

**Towards the Total Synthesis of Bruguierols A & B and
Uprolides D & E.**

A THESIS
SUBMITTED FOR THE DEGREE OF
DOCTOR OF PHILOSOPHY
(IN CHEMISTRY)

TO
UNIVERSITY OF PUNE

BY
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(Research Guide)

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OCTOBER 2007

**DEDICATED
TO
MY LATE FATHER,
MOTHER, BROTHERS,
SIS-IN-LAWS, SIS, BROTHER-IN-LAW,
PINKI, and PUTTA.**

DECLARATION

The research work embodied in this thesis has been carried out at National Chemical Laboratory, Pune under the supervision of **Dr. M. K. Gurjar**, Deputy Director, and Head, Organic Chemistry Division, National Chemical Laboratory, Pune - 411 008. This work is original and has not been submitted in part or full, for any degree or diploma of this or any other University.

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October 2007

(Mr. Sumantha)



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CERTIFICATE

The research work presented in thesis entitled “**Towards the Total Synthesis of Bruguierols A & B and Uprolides D & E**” has been carried out under my supervision and is a bonafide work of **Mr. Sumantha**. This work is original and has not been submitted for any other degree or diploma of this or any other University.

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- Sumanth.

DEFINATIONS AND ABBREVIATIONS

Ac	-	Acetyl
AcOH	-	Acetic acid
Ac ₂ O	-	Acetic anhydride
aq.	-	Aqueous
BINAP	-	2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl
Bn	-	Benzyl
BnBr	-	Benzyl bromide
BH ₃ .Me ₂ S	-	Boron dimethyl sulfide complex
BF ₃ .Et ₂ O	-	Boron trifluoride diethyl ether complex
BuLi	-	Butyl lithium
COD	-	Cyclooctadiene
Cp	-	Cyclopentadienyl
DCC	-	Dicyclohexyl carbodiimide
DCM	-	Dichloromethane
DET	-	Diethyl tartrate
DFT	-	Density functional theory
DIBAL-H	-	Diisobutylaluminiumhydride
DIPT	-	Diisopropyl tartrate
DMP	-	2,2-Dimethoxypropane
DMF	-	<i>N,N</i> -Dimethylformamide
DMAP	-	4-Dimethylaminopyridine
DMSO	-	Dimethyl sulfoxide
EDA	-	Ethylene diamine
EtOH	-	Ethanol
Et	-	Ethyl
Et ₂ O	-	Diethyl ether
EtOAc	-	Ethyl acetate
Et ₃ N	-	Triethylamine
HMDS	-	Hexamethyl disilazane

HOBt	-	N-Hydroxybenzotriazole
IBX	-	Iodoxybenzoic acid
Im	-	Imidazole
LDA	-	Lithium diisopropylamide
<i>m</i> -CPBA	-	<i>meta</i> -Chloroperbenzoic acid
MeOH	-	Methanol
MIC	-	Minimum inhibitory concentration
Ms	-	Methanesulfonyl
Me	-	Methyl
MeI	-	Methyl iodide
MTPA	-	α -Methoxytrifluorophenylacetic acid
NMO	-	<i>N</i> -Methyl morpholine <i>N</i> -oxide
NOESY	-	Nuclear overhauser effect spectroscopy
ORTEP	-	Oak ridge thermal ellipsoid plot
PDC	-	Pyridinium dichromate
PCC	-	Pyridinium chlorochromate
Ph	-	Phenyl
Py	-	Pyridine
PTSA	-	<i>para</i> -Toluenesulfonic acid
Red-Al	-	Sodium bis(2-methoxyethoxy)aluminumhydride
RCM	-	Ring-closing metathesis
r.t.	-	Room temperature
sat.	-	Saturated
TBDMS-Cl	-	<i>tert</i> -Butyldimethyl chlorosilane
TBHP	-	<i>tert</i> -Butyl hydroperoxide
TBS-OTf	-	<i>tert</i> -Butyldimethyl silyl trifluoromethane sulphonate
THF	-	Tetrahydrofuran
TPP	-	Triphenylphosphine
TMSOI	-	Trimethylsulfoxonium iodide
TPPTS	-	triphenylphosphine trisulfonate, sodium salt
TsCl	-	<i>para</i> -Toluenesulphonyl chloride

GENERAL REMARKS

- ^1H NMR spectra were recorded on AV-200 MHz, AV-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, and DRX-125 MHz spectrometer.
- EI Mass spectra were recorded on Finnigan MAT-1020 spectrometer at 70 eV using a direct inlet system.
- The X-Ray Crystal data were collected on *Bruker SMART APEX* CCD diffractometer using Mo K_α radiation with fine focus tube with 50 kV and 30 mA.
- 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.
- Melting points were recorded on Buchi 535 melting point apparatus and are uncorrected.
- 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 40 °C unless otherwise specified.
- Silica gel (60–120), (100-200), and (230-400) mesh were used for column chromatography.
- Different numbers were assigned for compounds in Abstract and Chapters.

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Abstract

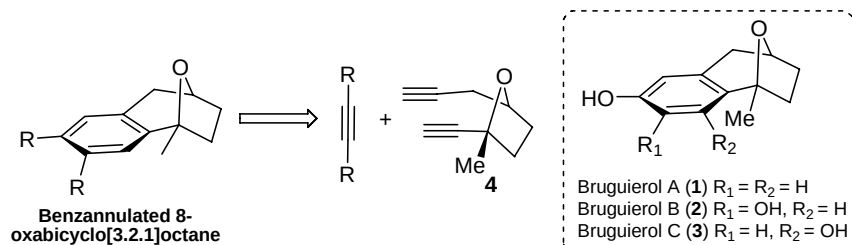
The thesis entitled “**Towards the Total Synthesis of Bruguiierols A & B and Uprolides D & E**” has been divided into two chapters. Each chapter again sub-divided in to two sections. Chapter I, section I describes an expeditious assembly of benzannulated 8-oxabicyclo[3.2.1]octane systems by [2+2+2] alkyne cyclotrimerization. Section II describes the synthetic studies towards bruguiierols A & B. Chapter II, Section I deals with the synthetic studies towards uprolide D and uprolide E, whereas section II describes a survey of some ring-closing metathesis approaches related to central core of uprolides D and E.

Chapter I:

Section I: An expeditious assembly of benzannulated-8-oxa-bicyclo[3.2.1]octane systems by [2+2+2] alkyne cyclotrimerization

Since the first disclosure by Reppe et. al, the transition metal-catalyzed [2+2+2] alkyne cyclotrimerization has become an integral component in the armory of organic synthetic methods. Though, the potential of [2+2+2] alkyne cyclotrimerization for linear fusion of aromatic compounds has seen great potential, however, the synthesis of bridged bicyclic systems through [2+2+2] cyclotrimerization has not yet explored.

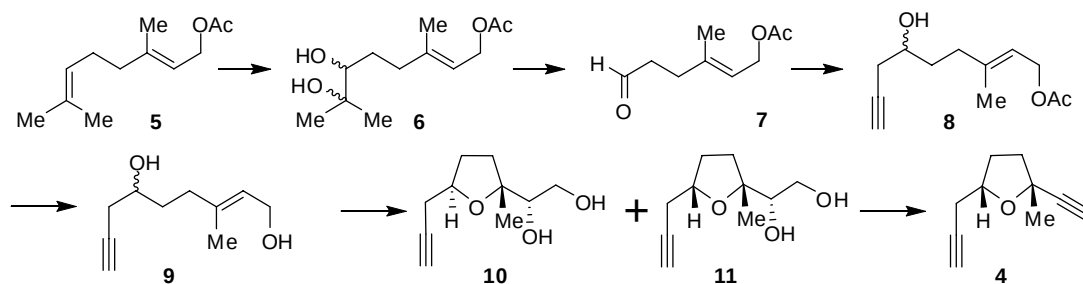
Scheme 1. Bruguiierols A –C and proposed [2+2+2] alkyne cyclotrimerization



Our initial foray in this area was stimulated by the three recently isolated natural products bruguiierols A–C (**1–3**) which comprise a rare 8-oxa bicyclo[3.2.1]octane skeleton and thus become excellent targets for our initial exploration. As depicted in the

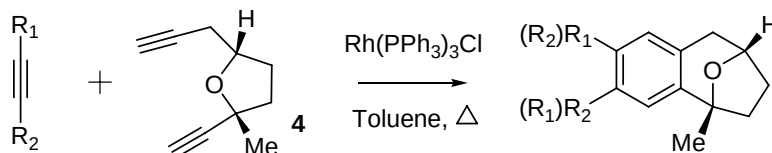
Scheme 1, we presumed these compounds can be accessed from a common key diyne **4** precursor and a suitable alkyne.

Scheme 2. Synthesis of key diyne 4



The key dialkyne **4** was prepared starting from geraniol acetate (**5**) in seven linear steps featuring Sharpless asymmetric epoxidation of racemic hexene diol **9**. The Wilkinson's catalyst was found to be superior for proposed [2+2+2] cross cyclotrimerization of diyne **4** with alkyne 2-butyne-1, 4-diol after screening various catalysts under different reaction conditions. In order to generalize, various alkynes were subjected to cyclotrimerization with the dialkyne **4** (Scheme 3). With unsymmetric alkynes like propargyl alcohol, phenyl acetylene, and 1-heptyne, cyclotrimerization resulted in equal ratios of inseparable regiomers, whereas with 4-oxopent-2-ynyl acetate, a 4:1 mixture was obtained.

Scheme 3. [2+2+2] Cross cyclotrimerization of diyne 4 with various alkynes



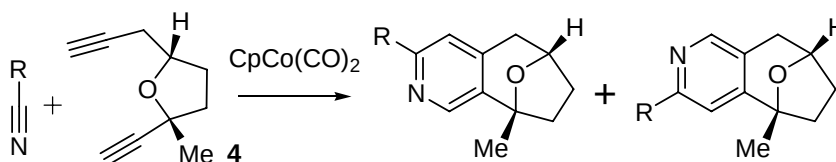
Entry	R ₁	R ₂	Product
1.	CH ₂ OH	CH ₂ OH	12
2.	H	H	13
3.	CH ₂ OAc	CH ₂ OAc	14
4.	CH ₂ OR ₃	CH ₂ OR ₃	15
5.	C(CH ₃) ₂ (OH)	C(CH ₃) ₂ (OH)	16
6.	CH ₂ OH	H	17/18
7.	Ph	H	19/20
8.	C ₅ H ₁₁	H	21/22
9.	CH ₂ OAc	Ac	23/24

R₃ =

Pyridine fused 8-oxabicyclo[3.2.1]octane systems by cyclotrimerization.

In order to extend the scope of this reaction the trimerization of dialkyne **4** was carried out with various nitriles and the regiomerically pyridines were obtained in equal ratios with moderate to good yields. The trimerization products of 4-chlorobenzonitrile were separated and the structures were confirmed with the help of 2D NMR.

Scheme 4. [2+2+2] Cross cyclotrimerization of diyne **4** with various nitriles

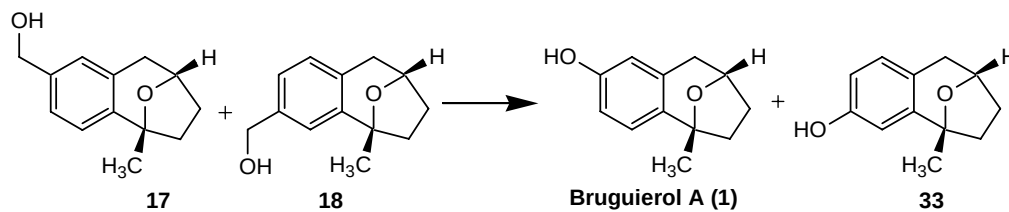


Entry	R	Product
1.	CH ₃	25/26
2.	Ph	27/28
3.	4-Cl-Bn	29/30
4.	3-Indole-CH ₂	31/32

Section II: Towards the total synthesis of bruguierols A & B.

After establishing the feasibility of [2+2+2]-cyclotrimerization reaction for the synthesis of benzannulated-8-oxa-bicyclo[3.2.1]octane systems, we next proceed for synthesis of bruguierol A using compounds **17/18**. Oxidation of **17/18** mixture with MnO₂ followed by treatment with *m*-chloroperoxybenzoic acid provided the bruguierol A (**1**) and **33** in 34% overall yield which were separated and characterized.

Scheme 5. Total synthesis of (–)-bruguierol A (**1**)

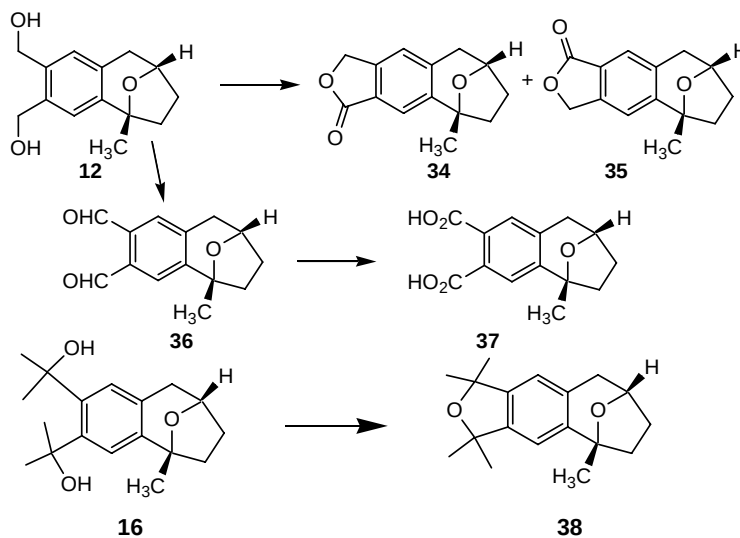


The spectroscopic data of synthetic bruguierol A (**1**) was in excellent agreement with those reported for the natural product. In addition, the single crystal X-ray structural analyses of **1** and **33** established their constitution beyond doubt. However, the optical rotation of synthetic sample was similar to reported opposite in sign which indicated that the synthetic sample was anti-pode of bruguierol A and established the absolute stereochemistry of bruguierol A (5*S*, 8*R*).

Attempted synthesis of bruguierol B

The following sequence of reactions with **12**, i.e., oxidation followed by Baeyer-Villiger reaction to obtain bruguierol B (**2**) was attempted. However, when treated with MnO₂, diol **12** gave mainly a mixture of lactone derivatives **34/35**. IBX oxidation of **12** yielded the *o*-dialdehyde **36**. Further, treatment of *o*-dialdehyde **36** with *m*-CPBA in dichloromethane resulted with rapid decomposition of the starting compound. On the other hand, hydrogen peroxide mediated oxidation of **36** catalyzed by diphenyl diselenide gave exclusively the *o*-diacid derivative **37**.

Scheme 6. Attempted synthesis of bruguierol B



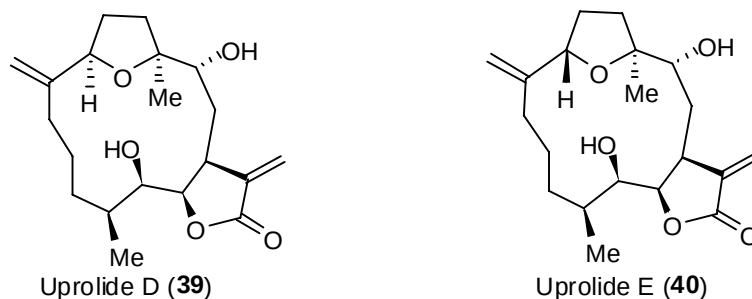
Attempted hydroperoxide rearrangement of **16** exclusively gave the cyclized product **38** under standard reaction condition.

Chapter II:

Synthetic studies towards Uprolides D and E

Uprolide D (**39**) and uprolide E (**40**) isolated from gorgonian species of the genus *Eunicea mammosa* showed promising antitumor activity against leukemia, colon, and breast cancer cells. Uprolides are characterized by their unique 4,7-oxa-bridged bicyclic skeleton and densely functionalized central 14-carbon core.

Figure 1. Structures of Uprolides D and E



The promising biological activity and unique structural features made uprolides as attractive targets for total synthesis and we approached the total synthesis of uprolides from two directions in this regard.

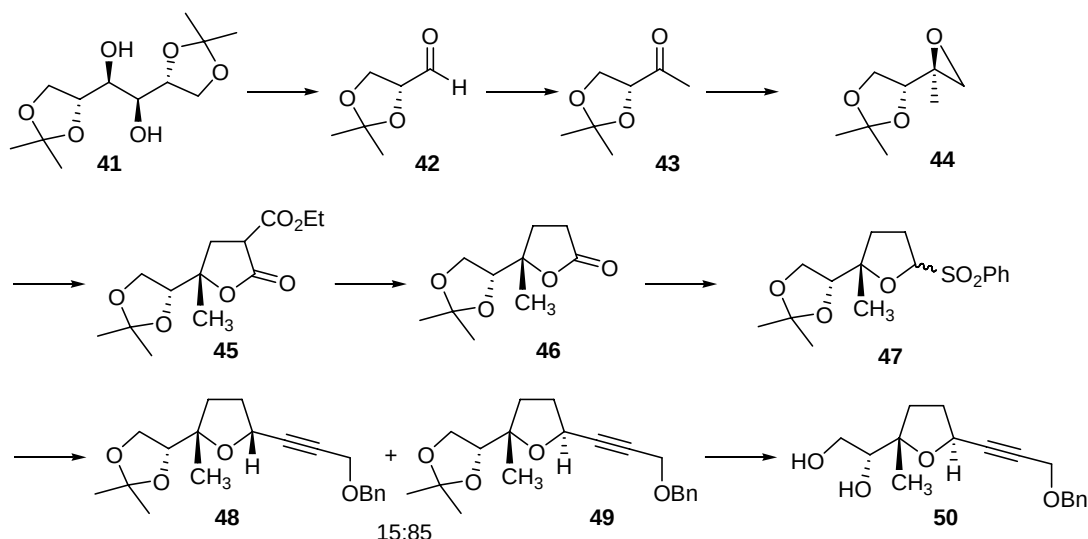
- Stereoselective construction of central 14 carbon unit (Section I)
- Examining the ease of ring closing metathesis reaction to form the bicyclic core of uprolides (Section II)

Section I. *Synthesis of the C1-C14 carbon unit of uprolide E*

Our initial synthetic study toward 14-carbon unit of Uprolide E consist of a couple of key reaction like intramolecular Horner-Wadsworth-Emmons cyclization, Yamaguchi protocol and Ley's sulphone displacement by alkynyl zinc species.

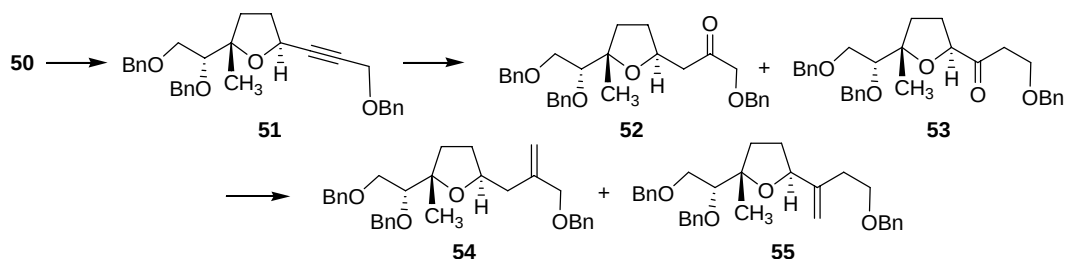
Scheme 7, silently describes the synthesis of epoxide **44**, an advanced intermediate in our strategy in enantiomeric pure form from 1,2:5,6-bis-O-isopropylidene-D-mannitol **41** and subsequent Ley's sulphone protocol for the construction of central 2,5-*anti*-configured tetrahydrofuran unit **50**.

Scheme 7. Synthesis of central 2,5-*anti*-configured tetrahydrofuran core of uprolide E



The epoxide **44** was treated with sodium salt of diethylmalonate to give β -ester lactone **45** which in turn was subjected to decarboxylation under modified Krapcho's condition to accomplish lactone **46**. Partial reduction of lactone **46** to lactol followed by treatment with benzenesulphinic acid afforded the sulphone derivative **47**. The sulfone **47** was treated with insitu generated dialkynyl zinc species derived from propargyl benzyl ether to give 85:15 ratio of 2,5-*anti* and *syn* configured tetrahydrofurans **48/49** in 69% yield. The diols were separated by chromatography and relative stereochemistry was assigned on the basis of NOESY experiments. The acetonide **49** was subjected to acid hydrolysis to give diol **50**.

Scheme 8. NaAuCl_4 mediated hydration and one carbon Wittig homologation

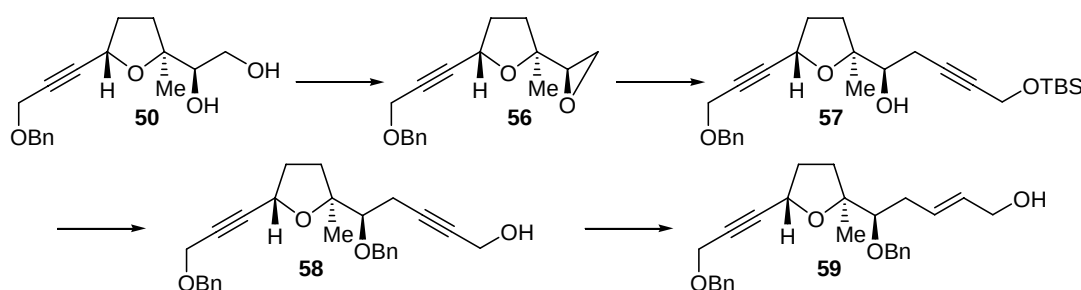


The gold/mercury mediated hydration reaction of **51** resulted in 1:1 mixture of inseparable regioisomers **52/53**. Even the one carbon Wittig homologation didn't separate the regioisomers **54/55**. Due to the problem of regioselectivity in hydration and

separation of the regiomers, we opted for constructing the molecule from the left hand side so that we can have the regioselectivity problem in the later stages of our synthesis.

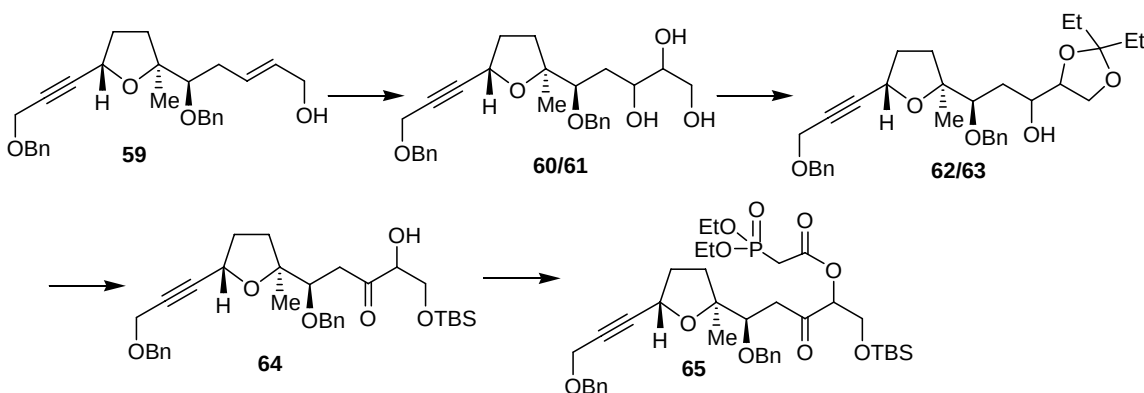
The diol **50** was transformed to epoxide **56** and then opened with propargyl TBS ether under Yamaguchi reaction condition to give the secondary alcohol **57**. The alcohol **57** was protected as its benzyl ether and the silyl protection was removed to give alkynol **58**. The alkynol **58** was chemoselectively reduced to *trans*-allylic alcohol **59** using LAH in moderate yield.

Scheme 9



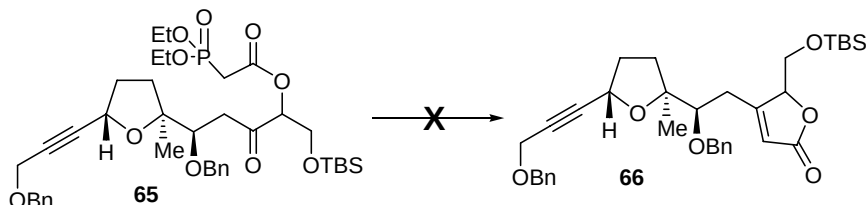
The attempted dihydroxylation of **59** under Sharpless asymmetric dihydroxylation condition or OsO₄/NMO surprisingly gave 1:1 mixture of inseparable diastereomers **60/61**. The mixture of triols **60/61** was subjected to 3-pentanone protection to give separable mixture of diastereomers **62/63**. We proceeded with one of the protected triol **62** for standardizing the reaction sequences. IBX oxidation, acetal deprotection followed by selective TBS protection gave keto alcohol **64** which was coupled with diethyl phosphonoacetic acid to give phosphonate **65**.

Scheme 10



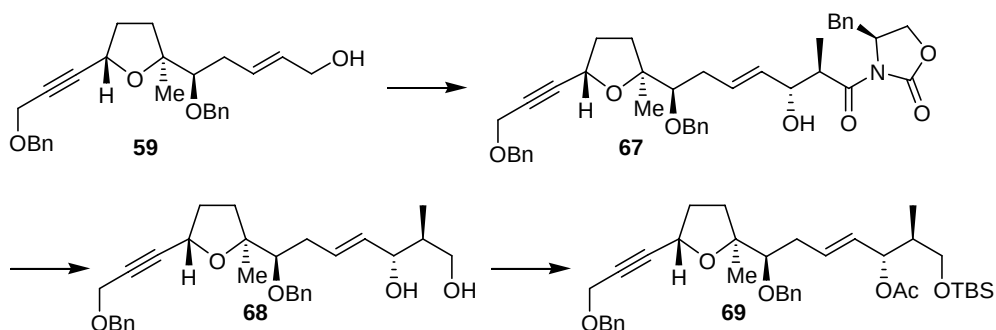
The attempted intramolecular Horner-Wadsworth-Emmons reaction of **65** using NaH/THF at 0 °C gave series of uncharacterizable products. The LiCl mediated reaction in acetonitrile didn't produce any cyclized product.

Scheme 11



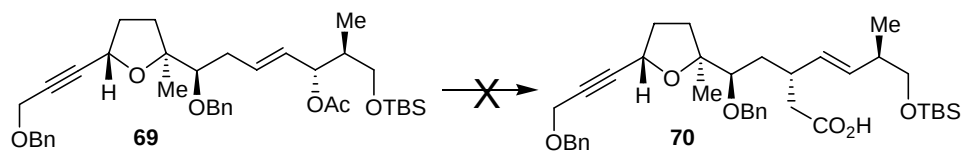
Since the attempted intramolecular Horner-Wadsworth-Emmons reaction for the construction of lactone was a failure, we planned an alternative strategy that involves an Ireland-Claisen rearrangement. The synthetic sequences started with MnO₂ oxidation of allylic alcohol **59**. The intermediate aldehyde was subjected to non-Evans *anti*-aldol reaction to furnish **67**, of which the chiral auxiliary was reductively removed to afford the diol **68**. Primary -OH in **68** was protected as its TBS ether and the secondary as acetate to afford allylic acetate **69**.

Scheme 12



The key Ireland-Claisen rearrangement of the fully elaborated allylic acetate **69** was studied under LiHMDS/TBS-Cl/THF at -78 °C to reflux temperature was found to be unsuccessful and in all the trials we could only recover the starting material. Similar results were obtained by employing LDA/TMS-Cl reaction conditions.

Scheme 13



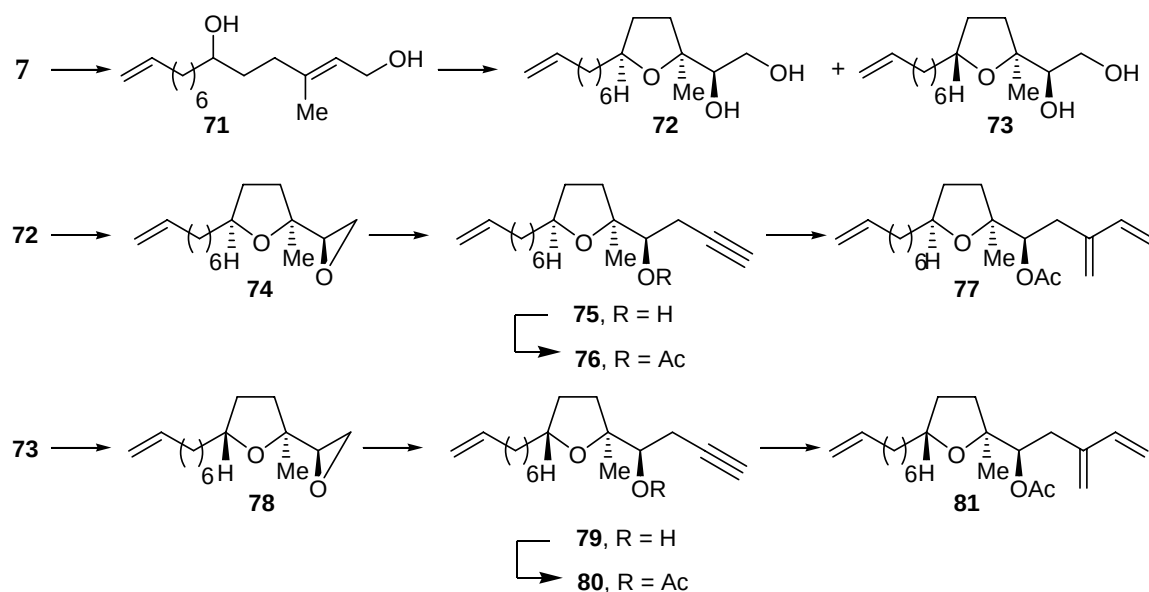
Section II: Central core of uprolides D and E: a survey of some ring-closing metathesis approaches

Our study related to construction of central bicyclic core Uprolides D and E and the lactone fused to it mainly deals with the metathetic approaches. The 14-membered carbocyclic uprolides become excellent targets for RCM and ene-yne RCM with properly placing the diene and ene-yne systems. The major issue in both the routes would be the feasibility of RCM with the 2,5-*anti*-configured tetrahydrofuran ring systems in general and the ease of an intramolecular ene-yne ring closing metathesis forming large ring systems in particular.

Ene-yne RCM approach towards uprolides:

In order to investigate an ene-yne RCM approach, the synthesis of the requisite tetrahydrofuran derivatives was carried out using the established kinetic resolution. Addition of 7-octenylmagnesium bromide to aldehyde **7** followed by acetate hydrolysis gave the dienol **71** in 73% yield. Sharpless asymmetric epoxidation of **71** using diisopropyl D-tartrate provided the diastereomeric tetrahydrofurans **72** and **73**. Regioselective tosylation of **72** followed by treatment with K_2CO_3 gave the epoxide **74** in 82% yield. Opening of **74** with lithium acetylide ethylenediamine complex in DMSO afforded the alkynol **75** in 81% yield. The ene-yne RCM reactions of alkynol **75** using Grubbs' 1st or 2nd generation catalyst under argon or ethylene in refluxing DCM were found to be unsuccessful. However, treatment of the corresponding acetate **76** with the 2nd generation Grubbs' catalyst in refluxing DCM under ethylene gave the triene **77** in 21% yield. In a similar manner, the ene-yne RCM of 2,5-*anti*-configured furan **80** prepared from **73** also resulted in the formation of the triene **81**.

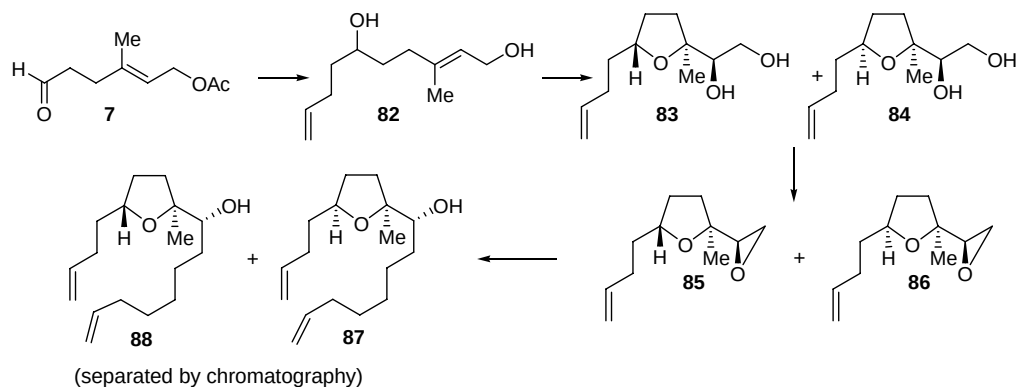
Scheme 14



RCM approach towards Urolides:

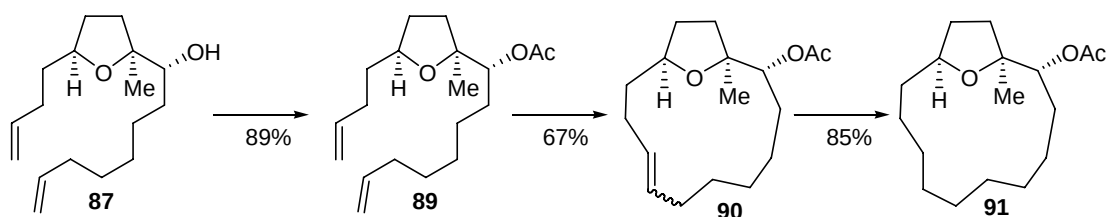
To complete the next intended RCM approach, the racemic dienol (**82**) was prepared by the addition of 3-butenylmagnesium bromide to **7**. The Sharpless asymmetric epoxidation of **82** using diisopropyl D-tartrate afforded the tetrahydrofurans **83** and **84** as an inseparable mixture (1:1). Regioselective tosylation of diols **83** and **84** followed by treatment with K_2CO_3 in methanol gave diastereomeric mixture of epoxides **85** and **86** which were treated with cuprate derived from 5-hexenyl magnesium bromide and CuI in THF at $-40^\circ C$ to afford dienol compounds **87** and **88** which were separated and characterized. The stereochemistry of tetrahydrofurans **87** and **88** were confirmed by NOESY spectra of corresponding acetates.

Scheme 15



The critical RCM reaction of diene **87** with 1st generation Grubbs' catalysts was unsatisfactory and only traces of macrocyclic derivative was isolated. The RCM reaction of the corresponding acetate **89** with the 1st generation Grubbs' catalyst was satisfactory and produced the 14-membered macrocyclic derivative **90** as an inseparable *E/Z* (1:1) mixture which was reduced to **91**, the central bicyclic core of uprolide D. Our attempted RCM approach for bicyclic core of uprolide E employing *anti*-configured furan **88** or its acetate was found to be a difficult proposition using either 1st or 2nd generation Grubbs' catalysts under several conditions attempted.

Scheme 16



Chapter I

Chapter I, Section I:

An Expeditious Assembly of Benzannulated 8-Oxa
Bicyclo[3.2.1]Octane Systems by [2+2+2] Alkyne
Cyclotrimerization.

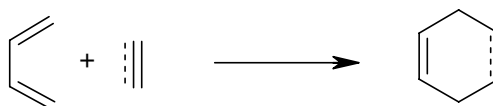
Introduction

Polysubstituted benzenes are highly useful compounds, which are widely used in industry as well as in the laboratory. The regioselective construction of polysubstituted benzenes has been mainly achieved by stepwise introduction of the substituents via electrophilic substitution reactions such as the Friedel-Crafts reaction. This is a useful method for the synthesis of polysubstituted benzenes. However, high regioselectivity (and yield) can only be achieved by the careful choice of the reagents and synthetic route. Furthermore, it is usually necessary to convert and/or protect-deprotect the substituents properly. Directed *ortho* metallation is another synthetic method which has been studied extensively, and this approach is a useful method for the introduction of a substituent at the *ortho* position. However, the scope of this reaction is clearly restricted by its nature. Compared to the transition metal-catalyzed methods, these approaches have some drawbacks from the viewpoint of atom economy or environmental concern.

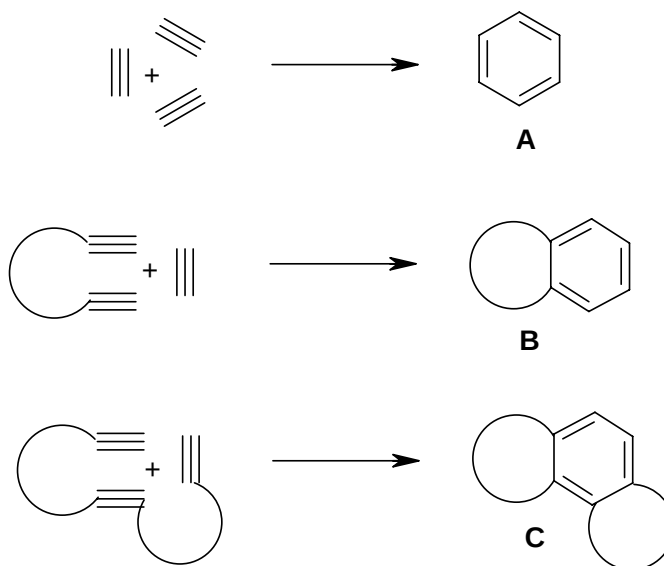
Cyclizations of unsaturated molecules are extensively studied reactions since they potentially afford a variety of substituted benzenes, heterocyclic and polycyclic compounds of paramount importance in chemical industry and pharmaceutical research. The rapid development of various transition-metal catalyzed reactions induced the innovation of organic synthesis. A large number of unique and efficient reactions developed by organometallic chemists have been widely used for the synthesis of various organic compounds such as drugs, natural products, and functionalized materials. The catalytic coupling reactions between unsaturated hydrocarbons such as [2+2+2] cyclotrimerization of alkynes and Diels–Alder-type reactions are particularly attractive, since complicated molecules are obtained in one step from simple unsaturated hydrocarbons (Scheme 1), which are usually less reactive compared to compounds bearing leaving groups such as a halogen atom. The reactions proceed with high atom economy and the product incorporates all of the atoms of the substrates and no unwanted products (such as inorganic salts) are produced, which is another attractive feature. The [2+2+2] cycloaddition strategy is complementary to the well known Diels-Alder reaction (Scheme 2).

Bertholet first discovered the formation of benzene by thermal cyclization of three acetylene molecules in 1866. Reppe et al. reported the first transition metal-catalyzed cyclotrimerization of acetylenes to benzene derivatives in 1948.¹ Since then, various transition metal catalysts based on Ni, Co, Pd, Cr, Rh, Fe, Zr, Nb, Ir, and Ta have been developed for the trimerization reaction involving alkynes. In addition to alkynes, other unsaturated components such as nitriles, isocyanates, olefins, carbonyl compounds, imines, and diimides have been shown to undergo cyclotrimerizations with alkynes to afford synthetically useful products.

Scheme 1. *Diels-Alder type reaction*



Scheme 2. *Cyclotrimerization of alkynes*



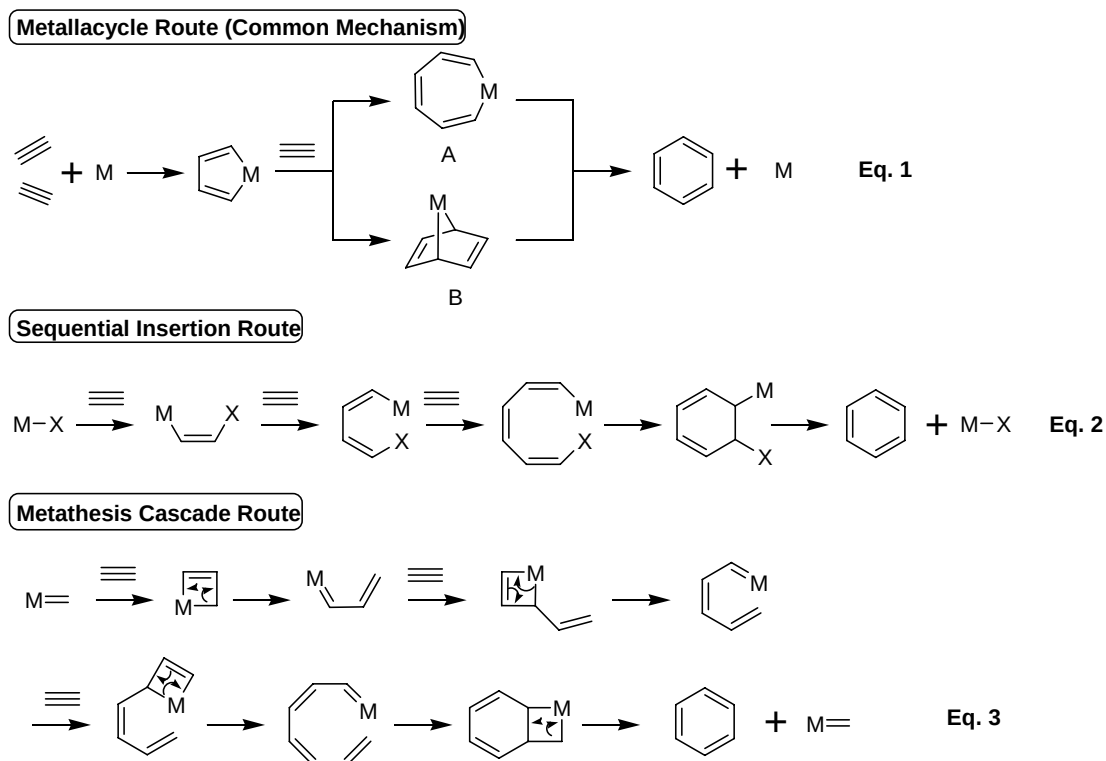
The acetylene trimerization by a symmetry-allowed [2+2+2] cycloaddition reaction is an exothermic process ($\Delta H = -594 \text{ kJmol}^{-1}$), but requires higher temperature or a catalyst because of entropic and kinetic factors. If two alkynes were tethered, annulated benzene derivative **B** would be generated, whilst if all three alkynes were

connected, a tricyclic ring **C** would be formed in an intramolecular fashion. Cyclotrimerization of suitably placed alkyne derivatives can provide otherwise difficult to prepare polysubstituted aromatic compounds. The catalytic control of chemoselectivity and regioselectivity of the product was a primary concern for this type of cycloadditions. These cyclotrimerization reactions can be performed in common organic solvents at temperatures ranging from r.t. to upwards. There are reports of cobalt-catalyzed alkyne trimerizations in supercritical water,² and in supercritical carbon dioxide.³

Mechanism of [2+2+2] alkyne cyclotrimerization

The mechanism of alkyne cyclotrimerization⁴ and cyclic cooligomerization (cyclizations involving two alkyne and one alkene)⁵ are reviewed thoroughly, but still a generality from these has not been achieved. Transition metal catalyzed alkyne cyclotrimerizations can be broadly divided into three categories on the basis of their reaction mechanisms (Scheme 3).^{4b}

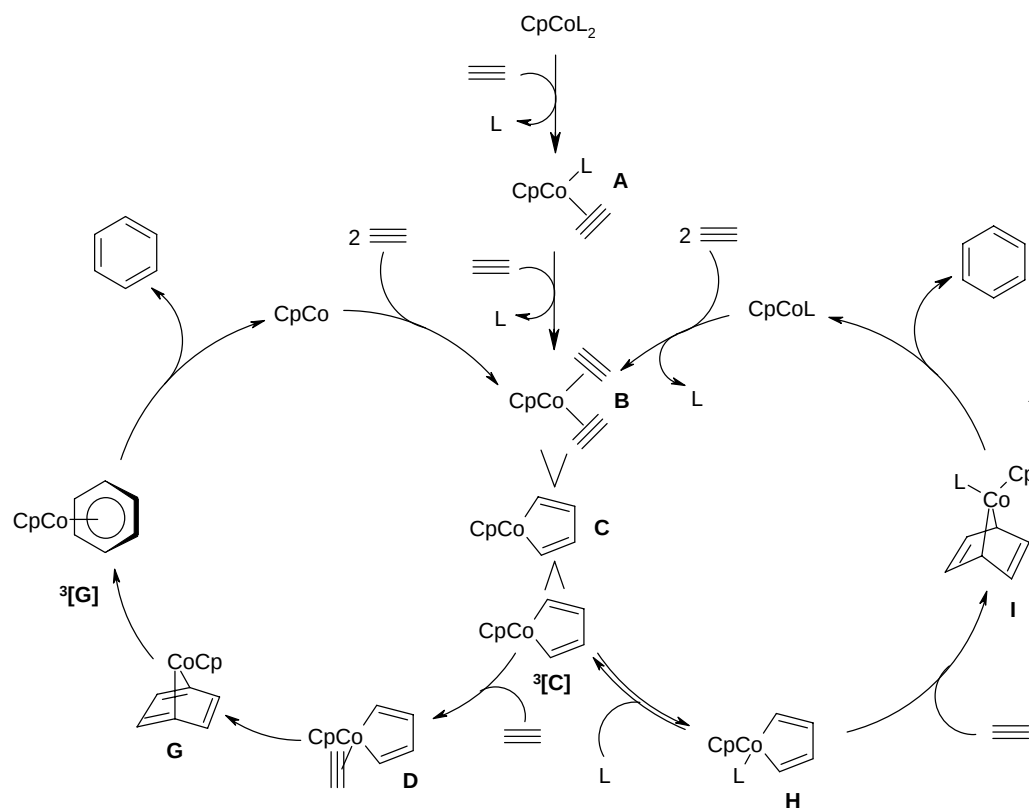
Scheme 3. Possible mechanisms of alkyne cyclotrimerization



The most widely accepted mechanism is the so-called “common mechanism” (Eq. 1, Scheme 3). Two alkyne moieties coordinate to the metal, and then coupling reaction proceeds to give the metallacycle A or B through an insertion or Diels-Alder type of addition. The benzene ring is formed by the reductive elimination of the metal. A sequential carbometallation mechanism (Eq. 2, Scheme 3) operates in cyclotrimerizations catalyzed by transition-metal hydrides or halides⁶. In addition, a metathesis cascade using Grubbs’ ruthenium carbene complex quite recently proved to be effective for the cyclization of triyne, regioselective coupling of diyne with monoyne, and the trimerization of carbohydrate-derived monoynes (Eq. 3, Scheme 3).⁷

Aubert and co-workers recently studied mechanism of the $\text{CpCo}(\text{L}_2)$ -catalyzed cyclotrimerization of acetylene on the basis of DFT computations, and proposed a parallel mechanism (Scheme 4).⁸

Scheme 4. *Two-state mechanism for the Co-catalyzed ethyne cyclotrimerization*

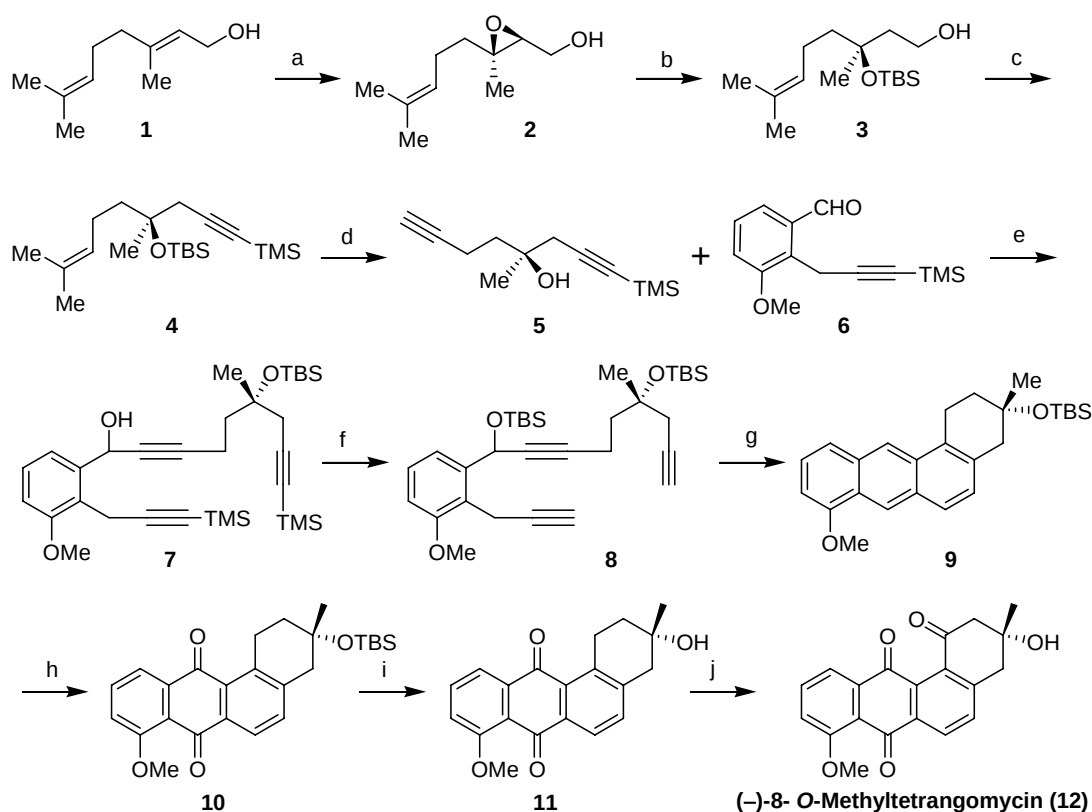


In the proposed parallel cycle, a bisalkyne complex (**B**) undergoes oxidative coupling to a cobaltacyclopentadiene (**C**), which spontaneously relaxes to the triplet ground state ($^3[\text{C}]$). The trapping of that species to give 18-electron complex **H** is faster with σ -donor ligands (PR_3 , CO, THF) than with π -donors (alkyne, alkene, arene). Therefore, for reactions in strong σ -donor solvents or employing $\text{CpCo}(\text{PR}_3)_2$ or $\text{CpCo}(\text{CO})_2$, the species **H** is a likely relay point. Subsequently, strongly dienophilic alkynes add to **H** by intermolecular $[4 + 2]$ cycloaddition to furnish cobaltanorbornadiene **I**. A change in the spin state results in the formation of the free arene and CpCoL . In the absence of strong σ -donors and electron poor alkynes, another catalytic cycle takes over: $^3[\text{C}]$ reacts with the alkyne to give **D**, which subsequently transforms into the $\text{CpCo}(\eta^4\text{-arene})$ complex **G** via intramolecular metal-assisted $[4 + 2]$ cycloaddition. A spin change transforms **G** into the 20-electron sandwich complex $^3[\text{G}]$, which dissociates to arene and CpCo .

Total Synthesis

Due to its operational simplicity, and ability to provide complex molecular structures, the transition metal catalyzed $[2+2+2]$ alkyne cyclotrimerization has become integral component in the armory of organic synthetic methods and has been reviewed thoroughly.⁹ The utility of this reaction is exemplified in the synthesis of a variety of complex natural products comprising aromatic rings featuring cyclotrimerization as the key step in the synthesis.¹⁰ Groth and co-workers reported stereoselective total synthesis of the natural antibiotic (–)-8-*O*-methyltetrangomycin (MM 47755) (**12**).^{10a} The essential steps for this convergent synthesis are the transformation of a geraniol epoxide **2** into a chiral octadiyne derivative (**5**), which was converted into a triyne **7** through a alkynylation process. The cobalt-mediated $[2+2+2]$ cycloaddition reaction of the triyne **8** in diethyl ether at $-78\text{ }^\circ\text{C}$ to r.t. led to a benz[*a*]anthracene system (Scheme 5), which was oxidized with $\text{Ag}(\text{Py})_2\text{MnO}_4$ to a benz[*a*]anthraquinone. Deprotection with aq. HF in acetonitrile and photooxidation afforded the desired natural product.

Scheme 5. Total synthesis of MM 47755

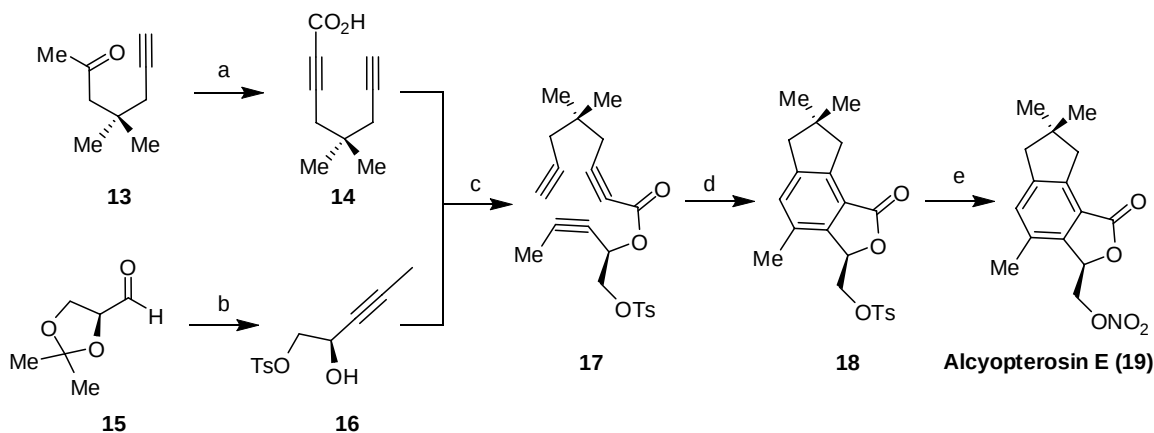


Reagents and conditions: (a) $\text{Ti}(\text{O}^i\text{Pr})_4$, TBHP, (+)-DET, CH_2Cl_2 , -25°C , 4 h, 93%. (b) i. Red-Al, THF, 0°C , THF, 92%; ii. BzCl , Et_3N , CH_2Cl_2 , 12 h, 98%; iii. TBSOTf, 2,6-lutidine, CH_2Cl_2 , 12 h, 96%; iv. NaOH , MeOH , r.t., 4 h, 95%. (c) i. $\text{SO}_3\cdot\text{Py}$, Et_3N , DMSO, r.t., 3 h, 93%; ii. PPh_3 , CBr_4 , Et_3N , CH_2Cl_2 , 12 h, 90%; iii. $n\text{-BuLi}$, Et_2O , -78°C , 2 h; iv. TMS-Cl , -78°C , 12 h (95%). (d) i. O_3 , Py , CH_2Cl_2 , -78°C , 1 h, then Me_2S , -78°C to r.t., 12 h, 85%; ii. PPh_3 , CBr_4 , Et_3N , CH_2Cl_2 , 12 h, 90%; iii. $n\text{-BuLi}$, Et_2O , -78°C , 3 h, then aq. NH_4Cl , 95%; iv. aq. HF , CH_3CN , 50°C , 6 h, 49%. (e) $n\text{-BuLi}$, Et_2O , -78°C , 3 h, then **6**, $\text{BF}_3\cdot\text{Et}_2\text{O}$, Et_2O , -78°C , 2 h, 70%. (f) i. K_2CO_3 , MeOH , r.t., 6 h, 90%; ii. TBSOTf, 2,6-lutidine, CH_2Cl_2 , 12 h, 96%. (g) $\text{CpCo}(\text{C}_2\text{H}_4)_2$, Et_2O , -78°C to r.t., 4 h, then cat. AcOH , 80%. (h) $\text{Ag}(\text{Py})_2\text{MnO}_4$, SiO_2 , CH_2Cl_2 , r.t., 7 h, 65%. (i) aq. HF , CH_3CN , 50°C , 5 h, 98%. (j) hv, air, CHCl_3 , r.t., 1 h, 58%.

The first synthesis of the marine illudalane sesquiterpenoid alcyopterosin E was reported by Witulski and co-workers through a concise ABC ring-formation strategy using a rhodium (I)-catalysed intramolecular alkyne cyclotrimerisation as key connection.^{10b} Acid **14** was obtained from known alkyne **13** over four steps and the propargylic alcohol **16** was synthesised from (*S*)-glyceraldehyde acetonide (**15**) within

four steps. The DCC mediated coupling of **14** and **16** provided the triyne ester **17**. Treatment of **17** with 10 mol% RhCl(PPh₃)₃ in DCM at 40 °C gave **18** as a single product in 72% yield. Finally, the first synthesis of alcyopterosin E (**19**) was completed by nucleophilic displacement of the tosyl protective group against a nitrate ester functionality (Scheme 6).

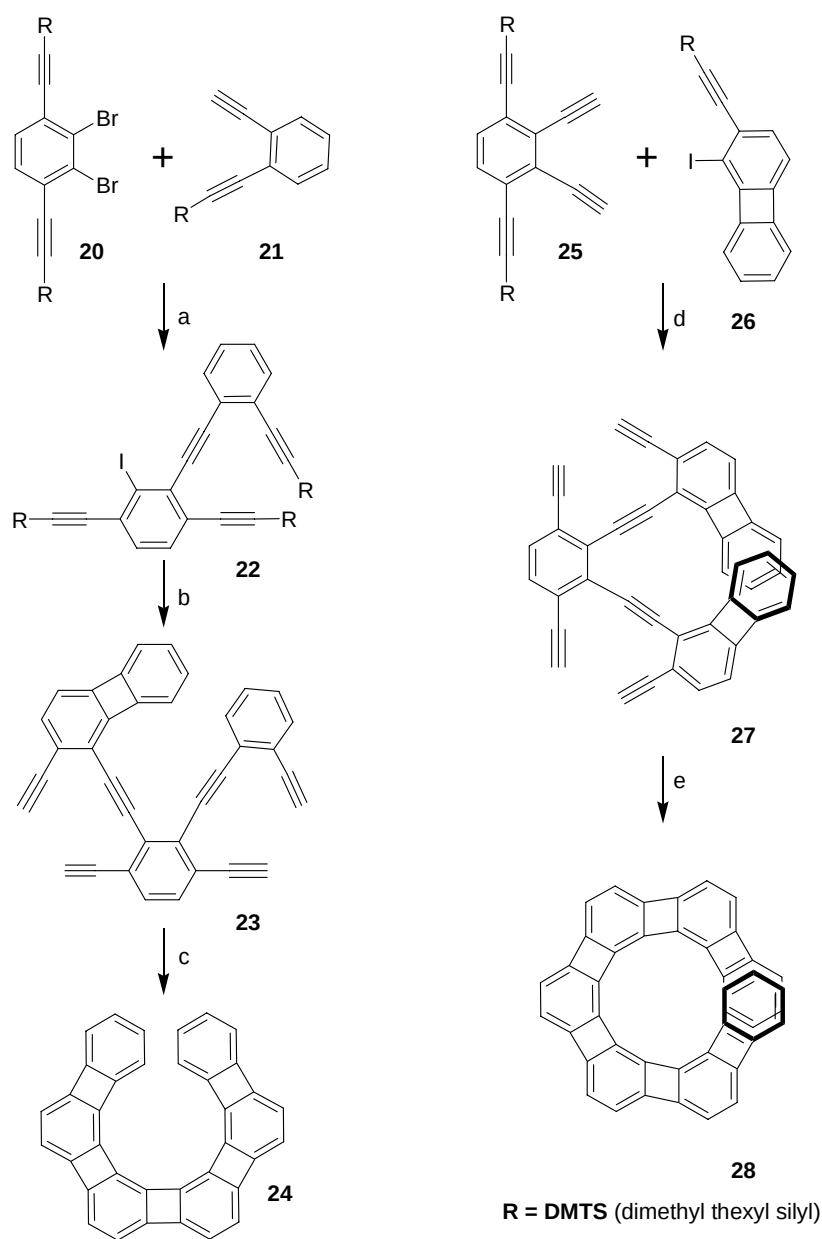
Scheme 6. Total synthesis of alcyopterosin E



Reagents and conditions: (a) i. LDA, THF, PhSiMe₂Cl, -78 °C, 98%; ii. LDA, THF, POCl(OEt)₂, -78 °C, 70%; iii. *n*-BuLi, THF, -40 °C, CO₂ (gas) 89%; iv. TBAF, THF, 0 °C, 94%. (b) i. Zn, CBr₄, PPh₃, CH₂Cl₂, 61%; ii. *n*-BuLi (2.2 equiv.), THF, -78 °C, then add MeI; iii. PTSA, MeOH, 61%; iv. TsCl, Py, CH₂Cl₂, 69%. (c) DCC, DMAP, CH₂Cl₂, -78 °C to r.t., 70%. (d) 10 mol% RhCl(PPh₃)₃, CH₂Cl₂, 40 °C, 72%. (e) NaNO₃ (10 equiv.), Bu₄NNO₃, toluene, 110 °C, 69%.

Vollhardt and co-workers reported total syntheses and structures of angular [6]- and [7] phenylene (heliphenes).^{10c} The synthesis started with Pd-catalyzed alkynylation of readily available dibromo compound **20** with alkyne **21** followed by replacement of bromo with iodo to furnish **22**. A second alkynylation with 1-ethynyl-2-(2-DMTS-ethynyl)biphenylene followed by global silyl deprotection gave hexayne **23**. Finally, cobalt-catalyzed intramolecular cyclotrimerization of **23** under photochemical condition in refluxing xylene furnished **24** as orange solid (Scheme 7).

Scheme 7. Synthesis of [6] and [7] phenylenes



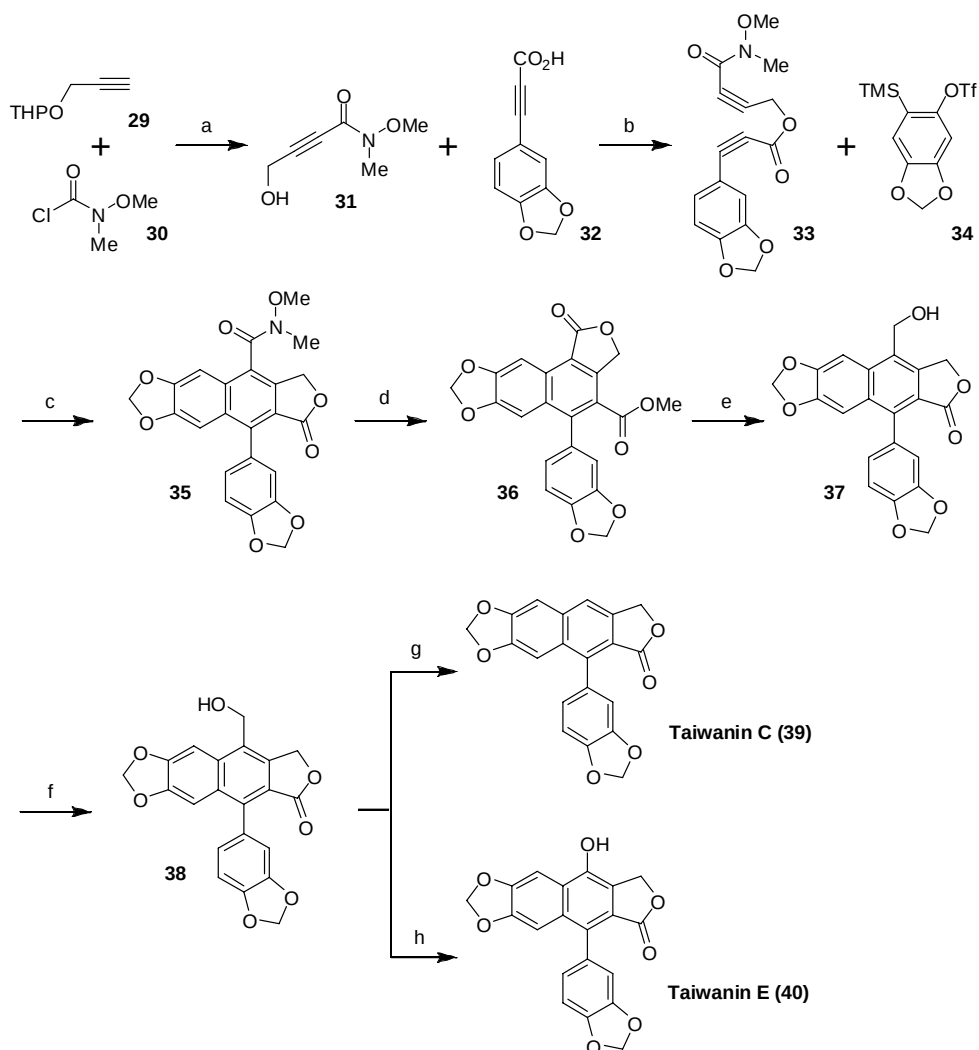
Reagents and conditions: (a) $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$, CuI , Et_3N , 70–85 °C, 14 h. (b) i. $n\text{-BuLi}$, Et_2O , –78 °C; ii. I_2 , Et_2O , –78 °C, 54%; ii. 1-ethynyl-2-(2-DMTS-ethynyl)biphenylene, $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$, CuI , Et_3N , 85 °C, 22 h; iii. $\text{Bu}_4\text{N}^+\text{F}^-$, THF, 23 °C, 40 min, 58%. (c) $\text{CpCo}(\text{CO})_2$, *m*-xylene, $h\nu$, Δ , 30 min, 12%. (d) i. $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$, CuI , Et_3N , 75 °C, 22 h; ii. $\text{Bu}_4\text{N}^+\text{F}^-$, THF, 23 °C, 40 min, 71%. (e) $\text{CpCo}(\text{CO})_2$, *m*-xylene, $h\nu$, Δ , 30 min, 8%.

In a similar fashion, synthesis of angular [7] phenylene was started with a double Sonogashira reaction of **25** with **26** to afford symmetric hexayne **27** after global silyl

deprotection. The final cobalt-catalyzed intramolecular cyclotrimerization of **27** afforded **28** as orange solid. The X-ray crystal structures of **24** and **28** exhibited bond parameters that are in excellent agreement with the calculations. The consideration and the fact that **24** and **28** constitute only the first two members of the helical series provided the impetus for tackling the synthetic challenge of assembling higher heliphenes systems.^{10d}

Soto and Mori et al. developed a novel method for the construction of aryl naphthalene skeletons through a Pd⁰–catalyzed [2+2+2] cocyclization of diynes and arynes. The cocyclization was the key step in the total synthesis of taiwanins C (**39**) and E (**40**) (Scheme 8).^{10e}

Scheme 8. Total synthesis of taiwanins C and E

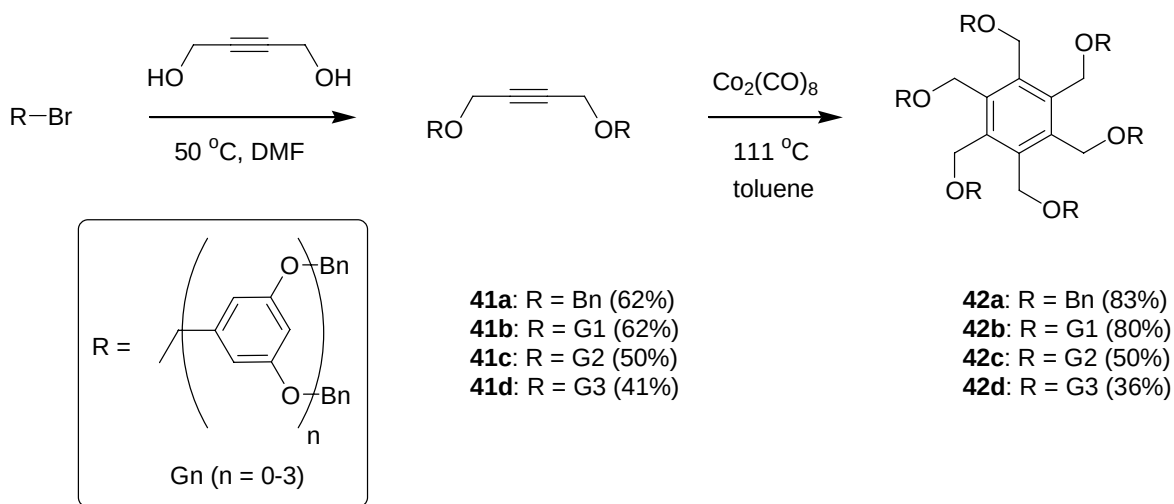


Reagents and conditions: (a) i. $\text{PdCl}_2(\text{CH}_3\text{CN})_2$, PPh_3 , CuI , Et_3N , $90\text{ }^\circ\text{C}$, 60%; ii. PTSA, MeOH , r.t., 86%. (b) DCC, DMAP, CH_2Cl_2 , r.t., 86%. (c) $\text{Pd}_2(\text{dba})_3$, $\text{P}(o\text{-tol})_3$, CsF , CH_3CN , r.t., 4 h, 61%. (d) NaH , MeOH , CH_2Cl_2 , r.t., 78%. (e) i. DIBAL-H, CH_2Cl_2 , $-78\text{ }^\circ\text{C}$, 63%; ii. NaBH_4 , MeOH , $0\text{ }^\circ\text{C}$ – r.t., 95%. (f) PCC, M.S. $4\text{ \AA}$, CH_2Cl_2 , $0\text{ }^\circ\text{C}$, 89%. (g) $\text{RhCl}(\text{PPh}_3)_3$, $\text{C}_2\text{H}_5\text{CN}$, reflux, 64%. (h) i. *m*-CPBA, CH_2Cl_2 , r.t.; ii. K_2CO_3 , MeOH , r.t., 88%.

Dendritic Ensembles

There are several reports on convergent synthesis of dendrimers in which the dendrimer core is generated from a dendritic precursor by an alkyne cyclotrimerization reaction.¹¹ Frechet and co-workers reported synthesis of novel benzene-core dendrimers via alkyne cyclotrimerization.^{11a} The substituted alkynes **41a–d** were synthesized by the Williamson ether coupling of 2-butyne-1,4-diol with appropriate polybenzyl ether-type dendritic bromides. The trimerization reaction of **41a–d** was carried out in refluxing toluene using dicobalt octacarbonyl as the catalyst to afford novel structures **42a – d** (Scheme 9).

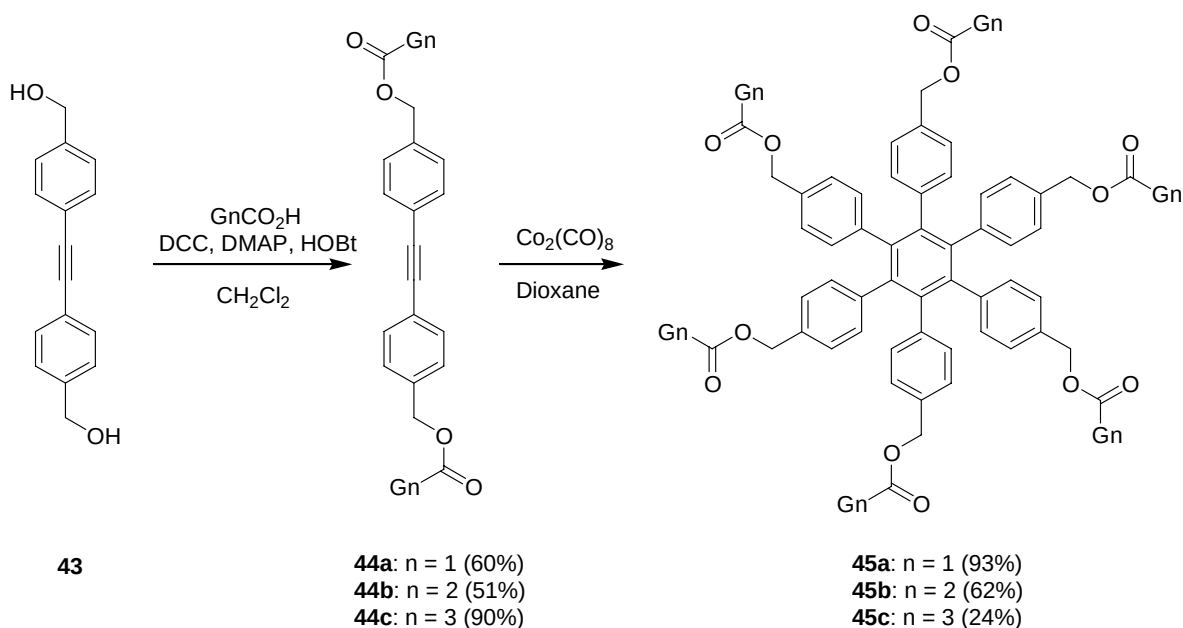
Scheme 9. Synthesis of dendritic assemblies



The synthesis of dendritic scaffolds substituted with multiple C_{60} moieties is quite challenging. Nierengarten and co-workers recently reported an efficient synthesis of fullerodendrimers^{11b} **45a–c** with hexaphenylbenzene cores and peripheral C_{60} units were prepared by metal-catalyzed cyclotrimerization of the corresponding dendritic *bis*-

(aryl)alkyne. The alkyne precursors **44a–c** were obtained by reaction of diol **43** with fullerodendron $G1CO_2H$, $G2CO_2H$, and $G3CO_2H$, respectively^{11e} under esterification condition. Treatment of **44a** with catalytic amount of $Co_2(CO)_8$ in dioxane at r.t. for 24 h afforded **45a** in 93% yield (Scheme 10). The same conditions were used for the preparation of the highest-generation dendrimers. The reaction of the second-generation derivative **44b** was finished after one day and compound **45b** was isolated in 62% yield. In contrast, the reaction of the highest-generation precursor **44c** was very slow, most probably as a result of steric effects and the product **45c** was isolated in 24% yield after 5 days.

Scheme 10. *Synthesis of fullerodendrimers*

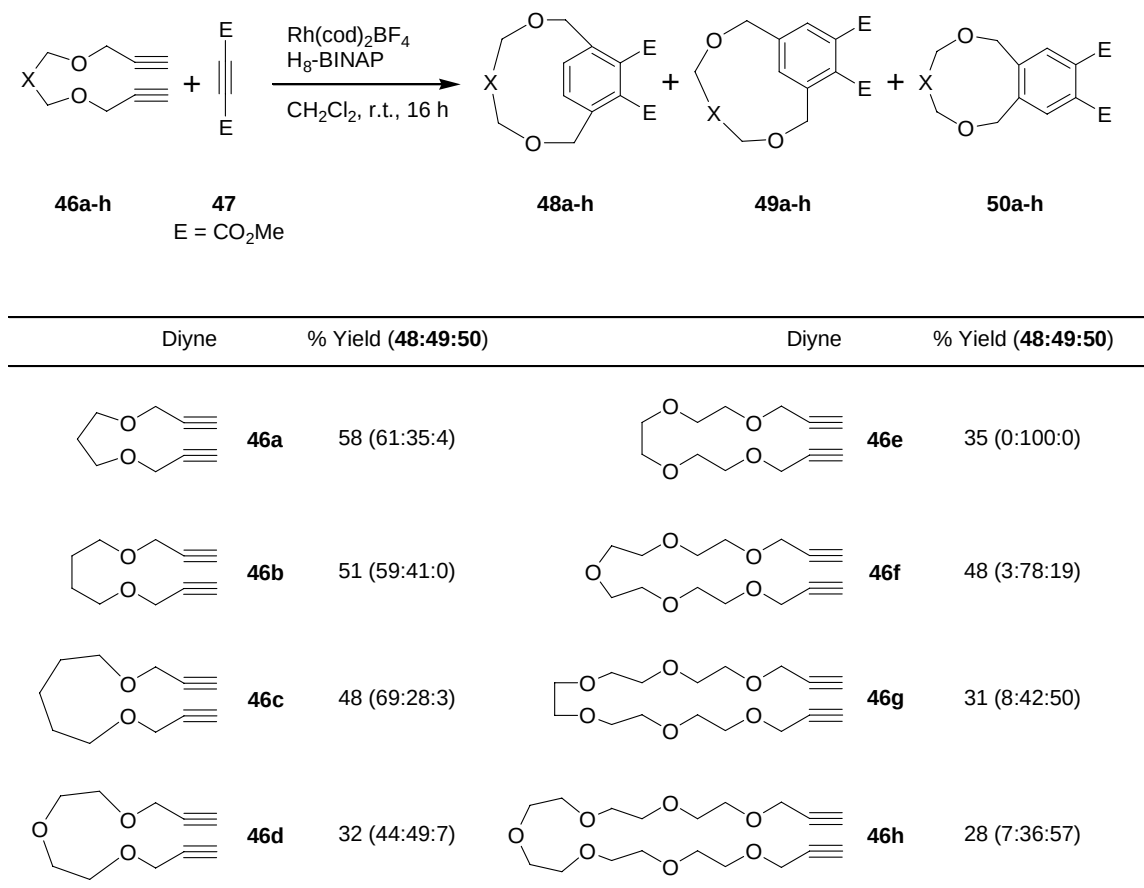


Cyclophanes

Cyclophanes are hydrocarbons consisting of an aromatic unit (typically a benzene ring) and an aliphatic chain that forms a bridge between two non-adjacent positions of the aromatic ring. More complex derivatives with multiple aromatic units and bridges forming cage-like structures are also known. Cyclophanes are well studied in organic chemistry because they adopt unusual conformations due to build-in strain. The

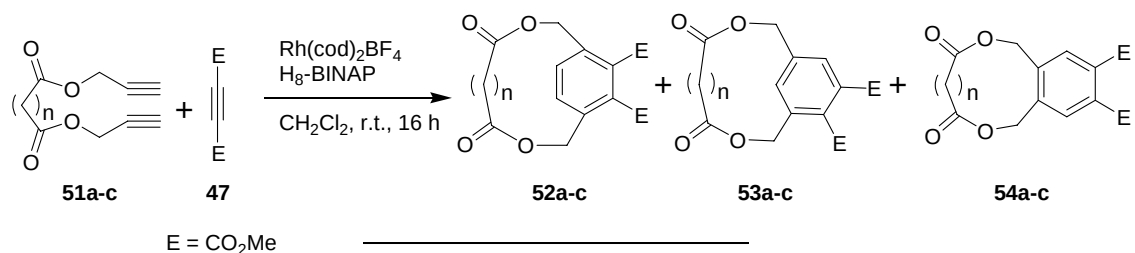
cyclophanes and their oxa, aza analogues are excellent targets through alkyne cyclotrimerization.¹² Tanaka et al. reported [7]–[21]polyether cyclophanes through a cross-cyclotrimerizations of ether-linked α,ω -diynes and dimethyl acetylene dicarboxylate in the presence of a catalytic amount of cationic rhodium(I)/H₈-BINAP complex (Scheme 11).^{12a}

Scheme 11. *Synthesis of [7]–[21] polyether cyclophanes*



[7]–[9]ester cyclophanes were also synthesized from the corresponding α,ω -diynes and dimethyl acetylene dicarboxylate (Scheme 12). The ratio of *para*-, *meta*-, and *ortho*-cyclophanes depends on the length and the structure of the α,ω -diyne tether chain, whilst the effect of concentration on the yield of polyether cyclophanes appears to be small.

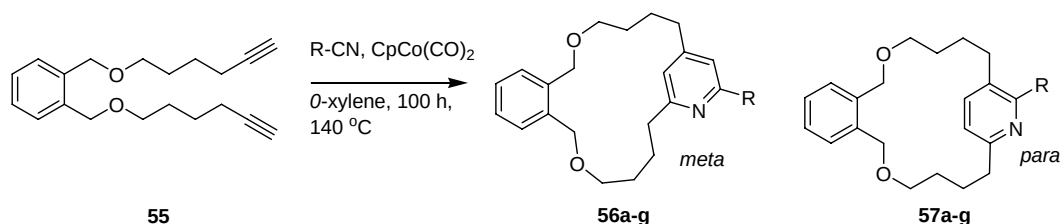
Scheme 12. *Synthesis of [7]–[9]ester cyclophanes*



Diyne	% yield (52:53:54)
51a (n = 1)	< 10 (100:0:0)
51b (n = 2)	53 (68:32:2)
51c (n = 3)	53 (39:55:6)

Maryanoff and co-workers synthesized pyridinophanes from α,ω -diyne **55** and various nitriles.^{12b} Nitriles conjugated to an arene, heteroarene, or alkene group underwent macrocyclization with diyne **55** with reasonable efficiency (Scheme 13).

Scheme 13. *Pyridinophanes from α,ω -diyne 55 and various nitriles*



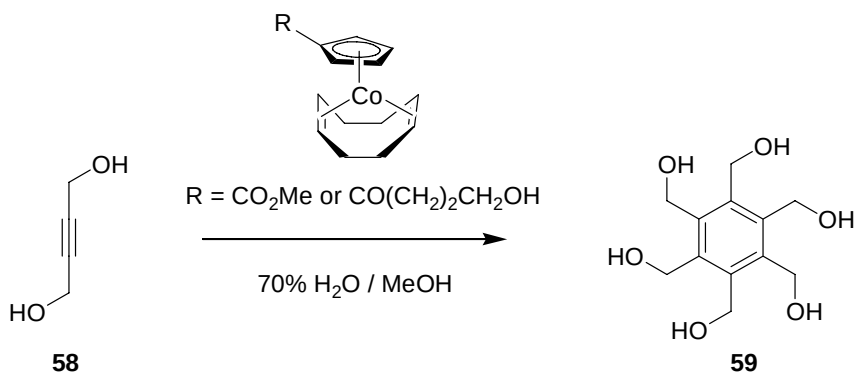
Entry	Nitrile	% yield (56:57)	Entry	Nitrile	% yield (56:57)
1		57 (1:1)	5		30 (2:1)
2		46 (2:1)	6		43 (1:2)
3		38 (1:3)	7		11 (>50:1)
4		33 (1:1)	8		Trace

Nitriles with phenyl (entries 1–2), furyl (entry 3), and pyridyl (entry 4) substituents gave moderate to good yields of pyridinophanes. The electronic nature of substituents on the phenyl ring showed a minor influence on yield, although an electronwithdrawing substituent favored the formation of the *meta* isomer (entry 2 vs 1). Nitriles conjugated to the cyclohexenyl (entry 5) and styrene units (entry 6) furnished pyridinophanes in moderate yields with the former preferentially generating the *meta* isomer. 1-Cyanoadamantane gave a yield of 11% (entry 7) with the macrocyclic product being essentially just the *meta* isomer.

Cyclotrimerization in aq. medium

For environmental reasons water is a preferred reaction medium. In addition, hydrophobic effects in organic reactions can provide substantial rate enhancements, chemoselectivity, and stereoselectivity. Another motivation for performing organometallic catalysis in aq. solution could entail merging biochemical and organometallic techniques to reveal new horizons in combinatorial chemistry. There are several reports on cyclotrimerization reaction on aq. medium.¹³ Sigman and co-workers describe a new cobalt catalyst that performs cyclotrimerization under mild conditions in water to prepare benzenes with unprotected functional groups (Scheme14).^{13a}

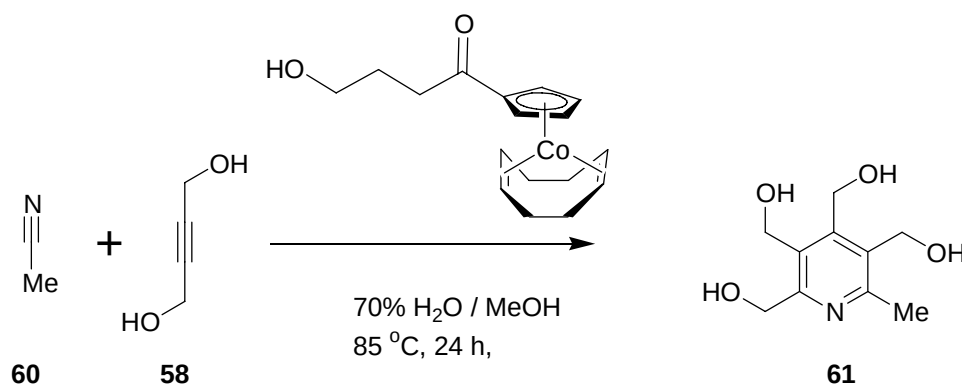
Scheme 14. Cobalt-catalyzed cyclotrimerization in aq. medium



They developed a $\text{CpCo-}\eta^4$ -cyclooctadiene complex where the Cp had attached a substituent that aided its water solubility and a cyclooctadiene that would control access to the cobalt coordination sphere.

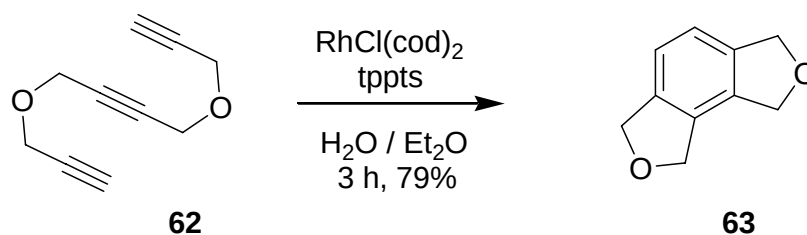
Eaton and co-workers reported alkyne-nitrile cyclotrimerization to form pyridines in aq. solution.^{13b} The Co-catalyst was found to be highly chemospecific and highly functionalized pyridines were synthesized (Scheme 15). Several different functional groups are well incorporated in this transformation, including unprotected alcohols, ketones, and amines.

Scheme 15. *Pyridines through cyclotrimerization in aq. medium*



A rhodium-catalyzed cyclotrimerization of triynes in a water-organic biphasic system has been explored by Oshima et al.^{13c} The biphasic system offers diluted reaction conditions for macrocyclization reactions. Selective cross-annulation between hydrophobic diynes and hydrophilic alkynes has also been achieved (Scheme 16).

Scheme 16. *Rhodium-catalyzed cyclotrimerization in water-organic biphasic system*

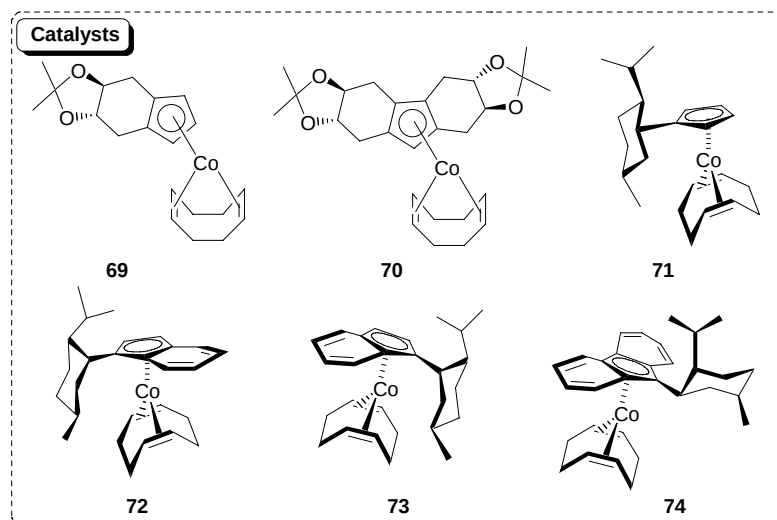
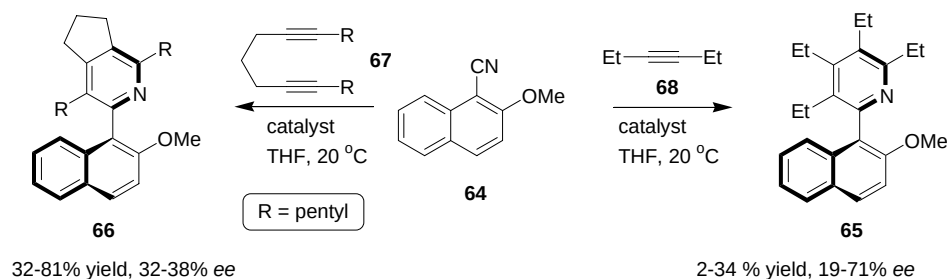


A water-soluble rhodium catalyst was prepared in situ from $\text{RhCl}(\text{cod})_2$ and the trisodium salt of tris(*m*-sulfonatophenyl)- phosphine (tppts) in water at 75 °C. The ability of this catalyst to promote cyclotrimerization in the biphasic system was examined with 4,9-dioxadodeca-1,6,11-triyne **62** and the tricyclic compound **63** was obtained in good yield.

Asymmetric version of cyclotrimerization

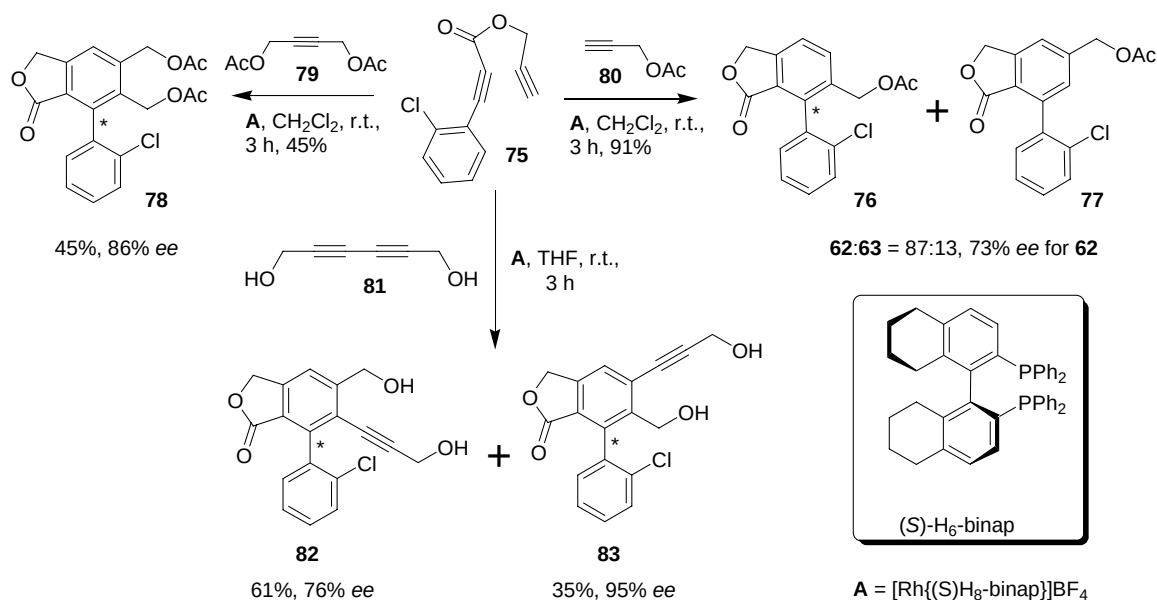
Although achiral version of cyclotrimerization reactions are well known, there are very few reports on catalytic asymmetric [2+2+2] homocyclizations yielding benzene derivatives with simultaneous introduction of an element of chirality.¹⁴ Heller and co-workers reported cobalt(I)-catalyzed asymmetric [2+2+2] cycloaddition of alkynes and nitriles to synthesize enantiomerically enriched atropoisomers of 2-arylpyridines (Scheme 17).^{14a}

Scheme 17. *Synthesis of atropoisomers of 2-arylpyridines*



Tanaka and co-workers reported enantioselective synthesis of axially chiral phthalides through cationic $[\text{Rh}(\text{H}_8\text{-binap})]$ -catalyzed cross alkyne cyclotrimerization of unsymmetrical 1,6-diynes and both terminal and internal alkynes (Scheme 18).^{14b} This method provides an easy access to axially chiral phthalides that bear one or two oxymethylene functionalities.

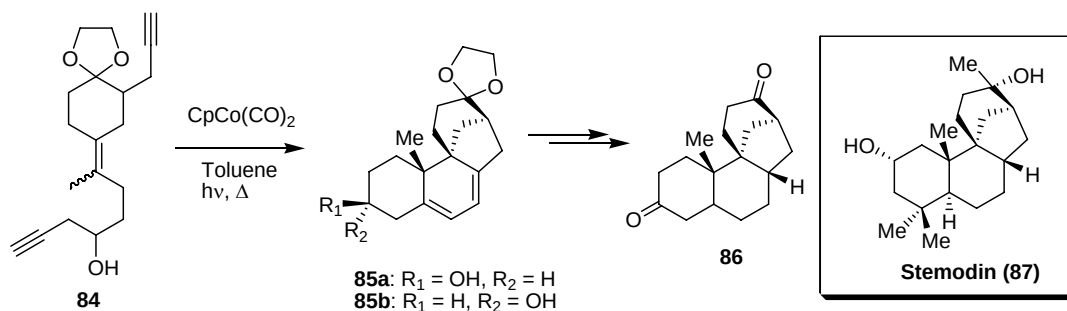
Scheme 18. *Synthesis of axially chiral phthalides*



Bicyclic systems by cyclotrimerization

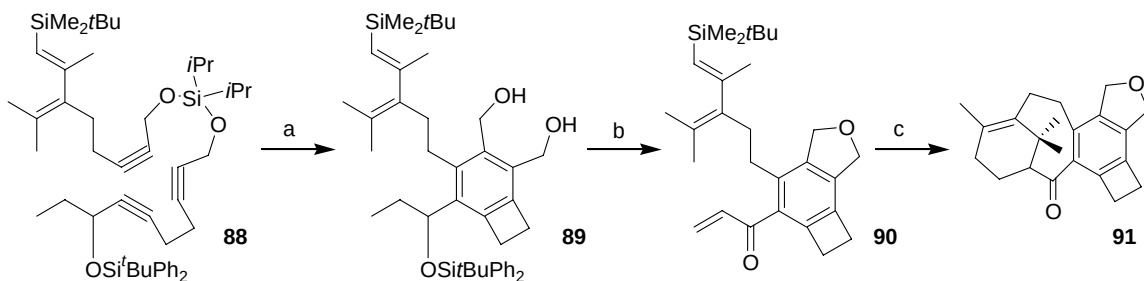
The scope of cyclotrimerization reaction in the synthesis of bridged bicyclic systems has seen limited potential. Vollhardt and co-workers showed the feasibility of the intramolecular $[2+2+2]$ cycloaddition reaction of enediynes for the synthesis of highly strained $[3.2.1]$ bicyclooctanes.¹⁵ The stereoselective assembly of **85** constitutes a novel application of the cobalt-catalyzed $[2+2+2]$ cycloaddition reaction furnishing a strained and highly sterically encumbered spirocyclic diene incorporating the stemodin framework that can be further elaborated into the natural product (Scheme 19)

Scheme 19. Synthesis of Stemodin framework



Malacria and co-workers explored the possibility of an intramolecular [2+2+2] cyclization approach for a tandem construction of B, C, D and E rings of polycyclic taxane system.¹⁶

Scheme 20. Synthesis of taxoid core



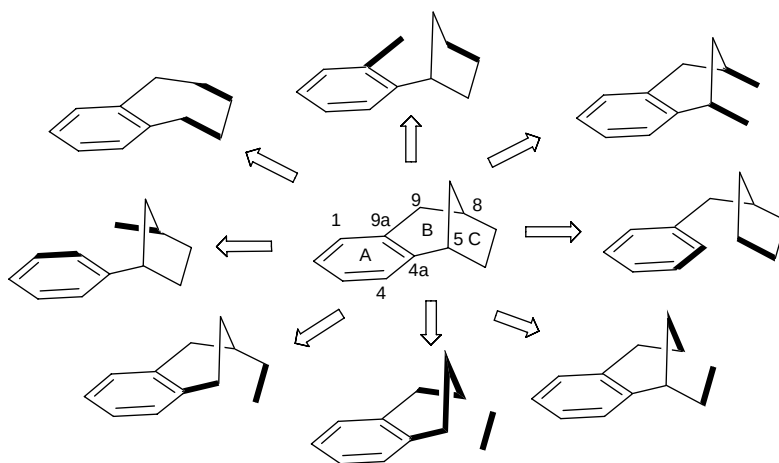
Reagents and conditions: (a) i. 5 mol% CpCo(CO)₂, xylenes, Δ, hv; ii. *n*Bu₄NF, THF, −78 °C to 0 °C; (b) i. *n*-BuLi, THF, −78 °C, TsCl, −78 °C to r.t.; ii. *n*Bu₄NF (1.2 equiv.), THF, reflux; iii. IBX, DMSO, r.t.; iv. NaHMDS, THF, −40 °C, PhSeCl, −40 °C to r.t.; v. NaIO₄, NaHCO₃, MeOH/H₂O; (c) BF₃·Et₂O (5 equiv.), CHCl₃, −50 °C.

Exposure of silaketal **88** to 5 mol% of CpCo(CO)₂ in boiling xylenes under irradiation led to the corresponding benzocyclobutene, which after opening of the silaketal afforded the diol **89** (Scheme 20). Monotosylation of **89** followed by selenation/oxidation/elimination sequence accomplished the tricyclic compound **90**. The latter was treated with 5 equiv. of BF₃·OEt₂ in chloroform to afford the desired cycloadduct, the taxoid core **91**.

Bridged polycyclic compounds have fascinated the organic chemists from the early part of the 20th century because of the occurrence of these units in many of the biologically active natural products. Bicyclic compounds such as camphor, norbornene, and tropinone are considered to be the simplest structures of this category. Tropinone belongs to this classical [3.2.1]bicyclic family and is inspirational in the early part of the last century for total synthesis where the first reported synthesis does involve more than 20 linear steps and later was prepared in a one step by the disclosure of a novel multicomponent reaction by Sir Robinson.

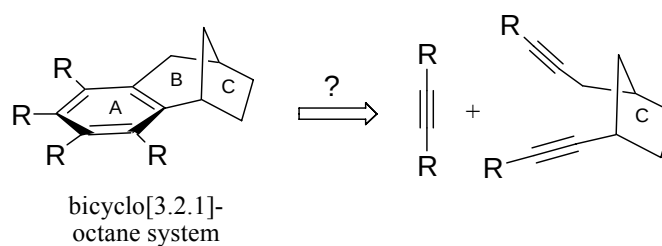
Benzene fused [3.2.1]-bicyclic system is a unique skeleton present in various classes of natural products and drug molecules with an appropriate ring carbon exchanged by either oxygen or nitrogen. Currently, the most general methods to access the aromatic fused *n*-oxa/aza[3.2.1]bicyclic systems are by [3 + 4] cycloadditions or annulations. A general retrosynthetic strategy is exemplified in the following figure which indicates playing around the benzene ring. It is clear from this that, there is not a single report so far, to construct aromatic ring with concomitant formation of the tricyclic frame work.

Figure 1. *Routine bond disconnection approaches for making a simple benzene fused bicyclo[3.2.1]octane skeleton*



Here in we propose an entirely novel strategy, which is identified by its flexibility for library synthesis. The key ingredient of our strategy is the construction of this highly strained ring system by [2+2+2] cross trimerization with simultaneous aromatic ring annulation (Fig. 2).

