Total Synthesis Guided Structural Revision of Peribysin Family Natural Products and Development of Novel Method for Enone Transposition

by

Paresh R. Athawale
10CC17J26033

A thesis submitted to the
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in
SCIENCE

Under the supervision of
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Certificate

This is to certify that the work incorporated in this Ph.D. thesis entitled, "*Total Synthesis Guided Structural Revision of Peribysin Family Natural Products and Development of Novel Method for Enone Transposition*", submitted by *Paresh R. Athawale* to the Academy of Scientific and Innovative Research (AcSIR) in fulfillment of the requirements for the award of the Degree of *Doctor of philosophy in science*, embodies original research work carried-out by the student. We, further certify that this work has not been submitted to any other University or Institution in part or full for the award of any degree or diploma. Research material(s) obtained from other source(s) and used in this research work has/have been duly acknowledged in the thesis. Image(s), illustration(s), figure(s), table(s) etc., used in the thesis from other source(s), have also been duly cited and acknowledged.

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(Research Supervisor)
26.08.2021

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I Mr. Paresh R. Athawale, a Ph.D. student of the Academy of Scientific and Innovative Research (AcSIR) with Registration No. 10CC17J26033 hereby undertake that, the thesis entitled "Total Synthesis Guided Structural Revision of Peribysin Family Natural Products and Development of Novel Method for Enone Transposition" 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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Signature of the Supervisor
Name : Dr. D. Srinivasa Reddy
Date : 26/08/2021
Place : Pune

Acknowledgement

During the entire tenure of my doctoral research, I have been accompanied and supported by many people. Herein I take this opportunity to express my gratitude to all of them.

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Finally, with immense respect and gratitude, I thank the almighty for all that has been offered to me. I am, and will remain thankful for everything that has ever happened in my life, the good and the bad; for everything that I have achieved and few that I have lost. Some were blessings and some were lessons worth learning.

Paresh R. Athawale

Abbreviations

AcOH	acetic acid
AcCl	acetyl chloride
Ac_2O	acetic anhydride
Å	angstrom
Ar	aryl
MeCN	acetonitrile
Bn	benzyl
Boc	*tertiary*-butyloxycarbonyl
Br	bromo
brs	broad singlet
Bu	butyl
t-Bu	*tertiary*-butyl
calcd.	Calculated
cm^{-1}	1/centimeter
C–C	carbon-carbon
C–H	carbon-hydrogen
C–N	carbon-nitrogen
C–O	carbon-oxygen
CH_2Cl_2	dichloromethane
$CHCl_3$	chloroform
CH3CN	acetonitrile
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DMAP	4-dimethyl aminopyridine
DMF	*N*,*N*-dimethylformamide
DMSO	dimethylsulphoxide

Abbreviations

DMSO-d_6	deutriated dimethylsulphoxide
dd	doublet of doublet
d	doublet (in NMR) or day(s) (in Scheme)
Et	ethyl
EtOAc	ethyl acetate
EtOH	ethanol
equiv	equivalent
g	gram(s)
h	hour(s)
Hz	hertz
IR	infrared
J	coupling constant (in NMR)
mass (ESI+)	electron spray ionization mass spectroscopy
min	minute(s)
m	multiplet
mL	milliliter(s)
mmol	millimole(s)
mp	melting point
m/z	mass to charge ratio
Me	methyl
MHz	megahertz
N	normality
nM	nanomolar(s)
NMR	nuclear magnetic resonance
Ph	phenyl

Abbreviations

ppm	parts per million
Pr	propyl
q	quartet
R_f	retention factor
rt	room temperature
s	singlet
S_N	nucleophilic substitution
sec	secondary
t	triplet
tert	tertiary
THF	tetrahydrofuran
TFA	trifluroacetic acid
TLC	thin layer chromatography
UV	ultraviolet
v/v	volume by volume
wt/v	weight by volume
^oC	degree celsius
µM	micromolar
mg	Milligram
µmol	Micromolar

General Remarks

- All reagents, starting materials, and solvents were obtained from commercial suppliers and used as such without further purification. Solvents were dried using standard protocols or through MBRAUN (MB SPS-800) solvent purification system (SPS).
- All reactions were carried out in oven-dried glassware under a positive pressure of argon or nitrogen unless otherwise mentioned with magnetic stirring.
- Air sensitive reagents and solutions were transferred via syringe or cannula and were introduced to the apparatus via rubber septa.
- Progress of reactions were monitored by thin layer chromatography (TLC) with 0.25 mm pre-coated silica gel plates (60 F254). Visualization was accomplished with either UV light, Iodine adsorbed on silica gel or by immersion in ethanolic solution of phosphomolybdic acid (PMA), *p*-anisaldehyde, 2,4-DNP, KMnO4, Ninhydrin solution followed by heating with a heat gun for ~15 sec.
- Column chromatography was performed on silica gel (100-200 or 230-400 mesh size).
- Melting points of solids were measured using scientific melting point apparatus (Buchi 565).
- Deuterated solvents for NMR spectroscopic analyses were used as received.
- All ^{1}H NMR, ^{13}C NMR spectra were obtained using a 200 MHz, 400 MHz, 500 MHz spectrometer. Coupling constants were measured in Hertz. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad.
- HRMS (ESI) were recorded on ORBITRAP mass analyzer (Thermo Scientific, QExactive).
- Infrared (IR) spectra were recorded on a FT-IR spectrometer as a thin film.
- Optical rotation values were recorded on P-2000 polarimeter at 589 nm.
- Chemical nomenclature (IUPAC) and structures were generated using Chem Bio Draw Ultra.

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 Chemical Sciences**
Name of the Candidate	**Paresh Ramesh Athawale**
Enrollment No. and Date	**10CC17J26033 02 January 2017**
Title of the Thesis	**Total Synthesis Guided Structural Revision of Peribysin Family Natural Products and Development of Novel Method for Enone Transposition**
Research Supervisor	**Dr. D. Srinivasa Reddy**
Research Co-Guide	

1. Introduction and Statement of Problem

Yamada and co-workers isolated peribysins (A-J) from *periconia byssoides* OUPS-N133 from a marine animal source (sea hare *Aplysia kurodai*).[1] All of which showed potent cell adhesion inhibitory activity compared to herbimycin (IC_{50} = 38.0 μm). All these natural products are useful leads for control of cancer metastasis, inflammation and sickle cell anemia. In 2007-08 Danishefsky group reported first total synthesis of peribysin E starting with carvone.[2] This study also revised the absolute stereostructure of peribysin E by making both the enantiomers from corresponding carvones. Since peribysins A-J were isolated from the same source, we postulated that remaining nine peribysins from this source may need stereochemical revision. Moreover, in recent publication by Hashimoto *et al*. the structurally similar peribysins were isolated from a plant source (*periconia macrospinosa* KT3863) and they claimed that the Danishefsky's peribysin E revision was erroneous.[3] Thus, we took up a challenging task to determine the stereochemical discrepancies (if present) in peribysins by achieving their total synthesis and to take up the related opportunities arising out of it.

2. Objectives

a. Total synthesis and structural revision of peribysin family natural products
b. Development of novel method for enone transposition
c. Development of DBU/CH_3CN mediated oxidation of dienones

3. Methodology

The thesis is divided into two major chapters. Initial part of **Chapter 1** introduces the role of total synthesis in structural revision of natural products, cell adhesion inhibitors, sickle cell anemia and background of peribysin family natural products. Further it describes the total synthesis and structural revision of peribysins A, B, C, F and G. The later part deals with attempts towards peribysin D along with synthesis of *ent*-peribysin Q. **Chapter 2** includes development of novel method for enone transposition and its application towards the synthesis of peribysin D. Second part deals with the development of DBU/CH_3CN mediated oxidation of dienones and its application to the synthesis of (±)-pleodendione.

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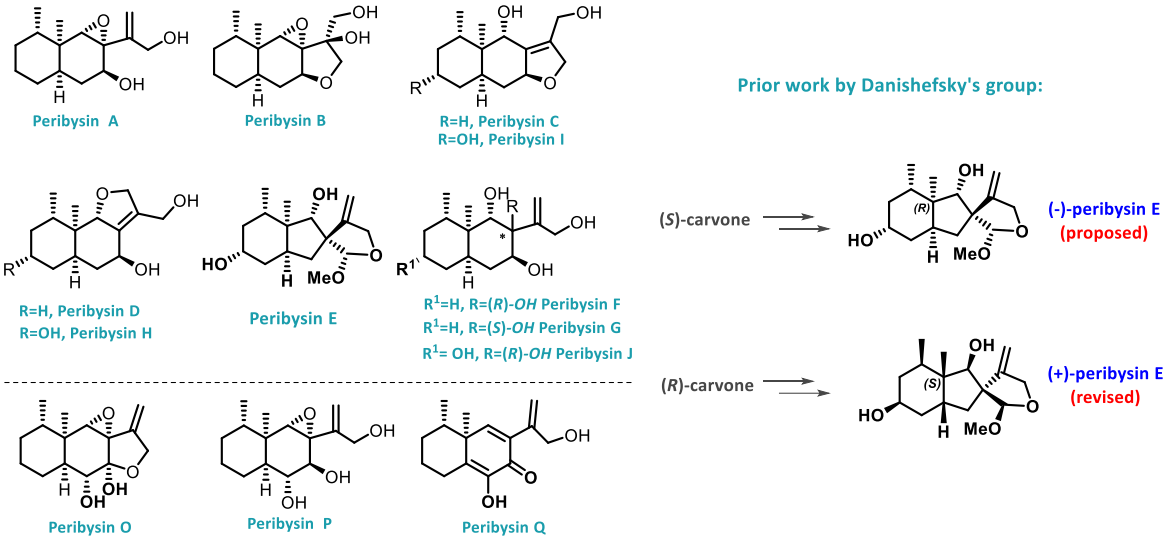
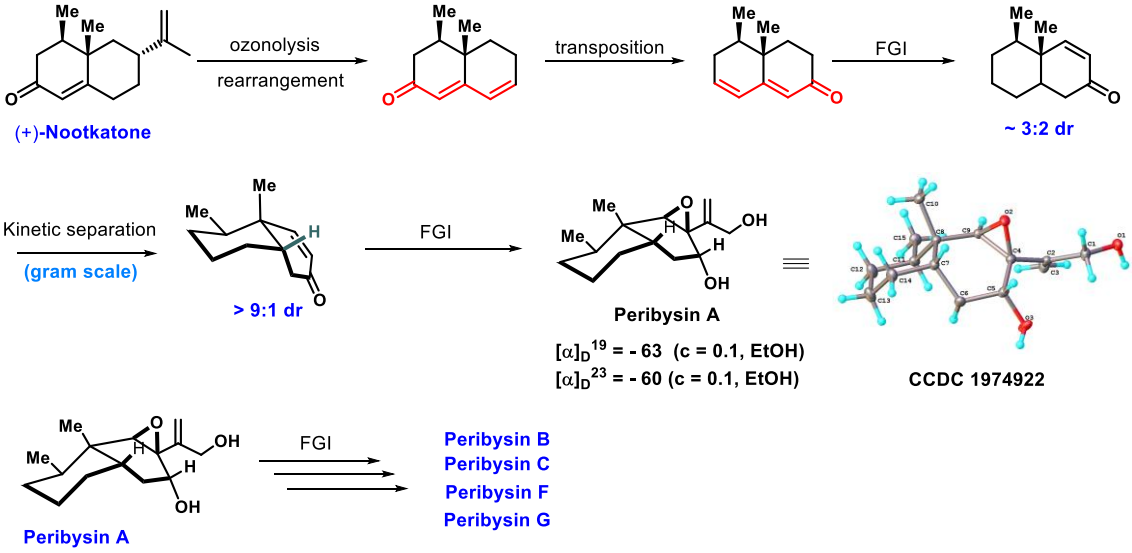
Chapter I: Total Synthesis Guided Structural Revision of Peribysin Family Natural Products



We started with the total synthesis of peribysin A (first member of this family) with commercially available starting material (+)-nootkatone. Ozonolysis followed by rearrangement of nootkatone and subsequent enone transposition afforded dienone product. Further via key kinetic separation of enone and functional group manipulations synthesis of target compound peribysin A was achieved. Based on specific optical rotation, NMR and single crystal X-ray data the structure of peribysin A was revised. Further peribysin A was used to prepare peribysin B, C, F and G (revised structures). In addition several attempts were made for the synthesis of peribysin D with no success.[4]

Total synthesis of peribysin A, B, C, F and G (revised structures)



Total synthesis of *ent*-peribysin Q

For absolute stereochemistry confirmation of recently isolated peribysins, peribysin Q was synthesized from one of the enone intermediate. Based on NMR, optical rotation and circular

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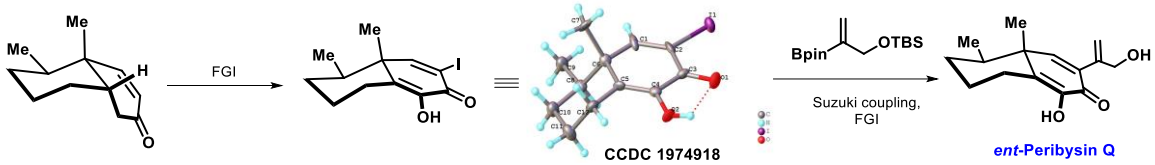
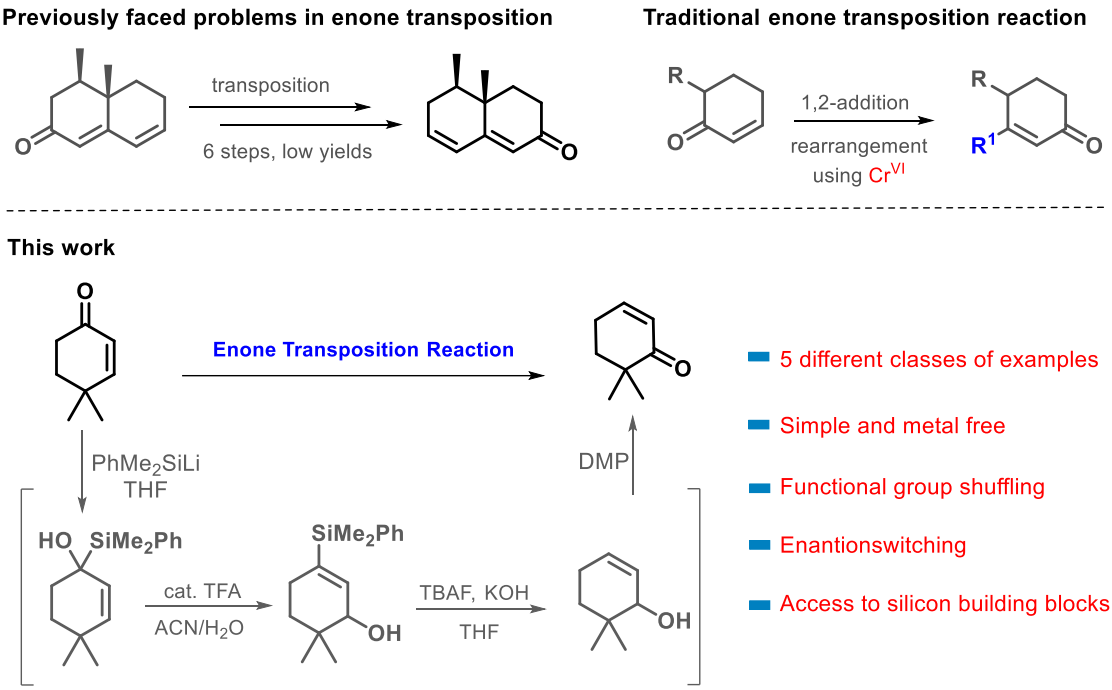
dichroism data it was concluded that we have synthesized *ent*-peribysin Q. During this process of total synthesis of six peribysin family natural products we created a library of several close analogues which are being screened in relevant biological assays.



Chapter II:
Section I: Development of Novel Method for Enone Transposition

During the synthesis of peribysin family natural products, we came across a situation where we wanted to perform an enone transposition. For this purpose, we screened several routes with no success and finally settled with a six step sequence with low yields. Classical enone transposition methods involves use of excess of chromium reagents, tedious workup procedures and low yields. In most of the cases the group added on the carbonyl group remains in the end product. Thus we envisioned to develop a reliable method for enone transposition and to apply it for the synthesis of useful building blocks and natural products. We decided to choose a masking group which can be detached easily after transposition.



After screening several conditions, we optimized the sequence by using 1,2 addition of $PhMe_2SiLi$ followed by rearrangement of tertiary allylic alcohol using catalytic TFA and finally cleavage of silicon moiety using TBAF and KOH. The scope of this method is being tested with various substrates. Interestingly 5-substituted cyclohexenones undergo enantio-switching and several other examples also undergo functional group shuffling when treated under these conditions. As an application the method is applied towards the synthesis of peribysin D which was not accomplished before.

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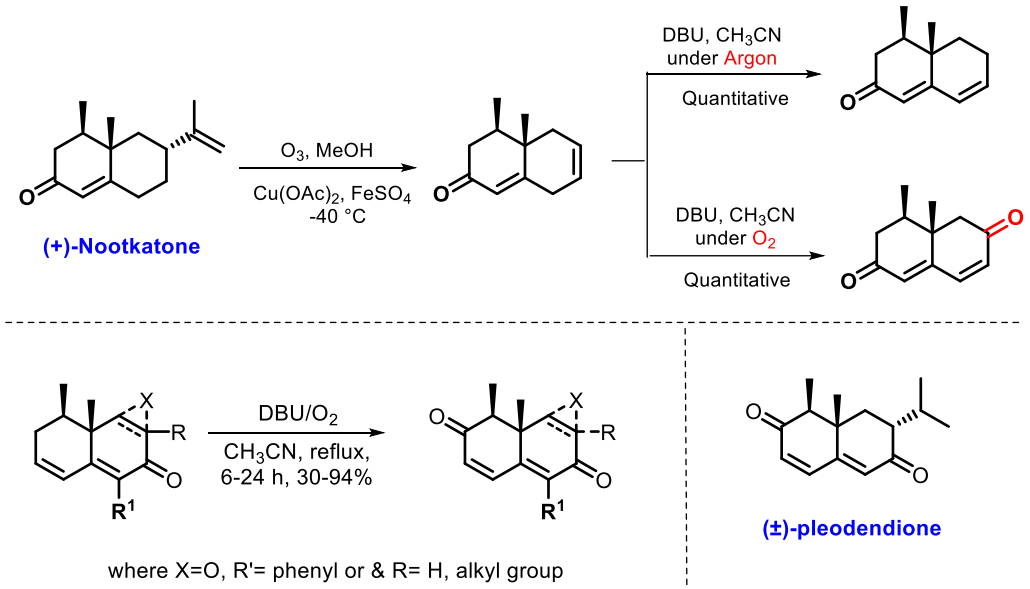
Section II: Development of DBU/CH_3CN mediated oxidation of dienones and its application to the synthesis of (±)-pleodendione

During the course of synthesis of peribysin A, we performed an ozonolysis of (+)-nootkatone and the resultant product was subjected for double bond migration using DBU in acetonitrile. Along with the expected conjugated dienone we observed the formation of diene-dione as by-product in trace amounts. Thus to verify the formation of this by-product we conducted controlled experiments under argon and oxygen atmosphere. Surprisingly we observed the exclusive formation of diene-dione under oxygen atmosphere. Thus we decided to explore this interesting method for synthesis of diene-diones using simple reagents.



After screening several conditions we found that the best yields were obtained when reaction was performed in oxygen atmosphere using DBU as a base in acetonitrile. We tested the scope of this method with more than 13 substrates with up to 94% isolated yield. The method was successfully applied for the synthesis of natural product (±)-pleodendione.

4. Summary

a) Accomplished the total synthesis of peribysin A, B, C, F, G and *ent*-peribysin Q for the first time in enantiopure form.
b) An unexpected but useful kinetic separation of enone was discovered during the synthetic sequence.
c) Structures of peribysins isolated from marine source (*periconia byssoides* OUPS-N133) were revised based on specific optical rotation and X-ray crystal structure data, whereas peribysins isolated from terrestrial source (*periconia macrospinosa* KT-3863) need no any revision.
d) Silicon mediated novel method for enone transposition was developed which was successfully tested on more than 10 substrates and applied towards the synthesis of peribysin D.
e) During the synthesis of peribysins a mild and efficient method for oxidation of dienones mediated by DBU/CH_3CN under oxygen atmosphere was discovered and it was tested on more than of 13 substrates and applied for the synthesis of (±)-pleodendione.

15/9/20

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5. Future directions

a. To test the synthesized peribysins and their analogs for their cell adhesion inhibitory activity
b. To expand the scope of enone transposition method.

6. Publications

a. Athawale, P. R.; Kalmode, H. P.; Motiwala, Z.; Kulkarni, K. A.; Reddy, D. S. *Org. Lett.* **2020**, *22*, 3104–3109.

7. References

A. (a) Yamada, T.; Minoura, K.; Tanaka, R.; Numata, A. *J. Antibiot*. **2006**, *59*, 345; (b) Yamada, T.; Iritani, M.; Minoura, K.; Kawai, K.; Numata, A. *Org. Biomol. Chem*. **2004**, *2*, 2131; (c) Yamada, T.; Doi, M.; Miura, A.; Harada, W.; Hiramura, M.; Minoura, K.; Tanaka, R.; Numata, A. *J. Antibiot.* **2005**, *58*, 185; (d) Yamada, T.; Minoura, K.; Tanaka, R.; Numata, A. *J. Antibiot*. **2007**, *60*, 370.

B. (a) Angeles, A. R.; Waters, S. P.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2008**, *130*, 13765. (b) Angeles, A. R.; Dorn, D. C.; Kou, C. A.; Moore, M. A. S.; Danishefsky, S. J. *Angew. Chem. Int. Ed*. **2007**, *46*, 1451.

C. Inose, K.; Tanaka, K.; Yamada, T.; Koshino, H.; Hashimoto, M. *J. Nat. Prod*. **2019**, *82*, 911.

D. Athawale, P. R.; Kalmode, H. P.; Motiwala, Z.; Kulkarni, K. A.; Reddy, D. S. *Org. Lett.* **2020**, *22*, 3104–3109.

D S Reddy 15/9/20

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Table of Content

Chapter 1

Total Synthesis Guided Structural Revision of Peribysin Family Natural Products

Table of Content

Chapter 2

Section I Development of Novel Method for Enone Transposition

Table of Content

Section II Development of DBU/CH_3CN mediated oxidation of dienones and its application to the synthesis of (±)-pleodendione

Chapter 1

Chapter 1 Total Synthesis Guided Structural Revision of Peribysin Family Natural Products

1.1 Introduction

Over the past few centuries natural product chemistry has evolved tremendously starting from the use of the herbs or plant extract for treating the illness/disease to multi-tonne manufacturing of the actual active ingredient without need of extraction or isolation from natural source.[1] For most of the drug discovery programmes across the world the basis for selection of targets is either natural products or their close derivatives. Some of the early natural medicines includes aspirin, morphine, quinine etc. where the journey started from the use of plant extracts for particular pharmacological action, evolved with isolation/identification of active ingredient and ended with the use in day-to-day life.[2] One famous example of this kind was the discovery and development of penicillin which revolutionized the area of antibiotics and modern drugs. This whole process of bringing the medicines from plant to pharmacy goes via a rigourous drug discovery process which starts with the isolation and structural identification of natural products.

Traditional structural elucidation of natural products was mainly dependent on chemical synthesis till mid of the 20th century. Isolation chemists used to perform derivatization and degradation studies (with large quantities in hand) followed by characterization using physical properties such as sharp melting points, boiling points, odour, colour, optical rotation etc. or comparison with the known compounds to look into the unknown structure of natural product.Thus the processes were lengthy and tedius to come up to a logical conclusion towards structure, but with the revolution of sophisticated techniques such as NMR spectroscopy, X-ray crystallography, circular dichroism, computational prediction softwares etc. the structural determination has become a day- to-day task with minimal or no requirement of chemical synthesis. Though there are several advanced techniques available, the errors in structural assignments can never be neglected (due to indirect nature of some of these techniques) especially with respect to absolute stereochemistry, which most of the techniques fail to determine. In this regard, total synthesis still offers the way to solve the puzzles that remain unaddressed during structural assignment.[3]

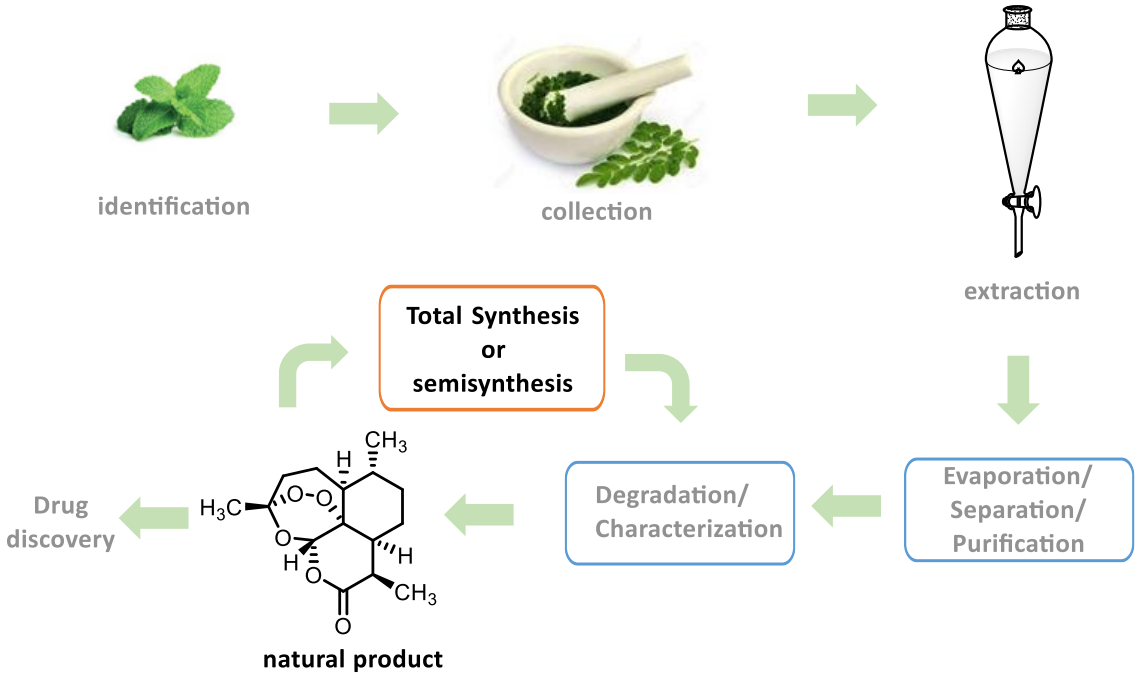
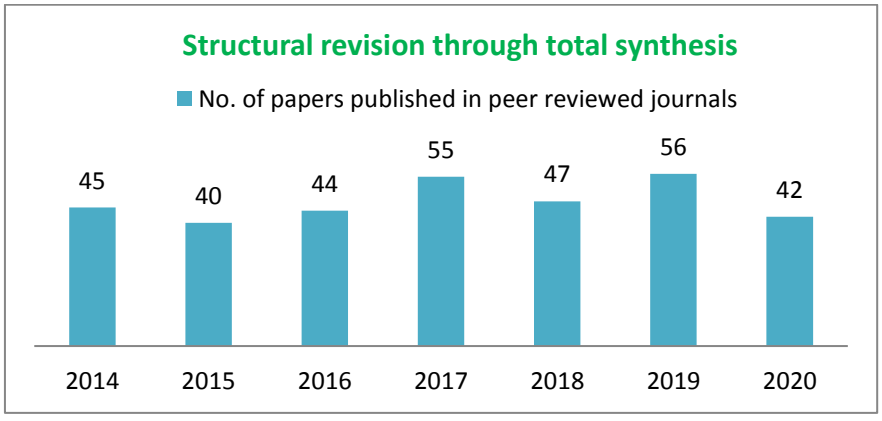


Figure 1.1 Role of total synthesis in traditional natural product isolation

1.1.1 Natural products revised by total synthesis

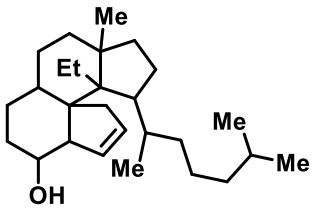
Over the years, several publications appeared in peer reviewed journals involving studies with structural reassignments/corrections by total synthesis.[4] These natural product revisions are mainly divided into two classes; first one is structural revisions where core structure/framework is revised and the second one is stereochemical revision where the absolute or relative stereochemistry is revised.



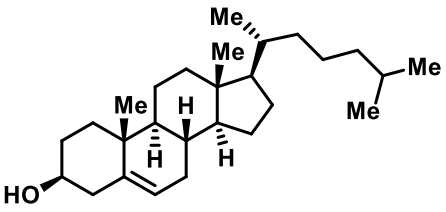
* = data collected up to December 2020

Figure 1.2 Structural revision through total synthesis

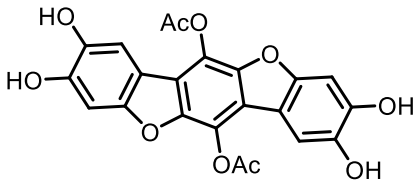
A classical example of structural misassignment was reported way back in 1927 by Windaus and Weiland on structure of cholesterol which was believed to be a hot topic at that time, later the structure was corrected in 1932 after X-ray crystal structure of ergosterol was published.[5] The originally proposed structure of cholesterol had 6/6/5/5 fused system whereas the revised structure had 6/6/6/5 skeleton. In second example the originally assigned structure of polyozellin contained *p*-diacetate substituted benzofuran moiety whereas the revised structure has *o*-diacetate substituted benzofuran moiety.[6] In 2005, B. B. Snider *et al*. reported the structural revision of epohelmin B where the proposed 9-oxa-4-azabicyclo[6.1.0]-nonane skeleton was reassigned to pyrrolizidin-1-ol structure.[7]



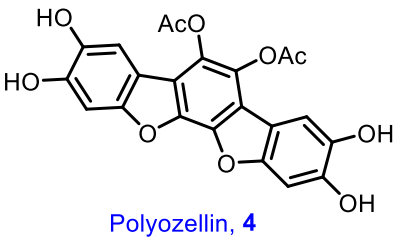
Cholesterol, **1**
proposed structure



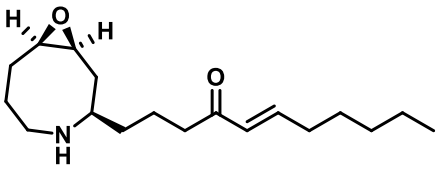
Cholesterol, **2**
revised structure



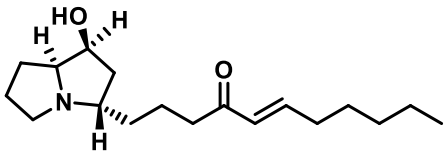
Polyozellin, **3**
proposed structure



Polyozellin, **4**
revised structure



Epohelmin B, **5**
proposed structure



Epohelmin B, **6**
revised structure

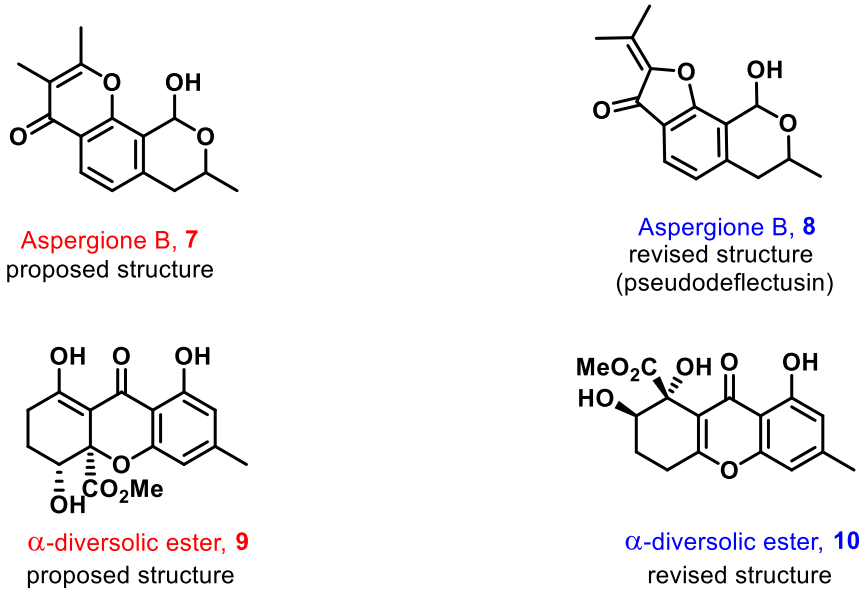
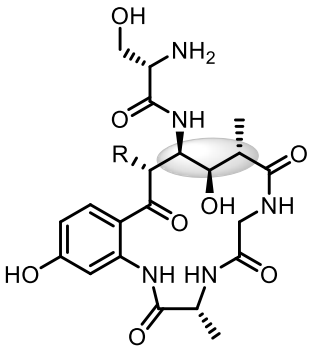


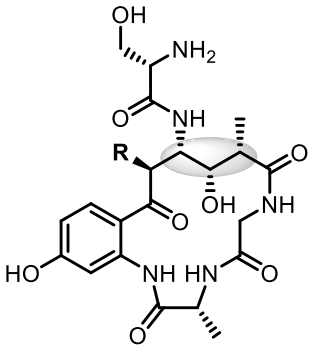
Figure 1.3 Selected examples of structural revisions

F. Saito *et al.* in 2006 while working on synthesis of pseudodeflectusin found that the synthesized natural product had the spectral data similar to spergione B. Thus they also synthesied putative structure of aspergione B and based on spectral data they concluded that, aspergione B and pseudodeflectusin B were the same compounds which resulted in the structural revision of the former.[8] Likewise there are hundreds of natural products revised so far and a few of them are captured in Figure 1.3.

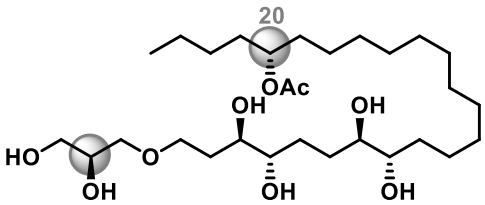
Two structural revisions reported from our group are captured in Figure 1.4. In case of solomonamides three chiral centers in un-natural amino acid part were corrected by synthesizing all possible (eight numbers) stereoisomers.[9] In case of mycalol secondary hydroxyl group stereochemistry and position of one of the acetate group was corrected by synthesizing the fragments with varying acetate group position.[10] Some of the recent examples include structural revision of Hydroxycurvularin by H. Choe *et al.*[11] and synthesis and revision of Aeruglnosin by K. Gademann and co-workers[12] where one chiral center was revised in both the cases.



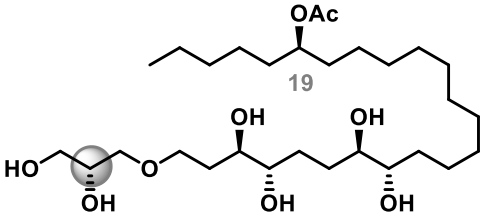
R = OH, Solomonamide A, **11**
R = H, Solomonamide B, **12**
proposed structures



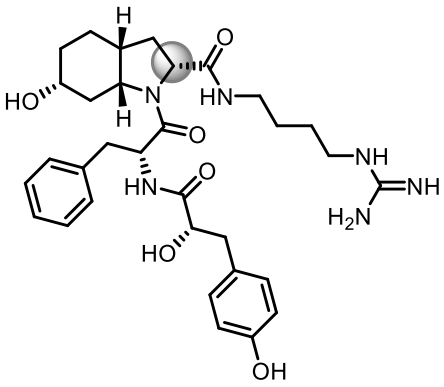
R = OH, Solomonamide A, **13**
R = H, Solomonamide B, **14**
revised structures



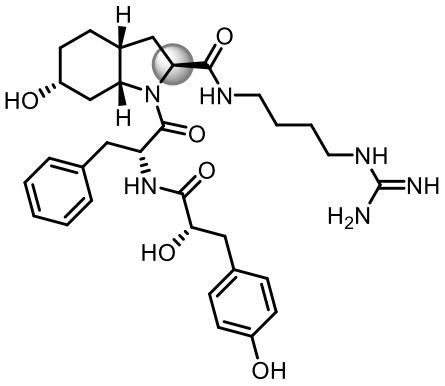
Mycalol, **15**
proposed structure



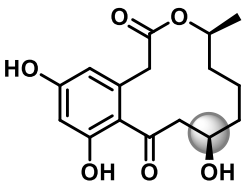
Mycalol, **16**
revised structure



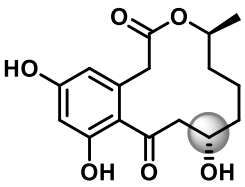
Aeruglnosin KT608A, **17**
proposed structure



Aeruglnosin KT608A, **18**
revised structure

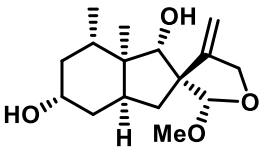


(-)-11a-Hydroxycurvularin, **19**
proposed structure

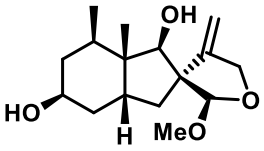


(-)-11a-Hydroxycurvularin, **20**
revised structure

..... and many more



Peribysin E, **21**
proposed structure



Peribysin E, **22**
revised structure

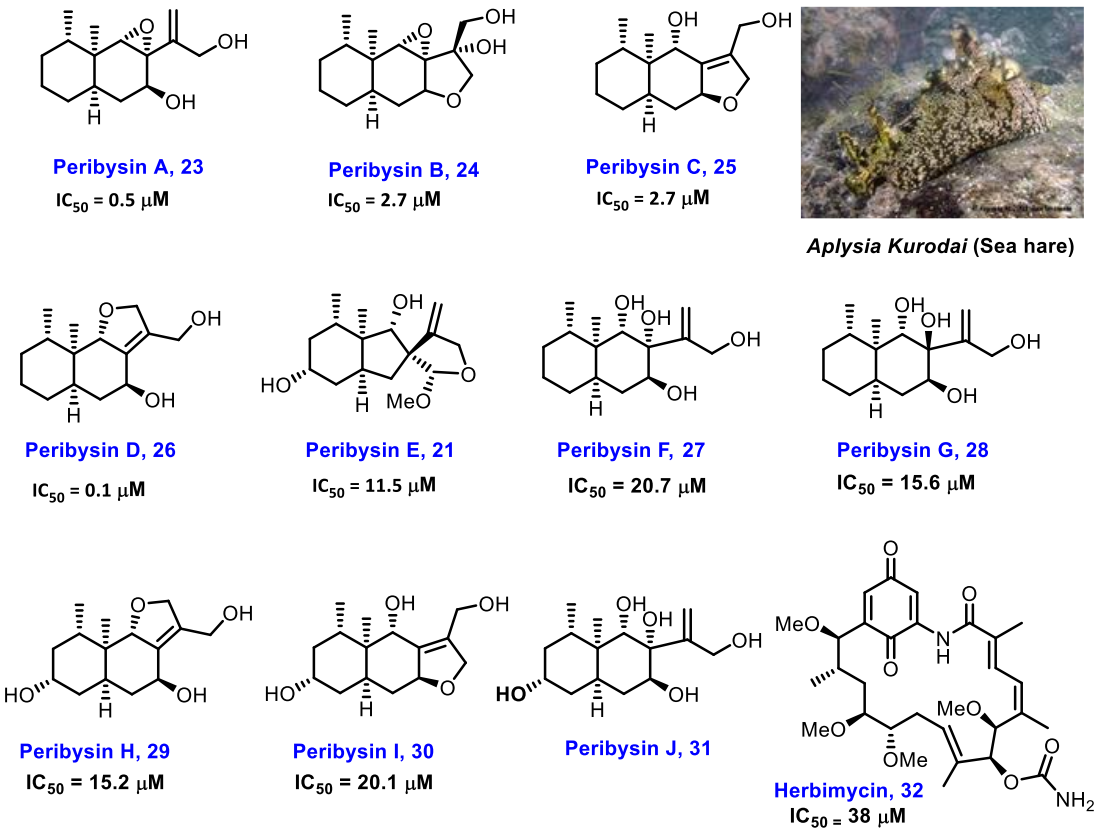
Figure 1.4 Selected examples of stereochemical revisions

Similarly the structure of natural product peribysin E, which was isolated from the strain of *Periconia byssoides* OUPS-N133 was revised by Danishefsky's group in 2007-08 in which all the stereocenters present in peribysin E were revised.[13] The actual natural product was the enantiomer of the proposed structure. They reported the synthesis of this spiro-eremophilane natural product by synthesizing both the enantiomers starting from respective enantiopure carvones without any ambiguity.

1.1.2 Natural products isolated from *Periconia byssoides* OUPS-N133

There are hundreds of eremophilane natural products isolated per year with various biological activities from various sources.[14] Yamada and co-workers isolated 10 such eremophilane natural products from the strain of *Periconia byssoides* OUPS-N133 which was originally separated from a sea hare *Aplysia Kurodai* and named as peribysins A-J.[15] Structures of all these natural products were determined by extensive NMR studies and derivatization. Structrally, all of them contain vicinal dimethyl groups and a *cis*-fused decalin junction except in peribysin E, which possess a hydrindane skeleton. Relative stereostructure of peribysin G was determined by single crystal X-ray diffraction and the absolute stereostructures of peribysins A, E, F and G were determined by either CD spectra, 2D NMR studies or derivatization for some of them. Based on these results and considering the same source of isolation, absolute stereochemistry of remaining natural products were assigned. All these natural products showed potent cell adhesion inhibitory activity compared to the standard drug herbimycin. Cell adhesion is a process where some specific proteins help the cells to bind to each other in order to maintain the regular functions of the tissue. But when it comes to the tumor cells, this process of cell adhesion needs to be inhibited in order to control the tumor formation. Thus cell adhesion inhibitors play a vital role in tumor cell

migration and cancer cell metastasis. Since there is a close relation between cell adhesion inhibiors for treating sickle cell anemia (SCA) and some of them are currently in clinical trials; we believed that these peribysin natural products with potent cell adhesion inhibitory activity may be useful leads for treating SCA.[16] These compounds can also be useful for treating inflammation and cancer cell metastasis.



IC_{50} values for cell adhesion potential compared to standard drug herbimycin

Figure 1.5 Proposed structures of peribysins isolated from *Periconia byssoides* OUPS-N133

1.1.3 **Sickle cell anemia**

Sickle cell anemia (SCA) is a genetic disorder related to red blood cells. The cells become sickled in shape as a result of which blood vessels get clogged which cause several disorders such as pain, anemia, bacterial infection or even stroke.[17] Out of all cases of sickle cell anemia 88% cases occur in Asia.[18] Till end of 2019 there was no approved drug for treating SCA, the only causative agent approved was hydroxyurea. Recently in November 2019 FDA approved Voxelator (trade name: Oxbryta) for

treatment of SCA in persons above age of 12 years.[19] Because of huge number of cases occurring in Asia, government of India initiated a programme to find the lead compounds for treating this disease (also known as sickle cell anemia mission-one of the major programme in CSIR-laboratories).

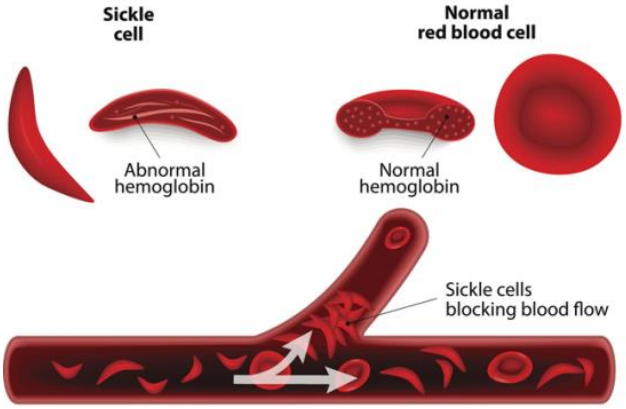


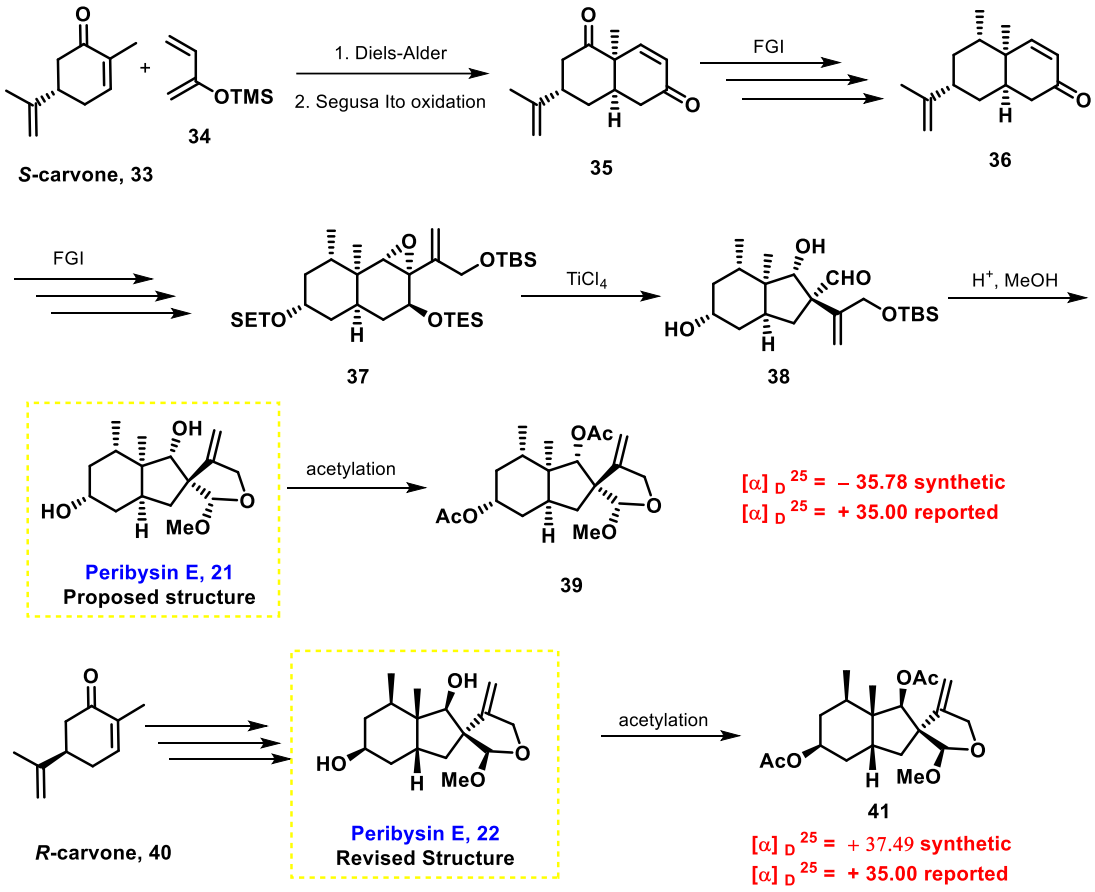
Figure 1.6 Sickel cell anemia schematic presentation[17]

1.1.4 **Previous work on peribysins**

Because of the structural features and interesting biological activities, peribysins gained a lot of attention from synthetic community. Early work involved synthesis of peribysin E, the only hydrindane core natural product from the family having a spiroacetal moiety and possessing seven chiral centers. In literature mainly three different groups reported work on peribysin E, one is enantiopure synthesis by Danishefsky's group and two are racemic synthesis from Sha's group and our group.[20] Later in 2018 our group reported first total synthesis of peribysin A and B in racemic form.[21] Work from all these groups is capured below in brief.

1.1.4.1 **Work done by Danishefsky group**

Danishefsky group was the first to achieve the total synthesis of peribysin E in enantiopure form in 2007.[13] But, after careful analysis of specific optical rotation of peribysin E and its diacetate derivative they concluded that peribysin E needs stereochemical revision since the optical rotation value obtained for the synthetic sample was with opposite sign.



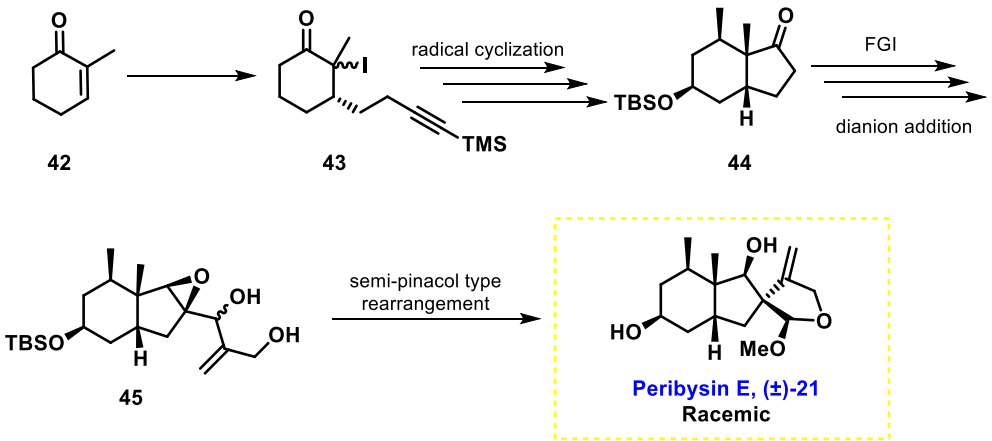
Scheme 1.1 Danishefsky's approach for peribysin E

Later, in 2008 same group synthesized both the enantiomers of peribysin E starting from carvone as a chiral pool starting material. Finally they concluded that the originally assigned structure of peribysin E by Yamada's group was *ent*-peribysin E. The synthesis relied on Diels Alder reaction to construct the *cis*-decalin framework **35** starting from carvone and Danishefsky diene. Compound **35** was then transformed into **36** by series of functional group interconversions. **36** was then subjected for key step of the synthesis semi-pinacol rearrangement using $TiCl_4$ to get hydrindane compound **38**. Finally acetal formation using methanol in acidic condition furnished target compound peribysin E. All the NMR spectral data for the synthetic compound was in complete agreement with the reported one but the specific optical rotation did not match. When recorded in ethanol at same concentration, the synthetic sample showed optical rotation $[\alpha]_D^{25} = -52.17$, whereas the reported value for natural peribysin E was $[\alpha]_D^{25} = -262.2$. Although the sign of the rotation was same, the difference in magnitude was

so large to conclude anything. Thus, they synthesized the di-acetate derivative, **39** and compared the optical rotation for the synthetic sample and the value obtained was –35.78 while the reported value for natural sample was + 35.00. With this result they were able to conclude that the originally assigned structure was *ent*-peribysin E. To prove this, they synthesized the other enantiomer using the same chemistry starting from *R*-carvone and prepared its diacetate derivative, which had the rotation value + 37.49. With this they revised structure of peribysin E by synthesizing both the enantiomers. One year later same group published a paper with a modified synthetic approach and synthesized both enantiomers again without any ambiguities in 18 step sequence.

1.1.4.2 **Work done by Sha's group**

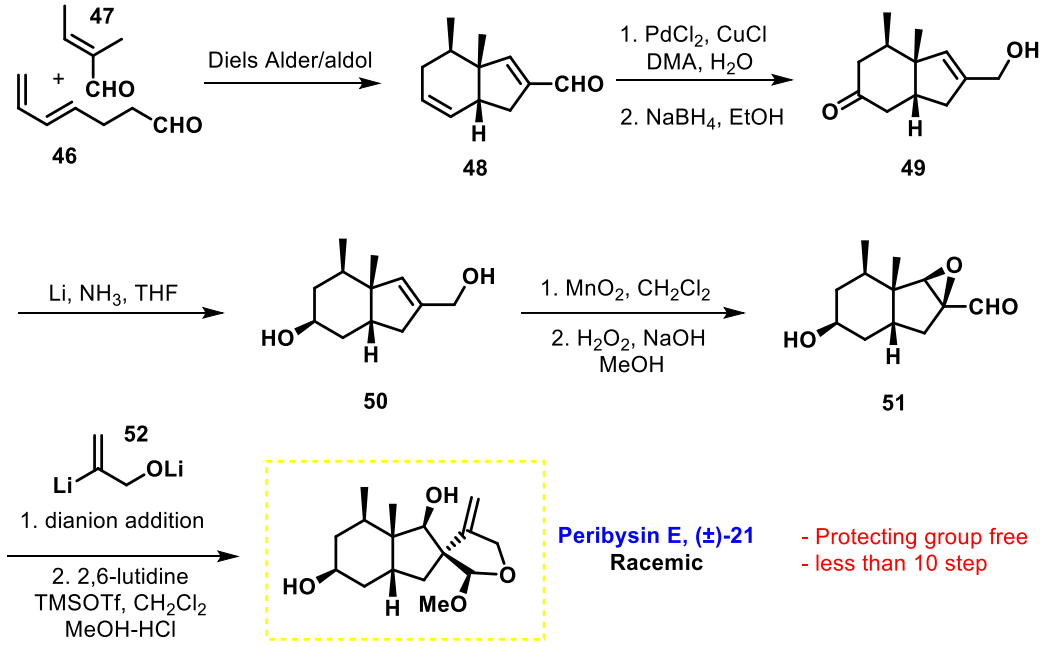
In 2011 Sha and co workers reported the approach for synthesis of racemic peribysin E starting from 2-methyl cyclohexanone using a protocol developed from their own group for radical cyclization of α-iodo ketones to construct *cis*-hydrindane skeleton **44**.[20b] After several functional group interconversions and dianion addition they reached upto intermediate **45** which upon semi-pinacol type rearrangement using 2,6-lutidine and TMSOTf followed by acetal formation using methanolic HCl they achieved the total synthesis of racemic peribysin E.



Scheme 1.2 Sha's approach for racemic peribysin E

1.1.4.3 **Work done by our group**

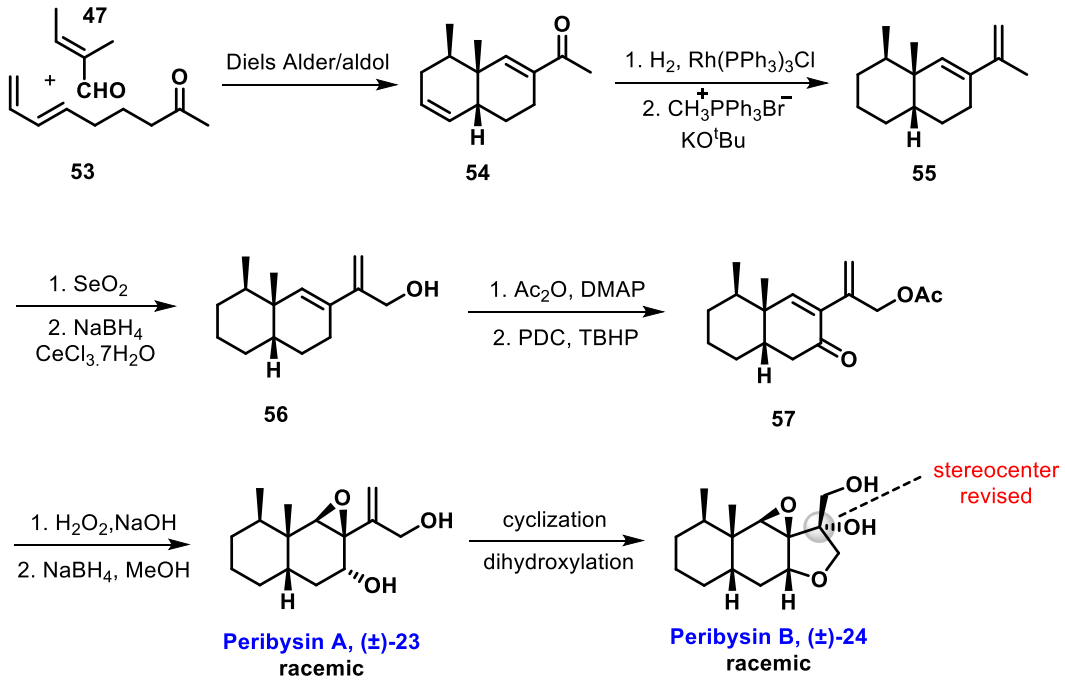
In our group, we have been actively working on the synthesis of decalin and hydrindane related natural products over the last decade.[22] Previously, our group developed a Diels Alder/aldol sequence for the construction of *cis*-decalin and hydrindane skeletons from tiglic aldehyde and suitable diene. In 2013, a short and protecting group free synthesis of racemic peribysin E using this chemistry was reported.[20a] The hydrindane compound **48** was prepared from tiglic aldehyde and diene **46** using Et_2AlCl as a Lewis acid to get selectively *cis* compound at lower temperature.



Scheme 1.3 Our group's approach for racemic peribysin E

Intermediate **48** was then then subjected for Wacker oxidation followed by chemoselective reduction of aldehyde carbonyl group using $NaBH_4$ at lower temperature furnished alcohol **49**. The keto group in compound **49** was selectively reduced using the Birch reduction condition to access alcohol **50**. The allylic alcohol **50** was oxidized using MnO_2 to get aldehyde. Finally, stereoselective epoxidation with H_2O_2-NaOH and dianion addition followed by acetal formation using TMSOTf gave peribysin E. During this synthesis, a library of analogues was generated for evaluation in biological assays.

In 2018, our group reported the first total synthesis of peribysin A and peribysin B in racemic form.[21]This time similar Diels Alder/ aldol chemistry was utilized by varying the diene to access *cis*-decalin moiety, **54** (scheme 1.4). Ketone **54** was then converted to diene **55** by selective hydrogenation of isolated double bond using Wilkinson's catalyst followed by one carbon Wittig reaction. Compound **55** was then subjected for Allylic oxidation using selenium dioxide to get aldehyde which was reduced to get allylic alcohol **56**. Primary alcohol group was then protected using Ac_2O and then allylic oxidation was achieved using low yielding PDC-TBHP condition to get ketone **57**. Finally epoxidation using H_2O_2-NaOH and reduction of carbonyl group using $NaBH_4$ provided racemic peribysin A. Peribysin A was then converted to peribysin B in a two step protocol first tosylation-cyclization followed by dihydroxylation. All the NMR spectral data of synthetic compound was matching with the natural peribysin B. But, interestingly after careful analysis of single crystal X-ray structure the stereochemistry of quaternary hydroxyl stereocenter was revised.



Scheme 1.4 Reddy's approach for racemic peribysins A and B

Both the natural products along with three close analogs were screened for their cell adhesion inhibition potential. The results were comparable with the reported biology results. This concludes all the reported approaches known so far for the synthesis of peribysins. Only peribysin E was synthesized in enantiopure form by Danishefsky

group, Sha and our group reported racemic peribysin E and also our group achieved racemic peribysin A and B synthesis.

1.1.5 **Natural products isolated from *Periconia Macrospinosa* KT-3863**

Ten years after Danishefsky's first paper on peribysin E revision appeared, two Japanese groups (Hashimoto and Yamada) reported isolation of three more peribysin natural products from *Periconia Macrospinosa* KT-3863 from a terrestrial herbaceous plant.[23]Although the source of isolation was completely different than that of the previously isolated peribysins, the natural prodcutswere named due to similarity in structure to those isolated previously by Yamada's group. The absolute stereostructures of these newly isolated natural products were assigned with the help of NMR studies and circular dichroism (CD) measurements. In addition to this, they also revisited peribysin E to have clarity on Danishefsky's claim of structural revision. After comparing the calculated and experimental CD spectra of newly isolated peribysins, they compared the calculated CD spectra of peribysin E and finally concluded that, the originally assigned structure of peribysin E (by Yamada group) was correct contrary to the results by Danishefsky's group. They supported their results with the assumption that peribysins isolated from same source can not have two different types of biogenetic pathways to produce opposite enantiomers.

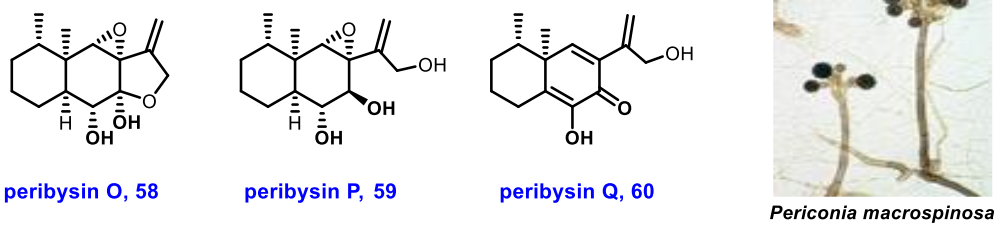


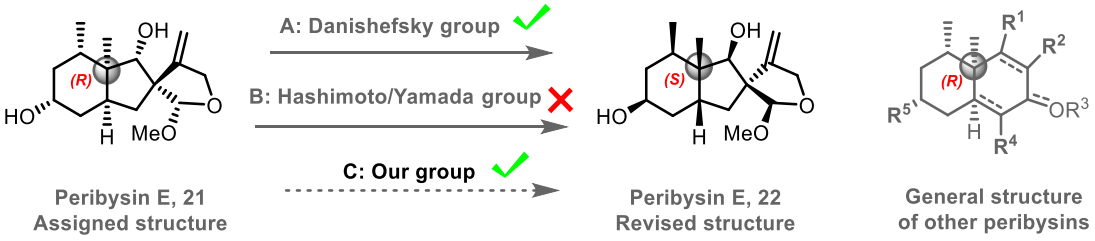
Figure 1.7 Peribysins isolated from *Periconia Macrospinosa* KT-3863

1.2 Present work

By considering great potential of peribysins as cell adhesion inhibitors, our group's continued interest in hydrindane and decalin natural products and to delineate the discrepancies in literature reports (about peribysin E) we decided to take up this challenging task of total synthesis of peribysin family natural products.

1.2.1 Views of different groups on peribysin E revision

Additional support for Hashimoto's recent publication was an argument that absolute stereochemistry of the natural products produced from same source belonging to a defined biogenetic pathway cannot be different.[23]In simple words peribysin E alone cannot possess opposite absolute stereochemistry. Since in our view Danishefsky group revised peribysin E unambiguously by preparing both the enantiomers starting with chiral pool, we made a hypothesis that whole peribysin family needs revision (based on isolation source).The hypothesis is captutered in Figure 1.8.



A: Structure of peribysin E was revised by total synthesis of both the enantiomers

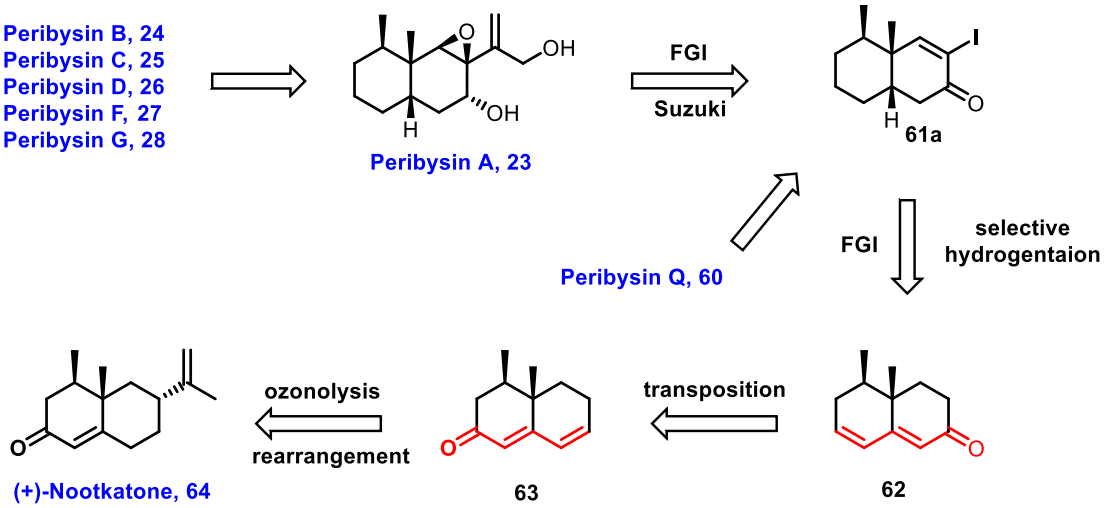
B: Danishefsky's revision of peribysin E was erroneous and peribysin E has structure like other peribysins

C: Danishefsky's peribysin E revision was right and remaining all peribysins needs revision

Figure 1.8 Hypothesis of peribysin family revision

1.2.2 Retrosynthesis of Peribysins

After making the hypothesis of peribysin family structural revision, we designed route as described retrosynthetic analysis so as to access all the natural product from this family and to generate a library of analogs. Since most of the peribysins can be derived from peribysin A itself, we first planned to synthesize peribysin A from a commercially available chiral pool starting material (+)-nootkatone, **64** which has a well established structure with X-ray crystallography.[24] Starting with (+)-nootkatone has an advantage that the dimethyl stereochemistry is already fixed thus the final outcome can be guessed without any ambiguity.

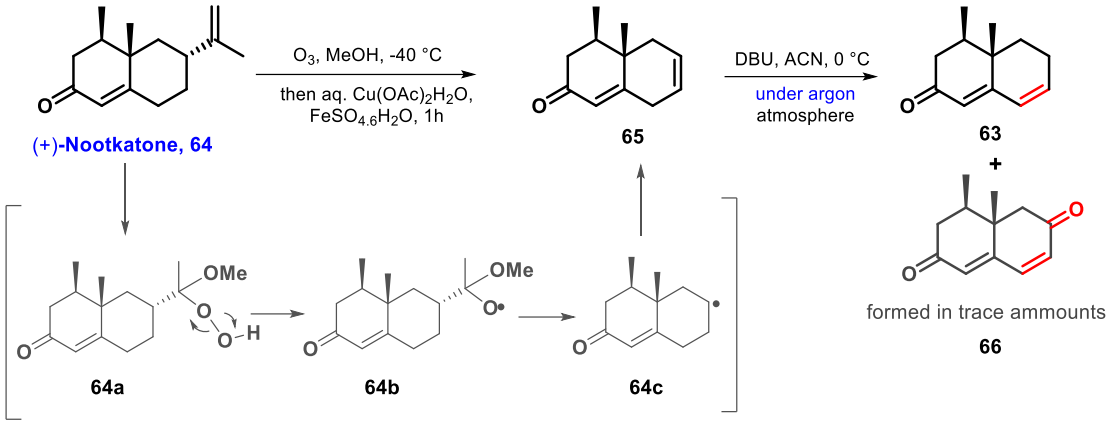


Scheme1.5 Retrosynthetic analysis for Peribysins

The target compound peribysin A was planned from iodo intermediate **61a** via Suzuki coupling followed by stereoselective operations. Iodo enone **61a** was planned from dienone **62** via selective hydrogenation to fix the stereochemistry of junction hydrogen and functional group interconversions. Dienone **62** was traced from dienone **63** by performing an enone transposition reaction/sequence. Finally dieneone **63** was planned from (+)-nootkatone by known ozonolysis reaction followed by rearrangement using base. The main challenge in the designed route was performing an enone transposition reaction and selective hydrogenation.

1.2.3 **Synthesis of dienone 62**

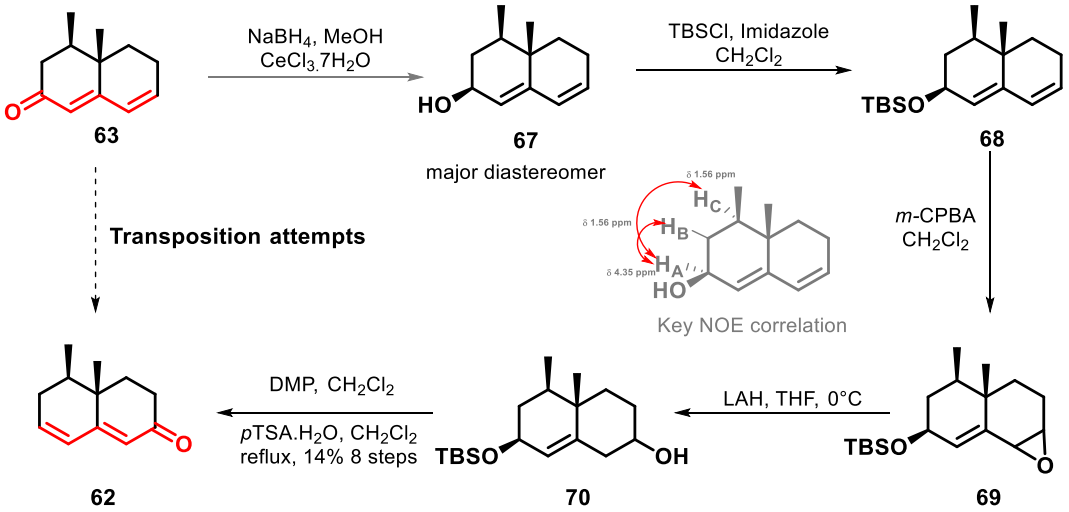
As per the plan, synthesis commenced with ozonolysis of (+)-nootkatone at –40 ^{o}C in methanol as a solvent which forms an methoxy-peroxide intermediate which upon β-fragmentation furnished alkyl radical which on hydrogen abstraction gave deconjugated dienone **65**. In the reported conditions by Newhouse and co-workers water soluble $Cu(BF_4)_2$ and $Fe(BF_4)_2$ salts were used for reductive quenching of methoxy peroxide.[25] But, in this case we observed that water insoluble and inexpensive $Cu(OAc)_2.2H_2O$ and $FeSO_4.6H_2O$ gave slightly better yields than reported one.[26] The reaction was performed on 20g scale batches without any difficulty.



Scheme 1.6 Ozonolysis of (+)-nootkatone

The crude enone **65** was subjected for double bond migration using DBU in acetonitrile at 0 °C for 4 hours under argon atmosphere to get compound **63**. The product was confirmed by checking TLC and dipping it in anisaldehyde solution which showed purple colour for product spot compared to greenish yellow colour for starting material. The ^{1}H NMR of compound **63** showed three protons in olefinic region and carbonyl signal appeared at δ 199.9 ppm in ^{13}C NMR which further confirmed the formation of dienone 63. In addition to compound **63** trace amount of compound **66** was observed which showed two carbonyl peaks in ^{13}C NMR. The reaction should be strictly performed with complete exclusion of oxygen to get conjugated dienone **63** exclusively. The reason for this will be visited again in chapter 2 section II.

Next task was to perform an enone transposition reaction from compound **63** to get compound **62**. For this purpose a six step sequence was adopted, first enone **63** was subjected for Luche reduction[27] to get allylic alcohol. The axial attack of hydride was favoured to give compound **67** as a major diastereomer. Although the stereochemical outcome of this reaction was not important at this stage, we assigned the stereochemistry of major diastereomer as shown in compound **67** (scheme 1.7) with the help of NOE experiment. The hydroxyl attached proton showed a correlation with adjacent methylene proton as well as methyl attached proton (Hc). Similar kind of diastereoselectivity was observed by S. D. Munari *et al.* during the synthesis of Androstane scaffold derivatives.[28]



Scheme 1.7 Dienone transposition

Next, the secondary alcohol was protected as TBS using TBSCl and imidazole to give compound **68** in quantitative yield over two steps. The less substituted double bond in compound **68** was epoxidised using *m*-CPBA in CH_2Cl_2 at 0 ^oC gave compound **69** as a major product which was carried as such for further reaction without any characterization. Epoxide **69** was then treated with LAH in THF at 0 ^oC to afford secondary alcohol **70**. Here LAH plays a dual role first to co-ordinate with epoxide to polarize the C-O bond of epoxide and opened from the side where positive charge is stabilized by double bond. The alcohol was then oxidied using Dess-Martin periodinane in CH_2Cl_2 to give ketone **71** (scheme 1.8) which showed a characteristic carbonyl carbon signal at δ 210 ppm. The ketone **71** was then treated with *p*-TSA.H_2O in CH_2Cl_2 under reflux for 4 hours to get dienone **62**. Here three reactions took place in one pot, TBS deprotection-hydroxyl group elimination and double bond migration. The compound showed four olefinic carbons at δ 163.3, 137.8, 127.9, 123.9 ppm and the carbonyl carbon appeared at d 199.9 ppm. Further comparison of this data was compared with the racemic compound previously reported by our group.[22b] Interestingly, this sequence of eight reactions starting with (+)-nootkatone can be performed with only one purification at dienone **62** stage. The overall yield after eight steps was found to be 14%. Although it was less yielding sequence, the amount was sufficient to go forward towards target compound. As this compound **62** is a vital intermediate which can be used for the synthesis of several natural products with the

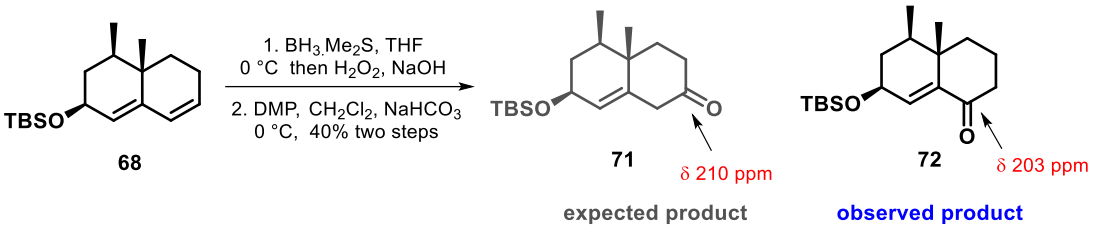
decalin skeleton, we wanted put more efforts by reducing number of steps and improving yields. Discussion in this direction are compiled in the following section.

1.2.4 **Failed attempts for enone transposition**

Before making enone **62** with the route mentioned in scheme 1.7, we also made a few attempts for enone transposition with no success. All these failed attempts are captured below in detail.

1.2.4.1 **Hydroboration-oxidation**

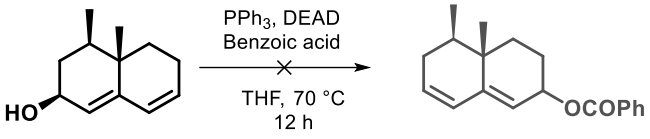
We envisioned that, the hydroboration-oxidation[29] reaction on less sterically hindered disubstituted double bond will happen first to give the required compound **71**. For this purpose compound **68** was treated with $BH_3.Me_2S$ and quenched with H_2O_2-NaOH mixture to give alcohol which was oxidized using DMP to give ketone compound. Surprisingly, the ketone product was highly uv active on TLC. Since, there are two possible products **71** and **72** one of them would be uv active because of the presence of enone moiety. After careful analysis of ^{13}C NMR finally it was concluded that the hydroboration-oxidation reaction gave the undesired ketone **72**. The carbonyl carbon appeared slighlt towards shielded region at δ 203 ppm vs expected shift of δ 210 ppm. Moreover the diastereotopic methylene protons in compound **71** would appear approximately in region of δ 2.4–3.0 ppm but in observed product they appeared at δ 2.2 to 2.5 ppm which further confirmed the formation of compound **72**.



Scheme 1.8 Hydroboration-oxidation attempt

1.2.4.2 **Mitsunobu reaction**

In second attempt, Mitsunobu reaction on doubly conjugated allylic alcohol, **67** was planned using standard Mitsunobu reaction condition assuming the distant attack of benzoate anion followed by saponification would give the desired transposition reaction similar to the reports by Cronje Grove *et al.*[30] Changing the sequence and rate of addition of reagents at 0 °C, room temperature or even at 70 °C did not give the desired product. Staring material was recovered completely in all the conditions.

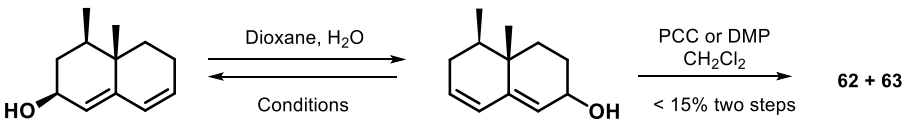


67 **73**

Scheme 1.9 Mitsunobu reaction attempt

1.2.4.3 **Water catalyzed transposition**

After failing in first two attempts, next we planned the water catalysed rearrangement as reported by Li *et al.*[31] Water at boiling temperature can act as a weak Bronsted acid which catalyzes the transposition of conjugated allylic alcohols. Thus, we treated allylic alcohol **67** in 9:1 mixture of 1,4-dioxane and water and refluxed the reaction mixture for 30 min. After 30 min. reaction was stopped and after isolation of product and analysis by ^{1}H NMR it was found that the desired rearranged allylic alcohol **74** and starting alcohol **67** were in equilibrium. The ratio was determined by NMR where separate peaks for oxygen attached proton were seen. This mixture was then oxidized with DMP which gave less than 15% yield of inseparable mixture of ketones **62** and **63**.



67 **74**

Scheme 1.10 Attempt for water catalysed transposition

To overcome this issue we thought of screening a few more reaction conditions to shift the equilibrium towards right side. All the conditions are captured below in Table 1.1. In first condition the reaction mixture was heated rapidly using microwave reactor at 100 ºC for 5 min. which showed the ratio of starting material and desired rearranged alcohol as 3:2.

Sr. No.	Temperature (ºC) Microwave	Time (min.)	Ratio of **67:74** (by NMR)
1	100	5	3:2
2	70	30	7:3
3	80	30	3:2
4	90	30	1:1
5	100	30	1:1
6	85*	12 h	1:1

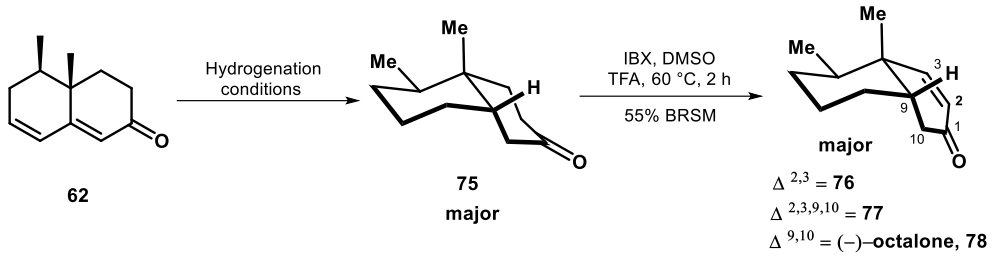
*reaction was performed in conventional heating condition

Table 1.1 Water catalyzed transposition

Further conditions 2 to 5 were performed by varying the temperature and keeping the reaction time fixed to 30 min. in microwave and condition 6 was performed in conventional heating at slightly lower temperature. In all the cases, the conversion to desired alcohol was not more than 50%.

1.2.5 **Synthesis of enone 76**

After various unsuccesful transposition attempts, we decided to go forward towards completion of synthesis using the same route described in Scheme 1.7. Although it is bit lengthy sequence, the dienone compound **62** was preparedupto 4.2 g scale. Now, as present in most of the peribysin family natural products we required a *cis*-fused decalin which was planned from the selective hydrogenation of enone **62** by taking the help of pre-organized axial methyl group as found in literature reports.[32]



Scheme 1.11 Synthesis of enone **76**

First we performed the conventional hydrogenation reaction using H_2 balloon and 10% Pd/C in methanol to get saturated ketone, **75** but only product observed was (–)-octalone,**78** where the enone double bond was intact. The product (–)-octalone was confirmed by comparing all the NMR spectral data with the reported data in literature.

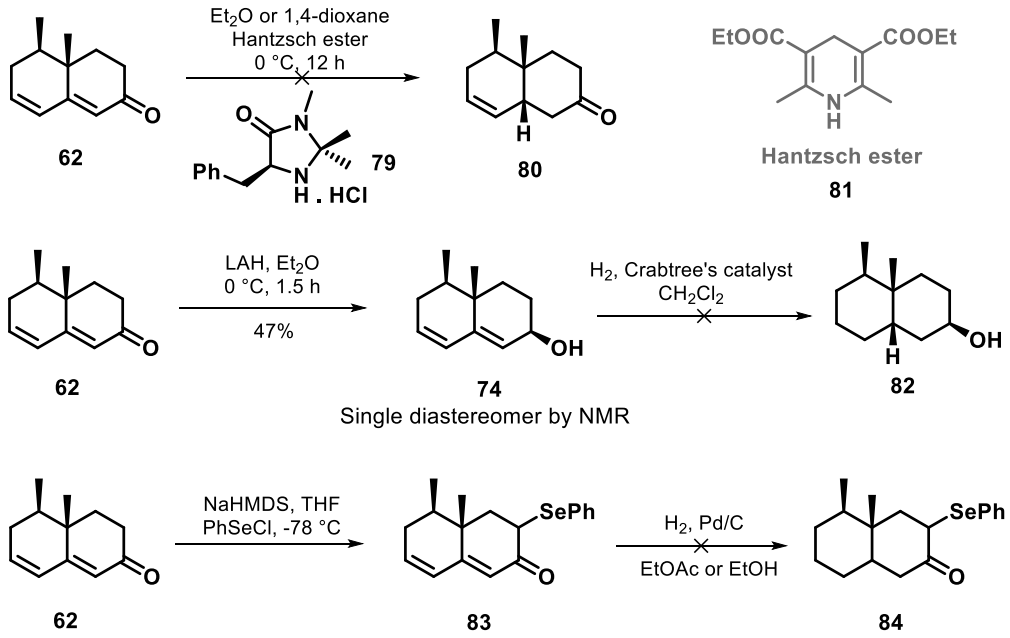
Sr. No.	Condition	Time	Product ratio*		
			***cis*-75**	**trans-75**	**(-)-octalone**
1	MeOH, H_2, Pd/C	12 h	ND	ND	100%
2	1% KOH in MeOH, H_2, Pd/C	12 h	60 %	40%	ND
3	ammonium formate, MeOH, Pd/C reflux	18 h	ND	ND	~ 50%
4	MeOH, H_2, Pd/C (800 psi, Parr reactor)	12 h	ND	ND	100%
5	$TiCl_4$, Et_3SiH, -78°C	2 h	60	40	ND
6	H_2, $RhCl(PPh_3)_3$ CH_2Cl_2	12 h	ND	ND	100%
7	1% KOH in EtOH, H_2, Pd/C	12 h	55%	45%	ND
8	2M HCl, CCl_4, H_2, Pd/C	12 h	Partially decomposed		

*Product ratio was confirmed by NMR after second step

Table 1.2 Attempts for selective hydrogenation

Furthermore the specific optical rotation was observed to be $[\alpha]_D^{24}$ = - 163.2 (c = 0.63, $CHCl_3$) which was comparable with the reported value$[\alpha]_D^{24}$ = - 169.2 (c = 2.1,

$CHCl_3$).[33] When the same hydrogenation was performed in presence of 1% methanolic KOH under hydrogen atmosphere it exclusively furnished the desired ketone **75**. At this stage the ratio of *cis* and *trans* isomers was not determined due to overlapping of peaks. Thus the crude material was forwarded for oxidation reaction using IBX in DMSO and catalytic amount of TFA which gave three different products.[34] Major one was (–)-octalone, then the required enone **76** and minor product was another natural product, **77** for which all the spectral data was perfectly matching with the reported data. [35] The ratio of enone *cis:trans* was found to be 60:40 by ^{1}H NMR. With this result we screened several conditions for selective hydrogenation using bulky Wilkinson's catalyst, $TiCl_4/Et_3SiH$ or in presence of catalytic mineral acid such as HCl and even under high pressure of hydrogen gas but the ratio did not improve more than 60:40.[36]



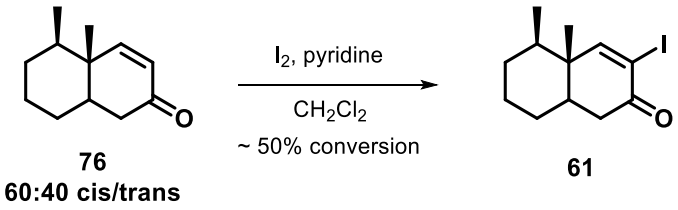
Scheme 1.12 Additional attempts for selective hydrogenation

Apart from the conditions listed in table 1.2, we also screened three more conditions. In first condition we treated dienone **62** with chiral imidazolidinone catalyst, **79** in presence of Hantzsch's ester in two different solvents at 0 °C but in both the cases starting material did not react at all. Even refluxing the reaction mixture did not give the required product. In second attempt we thought of taking help of a tethering group such as hydroxyl group which can bind with the metal catalyst to give the facial selectivity.[37]

For this purpose the dienone **62** was reduced to alcohol **74** which after purification showed a single diastereomer in NMR. This allylic alcohol was treated with Crabtree catalyst in CH_2Cl_2 under hydrogen atmosphere but the starting material was not consumed even after stirring the reaction for 24 hours. In the third attempt we prepared α-selenyl derivative of dienone **62** to get selenium derivative **83** which was subjected for hydrogenation using Pd/C under hydrogen atmosphere but the desired product was not observed. Instead, only deselenylated starting material was recovered.

1.2.6 **Iodination of enone 76**

With no good results of selective hydrogenation in hands we decided to move ahead in synthesis hoping that the two diasteromers may separate at some stage in the synthesis. Thus, both the natural products **77** and **78** were again recycled for hydrogenation and oxidation sequence to build up the quantity of enone **76**. After having gram scale quantity of compound **76**, it was treated for iodination using Johnson's protocol. For this purpose, we used one equivalent of iodine and two equivalents of pyridine at room temperature.[38]



Scheme 1.13 Iodination of enone **76**

After 12 hours, TLC analylsis showed about 50% consumption of starting material and formation of a slightly nonpolar product on TLC. Same ratio of both the compounds was observed when reaction was continued for 5 more hours.The rate of reaction was slow, adding excess of pyridine and iodine could improve the reaction rate to very less extent. Thus, we stopped the reaction by quenching with saturated solution of $Na_2S_2O_3$ and purified the mixture using column chromatography. After analysis of recovered starting material by ^{1}H NMR it was inferred that the diastereomeric ratio of recovered enone **76** was improved from 60:40 to 80:20. Both the enones showed clearly distinct chemical shift value for *β*-protons, in case of *cis* isomer it appeared at δ 6.8 ppm while

in case of *trans* isomer it appeared at δ 7.1 ppm. This observation clearly infers that one isomer has reacted faster compared to other.

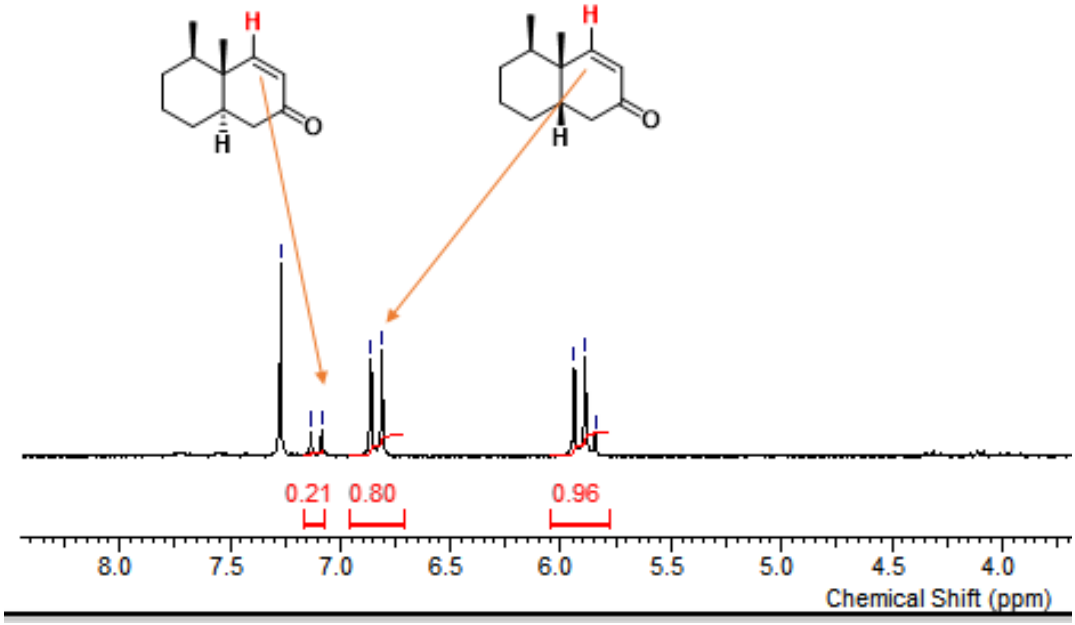
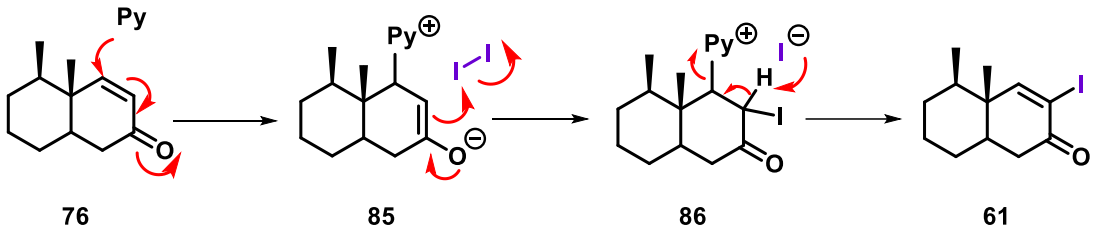


Figure 1.9 NMR analysis of recovered enone **76**

To see the reason for the difference in reactivity, we looked into the 3D structures of both the enones as shown in scheme 1.15. Moreover, according to literature reports mechanistically, pyridine first attacks at the *β*–position of enone to form enolate **85** which is trapped by iodine to give intermediate **86** and again elimination of pyridine gives iodo enone **61**.[38] In Danishefsky's synthesis of peribysin E they encountered a similar kind of intermediate which was very sluggish in iodination reaction which they assumed to be due to the presence of C-4 methyl group which might be creating steric hindrance for attack of pyridine at β-position.[13b]



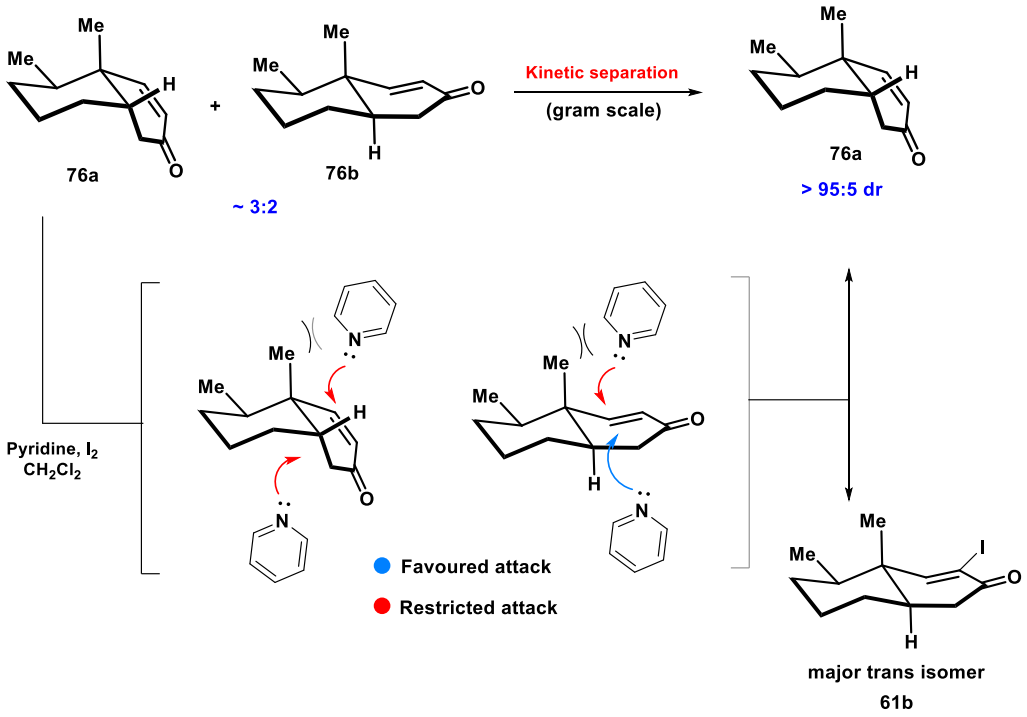
Scheme 1.14 Mechanism of α-iodination of enone

But in contrary, we have a mixture of *cis* and *trans* decalins both of which contains C-4 methyl group still one of the enone isomer was reacting faster as compared to other

enone which clearly tells that there is no any role of C-4 methyl group for the slower reactivity of enone **76**.

1.2.7 **Proposed model for kinetic iodination**

Thus we proposed a model for the difference in reactivity of enones based on the 3D structure. Here, *cis*-decalin **76a** has puckered structure compared to a flatter structure of *trans*-decalin **76b** which is responsible for difference in the reactivity (Figure 1.15). The attack of pyridine from top side is hindered because of the presence of C-4 methyl group in both the cases but the bottom side attack is more facile in case of *trans*-decalin. Thus, when the mixture of *cis* and *trans* enones is subjected for iodination in Johnson protocol, *trans* isomer reacts faster and slower reacting *cis* isomer gets enriched from 60:40 to more than 95:5 ratio.



Scheme 1.15 Model for kinetic iodination of enones

Thus, here we have encountered a novel kinetic separation of enones under Johnson protocol. After kinetic separation the stereochemistry of junction hydrogen was confirmed by recording 2D NMR. Strong NOE correlation was observed between junction methyl protons and junction hydrogen, for the *cis* isomer. Thus, under optimized condition when mixture of enones was treated with 1 equivalent of iodine

and six equivalents of pyridine for 24 hours at room temperature, it gave the kinetic separation with required isomer in more than 95:5 dr.

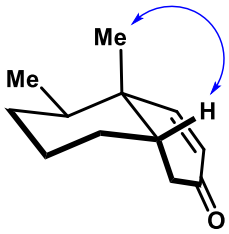
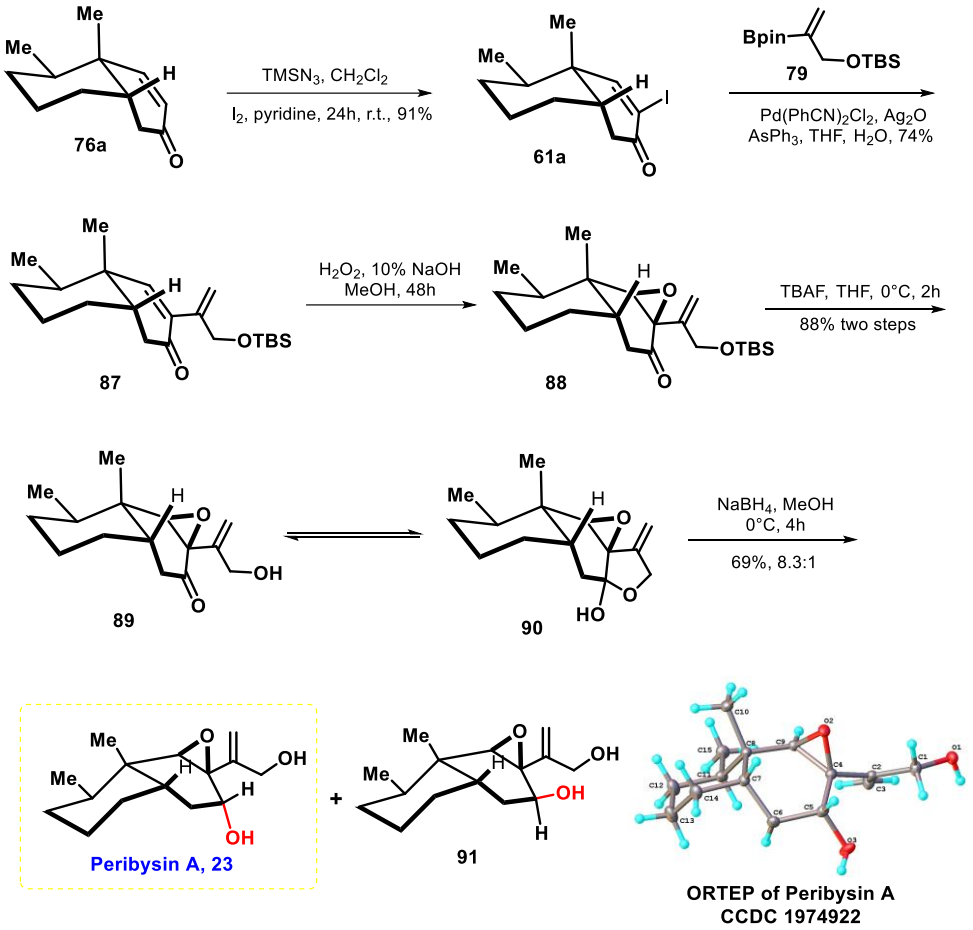


Figure 1.10 Key NOE correlation in enone **76a**

1.2.8 **Completion of peribysin A synthesis**

Since *cis*-enone **76a** was slow reacting in Johnson iodination protocol, we used $TMSN_3$ as used by Danishefsky's group.[13b] Using $TMSN_3$ has an advantage that, N_3 is a smaller nucleophile compared to pyridine and TMS helps to activate the enone towards facile enolate formation. Thus enone **76a** was converted to iodo enone **61a** using $TMSN_3$ and iodine in CH_2Cl_2. The iodo enone **61a** was then coupled with known boronate ester **79** using $Pd(PhCN)_2Cl_2$ as a catalyst in presence of Ph_3As as a ligand and Ag_2O as a base in THF and H_2O solvent mixture to get compound **87**. The ^1H NMR showed three olefinic peaks, one downfield signal for β-proton at δ 6.75 ppm and two terminal olefin protons appeared at δ 5.25 and 5.07 ppm. Further ^{13}C NMR of compound **87** showed four olefinic carbons which confirmed the formation of compound **87**. The α,β-unsaturated double bond in compound **87** was selectively epoxidized using H_2O_2-NaOH mixture to get compound **88**. In ^1H NMR only single diasteromer was observed which could be attributed to the presence of side chain which blocked the attack of peroxide anion from bottom face. One deshielded olefinic proton was vanished and a singlet appeared at δ3.24 ppm which corresponds to epoxide region which confirmed the formation of product **88**.

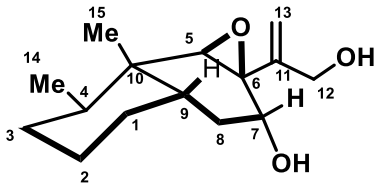


Scheme 1.16 Synthesis of peribysin A

TBS protecting group in **88** was then removed using 1M TBAF in THF which gave the free alcohol **89**. In ^{1}H NMR the alcohol **89** was observed in equilibrium with its acetal **90** which showed two sets of peaks of equal integration.The mixture of **89** and **90** was then treated with $NaBH_4$ in methanol at 0°C to get peribysin A, **23** and its minor diastereomer **91** in 8.3:1 ratio. All the NMR spectral data of synthetic peribysin A was perfectly matching with the data reported for natural peribysin A. Further the structure of synthesized compound was confirmed by HRMS which showed a peak for $[M+Na]^{+}$275.1616 which was comparable with the calculated value for formula $C_{15}H_{24}O_3Na$: 275.1618. After matching all the data we performed crystallization attempts and found good quality crystal in EtOAc/hexane mixture which after analysis using single crystal X-ray method with copper source gave confirmation for the synthesized structure.

After confirming the structure with all the spectral data we checked the specific optical rotation of the synthetic peribysin Awhich was found to be $[\alpha]_D^{23} = -59.3$ (c = 0.53, EtOH), the reported optical rotation for natural peribysin A was $[\alpha]_D^{19} = -63.0$ (c = 0.1, EtOH). Since we have synthesied the antipode of the proposed structure but the specific optical rotation of synthetic and natural peribysin A are exactly matching, it clearly concludes that the proposed structure of peribysin A is in fact *ent*-peribysin A and **we have revised the structure of peribysin A**. This clearly support the sterochemical revision of peribysin E by Danishefsky and our hypothesis of whole peribysin family revision. For making other peribysins, peribysin A was required in more quantities thus we scaled up the peribysin A upto 250 mg scale.

1.2.9 NMR comparison table of Natural and synthetic peribysin A, 23 (in $CDCl_3$):

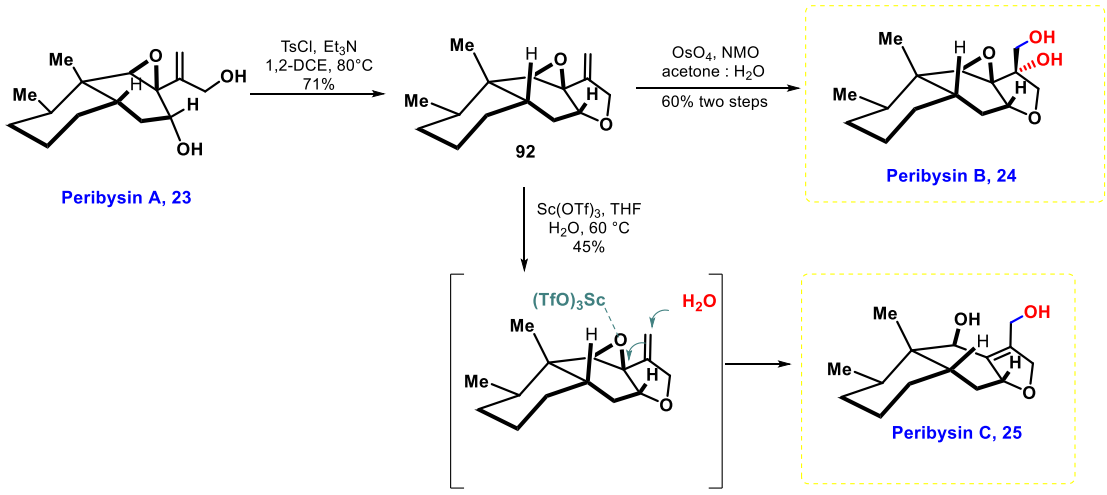


Peribysin A	^{1}H NMR δ ppm		^{13}C NMR δ ppm	
	isolation	synthesis	isolation	synthesis
1α	1.33	1.39	26.9	27.0
1β	1.68	1.69		
2	1.44	1.44	20.4	20.6
3α	1.46	1.50	30.7	30.8
3β	1.26	1.22		
4	1.95	1.93	31.9	31.1
5	3.18	3.19	35.7	35.9
6	-	-	69.9	69.9
7			67.5	67.3
8	3.98	4.02	68.4	68.7
9α	1.81	1.90-1.76	32.5	32.7
9β	1.50	1.50		
10	1.52	1.58	33.1	33.2
11	-	-	-	145.7
12α	4.12	4.19	63.7	64.4
12β	4.28	4.36	-	-
13A	5.19	5.22	117.3	117.5
13B	5.31	5.33	-	-
14	0.95	0.95	16.6	-
15	1.05	1.02	16.6	16.8
8-OH	4.23	3.02	-	-
12-OH	4.23	2.65	-	-

Table 1.3 NMR comparison table synthetic and natural peribysin A

1.2.10 **Synthesis of peribysin B and C**

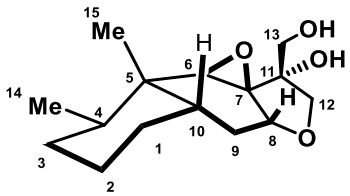
Next, we planned to make peribysin B, **24** from peribysin A by using a protocol already developed by our group during the synthesis of racemic peribysin B. For this purpose, peribysin A was treated with tosyl chloride and triethyl amine in 1,2-dichloroethane and refluxed for 12 h. The cyclized intermediate, **92** was confirmed by ^{1}H and ^{13}C NMR and HRMS which showed peak at 235.1694 calculated for molecular formula $C_{15}H_{23}O_2$ $[M+H]^+$: 235.1693. This compound **92**, was subjected for dihydroxylation using OsO_4 in acetone water mixture at room temperature. After purification by silica gel column chromatography peribysin B was obtained in 60% yield. All the NMR spectra data was matching with the reported data further with HRMS peak observed at 291.1565 calculated for the molecular formula $C_{15}H_{24}O_4Na$ $[M+Na]^+$: 291.1567 the structure was confirmed. After recording all the data we checked the specific optical rotation of the synthetic peribysin B $[\alpha]_D^{25}$ = –1.1 (c = 0.56, EtOH), the reported optical rotation for natural peribysin B was $[\alpha]_D^{25}$ = + 42.9 (c = 0.07, EtOH) thus we repurified the compound to eliminate possibility of any impurity and rechecked the rotation but the value observed was same as previous.



Scheme 1.17 Synthesis of peribysin B and C

Further to access peribysin C, same intermediate **92** was used and it was treated with $Sc(OTf)_3$ in THF-H_2O mixture to get the desired natural product. Here water stable Lewis acid $Sc(OTf)_3$ coordinates to epoxide oxygen and water molecule attacks at the terminal olefinic carbon to give the desired product **25**.

