Studies toward the total synthesis of Didemniserinolipid B, Notoryne and Kumausallene

A THESIS
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TO

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BY

Shyamsundar Das

Dr. C. V. Ramana

(Research Guide)

ORGANIC CHEMISTRY DIVISION
NATIONAL CHEMICAL LABORATORY
PUNE–411008

NOVEMBER–2014

Dedicated

To my

Family

DECLARATION

The research work embodied in this thesis has been carried out at National Chemical Laboratory, Pune under the supervision of **Dr. C. V. Ramana**, Organic Chemistry Division, National Chemical Laboratory, Pune – 411008. This work is original and has not been submitted in part or full, for any degree or diploma of this or any other university.

Organic Chemistry Division
National Chemical Laboratory
Pune – 411008
November –2014 **(Shyamsundar Das)**

Dr. C. V. Ramana

Phone: +91–20–25902577
+91–20–25902455
E–mail: vr.chepuri@ncl.res.in

CERTIFICATE

The research work presented in thesis entitled "***Studies toward the total synthesis of Didemniserinolipid B***, ***Notoryne and Kumausallene***" has been carried out under my supervision and is a bonafide work of **Mr. Shyamsundar Das**. This work is original and has not been submitted for any other degree or diploma of this or any other University.

Pune – 411008
November – 2014

Dr. C. V. Ramana
(Research Guide)

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Shyamsundar Das

DEFINATIONS AND ABREVIATIONS

Ac	–	Acetyl
Ac_2O	–	Acetic anhydride
AcOH	–	Acetic acid
AMP	–	1,3-diamino propane
Bu	–	Butyl
BnBr	–	Benzyl bromide
BzCl	–	Benzoyl chloride
$BF_3.Et_2O$	–	Boron trifluoride diethyl ether
n-BuLi	–	*n*-Butyl lithium
n-Bu_2SnO	–	*n*-Dibutyltin oxide
^{t}BuOH	–	Tertiary butyl alcohol
Cat.	–	Catalytic/catalyst
CH_3CN	–	Acetonitrile
DCM	–	Dichloromethane
Conc.	–	Concentrated
COESY	–	Correlation spectroscopy
2,2'-DMP	–	2,2'-Dimethoxypropane
DMP	–	Dess–Martin periodinane
DMF	–	*N*,*N*-Dimethylformamide
DMAP	–	*N*,*N*'-Dimethylaminopyridine
DMSO	–	Dimethyl sulfoxide
Et	–	Ethyl
EtOAc	–	Ethyl acetate
HRMS	–	High Resolution Mass Spectroscopy
IBX	–	2-Iodobenzoic acid
Liq.	–	Liquid
Me	–	Methyl
MsCl	–	Methane sulphonyl chloride
NMR	–	Nuclear Magnetic Resonance
NOESY	–	Nuclear Overhauser effect spectroscopy
piv	–	Pivoloyl
Py	–	Pyridine
p-TSA	–	*para*-Toluenesulfonic acid
Ph	–	Phenyl
i-PrOH	–	*iso*-Propanol
rt	–	Room temperature
Sat.	–	Saturated
TBAF	–	Tetra-*n*-butylammonium fluoride
THF	–	Tetrahydrofuran
TBS	–	*tert*-Butyldimethylsilyl
TPP	–	Triphenylphosphine

TMSCl	–	Trimethylsilyl chloride
TIPSCl	–	Triisopropylsilyl chloride
TMSOTf	–	Trimethylsilyl trifluromethanesulfonate

Abbreviations used for NMR spectral informations:

br	Broad	q	Quartet
d	Doublet	s	Singlet
m	Multiplet	t	Triplet

GENERAL REMARKS

- ^{1}H NMR spectra were recorded on AV–200 MHz, AV–400 MHz, JEOL AL-400 (400 MHz) and DRX–500 MHz spectrometer using tetramethylsilane (TMS) as an internal standard. Chemical shifts have been expressed in ppm units downfield from TMS.
- ^{13}C NMR spectra were recorded on AV–50 MHz, AV–100 MHz, JEOL AL-100 (100 MHz) and DRX–125 MHz spectrometer.
- Mass spectroscopy was carried out on PI QStar Pulsar (Hybrid Quadrupole-TOF LC/MS/MS) and High-resolution mass spectra (HRMS) were recorded on a Thermo Scientific Q-Exactive, Accela 1250 pump and also EI Mass spectra were recorded on Finngan MAT–1020 spectrometer at 70 *eV* using a direct inlet system.
- Infrared spectra were scanned on Shimadzu IR 470 and Perkin-Elmer 683 or 1310 spectrometers with sodium chloride optics and are measured in cm^{-1}.
- Optical rotations were measured with a JASCO DIP 370 digital polarimeter.
- All reactions are monitored by Thin Layer Chromatography (TLC) carried out on 0.25 mm E-Merck silica gel plates (60F–254) with UV light, I_2, and anisaldehyde in ethanol as developing agents.
- All reactions were carried out under nitrogen or argon atmosphere with dry, freshly distilled solvents under anhydrous conditions unless otherwise specified. Yields refer to chromatographically and spectroscopically homogeneous materials unless otherwise stated.
- All evaporations were carried out under reduced pressure on Buchi rotary evaporator below 45 °C unless otherwise specified.
- Silica gel (60–120), (100–200), and (230–400) mesh were used for column chromatography.

CONTENTS

ABSTRACT

Abstract

The thesis entitled ***"Studies toward the total synthesis of Didemniserinolipid B, Notoryne and Kumausallene"*** consists of two chapters. Each chapter was further divided into five parts – Introduction; Results; Discussion; Experimental; Spectra and References. Coming to the original contributions, which have been included in these two chapters; in the first chapter, the regioselectivity issues of the palladium mediated cycloisomerization of acyclic alkynols followed by the formal total synthesis of Didemniserinolipid B, have been presented. In the second chapter, the total synthesis of the proposed structure of Notoryne and the attempts towards the total synthesis of Kumausallene are described.

Chapter I:

Section A: Model studies on Pd-mediated cycloisomerization of acyclic alkynols

Didemniserinolipid B was isolated in 1999 by Gonzalez *et al.* The initially proposed structure has been revised as **1** by Steven Ley's group, who reported the first total synthesis of Didemniserinolipid B (**1**). Later, Burke and co-workers reported the second total synthesis of **1** by employing ketalization and ring closing metathesis as the key strategy for constructing the central bridged bicyclic core. Figures 1 saliently describes the key retro synthetic disconnections in the context of planned total synthesis of Didemniserinolipid B and the projected alkynol cycloisomerization as the key reaction to construct the central bridged bicyclic ketal core. The synthesis of key the alkynol **4** was planned from the coupling of epoxide **5** and the serinol coupled long-chain alkynol **6**.

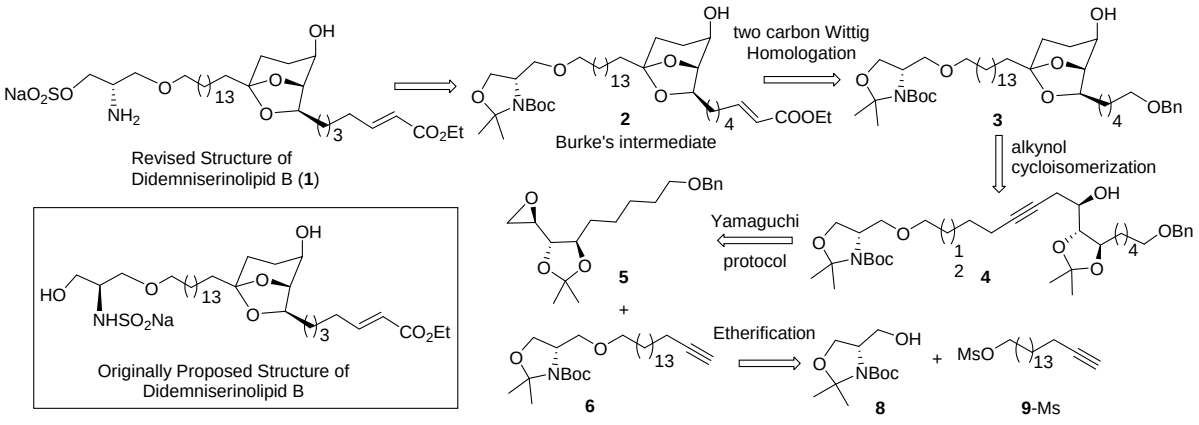


Figure 1. Retrosynthetic strategy for Didemniserinolipid B

Abstract

After the stereochemical comparisons, epoxide **5** synthesis has been planned from the known D-mannitol diacetonide **7**. Considering Williamson's etherification, the serinol **8** and the mesylate C_{17} alkynol **9**-Ms have been identified as first stage coupling partners. The synthesis of the corresponding C_{17} alkynol **9** has been envisioned from propargyl alcohol *via* alkylation with the requisite C_{14}-alkyl halide and a subsequent acetylenic Zipper reaction. The synthesis of the serinol derivative **8** has been already reported from D-serine.

The key issue of the cycloisomerization reactions is the mode of cyclization *i.e.exo*-dig *vs. endo*-dig. In this context, as a first step towards the total synthesis of didemniserinolipid B, an investigation on the substituent effect or the acyclic stereocontrol over the Pd-mediated alkynol cycloisomerization reactions has been undertaken and the compounds **11** – **14** were designed as the model substrates (Figure 2).

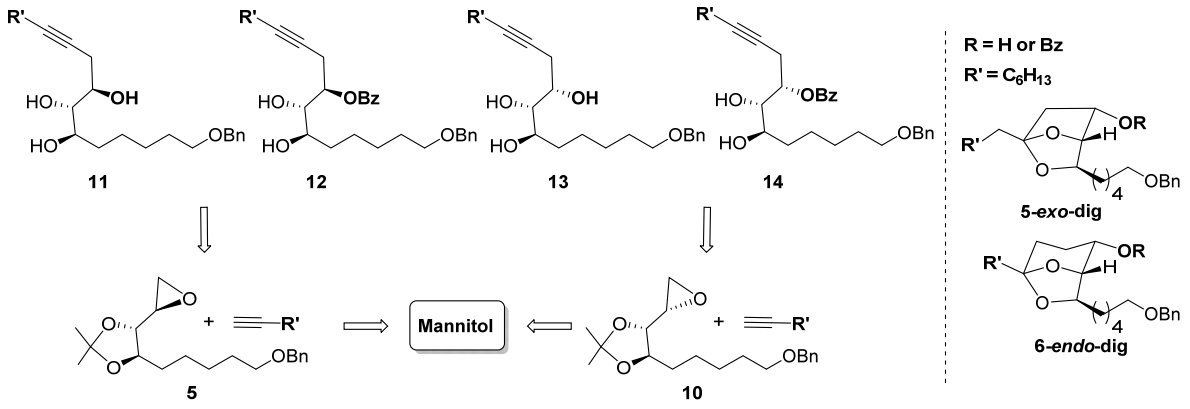
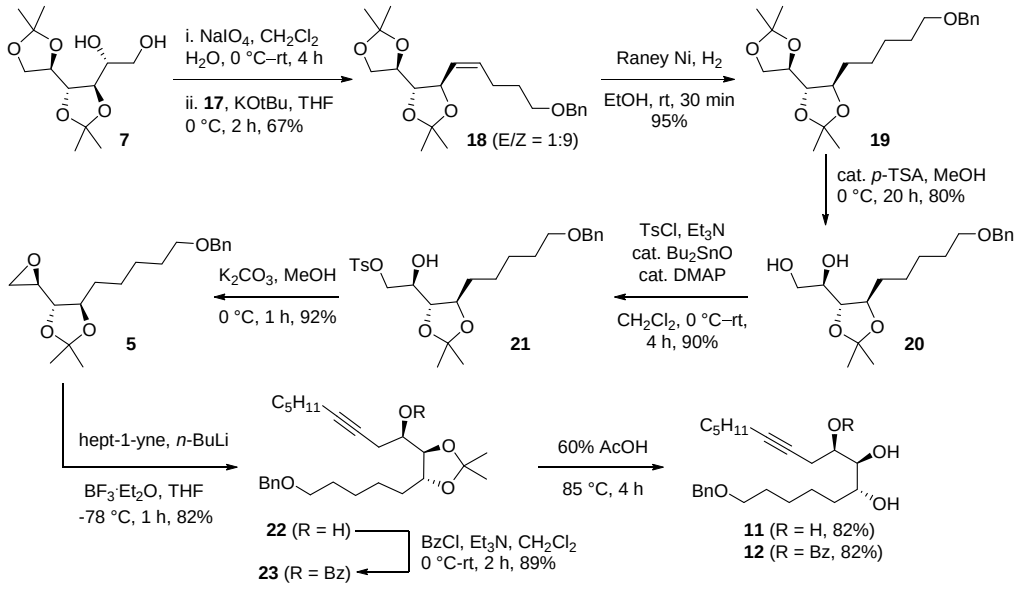


Figure 2. Model Substrates for understanding the substituent & stereo chemical control over the Pd(II)-mediated cycloisomerization reactions & the retrosynthetic analysis

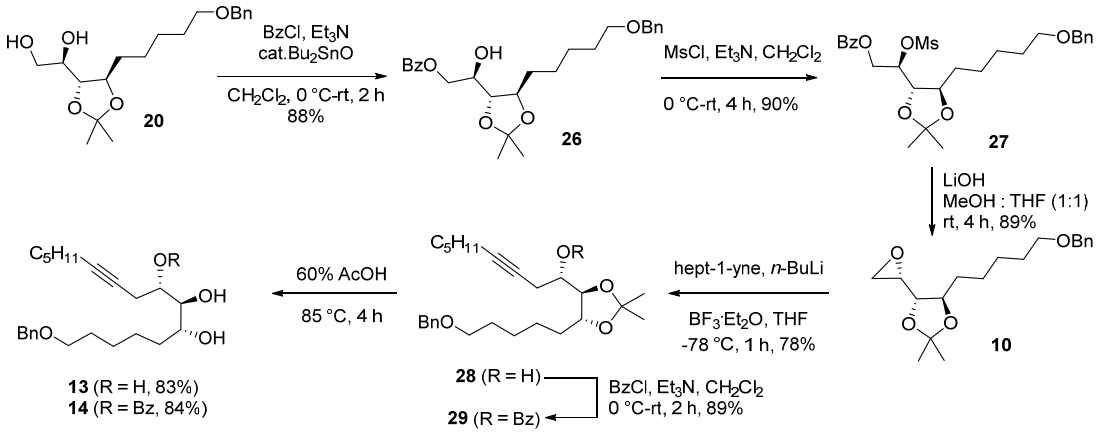
Synthesis of Model Substrates 11 –14:

Synthesis of key epoxide **5** started with the Wittig reaction of the arabinose diacetonide (prepared in 3 steps from D-mannitol) and 4-carbon ylide generated from the known phosphonium salt **17** (Scheme 1) to afford the *E*/*Z* mixture of **18**. The hydrogenation of **18** with Raney Ni followed by acetonide hydrolysis using *p*-TSA in MeOH resulted in diol **20**. The diol **20** was transformed into oxirane **5** by selective primary OH tosylation using *p*-TsCl, *n*-Bu_2SnO, and triethylamine in dichloromethane followed by cyclization using K_2CO_3 in methanol. Next, the epoxide was opened with the easily available 1-heptyne under Yamaguchi conditions to

procure the alkynol **22**, which, upon acetonide deprotection, gave the parent model compound **11**. Protection of the free –OH in **22** as its benzoate **23** followed by acetonide hydrolysis gave the model substrate **12**.



Scheme 1. Synthesis of key epoxide **5** and of model substrates **11**, **12**

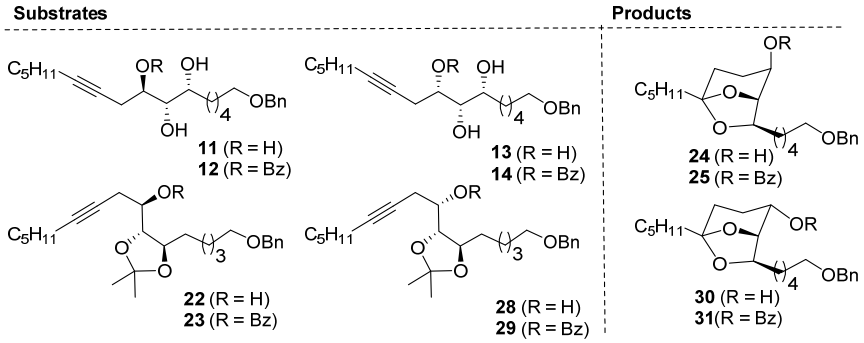


Scheme 3. Synthesis of **10** and of model substrates **13**, **14**

The synthesis of the model substrates **13** and its benzoate **14** was started with the diol **20**, the selective benzoylation of **20** followed by mesylation and LiOH treatment led to the obtaining of epoxide **10.** Opening of the epoxide **10** with lithiated 1-butyne gave **28** which, upon acetonide hydrolysis, provided the model substrate **13**. The model compound **14** was prepared by the benzoylation of **28** and the acetonide hydrolysis.

Abstract

The cycloisomerization of model compounds **11**–**14** was carried out under the optimized conditions [$Pd(CH_3CN)_2Cl_2$ in CH_3CN]. The results are given in *Table 1*. In all the cases, the reactions proceeded in a 6-*endo*-dig mode of cyclization and the corresponding [3,2,1]-bicyclic ketals were obtained in good yields. These results indicate that the stereochemistry of the substituent at the β-position to the alkyne seems to be not having much influence over the cycloisomerization, which is quite interesting.



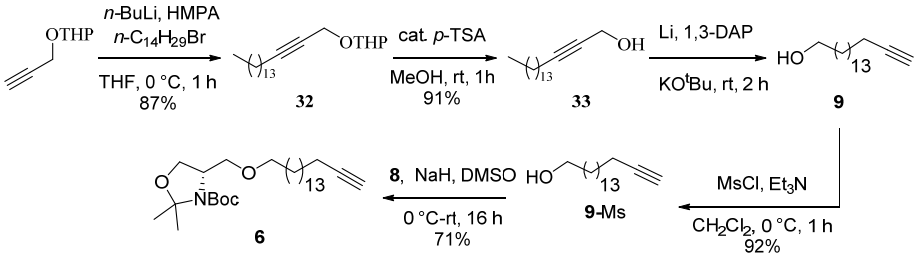
Entry	Reactants	Products	Yield (%)
1	**11**	**24**	67
2	**12**	**25**	80
3	**13**	**30**	81
4	**14**	**31**	73
5	**22**	**24**	65
6	**23**	–	–
7	**28**	**30**	71
8	**29**	–	–

Table 1. Pd-mediated cycloisomerization model substrates

Section B: **Formal synthesis of Didemniserinolipid B**

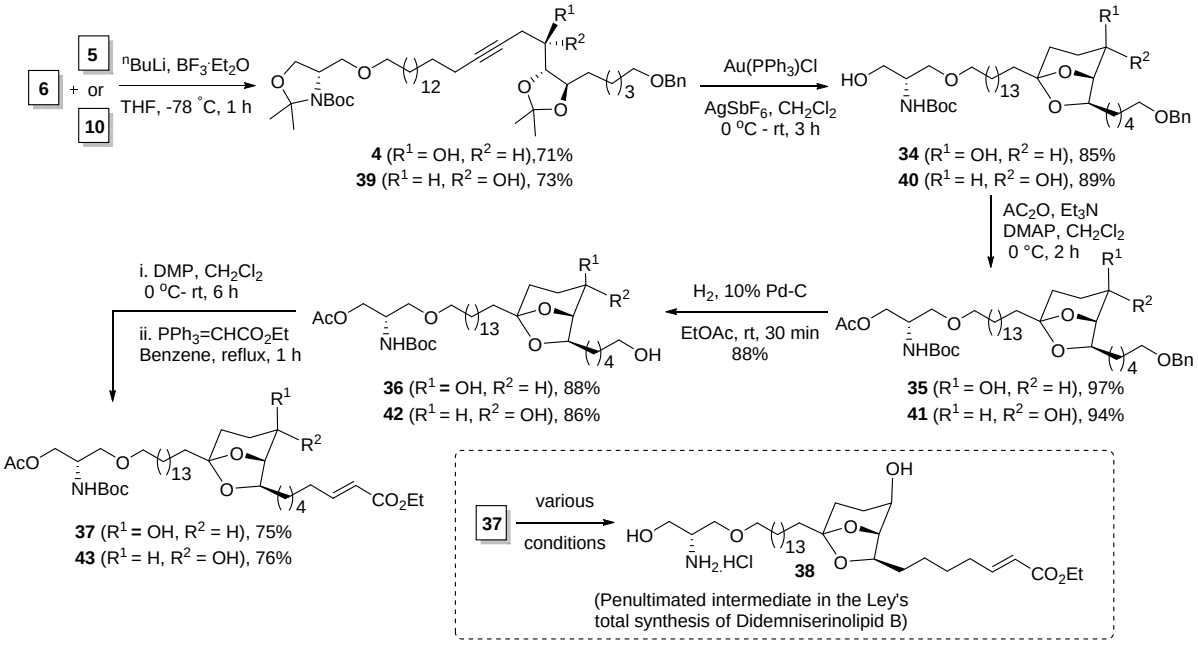
Next, we proceeded further to extend this strategy towards the synthesis of didemniserinolipid B (**1**). The synthesis of the key alkynol **4** was planned *via* the coupling of the epoxide **5** with the alkyne **6**. As mentioned previously, the key alkyne fragment **6** was planned by the coupling of protected serinol derivative **8** and the mesilyte of the C_{17}-alkynol **9**. The synthesis of alkyne **9** was started with the alkylation of commercially available propargyl alcohol THP ether with *n*-tetradecyl bromide to afford internal alkyne (Scheme 4). Subsequently, the

deprotection of THP group gave the substituted propargyl alcohol **33**, which upon the acetylenic zipper reaction employing Li rod in 1,3-diaminopropane as solvent at rt gave the C_{17}-alkynol **9.** Now, the alkynol **9** was mesylated to obtain the fragment **9**-Ms. Serinol derivative **8** was prepared according to the literature procedure and the key coupling reaction of **9**-MS and **8** was carried out successfully by the slow addition of **9**-Ms to a solution of serinol **8** and NaH in DMSO, maintaining the internal temperature strictly below 0 °C for 4 h, and afterwards, allowing the reaction to stir at rt for an additional 12 h to give compound **6**.



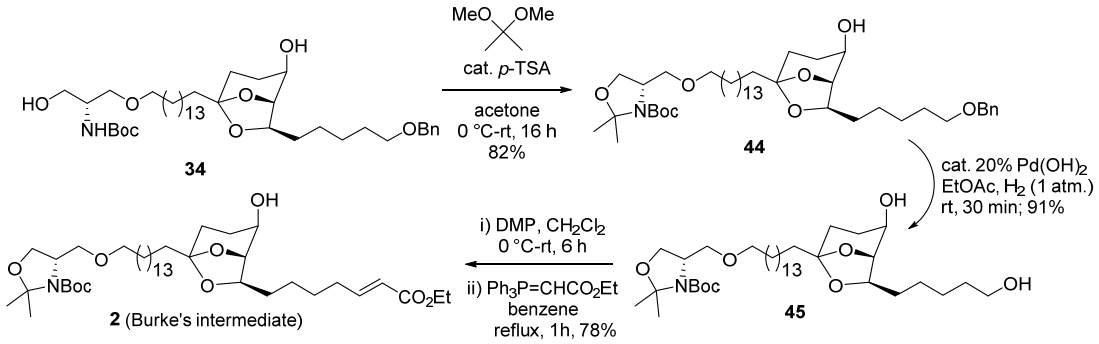
Scheme 4. Synthesis of C_{17}-alkyne fragment **6**

After having an easy access to alkyne **6**, we next proceeded for the synthesis of the key cycloisomerization substrate **4**. The coupling of epoxide **5** with lithiated alkyne **6** in the presence of $BF_3{\cdot}Et_2O$ delivered alkynol **4** in excellent yields (Scheme 5). The cycloisomerization of **4** needed substantial catalyst optimization. Under the standard conditions using the $Pd(CH_3CN)_2Cl_2$ complex, a complex mixture resulting from the formation of the requisite bicyclic ketal, the corresponding ketone, along with the deprotection of the acetonide group present in the serinol unit was observed. $Pd(PhCN)_2Cl_2$ was found to be ineffective for this transformation. Next, various electrophilic [Au]-complexes were screened for the cycloisomerization of **4**. To this end, the use of $Au(PPh_3)Cl$ (5 mol%) and $AgSbF_6$ (5 mol%) in CH_2Cl_2 led to the isolation of compound **34** resulting from the requisite cycloisomerization and the *insitu* the deprotection of serinol acetonide. Initially, to provide alternative final events in the total synthesis, we converted the compound 3**4** to the corresponding diacetate and subsequently carried out the debenzylation of **35** followed by the oxidation of the resulting alcohol **36** and Wittig homologation to obtain **37**. However, the deacetylation and Boc-deprotection of compound **37** has turned out to be a difficult proposition. A similar sequence has been carried out in parallel with the alkynol **39** (prepared by opening the epoxide **10** with alkyne **6**) in order to synthesize the *epi*-Didemniserinolipid B.



Scheme 5. Synthesis of requisite bicyclic ketal

Having met with difficulties in the deacetylation of the advanced intermediate **37** to arrive at the penultimate compound **38**, we revised our strategy to obtain the originally planned Burke's intermediate **2**. In this context, the intermediate ketal **34** obtained from the Au-catalyzed cycloisomerization was subjected for the acetonide protection by using dimethoxy propane and *p*-TSA (cat.) in acetone to obtain compound **44**, which subsequently transformed to **2** following the established 3 steps sequence - i. debenzylation ii. Oxidation and iii. Wittig homologation.



Scheme 6. Formal synthesis of Didemniserinolipid B

To conclude, a formal total synthesis of didemniserinolipid B was developed by employing a regioselective gold-mediated 6-*endo*-dig cycloisomerization. The interesting feature

of our approach is the [Au]-mediated cycloisomerization of an acetonide protected alkynediol unit that we executed. This has avoided several late stage protection deprotection events. Independent routes for the synthesis of both Ley's and Burke's intermediates have been explored from the resulting bicyclic ketal. The attempted synthesis of Ley's intermediate was not successful as the final deprotection turned out to be problematic. However, the Burke's intermediate has been successfully synthesized, thus conclusively ending this exercise as a formal total synthesis of didemniserinolipid B.

Chapter 2:

Section A: Studies toward the Total Synthesis of Notoryne:

A large number of halogenated C_{15} nonterpenoid ethers with a different kind of ring system were isolated from red algae of the genus *Larencia.* They contained a conjugated enyne or bromoallene moiety at the end of the molecule. The (3*Z*)-laurefucin (**49**), Notoryne (**46**) and Kumausallene (**47**) are some representative natural products isolated from the red algae of genus L*aurencia nipponica yamada* obtained from different sources. Considering, that all the natural products were comparable in terms of stereochemistry as well as the side chain enyne part, we endeavored to develop a common synthetic route for these three targets (fig 3). The key features of our retro synthesis are depicted in Fig 5. The two epimeric alkenediols **50** and **51** have been identified as the precursors for the synthesis of (3*Z*)-laurefucin (**49**), and Notoryne (**46**) employing a bromo etherification as the key skeletal construct albeit with a complementary regioselectivity. The synthesis of Kumausallene is a direct proposition from **51** *via* the known Tang's intermediate **48**. The synthesis of these two building blocks **50** and **51** was planned respectively from the epoxides **52** and **53**, which in turn were planned from the diol **54**.

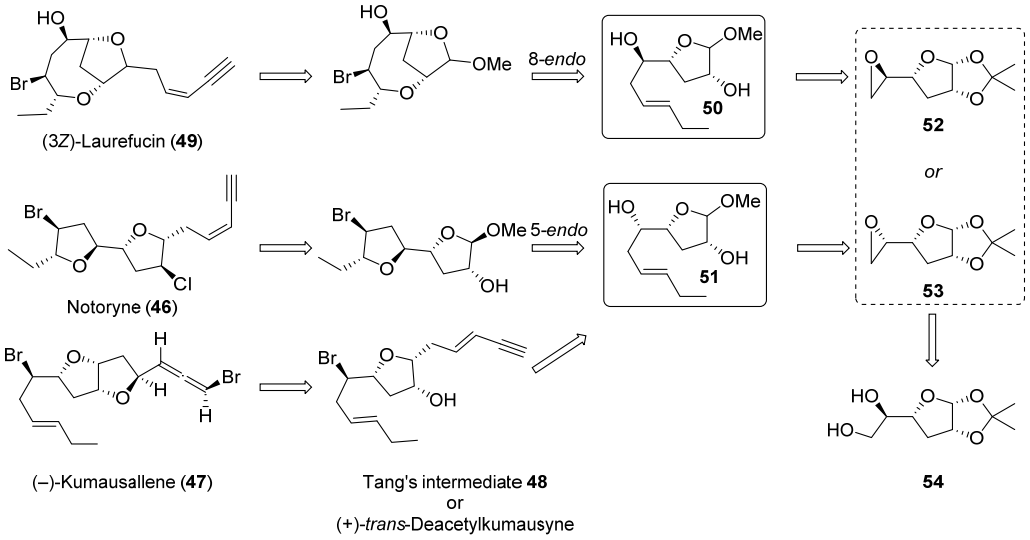
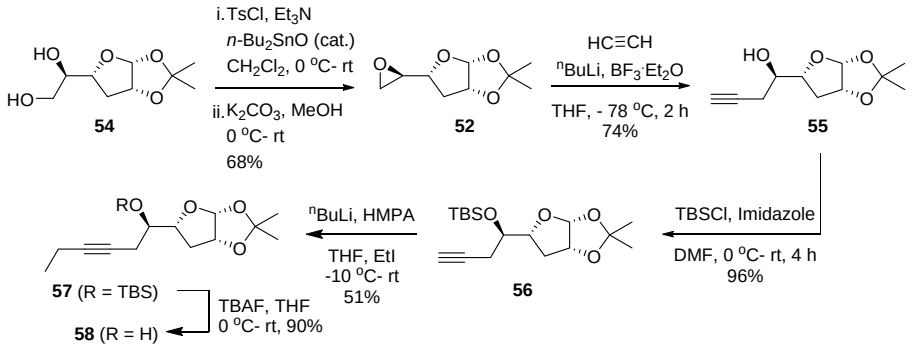


Figure 3. Structures of (3*Z*)-Laurefucin (**49**), Notoryne (**46**) and (–)-Kumausallene (**47**) and the proposed retro synthetic routes

Synthesis of Alkenediol 50:

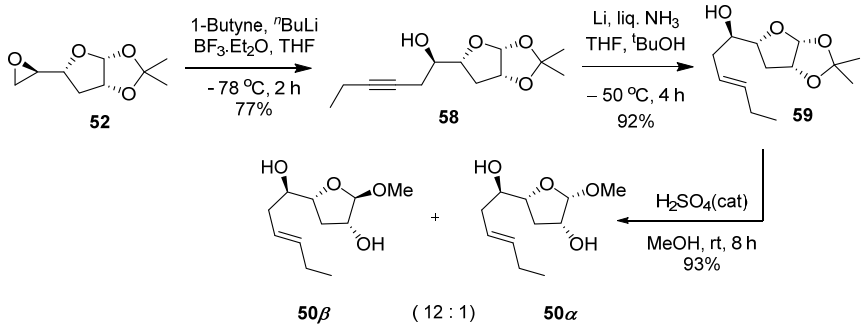
The synthesis of this building block was started from the preparation of **54** from D-glucose according to the literature procedure. The 1^{o}-OH of the diol **54** was selectively tosylated by using TsCl and $n$$Bu_2SnO$ (cat.) and subjected for base treatment to give the epoxide **52** which was converted to the homo-propargylic alcohol **55** by using lithium acetylide in the presence of $BF_3{\cdot}Et_2O$. Now the compound **55** was protected as its TBS ether and the alkylation reaction was carried out by using ethyl iodide in the presence of *n*-BuLi in HMPA to obtain **57** in moderate yields. The TBS group in compound **57** was selectively deprotected by using TBAF in THF to obtain the alkynol **58**.



Scheme 7. Synthesis of model substrate alkynol **58**

Abstract

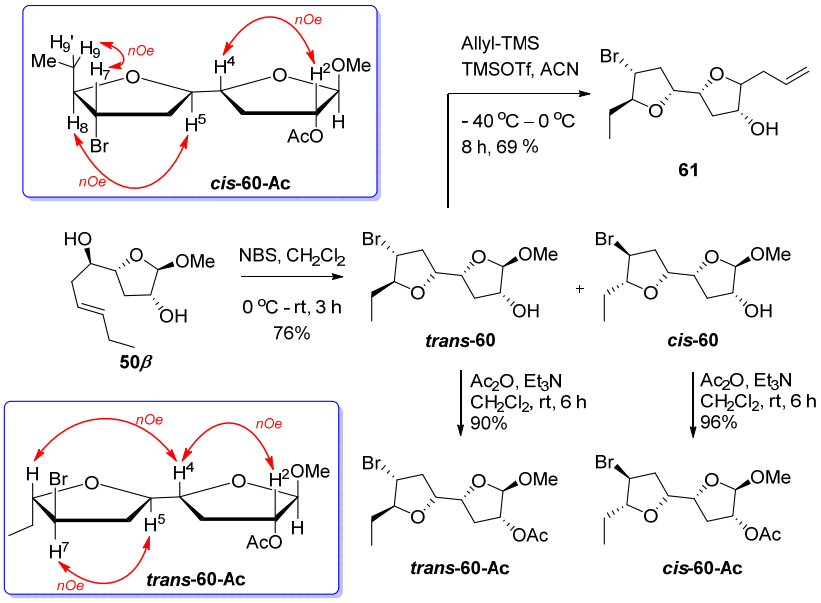
Considering the lengthy reaction sequence and moderate yields in the preparation of **58**, an alternative route for its synthesis has been developed. The compound **58** was synthesized alternatively by using expensive 1-butyne gas in place of acetylene to open the epoxide **52** under Yamaguchi conditions to obtain the intermediate alkynol **58**. The Birch reduction of the alkynol **58** employing Na or Li, in liquid NH_3 and THF at −78 ^oC gave the required *trans* alkene **59** in good yields. Finally, the 1,2 acetonide group in **59** was deprotected in the presence of H_2SO_4 in MeOH and obtained the methyl glycosides **50**α and **50**β.



Scheme 8. Synthesis of the key precursor **50**β for bromo etherification

To check the mode of cyclization, the bromo etherification of major **50**β was examined with NBS. Two products ***cis*-60** and ***trans*-60**, the latter being the major product, were obtained. The structural analysis of the corresponding acetates with the help of COSY and NOESY revealed that both these compounds possess a bis-furanyl skeleton present in Notoryne.

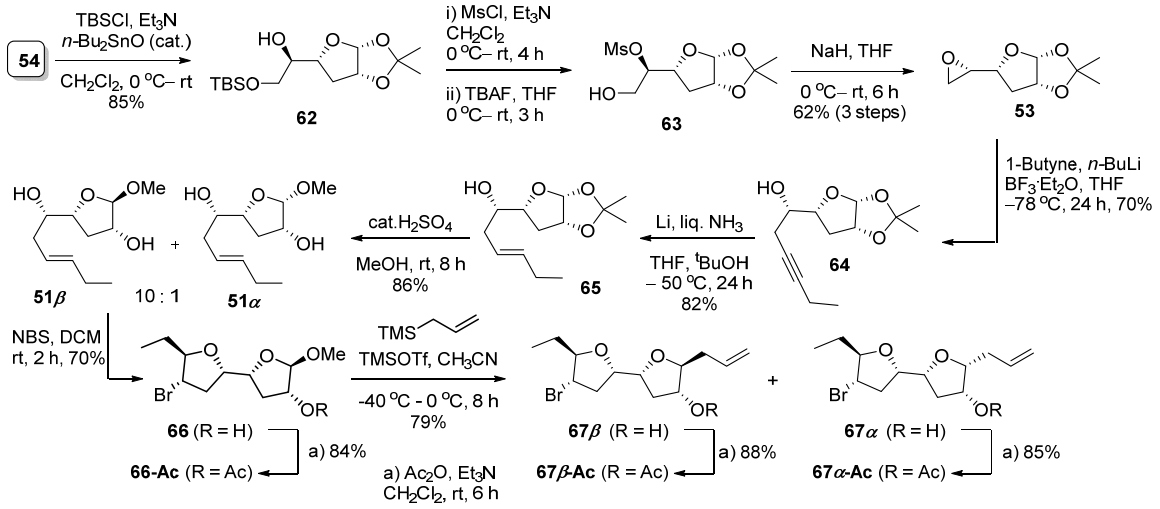
Since the relative stereochemistry of the newly generated furanyl unit in compound ***trans*-60** is matching with one of the natural products Notoryne **46**, its *C*-allylation was examined employing allyl trimethylsilane in the presence of TMSOTf and allyl product **61** was obtained in good yields as a single diastereomer.



Scheme 9. Synthesis of 2, 2'-bifuranyl skeleton **60**

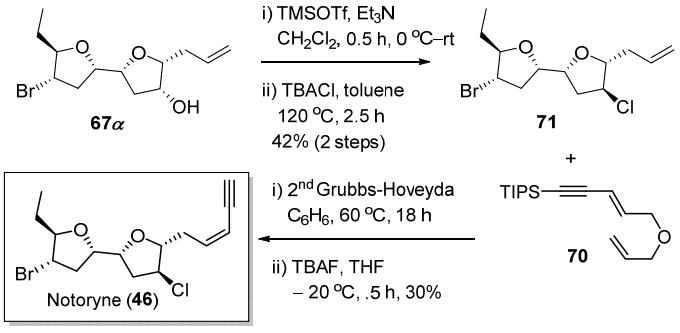
Synthesis of required homoallyl alcohol for Notoryne:

Having this initial promising result, we next proceeded for the synthesis of Notoryne **46** employing the sequence that has been established for **61**. This started with the conversion of diol **54** to the epoxide **53** following a sequence of the selective protection of 1^{o} hydroxy group as its TBS ether, mesylation, TBS-deprotection and base treatment**.** The epoxide **53** was opened with lithiated 1-butyne and the resulting alkynol **64** was subjected for Birch reduction to afford compound **65**. The acid catalyzed methanoloysis of **65** gave a mixture of methyl glycosides **51**α and **51**β. The bromo etherification of the major compound **51**β using NBS in dichloromethane gave the corresponding bis-furan **66** and the acetate **66-Ac**, which was subjected for extensive 2D NMR analysis to establish the stereochemistry of the newly generated stereo centers. The *C*-glycosidation of **66** under optimized conditions provided a mixture of **67**α and **67**β, which were acylated to establish their anomeric configurations. The desired α-*C*-glycoside **67**α was obtained as a major product.



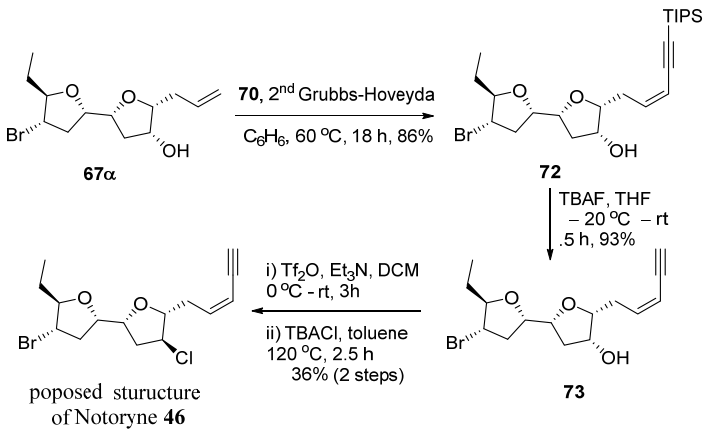
Scheme 10. Synthesis of required 2, 2'-bifuranyl skeleton **67α** of notoryne

After having the key *C*-glycoside **67α** in hand, the remaining work is to install the *cis*-enyne moiety and replacing the free –OH with a chloro group. Our initial plan was to introduce the chloro group first and then the cross-metathesis to install the enyne moiety. The treatment of the **67α** with TMSOTf and Et_3N in dichloromethane followed by the displacement of –OTf with Cl employing *n*-tetrabutyl ammonium chloride (TBACl) in toluene at reflux gave the penultimate chloro derivative **71**. The attempted cross metathesis reaction of **71** and dienyne **70** in the presence of Hoveyda-Grubbs 2nd generation catalyst resulted in an inseparable mixture of compounds which were subjected directly for the desilylation. The ^1H NMR of the resulting crude product revealed the presence of the characteristic peaks corresponding to the natural product Notoryne. However, the isolation of pure product was found to be a difficult task despite the sequence being repeated several times.



Scheme 11: Synthesis of chloroallyl compound **71**.

Considering this difficulties, the cross metathesis of intermediate **67**α and **70** has been carried out first to prepare the conjugated *cis*–enyne **72**, which was then subjected for the desilylation to obtain the penultimate intermediate **73**. Finally, the crucial chloro group introduction has been carried out by subjecting **73** for trifloylation and subsequent S_N2 displacement of the OTf with TBACl. The reaction was not clean and provided **46** in poor yields. Although, the spectral data is comparable, however, they were not exactly matched with the reported data revealing that the relative stereochemistry of chlorine bearing tetrahydrofuran in Notroyne has been wrongly assigned. Work in the direction of synthesizing the other possible diastereomers to determine the structure of Notoryne is under progress.



Scheme 12. Total synthesis of proposed structure of Notoryne

Section B: Studies toward the Total Synthesis of (–)-Kumausallene:

(–)-Kumausallene was isolated by Kurosawa *et al*. in 1983 from the coast of Hokkaido in Japan, and belongs to a family with a unique bromoallene moiety. The key retrosynthetic disconnections for the Kumausallene are provided in Figure 4.

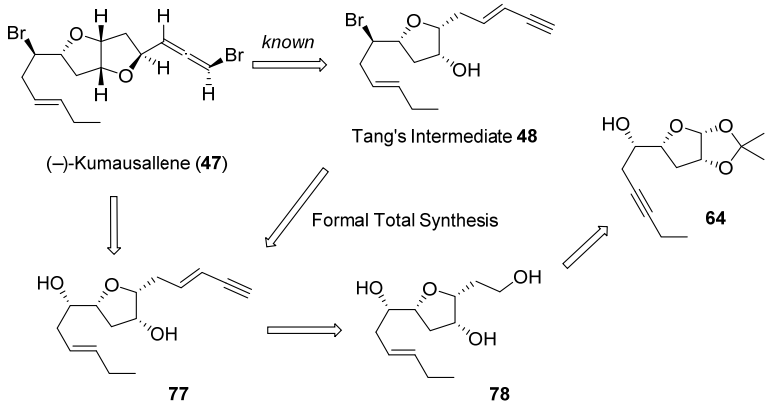
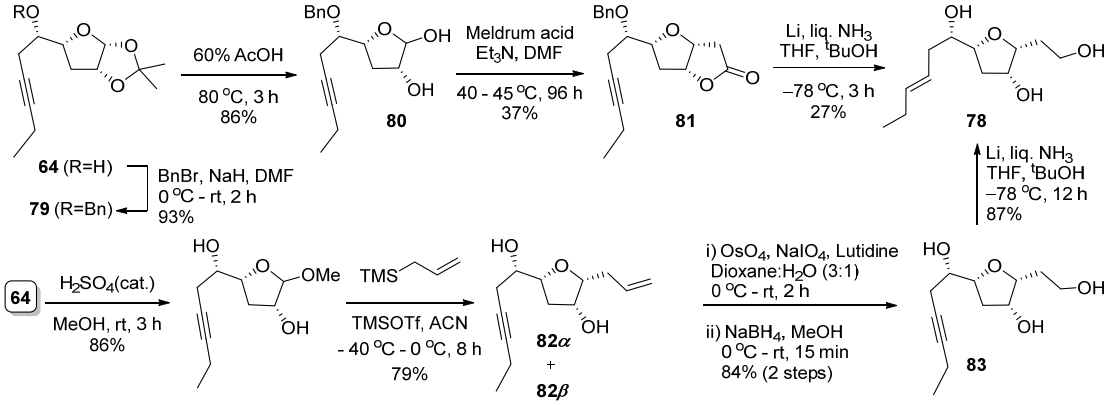


Figure 4. Retrosynthetic analysis for (–) Kumausallene **47**

Two options have been selected in this context, either the total synthesis or the synthesis of Tang's bromoenyne intermediate **48**. To have an alternative route that avoids the intermediate **48**, initially, we planned the bromoetherification of diol **77** followed by the Appel reaction (to introduce the bromine) as the final event in our total synthesis of Kumausallene. The synthesis of **77** was planned from the triol **78** which, in turn can be prepared from the alkynol **64** that we have synthesized as a part of the Notoryne synthesis.

Synthesis of Alkenetriol 78

Our synthetic journey for Kumausallene was started from compound **64** where the free hydroxyl group was benzylated by using BnBr and NaH in DMF. Acid treatment of **79** with AcOH gave the mixture of lactols **80** which ware transformed to lactone **81** by using meldrum acid in moderate yields. Next, the selective reduction of the internal triple bond to *trans*-alkene as well as debenzylation was examined under Birch reduction conditions employing Li and liq. NH_3 at –78 ^oC. To our surprise, in addition to the expected transformations, the lactone carbonyl was also reduced and the alkene triol **78** was obtained in 27% yield. This indicated the possible Bouveault-Blanc type reduction of lactone taking place in the present case.

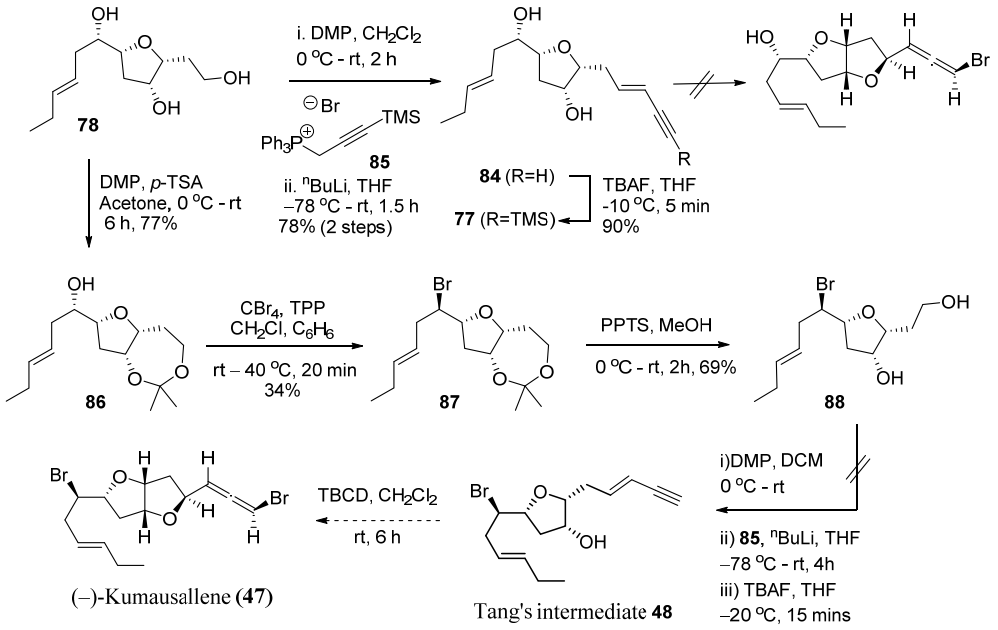


Scheme 13. Synthesis of required alkenetriol **78**

As the synthesis of key triol **78** on large scales turned out to difficult due to the poor yields at two stages, we revised our strategy for the synthesis of **78** *via* α-*C*-allyl glycoside. Consequently, the synthesis of **78** started with the deprotection of the 1,2 acetonide of alkynol **64** in the presence of MeOH in H_2SO_4 that led to a mixture of *O*-methyl glycosides. Now the mixture of *O*-glycosides was transformed to *C*-glycosides **82**α and **82**β by using allyl trimethylsilane and TMSOTf, in a 12:1 ratio in favor of the α- glycoside **82**α. The acetates of both the *C*-glycosides were prepared and are characterized with the help of 2D NMR spectra analysis. The alkene group of **82**α was chopped by using the modified Lemieux-Johnson oxidation protocol employing OsO_4 and $NaIO_4$ in the presence of 2,6-lutidine and the resulting aldehyde was reduced immediately using $NaBH_4$ in MeOH to procure the alkynetriol **83**. The Birch reduction of **83** proceeded smoothly to arrive at the key triol **78**.

Initially, the triol **78** was converted to the corresponding enyne diol **77** to avoid the Tang's intermediate in the planned total synthesis. However, key bromonium ion induced bromo etherification of **77** by employing NBS turned out to be a difficult proposition despite the fact that various conditions have been explored. The presence of two free hydroxyl groups in the substrate **77** was reasoned to be one of the primary causes for the problems associated with this key cycloetherification. We had to go back to our original proposal of placing the homo-allylic bromine group prior to conducting the key complexity building transform i.e – the synthesis of Tang's intermediate **48**. For that, the alken-triol **78** was converted to the corresponding acetonide by using DMP in the presence of *p*-TSA and the resulting **86** was subjected for the Appel reaction employing CBr_4, TPP and 2,6-di-tertbutylpyridine to obtain bromo-compound **87** in

moderate yield. Finally, the acetonide deprotection followed by selective 1°-OH oxidation and subsequent Witting homologation and the deprotection of alkynyl TMS has been attempted to arrive at Tang's bromoenyne intermediate or (+)-*trans*-Deacetylkumausyne **48**. Discouragingly, the reaction gave a complex mixture. Although the peaks corresponding to **48** could be seen on HRMS, efforts to obtain the pure samples of **48** for characterization met with failure. Currently, the optimization of the construction of the *trans*-enyne moiety and the total synthesis of Kumausallene is under progress.



Scheme 14. An attempted to synthesis of Tang's intermediate **48**

To conclude, efforts towards developing a unified approach for the synthesis of (3*Z*)-laurefucin (**49**), Notoryne (**46**) and Kumausallene (**47**) met with a partial success. The synthesis of the proposed structure of Notoryne has been completed and a penultimate intermediate for the synthesis of Tang's bromoenyne intermediate or (+)-*trans*-Deacetylkumausyne **48** has been accomplished**.**

CHAPTER I

The regioselectivity issues of the palladium mediated cycloisomerization of acyclic alkynols and formal total synthesis of Didemniserinolipid B

INTRODUCTION

The molecular complexity associated with the natural products manifest nature's ingenuity and the diverse biological activities that these natural products display reveals its foresight for the well being of all living organisms. Despite that fact that a few millions of natural products have been isolated and characterized, and millions of millions have yet to be traced, Nature has its own uniqueness in grouping these huge collections broadly into a few classes such as alkaloids, terpenoids, steroids, carbohydrates etc. These broadly categorised classes are further subdivided by the presence of some important sub-structural units and their integration in combination. The organization of these sub-structural units and the nature of the substituents that they hold, and their spacial relationships, vary extensively from species to species, and what also varies is the associated biological activity. Arguably, these substructural units have inspired the synthetic chemists to develop new methods for their assembly and the overall complexity of natural product, inspiring the design of innovative strategies for forging many such substructural units in consonance.

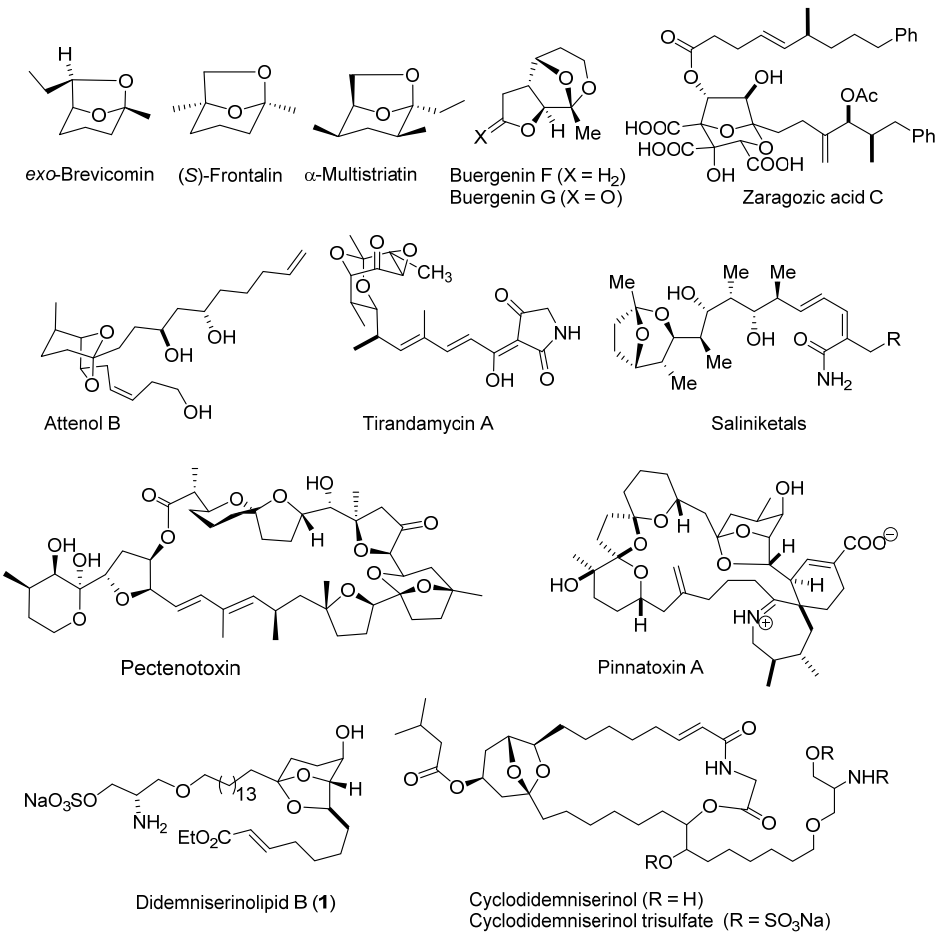


Figure 1: Natural products with the dioxa-bicyclo [3,2,l]octane core

The dioxa-bicyclo[3.2.1]octane core[1] (**F2. 1**) is an interesting structural unit that has been identified in the middle of last century, two decades before the isolation of a natural

product with this skeleton. Trivially known as bridged bicyclic ketal, the dioxa-bicyclo[3.2.1]octane core is characterized by the presence of ketal formed intramolecularly from a suitably positioned 1,2-diol unit. Whetstone patented the related bicyclicketal compound **F2.2** in 1950.[2] It has been reported that the heating of the Diels-Alder adduct 3,4-dihydro-1,2-pyran-2-carboxylic acid either at about 200 °C or at 70 °C in the presence of mineral acid gave **F2.2** with an unprecedented skeleton.

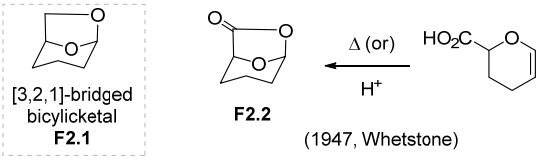
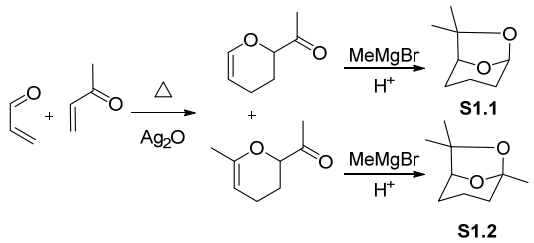


Figure 2: The dioxa-bicyclo [3,2,l]octane core **F2.1** and some early reported synthesis

The relatively simple derivatives of this family such as Frontalin and Brevicomin are the first ones to be characterized having this dioxa-bicyclo[3.2.1]octane core. These two compounds have been initially characterized as the aggregation pheromones of beetles and later it has been revealed that they are also secreted by elephants. Quite interestingly, the Frontalin or Brevicomin samples from the beetles are found to be the single enantiomers. However, when it comes to the elephant, the varying ratio of enantiomers change their sexual behaviour and their aggression is also affected. Figure **1** shows the structures of some selected natural products that have been isolated afterwards that possess this key dioxa-bicyclo[3.2.1]octane core either as main or as one of the substructural units present.[3] Also listed in Figure **1** are the diverse biological activities documented for these selected natural products. Cyclodidemniserinol trisulfate, the total synthesis of which is the objective of the present work, was isolated in 2000, by Faulkner and co-workers and showed promising HIV integrase inhibition with an IC_{50} of 60 μg/mL and also MCV topoisomerase inhibition with an IC_{50} value of 72 μg/mL.[4] Cyclodidemniserinol trisulfate is characterized by the presence of a 6,8-dioxa-bicyclo[3.2.1]octane moiety having functionalized long chain alkanes as substituents at C5 and C7. Given the objective of its total synthesis with a keen interest on developing new methods for the construction of the central bridged bicyclic ketal core, the following discussion will focus mainly on the various methods reported for constructing this core, taking the simple derivatives such as from the Frontalin and Brevicomin syntheses, which are further subdivided into three parts i. Acid Catalyzed Intramolecular Ketalization; ii. C–H Oxidative Transformations and iii. Metal-Catalyzed Transformations - depending upon how the key bicyclic core has been constructed. Subsequently discussed will be the salient features of the reported total synthesis of didemniserinolipid B.

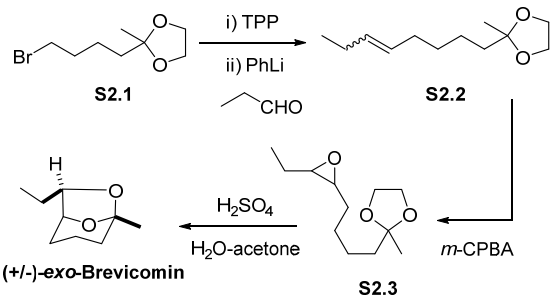
I. Dioxa-bicyclo[3.2.1]octane synthesis involing intramolecular ketalization:

As mentioned above, in the majority of the cases, an intramolecularacetal formation from a suitable keto-diol is a commonly employed method used for the construction of the bicyclic ketal core. In 1967, Naya's group reported the isolation of bicyclicketals **S1.1** and **S1.2** as the new constituents of hop oil and confirmed their structure by synthesis.[5] Quite interestingly, though these are the first ones of this family to be isolated, Naya has not given any name to these natural products. The synthesis of these two bicyclicketals involves a [4+2] cycloaddition of acryl aldehyde and MVK in the presence of silver oxide followed by Grignard reaction and acidic work up.



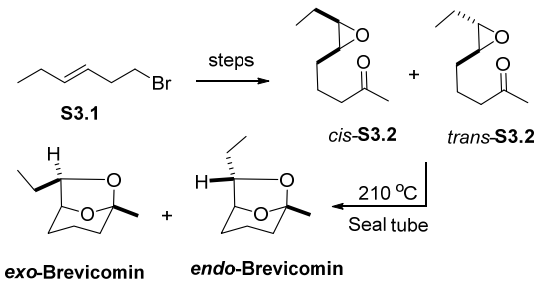
Scheme 1: Synthesis of naturally occurring **S1.1** and **S1.2** having dioxa-bicyclo [3,2,l]-octane core

In 1968, Silverstein's group documented the isolation of Brevicomin as the principal component of the sex attractant of the western pine beetle *dendroctonusbrevicomis*.[6] This is the simplest bicyclic ketal containing natural product that has been named first and its constitution was confirmed by the total synthesis. The total synthesis started from 6-bromohexan-2-one and the epoxide was made in normal reaction sequence i) protection of keto group ii) Witting homologation and iii) epoxidation by *m*-CPBA, leaded to the mixture of *cis* and *trans* epoxides. They separated both the epoxides by GC and the *cis*-epoxide was treated with aqueous H_2SO_4 to procure the first bicyclic ketal, *exo*-brevicomin.



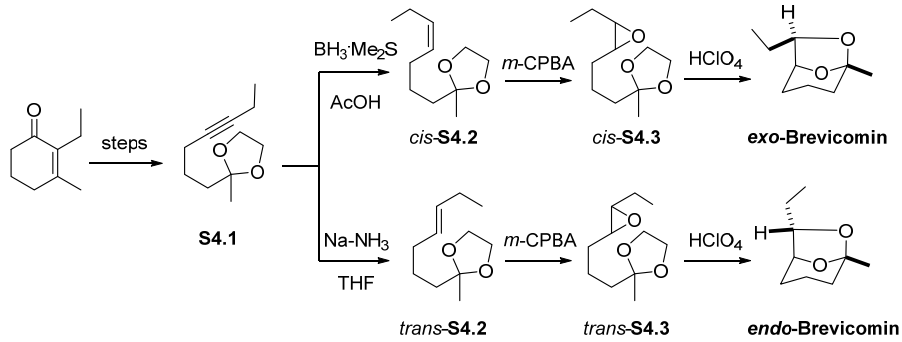
Scheme 2: Total synthesis of *exo*-brevicomin by Silverstein

In the next year, Barber's group documented a carbonyl epoxide rearrangement for synthesizing the [3.2.1]-bicyclic core of Brevicomin and related systems.[7] The *cis*-6,7-epoxynonan-2-one *cis*-**S3.2** predominately gives the *exo*-Brevicomin in 90% yield along with *endo* isomer and *vice versa*. Mechanistic studies revealed that during the thermolysis of the δ,ε-epoxy ketones, the epoxide ring undergoes opening predominantly with the inversion of configuration. The *endo*-brevomin is also a natural pheromone inhibitor produced by dendroctonus bark beetles.



Scheme 3: Barber's synthesis of *exo*- and *endo*-brevicomins

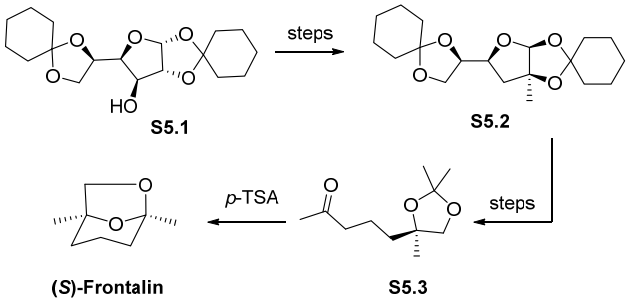
A large scale and stereospecific total synthesis of both *exo*-/*endo*-brevicomins was reported by Kocienski's group in 1975 and has its own origins from Silverstein's synthesis.[8] The key feature of this synthesis includes the selective synthesis of *cis*-/*trans*-olefin **S4.2** by manipulating the reduction of the intermediate alkyne **S4.1** in a stereoselective manner. The key cyclization of *cis*- and *trans*-epoxides **S4.3** has been accomplished by employing perchloric acid as a catalyst to obtain *exo*-/*endo*-brevicomins selectively. The total synthesis of (±)-*endo*-brevicomin has also been documented by Kenji Mori's featuring an alternative approach for the synthesis of the key epoxide *trans*-**S4.3**.[9]



Scheme 4: Kocienski's stereospecific total synthesis of *exo*-/*endo*-brevicomins

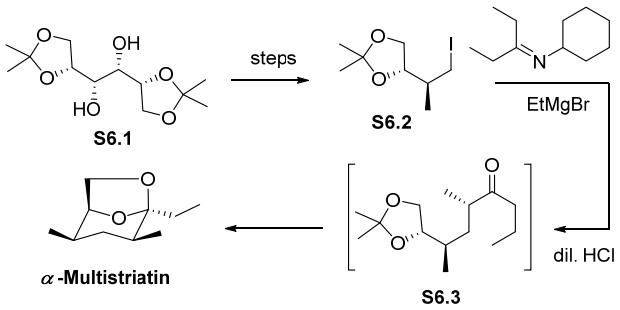
The first enantiospecific total synthesis of (*S*)-Frontalin has been documented by Emoto and co-workers.[10] D-glucose was used as the chiral-pool starting material and the key ketoacetonide **S5.2** was synthesized following a relatively lengthy sequence from the known

1,2:5,6-di-O-cyclohexylidene-α-D-gluco-hexofuranose **S5.1** and the key cyclization was performed by using *p*-TSA of **S5.3**.



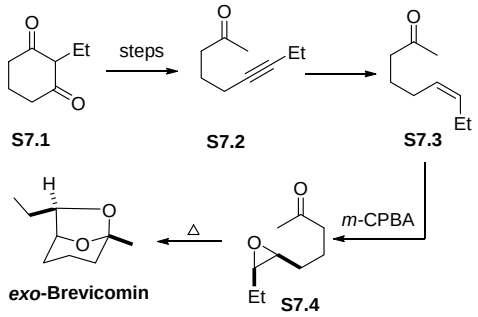
Scheme 5: Total synthesis of (*S*)-Frontalin by Emoto

In 1976, Mori and co-workers reported the total synthesis of optically active α-Multistriatin starting from D-mannitol.[11] The α-Multistriatin is one of essential components of an aggregation pheromone for the European elm bark beetle *Scolytusmultistriatus.* The key iodide **S6.2** was synthesised from the known mannitol diacetonide **S6.1**. The alkylation of the 3-pentanone enamine with **S6.2** in the presence of EtMgBr, followed by *in situ* enamine hydrolysis and cyclization leads to the natural product.



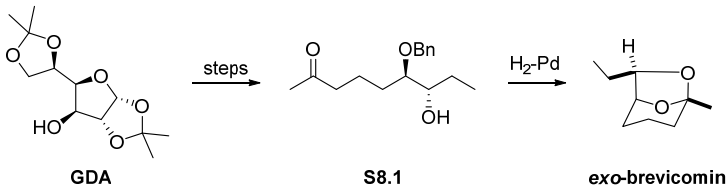
Scheme 6: Synthesis of α-Multistriatin by Kenji Mori *et al*

In the same year, Coke reported a new methodology for the synthesis of acetylenic ketone from 1,3 diketone **S7.1** through a β-halo-α,β-unsaturated ketone followed by thermal cleavage and has applied this methodology to the synthesis of *exo*-brevicomin.[12] The triple bond was reduced to the *cis* double bond followed by epoxidation, which gave the required epoxide **S7.4** which was transformed into *exo*-brevicomin through thermolysis. Coke's group has also applied this methodology to the synthesis of *exo*-brevicomin, the pheromone from *Dendroctonus breuicomis*.



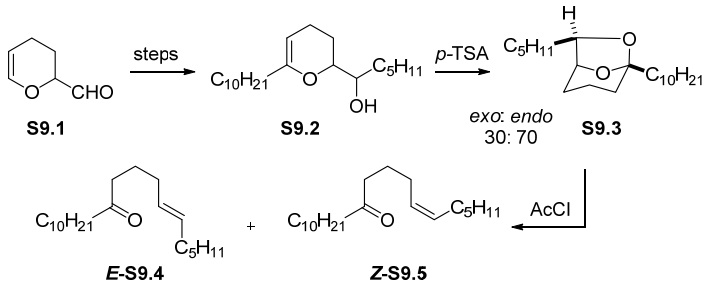
Scheme 7: Synthesis of *exo*-brevicomin by Coke and co-workers

In 1982, Fraser-Reid and co-workers documented the total synthesis of (+)-*exo*-brevicomin involving the preparation of the key intermediate **S8.1** from D-Glucose.[13] The key intramolecular ketalization was instantaneous when the benzyl ether deprotection occurred during the Pd-catalyzed hydrogenolysis.



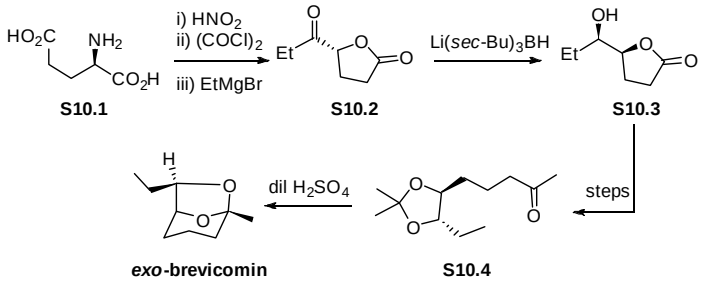
Scheme 8: Synthesis of (+)-*exo*-brevicomin by Bert Fraser-Reid *et al*

In 1985, Mundy and co-workers synthesized the (*E*/*Z*)-6-heneicosene-11-one **S9.4/ S9.5** the sex pheromone of the tussock moth.[14] The interesting feature of this synthesis was, that unlike with brevicomin and related bicyclic ketals, the synthesis where a keto-olefin was converted to the bicyclic ketal *via* an epoxide, in this a bicyclic ketal **S9.3** has been used as an intermediate to construct the ω-enone system through the acid catalyzed fragmentation. The active pheromone constituent has been identified as the (*Z*)-isomer **S9.5**. However, in the field tests, the (*E*)-isomer **S9.4** has also shown equivalent bioactivity. But the separate bioassay has revealed that the mixture of (*E*) : (*Z*) (60 : 40) was considerably more active as a pheromone than the pure material isolated from the female tussock moth.



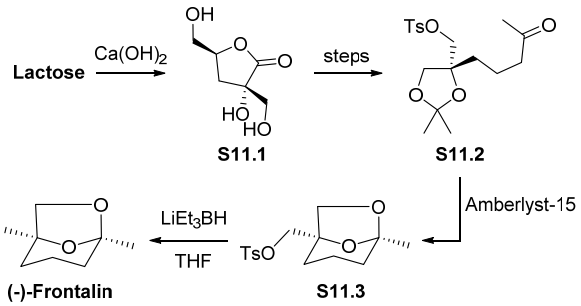
Scheme 9: Synthesis of 6-heneicosene-11-one by Mundy *et al*

In 1987, Larcheveque and co-workers documented the synthesis of (+)-*exo*-brevicomin from (–) glutamic acid **S10.1**.[15] The key-step of this synthesis was the selective reduction of ketone **S10.2** with L-selectride which gave the *syn*-product **S10.3**, with the subsequent acetonide deprotection of **S10.4** and *in situ* the ketalization happening in the presence of dil. H_2SO_4.



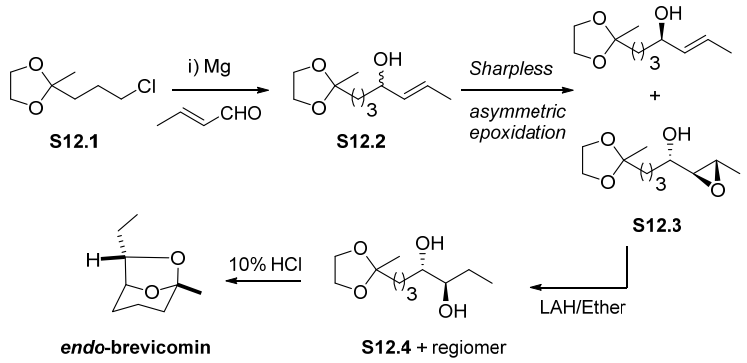
Scheme 10: Synthesis of (+)-*exo*-brevicomin by Larcheveque's group

Monneret and co-workers reported a chiral pool synthesis of (–)-Frontalin from *α*-D-isosaccharino-lactone **S11.1** that can be synthesized from D-lactose.[16] The key cyclization step of **S11.2** was performed by using the Amberlyst-15 ion-exchange resin followed by reduction of neopentyltosylate **S11.3** with lithium triethylborohydride which gave the aggregation pheromone of the southern pine beetle (–)-Frontalin.



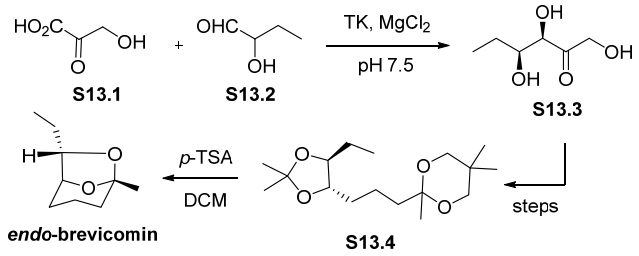
Scheme 11: Synthesis of (–)-Frontalin by Claude Monneret *et al*

In 1989, Yadav and co-workers documented a stereoselective synthesis of (1*S*,5*R*,7*R*) (–)-*endo*-brevicomin by employing the acid catalysed cyclization of diol **S12.4** which was prepared by the Sharpless Kinetic Resolution[18] of a suitable allylic alcohol **S12.3** followed by its subsequent reduction with LAH.[17] The allyl alcohol **S12.2** was prepared from the Grignard reagent derived from the chloride **S12.1** with the croton aldehyde.



Scheme 12: Synthesis of (–)-*endo*-brevicomin by J S Yadav *et al*

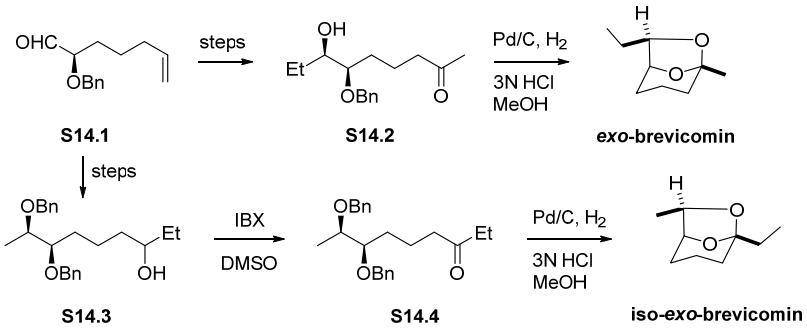
In 1991, Whitesides and co-workers described the total synthesis of naturally occurring (+)-*exo*-brevicomin by a strategy combining chemical and enzymatic steps.[19] The enzyme *Transketolase* (TK) was used for the condensation between *β*-hydroxypyruvic acid **S13.1** and 2-hydroxybutyraldehyde **S13.2** to furnish the vicinal diol **S13.3** possessing the D-*threo* configuration. The advanced acetonide **S13.4** was synthesized from **S13.3** following a sequence of reactions: i) acetonide protection of diol; ii) reduction of the keto group and $NaIO_4$ cleavage; iii) Witting homologation and iv) hydrogenation. Finally, the acetonide hydrolysis using *p*-TSA completed the total synthesis of (+)-*exo*-brevicomin.



Scheme 13: Synthesis of (+)-*exo*-brevicomin by G. M. Whitesides *et al*

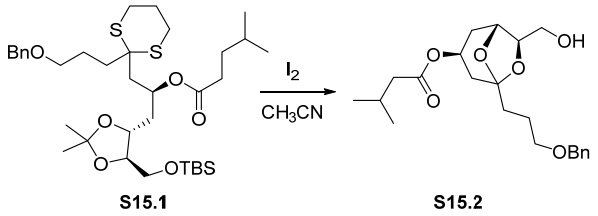
Prasad and co-workers documented the enantioselective synthesis of *α*-benzyloxy aldehyde **S14.1** containing a terminal alkene.[20] The reaction was carried out from a chiral pool L-(+)-tartaric acid and this common intermediate was used for the synthesis of pine beetle pheromones (+)-*exo*-brevicomin, (+)-iso-*exo*-brevicomin. The aldehyde **S14.1** was treated with ethylmagnesium bromide to yield the corresponding *threo* alcohol followed by oxidation of alkene with $PdCl_2$/CuCl which produced the ketone **S14.2** and was subjected for hydrogenolysis in methanolic HCl to obtain the (+)-*exo*-brevicomin. Similarly, for the synthesis of (+)-*iso*-*exo*-brevicomin, MeMgBr was added to the same aldehyde **S14.1** to furnish the *threo* alcohol which was converted to its benzyl ether **S14.3**. The ozonolysis of alkene followed by the treatment with ethylmagnesium bromide produce **S14.3** and the

oxidation of the alcohol procure the ketone **S14.4**, which was transformed into (+)-iso-*exo*-brevicomin under hydrogenation in acidic medium.



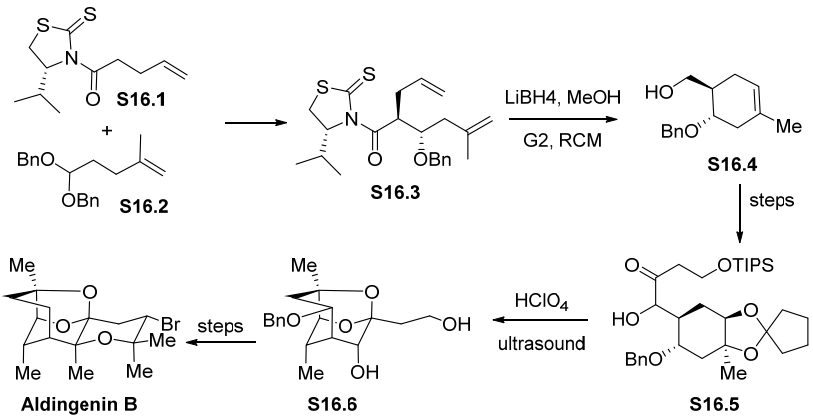
Scheme 14: Synthesis of (+)-*exo*-brevicomin & (+)-iso-*exo*-brevicomin by K.R. Prasad *et al*

In 2009, Long and co-workers reported the synthesis of the core structure of the natural product Cyclodidemniserinol trisulfate, a natural HIV-1 integrate inhibitor starting from butane diol.[21] From butane diol, they prepared advanced intermediate **S15.1** by using D-tartaric acid as a chiral source. The resulting thioketal **S15.1** was subjected for I_2-mediated thioketal and acetonide deprotection and intramolecular ketal **S15.2** formation in one pot.



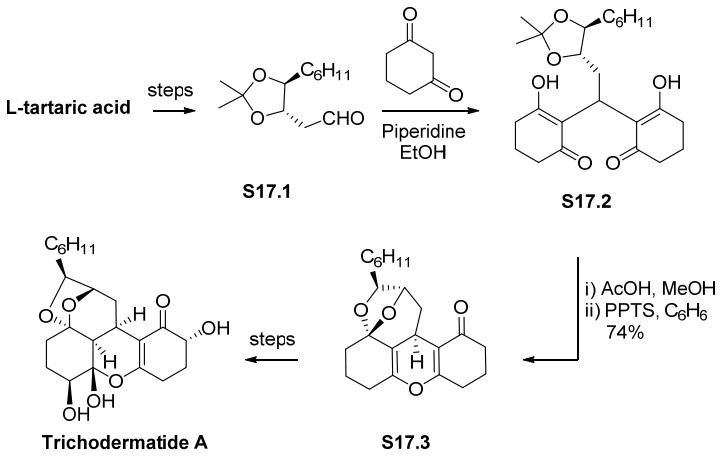
Scheme 15: Synthesis of cyclic core of Cyclodidemniserinol trisulfate

In 2012, Crimmins and co-workers reported the first total synthesis of the proposed structure of Aldingenin B from thiazolidinethione **S16.1**.[22] The key cyclohexene **S16.4** has been synthesized following the Evans aldol and RCM as the key reactions. Subsequently, the bicyclicketal unit **S16.6** has been prepared from the advanced intermediate **S16.5** by using $HClO_4$ under ultrasonic irradiation to ensure the proper mixing of the biphase on larger scales along with the deprotection of silyl ether. Following simple chemical transformations Aldingenin B with the proposed structure was synthesized from **S16.6** and a revision has been suggested.



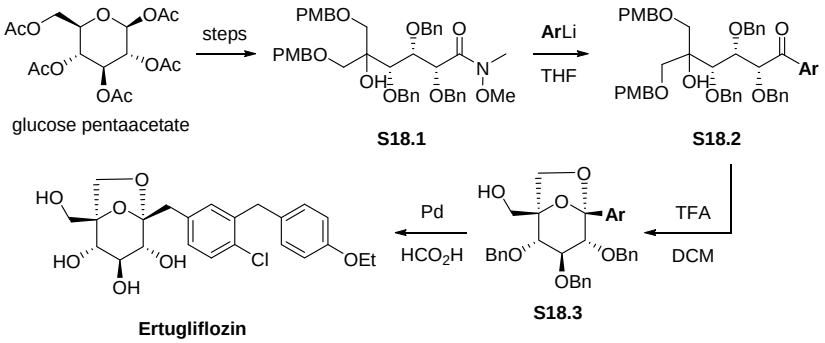
Scheme 16: Total synthesis of putative structure of Aldingenin by Crimmins'group

In 2013, Hiroya and co-workers reported the first total synthesis of Trichodermatide A starting from L-tartaric acid.[23] The aldehyde **S17.1** synthesized from L-tartaric acid was treated with 1,3-cyclohexanedione in the presence of piperidine in ethanol to provide the symmetric compound **S17.2**. The diastereoselective intramolecular ketal formation reaction and dehydrative pyran formation in the presence of aqueous acetic acid in methanol followed by treatment of the resulting intermediate with PPTS in benzene furnished the pentacyclic core **S17.3** which was subsequently transformed to Trichodermatide A.



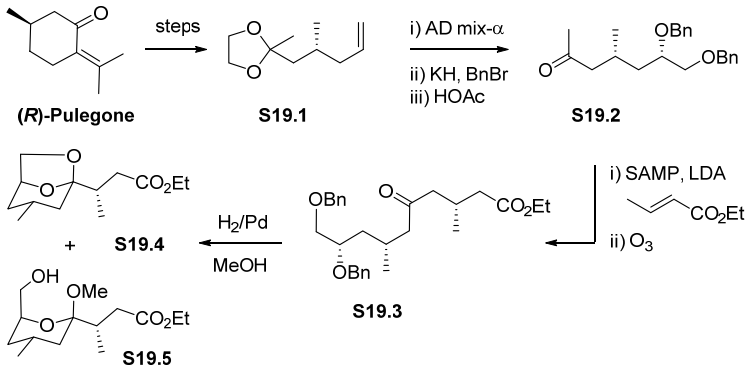
Scheme17: Synthesis of Trichodermatide A by Kou Hiroya *et al*

In 2014, Brandt and co-workers reported the synthesis of Ertugliflozin, a glucose-derived *C*-glycoside which contained a novel bridged bicyclic ketal motif and acted as a sodium-dependent glucose co-transporter (SGLT)2 inhibitor for the treatment of diabetes.[24] The nucleophillic addition of the appropriate organo-lithium reagent to the Weinreb amide **S18.1** in THF produced the equilibrium mixture of the corresponding cyclic lactol and acyclic ketone **S18.2**. The acid-promoted one-pot PMB removal followed by stereoselective intramolecular trapping of the putative oxonium ion intermediate provided the desired dioxa-bicyclo[3.2.1]octane **S18.3** ring system of Ertugliflozin.



Scheme 18: Synthesis of Ertugliflozin by T. A. Brandt *et al*

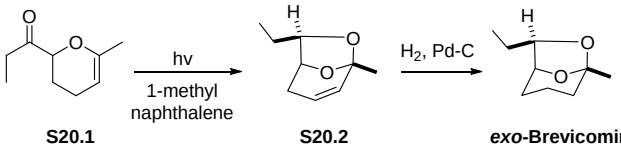
Kitching and co-workers documented the model studies toward the total synthesis of Pinnatoxin D.[25] Both the two compounds **S19.4** and **S19.5** having the bicyclic core of Pinnatoxin D have been synthesized from *R*-(+)-Pulegone. Both the model substrates were derived from the protected enone **S19.2** which was acquired from **S19.1**. Enone **S19.1** was treated with AD-mix-*α*, bezyl protection of which followed by ketone release yielded the advanced intermediate **S19.2**. The SAMP derivative ((*S*)-l-amino-2-methoxymethylpyrrolidine) of the ketone **S19.2** was deprotonated and was added to ethyl crotonate, followed by ozonolysis and the removal of hydrazones to yield the benzyl protected keto ester **S19.3** which was exposed to hydrogen in presence of palladium leading to the bicyclic ketal **S19.4**.



Scheme 19: Synthesis of bicyclic part of Pinnatoxin D by Kitching *et al*

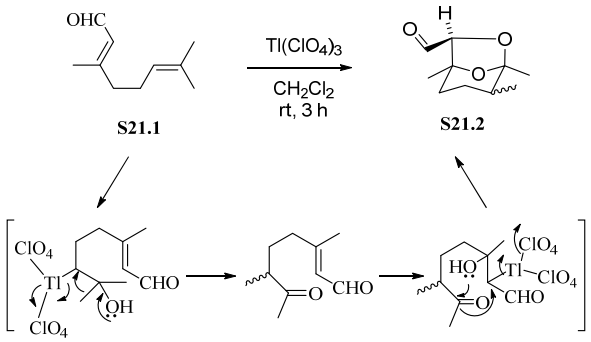
II. Oxidative Photochemical Transformations:

In 1977, Kossanyi and co-workers reported a novel photochemical approach for the total synthesis of *exo*-brevicomin.[26] The irradiation of the 2-propionyl-6-methyl-2,3-dihydro-4*H*-pyran **S20.1** provided the intermediate dehydro-*exo*-brevicomin **S20.2** that has been subjected for hydrogenation to provide a straightforward synthesis of the natural product.



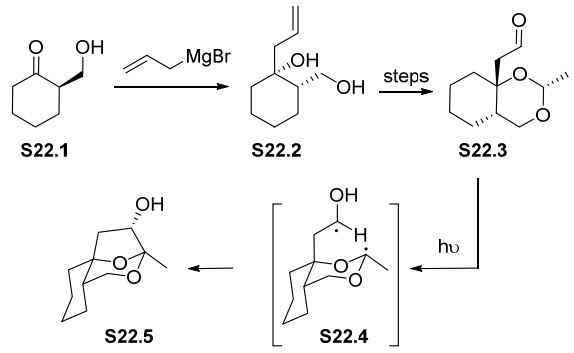
Scheme 20: Kossanyi's photochemical synthesis of *exo*-brevicomin

Yamada and co-workers reported a novel synthesis of the 6,8-dioxa-bicyclo[3.2.l]octane derivatives **S21.2** by the reaction of the citronellal **S21.1** with thallium perchlorate. [27]



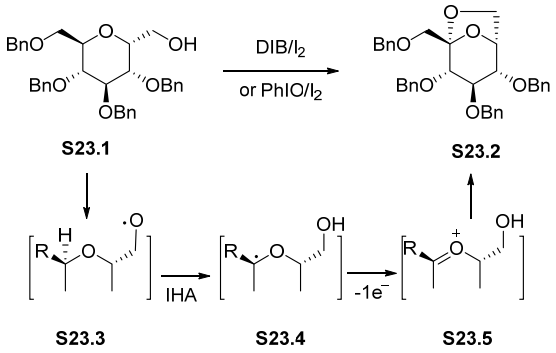
Scheme 21: Synthesis of dioxa-bicyclo [3,2,l] octane by Yamada *et al*

In 1996, Halcomb and co-workers[28] reported the synthesis of the dioxa-bicyclo[3.2.1]octane core of Zaragozic acids (a promising lead compound for the development of a new cholesterol-lowering drug) through a Norrish Type II [29] photochemical reaction. The synthesis started with the addition of allylmagnesium bromide to the ketone **S22.1** and subsequent protection of the diol unit as its acetal and then ozonolysis of the alkene to afford **S22.2**. Upon irradiation the aldehyde **S22.3** in benzene through a quartz filter provides bicyclic ketal **S22.5**. It has been proposed that this reaction proceeds through an unusual 1,6-hydrogen abstraction to generate a 1,5-biradical **S22.4** with subsequent cyclization.



Scheme 22: Synthesis of dioxa-bicyclo [3,2,l] octane by Halcomb *et al*

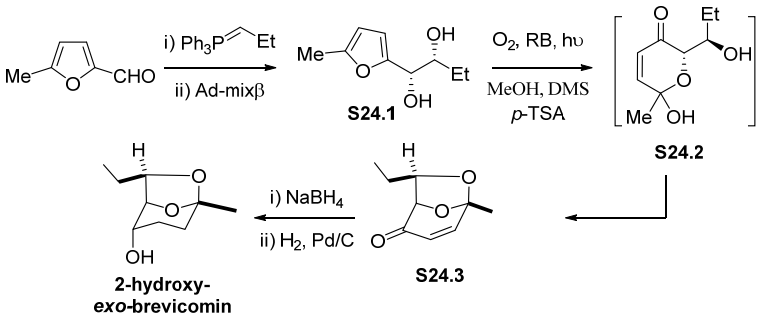
Suárez and co-workers described the synthesis of [2.2.1]- as well as [3.2.1] bicyclic ketals through an intramolecular hydrogen abstraction (IHA) reaction triggered by alkoxy radicals.[30] The compound **S23.3** was generated *in situ* by the reaction of alcohol with (diacetoxyiodo) benzene (DIB) or iodosyl benzene in the presence of iodine and *O*-radical to *C*-radical **S23.4** transformation was triggered by the IHA followed by oxidation, which yielded an oxycarbenium **S23.5** ion which was internally trapped by the nucleophillic alcohol and gave the [2.2.1] bicyclic system in case of tetrahydrofuran derivatives and the [3.2.1] bicyclic system **S23.2** from the tetrahydropyran moiety **S23.1**.



Scheme 23: Synthesis of dioxa-bicyclo [2.2.1] heptane and dioxa-bicyclo [3,2,l] octane

by E. Suárez *et al*

In 2011, Vassilikogiannakis and co-workers reported that photo oxygenation of 2-(*α,β*-dihydroxyalkyl)furan **S24.1** followed by *in situ* reduction and ketalization in presence of acid rapidly provides the 6,8-dioxa-bicyclo[3.2.1]oct-3-en-2-one **S24.3** framework through the intermediate **S24.2**.[31] Compound **S24.3** has been successfully converted to the 2-hydroxy-*exo*-brevicomin by simply reducing the keto group followed by hydrogenation.



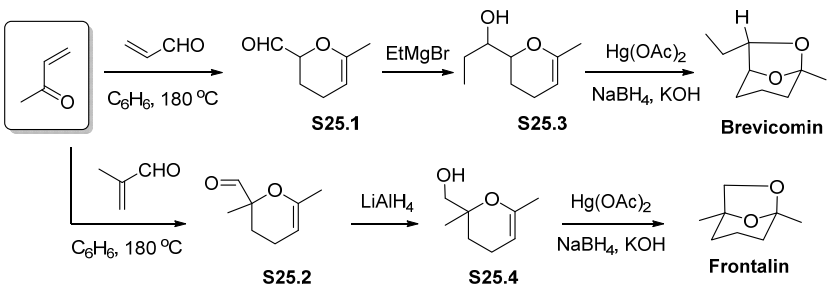
Scheme 24: Synthesis of 2-hydroxy-*exo*-brevicomin by Vassilikogiannakis

III. Metal-Catalyzed transformations of central bicyclic core

Broadly, the metalized reactions in the context of constructing the bicyclic ketal core can be categorized depending upon the nature of the newly formed bonds i. C–O bond or ii.

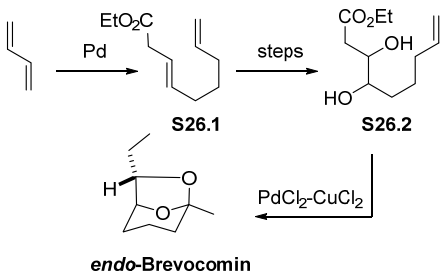
C–C bond. The former one mainly involves either the Pd-catalyzed Wacker oxidation[32] of olefin diol or the metal-mediated alkynediol cycloisomerization.[33] There are examples where the vinyl ethers have been functionalized intramolecularly to form the bicyclic ketals by employing metal-complexes. Indeed, as discussed earlier, the corresponding acid-catalyzed trapping of the glycals is one of the early approaches reported for the synthesis of the bicyclic ketal core.

In 1971, Mundy and co-workers reported a common approach for the total synthesis of diastereomers of Frontalin and Brevicomin.[34] The synthesis is similar to the one that has been reported by Naya's group.[5] The hetero Diels-Alder reaction between the methyl vinyl ketone and methacrolein or acrolein gave the corresponding intermediates **S25.1**/**S25.2**.[35] The pendant aldehyde in **S25.1**/**S25.2** has been subjected for reduction/Grignard addition gave **S25.3**/**S25.4**. The key ketalization step was performed by $Hg(OAc)_2$ in the presence of $NaBH_4$ and KOH.



Scheme 25: Mundy's total synthesis of Frontalin and Brevicomin

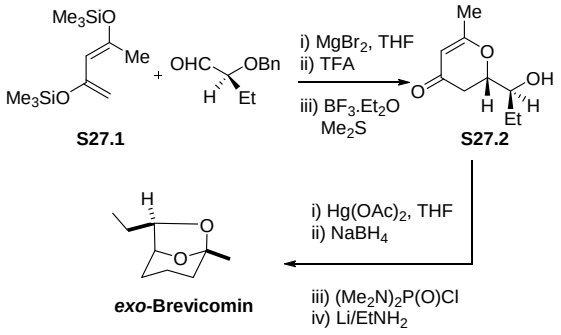
In 1976, Grigg reported a short total synthesis of racemic *endo*-brevicomin by employing the ethyl nona-3,8-dienoate **S26.1** that was prepared by the Pd-catalyzed dimerization of butadiene with concomitant carbonylation with ethanol.[36] This intermediate has been converted to **S26.2** by simple transformations and then subjected for the key Wacker-oxidation to provide the racemic *endo*-brevicomin.[32]



Scheme 26: Grigg's total synthesis of *endo*-brevicomin by employing Wacker-oxidation

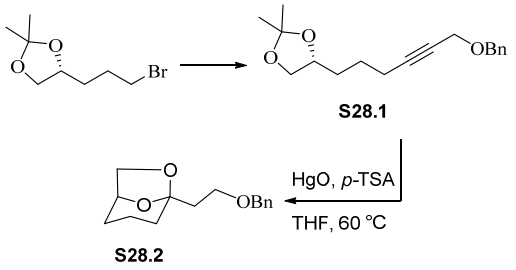
In 1984, Danishefsky and co-workers described a diastereo facial cyclocondensation reaction of aldehydes with activated dienes **S27.1** to procure the advance intermediate **S27.2**

which was employed for the synthesis of *exo*-brevicomin.[37] The bridged ketal was prepared by intramolecular oxymercuration in the presence of $NaBH_4$.



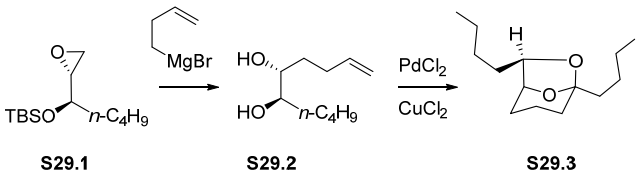
Scheme 27: Synthesis of *exo*-brevicomin by Danishefsky

The intrinsic nature of acetylenes as a carbonyl synthon was exploited by Katsuki's group (in 1991) wherein acetylene **S28.1** derived from L-ascorbic acid was subjected for alkynediol cycloisomerization with a catalytic amount of mercury(II) oxide and *p*-TSA to afford the bicyclic ketal **S28.2**.[38]



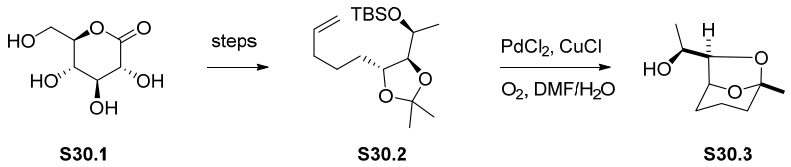
Scheme 28: Synthesis of bicyclic ketal *via* cycloisomerization by Katsuki

In 2002, Faber and co-workers demonstrated a short chemo enzymatic cascade-reaction route for the synthesis of the epoxide **S29.1** and demonstrated its application in the total synthesis of the constituent of Jamaican rum **S29.3**.[39] The enantio pure epoxide **S29.1** was opened by 3-butenylmagnesium bromide, with the removal of the TBS group giving the advance intermediate alkene diol **S29.2** that was subjected for Wacker oxidation by using $PdCl_2$ to procure the natural product **S29.3**. [32]



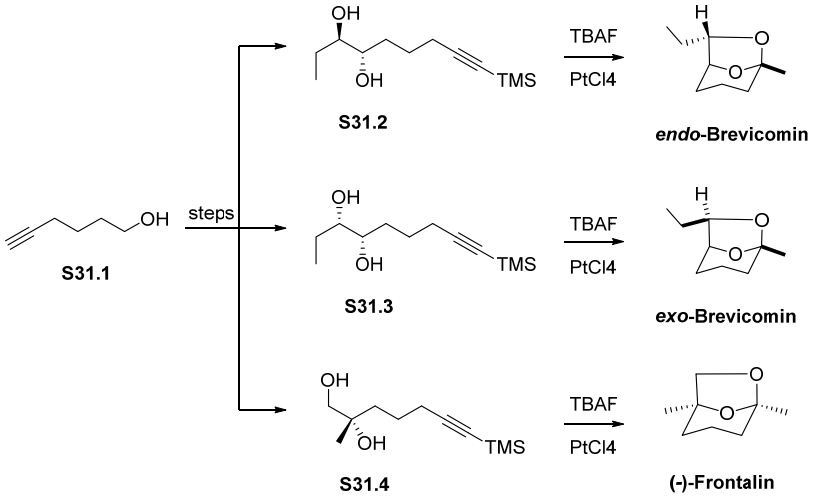
Scheme 29: Synthesis of Jamaican rum constituent by Faber

Yadav and co-workers reported the stereoselective synthesis of hydroxy-*exo*-brevicomin **S30.3** from D-glucono-*δ*-lactone **S30.1** as a chiral precursor.[40] The Wacker oxidation of **S30.2** followed by intra molecular ketalization led to the bicyclic ketal **S30.3**.



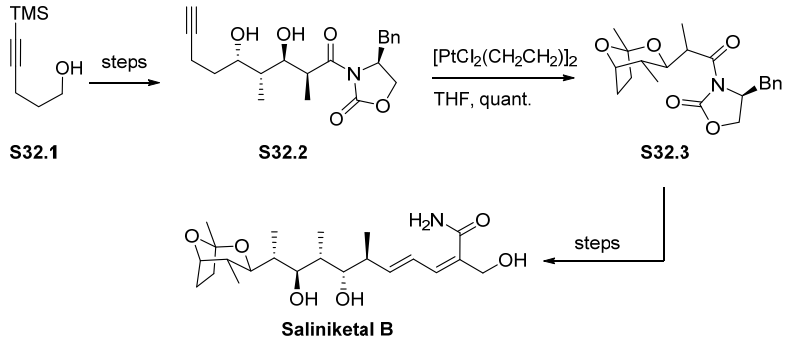
Scheme 30: Synthesis of 1-hydroxy-*exo*-brevicomin by J S Yadav *et al*

In 2009, there were three reports on the metal-catalyzed intra molecular ketalization of alkynediols for the construction of the [3.2.1]-bicyclic ketal core.[41] Hee-Yoon Lee and co-workers reported a facile total synthesis of (−)-*endo*-brevicomin, (−)-*exo*-brevicomin and (−)-Frontalin, through $PtCl_4$ catalyzed cycloisomerization or hydroalkoxylation reaction of suitable alkyne diols, **S31.2**, **S31.3**, **S31.4** respectively which were prepared from 5-hexynol **S31.1**.



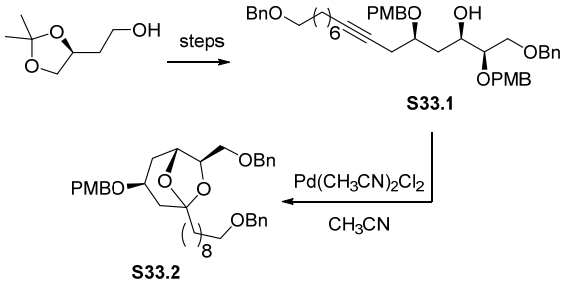
Scheme 31: Synthesis of (−)-Frontalin, (−)-*endo*-brevicomin and (−)-*exo*-brevicomin by Lee

Brabander and co-workers documented the total synthesis of Saliniketal B, employing the Pt(II)-catalyzed cycloisomerization of the suitable alkynol **S32.2** to construct the bicyclic ketal **S32.3** of Saliniketal B. [3d]



Scheme 32: Total synthesis of Saliniketal B by Brabander

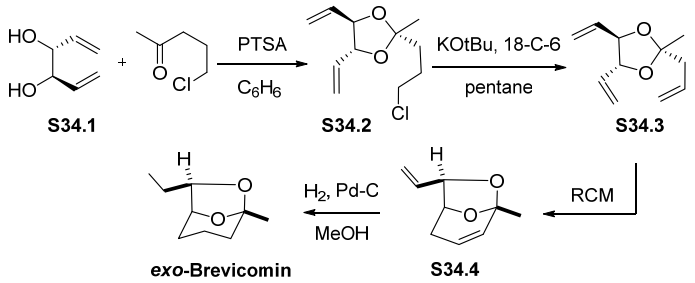
Our group has documented a Pd-mediated intra molecular ketalization of alkynediols **S33.1** for the construction of the central [3.2.1]-bicyclic ketal core **S33.2** of Cyclodidemniserinol trisulfate.[33f]



Scheme 33: Synthesis of Cyclodidemniserinol trisulfate by Ramana *et al*

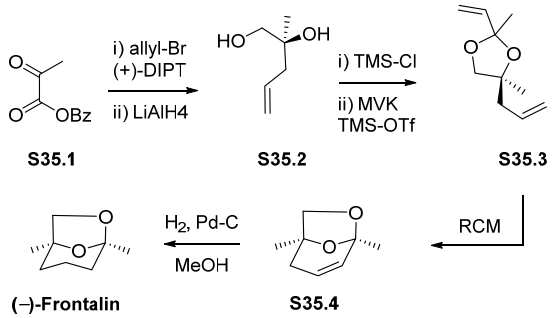
IV. RCM based approaches for the synthesis of bicyclic ketals

In 1999, Burke and co-workers documented a new route for the synthesis of (+)-*exo*- and *endo*-brevicomins using Ring Closing Metathesis (RCM) for the construction of the central 6,8-dioxa-bicyclo[3.2.1]octane. [42] For example, the synthesis of *exo*-brevicomin was started with the C_2-symmetric diol **S34.1** which was protected as ketal **S34.2** followed by elimination of the halide group, giving the advanced triene **S34.3**. Finally, triene **S34.3** was subjected for RCM followed by hydrogenation to complete the synthesis of *exo*-brevicomin.



Scheme 34: Synthesis of (+)-*exo*-brevicomin by Steven D. Burke *et al*

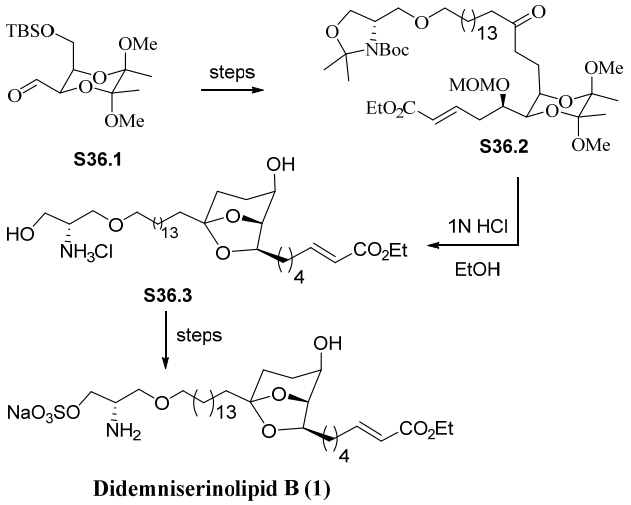
A similar approach has been reported by Grubbs and co-workers[43] for the total synthesis of the natural product (–)-Frontalin.



Scheme 35: Synthesis of (–)-frontalin by Grubbs

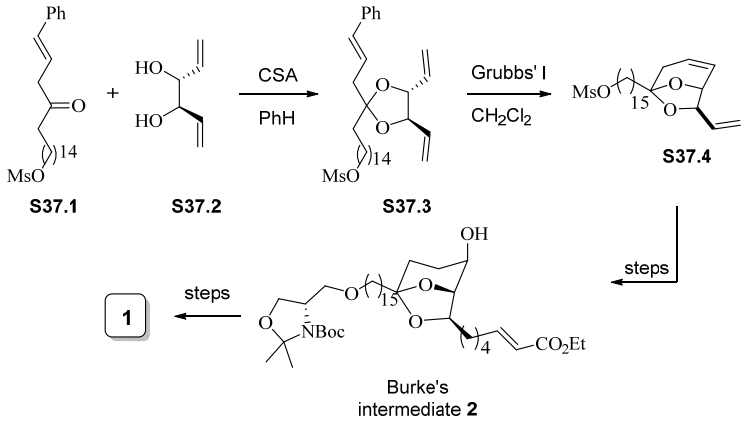
V. Salient features of the reported total syntheses of didemniserinolipid B

In 2002, Steven V. Ley and co-workers documented the first total synthesis, structure revision, and absolute configuration of (+)-Didemniserinolipid B **1**.[44] The synthesis started from the known butanediacetal (BDA)-protected aldehyde **S36.1**, from where they prepared the advanced intermediate **S36.2** which was exposed to 1N HCl to give the bicyclic ketal **S36.3** along with deprotection of all the protecting group (acetonide, Boc, BDA, and MOM).



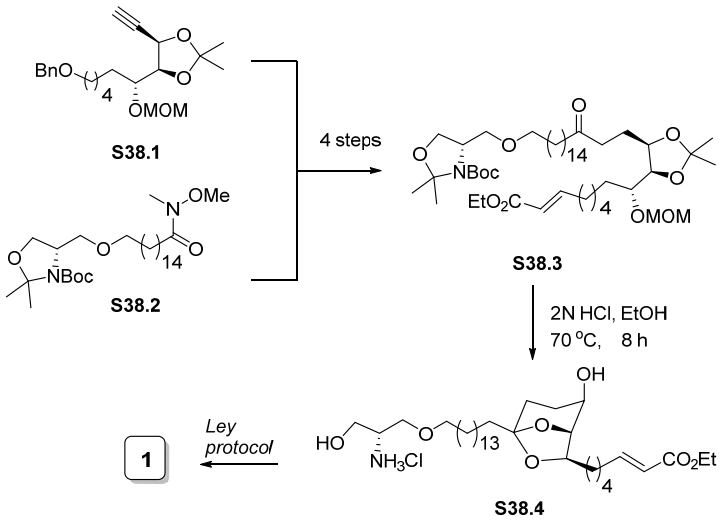
Scheme 36: Ley's protocol for Didemniserinolipid B synthesis

Burke and co-workers reported the modular synthesis of didemniserinolipid B **1** with the help of ketalization/ring-closing metathesis (K/RCM) strategy to establish the 6,8-dioxa-bicyclo[3.2.1]octane core **S37.4** from a suitable ketal **S37.3** which was prepared from ketone **S37.1** and the C_2-symmetric (*R*,*R*)-dienediol **S37.2**.[45] The C10 axial alcohol was established *via* a substrate-controlled epoxidation of the *endo*-cyclicalkene, followed by reductive *trans*-diaxial epoxide opening and the serinol and C1-C7 side chains could be appended in a modular fashion through a Williamson etherification and cross metathesis respectively procure the Burke's intermediate **2**.



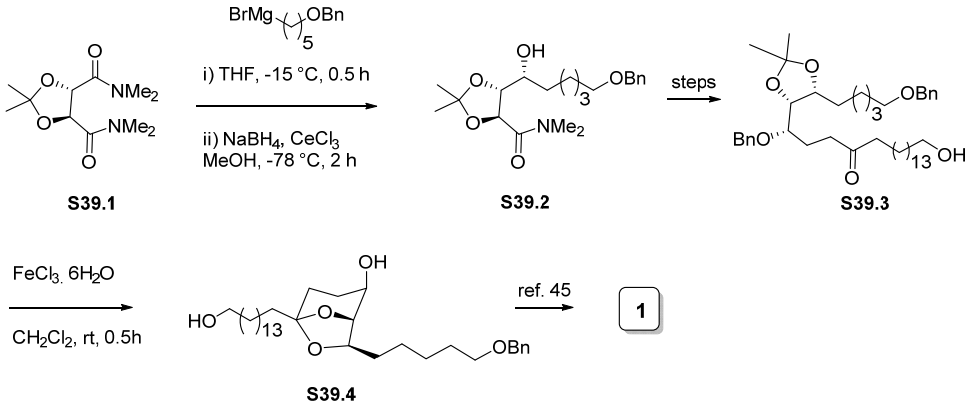
Scheme 37: Burke's protocol for Didemniserinolipid B synthesis

Chandrasekhar and co-workers documented the formal synthesis of Didemniserinolipid B **1** in a complete stereo controlled manner using the D-ribose as the chiral pool material.[46] The synthesis is modular and employs an addition alkynyl anion to Weinreb amide as the key skeletal construct. The key propargyl alcohol derivative **S38.1** has been prepared from D-ribose, and coupled with the Weinreb amide **S38.2** that was derived from D-serine. The resulting keto alkyne **S38.3** was subjected for hydrogenolysis to remove the benzyl as well as the triple bond reduction. The resulting terminal alcohol has been subjected for oxidation and two-carbon Witting homologation to prepare the key intermediate **S38.3** which upon acid catalysed hydrolysis afforded the **S38.4** from which the synthesis of **1** has been earlier reported by Ley's group.[44]



Scheme 38: S. Chandrasekhar's protocol for formal total synthesis of Didemniserinolipid B

Prasad and co-workers documented the formal total synthesis of (+)-Didemniserinolipid B, which was accomplished starting from L-(+)-tartaric acid.[47] The key transformations in the synthesis include the elaboration of a *γ*-hydroxy-amide **S39.2** readily obtained by desymmetrization of the tartaric acid *bis*-amide **S39.1** *via* the controlled addition of a Grignard reagent followed by stereo selective reduction of the resulting ketone. The core bicyclic ketal was prepared from a suitable ketone **S39.3** by using $FeCl_3$ where deprotection[48] of the acetonide with concomitant intra molecular ketalization furnished the bicyclic acetal **S39.4** in 93% yield.



Scheme 39: Prasad's protocol for the formal synthesis of the Didemniserinolipid B

PRESENT WORK

The giant marine environment is still a largely unexploited resource in terms of new biologically active compounds. Hundreds of new compounds have been reported every year from marine organisms by different groups. In recent decades, marine tunicates have been subjected to very close scrutiny and consequently, a large number of bioactive nitrogenous as well as non-nitrogenous metabolites with novel and complex structures showing significant biological activity have been described. Marine tunicates which belong to the genus Didemnum (Phylum Chordata, class Ascidiacea) have been identified as rich sources of complex molecules. Mainly, all metabolites are nitrogen-containing compounds which are derived from amino acids, and classified into two major categories: (1) cyclic and acyclic peptides (2) and aromatic alkaloids. Mollamide and cyclodidemnamide are the cytotoxic cyclic heptapeptides which have been isolated from *Didemnummolle*. Minalemines D–F are the first sulfamicacid containing acyclic peptide isolated from *Didemnumrodriguesi*. Aromatic alkaloids like didemnolines A–D isolated from the caribbean mangrove ascidian *Didemnumconchyliatum*, HIV protease inhibitors - didemnaketals A and B and the macrocycle containing HIV-integrase inhibitor cyclodidemniserinol trisulfate isolated from Palauan ascidian *Didemnumguttatumas* reveal the structural diversity and wide range of biological activities of natural products isolated from the genus *Didemnum*.[4]

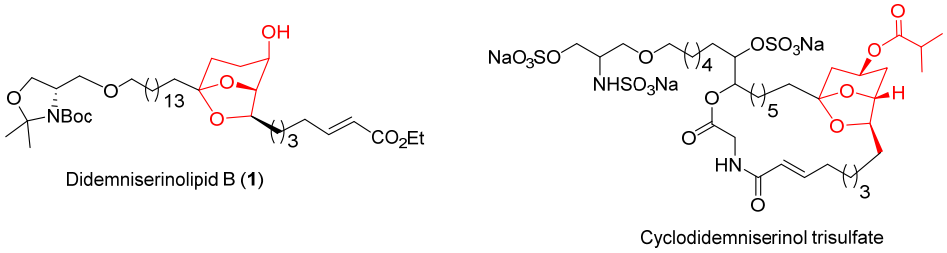


Figure 3. Structures of Didemniserniolipid B and of Cyclodidemniserinol trisulfate

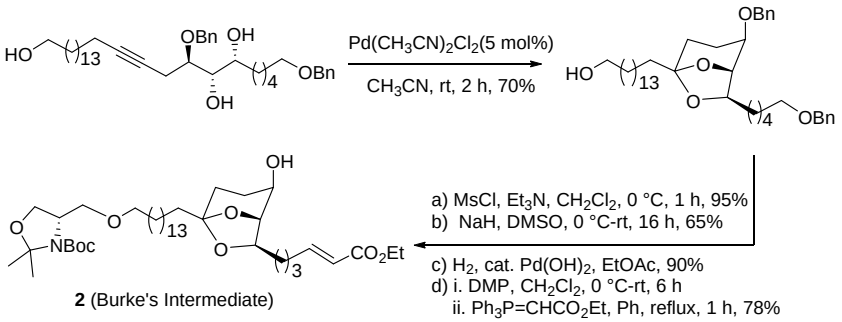
As part of a continuing search for biologically active secondary metabolites from ascidians, the tunicate *Didemnum sp.*, was collected from the coast of Sulawesi Island (Indonesia) with the aim of finding new cytotoxic agents against P388, A549, and HT29 tumor cell lines. While the initial methanolic extracts of these molecules show potent cytotoxic activity against several tumor cells, after further purification and isolation, none of the individual didemniserinolipids were found to be cytotoxic in the same assays. Though individual didemniserinolipids do not show any known biological activity, it has been reported that natural product containing 6,8-dioxa-bicyclo[3.2.1]octane moiety is biologically active.

The dioxa-bicyclic ketal, a common structural unit which is present in many natural products, has received substantial synthetic attention in recent years, due to the isolation of several new natural products having a bicyclic ketal unit as an integral part of their structures and the diverse biological activities reported, such as anti-fungal, anti-cancer, and anti-HIV.[4] The availabilty of the dioxa bicyclic ketal moiety in the large number of natural products suggest that development of a modular and efficient route for general structures of this type could be valuable in the context of diversity-oriented synthesis. As has been revealed in the Introduction, the intra-molecular acetal formation from a suitable keto-diol is a commonly employed method used for the construction of the bicyclic ketal core. The Wacker oxidation[32] of a suitably position alkenediol is another important reaction that has used in the synthesis of these bicyclic ketals. However, the prior protection of this diol unit and the deprotection of the same after oxidation is one of the draw-backs when one considers the number of transformations involved.

Quite interestingly, when an alkyne is placed in place of olefin, the corresponding sequential addition of heteroatoms is one of the most interesting and important reactions in organic chemistry. The intermolecular version of this reaction converting the alkynes to ketones has been known for a long time. Various metal complexes or Lewis acids have been employed either in catalytic or stoichiometric amounts. The intramolecular version of this reaction falls under the broad category of cycloisomerization reactions which are characterized by their complete atom economy and as well as recognized as an attractive tool for delivering complex molecular diversity. In 1983, Utimoto first reported the synthesis of a bicyclic ketal through cycloisomerization of ω-alkyne diols by using Pd-complexes.[49] After a long span, only during the last decade, this reaction has been examined by several groups and employing various transition metals like palladium, silver, gold, platinum, iridium, and mercury as catalysts.[33] Despite the fact that, this reaction occurs at rt and is tolerant towards many functional groups, there has been no report on the utilization of this metal-mediated alkynediol cycloisomerization in the synthesis of natural products having a bridged bicyclic ketal. Indeed, there was only a single report that employed the alkynediol cycloisomerization for the total synthesis of a natural product having a spiro bicyclic ketal.[33h]

One of the key issues of this alkynol cycloisomerization is the mode of cyclization i.e. *exo*-dig versus *endo*-dig. With a keen interest to extend the application of this approach in the synthesis of natural products, a systematic investigation dealing with the influence of electronic and steric factors on competitive 5-*exo*-dig versus 6-*endo*-dig and over the 6-*exo*-dig versus 7-*endo*-dig and also 5-*endo* vs 6-*exo*-dig mode of cyclizations employing

$Pd(CH_3CN)_2Cl_2$ complex as a catalyst has been carried out by our group.[33e, f, h, r] It has been shown that in case of competitive 5-*exo*-dig versus 6-*endo*-dig cyclization, the regioselectivity was influenced by the electronic nature of the substituents on the alkyne unit. In general, the presence of alkyl or aryl groups with +M groups as a substituents lead exclusively to 6-*endo* products. On the other hand, the 5-*exo*-cyclization is preferred over 6-*endo* when the substituents are electron with drawing in nature. When it comes to 5-*exo*-dig versus 6-*endo*-dig cyclization, the electronic factors have no influence and 6-*exo*-dig cyclization is favored over the 7-*endo*-dig cyclization.



Scheme 40: The regioselectivity of alkynol cycloisomerization in the synthesis of Didemniserinolipid B

Based on these results, we have recently documented the total synthesis of Cephalosporolides E/F executing the proposed 5-*exo*-dig cyclization successfully.[33h, r] Quite interestingly, when such an analogy has been extended in designing the substrate for the central 6,8-dioxa-bicyclo[3,2,1]octane core of Cyclodidemniserinol trisufate (featuring 6-*endo*-dig), the result was unexpected. The 5-*exo* product was obtained exclusively. In our revised strategy, we need to move the alkyne one carbon further and as expected the 6-*exo* is predominant and provides the requisite 6,8-dioxa-bicyclo[3,2,1]octane core of Cyclodidemniserinol trisufate.[33f] Intrigued by this observation, we have taken up a preliminary investigation to understand the acyclic stereocontrol over the regioselectivity of the alkynol cycloisomerization, with a keen interest to developing a second generation synthesis for Didemniserinolipid B.

Present work:

Didemniserinolipids A-C were isolated in 1999 by Gonzalez *et al.*.[3f] Didemniseriniolipids are characterized by their unusual serinolipid structure, which has been proposed with the help of extensive NMR analysis. In 2002, Steven Ley's group reported the synthesis of Didemniserinolipid B and revised its structure as **1** by amending the

stereochemistry of the serinol fragment. They proposed the position of the *O*-sulfate at C31.[44] Later, Burke and co-workers reported the second total synthesis of **1** by employing ketalization and ring closing metathesis as the key strategy for constructing the central bridged bicyclic core.[45]

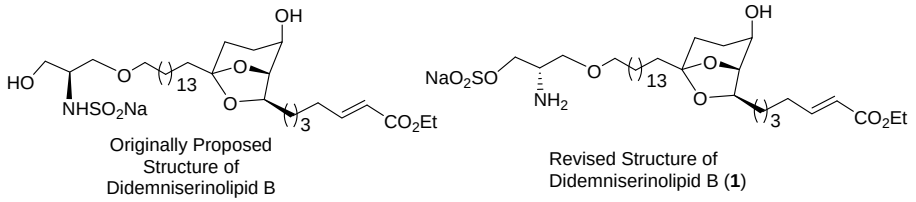


Figure 4. Proposed (1999) and revised (2002) structures of Didemniserinolipd B

Our basic idea behind this program is to provide sufficient scope for the library synthesis by functionalizing the alkyne end with a suitable functional group. Further, we want to check the stereochemical effect of the hydroxy group as well as the bulkiness of the substituent at the *β*-position to the alkyne for the Pd mediated cycloisomerization in acyclic systems. During this period, we have documented a formal total synthesis of Didemniserinolipid B (6-*endo*-dig).[33e] In the following section, we provide the complete details of our basic investigations related to the acyclic stereocontrol over the regiochemistry of these cyclizations, which has ultimately led us to arrive at the designing of the above key alkyne triol that has served as the key intermediate in our formal total synthesis of Didemniserinolipid B (**1**). The key features of our total synthesis program are depicted in the following retrosynthetic scheme.

Retrosynthesis of didemniserinolipid B (1):

The target molecule has been visualized from **2**, a key protected derivative of **1** that has been synthesized by Burke and co-workers.[45] The selective oxidation of the 1^{o}–OH in diol **3** and subsequent two-carbon Wittig homologation has been planned as the final event in the synthesis of **2**. The key bicyclic ketal intermediate **3** was planned by the cycloisomerization of the alkynol **4**. Keeping the knowledge that we acquired with the model cycloisomerization reactions of sugar alkynols in mind, the alkyne group has been positioned favorably for 6-*endo*-dig cyclization. The alkynol **4** was planned from the opening of the epoxide **5** with the alkyne **6**.

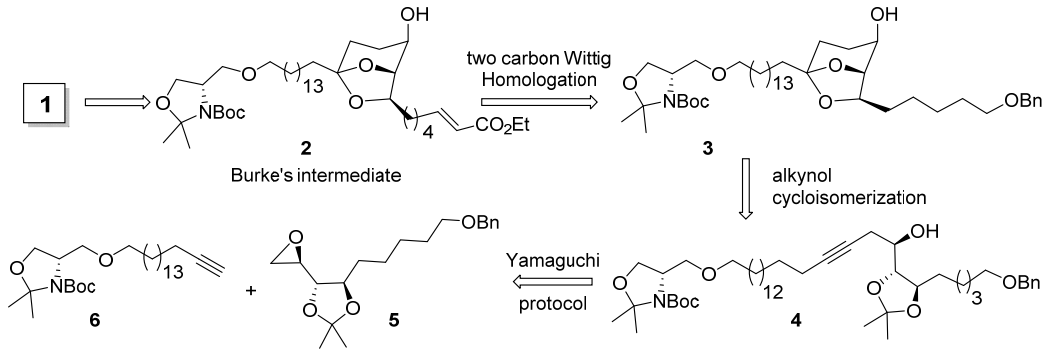


Figure 5. Key retrosynthetic disconnections for the total synthesis of Didemniserinolipid B (**1**) projecting a 6-*endo*-dig alkynol cycloisomerization for constructing the bicyclic ketal and a Yamaguchi protocol for building the key carbon framework.

After the stereochemical comparisons, epoxide **5** synthesis has been planned from known D-mannitol diacetonide **7**. The next disconnection is the ether link that combines the central lipid carbon framework and the serinol unit. Considering Williamson's etherification, the serinol **8** and the mesylate C_{17} alkynol **9**-Ms have been identified as first stage coupling partners. The synthesis of corresponding C_{17}-alkynol **9** has been envisioned from propargyl alcohol *via* alkylation with the requisite C_{14}-alkyl halide and a subsequent acetylenic Zipper reaction.[50] The synthesis of the serinol derivative **8** has been already reported from D-serine.[51]

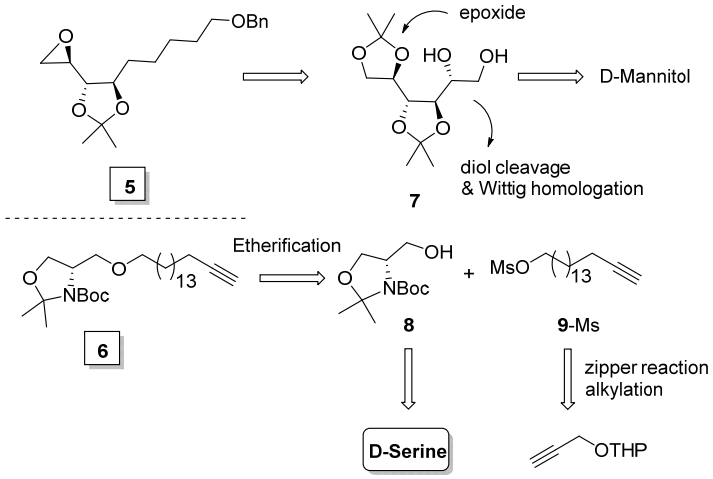


Figure 6. Planning for the synthesis of key building blocks **5** and **6**

Considering our observations in the synthesis of the central bicyclic core of Cyclodidemniserinol trisulfate, where we noticed an exclusive 5-*exo*-dig over the 6-*endo*-dig cyclization,[33f] we have initially designed the epimeric alkynols **11**, **13** and their benzoates **12**, **14** as model substrates in the context of the present total synthesis to learn about the possible acyclic stereocontrol over the regioselectivity of the alkynol-cycloisomerization. The synthesis of **13** and its benzoate **14** has planned from the epoxide **10**, which, in turn, can be

made from the penultimate intermediate that has been planned for preparing the original epoxide **5**.

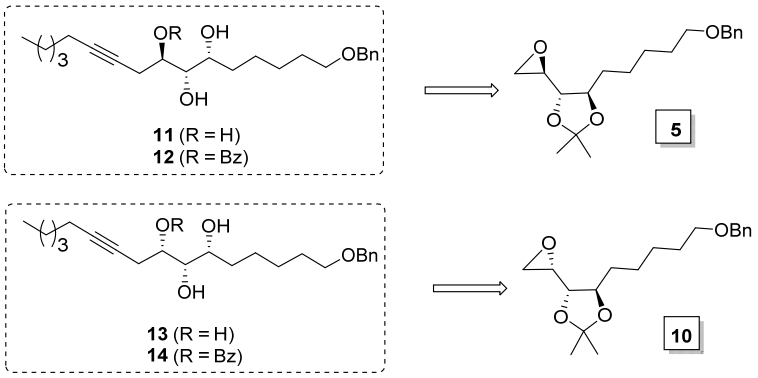
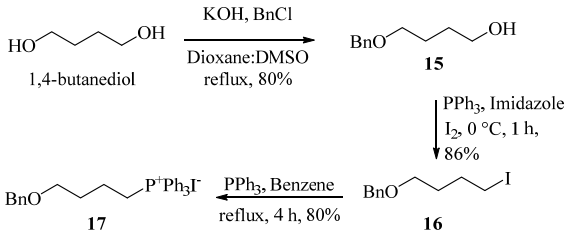


Figure 7. Model substrates designed for understanding possible acyclic stereocontrol over the regioselectivity of the alkynol-cycloisomerization.

Synthesis and cycloisomerization of model substrates:

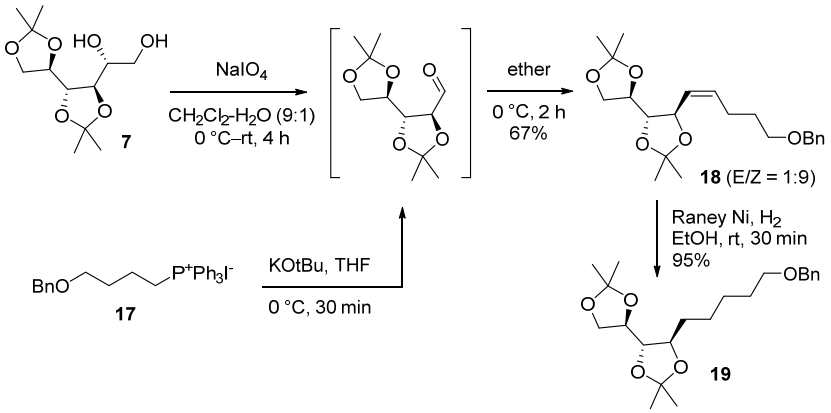
- **Synthesis of Wittig Salt 17**:

Our program in this context started with the idea of developing a route for the epimeric epoxides **5** and **10** from the known diacetonide **7**. The plan was to extend the right hand side following a sequence of diol cleavage and subsequent four-carbon Wittig homologation and hydrogenation of the resulting internal olefin. Then, selective terminal acetonide hydrolysis and conversion of either terminal or the internal –OH groups selectively to corresponding sulphonate followed by base mediated displacement should install the epoxide with either original or inverted configuration at the internal carbon of the epoxide unit. According to this plan, first we prepared the known four carbon Wittig salt **17** following the reported procedure.[53] The preparation of **17** involves the selective mono-benzylation of 1,4-butane diol and subsequent conversion of the free –OH group in the resulting **15** to the corresponding iodide **16** using triphenylphosphine, imidazole and iodine. Finally, the iodide **16** and triphenylphosphine were refluxed in benzene for 4 h to obtain **17** as a white powder. The spectral data of compound **17** was comparable with the data reported earlier.



Scheme 41: Preparation of Wittig Salt **17**

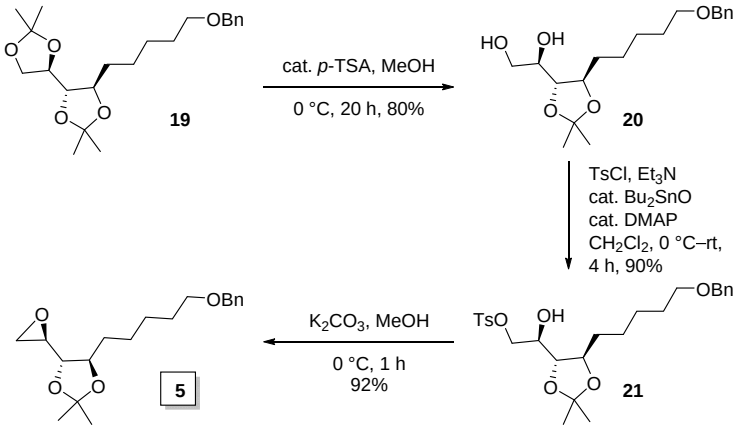
The diacetonide **7** was made from D-Mannitol following the reported two step[52] sequence – the preparation of triacetonide and selective hydrolysis of one of the terminal acetonides by employing 60% acetic acid. The oxidative cleavage of the diol in **7** was carried out using $NaIO_4$ and the intermediate aldehyde was immediately subjected for the Wittig reaction without purification. The requisite ylide was generated from the phosphonium salt **17** by using KO^{t}Bu as the base (Scheme 42) in THF. This solution was added slowly to a cooled solution of the above prepared aldehyde in ether at 0 ^oC to obtain the olefin **18** as a 9:1 *Z*/*E* mixture. In the ^1H NMR spectrum of **18**, the signal corresponding to olefinic protons of the major isomer resonated at δ 5.42 and 5.64 with a relatively small coupling constant of 10.7 Hz which indicated a *cis*-geometry for the major isomer. Five additional protons in the downfield region corresponding to the benzyl group were observed as multiplet at δ 7.27-7.35. The ^{13}C NMR spectrum of **18** showed two doublets of the olefinic carbons at 127.4 and 134.9 ppm. All other analytical data were in accordance with the assigned structure. Hydrogenation of the olefin **18** using Raney-Ni gave the saturated diacetonide **19**. The disappearance of the two olefinic protons in the downfield region and the upfield shift of the two protons to δ 1.41-1.74 in the ^1H NMR spectrum of compound **19** confirmed the reduction of the double bond. Further, in the ^{13}C NMR spectrum, two new triplets at 26.3 and 33.7 ppm corresponding to the newly formed methylene groups have been noticed.



Scheme 42: Four-carbon homologation of diacetonde **7**

The selective deprotection of the terminal acetonide in compound **19** was carried out using *p*-TSA in MeOH to obtain the diol **20**. In the ^1H NMR spectrum of compound **20**, the disappearance of the two singlets at δ 1.32 corresponding to the isopropylidene group and the corresponding quartets at 25.4 and 26.8 ppm and a singlet at 109.5 ppm in the ^{13}C NMR spectrum confirmed the removal of the acetonide group. Next, the key epoxide **5** was prepared from the diol **20** by following a sequence of selective monotosylation and base

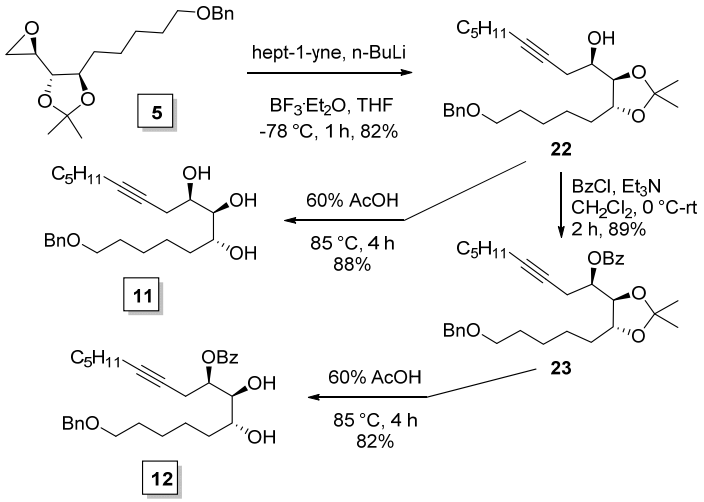
treatment. The selective tosylation 1°–OH of the diol **20** was carried out by using tosyl chloride, dibutyltinoxide and triethylamine as the base to afford **21**. In the ^{1}H NMR spectrum of **21**, the appearance of a singlet integrating for three protons at δ 2.45 corresponded to the methyl of the tosyl group. In addition, the protons of C*H*$_2$-OTs appeared at down filed at δ 4.01 and 4.25 as doublet of doublets, when compared to that in the starting diol [3.57–3.78 (m, 2H)], which clearly indicated the site of tosylation. The ^{13}C NMR spectrum showed a quartet at 21.7 ppm corresponding to the methyl of the tosyl group and two doublets at 127.6 and 129.9 ppm, each integrating for two carbons corresponding to the tosyl group along with that the carbon of *C*H$_2$-OTs is coming at 72.8 ppm as a triplet where as in diol it was came at 63.8 ppm. After confirming the structure of tosylate **21**, next it was subjected for the epoxide formation by employing K_2CO_3 in MeOH to afford the key epoxide **5** through a S_N2 displacement of the tosyl group. In the ^{1}H NMR spectrum of **5**, the characteristic oxirane protons resonated at upfield δ 2.63 (dd), 2.80 (dd), 2.94 (ddd), while a triplet and doublet at 45.1 and 51.5 ppm in the ^{13}C NMR spectrum suggesting the formation of the epoxide (Scheme 43).



