Synthetic studies toward the total synthesis of Aflastatin A, bruguierol A and preparation of some 10-diarylmethylidene anthraquinones

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Synthetic studies toward the total synthesis of Aflastatin A, bruguierol A and preparation of some 10-diarylmethylidene anthraquinones

Submitted by

Chandra Kiran Neella

To

Osmania University

For

The degree of Doctor of philosophy

Organic Chemistry: Technology
National Chemical Laboratory
Pune-411008
INDIA
June 2008

DEDICATED

TO

MY MUCH-LOVED PARENTS,
BROTHER, GRAND PARENTS,
PROF. DAVID KRUPADANAM,
Dr. M. K. GURJAR.

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**, former HOD, 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.

Division of Organic Chemistry
National Chemical Laboratory
Pune-411008
June 2008

(Mr. Chandra Kiran Neella)

CERTIFICATE

The research work presented in thesis entitled "**Synthetic studies toward the total synthesis of Aflastatin A, bruguierol A and preparation of some 10-diarylmethylidene anthraquinones**" has been carried out under my supervision and is a bonafide work of **Mr. Chandra Kiran Neella**. This work is original and has not been submitted for any other degree or diploma of this or any other University.

Pune-411008 **(Dr. M. K. Gurjar)**

June 2008 **Research Guide**

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Finally and most importantly I bow my head to lord shiva and goddess Saraswati by whom grace I acquired the wealthy knowledge especially in chemistry and wonderful family members.

Ac	-	Acetyl
AcOH	-	Acetic acid
Ac_2O	-	Acetic anhydride
aq.	-	Aqueous
Bn	-	Benzyl
BnBr	-	Benzyl bromide
$BH_3.Me_2S$	-	Boron dimethyl sulfide complex
BuLi	-	Butyl lithium
DCM	-	Dichloromethane
DIBAL-H	-	Diisobutylaluminiumhydride
DMAP	-	4-Dimethylaminopyridine
DMP	-	2,2-Dimethoxypropane
DMPOH	-	Dimetgyl propargyl alcohol
DMF	-	*N,N*-Dimethylformamide
DMSO	-	Dimethyl sulfoxide
EtOH	-	Ethanol
Et	-	Ethyl
Et_2O	-	Diethyl ether
EtOAc	-	Ethyl acetate
Et_3N	-	Triethylamine
HMPA	-	Hexamethylphosphoramide
Im	-	Imidazole
LAH	-	Lithium aluminium hydride
LiHMDS	-	Lithium hexamethyl disilazane
m-CPBA	-	*meta*-Chloroperbenzoic acid
MeOH	-	Methanol
Me	-	Methyl
MeI	-	Methyl iodide
MES	-	Mesitylenesulphonyl
Ms	-	Methanesulfonyl
NaHMDS	-	Sodium hexamethyl disilazane
n-Dec	-	n-Decyl

NEt_3	-	Triethyl amine
NMO	-	4-Methyl morpholine *N*-oxide
NOESY	-	Nuclear overhauser effect spectroscopy
OD	-	Optical Density
ORTEP	-	Oak ridge thermal ellipsoid plot
Ph	-	Phenyl
PMB	-	4-Methoxy benzyl
Py	-	Pyridine
PTSA	-	*para*-Toluenesulfonic acid
r.t.	-	Room temperature
sat.	-	Saturated
TBDMS-Cl	-	*tert*-Butyldimethyl chlorosilane
TBDMSOTf	-	*tert*-Butyldimethyl trifluoro methanesulphonate
THF	-	Tetrahydrofuran
TPP	-	Triphenylphosphine
TrCl	-	Trityl chloride
TsCl	-	*para*-Toluenesulphonyl chloride
WC	-	Wilkinson's Catalyst

GENERAL REMARKS

- ^{1}H 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 Finngan 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 Büchi 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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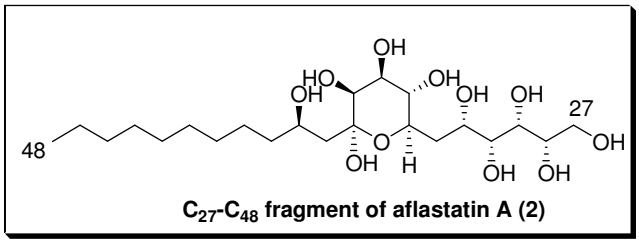
ABSTRACT

ABSTRACT

The thesis entitled "**Synthetic Studies Toward The Total Synthesis Of Aflastatin A, Bruguierol A And Preparation Of Some 10-Diarylmethylidene Anthraquinones**" is divided into three chapters and each chapter is further subdivided into introduction, present work, experimental, spectral data and references. The first chapter deliberates the synthetic efforts towards C_{27}-C_{48} fragment of aflastatin A. Chapter II discusses the application of [2+2+2] cross cyclotrimerization towards the enantioselective synthesis of (+)-bruguierol A and pyridine fused bicyclo[3.2.1]octane systems. Third chapter explicates the utility of double Suzuki coupling for the preparation of some 10-Diarylmethylidene 1, 8-dichloro anthraquinones.

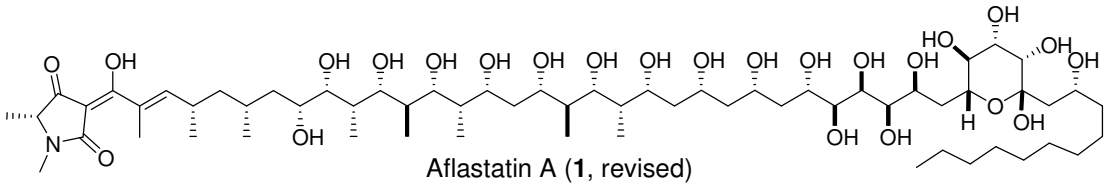
CHAPTER I: -

Synthetic studies toward C_{27}-C_{48} Fragment of Aflastatin A.



C_{27}-C_{48} fragment of aflastatin A (2)

Aflastatin A was isolated by Sakuda and co-workers from the mycelia of *Streptomyces sp.* MRI 142. Aflastatin A belongs to the class of polyol natural products and include a novel tetramic acid derivative with a long polyhydroxylated alkyl side chain and is acyclic except for a tetrahydropyran ring. Its strong inhibitory activity against aflatoxin production without significantly affecting the growth of *A. parasiticus* prompted vigorous structure elucidation effort culminating the absolute structure determination of aflastatin A (**1**).

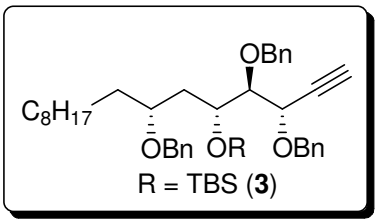


Aflastatin A (**1**, revised)

A convergent three pronged strategy was crafted for the synthesis: 1) Synthesis of alkyne fragment **3** (**Section I**): 2) synthesis of epoxide fragment **16** (**Section II**): and 3) Yamaguchi coupling of both the fragments followed by the construction of the pyran ring (**Section III**).

SECTION -I:

Chiron approach for the synthesis of alkyne fragment (3):

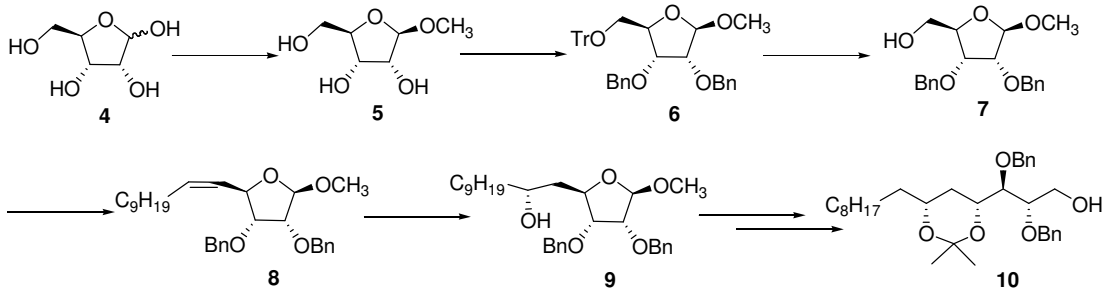


R = TBS (**3**)

Our journey began with the acetalization of D- ribose **4** (**Scheme 1**) with methanolic HCl under Fischer glycosidation conditions to deliver methyl ribopyranoside **5** whose primary hydroxyl was regioselectively tritylated with TrCl/NEt_3/DMAP in DMF which on dibenzylation of secondary hydroxyls delivered the dibenzyl ether **6**. Exposure of compound **6** to methanolic.HCl furnished the detritylated alcohol **7** which upon swern oxidation and subsequent Wittig reaction with decyl triphenylphosphorane in THF provided solely the *Z*-configured olefin **8**. As anticipated by the molecular models, hydroboration of *Z*-olefin with BH_3:DMS afforded the secondary alcohol **9** which was benzylated to obtain the compound **11**. The 1, 3 *syn* stereochemistry of the newly generated hydroxyl with the ring oxygen

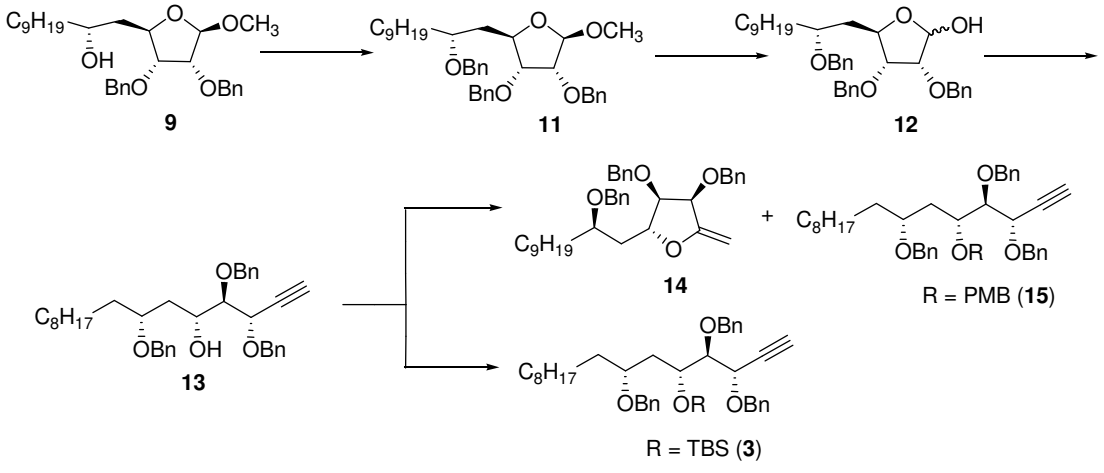
was established by converting **9** into isopropylidene derivative **10** whose spectral data is substantiated for the proposed structure.

Scheme 1:



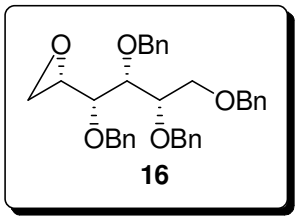
Acidic hydrolysis of **11** with conc. H_2SO_4 in refluxing dioxane and water delivered the hemiacetal **12** which was subjected to Ohira-Bestmann homologative alkynylation with [$(CH_3COC(N_2)PO(OMe)_2/K_2CO_3$ in MeOH] to furnish the key alkyne **13** (**Scheme 2**). Treatment of sodium alkoxide of **13** with PMBCl in DMF delivered a 1:1 mixture of required PMB ether **13** and undesired exocyclic olefine **14**. To circumvent this problem we altered the protecting group to TBS, accordingly reaction of alcohol **13** with TBSOTf and NEt_3 in DCM furnished the key alkyne fragment **3**.

Scheme 2:



SECTION-II:

Chiron approach for the synthesis of epoxide fragment (x)



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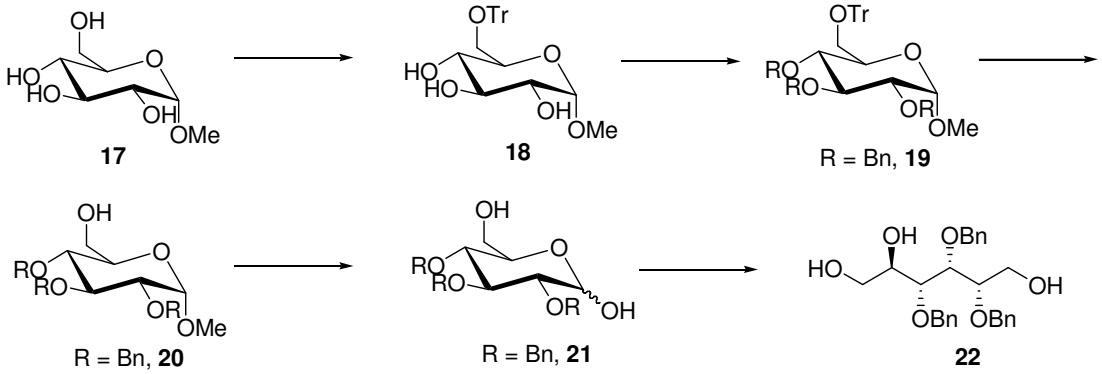
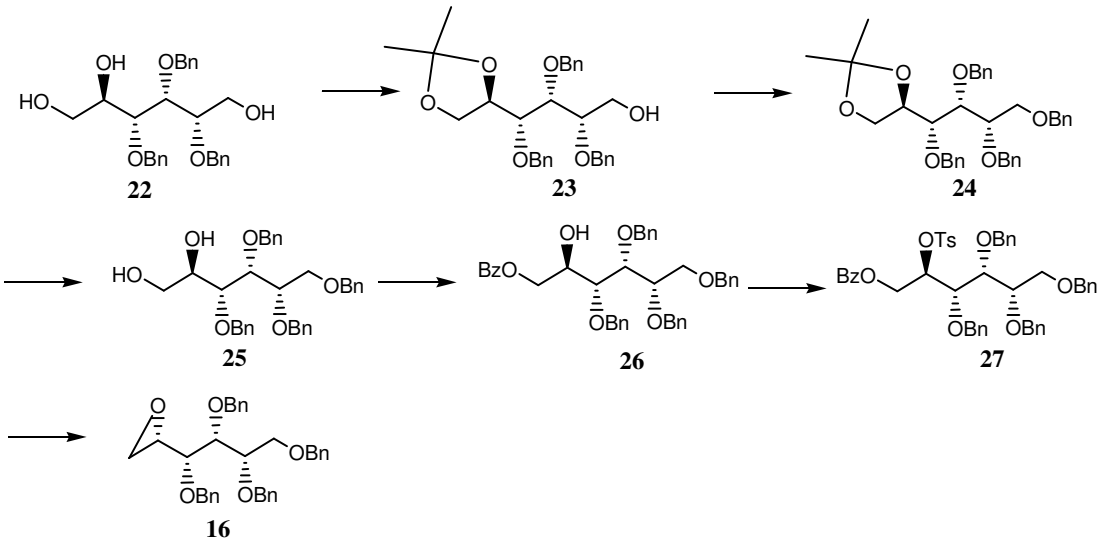
Our synthesis commenced with D-glucose (**Scheme 3**) which on Fischer glycosidation with methanolic HCl delivered methyl glucopyranoside **17** whose primary hydroxyl was regioselectively tritylated with TrCl/NEt_3/DMAP in DMF followed by benzylation of three secondary hydroxyls of **18** produced the tribenzyl ether **19**. Exposure of compound **19** to methanolic.HCl furnished the alcohol **20**. Acidic hydrolysis of **20** with conc. H_2SO_4 in refluxing dioxane and water provided the hemiacetal **21** which was reduced to triol **22** with LAH in THF.

Scheme 3:



Masking of the vicinal diol of triol **22** as its isopropylidene acetal **23** (**scheme 4**) followed by benzylation of the primary alcohol of **23** furnished the tetrabenzyl ether **24**. Acid mediated (p-TSA) de-isopropylidenation of compound **24** in MeOH delivered the diol **25**.

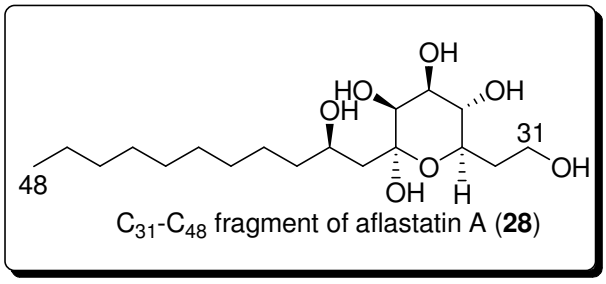
Scheme 4:



Regioselective primary alcohol protection of the vicinal diol **25** was accomplished by treating **25** with Bu_2SnO and BzCl in DCM to deliver the benzoate derivative **26**. Tosylation of hydroxyl benzoate **26** with TsCl and py in DCM provided the diester **27**. Exposure of diester **27** to K_2CO_3 in MeOH at ambient temperatures provided the epoxide fragment **16** with the requisite stereochemistry.

SECTION-III:

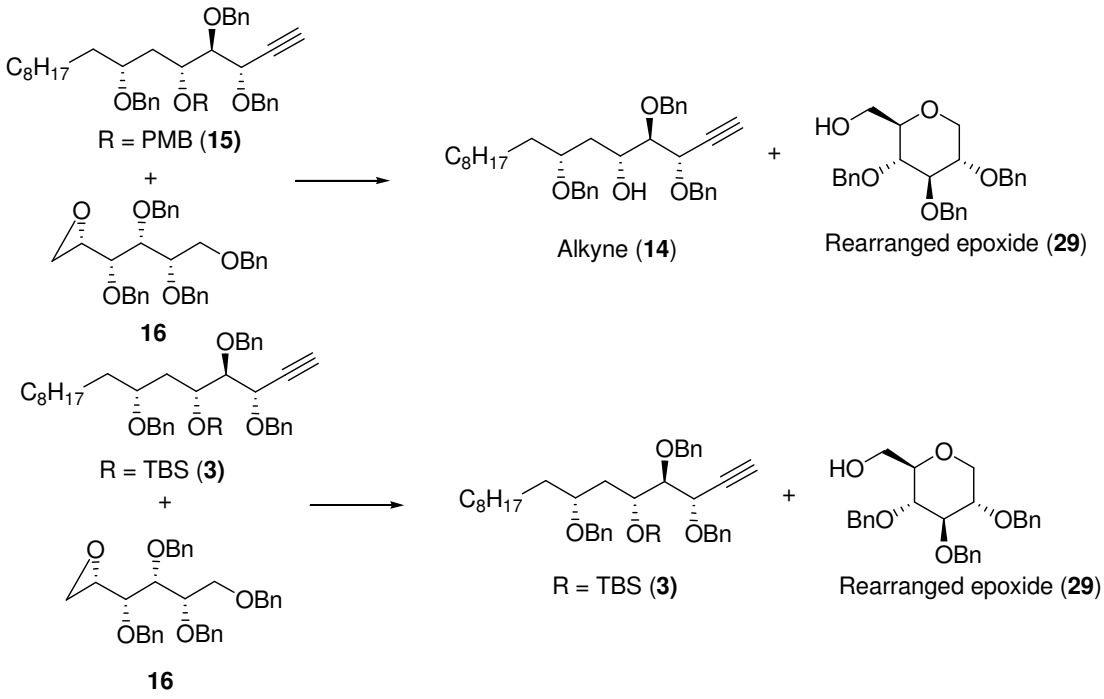
Synthesis of C_{31}-C_{48} fragment of aflastatin A



C_{31}-C_{48} fragment of aflastatin A (**28**)

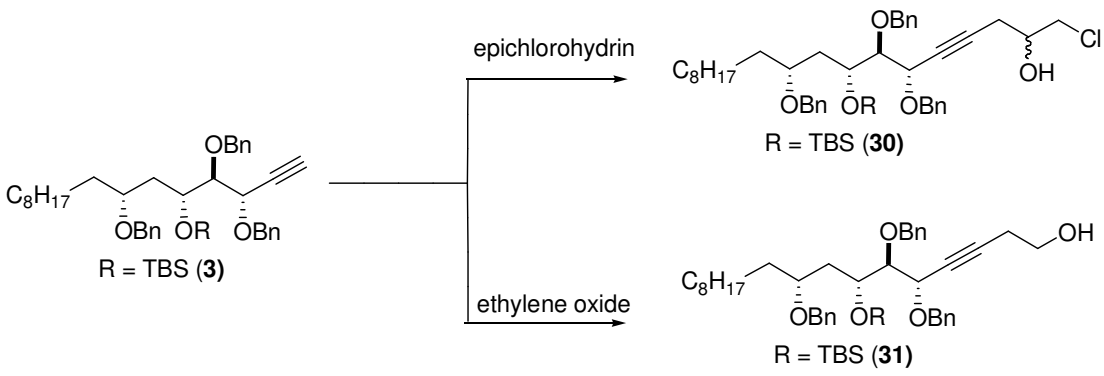
Having both the fragments in hand, now the stage is set for Yamaguchi's coupling of the alkynes **3** and **15** with the epoxide **16**, (**scheme 5**).

Scheme 5:



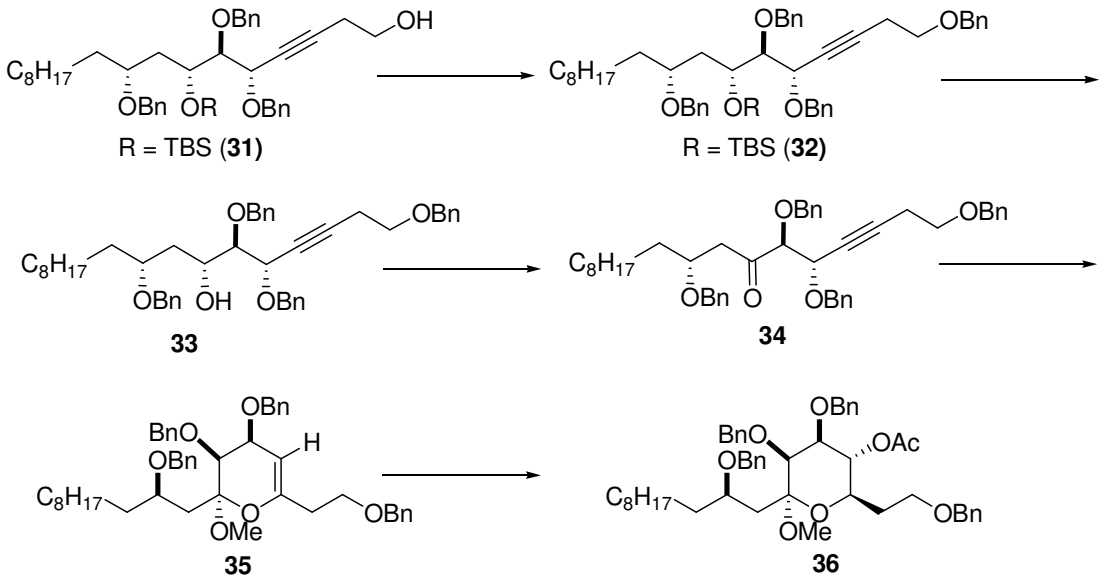
The products obtained were unmasked PMB derivative **14** and the rearranged epoxide **29**. The reaction of alkyne **3** with the epoxide **16**, under the indistinguishable reaction conditions as the previous reaction, also resulted into the rearranged epoxide **29** with the recovery of the alkyne **3**, which reveals the instability of epoxide **16** to the given reaction conditions.

Scheme 6:



To investigate this problem, we treated the alkyne **3** with couple of other epoxides (i.e. (±) epichlorohydrin and ethylene oxide) under the same set of reaction conditions as previous, furnished, not surprisingly, the required alcohols **30** and **31** respectively (**Scheme 6**), which reinforced our doubt of instability of the epoxide **16** under these reaction conditoins. After succeeding the reaction with ethylene oxide, we thought to synthesize the *cis*-juxtapositioned THP ring [C_{31}-C_{48} fragment (**28**)] of aflastatin A residing on Yamamoto's ω-alkynone cyclization (the pivotal transformation in the synthesis). Accordingly conversion of the primary alcohol of **31** to its benzyl ether **32** (**Scheme 7**) followed by exposure to TBAF in THF delivered the unmasked alcohol **33**. Oxidation of secondary alcohol of **33** with IBX in refluxing EtOAc furnished the ketone **34** which without purification treated with Pd $(OAc)_2$ in MeOH (to provoke the 6-*endo*-dig cyclization, Yamamoto's protocol) to deliver the suitably substituted dihydropyran derivative **35**.

Scheme 7:



After successfully performing the central transformation, next task in the synthetic endeavour was the regio and stereoselective hydroboration, for this we exposed dihydropyran **35** to BH_3:DMS in THF at 10 ^{0}C followed by oxidative workup with aq. NaOH and aq. H_2O_2 led to the secondary alcohol derivative with necessary stereochemistry. The crude alcohol was acetylated with Ac_2O and pyridine in DCM to furnish the final revised target **36** (C_{31}-C_{48} fragment). The compound **36** was substantiated for its structure by the correlative information from by ^{1}H NMR, ^{13}C NMR, DEPT, EI-MS, NOESY and IR.

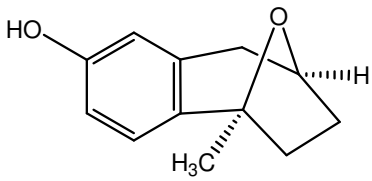
CHAPTER II:

Enantioselective total synthesis of (+)-Bruguierol A, Synthetic Studies Toward (+)- Bruguierol C and Pyridine Fused 8-oxa bicyclo[3.2.1]octane systems.

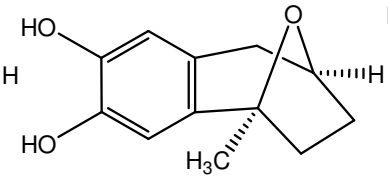
Five new aromatic compounds (**Figure 1**, **37-41**) were obtained by the phytochemical investigation of the stem of large leafed mangrove *Bruguiera gymnorrhiza* collected from the coast of Xiamen in the south china by Sattler and co-workers, of which bruguierols A-C (**37-39**), with the benzannulated 8-oxa bicyclo[3.2.1]octane structure, represent a new class of molecular skeleton in natural product chemistry. Among them bruguierol C showed moderate activity against Gram-positive and Gram-negative bacteria including mycobacteria and resistant strains (MICs 12.5 µg/ml).

Figure 1:

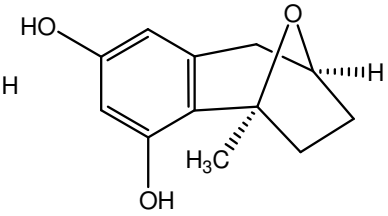
Aromatic compounds from *Bruguiera gymnorrhiza*



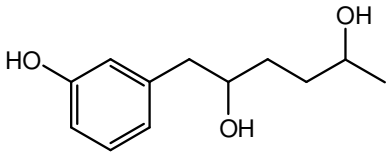
(+)-Bruguierol A (**37**)



(+)-Bruguierol B (**38**)



(+)-Bruguierol C (**39**)



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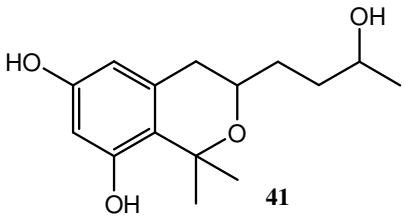

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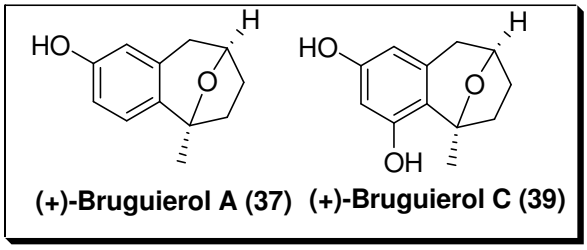
Intrigued by its molecular structure and moderate biological activity, we embarked on the synthesis of bruguierol A.

Section I :

Enantioselective Total synthesis of (+)-Bruguierol A and Synthetic Studies Toward (+)-Bruguierol C.

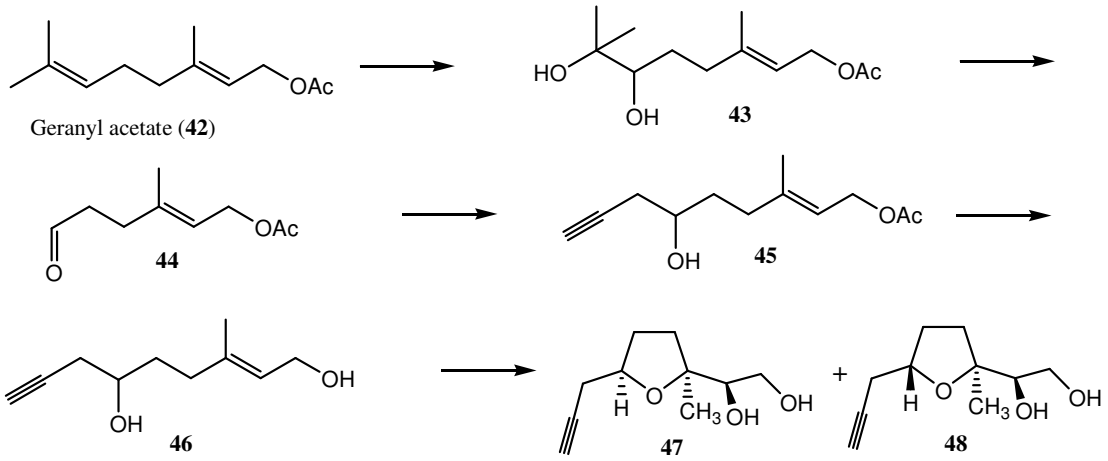


(+)-Bruguierol A (37) (+)-Bruguierol C (39)

Accordingly, our synthetic strategy hinges on [2+2+2] cross cyclotrimerization as a central transformation for bridged-bicycle construction, and Sharpless asymmetric epoxidation while envisaging the required chiral diyne precursor **50** to arise from the geranyl acetate through a series of manipulative transformations. Our synthesis began with regioselective dihydroxylation of electron rich double bond of

commercially available geranyl acetate **42** (**Scheme 1**) to racemic diol **43** followed by $NaIO_4$ assisted oxidative fission resulted into the aldehyde **44**. Propargylation of the aldehyde **44** under Barbier conditions (Zn/propargyl bromide, sat aq.NH_4Cl in THF) led to the homopropargyl alcohol **45**. Trans esterification of acetate functionality of **45** was accomplished with p-TSA in MeOH to afford the allylic alcohol **46**. The next endeavour is to perform the Sharpless Asymmetric Epoxidaton (SAE) of allylic alcohol **46** in advance of cyclotrimerization. Sharpless asymmetric epoxidation (SAE) of **46** was conducted at –20 °C in stoichiometric fashion in CH_2Cl_2 with t-butyl hydroperoxide as oxo donor

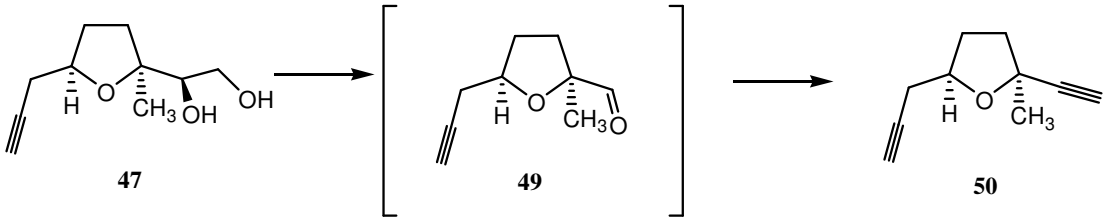
Scheme 1: -



and Ti(O*i*Pr)4– [D-(-)-DIPT] complex as chiral adjuvant to furnish a 1:1 seperable diastereomeric cis and trans furans **47** and **48** in 86% yield with 92% ee.

The diol functionality of requisite cis diastereomeric furan derivative **47** was oxidatively cleaved with $NaIO_4$ on silica to the somewhat volatile aldehyde **49** which was quickly subjected to Ohira-Bestmann reaction conditions [($CH_3COC(N_2)P(O)(OMe)_2$)/K_2CO_3/MeOH] to furnish the volatile dialkyne **50**,(with a typical terpene aroma) a key synthon for diverse cyclotrimerizations (**Scheme 2**).

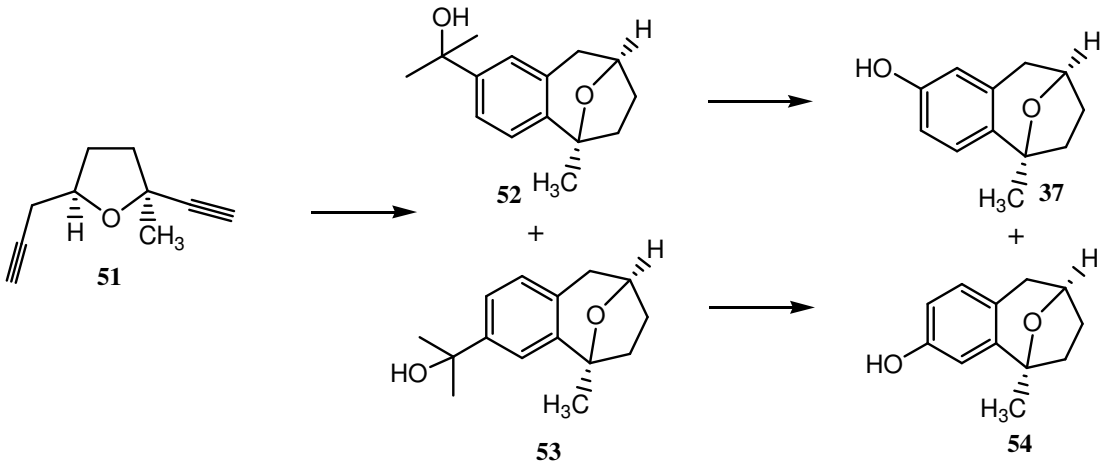
Scheme 2: -



47 **49** **50**

With the key dialkyne **50** in place, the penultimate step of our synthetic journey is cyclotrimerization of dialkyne **50** with dimethyl propargyl alcohol which was attempted with various metal catalysts in different solvents with a range of temperatures, but the reaction of dialkyne **50** with Wilkinson's catalyst (5 mol%) in refluxing EtOH (80 ^{0}C) was found to be the ideal reaction condition to deliver a 1:1 inseperable regiomeric alcohols **52** and **53** in 72% yield (**Scheme 3**).

Scheme 3: -



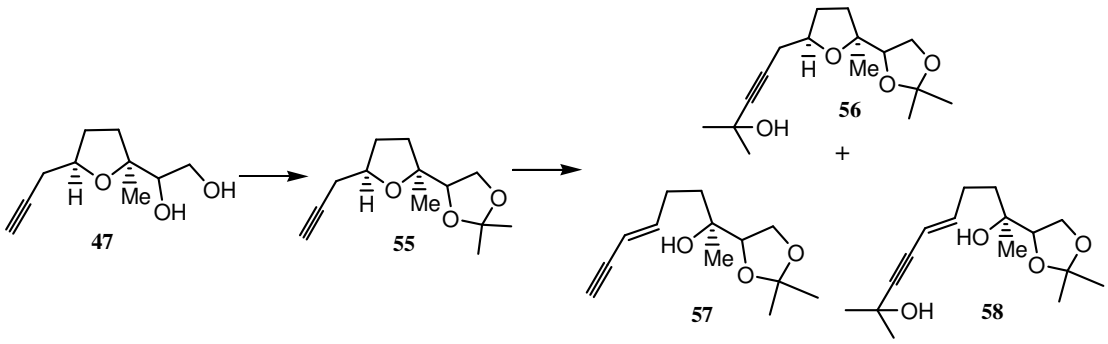
51 **52** **37** **53** **54**

The final step i.e. hydroperoxide rearrangement was accomplished by reacting regiomeric mixture of alcohols **52** and **53** with aq. H_2O_2 and a drop of conc. H_2SO_4 in benzene, at ambient temperatures to furnish (+)-bruguierol A (**37**) and its regiomer (**54**) in 84% yield. The synthetic compound is identical in all respects *viz.*, ^{1}H NMR,

^{13}C NMR, IR, EI, HRMS spectra, specific rotation and melting point with that of the natural sample.

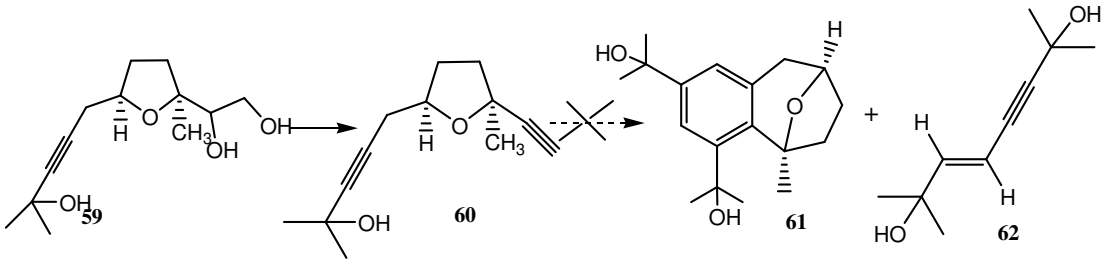
After accomplishing the synthesis of (+)-bruguierol A, next we paid our attention towards the synthesis of (+)-bruguierol C (**39**). Accordingly isopropylidenation of vicinal diol of **47** with 2, 2 DMP and cat p-TSA in DCM afforded the isopropylidene derivative **55**. Nucleophilic addition of lithium acetylide (generated from alkyne **55** and BuLi in THF) of **55** on acetone in THF at -20 ^{0}C furnished the required tertiary alcohol derivative **56** along with undesired THF ring opened products **57** and **58**. Required product **56** was obtained by performing the above said reaction at -78 ^{0}C under the same set of reaction conditions (**Scheme 4**).

Scheme 4: -



Transketalization of compound **56** in MeOH/p-TSA furnished the diol **59** which on oxidative C-C bond fission with $NaIO_4$/silica followed by one carbon homologative alkynylation with Ohira-Bestmann reagent delivered the dialkyne **60** (**Scheme 5**). Thus, this crucial transformation uneventfully framed the main skeleton with appropriate substitution and required stereochemistry for key cyclotrimerization. Thus

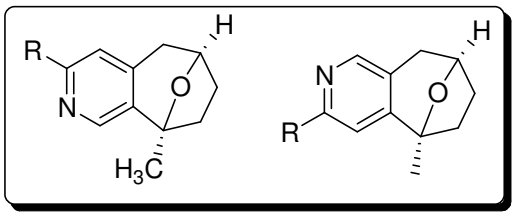
Scheme 5: -



cyclotrimerization of diyne **60** with dimethyl propargyl alcohol (DMPOH), with various catalysts in different solvents with a range of temperatures, could not deliver the required product **61** as the competitive self dimerization product **62** of DMPOH was isolated solely.

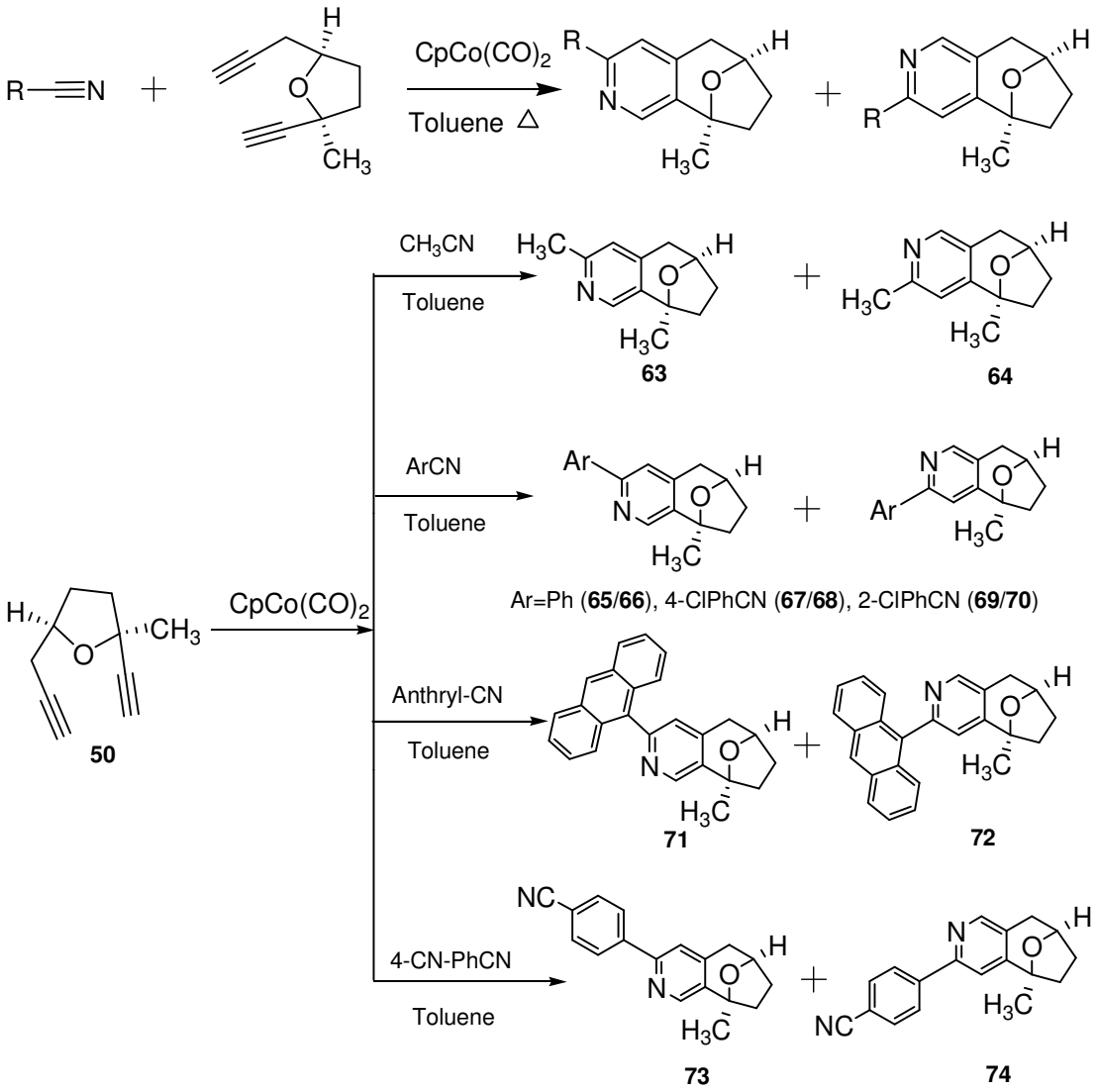
SECTION-II:

Synthesis of pyridine fused 8-oxa bicyclo[3.2.1]octane systems, A facile entry to the class of 8-oxa bicyclo[3.2.1]octane systems.



After being launched the viability of [2+2+2] alkyne cyclotrimerization for the synthesis of highly strained benzannulated 8-oxa bicyclo[3.2.1]octane systems and successfully applying to the total synthesis of natural bruguierol A, we later directed our attention to synthesize different pyridine fused bicyclic systems. The dialkyne **50** was expected to bring about the pyridines with different nitriles under the cyclotrimirization conditions. For that reason, dialkyne **53** was treated with different nitriles using 5 mol% $CpCo(CO)_2$ in toluene at 80 ^{0}C to afford pyridine fused 8-oxa bicyclo[3.2.1]octane systems (**63** to **74**) in good yields (**Scheme 6**).

Scheme 6:



Chapter III: -

Double Suzuki coupling for the syhthesis of 10 diarylmethylidene 1, 8-dichloro anthraquinones

Biochemists have been fascinated towards the anthraquinone substituted ligands as they inhibit Tau aggregation, dissolved Alzheimer's paired helical

fragments and display antimalarial, antifungal and anti leukemic properties in vitro and in cells. These have been used as electrochemically switched transport across model membranes. Derivatives of anthraquinones such as π-extended tetrathia fulvalenes (TTF's) are important building blocks for supra molecular and organic material chemistry. Substituted anthraquinones have been used for the mechanistic and rearrangement studies.

Rooted on the above said properties, we designed a basic skeleton, as depicted in **Figure 1**, to study the biological activity.