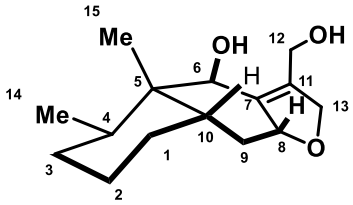
1.2.11 NMR comparison table of Natural and synthetic peribysin B, 24 (in $CDCl_3$):



Peribysin B	^{1}H NMR δ ppm		^{13}C NMR δ ppm	
	isolation	synthesis	isolation	synthesis
1α	1.36	1.39	27.0	27.0
1β	1.70	1.67		
2	1.46	1.41	20.6	20.6
3α	1.47	1.52	30.2	30.2
3β	1.26	1.32		
4	1.85	1.81	30.8	30.8
5	-	-	35.8	35.8
6	3.33	3.35	65.0	65.0
7	-	-	72.6	72.6
8	3.84	3.83	75.2	75.1
9α	1.87	1.91	30.9	30.9
9β	1.52	1.52		
10	1.34	1.32	32.5	32.5
11	-	-	77.6	77.6
12α	3.86	3.87	76.4	76.5
12β	3.98	3.98		
13A	3.54	3.55	64.2	64.2
13B	3.77	3.77		
14	0.96	0.96	16.9	16.9
15	1.07	1.07	16.5	16.5
8-OH	2.55	-	-	-
12-OH	2.28	-	-	-

Table 1.4 NMR comparison table synthetic and natural peribysin B

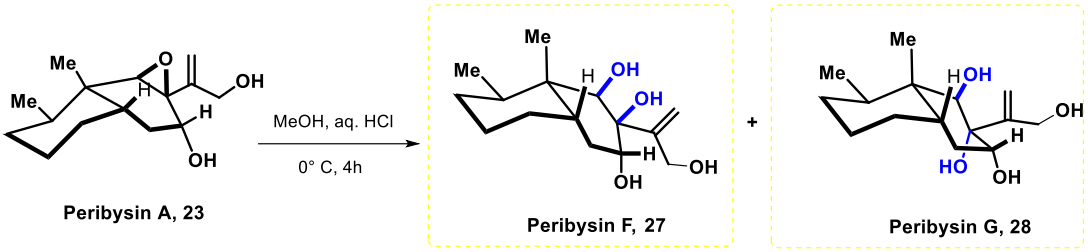
1.2.12 **NMR comparison table of Natural and synthetic peribysin C, 25 (in $CDCl_3$):**



Peribysin C	^{1}H NMR δ ppm		^{13}C NMR δ ppm	
	isolation	synthesis	isolation	synthesis
1α	1.32	1.34	26.4	26.4
1β	1.72	1.76	-	-
2α	1.44	1.44	20.2	20.2
2β	1.52	-	-	-
3α	1.40	1.37	30.8	30.8
3β	1.29	1.26	-	-
4	1.60	1.68	29.5	29.5
5	-	-	41.5	41.4
6	4.53	4.55	69.9	70.2
7	-	-	136.7	136.7
8	5.06	5.06	84.1	84.0
9α	1.90	1.86	35.2	35.3
9β	1.73	1.76	-	-
10	1.94	1.97	34.5	34.6
11	-	-	131.0	131.3
12α	4.78	4.79	76.4	76.4
12β	4.81	4.80	-	-
13A	4.15	4.25	56.0	56.4
13B	4.35	4.34	-	-
14	0.73	0.73	16.0	16.0
15	1.04	1.04	16.4	16.4

Table 1.5 NMR comparison table synthetic and natural peribysin C

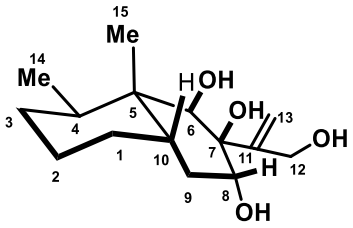
1.2.13 **Synthesis of peribysin F and G**



Scheme 1.18 Synthesis of peribysin F and G

Peribysin F, **27** and peribysin G, **28** has only difference at a quaternary hydroxyl chiral center both of which could be obtained from epoxide opening of peribysin A in acidic condition. Before making both these natural products few conditions were screened for their synthesis. In first condition, peribysin A was treated with $Sc(OTf)_3$ in water and THF mixture which after 3 days showed only ~10% conversion of starting material. In second condition when peribysin A was treated with catalytic H_2SO_4 in THF and H_2O it gave only peribysin G in less than 5% yield along with several unidentified by-products. Next, peribysin A was treated with aq. HCl in methanol at 0 °C for 4 hours gave a complex nature of TLC with several spots but after careful isolation using silica gel column chromatography peribysin G was isolated in 1.1 mg quantity and peribysin F was isolated in 2.3 mg quantity. Although the yield of this reaction was very less (less than 10%) we were able to record all the spectral data for both the natural products.^{1}H and ^{13}C NMR spectra of synthetic samples were exactly matching to those from the natural one. Additionally, the specific optical roration for peribysin F was observed to be $[\alpha]_D^{27} = -23.9$ (c = 0.09, EtOH), the reported optical rotation for natural peribysin F was $[\alpha]_D^{22} = -21.5$ (c = 0.1, EtOH**)** and peribysin G showed the specific optical rotation value of $[\alpha]_D^{23} = -0.65$ (c = 0.17, EtOH), the reported optical rotation for natural peribysin G was $[\alpha]_D^{22} = -1.3$ (c = 0.1, EtOH). This evidence concluded that we have revised the structures of peribysin F and peribysin G.

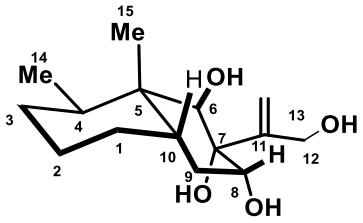
1.2.14 **NMR comparison table of Natural and synthetic peribysin F, 27 (in CD_3OD):**



Peribysin F	^{1}H NMR δ ppm		^{13}C NMR δ ppm	
	isolation	synthesis	isolation	synthesis
1α 1β	1.62	1.65	29.3	29.3
2α 2β	1.44	1.41	22.0	22.0
3α	1.48	1.50	31.7	31.7
3β	1.28	1.28	-	-
4	2.05	2.05	33.3	33.3
5	-	-	42.5	42.5
6	4.01	4.01	74.7	74.7
7	-	-	80.5	80.5
8	3.87	3.87	76.2	76.2
9α	1.97	1.90	33.8	33.8
9β	1.77	1.83-1.72	-	-
10	1.90	1.90	38.3	38.3
11	-	-	151.7	151.5
12α	4.22	4.22	64.7	64.7
12β	4.31	4.31	-	-
13A	5.43	5.44	116.8	116.8
13B	5.63	5.63	-	-
14	0.83	0.84	17.1	17.1
15	1.04	1.04	18.5	18.5

Table 1.6 NMR comparison table synthetic and natural peribysin F

1.2.15 **NMR comparison table of Natural and synthetic peribysin G, 28 (in CD_3OD):**

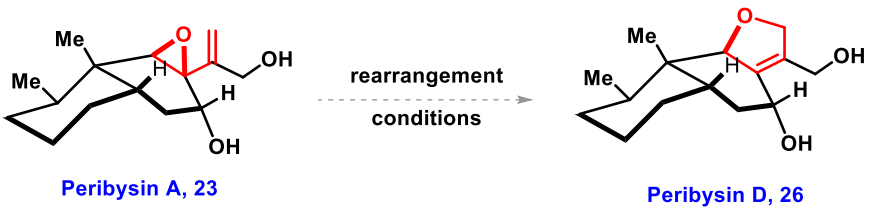


Peribysin G	^{1}H NMR δ ppm		^{13}C NMR δ ppm	
	isolation	synthesis	isolation	synthesis
1α	1.32	-	28.5	28.6
1β	1.77	1.77	-	-
2α	1.58	1.54	22.2	22.4
2β	1.44	1.45	-	-
3α 3β	1.32	-	32.2	32.4
4	2.80	2.88-2.76	30.7	30.8
5	-	-	42.1	42.2
6	3.60	3.60	79.0	79.2
7	-	-	80.9	81.0
8	4.17	4.17	70.2	70.4
9α	2.25	2.31	32.5	32.7
9β	1.32	-	-	-
10	1.80	1.81	37.6	37.8
11	-	-	154.7	155.1
12α 12β	4.29	4.28	65.1	65.3
13A	5.37	5.36	115.8	115.9
13B	5.45	5.46	-	-
14	0.81	0.81	17.3	17.3
15	0.92	0.92	18.1	18.2
12	4.29	4.28	65.1	65.3

Table 1.7 NMR comparison table synthetic and natural peribysin G

1.2.16 **Attempts for the synthesis of peribysin D, 26**

After making five natural products, next we turned our attention towards most potent natural product from this series peribysin D, **26**. It has a dihydrofuran moiety fused next to the junction methyl group which can be obtained from peribysin A by rearrangement of the allylic epoxide moiety as shown in Scheme 1.19.



Peribysin A, 23 Peribysin D, 26

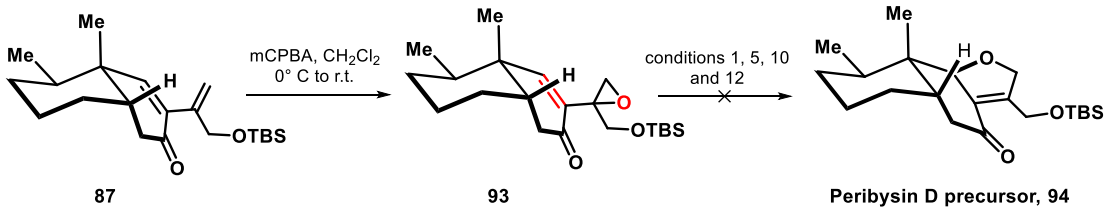
Scheme 1.19 Attempts for peribysin D using rearrangement of vinyl oxirane moiety

As per the plan we started screening with the known conditions using copper salts in particular $Cu(hfacac)_2$ which is known for this kind of transformation.[39] But under the known reaction conditions peribysin A was completely unreactive and starting material was recovered as such. Even after heating the reaction mixture to 180-200 °C did not give the desired product. Next, we screened different Cu(II) and Cu(I) catalysts but same result was observed. Then we screened various Lewis acids hoping that the Lewis acid may activate the epoxide moiety. In case of $ZnCl_2$ in DMF as a solvent at room temperature the decomposition of starting material was observed. In case of $BF_3.Et_2O$ and $TiCl_4$ complex TLC profile was observed whereas in case of Cp_2TiCl_2 epoxide eliminated corresponding olefin product, was observed.[40] In next few conditions we used different palladium catalysts which are known to give similar type of rearrangement via π-allyl complex but none of the conditions gave the desire product. In last two conditions we thought of using radical pathway to open the epoxide but SmI_2 failed to give peribysin D and when electrochemical condition was performed the starting material was decomposed. These are only selected conditions mentioned; apart from this changing solvent and temperature or in closed vessels few of the conditions were performed with no better results.

Sr. No.	Condition	Observation
1	$Cu(hfacac)_2$, toluene, 180 °C, MW	SM recovered
2	$Cu(acac)_2$, toluene, sealed tube 150 °C	SM recovered
3	CuCl, PhCN, sealed tube 160 °C	SM recovered
4	KI, $ZnCl_2$, DMF	Decomposed
5	$BF_3.Et_2O$, Et_2O, 0°C	complex mixture
6	$TiCl_4$, CH_2Cl_2, 0°C	complex mixture
7	Cp_2TiCl_2, Zn dust, THF	eliminated product at r.t.
8	$Sc(OTf)_3$, THF, reflux	SM recovered
9	$Pd(OAc)_2$, PPh_3, $KHPO_4$	SM recovered
10	$Pd(PPh_3)_4$, THF	SM recovered
11	$Pd_2(dba)_3$, THF	SM recovered
12	SmI_2, THF, -78 °C to 0°C	SM recovered
13	30 mA current, glassy carbon electrode, NaI, TEMPO, $TBABF_4$	Decomposed

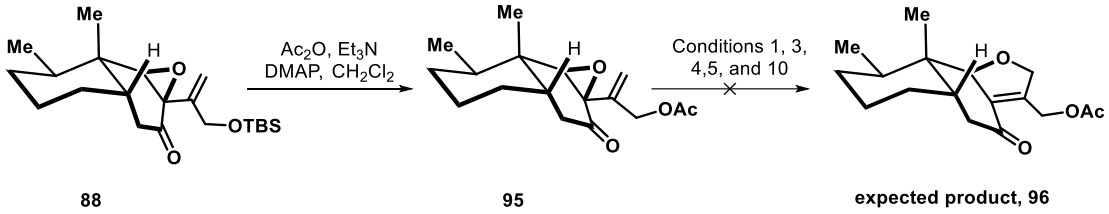
Table 1.8 Selected attempts for rearrangement of allylic epoxide

In our previous reactions (Johnson iodination and epoxidation) we observed that functionalization reaction next to C-4 methyl group was difficult or slower than other reactions. Thus, we prepared the epoxide on the other double bond than the α,β-unsaturated double bond. We prepared compound **93** by treating intermediated **87** with *m*CPBA in CH_2Cl_2 and it was again screened for condition No. 1, 5, 10, and 12 (shown in table 1.8) but no desired product was obtained.



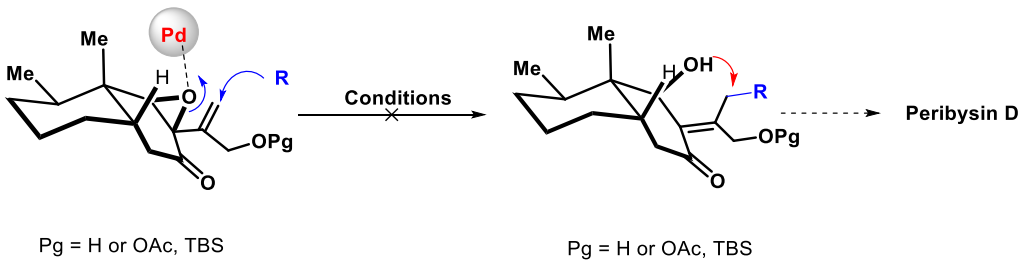
Scheme 1.20 Attempts towards peribysin D using switched epoxide

Since none of the above listed conditions worked, we then protected the free hydroxy groups present in compound **89** with acetate and to check whether free hydroxy groups were creating any problem for rearrangement and performed condition No. 1, 3, 4, 5, and 10 but in all the cases starting material remained unreacted.



Scheme 1.21 Attempts towards peribysin D

Next, we adopted a two step protocol, first 1,4-type addition of suitable R group (such as –OAc, -BPin, -I, -OH etc.) followed by cyclization from secondary hydroxyl group.[41]Some of the known conditions were screened directly on peribysin A or its diacetate derivative assuming the formation of π-allyl intermediate using palladium catalyst and subsequent trapping (Tsuji type reaction) with acetate, hydroxyl, iodo or –Bpin nucleophiles but all of them failed to give desired products. In condition No. 4 and 5 iodination of corresponding starting material failed in presence of $Sc(OTf)_3$ or PPh_3.Condition 6 was known to undergo formation of BPin radical which can add to double bond and open the epoxide moiety but in this case also desired product was not obtained the starting material was decomposed.

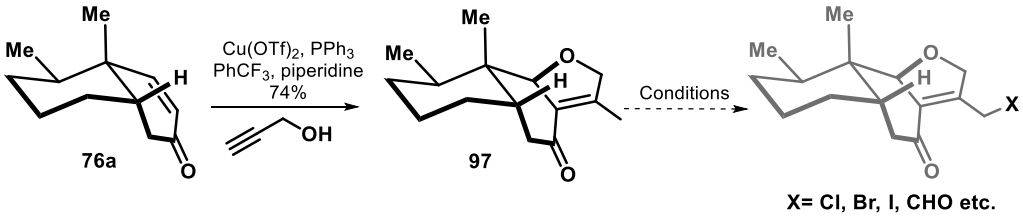


Scheme 1.22 Attempts for peribysin D

Sr. No.	Condition	Observation
1	$Pd(OAc)_2$, AcOH	SM recovered
2	$Pd(PPh_3)_4$, THF, H_2O	SM recovered
3	$Pd(PPh_3)_4$, THF, AcOH	SM recovered
4	$Sc(OTf)_3$, I_2, CH_2Cl_2	SM recovered
5	PPh_3, I_2, THF	SM recovered
6	B_2Pin_2, NaO^tBu, CuCl, toluene, MeOH	Decomposed
7	B_2Pin_2, $Pd(PPh_3)_4$, THF	SM recovered

Table 1.9 Selected attempts for allylic epoxide opening

1.2.17 **Attempts for peribysin D using allylic functionaliation strategy**



Scheme 1.23 Attempts towards peribysin D using allylic functionalization

With the failure in late stage functionalization of peribysin A towards peribysin D, we then thought of using one of the intermediate, enone **76a** which could be treated with propargyl alcohol under the condition reported by Fujie Tanaka *et al* for the synthesis of dihydrofuran moiety.[42]This intermediate **97** is a versatile intermediate which under various allylic functionalization conditions could give access to peribysin D. Thus, as per the plan we treated enone **76a** with $Cu(OTf)_2$, piperidine and PPh_3 in benzotrifluoride as solvent to get compound **97**. The structure of compound **97** was confirmed by observing singlet for olefin attached methyl in ^1H NMR and in ^{13}C NMR, two tetrasubstituted olefin peaks at δ 145.8 and 131.0 ppm and carbonyl carbon at δ 199.4 ppm were observed. Further HRMS gave the confirmation for product structure **97**.

First allylic bromination and chlorination attempts were performed using NBS, bromine or SO_2Cl_2 in presence of radical initiators such as AIBN, benzoyl peroxide but in most of the cases starting material was decomposed.[43] In condition 1 and 2 starting material was consumed completely thus to avoid any decomposition of bromo compound during purification, we subjected the crude material for hydrolysis using aq. $NaHCO_3$ in dioxane but desired hydroxyl compound was not observed. Apart from this well known allylic oxidation conditions using SeO_2 and PDC-TBHP[44] were used but in both the cases the more active allylic position next to oxygen was oxidized to give corresponding lactone product. Next, we turned our attention towards use of electrochemical condition developed by Baran's group for allylic oxidation.[45]We treated compound **97** under identical conditions reported by Baran's group using NHPI as mediator, $LiClO_4$ as a electrolyte and pyridine as a base at a constant current of 10 mA for 1 hour. After analysis by TLC only lactone product in trace amount was observed and remaining starting material was unreacted.

Sr. No.	Condition	Observation
1	NBS, CCl_4, benzoyl peroxide, reflux	decomposed
2	NBS, AIBN, CH_2Cl_2, 0°C to reflux	decomposed
3	Br_2, CH_2Cl_2, AIBN, 0°C to reflux	decomposed
4	SO_2Cl_2, CH_2Cl_2	SM recovered
5	SeO_2, 1,4-dioxane	Lactone product
6	PDC, TBHP	Lactone product
7	10 mA current, glassy carbon electrode, NHPI, pyridine, $LiClO_4$, acetone	Trace amount of lactone product and SM

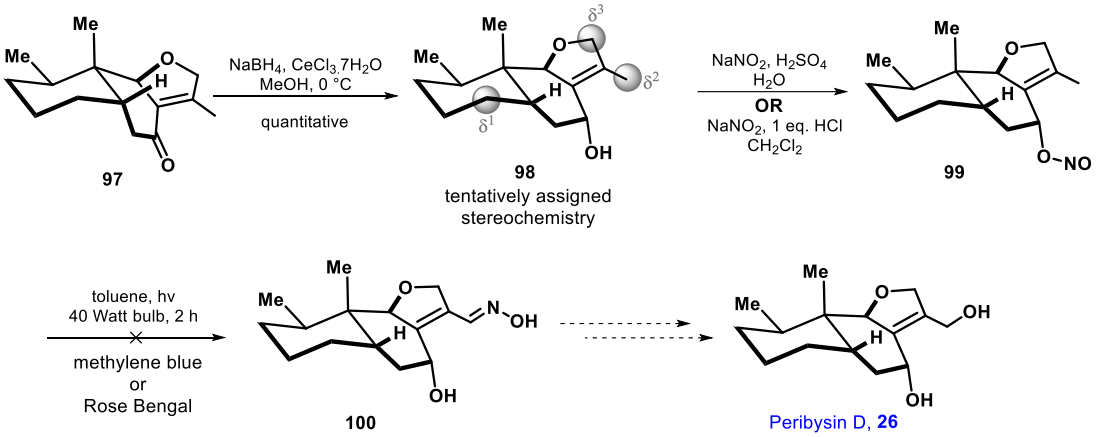
Table 1.9 Selected attempts for allylic oxidation

1.2.18 **Attempt for photochemical reaction towards peribysin D**

After doing several known and modified conditions towards peribysin D we took help of a photochemical reaction also known as Barton rearrangement.[46] In Barton reaction

corresponding *O*-nitroso compound having δ-hydrogen undergoes [1,5] shift when irradiated with light to give δ-nitroso compounds.

These δ-nitroso compounds are in equilibrium with their oxime forms which on hydrolysis provides compounds with oxygen functionality inserted at δ-position. With this in mind we preapared alcohol **98** from compound **97** by Luche reduction.

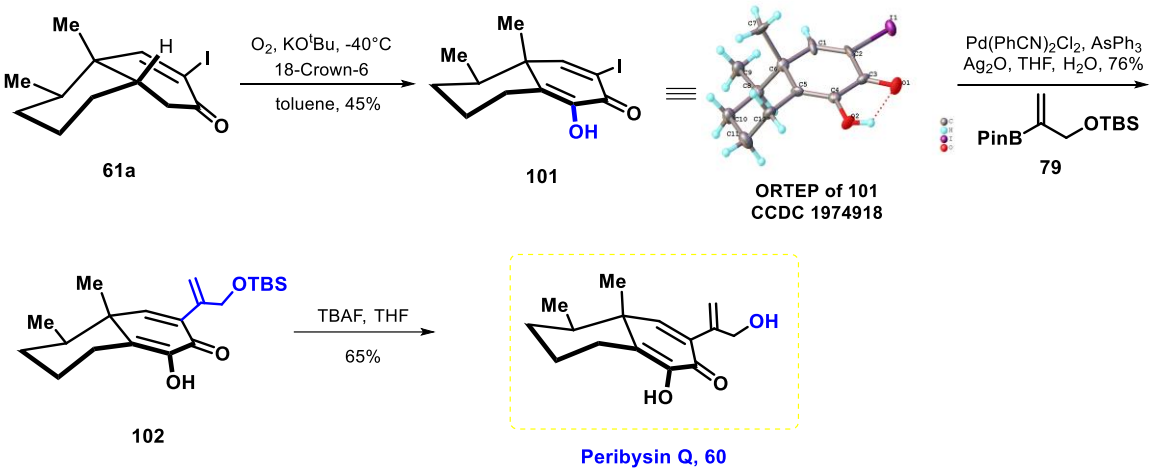


Scheme 1.24 Attempt towards peribysin D using Barton reaction

There are three potential δ-positions where nitroso group can migrate, but after looking at the 3D structure of alcohol, only position δ^2 seems to be more accessible. Thus, alcohol **98** was treated with $NaNO_2$ in presence of mineral acid to give O-nitroso compound **99**.[47] This compound **99** was unstable when kept outside for longer time giving back the starting material. Thus crude compound was immediately forwarded for next reaction. First compound **99** was irradiated with 40 Watt lamp for two hours in toluene in presence of methylene blue or Rose Bengal but in both the cases starting material and alcohol **98** was observed. Next, we performed the same reaction in acetonitrile and extra care was taken to exclude the oxygen from solvent but no better result was obtained. With this, more than 200 attempts were performed to access peribysin D with no success at the end. The successful attempts for peribysin D using an enone transposition sequence will be discussed in chapter 2 section 1. Thus, we decided to move ahead for synthesis of remaining peribysins recently isolated from plant source by Hashimoto's group.[23]

1.2.19 **Synthesis of peribysin Q**

Although all of them are named as peribysins based on structural similarities, they may possess different absolute stereochemistry and may not need stereochemical revision since they occur in completely different environment in nature.



Scheme 1.25 Synthesis of *ent*-peribysin Q

To check this, we planned the synthesis of peribysin Q, **60** from one of the iodo intermediate **61a**. Thus compound **61a** was treated with KO^{t}Bu in toluene in presence of 18-crown-6 and oxygen atmosphere at -40 °C to give enol **101**.[48] Structure of this enol intermediate was confirmed by single crystal X-ray analysis. Further coupling of this compound **101** with boronate ester **79** followed by deprotection of TBS group (as performed for the synthesis of peribysin A in Scheme 1.16) gave the target compound **60**. To our delight all the NMR spectral data for this synthetic compound matched completely with the data for natural peribysin Q. Further HRMS observed at 271.1300 calculated for molecular formula $C_{15}H_{20}O_3Na$ $[M+Na]^+$: 271.1305 gave the confirmation of compound structure **60**. But, when specific optical rotation was recorded for synthetic sample the value observed was $[\alpha]_D^{23} = -13.2$ (c = 0.74, $CHCl_3$), the reported optical rotation for natural peribysin Q was $[\alpha]_D^{20} = +18$ (c = 0.19, $CHCl_3$). This clearly conclude that we have prepared *ent*-peribysin Q and the original stereochemical assignment of peribysin Q by Hashimoto's group was correct. To support this argument we recorded CD spectra of synthetic peribysin Q in acetonitrile. Natural Peribysin Q was reported to possess first positive faint Cotton effect at λ 332 nm, a second negative cotton effect at λ 300 nm, and third positive cotton effect at 238

nm.[23] Whereas, in synthetic Peribysin Q we observed first negative faint Cotton effect at 333 nm, second positive cotton effect at 300 nm, and third negative at 237 nm.This concludes that the synthetic compound is *ent*-peribysin Q.

1.2.20 **Comparison of CD spectra of synthetic and natural peribysin Q**

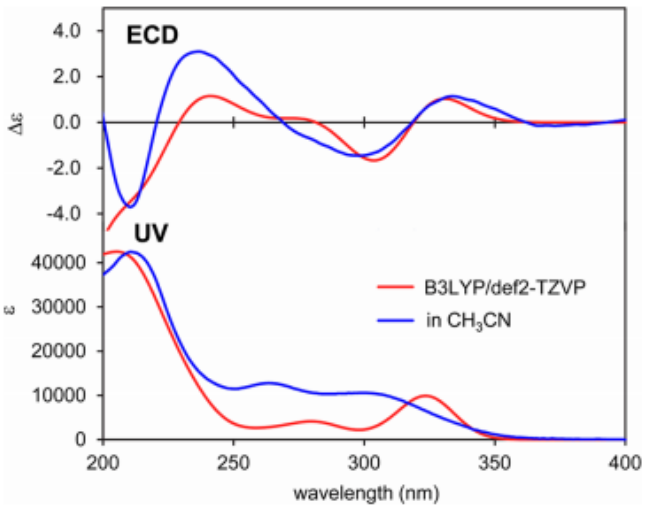


Figure 1.13 Experimental CD spectra of peribysin Q by Hashimoto's group [23]

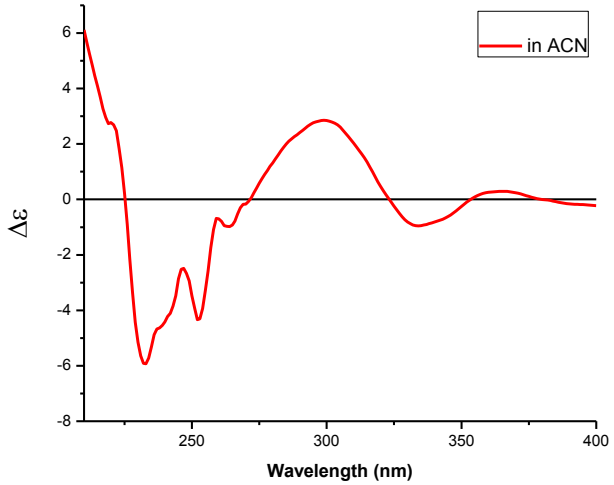
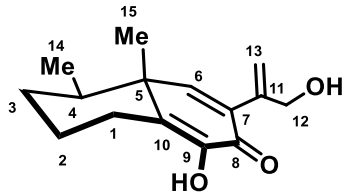


Figure 1.12 Experimental CD spectra of synthetic peribysin Q

1.2.21 **NMR comparison table of Natural and synthetic peribysin Q, 60 (in $CDCl_3$):**



Peribysin Q	^{1}H NMR δ ppm		^{13}C NMR δ ppm	
	isolation	Synthesis	isolation	synthesis
1α	2.01	2.04	23.7	23.7
-	3.09	3.12-3.03	-	-
2	1.94	1.95	27.0	26.9
-	1.34	1.61-1.33	-	-
3	1.48		30.5	30.4
-	1.58		-	-
4	1.47		41.9	41.8
5	-	-	43.3	43.3
6	7.20	7.21	156.6	156.6
7	-	-	135.4	135.4
8	-	-	180.4	180.4
9	-	-	141.8	141.7
10	-	-	138.3	138.4
11	-	-	145.8	145.7
12	4.29	4.29	65.2	65.1
13	5.33	5.34	117.9	117.9
-	5.36	5.37	-	-
14	1.10	1.10	16.9	16.8
15	1.17	1.18	17.1	17.1
OH	6.46	6.48	-	-

1.3 Conclusions

Our hypothesis of structural revision of peribysin family natural products was validated by achieving the total synthesis of peribysins A, B, C, F, G, and *ent*-peribysin Q for the first time in enatiopure form starting with commercially available (+)-nootkatone.[49] Our results were supported by single crystal X-ray analysis, specific optical rotation and CD spectra. Additionally, several attempts were made to access peribysn D with no success.

The key highlights of the synthesis are enone transposition and kinetic iodination of enone which ultimately resulted in separation of diastereomers. Our results coupled with Danishefsky's stereochemical revision of peribysin E finally concludes that structures of all the peribysins isolated form *periconia byssoides* OUPS-N133 which has a marine origin were revised and the peribysins isolated from *periconia macrospinosa* KT-3863 from a herbacdous plant source need not any stereochemical revision. Biological evaluation of all these natural products and their analogs (around 30 No.s) for cell adhesion potential and treating sickle cell anemia is currently ongoing.

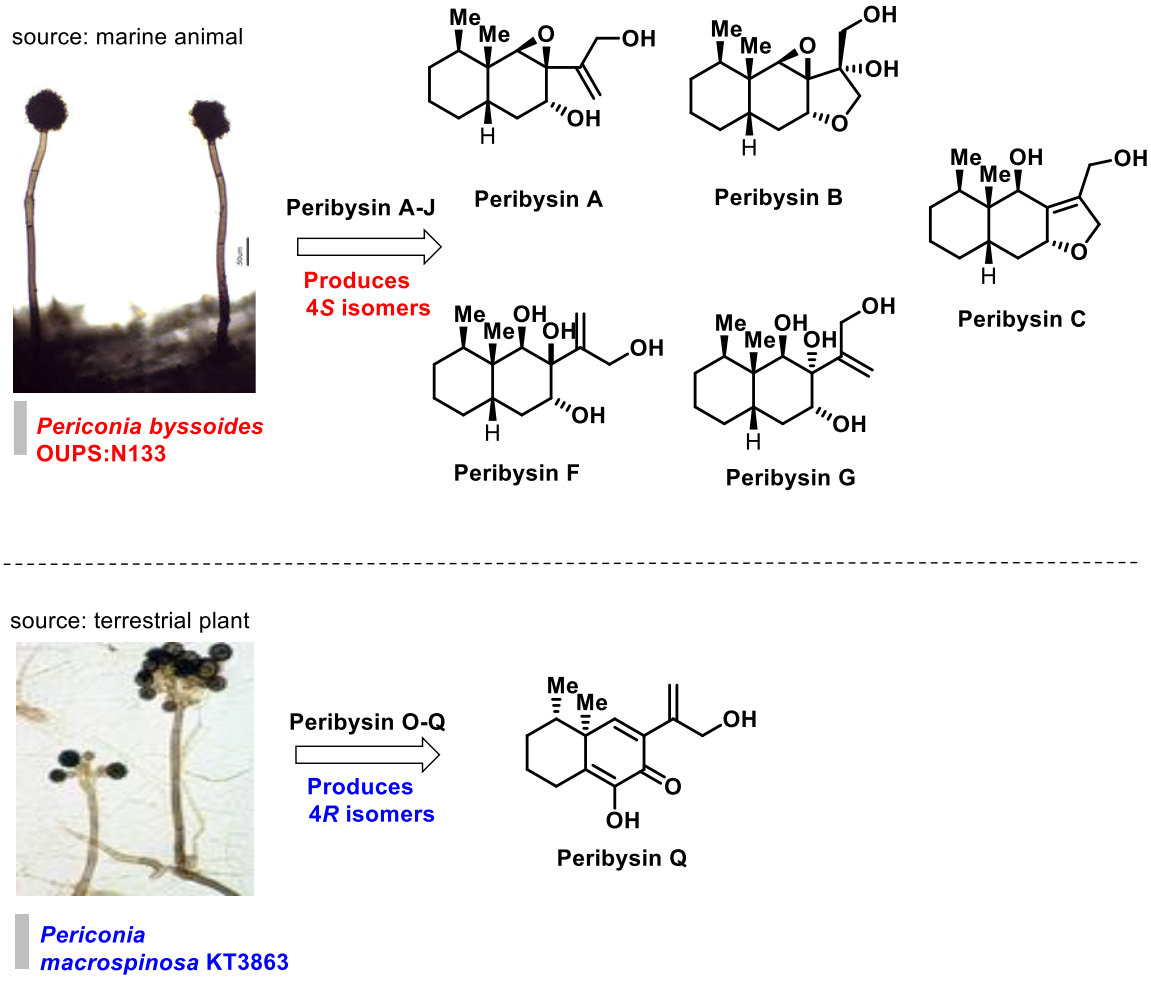
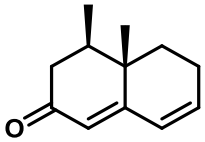


Figure 1.13 Overview of results from chapter 1

1.4 Experimental section



(4*R*,4a*S*)-4,4a-dimethyl-4,4a,5,6-tetrahydronaphthalen-2(3*H*)-one: 63

To a stirred solution of (+)-nootkatone, **64** (20.0 g, 91.74 mmol) in methanol (150 mL) was cooled to -40°C using dry ice-acetone bath. Ozone was bubbled through the solution keeping the temperature below -30°C until the starting material was completely consumed monitored by TLC (approx. 45 min). Then the excess ozone was ceased by bubbling oxygen for two minutes followed by purging the nitrogen for 4 min. Then 30% W/V solution of $Cu(OAc)_2.H_2O$ (27.5 g, 137.61 mmol) in water $FeSO_4.7H_2O$ (30.6 g, 110.09 mmol) in water were added sequentially over 4 min keeping the reaction temperature below 0 °C. The reaction mixture was allowed to warm to room temperature gradually and stirred for 1h. After 1h methanol was evaporated and the reaction mixture was diluted with ethyl acetate (200 mL), washed with water (80 mL), 1N HCl (100 mL) and brine (50 mL). The crude reaction mixture was dried over anhydrous sodium sulphate and concentrated in *vacuo* to give pale yellow oil **65** (15.4 g crude) which was used as such for further reaction. The above crude compound (15.4 g, 87.50 mmol) was taken in acetonitrile (80 mL) and purged argon through it for 15 min then at 0 °C DBU (13.3 mL, 87.5 mmol) was added and stirred the reaction mixture at room temperature for 4 hours. Then the acetonitrile was evaporated under reduced pressure and reaction mixture was diluted with EtOAc (150 mL), washed with water (60 mL), 1N HCl (80 mL) and brine (40 mL). The organic layer was dried over sodium sulphate, evaporated and purified by column chromatography (silica gel) (4% EtOAc: pet ether) to give **63,** 12.2 g (75% over two steps) as a pale yellow oil.

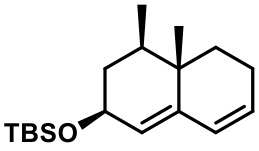
$[\alpha]_D^{23}$=+ 203.0 (*c* = 1.0, $CHCl_3$).

IR υ_{max}(film): cm^{-1} 2965, 2943, 1653, 1618, 1286.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.19 - 6.17 (m, 1 H), 6.10 - 6.08 (m, 1 H), 5.67 - 5.63 (m, 1 H), 2.34 - 2.22 (m, 4 H), 1.98 (qd, *J* = 6.5, 12.8 Hz, 1 H), 1.90 - 1.83 (m, 1 H), 1.30 (dt, *J* = 6.4, 12.1 Hz, 1 H), 0.96 (s, 3 H), 0.92 (d, *J* = 6.7 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 199.9, 163.3, 137.8, 127.9, 123.9, 42.4, 38.9, 36.3, 32.5, 23.4, 15.4, 14.8.

HRMS calculated for $C_{12}H_{17}O$ $[M+H]^+$: 177.1274, found 177.1273.

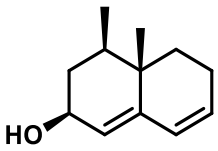


***tert*-butyl(((4*R*,4a*S*)-4,4a-dimethyl-2,3,4,4a,5,6-hexahydronaphthalen-2-yl)oxy)dimethylsilane: 68**

A solution of **63** (3.5 g, 19.880 mmol) in MeOH (40 mL) was cooled to 0°C and added $CeCl_3 \cdot 7H_2O$ (11.1 g, 29.830 mmol). After stirring the reaction mixture for 10 min, $NaBH_4$ (1.4 g, 39.772 mmol) was added portion wise over 10 min and the reaction mixture was stirred at 0 °C for 30 min. The reaction was quenched with saturated aqueous NH_4Cl solution (30 mL) and diluted with EtOAc (100 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate (2 × 50 mL). Then the combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, and concentrated under reduced pressure to obtain allylic alcohol **67** (3.5 g crude) as colourless oil. The obtained crude material was dissolved in CH_2Cl_2 (60 mL)and cooled at 0 °C; then imidazole (2.67 g, 39.32 mmol) was added followed by addition of DMAP (0.24 g, 1.96 mmol). Then TBSCl (2.12 g, 19.66 mmol) was added portion-wise at same temperature. After stirring the reaction mixture for 12 h, the reaction mixture was diluted with water (40 mL) washed with brine and extracted with CH_2Cl_2 (50 mL). The collective organic layer was washed with brine (25 mL) and concentrated. The crude product was purified by column chromatography (silica gel) to yield **68**, 3.6 g (63 % over two steps) as colourless oil.

Data for compound **67** (major isomer shown):

(2*S*,4*R*,4a*S*)-4,4a-dimethyl-2,3,4,4a,5,6-hexahydronaphthalen-2-ol: **67**



IR υ_{max}(film): cm^{-1} 3321, 2930, 2363, 1460.

^{1}H NMR (500 MHz, $CDCl_3$) δ= 5.96 - 5.94 (m, 1 H), 5.75 - 5.64 (m, 1 H), 5.38 – 5.28 (m, 1 H), 4.35 - 4.22 (m, 1 H), 2.25 - 2.08 (m, 2 H), 1.89 - 1.77 (m, 2 H), 1.62 - 1.48 (m, 2 H), 1.17 (dt, *J* = 5.7, 12.4 Hz, 1 H), 0.97 - 0.85 (m, 6 H).

^{13}C NMR (125 MHz, $CDCl_3$) δ = 143.6, 134.3, 129.1, 128.2, 128.1, 126.2, 124.9, 123.8, 67.9, 67.7, 37.8, 37.2, 37.1, 36.2, 35.5, 33.3, 29.4, 28.0, 23.2, 20.6, 17.0, 15.3.

HRMS calculated for $C_{12}H_{19}O$ $[M+H]^+$: 179.1430, found 179.1428.

Data for compound **68**:

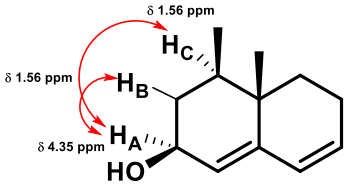
IR υ_{max}(film): cm^{-1} 2930, 2856, 1660, 1289.

^{1}H NMR (500 MHz, $CDCl_3$) δ = 5.95 (brs, 1 H), 5.69 (brs, 1 H), 5.31 (br. s., 1 H), 4.36 (brs, 1 H), 2.19 (brs, 1 H), 2.17 - 2.03 (m, 1 H), 1.86 - 1.74 (m, 1 H), 1.74 - 1.64 (m, 1 H), 1.63 - 1.51 (m, 2 H), 1.22 - 1.07 (m, 1 H), 0.97 - 0.82 (m, 15 H), 0.10 - -0.02 (m, 6 H).

^{13}C NMR (125 MHz, $CDCl_3$) δ = 142.6, 134.6, 128.6, 127.6, 127.5, 124.9, 68.9, 38.0, 37.3, 35.7, 33.5, 28.1, 26.0, 23.3, 20.7, 18.3, 17.1, 15.4, -4.4, -4.5.

HRMS calculated for $C_{17}H_{29}O_2Si$ $[M+Na]^+$: 293.1931, found 293.1928.

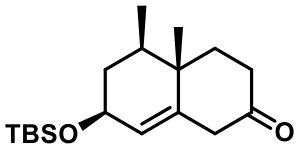
2D NMR analysis of compound 67:



major isomer shown

In the NOESY spectrum of compound **67** hydroxy group attached proton H_A (δ 4.35 ppm) showed a strong correlation with H_B (δ 1.56 ppm) and H_C (δ 1.56 ppm) protons. However, since H_B and H_C protons are overlapped with each other it is difficult to predict the stereochemistry firmly. Additionally H_A proton does not have any NOE

correlation with both methyl groups. Here the stereochemistry is assigned tentatively with the help of a literature reference.[28]



(*4aS*,5*R*)-7-((tert-butyldimethylsilyl)oxy)-4a,5-dimethyl-3,4,4a,5,6,7-hexahydronaphthalen-2(1*H*)-one: 71

To a stirred solution of compound **68** (4.0 g, 13.69 mmol) in CH_2Cl_2 (120 mL) at 0°C was added *m*-CPBA (~65%), (3.62 g, 13.69 mmol) and stirred the reaction mixture for 30 min at 0°C. Then saturated $NaHCO_3$ solution (40 mL) was added to reaction mixture and stirred for 10 min. Organic layer was separated and aqueous layer was extracted with CH_2Cl_2 (40 mL). The combined organic layer was dried over sodium sulphate and concentrated to give crude epoxide, **69** as pale yellow oil. To the crude epoxide (4.0 g, 12.987 mmol) in THF (60 mL) at 0°C was added LAH (1.2 g, 32.470 mmol) and stirred the reaction mixture at 0°C for 1 h. The reaction mixture was quenched with saturated Na_2SO_4 solution (10 mL) slowly over 5 min. The mixture was diluted with EtOAc (100 mL) and filtered through celite. The organic layer was washed with brine (30 mL), dried over sodium sulphate and evaporated to give crude alcohol (2.1 g) as colourless oil. To the above crude alcohol, **70** (1.9 g, 6.129 mmol) in CH_2Cl_2 (60 mL) at 0 °C was added solid $NaHCO_3$ (1.0 g) followed by DMP (3.9 g, 9.19 mmol) at 0 °C and the reaction mixture was allowed to warm to room temperature over 1 h and stirred for additional 1 h. The reaction mixture was quenched by adding saturated $NaHCO_3$ solution (25 mL). The organic layer was separated, washed with brine (30 mL) and evaporated. The crude product was purified by column chromatography (silica gel) to afford **71**, (1.8 g, 50% over three steps) as colourless oil.

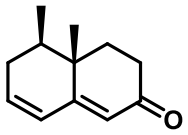
IR υ_{max}(film): cm^{-1} 2930, 2856, 1704, 1465, 1250.

^{1}H NMR (500 MHz, $CDCl_3$) δ = 5.29 (s, 1 H), 4.28 - 4.25 (m, 1 H), 3.29 (td, *J* = 2.7, 16.4 Hz, 1 H), 2.85 (dd, *J* = 2.3, 16.4 Hz, 1 H), 2.51 (dt, *J* = 5.9, 14.4 Hz, 1 H), 2.35 - 2.31 (m, 1 H), 2.06 - 2.02 (m, 1 H), 1.70 - 1.66 (m, 1 H), 1.57 - 1.49 (m, 2 H), 1.42 (dt,

J = 4.6, 13.5 Hz, 1 H), 1.15 (s, 3 H), 0.97 (d, *J* = 6.5 Hz, 3 H), 0.90 (m, 9 H), 0.09 - 0.08 (m, 6 H).

^{13}C NMR (125 MHz, $CDCl_3$) δ = 209.4, 140.3, 128.5, 68.6, 48.0, 38.1, 37.6, 37.4, 37.2, 36.5, 26.0, 17.3, 15.8, -4.5, -4.7.

HRMS calculated for $C_{18}H_{33}O_2Si$ $[M+H]^+$: 309.2244, found 309.2242.



(4a*S*,5*R*)-4a,5-dimethyl-4,4a,5,6-tetrahydronaphthalen-2(3*H*)-one: 62

To compound **71**(1.9 g, 6.129 mmol) in CH_2Cl_2 (40 mL) was added catalytic PTSA.H_2O (40 mg) at room temperature and refluxed the reaction mixture for 1 h. After 1 h solid $NaHCO_3$ was added to the reaction mixture and solvent was evaporated. The crude compound was purified by column chromatography (silica gel) to afford **62**(550 mg, 51 %) as pale yellow oil.

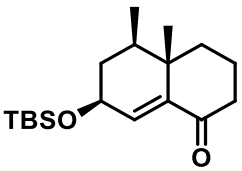
$[\alpha]_D^{19}$ = – 349.1 (*c* = 0.93, $CHCl_3$).

IR υ_{max}(film): cm^{-1} 2963, 2879, 1646, 1615, 1203.

^{1}H NMR (400 MHz,$CDCl_3$) δ = 6.21 - 6.17 (m, 1 H), 6.10 - 6.08 (m, 1 H), 5.63 (s, 1 H), 2.35 - 2.22 (m, 4 H), 1.98 (qd, *J* = 6.5, 12.8 Hz, 1 H), 1.87 - 1.83 (m, 1 H), 1.30 (dt, *J* = 6.4, 12.1 Hz, 1 H), 0.96 (s, 3 H), 0.92 (d, *J* = 6.7 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 199.9, 163.3, 137.8, 127.9, 123.9, 42.4, 38.9, 36.3, 32.5, 23.4, 15.4, 14.8.

HRMS calculated for $C_{12}H_{17}O_7$ $[M+H]^+$: 177.1274, found 177.1272.



(4a*S*,5*R*)-7-((tert-butyldimethylsilyl)oxy)-4a,5-dimethyl-3,4,4a,5,6,7-hexahydronaphthalen-1(2*H*)-one : 72

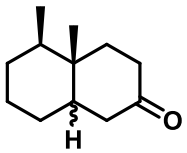
To a stirred solution of compound **68** (0.600 g, 2.054 mmol) in THF was added $BH_3.Me_2S$ (10M solution), (0.41 mL, 4.109 mmol) dropwise at 0°C. The reaction mixture was stirred at same temperature for 1 h. Then the reaction mixture was quenched with H_2O_2 (30% aq.) 1 mL in 2 mL of 2M NaOH solution and stirred the mixture for 10 min. Then the reaction mixture was diluted with EtOAc (30 mL), washed with water (20 mL) and brine (20 mL). The organic layer was dried over sodium sulphate; evaporated and crude compound was purified by column chromatography (silica gel) to afford alcohol (360 mg) as yellow oil. The above crude alcohol (0.200 g, 0.645 mmol) was dissolved in CH_2Cl_2 (15 mL) and added DMP (0.328 g, 0.774 mmol) at 0 °C and stirred the reaction mixture for 1 h. After 1 h saturated $NaHCO_3$ (10 mL) was added to the reaction mixture an extracted with CH_2Cl_2 (20 mL). The combined organic layer was dried over anhydrous sodium sulphate and purified by column chromatography (silica gel) to afford **72** as pale yellow oil (110 mg, 32% over two steps).

IR υ_{max}(film): cm^{-1} 2958, 2934, 2876, 1687, 1627, 1246.

^{1}H NMR (500 MHz, $CDCl_3$) δ = 6.14 (s, 1 H), 4.35 - 4.24 (m, 1 H), 2.57 - 2.49 (m, 1 H), 2.24 (ddd, *J* = 8.4, 11.5, 16.7 Hz, 1 H), 1.97 - 1.85 (m, 3 H), 1.73 - 1.60 (m, 2 H), 1.55 - 1.46 (m, 1 H), 1.37 (dt, *J* = 5.3, 12.4 Hz, 1 H), 0.93 - 0.89 (m, 6 H), 0.89 - 0.86 (m, 9 H), 0.06 (d, *J* = 3.4 Hz, 6 H).

^{13}C NMR (125 MHz, $CDCl_3$) δ = 202.7, 145.1, 134.6, 67.8, 40.3, 39.0, 38.8, 36.2, 35.9, 25.8, 19.4, 19.3, 18.1, 15.7, -4.7, -4.7.

HRMS calculated for $C_{18}H_{33}O_2Si$ $[M+H]^+$ 309.2244, found 309.2242.



(4a*S*,5*R*)-4a,5-dimethyloctahydronaphthalen-2(1*H*)-one: 75

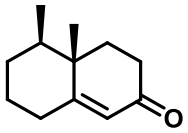
To compound **62**(4.1 g, 23.295 mmol) was added 1% KOH in MeOH (50 mL) followed by Pd/C (100 mg) (10% by wt) in Parr apparatus. The reaction mixture was stirred at room temperature under 250 psi pressure of H_2. After 12 h the Pd/C was filtered through a short pad of celite and washed with EtOAc. The combined organic layer was evaporated and crude pale yellow product **75** (4.1 g) which was used as such for further reaction.

IR υ_{max}(film): cm^{-1} 2923, 1710, 1455, 1170.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 2.65 - 2.58 (m, 1 H), 2.43 - 2.34 (m, 1 H), 2.30 - 2.19 (m, 1 H), 2.11 (dd, *J* = 4.3, 14.0 Hz, 2 H), 2.02 - 1.90 (m, 1 H), 1.86 - 1.70 (m, 2 H), 1.58 - 1.52 (m, 2 H), 1.44 - 1.24 (m, 4 H), 0.97 (s, 3 H), 0.88 (d, *J* = 6.7 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 213.3, 46.2, 44.7, 43.4, 42.6, 42.6, 38.5, 38.3, 37.4, 36.4, 35.0, 31.6, 30.6, 30.1, 29.4, 27.4, 26.3, 22.6, 21.3, 20.6, 15.6, 15.5, 14.1, 9.8.

HRMS calculated for $C_{12}H_{21}O$ $[M+H]^+$: 181.1587, found 181.1583.



(4a*S*,5*R*)-4a,5-dimethyl-4,4a,5,6,7,8-hexahydronaphthalen-2(3*H*)-one: 78

To compound **75** (0.1 g, 0.568 mmol) in MeOH (15 mL) followed by Pd/C (5 mg) (10% by wt) and the reaction mixture was stirred at room temperature under H_2 atmosphere (balloon pressure). After 12 h the Pd/C was filtered through a short pad of celite and washed with EtOAc. The combined organic layer was evaporated. The crude compound was purified by column chromatography (silica gel) to get (-)-octalone, **78** (78 mg, 77 %) as a colourless liquid.

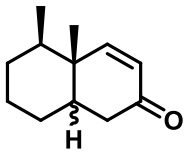
$[\alpha]_D^{24}$ = – 163.2 (*c* = 0.63, $CHCl_3$).

IR υ_{max}(film): cm^{-1} 2932, 2860, 1670, 1449.

^{1}H NMR (200 MHz, $CDCl_3$) δ = 5.74(s, 1 H), 2.48 - 2.21 (m, 4 H), 2.09 - 1.99 (m, 1 H), 1.90 - 1.67 (m, 3 H), 1.56 - 1.39 (m, 3 H), 1.11 (s, 3 H), 0.91 (d, *J* = 5.8 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 199.7, 171.4, 123.9, 43.1, 38.9, 35.4, 33.9, 33.3, 30.4, 26.4, 15.9, 15.1.

HRMS calculated for $C_{12}H_{19}O$ $[M+H]^+$: 179.1430, found 179.1430.



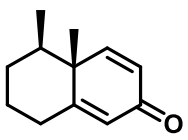
(4a*S*,5*R*)-4a,5-dimethyl-4a,5,6,7,8,8a-hexahydronaphthalen-2(1*H*)-one: 76

To a solution of ketone **75** (4.1 g, 22.777 mmol) in dry DMSO (40 mL) was added IBX (12.7 g, 45.555 mmol) followed by TFA (0.1 mL) at room temperature. The reaction mixture was stirred at 60 °C for 2 hours. After 2 hours reaction mixture was cooled to room temperature and EtOAc (100 mL) was added to it and filtered through a pad of celite. The organic layer was washed with H_2O (40 mL) and brine (40 mL). The organic layer was dried over anhydrous sodium sulphate and evaporated. Purification by column chromatography furnished **76** (1.2 g, 55% BRSM), compound **77**(0.3 g) and (-)-octalone**78** (1.6 g). The mixture of**77** and (-)-octalone, **78** were again subjected for hydrogenation using the procedure mentioned for the synthesis of **75** and again subjected to IBX reaction to build up the quantity of enone **76**. Enone ratio was observed as 3:2 (*cis:trans*)by ^{1}H NMR.

IR υ_{max}(film): cm^{-1} 2923, 2858, 1681, 1457.

^{1}H NMR (200 MHz,$CDCl_3$) δ = 6.84 (d, *J* = 10.1 Hz, 1 H), 6.00 - 5.77 (m, 1 H), 2.78 - 2.58 (m, 1 H), 2.50 - 1.98 (m, 3 H), 1.98 - 1.72 (m, 2 H), 1.58 - 1.33 (m, 5 H), 1.13 (s, 2 H), 0.99 (s, 1 H), 0.96 - 0.90 (m, 3 H).

HRMS calculated for $C_{12}H_{19}O$ $[M+H]^+$: 179.1430, found 179.1431.



(4a*R*,5*R*)-4a,5-dimethyl-5,6,7,8-tetrahydronaphthalen-2(4a*H*)-one: 77

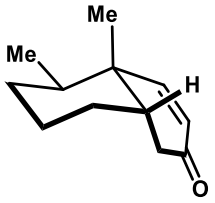
$[\alpha]_D^{25}$ = – 4.5 (*c* = 0.47, $CHCl_3$).

IR υ_{max}(film): cm^{-1} 2930, 1716, 1658, 1242.

^{1}H NMR (400 MHz,$CDCl_3$) δ = 7.05 (d, *J* = 10.1 Hz, 1 H), 6.23 (dd, *J* = 1.8, 10.1 Hz, 1 H), 6.07 (t, *J* = 1.6 Hz, 1 H), 2.41 - 2.34 (m, 2 H), 2.01 - 1.95 (m, 1 H), 1.58 - 1.45 (m, 3 H), 1.45 - 1.36 (m, 1 H), 1.13 (s, 3 H), 1.06 (d, J = 6.4 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 186.6, 169.1, 155.9, 127.4, 124.1, 43.7, 41.5, 33.1, 30.1, 28.0, 17.0, 16.1.

HRMS calculated for $C_{12}H_{17}O$ $[M+H]^+$: 177.1274, found 177.1272.



(4a*S*,5*R*,8a*S*)-4a,5-dimethyl-4a,5,6,7,8,8a-hexahydronaphthalen-2(1*H*)-one: 76a

To a mixture of enone **76** (1.2 g, 6.471 mmol) in dry CH_2Cl_2 was added I_2 (1.71 g, 6.471 mmol) followed by pyridine (3.6 mL) at room temperature. The reaction mixture was stirred at room temperature for 24 h then quenched by adding saturated $Na_2S_2O_3$ solution (25 mL) and extracted with CH_2Cl_2 (2 X 40 mL). The combined organic layer was washed with brine (25 mL) and dried over anhydrous sodium sulphate. Solvent was evaporated in *vacuo* and crude compound was purified by column chromatography (silica gel) to afford iodo enone **61b** (630 mg, as a mixture containing major trans isomer) and unreacted enone was recovered **76a** (590 mg, 49% with >95:5dr).

Data for recovered enone **76a**:

$[\alpha]_D^{25}$ = – 25.4 (*c* = 0.17, $CHCl_3$).

IR υ_{max}(film): cm^{-1} 2923, 2357, 1646, 1681, 1457.

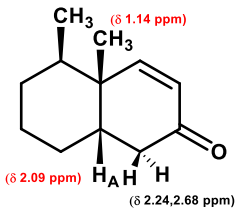
^{1}H NMR (500 MHz, $CDCl_3$) δ = 6.85 (d, *J* = 10.2 Hz, 1 H), 5.93 (dd, *J* = 0.7, 10.2 Hz, 1 H), 2.68 (dd, *J* = 12.7, 17.1 Hz, 1 H), 2.24 (dd, *J* = 4.3, 17.2 Hz, 1 H), 2.11 - 2.05 (m,

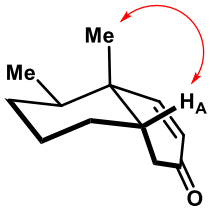
1 H), 1.86 - 1.75 (m, 2 H), 1.61 - 1.54 (m, 1 H), 1.54 - 1.46 (m, 2 H), 1.42 - 1.33 (m, 2 H), 1.14 (s, 3 H), 0.94 (d, *J* = 6.8 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$) δ = 161.4, 127.1, 39.9, 39.4, 38.8, 35.7, 30.1, 27.1, 20.5, 20.3, 15.9.

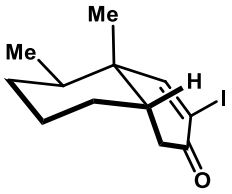
HRMS calculated for $C_{12}H_{19}O$ $[M+H]^+$: 179.1430, found 179.1431.

2D NMR analysis of compound 76a:





In the NOESY spectrum of compound **76a** the junction proton H_A (δ 42.09ppm) showed a strong correlation with junction methyl (δ 1.14 ppm) protons. This clearly tells that Junction methyl and junction hydrogen are *syn* to each other.



(4a*S*,5*R*,8a*S*)-3-iodo-4a,5-dimethyl-4a,5,6,7,8,8a-hexahydronaphthalen-2(1*H*)-one: 61a

To a solution of enone **76a** (570 mg, 0.320 mmol) in CH_2Cl_2 at 0 °C was added $TMSN_3$ (0.75 mL, 0.640 mmol) and stirred at 0 °C for 2 hours, then I_2 (1.65 g, 0.640 mmol) and pyridine (1.55 mL, 1.921 mmol) were added at 0 °C and reaction mixture was stirred at room temperature for 12 h. After completion of reaction, saturated $Na_2S_2O_3$ solution (20 mL) was added to reaction mixture and extracted with CH_2Cl_2 (2 X 40 mL). The combined organic layer was washed with brine (30 mL) and dried over anhydrous sodium sulphate. Solvent was evaporated in *vacuo* and the crude compound was purified by column chromatography (silica gel) to give iodo enone **61a** (870 mg, 89 %) as white solid.

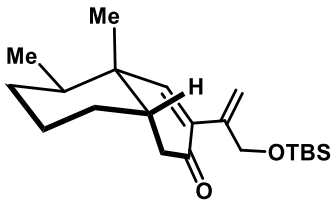
$[\alpha]_D^{25}$ = – 12.1 (*c* = 0.21, $CHCl_3$).

IR υ_{max}(film): cm^{-1} 2924, 2359, 1684, 1509.

^{1}H NMR (200 MHz, $CDCl_3$) δ = 7.63 (s, 1 H), 2.92 - 2.77 (m, 1 H), 2.56 - 2.46 (m, 1 H), 2.20 - 2.10 (m, 1 H), 1.97 - 1.67 (m, 2 H), 1.59 - 1.29 (m, 5 H), 1.15 (s, 3 H), 0.95 (m, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$) δ = 193.1, 169.5, 102.1, 44.1, 40.0, 38.4, 35.6, 30.1, 27.0, 20.3, 20.1, 16.0.

HRMS calculated for $C_{212}H_{18}OI$ $[M+H]^+$: 305.0397, found 305.0395.



(4a*S*,5*R*,8a*S*)-3-(3-((tert-butyldimethylsilyl)oxy)prop-1-en-2-yl)-4a,5-dimethyl-4a,5,6,7,8,8a-hexahydronaphthalen-2(1*H*)-one: 87

Iodo enone **61a** (0.7 g, 2.302 mmol) was taken in THF (9 mL) and water (1 mL), then Ag_2O (1.12 g, 3.683 mmol), $AsPh_3$ (80 mg, 0.345 mmol), $Pd(PhCN)_2Cl_2$ (176 mg, 0.460 mmol) and boronate **79** (1.02 g, 3.453 mmol) were added and reaction mixture was stirred at room temperature for 12 h under dark. After completion of reaction, saturated NH_4Cl solution (10 mL) was added to reaction mixture and stirred for 10 min. Then reaction mixture was extracted with EtOAc (2 X 30 mL) washed with brine (20 mL) and dried over anhydrous sodium sulphate. Solvent was evaporated in *vacuo* and crude compound was purified by column chromatography (silica gel) to afford **87** (670 mg, 84 %) as colourless oil.

$[\alpha]_D^{26}$ = – 34.2 (*c* = 0.90, $CHCl_3$)**.**

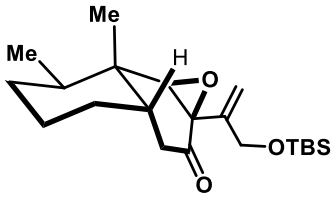
IR υ_{max}(film): cm^{-1} 2928, 2360, 1676, 1086.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.75 (s, 1 H), 5.25 (s, 1 H), 5.07 (s, 1 H), 4.34 - 4.26 (m, 2 H), 2.71 (dd, *J* = 12.8, 17.1 Hz, 1 H), 2.25 (dd, *J* = 4.3, 17.1 Hz, 1 H), 2.11 - 2.01

(m, 1 H), 1.84 (ddd, *J* = 3.7, 6.7, 10.4 Hz, 1 H), 1.79 - 1.69 (m, 1 H), 1.59 - 1.44 (m, 3 H), 1.40 - 1.26 (m, 2 H), 1.13 (s, 3 H), 0.96 - 0.88 (m, 12 H), 0.06 (s, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 199.2, 158.5, 146.4, 137.1, 113.7, 65.1, 40.1, 39.7, 39.0, 35.7, 30.2, 27.0, 25.9, 20.5, 20.5, 18.3, 16.0, -5.4.

HRMS calculated for $C_{21}H_{37}O_2Si$ $[M+H]^+$: 349.2557, found 349.2558.



(1a*R*,3a*S*,7*R*,7a*S*,7b*R*)-1a-(3-((tert-butyldimethylsilyl)oxy)prop-1-en-2-yl)-7,7a-dimethyloctahydronaphtho[1,2-b]oxiren-2(1a*H*)-one: 88

To a solution of compound **87** (660 mg, 1.896 mmol) in methanol (10 mL) was added 30% H_2O_2 (2.0 mL) followed by 10% NaOH solution (1.0 mL) at 0 °C. The reaction mixture was left at room temperature for 48 hours. After completion of reaction, saturated $NaHCO_3$ solution (10 mL) was added to the reaction mixture and extracted with EtOAc (3 X 20 mL). The combined organic layer was washed with brine (15 ml), dried over anhydrous sodium sulphate and purified by column chromatography (silica gel) to afford **88** (640 mg, 93 %) as colourless liquid.

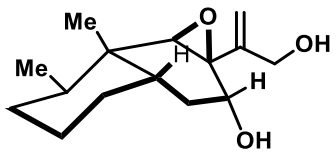
$[\alpha]_D^{26}$ = + 4.9 (*c* = 1.00, $CHCl_3$).

IR υ_{max}(film): cm^{-1} 2934, 2358, 1709, 1077, 1014.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.28 (m, 1 H), 5.19 (d, *J* = 1.4 Hz, 1 H), 4.37 - 4.27 (m, 2 H), 3.24 (s, 1 H), 2.50 - 2.42 (m, 1 H), 2.29 - 2.16 (m, 1 H), 2.12 - 2.00 (m, 1 H), 1.77 - 1.64 (m, 2 H), 1.55 - 1.48 (m, 1 H), 1.46 - 1.38 (m, 2 H), 1.34 - 1.24 (m, 2 H), 1.20 (s, 3 H), 0.96 (d, *J* = 6.4 Hz, 3 H), 0.92 - 0.89 (m, 9 H), 0.09 - 0.04 (m, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 204.8, 143.4, 112.2, 71.7, 64.0, 63.3, 38.8, 36.2, 33.4, 32.3, 30.0, 26.0, 25.6, 19.9, 18.5, 17.3, 16.4, -5.4, -5.5.

HRMS calculated for $C_{21}H_{37}O_3Si$ $[M+H]^+$: 365.2506, found 365.2508.



(1a*S*,2*R*,3a*S*,7*R*,7a*S*,7b*R*)-1a-(3-hydroxyprop-1-en-2-yl)-7,7a-dimethyldecahydronaphtho[1,2-b]oxiren-2-ol: 23

To a solution of compound **88** (610 mg, 1.676 mmol) in THF (20 mL) was added TBAF (1M in THF) (1.7 mL, 1.676 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 2 hours. After completion of reaction, saturated NH_4Cl solution (20 mL) was added to it and extracted with EtOAc (2 X 30 mL). The combined organic layer was washed with brine (25 mL), dried over anhydrous sodium sulphate and evaporated in *vacuo.* The crude compound **89** (370 mg, 88%) was used as such for further reaction.

To a solution of compound **89** (350 mg, 1.400 mmol) in THF (20 mL) at 0 °C was added $NaBH_4$ (54 mg, 1.400 mmol). The reaction mixture was stirred at 0 °C for 2 hours. After completion of reaction, saturated NH_4Cl solution (10 mL) was added to it and extracted with EtOAc (2 X 25 mL). The combined organic layer was washed with brine (15 mL), dried over sodium sulphate and evaporated in *vacuo*. The crude compound was purified by column chromatography (silica gel) to afford peribysin A, **23** (230 mg, 76%) as white solid, its minor diastereomers **91** (28 mg, 9%) as sticky solid and mixture (45 mg).

Data for Peribysin A: **23**

$[\alpha]_D^{23}$ = – 59.3 (*c* = 0.53, EtOH).

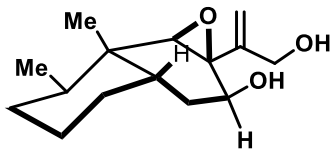
IR υ_{max}(film): cm^{-1} 2926, 2662, 1457, 1027.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.33 (s, 1 H), 5.22 (s, 1 H), 4.36 (d, *J* = 12.2 Hz, 1 H), 4.19 (d, *J* = 12.2 Hz, 1 H), 4.02 (dd, *J* = 6.7, 10.4 Hz, 1 H), 3.19 (s, 1 H), 3.02 (br. s., 1 H), 2.65 (br. s., 1 H), 2.02 - 1.93 (m, 1 H), 1.90 - 1.76 (m, 1 H), 1.69 (br. s., 1 H), 1.58 - 1.50 (m, 2 H), 1.50 - 1.44 (m, 3 H), 1.39 - 1.22 (m, 3 HS), 1.07 (s, 3 H), 0.95 (d, *J* = 6.7 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 145.7, 117.5, 69.9, 68.7, 67.3, 64.4, 35.9, 33.2, 32.7, 31.1, 30.8, 27.0, 20.6, 16.8.

HRMS calculated for $C_{15}H_{24}O_3Na$ $[M+Na]^+$: 275.1618, found 275.1616.

Data for other diastereomer: **91**



(1a*S*,2*S*,3a*S*,7*R*,7a*S*,7b*R*)-1a-(3-hydroxyprop-1-en-2-yl)-7,7a-dimethyldecahydronaphtho[1,2-b]oxiren-2-ol: 91

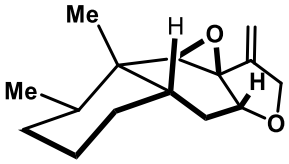
$[\alpha]_D^{26}$ = + 0.43 (*c* = 0.70, $CHCl_3$).

IR υ_{max}(film): cm^{-1} 2926, 2662, 1457, 1027.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.23 (d, *J* = 1.4 Hz, 1 H), 5.16 (s, 1 H), 4.38 - 4.25 (m, 1 H), 4.25 - 4.13 (m, 2 H), 3.24 (s, 1 H), 2.64 (br. s., 1 H), 2.32 (br. s., 1 H), 2.08 - 1.94 (m, 1 H), 1.81 - 1.69 (m, 2 H), 1.51 - 1.41 (m, 3 H), 1.35 - 1.25 (m, 4 H), 1.10 (s, 3 H), 0.93(d, *J* = 6.9 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 147.4, 113.9, 71.1, 66.5, 65.3, 63.9, 35.7, 32.4, 31.3, 30.7, 29.8, 26.5, 20.3, 17.3, 16.4.

HRMS calculated for $C_{15}H_{24}O_3Na$ $[M+Na]^+$: 275.1618, found 275.1617.



(1a*S*,4a*R*,5a*S*,9*R*,9a*S*,9b*R*)-9,9a-dimethyl-2-methylenedecahydro-7*H*-oxireno[2',3':3,4]naphtho[2,3-b]furan: 92

To a solution of peribysin A, **23** (28 mg, 0.111 mmol) in 1,2-dichloroethane (4 mL) were added Et_3N (0.16 mL, 1.110 mmol), tosyl chloride (105 mg, 0.555 mmol) at 0 °C and stirred for 30 min. Then the reaction mixture was refluxed for 12 hours. After 12 h

the solvent was evaporated and the crude compound was purified by column chromatography (silica gel) to afford **92** (16 mg, 62 %) as pale yellow oil.

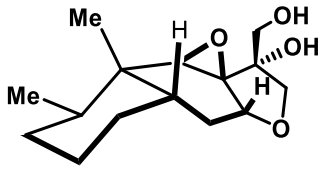
$[\alpha]_D^{26}$ = + 5.95(*c* = 0.53, $CHCl_3$).

IR υ_{max}(film): cm^{-1} 2922, 2358, 1258, 1015.

^{1}H NMR (200 MHz, $CDCl_3$) δ = 5.00 (td, *J* = 2.3, 11.6 Hz, 2 H), 4.52 - 4.50 (m, 2 H), 4.03 - 3.94 (m, 1 H), 3.28 (s, 1 H), 1.92 - 1.56 (m, 4 H), 1.51 - 1.29 (m, 6 H), 1.08 (s, 3 H), 0.93 (d, *J* = 6.7 Hz 3 H)

^{13}C NMR (100 MHz, $CDCl_3$) δ = 146.2, 105.1, 75.8, 70.5, 70.0, 60.7, 32.2, 31.2, 31.0, 30.9, 27.3, 20.8, 17.2, 16.7, 14.5.

HRMS calculated for $C_{15}H_{23}O_2$ $[M+H]^+$: 235.1693, found 235.1694.



(1a*S*,2*R*,4a*R*,5a*S*,9*R*,9a*S*,9b*R*)-2-(hydroxymethyl)-9,9a-dimethyldecahydro-7*H*-oxireno[2',3':3,4]naphtho[2,3-b]furan-2-ol: 24

To a solution of compound **92** (16 mg, 0.068 mmol) in acetone (3 mL) and H_2O (2 mL) at 0 °C was added OsO_4 (2.5% in *ter*-butanol) (0.1 mL) and NMO (16 mg, 0.137 mmol). The reaction mixture was stirred at room temperature for 4 hours. After completion of reaction saturated Na_2SO_3 solution (5 mL) was added to it and stirred for 15 min. The reaction mixture was extracted with EtOAc (2 X 20 mL), dried over anhydrous sodium sulphate and concentrated. The crude compound was purified by column chromatography (silica gel) to afford peribysin B, **24** (8 mg, 45%) as sticky solid.

$[\alpha]_D^{25}$ = – 1.1 (*c* = 0.56, EtOH).

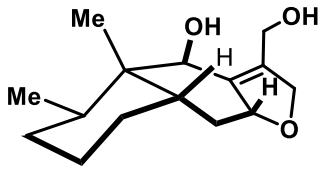
IR υ_{max}(film): cm^{-1} 3615, 2953, 2359, 1041.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 3.98 (d, *J* = 10.1 Hz, 1 H), 3.87 - 3.83 (m, 2 H), 3.77 (d, *J* = 11.9 Hz, 1 H), 3.55 (d, d, *J* = 11.9 Hz, 1 H), 3.35 (s, 1 H), 1.91 - 1.81 (m, 2 H),

1.76 - 1.67 (m, 2 H), 1.60 (ddd, *J* = 1.8, 6.8, 12.5 Hz, 2 H), 1.52 - 1.41 (m, 3 H), 1.39 - 1.32 (m, 3 H), 1.07 (s, 3 H), 0.96(d, d, *J* = 6.9 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 77.6, 76.5**,** 75.1, 72.6, 65.0, 64.2, 35.8, 32.5, 30.9, 30.8, 30.2, 27.0, 20.6, 16.9, 16.5.

HRMS calculated for $C_{15}H_{24}O_4Na$ $[M+Na]^+$: 291.1567, found 291.1565.



(4*R*,4a*S*,5*R*,8a*S*,9a*R*)-3-(hydroxymethyl)-4a,5-dimethyl-2,4,4a,5,6,7,8,8a,9,9a-decahydronaphtho[2,3-b]furan-4-ol: 25

To a solution of compound **92** (6 mg, 0.256 mmol) in THF (1 mL) and H_2O (0.1 mL) $Sc(OTf)_3$ (2.5 mg, 0.051 mmol) was added and the reaction mixture was stirred 70 °C for 5 hours. Reaction mixture was then diluted with EtOAc (12 mL) and washed with brine (5 mL). The combined organic layer was dried over anhydrous sodium sulphate and evaporated. Purification by column chromatography (silica gel) gave peribysin C, **25** (2.9 mg, 45 %).

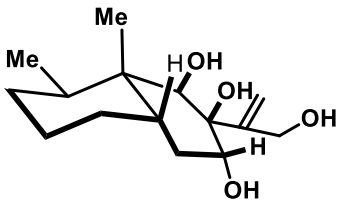
$[\alpha]_D^{23}$ = + 24.2 (*c* = 0.21, EtOH).

IR υ_{max}(film): cm^{-1} 3202, 2927, 2358, 1459, 1023.

^{1}H NMR (500 MHz, $CDCl_3$) δ = 5.09 - 5.04 (m, 1 H), 4.80 (s, 1 H), 4.79 (s, 1 H), 4.55 (s, 1 H), 4.34 (d, *J* = 12.6 Hz, 1 H), 4.25 (d, *J* = 12.6 Hz, 1 H), 1.97 - 1.86 (m, 2 H), 1.76 - 1.68 (m, 3 H), 1.44 - 1.37 (m, 2 H), 1.34 - 1.26 (m, 3 H), 1.04 (s, 3H), 0.73 (d, *J* = 6.5 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 136.7, 131.3, 84.0, 76.4, 70.2, 56.4, 41.4, 35.3, 34.6, 30.8, 29.5, 26.4, 20.2, 16.4, 16.0.

HRMS calculated for $C_{15}H_{24}O_3Na$ $[M+Na]^+$: 275.1618, found 275.1617.



(1*R*,2*S*,3*R*,4a*S*,8*R*,8a*S*)-2-(3-hydroxyprop-1-en-2-yl)-8,8a-dimethyldecahydronaphthalene-1,2,3-triol: 27

Peribysin A, **23** (45 mg, 0.18 mmol) was taken in MeOH (0.1 mL) and H_2O (2 mL) and cooled to 0°C. Then two drops of con. HCl were added to it and reaction mixture was allowed to warm to room temperature and stirred for additional 3 hours. Then reaction mixture was diluted with EtOAC (20 mL) and washed with saturated $NaHCO_3$ solution (5 mL) and brine (5 mL). The organic layer was dried over anhydrous sodium sulphate and purified by column chromatography (silica gel) to afford peribysin F, **27** (4.7 mg, 13%), peribysin G, **28** (1.1 mg, 3%) as sticky solid and peribsin A was recovered (8 mg).

Data for peribysin F: **27**

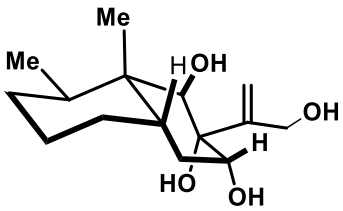
$[\alpha]_D^{27}$ = – 23.9 (*c* = 0.09, EtOH).

IR υ_{max}(film): cm^{-1} 3419, 2923, 2361, 1550.

^{1}H NMR (400 MHz, CD_3OD) δ = 5.63 (s, 1 H), 5.44 (s, 1 H), 4.31 (d, *J* = 5.3, 13.7 Hz, 1 H), 4.22(d, *J* = 13.7 Hz, 1 H), 4.01(s, 1 H), 3.87 (dd, *J* = 5.0, 8.8 Hz, 1 H), 2.05 (dd, *J* = 1.9, 6.5 Hz, 1 H), 1.90 (dt, *J* = 5.3, 9.2 Hz, 2 H), 1.83 - 1.72 (m, 1 H), 1.65 - 1.56 (m, 2 H), 1.50 - 1.41 (m, 3 H), 1.28 (d, *J* = 3.8 Hz, 1 H), 1.04 (s, 3 H), 0.84 (d, *J* = 6.9 Hz, 3 H).

^{13}C NMR (100 MHz, CD_3OD) δ = 151.5, 116.8, 80.5, 76.2, 74.7, 64.7, 42.5, 38.3, 33.8, 33.3, 31.7, 29.3, 22.0, 18.5, 17.1.

HRMS calculated for $C_{15}H_{26}O_4Na$ $[M+Na]^+$: 293.1723, found 293.1719.



(1*R*,2*R*,3*R*,4a*S*,8*R*,8a*S*)-2-(3-hydroxyprop-1-en-2-yl)-8,8a-dimethyldecahydronaphthalene-1,2,3-triol: 28

Data for peribysin G: **28**

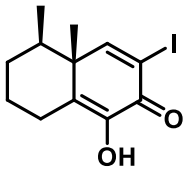
$[\alpha]_D^{22}$ = – 0.65 (*c* = 0.17, EtOH).

IR υ_{max}(film): cm^{-1} 3414, 2924, 2360, 1553, 1025.

^{1}H NMR (400 MHz, CD_3OD)δ = 5.46 (s, 1 H), 5.36 (s, 1 H), 4.28 (s, 2 H), 4.17 (dd, *J* = 4.9, 11.6 Hz, 1 H), 3.60 (s, 1 H), 2.88 - 2.76 (m, 1 H), 2.31 - 2.17 (m, 1 H), 1.81 (d, *J* = 14.0 Hz, 1 H), 1.77 - 1.68 (m, 2 H), 1.65 - 1.54 (m, 2 H), 1.45 (d, *J* = 11.6 Hz, 3 H), 0.92 (s, 3 H), 0.81 (d, *J* = 6.7 Hz, 3 H).

^{13}C NMR (100 MHz, CD_3OD) δ = 155.1, 115.9, 81.0, 79.2, 70.4, 65.3, 42.2, 37.8, 32.7, 32.4, 30.8, 28.6, 22.4, 18.2, 17.3.

HRMS calculated for $C_{15}H_{26}O_4Na$ $[M+Na]^+$: 293.1723, found 293.1721.



(4a*R*,5*R*)-1-hydroxy-3-iodo-4a,5-dimethyl-5,6,7,8-tetrahydronaphthalen-2(4a*H*)-one: 101

Iodo enone **61a** (250 mg, 0.82 mmol) was dissolved in dry toluene (80 mL) and purged with oxygen for 10 min. Then it was cooled to -78 °C and KO^tBu (276 mg, 2.467 mmol) and 18-crown-6 (195 mg, 0.74 mmol) were added to it. The reaction mixture was stirred at-78 °C under oxygen atmosphere for 2 hours. Then saturated NH_4Cl (25 mL) was added to it. The organic layer was separated and washed with brine (30 mL), dried over anhydrous sodium sulphate and concentrated in *vacuo*. The crude product was purified

by column chromatography (silica gel) to get **101** as white crystalline solid (128 mg, 49 %).

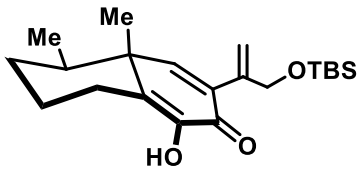
$[\alpha]_D^{26}$ = – 4.80 (*c* = 0.80, $CHCl_3$).

IR υ_{max}(film): cm^{-1} 3410, 2925, 1629, 1259.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.91 (s, 1 H), 6.25 (s, 1 H), 2.05 - 1.94 (m, 2 H), 1.56 - 1.40 (m, 3 H), 1.40 - 1.28 (m, 2 H), 1.17 (s, 3 H), 1.10 (d, *J* = 6.1 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 175.8, 166.5, 139.2, 138.7, 98.3, 48.3, 41.7, 30.3, 26.8, 23.8, 16.9, 16.8.

HRMS calculated for $C_{12}H_{15}O_2INa$ $[M+Na]^+$: 341.0009, found 341.0008.



(4a*R*,5*R*)-3-(3-((tert-butyldimethylsilyl)oxy)prop-1-en-2-yl)-1-hydroxy-4a,5-dimethyl-5,6,7,8-tetrahydronaphthalen-2(4a*H*)-one: 102

Iodo enone **101** (75 mg, 0.234 mmol) was taken in THF (4 mL) and water (0.5 mL), then Ag_2O (115 mg, 0.374 mmol), $AsPh_3$ (8 mg, 0.035 mmol), $Pd(PhCN)_2Cl_2$ (18 mg, 0.047 mmol) and boronate **79** (105 mg, 0.354 mmol) were added and reaction mixture was stirred at room temperature for 12 h under dark. After completion of reaction, saturated NH_4Cl solution (5 mL) was added to reaction mixture and stirred for 10 min. Then reaction mixture was extracted with EtOAc (2 X 20 mL) washed with brine (15 mL) and dried over anhydrous sodium sulphate. Solvent was evaporated in *vacuo* and crude compound was purified by column chromatography (silica gel) to afford **102** (58 mg, 68 %) as pale yellow oil.

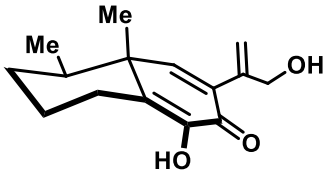
$[\alpha]_D^{23}$ = – 2.32 (*c* = 0.12, $CHCl_3$).

IR υ_{max}(film): cm^{-1} 2922, 2361, 2327, 1683.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.16 (s, 1 H), 6.53 (s, 1 H), 5.38 (q, *J* = 1.7 Hz, 1 H), 5.33 - 5.27 (m, 1 H), 4.47 - 4.39 (m, 2 H), 3.09 – 3.05 (m, 1 H), 2.04 - 1.90 (m, 2 H), 1.55 - 1.41 (m, 3 H), 1.36 - 1.22 (m, 3 H), 1.16 (s, 3 H), 1.09 (d, *J* = 6.4 Hz, 3 H), 0.90 (s, 9 H), 0.07 (s, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 179.6, 155.9, 145.2, 141.6, 136.6, 134.2, 114.7, 65.0, 42.8, 41.7, 30.5, 26.9, 25.9, 23.6, 18.3, 17.1, 16.8, -5.4.

HRMS calculated for $C_{21}H_{35}O_3Si$ $[M+Na]^+$: 363.2350, found 363.2353.



(4a*R*,5*R*)-1-hydroxy-3-(3-hydroxyprop-1-en-2-yl)-4a,5-dimethyl-5,6,7,8-tetrahydronaphthalen-2(4a*H*)-one: 60

To a solution of compound **102** (45 mg, 0.124 mmol) in THF (4 mL) at 0 °C was added TBAF (0.15 mL, 0.149 mmol) (1M in THF) and stirred at 0 °C for 1 hour. Reaction mixture was then diluted with EtOAc (25 mL) and washed with water (10 mL), followed by brine (10 mL). The combined organic layer was dried over anhydrous sodium sulphate and evaporated. Purification by column chromatography (silica gel) gave peribysin Q, **60** (18 mg, 57 %) as sticky liquid.

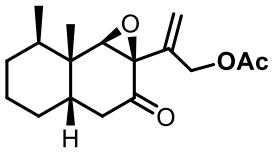
$[\alpha]_D^{23}$ = –13.2 (*c* = 0.74, $CHCl_3$).

IR υ_{max}(film): cm^{-1} 2926, 2365, 1745, 1101.

^{1}H NMR (500 MHz, $CDCl_3$) δ =7.21 (s, 1 H), 6.48 (s, 1 H), 5.37 - 5.34 (m, 2 H), 4.29 (s, 2 H), 3.12 - 3.03 (m, 1 H), 2.04 - 1.95 (m, 2 H), 1.61 - 1.55 (m, 1 H), 1.54 - 1.46 (m, 2 H), 1.39 - 1.33 (m, 2 H), 1.18 (s, 3 H), 1.10 (d, *J* = 6.1 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 180.4, 156.6, 145.7, 141.7, 138.4, 135.4, 117.9, 65.1, 43.3, 41.8, 30.4, 26.9, 23.7, 17.1, 16.8.

HRMS calculated for $C_{15}H_{20}O_3Na$ $[M+Na]^+$: 271.1305, found 271.1300.



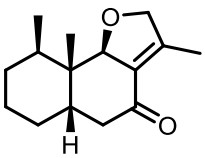
2-((1aR,3aS,7R,7aS,7bR)-7,7a-dimethyl-2-oxooctahydronaphtho[1,2-b]oxiren-1a(2H)-yl)allyl acetate: 95

To a solution of compound **88** (90 mg, 0.36mmol) in CH_2Cl_2 (6 mL) at 0 °C was added Et_3N (0.10 mL, 0.72 mmol) followed by Ac_2O (45 µL, 0.432mmol) and stirred at 0 °C for 2 hours. Reaction mixture was then diluted with CH_2Cl_2 (20 mL) and washed with water (10 mL), followed by brine (10 mL). The combined organic layer was dried over anhydrous sodium sulphate and evaporated. Purification by column chromatography (silica gel) compound **95** (94 mg, 89 %) as an white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ d = 5.42 - 5.24 (m, 2 H), 4.85 - 4.62 (m, 2 H), 3.25 (s, 1 H), 2.52 - 2.40 (m, 1 H), 2.26 (dd, *J* = 6.1, 18.8 Hz, 1 H), 2.10 (ddd, *J* = 2.4, 4.6, 11.6 Hz, 1 H), 2.07 - 2.02 (m, 3 H), 1.75 - 1.61 (m, 2 H), 1.56 - 1.48 (m, 1 H), 1.47 - 1.37 (m, 2 H), 1.36 - 1.24 (m, 2 H), 1.21 (s, 3 H), 0.98 (d, J = 6.8 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 204.8, 170.4, 138.8, 116.9, 72.0, 65.1, 63.1, 38.6, 36.3, 33.2, 32.4, 29.9, 25.5, 20.8, 19.8, 17.3, 16.3.

HRMS calculated for $C_{17}H_{24}O_4Na$ $[M+Na]^+$: 315.1572, found 315.1570.



(5aS,9R,9aS,9bR)-3,9,9a-trimethyl-5,5a,6,7,8,9,9a,9b-octahydronaphtho[1,2-b]furan-4(2H)-one: 97

$Cu(OTf)_2$ (7 mg, 0.02 mmol), PPh_3 (21 mg, 0.08 mmol), and $PhCF_3$ (1 mL) were mixed and stirred at room temperature for 5 min. Then compound **76a** (70 mg, 0.39mmol) in $PhCF_3$ (1 mL) and propargylalchohol (46 µL, 0.79 mmol) were added and the mixture was stirred at room temperature for 24 hours. Reaction mixture was then diluted with EtOAc (10 mL) and washed with water (5 mL), followed by brine (5 mL). The

combined organic layer was dried over anhydrous sodium sulphate and evaporated. Purification by column chromatography (silica gel) compound **97** (79 mg, 85 %) as an pale yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ= 5.41 (br. s., 1 H), 4.62 (dd, *J* = 3.7, 14.6 Hz, 1 H), 4.49 (dd, *J* = 5.5, 14.6 Hz, 1 H), 2.57 (dd, *J* = 6.1, 17.7 Hz, 1 H), 2.14 (d, *J* = 17.7 Hz, 1 H), 2.06 - 1.90 (m, 6 H), 1.61 - 1.49 (m, 2 H), 1.49 - 1.34 (m, 2 H), 1.34 - 1.21 (m, 2 H), 1.03 (d, *J* = 6.7 Hz, 3 H), 0.89 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ= 199.4, 145.8, 131.0, 87.0, 78.4, 44.6, 40.0, 37.0, 33.1, 29.9, 28.2, 20.5, 18.1, 14.7, 11.5.

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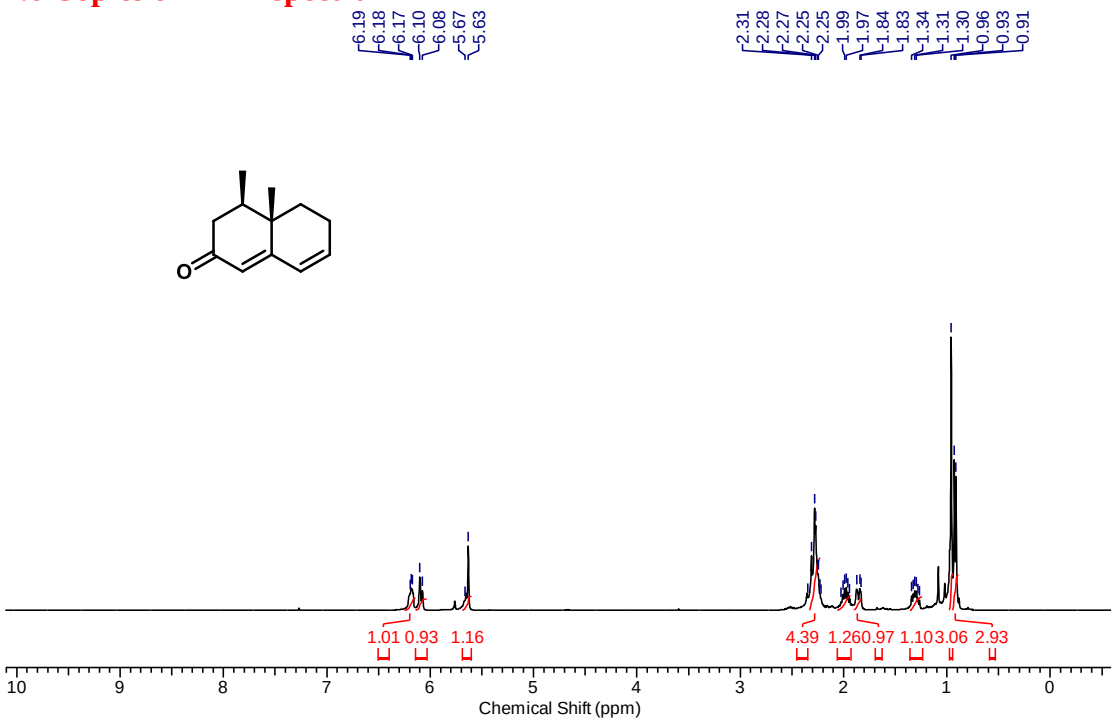
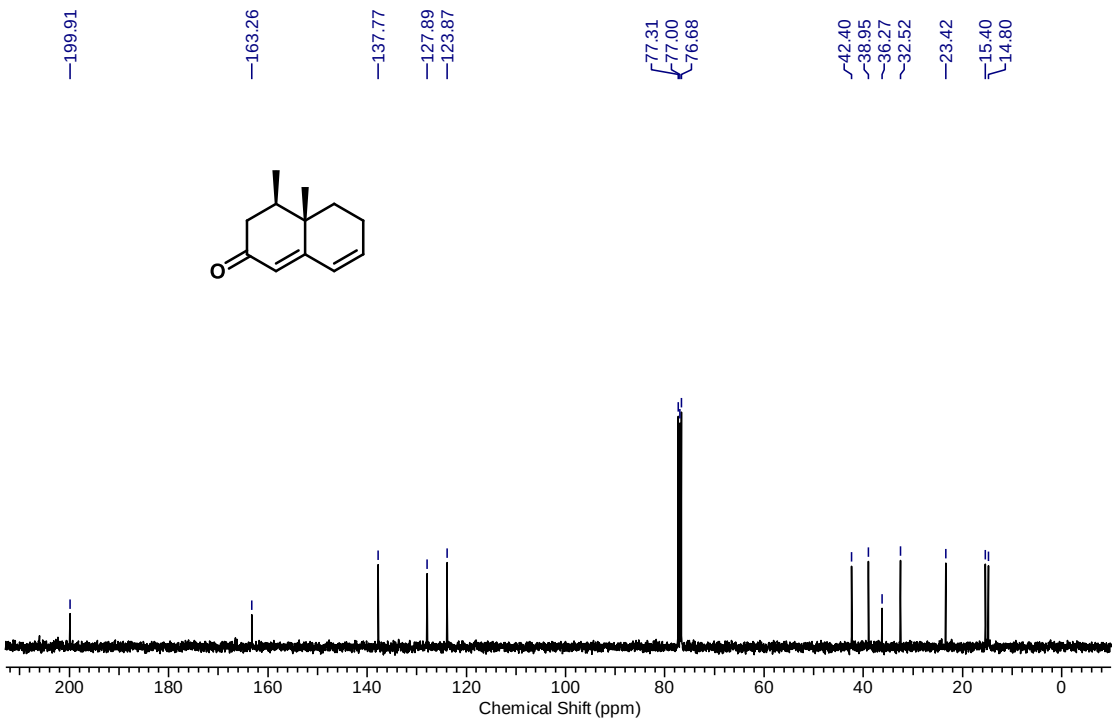
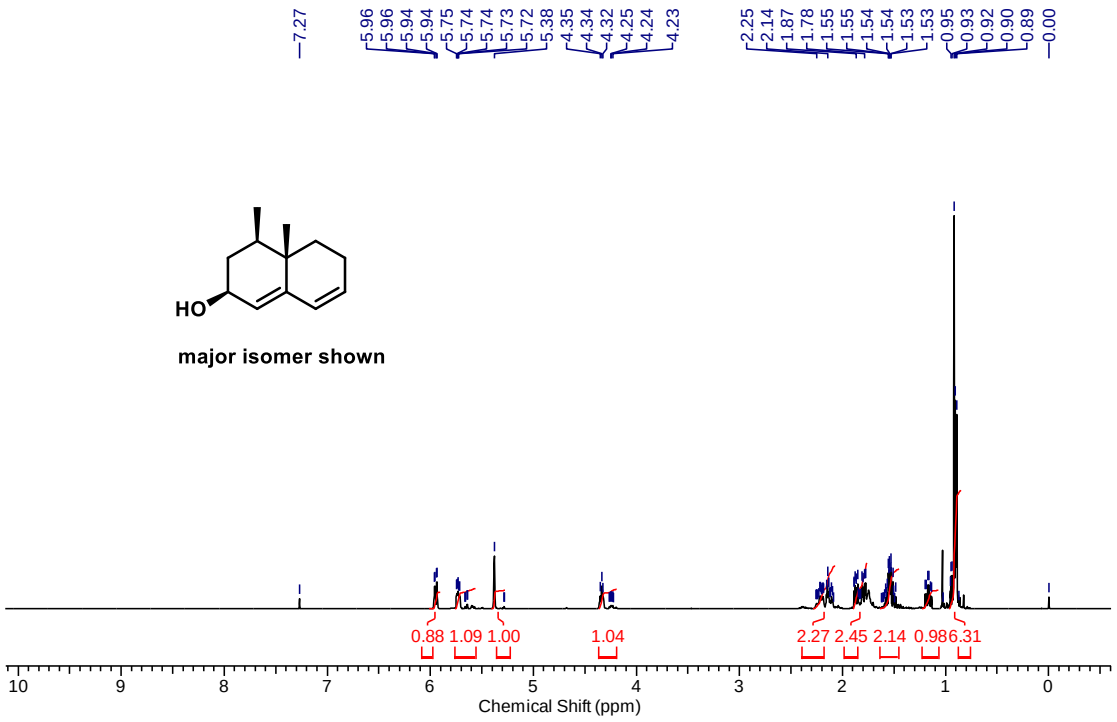
1.6 Copies of NMR spectra



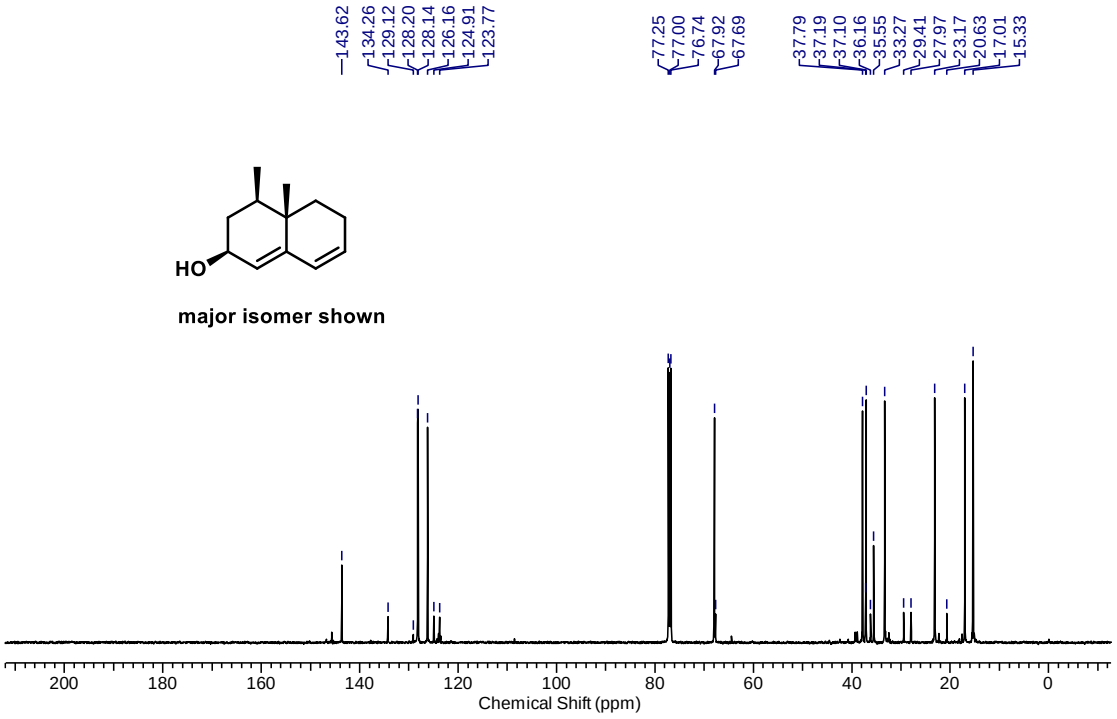
^{1}H NMR of Compound **63** in $CDCl_3$ at 400 MHz



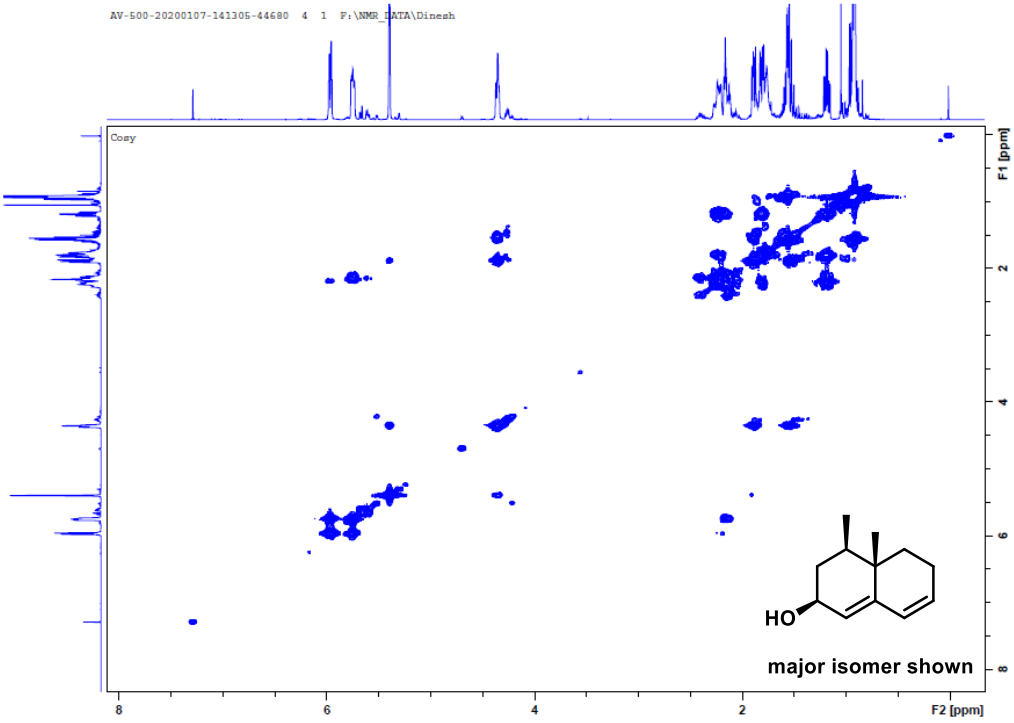
^{13}C NMR of Compound **63** in $CDCl_3$ at 100 MHz



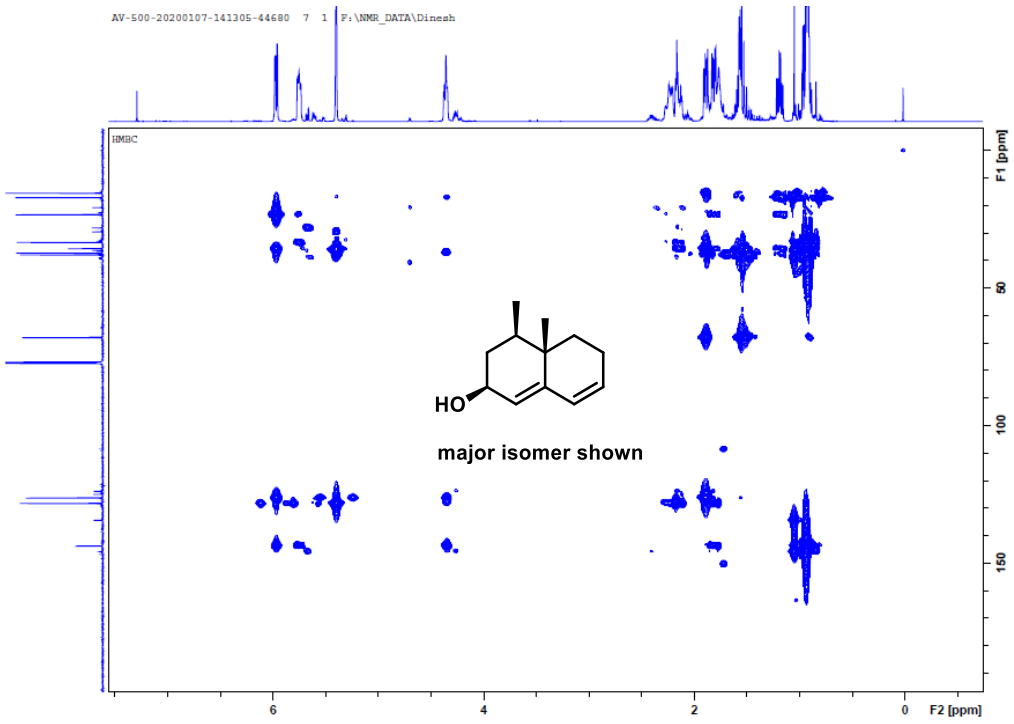
^{1}H NMR of Compound **67** in $CDCl_3$ at 500 MHz



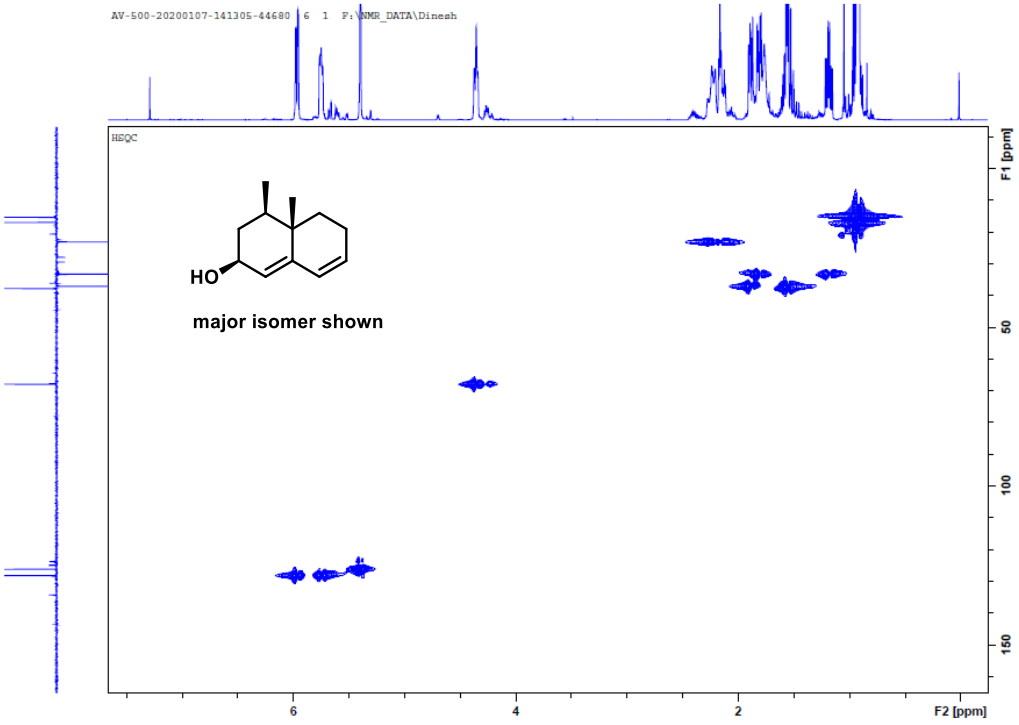
^{13}C NMR of Compound **67** in $CDCl_3$ at 125 MHz



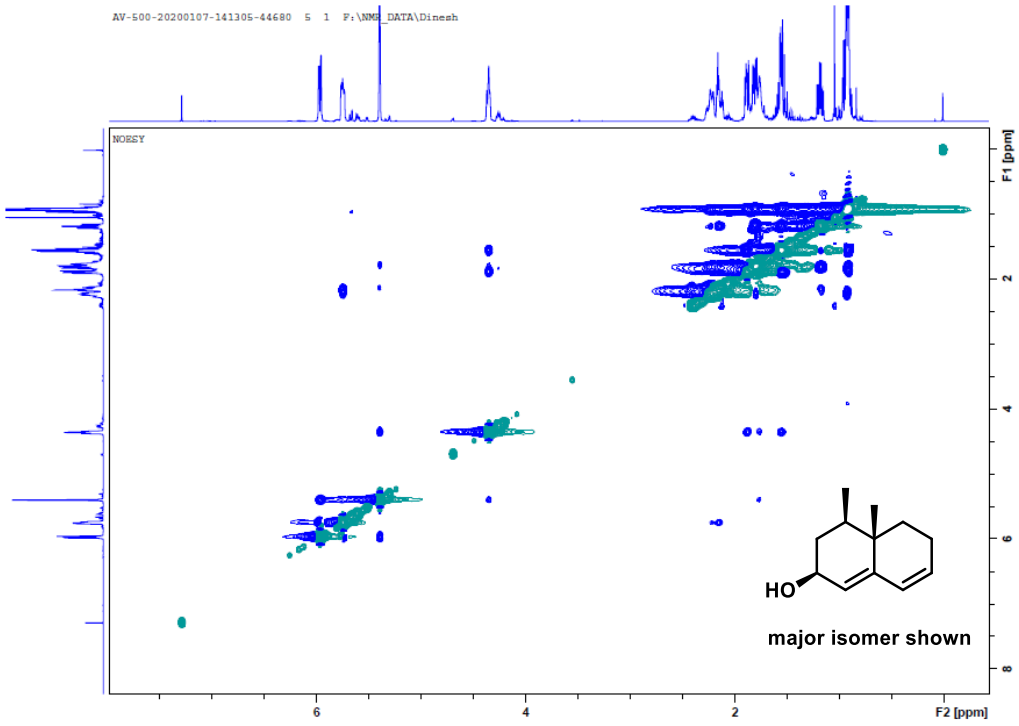
COSY spectra of Compound **67** in $CDCl_3$ at 100 MHz