Scheme 43: Synthesis of the epoxide fragment **5**

After having established the route for the synthesis of the key coupling partner epoxide **5**, we next proceeded to open the epoxide through the Yamaguchi protocol [54] and the preparation of model substrates **11** and **12**. Thus, the opening of epoxide **5** with the lithiated 1-heptyne under Yamaguchi conditions gave the homopropargylic alcohol **22**. The ^{1}H NMR spectrum of **22** showed the propargylic protons as multiplets at δ 2.11–2.16 and 2.46–2.50 (each integrating for two protons). The three protons of the C*H*$_3$ group have resonated at δ 0.9 as triplet. The ^{13}C NMR spectrum showed the presence of two singlets at 74.9 and 84.0 ppm corresponding to the acetylenic carbon and one quartet at 14.0 ppm for the *C*H$_3$ group. The IR spectrum showed the C≡C stretching at 2100 cm^{-1}. The alkynol **22** was protected as its

benzoate **23** by using benzoyl chloride and triethyl amine. The ^{1}H NMR spectrum showed the presence of five additional protons in the down field region corresponding to the benzoyl group and the proton of C*H*OBz was seen to resonate at δ 5.23 as a doublet of doublet. The ^{13}C NMR spectrum showed the presence of the carbonyl carbon at 165.6 ppm as a singlet as well as the carbon of *C*HOBz appeared at 72.9 as a doublet along with four peaks at aromatic region clearly indicate the presence of benzoyl group. The IR spectrum showed the C=O stretching at 1725 cm^{-1} corresponding to the carbonyl carbon of the benzoyl group (Scheme 44).



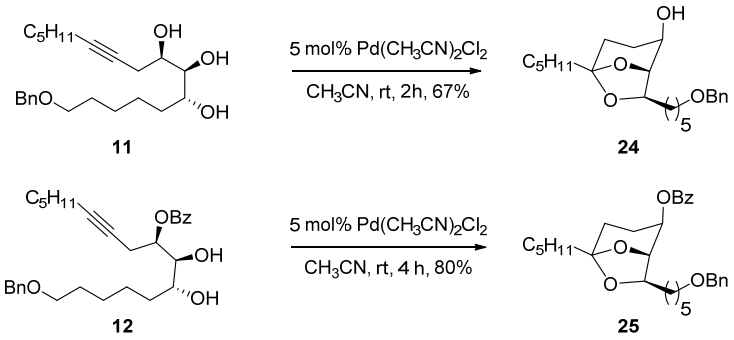
Scheme 44. Synthesis of model alkynol substrates **11** and **12**

The homopropargyl alcohol **22** was hydrolyzed by using 60% acetic acid in water to afford the triol **11**. In the ^{1}H NMR spectrum of **11**, the isopropylidene group C*H*$_3$ peaks at δ 1.35 and 1.38 were seen to disappear. In the ^{13}C NMR spectrum, quartets at 27.1 and 27.5 ppm and a singlet at 108.6 ppm corresponding to the isopropylidene group were seen to disappear. Similarly the benzoate **23** also hydrolysed by using 60% acetic acid in water to obtain the alkynediol **12**. The constitution of compound **12** was established with the help of spectral and analytical data. In the ^{1}H/^{13}C NMR spectra of **12**, peaks corresponding to the isopropylidene group were seen to disappear and that of the benzoate group are intact. The IR spectrum showed the O–H stretching at 3443 cm^{-1} and a C=O stretching at 1721 cm^{-1}, confirming the structure.

- **Mode of cyclization of model substrates 11-14**:

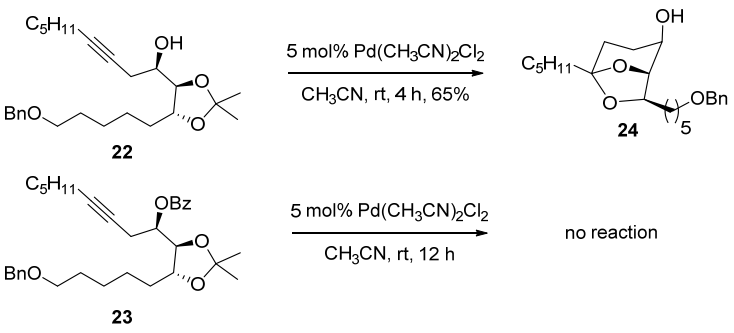
After having the key alkynols **11** and **12**, the stage was set for their cyclization by employing $Pd(CH_3CN)_2Cl_2$ as the catalyst. When employing $Pd(CH_3CN)_2Cl_2$ as the catalyst in acetonitrile, the cyclization of substrate **11** advanced smoothly with the disappearance of

the starting compound within 2 h and afforded the single product **24** exclusively. The constitution of the bicyclic ketal unit present in **24** was investigated with the help of spectral data analysis. In the ^{1}H NMR spectrum of **24**, the three characteristic methine protons of the ketal are present at δ 3.90, 3.93 and 4.19. The C*H*$_2$-C*H*$_2$ unit present in the bicyclic ketal was resonated separately from the rest of the alkane-H as multiplets at down field. The presence of the characteristic ketal carbon at 108.5 ppm in the ^{13}C NMR spectrum (Scheme 45) of compound **24** and two CH_2 s as triplets separately in the down field at 35.2 and 36.7 ppm indicated the presence of a [3.2.1] bicyclic ketal. The IR spectrum showed the O–H stretching at 3444 cm^{-1}, confirming the structure. Similarly, we performed the palladium mediated cyclization reaction for the benzoate protected alkynol **12**.



Scheme 45: Pd(II)-Catalyzed cycloisomerization of the alkynols **11** and **12**

In case of the benzoyl protected alkynediol **12**, the reaction advanced smoothly with the disappearance of the starting compound within 4 h and provided the [3.2.1]-bicyclic ketal unit. In the ^{1}H NMR spectrum of **25**, the three characteristic methine protons of the ketal are present at δ 3.76, 4.66 and 5.08. As expected, the C*H*$_2$-C*H*$_2$ unit of the bicyclic ketal ring was seen to resonate separately (as multiplets at δ 1.8–1.85 and 1.86–1.90) from the rest of the pendant alkane–CH_2 groups. Coming to the ^{13}C NMR spectrum of compound **25**, the presence of the characteristic ketal carbon at 110.7 ppm in the (Scheme 45) and of two well separated CH_2 triplets in the down field at 34.5 and 32.0 ppm, clearly indicated the presence of a [3.2.1] bicyclic ketal.

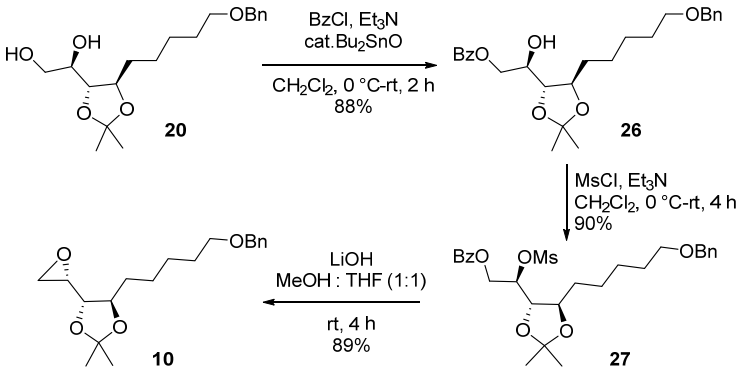


Scheme 46: Pd(II)-Catalyzed cycloisomerization of the acetonides **22** and **23**

Considering our previous experience on the cycloisomerization of sugar derived alkynols, where we noticed the participation of acetonide protected diols in the cycloisomerization, for curiosity, the acetonides **22** and **23** were subjected for the cycloisomerization under standard conditions. Quite interestingly, in case of **22**, the cycloisomerization was facile and the bicyclic ketal **24** was obtained in good yields. Interestingly, under these conditions, the benzoate **23** was intact even after the contents were kept for 24 hours.

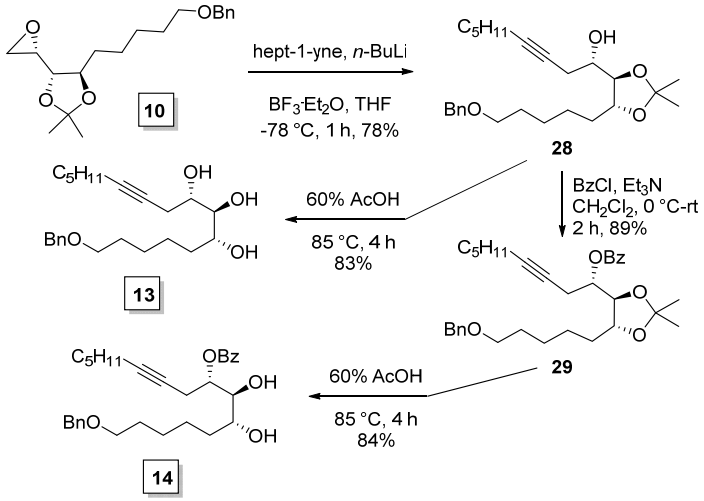
Next, we proceeded for the synthesis of the other set of model substrates **13** and **14** that we have designed to understand the acyclic stereocontrol over the cycloisomerization. The key epimeric epoxide **10** was prepared from **20** following a three-step sequence. The selective 1^{o}–OH benzoylation was performed by using benzoylchloride, dibutyltinoxide and triethylamine as the base in dichloromethane to afford **26**. In the ^{1}H NMR spectrum of compound **26**, the newly added benzoate protons resonated at δ 7.34–7.79 (m, 5H). In addition, the peaks corresponding to the CH_2-OBz were appeared at down filed at δ 4.39 and 4.58 as doublet of doublets, when compared to that in the compound **20** [3.57–3.78 (m, 2H)], which clearly indicated the site of benzoylation. The ^{13}C NMR spectrum showed the presence of a singlet at 167.0 ppm corresponding to the carbonyl carbon of the Bz group and the carbon of CH$_2$-OBz is coming at 66.8 ppm as a triplet (Scheme 47).

Next, the mesylation of compound **26** was carried out by using methanesulfonyl chloride and triethylamine as base to procure compound **27**. Subsequnetly, compound **27** was subjected for the hydrolysis of the benzoate group employing lithium hydroxide to obtain the epoxide **10** in very good yields. As expected, the oxirane protons resonated at up field as multiplets at δ 2.69 (dd), 2.79 (dd), 2.99 (ddd) in the ^{1}H NMR spectrum and also the corresponding carbons appeared shifted to up field (as triplet and doublet at 43.9 and 51.4 ppm respectively) in the ^{13}C NMR spectrum (Scheme 47).



Scheme 47: Synthesis of epoxide **10**

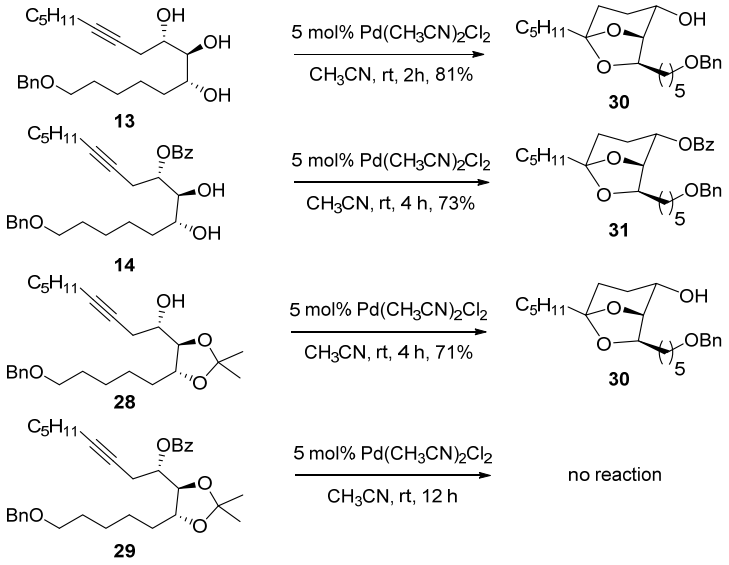
We followed a similar sequence that was employed in the preparation of model substrates **11** and **12** in order to prepare the other two model alkynols **13** and **14** from the epoxide **10**. First, the epoxide was opened with the lithiated 1-heptyne to obtain the homopropargylic alcohol **28**.



Scheme 48: Synthesis of model alkynols **13** and **14**.

The ^{1}H NMR spectrum of **28** showed the propargylic protons as triplet of triplet and multiplets at δ 2.14 and 2.38–2.50 (each integrating for two protons) respectively. The three protons of the CH_3 group were seen to resonate at δ 0.9 as triplet. In the ^{13}C NMR spectrum of compound **28**, the presence of two singlets at 75.5 and 83.0 ppm corresponding to the acetylenic carbons and one quartet at 14.0 ppm for CH_3 group are in support of the constitution of the product. The free –OH group in alkynol **28** was protected as its benzoate **29** by using benzoyl chloride and triethyl amine. The structure of the compound **29** was established with the help of spectral and analytical data. Next, the acetonide group present in the compound **28** was hydrolyzed by using 60% acetic acid in water to afford the alkyne triol **13**. Under similar conditions, the hydrolysis of compound **29** proceeded smoothly and provided the alkynediol **14**.

Next, the cycloisomerization of the alkynols **13** and **14**, and also of their starting acetonides **28** and **29** respectively, was examined under the established conditions employing $Pd(CH_3CN)_2Cl_2$ as the catalyst. With both model alkynols **13** and **14**, the reactions advanced smoothly with the disappearance of the starting compound within 2 – 4 h and afforded the corresponding [3.2.1]-bicyclicketals **30** and **31** respectively as single products in very good yields. As we had noticed earlier, the cyclization of acetonide **28** was also facile and provided **30** in good yield. Table 1 shows the comparative ^{1}H and ^{13}C NMR chemicals shifts selected protons of the ketals **24**/**25** and **30**/**31**.



Scheme 49: Pd(II)-catalyzed cycloisomerization of the alkynol **28** and alkyne diols **13**, **14**.

Thus, the model studies employing the model substrates **11** – **14** clearly indicated that the cycloisomerization proceeded with a complete 6-*endo*-dig mode of selectivity indicating that the stereochemistry as well as bulkiness of the substituent at the *β*-position to the alkyne seems to not be having much influence over the regioselectivity of the cycloisomerization. The facile cyclization of acetonides **22** and **28** having the free alcohol *β*-to the alkyne and no reaction of the benzoates **23** and **29** under similar reaction conditions indicates that the acetonide hydrolysis might be facilitated by the presence of an adjacent free-OH.

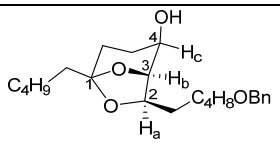
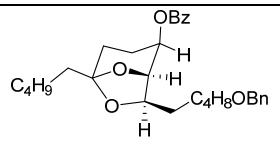
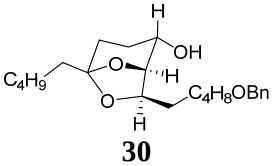
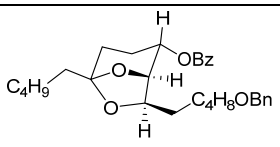
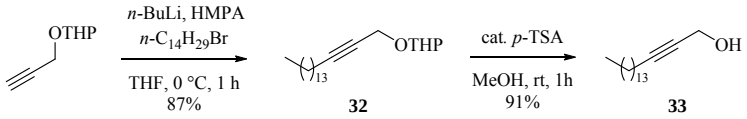
Compound	H_a–H_c	C_1–C_4
 **24**	3.90 (ddd, *J* = 5.5, 9.6, 18.2 Hz, 1H), 4.19 (dd, *J* = 5.6, 6.7 Hz, 1H), 3.93 (m, 1H)	66.5 (d), 80.8 (d), 75.7 (d), 108.5 (s)
 **25**	5.08 (ddd, *J* = 5.5, 7.3, 12.8 Hz,1H), 4.66 (d, *J* = 4.6, 1H), 3.76 (d, *J* = 5.4 Hz, 1H)	74.3 (d), 81.4 (d), 77.2 (d), 110.7 (s)
 **30**	3.90 (m, 1H), 4.20 (dd, *J* = 5.5, 7.3 Hz,1H), 3.94 (dd, *J* = 4.5, 7.1 Hz, 1H),	66.6 (d), 80.8 (d), 75.7 (d), 108.5 (s)
 **31**	5.08 (dt, *J* = 5.6, 7.1, 11.5 Hz, 1H), 4.66 (d, *J* = 4.4 Hz, 1H), 3.76 (d, *J* = 5.3, Hz, 1H)	74.3 (d), 81.4 (d), 77.2 (d), 110.7 (s)

Table 1: Comparative ^{1}H and ^{13}C NMR chemicals shift of cyclized ketal.

After having examined the regioselectivity of the key cycloisomerization reaction that was planned in our retrosynthetic scheme for the didemniserinolipid B, this information has been used in our group to arrive at the Burke's intermediate[45] by simply replacing the heptyne with a C_{17}-alkynol and adding the serinol unit at the final stages. However, one of the bottlenecks in this approach was the timing of this serinol coupling in the sequence as well as the difficulties that we faced for the optimization of this coupling. This has taken a substantial time as it needed repeated scale-up of a quite lengthy linear sequence. Considering this, in order to make the synthetic scheme more convergent, to provide the step-economy and to demonstrate the substrate flexibility, we have devised an alternate strategy (Fig. 5), featuring the serinol coupling with the C_{17}-alkynol followed by alkyne addition to the epoxide **5** and subsequent cycloisomerization of the resulting acetonide **4**. This approach thus should avoid the several intermediate protection and deprotection events. However, the cycloisomerization of **4** will be a challenging proposition as the hydrolysis of the other acetonide (of aminol unit) is going to be a potential side reaction that can possibly poison the electrophilic Pd-complex.

- **Synthesis of C17-alkynol fragment 9**:

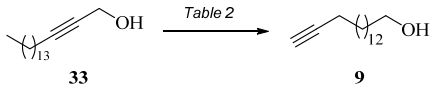
Our efforts in this direction started with the preparation of the C_{17}-alkynol **9** and its coupling with the serinol unit **8**. We have established Zipper reaction[50] as the reliable tool for the synthesis of **9**. The synthesis of **9** started with the alkylation of commercially available THP ether of propargyl alcohol, tetradecyl bromide using *n*-butyl lithium as a base to afford the substituted alkyne **32**. In the ^{1}H NMR spectrum of compound **32**, the propargylic protons of the aliphatic end resonated at δ 2.11–2.22 as multiplet while those on the THP end resonated at δ 4.14 and 4.25 as doublet of triplet. The acetylenic carbons resonated at 75.8 and 86.6 ppm as singlets in the ^{13}C NMR spectrum. The C≡C stretching was observed at 2100 cm^{-1} in the IR spectrum. The deprotection of the THP ether in **32** was effected using *p*-TSA and methanol to afford the alkylated propargyl alcohol **33**. In the ^{1}H NMR spectrum of compound **33**, the absence of triplet at δ 4.79 and of eight methylene protons in the up-field region of δ 1.46–1.58 corresponding to the THP ring confirmed the deprotection at the same time one triplet of triplet resonating at δ 2.18 for two protons, corresponds to CH_2OH. Also in the ^{13}C NMR spectrum of compound **33**, the absence of doublet at 96.4 ppm corresponding to the hemiacetal carbon of THP ring supported this and the carbon of *C*H$_2$OH appeared at upfield as a triplet at 51.32 ppm when compared to that in the compound **32** (54.55 ppm). The IR spectrum of **33** showed the O–H stretching at 3539 cm^{-1} (Scheme 50).



Scheme 50: Synthesis of Heptadec-2-yn-1-ol

- **Zipper reaction of Heptadec-2-yn-1-ol (33)**:

The isomerization of an internal alkyne to a terminal alkyne in the presence of a base is long known as the acetylenic zipper reaction.[50] After exploring a variety of bases and reaction conditions (Table 2), we concluded that the isomerization of alcohol **33** could be conducted successfully by employing lithium metal in combination with potassium butoxide in aminopropylamine as the solvent/base. The key alkynol **9** was obtained in 79% yield. The ^{1}H and ^{13}C NMR spectra of **9** evidenced the presence of terminal acetylene. For example, in the ^{1}H spectrum of compound **9**, the acetylenic–H resonated as a triplet at δ1.88 and the proapargylic protons resonated as dt at δ 2.16 ppm. The acetylenic carbons resonated as a doublet and a singlet at 68.2 and 84.6 ppm respectively in the ^{13}C NMR spectrum of compound **9**. The IR spectrum of compound **9** showed the O–H stretching at 3308 cm^{-1}.



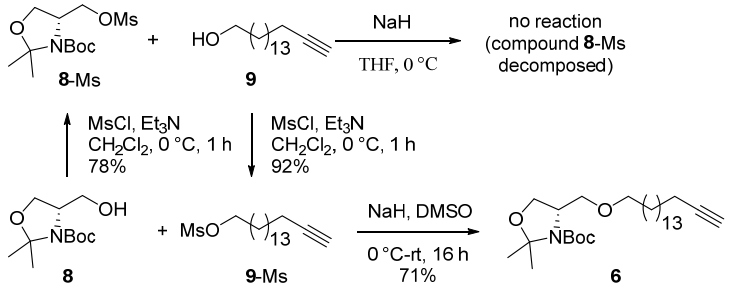
S. No.	Reaction conditions	Results obtained
1	KO^{t}Bu, DMSO, rt	Starting material recovered
2	Na, liq. NH_3, -78 °C	Starting material recovered
3	Li, liq. NH_3, -78 °C	Starting material recovered
4	KO^{t}Bu, DMSO, 80 °C	Starting material recovered
5	KH, 1,3diamino-propane. 0 ^{o}C - rt	< 5% conversion
6	Li, KO^{t}Bu, 1,3-diamino-propane, rt	Isomerization with 79% yield

Table 2. Conditions explored for the zipper reaction

- **Execution of the Serinol Coupling Event**:

After establishing the zipper reaction, our attention turned on the execution of the coupling of the appropriately protected serinol derivative **8** with alkynol. The known serinol derivative **8** required for the etherification was prepared from D-serine in 4 steps according to the literature procedures (Scheme 51).[51] The etherification of the serinol with the C_{17}-alkynol **9** was attempted in a number of ways. Initially, the etherification of the alkynol **9** was

attempted with the mesylate of the serinol **8**, but it did not result in the desired product. During this period, Burke's group [45] reported their synthesis of Didemniserinolipid B where it was shown that the coupling is effective with the mesylate of the alkynol and the serinol **8** using sodium hydride as the base, and importantly DMSO as solvent at 0 ^{o}C. Encouraged by this finding, we prepared the alkynol mesylated **9**-Ms and examined its coupling with serinol **8** following Burke's procedure. It needed substantial optimization to provide reproducible yields. The key to success was the slow addition of mesylate **9**-Ms to a solution of serinol **8** in DMSO at 0 °C or a little below during 4 h and afterwards, allowing the reaction to stir at rt for an additional 12 h. Under these conditions, the requisite building block **6** was obtained in 71% yield.



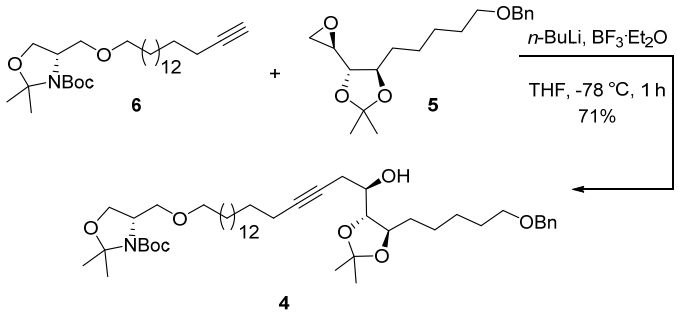
Scheme 51: Coupling of serinol with the mesylate of C_{17} alkynol.

In the ^{1}H NMR spectrum of compound **6**, the characteristic peaks of both the units – the alkyne triplet at δ 1.92 with coupling constant 2.7 Hz and the ^{t}Bu unit of the Boc group at δ 1.45 integrating for nine protons, two methyl singlets of acetonide at δ 1.50 and 1.55 have been seen to resonate at the expected positions. As expected, many of the singlets in the ^{13}C NMR spectrum of compound **6** are doubled due to the restricted rotation of the N–Boc group. The appearance of two triplets at 65.4, 65.7 (2t, 1C), 69.3, 70.1 (2t, 1C) ppm and one doublet at 56.3, 56.5 (2d, 1C) ppm of the serinol part and of the carbonyl carbon of the Boc group as a singlet at 151.7, 152.2 (2s, 1C) ppm, and of acetylenic carbons as doublet and singlet at 68.1 and 84.5 ppm respectively, in the ^{13}C NMR spectrum of **6** confirmed the etherification. Further, the IR spectrum showed the C=O stretching at 1694 cm^{-1}. All other analytical data were in total agreement with the assigned structure (Scheme 51).

- **Coupling of key fragments 5 and 6 and cycloisomerization:**

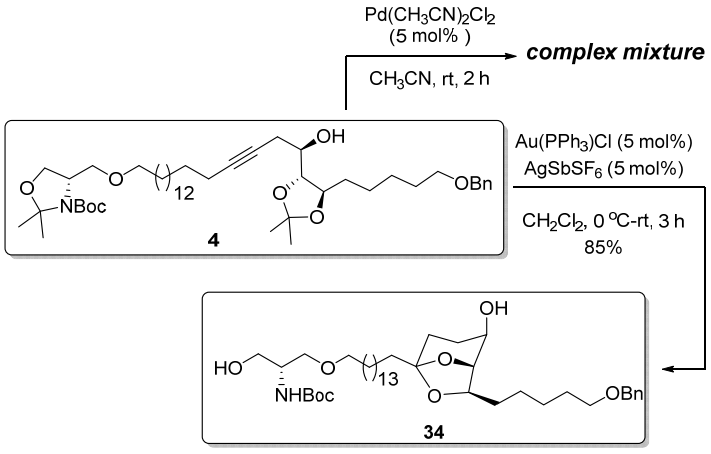
Having the key building block **6** in hand, the stage was now set for its coupling with the previously synthesized epoxide **5** and the cycloisomerization of the resulting alkynol **4**. The Yamaguchi coupling of the oxirane **5** with the alkyne-ether **6** proceeded smoothly under the previously optimized conditions and gave the key intermediate **4** in very good yields. The

constitution of the compound **4** was established with the help of spectral and analytical data. For example, in the ^{1}H NMR spectrum of compound **4**, two sets of propargylic protons appeared as triplet of triplet and multiplets at δ 2.14 and 2.43-2.48 (each integrating for two protons) respectively. The ^{13}C NMR spectrum showed the presence of two singlets at 74.9 and 83.9 ppm corresponding to the acetylene carbons.



Scheme 52: Key coupling event under Yamaguchi conditions

After having the key alkynol, **4** now the stage was set for executing the key complexity transform to build the requiste [3.2.1]-bicyclic ketal unit by employing the Pd-mediated alkynol cycloisomerization reaction. This alkynol cycloisomerization needs a special mention and also needed substantial catalyst optimization. When we employed $Pd(CH_3CN)_2Cl_2$ as the catalyst in acetonitrile, the reaction advanced smoothly with the disappearance of the starting compound within 2 h and provided a mixture of products. The LCMS analysis of the resulting complex mixture revealed the formation of the requisite bicyclicketals **2**, the corresponding ketone –the product resulting from the deprotection of the acetonide group present in the serinol unit. Even the freshly prepared catalyst and properly dried acetonitrile could not affect the yield. $Pd(PhCN)_2Cl_2$ was found to be ineffective for this transformation.

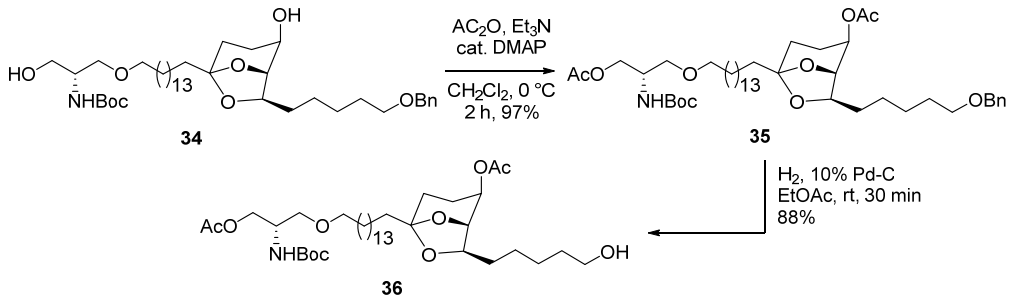


Scheme 53: The key cycloisomerization of the alkynol **4**

Having encountered failures in the Pd-catalyzed cycloisomerization, we assumed that the presence of the nitrogen group of serine part might be creating the problem in the cyclization reaction. The catalytic activity of palladium decreases as soon as nitrogen coordinates to the [Pd] complex. Hence, we oriented to the other electrophilic metal catalysts like Au which have very less affinity to form a complex with nitrogen compared to oxygen or the triple bond. Various electrophilic [Au]-complexes such as $AuCl_3$, $AuBr_3$, and $Au(PPh_3)Cl$ have been screened for the cycloisomerization of **4**.[55] To this end, the best results were obtained when $Au(PPh_3)Cl$ (5 mol %) was employed in combination with $AgSbSF_6$ (5 mol %) in dichloromethane. With this catalyst combination, the cycloisomerization of **4** gave exclusively one compound **34** in 85% yields. The analysis of its spectral and analytical data revealed that the compound **34** does not possess any acetonide group [55c] and is resulting from the requisite cycloisomerization followed by the deprotection of serinol acetonide. For example, in the ^{1}H NMR spectrum of **34**, the three characteristic methine protons of the ketal are present at δ 3.53, 3.65 and 3.85. The CH_2–CH_2 unit present in the bicyclic ketal was seen to resonate separately from the rest of the alkane-H as multiplets at down field. Two singlet peaks at δ 1.51 and 1.55 due to the isopropylidene group disappeared and in the ^{13}C NMR spectrum, quartets at 23.0 and 27.1 ppm and a singlet at 93.3, 93.7 (2s, 1C) ppm corresponding to the isopropylidene group were absent. The presence of the characteristic ketal carbon at 109.5 ppm in the ^{13}C NMR spectrum and two *C*H_2 s as triplets separately in the down field at 35.2 and 37.5 ppm indicated the presence of a [3.2.1] bicyclic ketal.

Having successfully demonstrated the feasibility of the key cycloisomerization on the originally planned substrate **4** with the desired regioselectivity, we next proceeded for the two carbon extension on the other side of the ketal. Our initial plan was to synthesize the penultimate intermediate **38** that has been reported by Ley in their total synthesis. This exercise was started with the protection of the free hydroxyl groups in compound **34** as their acetates by using acetic anhydride and triethyl amine in dichloromethane to obtain the diacetate **35**. In the ^{1}H NMR spectrum of **35**, the singlets of two acetyl groups resonated at δ 2.03 and 2.09 (each integrating for three protons) respectively, at the same time the proton of ring C*H*OAc resonating at δ 4.66 as a triplet and the two protons of remaining C*H*OAc are coming at 4.15 as a doublet of doublet. The ^{13}C NMR spectrum showed the presence of two singlets at 170.8 ppm corresponding to the two acetyl groups as well as two carbons of *C*HOAc coming at 63.7 (t) and 68.3 (d) respectively. Next, the compound **35** was subjected to debenzylation by using 10% Pd-C in ethyl acetate to afford the alcohol **36**. The absence of 5 aromatic protons and the characteristic benzylic protons at δ 4.47 in the ^{1}H NMR spectrum

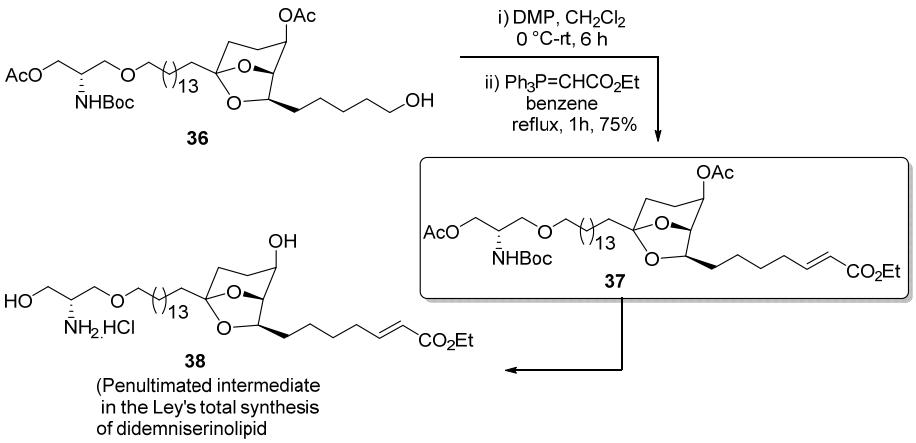
of **36** and the absence of four doublets and a singlet in the range of 127-138 ppm in its ^{13}C NMR spectrum confirmed the debenzylation.



Scheme 54: Synthesis of requisite alcohol

- **Wittig homologation of compound 36 and 40**:

The resulting primary alcohol in compound **36** was oxidized to aldehyde by using DMP as the oxidizing agent.[56] The aldehyde was used as such for the next step without further purification. The Wittig olefination of the aldehyde using the stable ylide $Ph_3P{=}CHCO_2Et$ in refluxing benzene afforded the desired α,β-unsaturated ester **37**. In the ^1H NMR spectrum of compound **37**, the two olefinic protons resonated at δ 5.80 (d) and 6.93 (dt) with a coupling constant of 15.6 Hz which clearly indicated the presence of a *trans* double bond. Also, the characteristic quartet corresponding methylene group of the ethyl ester was seen to appear at δ 4.17. In the ^{13}C NMR spectrum of compound **37**, the peaks corresponding to the olefinic carbons resonated as doublets at 121.5 and 148.9 ppm and of the ester carbonyl resonated at 166.7 ppm.

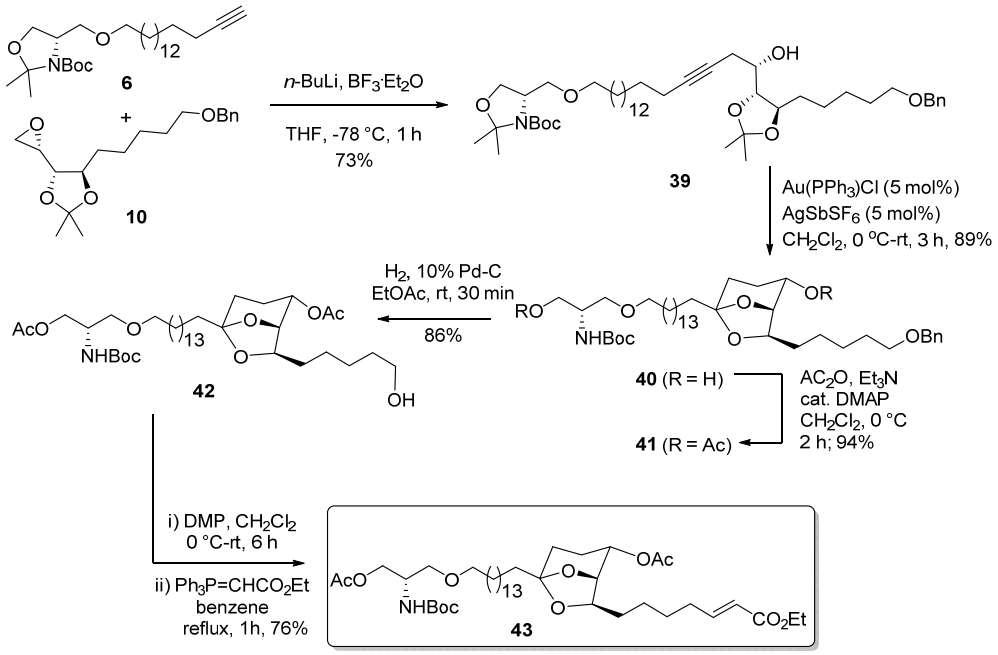


Scheme 55: Wittig homologation of compound **36** and attempted synthesis of Ley's intermediate **38**

Next we examined the deprotection of the acetate and Boc groups present in the compound **37** by employing various Lewis acids to arrive at the hydrochloride **38** that has

been used as the penultimate intermediate in the total synthesis of didemniserinolipid B by Ley and co-workers. However, the deacetylation of the compound **37** has turned out to be a difficult proposition.

As a part of this program, the synthesis of the *epi*-Didemniserinolipid B has been attempted in parallel by employing the epimeric epoxide **10** that we have prepared during our model studies. As shown in Scheme 56, the coupling of epoxide **10** with **6** proceeded smoothly under the established conditions and provided the alkynol **39**. The cyclo-isomerization of alkynol **39** was carried out with the Au-complex to obtain the bicyclic ketal **40** resulting from cyclization/serinol acetonide hydrolysis and was obtained in very good yields. Compound **40** was converted to the corresponding diacetate **41** by treating it with acetic anhydride in pyridine.

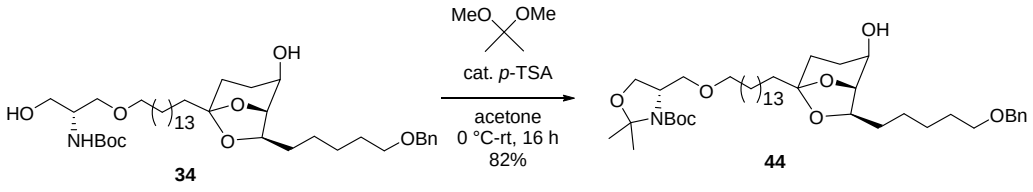


Scheme 56: Towards the synthesis of *epi*-Didemniserinolipid B

The resulting compound **41** was subjected to debenzylation by using Pd-C in methanol to afford the alcohol **42**. Subsequently, the two carbon homologation of **42** was carried out following a sequence of oxidation of the primary alcohol by using DMP and treatment of the resulting aldehyde with stable ylide $Ph_3P{=}CHCO_2Et$ in refluxing benzene to obtain the desired *α,β*-unsaturated ester **43**. The ^1H NMR spectrum revealed the presence of the olefinic protons at δ 5.80 (d) and 6.93 (dt) with a coupling constant of 15.7 Hz, indicative of a trans double bond. Also, the quartet at δ 4.17 was suggestive of the methylene group of the ethyl ester. The ^{13}C NMR spectrum showed doublets at 121.5 and 148.9 ppm corresponding to the olefinic carbons and the ester carbonyl resonated at 166.7 ppm. The IR

spectrum showed the C=O stretching at 1742 cm^{-1} for the ester. As it was noticed with **37**, even in case of **43**, the deacetylation was turned out to be a difficult proposition.

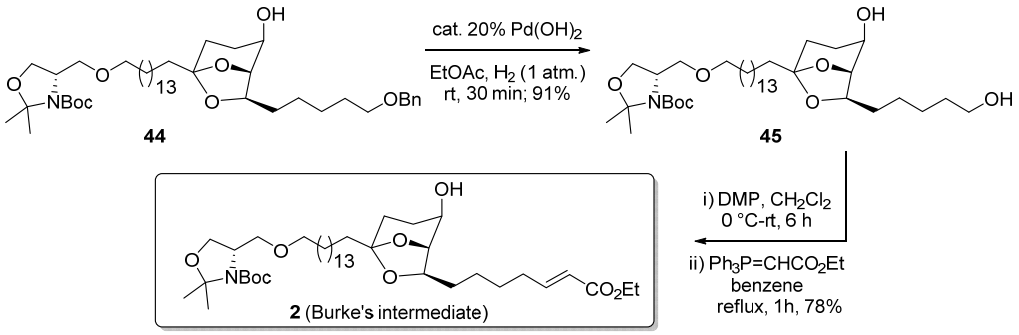
Having met with difficulties in the deacetylation of the advanced intermediates **37** and **43**, to arrive at the penultimate compound that was reported in the total synthesis of didemniserinolipid B by Ley's group, we revised our strategy to obtain the originally planned Burke's intermediate **2**. In this context, the intermediate ketal **34** obtained from the Au-catalyzed cycloisomerization was subjected for the acetonide protection by using dimethoxy propane and *p*-TSA (cat.) in acetone to obtain compound **44**. The ^{1}H NMR spectrum of **44** showed singlet peaks at δ 1.51 and 1.55 integrating for three protons each indicative of the acetonide unit of the serine part. In the ^{13}C NMR spectrum the acetonide the quaternary carbon resonated as a singlet at 93.2, 93.7 (2s, 1C) and two methyl groups were identified at 23.1, 24.4 (2q, 1C) and 26.7, 27.5 (2q, 1C) ppm respectively and confirmed the acetonide protection.



Scheme 57: Acetonide protection of compound **34**

The compound **44** was subjected to debenzylation by using $Pd(OH)_2$ in methanol to afford the alcohol **45**. The absence of five aromatic protons and the characteristic benzylic protons at δ 4.49 in the ^{1}H NMR spectrum of compound **45**, and of five aromatic carbon doublets and a singlet in the range of 127.5–138.8 ppm in its ^{13}C NMR spectrum confirmed the debenzylation. The primary alcohol was oxidized to the aldehyde by using DMP as the oxidizing agent. The aldehyde was used as such for the next step without further purification. The Wittig olefination of the aldehyde using the stable ylide $Ph_3P{=}CHCO_2Et$ in refluxing benzene afforded the desired α,β-unsaturated ester **2** – Burke's intermediate. The ^{1}H NMR spectrum revealed the presence of the olefinic protons at δ 5.80 (d) and 6.93 (dt) with a coupling constant of 15.7 Hz indicative of a *trans* double bond. Also, the quartet at δ 4.17 was suggestive of the methylene group of the ethyl ester. The ^{13}C NMR spectrum showed doublets at 121.5 and 148.9 ppm corresponding to the olefinic carbons and the ester carbonyl resonated at 166.7 ppm. The IR spectrum showed the C=O stretching at 1732 cm^{-1} for the ester. All other data was in total agreement with the reported values by the Burke group. The

specific rotation of the synthetic sample was found to be $[\alpha]_D^{25}$: +26.6 (c 0.4, $CHCl_3$), $[\alpha]_D^{25}$: +24.6 (*c* 0.5, $CHCl_3$),[33f] $[\alpha]_D^{25}$: +37.6 (*c* 0.98, $CHCl_3$).[45]

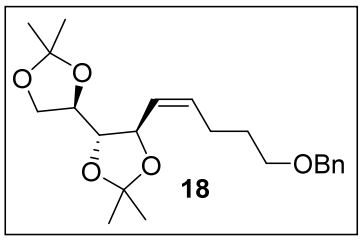


Scheme 58: Formal synthesis of Didemniserinolipid B (**1**)

To conclude, a formal total synthesis of didemniserinolipid B was developed by employing a regioselective gold-mediated 6-*endo*-dig cycloisomerization. The route we developed for the key alkyne diol (containing 30 out of 32 carbons of the complete framework) is synthesized in a highly modular fashion, featuring the risky serinol coupling event with the easily accessible C_{17}-alkynol and followed by coupling with the epoxide that has been synthesized in parallel from D-mannitol. The interesting feature of our approach is the [Au]-mediated cycloisomerization of an acetonide protected alkynediol unit that we executed. This has avoided several late stage protection deprotection events. Independent routes for the synthesis of both Ley's and Burke's intermediates have been explored from the resulting bicyclic ketal. The attempted synthesis of Ley's intermediate was not successful as the final deprotection turned out to be problematic. However, the Burke's intermediate has been successfully synthesized thus conclusively ending this exercise as a formal total synthesis of didemniserinolipid B.

EXPERIMENTAL & DATA

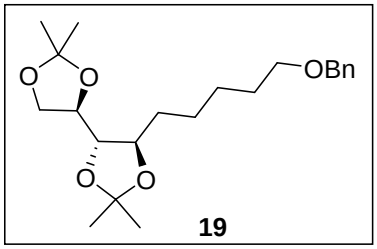
(4*S*,4'*R*,5*R*)-5-((*Z*)-5-(Benzyloxy)pent-1-enyl)-2,2,2',2'-tetramethyl-4,4'-bi(1,3-dioxolane) (18)



18

At 0 °C, a solution of the aldehyde (4.0 g, 17.4 mmol) in ether (20 mL) was treated with a solution of the ylide **17** [generated from $BnO(CH_2)_4P^+Ph_3I^-$ (28.8 g, 52.2 mmol) using KO^{t}Bu (4.9 g, 43.5 mmol) in THF (50 mL) at 0 °C] and stirred for 30 min. The reaction mixture was quenched with saturated NH_4Cl (25 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (2 x 25 mL). The combined organic layer was washed with brine, dried (Na_2SO_4) and concentrated. Purification of the crude product by column chromatography (90:10 petroleum ether/EtOAc) gave **18** (4.4 g, 67%) as colorless syrup: R_f (10% EtOAc/petroleum ether) 0.5; $[\alpha]^{25}_D$: +10.7 (*c* 1.3, $CHCl_3$); IR ($CHCl_3$) *v*: 2986, 1448, 1243, 1048, 847, 634, 467 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 1.31 (s, 3H), 1.36 (s, 3H), 1.38 (s, 3H), 1.41 (s, 3H), 1.67–1.75 (m, 2H), 2.22–2.31 (m, 2H), 3.48 (t, *J* = 6.4 Hz, 2H), 3.70 (dd, *J* = 6.4, 7.6 Hz, 1H), 3.89–3.95 (m, 1H), 4.01–4.10 (m, 2H), 4.50 (s, 2H), 4.68 (ddd, *J* = 0.7, 7.6, 8.7 Hz, 1H), 5.42 (tt, *J* = 1.5, 10.7 Hz, 1H), 5.64 (tt, *J* = 7.7, 10.9 Hz, 1H), 7.27–7.35 (m, 5H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 24.4 (t), 25.2 (q), 26.6 (q), 26.9 (q), 27.2 (q), 29.3 (t), 66.8 (t), 69.5 (t), 72.8 (t), 74.9 (d), 76.3 (d), 81.1 (d), 109.2 (s), 109.4 (s), 127.4 (d, 2C), 127.5 (d, 2C), 128.3 (d, 2C), 134.9 (d), 138.5 (s) ppm; MS (ESI) m/z = 399 $[M+Na]^+$; HRMS (ESI) calcd for $C_{22}H_{32}O_5$ $[M+Na]^+$ 399.2147, found 399.2148.

(4*S*,4'*R*,5*R*)-5-(5-(Benzyloxy)pentyl)-2,2,2',2'-tetramethyl-4,4'-bi(1,3-dioxolane) (19)

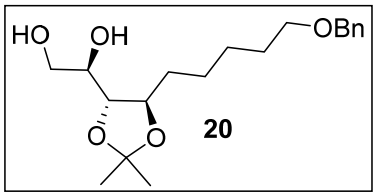


19

A suspension of the diacetonide **18** (2.1 g, 5.6 mmol), Raney-Ni (50 mg) in ethanol (20 mL) was flushed with hydrogen gas and stirred under hydrogen (20 *psi*) atmosphere for 30 min. The reaction mixture was filtered through celite, concentrated and the crude product was purified by column chromatography (90:10 petroleum ether/EtOAc) to procure **19** (2.0 g, 95%) as colorless syrup: R_f (10% EtOAc/petroleum ether) 0.52; $[\alpha]^{25}_D$: +18.7 (*c* 0.6, $CHCl_3$); IR ($CHCl_3$) *v*: 3018, 1496, 1372, 1216, 1064, 758, 668 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ1.32 (s, 6H), 1.36 (s, 3H), 1.38 (s, 3H), 1.41–1.72 (m, 8H),

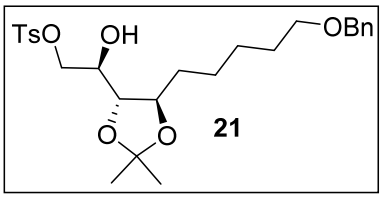
3.45 (t, *J* = 6.4 Hz, 2H), 3.45 (t, *J* = 7.7 Hz, 1H), 3.82–4.12 (m, 4H), 4.48 (s, 2H), 7.21–7.32 (m, 5H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 25.4 (q), 26.0 (t), 26.3 (t), 26.8 (q), 27.1 (q), 27.4 (q), 29.7 (t), 33.7 (t), 67.7 (t), 70.3 (t), 72.8 (t), 77.3 (d), 80.5 (d), 81.2 (d), 108.7 (s), 109.5 (s), 127.4 (d), 127.6 (d, 2C), 128.3 (d, 2C), 138.6 (s) ppm; MS (ESI) m/z = 401 $[M+Na]^+$; HRMS (ESI) calcd for $C_{22}H_{34}O_5$ $[M+Na]^+$ 401.2304, found 401.2271.

(*R*)-1-((4*R*,5*R*)-5-(5-(Benzyloxy)pentyl)-2,2-dimethyl-1,3-dioxolan-4-yl)ethane-1,2-diol (20)



To a solution of the diacetonide **19** (1.4 g, 3.7 mmol) in MeOH (10 mL), catalytic *p*-TSA (5 mg, 0.03 mmol) was added and the reaction mixture was stirred at 0 °C for 20 h. The reaction mixture was quenched by the addition of few drops of triethylamine and the solvent was evaporated. The crude residue was purified by column chromatography (65:35 petroleum ether/EtOAc) to obtain **20** (1.0 g, 80%) as a colorless oil: R_f (50% EtOAc/petroleum ether) 0.3; $[\alpha]^{25}_D$: +30.8 (*c* 1.0, $CHCl_3$); IR ($CHCl_3$) *v*: 3433, 2936, 1415, 1373, 1216, 1069, 759, 669 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz): δ1.35 (s, 3H), 1.37 (s, 3H), 1.40–1.49 (m, 2H), 1.45 (br s, 1H), 1.56–1.69 (m, 5H), 2.16 (br s, 1H), 2.53 (d, *J* = 4.0 Hz, 1H), 3.45 (t, *J* = 6.4 Hz, 2H), 3.57–3.78 (m, 4H), 3.92 (dt, *J* = 3.5, 7.7 Hz, 1H), 4.48 (s, 2H), 7.24–7.33 (m, 5H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 25.9 (t), 26.0 (t), 27.0 (q), 27.3 (q), 29.5 (t), 33.9 (t), 63.8 (t), 70.2 (t), 72.7 (d), 72.7 (t), 79.3 (d), 80.8 (d), 108.6 (s), 127.4 (d), 127.5 (d, 2C), 128.2 (d, 2C), 138.4 (s) ppm; MS (ESI) m/z = 361 $[M+Na]^+$; HRMS (ESI) calcd for $C_{19}H_{30}O_5$ $[M+Na]^+$ 361.1991, found 361.1972.

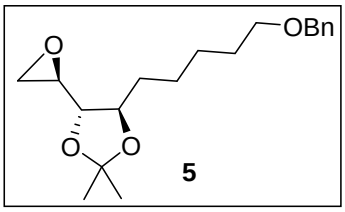
(*R*)-2-((4*R*,5*R*)-5-(5-(Benzyloxy)pentyl)-2,2-dimethyl-1,3-dioxolan-4-yl)-2-hydroxyethyl 4-methyl-benzenesulfonate (21)



To an ice cooled solution of the diol **20** (500 mg, 1.48 mmol) in CH_2Cl_2 (15 mL), were added Bu_2SnO (10 mg), DMAP (10 mg), and Et_3N (0.31 mL, 2.22 mmol) and stirred for 0.5 h at rt. The reaction mixture was cooled to 0 °C and treated with *p*-TsCl (280 mg, 1.48 mmol) and stirring was continued for 4 h at rt. Solvent was evaporated under reduced pressure, and the residue was purified by column chromatography (80:20 petroleum ether/EtOAc) to yield **21** (655 mg, 90%) as colorless syrup: R_f (30% EtOAc/petroleum ether)

0.46; $[\alpha]^{25}_{D}$: +33.0 (*c* 1.0, $CHCl_3$); IR ($CHCl_3$) *v*: 3434, 2984, 1560, 1375, 1247, 1047, 757, 668 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 1.28 (s, 3H), 1.32 (s, 3H), 1.35–1.44 (m, 3H), 1.48–1.69 (m, 5H), 2.45 (s, 3H), 2.47 (br s, 1H), 3.45 (t, *J* = 6.4 Hz, 2H), 3.48 (t, *J* = 3.4 Hz, 1H), 3.72–3.83 (m, 1H), 3.91 (dd, *J* = 3.2, 7.4 Hz, 1H), 4.01 (dd, *J* = 6.9, 10.5 Hz, 1H), 4.25 (dd, *J* = 2.8, 10.5 Hz, 1H), 4.48 (s, 2H), 7.23–7.32 (m, 5H), 7.34 (d, *J* = 8.2 Hz, 2H), 7.79 (d, *J* = 8.2 Hz, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 21.7 (q), 25.9 (t), 26.1 (t), 27.0 (q), 27.4 (q), 29.6 (t), 34.0 (t), 70.3 (t), 71.5 (d), 72.1 (t), 72.8 (t), 79.4 (d), 80.1 (d), 109.9 (s), 127.5 (d), 127.6 (d, 2C), 128.1 (d, 2C), 128.3 (d, 2C), 129.9 (d, 2C), 132.7 (s), 138.6 (s), 144.9 (s) ppm; MS (ESI) *m/z* = 515 $[M+Na]^+$; CHN calcd for $C_{26}H_{36}O_7S$: C, 63.39; H, 7.37; S, 6.51%, found C, 63.28; H, 7.20; S, 6.12%.

(4*R*,5*S*)-4-(5-(Benzyloxy)pentyl)-2,2-dimethyl-5-((*R*)-oxiran-2-yl)-1,3-dioxolane (5)

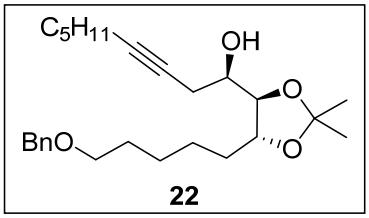


A suspension of the tosylate **21** (500 mg, 1.02 mmol) and K_2CO_3 (210 mg, 1.52 mmol) in MeOH (10 mL) was stirred at 0 °C under argon atmosphere for 1 h. The reaction mixture was filtered, concentrated and the residue was purified by silica gel chromatography (80:20 petroleum ether/EtOAc) to obtain **5** (300 mg, 92%) as colorless oil: R_f (30% EtOAc/petroleum ether) 0.5; $[\alpha]^{25}_{D}$: + 4.5 (*c* 1.2, $CHCl_3$); IR ($CHCl_3$) *v*: 2937, 2861, 1455, 1371, 1217, 1099, 876, 756, 698 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 1.40 (s, 6H), 1.42–1.53 (m, 3H), 1.57–1.71 (m, 5H), 2.64 (dd, *J* = 2.5, 5.0 Hz, 1H), 2.80 (dd, *J* = 3.9, 5.0 Hz, 1H), 2.95 (ddd, *J* = 2.5, 3.9, 6.3 Hz, 1H), 3.28 (dd, *J* = 6.3, 7.8 Hz, 1H), 3.47 (t, *J* = 6.5 Hz, 2H), 3.96 (dt, *J* = 4.7, 7.8 Hz, 1H), 4.49 (s, 2H), 7.22–7.34 (m, 5H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 25.6 (t), 26.1 (t), 26.6 (q), 27.1 (q), 29.5 (t), 33.1 (t), 45.1 (t), 51.5 (d), 70.2 (t), 72.7 (t), 79.5 (d), 81.1 (d), 109.0 (s), 127.4 (d), 127.5 (d, 2C), 128.2 (d, 2C), 138.6 (s) ppm; MS (ESI) m/z = 343 $[M+Na]^+$; HRMS (ESI) calcd for $C_{19}H_{28}O_4$ $[M+Na]^+$ 343.1886, found 343.1860.

General procedure for epoxide opening (A): At –78 °C, to a solution of 1-alkyne (4 mmol) in THF (15 mL) were added *n*-BuLi (4 mmol) and $BF_3.Et_2O$ (4 mmol) followed by a solution of the epoxide (1 mmol) in THF (8 mL) with a 15 minutes interval. The stirring was continued for another 30 min at –78 °C and then quenched with NH_4Cl (5 mL). The reaction mixture was allowed to reach rt and partitioned between ethyl acetate (25 mL) and water (25 mL). The aqueous layer was extracted with ethyl acetate (2 x 25mL) and the combined organic layer was washed

with brine, dried over Na_2SO_4 and concentrated. Purification of the crude alkynol product was carried out by column chromatography.

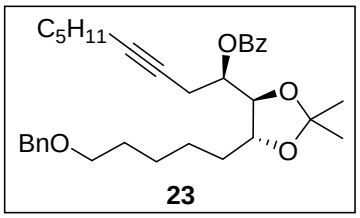
(*R*)-1-((4*R*,5*R*)-5-(5-(Benzyloxy)pentyl)-2,2-dimethyl-1,3-dioxolan-4-yl)non-3-yn-1-ol (22)



22

1-Heptyne (594 mg, 6.2 mmol), *n*-BuLi (3.9 mL, 6.2 mmol, 1.6 M in hexane), $BF_3{\cdot}Et_2O$ (0.77 mL, 6.2 mmol) and epoxide **5** (0.5 g, 1.6 mmol) were subjected to general procedure **A**. The crude product was purified by silica gel chromatography (85:15 petroleum ether/EtOAc) to afford **22** (530 mg, 82%) as a colorless syrup: R_f (10% EtOAc/petroleum ether) 0.57; $[\alpha]^{25}_D$: +37.3 (*c* 2.5, $CHCl_3$); IR ($CHCl_3$) *v*: 3546, 2934, 2861, 2401, 1455, 1370, 1217, 1101, 878, 769, 668 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 0.90 (t, 3H), 1.27–1.33 (m, 4H), 1.35 (s, 3H), 1.38 (s, 3H), 1.40–1.70 (m, 10H), 2.11–2.16 (m, 2H), 2.16 (br s, 1H), 2.45–2.50 (m, 2H), 3.46 (t, *J* = 6.6 Hz, 2H), 3.60–3.77 (m, 2H), 3.98 (dt, *J* = 3.5, 7.0 Hz, 1H), 4.49 (s, 2H), 7.24–7.33 (m, 5H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 14.0 (q), 18.7 (t), 22.2 (t), 24.3 (t), 26.1 (t), 26.3 (t), 27.1 (q), 27.5 (q), 28.6 (t), 29.7 (t), 31.1 (t), 34.5 (t), 70.4 (t), 70.9 (d), 72.9 (t), 74.9 (s), 78.9 (d), 81.9 (d), 84.0 (s), 108.6 (s), 127.5 (d), 127.7 (d, 2C), 128.4(d, 2C), 138.7 (s) ppm; MS (ESI) m/z = 439 $[M+Na]^+$; HRMS (ESI) calcd for $C_{26}H_{40}O_4$ $[M+Na]^+$ 439.2825, found 439.2826.

(*R*)-1-((4*S*,5*R*)-5-(5-(Benzyloxy)pentyl)-2,2-dimethyl-1,3-dioxolan-4-yl)non-3-ynyl benzoate (23)



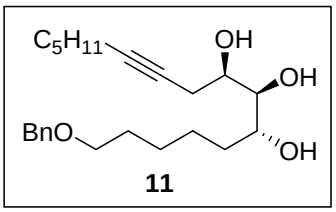
23

To an ice cooled solution of **22** (500 mg, 1.2 mmol), Et_3N (0.5 mL, 3.60 mmol) and DMAP (20 mg) CH_2Cl_2 (10 mL) was added benzoyl chloride (0.21 mL, 1.8 mmol) and stirred for 2 h at rt. The reaction mixture was poured into water (10 mL) and extracted with CH_2Cl_2 (2 x 10 mL). The combined organic layer was washed with brine, dried (Na_2SO_4) and concentrated under the reduced pressure. the resulting crude product was purified by column chromatography (90:10 petroleum ether/EtOAc) to afford the benzoate **23** (560 mg, 89%) as colorless syrup: R_f (10% EtOAc/petroleum ether) 0.5; $[\alpha]^{25}_D$: +51.2 (*c* 1.1, $CHCl_3$); IR ($CHCl_3$) *v*: 3019, 1717, 1214, 1111, 757, 711, 669 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 0.82 (t, *J* = 7.1 Hz, 3H), 1.19–1.34 (m, 8H), 1.36 (s, 3H), 1.41 (s, 3H), 1.46–1.70 (m, 6H),

2.09 (tt, *J* = 2.1, 6.8 Hz, 2H), 2.63–2.75 (m, 2H), 3.39 (t, *J* = 6.5 Hz, 2H), 3.96–4.07 (m, 2H), 4.45 (s, 2H), 5.23 (dd, *J* = 5.8,11.6 Hz, 1H), 7.26–7.35 (m, 5H), 7.41–7.45 (m, 2H),7.53–7.57 (m ,1H), 8.04 (d, *J* = 7.3 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 13.9 (q), 18.6 (t), 21.6 (t), 22.1 (t), 25.9 (t), 26.1 (t), 27.0 (q), 27.5 (q), 28.5 (t), 29.5 (t), 30.9 (t), 34.2 (t), 70.2 (t), 72.8 (t), 72.9 (d), 74.6 (s), 78.8 (d), 80.3 (d), 82.9 (s), 109.2 (s), 127.5 (d), 127.6 (d, 2C), 128.3 (d, 2C), 128.4 (d, 2C), 129.7 (d, 2C), 129.9 (s), 133.1 (d), 138.6 (s), 165.6 (s) ppm; MS (ESI) m/z = 543 $[M+Na]^+$; HRMS (ESI) calcd for $C_{33}H_{44}O_5$ $[M+Na]^+$ 543.3087, found 543.3043.

General procedure for acetonide deprotection (B): A solution of acetonide (1 mmol) in 60% AcOH in water (5 mL) was stirred at 80 °C for 2–4 h. The reaction mixture was evaporated. The crude residue wed with toluene (10 ml) three times. Then it was purified by column chromatography

(6*R*,7*S*,8*R*)-1-(Benzyloxy)tetradec-10-yne-6,7,8-triol (11)

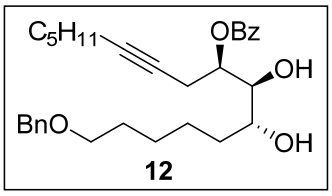


11

Acetonide **22** (150 mg, 0.36 mmol) was subjected to general procedure **B** and the crude product was purified by silica gel chromatography (15:85 petroleum ether/EtOAc) to obtain **11** (120 mg, 88%) as a white solid: R_f (80% EtOAc/petroleum ether) 0.35; Mp: 51–52 °C ; $[\alpha]^{31}_D$: +3.1 (*c* 2.9, $CHCl_3$); IR ($CHCl_3$) *v*: 3400, 2933, 2859, 1603, 1495, 1455, 1216, 1098, 756, 697, 666 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz):δ0.9 (t, *J* = 7.0, 3H), 1.28–1.35 (m, 5H), 1.37–1.44 (m, 3H), 1.46–1.55 (m, 3H), 1.59–1.65 (m, 3H), 2.14 (tt, *J* = 2.3, 7.1 Hz, 2H), 2.48–2.50 (m, 2H), 2.96–3.02 (m, 2H), 3.17 (br s, 1H), 3.47 (t, *J* = 6.6 Hz, 3H), 3.81 (q, *J* = 6.6 Hz, 1H), 3.98 (br s, 1H), 4.49 (s, 2H), 7.26–7.34 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ13.9 (q), 18.6 (t), 22.1 (t), 23.9 (t), 25.5 (t), 26.1 (t), 28.6 (t), 29.6 (t), 31.0 (t), 33.5 (t), 70.3 (d), 70.4 (t), 71.8 (d), 72.8 (t), 73.9 (d), 75.4 (s), 83.6 (s), 127.5 (d), 127.6 (d, 2C), 128.3 (d, 2C), 138.5 (s) ppm; MS (ESI) m/z = 399 $[M+Na]^+$; HRMS (ESI) calcd for $C_{23}H_{36}O_4$ $[M+Na]^+$ 399.2513, found 399.2512.

(6*R*,7*S*,8*R*)-1-(Benzyloxy)-6,7-dihydroxyhexadec-10-yn-8-yl benzoate (12)

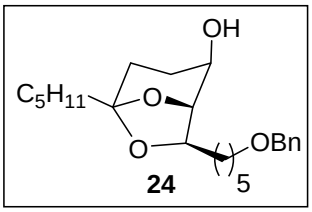
Acetonide **23** (200 mg, 0.38 mmol) was subjected to general procedure **B**. The crude product was purified by silica gel chromatography (40:60 petroleum ether/EtOAc) to obtain **12**



(152 mg, 82%) as a colorless thick syrup: R_f (50% EtOAc/petroleum ether) 0.5; $[\alpha]^{25}_D$: +20.2 (*c* 7.1, $CHCl_3$); IR ($CHCl_3$) *v*: 3443, 2932, 1721, 1452, 1272, 1113, 757, 712, 640, 668 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 0.81(t , *J* = 7.2 Hz, 3H), 1.12–1.67 (m, 14H), 2.03 (m, 2H), 2.55 (br d, *J* = 8.1 Hz, 1H), 2.74–2.82 (m, 2H), 2.9 (br s, 1H), 3.43 (t, *J* = 6.5 Hz, 2H), 3.55–3.65 (m, 2H), 4.46 (s, 2H), 5.08 (ddd, *J* = 4.6, 6.1, 10.7 Hz, 1H), 7.24–7.32 (m, 5H), 7.43 (dd, *J* = 1.4, 7.2 Hz, 1H), 7.46 (dd, *J* = 1.4, 7.7 Hz, 1H), 7.59 (tt, *J* = 2.5, 8.7 Hz, 1H), 8.07 (tt, *J* = 1.6, 7.2 Hz, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ13.9 (q), 18.6 (t), 21.7 (t), 22.1 (t), 25.7 (t), 26.2 (t), 28.5 (t), 29.6 (t), 30.9 (t), 33.0 (t), 69.3 (d), 70.2 (t), 72.8 (t), 73.2 (d), 73.5 (d), 75.1 (s), 82.7 (s), 127.4 (d), 127.6 (d, 2C), 128.3 (d, 2C), 128.4 (d, 2C), 129.5 (s), 129.9 (d, 2C), 133.4 (d), 138.6 (s), 167.1 (s) ppm; MS (ESI) m/z = 481 $[M+H]^+$; HRMS (ESI) calcd for $C_{30}H_{40}O_5$ $[M+Na]^+$ 503.2773, found 503.2799.

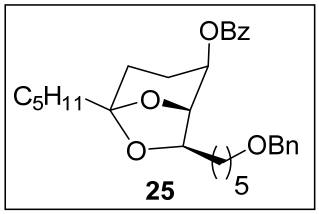
General procedure for cycloisomerization (Procedure C): A solution of the alkynol (1 mmol) and Pd $(CH_3CN)_2Cl_2$ (0.1 mmol) in acetonitrile (30 mL) was stirred at rt under argon atmosphere for 3–6 h. The reaction mixture was filtered through celite and the filtrate was concentrate under reduce pressure and the residue obtained was purified by silica gel chromatography

(1*R*,2*R*,5*S*,7*R*)-7-(5-(Benzyloxy)pentyl)-5-pentyl-6,8-dioxabicyclo[3.2.1]octan-2-ol (24)



Triol **11** (200 mg, 0.53 mmol) and Pd $(CH_3CN)_2Cl_2$ (7 mg, 0.03 mmol) were subjected to general procedure **C**. The crude product was purified by silica gel chromatography (80:20 petroleum ether/EtOAc) to obtain **24** (134 mg, 67%) as colorless syrup: R_f (15% EtOAc/petroleum ether) 0.4; $[\alpha]^{25}_D$: +25.0 (*c* 0.9, $CHCl_3$); IR ($CHCl_3$) *v*: 3444, 2930, 2857, 1722, 1455, 1216, 1100, 892, 753, 669 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 0.87 (t, *J* = 6.7, 3H), 1.24–1.34 (m, 5H), 1.36–1.44 (m, 6H), 1.61–1.65 (m, 9H), 1.90 (br s, 1H), 3.46 (t, *J* = 6.5 Hz, 2H), 3.90 (ddd, *J* = 5.5, 9.6, 18.2 Hz, 1H), 3.93 (m, 1H), 4.19 (dd, *J* = 5.6, 6.7 Hz, 1H), 4.49 (s, 2H), 7.26–7.34 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ14.0 (q), 22.6 (t), 22.9 (t), 25.4 (t), 26.0 (t), 26.6 (t), 29.6 (t), 31.9 (t), 33.7 (t), 35.2 (t), 36.7 (t), 66.5 (d), 70.3 (t), 72.8 (t), 75.7 (d), 80.8 (d), 108.5 (s), 127.5 (d), 127.6 (d, 2C), 128.3 (d, 2C), 138.6 (s) ppm; MS (ESI) m/z = 399 $[M+Na]^+$; HRMS (ESI) calcd for $C_{23}H_{36}O_4$ $[M+Na]^+$ 399.2513, found 399.2495.

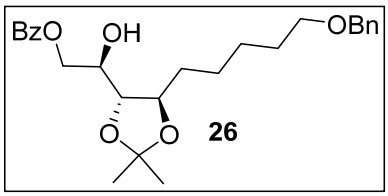
(1*R*,2*R*,5*S*,7*R*)-7-(5-(Benzyloxy)pentyl)-5-pentyl-6,8-dioxabicyclo[3.2.1]octan-2-ol (25)



25

Diol **12** (200 mg, 0.42 mmol) and $Pd(CH_3CN)_2Cl_2$ (5 mg, 0.02 mmol) were subjected to general procedure **C**. The crude product was purified by silica gel chromatography (78:22 petroleum ether/EtOAc) to procure **25** (161 mg, 80%) as colorless syrup: R_f (15% EtOAc/ petroleum ether) 0.43; $[\alpha]^{25}_D$: +32.9 (*c* 1.7, $CHCl_3$); IR ($CHCl_3$) *v*: 3448, 2929, 1717, 1274, 1273, 1113, 712, 617 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ0.86 (t, *J* = 7.1 Hz, 3H), 1.26–1.32 (m, 5H), 1.35–1.43 (m, 4H), 1.45–1.5 (m, 2H), 1.56–1.65 (m, 3H), 1.67–1.71 (m, 2H), 1.8–1.85 (m, 2H), 1.86–1.9 (dd, *J* = 6.9, 9.7 Hz, 2H), 3.42 (t, *J* = 6.5 Hz, 2H), 3.76 (d, *J* = 5.4 Hz, 1H), 4.46 (s, 2H), 4.66 (d, *J* = 4.6 Hz, 1H), 5.08 (ddd, *J* = 5.5, 7.3, 12.8 Hz,1H), 7.26–7.33 (m, 5H), 7.42 (dd, *J* = 1.6, 7.6 Hz, 2H), 7.53 (tt, *J* = 1.5, 8.7 Hz, 1H), 8.05 (tt, *J* = 1.6, 6.9 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ14.0 (q), 22.5 (t), 23.8 (t), 25.4 (t), 26.1 (t), 28.8 (t), 29.6 (t), 30.2 (t), 32.0 (t, 2C), 34.5 (t), 70.3 (t), 72.9 (t), 74.3 (d), 77.2 (d), 81.4 (d), 110.7 (s), 127.5 (d), 127.6 (d, 2C), 128.2 (d, 2C), 128.32 (d, 2C), 129.7 (d, 2C), 130.5 (s), 132.7 (d), 138.6 (s), 166.3 (s) ppm; MS (ESI) m/z = 481 $[M+H]^+$; HRMS (ESI) calcd for $C_{30}H_{40}O_5$ $[M+Na]^+$ 503.2773, found 503.2774.

(*R*)-2-((4*R*,5*R*)-5-(5-(Benzyloxy)pentyl)-2,2-dimethyl-1,3-dioxolan-4-yl)-2-hydroxyethyl benzoate (26)

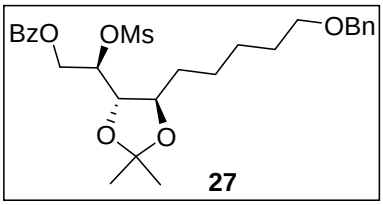


26

At 0 °C, to a cooled solution of the diol **20** (4 g, 11.8 mmol) in CH_2Cl_2 (50 mL), Bu_2SnO (50 mg), DMAP (50 mg), and Et_3N (5 mL, 35.5 mmol) were added and stirred for 30 min at the same temperature. To this, benzoyl chloride (1.51 ml, 13.0 mmol) was added drop-wise and the reaction mixture was further stirred for 8 h while warming to rt. Reaction mixture was poured into water (25 ml) and the aqueous layer was extracted with CH_2Cl_2 (2 x 25 mL). Combined organic layer was washed with brine dried (Na_2SO_4) and concentrated under reduce pressure. The residue was purified by column chromatography (85:15 petroleum ethe /EtOAc) to obtain **26** (4.6 g, 88%) as colorless syrup: R_f (10% EtOAc/petroleum ether) 0.46; $[\alpha]^{25}_D$: +36.0 (*c* 3.1, $CHCl_3$); IR ($CHCl_3$) *v*: 3444, 3019, 1719, 1372, 1276, 1215, 1047, 758, 668 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz):δ1.39 (s, 3H), 1.4 (s, 3H), 1.45–1.79 (m, 8H),

2.93 (brs, 1H), 3.45 (t, *J* = 6.6 Hz, 2H), 3.69 (t, *J* = 7 Hz, 1H), 3.91–4.1 (m, 2H), 4.39 (dd, *J* = 6.6, 11.8 Hz, 1H), 4.48 (s, 2H), 4.58 (dd, *J* = 3.2, 11.8 Hz, 1H), 7.23–7.32 (m, 5H), 7.34 (d, *J* =8.2 Hz, 2H), 7.57 (tt, *J* =1.4, 6.1 Hz, 1H), 7.79 (d, *J* = 8.2 Hz, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 25.9 (t), 26.1 (t), 27.0 (q), 27.4 (q), 29.5 (t), 34.1 (t), 66.8 (t), 70.3 (t), 71.6 (d), 72.8 (t), 79.3 (d), 80.3 (d), 108.9 (s), 127.4 (d), 127.6 (d, 2C), 128.3 (d, 2C), 128.4 (d, 2C), 129.6 (s), 129.7 (d, 2C), 133.2 (d), 138.5 (s), 167.0 (s); MS (ESI) m/z = 465 $[M+Na]^+$; HRMS (ESI) calcd for $C_{26}H_{34}O_6$ $[M+Na]^+$ 465.2253, found 465.2258

(*R*)-2-((4*S*,5*R*)-5-(5-(Benzyloxy)pentyl)-2,2-dimethyl-1,3-dioxolan-4-yl)-2-(methylsulfonyloxy)ethyl benzoate (27)

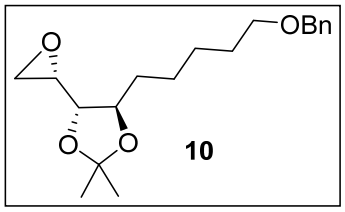


27

To an ice cooled solution of benzoate **26** (1.5 g, 3.4 mmol) in CH_2Cl_2 (15 mL) and Et_3N (1.43 mL, 10.2 mmol) was MsCl (0.4 mL, 5.1 mmol) and it was further stirred for 4 h rt. Reaction mixture was diluted with CH_2Cl_2 (15 mL) and washed with water, brine, dried (Na_2SO_4) and the Solvent was evaporated under reduced pressure. The resulting residue was purified by column chromatography (75:25 petroleum ether/EtOAc) to yield **27** (1.6 g, 90%) as colorless solid: R_f (20% EtOAc/petroleum ether) 0.5; $[\alpha]^{25}_D$: +28.4 (*c* 8.8, $CHCl_3$); IR ($CHCl_3$) *v*: 2934,1723, 1560, 1366, 1274, 1177, 925, 758, 667 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ1.41 (s, 6H), 1.45–1.77 (m, 8H), 3.05 (s, 3H), 3.45 (t, *J* = 7.4 Hz, 2H), 3.89 (t, *J* = 6.7 Hz, 1H), 4.12 (ddd, *J* = 2.9, 8.2, 10.1 Hz, 1H), 4.43 (d, *J* = 7.1 Hz, 1H), 4.46 (s, 2H), 4.75 (d, *J* = 12.5 Hz 1H), 5.01 (t, *J* = 6.6 Hz 1H), 7.23–7.32 (m, 5H), 7.42 (d, *J* =8.2 Hz, 2H), 7.54 (d, *J* =1.4, 6.1 Hz, 1H), 8.06 (d, *J* = 8.2 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 25.6 (t), 25.8 (t), 26.6 (q), 27.1 (q), 29.3 (t), 33.6 (t), 38.6 (q), 63.2 (t), 69.9 (t), 72.5 (t), 78.4 (d), 78.5 (d), 78.9 (d), 109.4 (s), 127.2 (d), 127.3 (d, 2C), 128.0 (d, 2C), 128.3 (d, 2C), 129.1 (s), 129.4 (d, 2C), 133.2 (d), 138.4 (s), 165.7 (s) ppm; MS (ESI) m/z = 543 $[M+Na]^+$; HRMS (ESI) calcd for $C_{27}H_{36}O_8S$ $[M+Na]^+$ 543.2029, found 543.2015.

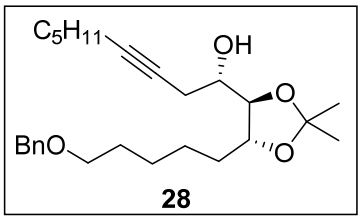
(4*R*,5*S*)-4-(5-(Benzyloxy)pentyl)-2,2-dimethyl-5-((S)-oxiran-2-yl)-1,3-dioxolane (10)

A solution of the mesylate **27** (2 g, 3.8 mmol), $LiOH{\cdot}H_2O$ (483 mg, 11.5 mmol) in MeOH:THF (2:3, 10 mL) was stirred at r.t. for 4 h. The reaction mixture was concentrated and



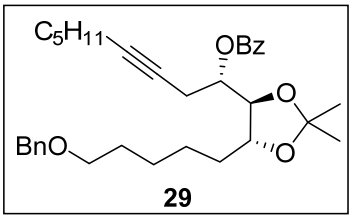
dissolved in ethyl acetate (25 mL), washed with brine, dried and concentrated under reduce pressure. The crude residue thus obtained was purified by silica gel chromatography (85:15 petroleum ether/EtOAc) to obtain **10** (1.1 g, 89%) as colorless oil: R_f (20% EtOAc/petroleum ether) 0.53; $[\alpha]^{25}_D$: +6.2 (*c* 0.9, $CHCl_3$); IR ($CHCl_3$) *v*: 2935, 2859, 1455, 1370, 1216, 1101, 878, 737, 698 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ1.38 (s, 6H), 1.42–1.66 (m, 8H), 2.69 (dd, *J* = 2.6, 5.2 Hz, 1H), 2.79 (dd, *J* = 4.4, 5.2 Hz, 1H), 2.99 (ddd, *J* = 2.7, 4.2, 6.8 Hz, 1H), 3.47 (m, 3H), 3.95 (dt, *J* = 4.9, 8.2 Hz, 1H), 4.49 (s, 2H), 7.22–7.34 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 25.8 (t), 26.2 (t), 26.6 (q), 27.2 (q), 29.6 (t), 33.0 (t), 43.9 (t), 51.4 (d), 70.2 (t), 72.9 (t), 77.8 (d), 81.2 (d), 109.2 (s), 127.5 (d), 127.6 (d, 2C), 128.3 (d, 2C), 138.6 (s) ppm; MS (ESI) m/z = 343 $[M+Na]^+$; HRMS (ESI) calcd for $C_{19}H_{28}O_4$ $[M+Na]^+$ 343.1886, found 343.1821.

(*R*)-1-((4*R*,5*R*)-5-(5-(Benzyloxy)pentyl)-2,2-dimethyl-1,3-dioxolan-4-yl)non-3-yn-1-ol (28)



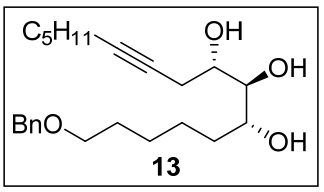
Epoxide **10** (400 mg, 1.25 mmol), 1-heptyne (480 mg, 5.0 mmol), $BF_3.Et_2O$ (0.63 mL, 5.0 mmol) and *n*-BuLi (3.1 mL, 5.0 mmol, 1.6 M in hexane), were subjected to general procedure **A**. The crude product was purified by silica gel chromatography (85:15 petroleum ether/EtOAc) to obtain alkynol **28** (410 mg, 78%) as a colorless syrup: R_f (10% EtOAc/petroleum ether) 0.58; $[\alpha]^{25}_D$: +55.8 (*c* 1.6, $CHCl_3$); IR ($CHCl_3$) *v*: 3431, 2935, 1453, 1380, 1276, 1068, 879, 714 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 0.90 (t, *J* = 6.9 Hz, 3H), 1.22–1.33 (m, 4H), 1.39 (s, 3H), 1.40 (s, 3H), 1.44–1.70 (m, 10H), 2.14 (tt, *J* = 2.2, 4.5, 6.9 Hz, 2H), 2.31–2.53 (m, 3H), 3.46 (t, *J* = 6.6 Hz, 2H), 3.61 (br s 1H), 3.75 (dd, *J* = 2.8, 8.1 Hz, 1H), 3.96 (dt, *J* = 3.5, 7.0 Hz, 1H), 4.49 (s, 2H), 7.24–7.33 (m, 5H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ14.0 (q), 18.7 (t), 22.2 (t), 25.3 (t), 25.9 (t), 26.3 (t), 26.9 (q), 27.5 (q), 28.6 (t), 29.6 (t), 31.0 (t), 33.1 (t), 69.0 (d), 70.2 (t), 72.8 (t), 75.5 (s), 77.8 (d), 81.8 (d), 83.0 (s), 108.8 (s), 127.5 (d), 127.6 (d, 2C), 128.3 (d, 2C), 138.6 (s) ppm; MS (ESI) m/z = 439 $[M+Na]^+$; HRMS (ESI) calcd for $C_{26}H_{40}O_4$ $[M+Na]^+$ 439.2824, found 439.2810.

(*S*)-1-((4*S*,5*R*)-5-(5-(Benzyloxy)pentyl)-2,2-dimethyl-1,3-dioxolan-4-yl)non-3-ynyl benzoate (29)



To a solution of **28** (600 mg, 1.40 mmol) in CH_2Cl_2 (10 mL) at 0 °C was added triethylamine (0.6 mL, 4.3 mmol), DMAP (10 mg) and stirred for 15 min. Benzoyl chloride (0.25 mL, 2.2 mmol) was added at 0 °C and stirred further for 2 h. Usual workup followed by purification of the crude product by column chromatography (90:10 petroleum ether/EtOAc) gave the benzoate **29** (665 mg, 89%) as colorless syrup: R_f (7% EtOAc/petroleum ether) 0.5; $[\alpha]^{25}_D$: 50.8 (*c* 1.2, $CHCl_3$); IR ($CHCl_3$) *v*: 3448, 2933, 1717, 1453, 1271, 1111, 877, 758, 666 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ0.83 (t, *J* = 7.1 Hz, 3H), 1.21–1.3 (m, 6H), 1.40 (s, 3H), 1.42 (s, 3H), 1.48–1.7 (m, 8H), 2.09 (tt, *J* = 2.4, 6.9 Hz, 2H), 2.67 (ddd, *J* = 2.3, 6.8, 9.1 Hz, 2H), 3.44 (t, *J* = 6.6 Hz, 2H), 3.84 (dt, *J* = 3.8, 8.1, 11.9 Hz, 1H), 4.01 (dd, *J* = 2.8, 8.7 Hz, 1H), 4.48 (s, 2H), 5.23 (dt, *J* = 2.7, 6.8, 9.5 Hz, 1H), 7.26–7.33 (m, 5H), 7.43 (tt, *J* = 1.5, 7.9 Hz, 2H), 7.56 (tt, *J* = 2.6, 7.3 Hz, 1H), 8.07 (tt, *J* = 1.5, 7.2 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ14.0 (q), 18.6 (t), 22.0 (t), 22.2 (t), 25.9 (t), 26.3 (t), 26.8 (q), 27.5 (q), 28.5 (t), 29.6 (t), 30.9 (t), 33.0 (t), 70.3 (t), 70.6 (d), 72.8 (t), 74.8 (s), 77.2 (d), 80.5 (d), 83.0 (s), 108.8 (s), 127.5 (d), 127.6 (d, 2C), 128.3 (d, 2C), 128.4 (d, 2C), 129.8 (d, 2C), 129.9 (s), 133.2 (d), 138.7 (s), 165.9 (s) ppm; MS (ESI) m/z = 543 $[M+Na]^+$; HRMS (ESI) calcd for $C_{33}H_{44}O_5$ $[M+Na]^+$ 543.3086, found 543.3096

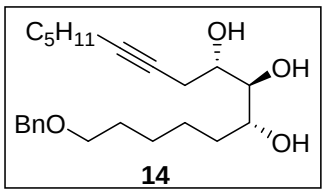
(6*R*,7*S*,8*S*)-1-(Benzyloxy)tetradec-10-yne-6,7,8-triol (13)



Acetonide **28** (140 mg, 0.34 mmol) was subjected to general procedure **B**. The crude product was purified by silica gel chromatography (15:85 petroleum ether/EtOAc) to obtain **13** (105 mg, 83%) as a white solid: R_f (80% EtOAc/petroleum ether) 0.36; Mp: 40–42 °C; $[\alpha]^{31}_D$: +8.1 (*c* 2.8, $CHCl_3$); IR ($CHCl_3$) *v*: 3422, 2932, 2859,1719,1602, 1453, 1275, 1070, 755, 697 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz):δ 0.9 (t, *J* = 7.1 Hz, 3H), 1.27–1.34 (m, 4H), 1.35–1.42 (m, 3H), 1.44–1.49 (m, 3H), 1.51–1.58 (m, 2H), 1.59–1.65 (m, 2H), 2.13 (tt, *J* = 2.3, 7.1 Hz, 2H), 2.42–2.5 (m, 2H), 2.89 (br s, 2H), 3.4 (br s, 1H), 3.46 (t, *J* = 6.6 Hz, 3H), 3.69 (br s, 1H), 3.79 (br s, 1H), 4.48 (s, 2H), 7.24–7.34 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ13.9 (q),

18.6 (t), 22.1 (t), 24.3 (t), 25.3 (t), 26.1 (t), 28.6 (t), 29.6 (t), 31.0 (t), 33.6 (t), 70.3 (t), 72.4 (d), 72.8 (t), 73.2 (d), 73.4 (d), 75.6 (s), 83.3 (s), 127.5 (d), 127.6 (d, 2C), 128.3 (d, 2C), 138.5 (s) ppm; MS (ESI) m/z = 399 $[M+Na]^+$; HRMS (ESI) calcd for $C_{23}H_{36}O_4$ $[M+Na]^+$ 399.2512. found 399.2516.

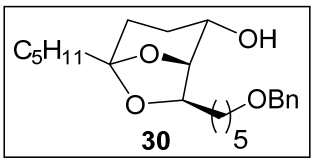
(6*R*,7*S*,8*S*)-1-(Benzyloxy)-6,7-dihydroxyhexadec-10-yn-8-yl benzoate (14)



14

Acetonide **29** (200 mg, 0.38 mmol) was subjected to general procedure **B**. The crude product was purified by silica gel chromatography (30:70 petroleum ether/EtOAc) to obtain **14** (155 mg, 84%) as a white syrup: R_f (60% EtOAc/ petroleum ether) 0.43; $[\alpha]^{25}_D$: + 4.7 (*c* 2.7, $CHCl_3$); IR ($CHCl_3$) *v*: 3448, 2932, 1718, 1451, 1273, 1114, 758, 668, 617 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz):δ 0.9 (t, J = 7.1 Hz, 3H), 1.27–1.36 (m, 4H), 1.42–1.49 (m, 6H), 1.59–1.62 (m, 2H), 1.80–1.83 (m, 2H), 2.12 (tt, J = 2.2, 7.1 Hz, 2H), 2.50 (m, 3H), 2.74 (br s, 1H), 3.44 (t, J = 6.6 Hz, 2H), 3.77(br s, 2H), 4.47 (s, 2H), 5.26 (ddd, J = 4.4, 6.1, 10.4 Hz, 1H), 7.24–7.34 (m, 5H), 7.43 (tt, J = 1.5, 7.1 Hz, 2H), 7.56 (tt, J = 2.3, 7.3 Hz, 1H), 8.06 (tt, J = 1.5, 7.1 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ13.9 (q), 18.6 (t), 22.1 (t), 24.5 (t), 25.2 (t), 26.0 (t), 28.6 (t), 29.5 (t), 30.7 (t), 31.1 (t), 70.0 (d), 70.2 (t), 72.8 (t), 73.6 (d), 75.2 (s), 75.3 (d), 83.7 (s), 127.4 (d), 127.6 (d, 2C), 128.3 (d, 2C), 128.4 (d, 2C), 129.7 (d, 2C), 130.1 (s), 133.1 (d), 138.6 (s), 166.6 (s) ppm; MS (ESI) m/z = 481 $[M+H]^+$; HRMS (ESI) calcd for $C_{30}H_{40}O_5$ $[M+Na]^+$ 503.2773. found 503.2781

(1*R*,2*R*,5*S*,7*R*)-7-(5-(Benzyloxy)pentyl)-5-pentyl-6,8-dioxabicyclo[3.2.1]octan-2-ol (30)

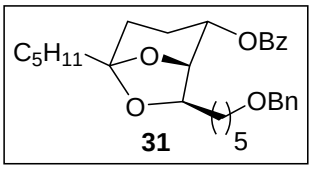


30

Triol **13** (150 mg, 0.36 mmol) and Pd $(CH_3CN)_2Cl_2$ (5.0 mg, 0.02 mmol) were subjected to general procedure **C**. The crude product was purified by silica gel chromatography (80:20 petroleum ether/EtOAc) to obtain **30** (125 mg, 81%) as colorless syrup: R_f (15% EtOAc/petroleum ether) 0.42; $[\alpha]^{28}_D$: +71.8 (*c* 0. 4, $CHCl_3$); IR ($CHCl_3$) *v*: 3421, 2932, 1602, 1456, 1029, 697, 617 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 0.90 (t, J = 7.0 Hz, 3H), 1.26–1.34 (m, 6H), 1.37–1.44 (m, 7H), 1.59–1.70 (m, 7H), 1.80–1.92 (m, 1H), 3.46 (t, J = 6.6 Hz, 2H), 3.90 (m, 1H), 3.94 (dd, J = 4.5, 7.1 Hz, 1H), 4.20 (dd, J = 5.5, 7.3 Hz,1H), 4.49 (br s, 2H), 7.25–7.35 (m,

5H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ14.0 (q), 22.6 (t), 22.9 (t), 25.4 (t), 26.1 (t), 26.7 (t), 29.7 (t), 32.0 (t), 33.8 (t), 35.2 (t), 36.7 (t), 66.6 (d), 70.4 (t), 72.9 (t), 75.7 (d), 80.8 (d), 108.5 (s), 127.5 (d), 127.6 (d, 2C), 128.3 (d, 2C), 138.7(s) ppm; MS (ESI) m/z = 399 $[M+Na]^+$; HRMS (ESI) calcd for $C_{23}H_{36}O_4$ $[M+Na]^+$ 399.2512, found 399.2498.

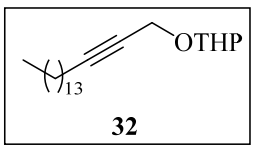
(1*S*,2*S*,5*S*,7*R*)-7-(5-(Benzyloxy)pentyl)-5-pentyl-6,8- dioxabicyclo[3.2.1]octan-2-yl benzoate (31)



31

Diol **14** (150 mg, 0.31 mmol) and Pd $(CH_3CN)_2Cl_2$ (4 mg, 0.02 mmol) were subjected to general procedure **C**. The crude product was purified by silica gel chromatography (80:20 petroleum ether/EtOAc) gave **31** (110 mg, 73%) as colorless syrup: R_f (10% EtOAc/petroleum ether) 0.45; $[\alpha]^{25}_D$: +36.8 (*c* 0.6, $CHCl_3$); IR ($CHCl_3$) *v*: 3418, 2930, 1716, 1602, 1274, 1112, 990, 712, 617 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz):δ0.85 (t, *J* = 7.0 Hz, 3H), 1.27–1.30 (m, 4H), 1.35–1.42 (m, 4H), 1.44–1.52 (m, 2H), 1.58–1.71 (m, 6H), 1.79–1.83 (m, 2H), 1.86–1.90 (m, 2H), 3.42 (t, *J* = 6.5 Hz, 2H), 3.76 (d, *J* = 5.3, Hz, 1H), 4.46 (br s, 2H), 4.66 (d, *J* = 4.4 Hz, 1H), 5.08 (dt, *J* = 5.6, 7.1, 11.5 Hz, 1H), 7.26–7.34 (m, 5H), 7.42 (tt, *J* = 1.5, 6.9 Hz, 2H), 7.53 (tt, *J* = 1.5, 7.1 Hz, 1H), 8.05 (dt, *J* = 1.6, 6.9 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ14.0 (q), 22.5 (t), 23.8 (t), 25.4 (t), 26.1 (t), 28.8 (t), 29.6 (t), 30.2 (t), 32.1 (t), 34.5 (t, 2C), 70.3 (t), 72.8 (t), 74.3 (d), 77.2 (d), 81.4 (d), 110.7 (s), 127.5 (d), 127.6 (d, 2C), 128.3 (d, 2C), 128.3 (d, 2C), 129.7 (d, 2C), 130.5 (s), 132.8 (d), 138.6 (s), 166.3 (s) ppm; MS (ESI) m/z = 503 $[M+Na]^+$; HRMS (ESI) calcd for $C_{30}H_{40}O_5$ $[M+Na]^+$ 503.2773, found 503.2628.

2-(Heptadec-2-ynyloxy)tetrahydro-2*H*-pyran (32)

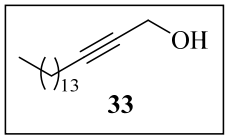


32

At –10 °C, a solution of the THP protected alkyne (1 g, 7.1 mmol) in THF (10 mL) was treated with *n*-BuLi (3.66 mL, 8.6 mmol) (2.34 M in hexane)] and stirred for 30 min. HMPA (1.53 mL, 8.6 mmol) was added and the reaction mixture was stirred at –10 °C for another 30 min. Myristyl bromide (2.37 g, 8.6 mmol) was dissolved in THF (20 mL) and stirred at –10 °C to which the solution of alkynyl lithium in THF was added and stirred for further 30 min. The reaction mixture was quenched with saturated NH_4Cl. The organic layer was separated and the aqueous layer was washed with ethyl

acetate, the combined organic layers were washed with ethyl acetate, brine, dried and concentrated. Purification of the crude product by column chromatography (90:10 petroleum ether/EtOAc) afforded **32** (2.1 g, 87%) as colorless oil: R_f (7% EtOAc/petroleum ether) 0.6; IR ($CHCl_3$)*v*: 2926, 1466, 1345, 1216, 1118, 1022, 903, 759, 668 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 0.88 (t, *J* = 6.7 Hz, 3H), 1.24–1.34 (m, 24H), 1.46–1.88 (m, 6H), 2.11–2.23 (m, 2H), 3.44–3.55 (m, 1H), 3.81 (ddd, *J* = 3.3, 8.5, 11.7 Hz, 1H), 4.14 (dt, *J* = 2.1, 15.3 Hz, 1H), 4.25 (dt, *J* = 2.1, 15.3 Hz, 1H), 4.79 (t, *J* = 2.9 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ14.2 (q), 18.4 (t), 18.9 (t), 19.1 (t), 22.7 (t), 25.5 (t), 28.5 (t), 28.6 (t), 28.8 (t), 28.9 (t), 29.2 (t), 29.4 (t), 29.6 (t), 29.7 (t), 29.7 (t), 30.3 (t), 32.0 (t), 54.5 (t), 61.8 (t), 75.8 (s), 86.6 (s), 96.4 (d) ppm; MS (ESI) *m/z* = 359 $[M+Na]^+$; CHN calcd for $C_{22}H_{40}O_2$: C, 78.51; H, 11.98%, found C, 78.40; H, 12.13%.

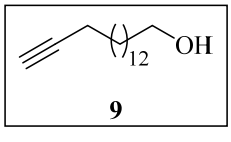
Heptadec-2-yn-1-ol (33)



33

To a solution of **32** (400 mg, 1.1 mmol) in MeOH (10 mL), *p*-TSA (7 mg) was added and the reaction mixture was stirred at rt for 30 min. The reaction mixture was quenched by the addition of few drops of triethylamine and the solvent was evaporated. The crude residue was purified by column chromatography (80:20 petroleum ether/EtOAc) to obtain **33** (275 mg, 91%) as a white solid: R_f (10% EtOAc/petroleum ether) 0.4; Mp: 48 – 49; IR ($CHCl_3$) *v*: 3539, 2944, 2254, 1631, 1444, 1376, 1040, 918, 759 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ0.87 (t, *J* = 6.7 Hz, 3H), 1.25–1.42 (m, 24H), 2.18 (tt, *J* = 2.1, 6.9 Hz, 2H), 4.22 (t, *J* = 2.1 Hz, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ14.2 (q), 18.8 (t), 22.7 (t), 28.6 (t), 28.9 (t), 29.2 (t), 29.4 (t), 29.6 (t), 29.7 (t, 5C), 32.0 (t), 51.3 (t), 78.4 (s), 86.5 (s) ppm; MS (ESI) m/z=275 $[M+Na]^+$; CHN calcd for $C_{17}H_{32}O$: C, 80.88; H, 12.78%, found C, 80.60; H, 12.73%.

Heptadec-16-yn-1-ol (9)

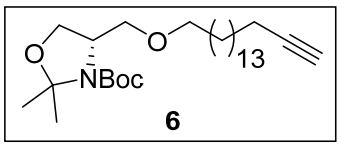


9

Lithium (3.3 g, 475.4 mmol) was added to freshly distilled 1,3-diaminopropane (250 mL) and stirred at rt till the reaction mixture turns into a deep purple suspension. The suspension was heated at 80 °C till the blue color disappears. The reaction mixture was cooled to rt and KO^{t}Bu (35.6 g, 316.9 mmol) was added and stirred for 30 min. Alkynol **33** (20 g, 79.2 mmol) was added to the reaction mixture and stirred at rt for 1 h. The reaction mixture was poured slowly on ice and partitioned between CH_2Cl_2 and water.

The aqueous layer was extracted with CH_2Cl_2 and combined CH_2Cl_2 layer was washed with brine, dried (Na_2SO_4), and concentrated. Purification of the residue by column chromatography (80:20 petroleum ether/EtOAc) afforded **9** (15.8 g, 79%) as white solid: R_f (10% EtOAc/petroleum ether) 0.45; Mp: 50 – 51; IR ($CHCl_3$) *v*: 3308, 2928, 1603, 1466, 1216, 1049, 758, 669 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ1.25–1.41 (m, 22H), 1.48–1.58 (m, 4H), 1.88 (t, *J* = 2.5 Hz, 1H), 2.15 (dt, *J* = 2.5, 6.8 Hz, 2H), 3.61 (t, *J* = 6.7 Hz, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ18.4 (t), 25.8 (t), 28.5 (t), 28.8 (t), 29.1 (t), 29.4 (t), 29.5 (t), 29.6 (t, 3C), 29.6 (t, 3C), 32.8 (t), 62.9 (t), 68.2 (d), 84.6 (s) ppm; HRMS (ESI) calcd for $C_{17}H_{32}O$ $[M+Na]^+$ 275.2350, found 275.2305.

(*S*)-*Tert*-butyl 4-((heptadec-16-ynyloxy)methyl)-2,2-dimethyloxazolidine-3-carboxylate (6)



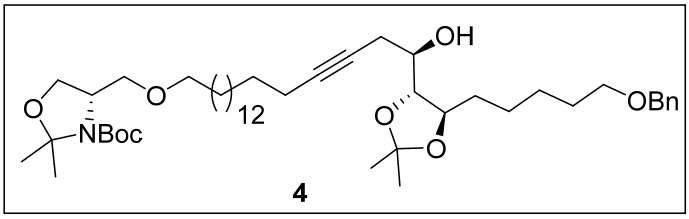
6

At 0 °C, triethylamine (6.7 mL, 47.5 mmol) was added to a solution of the **9** (4 g, 15.8 mmol) in CH_2Cl_2 and stirred for 30 min. MsCl (1.9 mL, 23.8 mmol) was added at 0 °C and stirred for 30 min. The reaction mixture was extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried (Na_2SO_4), concentrated and the resulting crude mesylate **9**-Ms (4.8 g, 92%) was used as such for the next step without purification.

Serinol derivative **8** (2.8 g, 12.1 mmol) was dissolved in dry DMSO (30 mL) and treated with NaH (581 mg, 60% dispersion in mineral oil, 14.5 mmol) and mesylate **9**-Ms (4.8 g, 14.5 mmol) was added sequentially. The reaction immediately changed color from nearly colorless to oranges' red. The reaction was stirred at room temperature for 16 h, and was then quenched by the ice and diluted with ethyl acetate. The two layers were separated and the aqueous layer extracted with ethyl acetate (5 x 15 mL). The combined organic layers were dried (Na_2SO_4) and concentrated in *vacuo*. Purification by flash column chromatography (85:15 petroleum ether/EtOAc) yielded the serinol ether **6** (4 g, 71%) as colorless oil: R_f (10% EtOAc/petroleum ether) 0.4; $[\alpha]^{25}_D$: +20.9 (*c* 1.1, $CHCl_3$); IR ($CHCl_3$) *v*: 3311, 2928, 2856, 1694, 1466, 1392, 1260, 1090, 847, 758, 629 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ1.23 (s, 24H), 1.45 (s, 9H), 1.43–1.49 (m, 2H), 1.50 (s, 3H), 1.55 (s, 3H), 1.92 (t, *J* = 2.7 Hz, 1H), 2.15 (dt, *J* = 2.6, 6.8 Hz, 2H), 3.22–3.36 (m, 1H), 3.42 (dd, *J* = 6.4, 12.1 Hz, 2H), 3.48–3.60 (m, 1H), 3.86–4.07 (m, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ18.4 (t), 23.1, 24.4 (2q, 1C), 26.1 (t), 26.8, 27.5 (2q, 1C), 28.5 (2q, 3C), 28.5 (t), 28.8 (t), 29.1 (t), 29.5 (t), 29.5 (t), 29.6 (t, 4C), 29.7 (t, 3C), 56.3, 56.5 (2d, 1C), 65.4, 65.7 (2t,

1C), 68.1 (d), 69.3, 70.1 (2t, 1C), 71.4 (t), 79.7, 80.2 (2s, 1C), 84.8 (s), 93.3, 93.7 (2s, 1C), 151.7, 152.2 (2s, 1C) ppm; MS (ESI) m/z = 488 $[M+Na]^+$; HRMS (ESI) calcd for $C_{28}H_{51}NO_4$ $[M+Na]^+$ 488.3716, found 488.3706.

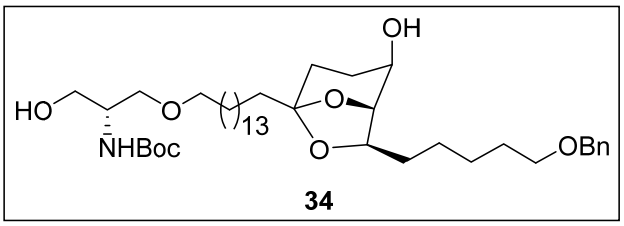
(*S*)-Tert-butyl 4-(((*R*)-19-((4*R*,5*R*)-5-(5-(benzyloxy)pentyl)-2,2-dimethyl-1,3-dioxolan-4-yl)-19-hydroxynonadec-16-ynyloxy)methyl)-2,2-dimethyloxazolidine-3-carboxylate (4)



4

Alkyne **6** (3.2 g, 6.9 mmol), *n*-BuLi (4.6 mL, 6.9 mmol, 1.6 M in hexane), $BF_3{\cdot}Et_2O$ (0.9 mL, 6.9 mmol), epoxide **5** (0.55 g, 1.7 mmol) were subjected to general procedure **A**. The crude product was purified by silica gel chromatography (80:20 petroleum ether/EtOAc) to obtain **4** (960 mg, 71%) as a colorless syrup: R_f (15% EtOAc/petroleum ether) 0.46; $[\alpha]^{25}_D$: +91.7 (*c* 0.9, $CHCl_3$); IR ($CHCl_3$) *v*: 3019, 2930, 1691, 1456, 1393, 1216, 1173, 759, 668 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ1.23 (s, 24H), 1.34 (s, 3H), 1.38 (s, 3H), 1.40–1.44 (m, 6H), 1.46 (s, 9H), 1.51 (s, 3H), 1.55 (s, 3H), 1.58 –1.62 (m, 4H), 2.14 (tt, *J* = 2.7, 6.8 Hz, 2H), 2.23 (d, *J* = 4.2 Hz, 1H), 2.43–2.48 (m, 2H), 3.25–3.38 (m, 1H), 3.41–3.48 (m, 4H), 3.54–3.76 (m, 3H), 3.86–4.03 (m, 4H), 4.48 (s, 2H), 7.24–7.34 (m, 5H);^{13}C NMR ($CDCl_3$, 50 MHz): δ18.7 (t), 23.0, 24.3 (q, 2C), 24.3 (t), 26.0 (t, 3C), 26.2 (t), 27.1, 27.4 (q, 2C), 28.4 (q, 3C), 28.9 (t, 3C), 29.1 (t), 29.4 (t), 29.6 (t, 7C), 34.4 (t), 56.3, 56.4 (2d, 1C), 65.4, 65.6 (2t, 1C), 69.2, 70.0 (2t, 1C), 70.3 (t), 70.8 (d), 71.3 (t), 72.8 (t), 74.9 (s), 78.8 (d), 79.7, 80.2 (2s, 1C), 81.8 (d), 83.9 (s), 93.2, 93.6 (2s, 1C), 108.6 (s), 127.4 (d), 127.6 (d, 2C), 128.3 (d, 2C), 138.6 (s), 151.7, 152.2 (2s, 1C) ppm; MS (ESI) m/z = 808 $[M+Na]^+$; HRMS (ESI) calcd for $C_{47}H_{79}NO_8$ $[M+Na]^+$ 808.5704, found 808.5649

***Tert*-butyl(*R*)-1-(15-((1*R*,2*R*,5*S*,7*R*)-7-(5-(benzyloxy)pentyl)-2-hydroxy-6,8-dioxabicyclo[3.2.1]octan-5-yl)pentadecyloxy)-3-hydroxypropan-2-ylcarbamate(34)**

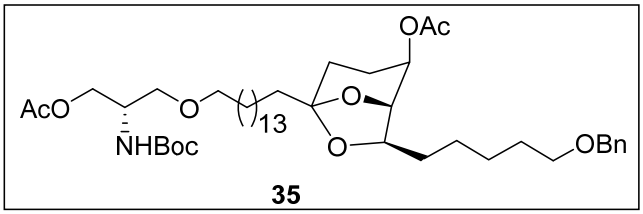


34

A solution of the acetonide **4** (120 mg, 0.15 mmol) in dry CH_2Cl_2 was degassed properly. Then $(C_6H_5)_3PAuCl$ (4 mg, 0.008 mmol) followed by $AgSbF_6$ (3 mg, 0.008

mmol) were added at 0 °C and stirred at rt under argon atmosphere for 3 h. The reaction mixture was concentrate under reduce pressure and the obtained residue was purified by silica gel chromatography (40:60 petroleum ether/EtOAc) to obtain **34** (92 mg, 85%) as colorless syrup: R_f (40% EtOAc/petroleum ether) 0.4; $[\alpha]^{25}_D$: +20.8 (*c* 3.6, $CHCl_3$); IR ($CHCl_3$) *v*: 3444, 2927, 2856, 1695, 1455, 1366, 1246, 1172, 1092, 755, 697 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ1.23 (s, 24H), 1.35–1.41 (m, 4H), 1.43 (s, 9H), 1.48 –1.55 (m, 4H), 1.60 –1.67 (m, 6H), 3.53 (dt, *J* = 5.6, 18.7 Hz, 1H), 1.91 –2.00 (m, 1H), 2.59 (br s, 1H), 3.40 (t, *J* = 6.7 Hz, 2H), 3.44 (t, *J* = 6.5 Hz, 2H), 3.53 (dd, *J* = 3.9, 9.5 Hz, 1H), 3.57 (dd, *J* = 3.6, 9.3 Hz, 2H), 3.65 (dd, *J* = 3.7, 10.2 Hz, 1H), 3.75–3.78 (m, 2H), 3.85 (dd, *J* = 5.4, 7.1 Hz, 1H), 4.03 (br s, 1H), 3.92 (br s, 1H), 4.47 (s, 2H), 5.19 (d, *J* = 5.5 Hz, 1H), 7.24–7.33 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 22.9 (t), 25.0 (t), 25.3 (t), 26.0 (t), 28.3 (q, 3C), 29.4 (t), 29.5 (t), 29.5 (t, 3C), 29.6 (t, 7C), 29.7 (t), 30.1 (t), 35.2 (t), 37.5 (t), 51.4 (d), 64.2 (t), 66.2 (d), 70.2 (t), 71.4 (t), 71.7 (t), 72.8 (t), 77.8 (d), 79.6 (s), 82.3 (d), 109.5 (s), 127.4 (d), 127.6 (d, 2C), 128.3 (d, 2C), 138.5 (s), 156.0 (s) ppm; MS (ESI) m/z = 728 $[M+Na]^+$; HRMS (ESI) calcd for $C_{41}H_{71}NO_8$ $[M+Na]^+$ 728.5078, found 728.5030.

(1*S*,2*R*,5*S*,7*R*)-5-(15-((*S*)-3-Acetoxy-2-(*tert*-butoxycarbonylamino)propoxy)pentadecyl)-7-(5-(benzyloxy)pentyl)-6,8-dioxabicyclo[3.2.1]octan-2-yl acetate (35)

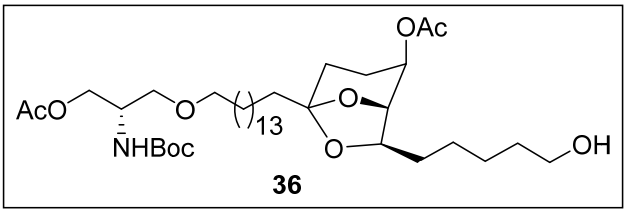


35

To a solution of **34** (80 mg, 0.11 mmol) in CH_2Cl_2 (10 mL) at 0 °C was added Et_3N (0.1 mL, 0.7 mmol), DMAP (2 mg) and stirred for 15 min. To this, acetic anhydride (0.03 mL, 0.34 mmol) was added at 0 °C and stirred further for 2 h. The reaction mixture was diluted with CH_2Cl_2 (10 mL) and washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. The resulting crude product was purified by column chromatography (60:40 petroleum ether/EtOAc) to afford the diaceate **35** (87 mg, 97%) as colorless syrup: R_f (30% EtOAc/petroleum ether) 0.43; $[\alpha]^{25}_D$: 19.6 (*c* 5.5, $CHCl_3$); IR ($CHCl_3$) *v*: 3447, 2928, 2855, 1739, 1497, 1366, 1244, 1114, 925, 756, 666 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ1.23 (s, 24H), 1.35–1.41 (m, 4H), 1.42 (s, 9H), 1.48 –1.54 (m, 4H), 1.57 –1.62 (m, 3H), 1.64 –1.71 (m, 3H), 1.77 (dt, *J* = 5.6, 18.7 Hz, 2H), 2.03(s, 3H), 2.09(s, 3H), 3.38 (t, *J* = 6.7 Hz, 2H), 3.44 (t, *J* = 6.6 Hz, 2H), 3.38 –3.49 (m, 2H), 3.88 (dd, *J* = 4.8, 7.3 Hz, 1H), 3.97 (br s, 1H), 4.09 (dd, *J* = 5.5, 10.8 Hz, 1H), 4.15 (dd, *J* = 6.2, 11.0 Hz, 2H), 4.47 (s, 2H), 4.66 (t, *J* =

2.3 Hz, 1H), 4.89 (d, J = 8.1 Hz, 1H), 7.24–7.33 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 20.8 (q), 21.3 (q), 22.5 (t), 22.7 (t), 25.3 (t), 26.0 (t), 26.0 (t), 28.3 (2q, 3C), 29.4 (t), 29.5 (t), 29.6 (t, 3C), 29.6 (t, 2C), 29.6 (t, 5C), 29.7 (t), 30.6 (t), 35.0 (t), 37.3 (t), 49.0 (d), 63.7 (t), 68.3 (d), 69.3 (t), 70.2 (t), 71.5 (t), 72.8 (t), 77.8 (d), 79.5 (s), 79.6 (d), 109.2 (s), 127.4 (d), 127.6 (d, 2C), 128.3 (d, 2C), 138.6 (s), 155.3 (s), 170.8 (s) ppm; MS (ESI) m/z = 812 $[M+Na]^+$; HRMS (ESI) calcd for $C_{45}H_{75}NO_{10}$ $[M+Na]^+$ 812.5289, found 812.5244.

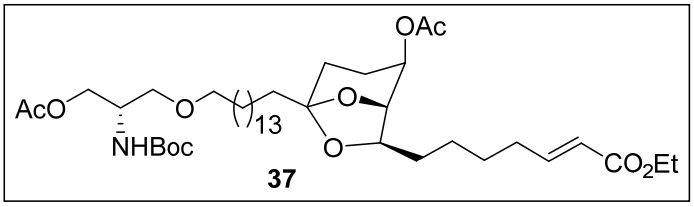
(1*S*,2*R*,5*S*,7*R*)-5-(15-((*S*)-3-Acetoxy-2-(*tert*-butoxycarbonylamino)propoxy)pentadecyl)-7-(5-hydroxypentyl)-6,8-dioxabicyclo[3.2.1]octan-2-yl acetate (36)



36

A suspension of **35** (200 mg, 0.3 mmol), Pd-C (5 mg) in ethyl acetate (5 mL) was flushed with hydrogen gas and stirred under hydrogen (20 *psi*) atmosphere for 30 min. The reaction mixture was filtered through celite, concentrated and the crude product by was purified column chromatography (50:50 petroleum ether/EtOAc) to yield **36** (175 mg, 88%) as colorless oil: R_f (30% EtOAc/petroleum ether) 0.4; $[\alpha]^{25}_D$: –47.4 (*c* 1.3, $CHCl_3$); IR ($CHCl_3$) *v*: 3448, 2928, 2855, 1735, 1499, 1366, 1244,1043, 756, 665 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ1.23 (s, 22H), 1.35–1.41 (m, 6H), 1.43 (s, 9H), 1.51 –1.58 (m, 6H), 1.61 –1.72 (m, 5H), 1.78 (dt, J = 5.6, 18.4 Hz, 1H), 2.04 (s, 3H), 2.10 (s, 3H), 3.38 (t, J = 6.4 Hz, 2H), 3.41 –3.49 (m, 2H), 3.63 (t, J = 6.4 Hz, 2H), 3.91 (t, J = 5.5 Hz, 1H), 3.97 (br s, 1H), 4.10 (dd, J = 5.3, 10.1 Hz, 1H), 4.13 –4.18 (m, 2H), 4.67 (br s, 1H), 4.88 (d, J = 7.1 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ20.8 (q), 21.3 (q), 22.5 (t), 22.7 (t), 25.3 (t), 25.5 (t), 26.0 (t), 28.3 (q, 3C), 29.4 (t), 29.5 (t), 29.6 (t, 3C), 29.6 (t, 2C), 29.7 (t, 5C), 29.7 (t), 30.6 (t), 32.6 (t), 35.0 (t), 37.3 (t), 49.0 (d), 62.8 (t), 63.7 (t), 68.4 (d), 69.3 (t), 71.6 (t), 77.8 (d), 79.6 (d), 109.3 (s), 155.4 (s), 170.9 (s) ppm; MS (ESI) m/z = 722 $[M+Na]^+$; HRMS (ESI) calcd for $C_{38}H_{69}NO_{10}$ $[M+Na]^+$ 722.4819, found 722.4765.

(*E*)-Ethyl 7-((1*S*,2*R*,5*S*,7*R*)-2-acetoxy-5-(15-((*S*)-3-acetoxy-2-(*tert* butoxycarbonylamino)propoxy)pentadecyl)-6,8-dioxabicyclo[3.2.1]octan-7-yl)hept-2-enoate (37)

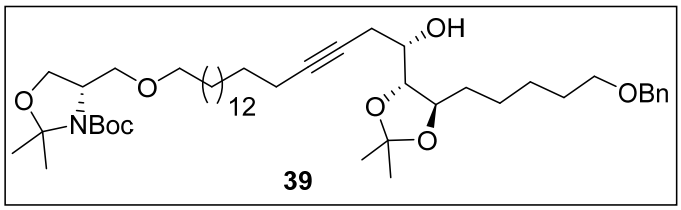


37

To an ice-cooled solution of the alcohol **36** (50 mg, 0.07 mmol) in CH_2Cl_2 (2 mL), DMP (0.36 g, 0.08 mmol) was added in small portions and stirred for 6 h. The reaction mixture was quenched with ice, partitioned between CH_2Cl_2, water and the organic layer was separated, washed with CH_2Cl_2, brine, dried (Na_2SO_4), and concentrated to afford the aldehyde (40 mg, 80%) as colorless syrup. The crude aldehyde was used for the next step without purification.

To a solution of the aldehyde (35 mg, 0.05 mmol) in benzene (2 mL), the ylide ((carbethoxymethylene) triphenyl phosphorane) (52 mg, 0.15 mmol) was added and refluxed for 1 h. Solvent was evaporated under reduced pressure and the crude residue was purified by column chromatography (80:20 petroleum ether/EtOAc) to yield **37** (29 mg, 75%) as colorless oil: R_f (10% EtOAc/petroleum ether) 0.4; $[\alpha]^{25}_D$: –83.4 (*c* 0.98, $CHCl_3$); IR ($CHCl_3$) *v*: 3367, 2927, 2854, 1720, 1500, 1465, 1244, 1042, 971, 775 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ1.23 (s, 24H), 1.27 (t, *J* = 7.2 Hz, 3H), 1.36–1.41 (m, 4H), 1.43 (s, 9H), 1.47 –1.56 (m, 6H), 1.65 –1.72 (m, 3H), 1.79 (dt, *J* = 5.8, 8.2 Hz, 1H), 2.05 (s, 3H), 2.10 (s, 3H), 2.19 (dd, *J* = 6.8, 13.6 Hz, 2H), 3.39 (t, *J* = 6.7 Hz, 2H), 3.42 –3.50 (m, 2H), 3.89 (dd, *J* = 5.1, 7.8 Hz, 1H), 3.97 (br s, 1H), 4.09 (dd, *J* = 5.6, 11.1 Hz, 1H), 4.14 –4.18 (m, 2H), 4.17 (q, *J* = 7.3 Hz, 2H), 4.67 (t, *J* = 2.0 Hz, 1H), 4.87 (d, *J* = 7.4 Hz, 1H), 5.80 (d, *J* = 15.6 Hz, 1H), 6.93 (dt, *J* = 7.0, 15.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ14.3 (q), 20.9 (q), 21.3 (q), 22.5 (t), 22.8 (t), 25.1 (t), 26.1 (t), 27.8 (t), 28.3 (q, 3C), 29.5 (t), 29.5, (t), 29.6 (t, 3C), 29.6 (t, 2C), 29.7 (t, 5C), 29.7 (t), 30.6 (t), 32.1 (t), 34.9 (t), 37.4 (t), 60.1 (t), 63.7 (t), 68.3 (d), 69.3 (t), 71.6 (t), 77.7 (d), 79.7 (d), 109.4 (s), 121.5 (d), 148.9 (d), 152.7 (s), 166.7 (s), 170.9 (s, 2C) ppm; MS (ESI) m/z = 790 $[M+Na]^+$; HRMS (ESI) calcd for $C_{42}H_{73}NO_{11}$ $[M+Na]^+$ 790.5082, found 790.5037.

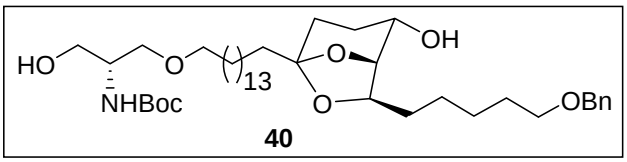
(S)-Tert-butyl 4-(((S)-19-((4R,5R)-5-(5-(Benzyloxy)pentyl)-2,2-dimethyl-1,3-dioxolan-4-yl)-19-hydroxynonadec-16-ynyloxy)methyl)-2,2-dimethyloxazolidine-3-carboxylate (39)



39

To a solution of alkyne **6** (0.58 g, 1.25 mmol) in THF (15 mL) at –78 °C, n-BuLi (0.8 mL, 1.25 mmol, 1.6 M in hexane) was added at –78 °C and stirred for an additional 15 min. To this, $BF_3{\cdot}Et_2O$ (0.16 mL, 1.25 mmol) was added and stirred again for 15 min. A solution of the epoxide **10** (0.1 g, 0.31 mmol) in THF (8 mL) was added at –78 °C and stirred further at the same temperature for another 30 min. The reaction mixture was quenched with THF-H_2O (1:1) at –78 °C. The organic layer was separated and the aqueous layer was washed with ethyl acetate. The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated. Purification of the residue by column chromatography (15% ethyl acetate in petroleum ether) afforded **39** (180 mg , 73%) as a colorless syrup. $[\alpha]^{25}_D$: +23.1 (*c* 6.9, $CHCl_3$); IR ($CHCl_3$) *v*: 3445, 2927, 2855, 1701, 1456, 1388, 1257, 1174, 1103, 848, 767cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz): δ1.23 (s, 24H), 1.38 (s, 3H), 1.39 (s, 3H), 1.40–1.44 (m, 6H), 1.45 (s, 9H), 1.50 (s, 3H), 1.55 (s, 3H), 1.58 –1.65 (m, 4H), 2.13 (tt, *J* = 2.4, 6.7 Hz, 2H), 2.35 (d, *J* = 8.1 Hz, 1H), 2.38–2.45 (m, 2H), 3.22–3.38 (m, 1H), 3.40–3.48 (m, 4H), 3.51–3.65 (m, 2H), 3.75 (dd, *J* = 2.8, 8.1 Hz, 1H), 3.85–4.04 (m, 4H), 4.48 (s, 2H), 7.24–7.33 (m, 5H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ18.7 (t), 23.1, 24.4 (2q, 2C), 25.2 (t), 25.9 (t), 26.1 (t), 26.2 (t), 26.9, 27.5 (2q, 2C), 28.4 (q, 3C), 28.9 (t), 28.9 (t), 29.1 (t), 29.4 (t), 29.6 (t, 4C), 29.6 (t, 5C), 33.1 (t), 56.3, 56.4 (2d, 1C), 65.34, 65.6 (2t, 1C), 69.1 (d), 69.2, 70.0 (2t, 1C), 70.2 (t), 71.3 (t), 72.8 (t), 75.5 (s), 77.2 (d), 79.6, 80.1 (2s, 1C), 81.8 (d), 83.0 (s), 93.2, 93.6 (2s, 1C), 108.7 (s), 127.4 (d), 127.5 (d, 2C), 128.3 (d, 2C), 138.6 (s), 151.7, 152.1 (2s, 1C), ppm; HRMS (ESI^+): Calculated for $[C_{47}H_{79}NO_8Na]^+$: 808.5704; found: 808.5649.

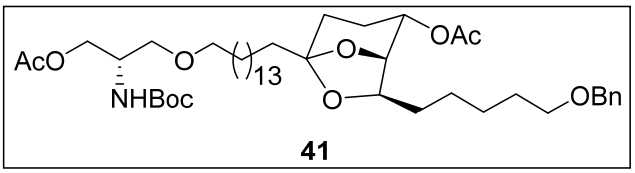
Tert-butyl (R)-1-(15-((1R,2S,5S,7R)-7-(5-(benzyloxy)pentyl)-2-hydroxy-6,8-dioxabicyclo[3.2.1]octan-5-yl)pentadecyloxy)-3-hydroxypropan-2-ylcarbamate (40)



40

A solution of the acetonide **39** (100 mg, 0.127 mmol) in dry dichloromehane was degassed properly. Then $(C_6H_5)_3PAuCl$ (3 mg, 0.006 mmol) followed by AgSbF6 (2 mg, 0.05 mmol) were added at 0 °C and keep stirring at rt under argon atmosphere for 3 h. The reaction mixture was concentrate under reduce pressure and the obtained residue was purified by silica gel chromatography (60% ethyl acetate in petroleum ether) to obtain **40** (74 mg, 82%) as colorless syrup. $[\alpha]^{25}_D$: +14.2 (*c* 2.9, $CHCl_3$); IR ($CHCl_3$) *v*: 3444, 2928, 2855, 1700, 1499, 1367, 1216, 1170, 756, 697 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ1.23 (s, 24H), 1.34–1.40 (m, 4H), 1.44 (s, 9H), 1.51 –1.55 (m, 4H), 1.60 –1.67 (m, 6H), 1.72 (br s, 1H), 1.83–1.91 (m, 2H), 2.83 (br s, 1H), 3.41 (t, *J* = 6.7 Hz, 2H), 3.46 (t, *J* = 6.5 Hz, 2H), 3.53 (dd, *J* = 3.9, 9.5 Hz, 1H), 3.58 (dd, *J* = 3.5, 9.6 Hz, 1H), 3.65–3.67 (m, 1H), 3.74–3.79 (m, 2H), 3.88 (br s, 1H), 3.92 (br s, 1H), 4.18 (t, *J* = 6.2 Hz, 1H), 4.48 (s, 2H), 5.18 (d, *J* = 5.5 Hz, 1H), 7.24–7.33 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ23.3 (t), 25.4 (t), 26.0 (t), 26.1 (t), 26.6 (t), 28.4 (q, 3C), 29.4 (t), 29.5 (t, 2C), 29.6 (t, 8C), 29.8 (t), 33.8 (t), 35.2 (t), 36.8 (t), 51.4 (d), 64.4 (t), 66.5 (d), 70.3 (t), 71.7 (t), 71.8 (t), 72.9 (t), 75.7 (d), 79.7 (s), 80.8 (d), 108.5 (s), 127.5 (d), 127.6 (d, 2C), 128.3 (d, 2C), 138.6 (s), 156.1 (s) ppm; HRMS (ESI^+) : Calculated for $[C_{41}H_{71}NO_8Na]^+$: 728.5078; found: 728.5027.

(1S,2S,5S,7R)-5-(15-((S)-3-Acetoxy-2-(tert-butoxycarbonylamino)propoxy)pentadecyl)-7-(5-(benzyloxy)pentyl)-6,8-dioxabicyclo[3.2.1]octan-2-yl acetate (41)



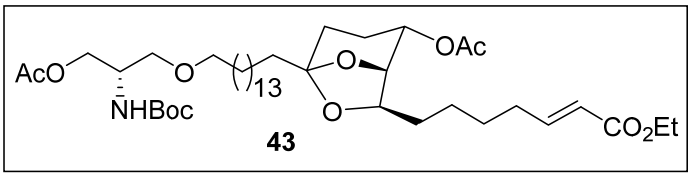
41

To a solution of **40** (100 mg, 0.141 mmol) in DCM (10 mL) at 0 °C was added triethylamine (0.12 mL, 0.85 mmol), DMAP (2 mg) and stirred for 15 min. Acetic anhydryde (0.04 mL, 0.425 mmol) was added at 0 °C and stirred further for 2 h. The reaction mixture was extracted with DCM. The combined organic extracts were washed with

brine, dried over Na_2SO_4, concentrated and the resulting crude product was purified by column chromatography (40% ethyl acetate in petroleum ether) to afford the acylate **41** (105 mg, 97 %) as colorless syrup. $[\alpha]^{25}_D$: +50.8 (*c* 1.2, $CHCl_3$); IR ($CHCl_3$) *v*: 3450, 2927, 1741, 1498, 1366, 1236, 1171, 1040, 942, 756, 698 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ1.23 (s, 24H), 1.36–1.41 (m, 6H), 1.42 (s, 9H), 1.48 –1.54 (m, 3H), 1.57 –1.69 (m, 6H),1.77 (dt, *J* = 6.5, 18.3 Hz, 1H), 2.01(s, 3H), 2.03 (s, 3H), 3.38 (t, *J* = 6.7 Hz, 2H), 3.45 (t, *J* = 6.5 Hz, 2H), 3.38 –3.49 (m, 2H), 3.97 (brs, 1H), 4.02 (d, *J* = 3.5 Hz, 1H), 4.08 (dd, *J* = 5.5, 10.8 Hz, 1H), 4.13 (d, *J* = 6.3 Hz, 1H), 4.15–4.18 (m, 1H), 4.48 (s, 2H), 4.85–4.90 (m, 2H), 7.24–7.33 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ20.8 (q), 21.0 (q), 23.1 (t), 23.2 (t), 25.3 (t), 26.0 (t), 26.0 (t), 28.3 (q, 3C), 29.4 (t), 29.5 (t), 29.5 (t), 29.5 (t), 29.6 (t), 29.6 (t), 29.6 (t, 4C), 29.7 (t), 29.7 (t), 33.6 (t), 34.9 (t), 36.7 (t), 49.0 (d), 63.7 (t), 68.6 (d), 69.3 (t), 70.2 (t), 71.5 (t), 72.8 (t), 76.4 (d), 78.0 (d), 79.5 (s), 108.9 (s), 127.4 (d), 127.5 (d, 2C), 128.3 (d, 2C), 138.6 (s), 155.3 (s), 170.1 (s), 170.8 (s); HRMS (ESI^+) : Calculated for $[C_{45}H_{75}NO_{10}Na]^+$: 812.5289; found: 812.5241.

(E)-Ethyl 7-((1S,2S,5S,7R)-2-acetoxy-5-(15-((S)-3-acetoxy-2-(tert-butoxycarbonylamino)propoxy)pentadecyl)-6,8-dioxabicyclo[3.2.1]octan-7-yl)hept-2-enoate (43)

A suspension of **41** (200 mg, 0.283 mmol), Pd-C (5 mg) in ethyl acetate (5 mL) was flushed with hydrogen gas and stirred under hydrogen (20 *psi*) atmosphere for 30 min. The reaction mixture was filtered through celite, concentrated and the crude product by was purified column chromatography (30% ethyl acetate in petroleum ether) to yield **42** (175 mg, 88%) as colorless oil.

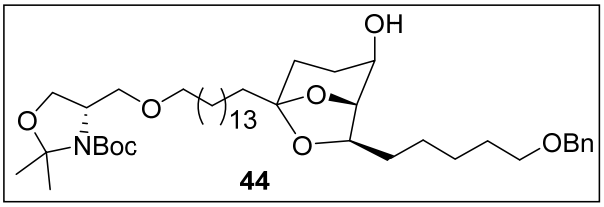


43

To an ice-cooled solution of the alcohol **42** (40 mg, 0.06 mmol) in DCM (2 mL), DMP (0.29 g, 0.07 mmol) was added in small portions and stirred for 6 h. The reaction mixture was quenched with ice, partitioned between DCM, water and the organic layer was separated, washed with DCM, brine, dried (Na_2SO_4), and concentrated to afford the aldehyde (31 mg, 78%) as colorless syrup. The crude aldehyde was used for the next step without purification.