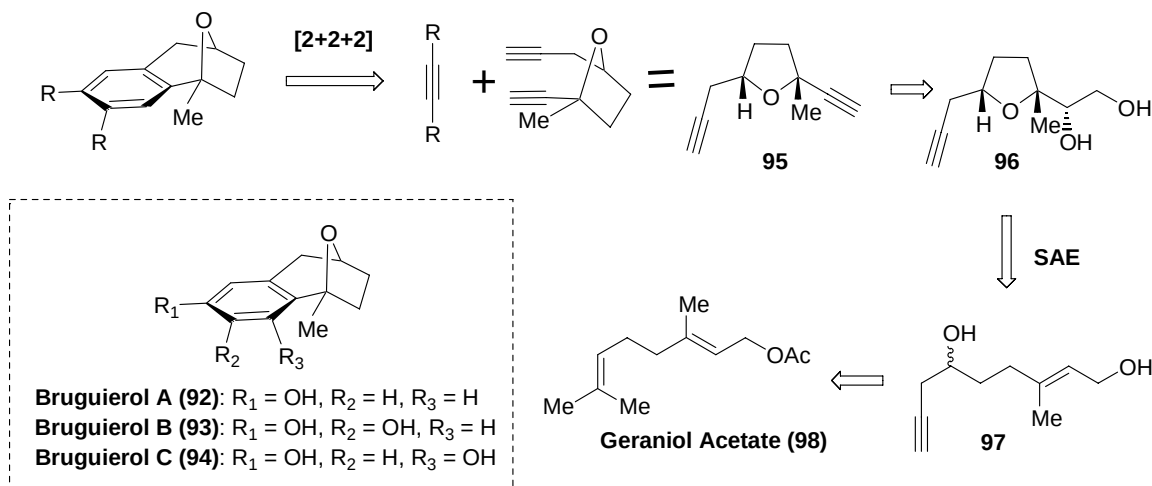
Figure 2. *Novel approach proposed for benzene fused [3.2.1]bicyclooctane skeleton*



Present Work

Alkyne cyclotrimerization in the synthesis of bicyclic systems has seen limited potential. To the best of our knowledge there are no reports concerning the syntheses of hetero bridgehead aromatic fused [2.2.1] and [3.2.1] bicyclic systems by co-trimerization approach. Our initial foray into this area was stimulated by the recently isolated natural products bruguierols A–C (**92–94**) which portrayed the benzannulated 8-oxabicyclo[3.2.1]octane structural skeleton.¹⁷ As outlined in the retrosynthesis (Scheme 1) benzannulated 8-oxa bicyclo[3.2.1]octane systems can be obtained by a cross alkyne cyclotrimerization of diyne (**95**) and with different alkynes. Since the absolute configuration of bruguierols were not known, we thought of proceeding with the chiral diyne **95**. The synthesis of the dialkyne **95** was planned from diol **96**, which in turn can be obtained by kinetic resolution of 6-substituted hex-2-en 1,6-diol **97** by means of Sharpless asymmetric epoxidation. Geraniol acetate (**98**) was chosen as starting material for **97**.

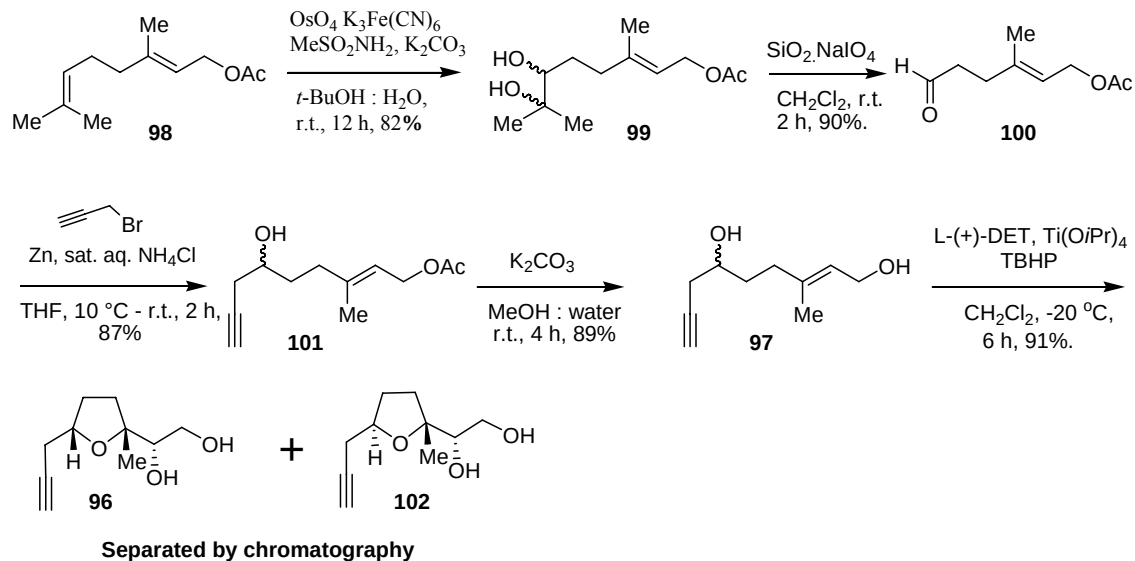
Scheme 1. Synthetic plan for benzannulated 8-oxa bicyclo[3.2.1]octane system



The synthetic sequences started with commercially available geraniol acetate **98**. Regioselective dihydroxylation under biphasic conditions gave racemic diol **99** in 70%

yield.¹⁸ Metaperiodate mediated cleavage of diol **99** afforded the aldehyde **100** in 91% yield. The ¹H NMR spectrum revealed the aldehyde proton at δ 9.78 as a triplet. The aldehydic carbon resonated at δ 201.4 in the ¹³C NMR spectrum. Propargylation of aldehyde **100** under zinc-mediated Barbier reaction¹⁹ conditions using THF-aq. NH₄Cl gave racemic alcohol **101** in 86% yield. The alkyne proton resonated as a triplet at δ 2.04 in ¹H NMR spectrum. The propargylic CH₂ protons resonated separately at δ 2.32 and 2.44 as a *ddds*. The ¹³C NMR spectrum showed the alkyne carbon signals at δ 70.5 & 80.6 and the propargyl CH₂ carbon resonated at δ 27.1 ppm. Rest of the analytical data are in full agreement with the assigned structure. Acetate hydrolysis of **101** using K₂CO₃ in methanol:water system gave racemic hexenol **97** in 89% yield. The following Sharpless asymmetric epoxidation²⁰ using Ti-complex of diethyl L-tartrate furnished the isomeric tetrahydrofurans **96** and **102** in 91% yield, which were separated by flash column chromatography (Scheme 2). In the ¹H NMR spectrums, the allylic proton of the starting allylic alcohol disappeared at δ 5.43. The *in situ* cyclization was further confirmed by non-availability of epoxide protons in the ¹H NMR spectrum. The quaternary methyl resonated at δ 1.15 and 1.18 respectively for **96** and **102**. Rest of the spectrum was in full agreement with the structures. IR and mass spectral analysis further confirmed the assigned structures of **96** and **102**.

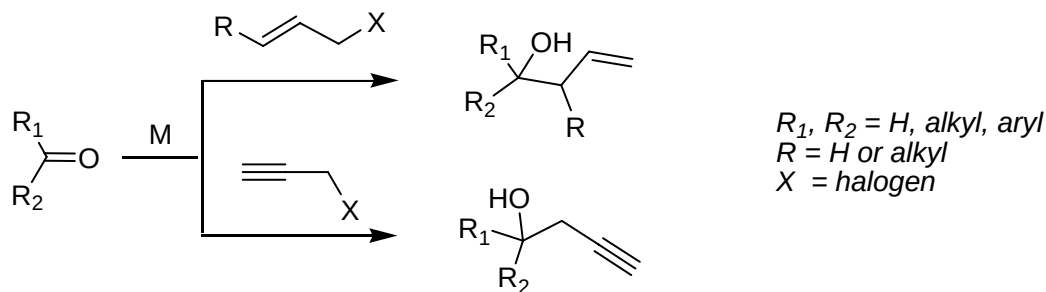
Scheme 2. Synthesis of tetrahydrofurans



Short account of Barbier reaction¹⁹

The reaction between an alkyl halide and a carbonyl group (aldehyde or a ketone) in the presence of metals like aluminium, zinc, indium, tin, samarium etc., or their salts is termed as Barbier reaction. The reaction product is a secondary or a tertiary alcohol. The reaction is similar to the Grignard reaction but the crucial difference is that the Barbier reaction is a one-pot synthesis whereas a Grignard reagent is prepared separately before addition of the carbonyl compound. Barbier reactions are nucleophilic addition reactions that take place with relatively inexpensive and water insensitive metals or metal compounds in contrast to Grignard reagents or organolithium reagents. For this reason it is possible in many cases to run the reaction in water, which makes this procedure part of green chemistry. The Barbier reaction is named after Victor Grignard's teacher Philippe Barbier.

Scheme 3

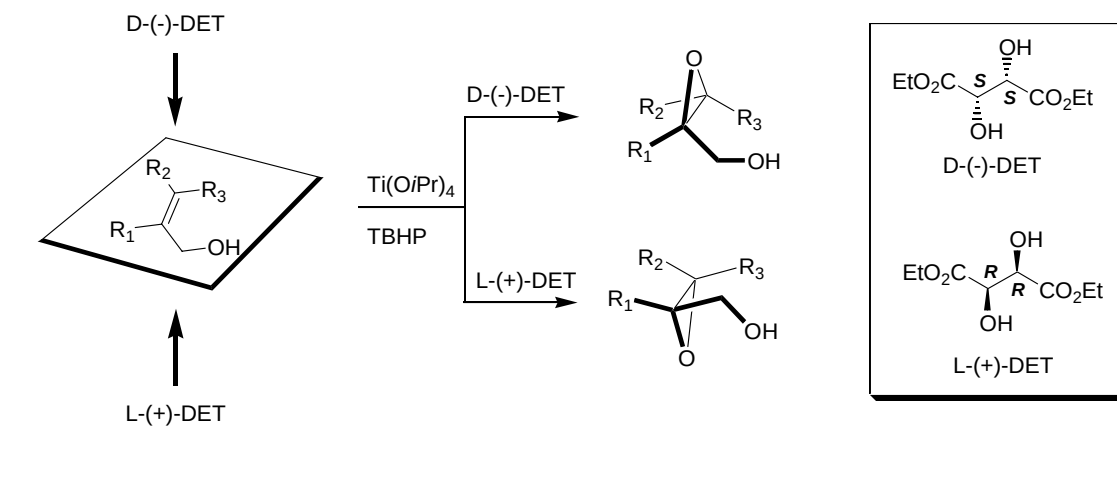


Sharpless Asymmetric Epoxidation (SAE)²⁰

Sharpless asymmetric epoxidation is one of the most popular reaction used for the enantioselective epoxidation of achiral allylic alcohols in organic synthesis. When a prochiral *Z*- or *E*-allylic alcohol is treated with dialkyl tartrate (generally Et or *i*-Pr), titanium tetrakisopropoxide and *t*-butylhydroperoxide, produces the corresponding chiral 2,3-epoxyalcohol with high ee. Easy availability of reagents involved, and high enantiomeric (or diastereomeric) excess obtained in the reaction made the Sharpless

asymmetric epoxidation to find wide spread application in the introduction of chirality in the complex target molecules. The easy and accurate prediction of stereochemical outcome irrespective of substitution on the allylic alcohol further asserted the reaction application.

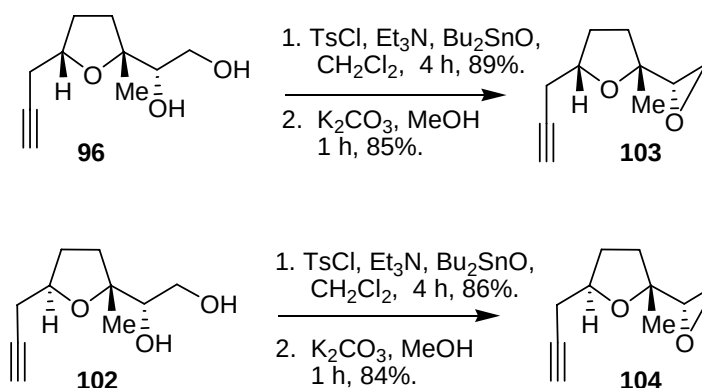
Scheme 4



Determination of relative and absolute stereochemistry:

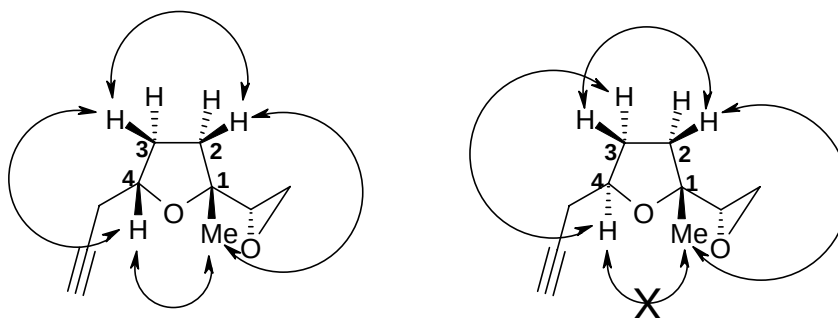
Once the *syn* and *anti*-tetrahydrofurans **96**, **102** in hand, we then proceeded to determine their relative and absolute stereochemistry. The diols **96** and **102** were independently subjected to regioselective tosylation²¹ by using tosyl chloride, triethylamine and catalytic dibutyl tin oxide in anhydrous DCM followed by treatment with K_2CO_3 in methanol to give the epoxides **103**, **104** in 85 and 84% yield respectively (Scheme 5). The formations of epoxides were supported by NMR analysis. The epoxide protons resonated at δ 2.64, 2.70, & 3.0 for **103** and 2.53, 2.69, & 2.98 for **104** as double doublets in the ^1H NMR spectrum. The ^{13}C NMR spectrum and other analytical data are in full agreement with the epoxides **103** and **104**. The NOESY-COSY experiments were performed on epoxides **103** and **104** and the correlations recorded are summarized in figure 1.

Scheme 5



It was found that in case of *syn*-tetrahydrofuran derived epoxide **103**, the C-1 β -quaternary methyl and C-4 β -proton are within the NOE proximity. Further C-2 β -proton is having spatial interactions with C-3 β -proton which in turn is having interaction with C-4 β -proton. The C-2 β -proton was also found to be in NOE proximity with C-1 methyl. In the case of *anti*-tetrahydrofuran derived epoxide **104**, it was found that there is negligible interaction between C-1 β -quaternary methyl and C-4 α -proton. The C-1 methyl is having spatial interaction with C-2 β -proton, which in turn is with in NOE proximity with C-3 β -proton. The C-4 α -proton was found to have NOE interaction with C-3 α -proton. All the NOE interactions observed are in full agreement with the assigned structure.

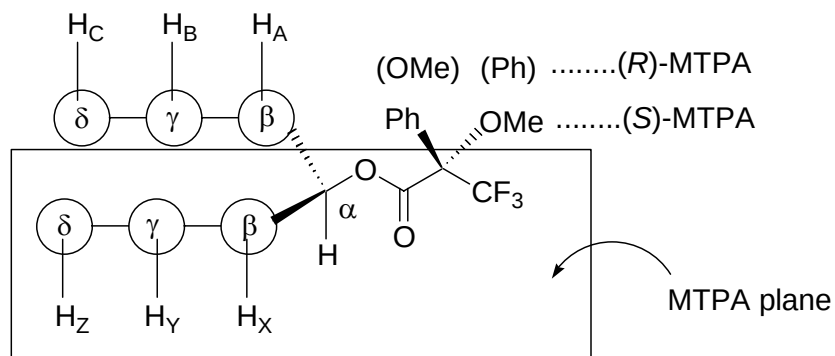
Figure 1. NOESY interactions observed



Modified Mosher's ester method for determining absolute stereochemistry²²

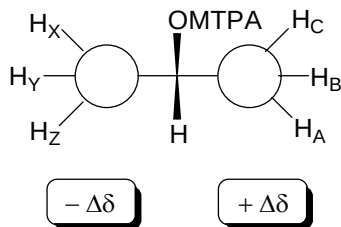
Determination of the absolute stereochemistry of organic compounds has become an important aspect in natural product synthesis. The limitations involved in physical methods such as exciton chirality method and X-ray crystallography forced synthetic chemists for a more reliable alternative. Although there are several chemical methods used to predict the absolute configuration of organic substances, Mosher's method using 2-methoxy-2-phenyl-2-(trifluoromethyl)acetic acid (MTPA) esters has been most frequently used. The modified Mosher's ester method (^1H) is one of the simple and efficient ways to determine the absolute stereochemistry of the secondary alcohols and amine stereo centers in organic molecules. Mosher proposed that, in solution, the carbinyl proton, ester carbonyl and trifluoromethyl group of the MTPA moiety lie in the same plane (Figure 3)

Figure 2. MTPA plane of a MTPA ester



The plane and the conformation of MTPA group was called as the MTPA plane and ideal conformation respectively. In the MTPA plane, H_A, H_B, H_C...and H_X, H_Y, H_Z...are on the right and left sides of the plane respectively. Due to the diamagnetic effect of the benzene ring, the H_A, H_B, H_C.... NMR signals of (R)-MTPA ester should appear upfield to those of the (S)-MTPA ester. The reverse should hold true for H_X, H_Y, H_Z.... Hence, the difference $\Delta\delta = (\delta_S - \delta_R) \times 1000$ should be positive for protons on the right side of the MTPA plane and the difference should be negative for those protons which were left side of the MTPA plane.

Figure 3. Model for determination of absolute stereochemistry

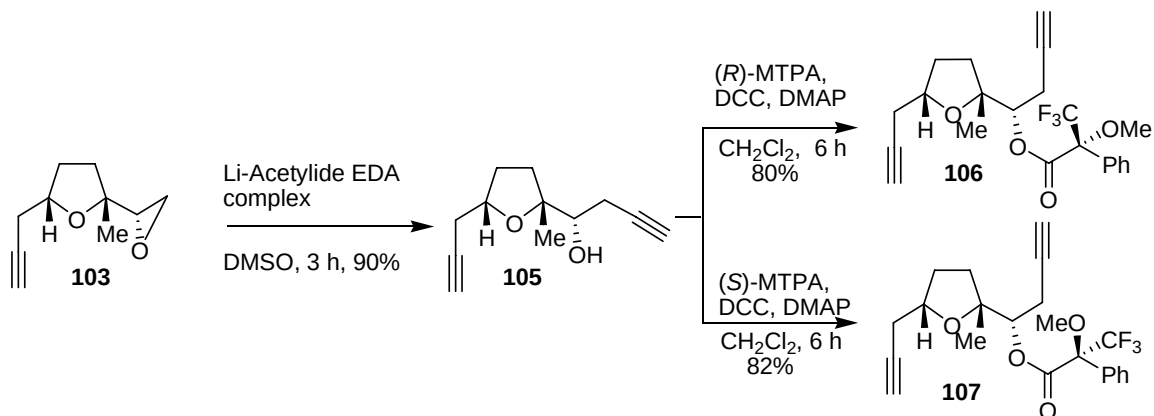


The Mosher's method can be summarized as follows:

- i. Assign as many proton signals as possible with respect to each of the (*R*) and (*S*) – MTPA esters
- ii. Obtain $\Delta\delta = (\delta_S - \delta_R) \times 1000$ values for all protons
- iii. Arrange the protons with positive $\Delta\delta$ values right side and those with negative $\Delta\delta$ values on the left side of the model.
- iv. Once the molecule satisfies all the conditions, the stereochemistry of the model is the absolute stereochemistry of the compound in question.

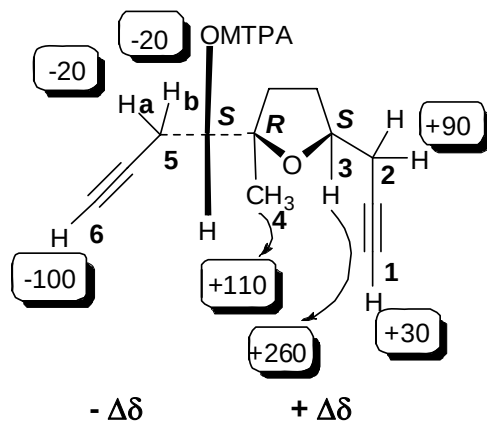
In order to determine the absolute stereochemistry and *ee*, epoxide **103** was treated with lithium acetylide.EDA complex in anhydrous DMSO to afford the alkynol **105** in 90% yield. The alcohol functionality in **105** was independently coupled with *R* and *S* Mosher acids using DCC, catalytic DMAP in anhydrous DCM to afford the respective Mosher esters **106** and **107** in 80 and 82% yields. (Scheme 6). ^1H NMR spectrum was recorded for the esters **106** and **107** and all possible protons were assigned. The difference $\Delta\delta = (\delta_S - \delta_R) \times 1000$ was calculated, and it was found that the molecule exactly fits into the Mosher model satisfying all the conditions (Figure 4).

Scheme 6. Mosher's ester synthesis

**Table 1:**

	1	2	3	4	5	6	
					a	b	
(S)-MTPA ester	1.99	2.40	4.01	1.25	2.48	2.77	1.91
(R)-MTPA ester	1.96	2.31	3.75	1.14	2.50	2.79	2.01
$\Delta\delta = (\delta S - \delta R) \times 1000$	+30	+90	+260	+110	-20	-20	-100

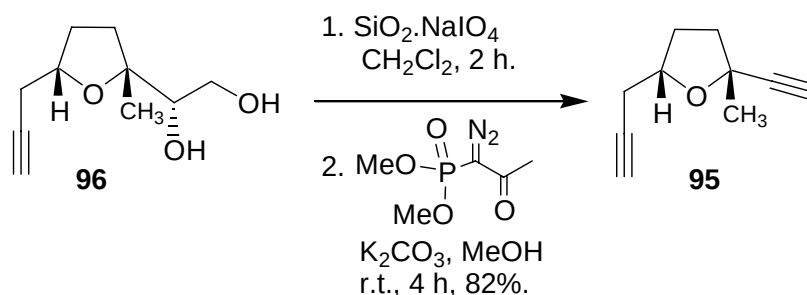
Figure 4



From the Mosher's model, the absolute stereochemistry of the hydroxyl center was found to be (*S*), from which we concluded that the absolute stereochemistry of adjacent quaternary center as (*R*) and the ring junction connected to propargyl group is (*S*).

After ascertaining the relative and absolute stereochemistries, we directed to synthesize the key diyne **95** starting from diol **96**. Metaperiodate mediated chopping of **96** in DCM afforded the intermediate aldehyde, which was immediately treated with Ohira–Bestmann reagent²³ using K₂CO₃ in methanol to accomplish dialkyne **95** in 82% yield.

Scheme 7. *Synthesis of dialkyne*



In the ¹H NMR spectrum of dialkyne (**95**), the two alkyne protons resonated at δ 1.95 and 2.39 as a triplet and singlet respectively. Further in ¹³C NMR spectrum, the four alkyne carbon signals were recorded at δ 69.68, 70.93, 80.85, and 87.76. Once the dialkyne structure was fully confirmed, we then proceeded to the much anticipated [2+2+2] cyclotrimerization reaction. With the fully elaborated diyne framework (**95**) in place, the task of cyclotrimerization with another alkyne was attempted using easily available 2-butyne-1,4-diol (**58**). The cyclotrimerization reaction was screened with different catalysts under different reaction conditions. Ni(cod)₂ / PPh₃ or Mo(CO)₆ in refluxing THF/ toluene solvent mixture gave the bicyclic diol (**108**) in 23 and 18% yields respectively. Whereas Wilkinson's catalyst²⁴ (3 mol%, toluene/ethanol at 80 °C for 3 h) was found to be superior and afforded the bicyclic diol in 85% yield. Cobalt-catalyzed reactions by using CoCl₂.6H₂O or CpCo(CO)₂ didn't produce any cyclized products (Scheme 8). The ¹H NMR spectrum of **108** showed the two aromatic protons as singlets at δ 7.02 and 7.10. Further the two C-benzylic protons appeared separately at δ 2.47 and 3.28 as doublet and doublet of doublet respectively. The quaternary methyl resonated at δ 1.69 as a singlet. In the ¹³C NMR spectrum, the benzene ring carbons appeared at δ

124.01, 130.51, 131.95, 137.08, 137.81, and 143.79. The structure was further confirmed by IR and mass spectroscopy.

Scheme 8. Optimization of cyclotrimerization condition

Entry	Catalyst	Solvent	Temp.	Time	yield
1.	Ni(cod) ₂ / PPh ₃	THF / Toluene	RT-reflux	10 h	23%
2.	Mo(CO) ₆	THF / Toluene	reflux	12 h	18%
3.	Rh(PPh ₃) ₃ Cl	Toluene-ethanol	80 °C	3 h	85%
4.	CoCl ₂ ·6H ₂ O / Zn	THF	reflux	-	-
5.	CpCo(CO) ₂	Xylene	140 °C	-	-

To further confirm the bicyclic structure, the diol **108** was treated with excess *p*-nitrobenzoyl chloride, triethylamine, and catalytic DMAP in anhydrous DCM to give the crystalline diester **109** (Scheme 9), whose single crystal X-ray was recorded which confirmed the structure beyond doubt (Figure 5).

Scheme 9. Derivatization of diol **108**

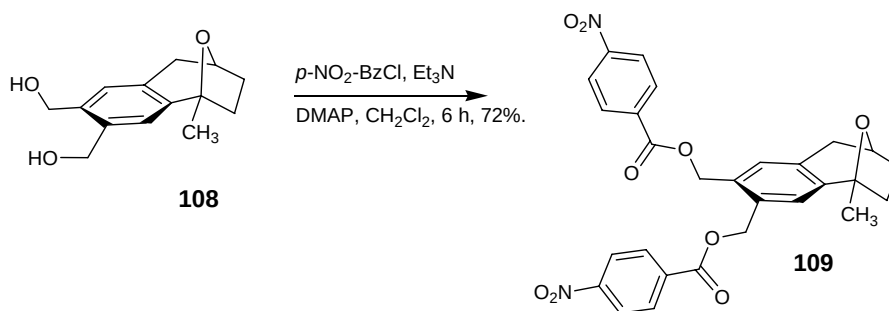
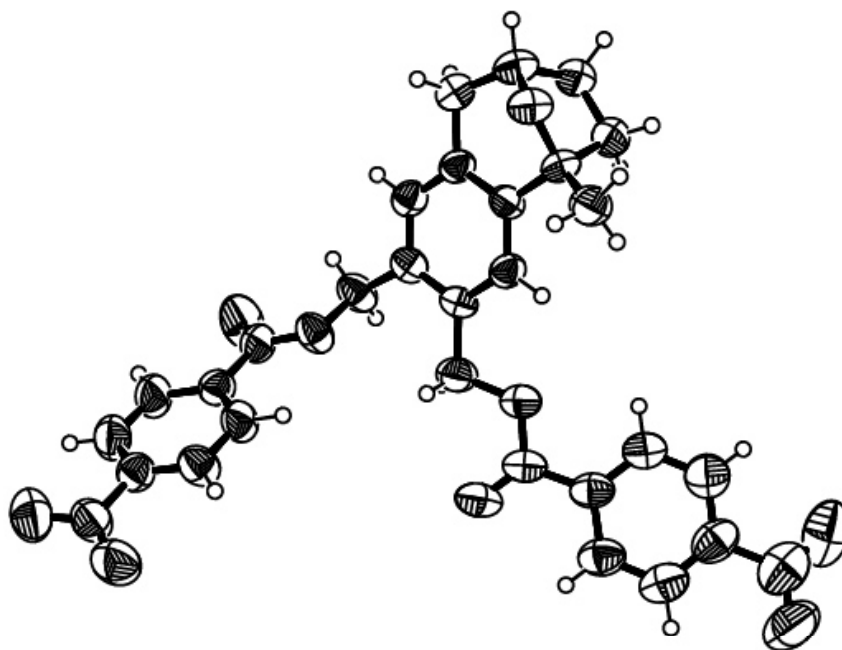
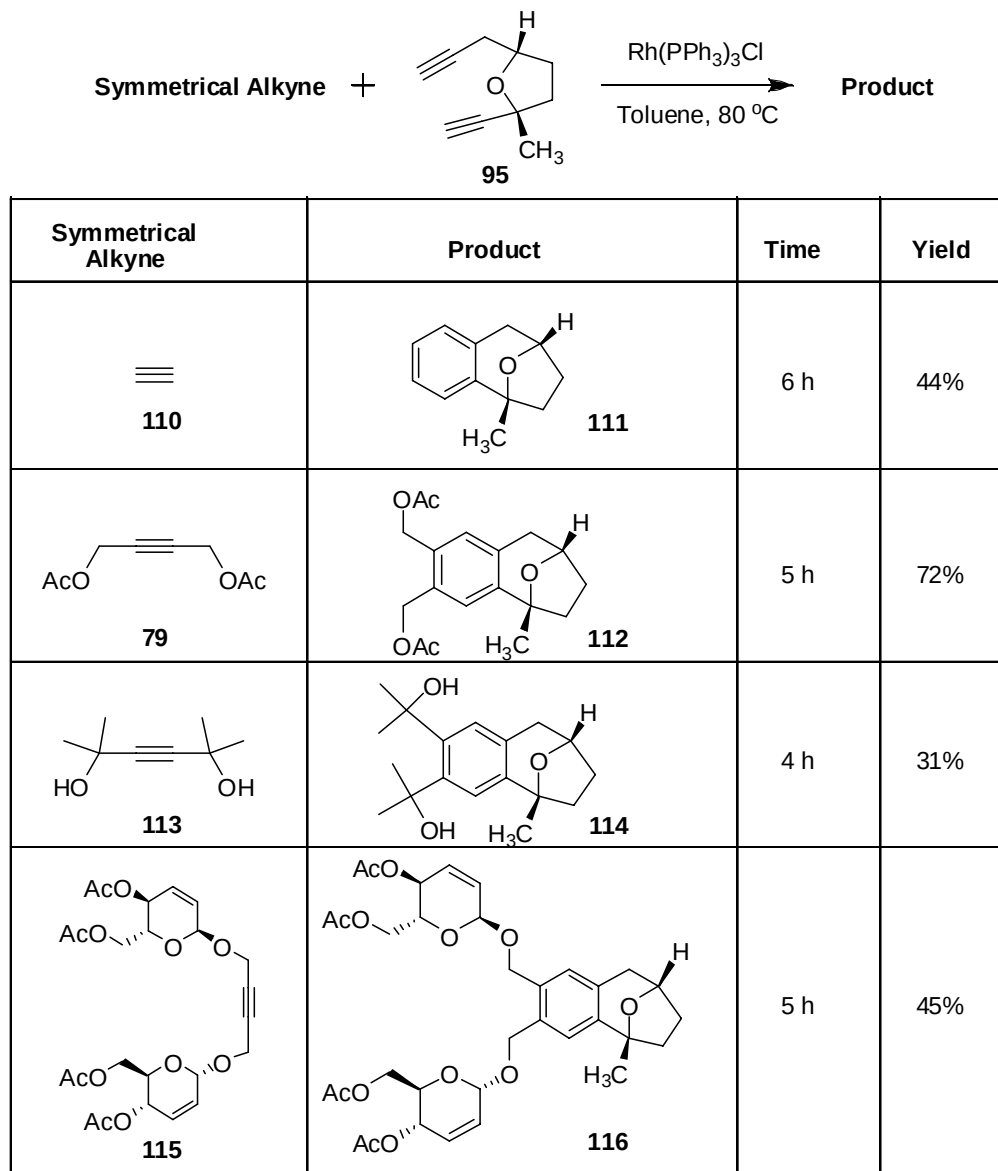


Figure 5. ORTEP structure of **109**



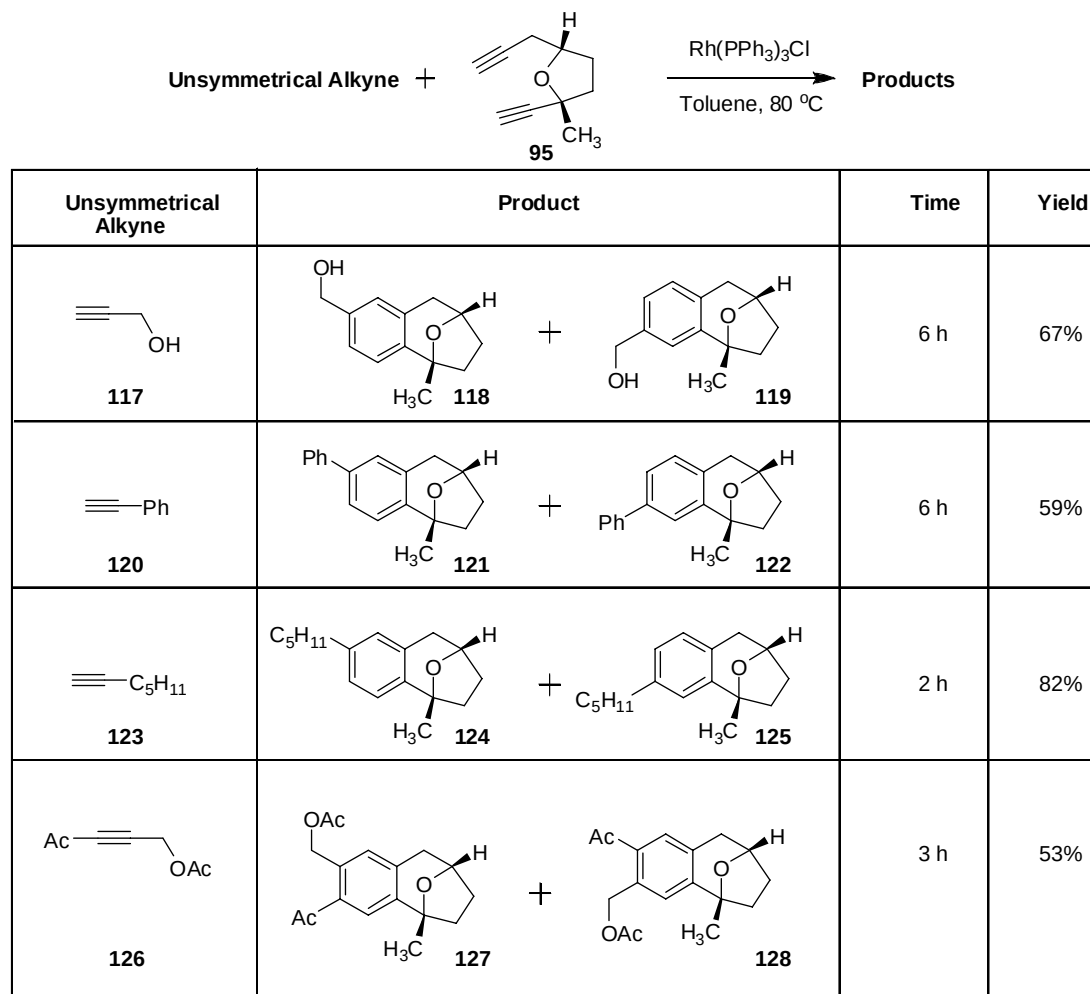
To illustrate the flexibility of our strategy, various alkynes were employed for trimerization reaction with diyne **95** using Wilkinson's catalyst and the results are summarized for symmetrical and unsymmetrical alkynes (Scheme 10 & Scheme 11). With simple acetylene (**110**), the reaction was carried out in a sealed tube to provide the 3,4-benzannulated-8-oxa-bicyclo[3.2.1]octane **111** in moderate yield (Scheme 10). With butyne diol diacetate (**79**) the cyclized product **112** was obtained in 72% yield. The cyclotrimerization with 2,5-dimethyl-3-hexyne-2,5-diol (**113**) and diglycal substrate **115**²⁵ furnished the cyclised products **114** and **116** in 31 and 45% yield respectively. Other symmetrical alkynes such as dimethylacetylene dicarboxylate, *bis*-trimethylsilyl acetylene and diphenylacetylene didn't produce any bicyclic products.

Scheme 10. *Cyclotrimerization of symmetrical alkynes*



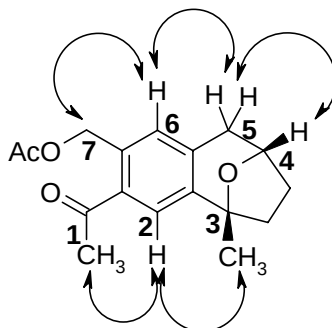
Unsymmetrical alkynes like propargyl alcohol (**117**), phenylacetylene (**120**), and hept-1-yne (**123**) gave 1:1 inseparable regiomer mixture of products in moderate to good yields. The ratio of regiomers were confirmed by ^1H and ^{13}C NMR analysis. The ^1H NMR spectrum of **118**, **119** mixture showed the quaternary methyl as two separate singlets at δ 1.73 and 1.75. Further, the ^{13}C NMR spectrum confirmed the equal ratio of regio-isomers.

Scheme 11. *Cyclotrimerization of unsymmetrical alkynes*



With 1-acetyloxy-2-pentyne-4-one (**126**), an inseparable 4:1 mixture of regiomer products were obtained and the constitution of the major isomer was deduced as indicated with the help of NOESY spectrum of **127/128** mixture. The observed NOESY interactions for **127** are summarized as follows. The acyl methyl 1 (refer fig. 6 for numbering) was found to be within NOE proximity with aromatic proton 2, which in turn is having interaction with the quaternary methyl 3. Similarly, the ring junction β -proton 4 is having spatial interaction with C-benzylic protons 5, which in turn is having interaction with aromatic proton 6. Also found that *O*-benzylic protons 7 are having interaction with 6. The above said interactions undoubtedly confirmed the assigned structure of **127**.

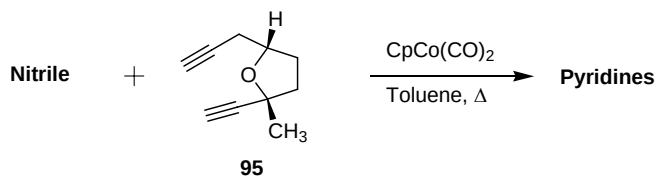
Figure 6. *NOESY Correlations of 127*

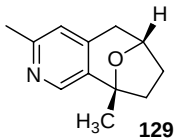
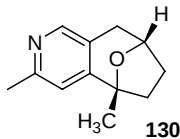
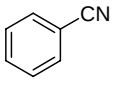
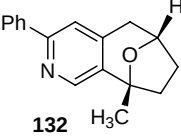
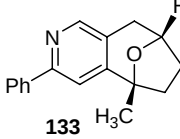
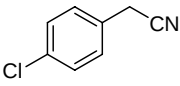
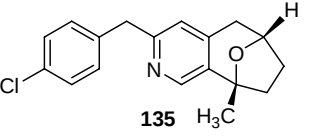
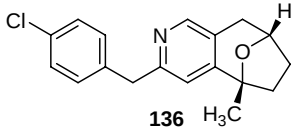
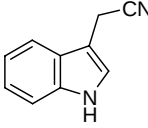
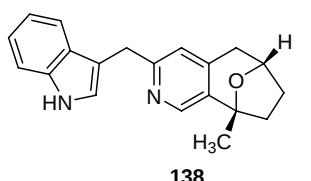
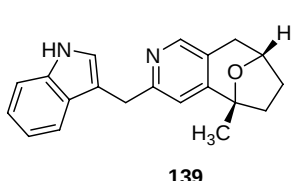


Synthesis of pyridine fused bicyclic systems by [2+2+2] cross alkyne cyclotrimerization: A novel entry to the class of pyridine fused 8-oxa bicyclo[3.2.1]octane system

After establishing the feasibility of [2+2+2] alkyne cyclotrimerization for the synthesis of highly strained benzannulated 8-oxa bicyclo[3.2.1]octane systems, we focused on the synthesis of pyridine fused bicyclic systems. The dialkyne **95** was expected to accomplish pyridines on treatment with different nitriles. Reports from the literature reveal that cobalt catalysts are efficient to bring about this type of cycloaddition for pyridine synthesis.²⁶ Different nitriles were treated with dialkyne **95** using 5 mol% of CpCo(CO)₂ in refluxing toluene temperature to give regiomer ic pyridines in equal ratio (Scheme 13). Initially the reaction conditions were standardized with acetonitrile (**60**) and it was found that CpCo(CO)₂ (5 mol%, 1.5 M solution in xylene) in refluxing toluene for 6 h gave the regiomer ic inseparable pyridines **129/130** in 64% yield. The products were extensively studied by spectral and analytical data. The ¹H NMR spectrum showed the aromatic protons α to the pyridine nitrogen at δ 8.18 and 8.26 as two separate singlets. The other aromatic proton resonated at δ 6.86 and 6.89 as two singlets. The methyl group α to the pyridine nitrogen resonated at δ 2.46 and 2.48 as two singlets. The two C-benzylic protons appeared at δ 3.25 and 2.47. The ring junction quaternary methyl resonated at δ 1.67 and 1.74 as two singlets. Further, the ¹³C NMR studies reveal the presence of equal ratio of regiomer ic pyridines. IR and mass spectral studies are in full agreement with the assigned structure.

Scheme 13. *CpCo(CO)₂* catalyzed [2+2+2] cyclotrimerization of dialkyne (**95**) with nitriles



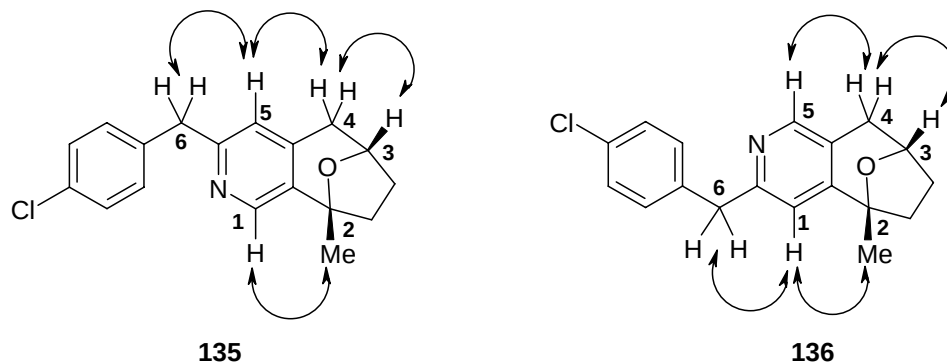
Nitrile	Product	Time	Yield
CH_3CN 60	 129 +  130	6 h	64%
 131	 132 +  133	8 h	44%
 134	 135 +  136	8 h	46%
 137	 138 +  139	5 h	39%

Later we subjected different nitriles like benzonitrile (**131**), 4-chloro benzyl cyanide (**134**) and indole-3-acetonitrile (**137**) for cycloaddition and the regiomer pyridines **132/133**, **135/136**, and **138/139** were obtained in 44, 46, and 39% yields respectively. All the products were characterized by spectral and analytical data. IR and mass spectral studies were in full agreement with the assigned structures. Further, the regiomer pyridines from **134** were separated by simple chromatography and are characterized independently.

The assigned structures of **135** and **136** were supported by their COSY-NOESY experiments. In the NOE spectrum of compound **135**, the observed interactions between

C1 proton (See figure 7 for numbering) and C2 methyl, C3 proton – C4 protons, C4 protons – C5 protons, and C5 proton – C6 protons established the assigned structure

Figure 7. Observed NOESY interactions for **135** and **136**



In the NOE spectrum of compound **136**, the observed interactions between C6 proton – C1 proton, C1 proton – C2 methyl, C3 proton – C4 protons, and C4 protons – C5 proton established the assigned structure.

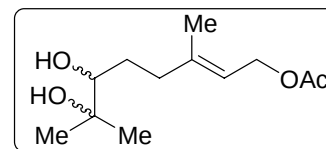
Conclusions

The chemistry described herein demonstrates the applicability of Wilkinson's catalyst catalyzed [2+2+2] cyclotrimerization for the construction of benzannulated-8-oxa-bicyclo[3.2.1]octane systems and its pyridine analogues using a $\text{CpCo}(\text{CO})_2$. As a result of minimal use of protecting groups and the late stage installation of key bicyclic system, the present approach leaves ample room for library synthesis. Considering the operational simplicity, this can be a potential methodology gaining entry into the synthesis of benzenefused bridged bicyclic systems, which are prevalent in various natural products and in some of the investigational drugs. The application of this novel methodology for the synthesis of bruguierol A has been discussed in section II.

Experimental

Experimental

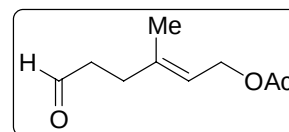
(E)-6,7-Dihydroxy-3,7-dimethyloct-2-enyl acetate (**99**):



A mixture of finely powdered potassium ferricyanide (50.39 g, 153 mmol), potassium carbonate (21.14 g, 153 mmol), methanesulfonamide (4.85 g, 51 mmol), osmium tetroxide (5.1 mL of 0.02 M soln. in toluene, 0.102 mmol), geranyl acetate **98** (10.0 g, 51 mmol) and 200 mL of 1:1 *t*-butanol-water was stirred at r.t. for 12 h. The reaction mixture was quenched by adding solid sodium bisulphite and the mixture was concentrated under reduced pressure. The residue was taken up in 400 mL of DCM, washed with 200 mL of 2M KOH, dried over Na₂SO₄, filtered and concentrated. The residue was purified by column chromatography (1:1 petroleum ether/ethyl acetate) to give diol **99** (9.62 g, 82%) as colorless oil

Mol. Formula	: C ₁₂ H ₂₂ O ₄
IR (CHCl₃) $\tilde{\nu}$	: 3441, 3019, 2977, 2932, 1726, 1368, 1239 cm ⁻¹ .
¹H NMR (CDCl ₃ , 200 MHz)	: δ 1.15 (s, 3H), 1.20 (s, 3H), 1.36–1.64 (m, 2H), 1.72 (s, 3H), 2.05 (s, 3H), 2.10–2.40 (m, 2H), 2.48 (br s, 2H), 3.32 (dd, <i>J</i> = 10.2, 2.2 Hz, 1H), 4.58 (d, <i>J</i> = 7.0 Hz, 2H), 5.38 (qt, <i>J</i> = 7.0, 1.3 Hz, 1H) ppm.
¹³C NMR (CDCl ₃ , 125 MHz)	: δ 16.1 (q), 20.6 (q), 22.9 (q), 26.0 (q), 29.2 (t), 36.2 (t), 61.0 (t), 72.7 (s), 77.5 (d), 118.2 (d), 141.7 (s), 170.8 (s) ppm.
ESI-MS (<i>m/z</i>)	: 253.41 [M+Na] ⁺ .
Elemental Analysis	Calcd.: C, 62.58; H, 9.63. Found: C, 62.39; H, 9.48.

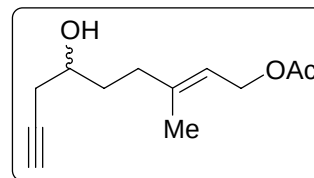
(E)-3-Methyl-6-oxohex-2-enyl acetate (**100**):



To a vigorously stirred suspension of silica gel-supported NaIO₄ (80 g) in DCM (300 mL) was added a solution of the diol **99** (9.0 g, 39.1 mmol) in DCM (100 mL). The reaction mixture was stirred at r.t. for 30 min, filtered through sintered glass funnel and the silica gel was thoroughly washed with DCM (3 X 100 mL). Combined filtrates were concentrated under reduced pressure to give aldehyde **100** (5.98 g, 90%) as a colorless oil, which was directly taken for the next step without further purification.

Mol. Formula	: C ₉ H ₁₄ O ₃
IR (Neat) $\tilde{\nu}$	: 3452, 2937, 2858, 1736, 1671, 1445, 1025 cm ⁻¹ .
¹H NMR (CDCl ₃ , 200 MHz)	: δ 1.73 (s, 3H), 2.05 (s, 3H), 2.38 (dd, J = 7.7, 6.9 Hz, 2H), 2.59 (m, 2H), 4.58 (d, J = 7 Hz, 2H), 5.36 (tq, J = 7.0, 1.3 Hz, 1H), 9.78 (t, J = 1.5 Hz, 1H) ppm.
¹³C NMR (CDCl ₃ , 50 MHz)	: δ 16.3 (q), 20.7 (q), 31.2 (t), 41.5 (t), 60.8 (t), 119.1 (d), 139.8 (s), 170.7 (s), 201.4 (d) ppm.
ESI-MS (m/z)	: 192.94 [M+Na] ⁺ .
Elemental Analysis	Calcd.: C, 63.51; H, 8.29. Found: C, 63.44; H, 8.25.

(E)-6-Hydroxy-3-methylnon-2-en-8-ynyl acetate (101):



To a vigorously stirred solution of aldehyde **100** (10 g, 58.8 mmol), propargyl bromide (15.7 mL, 176.4 mmol) and activated zinc powder (11.5 g, 176.4 mmol) in THF (100 mL) at 10 °C, was added sat aq. NH₄Cl solution (20 mL) drop wise over a period of 15 minutes. After stirring for 2 h at r.t., the reaction mixture was filtered through a *celite* bed and washed with DCM (100 mL). The filtrates were concentrated in *vacuo* and the crude product was purified by column chromatography (5:1 petroleum ether/ethyl acetate) to give **101** (10.75 g, 87%) as colorless oil.

Mol. Formula	: C ₁₂ H ₁₈ O ₃
IR (Neat) $\tilde{\nu}$	: 3453, 3296, 2939, 2118, 1736, 1236 cm ⁻¹ .
¹H NMR (CDCl ₃ , 200 MHz)	: δ 1.61–1.71 (m, 2H), 1.73 (s, 3H), 2.00 (br s, 1H), 2.04 (t, J = 2.7 Hz, 1H), 2.05 (s, 3H), 2.10–2.23 (m, 2H), 2.32 (ddd, J =

16.6, 6.4, 2.7 Hz, 1H), 2.44 (ddd, $J = 16.6, 5.2, 2.7$ Hz, 1H), 3.68–3.80 (m, 1H), 4.57 (d, $J = 7.1$ Hz, 2H), 5.37 (tq, $J = 7.1, 1.3$ Hz, 1H) ppm.

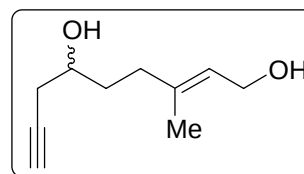
^{13}C NMR : δ 16.11 (q), 20.63 (q), 27.07 (t), 33.61 (t), 35.13 (t), 60.96 (t), (CDCl₃, 50 MHz) 68.97 (d), 70.52 (d), 80.66 (s), 118.41 (d), 141.35 (s), 170.70 (s) ppm

ESI-MS (m/z) : 233.15 [M+Na]⁺

Elemental Analysis Calcd.: C, 68.54; H, 8.63.

Found: C, 68.41; H, 8.51.

(E)-3-Methylnon-2-en-8-yne-1,6-diol (97):



To a solution of **101** (10.75 g, 51.2 mmol) in methanol (100 mL) and water (50 mL) was added potassium carbonate (10.61 g, 76.8 mmol) and the reaction mixture was stirred at r.t. for 4 h. The reaction mixture was concentrated in *vacuo* and partitioned between ethyl acetate (100 mL) and water (50 mL). The organic layer was separated and the aq. layer was extracted with ethyl acetate (50 mL). The combined organic layer was dried over Na₂SO₄, filtered and concentrated in *vacuo*. The crude product was purified by column chromatography (2:1 petroleum ether/ethyl acetate) to afford **97** (7.7 g, 90%) as colorless oil.

Mol. Formula : C₁₀H₁₆O₂

IR (Neat) $\tilde{\nu}$: 3410, 3014, 2939, 2119, 1955, 1432, 1216 cm⁻¹.

^1H NMR : δ 1.68 (s, 3H), 1.59–1.74 (m, 2H), 2.04 (t, $J = 2.7$ Hz, 1H), 2.09–2.19 (m, 2H), 2.34–2.40 (m, 2H), 2.71 (br s, 2H), 3.67–3.79 (m, 1H), 4.12 (d, $J = 6.9$ Hz, 2H), 5.43 (tq, $J = 6.9, 1.3$ Hz, 1H) ppm.

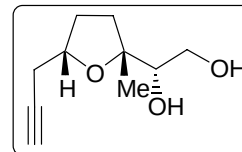
^{13}C NMR : δ 15.90 (q), 27.07 (t), 33.54 (t), 35.17 (t), 58.55 (t), 68.91 (d), 70.47 (d), 80.98 (s), 123.83 (d), 137.88 (s) ppm.

ESI-MS (m/z) : 191.30 [M+Na]⁺.

Elemental Analysis Calcd.: C, 71.39; H, 9.59.

Found: C, 71.23; H, 9.63.

(S)-1-((2R,5S)-2-Methyl-5-(prop-2-ynyl)tetrahydrofuran-2-yl)ethane-1,2-diol (96**):**



To a suspension of activated molecular sieves 4Å (2 g) in dry DCM (100 mL) was added diisopropyl-*L*-tartrate (11.7 g, 49.9 mmol) and cooled to -20°C . To this, titanium tetrakisopropoxide (11.82 g, 41.6 mmol) was added followed by drop wise introduction of *t*-butyl hydroperoxide solution (18.9 mL of 3.3 M solution in toluene, 62.4 mmol) and stirred at -20°C for 30 min. A solution of alcohol **97** (7 g, 41.6 mmol) in dry DCM (30 mL) was added slowly over a period of 20 min and stirring was continued for an additional 6 h at -20°C . The mixture was quenched by adding 10% aq. tartaric acid solution at -20°C and stirred at r.t. for 4 h. Organic layer was separated and the aq. layer was washed with DCM (2 X 75 mL). The combined organic extracts were dried over Na_2SO_4 , filtered and concentrated. The residue was purified by flash column chromatography (3:2 petroleum ether/ethyl acetate) to give *syn*-diol **96** (3.45 g, 45%) and *anti*-diol **102** (3.45 g, 45%) as colorless oils.

Mol. Formula : $\text{C}_{10}\text{H}_{16}\text{O}_3$

$[\alpha]_D$: -5.9 (*c* 1.9, CHCl_3).

IR (Neat) $\tilde{\nu}$: 3417, 2973, 2119, 1956, 1454 cm^{-1} .

^1H NMR : δ 1.15 (s, 3H), 1.45–1.59 (m, 1H), 1.76–1.90 (m, 1H), 2.00 (CDCl₃, 200 MHz) (t, J = 2.6 Hz, 1H), 2.04–2.21 (m, 2H), 2.38 (ddd, J = 16.8, 4.4, 2.6 Hz, 1H), 2.51 (ddd, J = 16.8, 5.6, 2.6 Hz, 1H), 2.73 (br s, 2H), 3.51 (dd, J = 11.7, 8.0 Hz, 1H), 3.63–3.71 (m, 2H), 4.04–4.16 (m, 1H) ppm.

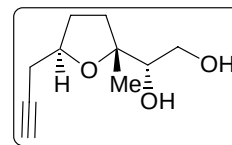
^{13}C NMR : δ 22.73 (q), 24.80 (t), 30.51 (t), 32.21 (t), 62.89 (t), 70.43 (CDCl₃, 50 MHz) (d), 75.14 (d), 76.69 (d), 80.73 (s), 85.28 (s) ppm.

ESI-MS (m/z) 185.29 $[\text{M}+1]^+$, 207.29 $[\text{M}+\text{Na}]^+$.

Elemental Analysis Calcd.: C, 65.19; H, 8.75.

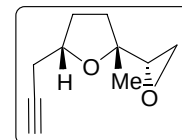
Found: C, 65.01; H, 8.90.

(S)-1-((2R,5R)-2-Methyl-5-(prop-2-ynyl)tetrahydrofuran-2-yl)ethane-1,2-diol (102):



Mol. Formula	: C ₁₀ H ₁₆ O ₃
[α]_D	: +16.9 (c 2.1, CHCl ₃).
IR (Neat) $\tilde{\nu}$	: 3411, 2972, 2118, 1956, 1453 cm ⁻¹ .
¹H NMR (CDCl ₃ , 200 MHz)	: δ 1.18 (s, 3H), 1.57–1.66 (m, 1H), 1.74–1.91 (m, 1H), 1.99 (t, <i>J</i> = 2.6 Hz, 1H), 2.02–2.15 (m, 2H), 2.41–2.46 (m, 2H), 2.74 (br s, 2H), 3.49 (dd, <i>J</i> = 12.1, 8.9 Hz, 1H), 3.64– 3.73 (m, 2H), 4.02–4.15 (m, 1H) ppm.
¹³C NMR (CDCl ₃ , 50 MHz)	: δ 23.69 (q), 25.57 (t), 30.90 (t), 32.67 (t), 63.05 (t), 69.91 (d), 76.75 (d), 78.05 (d), 80.75 (s), 84.95 (s) ppm.
ESI-MS (<i>m/z</i>)	: 185.30 [M+1] ⁺ , 207.30 [M+Na] ⁺ .
Elemental Analysis	Calcd.: C, 65.19; H, 8.75. Found: C, 64.98; H, 8.55.

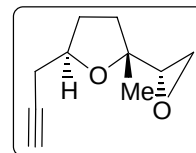
(2R,5S)-2-Methyl-2-((S)-oxiran-2-yl)-5-(prop-2-ynyl)tetrahydrofuran (103):



To a solution of diol **96** (2 g, 10.9 mmol) in dry DCM (20 mL) was added tosyl chloride (2.08 g, 10.9 mmol), dibutyl tin oxide (54 mg, 0.22 mmol) followed by triethylamine (3 mL, 21.8 mmol) and stirred at r.t. for 4 h. DCM was removed under reduced pressure and crude mixture was purified by column chromatography (7:3 petroleum ether/ethyl acetate) to give tosylate (3.26 g, 89%) as colorless oil which was taken in methanol (25 mL). Potassium carbonate (2.67 g, 19.3 mmol) was added and mixture was stirred at r.t. for 1 h. Methanol was removed under reduced pressure and crude was purified by column chromatography (4:1 petroleum ether/ethyl acetate) to procure epoxide **103** (1.36 g, 85%) as colorless oil.

Mol. Formula	: C ₁₀ H ₁₄ O ₂
[α]_D	: -22.1 (c 1.3, CHCl ₃).
IR (Neat) $\tilde{\nu}$	: 2972, 2118, 1956, 1453 cm ⁻¹ .
¹H NMR (CDCl ₃ , 200 MHz)	: δ 1.20 (s, 3H), 1.53–1.63 (m, 1H), 1.74–1.89 (m, 2H), 1.95 (t, <i>J</i> = 2.7 Hz, 1H), 2.00–2.13 (m, 1H), 2.33 (ddd, <i>J</i> = 16.6, 6.9, 2.7 Hz, 1H), 2.46 (ddd, <i>J</i> = 16.6, 5.3, 2.7 Hz, 1H), 2.64 (dd, <i>J</i> = 4.9, 2.8 Hz, 1H), 2.70 (dd, <i>J</i> = 4.9, 4.1 Hz, 1H), 3.0 (dd, <i>J</i> = 4.1, 2.8 Hz, 1H), 4.07–4.20 (m, 1H) ppm.
¹³C NMR (CDCl ₃ , 50 MHz)	: δ 23.36 (q), 25.04 (t), 30.61 (t), 32.49 (t), 44.30 (t), 56.59 (d), 69.58 (d), 76.85 (d), 80.82 (s), 81.84 (s) ppm.
ESI-MS (<i>m/z</i>)	: 189.02 [M+Na] ⁺ .
Elemental Analysis	Calcd.: C, 72.26; H, 8.49. Found: C, 72.10; H, 8.52.

(2*R*,5*R*)-2-Methyl-2-((*S*)-oxiran-2-yl)-5-(prop-2-ynyl)tetrahydrofuran (104**):**

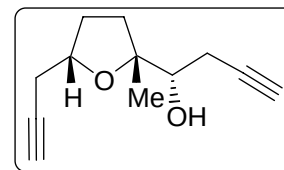


To a solution of diol **102** (2 g, 10.9 mmol) in dry DCM (20 mL) was added tosyl chloride (2.08 g, 10.9 mmol), dibutyl tin oxide (54 mg, 0.22 mmol) followed by triethylamine (3 mL, 21.8 mmol) and stirred at r.t. for 4 h. DCM was removed under reduced pressure and crude mixture was purified by column chromatography (7:3 petroleum ether/ethyl acetate) to give tosylate (3.15 g, 86%) as colorless oil which was taken in methanol (25 mL). Potassium carbonate (2.58 g, 18.6 mmol) was added and mixture was stirred at r.t. for 1 h. Methanol was removed under reduced pressure and crude was purified by column chromatography (4:1 petroleum ether/ethyl acetate) to give epoxide **104** (1.29 g, 84%) as colorless oil.

Mol. Formula	: C ₁₀ H ₁₄ O ₂
[α]_D	: +5.5 (c 1.7, CHCl ₃).
IR (Neat) $\tilde{\nu}$	: 2982, 2120, 1957, 1443 cm ⁻¹ .
¹H NMR	: δ 1.25 (s, 3H), 1.57–1.68 (m, 1H), 1.73–1.86 (m, 2H), 1.95

(CDCl ₃ , 200 MHz)	(t, <i>J</i> = 2.7 Hz, 1H), 2.01–2.14 (m, 1H), 2.35 (ddd, <i>J</i> = 16.7, 6.8, 2.7 Hz, 1H), 2.48 (ddd, <i>J</i> = 16.7, 5.1, 2.7 Hz, 1H), 2.53 (dd, <i>J</i> = 4.9, 2.8 Hz, 1H), 2.69 (dd, <i>J</i> = 4.9, 4.1 Hz, 1H), 2.98 (dd, <i>J</i> = 4.1, 2.8 Hz, 1H), 4.02–4.14 (m, 1H) ppm.
¹³ C NMR (CDCl ₃ , 50 MHz)	: δ 24.14 (q), 25.24 (t), 30.58 (t), 32.18 (t), 43.53 (t), 56.63 (d), 69.60 (d), 77.63 (d), 80.62 (s), 81.65 (s) ppm.
ESI-MS (<i>m/z</i>)	: 189.12 [M+1] ⁺ .
Elemental Analysis	Calcd.: C, 72.26; H, 8.49. Found: C, 72.20; H, 8.55.

(S)-1-((2R,5S)-2-Methyl-5-(prop-2-ynyl)tetrahydrofuran-2-yl)but-3-yn-1-ol (105):

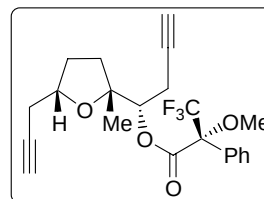


To a solution of epoxide **103** (500 mg, 3.01 mmol) in dry DMSO (5 mL) was added lithium acetylide-EDA complex (555 mg, 6.02 mmol) and stirred at r.t. for 3 h. The reaction mixture was quenched with ice, filtered and washed with ethyl acetate (25 mL). The organic phase was separated and washed with water (2 X 5 mL), brine (5 mL), dried over Na₂SO₄, filtered and concentrated in *vacuo*. The residue was purified by chromatography (4:1 petroleum ether/ethyl acetate) to give alkynol **105** (520 mg, 90%) as colorless oil.

Mol. Formula	: C ₁₂ H ₁₆ O ₂
[α]_D	: −18.1 (c 1.2, CHCl ₃).
IR (Neat) $\tilde{\nu}$	: 3411, 2982, 2120, 1957, 1443 cm ^{−1} .
¹ H NMR (CDCl ₃ , 200 MHz)	: δ 1.20 (s, 3H), 1.51–1.70 (m, 2H), 1.81–1.95 (m, 1H), 2.04 (t, <i>J</i> = 2.7 Hz, 1H), 2.06 (t, <i>J</i> = 2.7 Hz, 1H), 2.16–2.26 (m, 1H), 2.29–2.63 (m, 4H), 2.95 (br s, 1H), 3.79 (dd, <i>J</i> = 8.6, 4.0 Hz, 1H), 4.10–4.22 (m, 1H) ppm.
¹³ C NMR (CDCl ₃ , 50 MHz)	: δ 22.11 (t), 22.83 (q), 24.73 (t), 30.54 (t), 31.47 (t), 69.94 (d), 70.48 (d), 74.93 (d), 75.28 (d), 80.63 (s), 81.55 (s), 86.14 (s) ppm.

ESI-MS (m/z) : 215.11 $[M+Na]^+$.
Elemental Analysis Calcd.: C, 74.97; H, 8.39.
 Found: C, 74.88; H, 8.42.

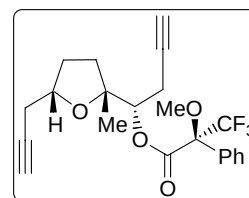
(R)-[(S)-1-((2R,5S)-2-Methyl-5-(prop-2-ynyl)tetrahydrofuran-2-yl)but-3-ynyl]3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (106):



To a solution of alcohol **105** (10 mg, 0.052 mmol) in dry DCM (2 mL) was added *R*-(–)-MTPA (15 mg, 0.062 mmol) and the reaction mixture was cooled to 0 °C. To this, DCC (16 mg, 0.078 mmol) was added in one portion followed by catalytic amount of DMAP and stirred at r.t. for 5 h. The reaction mixture was quenched with ice and the organic phase was separated, washed with water (3 X 5 mL), brine (1 X 5 mL), dried over Na_2SO_4 , filtered and concentrated. The residue obtained was purified by column chromatography (19:1 petroleum ether/ethyl acetate) to afford ester **106** (17 mg, 83%) as colorless oil.

Mol. Formula : $C_{22}H_{23}F_3O_4$
 1H NMR : δ 1.14 (s, 3H), 1.58–1.85 (m, 4H), 1.96 (t, $J = 2.7$ Hz, 1H),
 (CDCl₃, 200 MHz) 2.01 (t, $J = 2.7$ Hz, 1H), 2.29–2.34 (m, 2H), 2.50 (ddd, $J =$
 17.4, 9.0, 2.7 Hz, 1H), 2.79 (dt, $J = 17.4, 2.7$ Hz, 1H), 3.65 (q,
 $J = 1.2$ Hz, 3H), 3.69–3.81 (m, 1H), 5.28 (dd, $J = 9.0, 2.7$ Hz,
 1H), 7.36–7.44 (m, 3H), 7.55–7.67 (m, 2H) ppm.

(S)-[(S)-1-((2R,5S)-2-Methyl-5-(prop-2-ynyl)tetrahydrofuran-2-yl)but-3-ynyl]3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (107):

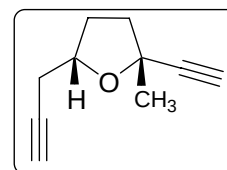


To a solution of alcohol **105** (10 mg, 0.052 mmol) in dry DCM (2 mL) was added *S*-(–)-MTPA (15 mg, 0.062 mmol) and the reaction mixture was cooled to 0 °C. To this, DCC (16 mg, 0.078 mmol) was added in one portion followed by catalytic amount of DMAP and stirred at r.t. for 6 h. The reaction mixture was quenched with ice the organic

phase was separated, washed with water (3 X 5 mL), brine (1 X 5 mL), dried over Na₂SO₄, filtered and concentrated. The residue obtained was purified by column chromatography (19:1 petroleum ether/ethyl acetate) to give (18 mg, 85%) of ester **107** as colorless oil.

Mol. Formula : C₂₂H₂₃F₃O₄
¹H NMR : δ 1.25 (s, 3H), 1.61–1.85 (m, 3H), 1.91 (t, *J* = 2.7 Hz, 1H),
 (CDCl₃, 200 MHz) 1.99 (t, *J* = 2.7 Hz, 1H), 2.02–2.11 (m, 1H), 2.29–2.47 (m, 2H), 2.48 (ddd, *J* = 17.4, 8.4, 2.7 Hz, 1H) 2.77 (dt, *J* = 17.4, 2.7 Hz, 1H), 3.53 (q, *J* = 1.0 Hz, 3H), 3.95–4.07 (m, 1H), 5.27 (dd, *J* = 8.5, 3.5 Hz, 1H), 7.39–7.44 (m, 3H), 7.58–7.63 (m, 2H) ppm.

(2R,5S)-2-Ethynyl-2-methyl-5-(prop-2-ynyl)tetrahydrofuran (95):

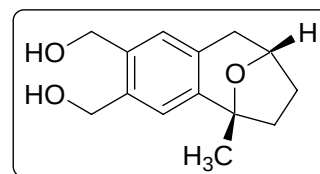


To a vigorously stirred suspension of silica gel-supported NaIO₄ (27 g) in DCM (75 mL) was added a solution of the diol **96** (2.5 g, 13.58 mmol) in DCM (20 mL) and stirred at r.t. for 2 h. After completion, the reaction mixture was filtered through sintered glass funnel and the silica gel was thoroughly washed with DCM (3 X 25 mL). Combined filtrate was concentrated under reduced pressure to yield intermediate aldehyde (1.92 g), which was taken in methanol (10 mL) and added potassium carbonate (2.61 g, 18.9 mmol) followed by Ohira–Bestmann reagent (2.91 g, 15.1 mmol). The reaction mixture was stirred at r.t. for 4 h. Diluted with water (10 mL) and diethyl ether (20 mL). The organic phase was separated and aq. layer extracted with ether (2 X 10 mL). The combined organic layer was washed with water, dried over Na₂SO₄, filtered and concentrated in *vacuo*. Purification of the crude by column chromatography (4:1 petroleum ether/ethyl acetate) afforded **95** (1.65 g, 82%) as colorless oil.

Mol. Formula : C₁₀H₁₂O
[α]_D : –60.4 (*c* 2.1, CHCl₃).
IR (Neat) $\tilde{\nu}$: 3303, 2982, 2120, 1957, 1443 cm^{–1}.

¹H NMR (CDCl ₃ , 200 MHz)	: δ 1.53 (s, 3H), 1.79–1.93 (m, 1H), 1.95 (t, <i>J</i> = 2.6 Hz, 1H), 2.00–2.09 (m, 1H), 2.16–2.33 (m, 2H), 2.39 (s, 1H), 2.45 (ddd, <i>J</i> = 16.5, 7.8, 2.6 Hz, 1H), 2.63 (ddd, <i>J</i> = 16.5, 5.6, 2.6 Hz, 1H), 4.13–4.27 (m, 1H) ppm.
¹³C NMR (CDCl ₃ , 50 MHz)	: δ 26.06 (t), 27.94 (q), 31.75 (t), 40.58 (t), 69.68 (d), 70.92 (d), 76.16 (s), 78.29 (d), 80.85 (s), 87.78 (s) ppm.
ESI-MS (<i>m/z</i>)	: 149.18 [M+1] ⁺ .
Elemental Analysis	Calcd.: C, 81.04; H, 8.16 Found: C, 80.96; H, 8.1.

(4-Hydroxymethyl-1-methyl-12-oxa-tricyclo[7.2.1.0^{2,7}]dodeca-2,4,6-trien-5-yl)-methanol (108):

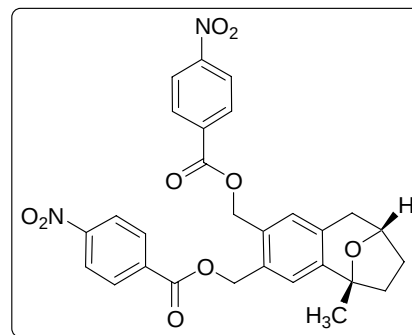


To a solution of dialkyne **95** (200 mg, 1.35 mmol) in dry toluene (10 mL) and dry ethanol (3 mL) was added 2-butyne-1,4-butyndiol (139 mg, 1.62 mmol) followed by Wilkinson's catalyst (37 mg, 41 μmol, 3 mol%). The reaction mixture was degassed with argon and heated to 80 °C for 3 h. Solvents were removed under reduced pressure and the crude product was purified by column chromatography (1:1 petroleum ether/ethyl acetate) to obtain diol **108** (269 mg, 85%) as colorless oil.

Mol. Formula	: C ₁₄ H ₁₈ O ₃
[α]_D	: −15.6 (<i>c</i> 1.0, CHCl ₃).
IR (Neat) $\tilde{\nu}$	: 3392, 3018, 1215 cm ^{−1} .
¹H NMR (CDCl ₃ , 200 MHz)	: δ 1.63–1.76 (m, 1H), 1.69 (s, 3H), 1.81–1.90 (m, 1H), 1.94–2.04 (m, 1H), 2.16–2.32 (m, 1H), 2.47 (d, <i>J</i> = 16.6 Hz, 1H), 3.23 (br s, 2H), 3.28 (dd, <i>J</i> = 16.6, 5.2 Hz, 1H), 4.62 (s, 2H), 4.64 (s, 2H), 4.67–4.74 (m, 1H), 7.02 (s, 1H), 7.10 (s, 1H) ppm.
¹³C NMR (CDCl ₃ , 125 MHz)	: δ 22.57 (q), 30.46 (t), 36.98 (t), 42.86 (t), 63.49 (t), 63.77 (t), 74.28 (d), 80.45 (s), 124.01 (d), 130.51 (d), 131.95 (s), 137.08 (s), 137.81 (s), 143.79 (s) ppm.

ESI-MS (m/z) : 257.39 $[M+Na]^+$.
Elemental Analysis Calcd.: C, 71.77; H, 7.74.
 Found: C, 71.55; H, 7.62.

***p*-Nitro benzoyl ester derivative (109):**



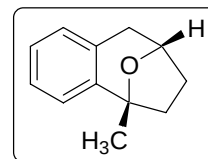
To a solution of diol **108** (40 mg, 0.17 mmol) in dry DCM (4 mL) was added dry triethylamine (95 μ L, 0.68 mmol) and catalytic DMAP. The reaction mixture was cooled to 0 $^{\circ}$ C and added *p*-nitrobenzoyl chloride (79 mg, 0.43 mmol) and stirred at r.t. for 6 h. The reaction mixture was diluted with DCM (4 mL) and water (4 mL). The organic phase was separated and washed with 10% NaHCO_3 solution (3 x 4 mL), water (4 mL), sat. brine solution (4 mL), dried over Na_2SO_4 , filtered and concentrated in *vacuo*. Purification of crude by chromatography (2:1 petroleum ether/ethyl acetate) gave diester **109** (65 mg, 72%) as pale yellow solid.

Crystal data: X-ray intensity data was collected on a Bruker SMART APEX CCD diffractometer with omega and phi scan mode, $\lambda_{\text{MoK}\alpha} = 0.71073 \text{ \AA}$ at $T = 297(2) \text{ K}$. All the data were corrected for Lorentzian, polarisation and absorption effects using Bruker's SAINT and SADABS programs. The crystal structures were solved by direct method using SHELXS-97 and the refinement was performed by full matrix least squares of F^2 using SHELXL-97 (G. M. Sheldrick, SHELX-97 program for crystal structure solution and refinement, University of Göttingen, Göttingen, Germany, 1997). Hydrogen atoms were included in the refinement as per the riding model. *Crystal data for 11* ($\text{C}_{28}\text{H}_{24}\text{N}_2\text{O}_9$): $M = 532.49$, crystal dimensions $0.56 \times 0.32 \times 0.11 \text{ mm}^3$, Orthorhombic, space group $P2_12_12_1$, $a = 7.0446(16)$, $b = 12.856(3)$, $c = 27.748(6) \text{ \AA}$, $V = 2512.9(10) \text{ \AA}^3$, $Z = 4$, $\rho_{\text{calcd}} = 1.407 \text{ g cm}^{-3}$, $\mu (\text{Mo-K}\alpha) = 0.106 \text{ mm}^{-1}$, $F(000) = 1112$, $2\theta_{\text{max}} = 50.00^{\circ}$, 18160 reflections collected, 4410 unique, 2917 observed ($I > 2\sigma(I)$) reflections, 353

refined parameters, R value 0.0541, $wR2 = 0.1219$ (all data $R = 0.0924$, $wR2 = 0.1389$), $S = 1.026$, minimum and maximum transmission 0.9429 and 0.9889 respectively, maximum and minimum residual electron densities +0.188 and $-0.152 \text{ e } \text{\AA}^{-3}$.

Mol. Formula	: $\text{C}_{28}\text{H}_{24}\text{N}_2\text{O}_9$
M. P.	: 201–203 °C.
$[\alpha]_D$	: -12 (c 1.7, CHCl_3).
IR (Neat) $\tilde{\nu}$	: 3020, 1726, 1530, 1349, 1269, 1215 cm^{-1} .
^1H NMR (CDCl_3 , 200 MHz)	: δ 1.68–1.81 (m, 1H), 1.75 (s, 3H), 1.87–2.11 (m, 2H), 2.22–2.37 (m, 1H), 2.56 (d, $J = 16.7 \text{ Hz}$, 1H), 3.37 (dd, $J = 16.7$, 5.1 Hz, 1H), 4.73–4.79 (m, 1H), 5.49 (s, 2H), 5.50 (s, 2H), 7.24 (s, 1H), 7.30 (s, 1H), 8.11–8.22 (m, 8H) ppm.
^{13}C NMR (CDCl_3 , 50 MHz)	: δ 22.62 (q), 30.54 (t), 37.06 (t), 42.80 (t), 64.95 (t), 65.41 (t), 74.18 (d), 80.24 (s), 123.49 (d), 125.39 (d), 130.72 (d), 130.74 (d), 131.50 (d), 131.52 (d), 132.54 (s), 133.79 (s), 135.10 (s), 135.14 (s), 145.32 (s), 150.55 (s), 164.31 (s) ppm.
ESI-MS (m/z)	: 533.6 $[\text{M}+1]^+$.
Elemental Analysis	Calcd.: C, 63.16; H, 4.54; N, 5.26. Found: 63.05; H, 4.42; N, 5.12.

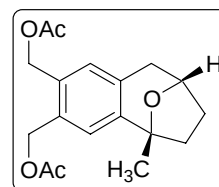
Cyclotrimerization product of acetylene (**111**):



A solution of dialkyne **95** (100 mg, 0.675 mmol) in dry toluene (6 mL) was cooled to ice-cold temperature in a glass ampule and purged acetylene gas till saturation. Added Wilkinson's catalyst (19 mg, 0.02 mmol, 3 mol%) and the ampule was fused and heated to 80 °C for 6 h. The ampule was cooled and the glass seal was broken. Toluene was removed under reduced pressure and the crude product was purified by column chromatography (4:1 petroleum ether/ethyl acetate) to give **111** (52 mg, 44%) as colorless oil.

Mol. Formula	: C ₁₂ H ₁₄ O
[α]_D	: -1.1 (c 0.7, CHCl ₃).
¹H NMR (CDCl ₃ , 500 MHz)	: δ 1.70–1.76 (m, 1H), 1.74 (s, 3H), 1.83–1.89 (m, 1H), 2.01–2.06 (m, 1H), 2.23–2.30 (m, 1H), 2.52 (d, <i>J</i> = 16.4 Hz, 1H), 3.37 (dd, <i>J</i> = 16.4, 5.2 Hz, 1H), 4.73–4.76 (m, 1H), 7.06–7.08 (m, 1H), 7.13–7.17 (m, 3H) ppm.
¹³C NMR (CDCl ₃ , 125 MHz)	: δ 22.72 (q), 30.51 (t), 37.33 (t), 42.95 (t), 74.42 (d), 80.46 (s), 122.68 (d), 125.92 (d), 126.65 (d), 129.32 (d), 131.93 (s), 143.96 (s) ppm.
Elemental Analysis	Calcd.: C, 82.72; H, 8.10. Found: C, 82.53; H, 8.18.

Cyclotrimerization product of butyne diol-diacetate (112):



To a solution of dialkyne **95** (100 mg, 0.68 mmol) in dry toluene (8 mL) was added butynediol diacetate (138 mg, 0.81 mmol) followed by Wilkinson's catalyst (19 mg, 0.02 mmol, 3 mol%). The reaction mixture was degassed with argon and heated to 80 °C for 5 h. Solvents were removed under reduced pressure and the crude product was purified by column chromatography (7:3 petroleum ether/ethyl acetate) to procure diacetate **112** (155 mg, 72%) as colorless oil.

Mol. Formula	: C ₁₈ H ₂₂ O ₅
[α]_D	: -11.8 (c 2.3, CHCl ₃).
IR (Neat) $\tilde{\nu}$	: 3018, 1736, 1216 cm ⁻¹ .
¹H NMR (CDCl ₃ , 200 MHz)	: δ 1.73 (s, 3H), 1.84–1.98 (m, 2H), 2.02–2.06 (m, 1H), 2.09 (s, 3H), 2.09 (s, 3H), 2.19–2.35 (m, 1H), 2.51 (d, <i>J</i> = 16.6 Hz, 1H), 3.34 (dd, <i>J</i> = 16.6, 5.2 Hz, 1H), 4.71–4.77 (m, 1H), 5.13 (s, 2H), 5.14 (s, 2H) 7.10 (s, 1H), 7.16 (s, 1H) ppm.
¹³C NMR (CDCl ₃ , 50 MHz)	: δ 20.94 (q), 22.62 (q), 30.52 (t), 37.06 (t), 42.87 (t), 63.57 (t), 63.96 (t), 74.16 (d), 80.25 (s), 124.80 (d), 130.98 (d),

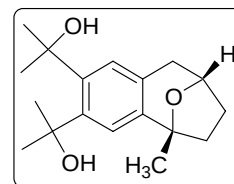
132.03 (s), 132.96 (s), 133.01 (s), 144.61 (s), 170.50 (s) ppm.

ESI-MS (*m/z*) : 319.5 [M+1]⁺, 341.5 [M+Na]⁺, 357.5 [M+K]⁺.

Elemental Analysis Calcd.: C, 67.91; H, 6.97.

Found: C, 67.88; H, 6.77.

Cyclotrimerization product of 2,5-dimethyl-3-hexyne-2,5-diol (114):



To a solution of dialkyne **95** (100 mg, 0.68 mmol) in dry toluene (8 mL) was added 2,5-dimethyl-3-hexyne-2,5-diol (115 mg, 0.81 mmol) followed by Wilkinson's catalyst (19 mg, 0.02 mmol, 3 mol%). The reaction mixture was degassed with argon and heated to 80 °C for 4 h. Solvents were removed under reduced pressure and the crude product was purified by column chromatography (1:1 petroleum ether/ethyl acetate) to give **114** (101 mg, 52%) as colorless oil.

Mol. Formula : C₁₈H₂₆O₃

[α]_D : −12.5 (c 1.8, CHCl₃).

IR (Neat) $\tilde{\nu}$: 3351, 2977, 2932, 1216 cm^{−1}.

¹H NMR : δ 1.65 (s, 3H), 1.68 (s, 9H), 1.70 (s, 3H), 1.71–1.77 (m, 1H),
(CDCl₃, 200 MHz) 1.86 (dd, *J* = 11.3, 7.2 Hz, 1H), 1.96–2.07 (m, 1H), 2.17–2.33 (m, 1H), 2.44 (d, *J* = 16.4, Hz, 1H), 3.26 (dd, *J* = 16.4, 5.2 Hz, 1H), 4.67–4.74 (m, 1H), 5.42 (br s, 2H), 6.97 (s, 1H), 7.05 (s, 1H) ppm.

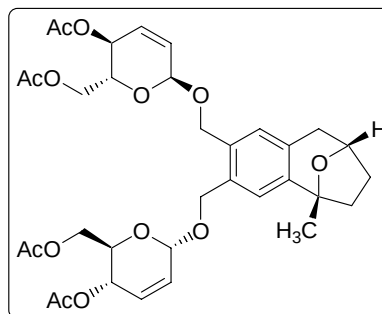
¹³C NMR : δ 22.44 (q), 30.51 (t), 33.70 (q), 33.73 (q), 33.89 (q) 2C,
(CDCl₃, 50 MHz) 36.85 (t), 42.72 (t), 74.37 (d), 74.54 (s), 74.67 (s), 80.30 (s), 122.21 (d), 128.92 (d), 129.57 (s), 141.57 (s), 143.35 (s), 144.07 (s) ppm.

ESI-MS (*m/z*) : 291.15 [M+1]⁺.

Elemental Analysis Calcd.: C, 74.45; H, 9.02.

Found: C, 74.23; H, 9.11.

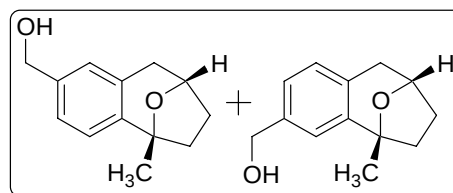
Cyclotrimerization product of glycoside dimer of 1,4-butyndiol (116):



To a solution of dialkyne **95** (100 mg, 0.68 mmol) in dry toluene (8 mL) was added glycoside dimer of 1,4-butyndiol (413 mg, 0.81 mmol) followed by Wilkinson's catalyst (19 mg, 0.02 mmol, 3 mol%). The reaction mixture was degassed with argon and heated to 80 °C for 5 h. Solvents were removed under reduced pressure and the crude product was purified by column chromatography (2:1 petroleum ether/ethyl acetate) to give **116** (240 mg, 54%) as colorless oil.

Mol. Formula	: C ₃₄ H ₄₂ O ₁₃
[α]_D	: +37.6 (c 1.0, CHCl ₃).
IR (Neat) $\tilde{\nu}$	: 3019, 2400, 1741, 1215 cm ⁻¹ .
¹H NMR (CDCl ₃ , 500 MHz)	: δ 1.66–1.72 (m, 1H), 1.74 (s, 3H), 1.84–1.90 (m, 1H), 1.98–2.03 (m, 1H), 2.08 (s, 3H), 2.09 (s, 3H), 2.10 (s, 3H), 2.12 (s, 3H), 2.21–2.30 (m, 1H), 2.52 (d, <i>J</i> = 16.6 Hz, 1H), 3.35 (dd, <i>J</i> = 16.6, 5.1 Hz, 1H), 4.07–4.15 (m, 3H), 4.22–4.31 (m, 3H), 4.62 (dd, <i>J</i> = 11.4, 10.4 Hz, 2H), 4.73–4.75 (m, 1H), 4.85 (d, <i>J</i> = 11.8 Hz, 1H), 4.90 (d, <i>J</i> = 11.8 Hz, 1H), 5.12 (t, <i>J</i> = 2.8 Hz, 2H), 5.33–5.35 (m, 2H), 5.80–5.83 (m, 2H), 5.88–5.91 (m, 2H), 7.11 (s, 1H), 7.17 (s, 1H) ppm.
¹³C NMR (CDCl ₃ , 125 MHz)	: δ 20.80 (q), 20.95 (q), 22.66 (q), 30.48 (t), 37.07 (t), 42.87 (t), 62.82 (t), 65.23 (d), 67.08 (d), 67.12 (d), 67.75 (t), 67.86 (t), 74.27 (d), 80.31 (s), 93.64 (d), 93.76 (d), 124.15 (d), 127.63 (d), 129.37 (d), 130.60 (d), 132.18 (s), 133.38 (s), 134.31 (s), 143.99 (s), 170.24 (s), 170.76 (s) ppm.
ESI-MS (<i>m/z</i>)	: 681.37 [M+Na] ⁺ .
Elemental Analysis	Calcd.: C, 62.00; H, 6.43. Found: C, 62.11; H, 6.30.

Cyclotrimerization products of propargyl alcohol (118/119):



To a solution of dialkyne **95** (100 mg, 0.68 mmol) in dry toluene (8 mL) was added propargyl alcohol (76 mg, 1.35 mmol) followed by Wilkinson's catalyst (19 mg, 0.02 mmol, 3 mol%). The reaction mixture was degassed with argon and heated to 80 °C for 6 h. Solvents were removed under reduced pressure and the crude product was purified by column chromatography (2:1 petroleum ether/ethyl acetate) to give inseparable **118** and **119** (92 mg, 67%) as colorless oil.

Mol. Formula : C₁₃H₁₆O₂

IR (Neat) $\tilde{\nu}$: 3390, 3018 cm⁻¹.

¹H NMR : δ 1.69–1.72 (m, 1H), 1.73, 1.75 (2s, 3H), 1.83–1.90 (m, 1H), 1.99–2.06 (m, 1H), 2.22–2.30 (m, 1H), 2.52 (2d, J = 16.5 Hz, 1H), 3.33–3.39 (m, 1H), 4.63, 4.65 (2s, 2H), 4.72–4.76 (m, 1H), 7.06–7.09 (m, 1H), 7.12–7.17 (m, 2H) ppm.

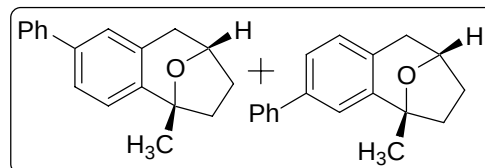
¹³C NMR : δ 22.64 (q), 30.40 (t), 37.08 (t), 37.27 (t), 42.85 (t), 64.92 (t), 65.19 (t), 74.29 (d), 74.31 (d), 80.42 (s), 80.53 (s), 121.42 (d), 122.84 (d), 124.65 (d), 125.41 (d), 127.92 (d), 129.42 (d), 131.26 (s), 132.15 (s), 138.55 (s), 139.27 (s), 143.25 (s), 144.02 (s) ppm.

ESI-MS (m/z) : 205.18 [M+1]⁺, 227.18 [M+Na]⁺.

Elemental Analysis Calcd.: C, 76.44; H, 7.90.

Found: C, 76.52; H, 8.01.

Cyclotrimerization products of phenyl acetylene (121/122):

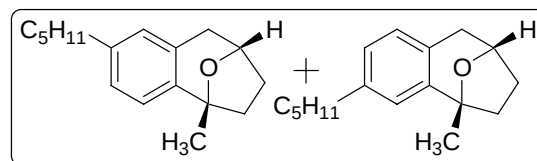


To a solution of dialkyne **95** (100 mg, 0.68 mmol) in dry toluene (8 mL) was added phenyl acetylene (83 mg, 0.81 mmol) followed by Wilkinson's catalyst (19 mg,

0.02 mmol, 3 mol%). The reaction mixture was degassed with argon and heated to 80 °C for 6 h. Solvents were removed under reduced pressure and the crude product was purified by column chromatography (4:1 petroleum ether/ethyl acetate) to give inseparable **121** and **122** (100 mg, 59%) as colorless oil.

Mol. Formula	: C ₁₈ H ₁₈ O
IR (Neat) $\tilde{\nu}$	: 3018, 1216 cm ⁻¹ .
¹H NMR (CDCl ₃ , 400 MHz)	: δ 1.73–1.83 (m, 1H), 1.77, 1.80 (2s, 3H), 1.88–1.97 (m, 1H), 2.04–2.11 (m, 1H), 2.22–2.37 (m, 1H), 2.53–2.63 (2d, J = 16.6 Hz, 1H), 3.35–3.49 (m, 1H), 4.74–4.81 (m, 1H), 7.13–7.21 (m, 1H), 7.29–7.33 (m, 1H), 7.36–7.48 (m, 4H), 7.54–7.59 (m, 2H) ppm.
¹³C NMR (CDCl ₃ , 100 MHz)	: δ 22.74 (q), 22.79 (q), 29.69 (t), 30.57 (t), 37.14 (t), 37.50 (t), 42.96 (t), 74.40 (d), 80.43 (s), 80.62 (s), 121.56 (d), 123.17 (d), 124.76 (d), 125.49 (d), 127.01 (d), 127.07 (d), 127.12 (d), 128.03 (d), 128.69 (d), 128.72 (d), 128.84 (s), 129.73 (d), 130.90 (s), 131.16 (s), 132.44 (s), 139.07 (s), 139.66 (s), 140.95 (s), 141.38 (s), 143.10 (s), 144.42 (s) ppm.
ESI-MS (m/z)	: 273.20 [M+1] ⁺ .
Elemental Analysis	Calcd.: C, 86.36; H, 7.25. Found: C, 86.52; H, 7.10.

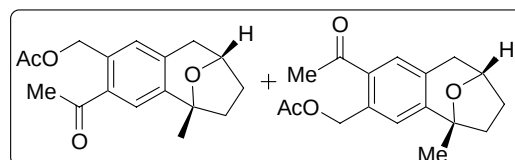
Cyclotrimerization products of 1-heptyne (124/125):



To a solution of dialkyne **95** (100 mg, 0.68 mmol) in dry toluene (8 mL) was added 1-heptyne (78 mg, 0.81 mmol) followed by Wilkinson's catalyst (19 mg, 0.02 mmol, 3 mol%). The reaction mixture was degassed with argon and heated to 80 °C for 2 h. Solvents were removed under reduced pressure and the crude product was purified by column chromatography (4:1 petroleum ether/ethyl acetate) to give inseparable **124** and **125** (135 mg, 82%) as colorless oil.

Mol. Formula	: C ₁₇ H ₂₄ O
IR (Neat) $\tilde{\nu}$	: 3018, 1216 cm ⁻¹ .
¹H NMR (CDCl ₃ , 200 MHz)	: δ 0.89 (t, <i>J</i> = 6.7 Hz, 3H), 1.28–1.35 (m, 4H), 1.51–1.62 (m, 2H), 1.68–1.77 (m, 1H), 1.71, 1.72 (2s, 3H), 1.82–1.91 (m, 1H), 1.97–2.08 (m, 1H), 2.17–2.31 (m, 1H), 2.43–2.58 (m, 3H), 3.27–3.37 (m, 1H), 4.68–4.75 (m, 1H), 6.86–7.06 (m, 3H) ppm.
¹³C NMR (CDCl ₃ , 50 MHz)	: δ 14.02 (q), 22.52 (t), 22.73 (q), 29.68 (t), 30.49 (t), 31.14 (t), 31.32 (t), 31.57 (t), 35.52 (t), 35.83 (t), 36.99 (t), 37.34 (t), 42.91 (t), 74.37 (d), 74.43 (d), 80.37 (s), 80.48 (s), 122.51 (d), 122.65 (d), 125.91 (d), 126.64 (d), 128.88 (s), 129.09 (d), 129.20 (d), 131.62 (s), 140.50 (s), 141.18 (s), 141.25 (s), 143.68 (s) ppm.
ESI-MS (<i>m/z</i>)	: 245.37 [M+1] ⁺ .
Elemental Analysis	Calcd.: C, 83.55; H, 9.90. Found: C, 83.33; H, 9.72.

Cyclotrimerization products of 1-acetyl 4-oxo-pent-2-ynyl-1-ol (127/128):



To a solution of dialkyne **95** (100 mg, 0.68 mmol) in dry toluene (8 mL) was added 1-acetyl 4-oxo-pent-2-ynyl-1-ol (114 mg, 0.81 mmol) followed by Wilkinson's catalyst (19 mg, 0.02 mmol, 3 mol%). The reaction mixture was degassed with argon and heated to 80 °C for 3 h. Solvents were removed under reduced pressure and the crude product was purified by column chromatography (7:3 petroleum ether/ethyl acetate) to give inseparable **127** and **128** (140 mg, 72%) as colorless oil.

Mol. Formula	: C ₁₇ H ₂₀ O ₄
IR (Neat) $\tilde{\nu}$	: 3019, 2979, 1736, 1680, 1215 cm ⁻¹ .
¹H NMR (CDCl ₃ , 200 MHz)	: δ 1.56–1.65 (m, 1H), 1.67, 1.70 (2s, 3H), 1.80–1.96 (m, 2H), 2.05, 2.06 (2s, 3H), 2.16–2.26 (m, 1H), 2.44–2.53 (d, <i>J</i> = 17.2 Hz, 1H), 2.50, 2.53 (2s, 3H), 3.30 (dd, <i>J</i> = 17.2, 5.1 Hz, 1H),

4.66–4.72 (m, 1H), 5.30, 5.31 (2s, 2H), 7.10, 7.18 (2s, 1H), 7.41, 7.48 (2s, 1H) ppm.

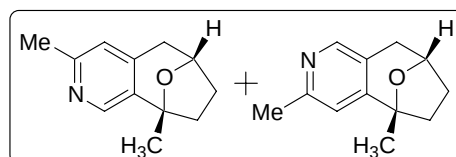
^{13}C NMR : δ 20.90 (q), 22.33 (q), 22.48 (q), 28.72 (q), 28.80 (q), 30.40 (t), 30.45 (t), 36.89 (t), 37.42 (t), 42.67 (t), 42.73 (t), 64.38 (t), 64.57 (t), 74.00 (d), 74.08 (d), 80.07 (s), 80.37 (s), 123.17 (d), 124.26 (d), 129.23 (d), 130.89 (d), 131.76 (s), 134.19 (s), 135.03 (s), 137.07 (s), 143.43 (s), 147.99 (s), 170.52 (s), 200.23 (s) ppm.

ESI-MS (m/z) : 289.31 $[\text{M}+1]^+$, 311.30 $[\text{M}+\text{Na}]^+$.

Elemental Analysis Calcd.: C, 70.81; H, 6.99.

Found: C, 70.63; H, 6.82.

Cyclotrimerization products of acetonitrile (129/130):



To a solution of dialkyne **95** (100 mg, 0.68 mmol) in dry toluene (10 mL) was added acetonitrile (0.1 mL, 2.04 mmol) followed by $\text{CpCo}(\text{CO})_2$ (27 μL , 1.25 M solution in xylenes, 5 mol%) and the reaction mixture was heated to reflux for 6 h. The solvents were removed under reduced pressure and the residue obtained was purified by column chromatography (1:1 petroleum ether/ethyl acetate) to give **129/130** (82 mg, 64%) as colorless oil.

Mol. Formula : $\text{C}_{12}\text{H}_{15}\text{NO}$

IR (CHCl_3) $\tilde{\nu}$: 3436, 3019, 1610, 1215 cm^{-1} .

^1H NMR : δ 1.57–1.65 (m, 1H), 1.67, 1.74 (2s, 3H), 1.82–2.06 (m, 2H), 2.19–2.31 (m, 1H), 2.44 (d, $J = 16.8$ Hz, 0.5 H), 2.47 (d, $J = 16.8$ Hz, 0.5 H), 2.46, 2.48 (2s, 3H), 3.25 (dd, $J = 16.8, 4.7$ Hz, 1H), 4.67–4.80 (m, 1H), 6.86, 6.89 (2s, 1H), 8.18, 8.26 (2s, 1H) ppm.