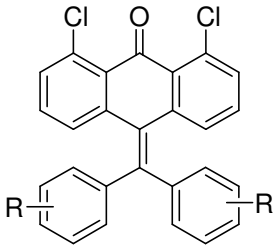
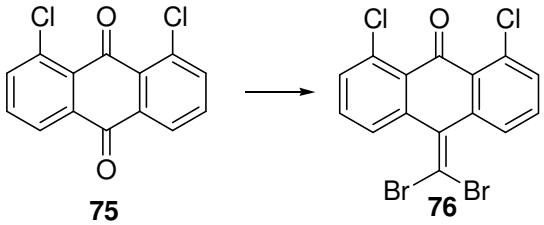


Figure 1

Because of the variable functionalities on the aromatic ring, the present approach, relied on double Suzuki coupling, leaves ample room for library synthesis.

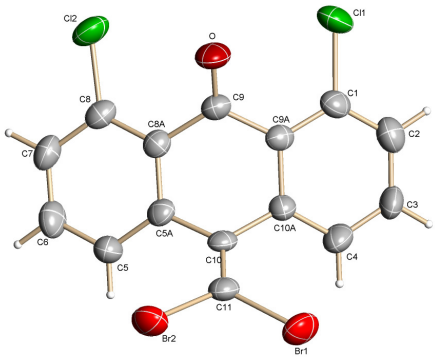
Scheme 1:



75 **76**

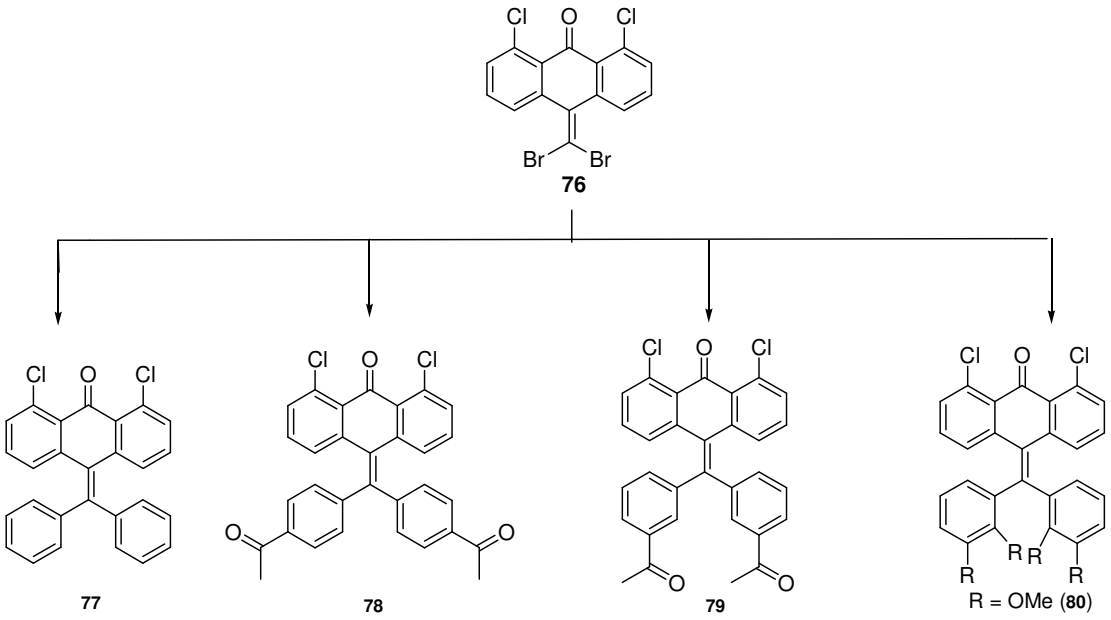
Accordingly, our library synthesis began with Corey-Fuchs dibromo-olefination (TPP/CBr_4 in DCM) of 1, 8 dichloro anthraquinone **75** to afford the dibromo derivative (**Scheme 1**) **76** whose structure was unambiguously determined by its single crystal x-ray structure.

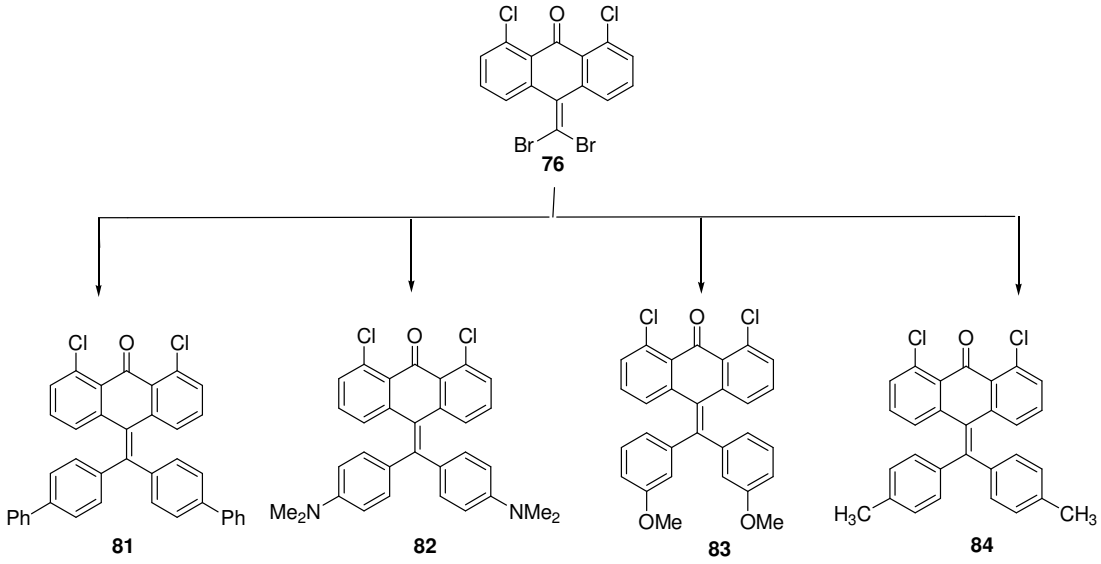
ORTEP diagram of dibromo compound



Pd (II) mediated standard Suzuki coupling of the dibromo olefin **76** with diverse boronic acids furnished a library of 10-diarylmethylidene-1, 8-dichloro anthraquinones (**77 to 84**) as depicted in **Scheme 2,** in good to excellent yields.

Scheme 2:





All the compounds are purified by column chromatography and the spectral data of all the compounds are in agreement with the proposed structure. A library of 8 compounds (**77 to 84**) were synthesized and submitted for biological screening.

CHAPTER – I

Synthetic studies toward C_{27}-C_{48} fragment of Aflastatin A

Introduction:

Introduction to mycotoxins: -

According to FAO estimates, 25% of the world crops are affected by mycotoxins each year.[1] Mycotoxins (Greek myco = fungus, toxin = poison) are toxic, secondary metabolites of low molecular weight produced by naturally occurring fungi (Chu, 1992).[2] Aflatoxins, trichothecenes, zearalenone, fumonisin, ochratoxins, slaframine etc. are diverse mycotoxins that affect the world crops, among which aflatoxins are probably the best known and most intensively researched mycotoxins in the world because they clearly have a potent carcinogenic effect on laboratory rats and their acute poisonous effects on humans.

Aflatoxins: - Origin, discovery and definition

In the 1960 more than 100,000 young turkeys on poultry farms in England died in the course of a few months from an apparently new disease that was termed **"Turkey X disease".**[3] It was soon found that the difficulty was not limited to turkeys. Ducklings and young pheasants were also affected and heavy mortality was experienced. A keen survey of the early outbreaks showed that they were all associated with feeds, namely **Brazilian peanut meal**.[4] An intensive investigation of the suspect peanut meal was undertaken and it was quickly found that this peanut meal was highly toxic to poultry and ducklings with symptoms typical of Turkey X disease. Speculations made during 1960 regarding the nature of the toxin suggested that it might be of fungal origin. In fact, the toxin-producing fungus was identified as *Asprgillus flavus* (1961) and the toxin was given the name Aflatoxin by virtue of its origin (*A.flavis*--> Afla).

Aflatoxins are potent toxic, carcinogenic, mutagenic, immunosuppressive agents, produced as secondary metabolites by the fungus *Aspergillus flavus* and *A. parasiticus* on variety of food products.[5] The fungi that produce aflatoxin grow on crops such as peanuts (especially), wheat, corn, beans and rice. Aflatoxin is a problem particularly in undeveloped and developing countries. Aflatoxin is a naturally occurring mycotoxin produced by two types of mold: *Aspergillus flavus* and *Aspergillus parasiticus*. *Aspergillus flavus* is common and widespread in nature and is most often found when certain grains are grown under

stressful conditions such as drought. The mold occurs in soil, decaying vegetation, hay, and grains undergoing microbiological deterioration and invades all types of organic substrates whenever and wherever the conditions are favourable for its growth. Favourable conditions include high moisture content and high temperature. At least 13 different types of aflatoxins are produced in nature with aflatoxin B1 considered as the most toxic.[7]

Physical and chemical properties of aflatoxins: -

Among 18 different types of aflatoxins identified, major members are aflatoxin B1, B2, G1 and G2. Aflatoxin B1 (AFB1) is normally predominant in amount in cultures as well as in food products.[6] Pure AFB1 is pale-white to yellow crystalline and odourless solid. Aflatoxins are soluble in methanol, chloroform, acetone, acetonitrile. *A. flavus* typically produces AFB1 and AFB2, where as *A. parasiticus* produce AFG1 and AFG2 as well as AFB1 and AFB2. Four other aflatoxins M1, M2, B2A, and G2A which may be produced in minor amounts were subsequently isolated from cultures of *A. flavus* and *A. parasiticus*. A number of closely related compounds namely aflatoxin GM1, parasiticol and aflatoxicol are also produced by *A. flavus*. Aflatoxin M1and M2 are major metabolites of aflatoxin B1 and B2 respectively, found in milk of animals that have consumed feed contaminated with aflatoxins.

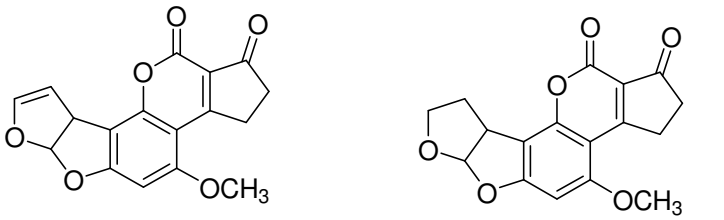


Figure 1: Structures of aflatoxins **B1, B2, G1** and **G2**

Aflatoxins are normally refers to the group of difuranocoumarins and classified into two broad groups according to their chemical structure (**Figure 1**); the difurocoumarocyclopentenone series (AFB1, AFB2, AFB2A, AFM1, AFM2, AFM2A and aflatoxicol) and the difurocoumarolactone series (AFG1, AFG2, AFG2A, AFGM1, AFGM2, AFGM2A and AFB3). The aflatoxins display potency of toxicity, carcinogenicity and mutagenicity in the order of AFB1 > AFG1 > AFB2 > AFG2 as illustrated by their LD_{50} values for day-old ducklings. Structurally the dihydrofuran moiety, containing double bond, and the substituents linked to the coumarin moiety are of importance in producing biological effects. The aflatoxins fluoresce strongly in ultraviolet light (ca. 365 nm); B1 and B2 produce a blue fluorescence where as G1 and G2 produce green fluorescence.

Biochemical mechanism of action of Aflatoxins: -

The various biological effects of mycotoxins, chiefly aflatoxins, are attributed largely to the alteration of basic metabolic processes.[8] Acutely affected processes are

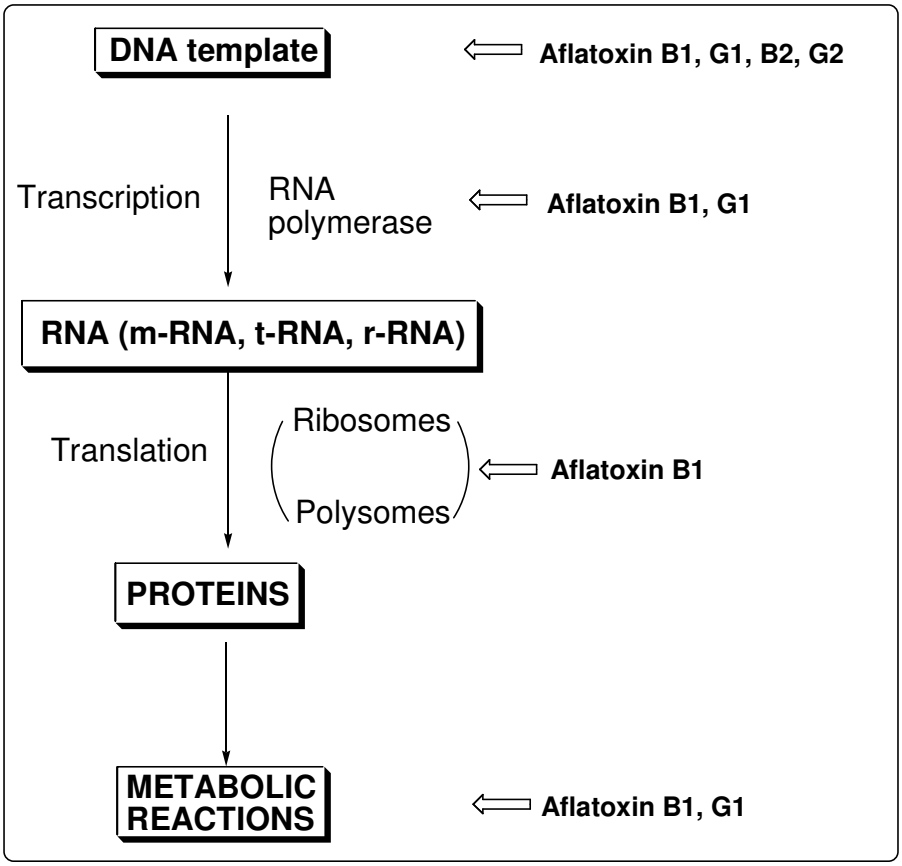


Figure 2: Aflatoxins affecting major sites in RNA and protein synthesis.

carbohydrate metabolism, mitochondrial functions, lipid and steroid metabolism and the biosynthesis of proteins and nucleic acids. The primary mechanism of action of an aflatoxin (**Figure 2**) may be to modify the DNA template, to impair the transcription process, or inhibit the translation process in protein synthesis. In certain cases the aflatoxin reacts directly with the enzyme protein or coenzyme. These entire primary events may lead to secondary effects in terms of modified enzyme activities and, hence, changes in metabolic activity and regulation. By understanding the mechanism of action of the aflatoxins on these processes it may ultimately be possible to develop methods for the control and prevention of aflatoxin problems. There are several structural similarities between aflatoxin B1 and sterigmatocystin, e.g. the dimensions and absolute configuration of the bis-dihydrofuran moiety are very similar. This suggests a metabolic activation on the same site, the C_2–C_3 double bond, as in aflatoxin B1. The mycotoxins may therefore operate by a common biochemical mechanism. Thus inhibition of DNA and RNA synthesis should be one of the primary modes of sterigmatocystin action.

a) Effects on DNA level: -

Two types of interactions have been shown to occur between aflatoxins and nucleic acids.[9] One is a non covalent, weak and reversal binding and the other is an irreversible covalent binding requiring mammalian metabolizing systems (**Figure 3**).[10] Crucial for the covalent binding is the C_2-C_3 unsaturated bond, which means that aflatoxins B1 and G1 are more active than B2 and G2.

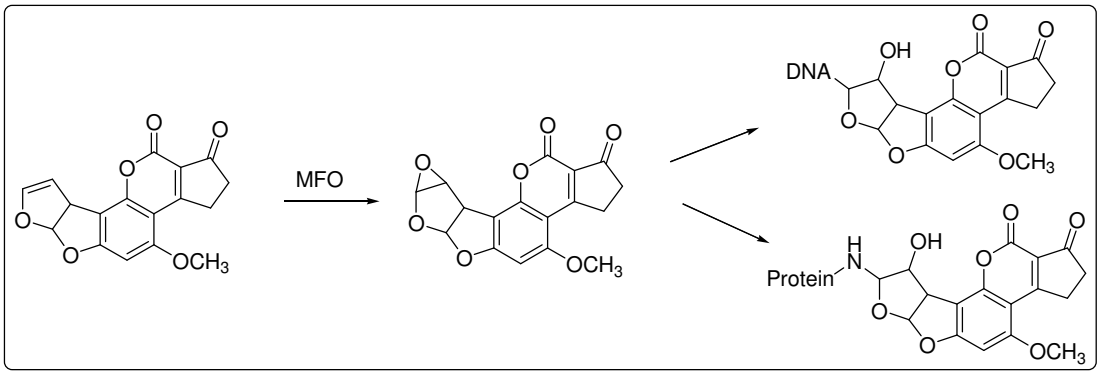


Figure 3: Metabolic activation of Aflatoxin B1 (and G1) by Mixed Function Oxidase (MFO)

Aflatoxins react with nucleic acids after first being converted to an epoxide by a cytochrome P450.[11] The epoxide reacts irreversibly with guanine in DNA and RNA

leading to depurination. The primary effect is to inhibit protein and DNA synthesis in the most active tissues, including the liver, the intestines, and the bone marrow. A strong correlation can be found between carcinogenicity, mutagenicity and the extent of covalent DNA binding amongst aflatoxins and their metabolites and precursors . Guanine in the DNA is the principal target for the attack of activated aflatoxins. The formation of mutations is made possible by the covalent binding to DNA which may lead to cancer. [12] The damage they do to DNA can be mutagenic, typically a GC to AT mutation, and also carcinogenic with liver cancer a common long-term effect of exposure. They have been listed as human carcinogens since 1988. One prominent effect of aflatoxin B administration to an animal is the decrease in RNA content and in RNA polymerase in the nuclei of the liver. Aflatoxin B1 was about three times as active as G, whereas had no effect at all, which led to the conclusion that the 2, 3 unsaturated double bond in the dihydrofuran moiety was important for activity.

Aflatoxin B is another mycotoxin that suppresses protein synthesis, whereas B2 and G2 '5 have not been found to inhibit in vivo synthesis.[13, 14] Polysome disaggregation may be the mechanism by which aflatoxin B1 disrupts protein synthesis. The simultaneously formed monosomes lack RNA and peptidyl t-RNA and contain only low levels of t-RNA.

Inhibition of Key enzymes in metabolic processes by Aflatoxins: -

Major biochemical effects of mycotoxins involve the modification of normal metabolic and other vital processes. The mode of their action appears to be based primarily on their ability to interact with macromolecules, sub cellular-organelles and organs. Many of these mycotoxin induced effects may be derived from and secondary to their disruption of nucleic acid or protein synthesis.

Carbohydrate metabolism: -

The effect of mycotoxins on carbohydrate metabolism (**Figure 4**) is generally discerned as reduced hepatic glycogen and increased blood glucose levels. Mycotoxins that can cause these effects are aflatoxins, ochratoxin A, rubratoxin B, cyclochlorotine and citreoviridin. Aflatoxin B, cyclochlorotine and citreoviridin all decrease the liver glycogen level, by inhibiting the biosynthetic enzymes such as glycogen synthetase and by increasing the activity of enzymes metabolizing glycogen

precursors, e.g. the NADP reducing enzyme glucose 6 phosphate dehydrogenase.[15] Aflatoxin B1 and cyclochlorotine inhibit glycogen synthesis by decreasing glycogen synthetase and transglycosylase activities, enzymes which catalyse elongation and

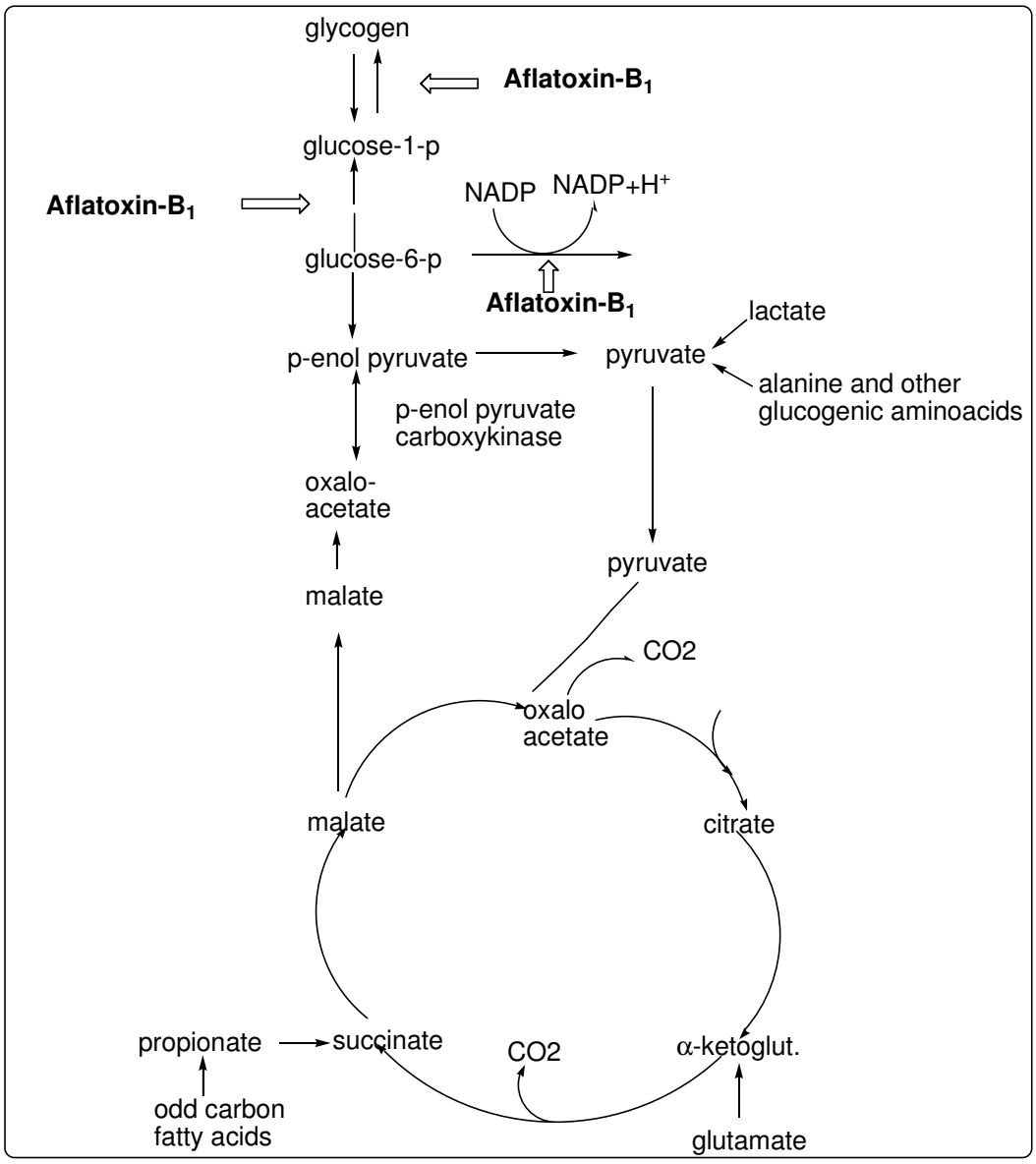


Figure 4: Sites where aflatoxins interfere with carbohydrate metabolism

rearrangement of the glycogen molecule. Aflatoxin B1 decreases the activity of phosphoglucomutase which reversibly converts glucose 6-phosphate into glucose 1-phosphate. Furthermore, aflatoxin B1 and cyclochlorotine reduce hepatic glycogen by accelerating glucose 6-phosphate oxidation.[16]

Effect on oxidative phosphorylation and other mitochondrial functions: -

Not unexpectedly, aflatoxins also fall in this category. Aflatoxin B1 inhibits electron transport in mitochondria both ADP-coupled and DNP-uncoupled.[17] Since the inhibition could be reversed by the electron acceptor TMPD, the site of inhibition must be situated between cytochrome b and c (**Figure 5).** Pai et al.[18] showed that aflatoxin M1 and B1 could act as uncouplers of oxidative phosphorylation. Obidoa and Siddiqui[19]

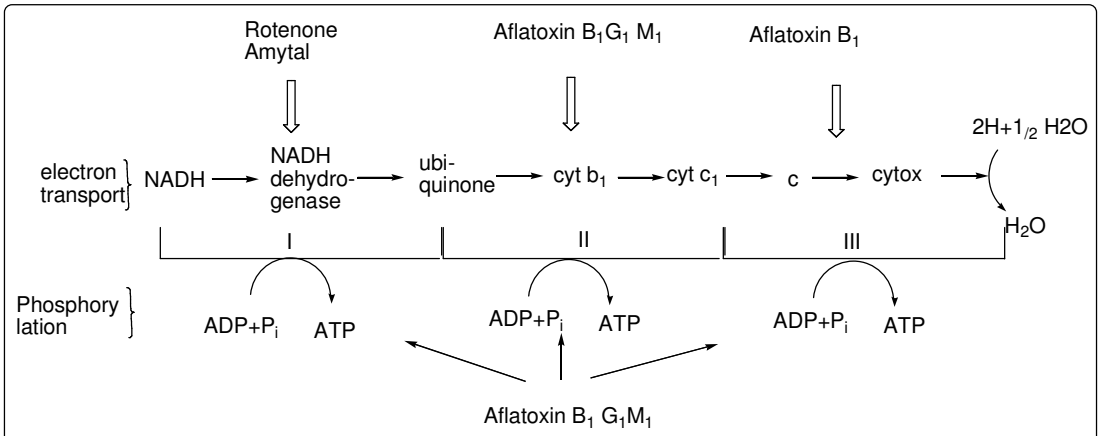


Figure 5: Interaction of aflatoxins with oxidative phosphorylation

showed that aflatoxin B is an inhibitor of electron transport at the cytochrome oxidase level.

Aflatoxins and Human Health: -

Humans are exposed to aflatoxins by consuming food contaminated with products of fungal growth. Such exposure is difficult to avoid because fungal growth in food is not easy to prevent. Even though heavily contaminated food supplies are not permitted in the market place in developed countries, concern still remains for the possible adverse effects resulting from long-term exposure to low levels of aflatoxins in the food supply. Evidence of acute aflatoxicosis in humans has been reported from many parts of the world, namely the Third World Countries, like Taiwan, Ouganda, India, and many others. The syndrome is characterized by vomiting, abdominal pain, pulmonary edema, convulsions, coma, and death with cerebral edema and fatty involvement of the liver, kidneys, and heart. Conditions increasing the likelihood of acute aflatoxicosis in humans include limited availability of food, environmental conditions

that favour fungal development in crops and commodities, and lack of regulatory systems for aflatoxin monitoring and control. Because aflatoxins, especially aflatoxin B1, are potent carcinogens in some animals, there is interest in the effects of long-term exposure to low levels of these important mycotoxins on humans. **In 1988, the IARC placed aflatoxin B1 on the list of human carcinogens.** This is supported by a number of epidemiological studies done in Asia and Africa that have demonstrated a **positive association between dietary aflatoxins and Liver Cell Cancer (LCC).** Additionally, the expression of aflatoxin-related diseases in humans may be influenced by factors such as age, sex, nutritional status, and/or concurrent exposure to other causative agents such as viral hepatitis (HBV) or parasite infestation.

Inhibitors of aflatoxins: -

Flavones, coumarins and anthraquinones have a significant influence on inhibition of aflatoxin B1 biotransformation to aflatoxin B1-8, 9-epoxide by cytochrome P450 enzymes of mouse liver.[20] Curcuminoids and structural analogues are potent inhibitors of aflatoxicol formation by chicken liver reductases.[21] Their α-diketone moieties linking two phenyl groups are essential for this inhibitory effect. These findings provide a basis for further study on relationships between naturally occurring compounds in the diet and reduced risk of aflatoxin-induced carcinogenesis in vivo. Dillapiol and its related essential oils like apiol and myristicin were found to inhibit the production of aflatoxin G_1 by *A. Parasiticus* without inhibiting that of aflatoxin B_1 or fungal growth. Hydrolysable tannins, present in a physical and chemical defensive tissue surrounding the edible portion of walnuts, in eliminating formation of aflatoxins. Dioctatin A (DotA), a metabolite of *Streptomyces* was found to inhibit aflatoxin production strongly by *Aspergillus parasiticus*, with an IC_{50} value of 4.0 μM.[22]

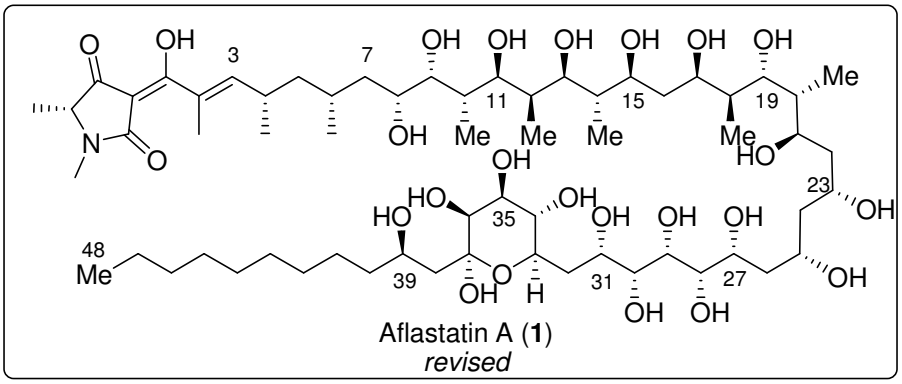
Aflastatin-A: A novel inhibitor of aflatoxin production[23]

Although there are diverse aflatoxin inhibitors, still there is a need for novel inhibitors at minimum concentration levels without significantly affecting the growth of the parasite. Aflastatin A (**1**), isolated by Sakuda and co-workers from the mycelia

of *Streptomyces sp*. MRI 142, was found to fit into this category.[24] Based on its inhibitory activity against aflatoxins and our constant interest in the total synthesis of complex polyol natural products,[25] aflastatin A (**1**) was selected as a specific target.

Determination of Absolute configuration of aflastatin A: -

Aflastatin A, a novel inhibitor of aflatoxin production of *Aspergillus parasiticus,* was isolated from a mycelial MeOH extract of the MRI 142 strains as a white powder whose molecular formula is $C_{62}H_{115}NO_{24}$. It has a novel tetramic acid derivative with a long highly oxygenated alkyl side chain and a pentasubstituted tetrahydropyran ring. The absolute configurations of 29 chiral centers of **1** were chemically elucidated by Sakuda et al. (**Figure 6).**[26]



Since crystals of **1** or its derivatives have not been obtained for X-ray analysis, Sakuda *et al* determined its absolute structure chemically (**Figure 6**). Three known fragments (**43-45**) along with two other fragments (**46-47**) were used for determination of the absolute configuration of **1.** By determining the absolute configurations of fragments **44-46**, absolute configuration at C_5, C_4 and C_6, C_{33} and C_{39} of **1** should be clarified. Since the fragment **43** is acyclic and all the chiral centers are present in a 1, 2 or 1, 3 methine systems, the relative configuration was determined by *J*-based configurational analysis which confirmed the relative configuration from C_{10} to C_{25} of **1**. The remaining relative configurations from C_6 to C_{10} and from C_{25} to C_{33} of **1** were determined by J-based method of their counterparts in **47**. By connecting the absolute configurations at C_6 and C_{33} of **1** with the relative configurations from C_6 to C_{33} and from C_{33} to C_{37} of **1**, the complete absolute configuration of **1** was determined. After establishment of the absolute structure,

many synthetic chemists were attracted towards its synthesis, although no total synthesis is reported till date.

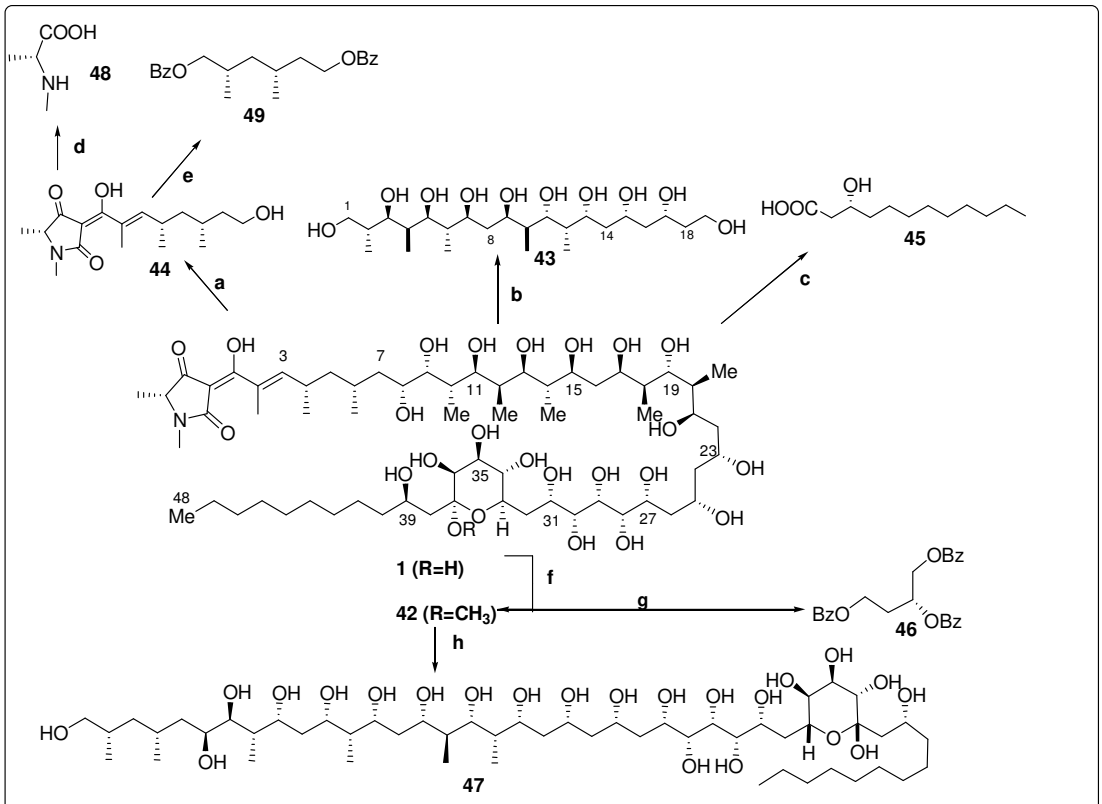


Figure 6: Procedures for the degradation of aflastatin A (1). (a) $NaIO_4$; $NaBH_4$. (b) $NaIO_4$; $NaBH_4$; Ac_2O; Py; NaOMe (c) $NaIO_4$. (d) $NaIO_4$; 3N HCl. (e) O_3; Me_2S; $LiAlH_4$; BzCN; tri-n-butyl amine. (f) 5% HCl-MeOH. (g) $NaIO_4$; $NaBH_4$; 3 N HCl; BzCl, pyridine. (h) O_3; $NaBH_4$; Ac_2O; Py; NaOMe; Dowex-50W (H^+).

Stereoselective Synthesis of C_9-C_{27} Polyol fragment of (-)-Aflastatin A

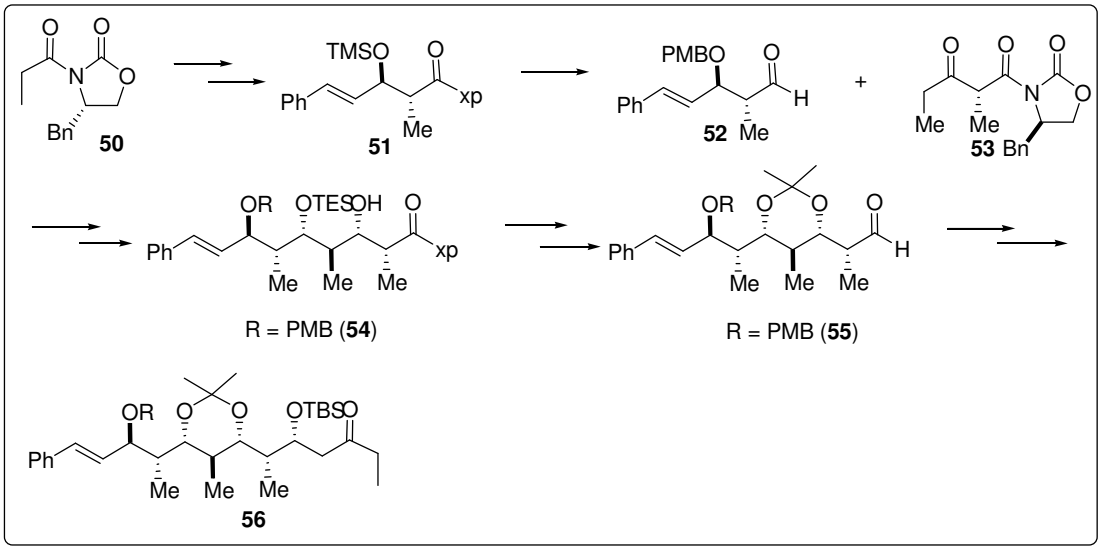
Evans *et al*. reported the synthesis of C_9-C_{27} fragment of aflastatin A, which relied on stereoselective aldol processes.[27] The synthesis include an *anti* aldol union of the (E) boron enolate **56** (C_8-C_{18} fragment) with the complex aldehyde **64** (C_{19}-C_{28} fragment).

Synthesis of C_8-C_{18} fragment of Aflastatin A:

The synthesis of C_8-C_{18} fragment was initiated with our recently reported $MgCl_2$-catalyzed direct aldol addition to provide the known *anti*-aldol adduct which was converted into the Weinreb amide **51**, protected as its PMB ether, and reduced to afford the C_8-C_{11} aldehyde **52 (Scheme 1)**. The C_{12}-C_{15} Carbon skeleton was introduced by a boron-mediated *anti*-aldol reaction between **52** and β-ketoimide **53**. The high selectivity observed in this reaction (>95:5 dr) was anticipated as a result of the matched double stereodifferentiating nature of the aldehyde and ketone

components. The hydroxy ketone was protected as its triethylsilyl (TES) ether followed by a chelation-controlled reduction mediated by $Zn(BH_4)_2$ to afford **54** as a single diastereomer with a 1,3-*syn* relationship between C_{11}-C_{13}. The high selectivity for this reduction can be rationalized through a bidentate chelate formed between C_{13} and C_{15} carbonyls, with the C_{14} methyl stereocenter controlling the subsequent hydride delivery. Protecting group interconversion, followed by $LiBH_4$ reduction and Dess-Martin oxidation, provided C_8-C_{15} aldehyde **55**. A methyl ketone aldol reaction,

Scheme 1: Synthesis of C_8-C_{18} fragment

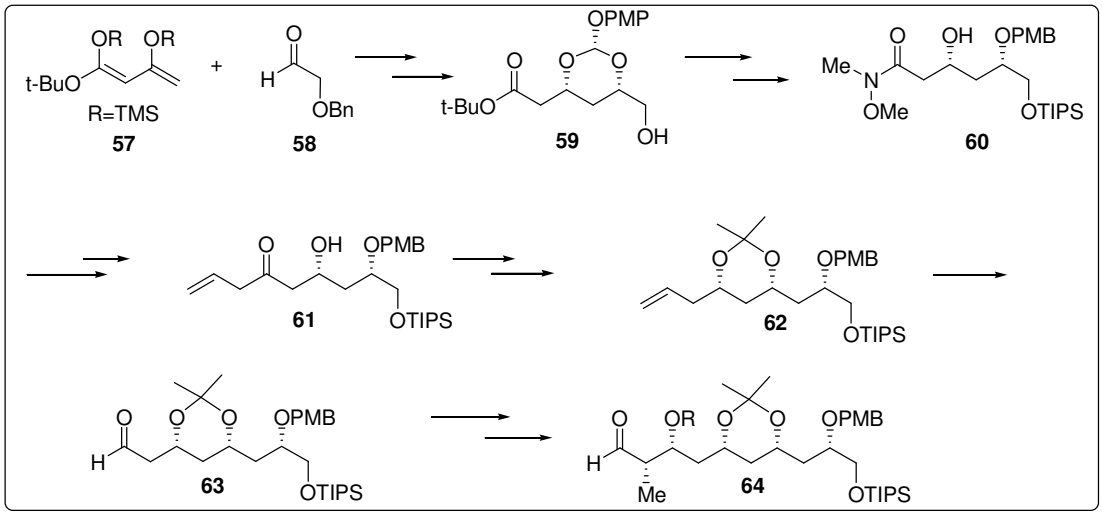


mediated by (-)-diisopinocampheylboron chloride (DIP-Cl), between **55** and 2-butanone furnished the desired aldol adduct with modest diastereoselectivity (4:1 favoring the Felkin product). Silylation of the aldol adduct afforded the C_8-C_{18} ethyl ketone fragment **56**.

Synthesis of the C_{19}-C_{28} fragment began with an enantioselective [Cu(S,S)-PhPybox)]$(SbF_6)_2$-catalyzed aldol union of **57** and **58** followed by *syn*-selective reduction to give the previously reported diol. Treatment of diol with anisaldehyde dimethylacetal afforded the PMP acetal, which underwent selective deprotection of the benzyl ether with Raney nickel to give hydroxy ester **59**. Silylation followed by transamidation provided the Weinreb amide **60**, which was an appropriate substrate for a carbonyl-directed acetal cleavage using $MgBr_2$ and Bu_3SnH. Allylation, Et_2BOMe-mediated *syn*-reduction, and acid-catalyzed acetonideformation furnished the protected all-*syn* triol derivative **62**. Ozonolysis

provided aldehyde **63**, which underwent an auxiliary controlled *syn*-aldol reaction with oxazolidinone **50** to deliver the corresponding aldol adduct as a single diastereomer. Cleavage of the imide auxiliary was achieved under standard conditions to provide Weinreb amide. Silylation with TBSOTf and 2,6-lutidine followed by DIBAL

Scheme 2: Synthesis of C_{19}-C_{28} fragment

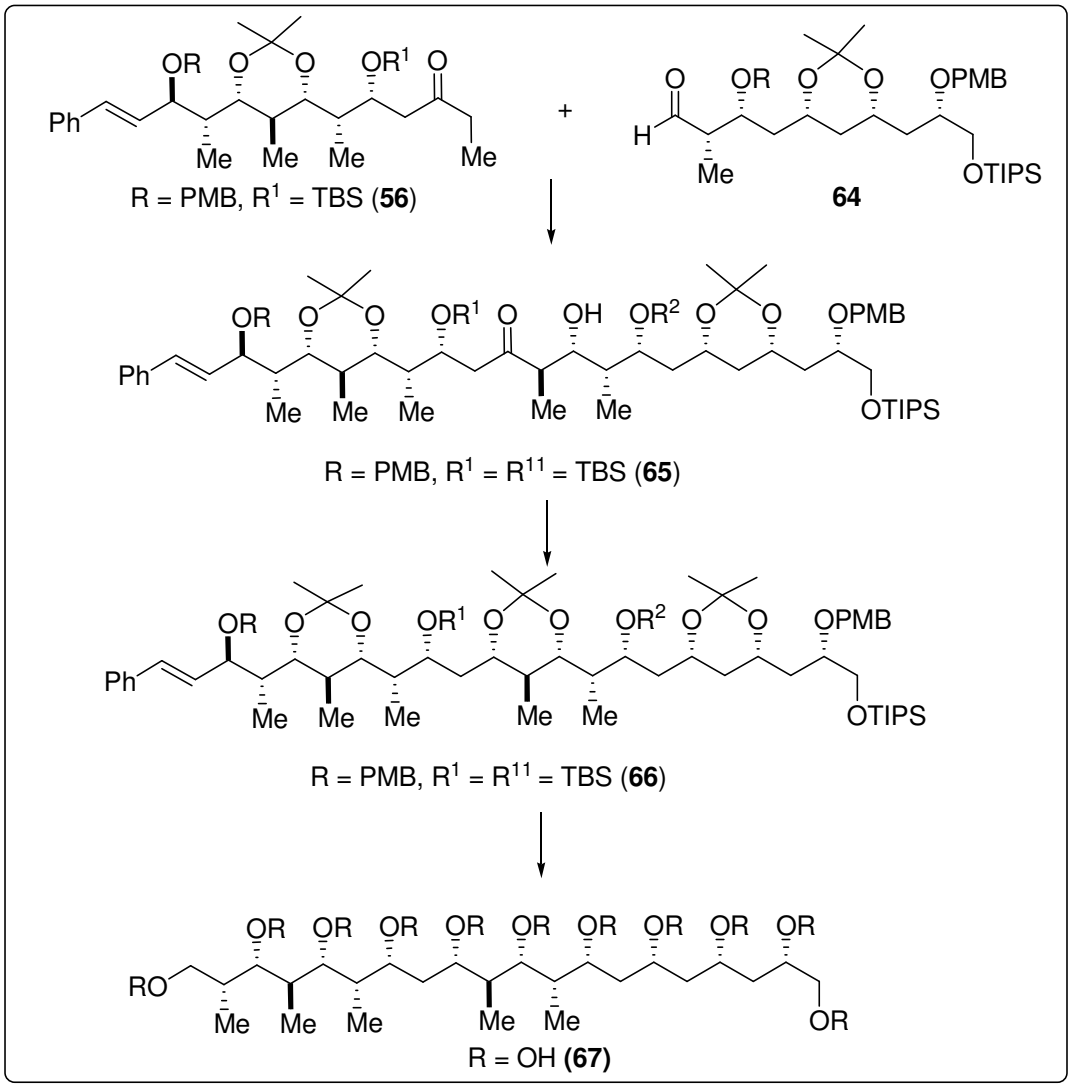


completed the synthesis of aldehyde **64** (**Scheme 2**)**.**

Synthesis of C_9-C_{27} polyol of Aflastatin A

Boron enolate mediated anti aldol union of ketone fragment **56** with the aldehyde fragment **64** resulted the required product **65** in moderate selectivity (4:1) (**Scheme 3**). $Zn(BH_4)_2$- mediated reduction of the major adduct afforded the C_{17}-C_{19} *syn*-diol, which was protected as its acetonide **66**. DDQ assisted deprotection resulted to over oxidised enone which on ozonolysis of the styrenyl double bond followed by in situ $NaBH_4$ reduction gave a triol intermediate. Selective deprotection of the primary TIPS ether with TBAF to provide the tetrol intermediate. $NaIO_4$- mediated diol cleavage of both termini followed by in situ $NaBH_4$ reduction furnished diol. Treatment of **66** with 80% aqueous acetic acid at room temperature afforded the C_9-C_{27} degradation polyol **67** in quantitative yield.