To a solution of the aldehyde (30 mg, 0.04 mmol) in benzene (2 mL), the ylide ((carbethoxymethylene) triphenyl phosphorane) (45 mg, 0.13 mmol) was added and refluxed for 1 h. Solvent was evaporated under reduced pressure and the crude residue was purified by column chromatography (20% ethyl acetate in petroleum ether) to yield **43** (27 mg, 82%) as colorless oil. $[\alpha]^{25}_{D}$: –83.4 (*c* .98, $CHCl_3$); IR ($CHCl_3$) *v*: 3449, 2927, 2855, 1742, 1500, 1463, 1367, 1235, 1040, 855, 776, 720 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ1.23 (s, 24H), 1.27 (t, *J* = 7.2 Hz, 3H), 1.36–1.41 (m, 4H), 1.43 (s, 9H), 1.47 –1.56 (m, 6H), 1.63 –1.68 (m, 3H), 1.76 (dt, *J* = 6.5, 18.3 Hz, 1H), 2.03 (s, 3H), 2.04 (s, 3H), 2.20 (dd, *J* = 6.8, 13.5 Hz, 2H), 3.39 (t, *J* = 6.7 Hz, 2H), 3.42 –3.50 (m, 2H), 3.97 (br s, 1H), 4.02 (d, *J* = 3.5 Hz, 1H), 4.09 (dd, *J* = 5.5, 10.8 Hz, 1H), 4.14 –4.18 (m, 2H), 4.17 (q, *J* = 7.2 Hz, 2H), 4.86 –4.91 (m, 2H), 5.80 (d, *J* = 15.7 Hz, 1H), 6.93 (dt, *J* = 7.0, 15.7 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ14.3 (q), 20.9 (q), 21.1 (q), 23.1 (t), 23.3 (t), 25.1 (t), 26.1 (t), 27.8 (t), 28.3 (q, 3C), 29.5 (t), 29.5(t), 29.6 (t, 2C), 29.6 (t), 29.6 (t), 29.7 (t, 4C), 29.8 (t), 32.1 (t), 33.5 (t), 34.8 (t), 36.7 (t), 49.1 (d), 60.2 (t), 63.7 (t), 68.6 (d), 69.3 (t), 71.6 (t), 76.3 (d), 78.1 (d), 79.6 (s), 109.1 (s), 121.5 (d), 148.9 (d), 155.4 (s), 166.7 (s), 170.2 (s), 170.9 (s), ppm; HRMS (ESI^+): Calculated for $[C_{42}H_{73}NO_{11}Na]^+$: 790.5082; found: 790.5034.

(4*S*)-*Tert*-butyl 4-((15-((1*R*,2*R*,5*S*)-7-(5-(benzyloxy)pentyl)-2-hydroxy-6,8-dioxabicyclo[3.2.1]octan-5-yl)pentadecyloxy)methyl)-2,2-dimethyloxazolidine-3-carboxylate (44)

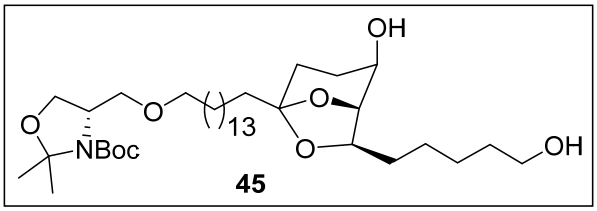


44

To a solution of diol **34** (100 mg, 0.14 mmol) in acetone, were added DMP (0.07 mL, 0.6 mmol) and *p*-TSA (5 mg) at 0 °C. The reaction mixture was stirred at rt for 2.5 h when TLC analysis indicates the reaction was complete then was treated with few drops of triethylamine and the solvent was removed under reduced pressure and the resulting crude product was purified by column chromatography (70:30 petroleum ether/EtOAc) to obtain **44** (87 mg, 82%) as a colorless thick syrup: R_f (35% EtOAc/petroleum ether) 0.4; $[\alpha]^{25}_{D}$: +28.7 (*c* 1.0, $CHCl_3$); IR ($CHCl_3$) *v*: 3404, 2925, 2854, 1702, 1459, 1388, 1103, 847, 770, 732, 697 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ1.24 (s, 24H), 1.38–1.44 (m, 6H), 1.46 (s, 9H), 1.51 (s, 3H), 1.55 (s, 3H), 1.53 –1.54 (m, 2H), 1.60 –1.69 (m, 6H), 1.76 (dt, *J* = 5.6, 18.4 Hz, 1H), 1.93 –2.00 (m, 1H), 2.37 (d, *J* = 6.3 Hz, 1H), 3.29 (dd, *J* = 9.5, 21.4 Hz, 1H), 3.41 (t, *J* = 6.7 Hz, 2H), 3.45 (t, *J* = 6.4

Hz, 2H), 3.37 –3.49 (m, 1H), 3.59 (br s, 1H), 3.85–3.92 (m, 3H), 3.98 (br s, 1H), 4.04 (br s, 1H), 4.49 (s, 2H), 7.24–7.35 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 23.0 (t), 23.1, 24.4 (2q, 1C), 25.1 (t), 25.4 (t), 26.0 (t), 26.1 (t), 26.7, 27.5 (2q, 1C), 28.4, 28.5 (2q, 3C), 29.5(t), 29.6 (t,5C), , 29.7(t, 4C), , 29.8 (t), 30.1 (t), 35.2 (t), 37.5 (t), 56.3, 56.5 (2q, 1C), 65.4, 65.7 (2t, 1C), 66.3 (d), 69.3, 70.0 (2t, 1C), 70.3 (t), 71.4 (t), 72.9 (t), 77.9 (d), 79.7, 80.2, (2s, 1C), 82.3 (d), 93.2, 93.7 (2s, 1C), 109.5 (s), 127.5 (d), 127.6 (d, 2C), 128.3 (d, 2C), 138.6 (s), 151.7, 152.2 (2s, 1C) ppm; MS (ESI) m/z = 768 $[M+Na]^+$; HRMS (ESI) calcd for $C_{44}H_{75}NO_8$ $[M+Na]^+$ 768.5391. found 768.5352.

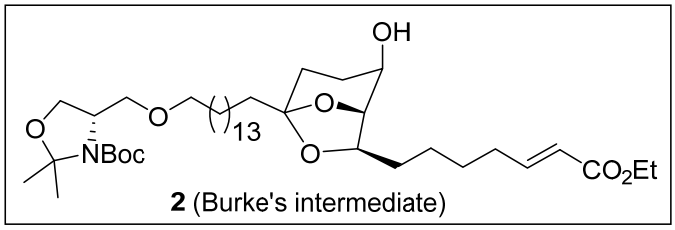
(4*S*)-*Tert*-butyl 4-((15-((1*R*,2*R*,5*S*)-2-hydroxy-7-(5-hydroxypentyl)-6,8-dioxabicyclo[3.2.1]octan-5-yl)pentadecyloxy)methyl)-2,2-dimethyloxazolidine-3-carboxylate (45)



45

A suspension of **44** (50 mg, 0.07 mmol), $Pd(OH)_2$ (5 mg) in ethyl acetate (5 mL) was flushed with hydrogen gas and stirred under hydrogen (20 *psi*) atmosphere for 30 min. The reaction mixture was filtered through celite, concentrated and the crude product by was purified column chromatography (60:40 petroleum ether/EtOAc) to yield **45** (40 mg, 91%) as colorless oil: R_f (40% EtOAc/petroleum ether) 0.4; $[\alpha]^{25}_D$: +36.3 (*c* 0.2, $CHCl_3$); IR ($CHCl_3$) *v*: 3436, 2928, 1690, 1406, 1394, 1216, 758, 668 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.24–1.35 (m, 24H), 1.37–1.44 (m, 6H), 1.46 (s, 9H), 1.51–1.59 (m, 11H), 1.62–1.71 (m, 3H), 1.77 (dt, *J* = 5.5, 12.3 Hz, 1H), 1.92–2.01 (m, 1H), 2.37 (d, *J* = 9.2 Hz, 1H), 3.26–3.50 (m, 2H), 3.39 (dd, *J* = 2.7, 8.1 Hz, 1H), 3.46 (dd, *J* = 2.9, 8.1 Hz, 1H), 3.60–3.66 (m, 1H), 3.63 (t, *J* = 6.4 Hz, 2H), 3.85–4.00 (m, 3H), 3.97–4.05 (m, 1H), 4.05 (br s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 22.7 (t), 22.9 (t), 23.1, 24.4 (2q, 1C), 25.0 (t), 25.3 (t), 25.6 (t), 26.1 (t), 26.7, 27.5 (2q, 1C), 28.4, 28.5 (2q, 3C), 29.1 (t), 29.3 (t), 29.4 (t), 29.6 (t, 2C), 29.6 (t, 3C), 29.8 (t), 30.1 (t), 31.9 (t), 32.6 (t), 35.2 (t), 37.5 (t), 56.3, 56.5 (2d, 1C), 62.8 (t), 65.4, 65.7 (2t, 1C), 66.3 (d), 69.3, 70.0 (2t, 1C), 71.4 (t), 77.8 (d), 79.7, 80.2 (2s, 1C), 82.4 (d), 93.3, 93.7 (2s, 1C), 109.6 (s), 151.7, 152.2 (2s, 1C) ppm; MS (ESI) m/z = 678 $[M+Na]^+$; HRMS (ESI) calcd for $C_{37}H_{69}NO_8$ $[M+Na]^+$678.4921, found 678.4874.

(4*S*)-*Tert*-butyl 4-((15-((1*R*,2*R*,5*S*)-7-((*E*)-7-ethoxy-7-oxohept-5-enyl)-2-hydroxy-6,8-dioxabicyclo[3.2.1]octan-5-yl)pentadecyloxy)methyl)-2,2-dimethyloxazolidine-3-carboxylate (2)

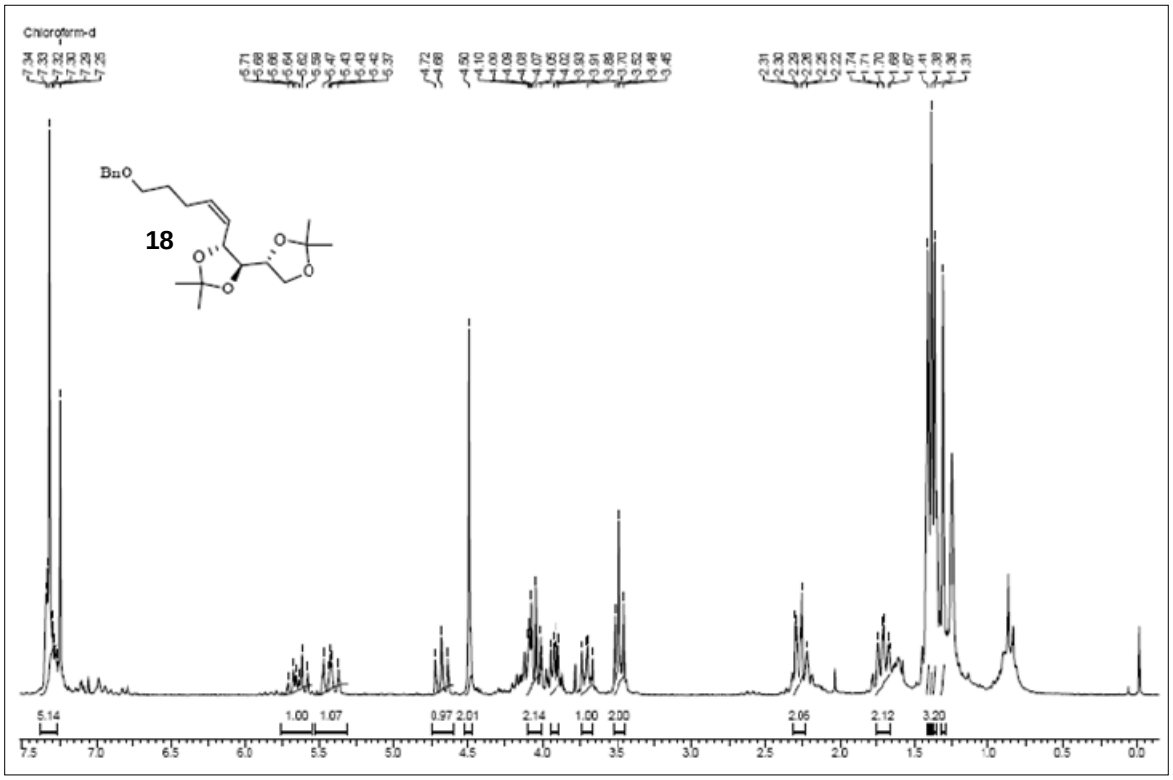


2 (Burke's intermediate)

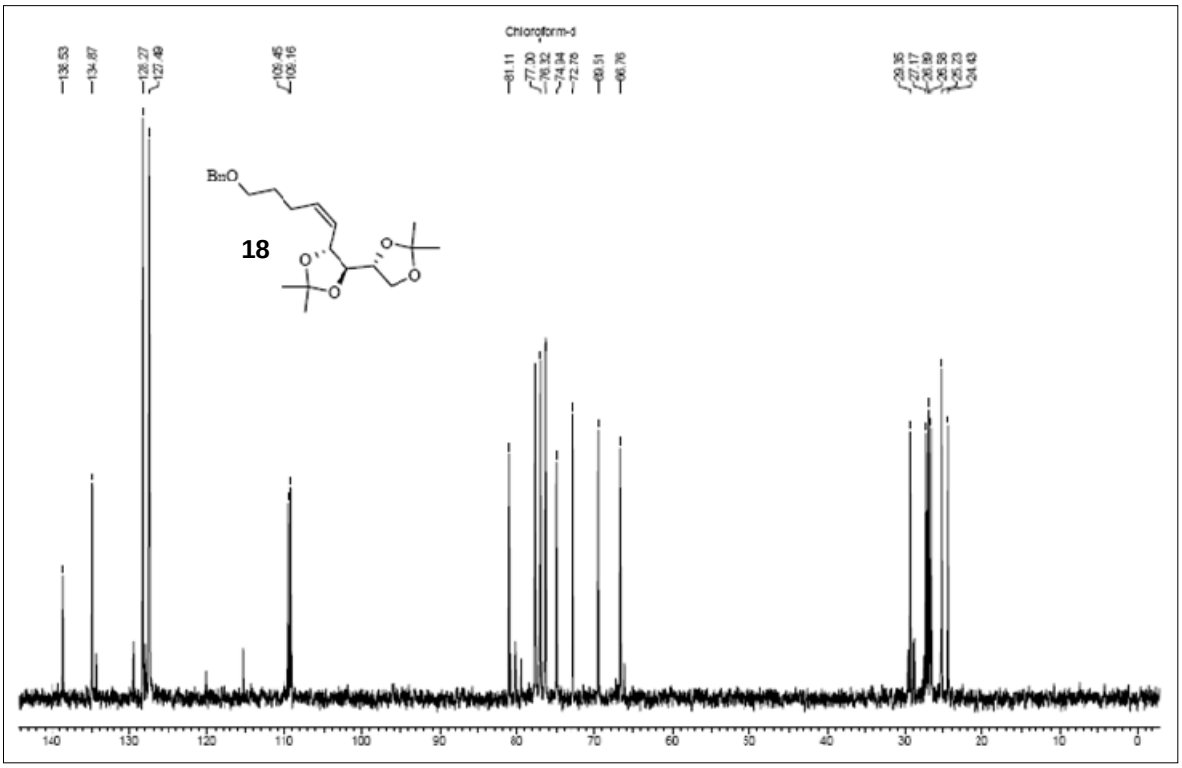
To an ice-cooled solution of the diol **45** (35 mg, 0.05 mmol) in CH_2Cl_2 (2 mL), DMP (27 mg, 0.6 mmol) was added in small portions and stirred for 6 h. The reaction mixture was quenched with ice, partitioned between CH_2Cl_2, water and the organic layer was separated, washed with CH_2Cl_2, brine, dried (Na_2SO_4), and concentrated to afford the aldehyde (30 mg, 85%) as colorless syrup. The crude aldehyde was used for the next step without purification.

To a solution of the aldehyde (30 mg, 0.05 mmol) in benzene (2 mL), the ylide ((carbethoxymethylene) triphenyl phosphorane) (56 mg, 0.16 mmol) was added and refluxed for 1 h. Solvent was evaporated under reduced pressure and the crude residue was purified by column chromatography (80:20 petroleum ether/EtOAc) to yield **2** (26 mg, 78%) as colorless oil: R_f (15% EtOAc/petroleum ether) 0.45; $[\alpha]^{25}_D$: +26.6 (*c* 0.4, $CHCl_3$); IR ($CHCl_3$) *v*: 3451, 2928, 1732, 1693, 1465, 1393, 1247, 1046, 758, 667 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ1.26 (s, 24H), 1.29 (t, *J* = 7.2 Hz, 3H), 1.34–1.46 (m, 7H), 1.48 (s, 9H), 1.47 –1.56 (m, 8H), 1.62 –1.71 (m, 4H), 1.79 (td, *J* = 5.5, 12.5 Hz, 1H), 1.95 –2.02 (m, 1H), 2.22 (dd, *J* = 7.3, 14.0 Hz, 2H), 3.28 –3.34 (m, 1H), 3.40 – 3.50 (m, 3H), 3.62 (br s, 1H), 3.89 (dd, *J* = 5.2, 7.6 Hz, 1H), 3.91 –3.94 (m, 2H), 3.99 –4.01 (m, 1H), 4.06 (br s, 1H), 4.19 (q, *J* = 7.2 Hz, 2H), 5.82 (dt, *J* = 1.5, 15.6 Hz, 1H), 6.96 (dt, *J* = 7.0, 15.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ14.3 (q), 23.0 (t), 23.1, 24.4 (2q, 1C), 25.0 (t), 25.1 (t), 26.1 (t), 26.7, 27.5 (2q, 1C), 27.8 (t), 28.4, 28.5 (2q, 3C), 29.4 (t), 29.6 (t), 29.6 (t, 9C), 29.8 (t), 30.1 (t), 32.1 (t), 35.1 (t), 37.5 (t), 56.3, 56.5 (2d, 1C), 60.2 (t), 65.4, 65.7 (2t, 1C), 66.3 (d), 69.3, 70.1 (2t, 1C), 71.4 (t), 77.7 (d), 79.7, 80.2 (2s, 1C), 82.4 (d), 93.3, 93.7 (2s, 1C), 109.7 (s), 121.5 (d), 148.9 (d), 166.7 (s) ppm; MS (ESI) m/z = 746 $[M+Na]^+$; HRMS (ESI) calcd for $C_{41}H_{73}NO_9$ $[M+Na]^+$ 746.5183. found 746.5129.

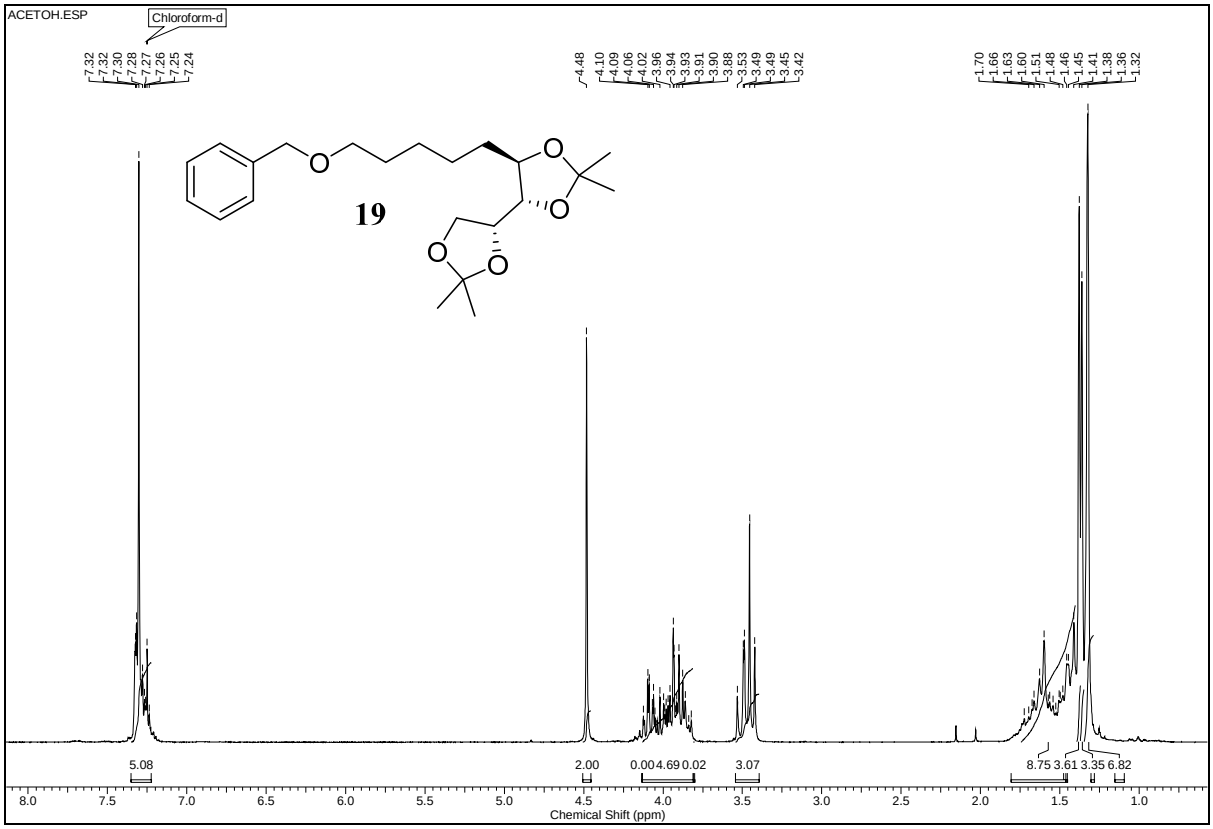
SPECTRA



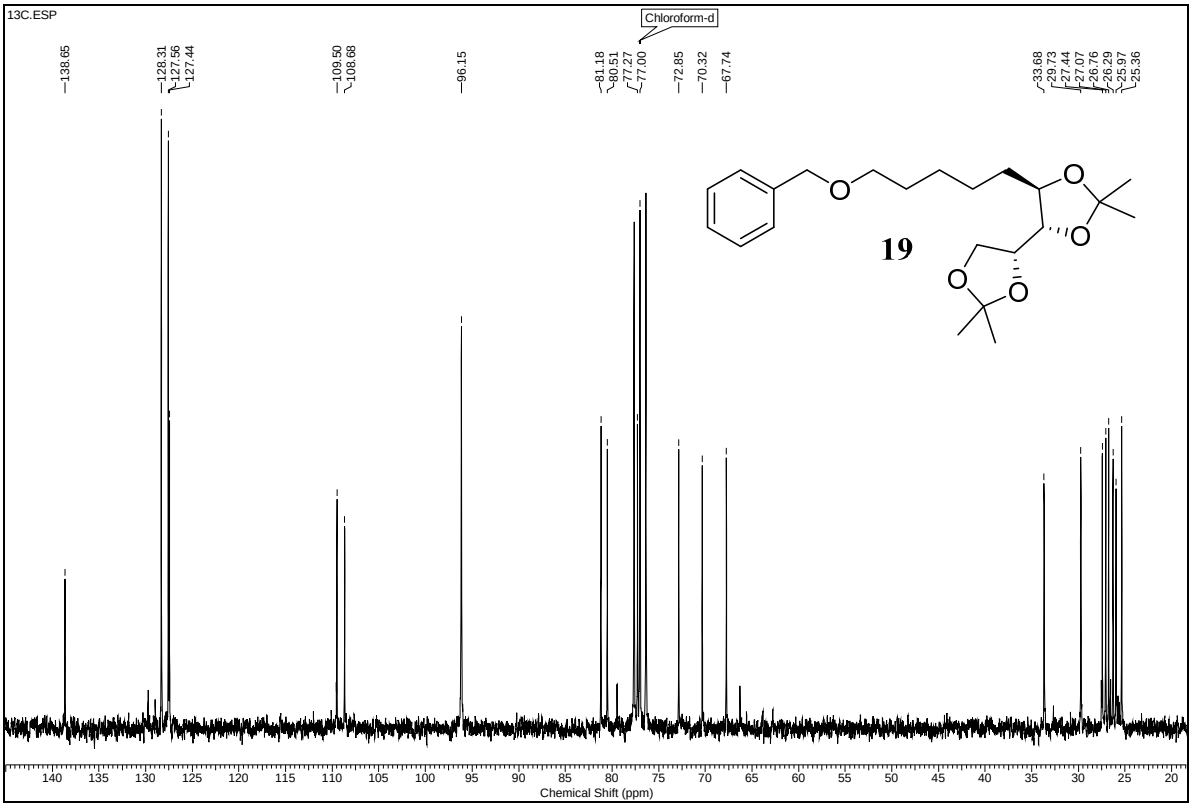
^{1}H NMR Spectrum of 18 in $CDCl_3$



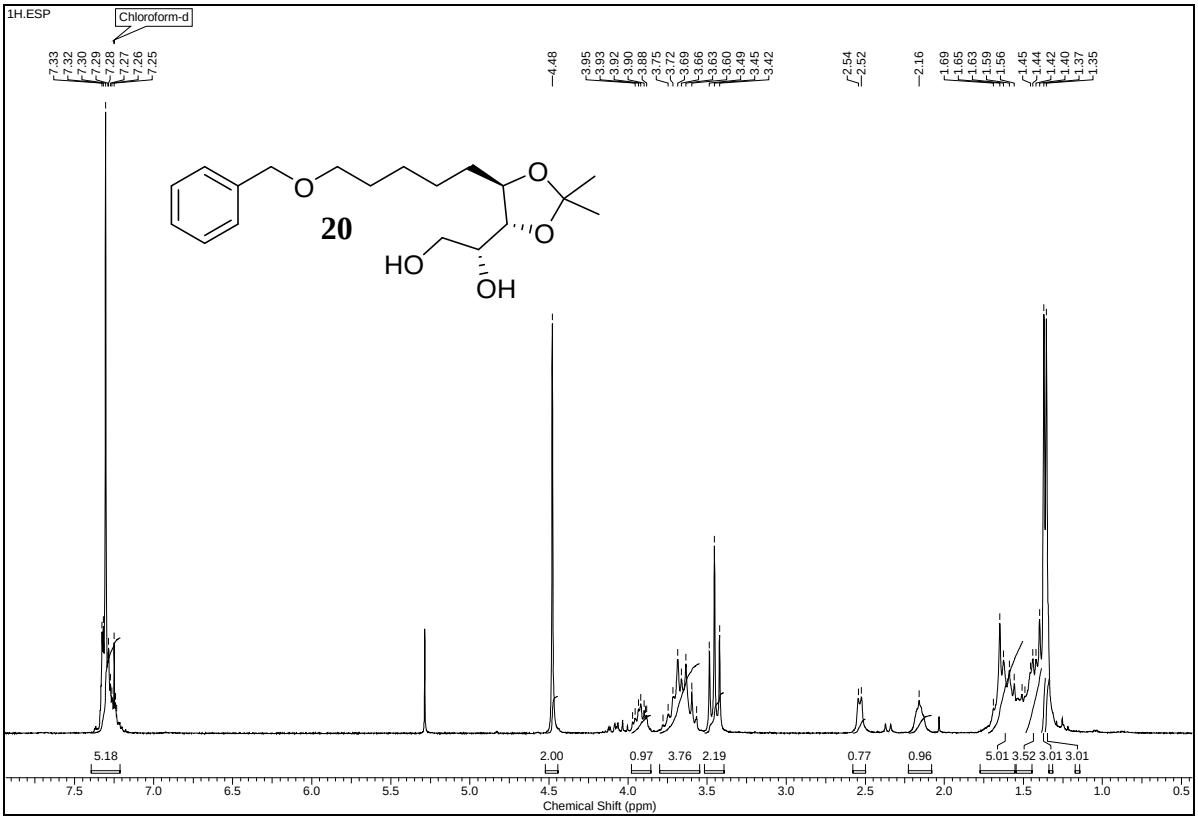
^{13}C NMR Spectrum of 18 in $CDCl_3$



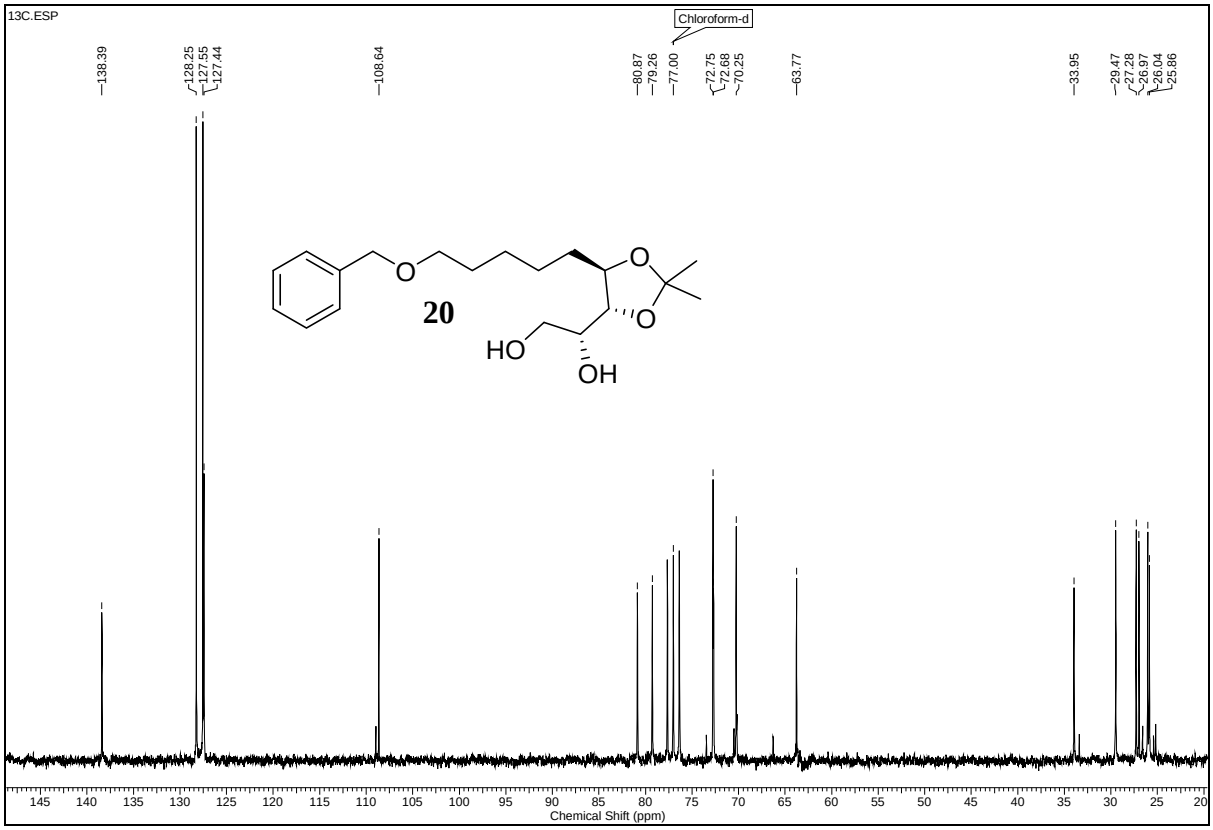
^{1}H NMR Spectrum of 19 in $CDCl_3$



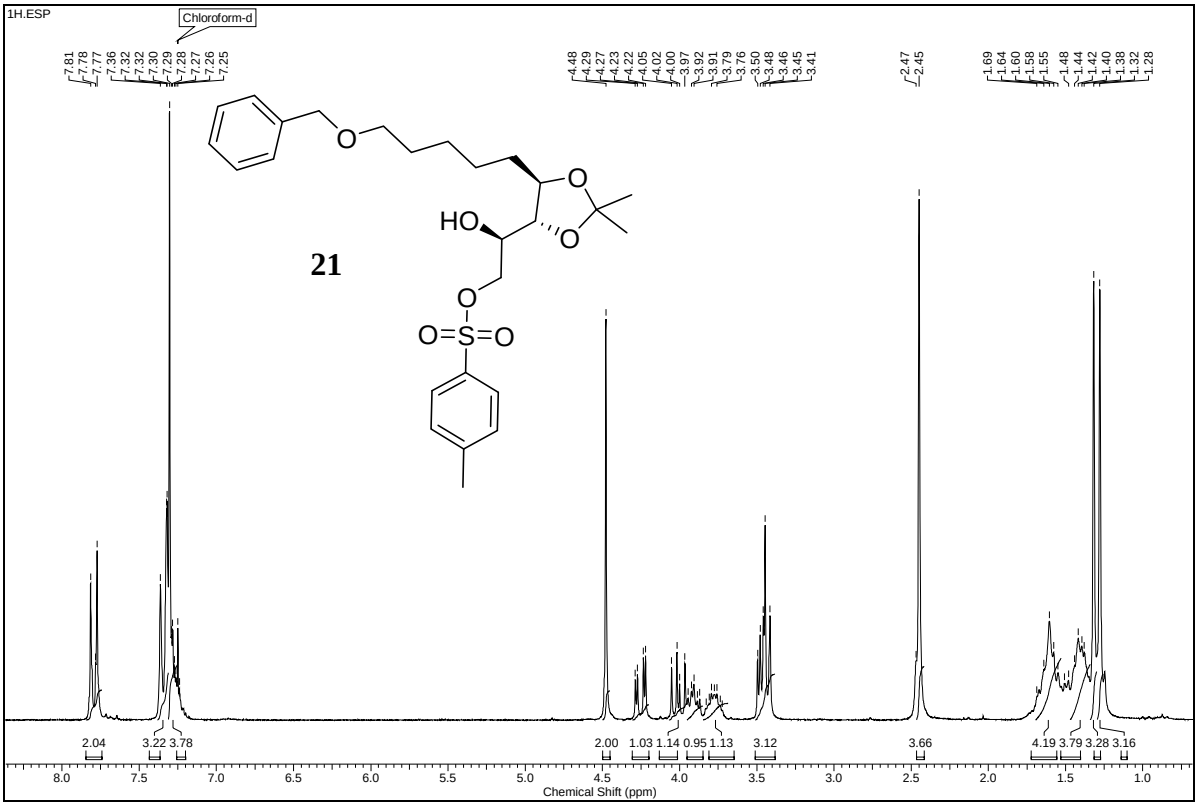
^{13}C NMR Spectrum of 19 in $CDCl_3$



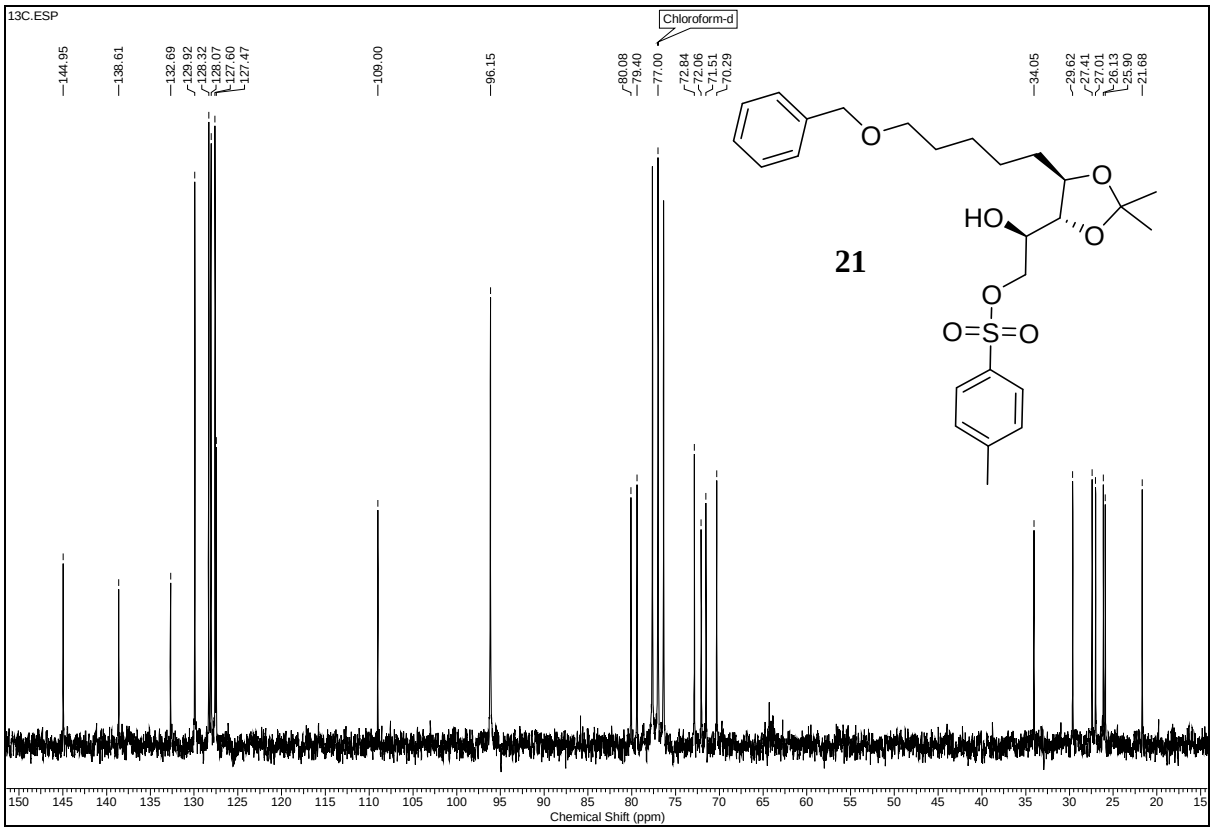
^{1}H NMR Spectrum of 20 in $CDCl_3$



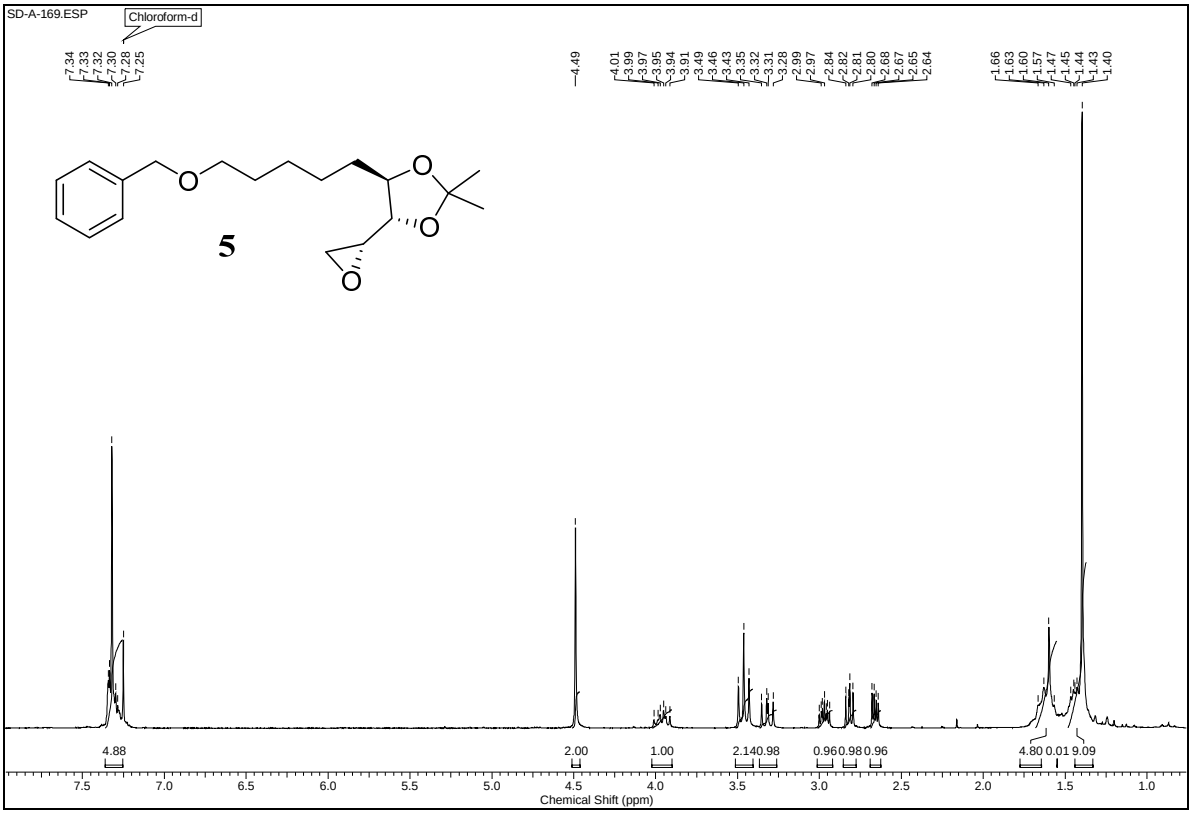
^{13}C NMR Spectrum of 20 in $CDCl_3$



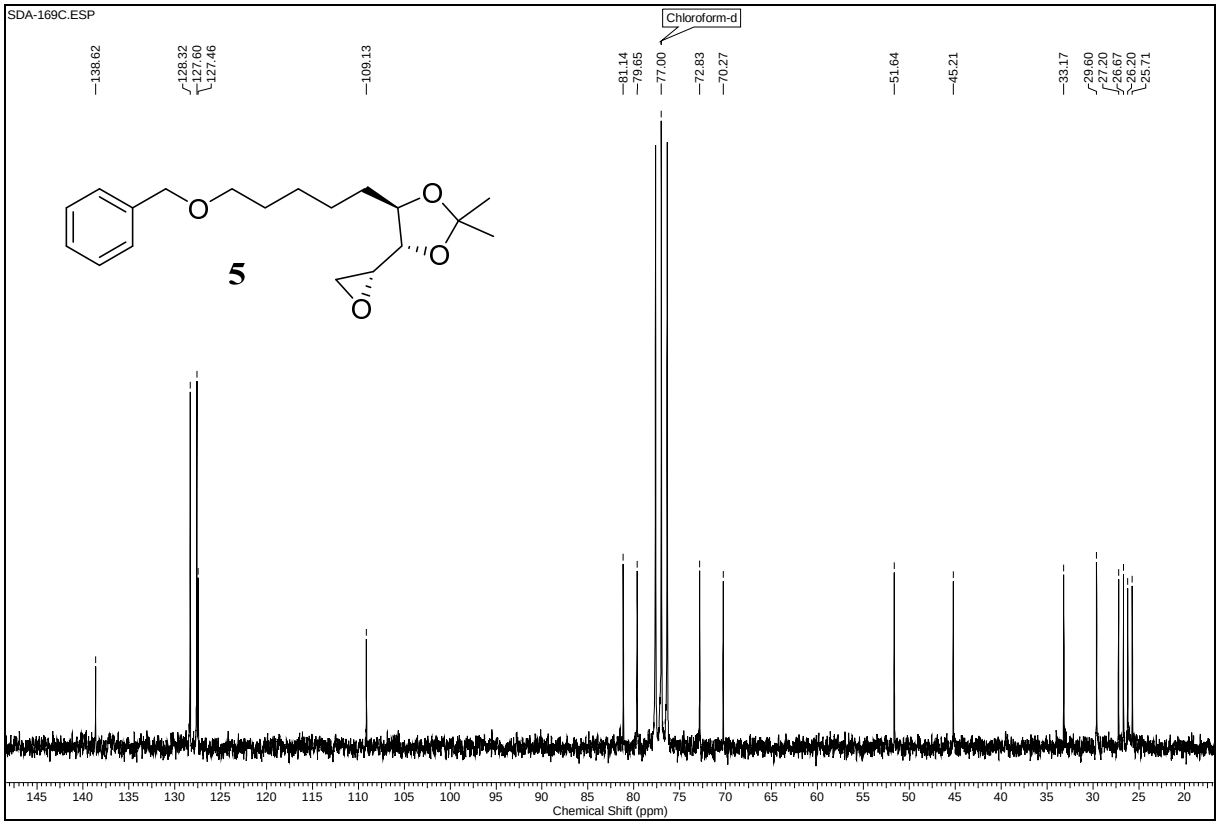
^{1}H NMR Spectrum of 21 in $CDCl_3$



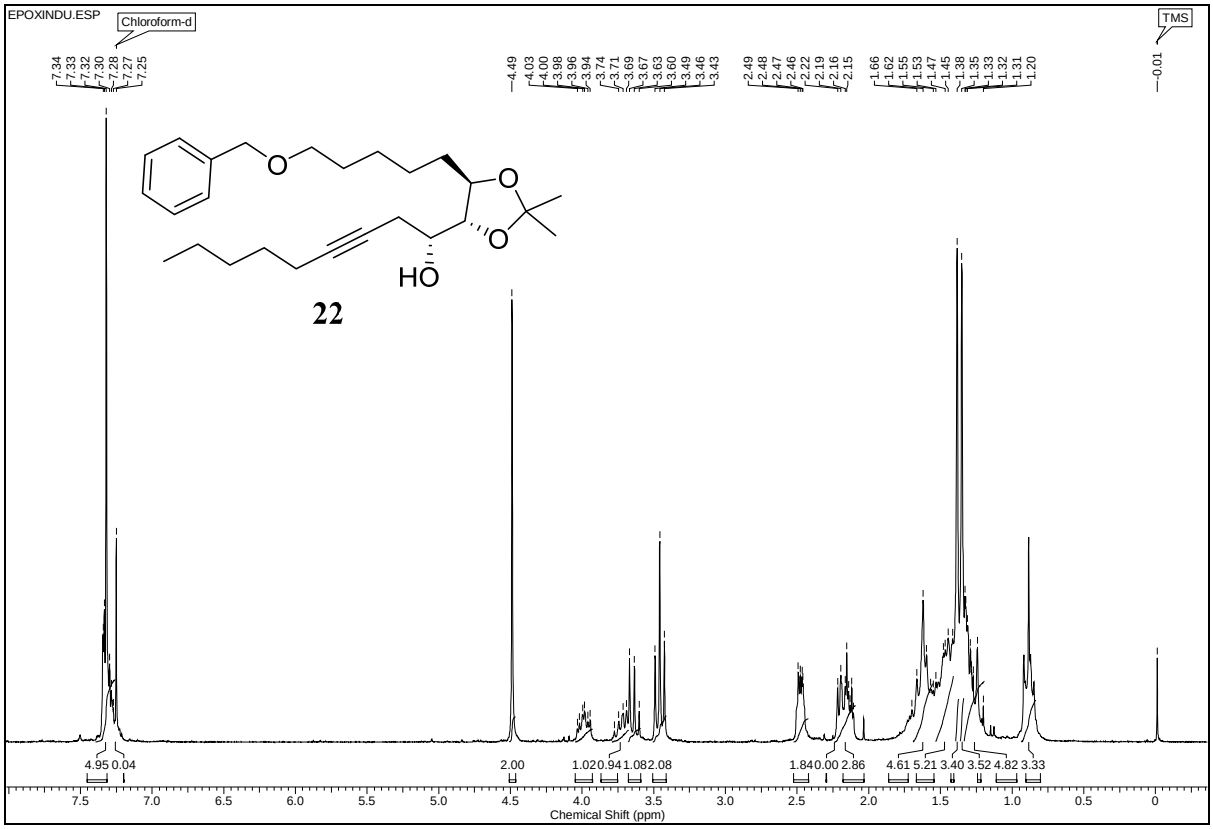
^{13}C NMR Spectrum of 21 in $CDCl_3$



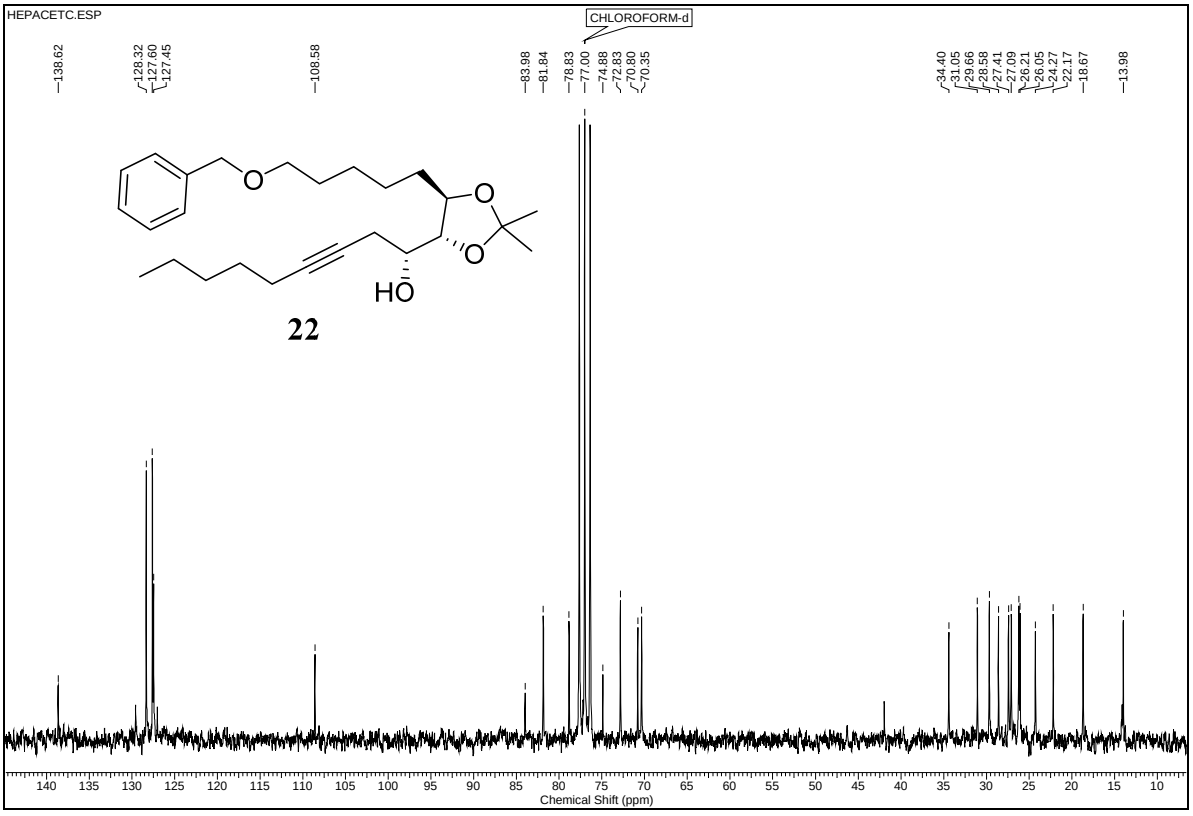
^{1}H NMR Spectrum of 5 in $CDCl_3$



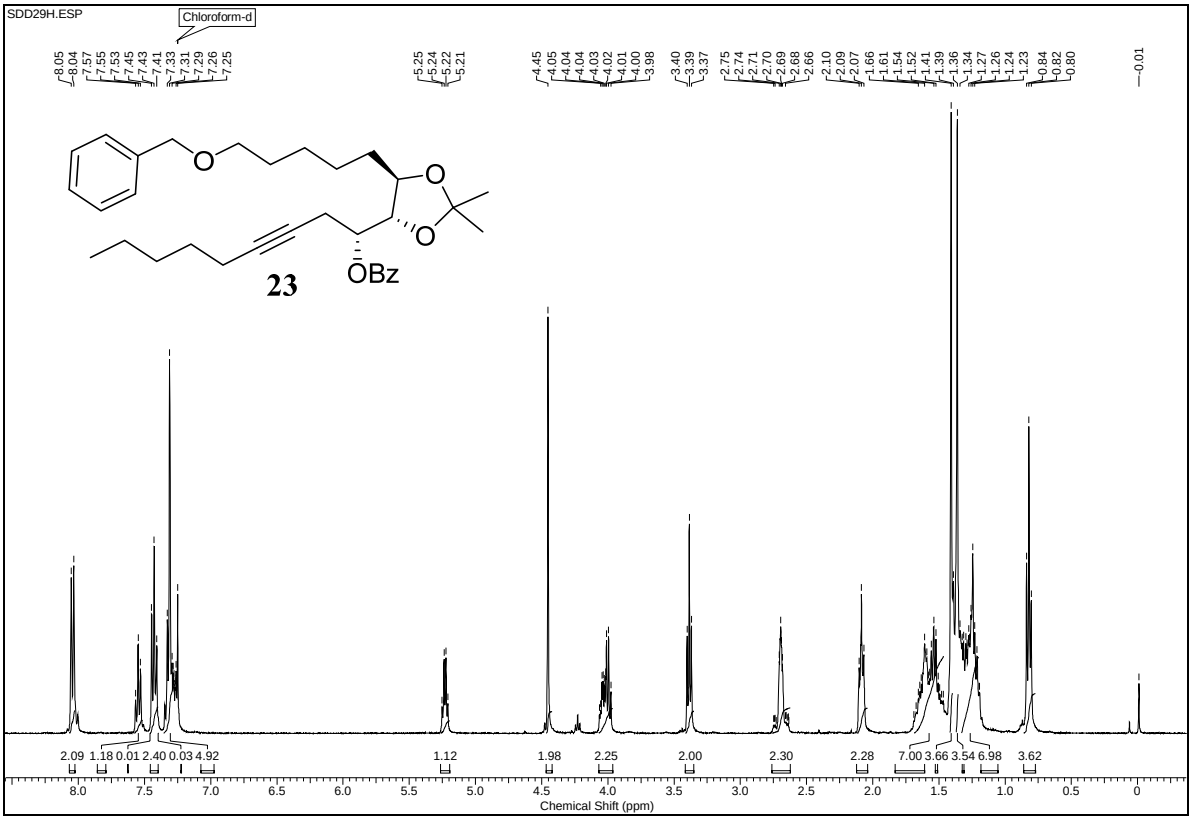
^{13}C NMR Spectrum of 5 in $CDCl_3$



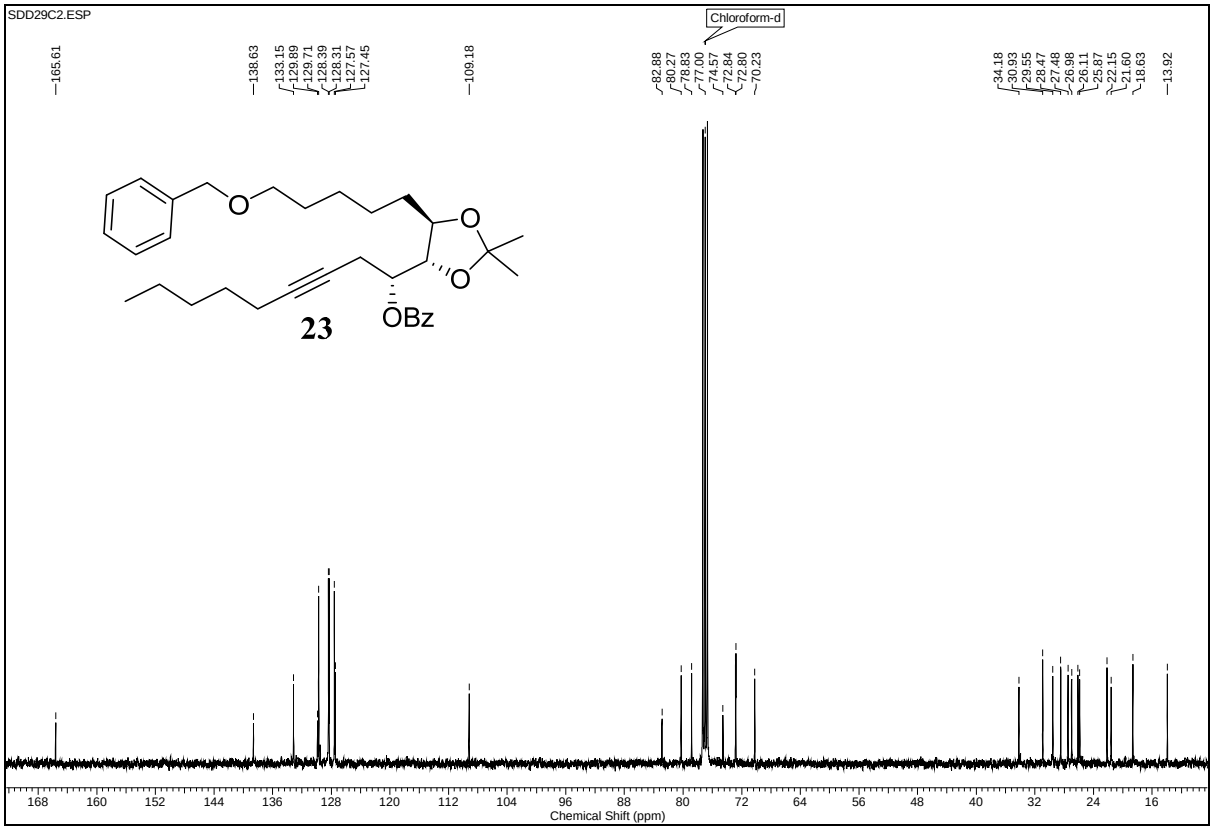
^{1}H NMR Spectrum of 22 in $CDCl_3$



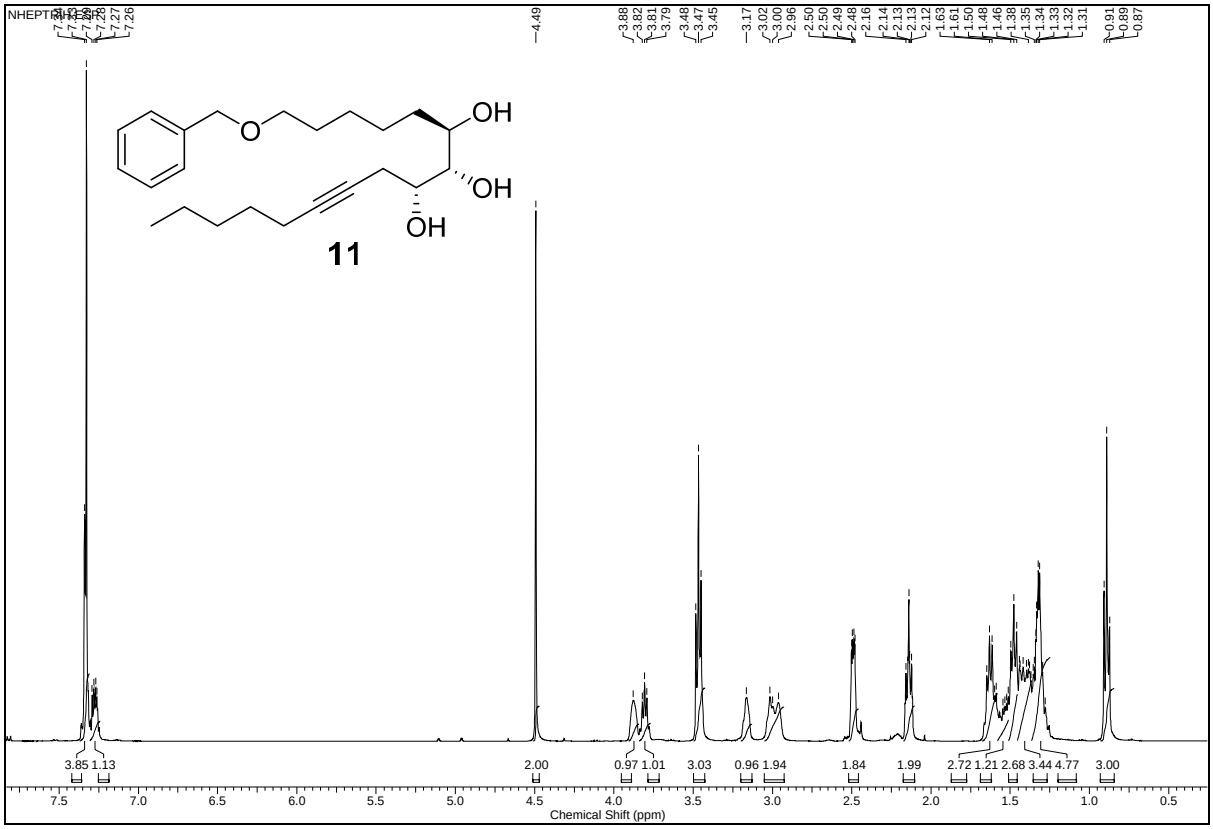
^{13}C NMR Spectrum of 22 in $CDCl_3$



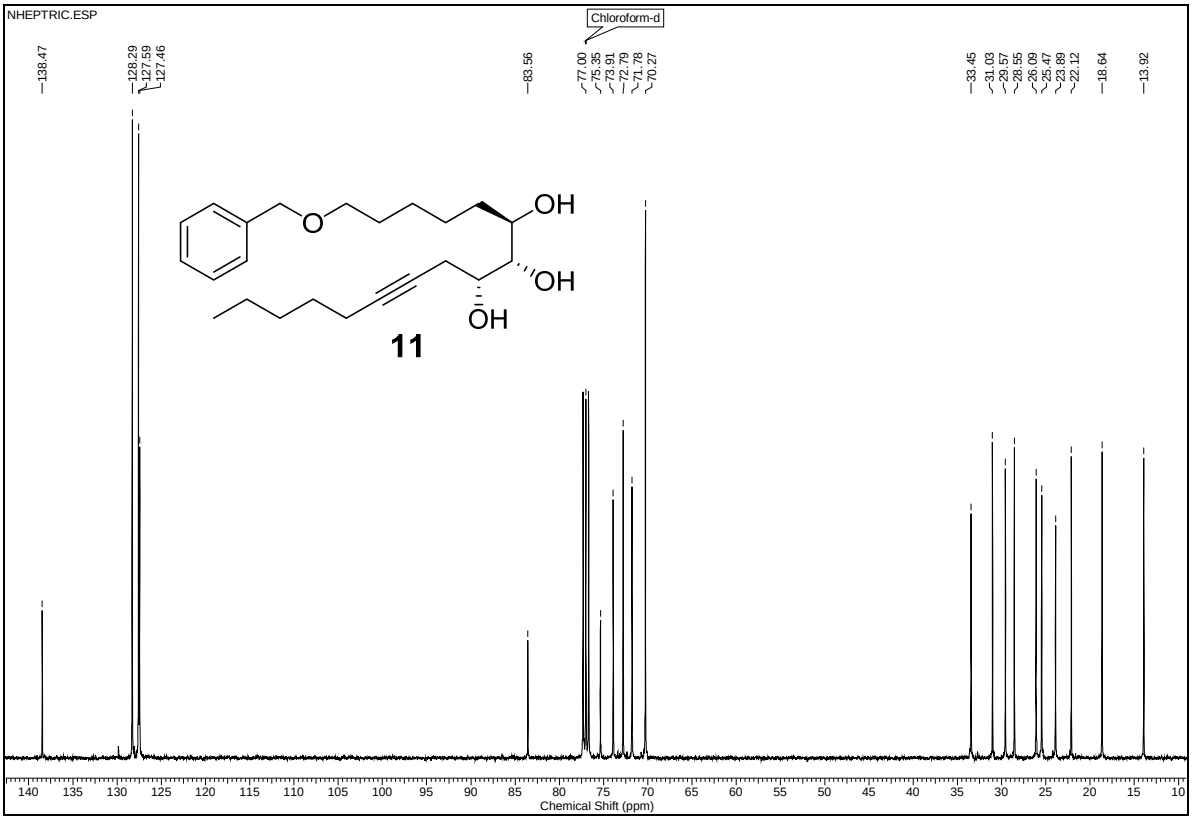
^{1}H NMR Spectrum of 23 in $CDCl_3$



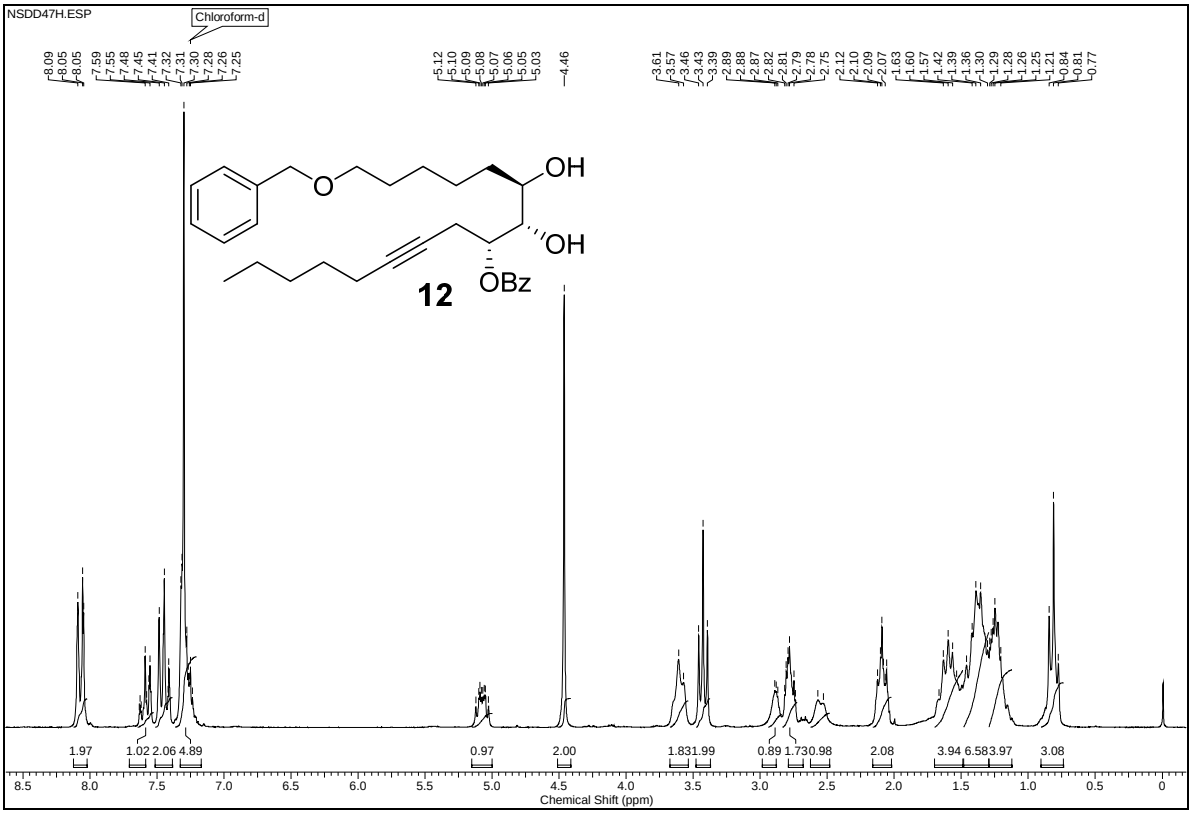
^{13}C NMR Spectrum of 23 in $CDCl_3$



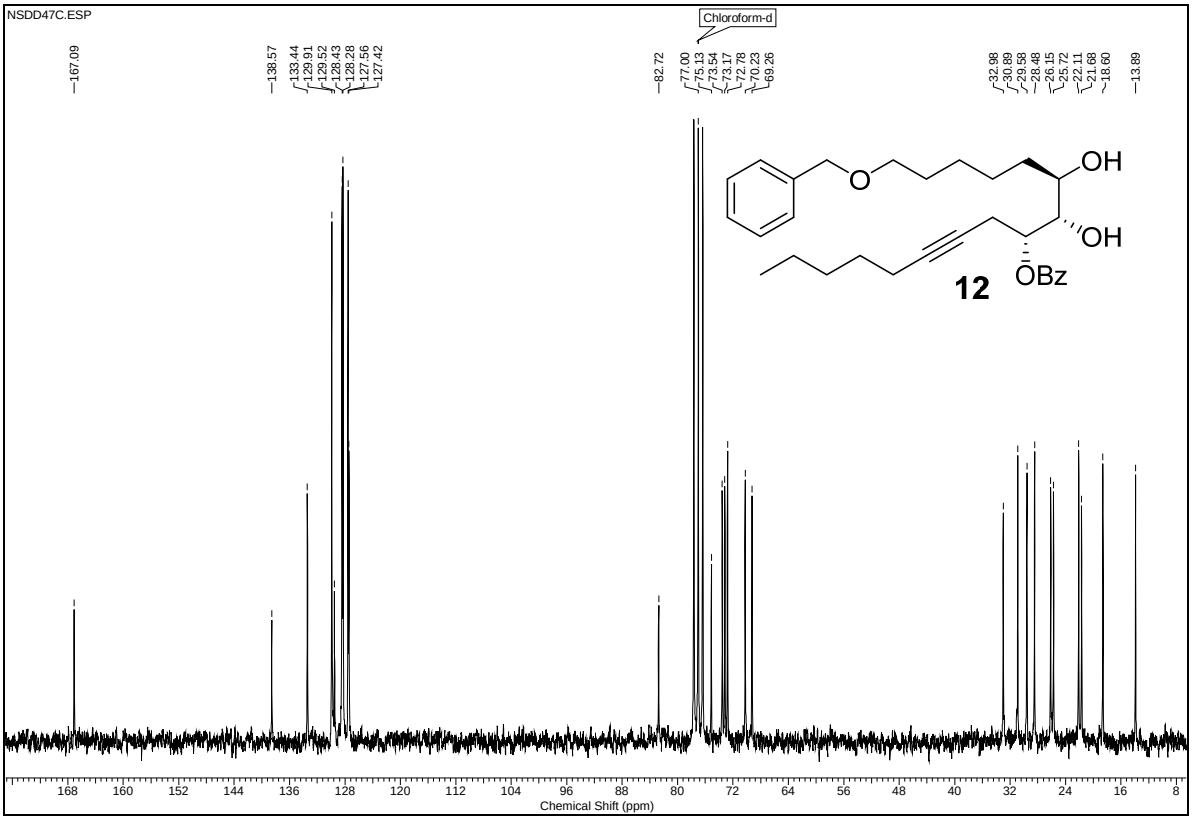
^{1}H NMR Spectrum of 11 in $CDCl_3$



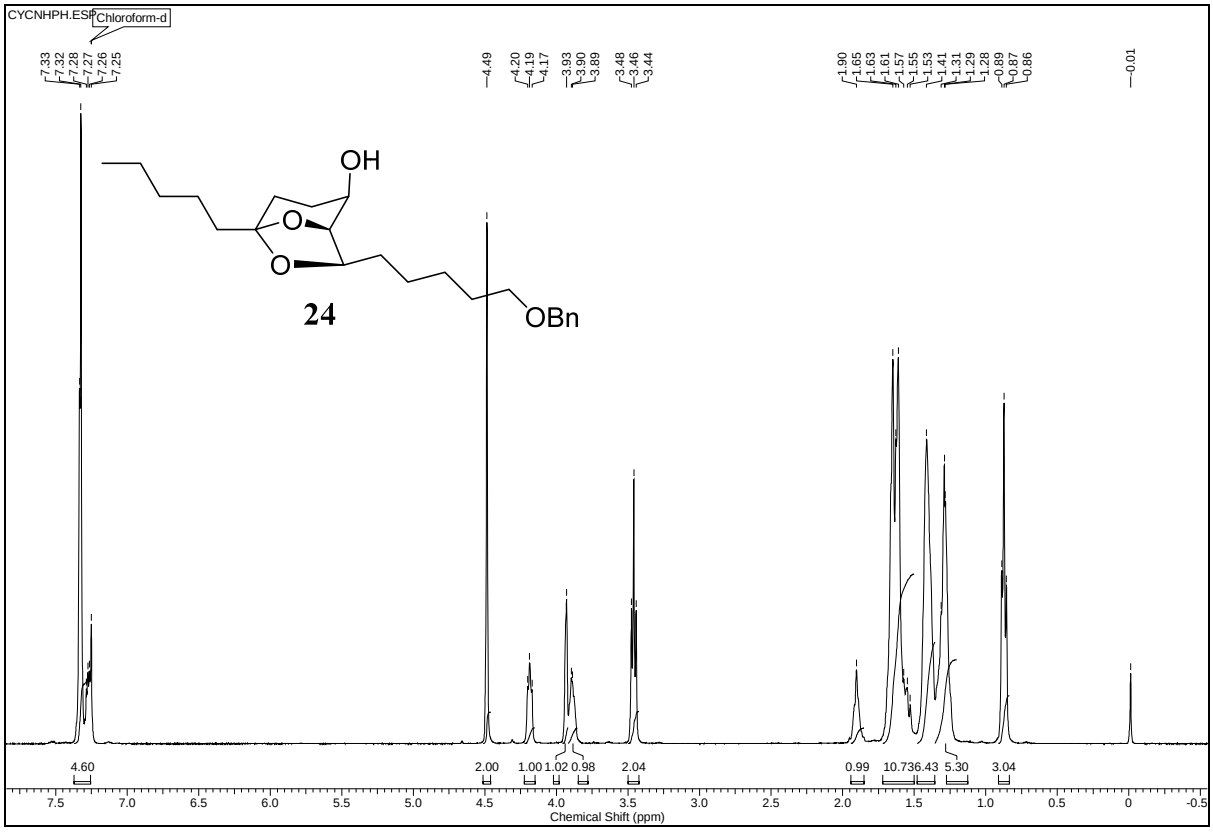
^{13}C NMR Spectrum of 11 in $CDCl_3$



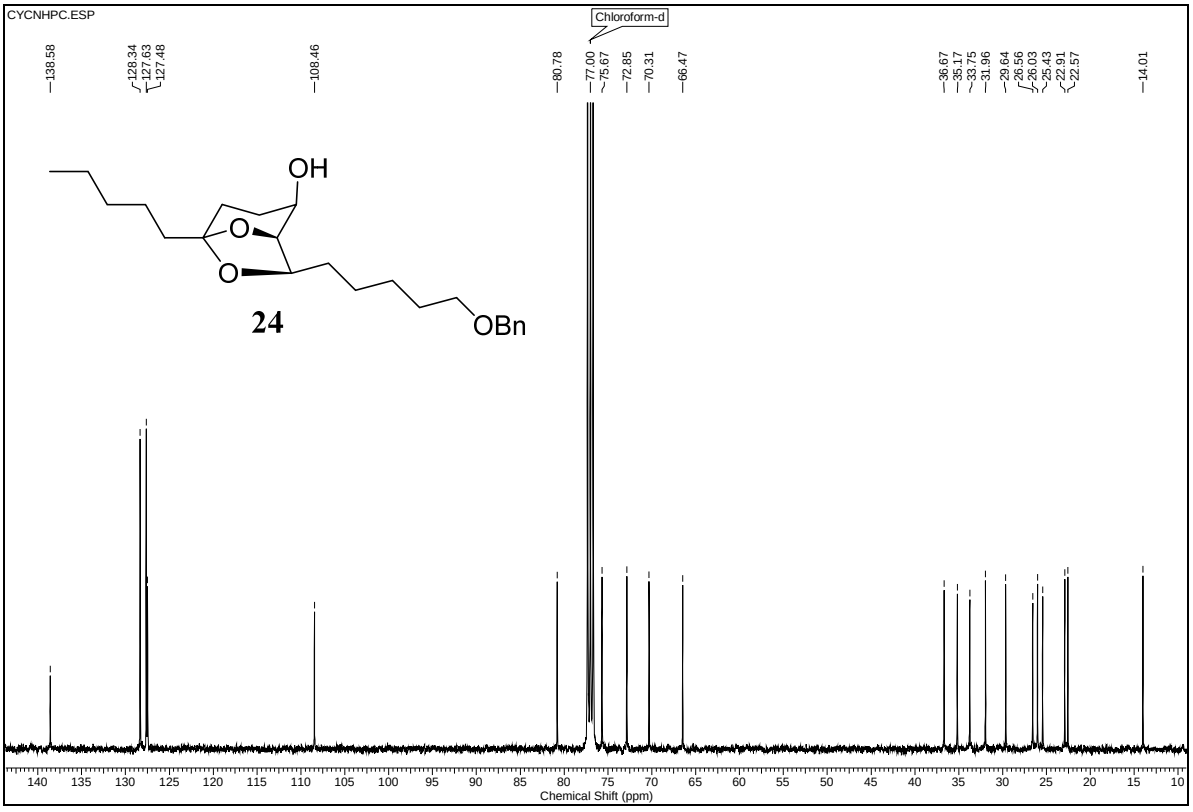
^{1}H NMR Spectrum of 12 in $CDCl_3$



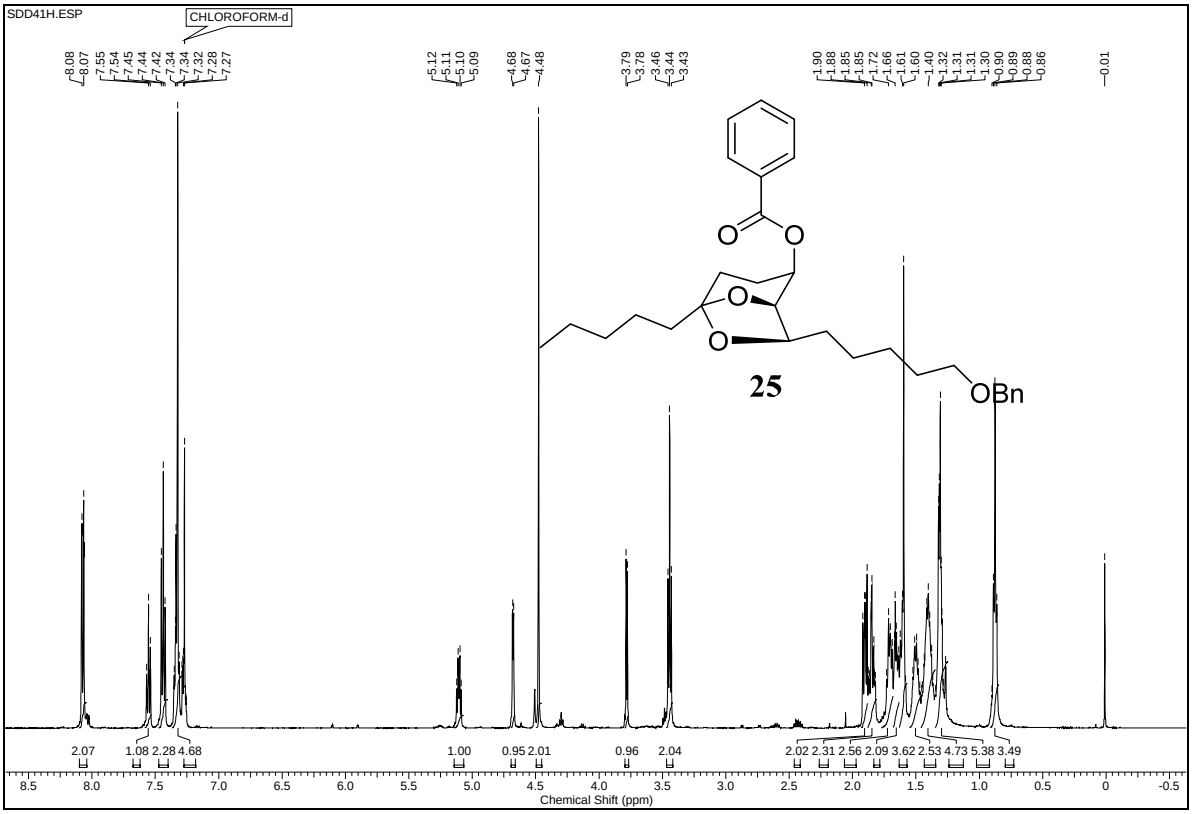
^{13}C NMR Spectrum of 12 in $CDCl_3$



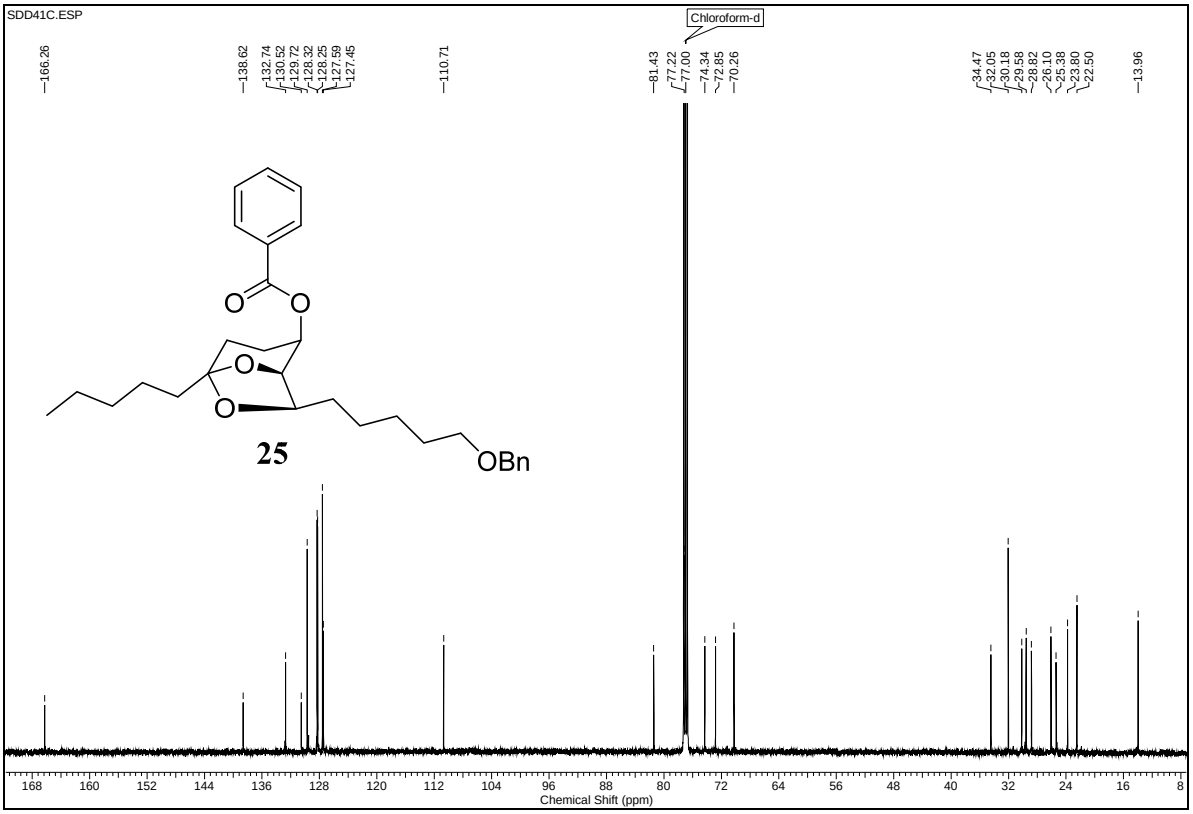
^{1}H NMR Spectrum of 24 in $CDCl_3$



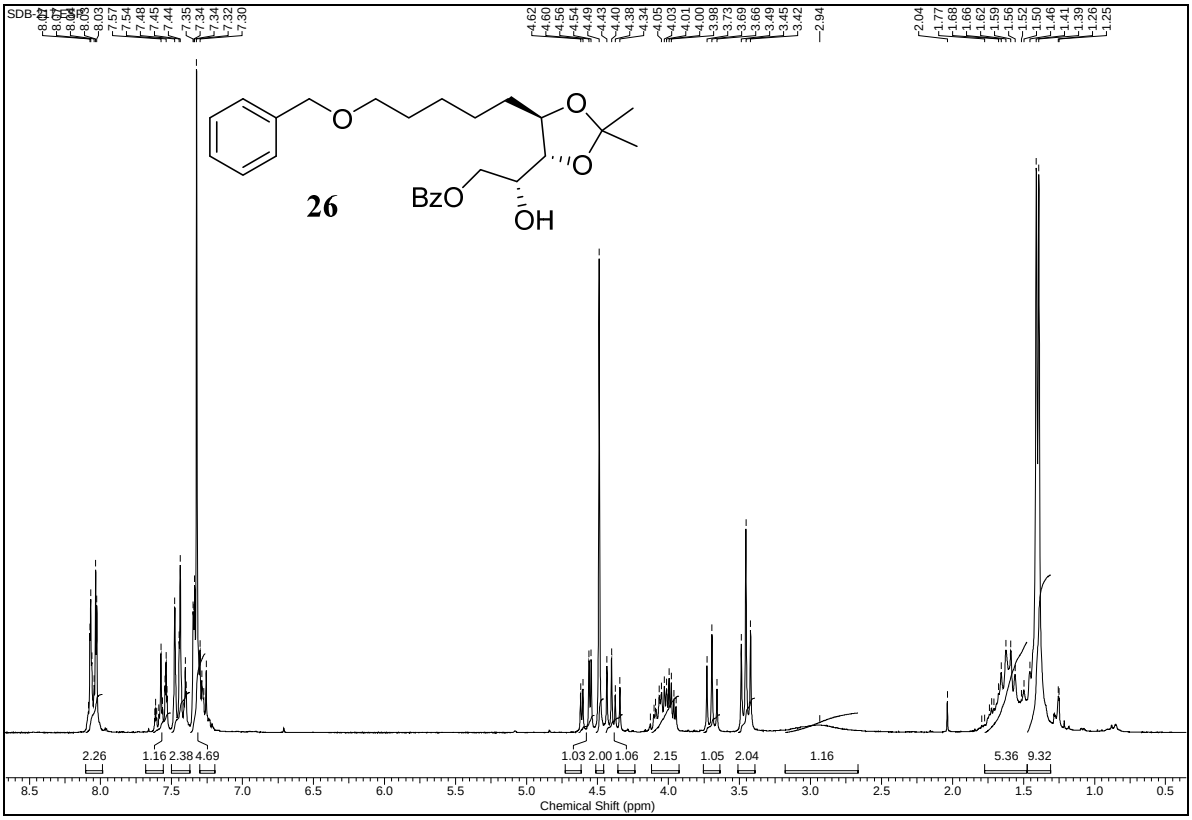
^{13}C NMR Spectrum of 24 in $CDCl_3$



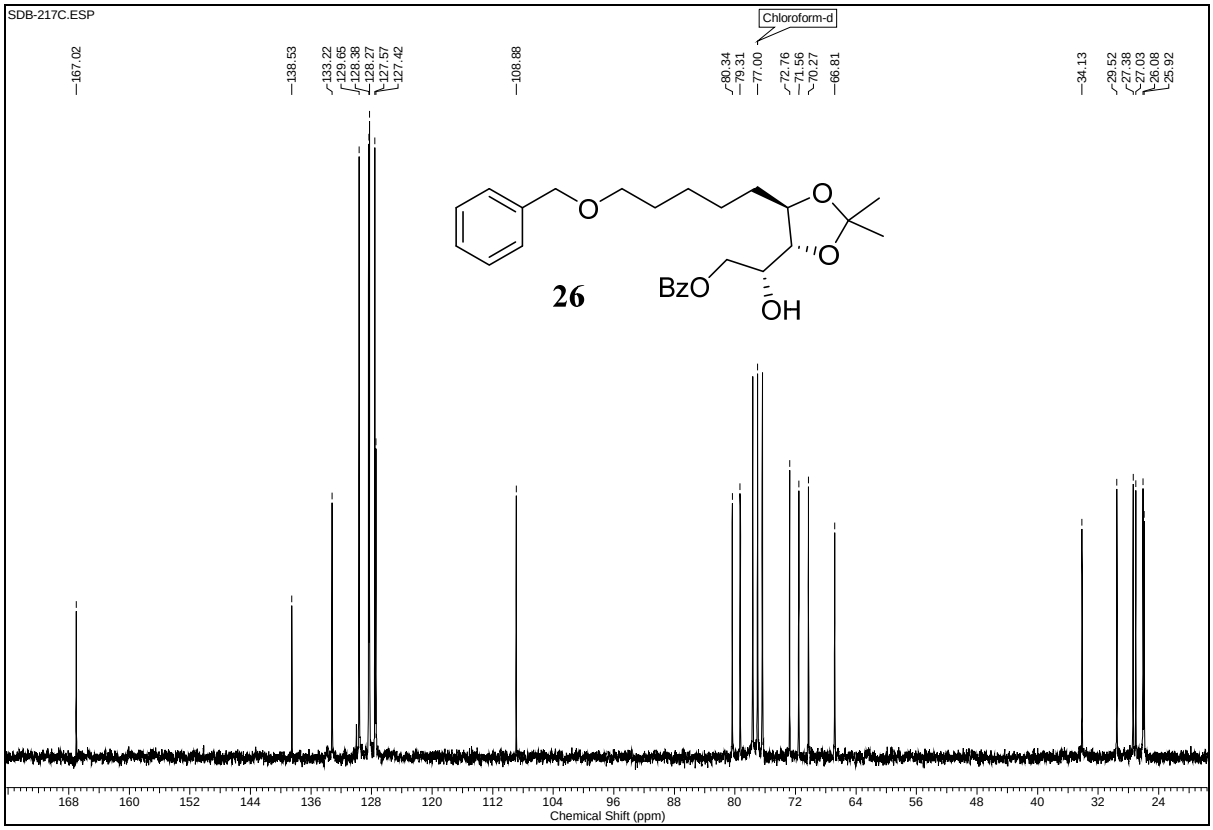
^{1}H NMR Spectrum of 25 in $CDCl_3$



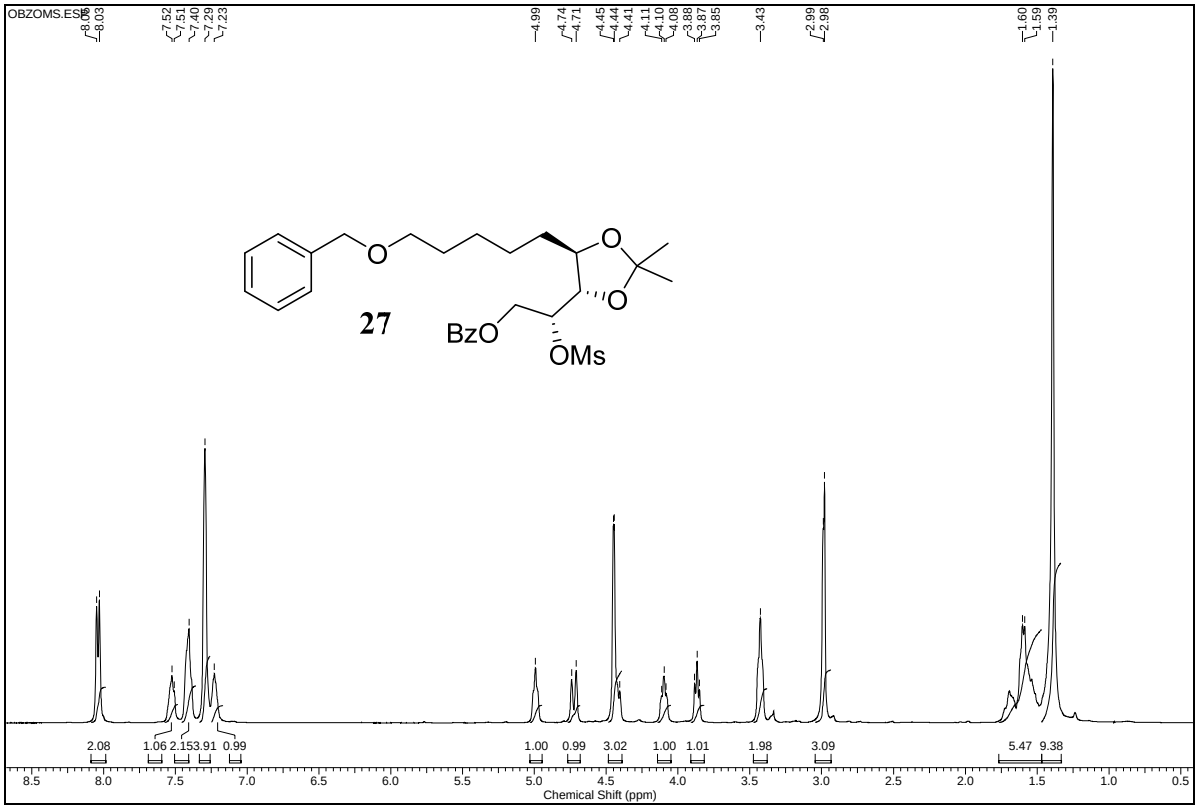
^{13}C NMR Spectrum of 25 in $CDCl_3$



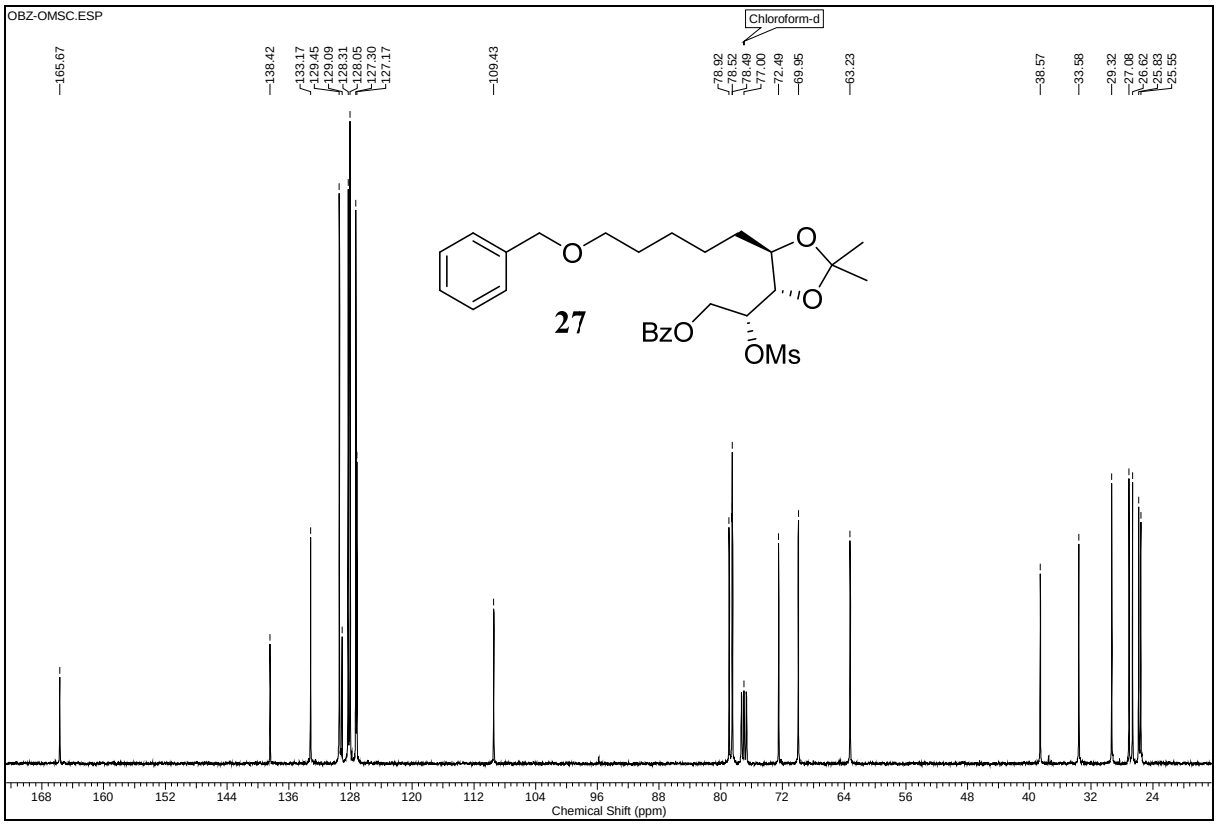
^{1}H NMR Spectrum of 26 in $CDCl_3$



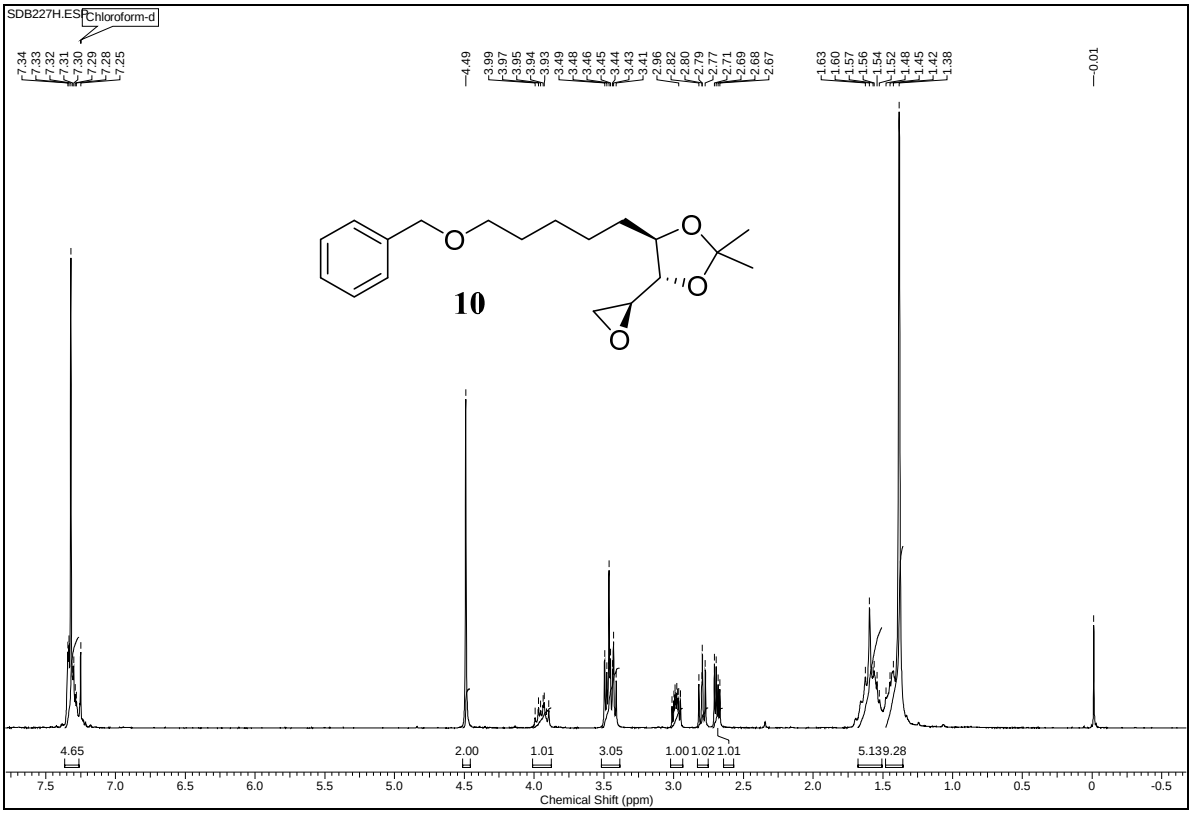
^{13}C NMR Spectrum of 26 in $CDCl_3$



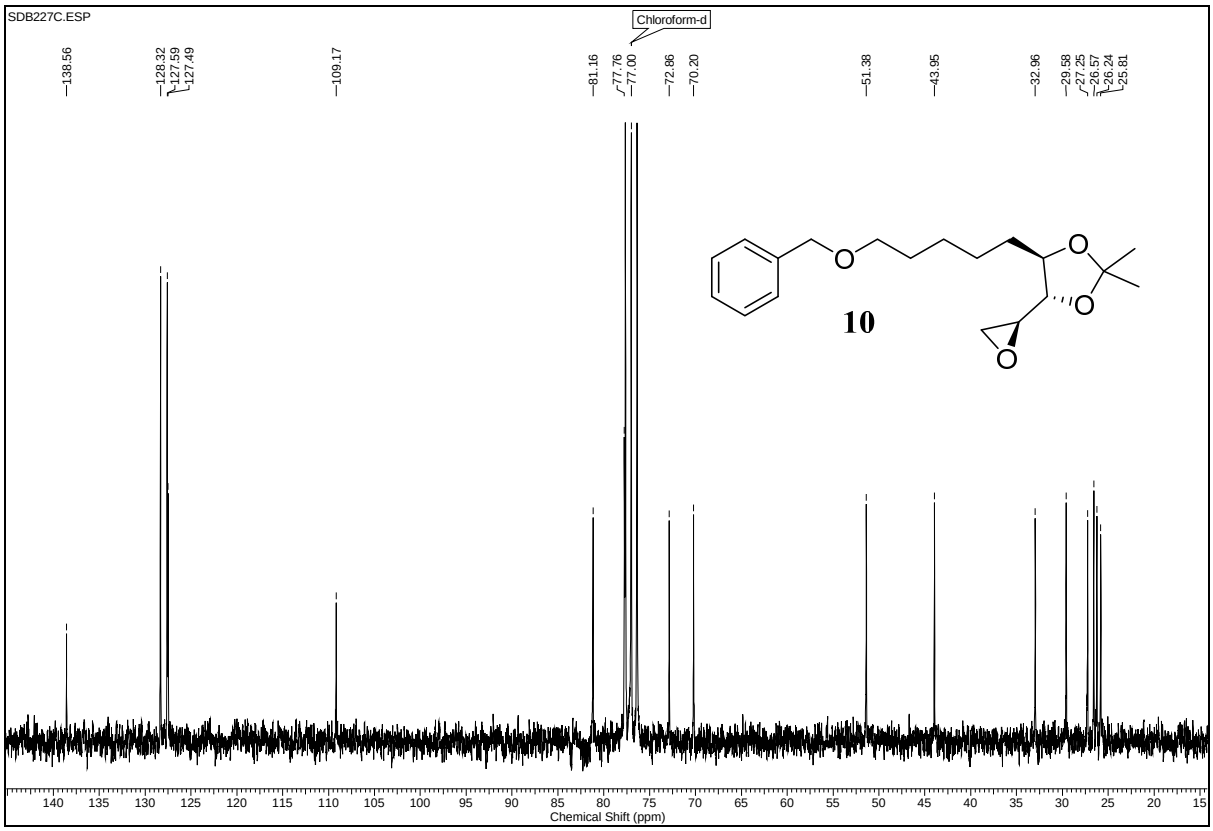
^{1}H NMR Spectrum of 27 in $CDCl_3$



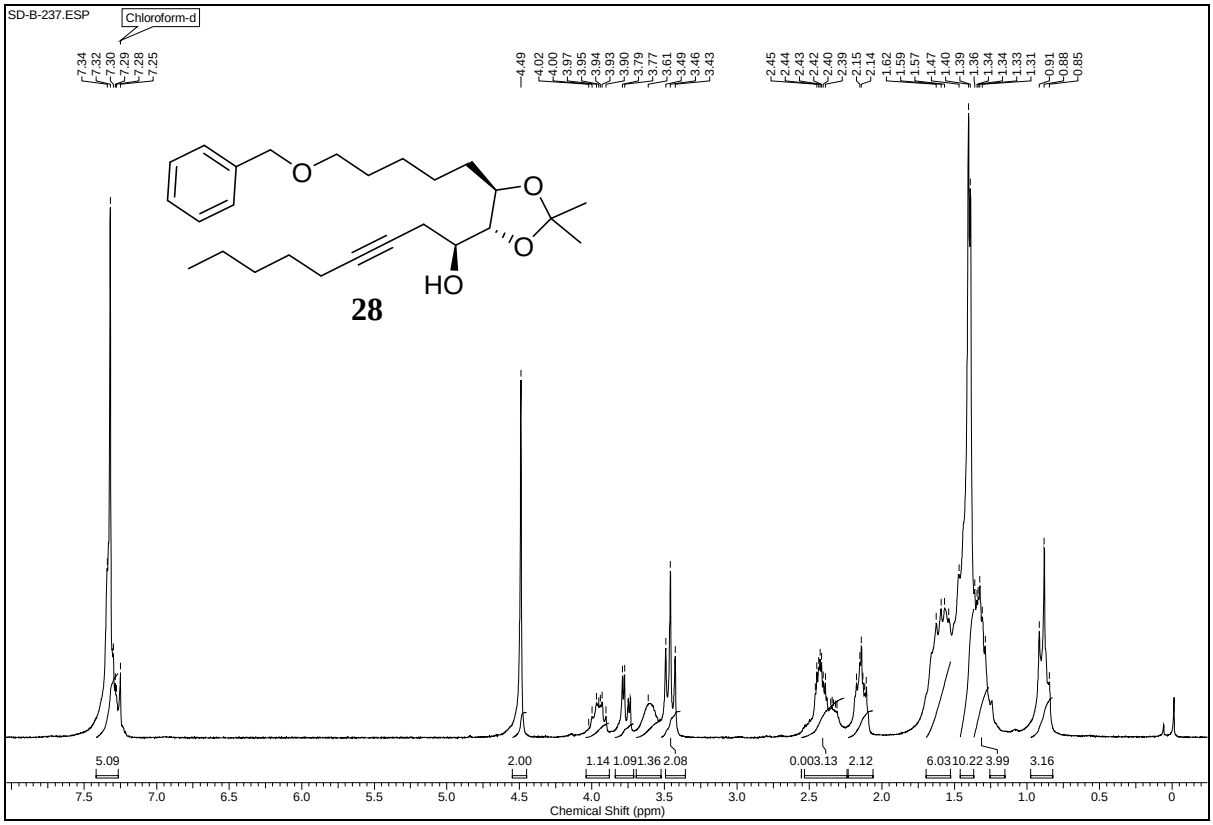
^{13}C NMR Spectrum of 27 in $CDCl_3$



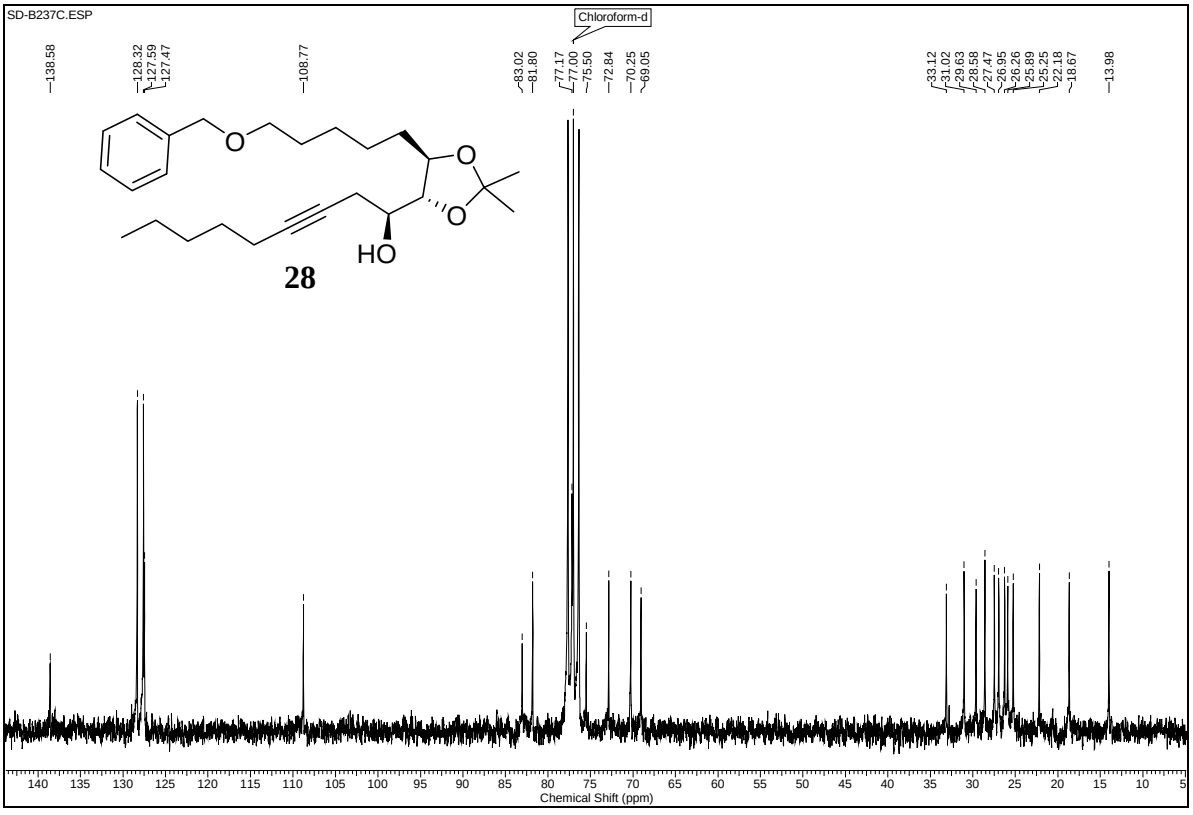
^{1}H NMR Spectrum of 10 in $CDCl_3$



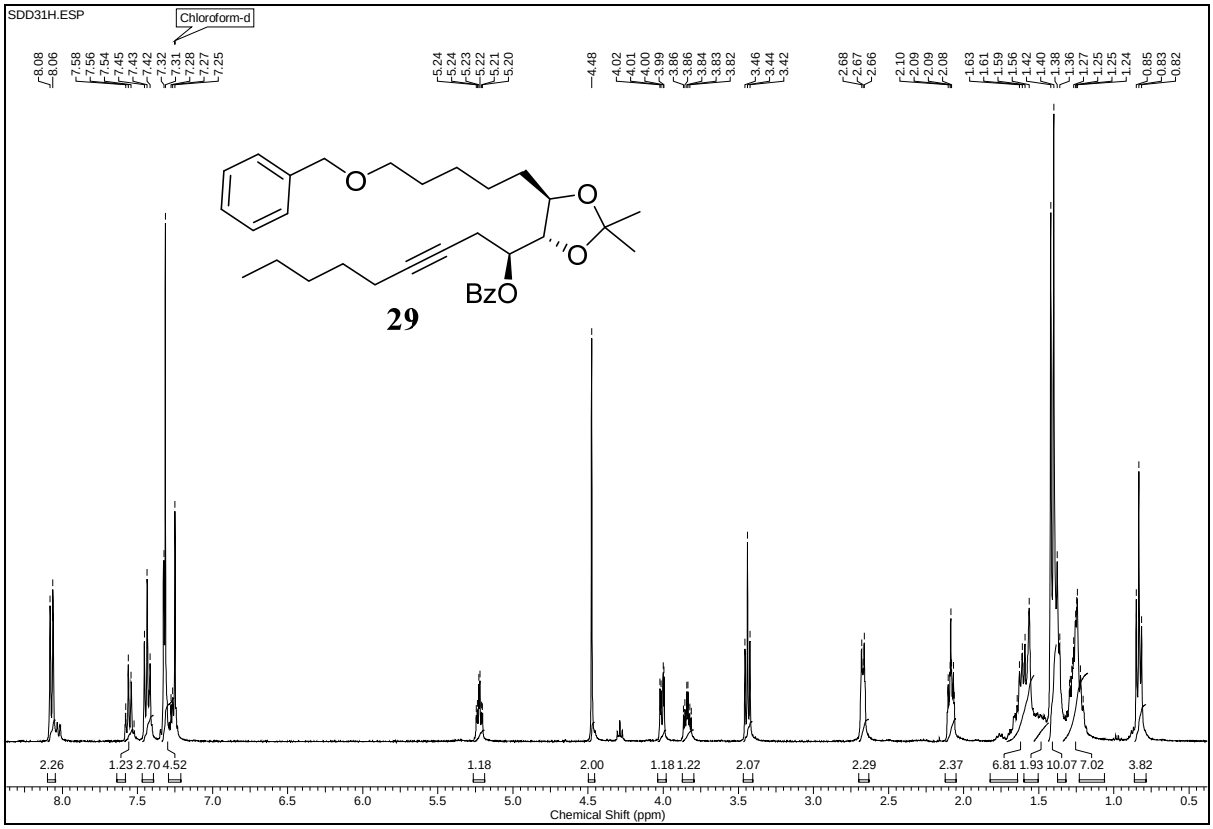
^{13}C NMR Spectrum of 10 in $CDCl_3$



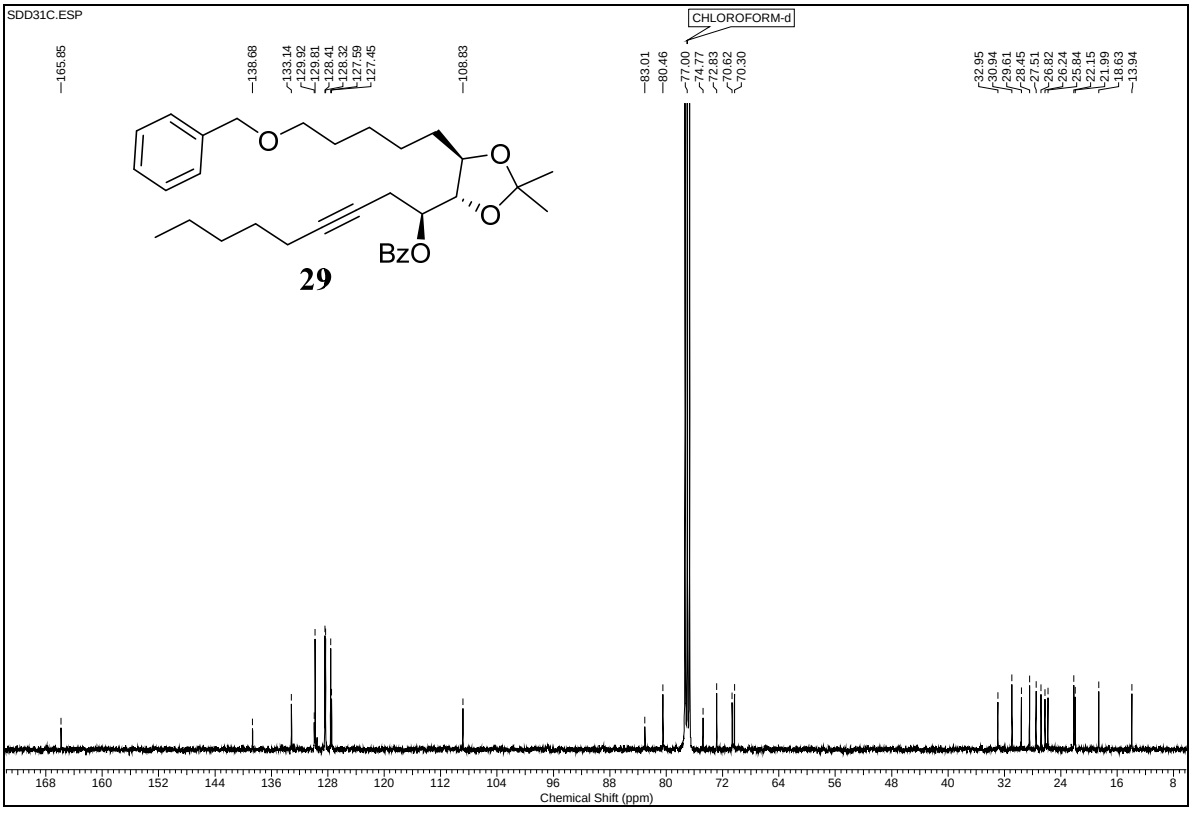
^{1}H NMR Spectrum of 28 in $CDCl_3$



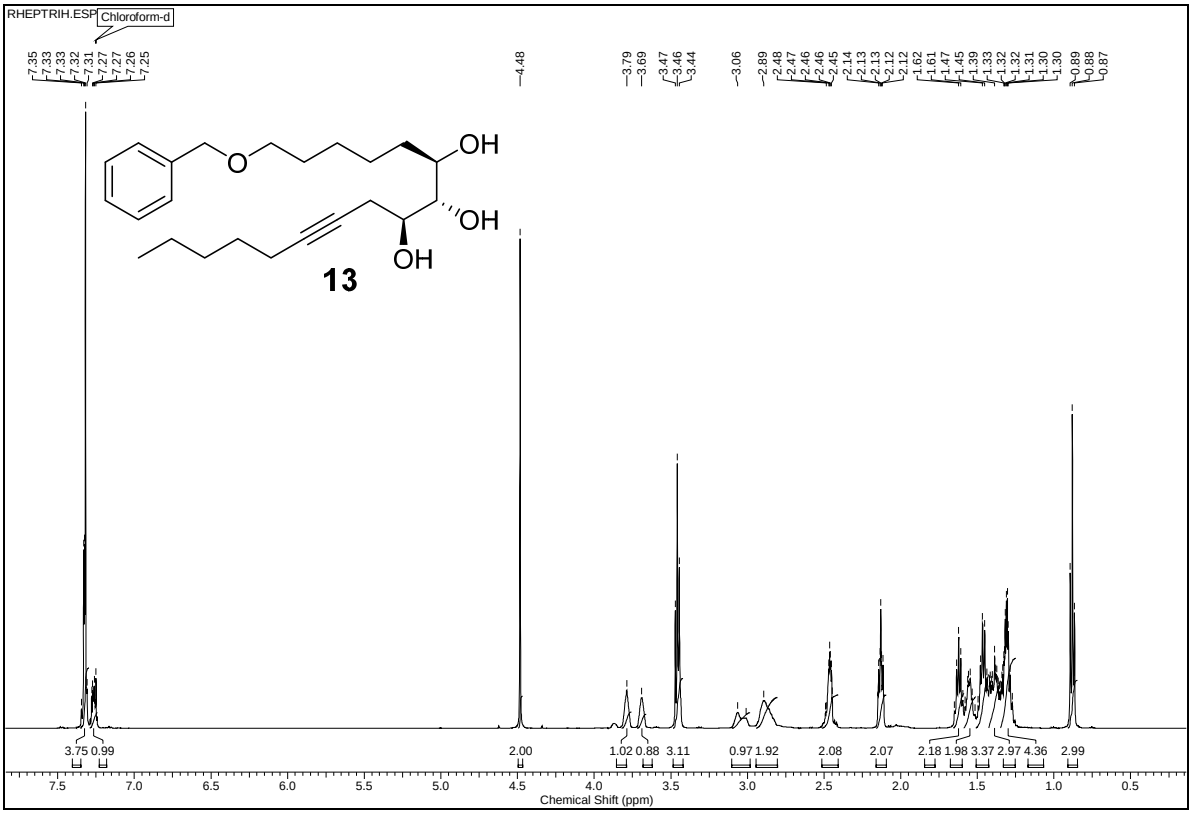
^{13}C NMR Spectrum of 28 in $CDCl_3$



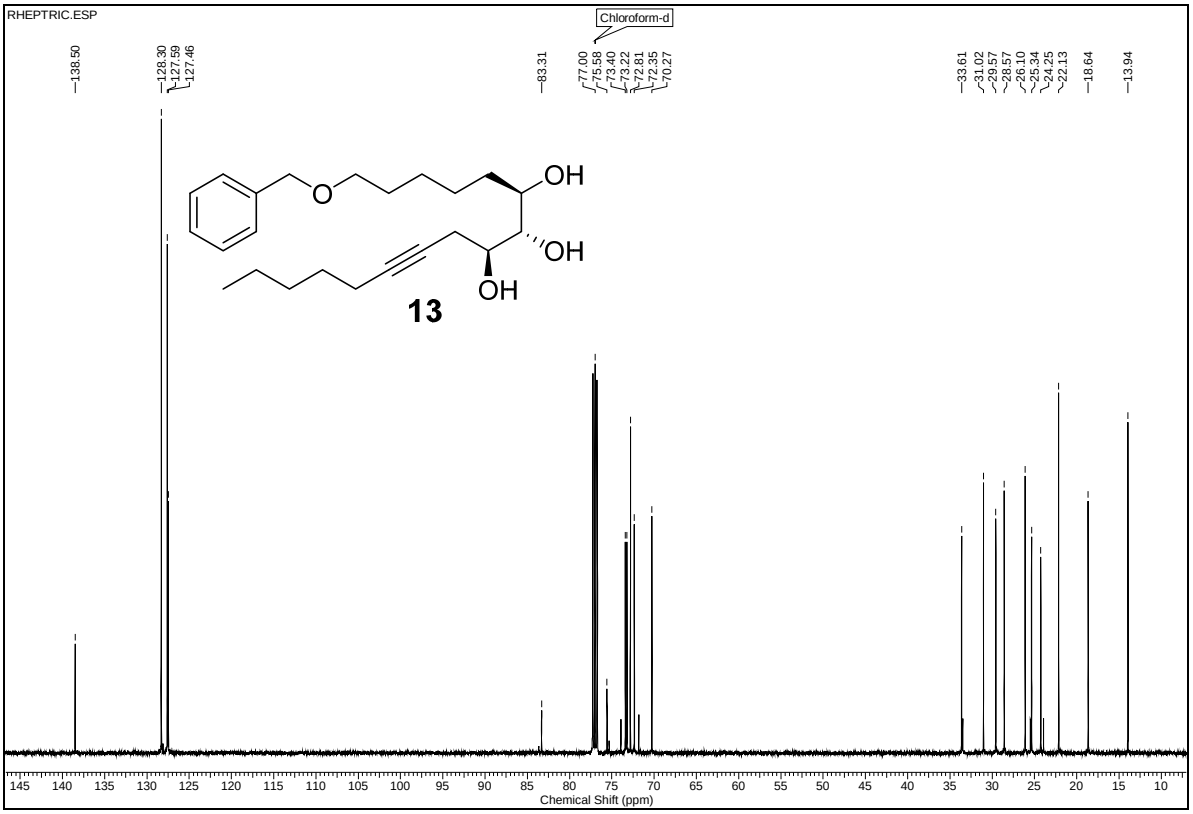
^{1}H NMR Spectrum of 29 in $CDCl_3$



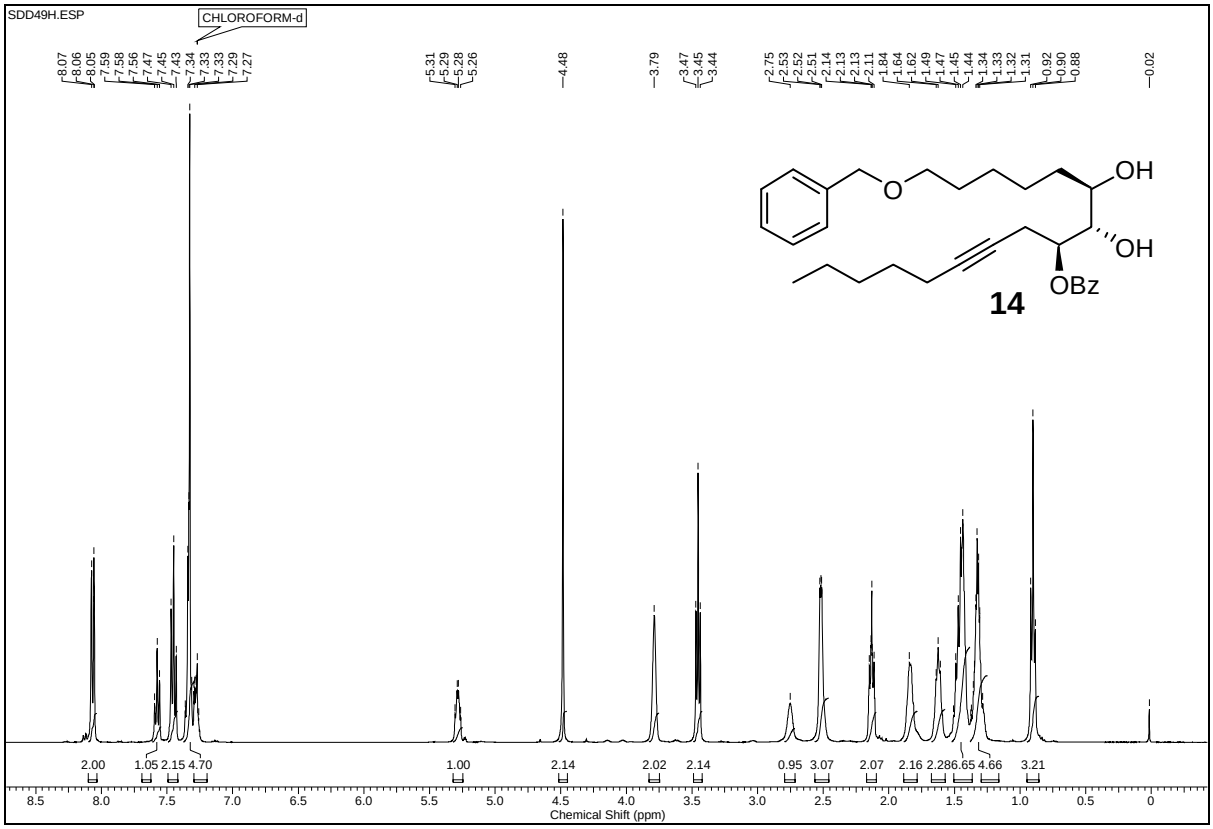
^{13}C NMR Spectrum of 29 in $CDCl_3$



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



^{13}C NMR Spectrum of 14 in $CDCl_3$



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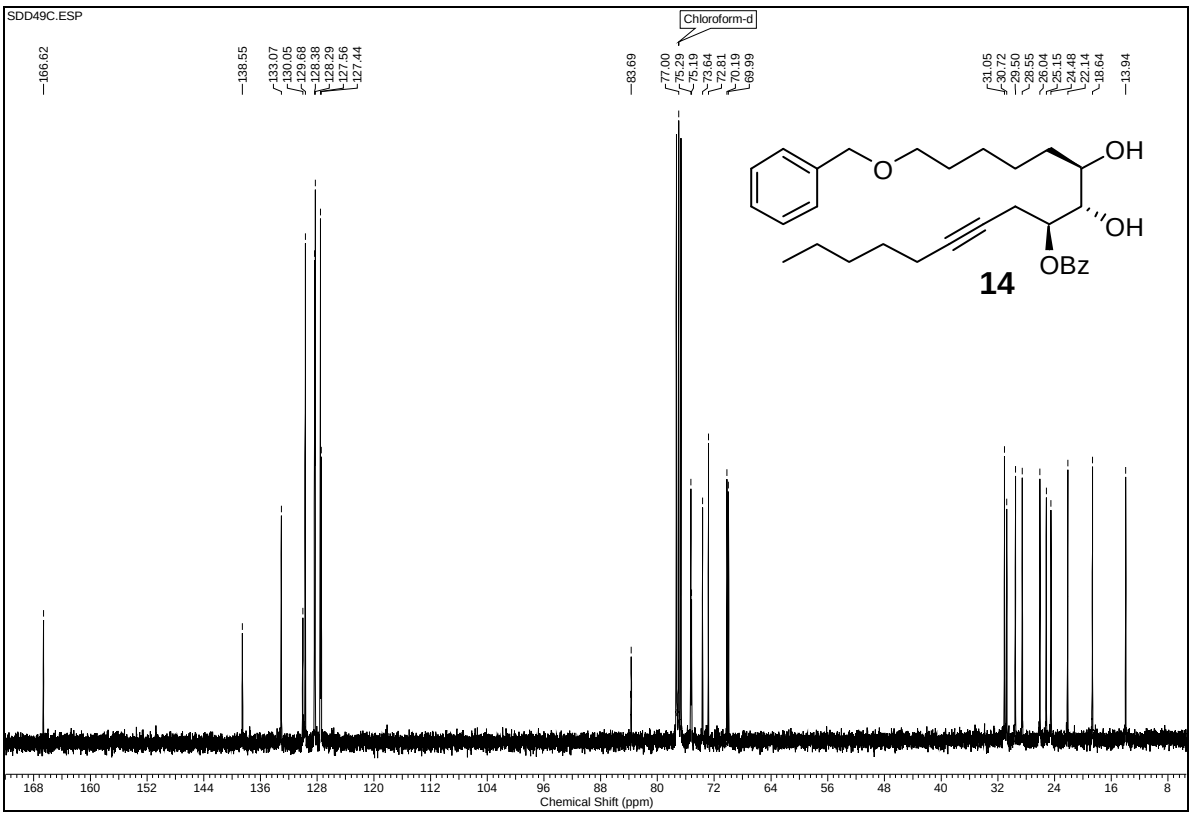
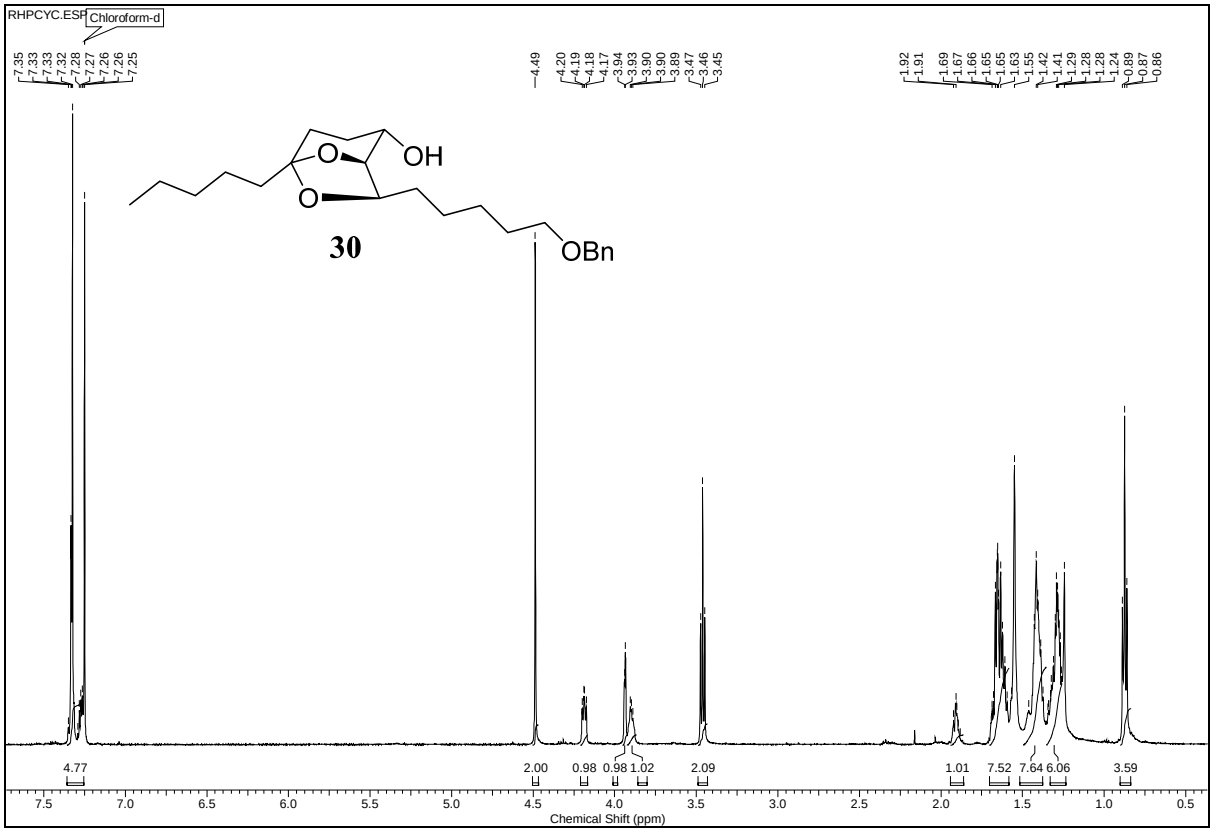
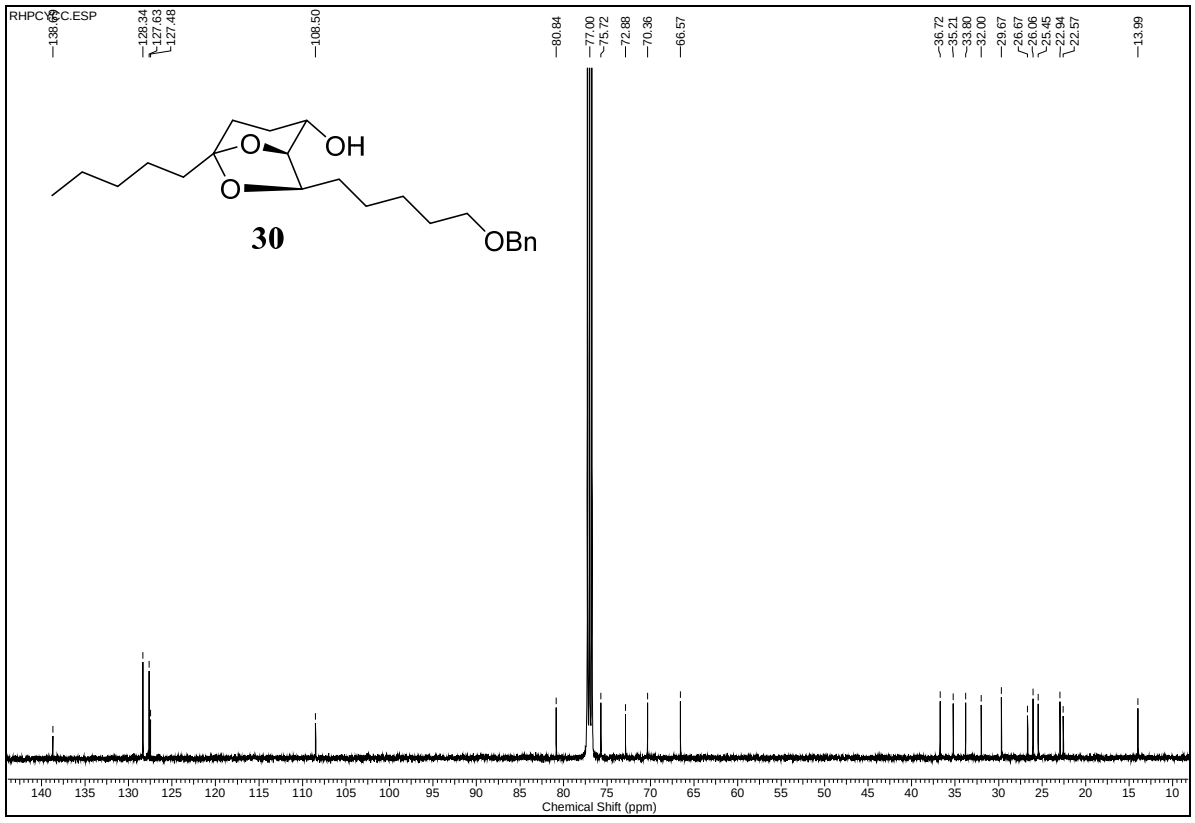