^{13}C NMR : δ 21.76 (q), 22.15 (q), 23.87 (q), 24.13 (q), 30.31 (t), 30.47 (t), 33.90 (t), 36.74 (t), 42.53 (t), 42.90 (t), 73.84 (d),

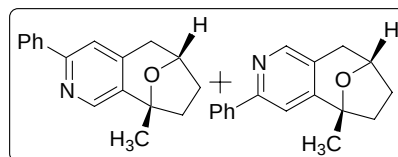
74.30 (d), 79.19 (s), 79.84 (s), 116.77 (d), 123.53 (d),
124.47 (s), 136.80 (s), 141.95 (s), 143.41 (d), 149.67 (d),
152.42 (s), 155.89 (s), 156.29 (s) ppm.

ESI-MS (*m/z*) : 190.15 [M+1]⁺

Elemental Analysis Calcd.: C, 76.16; H, 7.99; N, 7.40.

Found: C, 76.12; H, 7.83; N, 7.19.

**Cyclotrimerization products of benzonitrile
(132/133):**



To a solution of dialkyne **95** (100 mg, 0.68 mmol) in dry toluene (10 mL) was added benzonitrile (0.14 mL, 1.36 mmol) followed by CpCo(CO)₂ (25 μL, 1.25 M solution in xylenes, 5 mol%) and the reaction mixture was heated to reflux for 8 h. The solvents were removed under pressure and the residue obtained was purified by column chromatography (1:1 petroleum ether/ethyl acetate) to give **132/133** (75 mg, 44%) as colorless oil.

Mol. Formula : C₁₇H₁₇NO

IR (CHCl₃) $\tilde{\nu}$: 3435, 3019, 1607, 1215 cm⁻¹.

¹H NMR : δ 1.70–1.74 (m, 1H), 1.78, 1.81 (2s, 3H), 1.88–2.08 (m, 2H), 2.21–2.40 (m, 1H), 2.56 (d, *J* = 16.9 Hz, 1H), 3.34 (dd, *J* = 16.8, 5.6 Hz, 0.5 H), 3.36 (dd, *J* = 16.8, 5.6 Hz, 0.5 H), 4.73–4.85 (m, 1H), 7.38–7.49 (m, 5H), 7.92, 7.95 (2s, 1H), 8.39, 8.48 (2s, 1H) ppm.

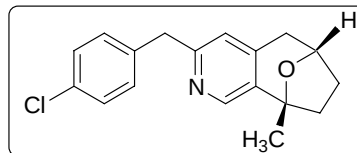
¹³C NMR : δ 21.81 (q), 22.09 (q), 30.37 (t), 30.48 (t), 34.04 (t), 36.97 (t), 42.53 (t), 42.87 (t), 73.83 (d), 74.22 (d), 79.22 (s), 80.00 (s), 114.22 (d), 120.88 (d), 126.22 (s), 126.66 (d), 126.71 (d), 128.61 (d), 139.11 (s), 139.52 (s), 142.35 (s), 144.05 (d), 150.31 (d), 152.84 (s), 155.48 (s), 155.64 (s) ppm.

ESI-MS (*m/z*) : 252.09 [M+1]⁺, 274.07 [M+Na]⁺

Elemental Analysis Calcd.: C, 81.24; H, 6.82; N, 5.57.

Found: C, 81.19; H, 6.59; N, 5.49.

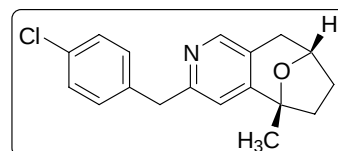
Cyclotrimerization product 4-chloro benzylcyanide (135):



To a solution of dialkyne **95** (100 mg, 0.68 mmol) in dry toluene (10 mL) was added 4-chloro benzylcyanide (205 mg, 1.36 mmol) followed by CpCo(CO)_2 (25 μL , 1.25 M solution in xylenes, 5 mol%) and the reaction mixture was heated to reflux for 8 h. The solvents were removed under reduced pressure and the residue obtained was purified by flash column chromatography (1:1 petroleum ether/ethyl acetate) to give **135** (46 mg, 23%) and **136** (46 mg, 23%) as colorless oil.

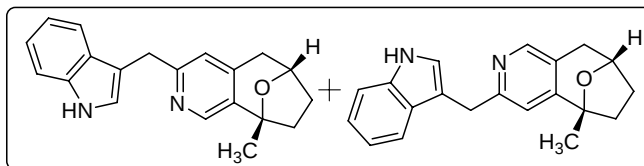
Mol. Formula	: $\text{C}_{18}\text{H}_{18}\text{ClNO}$
$[\alpha]_D$	: -10.6 (c 0.8, CHCl_3).
IR (CHCl_3) $\tilde{\nu}$	: 3400, 2987, 1600, 1216 cm^{-1} .
$^1\text{H NMR}$ (CDCl_3 , 400 MHz)	: δ 1.60–1.68 (m, 1H), 1.74 (s, 3H), 1.88 (dd, $J = 11.7$, 7.5 Hz, 1H), 2.01 (ddd, $J = 11.7$, 9.3, 2.4 Hz, 1H), 2.23–2.32 (m, 1H), 2.42 (d, $J = 17.3$ Hz, 1H), 3.22 (dd, $J = 17.3$, 5.1 Hz, 1H), 4.03 (s, 2H), 4.68–4.72 (m, 1H), 6.79 (s, 1H), 7.17 (d, $J = 8.3$ Hz, 2H), 7.25 (d, $J = 8.3$ Hz, 2H), 8.31 (s, 1H) ppm.
$^{13}\text{C NMR}$ (CDCl_3 , 125 MHz)	: δ 22.19 (q), 30.50 (t), 36.81 (t), 42.86 (t), 43.53 (t), 73.80 (d), 79.18 (s), 123.25 (d), 128.66 (d) 2C, 130.43 (d) 2C, 132.22 (s), 137.55 (s), 137.97 (s), 142.42 (s), 143.84 (d), 158.42 (s) ppm.
ESI-MS (m/z)	: 300.09 $[\text{M}+1]^+$
Elemental Analysis	Calcd.: C, 72.11; H, 6.05; Cl, 11.83; N, 4.67. Found: C, 72.09; H, 6.11; Cl, 11.56; N, 4.49.

Cyclotrimerization product 4-chloro benzylcyanide (136):



Mol. Formula	: C ₁₈ H ₁₈ ClNO
[α]_D	: +4.5 (c 0.7, CHCl ₃).
IR (CHCl₃) $\tilde{\nu}$	: 3401, 2976, 1602, 1216 cm ⁻¹ .
¹H NMR (CDCl ₃ , 400 MHz)	: δ 1.64 (s, 3H), 1.67–1.71 (m, 1H), 1.84 (dd, <i>J</i> = 11.7, 7.5 Hz, 1H), 1.96 (ddd, <i>J</i> = 11.7, 9.5, 2.6 Hz, 1H), 2.23–2.30 (m, 1H), 2.49 (d, <i>J</i> = 16.5 Hz, 1H), 3.25 (dd, <i>J</i> = 17.5, 5.1 Hz, 1H), 4.05 (s, 2H), 4.75–4.78 (m, 1H), 6.68 (s, 1H), 7.17 (d, <i>J</i> = 8.3 Hz, 2H), 7.25 (d, <i>J</i> = 8.3 Hz, 2H), 8.24 (s, 1H) ppm.
¹³C NMR (CDCl ₃ , 100 MHz)	: δ 21.79 (q), 30.39 (t), 33.97 (t), 42.55 (t), 43.70 (t), 74.27 (d), 79.87 (s), 125.42 (s), 128.63 (d) 2C, 130.28 (d) 2C, 130.86 (d), 132.15 (s), 138.18 (s), 150.16 (d), 152.93 (s), 157.96 (s) ppm.
ESI-MS (<i>m/z</i>)	: 300.13 [M+1] ⁺
Elemental Analysis	Calcd.: C, 72.11; H, 6.05; Cl, 11.83; N, 4.67. Found: C, 72.22; H, 6.02; Cl, 11.72; N, 4.62.

Cyclotrimerization product of indole-3-acetonitrile (138/139):



To a solution of dialkyne **95** (100 mg, 0.68 mmol) in dry toluene (10 mL) was added indole-3-acetonitrile (212 mg, 1.36 mmol) followed by CpCo(CO)₂ (25 μL, 1.25 M solution in xylenes, 5 mol%) and the reaction mixture was heated to reflux for 5 h. The solvents were removed under reduced pressure and the residue obtained was purified by flash column chromatography (3:7 petroleum ether/ethyl acetate) to give **138/139** (80 mg, 39%) as colorless oil.

Mol. Formula	: C ₂₀ H ₂₀ N ₂ O
IR (CHCl₃) $\tilde{\nu}$	: 3401, 2976, 1602, 1216 cm ⁻¹ .
¹H NMR (CDCl ₃ , 400 MHz)	: δ 1.60, 1.72 (2s, 3H), 1.64–1.70 (m, 1H), 1.80–1.94 (m, 2H), 2.22–2.31 (m, 1H), 2.39, 2.50 (2d, <i>J</i> = 17.4 Hz, 1H),

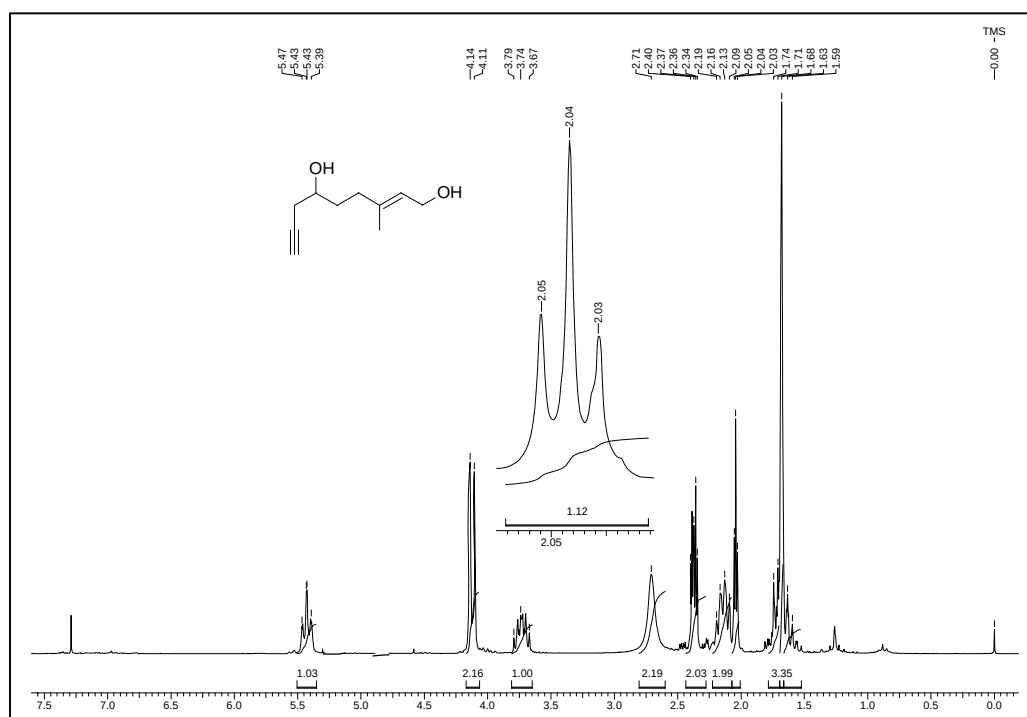
3.17–3.29 (m, 1H), 4.25 (s, 2H), 4.68–4.79 (m, 1H), 6.91, 7.00 (s, 1H), 7.05–7.09 (m, 1H), 7.13–7.20 (m, 1H), 7.34–7.37 (m, 1H), 7.52–7.55 (m, 1H), 7.70 (dd, $J = 5.6, 3.4$ Hz, 1H), 8.19–8.26 (m, 1H), 8.34 (br s, 1H) ppm.

^{13}C NMR : δ 22.66 (q), 22.96 (q), 30.35 (t), 31.90 (t), 33.59 (t), 33.97 (t), 36.87 (t), 38.72 (t), 42.47 (t), 42.84 (t), 73.84 (d), 74.26 (d), 77.20 (d), 79.22 (s), 111.13 (d), 113.57 (d), 113.95 (d), 116.61 (d), 119.12 (d), 119.44 (d), 122.05 (d), 122.80 (d), 123.19 (d), 127.40 (s), 128.79 (d), 130.24 (s), 130.87 (d), 132.44 (s), 136.39 (s), 139.28 (s), 140.36 (s), 142.95 (d), 149.36 (d) ppm.

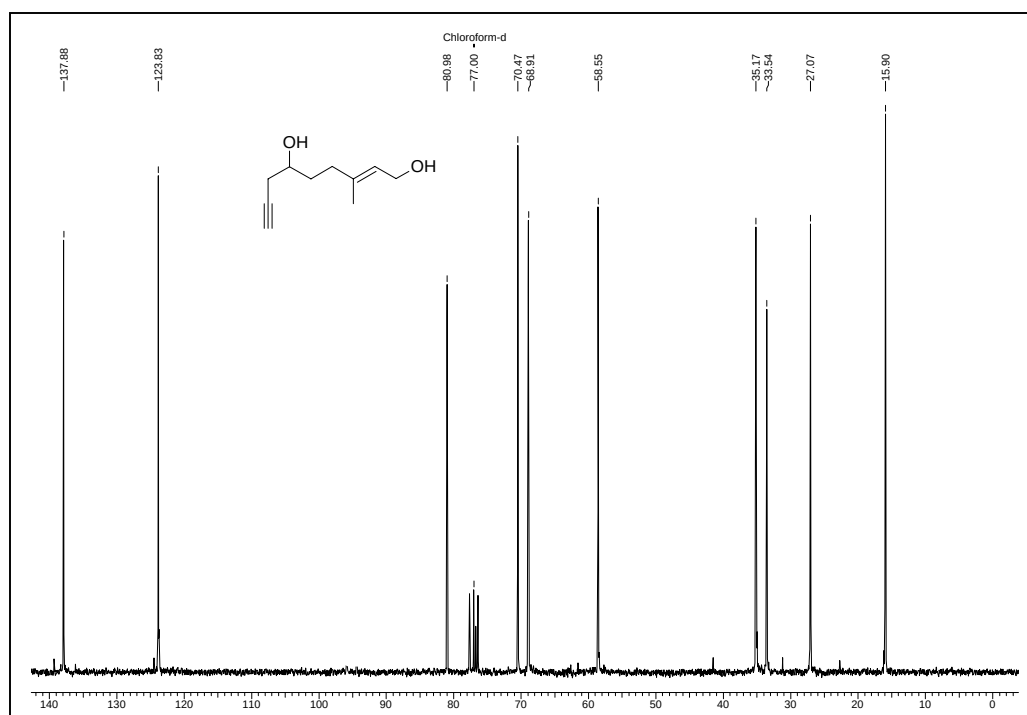
ESI-MS (m/z) : 305.18 $[\text{M}+1]^+$

Elemental Analysis Calcd.: C, 83.13; H, 6.98; N, 4.62.
Found: C, 83.22; H, 6.81; N, 4.55.

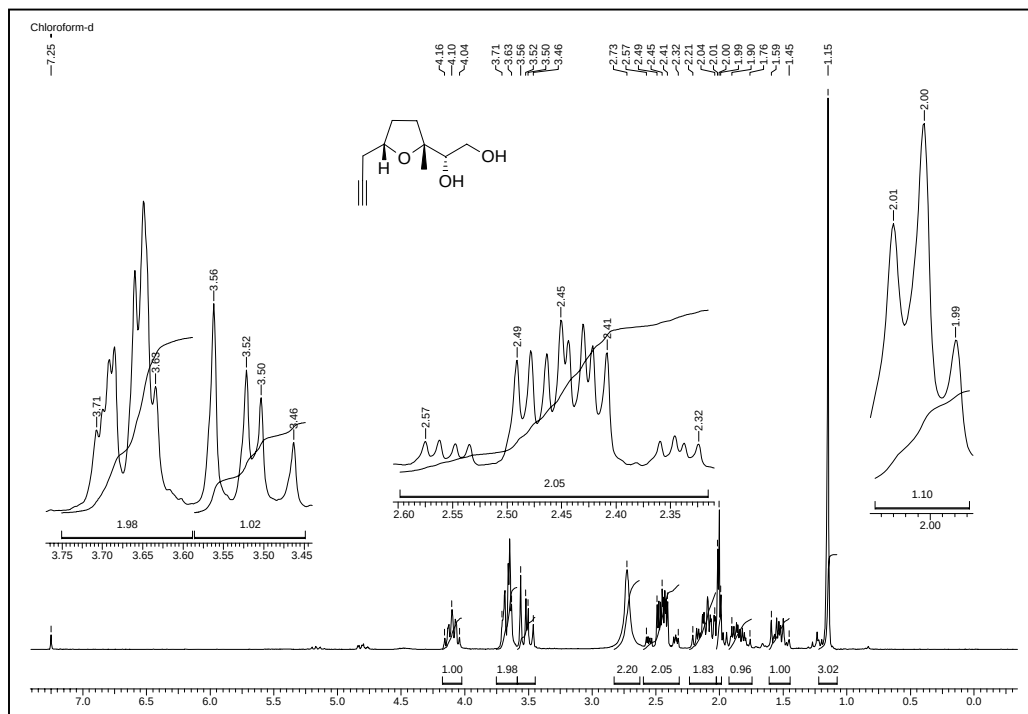
Spectra



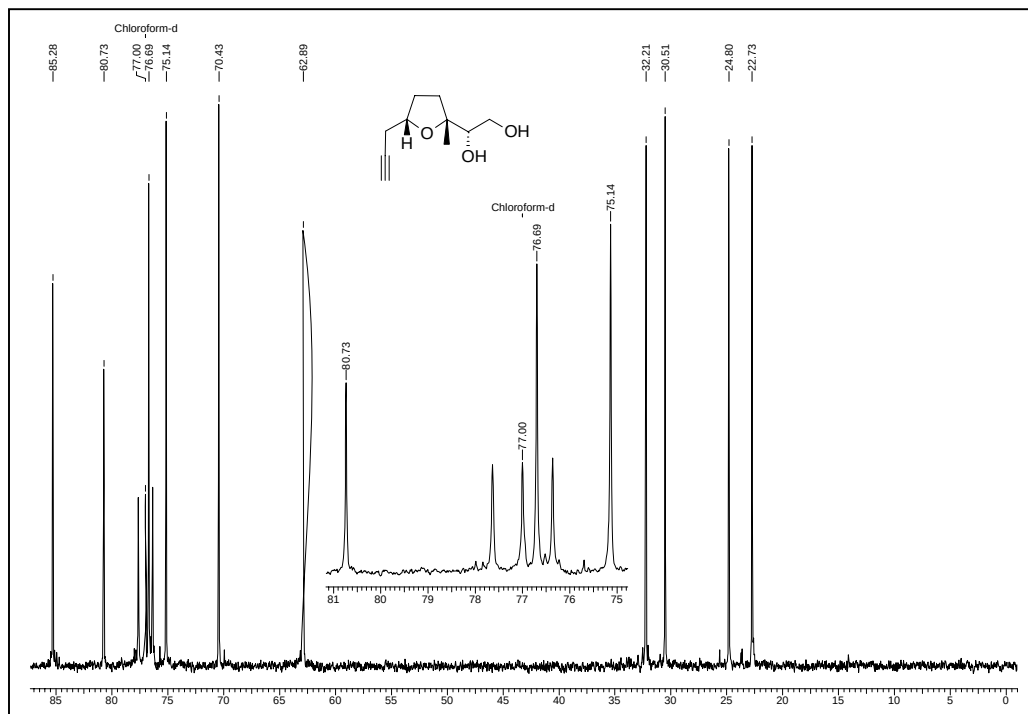
¹H NMR Spectrum of 97 in CDCl₃



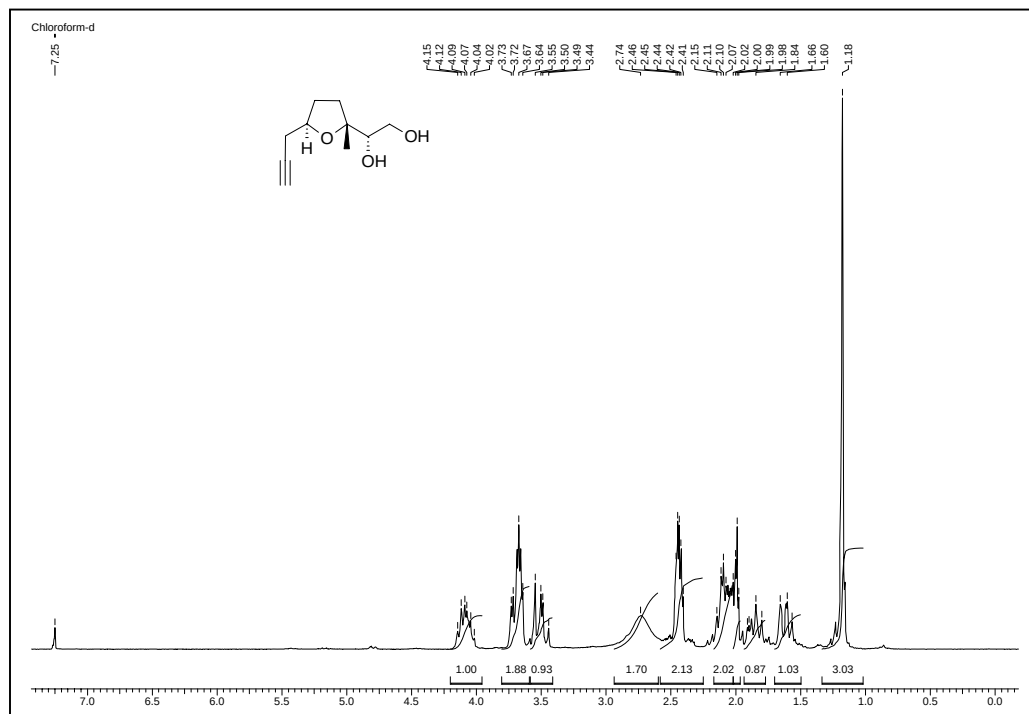
¹³C NMR Spectrum of 97 in CDCl₃



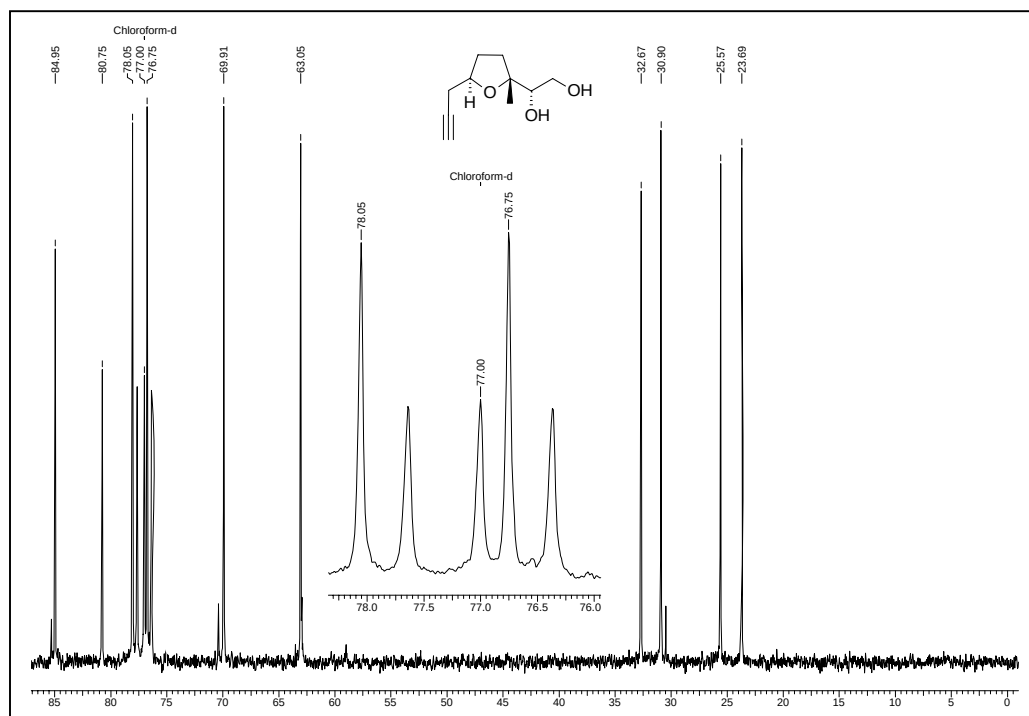
^1H NMR Spectrum of 96 in CDCl_3



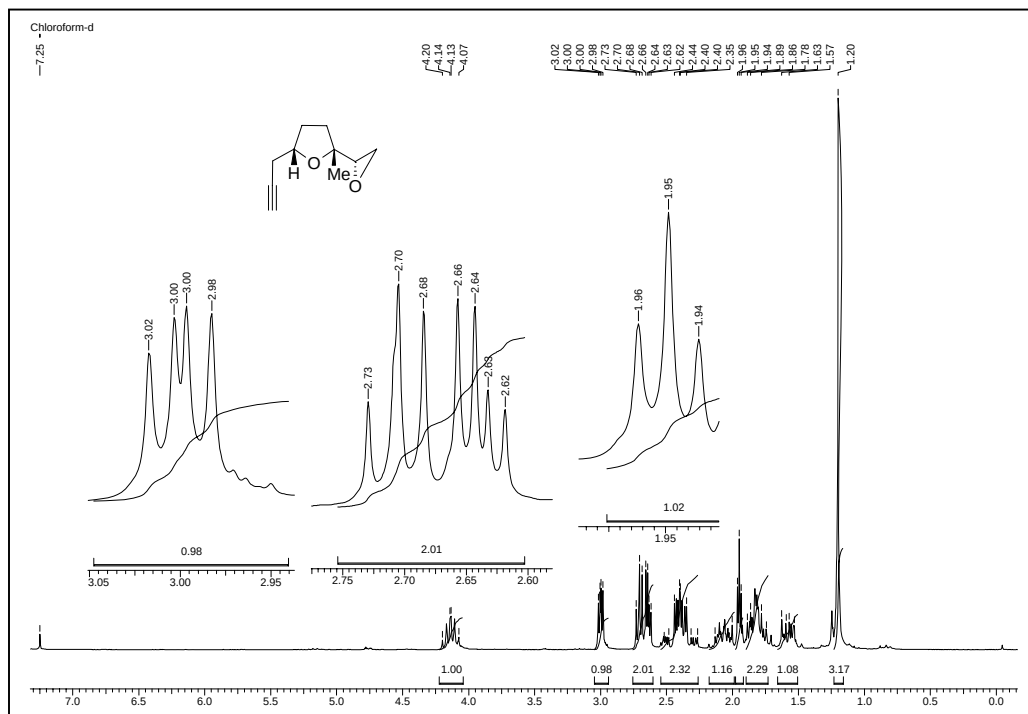
^{13}C NMR Spectrum of 96 in CDCl_3



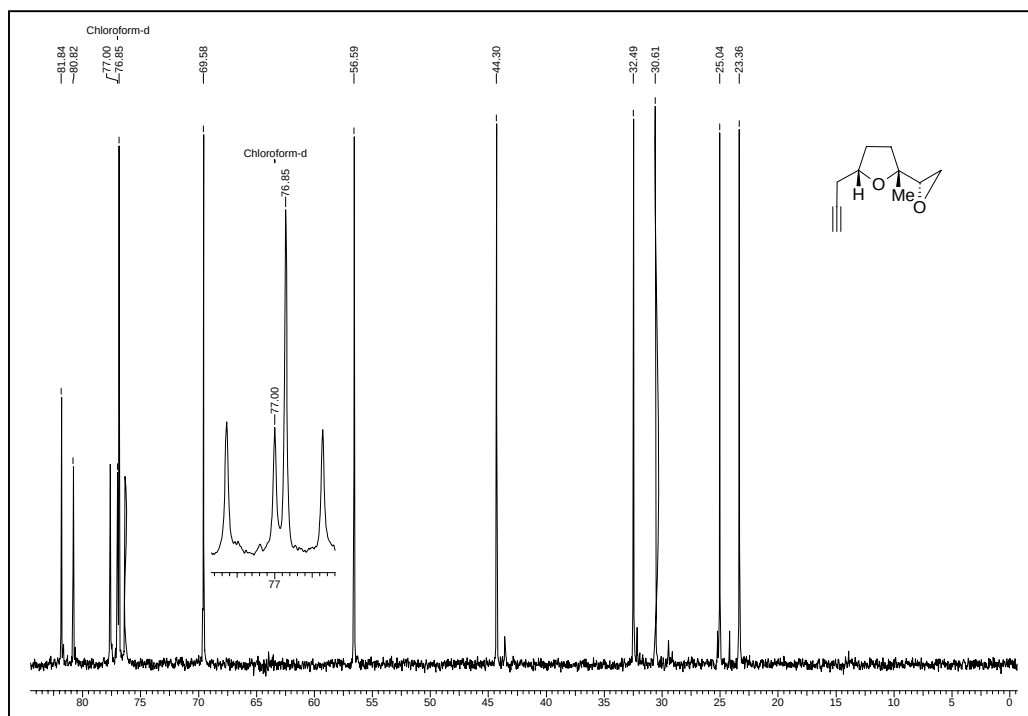
¹H NMR Spectrum of 102 in CDCl₃



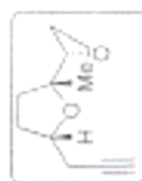
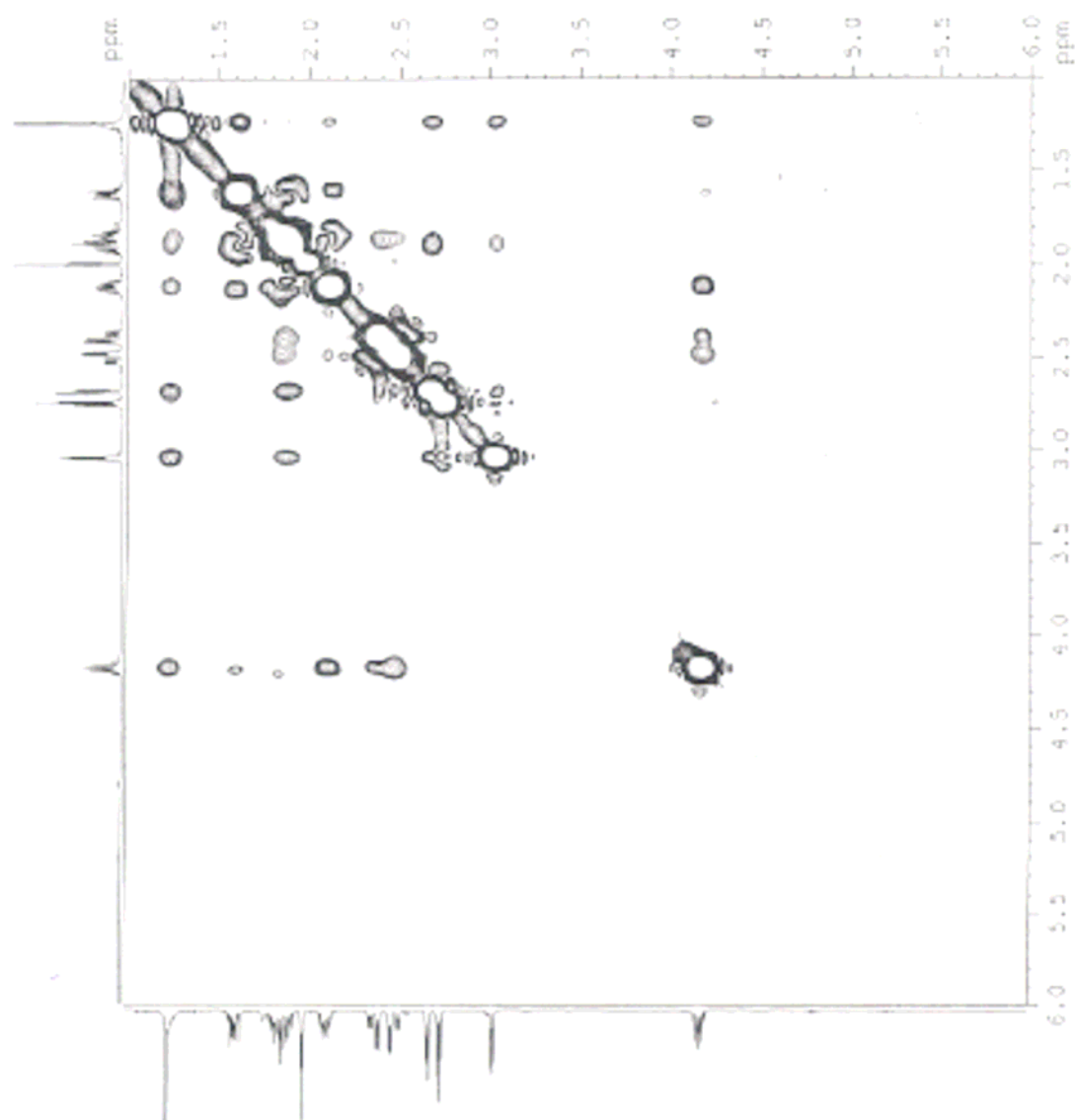
¹³C NMR Spectrum of 102 in CDCl₃



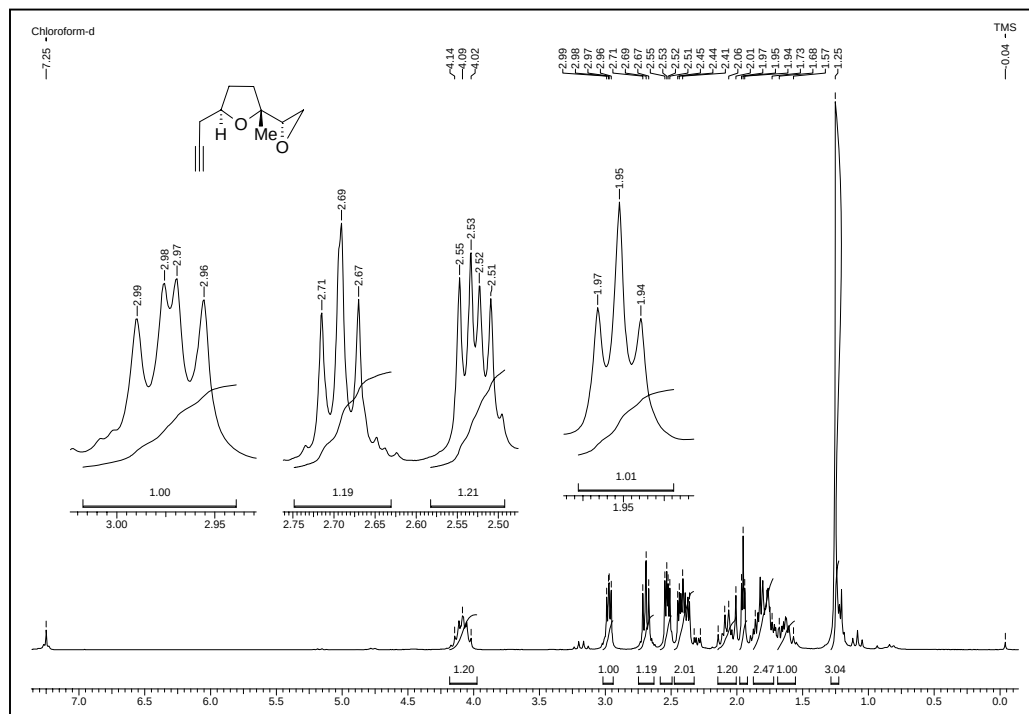
^1H NMR Spectrum of 103 in CDCl_3



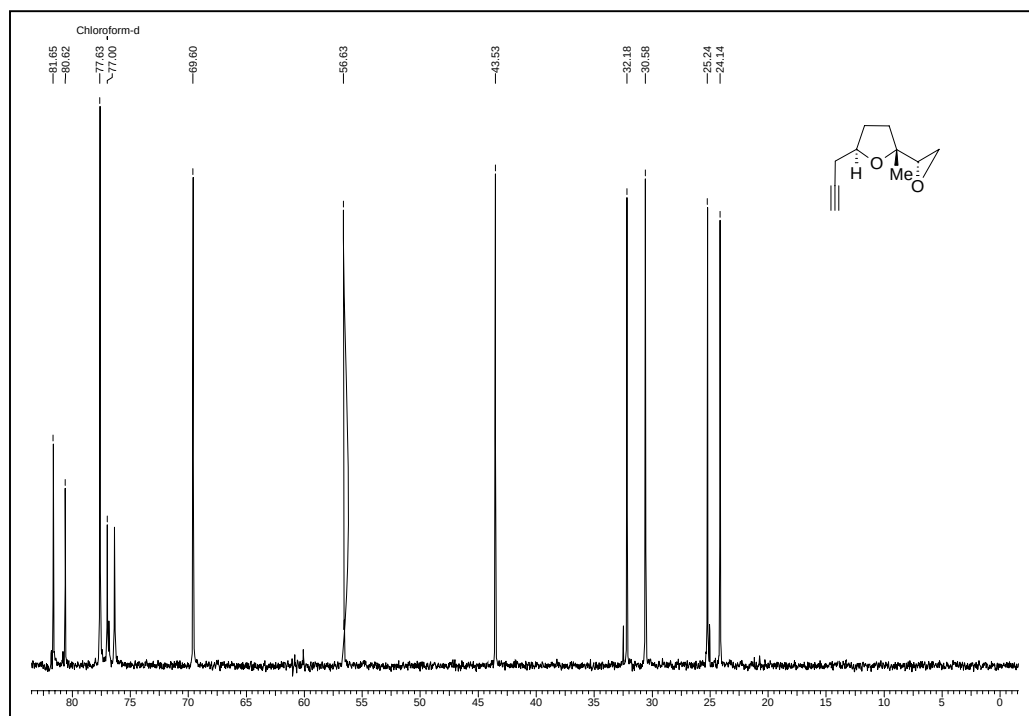
^{13}C NMR Spectrum of 103 in CDCl_3



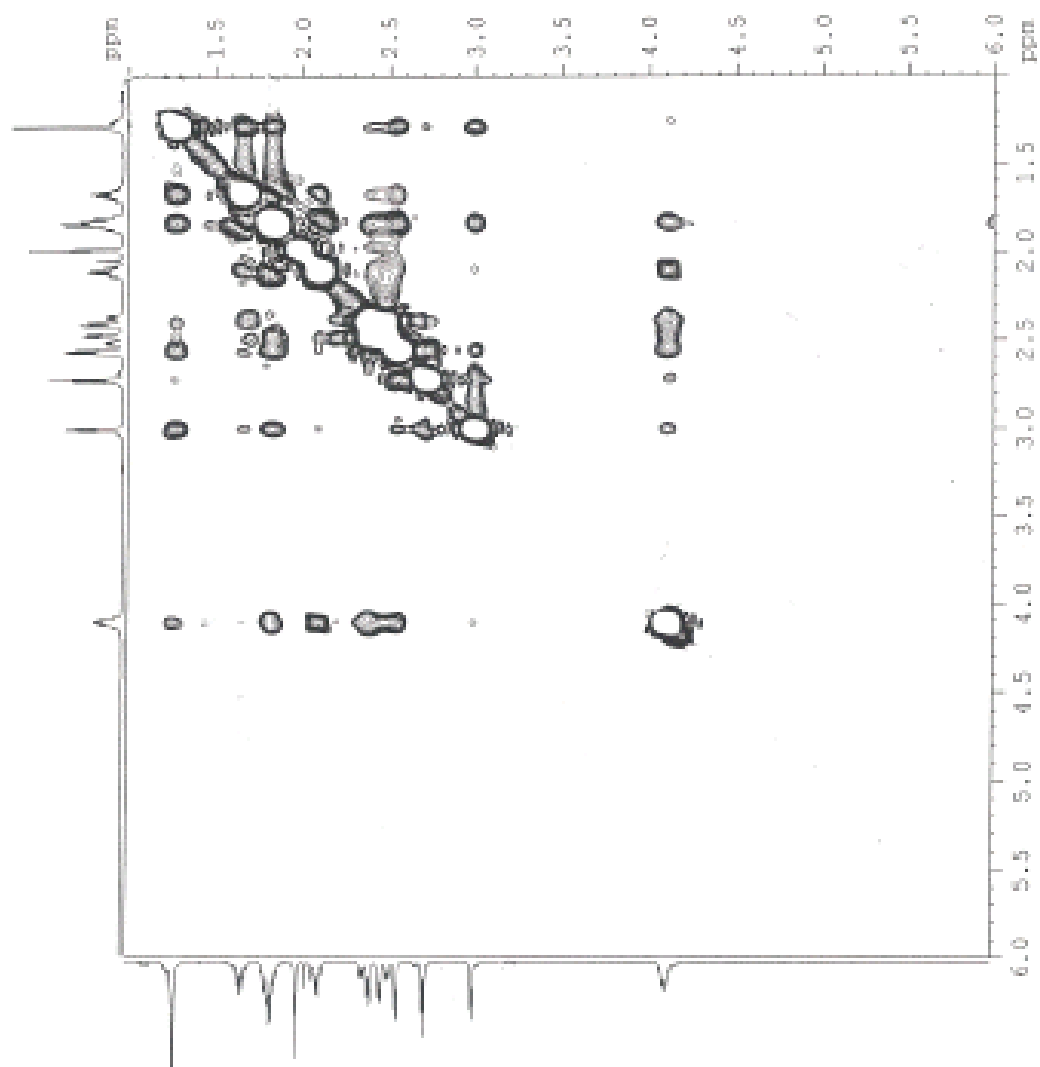
NOESY of compound 103



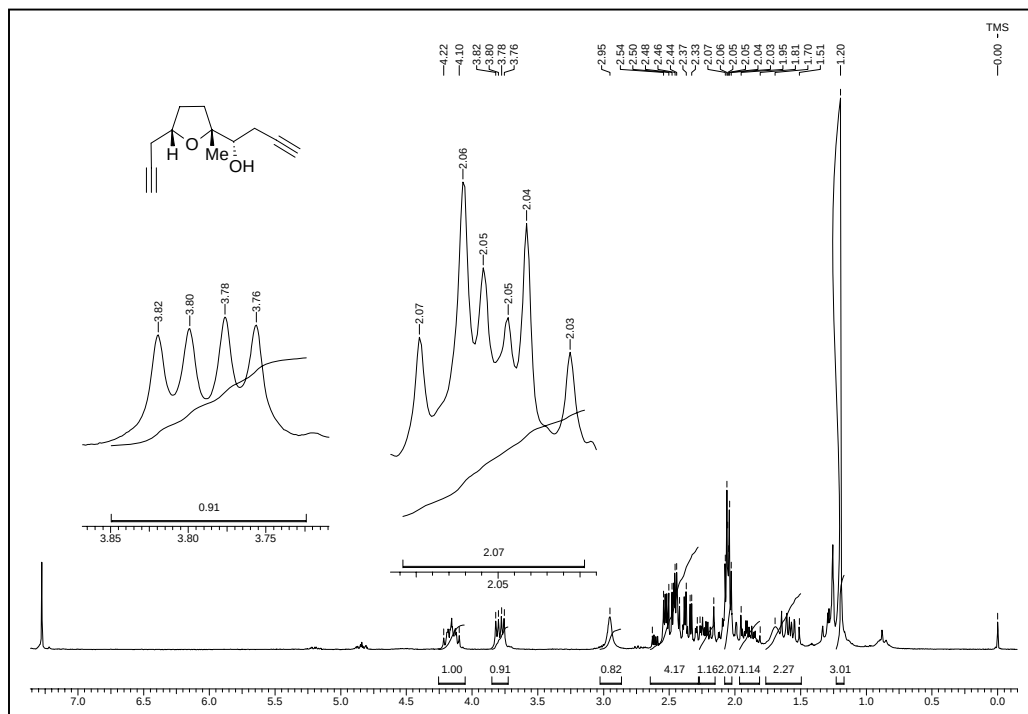
¹H NMR Spectrum of 104 in CDCl₃



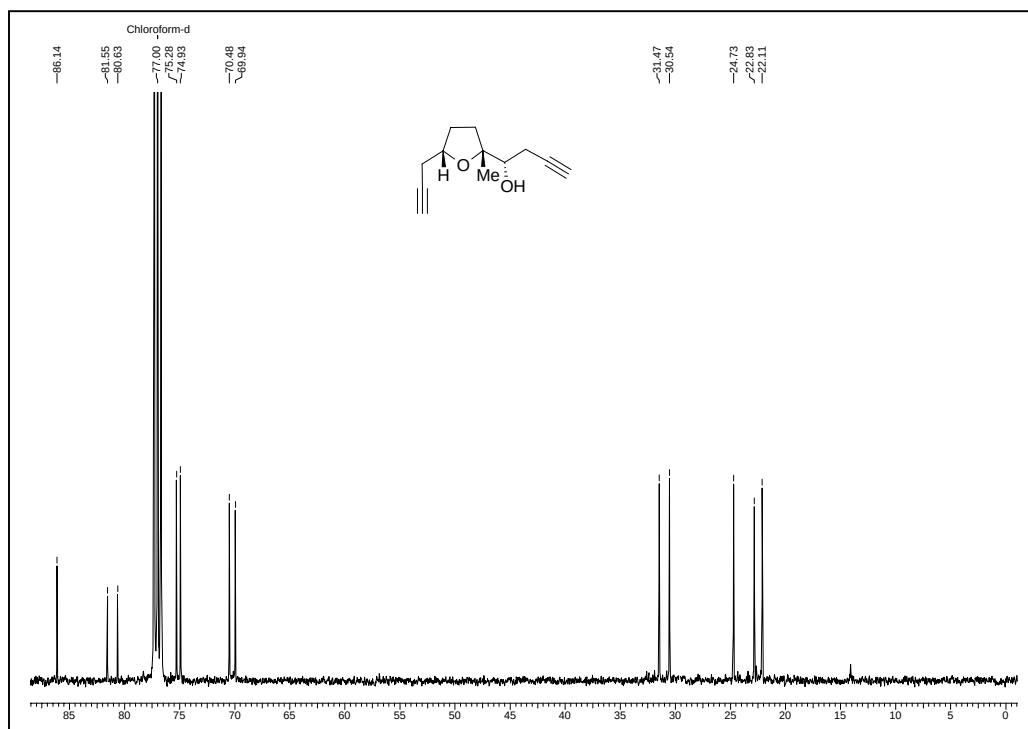
¹³C NMR Spectrum of 104 in CDCl₃



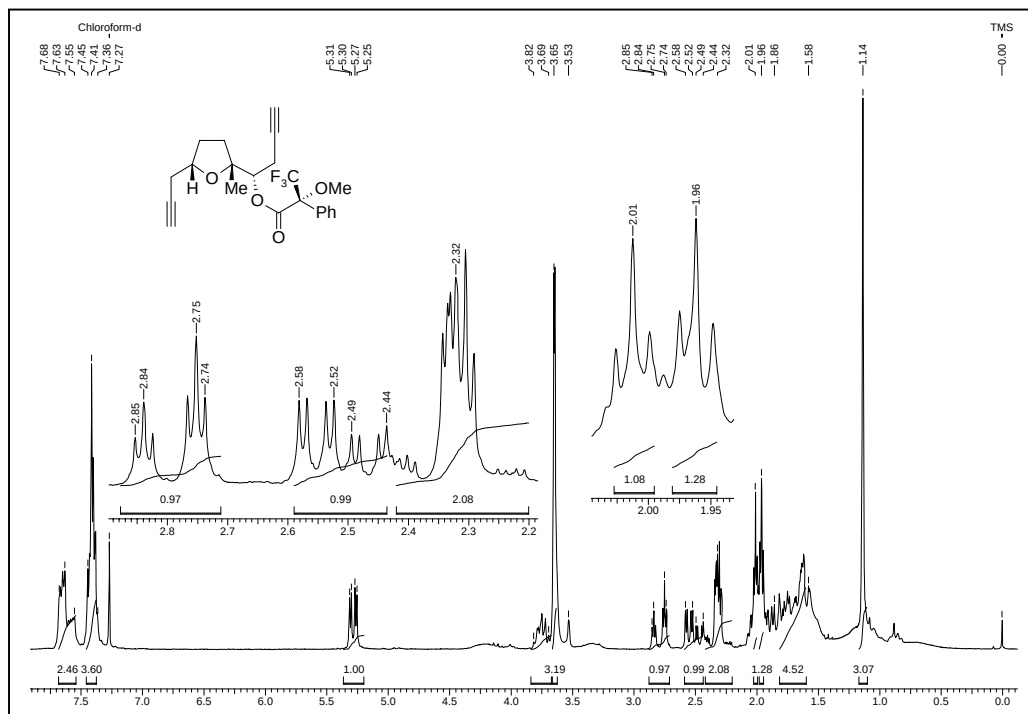
NOESY of compound 104



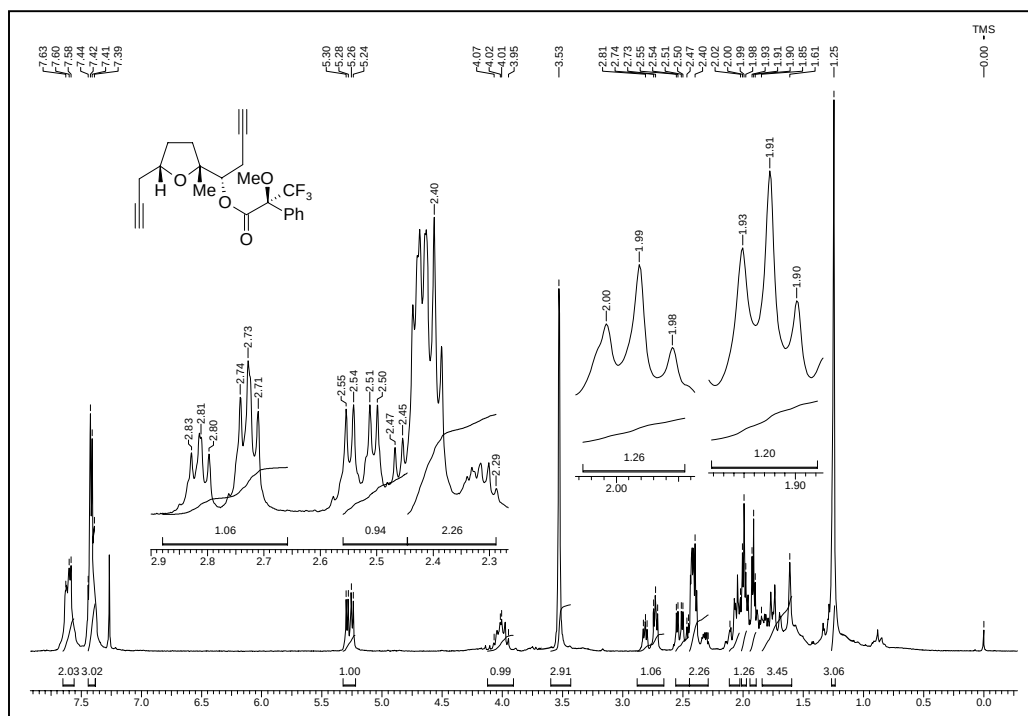
¹H NMR Spectrum of 105 in CDCl₃



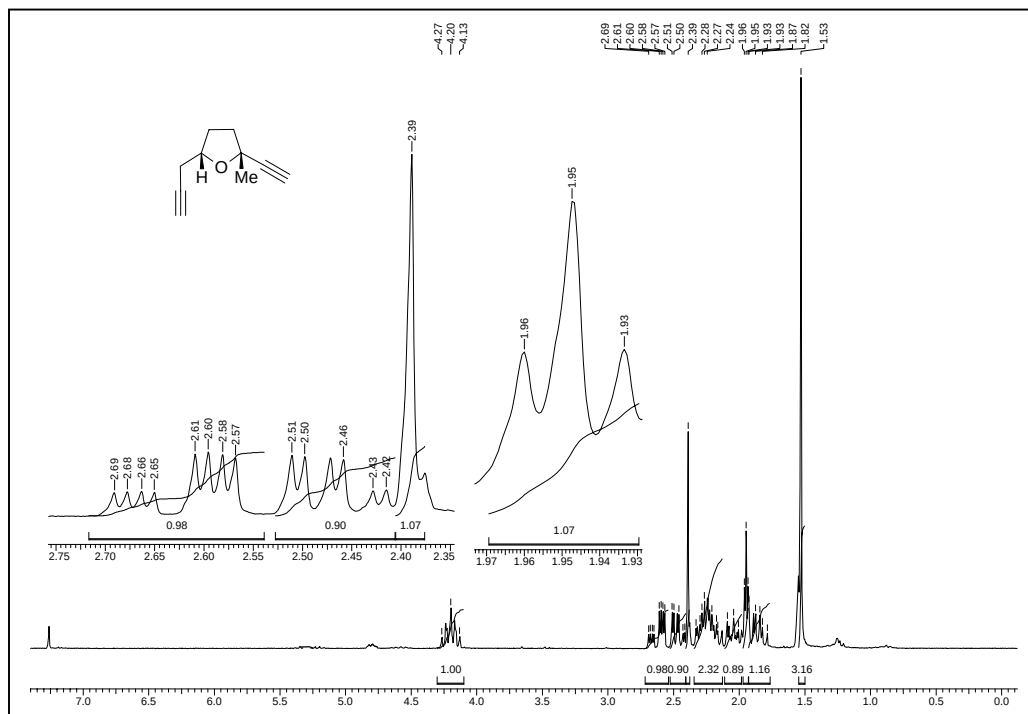
¹³C NMR Spectrum of 105 in CDCl₃



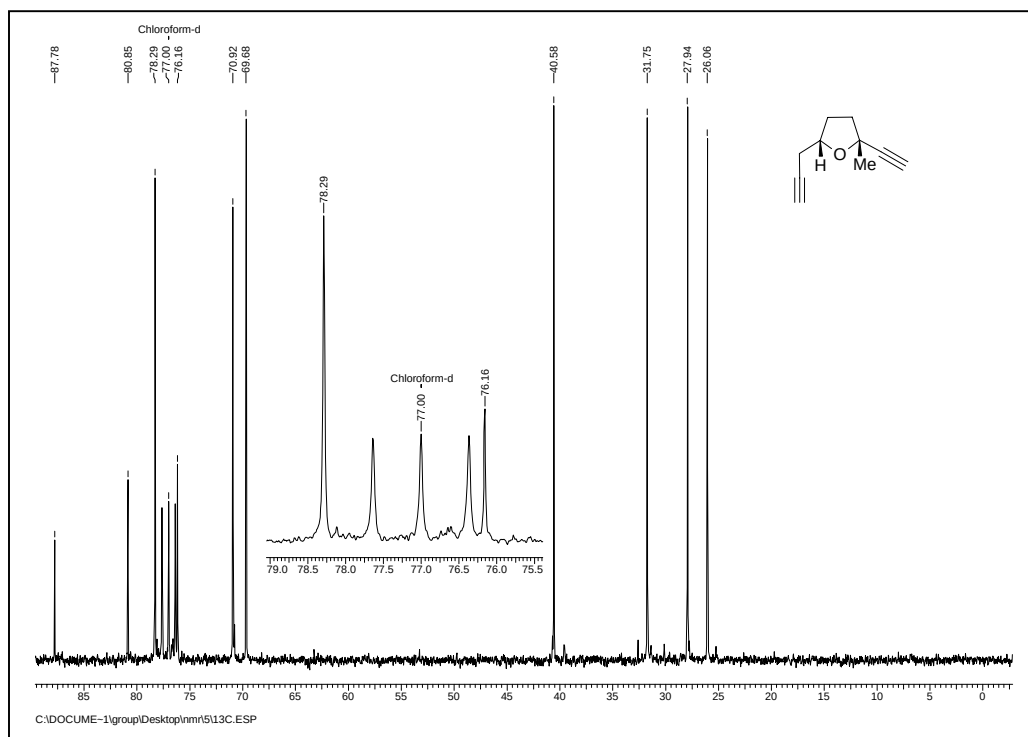
^1H NMR Spectrum of 106 in CDCl₃



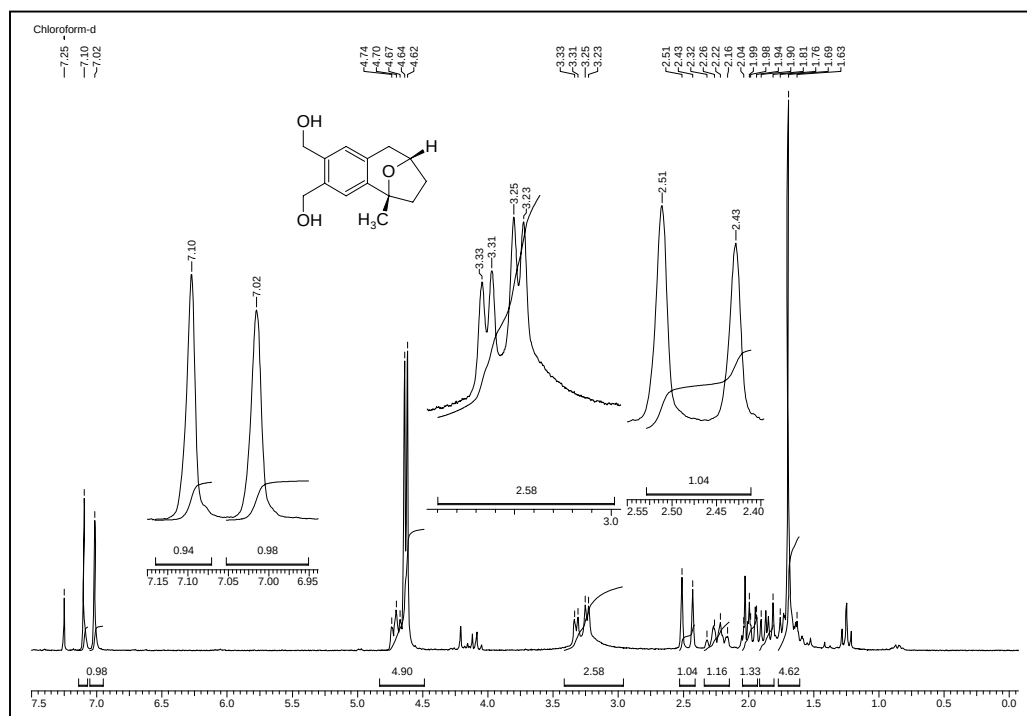
^1H NMR Spectrum of 107 in CDCl₃



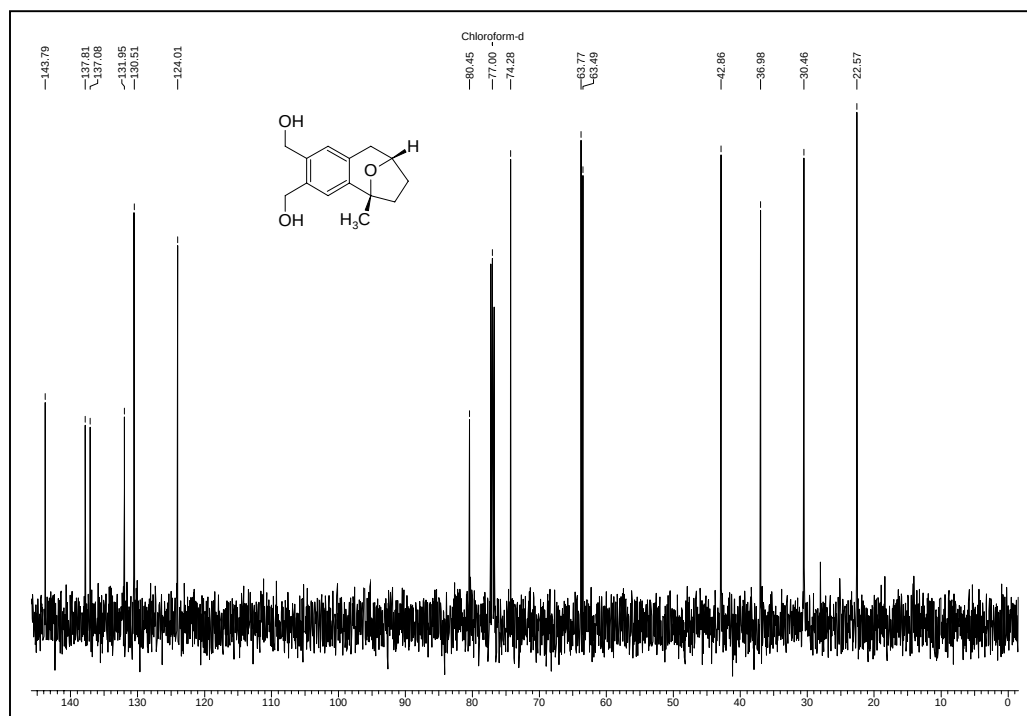
¹H NMR Spectrum of 95 in CDCl₃



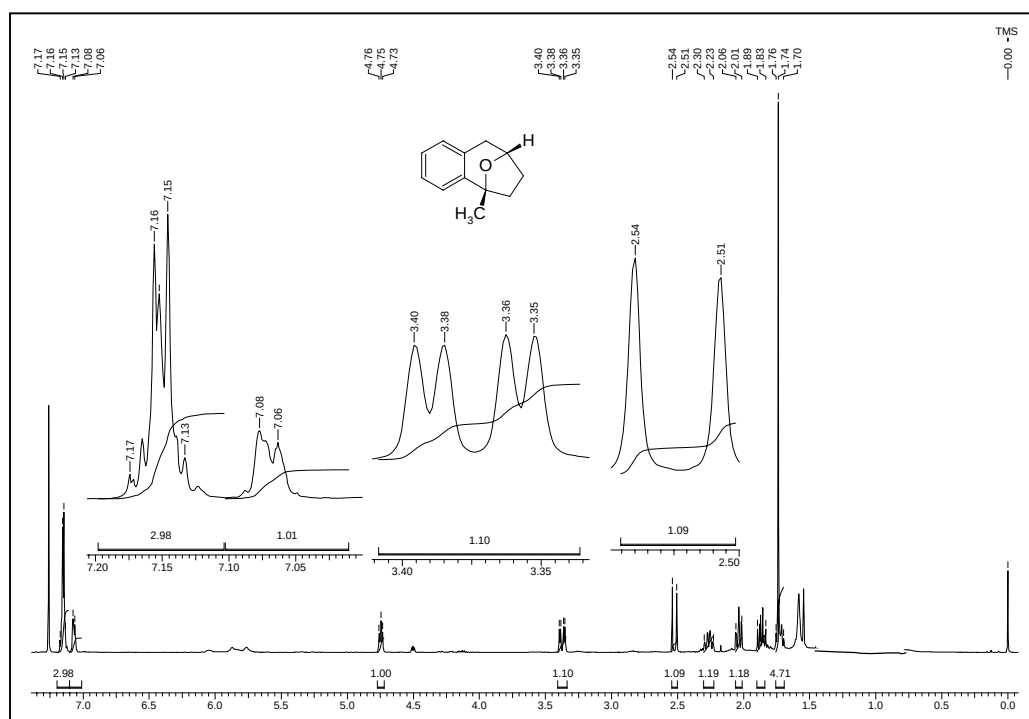
¹³C NMR Spectrum of 95 in CDCl₃



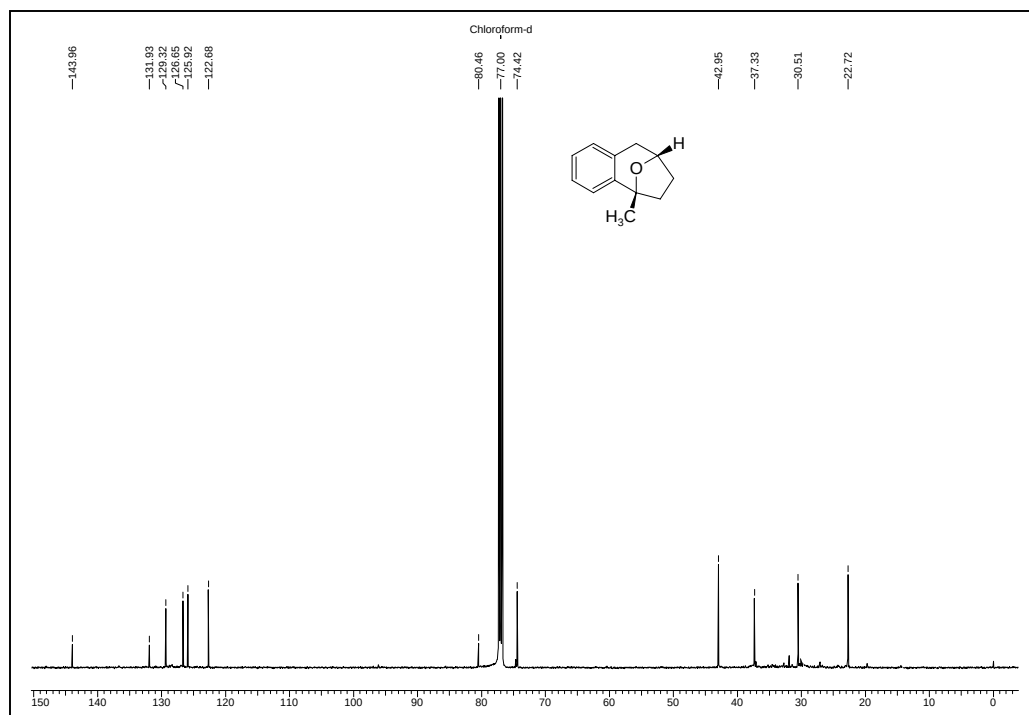
^1H NMR Spectrum of 108 in CDCl_3



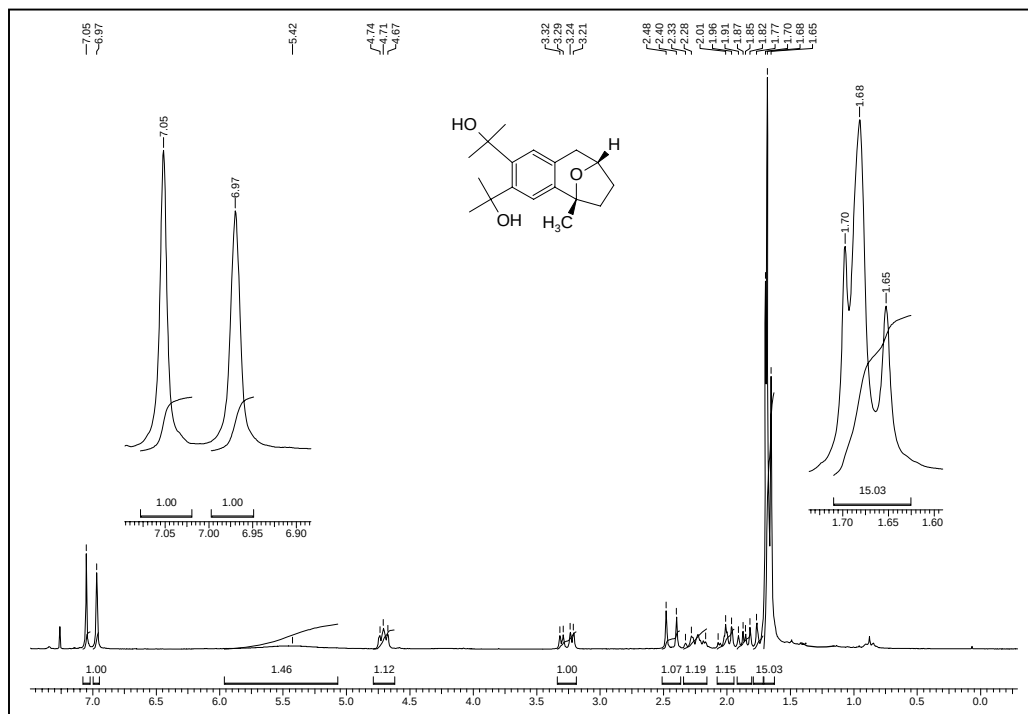
^{13}C NMR Spectrum of 108 in CDCl_3



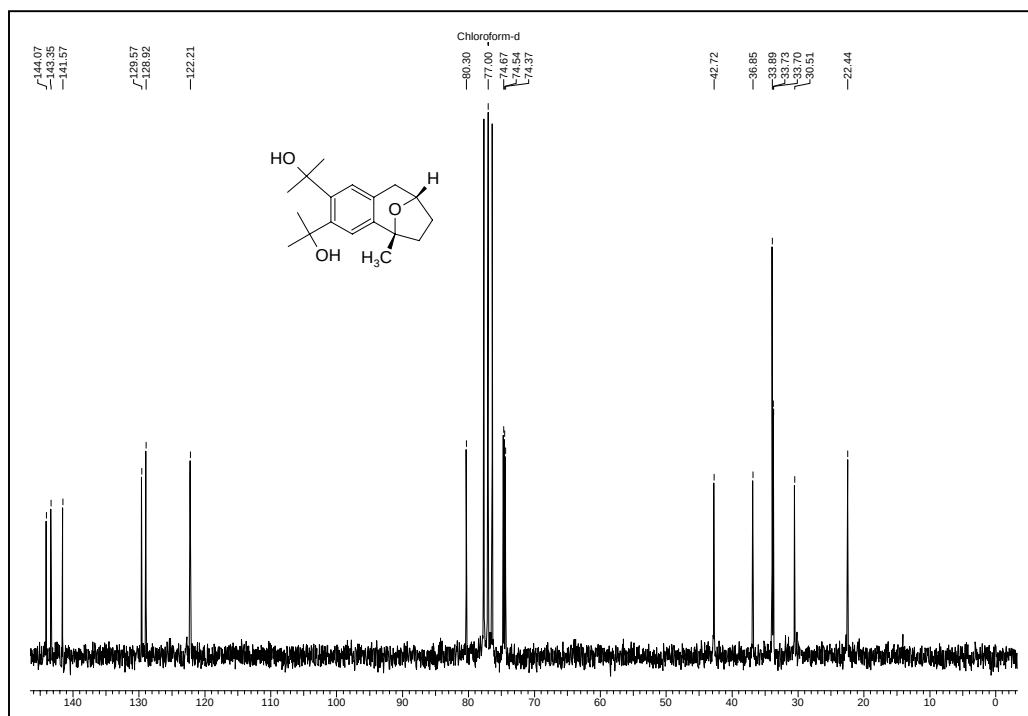
¹H NMR Spectrum of 111 in CDCl₃



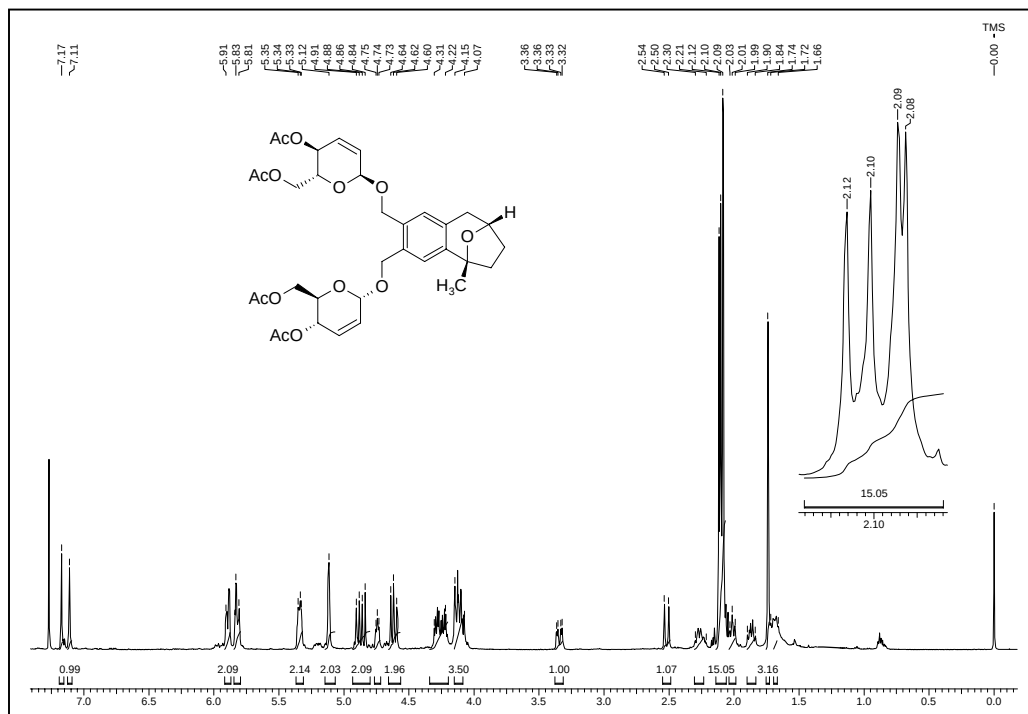
¹³C NMR Spectrum of 111 in CDCl₃



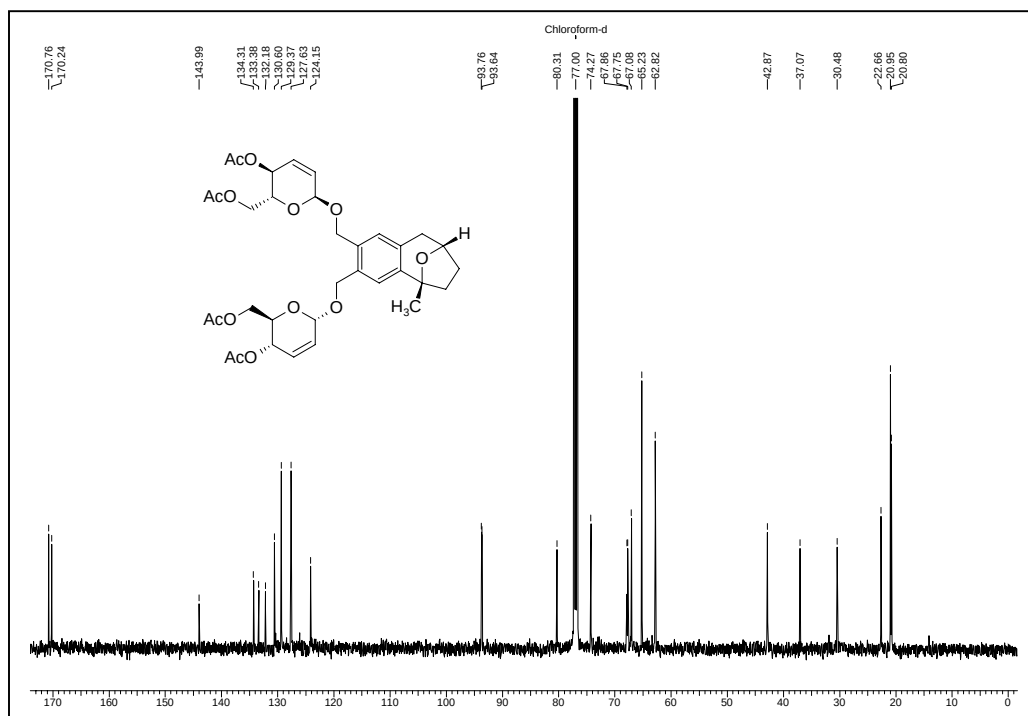
¹H NMR Spectrum of 114 in CDCl₃



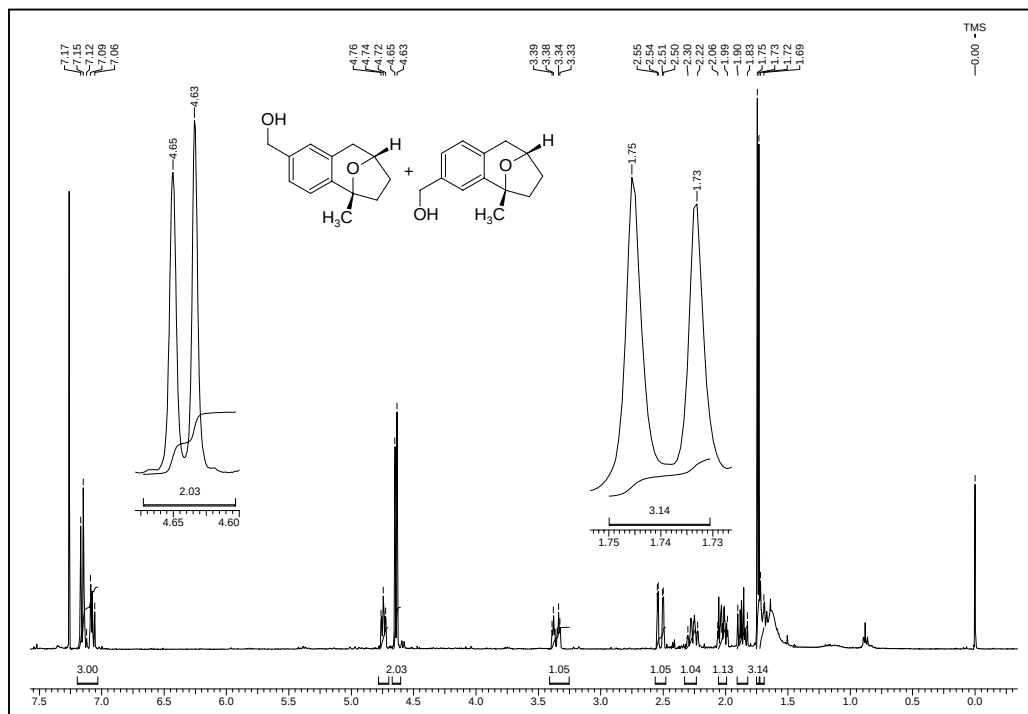
¹³C NMR Spectrum of 114 in CDCl₃



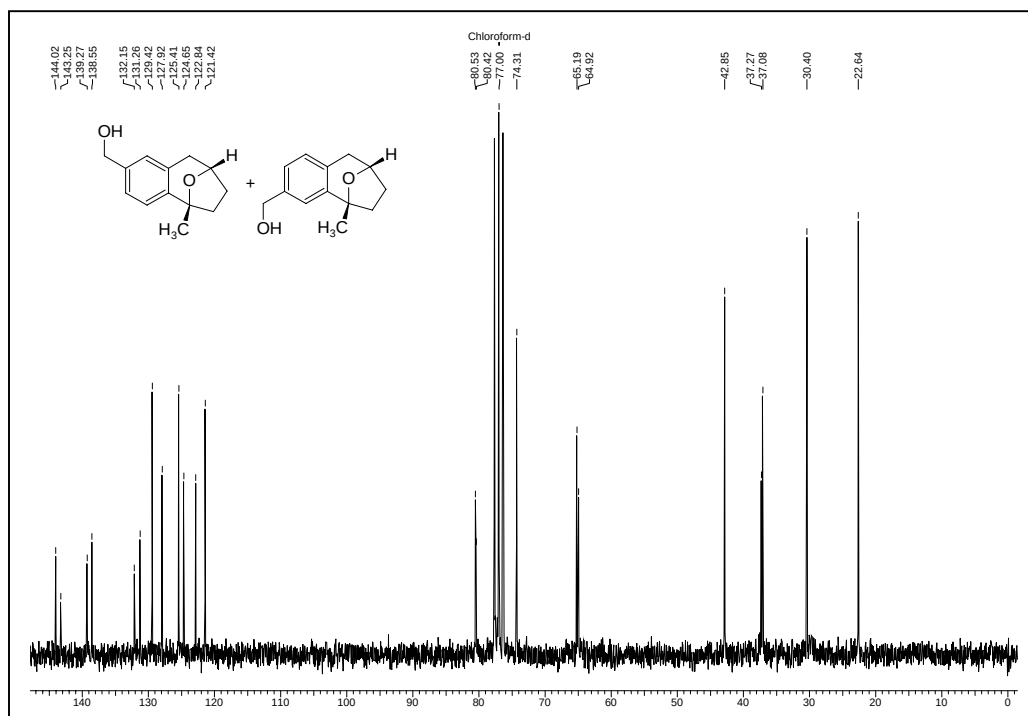
¹H NMR Spectrum of 116 in CDCl₃



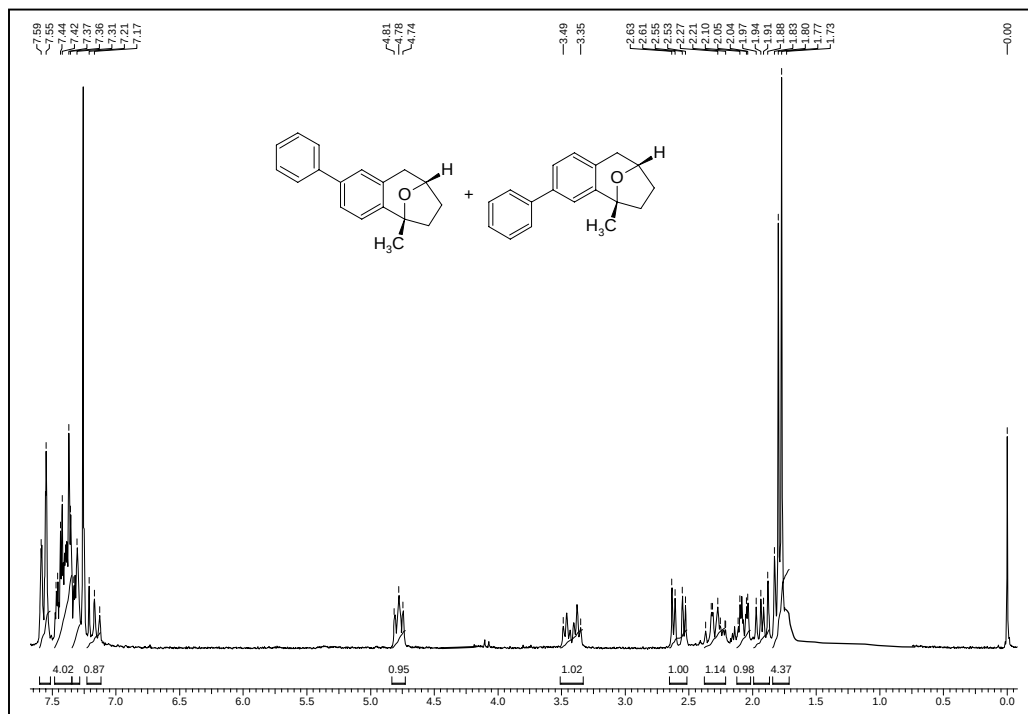
¹³C NMR Spectrum of 116 in CDCl₃



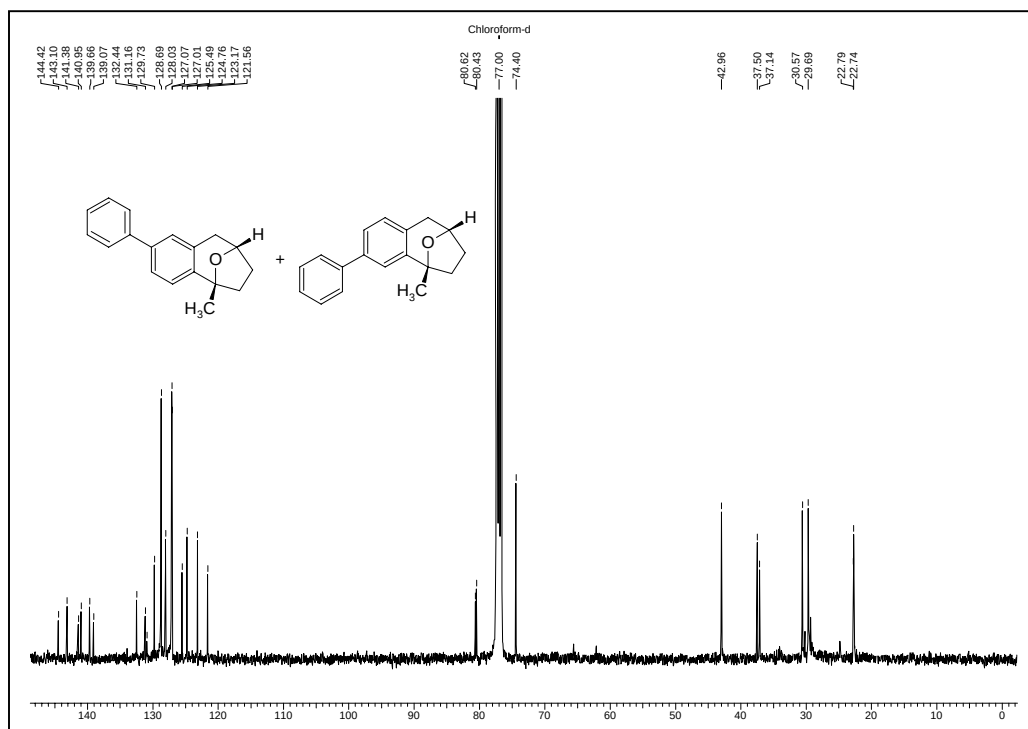
¹H NMR Spectrum of 118/119 in CDCl₃



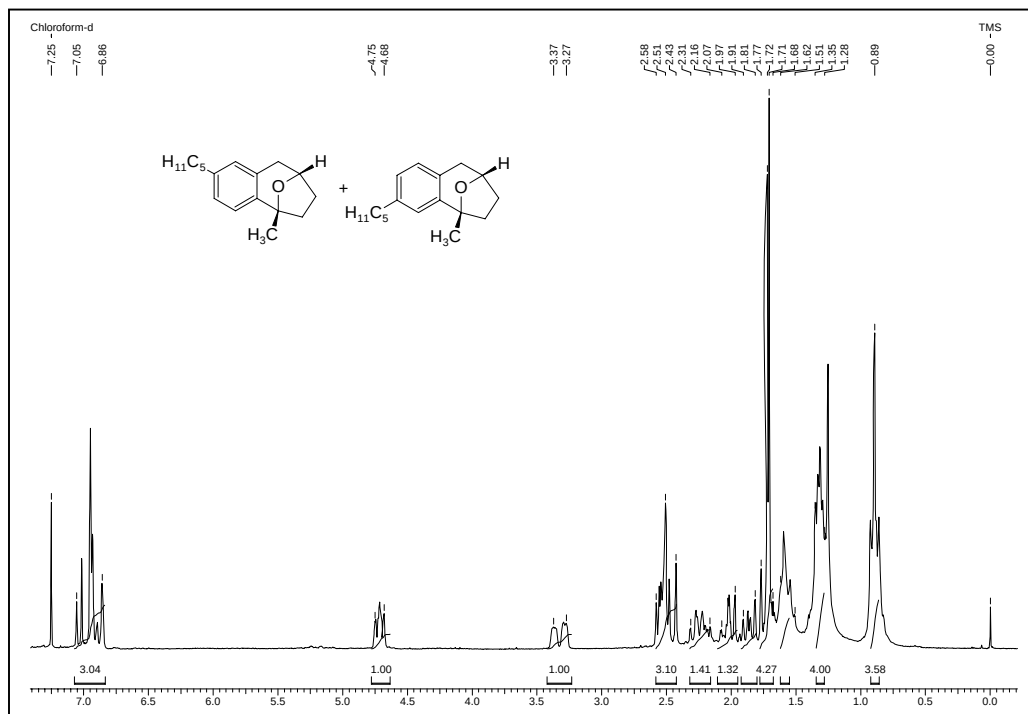
¹³C NMR Spectrum of 118/119 in CDCl₃



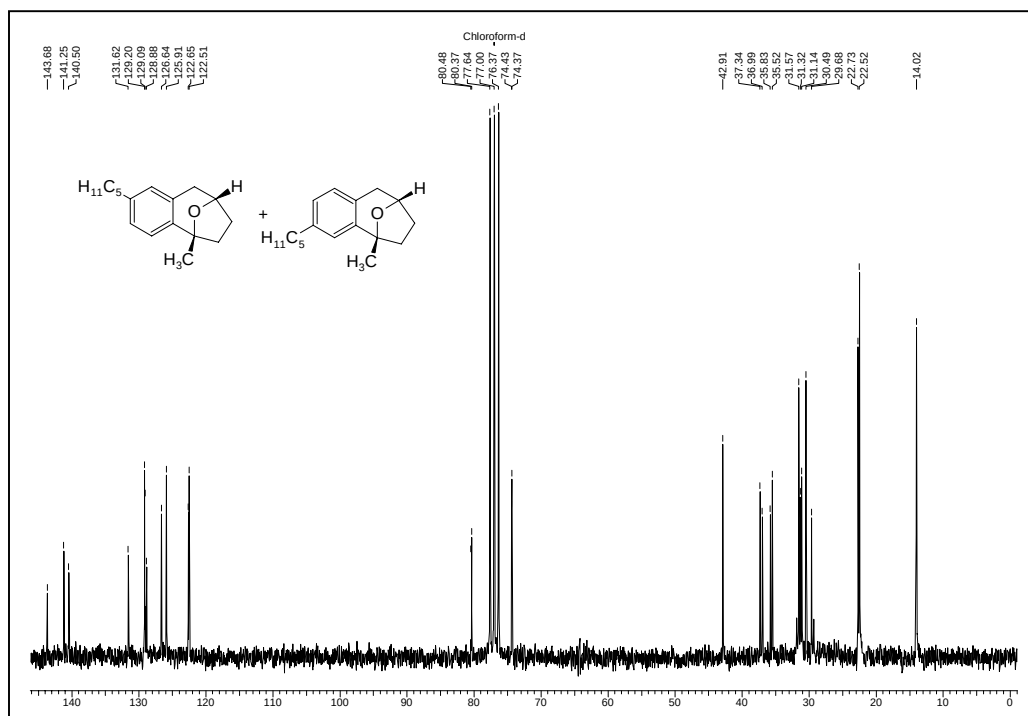
¹H NMR Spectrum of 121/122 in CDCl₃



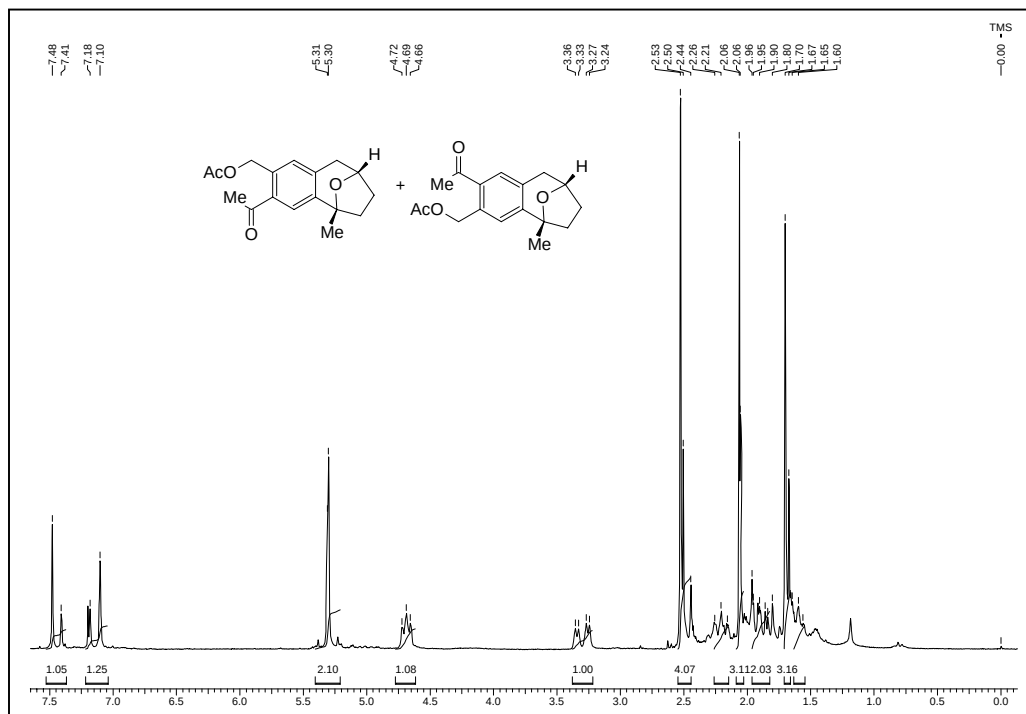
¹³C NMR Spectrum of 121/122 in CDCl₃



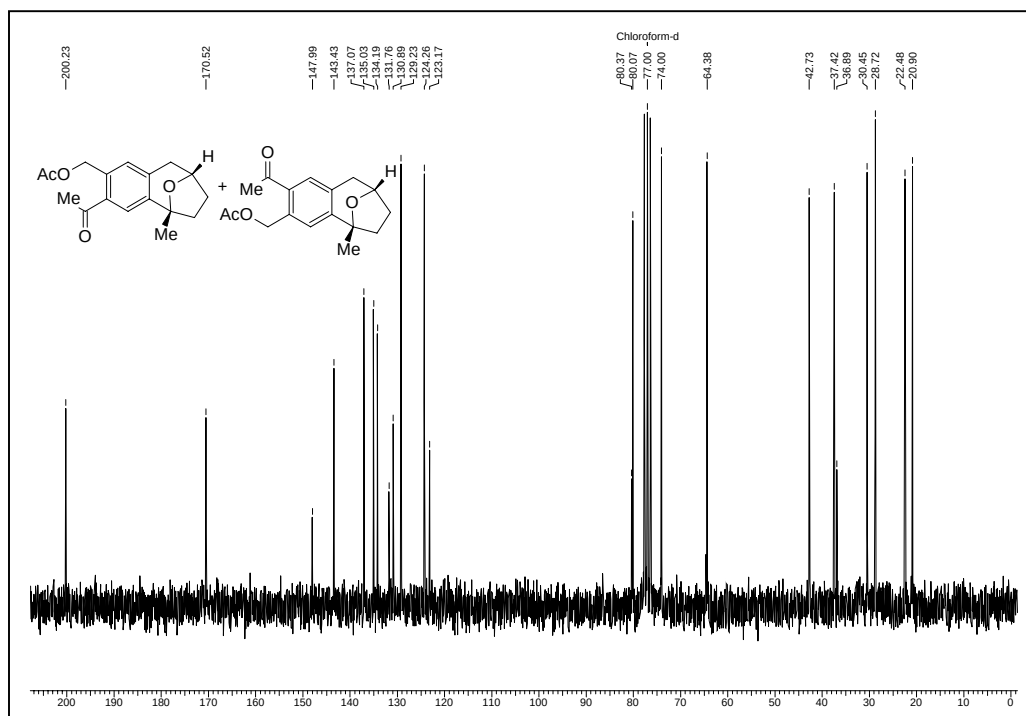
¹H NMR Spectrum of 124/125 in CDCl₃



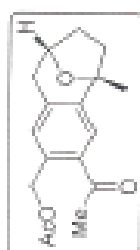
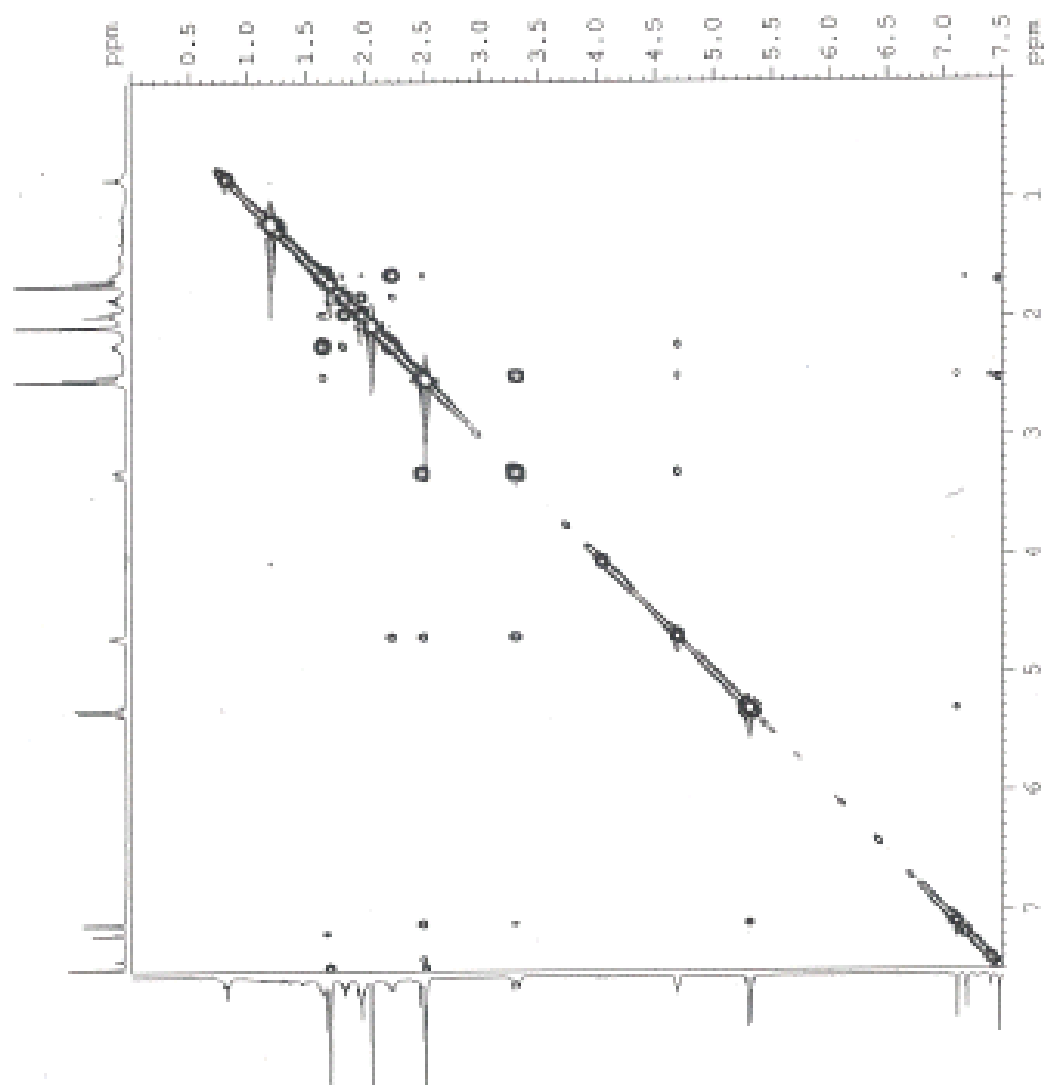
^{13}C NMR Spectrum of 124/125 in CDCl_3