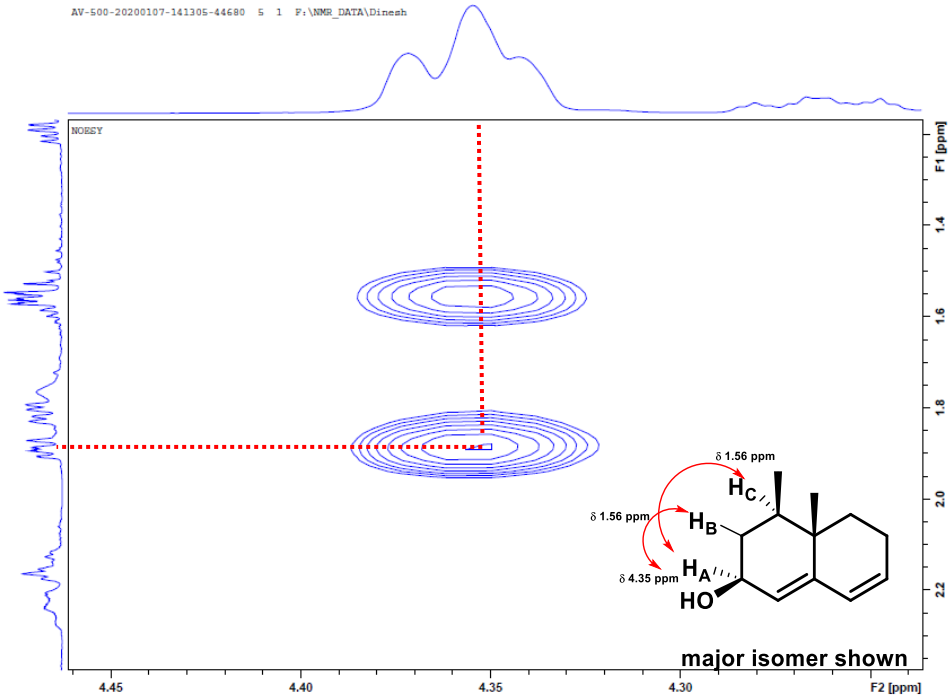
HMBC spectra of Compound **67** in $CDCl_3$ at 100 MHz



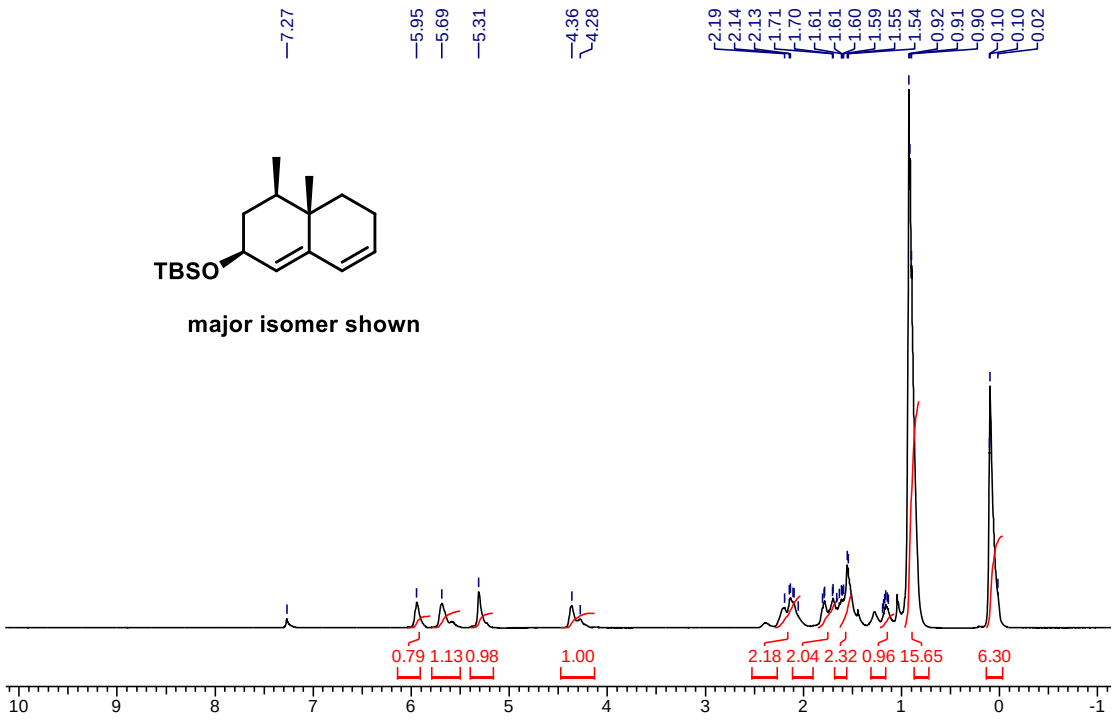
HSQC spectra of Compound **67** in $CDCl_3$ at 100 MHz



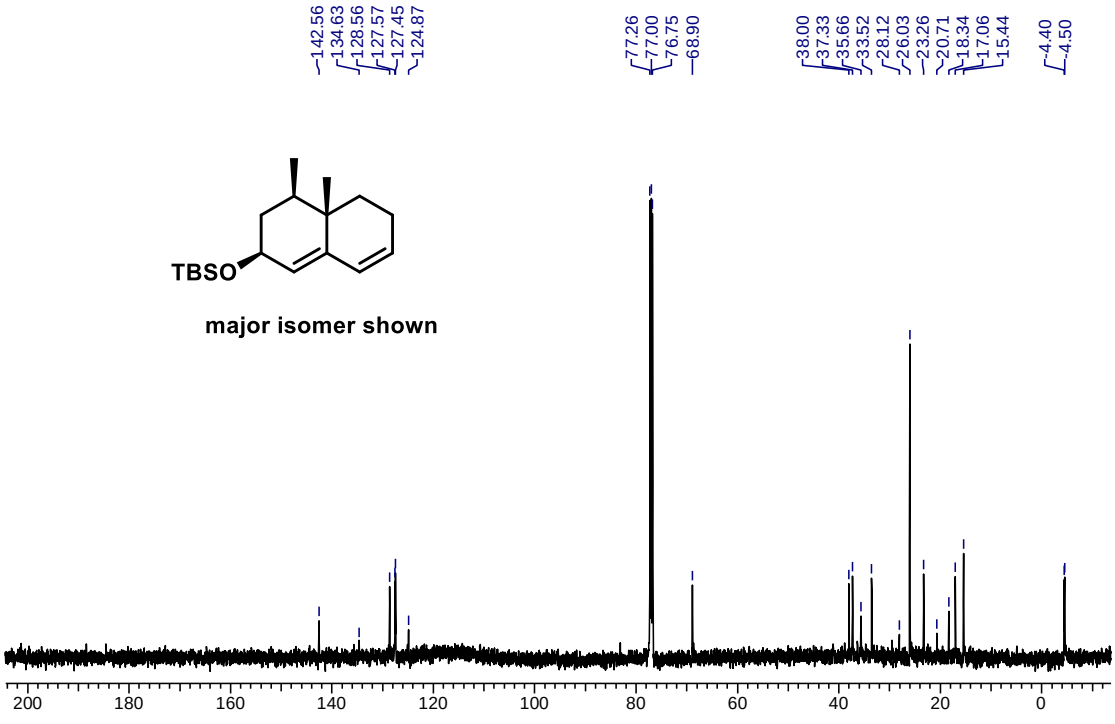
NOESY spectra of Compound **67** in $CDCl_3$ at 100 MHz



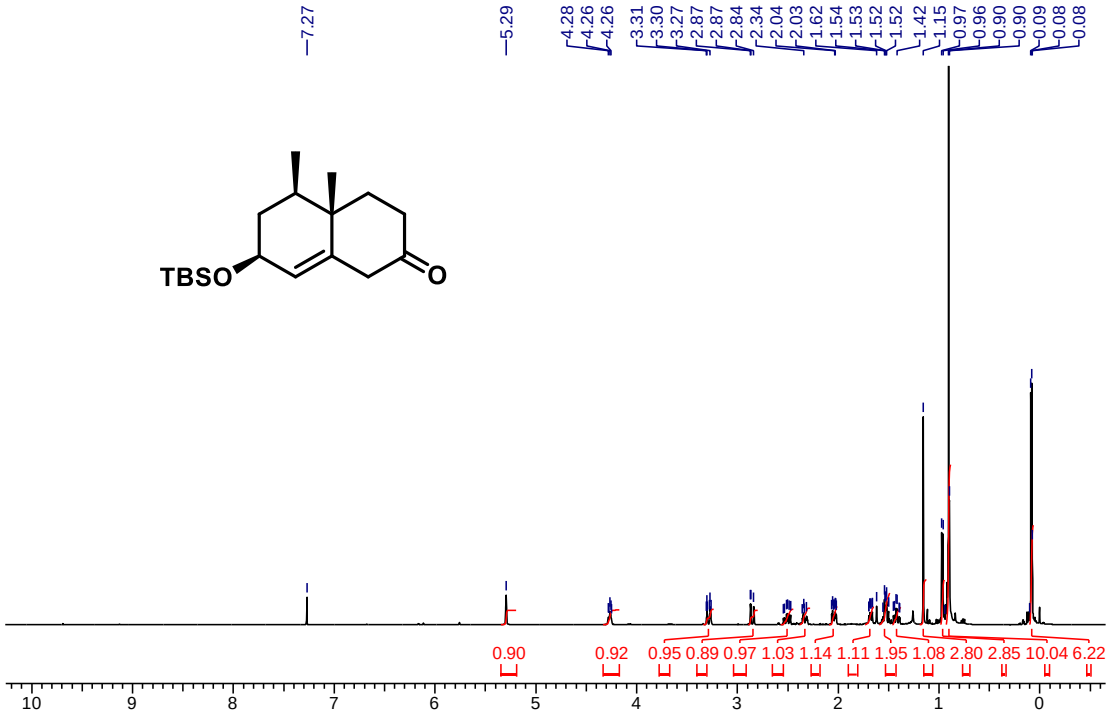
KEY NOESY correlation in Compound **67** in $CDCl_3$ at 100 MHz



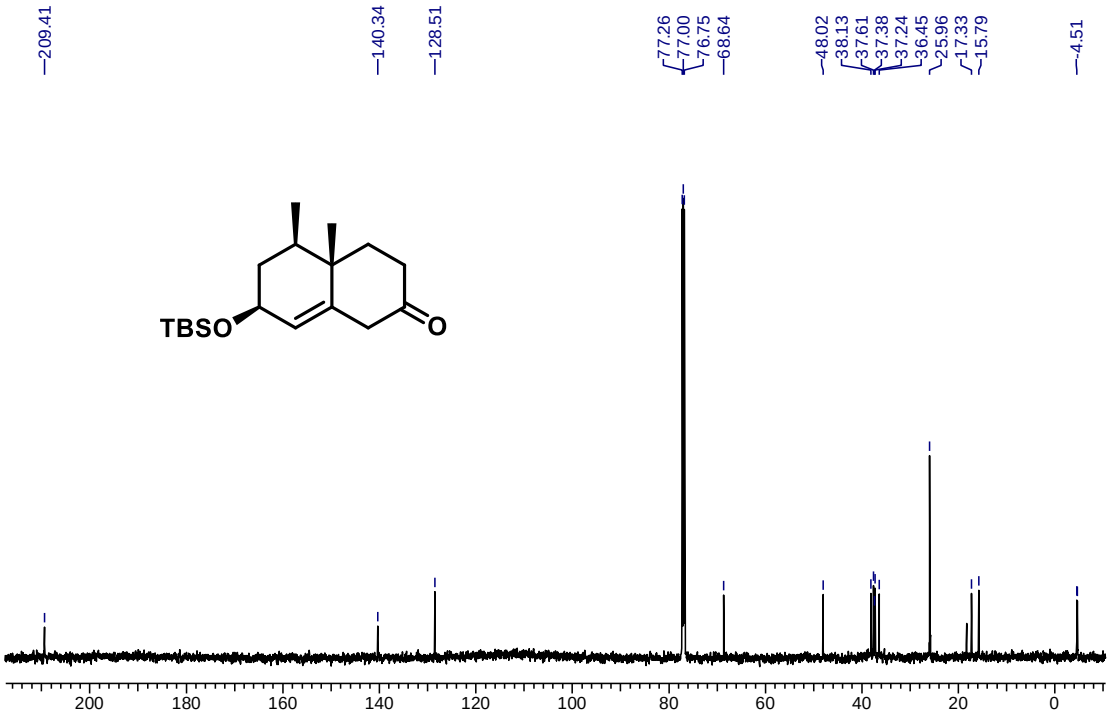
^{1}H NMR of Compound **68** in $CDCl_3$ at 500 MHz



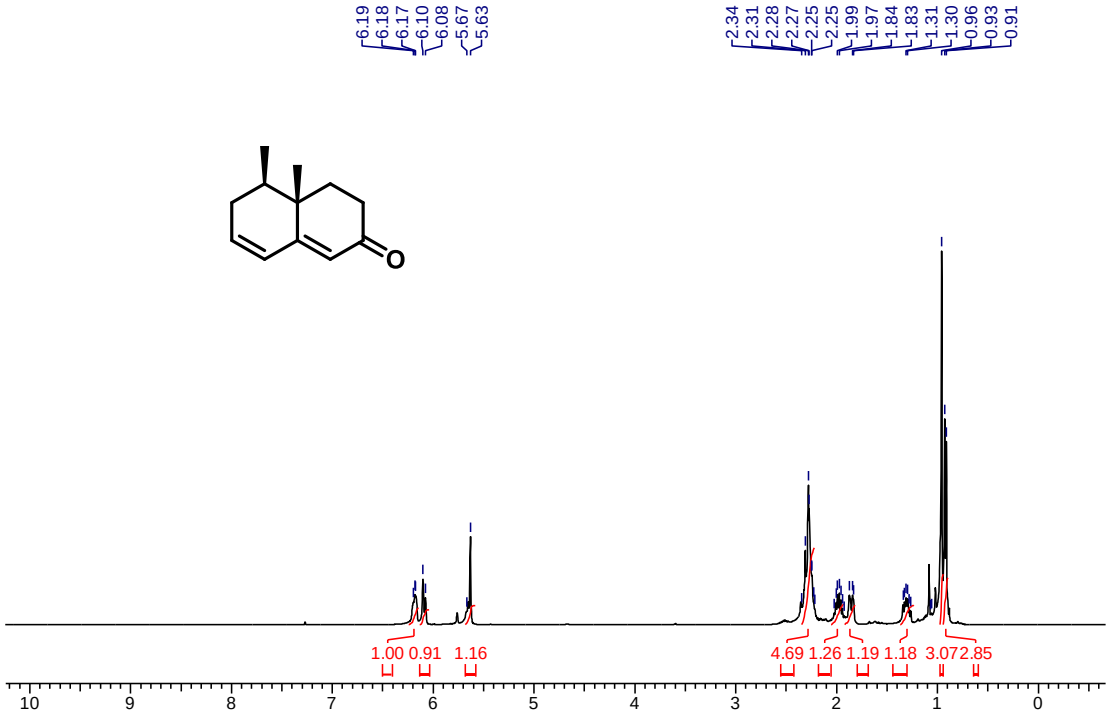
^{13}C NMR of Compound **68** in $CDCl_3$ at 125 MHz



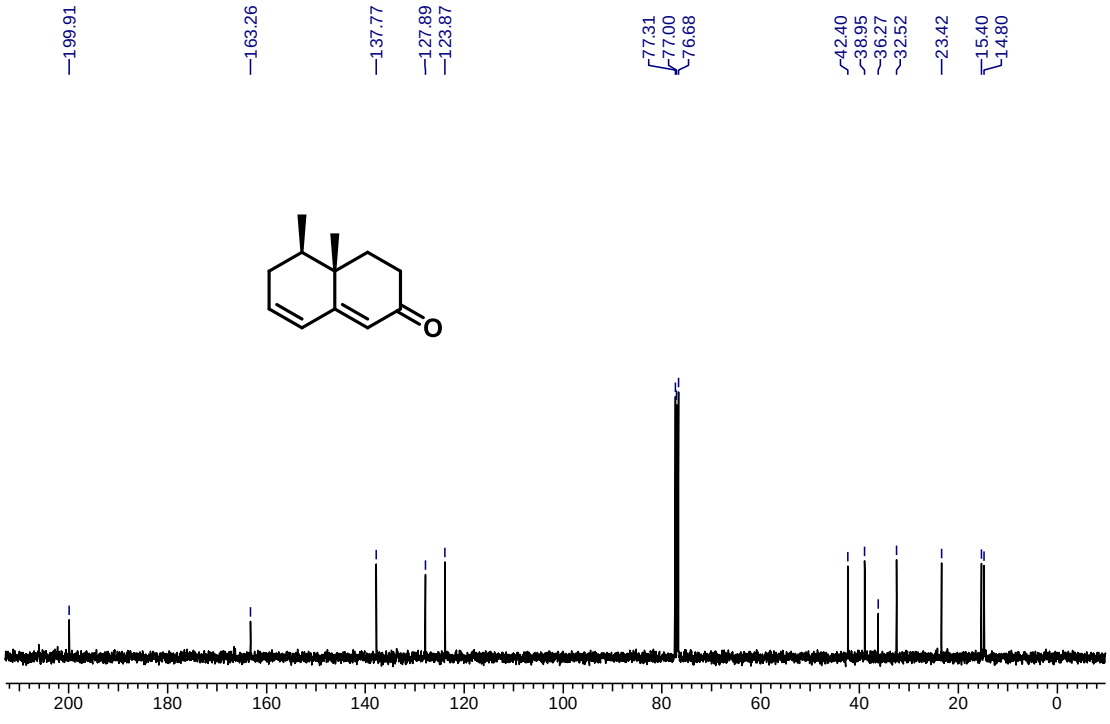
^{1}H NMR of Compound **71** in $CDCl_3$ at 500 MHz



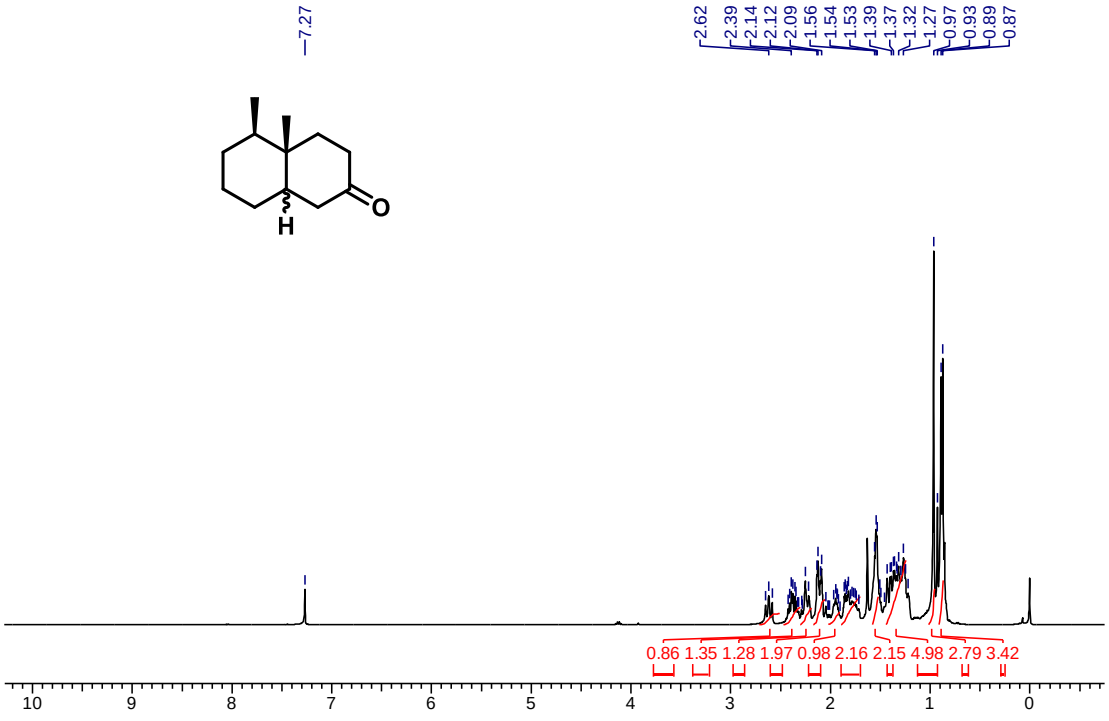
^{13}C NMR of Compound **71** in $CDCl_3$ at 125 MHz



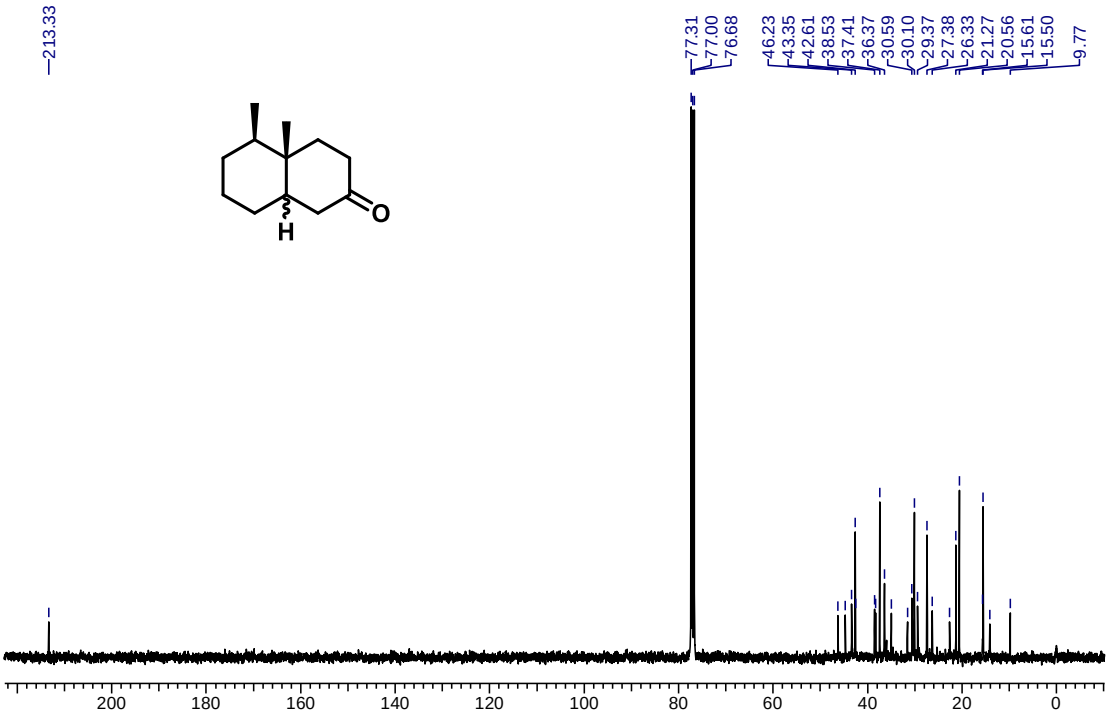
^{1}H NMR of Compound **62** in $CDCl_3$ at 400 MHz



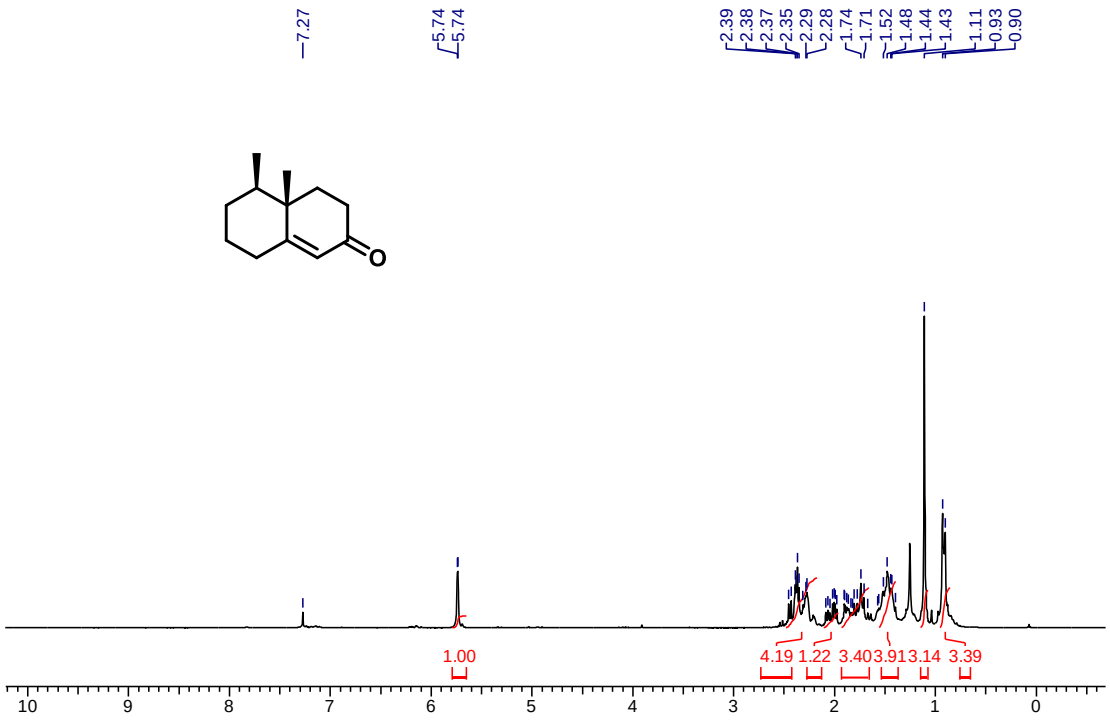
^{13}C NMR of Compound **62** in $CDCl_3$ at 100 MHz



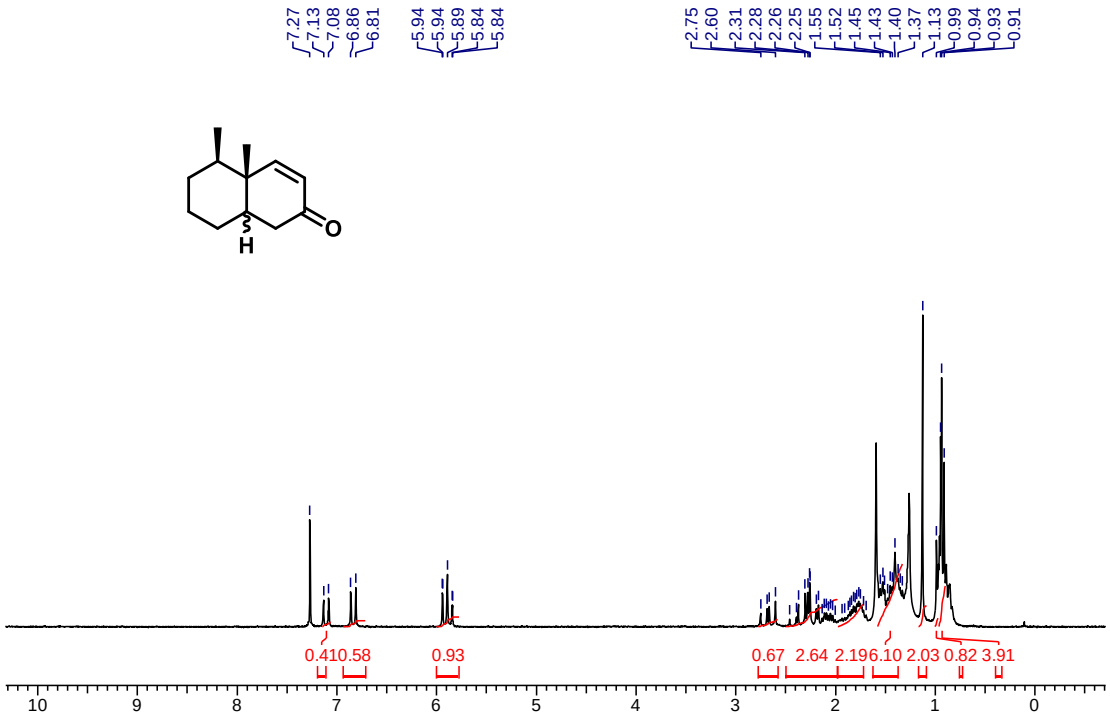
^{1}H NMR of Compound **75** in $CDCl_3$ at 400 MHz



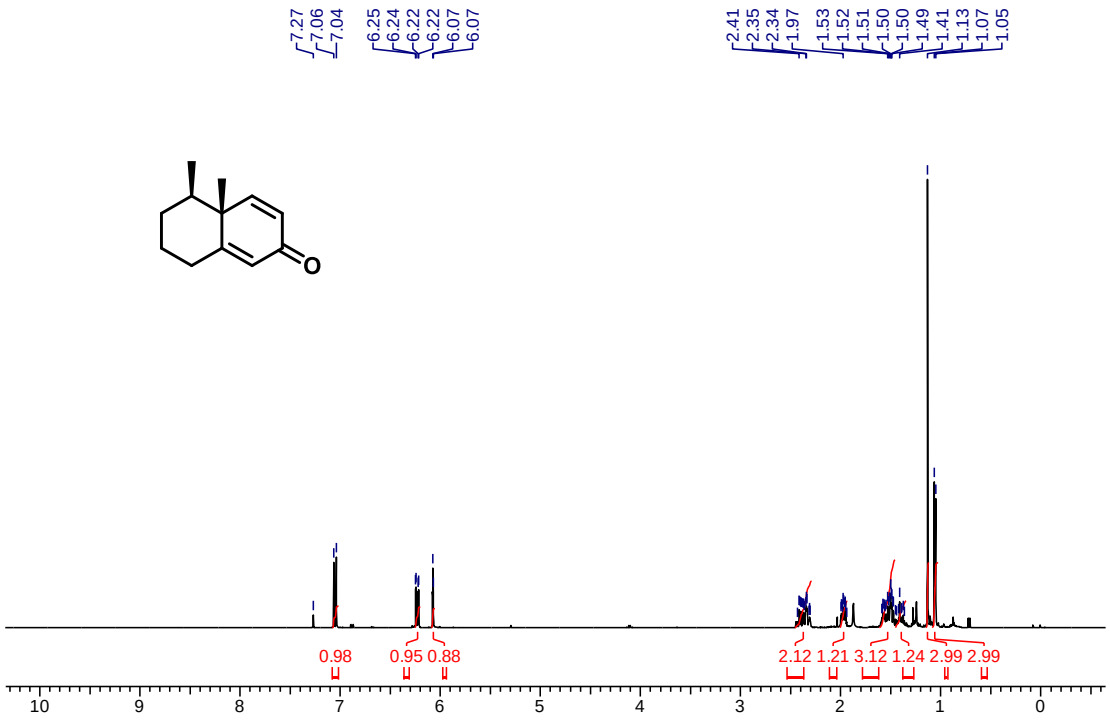
^{13}C NMR of Compound **75** in $CDCl_3$ at 100 MHz



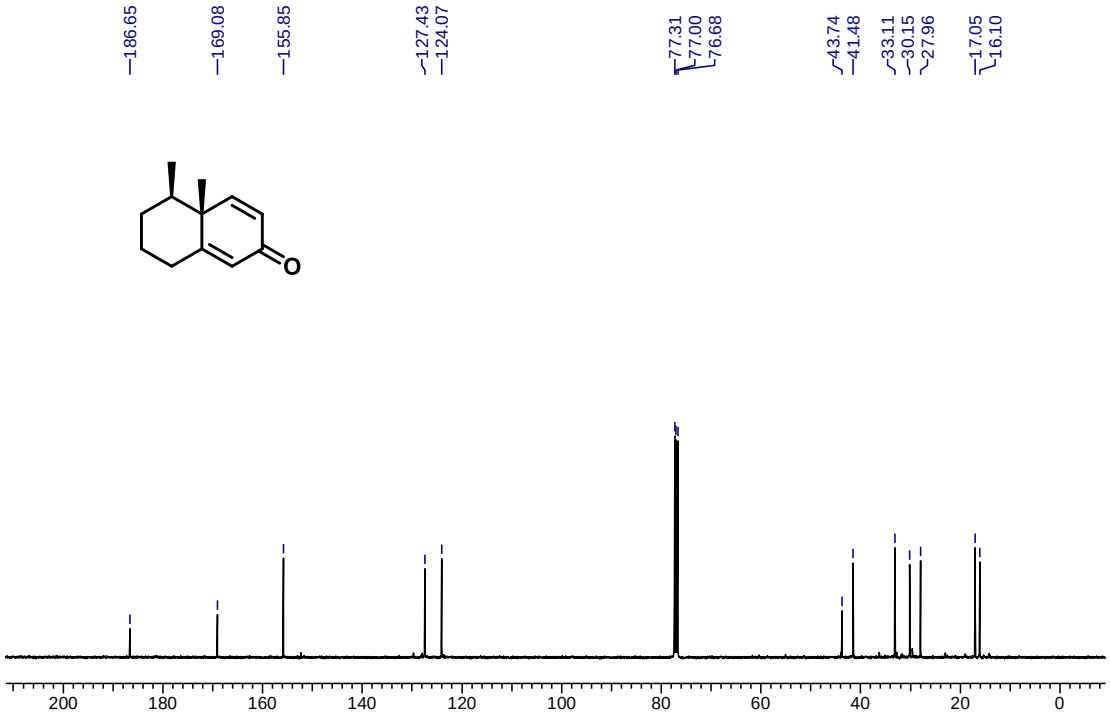
^{1}H NMR of (-)-Octalone**78** in $CDCl_3$ at 200 MHz



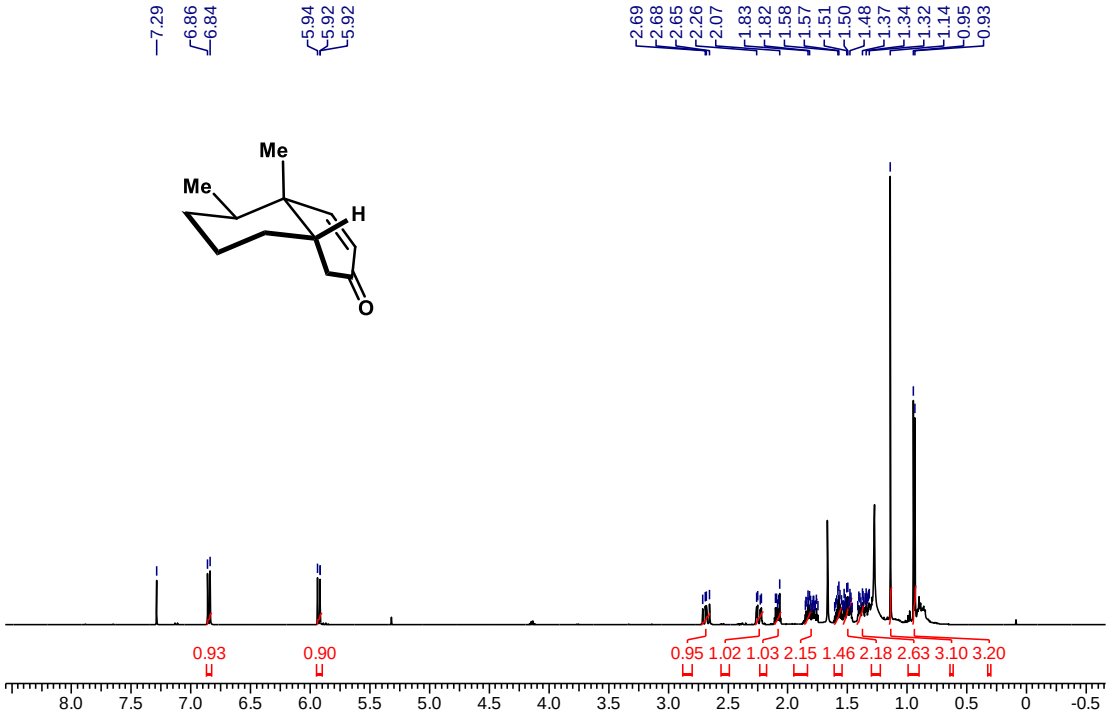
^{1}H NMR of Compound **76** in $CDCl_3$ at 200 MHz



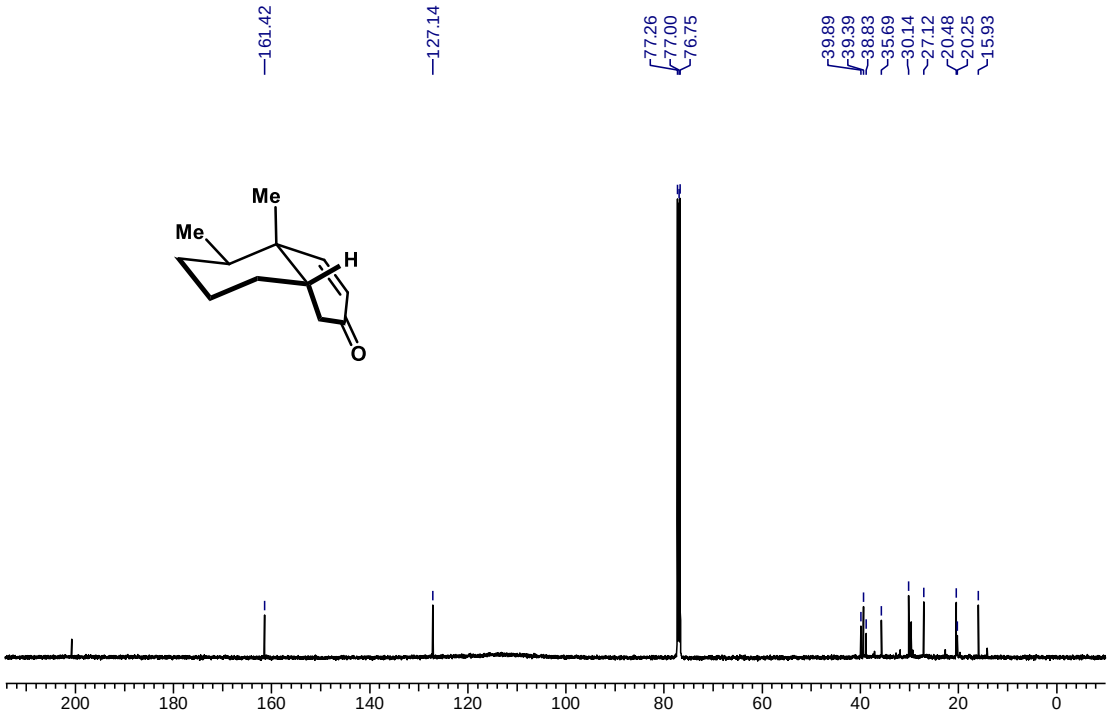
^{1}H NMR of Compound **77** in $CDCl_3$ at 400 MHz



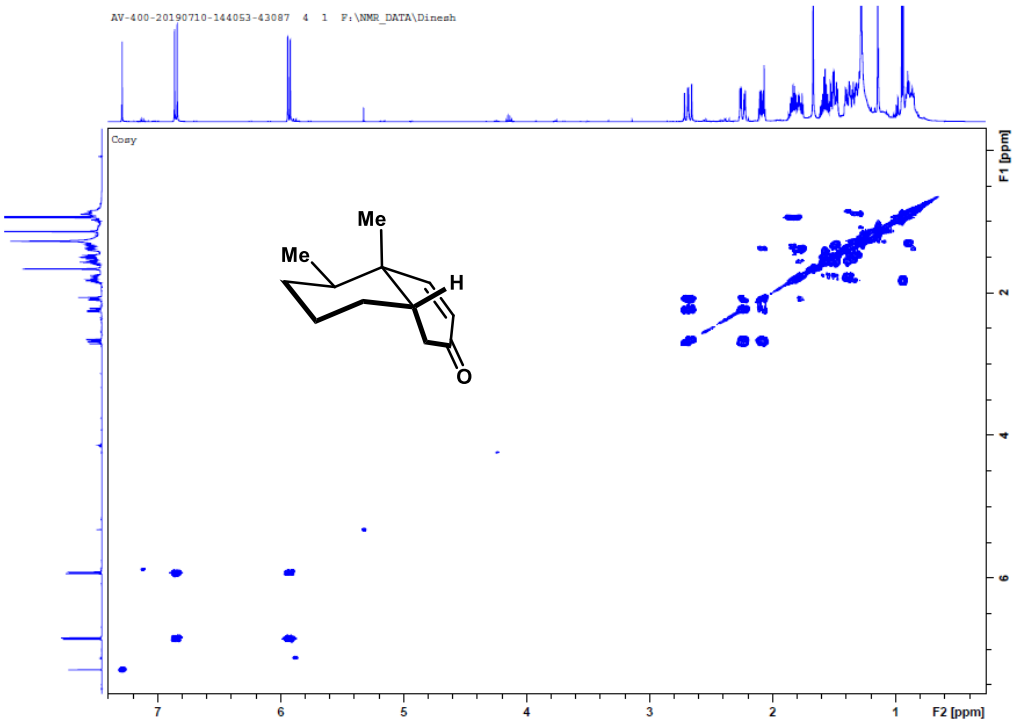
^{13}C NMR of Compound **77** in $CDCl_3$ at 100 MHz



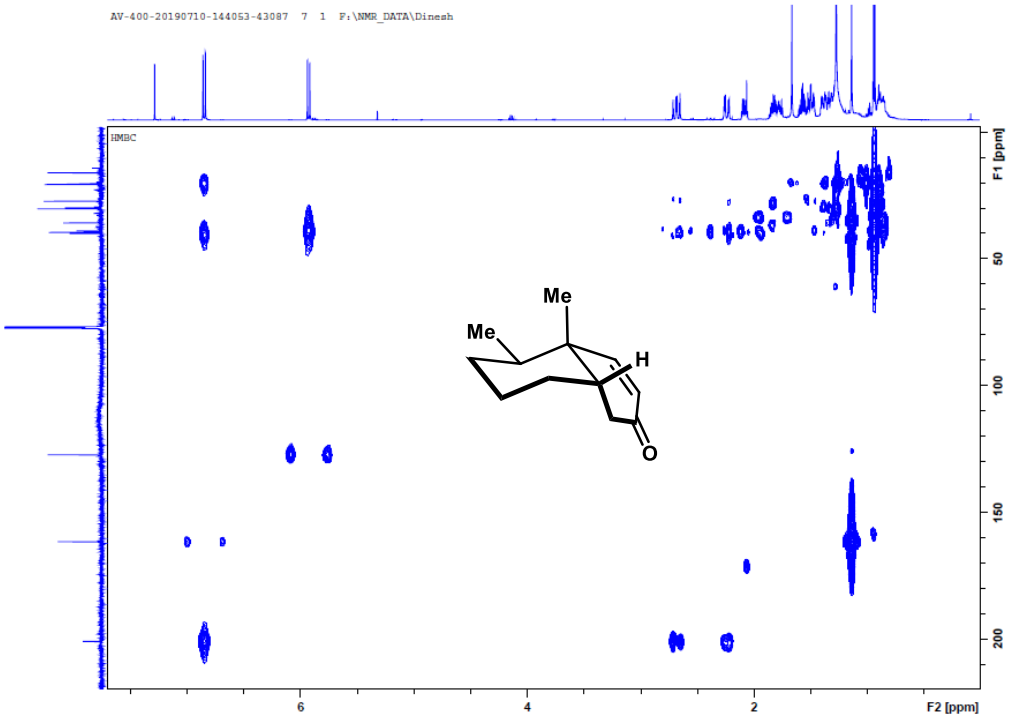
^{1}H NMR of Compound **76a** in $CDCl_3$ at 500 MHz



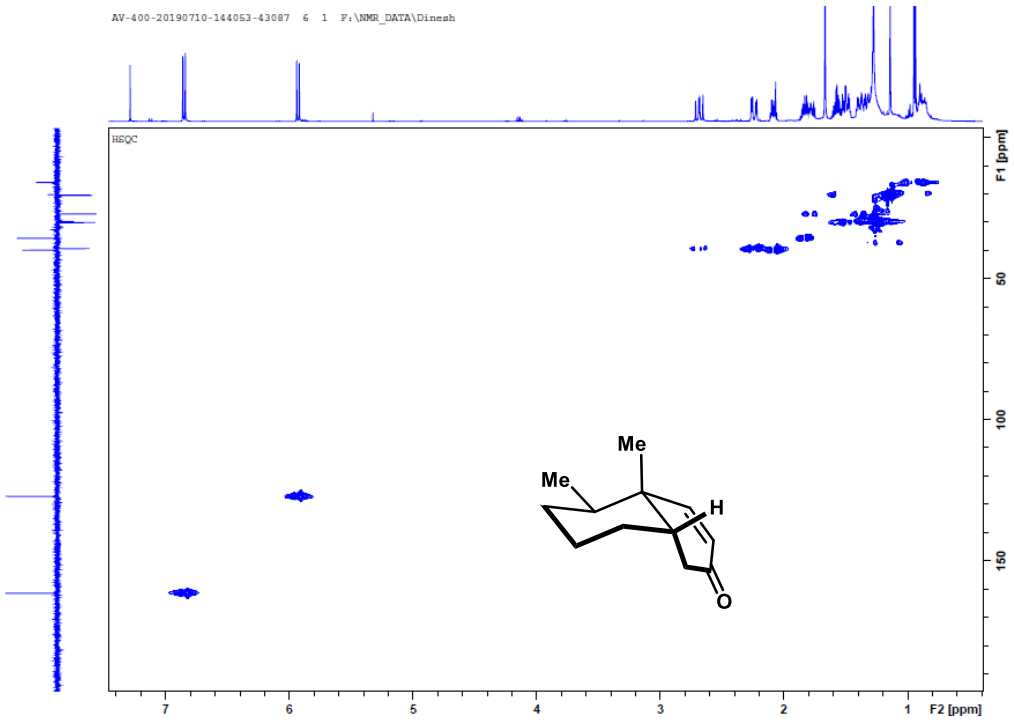
^{13}C NMR of Compound **76a** in $CDCl_3$ at 125 MHz



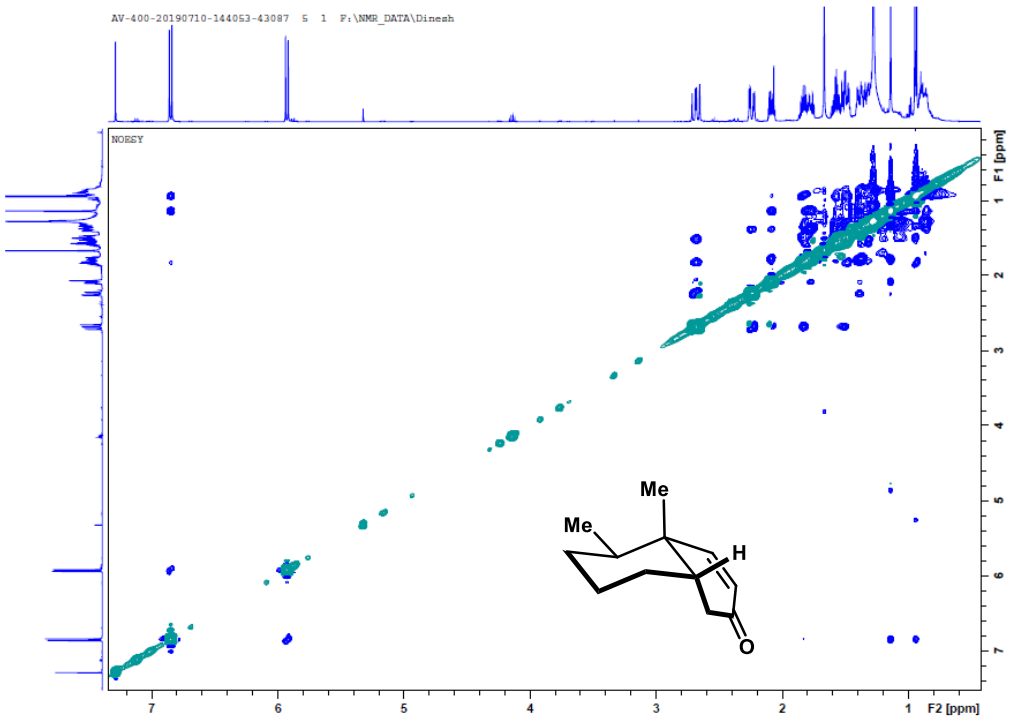
COSY spectra of Compound **76a** in $CDCl_3$ at 125 MHz



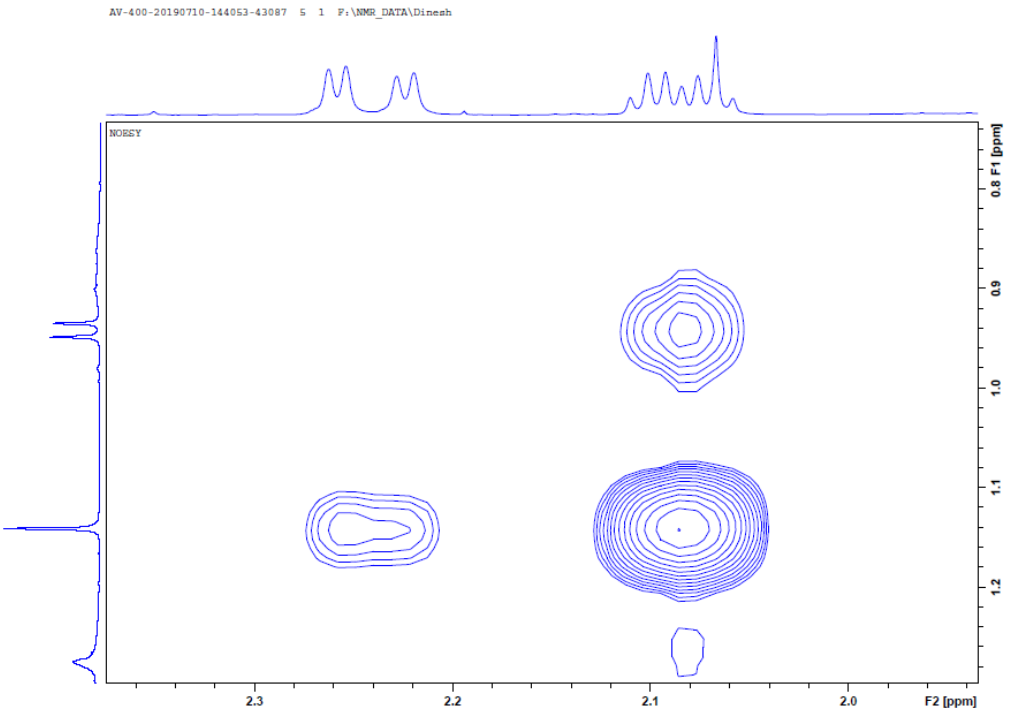
HMBC spectra of Compound **76a** in $CDCl_3$ at 125 MHz



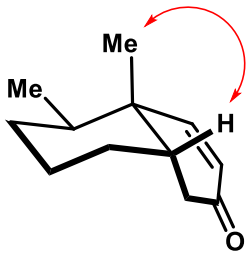
HSQC spectra of Compound **76a** in $CDCl_3$ at 125 MHz

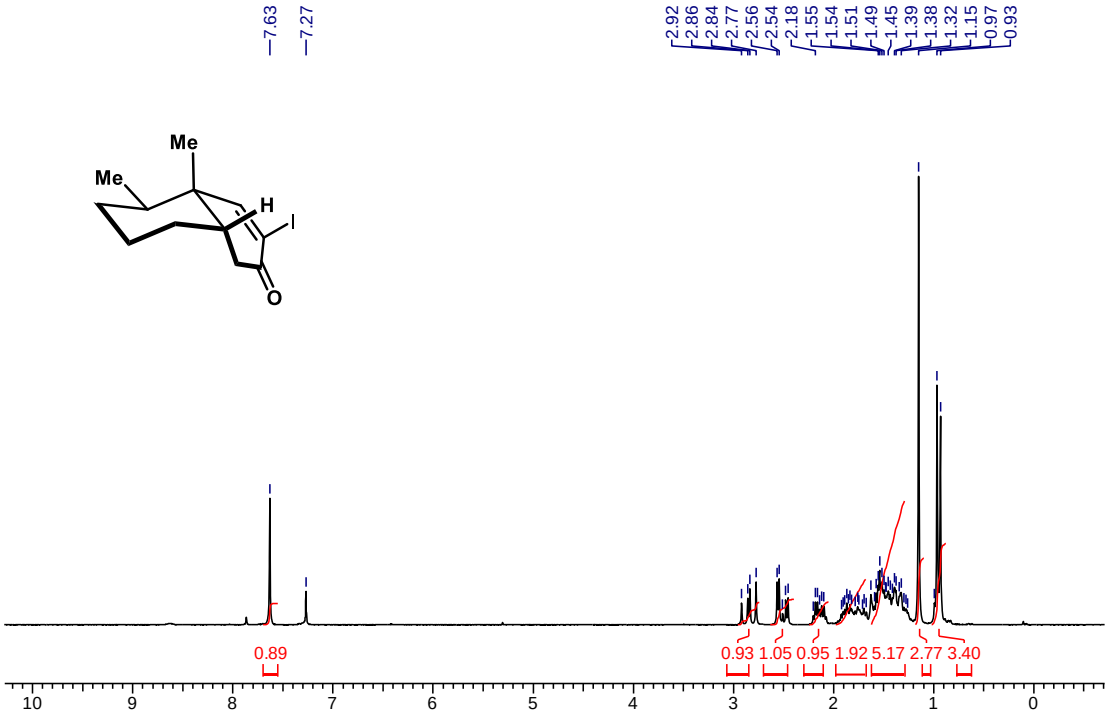


NOESY spectra of Compound **76a** in $CDCl_3$ at 125 MHz

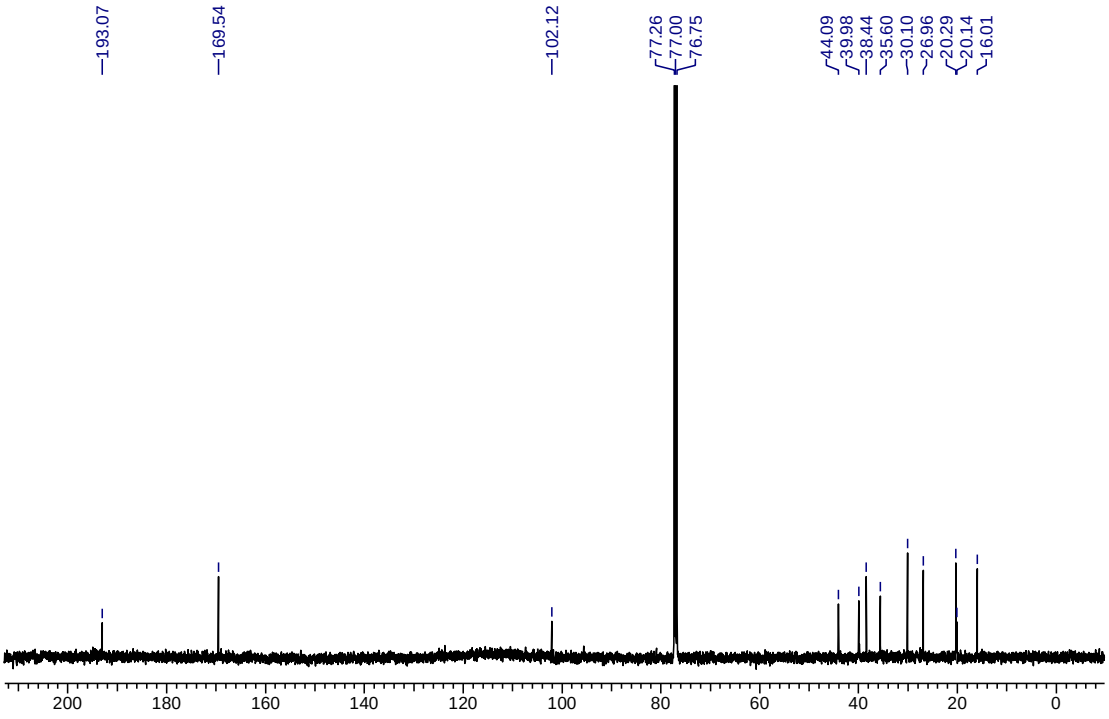


KEY NOE correlation in Compound **76a** in $CDCl_3$ at 125 MHz

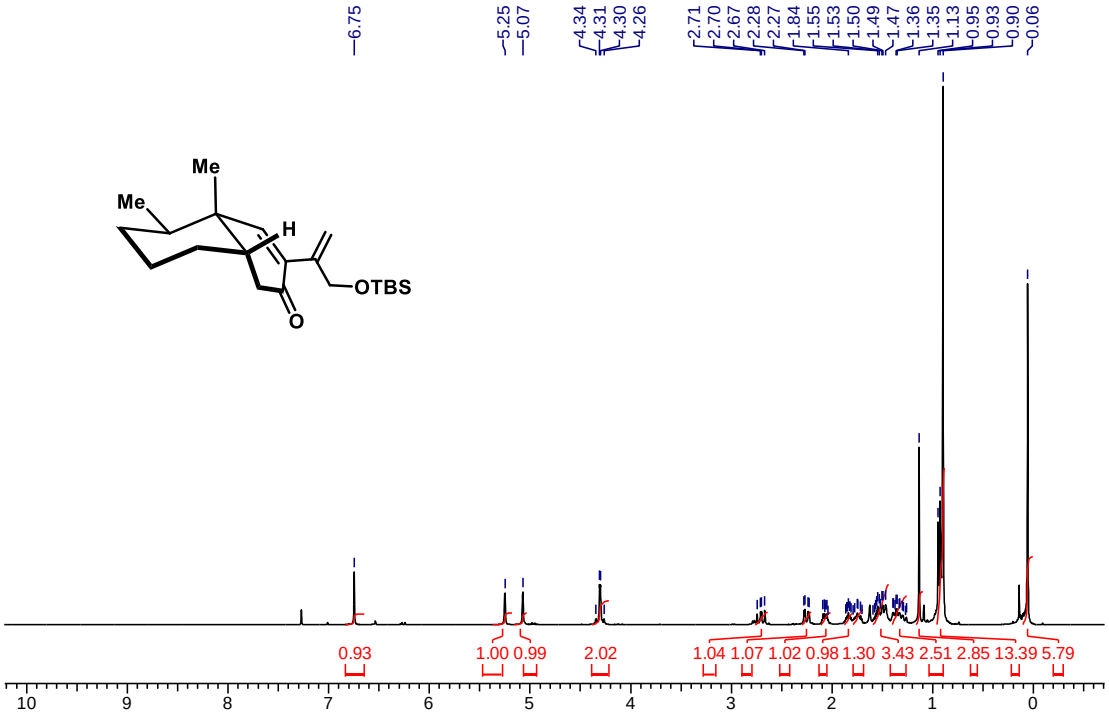




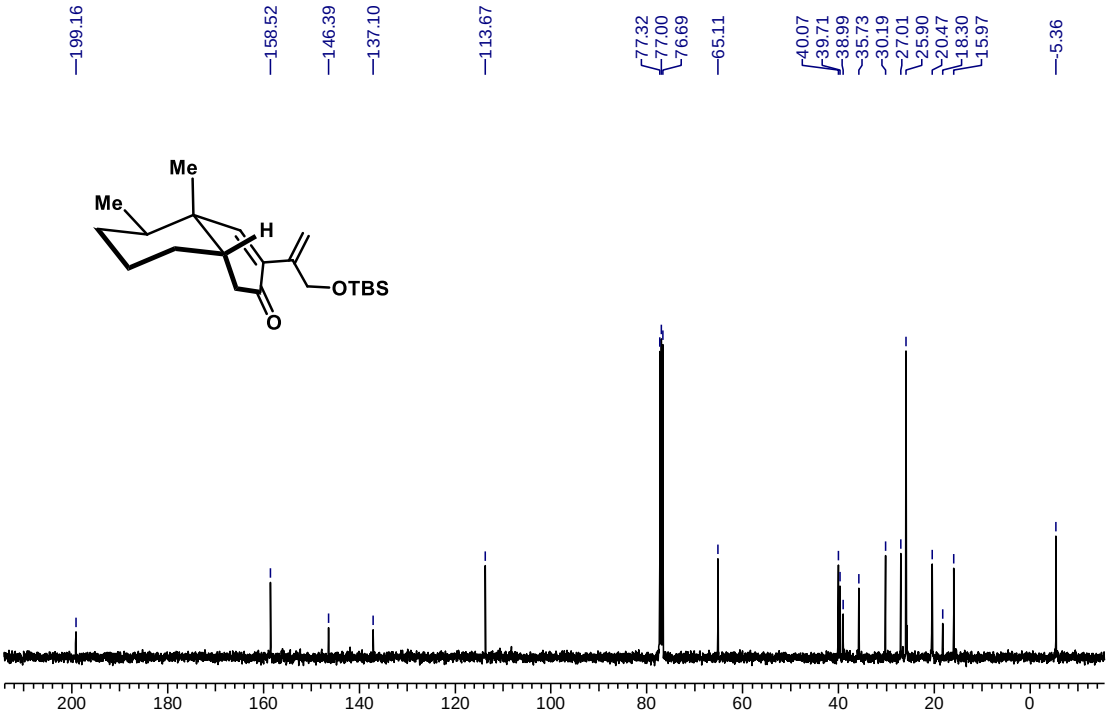
^{1}H NMR of Compound **61a**in $CDCl_3$ at 200 MHz



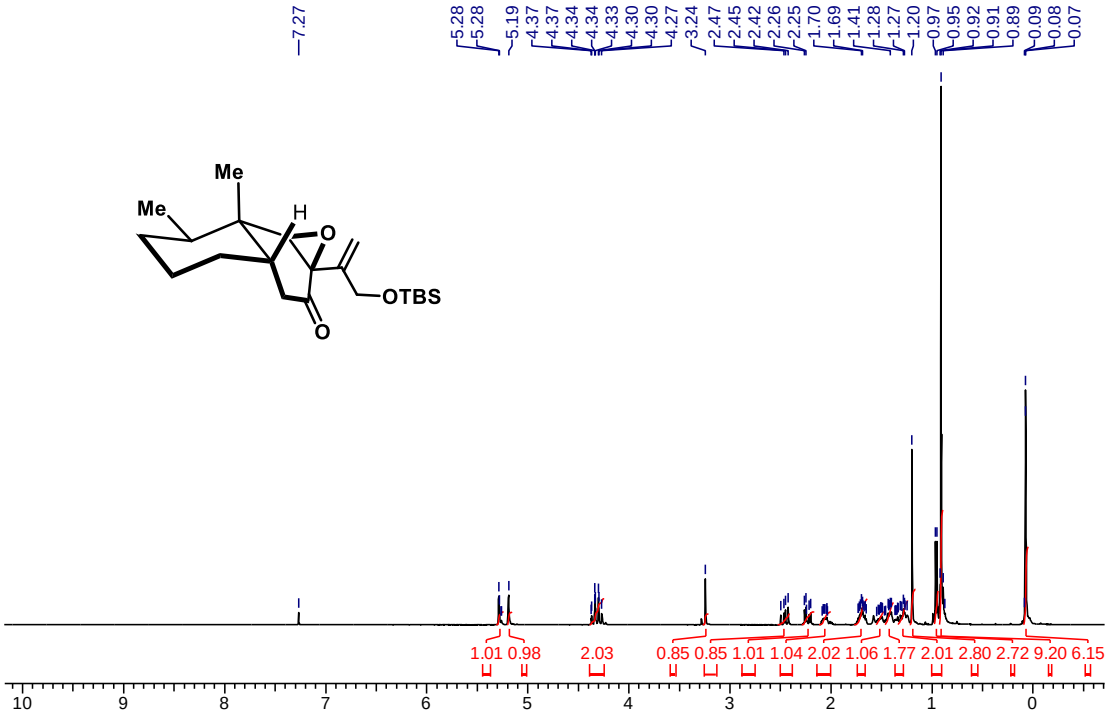
^{13}C NMR of Compound **61a** in $CDCl_3$ at 125 MHz



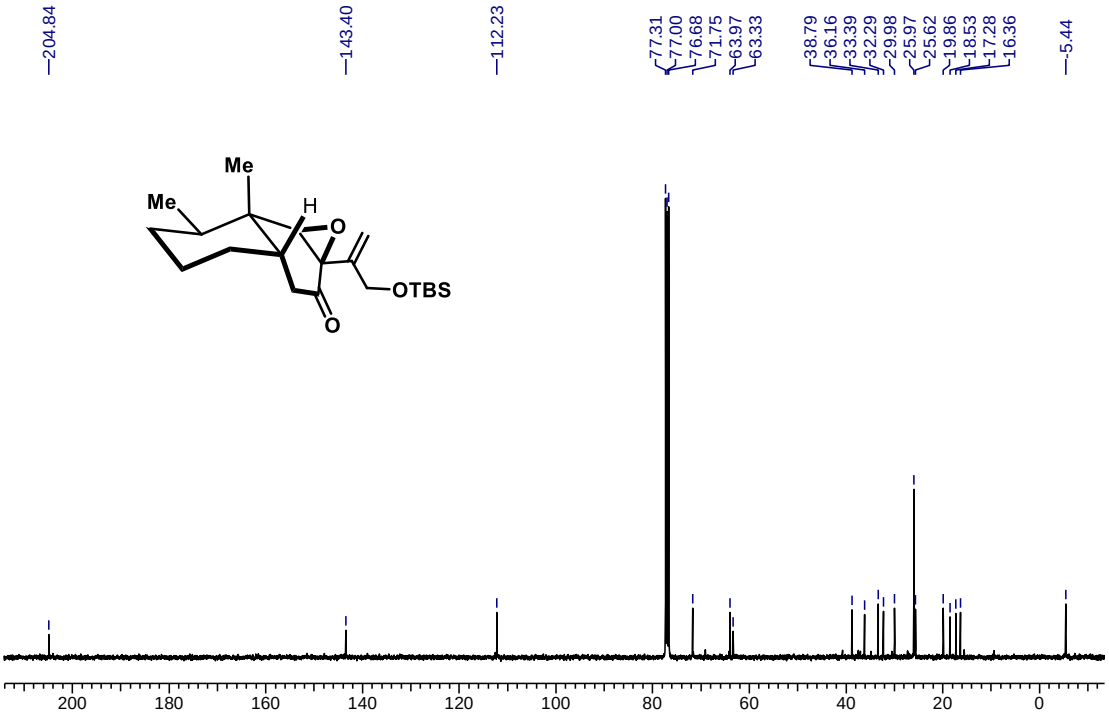
^{1}H NMR of Compound **87** in $CDCl_3$ at 400 MHz



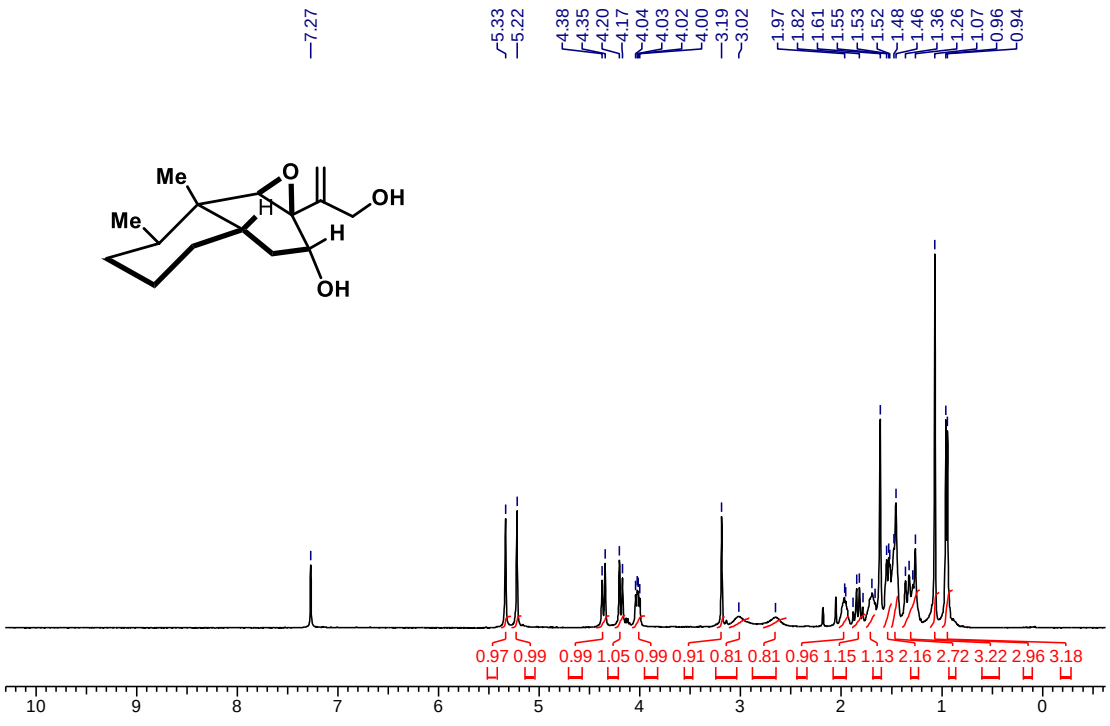
^{13}C NMR of Compound **87**in $CDCl_3$ at 100 MHz



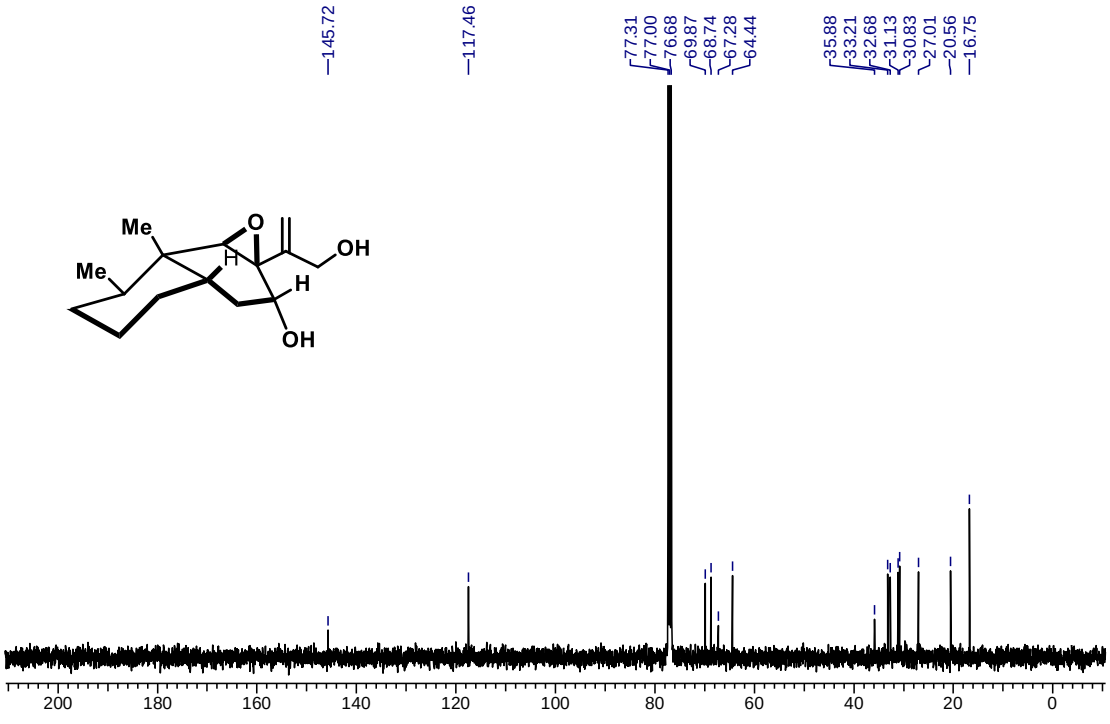
^{1}H NMR of Compound **88** in $CDCl_3$ at 400 MHz



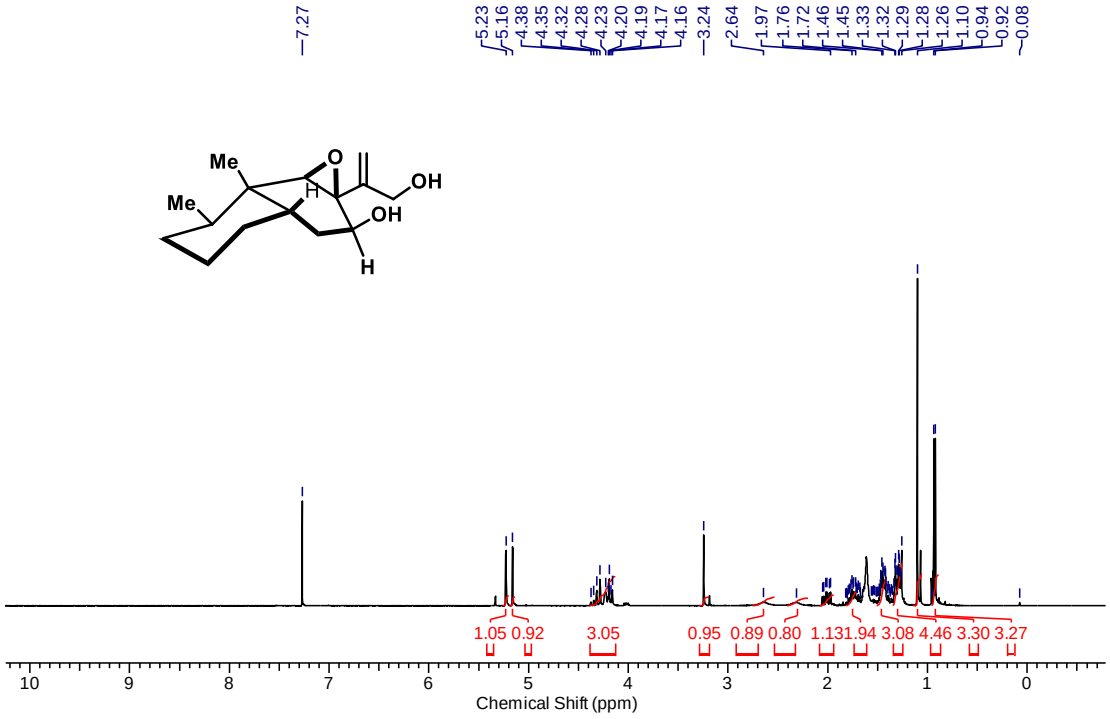
^{13}C NMR of Compound **22** in $CDCl_3$ at 100 MHz



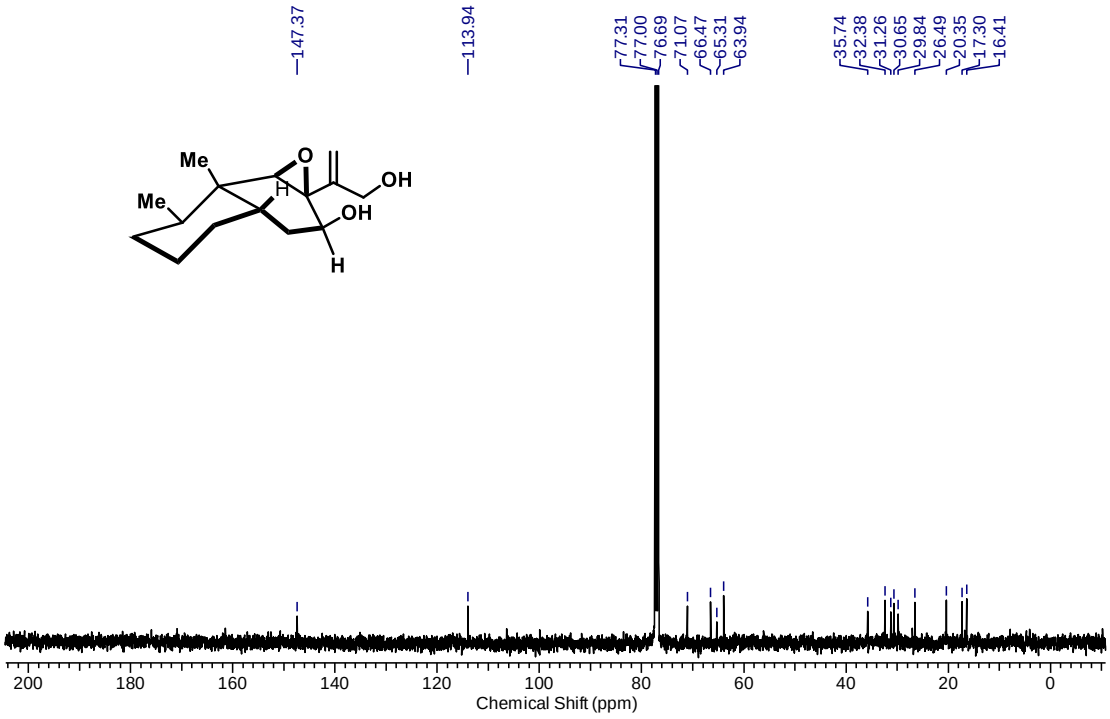
^{1}H NMR of Peribysin A, **23** in $CDCl_3$ at 400 MHz



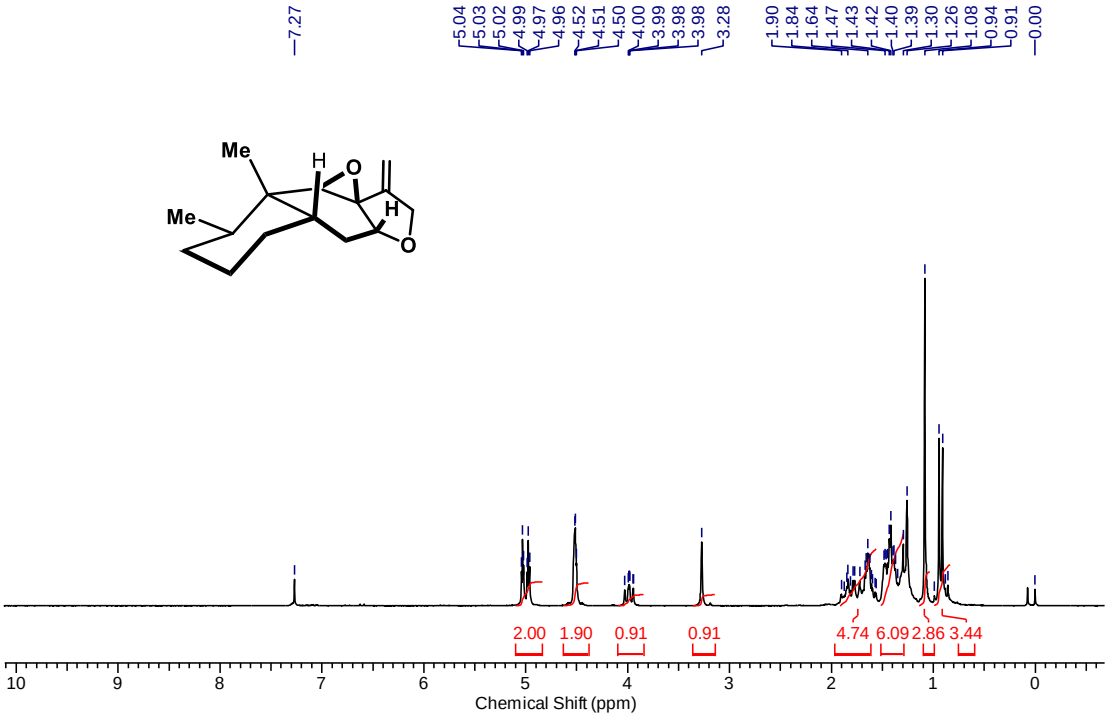
^{13}C NMR of Peribysin A, **23** in $CDCl_3$ at 100 MHz



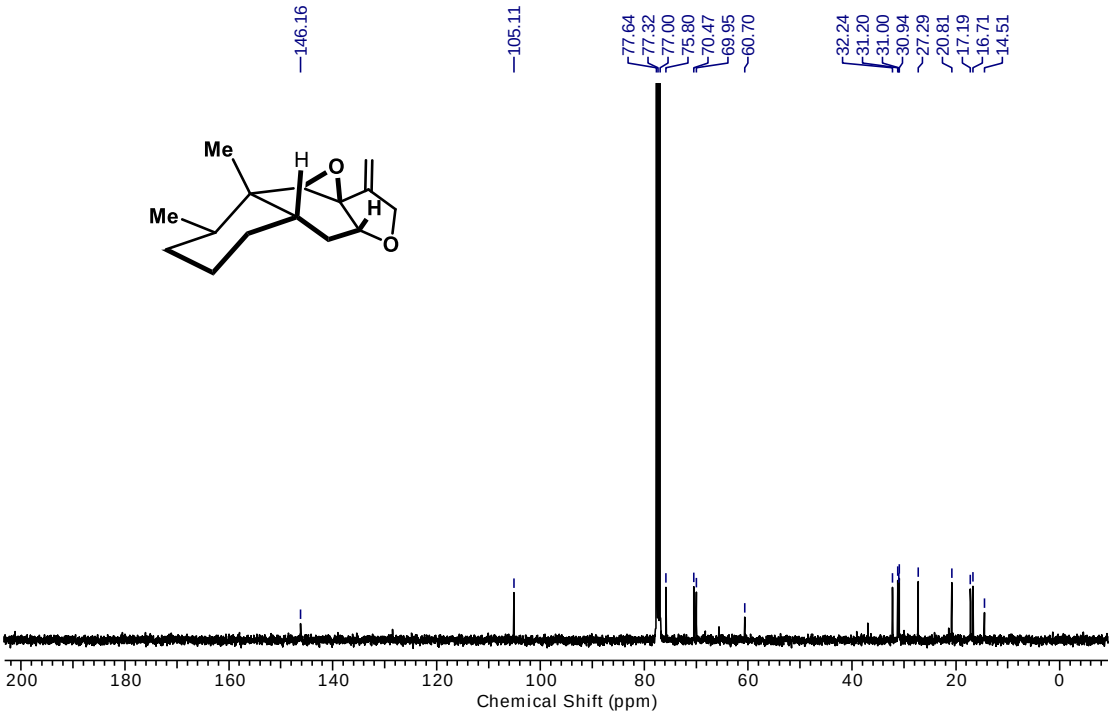
^{1}H NMR of Compound **91** in $CDCl_3$ at 400 MHz



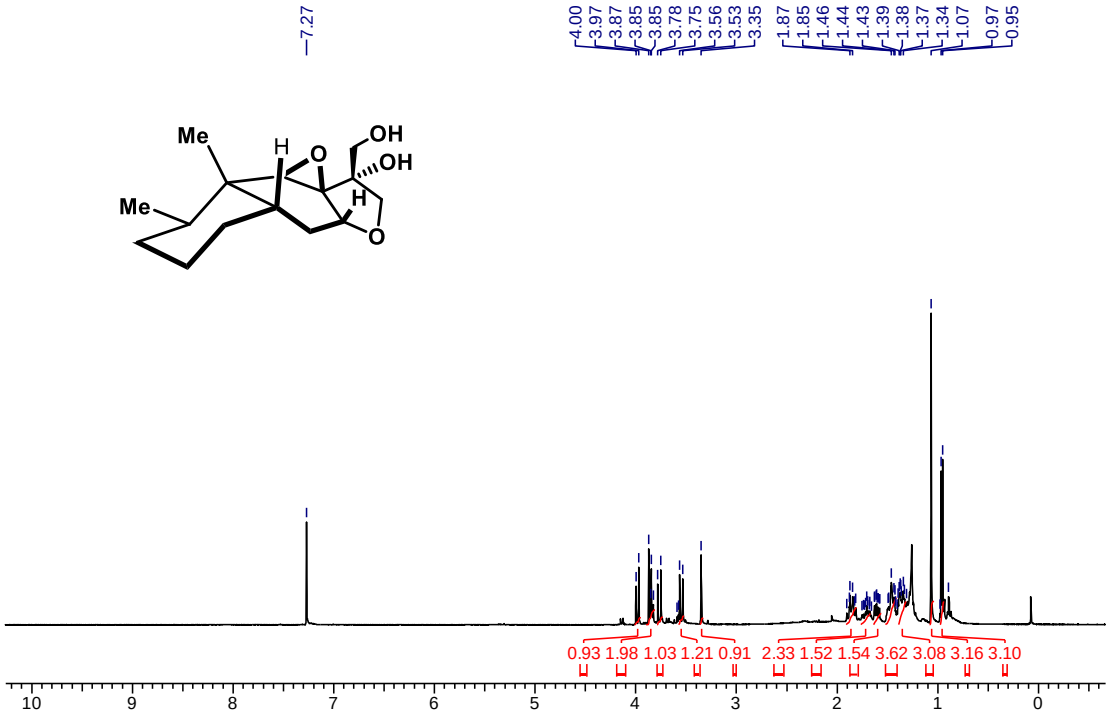
^{13}C NMR of Compound **91** in $CDCl_3$ at 100 MHz



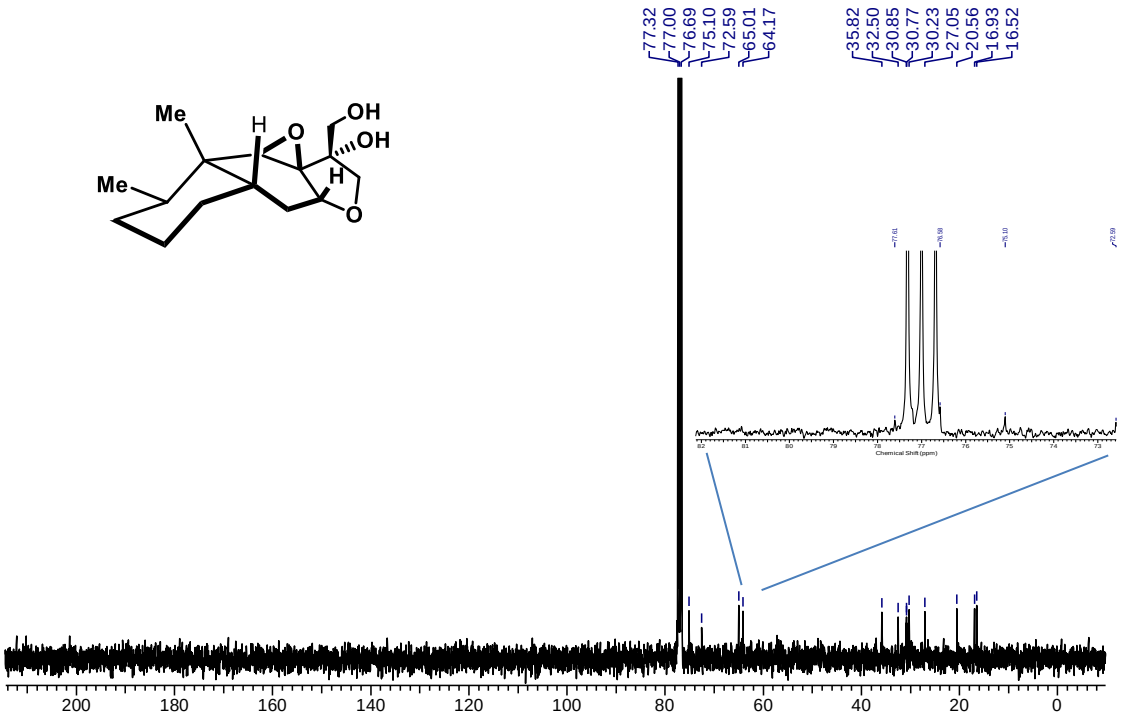
^{1}H NMR of Compound **92** in $CDCl_3$ at 200 MHz



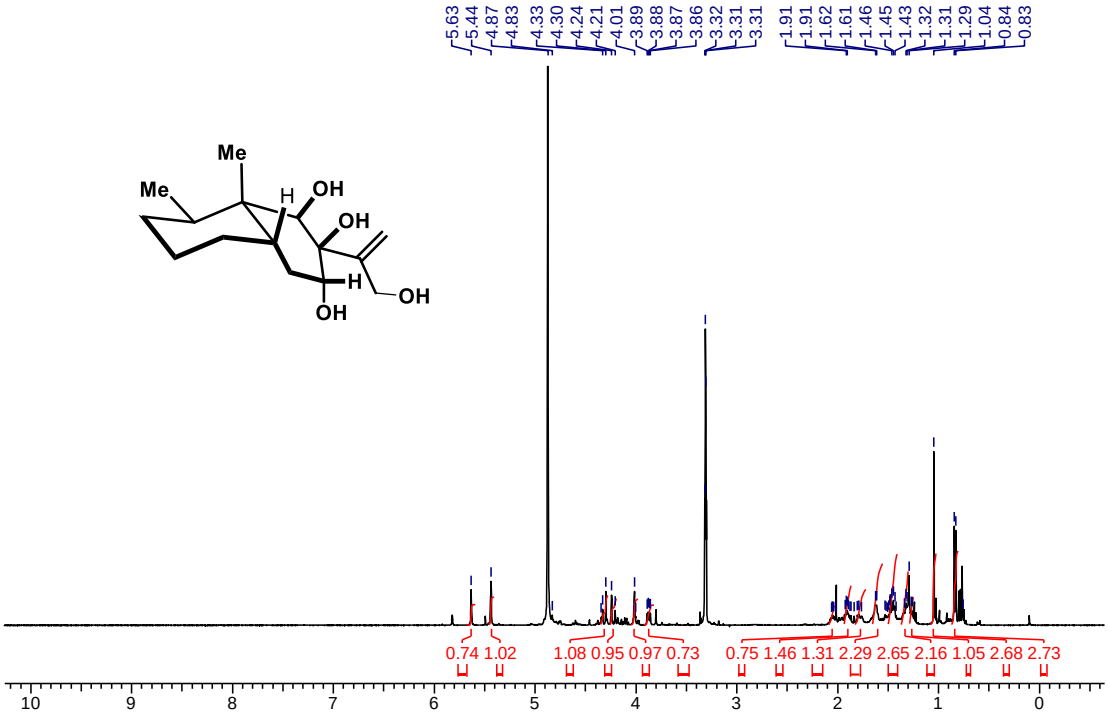
^{13}C NMR of Compound **92** in $CDCl_3$ at 100 MHz



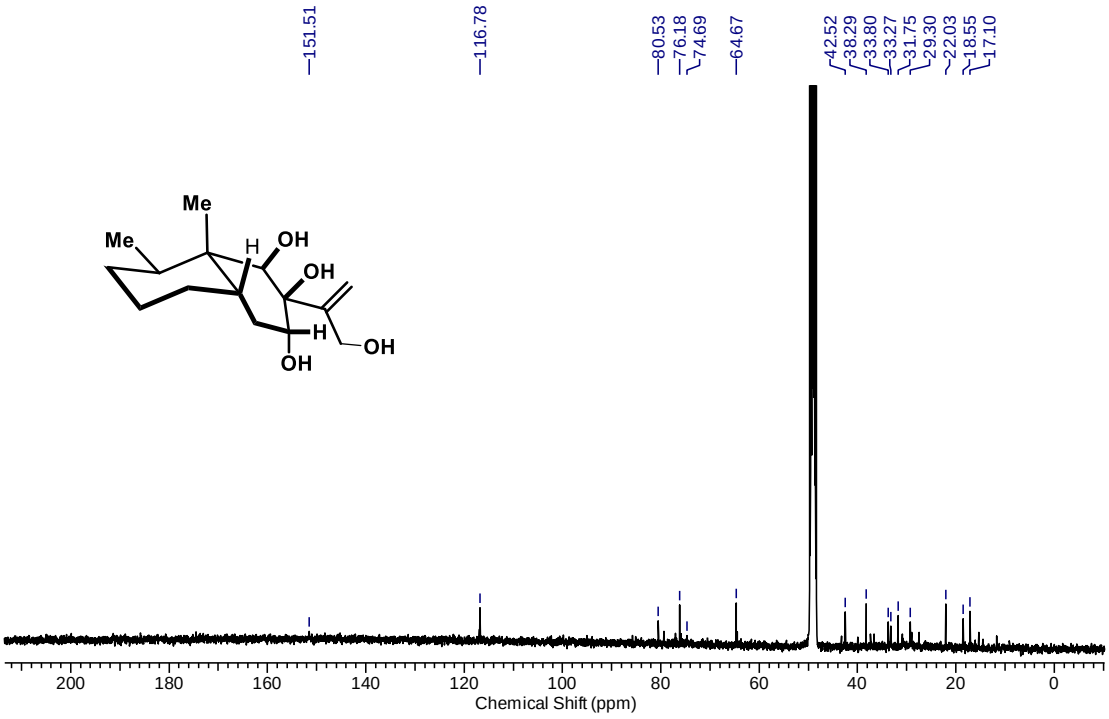
^{1}H NMR of Peribysin B, **24** in $CDCl_3$ at 400 MHz



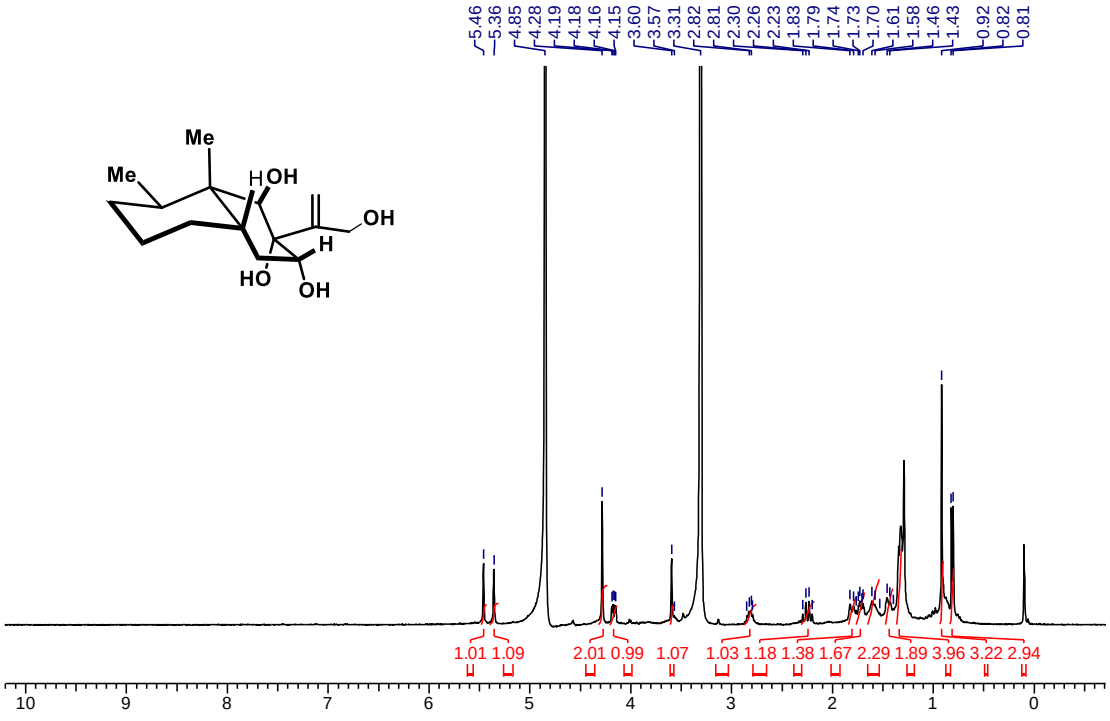
^{13}C NMR of Peribysin B, **24** in $CDCl_3$ at 100 MHz



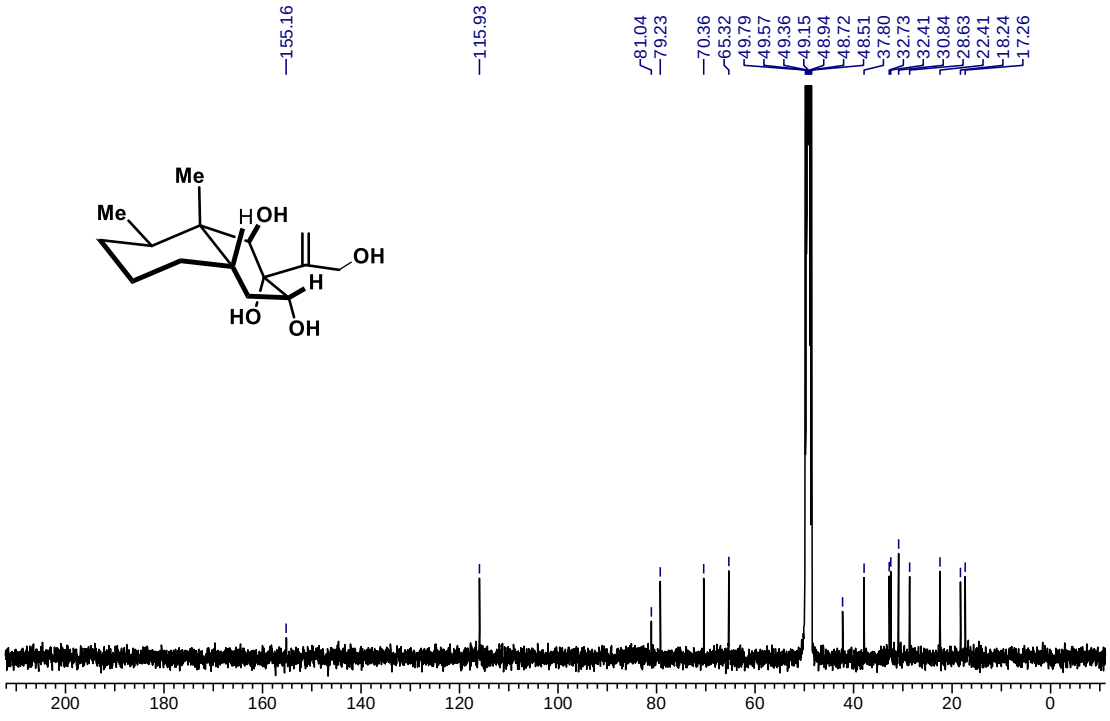
^{1}H NMR of Peribysin F, **27** in CD_3OD at 400 MHz



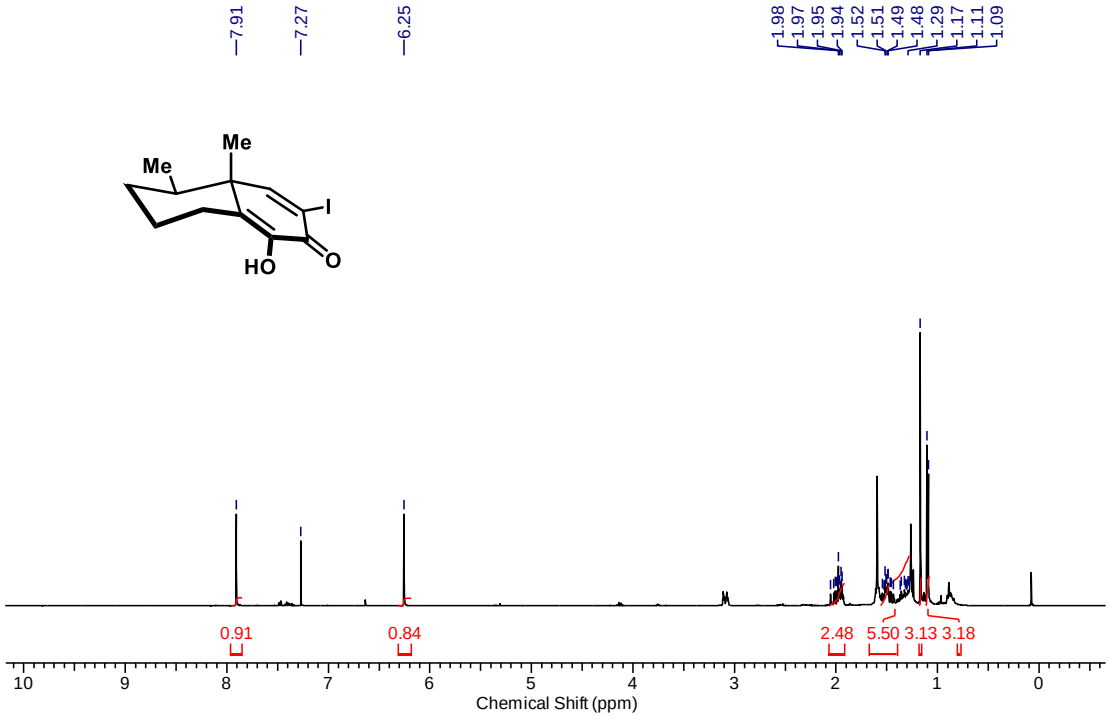
^{13}C NMR of Peribysin F, **27** in CD_3OD at 100 MHz



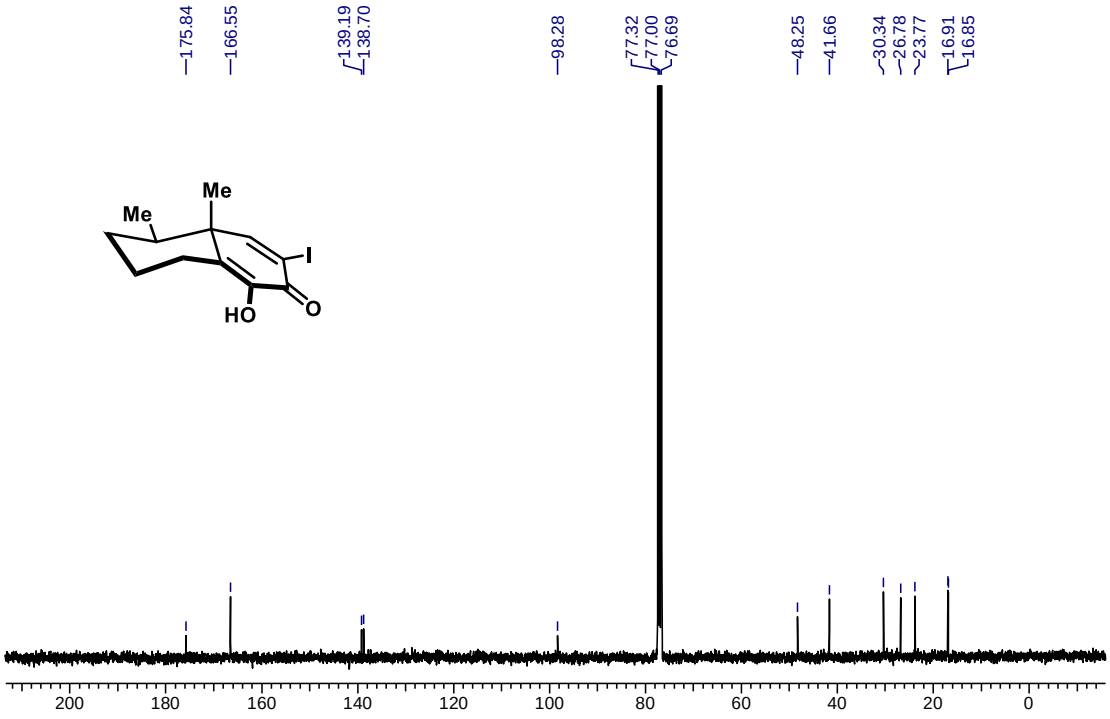
^{1}H NMR of Peribysin G, **28** in CD_3OD at 400 MHz



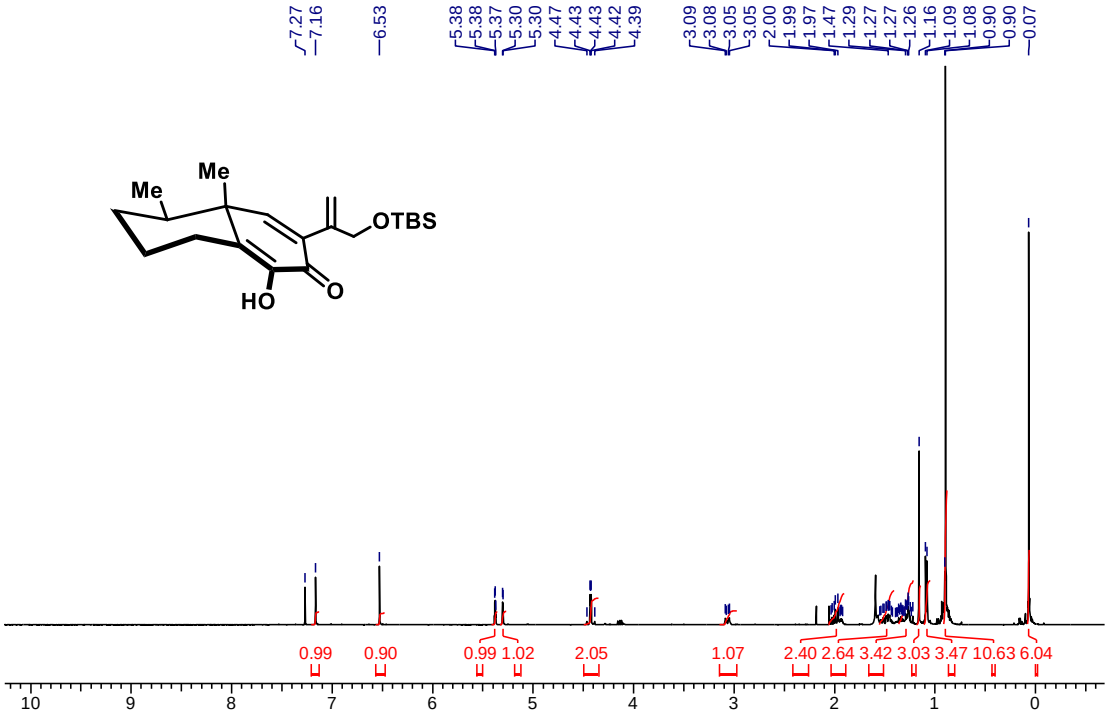
^{13}C NMR of Peribysin G, **28** in CD_3OD at 100 MHz