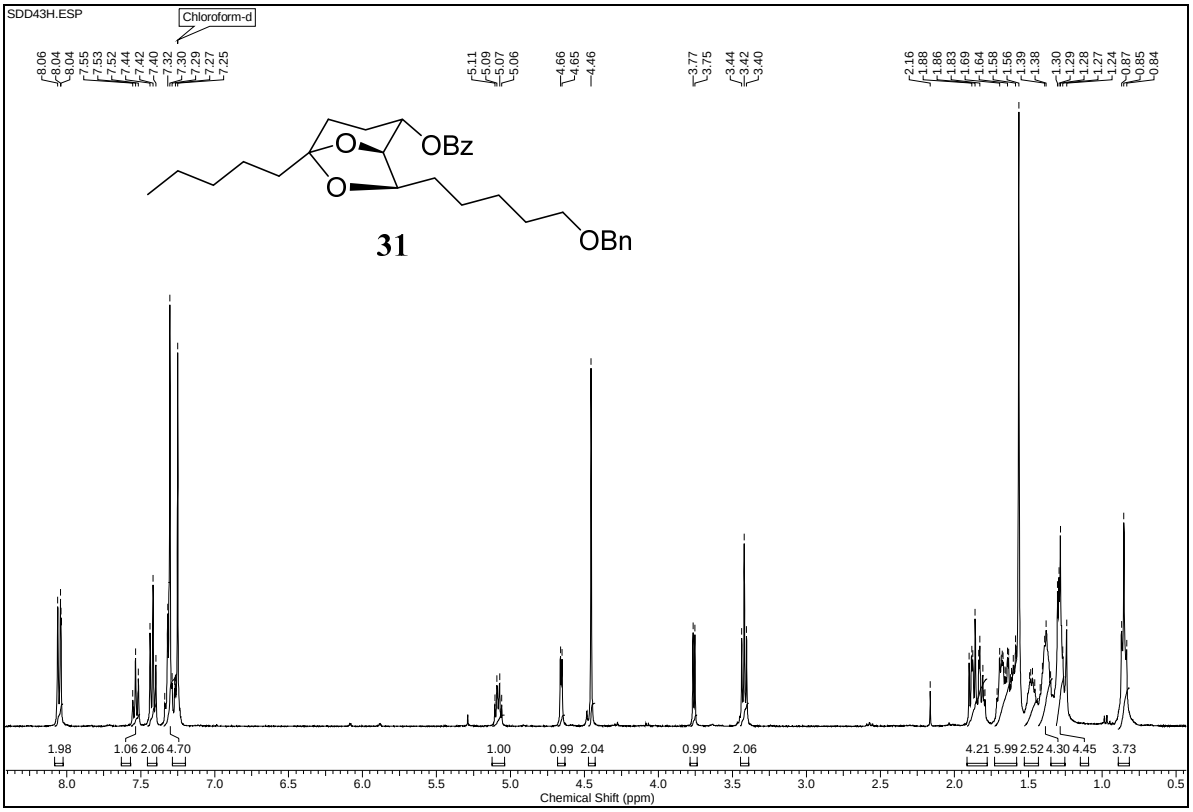
^{13}C NMR Spectrum of 14 in $CDCl_3$



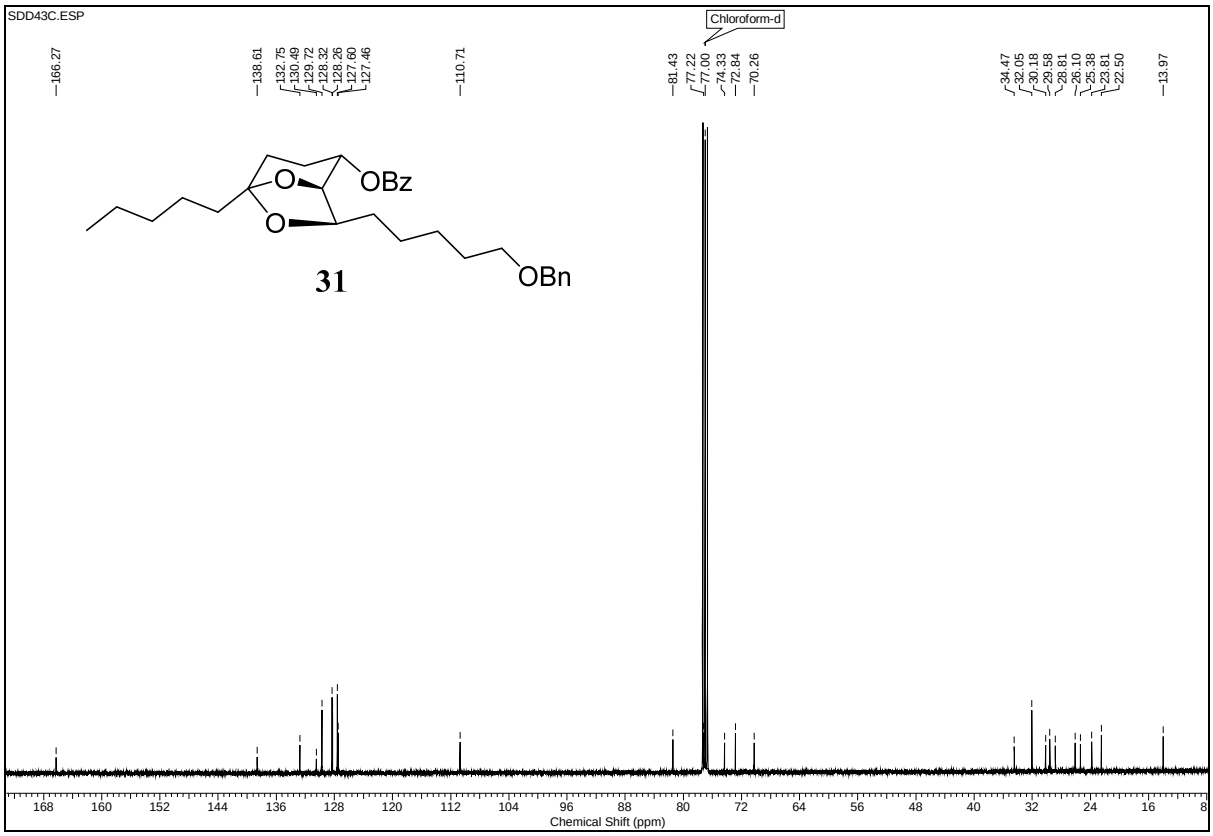
^{1}H NMR Spectrum of 30 in $CDCl_3$



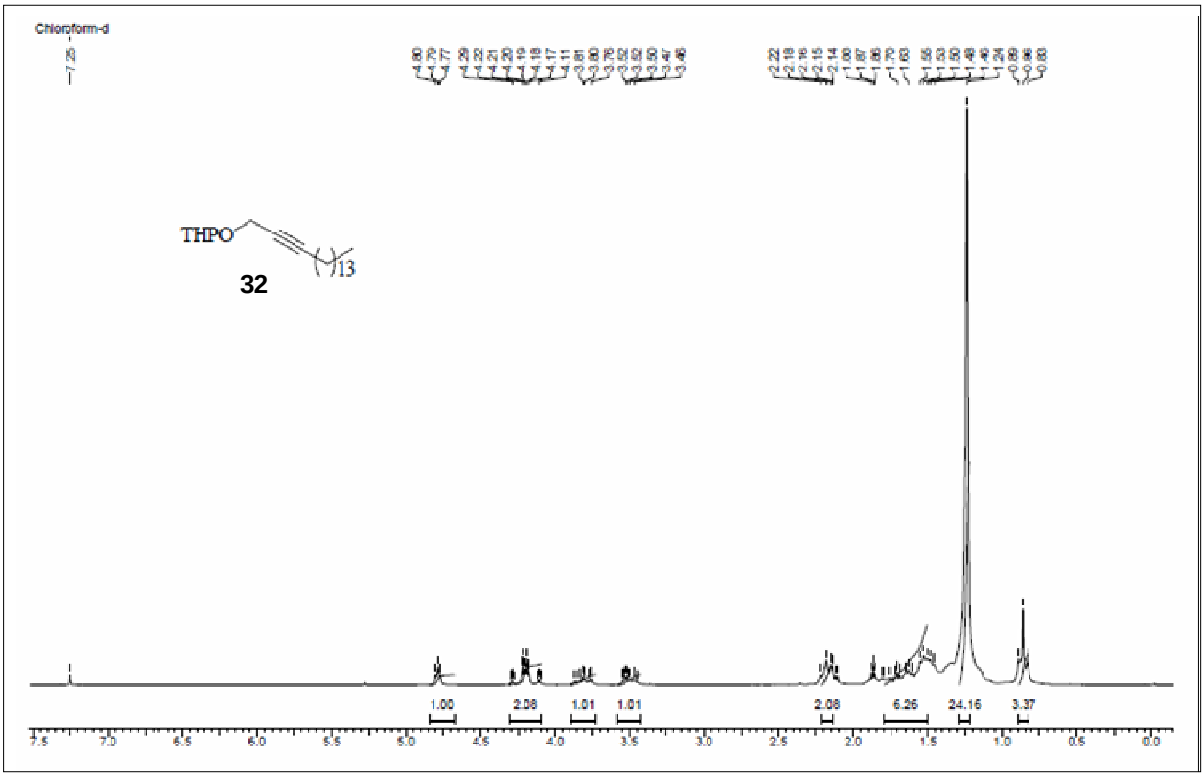
^{13}C NMR Spectrum of 30 in $CDCl_3$



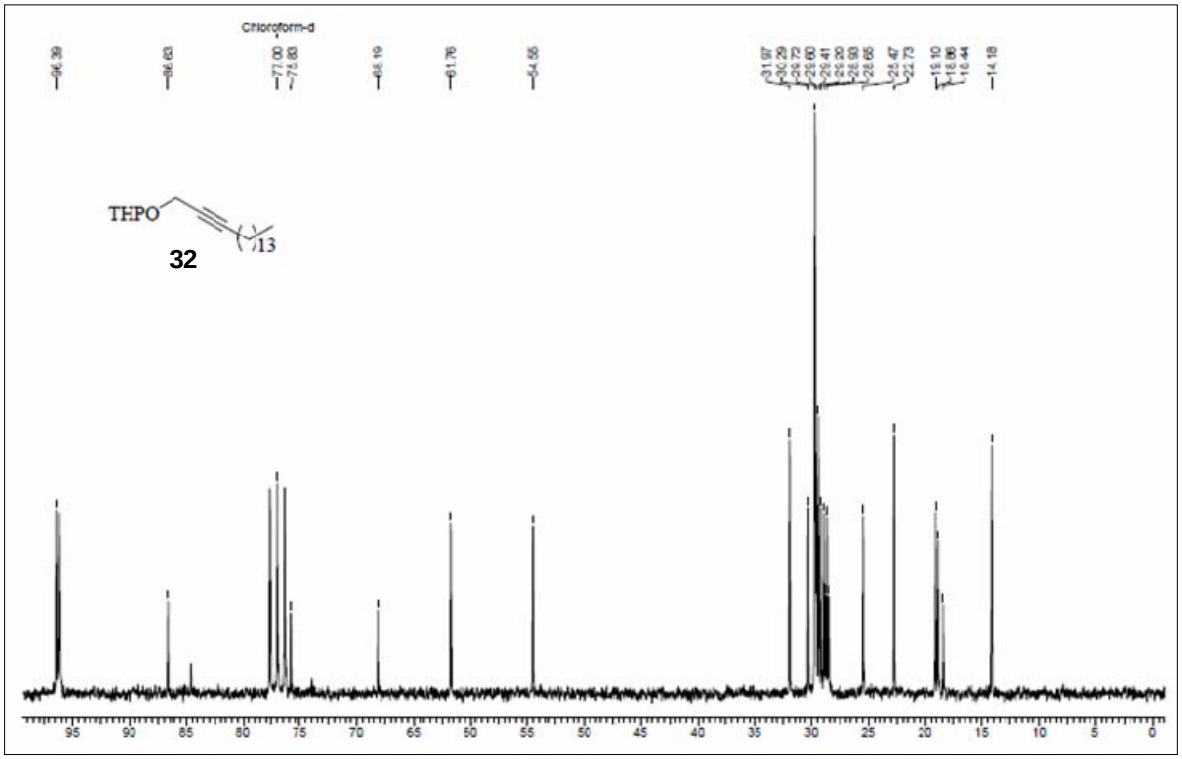
^{1}H NMR Spectrum of 31 in $CDCl_3$



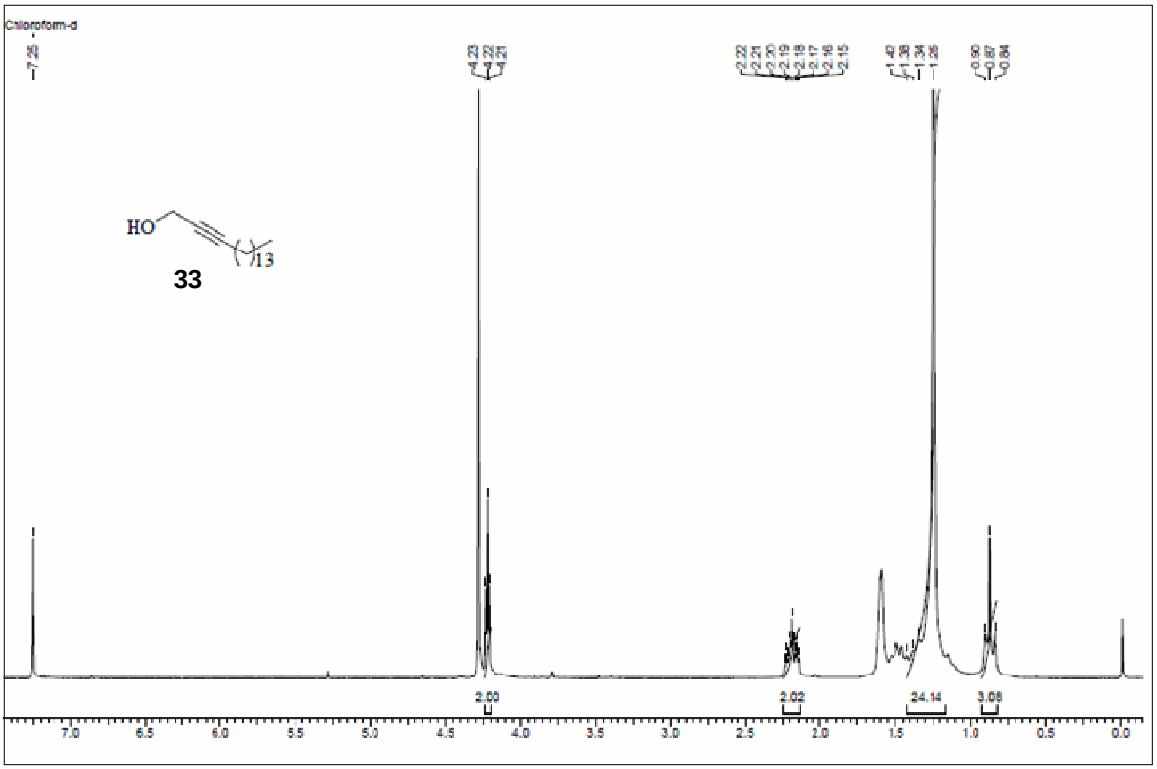
^{13}C NMR Spectrum of 31 in $CDCl_3$



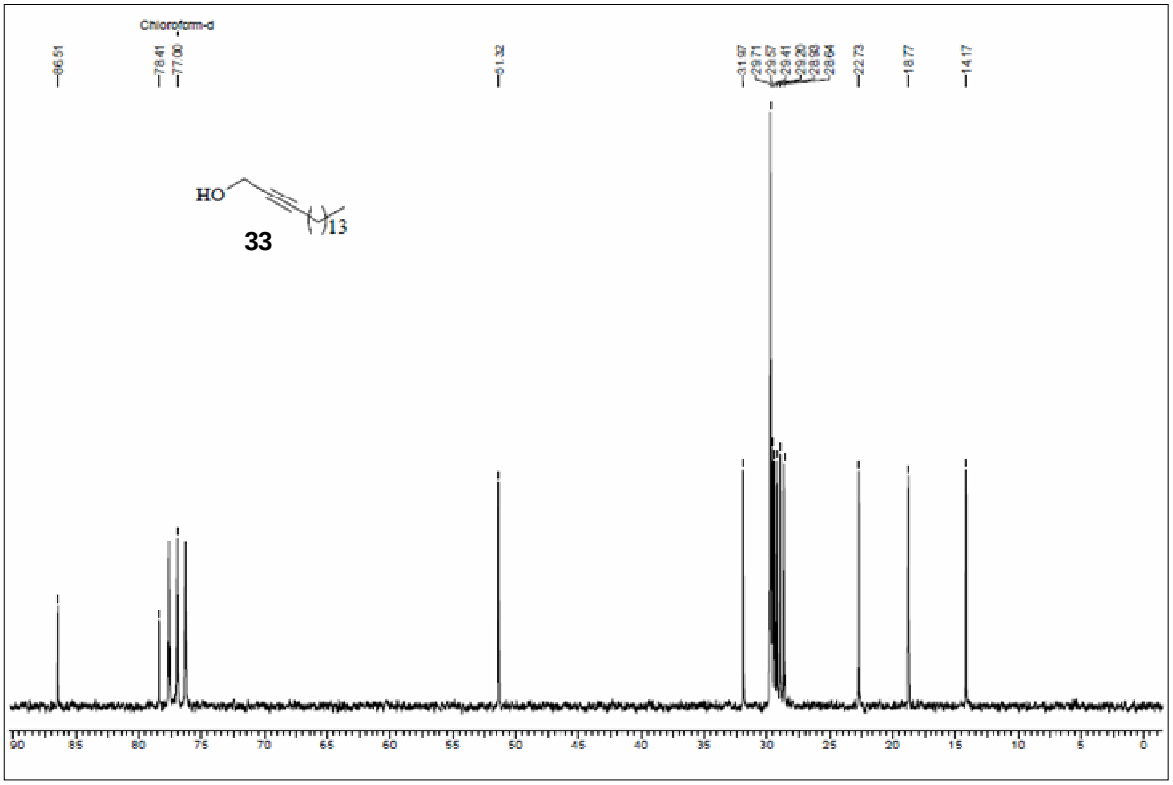
^{1}H NMR Spectrum of 32 in $CDCl_3$



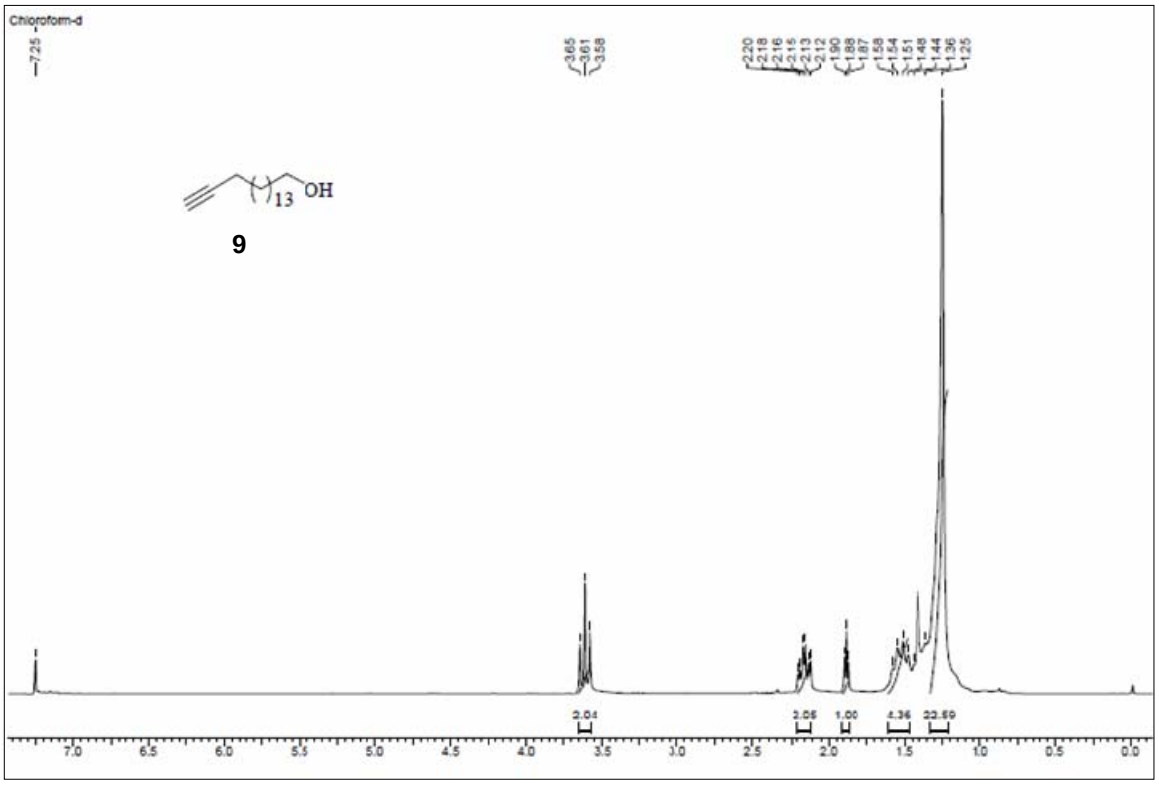
^{13}C NMR Spectrum of 32 in $CDCl_3$



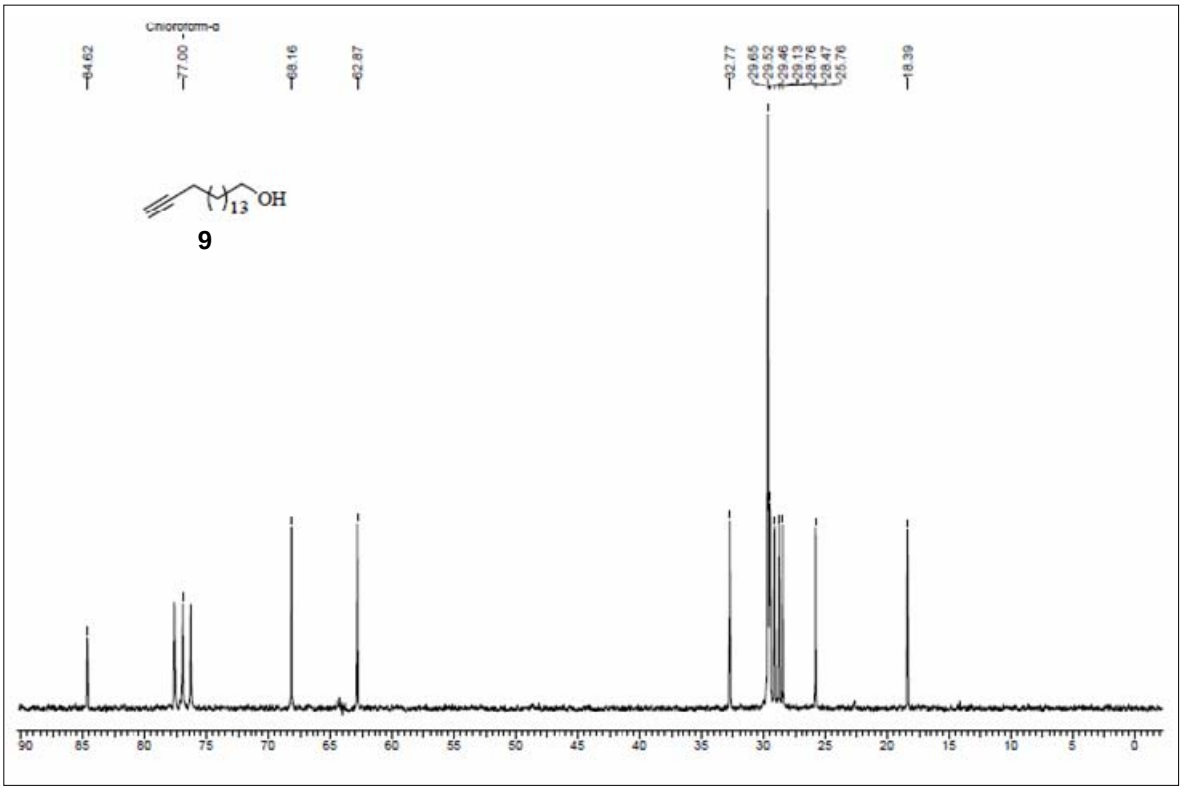
^{1}H NMR Spectrum of 33 in $CDCl_3$



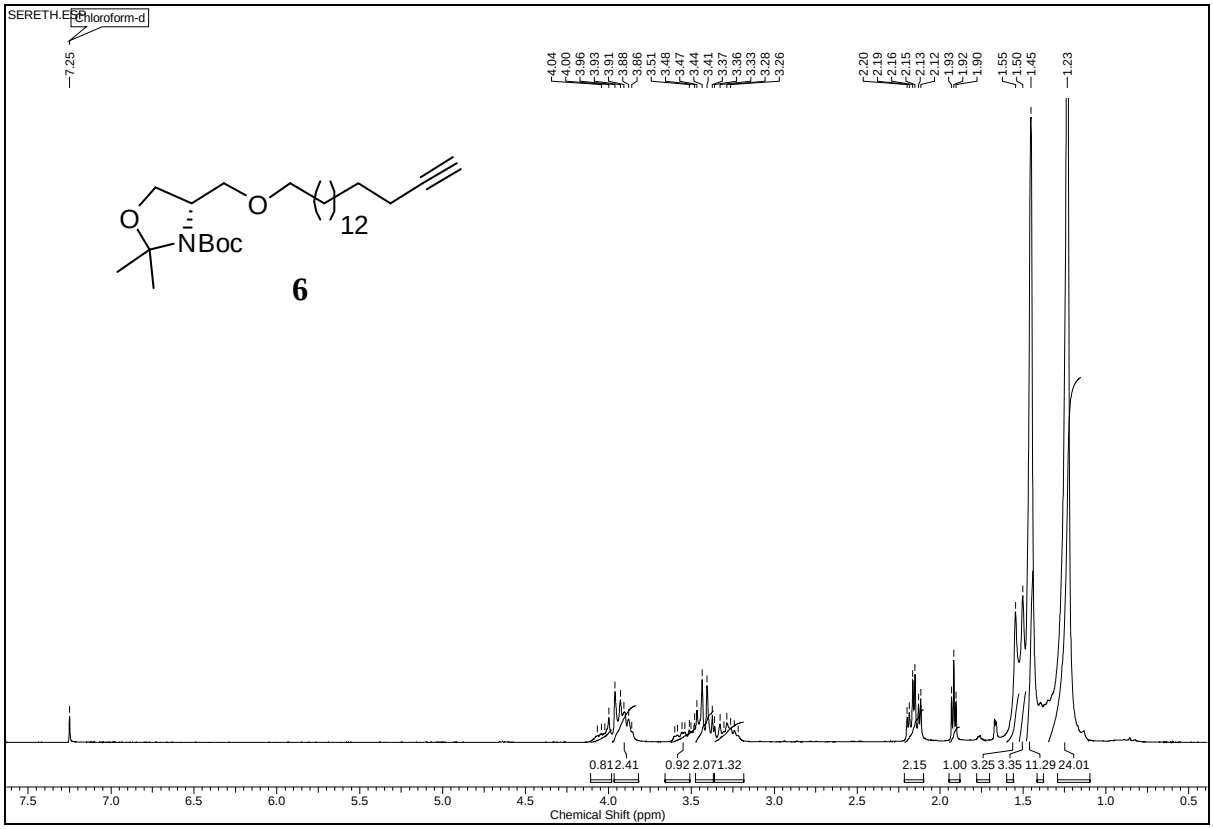
^{13}C NMR Spectrum of 33 in $CDCl_3$



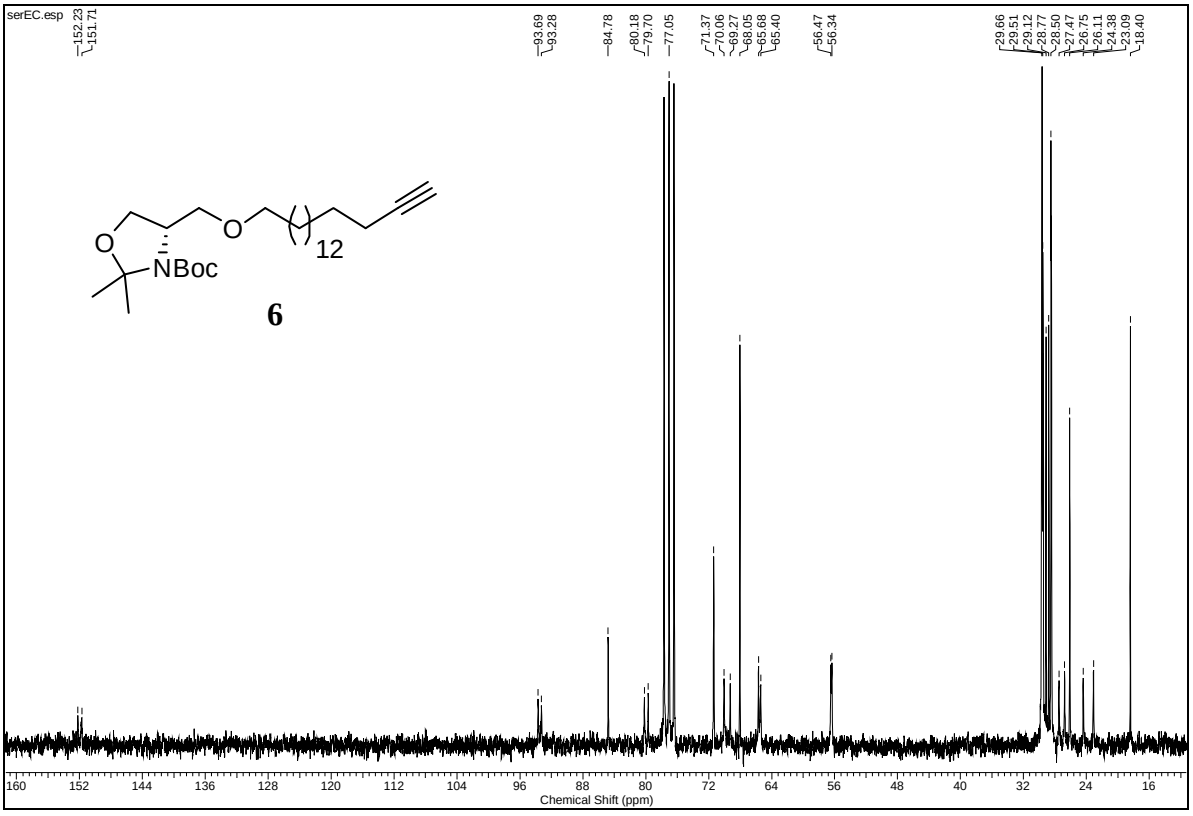
^{1}H NMR Spectrum of 9 in $CDCl_3$



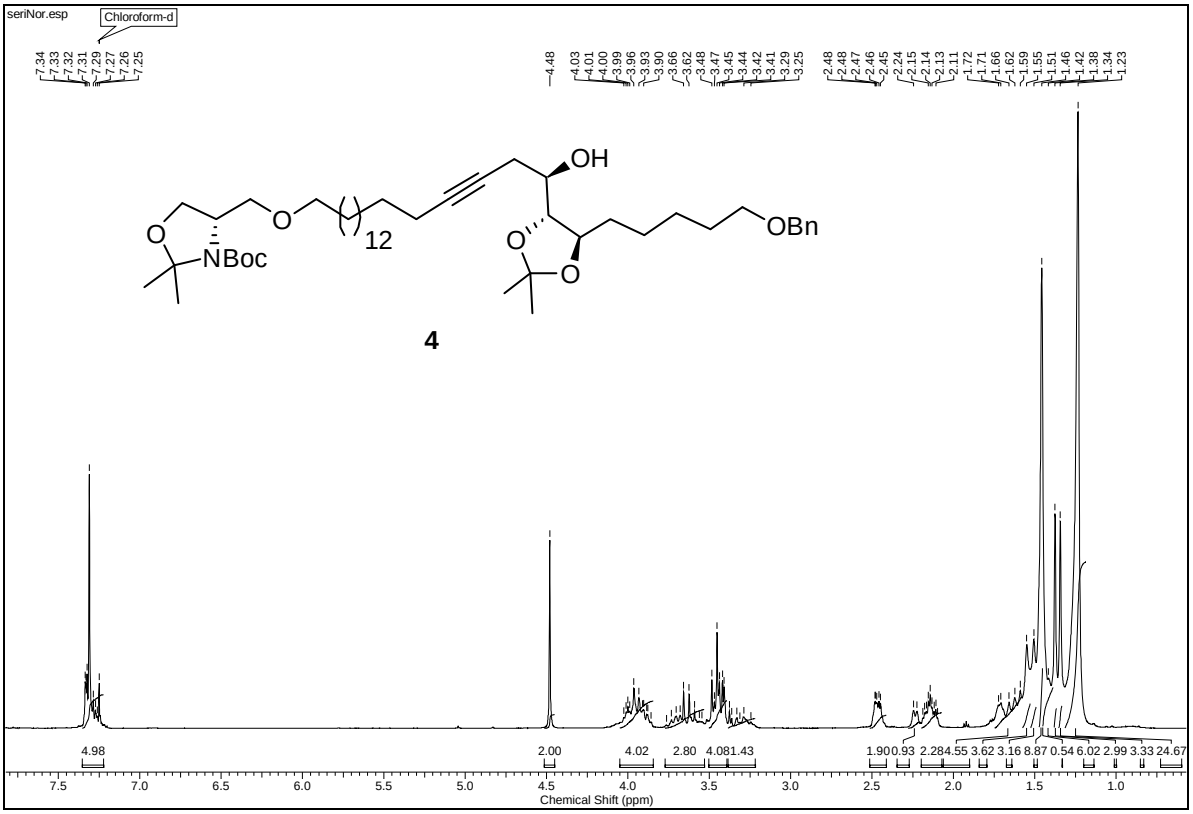
^{13}C NMR Spectrum of 9 in $CDCl_3$



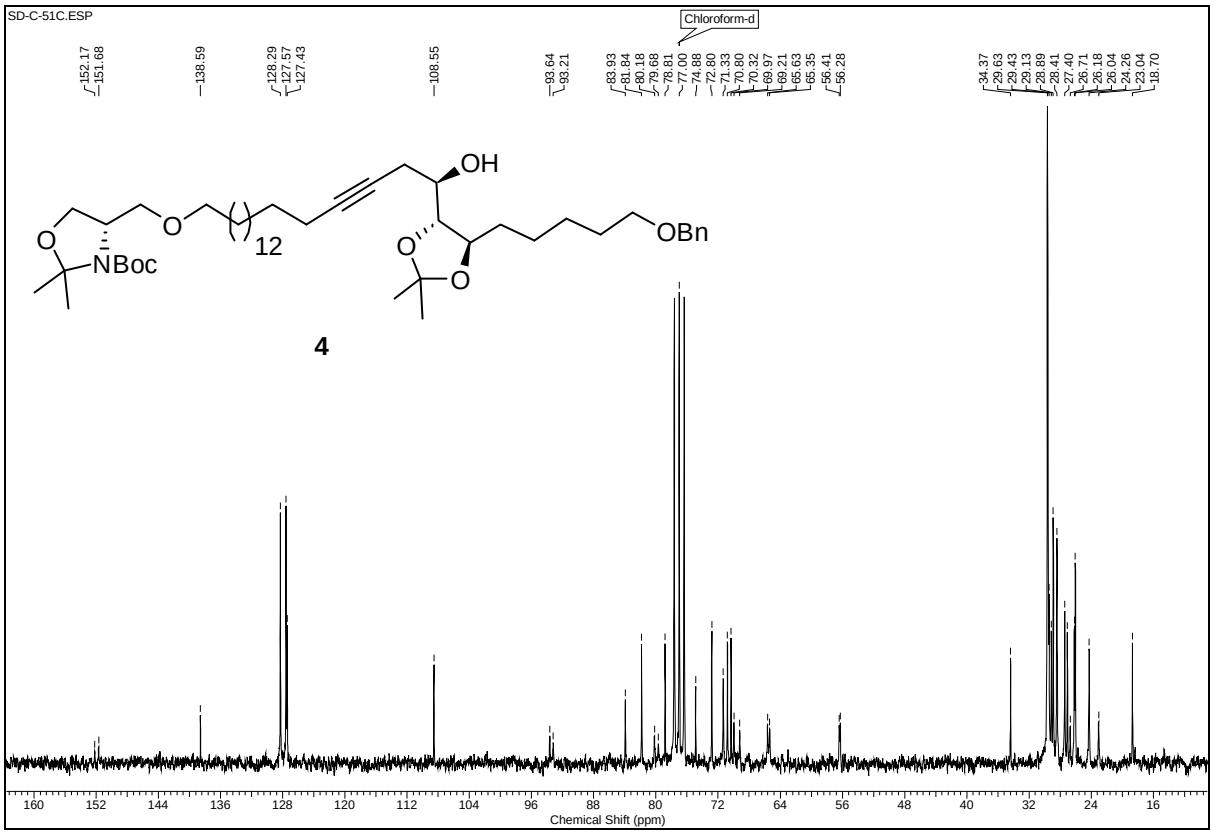
^{1}H NMR Spectrum of 6 in $CDCl_3$



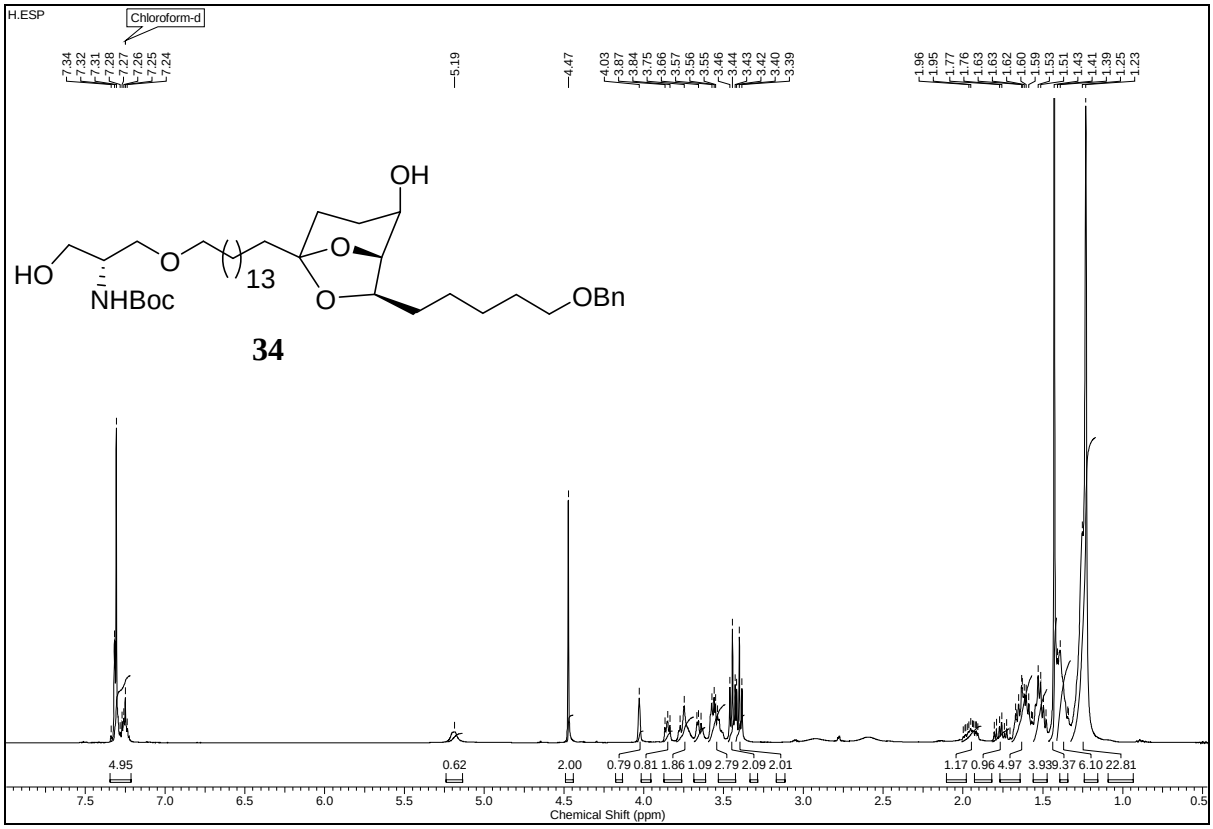
^{13}C NMR Spectrum of 6 in $CDCl_3$



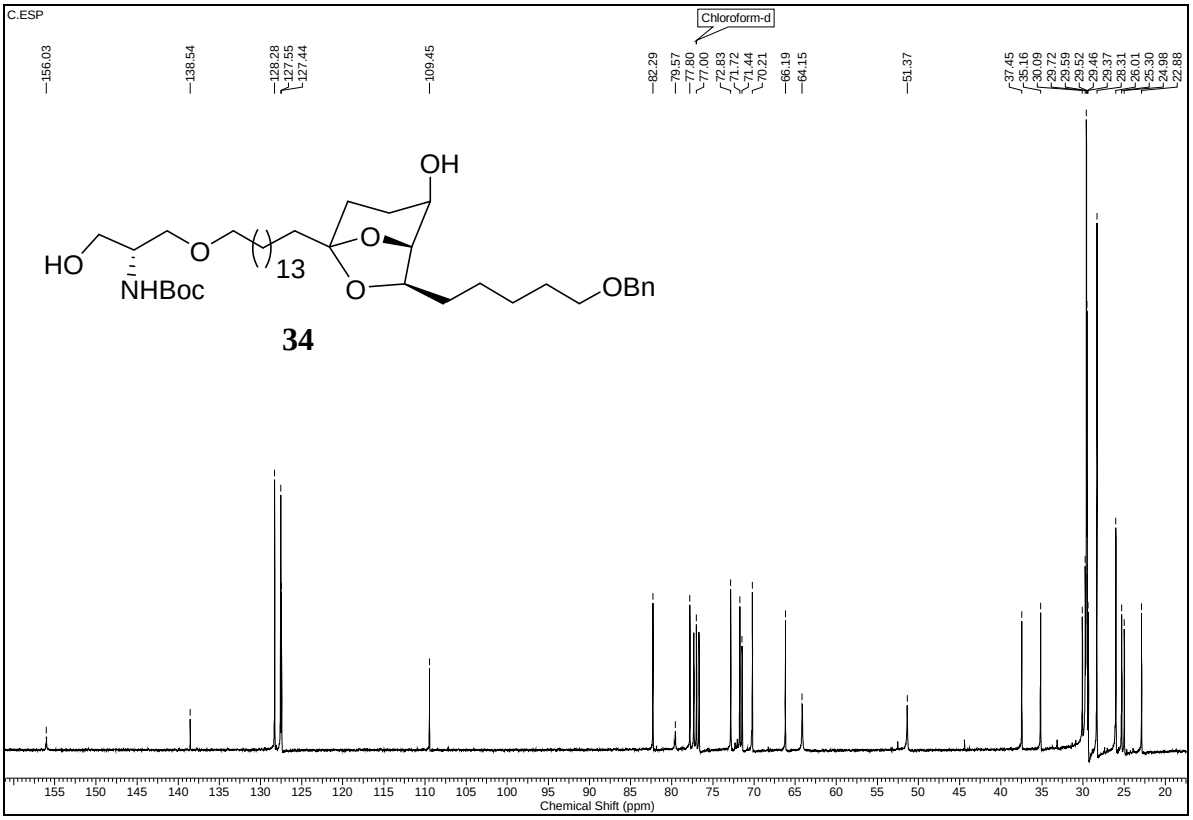
^{1}H NMR Spectrum of 4 in $CDCl_3$



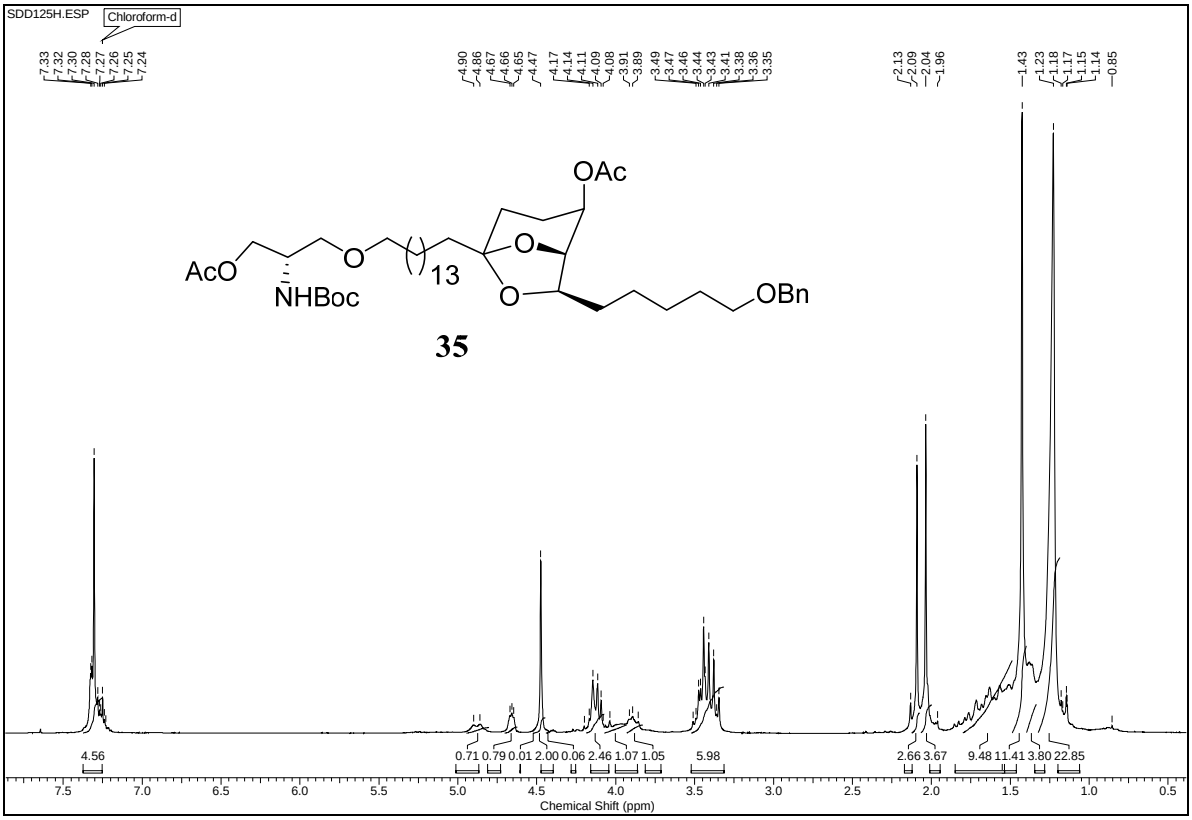
^{13}C NMR Spectrum of 4 in $CDCl_3$



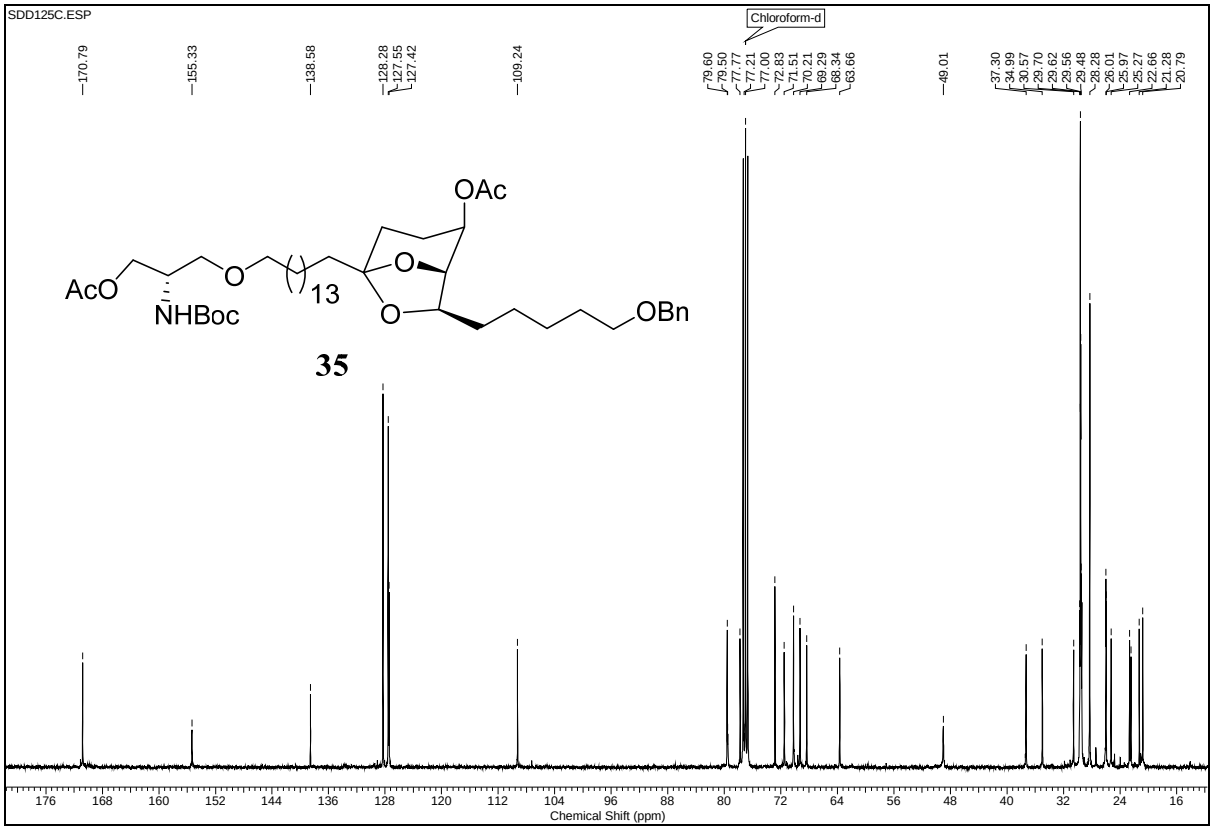
^{1}H NMR Spectrum of 34 in $CDCl_3$



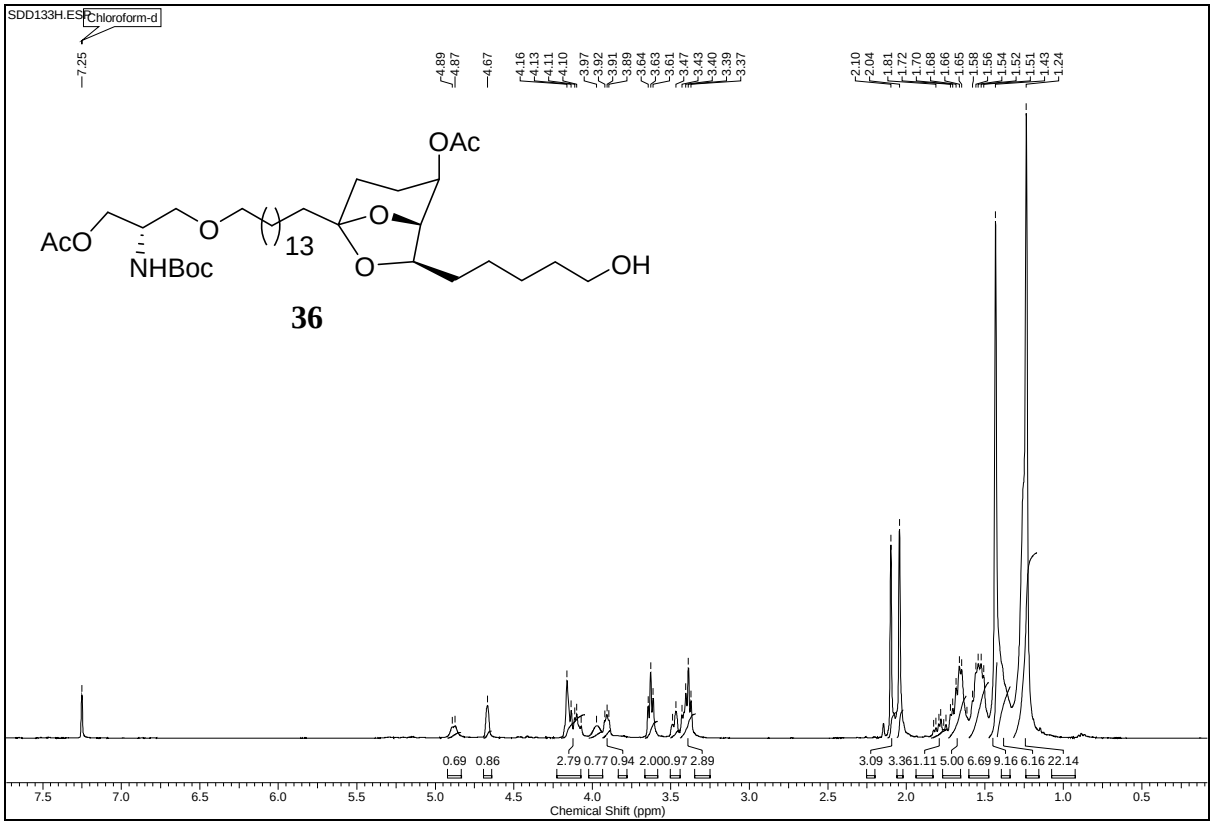
^{13}C NMR Spectrum of 34 in $CDCl_3$



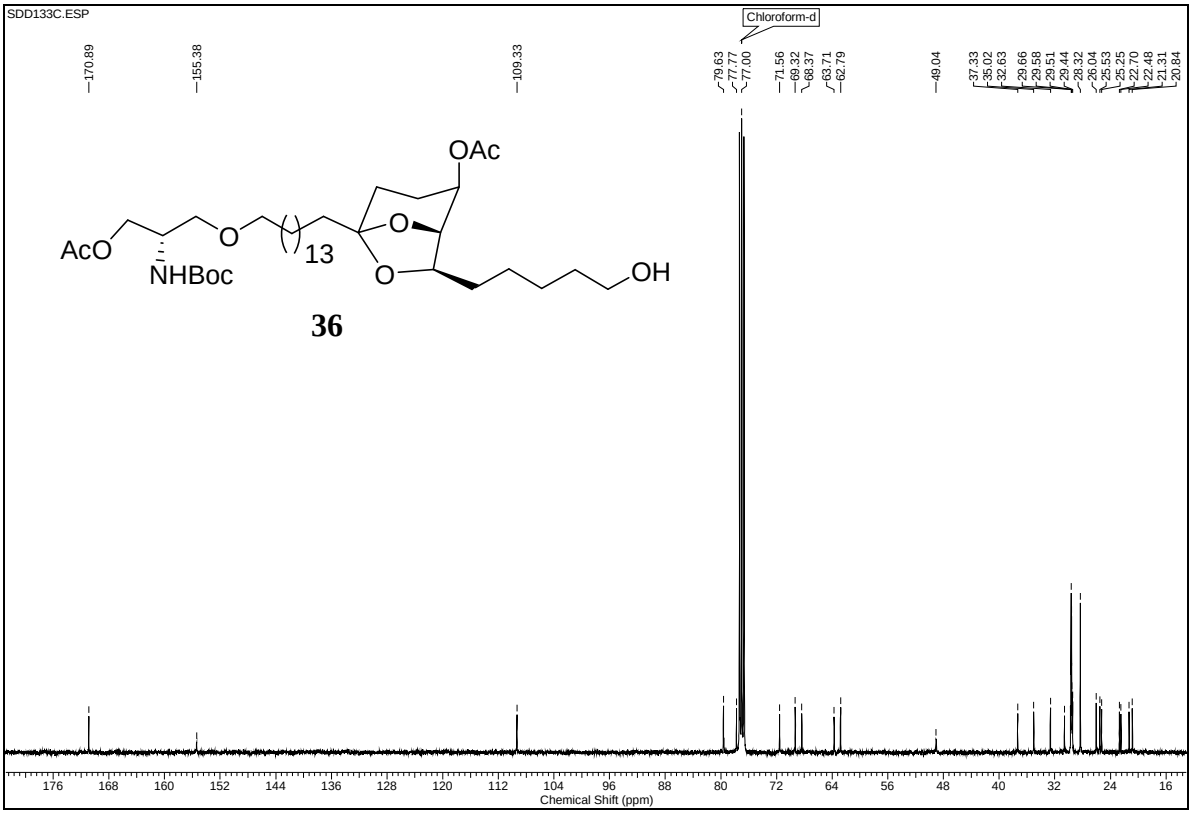
^{1}H NMR Spectrum of 35 in $CDCl_3$



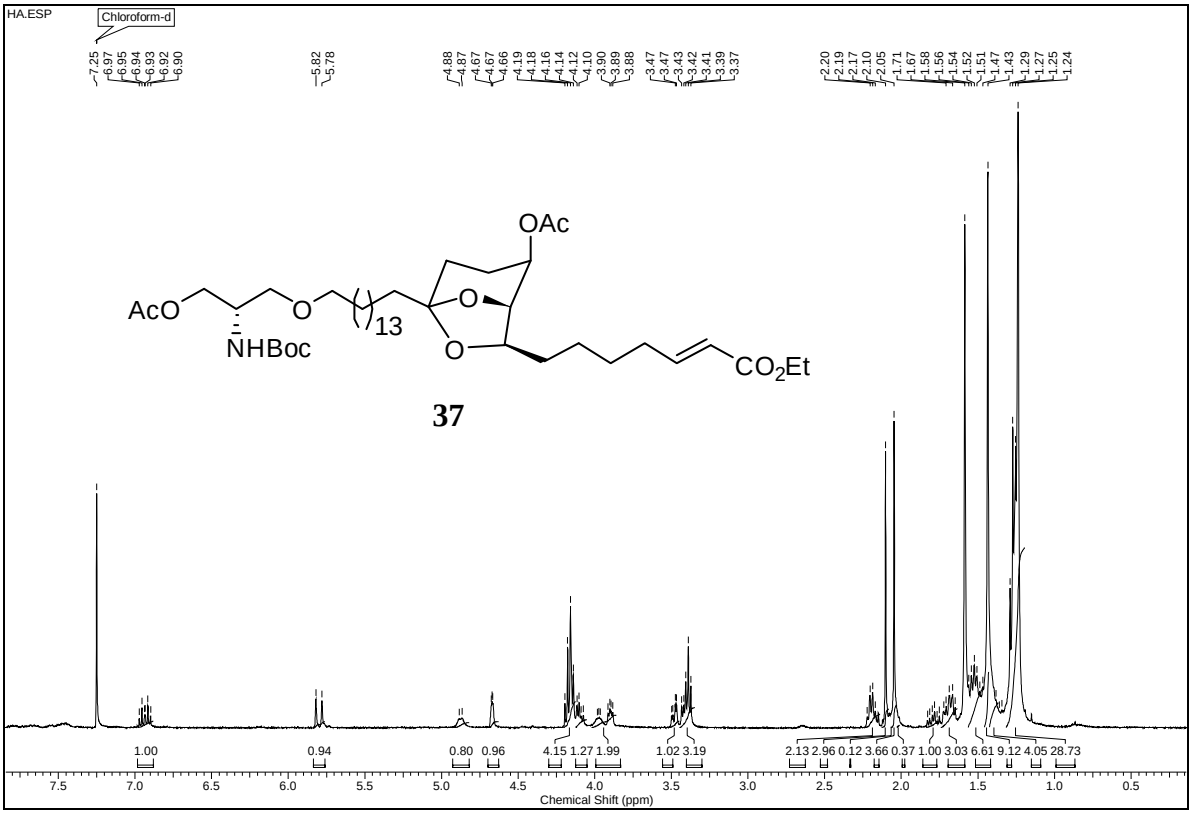
^{13}C NMR Spectrum of 35 in $CDCl_3$



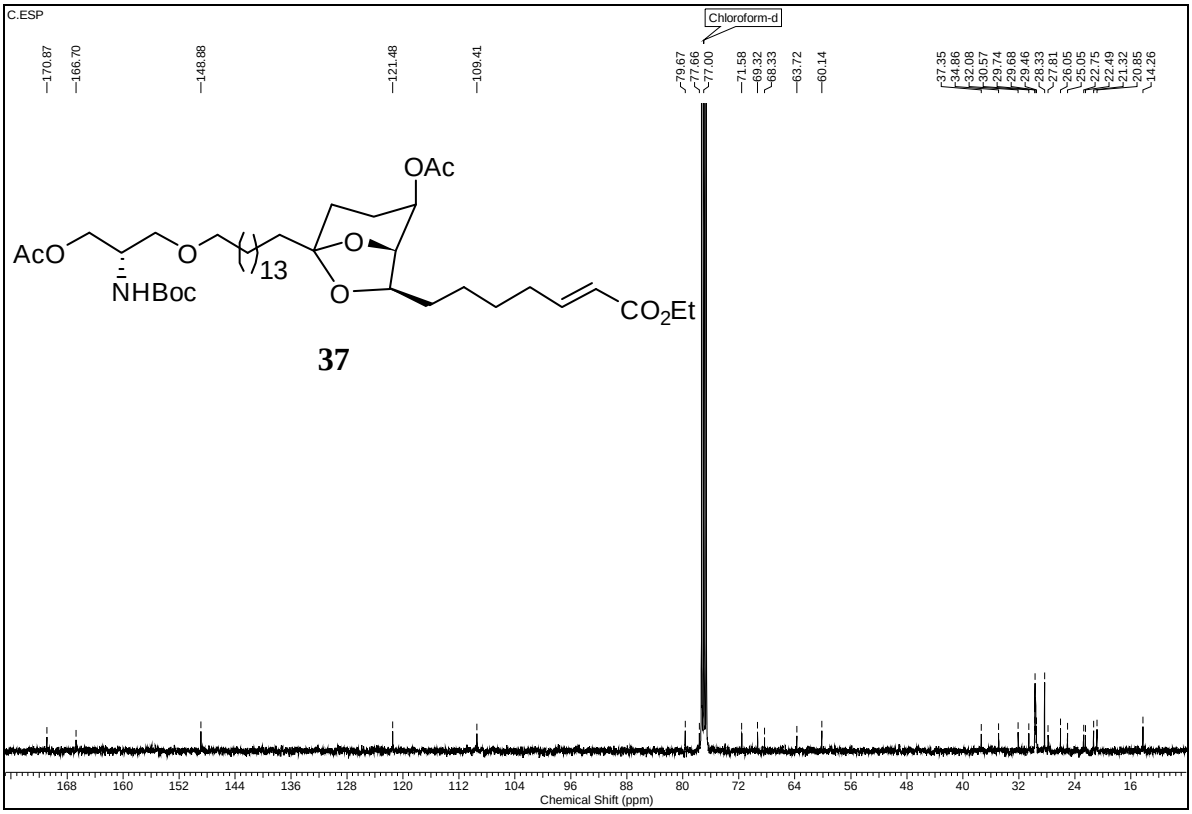
^{1}H NMR Spectrum of 36 in $CDCl_3$



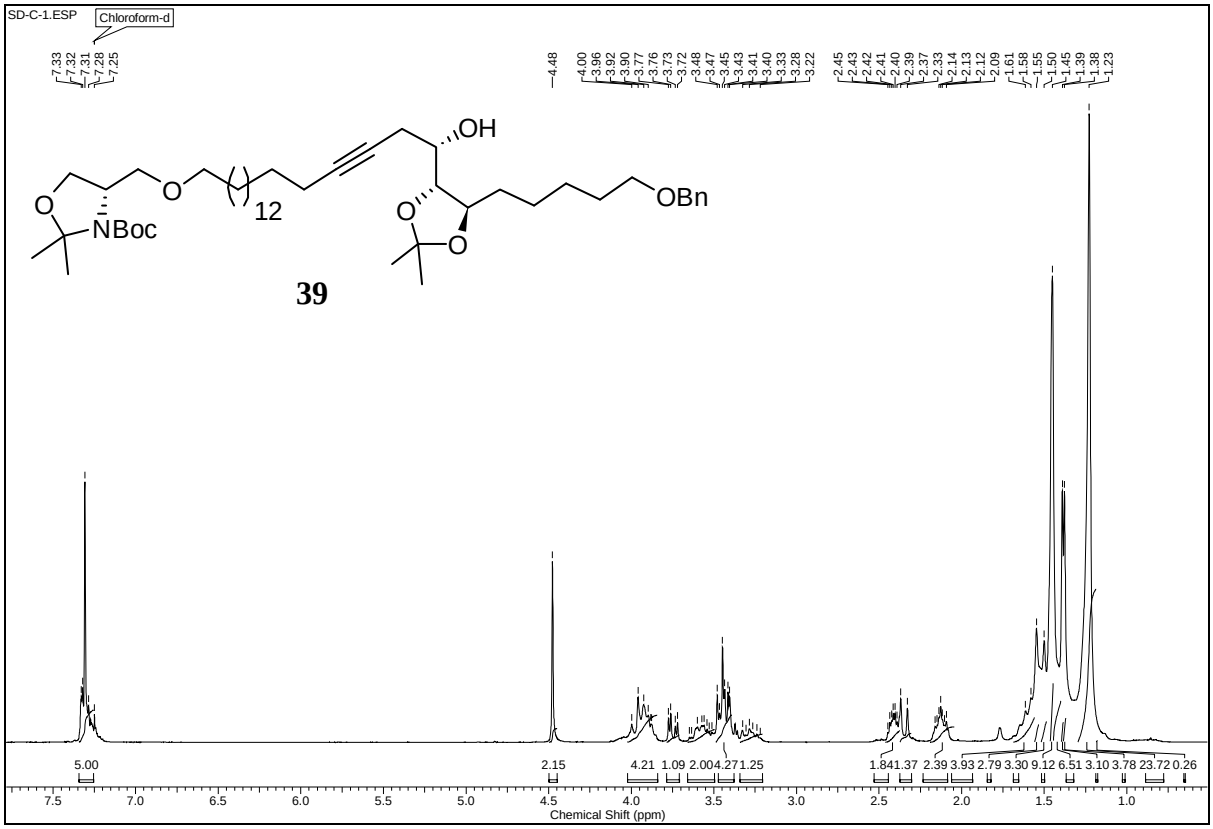
^{13}C NMR Spectrum of 36 in $CDCl_3$



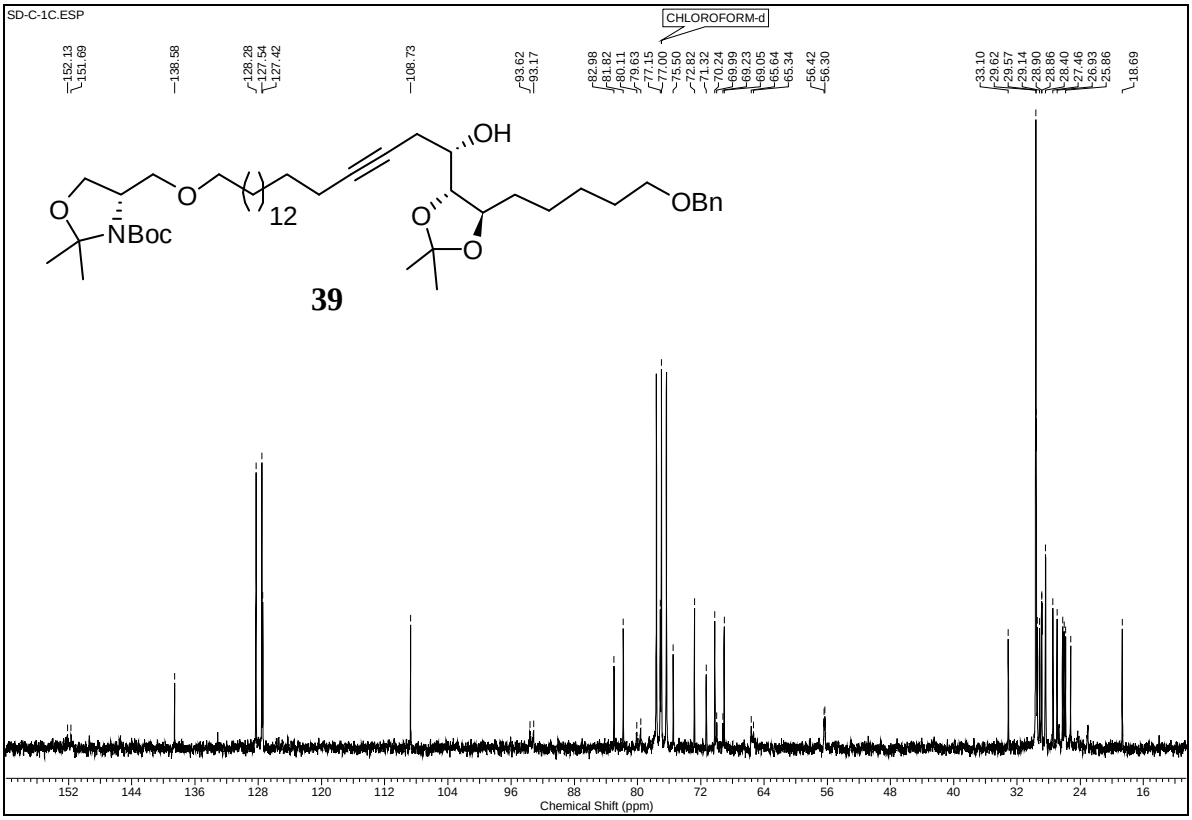
^{1}H NMR Spectrum of 37 in $CDCl_3$



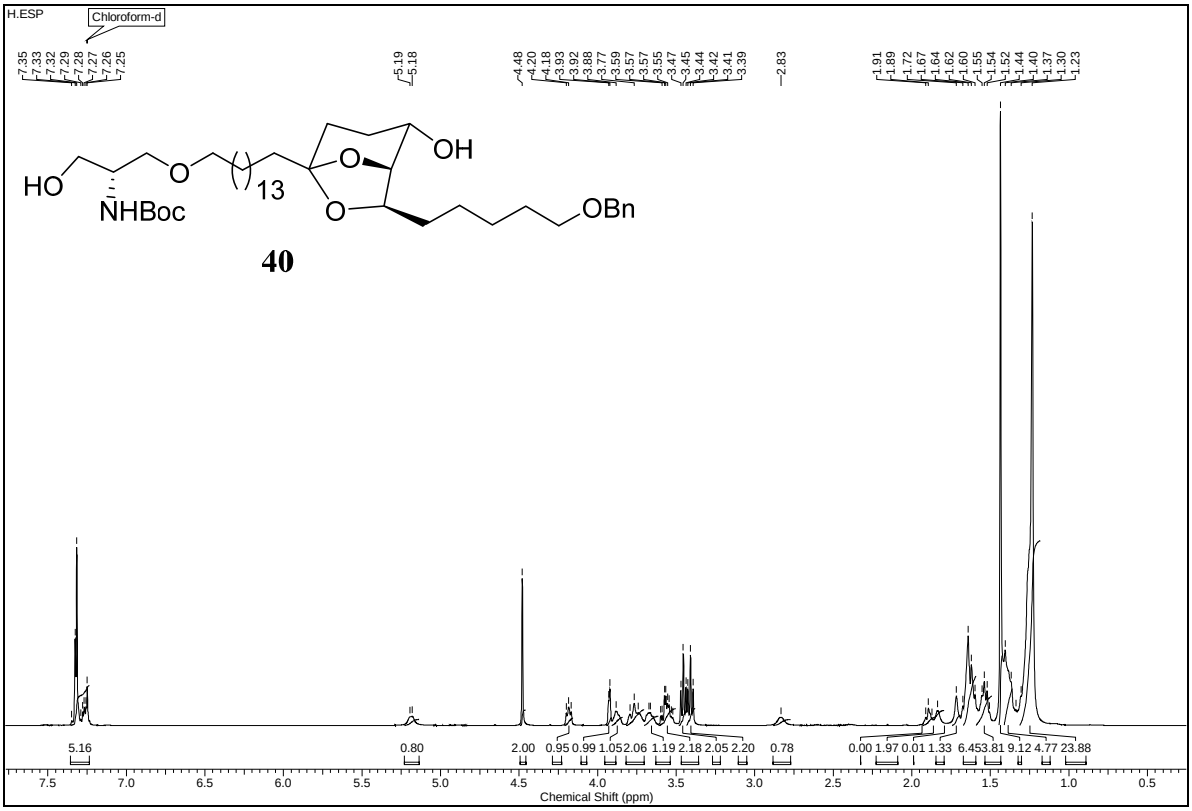
^{13}C NMR Spectrum of 37 in $CDCl_3$



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

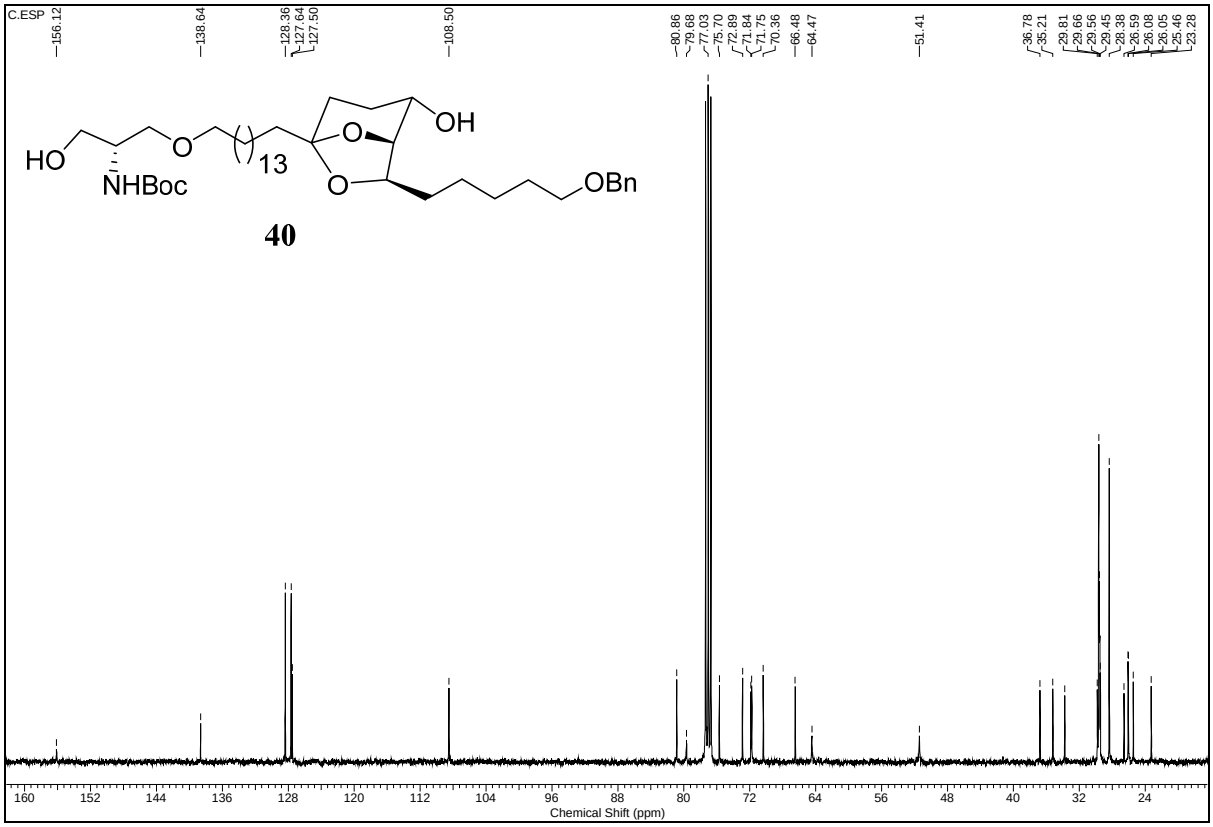


^{13}C NMR Spectrum of 39 in $CDCl_3$



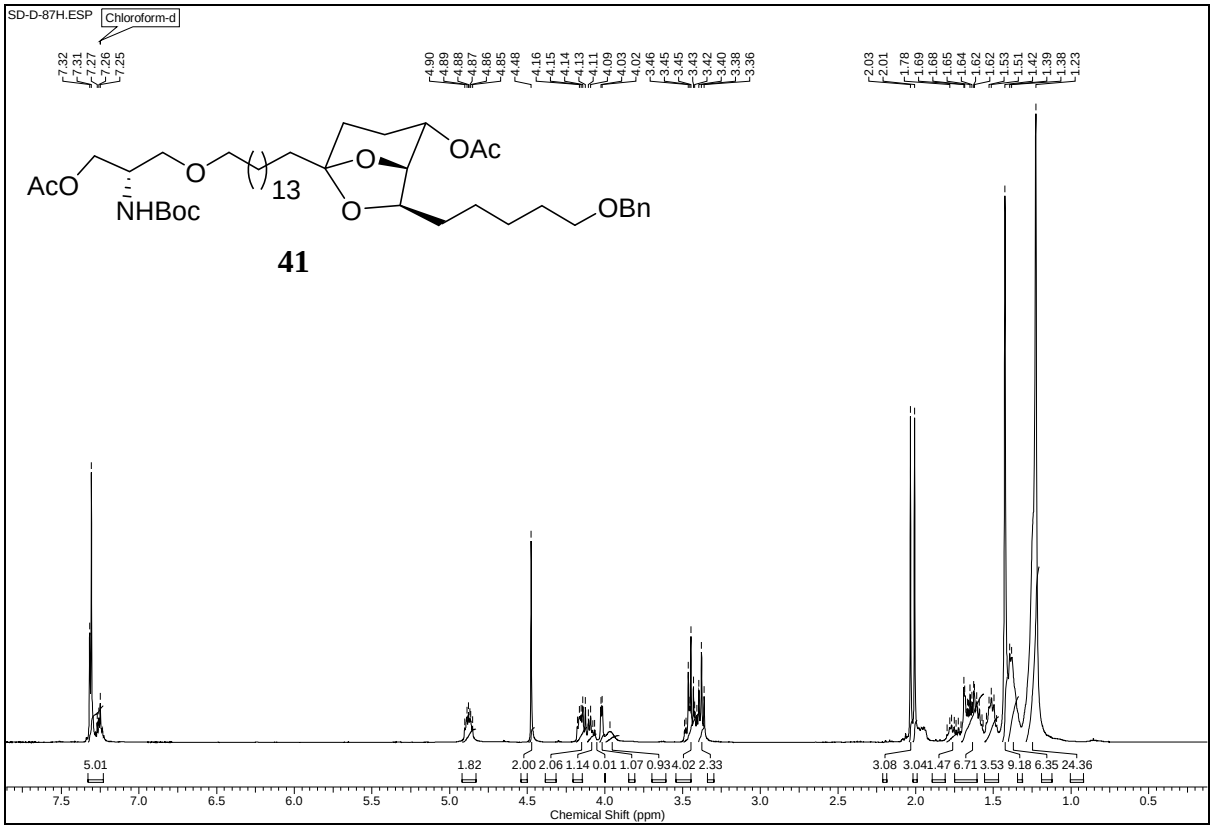
40

^{1}H NMR Spectrum of 40 in $CDCl_3$

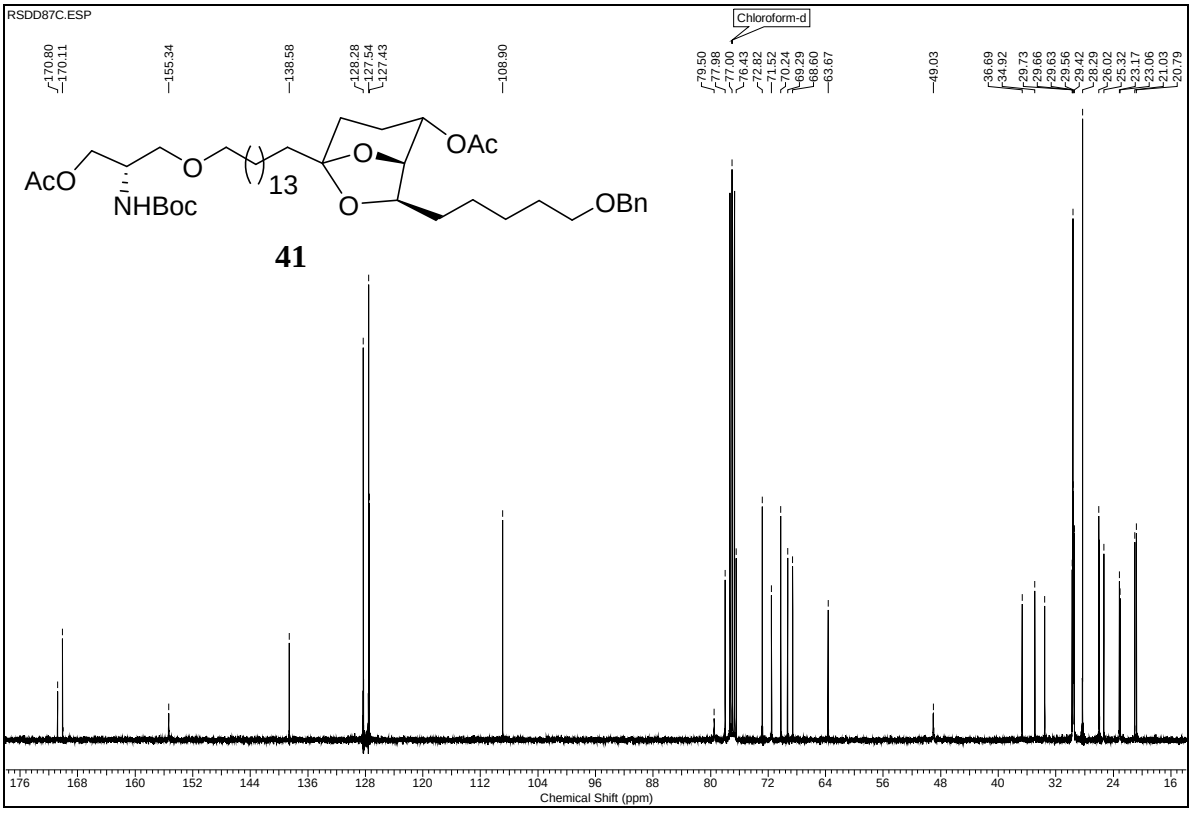


40

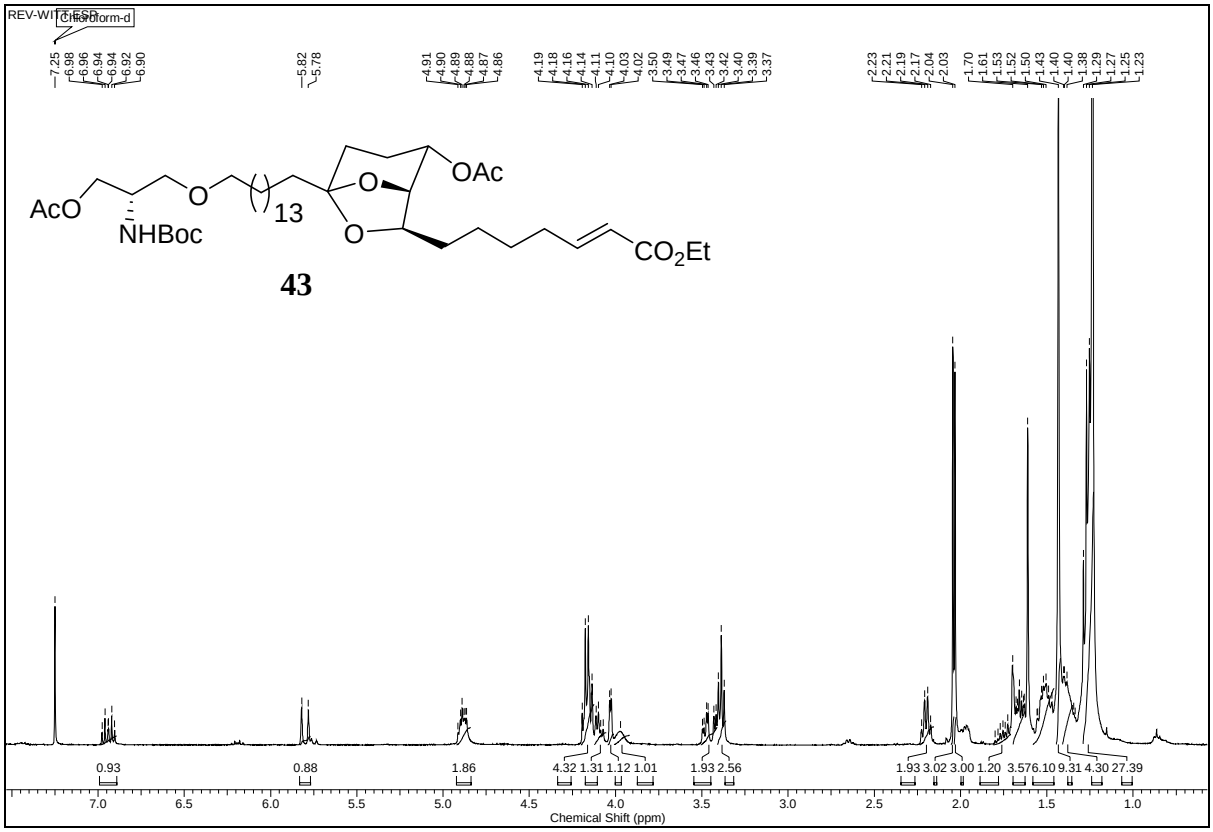
^{13}C NMR Spectrum of 40 in $CDCl_3$



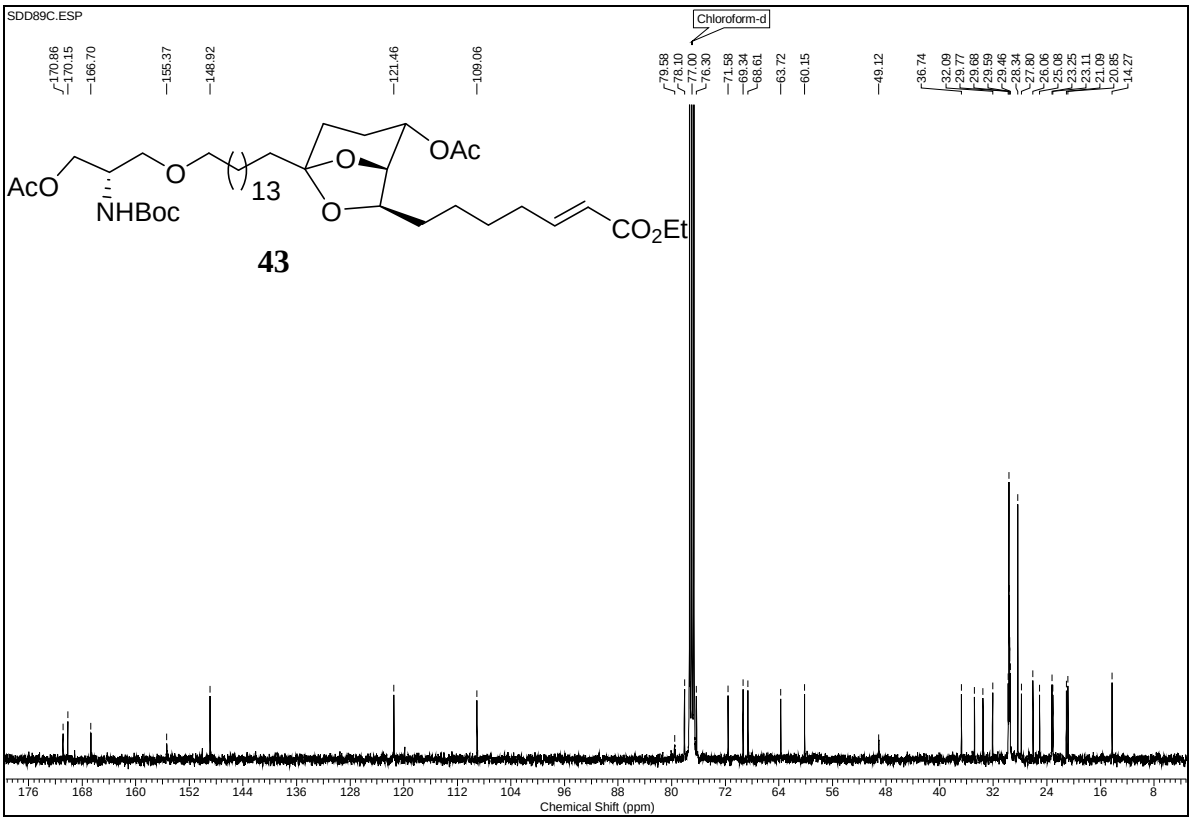
^{1}H NMR Spectrum of 41 in $CDCl_3$



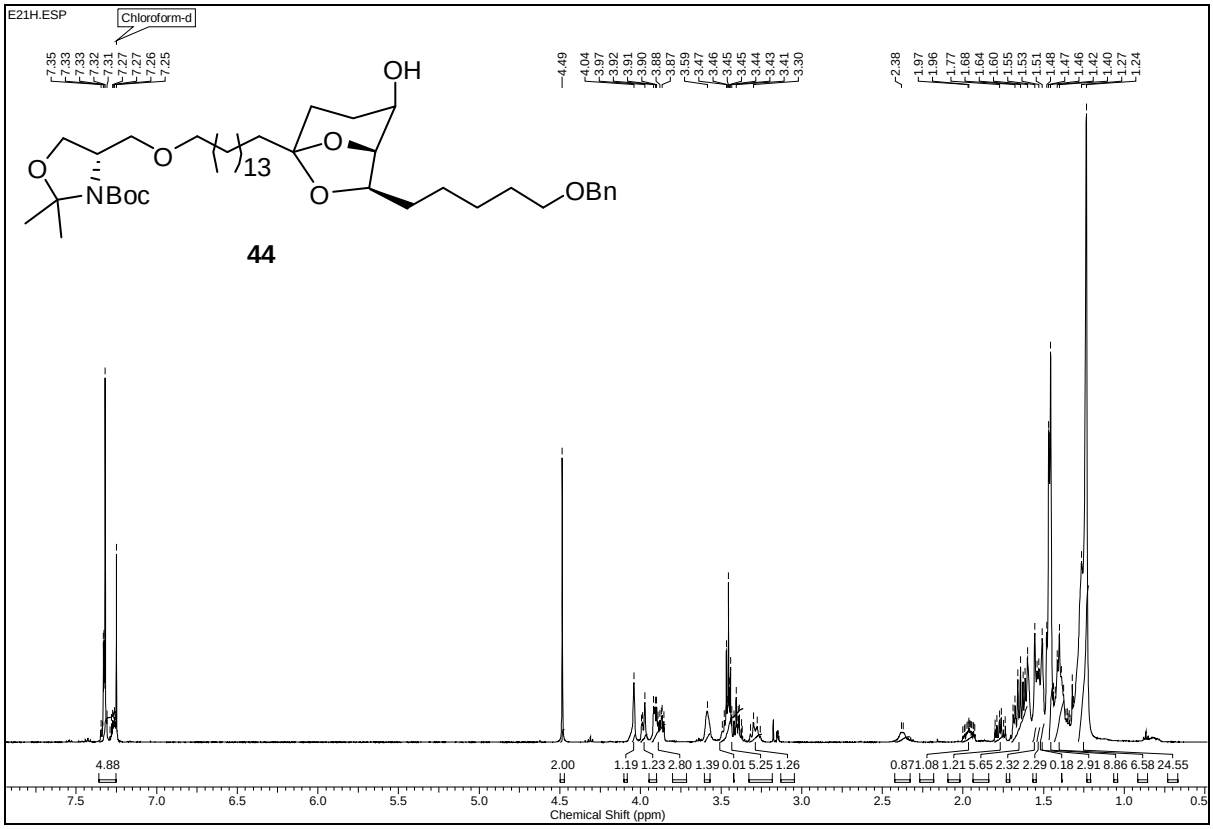
^{13}C NMR Spectrum of 41 in $CDCl_3$



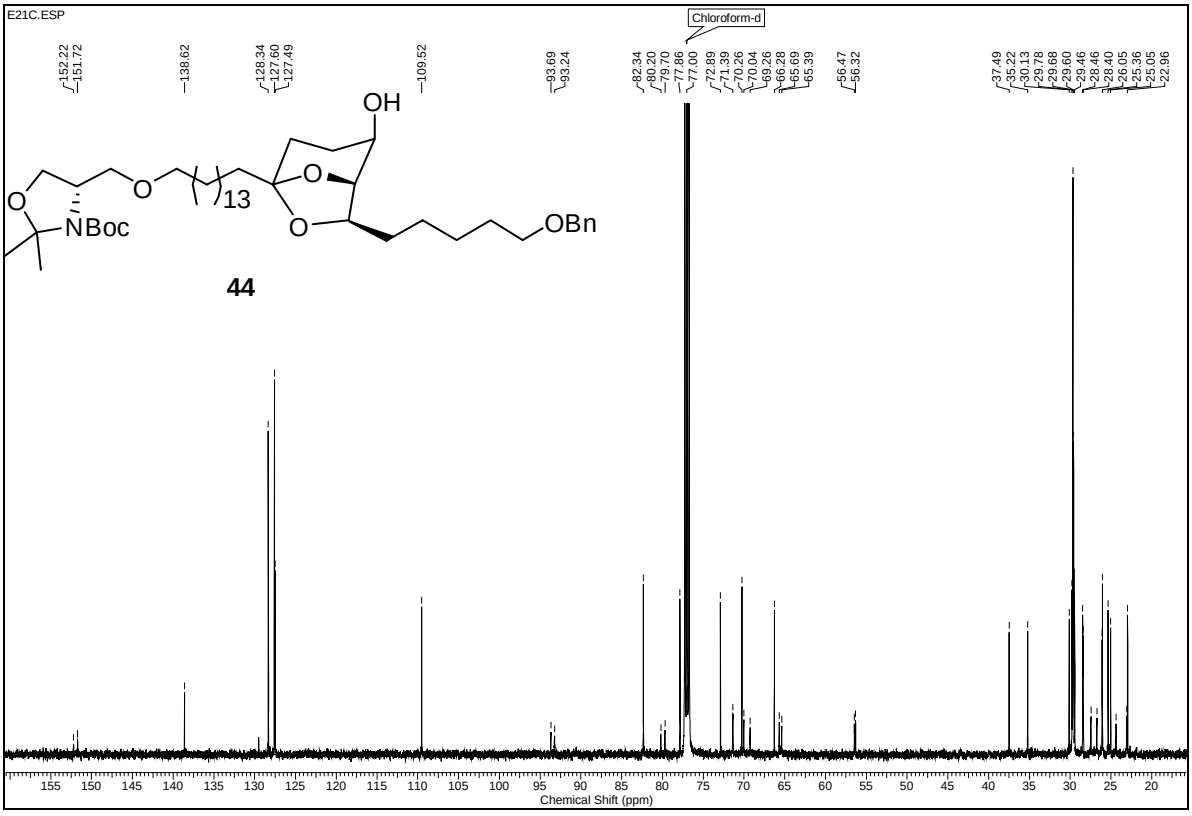
^{1}H NMR Spectrum of 43 in $CDCl_3$



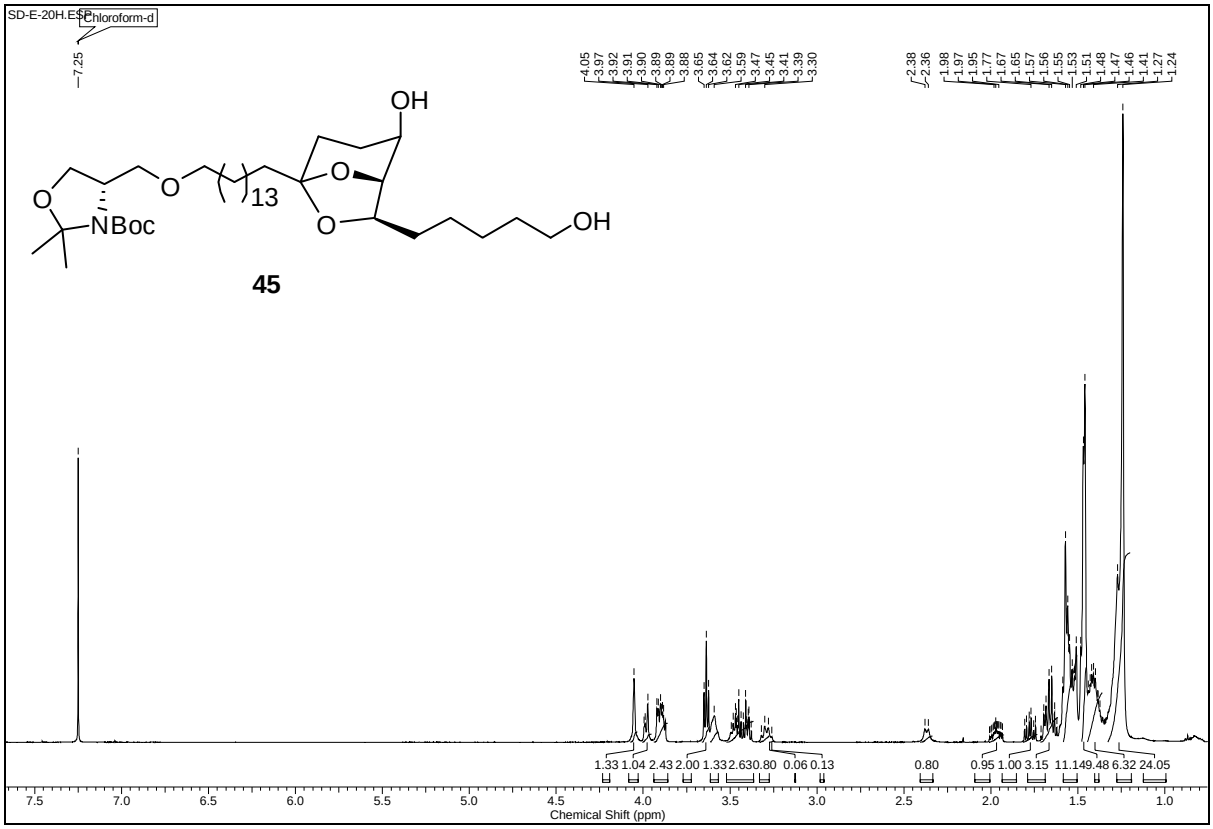
^{13}C NMR Spectrum of 43 in $CDCl_3$



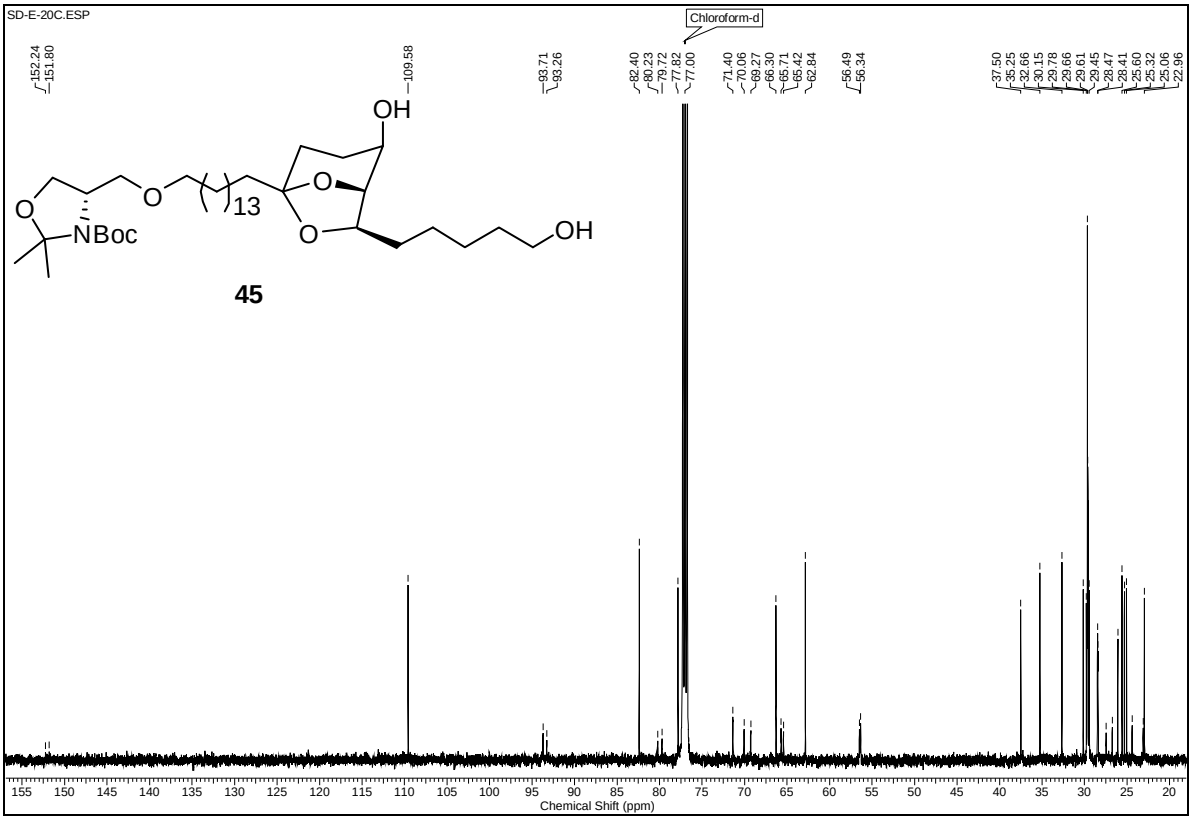
^{1}H NMR Spectrum of 44 in $CDCl_3$



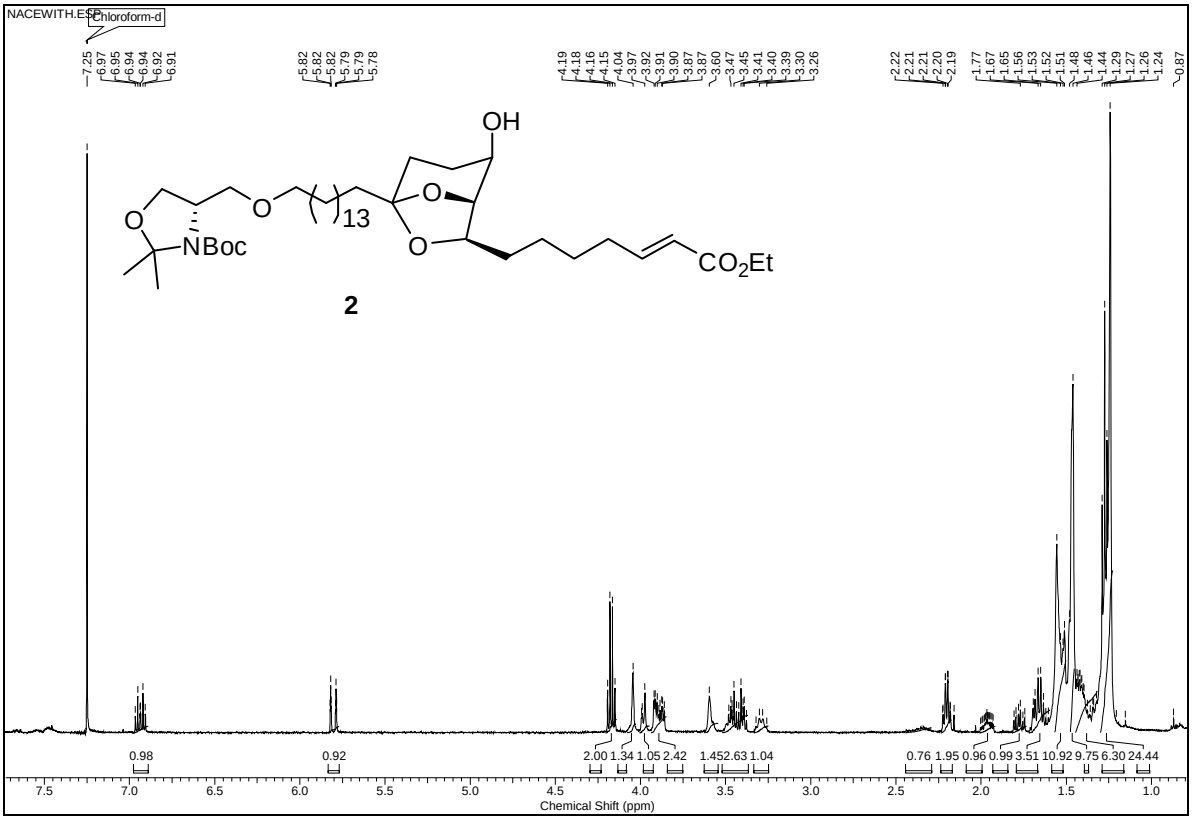
^{13}C NMR Spectrum of 44 in $CDCl_3$



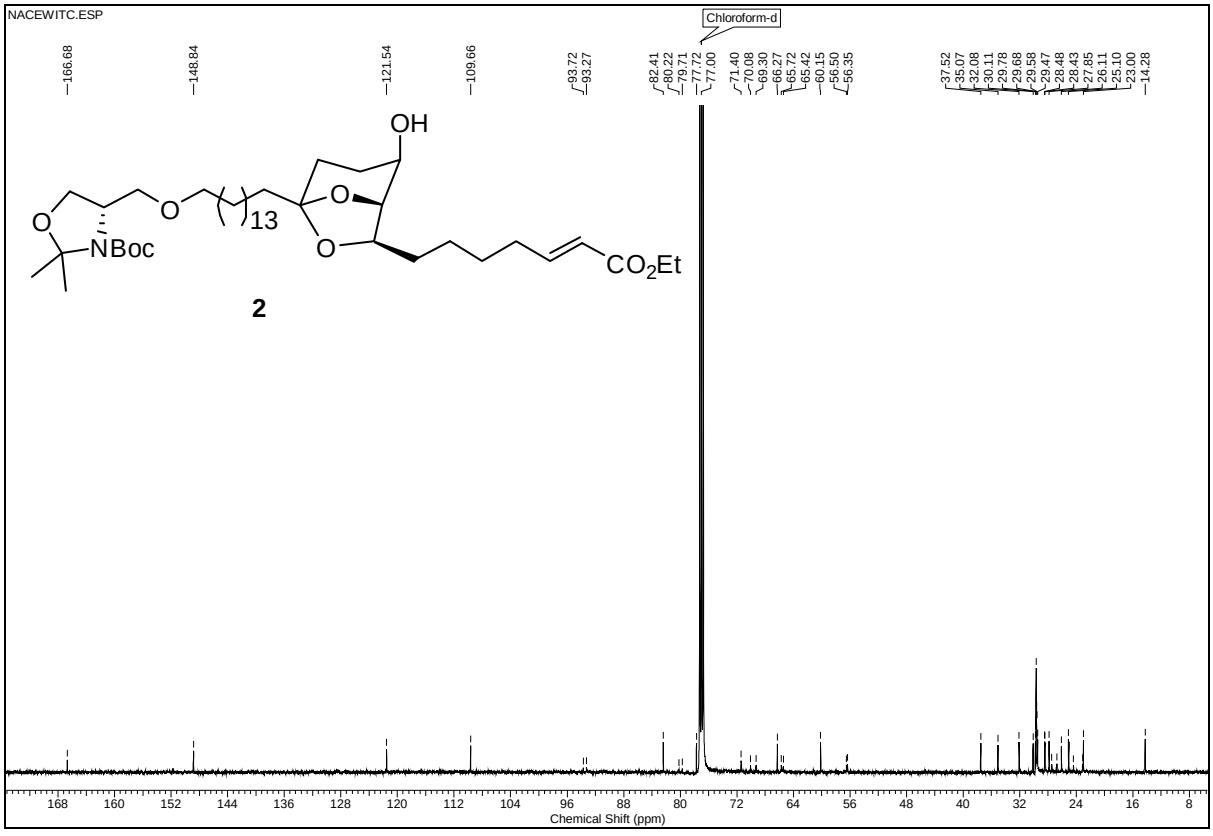
^{1}H NMR Spectrum of 45 in $CDCl_3$



^{13}C NMR Spectrum of 45 in $CDCl_3$



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



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

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CHAPTER II; SECTION A

The total synthesis of proposed structure of Notoryne

INTRODUCTION

The tetrahydrofuran (THF) ring is a commonly encountered ring in various natural products.[1] Quite interestingly there are several natural products which display two or more THF rings being arranged in various orientations.[2] Annonaceous acetogenins, polyether antibiotics, and macrodiolides are some of important classes which are characterized by the presence of multiple THF rings. For example, ionomycine, mucoxin, Jimenezin, NSC695222, Kumausallene and Notoryne are some representative natural products having the different types of relative arrangement of these furan rings across the complete molecular skeleton (Figure 8). This diversity in their arrangement and diverse biological activities that have been noticed and, most importantly, very limited supply of these natural products for further biological studies has attracted the attention of the synthetic organic chemists. There are many elegant approaches that have been developed to equip the molecular skeletons having the THF ring with the desired relative arrangement, yet the opportunities for the development of new methodologies with increased skeletal and stereo chemical flexibility continues. As this part of the thesis will be describing our efforts towards the synthesis of a couple of molecules belonging to the class of bis-furans, the following introductory part will be reserved mainly for providing the literature examples that deal with the synthesis of scaffolds which are similar to the ones that these two natural products possess.

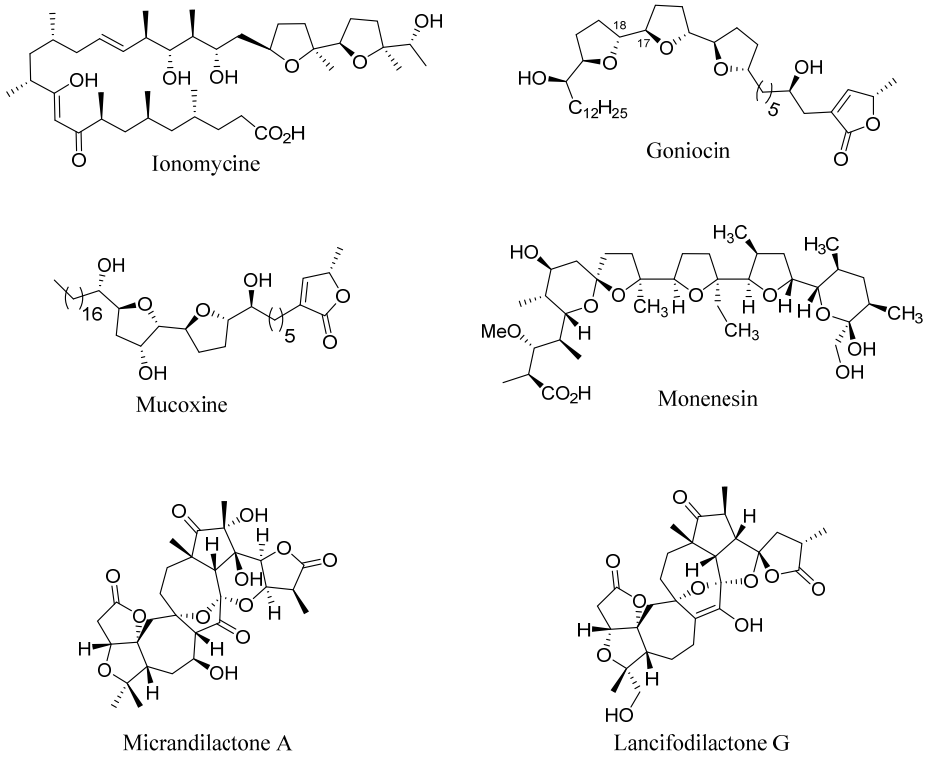


Figure 8: Structural diversity of in the natural products having multiple furan rings

Apart from the molecules of nature, there are several drugs which are identified with the presence of THF rings. 3'-Azido-3'-deoxythymidine (AZT) is one of the early drugs approved by FDA for the treatment of Acquired Immuno Deficiency Syndrome (AIDS) and has inspired the development a wide range of nucleoside analogues as potential retro viral.[3] In particular more emphasis has been placed on designing the conformationally restricted nucleoside derivatives as it has been understood that only one conformation of nucleosides binds to the target enzyme. Various nucleoside analogues containing the bicyclic carbohydrate moiety have been synthesized to lock the puckering of the furanose ring and study their biological activity. Darunavir, a conceptually new HIV-1 protease inhibitor having a bis-furan core, is one of the successful candidates that have been identified in this context.[4] It was proved that this bicyclic compound has shown anti-HIV activity through the inhibition of HIV reverse transcriptase. It has been shown that this bicyclic unit is involved in a network of hydrogen bonding interactions with the protein-backbone of the HIV-1 protease and that because of this Darunavir displays a superior resistance profile.[5]

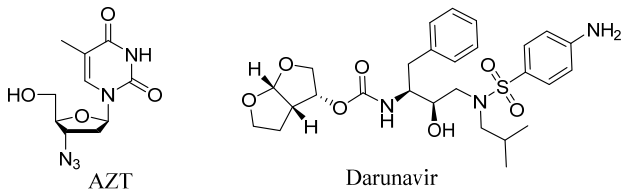


Figure 9: The structures of AZT and Darunavir

The molecules having multiple furan rings can be divided broadly into two classes as bis-furans and fused furan systems. The bis-furan systems can be further divided into two families as adjacent bis-furans, i.e. attached ring and non-adjacent 2,5 disubstituted (i.e. two furan rings are connected with a hydrocarbon chain). There are four types of fused furan rings possible according to their connection or fusion irrespective of stereochemistry. These are i) *syn*-furo[2,3-b]furan; ii) *anti*-furo[2,3-b]furan; iii) furo[2,3-c]furan; and iv) furo[3,4-c]furan. Considering the structures of Notoryne (**46**) and Kumausallene (**47**), the following discussion will be mainly on the synthesis of related systems in case of Notoryne and on the early total synthesis of Kumausllene.

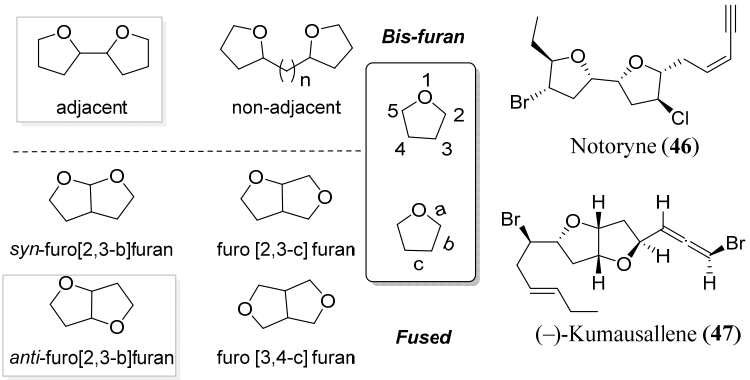


Figure 10: The classification of multiple furan arrangement and the structures of Notoryne and Kumausallene

1. Synthesis of adjacent bis-furan skeleton and of related natural products:

The complex chemistry and potent biological activity of the bis-furan unit containing molecules like Mucoxin, (+)-Parviflorin, ionomycine, Pamamycin-607, Uvaricin, Sylvaticin and (+)-Gigantecinan has created widespread interest. Sometime they act as an ionophore for transporting cations across the lipid barrier or sometimes they show multi drug-resistant power through the complexation with ubiquinone-linked NADH oxidase present in the plasma membrane of tumor cells. Plants of the family Annonaceaeuse produce significantly bioactive C_{35}–C_{37} fatty acid metabolites which contained mainly monoTHF, adjacent bis-THF, and nonadjacent bis-THF subunits. Mucoxin,[19] an adjacent bis-THFacetogenin, has shown the *in vitro* cytotoxicity assays against a panel of six human tumor cell lines and more potent and selective against MCF-7 (breast carcinoma) cell lines than adriamycin. Parviflorin,[15b] is an adjacent bis-THF acetogenin, was isolated from *Asiminapar Viflora Duanl* and from *Annonabullata Rich*, and shows significant selectivity in its cytotoxicity against certain human solid tumor cell lines. Squamocin D is a typical member of bis-THF acetogenins, which are known to be among the most potent annonaceous acetogenins in cytotoxicity tests. [2h] Annonaceous acetogenins help to reduce ATP levels *via* inhibition of complex I (NADH, ubiquinone oxidoreductase) of the mitochondrial transport systems of insects and mammals. As a result it disrupts the ATP-driven resistance mechanisms and builds up activity against multi drug-resistant tumor types. It also inhibits the NADH oxidase of the plasma membranes of tumor cells.

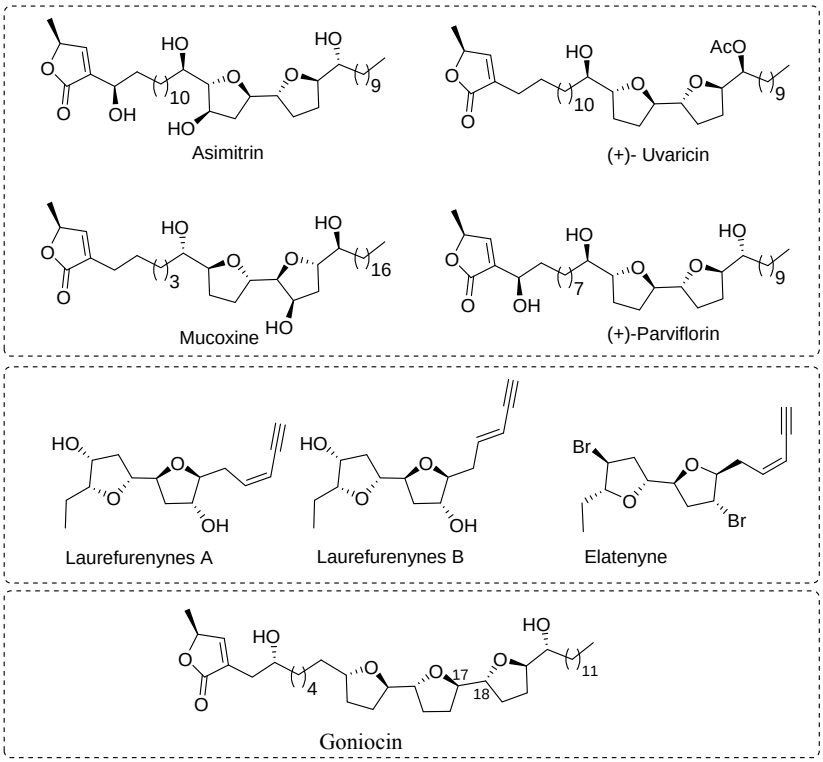


Figure 11: Selected natural products with adjacent *bis*-THF subunits

Considering the different approaches that have been employed in the context of installing the THF rings, the following discussion is subdivided into four parts depending upon the key reaction that has been employed. Each part will present a representative total synthesis stressing mainly on this particular transform and some of the other total syntheses wherein a similar approach employed will be mentioned.

The key transformations that have been employed in this context are:

1.1. Oxidative transformations of olefins.

1.2. Intramolecular additions of alcohols to epoxides.

1.3. Intramolecular S_N2 and S_N1 reactions of hydroxyl nucleophiles with alkyl halides.

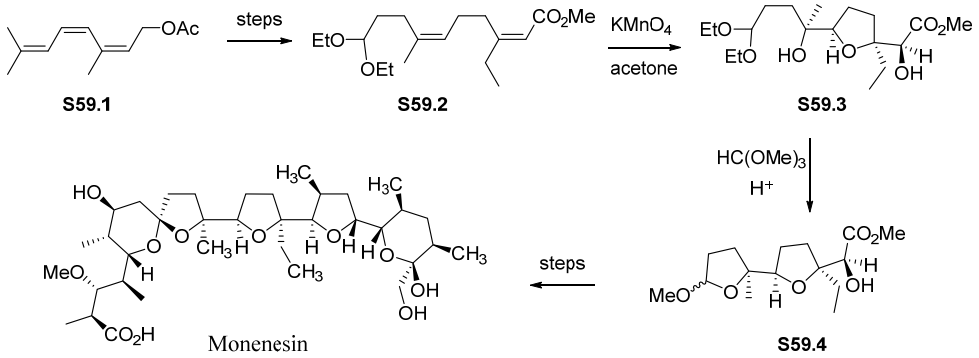
1.4. Halo etherification of multiple bonds.

1.5. Metal mediated cyclization.

1.1. Oxidative transformations of olefins:

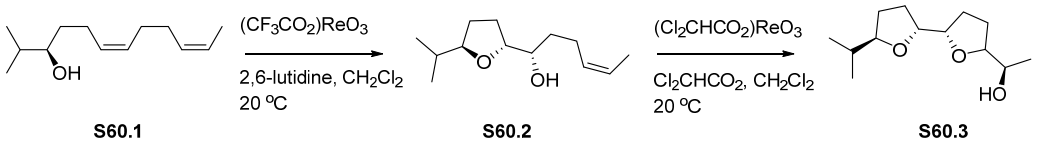
One of the early methods reported in the context of synthesis of the bis-THF core was the one-pot or sequential oxidation of polyenes. In 1965, Klein and Rojahn first demonstrated that a simple treatment of neryl acetate **S59.1** with $KMnO_4$ leads to a *cis*-2,5-disubstitutedfuran in a stereo specific way.[6] In 1980, Walba and co-workers used this potential methodology and synthesized the B and C ring of Monensine from neryl acetate

S59.1.[7] The advanced intermediate (*Z*,*Z*)-1,5-diene **S59.2** prepared from neryl acetate had been subjected for oxidation in the presence of $KMnO_4$ to procure the *cis*-2,5-substituted furan unit **S59.3** which was further exposed to acid to give **S59.4** having the BC ring of Monensine.



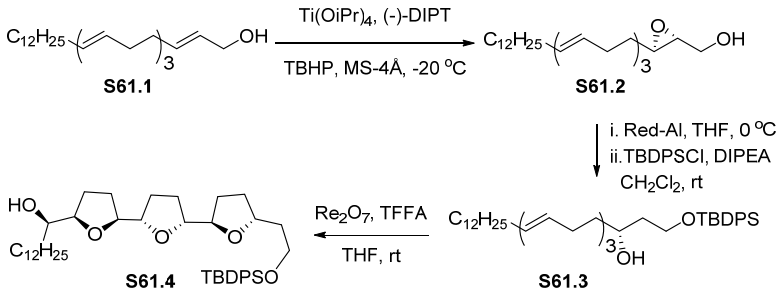
Scheme 59: Synthesis of Monensine by Walba *et al*

In 1995, McDonald and co-workers reported an acyl perrhenate-induced tandem [3 +2] *syn*-oxidative cyclization for the synthesis of bis-furan moiety from acid sensitive hydroxydienes **S60.1**.[8] A one-pot approach to generate the bis-furan moiety **S60.3** did not work because of coordinative interaction between the Lewis acidic rhenium atom and the tetrahydrofuran oxygen. Omission of base as well as addition of trifluoroacetic anhydride to regenerate the active trifluoroacetyl perrhenate catalyst led to the *trans*, *trans*-tetrahydrofurfuryl moiety **S60.3**.



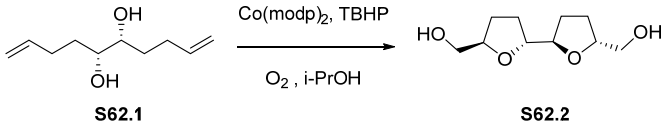
Scheme 60: Synthesis of bis-THF core by McDonald's group

In 1997, Sinha and co-workers reported a tandem oxidative cyclization reaction of a trienol using the Re(IV) reagent to install three adjacent THF rings with the creation of six new chiral centers aided by a single stereogenic centre present in the starting substrate.[9] The *trans*-4,8,12-trienol **S61.1** was transformed into the epoxy alcohol **S61.2** through asymmetric epoxidation followed by reductive cleavage of the epoxide ring using Red-Al and protection of 1^o–OH as its TBDPS ether **S61.3**. The treatment of trienol **S61.3** with Re_2O_7 in the presence of TFAA provided the tris-THF derivative **S61.4** as a single diastereomer which has been advanced further to synthesize the 17,18-*bisepi*-goniocin.



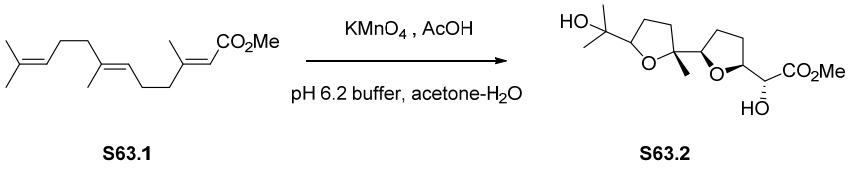
Scheme 61: A one-pot installation of tris-THF core of 17,18-*bisepi*-goniocin

In 1999, Wang and co-workers documented a simple method for the construction of the bis-THF **S62.2** unit from a suitable diol **S62.1** employing a Co-catalyzed oxidative cyclization of a dienediol employing the oxygen atmosphere. [10] The diol **S62.1** was prepared from *trans*-1,5,9-decatriene by using sharpless AD reactions.



Scheme 62: Synthesis of bis-THF core by Wang's group

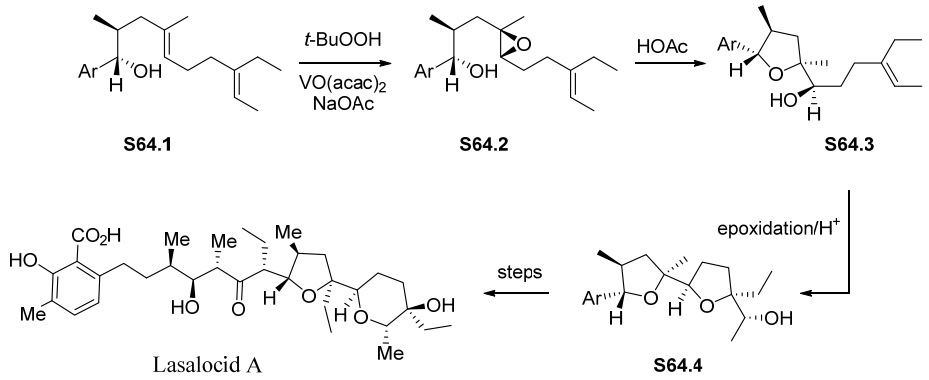
In 2002, Brown and co-workers documented the synthesis of the 2,2'-bifuranyl compound **S63.2** through a permanganate oxidation of *E,E*-methyl farnesoate **S63.1** with control of relative stereochemistry at four new stereocenters. [11]



Scheme 63: Synthesis of bis-THF core by Brown *et al*

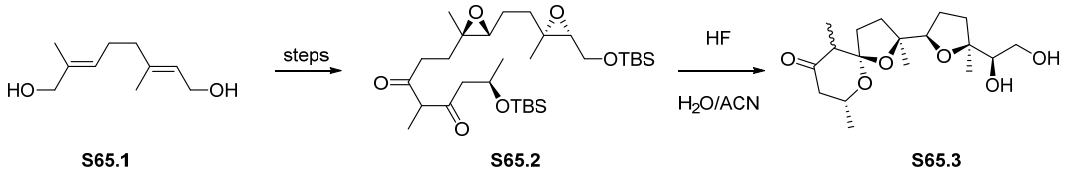
1.2. Intramolecular additions of alcohols to epoxides:

In 1978, Kishi and co-workers reported the first total synthesis of Lasalocid A which is produced by *Streptomyces lasaliensis*, and a member of the class of naturally occurring ionophores known as polyether antibiotics.[12] They have followed the epoxy-cyclization to build up *trans* 2,5 disubstituted furan **S64.3** from γ,δ-alkenol **S64.1** by using *t*-BuOOH in the presence of $VO(acac)_2$ followed by acid treatment. The same reaction sequence was repeated for the synthesis of the second furan ring in **S64.4**



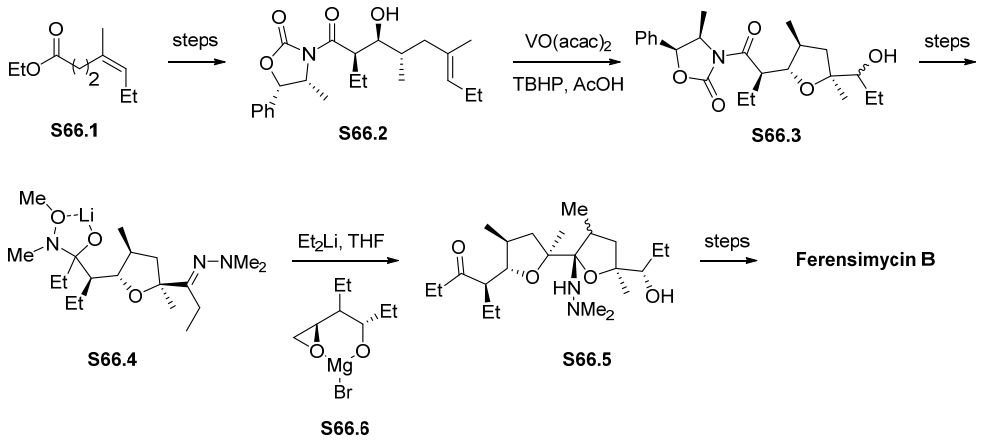
Scheme 64: Synthesis of Lasalocid A by Kishi *et al*

In 1989, Paterson and co-workers reported a controlled bisepoxide cyclization leads to bisfuran **S65.3** core by using suitable β-diketone **S65.2** which was prepared from 1,5 diene **S65.1**.[13] When TBS protected bis epoxide **S65.2** was treated with HF desilylation followed by cascade cyclization leads to bis-THFcore **S65.3**.



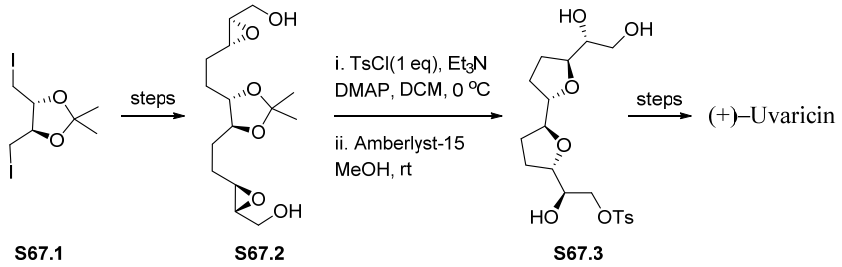
Scheme 65: Synthesis of bistetrahydrofuran core by Paterson *et al*

In 1991, Evans and co-workers documented a convergent asymmetric synthesis of polyether antibiotics Ferensimycin B.[14] For the preparation of THF ring they performed vanadium catalyzed epoxidation of bis-homoallylic alcohol **S66.2** followed by acid catalyzed ring opening of the intermediate epoxide, which afforded the diastereomeric tetrahydrofuran **S66.3**. The second THF ring was prepared by alkylation of the enamine **S66.4** to an activated epoxide **S66.6** followed by cyclization which led to the bis-furan **S66.5** core part of Ferensimycin B.