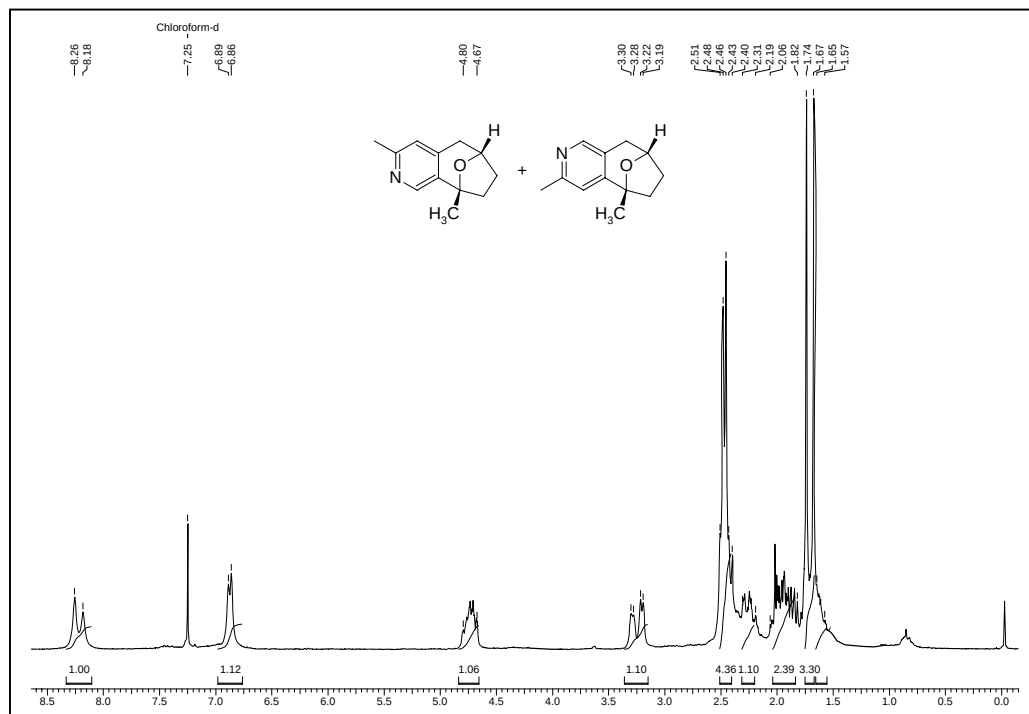
¹H NMR Spectrum of 127/128 in CDCl₃



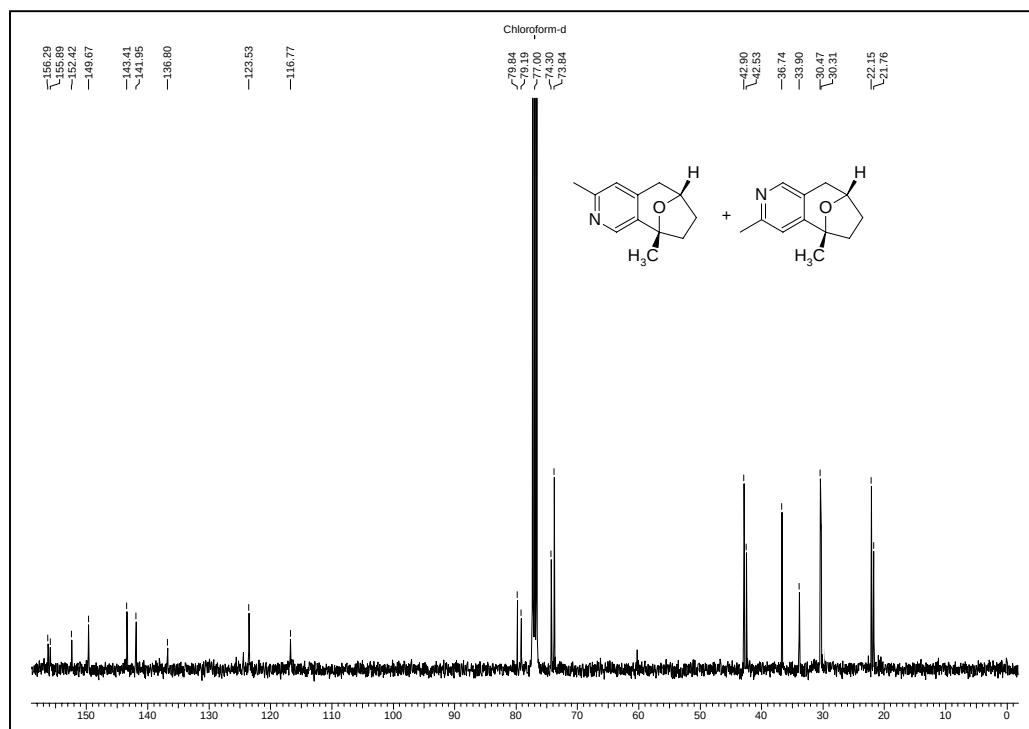
¹³C NMR Spectrum of 127/128 in CDCl₃



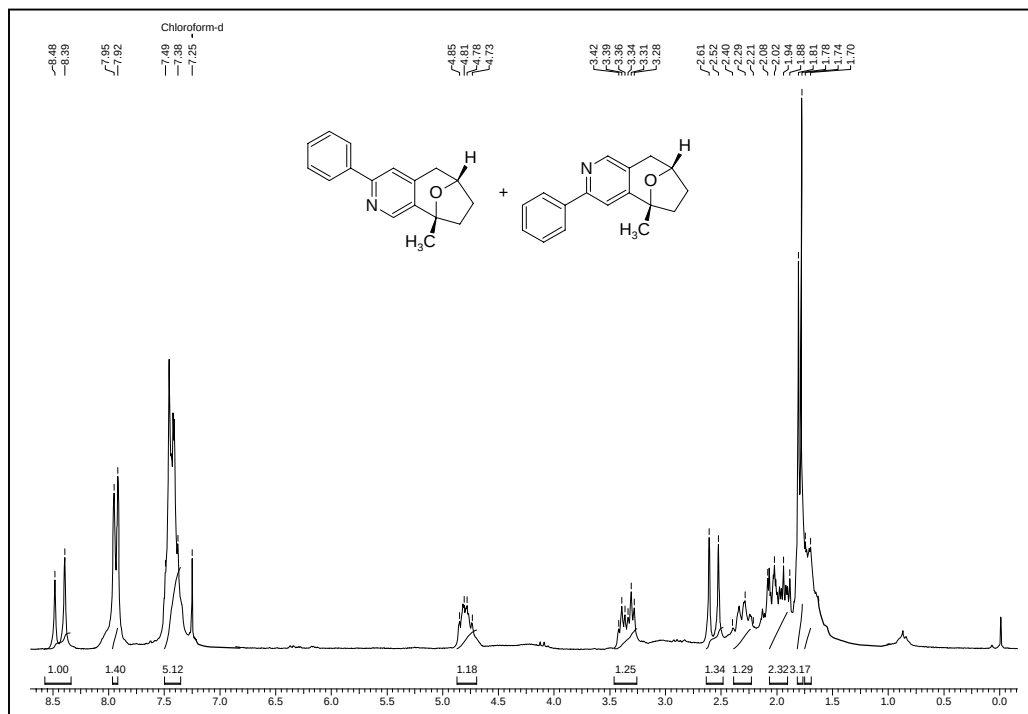
NOESY of compound 127



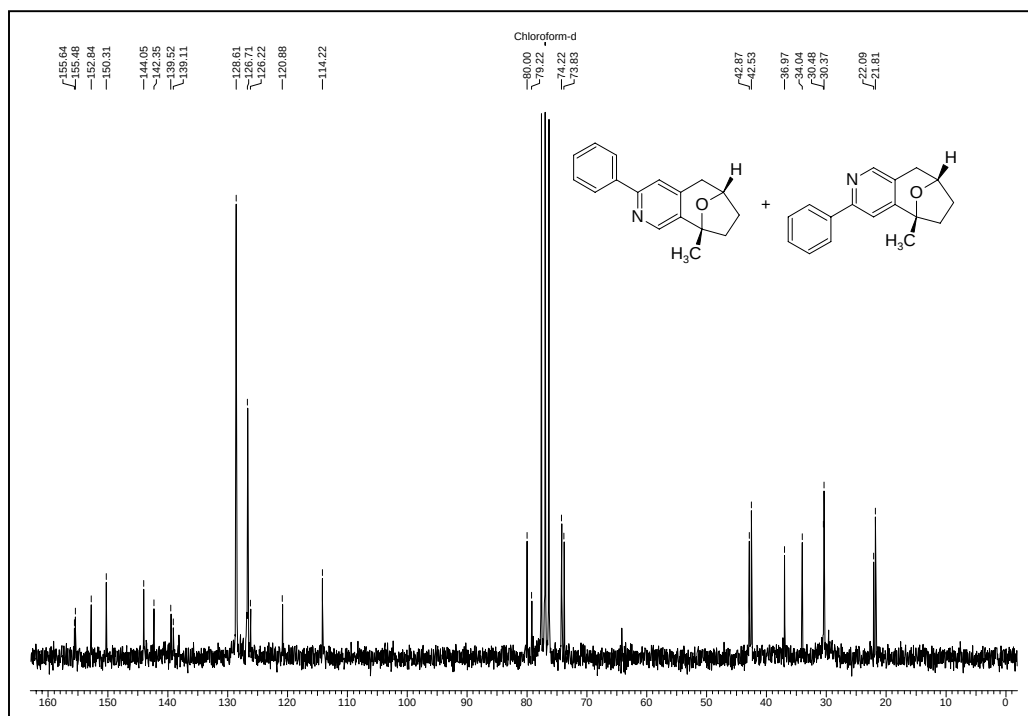
¹H NMR Spectrum of 129/130 in CDCl₃



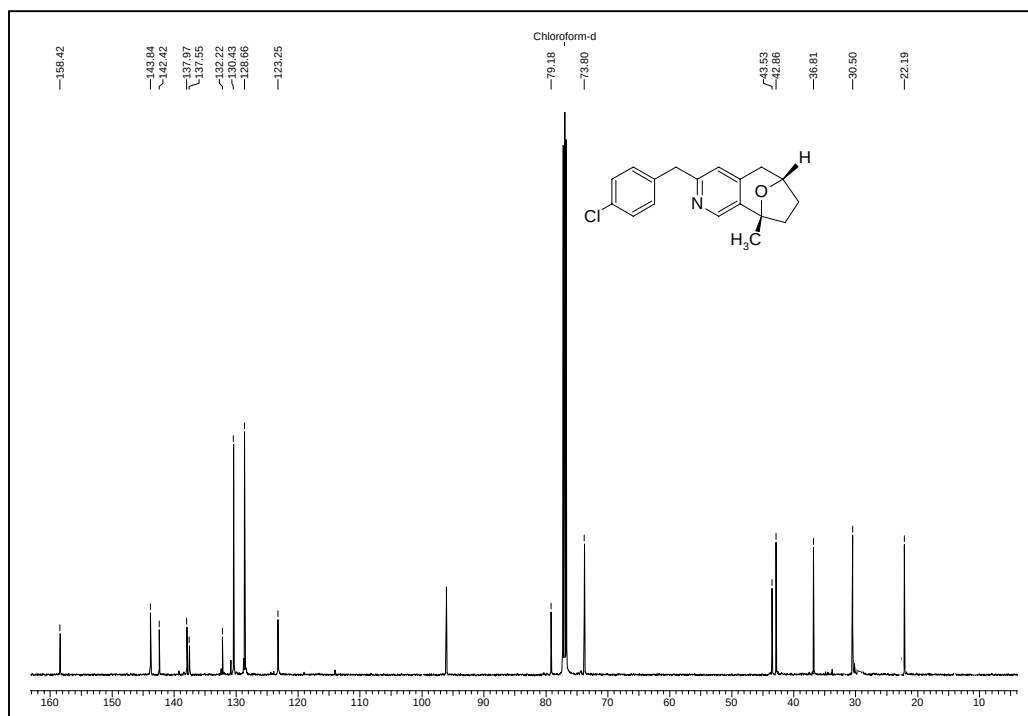
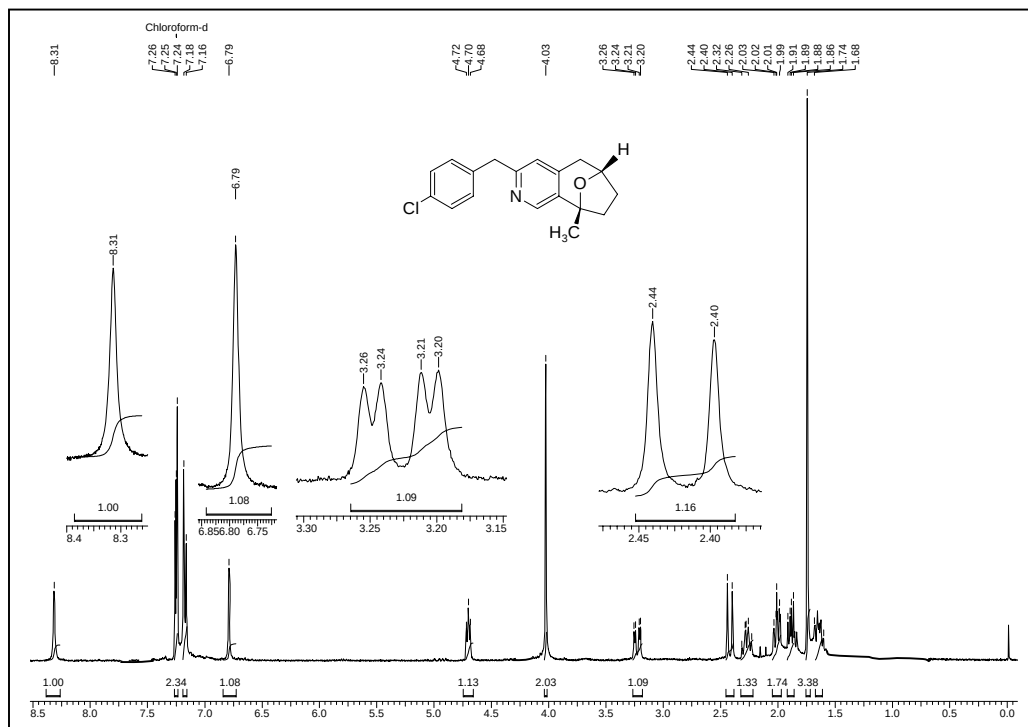
¹³C NMR Spectrum of 129/130 in CDCl₃

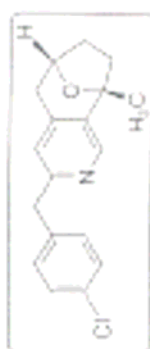
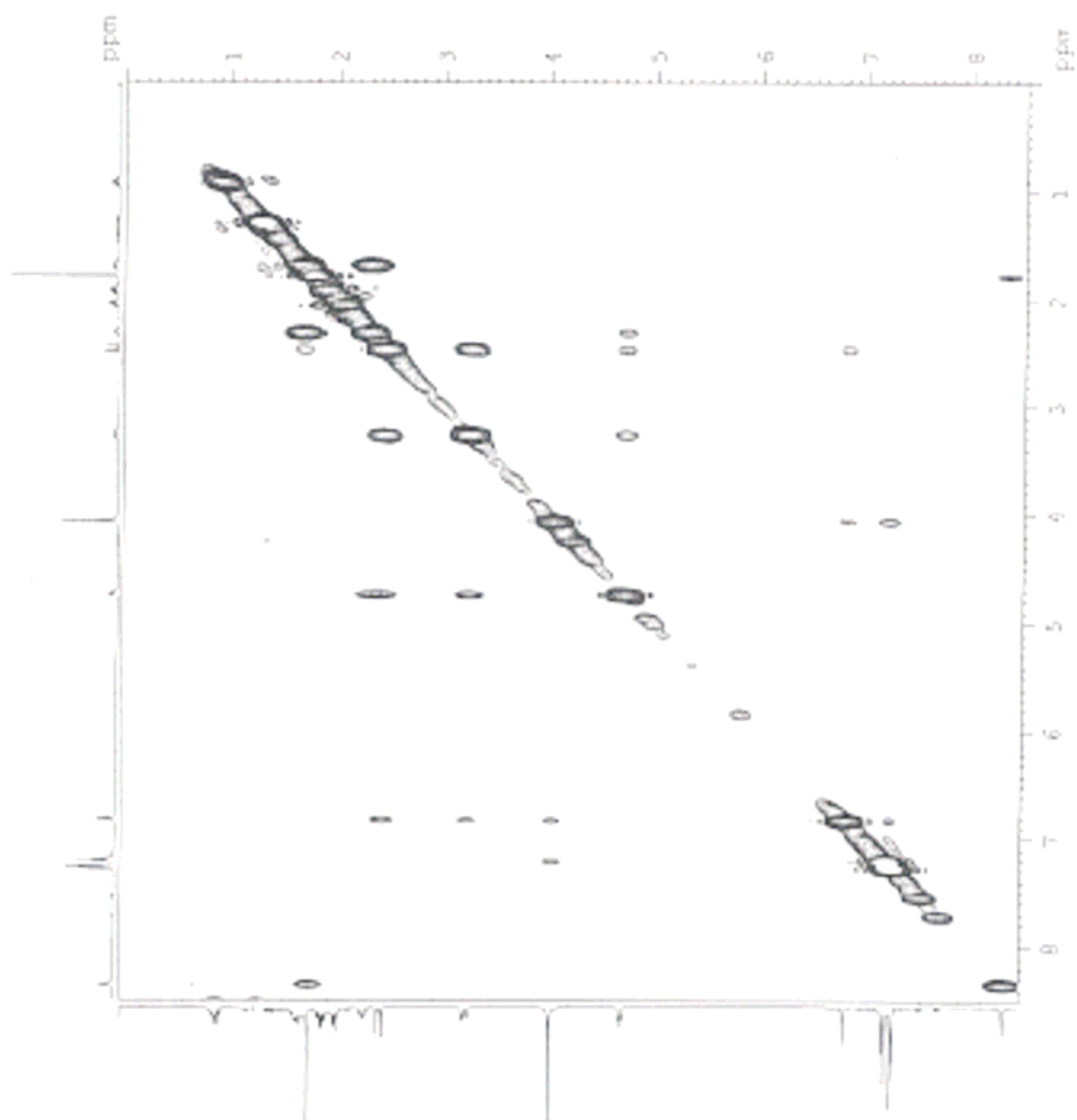


^1H NMR Spectrum of 132/133 in CDCl_3

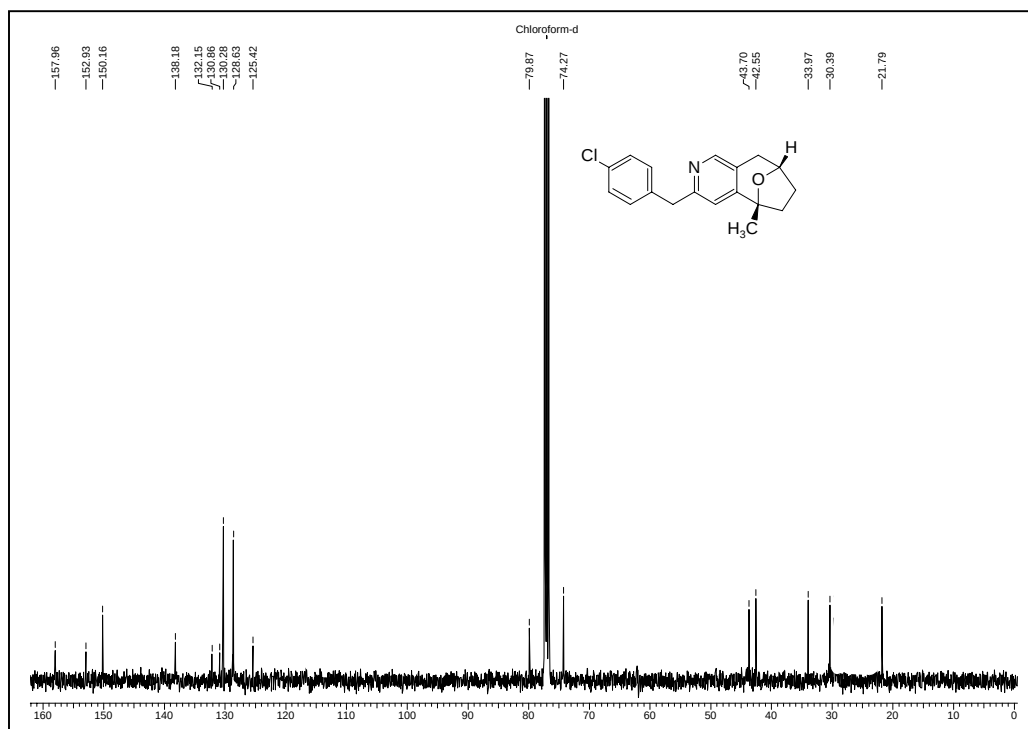
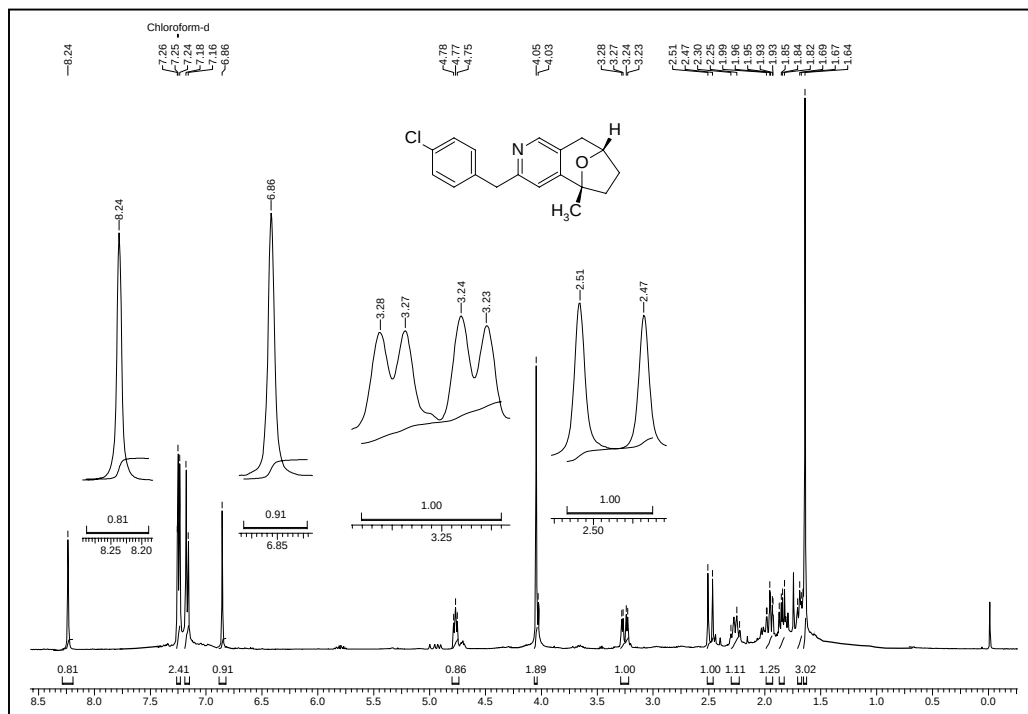


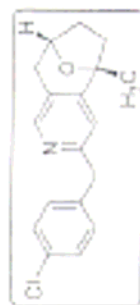
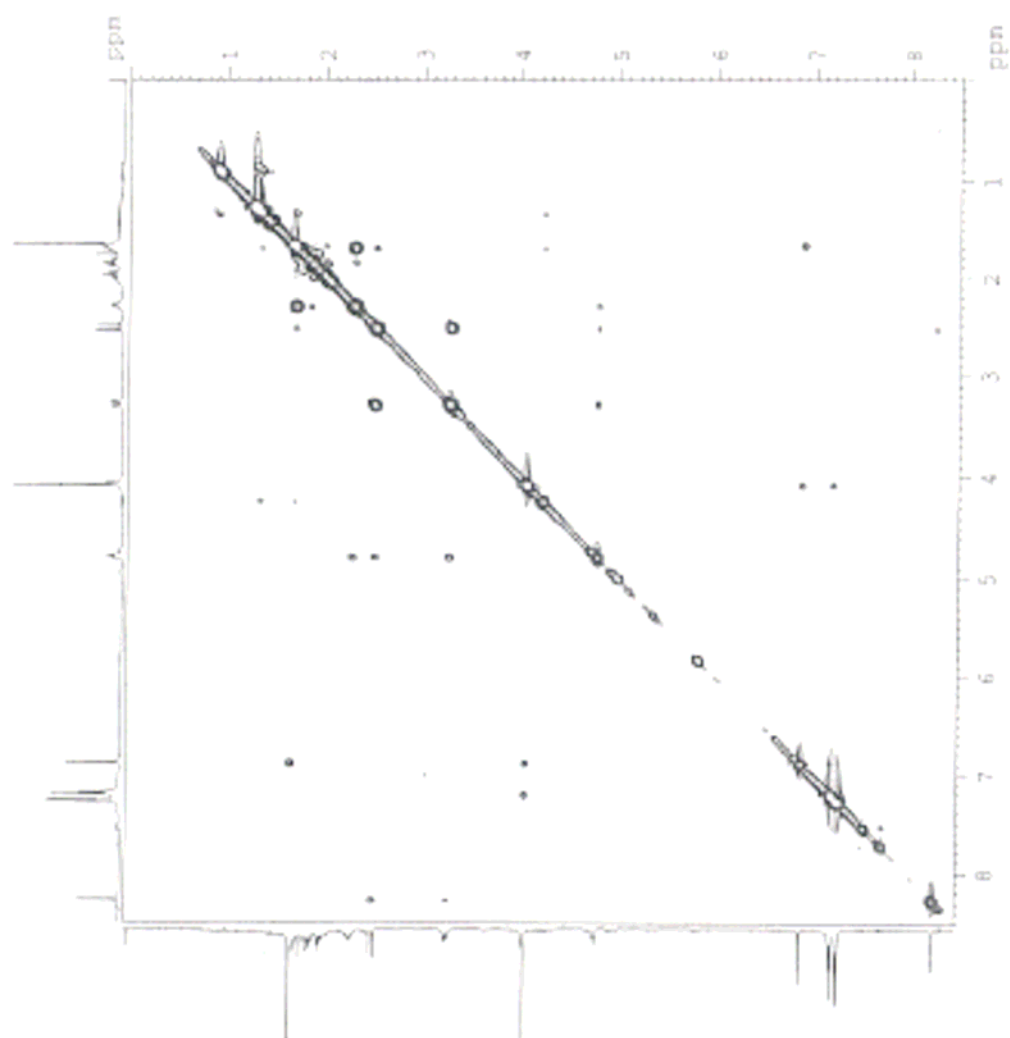
^{13}C NMR Spectrum of 132/133 in CDCl_3





NOESY of compound 135





NOESY of compound 136

Chapter I, Section II:

Towards the Total Synthesis of Bruguierols A and B

Introduction

For many years, traditional pharmacognosy was focused on the investigation and identification of medicinally important plants and animals in the terrestrial environment. With the development of the open-circuit self contained underwater breathing apparatus or SCUBA in the 1940's, some chemists turned to more pioneering work looking for new medicines in the marine environment. In the United States, the road has been long for the first FDA approval of a drug direct from the sea, but in 2004, the approval of ziconotide isolated from a marine cone snail has paved the way for other marine-derived compounds moving through clinical trials. With an estimated 75% of the earth's surface covered by water, research into the chemistry of marine organisms is relatively unexplored and represents a vast resource for new medicines to combat major diseases such as cancer, AIDS or malaria. Research typically focuses on slow moving or sessile organisms because of their inherent need for chemical defenses. Standard research involves an extraction of the organism in a suitable solvent followed by either an assay of this crude extract for a particular disease target or a rationally guided isolation of new chemical compounds using standard chromatography techniques.

The ocean environment is massively complex, consisting of extreme variations in pressure, salinity, temperature, and biological habitats. The biota of marine microorganisms has developed unique metabolic and physiological functions that not only ensure survival in extreme habitats but also offer a potential for the production of novel enzymes and bioactive metabolites for potential exploitation. It is estimated that less than 5% of the bacteria observed by microscopy are culturable under standard laboratory conditions. Out of the large number of species examined, only a fraction of marine bacteria have been isolated and cultured.

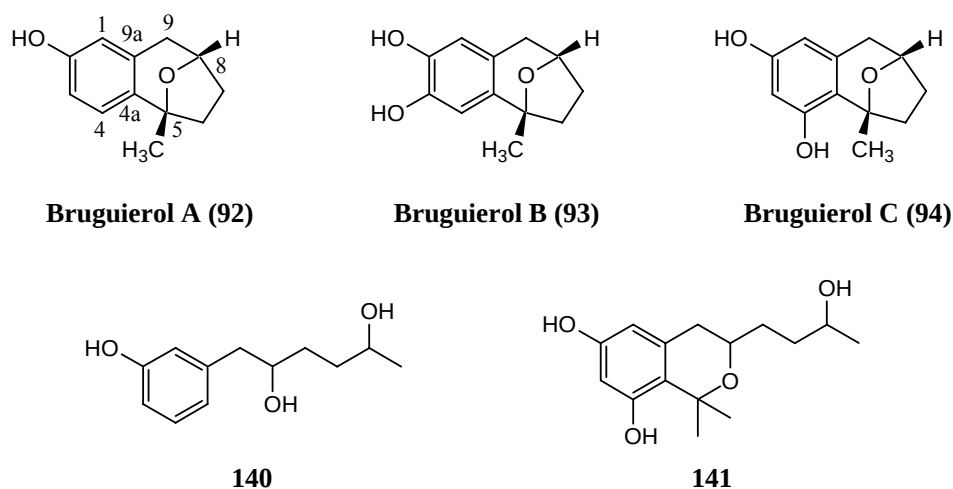
As a result of the potential for new drug discovery, marine natural products have attracted scientists from different disciplines, such as organic chemistry, bioorganic chemistry, pharmacology, biology and ecology.²⁷ This interest has led to the discovery of almost 8,500 marine natural products to date and many of the compounds have shown

very promising biological activity. The ocean is considered to be a great source of potential drugs.

The natural products from marine plants have been attracted by many natural product chemists. Mangrove trees in particular were found to be the source for a wide variety of natural products²⁸. Mangrove trees grow where no tree has grown before. They are able to survive inundation by salt water twice a day, and in "soil" which is unstable and poor in oxygen (anaerobic). They also have to deal with swollen rivers carrying silt during the wet season, as well as violent storms that hit the coasts. These include *Bruguiera*, *Sonneratia* and *Rhizophora*. A few can tolerate high levels of salt in their tissues and their sap can be up to one-tenth as salty as seawater. They then secrete the excess salt through special cells on their leaves.

In 2005, Sattler and co-workers isolated and characterized 5 new aromatic compounds by the phytochemical investigation of the stem of *Bruguiera gymnorhiza* (large-leafed mangrove) of mangrove family (*Rhizophoraceae*) collected from the coast of Xiamen in the south of China.¹⁷ Among these, bruguierols A–C (**92**–**94**) represent a new structural skeleton in natural product chemistry.

Figure 1. Aromatic compounds from *Bruguiera gymnorhiza*



Among these natural products, inclusion of *meta*-substituted hydroxyl groups is crucial for the antimicrobial activity. Bruguierol C (**94**) was shown to exhibit modest

antimicrobial activities (minimal inhibitory concentration, MIC: 12.5 $\mu\text{g/mL}$) against *Staphylococcus aureus* SG 511, *Micrococcus luteus* ATCC 10240, *Enterococcus faecalis* 1528 (vanA), *Escherichia coli* SG 458, and *Mycobacterium vaccae* (MT 10670).

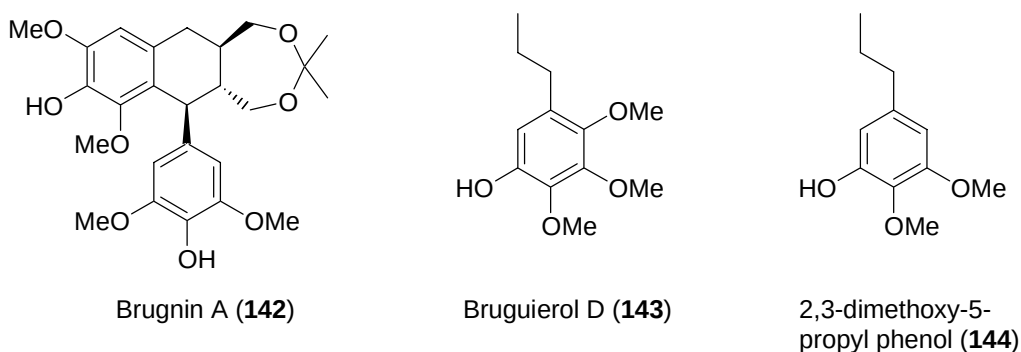
Isolation and structural elucidation

The finely powdered stem of *Bruguiera gymnorrhiza* collected in Xiamen, China was macerated with methanol at r.t. repeatedly and the combined methanolic extracts were concentrated to yield the crude product. A suspension of this crude extract in distilled water was extracted with EtOAc and *n*-BuOH to yield the dried extracts which were later subjected to repeated chromatographic techniques yielding bruguierols A–C (**92–94**), **140**, and **141**.

Despite the fact that extensive structural investigation with various 2D-NMR experiments were carried on **92–94** to elucidate their constitution and relative stereochemistry, however a complete absolute stereochemical characterization is hampered by the lack of a suitable functional group handle on the bicyclic frame work that can be derivatized according to either Mosher method or other related methods to establish the absolute configurations indirectly.

Very recently Lin and co-workers isolated a lignan brugnin A (**142**) and two other aromatic compounds brugueirol D (**143**) and 2,3-dimethoxy-5-propylphenol (**144**) from the branches of *Bruguiera gymnorrhiza*.²⁹ All the three natural products were extensively investigated by NMR and other analytical tools.

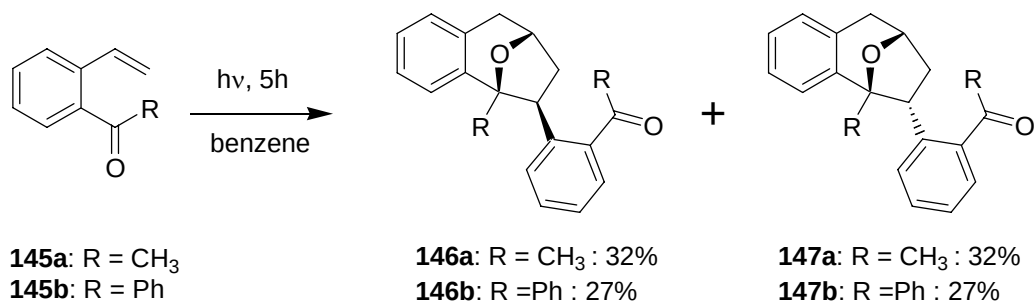
Figure 2. Aromatic compounds from the branches of *B. gymnorrhiza*



Chemistry of bridged bicyclic ethers were not studied much due to the risk factors associated such as higher ring strain and difficulty in accessing them. Bicyclic and tricyclic alkanes and their oxa, aza analogues form an interesting class of organic compounds due to their higher strain energies and greater reactivity. A wide variety of natural products and designed molecules represent these kind of systems. The simplest of among these is norbornane, or bicyclo[2.2.1]heptane. The 8-oxa bicyclo[3.2.1]octane system and its fused analogues form a fundamental class of compounds which include hydroazulenoid diterpene natural products.³⁰ Synthesis of bridged ethers incorporating stereocontrolled placement of functionality is of great synthetic interest. Particularly, aromatic fused bicyclic systems are very difficult to access and there are very few synthetic methods available. Currently, the most general methods to access the aromatic fused [2.2.1]- and [3.2.1] bicyclic systems are by [3+4] cycloadditions³¹ and annulations.³²

Some of the recent approaches towards the construction of 8-oxabicyclo[3.2.1]octane includes photodimerization of *o*-acyl styrenes by Oda and co-workers.³³ Irradiation of *o*-acyl styrenes afforded a pair of stereoisomers of photodimerized benzo-fused oxygen-bridged compounds, the 8-oxabicyclo[3.2.1]octane derivatives.

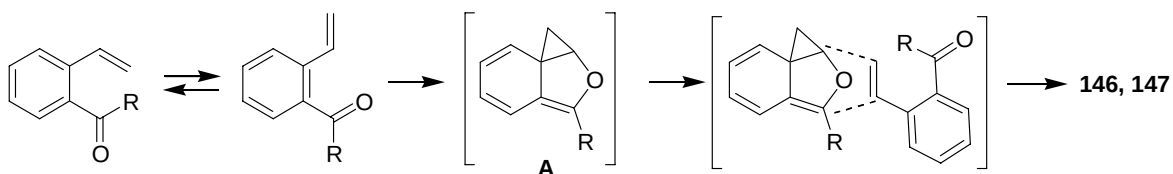
Scheme 1. Photodimerization of *o*-acyl styrenes



The formation of bicyclic system was explained as follows (Scheme 2). When the acyl group is an acetyl and a benzoyl, oxatricyclotriene intermediate **A** was exclusively generated, and it subsequently underwent addition with a vinyl moiety to give 8-

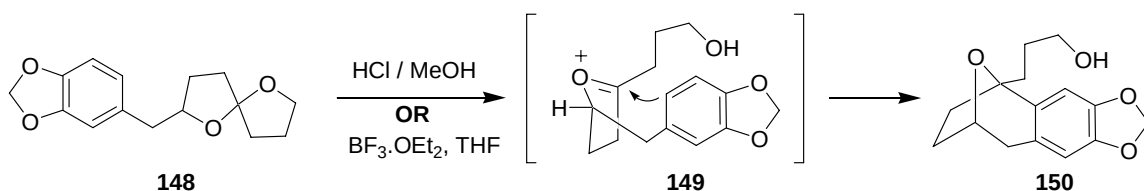
oxabicyclo[3.2.1]octanes **146**, **147**. The selective addition of vinyl moiety was explained by a steric factor associated with acyl group.

Scheme 2



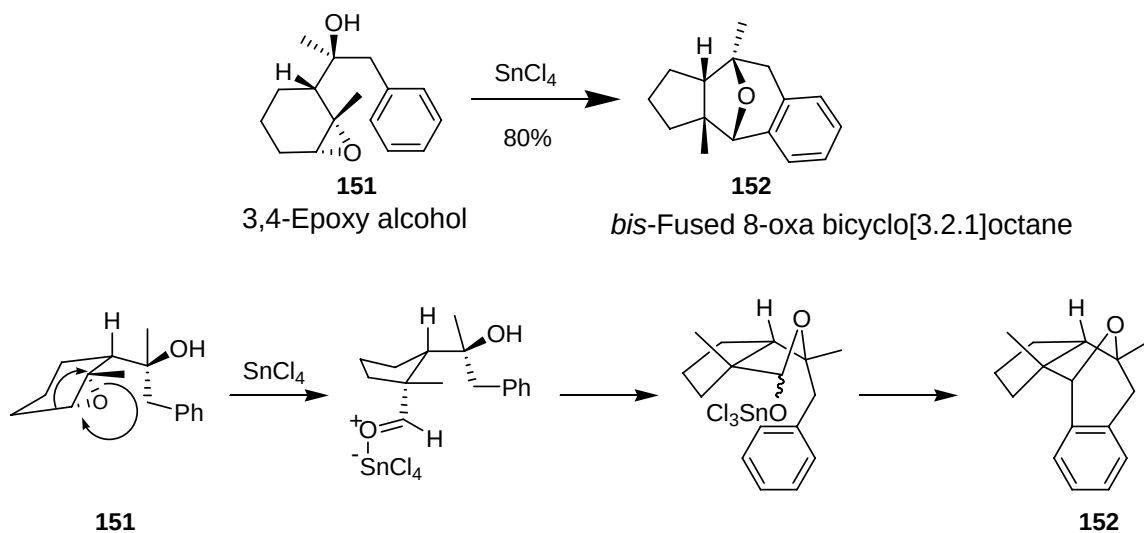
Fan and co-workers reported first examples of Friedel-Crafts alkylation using spiro-ketals as alkylating agents and accessed benzene fused 8-oxa bicyclo[3.2.1]octane system.³⁴ Slightly more than one equivalent of $\text{BF}_3 \cdot \text{OEt}_2$ in THF at refluxing temperature were found to be the most satisfactory conditions to achieve the desired cyclization. The formation of bicyclic system was satisfactorily explained through an oxonium intermediate **149** (Scheme 3), which immediately undergoes cyclization to **150**. An electron-donating group *para* to the position where cyclization will take place greatly facilitates the reaction.

Scheme 3. *Friedel-Crafts alkylation of spiro-ketals*



Marson and co-workers developed a novel general approach to bridged bicyclic ethers by SnCl_4 -catalysed tandem cyclisation involving 3,4-epoxy alcohols.³⁵ The above cyclization takes place by epoxide ring opening and ring contraction mediated by the Lewis acid (Scheme 5).

Scheme 4. *Cyclization of epoxy alcohol*

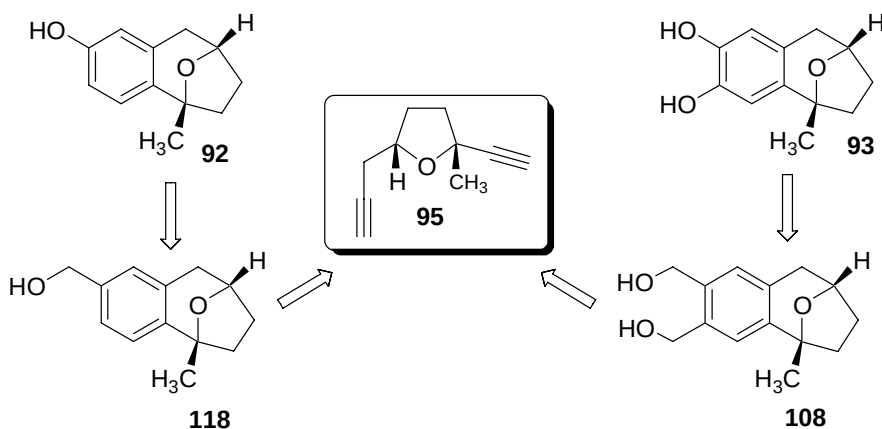


The configurations of the final products imply that the contraction is stereoselective and proceeds with inversion at the new quaternary center. The carbinol oxygen atom then participates in an intramolecular attack upon the activated carbonylic electrophile, resulting in a fused lactol intermediate. Lastly, the effect of SnCl_4 upon the lactol intermediate leads to an electrophile presumed to be the oxonium cation, which undergoes attack by the aryl or alkenyl π nucleophile.

Present Work

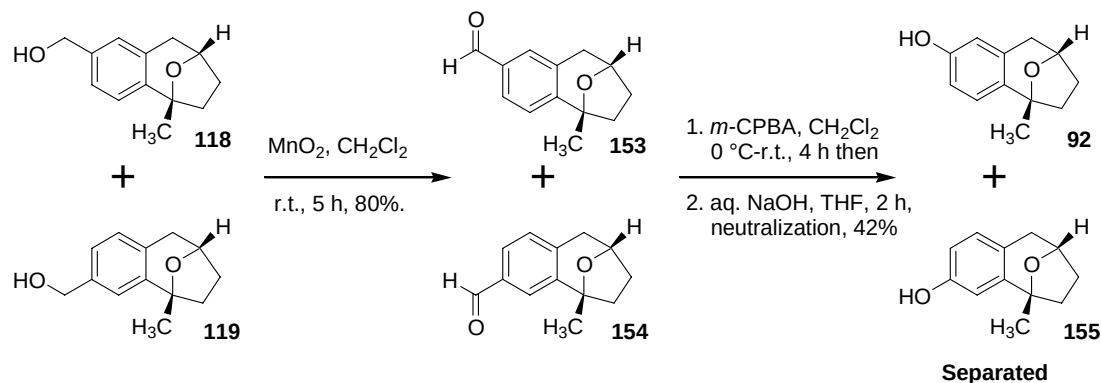
The interesting structural features of bruguierols encouraged us to make them as our synthetic targets. After establishing the feasibility of [2+2+2]-cyclotrimerization reaction for the synthesis of benzannulated-8-oxa-bicyclo[3.2.1]octane systems (Section I), we next planned for the synthesize the bruguierols by making use of this novel methodology. As depicted in the synthetic plan (Scheme 1), bruguierol A and B can be accessed from the cyclotrimerization products of propargyl alcohol and 2-butyne-1,4-diol through oxidation Baeyer-Villiger reaction sequences. Dialkyne **95** is the common starting material for [2+2+2] cyclotrimerization.

Scheme 1. Synthetic plan for bruguierols



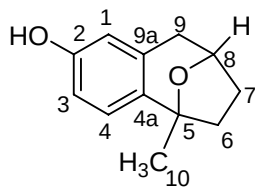
The cyclotrimerization of propargyl alcohol and 2-butyne-1,4-diol with **95** was discussed in detail in section I. Initially we attempted the synthesis of bruguierol A from cyclotrimerization products **118/119** of propargyl alcohol. The mixture of compounds **118/119** were subjected to MnO_2 oxidation in anhydrous DCM to give the intermediate aldehyde mixture **153/154**. The aldehyde mixture **153/154** was subjected to Baeyer-Villiger reaction using *m*-CPBA³⁶ in DCM at 0 °C to r.t. to furnish the intermediate formate ester mixtures which were subsequently hydrolysed using aq. NaOH in THF to give the easily separable mixture of phenols **92** and **155** in 34% overall yield (Scheme 2).

Scheme 2. Synthesis of bruguirol A and regio-bruguirol A

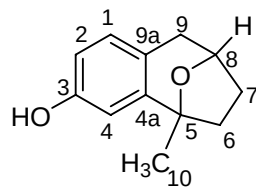


The spectroscopic data of synthetic bruguirol A (**92**) was in excellent agreement with those reported for the natural product (table 1)¹⁷.

Table 1. NMR comparison of synthetic bruguirol A and regio-bruguirol A with natural bruguirol A



Bruguirol A (92)



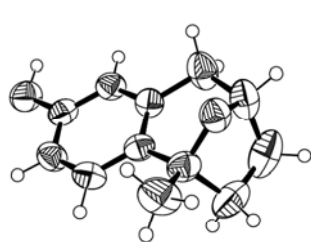
Regio-bruguirol A (155)

Carbon	Natural bruguirol A		Synthetic bruguirol A		Regio-bruguirol A	
	δ_H	δ_C	δ_H	δ_C	δ_H	δ_C
1	6.52	115.6	6.53	115.6	6.92	130.3
2	--	154.4	--	154.1	6.64	113.7
3	6.58	112.9	6.59	112.8	--	153.7
4	6.99	123.9	7.01	124.0	6.65	109.7
4a	--	136.2	--	136.5	--	145.2
5	--	80.4	--	80.3	--	80.5
6	1.84	42.9	1.85	42.9	1.84	42.8
	1.95		1.98		2.03	
7	2.25	30.4	2.24	30.4	2.24	30.4
	1.74		1.71		1.70	
8	4.69	74.2	4.70	74.2	4.73	74.6

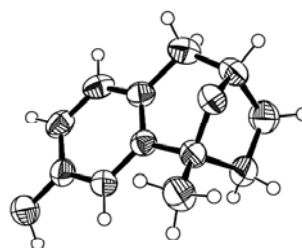
9	3.30	37.5	3.30	37.5	3.27	36.5
	2.44		2.45		2.44	
9a	--	133.5	--	133.6	--	123.7
10	1.68	22.8	1.69	22.8	1.69	22.6

Further, both the phenols were crystallized and the single crystal X-ray structural analyses established their constitution beyond the doubt (figure 1).

Figure 1. ORTEP structures of *bruguierol A (92)* and *155*



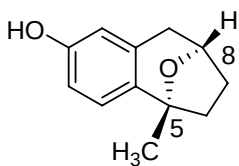
Bruguierol A (92)



Regio-bruguierol A (155)

The optical rotation of synthetic sample **92** $\{[\alpha]_D -19.8$ (*c* 1.0, CHCl_3) $\}$ was similar to reported value $\{[\alpha]_D +14.4$ (*c* 0.3, CHCl_3) $\}$ and opposite in sign which indicated that the synthetic sample was anti-pode of bruguierol A and established the absolute stereochemistry of bruguierol A as (5*S*, 8*R*).

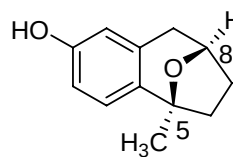
Figure 2. Absolute stereochemistry of *Bruguierol A*



(5*R*, 8*S*)

Synthetic Bruguierol A

$[\alpha]_D -19.8$ (*c* 1.0, MeOH)



(5*S*, 8*R*)

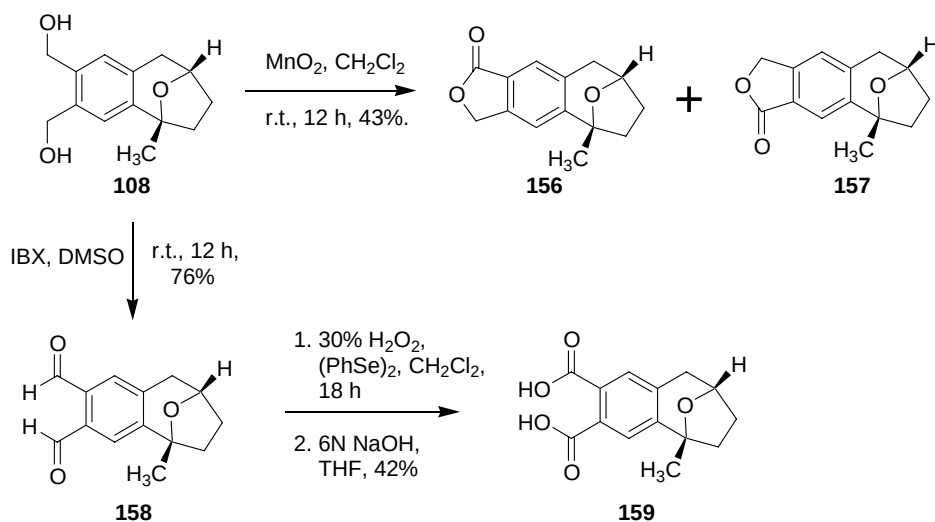
Natural Bruguierol A

$[\alpha]_D +14.4$ (*c* 0.3, MeOH)

Synthetic Studies Towards Bruguierol B (93)

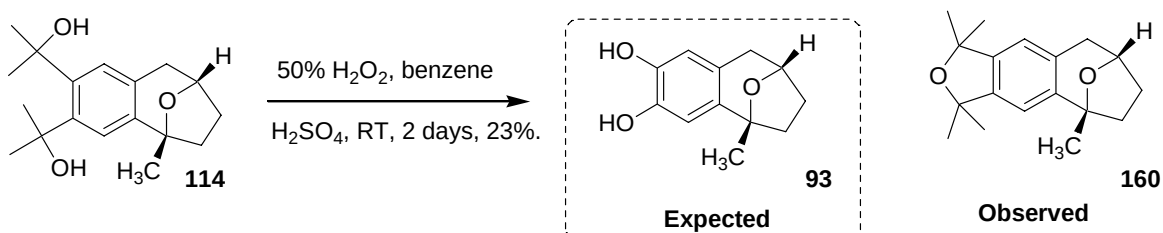
Once the total synthesis of (–) bruguierol A was accomplished, we next focussed on the synthesis of bruguierol B (**93**). The following sequence of reactions with **108**, i.e., oxidation followed by Baeyer-Villiger reaction to obtain bruguierol B (**93**) was attempted. However, when treated with MnO₂ in anhydrous DCM, diol **108** gave exclusively mixture of lactone derivatives **156/157**. The formation of lactone was confirmed by ¹H NMR and IR studies. In turn, IBX oxidation³⁷ of **108** in dry DMSO yielded the required *o*-dialdehyde **158** in 76% yield. The two aldehydic protons were shown by ¹H NMR spectrum at δ 10.47 and 10.57 as singlets. Further in ¹³C NMR spectrum, the carbonyl carbons resonated at δ 191.72 and 191.73. The IR spectrum further revealed the presence of aldehyde with a stretching at 1697 cm^{–1}. Treatment of *o*-dialdehyde **158** with *m*-CPBA in DCM resulted in rapid decomposition of the starting compound. On the other hand, hydrogen peroxide mediated oxidation of **158** catalyzed by diphenyl diselenide³⁸ gave exclusively the *o*-diacid derivative **159** (Scheme 3). The formation of diacid **159** was ascertained by its ¹H NMR and ¹³C NMR spectrum. The carboxylic acid protons resonated at δ 13.07 as a broad singlet in ¹H NMR spectrum. The carbonyl carbon resonated at δ 168.4 in ¹³C NMR spectrum. The structure was further confirmed by IR and mass spectral studies.

Scheme 3. Attempted synthesis of Bruguierol B



Once the planned strategy towards bruguierol B was a failure, we then focussed on possibility of a hydroperoxide rearrangement³⁹ on **114**, the cyclotrimerization product of 2,5-dimethyl 3-hexyne-2,5-diol. Exposure of **114** to H₂O₂ in benzene with catalytic sulfuric acid for 2 days gave the undesired cyclized product **160** in 23% yield (Scheme 4).

Scheme 4. *Hydroperoxide rearrangement of 114*



The cyclized product was in full agreement with spectral and analytical data. The ¹H NMR spectrum of **160** showed two aromatic protons at δ 6.77 and 6.84 as two singlets, whereas the same for **114** resonated at δ 6.97 and 7.05 as two singlets. Further the two hydroxy protons from **114**, which were observed as broad singlet at δ 5.42 were disappeared in the spectrum of **160**. The cyclization was further confirmed by IR and mass spectral studies.

Conclusions

An expedient total synthesis of bruguierol A has been completed with the novel application of [2+2+2] cross alkyne cyclotrimerization and established its absolute configuration. The attempted synthesis of bruguierol B met with over-oxidized products.

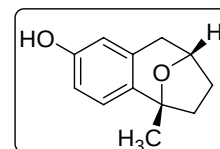
Experimental

Experimental

Oxidation & Baeyer-Villiger reaction of **118/119**:

To a solution of mixture of alcohols **118/119** (100 mg, 0.49 mmol) in dry DCM (8 mL) was added activated MnO₂ (85 mg, 0.98 mmol) and stirred at r.t. for 5 h. The reaction mixture was filtered through a pad of *celite*, washed with DCM (20 mL) and concentrated in *vacuo* to give mixture of aldehydes **153/154** (79 mg, 80%) which were taken in dry DCM (5 mL) and added *m*-CPBA (135 mg, 0.78 mmol) in ice-cold temperature and stirred at r.t. for 4 h. DCM was removed in *vacuo* and the crude product was dissolved in ethyl acetate (10 mL) and washed with 10% NaHCO₃ solution (4 x 5 mL). Organic phase was dried over Na₂SO₄, filtered and concentrated under reduced pressure. The crude material was taken on THF (4 mL) and added 2N NaOH (2 mL) solution, stirred at r.t. for 2 h. The reaction mixture was cooled to 10 °C and carefully neutralized with 6N HCl. THF was removed under reduced pressure and the aq. phase was extracted with DCM (2 x 5 mL). The combined organic phases were dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue obtained was purified by column chromatography (4:1 petroleum ether/ethyl acetate) to give **92** (16 mg, 21%) and **155** (16 mg, 21%) as colorless solids.

(-)-Bruguierol A (**92**):



Mol. Formula	: C ₁₂ H ₁₄ O ₂
M. P.	: 134–137 °C.
[α]_D	: -19.8 (c 1.0, CHCl ₃).
IR (CHCl₃) $\tilde{\nu}$	: 3395, 3020 cm ⁻¹ .
¹H NMR (CDCl ₃ , 400 MHz)	: δ 1.68–1.74 (m, 1H), 1.69 (s, 3H), 1.82–1.88 (m, 1H), 1.95–2.01 (m, 1H), 2.20–2.28 (m, 1H), 2.45 (d, <i>J</i> = 16.5 Hz, 1H), 3.30 (dd, <i>J</i> = 16.5, 5.1 Hz, 1H), 4.68–4.72 (m, 1H), 4.75 (br s, 1H), 6.53 (d, <i>J</i> = 2.5 Hz, 1H), 6.59 (dd, <i>J</i> = 8.4, 2.5 Hz, 1H), 7.01 (d, <i>J</i> = 8.4 Hz, 1H) ppm.

^{13}C NMR : δ 22.85 (q), 30.47 (t), 37.55 (t), 42.95 (t), 74.20 (d), 80.34 (CDCl₃, 100 MHz) (s), 112.86 (d), 115.67 (d), 124.01 (d), 133.69 (s), 136.55 (s), 154.17 (s) ppm.

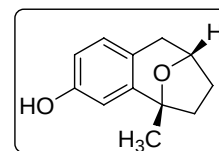
ESI-MS (m/z) : 191.18 [M+1]⁺, 213.18 [M+Na]⁺.

Elemental Analysis Calcd.: C, 75.76; H, 7.42.

Found: C, 75.59; H, 7.33.

Crystal data for 92 (C₁₂H₁₄O₂): $M = 190.23$, Crystal dimensions 0.82 x 0.26 x 0.09 mm³, Orthorhombic, space group $P2_12_12_1$, $a = 7.137(2)$, $b = 7.511(3)$, $c = 19.732(7)$ Å, $V = 1057.7(6)$ Å³, $Z = 4$; $\rho_{\text{calcd}} = 1.195$ gcm⁻³, μ (Mo-K α) = 0.080 mm⁻¹, $F(000) = 408$, $2\theta_{\text{max}} = 50.00^\circ$, 5307 reflections collected, 1859 unique, 1663 observed ($I > 2\sigma(I)$) reflections, 183 refined parameters, R value 0.0376, $wR2 = 0.0872$ (all data $R = 0.0434$, $wR2 = 0.0905$), $S = 1.093$, minimum and maximum transmission 0.9372 and 0.9930 respectively, maximum and minimum residual electron densities +0.141 and -0.122 eÅ⁻³.

Iso-bruguierol A (155):



Mol. Formula : C₁₂H₁₄O₂

M. P. : 160–162 °C.

$[\alpha]_D$: -16.2 (c 1.2, CHCl₃).

IR (CHCl₃) $\tilde{\nu}$: 3395, 3020 cm⁻¹.

^1H NMR : δ 1.64–1.75 (m, 1H), 1.69 (s, 3H), 1.80–1.88 (m, 1H), (CDCl₃, 400 MHz) 2.03 (ddd, $J = 11.6, 9.4, 2.4$ Hz, 1H), 2.20–2.28 (m, 1H), 2.44 (d, $J = 16.1$ Hz, 1H), 3.27 (dd, $J = 16.1, 5.1$ Hz, 1H), 4.72–4.75 (m, 1H), 5.16 (br s, 1H), 6.62–6.65 (m, 2H), 6.92 (d, $J = 7.8$ Hz, 1H) ppm.

^{13}C NMR : δ 22.60 (q), 30.39 (t), 36.47 (t), 42.78 (t), 74.56 (d), 80.47 (CDCl₃, 100 MHz) (s), 109.77 (d), 113.73 (d), 123.69 (s), 130.33 (d), 145.20

(s), 153.71 (s) ppm.

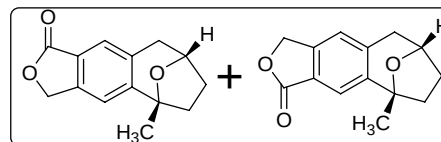
ESI-MS (*m/z*) : 191.20 [M+1]⁺, 213.19 [M+Na]⁺.

Elemental Analysis Calcd.: C, 75.76; H, 7.42.

Found: C, 75.53; H, 7.51.

Crystal data for 155 (C₁₂H₁₄O₂): *M* = 190.23, crystal dimensions 0.73 x 0.22 x 0.13 mm³, Orthorhombic, space group *P*2₁2₁2₁, *a* = 8.3141(11), *b* = 8.5663(12), *c* = 14.1453(19) Å, *V* = 1007.4(2) Å³, *Z* = 4; ρ_{calcd} = 1.254 gcm⁻³, μ (Mo–K α) = 0.084 mm⁻¹, *F*(000) = 408, 2 θ_{max} = 50.00°, 7223 reflections collected, 1765 unique, 1648 observed (*I* > 2 σ (*I*)) reflections, 183 refined parameters, *R* value 0.0302, *wR*2 = 0.0718 (all data *R* = 0.0326, *wR*2 = 0.0728), *S* = 1.086, minimum and maximum transmission 0.9410 and 0.9889 respectively, maximum and minimum residual electron densities +0.126 and – 0.123 e Å⁻³.

Lactones (156/157):



To a solution of diol **108** (70 mg, 0.30 mmol) in DCM (4 mL) was added MnO₂ (52 mg, 0.60 mmol) and the reaction mixture was stirred at r.t. for 12 h. The mixture was filtered through *celite* and washed with DCM (10 mL). The combined filtrates were concentrated and the residue obtained was purified by column chromatography (4:1 petroleum ether/ethyl acetate) to afford the mixture **156/157** (30 mg, 43%) as colorless oil.

Mol. Formula : C₁₄H₁₄O₃

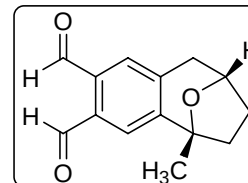
IR (CHCl₃) $\tilde{\nu}$: 2915, 1775, 1459 cm⁻¹

¹H NMR : δ 1.60–1.67 (m, 1H), 1.71, 1.73 (2s, 3H), 1.83–1.96 (m, 2H), 2.16–2.33 (m, 1H), 2.60 (d, *J* = 17.1 Hz, 1H), 3.40 (dd, *J* = 17.1, 4.8 Hz, 1H), 4.67–4.74 (m, 1H), 5.19, 5.20 (2s, 2H), 7.12, 7.20 (2s, 1H), 7.56, 7.66 (2s, 1H) ppm.

Elemental Analysis Calcd.: C, 73.03; H, 6.13

Found: C, 73.10; H, 6.01

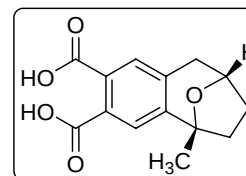
Dialdehyde 158:



To solution of diol **108** (100 mg, 0.43 mmol) in dry DMSO (4 mL) was added IBX (358 mg, 1.28 mmol) and the reaction mixture was stirred at r.t. for 6 h. The reaction mixture was quenched with water (4 mL), filtered through a *celite* bed and washed with diethyl ether (15 mL). The organic layer was separated and aq. layer was washed with ether (2 x 5 mL). The combined organic extracts were dried over Na₂SO₄, filtered and concentrated and the residue was purified by column chromatography (7:3 petroleum ether/ethyl acetate) to yield dialdehyde **158** (74 mg, 76%) as colorless oil.

Mol. Formula	: C ₁₄ H ₁₄ O ₃
[α]_D	: -14.5 (c 1.6, CHCl ₃).
IR (CHCl₃) $\tilde{\nu}$	: 3019, 2400, 1697, 1216 cm ⁻¹ .
¹H NMR (CDCl ₃ , 200 MHz)	: δ 1.63–1.74 (m, 1H), 1.81 (s, 3H), 1.91–2.10 (m, 2H), 2.25–2.40 (m, 1H), 2.67 (d, <i>J</i> = 17.4 Hz, 1H), 3.45 (dd, <i>J</i> = 17.4, 5.3 Hz, 1H), 4.75–4.82 (m, 1H), 7.67 (s, 1H), 7.76 (s, 1H), 10.47 (s, 1H), 10.51 (s, 1H) ppm.
¹³C NMR (CDCl ₃ , 50 MHz)	: δ 22.46 (q), 30.64 (t), 37.55 (t), 42.76 (t), 73.85 (d), 80.48 (s), 125.55 (d), 132.43 (d), 134.51 (s), 134.90 (s), 139.46 (s), 150.20 (s), 191.72 (d), 191.73 (d) ppm.
Elemental Analysis	Calcd.: C, 73.03; H, 6.13 Found: C, 73.12; H, 6.25.

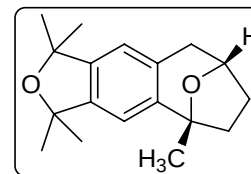
Diacid 159:



To a solution of the dialdehyde **158** (0.04 g, 0.17 mmol) in DCM (3 mL) were added diphenyl diselenide (2 mg, 7 μ mol) and 30% aq. hydrogen peroxide (0.1 mL, 0.85 mmol). The reaction mixture was stirred at ambient temperature for 18 h. The mixture was then diluted with water and ethyl acetate, washed with brine, dried over Na₂SO₄, and concentrated. The residue was dissolved in THF (3 mL), added 6N aq. NaOH (1 mL) and stirred at r.t. for 2 h. The reaction mixture was acidified to pH 1 with 1 N HCl and back-extracted with ethyl acetate. The organic extracts were washed with brine, dried over Na₂SO₄, filtered and concentrated. The diacid **159** (19 mg, 42%) crystallized out from ethyl acetate as colorless solid.

Mol. Formula	: C ₁₄ H ₁₄ O ₅
M. P.	: 174–176 °C.
[α]_D	: –5.4 (c 0.6, EtOH).
IR (Nujol) $\tilde{\nu}$	: 3390, 2924, 2854, 1732, 1664, 1456 cm ^{–1} .
¹H NMR (DMSO-d ₆ , 400 MHz)	: δ 1.56–1.63 (m, 1H), 1.63 (s, 3H), 1.71–1.79 (m, 1H), 1.89–1.96 (m, 1H), 2.11–2.19 (m, 1H), 2.58 (d, <i>J</i> = 17.2 Hz, 1H), 3.17 (dd, <i>J</i> = 17.2, 5.0 Hz, 1H), 4.62–4.65 (m, 1H), 7.36 (s, 1H), 7.48 (s, 1H), 13.07 (br s, 2H) ppm.
¹³C NMR (DMSO-d ₆ , 100 MHz)	: δ 22.25 (q), 29.92 (t), 36.46 (t), 42.35 (t), 73.05 (d), 79.68 (s), 122.95 (d), 129.23 (d), 130.29 (s), 131.46 (s), 135.34 (s), 146.18 (s), 168.36 (s), 168.46 (s) ppm.
ESI-MS (<i>m/z</i>)	: 263.15[M+1] ⁺ , 285.15 [M+Na] ⁺ .
Elemental Analysis	Calcd.: C, 64.12; H, 5.38. Found: C, 63.98; H, 5.48.

Cyclized product (160):

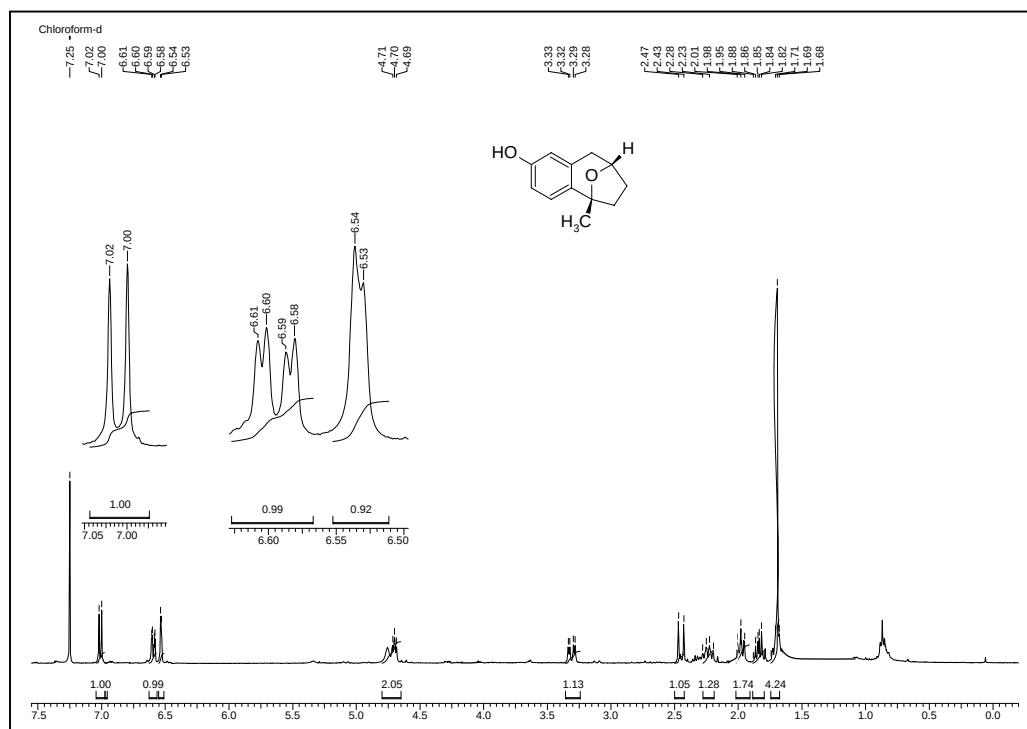


To a solution of diol **114** (50 mg, 0.172 mmol) in benzene (2 mL) was added 50% H₂O₂ (0.11 mL, 1.72 mmol) solution and the mixture was cooled to 0 °C. Added a drop of

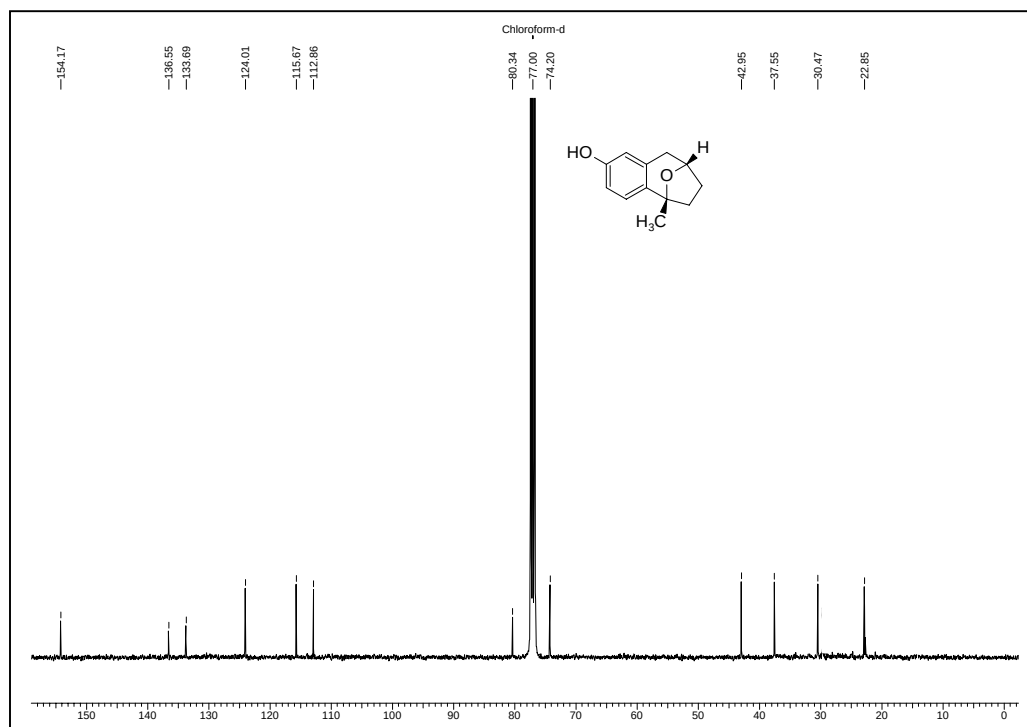
sulfuric acid and the mixture was stirred at r.t. for 2 days. The mixture was diluted with ether (5 mL), organic phase was separated washed with aq. NaHCO₃ solution (4 mL) and brine (3 mL), dried over Na₂SO₄, filtered and concentrated. The residue obtained was purified by column chromatography (4:1 petroleum ether/ethyl acetate) to give **160** (11 mg, 23%) as colorless oil.

Mol. Formula	: C ₁₈ H ₂₄ O ₂
[α]_D	: −7.6 (c 0.8, CHCl ₃).
IR (CHCl₃) $\tilde{\nu}$	: 3019, 2972, 1215 cm ^{−1} .
¹H NMR (CDCl ₃ , 400 MHz)	: δ 1.47 (s, 3H), 1.50 (s, 9H), 1.71–1.78 (m, 1H), 1.75 (s, 3H), 1.84–1.91 (m, 1H), 2.03–2.09 (m, 1H), 2.22–2.31 (m, 1H), 2.55 (d, <i>J</i> = 16.4, Hz, 1H), 3.37 (dd, <i>J</i> = 16.4, 5.3 Hz, 1H), 4.72–4.76 (m, 1H), 6.77 (s, 1H), 6.84 (s, 1H) ppm.
¹³C NMR (CDCl ₃ , 100 MHz)	: δ 23.07 (q), 30.58 (t), 30.73 (q), 30.79 (q), 30.84 (q), 30.96 (q), 37.54 (t), 42.90 (t), 74.32 (d), 80.65 (s), 83.82 (s), 84.04 (s), 114.85 (d), 121.41 (d), 131.34 (s), 143.53 (s), 144.06 (s), 144.66 (s) ppm.
Elemental Analysis	Calcd.: C, 79.37; H, 8.88. Found: C, 79.52; H, 8.63.

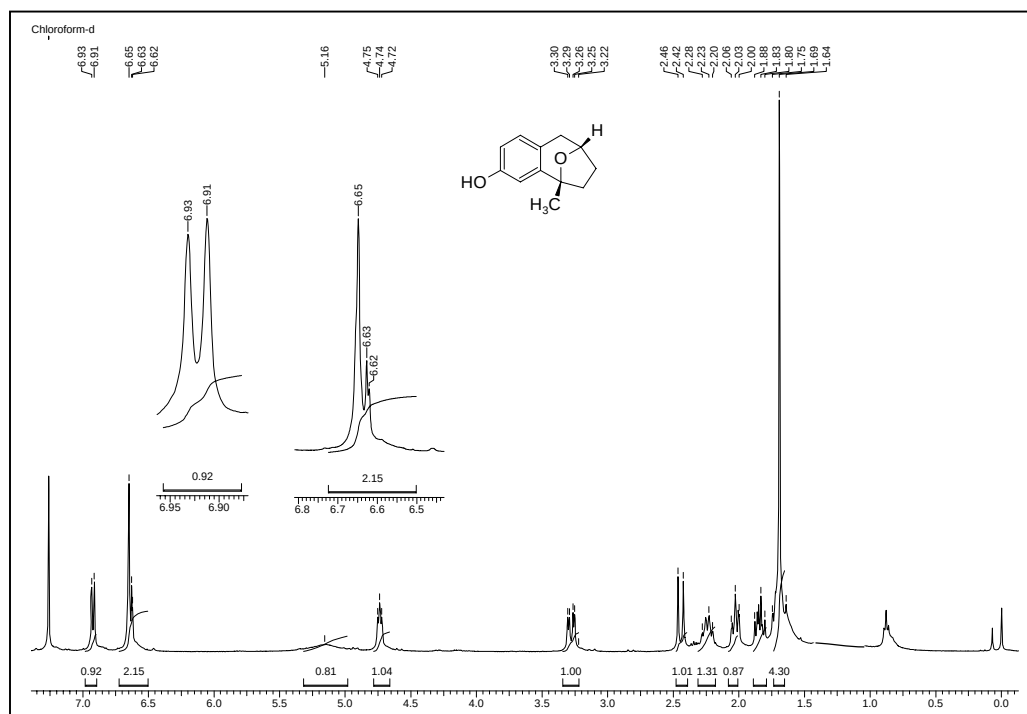
Spectra



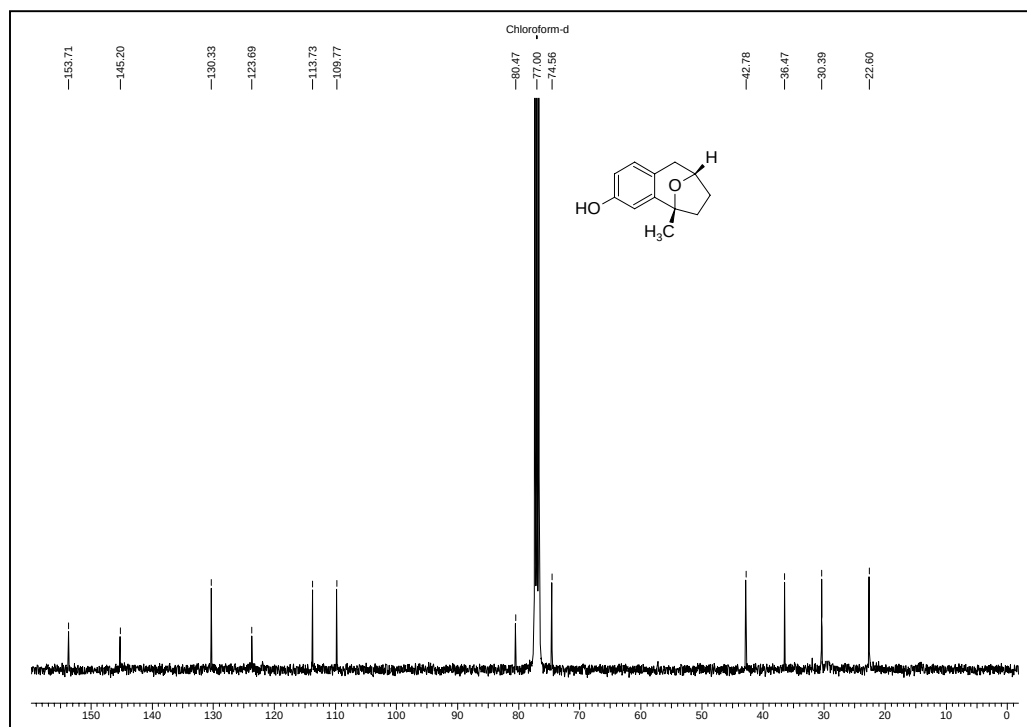
^1H NMR Spectrum of 92 in CDCl_3



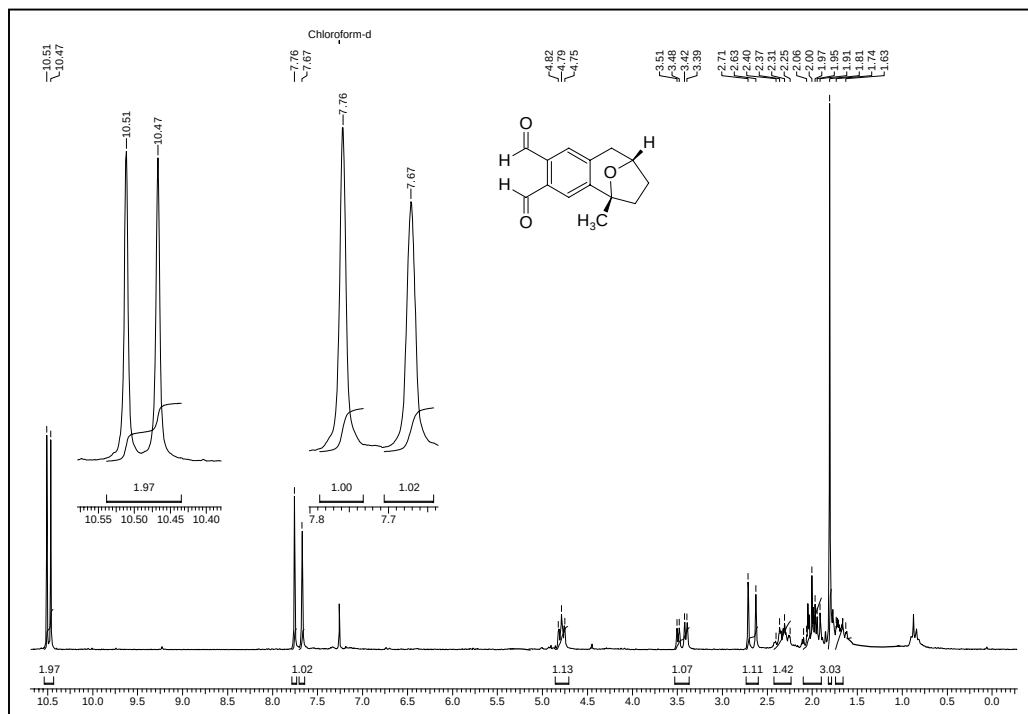
^{13}C NMR Spectrum of 92 in CDCl_3



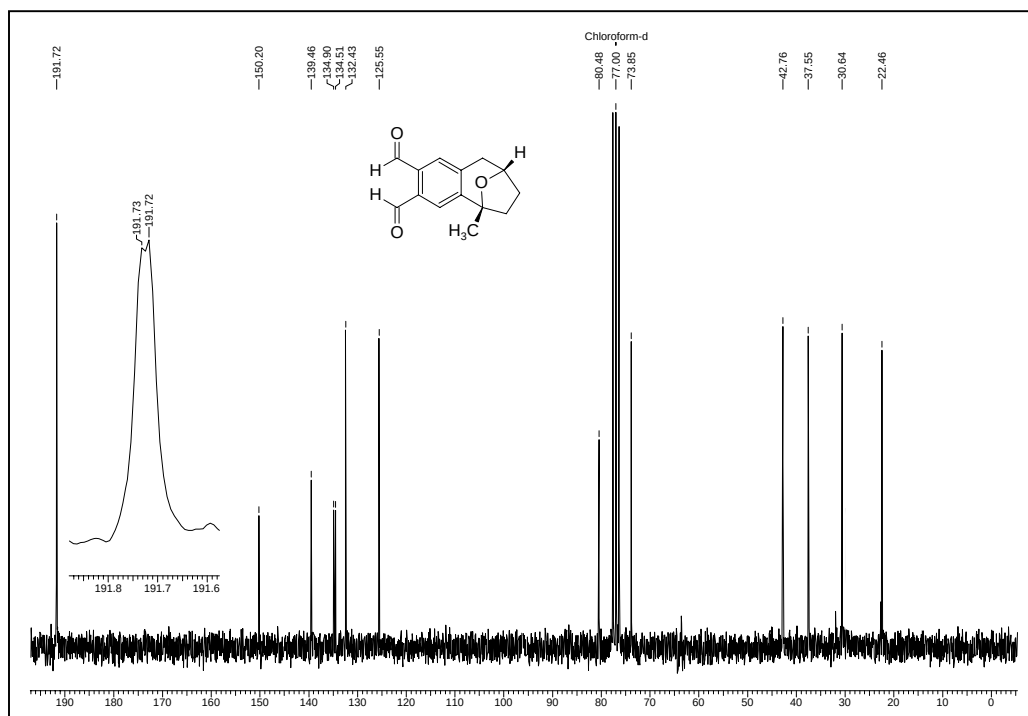
^1H NMR Spectrum of 155 in CDCl_3



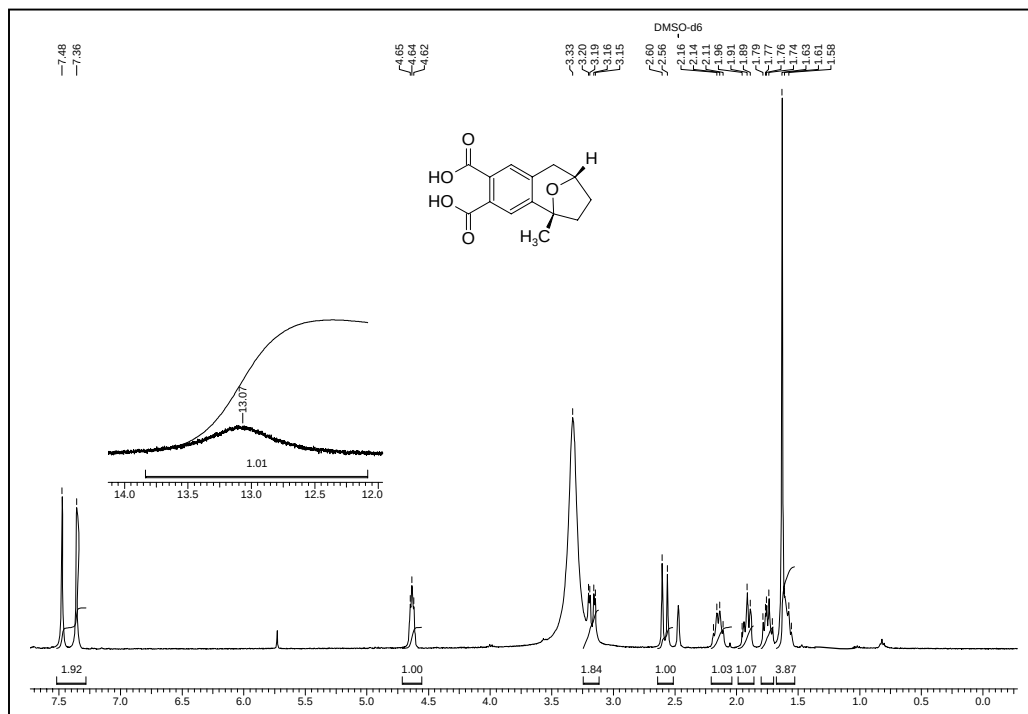
^{13}C NMR Spectrum of 155 in CDCl_3



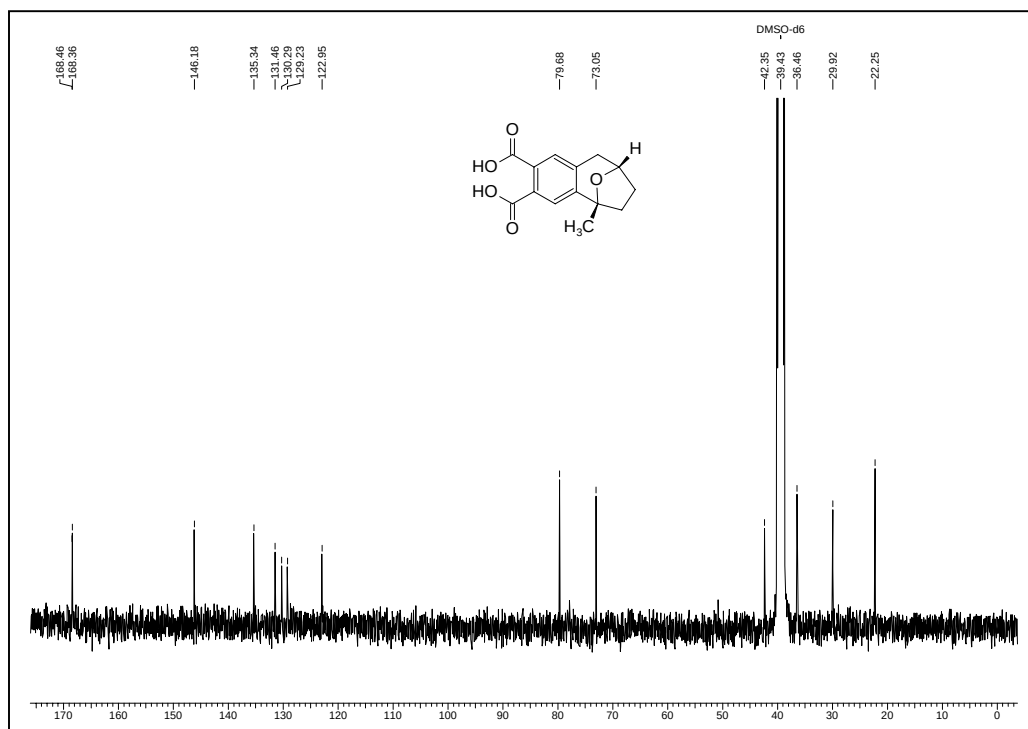
¹H NMR Spectrum of 158 in CDCl₃



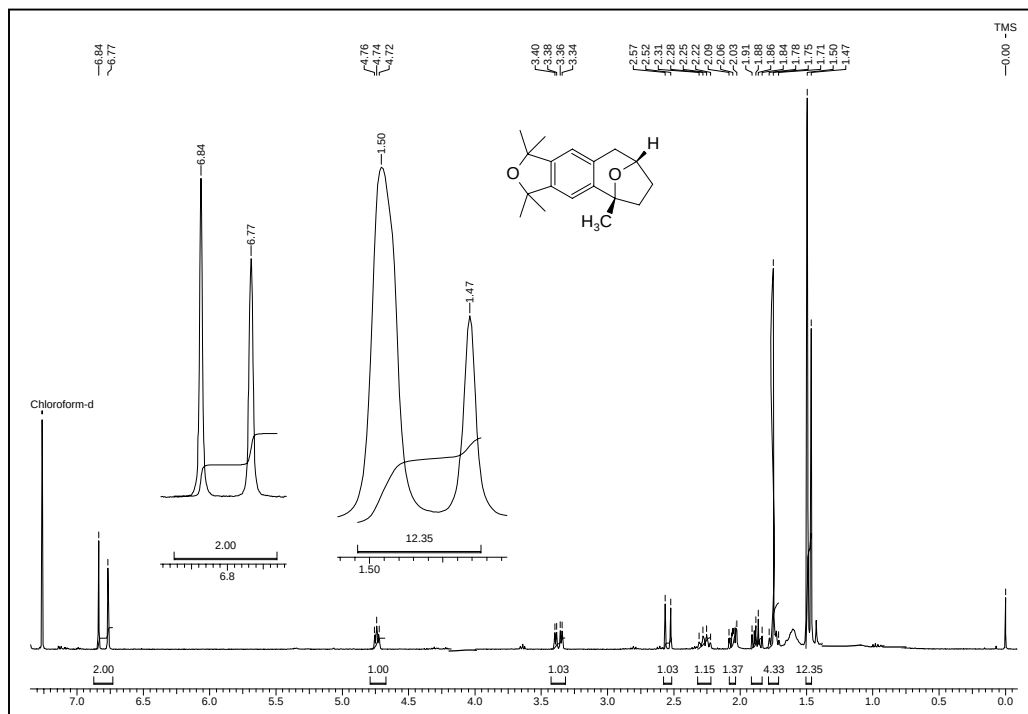
¹³C NMR Spectrum of 158 in CDCl₃



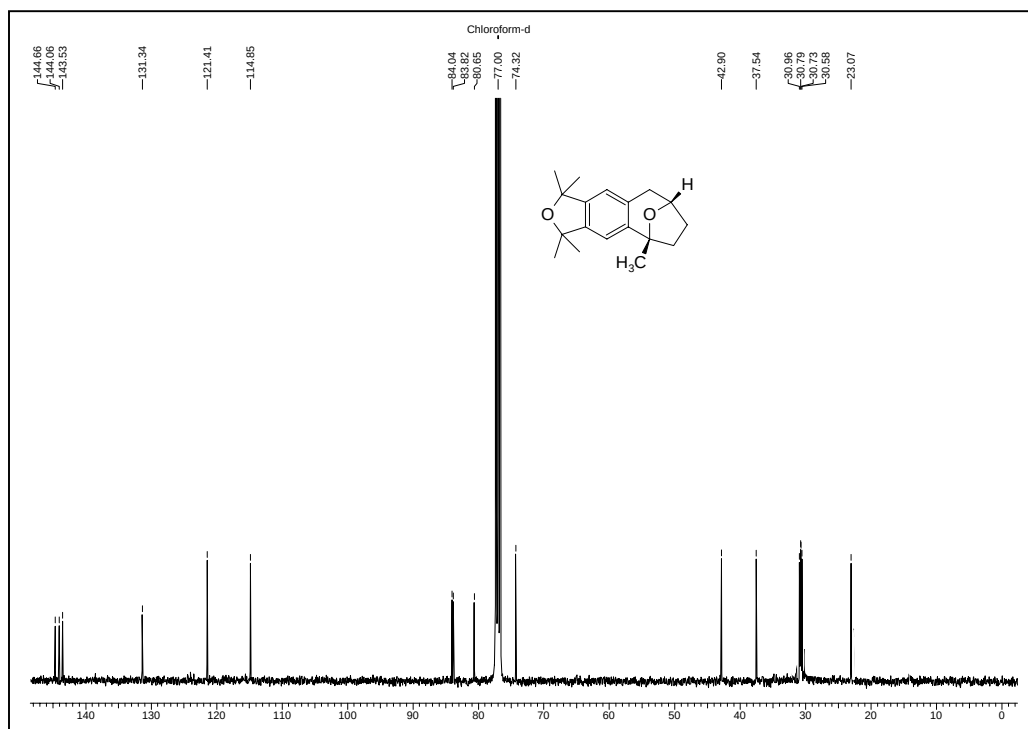
¹H NMR Spectrum of 159 in DMSO-d₆



¹³C NMR Spectrum of 159 in DMSO-d₆



¹H NMR Spectrum of 160 in CDCl₃



¹³C NMR Spectrum of 160 in CDCl₃

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Chapter II

Chapter II, Section I:

Synthesis of the C1-C14 carbon unit of Uprolide E

Introduction

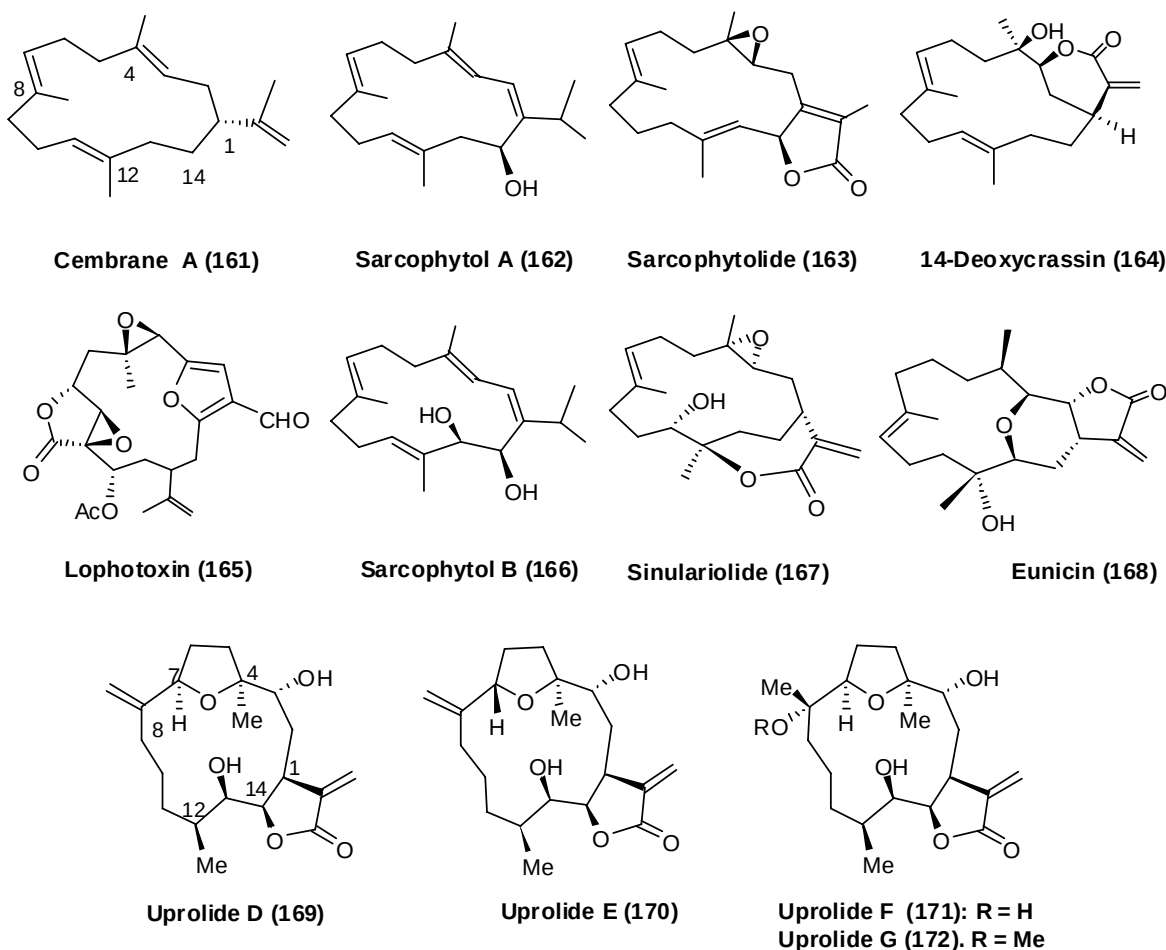
Terpenes are a large and varied class of hydrocarbons, produced primarily by a wide variety of plants, particularly conifers, and also by some insects such as swallowtail butterflies, which emit terpenes from their osmeterium. They are the major components of resin, and of turpentine produced from resin. The name "terpene" is derived from the word "turpentine". Terpenes are derived biosynthetically from units of isoprene. The isoprene units may be linked together "head to tail" to form linear chains or they may be arranged to form rings. One can consider the isoprene unit as one of nature's preferred building blocks. Isoprene itself does not undergo the building process, but rather activated forms, isopentenyl pyrophosphate (IPP or also isopentenyl diphosphate) and dimethylallyl pyrophosphate (DMAPP or also dimethylallyl diphosphate), are the components in the biosynthetic pathway.

When terpenes are modified chemically, such as by oxidation or rearrangement of the carbon skeleton, the resulting compounds are generally referred to as terpenoids. Degradation products of terpenoids in which carbon atoms have been lost through chemical or biochemical processes may contain different numbers of carbon atoms, but their overall structure will indicate their terpenoid origin and they will be still considered as terpenoids. Terpenoids constitute the largest class of naturally occurring molecules from the plant kingdom and a major means of communication between plants and their environment. Terpenoids also play key roles in animal development and physiology. Terpenoids are commercially important due to their use in a vast number of industrial products such as pharmaceuticals, flavoring agents, perfumes, insecticides, phytosanitary, coloring and anti-microbial agents. Some of the highly successful drugs from terpenoid family are Taxanes (cancer), Steroids (contraceptives, antiinflammatory), Artemisinin and derivatives (malaria).

Cembrene, or sometimes neocembrene, is a natural monocyclic diterpene. It is a colorless oil with a faint wax-like odor. Cembrene itself has little importance as chemical entity, being a trail pheromone for termites; however, the chemical structure of cembrene

is central to a very wide variety of other natural products found both in plants and in animals.