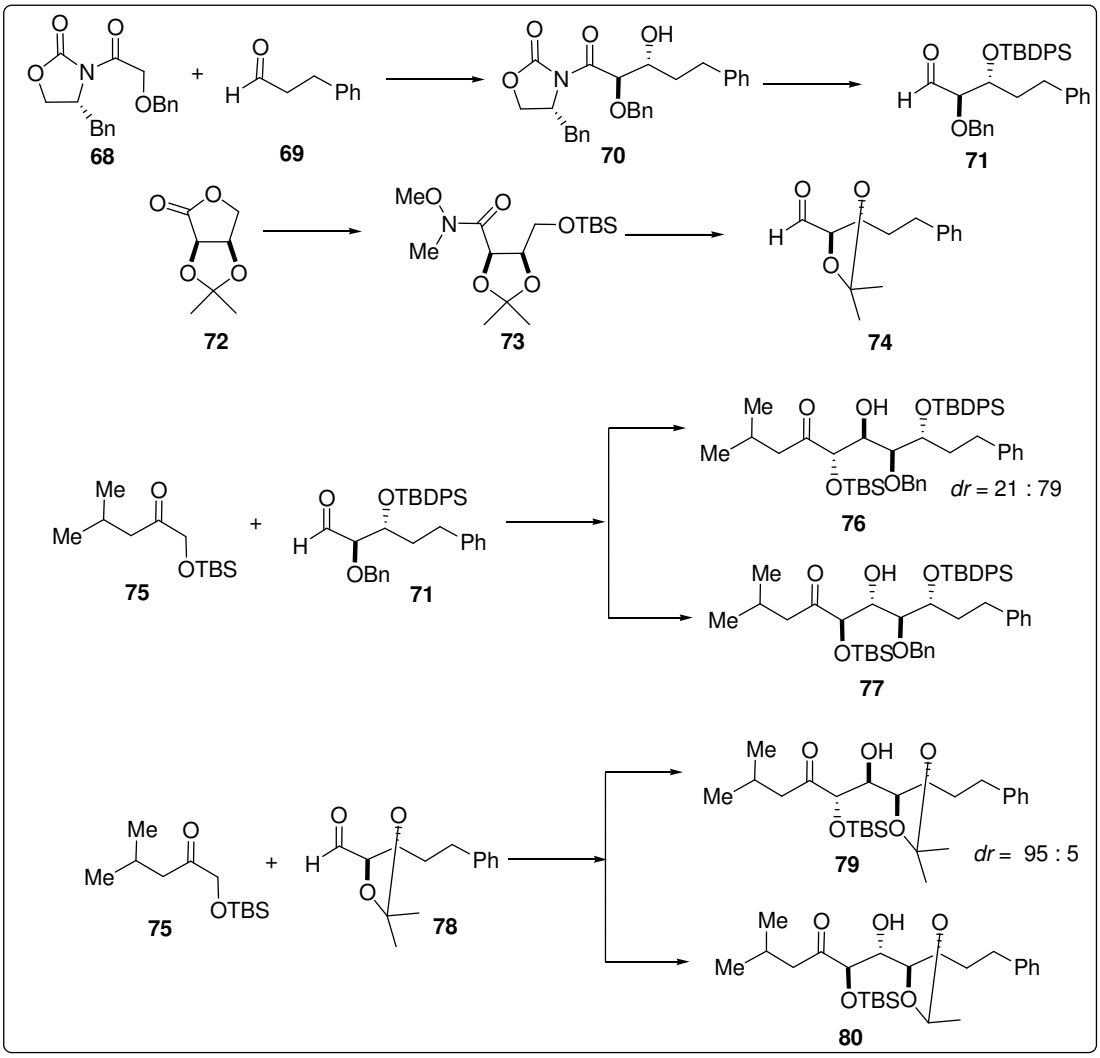
Scheme 3:



Synthesis of C_{33}-C_{36} region of Aflastatin A

Evans *et al*. reported the synthesis of C_{33}-C_{36} region based on the boron enolate mediated aldol reactions.[28] $Sn(OTf)_2$ mediated anti aldol reaction of oxazolidinone **68** and dihydrocinnamaldehyde **69** led to the anti product **70** in good diastereoselectivities. Cleavage of the imide auxiliary was achieved under standard conditions to provide Weinreb amide. Silylation with TBDPSOTf and 2, 6-lutidine followed by DIBAL reduction delivered the aldehyde **71.** The other acetonide protected aldehyde **74** was started from commercially available 2,3-O-isopropylidene-D-erythronolactone **72** which was converted to the weinreb amide followed by TBS protection and DIBAL reduction furnished the aldehyde **74**.

Scheme 4:

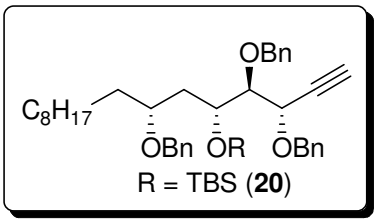


Ketone **75** was selected as an appropriate model to address the enolization. Thus treatment of boron enolate of ketone with the aldehyde **71** resulted to the required anti-Felkin product as the major product **76** (*dr* 79:21) along with unrequired Felkin product **77**. Changing the protecting group of hydroxyls to acetonide **78** resulted into the exclusive formation of *anti-syn-anti* stereoarray found in C_{33}-C_{36} region of aflastatin A (anti-Felkin product **79** as a sole product, *dr* 95:5).

CHAPTER-I

Section-I

Chiron approach for the synthesis of alkyne fragment



Present work

Present work:

Aflastatin A was isolated by Sakuda and co-workers from the mycelia of *Streptomyces* sp. MRI 142.[24] Aflastatin A belongs to the class of polyol natural products and contains a tetramic acid derivative with a long alkyl side chain which is highly oxygenated and a tetrahydropyran ring. Its strong inhibitory activity against aflatoxin production without significantly affecting the growth of *A. parasiticus* prompted vigorous structure elucidation efforts.[26] Sakuda and co-workers proposed the relative and absolute structure of aflastatin A (**Figure 1**) with the help of chemical degradation and extensive NMR studies.[29]

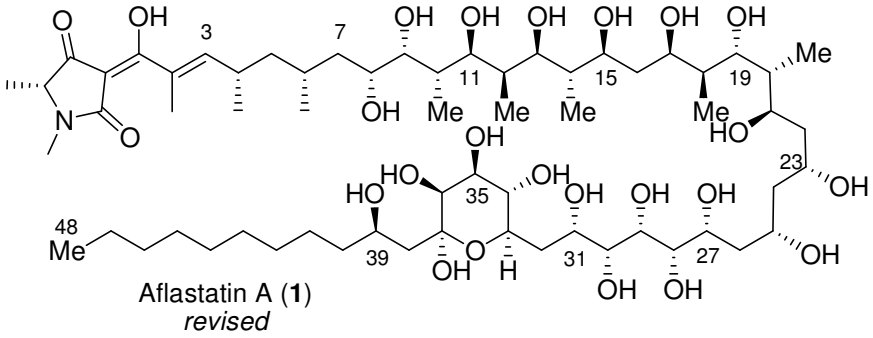


Figure 1: - Structure of aflastatin A (revised).

The assigned absolute stereochemistry of the degradation product C_9–C_{27} polyol has been cross checked by chemical synthesis and correlation studies by Evans *et al.*[27] The absolute stereochemistry of the tetrahydropyran ring moiety of aflastatin A was assigned based on the relative stereochemistry around the ring and the absolute configuration at C_{33}. Initially proposed configurations at the diol (C_8 and C_9) and pentanol (C_{25}–C_{29}) moieties have been recently cross checked by partial chemical synthesis and NMR correlations in light of the remarks from Kishi's group[29] and revised the absolute configuration of Aflastatin A as given in **Figure 1**.[30]Our constant interest in the area of total synthesis of complex polyol natural products[25] and the synthesis of small molecules by employing Pd-mediated cycloisomerization on sugar building blocks,[31] Aflastatin A was selected as a particular target. As a first step towards the total synthesis, herein we describe our preliminary efforts culminating a stereoselective approach for the synthesis of C_{31}-C_{48} fragment of aflastatin A. The retrosynthetic strategy for C_{27}-C_{48} fragment (**Figure 2**) is described in **Scheme 1**. The central issue of the synthesis of C_{27}-C_{48}

Retrosynthetic analysis of C_{27}-C_{48} fragment of Aflastatin A :

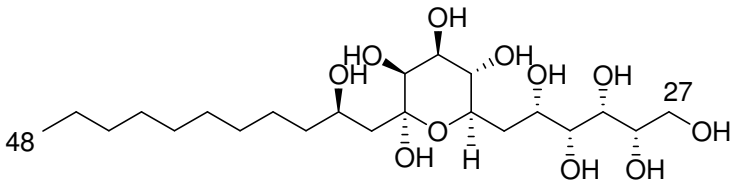
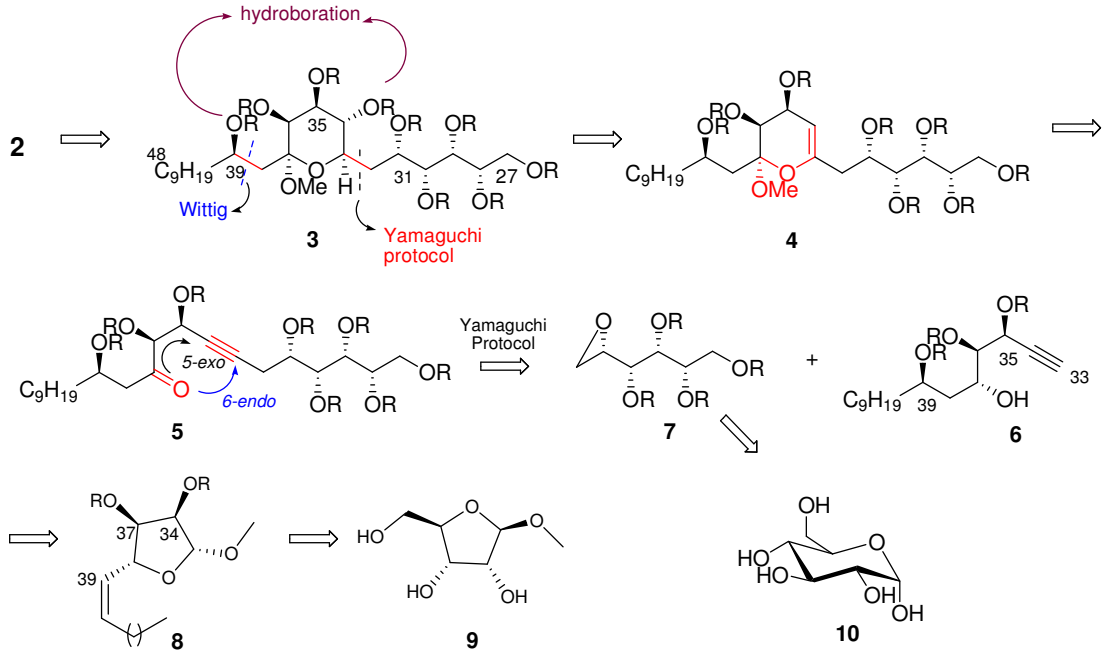


Figure 2: C_{27}-C_{48} fragment of Aflastatin A (2)

fragment is the construction of key pyran ring with requisite stereochemistry and we relied on the Pd-mediated ω-alkynone cycloisomerization[32] and a stereoselective hydroboration of resulting *C*-glycal[33] in this regard. Though, there exists two competitive pathways for the proposed cycloisomerization, considering our previous experience and some of the recent reports in this regard, a preference for 6-*endo*-dig over the 5-*exo*-dig cyclization was foreseen.[32] The preceding hydroboration of resulting *C*-glycal **4** can be expected from the opposite to the 3-hydroxyl groups thus ensuring the requisite stereochemistry at C_{33} and C_{34}.[33]

Scheme 1: - Retrosynthetic strategy



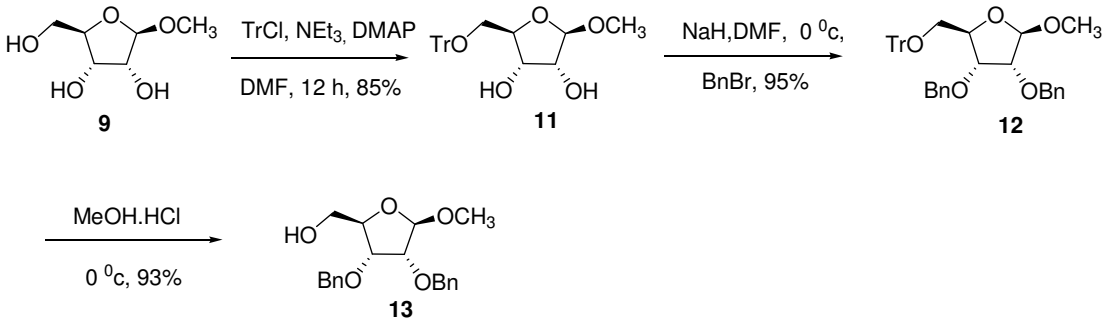
For synthesis of the key ω-ynone **5**, coupling of alkyne **6** and a suitable epoxide **7** following the Yamaguchi protocol[34] was identified as the principal coupling strategy in general. For the construction of the key alkyne **6**, D-ribose **9** containing

requisite stereochemistry at C(2) and C(3) matching with that of C(36) and C(35) respectively of Alfastatin A (**Figure 1**) selected as a chiral precursor. C(1) of ribose can be further extended to the alkyne C(33)-C(34) unit and C(4) to the carbonyl present at C(37). In order to introduce the hydroxyl group at C(39), a hydroboration-oxidation of a *Z*-olefin **8** was envisaged as there are several reports documented for the highly stereoselective addition reactions on 5,6-olefino aldofuranose derivatives.[35] For the synthesis of the epoxide fragment **7**, D-glucose **10** containing required stetreochemistry at C(2), C(3), C(4) and C(5) corresponding to that of C(27), C(28), C(29) and C(30, inversion) matching with that of Aflastatin A (**Figure 1**) choosen as a synthon.

Synthetic approach: -

Accordingly, our journey began with regioselective tritylation of primary hydroxyl of methyl-D-ribopyranoside[36] **9** with TrCl, NEt_3 and cat. DMAP in dry DMF afforded the monotrityl ether **11**[37] in 85% yield (**Scheme 2**). The product was confirmed by its ^{1}H NMR spectra in which 15 aromatic protons were resonated as a multiplet between 7.19-7.48 ppm and in ^{13}C NMR quaternary carbon of the trityl group was resonated at 86.3 ppm, a characteristic peak of trityl group.

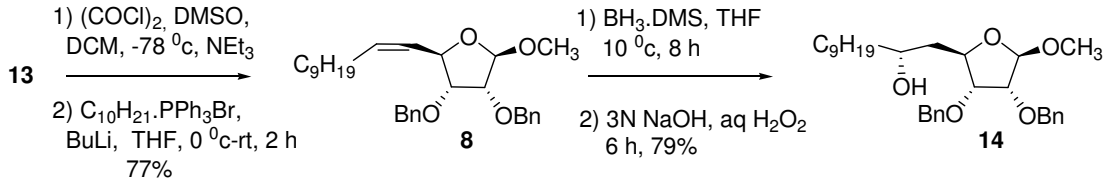
Scheme 2: -



Dibenzylation of **11** was achieved by treating the diol with NaH and BnBr in DMF to furnish dibenzylether **12** in 95% yield. Detritylation was affected with methanolicHCl at 0 ^{0}c to obtain the primary alcohol derivative **13** in 93% yield. Disappearance of 15 aromatic protons in ^{1}H NMR, absence of the quaternary carbon at 86.2 ppm in ^{13}C NMR and a peak at 587.8 $(M+1)^+$ in ESI-MS were indicative of the product. Swern oxidation of the primary alcohol of **13** with $(COCl)_2$, DMSO and NEt_3 in DCM

at -78 ^{0}c gave aldehyde which without purification quickly subjected to Wittig reaction with decyltriphenylphosphorane[38] generated from

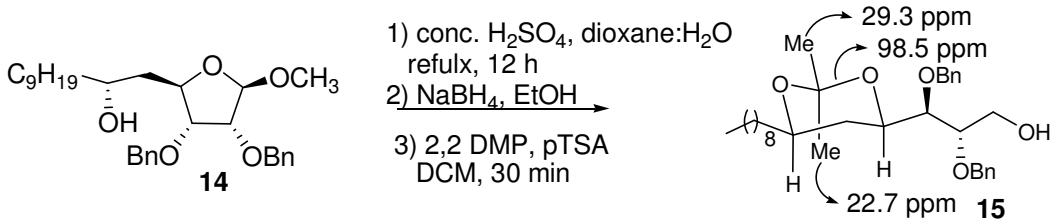
Scheme 3: -

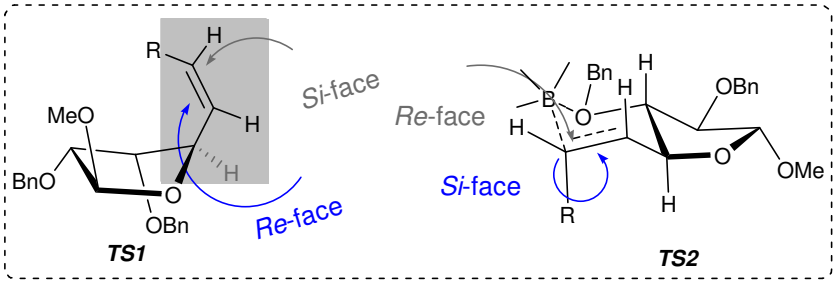


decyltriphenylphosphoniumbromide and BuLi in THF delivered the crucial *z*-configured olefin **8** in 77% yield (**Scheme 3**). The structure of the compound **8** was unambiguously confirmed from the spectral data. For example in ^{1}H NMR two *cis* olefinic protons were resonated downfield at 5.32 (J = 10.32 Hz) and 5.60 ppm (J = 10.32 Hz), while in ^{13}C NMR two olefinic carbons appeared at 129 and 134 ppm respectively. Molecular ion peak at 499.7 (M+23) in the ESI-MS spectrum was an additional support. Hydroboration of **8** by employing BH_3:DMS in THF at 10 ^{0}c followed by oxidative cleavage of the intermediate borane with 3N NaOH and aq. H_2O_2 delivered the alcohol **14** as a sole regio and diastereomer. Disappearance of olefinic protons and appearance of an additional proton (CHOH) at 3.47 ppm in ^{1}H NMR and in ^{13}C NMR carbon attached to hydroxyl resonated at 71.4 ppm, which confirmed the product structure.

The *syn* stereochemistry of newly generated asymmetric centre was confirmed by converting the alcohol **14** into acetonide derivative **15** by a

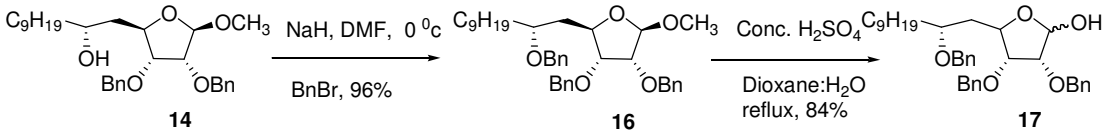
Scheme 4: - Stereoselectivity in hydroboration.





sequence of three reactions: acidic hydrolysis using conc. H_2SO_4 in refluxing 2:1 mixture of 1,4 dioxane and water, reduction of the resulted lactol using $NaBH_4$ in EtOH and acetonide protection of the diol using 2,2-DMP and cat pTSA in DCM (**Scheme 4**). In ^{13}C NMR the acetal carbon was resonated at 98.5 ppm and the two methyls at 22.7 and 29.3 ppm respectively are the characteristic features of the acetonide of a 1, 3-*syn* diol.[39] Stereoselectivity of hydroboration could be best explained by approach of the borane from the less hindered *Re*-face (***TS1***) or energetically demanding chair like transition state involving the boron atom coordinating with C(3)-oxygen and approaching the olefin from *Re*-face (***TS2***) as shown above.

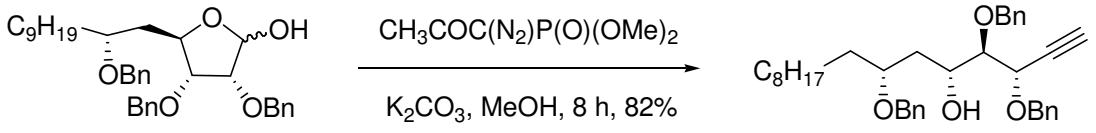
Scheme 5: - Synthesis of lactal **17**



14 **16** **17**

After the establishment of stereochemistry at C_6 in **14**, we proceeded further for the synthesis of alkyne **6**. For that compound **14** was converted to its benzyl ether **16** by treating with NaH and BnBr in DMF (**Scheme 5**). Acidic hydrolysis was achieved by refluxing compound **16** in a 2:1 mixture of 1,4-dioxane and H_2O with cat conc. H_2SO_4 to deliver the anomeric mixture of lactols **17** in 84% yield. ^1H NMR and ^{13}C NMR both showed the absence of -OMe peak, a molecular ion peak at 583.8 (M+23) in ESI-MS and a broad peak at 3496 cm^{-1} (due to anomeric OH) in IR spectrum were the confirmative features of the lactol **17**.

Scheme 6: - Synthesis of alkyne (**6**) empolying Ohira-Bestmann reaction

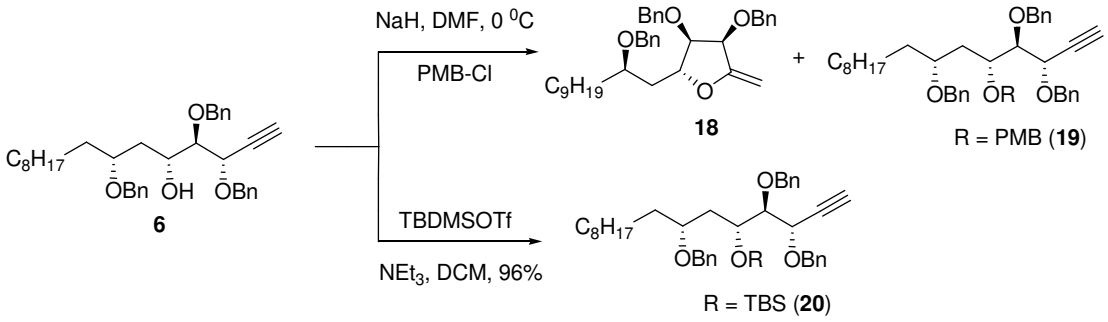


17 **6**

Our next step in the synthetic endeavour is alkynylation of the lactol under Ohira-Bestmann reaction conditions.[40] Accordingly exposure of lactols **17** to

$CH_3COC(N_2)P(O)(OMe)_2$ and K_2CO_3 in MeOH at ambient temperature for 8h furnished the terminal alkyne **6** in 82% yield (**Scheme 6**). The structure of the product was substantiated from the ^1H NMR, ^{13}C NMR, IR and mass spectra. In ^1H NMR alkyne proton ($C\equiv C-H$) was resonated as a doublet at 2.57 ppm (J = 2.14 Hz) while in ^{13}C NMR two alkyne carbons were resonated at 79.6 and 80.6 ppm respectively. An IR peak due to alkyne CH was observed at 3320 cm^{-1} and in mass spectrum molecular ion peak was seen at 579.4 $(M+23)^+$. The attempted PMB protection of free –OH in **6** using NaH and PMB-Cl in DMF gave major *exo*-olefin **18** (**Scheme 7**) resulting from the base mediated cycloisomerization in a 5-*exo*-dig fashion and minor required PMB ether **19**.[41] The structure of the product **18** was corroborated from its spectral data. In ^1H NMR

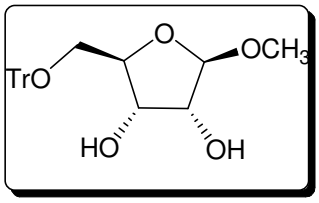
Scheme 7: -



two methylene protons, due to double bond, were seen at 4.13 and 4.52 ppm as doublets (J= 1.4Hz) and in ^{13}C NMR two olefinic carbons were resonated at 86 and 159 ppm respectively. As for the product PMB ether **19** is concerned its spectral data is in accordance with the structure, for example in ^1H NMR a peak due to methoxy group at 3.74 ppm and two doublets owing to two *ortho* protons of PMB group were seen at 6.75 and 7.10 ppm (J = 8.59 Hz) respectively. In order to circumvent this problem, we protected the free –OH of **6** as its TBS ether by treatment with TBSOTf and NEt_3 in DCM for 2h to deliver the key alkyne **20** in 96% yield. Two methyls attached to silicon atom were resonated at 0.01 and 0.04 ppm in ^1H NMR and at -4.33 and -4.18 ppm respectively in ^{13}C NMR while the methyls of t-butyl group were seen at 1.21 ppm in ^1H NMR and at 14.1 ppm in ^{13}C NMR were the indicative of the product. A peak at 694.1 in ESI-MS spectrum is an additional support.

Experimental

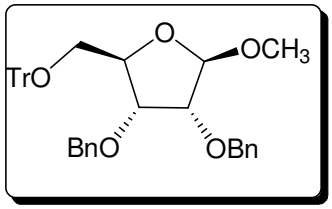
Methyl-6-O-trityl –β-ribofuranoside (11):-



Trityl chloride (14.1 g, 50.92 mmol), triethyl amine (9.7 ml, 69.45 mmol) and DMAP (0.283 g, 2.32 mmol) were added to a homogeneous solution of methyl ribopyranoside **9** (7.6 g, 46.3 mmol) in dry DMF (150 mL) at 0 ^{0}C warmed to rt and stirred for 12h. Reaction mixture was diluted with water (20 mL) and extracted into ethyl acetate (3x250 mL), dried over Na_2SO_4, evaporated to dryness and the crude was purified by column chromatography using ethyl acetate/hexane (1:1) as an eluent to yield the diol **11** (29.67 g, 85%) as a colourless oil.

Yield	: 85 %
Mol. Formula	: $C_{25}H_{26}O_5$
$[\alpha]_D^{25}$	: +52.62 (c 2.0, $CHCl_3$)
IR ($CHCl_3$) ν	: 3409, 3101, 2934, 2400, 1455, 1216, 1034, 699, 669 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 2.73 (brs, 1H), 3.15 (dd, *J* = 5.81, 4.04 Hz, 1H), 3.24 (dd, *J* = 5.04, 4.29 Hz, 2H), 3.30 (s, 3H), 3.96 (d, 4.67 Hz, 1H), 4.045 (t, *J* = 5.06, 4.67 Hz, 1H), 4.20 (t, *J* = 5.31, 5.18 Hz, 1H), 4.81 (s, 1H), 7.19-7.23 (m, 5H), 7.27-7.31 (m, 5H), 7.43-7.48(m, 5H).
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ 54.99 (q), 64.62 (t), 71.84 (d), 74.84 (d), 82.00 (d), 86.36 (s), 96.01 (s), 107.91 (d), 126.86 (d), 127.67 (d), 128.60 (d), 143.81 (s).
Elemental Analysis	Calcd.: C, 73.87; H, 6.84 Found: C, 73.79; H, 6.56
ESI-MS (m/z)	: 429.64 $(M+Na)^+$

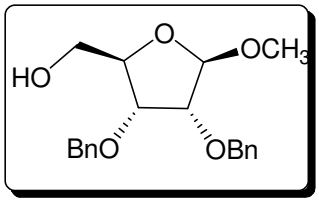
Methyl-2,3-di-O-benzyl-6-O-trityl –β-ribofuranoside (12): -



NaH (0.472 g, 19.68 mmol) was added in portions to an ice cooled solution of diol **11** (2 g, 4.92 mmol) in DMF (20 ml) over a period of 15 min. Benzyl bromide (1.75 ml, 14.76 mmol) was added. Reaction mixture was warmed to rt stirred overnight, cooled to 0 ^{0}c, quenched with ice and diluted with water. The reaction mixture was partitioned between water and ethyl acetate, combined organic layers were dried over Na_2SO_4, volatiles were removed and the crude was purified by column chromatography (1:9 ethyl acetate/hexane) to afford dibenzyl ether **12** as a colourless thick oil (2.73 g, 95%).

Yield	: 95 %
Mol. Formula	: $C_{39}H_{38}O_5$
$[\alpha]_D^{25}$	: +44.32 (c 1.2, $CHCl_3$)
IR ($CHCl_3$) ν	: 3101, 2934, 2400, 1455, 1216, 1034, 751, 669 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 3.115 (dd, *J* = 10.39, 4.32 Hz, 1H), 3.29 (d, *J* = 3.41 Hz, 1H), 3.34 (s, 3H), 3.83 (d, *J* = 4.37 Hz, 1H), 4.15 (dd, *J* = 7.33, 4.42 Hz, 1H), 4.285 (dd, *J* = 3.75,7.55 Hz, 1H), 4.35 (d, *J* = 11.87 Hz, 1H), 4.45 (d, *J* = 11.87 Hz, 1H), 4. 95 (d, *J* = 12.12 Hz, 1H), 4.67 (d, *J* = 12.12 Hz, 1H), 4.92 (s, 1H), 7.18-7.32 (m, 20H), 7.43-7.48 (m, 5H).
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ 55.14 (q), 63.82 (t), 72.22 (t), 72.34 (t), 77.99 (d), 79.63 (d), 80.47 (d), 86.26 (s), 106.14 (d), 126.87 (d), 127.71 (d), 127.90 (d), 128.25 (d), 128.34 (d), 128.68 (d), 137.70 (s), 137.81 (s), 143.97 (s)
Elemental Analysis	Calcd.: C, 79.84; H, 6.53 Found: C, 79.91; H, 6.49
ESI-MS (m/z)	: 587.83 $(M+1)^+$

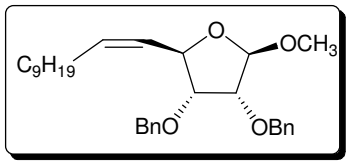
Methyl-2,3-di-O-benzyl–β-ribofuranoside (13):-



To an ice cold solution of dibenzyl ether **12** (2.5 g, 4.76 mmol) in MeOH (15 ml) was added methanolicHCl (10 ml) and stirred for 30 min, neutralized with NEt_3 (10 ml), solvent was removed under vacuum and the crude was chromatographed on silica gel (3.5:6.5 ethyl acetate/hexane) to furnish the primary alcohol **13** (1.36 g, 93%) as a colourless oil.

Yield	: 93 %
Mol. Formula	: $C_{20}H_{24}O_5$
$[\alpha]_D^{25}$	: +32.82 (c 4.75, $CHCl_3$)
IR ($CHCl_3$) ν	: 3561, 3101, 2921, 2406, 1719, 1465, 1216, 1044, 699, 667 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 1.91(brs, 1H), 3.35 (s, 3H), 3.54 (dd, *J* = 12.00, 3.52 Hz, 1H), 3.775 (dd, *J* = 12.00, 2.78 Hz, 2H), 4.09 (dd, *J* = 6.98, 4.76 Hz, 1H), 4.21-4.28 (m, 1H), 4.47 (d, *J* = 11.75 Hz, 1H), 4.56 (d, *J* = 11.75 Hz, 1H), 4. 58 (d, *J* = 12.15 Hz, 1H), 4.65 (d, *J* = 12.15 Hz, 1H), 4.86 (s, 1H), 7.30-7.35 (m, 10H).
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ 55.48 (q), 62.65 (t), 72.35 (t), 72.54 (t), 77.18 (d), 79.98 (d), 82.20 (d), 106.69 (d), 127.79 (d), 127.91 (d), 128.35 (d), 137.58 (s).
Elemental Analysis	Calcd.: C, 69.75; H, 7.02 Found: C, 69.91; H, 6.98
ESI-MS (m/z)	: 367.5 $(M+Na)^+$

Methyl-2,3-di-O-benzyl-5-deoxy-5-(1-decenyl)- β-ribopyranoside (8):-



Oxalyl chloride (2.76 ml, 31.74 mmol) was added slowly drop by drop to a stirred solution of DMSO (3.74 ml, 52.89 mmol) in DCM (25 ml) at – 78 ^{0}c, stirred for 15 min. A solution of alcohol **13** (3.6 g, 10.58 mmol) in DCM (15 ml) was cannulated into the reaction mixture and stirred for 30 min. NEt_3 (15 ml, 105.8 mmol) was added, stirred for 10 min, diluted with sat. NH_4Cl solution. Two layers were separated and the aqueous layer was extracted into DCM (3 x 75 ml), dried over Na_2SO_4, volatiles were removed and the crude was directly used for next reaction without purification.

P**reparation of Wittig salt: -**

n-decyl bromide (2.5 g, 10.62 mmol) in benzene (5 ml) was added to refluxing solution of TPP (2.78 g, 10.62 mmol) in benzene (5 ml) and the reaction mixture was refluxed for 48h. Benzene was removed and the crude was washed with dry ether (2 x 10 ml) and dried at 80 ^{0}c under high vacuum for 2h.

Wittig reaction: -

NaHMDS (5.86 ml, 5.86 mmol) was added to a vigorously stirred suspension of decyl triphenylphophonium bromide (4.24 g, 8.76 mm0l) in THF (25 ml) at 0 ^{0}c and the red colour solution was stirred at rt for 1h. Ylide was cannulated to a stirred solution of aldehyde (1 g, 2.93 mmol) in THF (20 ml) at 0 ^{0}c and Warmed to rt and stirred for 2h. The reaction mixture was quenched with sat NH_4Cl. THF was removed and the aqueous layer was extracted into ethyl acetate, combined organic layers were dried over Na_2SO_4, volatiles were removed and the crude was purified by column chromatography (5:95 ethyl acetate/hexane) to provide the Z olefin as a yellow coloured oil (1.06 g, 77%).

Yield : 77 %

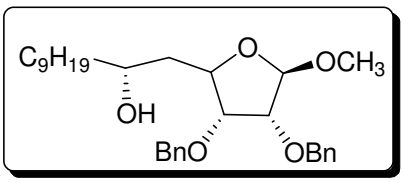
Mol. Formula : $C_{30}H_{42}O_4$

$[\alpha]_D^{25}$: -10.95 (c 1.6, $CHCl_3$)

IR ($CHCl_3$) ν : 3064.3 2954, 2854, 1715.86, 1606, 1465, 1455, 1145, 1046, 734, 697 cm^{-1}.

^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 0.88 (t, *J* = 6.6 Hz, 3H), 1.25 (m, 15H), 2.10-2.21 (m, 2H), 3.31 (s, 3H), 3.79-3.89 (m, 1H), 4. 47 (d, *J* = 12.1 Hz, 1H), 4.535 (d, *J* = 12.1 Hz, 1H), 4.61 (d, *J* = 12.13 Hz, 1H), 4.69 (d, *J* = 12.13 Hz, 1H), 4.84 (s, 1H), 4.91 (ddd, *J* = 9,0, 7.0, 0.8 Hz, 1H), 5.27-5.39 (m, 1H), 5.54-5.67(m, 1H). 7.28-7.34 (m, 10H).
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ 14.17 (q), 22.70 (t), 27.71 (t), 29.36 (t), 29.60 (t), 29.86 (t), 31.92 (t), 54.84 (d), 72.35 (t), 72.44 (t), 76.81 (d), 80.03 (d), 82.74 (d), 106.04 (d), 127.52 (d), 127.60 (d), 127.78 (d), 127.89 (d), 127.99 (d), 128.27 (d), 128.37 (d), 129.55 (d), 134.80 (d), 137.84 (s), 137.95 (s).
Elemental Analysis	Calcd.: C, 77.21; H, 9.07 Found: C, 77.34; H, 9.14
ESI-MS (m/z)	: 489.73 $(M+23)^+$

Methyl-2,3-di-O-benzyl-5-deoxy-5-(2R-hydroxydecyl)-β-ribopyranoside (14):-

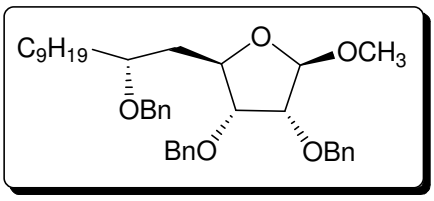


To an ice cold solution of olefin (0.8 g, 1.72 mmol) in THF was added BH_3.DMS (0.12 ml, 1.72 mmol) and stirred at 10 ^{0}c for 6h. Reaction mixture was cooled to 0 ^{0}c, 3N NaOH (4 ml) was added drop by drop, stirred for 10 min, 50% aq. H_2O_2 (4 ml) slowly added and stirred at rt for 6h. THF was removed and the aqueous layer was extracted into ethyl acetate, dried over Na_2SO_4 and purified by column chromatography (1: 9 ethyl acetate/hexane) to furnish the alcohol **14** (0.65 g, 79%) as a colourless oil.

Yield	: 79%
Mol. Formula	: $C_{30}H_{44}O_5$
Optical Rotation **$[\alpha]_D^{25}$**	: +11.29 (c 1.6, $CHCl_3$)
IR ($CHCl_3$) ν	: 3479, 31018, 2928, 2400, 1719, 1455, 1216, 1044, 699, 669 cm^{-1}.

^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 0.88 (t, *J* = 6.69 Hz, 3H), 1.25 (m, 15H), 1.48 (m, 3H), 3.31 (s, 3H), 3.47(m, 1H), 3.83 (m, 1H), 4.04-4.16 (m, 2H), 4.45 (d, *J* = 11.49 Hz, 1H), 4.545 (d, *J* = 11.49 Hz, 1H), 4.56 (d, *J* = 12.05 Hz, 1H), 4.64 (d, *J* = 12.05 Hz, 1H), 4.85 (s, 1H), 5.54-5.67(m, 1H), 7.25-7.35 (m, 10H).
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ 14.15 (q), 22.70 (t), 25.71 (t), 29.36 (t), 29.65 (t), 29.70 (t), 31.94 (t), 34.34 (t), 55.48 (q), 71.44 (d), 72.43 (t), 72.67 (t), 78.29 (d), 80.15 (d), 84.31 (d), 106.68 (d), 127.86 (d), 127.95 (d), 127.99 (d), 128.37 (d), 128.40 (d), 137.70 (s), 137.73 (s).
Elemental Analysis	Calcd.: C, 74.34; H, 9.15 Found: C, 74.23; H, 9.23
ESI-MS (m/z)	: 507.78 $(M+23)^+$

Methyl-2,3-di-O-benzyl-5-deoxy-5-(2R-benzyloxydecyl)-β-ribopyranoside (16):-

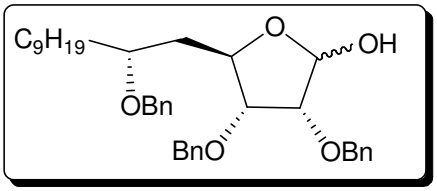


NaH (0,084 g, 3.47 mmol) was added in portions to an ice cooled solution of alcohol **15** (1.4 g, 2.89 mmol) in DMF (15 ml) over a period of 15 min. Benzyl bromide (0.3 ml, 3.18 mmol) was added. Reaction mixture was warmed to rt and stirred overnight, cooled to 0 ^{0}c, quenched with ice, diluted with water. The reaction mixture was partitioned between water and ethyl acetate, combined organic layers were dried over Na_2SO_4, volatiles were removed and the crude was purified by column chromatography (1:9 ethyl acetate/hexane) to afford tribenzyl ether **16** as a colourless thick oil (1.58 g, 96%).

Yield	: 96%
Mol. Formula	: $C_{37}H_{50}O_5$
$[\alpha]_D^{25}$	: +21.37 (c 1.6, $CHCl_3$)
IR ($CHCl_3$) ν	: 3019, 2927, 1653, 1454, 1215, 1045, 750, 669 cm^{-1}.

^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 0.88 (t, *J* = 6.82 Hz, 3H), 1.25 (m, 15H), 1.59 (m, 3H), 3.33 (s, 3H), 3.47(m, 1H), 3.845 (dd, *J* = 4.54, 0.73 Hz 1H), 4.03 (dd, *J* = 7.58, 4.54 Hz, 1H), 4.21(dd, *J* = 7.58, 4.53 Hz, 1H), 4.32 (d, *J* = 11.75 Hz, 1H), 4.50 (d, *J* = 11.75 Hz, 1H), 4.49-4.62 (m, 3H), 4.70 (d, *J* = 11.75 Hz, 1H), 4.93 (s, 1H), 7.26-7.38 (m, 15H).
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ 14.11 (q), 22.67 (t), 25.49 (t, 29.33 (t), 29.62 (t), 29.84 (t), 30.60 (t), 31.89 (t), 54.94 (q), 72.16 (t), 72.27 (t), 72.30 (t), 77.95 (d), 79.26 (d), 79.75 (d), 82.70 (d), 105.53 (d), 127.28 (d), 127.65 (d), 127.79 (d), 127.84 (d), 128.07 (d), 128.11 (d), 128.16 (d), 128.32 (d), 128.40 (d), 137.63 (s), 137.72 (s), 139.03 (s).
Elemental Analysis	Calcd.: C, 77.31; H, 8.77 Found: C, 77.38; H, 8.69
ESI-MS (m/z)	: 597.82 $(M+23)^+$

2,3-di-O-benzyl-5-deoxy-5-(2R-benzyloxydecyl)-β-ribopyranose (17):-

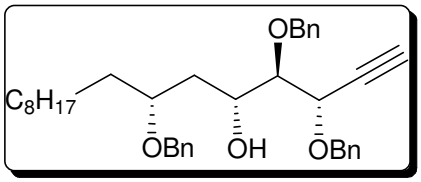


Conc. H_2SO_4 (2 ml) was added to cooled solution of compound **16** (1 g, 1.71 mmol) in dioxane and water (1:2, 20 ml) and heated on water bath for 9h. cooled to 0 ^{0}c and neutralized with NEt_3, two layers were separated and the aqueous layer was extracted into ethyl acetate, dried over Na_2SO_4, concentrated under reduced pressure and the crude was purified by column chromatography (1.5:8.5 ethyl acetate/hexane) to produce the lactal **17** (0.81g, 84%) as a colourless liquid.

Yield	: 84%
Mol. Formula	: $C_{36}H_{48}O_5$
$[\alpha]_D^{25}$	: +46.98 (c 1.6, $CHCl_3$)
IR ($CHCl_3$) ν	: 3496, 3019, 2927, 1653, 1454, 1215, 1045, 750, 669 cm^{-1}.