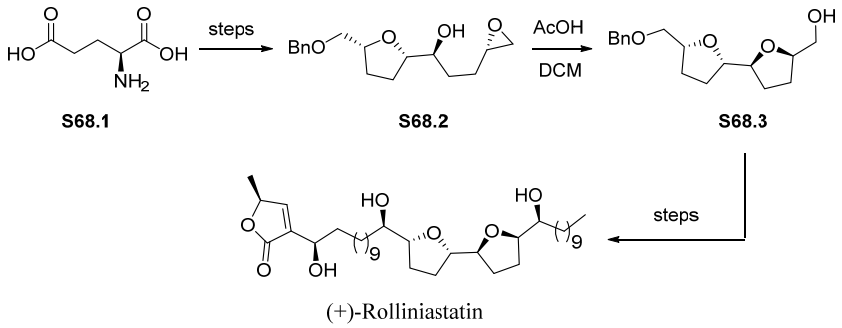
Scheme 66: Synthesis of Ferensimycin B by D. A. Evans *et al*

In the same year, Hoye and co-workers documented the synthesis of (+)-uvaricin by performing a cascade reaction of bis epoxide **S67.2** that was prepared by a two directional chain elongation of tartarate. [15a] The diiodide **S67.1** was converted into the C_2-symmetric diol **S67.2** through the Weiler dianion alkylation[16] and Sharpless asymmetric epoxidation.[17] Now, the diol **S67.2** was selectively mono-tosylated and then subjected for acid catalyzed acetonidede protection to afford the bis-THF core **S67.3** of (+)-Uvaricin. A similar approach for the (+)-Parviflorin has been reported by Hoye and co-workers in 1996.[15b]



Scheme 67: Synthesis of (+)-Uvaricin by Hoye's Group

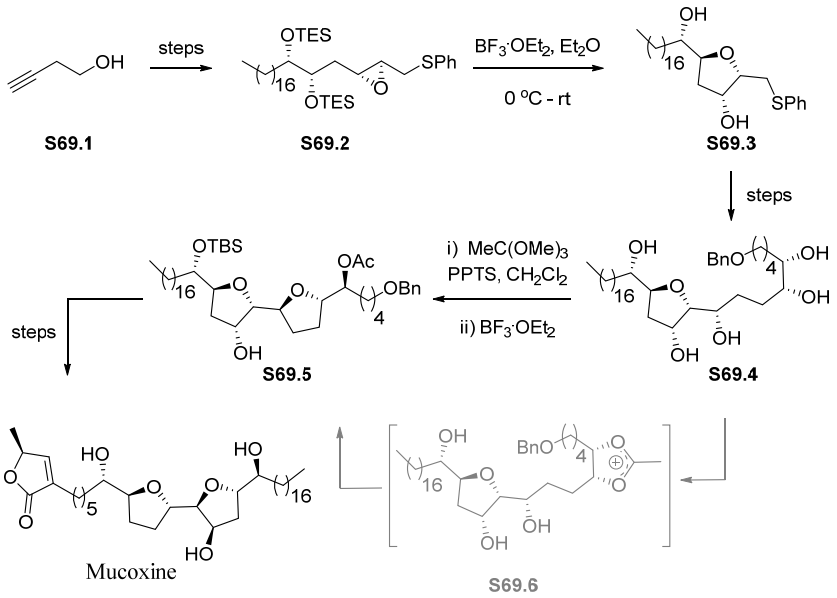
In 1994, Koert and co-workers described the first total synthesis of the naturally occurring acetogenin (+)-Rolliniastatin.[18] The advanced epoxy alcohol **S68.2** which was prepared from the L-glutamic acid **S68.1** and treated with AcOH to procure the desired bis-furan **S68.3** core of (+)-Rolliniastatin.



Scheme 68: Synthesis of (+)-Rolliniastatin by Koert's group

In 2005, Borhan and co-workers described an enantio selective total synthesis of the proposed structure of mucoxin *via* regio- and stereoselective THF ring-forming strategies.[19] Mucoxin is a highly potent and specific antitumor agent against MCF-7 (breast carcinoma) cell lines (ED_{50}= 3.7 X 10^{-3}µg/mL). The treatment of the bis-TES protected epoxydiol **S69.2** (prepared from 3-butynol **S69.1**) gave the THF-diol **S69.3** through a neighboring-group-assisted cyclization process. Subsequently, the THF-diol **S69.3** was employed for the synthesis of the advanced intermediate **S69.4** which was treated with trimethyl orthoacetate in

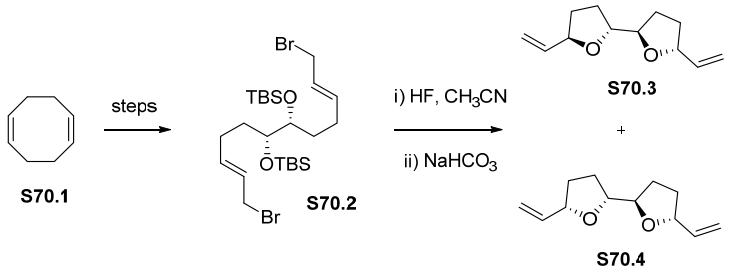
the presence of PPTS to afford the bis-THF **S69.5** part of Mucoxin through an *exo*-cyclization of the reactive acetoxonium intermediate **S69.6**.



Scheme 69: Synthesis of Mucoxin by B. Borhan *et al*

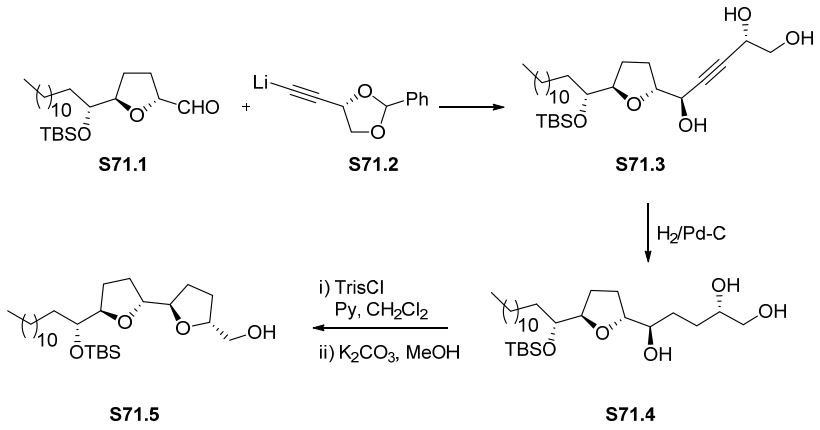
1.3. Intramolecular S_N2 and S_N2' reactions of hydroxyl nucleophiles with alkyl halides:

In 1999, Zhao and co-workers documented the synthesis of the bis-THF core of acetogenins through double intramolecular S_N2' *O*-cyclization reactions from a suitable protected diene-diol **S70.2** that was prepared from commercially available 1,5-cyclooctadiene **S70.1**. [20] The treatment of **S70.2** with HF followed by $NaHCO_3$ gave the desired *trans*, *trans*-bis-THF derivative **S70.3** as the major product along with the minor product **S70.4**.



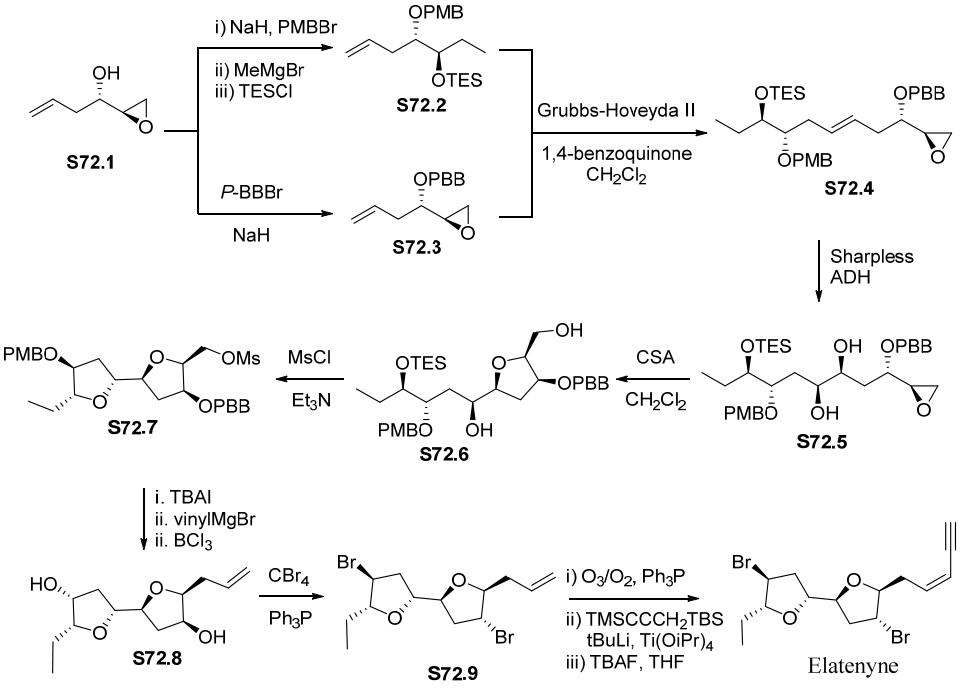
Scheme 70: Intramolecular $S_N2'$for synthesis of bis-THFcore

In 2004, Tanaka and co-workers documented the stereo divergent and reiterative synthesis of bis-THF ring core **S71.5** through an asymmetric alkynylation of the aldehyde **S71.1** with alkyne **S71.2** followed by hydrogenolysis and an intramolecular S_N2 displacement of diol **S71.4** in the presence of K_2CO_3 leading to the bis-THF moiety **S71.5**. [21]



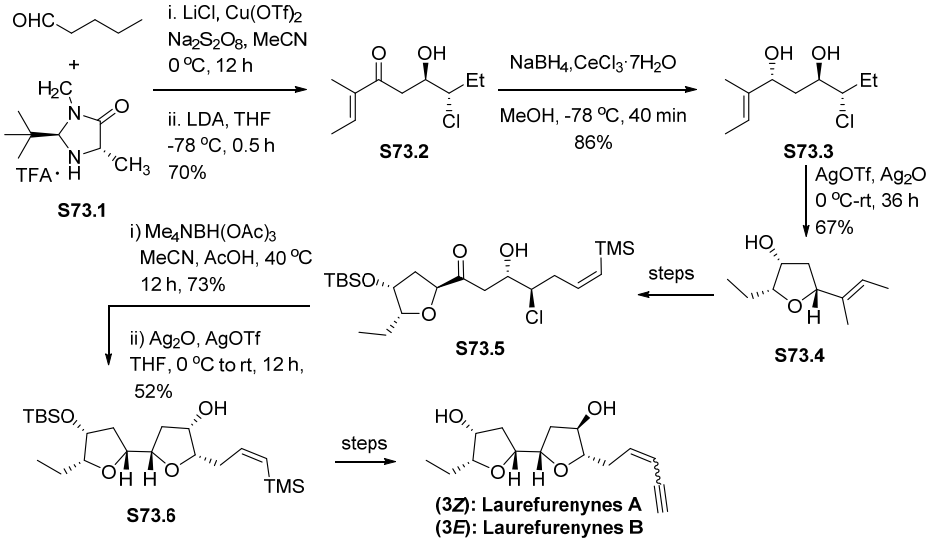
Scheme 71: Synthesis of bis-THF core by intramolecular S_N2 reaction

In 2012, Burton's group reported the first total synthesis and structural conformation of Elatenyne, a brominated natural product which was isolated from *Laurencia elata*.[22] The Sharpless asymmetric epoxidation/dihydroxylations (SAD) have been used to synthesize the key epoxide **S72.1** with the requisite stereochemically defined hydroxyl epoxide groups that were subjected for the acid catalyzed epoxide opening and a finally for an intramolecular S_N2 reaction. The journey started with the asymmetric epoxidation of readily available 1,5-hexadien-3-ol followed by cross metathesis and asymmetric dihydroxylation of the resulting internal *trans*-alkene **S72.4**. Now, the diol epoxide **S72.5** was forwarded for the acid catalyzed mono THF ring **S72.6** formation followed by S_N2 displacement to procure the bis-THF moiety **S72.7** of elatenyne.



Scheme 72: Total synthesis of elatenyne

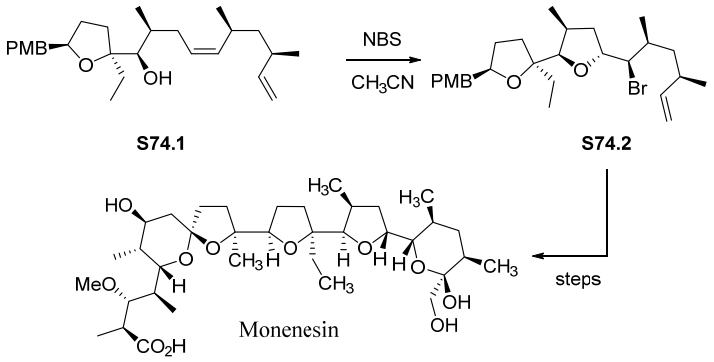
In 2013, Britton and co-workers documented the total synthesis and structural revision of Laurefurenynes A/B which were isolated from various *Laurencia sp*. red algae.[23] Stereochemically rich tetrahydrofuran **S73.4** was prepared through the AgI-promoted cyclization of a chlorodiol **S73.3** which was derived from the butanal *via* an aldol reaction[24] with the lithium enolate of 3-methyl-3-penten-2-one in presence of **S73.1** followed by 1,3-*anti*-selective reduction of the carbonyl group of **S73.2**. A similar strategy (*α*-chloroaldehyde, aldol, carbonyl reduction, and cyclization) was repeated for installing the next furan ring in **S73.6**.



Scheme 73: Total synthesis of Laurefurenynes A/B by Britton's group

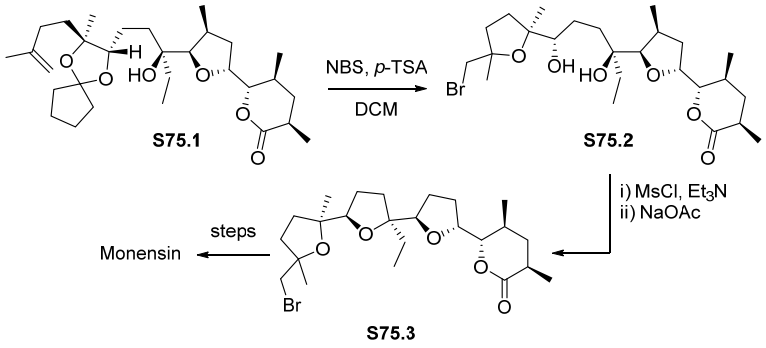
1.4. Halo etherification of multiple bonds:

In 1979, Kishi and co-workers documented the synthesis of the right half of Monensin in a stereo controlled manner.[25] NBS mediated bromo etherification was performed to get the bis-THF core **S74.2** from the advanced intermediate **S74.1**.



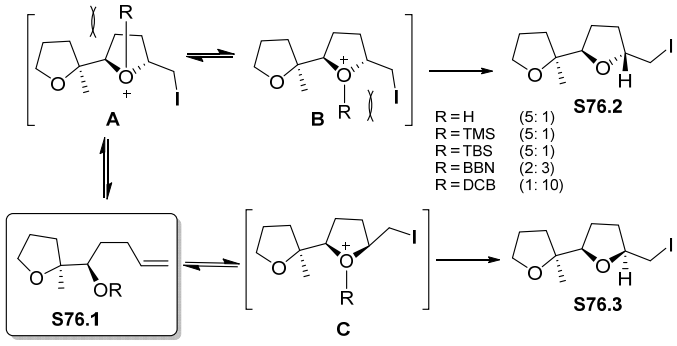
Scheme 74: Synthesis of Monensine by Kishi *et al*

In 1980, Clark Still and co-workers documented the synthesis of the polyether antibiotic Monensin.[26] One pot deketalization and halo etherification of **S75.1** gave the advanced intermediate **S75.2** which was mesylated selectively at the C13 position followed by solvolysis in buffered trifluoroethanol, resulting in the tetracyclic core **S75.3** of Monensin.



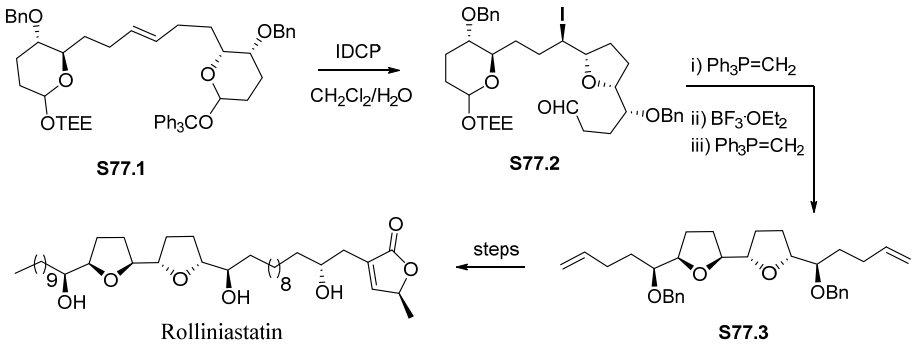
Scheme 75: Halo-etherification and Intramolecular S_N2 in synthesis of Monensine

In 1995, Brimble and co-workers documented the synthesis of *bis*-2,5-linked tetrahydrofuran through an iodo-etherification.[27] Iodoetherification of alcohol **S76.1** in the presence of I_2 and Na_2CO_3 afforded the mixture of bis-tetrahydrofurans **S76.2/S76.3**. The ratio of **S76.2/S76.3** depended on the nature of the ether substituent, **S76.2** being the major product for R=H, TMS, and TBS whereas **S76.3** was favoured when R= 4-bromobenzyl (BBN) or 2,6-dichlorobenzyl (DCB) due to 1,2-non bonded interactions.



Scheme 76: Protecting group dependent diastereoselectivity in halo-etherification

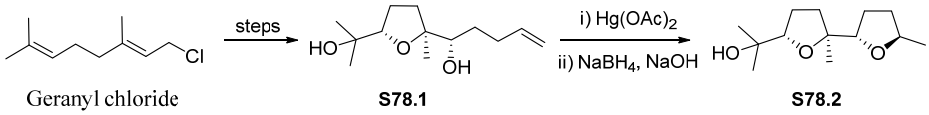
In 2000, Mootoo and co-workers documented a modular synthesis of the bis-THF core of rolliniastatin through an iodo-etherification of **S77.1** by using iodonium dicollidine perchlorate (IDCP) as a source of iodine.[28] The resulting iodo aldehyde **S77.2** was treated with methylene triphenylphosphorane followed by acid hydrolysis of the glycoside bond giving lactol which was directly employed for Witting olefination leading to the pseudo-symmetrical bis-THF diene **S77.3**.[29]



Scheme 77: Synthesis of Rolliniastatin by Mootoo's Group

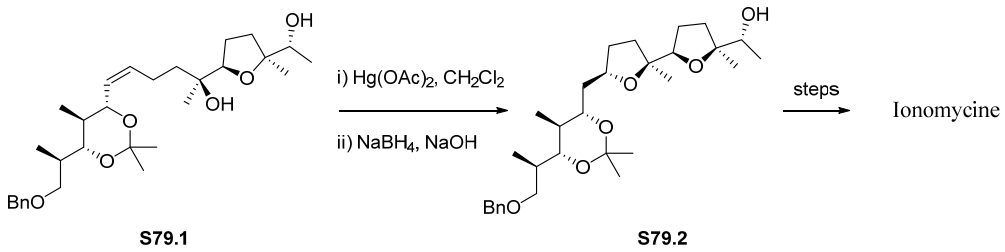
1.5. Metal mediated cyclization:

In 1981, Chastrett and co-workers documented a highly stereoselective route for the synthesis of a substituted bis-furan moiety **S78.2** from 1,5-diene. [30] Cyclization of **S78.1** was carried out with mercuric acetate in a mixture of water and THF (1:1) followed by demercuration with $NaBH_4$ which led to the bis-furan moiety **S78.2**.



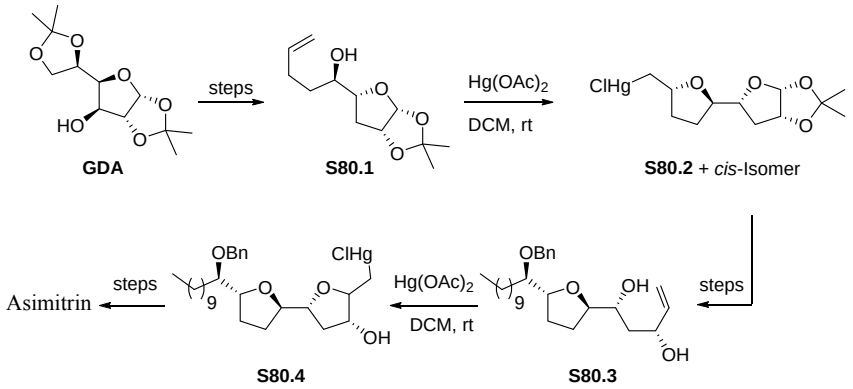
Scheme 78: Synthesis of bis-furan core by the oxymercuration reaction

In 1990, Evan and co-workers made the 2,2-bisfuryl moiety **S79.2** of Ionomycine from a suitable substituted furan **S79.1** by employing $Hg(OAc)_2$, followed by $NaBH_4$ reduction with a good diastereoselectivity. [31]



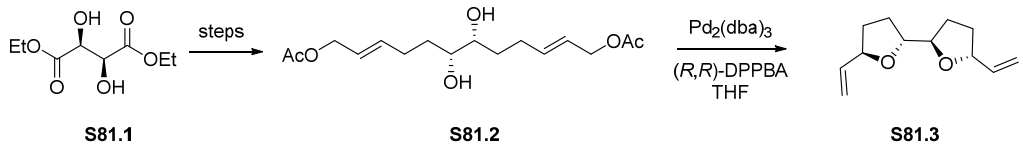
Scheme 79: Synthesis of Ionomycine by D. A. Evans *et al*

In 2007, Mohapatra and co-workers reported the synthesis of the C10–C34 fragment of Asimitrin by using a double stereoselective intramolecular oxymercuration reaction sequence.[32] The bis-homoallylic derivative **S80.1** prepared from commercially available GDA, was subjected to cyclization in the presence of $Hg(OAc)_2$ to give a mixture of cyclized products **S80.2**/*cis*-isomer. The same sequence has been repeated once to construct the second THF ring and arrive at the preparation of **S80.4** that served as an advanced intermediate in the total synthesis of asimitrin.



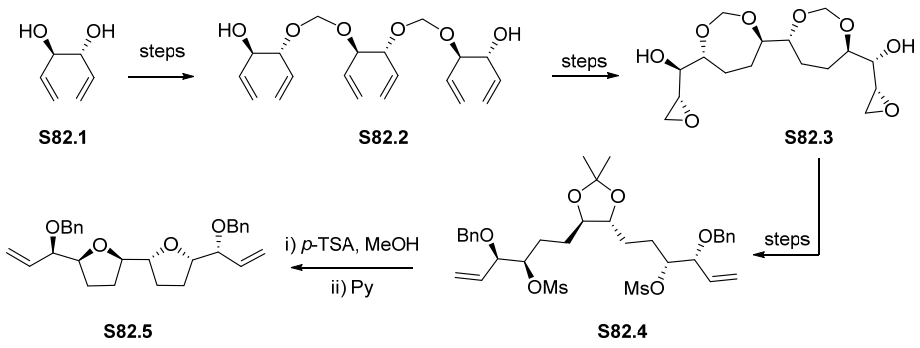
Scheme 80: Key steps in the synthesis of Asimitrin by Mahapatra's group

In 2001, Burke and co-workers documented the formal synthesis of Uvaricin through a palladium-mediated ligand controlled double cyclization from a suitable C_2-symmetric diene **S81.2**. [33] The bis-furan core **S81.3** was prepared from the double cyclization of **S81.2** which could potentially be derived from the commercially available diethyl D-tartrate **S81.1**.



Scheme 81: Pd-catalyzed S_N2' for synthesis of bis-furan core of Uvaricin

In 2010, Hou and co-workers documented the synthesis of bis-THF cores of annonaceous acetogenins from (3*R*,4*R*)-1,5-hexadiene-3,4-diol **S82.1** as the sole source of carbon atoms.[34] The C_2 diene-diol **S82.1** was transformed to the corresponding methylene acetal **S82.2** which could act as a linker/tether to facilitate the ring-closing metathesis. Two of the terminal alkenes out of six, were selectively transformed into the corresponding bis-epoxide and RCM was performed on remaining four double bonds, followed by hydrogenation which gave the advanced intermediate **S82.3**. Following this the bis-epoxide **S82.3** was converted into dimesylate **S82.4** by a known reaction sequence and finally acetonide deprotection and base treatment gave the bis-furan moiety **S82.5**.



Scheme 82: A metathesis and intramolecular S_N2 approach for bis-furan core by Hou *et al*

2. Natural products with *anti*-furo[2,3-b]furan core and some selected synthetic approaches:

Among the four possible arrangements of fused furofurans, the *anti*-furo[2,3-b]furan moiety takes a special role and is present in many biologically active natural products. For example, Aplysiallene[35] functions as a Na^+/K^+ ATPase inhibitor with IC_{50}= 0.7 μM. The natural product Furanodictine A, is unambiguously known to possess the ability to cause neuronal differentiation of rat pheochromocytoma (PC-12) cells, as well as act as an antitumor agent.[36] Manzamenone O shows antimicrobial activity against micrococcusluteus (MIC 4 μg/mL), aspergillisniger (IC_{50} 8 μg/mL), and trichophytonmentagrophytes (IC_{50} 8μg/mL) [37]. Neovibsanins A and B are the drugs for the treatment of neuro degenerative diseases such as Alzheimer's disease because they significantly promote the neuritis outgrowth of NGF mediated PC12 cells.[38] In the following pages, general methods that have been documented for the synthesis of this anti-furofuran core and also the details of the available total synthesis of this class of natural products will be described.

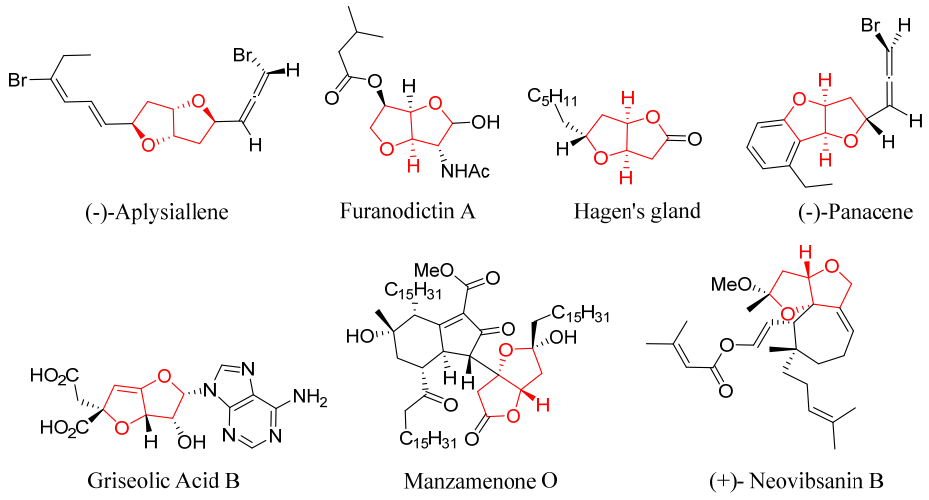
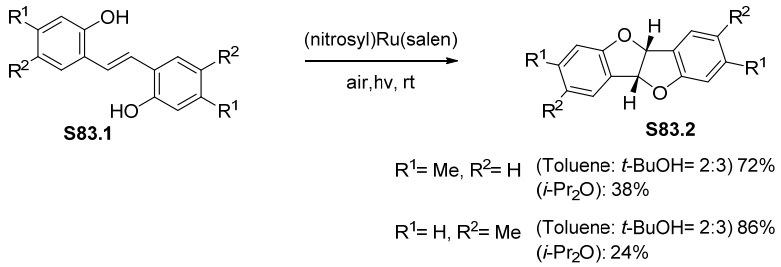


Figure 12: *Anti*-furo[2,3-b]furan subunit containing molecules

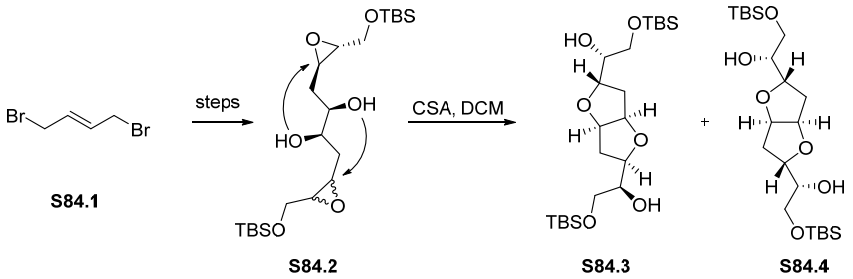
2.1. Synthesis of *anti*-furo[2,3-b]furan system:

In 2002, T. Katsuki and co-workers reported that aerobic oxidative cyclization of 2,2'–dihydroxy stilbenes **S83.1** in the presence of (nitrosyl)Ru(salen) as a catalyst, leads to the formation of the *anti*-furo[2,3-b]furan unit **S83.2**. [39] Here, solvent polarity plays a crucial role, in the case of a mixture of toluene and *t*-butanol giving good yields compared to only isopropylether or toluene, *t*-butanol.



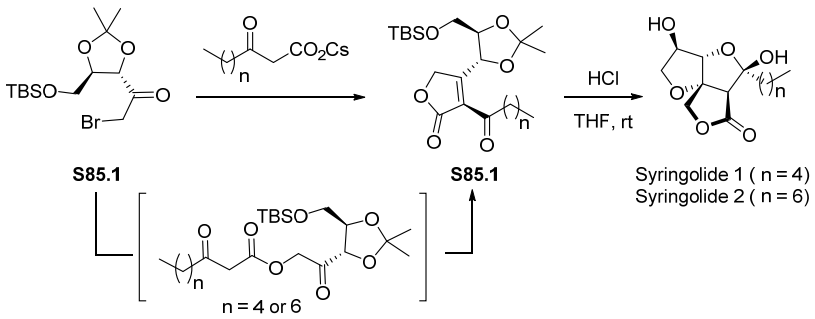
Scheme 83: Synthesis of *anti*-furo[2,3-b]furan unit by Katsuki *et al*

Martin and co-workers reported the synthesis of the *anti*-furo[2,3-b]furan unit **S84.3/S84.4** through an acid catalyzed double *exo*-cyclization of enantiomeric bis-epoxy-diols **S84.2** in a regio and stereoselective manner where all its six stereocenters could be controlled by Sharpless asymmetric epoxidation/dihydroxylation reactions of the appropriate bis-allylic alcohol which was prepared from **S84.1**.[40]



Scheme 84: Intramolecular bis-epoxide opening for the synthesis of *anti*-furo[2,3-b]furan unit by Martin and co-workers

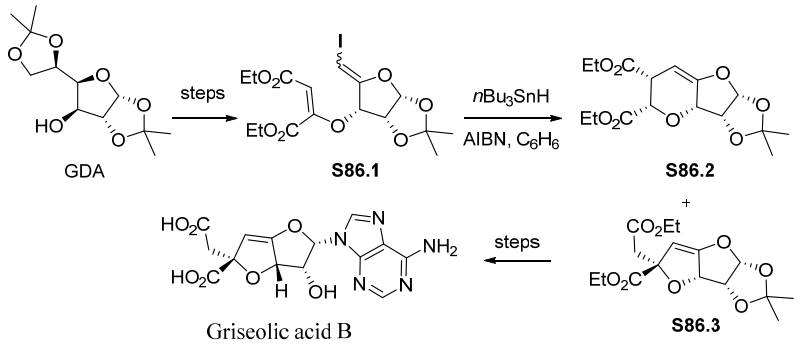
In 1986, Wood and co-workers documented a concise biomimetic asymmetric total synthesis of Syringolides **1** and **2** from **S85.1** (prepared from 2,3-O-isopropylidene-L-threitol), following an acylation with a suitable cesium carboxylated in DMF and intramolecular Claisen condensation and subsequent acetonide hydrolysis, cyclization resulted in the synthesis of naturally occurring butenolides syringolides.[41]



Scheme 85: Total synthesis of Syringolides **1** and **2** by Wood' group

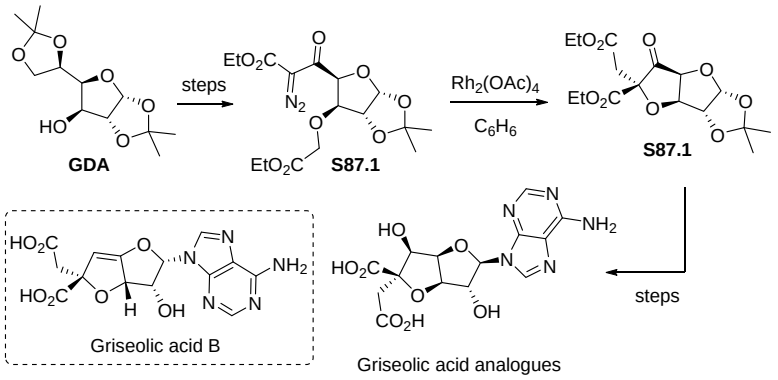
In 2001, Knapp and co-workers synthesized Griseolicacid B through a radical cyclization of a suitably functionalized vinyl iodide **S86.1** which was derived from glucose

diacetonide (GDA), and found that it affords the mixture of bicyclic vinyl ethers **S86.2**/**S86.3** with the required stereochemistry. [42]



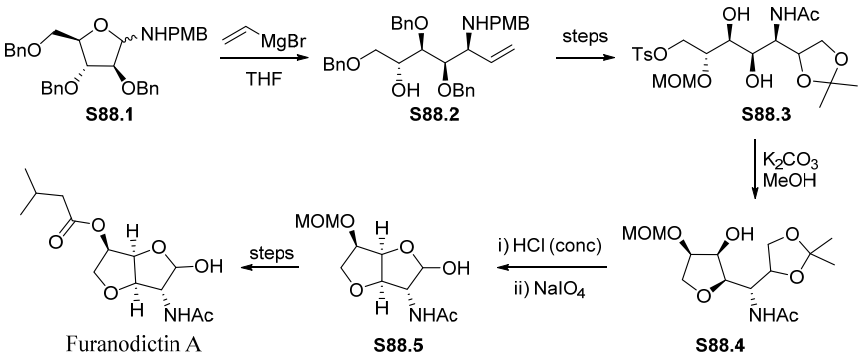
Scheme 86: Synthesis of Griseolic acid B by S. Knapp *et al*

In 2002, D. Dhavale and co-workers synthesized Griseolic acid analogues by a metal-carbenoide insertion across the C–H bond.[43] Thus, the *α*-diazo-*β*-ketoester **S87.1** was prepared from the glucose diacetonide which, when treated with rhodium acetate in benzene at reflux temperature led to obtain the furofuran **S87.2** with a complete *α*-facial selectivity in a [1,2]-migration leading eventually to the fused core **S87.1** that was converted subsequently to the analogue of Griseolic acid B.



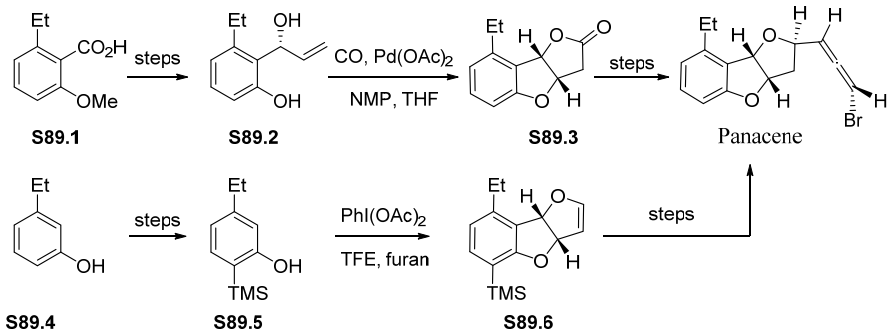
Scheme 87: Synthesis of Griseolic acid analogues by Dhavale *et al*

In 2004, Yoda and co-workers reported the total synthesis of Furanodictine A featuring the construction of the central furofuran unit through an intramolecular S_N2 reaction.[36] The key substrate **S88.3** for this transformation was synthesized from D-arabinose through a sequence of simple operations and then subjected for the S_N2 reaction using K_2CO_3 in methanol. The resulting furan **S88.4** upon acetonide hydrolysis and diol cleavage by periodates provided the lactol **S88.5** which was converted to the natural product by simple deprotection and acylation.



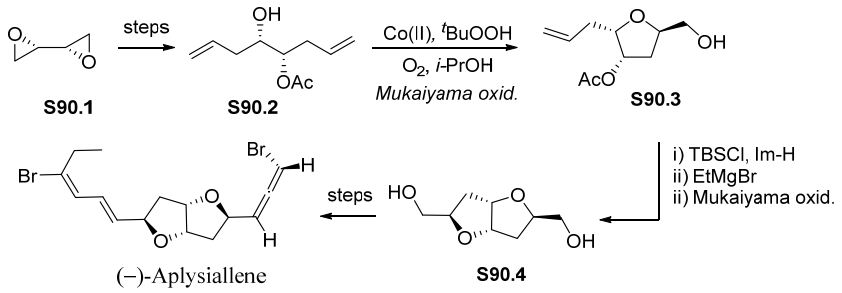
Scheme 88: Total synthesis of Furanodictine A by Yoda *et al*

In 2006, Boukouvalas and co-workers reported the total synthesis of Panacene from commercially available 2-methoxy-6-methylbenzoic acid.[44a] A Pd(II)-mediated tandem intra-molecular alkoxy carbonylation-lactonization has been used as the key skeletal construct to address the synthesis of the benzannulated furofuran **S89.3** unit. Later in 2008, Canesi and co-workers reported the synthesis of Panacene where the fused ring **S89.6** was derived from oxidative [2 + 3] cycloaddition between a substituted phenol **S89.5** which was derived from **S89.4** and furan by using PIFA.[44b]



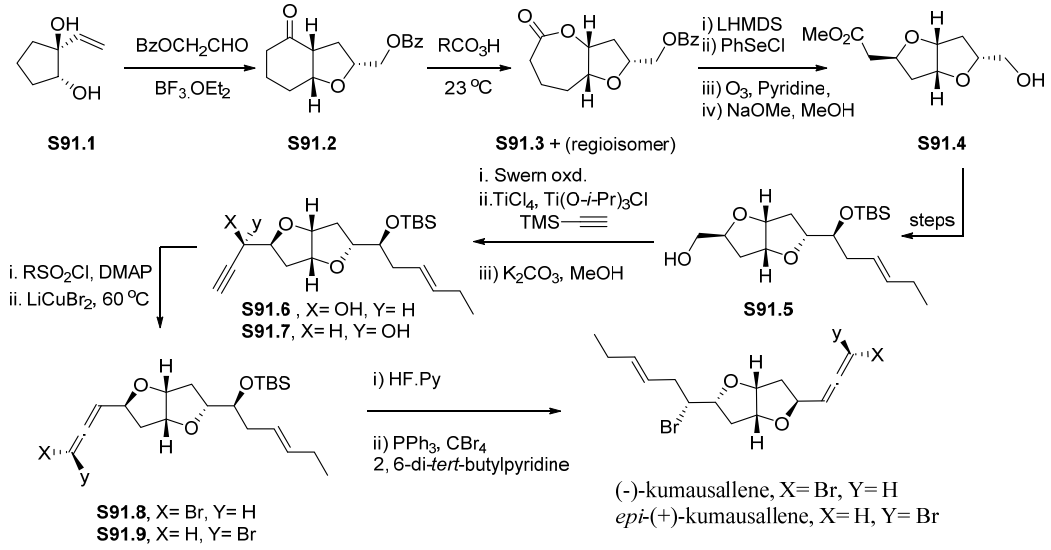
Scheme 89: Total syntheses of Panacene by Boukouvalas & Canesi groups

In 2007, Pagenkopf and co-workers documented the first total synthesis of (-)-Aplysiallene and reassigned the stereochemistry.[35] The repeated Mukaiyama aerobic oxidative cyclization of a suitably positioned enol has been used as the key step in the construction of the central furofuran core.[45] The synthesis began with the reaction of (*S*,*S*)-diepoxybutane **S90.1** with vinyl magnesium bromide in the presence of CuBr followed by selective mono acetylation to give the substrates **S90.2** that was subjected for the Co-catalyzed aerobic oxidative cyclization to construct the first furan ring **S90.3**. Simple manipulations and the second Mukaiyama oxidation gave the C_2-symmetric furofuran **S90.4** that was subsequently converted into the natural product by following simple synthetic transformations.



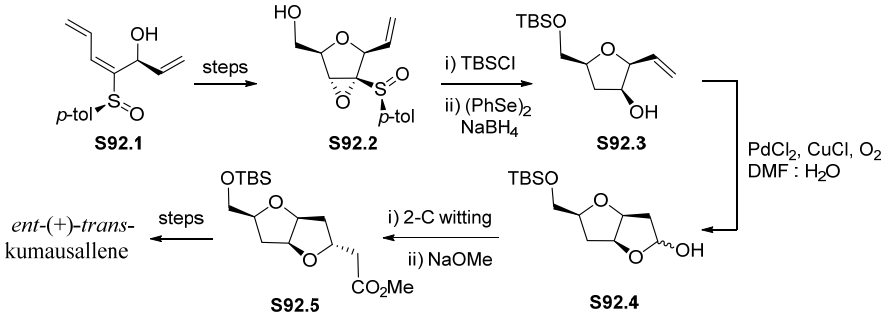
Scheme 90: Synthesis of (−)-Aplysiallene by B. L. Pagenkopf *et al*

In 1993, Overman's group reported the first total synthesis of (±)-Kumausallene through a ring-enlarging tetrahydrofuran annulation of cyclic, allylic diols as the central step.[46] A stereoselective, Lewis acid-catalyzed condensation of 1-vinylcyclopentane diol **S91.1** and α-(benzoy1oxy) acetaldehyde gave the key intermediate, hydrobenzofuranone **S91.2** which was oxidized with *m*-chloroperbenzoic acid to procure a mixture of lactone **S91.3**/ regioisomer. Then, the desired lactone **S91.3** was dehydrogenated by performing a selenation/selenoxide elimination procedure and lastly, methanolysis of lactone followed by tandem cyclization of the resulting hydroxy ester gave the *cis*-fused dioxabicyclo[3.3.0]octane **S91.4** with high stereoselectivity. The (*E*)-pentenyl appendage was installed by employing the Sakurai reaction followed by one carbon degradation, which led to the compound **S91.5** which was further employed for acetylide addition through Felkin-Anh stereo control.[49] Now, the derivative of propargyl alcohol **S91.6**/**S91.7** was transformed into bromoallene **S91.8**/**S91.9** through an *anti*-S_N2' displacement of a sulfonate by using a bromocuprate reagent. Finally, deprotection of TBS group followed by the Appel reaction lead to (±)-Kumausallene.



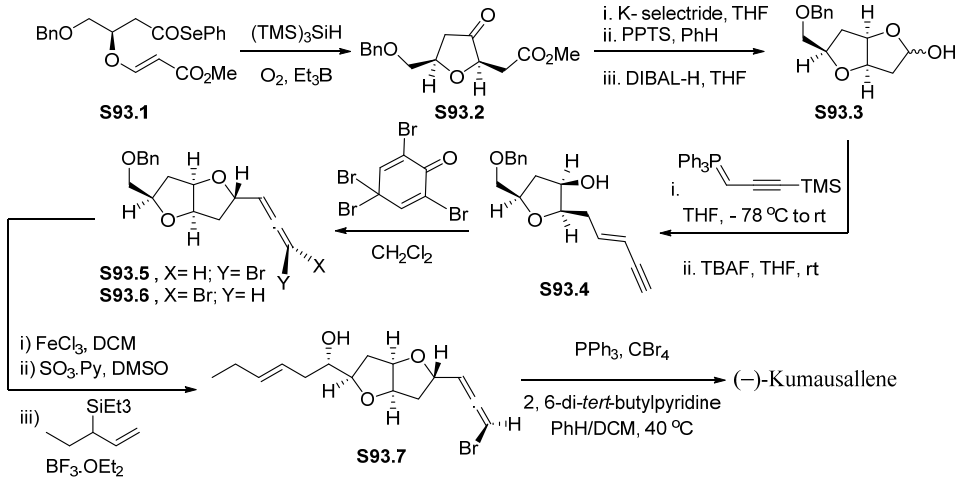
Scheme 91: Total synthesis of (±)-Kumausallene by Overman

In 1998, Pradilla and co-workers developed a sulfoxide-directed concise formal synthesis of enantiopure (+)-Kumausallene.[47] The key furofuran intermediate **S92.4** was constructed by a terminal-selective Wacker oxidation of **S92.3** (which was prepared from dienol **S92.1** through the construction of epoxy-THF **S92.2** through sequential epoxidation) followed by the two-carbon Witting homologation of the resulting lactol **S92.4** with concomitant THF ring **S92.5** formation *via* intramolecular1,4-nucliophilic addition to this *α*, *β*-unsaturated ester.



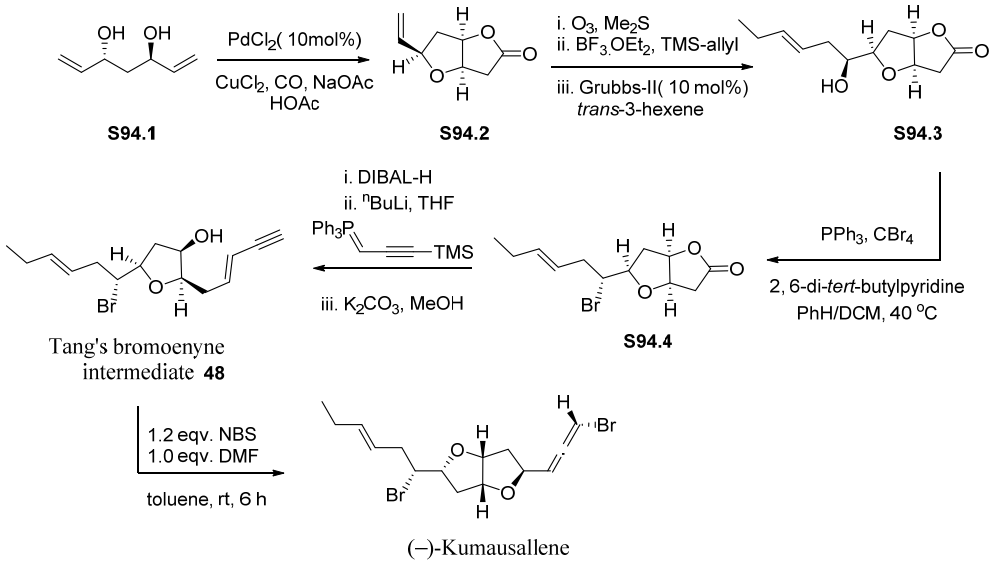
Scheme 92: Formal total synthesis of (+)-Kumausallene by Pradilla *et al*

In 1999, Evans and co-workers documented the enantioselective synthesis of the (–)-Kumausallene.[48] The 2,5-*cis*-substituted furan unit **S93.2** was prepared through a radical cyclization of acyl selenide **S93.1** and then converted into lactol **S93.3** by simple synthetic manipulations. The treatment of this lactol with Witting reagent followed by TMS deprotection leads to *trans*-enyne **S93.4**. A biomimetic electrophilic-type, intramolecular 1,4-addition of C-3 hydroxy of **S93.4** to an enyne in the presence of TBCD provided the bromoallenes **S93.5**/**S93.6**. The (*E*)-pentenyl appendage was introduced by employing the Sakurai reaction followed by the Appel reaction for converting the free hydroxyl into the bromo which completed the total synthesis of (−)-Kumausallene.



Scheme 93: Total synthesis of (–)-Kumausallene by Evans's Group

In 2011, Tang and co-workers documented the next approach for the total synthesis of (–)-Kumausallene.[50] The hidden symmetry present in (–)-Kumausallene has inspired this group to synthesize furanolactone **S94.2** by desymmetrizing a C_2-symmetric diol **S94.1** *via* a palladium catalyzed cascade reaction. This lactone **S94.2** was transformed into the derivative of homoallyl alcohol **S94.3** following simple synthetic manipulations. Finally performed Appel reaction on **S94.3** followed by witting reaction and TMS deprotection led to the Tang's bromoenyne intermediate **48**. Unlike the Evans's approach, here, the biomimetic cyclization to construct the fused furan unit with pendant bromoallene moiety was performed as the final step by employing NBS in DMF.



Scheme 94: Tang's total synthesis of (–)-Kumausallene

PRESENT WORK

The complexity of polyether Annonaceous acetogenins, Ionomycine, Mucoxin, and Jimenezin, Kumausallene and Notoryne has motivated more and more synthetic organic chemists in the research of new methods to introduce functionalities. The development of new methods for the stereo-controlled synthesis of biologically interesting compounds containing a number of hydroxy groups, contiguous stereogenic centres, a halo-ether unit or an enyne moiety continues to receive significant attention. Most challenging things for the synthetic chemist are the creation of contiguous stereogenic centres in both rigid and flexible systems and simultaneously controlling of regio- and stereochemistry. A rational insight into these factors has allowed improvement in the area of organic synthesis, particularly in planning synthetic strategies.

A large number of halogenated C_{15} nonterpenoid ethers with a different kind of ring system were isolated from red algae of the genus *Larencia*. This type of ethers mainly contained a conjugated enyne or bromoallene moiety at the end of the molecule. In 1991, Suzuki *et al.* reported that the specimen which was collected from the warm current region in Hokkaido at Noroto point contained (3*Z*)-laurefucin (**49**) as the major metabolite and a minor one named Notoryne (**46**). [51] Earlier, in 1983, Kurosawa *et al.* documented that a specimen which was collected at Kumausu, near Otaru, Hokkaido, contained five new bromo ethers and the major component named as Kumausallene (**47**). [52] All these three natural products were isolated from the same red algae of genus *Laurencia nipponica yamada* and it has been found that biosynthesis of nonterpenoids to be dependent upon the growth localities.

A careful examination of the structures of all these natural products indicates the fact that all the three natural products have a similar stereochemistry directly at two centers and indirectly (Br or Cl in place of –OH) at another two centres. Considering this, we reasoned that there is scope to develop a synthetic route where synthesis of these three natural products could be addressed from a common intermediate and it should be sufficiently flexible to permit late stage access for *cis*, *trans* enyne formation. In case of Notoryne and Laurefucin, controlling the mode of bromo-etherification i.e 5-*endo*-trig vs 8-*endo* trig should address the bis-furan moiety or bicyclic core present in these natural products respectively. The key features of our retro synthesis are depicted in Figure 13. The enyne part of all three natural products was planned from the *C*-glycoside by performing either cross metathesis [53, 22] or Witting homologation.[29] As shown in Figure 13, the synthesis of Notoryne (**46**)and Kumausellene (**47**) were planned from the common intermediate **51** whereas that of Laurefucin (**49**) was from the intermediate **50** which is epimeric at C5–OH. The epimeric

epoxides **52** and **53** that are planned from diol **54** should serve as the precursors respectively for **50** and **51**.

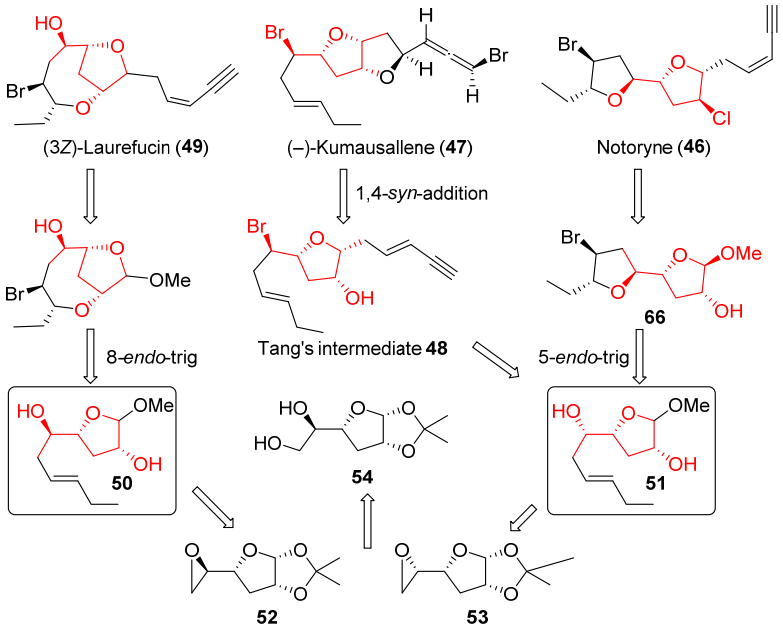
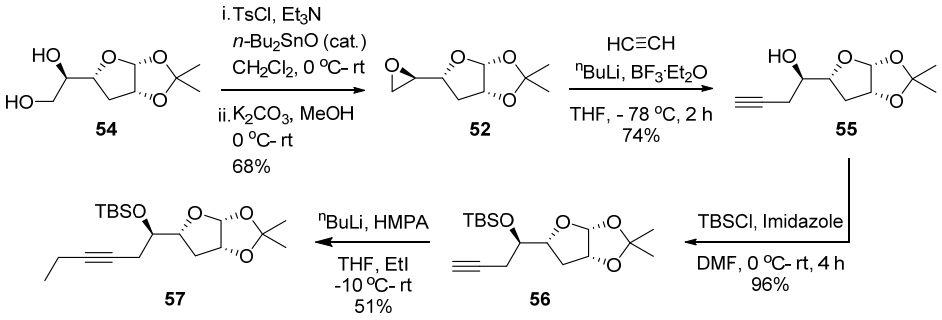


Figure13. Structures of Notoryne (**46**) and (–)-Kumausallene (**47**), (3*Z*)-Laurefucin (**49**) and the proposed retro synthetic route

Studies toward the total synthesis of Notoryne/Laurefucin

Our studies in this context were started with the preparation of the key furan intermediate **50** and checking its bromo etherification. The diol **54** was prepared in 4 steps according to the literature procedure from GDA (Scheme 95).[32] The diol **54** was advanced for the synthesis of epoxide **52** through the selective mono tosylation of 1°–OH by using 1 eq. of TsCl and cat. *n*-Bu_2SnO followed by base (K_2CO_3 in MeOH) treatment. The structure of the epoxide was confirmed with the help of spectral and analytical data. In the ^{1}H NMR spectrum of compound **52**, the characteristic protons of the oxirane were resonated at up field δ 2.57 (dd), 2.81 (dd) and 3.35 (ddd) and in the ^{13}C NMR the corresponding carbons are seen to resonate at 44.13 and 53.35 ppm as triplet and doublet. Next, the opening of the epoxide **52** with lithium acetylide in the presence of $BF_3{\cdot}Et_2O$ gave the homopropargylic alcohol **55**. In the ^{1}H NMR spectrum of compound **55**, the terminal alkyne–H resonated as a triplet at δ 2.99 (J = 2.7 Hz) and the propargylic-CH_2 as multiplets in the up field region of δ 2.39–2.51. The acetylenic carbons were resonated at 70.7 and 80.2 ppm as doublet and singlet respectively in the ^{13}C NMR spectrum.

In order to introduce the pendant ethyl group on the alkyne unit, the free homopropargylic alcohol was protected as its TBS ether by using TBSCl and imidazole in DMF. The key alkylation reaction was carried out by using ethyl iodide in the presence of *n*-BuLi in HMPA to obtain compound **57** in moderate yields. Using freshly distilled EtI or EtBr and dried HMPA did not affect the yields. The ^{1}H NMR spectrum of **57** showed the new propargylic protons as multiplets at δ 1.93–2.23. Protons of the CH_3 group resonated at δ 1.07 integrating for three and the ^{13}C NMR spectrum showed the presence of two singlets at 76.04 and 83.25 ppm corresponding to the acetylenic carbons and one quartet at 14.06 ppm corresponding to the CH_3 group.

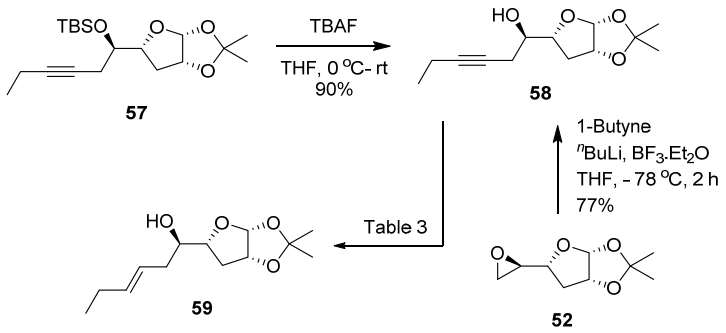


Scheme 95: Synthesis of **57**

We proceeded next to synthesizing the key homoallyl alcohol **59**. The TBS group was selectively deprotected by using TBAF in THF to obtain the alkynol **58**. As the yield of alkylation of the terminal alkyne was moderate, an alternate route using expensive 1-butyne gas in place of acetylene has been executed to open the epoxide **52** under Yamaguchi conditions to obtain the intermediate alkynol **58** directly.[54] In the ^{1}H NMR spectrum of compound **58**, the propargylic protons resonated as multiplets at δ 2.08–2.26 and 2.39–2.45 (each integrating for two protons) and the CH_3 group resonated at δ 1.1 as a triplet. In the ^{13}C NMR spectrum, the two internal acetylenic carbon singlets appeared at 74.88 and 84.11 ppm and one quartet at 14.07 ppm corresponding to the homo propargylic CH_3.

The selective *trans*-reduction of the internal alkyne in compound **58** has been examined employing various reducing agents under different reaction condition (Table 3). To this end, we could conclude that this reduction can be carried out by Birch reduction[55] employing either Na or Li in liquid NH_3 and THF at −78 ^{o}C giving the required *trans* alkene **59** in good yields. In the ^{1}H NMR spectrum of compound **59**, the two olefinic protons at δ 5.48 and 5.57 with the coupling constant of 15.4 Hz indicated the presence of a *trans* double bond. In the ^{13}C NMR spectrum of **59**, two doublets of the olefinic carbons appeared at

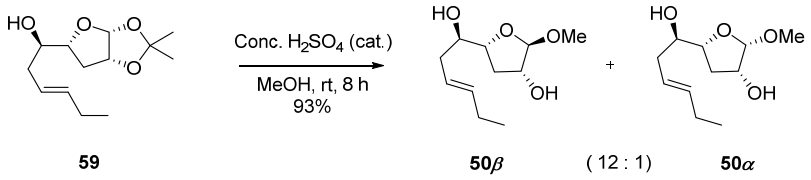
124.44 and 135.03 ppm. All other analytical data were in accordance with the assigned structure.



S. No.	Reaction conditions	Results obtained
1	$LiAlH_4$, THF, 0 °C– rt	Starting material recovered
2	$LiAlH_4$, THF, 65 °C	Starting material recovered
3	$LiAlH_4$, toluene, 110 °C	Starting material recovered
4	$LiAlH_4$, THF, Diglyme, 65 °C	Starting material recovered
5	Na, NH_3(l), ^{t}BuOH, THF, −78 °C	90% yields
6	Li, NH_3(l), ^{t}BuOH, THF, −78 °C	92% yields

Table 3: Synthesis of homoallyl alcohol **59** by employing Birch reduction

Next, the hydrolysis of the 1,2-acetonide group in alkenol **59** using cat. H_2SO_4 in MeOH provided a mixture of glycosides **50**α and **50**β, the latter being obtained as the major product. The major product of glycoside **50**β was confirmed by NMR study. The anomeric proton of the major product β-glycoside showed a singlet at δ 4.85 and in the ^{13}C NMR spectrum of **50**β, the anomeric carbon resonated at 106.12 ppm.

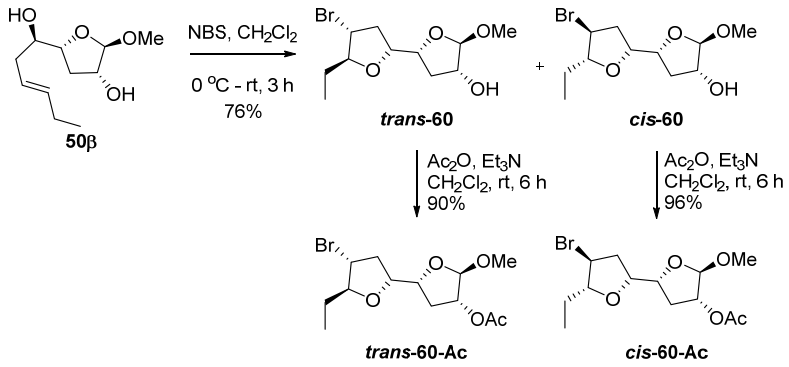


Scheme 96: Synthesis of *O*-methyl glycosides

- **Regioselectivity in NBS mediated bromo-etherification:**

After having the key akenol **50**β, the stage was set for examining the regioselectivity of the bromo-etherification reaction leading to either the [5.2.1]-bicyclic core of Laurefucin **49** or the 2,2-bisfuranyl unit for Notoryne **46**.[56] When employing freshly crystallised NBS in

CH_2Cl_2, the reaction advanced smoothly with the disappearance of the starting compound within 3 h and afforded the products ***cis*-60** and ***trans*-60** the latter being obtained as the major product. The presence of a bicyclic bis-furan core present in the ***trans*-60** and ***cis*-60** was established with the help of spectral data analysis.



Scheme 97: NBS mediated halo etherification of diol **50*β***

In the ^{1}H NMR spectrum of ***trans*-60**, the three characteristic methine protons of the new furan ring are present at δ 3.81, 3.91, and 4.02. The two carbons of the newly generated furan ring *C*HBr and CHBr*C*HEt are seen to resonate at 46.7 and 86.9 and also the presence of characteristic ether carbons at 78.1, 78.8 (C4 and C5), (>75 ppm)[57] ppm in the ^{13}C NMR spectrum (Scheme 97) and the carbon attached to bromine atom appeared as a doublet separately in the up field (46.7 ppm), indicating the presence of a 2, 2'-bisfuranyl unit. Coming to the minor isomer ***cis*-60**, three characteristic methine protons of the newly formed furan ring were seen to resonate at δ 3.97–4.03, 4.09–4.14, 4.20–4.23 as multiples in the ^{1}H NMR spectrum and the two carbons of the newly generated furan ring *C*HBr and CHBr*C*HEt at 49.0 and 89.1 and characteristic ether carbons at 77.80, 79.33 (C4 and C5), (>75 ppm) ppm in the ^{13}C NMR spectrum indicated its constitution as a 2, 2'-bisfuranyl unit.

Next, in order to fix the stereochemistry of the newly generated centers, the free hydroxyl group at C2 of both the regiomers was converted to the corresponding acetate by treating with Ac_2O in presence of Et_3N and the resulting ***trans*-60-Ac** and ***cis*-60-Ac** have been characterized with the help of the 1D and 2D spectral studies.

In the ^{1}H NMR spectrum of ***trans*-60-Ac**, the three characteristic methine protons of the new furan ring are present at δ 3.9, 4.01, and 4.08 and a singlet at 2.06 for three protons for the acyl group. Along with that, the proton, of C*H*OAc was seen to resonate at 5.03 as doublet of doublets. In the ^{13}C NMR spectrum of ***trans*-60-Ac**, the characteristic ether carbons resonated at 79.4, 79.9 (C4 and C5), (> 75 ppm) ppm and one singlet at 170.3 ppm

for acyl group (Scheme 97). In the NOESY of the ***trans*-60-Ac**, a strong n*O*e interaction between the C2-H^2, C4-H^4 and C8-H^8 and also between C5-H^5 and C7-H^7 was observed.

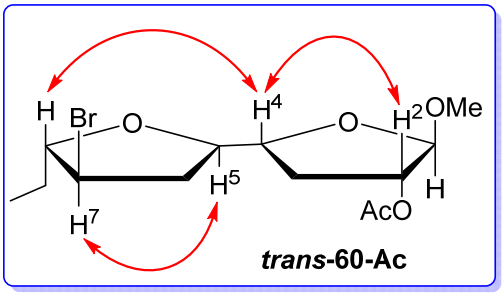


Figure 14: n*O*e interactions of the bromoether ***trans*-60-Ac**.

In case of ***cis*-60-Ac**, in the ^{1}H NMR spectrum, the three characteristic methine protons of the new furan ring are present at δ 4.02 (dt), 4.07–4.13 (m), 4.22 (q) and a singlet at 2.05 for three protons for the acyl group along with that the proton of C*H*OAc was seen to resonate at 5.02 as doublet of doublet. The presences of the characteristic ether carbons resonated at 79.36, 79.75 (C4 and C5), (> 75ppm) ppm and one singlet at 170.3 for acyl group in the ^{13}C NMR spectrum (Scheme 97). The bromo carbon came as doublet separately in the up field at 48.88 ppm, indicated the presence of a 2, 2'– bisfuranyl unit. The strong n*O*e interactions between the C2-H^2, C4-H^4 and C7-H^7, C9-$H^{9/9'}$ and between C5-H^5 and C8-H^8 noticed in the NOESY of compound ***cis*-60-Ac** are in support of its assigned structure.

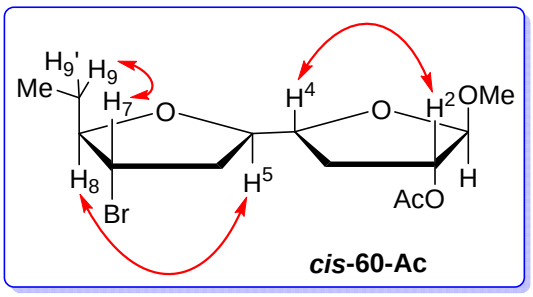
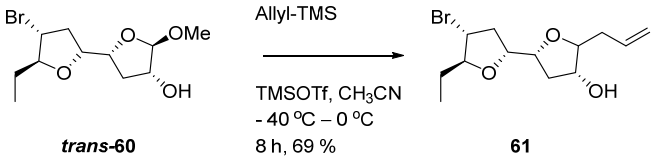


Figure 15: n*O*e interactions of the bromoether ***cis*-60-Ac**.

Although the key cyclization occurred in favour of the bis-furan formation, the stereochemistry of the free hydroxyl group that participates in cyclo etherification reaction needs to be inverted to get the natural product Notoryne. The initial attempt of inverting this centre under Mitsunobu conditions[58] resulted in the undesired product diene as a major product which revealed that we have to revise our strategy where the stereochemistry of hydroxyl group is inverted prior to the installation of the pendant olefin group. However, to examine the stereoselectivity of the key C–C bond formation, i.e from *O*-glycoside to *C*-

glycoside, the *C*-glycosidation of the major product ***trans*-60** was performed employing allyl-TMS along with TMSOTf in acetonitrile to give the allyl product **61** in good yields as a single diastereomer. In the ^{1}H NMR spectrum of the resulting compound **61**, the three olefinic protons resonated at δ 5.05 and 5.12 as doublet of doublet (dd) and one proton came as multiplet at 5.81–5.90, indicating the presence of an allyl double bond. The ^{13}C NMR spectrum of **58** showed one doublet and one triplet of the olefinic carbons at 135.1 and 116.78 ppm.

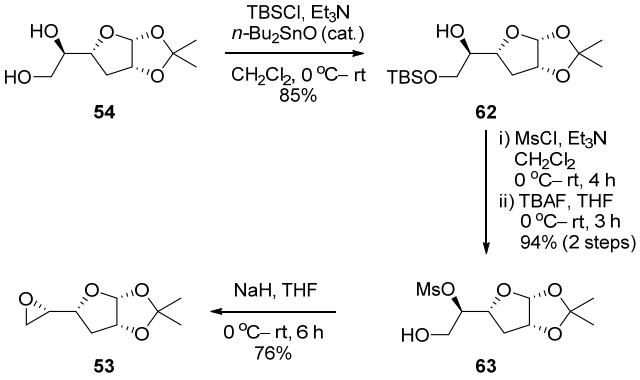


***trans*-60** **61**

Scheme 98: Synthesis of *C*-glycoside **61**

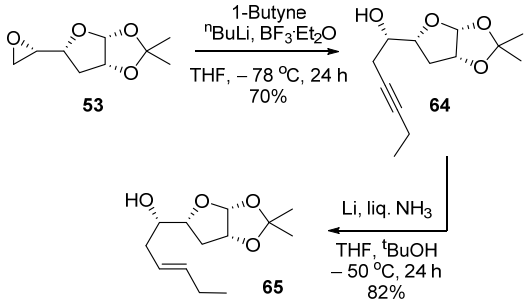
- **Synthesis of requisite 2,2' bisfuranyl unit of Notoryne**:

In order to start in the direction of employing the above protocol for Notoryne, the *epi*-epoxide **53** was prepared from diol **54** with a simple manipulation of both the hydroxyl groups. The 1^{o}–OH of diol **54** was selectively protected by TBSCl in the presence of cat. *n*-Bu_2SnO and Et_3N. In the ^{1}H NMR spectrum of **62**, the peaks corresponding to the TBS group resonated at δ 0.07 and 0.09 corresponding to the methyl and the tertiary butyl groups. In addition, the protons of CH_2-OTBS appeared at δ 3.64 and 3.71 as doublet of doublets, when compared to that in the starting diol [3.55(dd) and 3.74(dd)], which clearly indicated the site of silylation. The remaining free 2^{o}–OH was mesylated by using methanesulfonyl chloride and triethylamine and subjected for the TBS ether deprotection by using TBAF. The examination of the ^{1}H NMR of the resulting spectrum of resulting compound **63** (a singlet integrating for three protons at δ 3.20 corresponding to the CH_3 of mesyl group) revealed that only the TBS ether got deprotected. However, the anticipated epoxide formation had not occurred. Subsequently, the treatment of this mesylate **63** with NaH in THF yielded the epoxide **53**. In the ^{1}H NMR spectrum of compound **53**, the oxirane protons resonated at δ 2.67 (dd), 2.87 (dd), 3.31 (ddd) and a triplet and doublet at 47.3 and 53.1 ppm in its ^{13}C NMR spectrum which confirmed the formation of the epoxide (Scheme 99).



Scheme 99: Synthesis of *epi*-epoxide **53**

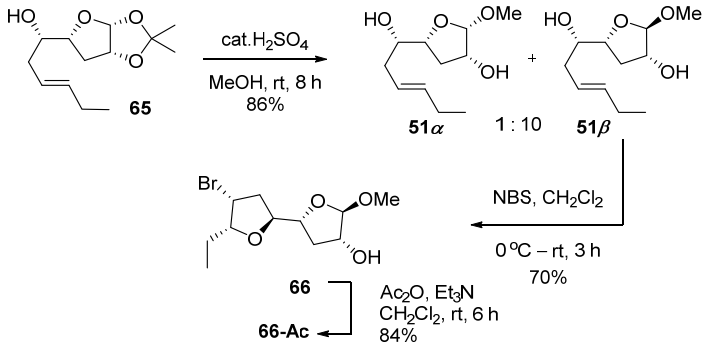
The homoallylic alcohol **65** was prepared from epoxide **53** following a procedure that we used for the preparation of compound **59**. Thus the opening of the epoxide **53** with lithiated 1-butyne in the presence of $BF_3{\cdot}Et_2O$ gave the substituted propargyl alcohol **64**. The triple bond was reduced under Birch reduction conditions employing Li and liq. NH_3 at −50 ^oC to obtain **65**. In the ^1H NMR spectrum of compound **65**, the presence of two olefinic protons at δ 5.48 and 5.57 with the coupling constant of 15.4 Hz was indicative of a *trans* double bond and in its ^{13}C NMR spectrum, the two doublets of the olefinic carbons appeared at 124.44 and 135.03 ppm. All other analytical data were in accordance with the assigned structure.



Scheme 100: Synthesis of homoallyl alcohol **65**

Now, the 1,2 acetonide of compound **65** was deprotected by using conc. H_2SO_4 in MeOH to procure an anomeric mixture of methyl glycosides **51** which were separated. The anomeric-H of the major isomer showed a singlet at δ 4.82 (C1 at 109.1 ppm) whereas that of the minor isomer appeared as a doublet at δ 4.74 (C1 at 102.3 ppm). Next, the NBS mediated bromo etherification reaction of the major isomer **51**$\boldsymbol{\beta}$ was carried out with freshly crystallised NBS in dichloromethane. The reaction advanced smoothly with the disappearance of the starting compound within 3 h and afforded exclusively compound **66**. The constitution of the bisfuranyl unit present in **66** was investigated with the help of spectral data analysis. In

the ^{1}H NMR spectrum of compound **66**, the three characteristic methine protons of the newly formed furan ring were seen to resonate at δ 3.90, 3.94, and 3.98. On the other hand, the two carbons of the newly generated furan ring *C*HBr and CHBr*C*HEt resonated at 46.2 and 88.09 along with the characteristic ether carbons at 78.49, 79.71 (>75 ppm)[57] ppm in the ^{13}C NMR spectrum (Scheme 101) which clearly indicated the presence of a 2, 2'-bisfuranyl unit.



Scheme 101: NBS mediated halo etherification of **51**β and acylation.

In order to fix the stereochemistry of the newly constructed furan ring and also that of the glycosidic linkage, the acetate **66-Ac** was prepared by treating **66** with Ac_2O in the presence of Et_3N. In the ^{1}H NMR spectrum of compound **66-Ac**, the three characteristic methine protons of the new furan ring are present at δ 3.90, 3.95, and 4.00. In the NOESY of compound **66-Ac**, the strong n*O*e interactions between the C1-H^{1}, C5-H^{5} and that between C2-H^{2}, C4-H^{4} and C8-H^{8} reaveled the *trans*-1,4 configuration of both the furan rings(fig. 16).

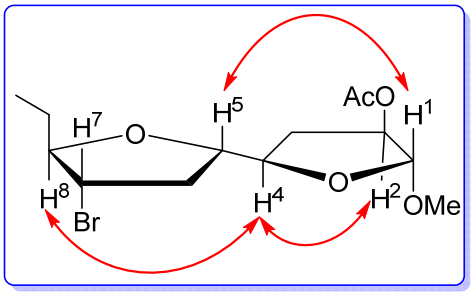
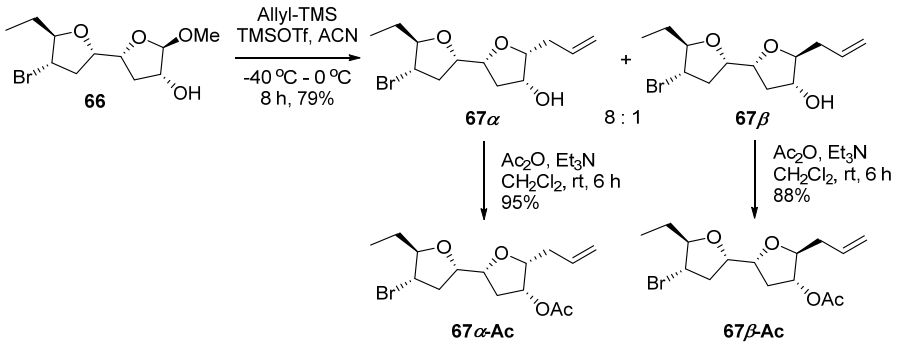


Figure 16: n*O*e interactions of the bromo etherproduct **66-Ac**.

- **Synthesis of *C*-glycosidation from *O*-glycoside 66**

After having the key cyclized product, the stage was then set for executing the key transformation from *O*-glycoside to the required *C*-glycoside. The *C*-glycosidation of **66** was performed in our optimized condition where allyl-TMS along with TMSOTf in acetonitrile at –40 ^{o}C gave the mixture of α and β allylglycosides **67**. Both the allyl glycosides were

separated by column chromatography and characterized as their acetates **67α-Ac** and **67β-Ac**, the former being the major product.



Scheme 102: Synthesis of *C*-glycosides and their acetate

In the ^{1}H NMR spectrum of the major compound **67α-Ac**, a singlet at δ 2.07 for three protons along with the proton of C*H*OAc was seen to resonate at down field at δ 5.27 (br t) and the anomeric proton came at δ 3.81 (ddd), when compared to that in the starting alcohol **67α** [δ 4.01–4.06 (m) and δ 3.67 (ddd) respectively]. In the ^{13}C NMR spectrum of compound **67α-Ac** the carbonyl singlet at 178.78 ppm, the *C*HOAc and anomeric doublets at 74.27 (d) and 81.27 ppm were noticed. The NOESY studies of **67α** revealed strong n*O*e interactions between the C4-H^{4}, C5-H^{5} and C7-H^{7} and also between C8-H^{8} and C10-H^{10} which suggested a 1,4-*cis* configuration in case of newly constructed furan ring (fig. 17).

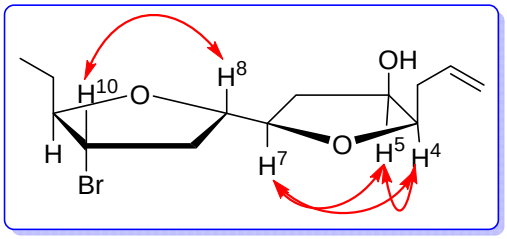


Figure 17: n*O*e interactions of the allyl product **67α**

Similarly in case of **67β-Ac** (minor), the ^{1}H NMR spectrum, showed the presence of a singlet at for three protons at δ 2.06, along with that the proton of C*H*OAc and anomeric proton were seen to resonate at down field at δ 5.02 (ddd) and 4.08 (ddd) when compared to the starting **67β** [δ 4.05–4.09 (m) and 3.99 (ddd) respectively]. The ^{13}C NMR spectrum of **67β-Ac** showed the one singlet carbonyl, *C*HOAc and anomeric carbons at 170.6, 77.51 and 83.07 ppm respectively. All other analytical data were in total agreement with the assigned structure. Furthermore stereo chemistry of the *C*-glycoside was confirmed by 2D spectra. The NOESY studies of **67β-Ac** revealed strong n*O*e interactions between the C3-H^{3}, C5-H^{5} and

C7-H[7] and that between C8-H[8] and C10-H[10] revealed the *trans*-1,4 configuration in case of newly constructed furan ring (fig. 18).

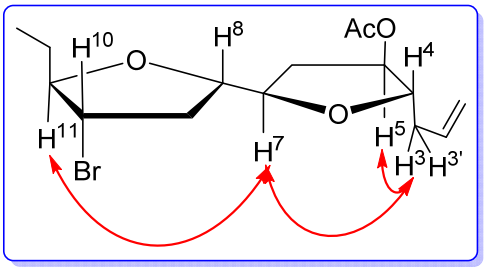
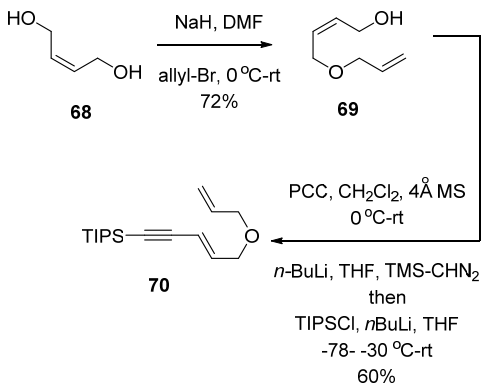


Figure 18: n*O*e interactions of the allyl product **67*β*-Ac**.

After having the key *C*-glycoside **67*α*** in hand, the remaining work is to install the *cis*-enyne moiety and replacing the free –OH with a chloro group. As mentioned in the introduction, the *cis*-enyne moiety can be introduced by subjecting a *C*-glycoside for the cross metathesis[53] with the enyne ether **70**. On the other hand, the –Cl group could be introduced by displacing the corresponding –OTf with Bu_4NCl. Our initial plan was the installation of chloro group first and then subjecting it for the cross-metathesis.

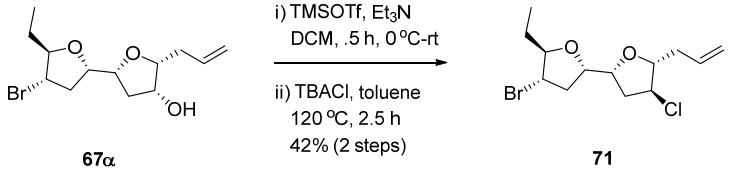
Accordingly, the enyne ether **70** was synthesised by following the known procedure[53a] – the selective allylation of *cis*-but-2-en-1,4-diol (**68**) followed by the oxidation of remaining –OH and subsequent alkynylation with TMS-diazomethane followed by *in situ* exchange of TMS with TIPS group. The spectral data of the compound **70** is in agreement with the data reported earlier. For example, in the ^{1}H NMR spectrum of **70**, the olefinic-H next to the triple bond appeared as doublet of triplet at δ 5.79 and 6.24 respectively (the large J = 16.02 Hz).



Scheme 103: Synthesis of TIPS enyne ether **70**

The key penultimate bis-furan building block **71** was synthesized from **67*α*** by following a two step-sequence for installing the chloride group – the conversion of the free hydroxyl group in **67*α*** to OTf by using TMSOTf and Et_3N in dichloromethane followed by the

displacement of –OTf with Cl employing *n*-tetrabutyl ammonium chloride (TBACl) in toluene at reflux.[57] In the ^{1}H NMR spectrum of **71** a characteristic proton came as doublet of doublets at δ 3.88 indicative of a C*H*Cl bond when compared to that in the starting alcohol [4.04 (ddd, 1H)], and in the ^{13}C NMR spectrum of **71** showing one carbon coming at the up field region as doublet at 62.35 ppm. All other analytical data were in accordance with the assigned structure.

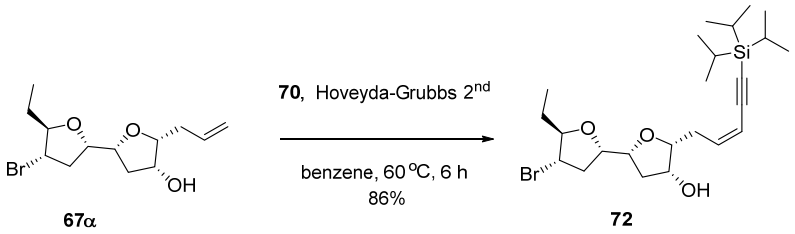


Scheme 104: Synthesis of chloroallyl compound **71**.

The attempted cross metathesis reaction of **71** and dienyne **70** employed in the presence of Hoveyda-Grubbs 2nd generation catalyst[59] resulted in an inseparable mixture of compounds which were subjected directly for the desilylation. The ^{1}H NMR of resulting crude product revealed the presence of the requisite peaks corresponding to the natural product Notoryne. However, the isolation of pure product was found to be a difficult task despite the sequence being repeated several times.

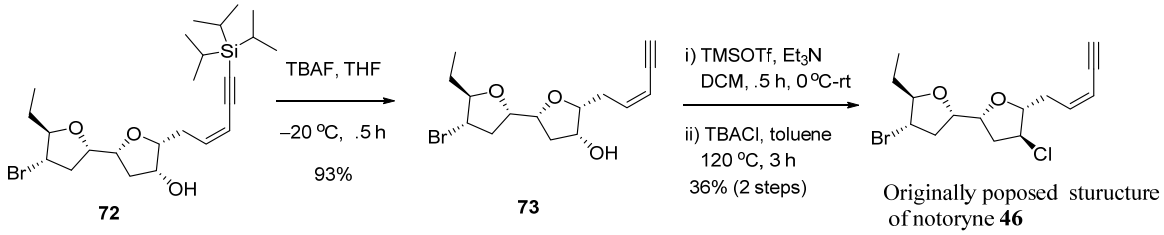
- **Execution of the cross metathesis event for the installation of *cis*-enyne part**:

Having met with failures at the final stage, we revised our strategy by planning the cross metathesis of intermediate **67α** to prepare the conjugated *cis*–enyne part and postponed the Appel reaction[60] for the installation of chloro group as the final event. The crucial cross metathesis was performed with the allyl compound **67α** and the TIPS enyne ether **70** in the presence of Hoveyda-Grubbs 2nd generation catalyst. This *cis* enyne **72** was characterized on the basis of NMR studies. In the ^{1}H NMR spectrum of compound **72**, the presence of two olefinic protons at δ 5.63 and 6.08 as br. doublet and doublet of triplet respectively, with the coupling constant of 10.8 Hz indicated the presence of a *cis* double bond. Furthermore, one singlet resonated at 1.09 ppm integrating for eighteen protons were indicative of a TIPS group. In the ^{13}C NMR spectrum of compound **72**, the two doublets corresponding to the olefinic carbons resonated at 111.4 and 140.8 ppm and two singlets at 95.8, 103.4 indicated the presence of an internal alkyne unit.



Scheme 105: Synthesis of *cis*-enyne **72** through cross metathesis

Next, the deprotection of the TIPS group in **72** by using TBAF in THF afforded the penultimate *cis*-enyne **73**. In the ^{1}H NMR spectrum of compound **73**, peaks corresponding to the TIPS group at δ 1.09 were absent and a doublet at 3.11 (d) with a coupling constant 1.96 Hz representing the terminal alkyne-H was present. All other analytical data of compound **73** were in accordance with the assigned structure (Scheme 106). Finally, the crucial chloro group introduction has been carried out by subjecting **73** for triflurylation and subsequent S_N2 displacement of the OTf with TBACl. The reaction was not clean and provided **46** in poor yields. Table 4 and 5 provides a comparison of the ^{1}H and ^{13}C signals of synthetic **46** with the reported data for Notoryne. Although, the peaks are comparable, however, were not exactly matched with the reported data revealing that the relative stereochemistry of chlorine bearing tetrahydrofuran has been wrongly assigned. Work in the direction of synthesising the other possible diastereomers to determine the structure of Notoryne is under progress.



Scheme 106: Synthesis of originally proposed Notoryne

Table 4. **Comparative ^{1}H NMR data of natural and synthetic Notoryne**

proton	Isolation (^{1}H NMR)	Synthetic (^{1}H HMR)
H1	3.13 (dd, *J* = 0.8, 2.4 Hz, 1H)	3.13 (d, *J* = 2.2 Hz, 1H)
H3	5.60 (dddd, *J* = 1.3, 1.3, 2.4, 10.8 Hz,1H)	5.61 (dt, *J* = 0.98, 10.76 Hz, 1H)
H4	6.08 (dddd, *J* = 0.8, 7.3, 7.3, 10.76 Hz, 1H)	6.07 (dt, *J* = 7.34, 10.76 Hz, 1H)
H5 H5’	2.59(dddd, *J* = 1.3, 7.0, 7.3, 14.8 Hz,1H) 2.67(m, 1H)	2.23–2.27 (m, 1H) 1.78 (dd, *J* = 7.4, 14.3 Hz, 1H)
H6	4.1(m, 1H)	4.48 (t, *J* = 3.67 Hz, 1H)
H7	4.1(m, 1H)	4.31 (dt, *J* = 5.6, 9.12 Hz, 1H)
H8 H8’	2.3 (m, 1H) 2.3(m, 1H)	2.32 (dd, *J* = 4.89, 9.05 Hz, 1H) 2.40 (dd, *J* = 6.1, 13.69 Hz, 1H)
H9	4.26 (ddd, *J* = 5.5, 7.3, 7.3 Hz, 1H)	4.20–4.25 (m, 1H)

H10	3.98(ddd, *J* = 5.5, 6.8, 8.3 Hz, 1H)	4.09–4.12 (m, 1H)
H11 H11’	2.66(ddd, *J* = 6.8, 6.8, 13.2 Hz, 1H) 2.17(ddd, *J* = 8.3, 8.3, 13.2 Hz, 1H)	2.63 (dt, *J* = 6.85, 14.18 Hz, 1H) 2.23–2.27 (m,1H)
H12	3.88(ddd, *J* = 6.8, 7.3, 8.3 Hz, 1H)	4.09–4.12 (m, 1H)
H13	3.91(ddd, *J* = 3.9, 7.2, 7.3 Hz, 1H)	3.91 (ddd, *J* = 2.93, 6.85, 9.54 Hz, 1H)
H14 H14’	1.49(dqd, *J* = 7.2, 7.3, 14.3 Hz, 1H) 1.76(dqd, *J* = 3.9, 7.3, 14.3 Hz, 1H)	1.45–1.49 (m, 1H) 1.70 (dd, *J* = 6.7, 14.2 Hz, 1H)
H15	1.00 (t, *J* = 7.3 Hz, 3H)	0.95 (t, *J* = 7.3 Hz, 3H)

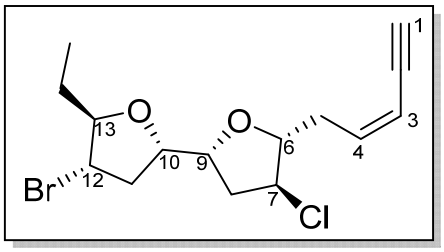
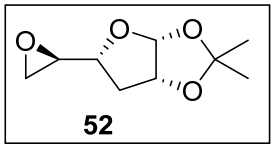


Table 5. **Comparative ^{13}C NMR data of natural and synthetic Notoryne**

	Isolation	Synthetic
C1	82.1(d)	82.3(d)
C 2	79.8(s)	80.1(s)
C 3	110.8(d)	111.1(d)
C 4	139.5(d)	139.8(d)
C 5	34.3(t)	34.6 (t)
C 6	79.9(d)	80.2 (d)
C 7	59.1(d)	59.4 (d)
C 8	39.3(t)	39.4 (t)
C 9	85.9(d)	84.2 (d)
C 10	87.0(d)	86.2(d)
C 11	38.0(t)	38.4 (t)
C 12	47.2(d)	47.4(d)
C 13	78.8(d)	78.6 (d)
C 14	25.4(t)	24.3 (t)
C 15	10.0(q)	10.0 (q)

EXPERIMENTAL & DATA

(3a*R*,5R,6aR)-2,2-dimethyl-5-((R)-oxiran-2-yl)tetrahydrofuro[2,3-d][1,3]dioxole (52)

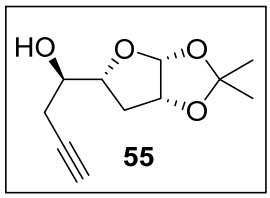


52

To an ice cooled solution of the diol **54** (16 g, 78 mmol) in CH_2Cl_2 (15 mL), were added Bu_2SnO (10 mg), DMAP (10 mg), and Et_3N (333 mL, 235 mmol) and stirred for 0.5 h at rt. The reaction mixture was cooled to 0 °C and treated with *p*-TsCl (16.4 g, 86 mmol) and stirring was continued for 4 h at rt. The reaction mixture was extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried (Na_2SO_4), concentrated and the resulting crude tosylate (25.5 g, 91%) was used as such for the next step without purification.

At 0 °C, a solution of the tosylate (25.5 g, 71 mmol), in dry THF (200 mL) was added NaH (4.1 g, 85 mmol) and stirred for 1h allowing the mixture to warm to room temperature. The reaction was cooled to 0 °C and quenched with water (50 mL) very slowly. The organic layer was extracted with brine (5 mL) and dried over Na_2SO_4 and concentrated under vacuo. The resulting crude product was purified by column chromatography (85:15 petroleum ether/EtOAc) to afford epoxide **52** (9 g, 68%) as a colorless oil: R_f (20% EtOAc/petroleum ether) 0.6; $[\alpha]^{25}_D$: −21.7 (*c* 3.1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz): δ1.33 (s, 3H), 1.56 (s, 3H), 2.05–2.14 (m, 1H), 2.18–2.32 (m, 1H), 2.57 (dd, *J* = 2.6, 4.8 Hz, 1H), 2.81 (dd, *J* = 4.2, 4.7 Hz, 1H), 3.35 (ddd, *J* = 2.7, 4.0, 7.1 Hz, 1H), 3.81 (ddd, *J* = 3.1, 7.4, 10.5 Hz, 1H), 4.74 (ddd, *J* = 1.3, 3.9, 5.3 Hz, 1H), 5.83 (d, *J* = 3.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ25.6 (q), 26.7 (q), 33.8 (t), 44.1 (t), 53.4 (d), 80.1 (d), 82.3 (d), 106.4 (d), 111.9 (s) ppm; MS (ESI) m/z = 209.79 $[M+Na]^+$; HRMS (ESI) calcd for $C_9H_{14}O_4$ $[M+Na]^+$ 209.0790, found 209.0781.

(R)-1-((3aR,5R,6aR)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-5-yl)but-3-yn-1-ol (55)

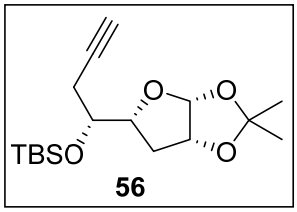


55

At −78 °C, acetylene gas was bubbled for 15 minutes. in THF (50 mL), after that were added *n*-BuLi (28.6 mL, 43 mmol, 1.5M in THF) and $BF_3.Et_2O$ (5.3 mL, 43 mmol) followed by a solution of the epoxide **52** (2 g, 10.7 mmol) in THF (10 mL) with a 15 minutes interval. The stirring was continued for another 1.5 h at −78 °C and then quenched with NH_4Cl (15 mL). The reaction mixture was allowed to reach rt and partitioned between ethyl acetate (25 mL) and water (25 mL). The aqueous layer was extracted with ethyl acetate (2 x 35mL) and the combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated. Purification of the crude product was carried out by column chromatography (80:20 petroleum ether/EtOAc) to afford the pure alkynol **55** (1.7 g, 74%) as a colorless oil: R_f (30%

EtOAc/petroleum ether) 0.47; $[\alpha]^{25}_{D}$: –25.6 (*c* 6.1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.32 (s, 3H), 1.56 (s, 3H), 2.05 (t, *J* = 2.7 Hz, 1H), 2.14 (dd, *J* = 2.7, 14.3 Hz, 1H), 2.27 (ddd, *J* = 6.3, 8.3, 14.6 Hz, 1H), 2.39–2.51 (m, 2H), 2.99 (d, *J* = 3.0 Hz, 1H), 3.92 (ddd, *J* = 2.8, 6.5, 12.9 Hz, 1H), 4.25 (ddd, *J* = 3.3, 7.3, 10.3 Hz, 1H), 4.77 (ddd, *J* = 1.3, 4.0, 6.1 Hz, 1H), 5.82 (d, *J* = 3.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ23.4 (t), 25.8 (q), 26.7 (q), 33.4 (t), 70.5 (d), 70.7(d), 80.2 (s), 80.6 (d), 83.0 (d), 106.1 (d), 112.5 (s), ppm MS (ESI) m/z = 235.16 $[M+Na]^+$; HRMS (ESI) calcd for $C_{11}H_{16}O_4$ $[M+Na]^+$ 235.0947, found 235.0939.

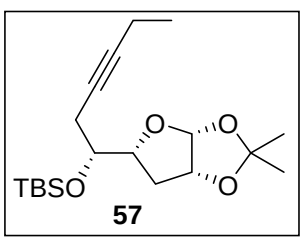
Tert-butyl(((R)-1-((3aR,5R,6aR)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-5-yl)but-3-yn-1-yl)oxy)dimethylsilane (56)



56

To a solution of **55** (7 g, 33 mmol) in DMF (100 mL) at 0 °C was added imidazole (11.23 g, 165 mmol), DMAP (20 mg) and stirred for 15 min. To this, TBSCl (9.94 g, 66 mmol) was added at 0 °C and stirred further for 5 h. The reaction mixture was diluted with EtOAc (50 mL) and washed with brine, dried (Na_2SO_4) and concentrated. The resulting crude product was purified by column chromatography (95:5 petroleum ether/EtOAc) to afford **56** (10.3 g, 96%) as colourless syrup: R_f (10% EtOAc/petroleum ether) 0.7; $[\alpha]^{25}_{D}$: –26.9 (*c* 6.8, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 0.12 (s, 6H), 0.90 (s, 9H), 1.33 (s, 3H), 1.56 (s, 3H), 1.97 (t, *J* = 2.7 Hz, 1H), 2.00–2.23 (m, 2H), 2.33 (ddd, *J* = 2.7, 5.7, 16.8 Hz, 1H), 2.52 (ddd, *J* = 2.7, 5.2, 16.8 Hz, 1H), 3.96 (dd, *J* = 5.8, 11.7 Hz, 1H), 4.07 (ddd, *J* = 6.4, 7.5, 13.9 Hz, 1H), 4.73 (ddd, *J* = 2.7, 4.0, 6.6 Hz, 1H), 5.71 (d, *J* = 4.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ–4.7 (q), –4.4 (q), 18.1 (s), 24.2 (t), 25.8 (q, 3C), 26.6 (q), 27.6 (q), 33.2 (t), 70.1 (d), 72.1 (d), 80.9 (d), 81.1 (s), 82.0 (d), 105.9 (d), 112.9 (s), ppm MS (ESI) m/z = 349.23 $[M+Na]^+$; HRMS (ESI) calcd for $C_{17}H_{30}O_4Si$ $[M+Na]^+$ 349.1811, found 349.1804.

Tert-butyl(((R)-1-((3aR,5R,6aR)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-5-yl)hex-3-yn-1-yl)oxy)dimethylsilane (57)

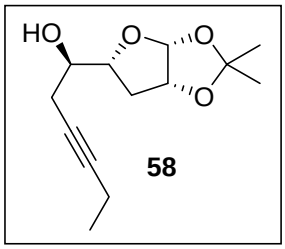


57

At –10 °C, a solution of the alkyne **56** (2 g, 6.13 mmol) in THF (50 mL) was treated with *n*-BuLi [(4.9 mL, 7.35 mmol) (1.5 M in hexane)] and stirred for 30 min. HMPA (1.23 mL, 7.35 mmol) was added and the reaction mixture was stirred at –10 °C for another 30

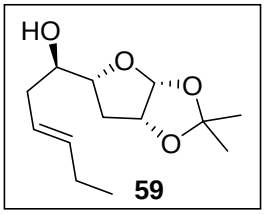
min. Ethyl bromide (0.9 mL, 12.2 mmol) was added to it at −10 °C and stirred for further 6 hours. The reaction mixture was quenched with saturated NH_4Cl. The organic layer was separated and the aqueous layer was washed with ethyl acetate, the combined organic layers were washed with ethyl acetate, brine, dried and concentrated. Purification of the crude product by column chromatography (90:10 petroleum ether/EtOAc) afforded **57** (1.1 g, 51%) as colorless oil: R_f (7% EtOAc/petroleum ether) 0.6; $[\alpha]^{25}_D$: −14.1 (*c* 5.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 0.11 (s, 6H), 0.9 (s, 9H), 1.09 (t, *J* = 7.5 Hz, 3H), 1.33 (s, 3H), 1.55 (s, 3H), 1.93–2.23 (m, 4H), 2.29 (dt, *J* = 2.3, 6.0 Hz, 1H), 2.37–2.50 (m, 1H), 3.87 (dd, *J* = 5.7, 11.5 Hz, 1H), 4.01 (dd, *J* = 6.6, 13.8 Hz, 1H), 4.70 (ddd, *J* = 2.9, 4.0, 6.8 Hz, 1H), 5.67 (d, *J* = 4.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ−4.7 (q), −4.4 (q), 12.4 (t), 14.1 (q), 18.1 (s), 24.4 (t), 25.9 (q, 3C), 26.7 (q), 27.7 (q), 33.4 (t), 72.8 (d), 76.0 (s), 81.0 (d), 82.1 (d), 83.3 (s), 105.9 (d), 112.9 (s), ppm MS (ESI) m/z = 377.28 $[M+Na]^+$; HRMS (ESI) calcd for $C_{19}H_{34}O_4Si$ $[M+Na]^+$ 377.2124, found 377.2115.

(R)-1-((3aR,5R,6aR)-2,2-Dimethyltetrahydrofuro[2,3-d][1,3]dioxol-5-yl)hex-3-yn-1-ol (58)



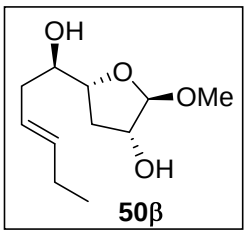
At −78 °C, to a solution of 1-butyne (26.8 mL, 188 mmol, 7M in THF) in THF (250 mL) were added *n*-BuLi (100.2 mL, 150 mmol, 1.5M in THF) and $BF_3.Et_2O$ (18.5 mL, 150 mmol) followed by a solution of the epoxide **52** (7 g, 37.6 mmol) in THF (20 mL) with a 15 minutes interval. The stirring was continued for another 1.5 h at −78 °C and then quenched with sat. NH_4Cl (15 mL). The reaction mixture was allowed to reach rt and partitioned between ethyl acetate (25 mL) and water (25 mL). The aqueous layer was extracted with ethyl acetate (2 x 50 mL) and the combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated. Purification of the crude product was carried out by column chromatography (85:15 petroleum ether/EtOAc) to afford the pure alkynol **58** (7 g, 77%) as a colorless oil: R_f (20% EtOAc/petroleum ether) 0.5; $[\alpha]^{25}_D$: −34.9 (*c* 2.6, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.1 (t, *J* = 7.5 Hz, 3H), 1.32 (s, 3H), 1.55 (s, 3H), 2.08–2.26 (m, 4H), 2.39–2.45 (m, 2H), 2.89 (d, *J* = 3.5 Hz, 1H), 2.83–2.94 (m, 1H), 4.23 (ddd, *J* = 3.7, 7.5, 11.0 Hz, 1H), 4.77 (ddd, *J* = 1.6, 4.0, 5.7 Hz, 1H), 5.81 (d, *J* = 3.9 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ12.4 (t), 14.1 (q), 23.9 (t), 26.0 (q), 27.0 (q), 33.7 (t), 71.2 (d), 74.9 (s), 80.8 (d), 83.2 (d), 84.1 (s), 106.1 (d), 112.5 (s), ppm MS (ESI) m/z = 262.93 $[M+Na]^+$; HRMS (ESI) calcd for $C_{13}H_{20}O_4$ $[M+Na]^+$ 263.1260, found 263.1254.

(R,E)-1-((3aR,5R,6aR)-2,2-Dimethyltetrahydrofuro[2,3-d][1,3]dioxol-5-yl)hex-3-en-1-ol (59)



At −78 °C, ammonia (300 mL) was condensed into two neck flask that was fitted with a dry ice condenser and the other neck was fitted with a gas delivery-tube running to the bottom of the flask. The gas delivery-tube was removed, and 390 mg (0.06 g-atoms) of lithium was added in small portions with vigorous stirring for 30 min. Then a solution of alkyne **58** (2.7 gm, 11.24 mmol) in THF (10 mL), followed by *tert*-butanol (4.3 mL, 45 mmol) were added to it very slowly. After the addition was complete, the reaction mixture was stirred at −78 °C for another 8 h. Then it was quenched by solid NH_4Cl (~2 gm), after that cooling bath was removed, and the ammonia was allowed to evaporate overnight. The reaction mixture was partitioned between ethyl acetate (50 mL) and water (50 mL). The aqueous layer was extracted with ethyl acetate (2 x 50 mL) and the combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated. Purification of the crude product was carried out by column chromatography (80:20 petroleum ether/EtOAc) to afford the pure alkenol **59** (2.5 g, 92%) as a colorless oil: R_f (25% EtOAc/petroleum ether) 0.5; $[\alpha]^{25}_D$: –9.7 (*c* 2.1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 0.98 (t, *J* = 7.45 Hz, 3H), 1.32 (s, 3H), 1.55 (s, 3H), 1.97–2.08 (m, 3H), 2.10–2.30 (m, 3H), 3.81 (td, *J* = 4.8, 7.6 Hz, 1H), 4.00 (td, *J* = 3.7, 8.1 Hz, 1H), 4.75 (ddd, *J* = 1.5, 3.9, 5.8 Hz, 1H), 5.48 (dt, *J* = 6.1, 15.4 Hz, 1H), 5.57 (dt, *J* = 5.3, 15.4 Hz, 1H), 5.80 (d, *J* = 3.9 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ13.7 (q), 25.6 (t), 26.1 (q), 27.1 (q), 33.6 (t), 36.6 (t), 72.6 (d), 80.8 (d), 83.9 (d), 106.1 (d), 112.5 (s), 124.4 (d), 135.0 (d), ppm; MS (ESI) m/z = 264.92 $[M+Na]^+$; HRMS (ESI) calcd for $C_{13}H_{22}O_4$ $[M+Na]^+$ 265.1416, found 265.1410.

(2R,3R,5R)-5-((R,E)-1-Hydroxyhex-3-en-1-yl)-2-methoxytetrahydrofuran-3-ol (50*β*)

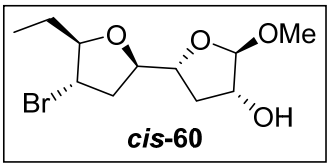


To an ice cooled solution of the acetonide **59** (1.5 gm, 6.19 mmol) in MeOH (25 mL), 4-5 drops of H_2SO_4 (conc) were added and stirred for overnight at rt. The reaction mixture was cooled to 0 °C and quenched with Et_3N. Solvent was evaporated under reduced pressure, and the residue was purified by column chromatography (75:25 petroleum ether/EtOAc) to yield the methyl glycoside **50*β*** (1.25 g, 93%) as colorless syrup: R_f (40% EtOAc/petroleum ether) 0.6; $[\alpha]^{25}_D$: –12.6 (*c* 4.3, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400

MHz): δ1.00 (t, *J* = 7.5 Hz, 3H), 1.80 (dd, *J* = 2.8, 13.8 Hz, 1H), 2.07 (dt, *J* = 7.3, 14.3 Hz, 2H), 2.21 (br s, 1H), 2.34–2.41 (m, 2H), 2.46 (ddd, *J* = 5.5, 9.8, 14.7 Hz, 1H), 3.35 (s, 3H), 3.56 (t, *J* = 6.7 Hz, 1H), 3.90 (br s, 1H), 4.06 (d, *J* = 4.3 Hz, 1H), 4.18 (dt, *J* =2.0, 9.7 Hz, 1H), 4.85 (s, 1H), 5.44 (dt, *J* =7.5, 15.1 Hz, 1H), 5.68 (dt, *J* =6.6, 15.1 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ13.6 (q), 25.6 (t), 34.7 (t), 37.3 (t), 54.3 (q), 72.2 (d), 73.9 (d), 79.2 (d), 109.5 (d), 124.5 (d), 137.1 (d) ppm; MS (ESI) m/z = 255.03 $[M+K]^+$; HRMS (ESI) calcd for $C_{11}H_{20}O_4$ $[M+Na]^+$ 239.126, found 239.1252.

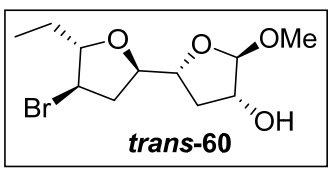
(2R,2'R,4R,4'S,5R,5'R)-4'-Bromo-5'-ethyl-5-methoxyoctahydro-[2,2'-bifuran]-4-ol (*cis*-60) and (2R,2'R,4R,4'R,5R,5'S)-4'-Bromo-5'-ethyl-5-methoxyoctahydro-[2,2'-bifuran]-4-ol (*trans*-60)

To a solution of the methylglycoside **50β** (150 mg, 0.69 mmol) in DCM (20 mL) at 0 °C, NBS (160 mg, 0.90 mmol) was added and stirred for 4 h at rt. The reaction mixture was concentrated under reduced pressure. Purification of the crude product by column chromatography (85:15 petroleum ether/EtOAc) gave ***cis*-60** as a minor diastereomer (20 mg, 10%) R_f (20% EtOAc/petroleum ether) 0.42 and further elution afforded the major diastereomer (135 mg, 66%) ***trans*-60** as colorless syrups: R_f (22% EtOAc/petroleum ether) 0.4.



***cis*-60**

Characterization data of compound *cis*-60: $[\alpha]^{25}_D$: −52.6 (*c*1.4, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ1.01 (t, *J* = 7.5 Hz, 3H), 1.52 (dd, *J* = 7.1, 14.1 Hz, 1H), 1.70–1.78 (m, 1H), 1.86 (dd, *J* = 1.6, 13.9 Hz, 1H), 2.27 (ddd, *J* = 5.3, 7.0, 12.9 Hz, 1H), 2.45 (ddd, *J* = 5.5, 10.3, 14.7 Hz, 1H), 2.67 (dt, *J* = 6.9, 13.5 Hz, 1H), 3.34 (s, 3H), 3.97–4.03 (m, 1H), 4.04–4.08 (m, 1H), 4.09–4.14 (m, 1H), 4.20–4.23 (m, 2H), 4.79 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ10.3 (q), 26.4 (t), 34.4 (t), 38.2 (t), 49.0 (d), 54.6 (q), 73.7 (d), 77.8 (d), 79.3 (d), 89.1 (d), 110.0 (d) ppm; MS (ESI) m/z = 317.03 $[M+Na]^+$; HRMS (ESI) calcd for $C_{11}H_{19}BrO_4$ $[M+Na]^+$ 317.0365, 319.0365 found 317.0357 and 319.0335.

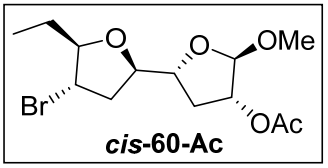


***trans*-60**

Characterization data of compound *trans*-60: $[\alpha]^{25}_D$: −102.9 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ1.01 (t, *J* = 7.4 Hz, 3H), 1.45 (d, *J* = 6.0 Hz, 1H), 1.49 (dd, *J* = 7.3, 14.3 Hz, 1H), 1.80 (dd, *J* = 2.3, 14.0 Hz, 1H), 1.87 (ddd, *J* = 3.3, 7.8 14.3 Hz, 1H), 2.43–2.51 (m, 1H), 2.56 (t, *J* = 8.5 Hz, 1H), 3.35 (s, 3H), 3.81 (q, *J* = 9.0 Hz, 1H),

3.91 (dd, *J* = 3.2, 8.8 Hz, 1H), 4.02 (dd, *J* = 5.5, 11.0 Hz, 1H), 3.97 (d, *J* = 8.5 Hz 1H), 4.19 (d, *J* = 10.8 Hz, 1H), 4.26 (d, *J* = 11.0 Hz, 1H), 4.84 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ10.1 (q), 25.0 (t), 34.6 (t), 38.2 (t), 46.7 (d), 54.6 (q), 73.6 (d), 78.1 (d), 78.8 (d), 86.9 (d), 109.8 (d) ppm; MS (ESI) m/z = 316.67, 318.74 $[M+Na]^+$; HRMS (ESI) calcd for $C_{11}H_{19}BrO_4$ $[M+Na]^+$317.0365, 319.0365 found 317.0356 and 319.0334.

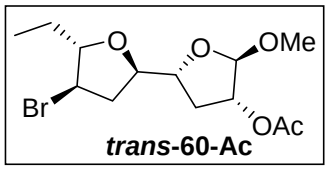
(2R,2'R,4R,4'S,5R,5'R)-4'-Bromo-5'-ethyl-5-methoxyoctahydro-[2,2'-bifuran]-4-yl acetate (*cis*-60-Ac)



***cis*-60-Ac**

To a solution of ***cis*-60** (20 mg, 0.06 mmol) in CH_2Cl_2 (10 mL) at 0 °C was added Et_3N (0.06 mL, 0.6 mmol), DMAP (2 mg) and stirred for 15 min. To this, acetic anhydride (0.02 mL, 0.3 mmol) was added at 0 °C and stirred further for 2 h. The reaction mixture was diluted with CH_2Cl_2 (10 mL) and washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. The resulting crude product was purified by column chromatography (90:10 petroleum ether/EtOAc) to afford the aceate ***cis*-60-Ac** (22 mg, 96%) as colorless syrup: R_f (20% EtOAc/petroleum ether) 0.6; $[\alpha]^{25}_D$: −35.8 (*c* 1.4, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ1.01 (t, *J* = 7.5 Hz, 3H), 1.60–1.71 (m, 3H), 2.07 (s, 3H), 2.22–2.33 (m, 2H), 2.46 (ddd, *J* = 7.0, 8.3, 14.6 Hz, 1H), 3.37 (s, 3H), 4.02 (dt, *J* = 5.3, 6.6 Hz, 1H), 4.07–4.13 (m, 2H), 4.22 (q, *J* = 7.0 Hz, 1H), 4.97 (s, 1H), 5.03 (dd, *J* = 2.0, 6.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ9.9 (q), 21.0 (q), 26.6 (t), 32.3 (t), 39.0 (t), 48.9 (d), 54.8 (q), 77.5 (d), 79.4 (d), 79.8 (d), 89.0 (d), 107.2 (d), 170.4 (s) ppm; MS (ESI) m/z = 359.00, 360.89 $[M+Na]^+$; HRMS (ESI) calcd for $C_{13}H_{21}BrO_5$ $[M+Na]^+$ 359.047, 361.047, found 359.0461 and 361.0439.

(2R,2'R,4R,4'R,5R,5'S)-4'-Bromo-5'-ethyl-5-methoxyoctahydro-[2,2'-bifuran]-4-yl acetate (*trans*-60-Ac)

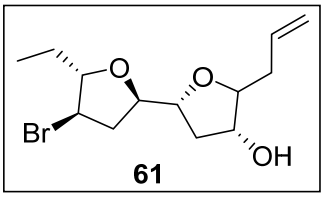


***trans*-60-Ac**

To a solution of ***trans*-60** (30 mg, 0.1 mmol) in CH_2Cl_2 (10 mL) at 0 °C was added Et_3N (0.09 mL, 0.6 mmol), DMAP (2 mg) and stirred for 15 min. To this, acetic anhydride (0.03 mL, 0.3 mmol) was added at 0 °C and stirred further for 2 h. The reaction mixture was diluted with CH_2Cl_2 (10 mL) and washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. The resulting crude product was purified by column chromatography (90:10 petroleum ether/EtOAc) to afford the aceate ***cis*-60-Ac** (31 mg, 90%) as colorless syrup: R_f (20% EtOAc/petroleum ether) 0.6; $[\alpha]^{25}_D$: −77.0 (*c* 0.76, $CHCl_3$); ^{1}H NMR ($CDCl_3$,

400 MHz): δ1.01 (t, *J* = 7.5 Hz, 3H), 1.56–1.59 (m, 1H), 1.63–1.64 (m, 1H), 1.72–1.82 (m, 1H), 2.06 (s, 3H), 2.08 (dt, *J* = 8.3, 13.2 Hz, 1H), 2.47 (ddd, *J* = 6.8, 8.5, 14.6 Hz, 1H), 2.65 (dt, *J* = 7.1, 13.3 Hz, 1H), 3.38 (s, 3H), 3.90 (dt, *J* = 7.6, 8.5 Hz, 1H), 4.01 (td, *J* = 4.5, 7.3 Hz, 1H), 4.08 (dd, *J* = 7.3, 15.1 Hz, 1H), 4.23 (ddd, *J* = 5.5, 7.7, 13.3 Hz, 1H), 4.97 (s, 1H), 5.04 (dd, *J* = 1.8, 6.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ9.7 (q), 21.0 (q), 25.1 (t), 32.0 (t), 39.1 (t), 46.9 (d), 54.8 (q), 77.4 (d), 79.4 (d), 80.0 (d), 86.7 (d), 107.1 (d), 170.3 (s) ppm; MS (ESI) m/z = 359.14, 361.30 $[M+Na]^+$; HRMS (ESI) calcd for $C_{13}H_{21}BrO_5$ $[M+Na]^+$ 359.047, 361.047, found 359.0460 and 361.0440.

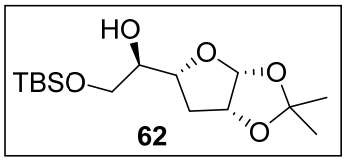
(2R,2'R,4R,4'R,5'S)-5-Allyl-4'-bromo-5'-ethyloctahydro-[2,2'-bifuran]-4-ol(61)



61

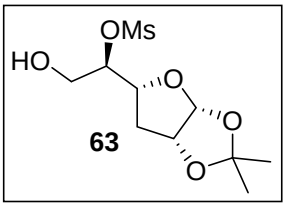
To a solution of methylglycoside ***trans*-60** (80 mg, 0.27 mmol) and allyltrimethylsilane (0.2 mL, 1.36 mmol) in acetonitrile (10 mL) was added drop wise an equimolar amount of trimethylsilyl triflate (0.05 mL, 0.27 mmol) at –40 °C. The solution was allowed to warm to 0 °C over 8 h. As soon as it reached to 0°C, a saturated aqueous solutions of $NaHCO_3$ (5 mL) was added. Reaction mixture was concentrate under reduced pressure to removed acetonitrile then the aqueous layer was extracted with EtOAc (4x 25 ml). The combined organic layers were dried over $NaSO_4$, filtrated, concentrated in vacuo and purified by column chromatography (petroleum ether:EtOAc, 90:10) to yield *C*-glycoside **61** (57 mg, 69%) as a colourless oil R_f (10% EtOAc/petroleum ether) 0.6; $[\alpha]^{25}_D$: –4.4 (*c* 0.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz): δ1.02 (t, *J* = 7.4 Hz, 3H), 1.53–1.62 (m, 2H), 1.72–1.77 (m, 1H), 2.00 (dd, *J* = 2.5, 14.1 Hz, 1H), 2.21 (ddd, *J* = 5.2, 7.1, 12.9 Hz, 1H), 2.34–2.44 (m, 2H), 2.61 (dt, *J* = 6.7, 13.4 Hz, 1H), 3.67–3.7 (m, 1H), 3.98 (br s, 1H), 4.02–4.06 (m, 2H), 4.08 (ddd, *J* = 1.4, 2.4, 10.5 Hz, 1H) 4.14 (ddd, *J* = 1.0, 7.3, 8.2 Hz, 1H), 5.05 (dd, *J* = 1.83, 10.07 Hz, 1H), 5.12 (dd, *J* = 1.8, 17.1 Hz, 1H), 5.81–5.90 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ10.4 (q), 26.6 (t), 33.9 (t), 37.8 (t), 38.2 (t), 49.3 (d), 71.2 (d), 76.9 (d), 80.0 (d), 84.0 (d), 89.2 (d), 116.8 (t), 135.1 (d) ppm; MS (ESI) m/z = 327.14, 328.88 $[M+Na]^+$; HRMS (ESI) calcd for $C_{13}H_{21}BrO_3$ $[M+H]^+$ 305.0754, 307.0754 and found 305.0745 and 307.0715.

(R)-2-((*Tert*-butyldimethylsilyl)oxy)-1-((3aR,5R,6aR)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-5-yl)ethan-1-ol (62)



To a solution of Diol **54** (6 g, 29.4 mmol) in CH_2Cl_2 (5 mL) at 0 °C was added imidazole (6 g, 88.1 mmol), cat. DMAP (10 mg), cat. *n*-Bu_2SnO (10 mg) and stirred for 15 min. TBSCl (4.4 g, 29.4 mmol) was added at 0 °C and stirred further for 4 h. The reaction mixture was diluted with CH_2Cl_2 (15 mL) and washed with brine, dried (Na_2SO_4) and concentrated. The resulting crude product was purified by column chromatography (80:20 petroleum ether/EtOAc) to afford silyl ether **62** (8 g, 85%) as a colorless oil: R_f (30% EtOAc/petroleum ether) 0.4; $[\alpha]^{25}_D$: −50.4 (*c* 1.3, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ − 0.07 (s, 6H), 0.09 (s, 9H), 1.33 (s, 3H), 1.56 (s, 3H), 2.16 (ddd, *J* = 2.0, 4.2, 14.2 Hz, 1H), 2.21 (dd, *J* = 6.1, 8.0 Hz, 1H), 2.79 (br s, 1H), 3.64 (dd, *J* = 6.1, 10.3 Hz, 1H), 3.71 (dd, *J* = 4.7, 10.3 Hz, 1H), 3.80 (ddd, *J* = 5.2, 6.5, 12.7 Hz, 1H), 4.24 (ddd, *J* = 4.0, 7.7, 11.7 Hz, 1H), 4.77 (dd, *J* = 2.0, 4.2, 6.1 Hz, 1H), 5.81 (d, *J* = 3.9 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ−5.4 (q, 2C), 18.3 (s), 25.9 (q, 3C), 26.1 (q), 27.0 (q), 33.6 (t), 64.4 (t), 72.8 (d), 80.8 (d), 81.7 (d), 106.8 (d), 112.5 (s) ppm; MS (ESI) m/z = 341.05 $[M+Na]^+$; HRMS (ESI) calcd for $C_{15}H_{30}O_5Si$ $[M+Na]^+$ 341.1761, found 341.1752.

(R)-1-((3aR,5R,6aR)-2,2-Dimethyltetrahydrofuro[2,3-d][1,3]dioxol-5-yl)-2-hydroxyethyl methanesulfonate (63)

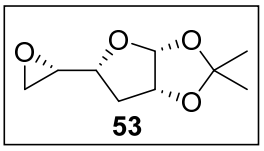


At 0 °C, a solution of the **62** (8 g, 25.1 mmol) and triethylamine (14.1 mL, 100.5 mmol) in CH_2Cl_2 was treated with MsCl (4.1 mL, 50.2 mmol) and stirred for 3 h. The reaction mixture was extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried (Na_2SO_4) and concentrated. The resulting crude mesylate (9 g, 90%) was used as such for the next step without purification.

To a cold (0 ºC) solution of the above mesylate **63** (9 g, 22.7 mmol) in dry tetrahydrofuran (150 mL) was added tetra-*n*-butylammonium fluoride (TBAF) (5.9 mL 22.7 mmol) and the resulting solution stirred for 2 h allowing the mixture to warm to room temperature. The reaction was quenched with water (50 mL). The organic layer was extracted with brine (5 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The resulting crude was purified by column chromatography (85:15 petroleum ether/EtOAc) to afford

mesylate **63** (6 g, 94%) as a colorless oil: R_f (30% EtOAc/petroleum ether) 0.5; $[\alpha]^{25}_D$: +29.4 (*c* 4.1, $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz): δ 1.29 (s, 3H), 1.56 (s, 3H), 2.19–2.25 (m, 2H), 2.91 (br s, 1H), 3.20 (s, 3H), 3.78 (dd, *J* = 3.5, 13.1 Hz, 1H), 3.94 (dd, *J* = 2.7, 13.3 Hz, 1H), 4.38–4.48 (m, 1H), 4.77 (t, *J* = 4.1 Hz, 1H), 4.88 (dt, *J* = 3.2, 9.2 Hz, 1H), 5.82 (d, *J* = 3.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ25.3 (q), 26.1 (q), 33.1 (q), 38.8 (t), 62.9 (t), 79.2 (d), 80.2 (d), 85.3 (d), 106.4 (d), 112.3 (s) ppm; MS (ESI) m/z = 305.21 $[M+Na]^+$; HRMS (ESI) calcd for $C_{10}H_{18}O_7S$ $[M+Na]^+$ 305.0671, found 305.0665.

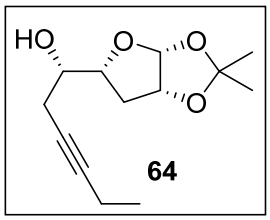
(3aR,5R,6aR)-2,2-Dimethyl-5-((S)-oxiran-2-yl)tetrahydrofuro[2,3-d][1,3]dioxole (53)



53

At 0 °C, a solution of the mesylate **63** (6 g, 21.2 mmol) in dry THF (50 mL) was treated with NaH (1.5g, 31.88 mmol) the resulting suspension was stirred for 1 h allowing to warm to room temperature. The reaction was cooled to 0 °C and quenched with water (50 mL) very slowly. The reaction mixture was extracted EtOAc (2 X 50 mL) and the combrined organic laywer was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The resulting crude was purified by column chromatography (85:15 petroleum ether/EtOAc) to afford epoxide **53** (3 g, 76%) as a yellow color oil: R_f (25% EtOAc/petroleum ether) 0.6; $[\alpha]^{25}_D$: −13.3 (*c* 0.14, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz): δ1.34 (s, 3H), 1.58 (s, 3H), 2.24 (ddd, *J* = 5.8, 8.2, 14.3 Hz, 1H), 2.34 (dd, *J* = 2.1, 14.3 Hz, 1H), 2.67 (dd, *J* = 2.6, 4.8 Hz, 1H), 2.87 (dd, *J* = 4.1, 4.7 Hz, 1H), 3.31 (ddd, *J* = 2.7, 3.9, 6.9 Hz, 1H), 3.77 (ddd, *J* = 2.1, 8.2, 9.8 Hz, 1H), 4.78 (dd, *J* = 4.1, 5.3 Hz, 1H), 5.83 (d, *J* = 4.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ25.8 (q), 27.1 (q), 34.7 (t), 47.3 (t), 53.1 (d), 80.7 (d), 82.3 (d), 106.8 (d), 112.4 (s) ppm; MS (ESI) m/z = 209.08 $[M+Na]^+$; HRMS (ESI) calcd for $C_9H_{14}O_4$ $[M+Na]^+$ 209.0790, found 209.0781.

(S)-1-((3aR,5R,6aR)-2,2-Dimethyltetrahydrofuro[2,3-d][1,3]dioxol-5-yl)hex-3-yn-1-ol (64)

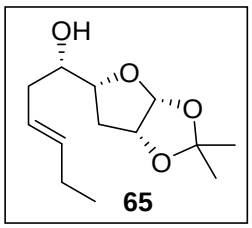


64

At −78 °C, a solution of 1-butyne (2.9 g, 53.7 mmol, 7.7 mL, 7M) in THF (25 mL) was treated with *n*-BuLi (28.6 mL, 42.96 mmol, 1.5M in THF) and $BF_3.Et_2O$ (5.3 mL, 42.96 mmol) followed by a solution of the epoxide **53** (2 gm, 10.74 mmol) in THF (8 mL) with a 15 minutes interval. The stirring was continued for another 1.5 h at−78 °C and then quenched with sat. NH_4Cl (5 mL). The reaction mixture was allowed to reach rt and partitioned between ethyl acetate (25 mL) and water (25 mL). The aqueous layer was extracted with ethyl acetate (2 x 30mL) and the combined organic layer was washed with brine,

dried over Na_2SO_4 and concentrated. Purification of the crude by column chromatography (80:20 petroleum ether/EtOAc) gave the alkynol **64** (1.8 g, 70 %) as a colorless oil: R_f (25% EtOAc/petroleum ether) 0.5; $[\alpha]^{25}_D$: 58.94 (*c* 3.7, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.1 (t, *J* = 7.45 Hz, 3H), 1.29 (s, 3H), 1.54 (s, 3H), 2.07–2.21 (m, 3H), 2.28–2.39 (m, 1H), 2.43–2.51 (m, 3H), 3.88–3.98 (m, 1H), 4.1 (ddd, *J* = 3.4, 7.9, 11.2 Hz, 1H), 4.74 (ddd, *J* = 1.5, 3.9, 5.9 Hz, 1H), 5.76 (d, *J* = 3.9 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ12.4 (t), 14.1 (q), 24.1 (t), 25.9 (q), 27.1 (q), 32.4 (t), 70.7 (d), 74.5 (s), 80.7 (d), 82.6 (d), 84.7 (s), 106.3 (d), 112.3 (s) ppm; MS (ESI) m/z = 262.75 $[M+Na]^+$; HRMS (ESI) calcd for $C_{13}H_{20}O_4[M+Na]^+$ 263.1260, found 263.1252.

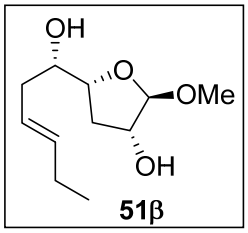
(S,E)-1-((3aR,5R,6aR)-2,2-Dimethyltetrahydrofuro[2,3-d][1,3]dioxol-5-yl)hex-3-en-1-ol (65)



65

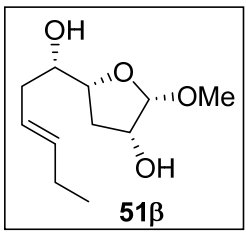
At −78 ^{o}C, ammonia (300 mL) was condensed into a two neck the flaskthat was fitted with a dry ice condenser and the other neck was fitted with a gas delivery-tube running to the bottom of the flask. The gas delivery-tube was removed, and 217 mg (0.03 g-atoms) of lithium was added in small portions with vigorous stirring for 30 min. Then a solution of alkyne **64** (1.5 g, 6.24 mmol) in THF (10 mL), followed by *t*-butanol(1.85 g, 25 mmol, 2.4 mL) were added to it very slowly. After the addition was complete, the reaction mixture was stirred at −50 °C for another 24 h. Then it was quenched by solid NH_4Cl(~2 gm), after that cooling bath was removed, and the ammonia was allowed to evaporate overnight. The reaction mixture was partitioned between ethyl acetate (50 mL) and water (50 mL). The aqueous layer was extracted with ethyl acetate (2 x 50mL) and the combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated. Purification of the crude by column chromatography (80:20 petroleum ether/EtOAc) gave the alkenol **65** (1.25 g, 82%) as a colorless oil: R_f (25% EtOAc/petroleum ether) 0.5.; $[\alpha]^{25}_D$: −25.4 (*c* 2.3, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz): δ0.97 (t, *J* = 7.5 Hz, 3H), 1.32 (s, 3H), 1.54 (s, 3H), 1.96–2.09 (m, 2H), 2.11–2.18 (m, 2H), 2.24–2.41 (m, 3H), 3.81–3.90 (m, 1H), 3.94–4.04 (m, 1H), 4.75 (ddd, *J* = 2.0, 3.9, 6.2 Hz, 1H), 5.41 (dt, *J* = 6.9, 15.4 Hz, 1H), 5.59 (dt, *J* = 5.9, 15.4 Hz, 1H), 5.74 (d, *J* =3.9 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ13.7 (q), 25.6 (t), 26.2 (q), 27.3 (q), 31.9 (t), 36.8 (t), 71.5 (d), 80.8 (d), 83.3 (d), 106.1 (d), 112.5 (s), 124.2 (d), 136.1 (d), ppm; MS (ESI) m/z = 264.88 $[M+Na]^+$; HRMS (ESI) calcd for $C_{13}H_{22}O_4$ $[M+Na]^+$ 265.1416, found 265.1410.

(2R,3R,5R)-5-((S,E)-1-Hydroxyhex-3-en-1-yl)-2-methoxytetrahydrofuran-3-ol (51*β*)



To an ice cooled solution of the acetonide **65** (1 g, 4.13 mmol) in MeOH (15 mL), 2 drops of conc. H_2SO_4 were added and stirred for overnight at rt. The reaction mixture was cooled to 0 °C and quenched with Et_3N. The solvent was evaporated under reduced pressure, and the residue was purified by column chromatography (75:25 petroleum ether/EtOAc) to yield a mixture of methyl glycoside **51*β*** (700 mg, 78%) as colorless syrup: R_f (40% EtOAc/petroleum ether) 0.5 and the isomer **51*α*** (70 mg, 8%) as colourless syrup: R_f (45% EtOAc/petroleum ether) 0.6.

Characterization data of compound 51*β*: $[\alpha]^{25}_D$: −107.8 (*c* 1.9, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz): δ0.96 (t, *J* = 7.3 Hz, 3H), 1.80 (dd, *J* = 2.5, 13.8 Hz, 1H), 2.01–2.09 (m, 3H), 2.13–2.2.17 (m, 1H), 2.26 (ddd, *J* = 5.5, 9.8, 14.1 Hz, 1H), 3.12 (br s, 2H), 3.33 (s, 3H), 3.87–3.90 (m, 1H), 4.05 (d, *J* = 5.5 Hz, 1H), 4.19 (d, *J* = 9.5 Hz, 1H), 4.82 (s, 1H), 5.38 (dt, *J* = 7.3, 15.3 Hz, 1H), 5.60 (dt, *J* = 6.5, 15.3 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ13.6 (q), 25.6 (t), 30.8 (t), 37.3 (t), 54.5 (q), 70.9 (d), 73.7 (d), 80.6 (d), 109.1 (d), 123.7 (d), 136.7 (d) ppm; MS (ESI) m/z = 239.00 $[M+Na]^+$; HRMS (ESI) calcd for $C_{11}H_{20}O_4$ $[M+Na]^+$ 239.126, found 239.1252.

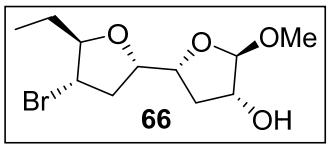


Characterization data of compound 51*α*: $[\alpha]^{25}_D$: +77.1 (*c* 2.6, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz): δ0.97 (t, *J* = 7.4 Hz, 3H), 1.86 (dt, *J* = 9.5, 12.2 Hz, 1H), 2.00–2.05 (m, 2H), 2.08–2.15 (m, 2H), 2.18 (dt, *J* = 7.5, 12.5 Hz, 1H), 2.44 (d, *J* = 10.4 Hz, 1H), 2.53 (br s, 1H), 3.50 (s, 3H), 3.75 (ddd, *J* = 3.9, 6.7, 10.0 Hz, 1H), 4.08 (ddd, *J* = 3.66, 7.0, 10.4 Hz, 1H), 4.20–4.26 (m, 1H), 4.74 (d, *J* = 4.3 Hz, 1H), 5.41 (dt, *J* = 7.0, 15.3 Hz, 1H) 5.57 (dt, *J* = 6.1, 15.3 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ13.7 (q), 25.6 (t), 30.2 (t), 35.9 (t), 55.9 (q), 71.8 (d), 72.7 (d), 80.7 (d), 102.3 (d), 124.2 (d), 135.5 (d) ppm; MS (ESI) m/z = 238.62 $[M+Na]^+$; HRMS (ESI) calcd for $C_{11}H_{20}O_4$ $[M+Na]^+$ 239.126, found 239.1252.