Figure 1. Simple Cembrane A, some of densley functionalised cembranolides and Uprolides D – G



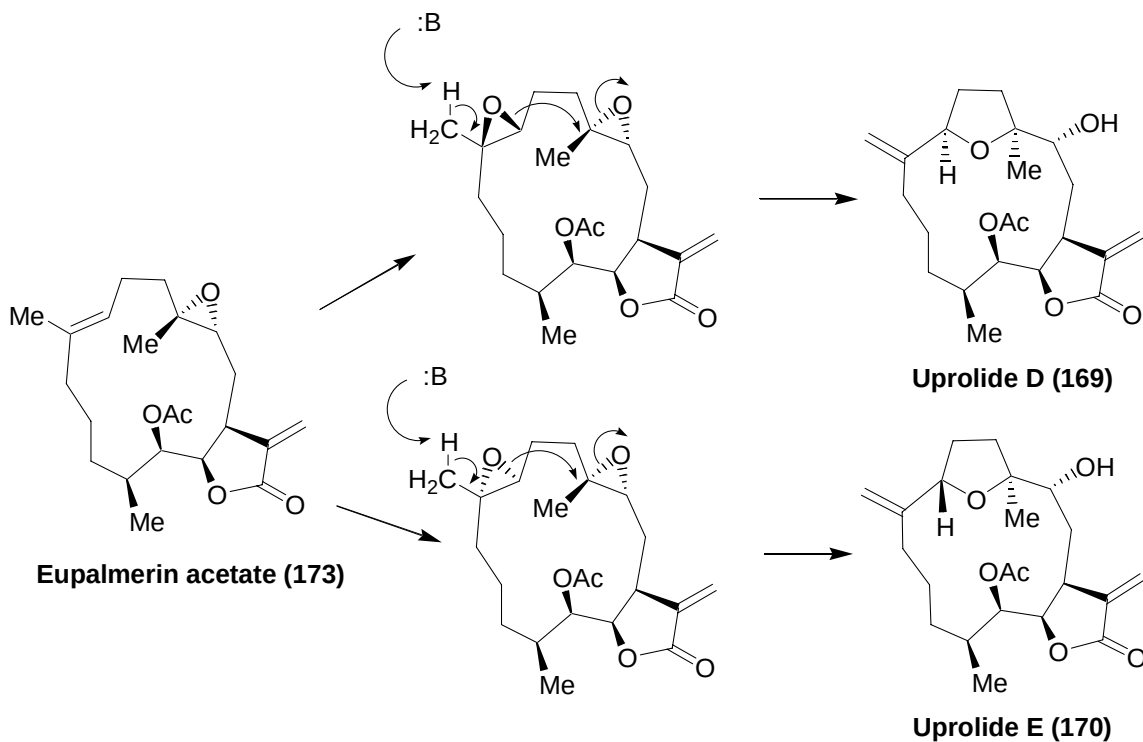
Cembranolides are a class of diterpenoids consisting of a 14-membered ring. Numerous cembranolides have been isolated from corals and other marine sources as well as from tobacco and other plants.¹ Cembrane diterpenoids, as a single class, represent the largest percentage of natural products isolated from *Eunicea* gorgonians. Among these new cembranolides some displayed moderate cytotoxicity against a variety of human cancer cell lines. The remarkable wide range of biological activity that has been recorded for these diterpenoids and their key role in the ecological behavior of soft

corals^{1d} has attracted the attention of both natural product isolation and synthetic chemists.²

Uprolides:

Rodriguez and co-workers in 1995, described the isolation of new cytotoxic cembranolides (Uprolides D and E, Figure 2) possessing a rare 4,7-oxa-bridged functionality from a species of gorgonian, *Eunicea mammosa* (Lamoroux).³ Gorgonians of the common Caribbean genus *Eunicea* were among the first marine invertebrates to be investigated chemically, with more than 15 species isolated. Throughout the last three decades these animals have been shown to be a rich source of several different skeletal classes of terpenes.

Figure 2. Possible Biosynthetic relationship between eupalmerin acetate and the uprolices



Eupalmerin acetate (**173**) was identified as the major constituent of the extract of the gorgonian, which is biosynthetically related to the uprolides. Eupalmerin acetate was originally isolated by Ciereszko and co-workers in the Caribbean gorgonian *Eunicea succinea* off the coast Florida.⁴ The structure of eupalmerin acetate (**173**) was elucidated originally by Rehm, primarily through chemical degradation methods and without knowledge of the stereochemical details.⁵ The absolute configuration of eupalmerin acetate was confirmed by Van der Helm and co-workers through an X-ray diffraction study and the relative stereochemistry was assigned by Rodriguez and co-workers based on 2D NMR analysis. The same spectroscopic techniques were used to ascertain the relative configurations of the biomimetically related uprolides.

Isolation

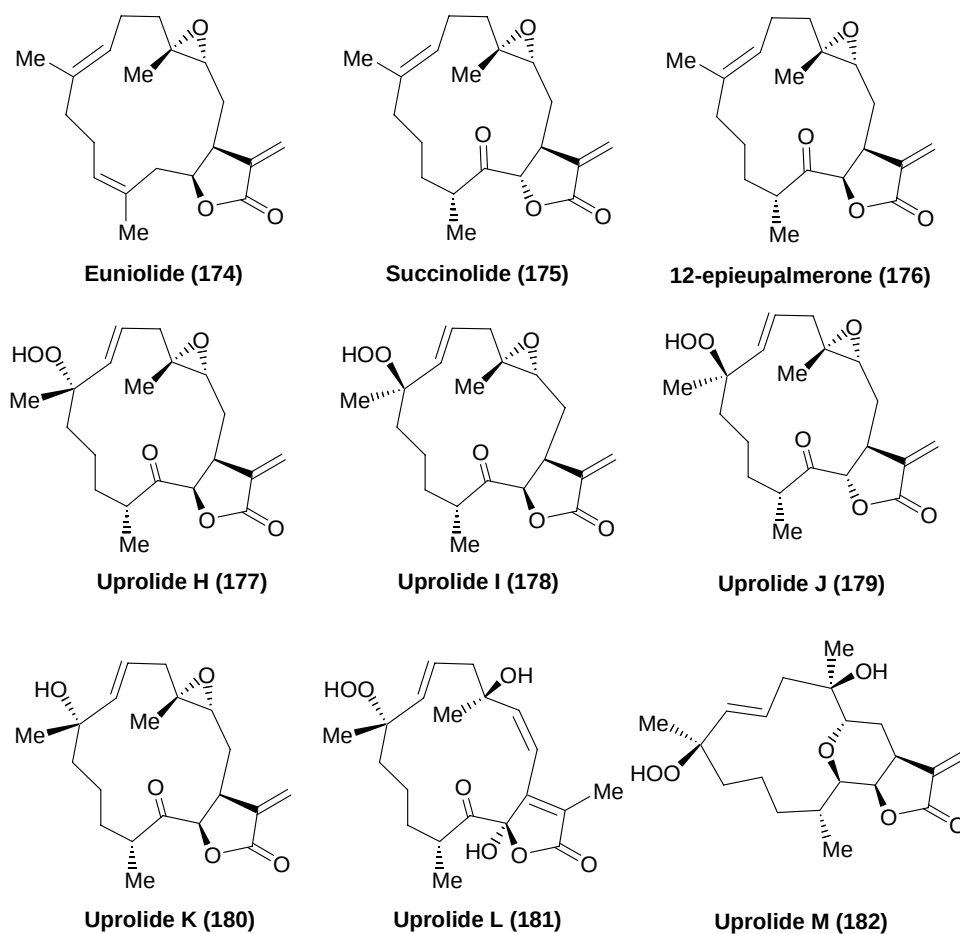
Fresh specimens of *Eunicea mammosa* collected at different locations around Puerto Rico (*Uprolide* is an acronym of *University of Puerto Rico*) was blended with MeOH:EtOAc (1:1), filtered and concentrated under vacuum to yield a crude residue which was partitioned between hexanes and water, and lastly between CHCl₃ and water. The hexane extract was concentrated to yield a green oil that was dissolved in toluene, filtered through *celite* and concentrated. The residue was chromatographed by size-exclusion chromatography on Bio-Beads SX-2 with toluene as the eluent. The combined terpenoid-rich fractions were concentrated to a yellow-orange oil that was chromatographed repeatedly on a silica gel column followed by normal phase HPLC to yield a major component of eupalmerin acetate followed by a minor polar fraction containing uprolides D-G. Each of the new metabolites was shown to possess the usual γ -lactone moiety and also a novel 4,7-oxa-bridged functionality.

Structural interpretation

The major structural features of uprolides were ascertained through spectroscopic data and by chemical correlation. The exact mass was found by HRMS corresponding to their molecular formula. The presence of two terminal methylene groups were shown in

NMR analysis with characteristic chemical shifts in the ^{13}C NMR spectrum at δ 147.5, 138.8, 122.4, and 115.7. The α -methylene- γ -lactone functionality was further supported by an IR stretch at 1770 cm^{-1} , by a UV absorption peak at $\lambda_{\text{max}} = 208\text{ nm}$ (MeOH), and two broad singlets in the ^1H NMR spectrum at δ 6.24 and 5.70. The relative stereochemistry of the tetrahydrofuran ring of uprolide D (**169**) was established as *cis* with the help of a NOESY experiment, in which the quaternary methyl at C-4 and the proton at C-7 are within NOE proximity. Since the absolute configuration of eupalmerin acetate had been established previously⁶ and because uprolide D (**169**) and uprolide E (**170**) are biosynthetically related, one can assume that they possess the same absolute configuration (Figure 2).

Figure 3. Uprolide class of cembranoids from *Eunicea pinta*⁷

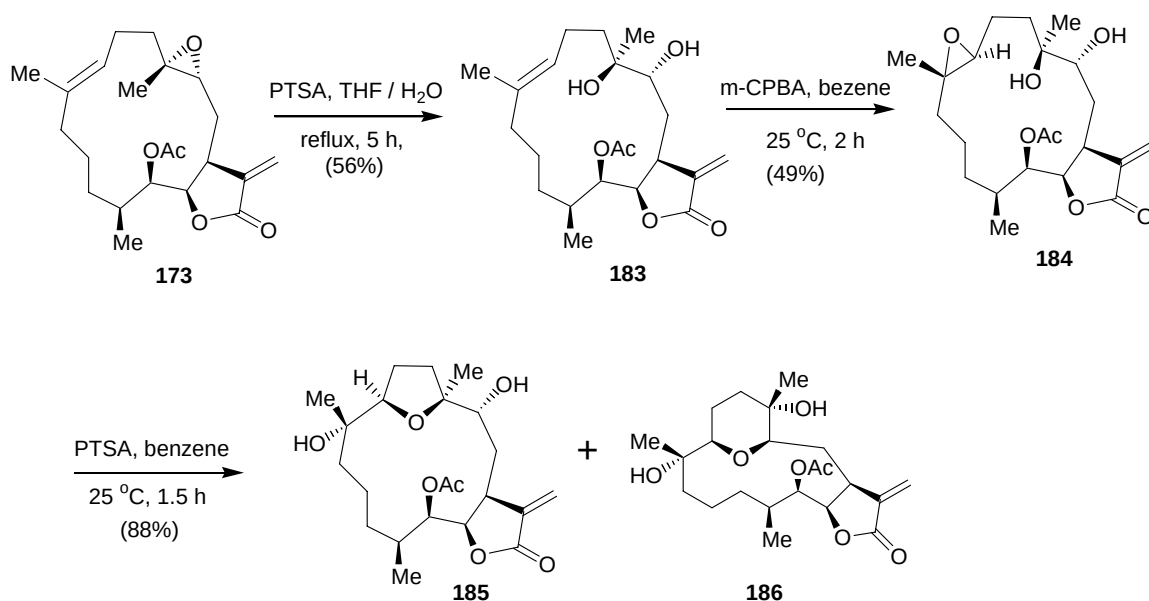


Biological Activity

The new uprolides displayed moderate cytotoxicity against HeLa cells: uprolide D acetate ($IC_{50} = 2.5 \mu\text{g/mL}$), uprolide D (**169**) ($IC_{50} = 5.0 \mu\text{g/mL}$), uprolide E (**170**) ($IC_{50} = 3.0 \mu\text{g/mL}$). Further, uprolide D acetate also displayed cytotoxicity against T-Cell leukemia ($IC_{50} = 7.0 \mu\text{g/mL}$), HCT 116 colon cancer ($IC_{50} = 7.0 \mu\text{g/mL}$), and MCF-7 breast adenocarcinoma ($IC_{50} = 0.6 \mu\text{g/mL}$).³

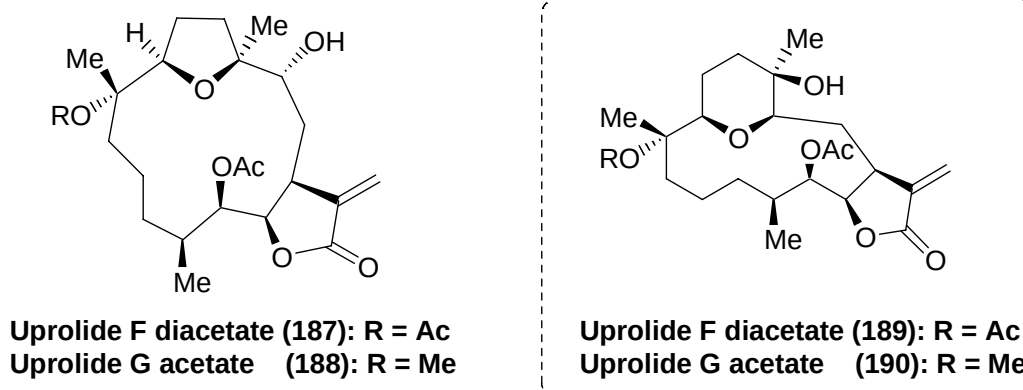
The structural features and biological activity of uprolides have stimulated substantial synthetic work, culminating in several approaches towards synthesis. Rodriguez and co-workers have synthesized uprolide D-G analogues and revised the structure of uprolide F diacetate and uprolide G acetate.⁸ Their original approach⁹ toward the synthesis of 4,7-oxa-bridged cembranolides was extended with some tactical modifications toward the synthesis of a structurally unique 3,7-oxa-bridged cembranolide analogue. Exposure of eupalmerin acetate (**173**) to PTSA in THF containing water at reflux temperature gave the kinetically favoured product **183**. The *m*-CPBA oxidation of **183** gave only one isomeric epoxide **184** in 49% yield. Subsequent treatment of **184** with PTSA in benzene gave the ethers **185** and **186** in 1.3:1 ratio.

Scheme 1. Conversion of eupalmarin acetate to uprolide F diacetate and uprolide G acetate



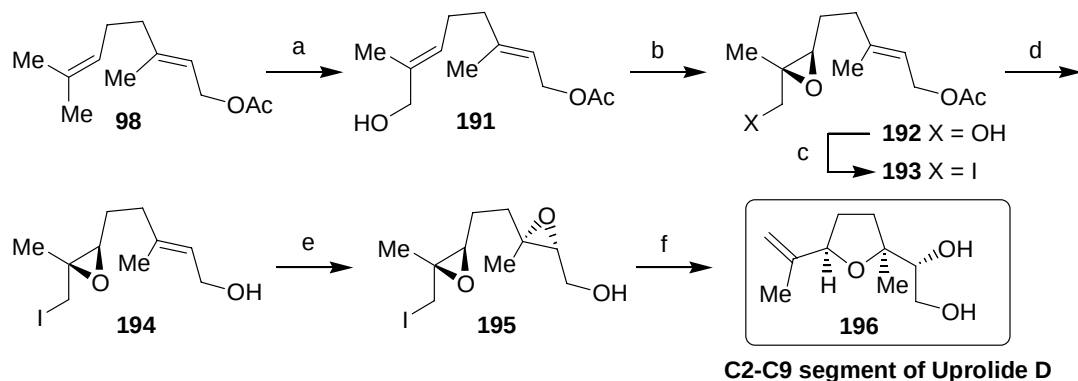
On the basis of synthetic interconversions and reinterpretation of spectral and chemical data, structures reported for uprolide F diacetate (**187**) and uprolide G acetate (**188**) were corrected to those of pyranethers **189** and **190** respectively (figure 4). The NMR analysis provided overwhelming support for their proposed structural assignments.

Figure 4. Revised structures for uprolide F diacetate and uprolide G acetate



Marshall and co-workers have synthesized C2-C9 segment of uprolides D by zinc mediated stereospecific elimination–cyclization of 1-iodomethyl-1,5-bis-epoxides.¹⁰ The precursor bis-epoxide was prepared starting from geraniol acetate. Geraniol acetate (**98**) was subjected to SeO₂ oxidation followed by Sharpless asymmetric epoxidation of the resulting allylic alcohol **191** using unnatural D-tartarate to furnish the epoxide **192**. Treatment of epoxy alcohol **192** with PPh₃.I₂ complex afforded the iodo acetate **193** which was subjected for Zemplen hydrolysis by employing potassium carbonate in methanol to procure the allylic alcohol **194**. Finally, the second Sharpless asymmetric epoxidation of **194** gave the key iodo methyl bis-epoxide **195**. The exo methylene was introduced through zinc-mediated stereospecific elimination cyclization of **195** in refluxing ethanol to give the 2,5-disubstituted tetrahydrofuran derivative **196**, the C2-C9 segment of uprolide D. (Scheme 2).

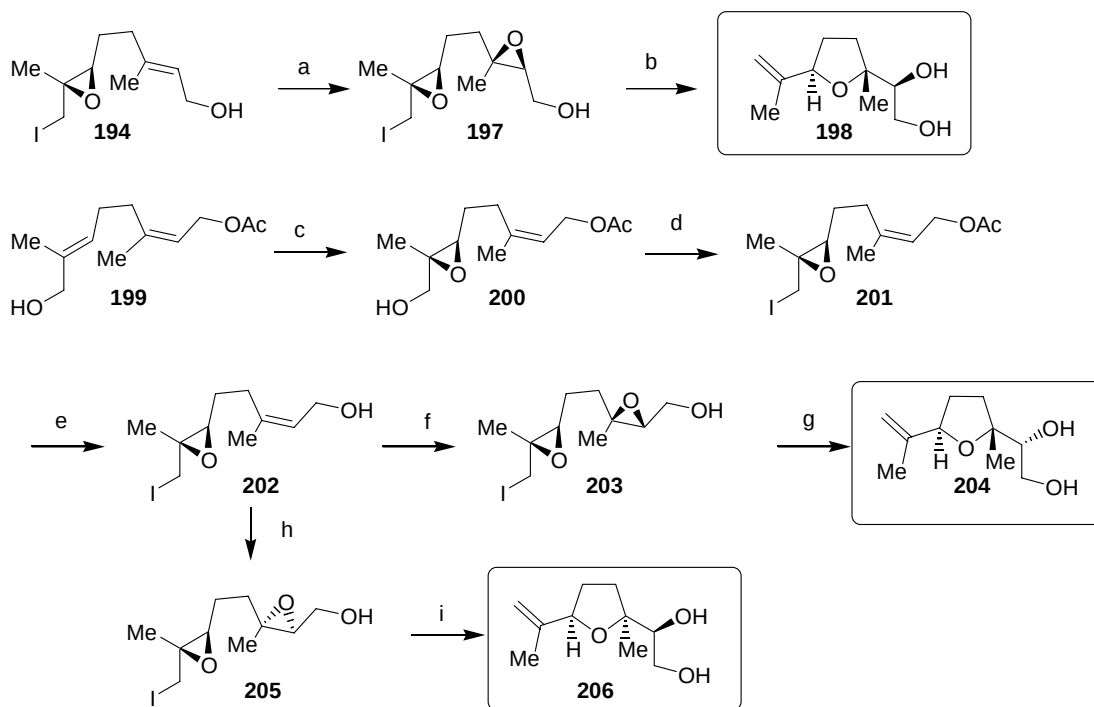
Scheme 2. C2-C9 segment of uprolide D



Reagents and conditions: (a) i. SeO_2 , $t\text{-BuOOH}$, CH_2Cl_2 ; ii. NaBH_4 , EtOH (55%). (b) D(-)DET, $\text{Ti}(\text{OiPr})_4$, $t\text{-BuOOH}$ (93%). (c) $\text{Ph}_3\text{P}\cdot\text{I}_2$, Im (83%). (d) K_2CO_3 , MeOH (94%). (e) D(-)DET, $\text{Ti}(\text{OiPr})_4$, $t\text{-BuOOH}$ (86%). (f) Zn, EtOH (95%).

All possible isomeric tetrahydrofurans were synthesized simply by changing the tartarate in Sharpless asymmetric epoxidation and changing the starting material from geraniol acetate to nerol acetate (Scheme 3).

Scheme 3. Synthesis of isomeric tetrahydrofurans



Reagents and conditions: (a) L(+)-DET, Ti(OiPr)₄, *t*-BuOOH (86%). (b) Zn, EtOH (95%). (c) D(-)-DET, Ti(OiPr)₄, *t*-BuOOH (95%). (d) Ph₃P.I₂, Im (70%). (e) K₂CO₃, MeOH (98%). (f) D(-)-DET, Ti(OiPr)₄, *t*-BuOOH (88%). (g) Zn, EtOH (86%). (h) L(+)-DET, Ti(OiPr)₄, *t*-BuOOH (85%). (i) Zn, EtOH (89%).

Despite exhibiting broad spectrum anti-cancer activity, the total synthesis of uprolide class of natural products has been not yet addressed except the preliminary work for the synthesis of central furan unit by Marshal and co-workers. This has prompted us to undertake this exercise with a focus on flexible strategies for the synthesis of related analogues with ease. Considering the novel skeleton of uprolides and densely functionalized central 14-carbon core we intended to approach the total synthesis of uprolides from two directions

- a. Stereoselective construction of central 14 carbon unit
- b. Examining the ease of ring closing metathesis reaction to form the bicyclic core of uprolides

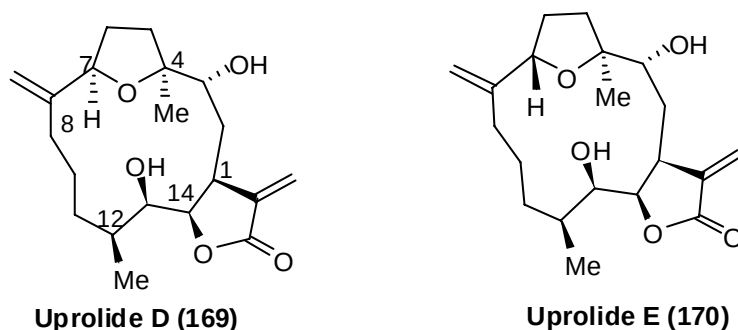
Accordingly, our efforts in this direction are summarized separately in two sections. Section I deals with the stereoselective construction of C1-C14 carbon unit of uprolide E with the requisite stereocenters and Section II provides the details about our efforts to construct the central bicyclic core of uprolides D and E using ring closing metathesis reactions.



Present Work

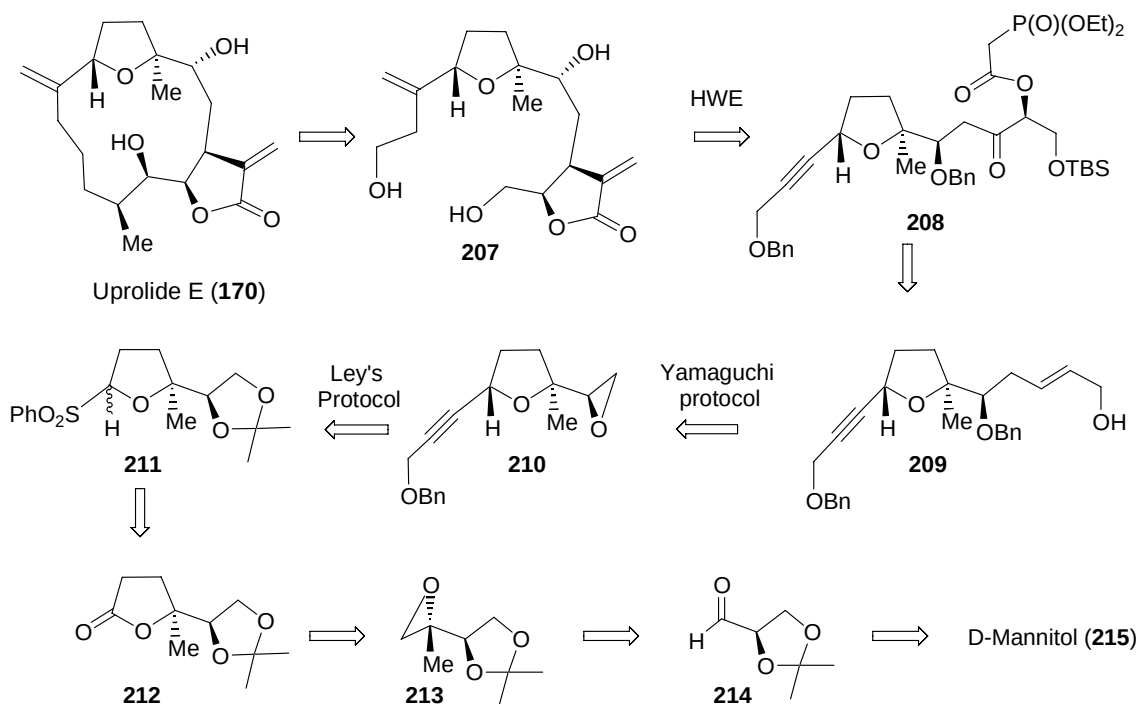
Cembranolide compounds in general, have exhibited a range of unique modes of action. While none of these metabolites have demonstrated a sufficient level of activity or spectrum of activity to be commercialized, several have served as templates for the design of synthetic compounds. Uprolides D (**169**) and E (**170**), the first representatives of a new family of furan integrated cembranolides, were recently isolated from the *Eunicea mammosa* collected at different locations around Puerto Rico.³ As explained in the introduction novel macrocyclic skeleton and the relative configuration of **169** and **170** were determined by extensive 2D NMR analyses. Biological testing of purified samples against different types of cancer cells revealed that these compounds have significant anticancer activity against HeLa cells, T-Cell leukemia, HCT 116 colon cancer, and MCF-7 breast adenocarcinoma. The combination of interesting anticancer activity and novel chemical structures makes the uprolices attractive targets for synthesis.

Figure 1. Uprolides D and E



Considering the novel skeleton of uprolices and densely functionalized central 14-carbon core we intended to approach the total synthesis of uprolices from two directions i.e. stereoselective construction of central 14 carbon unit and examining the ease of ring closing metathesis reaction to form the bicyclic core of uprolices. In this part, we describe our efforts in constructing the C1-C12 carbon unit of uprolide E, which has been selected considering our expertise in constructing the trans-configured furan rings by employing Steven Ley's sulphone protocol.

Scheme 1. Synthetic plan for uprolide E



As summarized in the retrosynthetic plan (Scheme 1), we envisaged an intramolecular Horner-Wadsworth-Emmons reaction for the construction of lactone from phosphonate (**208**). The phosphonate can be obtained from the trans allylic alcohol (**209**) through a couple of transformations. A Yamaguchi protocol of epoxide opening was planned on epoxide (**210**) for carbon chain extension. For the construction of 2,5-anti configured tetrahydrofuran, we thought of utilizing Ley's protocol (nucleophilic attack on oxonium ion generated insitu from a benzenesulfone at the anomeric position which was expected to give trans selectivity) on benzene sulfonate (**211**). The sulfone can be obtained from lactone (**212**) which in turn can be obtained from the epoxide (**213**) by a diethyl malonate opening. (*R*)-glyceraldehyde acetonide (**214**) was identified as an advanced starting point for the synthesis.

The synthetic sequences started with D-mannitol (Scheme 2). D-mannitol was treated with 2,2-dimethoxy propane in dry DMSO by employing catalytic PTSA to afford 1,2:5,6-*bis*-O-isopropylidene-D-mannitol (**216**) in 84% yield.¹¹ Oxidative cleavage of **216**

using silica gel impregnated sodium metaperiodate¹² gave the three-carbon synthon R-glyceraldehyde (**214**) in 93% yield. Subjecting **214** for methyl Grignard followed by PDC oxidation gave methyl ketone (**217**) in 65% overall yield (Scheme 2). The ¹H NMR spectrum and ¹³C NMR were in full agreement with assigned structure. The keto-methyl resonated at δ 2.22 in ¹H NMR spectrum. Further, ¹³C NMR spectrum shown the keto carbonyl carbon and the methyl at δ 208.51 and 26.05 respectively. To transform the keto derivative **217** to the epoxide **213**, we opted for Corey-Chayvosky reaction which was studied under various reaction conditions to control the diastereoselectivity. The combination of trimethyl sulfonium iodide and NaH in dry DMSO gave regiomeric 7:3 inseparable mixture of epoxides (**213/218**) in 35% yield.¹³ By little modification of the reaction condition (using trimethylsulfoxonium iodide in aq. sodium hydroxide as base) the yield can be improved up to 50% yield, however with similar diastereomeric selectivity.¹⁴ The ratio was ascertained by ¹H NMR spectrum. The geminal epoxide protons of major isomer resonated at δ 2.61 and 2.70 as doublets ($J = 4.8$ Hz), where as for minor isomer, they were observed at δ 2.57 and 2.78 ($J = 4.8$ Hz). Since, these epoxides are inseparable, in order to procure pure epoxide, we intended to prepare the respective diols **219** and **220**, where one of them (**219**) was reported to be a solid and the other one as syrup.¹³ Accordingly, treatment of the diastereomeric mixture of epoxides **213/218** with aq. sodium hydroxide provided the diols **219** and **220** mixture from which **219** could be separated by crystallization from a mixture of ethyl acetate-petroleum ether. The spectral as well as the analytical data of compound **219** was in agreement with the earlier reported data. Further, its single crystal X-ray structural analysis confirmed the assigned structure beyond the doubt (Figure 2).

After having access to pure diol **219**, we next focused our attention of converting back diol **219** to the pure epoxide **213** and its opening with the dimethyl malonate. Regioselective tosylation¹⁵ of **219** followed by treatment with sodium methoxide gave diastereomerically pure epoxide (**213**) in 85% yield. The NMR analysis and other analytical data were in full agreement with the assigned structure.

Scheme 2. Synthesis of chirally pure epoxide

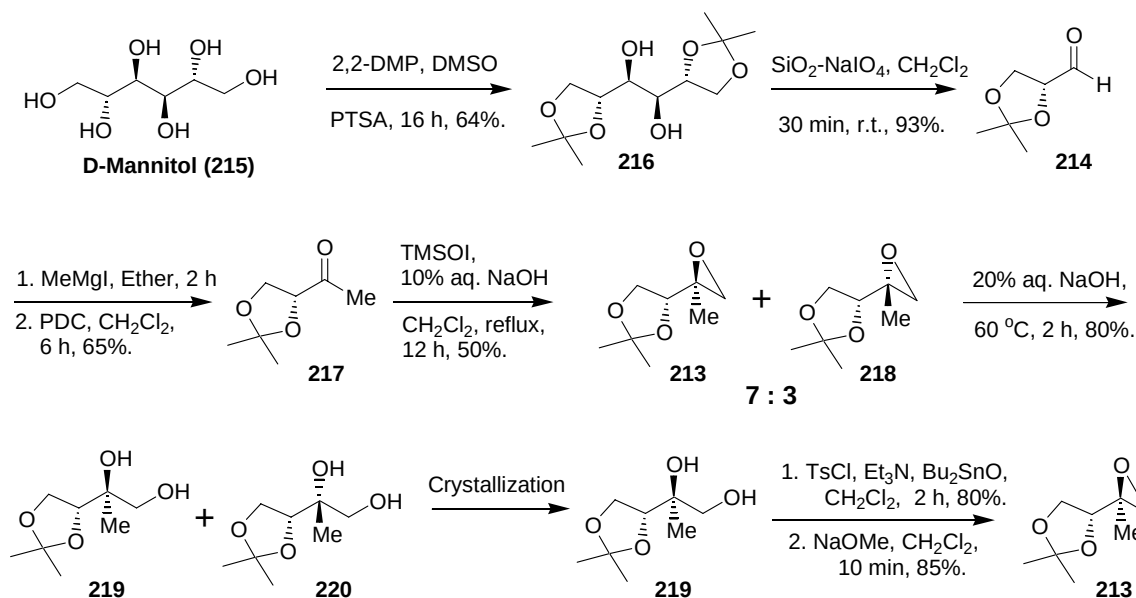
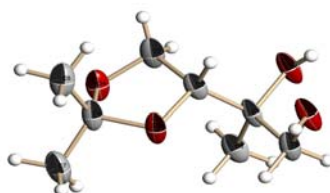


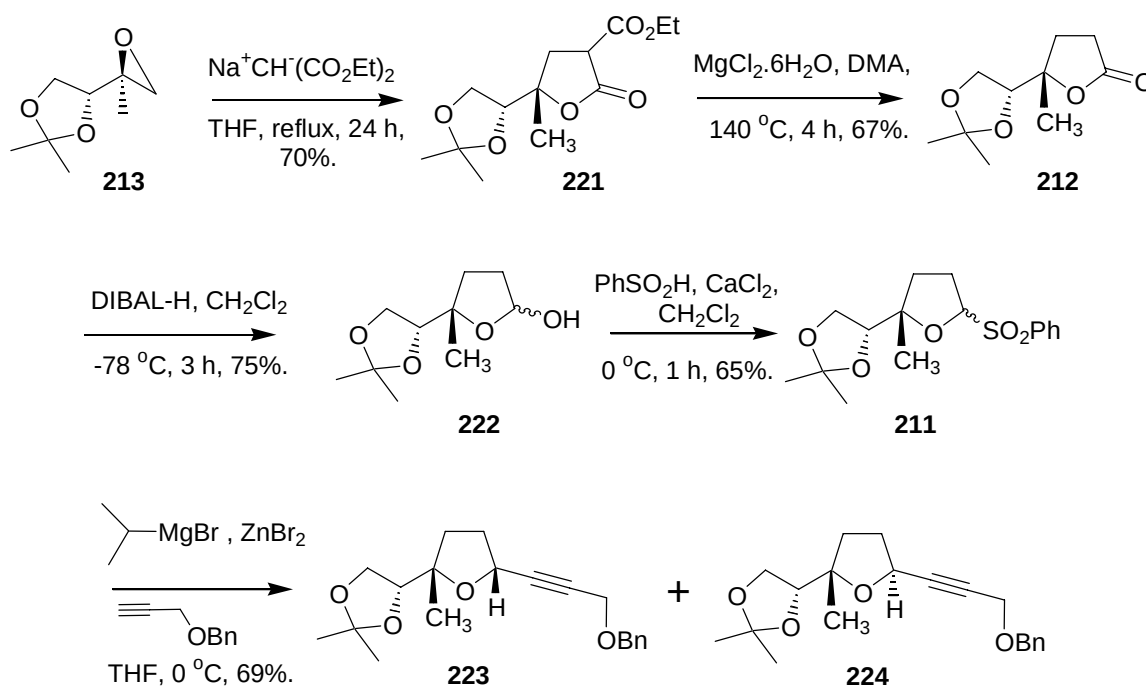
Figure 2. Crystal Structure of diol (219**)**



The epoxide (**213**) was treated with sodium salt of diethylmalonate in refluxing THF for 24 h to give β -ester lactone (**221**) in 70% yield.¹⁶ Decarboxylation of **221** under modified Krapcho's conditions¹⁷ afforded the lactone **212** in 67% yield. The structure was fully confirmed by ^1H and ^{13}C NMR analysis. Further in the IR spectrum of **212**, the characteristic C=O absorption of a γ -lactone carbonyl was observed at 1770 cm^{-1} . The lactone **212** was partially reduced with DIBAL-H and the resulting lactol **222** was treated with benzenesulphinic acid and calcium chloride in dry DCM to procure the key sulphone precursor **211** in 65% yield.¹⁸ In the ^1H NMR spectrum of **211**, peaks related to furan ring H-5 appeared as two sets of multiplets at δ 4.79 and 4.83 indicating the presence of

anomeric mixture. The aromatic protons of sulfone group appeared as two sets of multiplets at 7.52 and 7.81 ppm and rest of the spectrum was in complete agreement with the assigned structure. Subsequent C-C bond formation at C-2 by employing the proposed Ley's protocol was carried out by treating **211** with insitu generated dialkynyl zinc species¹⁹ derived from propargyl benzyl ether to give easily separable *cis* and *trans* isomers **223** and **224** in a 15:85 ratio (Scheme 3). The structures of both the tetrahydrofuran derivatives **223** and **224** were ascertained by spectral and analytical data. ¹H NMR spectrum of **223** showed the signal due the H-5 proton of tetrahydrofuran ring at δ 4.71 as a multiplet and the C-2 quaternary methyl was observed at δ 1.18 as a singlet. The propargylic CH₂ was observed at δ 4.20 as a doublet (J = 1.7 Hz). Similarly the ¹H NMR spectrum of **224** showed H-5 proton signal at δ 4.72 as a multiplet and C-2 methyl at δ 1.28 as a singlet. The propargylic CH₂ resonated at δ 4.19 as a doublet (J = 1.7 Hz).

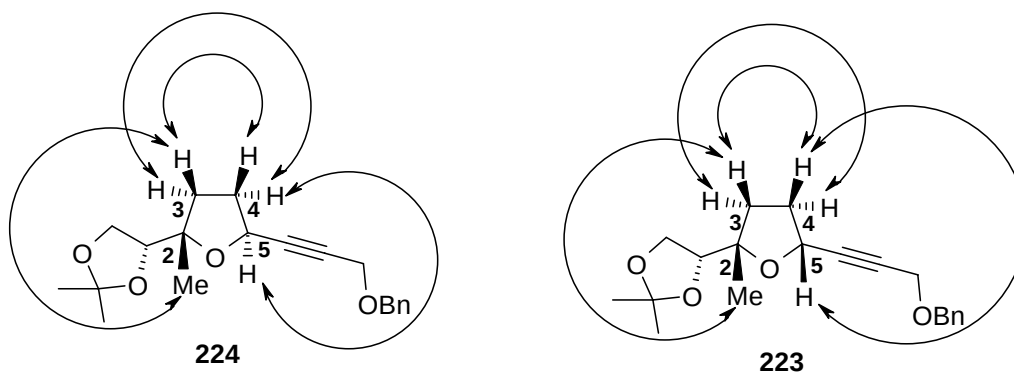
Scheme 3. Synthesis of 2,5-*anti*-configured tetrahydrofuran derivative



The assigned relative stereochemistry was confirmed by a NOESY experiment (Figure 2). In the NOESY experiment of the 2,5-*anti*-configured acetonide derivative

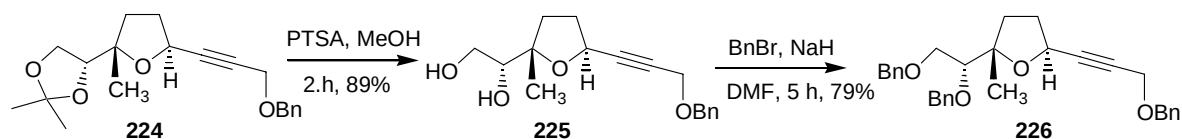
(**224**), we observed there is weak or negligible NOE between C-2 β -quaternary methyl and C-5 α -proton. It was found that C-2 methyl and C-3 β -proton are within NOE proximity, which in turn is having interaction with C-4 β -proton. Similarly there is interaction between C-5 α -proton and C-4 α -proton, which in turn is having space interaction with C-3 α -proton. In case of *syn*-tetrahydrofuran derivative (**223**), we observed that the C-2 β -quaternary methyl and C-5 α -proton are within the NOE proximity. There is NOE interaction between quaternary methyl and C-3 β -proton, which in turn is having interaction with C-3 β -proton. The C-3 β -proton is also having space interactions with C-4 β -proton. The C-3 α -proton was found to be within NOE proximity with C-4 α -proton (Figure 3). The observed correlations are in full agreement with the assigned structures.

Figure 3. NOESY correlations



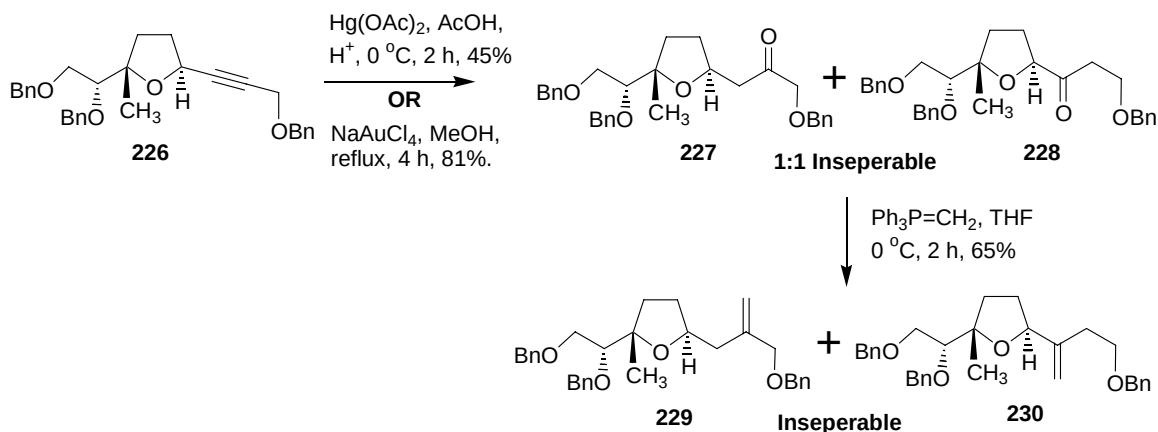
Before directly constructing the molecule from the left-hand side, we want to study the regioselectivity in hydration reaction of alkyne part. The acetone (**224**) was treated with PTSA in methanol at r.t. for 2 h gave diol (**225**) in 89% yield, which in turn was treated with 2 equivalents of benzyl bromide by using NaH in dry DMF for 5 h afforded the tribenzyl derivative (**226**) in 79% yield which is an ideal substrate for hydration reaction (Scheme 4). The ^1H NMR studies reveal the presence of three benzyl groups with a multiplet in the region 7.23-7.35 ppm integrating for 15 protons. Rest of the spectrum was in full agreement with the structure.

Scheme 4. Synthesis of tribenzyl derivative



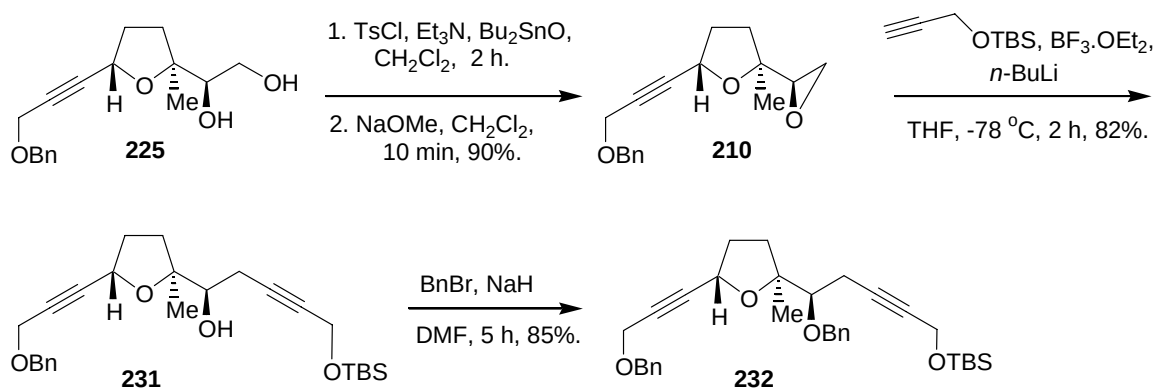
The tribenzyl derivative (**226**) was subjected to hydration reaction under standard reaction condition by using $\text{Hg}(\text{OAc})_2$ in acetic acid with catalytic sulfuric acid²⁰ unfortunately resulted in 1:1 mixture of inseparable regiomeric ketones **227** and **228** in 45% yield, which were fully confirmed by their spectral and analytical data. The C-5 methyl was observed as two singlets at δ 1.11, and 1.13 with equal intensity. ^{13}C NMR further confirmed the equal ratio of regiomers. Even the gold mediated hydration²¹ by using NaAuCl_4 in refluxing methanol resulted in same ratio of regiomers. The mixture of regiomeric ketones (**227/228**) were subjected to one carbon Wittig homologation by insitu generated ylide of methyl triphenylphosphonium bromide again gave the inseparable mixture of regio-exo methylene compounds (**229/230**) (Scheme 5). The exo-methylene protons were observed at δ 4.97 and 5.10 in the ^1H NMR spectrum of the mixture. ^{13}C NMR spectrum further confirmed the regiomeric mixture.

Scheme 5. Hydration of alkyne



Since the attempted hydration of alkyne (**226**) didn't give any regioselectivity, we opted for constructing the molecule from left-hand side so that we can have the selectivity problems of hydration in the later stages of our synthesis. Regioselective tosylation of **225** followed by treatment with K_2CO_3 in methanol gave epoxide (**210**) in 90% yield (Scheme 6). The epoxide protons were observed in 1H NMR spectrum at δ 2.50, 2.70, and 2.97. **210** was opened under Yamaguchi condition²² by using boronate of propargyl TBS ether gave the secondary alcohol **231** in 82% yield (Scheme 6). The 1H NMR showed disappearance of epoxide protons and the tertiary proton α to methylene was observed at δ 3.63 as a *dd* ($J = 8.7, 3.5$ Hz). The secondary hydroxyl group in **231** was protected as its benzyl ether by using benzyl bromide and NaH in dry DMF gave the dibenzyl O-TBS derivative **232** in 85% yield.

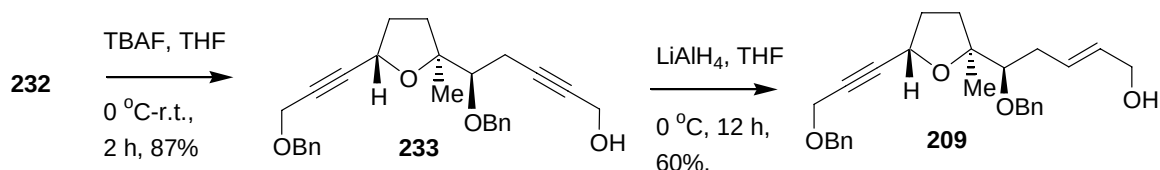
Scheme 6. Carbon chain extension by epoxide opening



The TBS functionality in **232** was deprotected by using TBAF in dry THF at 0 °C for 2 h gave alkynol **233** in 87% yield (Scheme 7). Our next intended partial reduction of alkynol to *trans*-alkenol²³ was studied thoroughly under different reaction conditions. Combination of Red-Al and ether or THF in different temperatures gave the *trans* allylic alcohol along with considerable amount of *cis* allylic alcohol. Reduction with LAH in refluxing THF gave exclusively the allene derivative along with some uncharacterisable products. After trial and error method, the combination of exactly one equiv of LAH in THF at 0 °C afforded the required *trans* allylic alcohol **209** in 60% yield. It was observed that, keeping the reaction mixture for longer period lowers the yield with allene type of

side products. ^1H NMR spectrum of **209** showed the olefinic protons at δ 5.55-5.74 as multiplet. The ^{13}C NMR analysis showed the olefinic carbons at δ 129.68, and 131.05. The product was further confirmed by IR and mass spectral studies.

Scheme 7. *Synthesis of trans allylic alcohol*



The trans allylic alcohol (**209**) was then subjected to Sharpless asymmetric dihydroxylation²⁴ condition by using AD-mix- α in *t*-butanol:water system surprisingly gave equal ratio of inseparable diastereomeric triols **234/235** (Scheme 8), which was confirmed by its ^1H and ^{13}C NMR spectral studies. The signal corresponding to C-2 methyl was observed at δ 1.30 and 1.32 as singlets with equal intensity in ^1H NMR spectrum. ^{13}C NMR further confirmed the equal ratio of diastereomers. The same ratio of diastereomers was observed with OsO_4/NMO condition (table 1).

Scheme 8. *Dihydroxylation of trans allylic alcohol*

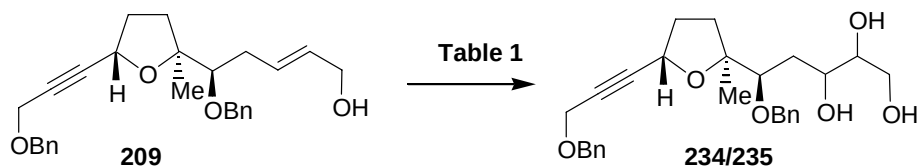
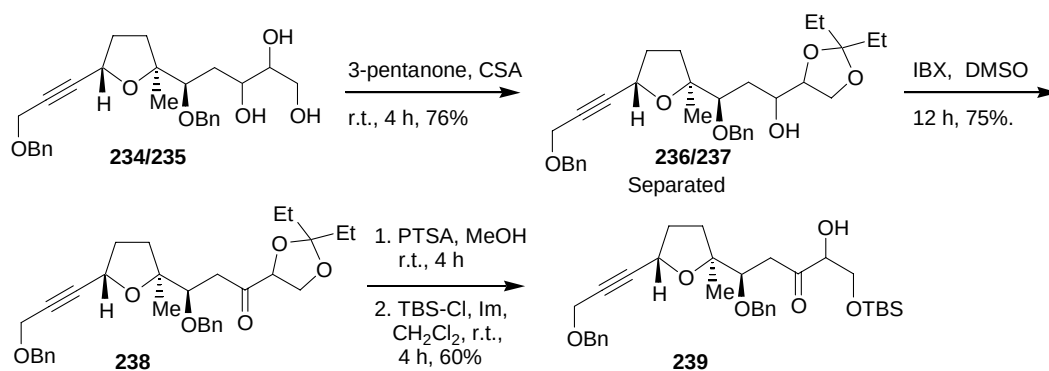


Table 1

Reagents	Temperature	Time	Ratio of diastereomers	yield (%)
AD-mix- α , <i>t</i> -BuOH:Water, MeSO_2NH_2	0 °C	7 h	1:1	67
OsO_4 , 50% aq. NMO Acetone:water	0 °C	5 h	1:1	58

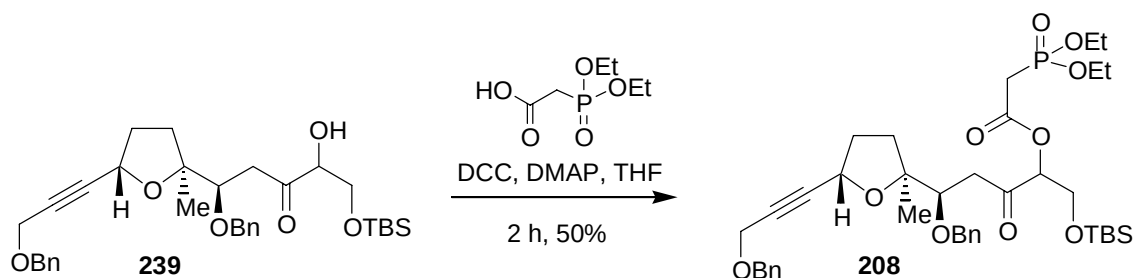
The mixture of triols (**234/235**) was subjected to 3-pentanone protection²⁵ using catalytic CSA to give separable mixture of diastereomers (**236/237**). We proceeded with one of the protected triol (**236**) for standardizing the reaction sequences. The secondary hydroxyl functionality in **236** was oxidized using IBX in dry DMSO to give keto compound (**238**) in 75% yield. The ¹H NMR spectrum showed the acetal methyl groups at δ 0.90 and 0.94 as two triplets ($J = 7.5$ Hz). The acetal CH₂'s were observed at 1.58-1.75 ppm as multiplet. Rest of the spectrum was in full agreement with the assigned structure. IR spectrum showed the carbonyl stretch at 1720 cm⁻¹, which confirmed the structure of **238** beyond doubt. Acetal deprotection in methanol-catalytic PTSA condition followed by selective primary TBS protection gave keto alcohol (**239**) in 60% overall yield (Scheme 9). The signals corresponding to TBS group was observed at δ 0.05 (6H), 0.86 (9H) as singlets in ¹H NMR spectrum. Rests of the signals are in full agreement with the assigned structure. Further, the ¹³C NMR analysis showed signal corresponding to carbonyl carbon at δ 209.53. The *t*-butyl group was observed at δ 25.88 and the two methyl groups attached to silicon resonated at δ -5.31 and -5.43. Rest of the spectrum was in full agreement with the assigned structure.

Scheme 9. Synthesis of keto alcohol



Coupling reaction of **239** with diethyl phosphonoacetic acid using DCC, catalytic DMAP in dry THF at 0 °C-r.t. gave phosphonate **208** in 50% yield (Scheme 12). The ¹H NMR showed the methylene group α to carbonyl and phosphonate at δ 3.07 as a doublet ($J = 21.5$ Hz). Rest of the spectrum was in full agreement with the structure.

Scheme 10. *Synthesis of phosphonate*



The much anticipated intramolecular Horner-Wadsworth-Emmons²⁶ reaction of phosphonate **208** was carried out using NaH in dry THF at 0 °C. To our surprise the reaction gave series of uncharacterisable spots and in every trial we observed decomposition of starting material (Scheme 11). The LiCl mediated reaction using diisopropyl ethylamine in acetonitrile didn't produce any cyclised product. Even the K₂CO₃ mediated cyclisation using 18-crown-6 in toluene resulted in decomposition of starting material.

Scheme 11. *Intramolecular Horner-Wadsworth-Emmons reaction*

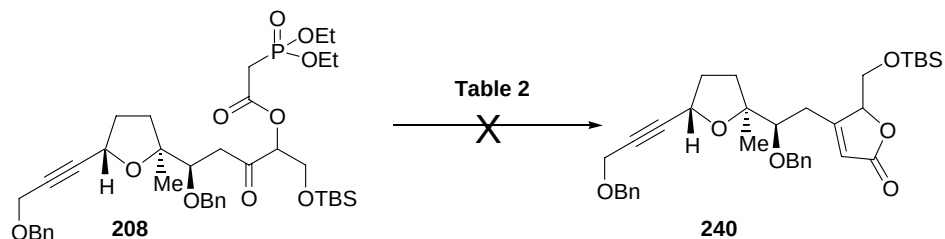
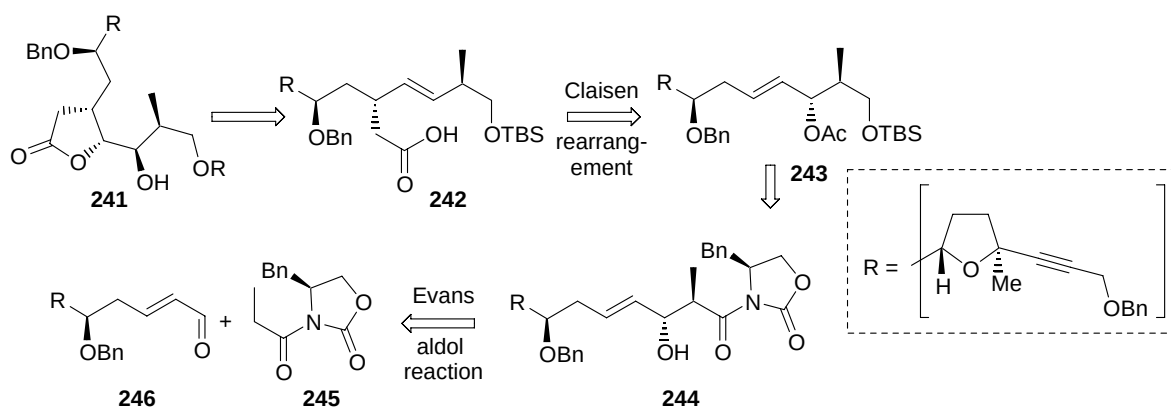


Table 2		
Condition	Temperature	Result
NaH, DME	0 °C- r.t.	SM decomposition
<i>i</i> -Pr ₂ NEt, LiCl CH ₃ CN	0 °C - r.t.	SM decomposition
K ₂ CO ₃ , 18-Crown-6 Toluene	r.t. - 80 °C	SM decomposition

Since the attempted intramolecular Horner-Wadsworth-Emmons reaction for the construction of lactone was a failure, we planned an alternative that involves an Ireland-

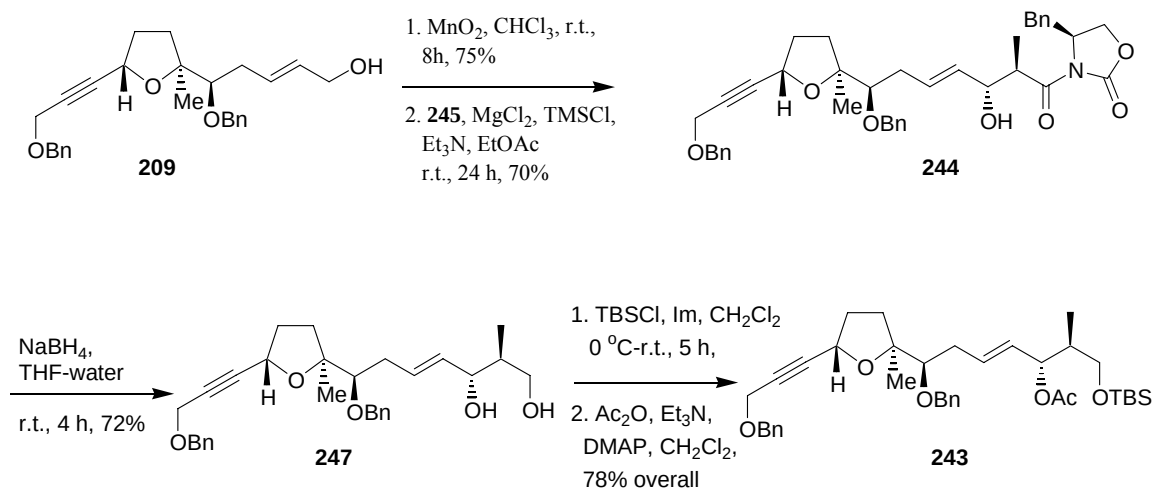
Claisen rearrangement. A short retrosynthetic strategy that addresses the construction of the butenolide ring along with the other requisite functional groups with the proposed stereochemistry was given in Scheme 12.

Scheme 12. *Alternative approach for uprolides funded upon Evans aldol and Claisen rearrangement*



The synthesis started with *trans* allylic alcohol (**209**). MnO_2 oxidation of **209** afforded allylic aldehyde **246** which was immediately subjected to non-Evans anti-Aldol reaction²⁷ using oxazolidinone derived from L-phenyl alanine (**245**) gave the aldol adduct in 70% yield. It was observed that the TMS ether was hydrolysed during work-up and we isolated the *anti*-hydroxy methyl compound **244**. The assigned structure was ascertained by its NMR analysis. The chiral auxiliary was reductively removed²⁸ by using NaBH_4 to afford **247** of which the primary hydroxyl functionality was protected as its TBS ether and the secondary hydroxyl group as its acetate to furnish the allylic acetate **243** in 78% overall yield (Scheme 13). In the ^1H NMR spectrum **243**, the acetate methyl was observed at δ 2.02 and the *tert*-butyl group of TBS functionality resonated at δ 0.87. Rest of the spectrum was in full agreement with the assigned structure.

Scheme 13. Non-Evans anti-Aldol reaction



The key Ireland-Claisen rearrangement²⁹ of the fully elaborated allylic acetate **243** under various conditions attempted was found to be unsuccessful and in most of the case we could only recover the starting material (Scheme 14).

Scheme 14. Ireland-Claisen rearrangement

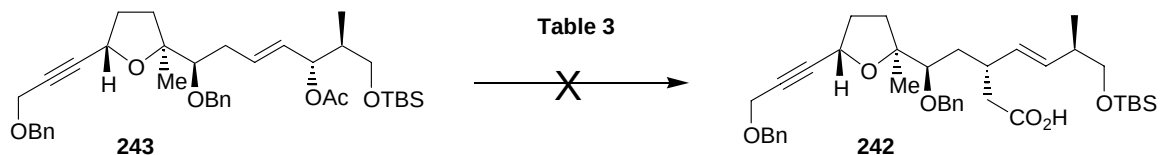


Table 3

Trial	Condition	Temperature	Result
1	LiHMDS , TBSCl , THF	-78°C -r.t., then reflux.	SM recovered
2	LDA , TMSCl , THF	-78°C -r.t., then reflux	SM recovered

Since the attempted Ireland-Claisen rearrangement was also unsuccessful, and considering the difficulty associated with material back-up and time constraints the Scheme from mannitol was terminated at this stage with the following conclusions

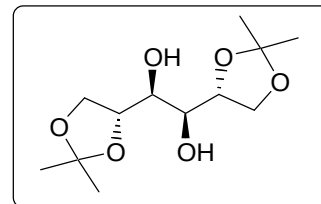
Conclusions:

A Ley's protocol was successfully utilized for the construction of 2,5-*anti* disubstituted tetrahydrofuran moiety present in Uprolide E. An intramolecular Horner-Wadsworth-Emmons approach for the construction of lactone fused to the Uprolide backbone was a failure. A complete carbon frame-work of uprolide E was constructed using non-Evans anti-Aldol reaction as key step.

Experimental

Experimental

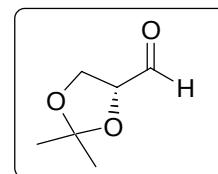
(1*S*,2*S*)-1,2-Bis((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)ethane-1,2-diol (**216**):



A mixture of powdered D-mannitol (60 g, 397 mmol), PTSA (0.31 g) and 2,2-dimethoxy propane (85.7 g, 823 mmol) in dry DMSO (100 mL) was stirred at r.t. under anhydrous nitrogen. Within one hour the suspended solid had dissolved and after 16 h the reaction mixture was poured into 3% aq. NaHCO₃ soln (300 mL). The mixture was extracted with ethyl acetate (4 X 500 mL) and the combined extracts in turn washed with water (1 x 500 mL). The organic layer was dried over Na₂SO₄, filtered and concentrated. The solid residue obtained was recrystallized (2:8, ethylacetate:pet ether) to give diacetonide **216** (52 g, 60%) as colorless solid.

Mol. Formula	: C ₁₂ H ₂₂ O ₆
¹H NMR (CDCl ₃ , 500 MHz)	: δ 1.35 (s, 6H), 1.41 (s, 6H), 2.62 (br s, 2H), 3.72 (d, <i>J</i> = 6.4 Hz, 2H), 3.96 (dd, <i>J</i> = 8.5, 5.6 Hz, 2H), 4.10 (dd, <i>J</i> = 8.5, 6.5 Hz, 2H), 4.16 (q, <i>J</i> = 6.4 Hz, 2H) ppm.
¹³C NMR (CDCl ₃ , 125 MHz)	: δ 25.29 (q), 26.77 (q), 66.76 (t), 71.17 (d), 76.07 (d), 109.28 (s) ppm.
Elemental Analysis	Calcd.: C, 54.95; H, 8.45. Found: C, 54.88; H, 8.29.

(*R*)-2,2-Dimethyl-1,3-dioxolane-4-carbaldehyde (**214**):

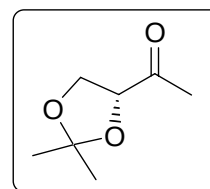


To a vigorously stirred suspension of silicagel-supported NaIO₄ (76 g) in DCM (400 mL) was added a solution of diol **216** (10 g, 38 mmol) in DCM (100 mL). The reaction was monitored by TLC until disappearance of the starting material. The mixture was filtered through a sintered glass funnel and washed thoroughly with DCM (400 mL).

The filtrate was concentrated to give aldehyde **214** (9.3 g, 93%) as colorless oil, which was directly taken for the next step without further purification.

Mol. Formula	: C ₆ H ₁₀ O ₃
¹H NMR	: δ 1.39 (s, 3H), 1.45 (s, 3H), 4.05-4.08 (m, 1H), 4.12-4.15 (CDCl ₃ , 200 MHz) (m, 1H), 4.33-4.35 (m, 1H), 9.68 (d, <i>J</i> = 2.0 Hz, 1H) ppm.
¹³C NMR	: δ 25.11 (q), 26.22 (q), 65.49 (t), 79.76 (d), 111.14 (s), (CDCl ₃ , 50 MHz) 201.53 (d) ppm.
Elemental Analysis	Calcd.: C, 55.37; H, 7.74. Found: C, 55.13; H, 7.55.

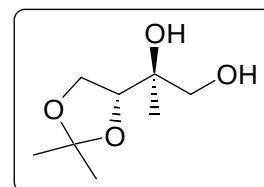
(R)-1-(2,2-Dimethyl-1,3-dioxolan-4-yl)ethanone (217):



To a solution of aldehyde **214** (15 g, 115 mmol) in dry ether (150 mL) was added freshly prepared solution of methyl magnesium iodide (230.5 mL, 1.0 M soln in ether, 230 mmol) slowly drop wise at 0 °C. The mixture was stirred for 2 h and the temperature was slowly raised to r.t.. Excess Grignard was quenched with careful addition of sat. NH₄Cl at 0 °C. The reaction mixture was diluted with ethyl acetate (100 mL) and water (100 mL). The organic phase was separated and the aq. phase was in turn washed with ethyl acetate (2 X 100 mL). The combined organic extracts were dried over Na₂SO₄, filtered and concentrated. The residue obtained was dissolved in dry DCM (200 mL) and added flame dried 4A° molecular sieves powder (20 g) and the reaction mixture was stirred at ice-cold temperature. Added PDC (86.5 g, 230 mmol) in portions at 0 °C followed by acetic anhydride (2 mL) and stirred at r.t. for 6 h. DCM was removed under reduced pressure and the residue obtained was dissolved in ethyl acetate (200 mL) and filtered through a pad of *celite*. The solid was washed with ethyl acetate (2 x 100 mL). The combined filtrates were concentrated and the residue was purified by column chromatography (7:3 petroleum ether/ethyl acetate) to give ketone **217** (10.8 g, 65%) as colorless oil.

Mol. Formula	: C ₇ H ₁₂ O ₃
[α]_D	: +65.1 (c 1.5, benzene).
¹H NMR (CDCl ₃ , 500 MHz)	: δ 1.36 (s, 3H), 1.46 (s, 3H), 2.22 (s, 3H), 3.95 (dd, <i>J</i> = 8.6, 5.6 Hz, 1H), 4.15 (t, <i>J</i> = 8.3 Hz, 1H), 4.35 (dd, <i>J</i> = 7.5, 5.6 Hz, 1H) ppm.
¹³C NMR (CDCl ₃ , 125 MHz)	: δ 25.01 (q), 26.05 (q), 66.38 (t), 80.45 (d), 110.88 (s), 208.51 (s) ppm.
Elemental Analysis	Calcd.: C, 58.32; H, 8.39. Found: C, 58.13; H, 8.25.

(S)-2-((R)-2,2-Dimethyl-1,3-dioxolan-4-yl)propane-1,2-diol (219**):**



To a solution of keto compound **217** (10 g, 69.36 mmol) in DCM (80 mL) was added trimethyl sulfoxonium iodide (15.26 g, 69.36 mmol) followed by a solution of 10% NaOH (27 mL). The reaction mixture was heated to reflux for 12 h and cooled. The organic phase was separated, dried over Na₂SO₄, filtered and concentrated. The inseparable mixture of epoxides (**213/218**) were taken in 20% sodium hydroxide solution (60 mL) and heated to 60 °C for 2 h. Added aq. sat. NH₄Cl solution (100 mL) with ice cooling and the reaction mixture was extracted with ethyl acetate (3 X 100 mL). The combined organic extracts were dried over Na₂SO₄, filtered and concentrated. The residue was purified by chromatography (1:1 petroleum ether/ethyl acetate) followed by crystallization to give diol **219** (3.1 g, 25.4% overall) as colorless solid.

Mol. Formula	: C ₈ H ₁₆ O ₄
M. P.	: 101 °C [lit 100-101 °C] ¹³
[α]_D	: +6.2 (c 1.0, CHCl ₃) [lit +5.14 (c 1.07, CHCl ₃)] ¹³
IR (CHCl₃) $\tilde{\nu}$	: 3339, 1374, 1215 cm ⁻¹ .
¹H NMR (CDCl ₃ , 500 MHz)	: δ 1.16 (s, 3H), 1.36 (s, 3H), 1.43 (s, 3H), 2.22 (br s, 2H), 3.45 (d, <i>J</i> = 11.3, Hz, 1H), 3.61 (d, <i>J</i> = 11.3, Hz, 1H), 3.91 (t, <i>J</i> = 7.6 Hz, 1H), 4.01 (d, <i>J</i> = 7.6, Hz, 1H), 4.08 (d, <i>J</i> =

6.8 Hz, 1H) ppm.

^{13}C NMR : δ 20.51 (q), 25.06 (q), 26.42 (q), 65.09 (t), 67.48 (t),
(CDCl_3 , 125 MHz) 72.34 (s), 79.63 (d), 109.04 (s) ppm.

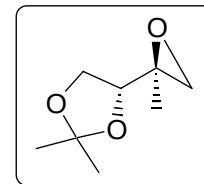
Elemental Analysis Calcd.: C, 54.53; H, 9.15.

Found: C, 54.35; H, 9.07.

Crystal data for 219 ($\text{C}_8\text{H}_{16}\text{O}_4$):

Formula weight	176.21
Temperature	297(2) K
Wavelength	0.71073 Å
Crystal system, space group	Triclinic, P-1
Unit cell dimensions	$a = 5.529(9)$ Å, $\alpha = 92.22(5)^\circ$. $b = 6.015(9)$ Å, $\beta = 96.18(8)^\circ$. $c = 15.45(2)$ Å, $\gamma = 114.62(3)^\circ$.
Volume	$462.4(12)$ Å ³
Z, Calculated density	2, 1.266 Mg/m ³
Absorption coefficient	0.100 mm ⁻¹
F(000)	192
Crystal size	0.86 x 0.09 x 0.08 mm
Theta range for data collection	4.09 to 25.10° deg.
Limiting indices	$-6 \leq h \leq 6$, $-7 \leq k \leq 7$, $-18 \leq l \leq 18$
Reflections collected / unique	3145 / 1341 [R(int) = 0.0397]
Completeness to $\theta = 25.10^\circ$	81.5 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9920 and 0.9187
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	1341 / 0 / 114
Goodness-of-fit on F^2	1.180
Final R indices [$I > 2\sigma(I)$]	$R_1 = 0.0914$, $wR_2 = 0.2819$
R indices (all data)	$R_1 = 0.1333$, $wR_2 = 0.3383$
Largest diff. peak and hole	0.227 and -0.242 e. Å ⁻³

(R)-2,2-Dimethyl-4-((R)-2-methyloxiran-2-yl)-1,3-dioxolane (213):



To a solution of diol **219** (2 g, 11.35 mmol) in dry DCM (20 mL) was added tosyl chloride (2.16 g, 11.35 mmol), dibutyl tin oxide (57 mg, 0.23 mmol) followed by triethylamine (3.2 mL, 22.7 mmol) and stirred at r.t. for 2 h. DCM was removed under reduced and crude mixture was purified by column chromatography (7:3 petroleum ether/ethyl acetate) to give monotosylate (3 g, 80%) as colorless oil. To a solution of tosylate (3 g, 9.08 mmol) in dry DCM (20 mL) was added sodium methoxide solution (250 mg of Na in 4 mL of methanol, 10.89 mmol) with cooling and stirred for 10 min. Added a sat. solution of NH₄Cl (5 mL) and the mixture was diluted with DCM (10 mL). The organic phase was separated and the aq. phase in turn was washed with DCM (2 X 10 mL). The combined organic extracts were dried over Na₂SO₄, filtered and concentrated. The crude residue was purified by column chromatography (4:1 petroleum ether/ethyl acetate) to furnish epoxide **213** (1.22 g, 85%) as colorless oil.

Mol. Formula : C₈H₁₄O₃

[α]_D : -2.07 (c 4.8, CHCl₃).

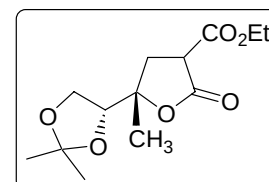
¹H NMR : δ 1.33 (s, 6H), 1.42 (s, 3H), 2.61 (d, *J* = 4.8 Hz, 1H), 2.71 (CDCl₃, 500 MHz) (d, *J* = 4.8 Hz, 1H), 3.83 (dd, *J* = 8.0, 6.4 Hz, 1H), 3.89 (t, *J* = 6.4 Hz, 1H), 4.02 (dd, *J* = 8.0, 6.8 Hz, 1H) ppm.

¹³C NMR : δ 16.73 (q), 25.01 (q), 26.14 (q), 52.29 (t), 56.14 (s), (CDCl₃, 125 MHz) 65.75 (t), 77.81 (d), 109.72 (s) ppm.

Elemental Analysis Calcd.: C, 60.74; H, 8.92.

Found: C, 60.53; H, 8.95.

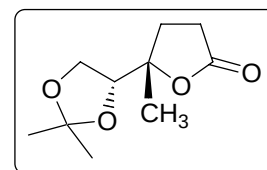
(5S)-Ethyl 5-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)-5-methyl-2-oxotetrahydrofuran-3-carboxylate(221):



To a solution of epoxide **213** (1.2 g, 7.58 mmol) in dry THF (10 mL) was added freshly prepared sodiodiethylmalonate (1.66 g, 9.1 mmol) and the mixture was heated to reflux for 24 h. The reaction mixture was cooled to ice-cold temperature and quenched with sat. aq. NH₄Cl solution (5 mL) and diluted with ethyl acetate (10 mL). The organic phase was separated and aq. phase in turn washed with ethyl acetate (10 mL). The combined organic extracts were dried over Na₂SO₄, filtered and concentrated. The residue was chromatographically purified (7:3 petroleum ether/ethyl acetate) to give **221** (1.44 g, 70%) as colorless oil.

Mol. Formula	: C ₁₃ H ₂₀ O ₆
IR (CHCl₃) $\tilde{\nu}$	: 2988, 1781, 1735 cm ⁻¹ .
¹H NMR (CDCl ₃ , 300 MHz)	: δ 1.30-1.38 (m, 6H), 1.41, 1.42 (2s, 3H), 1.45, 1.46 (2s, 3H), 2.20-2.73 (m, 2H), 3.62-3.71 (m, 1H), 3.77-3.86 (m, 1H), 4.00-4.09 (m, 1H), 4.19-4.29 (m, 3H) ppm.
¹³C NMR (CDCl ₃ , 50 MHz)	: δ 14.03 (q), 21.57 (q), 23.11 (q), 24.36 (q), 24.58 (q), 25.94 (q), 26.09 (q), 32.41 (t), 33.92 (t), 46.45 (d), 47.96 (d), 60.16 (t), 61.97 (t), 64.94 (t), 65.09 (t), 79.28 (d), 79.68 (d), 84.28 (s), 84.94 (s), 110.16 (s), 167.39 (s), 167.98 (s), 170.48 (s), 170.88 (s) ppm.
Elemental Analysis	Calcd.: C, 57.34; H, 7.40. Found: C, 57.12; H, 7.21.

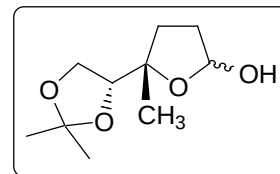
(S)-5-((R)-2,2-Dimethyl-1,3-dioxolan-4-yl)-5-methyldihydrofuran-2(3H)-one (212):



A mixture of β -ester lactone **221** (1.3 g, 4.77 mmol), MgCl₂.6H₂O (1.06 g, 5.25 mmol) in N,N-dimethyl acetamide (5 mL) was heated to 140 °C for 4 h. The reaction mixture was cooled to r.t. and added water (5 mL). The mixture was extracted with diethyl ether (3 X 10 mL), combined organic extracts were dried over Na₂SO₄, filtered and concentrated. The crude was purified by column chromatography purification (7:3 petroleum ether/ethyl acetate) to give lactone **212** (640 mg, 67%) as colorless oil.

Mol. Formula	: C ₁₀ H ₁₆ O ₄
[α]_D	: +1.40 (c 4.6, MeOH).
IR (CHCl₃) $\tilde{\nu}$	: 2987, 1776, 1211 cm ⁻¹ .
¹H NMR (CDCl ₃ , 500 MHz)	: δ 1.34 (s, 3H), 1.35 (s, 3H), 1.44 (s, 3H), 1.89-1.95 (m, 1H), 2.33 (ddd, <i>J</i> = 13.0, 10.4, 5.3 Hz, 1H), 2.55 (ddd, <i>J</i> = 17.9, 10.4, 5.3 Hz, 1H), 2.67 (ddd, <i>J</i> = 17.9, 10.4, 7.9 Hz, 1H), 3.72 (dd, <i>J</i> = 8.7, 6.3 Hz, 1H), 4.03 (dd, <i>J</i> = 8.7, 7.1 Hz, 1H), 4.18 (t, <i>J</i> = 6.7 Hz, 1H) ppm.
¹³C NMR (CDCl ₃ , 50 MHz)	: δ 22.38 (q), 24.36 (q), 25.98 (q), 29.03 (t) 2C, 65.02 (t), 79.46 (d), 85.56 (s), 109.86 (s), 176.03 (s) ppm.
Elemental Analysis	Calcd.: C, 59.98; H, 8.05. Found: C, 59.82; H, 8.11.

(S)-5-((R)-2,2-Dimethyl-1,3-dioxolan-4-yl)-5-methyltetrahydrofuran-2-ol (222):



To solution of lactone **212** (300 mg, 1.5 mmol) in dry DCM (10 mL) at –78 °C was added DIBAL-H (1.08 mL of 1.52 M solution in toluene, 1.65 mmol) stirred for 3 h. Added sat. solution of sodium potassium tartrate (3 mL) and the reaction mixture was vigorously stirred at r.t. for 6 h. The mixture was filtered through a pad of *celite* and washed with DCM (20 mL). The filtrates were concentrated and the residue was purified by column chromatography (3:2 petroleum ether/ethyl acetate) to give lactol **222** (227 mg, 75%) as colorless oil.

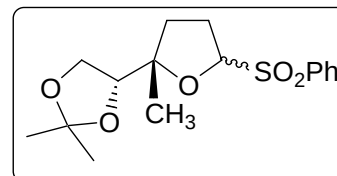
Mol. Formula	: C ₁₀ H ₁₈ O ₄
¹H NMR (CDCl ₃ , 200 MHz)	: δ 1.32, 1.35, 1.37, 1.41, 1.44, 1.48 (6s, 9H), 1.89-2.19 (m, 3H), 2.24-2.42 (m, 1H), 3.61-3.75 (m, 1H), 3.97-4.07 (m, 1H), 4.13-4.22 (m, 1H), 5.38-5.51 (m, 1H) ppm.
¹³C NMR (CDCl ₃ , 50 MHz)	: δ 22.30 (q), 22.93 (q), 24.14 (q), 24.36 (q), 24.66 (q), 26.02 (q), 29.10 (t), 29.88 (t), 33.48 (t), 33.88 (t), 65.53 (t), 65.86 (t), 79.87 (d), 80.38 (d), 84.35 (s), 84.54 (s), 98.50

(d), 98.72 (d), 109.16 (s), 109.31 (s) ppm.

Elemental Analysis Calcd.: C, 59.39; H, 8.97.

Found: C, 59.18; H, 8.81.

(R)-2,2-Dimethyl-4-((S)-2-methyl-5-phenylsulfonyltetrahydrofuran-2-yl)-1,3-dioxolane (211):



To a solution of lactol **222** (200 mg, 0.99 mmol) in dry DCM (5 mL) was added powdered CaCl_2 (150 mg, 1.49 mmol) and cooled to 0 °C. Added freshly prepared benzenesulfinic acid (154 mg, 1.09 mmol) in portion and stirred for 1 h at 0 °C. The mixture was filtered through a pad of *celite* and washed with DCM (10 mL). The filtrate was concentrated and residue obtained was purified by column chromatography (7:3 petroleum ether/ethyl acetate) to give sulphone **211** (210 mg, 65%) as colorless oil.

Mol. Formula : $\text{C}_{16}\text{H}_{22}\text{O}_5\text{S}$

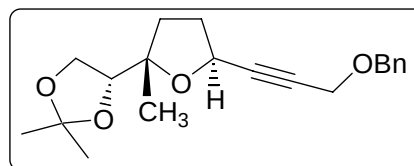
^1H NMR : δ 1.20 (s, 3H), 1.28 (s, 3H), 1.32 (s, 3H), 1.83-2.14 (m, 2H), 2.32-2.49 (m, 1H), 2.53-2.72 (m, 1H), 3.51 (dd, J = 7.5, 5.9 Hz, 1H), 3.82-3.96 (m, 2H), 4.71-4.86 (m, 1H), 7.44-7.62 (m, 3H), 7.78-7.85 (m, 2H) ppm.

^{13}C NMR : δ 22.34 (q), 24.45 (q), 25.91 (q), 29.45 (t), 31.65 (t), 65.71 (t), 80.11 (d), 89.36 (s), 94.92 (d), 109.38 (s), 128.67 (d) 2C, 129.25 (d) 2C, 133.46 (d), 137.00 (s) ppm.

Elemental Analysis Calcd.: C, 58.87; H, 6.79; S, 9.82.

Found: C, 58.69; H, 6.59; S, 9.64.

(R)-4-((2S,5S)-5-(3-(Benzyloxy)prop-1-ynyl)-2-methyltetrahydrofuran-2-yl)-2,2-dimethyl-1,3-dioxolane (224):

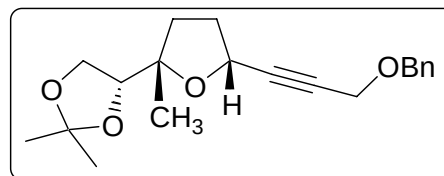


A freshly generated solution of isopropyl magnesium bromide (2.72 mL of 0.45 M solution in THF, 1.22 mmol) was treated with freshly prepared solution of anhydrous ZnBr_2 (0.68 mL of 1 M solution in THF, 0.67 mmol) at 0 °C for 30 min. Added a solution

propargyl benzyl ether (179 mg, 1.22 mmol), in THF (3 mL). The mixture was stirred at 0 °C for another 30 min. A solution of sulfone **211** (200 mg, 0.61 mmol) in dry THF (4 mL) was added slowly dropwise for a period of 10 min. The mixture was stirred at 0 °C for 4 h and quenched with sat. NH₄Cl solution (4 mL) and diluted with ethyl acetate (5 mL). The organic phase was separated and aq. phase in turn was washed with ethyl acetate (2 X 5 mL). The combined organic extracts were dried over Na₂SO₄, filtered and concentrated. The residue obtained was purified by flash column chromatography (7:3 petroleum ether/ethyl acetate) to give *anti*-acetone **224** (119 mg, 59%) and *syn*-acetone **223** (10 mg, 10%) as colorless oils.

Mol. Formula	: C ₂₀ H ₂₆ O ₄
[α]_D	: −4.08 (c 1.2, CHCl ₃).
¹H NMR (CDCl ₃ , 200 MHz)	: δ 1.28 (s, 3H), 1.33 (s, 3H), 1.42 (s, 3H), 1.81-1.90 (m, 1H), 2.01-2.30 (m, 3H), 3.71 (dd, <i>J</i> = 7.4, 5.7 Hz, 1H), 3.93-4.07 (m, 2H), 4.19 (d, <i>J</i> = 1.7 Hz, 2H), 4.57 (s, 2H), 4.69-4.75 (m, 1H), 7.29-7.34 (m, 5H) ppm.
¹³C NMR (CDCl ₃ , 50 MHz)	: δ 23.19 (q), 24.79 (q), 26.25 (q), 33.49 (t), 33.68 (t), 57.31 (t), 65.86 (t), 68.64 (d), 71.34 (t), 80.39 (s), 80.43 (d), 84.18 (s), 86.79 (s), 109.32 (s), 127.72 (d), 127.95 (d) 2C, 128.31 (d) 2C, 137.37 (s) ppm.
Elemental Analysis	Calcd.: C, 72.70; H, 7.93. Found: C, 72.60; H, 8.02.

(*R*)-4-((2*S*,5*R*)-5-(3-(Benzyloxy)prop-1-ynyl)-2-methyltetrahydrofuran-2-yl)-2,2-dimethyl-1,3-dioxolane (223):



Mol. Formula	: C ₂₀ H ₂₆ O ₄
[α]_D	: −6.3 (c 1.0, CHCl ₃).
¹H NMR (CDCl ₃ , 400 MHz)	: δ 1.17 (s, 3H), 1.33 (s, 3H), 1.42 (s, 3H), 1.71-1.78 (m, 1H), 2.01-2.09 (m, 1H), 2.13-2.28 (m, 2H), 3.90 (dd, <i>J</i> =

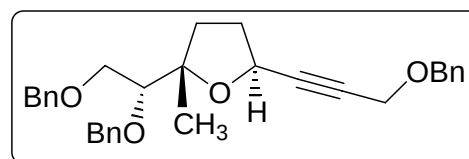
8.6, 6.2 Hz, 1H), 4.04 (dd, $J = 8.6, 6.9$ Hz, 1H), 4.14 (dd, $J = 6.9, 6.2$ Hz, 1H), 4.19 (d, $J = 1.6$ Hz, 2H), 4.57 (s, 2H), 4.70 (tt, $J = 6.4, 1.6$ Hz, 1H), 7.27-7.34 (m, 5H) ppm.

^{13}C NMR : δ 21.29 (q), 24.83 (q), 26.24 (q), 33.48 (t), 35.36 (t), 57.48 (t), 65.87 (t), 68.30 (d), 71.52 (t), 80.24 (d), 80.49 (s), 84.21 (s), 86.54 (s), 109.37 (s), 127.84 (d), 128.05 (d) 2C, 128.42 (d) 2C, 137.43 (s) ppm.

Elemental Analysis Calcd.: C, 72.70; H, 7.93.

Found: C, 72.66; H, 7.89.

(2S,5S)-5-(3-(Benzyloxy)prop-1-ynyl)-2-((R)-1,2-bis (benzyloxy) ethyl)-2 methyl tetrahydrofuran (226):



To a solution of acetonide **224** (100 mg, 0.30 mmol) in methanol (5 mL) was added PTSA (21 mg, 0.12 mmol) and the mixture was stirred at r.t. for 3 h. Added triethylamine (2 mL) and stirred for another 30 min. Methanol was removed in *vacuo* and the residue obtained was purified by column chromatography (1:1 petroleum ether/ethyl acetate) gave diol **225** (71 mg, 81%) as colorless oil. To a solution of diol (70 mg, 0.24 mmol) in dry DMF (2 mL) was added NaH (28 mg of 60% dispersed in mineral oil, 0.72 mmol) at ice-cold temperature. The mixture was stirred for 10 min and to the dark brown solution was added benzyl bromide (0.06 mL, 0.50 mmol) slowly dropwise and the mixture was stirred at r.t. 4 h. The mixture was quenched with ice and diluted with ethyl acetate (5 mL). The organic phase was separated and washed with water (3 X 3 mL), brine (3 mL), dried over Na_2SO_4 , filtered and concentrated. The residue was purified by column chromatography (4:1 petroleum ether/ethyl acetate) to give tribenzyl derivative **226** (98 mg, 85%) as colorless oil.

Mol. Formula : $\text{C}_{31}\text{H}_{34}\text{O}_4$

$[\alpha]_D$: -9.17 (c 2.5, CHCl_3).

IR (Neat) $\tilde{\nu}$: 2926, 2855, 1956, 1453 cm^{-1} .

^1H NMR : δ 1.27 (s, 3H), 1.71-1.81 (m, 1H), 1.97-2.24 (m, 3H),

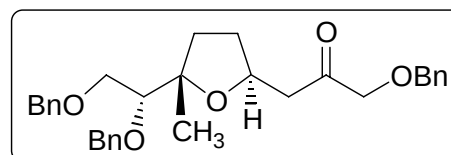
(CDCl₃, 200 MHz) 3.48-3.62 (m, 2H), 3.78 (dd, *J* = 9.8, 1.7 Hz, 1H), 4.19 (d, *J* = 1.4 Hz, 2H), 4.51 (s, 2H), 4.57 (s, 2H), 4.62-4.68 (m, 1H), 4.66 (d, *J* = 11.7 Hz, 1H), 4.83 (d, *J* = 11.7 Hz, 1H), 7.23-7.35 (m, 15H) ppm.

¹³C NMR : δ 23.68 (q), 33.51 (t), 34.42 (t), 57.18 (t), 68.34 (d), 71.16 (t), 71.80 (t), 73.21 (t), 73.58 (t), 80.13 (s), 83.14 (d), 85.07 (s), 86.78 (s), 127.17 (d), 127.30 (d), 127.57 (d), 127.78 (d), 127.99 (d), 128.13 (d), 137.31 (s), 138.15 (s), 138.78 (s) ppm.

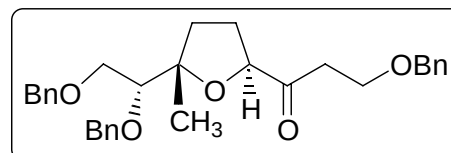
Elemental Analysis Calcd.: C, 79.12; H, 7.28.

Found: C, 79.08; H, 7.10.

1-(Benzyloxy)-3-((2*S*,5*S*)-5-((*R*)-1,2-bis(benzyloxy)ethyl)-5-methyl tetrahydrofuran-2-yl)propan-2-one (227):



3-(Benzyloxy)-1-((2*S*,5*S*)-5-((*R*)-1,2-bis(benzyloxy)ethyl)-5-methyl tetrahydrofuran-2-yl)propan-1-one (228):



To a mixture of alkyne **226** (100 mg, 0.212 mmol) and acetic acid (2 mL) added a drop of sulfuric acid at 0 °C and the mixture was stirred for 3 h. The mixture was diluted with water (3 mL) and acids were quenched with solid NaHCO₃. The mixture was extracted with ethyl acetate (2 X 10 mL), washed with brine (5 mL), dried over NaSO₄, filtered and concentrated. Column purification (7:3 petroleum ether/ethyl acetate) of crude residue gave inseparable mixture of keto compounds **227/228** (47 mg, 45%) as colorless oil.

Mol. Formula : C₃₁H₃₆O₅

IR (CHCl₃) $\tilde{\nu}$: 3031, 1726, 1453 cm⁻¹.

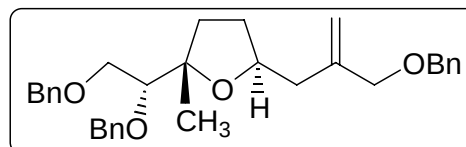
¹H NMR : δ 1.11, 1.13 (2s, 3H), 1.50-1.67 (m, 2H), 1.99-2.17 (m, 2H), 2.40-2.81 (m, 2H), 3.41-3.63 (m, 2H), 3.71-3.79 (m,

1H), 4.00 (d, $J = 3.6$ Hz, 1H), 4.08 (s, 1H), 4.23-4.38 (m, 1H), 4.50-4.58 (m, 4H), 4.63-4.87 (m, 2H), 7.27-7.35 (m, 15H) ppm.

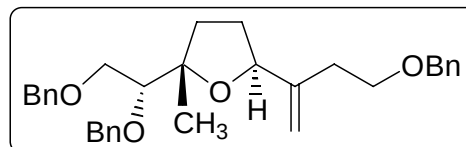
^{13}C NMR : δ 22.70 (q), 23.92 (q), 31.92 (t), 31.98 (t), 34.77 (t), 34.98 (t), 45.49 (t), 45.76 (t), 72.06 (t), 72.17 (t), 73.20 (t), 73.24 (t), 73.39 (t), 73.70 (t), 73.82 (t), 74.48 (d), 75.31 (t), 75.50 (t), 75.54 (d), 83.49 (d), 83.65 (d), 84.42 (s), 84.45 (s), 126.91 (d), 127.32 (d), 127.49 (d), 127.67 (d), 127.84 (d), 127.89 (d), 127.94 (d), 128.17 (d), 128.32 (d), 128.46 (d), 137.27 (s), 138.42 (s), 139.07 (s), 206.55 (s), 206.57 (s) ppm.

Elemental Analysis Calcd.: C, 76.20; H, 7.43
Found: C, 76.11; H, 7.30.

(2*S*,5*S*)-5-(2-(Benzyloxymethyl)allyl)-2-((*R*)-1,2-bis(benzyloxy)ethyl)-2-methyl tetrahydrofuran (229):



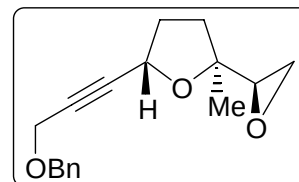
(2*S*,5*S*)-5-(4-(Benzyloxy)but-1-en-2-yl)-2-((*R*)-1,2-bis(benzyloxy)ethyl)-2-methyl tetrahydrofuran (230):



A solution of mixture of keto compounds **227/228** (40 mg, 0.082 mmol) in dry THF (4 mL) was treated with freshly prepared triphenyl phosphonium methylide (using 146 mg of $\text{PPh}_3^+\text{CH}_3\text{Br}^-$ 0.41 mmol, and 0.2 mL of 1.6 M *n*-BuLi 0.33 mmol in 4 mL of THF) at 0 °C and stirred for 2 h. Added a solution of sat. aq. NH_4Cl (3 mL) and the mixture was diluted with ethyl acetate (5 mL). The organic phase was separated and the aq. phase was washed with ethyl acetate (2 X 5 mL). The combined organic extracts were dried over Na_2SO_4 , filtered and concentrated. The residue was purified by column chromatography (1:9 petroleum ether/ethyl acetate) to give inseparable mixture of exomethylene compounds **229/230** (25 mg, 63%) as colorless oil.

Mol. Formula	: C ₃₂ H ₃₈ O ₄
¹H NMR (CDCl ₃ , 500 MHz)	: δ 1.14, 1.15 (2s, 3H), 1.50-1.66 (m, 2H), 1.90-1.98 (m, 1H), 2.05-2.13 (m, 1H), 2.17-2.24 (m, 1H), 2.32-2.39 (m, 1H), 3.48-3.56 (m, 1H), 3.58-3.64 (m, 1H), 3.79-3.86 (m, 1H), 3.92-3.99 (m, 2H), 4.07-4.14 (m, 1H), 4.47 (s, 2H), 4.52 (s, 2H), 4.68 (d, <i>J</i> = 11.7 Hz, 1H), 4.87 (dd, <i>J</i> = 11.7, 7.8 Hz, 1H), 4.97 (d, <i>J</i> = 15.7 Hz, 1H), 5.10 (d, <i>J</i> = 7.9 Hz, 1H), 7.25-7.35 (m, 15H) ppm.
¹³C NMR (CDCl ₃ , 125 MHz)	: δ 22.59 (q), 23.90 (q), 31.70 (t), 31.83 (t), 35.07 (t), 35.41 (t), 40.14 (t), 40.24 (t), 71.93 (t), 71.96 (t), 72.38 (t), 72.50 (t), 73.26 (t), 73.42 (t), 73.82 (t), 77.42 (d), 78.49 (d), 83.77 (d), 83.84 (d), 84.08 (s), 84.15 (s), 113.39 (t), 113.58 (t), 127.29 (d), 127.51 (d), 127.63 (d), 127.75 (d), 128.16 (d), 128.33 (d), 138.45 (s), 138.53 (s), 138.58 (s), 139.26 (s), 143.38 (s), 143.45 (s) ppm.
Elemental Analysis	Calcd.: C, 78.98; H, 7.87 Found: C, 78.85; H, 7.62.

(2*S*,5*S*)-5-(3-(Benzyloxy)prop-1-ynyl)-2-methyl-2-((*R*)-oxiran-2-yl)tetrahydrofuran (210):

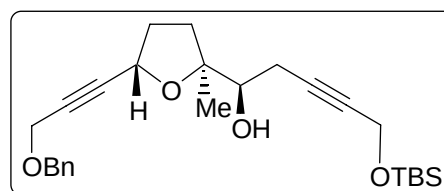


To a solution of diol **225** (4 g, 13.77 mmol) in dry DCM (40 mL) was added tosyl chloride (2.63 g, 13.77 mmol), dibutyltin oxide (68 mg, 0.28 mmol) followed by triethylamine (3.8 mL, 27.54 mmol) and stirred at r.t. for 6 h. DCM was removed under reduced pressure and the crude reaction mixture was taken in methanol (40 mL), added potassium carbonate (3.8 mg, 27.54 mmol) and stirred at r.t. for 30 min. Methanol was concentrated in *vacuo* and the crude product was diluted by adding water (50 mL) and ethyl acetate (75 mL). Organic phase was separated and aq. phase was washed with ethyl acetate (2 X 50 mL). The combined organic extracts were dried over Na₂SO₄, filtered,

concentrated, and the residue was purified by column chromatography (4:1 petroleum ether/ethyl acetate) to give epoxide **210** (3.75 g, 90%) as colorless oil.

Mol. Formula	: C ₁₇ H ₂₀ O ₃
[α]_D	: −8.7 (c 1.0, CHCl ₃).
IR (Neat) $\tilde{\nu}$	: 2978, 2118, 1956, 1453 cm ^{−1} .
¹H NMR (CDCl ₃ , 500 MHz)	: δ 1.35 (s, 3H), 1.72 (ddd, <i>J</i> = 12.5, 8.0, 6.6 Hz, 1H), 1.81 (ddd, <i>J</i> = 12.5, 8.0, 7.0 Hz, 1H), 2.01-2.08 (m, 1H), 2.20-2.26 (m, 1H), 2.50 (dd, <i>J</i> = 4.7, 2.7 Hz, 1H), 2.70 (t, <i>J</i> = 4.7 Hz, 1H), 2.97 (dd, <i>J</i> = 4.0, 2.7 Hz, 1H), 4.19 (d, <i>J</i> = 1.3 Hz, 2H), 4.57 (s, 2H), 4.67-4.71 (m, 1H), 7.26-7.34 (m, 5H) ppm.
¹³C NMR (CDCl ₃ , 125 MHz)	: δ 24.36 (q), 32.00 (t), 33.74 (t), 43.54 (t), 56.50 (d), 57.37 (t), 68.54 (d), 71.43 (t), 80.56 (s), 82.48 (s), 86.51 (s), 127.78 (d), 128.01 (d) 2C, 128.38 (d) 2C, 137.47 (s) ppm.
ESI-MS (<i>m/z</i>)	: 295.1 [M+Na] ⁺ .
Elemental Analysis	Calcd.: C, 74.97; H, 7.40. Found: C, 74.88; H, 7.26.