^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 0.82 (t, *J* = 6.82 Hz, 6H), 1.19 (m, 32H), 1.60 (m, 4H), 3.21 (t, *J* = 6.64, 6.22 Hz, 2H), 3.695 (d, *J* = 4.80 Hz, 2H), 3.83 (t, *J* = 4.70 Hz, 2H), 3.97 (dd, *J* = 6.82, 4.42 Hz 2H), 4.045 (d, *J* = 2.02 Hz, 1H), 4.075 (d, *J* = 1.52 Hz, 1H), 4.105 (d, *J* = 2.65 Hz, 1H), 4.18 (t, *J* = 2.40 Hz, 1H), 4.24-4.71 (m, 10H), 5.01-5.15(m, 2H), 7.05-7.29 (m, 30H).
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ 14.07 (q), 22.63 (t), 25.46 (t), 25.73 (t), 29.28 (t), 29.54 (t), 29.71 (t), 31.85 (t), 72.00 (t), 72.10 (t), 72.19 (t), 72.24 (t), 72.30 (t), 72.95 (t), 77.39 (d), 77.84 (d), 77.98 (d), 78.24 (d), 80.36 (d), 82.34 (d), 82.92 (d), 100.06 (d), 127.54 (d), 127.77 (d), 127.89 (d), 127.99 (d), 128.08 (d), 128.17 (d), 128.37 (d), 128.47 (d), 128.61 (d), 137.34 (s), 137.49 (s), 137.56 (s), 137.66 (s), 137.71 (s), 138.10 (s).
Elemental Analysis	Calcd.: C, 77.11; H, 8.63 Found: C, 77.17 H, 8.69
ESI-MS (m/z)	: 583.82 $(M+23)^+$

(3S,4R,5R,7R)-3,4,7-tris(benzyloxy)hexadec-1-yn-5-ol (6):-



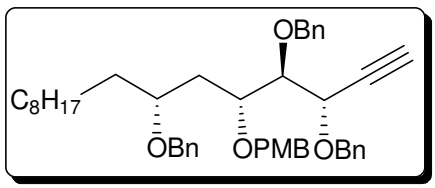
To a stirred solution of lactol **17** (0.55 g, 0.998mmol) in MeOH (5 ml) was added dimethyl 1-diazo-2-oxopropyl phosphonate (0.57 ml, 3 mmol) and K_2CO_3 (0.414 g, 3 mmol) and stirred for 8h. MeOH was removed and residue was partitioned between ethyl acetate and water, dried over Na_2SO_4. Volatiles were removed and the crude was purified by column chromatography (5:95 ethylacetate/hexane) to deliver the alkyne **6** as a colourless oil (0.45 g, 82%).

Yield : 82%

Mol. Formula : $C_{37}H_{48}O_4$

Optical Rotation $[\alpha]_D^{25}$	: +94.35 (c 1.6, $CHCl_3$)
IR ($CHCl_3$) ν	: 3548, 3306, 3031, 2926, 2855, 1496, 1454, 1216, 1067, 757, 697 cm^{-1}.
^1H NMR ($CDCl_3$, 200 MHz)	: δ 0.88 (t, *J* = 6.70 Hz, 3H), 1.25 (m, 17H), 1.64 (m, 2H), 2.57 (d, *J* = 2.14 Hz, 1H), 3.57 (dt, *J* = 9.06, 1.14 Hz, 1H), 3.69 (dt, *J* = 6.71, 1.14 Hz, 1H), 3.775 (dd, *J* = 8.97, 2.27 Hz, 1H), 4.17 (d, *J* = 11.37 Hz, 1H), 4.46-4.45 (m, 3H), 4.73 (t, *J* = 2.27 Hz, 1H), 4.94 (d, *J* = 11.75 Hz, 1H), 4.97 (d, *J* = 11.62 Hz, 1H), 7.20-7.41 (m, 15H).
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ 14.09 (q), 22.67 (t), 25.50 (t), 29.31 (t), 29.52 (t), 29.58 (t), 29.79 (t), 30.85 (t), 31.89 (t), 71.19 (t), 71.86 (t), 72.14 (d), 72.18 (d), 73.47 (t), 76.17 (s), 76.68 (d), 79.62 (s), 80.17 (d), 127.57 (d), 127.65 (d), 127.73 (d), 127.79 (d), 128.24 (d), 128.32 (d), 137.83 (s), 138.37 (s), 138.45 (s).
Elemental Analysis	Calcd.: C, 79.82; H, 8.63 Found: C, 79.71 H, 8.69
ESI-MS (m/z)	: 579.43 $(M+23)^+$

1-(3S,4R,5R,7R)-5-(4-methoxybenzyloxy)-3,4-bis(benzyloxy)hexadec-1-yn-7-yloxy)methyl)benzene (19):-



A solution of alkynol **6** (0.1 g, 0.18 mmol) and PMB-Cl (0.055 mg, 0.27 mmol) in DMF(2 ml) was cooled to 0 ^{0}c and NaH (0.0065 g, 0.27 mmol) was added and stirred for 30 min, quenched with ice, diluted with water and extracted into ethyl acetate (3 x 15 ml), dried over Na_2SO_4, concentrated under reduced pressure and the residue was purified by flash column chromatography (5:95 ethylacetate/hexane) to afford the PMB ether **19** as a colourless oil (0.08 g, 48%).

Yield : 48%

Mol. Formula : $C_{45}H_{56}O_5$

$[\alpha]_D^{25}$: +50.20 (c 1.3, $CHCl_3$)

IR ($CHCl_3$) ν : 3019, 2927, 1454, 1215, 757, 669 cm^{-1}.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 0.88 (t, *J* = 6.83 Hz, 3H), 1.25 (m, 15H), 1.54-1.58 (m, 2H), 2.585 (d, *J* = 2.02 Hz, 1H), 3.62-3.69 (m, 2H), 3.79 (s, 3H), 4.025 (dd, *J* = 6.32, 3.16 Hz, 1H), 4.46-4.63 (m, 7H), 4.665 (dd, *J* = 3.15, 2.40 Hz, 1H), 4.89 (d, *J* = 11.62 Hz, 1H), 4.96 (d, *J* = 11.50 Hz, 1H), 6.81 (d, *J* = 8.72 Hz, 2H), 7.18 (d, *J* = 8.72 Hz, 2H), 7.25-7.34 (m, 15H).

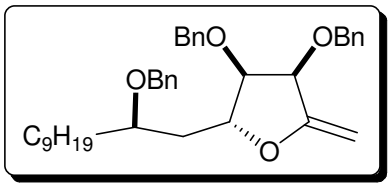
^{13}C NMR ($CDCl_3$, 50 MHz) : δ 14.12 (q), 22.68 (t), 25.81 (t), 29.34 (t), 29.60 (t), 29.81 (t), 30.92 (t), 31.90 (t), 55.21 (q), 70.99 (t), 71.26 (d), 72.25 (t), 73.69 (t), 74.19 (t), 75.95 (t), 79.08 (d), 80.39 (d), 80.53 (d), 80.59 (s), 113.58 (d), 127.31 (d), 127.39 (d), 127.63 (d), 127.84 (d), 127.94 (d), 127.99 (d), 128.16 (d), 128.32 (d), 129.75 (d), 130.59 (s), 137.66 (s), 138.64 (s), 139.00 (s), 159.10 (s).

Elemental Analysis Calcd.: C, 79.84; H, 8.34

Found: C, 79.90 H, 8.39

ESI-MS (m/z) : 699.89 $(M+23)^+$

(2R,3R,4R)-3,4-bis(benzyloxy)-2-((R)-2-(benzyloxy)undecyl)-tetrahydro-5-methylenefuran (18):-



Mol. Formula : $C_{37}H_{48}O_4$

$[\alpha]_D^{25}$: +50.64 (c 0.85, $CHCl_3$)

IR ($CHCl_3$) ν : 3306, 3019, 2927, 1514, 1215, 757, 669 cm^{-1}.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 0.88 (t, *J* = 6.83 Hz, 3H), 1.25 (m, 16H), 1.54-1.58 (m, 2H), 3.39-3.48 (m, 1H), 3.91 (dd, J = 7.08, 4.80 Hz, 1H), 4.125 (d, *J* = 1.39 Hz, 1H), 4.185 (d, *J* = 4.67 Hz,

1H), 4.29-4.65 (m, 7H), 4.75 (d, *J* = 12.12 Hz, 1H), 7.25-7.38 (m, 15H).

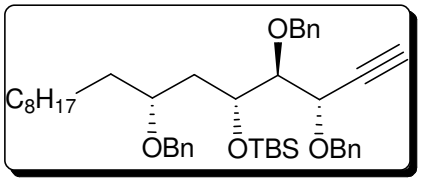
^{13}C NMR ($CDCl_3$, 50 MHz) : δ 14.09 (q), 22.65 (t), 25.60 (t), 25.65 (t), 29.30 (t), 29.51 (t), 29.57 (t), 29.66 (t), 29.69 (t), 30.29 (t), 31.87 (t), 69.79 (t), 71.81 (t), 72.11 (t), 74.89 (d), 76.93 (d), 77.35 (d), 83.49 (d), 86.02 (t), 127.55 (d), 127.74 (d), 127.87 (d), 128.00 (d), 128.14 (d), 128.24 (d), 128.32 (d), 128.37 (d), 137.42 (s), 137.71 (s), 138.39 (s), 159.10 (s).

Elemental Analysis Calcd.: C, 79.82; H, 8.63

Found: C, 79.71 H, 8.69

ESI-MS (m/z) : 579.43 $(M+23)^+$

(3S,4S,5R,7R)-3,4,7-tris(benzyloxy)hexadec-1-yn-5-yloxy)(tert-butyl)dimethylsilane (20):-



TBSOTf (0.058 ml, 0. 21 mmol) was added to a stirred solution of alkynol **6** (0.117 g, 0.210 mmol) and NEt_3 (0.042 ml), in DCM (5 ml) at 0 ^{0}c and stirred at rt for 2h, diluted with water, extracted into DCM dried over Na_2SO_4, solvent was removed and the crude was chromatographed on silica gel (5:95 ethyl acetate/hexane) to deliver the TBS ether (0.132 g, 96%) as a colourless thick oil.

Yield : 96%

Mol. Formula : $C_{43}H_{62}O_4Si$

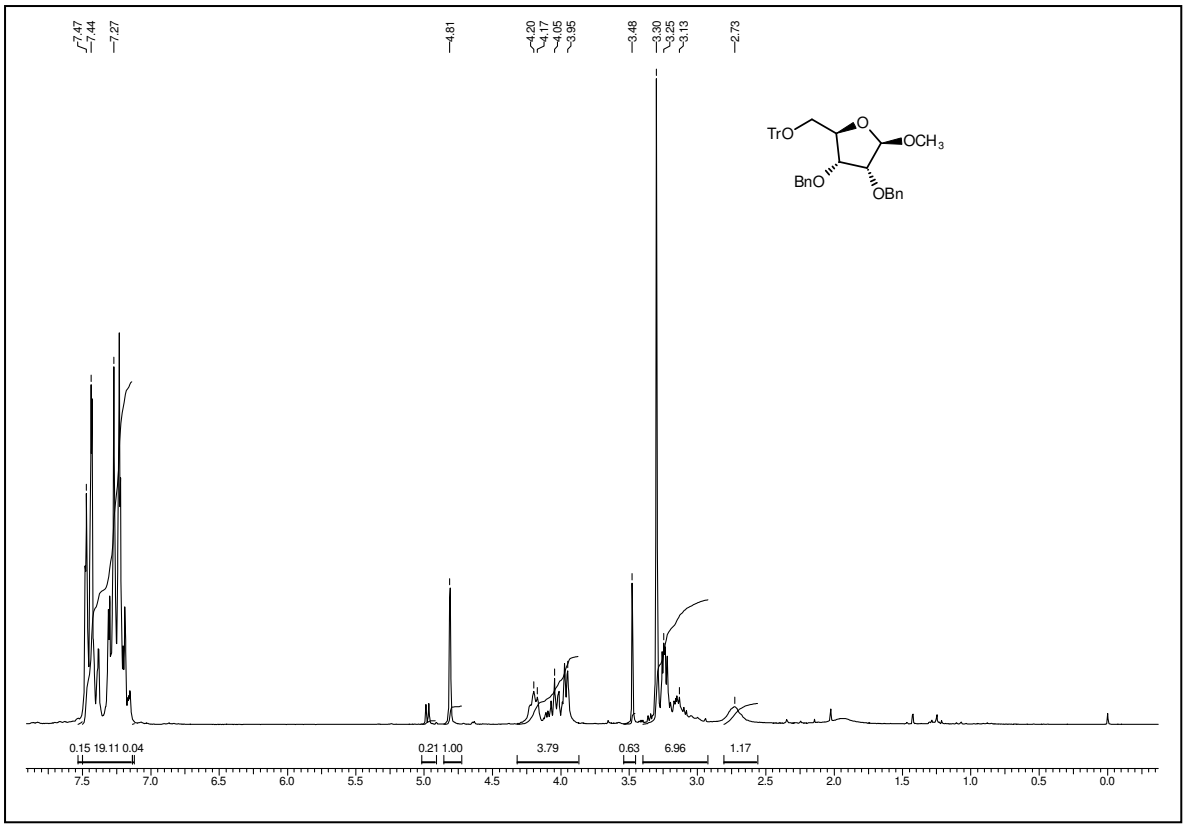
$[\alpha]_D^{25}$: +52.64 (c 1.3, $CHCl_3$)

IR ($CHCl_3$) ν : 3307, 2927, 2855, 1651, 1455, 1215, 1067, 757, 668 cm^{-1}.

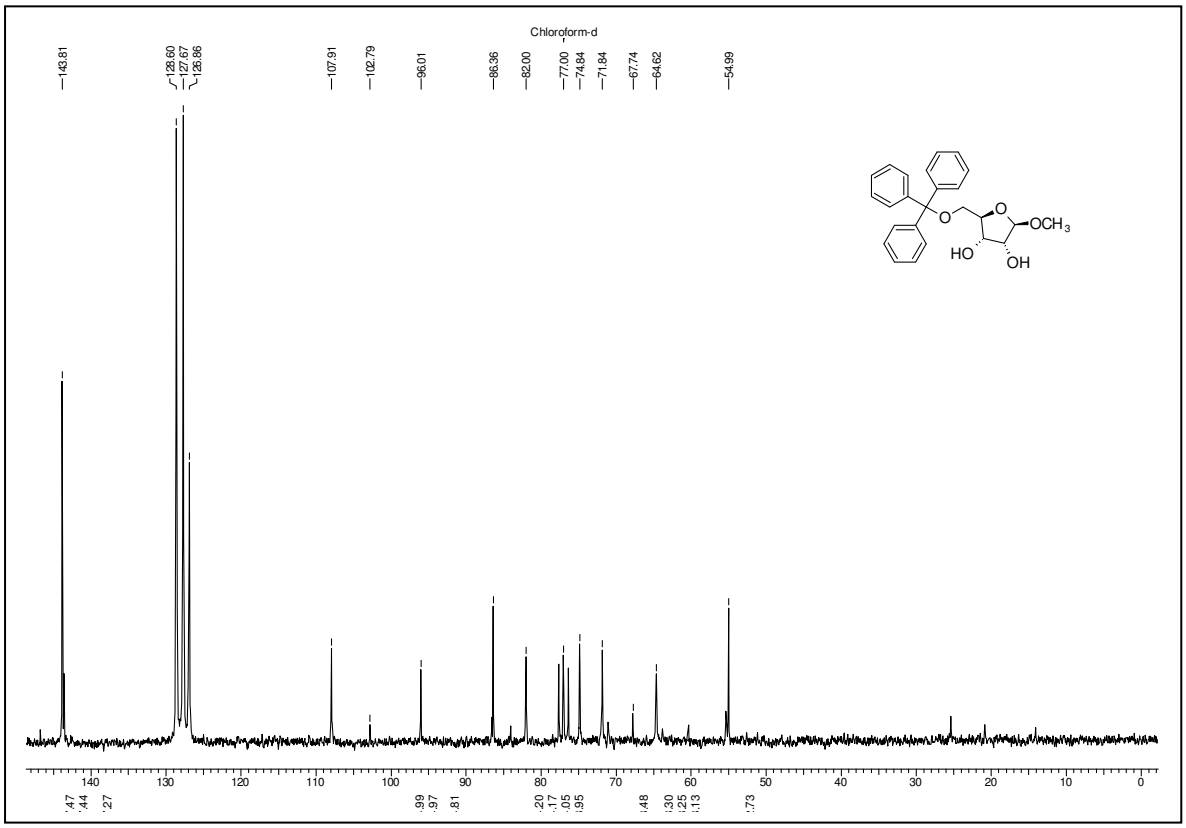
^{1}H NMR ($CDCl_3$, 200 MHz) : δ 0.01 (s, 3H), 0.04 (s, 3H), 0.83 (s, 9H), 0.84 (t, *J* = 6.57 Hz, 3H), 1.21-1.24 (m, 15H), 1.46-1.55 (m, 3H), 2.515 (d, *J* = 2.12 Hz, 1H), 3.50-3.58 (m, 1H), 3.84 (dd,

	J = 5.36, 4.27 Hz, 1H), 3.945 (dd, *J* = 5.41, 4.33 Hz, 1H), 4.40-4.52 (m, 3H), 4. 54-4.57 (m, 1H), 4.649 (d, *J* = 11.37 Hz, 1H), 4.865 (d, *J* = 11.62 Hz, 1H), 4.91 (d, *J* = 11.36 Hz, 1H), 7.24-7.40 (m, 15H).
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ δ -4.33 (q), -4.18 (q), 14.13 (q), 18.24 (s), 22.68 (t), 25.96 (t), 26.04 (q), 29.34 (t), 29.55 (t), 29.60 (t), 29.73 (t), 30.42 (t), 31.90 (t), 70.82 (t), 70.99 (d), 71.78 (t), 73.67 (d), 73.82 (t), 75.60 (s), 79.98 (d), 80.85 (s), 81.22 (d), 127.11 (d), 127.28 (d), 127.44 (d), 127.63 (d), 127.73 (d), 127.88 (d), 127.93 (d), 128.06 (d), 128.31 (d), 137.72 (s), 138.74 (s, 139.22 (s).
Elemental Analysis	Calcd.: C, 76.96; H, 9.31 Found: C, 76.96 H, 9.31
ESI-MS (m/z)	: 694.11 $(M+23)^+$

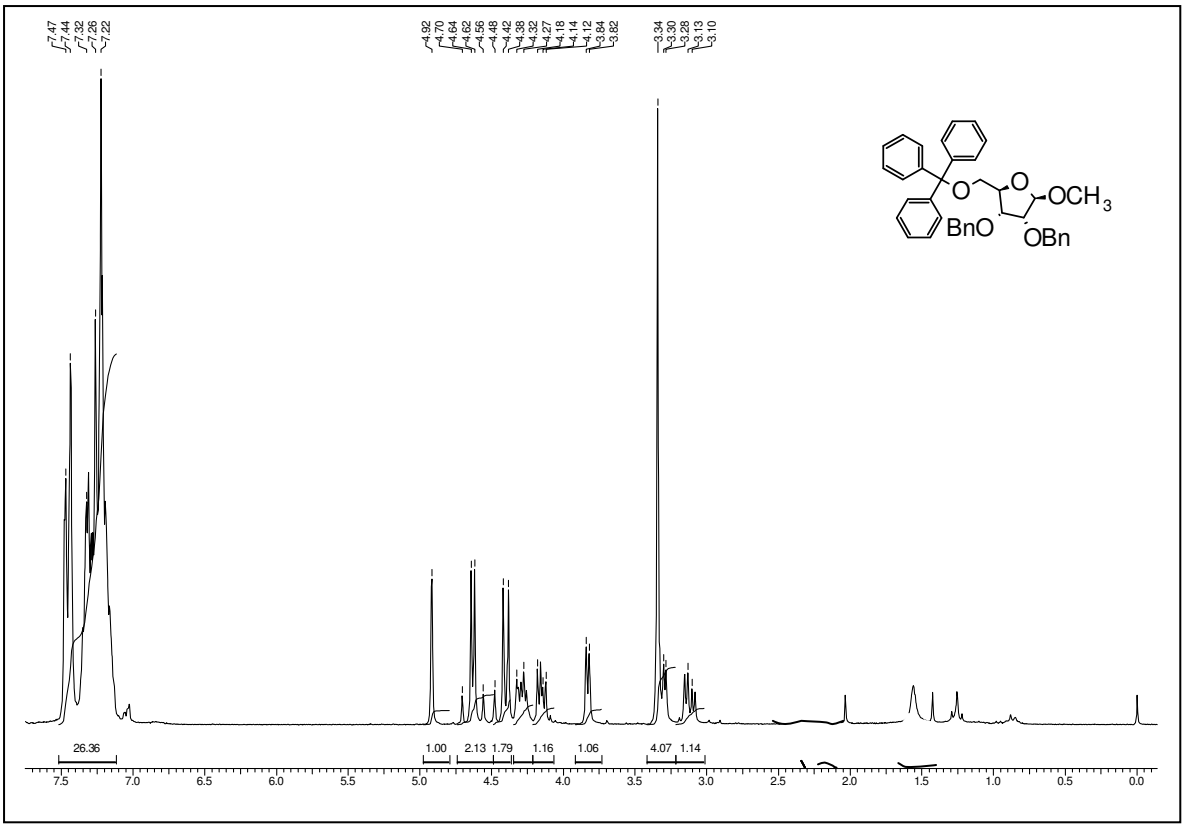
Spectral data



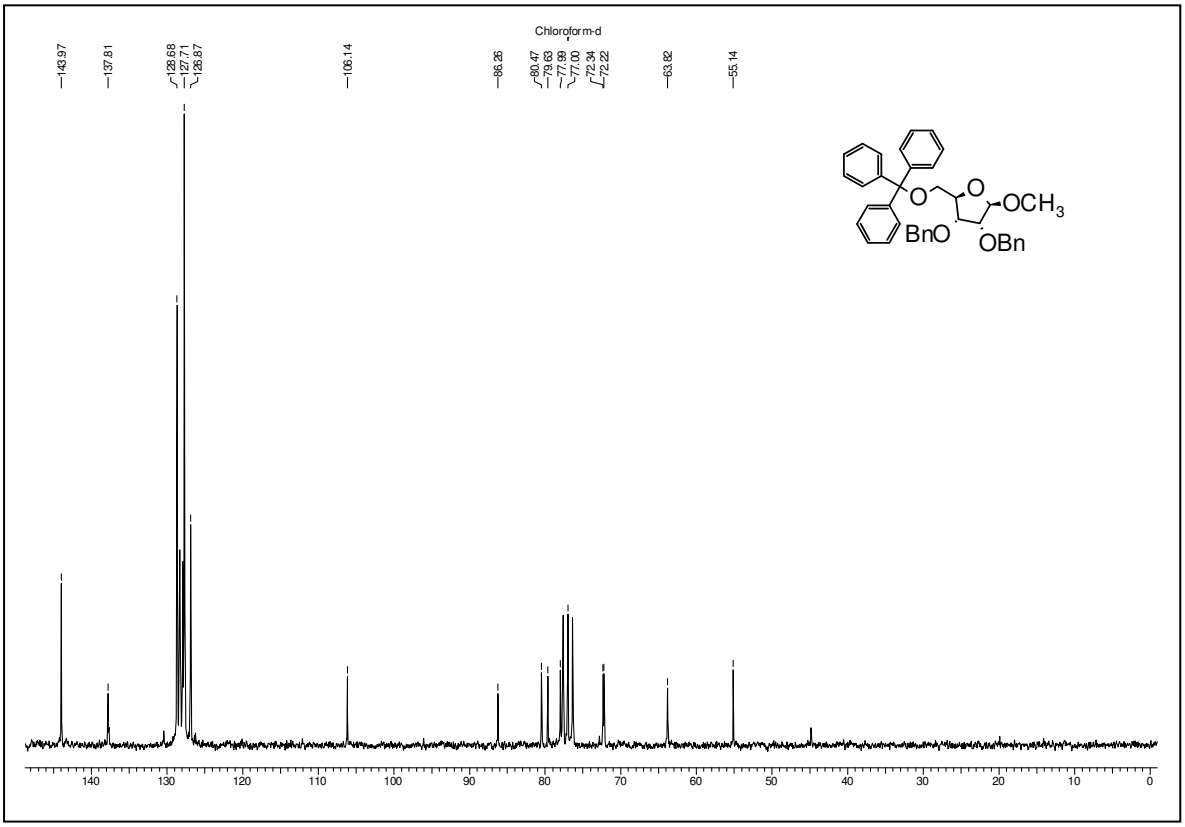
^{1}H NMR spectrum of compound 11 in $CDCl_3$



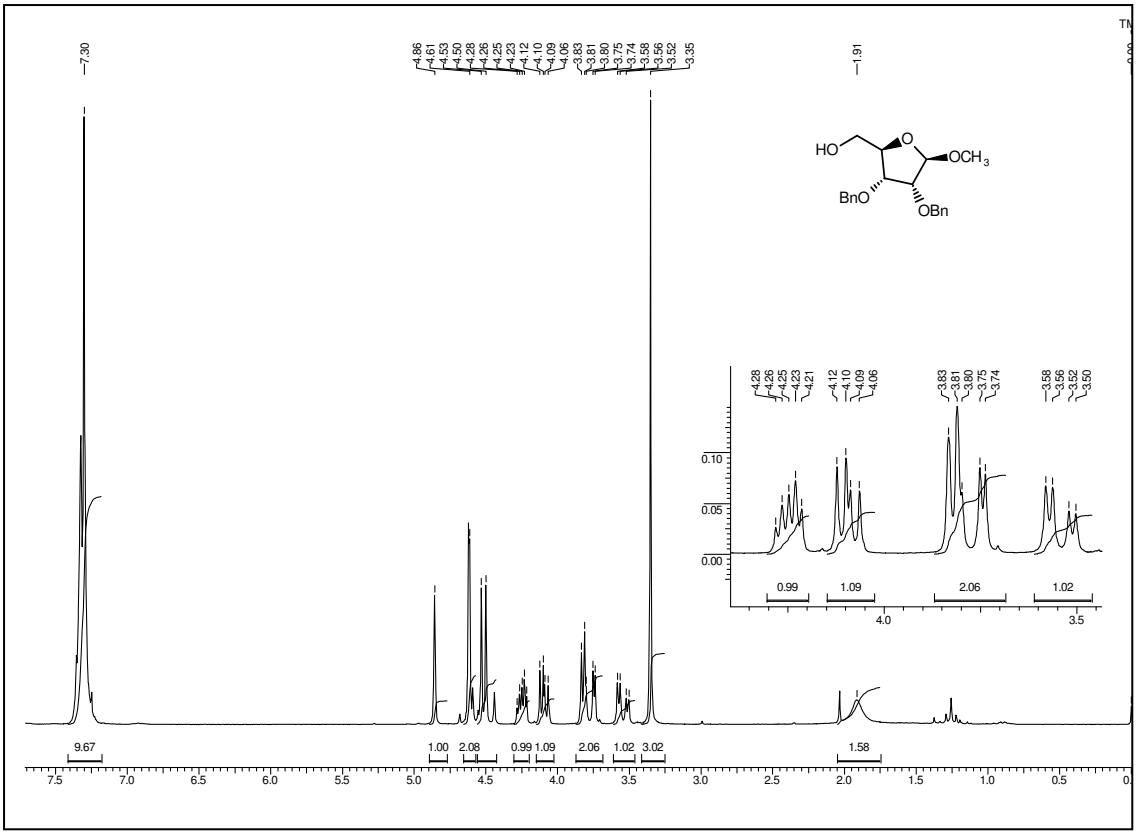
^{13}C NMR spectrum of compound 11 in $CDCl_3$



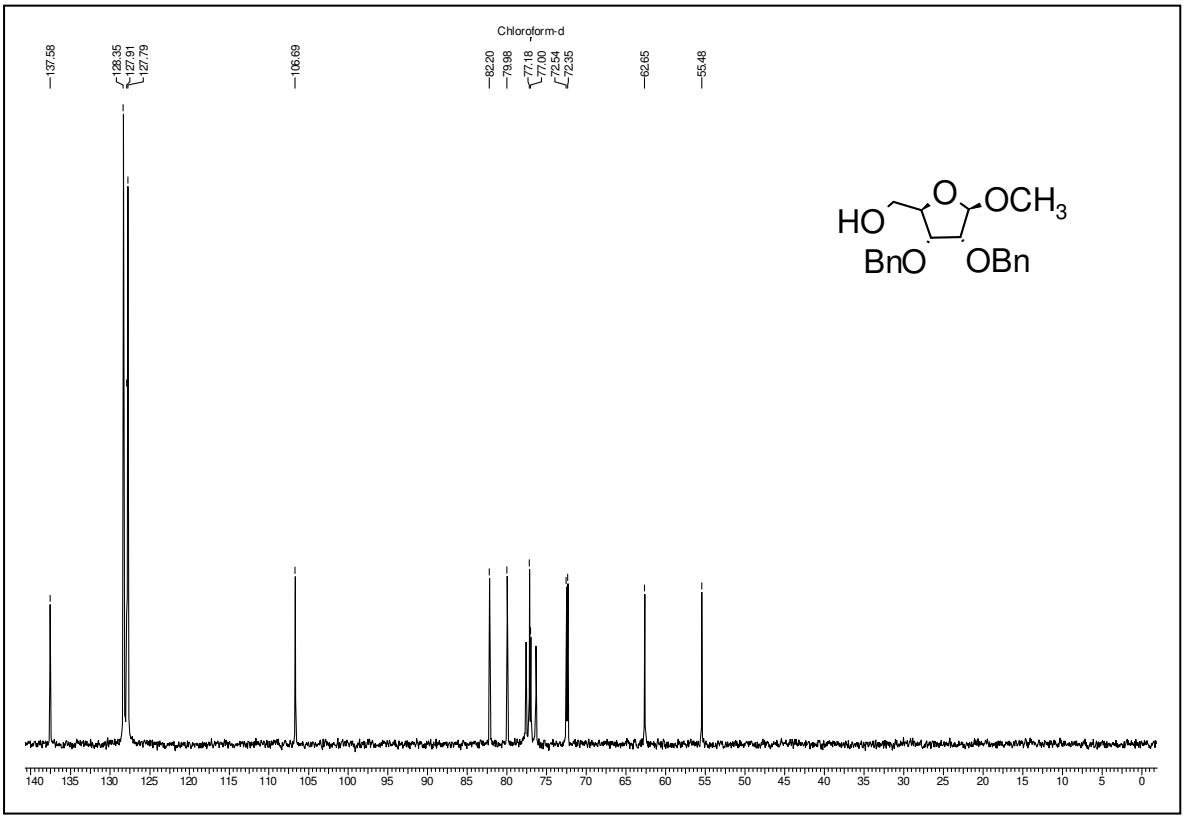
^{1}H NMR spectrum of compound 12 in $CDCl_3$



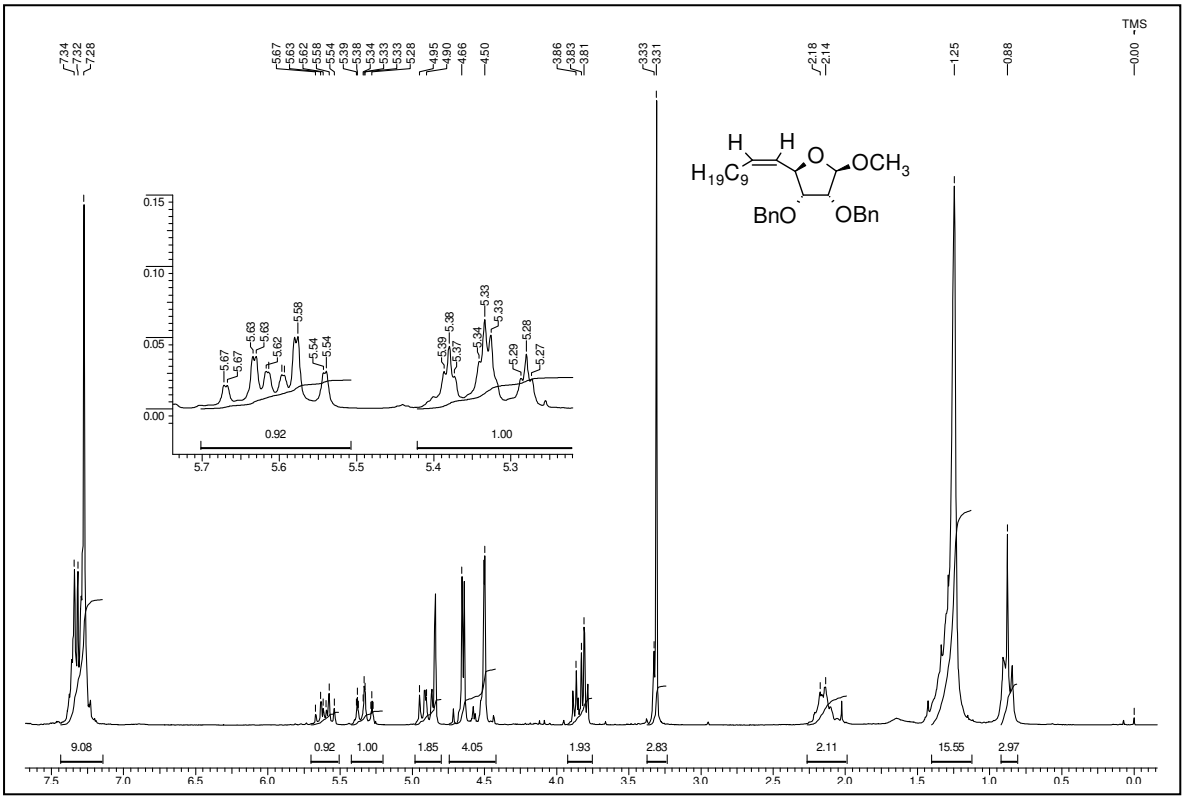
^{13}C NMR spectrum of compound 12 in $CDCl_3$



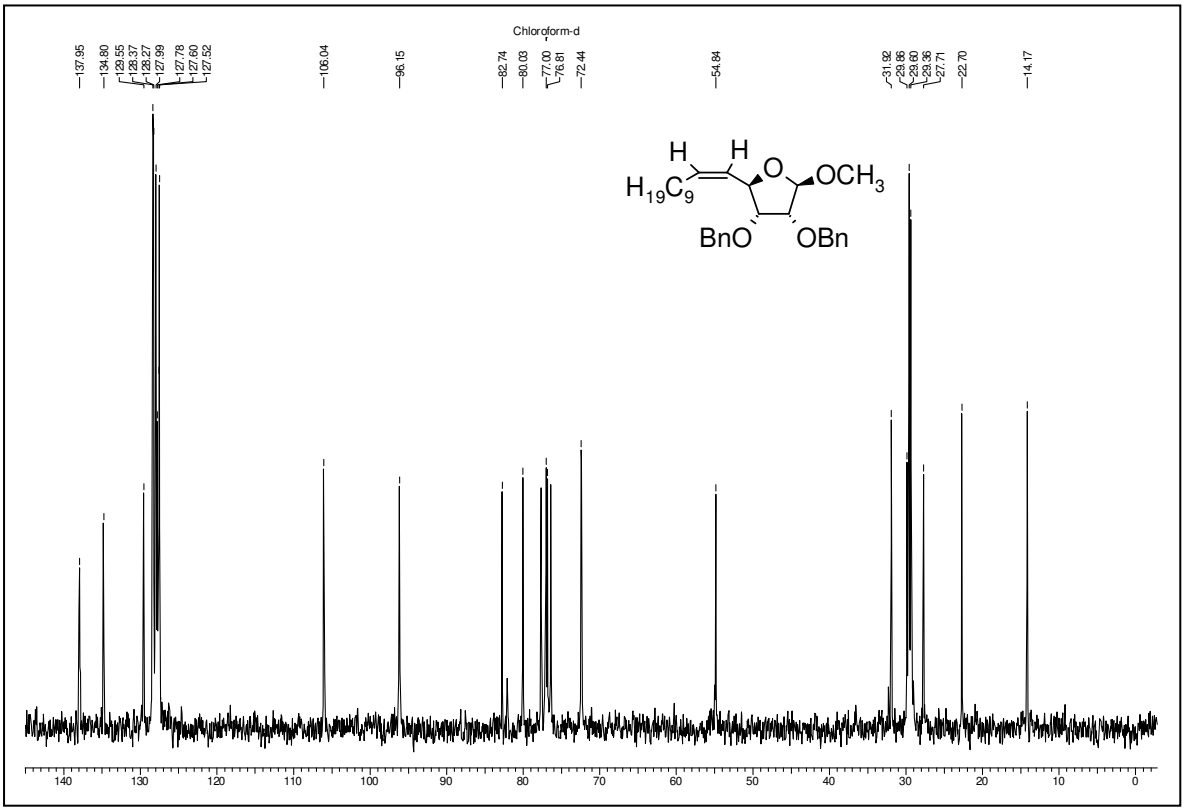
^{1}H NMR spectrum of compound 13 in $CDCl_3$



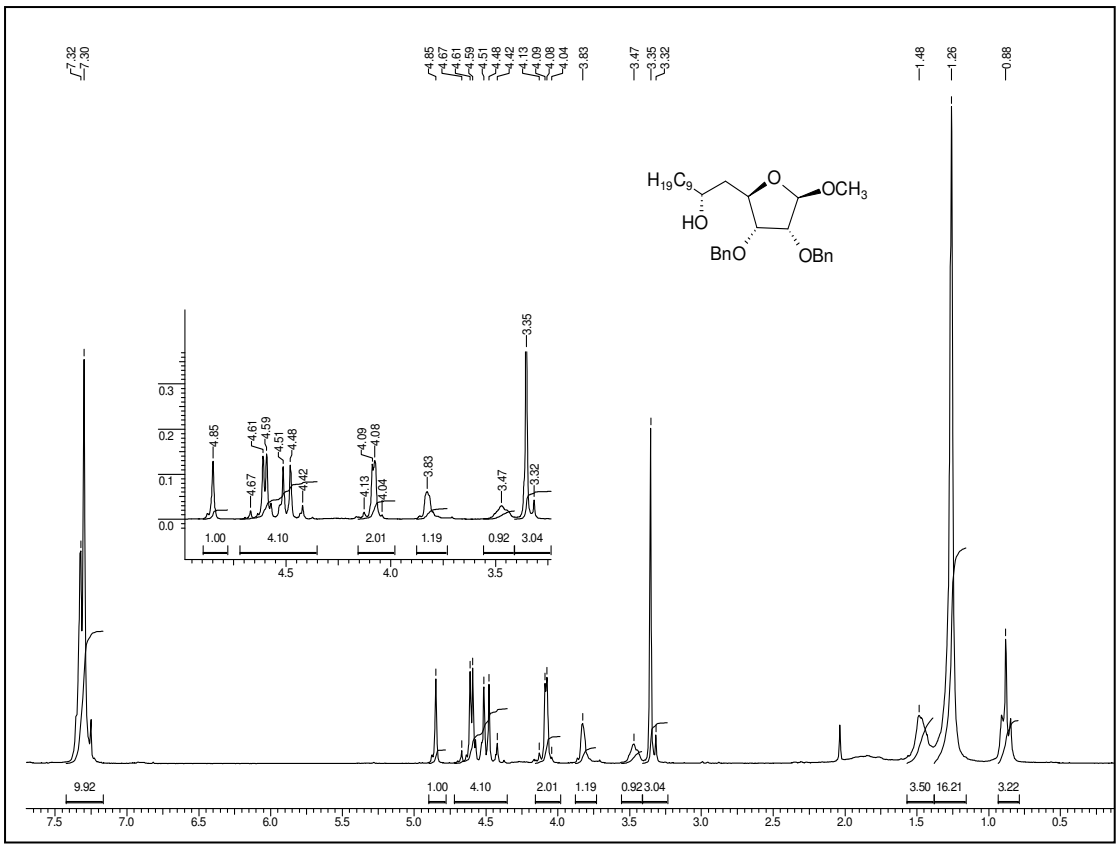
^{13}C NMR spectrum of compound 13 in $CDCl_3$



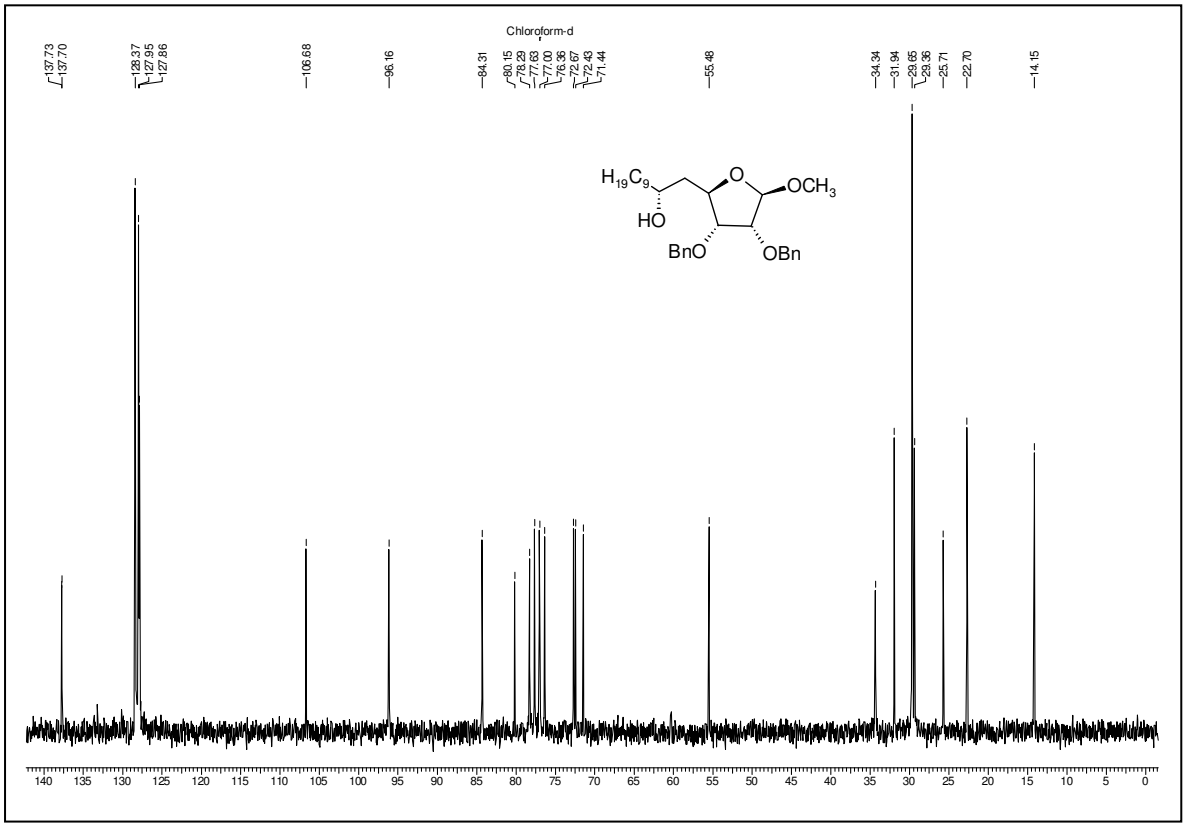
^{1}H NMR spectrum of compound 8 in $CDCl_3$



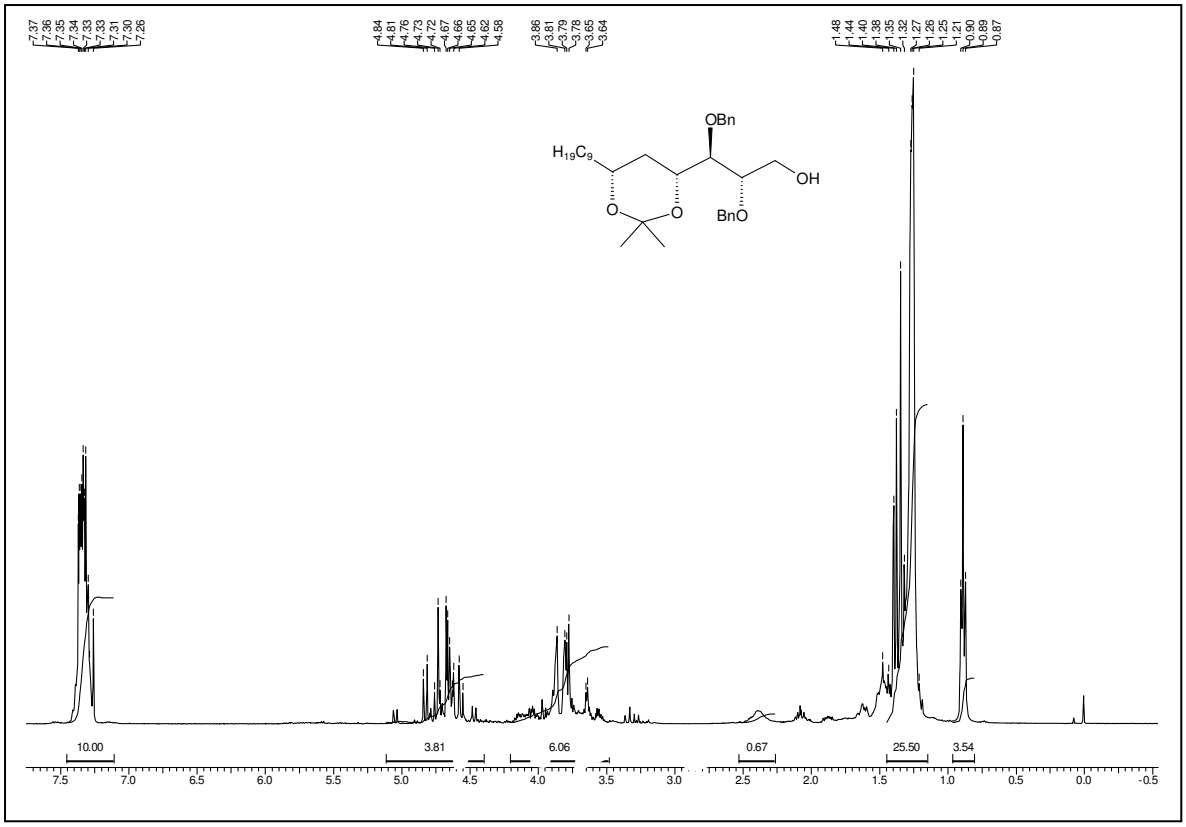
^{13}C NMR spectrum of compound 8 in $CDCl_3$