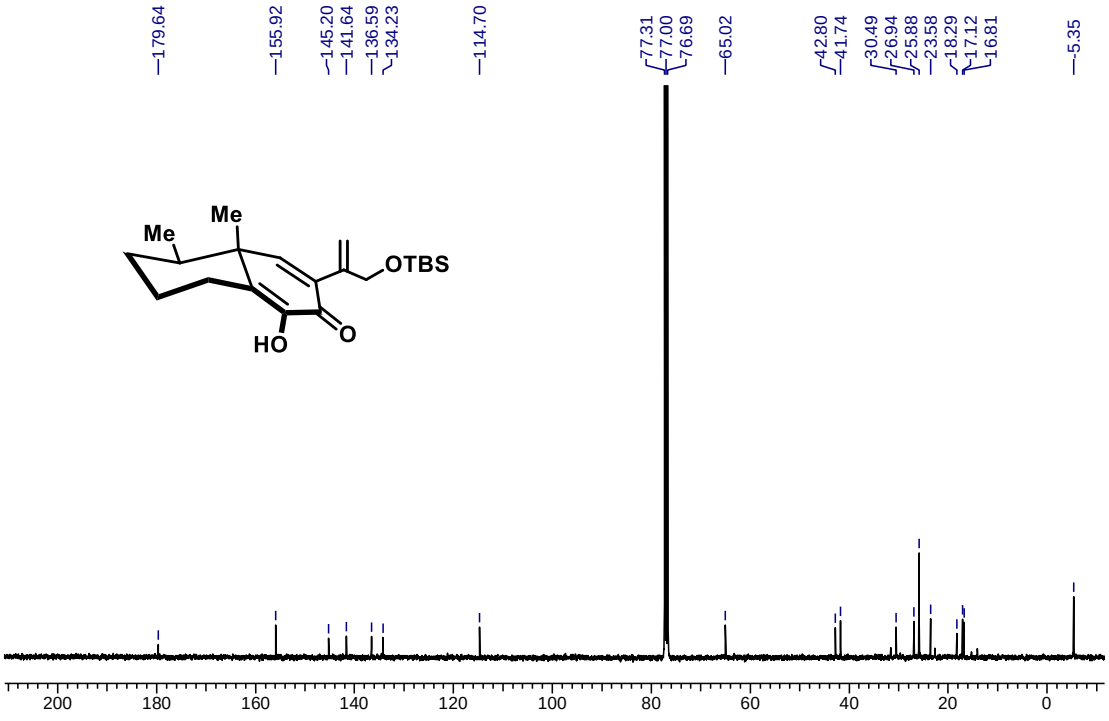
^{1}H NMR of Compound **101** in $CDCl_3$ at 400 MHz



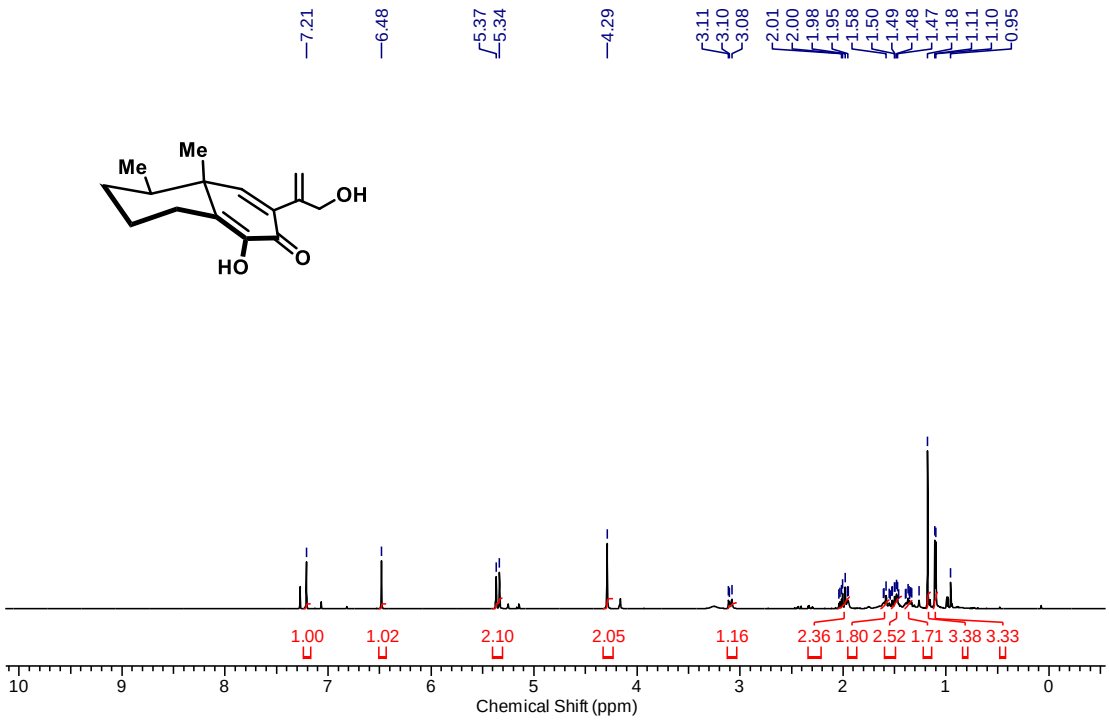
^{13}C NMR of Compound **101** in $CDCl_3$ at 100 MHz



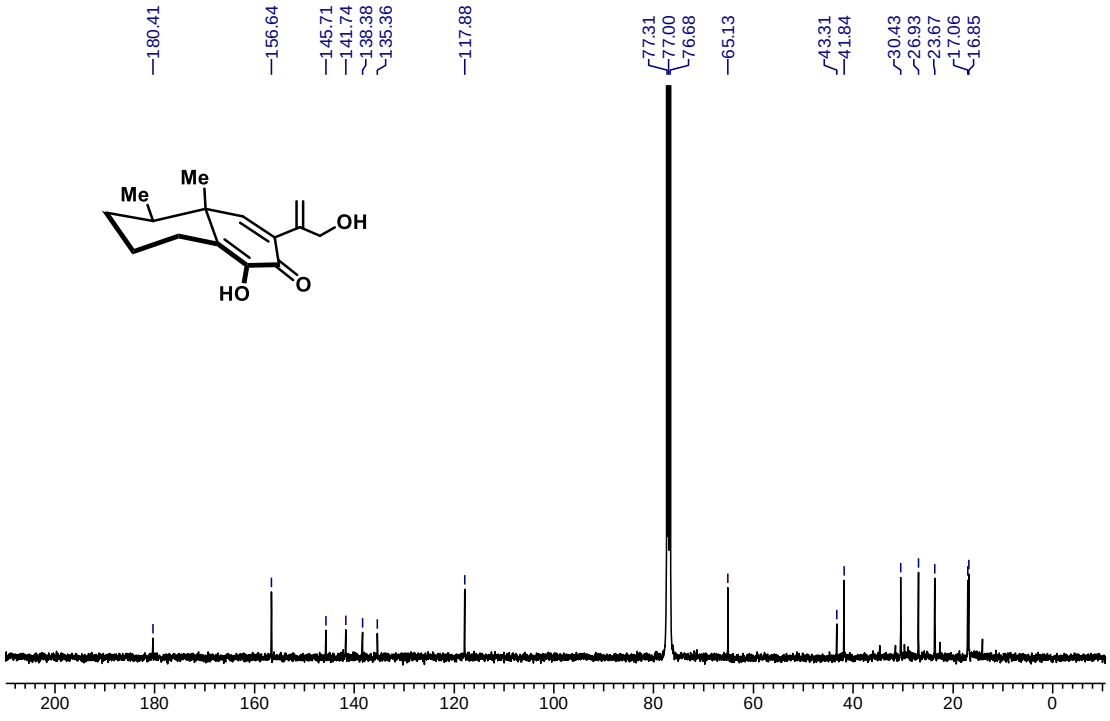
^{1}H NMR of Compound **102** in $CDCl_3$ at 400 MHz



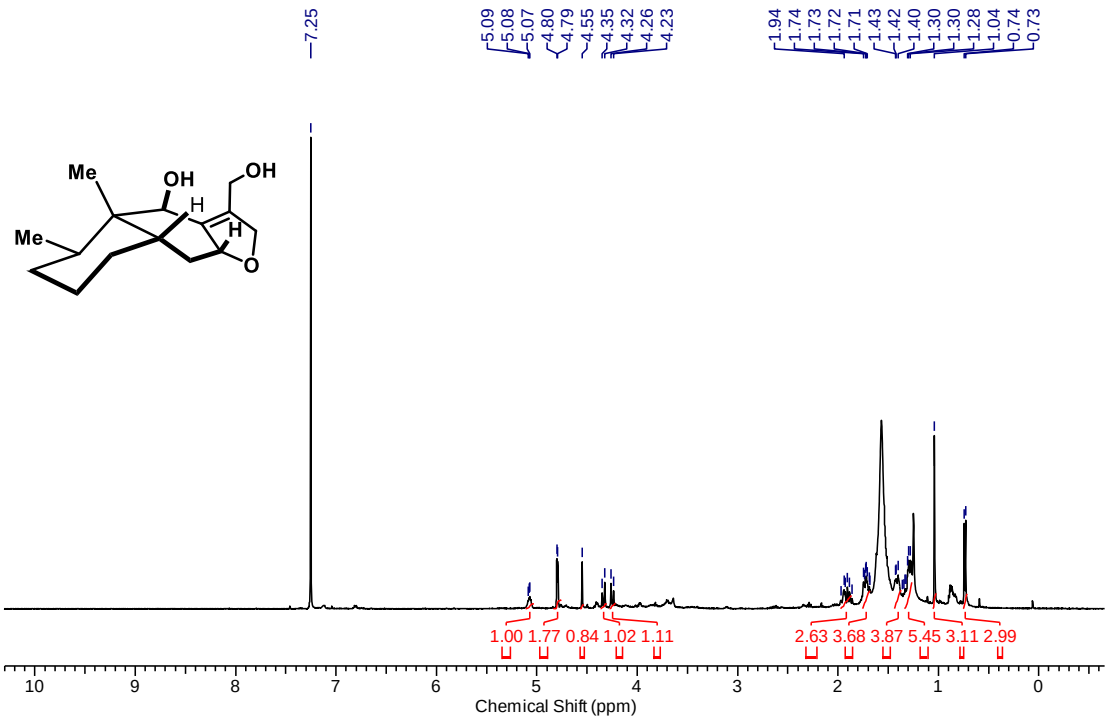
^{13}C NMR of Compound **102** in $CDCl_3$ at 100 MHz



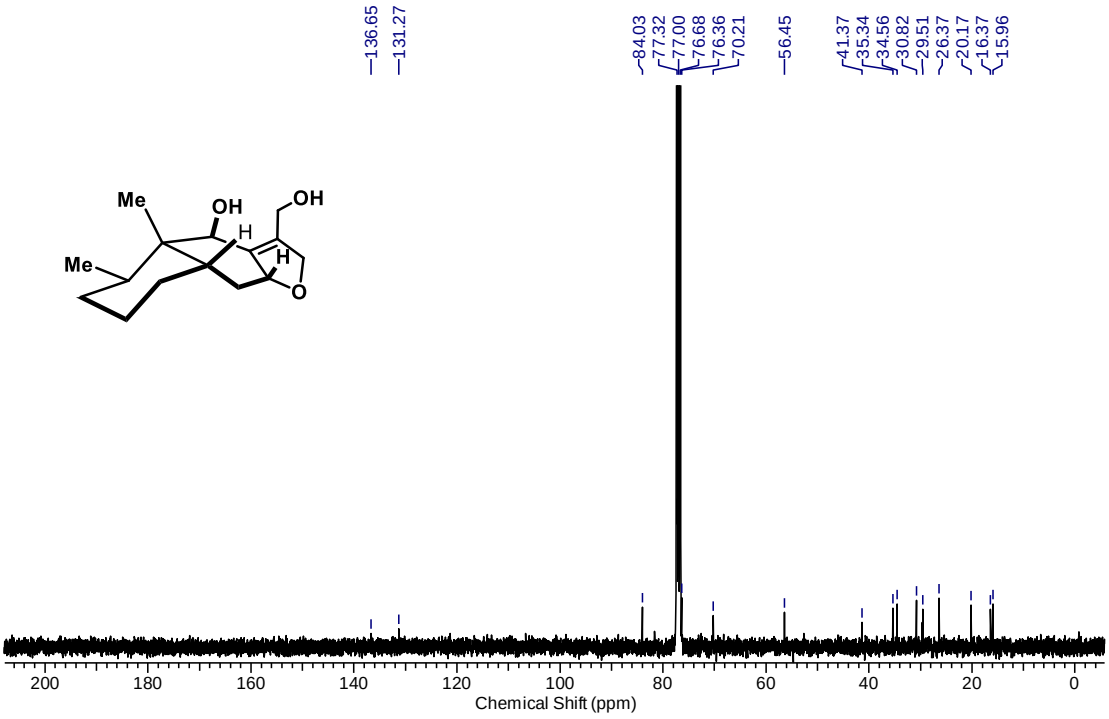
^{1}H NMR of Peribysin Q, **60** in $CDCl_3$ at 500 MHz



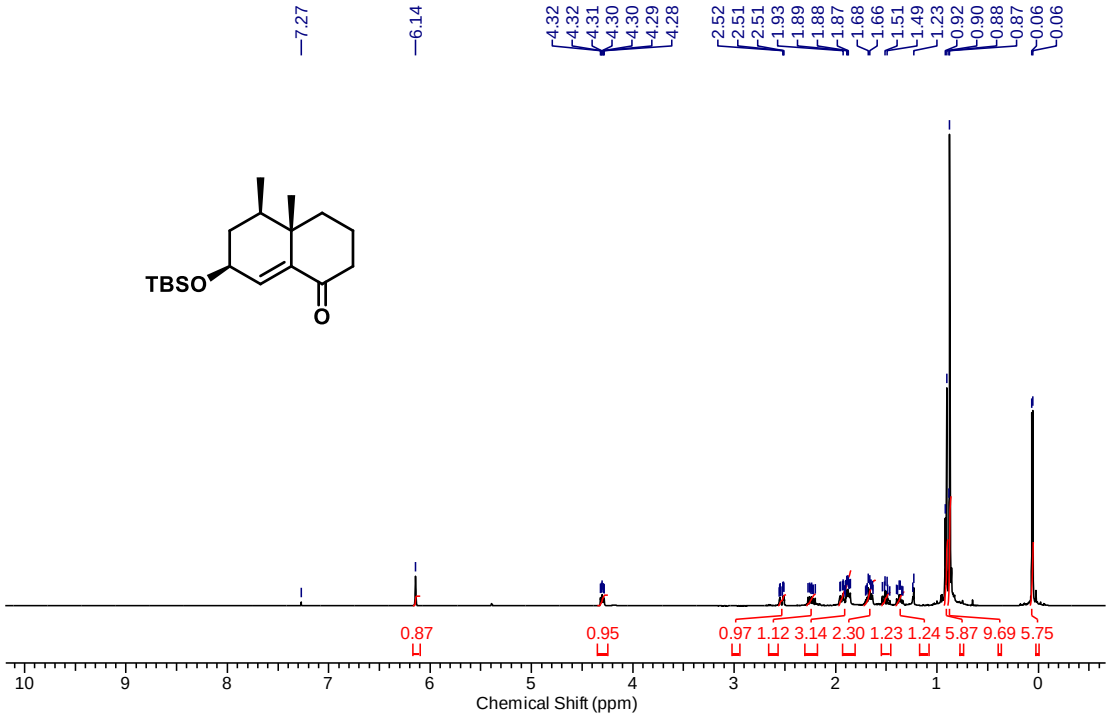
^{13}C NMR of Peribysin Q,**60** in $CDCl_3$ at 100 MHz



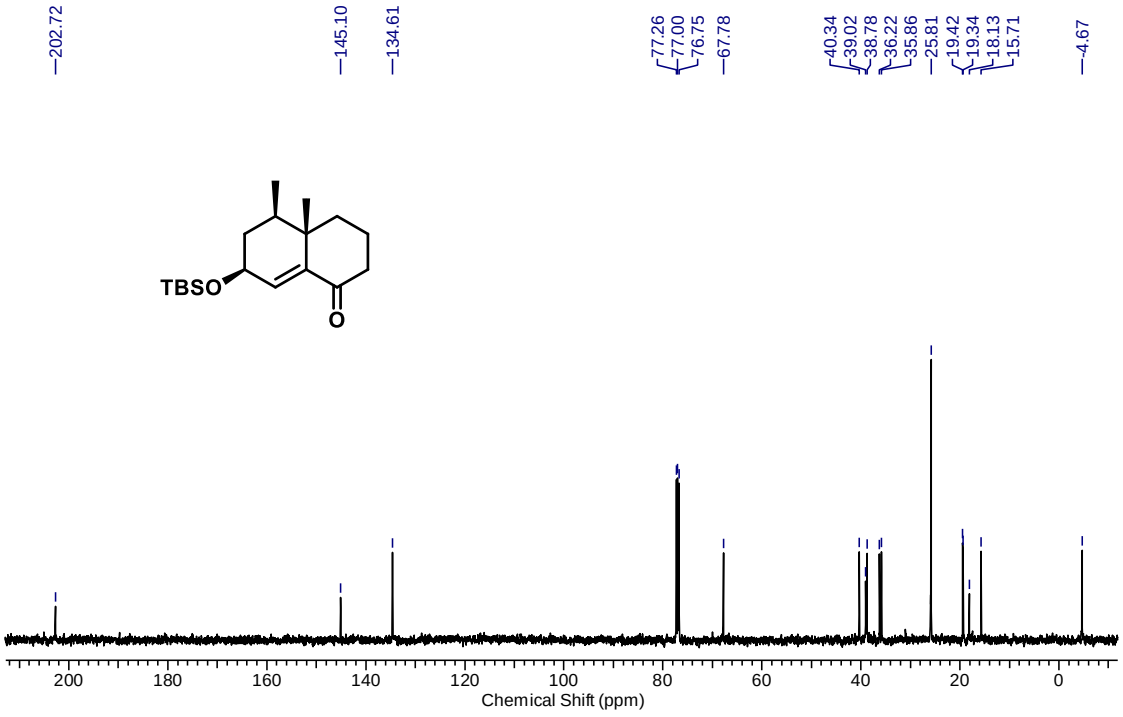
^{1}H NMR of Peribysin C, **25** in $CDCl_3$ at 500 MHz



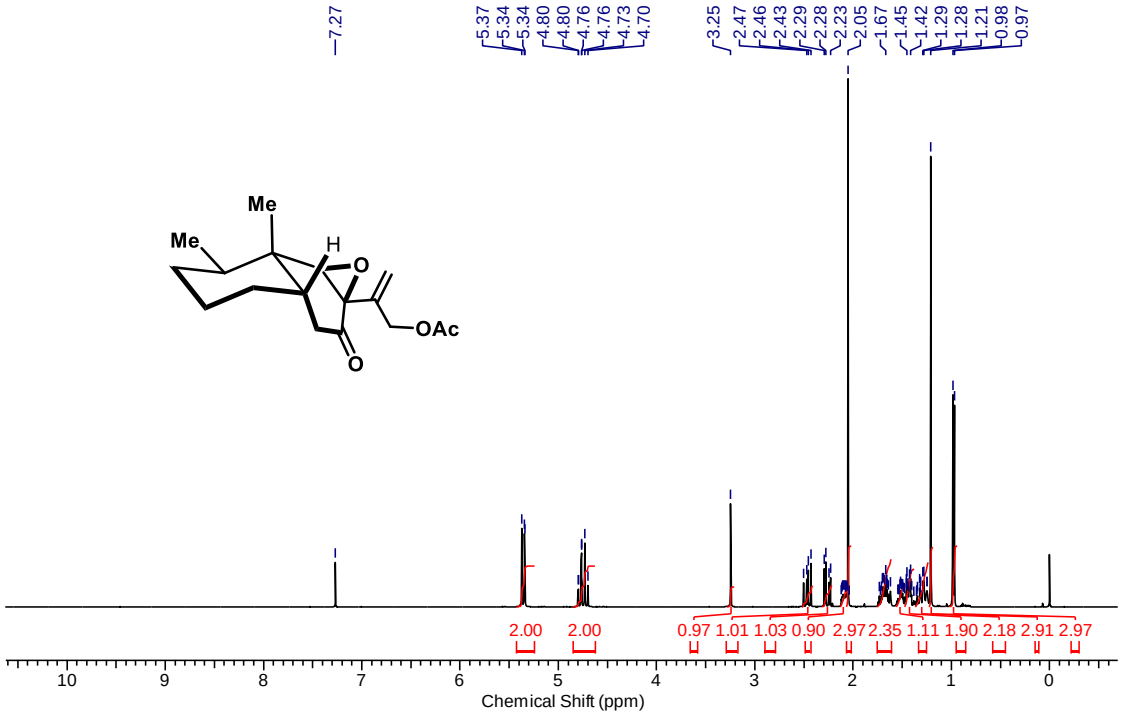
^{13}C NMR of Peribysin C, **25** in $CDCl_3$ at 100 MHz



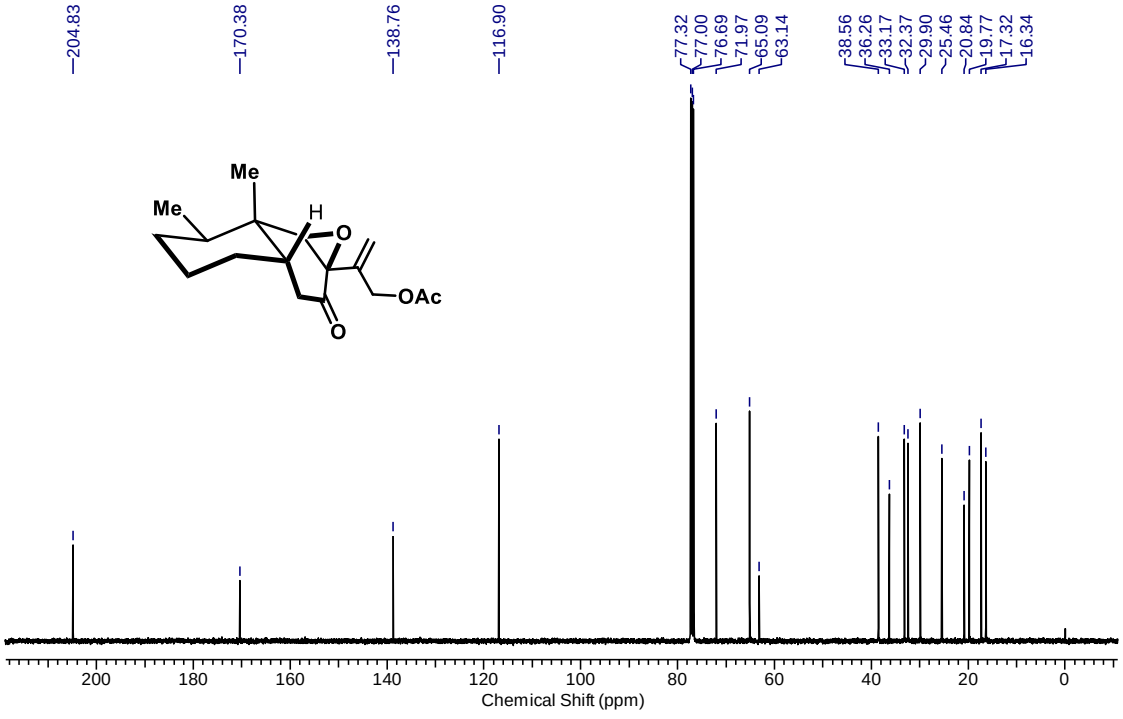
^{1}H NMR of Compound **72** in $CDCl_3$ at 500 MHz



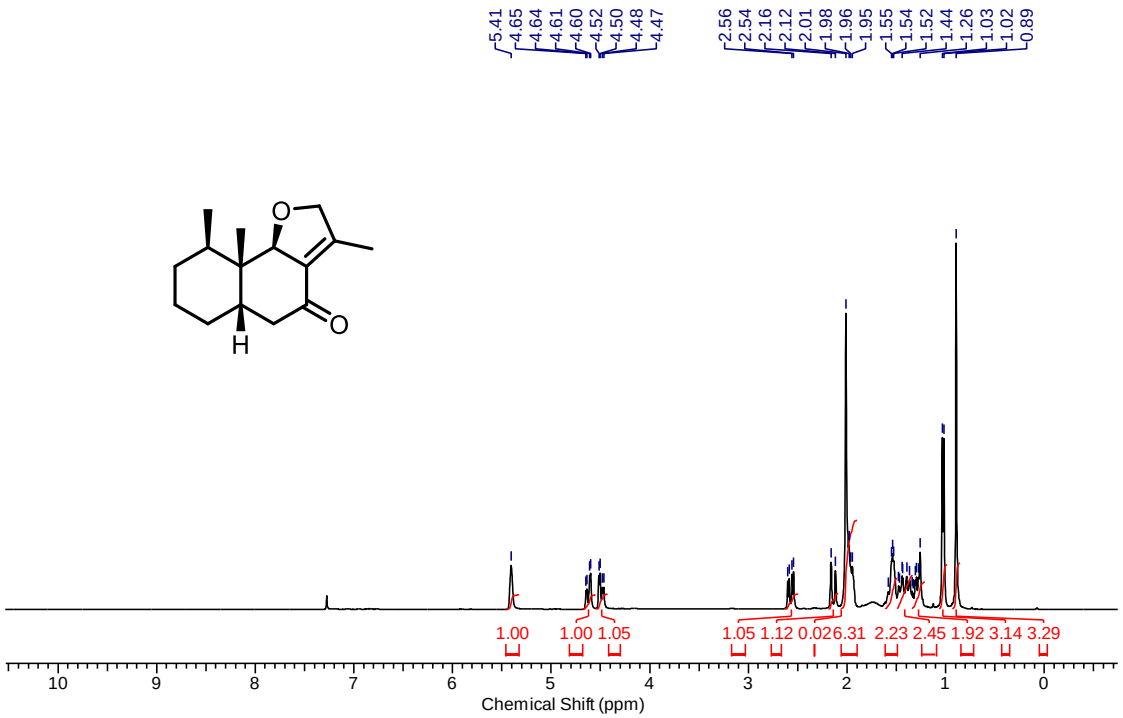
^{13}C NMR of Compound **72** in $CDCl_3$ at 125 MHz



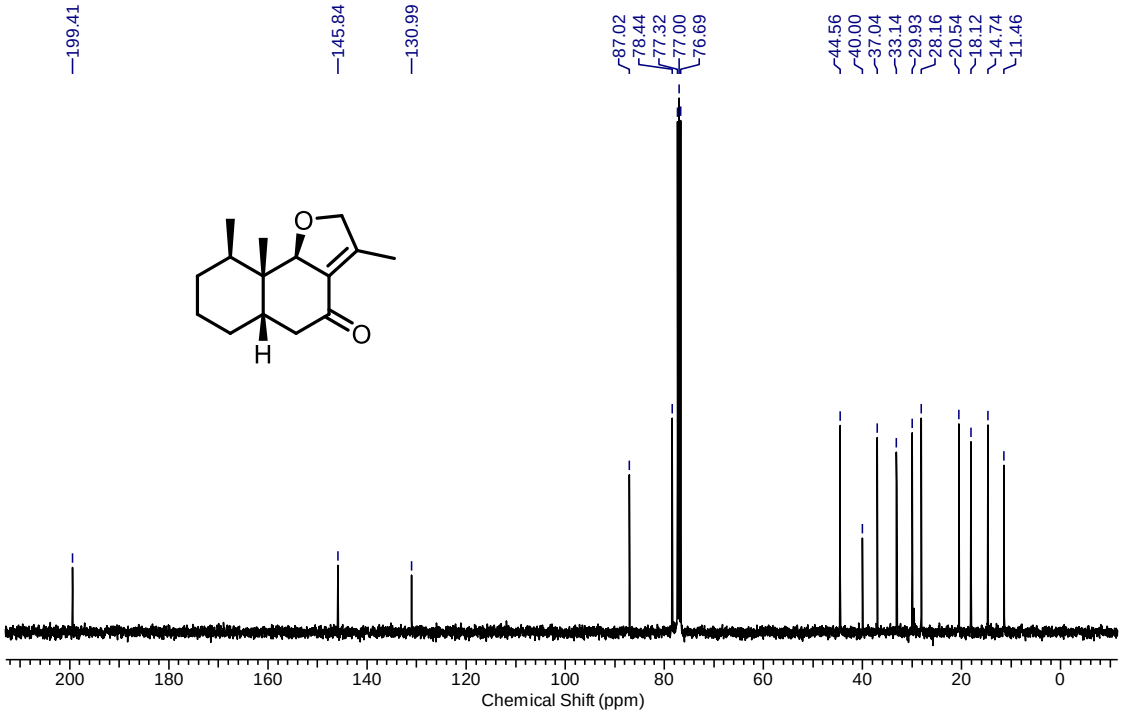
^{1}H NMR of Compound **95** in $CDCl_3$ at 400 MHz



^{13}C NMR of Compound **95** in $CDCl_3$ at 100 MHz



^{1}H NMR of Compound **97** in $CDCl_3$ at 500 MHz



^{13}C NMR of Compound **97** in $CDCl_3$ at 100 MHz

Chapter 2-Section 1

2.1.1. Introduction

Enones are one of the most useful functional groups encountered in natural product/API synthesis. The main reason for the choice is their multi-directional reactivity which makes them attractive and easy to manipulate and convert to the desired products.[1] All the three carbon atoms which are part of the enone moiety are reactive and can be functionalized with various types of reactions.[2] The carbonyl carbon of the enone can undergo addition reactions with various organometallic reagents and comparitively soft nucleophiles can react with the β-carbon of the enone moiety to give the 1,4-addition product. Various types of hydride reagents shows different reactivities with enone moiety to give either 1,2 or 1,4 reduction products depending on the reaction condition and the type of hydride reagent used.[3] Similarly the α-carbon of the enone moiety can be halogenated using SO_2Cl_2 or the Johnson iodination condition to give the halogen handles which can be useful for the cross-coupling reactions.[4]

The double bond of the enone system can also be reduced using hydrogenation conditions or it can undergo a [2+2] type of photochemical reaction using suitable conditions.[5] Though some reagents such as $NaBH_4$, $LiAlH_4$ can react at multiple centers at a time, tweaking the reaction parameters and use of combination of reagents can give the desired selectivity.[6] Some selected general reactions carried out with the enone moiety such as addition, reduction, alkylation, halogenation etc. are captured below in figure 2.1.1.

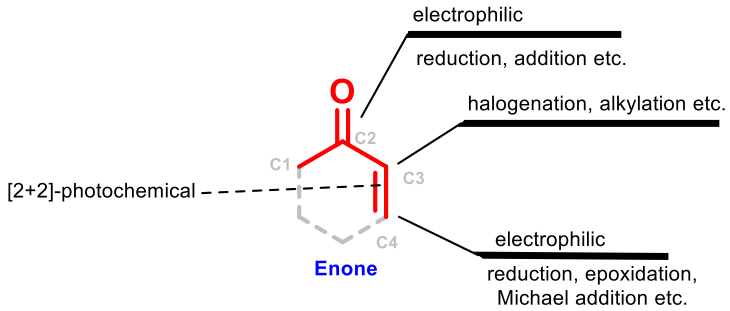
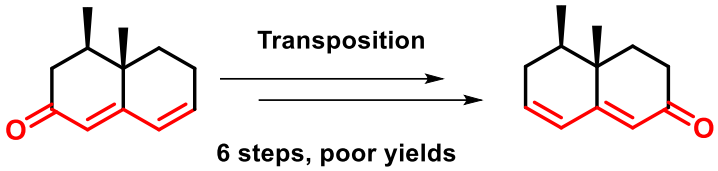


Figure 2.1.1 General reactions of enones

2.1.1.1 **Background of the work**

One such example of enone functionaliation was discussed in chapter 1 scheme 1.7 where we sought to perform an enone transposition reaction on compound **63** to get the compound **62** in order to get access to the peribysin family natural products. As discussed earlier, we made three different attempts for the rearrangement of enone moiety with no success and finally settled with a six steps sequence (scheme 2.1.1).



63 **62**

Scheme 2.1.1 General reactions of enones

Since the target at that time was to get access to peribysin family natural products, no further attempts were made for the rearrangement after getting the product **62** in sufficient quantity. But, looking at the presence of enone moiety in the natural product synthesis, it is highly desired to develop a reliable method for such kind of rearrangement.

2.1.1.2 **Known oxidative transposition reactions**

The most studied and utilized classical method for enone rearrangement is based on use of chromium based reagents such as PCC and PDC.[7] Babler *et al*. in 1976 have shown that when a allylic *ter*-alcohol is treated with a oxochromium reagent (Cr^{VI}), it forms a chromate ester which upon rearrangement followed by oxidation gives rearranged enone.[8] Several other methods capable of performing similar transformation includes use of TEMPO metaperiodate salt reported by Shibuya *et al*., use of aryl iodo sulphonate salt in combination with Oxone reported by Ishihara *et al*. or the use of IBX in DMSO under heating condition.[9] One of the well known reaction in this category includes Wharton reaction in which α-β-epoxy ketone is derived from an enone which on treatment with hydrazine gives the rearranged alcohol which can be further oxidized to give enone.[10] Hudlicky *et al* have reported Dauben–Michno type oxidative transposition of cyanohydrins

where several reagents are required to attain the transformation. In the same study, authors have converted *R*-carvone to *S*-carvone.[11]

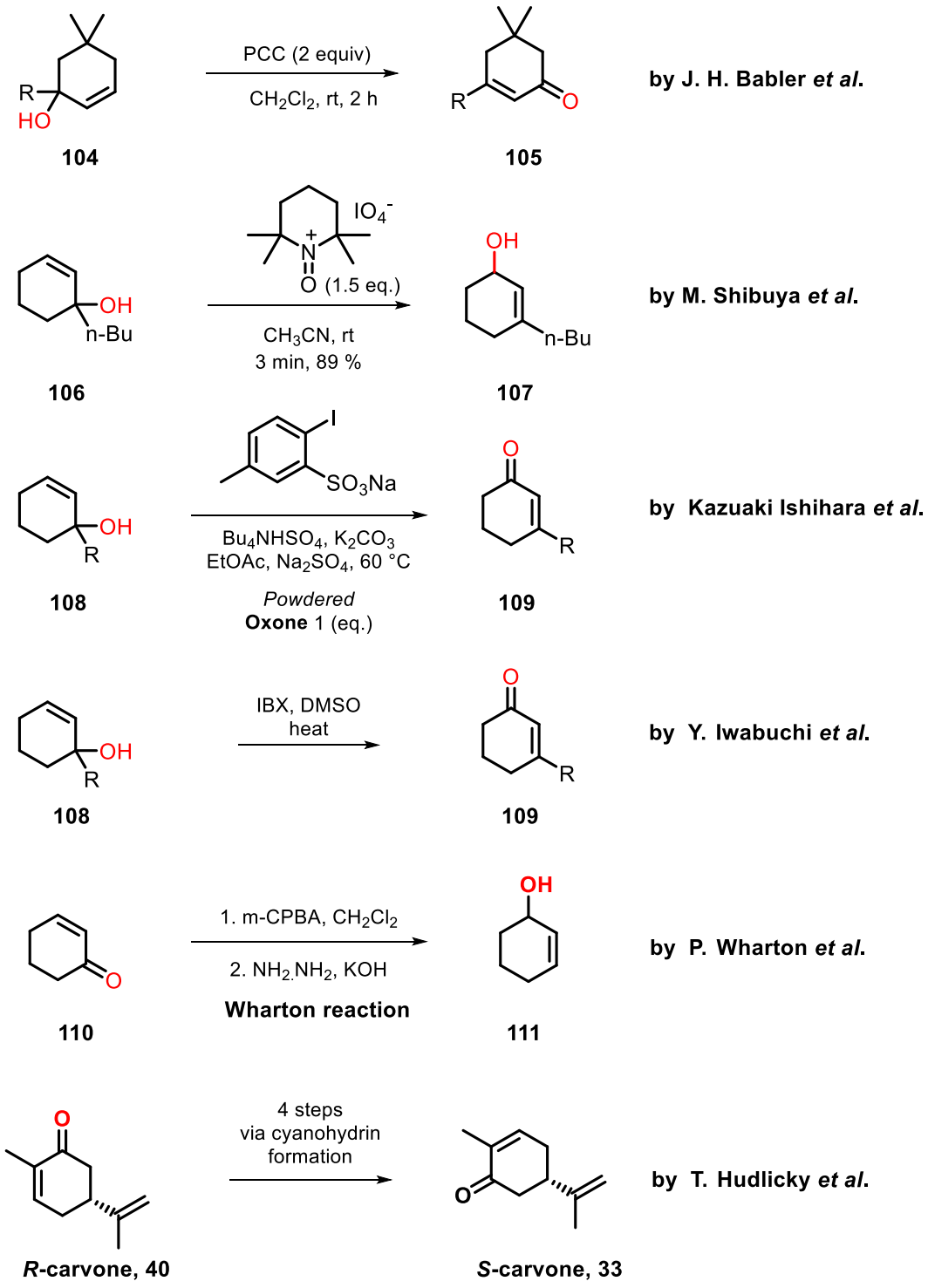


Figure 2.1.2 Selected examples of enone transposition

Though there are a bunch of methods available for the rearrangement of enones, or the oxidative rearrangement of *ter*-allylic alcohols, the general theme behind the rearrangement is addition of the organometallic or other suitable reagents to the carbonyl carbon in the first step. Then the rearrangement is performed using Cr(VI) based reagents such as PCC, PDC etc. to get the rearranged enone. But there are certain limitation to these methods in terms of productivity, the amount of Cr(VI) reagent required, and the metallic waste that is generated at the end of the reaction. The main disadvantage of these methods is that the group which is added to carbonyl group in the first step remains attached with the enone moiety. Hence these methods can not be called as the 'pure' enone rearrangement reactions.

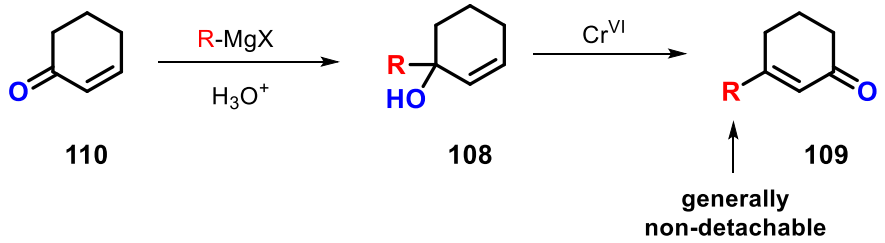


Figure 2.1.3 General theme of the classical oxidative rearrangements

2.1.2. Hypothesis for the use of silyl based masking group

With this background, considering the importance of enone moiety in the synthetic organic chemisty and our need for transformation of compound **63** to **62**, it is highly desirable to develop a general method for the enone transposition. For this purpose, a hypothesis was made which comprises of addition of suitable reagent (masking group) to the enone carbonyl in the first step, then performing the rearrangement and finally detaching the group which was added in the first step. Thus, choice of a suitable masking group is very important since it should be easy to prepare and readily added to carbonyl group. Further it should be stable during the rearrangement reaction and finaly it should be detachable after rearrangement.

Considering all these requirements a silicon based masking group was chosen. There are three main reasons for this as describes below.

a) Easy to prepare and are readily added to carbonyl group:

Preparation and addition of silyl lithium reagents is well documented in the literature and can be easily prepared and used.[12]

b) Helpful for rearrangement:

After the addition of silyl group to carbonyl of enone it forms a α-silyl *ter*-alcohol moiety. If this *ter*-alcohol is protonated and eliminated as a H_2O molecule then a *α*-silyl carbocation will be generated. Because of the silicon *α*-effect, the generated *α*-silyl carbocation will be highly unstable and it can undergo the rearrangement with the adjacent double bond to give the secondary allylic carbocation.[13]

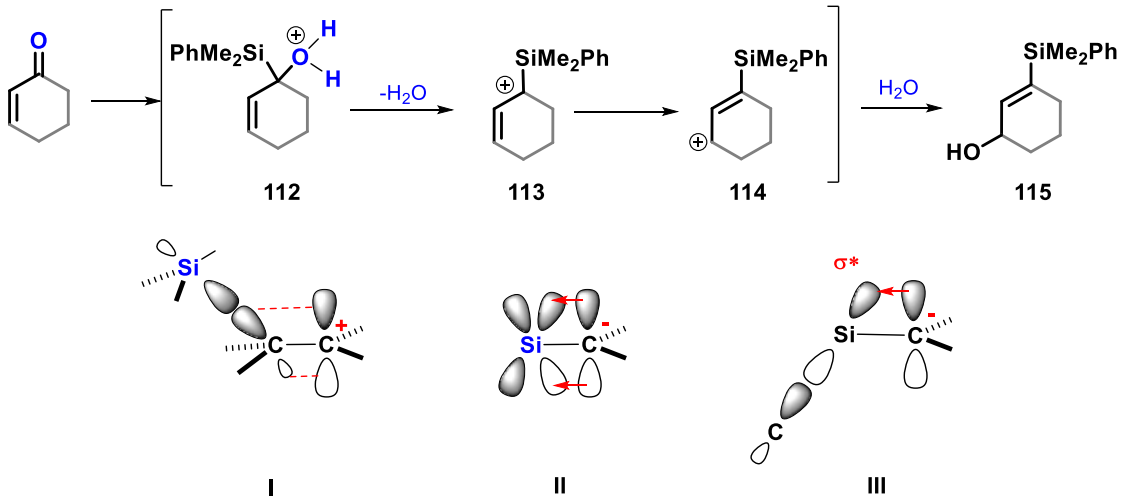


Figure 2.1.4 Silicon α and β-effect

(Orbital diagram reproduced from:

http://www-oc.chemie.uni-regensburg.de/OCP/ch/chb/oc5/Si_Organometallics.pdf)

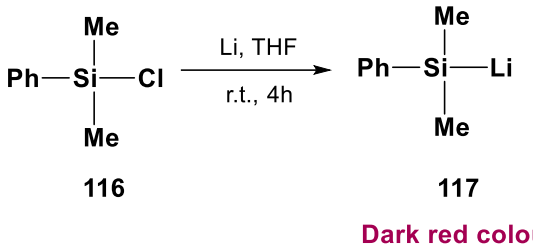
c) Easily detachable:

Silicon moiety is highly reactive towards fluorides, hydroxides and alkoxides which makes it easy to detach from the substrate.

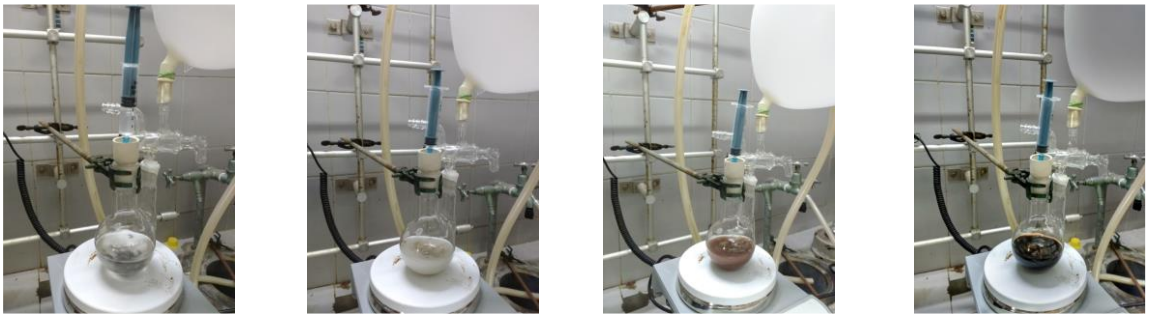
2.1.3. **Reaction optimization**

As per the hypothesis, initially, phenyl dimethyl silyl lithium ($PhMe_2SiLi$) reagent was prepared using the process described by Fleming *et al*.[12] First the lithium metal was taken in dry THF and $PhMe_2SiCl$ was added dropwise to it over 10 min. The reaction mixture becomes turbid after 10 min. of addition and starts becoming brown in color after 20 min.

After around 1-2 hours the reactions becomes dark reddish brown in color and can be used after 4 hours of stirring at room temperature.



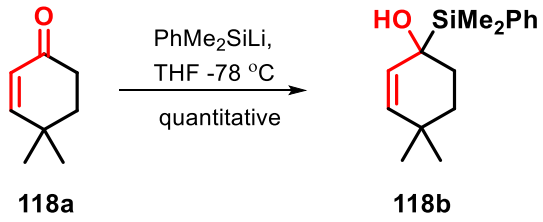
Scheme 2.1.2 Preparation of $PhMe_2SiLi$ reagent



5 min 10 min 20 min 2h

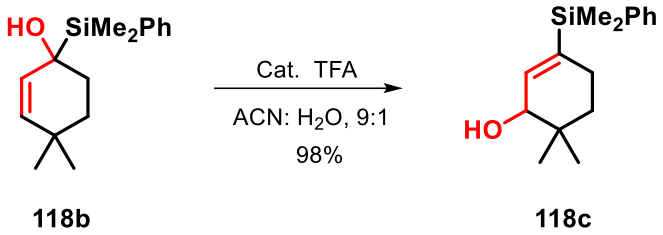
Figure 2.1.5 Preparation of $PhMe_2SiLi$ reagent

The freshly prepared $PhMe_2SiLi$ reagent (~ 0.5 M solution in THF) **117** was added to the model substrate 4,4-dimethyl cyclohexanone **118a** which gave the quantitative yield of the corresponding 1,2-addition product **118b** and no trace amount of Michael addition product was observed. In ^1H NMR both the olefinic C-H peaks were seen and five protons for phenyl ring were observed which gave the confirmation for the formation of the desired product.



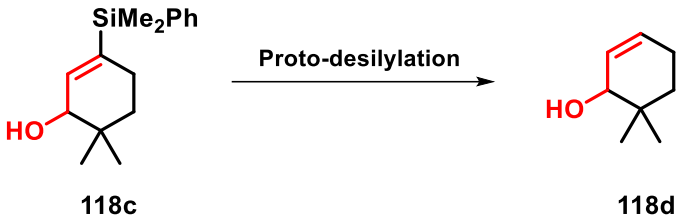
Scheme 2.1.3 Addition of $PhMe_2SiLi$ reagent to enone

Next, as per the hypothesis we treated the formed α-silyl *ter*-alcohol **118b** with catalytic TFA in 1:1 CH_3CN and H_2O mixture which gave the desired rearranged product **118c** in 55% yield. Further the ratio of solvents was optimized to 9:1 CH_3CN:H_2O which gave the best yield and no further optimization was needed. A similar kind of reaction was reported by Honda *et al*. to synthesize allyl ethers using methanol as a solvent.[14] In addition, Sakguchi *et al* have also used α-silyl *ter*-alcohols for the rearrangement.[13,15]



Scheme 2.1.4 Rearrangement of α-silyl *ter*-alcohol

After having the rearranged secondary alcohol **118c**, the next task was to perform proto-desilylation to get comound **118d.** For this purpose various conditions were screened to replace the $PhMe_2Si$ moiety with hydrogen. At first, some of the known conditions for proto-desilylation were screened starting with use of TFA in CH_2Cl_2 at room temperature. No product formation was observed in this condition, thus the reaction mixture was refluxed for 12 hours but the starting material was completely intact and recovered (Table 2.1.1, entry 1). Further use of BF_3·MeOH or BF_3·AcOH did not give the fruitful results and only starting material was recovered (entry 2-3). On treatment with HI in THF/H_2O mixture no reaction was observed, but when the reaction mixture was heated to reflux the starting material was decomposed.[16] Treatment with fluoride based reagents such as TBAF in THF or KF in DMSO at 80 ^oC did not give the desired product **118d**. When we screened the combination of TBAF and HMPA in DMSO, as reported by Muraoka *et al*. we observed 20% formation of the desired product **118d**.[17] Capperucci *et al*. have reported the use of TBAF and KOH combination for the desilylation of triphenyl silyl moiety hence we believed that similar condition can be used for removal of $PhMe_2Si$ moiety.[18] Thus compound **118c** was treated with TBAF and solid KOH in THF and refluxed for 12 hours which gave the isolated yield of 74%.



118c 118d

Scheme 2.1.5 Proto-desilylation of compound **118c**

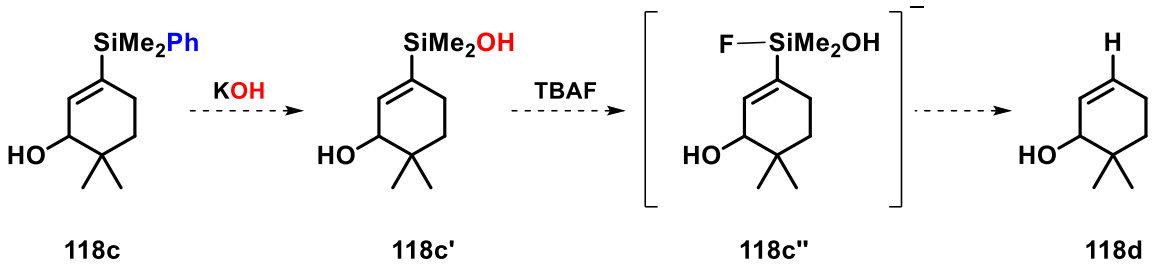
Sr. No.	Reagent	Solvent	Temperature	Time	Observation
1	TFA	CH_2Cl_2	reflux	12 h	No reaction
2	BF_3.MeOH	CH_2Cl_2	0 °C to r.t.	10 h	No reaction
3	BF_3.AcOH	AcOH	r.t.	10 h	No reaction
4	HI	THF/H_2O	r.t. to reflux	4 h	Decomposed
5	TBAF	THF	reflux	5 h	No reaction
6	KF	DMF	80 °C	2 h	No reaction
7	TBAF, HMPA	DMSO	80 °C	2 h	~ 20 %
8	TBAF, KOH	THF	reflux	12 h	74%
9	TBAF, KOH	THF	80 °C, MW	30 min	Quantitative

(All reactions were conducted on 100 mg scale. Yields mentioned in table are isolated yields.)

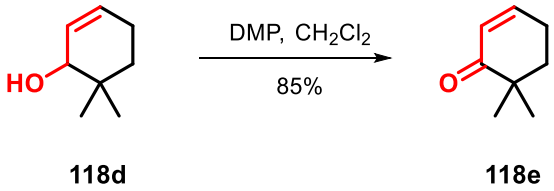
Table 2.1.1 Conditions screened for proto-desilylation of compound **118c**

Further when the reaction was conducted under microwave which gave the quantitative yield of the desired alcohol **118d**. Here it is interesting to note that by using the microwave condition the yield was increased and the reaction time was reduced sufficiently. During the proto-desilylation, when the reaction was monitored by TLC for every 5 minutes, a polar intermediate **118c'** was seen on TLC which was converting to the alcohol **118d** with time. This intermediate was isolated and after recording the ^{1}H and ^{13}C NMR spectra, peaks for phenyl ring were missing in the compound and rest of the peaks were present. Thus in

the mechanism for proto-desilylation, first the phenyl ring on silicon is replaced with OH group to give silanol intermediate **118c'** which on further reaction with fluoride ions gives the desilylated product **118d**.

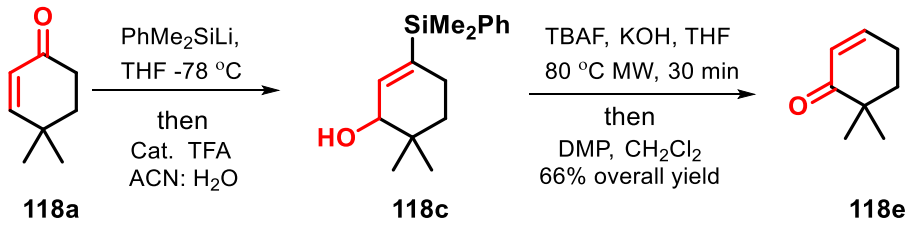


Scheme 2.1.6 Mechanism of proto-desilylation



Scheme 2.1.7 Oxidation of compound **118d**

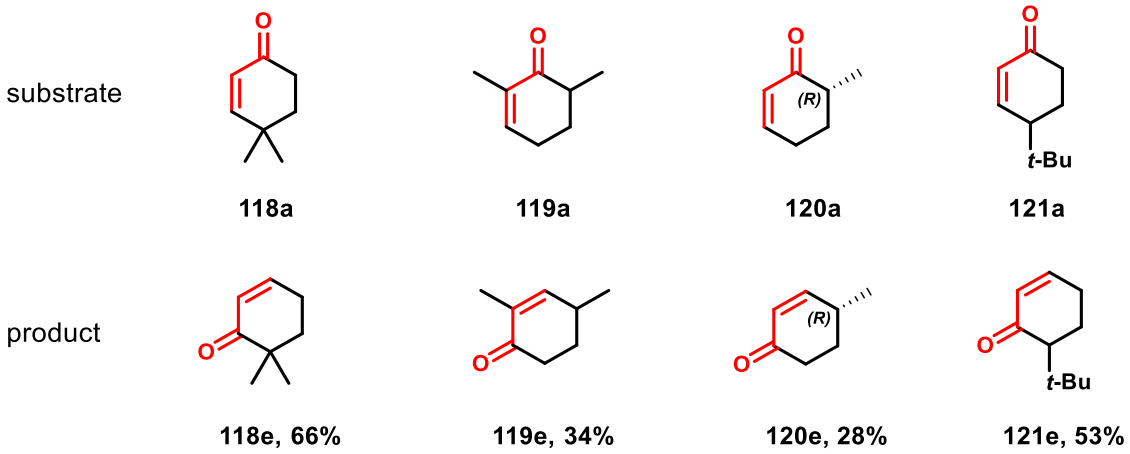
Finally the oxidation of allylic alcohol **118d** was performed using DMP in CH_2Cl_2 to give the enone **118e** in 85% yield. In ^{13}C NMR two olefinic carbons at δ 128.3, 148.6 ppm and the carbonyl carbon at δ 204.7 ppm were seen which gave the confirmation or the formation of enone **118e**. Here it is interesting to note that the starting material 4,4-dimethyl cyclohexanone gave 6,6-dimethyl cyclohexanone after rearrangement sequence which is an example of substituent shuffling. Thus a four steps sequence was optimized to perform the rearrangement of enones. Though there are four reactions required to perform the rearrangement, after further optimization, we clubbed first two steps and last two steps together eliminating the two purification steps.



Scheme 2.1.8 Final optimized condition

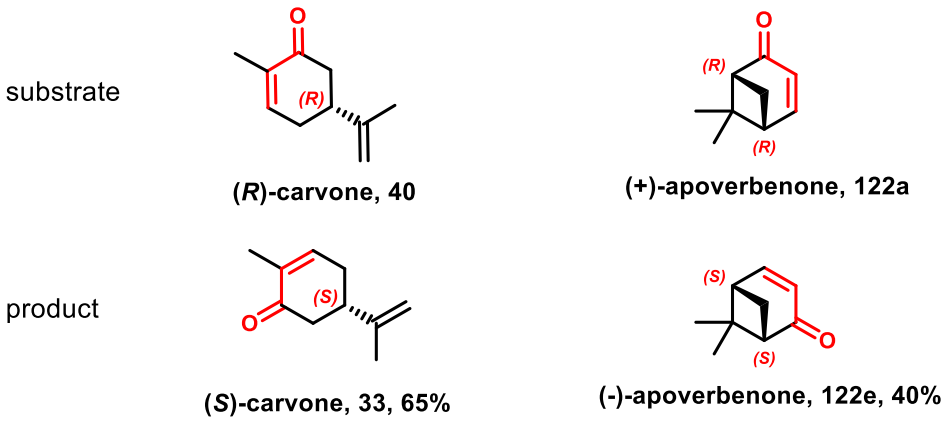
2.1.4 **Substrate Scope**

After having the optimized condition in hand the next task was to test the method on various classes of substrates having different functionalities. At first, the substrates based on cyclohexanone class were tested. Reaction of 2,6-dimethyl cyclohexanone **119a** under optimized sequence provided compound **119e** in 34% overall yield. The chiral starting material **120a** furnished rearranged enone **120e** in 28% yield. 4-*ter*-butyl substituted compound **121a** gave 53% overall yield. Here it is interesting to note that, in all these substrates, when a substituent is present at 2 or 4 position on the cyclohexenone ring their positions are exchanged in the end result. Hence, these are the examples of substituent shuffling.



Scheme 2.1.9 Substituted cyclohexenones

Next, we focused on the 3-substituted derivatives and for this purpose, *R*-carvone was treated under optimized condition which resulted in the formation of *S*-carvone (scheme 2.1.10). This is an interesting example of the enantio-switching. In natural product chemistry, chiral pool starting materials play a vital role and sometimes it is difficult to access a particular enantiomer because of the non-existance in nature or the higher cost of particular enantiomer. Thus this method can be useful to interconvert such 3-substituted chiral cyclohexenone derivatives. Another interesting example of this kind was the interconversion of (+)-apoverbenone **122a** (derived from pinene in 2-steps) to (-)-apoverbenone **122e**.



Scheme 2.1.10 Enantio-switching of carvone and apoverbenone

After screening the cyclohexenone derivatives next, few acyclic enones were prepared using the known literature protocols.[19] The reaction of commercially available 3-decen-2-one **123a** under optimized conditions furnished rearranged enone **123e** in 70% yield. Interestingly, after careful analysis by NMR and literature reports, the obtained product was found to possess *Z*-geometry of the double bond. The probable eason for the selectivity could be traced back to the bulky $PhMe_2Si$ group which prefers the less sterically hindered position after the rearrangement of the carbocation and locks the conformation to *E*-isomer. After the desilylation the geometry does not change and *Z*-alcohol is obtained (scheme 2.1.11). Next, three more enones were derived from *R*-citronellal, cyclohexane carboxaldehyde and hexanal by Wittig reaction to get **124a**, **125a** and **126a**. Further treatment of these three enones under optimized conditions furnished corresponding *Z*-enones **124e**, **125e** and **126e** with overall yields of 46, 44 and 43% respectively. Two more enones **127a** and **128a** were synthesized starting from hydrocinnamladehyde using known procedures.[20, 21] Both the enones were successfully rearranged under optimized conditions to give 40 and 61% yields respectively.

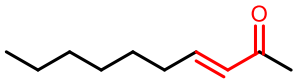
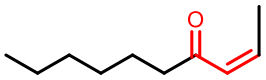
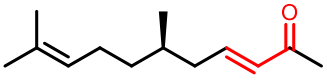
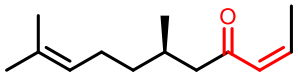
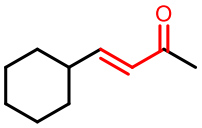
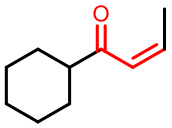
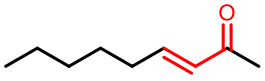
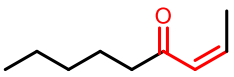
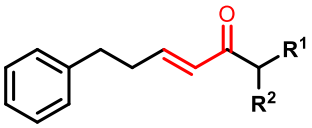
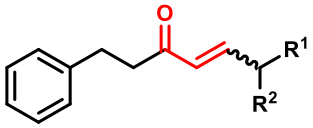
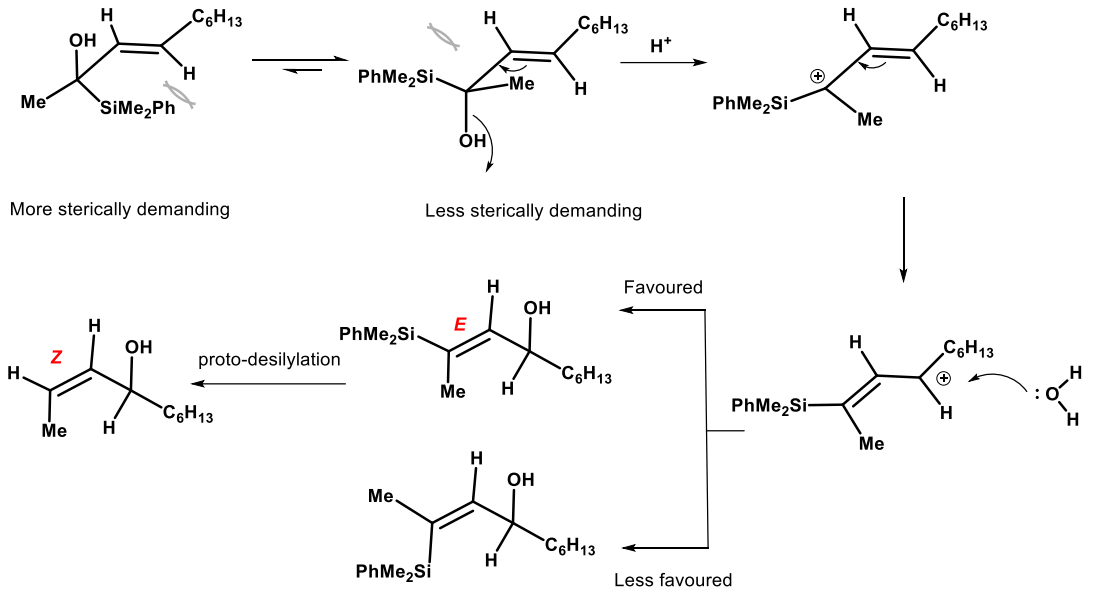
substrate	product	*Z*:*E* ratio, yield
 123a	 123e	> 95:5, , 56%
 124a	 124e	> 95:5, 46%
 125a	 125e	> 92:8, 44%
 126a	 126e	> 95:5, 43%
 $R^1 = R^2 = H$, 127a $R_1 = R_2 = CH_3$, 128a	 127e 128e	> 92:8, 40% exclusively *E*, 61%

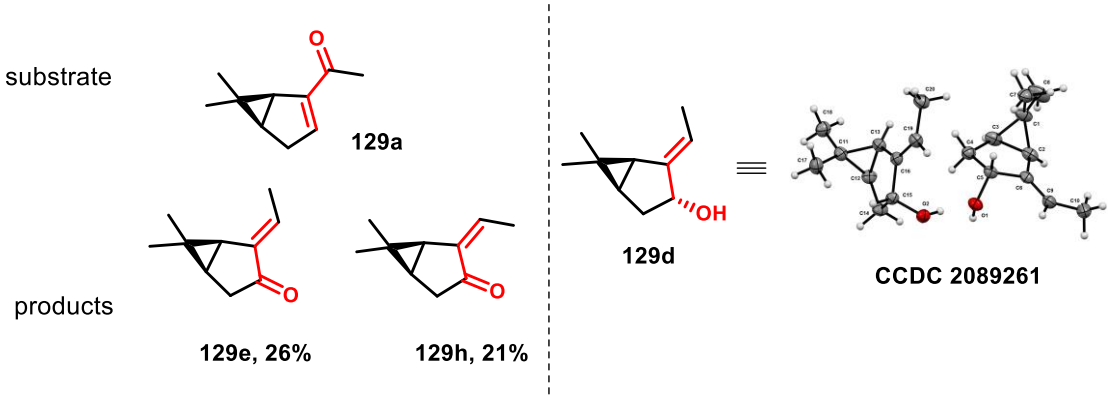
Table 2.1.2 long chain and aliphatic enone substrates

Here, in all the cases more than 90% of the *Z*–isomer was obtained except for the isopropyl group containing enone **128a** which furnished exclusively *E*-isomer. The probable reason for the reverse selectivity could be presence of the comparitively more bulky isopropyl group than the methyl group present in other substrates (scheme 2.1.11). After screening the long chain and aliphatic substrates, next we synthesized two bicyclic enones **129a** and **130a**. The enone **129a** was synthesized starting from (+)-3-carene in two steps using known protocol.[22] Enone **129a** after silyl addition gave compound **129b** which when treated with catalytic TFA in CH_3CN, furnished two different products which were forwarded separately for the next sequence to give two enones **129e** and **129h**.



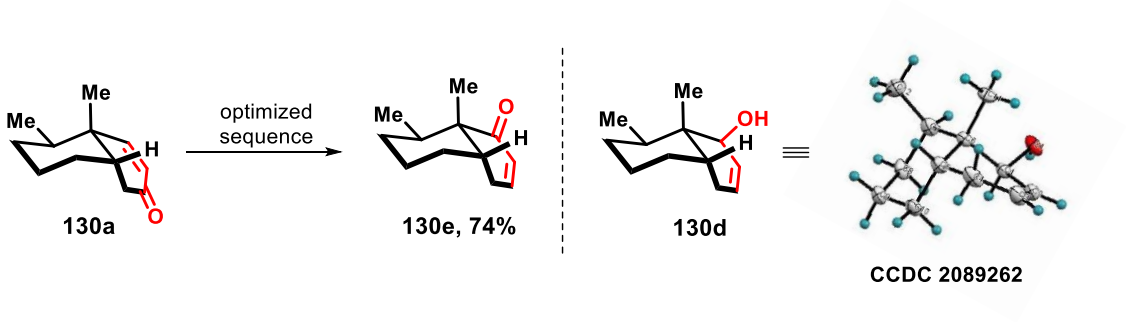
Scheme 2.1.11 Possible explanation for the *Z*-selectivity

The structure of the *E*-enone **129d** was confirmed by single crystal X-ray diffraction method which helped us to fix the stereochemistry of the hydroxy center and the geometry of the double bond. Both these enones **129e**, **129h** and their intermediates are useful building blocks and can be used in synthesis of natural products. A decalin enone **130a** was synthesized by following the previously developed procedures in our group. Treatment of this enones **130a** under optimized conditions provided the rearranged enone **130e** in 39% overall yield.



Scheme 2.1.12 Enone derived from (+)-3-carene

The structure of the intermediate alcohol **130d** was confirmed by the single crystal X-ray diffraction method. Interestingly, compound **130d** mimics the core structure of peribysin D with all the four chiral centers having same relative stereochemistry as present in peribysin D. Since, in our previous attempts on synthesis of peribysin D (chapter I section 1.2.16) we failed to install the hydroxyl group at the carbon next to the decalin junction carbon; here we found an opportunity to address this problem by using the developed method for the synthesis of peribysin D.



Scheme 2.1.13 Bicyclic enone substrate

2.1.5. Application of the developed method

2.1.5.1 Synthesis of peribysin D

Peribysin D is the most potent cell adhesion inhibitor from the peribysin family. Yamada and co-workers originally proposed a tetracyclic structure for peribysin D, **131** which was later corrected by Koshino *et al*. to tricyclic structure, **26** with the help of NMR studies (scheme 2.1.14).[23,24] From our previous work on peribysins, we knew that peribysin D may need structural revision. Thus it was necessary to address this descrepancy by achieving its total synthesis.

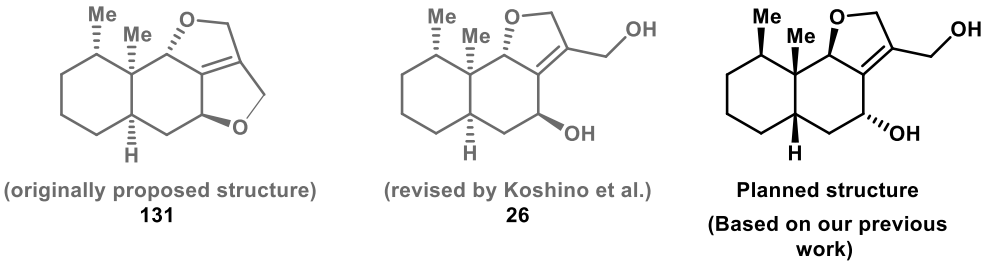
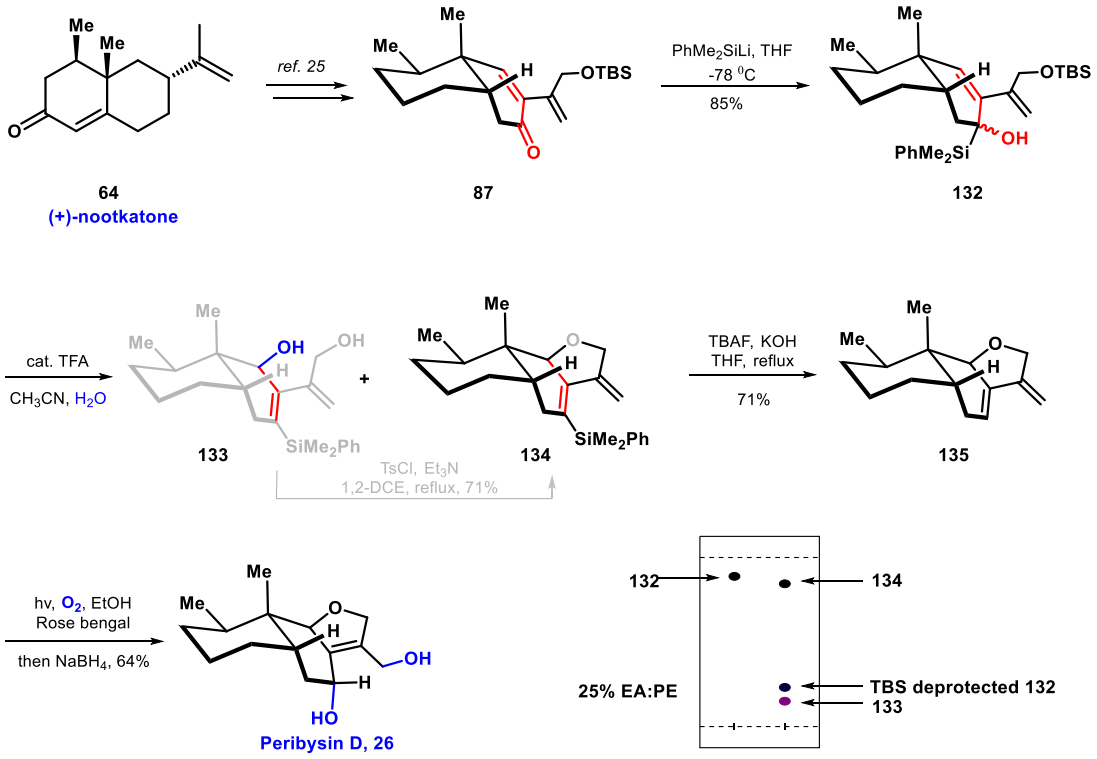


Figure 2.1.6 Proposed and revised structures of peribysins

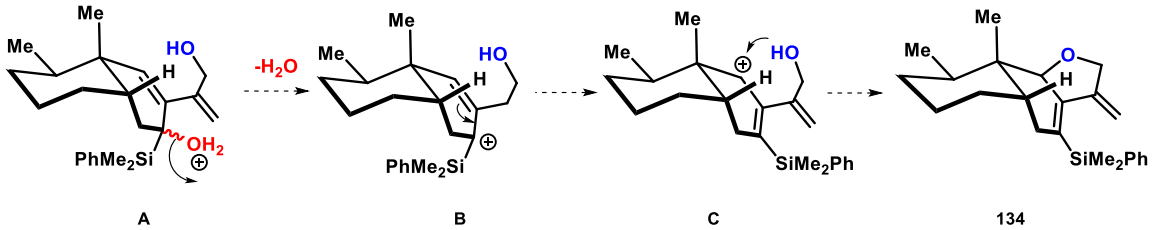
As we planned to access the revised structure of peribysin D using the developed method. For this purpose we synthesized compound **87** staring from (+)-nootkatone, **64** using our previously optimized route.[25] To this compound **87** we added freshly prepared $PhMe_2SiLi$ reagent at -78°C to get 1,2 addition product **132**. Compound **132** was then treated with catalytic TFA in CH_3CN and H_2O mixture to get the rearranged alcohol **133**. In ^1H NMR one new proton appeared at δ 4.04 ppm which corresponds to hydroxyl group adjacent C-H. In the ^{13}C NMR of compound **133** oxygen attached methyne carbon was observed at δ 72.4 ppm which infers the formation of secondary alcohol product and hence the formation of compound **133**. Further HRMS peak observed at 393.2214 calculated for the molecular formula $C_{23}H_{34}O_2SiNa$ $[M+Na]^+$: 393.2220 gave the confirmation. In addition to the expected product **133** we isolated a non-polar compound from the same reaction mixture



Scheme 2.1.14 Synthesis of peribysin D

in 27% yield. The HRMS of this compound showed peak at 353.2292 calculated for the molecular formula $C_{23}H_{33}OSi$ $[M+H]^+$: 353.2295. Thus there is a possibility of a cyclized product **134** by loss of H_2O molecule. All the NMR data was in accordance with the

cyclized structure **134**. To further confirm the product **134** we treated diol **133** with Et_3N and TsCl to get cyclic ether **134**. After comparison of NMR spectra the structure was confirmed to be compound **134**. The probable mechanism for the direct formation of compound **134** from compound **133** is depicted in scheme 2.1.15. First the TBS group in compound **133** gets removed under acidic medium followed by protonation of *ter*-alcohol produces intermediate **A**. Removal of H_2O molecule followed by rearrangement of carbocation gives intermediate **C**. The carbocation **C** can be attacked by two different nucleophiles; H_2O molecule present in the reaction medium to give compound **133** or

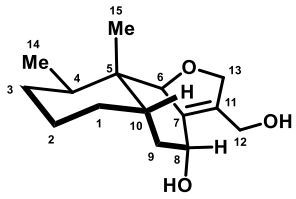


Scheme 2.1.15 Possible mechanism for the direct formation of compound **134**

the internally present OH group can produce cyclized product **134**. Compound **134** was then subjected for proto-desilylation to get diene **135** in 71% yield. In the ^1H and ^{13}C NMR of the obtained product peaks for $PhMe_2Si$ group were missing and an addition olefinic proton appered at δ 5.93 ppm which confirmed the formation of diene **134**. Finally, the diene **134** was subjected for [4+2] reaction with singlet oxygen in presence of Rose Bengal to get the cyclic peroxide intermediate which was *in-situ* reduced to diol using $NaBH_4$ to get the target compound **26**.[23] All the NMR spectral data for the synthetic compound **26** was matching with the natural peribysin D. Further HRMS peak was observed at 275.1617 calculated for the molecular formula $C_{15}H_{24}O_3Na$ $[M+Na]^+$: 275.1618, gave the confirmation for the structure **26**. The specific optical rotation was recorded in ethanol solvent which gave the value of -1.8° whereas the reported optical rotation was +4.6° in ethanol. Since the magnitude of the rotation was very small and close to zero, we wanted to have additional we recorded the CD spectra for the synthetic compound. To our delight, the CD spectra for the synthetic peribysin and natural peribysin were in complete agreement. Since we synthesized the antipode of the proposed structure, and CD spectra of

both of them are matching, we revised the structure of the peribysin D as per the hypothesis (chapter I section 1.2.1).

Table 2.1.3 NMR comparison Table of synthetic and natural peribysin D



Peribysin D	^{1}H NMR δ ppm		Difference	^{13}C NMR δ ppm		Difference
	isolation	Synthesis		isolation	synthesis	
1α	1.92	1.92	-	30.20	30.26	0.06
1β	1.46	1.46	-	-	-	-
2α	1.51	1.51	-	20.98	21.02	0.04
2β	1.48	1.48	-	-	-	-
3α	1.25	overlapped	-	20.89	overlapped	-
3β	1.35	1.34	0.01	-	-	-
4	1.94	1.94	-	33.48	33.55	0.07
5	-		-	42.35	42.26	0.09
6	5.40	5.39	0.01	85.95	85.91	0.04
7	-	-	-	136.6	136.5	0.10
8	4.77	4.73	0.04	63.69	64.10	0.41
9α	1.61	1.62	0.01	34.52	34.74	0.22
9β	1.85	1.87	0.02	-	-	-
10	1.67	1.67	-	37.21	37.23	0.02
11	-	-	-	132.82	133.24	0.42
12A	4.15	4.29	0.14	55.68	56.44	0.24
12B	4.40	4.38	0.02	-	-	-
13A	4.55	4.60	0.05	76.36	76.26	0.10
13B	4.78	4.79	0.01	-	-	-
14	0.96	0.95	0.01	15.17	15.21	0.04
15	0.71	0.72	0.01	17.78	17.84	0.04

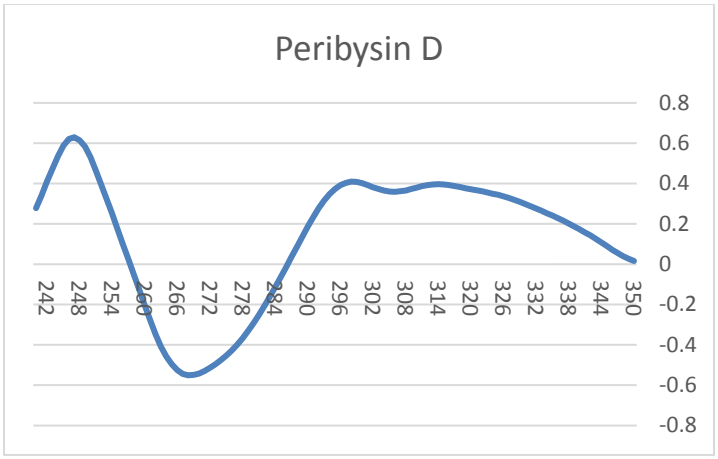


Figure 2.1.7 CD spectra of synthetic peribysin D

In natural peribysin D faint first positive Cotton effect at was observed at 297 nm and second negative cotton effect at 264 nm. Whereas, in synthetic Peribysin D first positive Cotton effect at 296 nm, second negative Cotton effect was observed at 267 nm.This information suggests that the synthesized structure is natural peribysin D and the originally assigned structure needs to be revised.

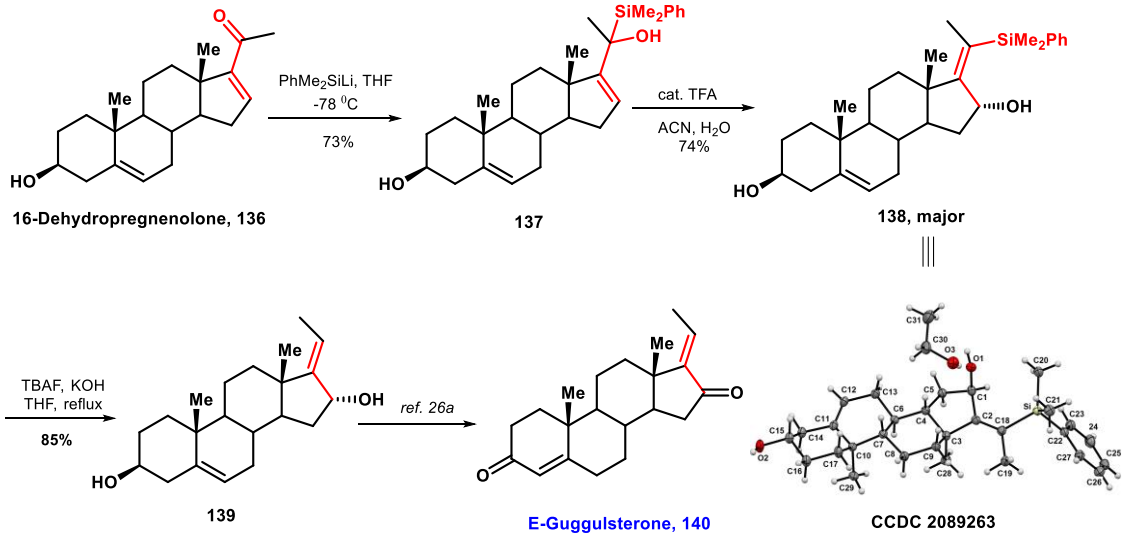
2.1.5.2 **Formal synthesis of *E*-guggulsterone and *E*-volkendousin**

To further expand the scope of the method we chose two more natural products guggulsterone, **140** and volkendousin, **141** from the steroidal family possessing enone moiety. Guggulsterone is a plant sterol which is obtained from the gum resin of *Commiphora wightii*. The resin obtained from the guggul plant has been used to treat various disorders tumors, obesity, edema etc. for thousands of years in Ayurveda.[26] Structurally, guggulsterone exists in both *E* and *Z*-forms in nature. In recent studies, the *E*-form was found to be superior than *Z*-form.[27]

Figure 2.1.8 Guggul plant and resin

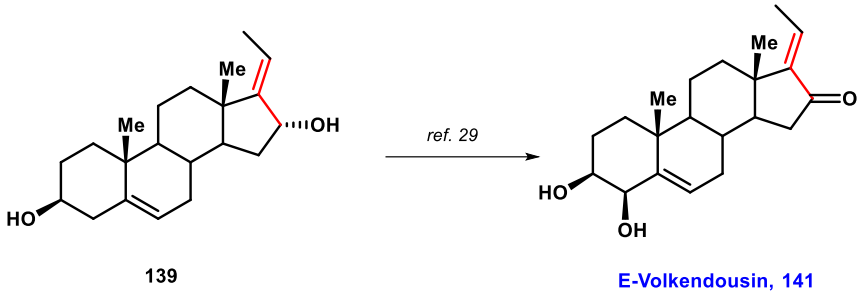
(Image source: https://gafacom.website/guggulu-commiphora-wightii-medicinal-uses/)

One more structurally similar steroid natural product volkendousin was isolated by Rogers *et al*. in 1998.[28] *E*-volkendousin possessing anticancer activity has been synthesied previously by Snider *et al*.[29] Thus, we thought of accessing both the natural products using the developed strategy from commercially available 16-dehydropregnenolone **136**. For this purpose, compound **136** was treated with freshly prepared $PhMe_2SiLi$ reagent to get 1,2-addition product **137**. Treatment of compound **137** with catalytic TFA furnished **138** as a major product (scheme 2.1.16). In the ^1H NMR one olefinic peak was vanished and an extra proton was observed at δ 4.40 ppm which correspons to the OH attached proton which confirmed the formation of product **138**.



Scheme 2.1.16 Formal synthesis of *E*-guggulsterone

To confirm the stereochemistry of the OH chiral center we recorded the single crystal X-ray structure of compound **138**. Thus, we were able to assign the double bond geometry and the stereochemistry as depicted in scheme 2.1.16. The proto-desilylation reaction of compound **138** provided diol **139** in 85% yield. The NMR spectral data and specific optical rotation was compared with the reported data by Ham *et al*. and found to be matching.[26a] This diol **139** was previously conveted to *E*-guggulsterone and *E*-volkendousin in one steps each. Thus here we have achieved formal synthesis of both the natural products in a very short synthetic sequence (scheme 2.1.17).



Scheme 2.1.17 Formal **s**ynthesis of *E*-volkendousin

2.1.6. **Other potential applications from developed method**

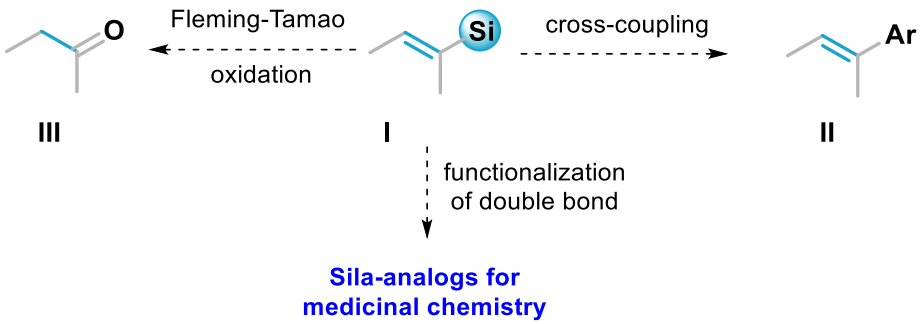


Figure 2.1.9 Potential synthetic utility of vinyl silanes

In the process for the synthesis of substrates and their rearrangement, we have generated a library of vinyl silanes (I) (Figure 2.1.9). These vinyl silanes can act as handles for cross coupling such as Hiyama coupling with variety of coupling partners. Moreover, vinyl silanes can undergo various types of other reactions including Fleming-Tamao oxidation and other reactions of carbon-carbon double bond (figure 2.1.9).[16] Silicon incorporated organic compounds also has an importance with medicinal chemistry point of view. In last

few years, lot of research has been conducted on silicon incorporated drugs because of he unique properties such as high lipophilicity afforded by sila analogs.[30-36] Thus sila intermediates generated during this work might be useful for various purposes in organic synthesis and medicinal chemistry.

2.1.7. **Conclusions**

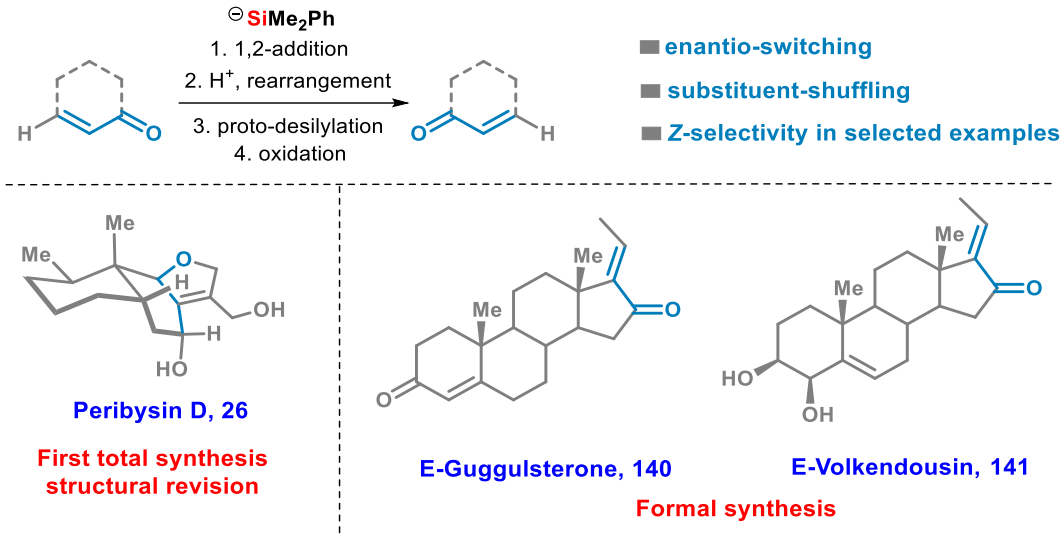


Figure 2.1.10 Summary of Chapter 2 Section I

In summary, a new method for the rearrangement of enones has been developed by using a masked silicon group. The method involves preparation of α-silyl *ter*-alcohol intermediate followed by *in-situ* generaion and rearrangement of α-silyl carbocation. The rearrangement of α-silyl carbocation was facilitated by silicon α-effect. Further proto-desilylation using fluoride source in basic condition followed by oxidation gave the rearranged enone. The method was successfully applied for the transposition of 14 substrates. Additionally, enantio-switching of carvone and apoverbenone was achieved using this mehod. Another pleasing outcome from this method is our previously unaddressed problem of peribysin D total synthesis was addressed by applying the current method for the first total synthesis and stereochemical revision of peribysin D. Moreover, formal synthesis of steroidal bioactive natural products, *E*-guggulsterone and *E*-

volkendousin was achieved in very short reaction sequence. During this exercise, a library of functional building blocks (vinyl silanes) was generated which might be used for various applications in synthetic organic chemistry. A summary is captured below in figure 2.1.9.

2.1.8. **Experimental section (Data for selected compounds)** Remaining data can be found in doi.org/10.1021/acs.orglett.1c02173

2.1.8.1. **General procedure for preparation of $PhMe_2SiLi$ reagent**

(Slightly modified procedure reported by Fleming *et al.* and Studer *et al.*)[12]

Lithium metal (448 mg, 74.66 mmol, 5 eq.) was cut into small pieces and taken into a two necked round-bottom flask under nitrogen atmosphere. Then dry THF (25 mL) was added to it via syringe. To this mixture, chlorodimethylphenylsilane **116** (2.5 mL, 14.70 mmol, 1 eq.) was added dropwise over 5 min at room temperature. The reaction mixture was stirred at room temperature for 3-4 hours. After 3 hours, dark brown coloured $PhMe_2SiLi$ reagent, **117** in THF was generated, which was used as such for the further reactions.

2.1.8.2. **General procedure for 1,2-addition of $PhMe_2SiLi$ reagent**

To the stirred solution of enone **118a** (1.5 g, 12.09 mmol, 1 equiv.) in THF at -78 °C under nitrogen atmosphere was added freshly prepared $PhMe_2SiLi$ reagent in THF dropwise via syringe. The resulting solution was stirred for 30 min at -78 °C. The reaction progress was monitored by TLC. If reaction is incomplete, the more amount of $PhMe_2SiLi$ can be added. After complete conversion of starting material, reaction mixture was quenched with sat. aq. NH_4Cl (30 mL) and extracted with EtOAc (2 X 50 mL). The combined organic layer was washed with brine (40 mL), and dried over Na_2SO_4. The solvent was evaporated and the mixture was purified by column chromatography (silica gel) to give pure compound **118b** (1.82 g, 84%).

Similar procedure was followed for the preparation of compounds **119b**, **120b, 121b, 122b**, …, etc. from compounds **119a, 120a, 121a, 122a,** …, etc. respectively.

2.1.8.3. **General procedure for transposition**

Compound **118b** (800 mg, 3.07 mmol, 1 equiv.) was taken in CH_3CN: H_2O (9:1) (30 mL) in a round bottom flask. Catalytic amount of TFA (50 μL) was added to it. Reaction mixture

was then stirred for overnight (or till complete consumption of starting material monitored by TLC). After completion of reaction, reaction mixture was quenched with sat. aq. $NaHCO_3$ (20 ml) and extracted with EtOAc (2 x 30 mL). The organic layer was washed with brine (25 mL) and dried over Na_2SO_4 and concentrated under reduced pressure. Crude product was purified using column chromatography (silica gel) to afford pure compound **118c** (758 mg, 95%).

Similar procedure was followed for the preparation of compounds **119c**, **120c**, **121c**, **122c**, …, etc. from compounds **119b**, **120b**, **121b**, **122b**, …, etc. respectively.

2.1.8.4. **General procedure for proto-desilylation**

To the microwave vial containing compound **118c** (750 mg, 2.8 mmol, 1 equiv.) in dry THF, added KOH (323 mg, 5.7 mmol, 2 equiv.) at room temperature. Subsequently, TBAF (4.2 mL, 1.5equiv.) (1M in THF) was added to the reaction mixture. The reaction mixture was subjected to microwave irradiation for 30 min at 85 °C. After completion of reaction, vial was cooled to 0 °C in ice bath. Reaction mixture was quenched with aq. 1N HCl (20 mL) and extracted with EtOAc (2 x 50 mL). The organic layer was washed with brine (30 mL) and dried over Na_2SO_4, and concentrated under reduced pressure. Purification of crude product by using column chromatography (silica gel) afforded the proto-desilylated pure product **118d** (356 mg, 98%).

Similar procedure was followed for the preparation of compounds **119d**, **120d**, **121d**, **122d**, …, etc. from compounds **119c**, **120c**, **121c**, **122c**, …, etc. respectively.

2.1.8.5. **General procedure for oxidation**

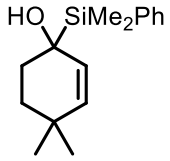
Compound **118d** (200 mg, 1.59 mmol) was taken in dry CH_2Cl_2 (20 mL) under nitrogen atmosphere. Then solid $NaHCO_3$ (50 mg) was added to the reaction mixture at 0 °C followed by the addition of DMP (807 mg, 1.90 mmol, 1.2 equiv.) reagent. After addition, reaction mixture was stirred at room temperature for the next 1-2 hours. Reaction progress was monitored by using TLC, and after completion of reaction, CH_2Cl_2 (20 mL) was added to the reaction mixture and the organic layer was washed with sat. $NaHCO_3$ (25 mL) followed by brine (25 mL). The solvent was evaporated and the crude product was

subjected to column chromatography (silica gel) which afforded the final enone transposition product **118e** (171 mg, 85%).

Similar procedure was followed for the preparation of compounds **119e**, **120e**, **121e**, **122e**, …, etc. from compounds **119d**, **120d**, **121d**, **122d**, …, etc. respectively.

Note: For the purification of volatile compounds pentane and diethyl ether system was used to minimize the loss of yield during evaporation.

2.1.8.6. **Compound characterization data for selected compounds: Data for remaining compounds can be found at https://doi.org/10.1021/acs.orglett.1c02173**



1-(dimethyl(phenyl)silyl)-4,4-dimethylcyclohex-2-en-1-ol: 118b

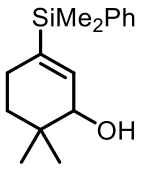
Yield: 1.82 g, 84%

IR υ_{max}(film): cm^{-1} 3444, 2952, 1427, 1250, 1112;

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.65 - 7.61 (m, 2 H), 7.41 - 7.37 (m, 3 H), 5.61 - 5.55 (m, 2 H), 1.89 - 1.85 (m, 1 H), 1.68 (ddd, *J* = 3.4, 7.3, 14.0 Hz, 1 H), 1.49 (ddd, *J* = 3.2, 10.8, 13.5 Hz, 1 H), 1.35 - 1.23 (m, 2 H), 1.01 (s, 3 H), 0.82 (s, 3 H), 0.42 - 0.40 (m, 6 H);

^{13}C NMR (100 MHz, $CDCl_3$) δ = 140.3, 136.3, 134.6, 129.2, 127.7, 127.6, 64.6, 32.3, 31.5, 30.0, 29.9, 27.5, -5.7, -6.0;

HRMS calculated for $C_{16}H_{25}OSi$ $[M+H]^+$: 261.1669, found 261.1660.



3-(dimethyl(phenyl)silyl)-6,6-dimethylcyclohex-2-en-1-ol: 118c

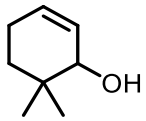
Yield: 758 mg, 95%

IR υ_{max}(film): cm^{-1} 3356, 2957, 1427, 1251, 1110;

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.52 - 7.49 (m, 2 H), 7.37 - 7.35 (m, 3 H), 5.97 (q, *J* = 2.3 Hz, 1 H), 3.81 (q, *J* = 2.6 Hz, 1 H), 2.04 – 2.01 (m, 2 H), 1.48 - 1.38 (m, 3 H), 0.96 (s, 3 H), 0.88 (s, 3 H), 0.36 (d, *J* = 1.8 Hz, 6 H);

^{13}C NMR (100 MHz, $CDCl_3$) δ = 139.3, 139.1, 137.9, 133.8, 129.0, 127.8, 75.0, 33.8, 33.3, 26.8, 24.8, 20.5, -3.7;

HRMS calculated for $C_{16}H_{25}OSi$ $[M+H]^+$: 261.1669, found 261.1658.



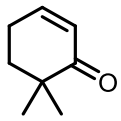
6,6-dimethylcyclohex-2-en-1-ol: 118d

Yield: 356 mg, 98%

^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.73 (dtd, *J* = 1.4, 3.5, 10.0 Hz, 1 H), 5.61 (tdd, *J* = 2.1, 3.1, 10.0 Hz, 1 H), 3.72 (s, 1 H), 2.07 - 1.90 (m, 2 H), 1.46 (td, *J* = 5.9, 13.5 Hz, 1 H), 1.33 (td, *J* = 6.7, 13.5 Hz, 2 H), 1.22 (br. s., 1 H), 0.92 (s, 3 H), 0.85 (s, 3 H);

^{13}C NMR (100 MHz, $CDCl_3$) δ = 129.3, 129.1, 73.9, 33.5, 32.5, 26.2, 23.0, 21.6;

HRMS calculated for $C_8H_{14}ONa$ $[M+Na]^+$: 149.0942, found 149.0240.



6,6-dimethylcyclohex-2-en-1-one: 118e

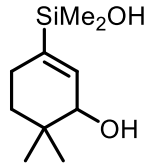
Yield: 171 mg, 85%

IR υ_{max}(film): cm^{-1} 2958, 2924, 1676, 1260, 1156;

^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.81-6.85 (dt, *J* = 10.07, 3.91 Hz, 1 H), 5.86-5.90 (dt, *J* = 10.04, 2.05 Hz, 1 H), 2.32 - 2.36 (tdd, *J* = 6.05, 6.05, 3.97, 2.06 Hz, 2 H), 1.80 (t, *J* = 6.07 Hz, 2 H), 1.08 (s, 6 H) ;

^{13}C NMR (100 MHz, $CDCl_3$) δ = 204.7, 148.6, 128.3, 41.4, 36.2, 24.1, 23.4;

HRMS calculated for $C_8H_{13}O$ $[M+H]^+$: 125.0966, found 125.0970.



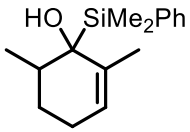
(3-hydroxy-4,4-dimethylcyclohex-1-en-1-yl)dimethylsilanols: 118c'

IR υ_{max}(film): cm^{-1} 3413, 3308, 2911, 1458, 1253, 1069;

^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.97 - 5.90 (m, 1 H), 3.77 - 3.66 (m, 1 H), 2.07 – 2.04 (m, 2 H), 1.68 (br. s, 1 H), 1.48 - 1.43 (m, 1 H), 1.36 (ddd, *J* = 6.5, 7.7, 13.7 Hz, 1 H), 0.92 (s, 3 H), 0.84 (m, 3 H), 0.17 - 0.09 (m, 6 H);

^{13}C NMR (100 MHz, $CDCl_3$) δ = 140.3, 138.4, 74.7, 33.6, 33.2, 26.8, 24.0, 20.5, -1.1, -1.1;

LCMS calculated for $C_{10}H_{19}O_2Si$ $[M-H]^+$: 199.1, found 199.0.



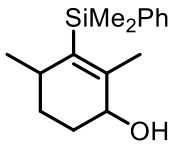
1-(dimethyl(phenyl)silyl)-2,6-dimethylcyclohex-2-en-1-ol: 119b

Yield: 873 mg, 87%, d.r. = 7 : 3

IR υ_{max}(film): cm^{-1} 3603, 2928, 1443, 1254, 1110;

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.61 - 7.56 (m, 2 H), 7.38 - 7.33 (m, 3 H), 5.43 - 5.40 (m, 0.3 H), 5.34 - 5.31 (m, 0.7 H), 2.09 - 2.04 (m, 1 H), 2.02 - 1.93 (m, 1 H), 1.82 - 1.76 (m, 1 H), 1.76 - 1.73 (m, 1 H), 1.66 - 1.63 (m, 3 H), 1.44 - 1.35 (m, 1 H), 0.89 (d, *J* = 6.8 Hz, 1.5 H), 0.85 (d, *J* = 6.6 Hz, 1.5 H), 0.44 - 0.41 (m, 4 H), 0.38 (s, 2 H);

HRMS calculated for $C_{16}H_{25}OSi$ $[M-H]^+$: 259.1518, found 259.1526.



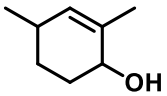
3-(dimethyl(phenyl)silyl)-2,4-dimethylcyclohex-2-en-1-ol: 119c

Yield: 467 mg, 67%; d.r. = ~ 1 : 1

IR υ_{max}(film): cm^{-1} 3320, 2935, 1430, 1254, 1107;

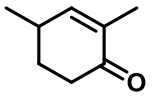
^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.54 - 7.50 (m, 2 H), 7.38 - 7.34 (m, 3 H), 4.04 (br. s, 0.45 H), 3.81 (br. s, 0.55 H), 2.47 - 2.42 (m, 1 H), 2.03 - 1.92 (m, 1 H), 1.89 - 1.78 (m, 2 H), 1.75 (d, *J* = 1.5 Hz, 1.6 H), 1.70 (s, 1.4 H), 1.56 – 1.51 (m, 0.45 H), 1.44 - 1.38 (m, 0.6 H), 1.06 (d, *J* = 6.9 Hz, 1.4 H), 0.99 (d, *J* = 6.9 Hz, 1.6 H), 0.42 (s, 4 H), 0.40 (s, 2 H);

HRMS calculated for $C_{16}H_{25}OSi$ $[M-H]^+$: 259.1518, found 259.1536.



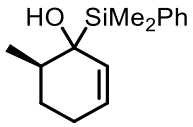
2,4-dimethylcyclohex-2-en-1-ol: 119d

Yield: 232 mg, 74%; d.r. = ~ 1 : 1; Check ref. 37 for known compound data.



2,4-dimethylcyclohex-2-en-1-one: 119e

Yield: 84 mg, 78%; Check Ref. 37 for known compound data.



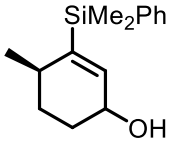
(6*R*)-1-(dimethyl(phenyl)silyl)-6-methylcyclohex-2-en-1-ol: 120b

Yield: 782 mg, 71%; d.r. = 7 : 3

IR υ_{max}(film): cm^{-1} 3438, 3398, 2955, 1427, 1254, 1114;

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.57 - 7.52 (m, 2 H), 7.32 - 7.27 (m, 3 H), 5.74 (ddd, *J* = 2.8, 4.7, 10.0 Hz, 0.7 H), 5.65 (m, 0.3 H), 5.58 (td, *J* = 2.0, 10.0 Hz, 0.7 H), 5.51 (m, 0.3 H), 2.00 - 1.91 (m, 1 H), 1.90 - 1.64 (m, 2 H), 1.38 (dtd, *J* = 3.1, 5.3, 13.4 Hz, 1 H), 1.32 - 1.15 (m, 1 H), 0.93 (d, *J* = 7.0 Hz, 1 H), 0.85 (d, *J* = 6.9 Hz, 2 H), 0.36 (d, *J* = 8.3 Hz, 2 H), 0.33 (d, *J* = 3.6 Hz, 4 H);

HRMS calculated for $C_{12}H_{17}OSiNa$ $[M+Na]^+$: 269.1332, found 269.1322.



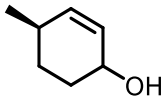
(4*R*)-3-(dimethyl(phenyl)silyl)-4-methylcyclohex-2-en-1-ol: 120c

Yield: 172 mg, 75%; d.r. = 3 : 2

IR υ_{max}(film): cm^{-1} 3356, 3060, 2946, 1428, 1254, 1111;

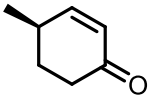
^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.53 - 7.50 (m, 2 H), 7.37 - 7.33 (m, 3 H), 6.08 - 6.07 (m, 0.4 H), 6.04 - 6.03 (m, 0.6 H), 4.20 - 4.13 (m, 1 H), 2.33 - 2.27 (m, 1 H), 2.04 - 1.97 (m, 0.5 H), 1.88 - 1.70 (m, 1.5 H), 1.70 - 1.61 (m, 1 H), 1.61 - 1.51 (m, 1 H), 1.51 - 1.43 (m, 0.6 H), 1.33 – 1.29 (m, 0.4 H), 0.97 (d, *J* = 7.1 Hz, 2 H), 0.89 (d, *J* = 7.1 Hz, 1 H), 0.42 - 0.37 (m, 6 H);

HRMS calculated for $C_{15}H_{22}OSiNa$ $[M+Na]^+$: 269.1332, found 269.1331.



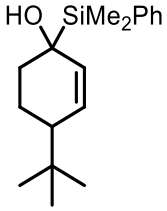
(4*R*)-4-methylcyclohex-2-en-1-ol: 120d

Yield: 128 mg, 71%; d.r. = ~ 2:1; Check ref. 38 for known compound data



(*R*)-4-methylcyclohex-2-en-1-one: 120e

Yield: 73 mg, 75%; Check ref. 39 for more details.



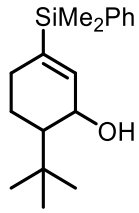
4-(tert-butyl)-1-(dimethyl(phenyl)silyl)cyclohex-2-en-1-ol: 121b

Yield: 766 mg, 81%

IR υ_{max}(film): cm^{-1} 3445, 2953, 1249, 1112;

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.64 - 7.59 (m, 2 H), 7.40 - 7.36 (m, 3 H), 5.94 - 5.88 (m, 1 H), 5.82 - 5.77 (m, 1 H), 1.84 - 1.79 (m, 1 H), 1.68 - 1.62 (m, 1 H), 1.61 - 1.58 (m, 1 H), 1.58 - 1.53 (m, 1 H), 1.40 - 1.33 (m, 1 H), 0.89 (s, 9 H), 0.36 (d, *J* = 5.1 Hz, 6 H);

HRMS calculated for $C_{18}H_{28}OSiNa$ $[M+Na]^+$: 311.1807, found 311.1834.



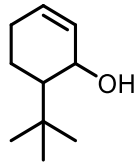
6-(tert-butyl)-3-(dimethyl(phenyl)silyl)cyclohex-2-en-1-ol: 121c

Yield: 426 mg, 85%; d.r. = 8.5:1.5

IR υ_{max}(film): cm^{-1} 3442, 2950, 1424, 1248, 1110;

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.48 - 7.45 (m, 2 H), 7.35 - 7.32 (m, 3 H), 6.16 (ddd, *J* = 1.3, 2.6, 5.3 Hz, 0.85 H), 5.90 (m, 0.15 H) 4.21 (br. s., 0.85 H), 4.16 (br. s., 0.15 H), 2.26 - 2.20 (m, 1 H), 1.92 (m, 1 H), 1.47 - 1.31 (m, 2 H), 1.13 - 1.09 (m, 1 H), 0.97 (s, 7.5 H), 0.96 (s, 1.5 H), 0.32 (s, 5 H), 0.31 (s, 1 H);

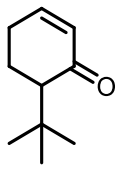
HRMS calculated for $C_{18}H_{28}OSiNa$ $[M+Na]^+$: 289.1982, found 289.1969.



6-(tert-butyl)cyclohex-2-en-1-ol: 121d

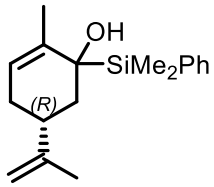
Yield: 142 mg, 89%; d.r. = 8.5:1.5; Check ref. 40 for known compound data.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.81 - 5.73 (m, 2 H), 3.97 (br. s., 0.85 H), 3.90 (br. s., 0.15 H), 1.79 - 1.73 (m, 1 H), 1.68 - 1.63 (m, 1 H), 1.54 - 1.48 (m, 1 H), 1.39 - 1.23 (m, 3 H), 0.77 (s, 8 H), 0.73 (s, 1 H);



6-(tert-butyl)cyclohex-2-en-1-one: 121e

Yield: 86 mg, 87%; Check ref. 37 for more details.