(R)-1-((2S,5S)-5-(3-(Benzyloxy)prop-1-ynyl)-2-methyltetrahydrofuran-2-yl)-5-(tert-butyldimethylsilyloxy)pent-3-yn-1-ol (231):

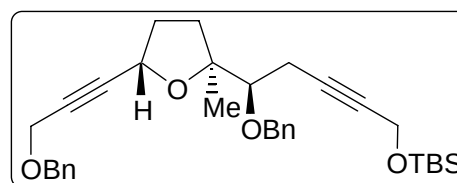


To a solution of propargyl TBS ether (1.74 g, 10.2 mmol) in dry THF (10 mL) was added *n*-BuLi (6 mL of 1.6 M in hexanes, 9.54 mmol) at −78 °C. The mixture was stirred for 30 min and added a solution of epoxide **210** (927 mg, 3.4 mmol) slowly dropwise followed by BF₃·OEt₂ (0.86 mL, 6.8 mmol). After stirring the mixture for 2h at −78 °C, the mixture was quenched with sat. aq. NH₄Cl solution (5 mL) carefully and the temperature was raised to r.t. slowly. The mixture was diluted with ethyl acetate (10 mL). The organic phase was separated and the aq. phase was washed with ethyl acetate (2 X 10 mL). The combined organic extracts were dried over Na₂SO₄, filtered and concentrated.

The residue was purified by column chromatography (4:1 petroleum ether/ethyl acetate) to give alcohol **231** (1.23 g, 82%) as colorless oil.

Mol. Formula	: C ₂₆ H ₃₈ O ₄ Si
[α]_D	: -9.87 (c 1.0, CHCl ₃).
IR (CHCl₃) $\tilde{\nu}$	: 3444, 2972, 2118, 1453 cm ⁻¹ .
¹H NMR (CDCl ₃ , 200 MHz)	: δ 0.11 (s, 6H), 0.90 (s, 9H), 1.29 (s, 3H), 1.74-1.82 (m, 1H), 2.04-2.37 (m, 4H), 2.46-2.57 (m, 1H), 3.63 (dd, <i>J</i> = 8.7, 3.5 Hz, 1H), 4.19 (s, 2H), 4.29 (q, <i>J</i> = 1.8 Hz, 2H), 4.57 (s, 2H), 4.64-4.70 (m, 1H), 7.27-7.35 (m, 5H) ppm.
¹³C NMR (CDCl ₃ , 50 MHz)	: δ -5.08 (q) 2C, 18.35 (s), 22.72 (t), 23.06 (q), 25.89 (q) 3C, 32.96 (t), 33.77 (t), 51.88 (t), 57.39 (t), 68.78 (d), 71.50 (t), 74.80 (d), 80.67 (s), 80.90 (s), 82.03 (s), 85.99 (s), 86.71 (s), 127.82 (d), 128.03 (d) 2C, 128.40 (d) 2C, 137.43 (s) ppm.
ESI-MS (<i>m/z</i>)	: 443.3 [M+1] ⁺ , 465.3 [M+Na] ⁺ .
Elemental Analysis	Calcd.: C, 70.55; H, 8.65. Found: C, 70.39; H, 8.41.

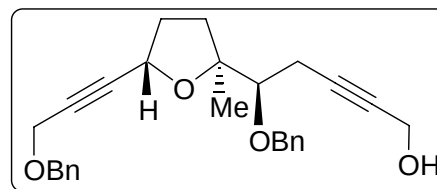
((*R*)-5-(Benzyloxy)-5-((2*S*,5*S*)-5-(3-(benzyloxy)prop-1-ynyl)-2-methyl tetrahydrofuran-2-yl)pent-2-ynyloxy)(tert-butyl)dimethylsilane (232**):**



To a solution of alcohol **231** (530 mg, 1.2 mmol) in dry DMF (5 mL) was added NaH (58 mg of 60% in mineral oil, 1.44 mmol) at ice-cold temperature. The mixture was stirred for 10 min and to the dark brown solution was added benzyl bromide (0.285 mL, 2.4 mmol) slowly dropwise and the mixture was stirred at r.t. 5 h. The mixture was quenched with ice and diluted with ethyl acetate (15 mL). The organic phase was separated and washed with water (3 X 10 mL), brine (10 mL), dried over Na₂SO₄, filtered and concentrated. Chromatographic purification of residue (9:1 petroleum ether/ethyl acetate) gave benzyl derivative **232** (504 mg, 79%) as colorless oil.

Mol. Formula	: C ₃₃ H ₄₄ O ₄ Si
[α]_D	: −10.7 (c 3.3, CHCl ₃).
IR (CHCl₃) $\tilde{\nu}$	: 3012, 2953, 2234, 1216 cm ^{−1} .
¹H NMR (CDCl ₃ , 200 MHz)	: δ 0.10 (s, 6H), 0.90 (s, 9H), 1.29 (s, 3H), 1.71-1.85 (m, 1H), 1.98-2.22 (m, 3H), 2.29-2.43 (m, 1H), 2.54-2.66 (m, 1H), 3.49 (dd, <i>J</i> = 7.8, 3.5 Hz, 1H), 4.19 (d, <i>J</i> = 1.2 Hz, 2H), 4.29 (t, <i>J</i> = 1.8 Hz, 2H), 4.57 (s, 2H), 4.59-4.67 (m, 1H), 4.67 (d, <i>J</i> = 11.4 Hz, 1H), 4.87 (d, <i>J</i> = 11.4 Hz, 1H), 7.23-7.35 (m, 10H) ppm.
¹³C NMR (CDCl ₃ , 50 MHz)	: δ -5.07 (q) 2C, 18.38 (s), 21.52 (t), 23.71 (q), 25.92 (q) 3C, 29.75 (t), 33.86 (t), 51.97 (t), 57.46 (t), 68.63 (d), 71.49 (t), 74.08 (t), 80.03 (s), 80.38 (s), 82.95 (d), 83.19 (s), 86.20 (s), 86.82 (s), 127.52 (d), 127.82 (d), 127.89 (d) 2C, 128.05 (d) 2C, 128.25 (d) 2C, 128.40 (d) 2C, 137.48 (s), 138.65 (s) ppm.
ESI-MS (<i>m/z</i>)	: 555.6 [M+Na] ⁺ .
Elemental Analysis	Calcd.: C, 74.39; H, 8.32. Found: C, 74.22; H, 8.41.

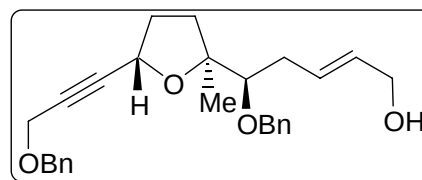
(*R*)-5-(Benzyloxy)-5-((2*S*,5*S*)-5-(3-(benzyloxy)prop-1-ynyl)-2-methyl tetrahydrofuran-2-yl)pent-2-yn-1-ol (233):



To a solution of O-TBS derivative **232** (500 mg, 0.94 mmol) in dry THF (10 mL) at 0 °C added slowly dropwise a solution of TBAF (1.41 mL of 1 M solution on THF, 1.41 mmol) and stirred at r.t. for 1 h. The mixture was quenched with ice and diluted with ethyl acetate (10 mL). The organic phase was separated and the aq. phase was washed with ethyl acetate (2 X 10 mL). The combined organic extracts were dried over Na₂SO₄, filtered and concentrated. Silica gel column chromatography purification of crude residue (4:1 petroleum ether/ethyl acetate) gave alkynol **233** (322 mg, 82%) as colorless oil.

Mol. Formula	: C ₂₇ H ₃₀ O ₄
[α]_D	: −16.3 (c 2.2, CHCl ₃).
IR (CHCl₃) $\tilde{\nu}$	: 3439, 3017, 2401, 1453 cm ^{−1} .
¹H NMR (CDCl ₃ , 20 MHz)	: δ 1.29 (s, 3H), 1.59 (br s, 1H), 1.73-1.85 (m, 1H), 1.97-2.23 (m, 3H), 2.30-2.44 (m, 1H), 2.53-2.65 (m, 1H), 3.49 (dd, <i>J</i> = 7.8, 3.5 Hz, 1H), 4.19 (d, <i>J</i> = 1.3 Hz, 4H), 4.57 (s, 2H), 4.60-4.70 (m, 1H), 4.68 (d, <i>J</i> = 11.5 Hz, 1H), 4.85 (d, <i>J</i> = 11.5 Hz, 1H), 7.26-7.38 (m, 10H) ppm.
¹³C NMR (CDCl ₃ , 50 MHz)	: δ 21.02 (t), 23.27 (q), 33.41 (t), 33.46 (t), 50.49 (t), 57.07 (t), 68.24 (d), 71.12 (t), 73.79 (t), 79.77 (s), 80.10 (s), 82.56 (d), 83.27 (s), 85.91 (s), 86.45 (s), 127.23 (d), 127.47 (d), 127.56 (d) 2C, 127.67 (d) 2C, 127.92 (d) 2C, 128.03 (d) 2C, 137.03 (s), 138.18 (s) ppm.
ESI-MS (<i>m/z</i>)	: 441.2 [M+Na] ⁺ .
Elemental Analysis	Calcd.: C, 77.48; H, 7.22 Found: C, 77.32; H, 7.15.

(*R,E*)-5-(Benzyloxy)-5-((2*S*,5*S*)-5-(3-(benzyloxy)prop-1-ynyl)-2-methyl tetrahydrofuran-2-yl)pent-2-en-1-ol (209**):**

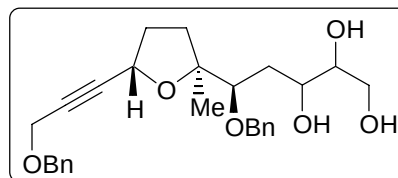


A solution of alkynol **233** (300 mg, 0.72 mmol) in dry THF (15 mL) was cooled 0 °C and added LiAlH₄ (27 mg, 0.72 mmol) in portions and the mixture was stirred at the same temperature for 12 h. The mixture was quenched with ice and the residue was filtered through a pad of *celite*. The cake was washed with ethyl acetate (25 mL). The filtrate was concentrated and the residue obtained was purified by column chromatography (4:1 petroleum ether/ethyl acetate) to give alkenol **209** (121 mg, 40%) as colorless oil.

Mol. Formula	: C ₂₇ H ₃₂ O ₄
[α]_D	: −4.2 (c 1.4, CHCl ₃).
IR (CHCl₃) $\tilde{\nu}$	: 3436, 3014, 2972, 2118, 1453 cm ^{−1} .

¹H NMR (CDCl ₃ , 200 MHz)	: δ 1.29 (s, 3H), 1.66-1.79 (m, 1H), 1.76 (br s, 1H), 1.98-2.37 (m, 5H), 3.37 (dd, <i>J</i> = 8.8, 3.3 Hz, 1H), 3.99 (d, <i>J</i> = 2.7 Hz, 2H), 4.20 (d, <i>J</i> = 1.6 Hz, 2H), 4.57 (s, 2H), 4.63 (d, <i>J</i> = 6.6 Hz, 2H), 4.65-4.71 (m, 1H), 5.55-5.74 (m, 2H), 7.24-7.34 (m, 10H) ppm.
¹³C NMR (CDCl ₃ , 50 MHz)	: δ 24.67 (q), 33.10 (t), 34.00 (t), 34.60 (t), 57.43 (t), 63.39 (t), 68.50 (d), 71.46 (t), 74.36 (t), 80.30 (s), 84.53 (d), 86.91 (s), 87.11 (s), 127.46 (d), 127.75 (d), 127.89 (d) 2C, 127.98 (d) 2C, 128.21 (d) 2C, 128.34 (d) 2C, 129.68 (d), 131.05 (d), 137.44 (s), 138.85 (s) ppm.
ESI-MS (<i>m/z</i>)	: 443.1 [M+Na] ⁺ .
Elemental Analysis	Calcd.: C, 77.11; H, 7.67 Found: C, 77.23; H, 7.55.

(*R*)-5-(Benzyloxy)-5-((2*S*,5*S*)-5-(3-(benzyloxy)prop-1-ynyl)-2-methyl tetrahydrofuran-2-yl)pentane-1,2,3-triol (234/235):



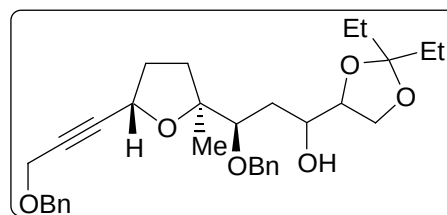
Method A: To a mixture of *t*-butyl alcohol (4 mL) and water (4 mL) was added AD-mix- α (0.67 g), MeSO₂NH₂ (46 mg, 0.48 mmol) and the mixture was stirred at r.t. until both phases are clear and then cooled to 0 °C. Allylic alcohol **209** (200 mg, 0.48 mmol) was added at once and stirred vigorously at 0 °C for 7 h. The mixture was quenched by adding sodium sulfite (0.5 g) at 0 °C, warmed to r.t. and stirred for 1 h. The mixture was extracted with ethyl acetate (3 x 5 mL). The combined organic extracts were washed with 2N KOH (5 mL), dried over Na₂SO₄, filtered and concentrated. The residue obtained was purified by column chromatography (3:7 petroleum ether/ethyl acetate) to furnish inseparable diastereomeric mixture of triols **234/235** (145 mg, 67%) as colorless oil.

Method B: To a solution of allylic alcohol **209** (200 mg, 0.475 mmol) in 5:1 acetone-water mixture (6 mL) was added 50% aq. NMO (0.2 mL, 0.95 mmol) and the mixture was cooled to 0 °C. Added 2 drops of a 0.2 M solution of OsO₄ in toluene and the mixture was stirred at 0 °C for 5 h. The mixture was quenched with the addition solid sodium

sulfite (1 g). Acetone was removed in *vacuo* and the residue obtained was diluted with ethyl acetate (10 mL). The organic phase was separated and the aq. phase in turn was washed with ethyl acetate (2 X 5 mL). The combined organic extracts were dried over Na₂SO₄, filtered, concentrated, and the residue was purified by column chromatography (3:7 petroleum ether/ethyl acetate) to give inseparable diastereomeric mixture of triols **234/235** (125 mg, 58%) as colorless oil.

Mol. Formula	: C ₂₇ H ₃₄ O ₆
IR (CHCl₃) $\tilde{\nu}$	: 3436, 3014, 2118, 1453 cm ⁻¹ .
¹H NMR (CDCl ₃ , 200 MHz)	: δ 1.30, 1.32 (2s, 3H), 1.48-1.88 (m, 3H), 2.00-2.25 (m, 3H), 2.59 (br s, 3H), 3.39-3.48 (m, 1H), 3.56-3.85 (m, 4H), 4.21 (t, <i>J</i> = 1.6 Hz, 2H), 4.58 (s, 2H), 4.62-4.90 (m, 3H), 7.27-7.36 (m, 10H) ppm.
¹³C NMR (CDCl ₃ , 50 MHz)	: δ 24.21 (q), 24.71 (q), 32.85 (t), 33.66 (t), 33.84 (t), 34.84 (t), 35.42 (t), 57.45 (t), 64.61 (t), 64.70 (t), 68.56 (d), 69.70 (d), 71.52 (t), 71.56 (t), 71.98 (d), 73.65 (d), 74.41 (t), 74.63 (t), 80.58 (s), 80.65 (s), 81.45 (d), 83.94 (d), 86.71 (s), 86.77 (s), 87.30 (s), 87.73 (s), 127.68 (d), 127.83 (d), 127.95 (d), 128.03 (d), 128.11 (d), 128.40 (d), 128.57 (d), 137.42 (s), 137.96 (s), 138.71 (s) ppm.
Elemental Analysis	Calcd.: C, 71.34; H, 7.54. Found: C, 71.25; H, 7.65.

(3*R*)-3-(Benzyloxy)-3-((2*S*,5*S*)-5-(3-(benzyloxy)prop-1-ynyl)-2-methyl tetrahydrofuran-2-yl)-1-(2,2-diethyl-1,3-dioxolan-4-yl)propan-1-ol (236/237):



To a solution of mixture of triols **234/235** (100 mg, 0.219 mmol) in 3-pentanone (5 mL) was added catalytic camphor sulfonic acid and the mixture was stirred at r.t. for 4 h. The reaction mixture was quenched with triethylamine (1 mL) and the solvents were removed in *vacuo*. The residue obtained was purified by flash column chromatography

(7:3 petroleum ether/ethyl acetate) to separate the diastereomers **236** (44 mg, 38%) and **237** (44 mg, 38%) as colorless oils.

236:

Mol. Formula	: C ₃₂ H ₄₂ O ₆
[α]_D	: −10.3 (c 1.0, CHCl ₃).
IR (CHCl₃) $\tilde{\nu}$	: 3430, 3010, 2115, 1453 cm ^{−1} .
¹H NMR (CDCl ₃ , 200 MHz)	: δ 0.89 (t, <i>J</i> = 7.4 Hz, 3H), 0.90 (t, <i>J</i> = 7.4 Hz, 3H) 1.30 (s, 3H), 1.55-1.78 (m, 7H), 2.00-2.33 (m, 4H), 3.59-3.75 (m, 3H), 3.88-4.00 (m, 2H), 4.20 (d, <i>J</i> = 1.6 Hz, 2H), 4.58 (s, 2H), 4.60-4.69 (m, 1H), 4.67 (d, <i>J</i> = 11.4 Hz, 1H), 4.78 (d, <i>J</i> = 11.4 Hz, 1H), 7.26-7.34 (m, 10H) ppm.
¹³C NMR (CDCl ₃ , 50 MHz)	: δ 8.02 (q), 8.21 (q), 24.50 (q), 29.32 (t), 29.65 (t), 33.22 (t), 33.97 (t), 35.76 (t), 57.48 (t), 66.46 (t), 68.53 (d), 68.99 (d), 71.51 (t), 74.99 (t), 79.74 (d), 80.37 (s), 81.11 (d), 86.95 (s), 87.18 (s), 113.23 (s), 127.55 (d), 127.78 (d), 127.87 (d) 2C, 128.03 (d) 2C, 128.33 (d) 2C, 128.37 (d) 2C, 137.51 (s), 138.98 (s) ppm.
Elemental Analysis	Calcd.: C, 73.53; H, 8.10. Found: C, 73.45; H, 7.98.

237:

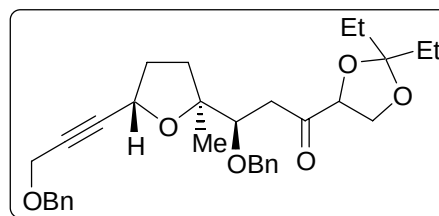
Mol. Formula	: C ₃₂ H ₄₂ O ₆
[α]_D	: + 2.4 (c 1.0, CHCl ₃).
IR (CHCl₃) $\tilde{\nu}$	: 3429, 3015, 2115, 1453 cm ^{−1} .
¹H NMR (CDCl ₃ , 200 MHz)	: δ 0.87 (t, <i>J</i> = 7.4 Hz, 3H), 0.90 (t, <i>J</i> = 7.4 Hz, 3H) 1.30 (s, 3H), 1.52-1.79 (m, 7H), 2.02-2.29 (m, 3H), 3.15 (br s, 1H), 3.62-3.80 (m, 3H), 3.88-4.02 (m, 2H), 4.22 (d, <i>J</i> = 1.6 Hz, 2H), 4.59 (s, 2H), 4.60-4.70 (m, 1H), 4.66 (d, <i>J</i> = 11.4 Hz, 1H), 4.81 (d, <i>J</i> = 11.4 Hz, 1H), 7.27-7.37 (m, 10H) ppm.
¹³C NMR (CDCl ₃ , 50 MHz)	: δ 8.07 (q), 8.23 (q), 24.49 (q), 29.05 (t), 29.54 (t), 33.12 (t), 33.87 (t), 34.67 (t), 57.46 (t), 66.01 (t), 68.53 (d), 70.71

(d), 71.56 (t), 74.16 (t), 78.45 (d), 80.50 (s), 82.96 (d), 86.83 (s), 87.58 (s), 113.08 (s), 127.80 (d), 127.83 (d), 128.04 (d) 2C, 128.11 (d) 2C, 128.40 (d) 2C, 128.48 (d) 2C, 137.44 (s), 138.26 (s) ppm.

Elemental Analysis Calcd.: C, 73.53; H, 8.10.

Found: C, 73.51; H, 8.21.

(3R)-3-(Benzyloxy)-3-((2S,5S)-5-(3-(benzyloxy)prop-1-ynyl)-2-methyl tetrahydrofuran-2-yl)-1-(2,2-diethyl-1,3-dioxolan-4-yl)propan-1-one (238):



To a suspension of alcohol **236** (80 mg, 0.153 mmol) in dry DMSO (2 mL) was added IBX (86 mg, 0.306 mmol) and the mixture was stirred at r.t. for 12 h. Added water (2 mL) and the solid obtained was filtered through *celite* and washed with ethyl acetate (10 mL). The filtrate was concentrated and the residue was purified by column chromatography (4:1 petroleum ether/ethyl acetate) to give **238** (60 mg, 75%) as colorless oil.

Mol. Formula : C₃₂H₄₀O₆

[α]_D : −8.3 (c 1.0, CHCl₃).

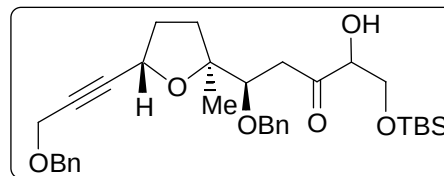
IR (CHCl₃) $\tilde{\nu}$: 3019, 2400, 1720, 1215 cm^{−1}.

¹H NMR : δ 0.90 (t, *J* = 7.5 Hz, 3H), 0.94 (t, *J* = 7.5 Hz, 3H) 1.30 (s, 3H), 1.58-1.88 (m, 5H), 1.96-2.24 (m, 3H), 2.73-2.94 (m, 2H), 3.90-3.99 (m, 2H), 4.12-4.20 (m, 1H), 4.19 (d, *J* = 1.6 Hz, 2H), 4.41 (t, *J* = 7.3 Hz, 1H), 4.49-4.65 (m, 5H), 7.23-7.35 (m, 10H) ppm.

Elemental Analysis Calcd.: C, 73.82; H, 7.74

Found: C, 73.65; H, 7.83

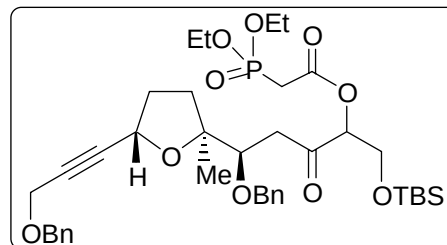
(1R)-1-(Benzyloxy)-1-((2S,5S)-5-(3-(benzyloxy)prop-1-ynyl)-2-methyl tetrahydrofuran-2-yl)-5-(tert-butyl dimethylsilyloxy)-4-hydroxypentan-3-one (239):



To a solution of **238** (60 mg, 0.115 mmol) in methanol (4 mL) was added PTSA (8 mg, 0.046 mmol) and the mixture was stirred at r.t. for 4 h and quenched with triethylamine (1 mL). The residue was taken in dry DCM (5 mL) and cooled to 0 °C. Added imidazole (16 mg, 0.23 mmol) followed by TBS-Cl (21 mg, 0.138 mmol) and stirred for 4 h. The mixture was quenched with sat. aq. NH₄Cl solution (1 mL). The organic phase was separated and the aq. phase was washed with DCM (2 X 5 mL). The combined organic extracts were dried over Na₂SO₄, filtered and concentrated. The residue obtained was purified by column chromatography (4:1 petroleum ether/ethyl acetate) to give keto alcohol **239** (39 mg, 60%) as colorless oil.

Mol. Formula	: C ₃₃ H ₄₆ O ₆ Si
[α]_D	: −6.4 (c 1.0, CHCl ₃).
IR (CHCl₃) $\tilde{\nu}$	: 3430, 2118, 1720, 1453 cm ^{−1} .
¹H NMR (CDCl ₃ , 200 MHz)	: δ 0.05 (s, 6H), 0.86 (s, 9H) 1.31 (s, 3H), 1.56 (br s, 1H), 1.78-1.86 (m, 1H), 1.97-2.26 (m, 3H), 2.67 (dd, <i>J</i> = 16.4, 8.4 Hz, 1H), 2.87 (dd, <i>J</i> = 16.4, 3.6 Hz, 1H), 3.79 (dd, <i>J</i> = 10.8, 4.0 Hz, 1H), 3.91-4.00 (m, 2H), 4.06-4.14 (m, 1H), 4.19 (d, <i>J</i> = 1.5 Hz, 2H), 4.54-4.63 (m, 5H), 7.22-7.35 (m, 10H) ppm.
¹³C NMR (CDCl ₃ , 50 MHz)	: δ -5.43 (q), -5.31 (q), 18.28 (s), 23.31 (q), 25.88 (q) 3C, 33.73 (t), 34.42 (t), 40.61 (t), 57.45 (t), 64.53 (t), 68.48 (d), 71.52 (t), 74.23 (t), 78.42 (d), 80.35 (d), 80.49 (s), 86.07 (s), 86.78 (s), 127.63 (d), 127.80 (d) 2C, 127.84 (d), 128.06 (d) 2C, 128.35 (d) 2C, 128.43 (d) 2C, 137.51 (s), 138.49 (s), 209.53 (s) ppm.
Elemental Analysis	Calcd.: C, 69.93; H, 8.18. Found: C, 69.88; H, 8.07.

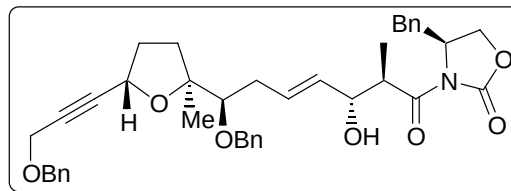
(5*R*)-5-(Benzyloxy)-5-((2*S*,5*S*)-5-(3-(benzyloxy)prop-1-ynyl)-2-methyl tetrahydrofuran-2-yl)-1-tert-butyl dimethylsilyloxy)-3-oxopentan-2-yl 2-(diethoxyphosphoryl) acetate (208):



To a solution of alcohol **239** (40 mg, 0.071 mmol) in dry THF (2 mL) was added diethyl phosphono acetic acid (125 mg, 0.639 mmol) and cooled to 0 °C. Added DCC (132 mg, 0.639 mmol) in one portion followed by catalytic amount of DMAP. The mixture was then brought to r.t. and stirred for 2 h. Added water (2 mL) and ethyl acetate (2 mL) The organic phase was separated and washed with water (2 X 2 mL), brine (2 mL), dried over Na₂SO₄, filtered and concentrated. The residue obtained was purified by column chromatography (3:2 petroleum ether/ethyl acetate) to give phosphonate **208** (26 mg, 60%) as colorless oil.

Mol. Formula	: C ₃₉ H ₅₇ O ₁₀ PSi
[α]_D	: -15.9 (c 1.0, CHCl ₃).
IR (CHCl₃) $\tilde{\nu}$	: 3019, 2400, 1731, 1215 cm ⁻¹ .
¹H NMR (CDCl ₃ , 400 MHz)	: δ 0.04 (s, 6H), 0.86 (s, 9H) 1.29 (s, 3H), 1.31-1.36 (m, 6H), 1.79-1.84 (m, 1H), 1.99-2.11 (m, 2H), 2.14-2.20 (m, 1H), 2.73-2.91 (m, 2H), 3.07 (d, <i>J</i> = 21.5 Hz, 2H), 3.89-4.04 (m, 3H), 4.14-4.22 (m, 6H), 4.51-4.65 (m, 5H), 5.17 (t, <i>J</i> = 3.9 Hz, 1H), 7.26-7.35 (m, 10H) ppm.
¹³C NMR (CDCl ₃ , 100 MHz)	: δ -5.52 (q) 2C, 16.31 (q), 16.37 (q), 18.20 (s), 23.00 (q), 25.73 (q) 3C, 29.68 (t), 33.59 (t), 34.56 (t), 34.65 (t), 41.74 (t), 57.51 (t), 62.41 (t), 62.84 (t), 68.38 (d), 71.54 (t), 73.54 (t), 78.94 (d), 80.23 (s), 80.61 (d), 85.79 (s), 86.86 (s), 127.39 (d), 127.63 (d), 127.70 (d), 127.82 (d), 128.04 (d) 2C, 128.18 (d) 2C, 128.41 (d) 2C, 137.46 (s), 138.72 (s), 165.14 (s), 203.71 (s) ppm.
Elemental Analysis	Calcd.: C, 62.88; H, 7.71 Found: C, 62.69; H, 7.53.

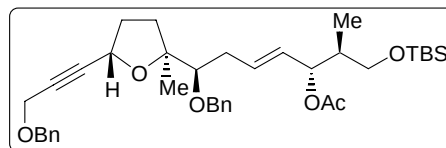
4-Benzyl-3-{7-benzyloxy-7-[5-(3-benzyloxy-prop-1-ynyl)-2-methyl-tetrahydro-furan-2-yl]-3-hydroxy-2-methyl-hept-4-enoyl}-oxazolidin-2-one (244):



To a solution of allylic alcohol **209** (100 mg, 0.24 mmol) in chloroform (5 mL) was added MnO_2 (42 mg, 0.48 mmol) and the mixture was stirred at r.t. for 8 h. The mixture was filtered through a pad of *celite* and washed with chloroform (10 mL). The filtrates were concentrated to yield allylic aldehyde (75 mg, 75%), which was directly taken to next step without further purification. To a solution of oxazolidinone (42 mg, 0.18 mmol) in dry ethyl acetate (3 mL) was added MgCl_2 (4 mg, 0.04 mmol), triethylamine (50 μL , 0.36 mmol) and aldehyde (75 mg, 0.18 mmol) in dry ethyl acetate (1 mL) followed by TMS-Cl (34 μL , 0.27 mmol) and the mixture was stirred at r.t. for 24 h. Added sat. aq. NH_4Cl (1 mL) and organic phase was separated. The aq. phase was washed with ethyl acetate (2 X 2 mL). The combined organic extracts were dried over Na_2SO_4 , filtered, concentrated and the residue obtained was purified by column chromatography (3:2 petroleum ether/ethyl acetate) to furnish **244** (72 mg, 62%) as colorless oil.

Mol. Formula	: $\text{C}_{40}\text{H}_{45}\text{NO}_7$
$[\alpha]_D$	: -25.3 (c 1.0, CHCl_3).
$^1\text{H NMR}$ (CDCl_3 , 200 MHz)	: δ 1.28 (d, $J = 7.5$ Hz, 3H), 1.30 (s, 3H), 1.68-1.76 (m, 1H), 2.10-2.54 (m, 5H), 2.75 (dd, $J = 13.4, 9.6$ Hz, 1H), 3.24-3.44 (m, 2H), 3.88-4.10 (m, 2H), 4.14-4.19 (m, 2H), 4.21 (d, $J = 1.5$ Hz, 2H), 4.37-4.52 (m, 1H), 4.59 (s, 2H), 4.63-4.73 (m, 3H), 5.53-5.91 (m, 2H), 7.21-7.36 (m, 15H) ppm.
Elemental Analysis	Calcd.: C, 73.71; H, 6.96; N, 2.15. Found: C, 73.69; H, 7.14; N, 2.34.

Acetic acid 5-benzyloxy-5-[5-(3-benzyloxy-prop-1-ynyl)-2-methyl-tetrahydro-furan-2-yl]-1-[2-(tert-butyl-dimethyl-silanyloxy)-1-methyl-ethyl]-pent-2-enyl ester (243):



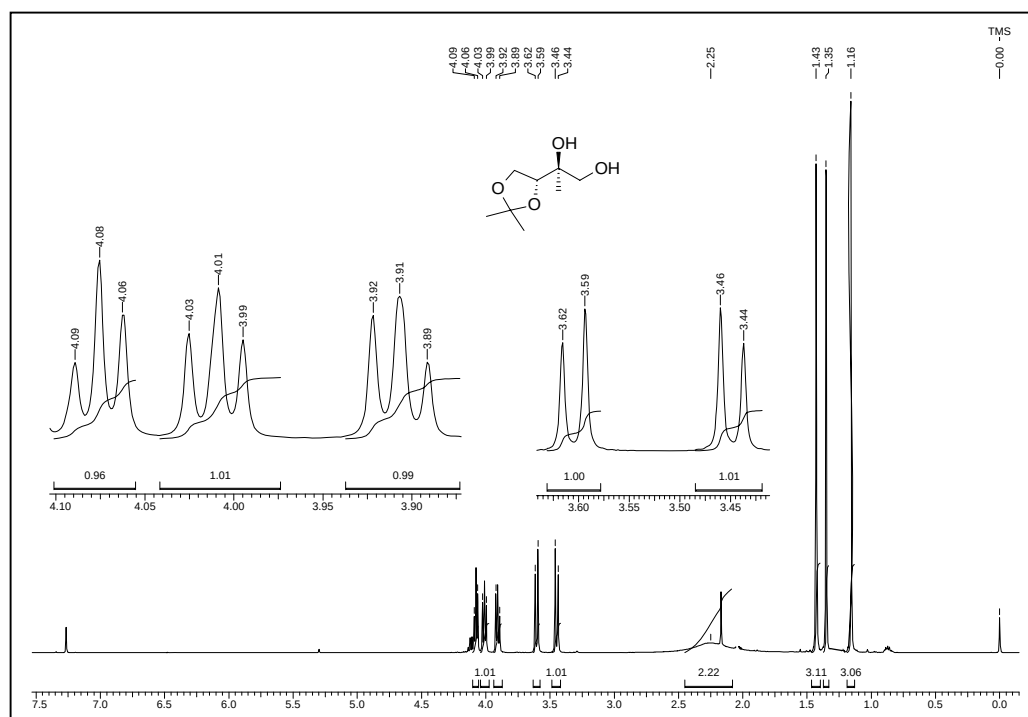
To a solution of **244** (60 mg, 0.09 mmol) in THF (2 mL) was added a solution of sodium borohydride (14 mg, 0.36 mmol) in water (0.5 mL) at a rate to maintain the internal temperature at 20-25 °C. The mixture was stirred at r.t. for 4 h, and the completion of the reaction was monitored by tlc. To the reaction mixture was added 2 N HCl (0.5 mL) at a rate to maintain the internal temperature at 20-25 °C. The reaction mixture was extracted with ethyl acetate (2 X 5 mL) washed with brine (3 mL), concentrated under vacuum, and the residue obtained was purified by silica gel chromatography to yield diol **247** (32 mg, 72%) as colorless oil. To a solution of diol (32 mg, 0.07 mmol) in dry DCM (2 mL) was added imidazole (10 mg, 0.14 mmol) and the mixture was cooled to 0 °C. Added TBS-Cl (11 mg, 0.07 mmol) and the temperature of the mixture was brought to r.t. slowly and stirred for 5 h. Added sat. aq. NH₄Cl (1 mL) and the organic layer was separated and the aq. layer in turn washed with DCM (3 mL). The combined organic extracts were washed with water (3 mL), brine (3 mL), dried over Na₂SO₄, filtered and concentrated. The residue obtained was taken in dry DCM (2 mL) and added triethylamine (20 µL, 0.14 mmol) followed by acetic anhydride (7 µL, 0.07 mmol) and catalytic DMAP. The mixture was stirred at r.t. for 1 h and the solvents were removed under reduced pressure. The residue was purified by chromatography (7:3 petroleum ether/ethyl acetate) to give **243** (29 mg, 68%) as colorless oil.

Mol. Formula : C₃₈H₅₄O₆Si

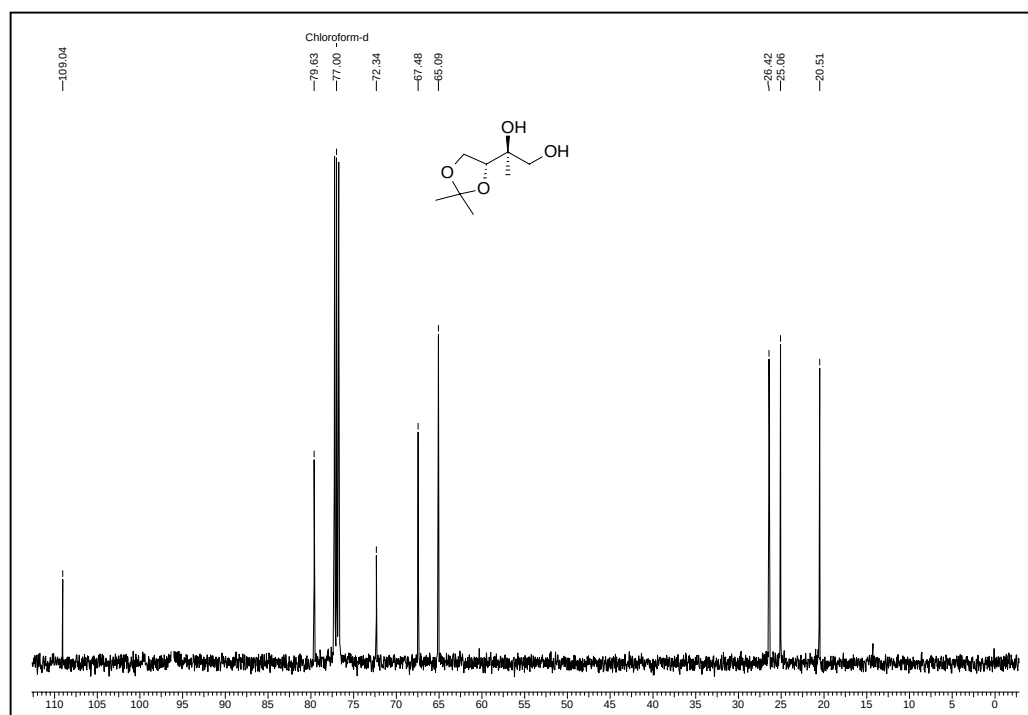
[α]_D : -11.2 (c 1.0, CHCl₃).

¹H NMR : δ 0.01 (s, 6H), 0.87 (s, 9H), 0.99 (d, *J* = 7.2 Hz, 3H), (CDCl₃, 400 MHz) 1.28 (s, 3H), 1.69-1.74 (m, 1H), 1.79-1.84 (m, 1H), 1.91 (s, 3H), 2.00-2.06 (m, 1H), 2.11-2.21 (m, 3H), 2.33-2.37 (m, 1H), 3.34-3.43 (m, 2H), 3.49-3.52 (m, 1H), 4.21 (d, *J* = 1.4 Hz, 2H), 4.58 (s, 2H), 4.60-4.85 (m, 3H), 5.20-5.33 (m, 1H), 5.44-5.56 (m, 1H), 5.74-5.85 (m, 1H), 7.27-7.34 (m, 10H) ppm.

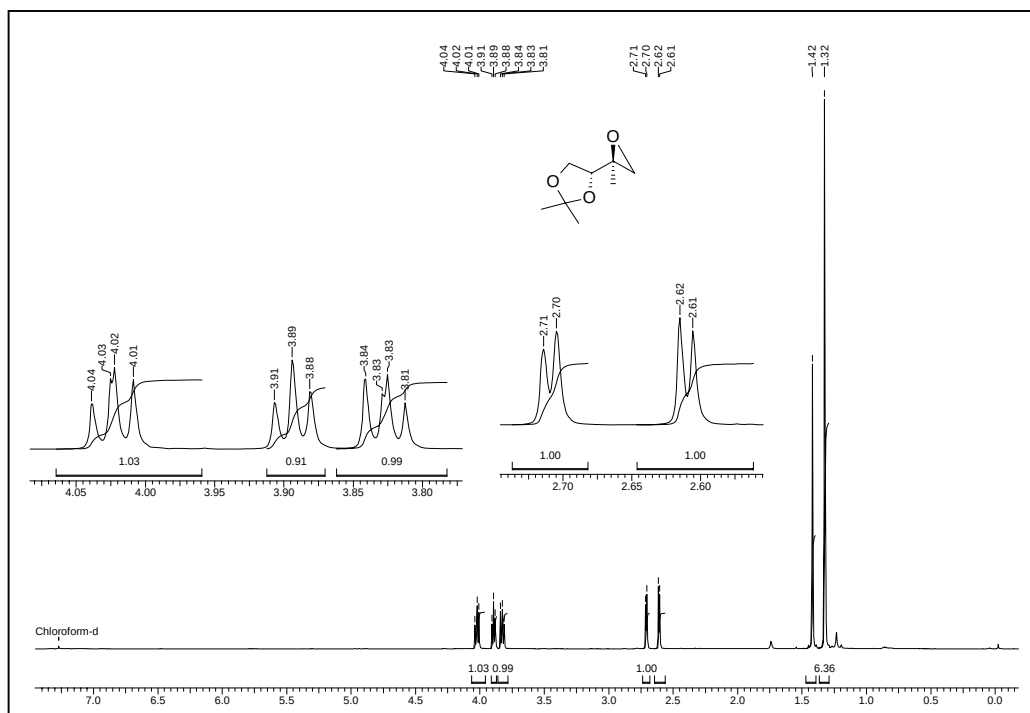
Spectra



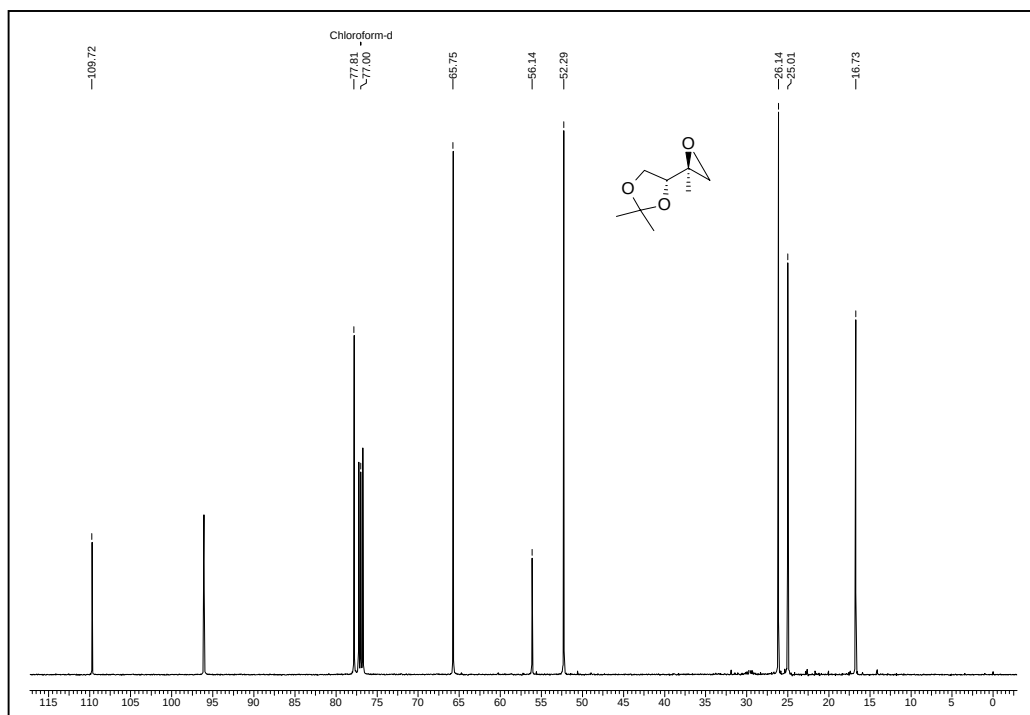
¹H NMR Spectrum of 219 in CDCl₃



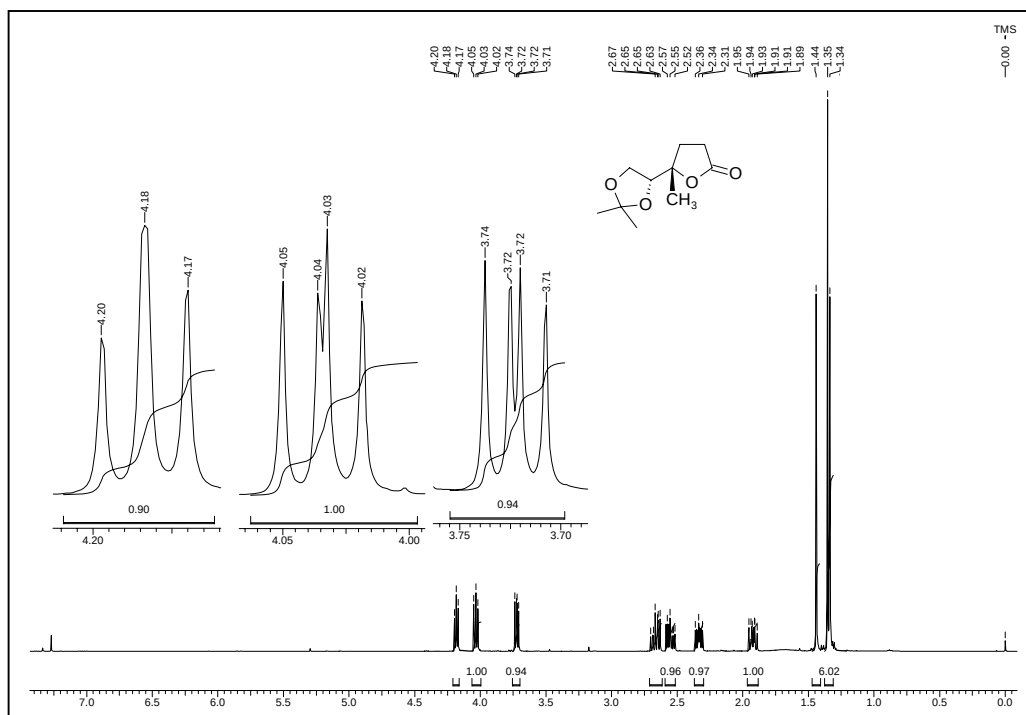
¹³C NMR Spectrum of 219 in CDCl₃



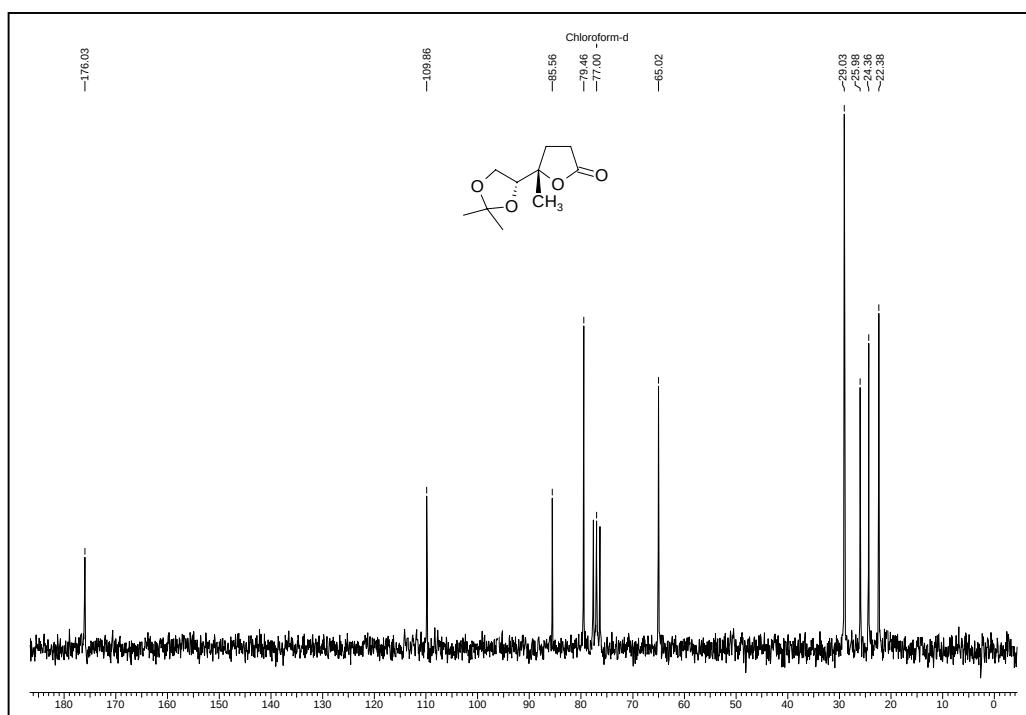
¹H NMR Spectrum of 213 in CDCl₃



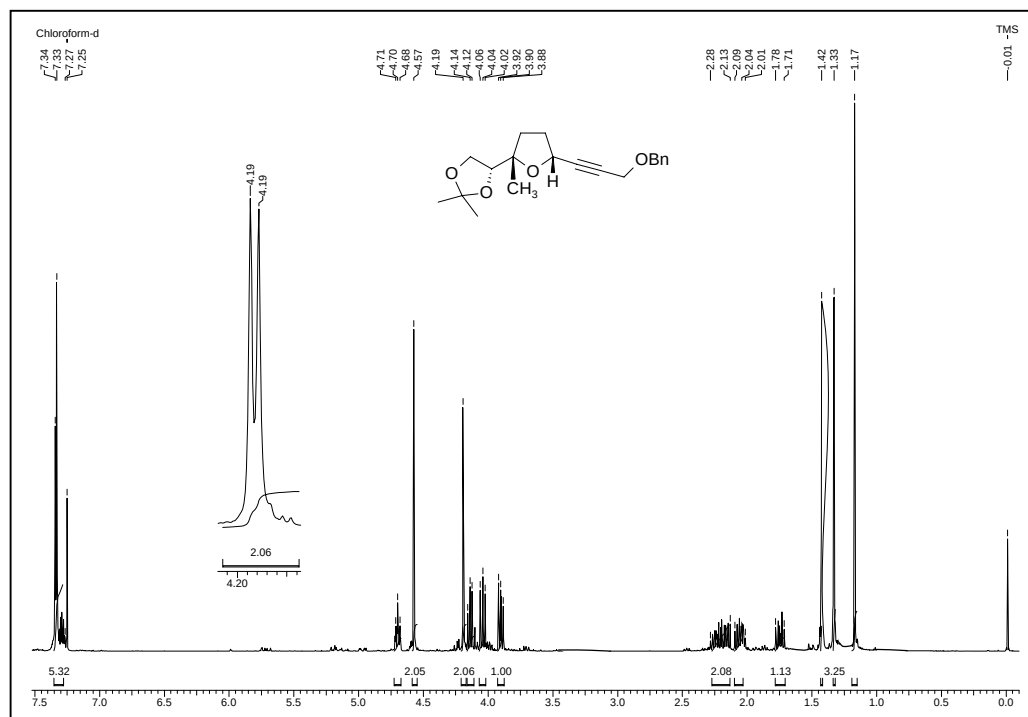
¹³C NMR Spectrum of 213 in CDCl₃



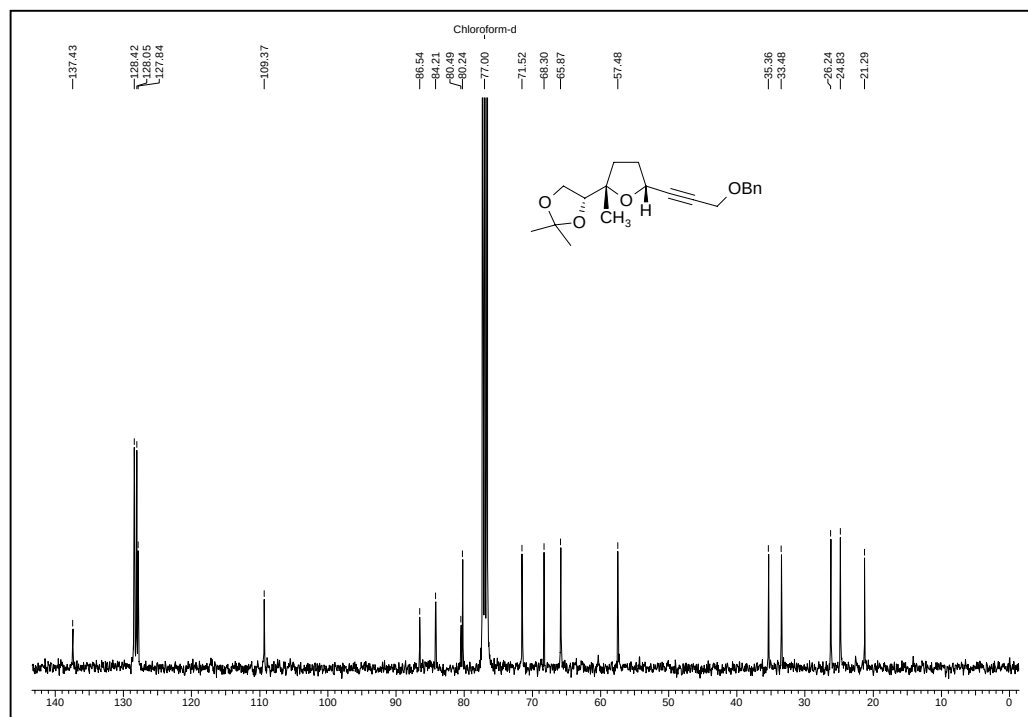
¹H NMR Spectrum of 212 in CDCl₃



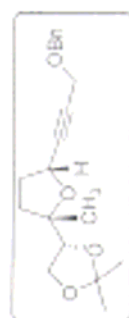
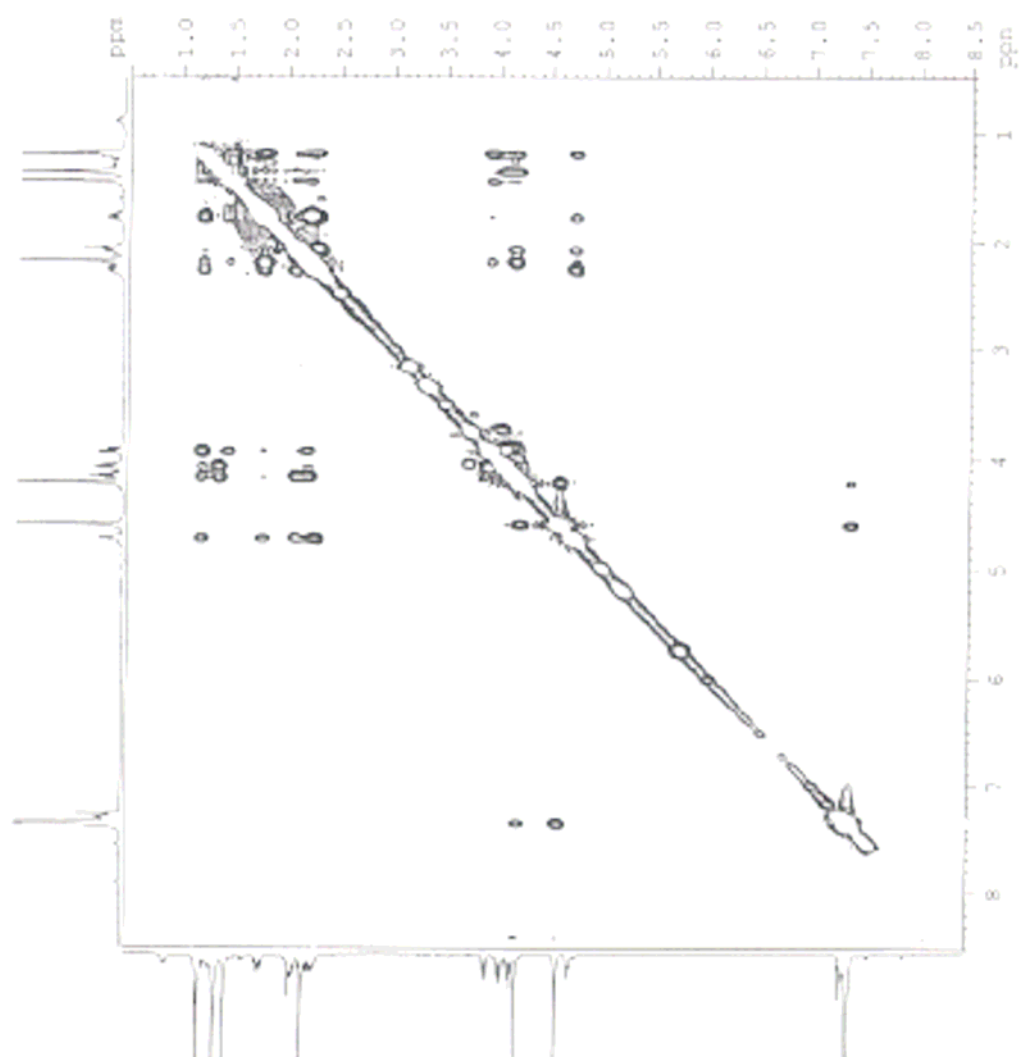
¹³C NMR Spectrum of 212 in CDCl₃



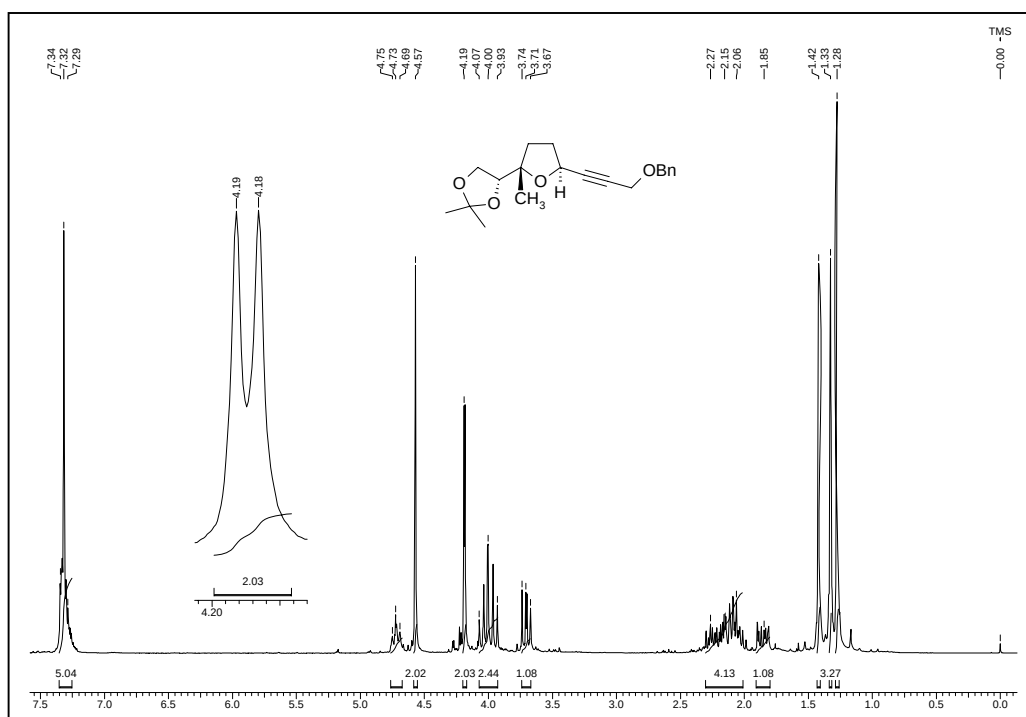
^1H NMR Spectrum of 223 in CDCl_3



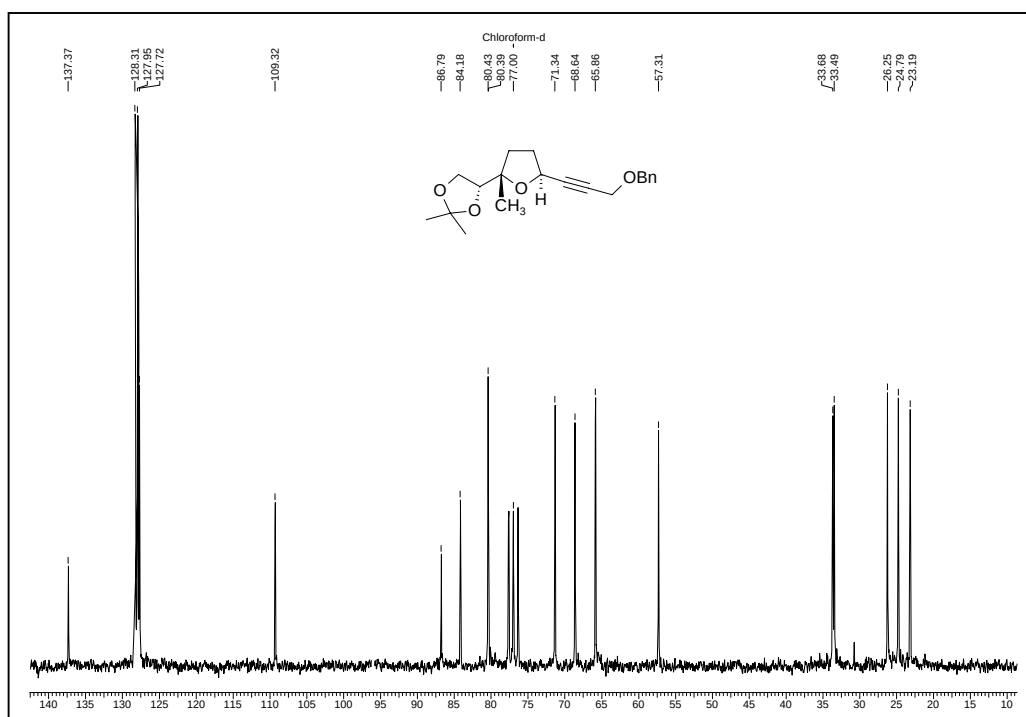
^{13}C NMR Spectrum of 223 in CDCl_3



NOESY of compound 223



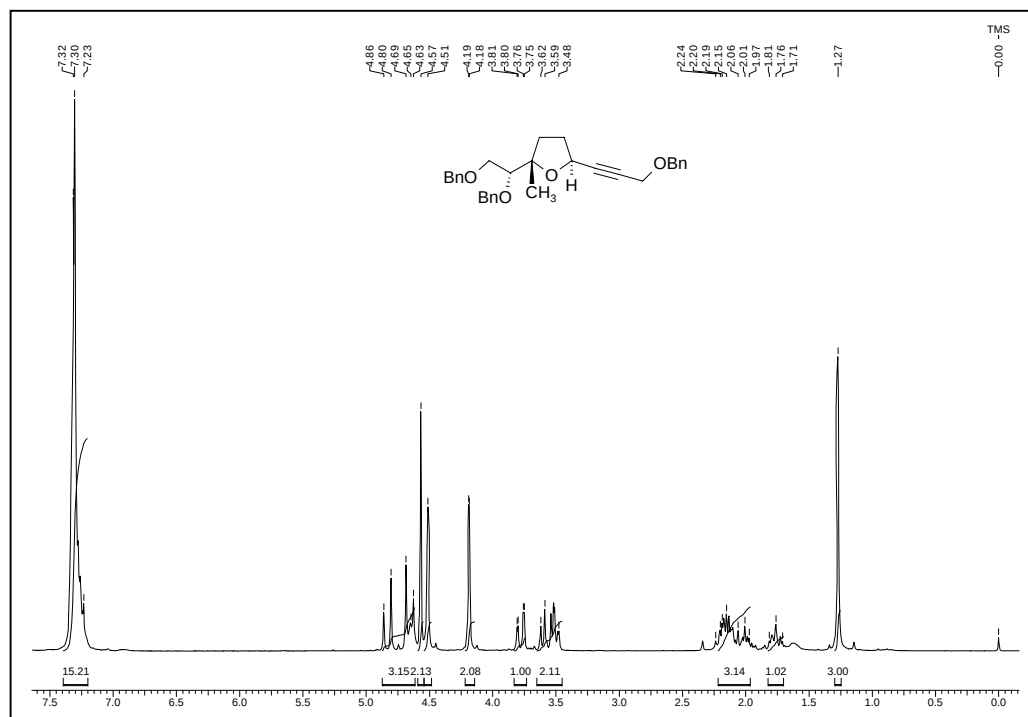
¹H NMR Spectrum of 224 in CDCl₃



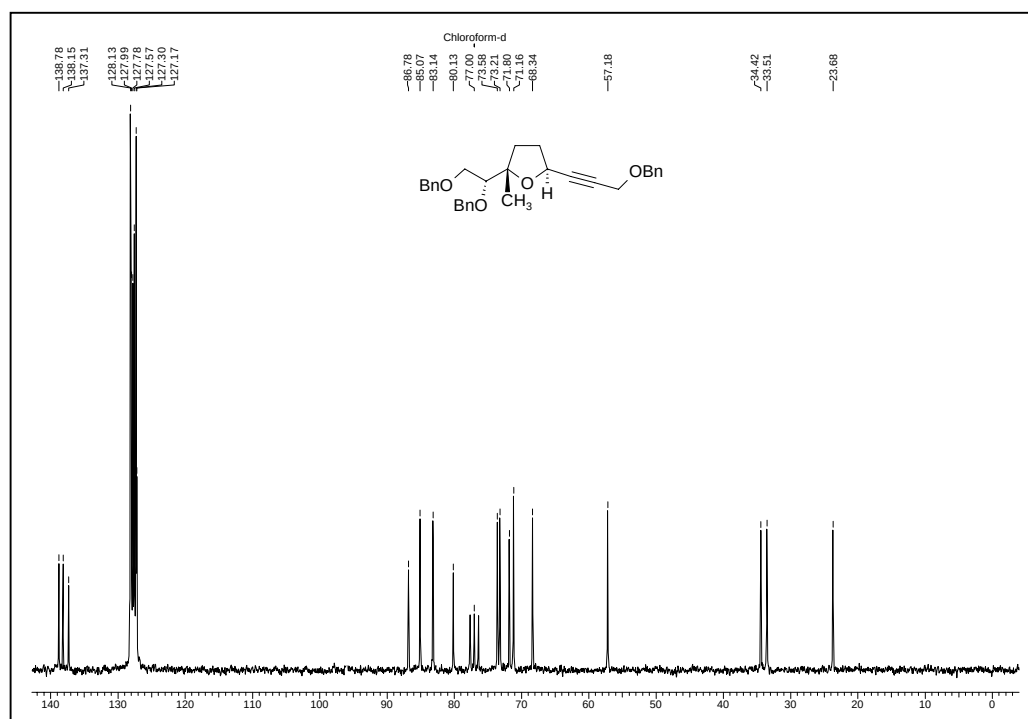
¹³C NMR Spectrum of 224 in CDCl₃



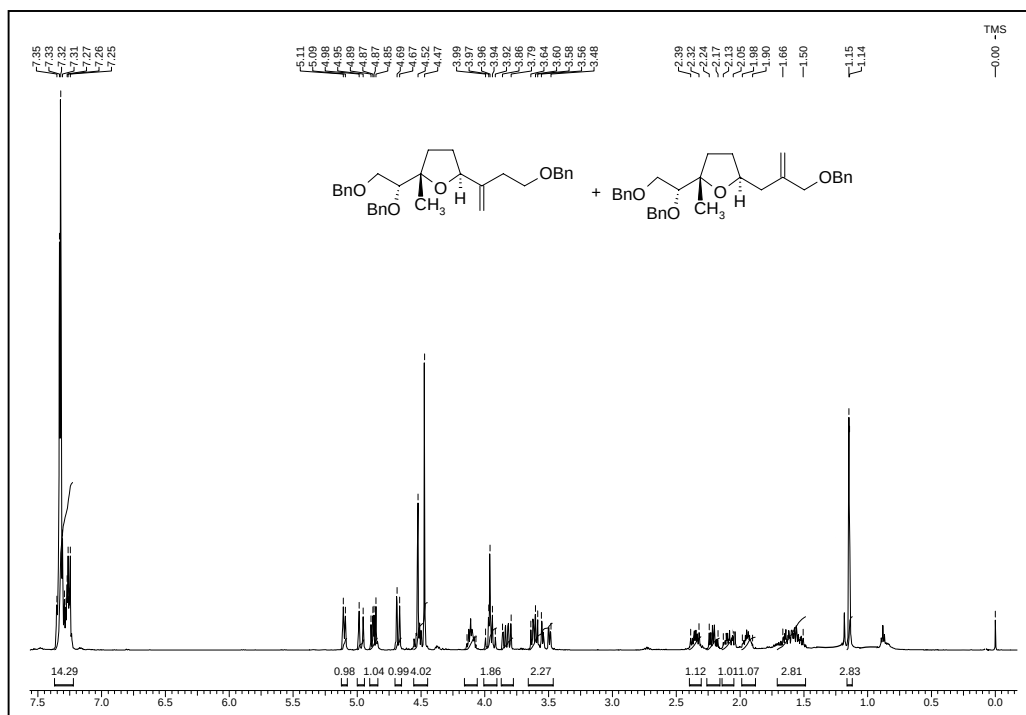
NOESY of compound 22a



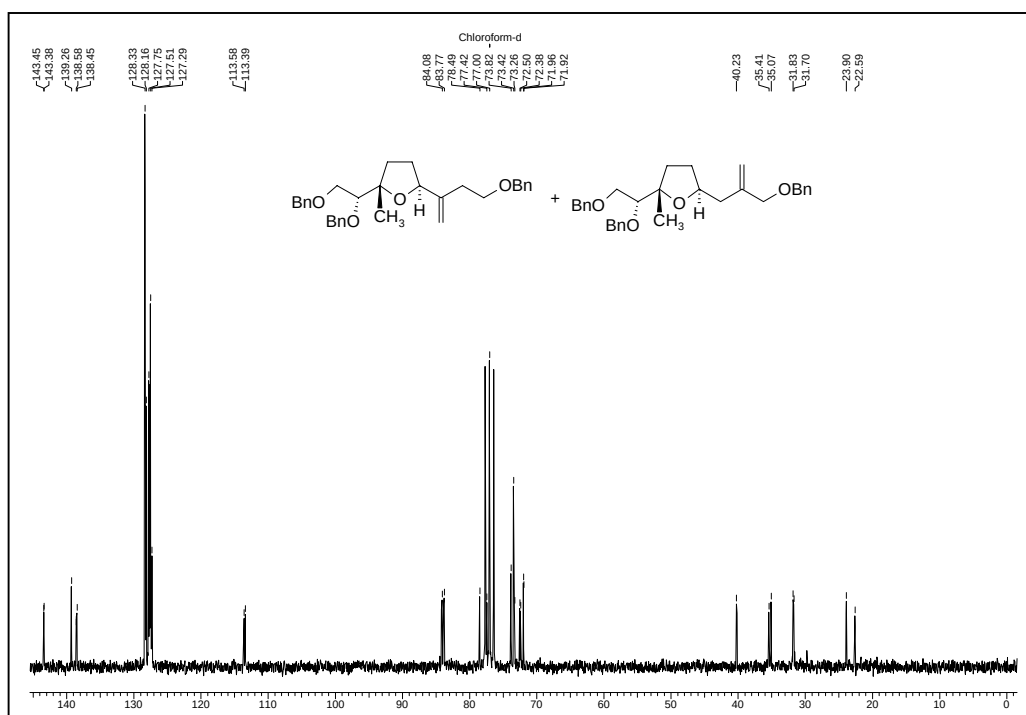
¹H NMR Spectrum of 226 in CDCl₃



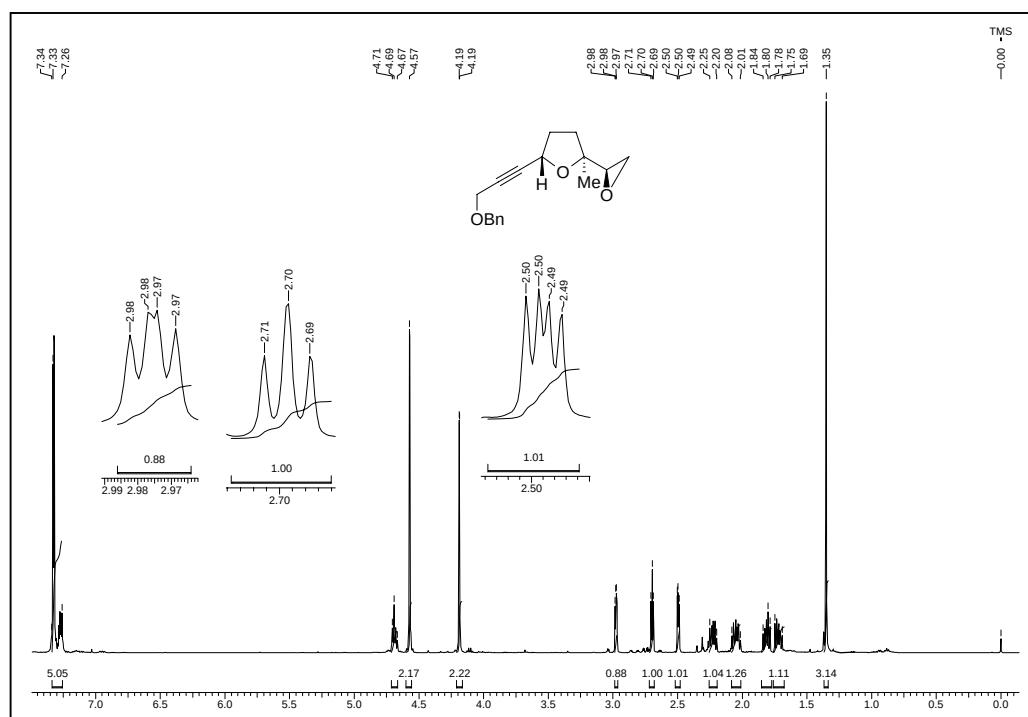
¹³C NMR Spectrum of 226 in CDCl₃



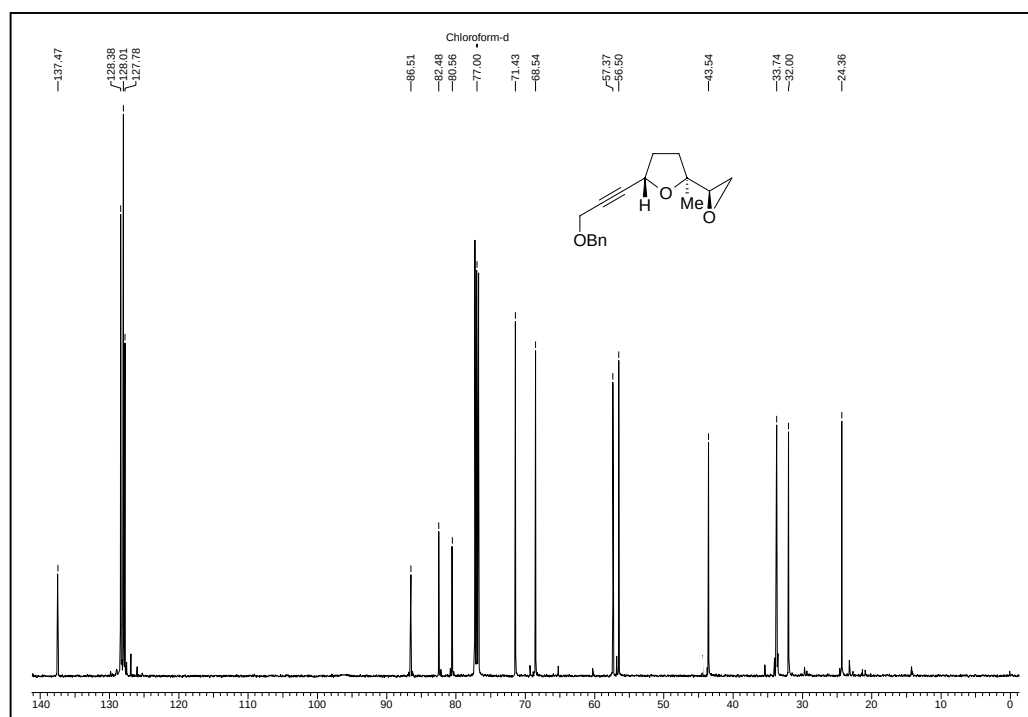
^1H NMR Spectrum of 229/230 in CDCl_3



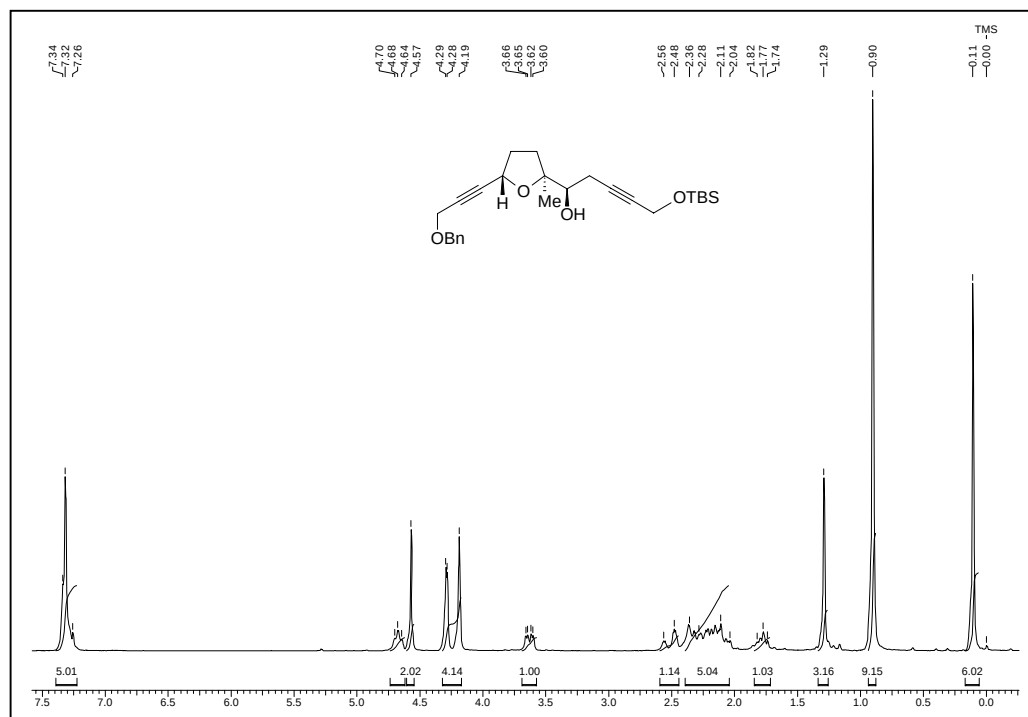
^{13}C NMR Spectrum of 229/230 in CDCl_3



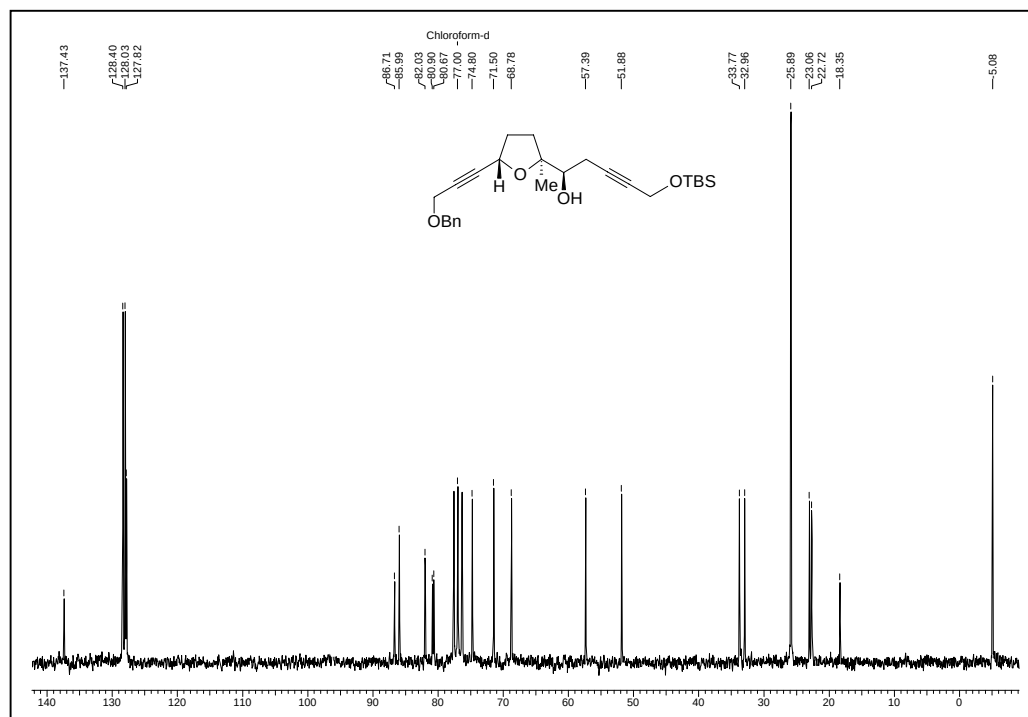
¹H NMR Spectrum of 210 in CDCl₃



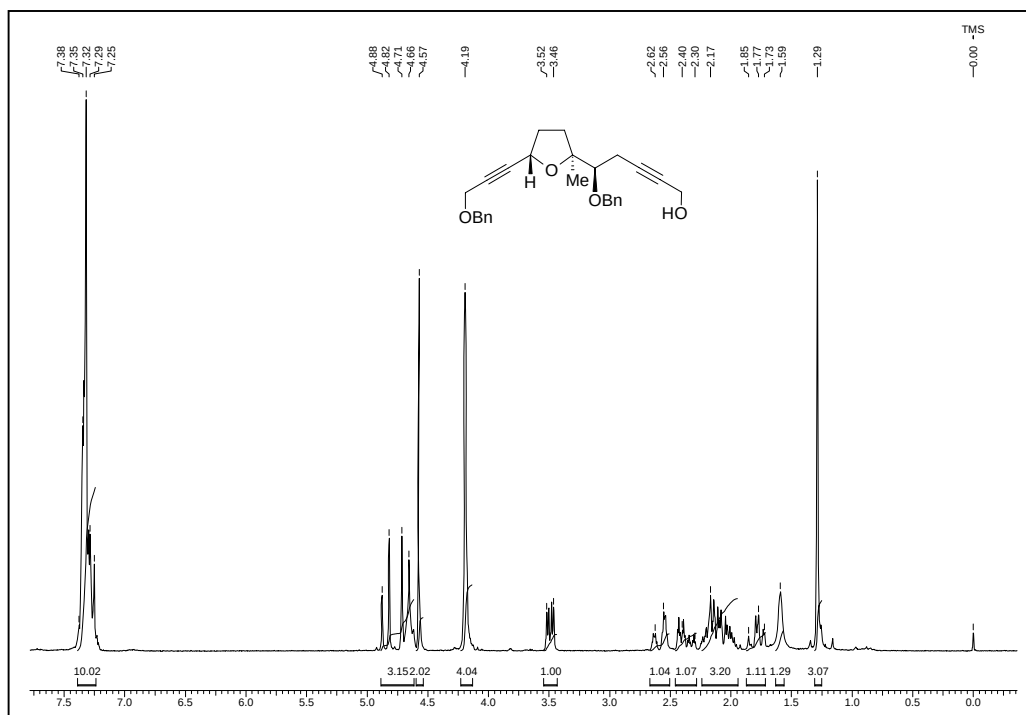
¹³C NMR Spectrum of 210 in CDCl₃



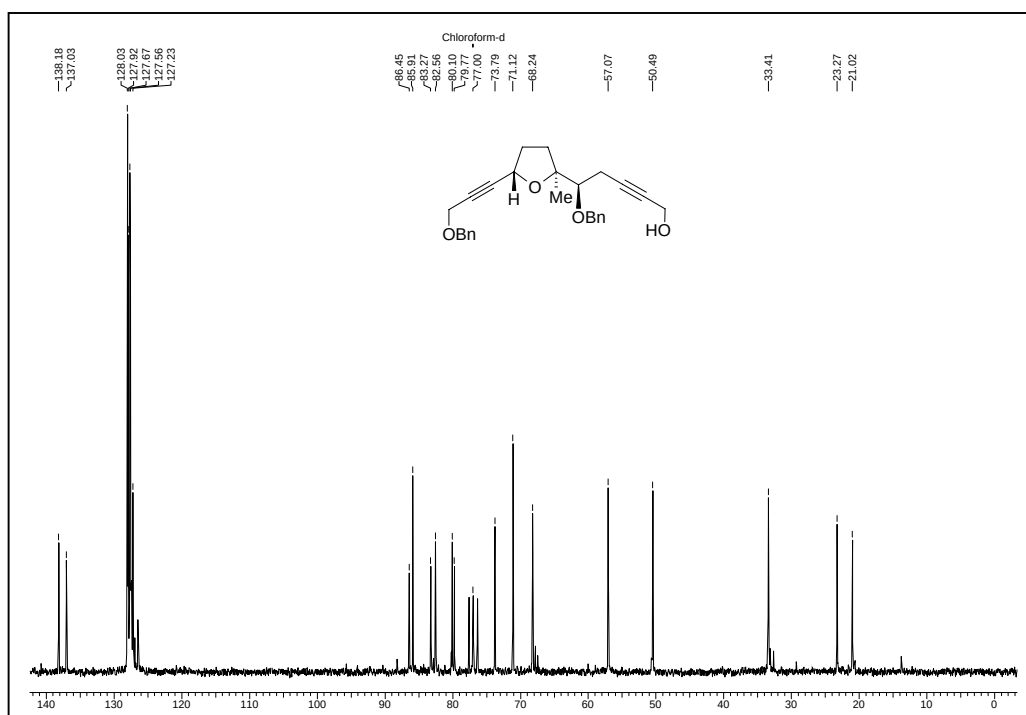
¹H NMR Spectrum of 231 in CDCl₃



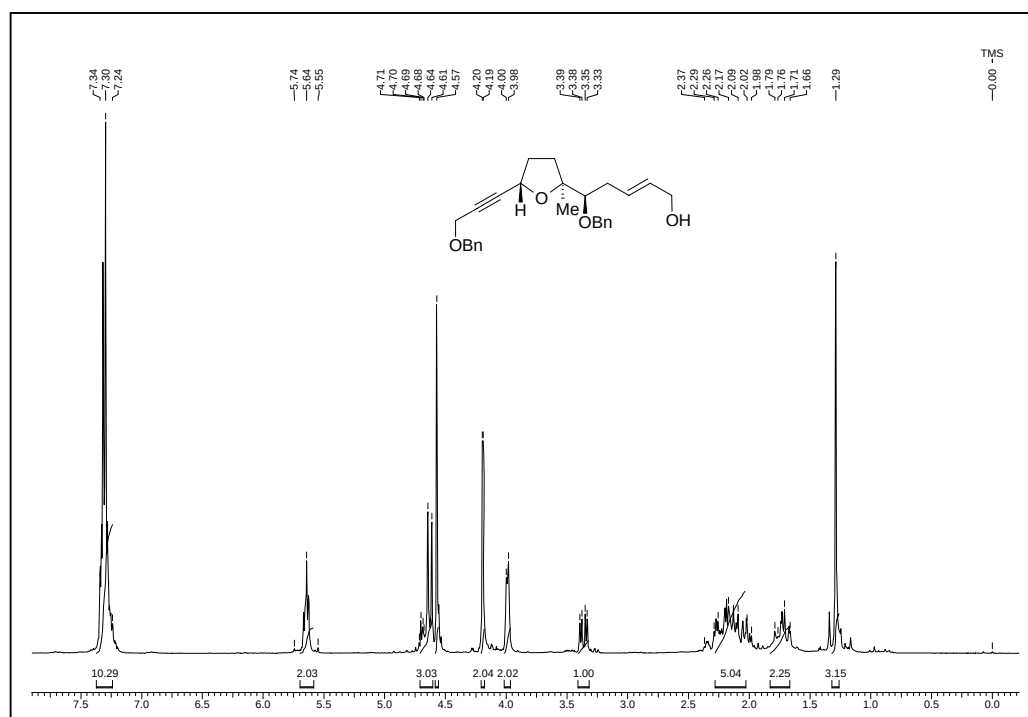
¹³C NMR Spectrum of 231 in CDCl₃



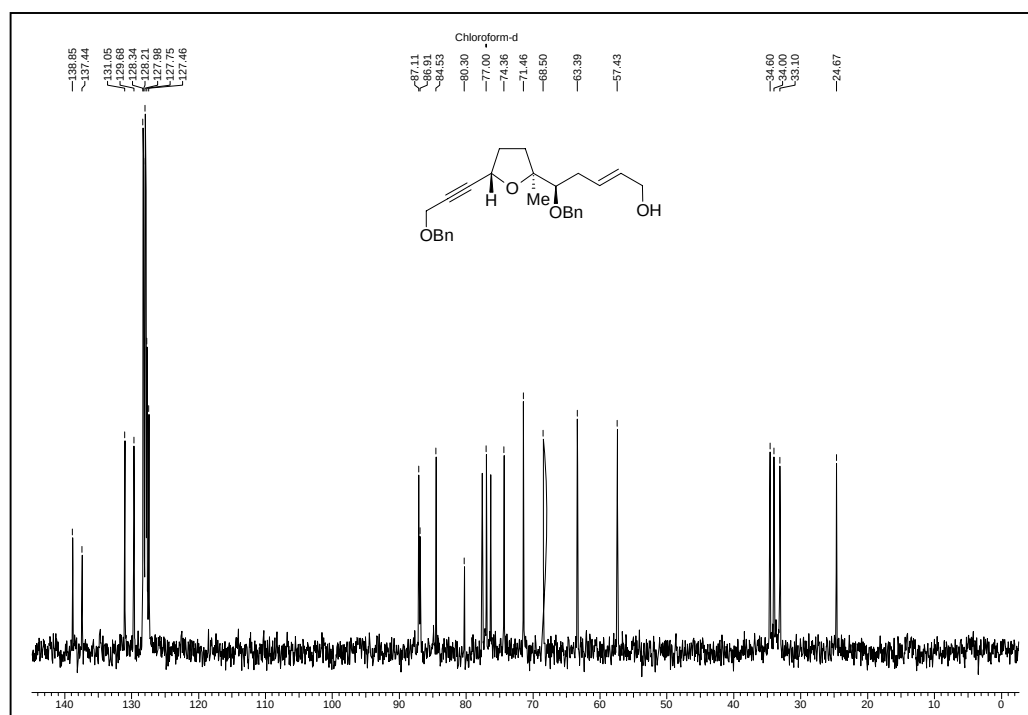
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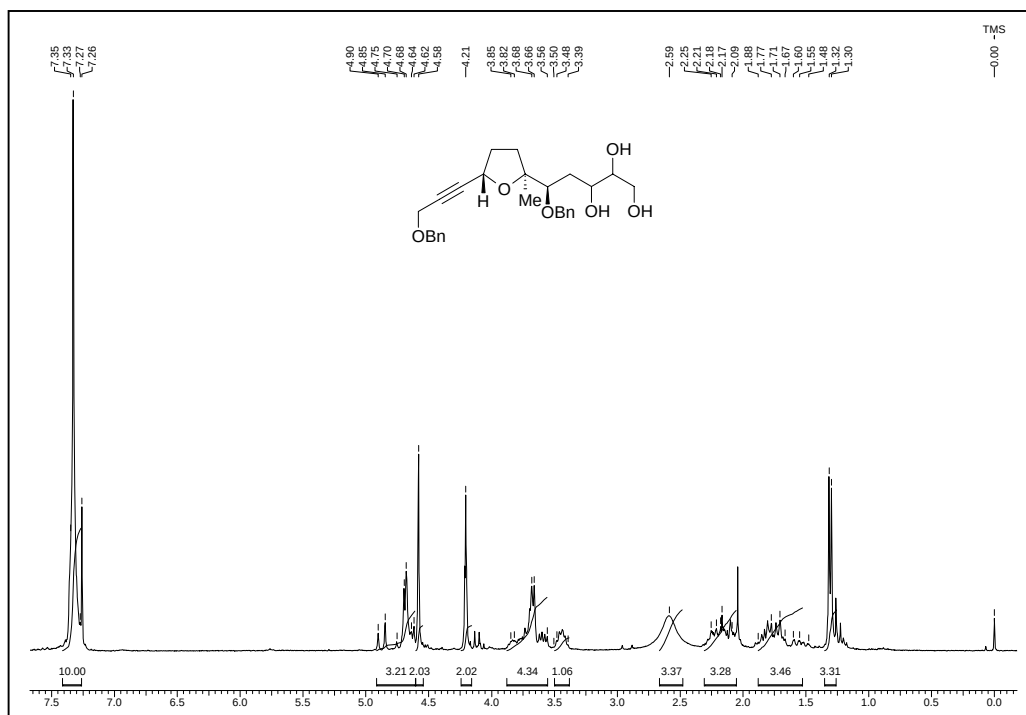
¹³C NMR Spectrum of 233 in CDCl₃



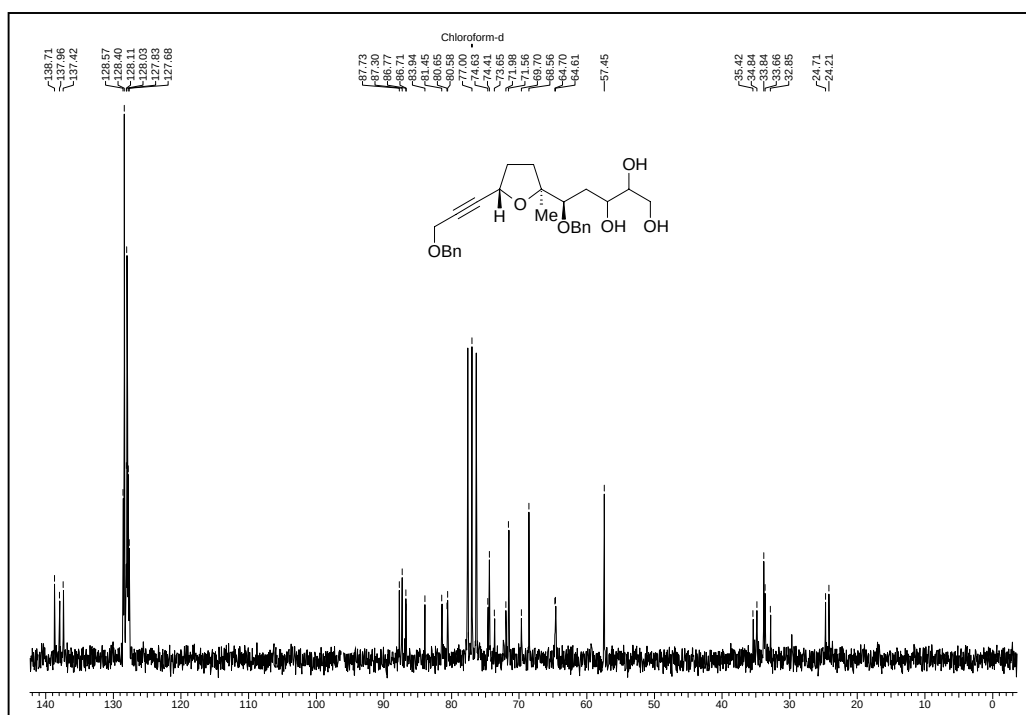
¹H NMR Spectrum of 209 in CDCl₃



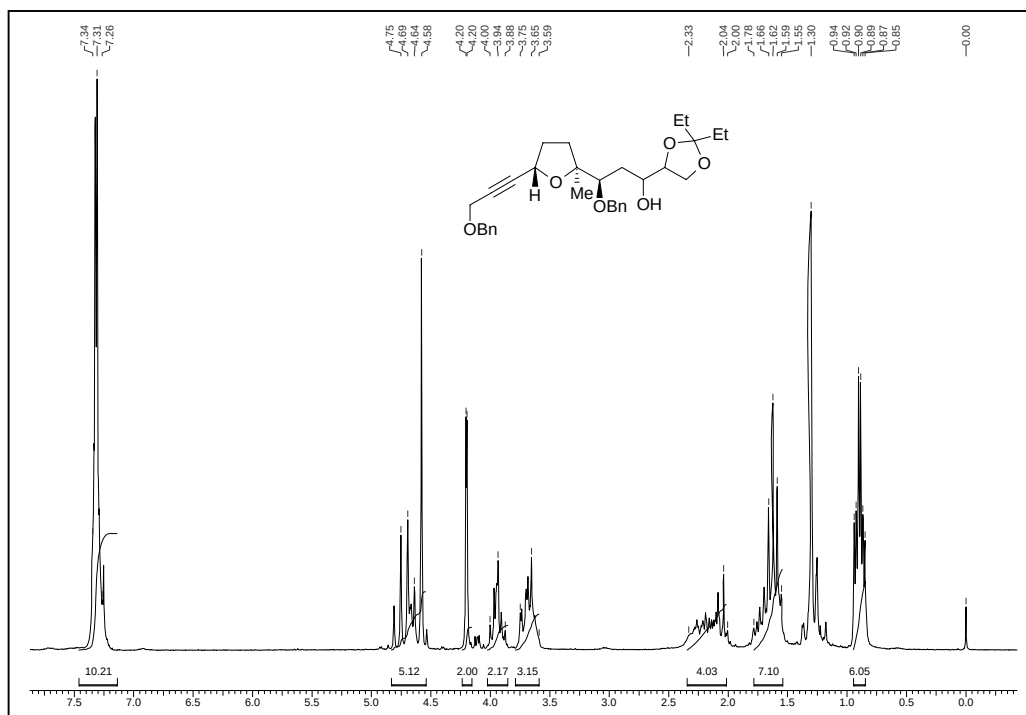
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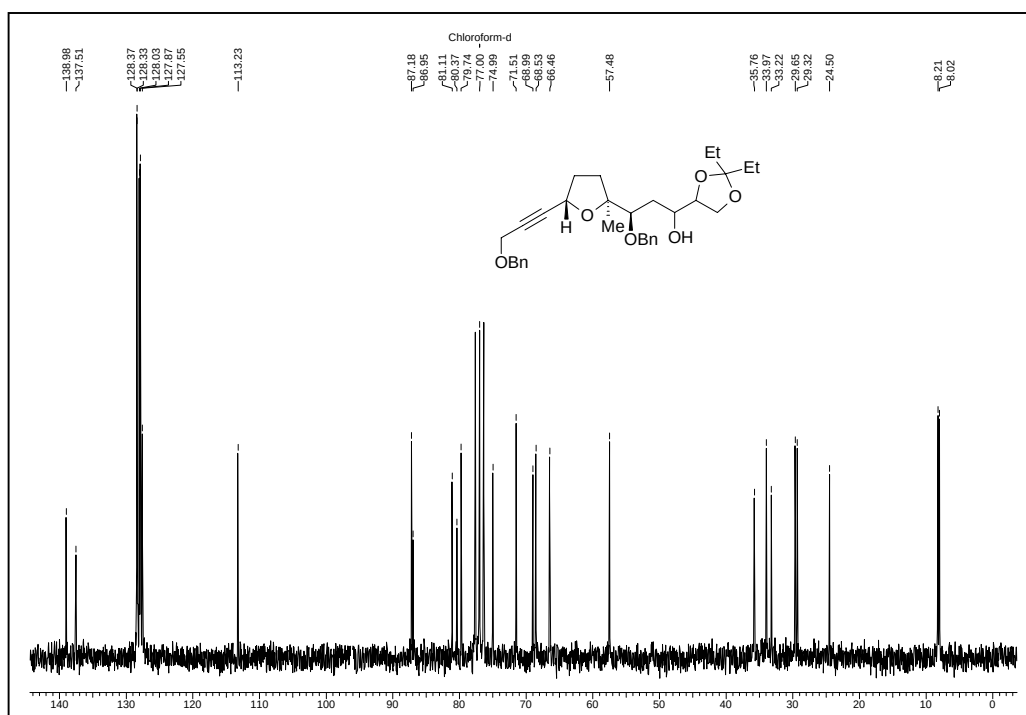
¹H NMR Spectrum of 234/235 in CDCl₃



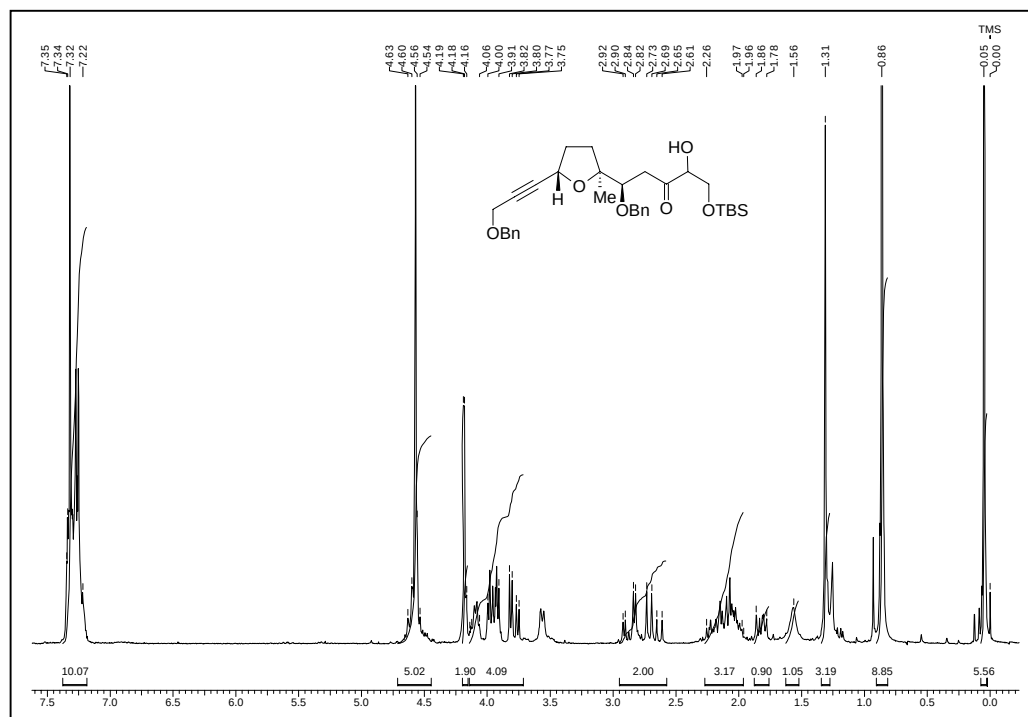
¹³C NMR Spectrum of 234/235 in CDCl₃



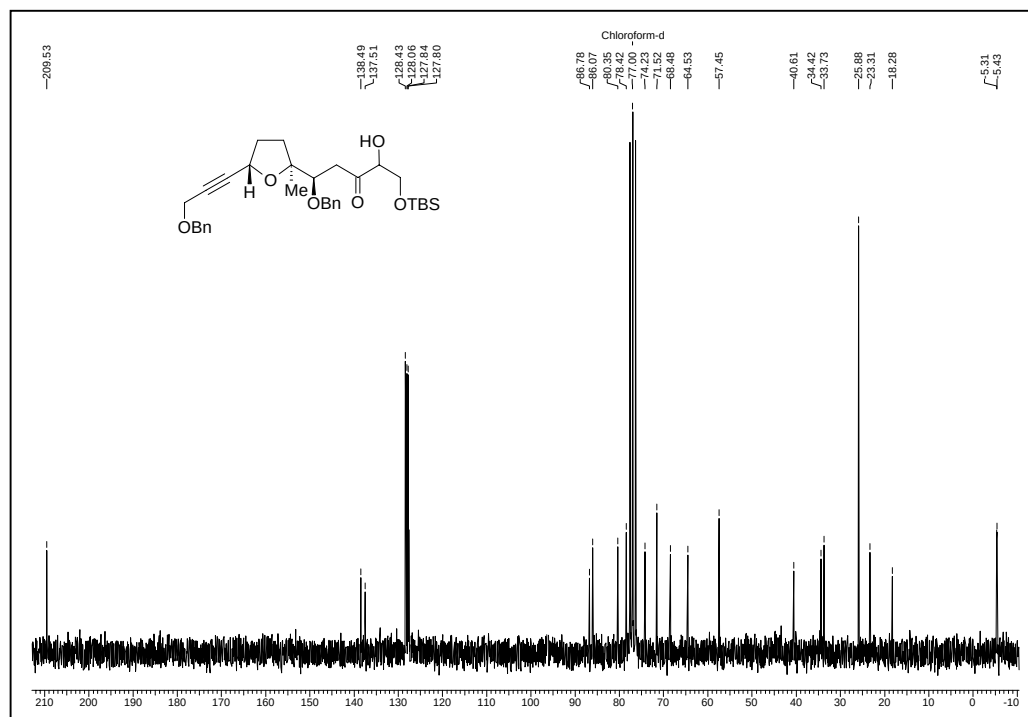
¹H NMR Spectrum of 236 in CDCl₃



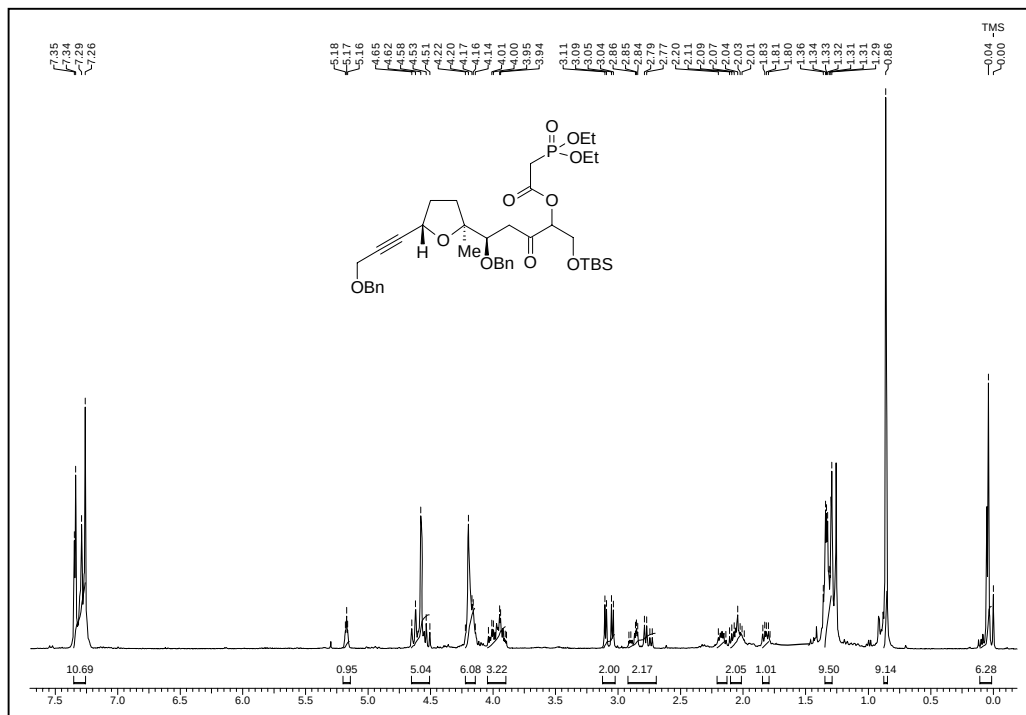
¹³C NMR Spectrum of 236 in CDCl₃



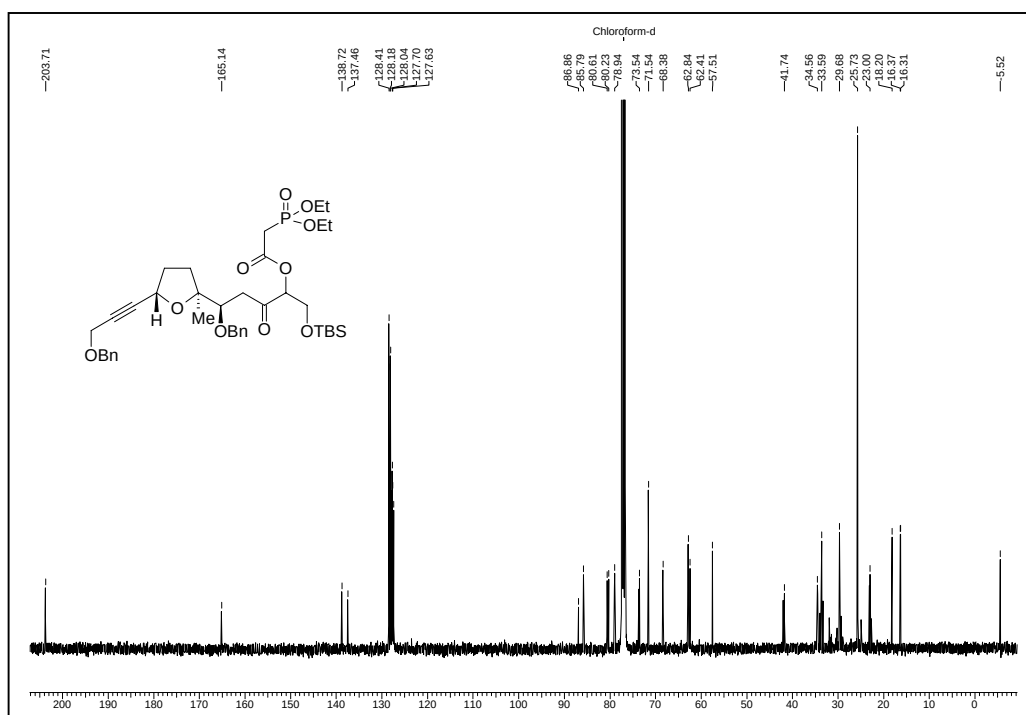
¹H NMR Spectrum of 239 in CDCl₃



¹³C NMR Spectrum of 239 in CDCl₃



¹H NMR Spectrum of 208 in CDCl₃



¹³C NMR Spectrum of 208 in CDCl₃

Chapter II, Section II:

Central Core of Uprolides D and E: A Survey of Some
Ring-Closing Metathesis Approaches

Introduction

Considering the novel skeleton of uprolides and densely functionalized central 14-carbon bicyclic core, as indicated in the first part of this chapter, in parallel to the construction of the C1-C14 of uprolide core, we initiated to explore ring closing metathesis reaction to form the bicyclic core. In this part, we describe our efforts in constructing the central bicyclic core of uprolide D and E, which has been selected considering our expertise in constructing the bicyclic rings by employing ring closing metathesis.