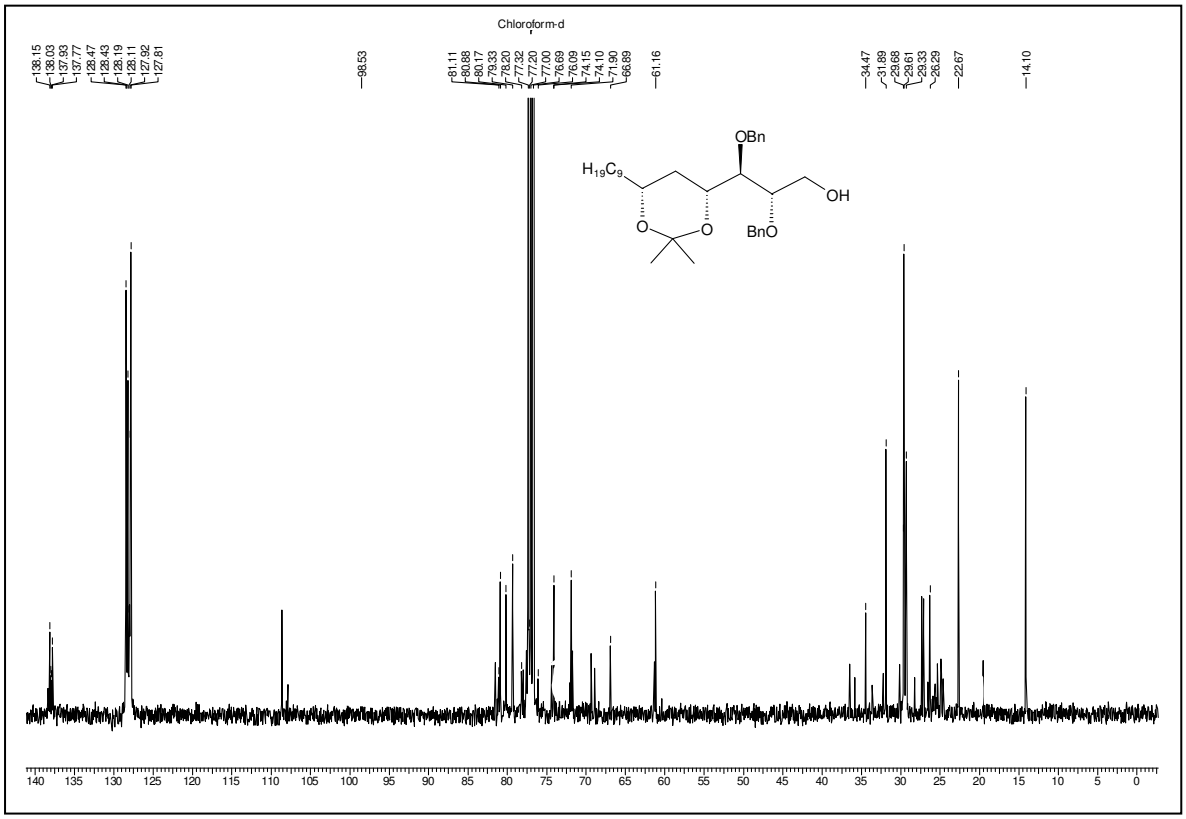
^{1}H NMR spectrum of compound 14 in $CDCl_3$



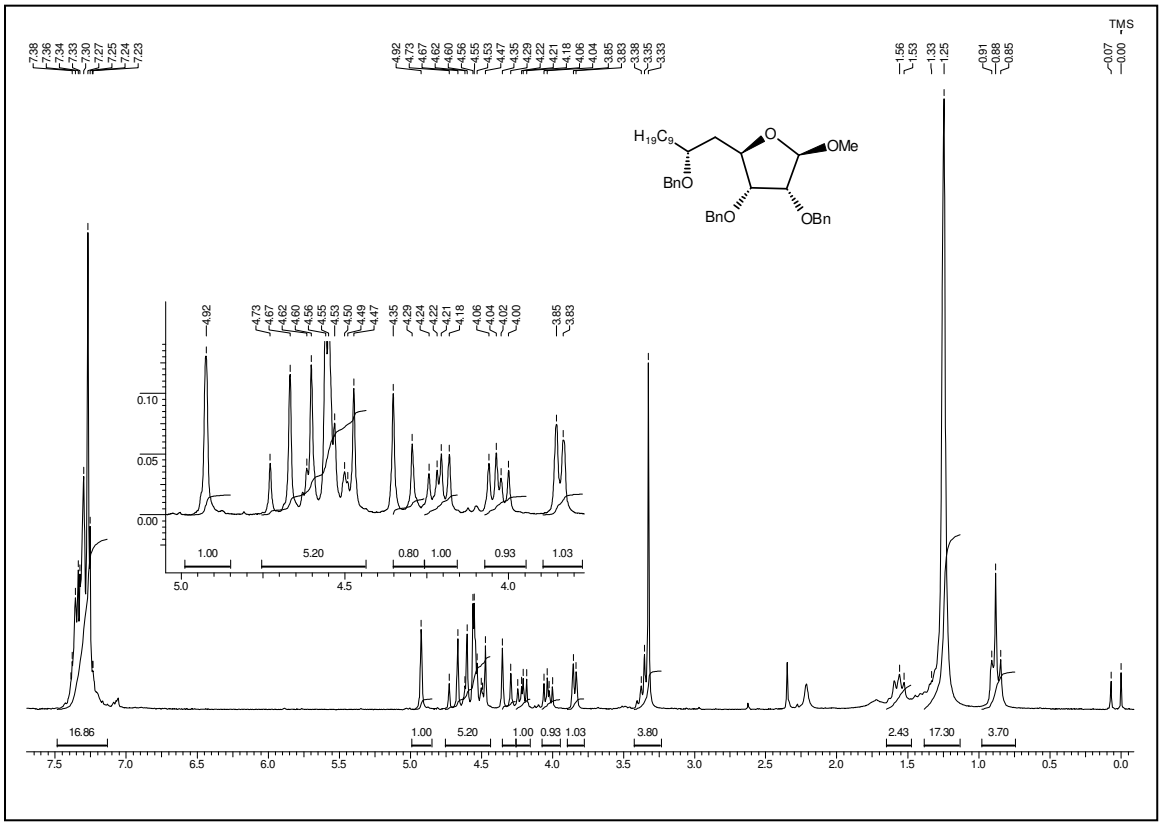
^{13}C NMR spectrum of compound 14 in $CDCl_3$



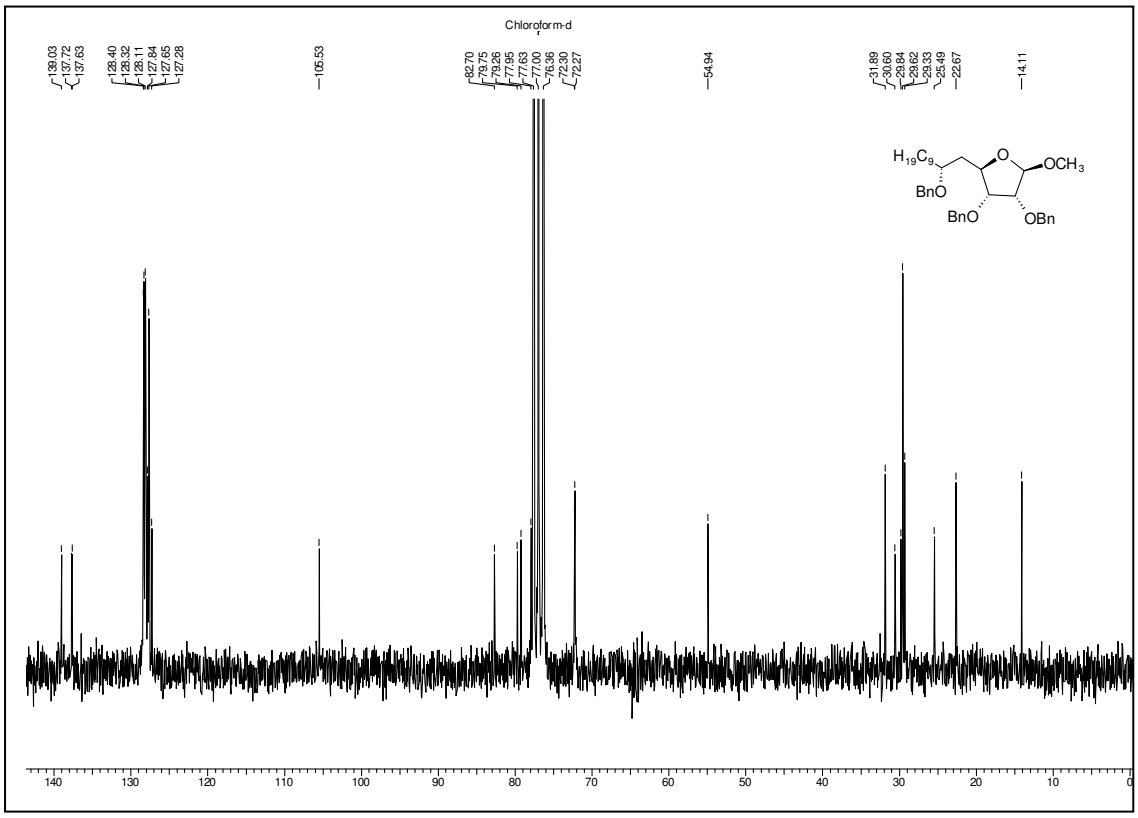
^{1}H NMR spectrum of compound 15 in $CDCl_3$



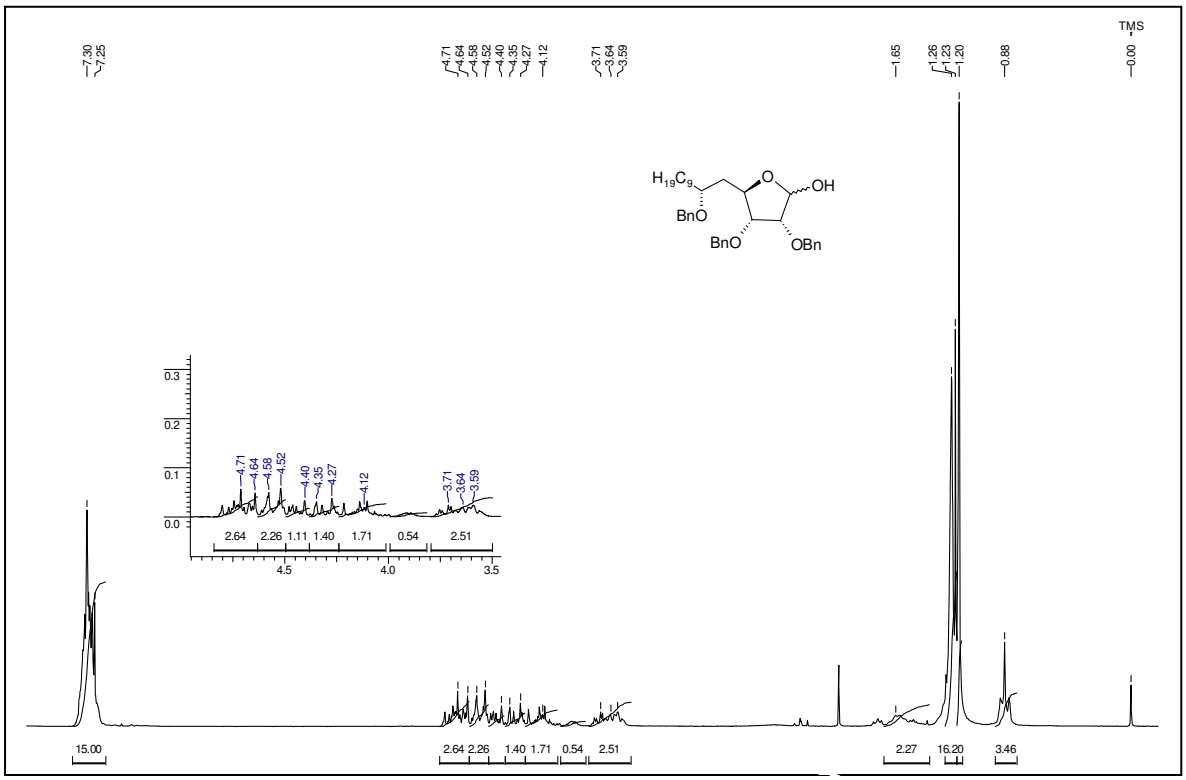
^{13}C NMR spectrum of compound 15 in $CDCl_3$



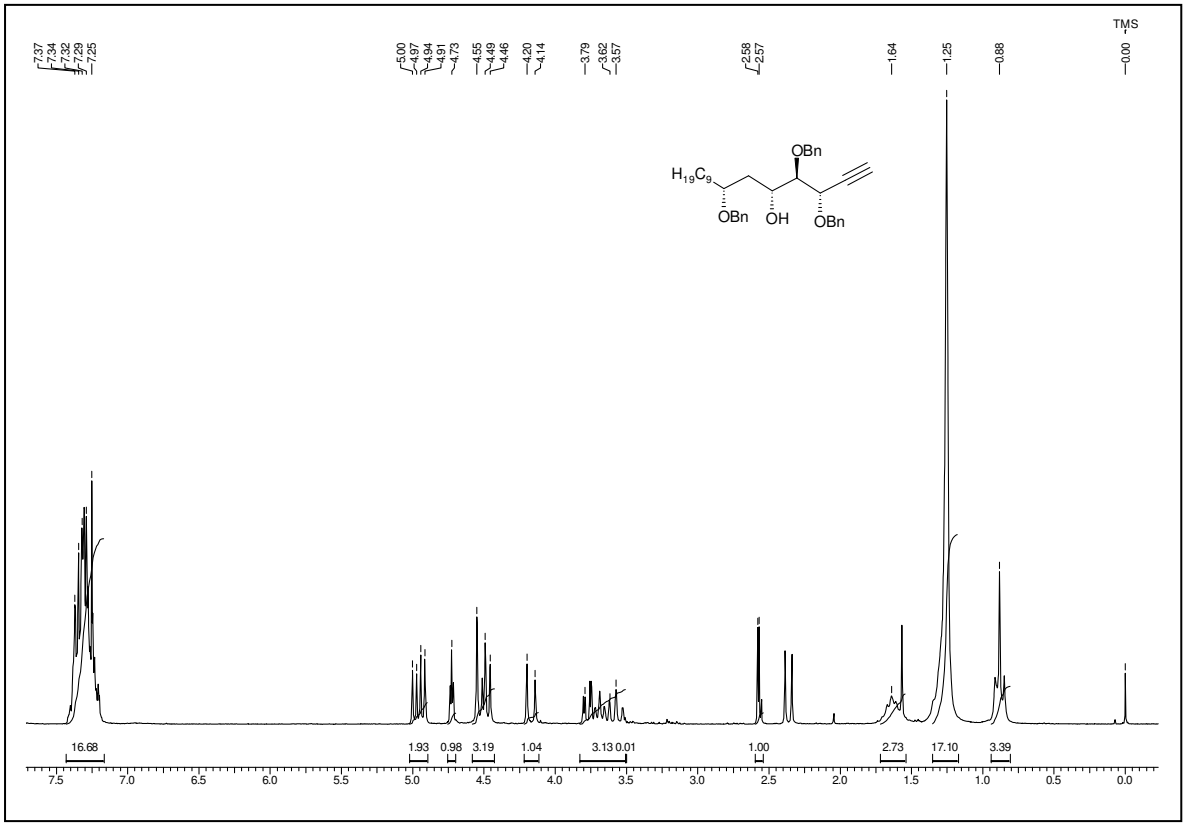
^{1}H NMR spectrum of compound 16 in $CDCl_3$



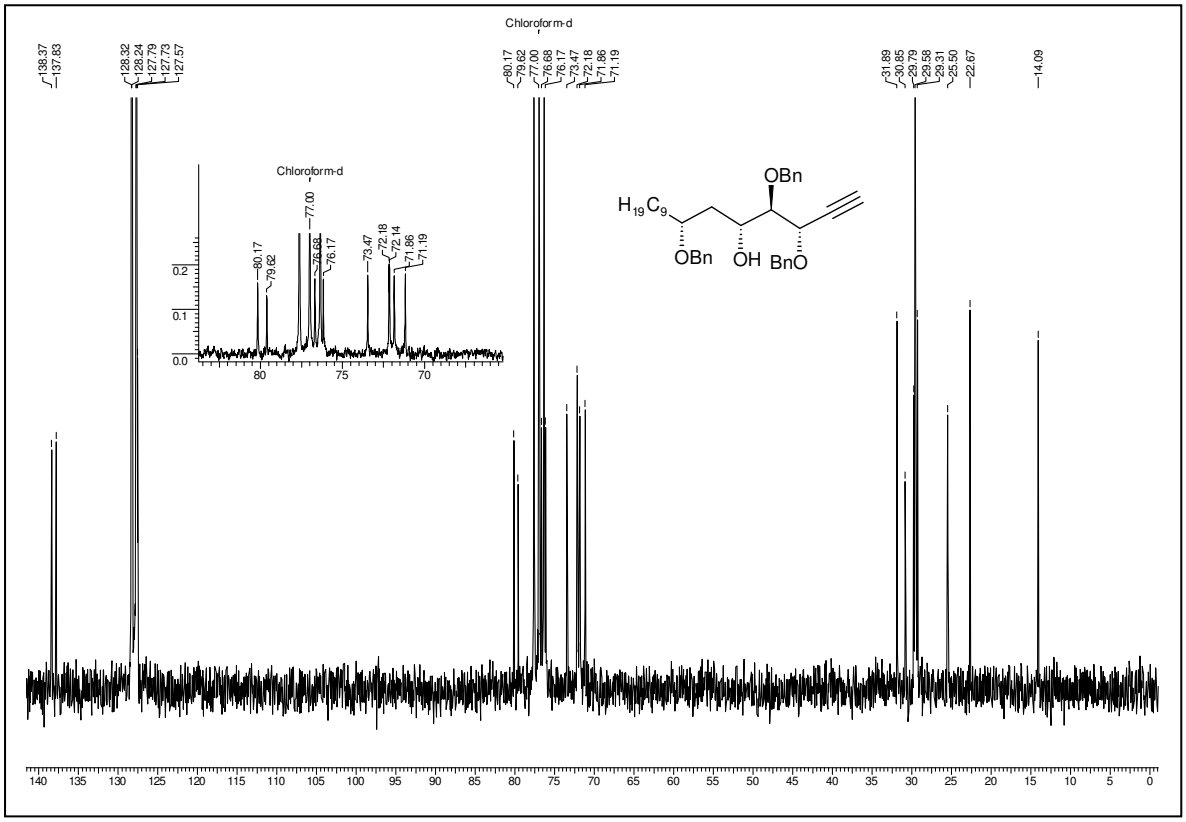
^{13}C NMR spectrum of compound 16 in $CDCl_3$



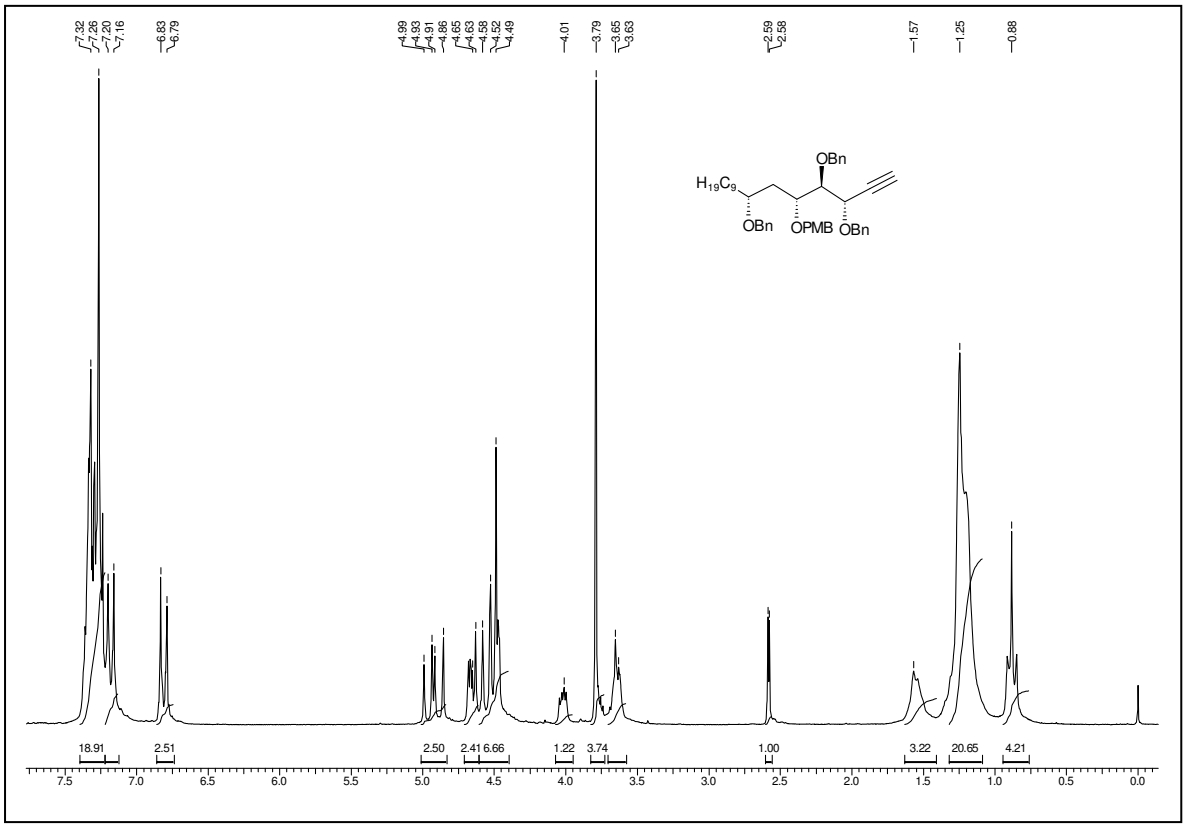
^{1}H NMR spectrum of compound 17 in $CDCl_3$



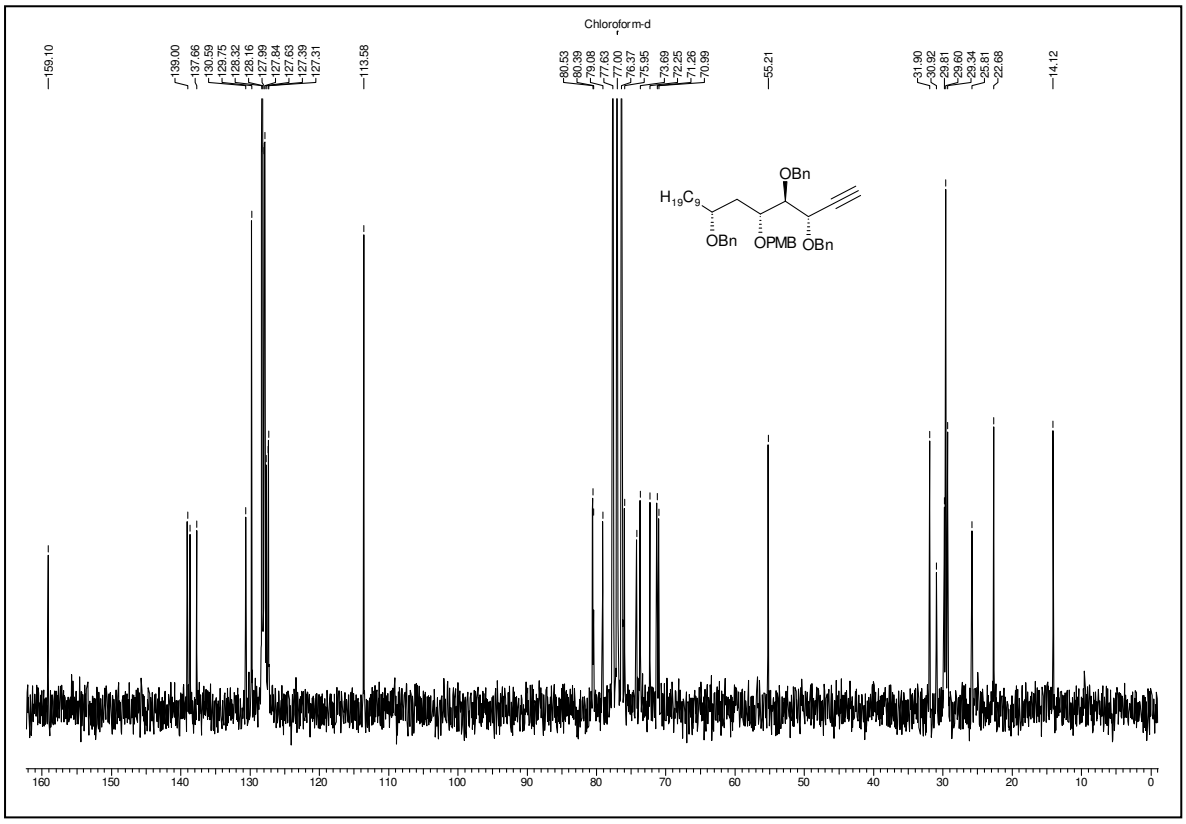
^{1}H NMR spectrum of compound 6 in $CDCl_3$

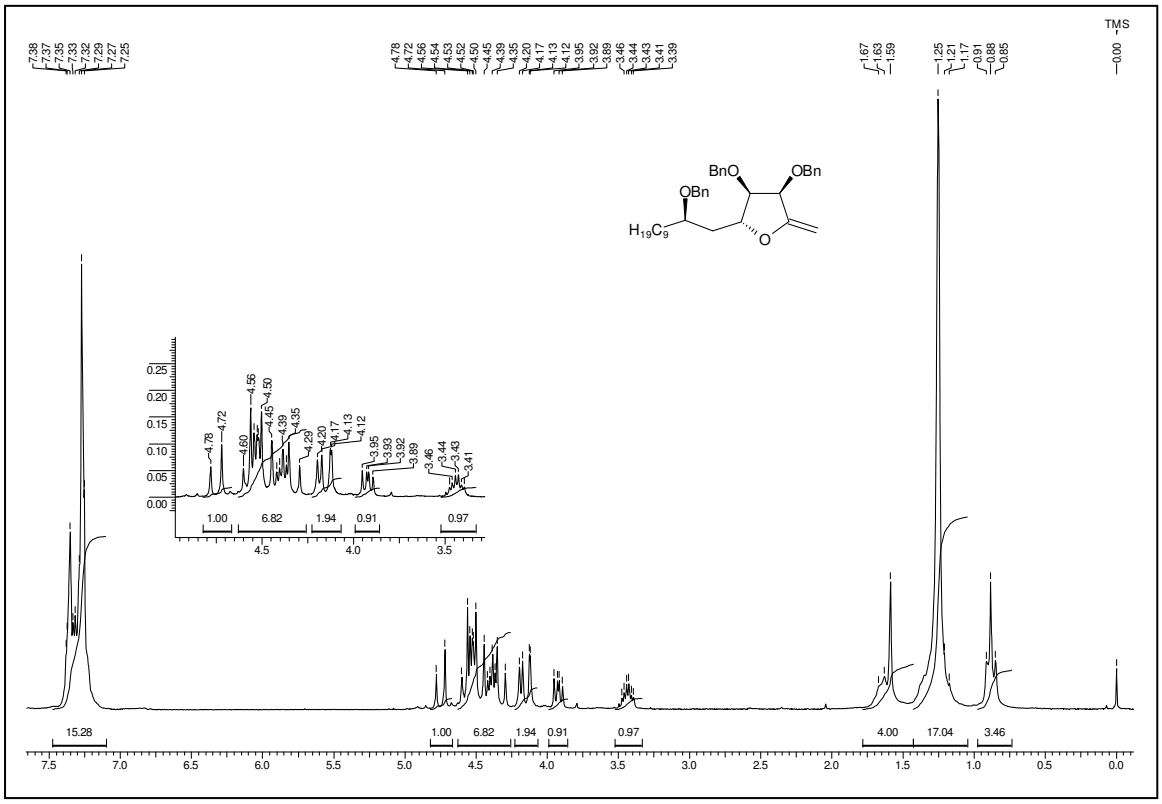


^{13}C NMR spectrum of compound 6 in $CDCl_3$

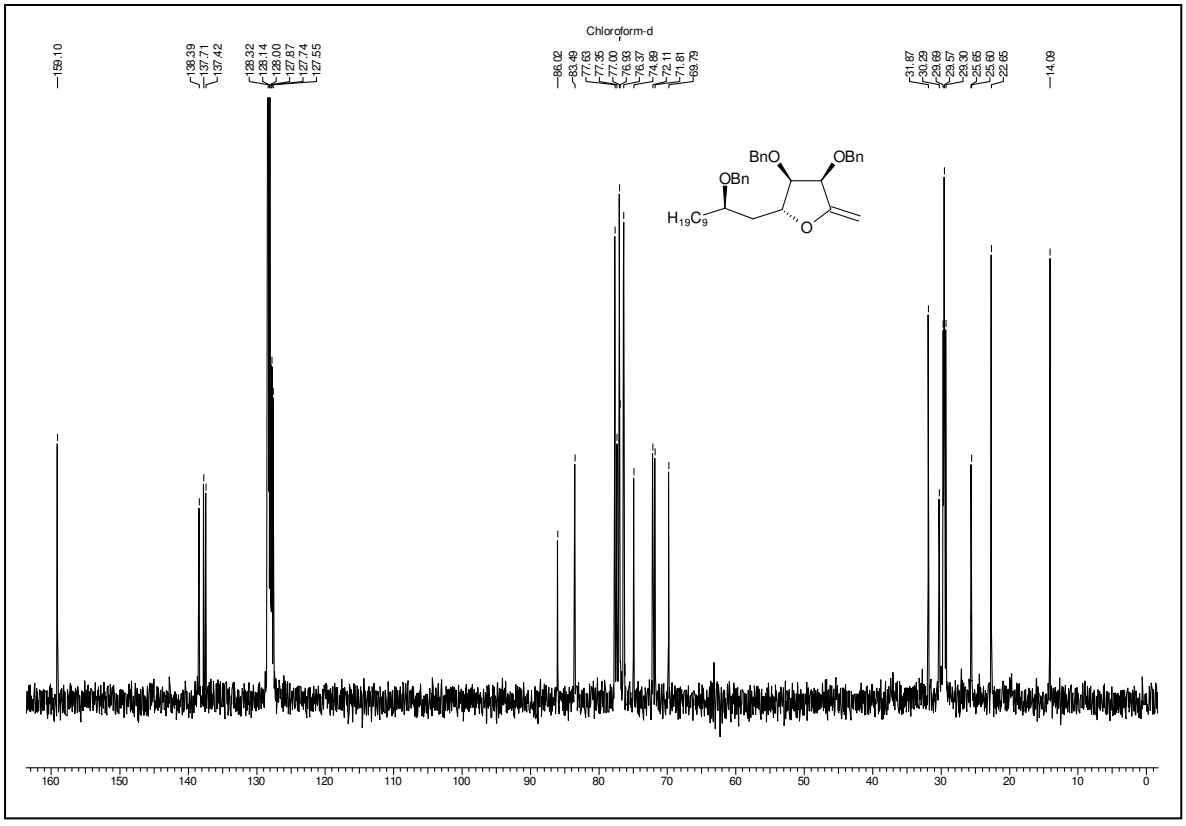


^{1}H NMR spectrum of compound 19 in $CDCl_3$

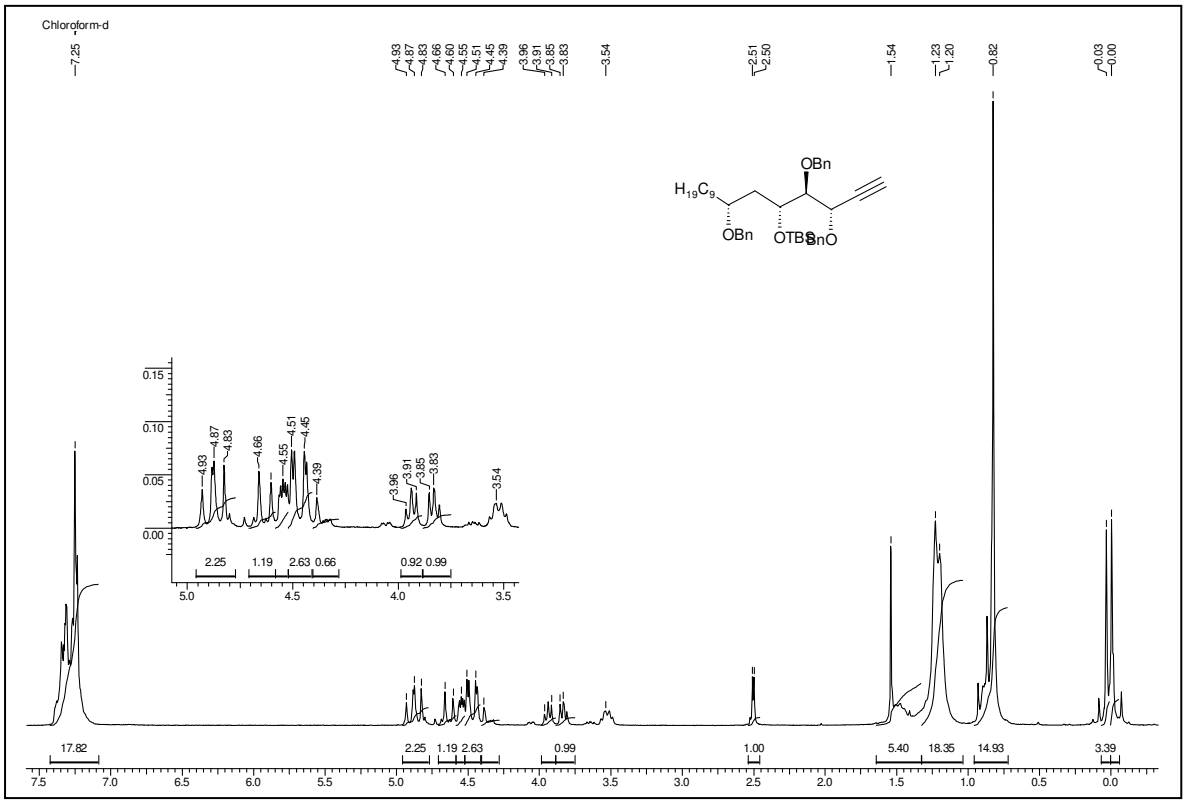




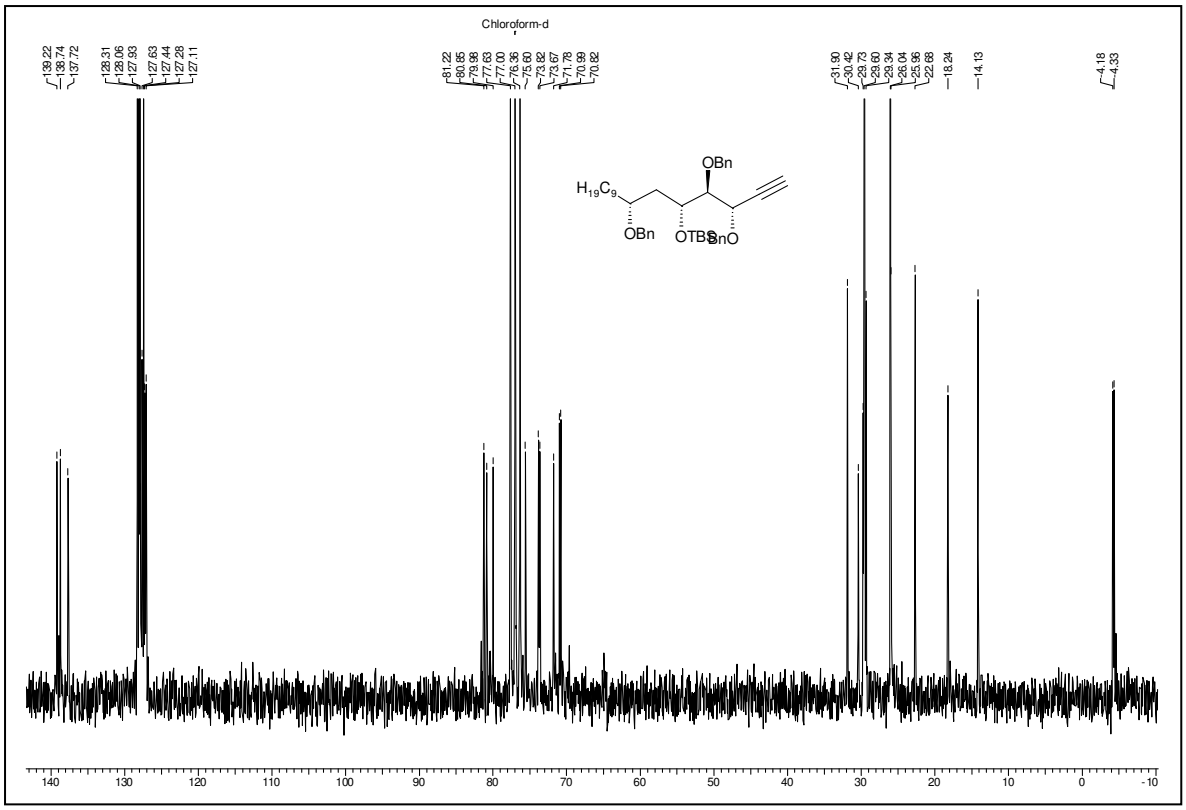
^{1}H NMR spectrum of compound 18 in $CDCl_3$



^{13}C NMR spectrum of compound 18 in $CDCl_3$



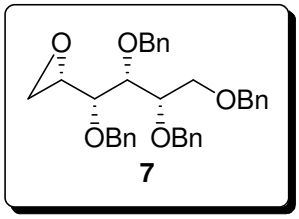
^{1}H NMR spectrum of compound 20 in $CDCl_3$



^{13}C NMR spectrum of compound 20 in $CDCl_3$

Section-II

Chiron approach for synthesis of epoxide fragment

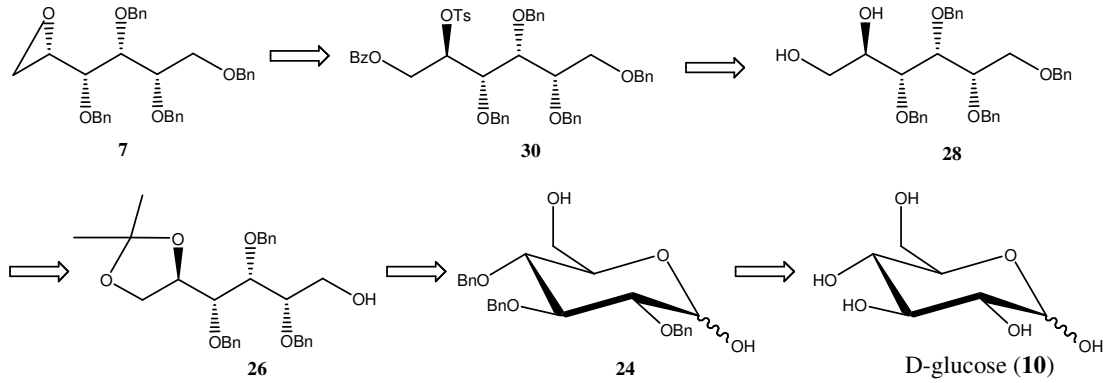


7

Retrosynthetic analysis

D-Glucose was choosen as synthon for the synthesis of epoxide fragment **7** as the absolute stereochemistries of aflastatin A at C_{28}, C_{29} and C_{30} are exactly matching with the C_2, C_3 and C_4 stereochemistries of D-glucose. Asymmetric center at C_{31} of aflastatin A could be obtained by inverting the C_5 stereocenter of D-glucose. Retrosynthetically epoxide **7** was envisaged its construction from the diester **30** by base mediated hydrolysis and SN^2 displacement of tosyl group. Diester **30** could

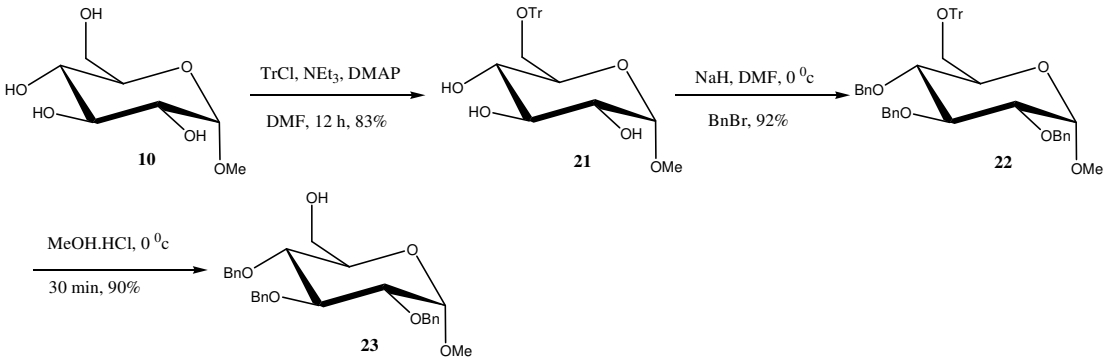
Scheme 8: - Retrosynthesis of epoxide fragment (7):



be easily obtainable from diol **28** which in turn could be obtained from lactol **24** through functional group interconversions. Lactol **24**, with all the stereocenters exactly matching with that of D-glucose, reveals D-glucose (**10**) as a synthon.

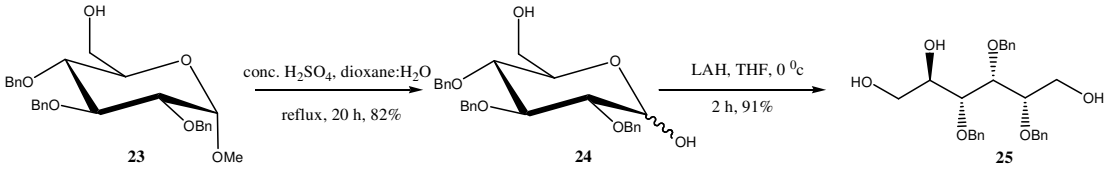
Our synthesis commenced with regioselective tritylation of primary hydroxyl of methyl-D-glucopyranoside **10** with TrCl, NEt_3 and cat. DMAP in dry DMF afforded the previously reported monotrityl ether **21** in 83% yield (**Scheme 9**).[42] The structure of the product **21** was confirmed by its ^1H NMR spectra in which 15 aromatic protons were resonated as a multiplet between 7.19-7.48 ppm and in ^{13}C NMR quaternary carbon of the trityl group was resonated at 86.6 ppm, a characteristic peak of trityl group. Tribenzylation of **21** was achieved by treating the compound **21** with NaH and BnBr in DMF to furnish the tribenzyl ether **22** in 92% yield. In ^1H NMR appearance of six-benzylic protons between 4.6-4.9 ppm, in ^{13}C NMR three CH_2 groups were seen at 72.8, 73.6 and 75.8 ppm respectively and a $(M+1)^+$ peak at 587.8 in ESI-MS spectrum are the confirmative features of the product. Detritylation was accomplished upon exposure of **22** to methanloic.HCl in MeOH at 0 ^{0}c for 30 min to deliver the alcohol **23** whose structure was deduced from ^1H NMR,

Scheme 9: -



^{13}C NMR, ESI-MS and IR spectra. Disappearance of aromatic protons, due to trityl group, in ^{1}H NMR and the quaternary carbon in ^{13}C NMR was pinpointed the conversion, duly supported by ESI-MS [$(M+23)^+$ at m/z 487.8] and IR spectra (CH_2O-H stretching at 3561 cm^{-1}). Conc. H_2SO_4 catalysed hydrolysis of compound **23** in a 2:1 solvent mixture of dioxane and water on waterbath resulted to the lactol **24** (**Scheme 10**) in 82% Yield. Lactol **24** was substantiated for its structure from the spectral data. For example absence of methoxy signal in both ^{1}H NMR and ^{13}C NMR, the –OH stretching in IR at 3405 cm^{-1} and a mass peak at m/z 451.64 $(M+1)^+$ in ESI-MS spectrum were the indicative of lactol **24**. Conversion of the lactol **24** to triol **25** was accomplished by treating the lactol **24** with LAH in THF at rt for 2h to deliver the triol **25** in 91% yield.