(2R,2'S,4R,4'S,5R,5'R)-4'-Bromo-5'-ethyl-5-methoxyoctahydro-[2,2'-bifuran]-4-ol (66)

To a solution of the methylglycoside **51*β*** (115 mg, 0.53 mmol) in CH_2Cl_2 (20 mL) at 0 °C, NBS (123 mg, 0.69 mmol) was added and stirred for 4 h at rt. The reaction mixture was

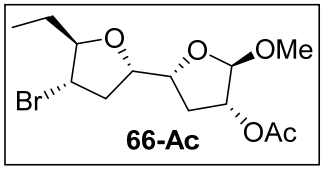
concentrated under reduced pressure. Purification of the crude product by column chromatography (85:15 petroleum ether/EtOAc) gave **66** (110 mg, 70%) as colorless syrup:R_f (20% EtOAc/petroleum ether) 0.4; $[\alpha]^{25}_D$: 26.8 (*c* 4.1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ1.01 (t, *J* = 7.5 Hz, 3H), 1.51–1.57 (m, 1H), 1.80–1.87 (m, 2H), 1.94 (dd, *J* = 10.5, 12.8 Hz, 1H), 2.33–2.40 (m, 1H), 2.64 (dt, *J* = 6.4, 12.8 Hz, 1H), 3.34 (s, 3H), 3.90 (dd, *J* = 6.7, 8.2 Hz, 1H), 3.94 (dd, *J* = 2.7, 9.2 Hz, 1H), 3.98 (ddd, *J* = 3.6, 8.0, 11.7 Hz, 1H), 4.05 (br s, 1H), 4.24–4.28 (m, 2H), 4.85 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ10.0 (q), 25.4 (t), 31.3 (t), 39.8 (t), 46.1 (d), 55.6 (q), 73.4 (d), 78.4 (d), 79.6 (d), 88.0 (d), 109.6 (d) ppm; MS (ESI) m/z = 317.03 $[M+Na]^+$; HRMS (ESI) calcd for $C_{11}H_{19}BrO_4$ $[M+Na]^+$ 317.0365, 319.0365 found 317.0356 and 319.0334.



66

(2R,2'S,4R,4'S,5R,5'R)-4'-Bromo-5'-ethyl-5-methoxyoctahydro-[2,2'-bifuran]-4-yl acetate (66-Ac)

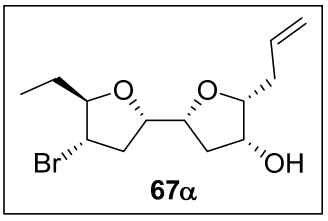
To a solution of **66** (30 mg, 0.1 mmol) in CH_2Cl_2 (10 mL) at 0 °C was added Et_3N (0.08 mL, 0.6 mmol), DMAP (2 mg) and stirred for 15 min. To this, acetic anhydride (0.03 mL, 0.3 mmol) was added at 0 °C and stirred further for 2 h. The reaction mixture was diluted with CH_2Cl_2 (10 mL) and washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. The resulting crude product was purified by column chromatography (90:10 petroleum ether/EtOAc) to afford the aceate **66-Ac** (29 mg, 84%) as colorless syrup: R_f (20% EtOAc/petroleum ether) 0.6; $[\alpha]^{25}_D$: −37.5 (*c* 0.45, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ1.01 (t, *J* = 7.4 Hz, 3H), 1.50–1.57 (m, 1H), 1.71–1.79 (m, 1H), 1.85 (ddd, *J* = 1.2, 5.1, 14.2 Hz, 1H), 2.07 (s, 3H), 2.23–2.31 (m, 1H), 2.46–2.54 (m, 1H), 2.71 (dt, *J* = 6.8, 13.7 Hz, 1H), 3.36 (s, 3H), 3.91 (dd, *J* = 7.6, 15.5 Hz, 1H), 3.96 (dd, *J* = 7.3, 10.8 Hz, 1H), 3.99 (dd, *J* = 6.9, 14.2 Hz, 1H), 4.18–4.23 (m, 1H), 4.93 (s, 1H), 5.05 (dd, *J* = 1.5, 6.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 9.9 (q), 21.1 (q), 25.4 (t), 32.6 (t), 39.6 (t), 47.4 (d), 54.6 (d), 77.6 (d), 79.2 (d), 80.1 (d), 87.0 (d), 107.0 (d), 170.3 (s) ppm; MS (ESI) m/z = 359.14, 361.30 $[M+Na]^+$; HRMS (ESI) calcd for $C_{13}H_{21}BrO_5$ $[M+Na]^+$ 359.047, 361.047, found 359.0462 and 361.0439.



66-Ac

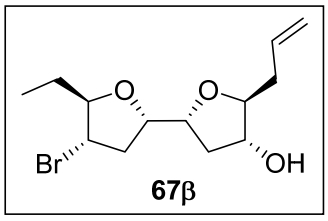
(2R,2'S,4R,4'S,5R,5'R)-5-Allyl-4'-bromo-5'-ethyloctahydro-[2,2'-bifuran]-4-ol (67α) and (2R,2'S,4R,4'S,5S,5'R)-5-Allyl-4'-bromo-5'-ethyloctahydro-[2,2'-bifuran]-4-ol(67β)

To a solution of methylglycoside **66** (220 mg, 0.74 mmol) and allyltrimethylsilane (0.59 mL, 3.73 mmol) in acetonitrile (10 mL), was added drop wise an equimolar amount of trimethylsilyl triflate (0.14 mL, 0.74 mmol) at –40 °C. The solution was allowed to warm to 0 °C over 8 h. As soon as it reached to 0 °C, a saturated aqueous solution of $NaHCO_3$ (5 mL) was added.The reaction mixture was concentrated under reduced pressure and was extracted with EtOAc (4x 25 ml). The combined organic layers were dried over $NaSO_4$ and concentrated under reduced pressure. The resulting crude was purified by column chromatography (petroleum ether:EtOAc, 90:10) to yield *C*-glycoside **67α** as a major diastereomer (150 mg, 66%) R_f (10% EtOAc/petroleum ether) 0.6 and further elution afforded the minor *C*-glycoside **67β** (30 mg, 13%) as colorless syrup:R_f (10% EtOAc/petroleum ether) 0.61.



67α

Characterization data of compound 67α: $[\alpha]^{25}_D$: +23.1 (*c* 6.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz): δ1.03 (t, *J* = 7.6 Hz, 3H), 1.51–1.57 (m, 1H), 1.80–1.87 (m, 1H), 1.88–1.98 (m, 2H), 2.28 (ddd, *J* = 5.2, 10.1, 19.2 Hz, 1H), 2.41–2.52 (m, 2H), 2.61 (dt, *J* = 6.4, 12.8 Hz, 1H), 3.67 (ddd, *J* = 2.1, 8.8, 13.7 Hz, 1H), 3.81 (d, *J* = 11.0 Hz, 1H), 3.85–3.90 (m, 1H), 3.96 (ddd, *J* = 3.7, 8.3, 16.5 Hz, 1H), 4.04 (ddd, *J* = 2.4, 4.8, 10.7 Hz, 1H), 4.14 (dt, *J* = 2.1, 9.8 Hz, 1H), 4.22 (ddd, *J* = 1.2, 6.1, 10.7 Hz, 1H), 5.08 (dd, *J* = 1.2, 10.1 Hz, 1H), 5.17 (dd, *J* = 1.2, 17.1 Hz, 1H), 5.83–5.92 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ10.1 (q), 25.5 (t), 33.5 (t), 34.7 (t), 39.8 (t), 46.3 (d), 70.9 (d), 79.0 (d, 2C), 83.7 (d), 87.9 (d), 116.9 (t), 134.9 (d) ppm; MS (ESI) m/z = 327.07 $[M+Na]^+$; HRMS (ESI) calcd for $C_{13}H_{21}BrO_3$ $[M+Na]^+$ 327.0572, 329.0572 and found 327.0565 and 329.0542.

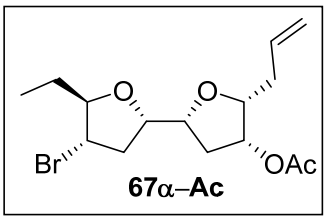


67β

Characterization data of compound 67β: $[\alpha]^{25}_D$: –66.2 (*c* 0.3, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz): δ1.0 (t, *J* = 7.4 Hz, 3H), 1.53 (dd, *J* = 7.3, 14.3 Hz, 1H), 1.77–1.85 (m, 1H), 1.92–1.96 (m, 2H), 2.11–2.22 (m, 2H), 2.23 (ddd, *J* = 5.3, 8.8, 14.6 Hz, 1H), 2.63 (dt, *J* = 6.4, 12.8 Hz, 1H), 3.88–3.93 (m, 2H), 3.99 (ddd, *J* = 3.7, 7.8, 11.7 Hz, 1H), 4.05–4.09 (m, 2H), 4.20–4.23 (m, 2H), 5.09 (dd, *J* = 1.4, 8.9 Hz, 1H), 5.11 (dd, *J* = 1.4, 17.1 Hz, 1H), 5.77–5.85 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ10.0 (q), 25.5 (t), 33.6 (t), 37.8 (t), 39.9 (t),

46.4 (d), 74.3 (d), 79.5 (d, 2C), 87.0 (d), 87.9 (d), 117.3 (t), 134.2 (d) ppm; MS (ESI) m/z = 327.05 $[M+Na]^+$; HRMS (ESI) calcd for $C_{13}H_{21}BrO_3$ $[M+Na]^+$ 327.0572, 329.0572 and found 327.0564 and 329.0540.

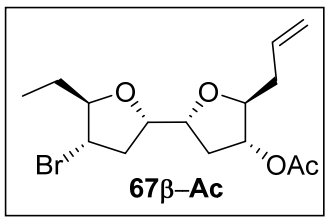
(2R,2'S,4R,4'S,5R,5'R)-5-Allyl-4'-bromo-5'-ethyloctahydro-[2,2'-bifuran]-4-yl acetate (67α–Ac)



67α–Ac

To a solution of **67α** (25 mg, 0.09 mmol) in CH_2Cl_2 (10 mL) at 0 °C was added Et_3N (0.07 mL, 0.49 mmol), DMAP (2 mg) and stirred for 15 min. To this, acetic anhydride (0.02 mL, 0.24 mmol) was added at 0 °C and stirred further for 2 h. The reaction mixture was diluted with CH_2Cl_2 (10 mL) and washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. The resulting crude product was purified by column chromatography (95:5 petroleum ether/EtOAc) to afford the aceate **67α–Ac** (27 mg, 95%) as colorless syrup: R_f (10% EtOAc/petroleum ether) 0.64; $[\alpha]^{25}_D$: −11.1 (*c* 0.6, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ1.00 (t, *J* = 7.3 Hz, 3H), 1.51 (dd, *J* = 7.3, 14.4 Hz, 1H), 1.70–1.80 (m, 1H), 1.87 (dd, *J* = 1.4, 5.4, 14.4 Hz, 1H), 2.07 (s, 3H), 2.28–2.50 (m, 4H), 2.71 (dt, *J* = 6.6, 13.2 Hz, 1H), 3.84 (ddd, *J* = 4.2, 6.9, 10.8 Hz, 1H), 3.95 (d, *J* = 6.8 Hz, 1H), 3.91–3.94 (m, 1H), 3.95–3.97 (m, 1H), 3.99–4.03 (m, 1H), 5.05–5.12 (m, 2H), 5.27 (br t, 1H), 5.75–5.85 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ9.9 (q), 21.0 (q), 25.5 (t), 33.6 (t), 36.2 (t), 39.4 (t), 47.7 (d), 74.3 (d), 79.5 (d), 79.7 (d), 81.3 (d), 87.0 (d), 117.1 (t), 134.2 (d), 178.8 (s) ppm; MS (ESI) m/z = 369.02, 370.91 $[M+Na]^+$; HRMS (ESI) calcd for $C_{15}H_{23}BrO_4$ $[M+Na]^+$ 369.0678, 371.0678 and found 369.0668 and 371.0646.

(2R,2'S,4R,4'S,5S,5'R)-5-allyl-4'-bromo-5'-ethyloctahydro-[2,2'-bifuran]-4-yl acetate (67β–Ac)

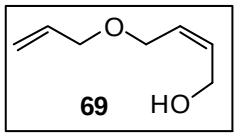


67β–Ac

To a solution of **67β** (15 mg, 0.05 mmol) in CH_2Cl_2 (10 mL) at 0 °C was added Et_3N (0.04 mL, 0.29 mmol), DMAP (2 mg) and stirred for 15 min. To this, acetic anhydride (0.01 mL, 0.14 mmol) was added at 0 °C and stirred further for 2 h. The reaction mixture was diluted with CH_2Cl_2 (10 mL) and washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. The resulting crude product was purified by column chromatography (95:5 petroleum ether/EtOAc) to afford the diaceate **67β–Ac** (15 mg, 88%) as colorless syrup: R_f (10% EtOAc/petroleum ether) 0.65;

$[\alpha]^{25}_{D}$: −5.8 (*c* 0.6, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz): δ1.00 (t, *J* = 7.5 Hz, 3H), 1.52 (dt, *J* = 7.3, 14.1 Hz, 1H), 1.70–1.78 (m, 1H), 1.96 (ddd, *J* =3.4, 5.3, 14.1 Hz, 1H), 2.06 (s, 3H), 2.24 (dt, *J* = 8.0, 13.4 Hz, 1H), 2.29 (t, *J* =6.8 Hz, 2H), 2.46 (dt, *J* = 7.3, 14.1 Hz, 1H), 2.70 (dt, *J* = 6.9, 13.4 Hz, 1H), 3.91 (dd, *J* =7.3, 15.3 Hz, 1H), 3.94 (dd, *J* =3.1, 7.3 Hz, 1H), 3.99 (dd, *J* = 7.0, 14.4 Hz, 1H), 4.08 (ddd, *J* = 3.1, 6.5, 9.5 Hz, 1H), 4.13 (td, *J* = 5.3, 7.3 Hz, 1H), 5.02 (dd, *J* = 3.0, 6.5 Hz, 1H), 5.09–5.15 (m, 2H), 5.77–5.85 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ9.9 (q), 21.1 (q), 25.5 (t), 34.2 (t), 37.4 (t), 39.8 (t), 47.6 (d), 77.5 (d), 79.3 (d), 80.1 (d), 83.1 (d), 87.0 (d), 117.7 (t), 133.6 (d), 170.6 (s) ppm; MS (ESI) m/z = 345.14 $[M-H]^+$; HRMS (ESI) calcd for $C_{15}H_{23}BrO_4$ $[M+Na]^+$ 369.0678, 371.0678 and found 369.0672 and 371.0649.

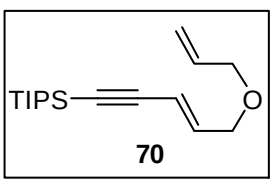
(*Z*)-4-(Allyloxy)but-2-en-1-ol (69)



69

The *cis*-2-butene-1,4-diol (10 g, 113.5 mmol) was dissolved in DMF (150 mL) under a N_2 atmosphere and cooled to 0 °C. To this, NaH (5.45 g, 136.2 mmol) was added followed by allyl bromide (8.83 mL, 102.1 mmol) after 15 minutes and then reaction mixture was allowed to warm to room temperature. After four hours, as indicated by TLC the reaction was complete. The reaction mixture was quenched very slowly with sat. NH_4Cl solution at 0 ^oC. The organic material was extracted with ether and washed with brine solution. The organic layer was dried with Na_2SO_4 and concentrated. Purification of the crude by column chromatography (80:20 petroleum ether/EtOAc) gave the pure monoallyl ether **69** (10.5 g, 72%) as a colorless oil: R_f (30% EtOAc/petroleum ether) 0.56; ^{1}H NMR ($CDCl_3$, 200 MHz): δ2.71 (br s, 1H), 3.96 (dt, *J* = 1.4, 5.7 Hz, 2H), 4.02 (dd, *J* = 0.8, 5.8 Hz, 2H), 4.16 (d, *J* = 5.9 Hz, 2H), 5.17 (ddd, *J* = 1.3, 2.9, 10.4 Hz, 1H), 5.26 (ddd, *J* = 1.6, 3.2, 17.2 Hz, 1H), 5.59–5.98 (m, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ58.3 (d), 65.5 (t), 71.2 (t), 117.3 (t), 127.8 (d), 132.3 (d), 134.3 (d) ppm; MS (ESI) m/z = 151.12 $[M+Na]^+$; HRMS (ESI) calcd for $C_7H_{12}O_2$ $[M+Na]^+$ 151.0735, found 151.0726.

(*E*)-(5-(allyloxy) pent-3-en-1-yn-1-yl)triisopropylsilane (70)



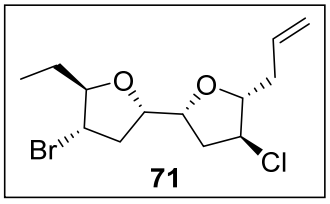
70

To a solution of **69** (100 mg, 0.78 mmol) in dry CH_2Cl_2 under N_2 atmosphere and PCC (219 mg, 1.01 mmol) mixed with 4 Å mol sieves (1 g) was added. The reaction mixture was stirred at rt until TLC indicated complete consumption of starting material. The chromium salts were removed by filtering through a large plug of silica gel and washing with

diethyl ether. The aldehyde was further purified by flash column chromatography (90:10 petroleum ether/EtOAc) to afford the pure aldehyde (90 mg, 91%) which was used directly for for next reaction.

At −78 °C, a solution of TMS-diazomethane (0.4 mL, 2.0 M solution in hexane) in THF (15 mL) was treated with *n*-BuLi (0.6 mL, 1.5 M solution in hexane) and stirred for 15 min. To this the above prepared aldehyde (90 mg, 0.71 mmol) was added and stirred for another 10 min by then the TLC showed the complete disappearance of aldehyde. The reaction was allowed to warm to −30 °C wherein the TLC showed a new UV-active, non-polar spot. The reaction mixture was again cooled to −78 °C and an additional 0.6 mL of n-BuLi was added and stirring 10 min before introducing the TIPSCl (0.23 mL, 1.07 mmol). Then the the reaction was allowed to warm to room temperature over 1 h. The reaction was quenched with a small amount of water, and dried with $MgSO_4$ and concentrated. The resulting crude was purified by column chromatography (98:2 petroleum ether/EtOAc) to afford the pure allyl ether **70** (120 mg, 60%) as a colorless oil: R_f (10% EtOAc/petroleum ether) 0.73; ^{1}H NMR ($CDCl_3$, 200 MHz): δ1.06 (s, 3H), 1.08 (s, 18H), 4.00 (dt, *J* = 1.5, 5.6 Hz, 2H), 4.04 (dd, *J* = 1.6, 5.4 Hz, 2H), 5.21 (ddd, *J* = 1.4, 3.0, 10.4 Hz, 1H), 5.30 (ddd, *J* = 1.6, 3.3, 17.2 Hz, 1H), 5.79 (dt, *J* = 1.8, 16.0 Hz, 1H), 5.85–6.01 (m, 1H), 6.24 (dt, *J* = 5.4, 16.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ11.3 (d, 3C), 18.6 (q, 6C), 69.7 (t), 71.3 (t), 96.2 (s), 104.9 (s), 112.0 (d), 117.1 (t),134.5 (d), 140.2 (d) ppm; MS (ESI) m/z = 278.93 $[M+H]^+$; HRMS (ESI) calcd for $C_{17}H_{30}OSi[M+Na]^+$ 301.1964, found 301.1405.

(2R,2'S,4S,4'S,5R,5'R)-5-allyl-4'-bromo-4-chloro-5'-ethyloctahydro-2,2'-bifuran (71)

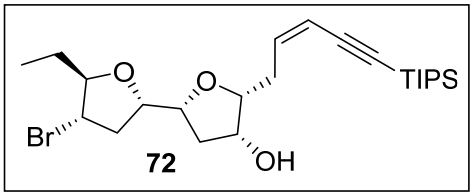


71

To a stirred solution of the alcohol **67**α (60 mg, 0.2 mmol) in CH_2Cl_2 (10 mL) at 0 °C was added pyridine (0.16 mL, 2 mmol) and trifluoromethanesufonic anhydride (0.1 mL, 0.6 mmol). The reaction mixture was stirred at rt for 0.5 h and then quenched by the addition of saturated aqueous $NaHCO_3$ (5 mL). The organic phase was separated and the aqueous phase was extracted with CH_2Cl_2 (2 × 10 mL). The organic phases were washed with saturated aqueous $CuSO_4$ solution (2 × 10 mL) and dried ($MgSO_4$). The solvent was removed in *vacuo* and the crude triflate was briefly dried under high vacuum. Tetra-*n*-butylammonium chloride (152 mg, 0.55 mmol) and toluene (20 mL) were added to the

crude triflate and the resulting suspension was placed in a preheated oil bath (120 °C) and reflux for 2.5 h. The cooled reaction mixture was filtered through a silica gel plug and washed with ether. The solvent was removed and the residue was dissolved in methanol (30 mL), and Amberlyst IR-120 was added and the reaction mixture was stirred overnight. The reaction mixture was filtered and the solvent was removed in *vacuo*. Purfication by the crude flash chromatography (petroleum ether:EtOAc, 95:5) gave the title compound **71** as a clear and colourless oil (27 mg, 42%); R_f (10% EtOAc/petroleum ether) 0.6; $[\alpha]^{25}_D$: +113.4 (*c* 0.14, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz): δ1.00 (t, *J* = 7.3 Hz, 3H), 1.48–1.54 (m, 1H), 1.71–1.78 (m, 1H), 2.14 (dt, *J* = 8.5, 13.1 Hz, 1H), 2.31 (ddd, *J* = 4.6, 9.5, 14.0 Hz, 1H), 2.39 (d, *J* = 6.1 Hz, 1H), 2.42–2.49 (m, 1H), 2.51–2.57 (m, 1H), 2.67 (dt, *J* = 6.7, 13.2 Hz, 1H), 3.88 (dd, *J* = 7.6, 15.6 Hz, 1H), 3.91–3.95 (m, 1H), 4.02–4.07 (m, 2H), 4.41 (dt, *J* = 5.5, 9.4 Hz, 1H) 4.48 (t, *J* = 3.4 Hz, 1H), 5.10 (d, *J* = 10.4 Hz, 1H), 5.19 (d, *J* = 17.4 Hz, 1H), 5.76–5.84 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 9.9 (q), 25.4 (t), 35.7 (t), 39.0 (t), 39.5 (t), 47.3 (d), 62.4 (d), 79.3 (d, 2C), 82.1 (d), 87.2 (d), 117.8 (t), 133.5 (d) ppm; MS (ESI) m/z = 345.06 $[M+Na]^+$; HRMS (ESI) calcd for $C_{13}H_{20}BrClO_2$ $[M+Na]^+$ 345.0233, 347.0233 and found 345.0225 and 347.0198.

(2R,2'S,4R,4'S,5R,5'R)-4'-bromo-5'-ethyl-5-((Z)-5-(triisopropylsilyl)pent-2-en-4-yn-1-yl)octahydro-[2,2'-bifuran]-4-ol(72)

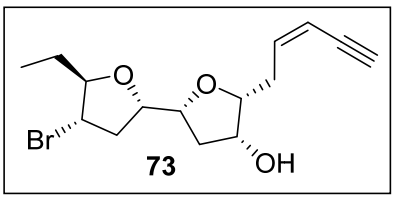


72

To a solution of **67**α (36 mg, 0.12 mmol, 1.0 eq.) in dry benzene (5 mL) were added TIPS-enyne **70** (98.5 mg, 0.35 mmol) in benzene (1 mL) and Hoveyda-Grubbs 2nd generation catalyst (15 mg, 0.02 mmol) in benzene (1 mL) at rt under nitrogen atmosphere. The reaction mixture was stirred at 60 °C for 1.5 h. Addition of TIPS-enyne **70** (98.5 mg, 0.35 mmol) in benzene (1 mL) and catalyst (15 mg, 0.02 mmol) in benzene (1 mL) was repeated three times for every 1.5 h. Dimethyl sulfoxide (0.4 mL, 50 equiv per 1 equiv Grubbs' cat.) was added to the solution, and it was stirred open to the air for 15 h. The reaction mixture was concentrated in vacuo. The residue was purified by column chromatography (petroleum ether:EtOAc, 92:8) to yield *cis*-enyne **72** (49 mg, 86%) as a colourless oil R_f (10% EtOAc/petroleum ether) 0.64; $[\alpha]^{25}_D$: +20.8 (*c* 0.4, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz): δ1.03 (t, *J* = 7.5 Hz, 3H), 1.09 (s, 21H), 1.53 (ddd, *J* = 7.3, 14.9, 21.5 Hz, 1H), 1.80–1.88 (m, 1H), 1.92–1.97 (m, 2H), 2.26 (ddd, *J* = 5.1, 9.8, 14.9 Hz, 1H), 2.61 (dt, *J* = 6.4, 12.9 Hz, 1H), 2.68–2.80 (m, 2H), 3.73 (ddd, *J* = 2.4, 6.4, 8.8 Hz, 1H), 3.76 (d, *J* = 10.5 Hz, 1H), 3.87 (ddd, *J* = 6.9, 10.3, 15.4 Hz, 1H), 3.95 (td, *J* = 3.4, 8.3 Hz,

1H), 4.02 (ddd, *J* = 2.2, 4.7, 10.0 Hz, 1H), 4.12 (dt, *J* = 2.5, 9.8, Hz, 1H), 4.22 (ddd, *J* = 2.0, 6.1, 10.6 Hz, 1H), 5.63 (dt, *J* = 1.2, 10.8 Hz, 1H), 6.08 (dt, *J* = 7.6, 10.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ10.1 (q), 11.3 (d, 3C), 18.6 (q, 6C), 25.5 (t), 30.3 (t), 34.7 (t), 39.7 (t), 46.4 (d), 71.3 (d), 79.1 (d), 79.1 (d), 83.2 (d), 87.8 (d), 95.8 (s), 103.4 (s), 111.4 (d), 140.8 (d) ppm; MS (ESI) m/z = 506.79 $[M+Na]^+$; HRMS (ESI) calcd for $C_{24}H_{41}BrO_3Si$ $[M+Na]^+$ 507.1906, 509.1906 and found 507.1902 and 509.1881.

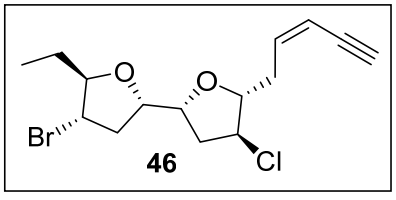
(2R,2'S,4R,4'S,5R,5'R)-4'-bromo-5'-ethyl-5-((Z)-pent-2-en-4-yn-1-yl)octahydro-[2,2'-bifuran]-4-ol (73)



73

To an ice cooled solution of the TIPS-enyne **72** (25 mg, 0.05 mmol) in THF (10 mL), TBAF (20 mg, 0.08 mmol) was added and stirred for 0.5 h at –20 ^{o}C. The reaction mixture was quenched by adding few drops of Et_3N. Solvent was evaporated under reduced pressure, and the residue was purified by column chromatography (90:10 petroleum ether/EtOAc) to afford **75** (12 mg, 93%) as colorless syrup: R_f (20% EtOAc/petroleum ether) 0.6; $[\alpha]^{25}_D$: –44.7 (*c* 0.75, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ1.03 (t, *J* = 7.5 Hz, 3H), 1.54 (dt, *J* = 7.1, 14.2 Hz, 1H), 1.79–1.87 (m, 1H), 1.89–2.00 (m, 2H), 2.29 (ddd, *J* = 5.1, 10.0, 14.9 Hz, 1H), 2.62 (dt, *J* = 6.4, 12.9 Hz, 1H), 2.67–2.80 (m, 2H), 3.11 (d, *J* = 2.0 Hz, 1H), 3.71 (ddd, *J* = 2.5, 6.9, 9.4 Hz, 1H), 3.79 (d, *J* = 10.5 Hz, 1H), 3.87 (ddd, *J* = 7.1, 10.0, 15.2 Hz, 1H), 3.96 (ddd, *J* = 3.4, 8.1, 11.7 Hz, 1H), 4.05 (br s, 1H), 4.12 (dt, *J* = 2.5, 9.8 Hz, 1H), 4.21 (ddd, *J* = 2.0, 6.1, 10.5 Hz, 1H), 5.56 (dt, *J* = 1.0, 11.0 Hz, 1H), 6.14 (dt, *J* = 7.6, 11.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ10.1 (q), 25.5 (t), 30.2 (t), 34.8 (t), 39.8 (t), 46.4 (d), 71.2 (d), 79.1 (d), 79.1 (d), 80.2 (s), 82.1 (s), 83.0 (d), 87.9 (s), 110.0 (d), 141.8 (d) ppm; MS (ESI) m/z = 351.03 $[M+Na]^+$; HRMS (ESI) calcd for $C_{15}H_{21}BrO_3$ $[M+Na]^+$ 351.0572, 353.0572 and found 351.0562 and 353.0540.

(2S,2'R,4S,4'S,5R,5'R)-4-bromo-4'-chloro-5-ethyl-5'-((Z)-pent-2-en-4-yn-1-yl)octahydro-2,2'-bifuran (46)

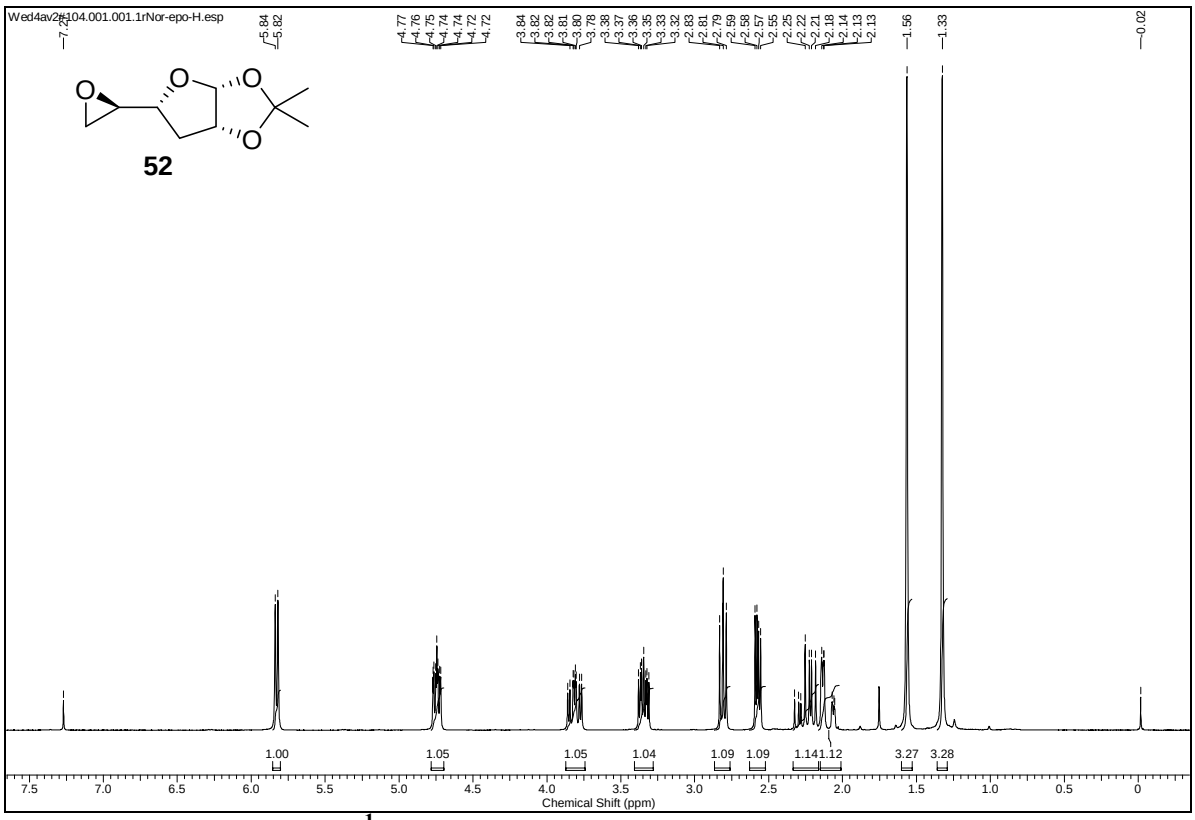


46

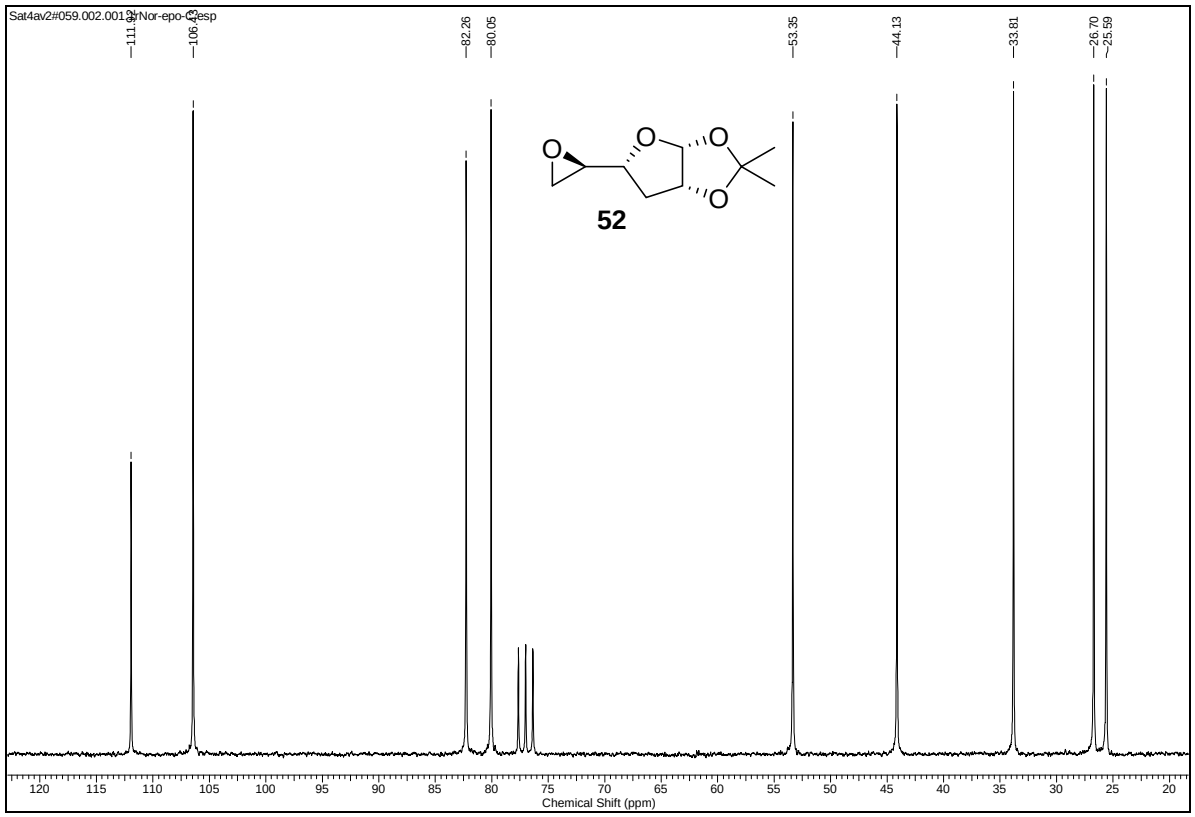
The procedure used in the preparation of **71** has been adopted for the convertion of alcohol **73** (50 mg, 0.15 mmol) in into the title compound **46** as a clear and colourless oil (17 mg, 32%); R_f (10% EtOAc/petroleum ether) 0.55; $[\alpha]^{25}_D$: –0.96 (*c* 0.13, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ0.95 (t, *J* = 7.3 Hz, 3H), 1.45–1.49 (m,

1H), 1.70 (dd, *J* = 6.7, 14.2 Hz, 1H), 1.78 (dd, *J* = 7.4, 14.3 Hz, 1H), 2.23–2.27 (m, 2H), 2.32 (dd, *J* = 4.9, 9.1 Hz, 1H), 2.40 (dd, *J* = 6.1, 13.7 Hz, 1H), 2.63 (dt, *J* = 6.9, 14.2 Hz, 1H), 3.13 (d, *J* = 2.2 Hz, 1H), 3.91 (ddd, *J* = 2.9, 6.9, 9.5 Hz, 1H), 4.09–4.12 (m, 2H), 4.20–4.25 (m, 1H), 4.31 (dt, *J* = 5.6, 9.1 Hz, 1H), 4.48 (t, *J* = 3.7 Hz, 1H), 5.61 (dt, *J* = 1.0, 10.8 Hz, 1H), 6.07 (dt, *J* = 7.3, 10.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ10.1 (q), 24.3 (t), 34.6 (t), 38.4 (t), 39.4 (t), 47.4 (d), 59.4 (d), 78.6 (d), 80.1 (d), 80.2 (d), 82.3 (d), 84.2 (d), 86.2 (d), 111.1 (d), 139.8 (d) ppm; HRMS (ESI) calcd for $C_{15}H_{20}BrClO_2$ $[M+Na]^+$ 369.0233, 371.0233 and found 369.0231 and 371.0207.

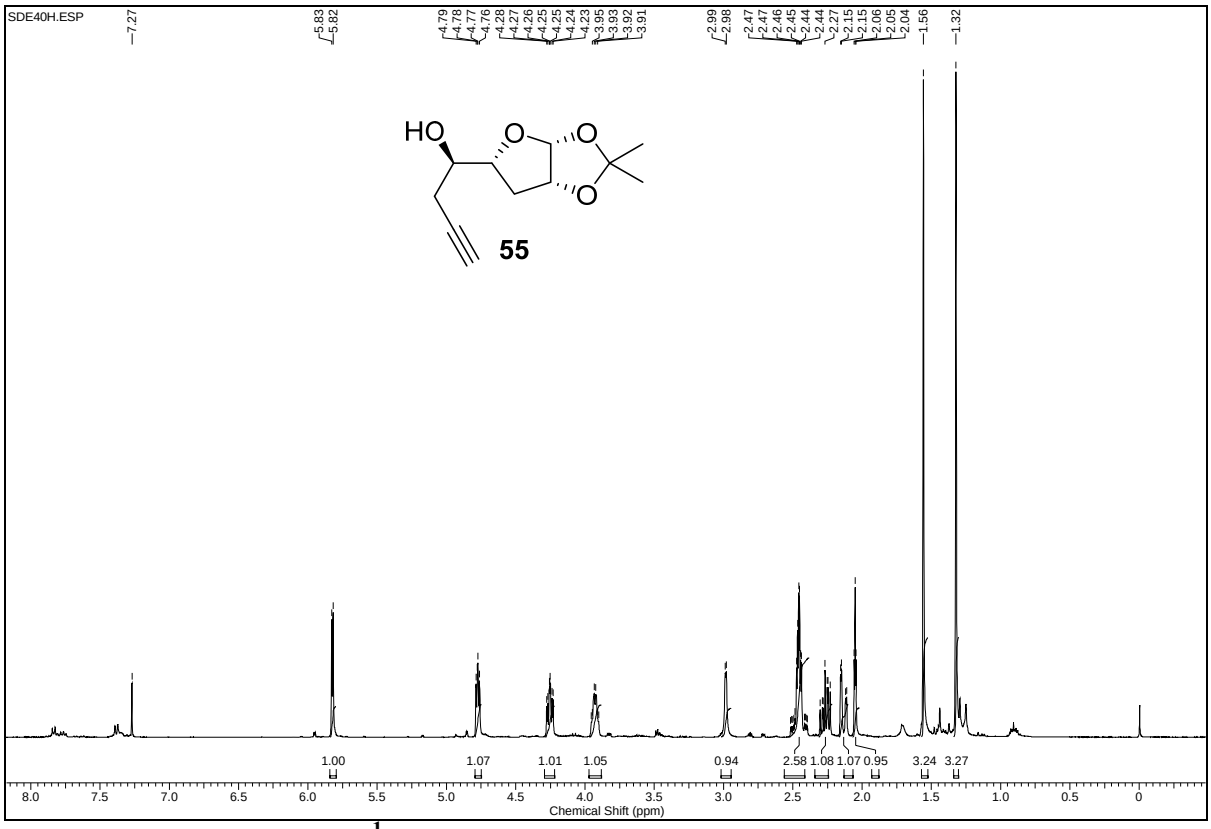
SPECTRA



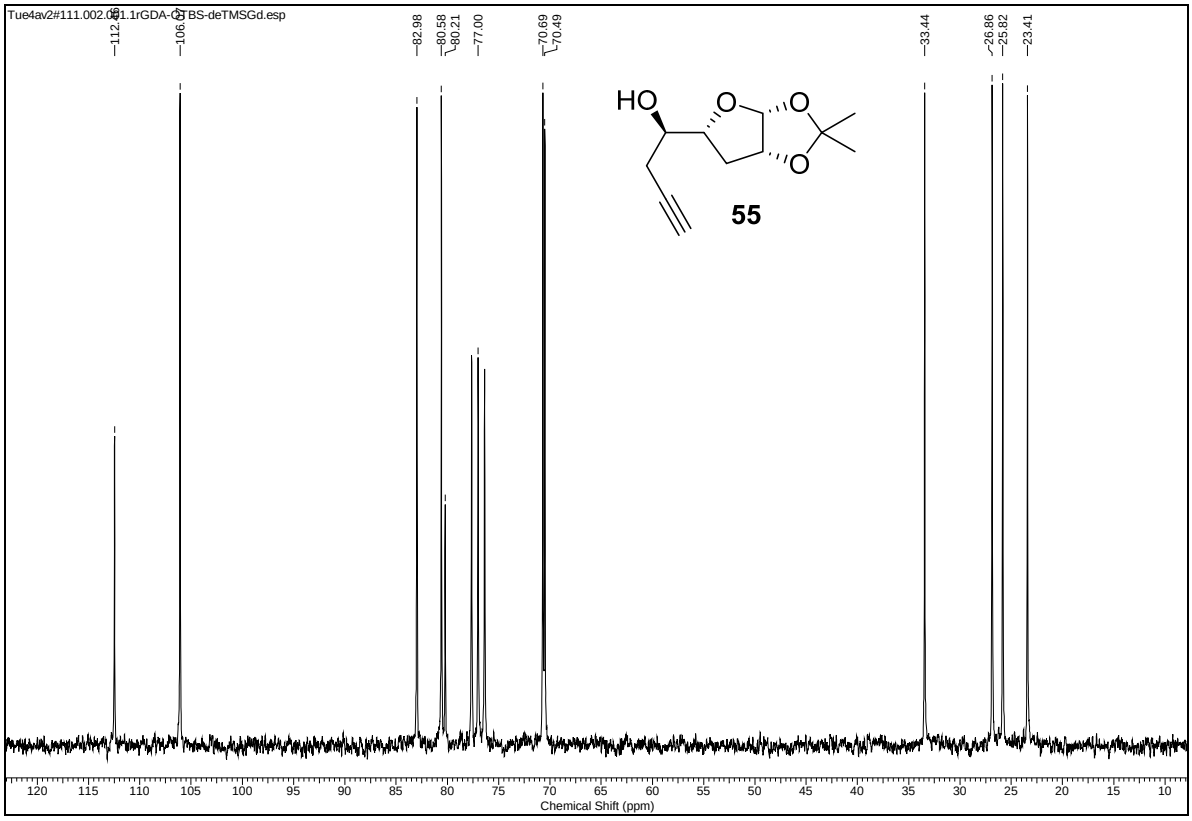
^{1}H NMR Spectrum of 52 in $CDCl_3$



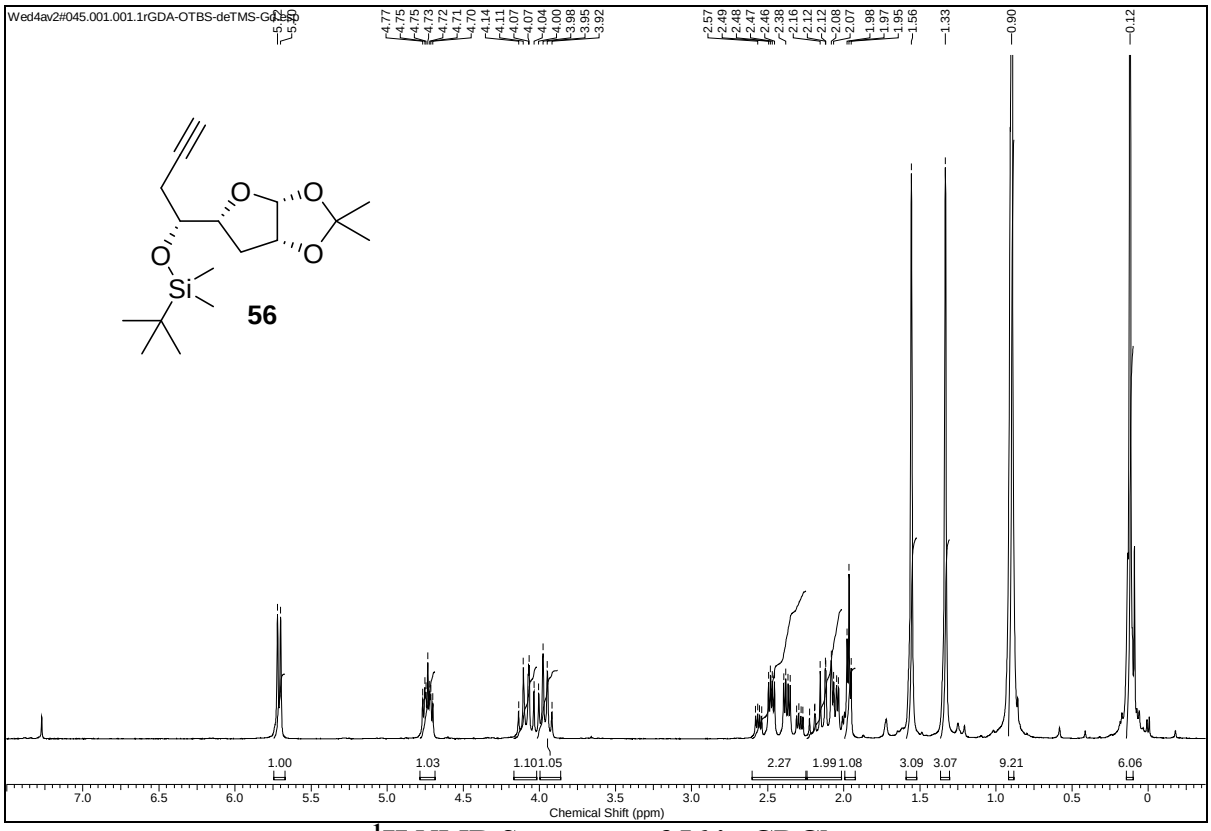
^{13}C NMR Spectrum of 52 in $CDCl_3$



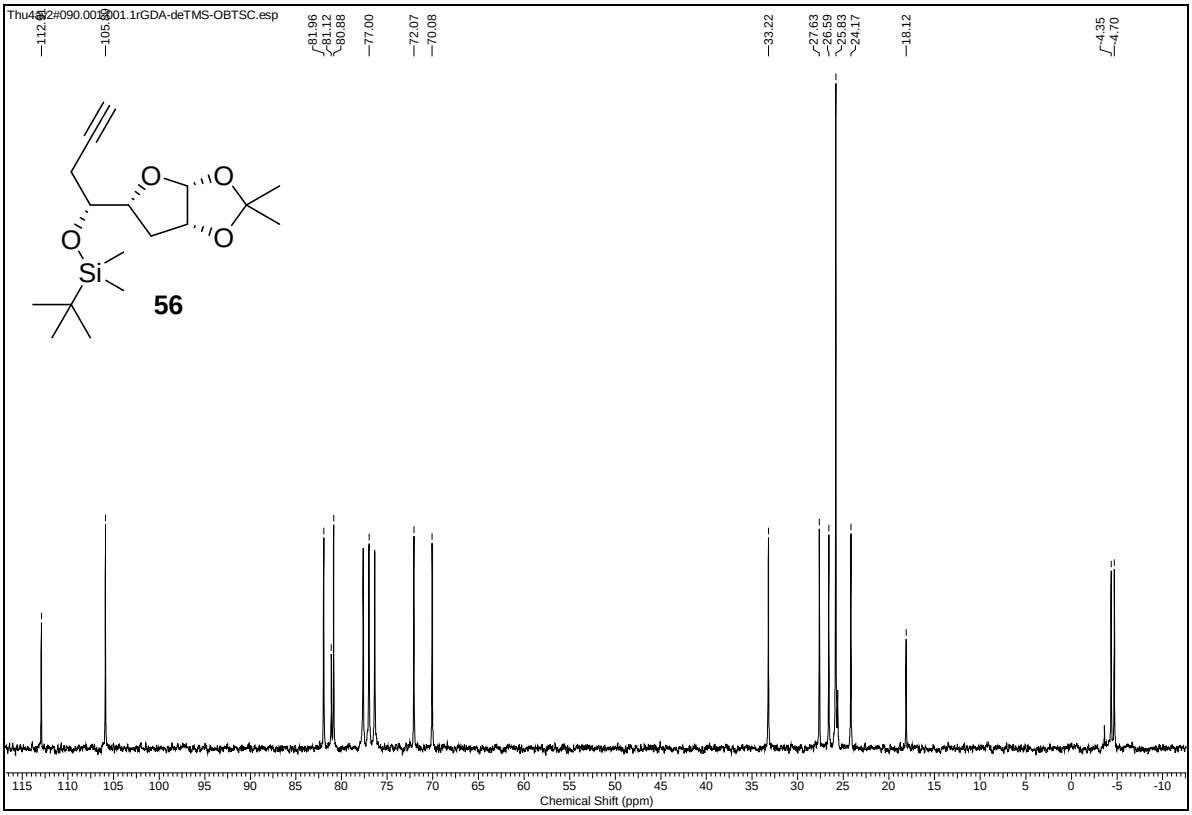
^{1}H NMR Spectrum of 55 in $CDCl_3$



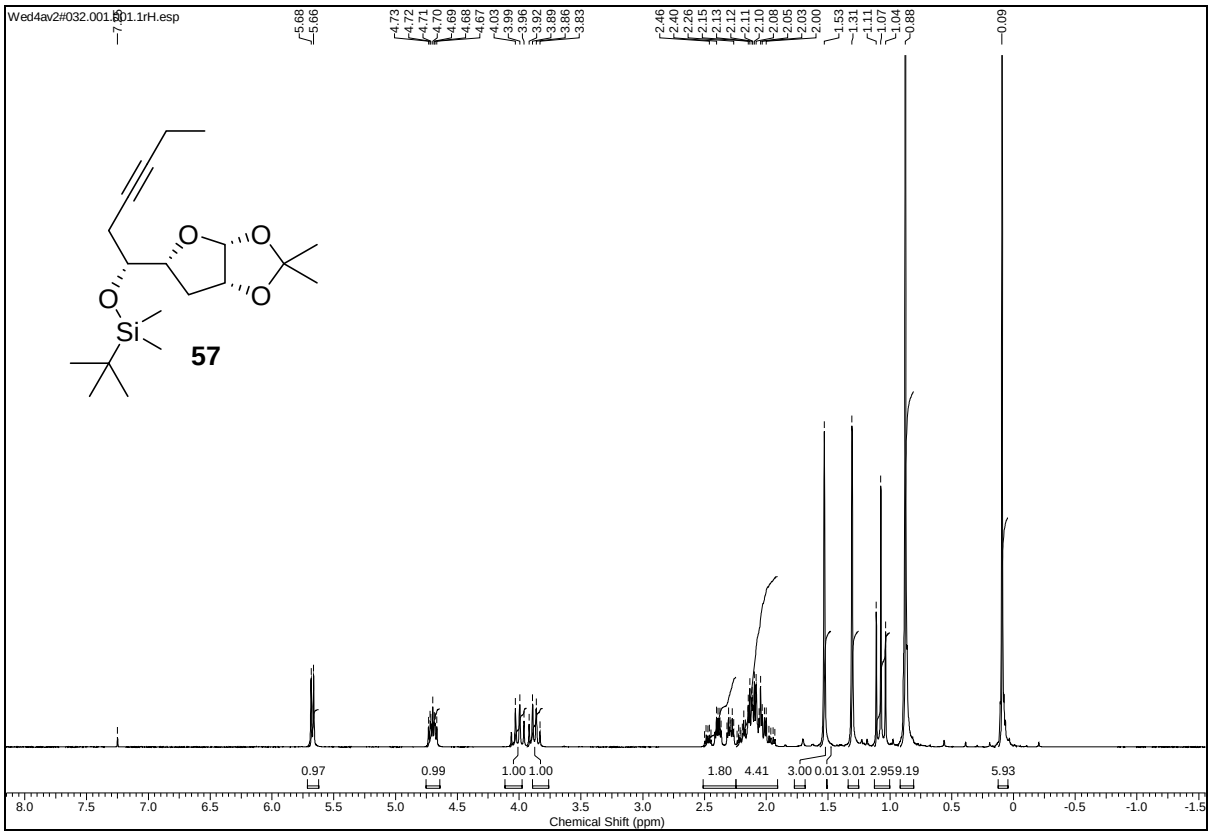
^{13}C NMR Spectrum of 55 in $CDCl_3$



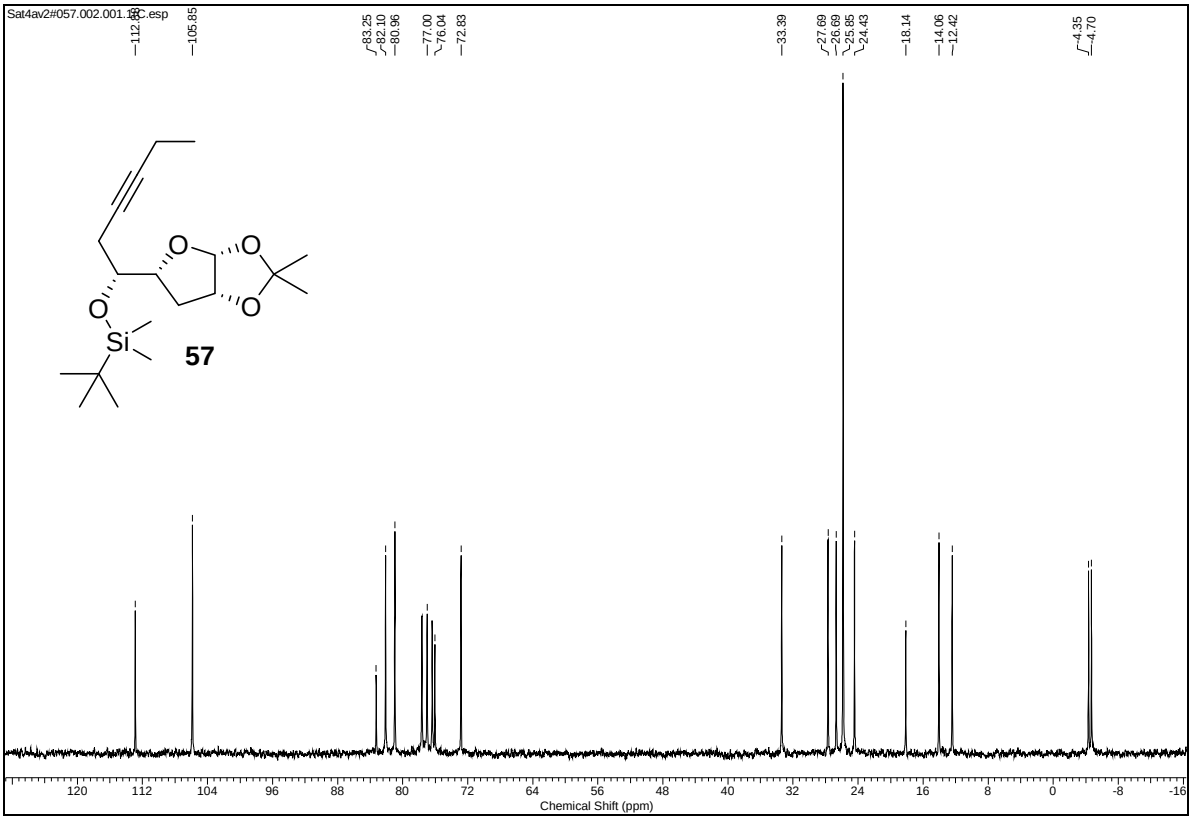
^{1}H NMR Spectrum of 56 in $CDCl_3$



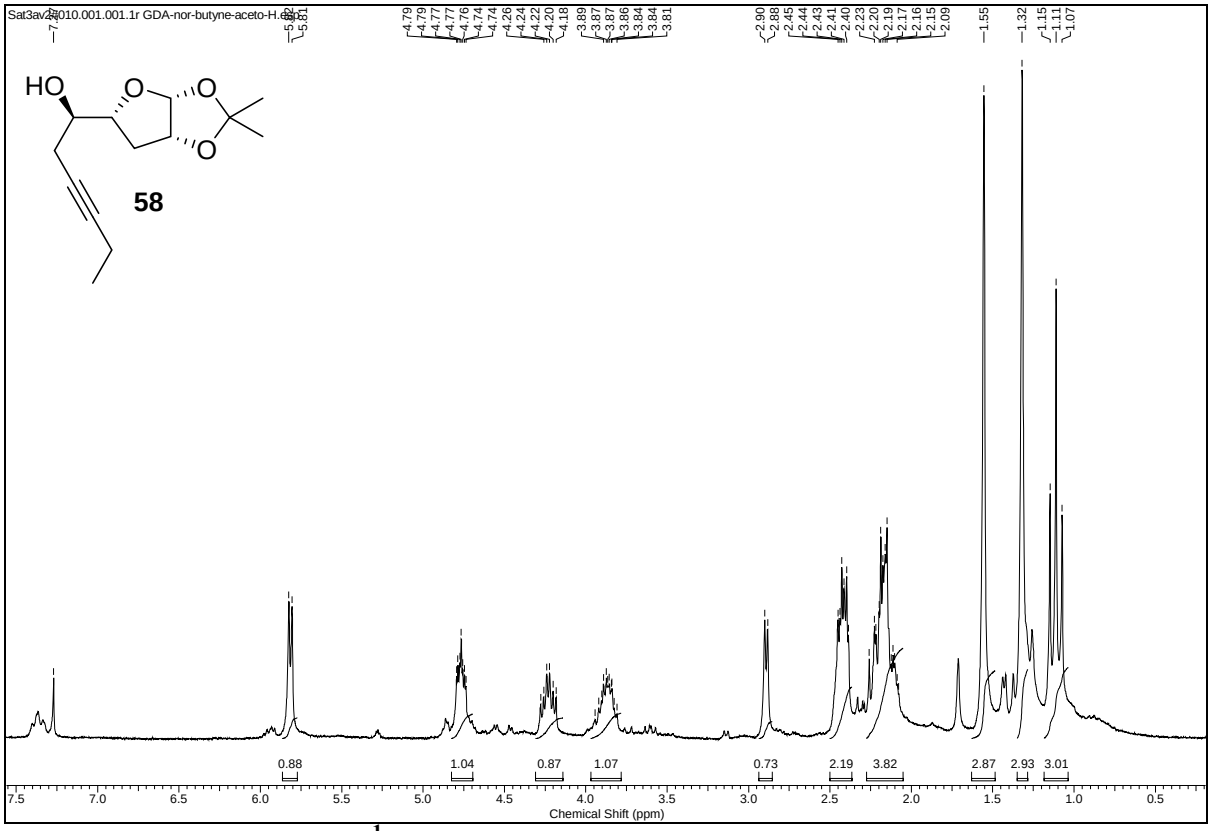
^{13}C NMR Spectrum of 56 in $CDCl_3$



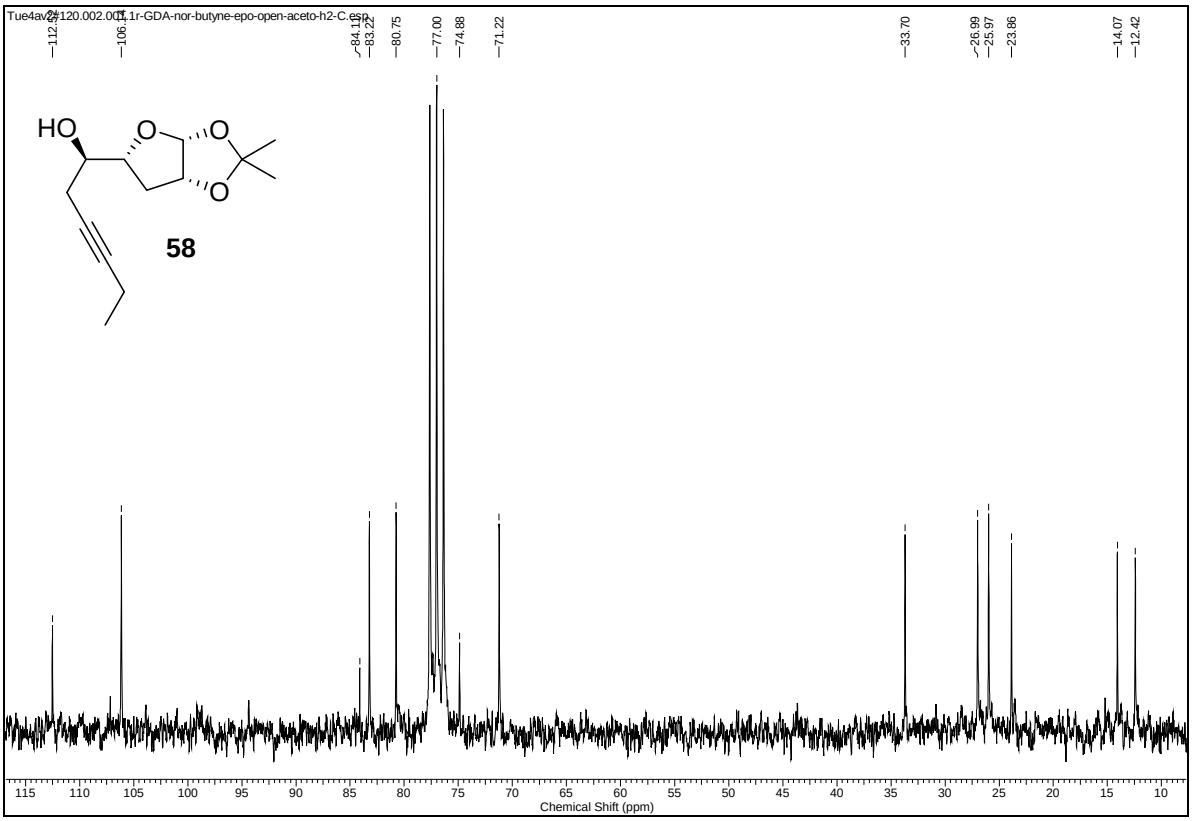
^{1}H NMR Spectrum of 57 in $CDCl_3$



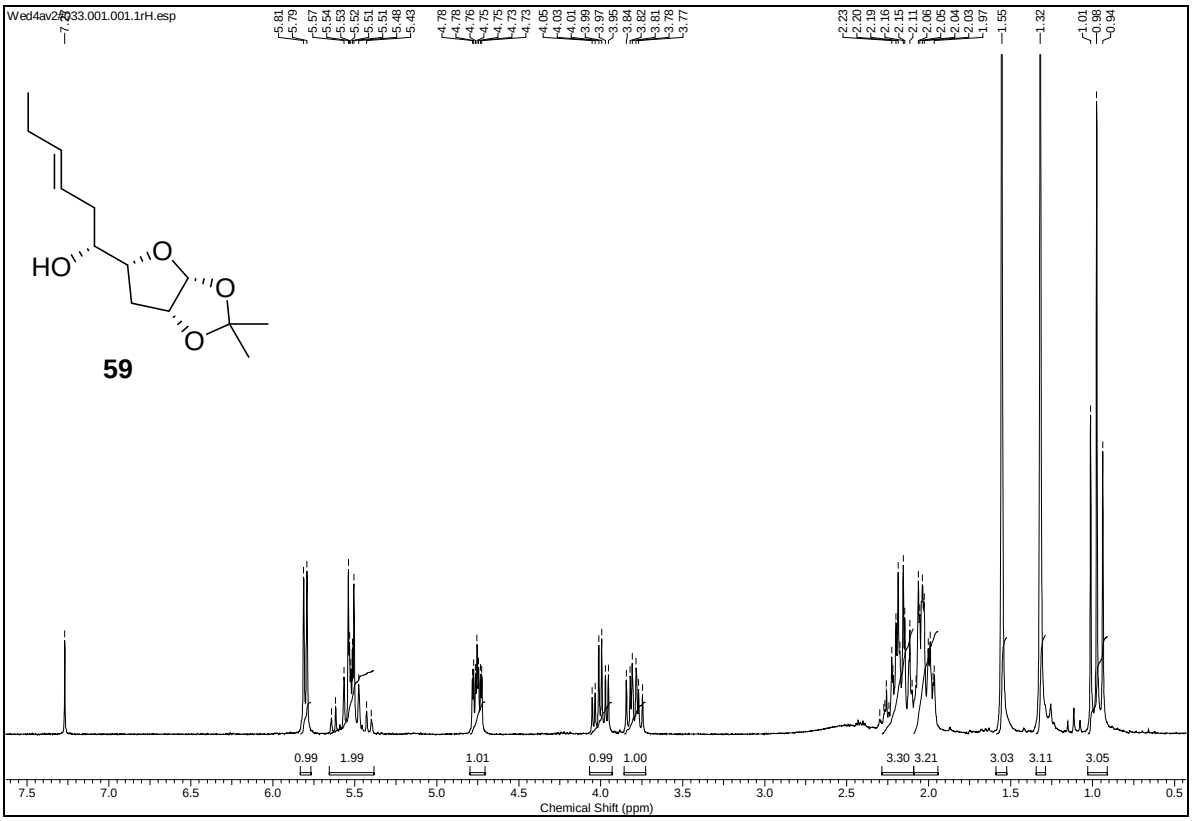
^{13}C NMR Spectrum of 57 in $CDCl_3$



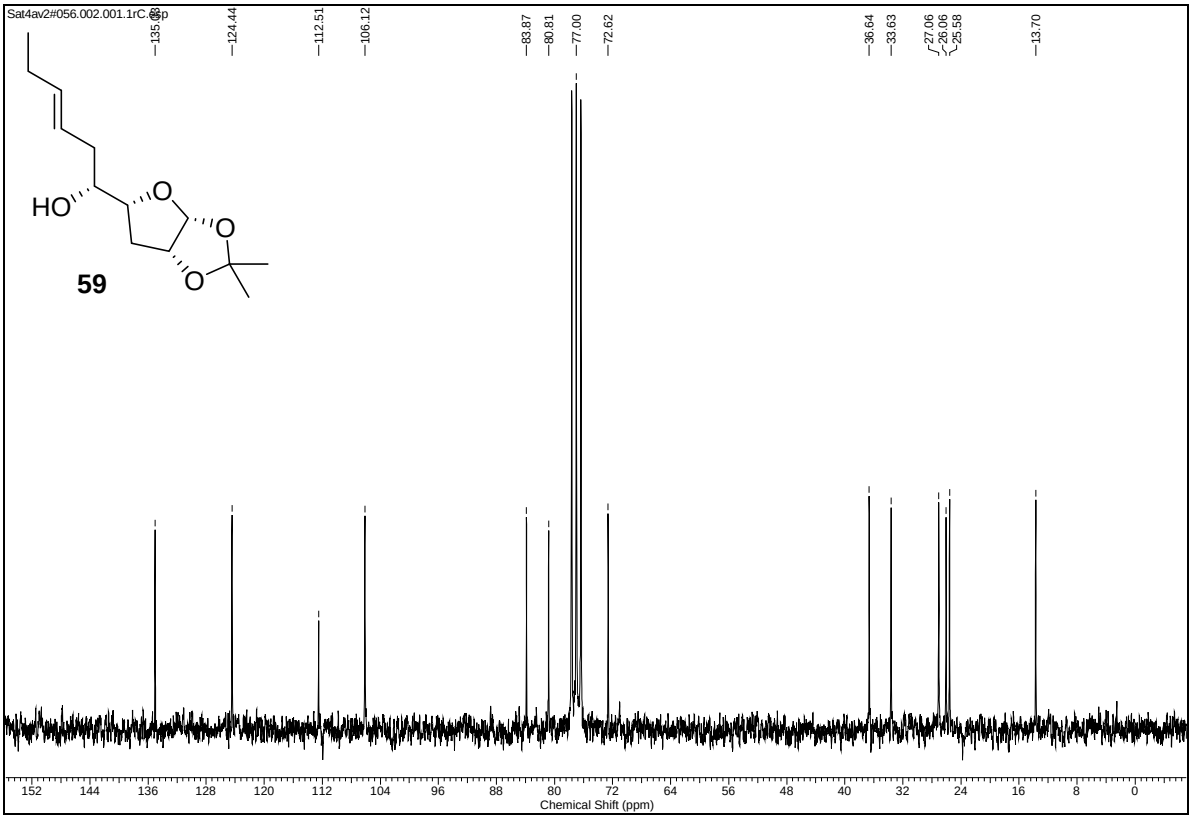
^{1}H NMR Spectrum of 58 in $CDCl_3$



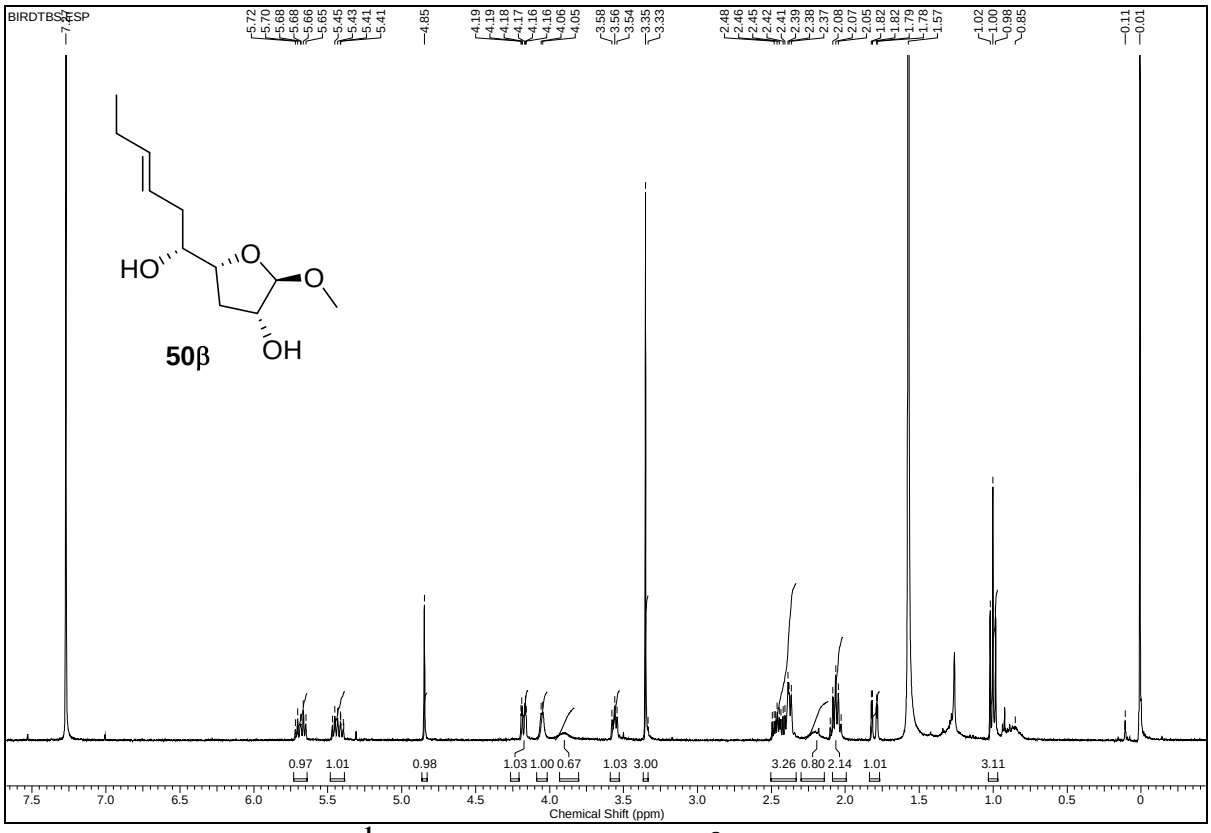
^{13}C NMR Spectrum of 58 in $CDCl_3$



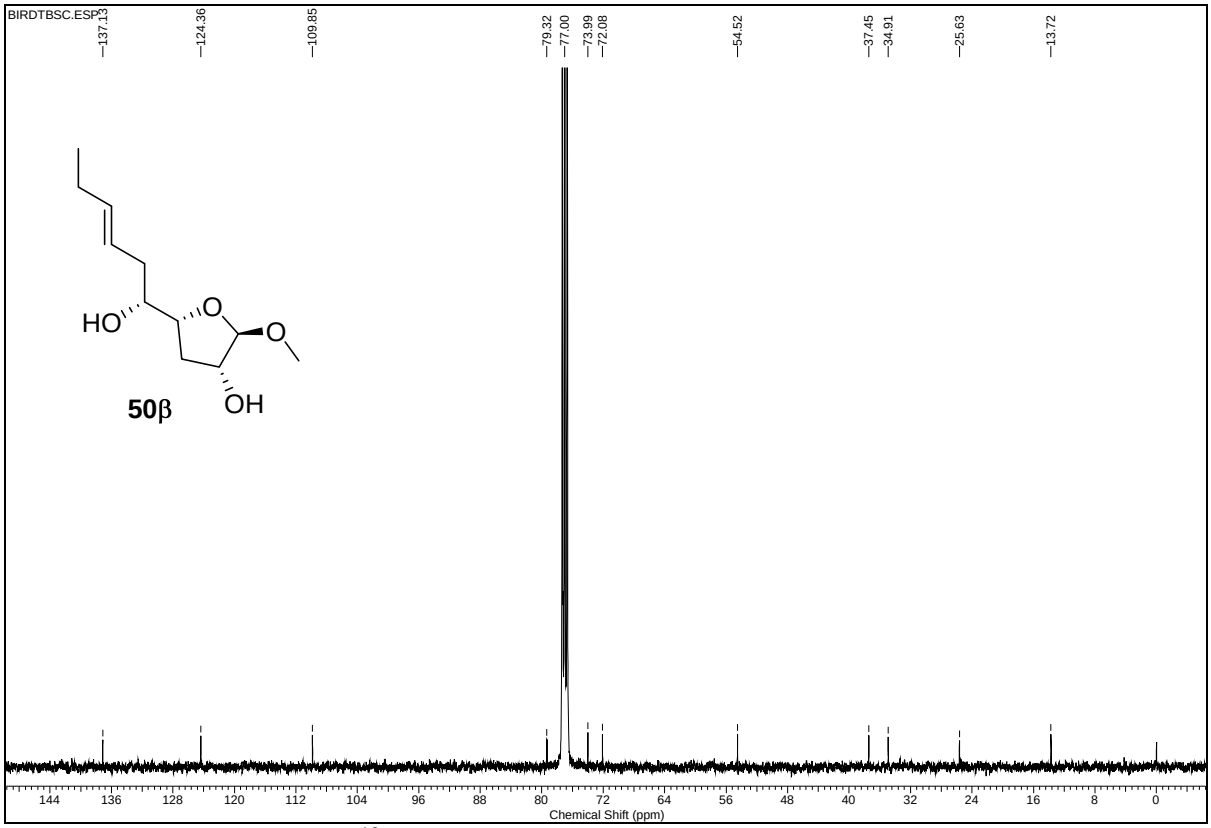
^{1}H NMR Spectrum of 59 in $CDCl_3$



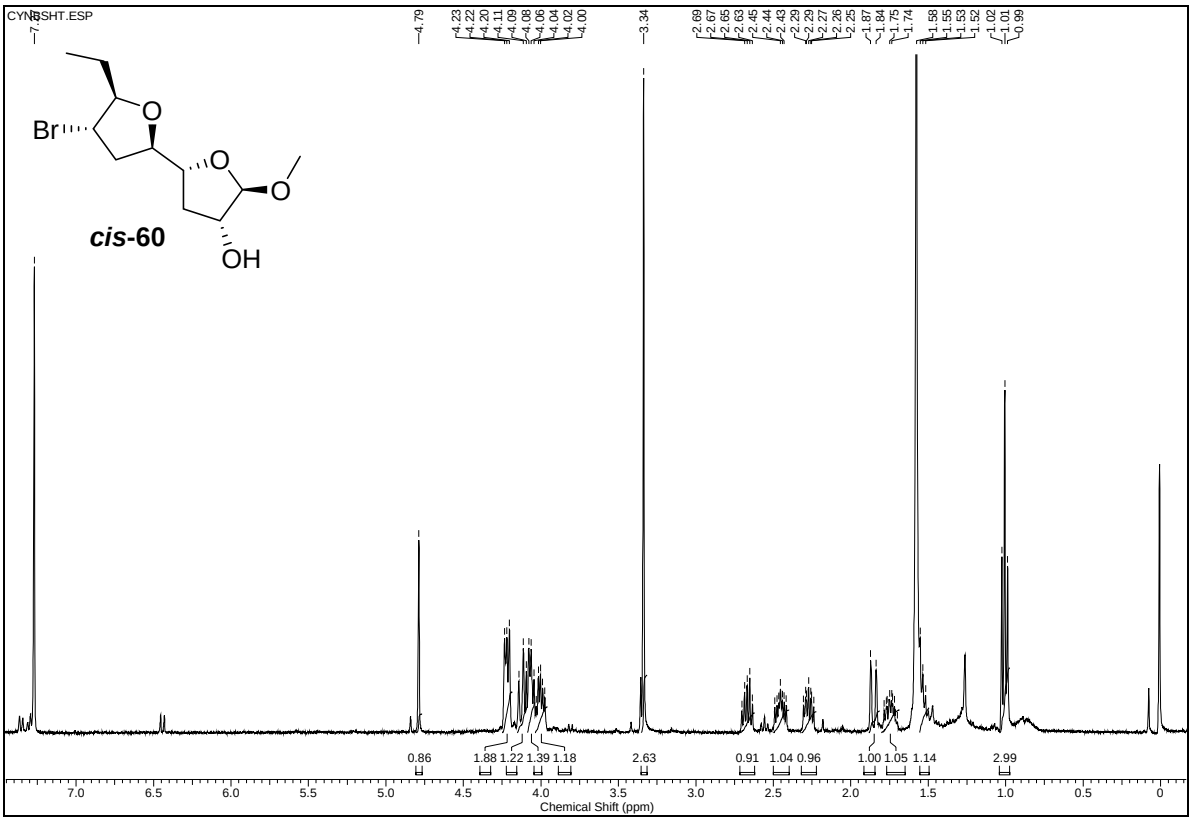
^{13}C NMR Spectrum of 59 in $CDCl_3$



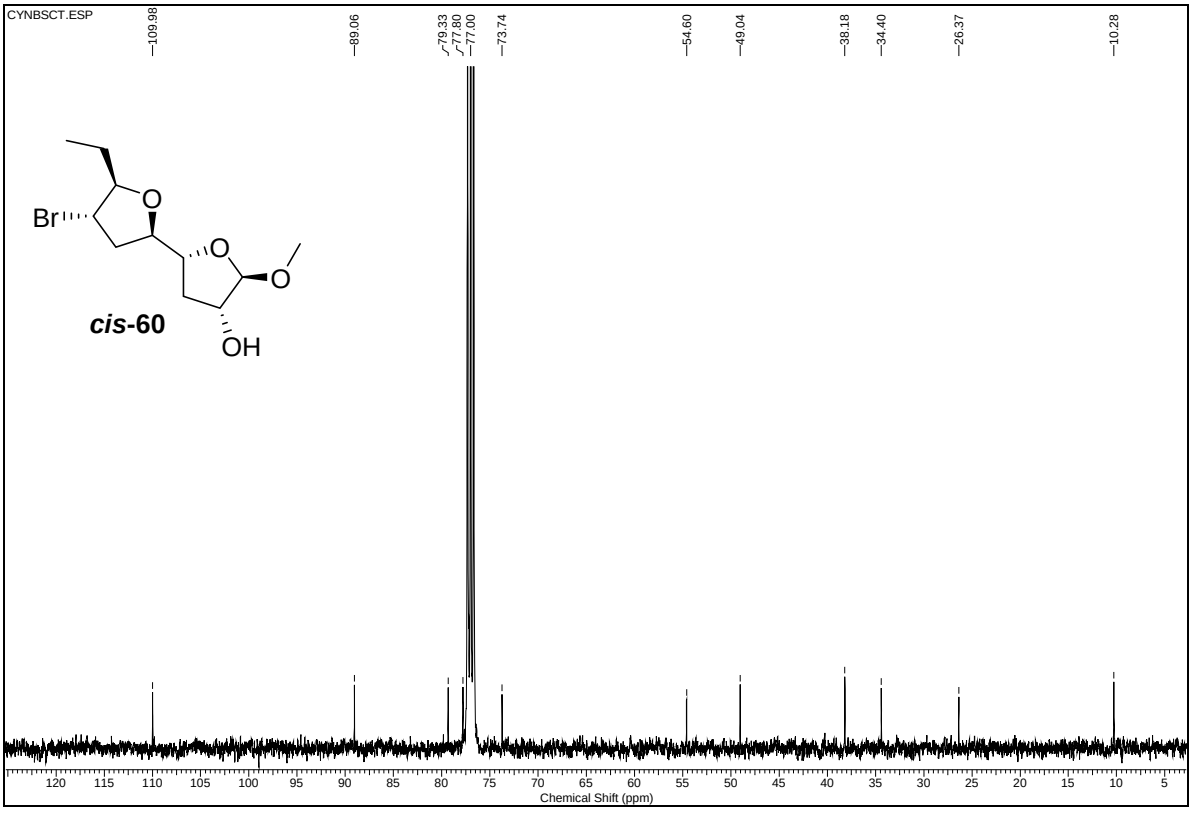
^{1}H NMR Spectrum of 50β in $CDCl_3$



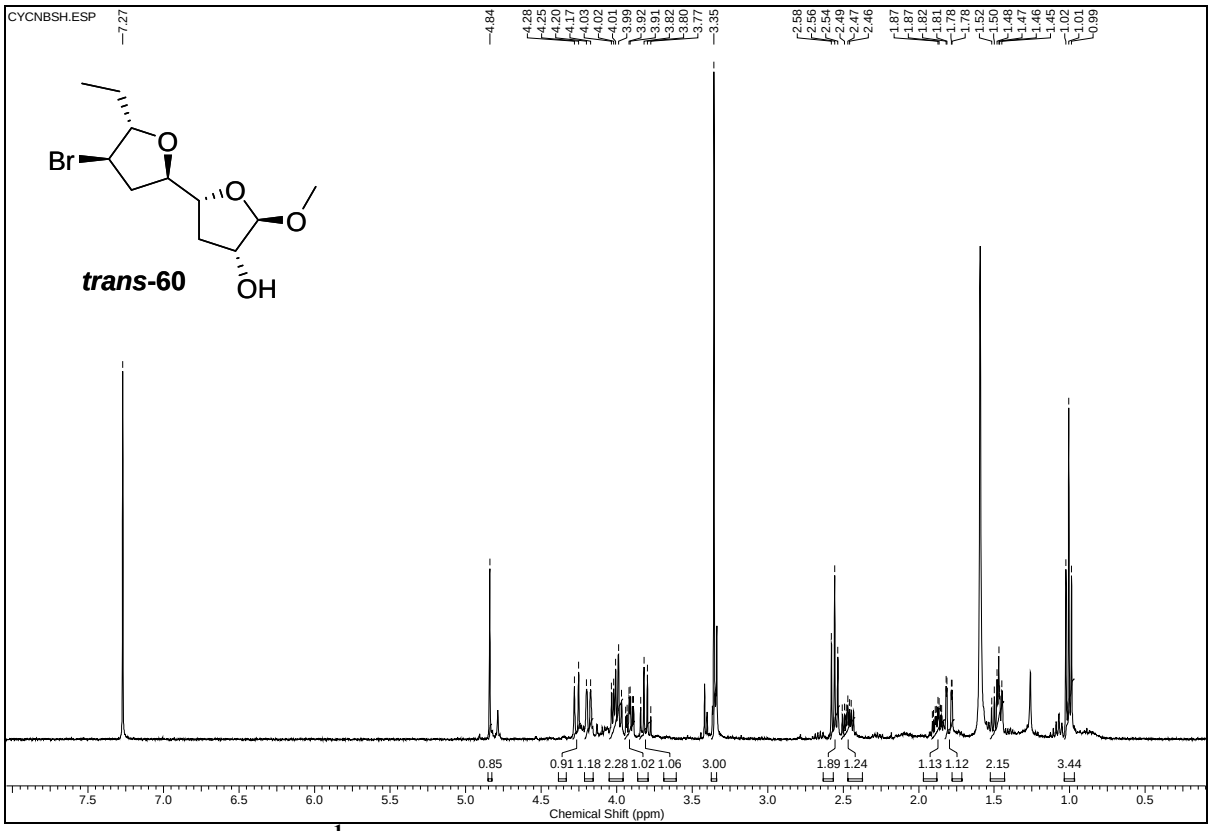
^{13}C NMR Spectrum of 50β in $CDCl_3$



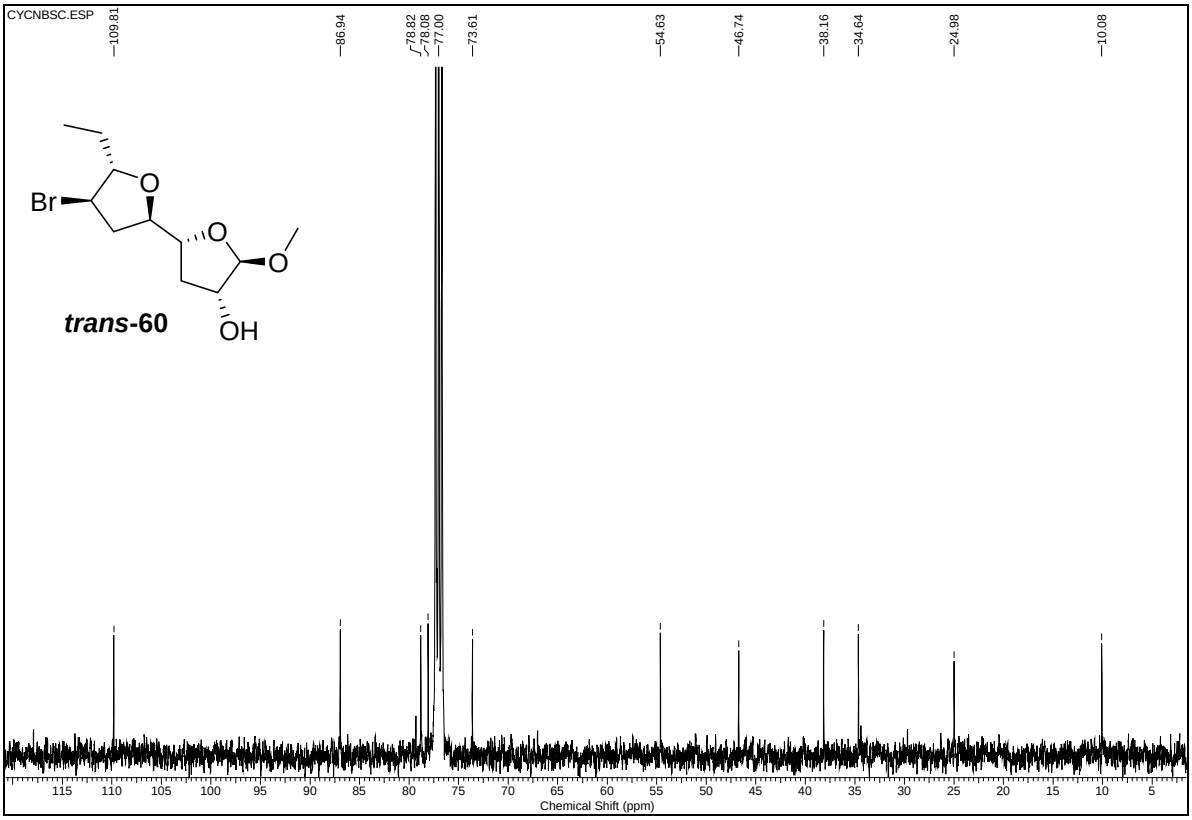
^{1}H NMR Spectrum of *cis*-60 in $CDCl_3$



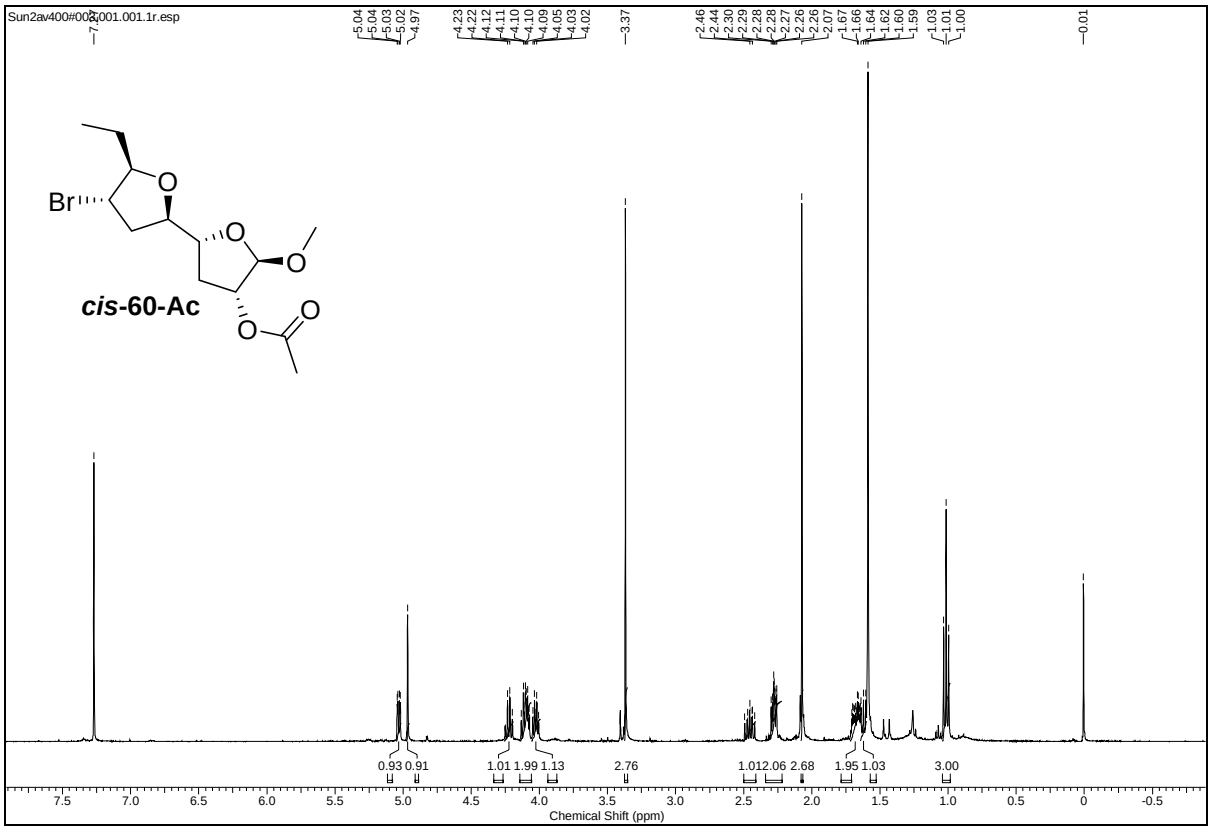
^{13}C NMR Spectrum of *cis*-60 in $CDCl_3$



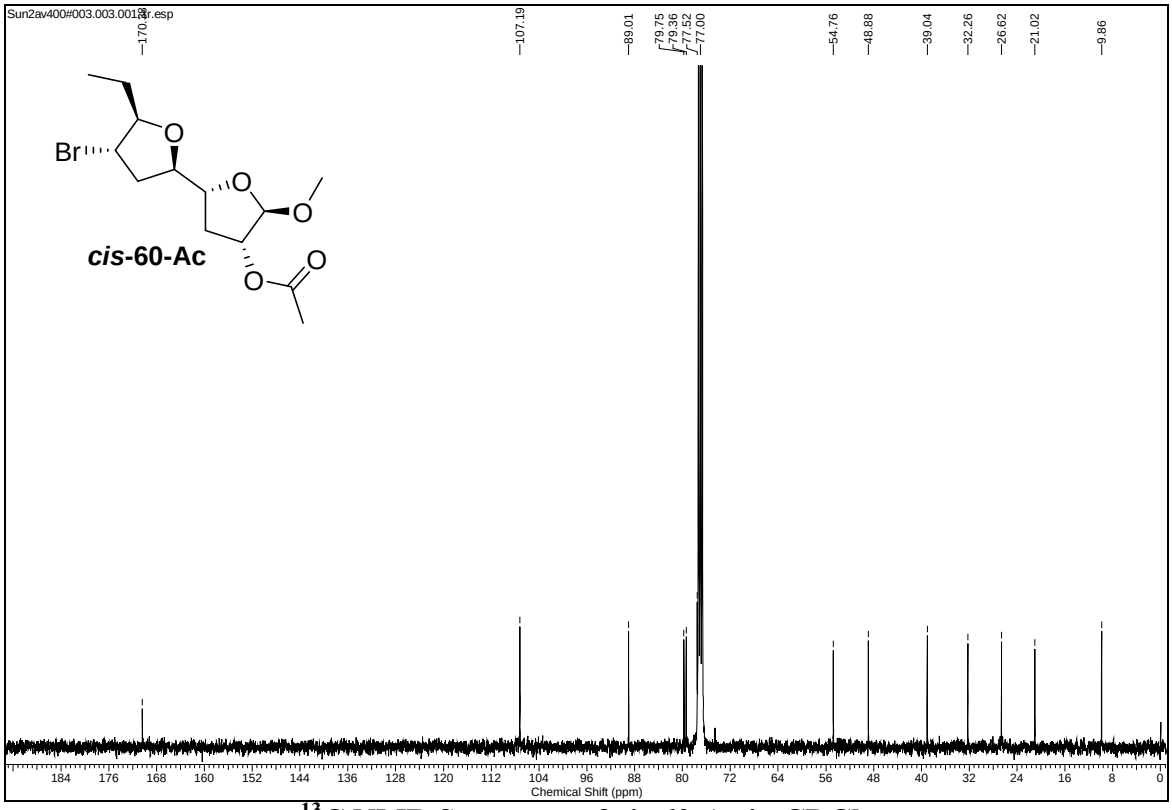
^{1}H NMR Spectrum of *trans*-60 in $CDCl_3$



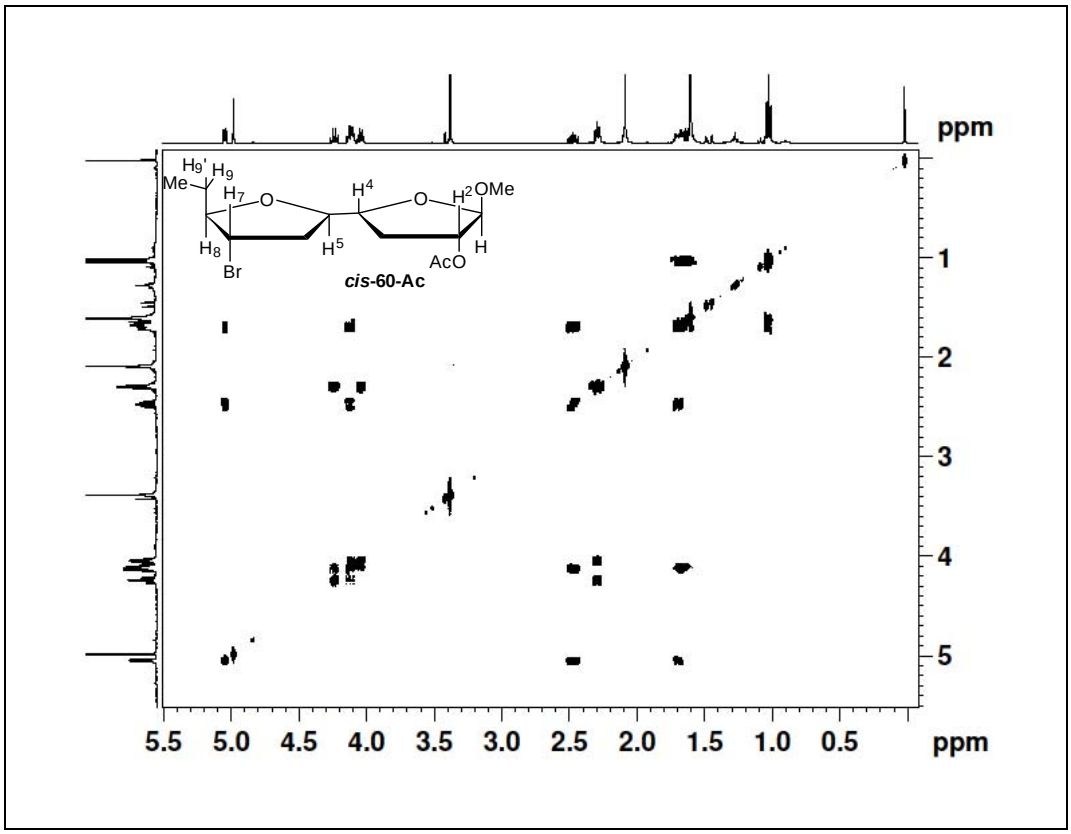
^{13}C NMR Spectrum of *trans*-60 in $CDCl_3$



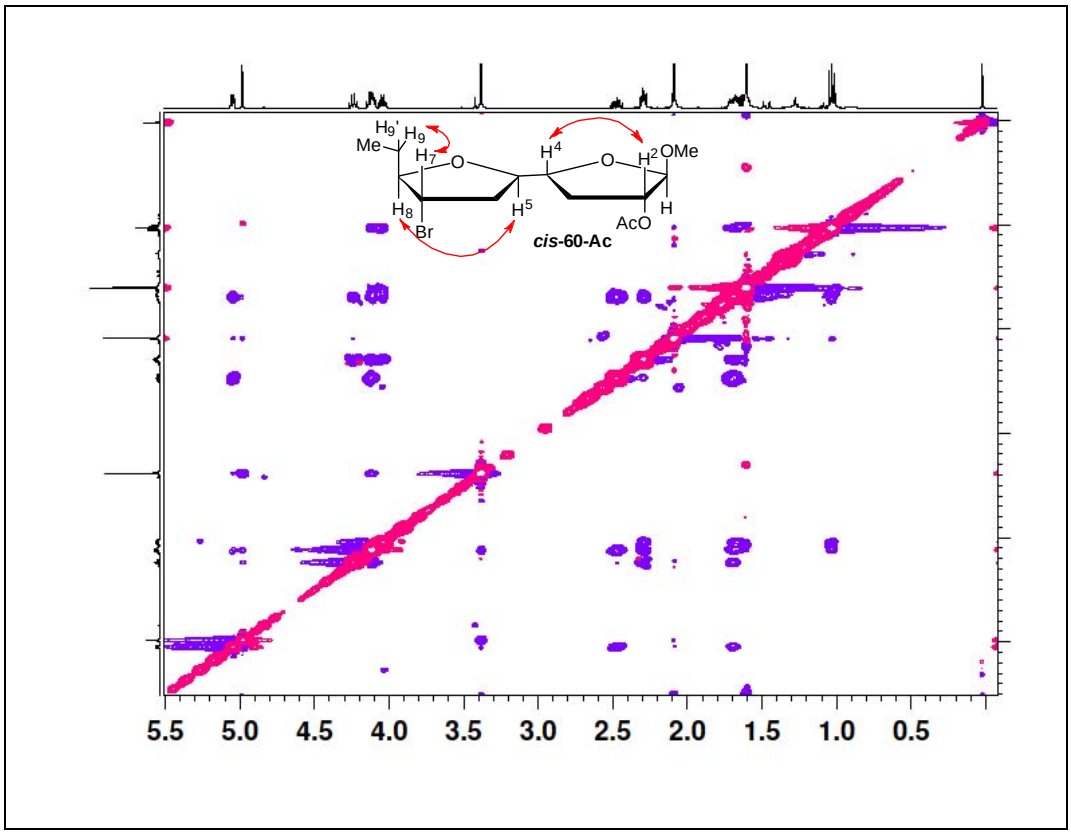
^{1}H NMR Spectrum of *cis*-60-Ac in $CDCl_3$



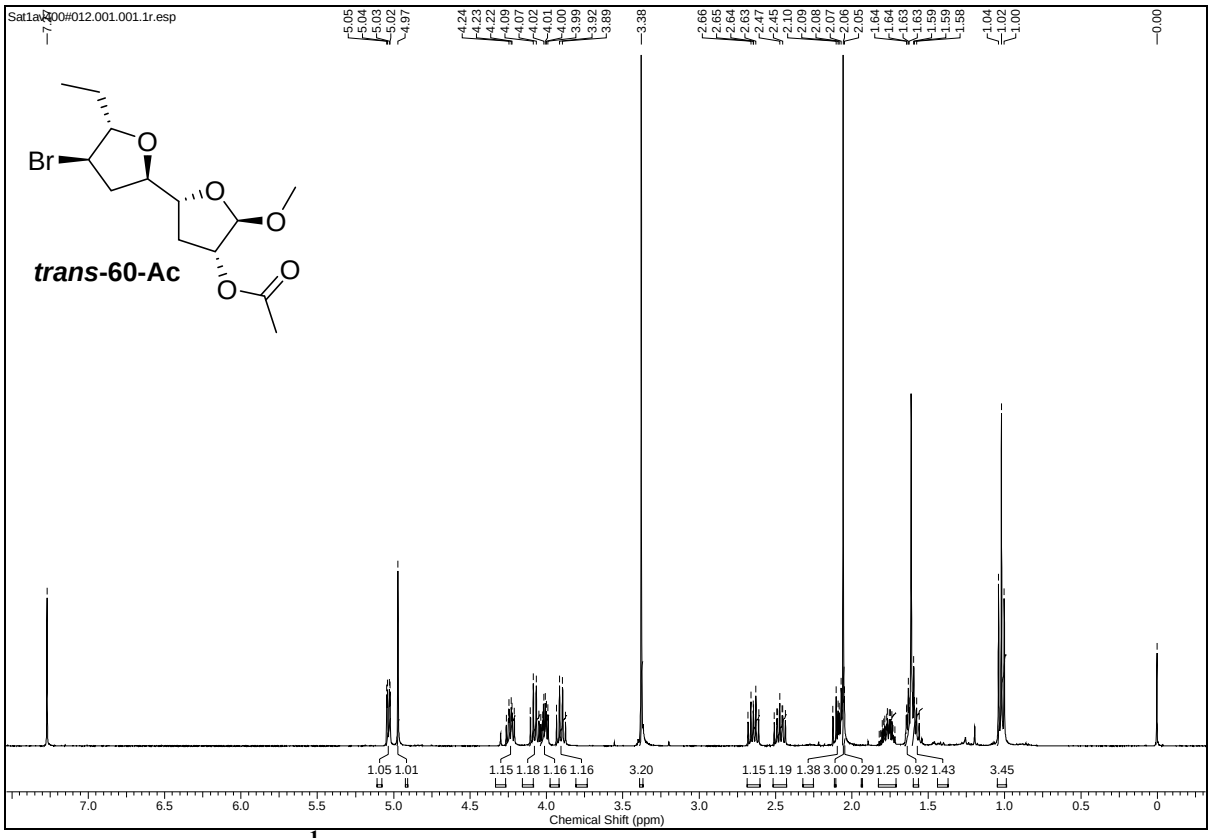
^{13}C NMR Spectrum of *cis*-60-Ac in $CDCl_3$



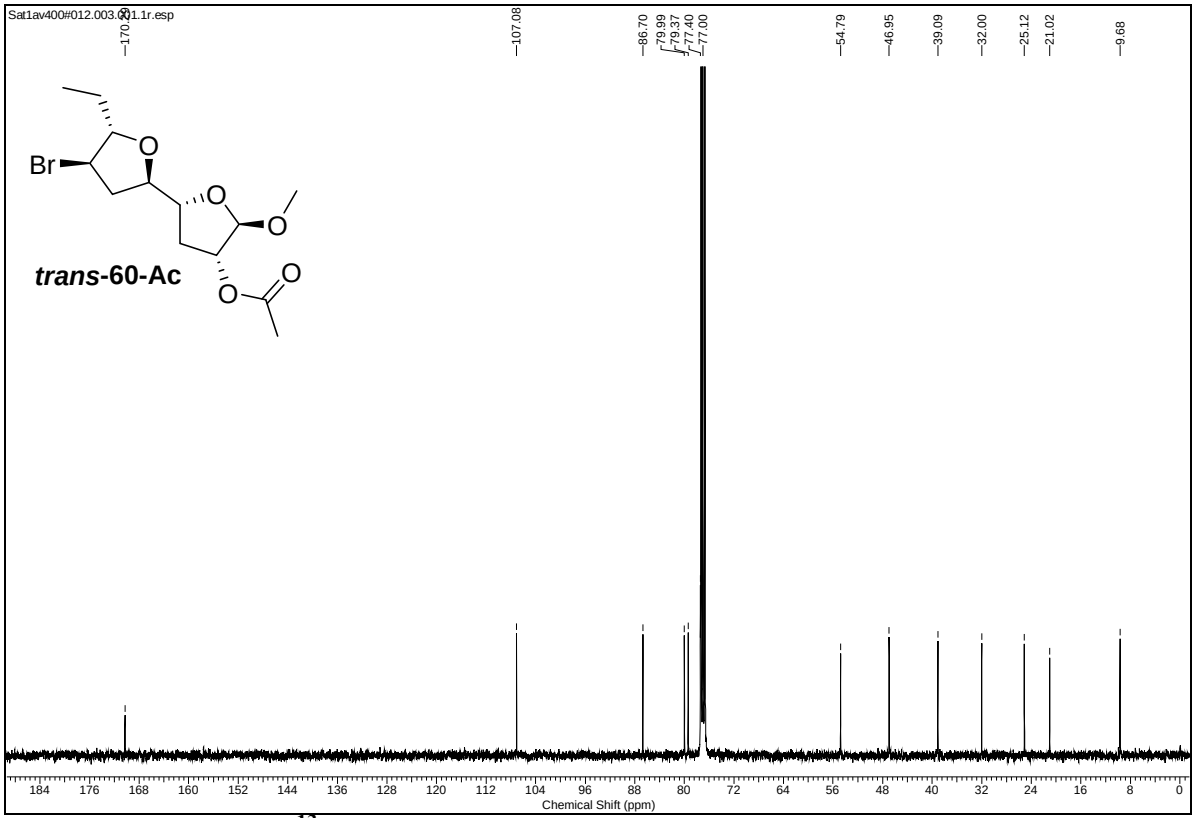
COSY of compound *cis*-60-Ac



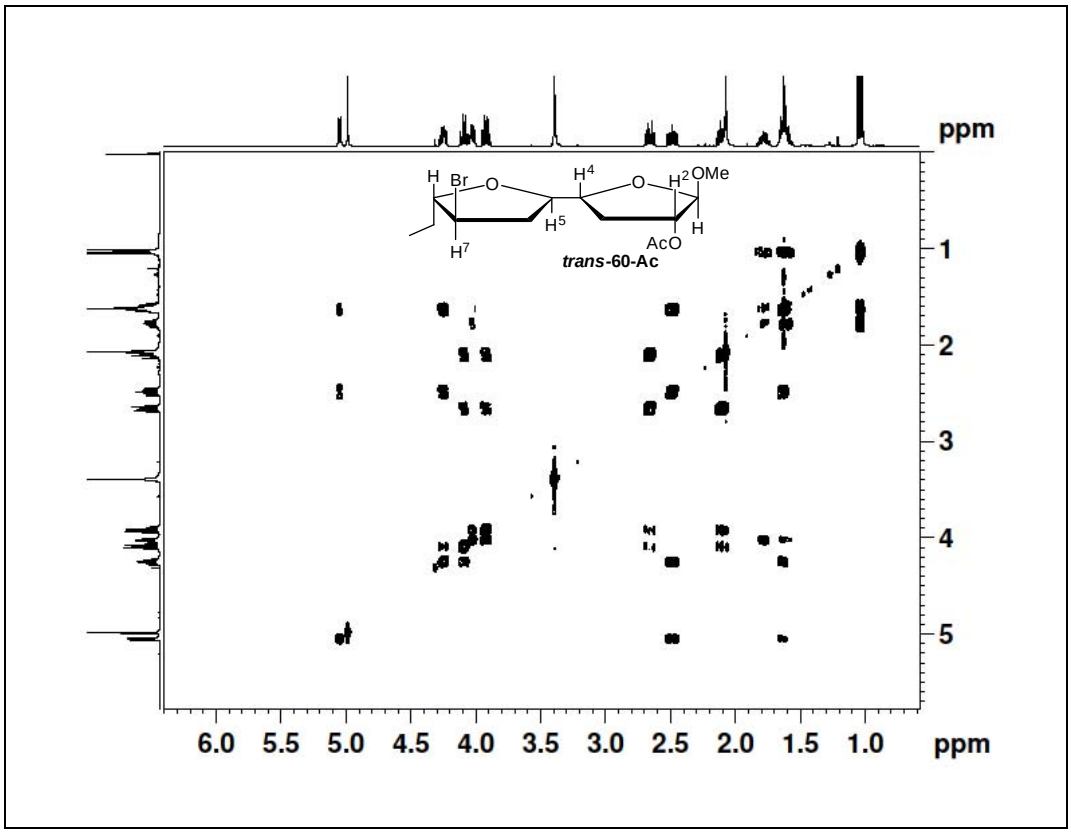
NOESY of compound *cis*-60-Ac



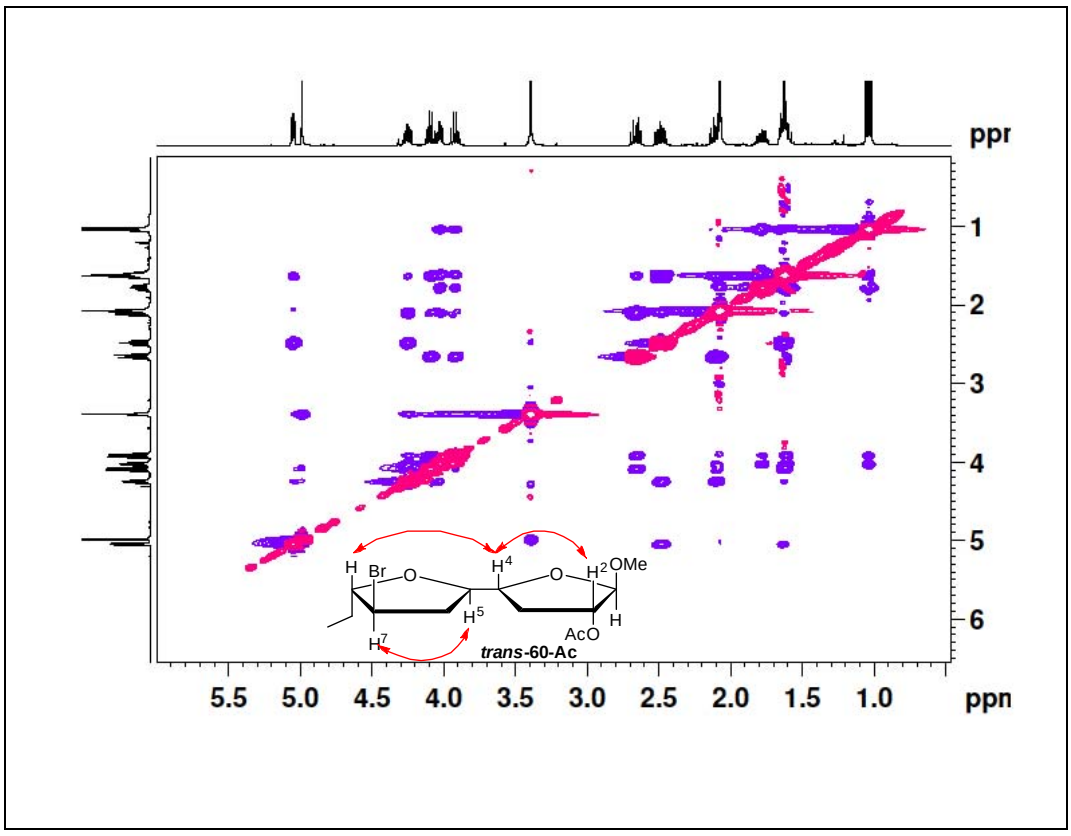
^{1}H NMR Spectrum of *trans*-60-Ac in $CDCl_3$



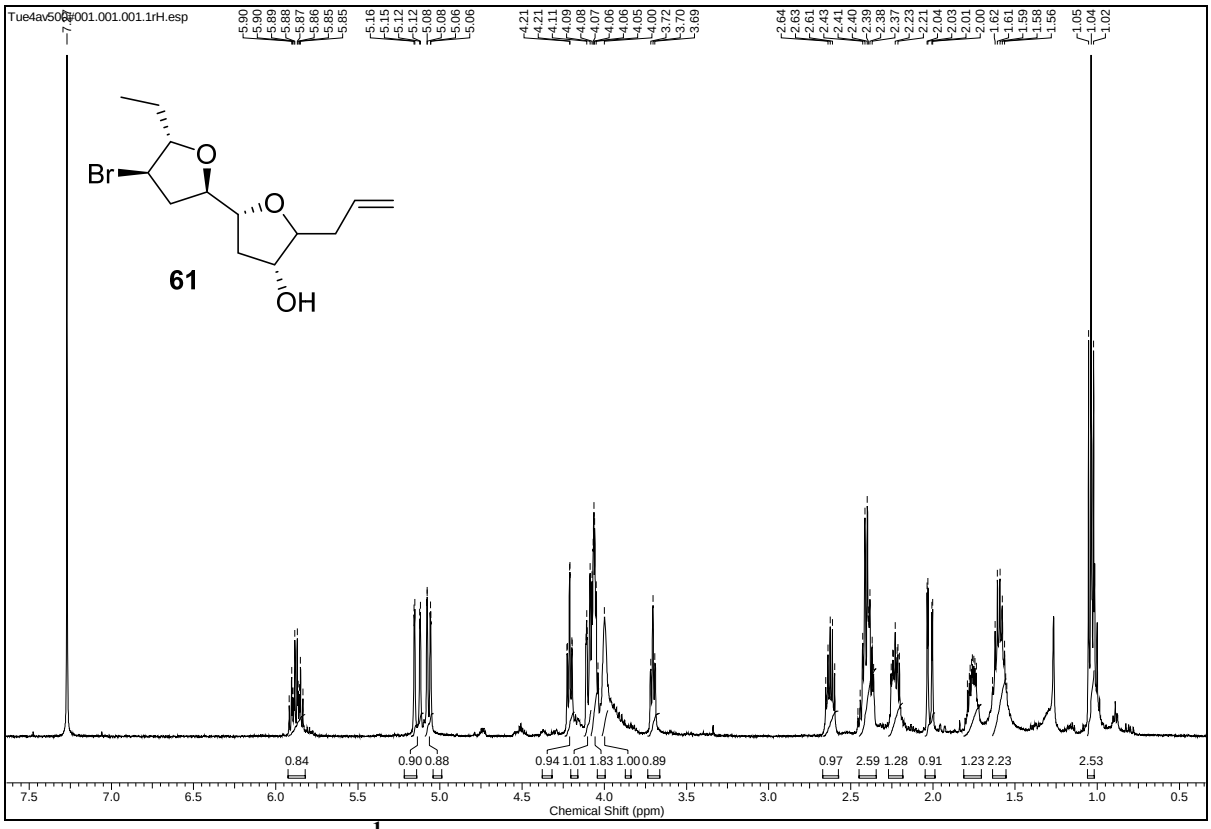
^{13}C NMR Spectrum of *trans*-60-Ac in $CDCl_3$



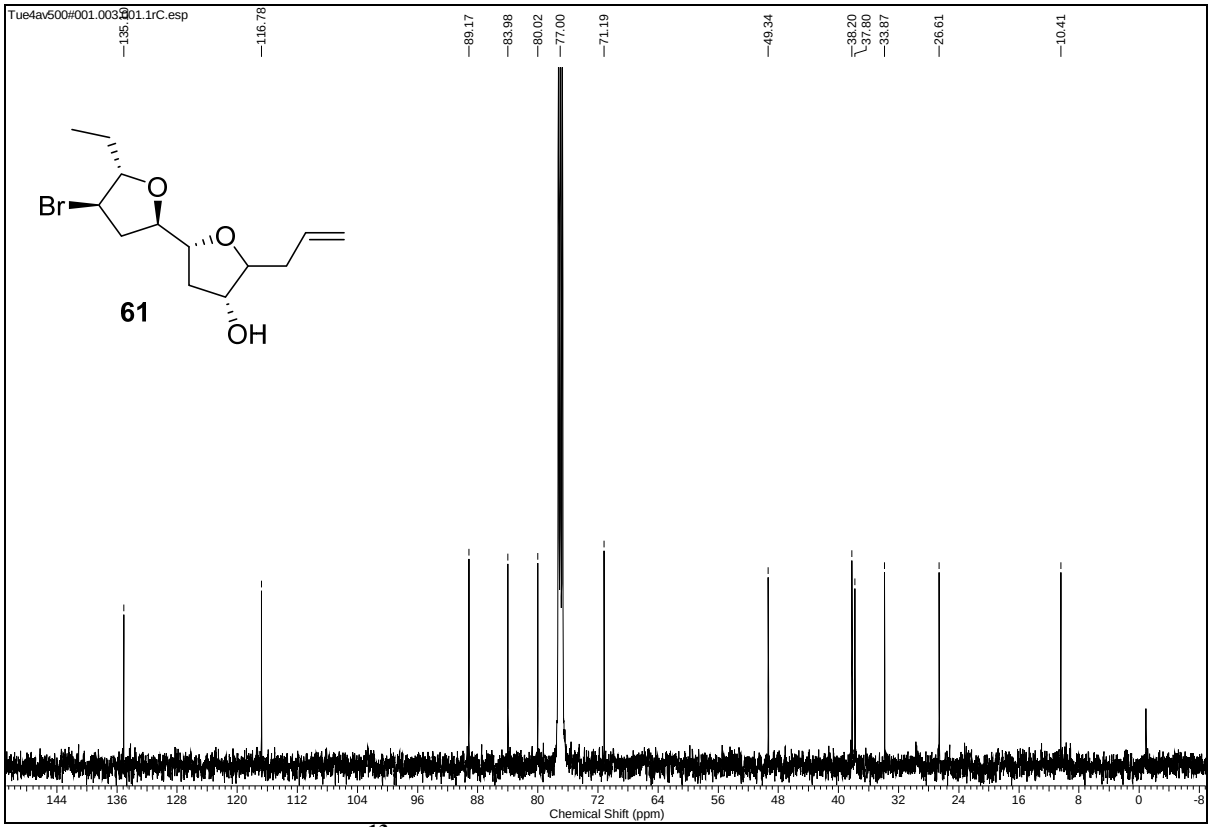
COSY of compound *trans*-60-Ac



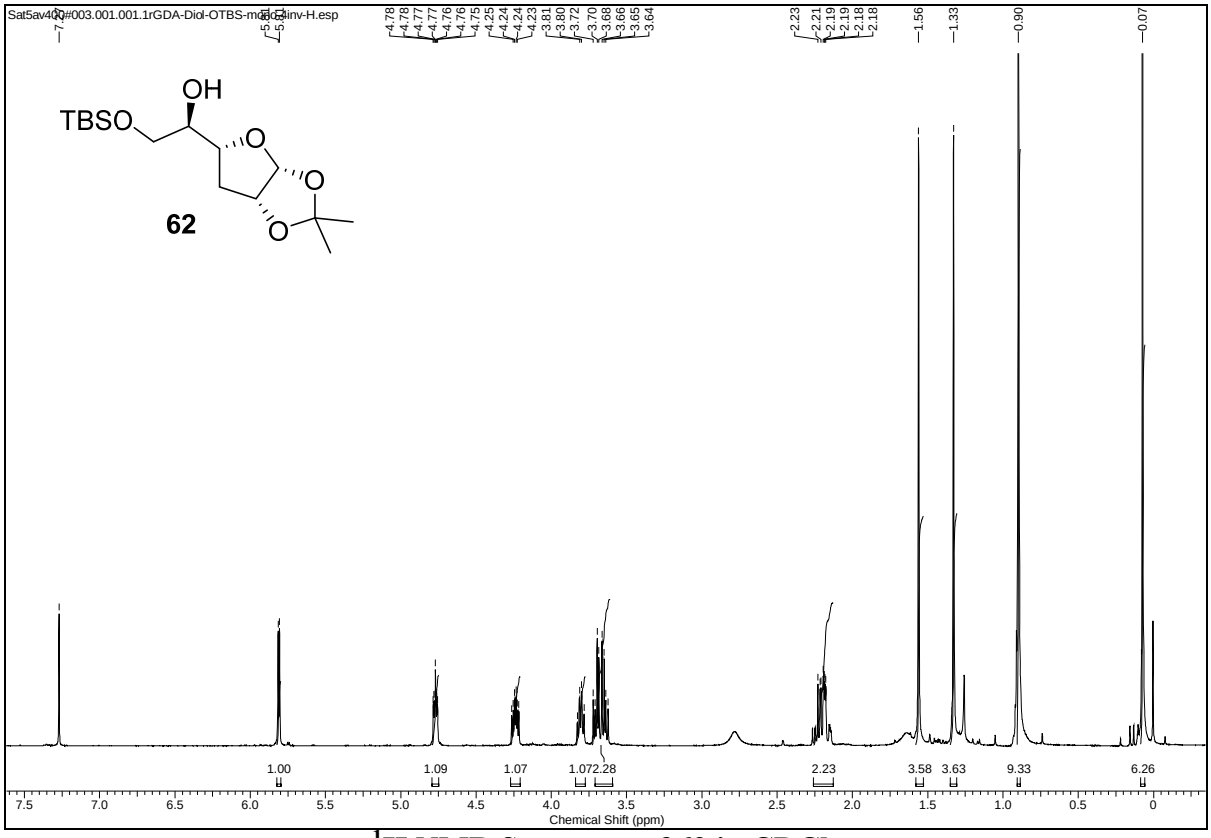
NOESY of compound *trans*-60-Ac



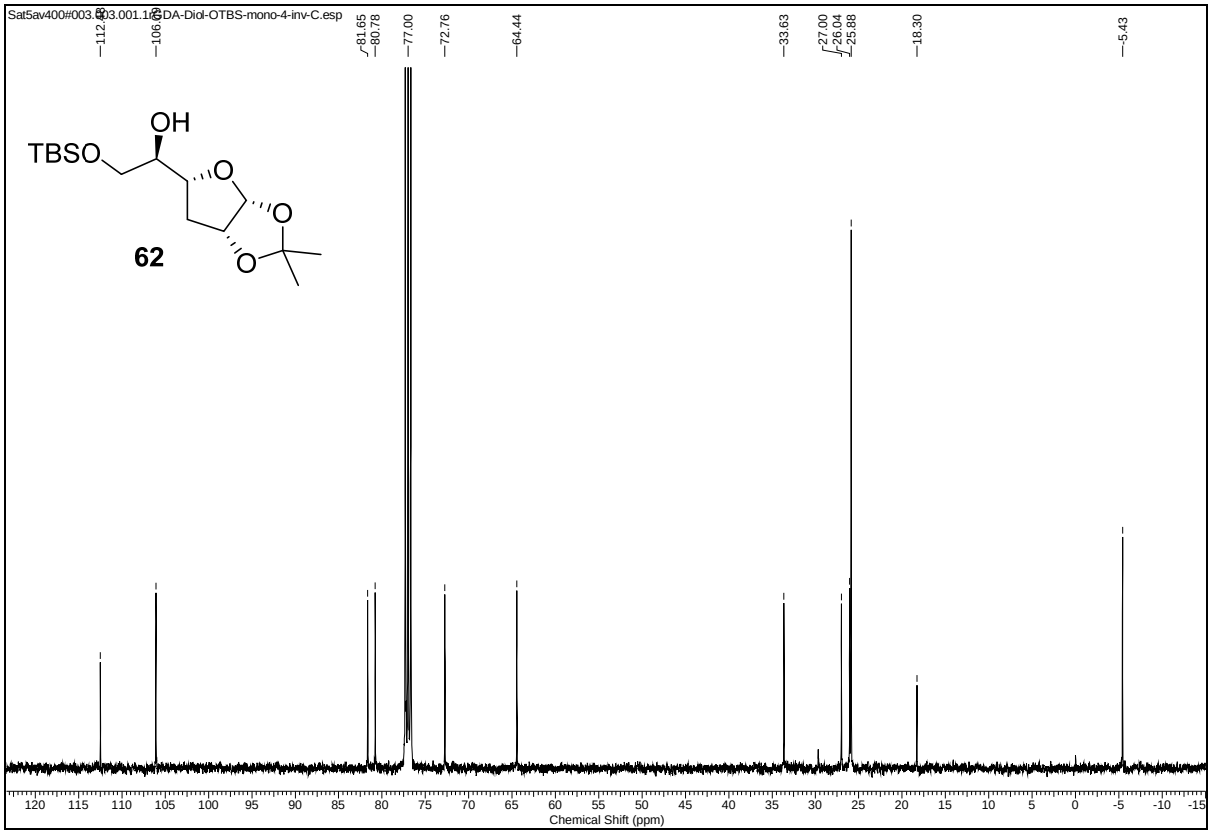
^{1}H NMR Spectrum of 61 in $CDCl_3$



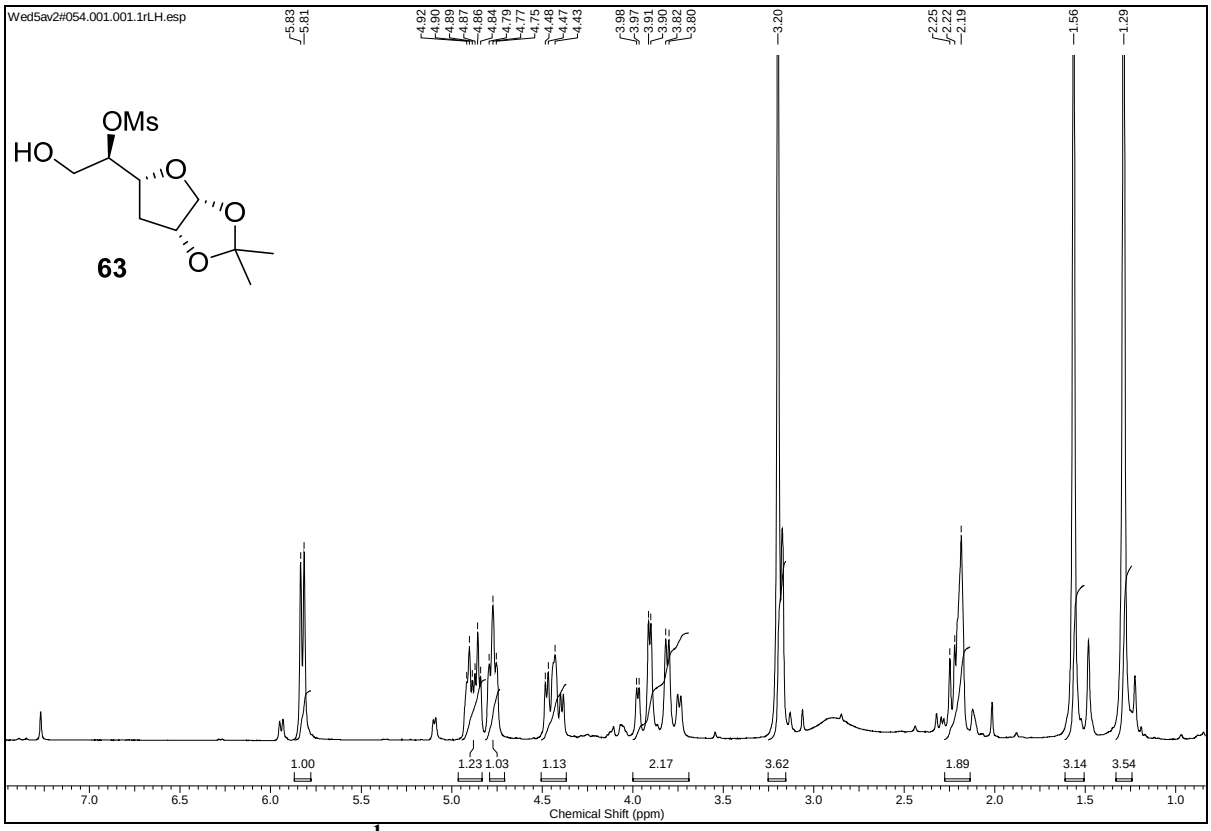
^{13}C NMR Spectrum of 61 in $CDCl_3$



^{1}H NMR Spectrum of 62 in $CDCl_3$



^{13}C NMR Spectrum of 62 in $CDCl_3$



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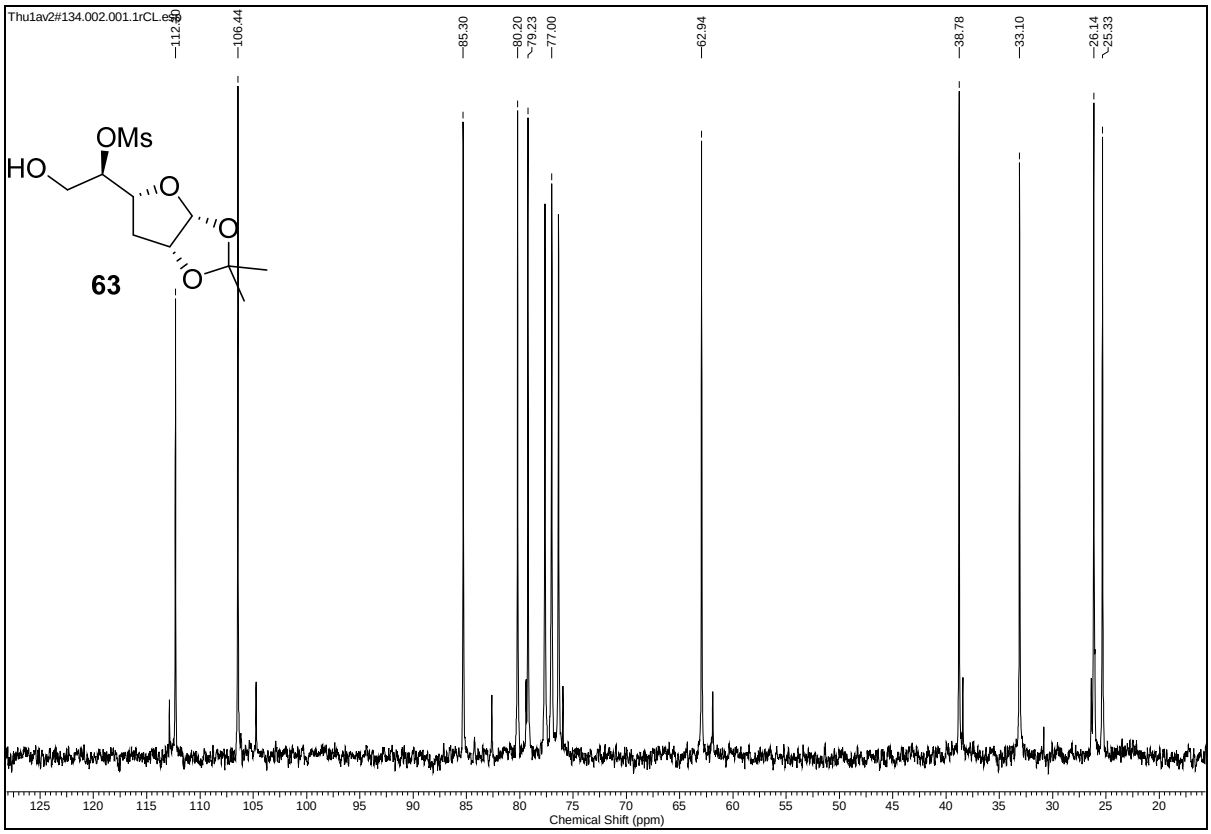