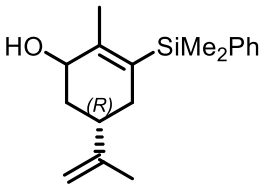
(5*R*)-1-(dimethyl(phenyl)silyl)-2-methyl-5-(prop-1-en-2-yl)cyclohex-2-en-1-ol: 40b

Yield: 1.85 g, 97%; d.r. = 6.5:3.5

IR υ_{max}(film): cm^{-1} 3463, 2959, 1657, 1436, 1253, 1113;

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.62 - 7.57 (m, 2 H), 7.40 - 7.34 (m, 3 H), 5.59 – 5.57 (m, 0.35 H), 5.40 (ddd, *J* = 1.6, 2.9, 4.2 Hz, 0.65 H), 4.73 - 4.71 (m, 0.6 H), 4.65 - 4.62 (m, 1.5 H), 2.28 - 2.21 (m, 1 H), 2.07 - 2.03 (m, 1 H), 1.97 - 1.93 (m, 2 H), 1.82 - 1.77 (m, 2 H), 1.71 (td, *J* = 1.7, 3.5 Hz, 3 H), 1.69 (s, 1 H), 1.58 (s, 2 H), 0.46 (s, 2 H), 0.41 - 0.40 (m, 4 H);

HRMS calculated for $C_{18}H_{25}OSi$ $[M+H]^+$: 285.1674, found 285.1681.



(5*R*)-3-(dimethyl(phenyl)silyl)-2-methyl-5-(prop-1-en-2-yl)cyclohex-2-en-1-ol: 40c

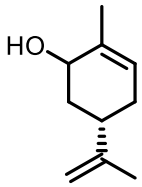
Yield: 1.6 g, 94%; d.r. = ~4:1

IR υ_{max}(film): cm^{-1} 2926, 1655, 1435, 1254, 1111;

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.54 - 7.50 (m, 2 H), 7.37 - 7.34 (m, 3 H), 4.77 - 4.74 (m, 2 H), 4.21 – 4.16 (m, 0.2 H), 3.99 (br. s., 0.8 H), 2.35 - 2.26 (m, 2 H), 1.99 - 1.93 (m,

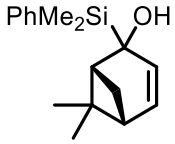
1 H), 1.92 - 1.84 (m, 1 H), 1.82 - 1.79 (m, 2.5 H), 1.76 (s, 3.5 H), 1.63 (dt, *J* = 4.1, 13.1 Hz, 1 H), 0.42 (s, 3 H), 0.41 (s, 3 H);

HRMS calculated for $C_{18}H_{26}OSiNa$ $[M+Na]^+$: 309.1645, found 309.1640.



(5*S*)-2-methyl-5-(prop-1-en-2-yl)cyclohex-2-en-1-ol: 40d

Yield: 255 mg, 80%; d.r. = 4:1; Check ref. 41 for known compound data.



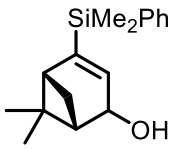
(1*R*,5*R*)-2-(dimethyl(phenyl)silyl)-6,6-dimethylbicyclo[3.1.1]hept-3-en-2-ol: 122b

Yield: 1.25 g, 78%

IR υ_{max}(film): cm^{-1} 3449, 3058, 2953, 1419, 1254, 1113;

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.56 - 7.53 (m, 2 H), 7.36 - 7.33 (m, 3 H), 6.28 - 6.24 (m, 1 H), 5.68 - 5.65 (m, 1 H), 2.33 - 2.25 (m, 2 H), 2.06 (q, *J* = 5.6 Hz, 1 H), 1.60 (s, 1 H), 1.35 (d, *J* = 8.8 Hz, 1 H), 1.28 (s, 3 H), 1.09 (s, 3 H), 0.36 (d, *J* = 9.0 Hz, 6 H)

HRMS calculated for $C_{17}H_{25}OSi$ $[M+H]^+$: 273.1669, found 273.1667.



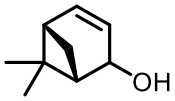
(1*S*,5*R*)-4-(dimethyl(phenyl)silyl)-6,6-dimethylbicyclo[3.1.1]hept-3-en-2-ol: 122c

Yield: 384 mg, 77%; d.r. = 9:1

IR υ_{max}(film): cm^{-1} 3327, 2919, 1593, 1462, 1250, 1109;

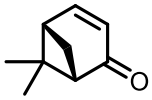
^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.50 - 7.47 (m, 2 H), 7.38 - 7.33 (m, 3 H),6.03 - 6.01 (m, 0.1 H) 6.00 - 5.95 (m, 0.9 H), 4.52 (t, *J* = 2.9 Hz, 0.1 H), 4.33 (t, *J* = 2.9 Hz, 0.9 H), 2.33 - 2.31 (m, 1 H), 2.29 - 2.23 (m, 1 H), 2.22 - 2.19 (m, 1 H), 1.30 (s, 3 H), 0.81 (s, 3 H), 0.33 (s, 3 H), 0.32 (s, 3 H);

HRMS calculated for $C_{17}H_{24}OSiNa$ $[M+Na]^+$: 295.1489, found 295.1487.



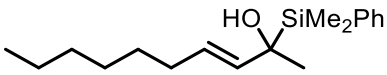
(1*S*,5*S*)-6,6-dimethylbicyclo[3.1.1]hept-3-en-2-ol: 122d

Yield: 144 mg, 81%; d.r. = 9:1; Check ref. 42 for known compound data.



(1*S*,5*S*)-6,6-dimethylbicyclo[3.1.1]hept-3-en-2-one: 122e

Yield: 79 mg, 80%; Check ref. 43 for more details.



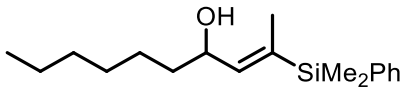
(*E*)-2-(dimethyl(phenyl)silyl)dec-3-en-2-ol: 123b

Yield: 760 mg, 80%

IR υ_{max}(film): cm^{-1} 3407, 2924, 1430, 1251, 1112;

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.54 - 7.52 (m, 2 H), 7.38 - 7.30 (m, 3 H), 5.51 (dt, *J* = 1.3, 15.5 Hz, 1 H), 5.32 (dt, *J* = 6.8, 15.5 Hz, 1 H), 2.03 - 1.97 (m, 2 H), 1.33 - 1.25 (m, 8 H), 1.22 (s, 3 H), 1.03 (s, 1 H), 0.89 - 0.85 (t, 3 H), 0.30 (d, *J* = 2.9 Hz, 6 H);

HRMS calculated for $C_{18}H_{30}OSiNa$ $[M+Na]^+$: 313.1958, found 313.1956.



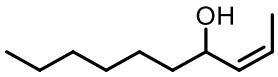
(*E*)-2-(dimethyl(phenyl)silyl)dec-2-en-4-ol: 123c

Yield: 460 mg, 92%; Z:E = ~1:9

IR υ_{max}(film): cm^{-1} 3353, 2932, 1435, 1253, 1113;

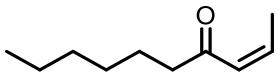
^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.45 - 7.41 (m, 2 H), 7.33 - 7.22 (m, 3 H), 5.95 – 5.92 (m, 0.1 H), 5.70 (qd, *J* = 1.7, 8.1 Hz, 0.9 H), 4.49 - 4.43 (m, 0.9 H), 4.00 – 3.95 (m, 0.1 H), 1.79 (d, *J* = 1.8 Hz, 0.4 H), 1.64 (d, *J* = 1.8 Hz, 2.6 H), 1.58 - 1.48 (m, 2 H), 1.42 - 1.31 (m, 1 H), 1.29 - 1.17 (m, 7 H), 0.83 - 0.79 (m, 3 H), 0.34 (d, *J* = 2.6 Hz, 0.8 H), 0.31 - 0.23 (m, 5.2 H);

HRMS calculated for $C_{18}H_{30}OSiNa$ $[M+Na]^+$: 313.1958, found 313.1959.



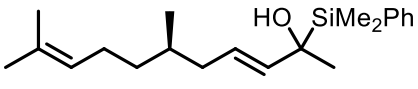
(*Z*)-dec-2-en-4-ol: 123d

Yield: 190 mg, 88%;Z:E = ~9:1



(*Z*)-dec-2-en-4-one: 123e

Yield: 93 mg, 86%; Check ref. 44 for more details.



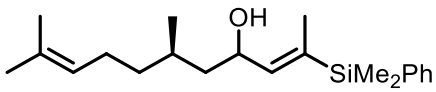
(6*R*,*E*)-2-(dimethyl(phenyl)silyl)-6,10-dimethylundeca-3,9-dien-2-ol: 124b

Yield: 710 mg, 84%

IR υ_{max}(film): cm^{-1} 3437, 3138, 2956, 1432, 1255, 1057;

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.59 - 7.56 (m, 2 H), 7.40 - 7.34 (m, 3 H), 5.54 (d, *J* = 15.5 Hz, 1 H), 5.39 - 5.32 (m, 1 H), 5.13 - 5.07 (m, 1 H), 2.08 - 1.80 (m, 4 H), 1.70 (s, 3 H), 1.62 (s, 3 H), 1.48 (dd, *J* = 6.8, 12.9 Hz, 1 H), 1.40 - 1.30 (m, 1 H), 1.26 (d, *J* = 1.8 Hz, 3 H), 1.18 - 1.11 (m, 1 H), 0.87 (dd, *J* = 2.0, 6.6 Hz, 3 H), 0.35 - 0.33 (m, 6 H);

HRMS calculated for $C_{21}H_{34}OSi$ $[M+Na]^+$: 353.2276, found 353.2275.



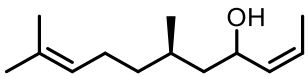
(6*R*,*E*)-2-(dimethyl(phenyl)silyl)-6,10-dimethylundeca-2,9-dien-4-ol: 124c

Yield: 596 mg, 92%

IR υ_{max}(film): cm^{-1} 3447, 2917, 1622, 1436, 1251, 1111;

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.54 - 7.48 (m, 2 H), 7.39 - 7.33 (m, 3 H), 5.81 - 5.73 (m, 1 H), 5.13 – 5.08 (m, 1 H), 4.68 - 4.64 (m, 1 H), 2.04 - 1.93 (m, 2 H), 1.74 - 1.72 (m, 3 H), 1.70 - 1.67 (m, 3 H), 1.61 (d, *J* = 3.5 Hz, 3 H), 1.49 - 1.42 (m, 1 H), 1.40 - 1.35 (m, 1 H), 1.23 - 1.16 (m, 2 H), 0.94 (dd, *J* = 6.4, 8.3 Hz, 3 H), 0.36 (d, *J* = 1.9 Hz, 6 H);

HRMS calculated for $C_{21}H_{34}OSi$ $[M+Na]^+$: 353.2276, found 353.2275.

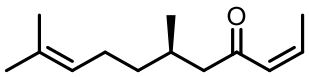


(6*R*,*Z*)-6,10-dimethylundeca-2,9-dien-4-ol: 124d

Yield: 265 mg, 88%

^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.60 - 5.50 (m, 1 H), 5.45 - 5.33 (m, 1 H), 5.10 (t, *J* = 7.1 Hz, 1 H), 4.61 - 4.55 (m, 1 H), 2.05 - 1.93 (m, 2 H), 1.73 - 1.66 (m, 6 H), 1.61 (s, 3 H), 1.40 - 1.30 (m, 2 H), 1.24 - 1.15 (m, 1 H), 0.96 - 0.91 (m, 3 H);

HRMS calculated for $C_{13}H_{24}ONa$ $[M+Na]^+$: 219.1725, found 219.1724.



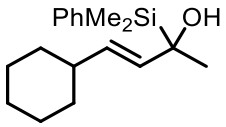
(*R*,*Z*)-6,10-dimethylundeca-2,9-dien-4-one: 124e

Yield: 110 mg, 74%

$[\alpha]_D^{23}$ = –3.98 (*c* = 0.21, $CHCl_3$);

^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.17 - 6.07 (m, 2 H), 5.06 (tdt, *J* = 1.3, 2.8, 7.1 Hz, 1 H), 2.41 (dd, *J* = 5.7, 15.3 Hz, 1 H), 2.20 (dd, *J* = 8.2, 15.3 Hz, 1 H), 2.11 - 2.04 (m, 3 H), 2.03 - 1.89 (m, 3 H), 1.65 (d, *J* = 1.1 Hz, 3 H), 1.56 (s, 3 H), 1.34 - 1.26 (m, 1 H), 1.20 - 1.14 (m, 1 H), 0.88 (d, *J* = 6.6 Hz, 3 H);

HRMS calculated for $C_{13}H_{23}O$ $[M+H]^+$: 195.1749, found 195.1748.



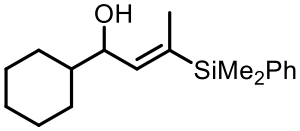
(*E*)-4-cyclohexyl-2-(dimethyl(phenyl)silyl)but-3-en-2-ol: 125b

Yield: 710mg, 86%

IR υ_{max}(film): cm^{-1} 3406, 2925, 1626, 1436, 1254, 1116;

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.57 - 7.52 (m, 2 H), 7.41 - 7.33 (m, 3 H), 5.52 - 5.48 (m, 1 H), 5.29 (dd, *J* = 6.8, 15.7 Hz, 1 H), 1.95 (tdd, *J* = 3.5, 7.2, 10.8 Hz, 1 H), 1.76 - 1.62 (m, 5 H), 1.33 - 1.28 (m, 1 H), 1.25 (s, 3 H), 1.21 - 1.12 (m, 1 H), 1.11 - 1.00 (m, 3 H), 0.33 (d, *J* = 2.6 Hz, 6 H);

HRMS calculated for $C_{18}H_{28}OSiNa$ $[M+Na]^+$: 311.1807, found 311.1816.



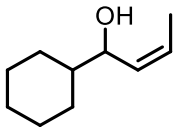
(*E*)-1-cyclohexyl-3-(dimethyl(phenyl)silyl)but-2-en-1-ol: 125c

Yield: 574 mg, 89%

IR υ_{max}(film): cm^{-1} 3431, 2922, 1438, 1251, 1110;

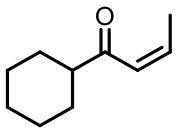
^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.50 - 7.46 (m, 2 H), 7.34 - 7.31 (m, 3 H), 5.75 (dq, *J* = 1.7, 8.5 Hz, 1 H), 4.23 (t, *J* = 7.8 Hz, 1 H), 1.92 - 1.87 (m, 1 H), 1.76 - 1.71 (m, 2 H), 1.68 – 1.67 (d, *J* = 1.6 Hz, 3 H), 1.63 (br. s., 1 H), 1.42 - 1.32 (m, 2 H), 1.27 - 1.06 (m, 4 H), 0.99 - 0.85 (m, 2 H), 0.33 (d, *J* = 1.5 Hz, 6 H);

HRMS calculated for $C_{18}H_{29}OSi$ $[M+H]^+$: 289.1988, found 289.1987.



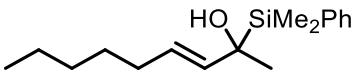
(*Z*)-1-cyclohexylbut-2-en-1-ol: 125d

Yield: 174 mg, 72%; Z:E = ~9:1; Check ref. 45 for known compound data.



(*Z*)-1-cyclohexylbut-2-en-1-one: 125e

Yield: 78 mg, 79%



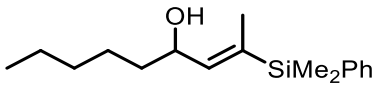
(*E*)-2-(dimethyl(phenyl)silyl)non-3-en-2-ol: 126b

Yield: 902 mg, 92%

IR υ_{max}(film): cm^{-1} 3448, 2925, 1440, 1251, 1110;

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.60 - 7.57 (m, 2 H), 7.43 - 7.35 (m, 3 H), 5.56 (td, *J* = 1.3, 15.5 Hz, 1 H), 5.37 (td, *J* = 6.8, 15.5 Hz, 1 H), 2.08 - 2.02 (m, 2 H), 1.41 - 1.28 (m, 6 H), 1.27 (s, 3 H), 1.09 (s, 1 H), 0.92 (t, *J* = 6.9 Hz, 3 H), 0.36 (d, *J* = 2.9 Hz, 6 H);

HRMS calculated for $C_{17}H_{29}OSi$ $[M+H]^+$: 277.1982, found 277.1980.



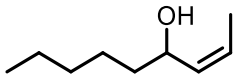
(*Z*)-2-(dimethyl(phenyl)silyl)non-2-en-4-ol: 126c

Yield: 523 mg, 65%; Z:E = ~1:9.

IR υ_{max}(film): cm^{-1} 3350, 2932, 1426, 1251, 1112;

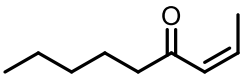
^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.52 - 7.49 (m, 2 H), 7.41 - 7.34 (m, 3 H), 5.79 (qd, *J* = 1.7, 8.1 Hz, 1 H), 4.57 - 4.54 (m, 1 H), 1.73 (d, *J* = 1.6 Hz, 3 H), 1.64 - 1.57 (m, 1 H), 1.49 - 1.42 (m, 2 H), 1.35 - 1.29 (m, 5 H), 0.92 - 0.89 (m, 3 H), 0.37 (d, *J* = 2.3 Hz, 6 H);

HRMS calculated for $C_{17}H_{28}OSiNa[M+N]^+$: 299.1802, found 299.1799.



(*Z*)-non-2-en-4-ol: 126d

Yield: 194 mg, 88%; Z:E = ~9:1; Check ref. 46 for more details.



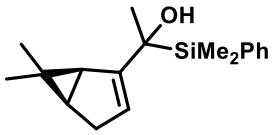
(*Z*)-non-2-en-4-one: 126e

Yield: 96 mg, 81%;Z:E = ~9:1.

IR υ_{max}(film): cm^{-1} 2925, 2855, 1702, 1451, 1255;

^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.89 – 6.80 (m, 0.2 H), 6.21 - 6.10 (m, 1.8 H), 2.53 - 2.42 (m, 2 H), 2.12 - 2.10 (m, 2.6 H), 1.90 (dd, *J* = 1.7, 6.8 Hz, 0.4 H), 1.64 - 1.59 (m, 1 H), 1.37 - 1.27 (m, 5 H), 0.91 - 0.88 (m, 3 H);

LCMS calculated for $C_9H_{17}O[M+H]^+$: 141.1, found 141.1.



1-(dimethyl(phenyl)silyl)-1-((1*S*,5*R*)-6,6-dimethylbicyclo[3.1.0]hex-2-en-2-yl)ethan-1-ol: 127b

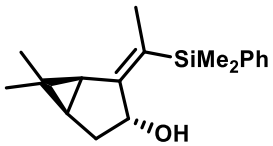
Yield: 1.15 g, 77%

IR υ_{max}(film): cm^{-1} 3447, 2954, 1667, 1427, 1251, 1111;

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.62 - 7.60 (m, 2 H), 7.37 - 7.33 (m, 3 H), 5.08 (dd, *J* = 0.8, 1.3 Hz, 1 H), 2.42 (ddd, *J* = 2.3, 7.9, 18.0 Hz, 1 H), 2.11 - 2.04 (m, 1 H), 1.52 (dd, *J* = 3.0, 6.6 Hz, 1 H), 1.32 (s, 3 H), 1.30 - 1.26 (m, 1 H), 0.98 (s, 3 H), 0.78 (s, 3 H), 0.38 (s, 3 H), 0.35 (s, 3 H);

^{13}C NMR (100 MHz, $CDCl_3$) δ = 150.6, 136.8, 134.7, 129.1, 127.5, 120.9, 69.2, 58.2, 37.9, 32.0, 29.2, 26.2, 25.3, 19.4, 13.5, -5.2, -5.3;

HRMS calculated for $C_{18}H_{26}OSiNa$ $[M+Na]^+$: 309.1645, found 309.1644.



(1*S*,3*R*,5*R*,*Z*)-2-(1-(dimethyl(phenyl)silyl)ethylidene)-6,6-dimethylbicyclo[3.1.0]hexan-3-ol : 127c

Yield: 260 mg, 26%

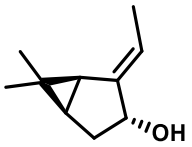
$[\alpha]_D^{30}$ = – 5.66 (*c* = 0.2, $CHCl_3$);

IR υ_{max}(film): cm^{-1} 3419, 2925, 1457, 1255, 1051;

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.57 - 7.54 (m, 2 H), 7.38 - 7.35 (m, 3 H), 4.25 (d, *J* = 5.0 Hz, 1 H), 1.87 (d, *J* = 6.9 Hz, 1 H), 1.83 (s, 3 H), 1.77 - 1.67 (m, 2 H), 1.51 - 1.45 (m, 1 H), 1.11 (s, 3 H), 0.76 (s, 3 H), 0.43 (s, 6 H);

^{13}C NMR (100 MHz, $CDCl_3$) δ = 157.5, 140.0, 133.6, 130.2, 129.1, 128.1, 79.2, 35.5, 33.8, 30.2, 27.0, 24.2, 20.5, 15.5, -1.0, -1.6.

HRMS calculated for $C_{18}H_{26}OSiNa$ $[M+Na]^+$: 309.1645, found 309.1641.



(1*S*,3*R*,5*R*,*E*)-2-ethylidene-6,6-dimethylbicyclo[3.1.0]hexan-3-ol: 127d

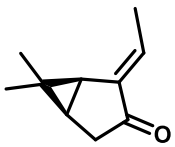
Yield: 94 mg, 85%

$[\alpha]_D^{30}$ = –219.98 (*c* = 0.18, $CHCl_3$);

IR υ_{max}(film): cm^{-1} 3522, 2959, 1258, 1019;

^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.67 - 5.62 (m, 1 H), 4.25 - 4.24 (m, 1 H), 2.02 (ddd, *J* = 1.4, 6.7, 14.7 Hz, 1 H), 1.85 - 1.79 (m, 1 H), 1.79 - 1.75 (m, 1 H), 1.72 (td, *J* = 0.8, 6.7 Hz,

HRMS calculated for $C_{10}H_{17}O$ $[M+H]^+$: 153.1274, found 153.1274.



(1*S*,5*R*,*E*)-2-ethylidene-6,6-dimethylbicyclo[3.1.0]hexan-3-one: 127e

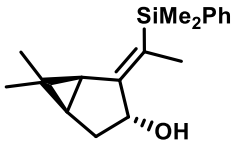
Yield: 42 mg, 65%

$[\alpha]_D^{31}$ = –72.71 (*c* = 0.72, $CHCl_3$);

IR υ_{max}(film): cm^{-1} 2922, 1729, 1643, 1455;

^{1}H NMR (500 MHz, $CDCl_3$) δ = 6.60 (dq, *J* = 1.3, 7.2 Hz, 1 H), 2.57 (dd, *J* = 7.1, 19.6 Hz, 1 H), 2.32 - 2.28 (m, 1 H), 1.93 (d, *J* = 7.6 Hz, 1 H), 1.89 (d, *J* = 7.2 Hz, 3 H), 1.50 (t, *J* = 7.1 Hz, 1 H), 1.18 (s, 3 H), 0.83 (s, 3 H);

HRMS calculated for $C_{10}H_{15}O$ $[M+H]^+$: 151.1117, found 151.1118.



(1*S*,3*R*,5*R*,*E*)-2-(1-(dimethyl(phenyl)silyl)ethylidene)-6,6-dimethylbicyclo[3.1.0]hexan-3-ol: 127f

Yield: 210 mg, 21%

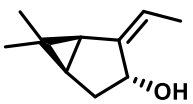
$[\alpha]_D^{30}$ = –53.97 (*c* = 0.26, $CHCl_3$);

IR υ_{max}(film): cm^{-1} 3411, 2948, 1428, 1252, 1049;

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.55 - 7.52 (m, 2 H), 7.37 - 7.34 (m, 3 H), 4.63 (dd, *J* = 1.4, 6.1 Hz, 1 H), 2.01 - 1.92 (m, 1 H), 1.90 (d, *J* = 0.6 Hz, 3 H), 1.88 - 1.83 (m, 1 H), 1.67 (d, *J* = 6.8 Hz, 1 H), 1.46 (dt, *J* = 1.9, 6.9 Hz, 1 H), 0.88 (s, 3 H), 0.69 (s, 3 H), 0.43 - 0.41 (m, 6 H);

^{13}C NMR (100 MHz, $CDCl_3$) δ = 156.7, 139.4, 133.8, 133.0, 130.0, 128.8, 127.8, 78.3, 35.9, 34.3, 31.4, 26.2, 23.4, 18.9, 16.1, -1.4, -1.7;

HRMS calculated for $C_{18}H_{26}OSiNa$ $[M+Na]^+$: 309.1645, found 309.1644.



(1*S*,3*R*,5*R*,*Z*)-2-ethylidene-6,6-dimethylbicyclo[3.1.0]hexan-3-ol: 127g

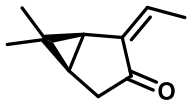
Yield: 71 mg, 75%

$[\alpha]_D^{31}$ = –76.40 (*c* = 0.12, $CHCl_3$);

IR υ_{max}(film): cm^{-1} 33372, 2927, 1456, 1018;

^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.55 (tq, *J* = 1.3, 7.0 Hz, 1 H), 4.53 (br. s., 1 H), 2.07 (ddd, *J* = 1.4, 6.7, 15.1 Hz, 1 H), 1.89 (ddd, *J* = 2.4, 7.1, 15.1 Hz, 1 H), 1.78 (td, *J* = 0.8, 7.0 Hz, 3 H), 1.74 (d, *J* = 6.6 Hz, 1 H), 1.44 - 1.40 (m, 1 H), 1.00 (s, 3 H), 0.75 (s, 3 H);

LCMS calculated for $C_{10}H_{17}O$ $[M+H]^+$: 153.1, found 153.0.



(1*S*,5*R*,*Z*)-2-ethylidene-6,6-dimethylbicyclo[3.1.0]hexan-3-one: 127h

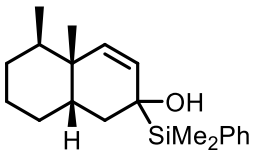
Yield: 31 mg, 70%

$[\alpha]_D^{31}$ = –64.72 (*c* = 0.15, $CHCl_3$);

IR υ_{max}(film): cm^{-1} 2924, 1721, 1640, 1020;

^{1}H NMR (500 MHz, $CDCl_3$) δ = 6.12 (q, *J* = 7.2 Hz, 1 H), 2.59 (dd, *J* = 6.9, 19.8 Hz, 1 H), 2.32 (d, *J* = 19.5 Hz, 1 H), 2.14 (d, *J* = 7.2 Hz, 3 H), 1.87 (d, *J* = 7.2 Hz, 1 H), 1.42 (t, *J* = 7.1 Hz, 1 H), 1.11 (s, 3 H), 0.89 (s, 3 H);

LCMS calculated for $C_{10}H_{15}O$ $[M+H]^+$: 151.1, found 151.1.



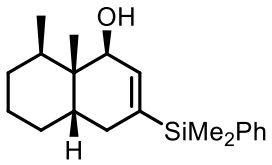
(4a*S*,5*R*,8a*S*)-2-(dimethyl(phenyl)silyl)-4a,5-dimethyl-1,2,4a,5,6,7,8,8a-octahydronaphthalen-2-ol: 128b

Yield: 565 mg, 80%; d.r. = 7:3;

IR υ_{max}(film): cm^{-1} 2929, 1675, 1253, 1053;

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.59 - 7.57 (m, 2 H), 7.40 - 7.35 (m, 3 H), 5.80 – 5.77 (d, *J* = 10.1 Hz, 0.3 H), 5.70 - 5.63 (m, 1 H), 5.50 (d, *J* = 10.1 Hz, 0.7 H), 2.13 – 2.06 (m, 0.3 H), 1.96 - 1.87 (m, 0.7 H), 1.75 - 1.62 (m, 2 H), 1.45 - 1.32 (m, 3 H), 1.31 - 1.19 (m, 2 H), 1.19 - 1.13 (m, 2 H), 0.94 (s, 0.8 H), 0.81 (d, *J* = 6.8 Hz, 2.2 H), 0.78 (s, 2.2 H), 0.75 (d, *J* = 6.1 Hz, 0.8 H), 0.43 - 0.40 (m, 2.2 H), 0.40 - 0.36 (m, 3.8 H);

HRMS calculated for $C_{20}H_{30}OSi$ $[M]^+$: 314.2065, found 314.2065.



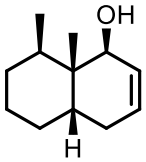
(4a*S*,8*R*,8a*S*)-3-(dimethyl(phenyl)silyl)-8,8a-dimethyl-1,4,4a,5,6,7,8,8a-octahydronaphthalen-1-ol: 128c

Yield: 337 mg, 84%

IR υ_{max}(film): cm^{-1} 3421, 2917, 1250, 1049;

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.60 - 7.43 (m, 2 H), 7.43 - 7.29 (m, 3 H), 6.03 - 5.87 (m, 1 H), 4.43 (br. s., 1 H), 2.27 - 2.15 (m, 1 H), 1.93 (dd, *J* = 3.4, 6.8 Hz, 1 H), 1.85 - 1.69 (m, 3 H), 1.56 - 1.42 (m, 2 H), 1.38 - 1.23 (m, 5 H), 0.93 (d, *J* = 7.1 Hz, 3 H), 0.86 (s, 3 H), 0.37 - 0.32 (m, 6 H);

HRMS calculated for $C_{20}H_{30}OSi$ $[M+Na]^+$: 337.1963, found 337.1962.



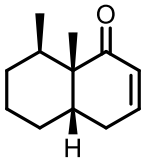
(4a*S*,8*R*,8a*S*)-8,8a-dimethyl-1,4,4a,5,6,7,8,8a-octahydronaphthalen-1-ol: 128d

Yield: 92 mg, 75%

IR υ_{max}(film): cm^{-1} 3414, 2920, 2943, 1661, 1460, 1047;

^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.67 - 5.65 (m, 1 H), 5.59 – 5.56 (d, *J* = 9.6 Hz, 1 H), 4.31 (s, 1 H), 2.18 (d, *J* = 16.9 Hz, 1 H), 1.85 (br. s., 1 H), 1.75 - 1.73 (d, 3 H), 1.58 (s, 3 H), 1.47 - 1.46 (m, 2 H), 1.17 (s, 1 H), 0.88 - 0.82 (m, 6 H)

HRMS calculated for $C_{12}H_{19}O$ $[M-H]^+$: 179.1436, found 179.1431.



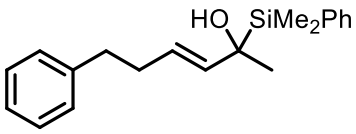
(4a*S*,8*R*,8a*S*)-8,8a-dimethyl-4a,5,6,7,8,8a-hexahydronaphthalen-1(4H)-one: 128e

Yield: 62 mg, 78%

IR υ_{max}(film): cm^{-1} 2952, 2859, 1726, 1460, 1161;

^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.76 – 6.71 (td, *J* = 4.0, 10.1 Hz, 1 H), 5.88 (td, *J* = 2.1, 10.1 Hz, 1 H), 2.41 - 2.28 (m, 2 H), 2.12 (dd, *J* = 5.9, 10.4 Hz, 1 H), 2.07 - 2.02 (m, 1 H), 1.55 - 1.44 (m, 3 H), 1.43 - 1.33 (m, 2 H), 1.29 (m, *J* = 6.4, 13.2 Hz, 1 H), 1.05 (s, 3 H), 0.77 (d, *J* = 7.1 Hz, 3 H);

HRMS calculated for $C_{12}H_{18}O$ $[M+H]^+$: 179.1435, found 179.1435.



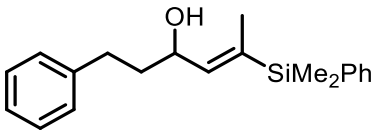
(*E*)-2-(dimethyl(phenyl)silyl)-6-phenylhex-3-en-2-ol: 129b

Yield: 640 mg, 72%

IR υ_{max}(film): cm^{-1} 3341, 3027, 2953, 1437, 1253, 1114;

^{1}H NMR (400 MHz, $CDCl_3$) δ = 0.26 – 0.27 (d, *J* = 5.63 Hz, 6 H), 1.20 (s, 3 H), 2.32 – 2.37 (m, 2 H), 2.65 (t, *J* = 7.69 Hz, 2 H), 5.36 (dt, *J* =15.51, 1 H), 5.53 (dt, *J* = 15.57, 1 H), 7.15 (m, 3 H), 7.25 (m, 2 H), 7.34 (m, 3 H), 7.48 (m, 2 H);

HRMS calculated for $C_{20}H_{26}OSiNa$ $[M+Na]^+$: 333.1645, found 333.1648.



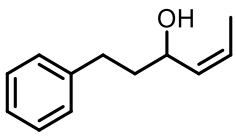
(*E*)-5-(dimethyl(phenyl)silyl)-1-phenylhex-4-en-3-ol: 129c

Yield: 510 mg, 91%

IR υ_{max}(film): cm^{-1} 3337, 3024, 2948, 1607, 1430, 1251;

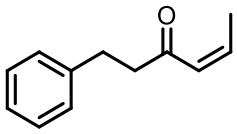
^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.55 - 7.53 (m, 2 H), 7.41 - 7.38 (m, 3 H), 7.34 - 7.31 (m, 2 H), 7.25 - 7.21 (m, 3 H), 5.86 (qd, *J* = 1.7, 8.1 Hz, 1 H), 4.63 - 4.57 (q, 1 H), 2.82 - 2.66 (m, 2 H), 2.02 - 1.91 (m, 1 H), 1.89 - 1.77 (m, 1 H), 1.72 (d, *J* = 1.6 Hz, 3 H), 1.58 (br. s., 1 H), 0.40 (s, 6 H);

HRMS calculated for $C_{20}H_{27}OSi$ $[M+H]^+$: 311.1831, found 311.1818.



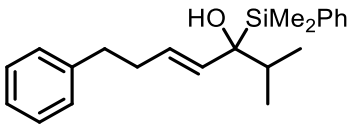
(*Z*)-1-phenylhex-4-en-3-ol: 129d

Yield: 179 mg, 79%; Z:E = ~9.5:0.5; Check ref. 47 for known compound data.



(*Z*)-1-phenylhex-4-en-3-one: 129e

Yield: 69 mg, 78%;Check ref. 48 for known compound data.



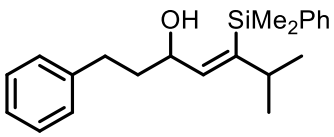
(*E*)-3-(dimethyl(phenyl)silyl)-2-methyl-7-phenylhept-4-en-3-ol: 130b

Yield: 829 mg, 99%

IR υ_{max}(film): cm^{-1} 3412, 2955, 1441, 1252, 1054;

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.61 - 7.50 (m, 2 H), 7.36 - 7.25 (m, 5 H), 7.19 - 7.15 (m, 3 H), 5.58 (td, *J* = 1.3, 15.5 Hz, 1 H), 5.37 (td, *J* = 6.7, 15.5 Hz, 1 H), 2.70 - 2.66 (m, 2 H), 2.45 - 2.39 (m, 2 H), 1.86 - 1.80 (m, 1 H), 0.76 (d, *J* = 6.6 Hz, 3 H), 0.78 (d, *J* = 6.8 Hz, 3 H), 0.31 (d, *J* = 3.8 Hz, 6 H);

HRMS calculated for $C_{22}H_{29}OSi$ $[M-H]^+$: 337.1987, found 337.1986.



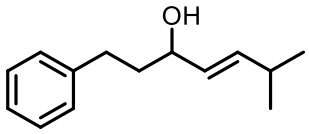
(*Z*)-5-(dimethyl(phenyl)silyl)-6-methyl-1-phenylhept-4-en-3-ol: 130c

Yield: 709 mg, 96%

IR υ_{max}(film): cm^{-1} 3457, 2924, 1453, 1254, 1040;

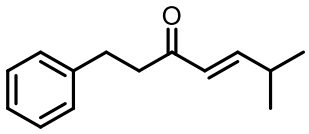
^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.46 - 7.40 (m, 2 H), 7.35 - 7.30 (m, 3 H), 7.24 - 7.12 (m, 3 H), 7.05 - 7.03 (m, 2 H), 6.03 - 5.97 (m, 1 H), 4.05 (dt, *J* = 4.6, 8.8 Hz, 1 H), 2.55 - 2.43 (m, 2 H), 2.35 (ddd, *J* = 6.9, 9.7, 13.7 Hz, 1 H), 1.71 (dddd, *J* = 5.1, 8.3, 9.8, 13.4 Hz, 1 H), 1.52 - 1.46 (m, 1 H), 1.05 (d, *J* = 6.8 Hz, 3 H), 1.00 (d, *J* = 6.9 Hz, 3 H), 0.34 (s, 3 H), 0.26 (s, 3 H);

HRMS calculated for $C_{22}H_{30}OSiNa$ $[M+Na]^+$: 361.1963, found 361.1966.



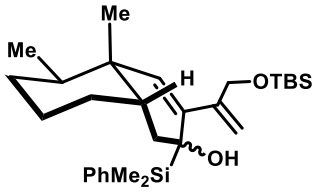
(*E*)-6-methyl-1-phenylhept-4-en-3-ol: 130d

Yield: 312 mg, 82%; Check ref. 49 for known compound data.



(*E*)-6-methyl-1-phenylhept-4-en-3-one: 130e

Yield: 186 mg, 86%; Check ref. 50 for known compound data.



(4a*S*,5*R*,8a*S*)-3-(3-((tert-butyldimethylsilyl)oxy)prop-1-en-2-yl)-2-(dimethyl(phenyl)silyl)-4a,5-dimethyl-1,2,4a,5,6,7,8,8a-octahydronaphthalen-2-ol: 132

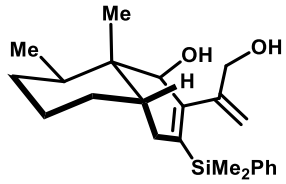
Compound **132**(141 mg, 85%) was obtained (as a pale-yellow oil) by following the general procedure 2.1.6.2.

IR υ_{max}(film): cm^{-1} 3430, 3365, 2926, 1669, 1447, 1114;

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.60 - 7.55 (m, 2 H), 7.37 - 7.32 (m, 3 H), 5.67 – 5.60 (m, 1 H), 5.04 – 4.82 (m, 2 H), 4.45 (d, *J* = 13.3 Hz, 1 H), 4.16 (d, *J* = 13.4 Hz, 1 H), 3.53 (s, 1 H), 2.03 - 1.90 (m, 1 H), 1.74 (ddd, *J* = 3.0, 6.9, 11.8 Hz, 1 H), 1.53 (dt, *J* = 2.9, 6.9 Hz, 1 H), 1.40 - 1.29 (m, 3 H), 1.19 - 1.08 (m, 1 H), 0.93 - 0.88 (m, 9 H), 0.87 - 0.78 (m, 6 H), 0.42 - 0.32 (m, 6 H), 0.09 - 0.00 (m, 6 H);

^{13}C NMR (100 MHz, $CDCl_3$) δ = 153.4, 152.4, 143.1, 140.5, 139.5, 138.5, 137.9, 134.9, 134.6, 133.0, 128.9, 128.8, 127.7, 127.4, 127.2, 112.7, 112.2, 71.2, 67.5, 67.0, 65.9, 39.8, 37.8, 37.6, 36.8, 36.3, 34.8, 34.7, 33.6, 31.6, 31.4, 30.5, 28.2, 27.2, 25.8, 22.6, 21.4, 21.4, 20.1, 20.0, 18.2, 18.1, 16.4, 16.1, 14.1, -2.9, -3.6, -4.4, -4.5, -5.1, -5.2, -5.4, -5.5;

HRMS calculated for $C_{29}H_{49}O_2Si_2$ $[M+H]^+$: 485.3266, found 485.3256.



(1*R*,4a*S*,8*R*,8a*S*)-3-(dimethyl(phenyl)silyl)-2-(3-hydroxyprop-1-en-2-yl)-8,8a-dimethyl-1,4,4a,5,6,7,8,8a-octahydronaphthalen-1-ol: 133

Compound **133** (32 mg, 38%) was obtained by following the general procedure 2.1.6.3.

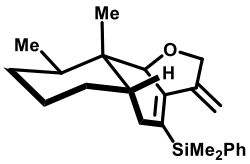
$[\alpha]_D^{23}$ = –1.11 (*c* = 0.23, $CHCl_3$);

IR υ_{max}(film): cm^{-1} 3360, 2922, 1427, 1250, 1051;

^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.51 - 7.45 (m, 2 H), 7.37 - 7.32 (m, 3 H), 5.03 (m, 1 H), 4.87 (s, 1 H), 4.04 (br. s., 1 H), 3.95 (d, *J* = 13.7 Hz, 1 H), 3.82 (d, *J* = 13.7 Hz, 1 H), 2.27 - 2.21 (m, 1 H), 2.13 - 2.05 (m, 1 H), 1.88 - 1.82 (m, 1 H), 1.74 - 1.66 (m, 1 H), 1.54 - 1.49 (m, 2 H), 1.36 - 1.28 (m, 2 H), 0.95 (s, 3 H), 0.81 (d, *J* = 6.9 Hz, 4 H), 0.38 (d, *J* = 2.3 Hz, 6 H);

^{13}C NMR (125 MHz, $CDCl_3$) δ = 151.0, 148.6, 139.8, 134.0, 128.9, 127.6, 114.8, 72.4, 66.0, 38.1, 32.5, 31.2, 29.7, 29.4, 20.2, 17.4, 15.1, 0.0, -0.8;

HRMS calculated for $C_{23}H_{34}O_2SiNa$ $[M+Na]^+$: 393.2220, found 393.2214.



((5a*S*,9*R*,9a*S*,9b*R*)-9,9a-dimethyl-3-methylene-2,3,5,5a,6,7,8,9,9a,9b-decahydronaphtho[1,2-b]furan-4-yl)dimethyl(phenyl)silane: 134

Compound **134** (22 mg, 27%) was obtained by following the general procedure 2.1.6.3.

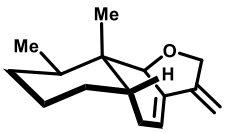
$[\alpha]_D^{31}$ = –27.64 (*c* = 0.1, $CHCl_3$);

IR υ_{max}(film): cm^{-1} 2922, 1646, 1544, 1084;

^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.51 - 7.48 (m, 2 H), 7.35 - 7.33 (m, 3 H), 4.93 (s, 1 H), 4.78 (s, 1 H), 4.58 (br. s., 1 H), 4.37 - 4.34 (m, 1 H), 4.28 (td, *J* = 2.3, 12.6 Hz, 1 H), 2.59 - 2.52 (m, 1 H), 2.41 - 2.37 (m, 1 H), 2.04 - 1.95 (m, 2 H), 1.78 - 1.74 (m, 2 H), 1.46 - 1.39 (m, 4 H), 1.01 (d, *J* = 6.9 Hz, 3 H), 0.81 (s, 3 H), 0.44 (s, 3 H), 0.38 (s, 3 H);

^{13}C NMR (100 MHz, $CDCl_3$) δ = 145.0, 139.0, 133.6, 130.2, 128.8, 127.9, 127.6, 127.1, 125.9, 107.4, 80.3, 70.9, 46.0, 37.3, 37.1, 35.3, 33.1, 29.7, 28.6, 20.6, 18.7, 14.4, -1.1, -2.7;

HRMS calculated for $C_{23}H_{33}OSi$ $[M+H]^+$: 353.2295, found 353.2292.



(5a*S*,9*R*,9a*S*,9b*R*)-9,9a-dimethyl-3-methylene-2,3,5,5a,6,7,8,9,9a,9b-decahydronaphtho[1,2-b]furan: 135

Compound **135** (9.6 mg, 71%) was obtained by following the general procedure 2.1.6.4.

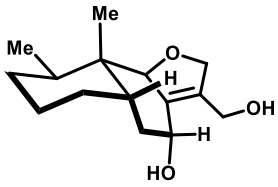
IR υ_{max}(film): cm^{-1} 3566, 2923, 1651, 1458, 1021;

$[\alpha]_D^{30}$ = - 9.78 (*c* = 0.13, $CHCl_3$);

^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.94 - 5.91 (m, 1 H), 5.27 (s, 1 H), 4.83 (s, 1 H), 4.59 - 4.57 (m, 1 H), 4.44 (td, *J* = 1.9, 12.9 Hz, 1 H), 4.32 (td, *J* = 2.6, 12.9 Hz, 1 H), 2.49 - 2.40 (m, 1 H), 2.07 - 1.95 (m, 2 H), 1.84 - 1.74 (m, 2 H), 1.54 - 1.48 (m, 2 H), 1.40 - 1.31 (m, 3 H), 1.01 (d, *J* = 7.4 Hz, 3 H), 0.76 (s, 3 H);

^{13}C NMR (100 MHz, $CDCl_3$) δ = 145.3, 135.2, 116.5, 99.7, 79.2, 71.0, 38.0, 35.0, 33.2, 31.1, 30.1, 28.7, 20.6, 18.4, 14.6;

HRMS calculated for $C_{15}H_{23}O_2$ $[M+H]^+$: 219.1749, found 219.1744.



(4*R*,5a*S*,9*R*,9a*S*,9b*R*)-3-(hydroxymethyl)-9,9a-dimethyl-2,4,5,5a,6,7,8,9,9a,9b-decahydronaphtho[1,2-b]furan-4-ol: 26

Compound **135** (3.2 mg) was taken in EtOH (2 mL) and Rose Bengal (0.2 mg) was added to it. The flask was fitted with a small condenser and a steady stream of oxygen bubbles was introduced using oxygen balloon and a needle. Then the reaction mixture was irradiated with a 200 Watt tungsten lamp for 3 hours. The consumption of starting material was monitored by TLC. After complete consumption of starting material, reaction was cooled to 0 ^oC and bubbled with nitrogen gas for two minutes to expel out the dissolved oxygen from the reaction mixture.

To this crude reaction mixture $NaBH_4$ (15 mg) was added portion wise. After complete consumption of starting material the reaction mixture was quenched with saturated NH_4Cl (3 mL) and extracted with EtOAc (3 X 5 mL). The combined organic layer was washed with brine (5 mL) and dried over sodium sulphate. The solvent was evaporated and the

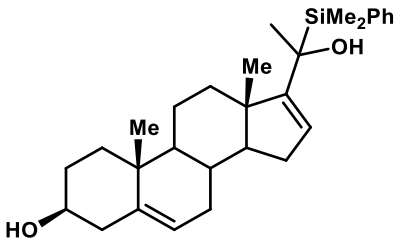
crude compound was purified by column chromatography (silica gel) to give peribysin D (2.3 mg, 64 %).

$[\alpha]_D^{23}$ = – 1.89 (*c* = 0.1, EtOH);

^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.39 (dd, *J* = 4.1, 5.1 Hz, 1 H), 4.79 (m, 1 H), 4.73 (dd, *J* = 3.9, 12.4 Hz, 1 H), 4.60 (dd, *J* = 6.0, 12.4 Hz, 1 H), 4.38 (d, *J* = 12.6 Hz, 1 H), 4.29 (d, *J* = 12.6 Hz, 1 H), 1.95 - 1.91 (m, 1 H), 1.89 (d, *J* = 4.8 Hz, 1 H), 1.88 - 1.83 (m, 1 H), 1.76 - 1.70 (m, 1 H), 1.66 (m, 1 H), 1.63 - 1.57 (m, 1 H), 1.48 (m, 1 H), 1.47 - 1.45 (m, 1 H), 1.44 - 1.41 (m, 1 H), 1.36 - 1.32 (m, 1 H), 0.95 (d, *J* = 7.4 Hz, 4 H), 0.72 (s, 3 H);

^{13}C NMR (100 MHz, $CDCl_3$) δ = 136.5, 133.2, 85.9, 76.3, 64.1, 56.4, 42.3, 37.2, 34.7, 33.5, 30.3, 28.9, 21.02, 17.8, 15.2;

HRMS calculated for $C_{15}H_{24}O_3Na$ $[M+Na]^+$: 275.1618, found 275.1617.



(3*S*,10*R*,13*S*)-17-(1-(dimethyl(phenyl)silyl)-1-hydroxyethyl)-10,13-dimethyl-2,3,4,7,8,9,10,11,12,13,14,15-dodecahydro-1H-cyclopenta[a]phenanthren-3-ol: 137

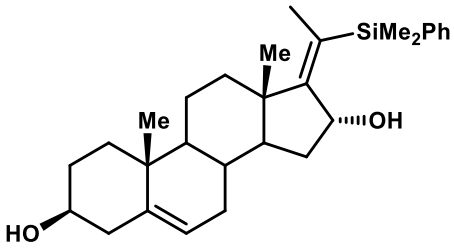
Compound **137** (520 mg, 73%) was obtained by following the general procedure 2.1.6.2. ($PhMe_2SiLi$ reagent was required in 2.5 equivalent for this substrate).

IR υ_{max}(film): cm^{-1} 3420, 3372, 2933, 1658, 1429, 1051;

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.56 - 7.52 (m, 2 H), 7.40 - 7.31 (m, 3 H), 5.36 (d, *J* = 5.1 Hz, 1 H), 5.06 (dd, *J* = 1.7, 3.1 Hz, 1 H), 3.56 - 3.48 (m, 1 H), 2.34 - 2.19 (m, 2 H), 2.12 - 1.93 (m, 3 H), 1.87 - 1.75 (m, 3 H), 1.65 - 1.55 (m, 3 H), 1.54 - 1.44 (m, 3 H), 1.42

(S, 3 H), 1.35 - 1.27 (m, 1 H), 1.17 - 1.02 (m, 3 H), 1.00 (s, 3 H), 0.92 (s, 3 H), 0.41 - 0.31 (m, 6 H);

HRMS calculated for $C_{29}H_{42}O_2SiNa$ $[M+Na]^+$: 473.2846, found 473.2845.



(3*S*,10*R*,13*S*,16*R*,*Z*)-17-(1-(dimethyl(phenyl)silyl)ethylidene)-10,13-dimethyl-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1H-cyclopenta[a]phenanthrene-3,16-diol: 138

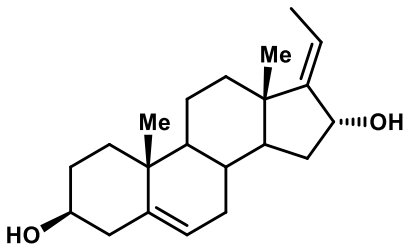
Compound **138** (368 mg, 74%) was obtained by following the general procedure 2.1.6.3.

$[\alpha]_D^{31}$ = – 31.76 (*c* = 0.51, EtOH);

IR υ_{max}(film): cm^{-1} 3367, 3302, 2925, 1445, 1054;

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.56 - 7.53 (m, 2 H), 7.438 - 7.34 (m, 3 H), 5.36 (d, *J* = 4.6 Hz, 1 H), 4.40 (d, *J* = 5.3 Hz, 1 H), 3.58 - 3.50 (m, 1 H), 2.47 - 2.44 (m, 1 H), 2.34 - 2.21 (m, 3 H), 2.05 - 1.95 (m, 1 H), 1.90 (s, 3 H), 1.88 - 1.81 (m, 3 H), 1.69 - 1.64 (m, 3 H), 1.52 - 1.37 (m, 4 H), 1.10 (dd, *J* = 4.6, 9.9 Hz, 2 H), 1.03 (s, 3 H), 0.96 (s, 3 H), 0.46 (d, *J* = 6.1 Hz, 6 H);

HRMS calculated for $C_{29}H_{42}O_2SiNa$ $[M+Na]^+$: 473.2846, found 473.2843.



(3*S*,10*R*,13*S*,16*R*,*E*)-17-ethylidene-10,13-dimethyl-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1H-cyclopenta[a]phenanthrene-3,16-diol : 139

Compound **139** (106 mg, 85%) was obtained by following the general procedure 2.1.6.4.

$[\alpha]_D^{31}$ = –73.24 (*c* = 0.20, EtOH);

IR υ_{max}(film): cm^{-1} 3371, 3322, 2928, 1452, 1057;

^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.60 (dq, *J* = 1.3, 7.2 Hz, 1 H), 5.38 - 5.36 (m, 1 H), 4.45 - 4.444 (m, 1 H), 3.57 - 3.51 (m, 1 H), 2.33 - 2.24 (m, 3 H), 2.03 - 1.98 (m, 1 H), 1.89 - 1.82 (m, 2 H), 1.76 - 1.74 (m, 3 H), 1.68 - 1.47 (m, 10 H), 1.13 - 1.06 (m, 1 H), 1.03 (s, 3 H), 0.90 (s, 3 H);

Check ref. 26 for known compound data.

2.1.9. SC-XRD Data:

The single crystal X-ray diffraction measurements were performed to determine the crystal structure of compounds **127d**, **128D** and **138** at 100 K using APEX3 (Bruker, 2016; Bruker D8 VENTURE Kappa Duo PHOTON II CPAD) diffractometer having graphite-monochromatized (CuKα = 1.54178 Å). The X-ray generator was operated at 50 kV and 30 mA. Compound **127d** crystallizes in a monoclinic system in the C_2 space group with two independent molecules in the asymmetric unit obtained from the ethyl acetate solvent.

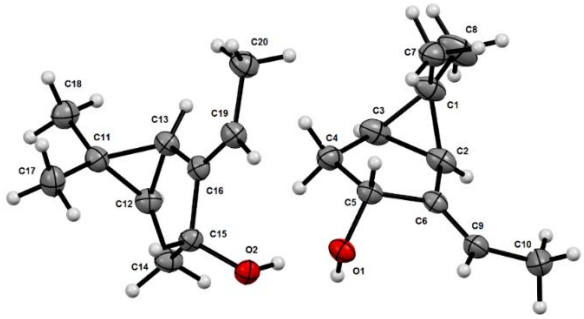


Figure 2.1.11 ORTEP diagram of compound **127d**, the asymmetric unit, contains two molecules. Herein, the ellipsoids are drawn with a 50% probability.

Compound **128d** crystallizes in the trigonal *R*-3 space group with one molecule in the asymmetric unit obtained from the ethyl acetate solvent.

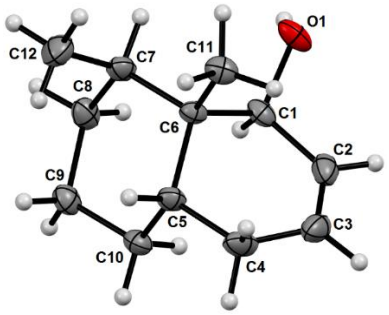


Figure 2.1.12 ORTEP diagram of compound **128d**, the asymmetric unit, contains a single molecule. Herein, the ellipsoids are drawn with a 50% probability.

Compound **138** crystallizes in the Orthorhombic $P2_12_12_1$ space group with one molecule of compound **138** and one molecule of MeOH solvent in the asymmetric unit obtained from MeOH solvent.

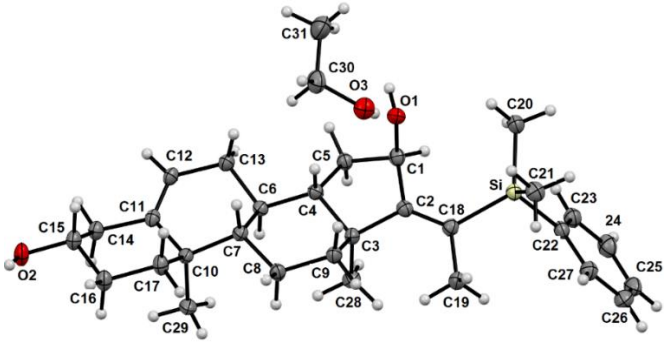


Figure 2.1.13. ORTEP diagram of compound 19, the asymmetric unit, contains a single molecule of compound **138** and a MeOH molecule. Herein, the ellipsoids are drawn with a 50% probability.

Table 2.1.4 Crystallographic information details of compounds **127d**, **128d**, and **138**.

Crystal data	Compound **127d**	Compound **128d**	Compound **138**
Chemical formula	$C_{10}H_{16}O$	$C_{12}H_{20}O$	$C_{31}H_{48}O_3Si$
Formula weight (M_r)	152.23	180.28	496.78
Crystal system	Monoclinic	Trigonal	Orthorhombic
Space group	C_2	*R*-3	$P2_12_12_1$
Temperature T (K)	100(2)	100(2)	100(2)
a (Å)	25.9690(11)	13.1029(3)	6.3692(3)
b (Å)	6.3140(3)	13.1029(3)	20.3113(10)

c (Å)	11.8097(5)	32.0879(8)	22.0459(10)
α (°)	90	90	90
β (°)	105.762(2)	90	90
γ (°)	90	120	90
Z	8	18	4
Volume ($Å^3$)	1863.60(14)	4771.0(2)	2852.0(2)
Source of radiation	CuKα	CuKα	CuKα
D_{calc} (g cm^{-3})	1.085	1.129	1.157
Crystal size (mm)	0.38x 0.27x 0.12	0.34x 0.2x 0.18	0.36x 0.21x 0.12
μ (mm^{-1})	0.521	0.527	0.940
Flack parameter	-0.09(12)	-	0.018(10)
Data collection			
Diffractometer	Bruker D8 VENTURE Kappa Duo PHOTON II CPAD	Bruker D8 VENTURE Kappa Duo PHOTON II CPAD	Bruker D8 VENTURE Kappa Duo PHOTON II CPAD
Absorption correction	Multi-scan (SADABS; Bruker, 2016)	Multi-scan (SADABS; Bruker, 2016)	Multi-scan (SADABS; Bruker, 2016)
T_{min}, T_{max}	0.6176, 0.7536	0.6634, 0.7520	0.789, 0.893
No. of measured, independent and observed [I > 2σ(I)] reflections	38792, 3692, 3239	29878, 1631, 1496	118193, 6073, 5332
Theta range (°)	3.54-72.48	4.13- 61.16	2.96-79.80
R_{int}	0.0903	0.1005	0.0916
Refinement			
R[F^2 > 2σ (F^2)], wR(F^2)	0.0391	0.0397	0.0447
GOF on F^2	1.027	1.081	1.099
No. of independent reflections	3239	1496	5332
No. of parameters	208	125	326
F_000	672	1800	1088
No. of restraints	1	0	0
H-atom treatment	constr	constr	Constr
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (e $A^{\circ -3}$)	0.199, -0.177	0.229, -0.214	0.265, -0.266
CCDC number	2089261	2089262	2089263

2.1.10. **Refrences**

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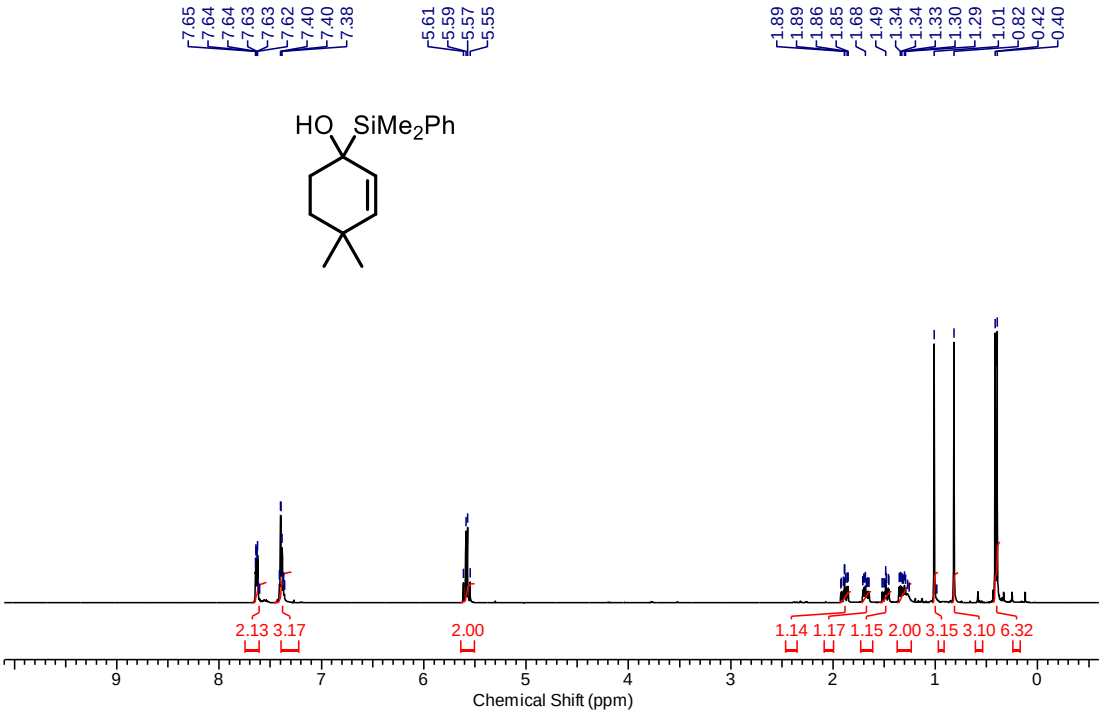
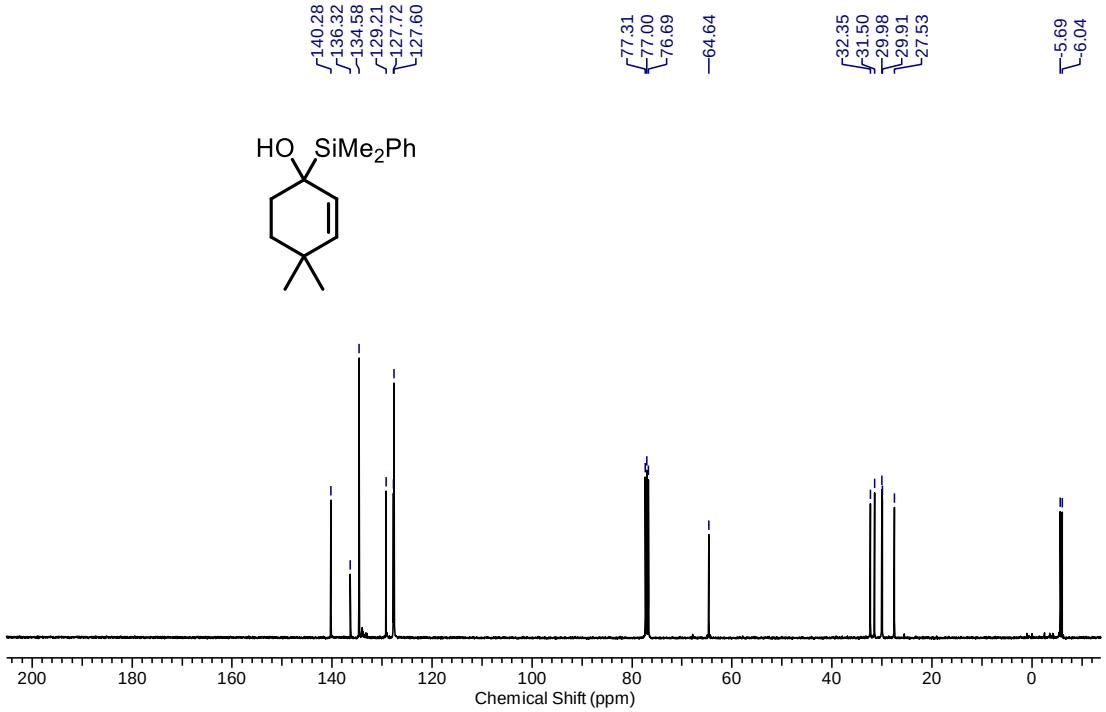
2.1.10. **Copies of selected NMR spectra**



^{1}H NMR of Compound **118b** in $CDCl_3$ at 400 MHz



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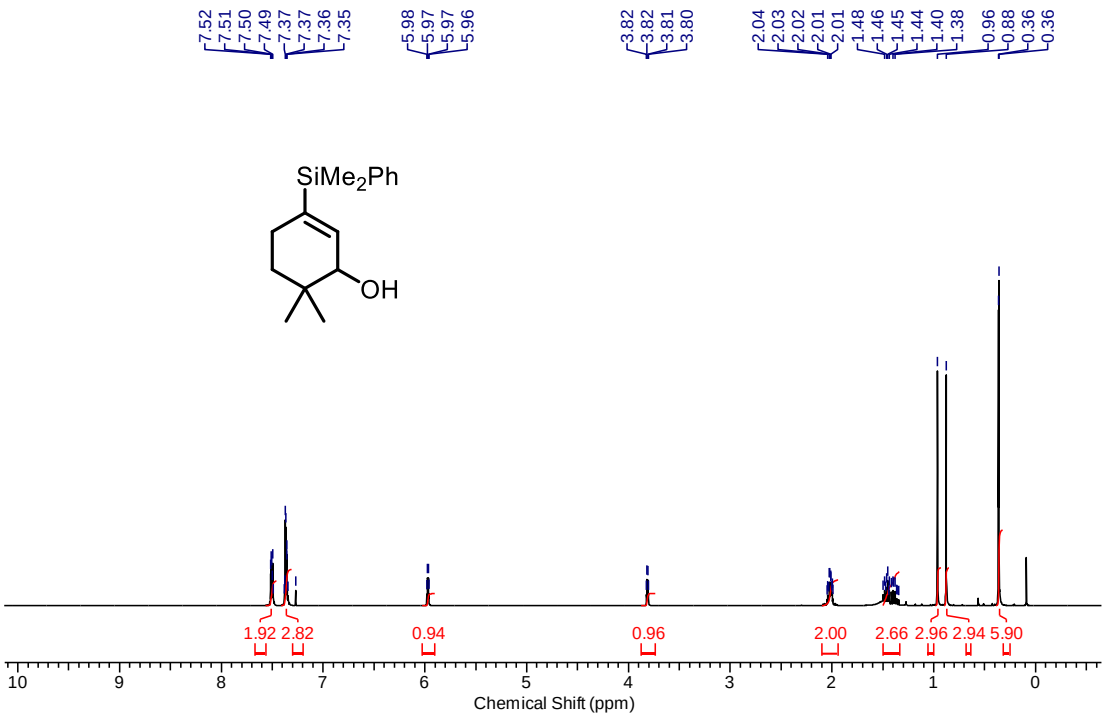

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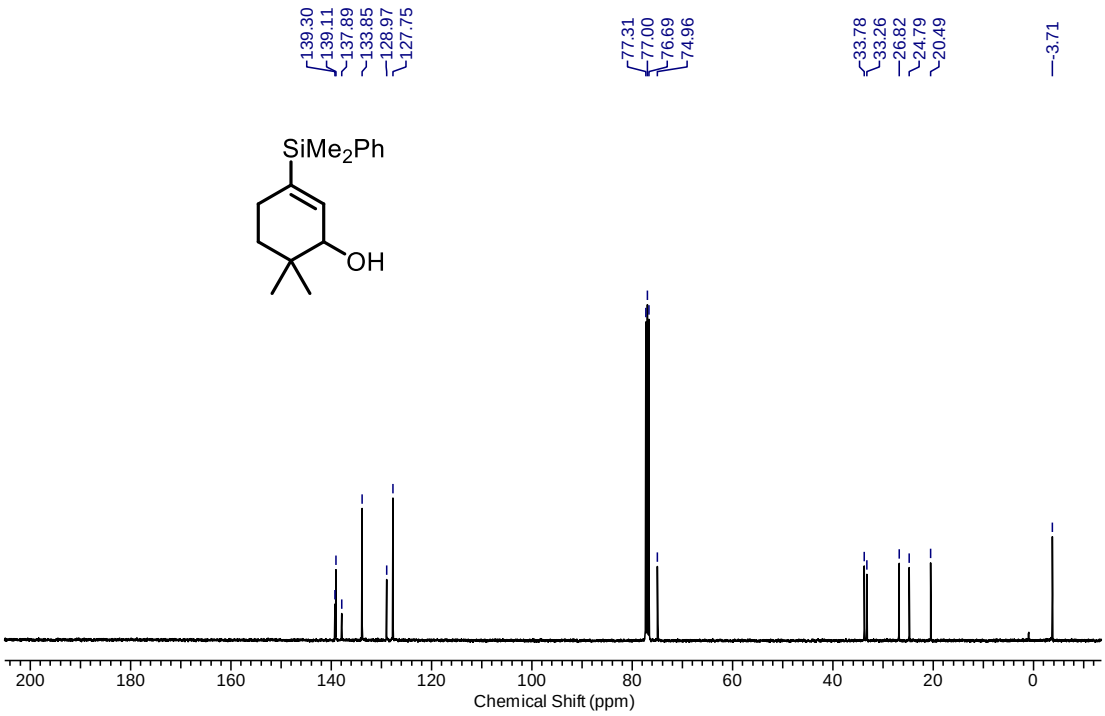

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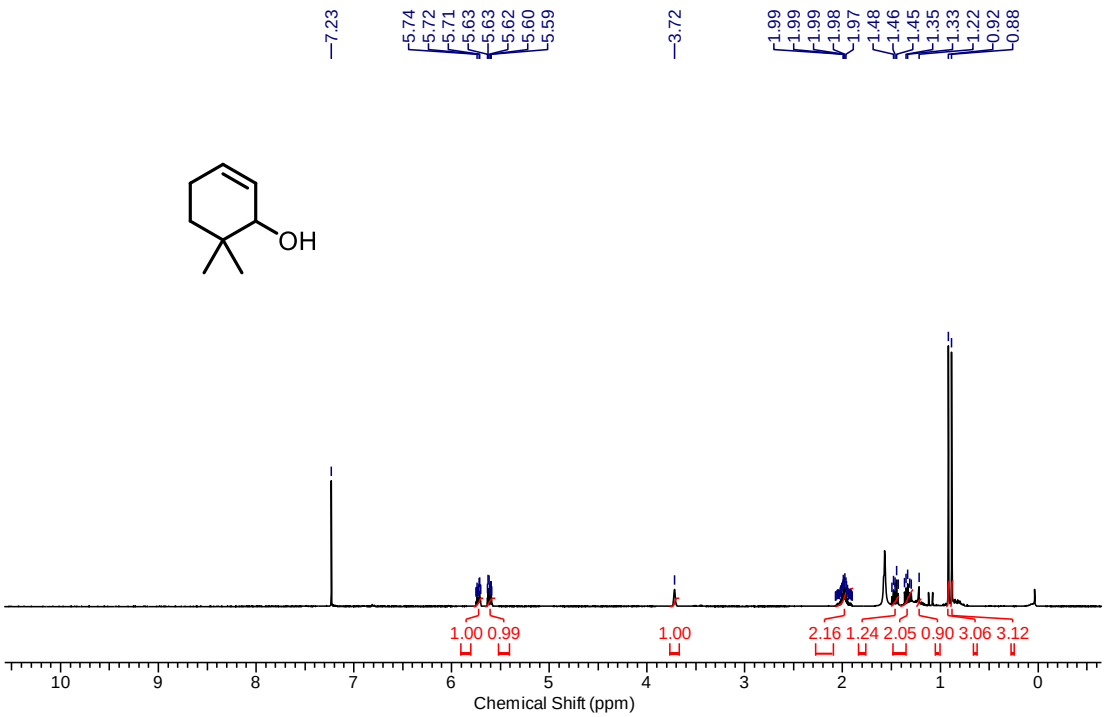

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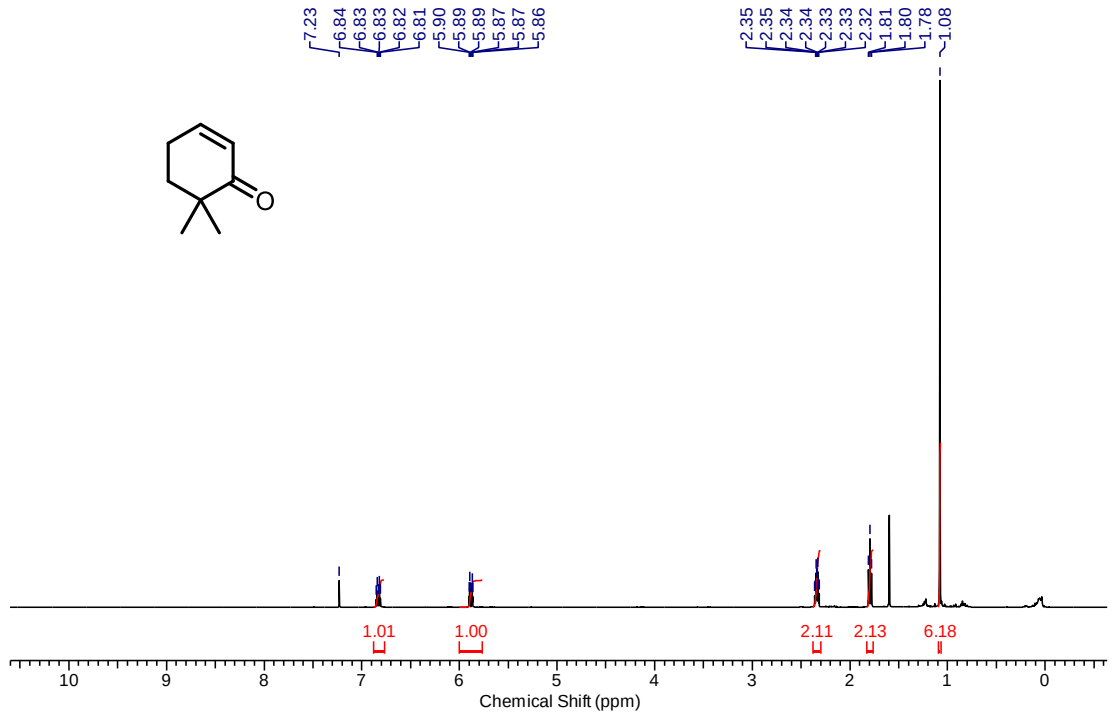
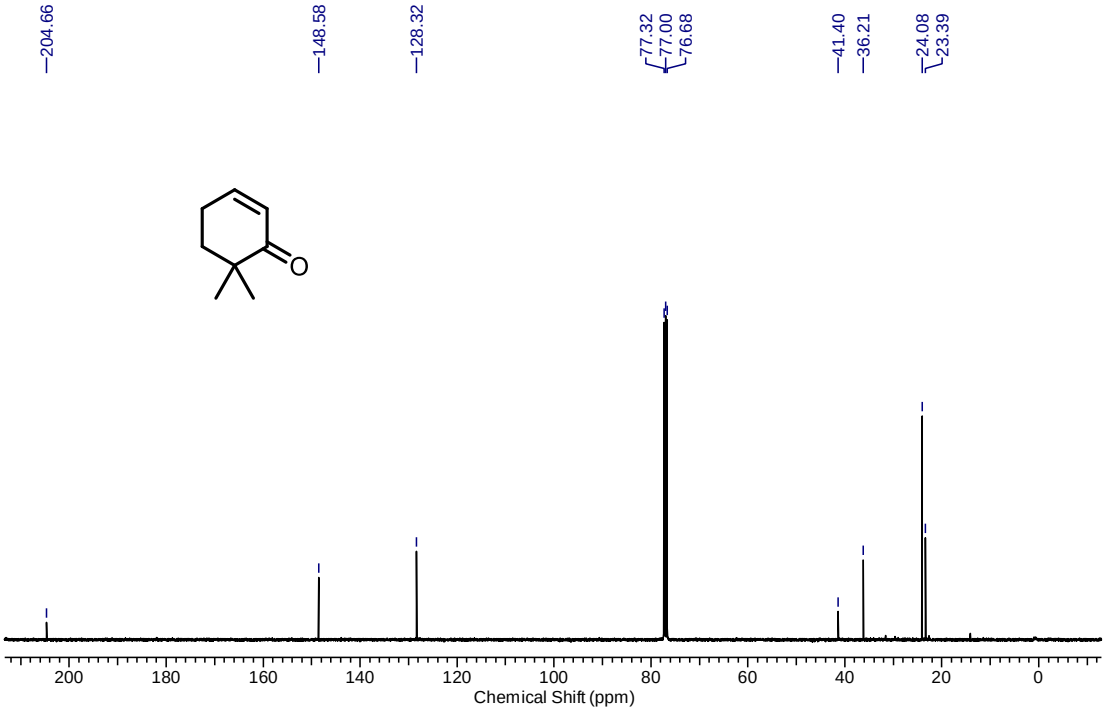


^{1}H NMR of Compound **118e** in $CDCl_3$ at 400 MHz



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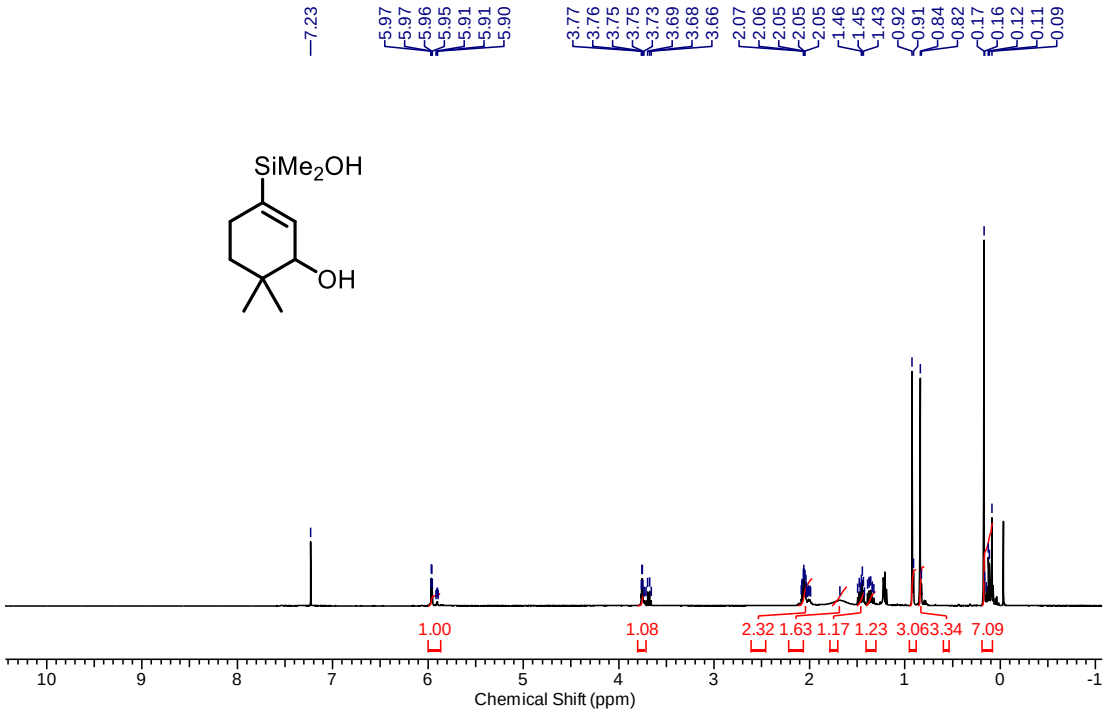
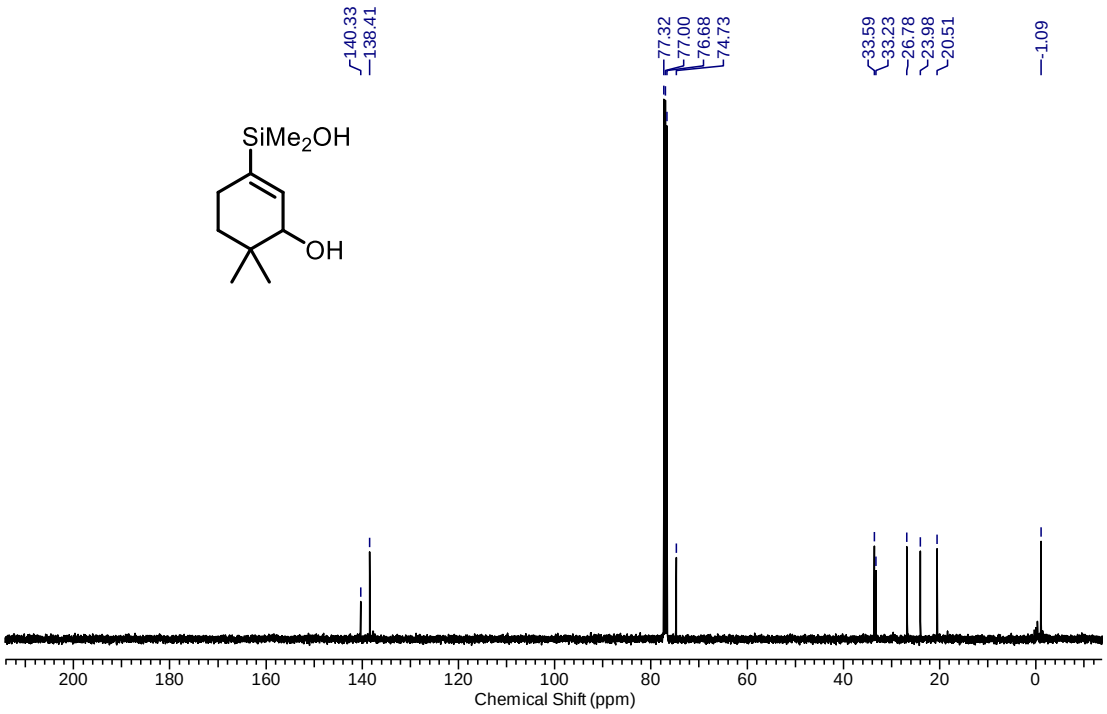


^{1}H NMR of Compound **118c'** in $CDCl_3$ at 400 MHz



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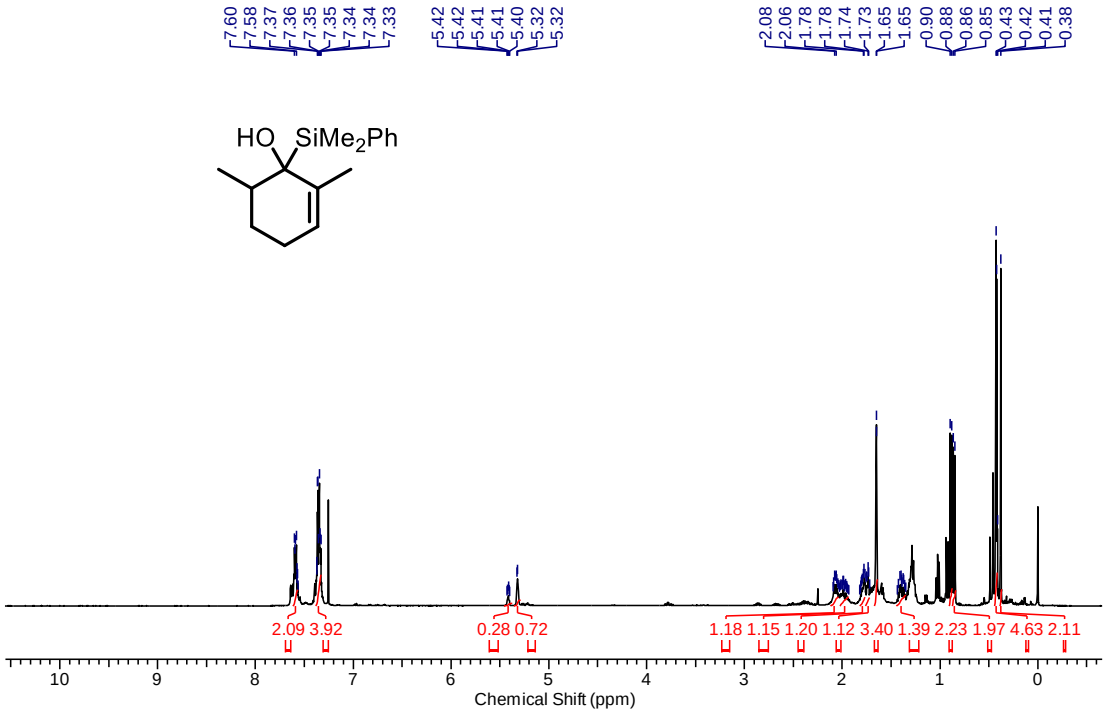

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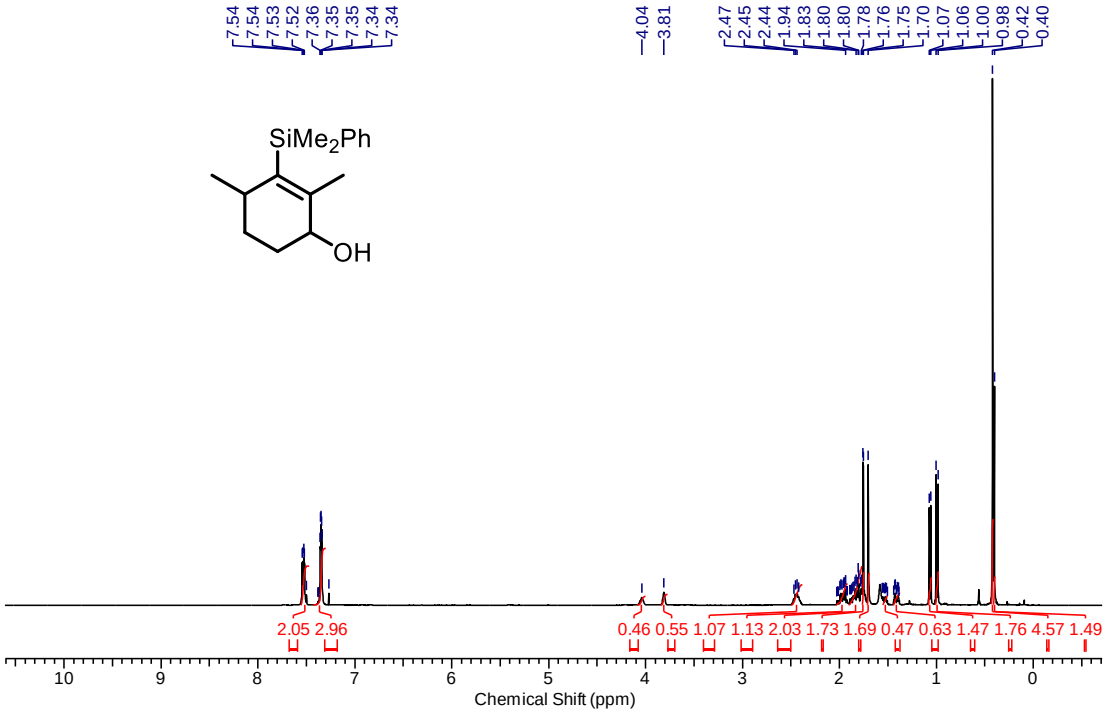

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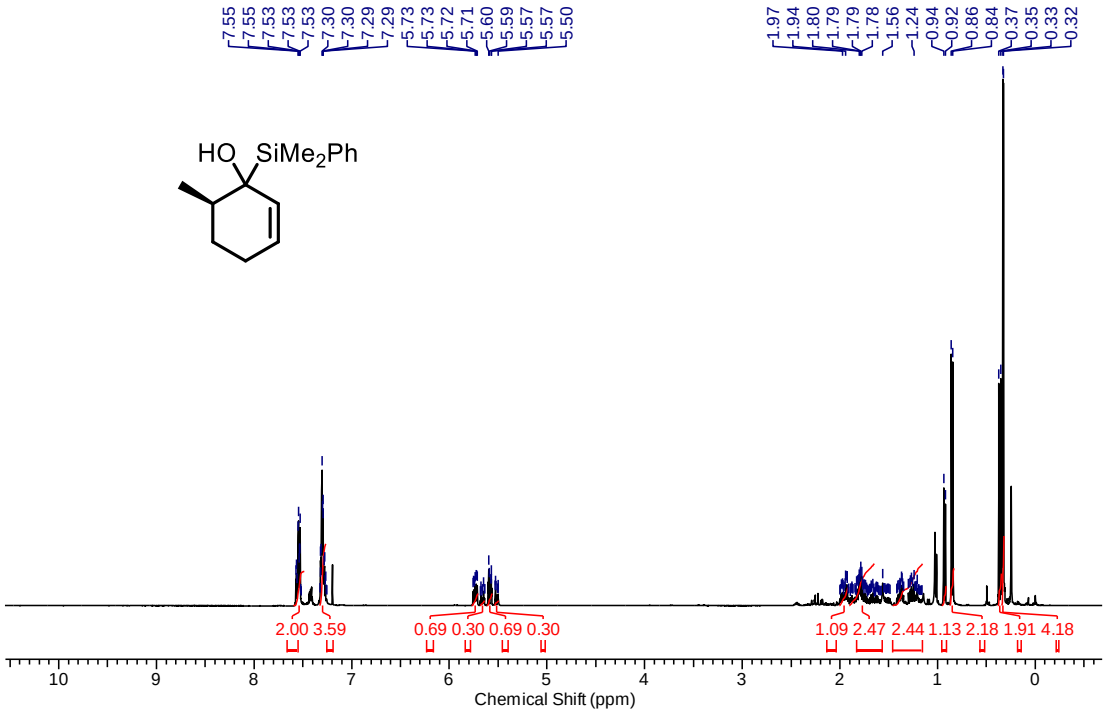

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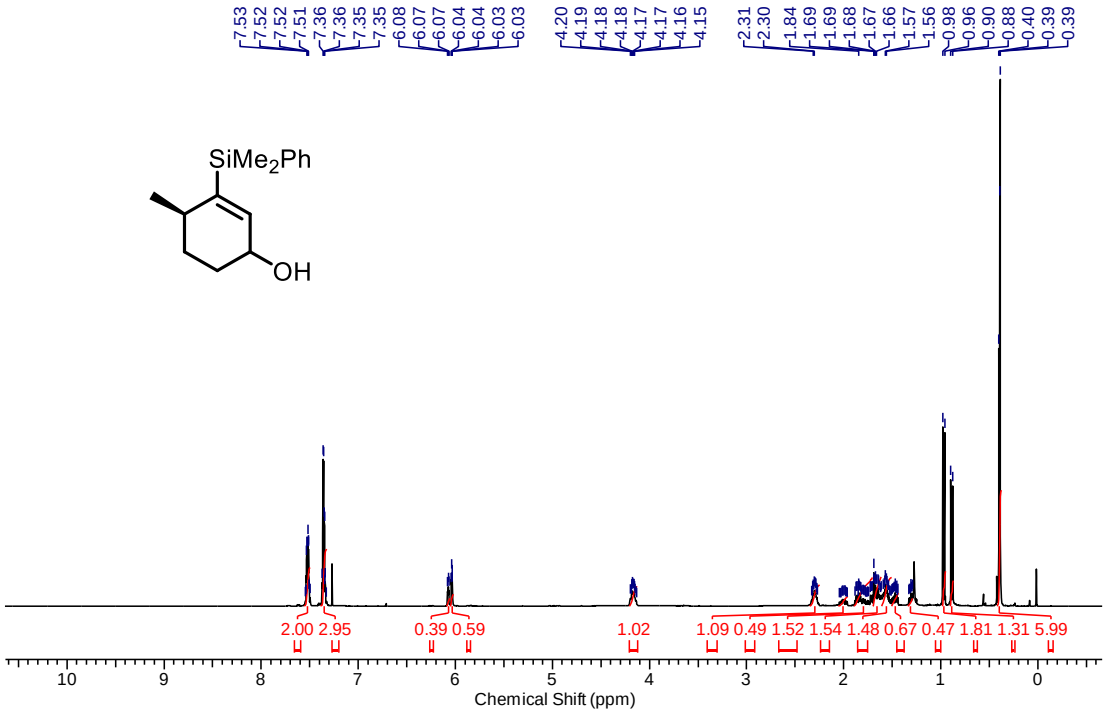

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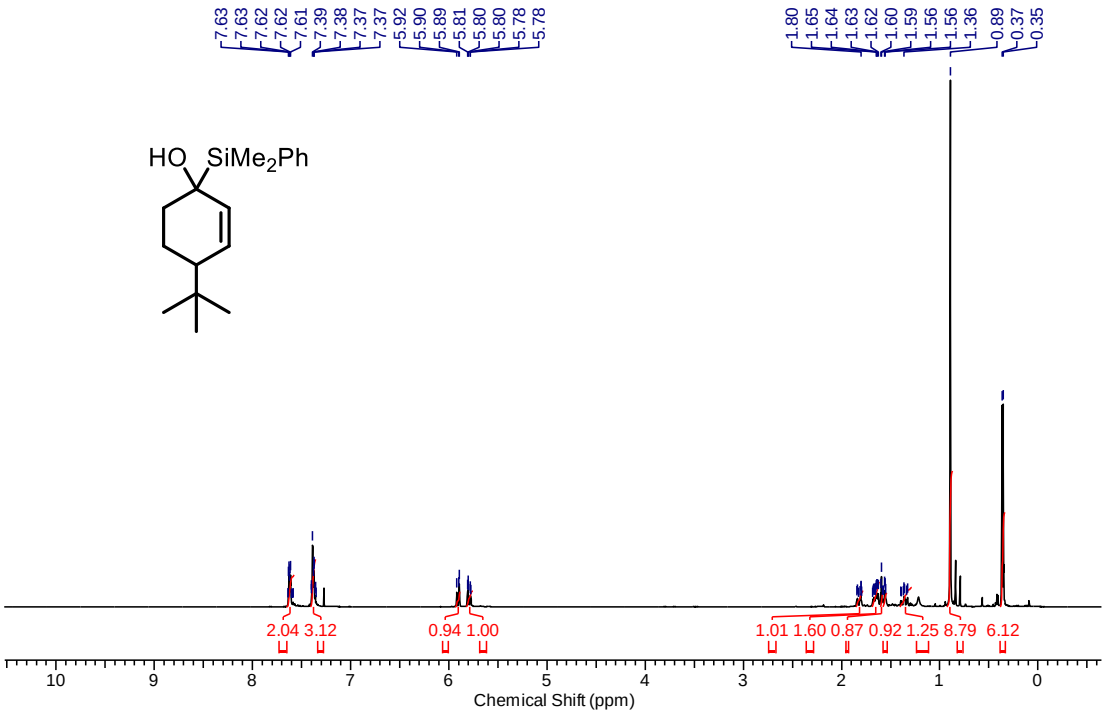

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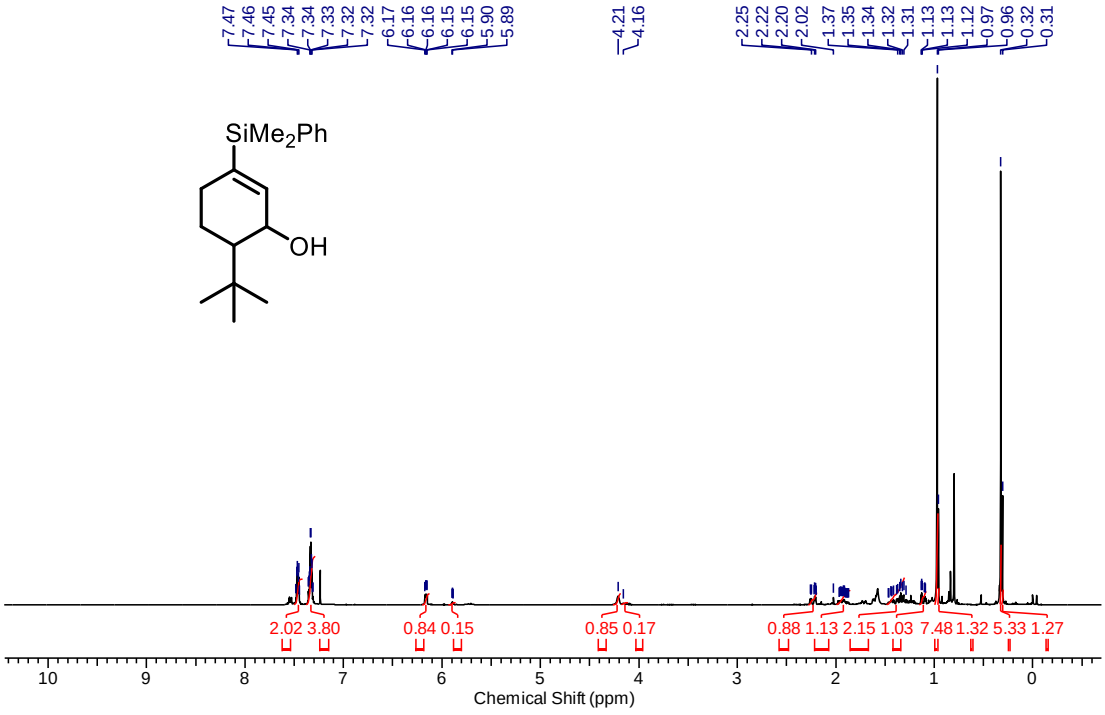

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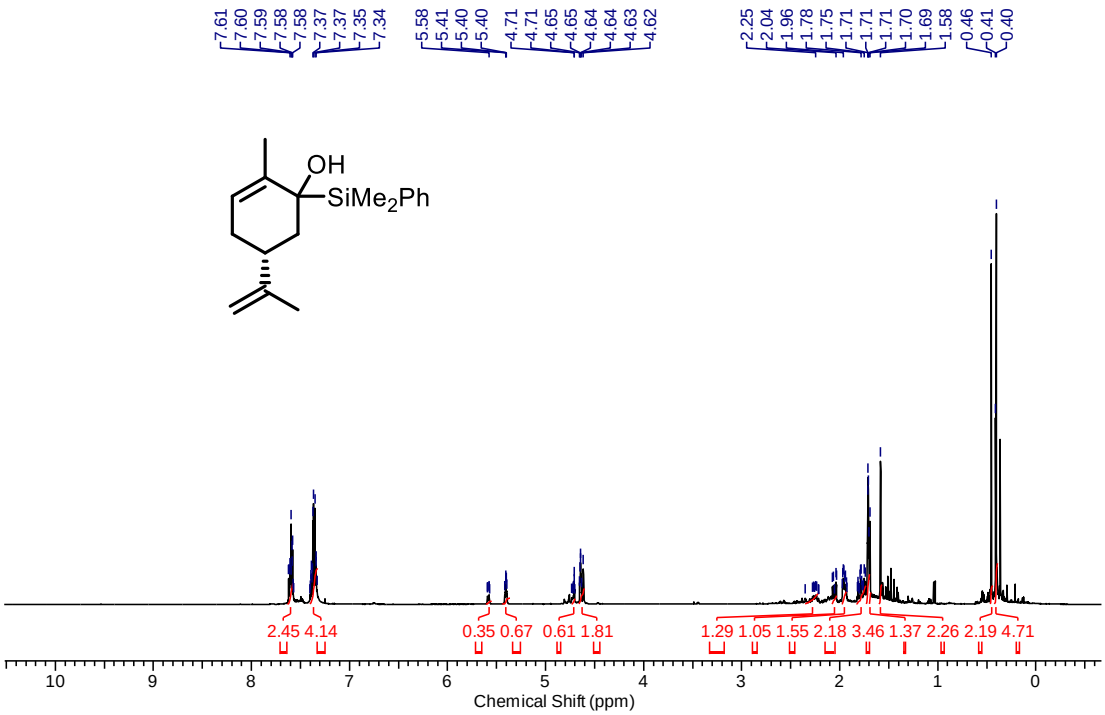

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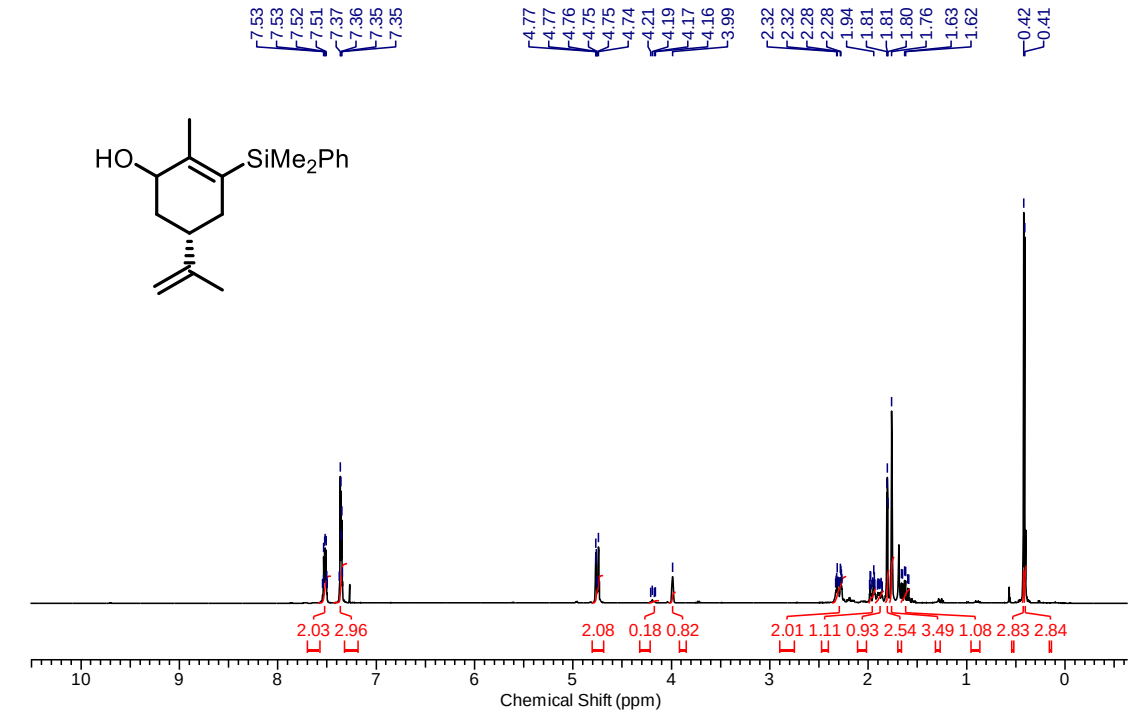

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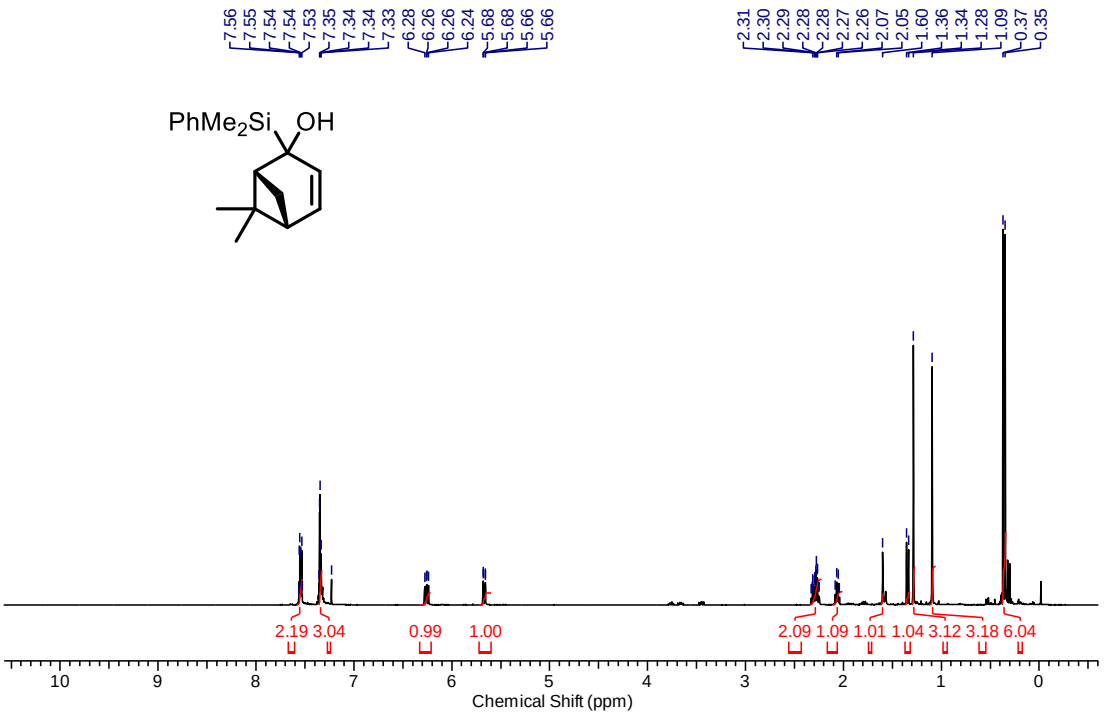

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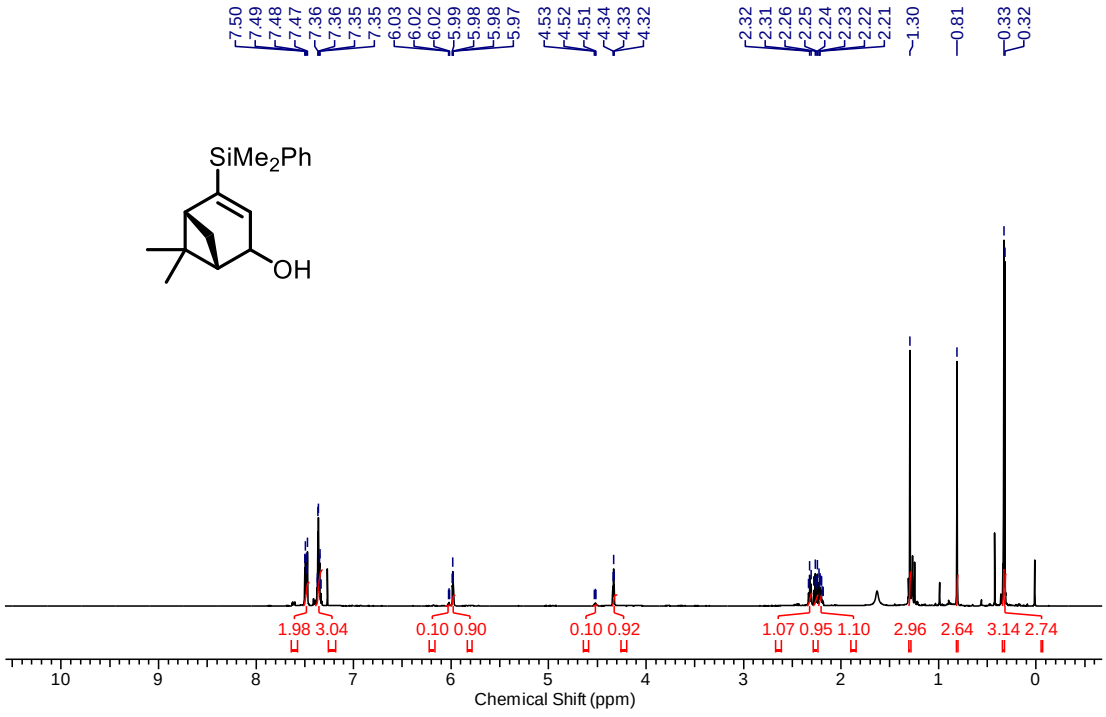