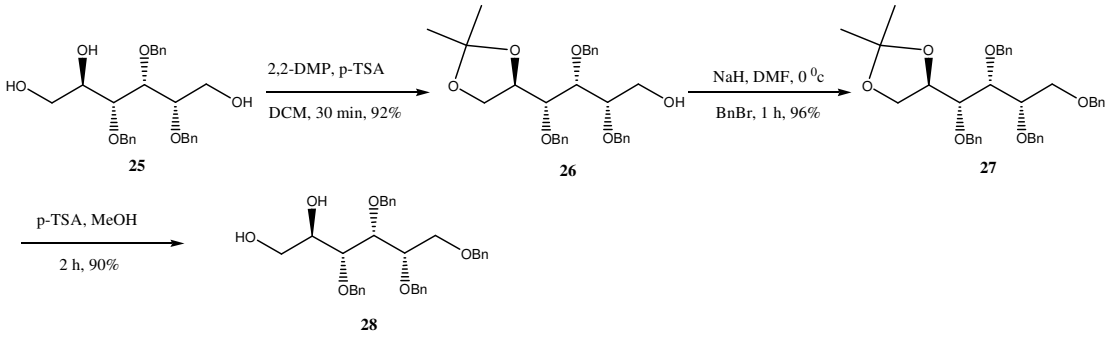
Scheme 10: - Synthesis of triol 25



The structure of triol **25** was confirmed by its spectral data. Absence of the anomeric proton in ^{1}H NMR and anomeric carbon in ^{13}C NMR, a broad peak in IR spectrum between 3560-3490 cm^{-1} and m/z peak at 475.6 $(M+23)^+$ in ESI-MS spectrum hint at the structure. The vicinal diol of the triol **25** was protected as its isopropylidene ketal by using 2,2-dimethoxy propane and cat. p-TSA in DCM for 30 min to afford the compound **26** in 92% yield (**Scheme 11**), whose structure was unambiguously assigned based on spectral data. In ^{1}H NMR two gem-dimethyls of isopropylidene ketal appeared as two singlets at 1.29 and 1.41 ppm, while the –OH proton as a broad

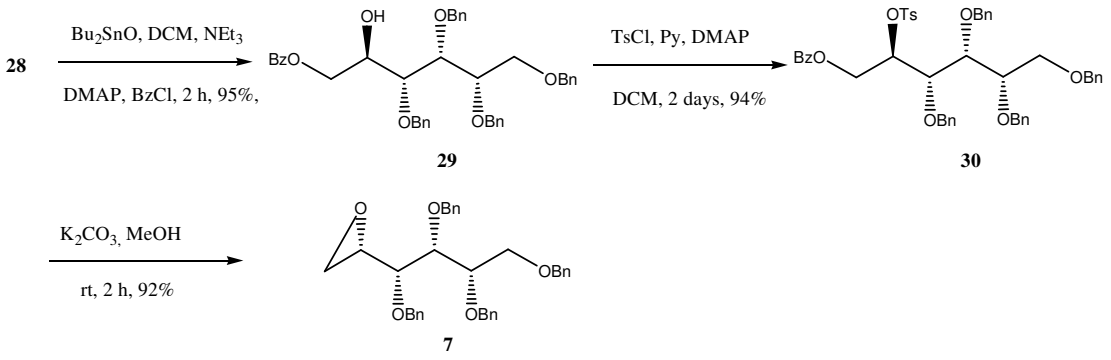
singlet at 3.49 ppm. ^{13}C NMR showed two peaks at 24.9 and 26.4 ppm corresponding to two methyl groups and a peak due to quaternary carbon at 108.8 ppm. A peak in mass spectrm at m/z 493.6 $(M+1)^+$ is an additional support.

Scheme 11: - Synthesis of epoxide precursor



Primary alcohol of compound **26** was protected as its benzyl ether by treating with NaH and benzyl bromide in DMF at 0 ^{0}c for 1h to furnish the tetrabenzyl ether **27** in 96% yield. Disappearance of a broad peak due to –OH in IR spectra, appearance of two additional protons between 4.5-4.8 ppm and five aromatic protons between 7.2-7.4 ppm and a peak in mass spectrum at m/z 605.4 $(M+23)^+$ were the indicative of the product **27**. Transketalization of compound **27** was achieved upon exposure to p-TSA in MeOH for 2h to deliver the diol **28** in 90% yield. The structural features were unambiguously corroborated from the combined spectral data *viz*. ^1H NMR, ^{13}C NMR, IR and ESI-MS spectra. The peaks owing to isopropylidene group disappeared in the ^1H NMR and ^{13}C NMR spectra. The ESI mass spectrum gave a highest mass peak at (*m/z*) 565.7 $(M+23)^+$ and a broad peak in IR spectrum at 3510 cm^{-1} was observed.

Scheme 12: - Synthesis of epoxide (7)

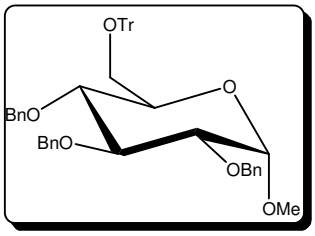


The next step of regioselective benzoylation of diol **28** to benzoate ester **29** was conveniently achieved with Bu_2SnO, NEt_3, cat. DMAP and BzCl in DCM as per the literature procedure.[43] In ^1H NMR peaks owing to benzoate were observed at 7.4 (2H), 7.5 (1H) and 8.0 ppm (2H) respectively, ^{13}C showed a carbonyl peak corresponding to the benzoate at 166.5 ppm and IR spectrum indicated the ester stretching frequency at 1715 cm^{-1}. Tosylation of secondary alcohol of **29** was performed using TsCl, Py and DMAP in DCM for 2 days to furnish the diester **30** in 94% yield. The diester **30** was confirmed by the presence of additional peaks in ^1H NMR due to tosylate group i.e., a singlet at 2.2 ppm for aryl methyl and two doublets at 7.0 and 7.62 ppm of A_2B_2 pattern. ESI-MS spectrum gave a peak at m/z 824.3 $(M+23)^+$ is an added support. The epoxide **7** was derived out of diester in 92% yield on exposure to K_2CO_3 in MeOH at rt for 2h. The product was readily confirmed by the ^1H NMR spectrum with substantial information from ^{13}C NMR, IR, EI and Mass spectral studies. While the protons specifying -OTs and -Bz groups were no more, new peaks in the region of 2.2-3.00 ppm, characteristic of terminal epoxy protons were observed in the ^1H NMR spectrum and in the ^{13}C NMR carbons of epoxy group were seen at 42.7 and 53.4 ppm respectively. The ESI mass spectrum gave a molecular ion peak at (*m*/*z*) 525.7 $(M+1)^+$.

Experimental

Section-II; Experimental

Methyl-2,3,4-tri-O-benzyl-6- O-trityl-α/β-D-glucopyranoside (22) : -



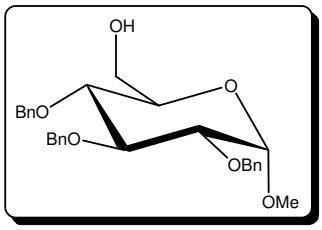
NaH (1.71 g, 71.2 mmol) was added in portions to an ice cooled solution of triol **21** (10 g, 22.9 mmol) in DMF (100 ml) over a period of 10 min. Benzyl bromide (8.5 ml, 71. 2 mmol) in DMF (15 ml) was added slowly drop by drop over a period of 10 min. Reaction mixture was warmed to rt and stirred overnight, cooled to 0 ^{0}c, quenched with ice and diluted with water. The reaction mixture was partitioned between water and ethyl acetate, combined organic layers were dried over Na_2SO_4, volatiles were removed and the crude was purified by column chromatography (1:9 ethyl acetate/hexane) to afford the tribenzyl ether **22** as a colourless thick oil (1.49 g, 92%).

Yield	: 92%
Mol. Formula	: $C_{47}H_{46}O_6$;
$[\alpha]_D^{25}$	: +71.0 (c 2.7, $CHCl_3$)
IR (CHCl3) ν	: 3101, 2934, 2400, 1455, 1216, 1034, 751, 669 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 3.15-3.18 (m, 1H), 3.34 (s, 3H), 3.53-3.64 (m, 2H), 3.67 (s, 1H), 3.78-4.17 (m, 2H), 4.26-4.39 (m, 1H), 4.56-5.01 (m, 6H), 7.17-7.55 (m, 30H).
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ 44.72 (d), 54.78 (d), 56.41 (d), 62.19 (t), 62.48 (t), 70.14 (d), 71.91 (t), 72.72 (d), 73.17 (t), 74.40 (d), 74.67 (t), 74.83 (t), 74.88 (t), 75.81 (t), 78.00 (s), 80.13 (d), 82.15 (d), 82.47 (d), 84.52 (d), 86.18 (d), 86.22 (d), 97.76 (d), 104.45 (d), 126.80 (d), 127.53 (d), 127.65 (d), 127.89 (d), 128.01 (d), 128.28 (d), 128.64 (d), 137.75 (s), 137.81 (s), 138.12 (s), 138.16 (s), 138.42 (s), 138.52 (s), 138.58 (s), 143.81 (s).
Elemental Analysis	Calcd.: C, 76.86; H, 6.56

Found: C, 76.91 H, 6.49

ESI-MS (m/z) : 587.83 $(M+1)^+$

Methyl-2,3,4-tri-O-benzyl-α-D-glucopyranoside (23) : -



To an ice cold solution of tribenzyl ether **22** (3 g, 4.244 mmol) in MeOH (50 ml) was added methanolicHCl (20 ml) and stirred for 30 min, neutralized with NEt_3 (10 ml), solvent was removed under vacuum and the crude was chromatographed on silica (3.5:6.5 ethyl acetate/hexane) to yield the primary alcohol **23** (1.77 g, 90%) as a colourless oil.

Yield : 90%

Mol. Formula : $C_{28}H_{32}O_6$;

$[\alpha]_D^{25}$: +28.28 (c 0.95, $CHCl_3$)

IR ($CHCl_3$) ν : 3561, 3101, 2921, 2406, 1719, 1465, 1216, 1044, 699, 667 cm^{-1}.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 3.23 (s, 3H), 3.50-3.59 (m, 1H), 3.66-3.76 (m, 3H), 3.79-3.95 (m, 2H), 4.56 (s, 2H), 4.58-4.64 (m, 4H), 4.72 (d, J = 12.38 Hz, 1H), 4.875 (d, J = 10.99 Hz, 1H), 7.22-7.27 (m, 15H).

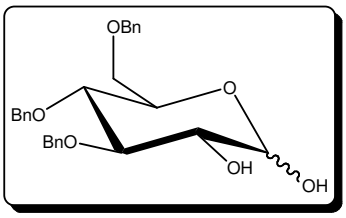
^{13}C NMR ($CDCl_3$, 50 MHz) : δ 54.65 (q), 62.17 (d), 71.99 (d), 72.10 (t), 72.86 (t), 74.58 (d), 74.69 (d), 75.09 (t), 80.08 (d), 99.19 (d), 127.49 (d), 127.61 (d), 127.65 (d), 127.80 (d), 127.93 (d), 128.30 (d), 138.09 (s), 138.31 (s), 138.35 (s).

Elemental Analysis Calcd.: C, 72.39; H, 6.94

Found: C, 72.46 H, 6.54

ESI-MS (m/z) : 487.83 $(M+23)^+$

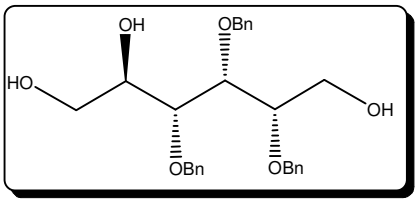
2,3,4-tri-O-benzylα/β-D-glucopyranose (24): -



Conc. H_2SO_4 (1 ml) was added to cooled solution of compound **23** (2 g, 4.30 mmol) in dioxane and water (2:1, 40 ml) and heated on water bath for 20 h, cooled to 0 ^{0}c and neutralized with NEt_3, two layers were separated and the aqueous layer was extracted into ethyl acetate, dried over Na_2SO_4, concentrated under reduced pressure and the crude was purified by column chromatography (1.5:8.5 ethyl acetate/hexane) to produce the lactal **24** (1.58 g, 82%) as a colourless liquid.

Yield	: 82%
Mol. Formula	: $C_{27}H_{30}O_6$;
$[\alpha]_D^{25}$	: +23.37 (c 3.0, $CHCl_3$)
IR (CHCl3) ν	: 3405, 3101, 2934, 2400, 1455, 1216, 1034, 751, 669 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 3.32-3.44 (m, 1H), 3.48-3.57 (m, 2H), 3.62-3.72 (m, 2H), 3.76-3.78 (m, 1H), 3.90-4.13 (m, 2H), 4.58-4.72 (m, 3H), 4.82-4.98 (m, 3H), 5.17 (d, J = 3.16 Hz, 1H), 7.25-7.32 (m, 15H).
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ 65.23 (d), 65.37 (d), 71.13 (t), 71.72 (t), 71.98 (t), 74.34 (d), 76.05 (d), 76.16 (d), 76.81 (d), 100.56 (d), 126.90 (d), 127.55 (d), 127.69 (d), 127.79 (d), 127.91 (d), 128.06 (d), 128.09 (d), 128.39 (d), 128.48 (d), 137.79 (s), 137.83 (s), 137.87 (s).
Elemental Analysis	Calcd.: C, 71.98; H, 6.71 Found: C, 72.06 H, 6.64
ESI-MS (m/z)	: 451.64 $(M+1)^+$

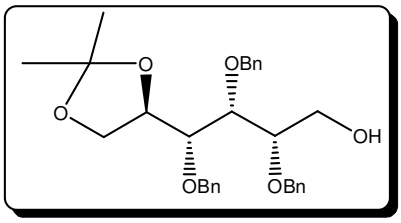
(2R,3R,4R,5S)-3,4,5-tris(benzyloxy)hexane-1,2,6-triol (25): -



LAH (0.606 g, 15.98 mmol) was added to a vigorously stirred solution of lactol **24** (7.2 g, 15.98 mmol) in THF (50 ml) at 0 ^{0}c and stirred at rt for 2h, cooled to 0 ^{0}c and quenched with sat. Na_2SO_4, solvent was decanted and washed with ethyl acetate, combined organics were dried over Na_2SO_4, volatiles were removed and the residue was purified by column chromatography (1:1 ethyl acetate/hexanes) to furnish the triol **25** (6.58 g, 91%) as a colourless liquid.

Yield	: 91%
Mol. Formula	: $C_{27}H_{32}O_6$;
$[\alpha]_D^{25}$	+13.34 (c 2.45, $CHCl_3$)
IR ($CHCl_3$) ν	: 3560-3490, 3101, 2934, 2400, 1449, 1215, 1034, 756, 667 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 1.91 (s, 1H), 2.32 (s, 1H), 2.43 (s, 1H), 3.51 (d, J = 3.31 Hz, 1H), 3.65-3.75 (m, 4H), 3.82-3.90 (m, 3H), 4.59 (s, 2H), 4.65 (s, 2H), 4.97 (s, 2H), 7.29-7.32 (m, 15H).
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ 61.60 (t), 63.46 (t), 71.66 (d), 73.09 (t), 73.55 (t), 74.21 (t), 76.87 (d), 79.10 (d), 79.20 (d), 127.89 (t), 127.97 (t), 128.07 (t), 128.13 (t), 128.36 (t), 128.48 (t), 137.49 (s), 137.54 (s), 137.79 (s).
Elemental Analysis	Calcd.: C, 71.66; H, 7.13 Found: C, 71.72; H, 7.21
ESI-MS (m/z)	475.64 $(M+23)^+$

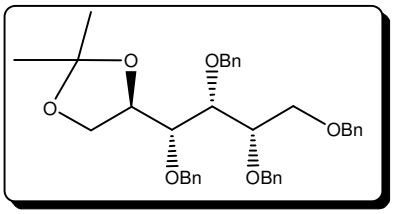
(2S,3R,4R)-2,3,4-tris(benzyloxy)-4-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)butan-1-ol (26): -



To a stirred solution of triol **25** (0.69 g, 1.52 mmol) in DCM (10 ml) was added 2,2 DMP (0.23 ml, 1.83 mmol) and cat. p-TSA, stirred for 30 min, neutralized with NEt_3, solvent was removed and the crude was purified by column chromatography (2:8 ethyl acetate/hexanes) to deliver the alcohol **26** (0.69 g, 92%).

Yield	: 92%
Mol. Formula	: $C_{30}H_{36}O_6$;
$[\alpha]_D^{25}$	+12.97 (c 1.0, $CHCl_3$)
IR ($CHCl_3$) ν	: 3510, 3101, 2934, 2400, 1454, 1216, 1034, 756, 669 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 1.29 (s, 3H), 1.41 (s, 3H), 3.49 (brs, 1H), 3.65-3.74 (m, 3H), 3.88-4.04 (m, 3H), 4.09-4.24 (m, 2H), 4.57-4.69 (m, 4H), 4.74 (d, J = 11.37 Hz, 1H),), 4.82 (d, J = 11.37 Hz, 1H), 7.26-7.31 (m, 15H).
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ 24.91 (q), 26.48 (q), 61.53 (t), 65.85 (t), 72.92 (t), 73.95 (t), 74.67 (t), 77.06 (d), 78.10 (d), 79.52 (d), 79.59 (d), 108.18 (s), 127.69 (t), 127.79 (t), 127.88 (t), 127.97 (t), 128.24 (t), 128.32 (t), 128.36 (t), 128.44 (t), 137.99 (s), 138.11 (s), 138.13 (s).
Elemental Analysis	Calcd.: C, 72.15; H, 7.37 Found: C, 73.21; H, 7.31
ESI-MS (m/z)	493.64 $(M+1)^+$

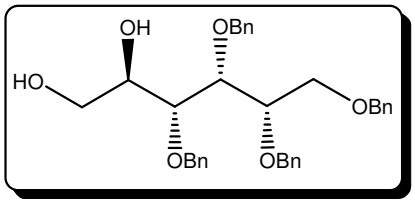
(R)-4-((1R,2R,3S)-1,2,3,4-tetrakis(benzyloxy)butyl)-2,2-dimethyl-1,3-dioxolane (27): -



To an ice cooled solution of alcohol **26** (1.15 g, 2.334 mmol) in DMF (15 ml) was added NaH (0.084 g, 3.50 mmol) and stirred for 10 min, benzyl bromide (0.33 ml, 2.801 mmol) was added and stirred at rt for 1h, cooled to 0 ^{0}c and quenched with ice, diluted with water, extracted into ethyl acetate, dried over Na_2SO_4, volatiles were removed and the crude was purified by column chromatography (1:9 ethyl acetate/hexanes) to yield the tetrabenzyl ether **27** (1.30 g, 96%) as a colourless.

Yield	: 96%
Mol. Formula	: $C_{37}H_{42}O_6$;
$[\alpha]_D^{25}$	+18.92 (c 1.0, $CHCl_3$)
IR ($CHCl_3$) ν	: 3091, 2934, 2400, 1454, 1216, 756, 676 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 1.29 (s, 3H), 1.41 (s, 3H), 3.46 (dd, *J* = 10.43, 5.17 Hz, 1H), 3.635 (dd, *J* = 10.43, 3.15 Hz, 1H), 3.715 (dd, *J* = 5.94, 4.29 Hz, 1H), 3.845 (dd, *J* = 5.70, 3.29 Hz, 1H), 3.90-4.02 (m, 2H), 4.07-4.22 (m, 2H), 4.42 (s, 2H), 4.52-4.64 (m, 3H), 4.69-4.79 (m, 3H), 7.27-7.36 (m, 20H).
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ 24.98 (q), 26.48 (q), 65.80 (t), 69.95 (t), 72.90 (t), 73.26 (t), 74.05 (td), 74.67 (t), 77.17 (d), 78.40 (d), 78.74 (d), 79.68 (d), 108.11 (s), 127.49 (d), 127.53 (d), 127.59 (d), 127.71 (d), 127.92 (d), 128.23 (d), 128.33 (d), 138.18 (s), 138.32 (s), 138.45 (s), 138.55 (s).
Elemental Analysis	Calcd.: C, 76.26; H, 7.26 Found: C, 76.32; H, 7.30
ESI-MS (m/z)	605.4 $(M+23)^+$

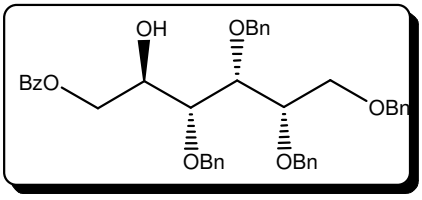
(2R,3R,4R,5S)-3,4,5,6-tetrakis(benzyloxy)hexane-1,2-diol (28) : -



To a stirred solution of compound **27** (1 g, 1.717 mmol) in MeOH (10 ml) was added cat. p-TSA and stirred at rt for 2h, neutralized with NEt_3, solvent was removed under reduced pressure and the residue was purified by column chromatography (4:6 ethyl acetate/hexanes) to furnish the diol **28** (0.838 g, 90%) as a colourless oil.

Yield	: 90%
Mol. Formula	: $C_{34}H_{38}O_6$;
$[\alpha]_D^{25}$	+12.27 (c 0.55, $CHCl_3$)
IR ($CHCl_3$) ν	: 3510, 3101, 2934, 2400, 1454, 1216, 1034, 756, 669 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 3.36 (brs, 1H), 3.59-3.62 (m, 3H), 3.65-3.71 (m, 2H), 3.74-3.83 (m, 2H), 3.90-3.97 (m, 1H). 4.41 (s, 2H), 4.53-4.66 (m, 5H), 4.72 (s, *J* = 11.50 Hz, 1H), 7.22-7.32 (m, 20H).
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ 60.35 (t), 63.66 (t), 69.46 (d), 71.82 (d), 73.12 (t), 73.26 (t), 73.58 (t), 73.84 (t), 77.37 (d), 78.26 (d), 127.68 (d), 127.80 (d), 127.85 (d), 127.97 (d), 128.07 (d), 128.13 (d), 128.44 (d), 137.75 (s), 137.91 (s), 137.97 (s), 138.12 (s).
Elemental Analysis	Calcd.: C, 75.25; H, 7.06 Found: C, 75.32; H, 7.10
ESI-MS (m/z)	565.72 $(M+23)^+$

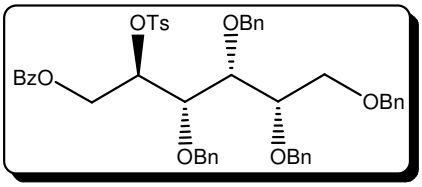
(2R,3R,4R,5S)-3,4,5,6-tetrakis(benzyloxy)-2-hydroxyhexyl benzoate (29) : -



To an ice cold solution of diol **28** (0.75 g, 1.382 mmol) in DCM (20 ml) was added Bu_2SnO (0.035 g, 0.1382 mmol) and stirred for 10 min. NEt_3 (0.212 ml, 1.52 mmol), BzCl (0.16 ml, 1.382 mmol) and cat. DMAP were added and stirred for 2h, diluted with water, two layers were separated, aq layer was extracted into DCM. Combined organics were dried over Na_2SO_4, volatiles were removed and the crude was purified by column (1.5:8.5 ethyl acetate/hexanes) to accomplish the benzoate **29** (0.849 g, 95%) as a colourless oil.

Yield	: 95%
Mol. Formula	: $C_{41}H_{42}O_7$;
$[\alpha]_D^{25}$	+16.60 (c 1.3, $CHCl_3$)
IR ($CHCl_3$) ν	: 3490, 3101, 2934, 2400, 1715, 1454, 1216, 1034, 756, 669 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 3.31 (brs, 1H), 3.65 (dd, *J* = 5.31, 3.03 Hz, 1H), 3.76 (dd, *J* = 7.07, 4.55 Hz, 2H), 3.93 (t, J = 4.40 Hz, 1H), 3.99 (t, J = 4.40 Hz, 1H), 4.07-4.17 (m, 2H), 4.35-4.78 (m, 8H), 7.23-7.33 (m, 20H), 7.44 (dt, , *J* = 7.58, 1.39 Hz, 2H), 7.55 (dt, , *J* = 7.45, 1.39 Hz, 1H), 8.015 (dt, *J* = 7.07, 1.52 Hz, 2H).
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ 66.31 (t), 69.50 (t), 70.40 (d), 73.10 (t), 73.26 (t), 73.36 (t), 74.08 (t), 77.47 (d), 78.10 (d), 127.68 (d), 127.74 (d), 127.82 (d), 127.94 (d), 128.10 (d), 128.14 (d), 128.30 (d), 128.36 (d), 128.48 (d), 129.68 (d), 130.10 (s), 132.96 (d), 137.67 (s), 137.71 (s), 137.97 (s), 138.10 (s), 166.65 (s).
Elemental Analysis	Calcd.: C, 76.14; H, 6.56 Found: C, 76.18; H, 6.62
ESI-MS (m/z)	669.83 $(M+23)^+$

(2R,3S,4R,5S)-1-(benzoyloxy)-3,4,5,6-tetrakis(benzyloxy)hexan-2-yl 4-methylbenzenesulfonate (30) : -

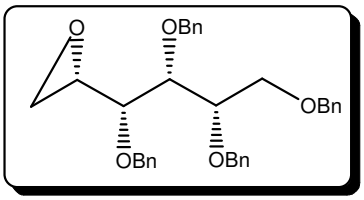


To a stirred solution of alcohol **29** (0.80 g, 1.23 mmol) in DCM (5 ml) was added TsCl (0.235 g, 1.23 mmol) , pyridine (0.116 ml, 1.23 mmol) and cat. DMAP and stirred at rt for 2days. Reaction mixture was diluted with water, two layers were separated and the aq layer was extracted into DCM. Combined organics were dried over Na_2SO_4, evaporated to dryness and the crude was purified by column (1:9 ethyl acetate/hexanes) to deliver the diester **30** (0.931 g, 94%) as a light yellow colour oil.

Yield	: 94%
Mol. Formula	: $C_{48}H_{48}O_9S$;
$[\alpha]_D^{25}$	+23.34 (c 0.9, $CHCl_3$)
IR ($CHCl_3$) ν	: 3490, 3101, 2934, 2400, 1715, 1454, 1216, 1034, 756, 669 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 2.26 (s, 3H), 3.61 (dd, *J* = 10.40, 6.05 Hz, 1H), 3.67-3.76 (m, 2H), 3.85-3.92 (m, 1H), 4.20 (dd, , *J* = 6.44, 1.77 Hz, 1H), 4.49-4.81 (m, 10H), 5.12-5.18 (m, 1H), 7.01 (d, *J* = 8.34 Hz, 2H), 7.17-7.38 (m, 22H), 7.51 (dt, *J* = 7.33, 1.77 Hz, 1H), 7.61 (d, , *J* = 8.34 Hz, 2H), 7.66-7.70 (m, 2H).
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ 21.58 (q), 63.34 (t), 69.76 (t), 73.10 (t), 73.32 (t), 74.52 (t), 75.20 (t), 78.29 (d), 79.17 (d), 80.64 (d), 127.47 (d), 127.59 (d), 127.68 (d), 127.73 (d), 127.79 (d), 128.08 (d), 128.24 (d), 128.31 (d), 128.35 (d), 129.58 (d), 129.66 (d), 129.72 (d), 132.87 (d), 133.82 (s), 137.85 (s), 137.89 (s), 138.21 (s), 138.26 (s), 144.38 (s), 165.87 (s).
Elemental Analysis	Calcd.: C, 71.98; H, 6.04 Found: C, 71.92; H, 6.09

ESI-MS (m/z) 824.04 $(M+23)^+$

(S)-2-((1R,2R,3S)-1,2,3,4-tetrakis(benzyloxy)butyl)oxirane (7) : -



K_2CO_3 (0.082 g, 0.624 mmol) was added to an ice cold solution of diester **30** (0.5 g, 0.624 mmol) in MeOH (10 ml) and stirred at rt for 2 h, MeOH was evaporated and the crude was purified by column chromatography (1:9 ethyl acetate/hexanes) to furnish the epoxide **7** (0.37 g, 92%) as a colorless liquid.

Yield : 92%

Mol. Formula : $C_{34}H_{36}O_5$;

$[\alpha]_D^{25}$ +18.54 (c 1.0, $CHCl_3$)

IR ($CHCl_3$) ν : 3490, 3101, 2934, 2400, 1715, 1454, 1216, 1034, 756, 669 cm^{-1}.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 2.25-2.28 (m, 1H), 2.37-2.42 (m, 1H), 3.09-3.10 (m, 2H), 3.325 (dd, *J* = 10.36, 4.80 Hz, 1H), 3.545 (dd, *J* = 10.36, 3.41 Hz, 1H), 3.69-3.76 (m, 1H), 3.88-3.97 (m, 1H), 4.26-4.81 (m, 8H), 7.23-7.32 (m, 20H).

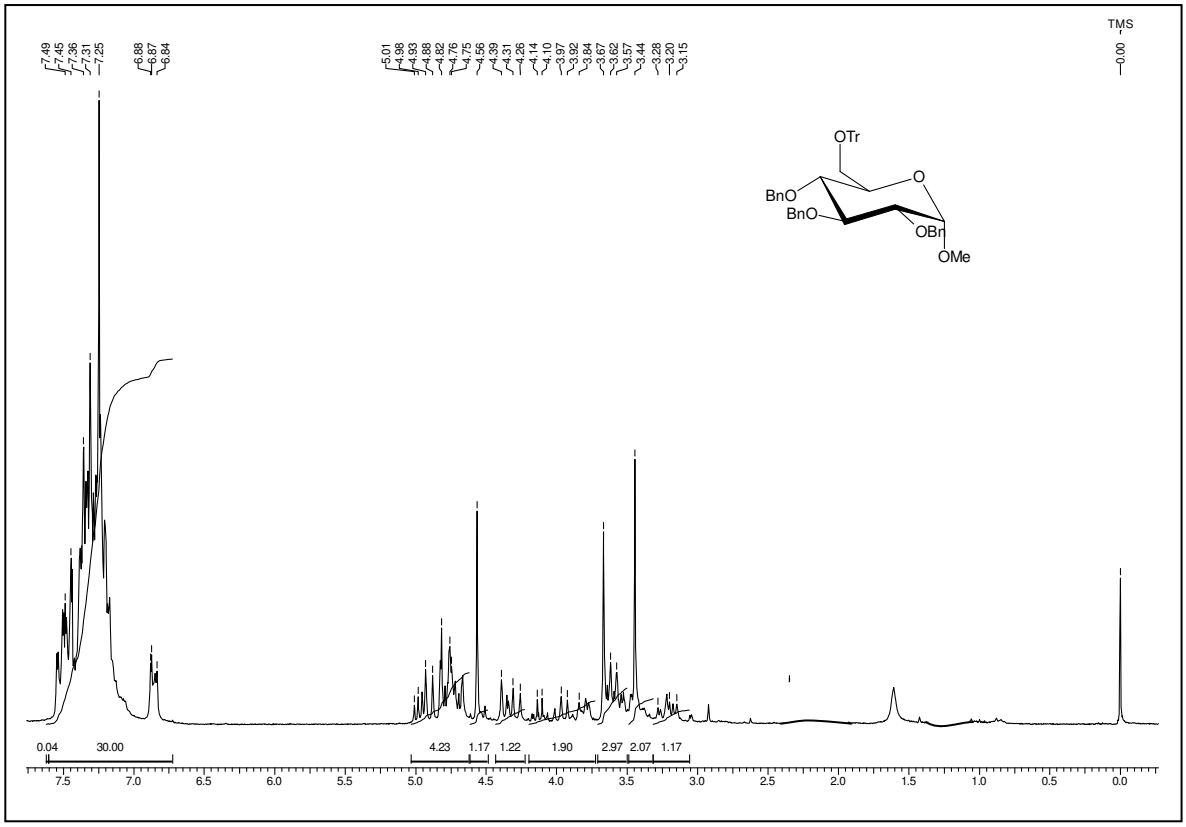
^{13}C NMR ($CDCl_3$, 50 MHz) : δ 42.73 (t), 53.40 (d), 69.39 (t), 71.87 (t), 72.87 (t), 73.23 (t), 74.63 (t), 78.82 (d), 79.36 (d), 79.84 (d), 127.53 (d), 127.57 (d), 127.60 (d), 127.71 (d), 127.74 (d), 127.92 (d), 128.19 (d), 128.27 (d), 128.63 (d), 137.96 (s), 138.04 (s), 138.14 (s), 138.50 (s).