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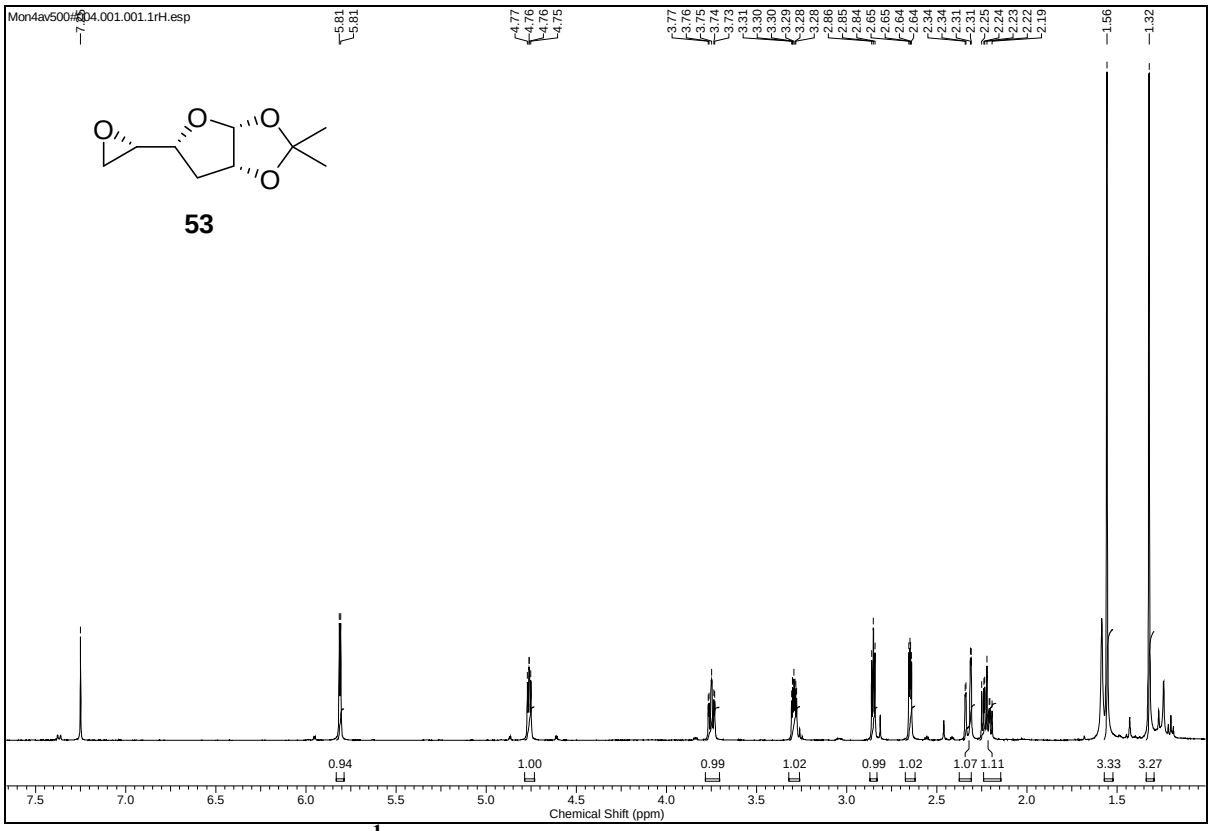
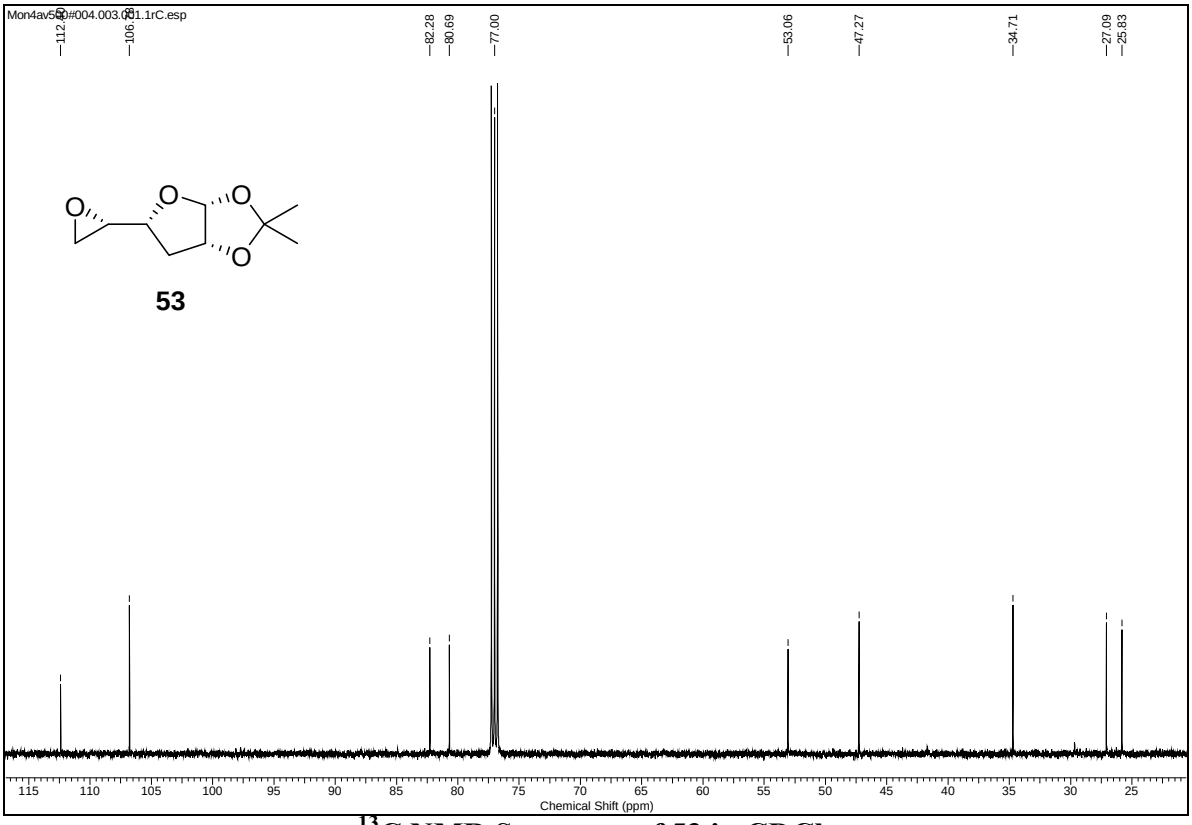
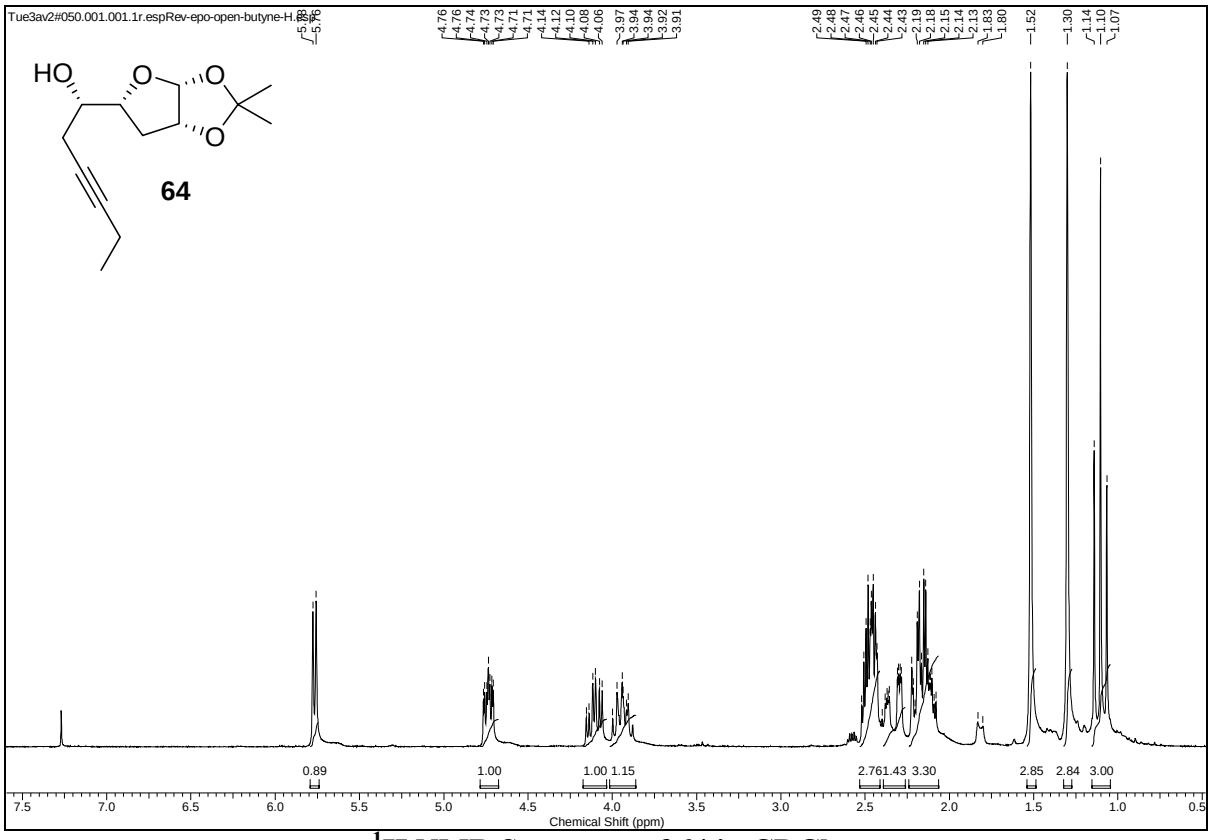


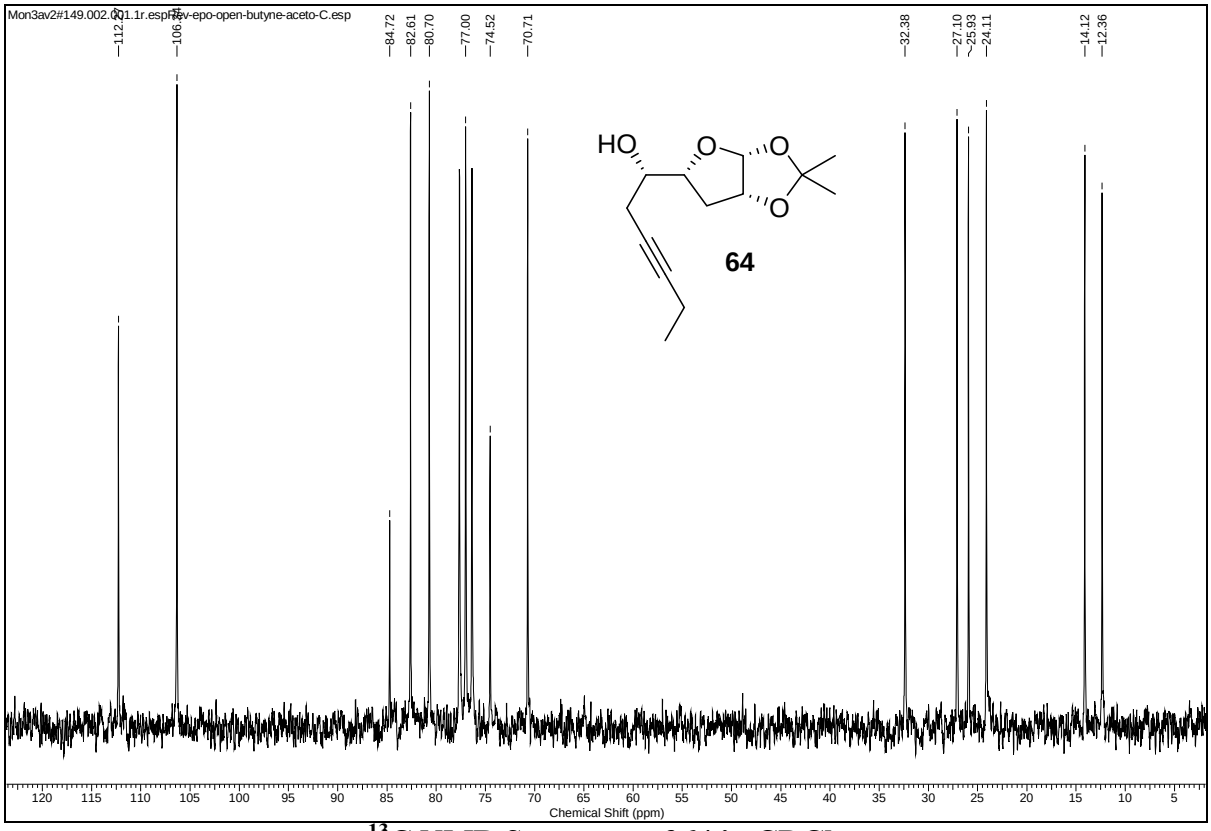
^{1}H NMR Spectrum of 53 in $CDCl_3$



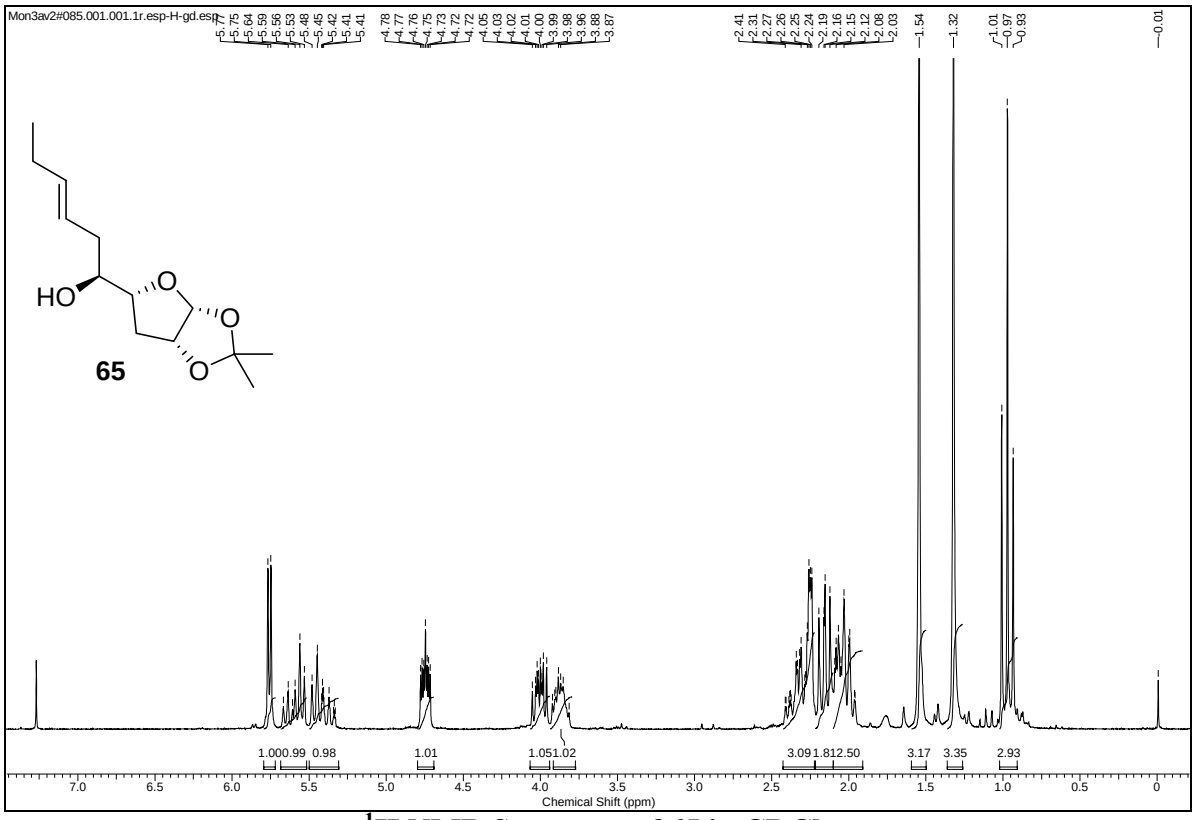
^{13}C NMR Spectrum of 53 in $CDCl_3$



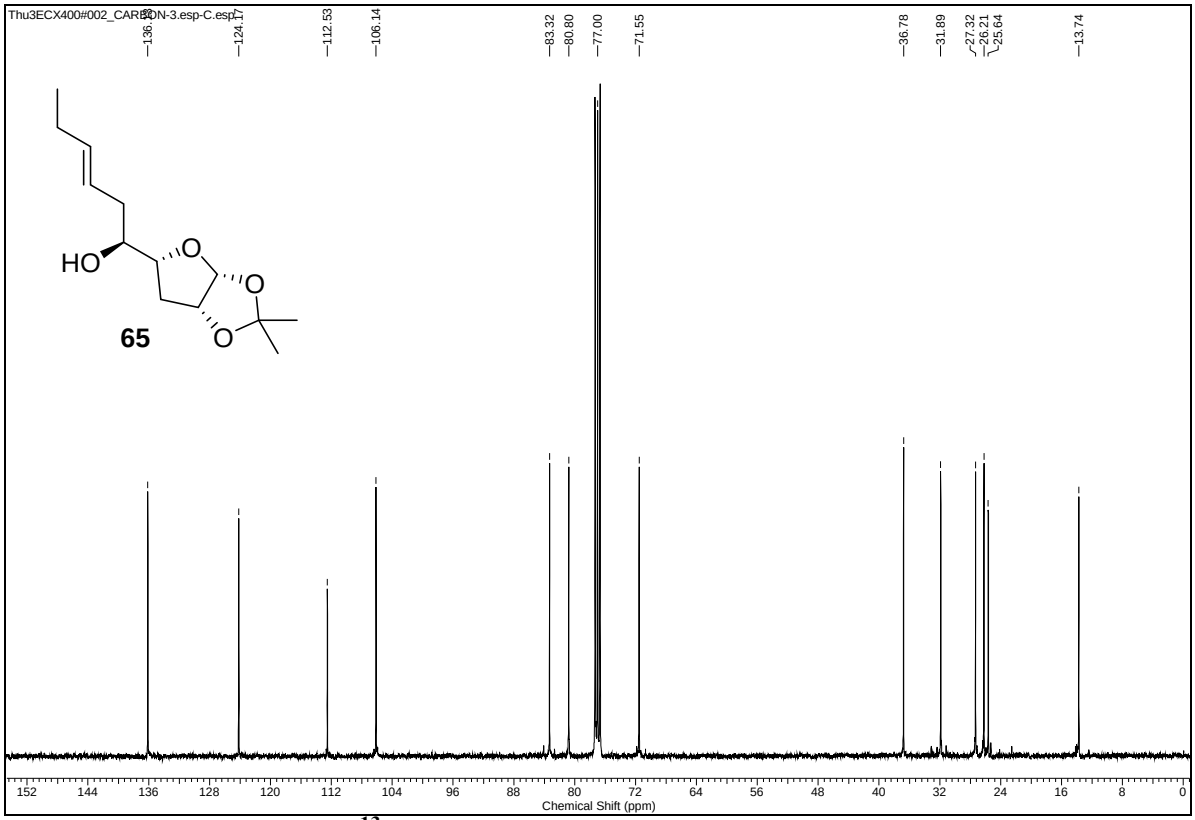
^{1}H NMR Spectrum of 64 in $CDCl_3$



^{13}C NMR Spectrum of 64 in $CDCl_3$



^{1}H NMR Spectrum of 65 in $CDCl_3$



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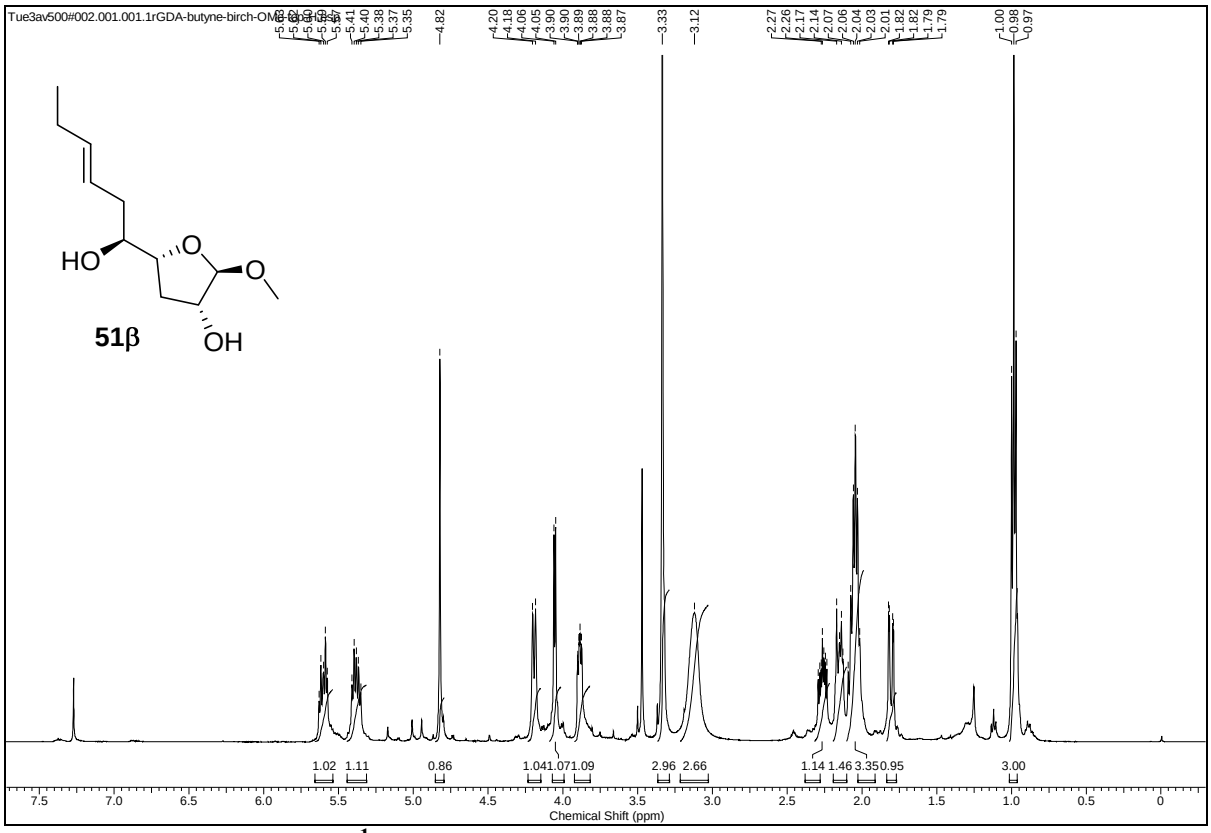
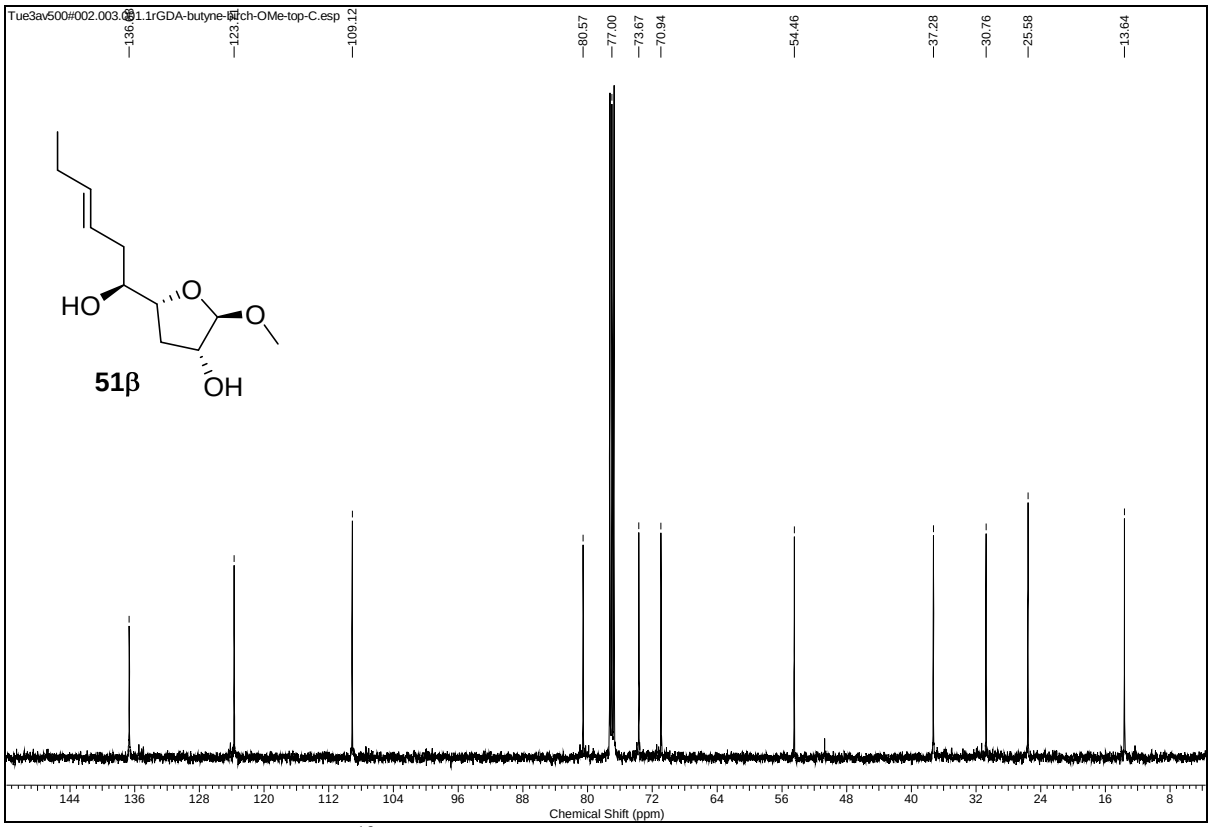
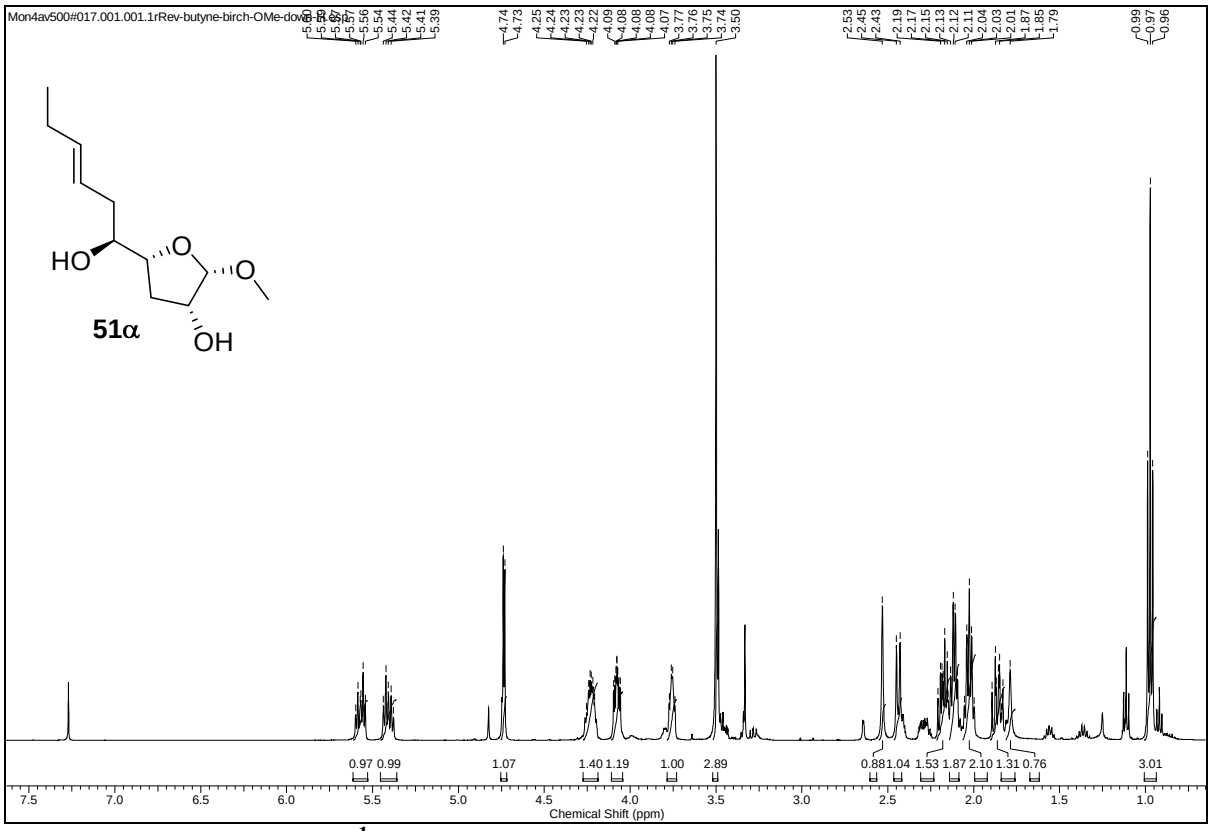


^{1}H NMR Spectrum of 51β in $CDCl_3$



^{13}C NMR Spectrum of 51β in $CDCl_3$



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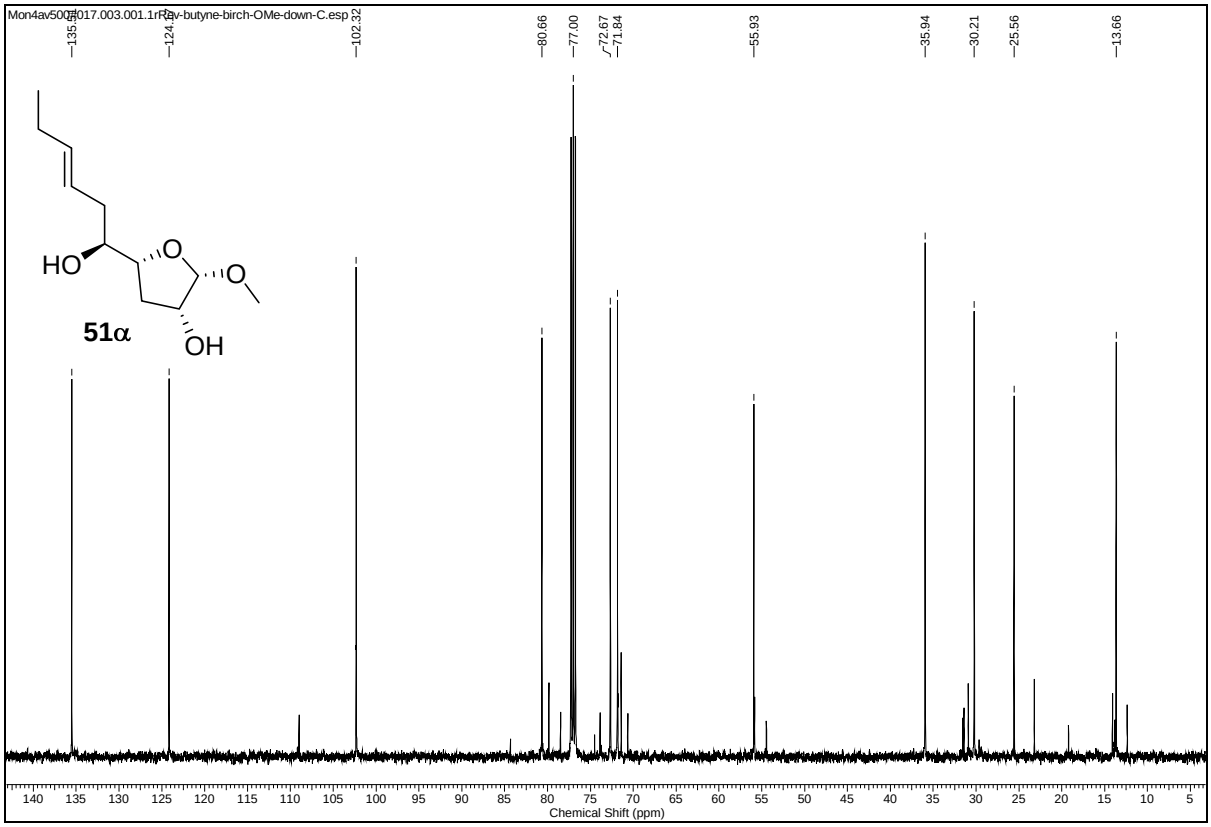
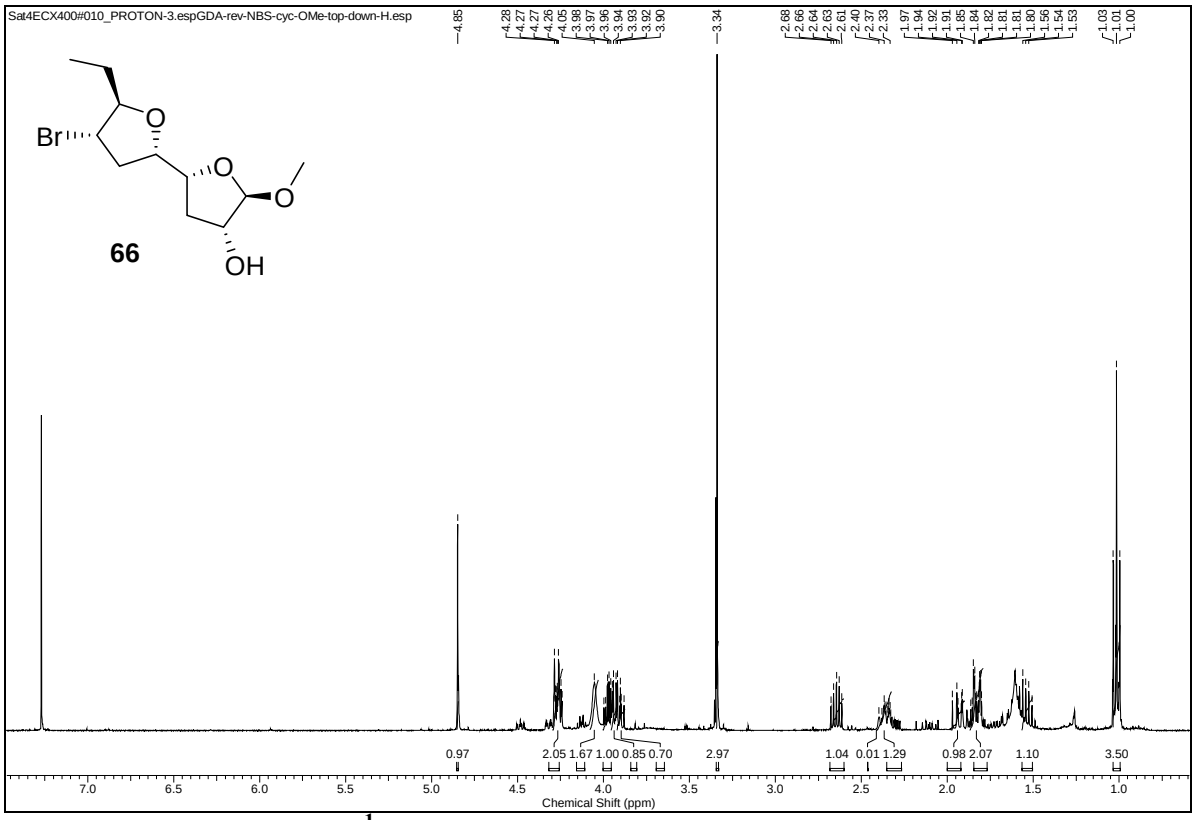
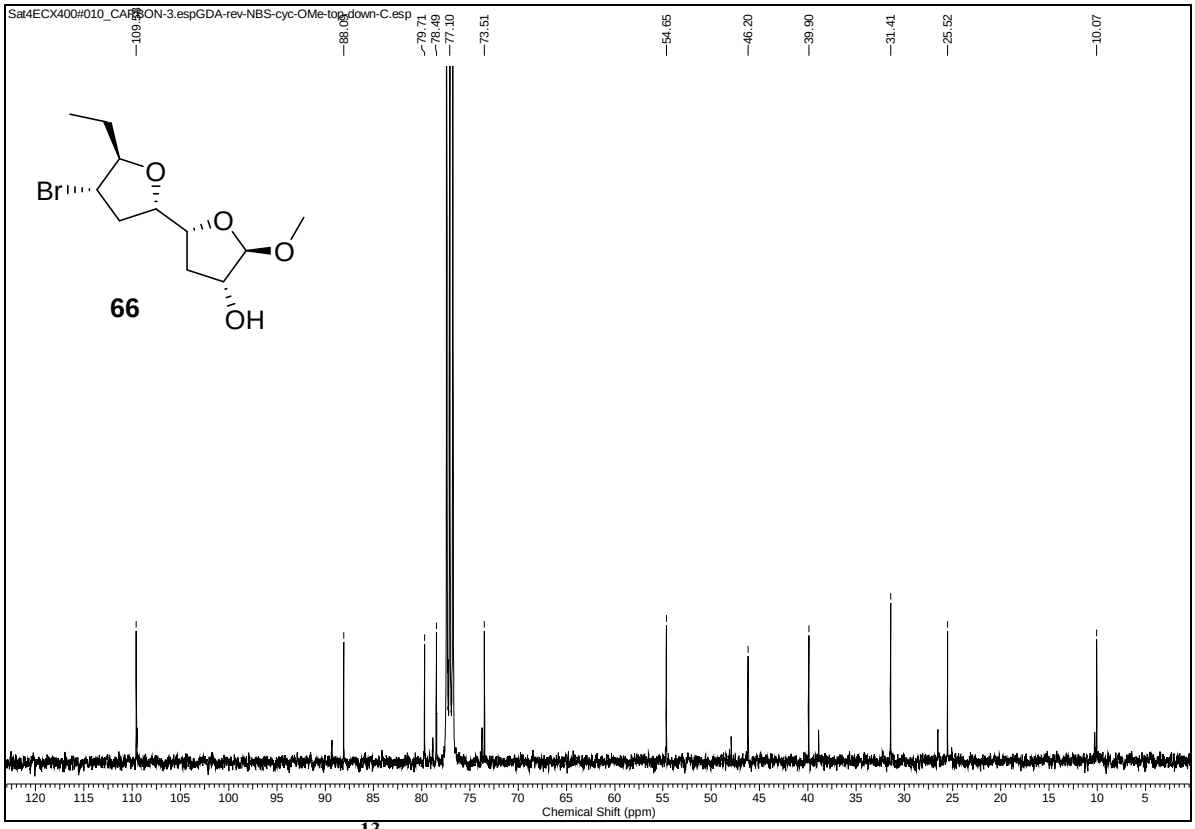


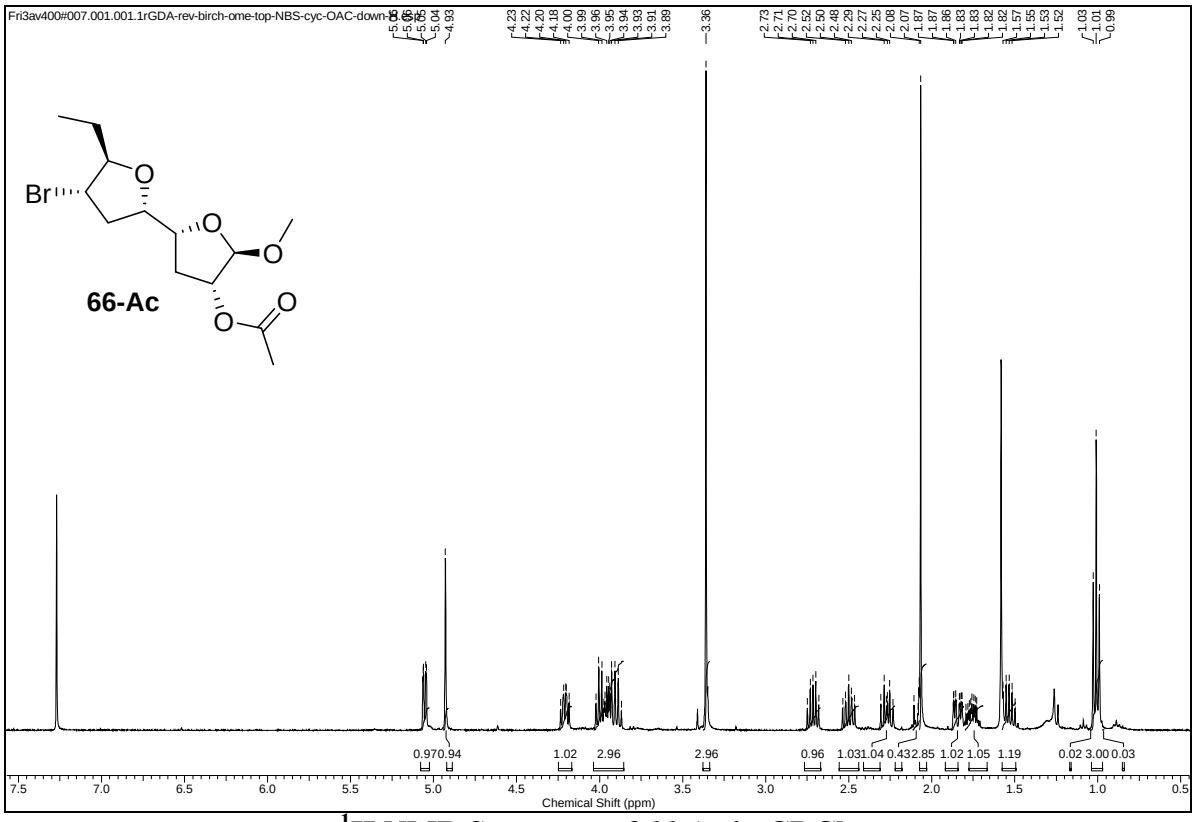
^{13}C NMR Spectrum of 51α in $CDCl_3$



^{1}H NMR Spectrum of 66 in $CDCl_3$



^{13}C NMR Spectrum of 66 in $CDCl_3$



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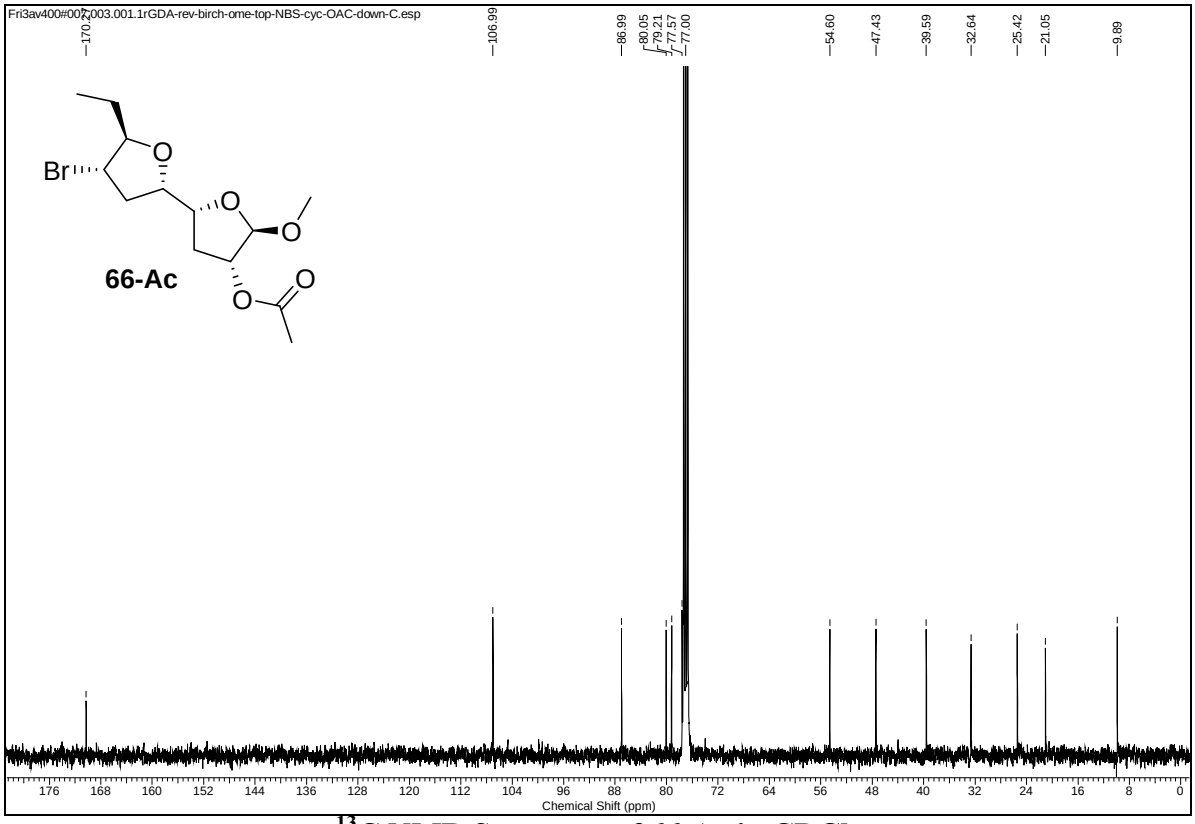
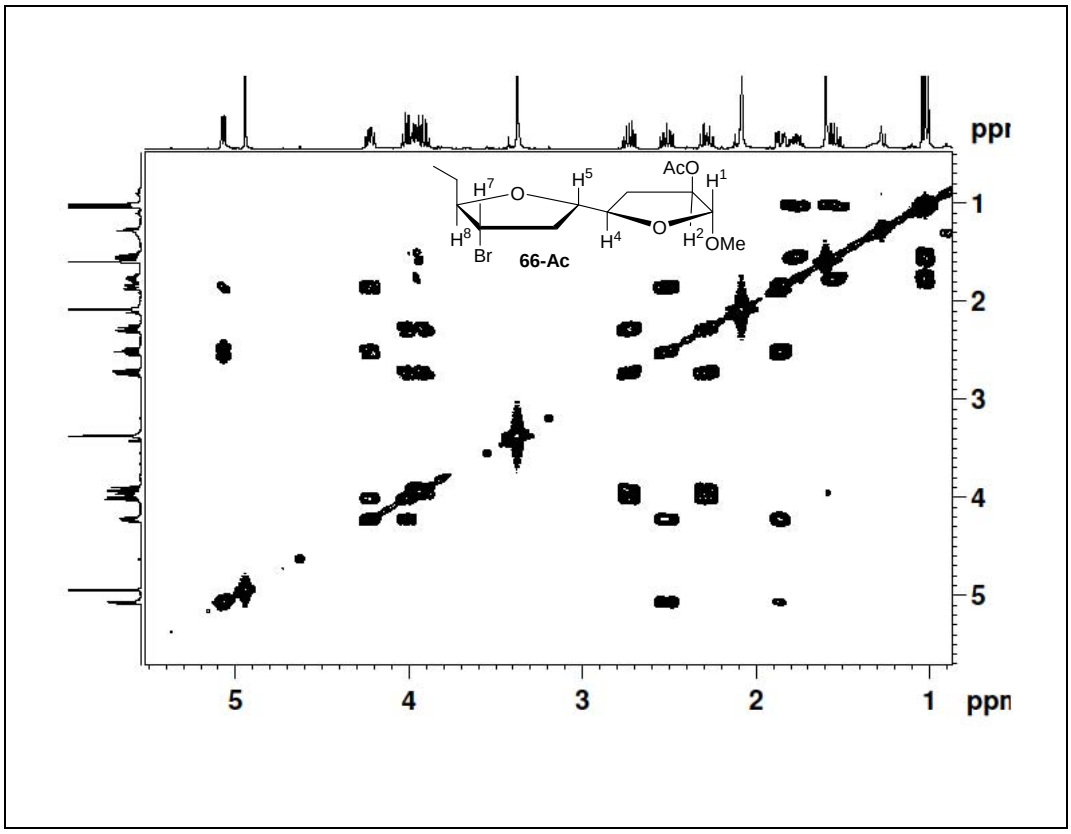
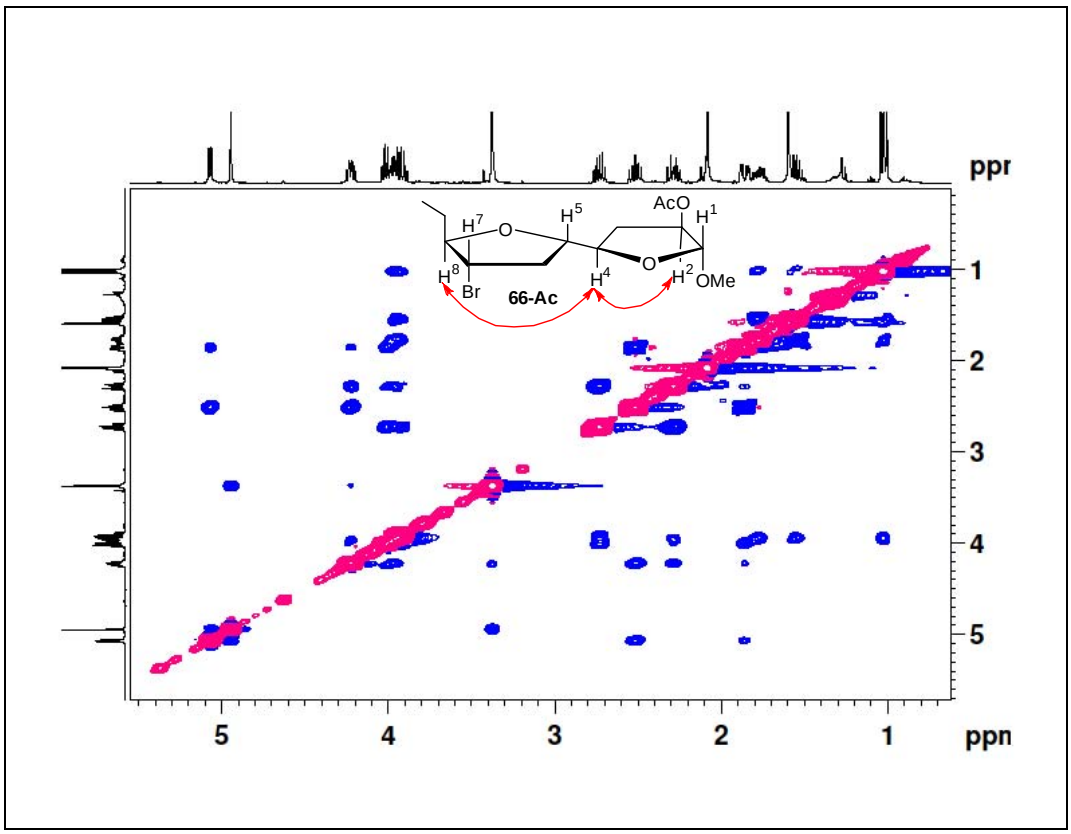


^{13}C NMR Spectrum of 66-Ac in $CDCl_3$



COSY of compound 66-Ac



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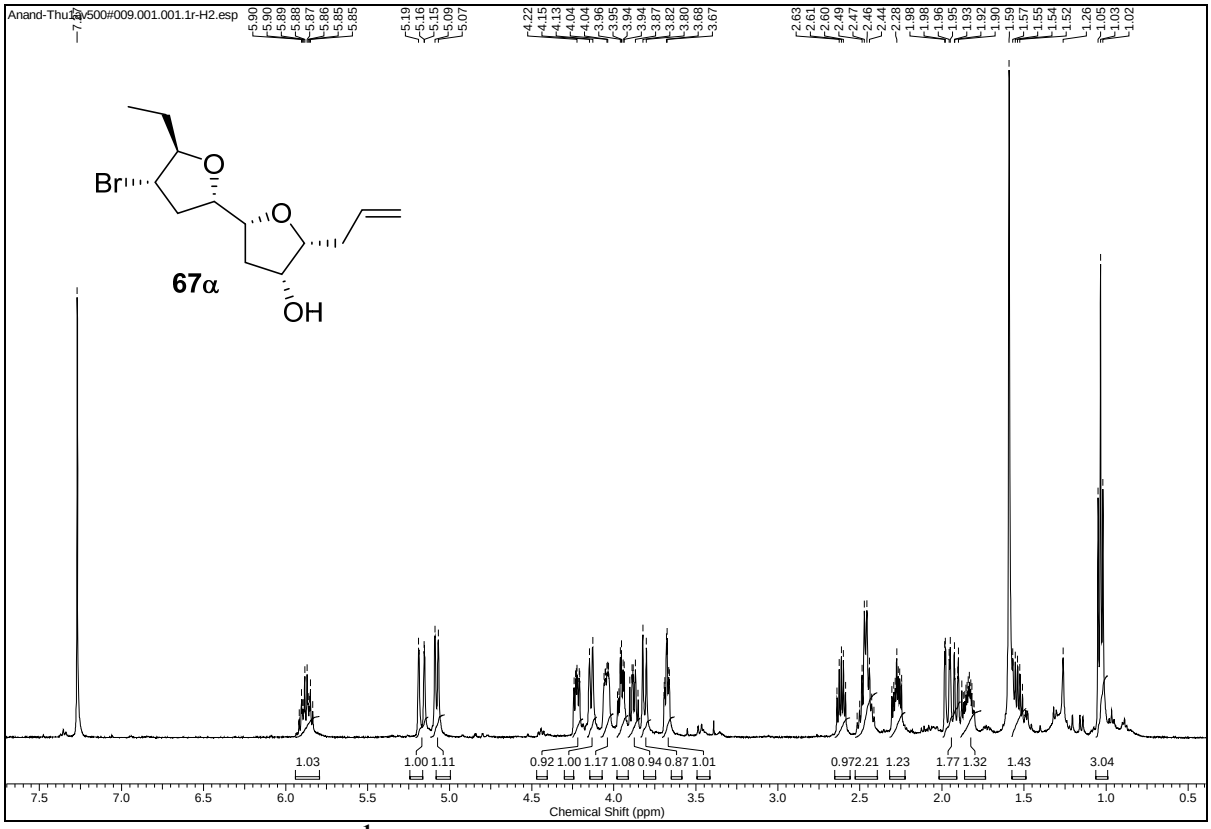
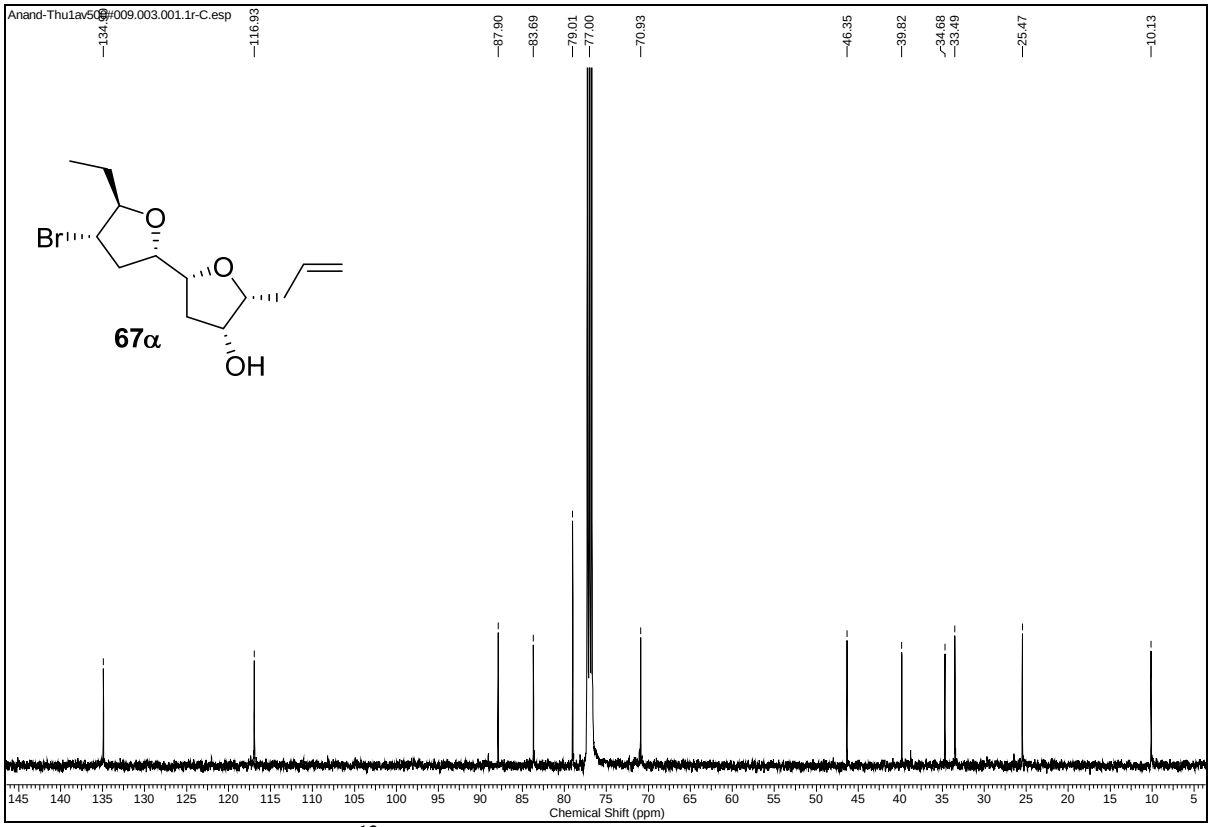


^{1}H NMR Spectrum of 67α in $CDCl_3$



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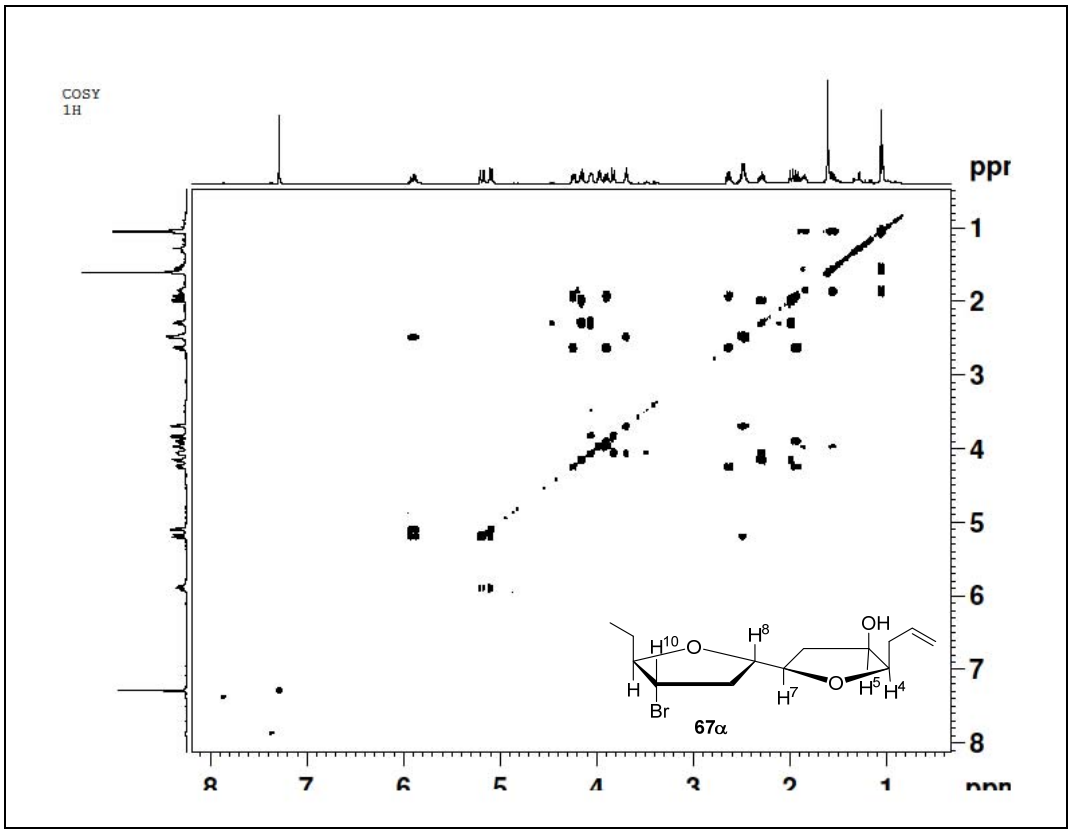

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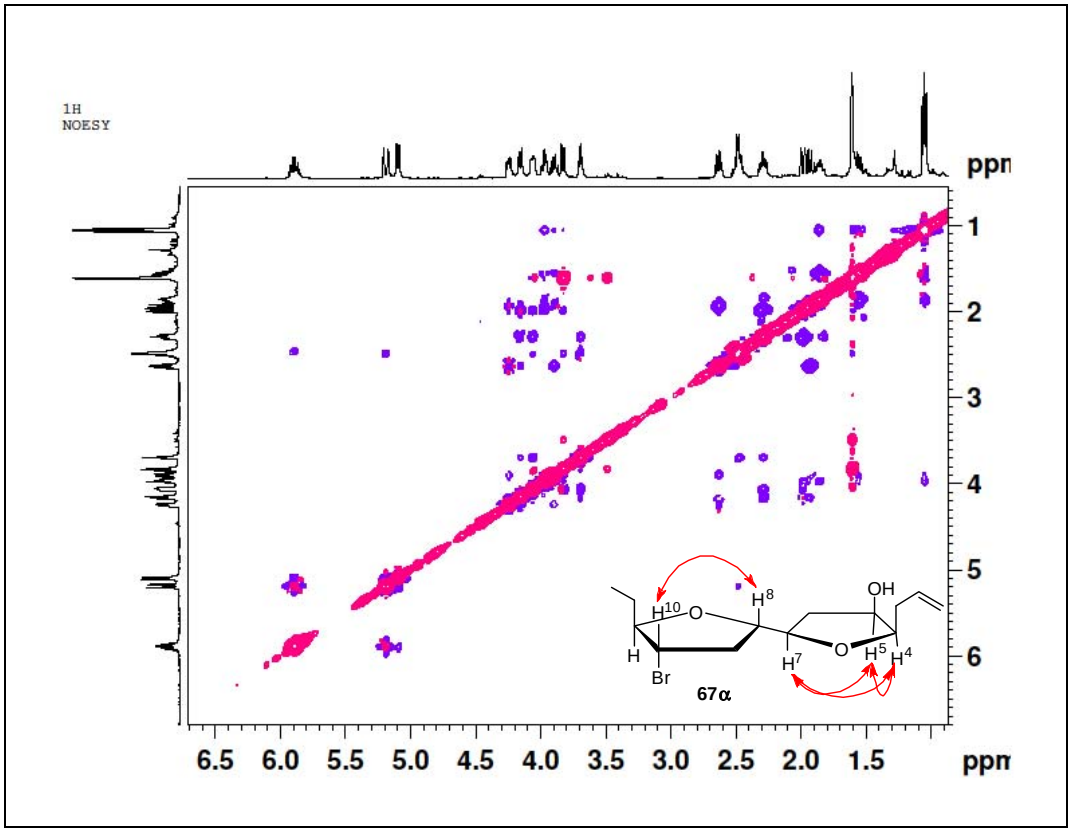

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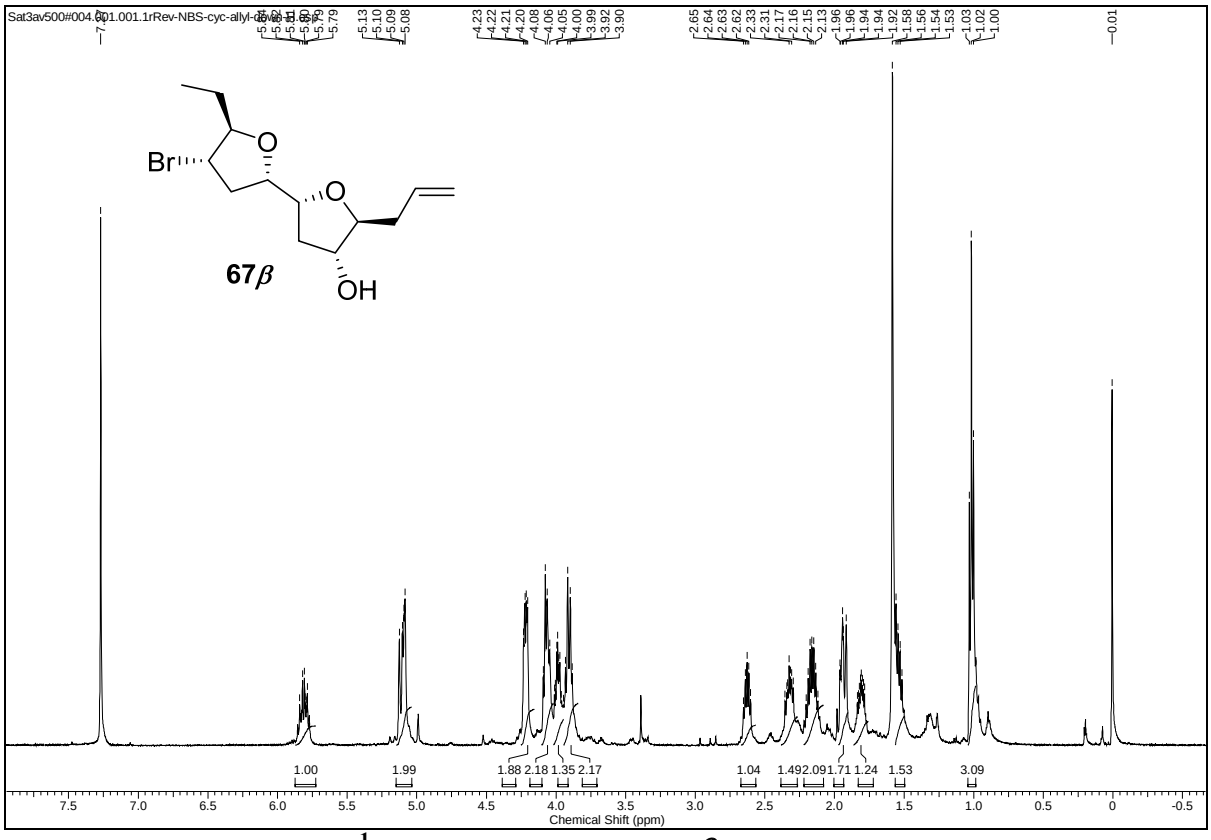
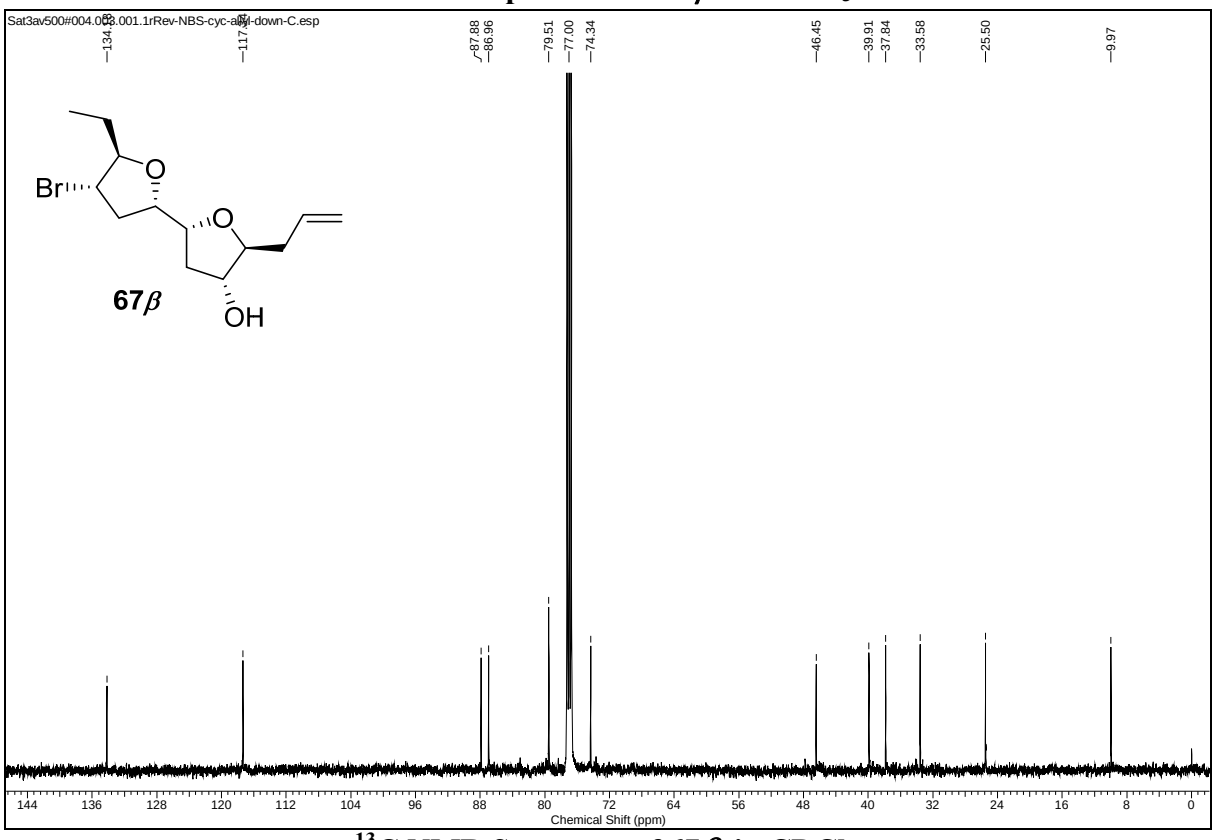


^{1}H NMR Spectrum of 67β in $CDCl_3$



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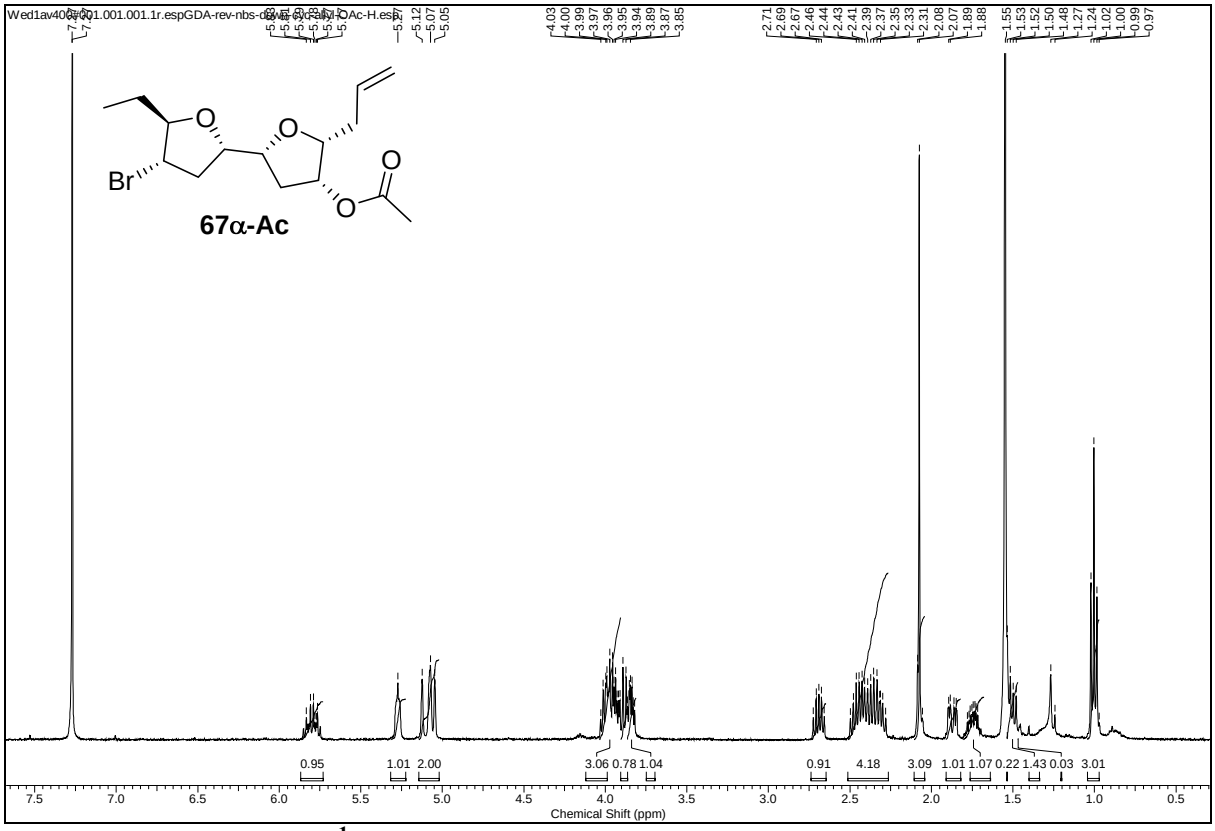
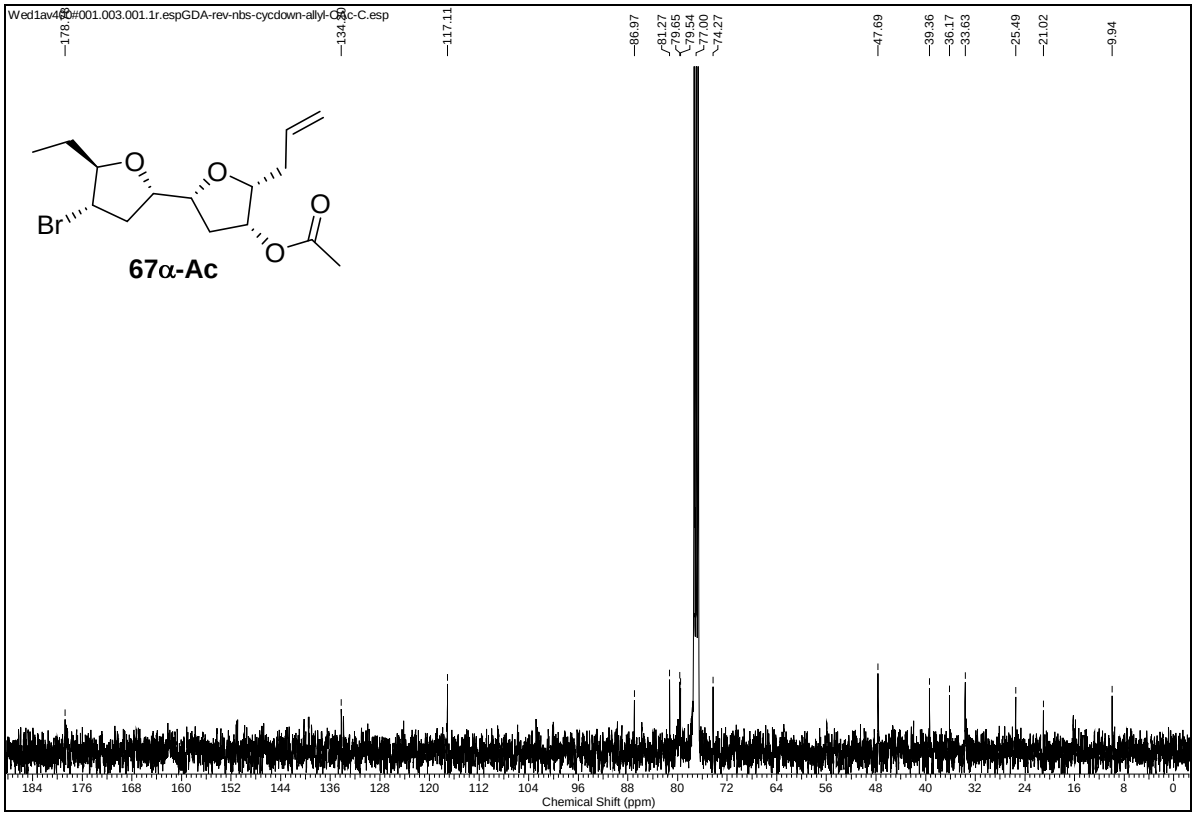
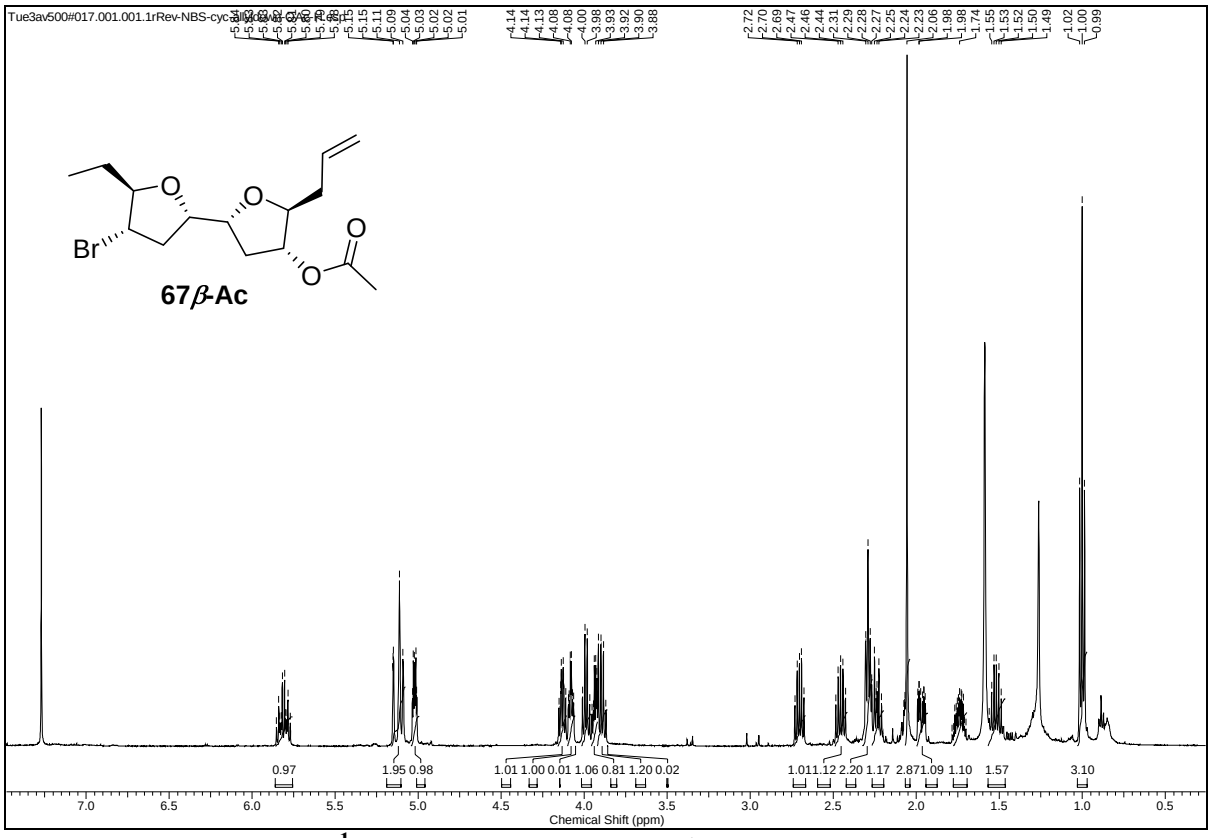


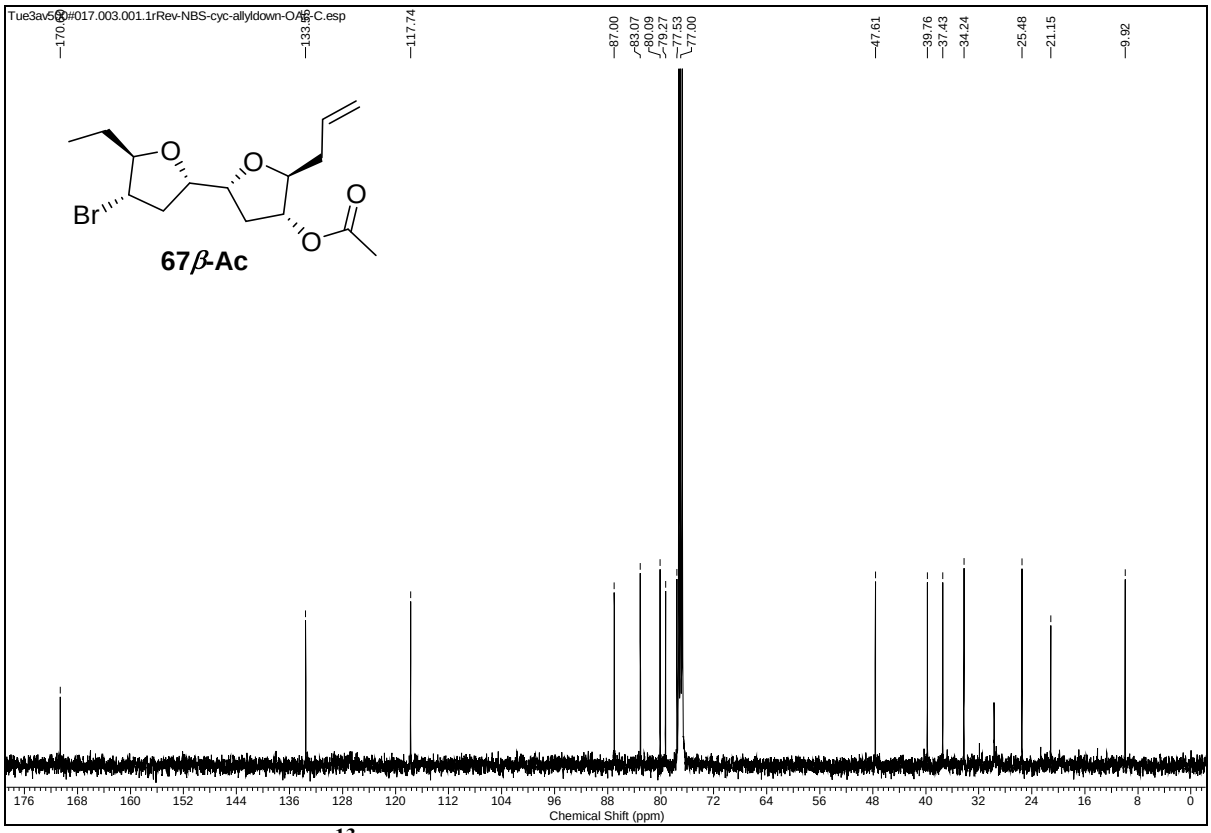
^{1}H NMR Spectrum of 67α-Ac in $CDCl_3$



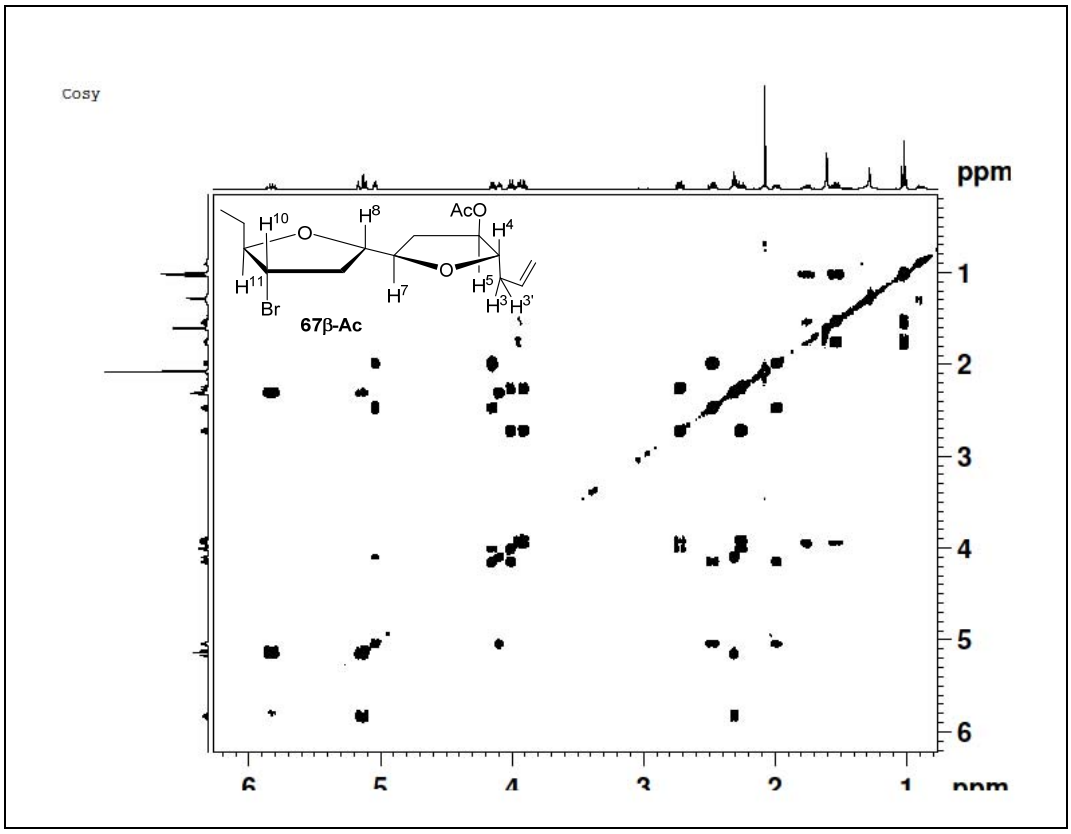
^{13}C NMR Spectrum of 67α-Ac in $CDCl_3$



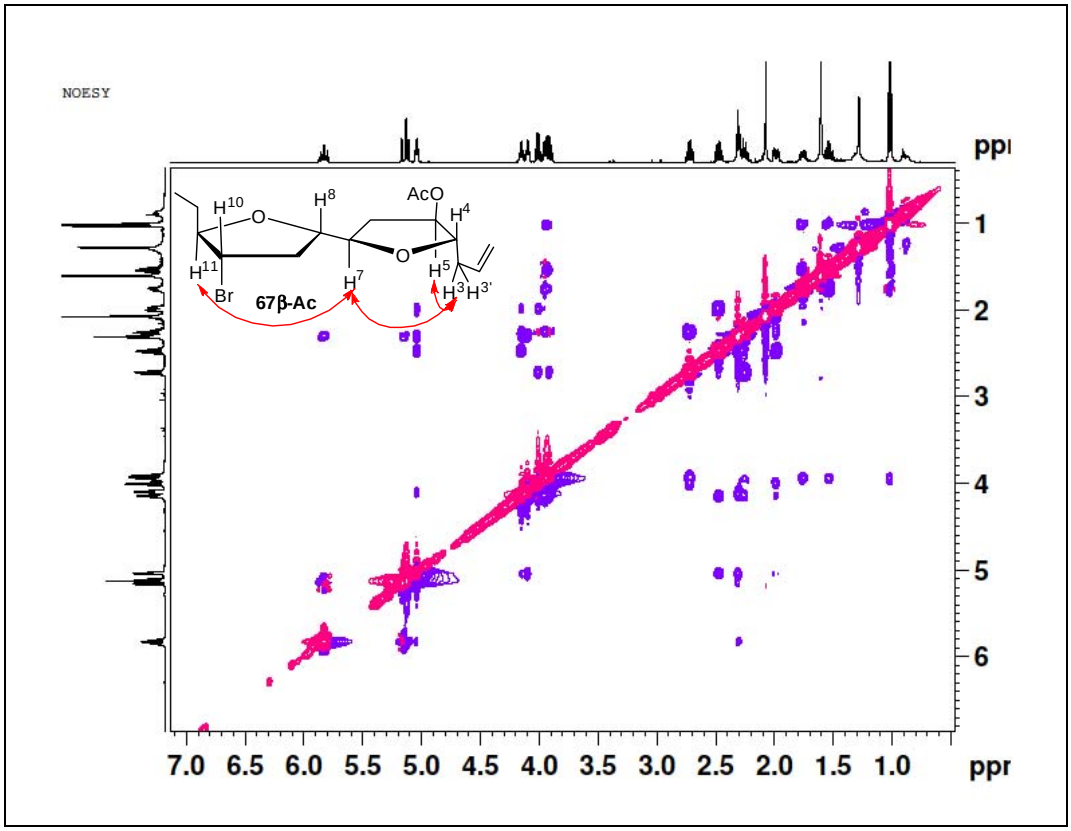
^{1}H NMR Spectrum of 67β-Ac in $CDCl_3$



^{13}C NMR Spectrum of 67β-Ac in $CDCl_3$



COSY of compound 67β-Ac



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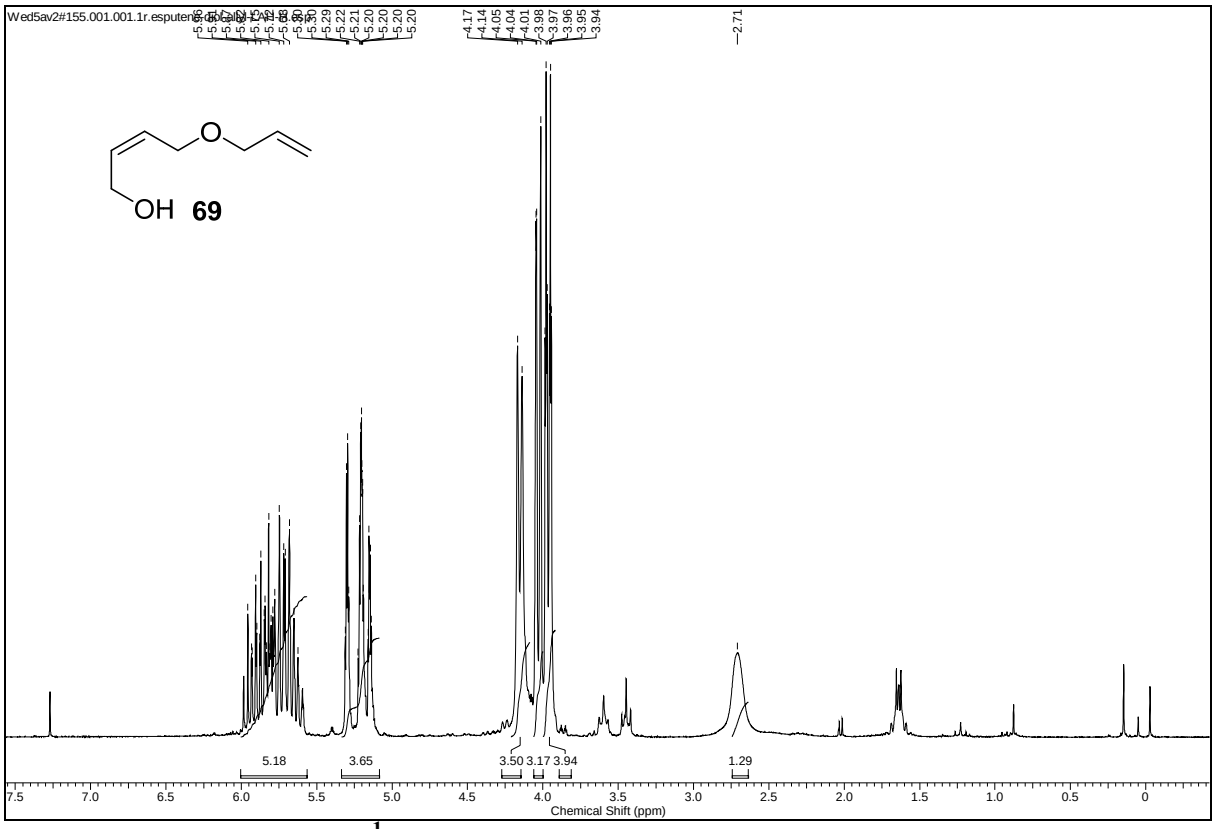
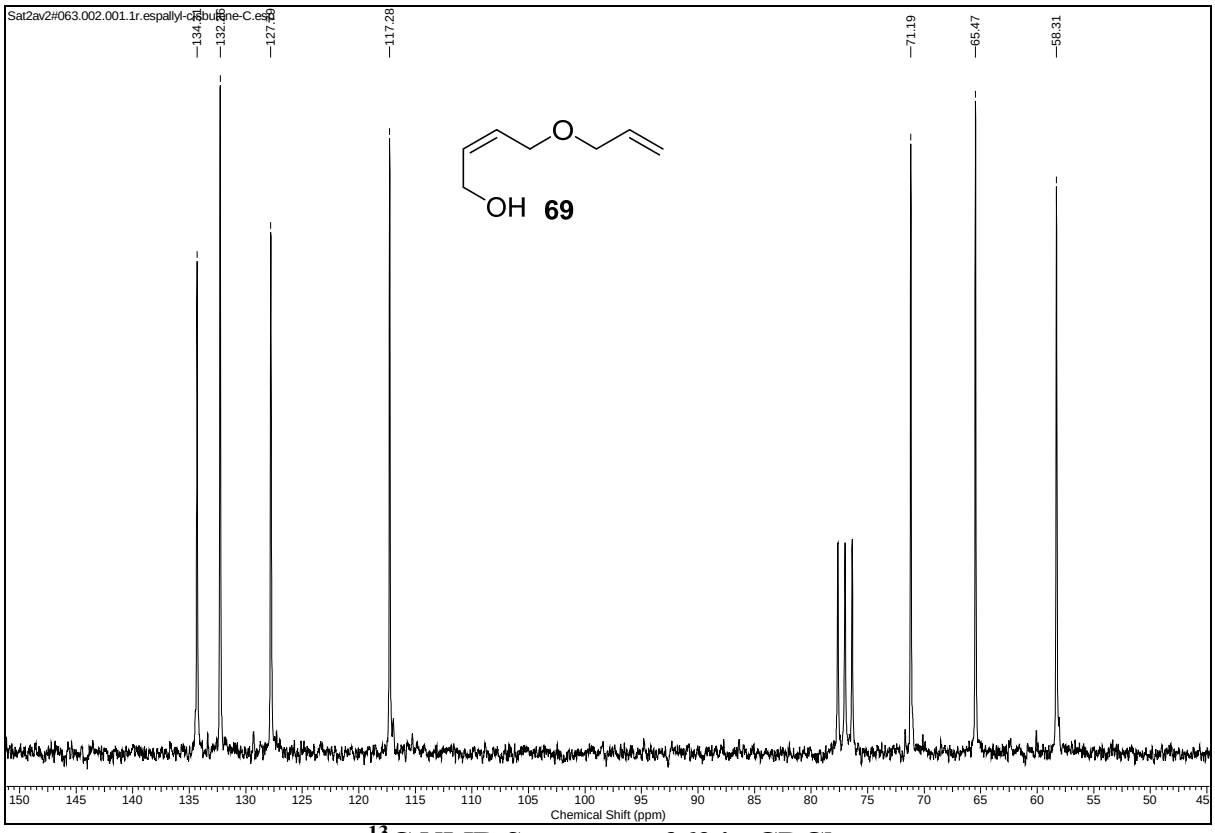
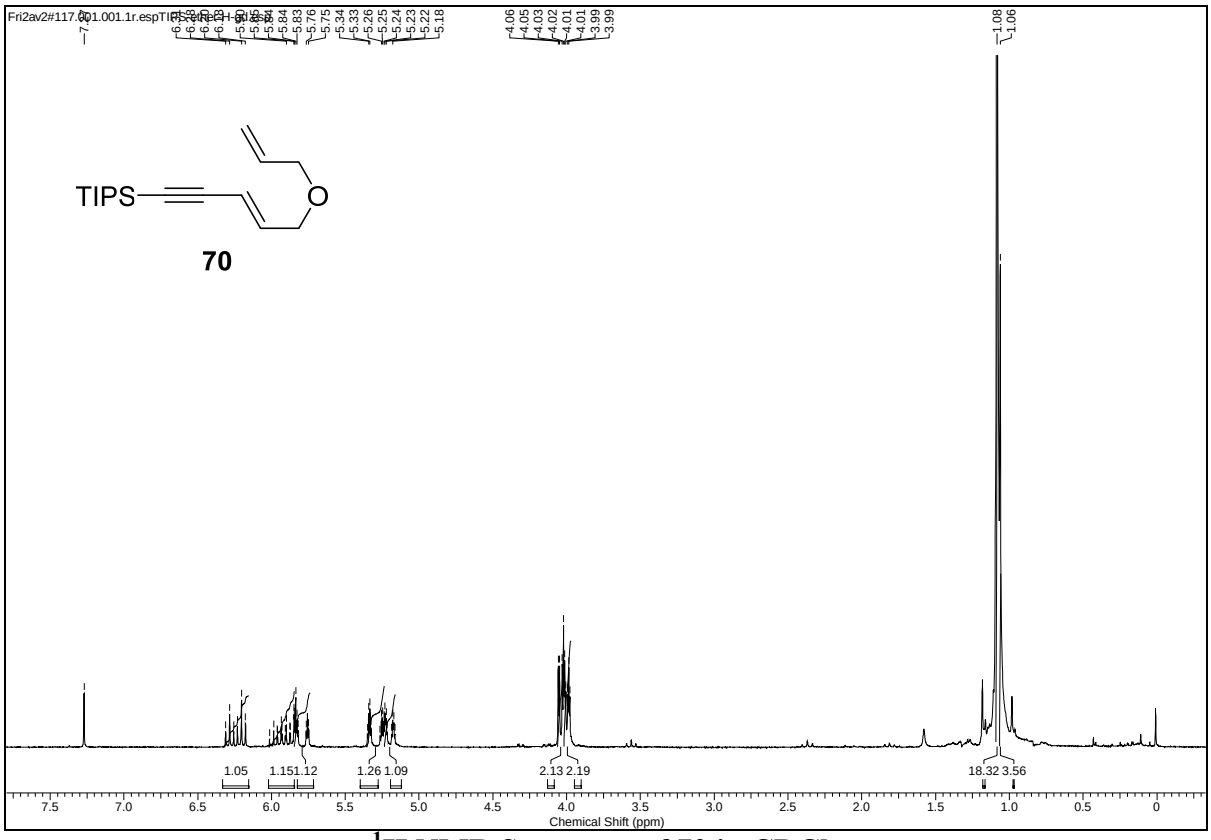


^{1}H NMR Spectrum of 69 in $CDCl_3$



^{13}C NMR Spectrum of 69 in $CDCl_3$



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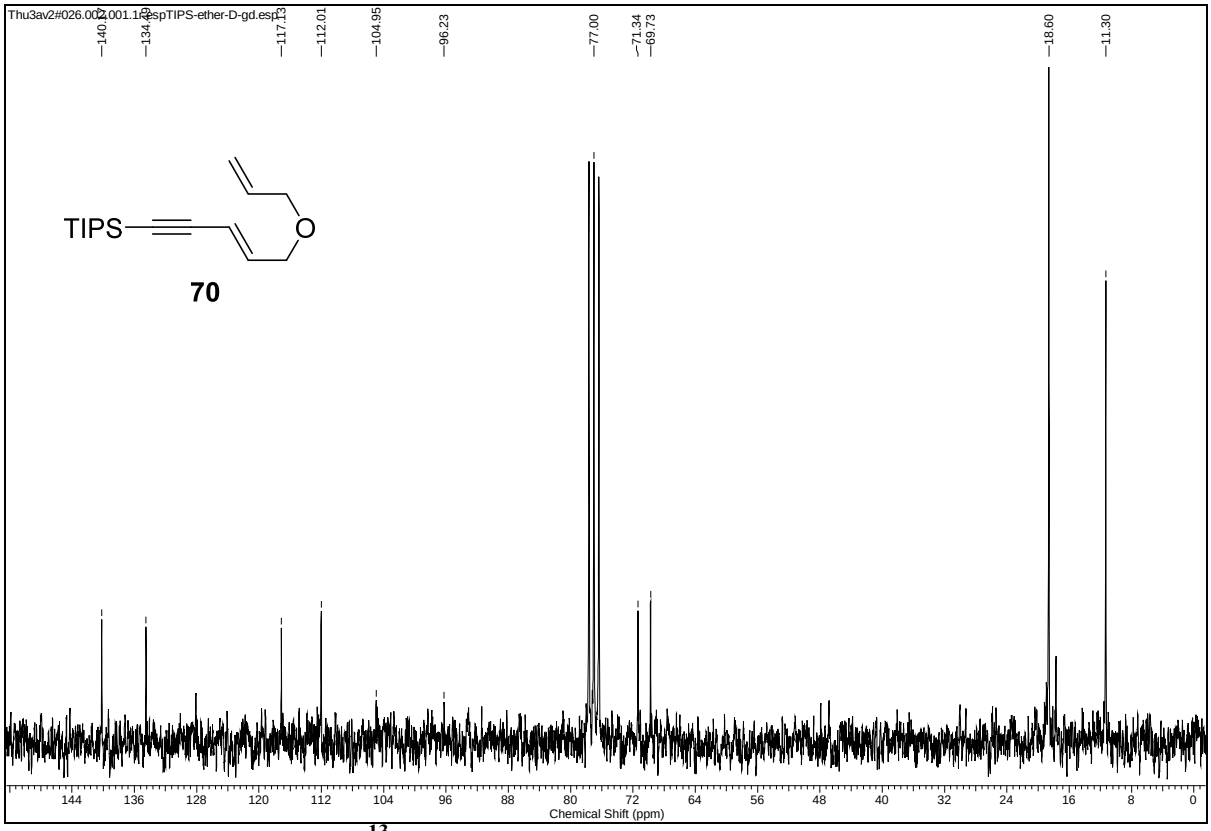

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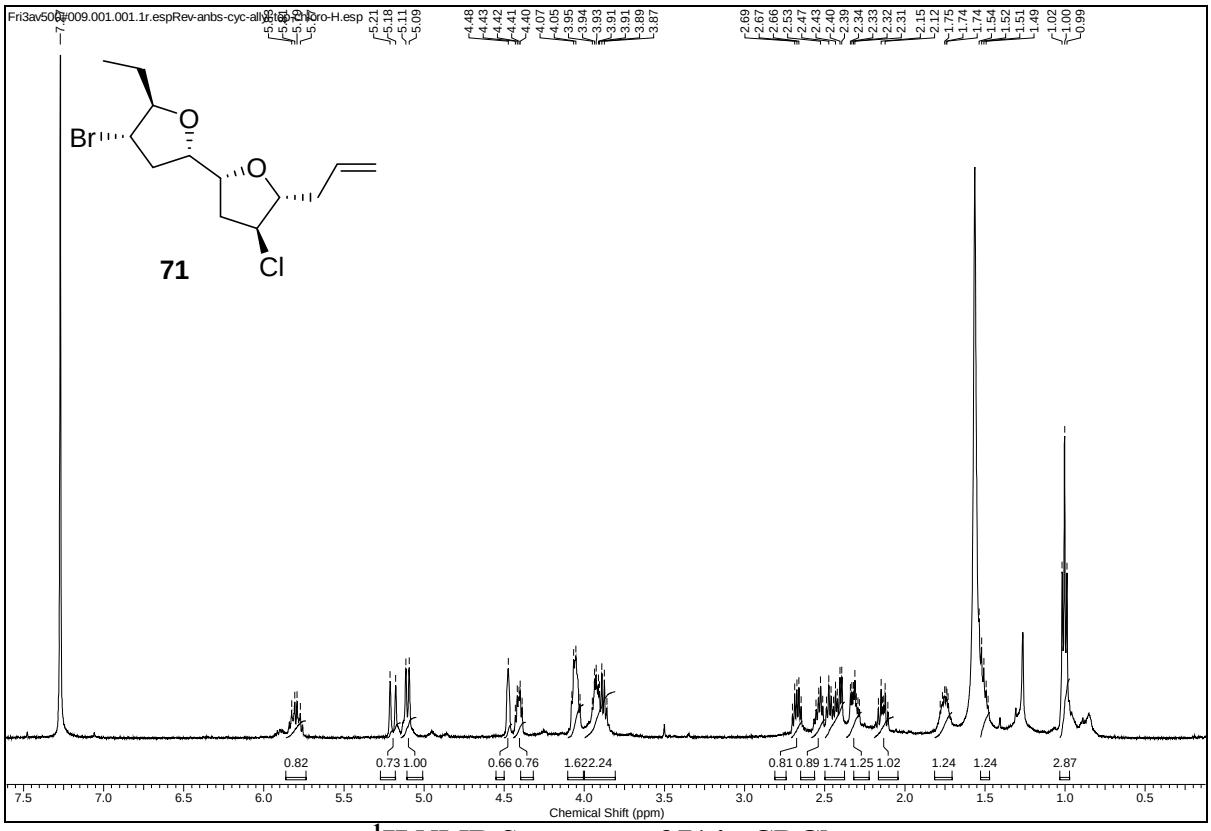

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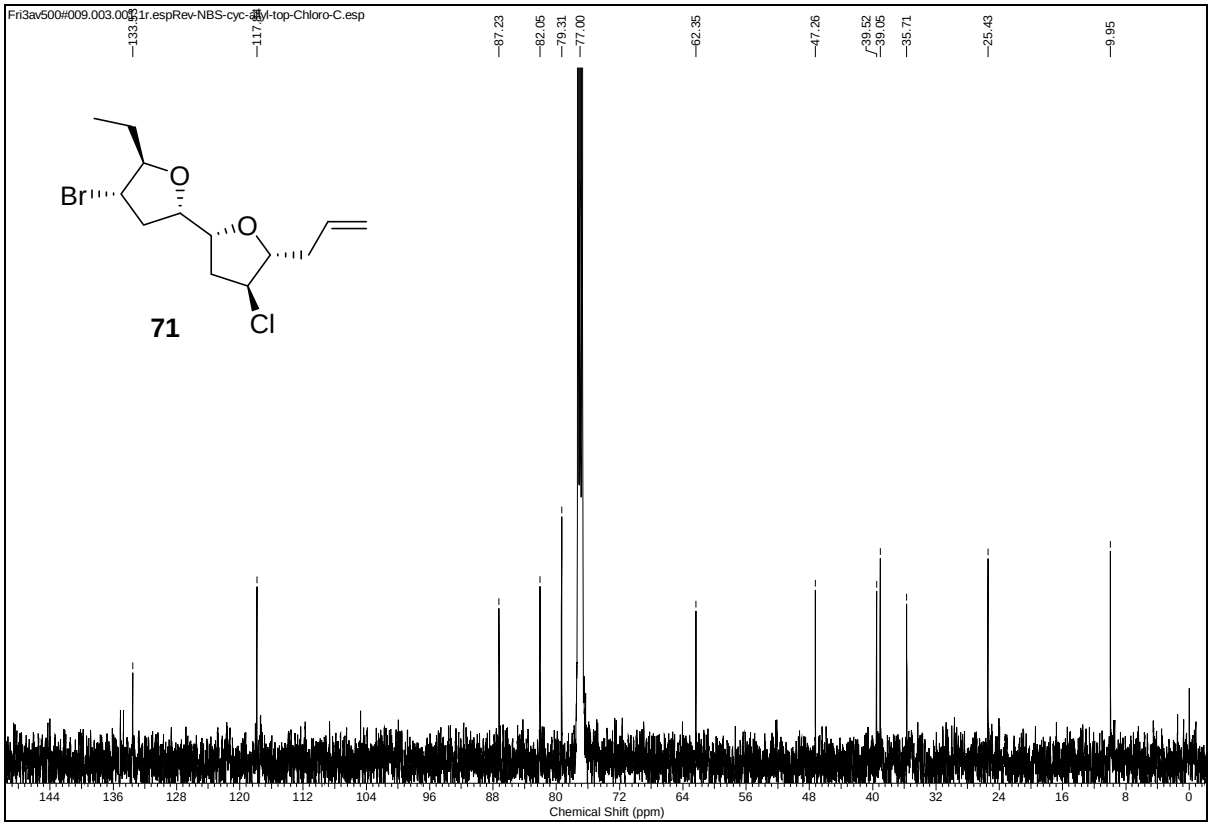

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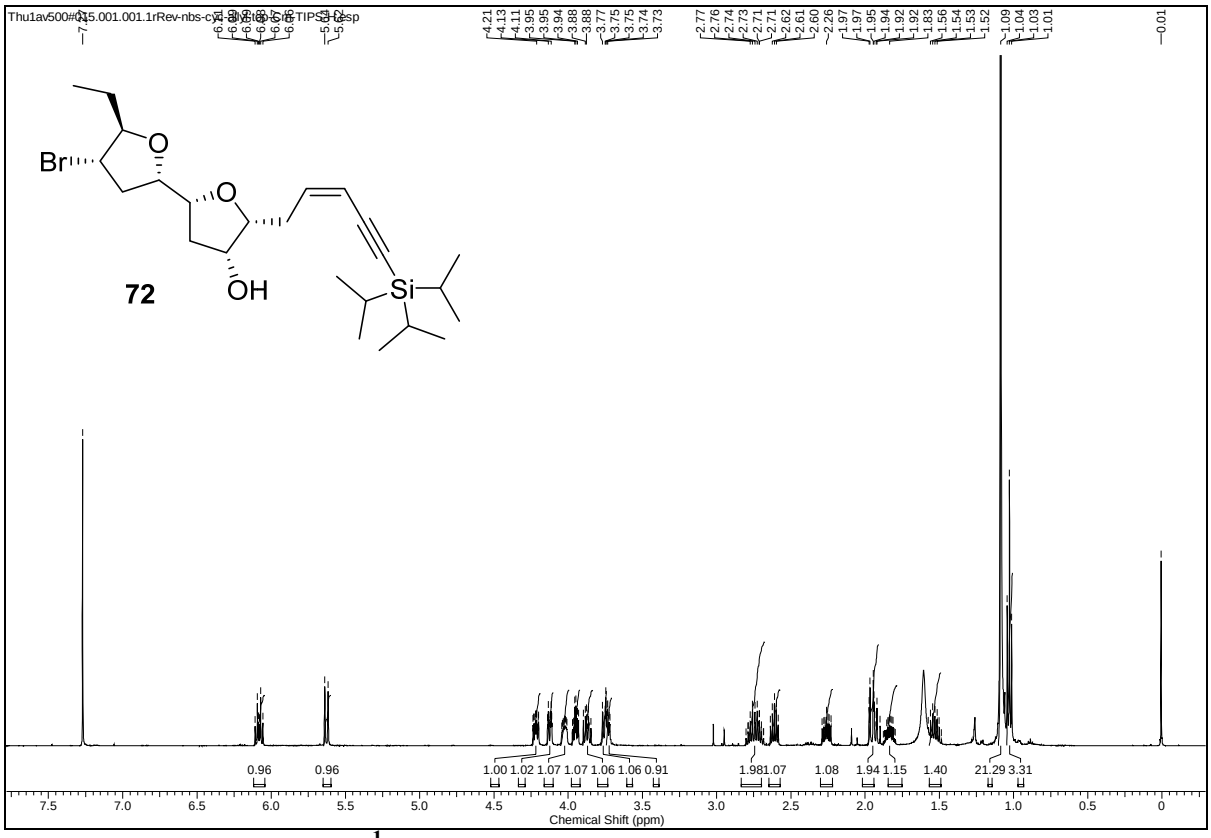

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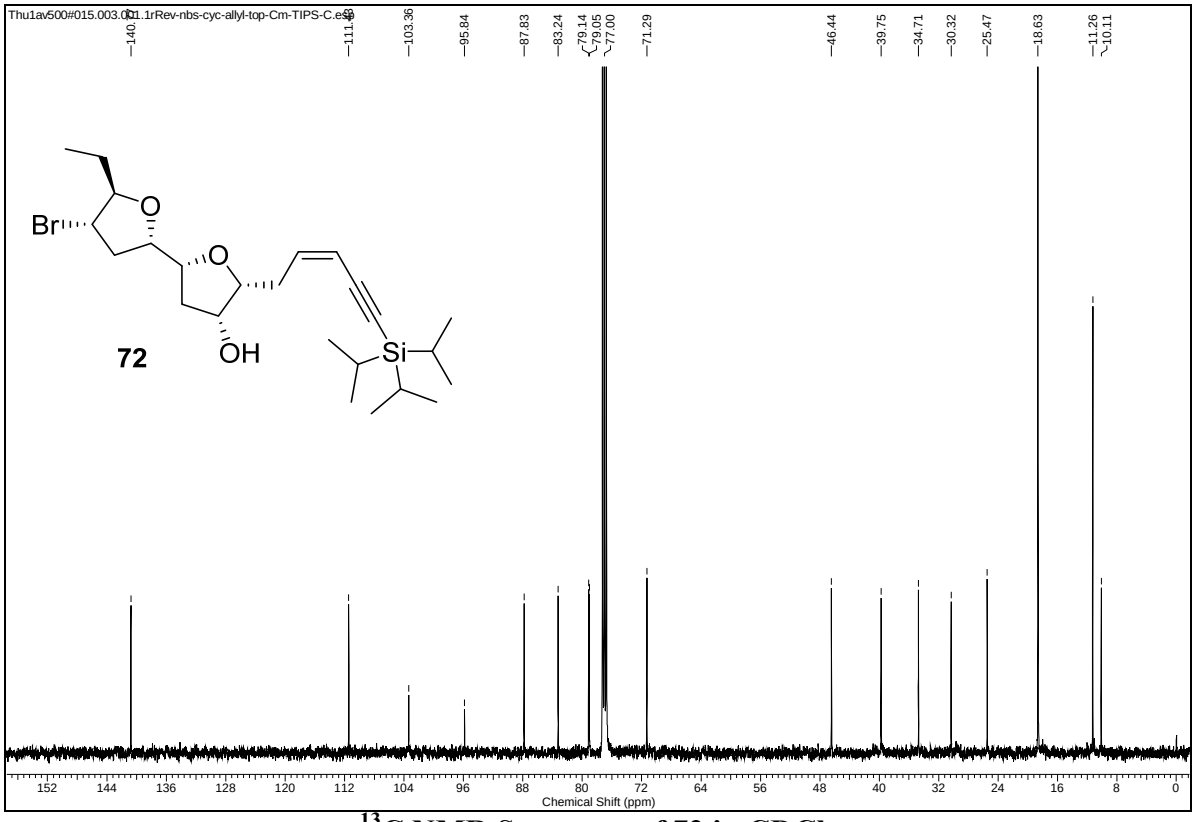
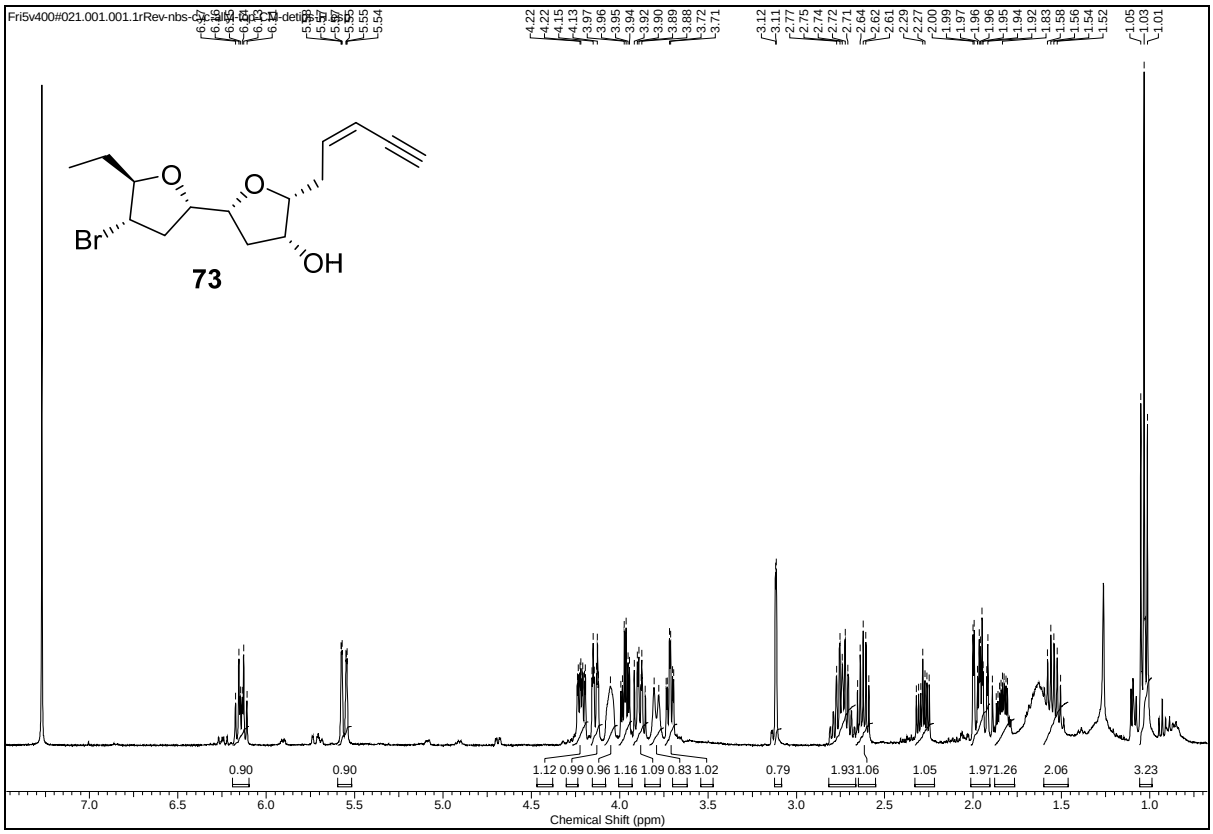
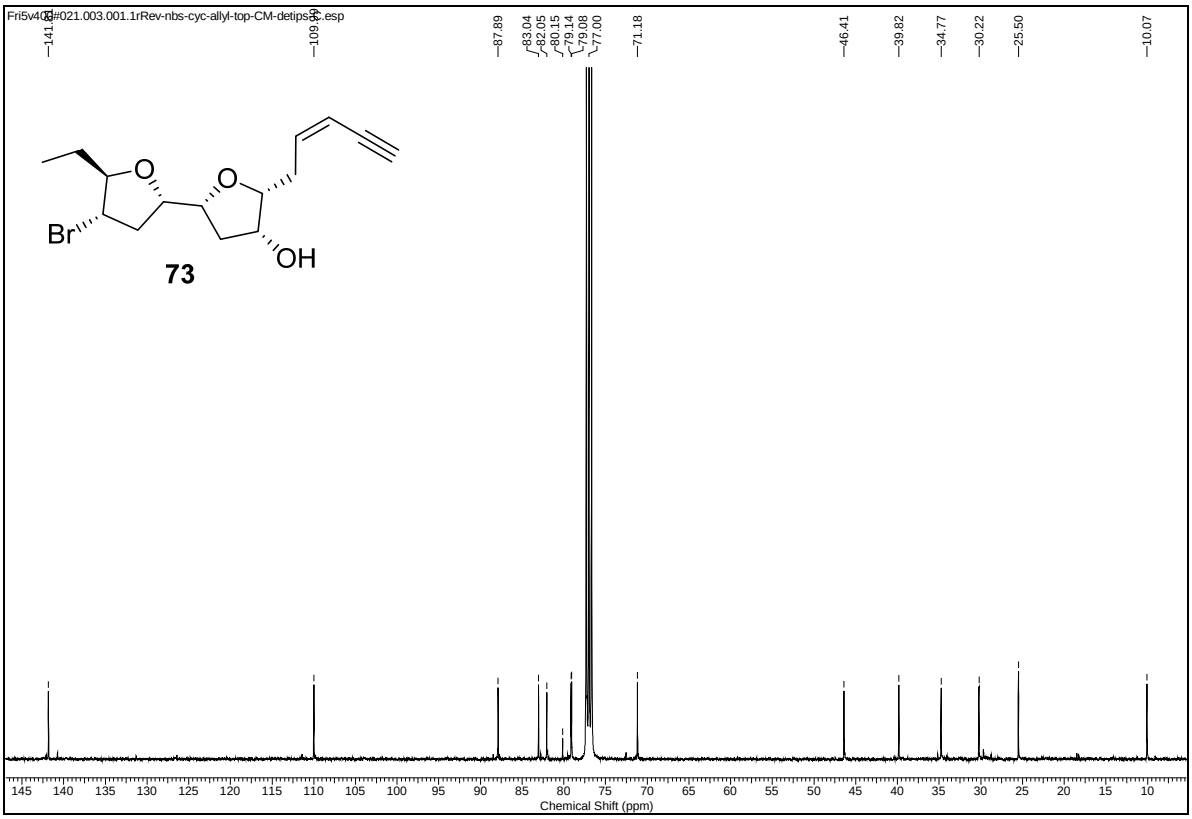


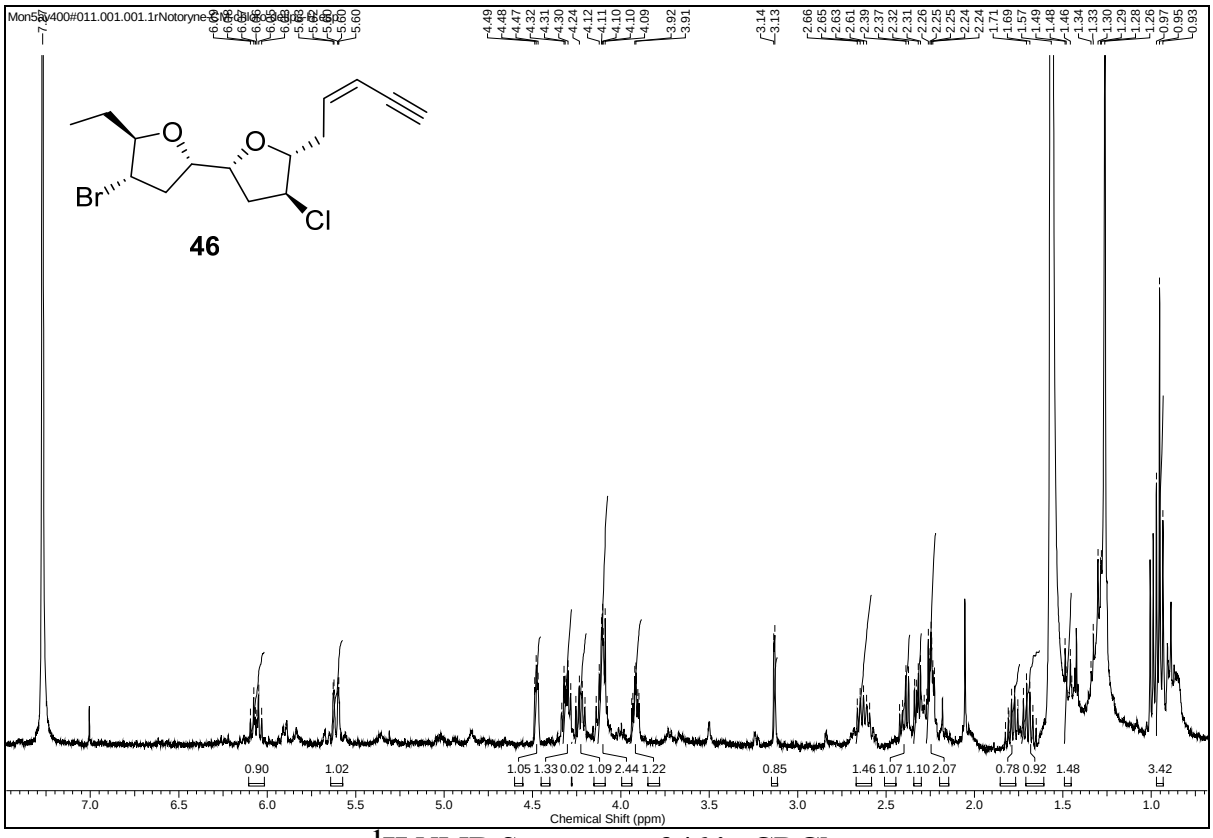
^{13}C NMR Spectrum of 72 in $CDCl_3$



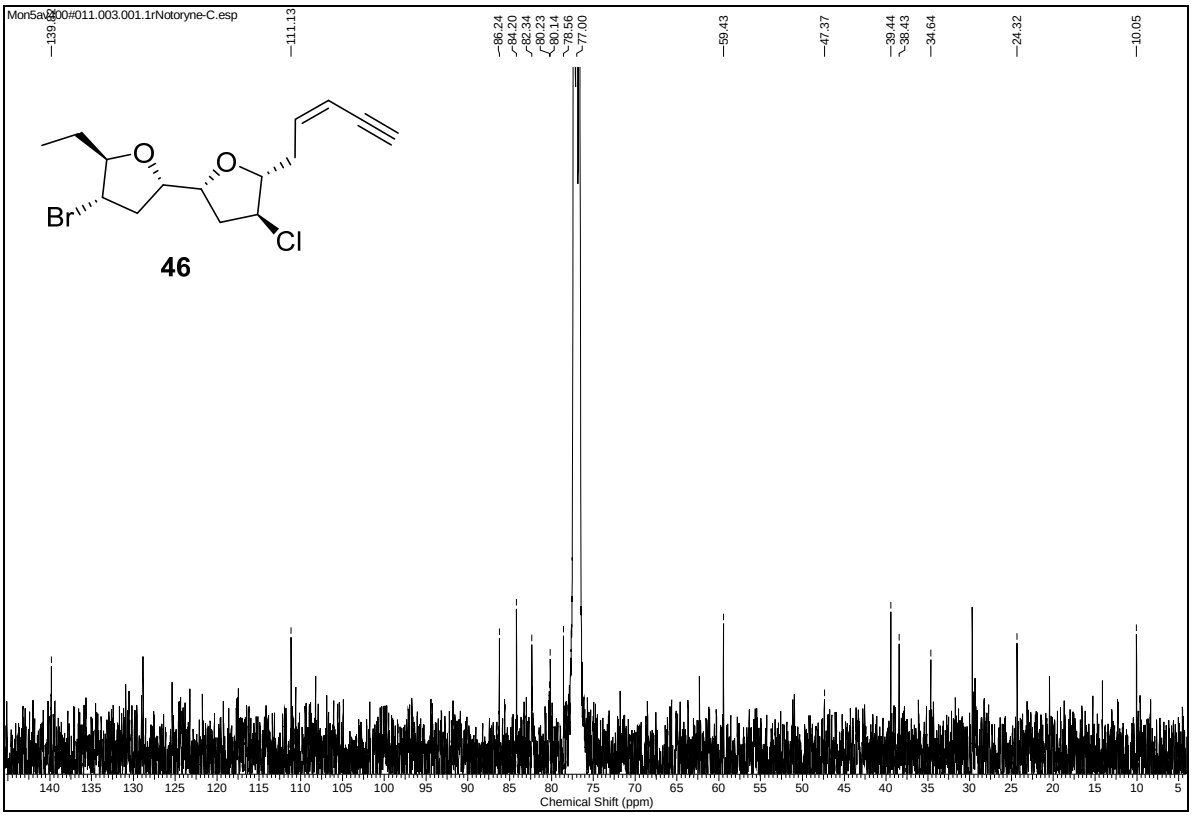
^{1}H NMR Spectrum of 73 in $CDCl_3$



^{13}C NMR Spectrum of 73 in $CDCl_3$



^{1}H NMR Spectrum of 46 in $CDCl_3$



^{13}C NMR Spectrum of 46 in $CDCl_3$

CHAPTER II; SECTION B

Studies toward the total synthesis of Kumausallene

PRESENT WORK

While the work in the direction of Notoryne (**46**) synthesis was in progress, in parallel, the total synthesis of Kumausallene (**47**) was also attempted. As mentioned previously, considering the similar stereochemistry of one of the THF units of Kumausallene with Notoryne, one of the advanced intermediate that we have prepared as part of the Notoryne synthesis has been identified as the starting point for the total synthesis of Kumausallene. Kumausallene belongs to a family of non isoprenoid sesquiterpenes which contain a dioxa-bicyclo [3.3.0] octane core along with a unique *exo*-cyclic bromoallene moiety. In 1983, Kurosawa and co-workers reported the isolation of Kumausallene from the red algae *Laurencia Nipponica Yamada* indigenous to the coast of Hokkaido in Japan.[52] Its Structure was characterized with the help of extensive NMR analysis. Kumausallene belongs to the class of furofuran natural products and, more importantly, it displays a chiral bromoallene motif.

The first total synthesis of Kumausallene was reported by Overman's group.[46b] As was described in the Introduction, the bromo allene motif was constructed through a S_N2' displacement by using $LiCuBr_2$. The second synthesis was documented by Evans' group.[48] A late stage electrophilic cyclization comprising the addition of the C3 hydroxy group on to the enyne side chain had been employed as the key reaction to install the bromoallene part of Kumausallene. Recently, Tang and co-workers [50] documented the synthesis of Kumausallene in which a DMF-promoted biomimetic 1, 4-bromocyclization of a conjugated enynehas been employed as the key reaction to address the bromoallene synthesis. As shown in Figure 19, we are interested to explore the bromonium ion induced cyclo etherification of a conjugated enyne for the construction of the bicyclic core part as well as the *exo* cyclic bromoallene part of this natural product that has been applied earlier by Evans group. The key features of our retro synthesis aredepicted in Figure 19.

Retrosynthesis:

Two options have been selected in this context - either the total synthesis or the synthesis of Tang's bromoenyne intermediate **48**. To have an alternative route that avoids the intermediate **48**, we planned the bromoetherification of diol **75** followed by Appel reaction to introduce the bromine as the final event in our total synthesis of Kumausallene. The synthesis of **75** was planned from the triol **76** which, in turn can be prepared from the alkynol **64** that we have synthesized as a part of the Notoryne synthesis.

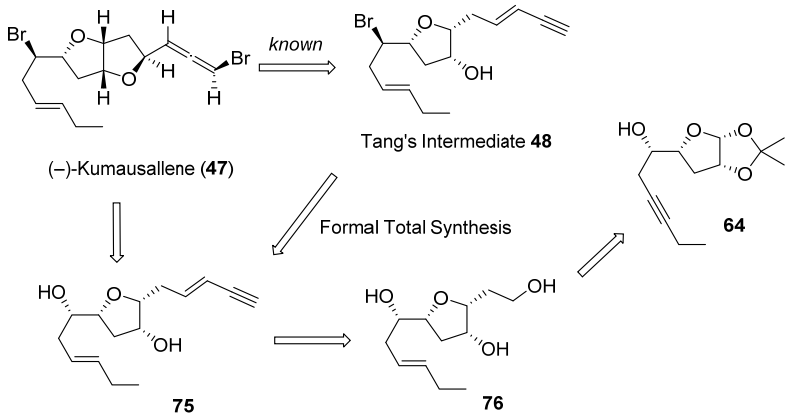
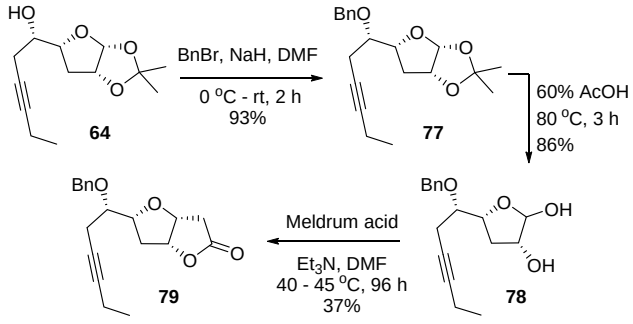


Figure 19. The proposed retrosynthetic route for (–)-Kumausallene (**47**)

Synthesis of the alkentriol 76

The synthesis of the key alkenetriol **76** started from the alkynol **64** that has been synthesized earlier as a part of Notoryne synthesis. The protection of the free –OH group in **64** as its benzyl ether was carried outby using BnBr and NaH in DMF to obtain **77**. In the ^{1}H NMR spectrum of compound **77**, the presence of five Ar-H in the downfield region at δ 7.28-7.43 and of two doublets at δ 4.6 and 4.84 with a large coupling constant of 11.4 Hz corresponding to the benzyl group confirmed the benzylation.

The 1,2-acetonide group in compound **77** was hydrolyzed by employing 60% AcOH at 80 °C to procure the lactols **78**. The absence of two methyl singlets at δ 1.30 and 1.46 in the ^{1}H NMR and of two quartets at 25.8, 26.9 ppm in the ^{13}C NMR confirmed the acetonide group deprotection.

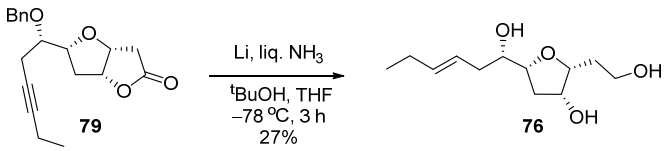


Scheme 107: Synthesis of the lactone **79**

Now, the lactols **78** was treated with Meldrum acid in DMF in the presence of Et_3N (cat.) to obtain lactone **79** in moderate yields. In the ^{1}H NMR spectrum of lactone **79**, two additional protons were seen to resonate in the upfield region at δ 2.73–2.74 and the C2 proton has been shifted to δ 5.04 as doublet of doublet of doublet (ddd). In addition, in the ^{13}C

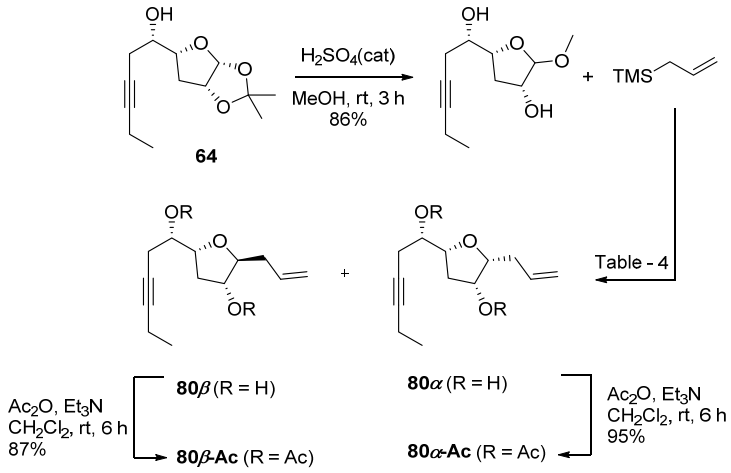
NMR spectrum compound **79**, the two newly added two carbons appeared as triplet at 36.55 ppm and a singlet at 175.31 ppm, which confirmed the lactone formation. All other analytical data were in accordance with the assigned structure.