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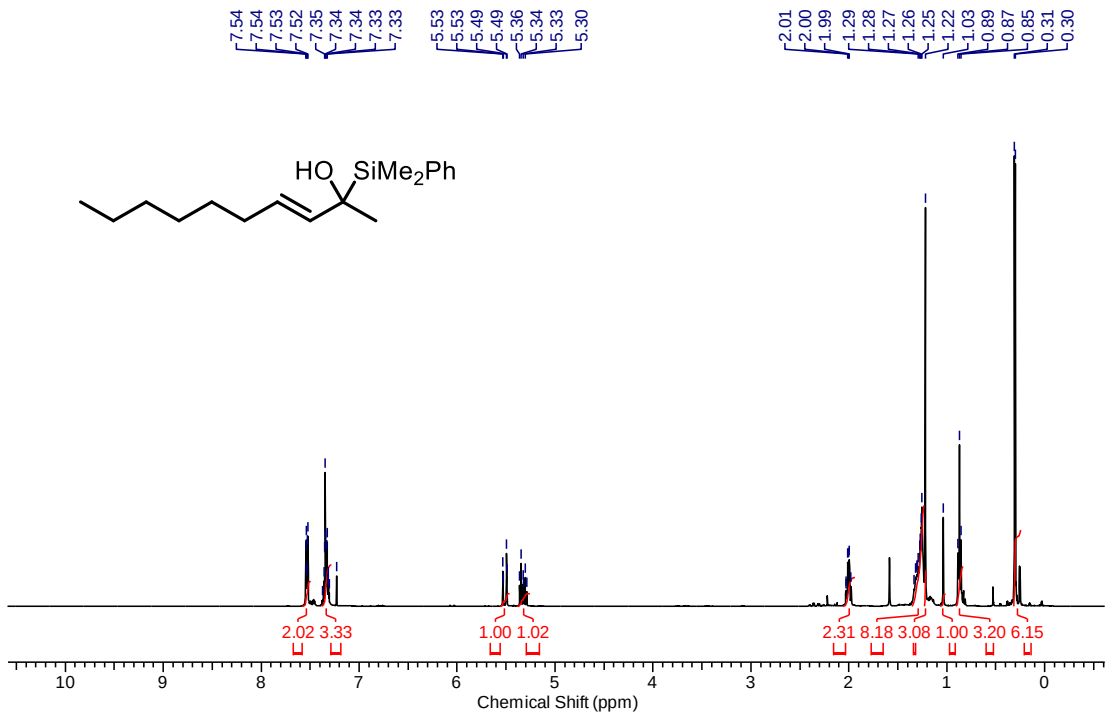

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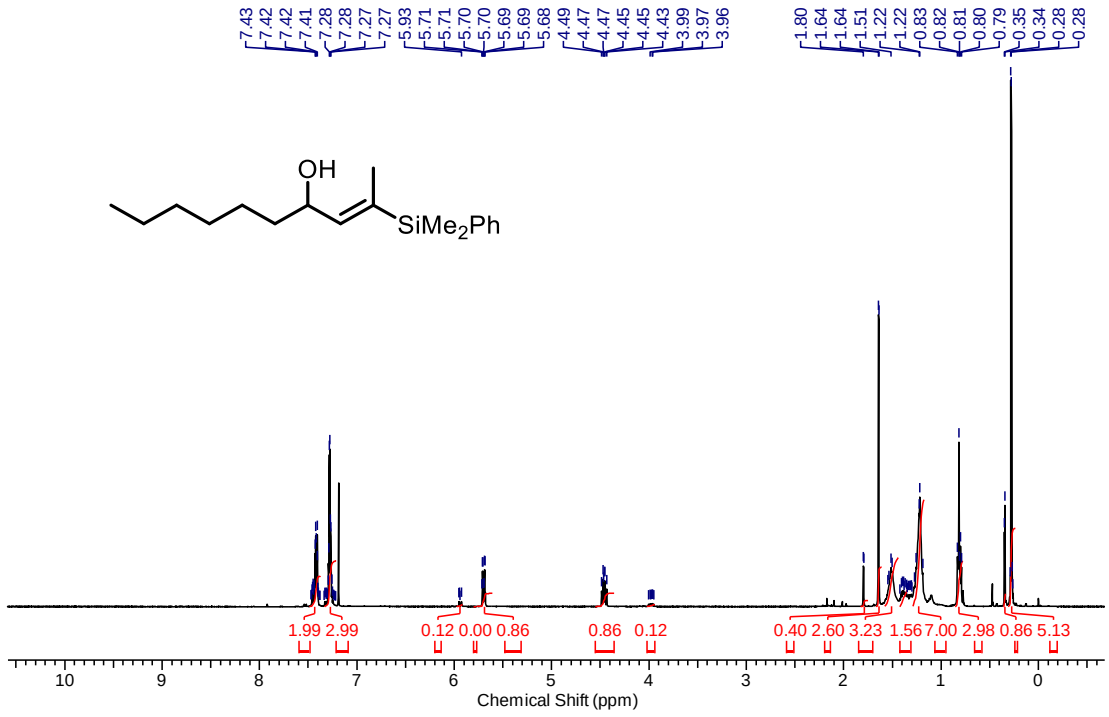

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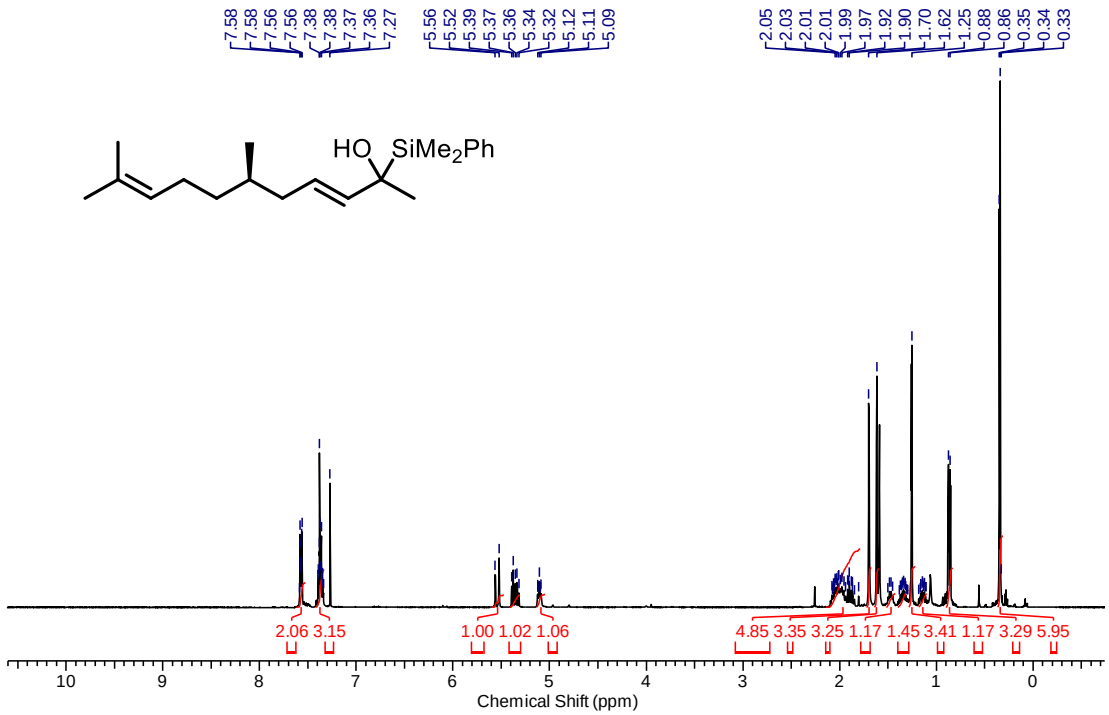

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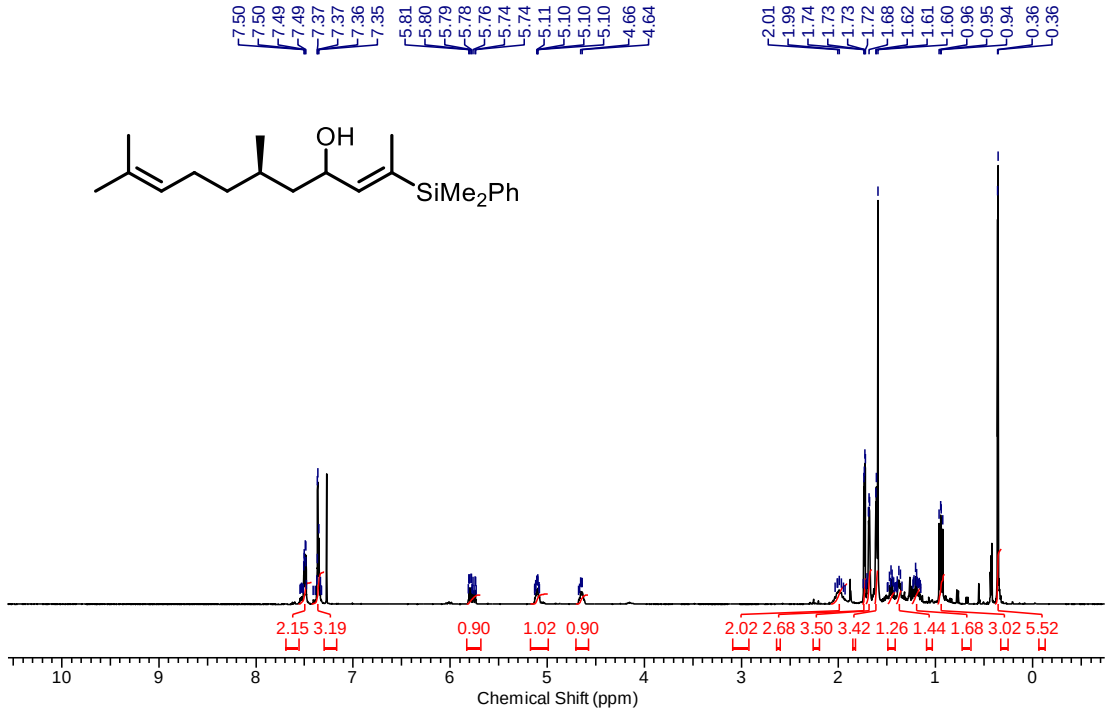

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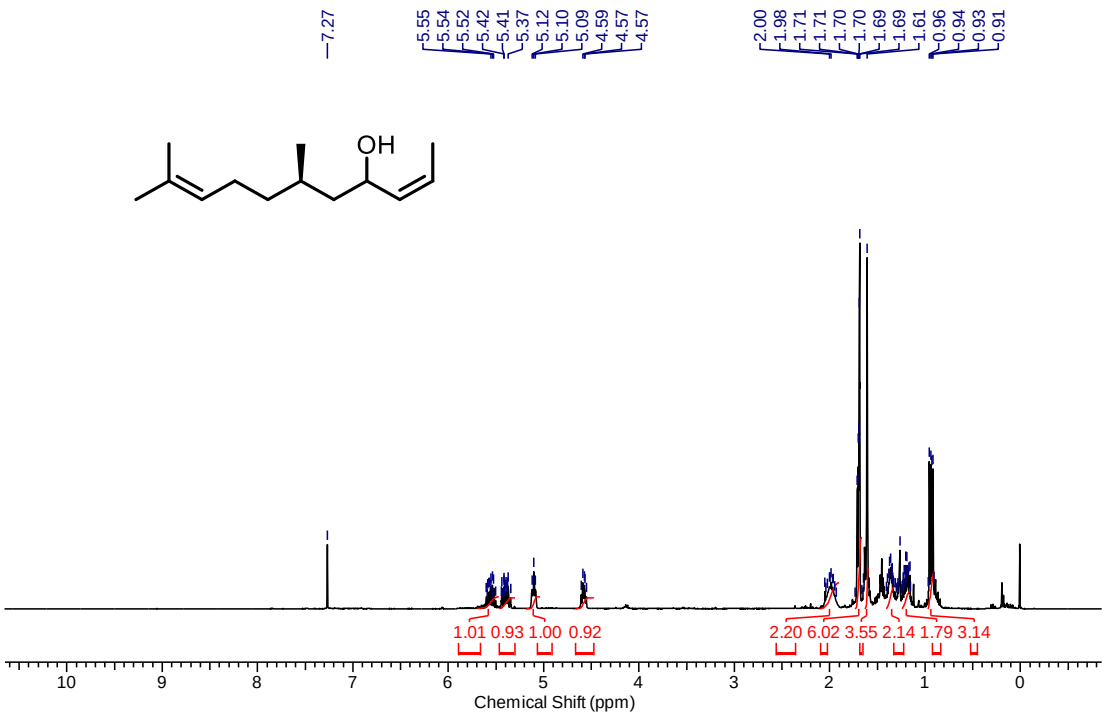
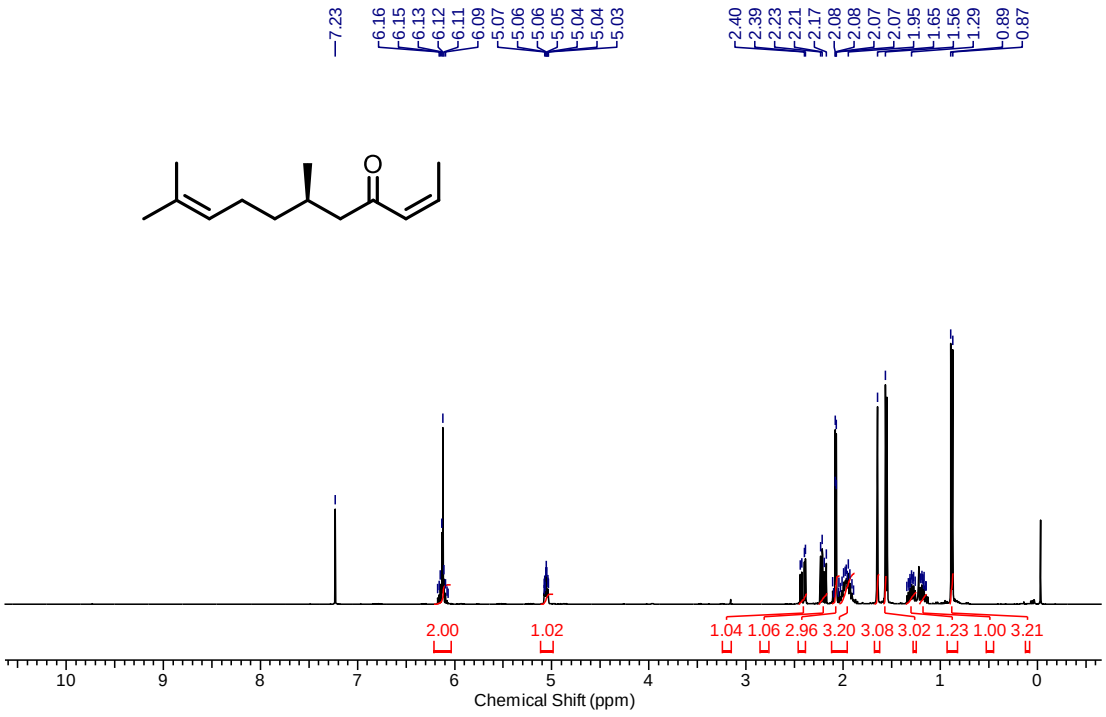
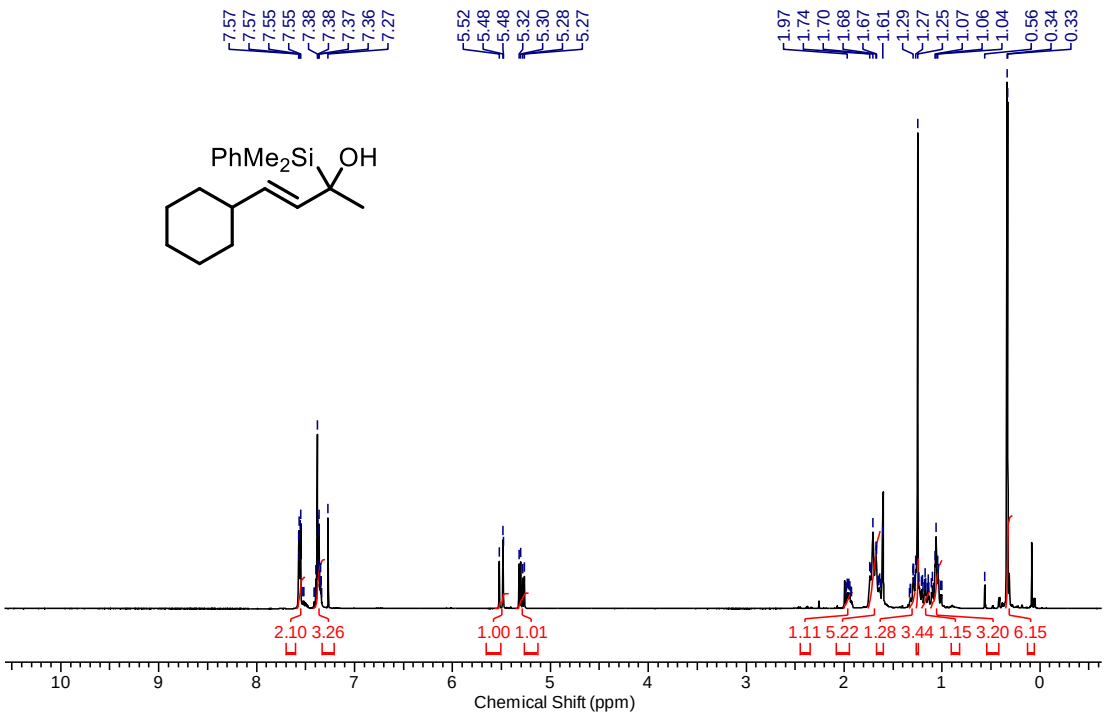


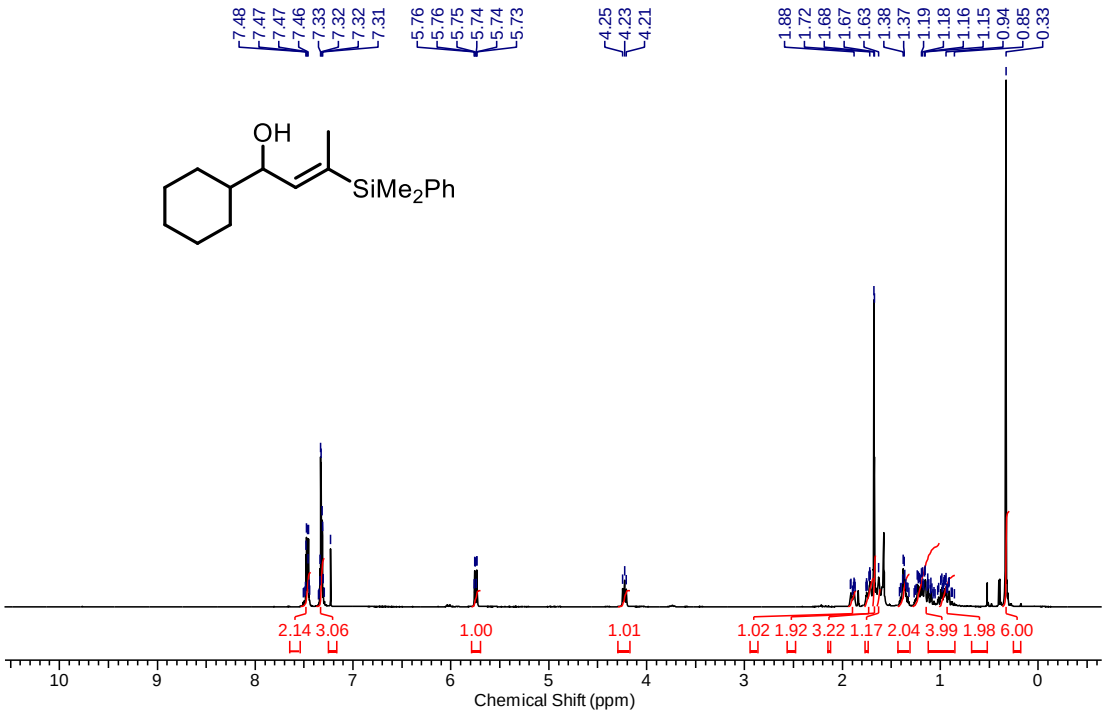
^{1}H NMR of Compound **124d** in $CDCl_3$ at 400 MHz



^{1}H NMR of Compound **124e** in $CDCl_3$ at 400 MHz



^{1}H NMR of Compound **125b** in $CDCl_3$ at 400 MHz



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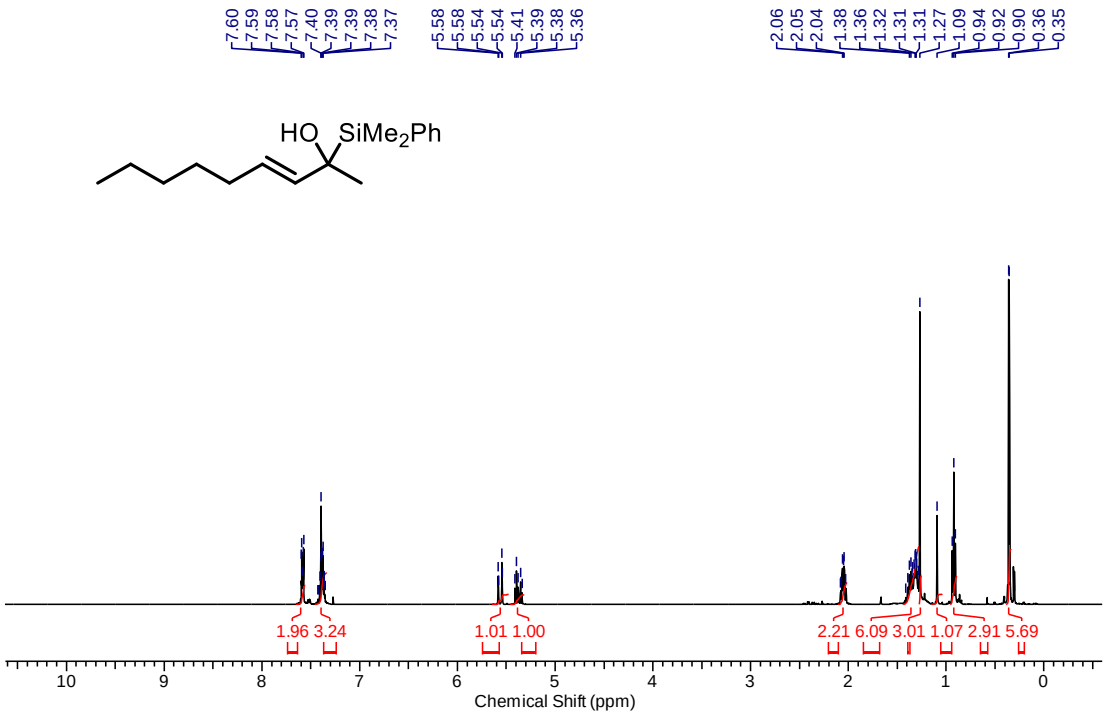

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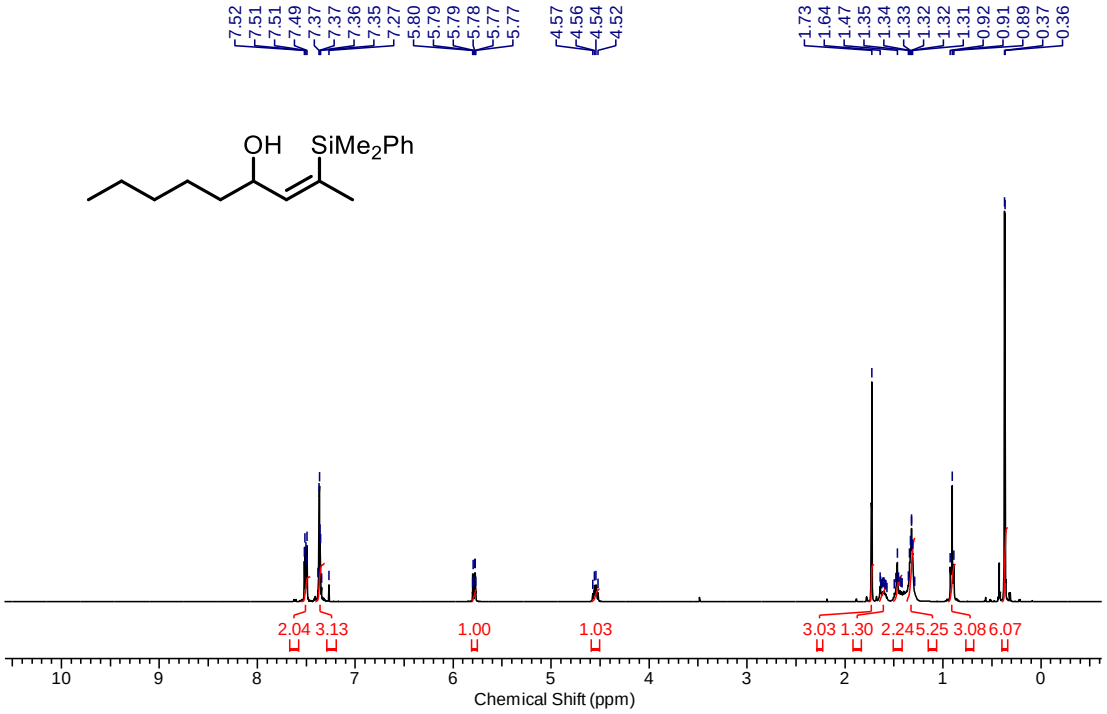
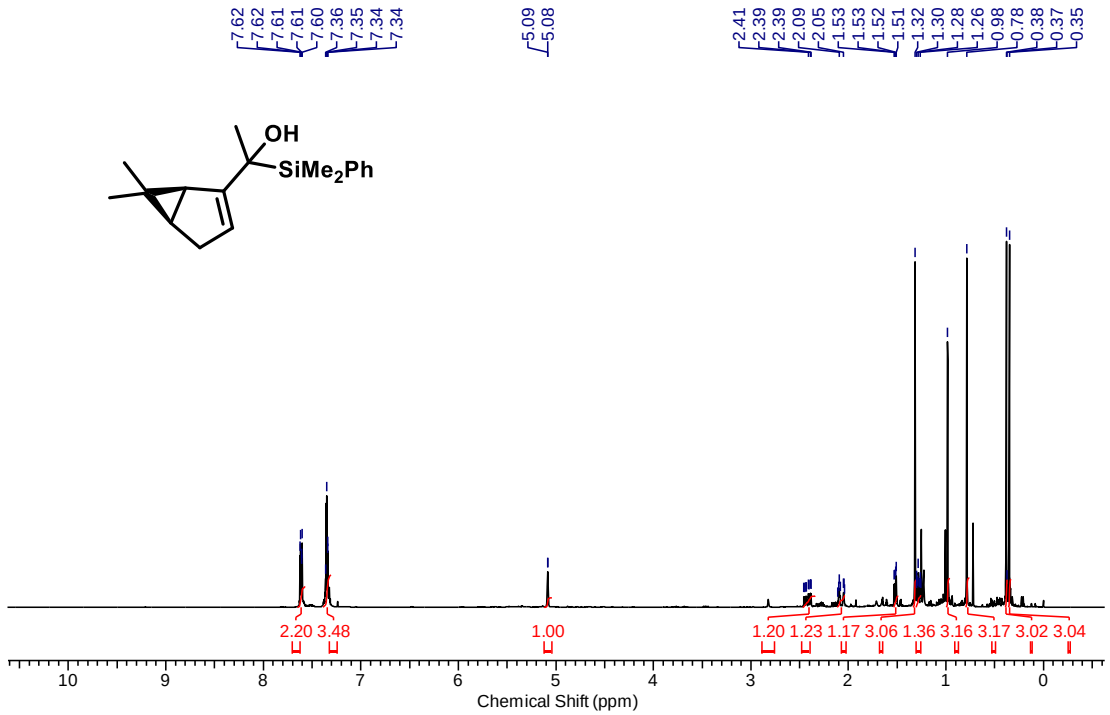


^{1}H NMR of Compound **126c** in $CDCl_3$ at 400 MHz



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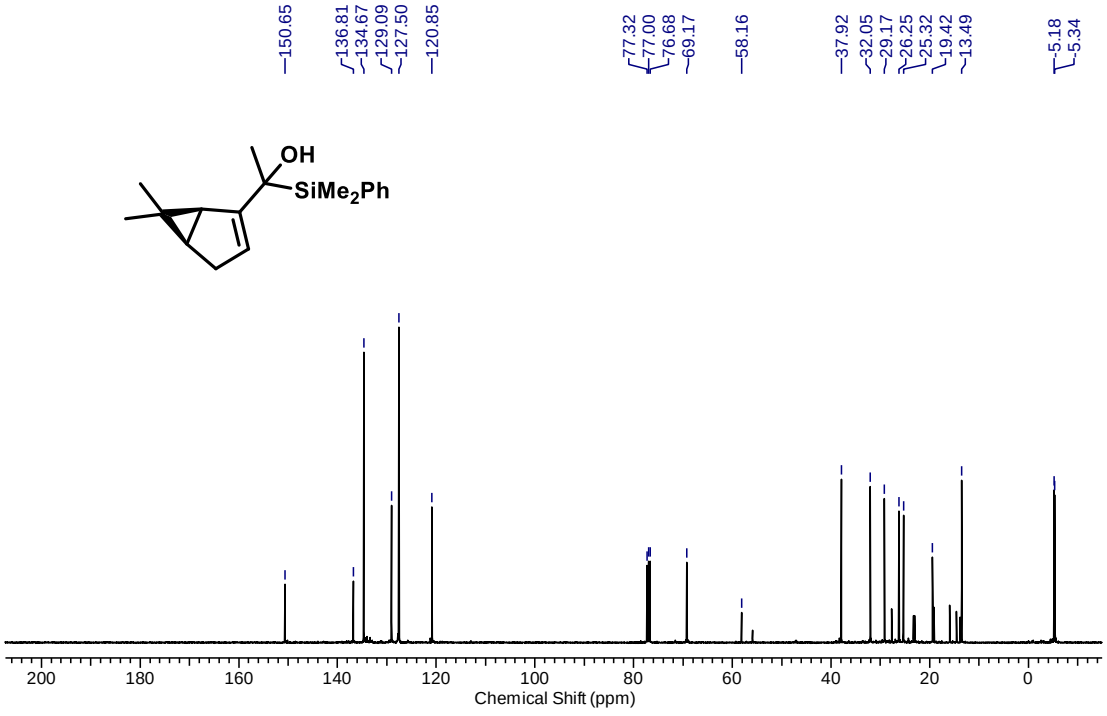
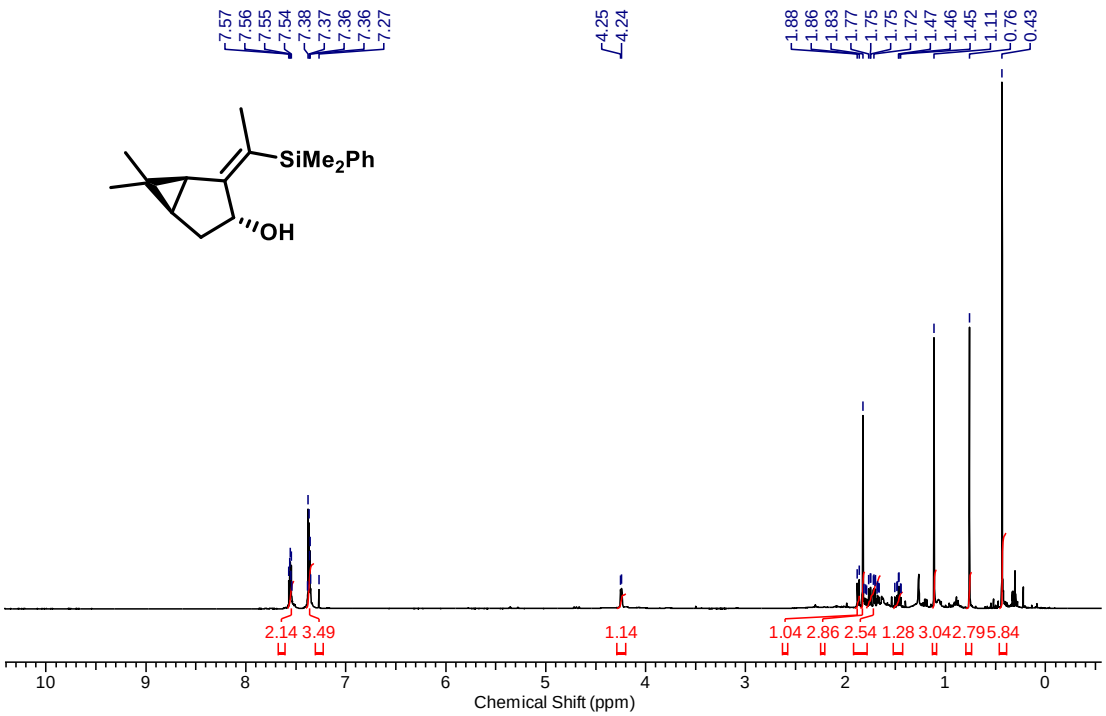
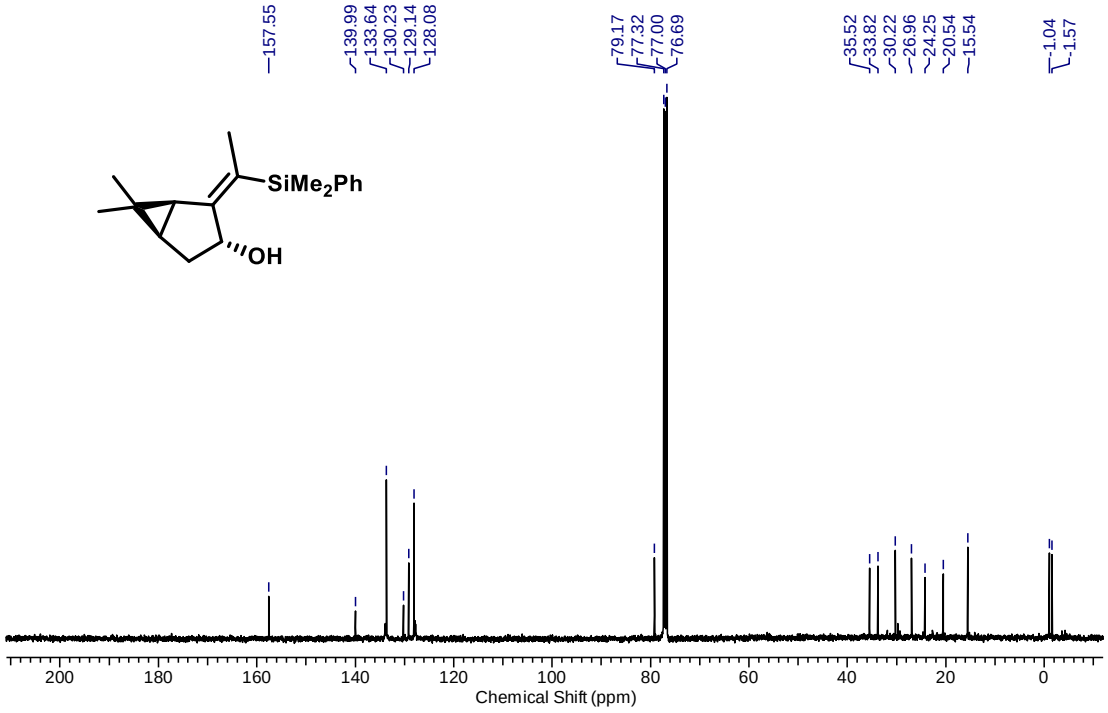


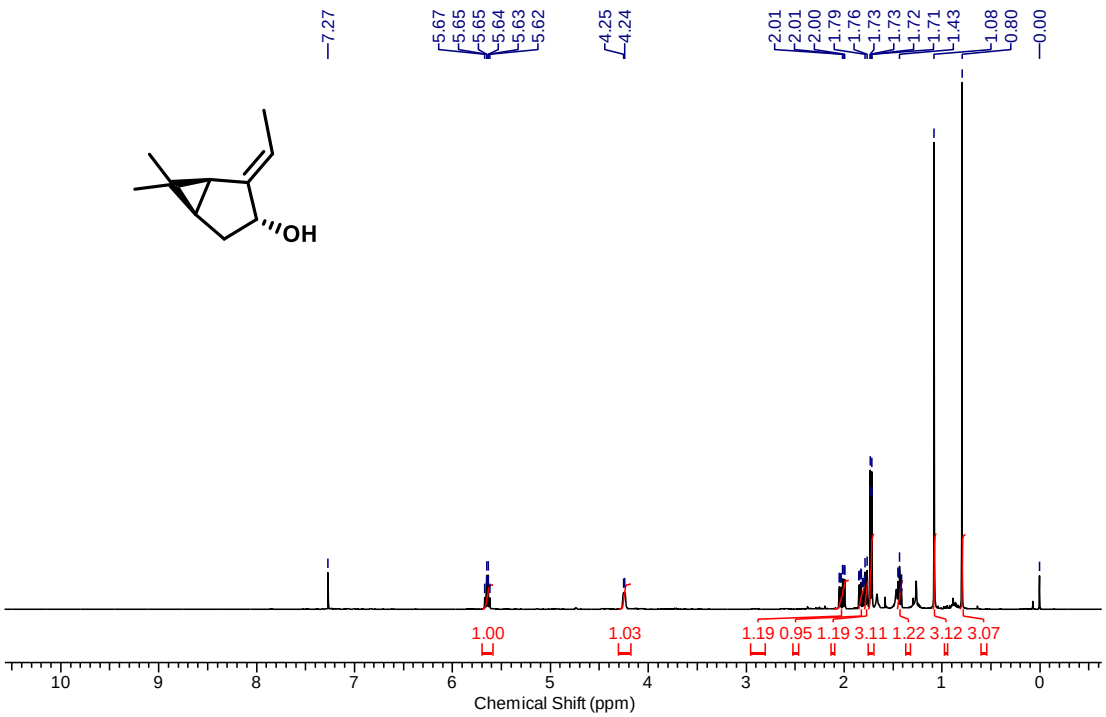
^{13}C NMR of Compound **127b** in $CDCl_3$ at 100 MHz



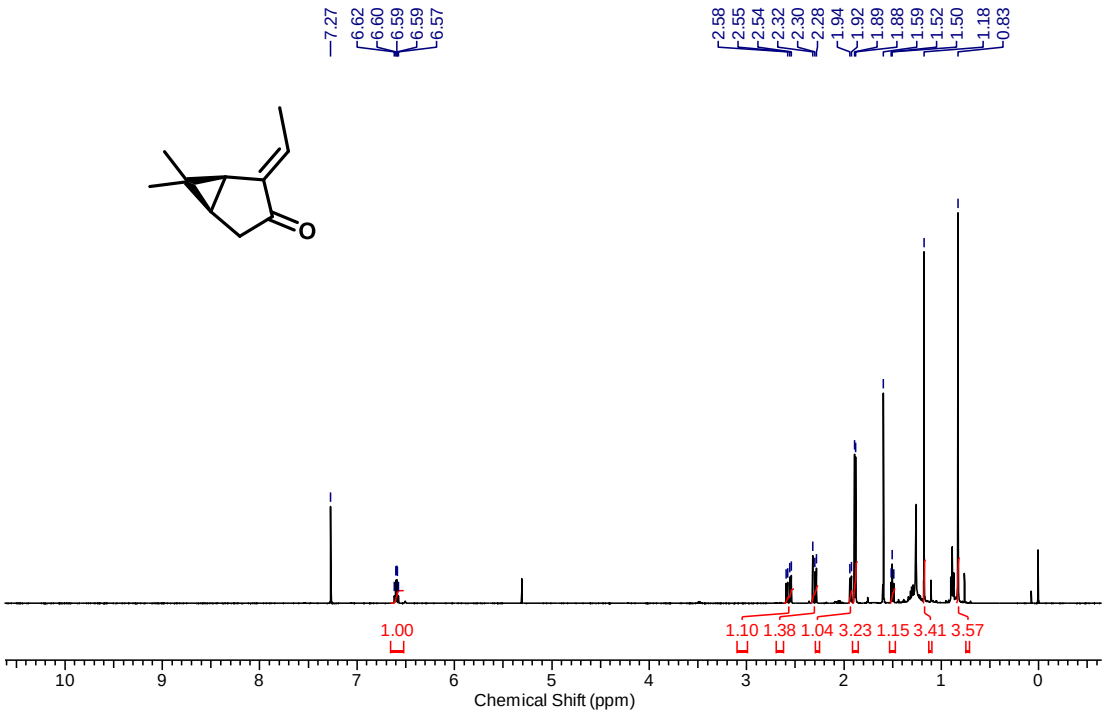
^{1}H NMR of Compound **127c** in $CDCl_3$ at 400 MHz



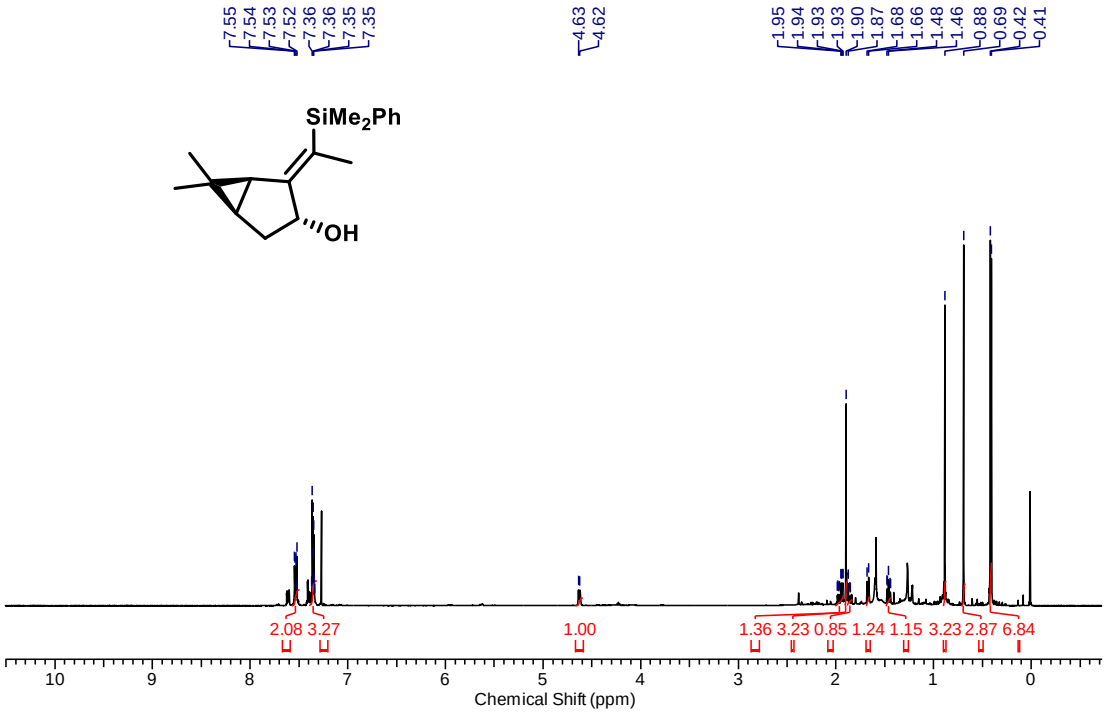
^{13}C NMR of Compound **127c** in $CDCl_3$ at 100 MHz



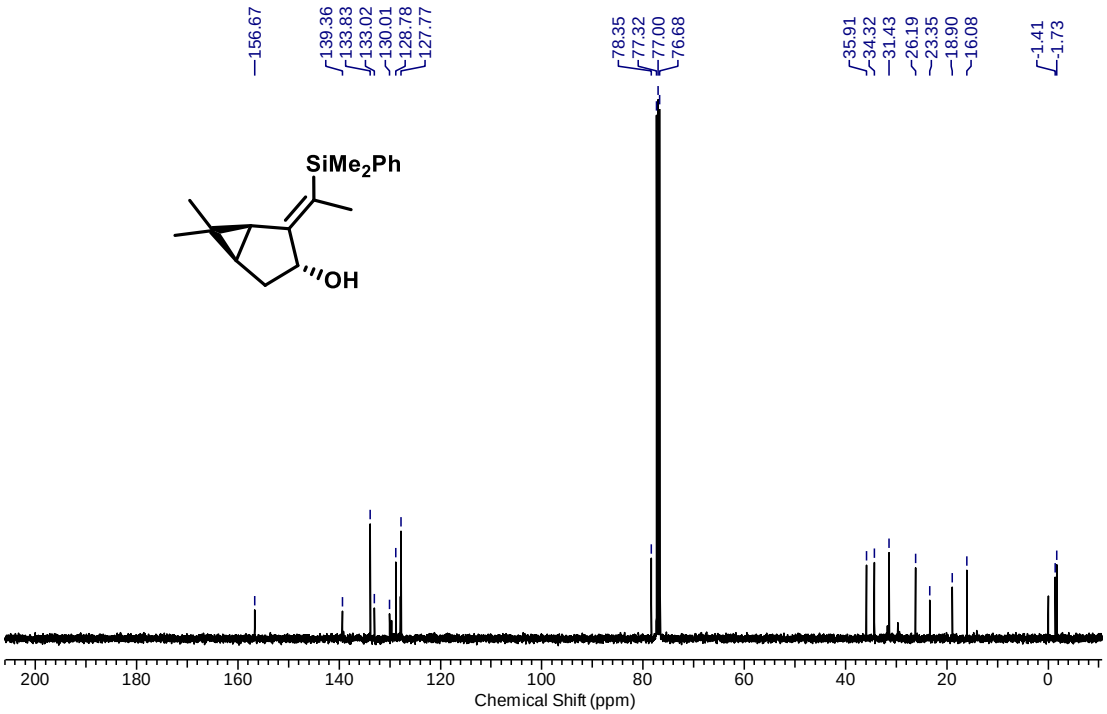
^{1}H NMR of Compound **127d** in $CDCl_3$ at 400 MHz



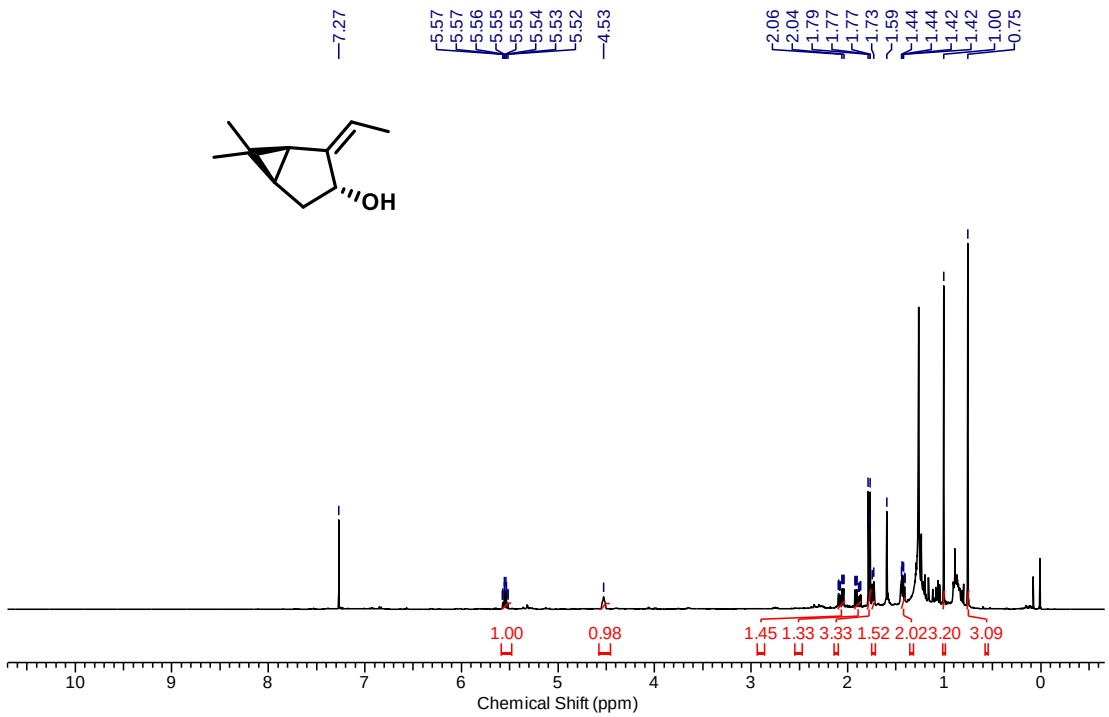
^{1}H NMR of Compound **127e** in $CDCl_3$ at 500 MHz



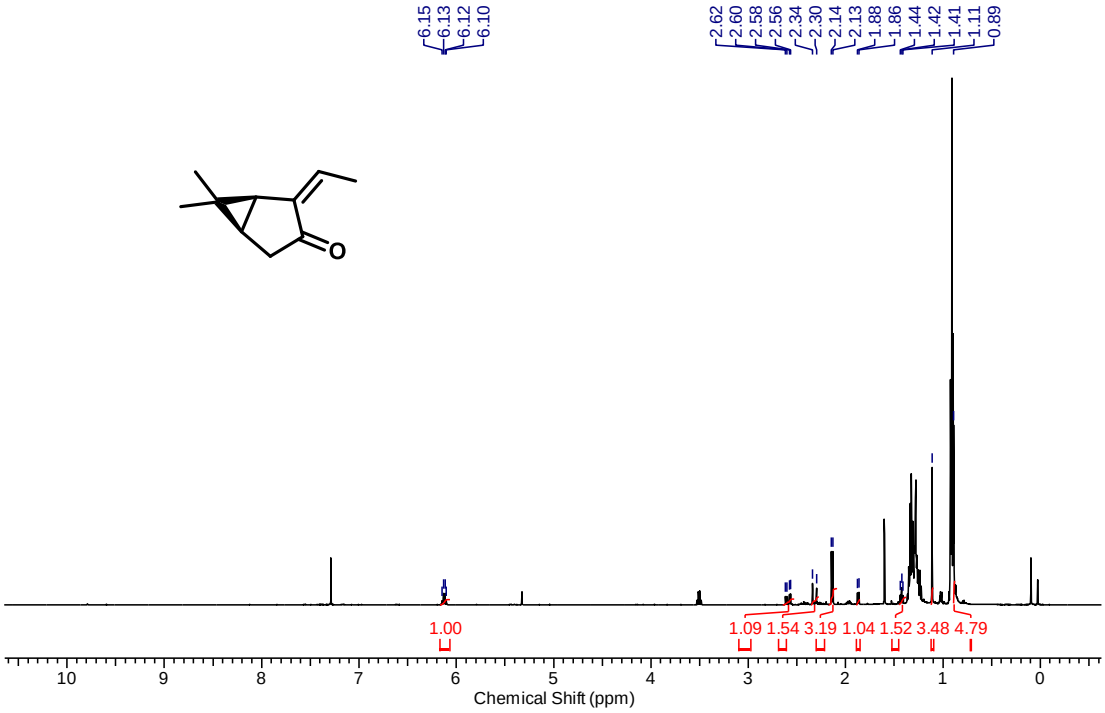
^{1}H NMR of Compound **127f** in $CDCl_3$ at 400 MHz



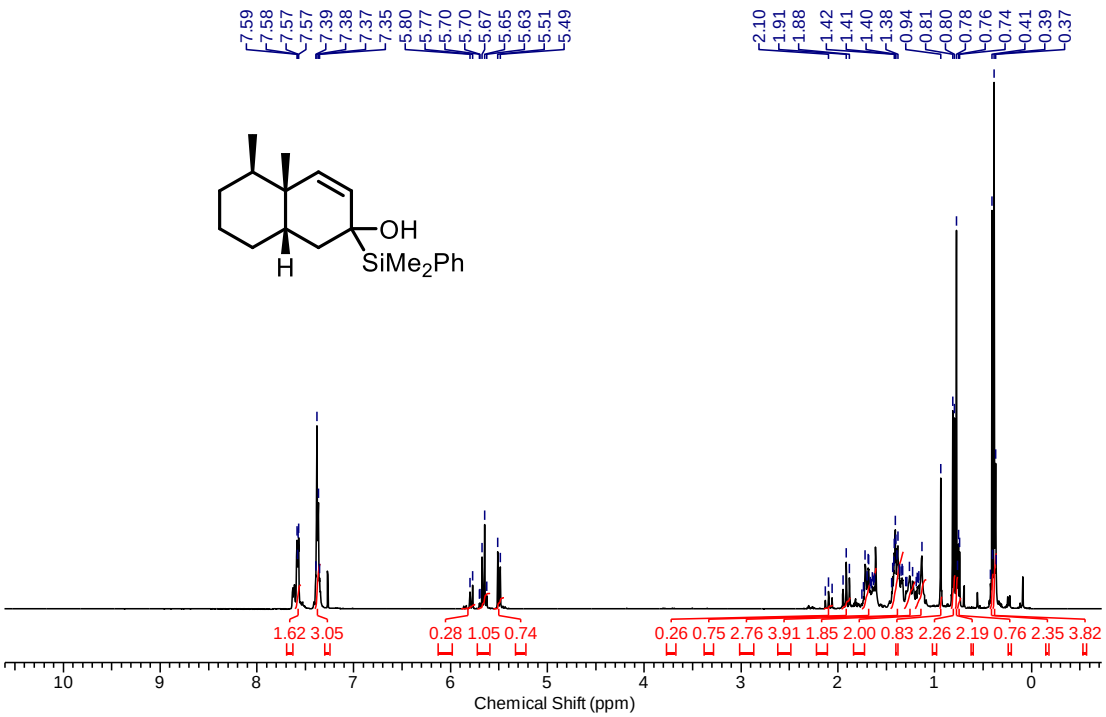
^{13}C NMR of Compound **127f** in $CDCl_3$ at 100 MHz



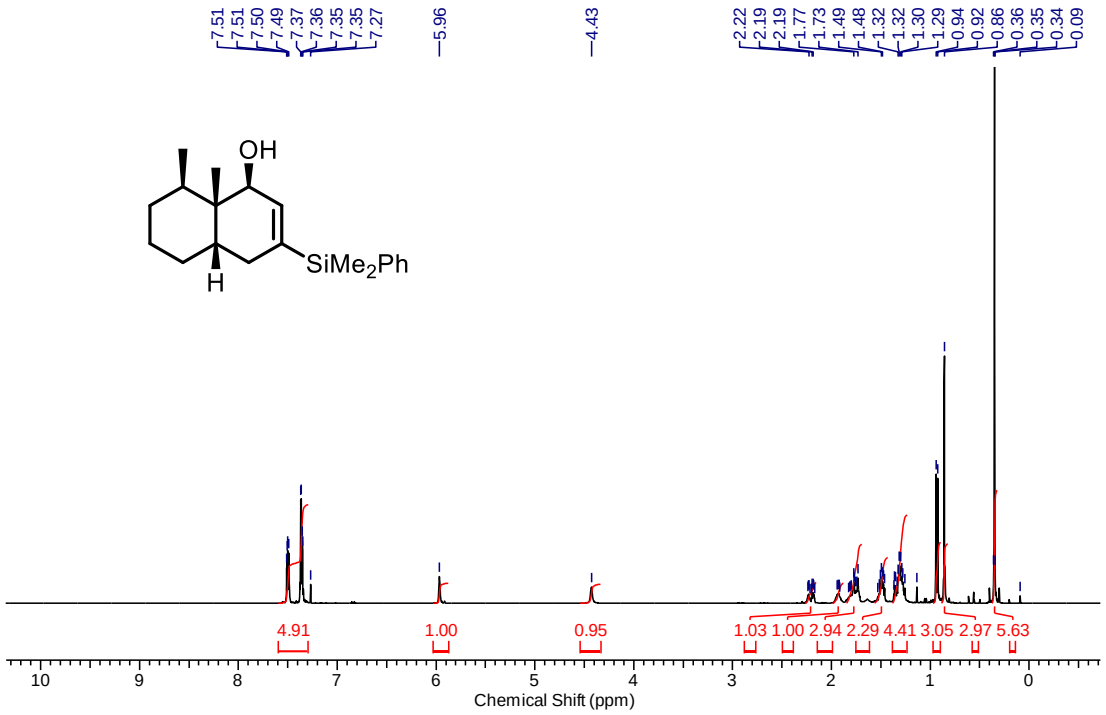
^{1}H NMR of Compound **127g** in $CDCl_3$ at 400 MHz



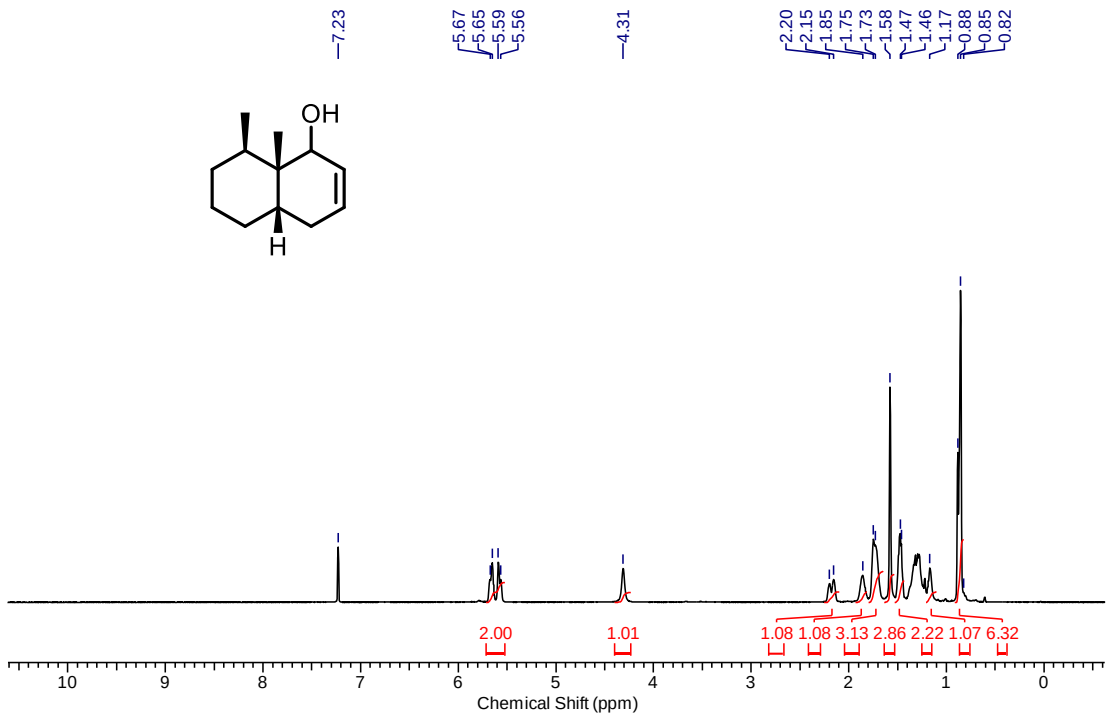
^{1}H NMR of Compound **127h** in $CDCl_3$ at 500 MHz



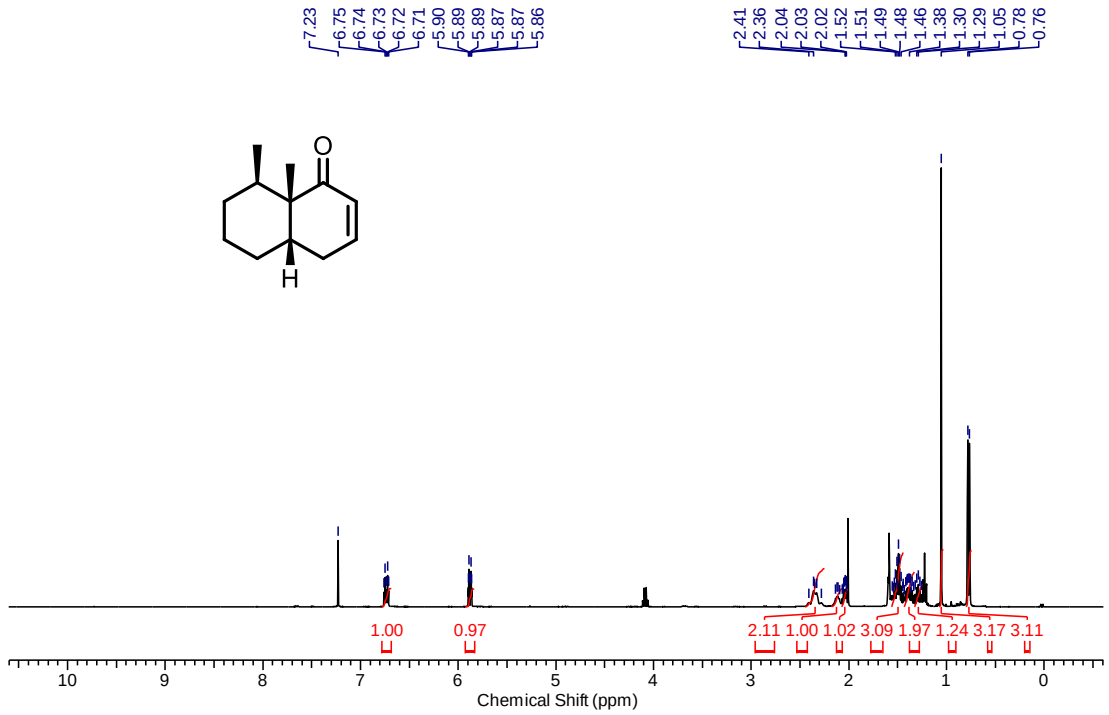
^{1}H NMR of Compound **128b** in $CDCl_3$ at 400 MHz



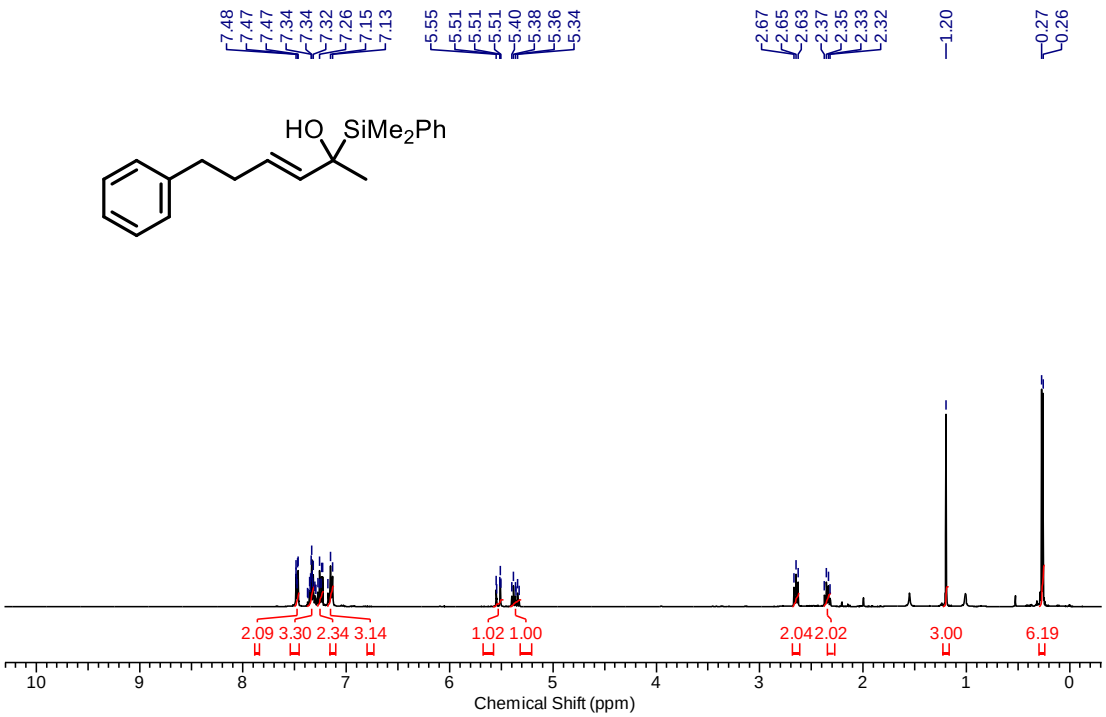
^{1}H NMR of Compound **128c** in $CDCl_3$ at 400 MHz



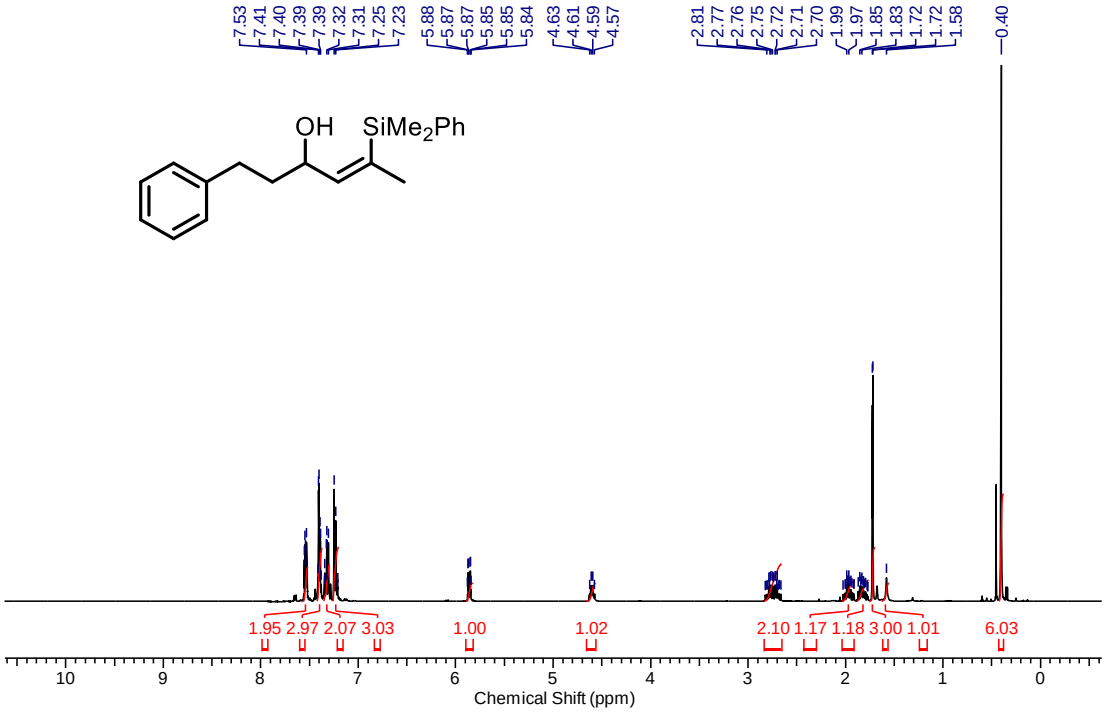
^{1}H NMR of Compound **128d** in $CDCl_3$ at 400 MHz



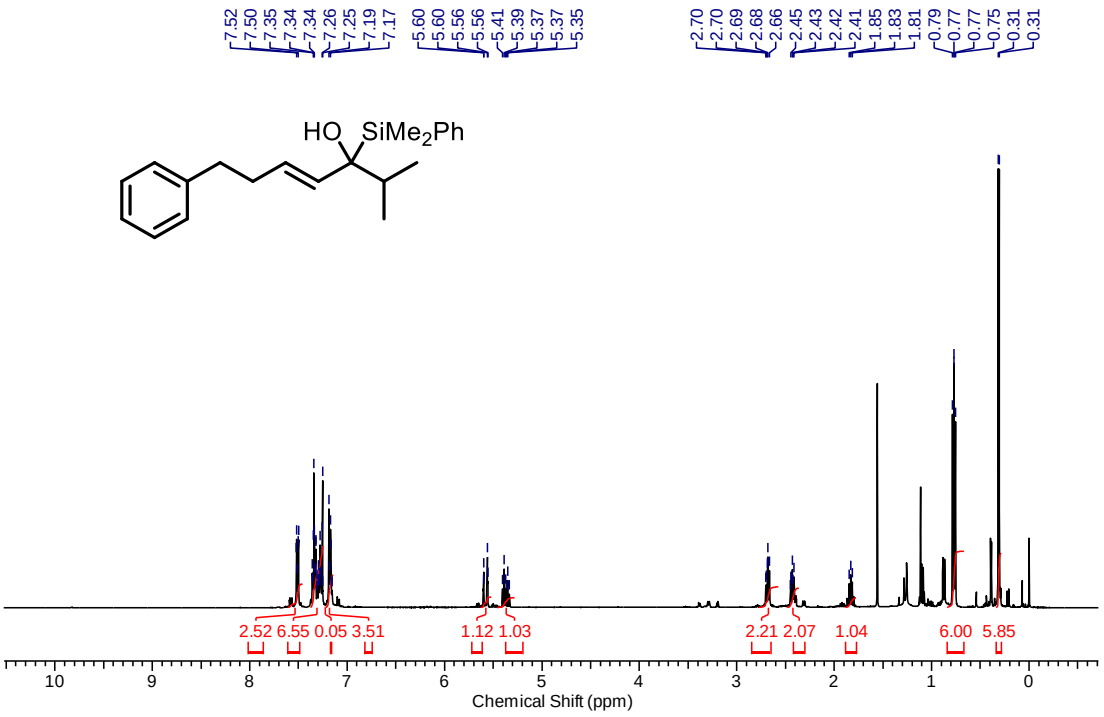
^{1}H NMR of Compound **128e** in $CDCl_3$ at 400 MHz



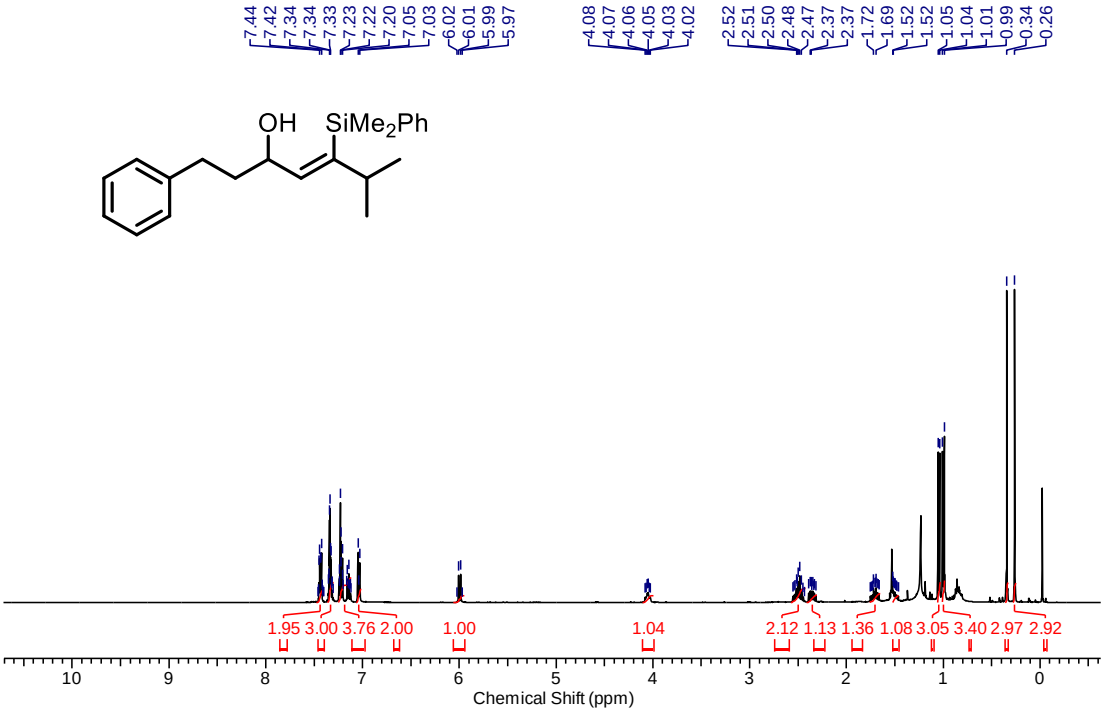
^{1}H NMR of Compound **129b** in $CDCl_3$ at 400 MHz



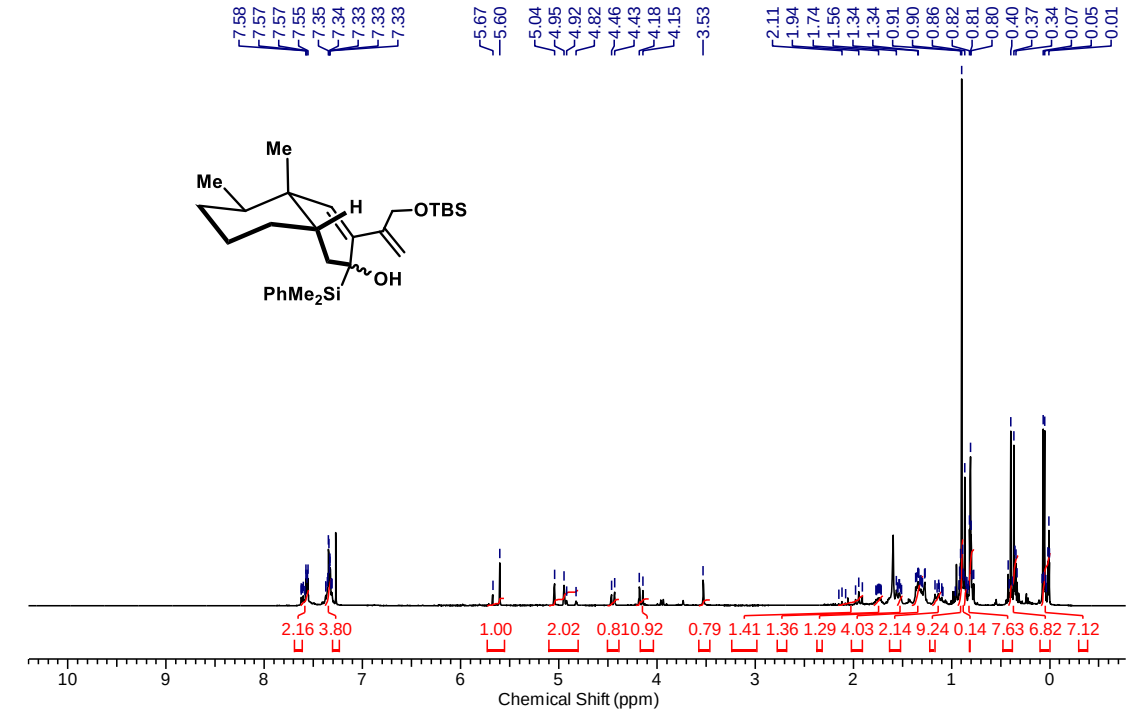
^{1}H NMR of Compound **129c** in $CDCl_3$ at 400 MHz



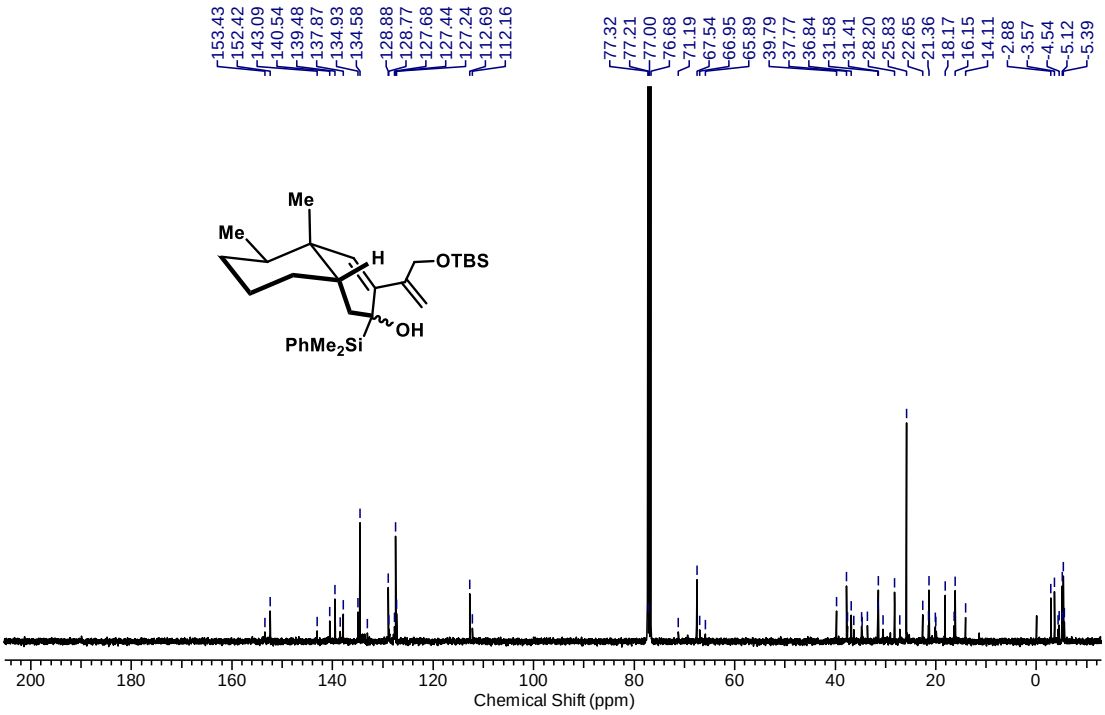
^{1}H NMR of Compound **130b** in $CDCl_3$ at 400 MHz



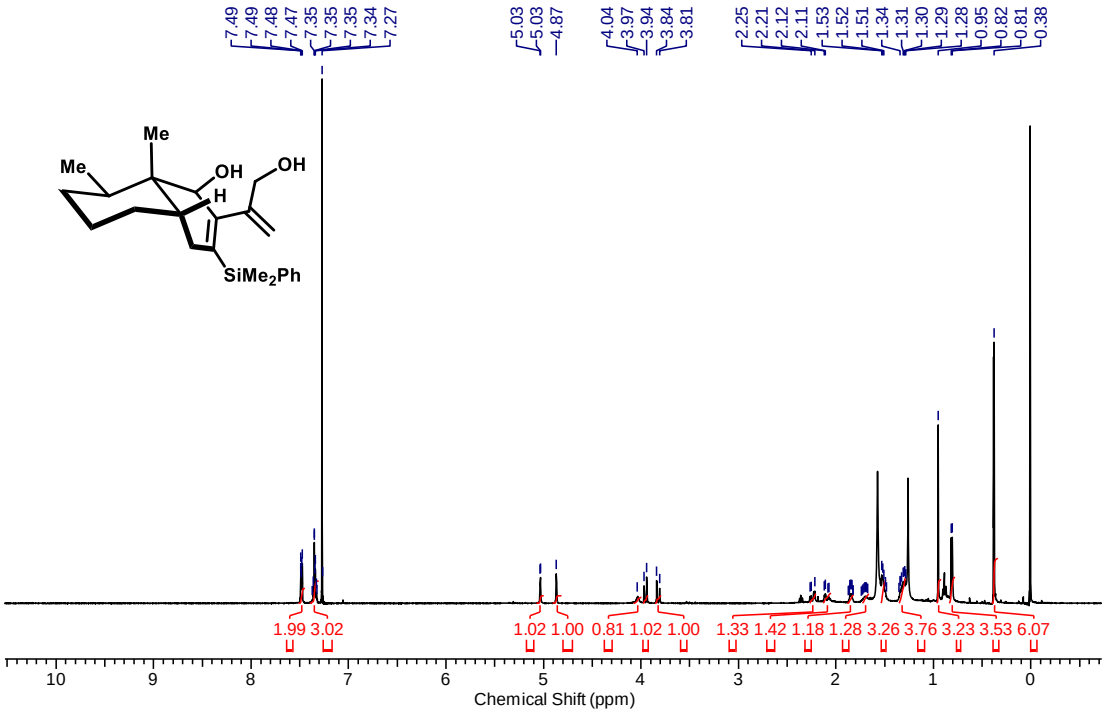
^{1}H NMR of Compound **130c** in $CDCl_3$ at 400 MHz



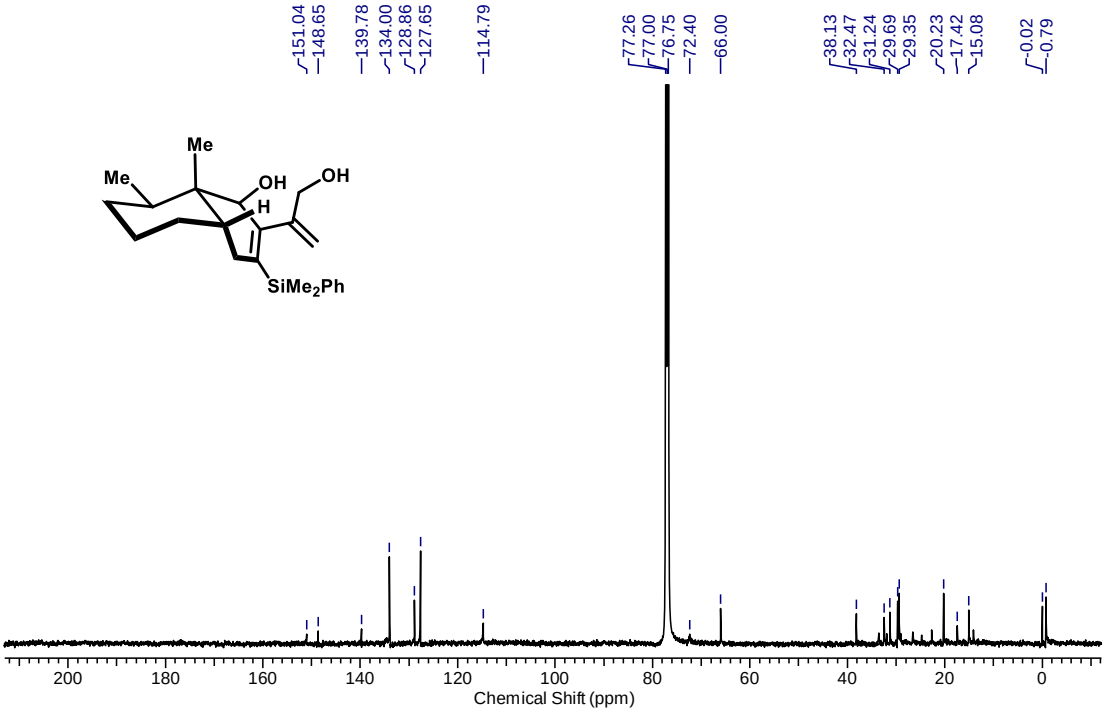
^{1}H NMR of Compound **132** in $CDCl_3$ at 400 MHz



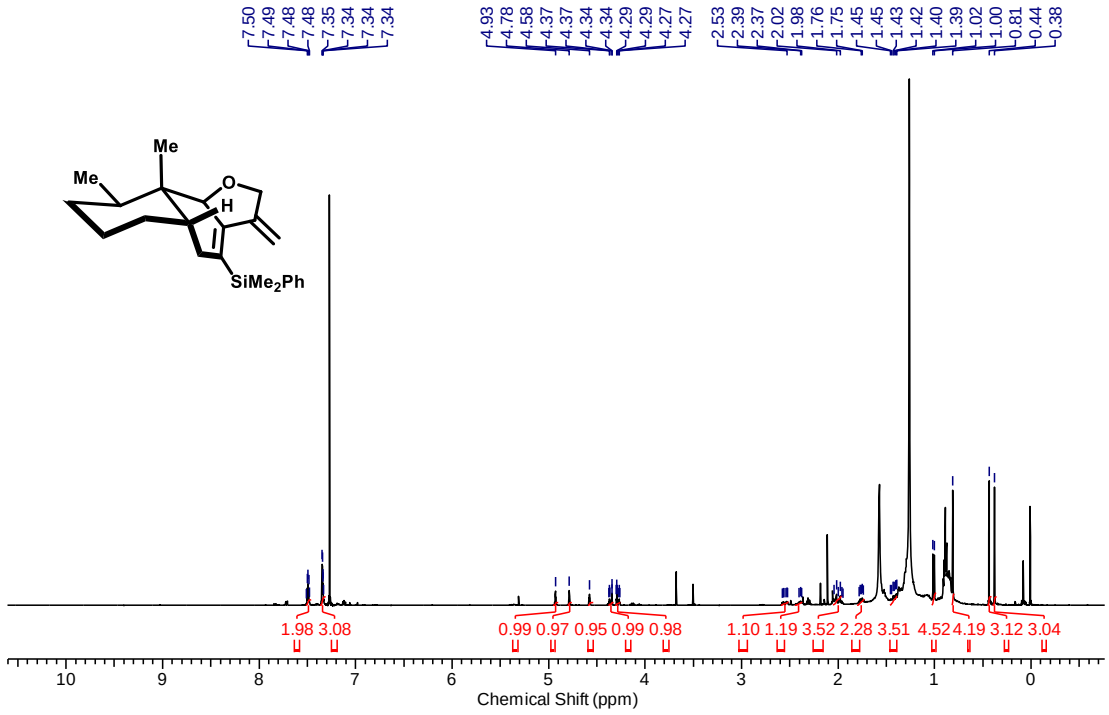
^{13}C NMR of Compound **132** in $CDCl_3$ at 100 MHz



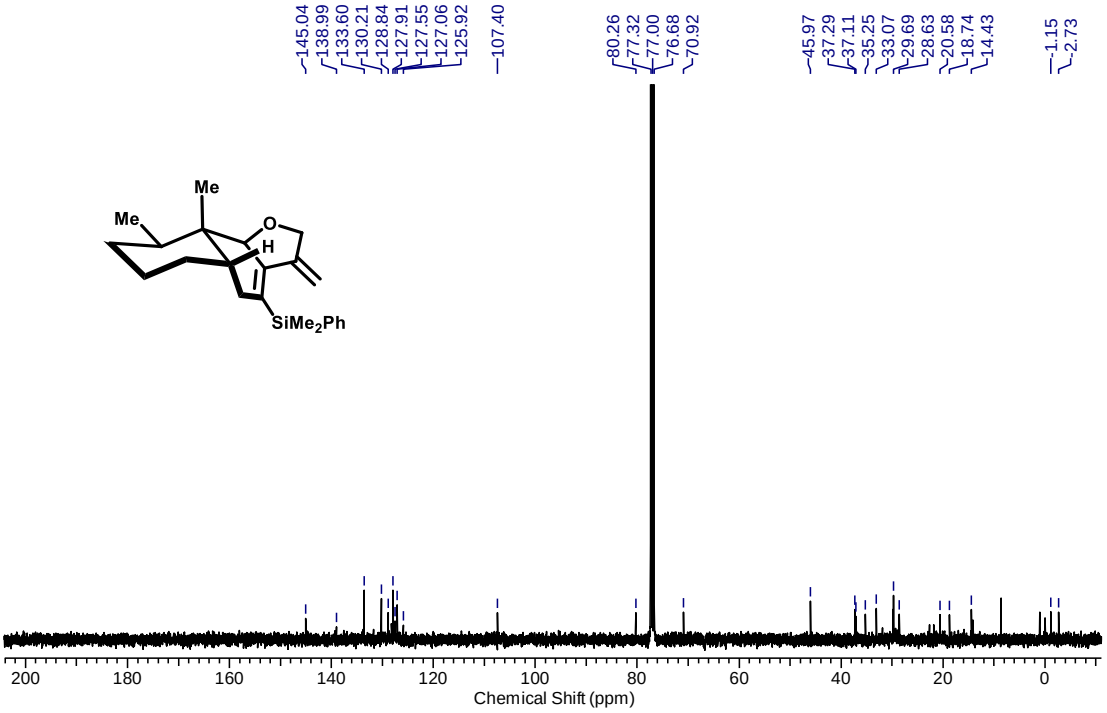
^{1}H NMR of Compound **133** in $CDCl_3$ at 400 MHz



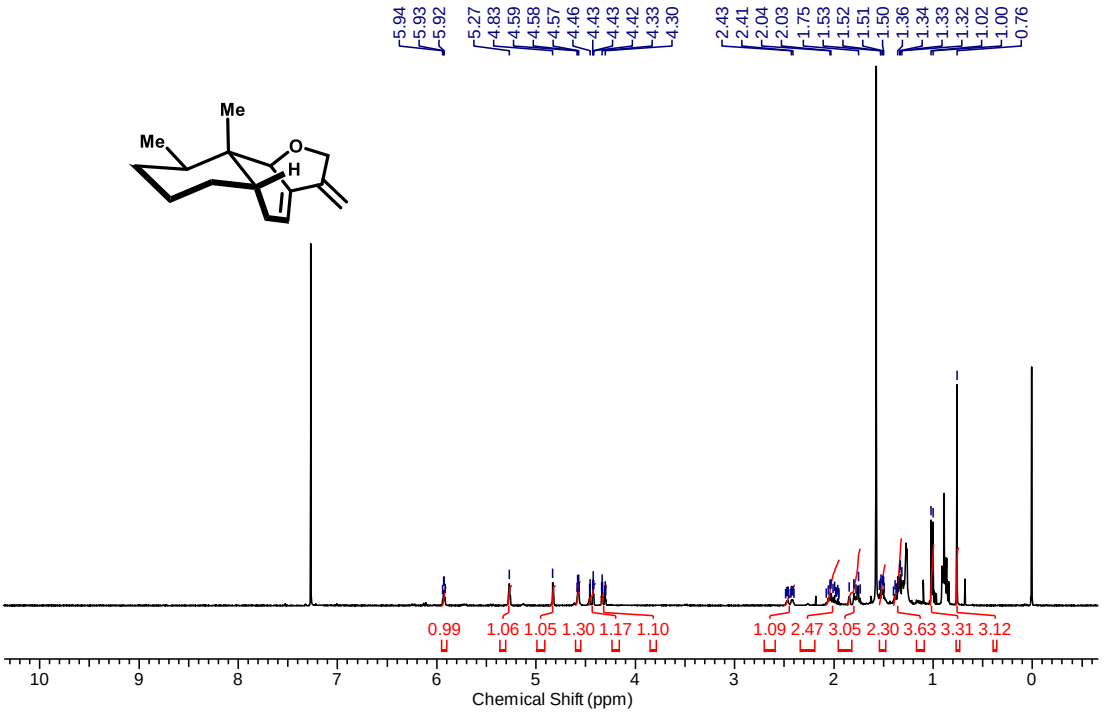
^{13}C NMR of Compound **133** in $CDCl_3$ at 100 MHz



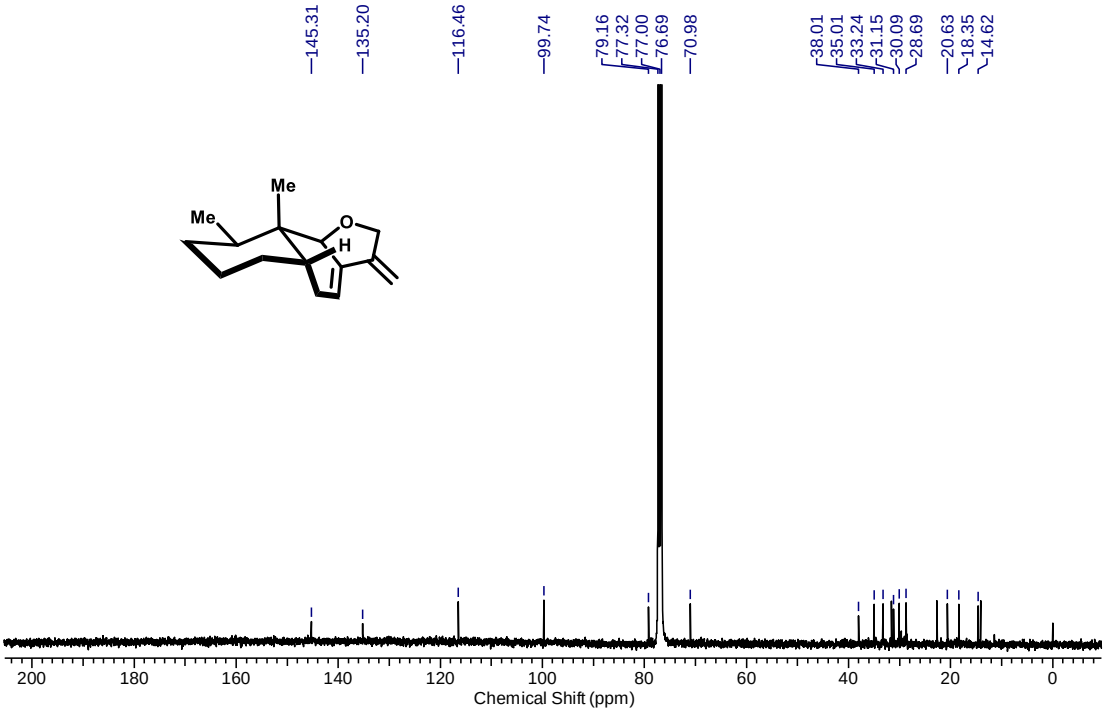
^{1}H NMR of Compound **134b** in $CDCl_3$ at 400 MHz



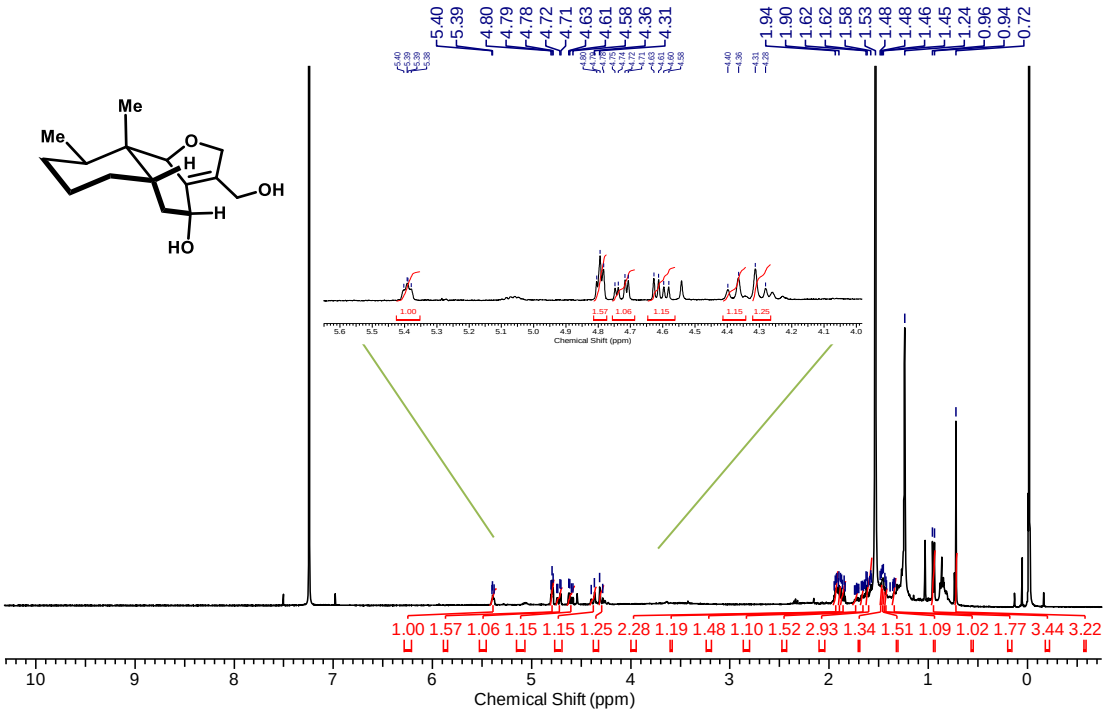
^{13}C NMR of Compound **134b** in $CDCl_3$ at 100 MHz



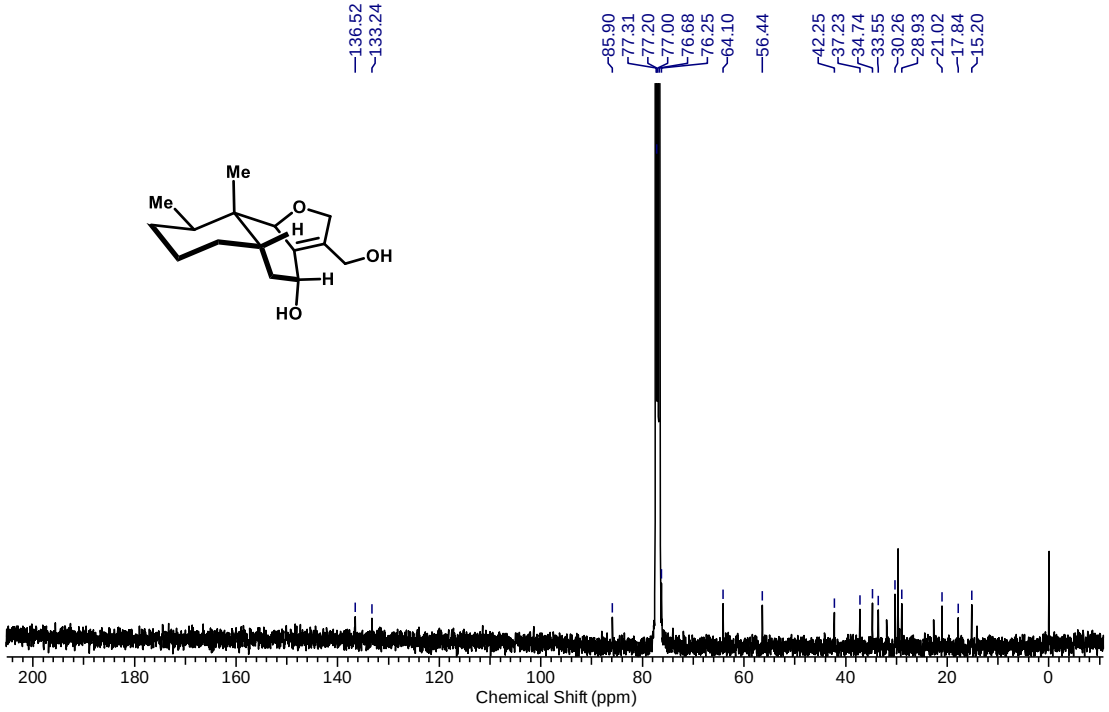
^{1}H NMR of Compound **135** in $CDCl_3$ at 400 MHz



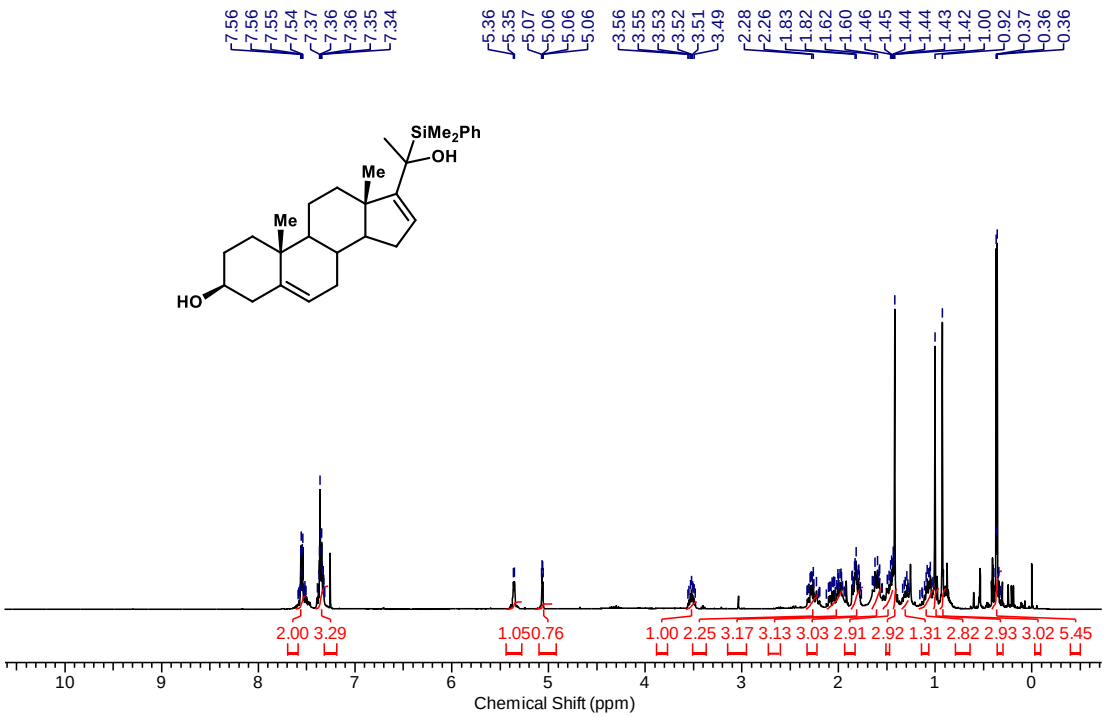
^{13}C NMR of Compound **135** in $CDCl_3$ at 100 MHz



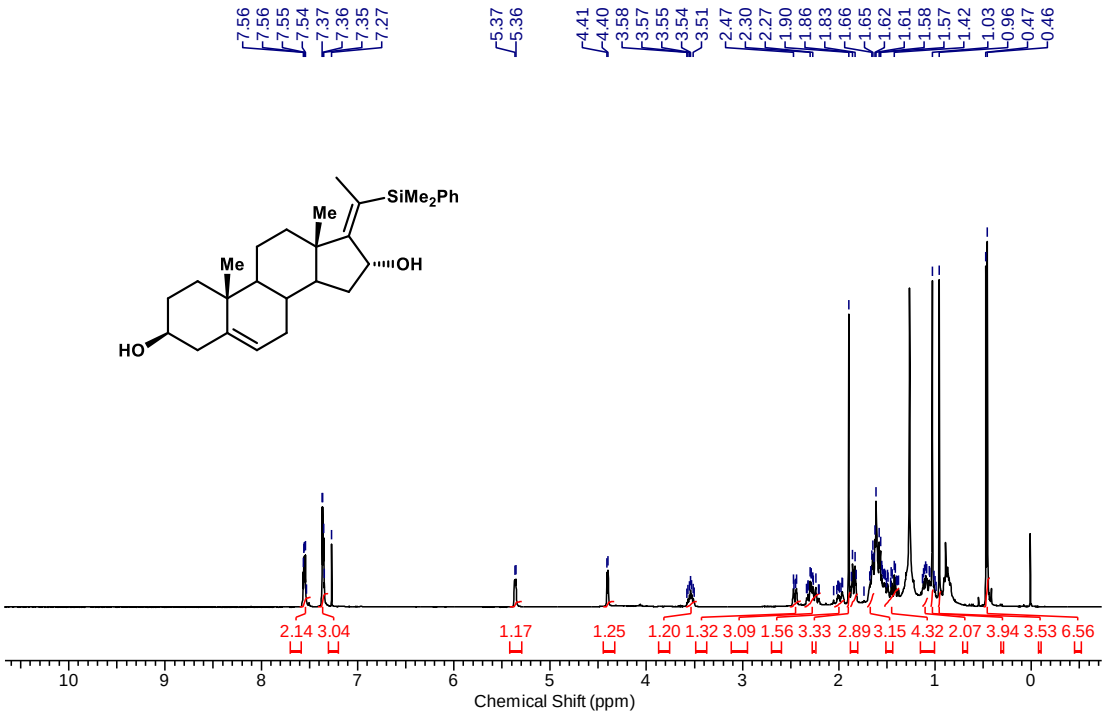
^{1}H NMR of Compound **26** in $CDCl_3$ at 400 MHz



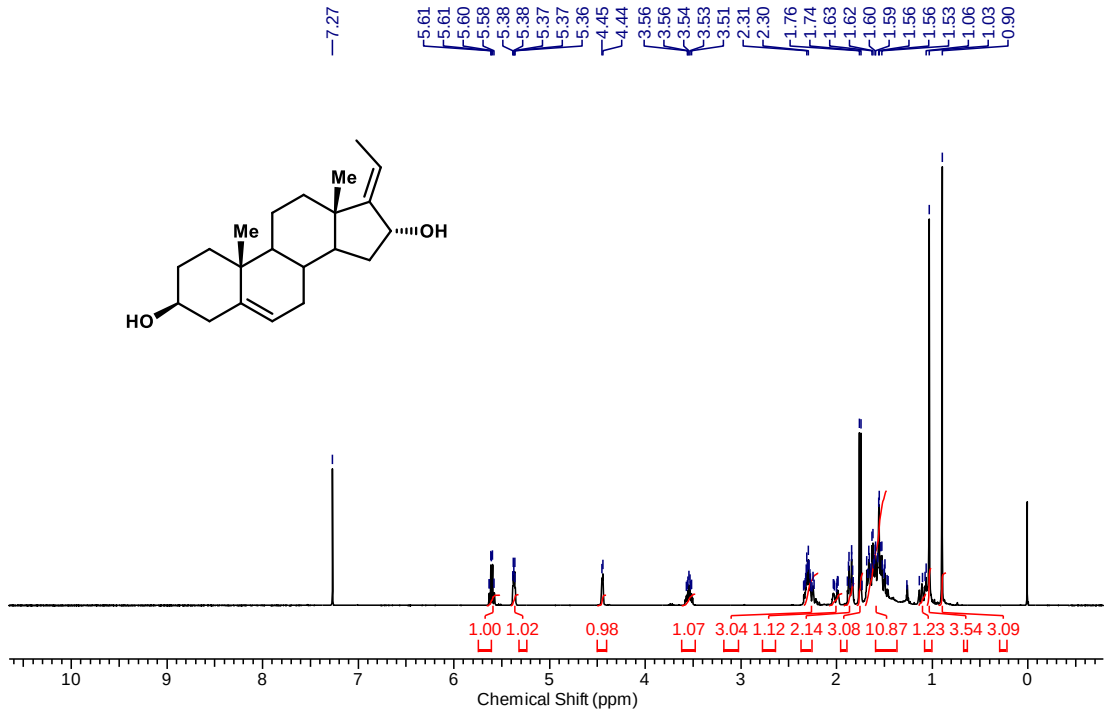
^{13}C NMR of Compound **26** in $CDCl_3$ at 100 MHz



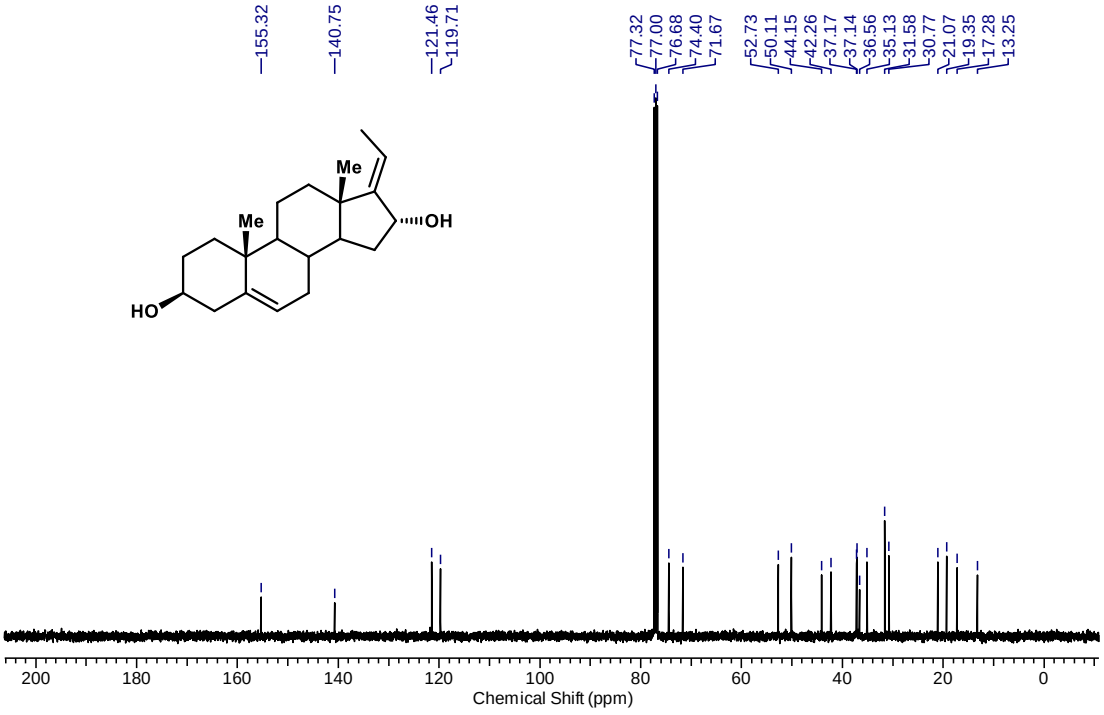
^{1}H NMR of Compound **137** in $CDCl_3$ at 400 MHz



^{1}H NMR of Compound **138** in $CDCl_3$ at 400 MHz



^{1}H NMR of Compound **139** in $CDCl_3$ at 400 MHz



^{13}C NMR of Compound **139** in $CDCl_3$ at 100 MHz

Chapter 2-Section 2

2.2.1 Introduction

Allylic oxidation reaction is one of the popular reactions in organic synthesis and has great impact on chemistry of natural products and pharmaceutically vital molecules.[1] The scouting of newer methods for allylic oxidations is an active and ever developing area from past few decades.[2] Till date hundreds of different reagents and conditions have been developed (majority of them are metal based). However, due to limitations such as poor chemoselectivity, regioselectivity and the requirement of stoichiometry of toxic metallic reagents have impacted largely on use of these methods on industrial scale.[3] Generally, in these type of reactions double bond co-ordinates to the metal catalysts and activates allylic C-H bond which in turn assist the installation of oxygen functionality at allylic carbon.