Elemental Analysis Calcd.: C, 77.84; H, 6.92

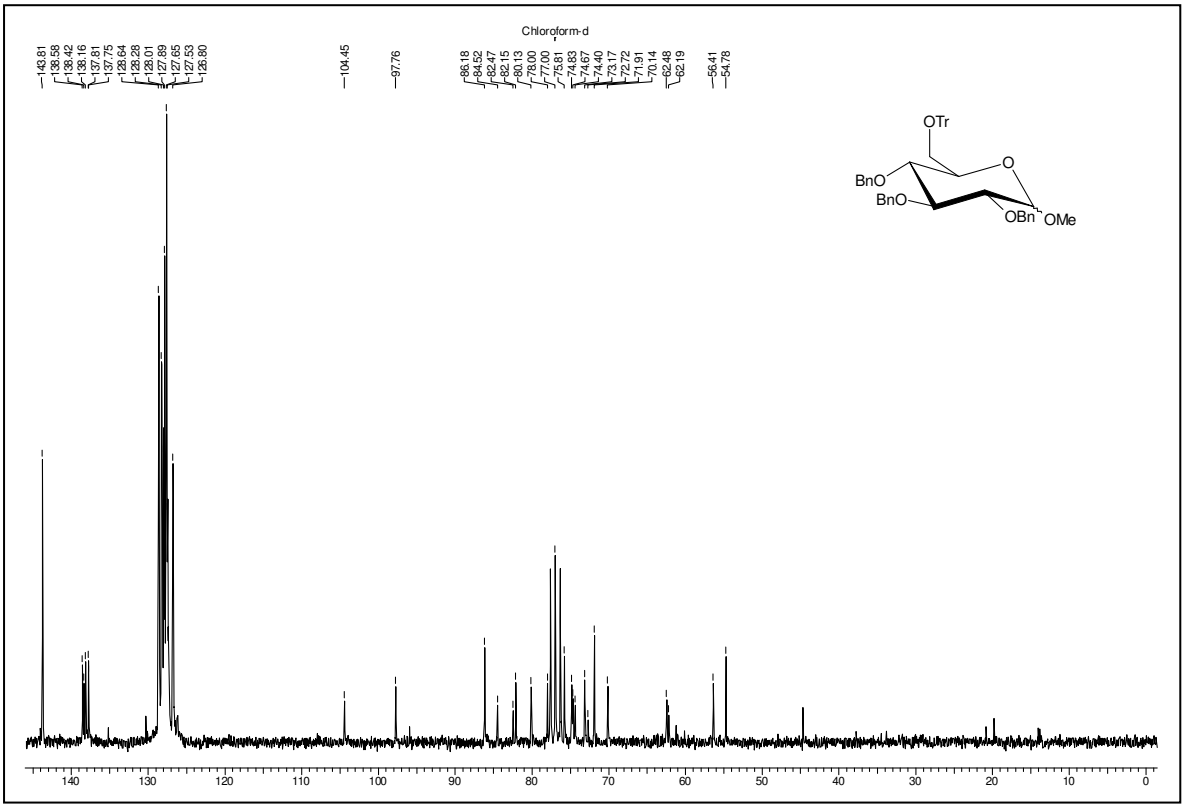
Found: C, 77.92; H, 6.89

ESI-MS (m/z) 525.72 $(M+23)^+$

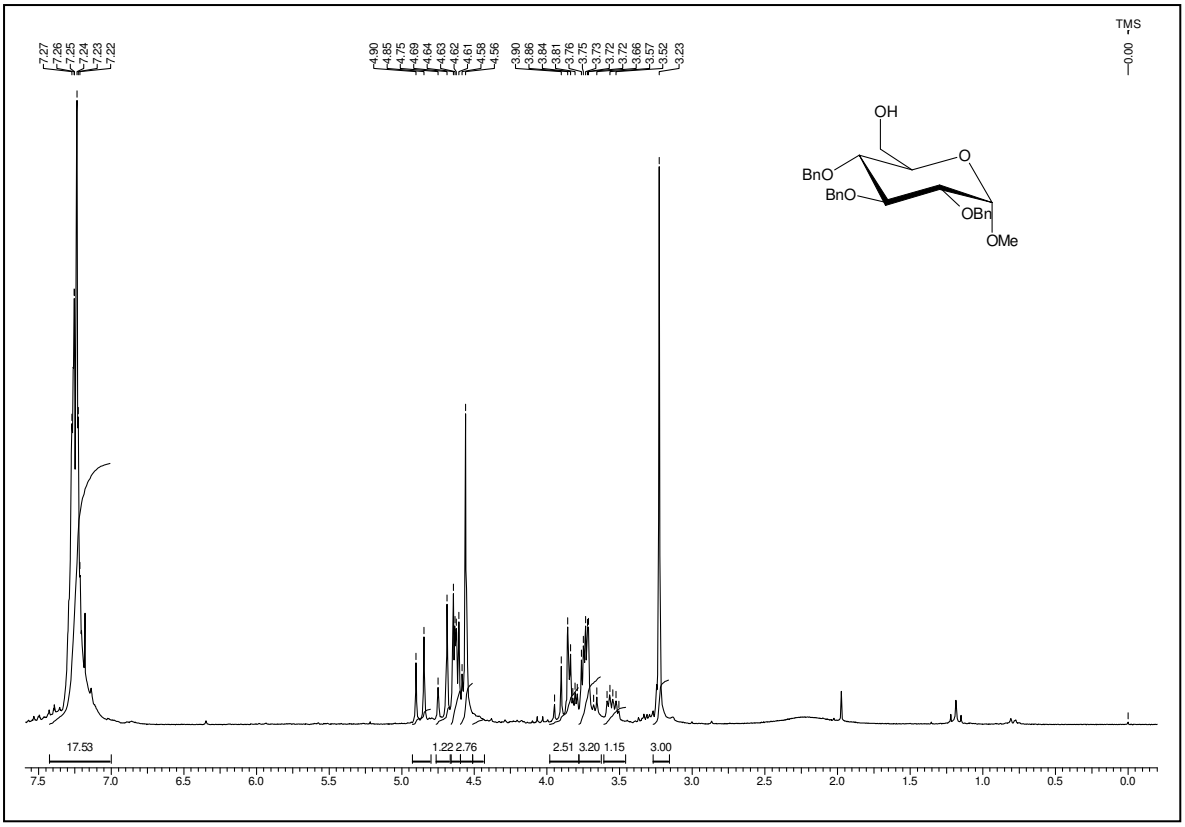
Spectral data



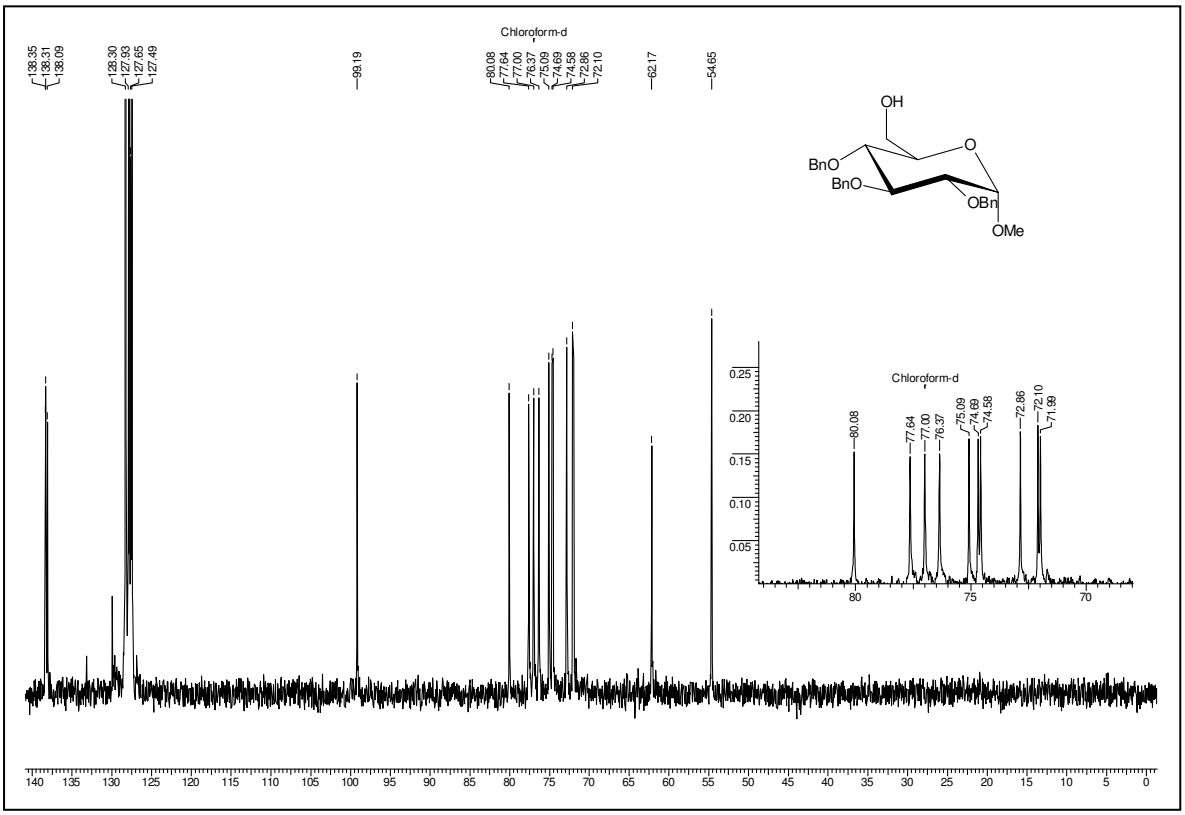
^{1}H NMR of compound 22 in $CDCl_3$



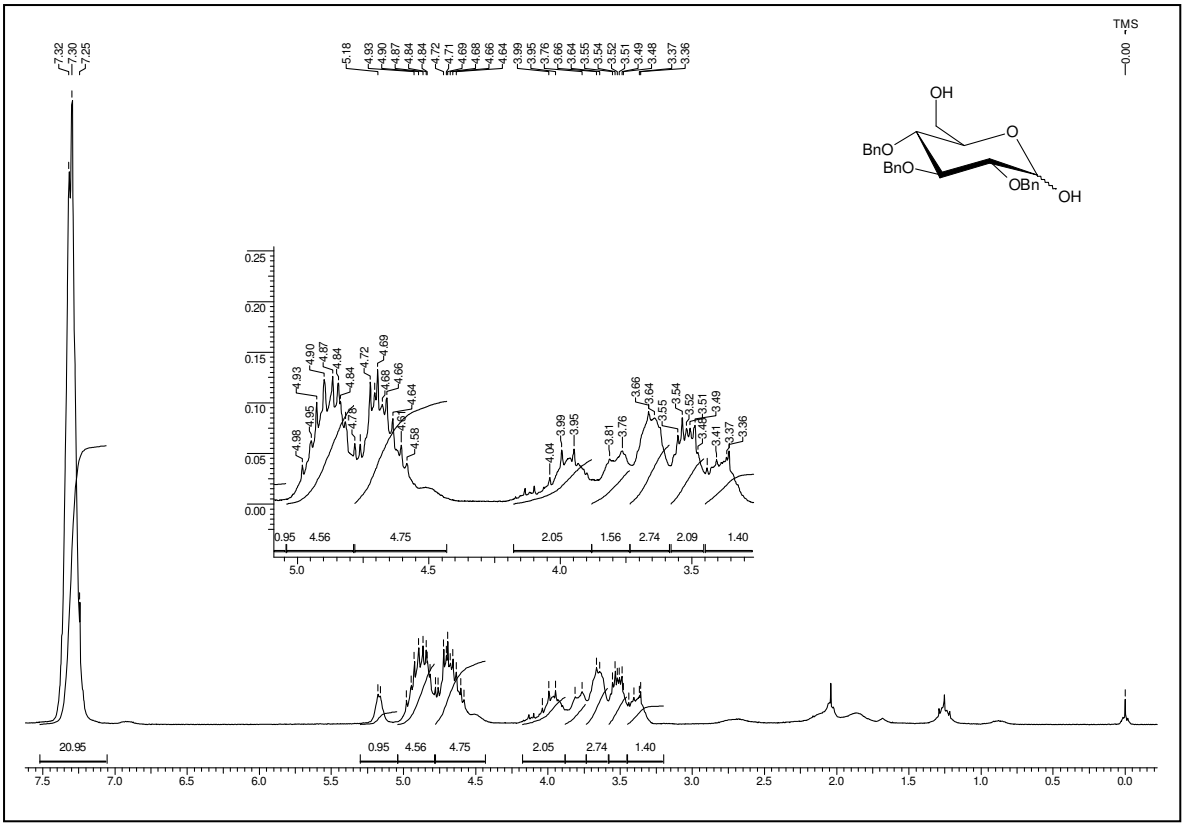
^{13}C NMR of compound 22 in $CDCl_3$



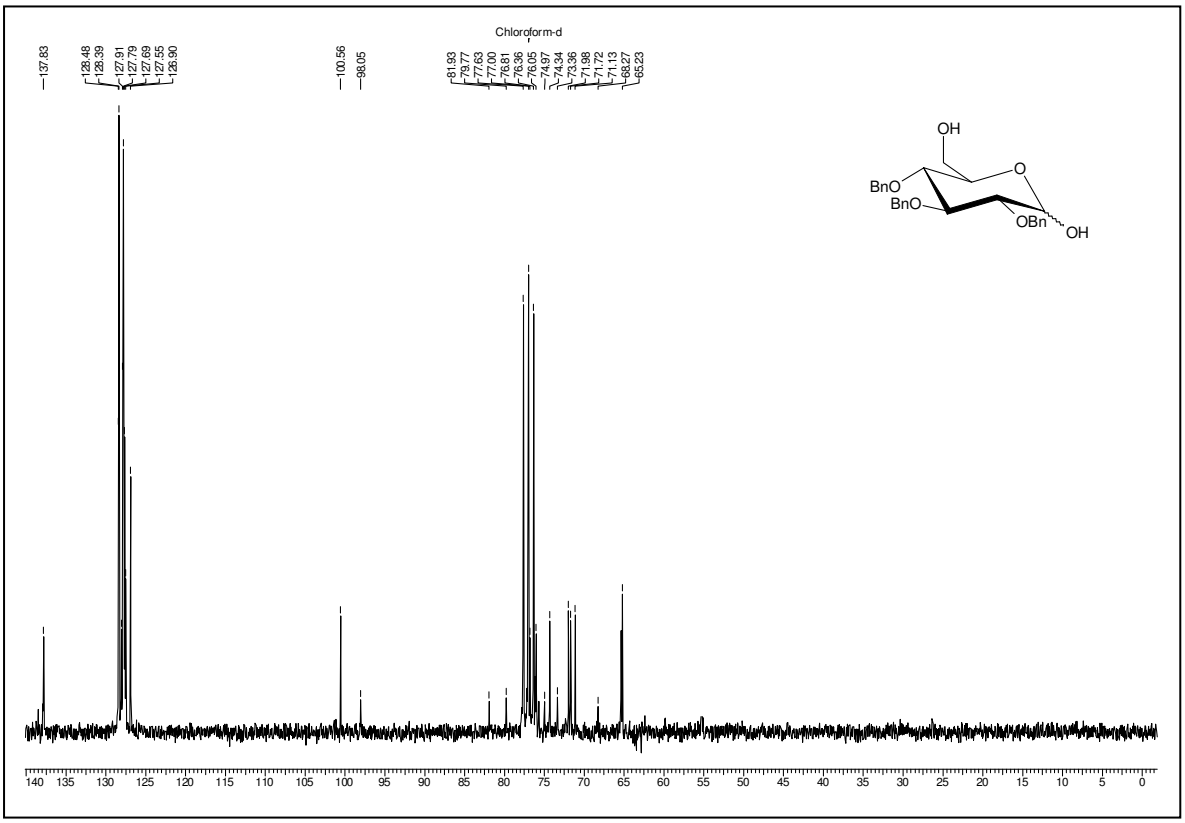
^{1}H NMR of compound 23 in $CDCl_3$



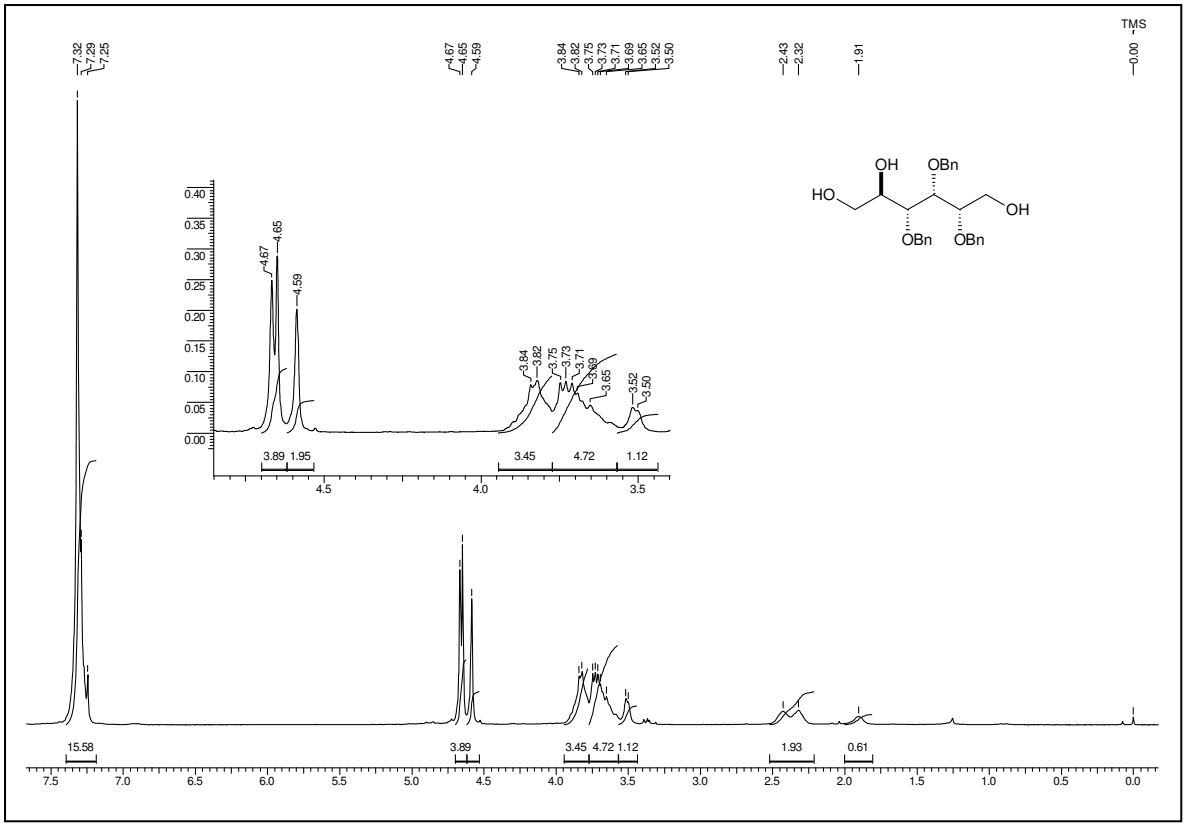
^{13}C NMR of compound 23 in $CDCl_3$



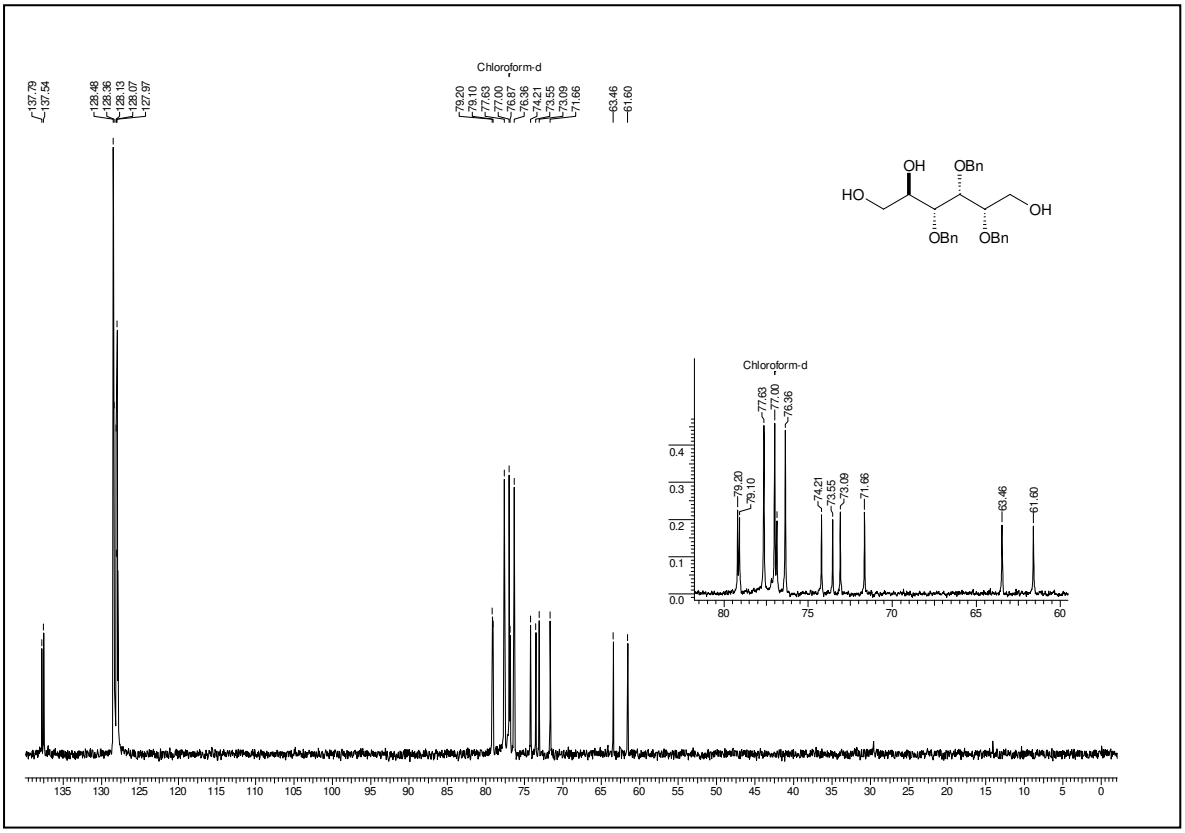
^{1}H NMR of compound 24 in $CDCl_3$



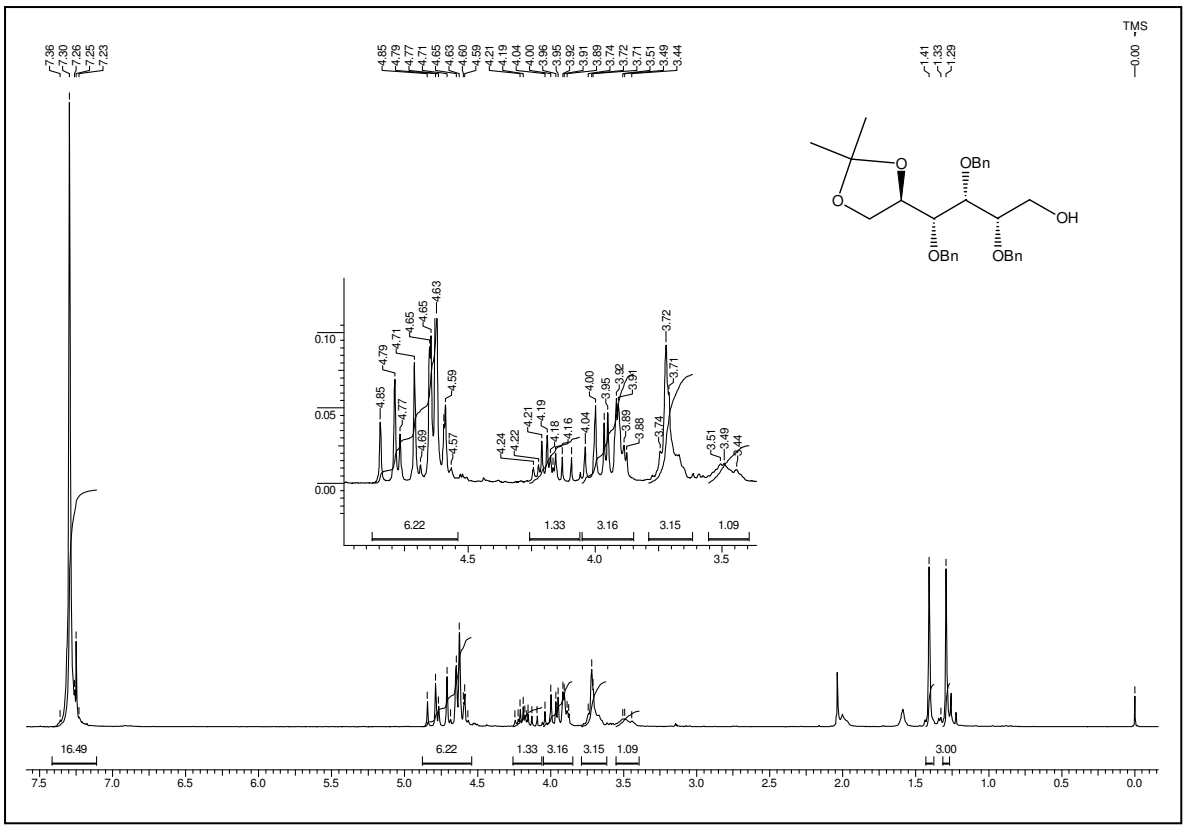
^{13}C NMR of compound 24 in $CDCl_3$



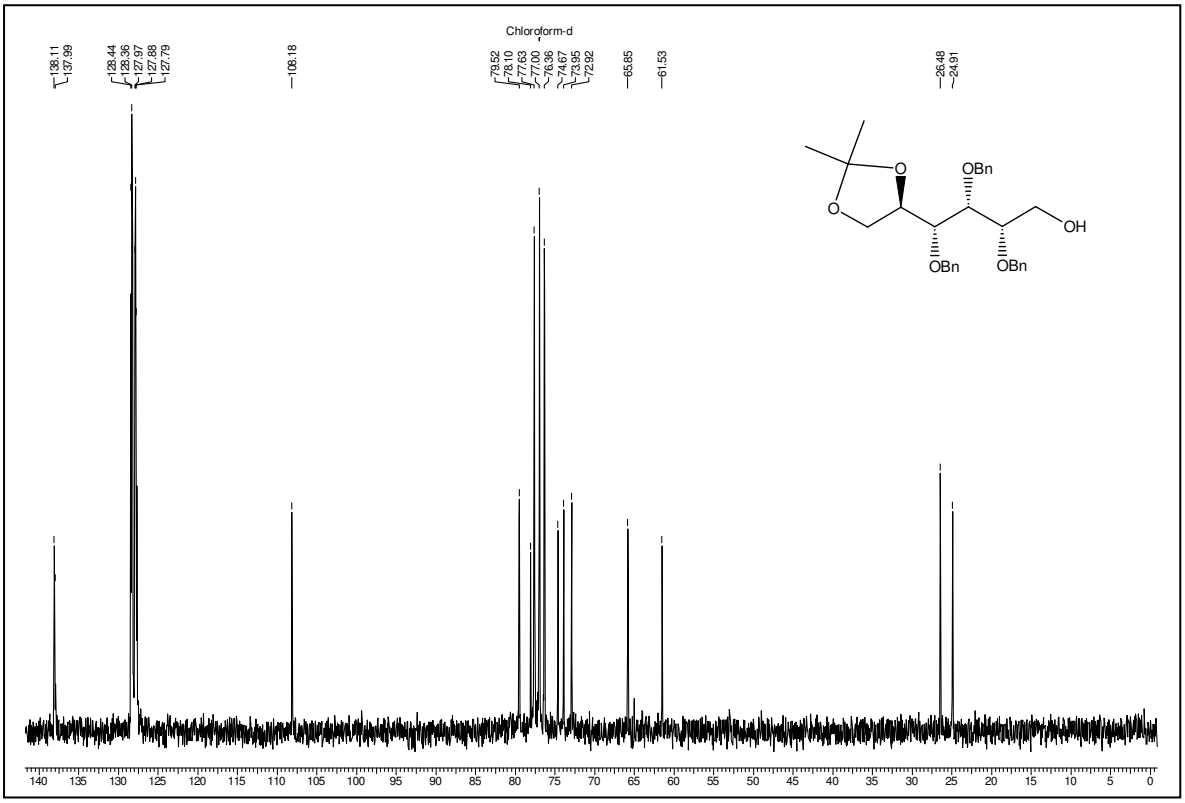
^{1}H NMR of compound 25 in $CDCl_3$



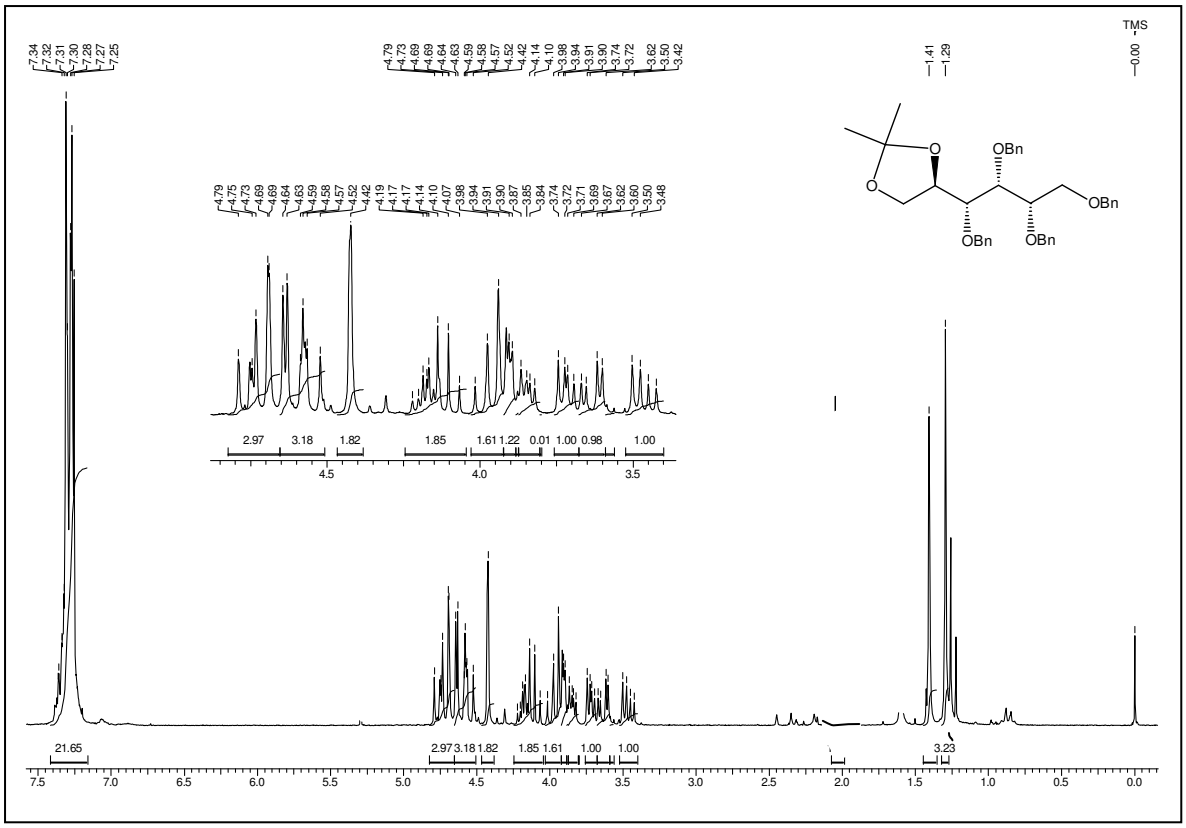
^{13}C NMR of compound 25 in $CDCl_3$



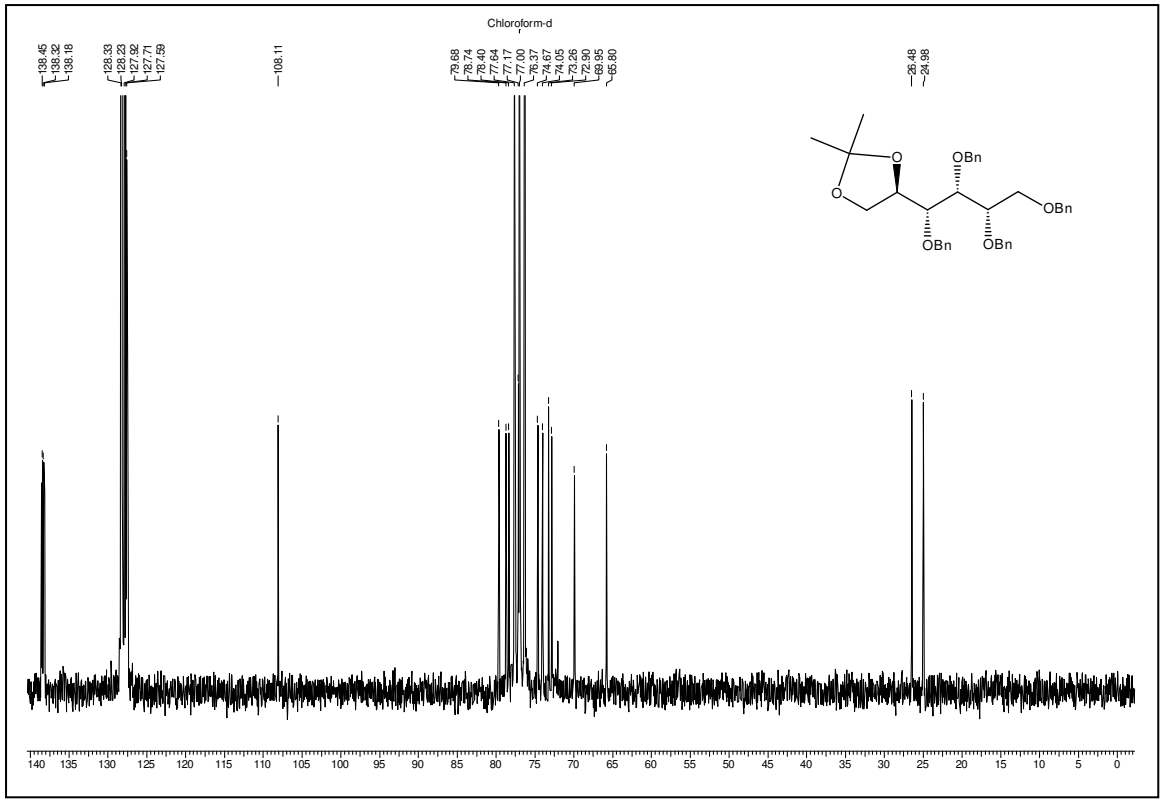
^{1}H NMR of compound 26 in $CDCl_3$



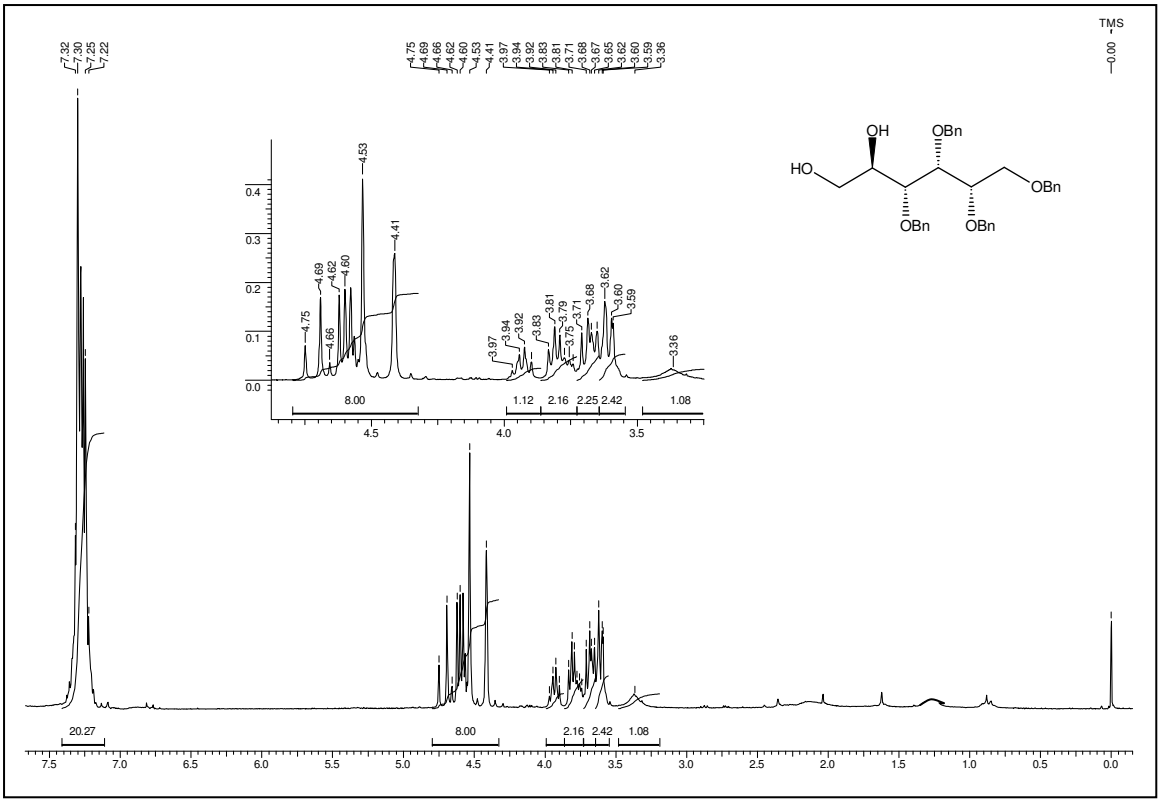
^{13}C NMR of compound 26 in $CDCl_3$



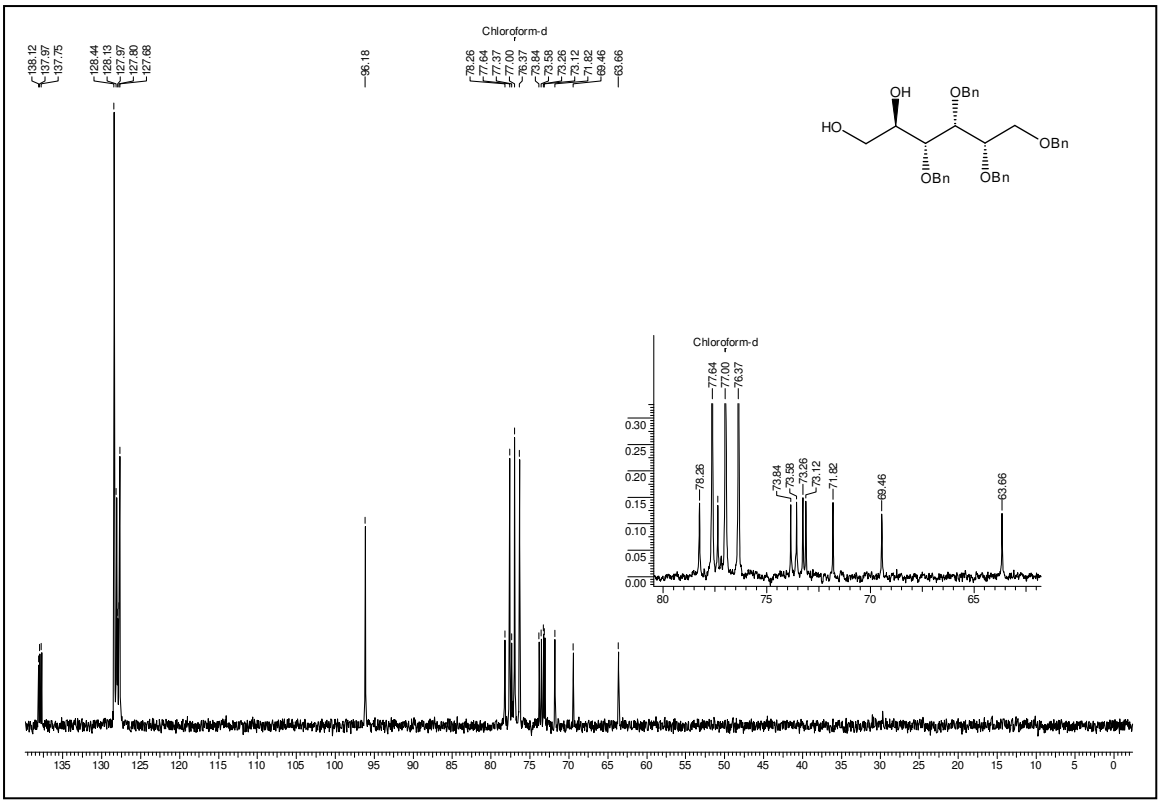
^{1}H NMR of compound 27 in $CDCl_3$



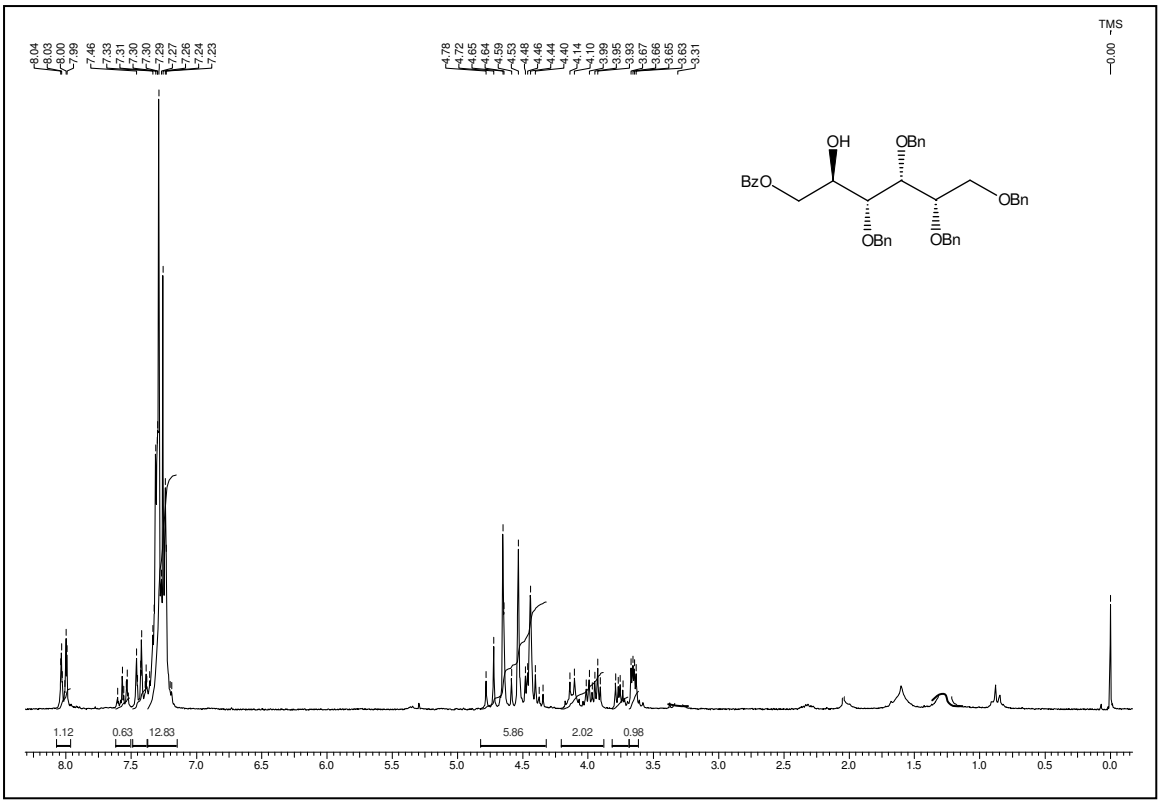
^{13}C NMR of compound 27 in $CDCl_3$



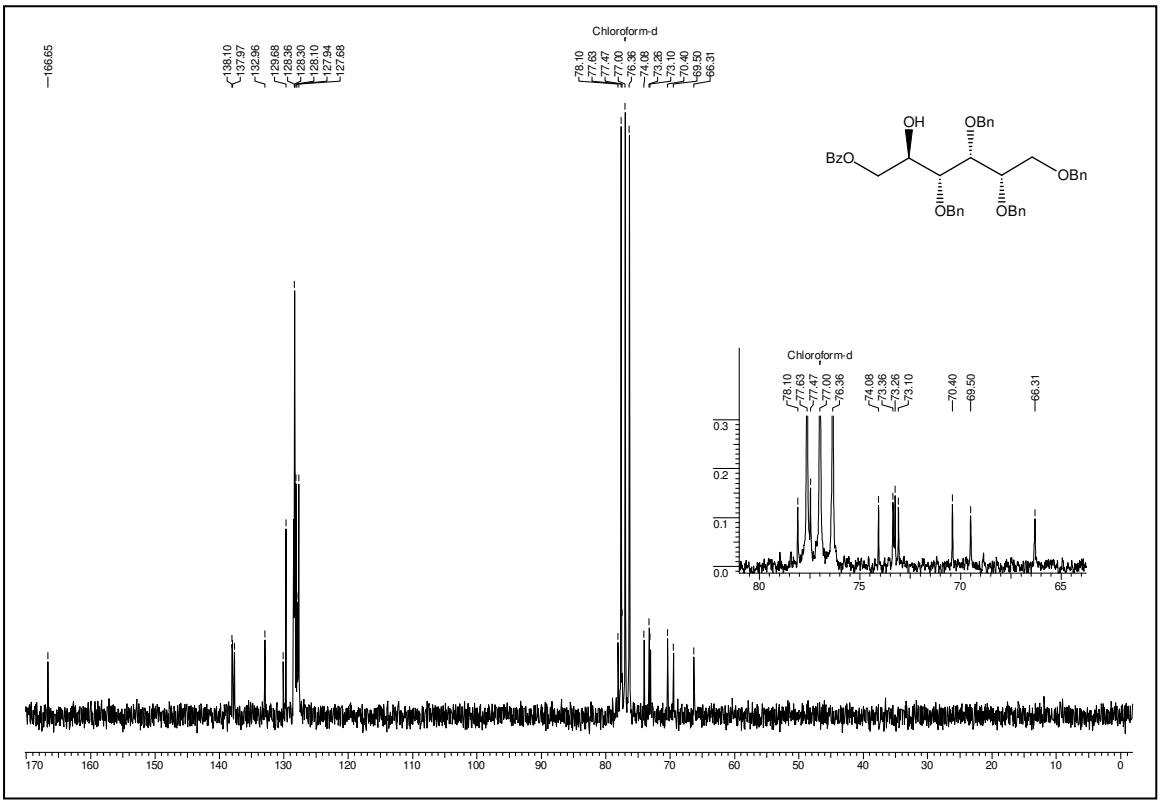
^{1}H NMR of compound 28 in $CDCl_3$



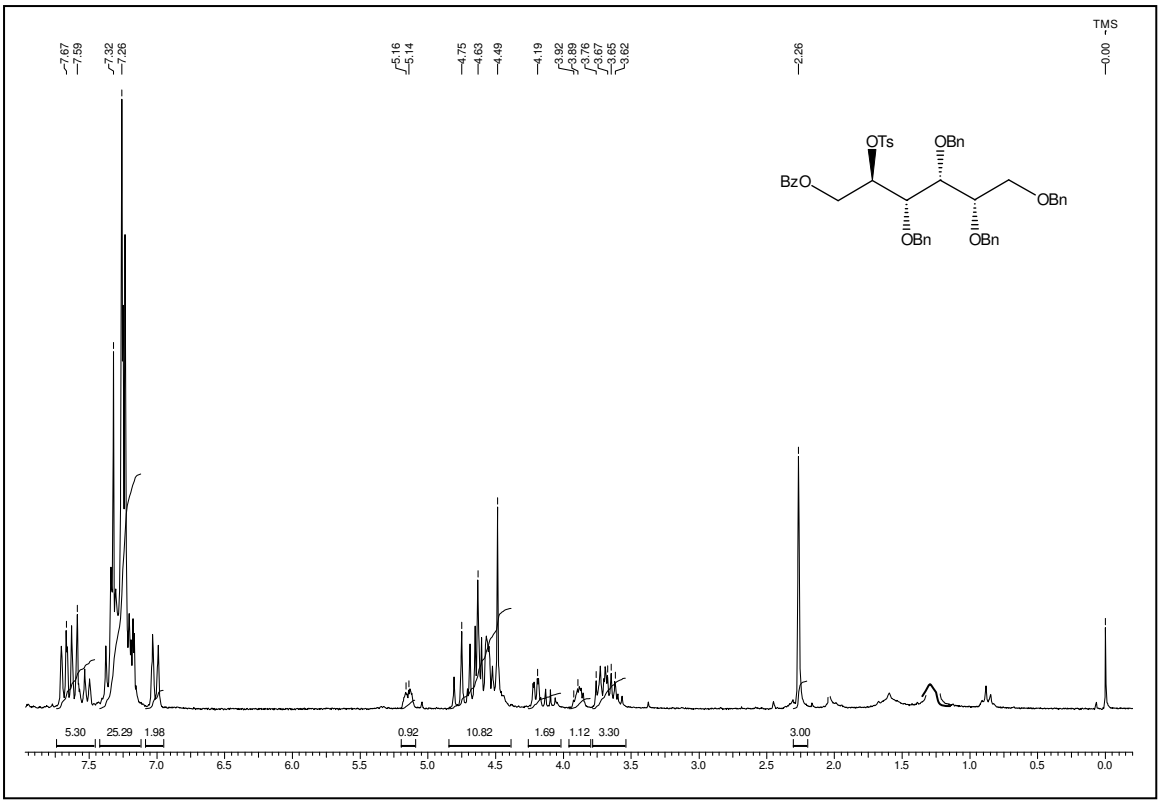
^{13}C NMR of compound 28 in $CDCl_3$



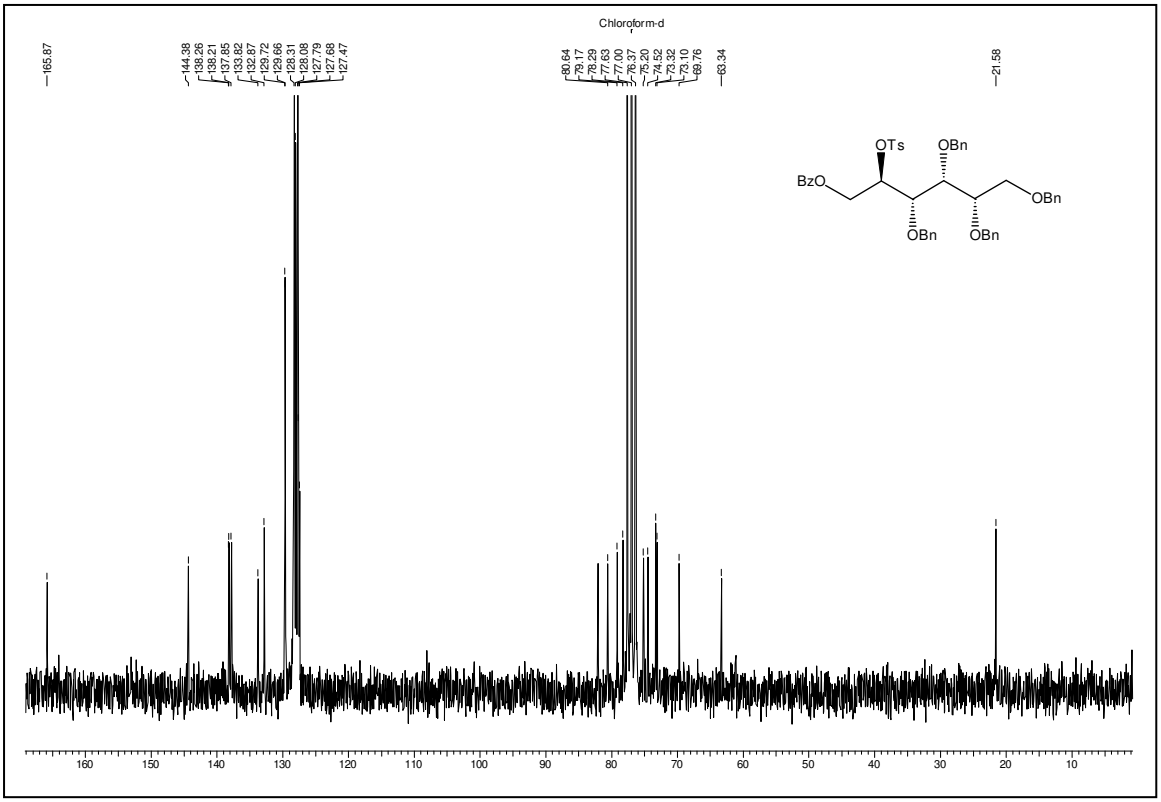
^{1}H NMR of compound 29 in $CDCl_3$



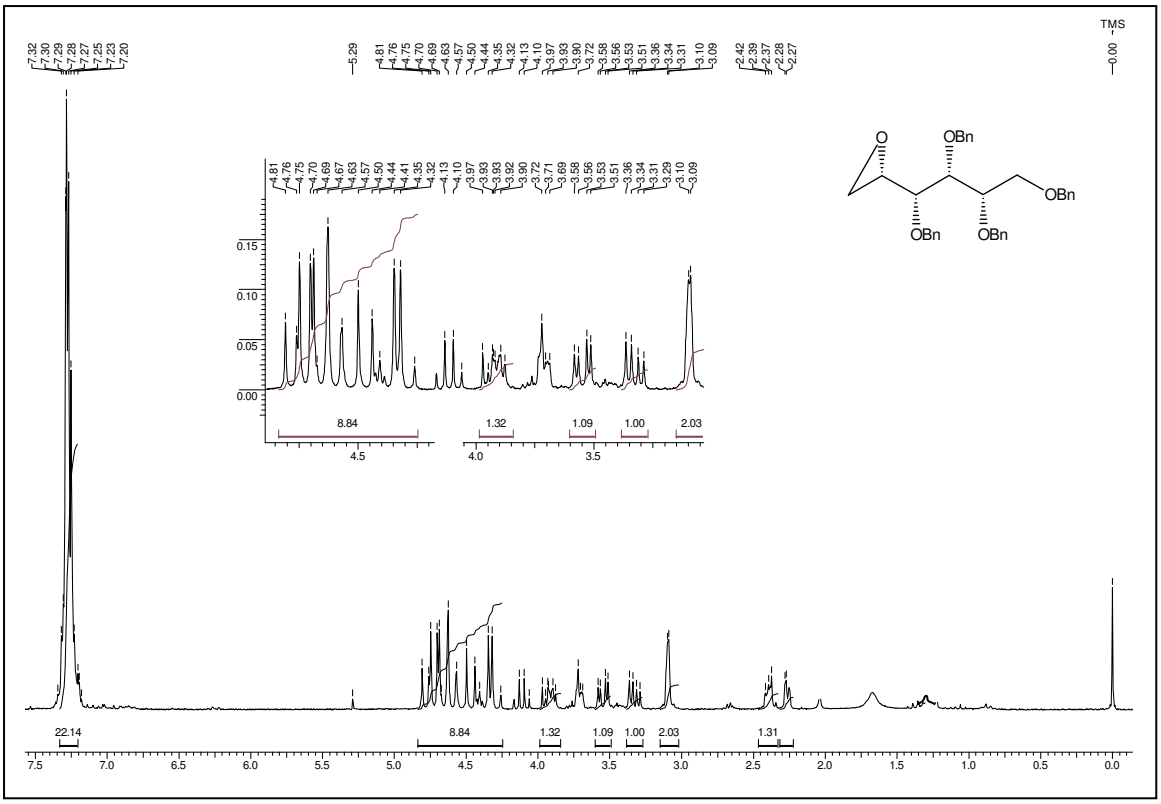
^{13}C NMR of compound 29 in $CDCl_3$



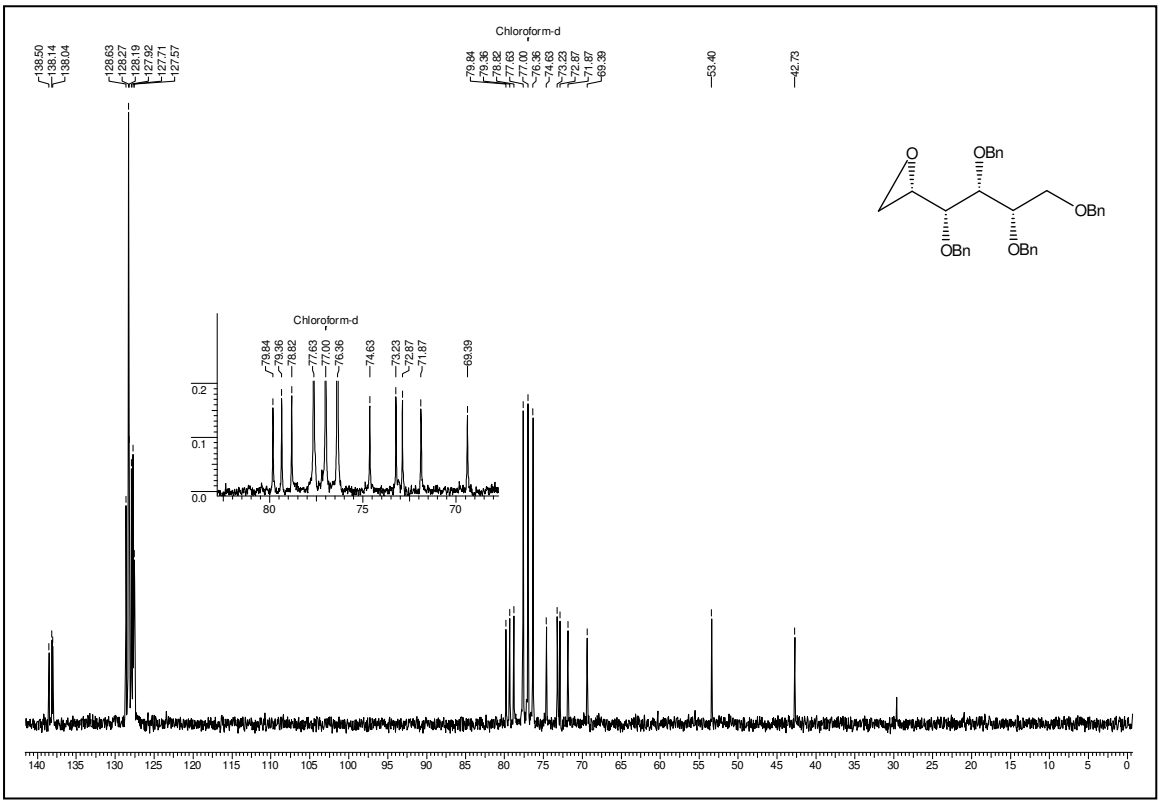
^{1}H NMR of compound 30 in $CDCl_3$



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



^{1}H NMR of compound 7 in $CDCl_3$



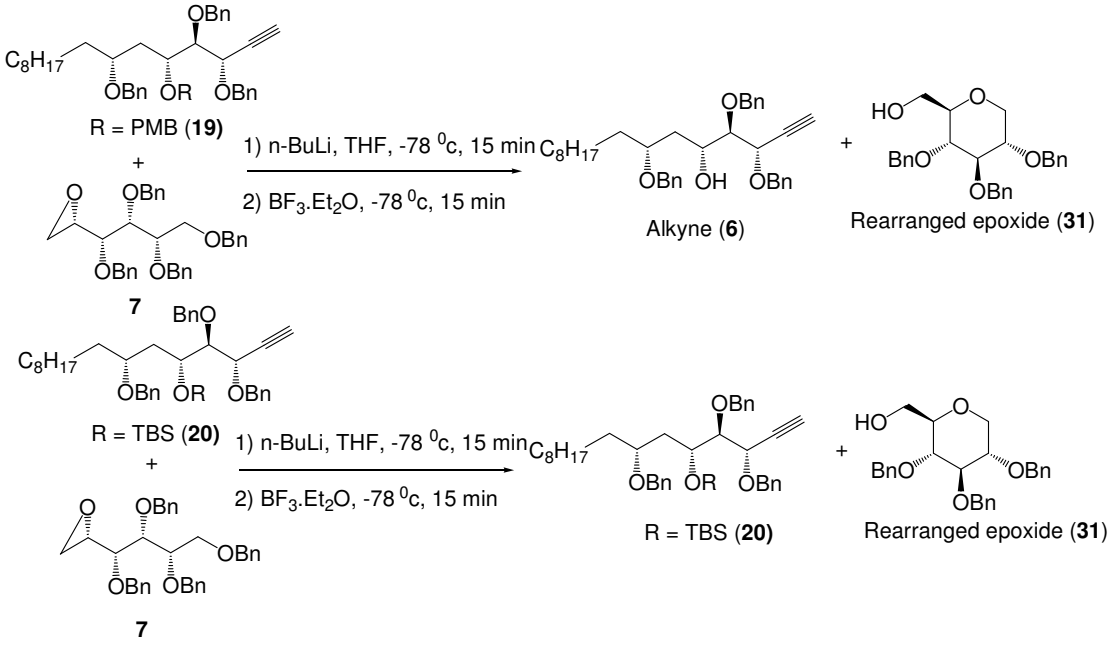
^{13}C NMR of compound 7 in $CDCl_3$

Section-III

Studies on Yamaguchi coupling of both the fragments and synthesis of C_{31}-C_{48} fragment of Aflastatin A