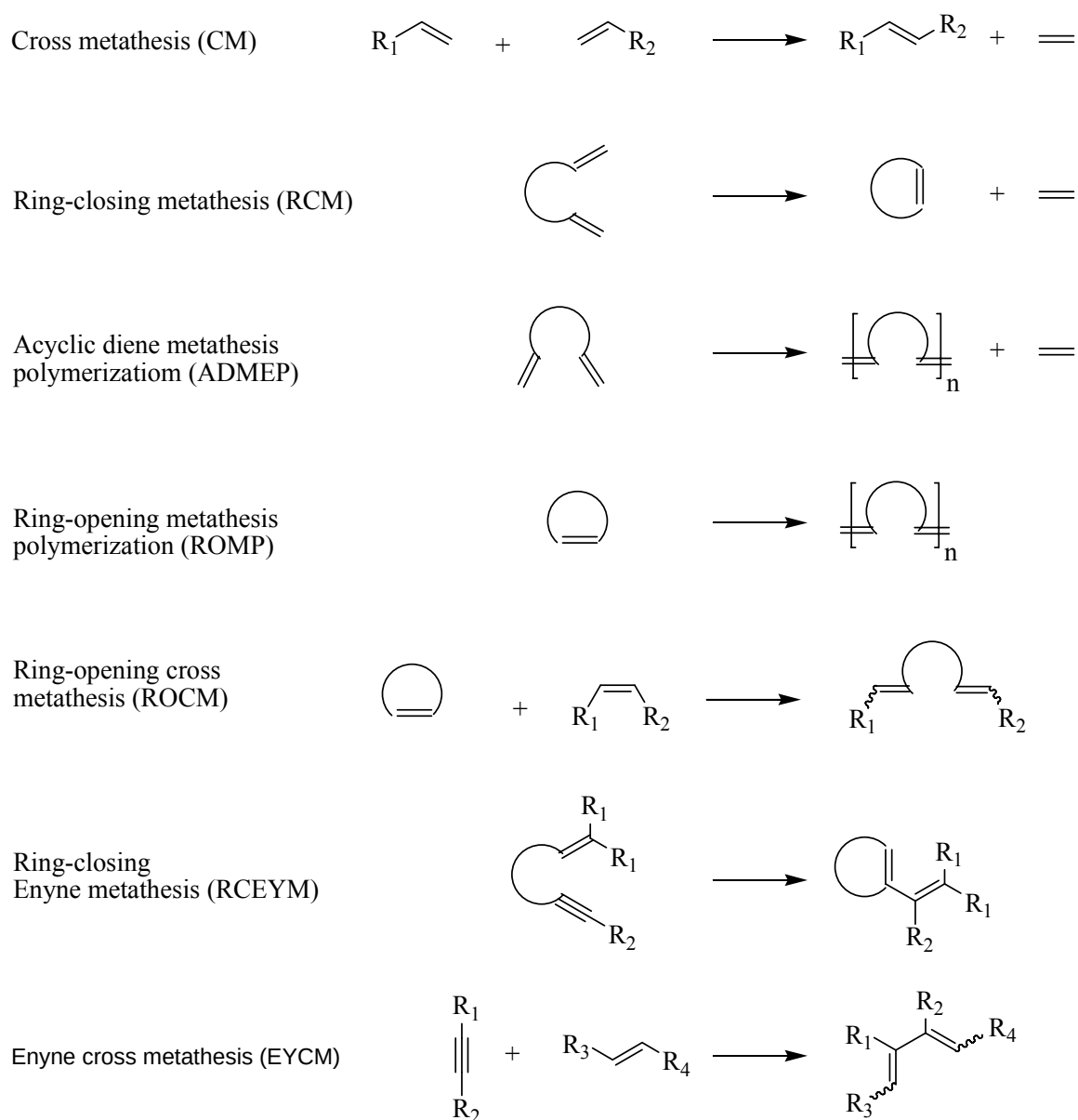
The Nobel Prize in chemistry 2005 was equally shared by Dr. Yves Chauvin, Professor Robert H. Grubbs, and Professor Richard R. Schrock for their pioneering contribution in the “development of *the metathesis method in organic synthesis*”.

The very foundation of organic synthesis consists of reactions that can reliably and efficiently form carbon-carbon bonds. In recent years, the olefin metathesis reaction has attracted widespread attention as a versatile carbon-carbon bond-forming method. Derived from the Greek words *meta* (change) and *thesis* (position), metathesis is the exchange of parts of two substances. The olefin metathesis reaction can be thought of as a reaction in which all the carbon-carbon double bonds in an olefin (alkene) are cut and then rearranged in a statistical fashion.

In 1950s the first metal catalysed metathesis reaction was discovered by Ziegler (Nobel prize in chemistry 1963), i.e. polymerization of ethylene. Metathesis, with its multiple facets, has become one of the most important chemical transformations. The olefin metathesis has been broadly divided as cross metathesis (CM), ring-closing metathesis (RCM), acyclic diene metathesis polymerization (ADMEP), ring-opening metathesis polymerization (ROMP), enyne metathesis (EYM), and ring opening cross metathesis (ROCM) (figure 1). Through these reactions, olefin metathesis provides a route to unsaturated molecules that are often challenging or impossible to prepare by any other means. Some of the most impressive achievements include the use of ROMP to make functionalized polymers, the synthesis of small to large heterocyclic systems by RCM, and the CM of olefins with pendant functional groups. A number of reviews have been published in this area, all of which focus on the ever-increasing uses of olefin

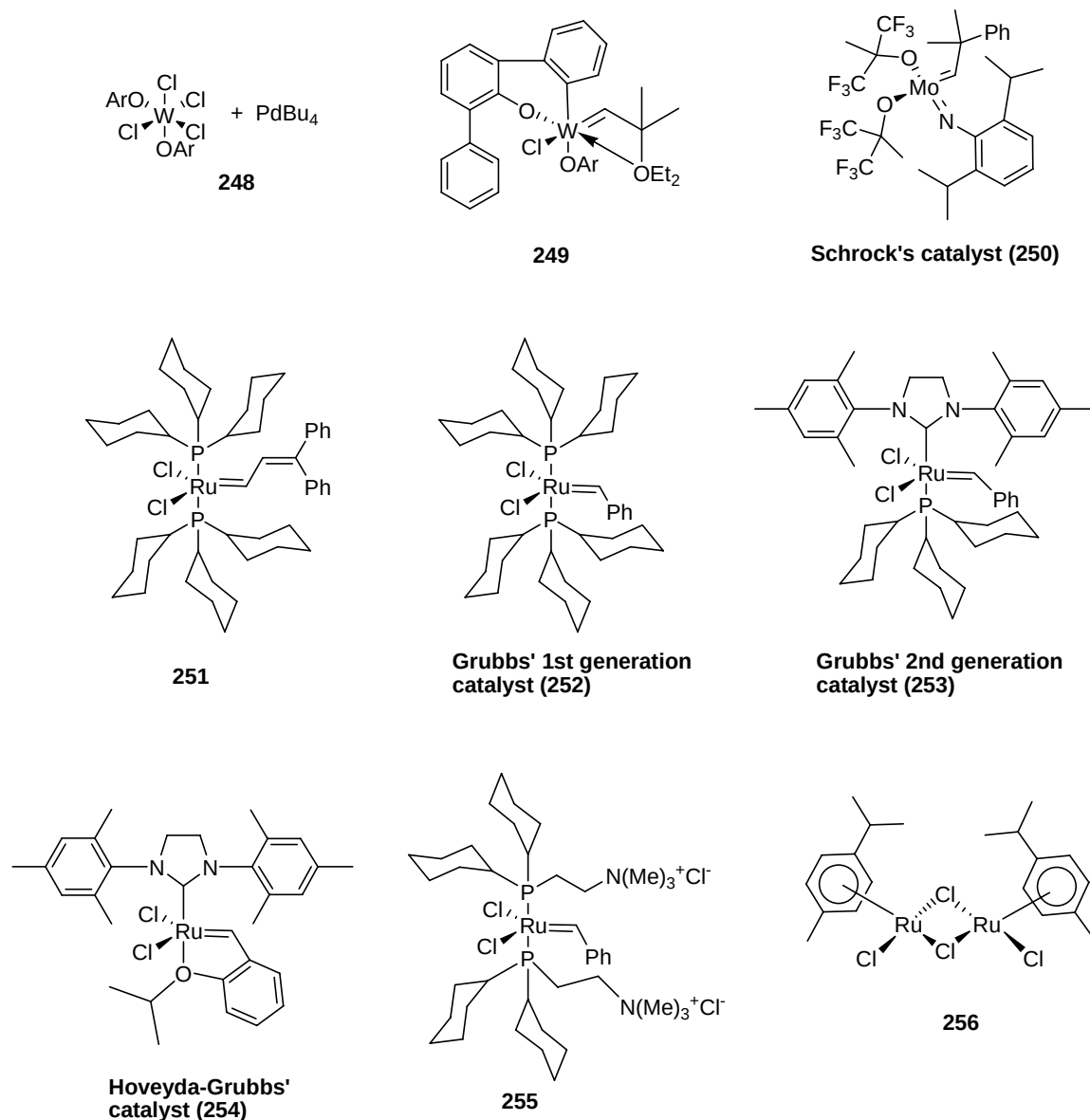
metathesis in organic synthesis and polymer chemistry.³⁰ However until a few years ago, the scope of the reaction was quite limited because of insufficient catalyst performance. It is only through major advances in catalyst design that tremendously expanded applications have recently become possible. To a large extent, these efforts to improve catalyst performance have been motivated and inspired by the desire to apply olefin metathesis to new synthetic challenges.

Scheme 1. *Olefin metathesis reactions*



Olefin metathesis does not require the use of any additional reagents except for a catalytic amount of metal carbene, and the only by-product that forms is volatile ethylene gas. The early examples of olefin metathesis employed classical catalysts, which usually included a tungsten chloride or oxychloride and an alkyl metal species.

Figure 1. Catalysts for olefin metathesis



These catalysts were less reactive to olefins due to their increased stability and yields were generally found to be low.³¹ The other established catalyst is dichlorobis(2,6-

dibromophenoxy)oxotungsten, $\text{Cl}_2(\text{ArO})_2\text{W}=\text{O}$.³² Although this system shows good functional group tolerance and has been used for many syntheses, it is considered to be unsuitable for industrial applications owing to its complexity and cost. Olefin metathesis began to receive more attention in 1993, when Basset and co-workers developed and applied the tungsten catalysts **248** and **249** for cross metathesis reactions.³³

One of the most useful catalysts for olefin metathesis reactions is the molybdenum catalyst (**250**) developed by Schrock et al.³⁴ Although the major advantage of **250** is its high reactivity towards a broad range of substrates having a variety of functional groups, this catalyst also has some limitations. Its major drawbacks are that it is air sensitive and has moderate to poor functional group tolerance. Much work on the development of catalytic systems has been done by Grubbs' and coworkers using four very important ruthenium based catalysts, **251**,³⁵ **252**,³⁶ **253**,³⁷ and **254**. The Schrock catalyst is more active and is useful in the conversion of sterically demanding substrates, while the Grubbs' catalysts tolerate a wide variety of functional groups. The second-generation Grubbs' catalysts are even more stable and more active than the original versions. Although all the three catalysts benefit from the same impressive tolerance to air, moisture and various functional groups, catalyst **252** provides improved initiation rates and can be prepared easily. In addition to the catalytic systems discussed above, a few other transition metal catalysts have been prepared for olefin metathesis reactions. Among them, the water soluble ruthenium catalyst **255**,³⁸ also developed by Grubbs and coworkers, and a photoinducible dichloro(*p*-cymene)ruthenium(II) dimer (**256**), developed by Fürstner and Ackermann,³⁹ are noteworthy.

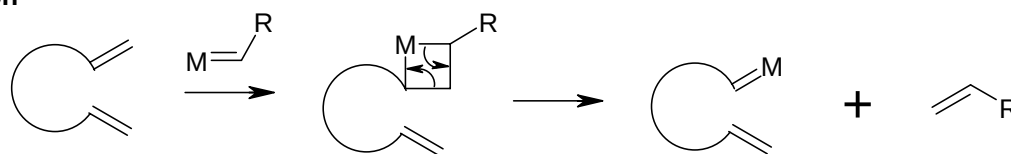
Ring-closing metathesis (RCM):

RCM is simply an intramolecular olefin metathesis with a Grubbs' catalyst yielding the cycloalkene and a volatile ethene. The Ring-closing metathesis (RCM) allows synthesis of 5- up to 30-membered cyclic alkenes. The *E/Z*-selectivity depends on the ring strain. The Ru-catalysts used tolerate a variety of functional groups, but normally the molecule must have polar side chains that are able to build a template for the catalyst. The modern 2nd generation Grubbs' catalysts are more versatile.

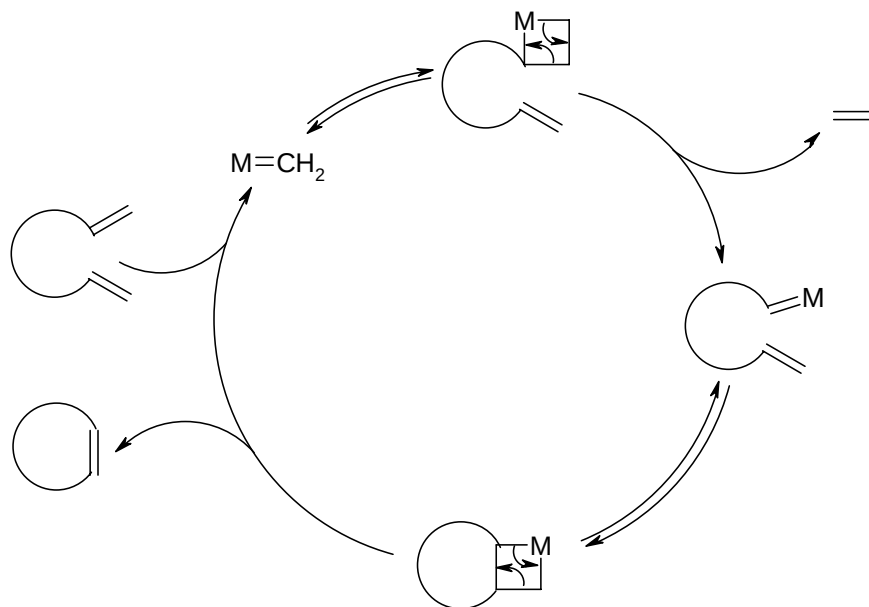
The postulated mechanism involves an iterative process of [2+2] cycloaddition and cycloreversion between the olefins, metal alkylidene and metallocyclobutane species.⁴⁰ The initial retro-type intermolecular [2+2] cycloaddition between the catalyst and one of the olefins of diene leads to the incorporation of the metal alkylidene in the substrate. The second cycloaddition takes place in a facile intramolecular fashion and ring opening of resulting metallocyclobutane leads to the cycloalkene and regeneration of the metal carbene, which takes up another diene molecule and acts in same fashion. The key intermediate is a metallacyclobutane, which can undergo cycloreversion either towards products or back to starting materials. The volatile nature of the alkene by-product (the ethene in most cases) tends the reaction to proceed forward thermodynamically. When the olefins of the substrate are terminal, the driving force for RCM is the removal of ethene from the reaction mixture.

Scheme 2. *Chauvin's mechanism of RCM*

Initiation



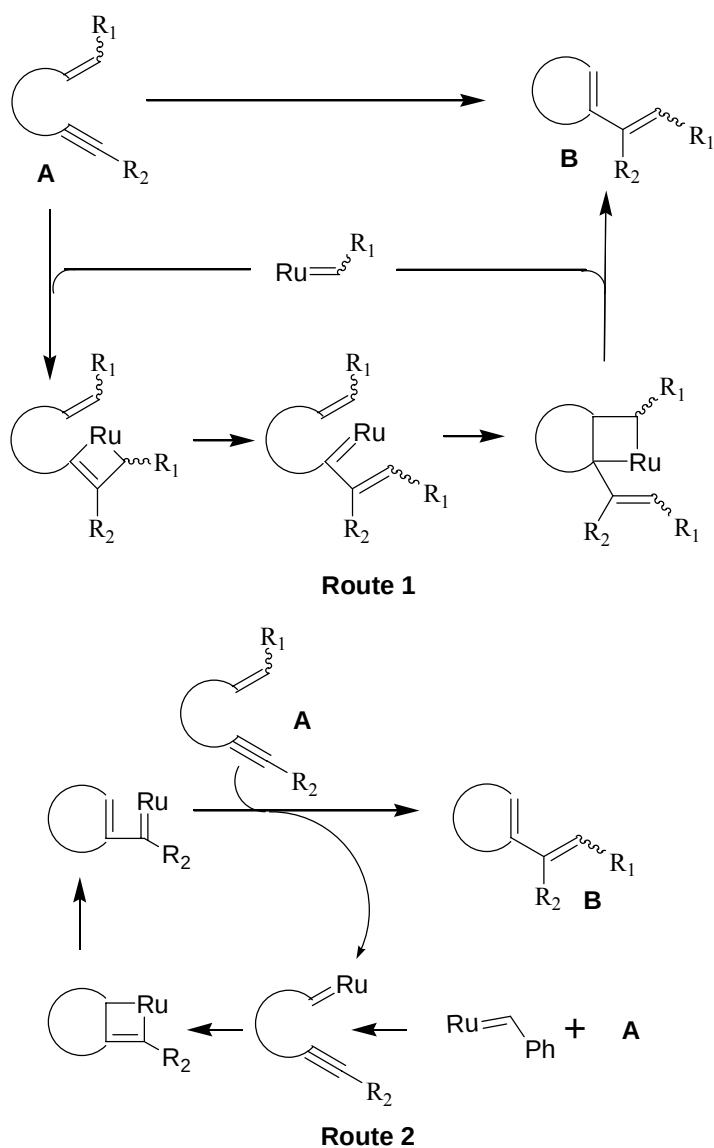
Catalytic cycle



Ene-yne metathesis:

The reaction between an alkyne and an alkene with a metal carbene catalyst forming a butadiene is termed as enyne metathesis. This reaction is a variation of olefin metathesis. The first enyne metathesis was reported by Katz,⁴¹ who used a Fischer tungsten carbene complex. It was found that ruthenium carbene complexes **252**, **253**, and **254** are very effective for enyne metathesis.

Scheme 3. *Ring-closing enyne metathesis*



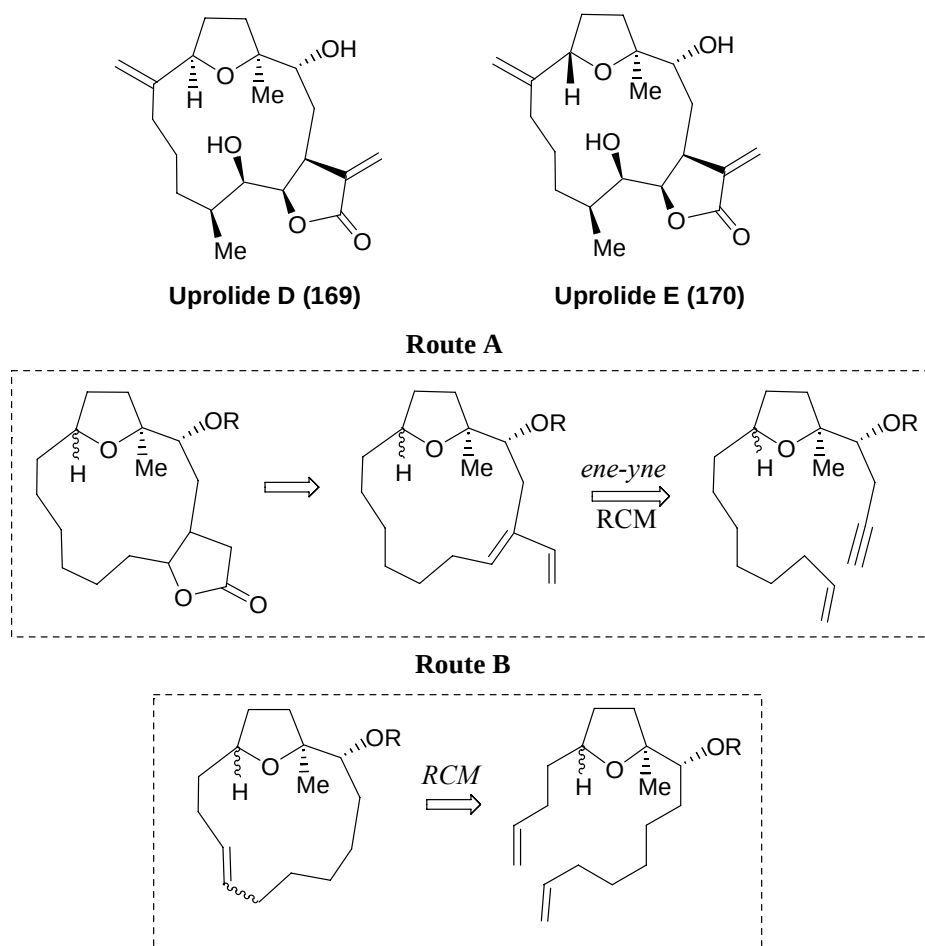
In eneyne metathesis, the double bond is cleaved, a carbon-carbon bond is formed between the double and triple bonds, and the cleaved alkylidene part of the double bond migrates onto the alkyne carbon to produce a cyclic compound having a diene moiety (Scheme 3).⁴² The reaction may proceed by a [2+2] cycloaddition of a ruthenium carbene complex with an alkyne part to produce a ruthenacyclobutene, and ring opening of this affords a ruthenium carbene complex, which reacts with an alkene part to produce a ruthenacyclobutane, and ring opening of this gives a cyclized compound and a ruthenium carbene complex is regenerated (Route 1). Another mechanism is also considered by which an alkene part of the enyne reacts at first with the ruthenium carbene complex (Route 2).



Present Work

Our study related to construction of central bicyclic core of both the Uprolides D and E and the lactone fused to it mainly deals with the metathetic approaches. The 14-membered carbocyclic uprolides become excellent targets for RCM and ene-yne RCM with proper orientation of the diene and ene-yne systems. The retro synthetic analysis is represented by two closely related metathetic approaches *viz* route-A and route-B.

Scheme 1. *Metathetic approaches for uprolides*

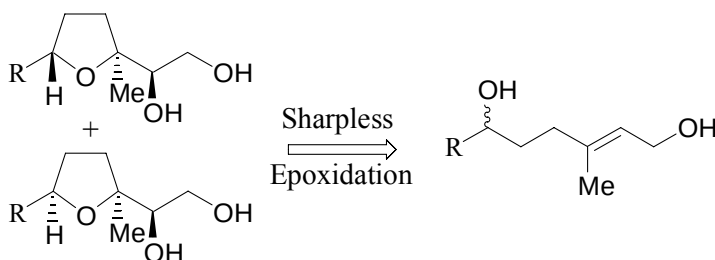


To construct a bicyclic core of uprolides and the lactone fused to it, we planned to have a 1,3-diene as shown in route A (Scheme 1), which in turn can be obtained from ene-yne RCM of a suitable precursor. The other RCM approach was expected to be

straightforward from a diene as depicted in route B. The major issue in both the routes would be the feasibility of RCM with the 2,5-*anti*-configured tetrahydrofuran ring systems in general and the ease of an intramolecular ene-yne RCM forming large ring systems in particular.

Having opted for the ring closing metathetic approaches for the central bicyclic core of uprolides D and E, we required to examine good number of substrates to explore this key reaction. Considering the lengthy sequence that has been adopted in our previous endeavor, we were forced to develop a more reliable and flexible strategy to build the key tetrahydrofuran building units with the desired 2,5-*cis*- and 2,5-*trans*-configuration at the ring junctions. In this context we have devised a strategy which is funded on kinetic resolution of 6-substituted hex-2-en-1,6-diol by means of Sharpless asymmetric epoxidation (Scheme 2) to address the synthesis of the key 2,5-*syn*- and *anti*-configured tetrahydrofurans with the required side chain at C-5 of furan ring.

Scheme 2. Sharpless asymmetric epoxidation route for 2,5-*syn*- and *anti*-configured central tetrahydrofuran core of uprolides

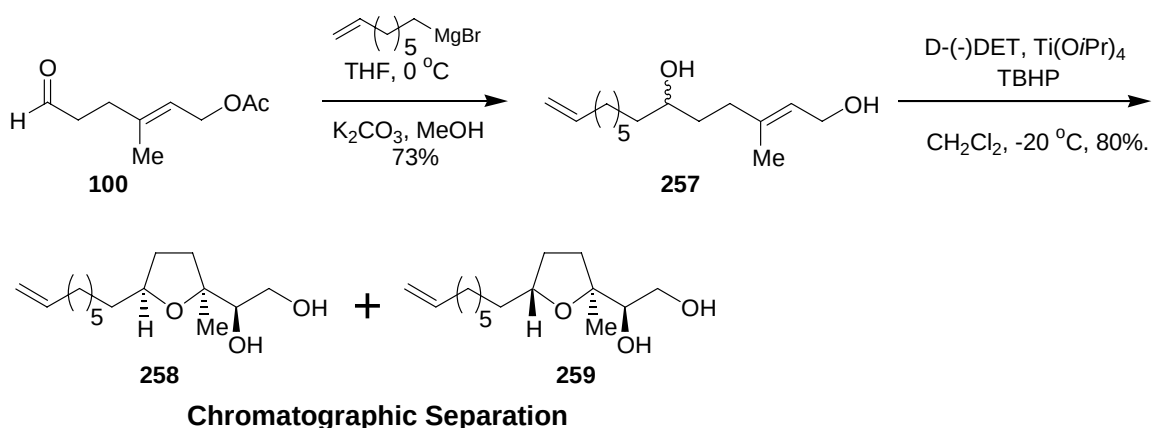


Ene-yne RCM approach towards uprolides

The synthetic sequences started with the known aldehyde **100** that can be prepared from the geraniol acetate following a two step sequence as described earlier in first section of chapter I. Addition of 7-octenyl-magnesium bromide to aldehyde **100** in dry THF at 0 °C for 4 h followed by acetate hydrolysis using K₂CO₃ in methanol at r.t. for 3 h gave the dienol **257** in 73% yield (Scheme 3). ¹H and ¹³C NMR analysis supported the formation of **257**. The ¹H NMR spectrum showed the signal corresponding to allylic proton at δ 5.45 and the terminal vinylic protons showed resonances at δ 4.96 and 5.80.

Rest of the spectrum was in full agreement with the structure. The ^{13}C NMR spectrum showed the signals corresponding to vinylic carbons at δ 113.9 and 138.8. The allyl olefinic carbons resonated at δ 123.6 and 138.6. IR and mass spectral studies further confirmed the structure. The following Sharpless asymmetric epoxidation of **257** using diethyl D-tartrate provided the diastereomeric tetrahydrofurans **258** and **259** (Scheme 3), which were separated by flash column chromatography. The ^1H NMR analysis of **258** showed the disappearance of allylic protons in the olefinic region and no protons corresponding to epoxide were observed. The C-2 quaternary methyl resonated at δ 1.19 as a singlet, and the C-5 ring proton was observed at δ 3.95 as a multiplet. The terminal vinylic protons resonated at δ 4.96 and 5.80. The ^{13}C NMR spectrum showed C-2 methyl at δ 22.4. The vinylic carbons resonated at δ 114.0 and 138.9. Similarly, in the ^1H NMR spectrum of **259**, the signal corresponding to C-2 methyl was observed at δ 1.16 as a singlet, and the C-5 ring proton at δ 3.89 as a multiplet. The vinylic protons were observed at δ 4.96 and 5.80. The ^{13}C NMR spectrum showed the C-2 methyl at δ 23.8. The vinylic carbons resonated at δ 114.0 and 138.9. Rest of the spectrum was in full agreement with the assigned structure. The structures **258** and **259** were further confirmed by IR and mass spectral studies.

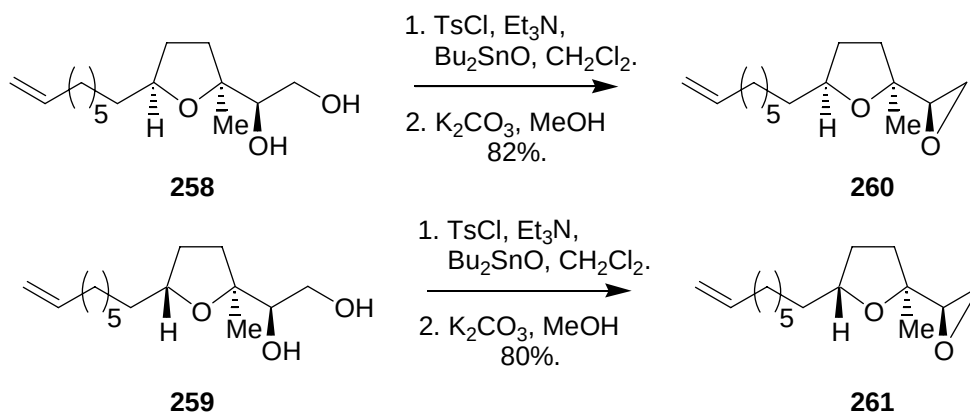
Scheme 3. Kinetic resolution of hexene diol



To establish the relative stereochemistries of tetrahydrofurans **258** and **259**, both the diols were independently subjected to regioselective tosylation by using tosyl

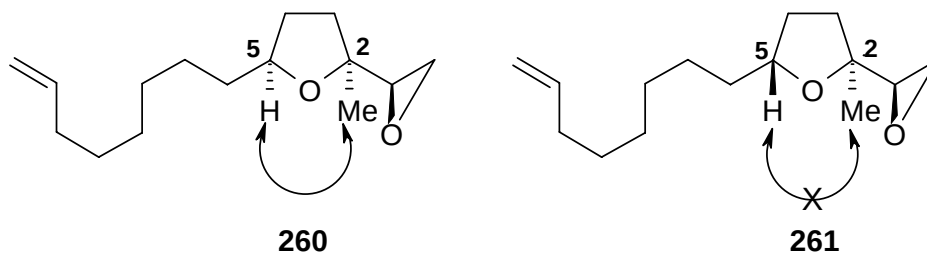
chloride, triethyl amine and catalytic di *n*-butyl tin oxide in anhydrous DCM to give the intermediate O-tosylates which in turn was treated with K₂CO₃ in methanol to accomplish the epoxides **260** and **261** in 80 and 82% yields respectively (Scheme 4). The NMR analysis confirmed the formation of epoxides. The ¹H NMR spectrum of **260** showed signals corresponding to the epoxide protons at δ 2.64, 2.73, and 2.98. Similarly, the epoxide protons of **261** resonated at δ 2.56, 2.72, and 3.00. The structures were further confirmed by ¹³C NMR, IR and mass spectral studies.

Scheme 4. *Synthesis of epoxides*



NOESY-COSY experiments were carried out on epoxides **260** and **261** and the interactions observed are shown below (figure 1). It was found that in case of *syn*-tetrahydrofuran derived epoxide (**260**), the C-2 α -quaternary methyl and C-5 α -proton are within NOE proximity. There is negligible or no spatial interaction observed between C-2 α -quaternary methyl and C-5 β -proton in case of *anti*-tetrahydrofuran derived epoxide (**261**). Rest of the interactions are too complex to explain as tetrahydrofuran and side chain protons are merging together. The observed spatial interactions ambiguously confirmed the relative stereochemistries of 2,5-disubstituted tetrahydrofurans **260** and **261** as *syn* and *anti* respectively.

Figure 1. Observed NOESY interactions



Once we were thorough with the relative stereochemistry, we then directed to assign the absolute stereochemistry by modified Mosher's ester method as described in chapter I, section I. The *syn*-epoxide **260** when opened with lithium acetylide ethylenediamine complex in dry DMSO at r.t. for 2 h furnished alkynol **262** in 81% yield. The ^1H NMR spectrum showed the disappearance of epoxide protons and the alkyne proton resonated at δ 2.01 as a triplet ($J = 2.7$ Hz). The propargylic CH_2 protons were seen separately at δ 2.30 and 2.48 as ddd. The alkyne carbons resonated at δ 70.0 and 81.8 in ^{13}C NMR spectrum. The secondary hydroxyl functionality of **262** was independently coupled with (*R*)- and (*S*)-MTPA acids by using DCC and catalytic DMAP in anhydrous DCM to give their respective MTPA esters **263**, **264** in 80 and 82% yields respectively (Scheme 5). ^1H NMR spectrum of both the esters **263** and **264** were recorded and all the possible protons were assigned. The $\Delta\delta = (\delta S - \delta R) \times 1000$ values were calculated for as many protons as possible. A molecular model was constructed by arranging part of the molecule with $-\Delta\delta$ on left hand side and the one with $+\Delta\delta$ on the right hand side. On the basis of the model (Figure 2) we have assigned the absolute stereochemistry of side chain hydroxyl center of **262** as (*R*), which ultimately confirmed the absolute stereochemistry at quaternary C-2 centre as (*S*) and C-5 as again (*S*). The diastereomeric excess was found to be 93% by ^{19}F NMR analysis of (*R*)-MTPA ester.

Scheme 5. *Synthesis of (R) and (S) MTPA esters*

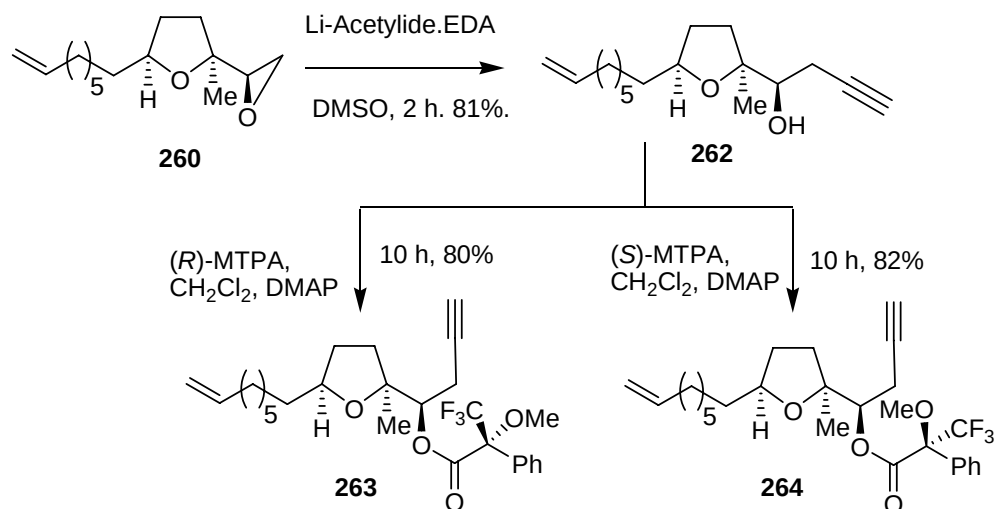
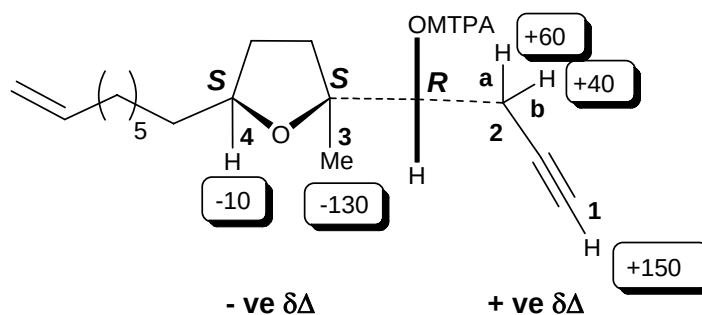


Figure 2. *Determination of absolute stereochemistry*

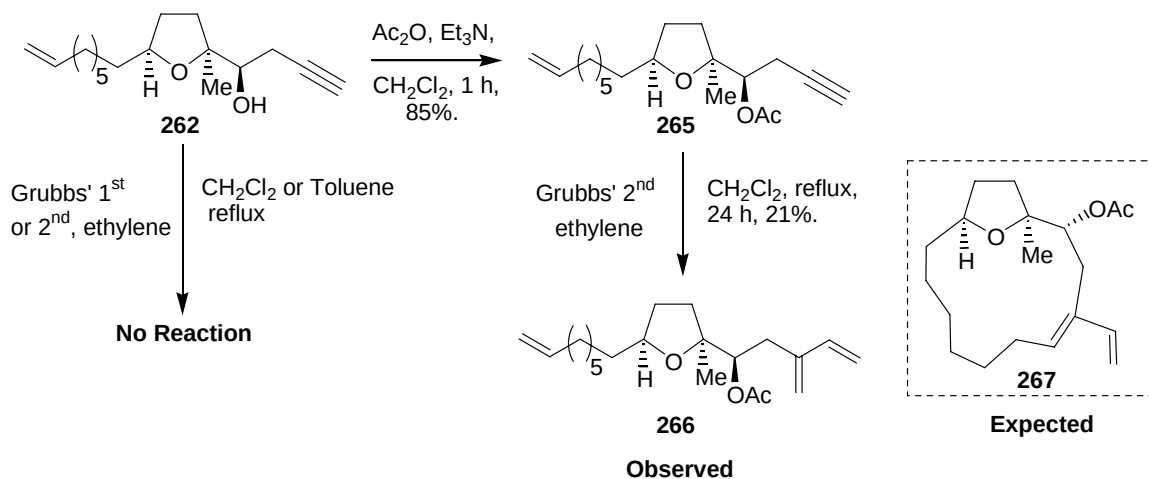
	1	2		3	4
		a	b		
(S)-MTPA ester	1.99	2.52	2.84	1.06	3.91
(R)-MTPA ester	1.84	2.48	2.78	1.19	3.93
$\delta\Delta = (\delta S - \delta R) \times 1000$	+150	+40	+60	-130	-10



Our next concern, the ene-yne RCM reaction was initially studied on alkynol **262**. Exposure of **262** to ethylene using Grubbs' 1st generation catalyst (**252**) in refluxing

DCM didn't procure any cyclised product. The attempted reaction with Grubbs' 2nd generation catalyst (**253**) under ethylene in refluxing toluene was again a failure (Scheme 6). However, once the alcohol functionality in **262** was protected as its acetate **265**, the treatment of this acetate with 2nd generation Grubbs' catalyst (**253**) in refluxing DCM under ethylene atmosphere gave the intermediate triene **266** in 21% yield. However it did not produce traces of expected macrocyclic 1,3-diene (**267**) (Scheme 6). The structure **266** was established on the basis of its spectral and analytical data. In the ¹H NMR spectrum the 1,3 diene protons were seen at δ 5.01 as a singlet (2H), 5.10 as a doublet (J = 10.8 Hz), 5.29 as a doublet (J = 17.6), and 6.34 as a double doublet (J = 17.6, 10.8 Hz). The terminal vinylic protons resonated at δ 4.93 and 5.78. ¹³C NMR spectrum showed the signals corresponding to the diene system at δ 113.9, 117.9, 138.4, and 143.1. The carbons corresponding to terminal vinyl group resonated at δ 114.3 and 139.0.

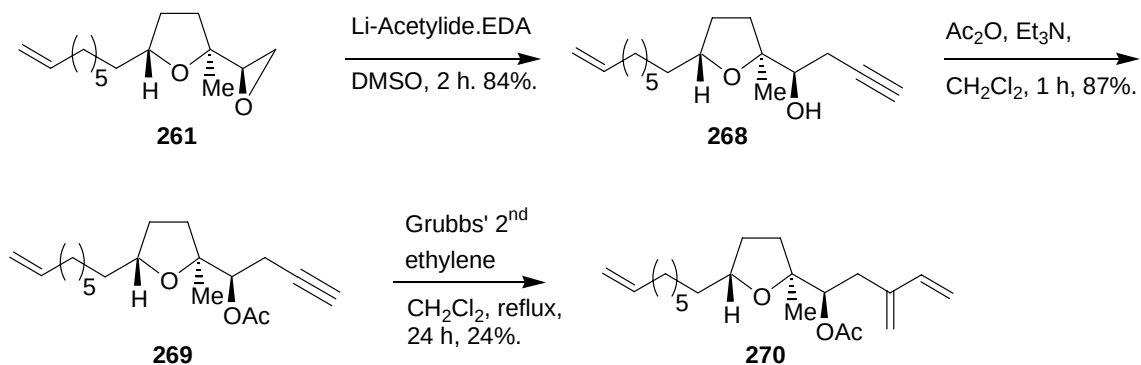
Scheme 6. Attempted ene-yne RCM reaction



Though, the attempted enyne reaction of **265** resulted in an exclusive triene formation, we also explored the possibility of the ene-yne RCM reaction of the 2,5-*anti*-configured furan, which is a model substrate for the synthesis of uprolide E. The epoxide **261** was opened with lithium acetylide ethylenediamine complex in dry DMSO at r.t. for 2 h to give alkynol **268** in 84% yield. Hydroxy functionality in **268** was treated with acetic anhydride using triethylamine, catalytic DMAP to afford the corresponding acetate **269** in 87% yield. The acetate was subjected to ene-yne RCM reaction by using 2nd

generation Grubbs' catalyst in refluxing DCM under ethylene atmosphere to afford the corresponding intermediate triene **270** in 21% yield (Scheme 7).

Scheme 7. *Enyne-RCM approach for the anti-2,5-disubstituted ene-yne*

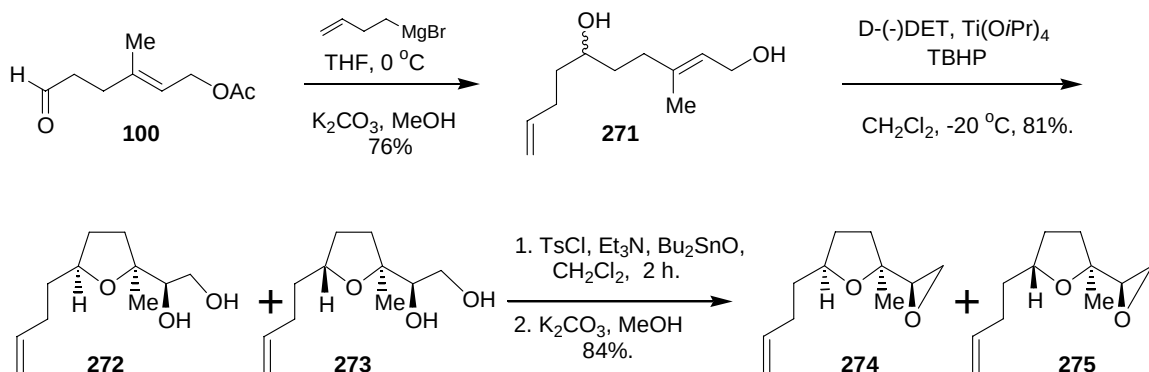


Ring closing metathesis approach towards uprolides

Since the ene-yne RCM approach towards uprolides resulted in exclusive triene products, we then focused on RCM possibilities for the bicyclic core of uprolides. The synthetic sequence started with the aldehyde **100**. Addition of 3-butenylmagnesium bromide to **100** followed by acetate hydrolysis using K₂CO₃ in methanol gave key dienol **271** in 76% overall yield. In the ¹H NMR spectrum, the aldehydic proton had disappeared and the signals corresponding to terminal olefinic protons are observed at δ 4.96 and 5.80. The allylic olefinic proton resonated at δ 5.38. ¹³C NMR spectrum showed the terminal olefinic carbons at δ 114.3 and 138.3, and the internal olefinic carbons resonated at δ 123.5 and 138.3. The structure was further confirmed by IR and mass spectral studies. The racemic dienol **271** was subjected to Sharpless asymmetric epoxidation using diisopropyl D-tartrate to afford tetrahydrofurans **272** and **273** as an inseparable mixture (1:1). The cyclization was initially confirmed by ¹H NMR analysis of the mixture **272/273**. The allylic olefinic proton had disappeared and no epoxide protons were seen in the spectrum. The furan ring protons resonated as set of multiplets from δ 1.52-1.78 and 1.96-2.16 along with the side chain aliphatic protons. The C-2 methyls appeared at δ 1.17 and 1.18 as singlets with equal integration. The two hydroxyl protons resonated at δ 2.77

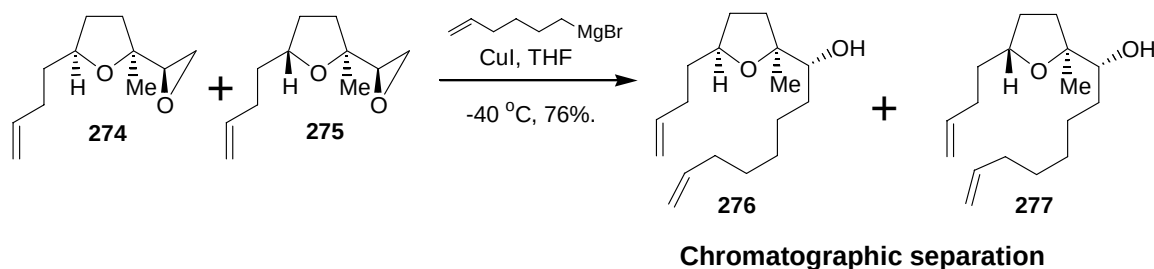
as a broad singlet. The equal ratio of diastereomers was further confirmed by ^{13}C NMR analysis. Regioselective tosylation of diols **272/273** followed by treatment with K_2CO_3 in methanol gave inseparable mixture of diastereomeric epoxides **274/275** in 84% yield (Scheme 8). The formation of epoxides were confirmed by their spectral analysis. In the ^1H NMR analysis, the epoxide protons were seen at δ 2.56, 2.69, and 2.96. Rest of the spectrum was in full agreement with the assigned structure. ^{13}C NMR, IR and mass spectral studies further confirmed the epoxide structures beyond reasonable doubt.

Scheme 8. *Kinetic resolution of hexenol*



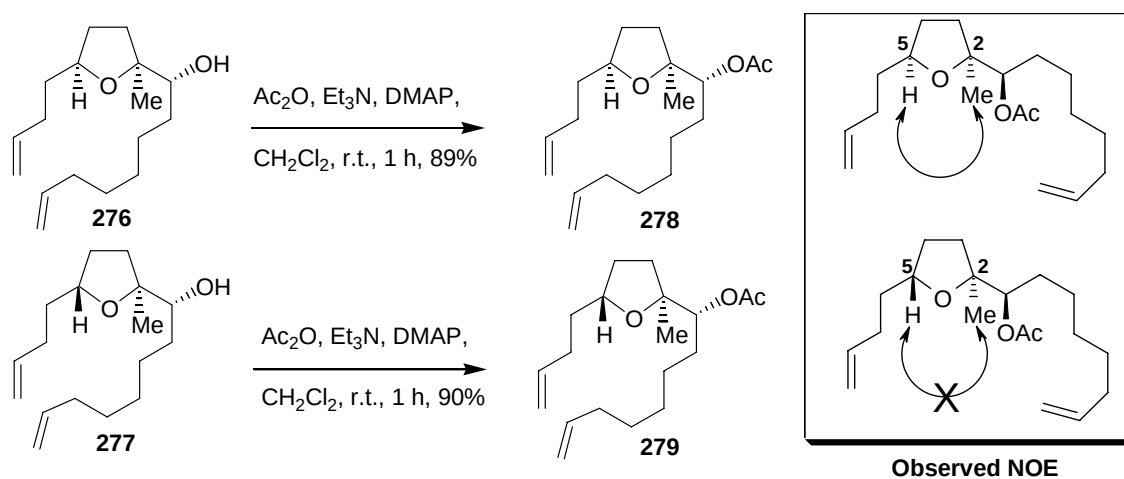
The mixture of epoxides **274/275** were treated with cuprate derived from 5-hexenyl magnesium bromide and CuI in THF at $-40\text{ }^\circ\text{C}$ to afford dienol compounds **276** and **277** in 76% yield (Scheme 9). These were separated and characterized by spectral and analytical data. The signals corresponding to epoxide protons disappeared in ^1H NMR spectrum of **276** and the $-\text{CH}-$ proton attached to hydroxyl group resonated at δ 3.50 as a double doublet. The rest of the spectrum was in full agreement with the structure. In the ^1H NMR spectrum of **277** the $-\text{CH}-$ proton attached to hydroxyl group resonated at δ 3.45 as a double doublet. ^{13}C NMR, IR and mass spectral studies further confirmed the assigned structure.

Scheme 9. Synthesis of dienes



To confirm the relative stereochemistries of **276** and **277**, both the alcohols were independently treated with acetic anhydride using triethylamine, catalytic DMAP in anhydrous DCM to afford the corresponding acetates **278** and **279** (Scheme 10). The structures **278** and **279** were established by spectral analysis. In the ^1H NMR spectrum, the acetate methyl for **278** and **279** were observed at δ 2.06 as a singlet. The ^{13}C NMR spectrum showed the carbonyl carbon at δ 170.3 for both **278** and **279**. Rest of the spectral and analytical data were in full agreement with the structures **278** and **279**.

Scheme 10. Determination of relative stereochemistry

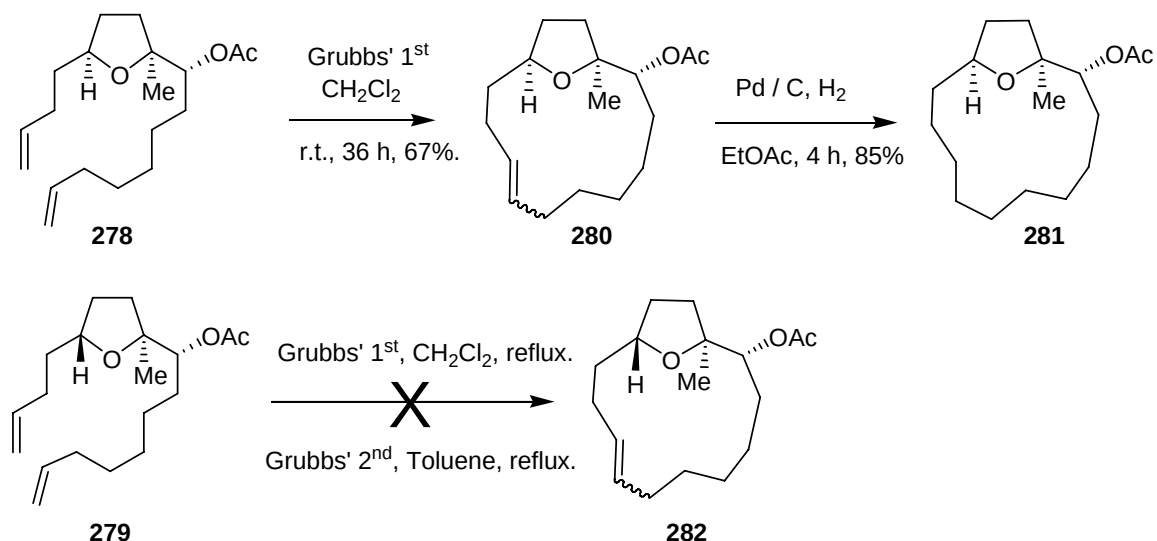


In case of *syn*-tetrahydrofuran derived acetate **278**, the C-2 α -quaternary methyl and C-5 α -proton have spatial interactions. There is negligible or no spatial interaction observed between C-2 α -quaternary methyl and C-5 β -proton in case of *anti*-

tetrahydrofuran derived acetate **279**. Rest of the interactions are too complex to explain since tetrahydrofuran and side chain protons merge together in the NMR spectra.

The next endeavor was to study the critical RCM reaction of dienol **276**. Treating **276** with 1st generation Grubbs' catalysts in refluxing DCM or 2nd generation Grubbs' catalysts in refluxing benzene didn't produce any cyclized product. The RCM reaction of the corresponding acetate **278** with the 1st generation Grubbs' catalyst in DCM at r.t. under high dilution condition was satisfactory and produced the 14-membered macrocyclic derivative **280** as an inseparable *E/Z* (1:1) mixture in 67% yield (Scheme 11). The product was confirmed by its ¹H NMR analysis. The four protons corresponding to the terminal olefinic system had disappeared and two protons were observed at δ 5.14-5.46 as a multiplet. The C-2 methyl resonated at δ 1.14 and 1.20 as two distinct singlets with equal integration that unambiguously confirmed the 1:1 ratio of *E/Z* isomers. Hydrogenation of **280** using Pd/C in ethyl acetate gave the reduced bicyclic core of uprolide D **281** in 85% yield. The spectral and analytical data of **281** was in agreement with the assigned structure

Scheme 11. Ring-closing metathesis reaction

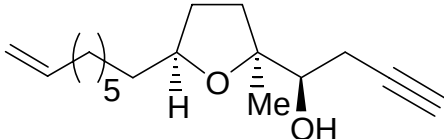
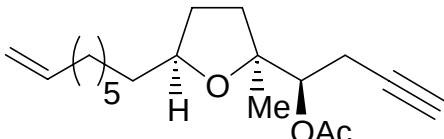
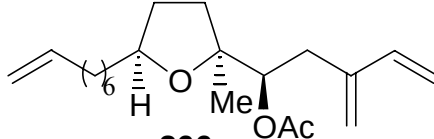
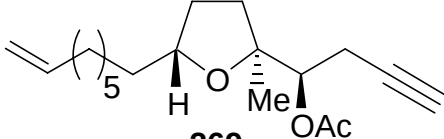
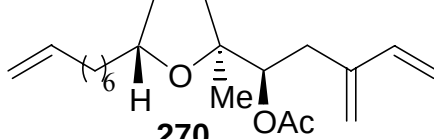


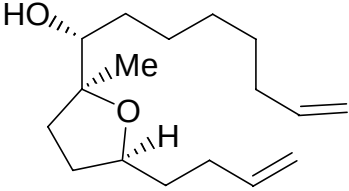
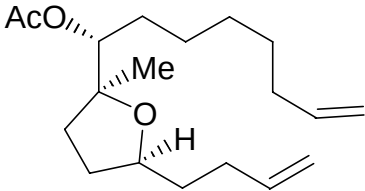
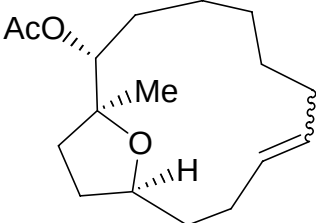
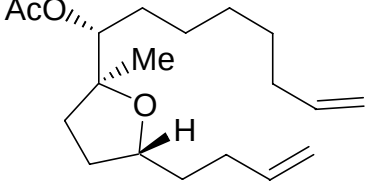
After having established the feasibility of RCM in accessing the central bicyclic core of uprolide D, next we turned our attention to implement the same with furan

derivative **277**, which is a model substrate for the synthesis of uprolide E. However, the RCM of *anti*-configured furan **277** or its acetate **279** was found to be a difficult proposition using either 1st or 2nd generation Grubbs' catalysts under several conditions attempted such as running the reaction in refluxing DCM, benzene or toluene (Scheme 11).

Conclusions

As indicated in the following table, a variety of substrates were explored to examine the feasibility of RCM to build the macrocyclic core of uprolides D and E. It was concluded that only in case of a 2,5-*syn*-configured tetrahydrofuran derivative (model substrate for the uprolide D), the RCM reaction was feasible. However, a RCM approach to the bicyclic core of uprolide E or an ene-yne RCM approach for both uprolides D and E were unsuccessful.

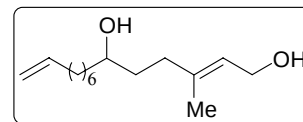
Substrate	Reaction Condition	Product
 262	G 1, DCM, Ethylene Reflux	No Reaction
	G 2, Toluene, Ethylene Reflux	No Reaction
 265	G 2, DCM, Ethylene, Reflux	 266
 269	G 2, DCM, Ethylene, Reflux	 270

 276	G 1, DCM, Reflux	Dimer
	G 2, Benzene, Reflux	Dimer
 278	G 1, DCM, r.t.	 280
 279	G 1, DCM, Reflux	Dimer
	G 2, Benzene, Reflux	Dimer

Experimental

Experimental

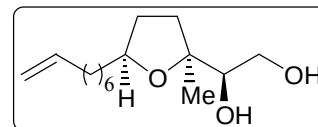
(E)-3-Methyltetradeca-2,13-diene-1,6-diol (257):



A solution of 7-octenyl magnesium bromide [freshly prepared using 7-octenyl bromide (10.34 g, 54 mmol) and magnesium (1.73 g, 72.2 mmol) in dry THF (40 mL)] was added drop wise to a solution of aldehyde **100** (6.13 g, 36.1 mmol) in dry THF (50 mL) at 0 °C. After 2 h the reaction mixture was quenched by the addition of sat. aq. NH₄Cl solution. Ethyl acetate (50 mL) was added and the organic phase was separated. The aq. phase was washed with ethyl acetate (1 X 50 mL) and the combined organic extracts were dried over Na₂SO₄, filtered and concentrated. The crude Grignard product was taken in methanol (50 mL), potassium carbonate (9.97 g, 72.2 mmol) was added and stirred at r.t. for 4 h. Methanol was removed under reduced pressure and water (30 mL) was added to the residue and extracted with ethyl acetate (2 X 100mL). The combined organic extracts were dried over Na₂SO₄, filtered, and concentrated. The residue was purified by column chromatography (1:1 petroleum ether/ethyl acetate) to afford dienol **257** (6.31 g, 73% overall) as colorless oil.

Mol. Formula	: C ₁₅ H ₂₈ O ₂
IR (CHCl₃) $\tilde{\nu}$	: 3360, 3076, 2930, 2856, 1640, 1439 cm ⁻¹ .
¹H NMR (CDCl ₃ , 200 MHz)	: δ 1.26-1.49 (m, 10H), 1.53-1.64 (m, 4H), 1.69 (s, 3H), 2.00-2.23 (m, 4H), 3.52-3.64 (m, 1H), 4.15 (d, <i>J</i> = 6.9 Hz, 2H), 4.89-5.05 (m, 2H), 5.45 (qt, <i>J</i> = 7.0, 1.3 Hz, 1H), 5.80 (ddt, <i>J</i> = 16.8, 13.3, 6.6 Hz, 1H) ppm.
¹³C NMR (CDCl ₃ , 50 MHz)	: δ 16.0 (q), 25.4 (t), 28.6 (t), 28.9 (t), 29.3 (t), 33.5 (t), 34.9 (t), 35.5 (t), 37.2 (t), 58.7 (t), 71.1 (d), 113.9 (t), 123.6 (d), 138.6 (s), 138.8 (d) ppm.
ESI-MS (<i>m/z</i>)	: 263.22 [M+Na] ⁺ .
Elemental Analysis	Calcd.: C, 74.95; H, 11.74. Found: C, 74.72; H, 11.84.

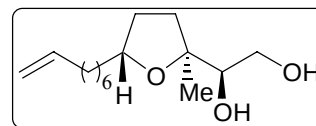
(R)-1-((2S,5S)-2-Methyl-5-(oct-7-enyl)tetrahydrofuran-2-yl)-ethane-1,2-diol (258):



To a suspension of activated MS 4Å in dry DCM (50 mL) was added diisopropyl D-tartrate (5.28 g, 22.57 mmol) and cooled to -20°C . Titanium tetraisopropoxide (5.35 g, 18.81 mmol) was added and stirred for 10 min. Added slowly drop wise *t*-butyl hydroperoxide solution (11.4 mL of 3.3 M soln in toluene, 37.62 mmol) and stirred for half an hour. A solution of allylic alcohol **257** (4.52 g, 18.81 mmol) in dry DCM (25 mL) was added slowly drop wise over a period of 10 min and was stirred at -20°C for 8 h. The reaction mixture was quenched by adding 10% aq. tartaric acid solution at -20°C and stirred at r.t. for another 4 h. Organic layer was separated and the aq. layer was washed with DCM (2 X 50 mL). The combined organic extracts were dried over Na_2SO_4 , filtered and concentrated. The residue obtained was purified by flash silica gel column chromatography (3:2 petroleum ether/ethyl acetate) to give *syn*-diol **258** (1.88 g, 39%) and *anti*-diol **259** (1.88 g, 39%) as colorless oils.

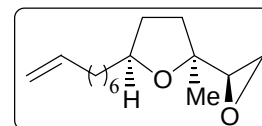
Mol. Formula	: $\text{C}_{15}\text{H}_{28}\text{O}_3$
$[\alpha]_D$	: -1.17 (c 1.4, CHCl_3).
IR (Neat) $\tilde{\nu}$	: 3435, 3077, 2973, 2930, 2857, 1216 cm^{-1} .
^1H NMR (CDCl_3 , 200 MHz)	: δ 1.19 (s, 3H), 1.23-1.45 (m, 10H), 1.49-1.59 (m, 2H), 1.99-2.09 (m, 4H), 2.60 (br s, 2H), 3.54-3.75 (m, 3H), 3.89-4.00 (m, 1H), 4.90-5.05 (m, 2H), 5.80 (ddt, $J = 16.8$, 13.3, 6.6 Hz, 1H) ppm.
^{13}C NMR (CDCl_3 , 50 MHz)	: δ 22.4 (q), 25.9 (t), 28.6 (t), 28.8 (t), 29.3 (t), 31.4 (t), 32.8 (t), 33.6 (t), 35.7 (t), 63.0 (t), 76.3 (d), 78.1 (d), 84.1 (s), 114.0 (t), 138.9 (d) ppm.
ESI-MS (m/z)	: 279.41 $[\text{M}+\text{Na}]^+$.
Elemental Analysis	Calcd.: C, 70.27; H, 11.01. Found: C, 70.11; H, 10.89.

(R)-1-((2S,5R)-2-Methyl-5-(oct-7-enyl)tetrahydrofuran-2-yl)ethane-1, 2-diol (259):



Mol. Formula	: C ₁₅ H ₂₈ O ₃
[α]_D	: -9.61 (c 1.0, CHCl ₃).
IR (Neat) $\tilde{\nu}$	: 3401, 2971, 2928, 2856, 1640, 1456 cm ⁻¹ .
¹H NMR (CDCl ₃ , 200 MHz)	: δ 1.16 (s, 3H), 1.25-1.45 (m, 10H), 1.58-1.70 (m, 2H), 1.98-2.08 (m, 4H), 2.50 (br s, 2H), 3.52-3.76 (m, 3H), 3.84-3.96 (m, 1H), 4.89-5.05 (m, 2H), 5.80 (ddt, <i>J</i> = 16.8, 13.3, 6.6 Hz, 1H) ppm.
¹³C NMR (CDCl ₃ , 50 MHz)	: δ 23.8 (q), 25.8 (t), 28.1 (t), 28.9 (t), 29.4 (t), 31.5 (t), 33.0 (t), 33.6 (t), 36.5 (t), 63.1 (t), 76.7 (d), 80.6 (d), 83.8 (s), 114.0 (t), 138.9 (d) ppm.
ESI-MS (<i>m/z</i>)	: 278.6 [M+Na] ⁺ .
Elemental Analysis	Calcd.: C, 70.27; H, 11.01. Found: C, 70.32; H, 11.00.

(2S,5S)-2-Methyl-5-(oct-7-enyl)-2-((R)-oxiran-2-yl)-tetrahydrofuran (260):

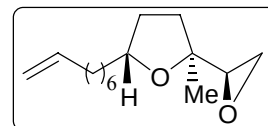


To a solution of diol **258** (350 mg, 1.37 mmol) in dry DCM (10 mL) was added tosyl chloride (260 mg, 1.37 mmol), dibutyl tin oxide (7 mg, 0.027 mmol) followed by triethylamine (0.38 mL, 2.73 mmol) and stirred at r.t. for 4 h. DCM was removed under reduced pressure and the crude reaction mixture was taken in methanol (10 mL). Potassium carbonate (377 mg, 2.73 mmol) was added to it and stirred at r.t. for 30 min. Methanol was concentrated in *vacuo* and the crude product was diluted by adding water (10 mL) and ethyl acetate (50 mL). Organic phase was separated and aq. phase was extracted with ethyl acetate (1 X 20 mL). The combined organic extracts were dried over Na₂SO₄, filtered and concentrated. Column chromatography purification (4:1 petroleum

ether/ethyl acetate) of crude residue gave epoxide **260** (266 mg, 82% overall) as colorless oil.

Mol. Formula	: C ₁₅ H ₂₆ O ₂
[α]_D	: + 7.99 (<i>c</i> 2.2, CHCl ₃).
IR (CHCl₃) $\tilde{\nu}$	: 3016, 2974, 2930, 2858, 1639, 1456, 1216 cm ⁻¹ .
¹H NMR (CDCl ₃ , 200 MHz)	: δ 1.22 (s, 3H), 1.26-1.42 (m, 9H), 1.53-1.64 (m, 3H), 1.82-1.89 (m, 1H), 1.96-2.06 (m, 3H), 2.64 (dd, <i>J</i> = 5.0, 2.8 Hz, 1H), 2.73 (dd, <i>J</i> = 5.0, 4.2 Hz, 1H), 2.98 (dd, <i>J</i> = 4.2, 2.8 Hz, 1H), 3.94-4.00 (m, 1H), 4.91-5.01 (m, 2H), 5.80 (ddt, <i>J</i> = 16.8, 13.3, 6.6 Hz, 1H) ppm.
¹³C NMR (CDCl ₃ , 100 MHz)	: δ 23.5 (q), 25.9 (t), 28.8 (t), 29.0 (t), 29.5 (t), 31.7 (t), 33.5 (t), 33.7 (t), 35.8 (t), 44.4 (t), 57.1 (d), 79.3 (d), 80.7 (s), 114.1 (t), 139.1 (d) ppm.
ESI-MS (<i>m/z</i>)	: 239.38 [M+1] ⁺ , 261.35 [M+Na] ⁺ .
Elemental Analysis	Calcd.: C, 75.58; H, 10.99. Found: C, 75.29; H, 10.87.

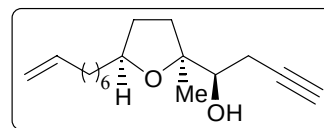
(2*S*,5*R*)-2-Methyl-5-(oct-7-enyl)-2-((*R*)-oxiran-2-yl)tetrahydrofuran (261):



To a solution of diol **259** (400 mg, 1.56 mmol) in dry DCM (10 mL) was added tosyl chloride (297 mg, 1.56 mmol), dibutyl tin oxide (8 mg, 0.031 mmol), triethylamine (0.435 mL, 3.12 mmol) and was stirred at r.t. for 4 h. DCM was removed under reduced pressure and the crude reaction mixture was taken in methanol (10 mL). Potassium carbonate (431 mg, 3.12 mmol) was added to it and stirred at r.t. for 30 min. Methanol was removed under reduced pressure and the crude product was dissolved by adding water (10 mL) and ethyl acetate (50 mL). Organic phase was separated and aq. phase was washed with ethyl acetate (1 X 20 mL). The combined organic extracts were dried over Na₂SO₄, filtered and concentrated. The residue was purified by column chromatography (4:1 petroleum ether/ethyl acetate) to give epoxide **261** (297 mg, 80% overall) as colorless oil.

Mol. Formula	: C ₁₅ H ₂₆ O ₂
[α]_D	: + 2.26 (<i>c</i> 2.6, CHCl ₃)
IR (CHCl₃) $\tilde{\nu}$	: 3016, 2974, 2930, 2857, 1640, 1462 cm ⁻¹ .
¹H NMR (CDCl ₃ , 200 MHz)	: δ 1.25 (s, 3H), 1.31-1.40 (m, 9H), 1.54-1.64 (m, 3H), 1.80-1.85 (m, 1H), 1.95-2.07 (m, 3H), 2.56 (dd, <i>J</i> = 5.0, 2.7 Hz, 1H), 2.72 (dd, <i>J</i> = 5.0, 4.0 Hz, 1H), 3.00 (dd, <i>J</i> = 4.0, 2.7 Hz, 1H), 3.88-3.94 (m, 1H), 4.92-5.02 (m, 2H), 5.80 (ddt, <i>J</i> = 16.8, 13.3, 6.6 Hz, 1H) ppm.
¹³C NMR (CDCl ₃ , 100 MHz)	: δ 24.5 (q), 25.8 (t), 28.8 (t), 28.9 (t), 29.5 (t), 31.4 (t), 32.7 (t), 33.7 (t), 36.0 (t), 43.6 (t), 57.0 (d), 80.2 (d), 80.5 (s), 114.0 (t), 139.1 (d) ppm.
ESI-MS (<i>m/z</i>)	: 239.03 [M+1] ⁺ , 260.99 [M+Na] ⁺ .
Elemental Analysis	Calcd.: C, 75.58; H, 10.99. Found: C, 75.26; H, 11.10.

(R)-1-((2S,5S)-2-Methyl-5-(oct-7-enyl)tetrahydrofuran-2-yl)but-3-yn-1-ol (262):



To a solution of epoxide **260** (180 mg, 0.76 mmol) in dry DMSO (4 mL) was added lithium acetylide-EDA complex (209 mg, 2.27 mmol) and stirred at r.t. for 2 h. The reaction mixture was quenched with ice, filtered, and washed with ethyl acetate (25 mL). The organic phase was separated and washed with water (2 X 5 mL) and brine (5 mL), dried over Na₂SO₄, filtered and concentrated in *vacuo*. Purification of crude by chromatography (7:3 petroleum ether/ethyl acetate) gave alkynol **262** (162 mg, 81%) as colorless oil.

Mol. Formula	: C ₁₇ H ₂₈ O ₂
[α]_D	: +1.98 (<i>c</i> 1.2, CHCl ₃).
IR (CHCl₃) $\tilde{\nu}$	: 3583, 3309, 2930, 2119, 1640, 1457 cm ⁻¹ .
¹H NMR (CDCl ₃ , 200 MHz)	: δ 1.17 (s, 3H), 1.25-1.61 (m, 13H), 1.98-2.11 (m, 4H), 2.01 (t, <i>J</i> = 2.7 Hz, 1H), 2.30 (ddd, <i>J</i> = 16.8, 8.6, 2.7 Hz,

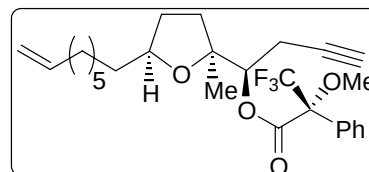
1H), 2.48 (ddd, $J = 16.8, 4.0, 2.7$ Hz, 1H), 3.65 (dd, $J = 8.6, 4.0$ Hz, 1H), 3.89-4.01 (m, 1H), 4.88-5.03 (m, 2H), 5.80 (ddt, $J = 16.8, 13.3, 6.6$ Hz, 1H) ppm.

^{13}C NMR : δ 22.1 (t), 22.3 (q), 26.0 (t), 28.8 (t), 29.0 (t), 29.5 (t), (CDCl₃, 125 MHz) 31.6 (t), 32.3 (t), 33.7 (t), 35.9 (t), 70.0 (d), 74.8 (d), 78.4 (d), 81.8 (s), 84.6 (s), 114.3 (t), 138.9 (d) ppm.

ESI-MS (m/z) : 265.36 [M+1]⁺, 287.34 [M+Na]⁺.

Elemental Analysis Calcd.: C, 77.22; H, 10.67.
Found: C, 77.51; H, 10.47.

(R)-((R)-1-((2S,5S)-2-Methyl-5-(oct-7-enyl) tetrahydrofuran-2-yl)but-3-ynyl) 3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (263):

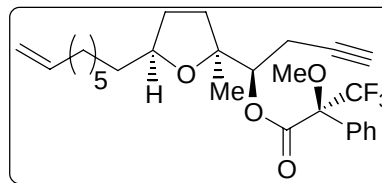


To a solution of alcohol **262** (10 mg, 0.038 mmol) in dry DCM (2 mL) was added *R*-(+)-MTPA (9 mg, 0.038 mmol) and the reaction mixture was cooled to 0 °C. DCC (12 mg, 0.056 mmol) was added in one portion followed by catalytic amount of DMAP. The mixture was brought to r.t. and stirred for 10 h and then quenched with ice. The organic phase was separated, washed with water (3 X 5 mL), brine (1 X 5 mL), dried over Na₂SO₄, filtered and concentrated. The residue obtained was purified by column chromatography (7:3 petroleum ether/ethyl acetate) to furnish ester **263** (12 mg, 67%) as colorless oil.

Mol. Formula : C₂₇H₃₅F₃O₄

^1H NMR : δ 1.19 (s, 3H), 1.23-1.38 (m, 8H), 1.62-1.71 (m, 4H), 1.84 (t, $J = 2.7$ Hz, 1H), 1.93-2.08 (m, 4H), 2.48 (ddd, $J = 17.4, 9.1, 2.7$ Hz, 1H), 2.78 (dt, $J = 17.4, 2.7$ Hz, 1H), 3.53 (q, $J = 1.1$ Hz, 3H), 3.87-3.99 (m, 1H), 4.88-5.04 (m, 2H), 5.16 (dd, $J = 9.1, 3.0$ Hz, 1H), 5.79 (ddt, $J = 16.8, 13.4, 6.7$ Hz, 1H), 7.37-7.43 (m, 3H), 7.54-7.62 (m, 2H) ppm.

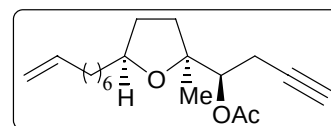
(S)-((R)-1-((2S,5S)-2-Methyl-5-(oct-7-enyl)tetrahydrofuran-2-yl)but-3-ynyl) 3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (264):



To a solution of alcohol **262** (10 mg, 0.038 mmol) in dry DCM (2 mL) was added *S*-(–)-MTPA (9 mg, 0.038 mmol) and the reaction mixture was cooled to 0 °C. DCC (12 mg, 0.056 mmol) was added in one portion followed by catalytic amount of DMAP. The mixture was brought to r.t. and stirred for 10 h and then quenched with ice. The organic phase was separated, washed with water (3 X 5 mL), brine (1 X 5 mL), dried over Na₂SO₄, filtered and concentrated. Column chromatography purification (7:3 petroleum ether/ethyl acetate) afforded ester **264** (13 mg, 72%) as colorless oil.

Mol. Formula : C₂₇H₃₅F₃O₄
¹H NMR : δ 1.06 (s, 3H), 1.26-1.34 (m, 8H), 1.50-1.55 (m, 2H),
 (CDCl₃, 200 MHz) 1.67-1.75 (m, 2H), 1.82-1.92 (m, 2H), 1.99 (t, *J* = 2.7 Hz, 1H), 2.03-2.09 (m, 2H), 2.52 (ddd, *J* = 17.4, 9.3, 2.7 Hz, 1H), 2.84 (dt, *J* = 17.4, 2.7 Hz, 1H), 3.62 (q, *J* = 1.3 Hz, 3H), 3.87-3.97 (m, 1H), 4.90-5.05 (m, 2H), 5.20 (dd, *J* = 9.3, 2.7 Hz, 1H), 5.81 (ddt, *J* = 16.9, 13.4, 6.7 Hz, 1H), 7.37-7.44 (m, 3H), 7.53-7.60 (m, 2H) ppm.

(R)-1-((2S,5S)-2-Methyl-5-(oct-7-enyl)tetrahydrofuran-2-yl)but-3-ynyl acetate (265):

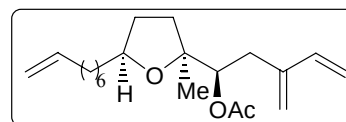


To a solution of alcohol **262** (150 mg, 0.57 mmol) in dry DCM (5 mL) was added acetic anhydride (70 mg, 0.68 mmol) followed by triethylamine (0.16 mL, 1.14 mmol) and catalytic DMAP. The reaction mixture was stirred for an hour and then quenched with ice. The organic phase was separated and washed with water, brine, dried over Na₂SO₄, filtered and concentrated. The residue obtained was purified by column

chromatography (4:1 petroleum ether/ethyl acetate) to furnish acetate **265** (148 mg, 85%) as colorless oil.

Mol. Formula	: C ₁₉ H ₃₀ O ₃
[α]_D	: −9.85 (<i>c</i> 1.0, CHCl ₃).
IR (CHCl₃) $\tilde{\nu}$	: 3077, 2974, 2929, 2857, 2123, 1746, 1237 cm ^{−1} .
¹H NMR (CDCl ₃ , 200 MHz)	: δ 1.18 (s, 3H), 1.26-1.41 (m, 8H), 1.49-1.68 (m, 4H), 1.90 (t, <i>J</i> = 2.7 Hz, 1H), 1.96-2.05 (m, 4H), 2.11 (s, 3H), 2.44 (ddd, <i>J</i> = 17.1, 9.1, 2.7 Hz, 1H), 2.60 (ddd, <i>J</i> = 17.1, 3.5, 2.7 Hz, 1H), 3.87-3.98 (m, 1H), 4.89-5.03 (m, 3H), 5.80 (ddt, <i>J</i> = 16.8, 13.3, 6.6 Hz, 1H) ppm.
¹³C NMR (CDCl ₃ , 100 MHz)	: δ 19.7 (t), 20.9 (q), 22.0 (q), 26.0 (t), 28.8 (t), 29.0 (t), 29.5 (t), 31.3 (t), 33.7 (t), 35.1 (t), 36.0 (t), 69.6 (d), 75.2 (d), 79.3 (d), 80.7 (s), 82.8 (s), 114.2 (t), 138.9 (d), 170.0 (s) ppm.
ESI-MS (<i>m/z</i>)	: 307.03 [M+1] ⁺ , 329.01 [M+Na] ⁺ .
Elemental Analysis	Calcd.: C, 74.47; H, 9.87. Found: C, 74.32; H, 10.01.

(*R*)-1-((2*S*, 5*S*)-2-Methyl-5-(oct-7-enyl)tetrahydrofuran-2-yl)-3-methylenepent-4-enyl acetate (266**):**

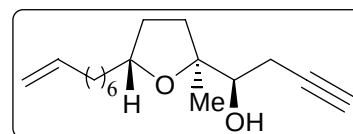


To a solution of acetate **265** (100 mg, 0.32 mmol) in dry DCM (20 mL), Grubbs' 2nd generation catalyst (26 mg, 0.032 mmol) was added, degassed with ethylene. The contents were heated to reflux for 24 h under ethylene atmosphere. The reaction mixture was cooled to r.t. and concentrated under reduced pressure. Column chromatography purification (4:1 petroleum ether/ethyl acetate) of crude gave triene acetate **266** (23 mg, 21%) as colorless oil.

Mol. Formula	: C ₂₁ H ₃₄ O ₃
[α]_D	: − 2.9 (<i>c</i> 1.0, CHCl ₃).
IR (CHCl₃) $\tilde{\nu}$	: 3394, 3019, 2930, 2400, 1731, 1216 cm ^{−1} .

¹H NMR (CDCl ₃ , 200 MHz)	: δ 1.22 (s, 3H), 1.25-1.40 (m, 10H), 1.52-1.68 (m, 3H), 1.87-1.95 (m, 1H), 1.99 (s, 3H), 2.01-2.11 (m, 2H), 2.26 (dd, <i>J</i> = 14.2, 10.7 Hz, 1H), 2.72 (td, <i>J</i> = 14.2, 1.2 Hz, 1H), 3.90-4.03 (m, 1H), 4.89-4.97 (m, 2H), 5.01 (br s, 3H), 5.10 (d, <i>J</i> = 10.8 Hz, 1H), 5.29 (d, <i>J</i> = 17.6 Hz, 1H), 5.78 (ddt, <i>J</i> = 16.8, 13.3, 6.6 Hz, 1H), 6.34 (dd, <i>J</i> = 17.6, 10.8 Hz, 1H) ppm.
¹³C NMR (CDCl ₃ , 100 MHz)	: δ 21.0 (q), 21.9 (q), 26.2 (t), 28.9 (t), 29.1 (t), 29.6 (t), 31.5 (t), 31.9 (t), 33.8 (t), 35.3 (t), 36.3 (t), 75.9 (d), 79.5 (d), 83.3 (s), 113.9 (t), 114.3 (t), 117.9 (t), 138.4 (d), 139.0 (d), 143.1 (s), 170.1 (s) ppm.
ESI-MS (<i>m/z</i>)	: 335.41 [M+1] ⁺ , 357.41 [M+Na] ⁺ .
Elemental Analysis	Calcd.: C, 75.41; H, 10.25. Found: C, 75.23; H, 10.10.

(*R*)-1-((2*S*,5*R*)-2-Methyl-5-(oct-7-enyl)tetrahydrofuran-2-yl)but-3-yn-1-ol (268**):**



To a solution of epoxide **261** (200 mg, 0.84 mmol) in dry DMSO (4 mL) was added lithium acetylide-EDA complex (232 mg, 2.52 mmol) and stirred at r.t. for 2 h. The reaction mixture was quenched with ice, filtered and washed with ethyl acetate (25 mL). The organic phase was separated and washed with water (2 X 5 mL), brine (5 mL), dried over Na₂SO₄, filtered and concentrated in *vacuo*. The crude product was purified by column purification (7:3 petroleum ether/ethyl acetate) to afford alkynol **268** (186 mg, 84%) as colorless oil.

Mol. Formula	: C ₁₇ H ₂₈ O ₂
[α]_D	: − 4.77 (<i>c</i> 1.0, CHCl ₃).
IR (CHCl ₃) $\tilde{\nu}$	: 3461, 3310, 3076, 2928, 2856, 2119, 1640, 1457 cm ^{−1} .
¹H NMR (CDCl ₃ , 200 MHz)	: δ 1.16 (s, 3H), 1.26-1.41 (m, 9H), 1.57-1.67 (m, 3H), 1.94-2.10 (m, 5H), 2.04 (t, <i>J</i> = 2.6 Hz, 1H), 2.31 (ddd, <i>J</i> =

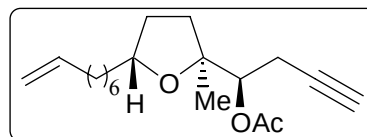
16.8, 8.6, 2.7 Hz, 1H), 2.50 (ddd, $J = 16.8, 3.8, 2.7$ Hz, 1H), 3.70 (dd, $J = 8.6, 3.8$ Hz, 1H), 3.83-3.93 (m, 1H), 4.89-5.04 (m, 2H), 5.80 (ddt, $J = 16.8, 13.3, 6.6$ Hz, 1H) ppm.

^{13}C NMR : δ 22.2 (t), 23.5 (q), 25.9 (t), 28.7 (t), 28.9 (t), 29.5 (t), (CDCl₃, 100 MHz) 31.7 (t), 32.7 (t), 33.7 (t), 36.6 (t), 69.9 (d), 75.1 (d), 80.8 (d), 81.8 (s), 84.3 (s), 114.1 (t), 139.0 (d) ppm.

ESI-MS (m/z) : 265.38 [M+1]⁺, 287.37 [M+Na]⁺.

Elemental Analysis Calcd.: C, 77.22; H, 10.67.
Found: C, 76.93; H, 10.92.

(R)-1-((2S,5R)-2-Methyl-5-(oct-7-enyl)tetrahydrofuran-2-yl)but-3-ynyl acetate (269):



To a solution of alcohol **268** (150 mg, 0.57 mmol) in dry DCM (5 mL) was added acetic anhydride (70 mg, 0.68 mmol) followed by triethylamine (115 mg, 1.14 mmol) and catalytic DMAP. The reaction mixture was stirred for an hour and quenched with ice. The organic phase was separated and washed with water, brine, dried over Na₂SO₄, filtered and concentrated. The residue was purified by column chromatography (4:1 petroleum ether/ethyl acetate) to furnish ene-yne acetate **269** (153 mg, 88%) as colorless oil.

Mol. Formula : C₁₉H₃₀O₃
[α]_D : -13.93 (c 2.3, CHCl₃).
IR (CHCl₃) $\tilde{\nu}$: 3077, 2974, 2929, 2123, 1745, 1640, 1461, 1237 cm⁻¹.
 ^1H NMR : δ 1.17 (s, 3H), 1.26-1.38 (m, 10H), 1.53-1.66 (m, 3H), (CDCl₃, 200 MHz) 1.90 (t, $J = 2.6$ Hz, 1H), 1.94-2.07 (m, 3H), 2.10 (s, 3H), 2.40 (ddd, $J = 17.1, 9.1, 2.7$ Hz, 1H), 2.65 (ddd, $J = 17.1, 3.5, 2.7$ Hz, 1H), 3.82-3.95 (m, 1H), 4.88-5.09 (m, 3H), 5.80 (ddt, $J = 16.8, 13.3, 6.6$ Hz, 1H) ppm.
 ^{13}C NMR : δ 20.0 (t), 20.9 (q), 22.9 (q), 25.9 (t), 28.8 (t), 29.0 (t), (CDCl₃, 50 MHz) 29.5 (t), 31.4 (t), 33.7 (t), 35.3 (t), 36.2 (t), 69.6 (d), 75.3

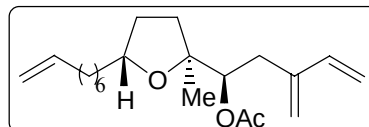
(d), 80.4 (d), 80.7 (s), 82.7 (s), 114.2 (t), 138.9 (d), 170.2 (s) ppm.

ESI-MS (*m/z*) : 307.03 [M+1]⁺, 329.01 [M+Na]⁺.

Elemental Analysis Calcd.: C, 74.47; H, 9.87.

Found: C, 74.17; H, 9.69.

(R)-1-((2S,5R)-2-Methyl-5-(oct-7-enyl)tetrahydrofuran-2-yl)-3-methylenepent-4-enyl acetate (270):



A solution of acetate **269** (100 mg, 0.32 mmol) in dry DCM (20 mL), Grubbs' 2nd generation catalyst (26 mg, 0.032 mmol) was added and degassed with ethylene. The contents were heated to reflux for 24 h under ethylene atmosphere. The reaction mixture was cooled to r.t. and concentrated under reduced pressure. The residue obtained was purified by column chromatography (4:1 petroleum ether/ethyl acetate) to afford triene acetate **270** (27 mg, 25%) as colorless oil.

Mol. Formula : C₂₁H₃₄O₃

[α]_D : − 8.2 (*c* 1.0, CHCl₃).

IR (CHCl₃) $\tilde{\nu}$: 3077, 2974, 2929, 2857, 2123, 1745, 1640, 1461 cm^{−1}.