Conventionally, various chromium (VI) based reagents such as pyridiniumchlorochromate (PCC), pyridinium dichromate (PDC), PDC/TBHP combination, CrO_3–pyridine complex, CrO_3–3,5-dimethylpyrazole, sodium chromate or dichromate in acetic acid, pyridiniumfluorochromate, etc. have been widely used by synthetic chemists to attain allylic oxidation reactions.[4] Some of the other metallic reagents include MnO_2, $Mn(OAc)_3$, selenium dioxide, potassium permanganate which are required in stoichiometric amount.[5] Some of the efficient catalytic methods include palladium, rhodium, iron, copper or cobalt based catalysts majority of which are costly, and must not be present above certain ppm levels in the pharmaceutical products due to their toxic effects.[3]

Although, a lot of research has already been conducted on development of such reagents, they become less preferred for the industrial scale production because of the quantities of reagents required, higher volumes of solvent required and tedious work-up procedures. In addition, stoichiometric metallic waste is generated during the course of the reaction. Some of the reported methods for allylic oxidation in natural product synthesis are captured in Figure 2.2.1.Omura *et al*. during the synthesis of (+)-pyripyropene A used SeO_2 in dioxane for allylic C-H oxidation which gave allylic alchohol which on further oxidation with PCC gave compound **144**.[6]

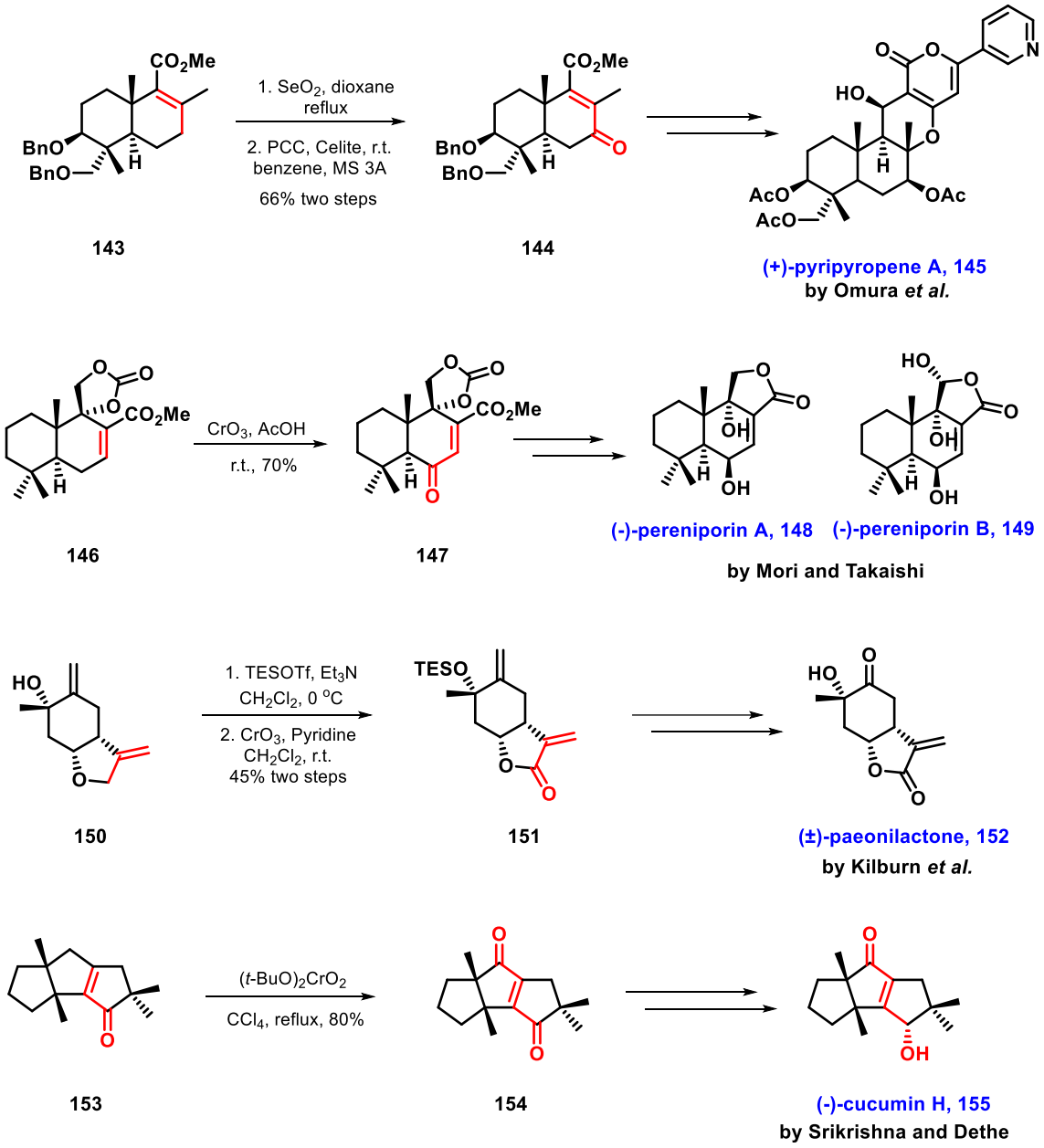


Figure 2.2.1 Selected examples of selenium and chromium based allylic oxidations in natural product synthesis

Mori and Takaishi used CrO_3 in acetic acid to obtain enone **147** which they further transformed into pereniporin A and B. Kilburn and co-workers wanted to perform selective allylic oxidation next to oxygen functionality during their synthesis of paeonilactone where they took help of CrO_3-Pyridine condition for accessing the desired product **151**. In the

synthesis of cucumin H, Srikrishna and Dethe used $(t\text{-BuO})_2CrO_2$ as an oxidizing agent to get selectively 1,4-diketo functionality, **154**. Apart from these there are several other non-chromium based metallic reagents widely used for this purpose which are captured Figure 2.2.2.[7] Sutherland *et al*. during the synthesis of an alkaloid (+)-physoperuvine used Pd/C and TBHP combination to generate enone functionality **157**.[8]

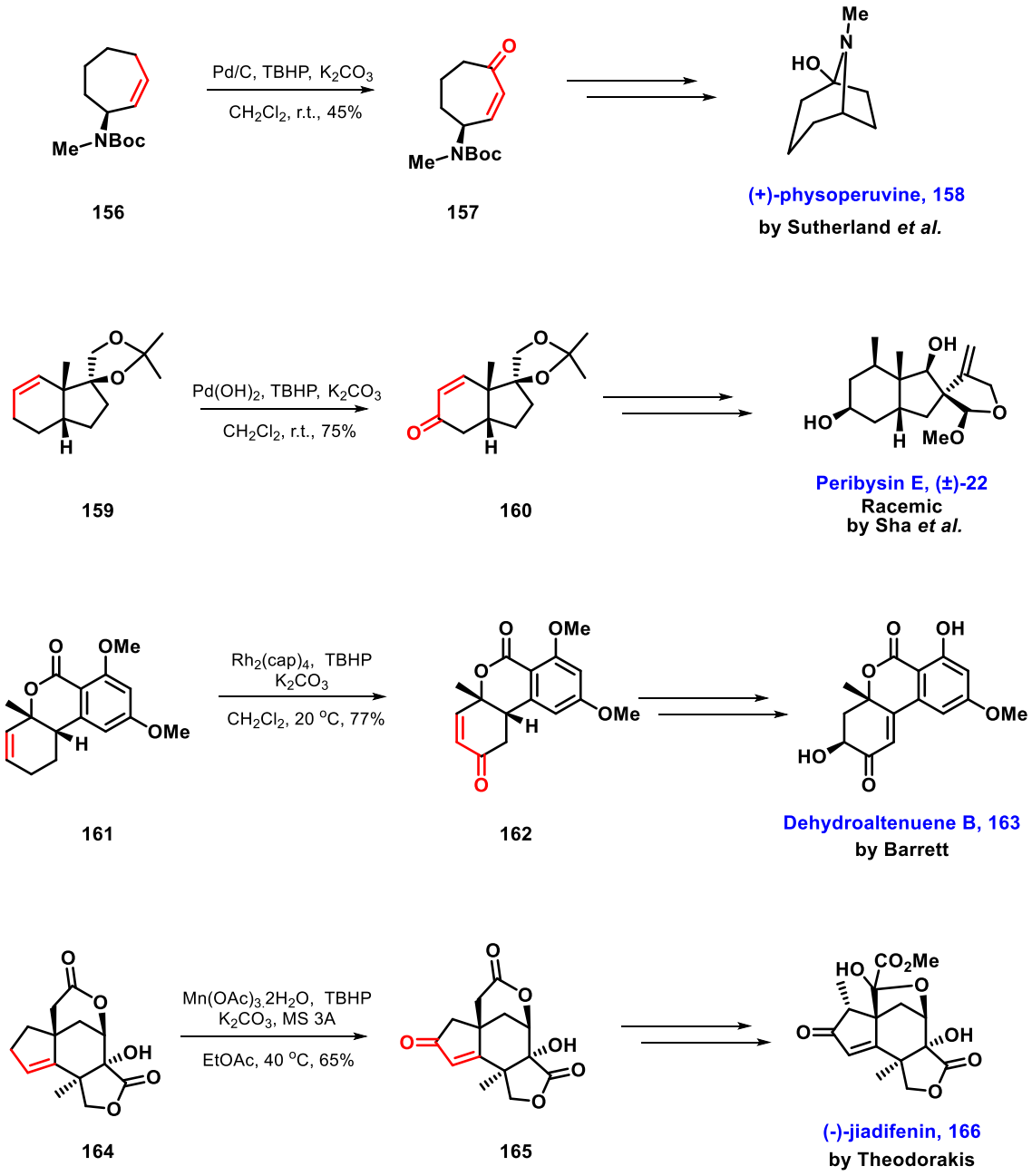
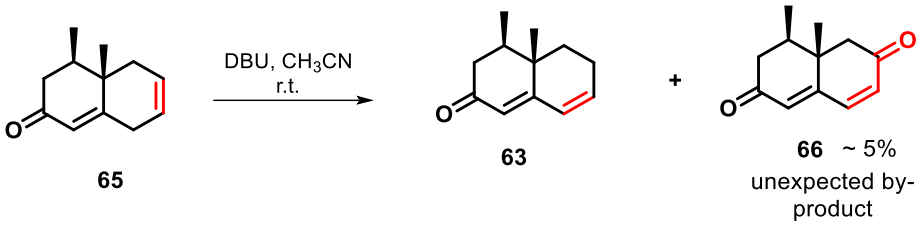


Figure 2.2.2 Pd, Rh and Mn based allylic oxidations in natural product synthesis

As discussed earlier (in chapter 1 figure 1.4) Sha and co-workers used $Pd(OH)_2$ and TBHP combination in presence of K_2CO_3 to get enone **160**. Here basic condition was used in order to keep acetonide functionality intact. Dehydroaltenuene B synthesis was accomplished by Barrett *et al*. where they employed $Rh_2(cap)_4$ and TBHP combination to perform allylic oxidation. Theoderakis and group used $Mn(OAc)_3.2H_2O$ and TBHP in presence of 3Å molecular sieves to perform allylic oxidation on substrate **165** having other sensitive functional groups.

2.2.2 Background of the work

Although there are various allylic oxidations reported in the literature,[9] the development of metal-free, eco-friendly synthetic transformations are highly desirable.[10] In this context, while we were working on synthesis of peribysin family natural products, we made an interesting observation when we wanted to perform a double bond migration reaction in compound **65** to get compound **63**.[11] During the synthesis of peribysin family of natural products a double bond migration reaction was performed using DBU in acetonitrile to get the conjugated dienone **63**. Surprisingly, in addition to the expected product **63** we observed formation of side-product **66** in approximately 5% yield. The structure of side product **66** was confirmed by ^1H and ^{13}C NMR where two carbonyl carbons at δ 197.8 and 198.6 ppm were observed and one allylic methylene group was absent. Further, the HRMS peak was observed at 191.1064 calculated for the molecular formula $C_{12}H_{15}O_2$ $[M+H]^+$ 191.1067.



65 **63** **66** ~ 5% unexpected by-product

Scheme 2.2.1 Unexpected side-product observed during double bond migration reaction

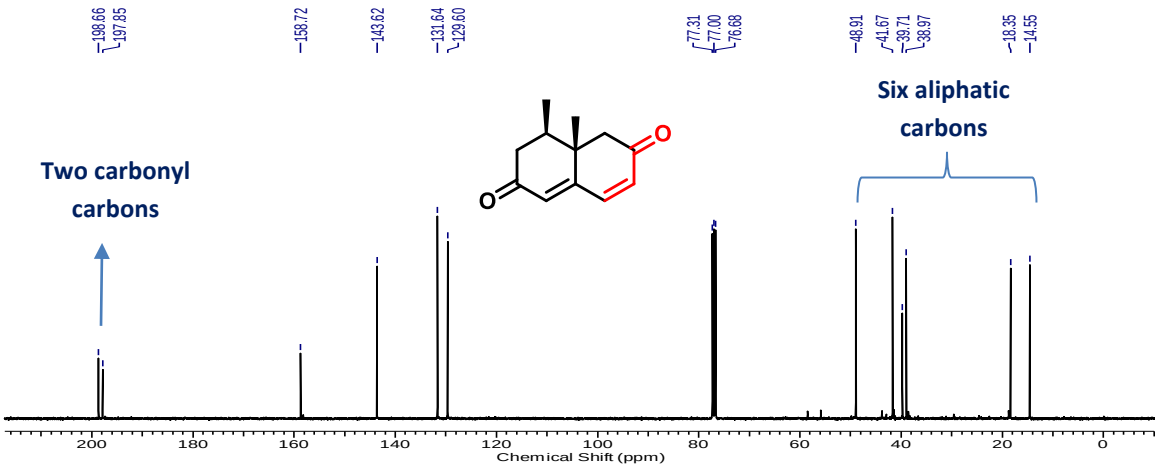
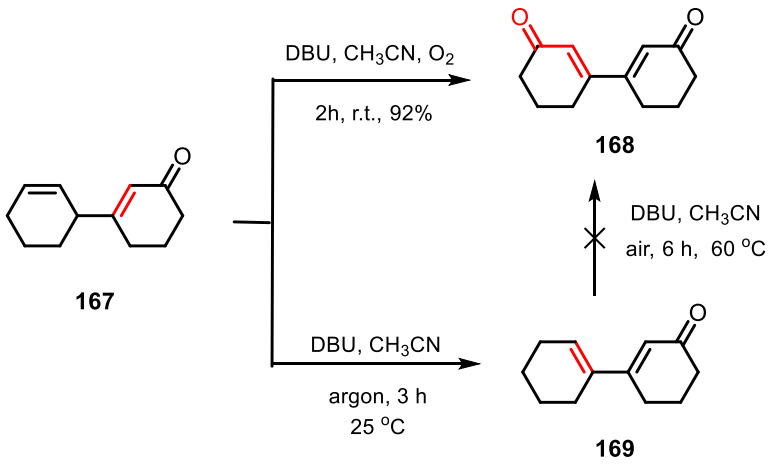


Figure 2.2.3 Characterization of observed side-product

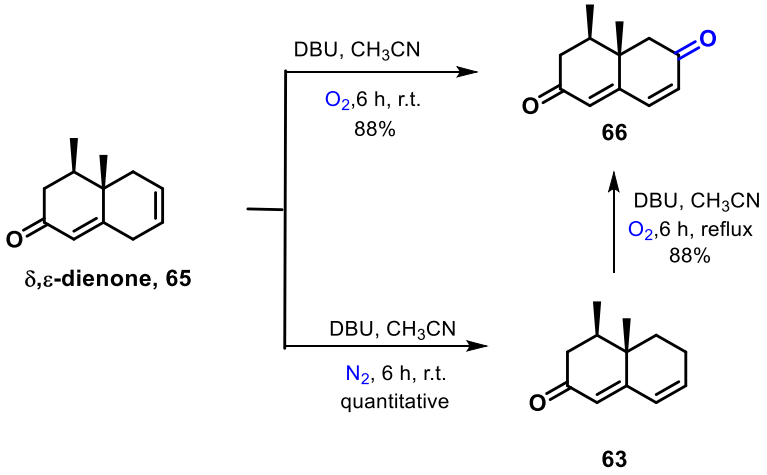
Based on literature survey, we found that a similar kind of observation was reported by P. L Fuchs et al. in 1994.[12] In this report, authors reported that when compound **167** was treated with DBU in acetonitrile under air (in presence of oxygen) the oxidized 2,6-dione **168** was observed in 92% yield. The same compound under innert atmosphere when treated with DBU in acetonitrile gave double bond migrated compound **169**. Further conversion of **169** to **168** was not successful when heated at 60 °C for six hours.



Scheme 2.2.2 Literature report by P. L. Fuchs *et al.*

With this background, we decided to conduct control experiments on our substrate **65** under innert and oxygen atmosphere. For this purpose, the starting material **65** was taken in two different round bottom flasks in dry acetonitrile. The first reaction mixture was purged with

oxygen for 10 min and second reaction mixture with nitrogen gas for 10 min. After 10 min DBU was added to both the reaction mixtures at room temperature. The reaction under oxygen atmosphere gave compound **66** in 88% yield whereas the reaction under nitrogen atmosphere gave quantitative yield of **63**. Further we heated **63** under oxygen atmosphere for six hours to check the possibility of conversion of **63** to **66** (because in majority of the cases it is difficult to produce deconjugated enone). To our delight we observed 88 % formation of **66** after refluxing for six hours. With all these experiments, we concluded that the dissolved oxygen was acting as a oxidant and giving the 2,6-dione derivatives with conjugated as well as deconjugated enone.



Scheme 2.2.3 Control experiment

In our previous work, we employed this un-optimized reaction condition for the total synthesis of a natural product (±)-periconianone A having 2,6-dione skeleton.[13] There are dozens of natural products isolated every year with various biological activities and which posseses 2,6-dione skeleton. A few selected natural products having naphthalene-2,6-dione skeleton are captured in figure 2.2.7.[14]

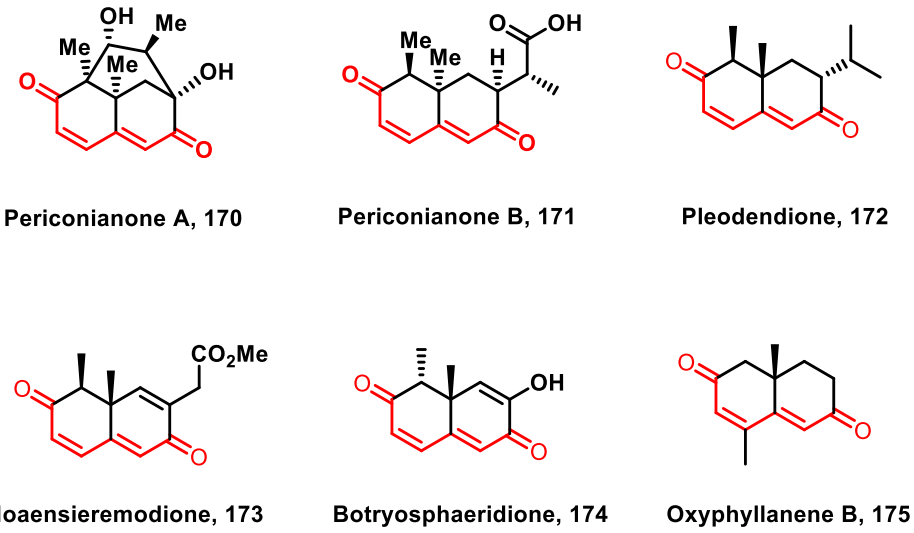
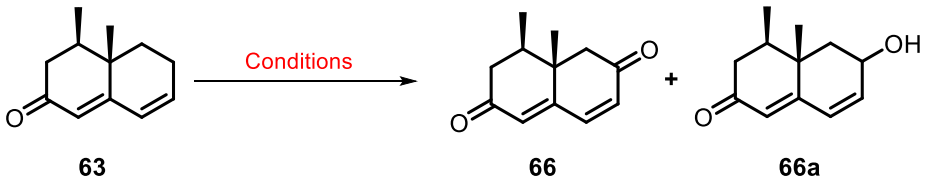


Figure 2.2.4 Natural products having 2, 6-oxygen functionality

2.2.3 **Reaction Optimization**

With this background and considering the wide presence of natural products with 2,6-dione skeleton we decided to study the method for accessing these moieties by using DBU/O_2 condition. For this purpose we selected compound **63** as our model substrate since we had easy access to good quantity of this compound.



Scheme 2.2.4 Reaction optimization

First, to compare our reaction condition with well known condition, we treated compound **63** with 5 equivalents of PDC and 5 equivalents of TBHP (Table 2.2.1, entry 1) in benzene as a solvent which gave only 28% isolated yield of the desired product **65** and 40% of the starting material was recovered.[15] Next, we moved to our reaction condition using 1.5 eq. of DBU (entry 2) in acetonitrile under oxygen atmosphere (balloon pressure) at 80 ^oC for 12 hours. After the workup and isolation using column chromatography, two products were characterized compound **66** and alcohol **66a** along with 45% of the starting material. Then we increased the equivalents of DBU from 1.5 to 2.5 equivalents, it gave 46% yield of

Table 2.2.1. Optimization of Reaction Conditions[a]

Sr. No.	catalyst/base (equiv.)	oxidant/ promoter (equiv.)	solvent	temp (ºC)	time (h)	yield (%)[c]		
						product **66**	starting **63**	alcohol **66a**
1	-	PDC(5)/ TBHP(5)	Benzene	rt	16	28%	40%	-
2	DBU (1.5)	-	CH_3CN	80	12	36%	45%	<10%
3	DBU (2.5)	-	CH_3CN	80	6	46%	32%	<5%
4	**DBU (2.5)**	**-**	**CH_3CN**	**80**	**12**	**94%**	**ND**	**ND**
5	DBU (2.5)	-	1,4-dioxane	80	12	49%	46%	<5%
6	DBU (2.5)	-	THF	reflux	12	trace	~92%	ND
7	DBU (2.5)	-	EtOAc	reflux	12	18%	77%	trace
8	DBU (2.5)	-	DMSO	80	12	decomposed		
9	DBU (2.5)	-	1,2-DCE	80	12	4%	90%	ND
10	DBU (2.5)	-	Toluene	80	12	9%	86%	trace
11	DBU (2.5)	-	DMF	80	12	decomposed		
12	NMM (2.5)	-	CH_3CN	80	12	trace	90%	ND
13	DIPEA (2.5)	-	CH_3CN	80	12	ND	98%	ND
14	DABCO (2.5)	-	CH_3CN	80	12	ND	95%	ND
15[b]	-	-	CH_3CN	80	12	ND	98%	ND
16	$Pd(OH)_2/C(0.05)/K_2CO_3(0.5)$	TBHP (5)	CH_2Cl_2	rt	12	trace	91%	ND

[a] Reaction conditions: dienone (**63**, 1.0 mmol), catalyst (0.05 mmol) or and base (0.5-2.5 mmol) or oxidant (5 mmol) and promoter (5 mmol), solvent (10 mL) were stirred at r.t. to reflux for 6-24 h. [b] In the absence of catalyst or base. [c] Isolated yields. Abbreviations: PDC = pyridinium dichromate, TBHP = *tert*-butyl hydroperoxide, DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, NMM = *N*-methylmorpholine, DIPEA = *N*,*N*-diisopropylethylamine, DABCO = 1,4-diazabicyclo[2.2.2]octane, ND = not detected.

compound **66** after 6 hours and under same condition it gave 94% yield when heated for 12 hours (entry 3 and 4).To optimize the reaction further in order to get the quantitative yield of **66**, we then screened with various solvents such as 1,4-dioxane, THF, EtOAc, DMSO, 1,2-DCE, toluene, DMF etc. but no better yields were obtained (entries 5 to 11). Then by keeping the solvent fixed to acetonitrile, we then screened with various bases such as NMM, DIPEA, DABCO etc. but none of the bases gave the desired product **66**. Instead, we recovered the starting material in all the cases (entries 12 to 14). Next, we performed a reaction in absence of base keeping all the other parameters constant, but no product formation was observed. Finally, to compare our method with one more reported method, we treated compound **63** with $Pd(OH)_2$ and TBHP but no desired product was obtained (entry 16).[16] After screening all the conditions listed in Table 2.2.1 we finally settled for condition no. 4 as the best condition for this transformation.

2.2.4 **Substrate Scope**

After getting the best conditions for obtaining 2,6-diones, we then next focused on testing this method with a variety of substrates. For this purpose, we divided the starting materials into two categories. One category having de-conjugated systems and another category having conjugated systems. In case of α-ionone, the deconjugated double bond migrated followed by oxidation when stirred at room temperature for 12 h to give 76% isolated yield of **176b**. In ^{13}C NMR of compound **176b** two carbonyl carbons were observed at δ 198.3 and 197.2 ppm which further gave the confirmation for formation of diketo compound. Next we prepared deconjugated ethyl sorbate by using known procedure which under optimized condition gave 30% (90% brsm) of the expected product **177b**. Here the reaction was found to be sluggish and needs heating for 24 h. When acyclic dienone **178a** was subjected for oxidation under optimized condition, it gave 48% yield of the corresponding diketo compound **178b**. Similarly, reactions of *β*-ionone and conjugated enone **180a** underwent oxidation smoothly to give 68% and 54% yields respectively. Here it is interesting to note that the reaction of corresponding deconjugated substrate *α*-ionone gave slightly better yields than the conjugated substrate *β*-ionone. In case of tricyclic enone **180a** we observed hydroxylated diketo compound **180b** in 52% yield which was completely

characterized by spectral means. In the ^{13}C NMR of the product **180b** an additional carbonyl peak appeared compared to starting material and an OH attached quaternary carbon was observed at δ 66.5 ppm which was in accordance with the structure **180b**.

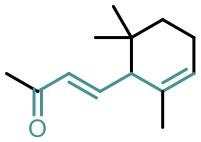
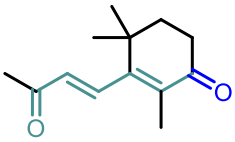
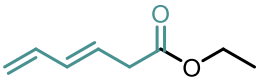
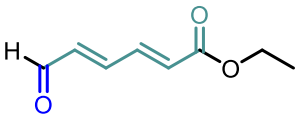
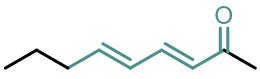
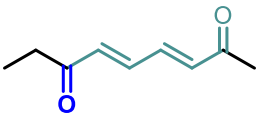
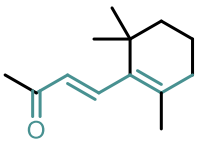
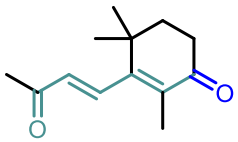
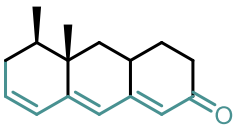
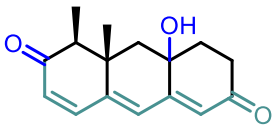
Substrate	Product	time/temp.	Yield
 α-ionone, 176a	 176b	12h, r.t.	76 %
 177a	 177b	24h, reflux	90% brsm (30%)
 178a	 178b	12h	48%
 β–ionone, 179a	 176b	12h	68%
 180a	 180b	19h	52%

Table 2.2.3 Substrate scope

After completing the deconjugated substrates, next we focused on reaction of conjugated enones, and for this purpose we prepared few starting materials with dienone moiety using

the Diels-Alder strategy developed in our group for the construction of decalin skeleton (substrates **185a** to **189a** in Table 2.2.4).[17a] The benzyl substituted enone was prepared by the procedure similar to the one reported by Yadav *et al*.[17b]

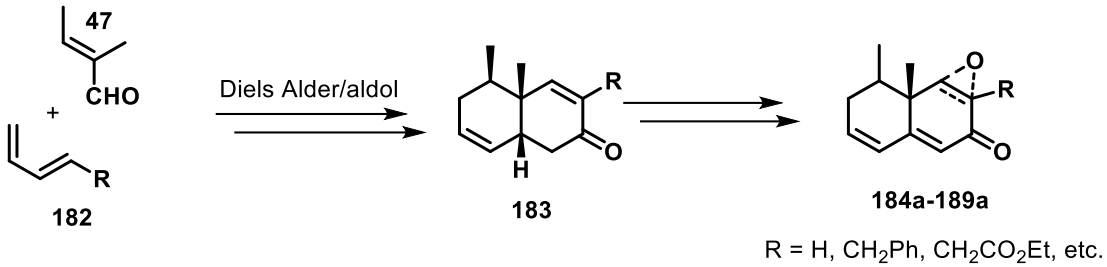


Figure 2.2.5 Synthesis of dienone starting materials

Reaction of benzyl substituted enone **184a** under standardized condition gave the expected oxidized product **184b** in 79% yield. Although, we were sure about the assigned structure of the product, we further confirmed it through analysis using single crystal X-ray structure which clearly indicated that no other regioisomer was formed (figure 2.2.9). The oxidation reaction of trienone **185a** and epimerized trienone **185b** underwent smoothly to give 75% and 44% yield respectively. Next, we tested the substrates having epoxy, allyl, ester and *tert*-alchohol functional groups which gave the corresponding oxidized products (**187a** to **190a**) in yields ranging from 44 to 63%. In ^{13}C NMR of compound 187b an methylene CH_2 was vanished and an additional carbonyl carbon appeared at δ 197.88 ppm and in the ^{1}H NMR epoxide peaks were observed at δ 3.48 and 3.68 ppm which further confirmed the product **187b**.

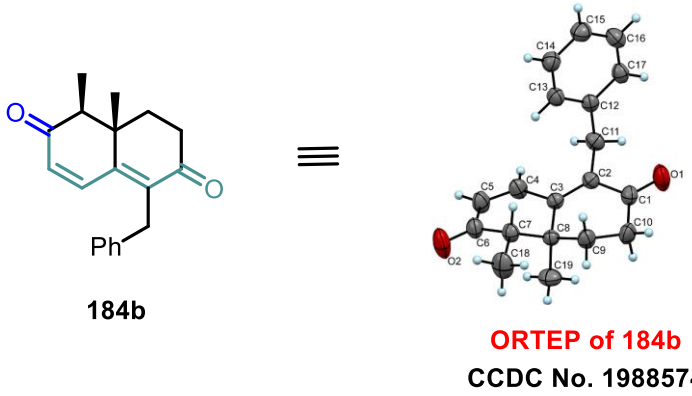


Figure 2.2.6 Single crystal X-ray structure of compound **184b**

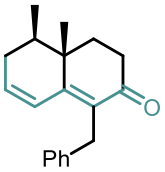
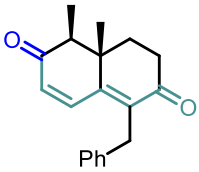
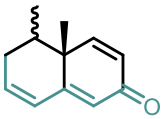
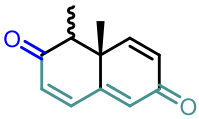
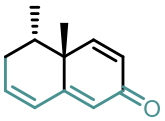
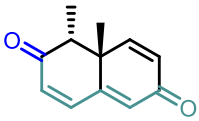
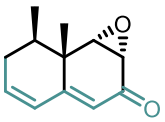
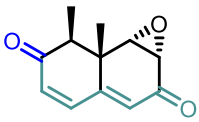
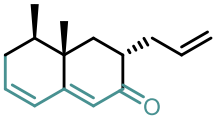
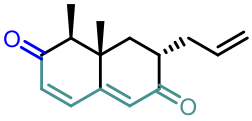
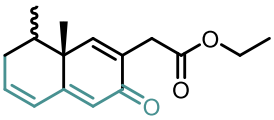
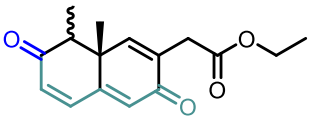
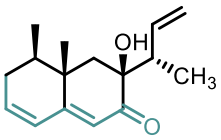
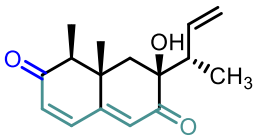
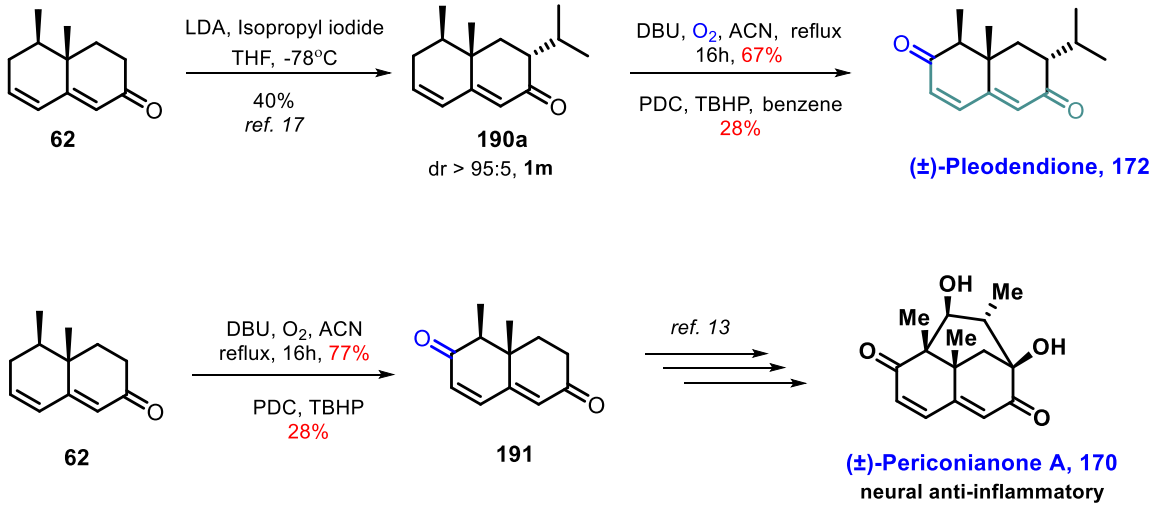
Substrate	Product	time[a]	Yield
 184a	 184b	14h	79%
 185a	 185b	12h	94%
 186a	 186b	8h	75%
 187a	 187b	10h	44%
 188a	 188b	13h	61%
 189a	 189b	16h	63%
 190a	 190b	18h	48%

Table 2.2.4 Substrate scope

2.2.5. Applications of the developed method:

2.2.5.1. Synthesis of (±)-Pleodendione

After successfully testing the scope of the method with various substrates we then focused on the application of this method in natural product synthesis. For this purpose we selected a natural product pleodendione which was previously synthesized in our group employing PDC-TBHP method for allylic oxidation. For this purpose we prepared compound **190**a following the literature protocol and then the dienone **190a** was subjected for the oxidation using the optimized condition.[17] To our delight, the natural product (±)-Pleodendione, **172** was obtained in 67% isolated yield for which all the spectral data was in complete agreement with the literature report.[18] Here it is interesting to note that, the yield of the product using current method was more than two fold as compared to the standard PDC-TBHP method. Apart from this, the same method was previously employed for the total synthesis of (±)-Periconianone A where the yield of dienone **191** was obtained more than two fold than the reported method.[17]

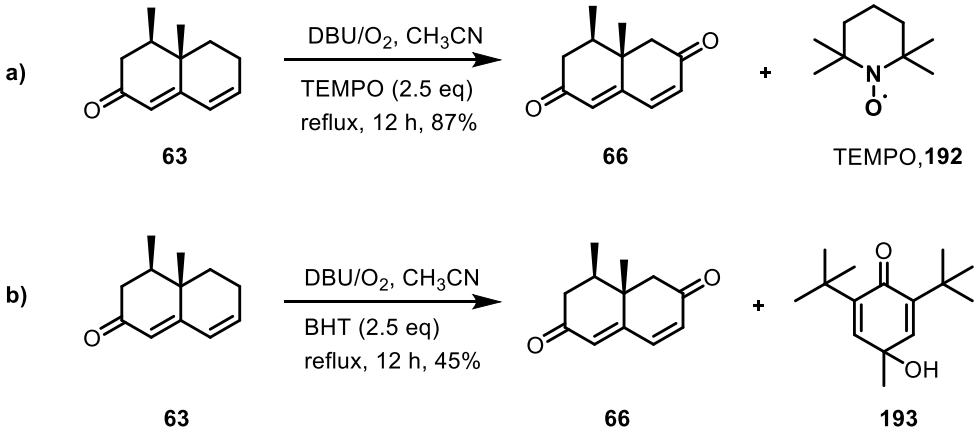


Scheme 2.2.5 Synthesis of (±)-Pleodendione

2.2.6. Mechanistic investigation of the oxidation reaction:

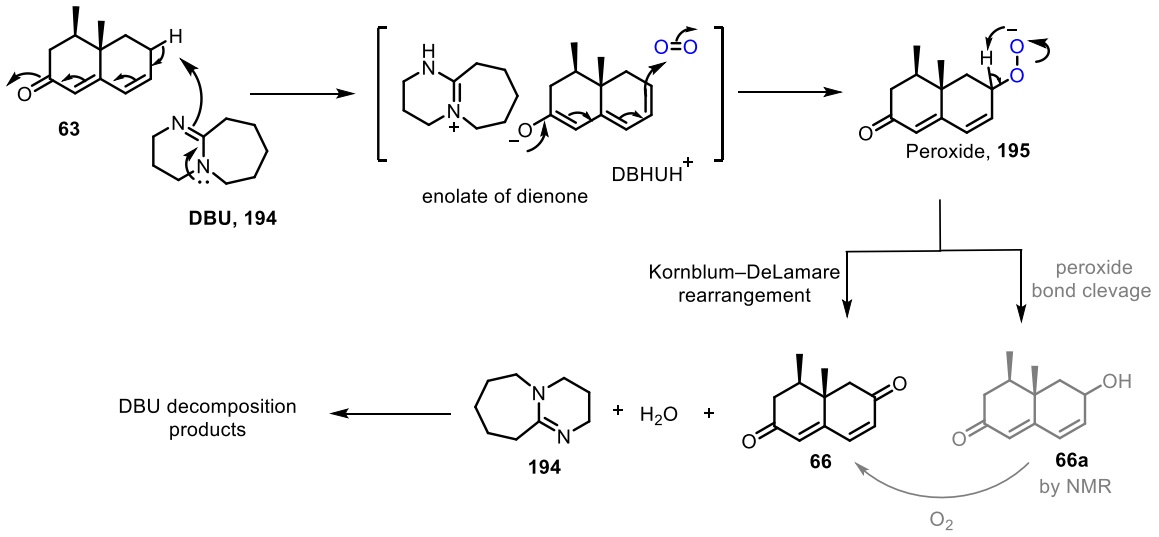
After testing the substrate scope of the reaction, our next task was to gain some insight into the reaction mechanism. From the initial experiments from scheme 2.2.3 we knew that the dissolved oxygen is acting as an oxidant in this reaction. Thus to check for the possibility

that whether the reaction is proceeding through a radical pathway; we performed the reaction in presence of radical scavenger 2,2,6,6-tetramethyl-1-piperidinoxyl (TEMPO, 2.5 equiv.) or butylated hydroxytoluene (BHT, 2.5 equiv.). In both the reactions we observed formation of the product **66** in 87 and 45% yield respectively. This experiment confirmed that the reaction is not proceeding through a radical pathway. Thus there remains a possibility of an ionic mechanism as proposed in scheme 2.2.7 based on literature reports.[19]



Scheme 2.2.6 Control experiments

DBU on reaction with the dienone, abstracts allylic hydrogen to give the enolate which traps oxygen molecule to form peroxide **195**. This peroxide on Kornblum-DeLamare type rearrangement affords the product 2,6-dione and DBU decomposition compounds as side products. In addition, the peroxide intermediate **195** cleaves to give alchoho l**66a** which was fully characterized by spectral means.



Scheme 2.2.7 Proposed Reaction Mechanism

2.2.7. Conclusions

In summary, a convenient method for the allylic oxidation of dienones was developed. The reaction involves oxygen as an oxidant and an inexpensive base DBU in acetonitrile solvent. The reaction is metal-free and easy to operate. The scope of the reaction was tested with non-cojugated as well as conjugated dienones with moderate to good yields. In most of the substartes we observed more than two fold yield improvement as compared to well known PDC-TBHP method. As a synthetic application, reaction was successfully applied for the synthesis of (±)-pleodendione and for the formal synthesis of (-)-periconianone A. Isolation of an reaction intermediate revealed that this transformation goes via a peroxide intermediate which further undergoes Kornblum-DeLamare rearrangement to give 2,6-diones.

2.2.8. Experimental section

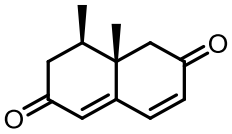
2.2.8.1. General procedure for oxidation of dienones

To a stirred solution of **63 (or 176a to 190a)** (1 mmol) in dry acetonitrile (10 mL) oxygen gas was bubbled for a period of 10 min at room temperature. DBU (2.5 mmol) was added dropwise and the reaction mixture was refluxed for a period of 6-24 h under O_2 atmosphere. The reaction mass was diluted with ice cold water (20 mL) and extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with water, dried over Na_2SO_4, filtered and concentrated to give crude product.

Which was purified by column chromatography (ethyl acetate-petroleum ether) to obtain **66 (or 176b to 190b)** in 30-94% yield.

2.2.8.2. **Compound characterization data for selected compounds: Data for remaining compounds can be found at** (*J. Org. Chem.* **2021**, *86*, 9200–9205).

(1*R,8a*R**)-1,8a-dimethyl-1,7,8,8a-tetrahydronaphthalene-2,6-dione (66):**



Off white solid

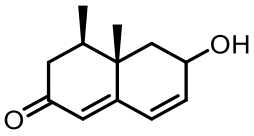
IRυ_{max}(film): 1655, 1607, 1574, 755 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.07 (dd, *J* = 0.6, 9.9 Hz, 1 H), 6.22 (d, *J* = 9.9 Hz, 1 H), 6.10 (s, 1 H), 2.71 (d, *J* = 15.6 Hz, 1 H), 2.50 - 2.34 (m, 2 H), 2.33 - 2.22 (m, 2 H), 1.18 (d, *J* = 0.9 Hz, 3 H), 1.03 (d, *J* = 6.5 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 198.7, 197.8, 158.7, 143.6, 131.6, 129.6, 48.9, 41.7, 39.7, 39.0, 18.4, 14.5.

HRMS (ESI) calc. for $C_{12}H_{15}O_2$ $[M+H]^+$ 191.1067, found 191.1064.

(4R,4aS)-6-hydroxy-4,4a-dimethyl-4,4a,5,6-tetrahydronaphthalen-2(3H)-one (66a):



Pale yellow liquid.

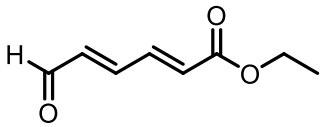
IRυ_{max}(film): 3378, 2958, 1651, 1287, 1041 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.29 - 6.11 (m, 2 H), 5.79 (s, 1 H), 4.54 (br. s., 1 H), 2.39 - 2.30 (m, 3 H), 2.16 - 2.04 (m, 1 H), 1.69 - 1.60 (m, 1 H), 1.07 (s, 3 H), 1.01 (d, *J* = 6.9 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 199.5, 161.5, 140.1, 128.5, 125.2, 66.1, 43.1, 41.6, 38.6, 37.9, 16.5, 14.8.

HRMS (ESI) calc. for $C_{12}H_{17}O_2$ $[M+H]^+$ 193.1228, found 193.1228.

Ethyl (2*E*,4*E*)-6-oxohexa-2,4-dienoate (177b):



Yellowish oily liquid.

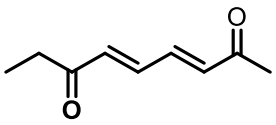
IRυ_{max} (film): 2957, 2853, 1716, 1690, 1642, 1603, 1461, 1367, 1272, 1178, 1095, 1030, 969, 764 cm^{-1}.

^{1}H NMR (**400 MHz**, **$CDCl_3$**) δ 9.68 (d, *J* = 8.0 Hz, 1H), 7.42 (dd, *J* = 15.6, 11.2 Hz, 1H), 7.17 (dd, *J* = 15.2, 11.2 Hz, 1H), 6.43 (dd, *J* = 15.2, 8.0 Hz, 1H), 6.31 (d, *J* = 15.2 Hz, 1H), 4.27 (q, *J* = 7.2 Hz, 2H), 1.33 (t, *J* = 7.6 Hz, 3H).

^{13}C NMR (**100 MHz, $CDCl_3$**) δ 192.9, 165.4, 147.2, 140.3, 136.9, 129.9, 61.1, 14.2.

HRMS (ESI) calc. for $C_8H_{10}O_3Na$ $[M+Na]^+$177.0522, found 177.0516.

(3E,5E)-nona-3,5-diene-2,7-dione (178b):



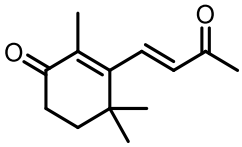
Pale yellow liquid.

IRυ_{max} (film): 2927, 1678, 1590, 1251cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$)δ= 7.24 - 7.08 (m, 2 H), 6.57 - 6.39 (m, 2 H), 2.64 (q, *J* = 7.3 Hz, 2 H), 2.33 (s, 3 H), 1.14 (t, *J* = 7.3 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 200.2, 197.7, 139.8, 138.6, 136.6, 135.9, 34.5, 29.7, 27.8; **HRMS (ESI)** calc. for $C_9H_{13}O_2$ $[M+H]^+$153.0915, found 153.0915.

(*E*)-2,4,4-trimethyl-3-(3-oxobut-1-en-1-yl)cyclohex-2-en-1-one (176b):



Yellowish oily liquid.

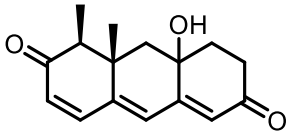
IRυ_{max} (film): 2962, 1694, 1666, 1613, 1353, 1312, 1249, 1174, 1141, 1093, 1025 cm^{-1}.

^{1}H NMR (**400 MHz**, **$CDCl_3$**) δ 7.17 (d, *J* = 16.4 Hz, 1H), 6.11 (d, *J* = 16.4 Hz, 1H), 2.45 (t, *J* = 7.2 Hz, 2H), 2.28 (s, 3H), 1.82 (t, *J* = 6.8 Hz, 2H), 1.72 (s, 3H), 1.12 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 198.3, 197.2, 157.6, 140.1, 133.4, 131.1, 37.1, 35.3, 33.9, 27.7, 27.1 (2C), 13.2.

HRMS (ESI) calc. for $C_{13}H_{19}O_2$ $[M+H]^+$207.1380, found 207.1378.

(1*R,9a*R**)-8a-hydroxy-1,9a-dimethyl-1,7,8,8a,9,9a-hexahydroanthracene-2,6-dione (180b):**



Pale yellow solid.

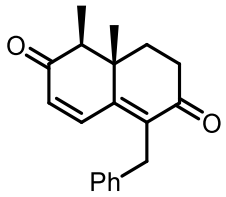
IRυ_{max} (film): 3409, 2923, 1647, 1596, 1452, 1323, 1260, 1218, 1075, 997, 952, 910, 755 $cm^{-1.}$

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.03 (d, *J* = 9.2 Hz, 1H), 6.41 (s, 1H), 6.14 (d, *J* = 9.6 Hz, 1H), 5.91 (s, 1H), 2.89 (td, *J* = 15.6, 5.2 Hz, 1H), 2.52 (s, 1H), 2.48-2.43 (m, 1H), 2.19 (d, *J* = 14.8 Hz, 2H), 2.06 (dd, *J* = 13.4, 4.4 Hz, 2H), 1.71 (d, *J* = 14.0 Hz, 1H), 1.34 (s, 3H), 1.15 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 200.4, 199.4, 153.1, 149.8, 142.8, 129.5, 129.0, 126.5, 66.5, 53.3, 47.2, 40.6, 37.5, 33.1, 20.9, 7.1.

HRMS (ESI) calc. for $C_{16}H_{19}O_3$ $[M+H]^+$259.1329, found 259.1327.

(1*R,8a*R**)-5-benzyl-1,8a-dimethyl-1,7,8,8a-tetrahydronaphthalene-2,6-dione (184b):**



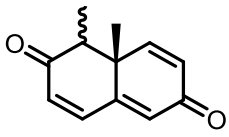
IRυ_{max} (film): 2971, 1716, 1663, 1599, 1492, 1453, 1317, 1183, 1112, 848, 735, 703 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (d, *J* = 10.4 Hz, 1H), 7.29-7.27 (m, 2H), 7.21 (d, *J* = 6.8 Hz, 1H), 7.14 (d, *J* = 7.2 Hz, 2H), 6.23 (d, *J* = 9.6 Hz, 1H), 3.89 (s, 2H), 2.66-2.64 (m, 3H), 2.13 (d, *J* = 12.8 Hz, 1H), 2.04 (dd, *J* = 12.0, 7.2 Hz, 1H), 1.23 (s, 3H), 1.18 (d, *J* = 6.4 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 199.9, 197.5, 153.7, 139.4, 139.3, 137.4, 131.5, 128.6 (2C), 127.9 (2C), 126.2, 52.4, 40.9, 33.6, 33.4, 30.3, 17.8, 6.9.

HRMS (ESI) calc. for $C_{19}H_{21}O_2$ $[M+H]^+$281.1542, found 281.1544.

(8a*R)-1,8a-dimethyl-1,8a-dihydronaphthalene-2,6-dione (185b):**



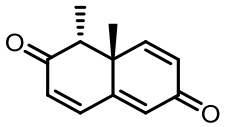
IRυ_{max} (film): 2973, 1653, 1625, 1452, 1215, 899, 750 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 (d, *J* = 8.0 Hz, 1H), 6.81 (d, *J* = 8.0 Hz, 1H), 6.52 (s, 1H), 6.41 (d, *J* = 12.0 Hz, 1H), 6.15 (d, *J* = 12.0 Hz, 1H), 2.63 (q, *J* = 8.0 Hz, 1H), 1,36 (s, 3H), 0.93 (d, *J* = 8.0 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 198.3, 185.2, 157.6, 153.3, 142.4, 131.2, 128.9, 128.5, 49.6, 44.3, 22.2, 7.8.

HRMS (ESI) calc. for $C_{12}H_{13}O_2$ $[M+H]^+$189.0910, found 189.0907.

(1*S,8a*R**)-1,8a-dimethyl-1,8a-dihydronaphthalene-2,6-dione (186b):**



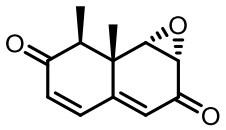
IRυ_{max} (film): 2974, 1667, 1649, 1618, 1597, 1452, 1307, 1187, 876, 787 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 (d, *J* = 12.0 Hz, 1H), 6.81 (d, *J* = 12.0 Hz, 1H), 6.53 (s, 1H), 6.42 (d, *J* = 12.0 Hz, 1H), 6.16 (d, *J* = 12.0 Hz, 1H), 2.63 (q, *J* = 8.0 Hz, 1H), 1.37 (s, 3H), 0.94 (d, *J* = 8.0 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 201.2, 185.9, 154.8, 154.5, 142.5, 131.1, 129.6, 129.1, 52.3, 45.0, 28.1, 15.6.

HRMS (ESI) calc. for $C_{12}H_{13}O_2$ $[M+H]^+$189.0916, found 189.0925.

(1a*R,7*R**,7a*R**,7b*R**)-7,7a-dimethyl-1a,7,7a,7b-tetrahydronaphtho[1,2-*b*]oxirene-2,6-dione (187b):**



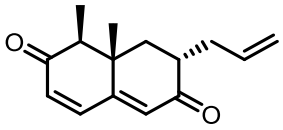
IRυ_{max} (film): 2919, 1710, 1676, 1463, 1215, 1094, 755, 667 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.13 (d, *J* = 8.0 Hz, 1H), 6.21 (d, *J* = 12.0 Hz, 1H), 6.02 (s, 1H), 3.68 (d, *J* = 3.6 Hz, 1H), 3.48 (dd, *J* = 3.2, 2.0 Hz, 1H), 2.74 (q, *J* = 7.2 Hz, 1H), 1.36 (s, 3H), 1.35 (d, *J* = 7.2 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 197.88, 191.43, 157.13, 142.62, 131.76, 124.39, 60.76, 54.19, 49.32, 40.82, 19.02, 7.64.

HRMS (ESI) calc. for $C_{12}H_{13}O_3$ $[M+H]^+$205.0859, found 205.0858.

(1*R,7*R**,8a*R**)-7-allyl-1,8a-dimethyl-1,7,8,8a-tetrahydronaphthalene-2,6-dione (188b):**



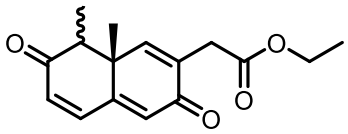
IRυ_{max} (film): 2922, 1718, 1665, 1612, 1580, 1388, 1161, 913, 882 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.01 (d, *J* = 9.6 Hz, 1H), 6.22 (d, *J* = 10.0 Hz, 1H), 6.05 (s, 1H), 5.83-5.73 (m, 1H), 5.12-5.07 (m, 2H), 2.77-2.72 (m, 1H), 2.64-2.47 (m, 2H), 2.21 (dd, *J* = 14.6, 8.4 Hz, 1H), 2.14 (dd, *J* = 13.0, 5.2 Hz, 1H), 1.70 (t, *J* = 13.6 Hz, 1H), 1.17 (s, 3H), 1.14 (d, *J* = 6.4 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 199.8, 199.6, 158.7, 142.1, 135.5, 132.0, 128.8, 117.3, 52.2, 41.4, 40.4, 39.9, 33.5, 18.6, 6.9.

HRMS (ESI) calc. for $C_{15}H_{19}O_2$ $[M+H]^+$231.1380, found 231.1378.

Ethyl 2-((8a*R)-8,8a-dimethyl-3,7-dioxo-3,7,8,8a-tetrahydronaphthalen-2-yl)acetate (189b):**



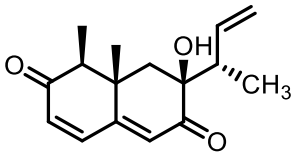
IRυ_{max} (film): 2976, 1730, 1662, 1632, 1452, 1256, 1163, 1027, 839, 727 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 (dd, *J* = 10.0, 5.6 Hz, 1H), 6.71 (s, 1H), 6.54 (s, 1H), 6.15 (d, *J* = 10.0 Hz, 1H), 4.18-4.11 (m, 2H), 3.44 (d, *J* = 16.4 Hz, 1H), 3.30 (d, *J* = 16.4 Hz, 1H), 2.62 (q, *J* = 7.2 Hz, 1H), 1.36 (s, 3H), 1.24 (t, *J* = 6.8 Hz, 3H), 0.95 (d, *J* = 7.2 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 201.2, 198.3, 184.8, 184.2, 170.7, 170.6, 157.5, 154.8, 152.5, 151.2, 142.3, 142.1, 133.8, 132.7, 131.2, 130.3, 129.1, 128.3, 60.9, 52.4, 49.5, 45.1, 44.3, 34.9, 34.6, 29.6, 27.9, 22.3, 15.5, 14.1, 7.8.

HRMS (ESI) calc. for $C_{16}H_{19}O_4$ $[M+H]^+$275.1283, found 275.1292.

(1*R,7*R**,8a*R**)-7-((*R**)-but-3-en-2-yl)-7-hydroxy-1,8a-dimethyl-1,7,8,8atetrahydronaphthalene-2,6-dione (190b):**



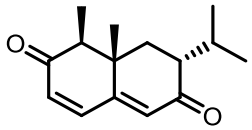
IRυ_{max} (film):3412, 1720, 1666, 721 cm^{-1}.

^{1}H NMR (**400 MHz, $CDCl_3$**) δ 7.04 (d, *J* = 10.0 Hz, 1H), 6.25 (d, *J* = 10.0 Hz, 1H), 6.18 (s, 1H), 5.98-5.89 (m, 1H), 5.22 (d, *J* = 10.8 Hz, 1H), 5.16 (d, *J* = 16.8 Hz, 1H), 3.49 (q, *J* = 7.6 Hz, 1H), 2.79-2.73 (m, 1H), 2.61 (q, *J* = 6.8 Hz, 1H), 2.33 (s, 1H), 2.06-1.95 (m, 1H), 1.26 (s, 3H), 1.18 (d, *J* = 6.8 Hz, 3H), 0.95 (d, *J* = 6.0 Hz, 3H).

^{13}C NMR (**100 MHz, $CDCl_3$**) δ 200.1, 199.7, 160.5, 141.7, 137.6, 132.4, 127.9, 117.5, 75.5, 52.1, 45.9, 40.3, 39.5, 22.8, 14.6, 7.3.

HRMS (ESI) calc. for $C_{16}H_{20}O_3Na$ $[M+Na]^+$283.1305, found 283.1298.

(1*R,7*S**,8a*R**)-7-isopropyl-1,8a-dimethyl-1,7,8,8a-tetrahydronaphthalene-2,6-dione (172):**



IRυ_{max} (film): 2925, 1721, 1665, 1580, 1461, 1386, 1208, 1004, 879, 753 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.0 (d, *J* = 9.6 Hz, 1H), 6.22 (d, *J* = 9.6 Hz, 1H), 6.03 (s, 1H), 2.65-2.57 (m, 2H), 2.40-2.34 (m, 1H), 2.01 (dd, *J* = 13.0, 4.8 Hz, 1H), 1.77 (t, *J* = 13.6 Hz, 1H), 1.26 (s, 3H), 1.16 (d, *J* = 2.4 Hz, 3H), 1.00 (d, *J* = 7.2 Hz, 3H), 0.86-0.84 (m, 3H)

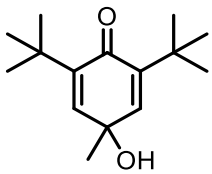
^{13}C NMR (100 MHz, $CDCl_3$) δ 200.1, 199.9, 158.2, 142.2, 131.9, 129.5, 52.3, 47.2, 40.1, 34.2, 25.8, 20.1, 18.4, 17.6, 7.0.

HRMS (ESI) calc. for $C_{15}H_{21}O_2$ $[M+H]^+$233.1536, found 233.1533.

2.2.6 Control experiment procedure

To a stirred solution of **63** (1 mmol) in dry acetonitrile (10 mL) oxygen gas was bubbled for a period of 10 min at rt. DBU (2.5 mmol) was added dropwise followed by portion wise addition of 2,2,6,6-tetramethyl-1-piperidinoxyl (TEMPO, 2.5 mmol) or 2,6-di-*tert*-butyl-4-methylphenol (BHT, 2.5 mmol). The reaction mixture was refluxed for a period of 12 h under O_2 atmosphere. The reaction mass was diluted with ice cold water (20 mL) and extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with water, brine, dried over Na_2SO_4, filtered and concentrated to give crude product. Which was purified by column chromatography (ethyl acetate-petroleum ether, 17:83, v/v as a eluent) to obtain **66** in 87 or 45% yield along with formation of **193** in case of BHT.

2,6-di-*tert*-butyl-4-hydroxy-4-methylcyclohexa-2,5-dien-1-one (193):



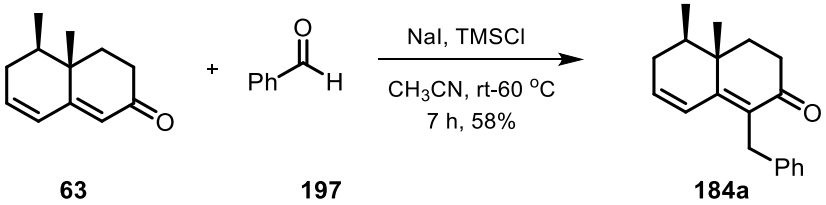
IRυ_{max} (film): 3330, 2925, 1665, 1644, 1363, 1215, 1047, 877, 748 cm^{-1}.

^{1}H NMR (**500 MHz**, **$CDCl_3$**) δ 6.56 (s, 2H), 1.85 (br s, 1H), 1.42 (s, 3H), 1.22 (s, 18H).

^{13}C NMR (**125 MHz, $CDCl_3$**) δ 186.0, 145.4 (2C), 143.2 (2C), 67.4, 34.5 (2C), 29.4 (6C), 28.0.

HRMS (ESI) calc. for $C_{15}H_{25}O_2$ $[M+H]^+$237.1855, found 237.1862.

Synthesis of compound 184a:[17b]



63 **197** **184a**

Scheme 2.2.8: Synthesis of compound 1h

(4aS,5R)-1-benzyl-4a,5-dimethyl-4,4a,5,6-tetrahydronaphthalen-2(3H)-one:

To a stirred solution of compound **63** (1 g, 5.68 mmol), and benzaldehyde (1.2 mL, 11.36 mmol) in CH_3CN (25 mL was added NaI (0.852 g, 5.68 mmol) followed by dropwise addition of TMSCl (0.73 mL, 5.68 mmol). The reaction mixture was then stirred for 1 hour at room temperature then it was heated to 60 °C for six more hours. The reaction mixture was then cooled and diluted with EtOAc (30 mL) and saturated $Na_2S_2O_3$ solution was added to it. The organic layer was extracted with EtOAc (2 X 25 mL), washed with brine (25 mL) and dried over Na_2SO_4. Solvent was evaporated and the crude compound was purified by column chromatography (silica gel) to give compound **184a**, 0.88 g.

2.2.9. Refrences

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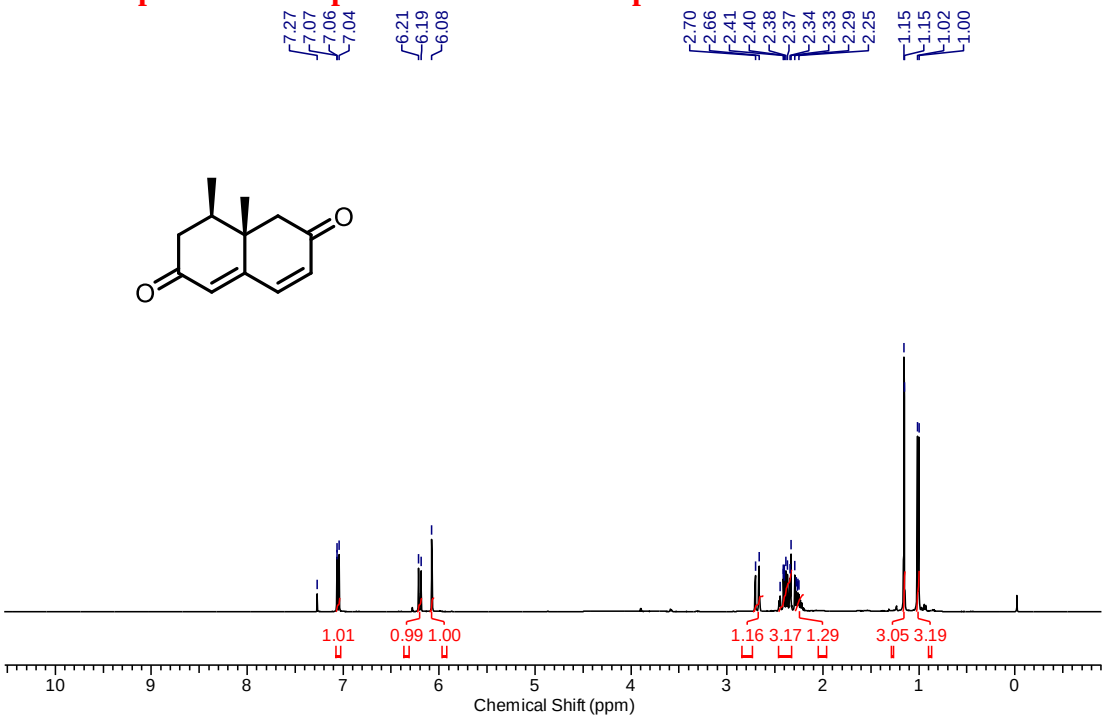
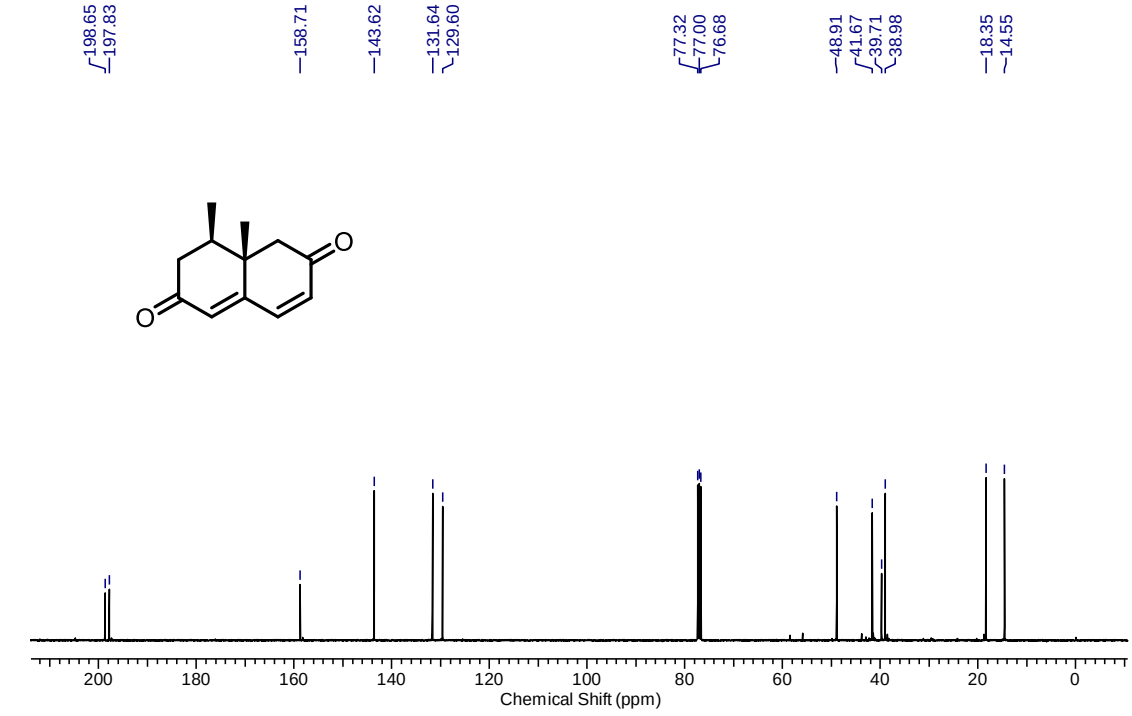
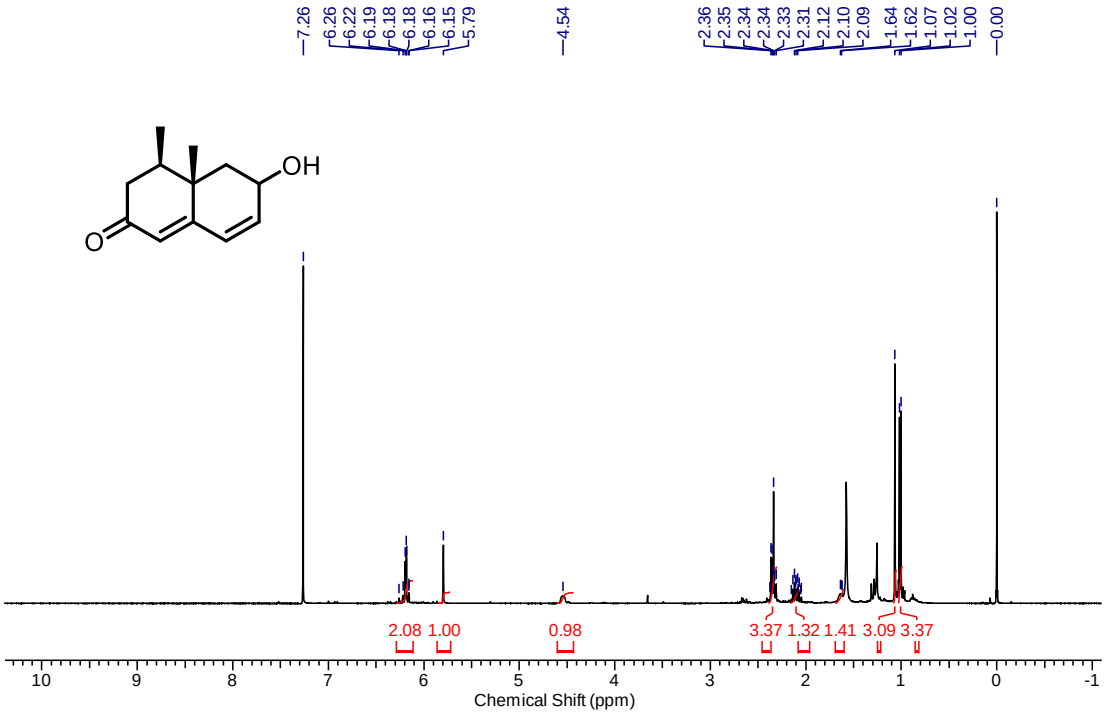
2.2.10. Copies of NMR spectra of selected compounds



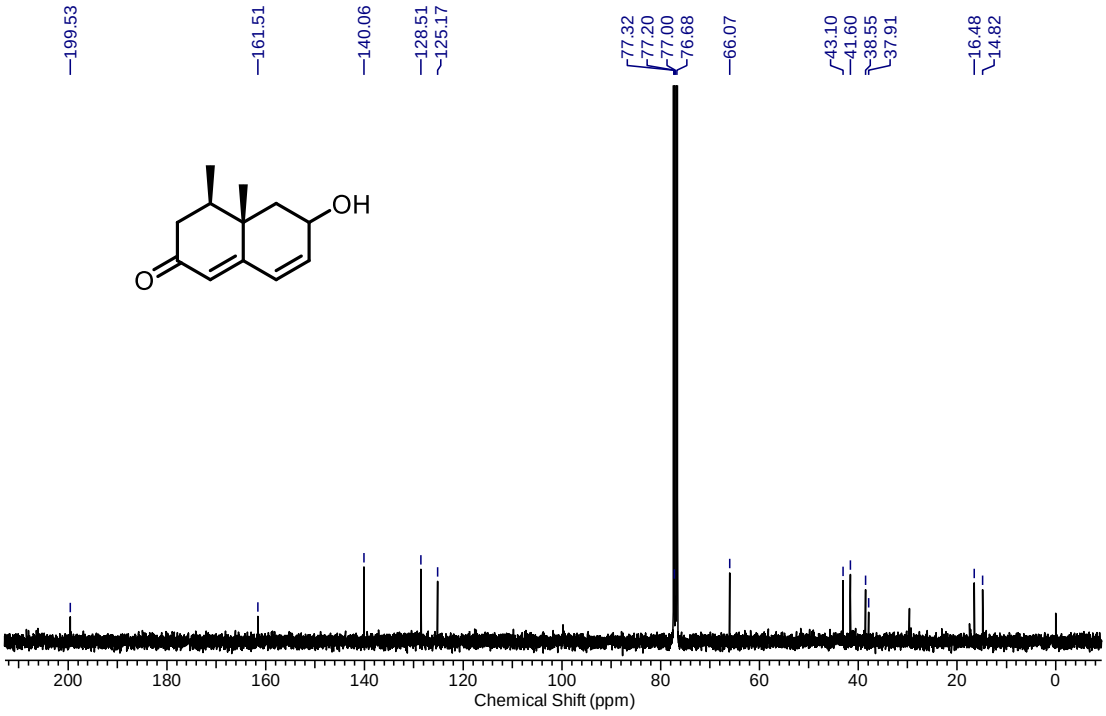
^{1}H NMR of Compound **66** in $CDCl_3$ at 400 MHz



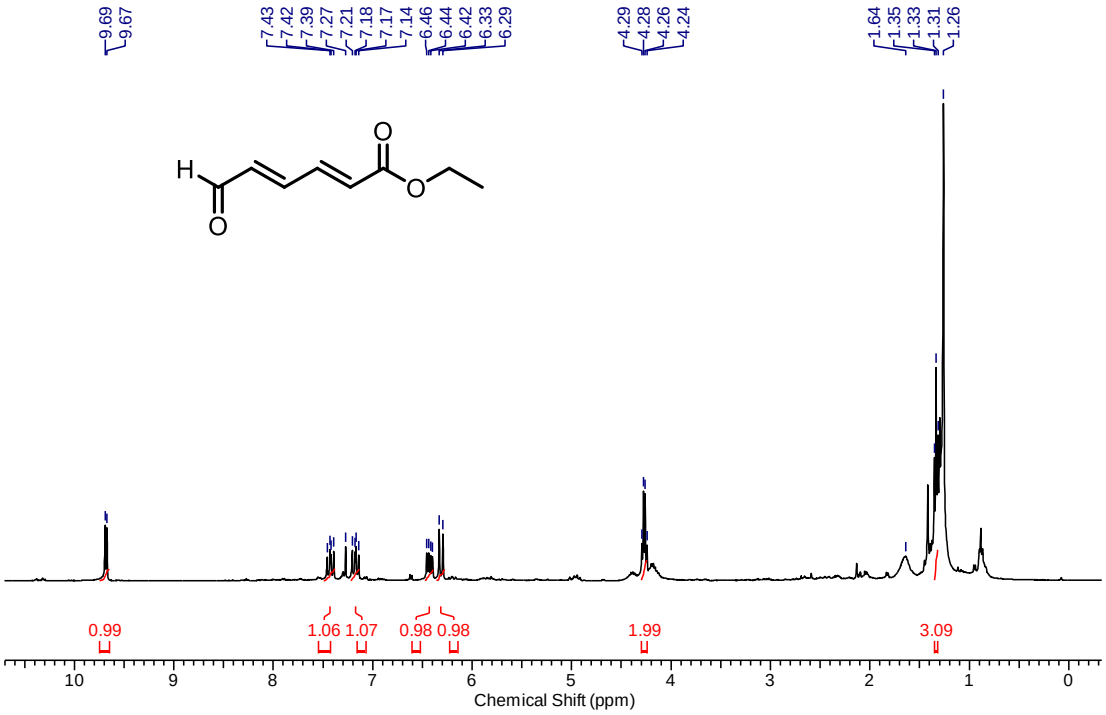
^{13}C NMR of Compound **66** in $CDCl_3$ at 100 MHz



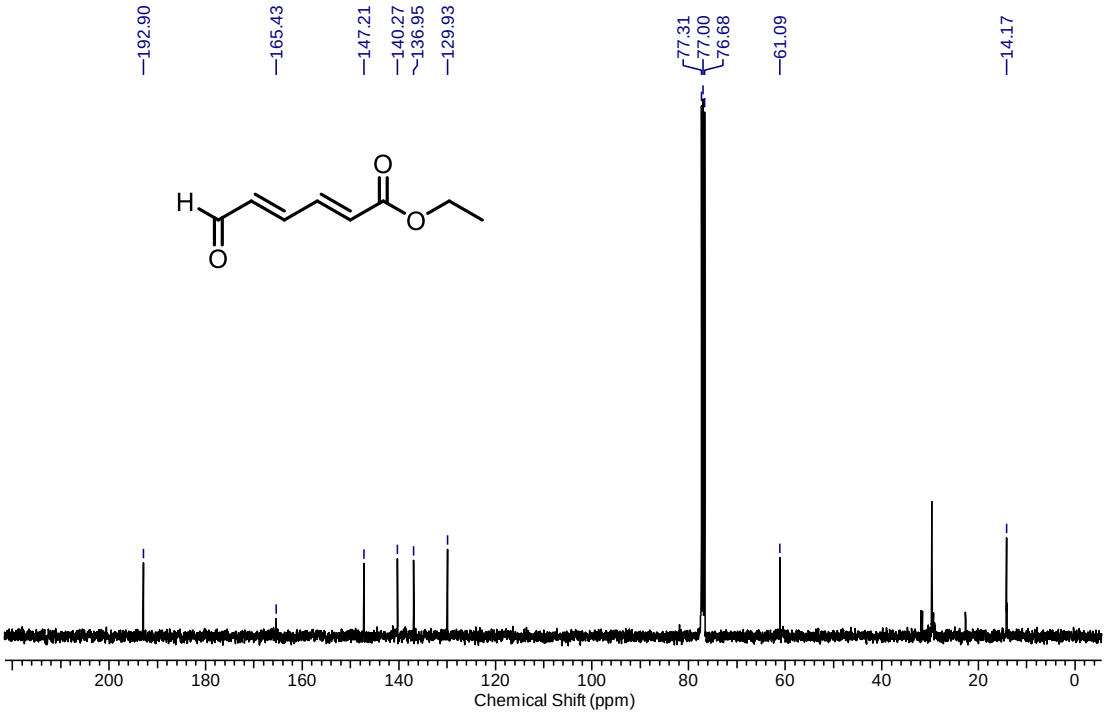
^{1}H NMR of Compound **66a** in $CDCl_3$ at 400 MHz



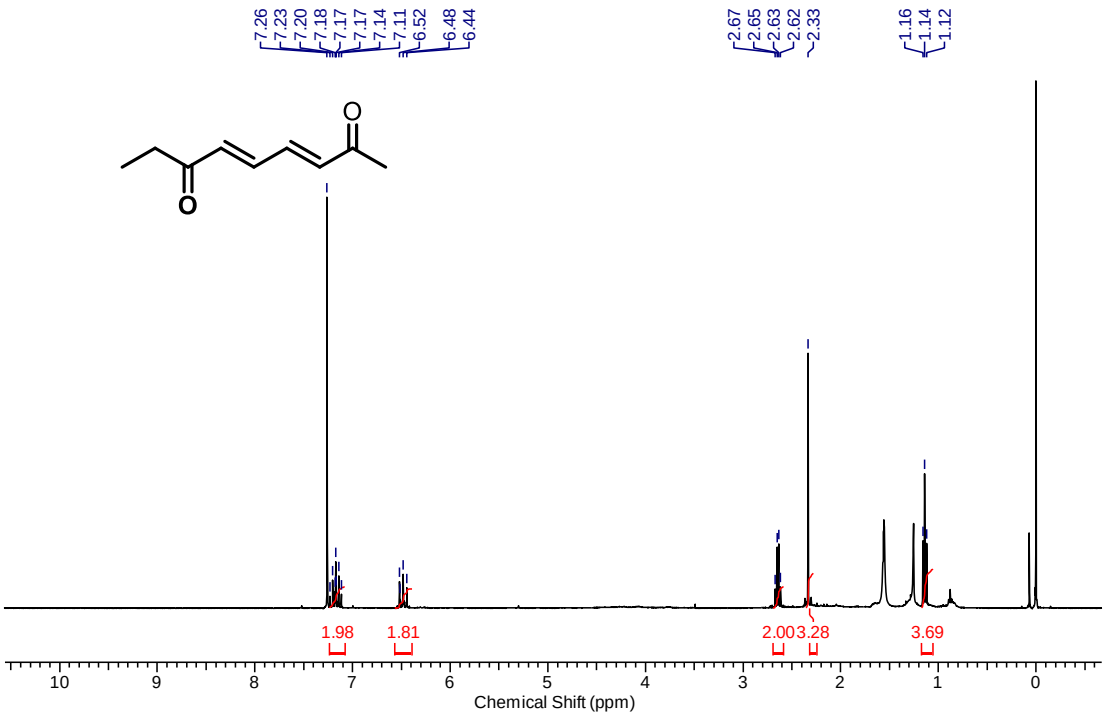
^{13}C NMR of Compound **66a** in $CDCl_3$ at 100 MHz



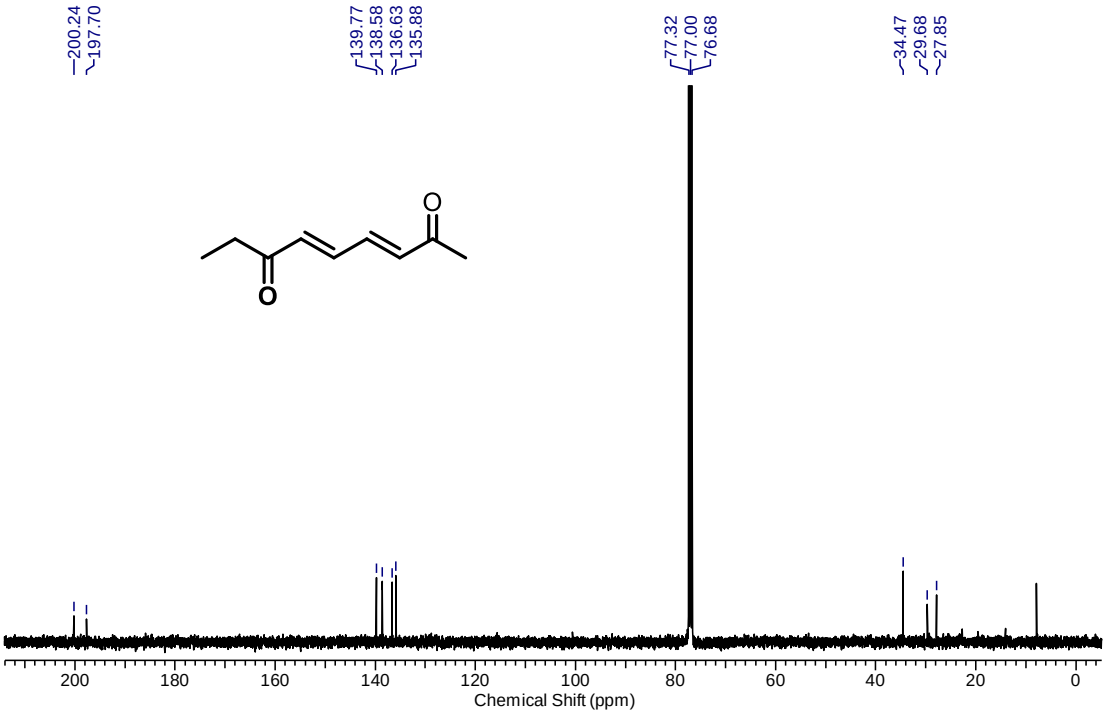
^{1}H NMR of Compound **177b** in $CDCl_3$ at 400 MHz



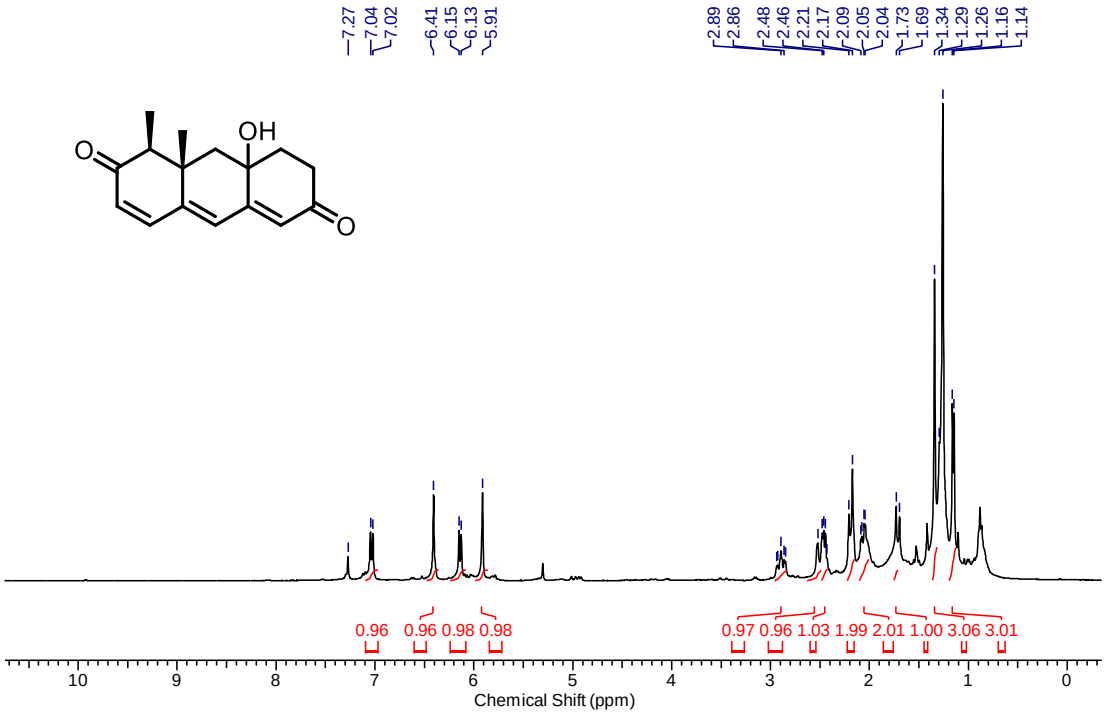
^{13}C NMR of Compound **177b** in $CDCl_3$ at 100 MHz



^{1}H NMR of Compound **178b** in $CDCl_3$ at 400 MHz



^{13}C NMR of Compound **178b** in $CDCl_3$ at 100 MHz



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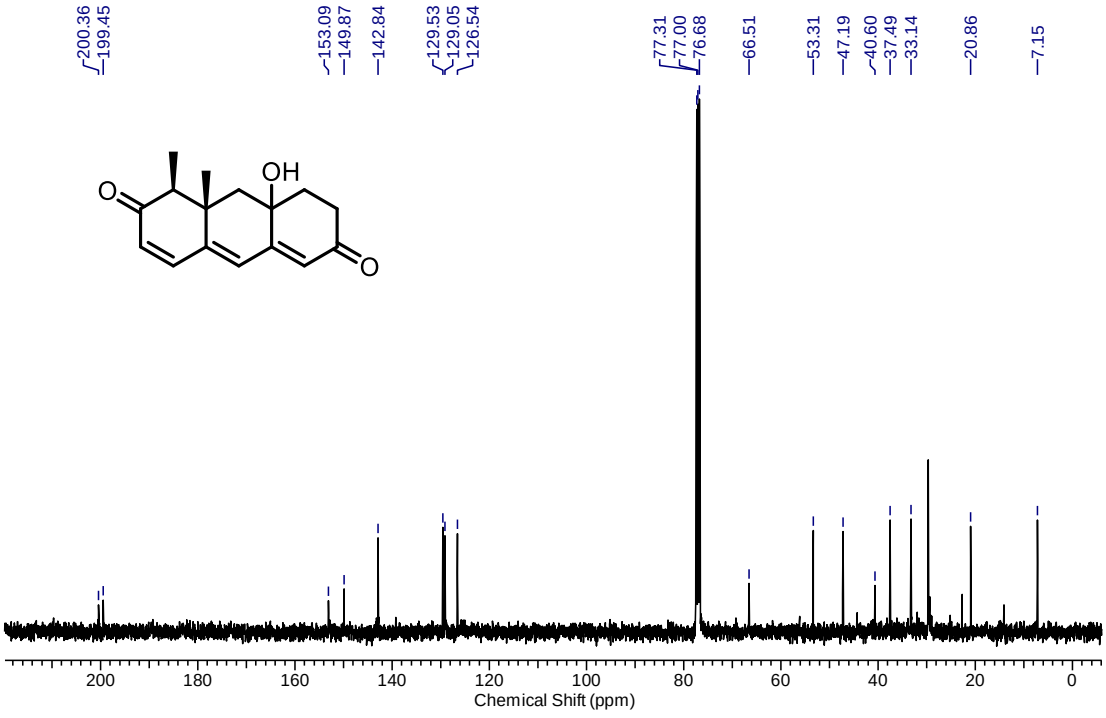
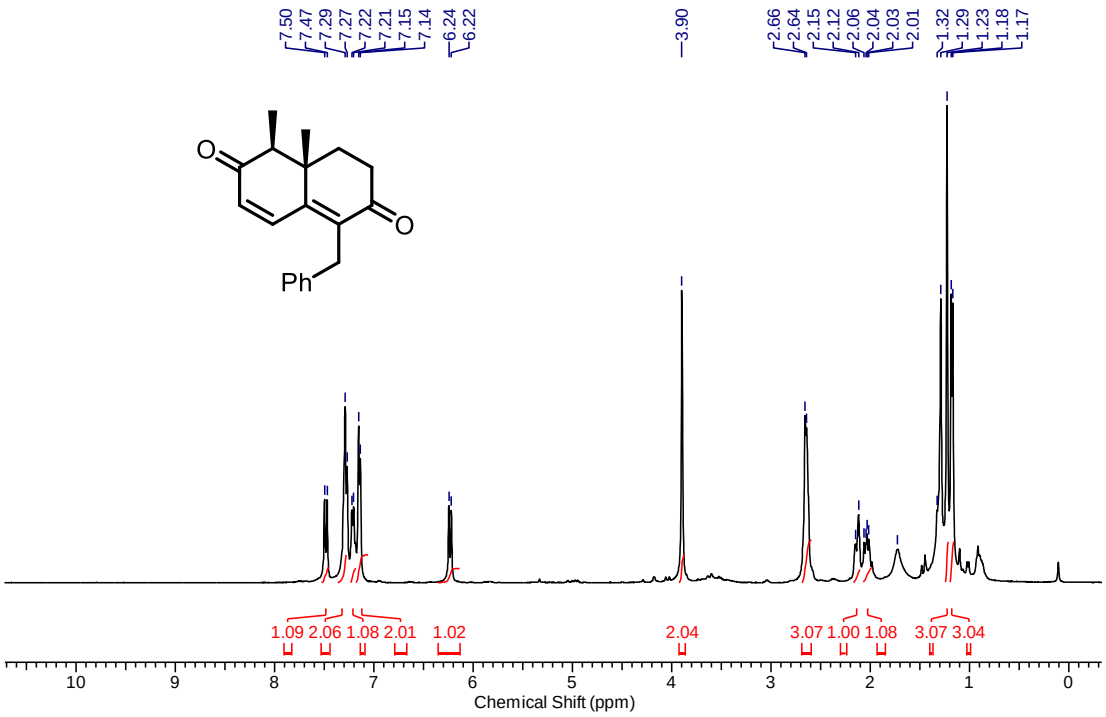
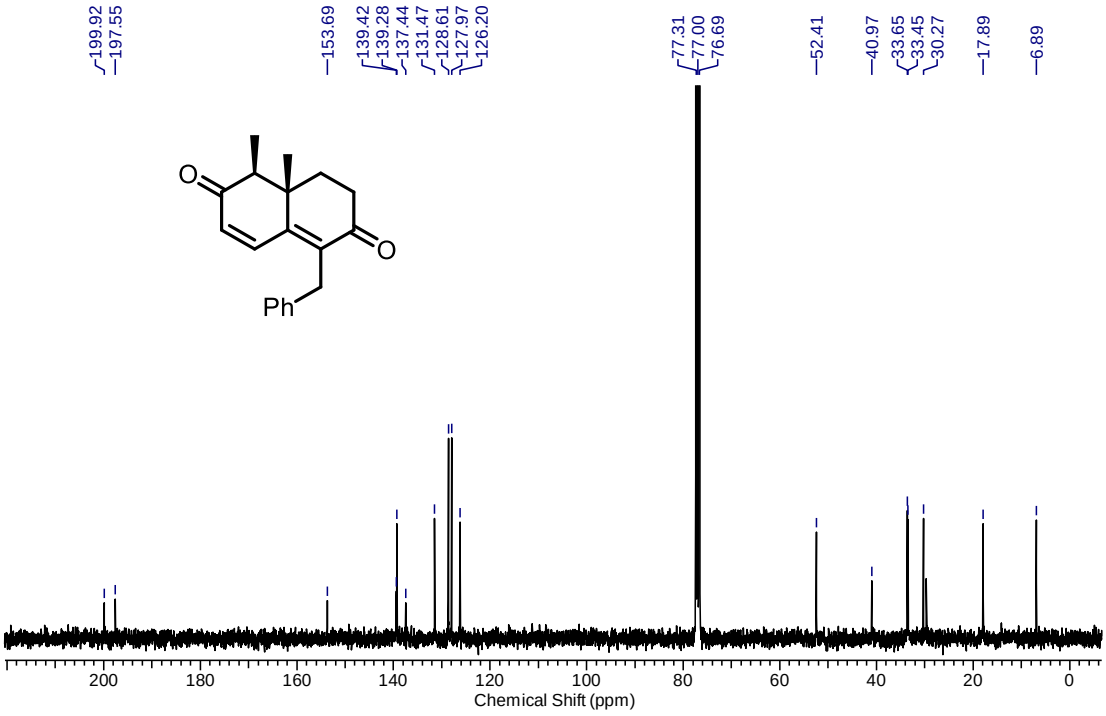


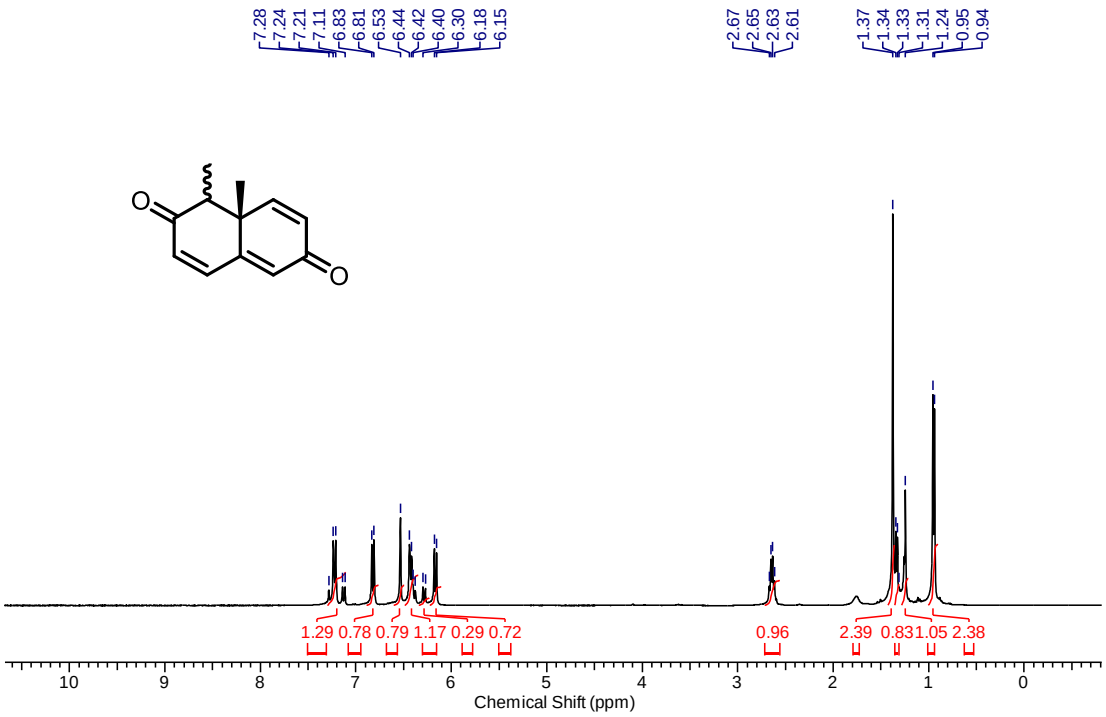
^{13}C NMR of Compound **180b** in $CDCl_3$ at 100 MHz



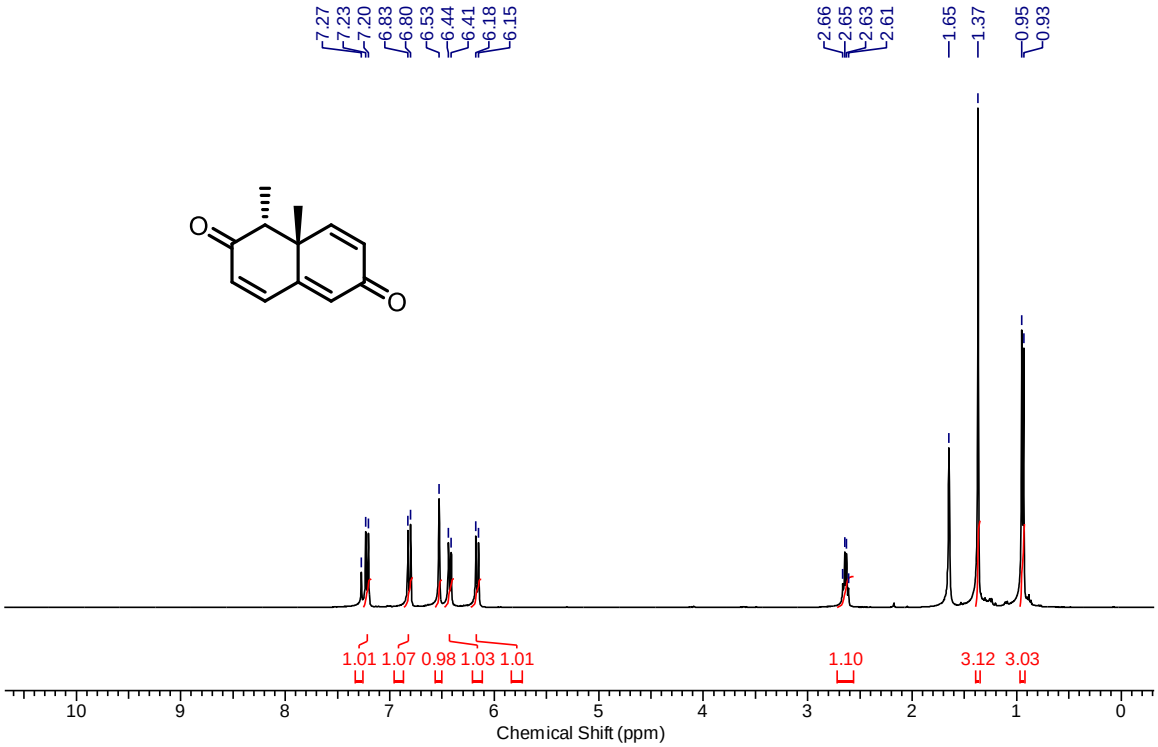
^{1}H NMR of Compound **184b** in $CDCl_3$ at 400 MHz



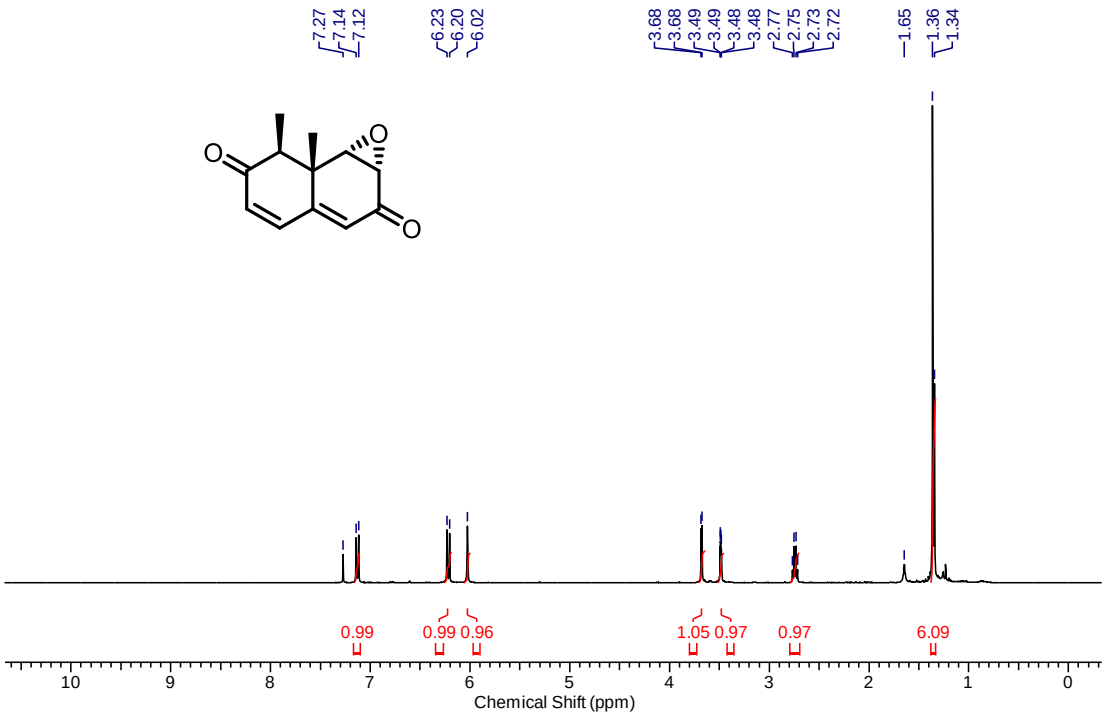
^{13}C NMR of Compound **184b** in $CDCl_3$ at 100 MHz



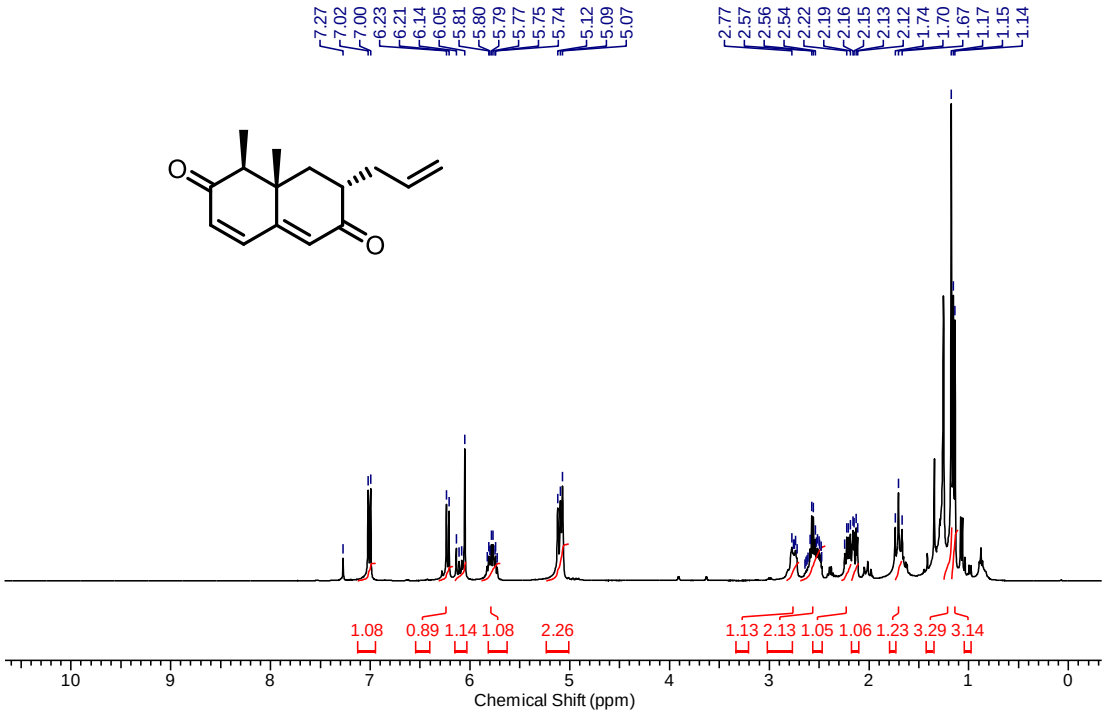
^{1}H NMR of Compound **185b** in $CDCl_3$ at 400 MHz



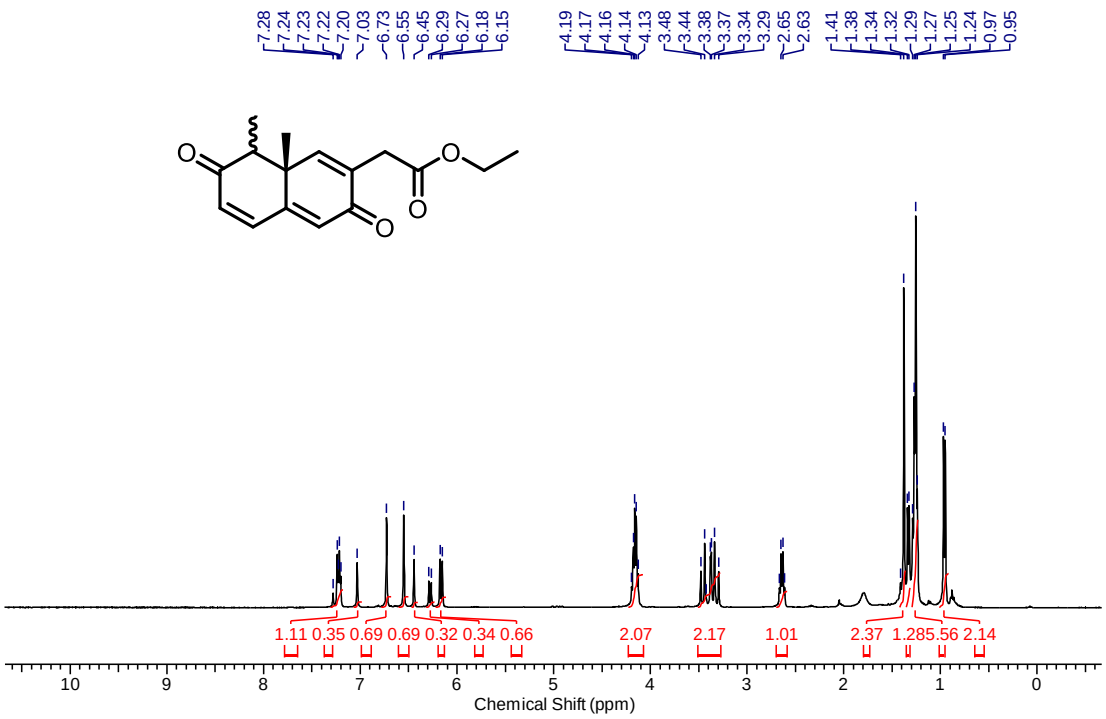
^{1}H NMR of Compound **186b** in $CDCl_3$ at 400 MHz



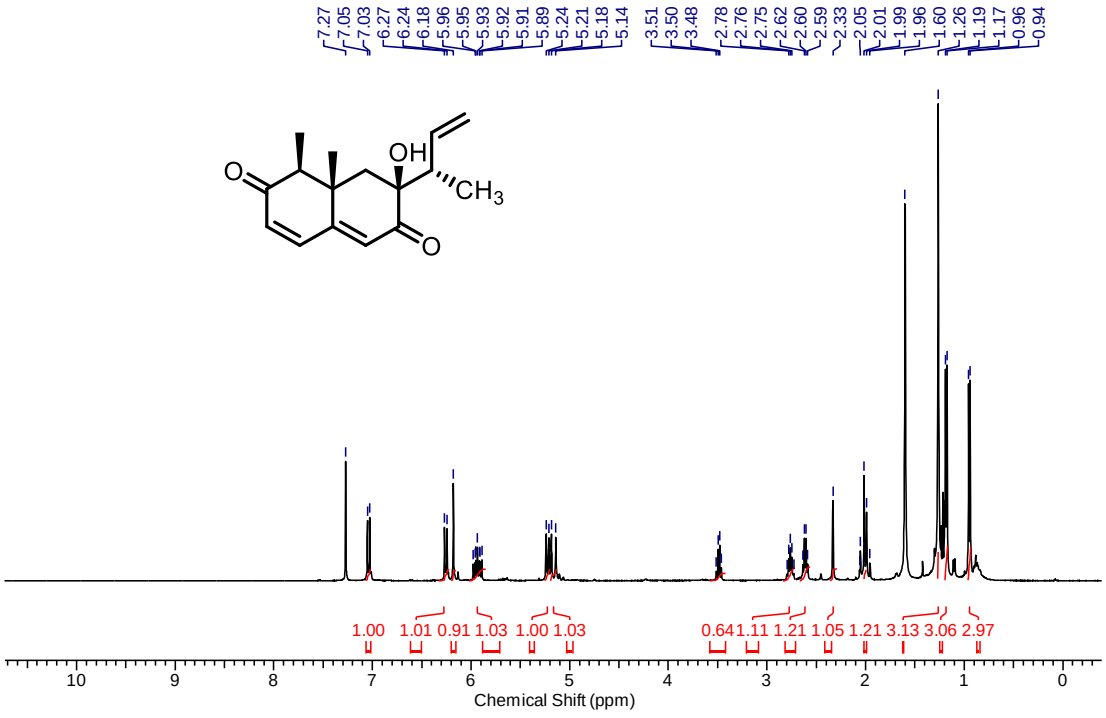
^{1}H NMR of Compound **187b** in $CDCl_3$ at 400 MHz



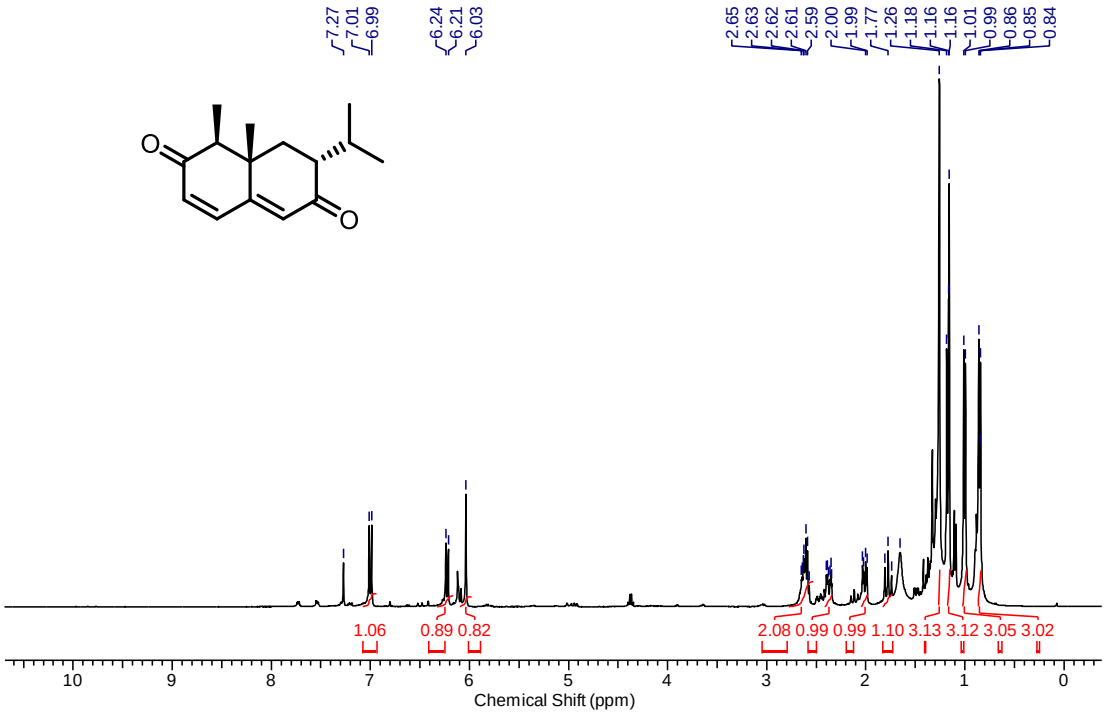
^{1}H NMR of Compound **188b** in $CDCl_3$ at 400 MHz



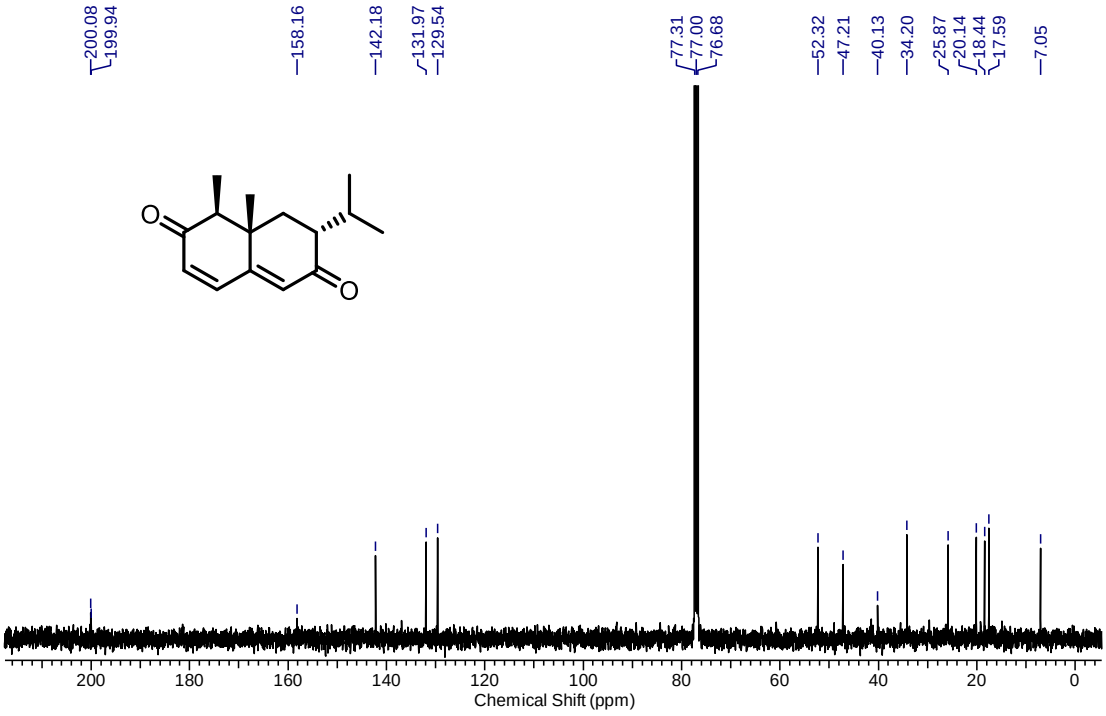
^{1}H NMR of Compound **189b** in $CDCl_3$ at 400 MHz



^{1}H NMR of Compound **190b** in $CDCl_3$ at 400 MHz



^{1}H NMR of Compound **172** in $CDCl_3$ at 400 MHz

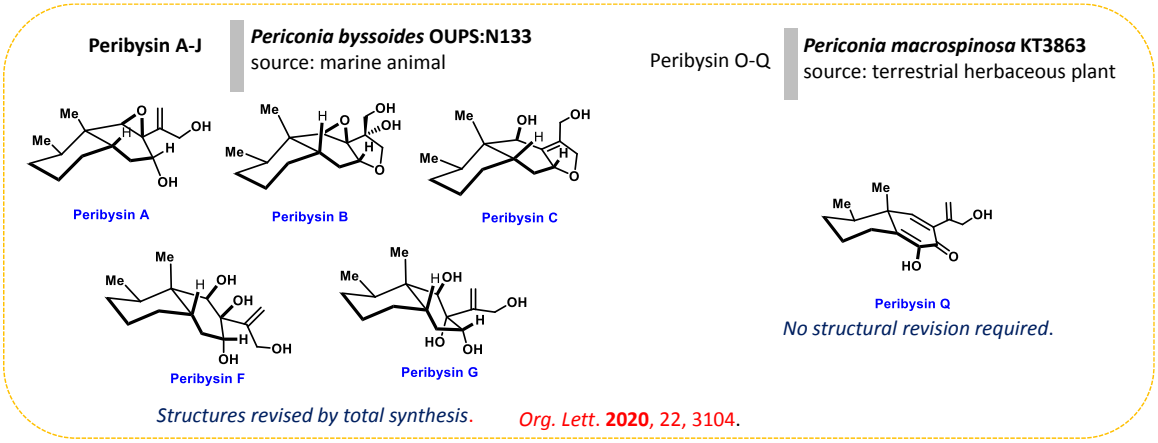


^{13}C NMR of Compound **172** in $CDCl_3$ at 100 MHz

Thesis Summary

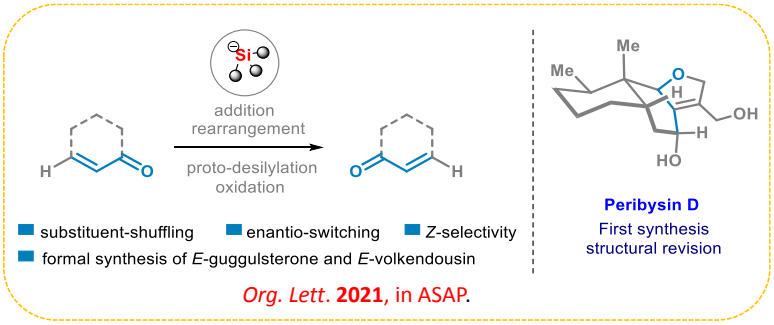
In the search for the medicinally important compounds inspired from the nature, we selected peribysins, a family of natural products possessing potent cell adhesion inhibitory activity for the present study. At first, the structural re-assignment of peribysins isolated from marine source was achieved by means of total synthesis of five natural products from the series. During this exercise, two methodologies were developed having high synthetic utility. The salient features of the work are capturd below.