Next, the selective reduction of the internal triple bond to *trans*-alkene as well as debenzylation was examined under Birch reduction conditions employing Li and liq. NH_3 at –78 ^oC. To our surprise, in addition to the expected transformations, the lactone carbonyl also reduced and the alkene triol **76** was obtained in 27% yield. This indicated the possible Bouveault-Blanc type reduction of lactone taking place in the present case.[61] In the ^1H NMR spectrum compound **76**, the two olefinic protons resonated at δ 5.38 and 5.57 as doublet of triplets (dt) with the coupling constant of 15.4 Hz indicative of a *trans* double bond. In the ^{13}C NMR spectrum of **76**, the corresponding two doublets of the olefinic carbons resonated at 124.01 and 136.16 ppm.



Scheme 108: Birch reduction of lactone **79**

As the synthesis of key triol **76** on large scales turned out to difficult due to the poor yields at two stages, we revised our strategy for the synthesis of **76** *via* α-*C*-allyl glycoside. Consequently, the synthesis of **76** started with the deprotection of 1,2 acetonide of alkynol **64** in the presence of MeOH in H_2SO_4 that led to a mixture of *O*-methyl glycosides. This mixture was directly used for the *C*-glycosidation. The *C*-glycosidation needed employing allylTMS and TMSOTf substantial optimization of solvents/conditions to control the selectivity and yield. As shown in Table 6, in acetonitrile at 0 ^oC, a mixture of α- and β-*C*-allyl glycosides respectively **80**α and **80**β were obtained in 1:3 ratios. When the same reaction was carried out at –40 °C, it gave the same mixture in a 12:1 ratio in favor of the α- glycoside **80**α. These α- and β-*C*-allyl glycosides respectively, **80**α and **80**β were separated by column chromatography and subjected for the acetylation for further characterization with the help of 2D NMR spectral data analysis.



S. No.	Reaction conditions	Results obtained
1	$BF_3.Et_2O$, DCM, 0 ^oC– rt	Decomposition
2	$BF_3.Et_2O$, ACN, 0 ^oC– rt	Decomposition
3	$ZnBr_2$, toluene, 110 ^oC	Decomposition
4	TMSOTf, DCM, 0 ^oC– rt	Complex reaction mixture
5	TMSOTf, ACN, 0 ^oC– rt	76% α: β (1: 3)
6	TMSOTf, ACN, –40 ^oC– 0 ^oC	84% , α: β (12: 1)

Table 6: Synthesis of *C*-glycosides **80α** and **80β** *via O*-glycoside

In the ^{1}H NMR spectrum of **80α-Ac**, two singlets at 2.09 and 2.10 integrating each for three protons and two C*H*OAc at 5.01 (C2, ddd) and 5.22 (C6, ddd) were seen. The strong n*O*e interactions noticed in between the C4-H^4, C5-H^5 and C7-H^7 revealed that they are on the same side and that the anomeric configuration was alpha. Similarly, in the ^{1}H NMR spectrum of **80β-Ac**, two singlets at 2.07 and 2.10 for three protons each along with two C*H*OAc seen to resonate at down field at 4.98 (C2, ddd) and 5.03 (C6, ddd). In the ^{13}C NMR spectrum, two singlets at 170.14 and 170.76 ppm acknowledge the acyl group as well as two carbons of *C*HOAc coming at 77.19 (C2) and 72.64 (C6) as doublet (Scheme 3). In the NOESY of **80β-Ac**, the observed strong n*O*e interactions between the C3-H^3, C5-H^5 and C7-H^7 suggested a beta-configuration at the glycoside carbon (figure. 20).

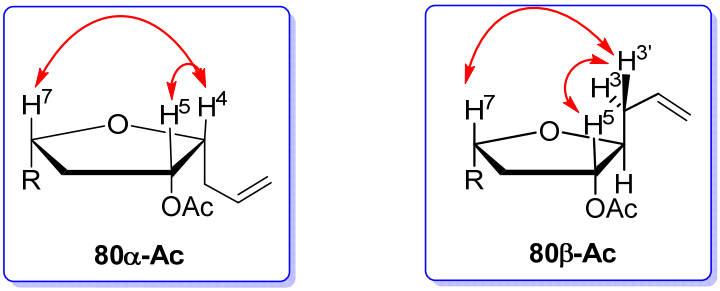
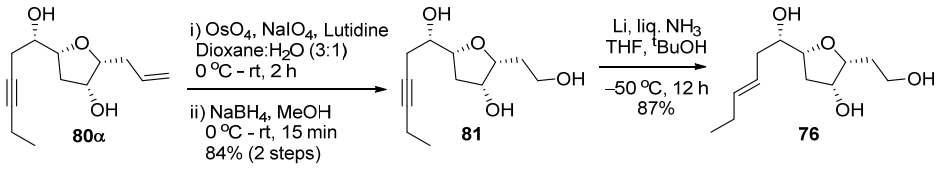


Figure 20: The strong n*O*es noticed in the **80*α*-Ac** and **80*β*-Ac**.

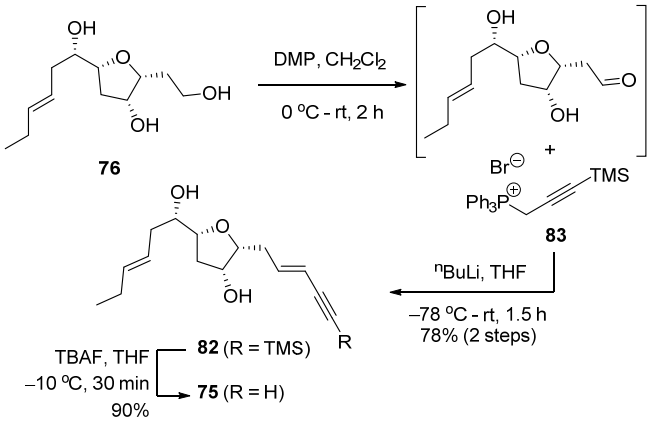
After having the key *C*-glycoside **80*α***, the next task was preparing the key alkenetriol **76**. The synthesis of the key alkenetriol **76** started with the oxidative olefin cleavage of **80*α***, under the modified Lemieux-Johnson oxidation protocol employing OsO_4 and $NaIO_4$ in the presence of 2,6-lutidine. [62] The resulting aldehyde was reduced immediately using $NaBH_4$ in MeOH to procure the alkynetriol **81**. The appearance of a new multiplet resonating at δ 3.67–3.73 in ^{1}H NMR and new *C*H_2 triplet at 59.6 ppm in ^{13}C NMR were in supportive of the assigned structure of compound **81**. Subsequently, the triple bond of triol **81** was reduced to *trans*-alkene **76** under Birch reduction conditions employing Li and NH_3 at –50 ^{o}C. The spectral data of **76** was in agreement with the data that we obtained earlier.



Scheme 109: Synthesis of key alkenetriol **76**

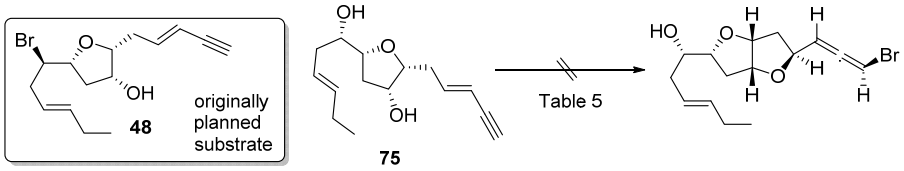
Having established a scalable route for the alkenetriol **76**, we proceeded further for the installation of a *trans*-enyne moiety. The eneyne **75** was synthesized from the alkenetriol **76** following a two-step sequence. The selective oxidation of 1^o– OH to aldehyde by using Dess-Martin periodinane [63] and the 3 carbon Wittig olefination [29, 50] of the resulting aldehyde with the ylide **83** gave the TMS protected enyne **82**. The ^{1}H NMR spectrum of the enyne **82**, showed that olefinic-H resonated as a doublet (d) at δ 5.64 and a doublet of triplet (dt) at 6.26 ppm with a large coupling constant of 15.9 Hz indicating *E*-configured olefin. Also, in the ^{13}C NMR spectrum, doublets at 111.96 and 141.90 ppm, and alkyne singlets at 93.27 and 103.82 ppm and TMS quartet at –0.08 ppm for three carbons confirmed the presence of the TMS-protected enyne group. Next, the deprotection of the TMS group in **82** by using TBAF in THF afforded the advanced intermediate enyne **75**. In the ^{1}H NMR spectrum of compound

75, peaks corresponding to the TMS group at δ –0.17 are absent and a doublet at 2.80 (d) with a coupling constant 1.9 Hz representing the terminal alkyne-H was present. All other analytical data of compound **75** were in accordance with the assigned structure (Scheme 110).



Scheme 110: Synthesis of key enyne intermediate **75**

Having this compound enyne diol **75** in hand, initially we explored the possibility of executing the key complexity transformation - bromonium ion induced bromo etherification of **75** to install the fused furofuran unit along with placing the pendant bromoallene tether, then carrying out the Appel reaction to introduce the bromo-group at the homoallylic position. This turned out to be a problematic proposition. Various sources of bromonium ion have been explored and their screening in different solvents has been investigated. In all the cases, the reactions led to complex mixtures and the isolation of one of the cyclized products turned out to be difficult. The use of freshly crystallized reagents and properly dried solvents like CH_3CN, DCM, and acetone could not lead to any success. The presence of two free hydroxyl groups in the substrate was reasoned to be one of the primary causes for the problems associated with this key cycloetherification. We have to go back to our original proposal of placing the homo-allylic bromine group prior to conducting the key complexity building transform i.e – the synthesis of Tang's intermediate **48**.

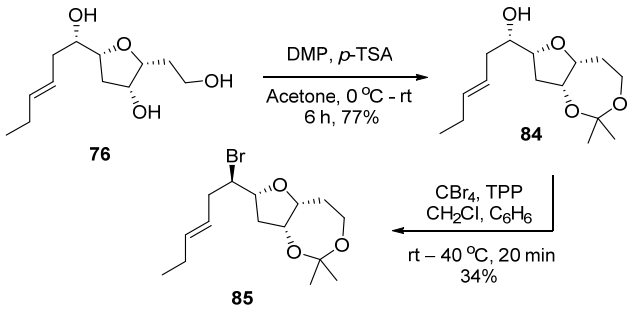


S. No.	Reaction conditions	Results obtained
1	NBS, DCM, 0 °C– rt	Complex reaction mixture

2	NBS, ACN, 0 ^{o}C– rt	Complex reaction mixture
3	NBS, acetone, 0 ^{o}C– rt	Complex reaction mixture
4	TBCD, DCM, 0 ^{o}C– rt	Complex reaction mixture
5	NBS, DMF, toluene, rt	Complex reaction mixture

Table 7. Attempted bormonium-ion induced cycloetherification of diol **75**

Our efforts in this direction started with the conversion of the alkene triol **76** to the corresponding acetonide **84** by using 2,2- dimethoxypropane in the presence of *p*-TSA (cat.). The ^{1}H NMR spectrum of **84** showed the singlet peaks at δ 1.36 and 1.38 integrating for three protons each acknowledging the acetonide unit. In the ^{13}C NMR spectrum the acetonide quaternary carbon resonated as a singlet at 101.34 and two methyl groups were characterized at 24.68 and 24.85 ppm as a quartet respectively and confirmed the acetonide protection.

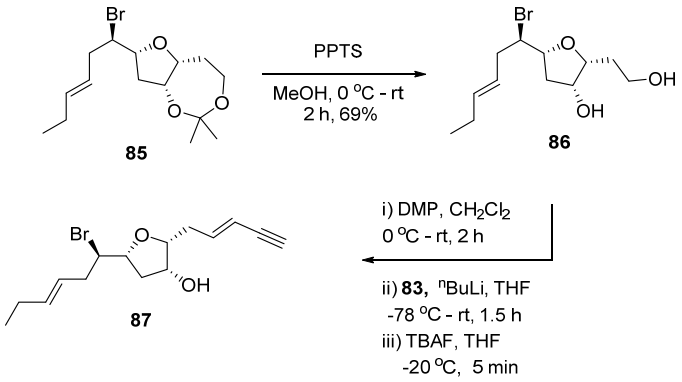


Scheme 111: Synthesis of compound **85**

Next, the Appel reaction[46, 50, 60] of the resulting **84** was carried out employing CBr_4, TPP and 2,6-di-tertbutylpyridine. The corresponding bromo-compound **85** was obtained in moderate yield. The ^{1}H NMR spectrum of **85** showed the peaks of the C*H*Br at 4.51 as a doublet of triplet and the allylic protons of CHC*H*$_2$CHBr are well separated, resonating at 2.31 and 2.48 as doublet of triplets. In the ^{13}C NMR spectrum, the *C*HBr comes as a doublet at 59.0 ppm along with the allylic carbon of CH*C*H$_2$CHBr coming at 36.66 ppm as a triplet compared to the starting alcohol which came at 32.71 ppm. All other analytical data were in accordance with the assigned structure.

The attempts to improve the yield of the Appel reaction were not successful. Despite the poor yield at this stage, we proceeded for the synthesis of bromoenyne **48** so that a formal total synthesis of Kumausallene could be completed. Accordingly, the compound **85** was subjected for acetonide hydrolysis employing PPTS in methanol at rt to obtain the diol **86** in 69% yield. The absence of the methyl singlets both in ^{1}H NMR (δ 1.34 and 1.38 ppm) and

^{13}CNMR [24.29 (q), 25.12(q) and 101.08 (s) ppm] clearly indicated the acetonide hydrolysis. Next, the resulting diol **86** was subjected for the selective oxidation of 1°–OH employing DMP in dichloromethane and the intermediate aldehyde was immediately treated with the ylide generated from the phosphonium salt **83** employing the *n*-butyl lithium. Discouragingly, the reaction gave a complex mixture. Although the peaks corresponding to **87** could be seen on HRMS, efforts to obtain the pure samples of **87** for characterization met with failure.

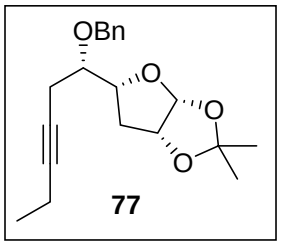


Scheme 112: An attempts for the formal total synthesis of Kumausallene

The failures that we encountered across the various approaches that we explored for the synthesis of Notoryne and Kumausallene have revealed that the problems are mainly associated either with during the introduction of halo-group or during the bromoetherification event, in the latter case. One of the important messages that we have learned out of this exercise was that the construction or the manipulation of the enyne group after installing the halo-group is problematic. This should be addressed by holding the –OH group until the end and with a proper protecting group and also the key enyne or allene moieties should be introduced prior to the introduction of the bromo-group. Currently, work in this direction is in progress.

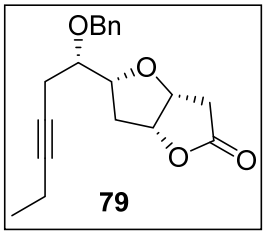
EXPERIMENTAL & DATA

(3aR,5R,6aR)-5-((S)-1-(benzyloxy)hex-3-yn-1-yl)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxole (77)



To an ice cooled solution of the alcohol **64** (2.5 g, 10.4 mmol) in DMF (25 mL) was added NaH (50%, 850 mg, 17.7 mmol) and stirred for 0.5 h at rt. The reaction mixture was cooled to 0 °C and treated with benzyl chloride (1.9 mL, 15.6 mmol) and stirring was continued for 4 h at rt. The reaction mixture was quenched with ice, partitioned between ethyl acetate, water and the organic layer was separated and aqueous layer was extracted. The combined organic layer was washed with brine, dried (Na_2SO_4), and concentrated. The crude was purified by column chromatography (95:5 petroleum ether/EtOAc) to afford **77** (3.2 g, 93%) as colorless syrup, R_f (10% EtOAc/petroleum ether) 0.6 $[\alpha]^{25}_D$: –5.5 (*c* 2.9, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz): δ1.13 (t, *J* = 7.5 Hz, 3H), 1.30 (s, 3H), 1.46 (s, 3H), 2.06–2.26 (m, 3H), 2.32 (dd, *J* = 2.4, 14.1 Hz, 1H), 2.44–2.57 (m, 1H), 2.65–2.78 (m, 1H), 3.83 (ddd, *J* = 4.0, 5.2, 9.1 Hz, 1H), 4.18 (ddd, *J* = 2.9, 8.4, 11.4 Hz, 1H), 4.6 (d, *J* = 11.4 Hz, 1H), 4.73 (ddd, *J* = 1.1, 4.0, 5.6 Hz, 1H), 4.84 (d, *J* = 11.4 Hz, 1H), 5.79 (d, *J* = 4.0 Hz, 1H), 7.28–7.43 (m, 5H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ12.5 (t) 14.2 (q), 21.1 (t), 25.8 (q), 26.9 (q), 33.3 (t), 72.1(t), 75.4 (s), 77.92 (d), 80.6 (d), 81.0 (d), 83.4 (s), 106.6 (d), 111.9 (s), 127.7 (d), 128.1 (d, 2C), 128.3 (d, 2C), 138.2 (s) ppm; MS (ESI) m/z = 352.94 $[M+Na]^+$; HRMS (ESI) calcd for $C_{20}H_{26}O_4$ $[M+Na]^+$ 353.1729, found 353.1722.

(3aR,5R,6aR)-5-((S)-1-(Benzyloxy)hex-3-yn-1-yl)tetrahydrofuro[3,2-b]furan-2(3H)-one (79)



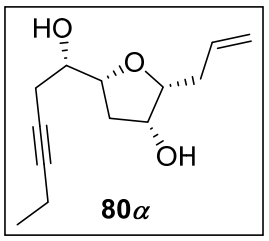
A solution of compound **77** (2.5 g, 7.5 mmol) in 20 mL of 60% acetic acid was heated at 80 °C for 3h. The solvent was removed in vacuum using toluene as a co-solvent, the resulting crude lactol **78** (2 g, 91%) was used as such for the next step without purification.

To a stirred solution of **78** (2 g, 7 mmol) in dry DMF (20 mL), Meldrum's acid (2 g, 17 mmol) and Et_3N (0.1 mL) were added at 0 ^oC and the reaction mixture was stirred at 40 ^oC for 16 h. The solvent was removed in vacuum using toluene as a co-solvent. Purification of the crude product was carried out by column chromatography (95:5 petroleum ether/EtOAc) to afford the pure lactone **79** (800 mg, 37%) as a colorless oil: R_f (10% EtOAc/petroleum ether) 0.55; $[\alpha]^{25}_D$: + 62.4 (*c* 0.6, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ1.12 (t, *J* = 7.5 Hz, 3H),

2.14–2.21 (m, 2H), 2.31–2.44 (m, 2H), 2.46–2.50 (m, 2H), 2.73–2.74 (m, 2H), 3.58 (dd, *J* = 5.5, 11.3 Hz, 1H), 4.19 (dd, *J* = 6.8, 14.1 Hz, 1H), 4.57–4.61 (m, 2H), 4.73 (d, *J* = 11.5 Hz, 1H), 5.04 (ddd, *J* =2.0, 4.3, 6.3 Hz, 1H), 7.29–7.36 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ12.5 (t), 14.1 (q), 21.7 (t), 34.0 (t), 36.6 (t), 72.5 (t), 74.9 (s), 78.4 (d), 78.9 (d), 81.1 (d), 83.8 (s), 84.4 (d), 127.8 (d), 128.0 (d, 2C), 128.4 (d, 2C), 138.0 (s), 175.3 (s) ppm; MS (ESI) m/z = 337.36 $[M+Na]^+$; HRMS (ESI) calcd for $C_{19}H_{22}O_4$ $[M+Na]^+$ 337.1416, found 337.1404.

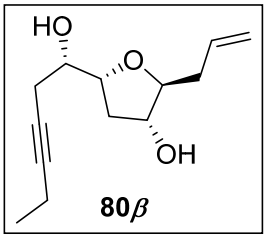
(2R,3R,5R)-2-Allyl-5-((S)-1-hydroxyhex-3-yn-1-yl)tetrahydrofuran-3-ol (80α)

At –40 °C, a solution of methylglycosides of compound **64** (1 g, 4.7 mmol) and allyl trimethylsilane (3.7 mL, 23.3 mmol) in acetonitrile (30 mL) was treated drop wise with trimethylsilyl triflate (0.9 mL, 4.7 mmol) . The solution was allowed to warm to 0 °C over 8 h. As soon as it reached to 0 °C, a saturated aqueous solutions of $NaHCO_3$ (10 mL) was added and the reaction mixture was concentrated under reduced pressure and the aqueous layer was extracted with EtOAc (4x 25 ml). The combined organic layer was dried over $NaSO_4$ and concentrated under reduced pressure. The crude was purified by column chromatography (petroleum ether:EtOAc, 80:20) to yield α-*C*-glycoside **80α** (900 mg, 86%) as a colourless oil, R_f (35% EtOAc/petroleum ether) 0.6; along with β-*C*-glycoside **80β** (80 mg, 7%); R_f (35% EtOAc/petroleum ether) 0.58.



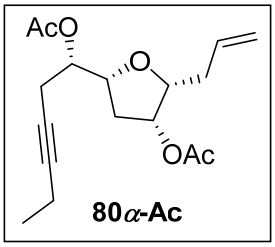
80α

Characterization data of compound 80α: $[\alpha]^{25}_D$: +131.8 (*c* 1.7, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz): δ1.12 (t, *J* = 7.5 Hz, 3H), 1.99 (dd, *J* = 3.1, 14.1 Hz, 1H), 2.15–2.19 (m, 2H), 2.20–2.27 (m, 1H), 2.29–2.36 (m, 3H), 2.42–2.51 (m, 3H), 3.68 (ddd, *J* = 2.4, 7.0, 9.2 Hz, 1H), 3.99 (ddd, *J* = 2.1, 7.3, 8.5 Hz, 1H), 4.08 (dd, *J* = 2.1, 4.9 Hz, 1H), 4.16 (dt, *J* = 2.4, 9.7 Hz, 1H), 5.08 (d, *J* = 10.1 Hz, 1H), 5.17 (dd, *J* = 0.9, 17.1 Hz, 1H), 5.84–5.92 (m, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ12.4 (t), 14.1 (q), 24.3 (t), 33.5 (t), 34.1 (t), 70.8 (d), 71.2 (d), 74.4 (s), 79.3 (d), 83.2 (d), 84.8 (s), 117.0 (t), 134.9 (d) ppm; MS (ESI) m/z = 246.83 $[M+Na]^+$; HRMS (ESI) calcd for $C_{13}H_{20}O_3$ $[M+Na]^+$ 247.1310, found 247.1304.



Characterization data of compound 80β: $[\alpha]^{25}_D$: –36.2 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz): δ1.12 (t, *J* = 7.6 Hz, 3H), 1.95 (ddd, *J* = 2.0, 3.4, 13.9 Hz, 1H), 2.12–2.22 (m, 4H), 2.26 (ddd, *J* = 5.9, 9.1, 15.2 Hz, 1H), 2.30–2.33 (m, 2H), 2.97 (br s, 1H), 3.61 (br s, 1H), 3.97 (ddd, *J* = 2.9, 6.9, 9.5 Hz, 1H), 4.05 (ddd, *J* = 1.4, 6.9, 8.2 Hz, 1H), 4.08 (d, *J* = 5.9 Hz, 1H), 4.22 (dt, *J* = 3.4, 9.1 Hz, 1H), 5.09–5.14 (m, 2H), 5.78–5.86 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ12.4 (t), 14.1 (q), 24.3 (t), 33.0 (t), 37.9 (t), 71.3 (d), 74.5 (s), 74.6 (d), 79.7 (d), 84.7 (s), 86.5 (d), 117.4 (t), 134.2 (d) ppm; MS (ESI) m/z = 246.89 $[M+Na]^+$; HRMS (ESI) calcd for $C_{13}H_{20}O_3$ $[M+Na]^+$ 247.1310, found 247.1305.

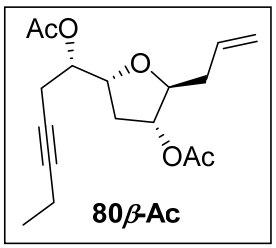
(S)-1-((2R,4R,5R)-4-acetoxy-5-allyltetrahydrofuran-2-yl)hex-3-yn-1-yl acetate (80α–Ac)



To a solution of **80α** (60 mg, 0.27 mmol) in CH_2Cl_2 (10 mL) at 0 °C was added Et_3N (0.2 mL, 1.6 mmol), DMAP (2 mg) and stirred for 15 min. To this, acetic anhydride (0.08 mL, 0.8 mmol) was added at 0 °C and stirred further for 2 h. The reaction mixture was diluted with CH_2Cl_2 (10 mL) and washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. The resulting crude was purified by column chromatography (90:10 petroleum ether/EtOAc) to afford the diaceate **80α–Ac** (75 mg, 91%) as colorless syrup: R_f (15% EtOAc/petroleum ether) 0.64; $[\alpha]^{25}_D$: –3.0 (*c* 0.54, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ1.11 (t, *J* = 7.5 Hz, 3H), 1.91 (ddd, *J* = 1.8, 5.0, 14.6 Hz, 1H), 2.09 (s, 3H), 2.10 (s, 3H), 2.13–2.18 (m, 2H), 2.33–2.42 (m, 3H), 2.47–2.63 (m, 2H), 3.89 (ddd, *J* = 4.0, 7.0, 10.8 Hz, 1H), 4.11 (ddd, *J* = 5.3, 7.0, 12.0 Hz, 1H), 5.01 (ddd, *J* = 5.3, 6.4, 11.8 Hz, 1H), 5.04–5.12 (m, 2H), 5.22 (ddd, *J* = 1.8, 3.8, 5.7 Hz, 1H), 5.72–5.83 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ12.4 (t), 14.1 (q), 21.1 (t, 2C), 21.4 (t), 33.8 (t), 34.9 (t), 72.9 (d), 73.9 (d), 74.3 (s), 77.1 (d), 81.3 (d), 83.8 (s), 117.2 (t), 134.0 (d), 170.2 (s), 170.6 (s) ppm; MS (ESI) m/z = 331.18 $[M+Na]^+$; HRMS (ESI) calcd for $C_{17}H_{24}O_5$ $[M+Na]^+$ 331.1522, found 331.1510.

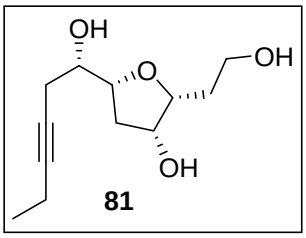
(S)-1-((2R,4R,5S)-4-Acetoxy-5-allyltetrahydrofuran-2-yl)hex-3-yn-1-yl acetate (80β–Ac)

To a solution of **80β** (40 mg, 0.18 mmol) in CH_2Cl_2 (10 mL) at 0 °C was added Et_3N (0.15 mL, 1.0 mmol), DMAP (2 mg) and stirred for 15 min. To this, acetic anhydride (0.05 mL, 0.5 mmol) was added at 0 °C and stirred further for 2 h. The reaction mixture was



diluted with CH_2Cl_2 (10 mL) and washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. The resulting crude was purified by column chromatography (90:10 petroleum ether/EtOAc) to afford the diaceate **80β–Ac** (48 mg, 87%) as colorless syrup: R_f (15% EtOAc/petroleum ether) 0.6; $[\alpha]^{25}_D$: + 42.2 (*c* 4.6, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): δ1.11 (t, *J* = 7.6 Hz, 3H), 1.90–1.95 (m, 1H), 2.07 (s, 3H), 2.10 (s, 3H), 2.12–2.18 (m, 2H), 2.28–2.31 (m, 2H), 2.34–2.43 (m, 1H), 2.48–2.62 (m, 2H), 4.07 (ddd, *J* = 2.6, 6.1, 8.9 Hz, 1H), 4.23–4.28 (m, 1H), 4.98 (dd, *J* = 3.2, 6.6 Hz, 1H), 5.03 (dd, *J* = 5.4, 11.7 Hz, 1H), 5.09–5.15 (m, 2H), 5.75–5.85 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ12.4 (t), 14.1 (q), 21.1 (t), 21.1 (t), 21.5 (t), 33.4 (t), 37.5 (t), 72.6 (d), 74.1 (s), 77.2 (d), 77.6 (d), 82.9 (d), 83.9 (s), 117.8 (t), 134.0 (d), 170.1 (s), 170.8 (s) ppm; MS (ESI) m/z = 331.23 $[M+Na]^+$; HRMS (ESI) calcd for $C_{17}H_{24}O_5$ $[M+Na]^+$ 331.1522, found 331.1509.

(2R,3R,5R)-2-(2-hydroxyethyl)-5-((S)-1-hydroxyhex-3-yn-1-yl)tetrahydrofuran-3-ol (81)

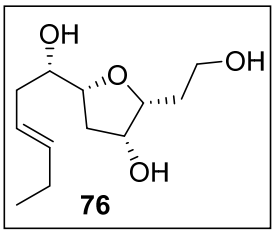


At 0 °C, to a solution of compound **80α** (560 mg, 2.5 mmol) in dioxane-water (3:1, 8 mL) were added 2,6-lutidine (0.58 mL, 5 mmol), OsO_4 (1 mL, 0.05 mmol, 0.05M in toluene) and $NaIO_4$ (2.1 g, 10 mmol). The reaction was stirred at 25 °C and monitored by TLC. After the reaction was complete, water (10 mL) and CH_2Cl_2 (20 mL) were added. The organic layer was separated, and the water layer was extracted by CH_2Cl_2 (10 mL) three times. Organic layers were concentrated and the resulting crude aldehyde (530 mg, 94%) was used as such for the next step without purification.

To a solution of crude aldehyde (530 mg, 2.34 mmol) in dry methanol at 0 °C, $NaBH_4$ (354 mg, 9.4 mmol) was added in portion wise. After complete the addition reaction mixture was stirred for 3 h at rt. The reaction mixture was concentrated under reduced pressure and the resulting crude product was purified by column chromatography (60:40 petroleum ether/EtOAc) to afford **81** (500 mg, 93%) as colourless syrups, R_f (80% EtOAc/petroleum ether) 0.46; $[\alpha]^{25}_D$: –14.4 (*c* 3.5, $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz): δ1.03 (t, *J* = 7.4 Hz, 3H), 1.78–1.91 (m, 3H), 2.05–2.10 (m, 2H), 2.12–2.19 (m, 2H), 2.26–2.31 (m, 1H), 3.46 (br s, 3H), 3.60–3.64 (m, 1H), 3.67–3.73 (m, 2H), 3.82 (t, *J* = 6.4 Hz, 1H), 4.04 (s, 1H), 4.14–4.16 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ12.1 (t), 13.8 (q), 24.0 (t), 31.2 (t), 33.5 (t),

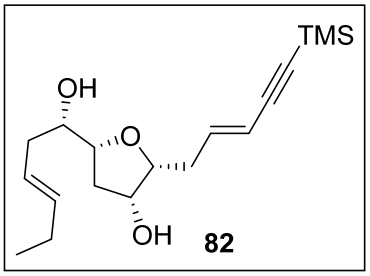
59.6 (t), 70.4 (d), 71.3 (d), 74.7 (s), 79.3 (d), 82.0 (d), 83.9 (s) ppm; MS (ESI) m/z = 250.86 $[M+Na]^+$; HRMS (ESI) calcd for $C_{12}H_{20}O_4$ $[M+Na]^+$ 251.126, found 251.1252.

(2R,3R,5R)-2-(2-hydroxyethyl)-5-((S,E)-1-hydroxyhex-3-en-1-yl)tetrahydrofuran-3-ol (76)



The procedure used in the preparation of compound 65 has been adopted for the Birch reduction of alkyne **81** (200 mg, 0.87 mmol) in to obtain the alkenol **76** (175 mg, 87%) as a colorless oil: R_f (80% EtOAc/petroleum ether) 0.4; $[\alpha]^{27}_D$: –13.6 (*c* 2.1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ0.98 (t, *J* = 7.4 Hz, 3H), 1.89–1.96 (m, 1H), 1.99–2.07 (m, 4H), 2.08–2.2.13 (m, 1H), 2.2 (ddd, *J* = 5.0, 9.3, 14.3 Hz, 1H), 3.19 (s, 3H), 3.75–3.85 (m, 4H), 4.06 (d, *J* = 9.3 Hz, 2H), 4.12 (br s, 1H), 5.38 (dt, *J* = 7.1, 15.4 Hz, 1H), 5.58 (dt, *J* = 6.1, 15.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ13.7 (q), 25.6 (t), 31.5 (t), 33.8 (t), 37.2 (t), 60.4 (t), 71.5 (d), 71.8 (d), 80.1 (d), 82.8 (d), 124.0 (d), 136.2 (d) ppm; MS (ESI) m/z = 253.12 $[M+Na]^+$; HRMS (ESI) calcd for $C_{12}H_{22}O_4$ $[M+Na]^+$ 253.1416, found 253.1406.

(2R,3R,5R)-5-((S,E)-1-hydroxyhex-3-en-1-yl)-2-((E)-5-(trimethylsilyl)pent-2-en-4-yn-1-yl)tetrahydrofuran-3-ol (82)

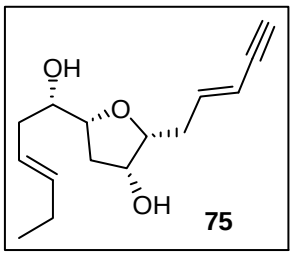


To an ice-cooled solution of the triol **76** (100 mg, 0.43 mmol) in CH_2Cl_2 (10 mL), DMP (240 mg, 0.56 mmol) was added in small portions and stirred for 3 h. The reaction mixture was quenched with ice, partitioned between CH_2Cl_2, water and the organic layer was separated, washed with brine, dried (Na_2SO_4), and concentrated to afford the aldehyde (90 mg, 91%) as colorless syrup. The crude aldehyde was used for the next step without purification.

At –78 ^{o}C, a solution of (trimethylsilylpropargyl)triphenylphosphonium bromide **83** (715 mg, 1.6 mmol) in THF (20.0 mL) was treated with *n*BuLi (0.9 mL, 1.5 M 1.4 mmol) and stirred for 15 minutes at the same temperatures and then warmed to room temperature and stirred for another one hour. To this, a solution of the above aldehyde in THF (5 mL) was added slowly. The reaction was allowed to stirr for 8 h and then quenched with water, and

extracted with Et_2O (3 x 20 mL). The combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. Purification of the crude by column chromatography (70:30 petroleum ether/EtOAc) gave alkenol **82** (110 mg, 86%) as a colorless oil: R_f (60% EtOAc/petroleum ether) 0.53; $[\alpha]^{25}_D$: −4.5 (*c* 1.1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz): δ –0.17 (s, 9H), 0.99 (t, *J* = 7.3 Hz, 3H), 1.96 (dd, *J* = 2.8, 14.0 Hz, 1H), 1.99–2.07 (m, 4H), 2.12–2.22 (m, 3H), 2.49 (td, *J* = 2.6, 7.1 Hz, 2H), 3.63 (ddd, *J* = 2.1, 6.7, 8.5 Hz, 1H), 3.84–3.86 (m, 1H), 4.05 (d, *J* = 6.4 Hz, 2H), 5.37 (dt, *J* = 7.3, 15.4 Hz, 1H), 5.61 (dt, *J* = 7.3, 15.4 Hz, 1H), 5.64 (d, *J* = 15.9 Hz, 1H), 6.26 (dt, *J* = 7.6, 15.9 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ –0.08 (q, 3C), 13.7 (q), 25.6 (t), 32.8 (t), 34.1 (t), 37.1 (t), 71.1 (d), 71.4 (d), 79.9 (d), 82.6 (d), 93.3 (s), 103.8 (s), 112.0 (d), 123.8 (d), 136.8 (d), 141.9 (d) ppm; MS (ESI) m/z = 345.21 $[M+Na]^+$; HRMS (ESI) calcd for $C_{18}H_{30}O_3Si$ $[M+Na]^+$ 345.1862, found 345.1852.

(2R,3R,5R)-5-((S,E)-1-hydroxyhex-3-en-1-yl)-2-((E)-pent-2-en-4-yn-1-yl)tetrahydrofuran-3-ol (75)

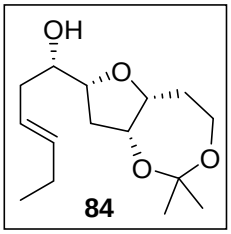


75

To an ice cooled solution of the TMS-diol **82** (20 mg, 0.06 mmol) in THF (10 mL), TBAF (24 mg, 0.09 mmol) was added and stirred for 1 h at rt. The reaction mixture was quenched by few drops of Et_3N. Solvent was evaporated under reduced pressure, and the residue was purified by column chromatography (80:20 petroleum ether/EtOAc) to yield **75** (14 mg, 90%) as colorless syrup: R_f (30% EtOAc/petroleum ether) 0.46; $[\alpha]^{25}_D$: −44.7 (*c* 0.75, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.99 (t, *J* = 7.5 Hz, 3H), 1.95–1.99 (m, 1H), 2.01–2.09 (m, 4H), 2.13–2.24 (m, 3H), 2.26–2.33 (m, 1H), 2.47–2.53 (m, 1H), 2.80 (d, *J* = 1.9 Hz 1H), 3.65 (ddd, *J* = 2.4, 6.9, 9.3 Hz, 1H), 3.86 (ddd, *J* = 1.9, 6.8, 9.3 Hz, 1H), 4.04–4.08 (m, 2H), 5.34–5.41 (m, 1H), 5.55–5.65 (m, 2H), 3.86 (dt, *J* = 7.3, 15.9 Hz, 1H) ; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 13.7 (q), 25.6 (t), 32.8 (t), 34.1 (t), 37.1 (t), 71.1 (d), 71.4 (d), 76.2 (s), 77.2 (d), 77.0 (d), 82.5 (d), 110.8 (d), 123.7 (d), 136.9 (d), 142.6 (d) ppm; MS (ESI) m/z = 272.93 $[M+Na]^+$; HRMS (ESI) calcd for $C_{15}H_{22}O_3$ $[M+Na]^+$ 273.1467, found 273.1457.

(S,E)-1-((5aR,7R,8aR)-2,2-dimethylhexahydrofuro[3,2-d][1,3]dioxepin-7-yl)hex-3-en-1-ol (84)

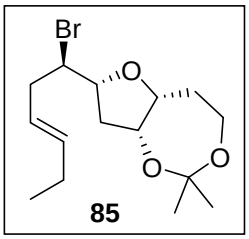
To a solution of triol **76** (100 mg, 0.43 mmol) in acetone, were added DMP (0.21 mL, 1.7 mmol) and *p*-TSA (5 mg) at 0 °C. The reaction mixture was stirred at rt for 2.5 h when



84

TLC indicated the reaction was complete then was treated with few drops of triethylamine and concentrate under reduced pressure and the resulting crude product was purified by column chromatography (85:15 petroleum ether/EtOAc) to obtain **84** (90 mg, 77%) as a colorless thick syrup: R_f (25% EtOAc/petroleum ether) 0.5; $[\alpha]^{25}_D$: –0.7 (*c* 7.2, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz): δ0.98 (t, *J* = 7.5 Hz, 3H), 1.36 (s, 3H), 1.38 (s, 3H), 1.87 (ddd, *J* = 4.7, 9.4, 14.8 Hz, 1H), 1.92–2.28 (m, 7H), 3.17 (br s, 1H), 3.52 (dt, *J* = 4.8, 12.1 Hz, 1H), 3.79 (ddd, *J* = 2.6, 4.4, 7.0 Hz, 1H), 3.86 (dd, *J* = 2.4, 7.1 Hz, 1H), 3.92–4.04 (m, 2H), 4.41 (dt, *J* = 2.4, 5.7 Hz, 1H), 5.43 (dt, *J* = 6.4, 15.4 Hz, 1H), 5.57 (dt, *J* = 5.7, 15.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ13.7 (q), 24.7 (q), 24.9 (q), 25.6 (t), 32.3 (t), 32.7 (t), 37.2 (t), 57.8 (t), 71.8 (d), 72.5 (d), 78.8 (d), 79.1 (d), 101.3 (s), 124.6 (d), 135.0 (d) ppm; MS (ESI) m/z = 293.10 $[M+Na]^+$; HRMS (ESI) calcd for $C_{15}H_{26}O_4$ $[M+Na]^+$ 293.1729, found 293.1718.

(5aR,7R,8aR)-7-((R,E)-1-bromohex-3-en-1-yl)-2,2-dimethylhexahydrofuro[3,2-d][1,3]dioxepine (85)



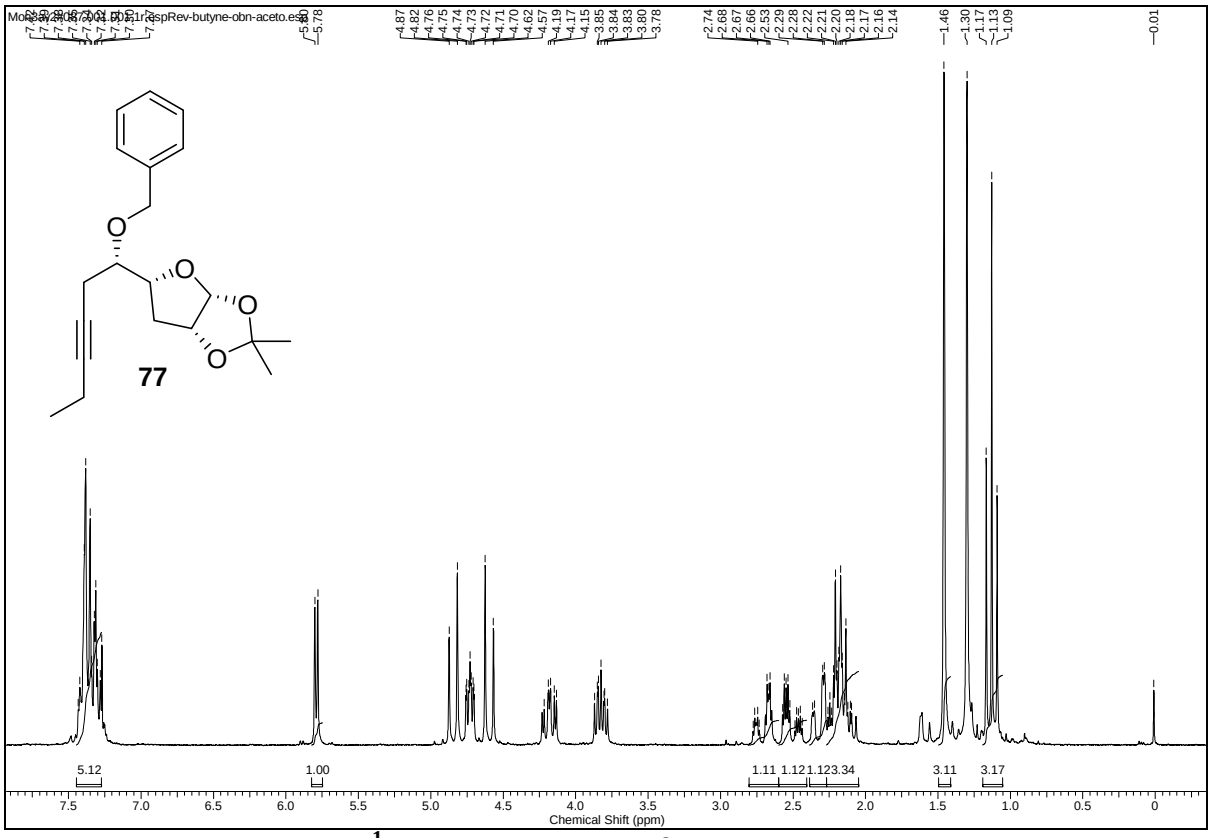
85

A solution of freshly sublimed CBr_4 (300 mg, 0.9 mmol) in CH_2Cl_2 (5 mL) was degassed under N_2 for 30 min and then filtered through a short column of basic alumina, rinsing the flask and column with CH_2C1_2 (2 X 3 mL). The resulted solution (final volume: 6 mL, 0.15 M in CBr_4) was stirred over anhydrous K_2CO_3 until use.

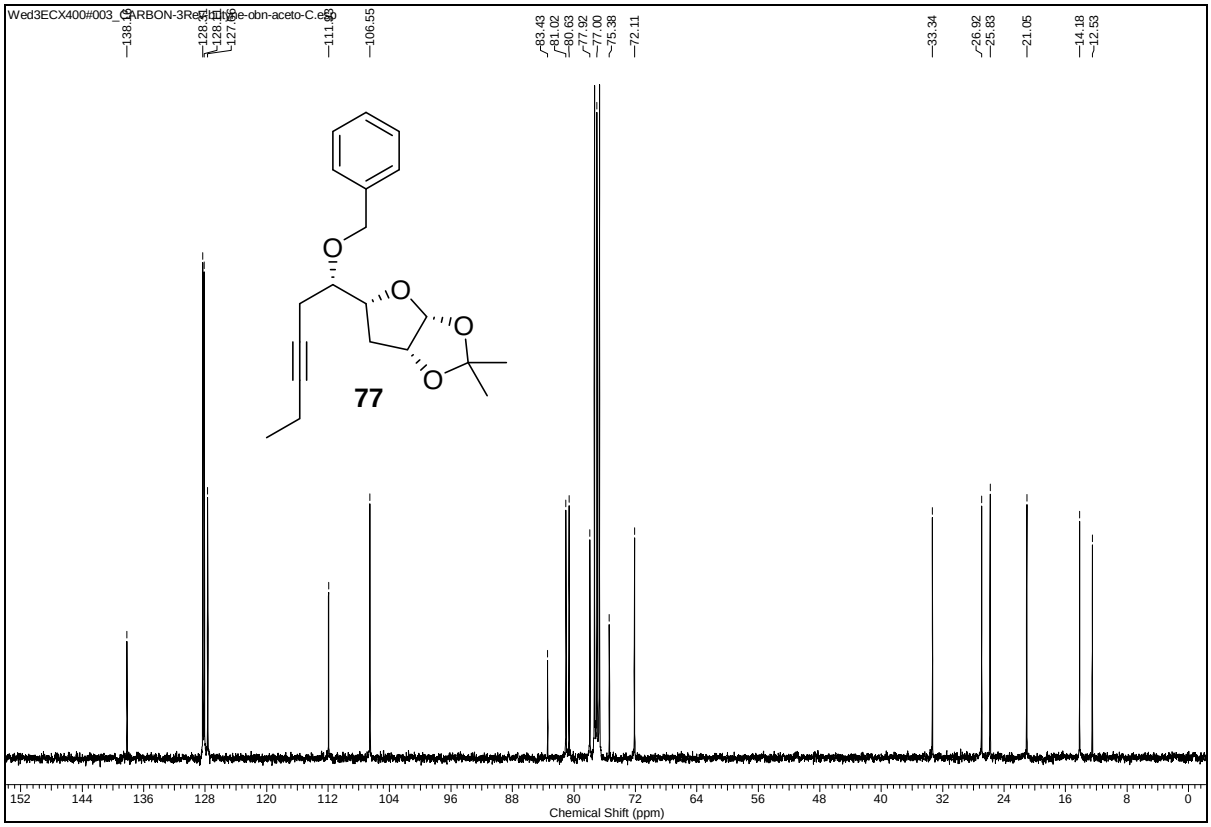
To a solution of **84** (50 mg, 0.18 mmol) Ph_3P (194 mg, 0.74 mmol, 4 eq) and 2, 6-di-tertbutylpyridine (141 mg, 0.157.2 mL, 0.74 mmol)in benzene (5 mL) was added A solution of CBr_4 (245 mg, 0.74 mmol) in CH_2Cl_2 (4.9 mL; 0.15 M) and then heated to 40 ^{o}C for 20 minutes. The reaction mixture was cooled to room temperature and concentrate and the crude was immediately purified by column chromatography (90:10 petroleum ether/EtOAc) to obtain **85** (21 mg, 34%) as a colorless thick syrup: R_f (20% EtOAc/petroleum ether) 0.6; $[\alpha]^{25}_D$: 7.5 (*c* 0.2, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz): δ1.00 (t, *J* = 7.5Hz, 3H), 1.34 (s, 3H), 1.38 (s, 3H), 1.77 (ddd, *J* = 4.9, 8.6, 13.3 Hz, 1H), 1.88 (ddd, *J* = 4.8, 9.8, 14.1 Hz, 1H), 2.02–2.08 (m, 2H), 2.20–2.27 (m, 1H), 2.31 (dt, *J* = 6.6, 13.2 Hz, 1H), 2.48 (dt, *J* = 7.6, 14.9 Hz, 1H), 2.66–2.71 (m, 1H), 3.60 (ddd, *J* = 5.6, 9.1, 14.9 Hz, 1H), 3.93–4.00 (m, 2H), 4.02–4.07 (m, 2H), 4.51 (dt, *J* = 4.9, 7.2 Hz, 1H), 5.49 (dt, *J* = 6.4, 15.4 Hz, 1H), 5.59 (dt, *J* = 6.1, 15.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ13.7 (q), 24.3 (q), 25.1 (q), 25.6 (t), 31.4 (t),

36.7 (t), 37.6 (t), 57.4 (d), 59.0 (t), 72.7 (d), 79.8 (d), 80.0 (d), 101.1 (s), 124.8 (d), 135.7 (d) ppm; MS (ESI) m/z = 354.85 $[M+Na]^+$; HRMS (ESI) calcd for $C_{15}H_{25}BrO_3$ $[M+Na]^+$ 355.0885, 357.0885 found 355.0875, 357.0853.

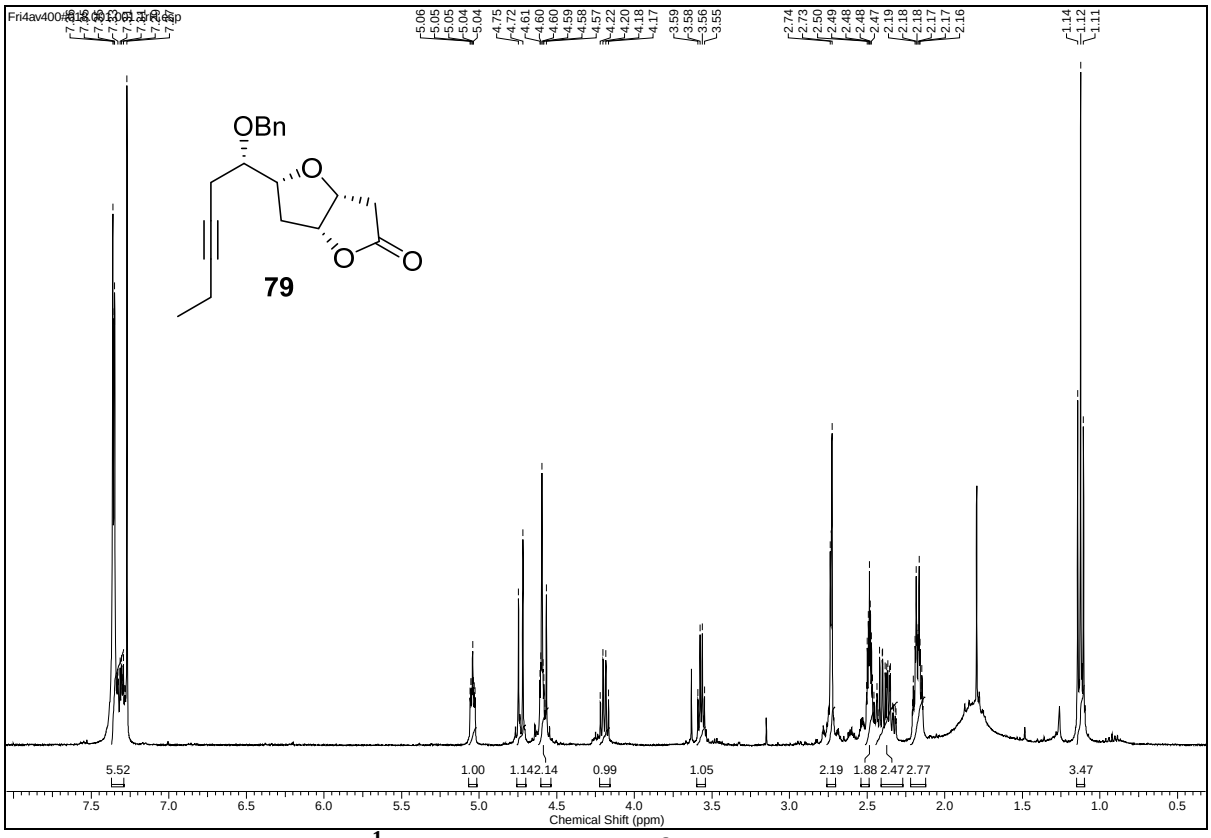
SPECTRA



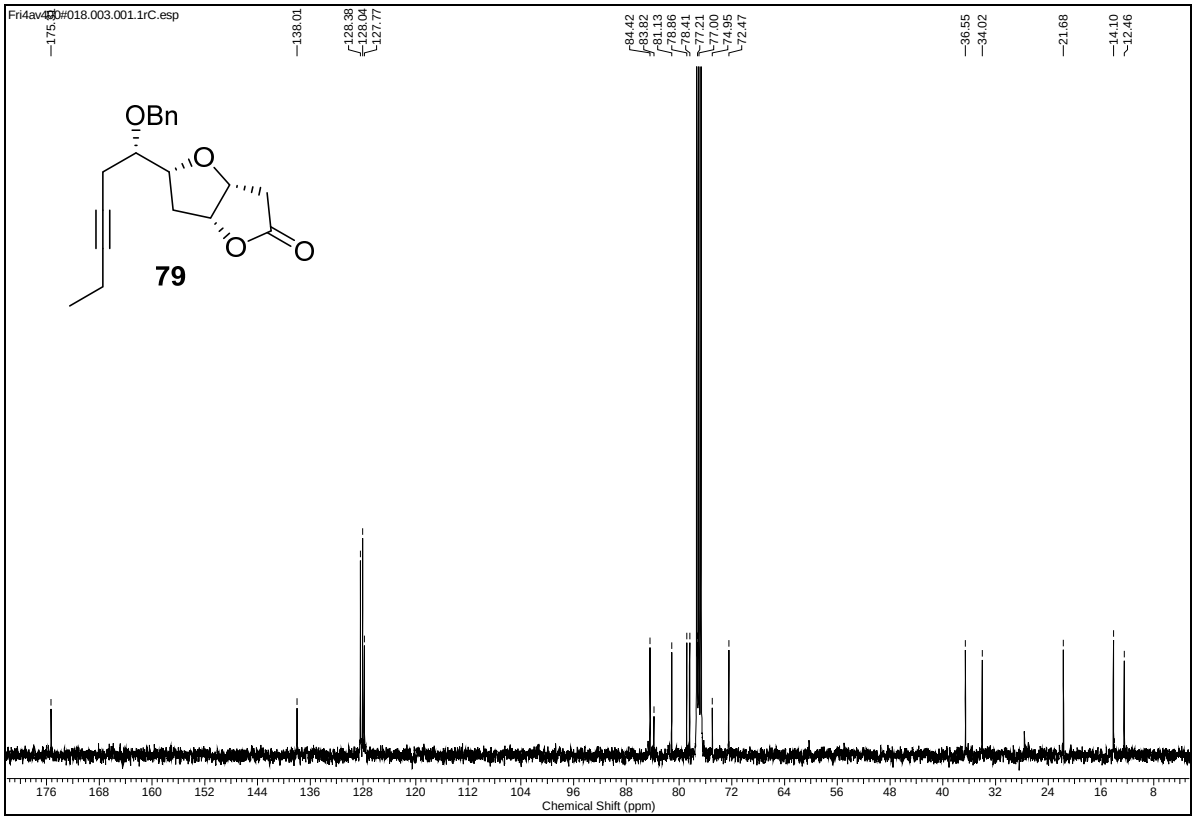
^{1}H NMR Spectrum of 77 in $CDCl_3$



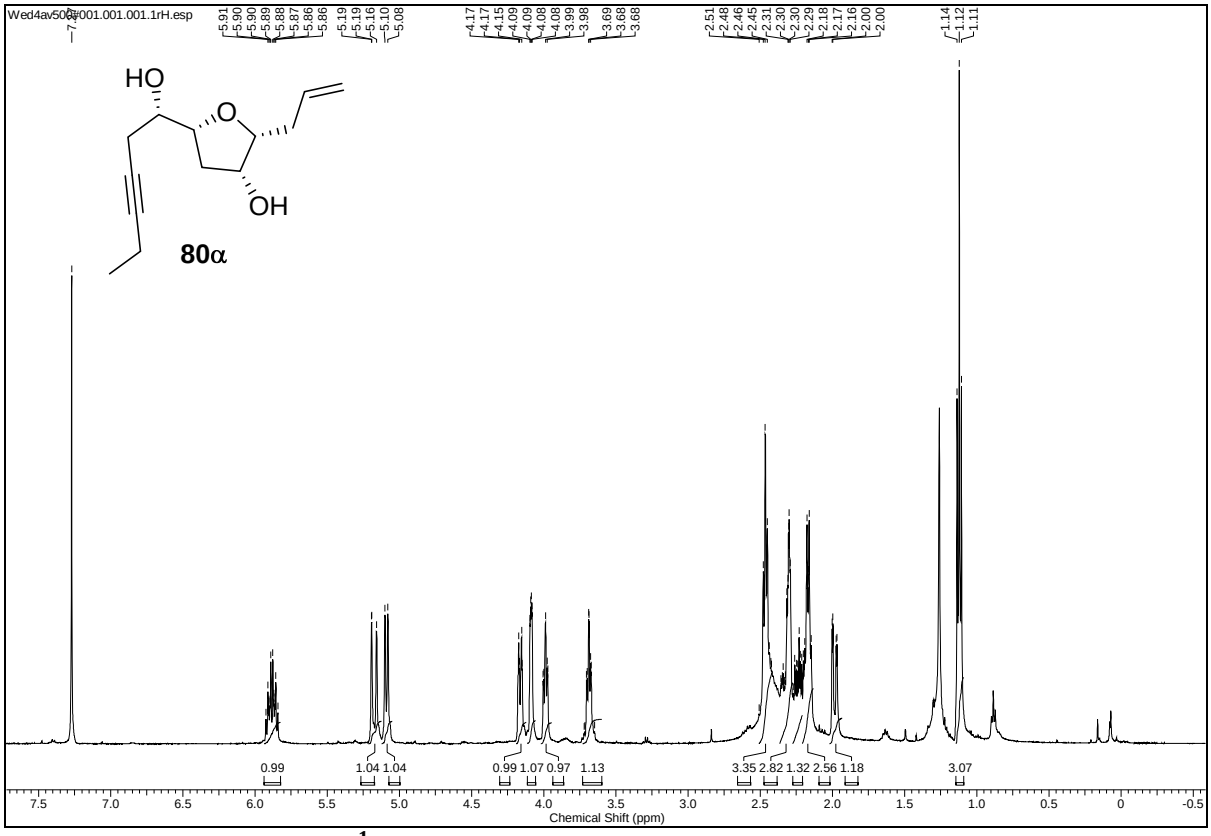
^{13}C NMR Spectrum of 77 in $CDCl_3$



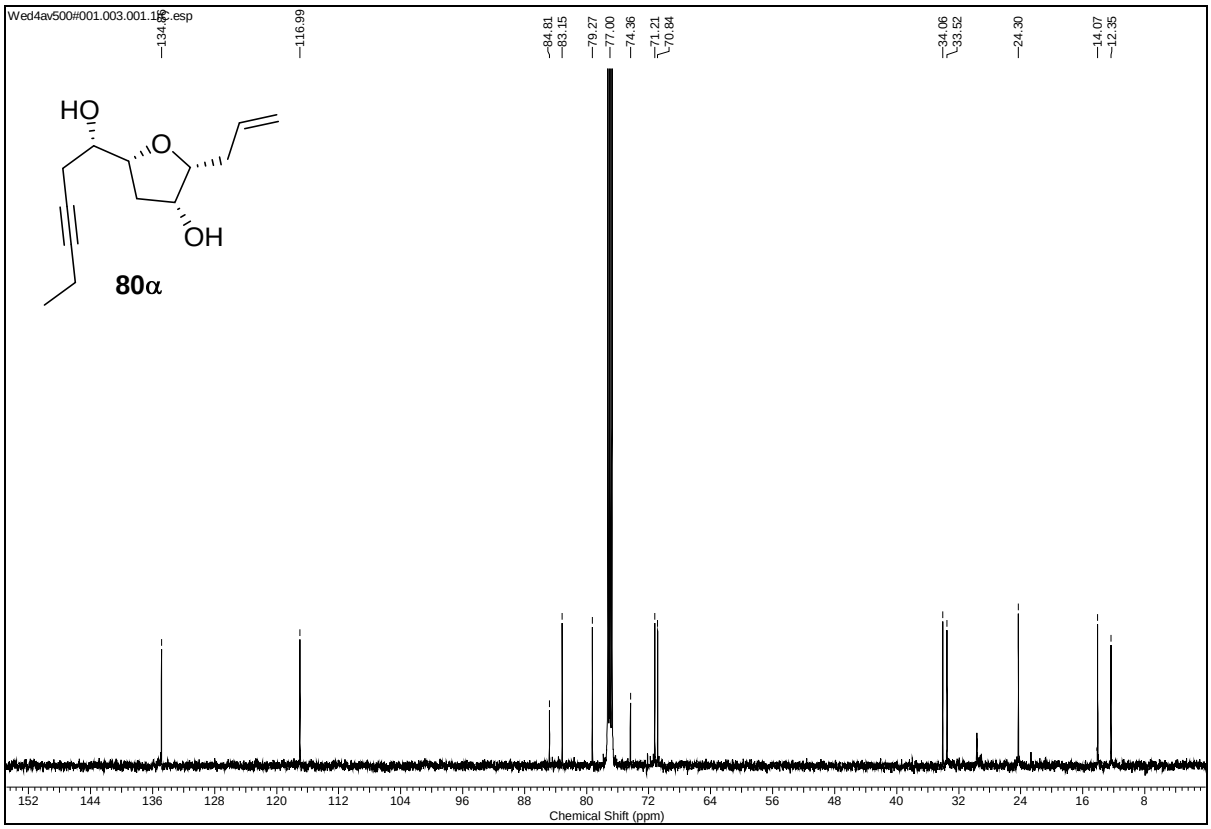
^{1}H NMR Spectrum of 79 in $CDCl_3$



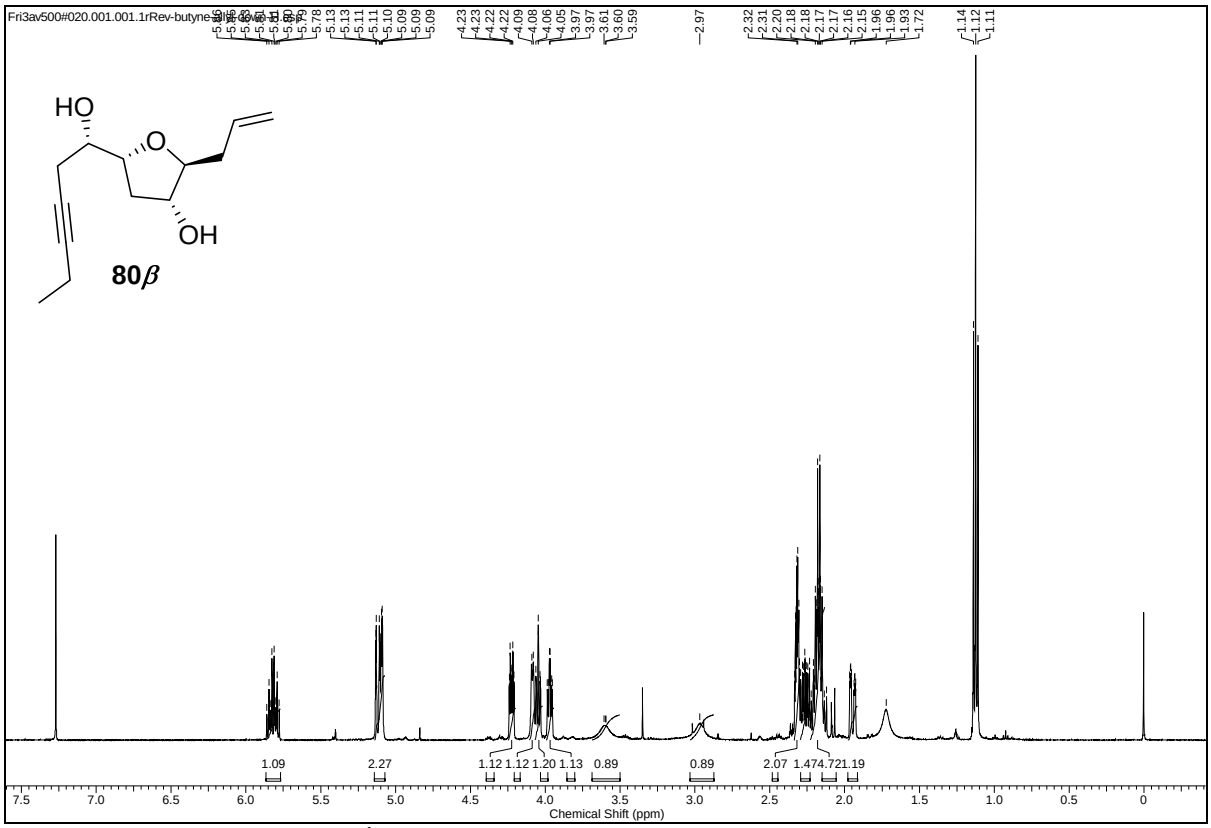
^{13}C NMR Spectrum of 79 in $CDCl_3$



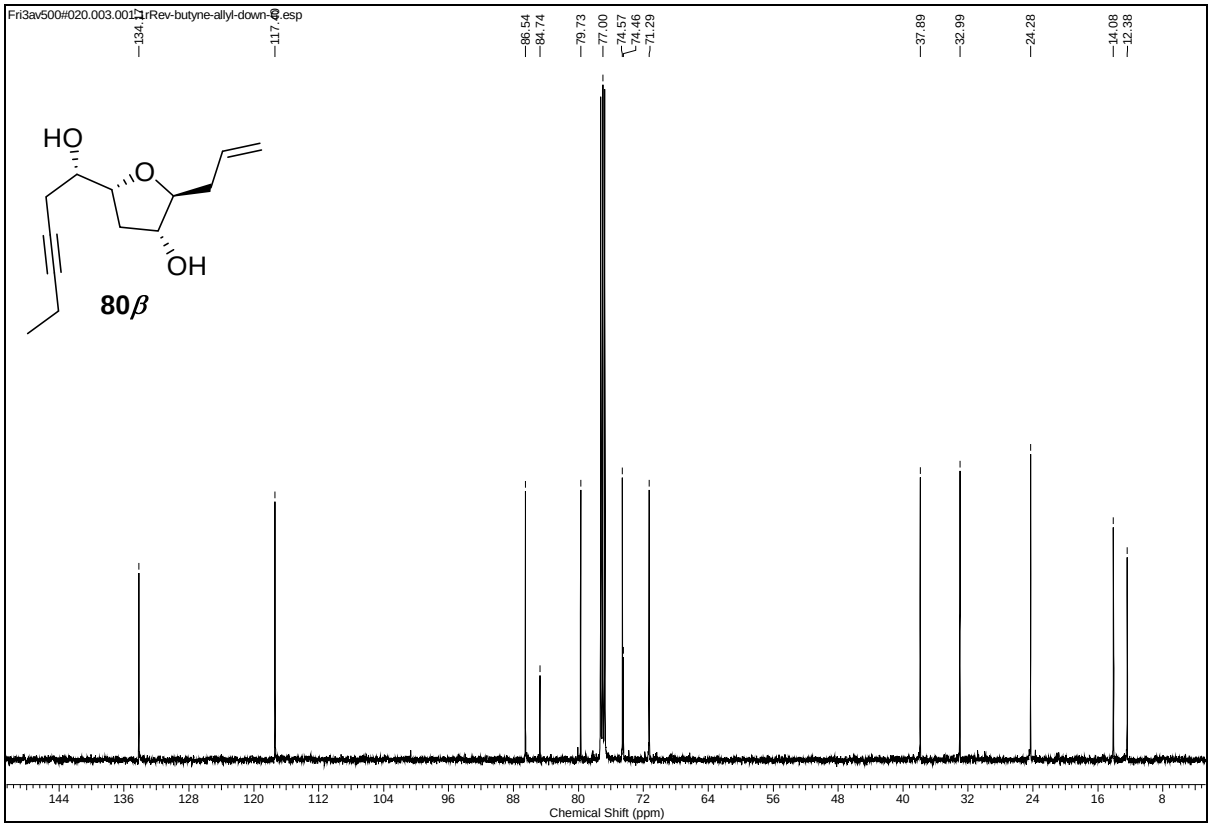
^{1}H NMR Spectrum of 80α in $CDCl_3$



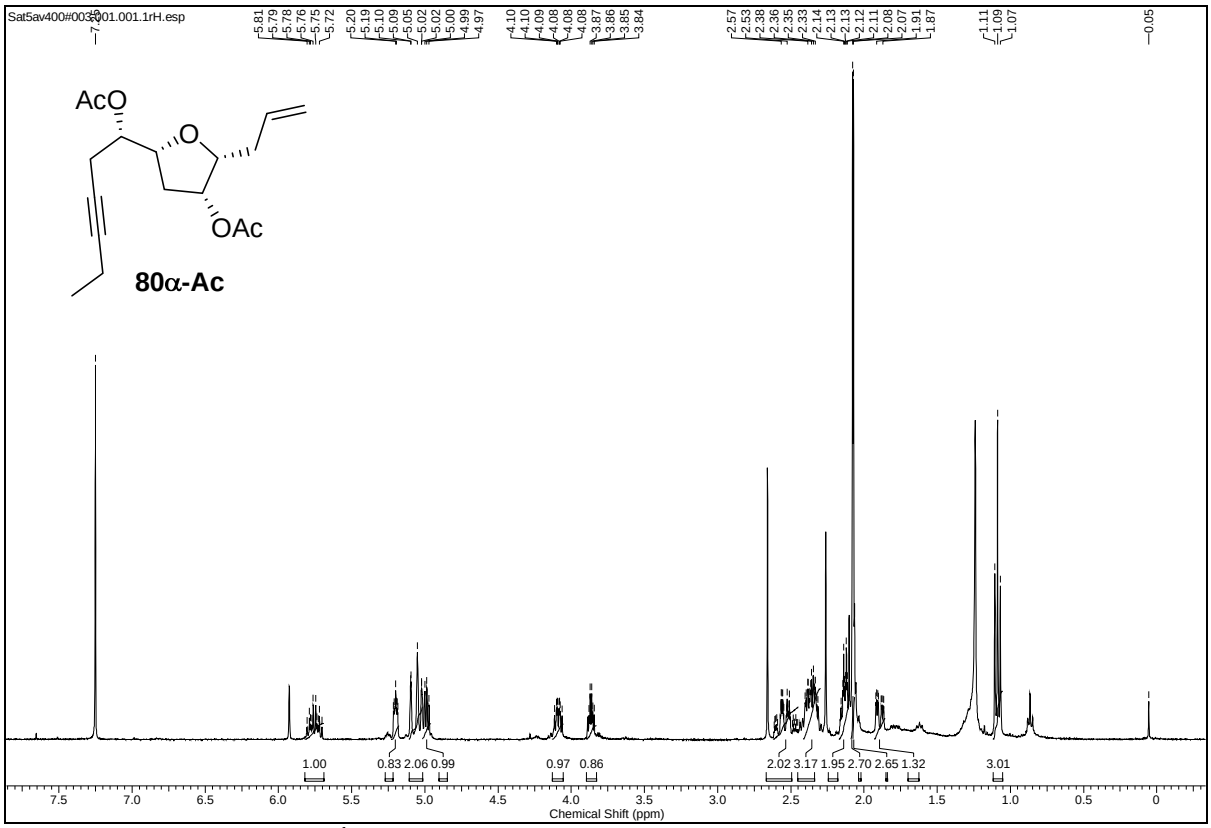
^{13}C NMR Spectrum of 80α in $CDCl_3$



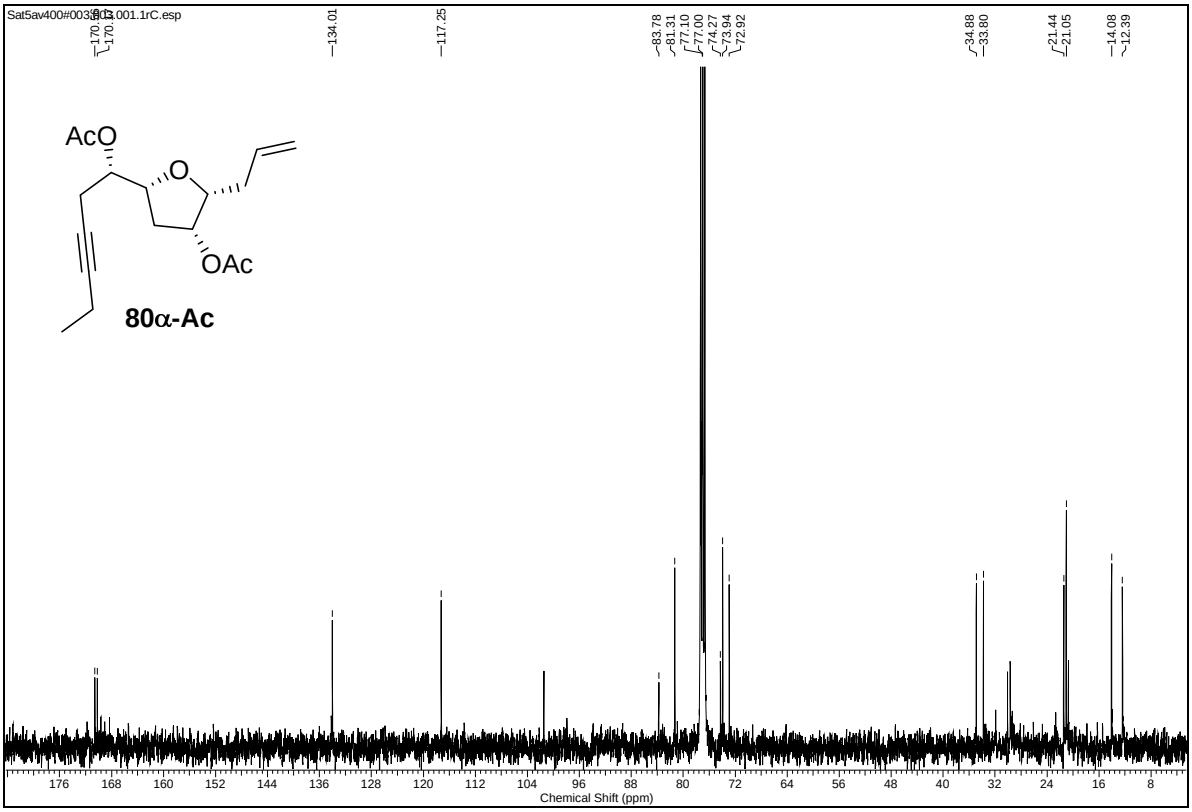
^{1}H NMR Spectrum of 80β in $CDCl_3$



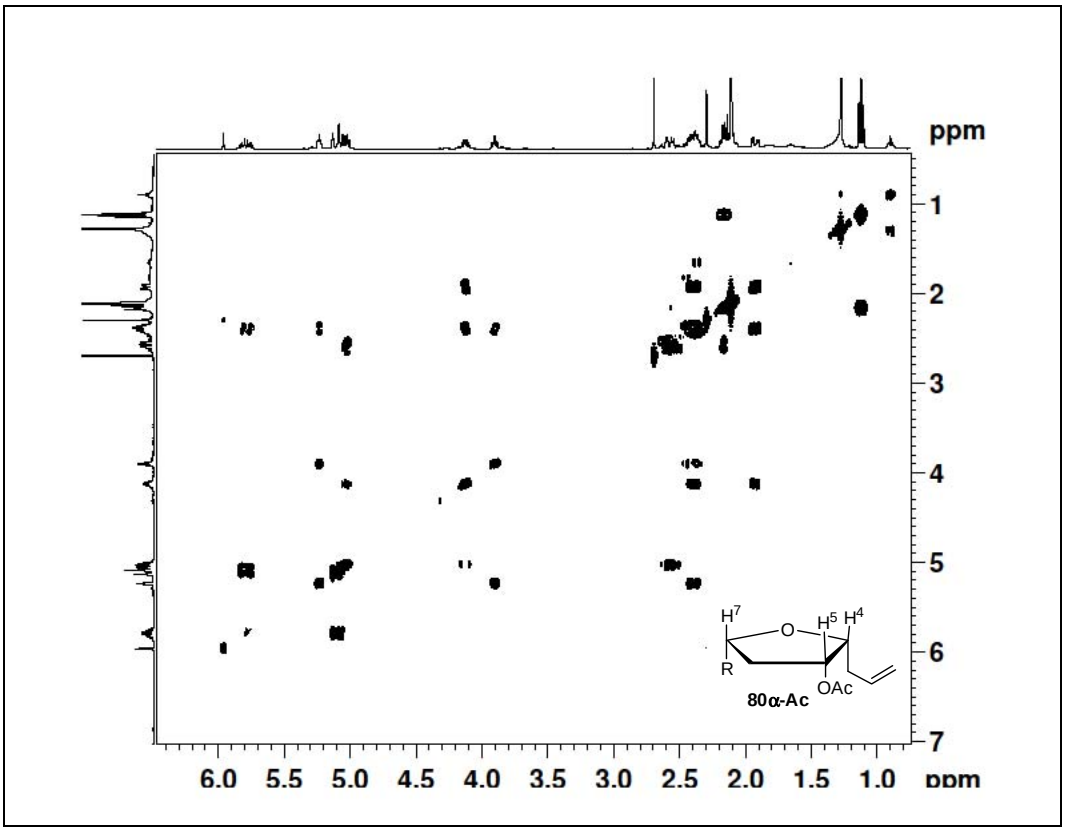
^{13}C NMR Spectrum of 80β in $CDCl_3$



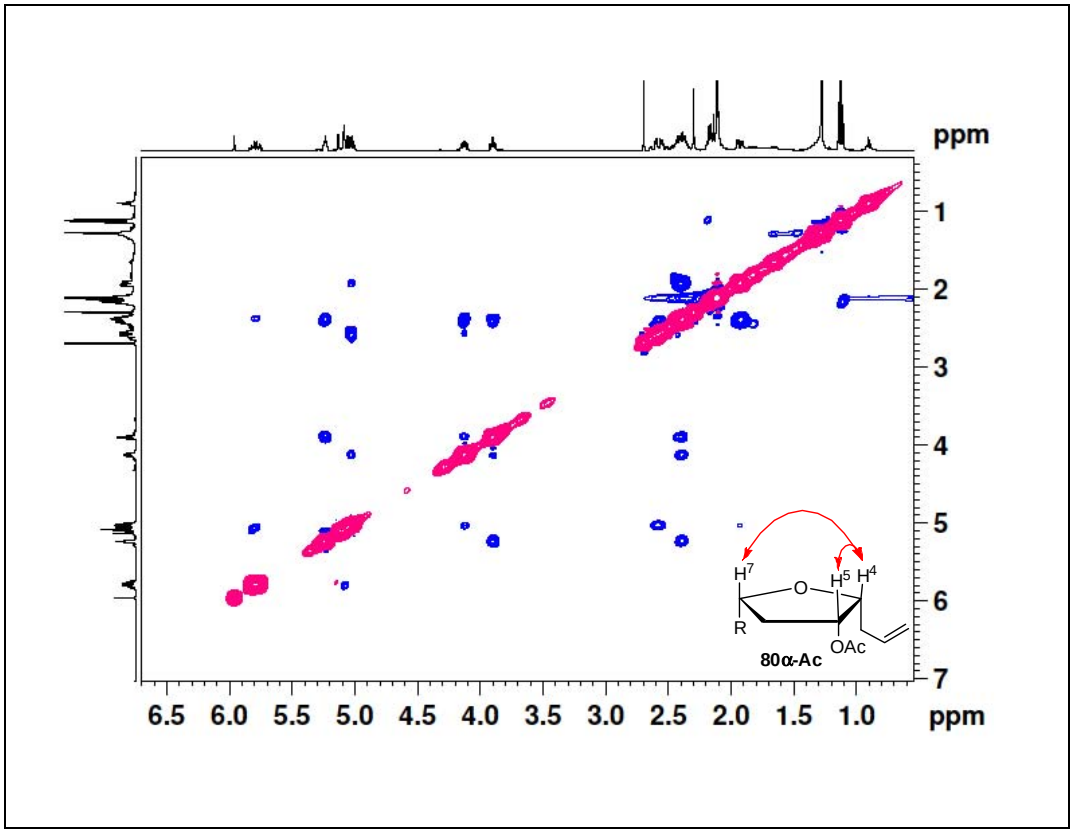
^{1}H NMR Spectrum of 80α-Ac in $CDCl_3$



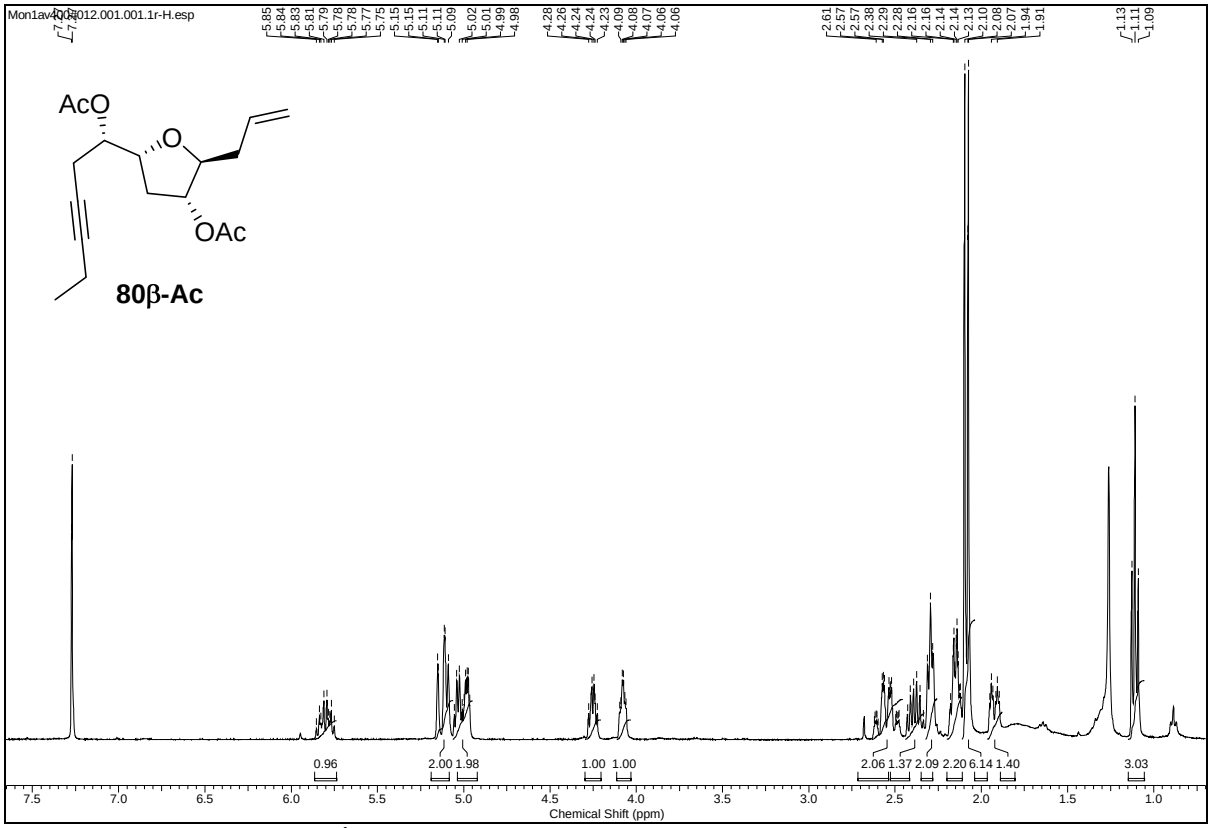
^{13}C NMR Spectrum of 80α-Ac in $CDCl_3$



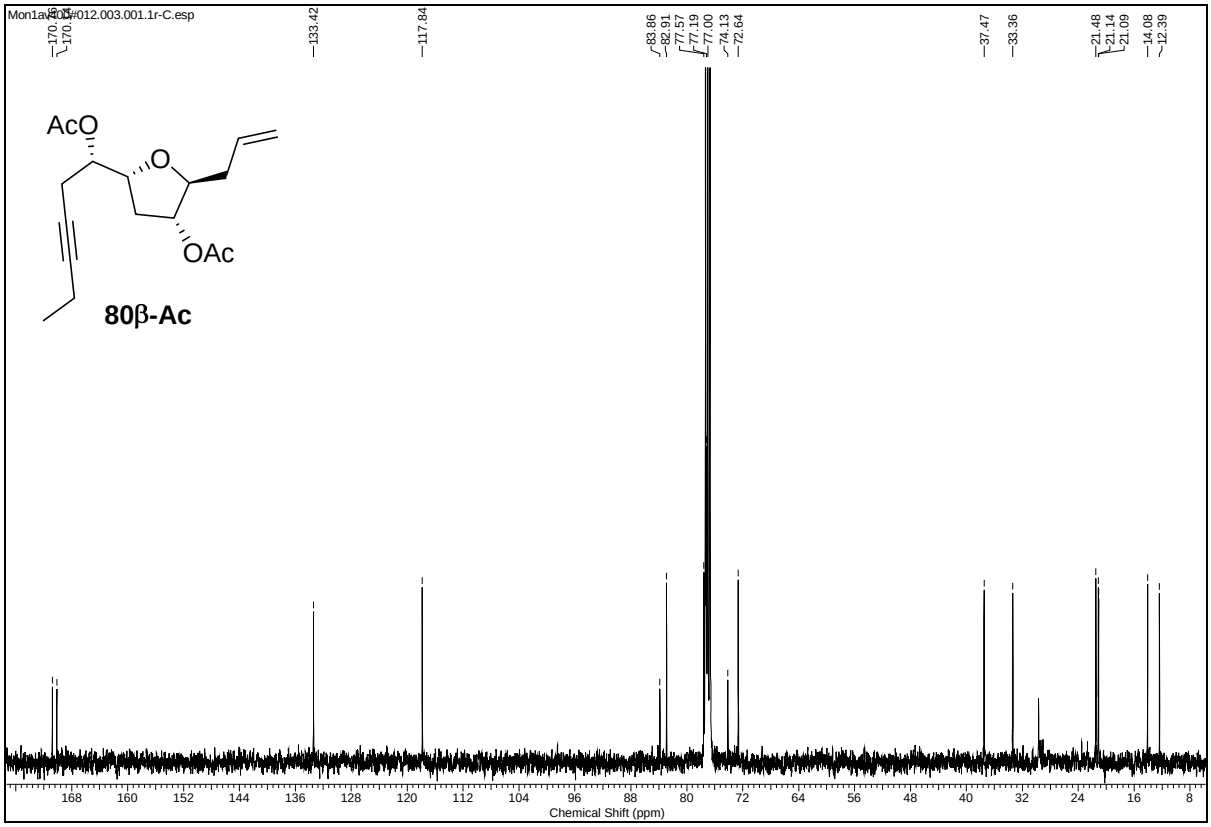
COSY of compound 80*α*-Ac



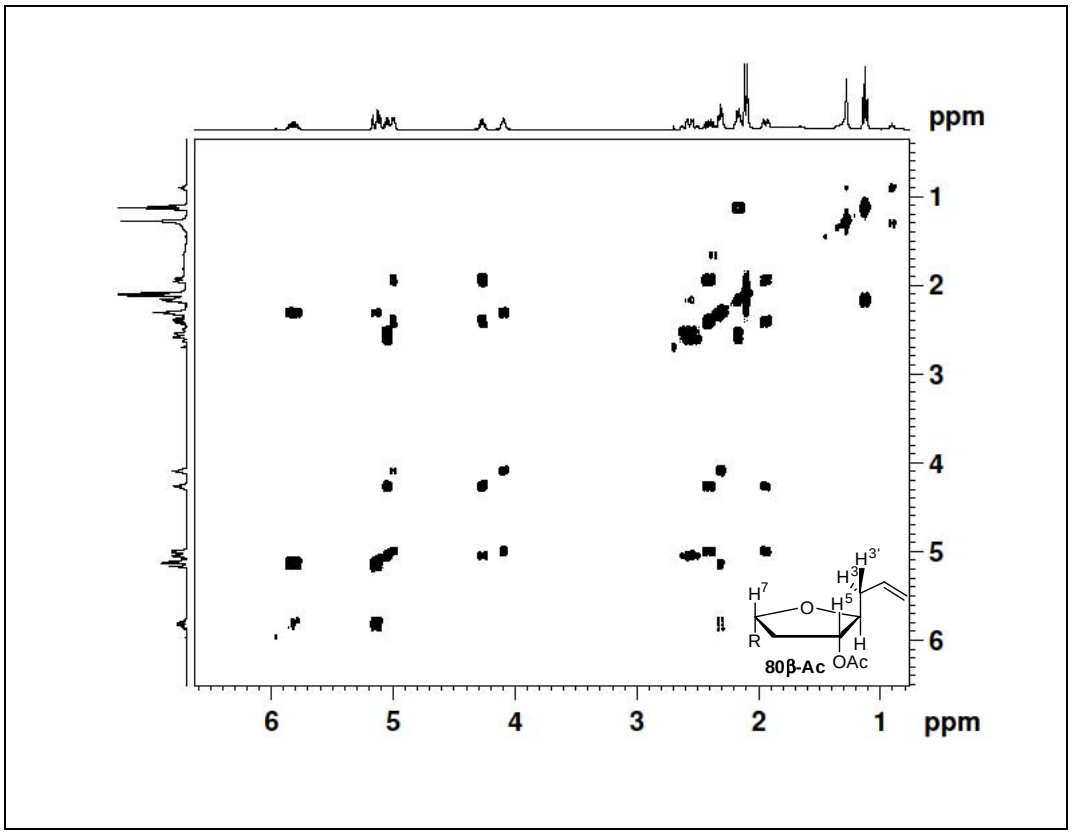
NOESY of compound 80*α*-Ac



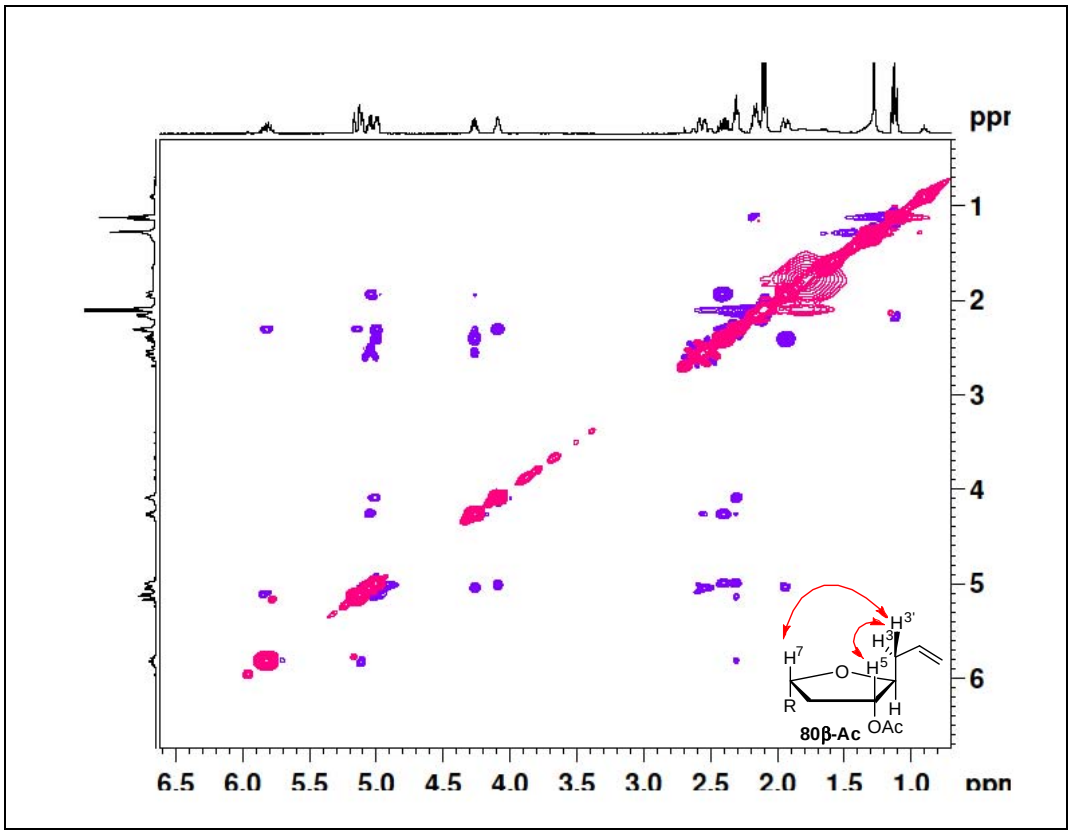
^{1}H NMR Spectrum of 80β-Ac in $CDCl_3$



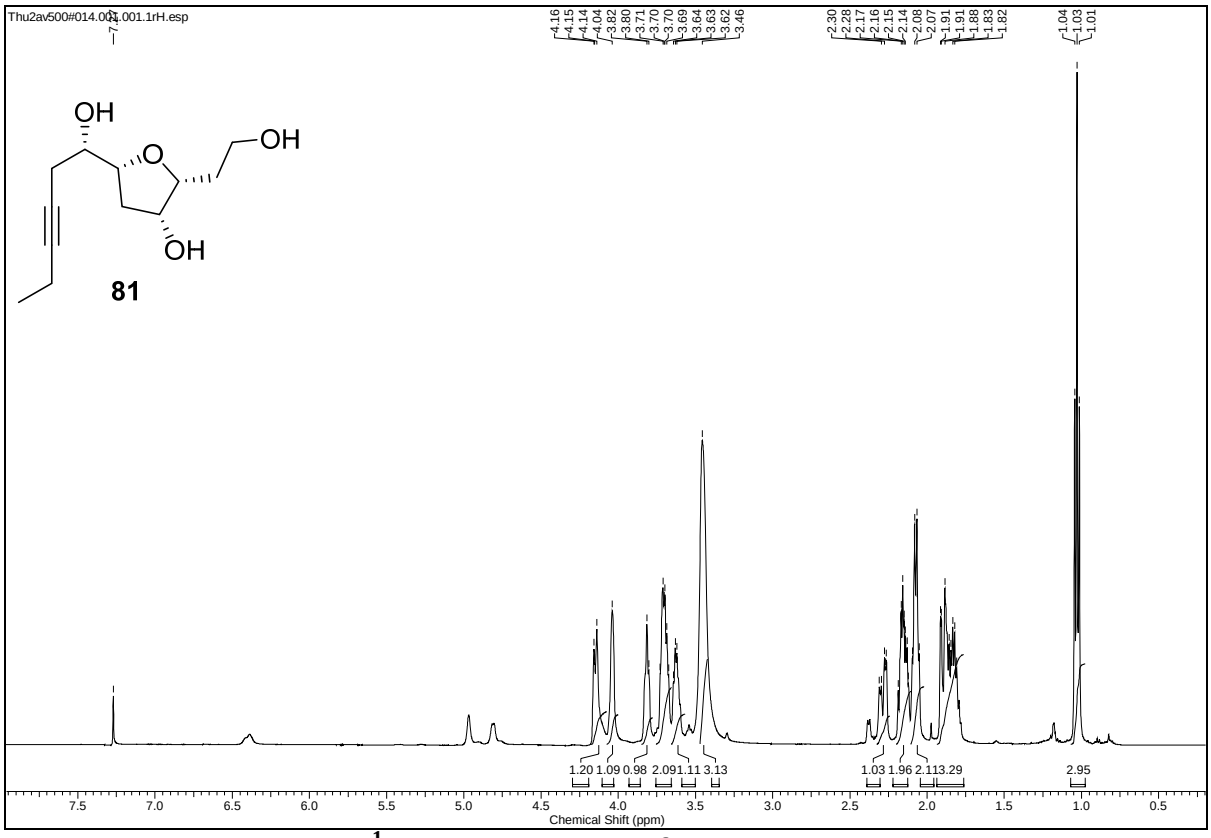
^{13}C NMR Spectrum of 80β-Ac in $CDCl_3$



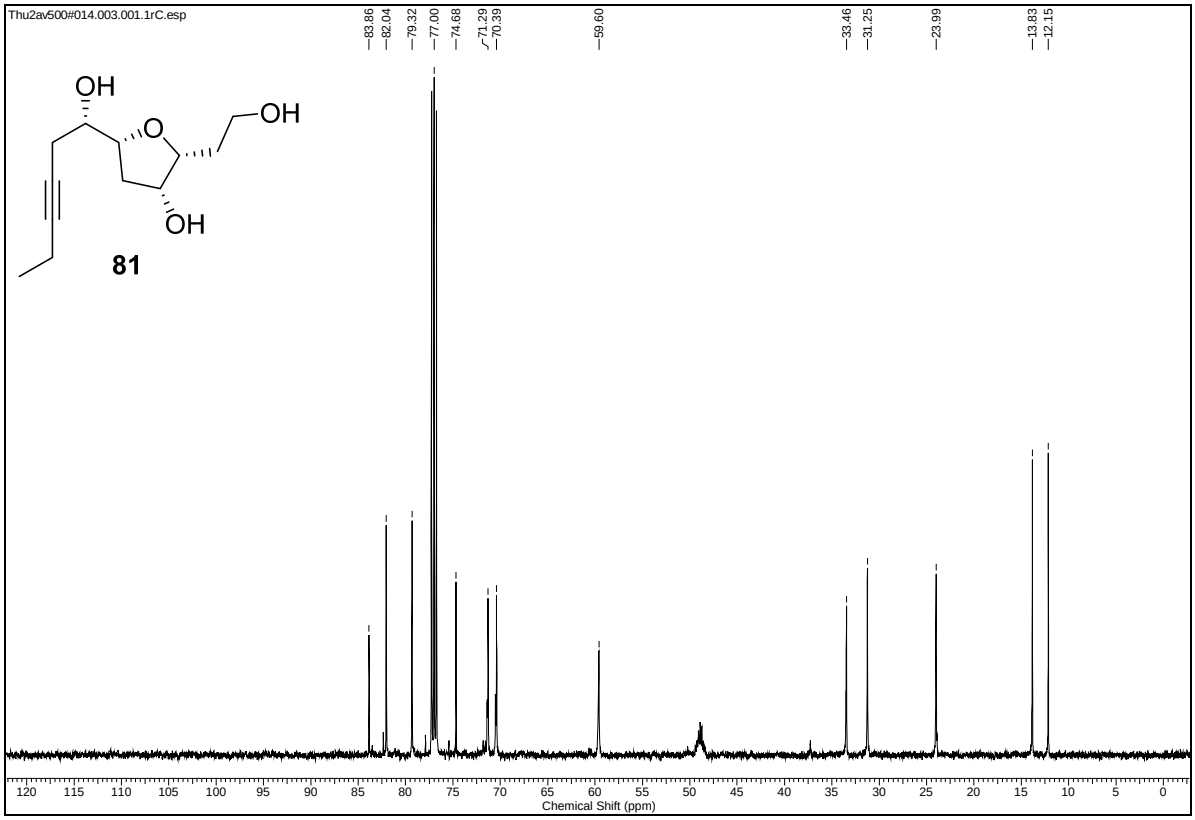
COSY of compound 80β-Ac



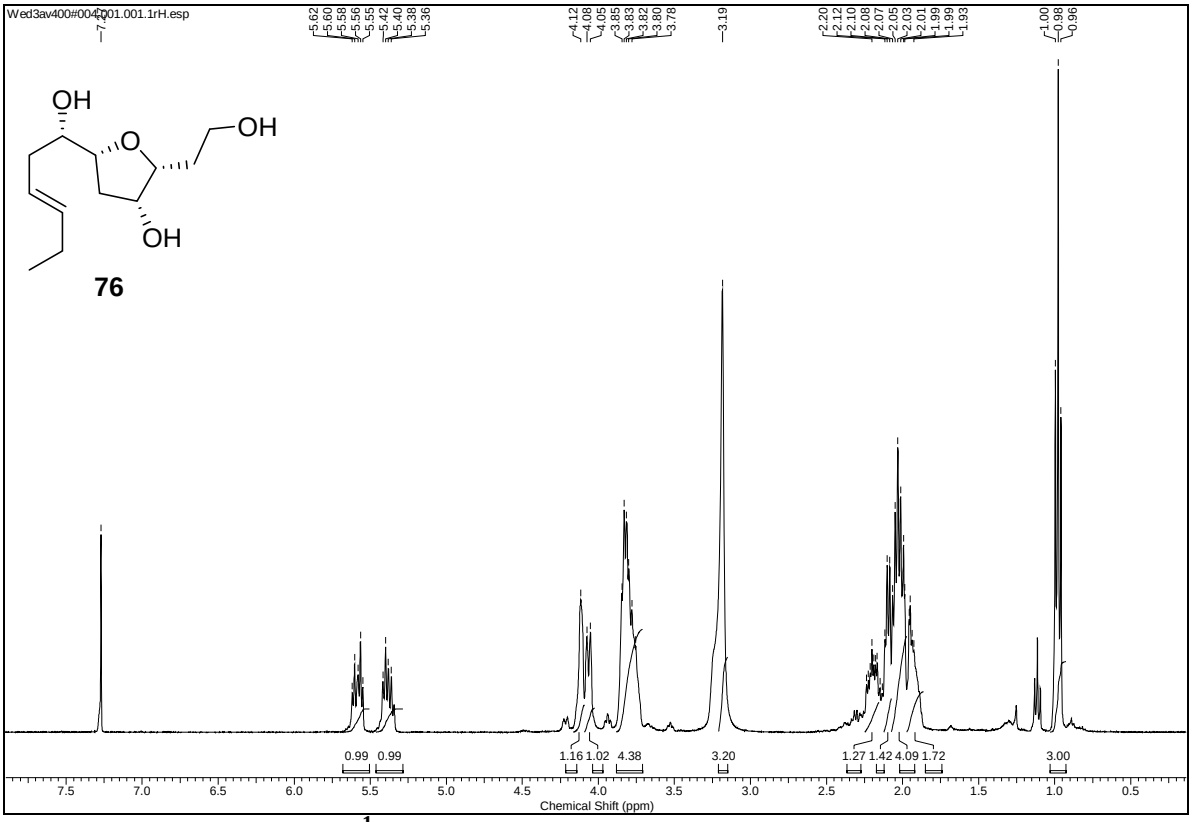
NOESY of compound 80β-Ac



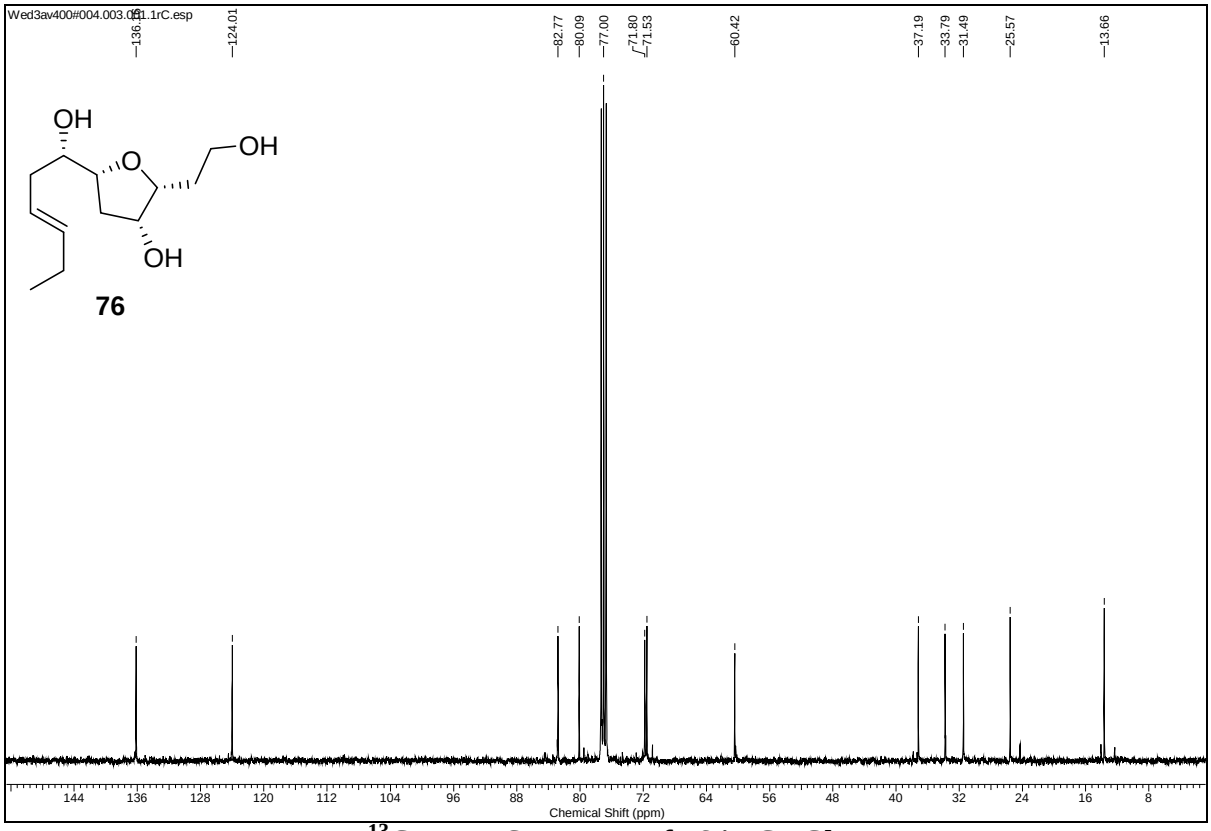
^{1}H NMR Spectrum of 81 in $CDCl_3$



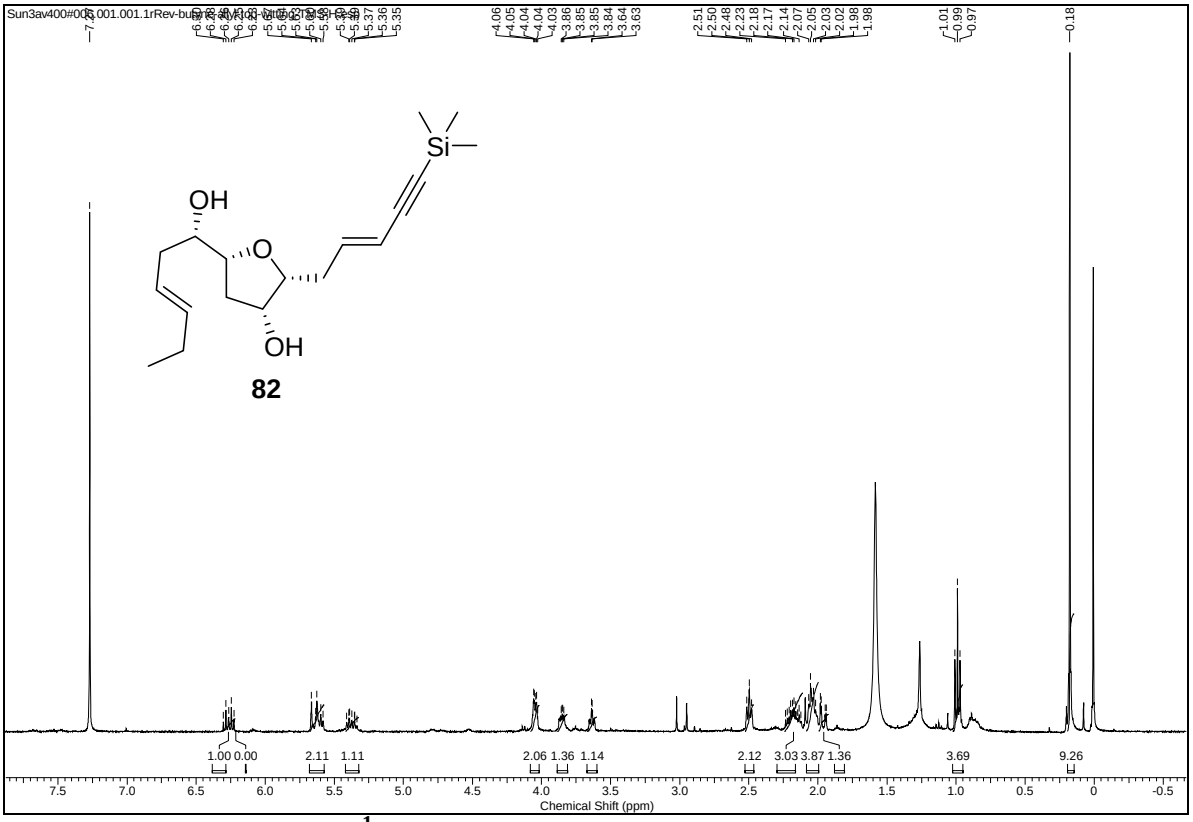
^{13}C NMR Spectrum of 81 in $CDCl_3$



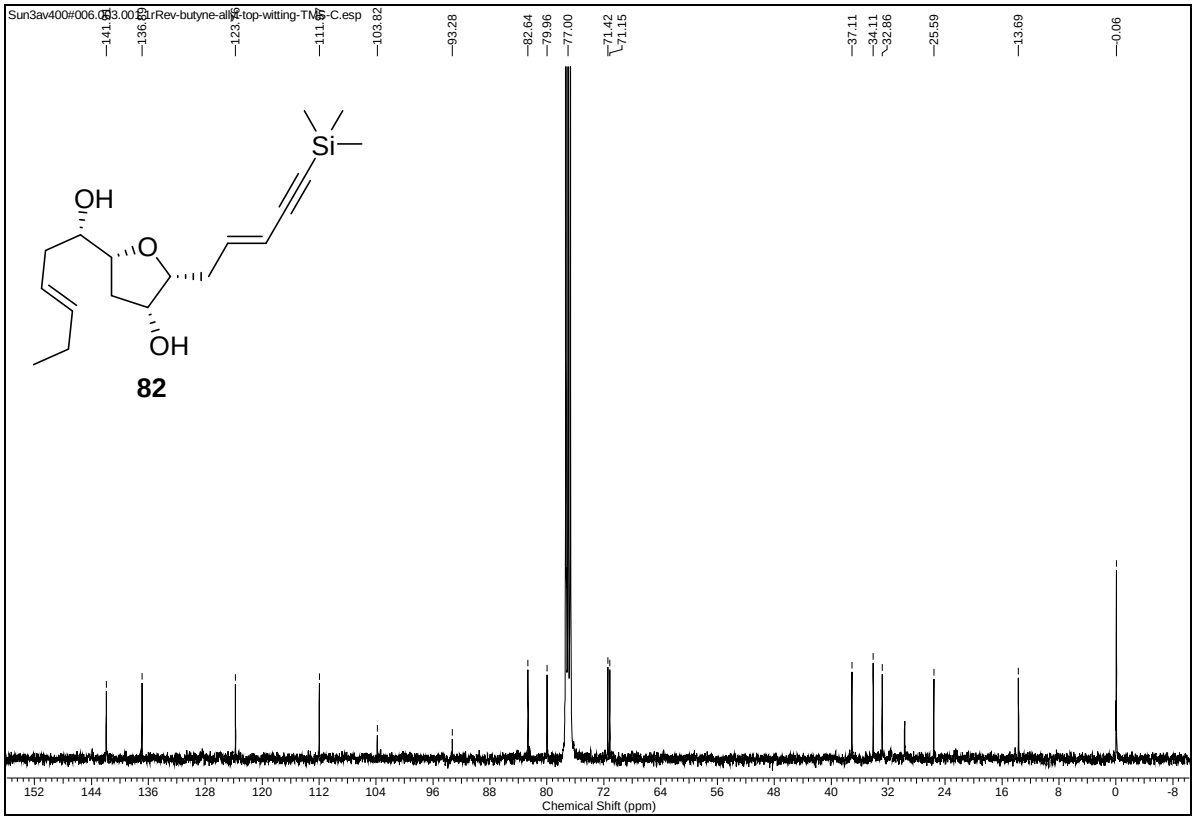
^{1}H NMR Spectrum of 76 in $CDCl_3$



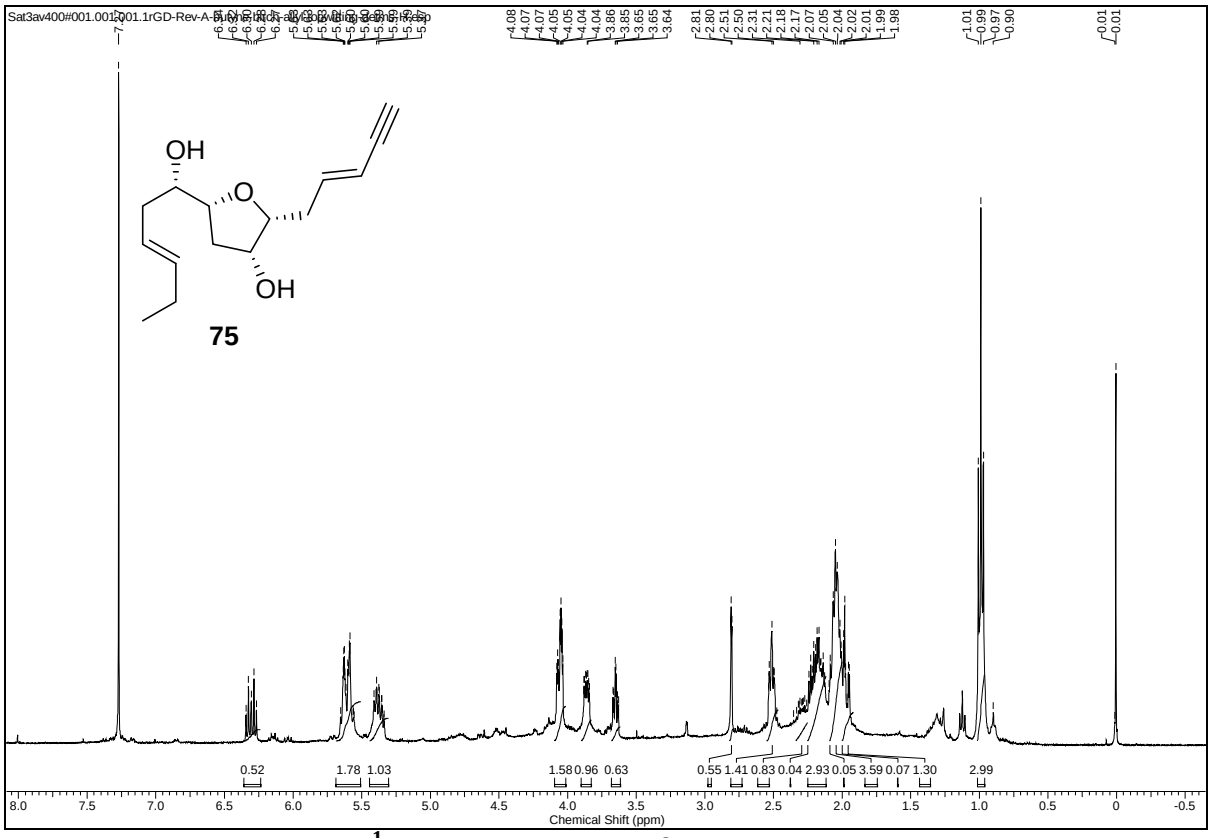
^{13}C NMR Spectrum of 76 in $CDCl_3$



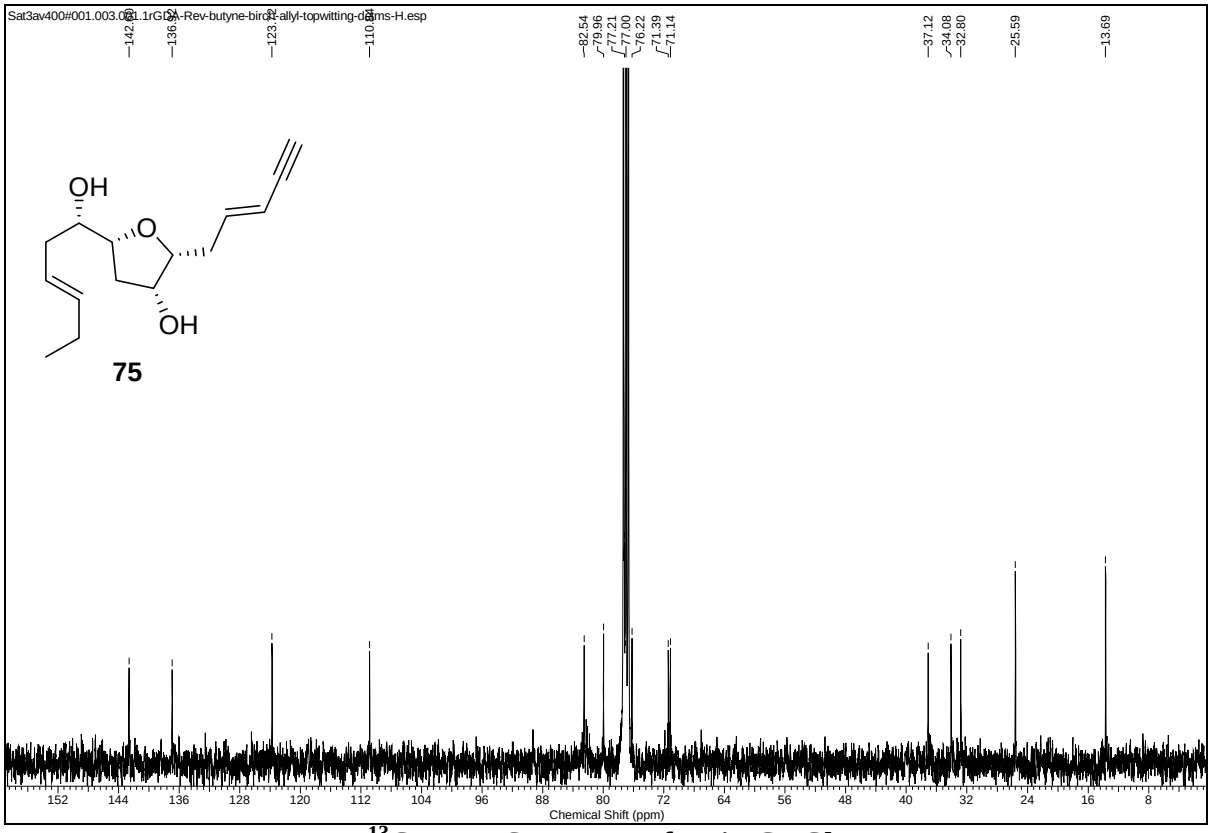
^{1}H NMR Spectrum of 82 in $CDCl_3$



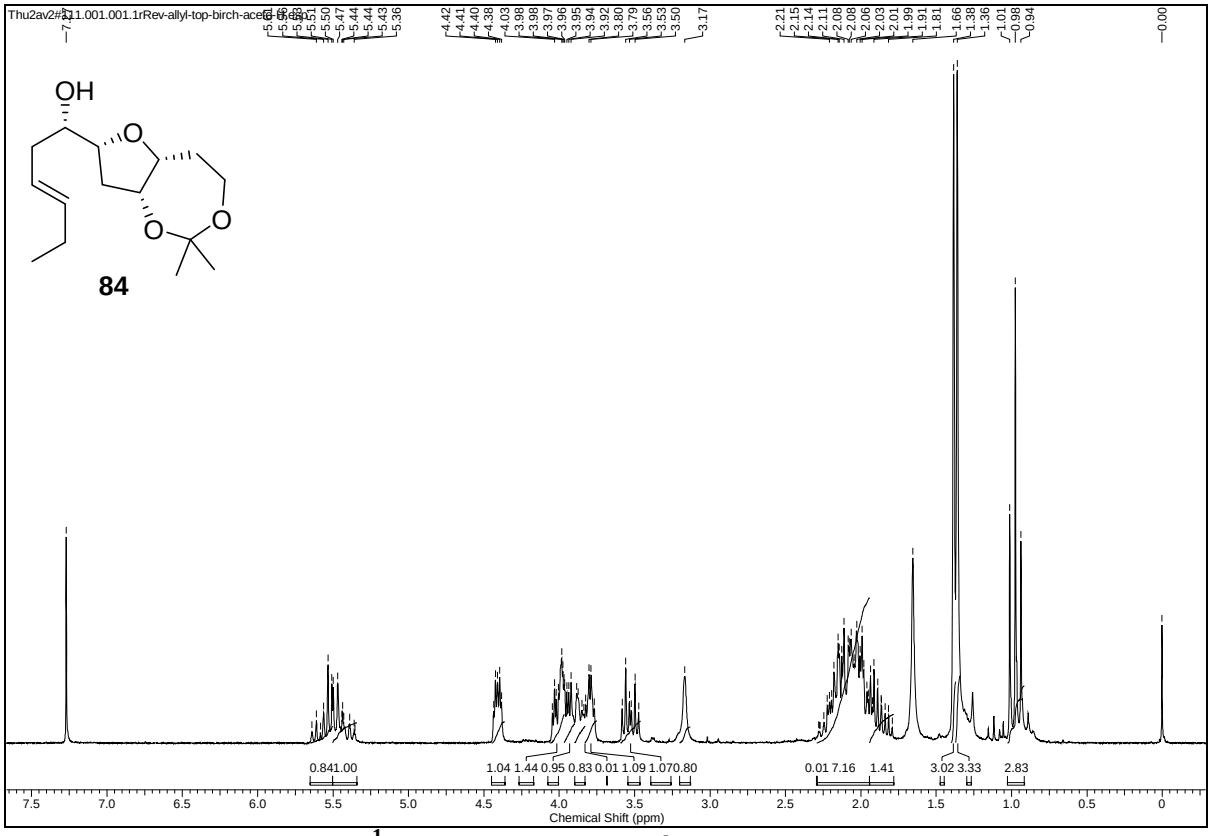
^{13}C NMR Spectrum of 82 in $CDCl_3$



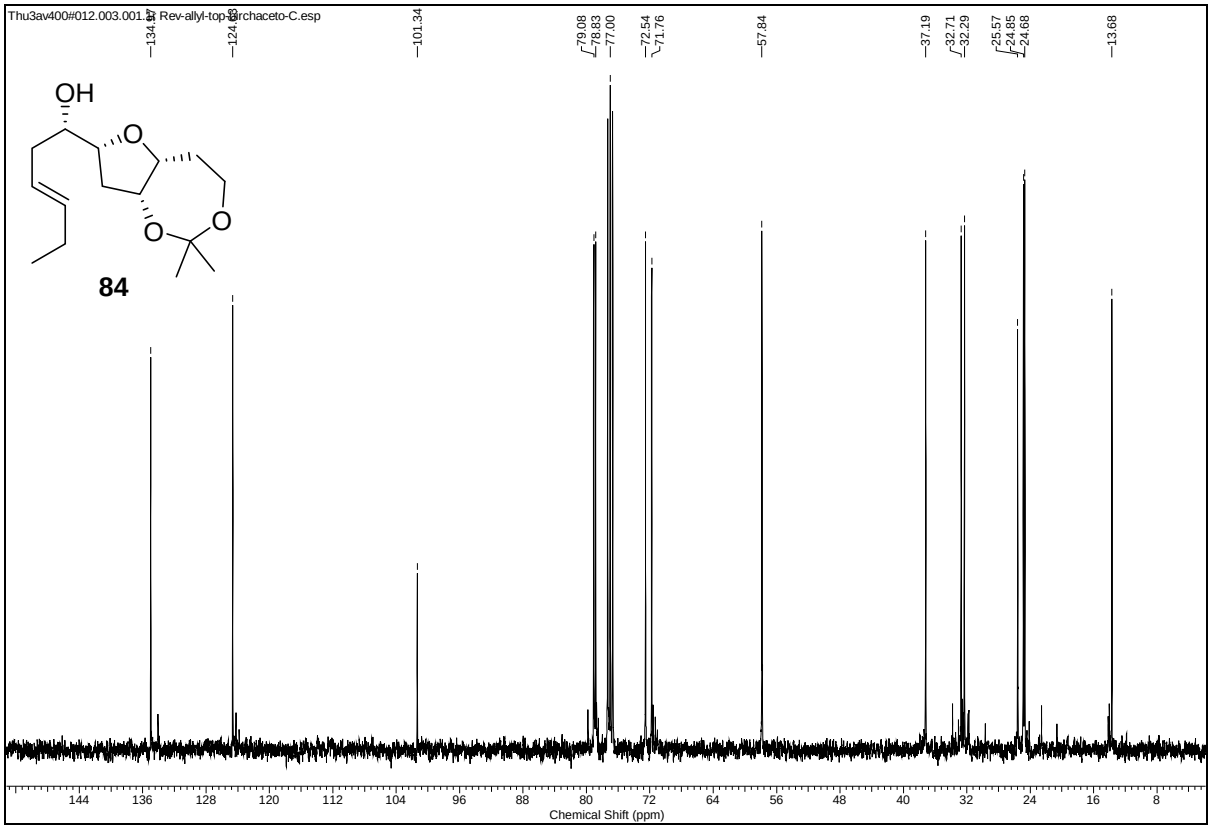
^{1}H NMR Spectrum of 75 in $CDCl_3$



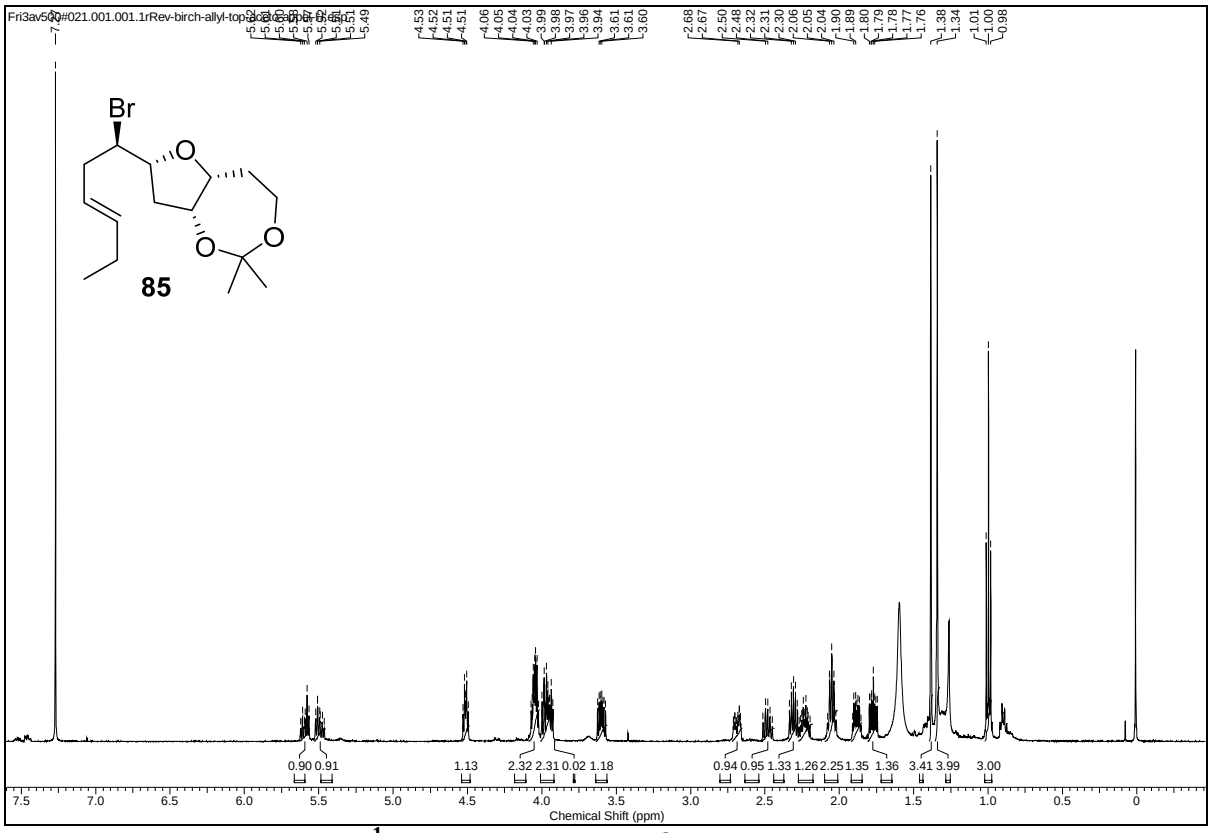
^{13}C NMR Spectrum of 75 in $CDCl_3$



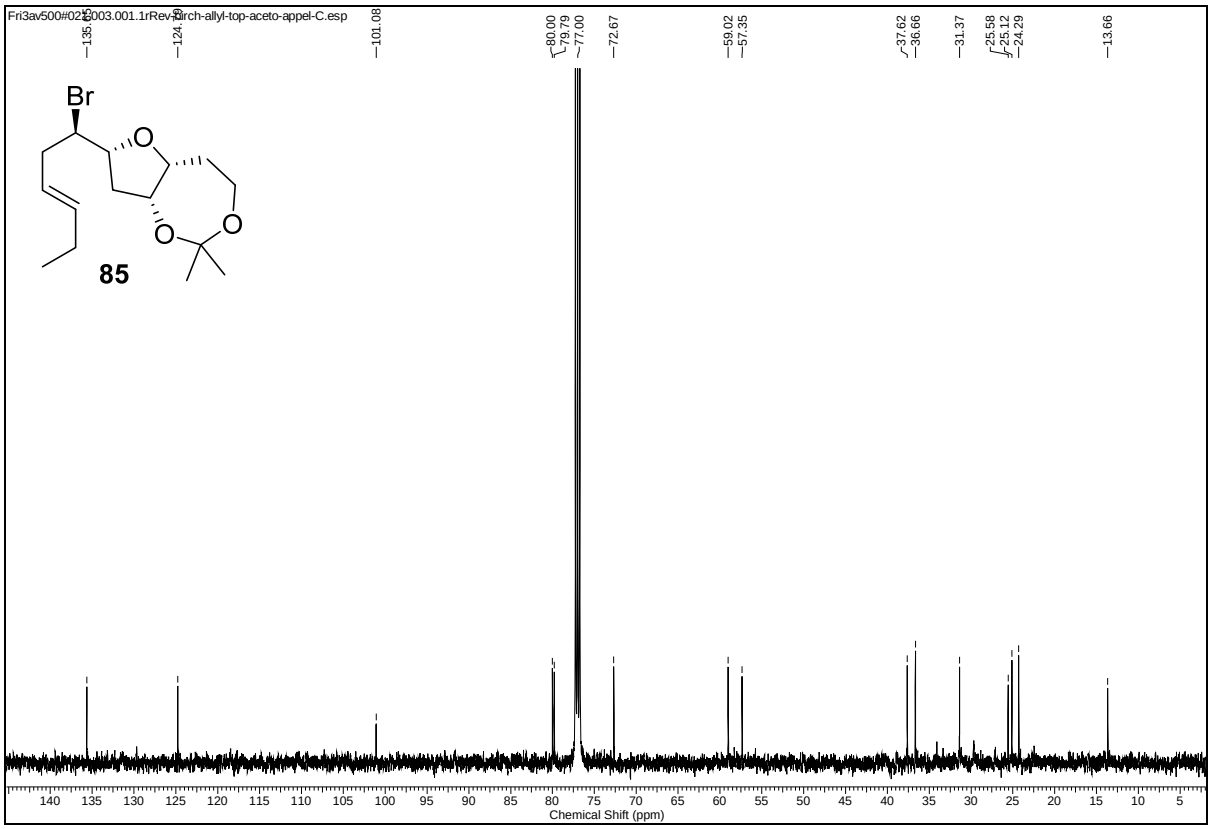
^{1}H NMR Spectrum of 84 in $CDCl_3$



^{13}C NMR Spectrum of 84 in $CDCl_3$



^{1}H NMR Spectrum of 85 in $CDCl_3$



^{13}C NMR Spectrum of 85 in $CDCl_3$

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LIST OF PUBLICATIONS:

- ☆ “Metal-mediated alkyne diol cycloisomerization: first and second generation formal total syntheses of didemniserinolipid B” **Shyamsundar Das**, Boddeti Induvadana, C.V. Ramana. *Tetrahedron* **2013**, *69*, 1881-1896.

- ☆ “First total synthesis of proposed structure of Notoryne” **Shyamsundar Das**, C.V. Ramana., to be communicated.

- ☆ “A chiral pool approach for total syntheses of (–) Kumausallene” **Shyamsundar Das**, C.V. Ramana., to be communicated

Erratum