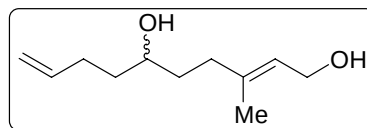
¹H NMR (CDCl₃, 400 MHz) : δ 1.23 (s, 3H), 1.27-1.38 (m, 10H), 1.54-1.67 (m, 3H), 1.86-1.94 (m, 1H), 2.01 (s, 3H), 2.02-2.07 (m, 2H), 2.28 (dd, *J* = 14.2, 10.7 Hz, 1H), 2.73 (td, *J* = 14.2, 1.2 Hz, 1H), 3.88-3.95 (m, 1H), 4.90-4.98 (m, 2H), 5.03 (br s, 3H), 5.11 (d, *J* = 10.8 Hz, 1H), 5.30 (d, *J* = 17.6 Hz, 1H), 5.82 (ddt, *J* = 16.8, 13.3, 6.6 Hz, 1H), 6.37 (dd, *J* = 17.6, 10.8 Hz, 1H) ppm.

¹³C NMR (CDCl₃, 100 MHz) : δ 21.1 (q), 22.7 (q), 26.0 (t), 28.9 (t), 29.1 (t), 29.6 (t), 31.5 (t), 31.9 (t), 33.8 (t), 35.4 (t), 36.2 (t), 75.9 (d), 80.4 (d), 83.2 (s), 113.8 (t), 114.1 (t), 117.9 (t), 138.4 (d), 139.1 (d), 143.1 (s), 170.5 (s) ppm.

ESI-MS (*m/z*) : 357.15 [M+Na]⁺.

Elemental Analysis Calcd.: C, 75.41; H, 10.25.
Found: C, 75.53; H, 10.47.

(E)-3-Methyldeca-2, 9-diene-1,6-diol (271):



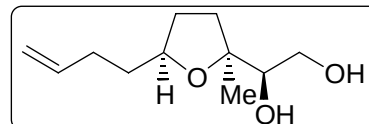
A solution of 3-butenylmagnesium bromide [freshly generated using 3-butenyl bromide (9.48 g, 70.2 mmol) and magnesium (2.52 g, 105.3mmol) in dry THF (30 mL)] was added slowly to a solution of aldehyde **100** (5.98 g, 35.1 mmol) in dry THF (50 mL) at 0 °C. After 2 h, the reaction mixture was quenched with sat. aq. NH₄Cl solution and diluted with ethyl acetate (50 mL). The organic phase was separated and the aq. phase was washed with ethyl acetate (1 X 50 mL). The combined organic extracts were dried over Na₂SO₄, filtered and concentrated. The crude product was dissolved in methanol (40 mL), and potassium carbonate (9.7 g, 70.2 mmol) was added followed by stirring at r.t. for 4 h. Methanol was removed under pressure and water (30 mL) was added. The mixture was extracted with ethyl acetate (2 X 100 mL) and the combined organic extracts were dried over Na₂SO₄, filtered and concentrated. The residue obtained was purified by silica gel column chromatography (1:1 petroleum ether/ethyl acetate) to afford dienol **271** (4.92 g, 76%) as colorless oil.

Mol. Formula	: C ₁₁ H ₂₀ O ₂
IR (CHCl₃) $\tilde{\nu}$	: 3379, 3078, 3012, 2936, 1640, 1447, 1216, 996 cm ⁻¹ .
¹H NMR (CDCl ₃ , 200 MHz)	: δ 1.45-1.58 (m, 4H), 1.64 (s, 3H), 2.00-2.20 (m, 4H), 2.59 (br s, 2H), 3.51-3.63 (m, 1H), 4.09 (d, J = 6.8 Hz, 2H), 4.90-5.07 (m, 2H), 5.38 (qt, J = 2.5, 1.2 Hz, 1H), 5.80 (ddt, J = 16.8, 13.3, 6.6 Hz, 1H) ppm.
¹³C NMR (CDCl ₃ , 50 MHz)	: δ 15.9 (q), 29.7 (t), 34.8 (t), 35.4 (t), 36.2 (t), 58.6 (t), 70.4 (d), 114.3 (t), 123.5 (d), 138.3 (d) 2C ppm.
ESI-MS (m/z)	: 185.41 [M+1] ⁺ .

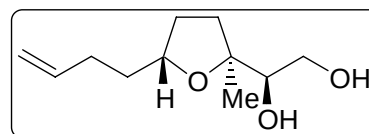
Elemental Analysis Calcd.: C, 71.70; H, 10.94.

Found: C, 71.59; H, 10.90.

(R)-1-((2S,5S)-5-(But-3-enyl)-2-methyltetrahydrofuran-2-yl)ethane-1, 2-diol (272)



(R)-1-((2S,5R)-5-(But-3-enyl)-2-methyltetrahydrofuran-2-yl)ethane-1, 2-diol (273):



To a suspension of activated MS 4Å in dry DCM (50 mL) was added diisopropyl-D-tartrate (5.54 g, 23.6 mmol) and the mixture was cooled to -20°C . To this, titanium tetrakisopropoxide (5.59 g, 19.69 mmol) was added and stirred for 10 min after which *t*-butyl hydroperoxide solution (8.95 mL of 3.3 M soln in toluene, 29.5 mmol) was introduced slowly. After stirring for another half an hour, a solution of allylic alcohol **271** (3.63 g, 19.69 mmol) in dry DCM (20 mL) was added slowly drop wise over a period of 10 min and stirred at -20°C for 6 h. The reaction mixture was quenched by adding 10% aq. tartaric acid solution at -20°C and stirred at r.t. for another 4 h. Organic layer was separated and the aq. layer was washed with DCM (2 X 50 mL). The combined organic extracts were dried over Na_2SO_4 , filtered and concentrated. The residue was purified by column chromatography (1:1 petroleum ether/ethyl acetate) to procure diols **272/273** (3.19 g, 81%) as colorless oil.

Mol. Formula : $\text{C}_{11}\text{H}_{20}\text{O}_3$

IR (CHCl_3) $\tilde{\nu}$: 3412, 3017, 2975, 2935, 1216 cm^{-1} .

^1H NMR : δ 1.17, 1.18 (2s, 3H), 1.46-1.78 (m, 4H), 1.96-2.17 (m, 4H), 2.77 (br s, 2H), 3.48-3.76 (m, 3H), 3.89-4.01 (m, 1H), 4.93-5.08 (m, 2H), 5.82 (ddt, J = 16.8, 13.3, 6.6 Hz, 1H) ppm.

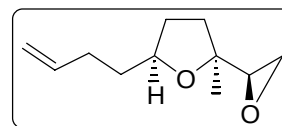
^{13}C NMR : δ 22.3 (q), 23.6 (q), 30.0 (t), 30.1 (t), 31.3 (t), 31.4 (t), 32.9 (t), 33.1 (t), 34.7 (t), 35.5 (t), 63.0 (t), 63.1 (t), 76.4 (d), 76.7 (d), 77.5 (d), 79.8 (d), 83.9 (s), 84.1 (s), 114.4 (t), 114.5 (t), 138.0 (d), 138.1 (d) ppm.

ESI-MS (*m/z*) : 200.96 [M+1]⁺, 222.92 [M+Na]⁺.

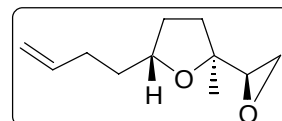
Elemental Analysis Calcd.: C, 65.97; H, 10.07.

Found: C, 65.83; H, 10.15.

(2*S*,5*S*)-5-(But-3-enyl)-2-methyl-2-((*R*)-oxiran-2-yl)tetrahydrofuran (274):



(2*S*,5*R*)-5-(But-3-enyl)-2-methyl-2-((*R*)-oxiran-2-yl)tetrahydrofuran (275):



To a solution of mixture of diols **272/273** (1.9 g, 9.48 mmol) in dry DCM (20 mL) was added tosyl chloride (1.8 g, 9.48 mmol), dibutyl tin oxide (47 mg, 0.19 mmol) followed by triethylamine (2.64 mL, 18.96 mmol) and stirred at r.t. for 4 h. DCM was removed under reduced pressure and the crude reaction mixture was taken in methanol (20 mL). Potassium carbonate (2.62 g, 18.96 mmol) was added and stirred at r.t. for 30 min. Methanol was concentrated in *vacuo* and the crude product was dissolved by adding water (20 mL) and ethyl acetate (50 mL). Organic phase was separated and aq. phase was washed with ethyl acetate (1 X 40 mL). The combined organic extracts were dried over Na₂SO₄, filtered and concentrated. Column chromatography purification (4:1 petroleum ether/ethyl acetate) of the crude furnished mixture of inseparable epoxides **274/275** (1.45 g, 84%) as colorless oil.

Mol. Formula : C₁₁H₁₈O₂

IR (CHCl₃) $\tilde{\nu}$: 3017, 2977, 2932, 1640, 1449, 1216 cm⁻¹.

¹H NMR : δ 1.23, 1.26 (2s, 3H), 1.48-1.69 (m, 5H), 1.95-2.18 (m, 3H), 2.56 (ddd, *J* = 14.7, 5, 2.8 Hz, 1H), 2.69 (m, 1H), 2.96 (dd, *J* = 3.9, 2.8 Hz, 1H), 3.86-4.04 (m, 1H), 4.91-5.08 (m, 2H), 5.73-5.93 (m, 1H) ppm.

¹³C NMR : δ 23.2 (q), 24.3 (q), 29.9 (t), 30.0 (t), 31.2 (t), 31.4 (t), 32.3 (t), 33.0 (t), 34.7 (t), 34.9 (t), 43.0 (t), 43.9 (t), 56.5 (d), 56.6 (d), 78.2 (d), 79.1 (d), 80.3 (s), 80.6 (s), 114.2 (t), 138.0 (d) ppm.

ESI-MS (m/z) : 183.24 $[M+1]^+$, 205.23 $[M+Na]^+$.

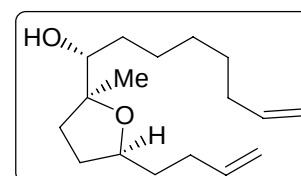
Elemental Analysis Calcd.: C, 72.49; H, 9.95.

Found: C, 72.29; H, 9.71.

Opening of epoxides 274/275 with 5-hexenylmagnesium bromide:

To a solution of dried cuprous iodide (313 mg, 1.65 mmol) in dry THF (5 mL) was added slowly drop wise a freshly generated solution of 5-hexenylmagnesium bromide [prepared from magnesium (479 mg, 19.75 mmol), and 5-hexenyl bromide (2.68 g, 16.46 mmol) in 10 mL of dry THF] at $-40\text{ }^{\circ}\text{C}$ and stirred for half an hour. A solution of epoxides **274/275** (600 mg, 3.29 mmol) in dry THF (4 mL) was added slowly and stirred at same temperature for 3 h. The temperature was then raised to $0\text{ }^{\circ}\text{C}$, quenched with sat. NH_4Cl solution and brought to r.t.. Ethyl acetate (20 mL) was added and the organic phase was separated. The aq. phase extracted with ethyl acetate (1 X 20 mL). The combined organic extracts were dried over Na_2SO_4 , filtered and concentrated. The residue thus obtained was purified by flash column chromatography (7:3 petroleum ether/ethyl acetate) to afford *syn*-dienol **276** (332 mg, 38%), and *anti*-dienol **277** (333 mg, 38%) as colorless oils.

(*R*)-1-((2*S*,5*S*)-5-(But-3-enyl)-2-methyltetrahydrofuran-2-yl) oct-7-en-1-ol (**276**):



Mol. Formula : $\text{C}_{17}\text{H}_{30}\text{O}_2$

$[\alpha]_D$: -3.4 (c 1.2, CHCl_3).

IR (CHCl_3) $\tilde{\nu}$: 3568, 3014, 2929, 2858, 1640, 1455 cm^{-1} .

^1H NMR : δ 1.12 (s, 3H), 1.26-1.41 (m, 6H), 1.51-1.73 (m, 6H),
(CDCl_3 , 200 MHz) 1.97-2.13 (m, 6H), 2.27 (br s, 1H), 3.50 (dd, $J = 9.5$, 2.0 Hz, 1H), 3.85-3.98 (m, 1H), 4.90-5.07 (m, 4H), 5.71-5.93 (m, 2H) ppm.

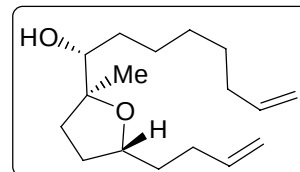
^{13}C NMR : δ 24.6 (q), 26.6 (t), 28.8 (t), 29.1 (t), 30.2 (t), 31.0 (t),

(CDCl₃, 125 MHz) 31.5 (t), 31.9 (t), 33.7 (t), 35.9 (t), 76.6 (d), 80.3 (d), 85.6 (s), 114.1 (t), 114.4 (t), 138.3 (d), 139.0 (d) ppm.

ESI-MS (*m/z*) : 267.13 [M+1]⁺, 289.10 [M+Na]⁺.

Elemental Analysis Calcd.: C, 76.64; H, 11.35.
Found: Found C, 76.41; H, 11.72.

(R)-1-((2S,5R)-5-(But-3-enyl)-2-methyltetrahydrofuran-2-yl) oct-7-en-1-ol (277):



Mol. Formula : C₁₇H₃₀O₂

[α]_D : +10.7 (*c* 2.5, CHCl₃).

IR (CHCl₃) $\tilde{\nu}$: 3583, 3016, 2930, 1640, 1216 cm⁻¹.

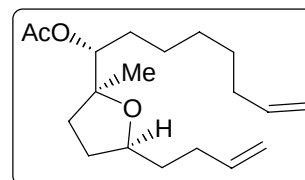
¹H NMR : δ 1.12 (s, 3H), 1.26-1.69 (m, 12H), 1.94-2.17 (m, 6H), 2.37 (br s, 1H), 3.47 (dd, *J* = 9.7, 2.0 Hz, 1H), 3.91-4.04 (m, 1H), 4.88-5.07 (m, 4H), 5.69-5.91 (m, 2H) ppm.

¹³C NMR : δ 23.2 (q), 26.6 (t), 28.8 (t), 29.2 (t), 30.2 (t), 30.3 (t), 31.5 (t), 31.7 (t), 33.7 (t), 35.0 (t), 75.9 (d), 77.2 (d), 85.9 (s), 114.2 (t), 114.7 (t), 138.2 (d), 138.9 (d) ppm.

ESI-MS (*m/z*) : 267.13 [M+1]⁺, 289.11 [M+Na]⁺.

Elemental Analysis Calcd.: C, 76.64; H, 11.35.
Found: C, 76.34; H, 11.59.

(R)-1-((2S,5S)-5-(But-3-enyl)-2-methyltetrahydrofuran-2-yl) oct-7-enyl acetate (278):

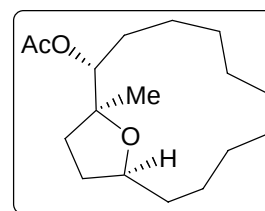


To a solution of alcohol **276** (250 mg, 0.939 mmol) in dry DCM (5 mL) was added acetic anhydride (106 mg, 1.03 mmol) followed by triethylamine (190 mg, 1.87 mmol) and catalytic DMAP. The reaction mixture was stirred for an hour and quenched

with ice. The organic layer was separated and washed with water (5 mL), and brine (5 mL), dried over Na₂SO₄, filtered and concentrated. The crude product was subjected for chromatographic purification (4:1 petroleum ether/ethyl acetate) to procure diene-acetate **278** (257 mg, 89%) as colorless oil.

Mol. Formula	: C ₁₉ H ₃₂ O ₃
[α]_D	: + 7.67 (<i>c</i> 1.5, CHCl ₃).
IR (CHCl₃) $\tilde{\nu}$	: 3019, 2931, 2859, 1729, 1247, 1216 cm ⁻¹ .
¹H NMR (CDCl ₃ , 200 MHz)	: δ 1.15 (s, 3H), 1.26-1.37 (m, 6H), 1.49-1.70 (m, 6H), 1.85-2.10 (m, 6H), 2.06 (s, 3H), 3.80-3.93 (m, 1H), 4.85- 5.05 (m, 5H), 5.68-5.90 (m, 2H) ppm.
¹³C NMR (CDCl ₃ , 50 MHz)	: δ 20.9 (q), 23.2 (q), 25.8 (t), 28.6 (t), 28.8 (t), 29.6 (t), 30.1 (t), 31.3 (t), 33.5 (t), 34.7 (t), 35.3 (t), 77.6 (d), 79.4 (d), 83.2 (s), 114.2 (t), 114.3 (t), 138.2 (d), 138.6 (d), 170.3 (s) ppm.
ESI-MS (<i>m/z</i>)	: 309.39 [M+1] ⁺ , 331.36 [M+Na] ⁺ .
Elemental Analysis	Calcd.: C, 73.98; H, 10.46. Found: C, 73.68; H, 10.45.

(1*S*,2*R*,12*S*)-1-methyl-15-oxabicyclo[10.2.1]pentadecan-2-yl acetate (281):

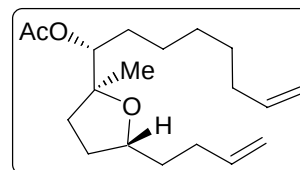


To a solution of diene-acetate **278** (100 mg, 0.32 mmol) in dry DCM (125 mL), Grubbs' 1st generation catalyst (26.0 mg, 0.032 mmol) was added, degassed with argon and stirred at r.t. for 36 h. DCM was removed under reduced pressure. The crude product was purified by column chromatography (4:1 petroleum ether/ethyl acetate) to afford cyclized product **280** (62 mg, 67%) as 1:1 mixture of *E/Z* isomers. To a solution of **280** (62 mg, 0.24 mmol) in ethyl acetate (5 mL) was added 10% palladium in charcoal (10 mg) and the suspension was stirred at r.t. under balloon hydrogen pressure for 4 h. The reaction mixture was filtered through a pad of *celite* and washed with ethyl acetate

(5mL). The combined washings were concentrated and purified by column chromatography (4:1 petroleum ether/ethyl acetate) to furnish reduced product **281** (50 mg, 85%) as colorless oil.

Mol. Formula	: C ₁₇ H ₃₀ O ₃
[α]_D	: −14.8 (c 1.2, CHCl ₃).
IR (CHCl₃) $\tilde{\nu}$	: 2927, 1730, 1248 cm ^{−1} .
¹H NMR (CDCl ₃ , 400 MHz)	: δ 1.18 (s, 3H), 1.24-1.33 (m, 10H), 1.42-1.51 (m, 4H), 1.54-1.62 (m, 2H), 1.65-1.73 (m, 4H), 1.80-1.86 (m, 1H), 1.90-1.98 (m, 1H), 2.04 (s, 3H), 3.90-3.97 (m, 1H), 4.90 (t, <i>J</i> = 6 Hz, 1H) ppm.
¹³C NMR (CDCl ₃ , 100 MHz)	: δ 21.3 (q), 21.9 (q), 23.8 (t), 24.7 (t), 25.7 (t), 25.9 (t), 26.3 (t), 26.6 (t), 27.5 (t), 29.5 (t), 33.1 (t), 34.8 (t), 37.3 (t), 76.4 (d), 78.9 (d), 82.8 (s), 170.8 (s) ppm.
ESI-MS (<i>m/z</i>)	: 283.15 [M+1] ⁺ , 305.13 [M+Na] ⁺ .
Elemental Analysis	Calcd.: C, 72.30; H, 10.71. Found: C, 72.01; H, 10.50.

(*R*)-1-((2*S*,5*R*)-5-(But-3-enyl)-2-methyltetrahydrofuran-2-yl) oct-7-enyl acetate (279**):**

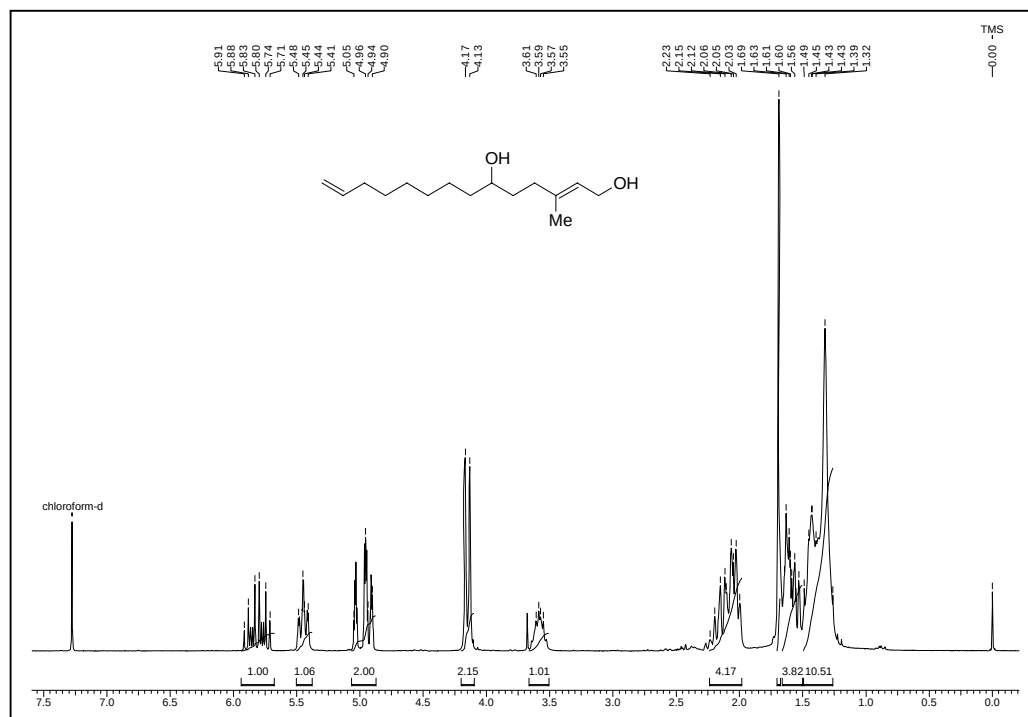


To a solution of alcohol **277** (250 mg, 0.939 mmol) in dry DCM (5 mL) was added acetic anhydride (106 mg, 1.03 mmol) followed by triethylamine (0.26 mL, 1.87 mmol) and catalytic DMAP. The reaction mixture was stirred for an hour and quenched with ice. The organic layer was separated and washed with water and brine, dried over Na₂SO₄, filtered and concentrated. The crude product was purified by column chromatography (4:1 petroleum ether/ethyl acetate) to afford diene-acetate **279** (246 mg, 85%) as colorless oil.

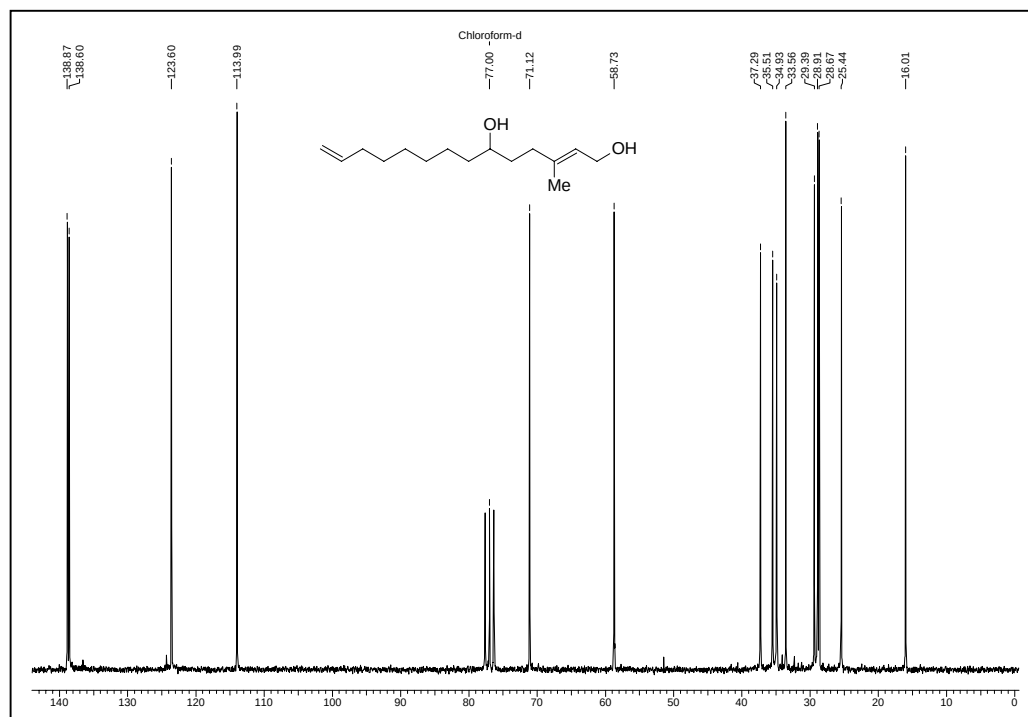
Mol. Formula	: C ₁₉ H ₃₂ O ₃
[α]_D	: +11.8 (<i>c</i> 1.0, CHCl ₃).
IR (CHCl₃) $\tilde{\nu}$	: 3019, 2930, 2859, 1729, 1245 1216 cm ⁻¹ .
¹H NMR (CDCl ₃ , 200 MHz)	: δ 1.16 (s, 3H), 1.26-1.38 (m, 6H), 1.43-1.70 (m, 8H), 1.85-2.04 (m, 4H), 2.06 (s, 3H), 3.89-4.02 (m, 1H), 4.82- 5.05 (m, 5H), 5.68-5.90 (m, 2H) ppm.
¹³C NMR (CDCl ₃ , 50 MHz)	: δ 21.0 (q), 22.3 (q), 25.9 (t), 28.6 (t), 28.8 (t), 29.5 (t), 30.2 (t), 31.2 (t), 33.6 (t), 34.4 (t), 35.3 (t), 77.4 (d), 78.2 (d), 83.5 (s), 114.2 (t), 114.4 (t), 138.2 (d), 138.7 (d), 170.3 (s) ppm.
ESI-MS (<i>m/z</i>)	: 309.51 [M+1] ⁺ , 331.52 [M+Na] ⁺ .
Elemental Analysis	Calcd.: C, 73.98; H, 10.46. Found: C, 73.80; H, 10.39.



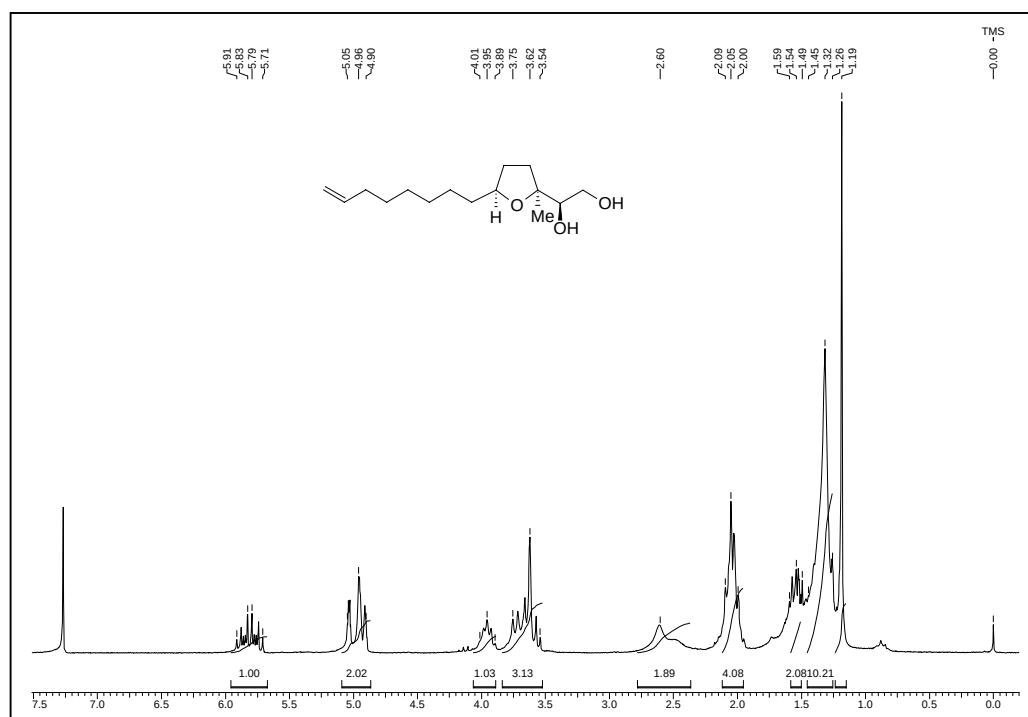
Spectra



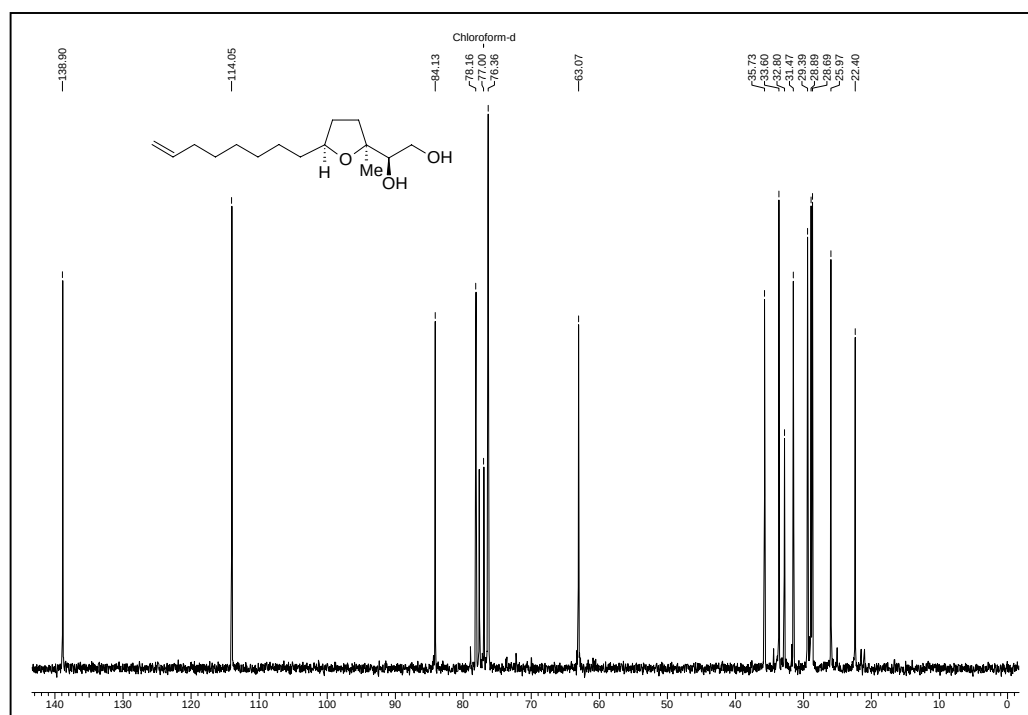
¹H NMR Spectrum of 257 in CDCl₃



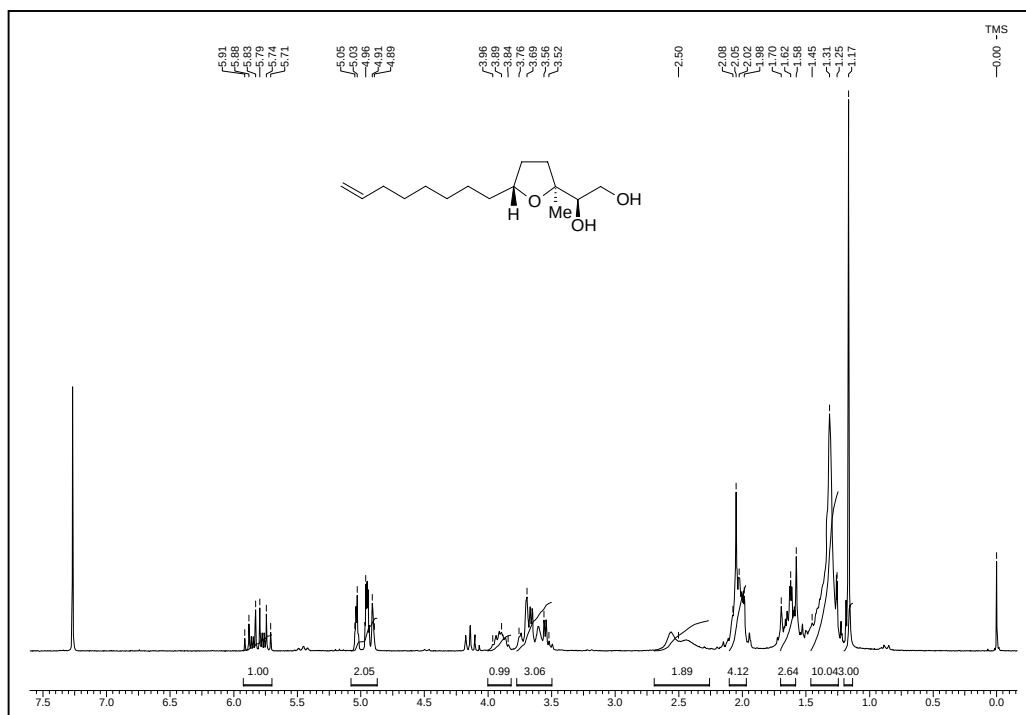
¹³C NMR Spectrum of 257 in CDCl₃



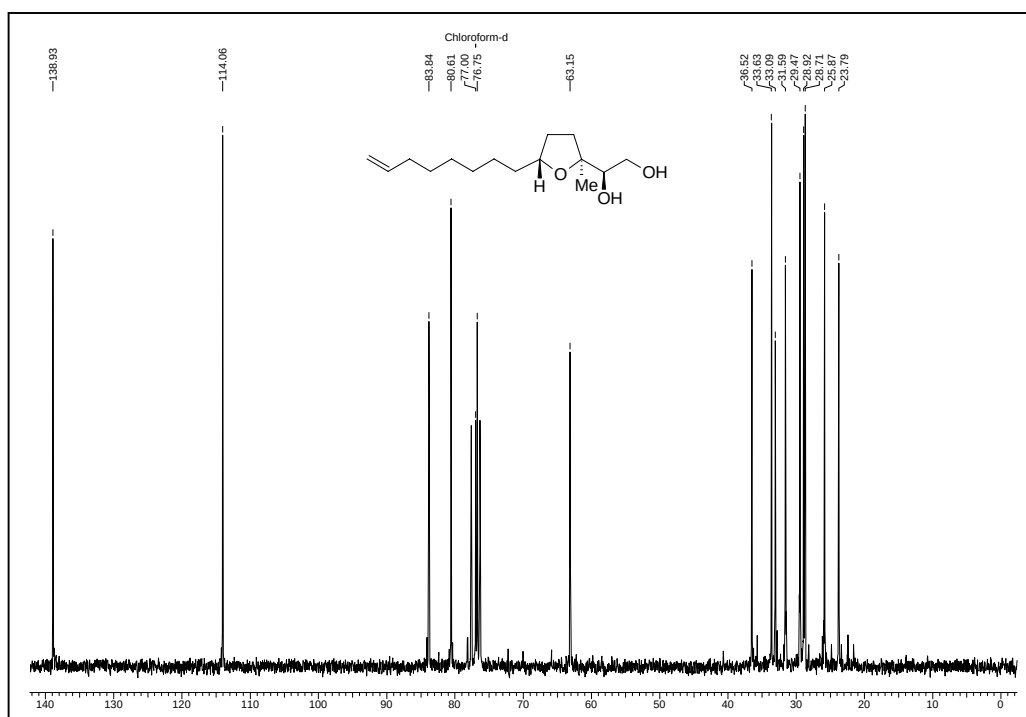
¹H NMR Spectrum of 258 in CDCl₃



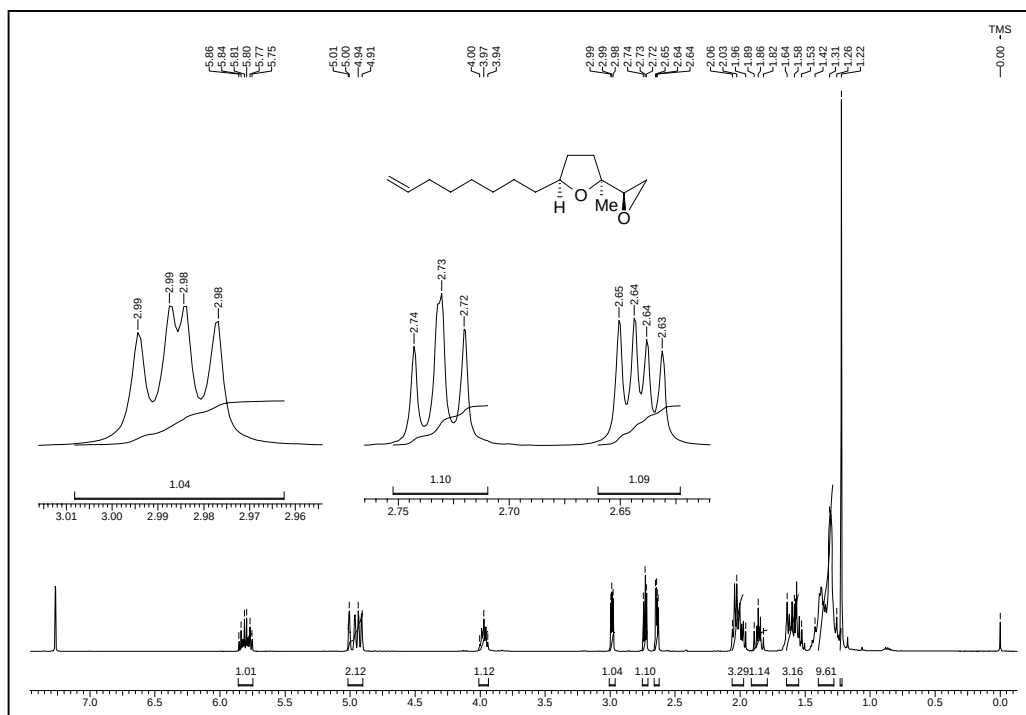
¹³C NMR Spectrum of 258 in CDCl₃



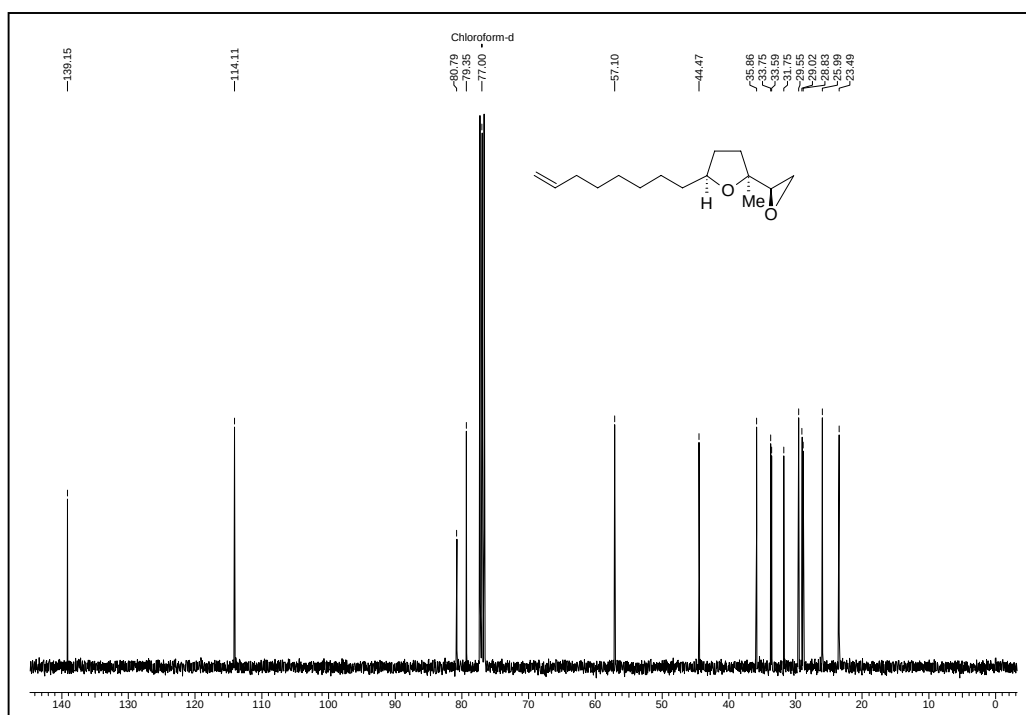
¹H NMR Spectrum of 259 in CDCl₃



¹³C NMR Spectrum of 259 in CDCl₃



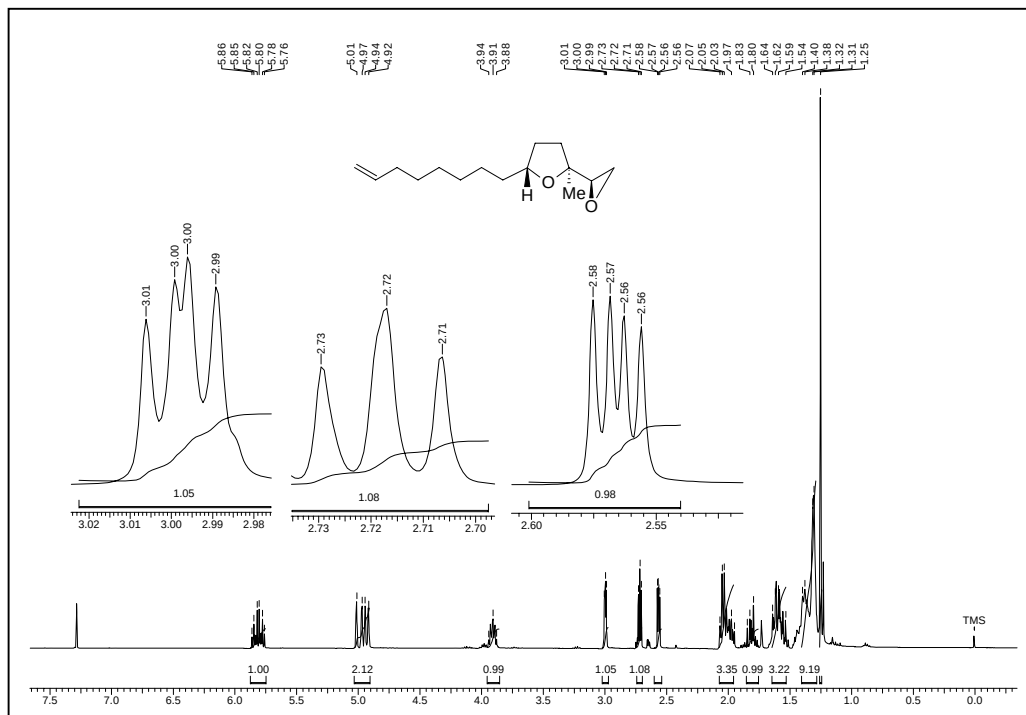
¹H NMR Spectrum of 260 in CDCl₃



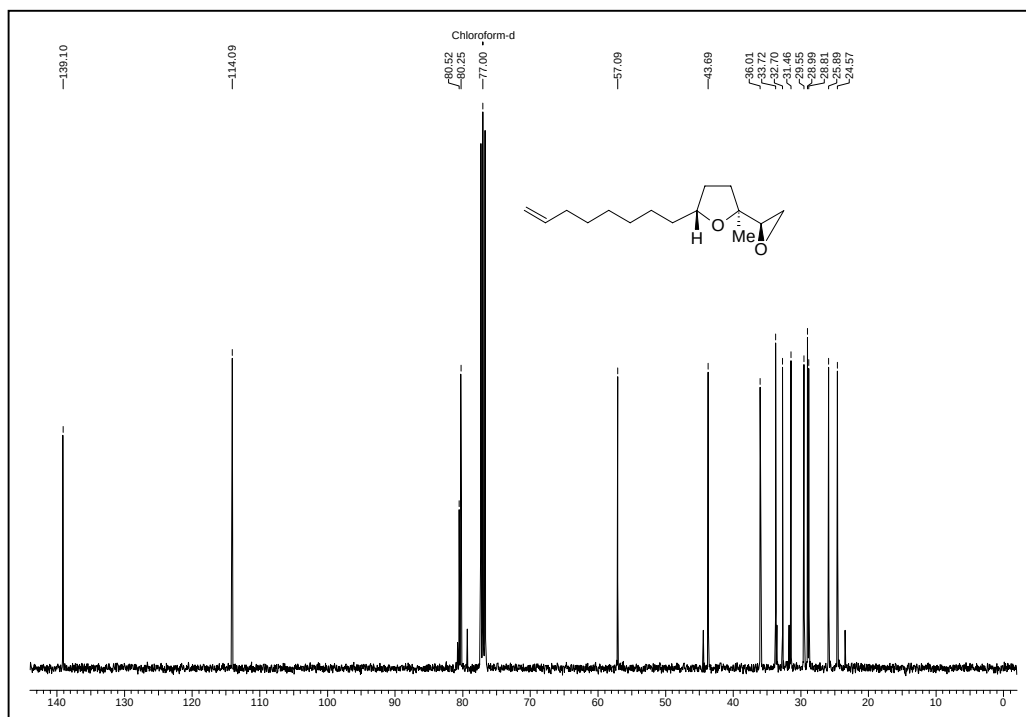
¹³C NMR Spectrum of 260 in CDCl₃



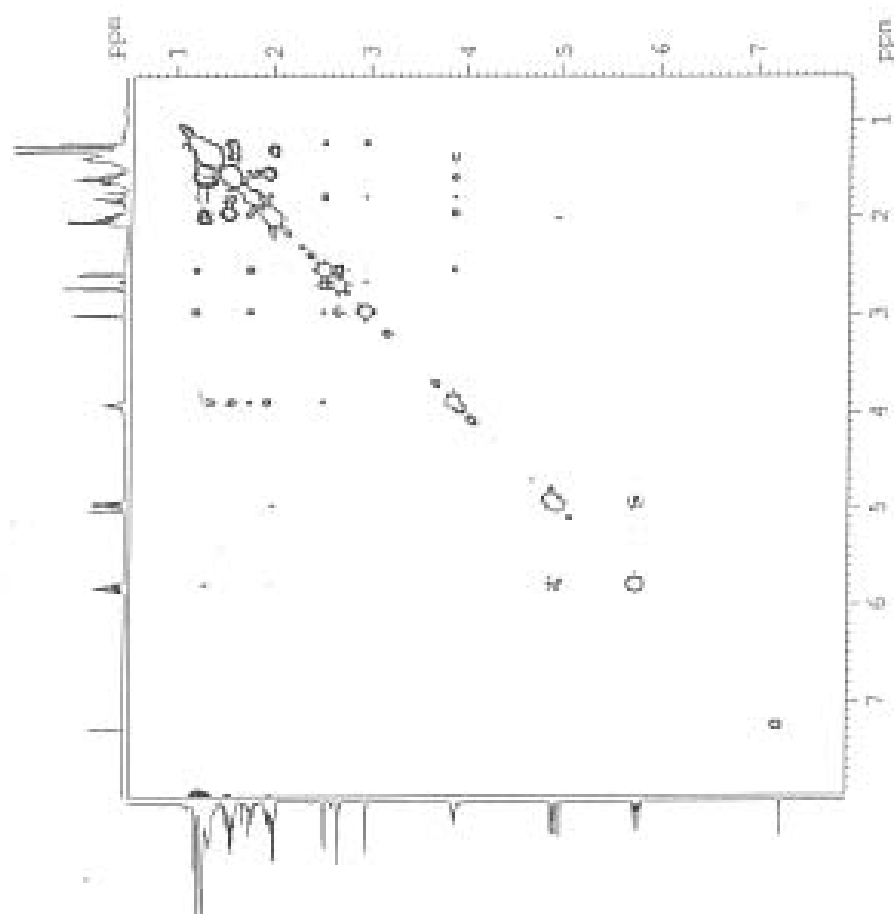
NOESY of compound 2d0



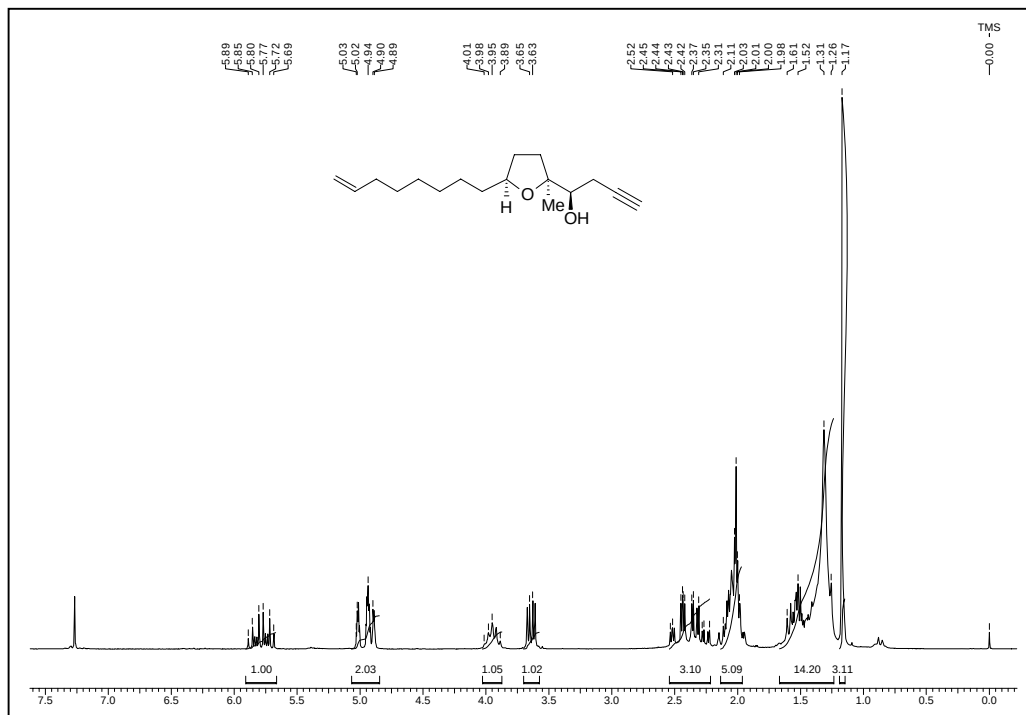
¹H NMR Spectrum of 261 in CDCl₃



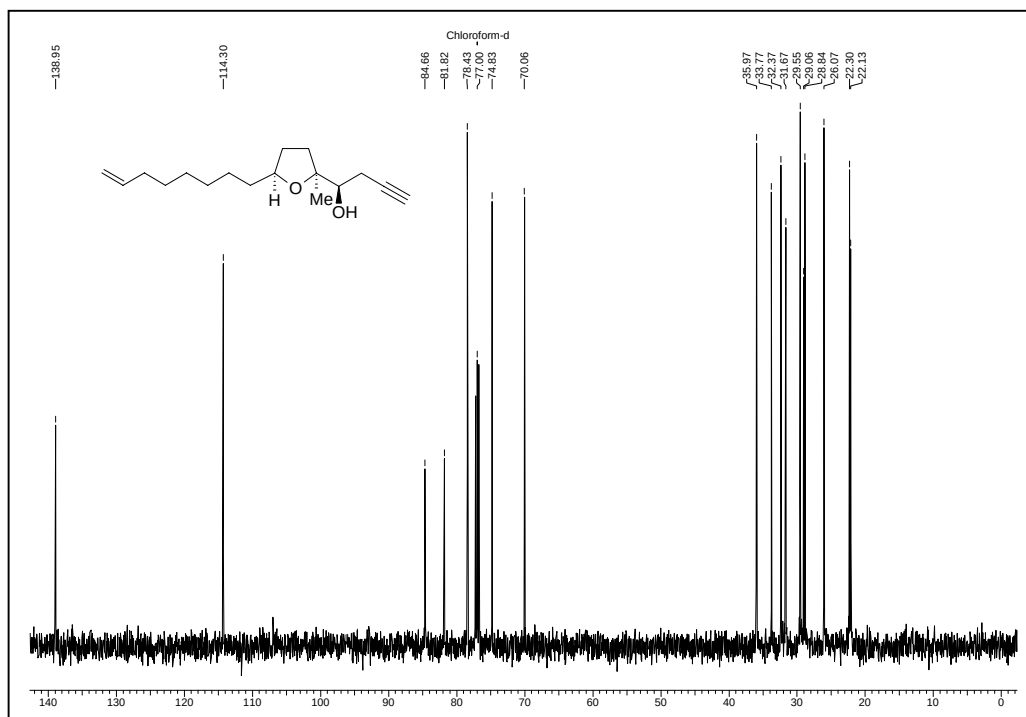
¹³C NMR Spectrum of 261 in CDCl₃



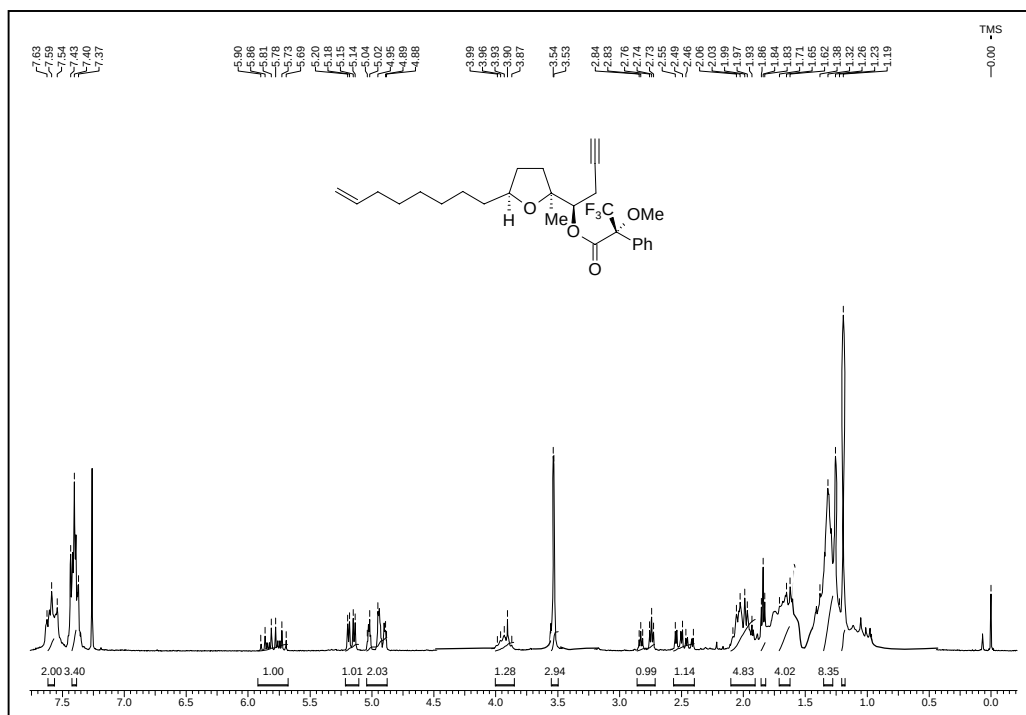
NOESY of compound 261



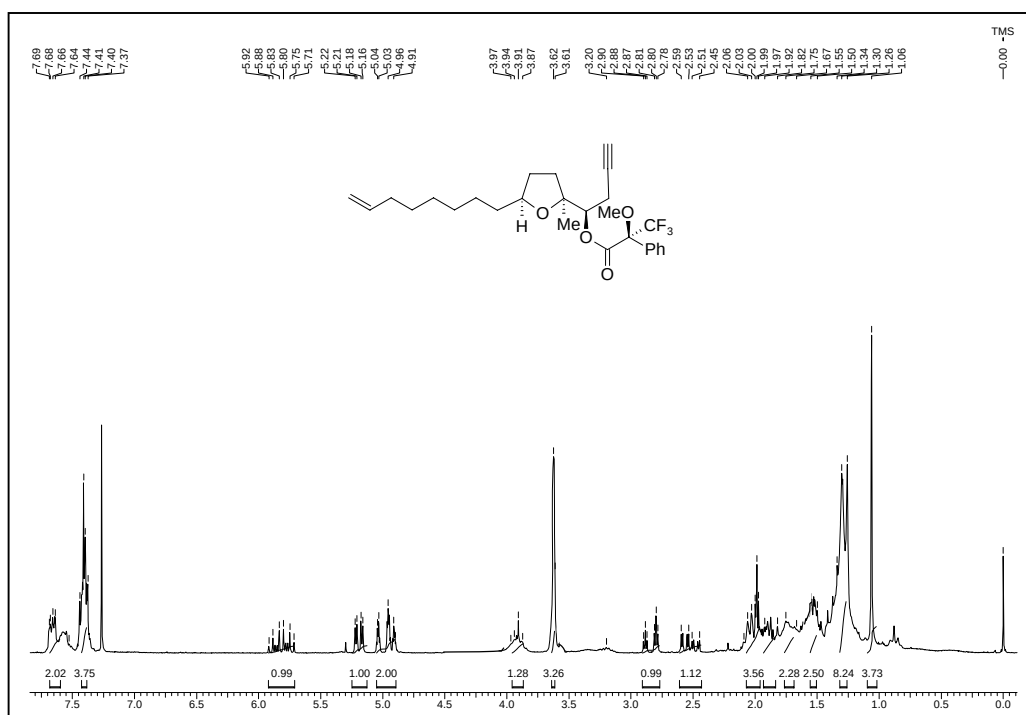
¹H NMR Spectrum of 262 in CDCl₃



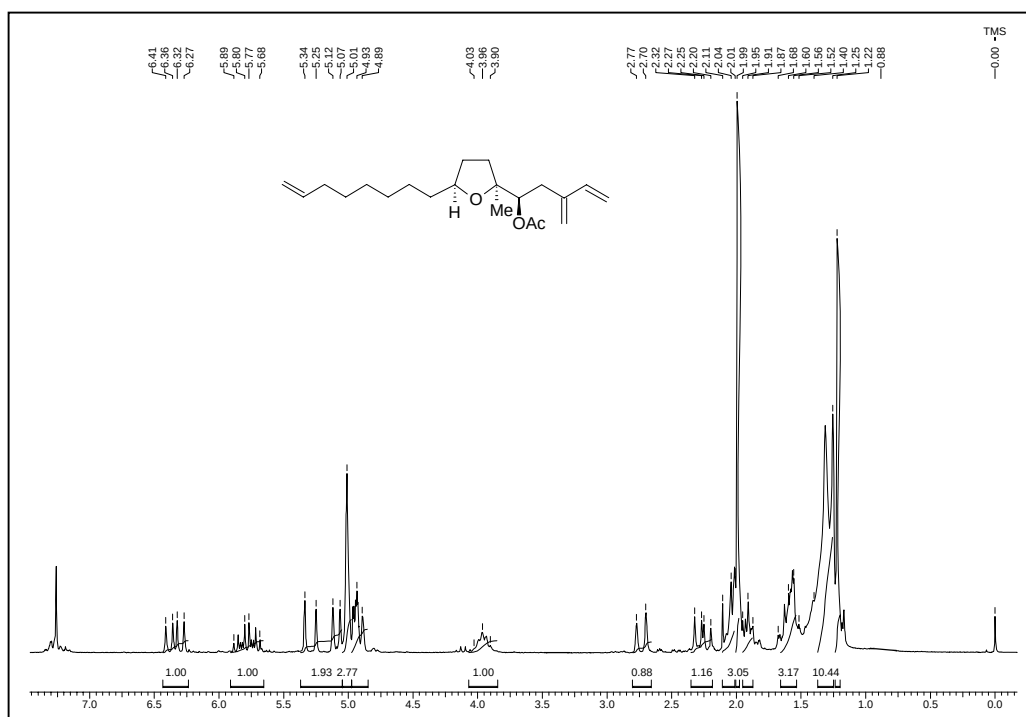
¹³C NMR Spectrum of 262 in CDCl₃



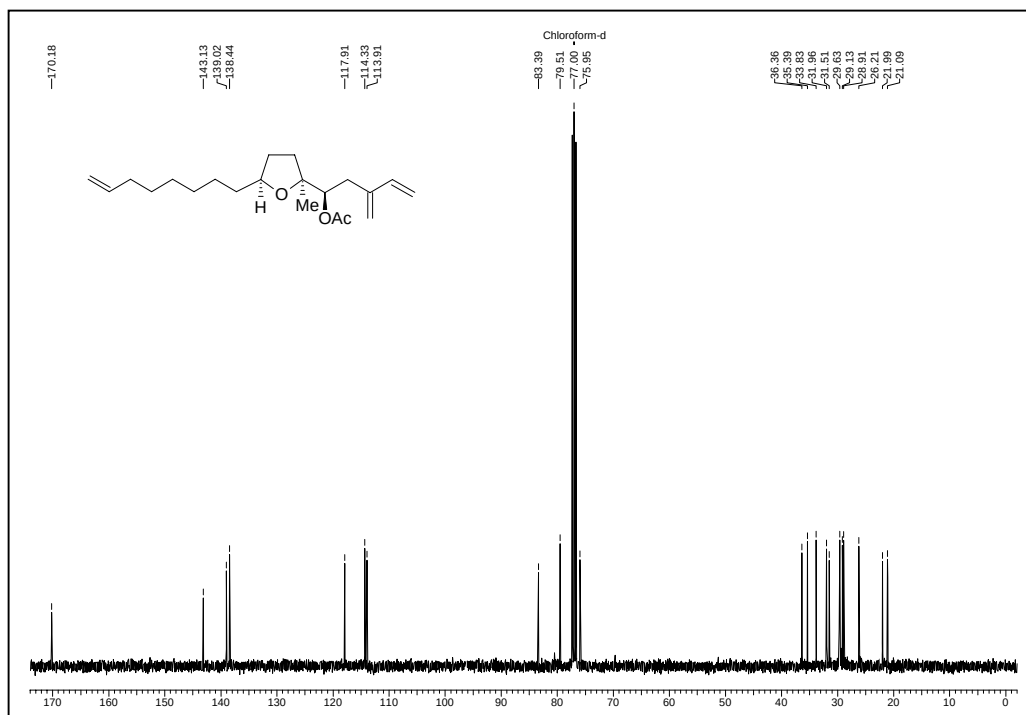
¹H NMR Spectrum of 263 in CDCl₃



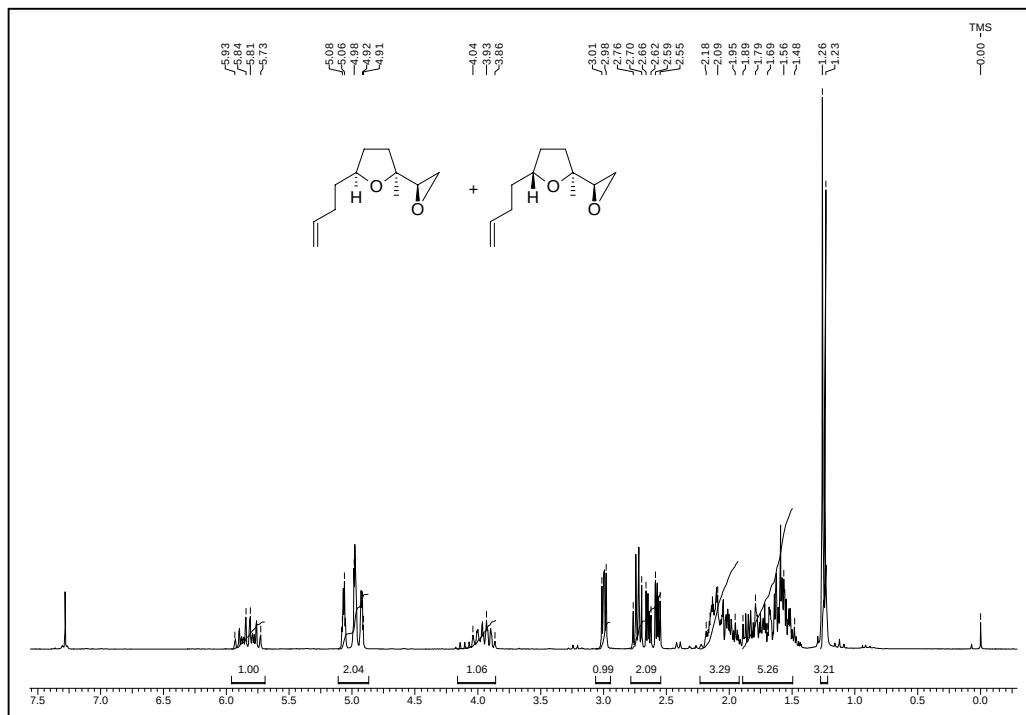
¹H NMR Spectrum of 264 in CDCl₃



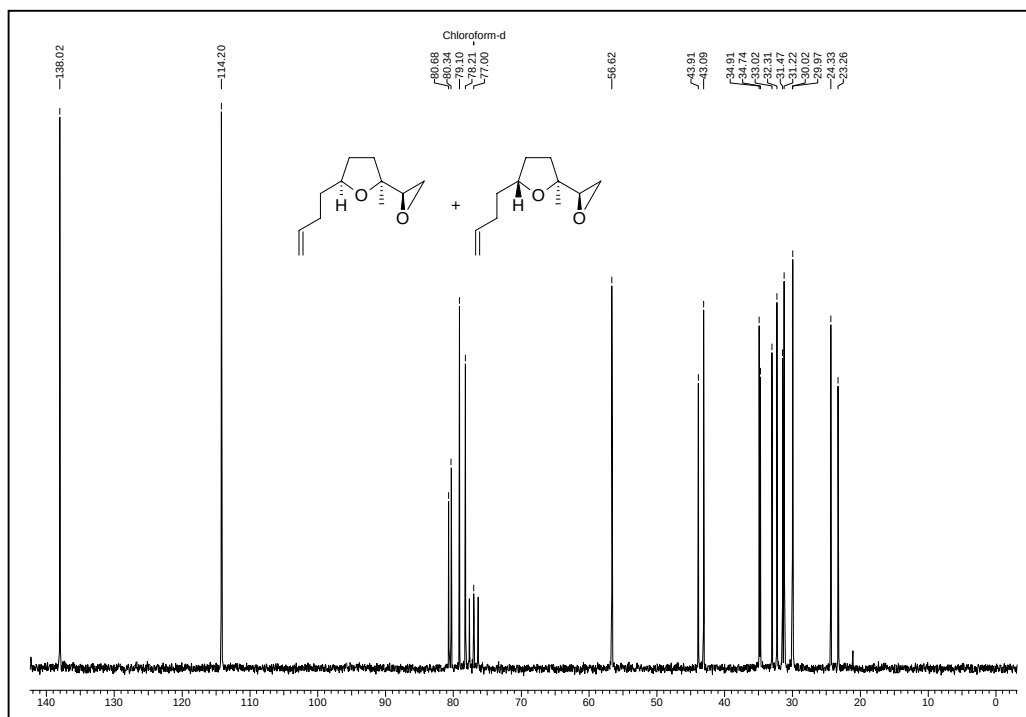
¹H NMR Spectrum of 266 in CDCl₃



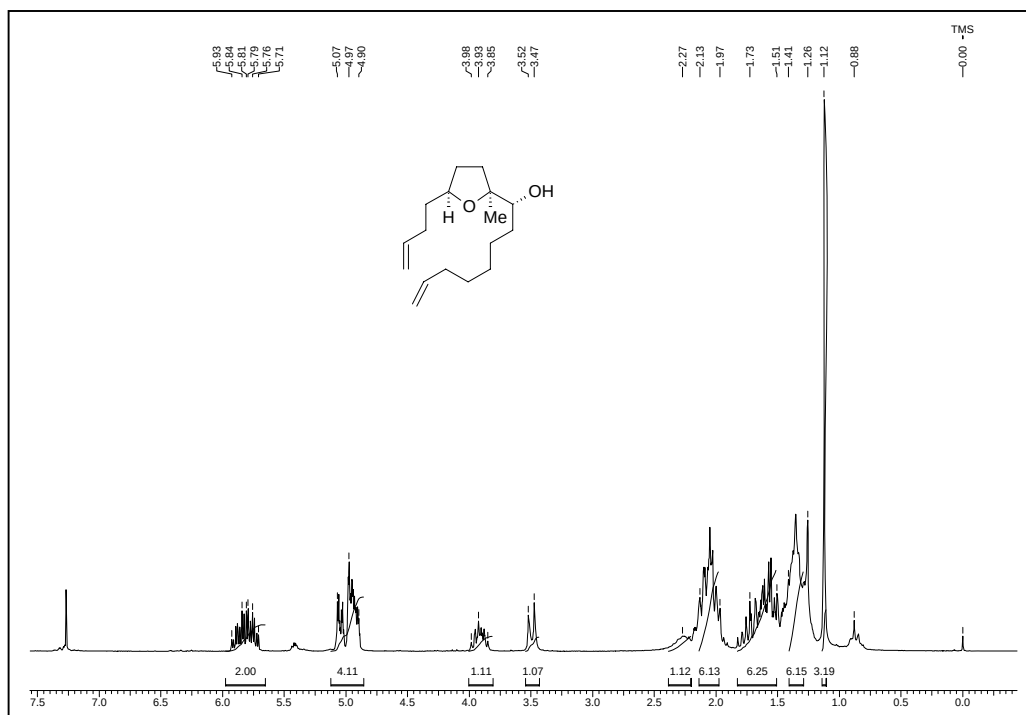
¹³C NMR Spectrum of 266 in CDCl₃



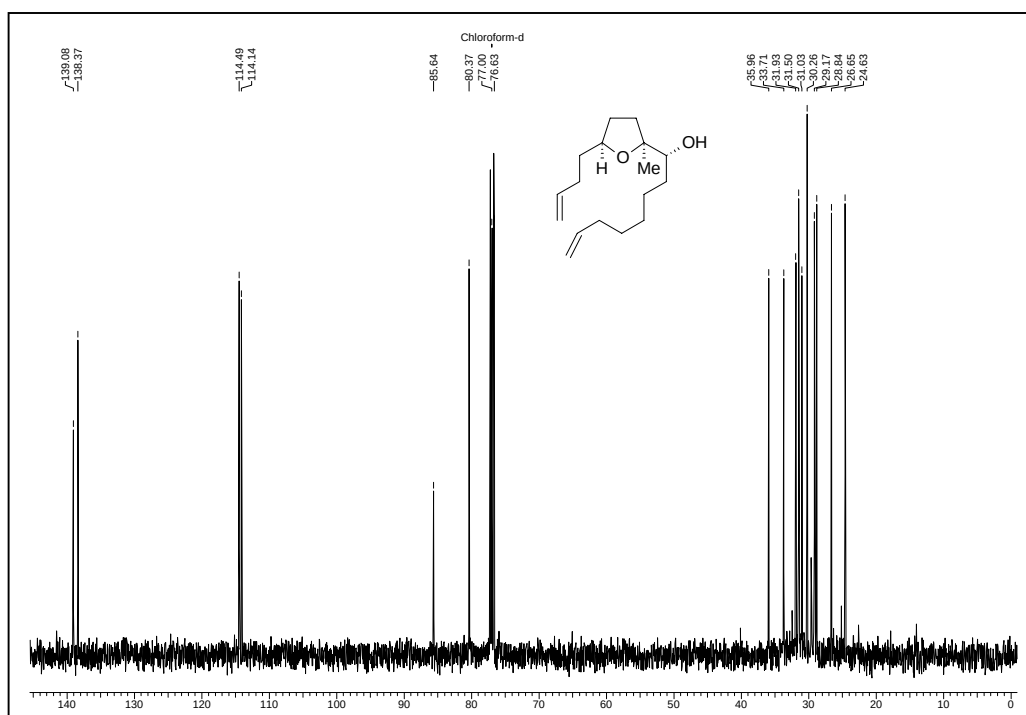
^1H NMR Spectrum of 274/275 in CDCl_3



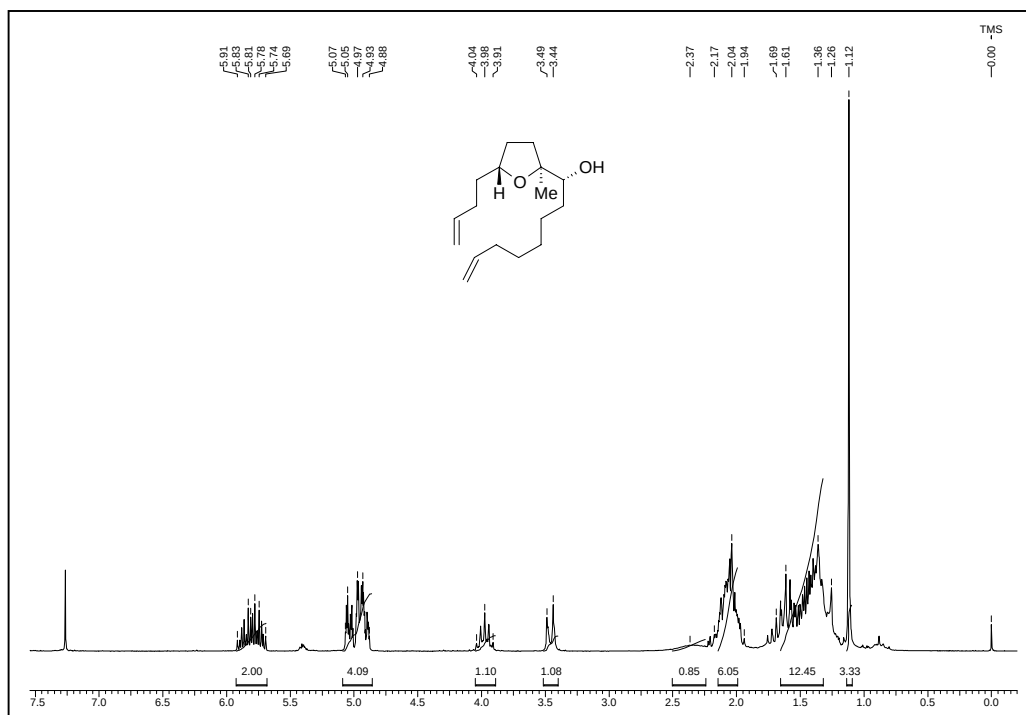
^{13}C NMR Spectrum of 274/275 in CDCl_3



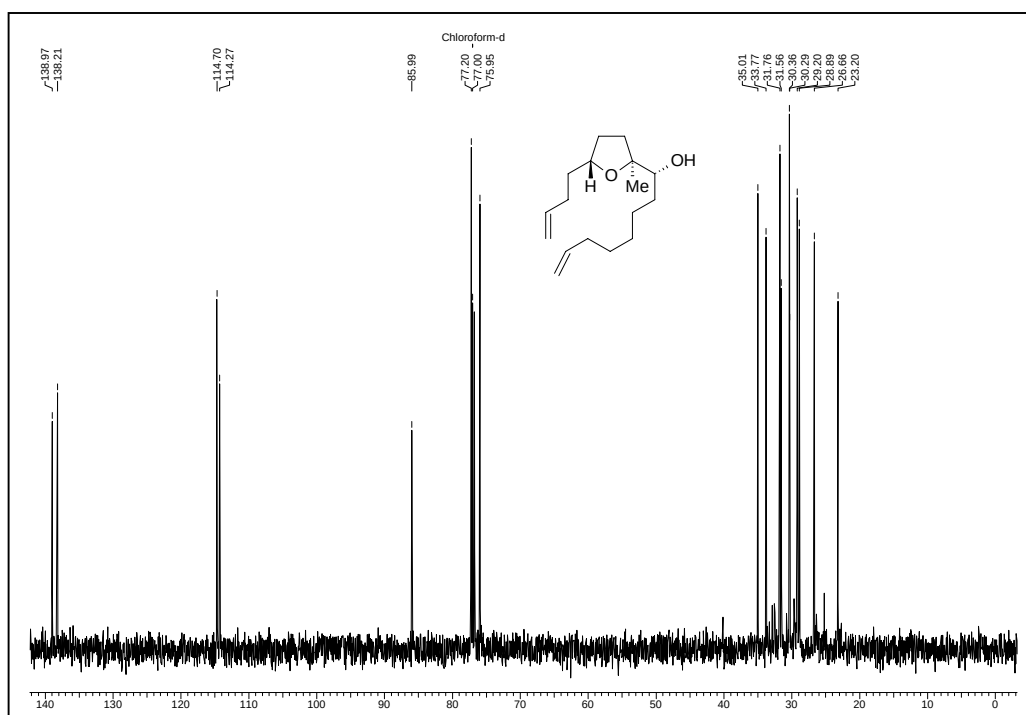
¹H NMR Spectrum of 276 in CDCl₃



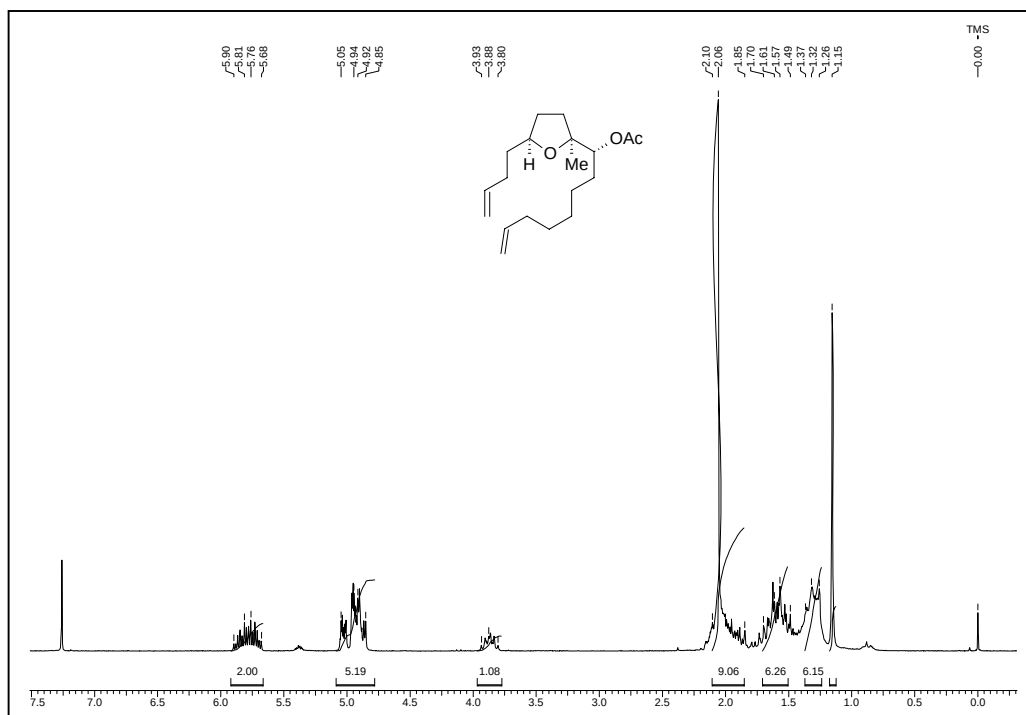
¹³C NMR Spectrum of 276 in CDCl₃



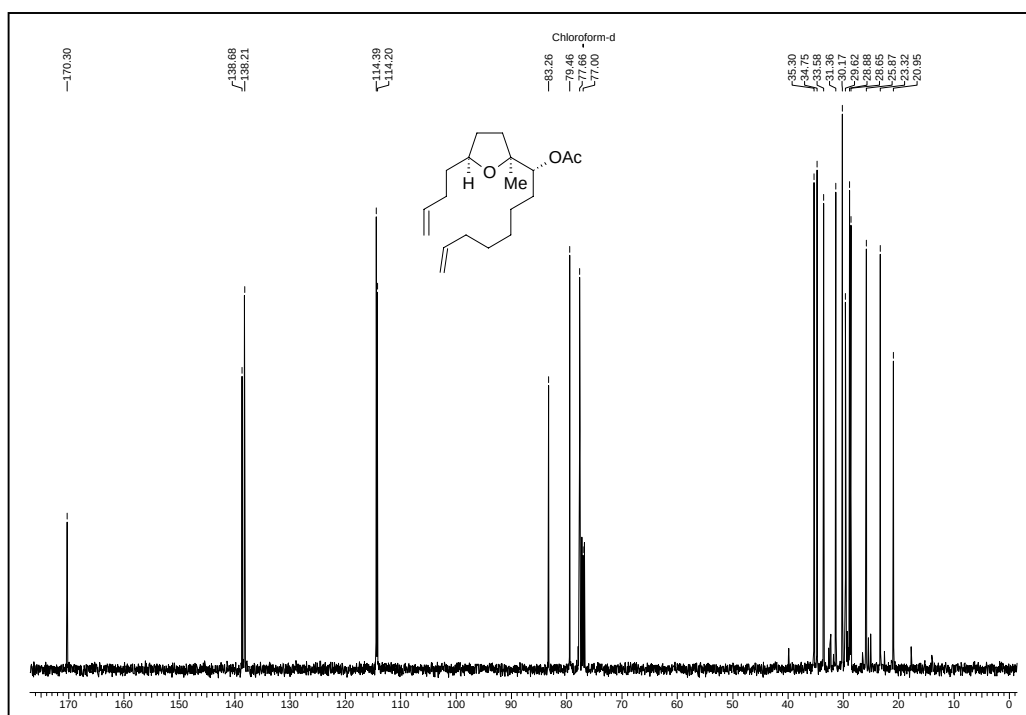
¹H NMR Spectrum of 277 in CDCl₃



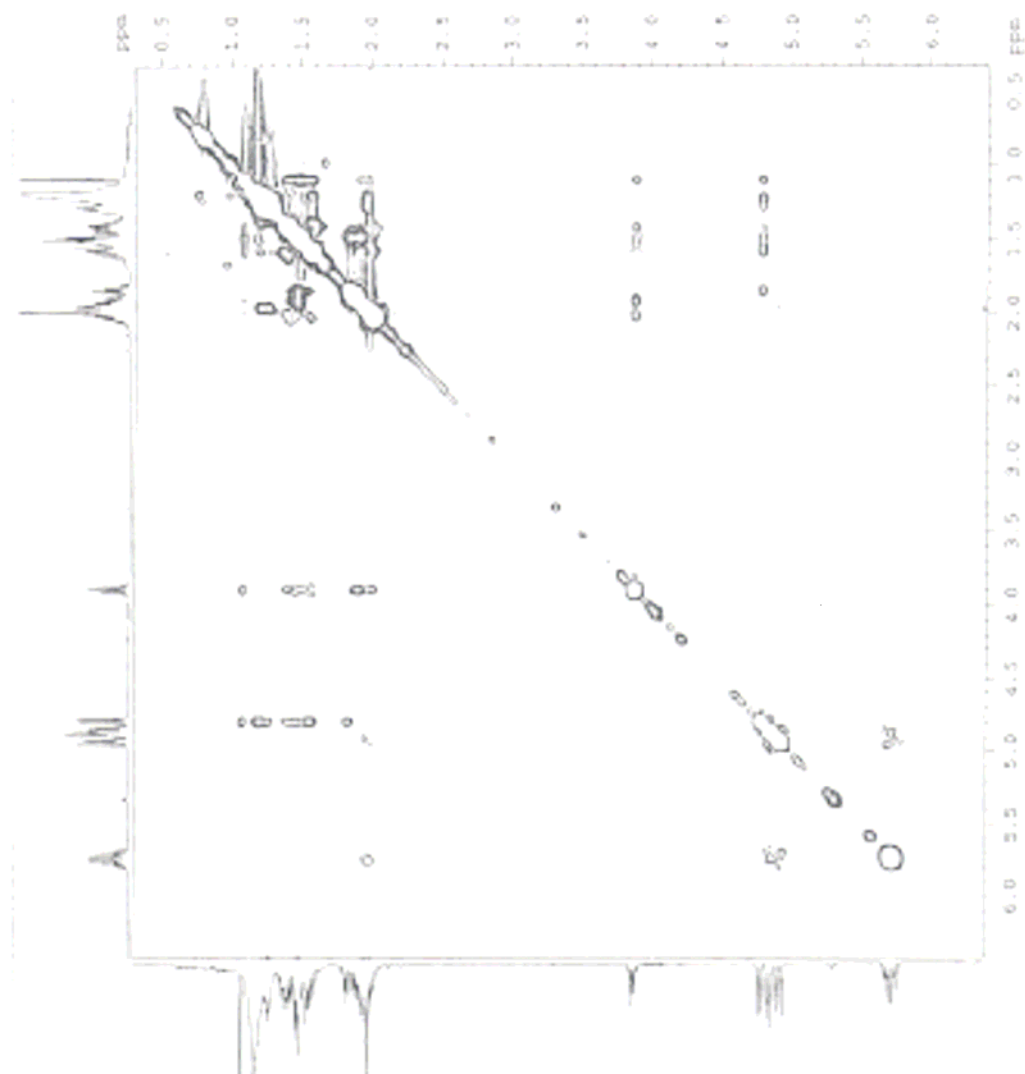
¹³C NMR Spectrum of 277 in CDCl₃



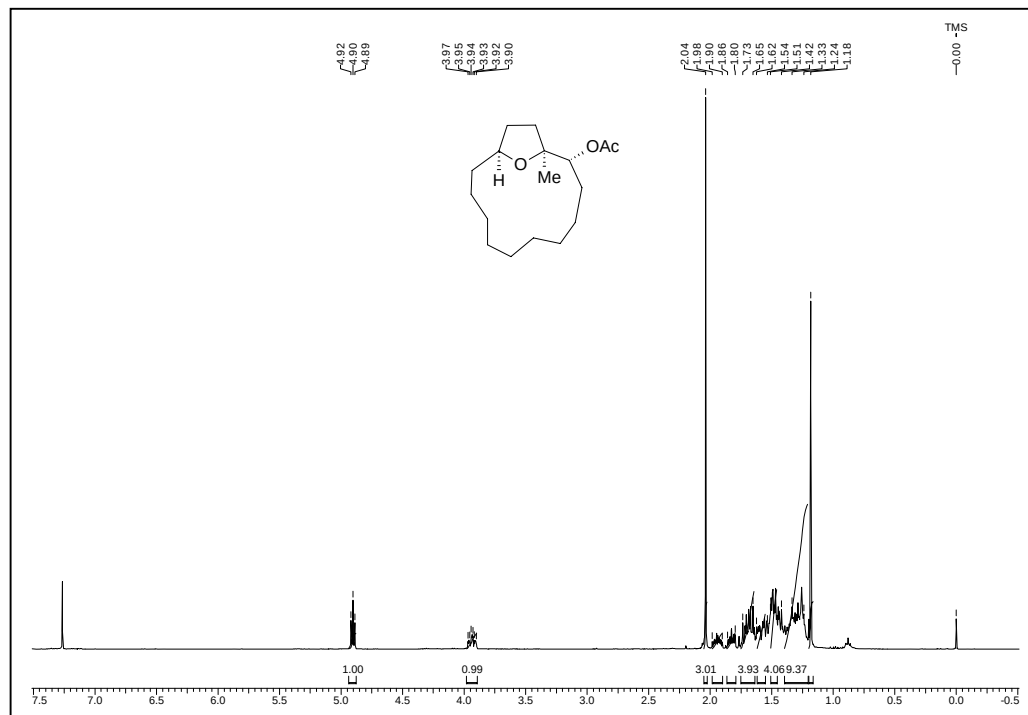
¹H NMR Spectrum of 278 in CDCl₃



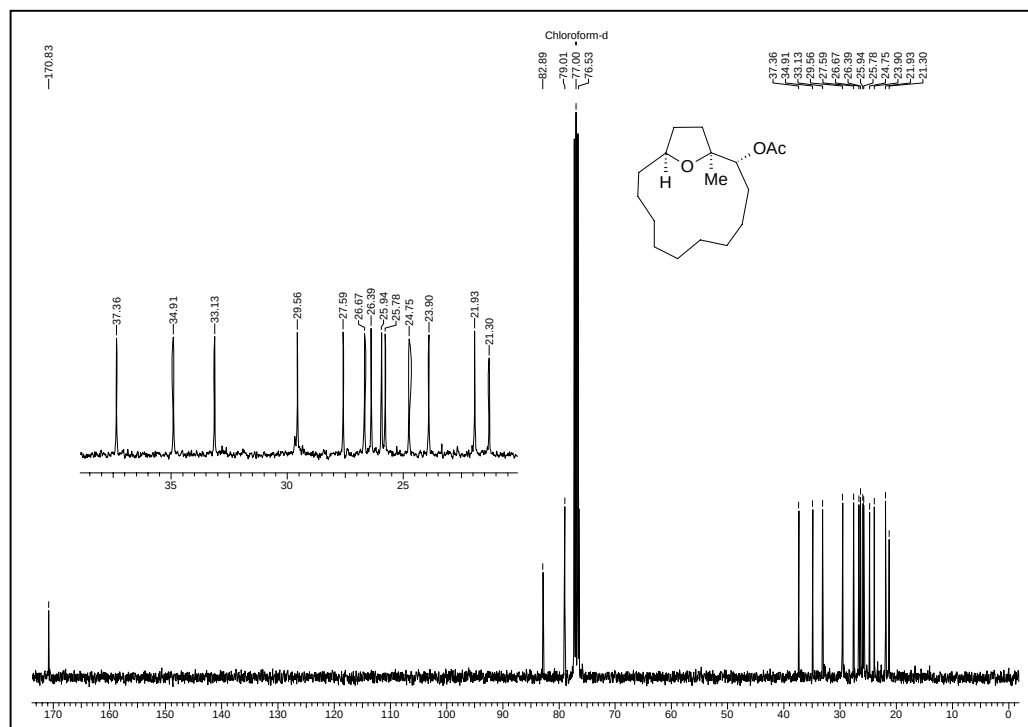
¹³C NMR Spectrum of 278 in CDCl₃



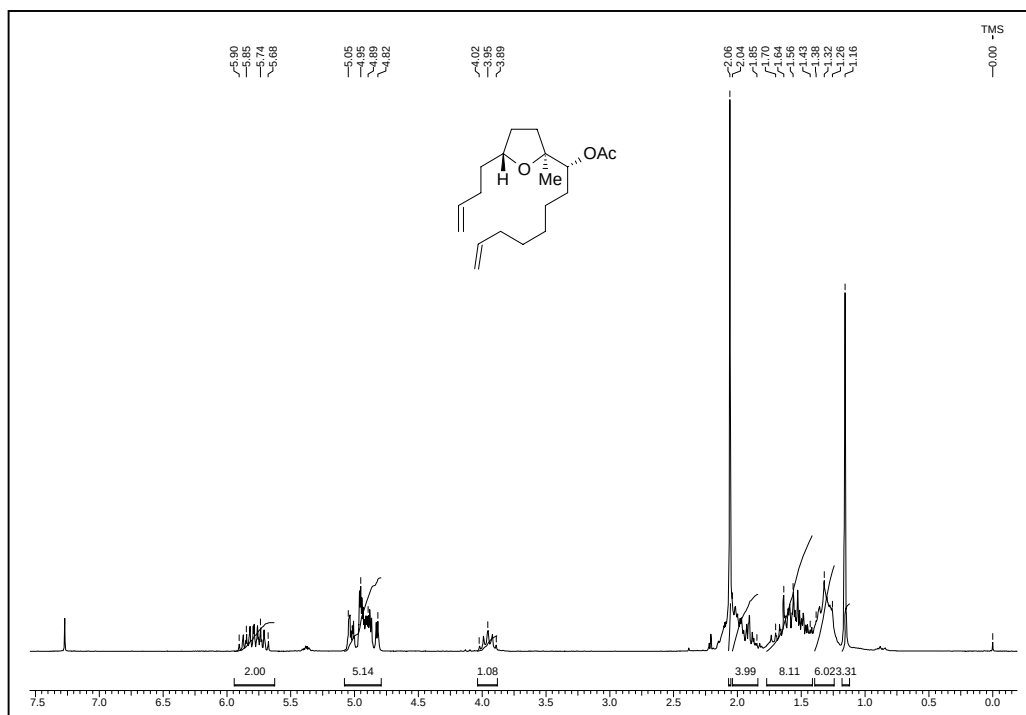
NOESY of compound 278



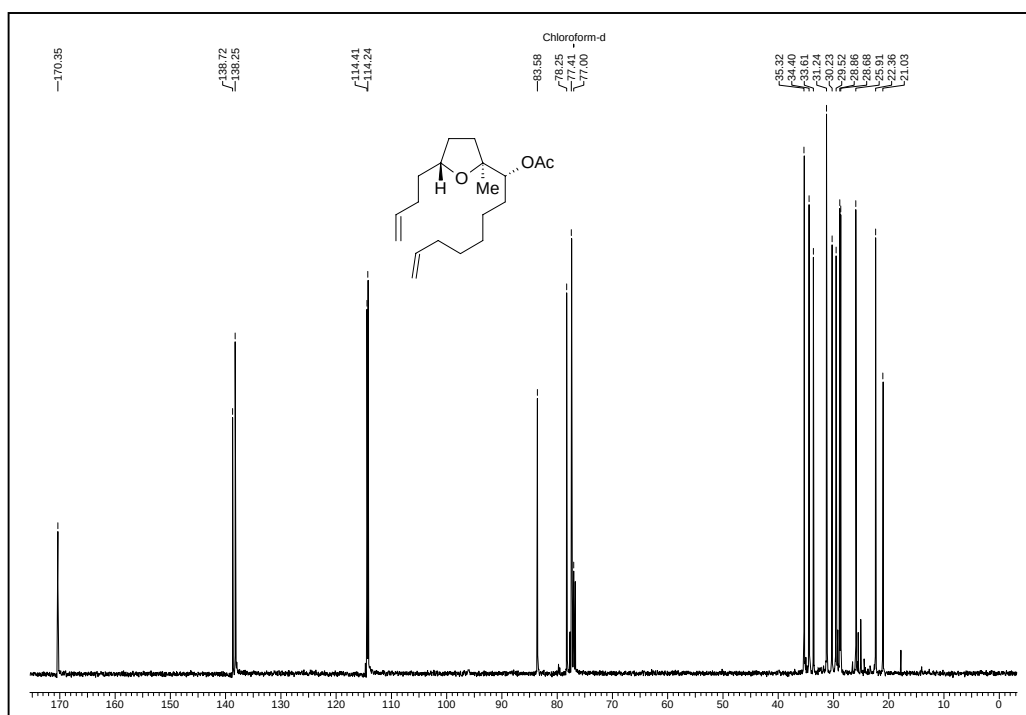
¹H NMR Spectrum of 281 in CDCl₃



¹³C NMR Spectrum of 281 in CDCl₃

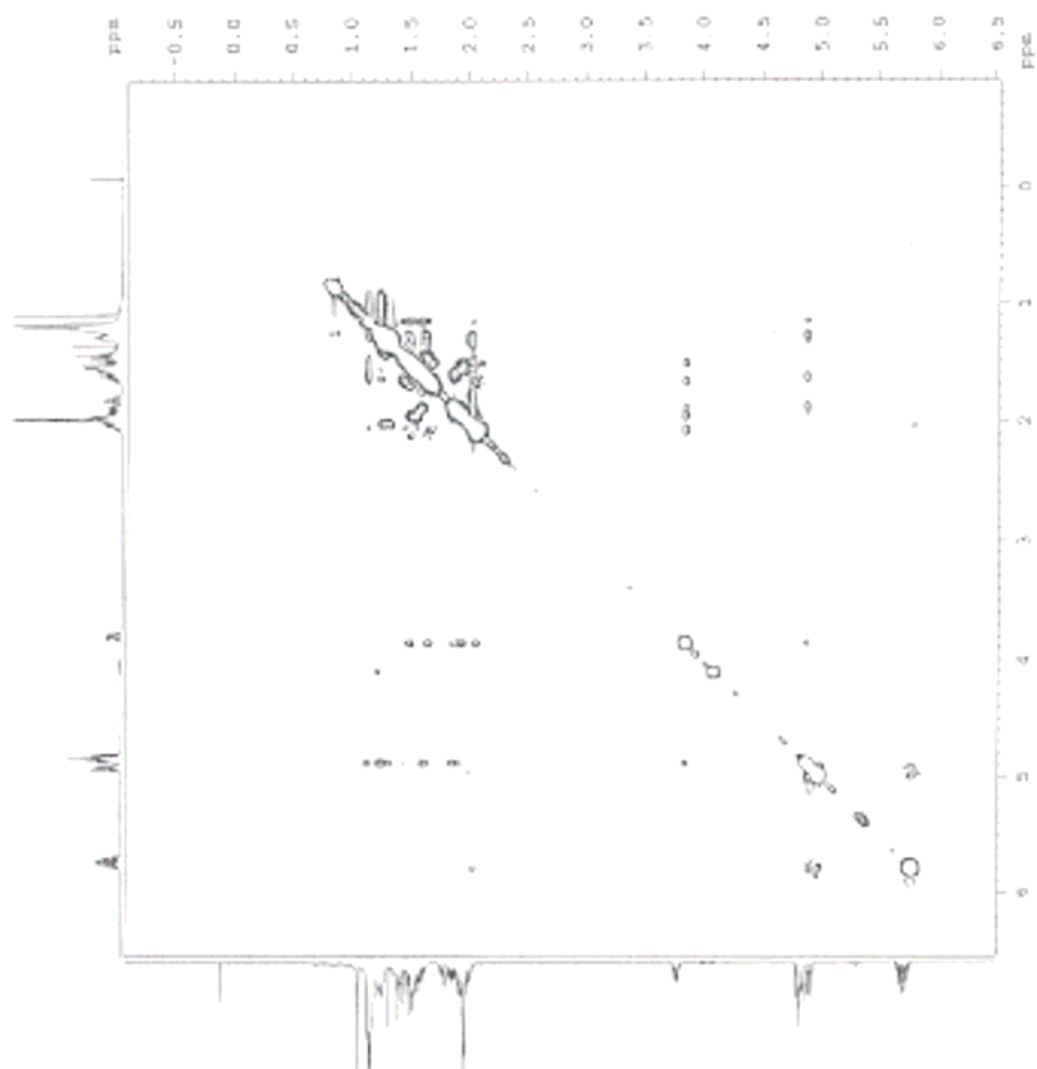


¹H NMR Spectrum of 279 in CDCl₃



¹³C NMR Spectrum of 279 in CDCl₃

Noesy



NOESY of compound 279

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List of Publications

LIST OF PUBLICATIONS

1. Central core of uprolides D and E: a survey of some ring closing metathesis approaches- C. V. Ramana, **Sumanth R. Salian**, and Mukund K. Gurjar, *Tetrahedron Lett.* **2007**, *48*, 1013-1016.
2. An Expeditious Assembly of 3,4-Benzannulated 8-Oxabicyclo[3.2.1]octane Systems by [2+2+2] Alkyne Cyclotrimerisation: Total Synthesis of (–)-Bruguierol A- C. V. Ramana, **Sumanth R. Salian**, and Rajesh G. Gonnade, *Eur. J. Org. Chem*, **2007**, *in press*.