- We developed a unified strategy to access all the peribysins from (+)-nootkatone.
- Kinetic iodination of the enone resulting in separation of diastereomers is the key step of the sequence.
- Based on single crystal X-ray data of peribysin A, optical rotation values and prior work by Danishefsky's group we revised the structures of peribysin A, B, C, F and G by total synthesis.
- The study also concluded that peribysins isolated from marine source need stereochemical revision and the peribysins isolated from plant source need no any revision.

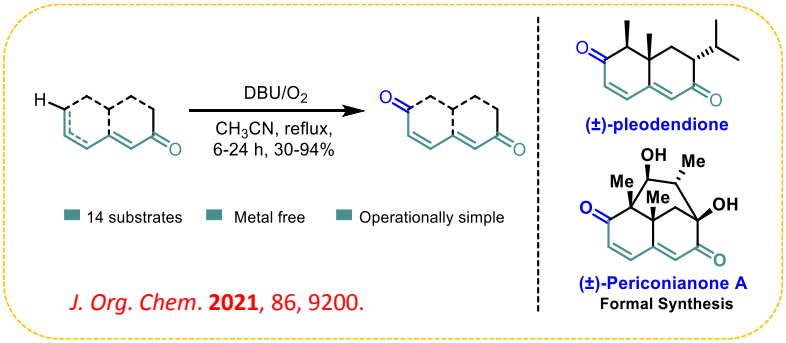


- We developed a general method for enone transposition mediated by silyl masking group.
- Method was tested with 15 different substrates with interesting outcomes such as substituent shuffling, enantio-switching, *Z*-selectivity etc.

- Method was successfully applied for the first total synthesis (with structural revision) of peribysin D and for the formal synthesis of *E*-guggulsterone and *E*-volkendousin.



- A mild and efficient method mediated by DBU/O_2 in CH_3CN for the oxidation of dienones was developed.
- The method is operationally simple and tested with 14 substrates with up to 94% isolated yield.
- The method was successfully applied for the synthesis of natural product (±)-pleodendione with improved yields over the traditional PDC/TBHP method.



ABSTRACT

Name of the Student: Paresh R. Athawale **Registration No.:** 10CC17J26033

Faculty of Study: Chemical Science **Year of Submission:** 2021

AcSIR academic centre/CSIR Lab: CSIR-National Chemical Laboratory, Pune **Name of the Supervisor:** Dr. D. Srinivasa Reddy

Title of the thesis: Total Synthesis Guided Structural Revision of Peribysin Family Natural Products and Development of Novel Method for Enone Transposition

The work included in this thesis is mainly based on the total synthsis of the natural products and development of useful synthetic methods. Herein we have developed a unified strategy to access the peribysin family natural products which possess potent cell adhesion inhibitory activities. The structures of the peribysins A, B, C, F, and G were revised based on NMR, optical rotation and single crystal X-ray data. With this exercise we were able to conclude that the peribysins isolated from marine animal source needs stereochemical revision and those isolated from terrestrial plant source does not need any revision.

During the synthesis of peribysins we sought to develop a method for enone transposition which was achieved with help of silyl masking group. The highlights of the method includes *Z*-selectivity, enantio-switching and functional group shuffling in selected examples. The method was successfully tested with more than 14 substrates and applied for the total synthesis along with structural revision of peribysin D. Additionally, formal synthesis of *E*-guggulsterone and *E*-volkendousin was achieved.

Lastly, an unexpected but useful transformation of dienones to diene-diones discovered during a double bond migration reaction using DBU in acetonitrile. Further, method was tested with 14 substrates and applied for the synthesis of (±)-pleodendione with improved yields.

List of Publications Emanating from the Thesis Work

1. **Athawale**, **P. R.;** Zade, V. M.; Gamidi, R. K.; Reddy, D. S. Tuning of α-Silyl Carbocation Reactivity into Enone Transposition: Application to the Synthesis of Peribysin D, *E*-Volkendousin, and *E*-Guggulsterone *Org. Lett.* **2021**, *doi.org/10.1021/acs.orglett.1c02173.*
2. **Athawale**, **P. R.;** Kalmode, H. P.; Reddy, D. S. DBU/O_2-Mediated Oxidation of Dienones *J. Org. Chem.* **2021**, *86*, 9200-9205.
3. **Athawale**, **P. R.**; Kalmode, H. P.; Motiwala, Z.; Kulkarni, K. A.; Reddy, D. S. Overturning the Peribysin Family Natural Products Isolated from Periconia byssoides OUPS-N133: Synthesis and Stereochemical Revision of Peribysins A, B, C, F, and G *Org. Lett.* **2020**, *22*, 3104–3109.

List of Publications Non-Emanating from the Thesis Work

1. Atapalkar, R. S.; **Athawale**, **P. R.**; Reddy, D. S.; Kulkarni, A. A. Scalable, sustainable and catalyst-free continuous flow ozonolysis of fatty acids *Green Chem.* **2021**, *23*, 2391-2396. (equal contribution).
2. Jachak, G. R.; **Athawale**, **P. R.;** Choudhury, R.; Reddy, D. S. Access to a Stereoisomer Library of Solomonamide Macrocycles *Chem. Asian J.* **2019**, *14*, 4572-4576.
3. **Athawale**, **P. R.**; Kumari, N.; Dandawate, M.; Kashinath, K.; Reddy D. S. Synthesis of Chiral Tetrahydrofuran Building Blocks from Pantolactones: Application in the Synthesis of Empagliflozin and Amprenavir Analogs *Eur. J. Org. Chem.* **2019**, 4805.
4. Kalmode, H. P.; Patil, S. S.; Handore, K. L.; **Athawale**, **P. R.**; Dandela, R.; Verma, A. K.; Basu, A.; Reddy, D. S. Neural Anti-Inflammatory Natural Product Periconianone A: Total Synthesis and Biological Evaluation *Eur. J. Org. Chem.* **2019**, 2376–2381.
5. Jachak, G. R.; **Athawale**, **P. R.**; Agarwal, H.; Barthwal, M. K.; Lauro, G.; Bifulco, G.; Reddy, D. S. Total synthesis of the potent anti-inflammatory natural product solomonamide A along with structural revision and biological activity evaluation *Org. Biomol. Chem.* **2018**, *16*, 9138.
6. **Athawale**, **P. R.**; Jachak, G. R.; Shukla, A.; Shanmugam, D.; Reddy, D. S. Efforts To Access the Potent Antitrypanosomal Marine Natural Product Janadolide: Synthesis of Des-*tert*-butyl Janadolide and Its Biological Evaluation *ACS Omega***,**

2018, *3*, 2383.

7. **Athawale**, **P. R.**; Kashinath, K.; Reddy, D. S. Enantiospecific Formal Synthesis of Inthomycin C *Chemistry Select.* **2016**, 3, 495.
8. Kashinath, K.; Jachak, G. R.; **Athawale**, **P. R.**; Marelli, U. K.; Gonnade, R. G.; Reddy, D. S. Total Synthesis of the Marine Natural Product Solomonamide B Necessitates Stereochemical Revision *Org. Lett.* **2016**, 18, 3178. (equal contribution).

Patents

1. A process for the oxidation of fatty acids (**WO2020240596A1**).
2. Decalin derivatives, a process for the preparation and pharmaceutical composition thereof (**PCT/IN2019/050779**).
3. A process for the preparation of benofuran-6-carboxylic acid (**INV-2019-32**)

List of Posters Presented with Details

1. National Science Day Poster presentation at CSIR-National Chemical Laboratory, Pune (February 25-27, **2018**):

   Title: Efforts toward Total Synthesis of Potent Anti-Parasitic Natural Product Janadolide

   Abstract: To identify novel anti-parasitic agents based on Janadolide, a potent macrocyclic polyketide-peptide hybrid natural product, two macrocyclization strategies (ring closing metathesis and macrolactonization) were explored. Whereas, macrocyclization in the vicinity of *tert*-butyl group was unsuccessful in both the cases. In this project, we achieved the first total synthesis of des-*tert*-butyl Janadolide (which has all the functionalities in place except *tert*-butyl group) using Shiina macrolactonization strategy.

List of Conference Attended with Details

1. Oral presentation at Department of Chemistry, University of Delhi, (October 18-21, **2019**)

   Title: Total synthesis guided stereochemical revision of peribysin family natural products

   Abstract: Peribysins (A–I, O-Q) were isolated by Yamada's group from a strain of *Periconia byssoides* OUPS-N133, originally separated from the sea hare, *Aplysia kurodai*. All the peribysins showed potent cell-adhesion inhibitory activity and they are useful leads for the control of cancer metastasis, inflammation and sickle cell anemia. Based on this assumption and the ground work done by Danishefsky's group, we defined the problem that all the remaining peribysins may need stereochemical revision. Accordingly, we developed a general route to access all the peribysins from (+)-nootkatone in an enantiospecific manner. Firstly, peribysin A was synthesized and absolute stereochemistry was revised based on NMR spectral data and specific optical rotation.

2. NCL-RF Annual Students' Conference, CSIR-National Chemical Laboratory, 2019 (delivered oral presentation).

   Title: Total synthesis guided stereochemical revision of peribysin family natural products

Abstract: Peribysins (A–I) were isolated by Yamada's group from a strain of Periconia byssoides OUPS-N133, originally separated from the sea hare, Aplysia kurodai.1 All the peribysins showed potent cell-adhesion inhibitory activity and they are useful leads for the control of cancer metastasis, inflammation and sickle cell anemia. Danishefsky's group reported the elegant first total synthesis of peribysin E along with stereochemical revision in 2007-08. Their findings pointed out that the absolute stereochemistry of peribysin E was incorrect; the revised structure was exact antipode of the proposed structure. Since all the peribysins were isolated from same species, it is most likely that they all are biosynthesized from the same precursor. Based on this assumption and the ground work done by Danishefsky's group,2 we defined the problem that all the remaining peribysins may need stereochemical revision. Accordingly, we developed a general route to access all the peribysins from (+)-nootkatone in enantiospecific manner. Firsty, peribysin A was synthesized and absolute stereochemistry was revised based on NMR spectral data and specific optical rotation.

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Overturning the Peribysin Family Natural Products Isolated from *Periconia byssoides* OUPS-N133: Synthesis and Stereochemical Revision of Peribysins A, B, C, F, and G

Paresh R. Athawale, Hanuman P. Kalmode, Zenia Motiwala, Kiran A. Kulkarni,* and D. Srinivasa Reddy*

Cite This: *Org. Lett.* 2020, 22, 3104–3109 Read Online

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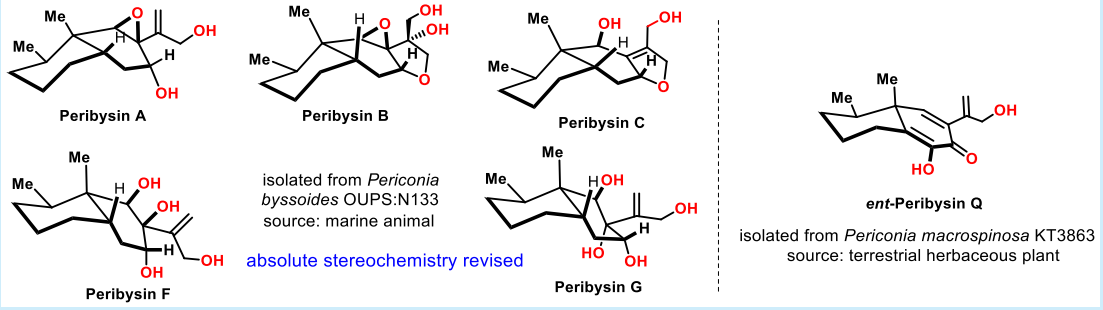

ABSTRACT: Herein we report the stereochemical revision of peribysins A, B, C, F, and G, guided by enantiospecific total synthesis starting from (+)-nootkatone. Furthermore, we reconfirmed the absolute stereochemistry of peribysin Q. The highlights of the synthesis are enone transposition and kinetic iodination resulting in separation of diastereomers. Our findings coupled with synthetic and biological data previously reported by Danishefsky's group suggest that the original stereochemistries of peribysins A, B, C, F, and G were misassigned.

The field of structural elucidation of natural products has changed significantly over the last century. Until the mid-20th century, most of the structural explorations of natural products were based on total synthesis, derivatization, and degradation studies. However, advancements in NMR spectroscopy, X-ray crystallography, and several other techniques have reduced the dependence on chemical synthesis to delineate the absolute structure of natural products. However, despite these advancements, the structural interpretations are still prone to errors due to the indirect nature of some of these techniques. The fallibility in interpretation is exemplified by several reports of structural revisions over the years.[1] In this regard, total synthesis of natural products has served as an autocorrect tool to rectify the errors that remain unaddressed in the canonical isolation-based structural elucidations. In this pursuit, the Danishefsky group reported the stereochemical revision of peribysin E by synthesizing (+)- and (−)-peribysins starting from (*R*)- and (*S*)-carvones, respectively, using a chiral-pool approach (Figure 1B).[2] Recently, Hashimoto et al. reported the isolation of three new members of this family, peribysins O−Q, from *Periconia macrospinosa* KT3863 (a terrestrial herbaceous plant), in addition to the previously reported peribysins A−J from *Periconia byssoides* OUPS-N133 (from the sea hare *Aplysia kurodai*) by the Yamada group (Figure 1A).[3] Additionally, the study by Hashimoto et al. revisited the absolute stereochemistry of peribysin E, and on the basis of circular dichroism (CD) studies it was inferred that the original stereochemical assignment of the molecule by their group was correct. This inference was also supported by an argument that the absolute stereochemistry of peribysins from a particular isolation source, belonging to defined biogenetic pathways, generally remains invariant, particularly, with respect to absolute stereochemistry. In view of the biological potential of peribysins as cell adhesion inhibitors, they are one of the focus areas of our research[4] (in particular, a major program, the Sickle Cell Anemia Mission, is ongoing), it is imperative to address this discrepancy. In the present work, we set out to conclusively delineate the absolute stereochemistries of peribysins. We employed the total synthesis technique to revise the structures of all of the known members of the peribysin family. Accordingly, we planned the antipodes of the proposed structures from a chiral-pool starting material, (+)-nootkatone (with well-established absolute stereochemistry),[6] to eliminate the ambiguities and have access to a maximum number of natural products from this family (Figure

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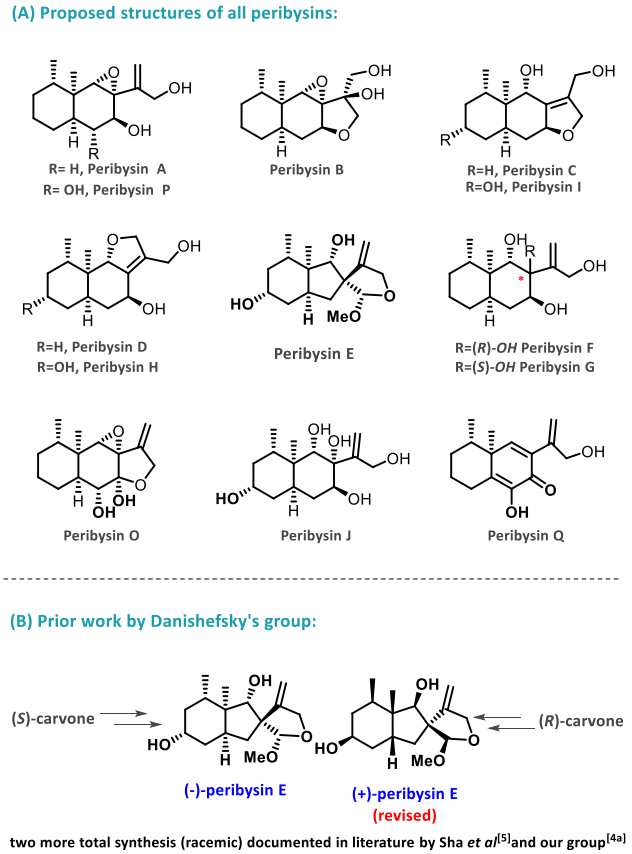

Figure 1. (A) Proposed structures of the peribysins. (B) Prior work.

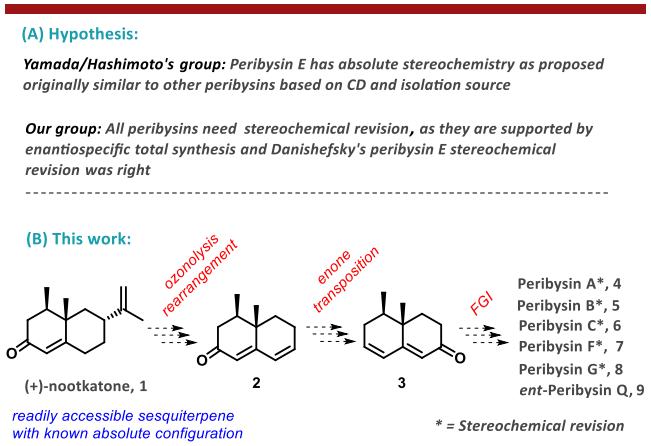

Figure 2. (A) Hypothesis. (B) This work.

2B). Since most of the peribysins can be obtained from peribysin A via functional group manipulations, we prioritized synthesis of peribysin A to validate our hypothesis.

As per the plan, synthesis commenced from ozonolysis of commercially available (+)-nootkatone (**1**) in methanol to form the methoxy peroxide intermediate, which upon quenching with Cu(II) and Fe(II) salts gave olefin compound **10** (Scheme 1).[7] The crude olefin was subjected to double-bond migration using DBU in acetonitrile to obtain dienone **2**. The reaction was done in 20 g scale batches in 75% yield over the two steps. Enone **2** was subjected to Luche reduction followed by TBS protection of the resulting allylic alcohol to afford compound **12**. Although it is not required for the present purpose, the stereochemistry of the allylic alcohol was tentatively assigned (see the Supporting Information for details). Selective epoxidation of the less hindered double bond in **12** followed by regioselective opening of the epoxide furnished an alcohol, which was oxidized with DMP to give compound **13**. Treatment of **13** with a catalytic amount of *p*TSA·H_2O in CH_2Cl_2 furnished the desired compound **3**, a vital intermediate for synthesis of several natural products. Three steps took place in this one experimental operation: TBS deprotection, hydroxyl group elimination, and double-bond migration. The entire sequence of transformations was performed with crude materials, and just a single purification was needed at the end, affording enone **3** in 14% overall yield over eight steps starting from (+)-nootkatone. At this stage, for enone transposition from **2** to **3**, we attempted various approaches (viz., hydroboration−oxidation, **12** to **13**/**18**;[8] Mitsunobu reaction, **11** to **11a**;[9] and water-catalyzed allylic rearrangement, **11** to **19**)[10] but had no practical success to move forward toward total synthesis (Scheme 1).

Compound **3** was then subjected to hydrogenation using Pd/C in 1% methanolic KOH to give saturated ketone **14**. Several conditions were screened for selective hydrogenation of enone **3** to get the *cis* geometry of the junction. The maximum selectivity (3:2 *cis*:*trans*) was obtained in 1% KOH in methanol under a hydrogen pressure of 250 mbar, in which the major isomer was the required one (see the Supporting Information for additional details).[11] When enone **3** was subjected to hydrogenation with Pd/C without using any base, it furnished exclusively (−)-octalone (**16**). Ketone **14** was then subjected to oxidation using IBX in DMSO[12] and catalytic TFA, which yielded the required enone **15** along with two more natual products, **16** and overoxidized product **17**. All of the data, including specific optical rotation, were in agreement with the literature reports.[13,14]

At this stage, the *cis*:*trans* ratio of enone **15** was found to be 3:2 by ^{1}H NMR analysis. When enone **15** having a *cis*:*trans* ratio of 3:2 was subjected to iodination with iodine and pyridine, the reaction became sluggish after approximately 50% conversion of the starting material. Even adding more equivalents of iodine and pyridine could not accelerate the reaction to a considerable extent. At this point, the reaction was stopped, and unreacted enone was recovered. To our delight, after careful analysis of the enone by ^{1}H NMR spectroscopy, the *cis*:*trans* ratio was found to be 4:1, which clearly indicates that there is a difference between the reactivities of the enone isomers toward iodination. The reason for this improved diastereomeric ratio could be the rigid structures of the two enones (Scheme 2). The *cis* isomer has a puckered structure compared with the flatter structure of the *trans* isomer, which enables more favorable attack of pyridine at the *β*-position in the *trans* isomer. Moreover, the presence of the junction methyl group provides steric hindrance for the top-face nucleophilic attack at the *β*-position (similar to the observation made by Danishefsky's group[2]) in both isomers, which ultimately results in kinetic iodination of the *trans* isomer while keeping the *cis* isomer unreacted. The use of 1 equiv of iodine and 6 equiv of pyridine at room temperature for 24 h resulted in kinetic separation to give the required enone **15a** with a >95:5 diastereomeric ratio. The stereochemistry of **15a** was further confirmed by the strong NOE correlation between the junction methyl and junction hydrogen (Scheme 2).

Enone **15a** was subjected to iodination with $TMSN_3$ and iodine followed by Suzuki cross coupling with known boronate

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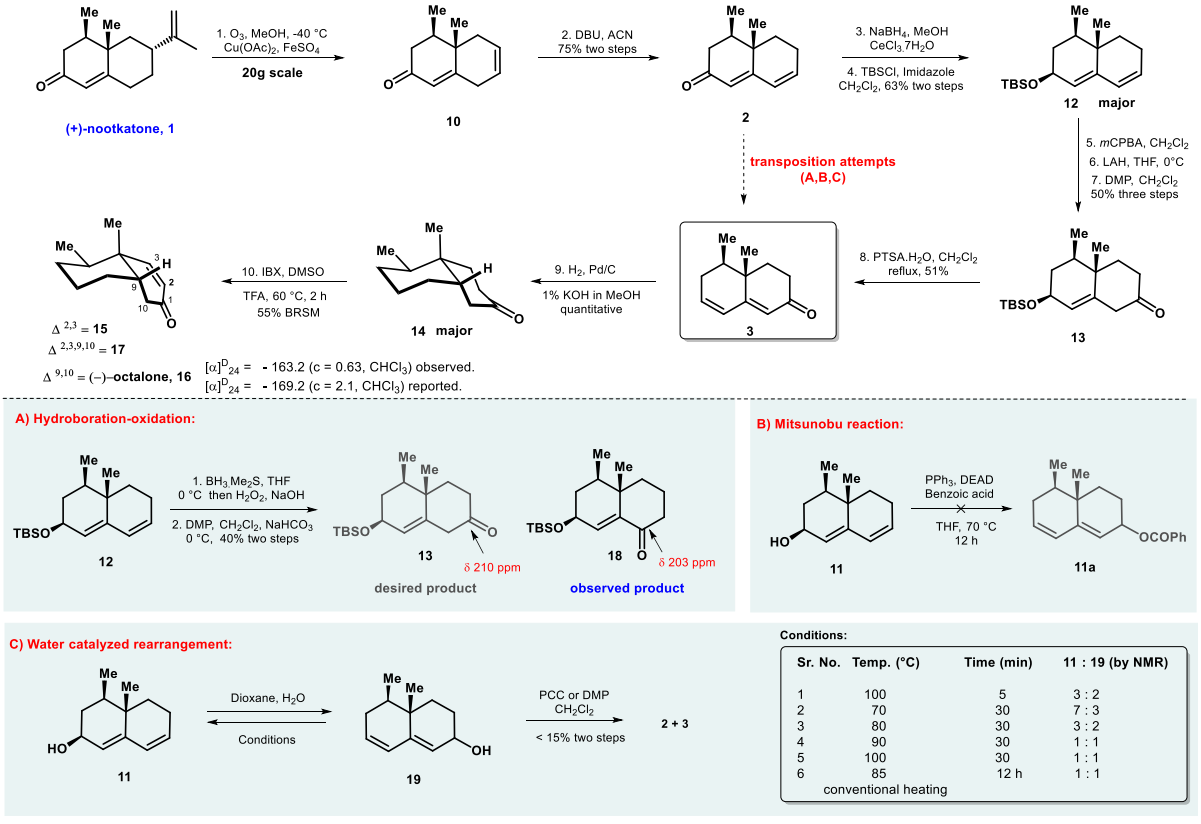
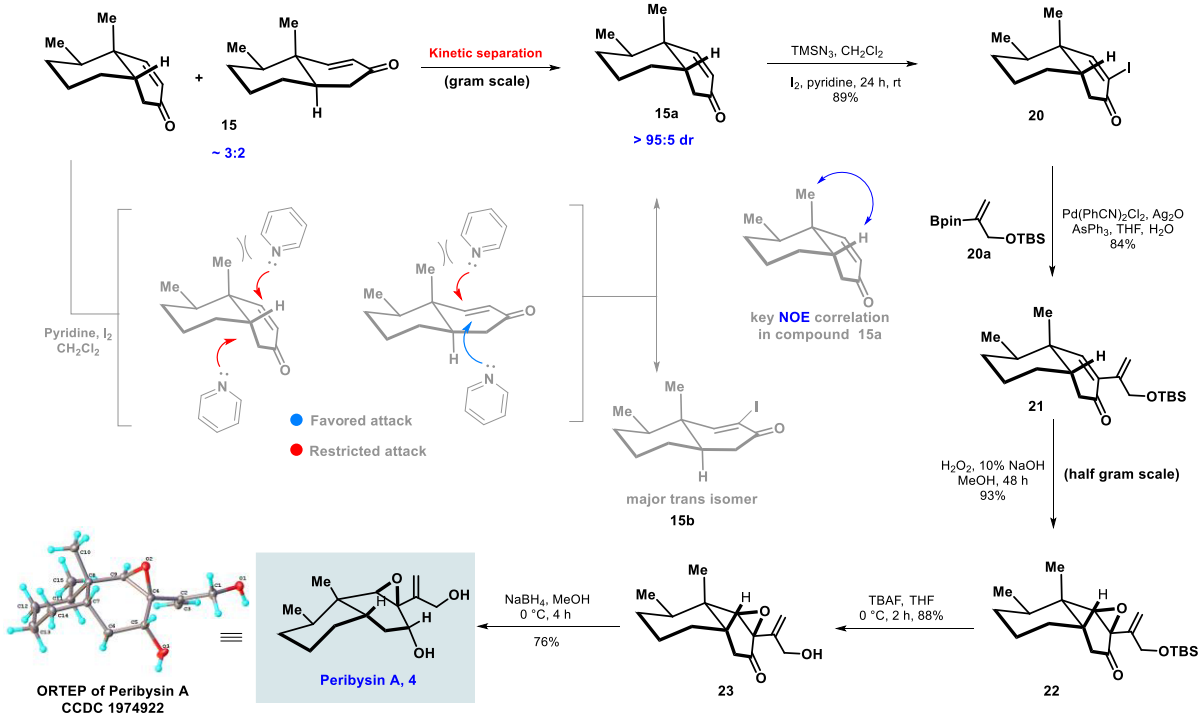
Org. Lett. 2020, 22, 3104−3109

Scheme 1. Synthesis of Enone 15 from (+)-Nootkatone and Transposition Attempts



Scheme 2. Total Synthesis of Peribysin A



ester **20a**[15] to furnish compound **21** in excellent yield. Compound **21** was subjected to epoxidation using H_2O_2 and NaOH to obtain **22** in 93% yield. Here epoxidation occurred stereoselectively from the top face to give a single diastereomer. TBS deprotection of compound **22** was achieved using TBAF, and ketone reduction using $NaBH_4$ in MeOH gave peribysin A (**4**) and its diastereomer **4a** in an 8.4:1 ratio). All of the NMR spectral data for the synthetic sample of peribysin A perfectly matched those in the literature report. Furthermore, the structure was confirmed by single-crystal X-

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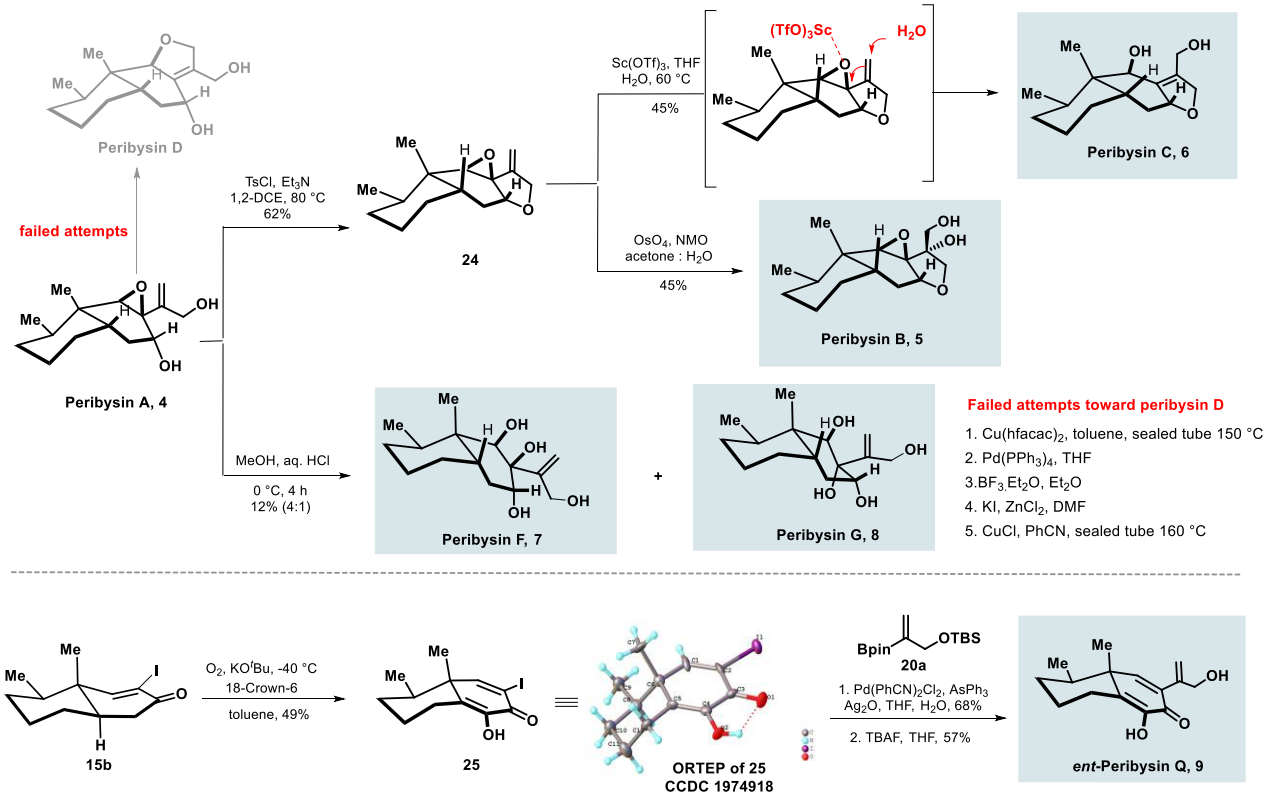
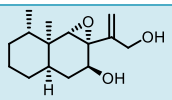
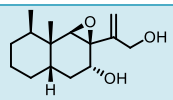
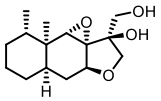
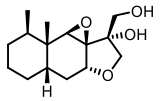
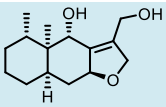
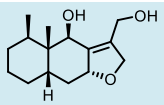
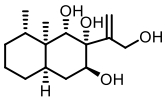
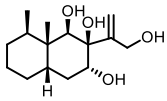
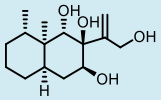
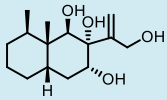
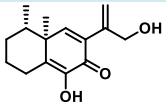
Org. Lett. 2020, 22, 3104−3109

Scheme 3. Total Synthesis of Peribysins B, C, F, G, and Q



Scheme 4. Summary of This Work: Proposed and Revised Structures of Peribysins

Proposed structure	Compound	Revised structure
	Peribysin A	
	Peribysin B	
	Peribysin C	
	Peribysin F	
	Peribysin G	
	Peribysin Q	no revision required

ray analysis to eliminate any ambiguities. The specific optical rotation of synthetic peribysin A was recorded in ethanol and found to be −59.3°, whereas the reported value is −63.7°. As we synthesized the antipode of the proposed structure of peribysin A and the optical rotations match, we conclude that peribysin A needs stereochemical revision, as per our hypothesis in Figure 2A. The proposed structure is in fact *ent*-peribysin A, similar to the report by the Danishefsky group in the peribysin E revision.

Inspired by this outcome, next we turned our attention to the remaining peribysins. To synthesize other members of the family, peribysin A was required in greater quantities, so the synthesis of peribysin A was scaled up to the 250 mg scale. Peribysin A was treated with tosyl chloride and triethylamine in 1,2-dichloroethane (1,2-DCE) at 80 °C to give compound **24**, which upon dihydroxylation using NMO and catalytic OsO_4 in aqueous acetone furnished peribysin B (**5**) in moderate yield (Scheme 3). The same compound **24** was treated with $Sc(OTf)_3$ in THF/H_2O to give another natural product, peribysin C (**6**), in 45% yield. All of the spectral data for the synthesized peribysins **5** and **6** were in complete agreement with the reported data, but the optical rotation value for peribysin B was not comparable.[16] To access peribysins F and G, the epoxide moiety in peribysin A was opened under acidic conditions to give the more stable carbocation intermediate, which upon reaction with H_2O resulted in both of the desired natural products F and G. Again, all of the spectral data (NMR and optical rotation) were compared to the literature values and found to be identical, suggesting that the structures of peribysins F and G have to be revised. To access peribysin D, we attempted several conditions[17] for rearrangement of the allylic epoxide moiety present in peribysin A to the dihydrofuran moiety, but none of them gave the desired product (selected conditions are mentioned in Scheme 3). Finally, we focused on synthesis of newly isolated peribysins O−Q. For this purpose, iodoenone

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Org. Lett. 2020, 22, 3104−3109

15b obtained during the diastereomeric separation was treated with KO^{t}Bu and 18-crown-6 under an oxygen atmosphere[18] to afford enol **25**, which upon Suzuki cross coupling followed by TBS deprotection furnished peribysin Q (**9**). All of the NMR spectral data were in complete agreement with the reported ones, but the specific optical rotation was found to be exactly opposite. The CD spectrum of peribysin Q was recorded, from which it was inferred that the absolute stereochemistry assigned for peribysin Q was correct.

Thus, we have addressed the stereochemical discrepancies in peribysins isolated from a marine source through enantiospecific total syntheses and revised the structures of several peribysin family natural products, including peribysins A, B, C, F, and G. Accordingly, we suggest that the peribysins isolated from the marine source need stereochemical revision, whereas peribysins isolated from the herbaceous plant need no stereochemical revision (Scheme 4). During the synthesis, we discovered an unexpected but useful kinetic iodination of enone **15** that resulted in diastereomeric separation. Screening of peribysins and their analogues for their cell adhesion potential is currently ongoing.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c00857.

Experimental procedures; NMR comparison table for peribysins A, B, C, F, G, and Q; NMR spectra; crystallographic data for **4** and **25**; and CD spectra of *ent*-peribysin Q (PDF)

Accession Codes

CCDC 1974918 and 1974922 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, U.K.; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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(16) The specific optical rotation value for synthetic peribysin B was found to be $[\alpha]_D^{25} = -1.1$ (c = 0.56, EtOH) after repeated checking. The reported value is $[\alpha]_D^{25} = +42.9$ (c = 0.07, EtOH).
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DBU/O_2-Mediated Oxidation of Dienones

Paresh R. Athawale,[‖] Hanuman P. Kalmode,[‖] and D. Srinivasa Reddy*

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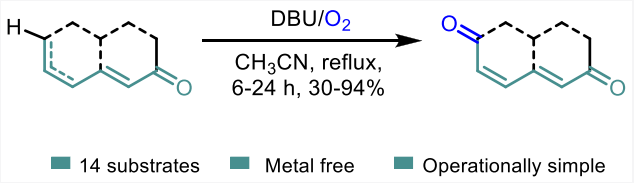
ABSTRACT: Herein, we describe a DBU/O_2-promoted novel method for oxidation of dienones to 2,6-dione derivatives. The reaction involves treatment of a dienone with DBU in acetonitrile employing molecular oxygen as the oxidant. Metal free conditions and an eco-friendly reagent are the striking features of this protocol. This transformation proceeds through a peroxide intermediate that upon Kornblum−DeLaMare rearrangement produces 2,6-diones. The method was successfully utilized for the synthesis of (±)-pleodendione with improved yields versus those of the traditional PDC-TBHP method.



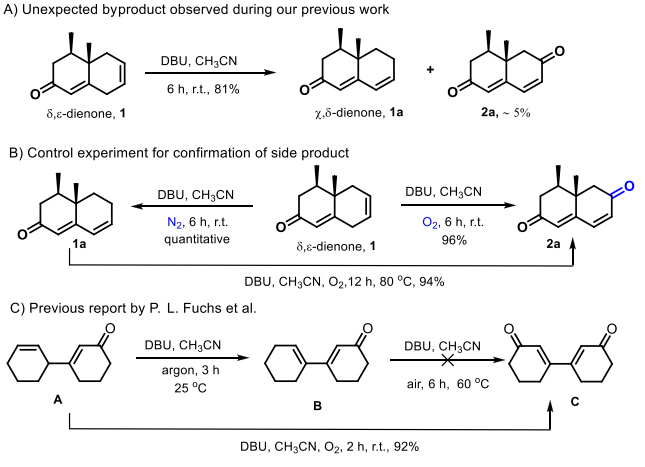
In organic synthesis, the discovery of new methods for allylic oxidation is an ever developing active area. Generally, a double bond present in the system activates the allylic carbon hydrogen bond that aids in the selective installation of the oxygen functionality.[1] These types of reactions are fundamental methods for allylic functionalization and have a great impact on the synthetic chemistry of molecules having commercial value.[2,3] In natural product synthesis, allylic oxidation is greatly important, and to date, a variety of reagents and conditions have been reported. However, there are certain limitations in terms of productivity and chemo- and regioselectivity because of the structural diversity of natural products.

Conventionally, reagents based on chromium(VI) such as pyridinium chlorochromate (PCC), pyridinium dichromate (PDC), PDC-*tert*-butyl hydroperoxide, the CrO_3-pyridine complex, CrO_3 and 3,5-dimethylpyrazole, sodium chromate, sodium dichromate in acetic acid, pyridinium fluorochromate, 3,5-dimethylpyrazolium fluorochromate, and a combination of an *N*-hydroxydicarboxylic acid imide with a chromium-containing oxidant have been used to perform allylic oxidations.[4] Manganese dioxide, potassium permanganate, and selenium dioxide are the other classical methods that use a stoichiometric amount of the reagent.[5] However, these reagents have become less preferred for industrial scale production based on the quantities of reagents required, the volume of solvent used, and tedious workup procedures of the environmentally hazardous metal residues and/or byproducts. Other catalytic methods involve rhodium, iron, copper, cobalt, and palladium as catalysts, most of which are costly, toxic, and avoided in the final stages of API synthesis.[2]

Although various allylic oxidations have been reported in the literature,[6] the development of metal free, eco-friendly synthetic transformations is highly desirable.[7] In this context, while we were working on the synthesis of the peribysin family of natural products,[8] we made an interesting observation when we wanted to perform a double bond migration reaction in compound **1** to obtain compound **1a**.

When the reaction was conducted under the standard protocol using DBU as a base in CH_3CN, we observed compound **2a** in ∼5% yield in addition to expected product **1a** (Scheme 1A). This was quite surprising because no oxidant or metal catalyst was utilized in this reaction. Thus, the only possible oxygen source could be dissolved oxygen from the solvent. To confirm this, we conducted two control experiments, one reaction under a completely inert atmosphere of

Scheme 1. Background



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nitrogen and another reaction in the presence of oxygen. To our delight, the reaction under a nitrogen atmosphere exclusively gave double bond migrated compound **1a** while the reaction under an oxygen atmosphere exclusively furnished oxygenated compound **2a** (Scheme 1B). This experiment confirmed that oxygen acted as an oxidant in this reaction. A similar kind of observation was made by P. L. Fuchs et al. using DBU and oxygen in CH_3CN (Scheme 1C).[9] However, the corresponding conjugated compound (**B**) did not give an oxidized product even after heating at 60 °C. Thus, to confirm this, we applied this method on our substrate **1a** having a conjugated system. At 60 °C, only a trace amount of product was observed, but when the temperature was increased to 80 °C, a 94% yield of the diketo product **2a** was isolated. This unoptimized condition was previously employed by our group for the synthesis of (±)-periconianone A.[10]

Inspired with this result in hand and considering the presence of a naphthalene-2,6-dione skeleton in natural products,[11] we decided to optimize this method and test it with various substrates (selected natural products are captured in Figure 1). For this purpose, compound **1a** was chosen as a

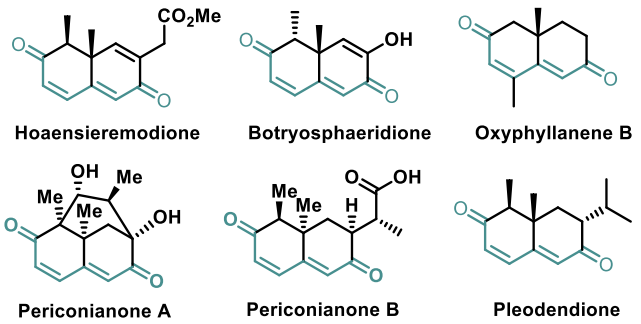

Figure 1. Natural products having 2,6-dione functionality.

model substrate. In our preliminary observations, we obtained desired product **2a** in 46% yield along with <10% formation of 8-hydroxy dienone (**2a′**) and the starting material (**1a**, 45%) was recovered (Table 1, entry 2). To further optimize the reaction condition, we increased the amount of DBU (1.5−2.5 equiv) and observed the formation of **2a** in 94% yield (Table 1, entries 3 and 4). To check the possibility of a further increase in the yield of **2a**, various solvents such as 1,4-dioxane, THF, EtOAc, and DMSO were screened (Table 1, entries 5−8, respectively). The use of 1,4-dioxane and EtOAc as the solvent resulted in a moderate to low yield of **2a**, 49% and 18%, respectively, along with recovery of the starting material (entries 5 and 7, respectively). A trace amount of **2a** was formed in THF, whereas in the case of DMSO, decomposition of the starting material was observed (entries 6 and 8). 1,2-Dichloroethane and toluene gave a low yield of **2a**, while in DMF, the product was not formed (entries 9−11).

Various bases such as NMM, DIPEA, and DABCO were also used for the allylic oxidation reaction (Table 1, entries 12−14, respectively). However, using these bases, no product formation was observed, and only the starting material was recovered. We also tried the reaction of dienone (**1a**) without the use of base, but in that case, only the starting material was recovered (entry 15). Only a trace amount of tetrahydronaphthalene-2,6-dione (**2a**) was observed by oxidation of dienone (**1a**) using Pearlman's catalyst (entry 16). Corey's group has explored this highly selective method for the oxidation of α,β-enones to 1,4-enediones, and very recently, the Wang group reported a highly step and atom economic Pd/Cu combination for accessing 1,4-enediones under aerobic conditions.[12] Therefore, the optimal reaction condition for the preparation of 2,6-dione derivatives (**2a**) was found to be DBU as a base and molecular O_2 as the oxidant in acetonitrile at the reflux temperature.

Considering the importance of this method in total synthesis[12] and to explore the generality of this protocol for the synthesis of 2,6-dione derivatives (**2a**), various dienones (**1**) synthesized using known procedures[13] were examined under the optimized reaction conditions (Table 2). Trienone (**1b**) via the allylic oxidation reaction under optimized conditions gave compound **2b** in a good yield (78%). The oxidation reaction of epimerized trienone and epoxy dienones (**1c** and **1d**) went smoothly to afford the corresponding products (**2c** and **2d**, respectively) in 75% and 44% yields, respectively. The regioselective allylic oxidation of dienones (**1e−h**) having alkenyl, ester, hydroxy alkenyl, and benzyl substituents on a decalin skeleton resulted in good to moderate yields (48−79%) of diketones (**2e−h**). Although the structure of diketone **2h** was proposed on the basis of NMR analysis, it was further confirmed by X-ray analysis (see Table 2 for the ORTEP diagram).

Encouraged by these results in hand, we extended the scope of the reaction to the extended trienone of hexahydroanthracene (**1i**) and found that along with allylic oxidation hydroxylation was observed (**2i**, 52%), which was confirmed by ^1H and ^{13}C NMR in which one of the quaternary carbons at δ 66.5 was observed (no further studies were performed to determine the stereochemistry of the new quaternary center). Additionally, the substrate scope was extended to an alicyclic system such as α-ionone and β-ionone. In both cases, we observed the formation of dione (**2j**) in 76% and 68% yields, respectively. It means α-ionone was converted to β-ionone first and then allylic oxidation occurred.

Similarly, in the case of aliphatic dienone **1k**, the reaction proceeded smoothly to give **2k** in 48% yield. In addition, the reaction of ethyl sorbate and deconjugated ethyl sorbate under optimized conditions gave a moderate yield of the product (**2l**). Here, it is interesting to note that natural product (±)-pleodendione (**2m**) was obtained in 67% isolated yield compared to our previous report using the conventional PDC-TBHP method (46%) (Scheme 2).[13] An ionic mechanism was proposed on the basis of the literature reports and control experiments (see the Supporting Information).[14]

In summary, we have developed a mild and efficient method for the oxidation of dienones to form 2,6-diones, which might find application in the synthesis of natural products and bioactive molecules. Additionally, employing inexpensive DBU as the base and O_2 (balloon) as the oxidant makes this reaction more practical and sustainable. The method was successfully applied for the synthesis of (±)-pleodendione with an improved yield. Further synthetic exploration of this method is underway in our laboratory.

■ EXPERIMENTAL SECTION

General Information. All reactions were carried out in oven-dried glassware under a positive pressure of argon or nitrogen unless otherwise mentioned with magnetic stirring. Air sensitive reagents and solutions were transferred via syringe or cannula and introduced into the apparatus via rubber septa. All reagents, starting materials, and solvents were obtained from commercial suppliers and used as such

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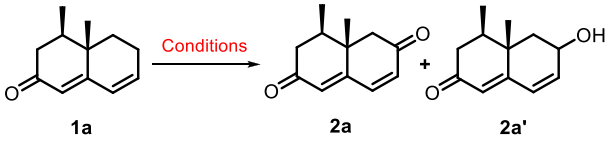
J. Org. Chem. 2021, 86, 9200−9205

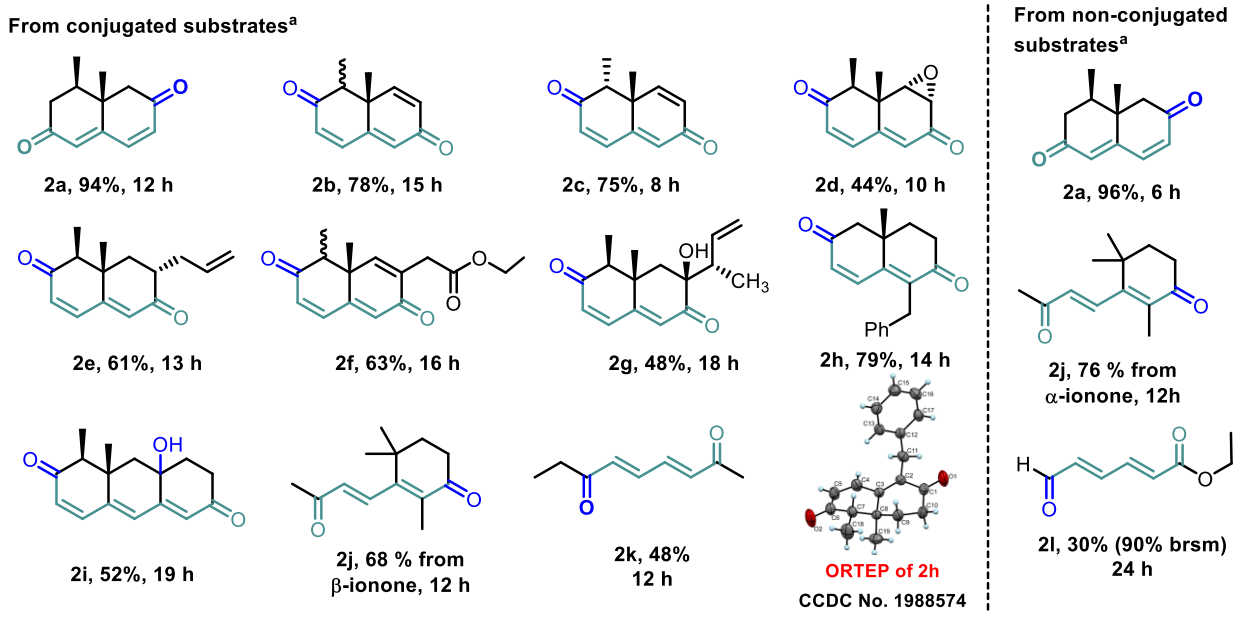
Table 1. Optimization of Reaction Conditions[a]



entry	catalyst/base (equiv)	promoter/oxidant (equiv)	solvent	temp (°C)	time (h)	yield (%)[c] 2a	1a	2a′
1	–	PDC (5)/TBHP (5)	benzene	rt	16	28		–
2	DBU (1.5)	–	CH_3CN	reflux	12	36	45	<10
3	DBU (2.5)	–	CH_3CN	reflux	6	46	32	<5
4	DBU (2.5)	–	CH_3CN	reflux	12	94	ND	ND
5	DBU (2.5)	–	1,4-dioxane	80	12	49	46	<5
6	DBU (2.5)	–	THF	reflux	12	trace	~92	ND
7	DBU (2.5)	–	EtOAc	reflux	12	18	77	trace
8	DBU (2.5)	–	DMSO	80	12		decomposed	
9	DBU (2.5)	–	1,2-DCE	80	12	4	90	ND
10	DBU (2.5)	–	toluene	80	12	9	86	trace
11	DBU (2.5)	–	DMF	80	12		decomposed	
12	NMM (2.5)	–	CH_3CN	reflux	12	trace	90	ND
13	DIPEA (2.5)	–	CH_3CN	reflux	12	ND	98	ND
14	DABCO (2.5)	–	CH_3CN	reflux	12	ND	95	ND
15[b]	–	–	CH_3CN	reflux	12	ND	98	ND
16	$Pd(OH)_2/C$ (0.05), K_2CO_3 (0.5)	TBHP (5)	CH_2Cl_2	rt	12	trace	91	ND

[a]Reaction conditions: dienone (**1a**, 1.0 mmol), catalyst (0.05 mmol) or base (0.5−2.5 mmol) or oxidant (5 mmol) and promoter (5 mmol), solvent (10 mL) stirred at rt to reflux for 6−12 h under an oxygen atmosphere. Abbreviations: PDC, pyridinium dichromate; TBHP, *tert*-butyl hydroperoxide; DBU, 1,8-diazabicyclo[5.4.0]undec-7-ene; NMM, *N*-methylmorpholine; DIPEA, *N,N*-diisopropylethylamine; DABCO, 1,4-diazabicyclo[2.2.2]octane; ND, not detected. [b]In the absence of a catalyst or base. [c]Isolated yields.

Table 2. Scope of the Method



[a]The carbonyl group/OH group is from the reaction with DBU, and O_2 is colored blue.

without further purification. Reactions were monitored by thin layer chromatography (TLC) with 0.25 mm precoated silica gel plates (60 F254). Visualization was accomplished either with UV light or by immersion in an ethanolic solution of phosphomolybdic acid (PMA), *p*-anisaldehyde, 2,4-DNP, a $KMnO_4$ solution, or iodine adsorbed on silica gel followed by heating with a heat gun for ~15 s. Column chromatography was performed on silica gel (100−200 or 230−400 mesh). Melting points were determined using a Bruker capillary melting point apparatus and are uncorrected. *S**/*R** nomenclature is used to show the relative stereochemistry of the product. Deuterated solvents for NMR spectroscopic analyses were used as received. All ^1H and ^{13}C NMR spectra were recorded using a Jeol/Bruker 400 MHz or Bruker 500 MHz spectrometer. Coupling constants are reported in hertz. Chemical shifts are quoted in parts per million, relative to TMS, using the residual solvent peak as a reference standard. The following abbreviations were used to explain the

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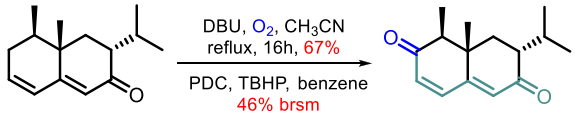
J. Org. Chem. 2021, 86, 9200−9205

Scheme 2. Synthesis of (±)-Pleodendione



multiplicities: br s, broad singlet; s, singlet; d, doublet; dd, doublet of doublets; t, triplet; td, triplet of doublets; q, quartet; m, multiplet. HRMS (ESI) spectra were recorded on an ORBITRAP mass analyzer (Thermo Scientific, QExactive). Infrared (IR) spectra were recorded on an FT-IR spectrometer as a thin film. The chemical nomenclature was generated using Chem Bio Draw Ultra 14.0.

General Procedure for the Oxidation of Dienones. Into a stirred solution of **1a−m** (1 mmol, 1 equiv) in dry acetonitrile (10 mL) was bubbled oxygen gas for 10 min at room temperature. DBU (2.5 mmol, 2.5 equiv) was added dropwise, and the reaction mixture was refluxed for a period of 6−24 h (using an oil bath as the heating source) under an O_2 atmosphere. The reaction mixture was diluted with ice-cold water (20 mL) and extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with water, dried over Na_2SO_4, filtered, and concentrated to give the crude product that was purified by column chromatography (ethyl acetate/petroleum ether) to afford **2a−m** in 30−94% yield.

(1R,8aR*)-1,8a-Dimethyl-1,7,8,8a-tetrahydronaphthalene-2,6-dione (**2a**).* Purified by silica gel column chromatography (80:20 petroleum ether/ethyl acetate): isolated yield of 0.122 g, 94%; off-white solid; IR υ_{max} (film) 1655, 1607, 1574, 755 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.05 (dd, J = 0.6, 9.9 Hz, 1 H), 6.20 (d, J = 9.9 Hz, 1 H), 6.08 (s, 1 H), 2.68 (d, J = 15.6 Hz, 1 H), 2.46−2.32 (m, 3 H), 2.26 (dd, J = 4.0, 6.4 Hz, 1 H), 1.17−1.14 (m, 3 H), 1.01 (d, J = 6.5 Hz, 3 H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 198.6, 197.8, 158.7, 143.6, 131.6, 129.6, 48.9, 41.7, 39.7, 39.0, 18.4, 14.6; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{12}H_{15}O_2$191.1067, found 191.1064.

*(4R,4aS)-6-Hydroxy-4,4a-dimethyl-4,4a,5,6-tetrahydronaphthalen-2(3H)-one (**2a′**).* Purified by silica gel column chromatography (72:28 petroleum ether/ethyl acetate): isolated yield of 0.148 g; pale yellow liquid; IR υ_{max} (film) 3378, 2958, 1651, 1287, 1041 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.29−6.11 (m, 2 H), 5.79 (s, 1 H), 4.54 (br s, 1 H), 2.39−2.30 (m, 3 H), 2.16−2.04 (m, 1 H), 1.69−1.60 (m, 1 H), 1.07 (s, 3 H), 1.01 (d, J = 6.9 Hz, 3 H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 199.5, 161.5, 140.1, 128.5, 125.2, 66.1, 43.1, 41.6, 38.6, 37.9, 16.5, 14.8; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{12}H_{17}O_2$ 193.1228, found 193.1228.

(8aR)-1,8a-Dimethyl-1,8a-dihydronaphthalene-2,6-dione (**2b**) (dr 7:3).* Purified by silica gel column chromatography (75:25 petroleum ether/ethyl acetate): isolated yield of 0.114 g, 78%; colorless solid; IR υ_{max} (film) 2973, 1653, 1625, 1452, 1215 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.28−7.11 (m, 1.2 H), 6.82 (d, J = 9.8 Hz, 1 H), 6.53 (s, 0.7 H), 6.45−6.38 (m, 1.2 H), 6.28 (d, J = 9.8 Hz, 0.3 H), 6.17 (d, J = 9.8 Hz, 1 H), 2.67−2.60 (m, 1 H), 1.37 (s, 2 H), 1.35−1.31 (m, 1 H), 1.24 (s, 1 H), 0.94 (d, J = 7.3 Hz, 2 H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 201.2, 198.3, 185.8, 185.2, 157.5, 154.8, 154.5, 153.3, 142.5, 142.4, 131.2, 131.0, 129.5, 129.1, 128.9, 128.5, 52.2, 49.5, 45.0, 44.3, 29.6, 28.0, 15.6, 7.8; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{12}H_{13}O_2$ 189.0910, found 189.0907.

(1S,8aR*)-1,8a-Dimethyl-1,8a-dihydronaphthalene-2,6-dione (**2c**).* Purified by silica gel column chromatography (75:25 petroleum ether/ethyl acetate): isolated yield of 0.093 g, 75%; white solid; IR υ_{max} (film) 2974, 1667, 1649, 1618, 1597, 1452, 1307, 1187 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.21 (d, J = 12.0 Hz, 1 H), 6.81 (d, J = 12.0 Hz, 1 H), 6.53 (s, 1 H), 6.42 (d, J = 12.0 Hz, 1 H), 6.16 (d, J = 12.0 Hz, 1 H), 2.63 (q, J = 8.0 Hz, 1 H), 1.37 (s, 3 H), 0.94 (d, J = 8.0 Hz, 3 H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 201.2, 185.9, 154.8, 154.5, 142.5, 131.1, 129.6, 129.1, 52.3, 45.0, 28.1, 15.6; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{12}H_{13}O_2$ $[M + H]^+$ 189.0916, found 189.0925.

(1aR,7R*,7aR*,7bR*)-7,7a-Dimethyl-1a,7,7a,7b-tetrahydronaphtho[1,2-b]oxirene-2,6-dione (**2d**).* Purified by silica gel column chromatography (77:23 petroleum ether/ethyl acetate): isolated yield of 0.045 g, 44%; yellowish oily liquid; IR υ_{max} (film) 2919, 1710, 1676, 1463, 1215, 1094 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.13 (d, J = 8.0 Hz, 1 H), 6.21 (d, J = 12.0 Hz, 1 H), 6.02 (s, 1 H), 3.68 (d, J = 3.6 Hz, 1 H), 3.48 (dd, J = 3.2, 2.0 Hz, 1 H), 2.74 (q, J = 7.2 Hz, 1 H), 1.36 (s, 3 H), 1.35 (d, J = 7.2 Hz, 3 H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 197.9, 191.4, 157.1, 142.6, 131.8, 124.4, 60.76, 54.2, 49.3, 40.8, 19.0, 7.6; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{12}H_{13}O_3$ 205.0859, found 205.0858.

(1R,7R*,8aR*)-7-Allyl-1,8a-dimethyl-1,7,8,8a-tetrahydronaphthalene-2,6-dione (**2e**).* Purified by silica gel column chromatography (75:25 petroleum ether/ethyl acetate): isolated yield of 0.094 g, 61%; light yellow solid; IR υ_{max} (film) 2922, 1718, 1665, 1612, 1580, 1388, 1161 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.01 (d, J = 9.6 Hz, 1 H), 6.22 (d, J = 10.0 Hz, 1 H), 6.05 (s, 1 H), 5.83−5.73 (m, 1 H), 5.12−5.07 (m, 2 H), 2.77−2.72 (m, 1 H), 2.64−2.47 (m, 2 H), 2.21 (dd, J = 14.6, 8.4 Hz, 1 H), 2.14 (dd, J = 13.0, 5.2 Hz, 1 H), 1.70 (t, J = 13.6 Hz, 1 H), 1.17 (s, 3 H), 1.14 (d, J = 6.4 Hz, 3 H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 199.8, 199.6, 158.7, 142.1, 135.5, 132.0, 128.8, 117.3, 52.2, 41.4, 40.4, 39.9, 33.5, 18.6, 6.9; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{15}H_{19}O_2$ 231.1380, found 231.1378.

Ethyl 2-[(8aR)-8,8a-Dimethyl-3,7-dioxo-3,7,8,8a-tetrahydronaphthalen-2-yl]acetate (**2f**) (dr 7:3).* Purified by silica gel column chromatography (70:30 petroleum ether/ethyl acetate): isolated yield of 0.086 g, 63%; yellowish oily liquid; IR υ_{max} (film) 2976, 1730, 1662, 1632, 1452, 1256, 1163, 1027 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.28−7.20 (m, 1 H), 7.03 (s, 0.3 H), 6.73 (s, 0.7 H), 6.55 (s, 0.7 H), 6.45 (s, 0.3 H), 6.28 (d, J = 9.8 Hz, 0.3 H), 6.16 (d, J = 9.8 Hz, 0.7 H), 4.19−4.13 (m, 2 H), 3.48−3.29 (m, 2 H), 2.64 (q, J = 6.7 Hz, 1 H), 1.38 (s, 2 H), 1.33 (d, J = 6.7 Hz, 1 H), 1.29−1.23 (m, 4 H), 0.96 (d, J = 7.3 Hz, 2 H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 201.2, 198.3, 184.8, 184.2, 170.7, 170.6, 157.5, 154.8, 152.5, 151.2, 142.3, 142.1, 133.8, 132.7, 131.2, 130.3, 129.1, 128.3, 60.9, 52.4, 49.5, 45.1, 44.3, 34.9, 34.6, 29.6, 27.9, 22.3, 15.5, 14.1, 7.8; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{16}H_{19}O_4$ 275.1283, found 275.1292.

(1R,7R*,8aR*)-7-[(R*)-But-3-en-2-yl]-7-hydroxy-1,8a-dimethyl-1,7,8,8a-tetrahydronaphthalene-2,6-dione (**2g**).* Purified by silica gel column chromatography (80:20 petroleum ether/ethyl acetate): isolated yield of 0.089 g, 48%; off-white solid; IR υ_{max} (film) 3412, 1720, 1666 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.04 (d, J = 10.0 Hz, 1 H), 6.25 (d, J = 10.0 Hz, 1 H), 6.18 (s, 1 H), 5.98−5.89 (m, 1 H), 5.22 (d, J = 10.8 Hz, 1 H), 5.16 (d, J = 16.8 Hz, 1 H), 3.49 (q, J = 7.6 Hz, 1 H), 2.79−2.73 (m, 1 H), 2.61 (q, J = 6.8 Hz, 1 H), 2.33 (s, 1 H), 2.06−1.95 (m, 1 H), 1.26 (s, 3 H), 1.18 (d, J = 6.8 Hz, 3 H), 0.95 (d, J = 6.0 Hz, 3 H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 200.1, 199.7, 160.5, 141.7, 137.6, 132.4, 127.9, 117.5, 75.5, 52.1, 45.9, 40.3, 39.5, 22.8, 14.6, 7.3; HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{16}H_{20}O_3Na$ 283.1305, found 283.1298.

(1R,8aR*)-5-Benzyl-1,8a-dimethyl-1,7,8,8a-tetrahydronaphthalene-2,6-dione (**2h**).* Purified by silica gel column chromatography (70:30 petroleum ether/ethyl acetate): isolated yield of 0.075 g, 79%; colorless solid; IR υ_{max} (film) 2971, 1716, 1663, 1599, 1492, 1453, 1317, 1183 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.48 (d, J = 10.4 Hz, 1 H), 7.29−7.27 (m, 2 H), 7.21 (d, J = 6.8 Hz, 1 H), 7.14 (d, J = 7.2 Hz, 2 H), 6.23 (d, J = 9.6 Hz, 1 H), 3.89 (s, 2 H), 2.66−2.64 (m, 3 H), 2.13 (d, J = 12.8 Hz, 1 H), 2.04 (dd, J = 12.0, 7.2 Hz, 1 H), 1.23 (s, 3 H), 1.18 (d, J = 6.4 Hz, 3 H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 199.9, 197.5, 153.7, 139.4, 139.3, 137.4, 131.5, 128.6 (2C), 127.9 (2C), 126.2, 52.4, 40.9, 33.6, 33.4, 30.3, 17.8, 6.9; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{19}H_{21}O_2$ 281.1542, found 281.1544.

(1R,9aR*)-8a-Hydroxy-1,9a-dimethyl-1,7,8,8a,9,9a-hexahydroanthracene-2,6-dione (**2i**).* Purified by silica gel column chromatography (65:35 petroleum ether/ethyl acetate): isolated yield of 0.069 g, 52%; pale yellow solid; IR υ_{max} (film) 3409, 2923, 1647, 1596, 1452, 1323, 1260, 1218 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.03 (d, J = 9.2 Hz, 1 H), 6.41 (s, 1 H), 6.14 (d, J = 9.6 Hz, 1 H), 5.91 (s, 1 H), 2.89 (td, J = 15.6, 5.2 Hz, 1 H), 2.52 (s, 1 H), 2.48−2.43 (m, 1 H), 2.19 (d, J = 14.8 Hz, 2 H), 2.06 (dd, J = 13.4, 4.4

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J. Org. Chem. 2021, 86, 9200−9205

Hz, 2 H), 1.71 (d, J = 14.0 Hz, 1 H), 1.34 (s, 3 H), 1.15 (d, J = 6.8 Hz, 3 H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 200.4, 199.4, 153.1, 149.8, 142.8, 129.5, 129.0, 126.5, 66.5, 53.3, 47.2, 40.6, 37.5, 33.1, 20.9, 7.1; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{16}H_{19}O_3$ 259.1329, found 259.1327.

*(E)-2,4,4-Trimethyl-3-(3-oxobut-1-en-1-yl)cyclohex-2-en-1-one (**2j**).* Purified by silica gel column chromatography (80:20 petroleum ether/ethyl acetate): isolated yield of 0.146 g, 68%; yellowish oily liquid; IR υ_{max} (film) 2962, 1694, 1666, 1613, 1353, 1312, 1249, 1174 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.17 (d, J = 16.4 Hz, 1 H), 6.11 (d, J = 16.4 Hz, 1 H), 2.45 (t, J = 7.2 Hz, 2 H), 2.28 (s, 3 H), 1.82 (t, J = 6.8 Hz, 2 H), 1.72 (s, 3 H), 1.12 (s, 6 H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 198.3, 197.2, 157.6, 140.1, 133.4, 131.1, 37.1, 35.3, 33.9, 27.7, 27.1 (2C), 13.2; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{13}H_{19}O_2$ 207.1380, found 207.1378.

*Ethyl (2E,4E)-6-Oxohexa-2,4-dienoate (**2k**) (see ref 15 for literature data).* Purified by silica gel column chromatography (70:30 petroleum ether/ethyl acetate): isolated yield of 0.080 g, 48%; yellowish oily liquid; IR υ_{max} (film) 2957, 2853, 1716, 1690, 1642, 1603, 1461, 1367, 1272, 1178, 1095, 1030, 969, 764 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.68 (d, J = 8.0 Hz, 1 H), 7.42 (dd, J = 15.6, 11.2 Hz, 1 H), 7.17 (dd, J = 15.2, 11.2 Hz, 1 H), 6.43 (dd, J = 15.2, 8.0 Hz, 1 H), 6.31 (d, J = 15.2 Hz, 1 H), 4.27 (q, J = 7.2 Hz, 2 H), 1.33 (t, J = 7.6 Hz, 3 H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 192.9, 165.4, 147.2, 140.3, 136.9, 129.9, 61.1, 14.2; HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_8H_{10}O_3Na$ 177.0522, found 177.0516.

*(3E,5E)-Nona-3,5-diene-2,7-dione (**2l**) (see ref 16 for literature data).* Purified by silica gel column chromatography (85:15 petroleum ether/ethyl acetate): isolated yield of 0.165 g, 30% (90% brsm); pale yellow liquid; IR υ_{max} (film) 2927, 1678, 1590, 1251 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.24−7.08 (m, 2 H), 6.57−6.39 (m, 2 H), 2.64 (q, J = 7.3 Hz, 2 H), 2.33 (s, 3 H), 1.14 (t, J = 7.3 Hz, 3 H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 200.2, 197.7, 139.8, 138.6, 136.6, 135.9, 34.5, 29.7, 27.8; HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_8H_{10}O_3Na$ 177.0522, found 177.0516.

(1R,7S*,8aR*)-7-Isopropyl-1,8a-dimethyl-1,7,8,8a-tetrahydronaphthalene-2,6-dione (**2m**).* Purified by silica gel column chromatography (78:22 petroleum ether/ethyl acetate): isolated yield of 0.107 g, 67%; colorless oil; IR υ_{max} (film) 2925, 1721, 1665, 1580, 1461, 1386, 1208 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.0 (d, J = 9.6 Hz, 1 H), 6.22 (d, J = 9.6 Hz, 1 H), 6.03 (s, 1 H), 2.65−2.57 (m, 2 H), 2.40−2.34 (m, 1 H), 2.01 (dd, J = 13.0, 4.8 Hz, 1 H), 1.77 (t, J = 13.6 Hz, 1 H), 1.26 (s, 3 H), 1.16 (d, J = 2.4 Hz, 3 H), 1.00 (d, J = 7.2 Hz, 3 H), 0.86−0.84 (m, 3 H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 200.1, 199.9, 158.2, 142.2, 131.9, 129.5, 52.3, 47.2, 40.1, 34.2, 25.8, 20.1, 18.4, 17.6, 7.0; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{15}H_{21}O_2$ 233.1536, found 233.1533.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.1c00529.

^1H and ^{13}C NMR spectra of all compounds (PDF)

Accession Codes

CCDC 1988574 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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Tuning of α-Silyl Carbocation Reactivity into Enone Transposition: Application to the Synthesis of Peribysin D, *E*-Volkendousin, and *E*-Guggulsterone

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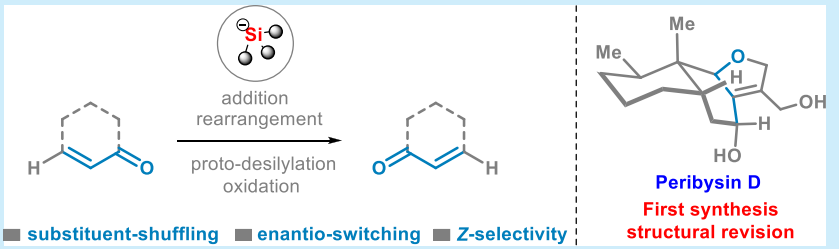

ABSTRACT: A reliable method for enone transposition has been developed with the help of silyl group masking. Enantio-switching, substituent shuffling, and *Z*-selectivity are the highlights of the method. The developed method was applied for the first total synthesis of peribysin D along with its structural revision. Formal synthesis of *E*-guggulsterone and *E*-volkendousin was also claimed using a short sequence.

The multidirectional reactivity of the enone moiety makes it an attractive functional group in organic synthesis. All three carbon atoms and the oxygen present in the enone system can be manipulated as per the requirement.[1] Transposition of both the carbonyl group and the olefinic bond further enhances the synthetic utility of the enone synthons and thereby offers a high degree of opportunity in organic synthesis. On the contrary, dealing with these types of compounds becomes difficult.[2] Over the past few decades, enones served as vital intermediates in natural product synthesis.[3] One such type of enone rearrangement was attempted by our group during the synthesis of peribysin family natural products.[4] We wanted to achieve an enone transposition reaction from compound **1** to compound **2** (Figure 1A). However, after screening a few conditions, we settled for a six-step sequence with poor yields. The most studied transformation of this kind is the oxidative rearrangement of *ter*-alcohols to enones using Cr^{VI}-based reagents,[5] but the main drawback of this transformation is that the group added to enone carbonyl is not detachable after rearrangement (Figure 1B). Apart from this, there are a few known methods in the literature; each has certain advantages and limitations.[6] One such type of reaction is Wharton reaction, wherein α,β-epoxy ketone is rearranged to the corresponding allylic alcohol using hydrazine.[7] With this background, we decided to develop a transposition method using a silicon-based masking group (Figure 1C) because a silyl lithium reagent can be easily prepared and added to the carbonyl group, wherein an α-silyl tertiary carbocation can be generated in situ. If a double bond is present in conjugation, then it can undergo rearrangement because of the favored tertiary to secondary carbocation rearrangement and silicon α-effect (Figure 1D).[8]

In addition, the silyl groups are reactive toward various nucleophiles such as hydroxides, alkoxides, and fluorides, which make them easy to detach from the substrate. A similar kind of rearrangement of α-silyl alcohols was reported by Honda and co-workers during the synthesis of allyl ethers.[9] A few more useful rearrangements of α-silyl alcohols were reported by Sakaguchi et al., and a Cr(VI)-mediated oxidative rearrangement was reported by Song et al.[10] With this background, we first prepared the $PhMe_2SiLi$ reagent as described by Fleming et al. and added it to a model substrate 4,4-dimethyl-2-cyclohexen-1-one (**3a**).[11] The reaction gave an 84% yield of the desired 1,2-addition product **3b** (Scheme 1). The next task was to perform the rearrangement of compound **3b** to obtain compound **3c**. Here, we used acetonitrile and H_2O as a mixture of solvents (in a 1:1 ratio), and a few drops of TFA was added. The rearranged product was observed in 55% yield. Further tweaking the ratio of solvents (9:1 CH_3CN/H_2O) gave a 95% yield of the rearranged alcohol (Scheme 1). In addition, for proto-desilylation of compound

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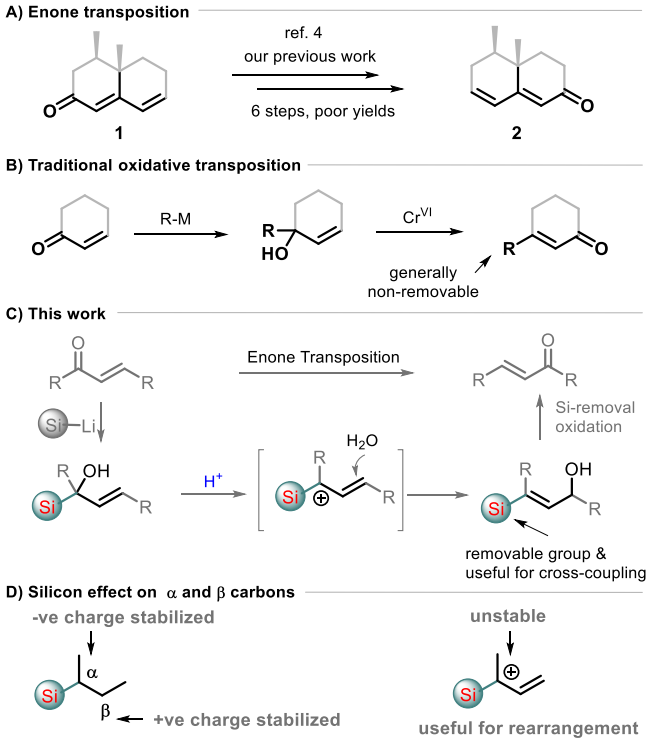
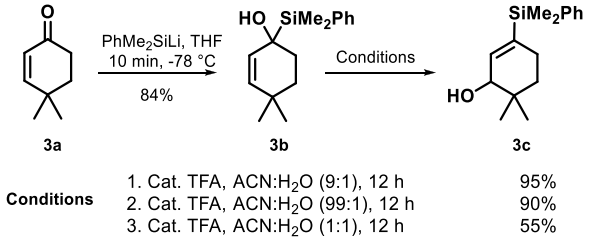


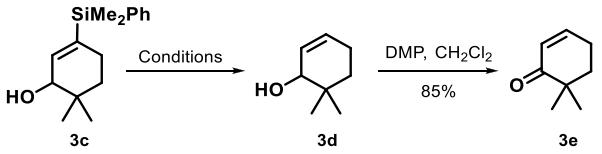
Figure 1. (A) Our previous work. (B) Traditional oxidative transposition. (C) This work. (D) Silicon α and β effects.

Scheme 1. Optimization of Silyl Addition and Transposition Reaction



3c to obtain compound **3d** (Scheme 2), reaction with TFA, BF_3·MeOH, or BF_3·AcOH did not give the desired product **3d**.

Scheme 2. Optimization of Proto-desilylation



Instead, the starting material was recovered completely (Table 1, entries 1−3). Reaction with HI resulted in partial decomposition of the starting material. In addition, fluoride- and alkoxide-based reagents were unsuccessful in the desilylation reaction (Table 1, conditions 5−7).[12] The use of HMPA along with TBAF as reported by Muraoka et al. gave an ∼20% yield of the desired product.[13] Capperucci et al. have reported a condition under which TBAF and KOH were used in combination for the proto-desilylation of the triphenyl silyl group.[14] Under the same condition, we observed successful removal of the phenyl dimethyl silyl group, which furnished product **3d** in 64% yield when refluxed in THF for 16 h. The

Table 1. Optimization of Proto-desilylation

	reagent[a]	solvent	temp	time (h)	observation
1	TFA	CH_2Cl_2	reflux	12	NR
2	BF_3·MeOH	CH_2Cl_2	0 °C to rt	10	NR
3	BF_3·AcOH	AcOH	rt	10	NR
4	HI	THF/H_2O	rt to 70 °C	4	decomposed
5	TBAF	THF	reflux	5	NR
6	KF	DMF	80 °C	2	NR
7	NaOMe	MeOH	reflux	6	NR
8	TBAF/HMPA	DMSO	80 °C	2	∼20%
9	TBAF, KOH	THF	reflux	16	64%[b]
10	TBAF, KOH	THF	85 °C, MW	0.5	98%[b]

[a]Reaction performed on a 100 mg scale. NR indicates no reaction, and MW indicates microwave irradiation. [b]Isolated yield.

reaction time was significantly decreased when the reaction was carried out in a microwave at 85 °C with an excellent yield of 98% (Table 1, entry 10). The mechanism of proto-desilylation is the replacement of the phenyl ring on silicon with the hydroxide to give silanol.[15] In addition, the silanol intermediate on reaction with fluoride ions gives the desilylated alcohol **3d**.

Finally, the allylic alcohol was oxidized using DMP to give rearranged enone **3e** in 85% yield. The whole sequence can be performed with only two purification steps after rearrangement and after a final oxidation step with an overall yield of 66%. It is interesting to note that, when the reaction was started with 4,4-dimethyl cyclohexenone, the end product is 6,6-dimethyl cyclohexenone (an example of substituent shuffling). After having the optimized reaction sequence in hand, we first screened substituted cyclohexenones. The reaction of 2,6-cyclohexenone of 2,4-dimethyl cyclohexenone. Similarly, 4-*tert*-butyl cyclohexenone was transformed into 6-*tert*-butyl cyclohexenone in 53% overall yield. Chiral substrate **5a** gave compound **5e** in 28% overall yield. Here it is clear from these four examples that when the substituent is present at positions 4 and 6 on cyclohexenones, in the end, the positions of these substituents are exchanged. Next, we prepared two bicyclic enones **7a** and **8a**. Enone **7a** was derived from (+)-3-carene in two steps that under the optimized conditions gave two different enones, **7e** and **7h**. The structure of *E*-enone **7e** was confirmed by single-crystal X-ray diffraction during the alcohol stage. These two enones and their intermediates can be utilized as building blocks for natural product synthesis. Bicyclic enone **8a** underwent smooth rearrangement to give enone **8e** in 39% overall yield. The structure of intermediate **8d** of enone **8e** was confirmed via single-crystal X-ray diffraction, where the equatorial hydroxyl group was observed after the rearrangement reaction (Scheme 3). In addition, we tested the method on our original target compound (conversion of compound **1** to **2**) but it failed to give the desired product.

Next, we tested the commercially available enone **9a**, which gave a 56% overall yield of **9e**. Here, interestingly, the *Z*-enone was observed as the major product. The selectivity arose during the rearrangement reaction where the bulky silyl group prefers the less sterically crowded side to give alcohol **9c** having *E*-geometry. After deprotection, the geometry remained unchanged to give the *Z*-enone. Hydrocinnamaldehyde-derived enone **10a** furnished the desired rearranged enone **10e** with a 92:8 *Z*:*E* selectivity, whereas the corresponding

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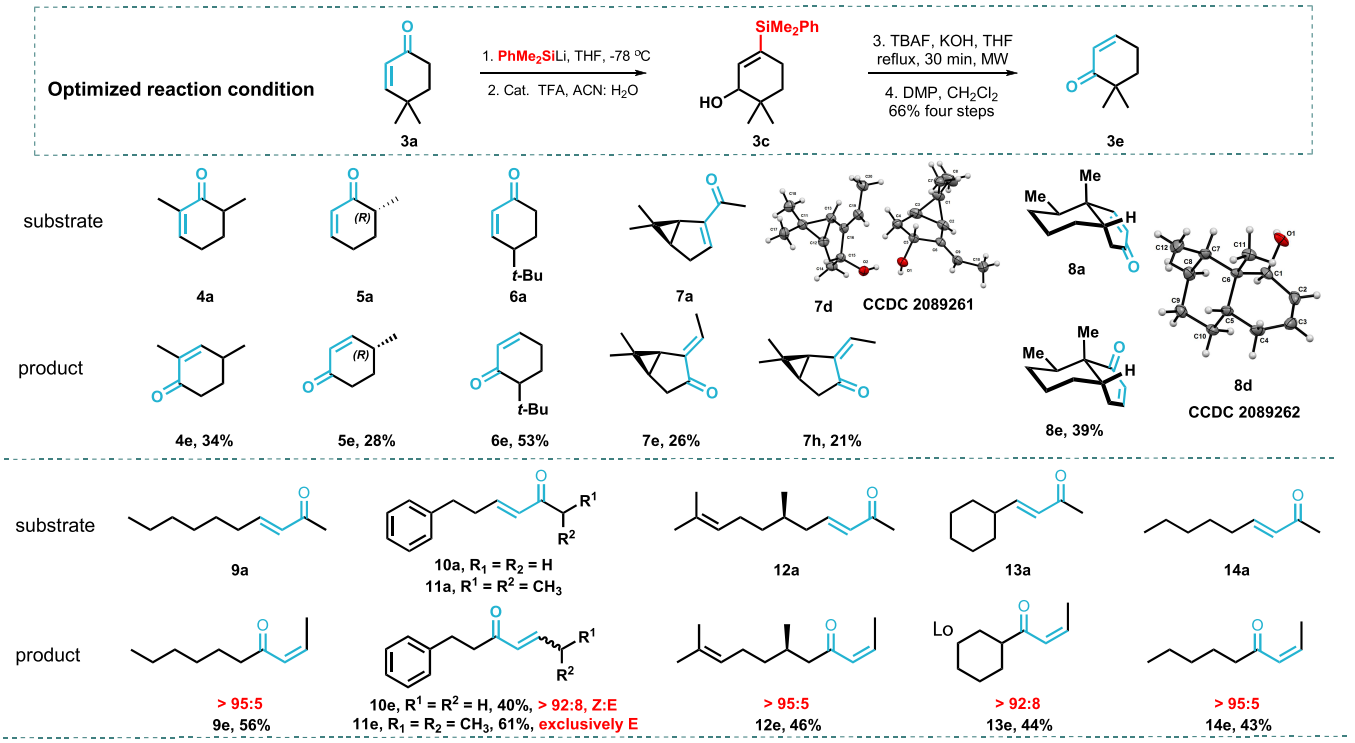
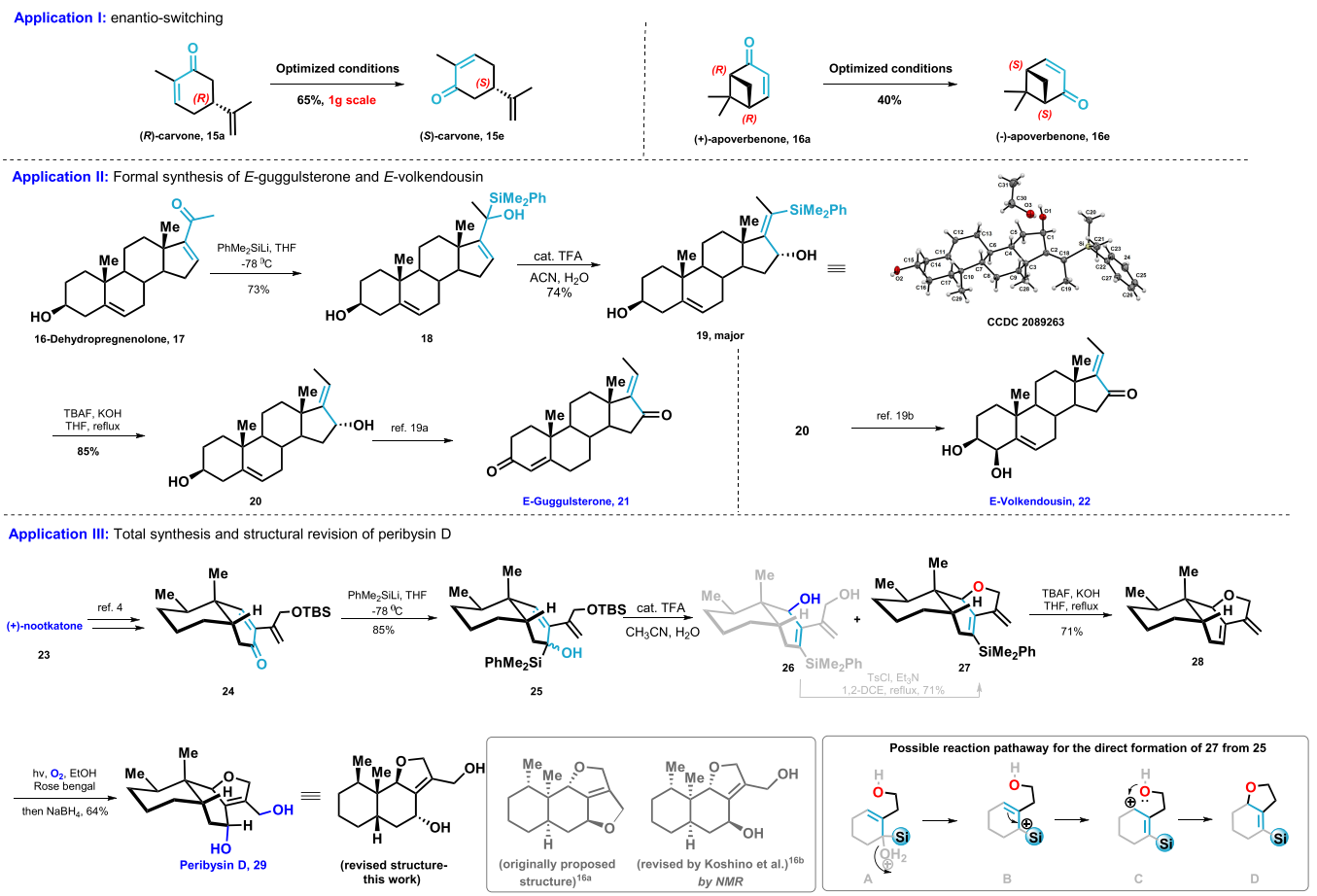
Org. Lett. XXXX, XXX, XXX−XXX

Scheme 3. Substrate Scope of Enone Transposition



Scheme 4. Various Applications of the Developed Method



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isopropyl ketone **11a** exclusively provided *E*-enone **11e**. Here the steric bulk of the isopropyl group was responsible for the exclusive *E*-selectivity. Next, three more enones (**12a−14a**) derived from *R*-citronellal, cyclohexane carboxaldehyde, and hexanal were converted to their corresponding *Z*-enones (**12e−14e**, respectively) in 46%, 44%, and 43% yields, respectively. In the literature, few other metal-based methods are available such as the Rh(I)-catalyzed reaction reported by Zhuo et al. for *Z*-enone synthesis.[16] Also, several other methods of olefin isomerization are available, the majority of which gives *E*-alkenes.[17] Thus, we believe that the current method will be more useful for accessing the *Z*-enones, which are difficult to access by other methods.

During the synthesis of substrates, we have generated a library of functional building blocks having a silicon handle. These vinyl silanes can be used for various purposes in organic synthesis.[12] Furthermore, the silicon-incorporated organic compounds can be used in medicinal chemistry programs because of the unique properties of the silicon-incorporated compounds.[18] Access to the enantiopure starting materials is one of the key factors in the chiral pool synthesis of natural products. Sometimes, it is difficult to access a particular enantiomer for the synthesis because some compounds exist in nature in only one enantiomeric form, or one of the isomers is costly in most of the cases. Here we have demonstrated an exciting application of the developed method for the interconversion of *R*-carvone to *S*-carvone with an overall yield of 65%. Similarly, the enantio-switching of (+)-apoverbenone to (−)-apoverbenone gave a 40% overall yield (Scheme 4). To further expand the scope of the method, we focused on the synthesis of two bioactive steroidal natural products guggulsterone (having mineralocorticoid, androgen, estrogen, etc., receptor antagonist and activities) and volkendousin (having anticancer activity).[19] We treated 16-dehydropregnenolone with $PhMe_2SiLi$, which gave a 90% yield of silyl addition product **18**. Treatment of compound **18** with catalytic TFA in a CH_3CN/H_2O mixture furnished **19** as a major product. The structure of compound **19** was confirmed by single-crystal X-ray diffraction, which helped us to fix the double bond geometry and the newly generated chiral center. Proto-desilylation of compound **19** furnished alcohol **20**. All of the data for compound **20** were in agreement with the reported data. Compound **20** was previously transformed into *E*-guggulsterone and *E*-volkedousin in one step each.[19] Thus, here, we have accomplished the formal synthesis of *E*-guggulsterone and *E*-volkedousin using a short sequence. Recently, we accomplished the synthesis and structural revision of five peribysin family natural products isolated from *Periconia byssoides* OUPS-N133 by Yamada and co-workers.[4,20a] The most potent member from this series is peribysin D having an IC_{50} value of 0.1 μM.

The originally proposed structure (tetracyclic) of peribysin D was revised by Koshino et al. to a tricyclic structure on the basis of the NMR studies.[20b] In addition to the impressive biological activity, the structure of peribysin D was also associated with some ambiguity, which necessitates the total synthesis of the same. In our previous attempts to synthesize peribysin D, we encountered challenges in installing the oxygen functionality at the carbon next to the quaternary methyl center. Here, we envisioned installing the oxygen functionality at the desired position by using the method presented here (Scheme 4, application III). Thus, we synthesized compound **24** by our previously developed protocol.[4] To compound **24** was added $PhMe_2SiLi$ to give addition product **25**, which was then subjected to catalytic TFA in CH_3CN/H_2O, which gave the desired product **26**. In addition to diol **26**, a nonpolar compound observed in the same reaction mixture after characterization was found to be compound **27**. In addition, the structure of compound **27** was confirmed by conversion of **26** to **27** using TsCl and Et_3N. Mechanistically, the TBS group in compound **25** first is deprotected to give free alcohol. Protonation of *ter*-alcohol followed by elimination of a H_2O molecule generates α-silyl carbocation **B**, which rearranges to give intermediate **C** (Scheme 4). Subsequent trapping of the carbocation by free alcohol offers cyclized product **D**. Here, H_2O and free alcohol compete as nucleophiles to provide two different products, **26** and **27**. Compound **27** after desilylation using TBAF and KOH furnished diene **28** in 80% yield. Finally, diene **28** upon reaction with molecular oxygen in the presence of Rose Bengal in EtOH resulted in cyclic peroxide, which was reduced in situ with $NaBH_4$ to give peribysin D.[21] All of the spectral data, including ^1H and ^{13}C NMR data, were in agreement with the literature report.[17] It was clear from our previous work that the structure of peribysin D may need to be stereochemically revised (see ref 4). Thus, CD spectra were recorded, which matched those reported by Yamada et al.[20,22] On the basis of all of these observations, spectral data, CD spectra, and our previous work, the structure of peribysin D was revised.

In summary, we have developed a method for enone transposition having potentially high synthetic utility. A silyl-based masking group was chosen for in situ generation and rearrangement of α-silyl carbocation species. The developed method was successfully tested with a variety of substrates with exciting outcomes such as substituent shuffling, enantio-switching, and *Z*-selectivity. A library of vinyl silanes having potentially high synthetic utility were generated during the course of making the substrates. Using the developed method, the first synthesis of peribysin D was achieved along with its structural revision. Additionally, formal synthesis of two bioactive natural products, *E*-guggulsterone and *E*-volkendousin, was accomplished in a short sequence. Further applications of the method are currently underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c02173.

General and experimental procedures, compound characterization data, single-crystal X-ray data of compounds **7d**, **8d**, and **19** and NMR spectra of selected compounds (PDF)

Accession Codes

CCDC 2089261−2089263 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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Org. Lett. XXXX, XXX, XXX−XXX