After successfully synthesizing both the fragments, our next goal in the synthetic endeavour was to couple both the fragments under Yamaguchi-Hirao protocol.[34] Accordingly reaction of alkynyl borane (formed by treating alkyne **19** with BuLi in THF at -78 ^{0}C followed by $BF_3.Et_2O$ in THF) with

Scheme 13: Yamaguchi coupling of alkyne 19 with epoxide 7



the epoxide **7** met with failure. The products obtained were unmasked PMB derivative **6** and the rearranged epoxide **31**. The reaction of alkyne **20** with the epoxide **7**, under the indistinguishable reaction conditions as the previous reaction, also resulted into the rearranged epoxide **31** with the recovery of the alkyne **20**, which reveals the instability of epoxide **7** to the given reaction conditions (**Scheme 13**).

The instability of the epoxide **7** under the Yamaguchi reaction conditions is attributed

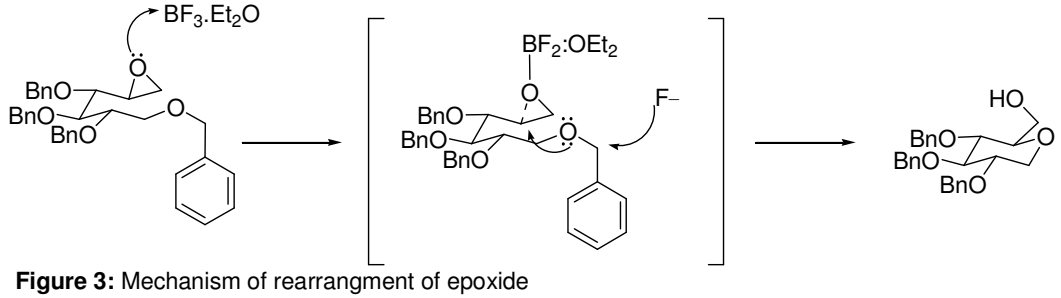
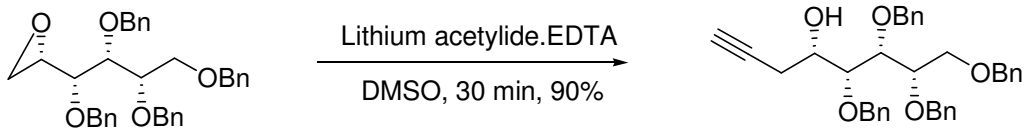


Figure 3: Mechanism of rearrangment of epoxide

to its rapid rearrangement to the stable THP derivative **31**. The mechanism of the rearrangement is shown in a box (**Figure 3**) in which co-ordination of epoxy oxygen with $BF_3.Et_2O$ activates the carbon oxygen bond towards the nucleophilic attack of

nearby oxygen (i.e. primary benzyloxy group) leading to the formation of THP derivative **31**. Such rearrangement reactions are reported with free –OH group.[44] The structure of the compound **31** was confirmed by its spectral data. For example absence of epoxy protons between 2.5-3.0 ppm, benzylic $-CH_2$ and five aromatic protons in ^1H NMR and respective carbons in ^{13}C NMR, a peak at m/z 457.32 $(M+23)^+$ and a broad IR peak at 3510 cm^{-1} are the indicatives of the product. Under basic conditions

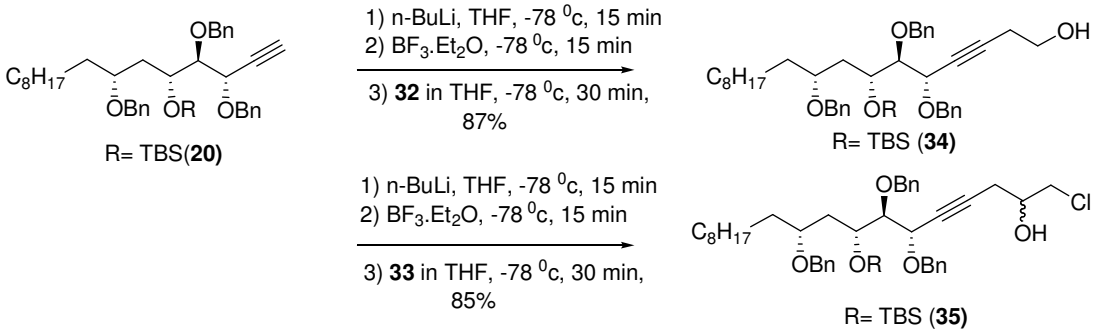
Scheme 14:



7 **41**

epoxide 7 is quite stable for example it react rapidly with lithium acetylide:EDTA complex in DMSO and furnished the epoxide opened product **41** in 92% of yield (**Scheme 14**). The product structure was confirmed by its ^1H NMR spectrum. In ^1H NMR disappearance of epoxy protons, resonance of a alkyne CH as a doublet at 1.95 (J = 2.66 Hz) and propargylic CH_2 as a doublet of triplet at 2.35 (J = 6.53, 2.66 Hz). To check the instability of the epoxide **7**, we treated the alkyne **20** with couple of other simple epoxides like ethylene oxide (**32**) and *rac*-epichlorohydrin (**33**) under the same set of reaction conditions (**Scheme 15**). Thus reaction of lithium acetylide of **20** with ethylene oxide **32** and *rac*-epichlorohydrin **33** under the same reaction conditions furnished, not surprisingly, the required alcohols **34** and **35** in 87 and 85% yields respectively.

Scheme 15: Yamaguchi coupling of alkyne **20** with epoxides **32** and **33**



The structure of the compound **34** was substantiated from all the spectral data. In ^1H NMR, lack of terminal alkyne proton, resonance of propargylic $-CH_2$ as a doublet of

triplet at 2.4 ppm (J = 6.07, 1.75 Hz) and an additional two protons between 3.5 to 4.0 ppm, were the pinpoint of the conversion, while in ^{13}C NMR two internal alkyne carbons were seen at 79.6 and 84.6 ppm respectively. A peak at m/z 738.2 in EIS-MS spectrum is further support of **34**. As for the product **35** is concerned, its all spectral data is in agreement with the structure.

After succeeding the Yamaguchi coupling of alkyne **20** with ethylene oxide (**32**), we wanted to complete the synthesis of C_{31}-C_{48} fragment (**36**) of

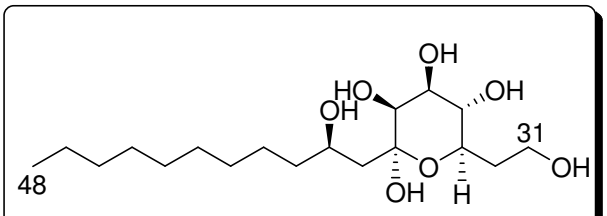
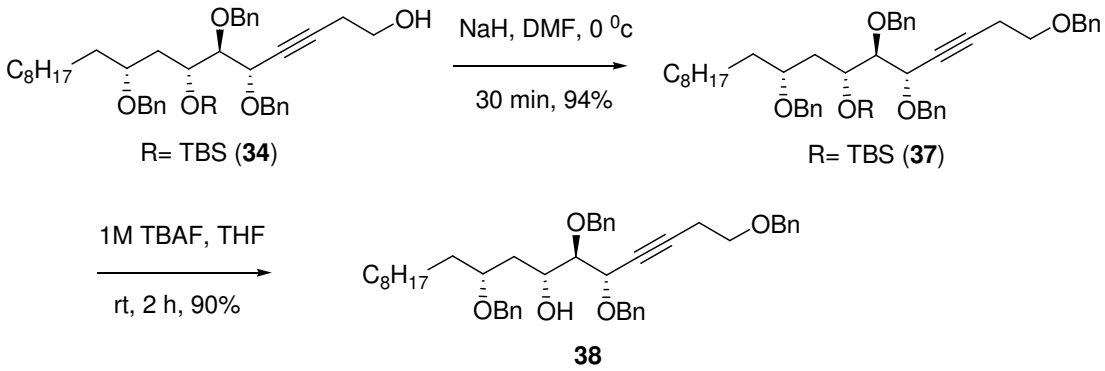


Figure 4: C_{31}-C_{48} fragment of Aflastatin A (**36**)

Aflastatin A by employing Yamamoto's 6-*endo*-dig cyclization[32] and the stereo and regioselective hydroboration of the resulted C-glycal. In this direction, the primary alcohol of **34** was protected as its benzyl ether **37** in 94% yield upon treatment with NaH and BnBr in DMF for 30 min (**Scheme 16**). Product **37** structure was determined based on its ^1H NMR and mass spectra. In ^1H NMR, two additional protons between 4.3 to 4.7 ppm and five aromatic protons in the range of 7.2-7.4 ppm, indicated the

Scheme 16:

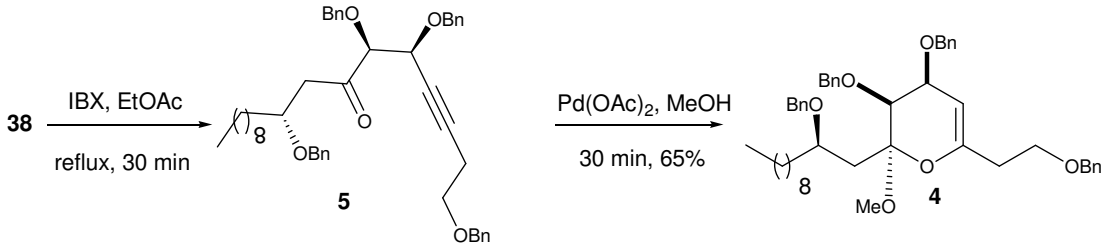


product. Additional support was gained from mass spectrum, in which a peak at m/z 828.2 $(M+23)^+$ corresponding to the product was seen, and IR spectrum showed lack of –OH stretching. Exposure of the compound **37** to a 1M solution of TBAF in THF for 2 h delivered the TBS deprotected compound **38** in 90% yield. The product structure was identified by its ^1H NMR and ^{13}C NMR spectra in which peaks due to

TBS group (i.e. two singlet methyls and a t-butyl group) were vanished. A highest peak at m/z 711.5 $(M+23)^+$ in ESI-MS spectrum is an extra support.

The cyclization precursor ω-ynone **5** was accomplished from the alcohol derivative **38** by oxidizing with IBX in refluxing ethyl acetate for 30

Scheme 17: Pd(II) Catalized Yamamoto' s 6-*endo*-dig cyclization of 5



min which without purification was subjected to Yamamoto' s cyclization conditions [$Pd(OAc)_2$ in MeOH] for 30 min to deliver the dihydropyran **4** in good yields (65%) (**Scheme 17**). The structure of dihydropyran **4** was unambiguously assigned based on its spectral and analytical data. ^{1}H NMR of **4** reveals two characteristic peaks, one of which is the olefinic-H, which was resonated as doublet (J = 4.8 Hz) at 4.80 ppm and a singlet at 3.23 ppm due to methoxy group, while ^{13}C NMR of **4** showed two olefinic carbons resonating at 97.1 and 149.9 ppm respectively. In mass spectrum a peak at m/z 740.07 $(M+23)^+$ is a further support of product **4**.

Figure 5 shows the mechanism of cyclization in which Pd(II) acts as a dual activator (i.e. activates both keto and alkyne). Initially higher reactivity of keto prone MeOH to attack from the *Re* face of the carbonyl compound **5**

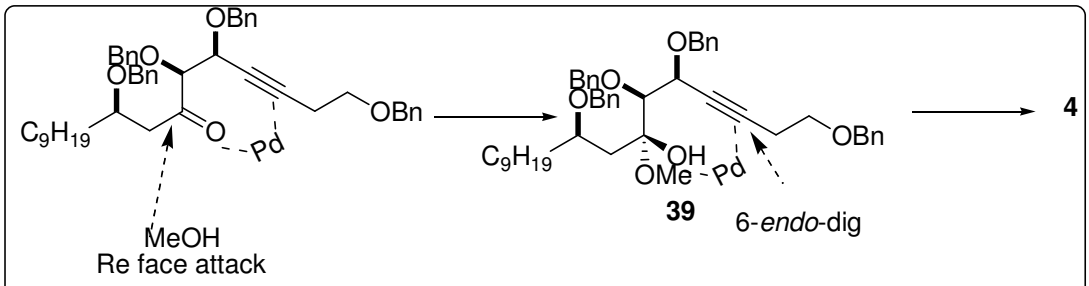


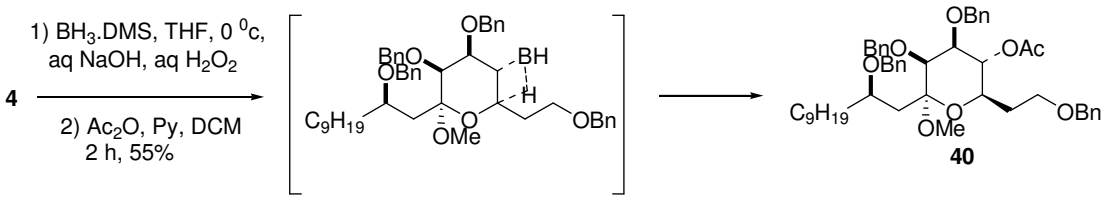
Figure 5: Mechanism of 6-*endo*-dig-cyclization

leading to hemiacetal **39** which undergoes preferentially 6-*endo*-dig over 5-*exo*-dig cyclization to deliver the dihydropyran **4**. The exact reason for regioselectivity is not

yet known but –I effect of the alkoxy groups facilitating the *endo* cyclization.

The final frontier in the synthesis is the regio and stereoselective hydroboration of DHP derivative **4** which was carried out with BH_3:DMS in THF followed by $NaOH/H_2O_2$ oxidation afforded the tetrahydrop

Scheme 18: Hydroboration of C-glycal 4

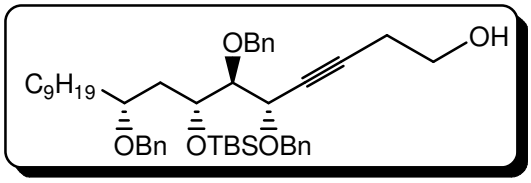


derivative which was converted to corresponding acetyl derivative **40** for structural characterization by treatment with Ac_2O and py in DCM for 2h (S**cheme 18**). In the ^1H NMR of **40**, olefinic proton was no more and C-H attached to acetate appeared down field at 5.25 ppm with two diaxial coupling constants (J = 9.3, 9.0 Hz) indicating a *trans*-orientation with respect to the adjacent C-Hs and in ^{13}C NMR two olefinic carbons were disappeared. An additional support was gained from mass spectrum which gave a peak at m/z 804.07 $(M+23)^+$. Further, in the NOESY spectrum of **40**, a peak corresponding to the OCH_3 at 3.39 ppm is showing nOe with H at 3.51 .Boron being electron deficient (Lewis acidic) reacts with the electron rich β-carbon from the less hindered site i. e. opposite to the adjacent benzyloxy groups, of the enol ether **4** thus producing the required alcohol **36** in moderately good yields.

Experimental

Section- III; Experimental

(5S,6R,7R,9R)-5,6,9-tris(benzyloxy)-7-tertiarybutyldimethylsilloxy-octadec-3-yne-1-Ol (34):



BuLi (0.36 ml, 0.858mmol) was added to stirred solution of alkyne **20** (0.52 g, 0.71 mmol) in THF (5 ml) at -78 ^{0}c and stirred for 30 min. To this reaction mixture, a solution of ethylene oxide in THF (2 ml of 4M) and $BF_3{\cdot}Et_2O$ (0.095 ml, 0.77 mmol) were successively added and stirred for 30 min. Reaction mixture was quenched with sat aq. NH_4Cl, warmed to rt, two layers were separated and aq. layer was extracted into ethyl acetate. Combined organic layers were dried over Na_2SO_4, concentrated under reduced pressure and the residue was purified by column chromatography (15:85 ethyl acetate/hexane) to afford the alcohol **34** (0.476 g, 87%) as colourless oil.

Yield : 87%

Mol. Formula : $C_{45}H_{66}O_5Si$;

$[\alpha]_D^{25}$ +31.84 (c 0.9, $CHCl_3$)

IR ($CHCl_3$) ν : 3434, 2927, 2856, 1454, 1216, 1095, 758, 668 cm^{-1}.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 0.00 (s, 3H), 0.03 (s, 3H), 0.83 (s, 9H), 0.87 (t, *J* = 5.94 Hz, 3H), 1.21-1.23 (m, 17H), 1.45-1.56 (m, 3H), 1.91 (s, 2H), 2.495 (dt, *J* = 6.07, 1.76 Hz, 2H), 3.835 (dd, *J* = 5.67, 4.02 Hz, 1H), 3.925 (dd, *J* = 5.58, 4.30 Hz, 1H), 4.40-4.68 (m, 5H), 4.82 (d, *J* = 12.25 Hz, 1H), 4.885 (d, *J* = 11.62 Hz, 1H), 7.25-7.38 (m, 15H).

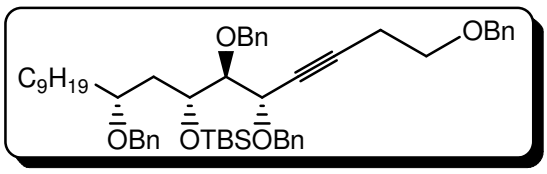
^{13}C NMR ($CDCl_3$, 50 MHz) : δ -4.40 (q), -4.16 (q), 14.11 (q), 18.21 (s), 22.67 (t), 23.44 (t), 26.00 (q), 26.09 (t), 29.33 (t), 29.60 (t), 29.74 (t), 30.41 (t), 31.90 (t), 60.95 (t), 70.81 (t), 71.52 (d), 71.80 (t), 73.41 (d), 73.79 (t), 79.60 (s), 80.17 (d), 81.71 (d), 84.62 (d), 127.15 (d), 127.34 (d), 127.50 (d), 127.57 (d), 127.84 (d), 127.93 (d), 128.10 (t), 128.30 (d), 138.01 (s), 138.74 (s), 139.20 (s).

Elemental Analysis Calcd.: C, 75.58; H, 9.30

Found: C, 75.69; H, 9.39

ESI-MS (m/z) 738.29 $(M+23)^+$

(5S,6S,7R,9R)-1,5,6,9-tetrakis(benzyloxy)octadec-3-yn-7-yloxy)(tert-butyl)dimethylsilane (37) :-



NaH (0.02 g, 0.839 mmol) was added in portions to an ice cooled solution of alcohol **34** (0.5 g, 0.699 mmol) in DMF (5 ml) over a period of 10 min. Benzyl bromide (0.09 ml, 0.768 mmol) was added and the reaction mixture was warmed to rt and stirred for 30 min, cooled to 0 ^{0}c, quenched with ice and diluted with water. The reaction mixture was partitioned between water and ethyl acetate, combined organic layers were dried over Na_2SO_4, volatiles were removed and the crude was purified by column chromatography (1:9 ethyl acetate/hexane) to afford tetrabenzyl ether **37** as a colourless thick oil (0.52 g, 94%).

Yield : 94%

Mol. Formula : $C_{52}H_{72}O_5Si$;

$[\alpha]_D^{25}$ +41.73 (c 1.2, $CHCl_3$)

IR ($CHCl_3$) ν : 3019, 2925, 2856, 1464, 1215, 1095, 757, 669 cm^{-1}.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 0.00 (s, 3H), 0.04 (s, 3H), 0.84 (s, 9H), 0.88 (t, *J* = 6.19 Hz, 3H), 1.20-1.24 (m, 15H), 1.46-1.56 (m, 4H), 2.585 (dt, *J* = 7.20, 1.77 Hz, 2H), 3.50-3.63 (m, 3H), 3.78 (t, *J* = 4.80 Hz, 1H), 3.94 (t, *J* = 4.93 Hz, 1H), 4.39-4.92 (m, 8H), 7.23-7.39 (m, 20H).

^{13}C NMR ($CDCl_3$, 50 MHz) : δ -4.35 (t), -4.22 (t), 14.11 (t), 18.25 (s), 20.40 (t), 22.67 (t), 25.92 (t), 26.05 (q), 29.33 (t), 29.60 (t), 29.75 (t), 31.89 (t), 63.28 (t), 68.59 (t), 70.64 (t), 71.15 (d), 71.91 (t), 72.93 (d), 74.01 (d), 78.29 (s), 80.13 (d), 81.64 (d), 84.34 (s), 127.06 (t), 127.17 (t), 127.44 (t),

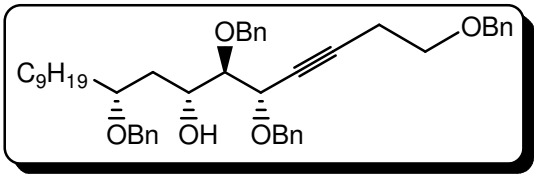
127.60 (t), 127.85 (t), 127.92 (t), 128.00 (t), 128.04 (t), 128.22 (t), 128.36 (t), 138.10 (s), 138.98 (t), 139.32 (s).

Elemental Analysis Calcd.: C, 77.56; H, 9.01

Found: C, 77.65; H, 9.09

ESI-MS (m/z) 828.29 $(M+23)^+$

(5S,6R,7R,9R)-1,5,6,9-tetrakis(benzyloxy)octadec-3-yn-7-ol (38) :-



TBAF (0.12 ml, 0.316 mmol) was added to an ice cooled solution of TBS ether **37** (0.17 g, 0.177 mmol) in THF (5 ml) and stirred at rt for 2h, diluted with water, two layers were separated and aq layer was extracted into ethyl acetate, dried over Na_2SO_4, solvent was evaporated and the crude was purified by column chromatography (15:85 ethyl acetate: hexane) to yield alcohol **38** (0.136 g, 90%) as a colourless oil.

Yield : 90%

Mol. Formula : $C_{46}H_{58}O_5$;

$[\alpha]_D^{25}$ +39.64 (c 1.2, $CHCl_3$)

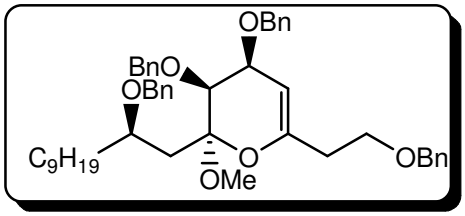
IR ($CHCl_3$) ν : 3475, 3018, 2925, 1454, 1215, 1095, 759, 667 cm^{-1}.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 0.88 (t, *J* = 6.69 Hz, 3H), 1.25 (m, 16H), 1.53-1.69 (m, 3H), 2.605 (dt, *J* = 7.08, 1.89 Hz, 2H), 3.59-3.69 (m, 3H), 3.75 (dd, *J* = 8.84, 2.80 Hz, 1H), 4.215 (d, *J* = 11.24 Hz, 1H), 4.46-4.52 (m, 5H), 4.67-4.70 (m, 1H), 4.90 (d, *J* = 11.75 Hz, 1H), 4.95 (d, *J* = 11.50 Hz, 1H), 7.21-7.34 (m, 20H).

^{13}C NMR ($CDCl_3$, 50 MHz) : δ 14.10 (q), 20.43 (t), 22.66 (t), 25.57 (t), 29.32 (t), 29.55 (t), 29.60 (t), 29.66 (t), 29.81 (t), 30.98 (t), 31.89 (t), 68.56 (t), 70.91 (t), 71.95 (t), 72.26 (d), 72.40 (d), 72.95 (t), 73.32 (t), 76.91 (d), 80.41 (s), 85.33 (s), 127.47 (t), 127.51 (t), 127.60 (t), 127.73 (t), 127.76 (t),

	128.20 (t), 128.29 (t), 128.36 (t), 138.08 (s), 138.12 (s), 138.47 (st), 138.63 (s).
Elemental Analysis	Calcd.: C, 80.20; H, 8.19 Found: C, 80.29; H, 8.24
ESI-MS (m/z)	711.56 $(M+23)^+$

(2S,3S,4S)-3,4-bis(benzyloxy)-6-(2-(benzyloxy)ethyl)-2-((R)-2-(benzyloxy)undecyl)-3,4-dihydro-2-methoxy-2H-pyran (3):

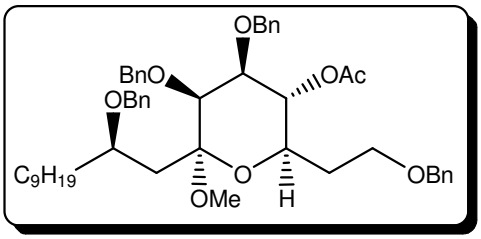


A suspension of alcohol **38** (0.095 g, 0.1375 mmol) and IBX (0.115 g, 0.412 mmol) in EtOAc (10 ml) was heated to reflux for 30 min, cooled to 0 ^{0}c, filtered over celite and concentrated under vacuum. To this residue in MeOH (5 ml) was added $Pd(OAc)_2$ (0.003 g, 0.01375 mmol) and strirred at rt for 30 min, MeOH was removed and the crude was purified by flash column (2:8 ethyl acetate/hexane) to deliver the dihydro pyran **4** (0.064 g, 65%) as a colourless oil.

Yield	: 65%
Mol. Formula	: $C_{47}H_{60}O_6$;
$[\alpha]_D^{25}$	+29.42 (c 0.3, $CHCl_3$)
IR ($CHCl_3$) ν	: 3018, 2925, 1454, 1215, 1095, 759, 667 cm^{-1}.
^{1}H NMR ($CDCl_3$, 400 MHz)	: δ 0.81 (t, *J* = 6.78 Hz, 3H), 1.19 (m, 15H), 1.40-1.55 (m, 2H), 1.90 (dd, *J* = 14.81, 4.77 Hz, 1H), 2.265 (dd, *J* = 14.81, 7.28 Hz, 1H), 2.32 (t, *J* = 6.78 Hz, 2H), 3.23 (s, 3H), 3.46-3.50 (m, 1H), 3.55 (t, *J* = 6.78 Hz, 1H), 3.705 (d, *J* = 5.27 Hz, 1H), 3.81(t, *J* = 5.02 Hz, 1H), 4.23-4.54 (m, 8H), 4.805 (d, *J* = 4.77 Hz, 1H), 7.161-7.28 (m, 20H).

^{13}C NMR ($CDCl_3$, 100 MHz)	: δ 14.10 (q), 22.67 (t), 24.74 (t), 29.34 (t), 29.61 (t), 29.69 (t), 29.89 (t), 31.90 (t), 34.28 (t), 34.40 (t), 35.66 (t), 49.27 (q), 65.96 (d), 67.48 (t), 70.75 (t), 70.88 (t), 72.03 (t), 72.95 (t), 75.67 (d), 77.20 (d), 97.17 (d), 100.22 (s), 127.35 (t), 127.47 (t), 127.65 (t), 127.77 (t), 128.08 (t), 128.14 (t), 128.22 (t), 128.26 (t), 128.37 (t), 138.15 (s), 138.22 (s), 138.81 (s), 139.12 (s), 149.89 (s).
Elemental Analysis	Calcd.: C, 78.30; H, 8.39 Found: C, 78.25; H, 8.45
ESI-MS (m/z)	744.07 $(M+23)^+$

(2R,3R,4S,5S,6S)-4,5-bis(benzyloxy)-2-(2-(benzyloxy)ethyl)-6-((R)-2-(benzyloxy)undecyl)-tetrahydro-6-methoxy-2H-pyran-3-yl acetate (40):

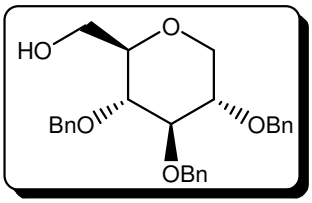


To a stirred solution of dihydro pyran **4** (0.01 g, 0.013 mmol) in THF (2 ml) was added BH_3:DMS (0.008 ml, 0.013 mmol) at 0 ^{0}c and stirred for 2h. 3N NaOH (1 ml) and aq. H_2O_2 (1 ml) were added, warmed to rt and stirred for 6h. THF was removed and the aq layer was extracted into ethyl acetate, dried over Na_2SO_4 and concentrated under vacuuo. To the crude in DCM (1 ml) was added Ac_2O (0.1 ml) and pyridine (0.1 ml) and stirred for 2h, volatiles were removed and the residue was purified by flash column (1:9 ethyl acetate/hexane) gave the THP derivative **40** (0.006 g, 55%) as a colourless oil.

Yield	: 55%
Mol. Formula	: $C_{49}H_{64}O_8$;
$[\alpha]_D^{25}$	+37.90 (c 0.3, $CHCl_3$)
IR ($CHCl_3$) ν	: 3018, 2925, 1736, 1459, 1216, 1095, 767, 669 cm^{-1}.
^{1}H NMR ($CDCl_3$, 400 MHz)	: δ 0.81 (t, *J* = 6.78 Hz, 3H), 1.25-1.27 (m, 16H), 1.38 (t, *J* = 7.53, 7.28 Hz, 1H), 1.765 (dd, *J* = 15.56, 4.52

	Hz, 1H), 1.84-1.91 (m, 1H), 1.99-2.04 (m, 1H), 2.01 (s, 3H), 3.36 (s, 3H), 3.39-3.44 (m, 1H), 3.51-3.65 (m, 3H), 3.765 (d, *J* = 3.01 Hz, 1H), 4.315 (d. *J* = 12.30 Hz, 1H), 4.38-4.50 (m, 6H), 4.715 (d, *J* = 12.04 Hz, 1H), 4.815 (d, *J* = 12.04 Hz, 1H), 5.245 (t, *J* = 9.29, 9.03 Hz, 1H), 7.17-7.39 (m, 20H).
^{13}C NMR ($CDCl_3$, 100 MHz)	14.11 (q), 21.10 (q), 22.69 (t), 24.87 (t), 29.35 (t), 29.69 (t), 29.87 (t), 31.91 (t), 32.45 (t), 34.91 (t), 36.16 (t), 50.11 (q), 66.08 (t), 69.39 (d), 71.26 (t), 71.52 (t), 71.78 (d), 73.00 (t), 74.59 (t), 75.33 (d), 76.68 (d), 77.20 (d), 77.34 (d), 100.78 (s), 127.34 (d), 127.49 d), 127.68 (d), 128.04 (d), 128.31 (d), 138.13 (s), 138.45 (s), 138.68 (s), 138.81 (s), 169.92 (s).
Elemental Analysis	Calcd.: C, 75.35; H, 8.26 Found: C, 75.34; H, 8.35
ESI-MS (m/z)	803.5 $(M+23)^+$

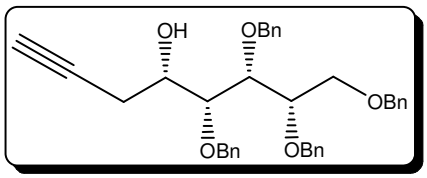
((2R,3R,4R,5S)-3,4,5-tris(benzyloxy)-tetrahydro-2H-pyran-2-yl)methanol (31): -



Yield	: 75%
Mol. Formula	: $C_{27}H_{30}O_5$;
$[\alpha]_D^{25}$	+63.80 (c 1.3, $CHCl_3$)
IR ($CHCl_3$) ν	: 3510, 3030, 2923, 2400, 1720, 1453, 1218, 1088, 768, 695 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 3.54-3.61 (m, 1H), 3.62-3.70 (m, 2H), 3.75 (dd, *J* = 11.88, 2.52 Hz, 1H), 3.92 (d, *J* = 3.67 Hz, 1H), 3.96-4.02 (m, 2H), 4.15-4.22 (m, 1H), 4.32-4.59 (m, 6H), 7.20-7.28 (m, 15H).

^{13}C NMR ($CDCl_3$, 100 MHz)	: δ 62.93 (t), 68.15 (t), 71.62 (t), 71.87 (t), 73.46 (t), 79.96 (t), 80.03 (d), 82.25 (d), 82.73 (d), 84.49 (d), 127.56 (t), 127.67 (t), 127.75 (t), 127.83 (t), 127.92 (t), 128.35 (t), 128.46 (t), 128.50 (t), 128.55 (t), 137.38 (s), 137.53 (s), 137.91 (s).
Elemental Analysis	Calcd.: C, 74.63; H, 6.96 Found: C, 74.72; H, 7.02
ESI-MS (m/z)	457.32 $(M+23)^+$

(4S,5R,6R,7S)-5,6,7,8-tetrakis(benzyloxy)oct-1-yn-4-ol (41) :

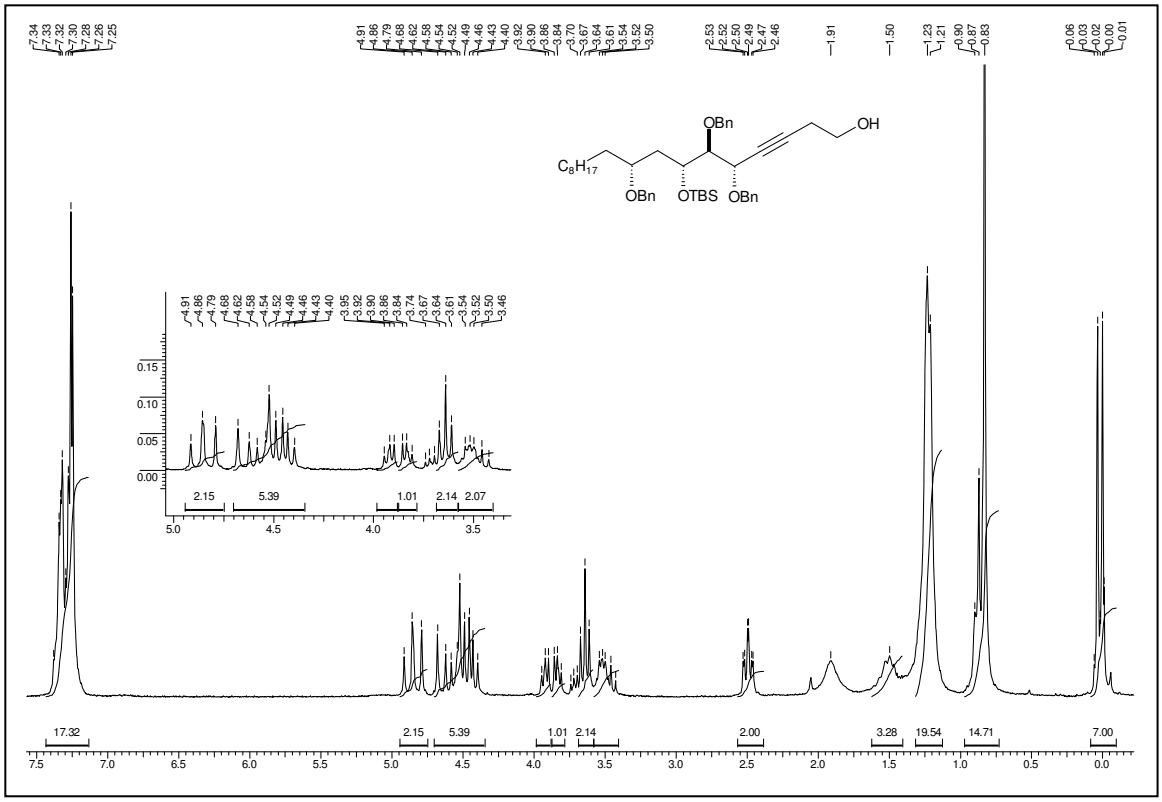


To a stirred solution of epoxide (0.05 g, 0.095 mmol) in dry DMSO (2 ml) was added excess lithium acetylide EDTA complex at 0 ^{0}c and stirred for 30 min, quenched with ice and extracted into ethyl acetate. Combined organics were dried over Na_2SO_4, volatiles were removed and the residue was purified by column (1.5:8.5 ethyl acetate/hexanes) to furnish the alkynol **41** (0.049 g, 93%) as a colorless oil.

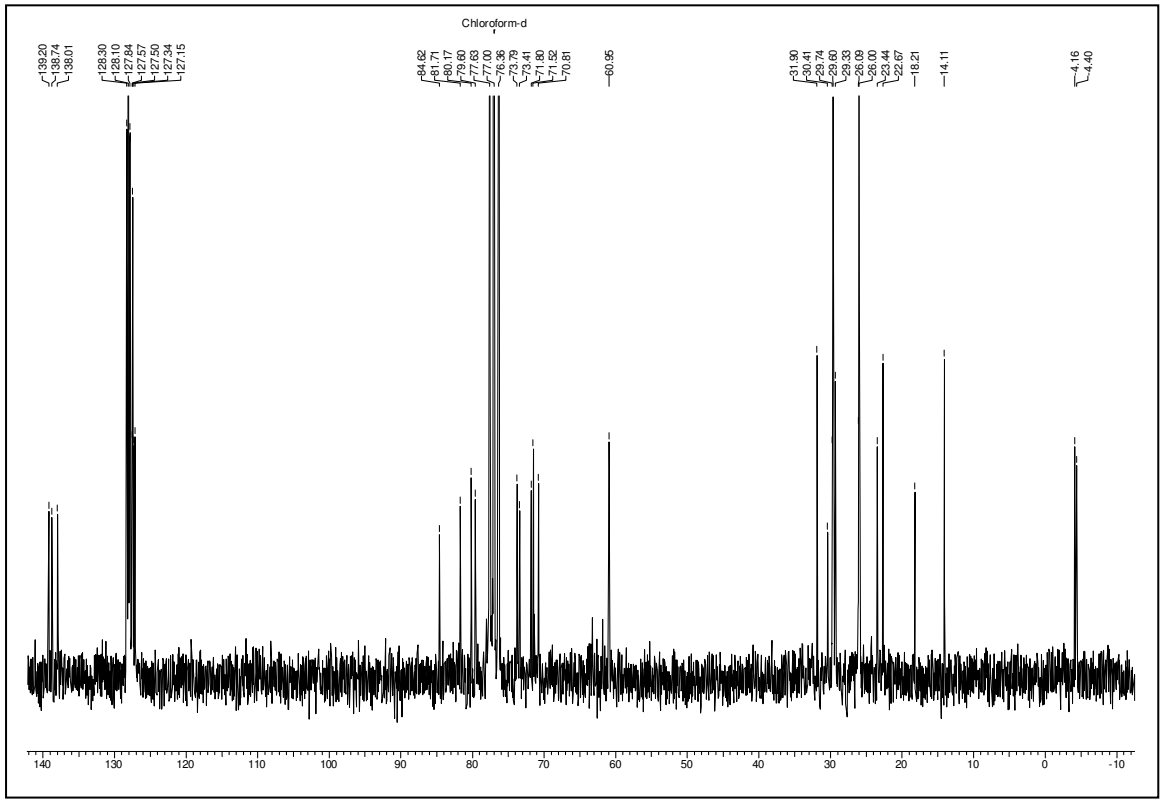
Yield	: 93%
Mol. Formula	: $C_{36}H_{38}O_5$;
Optical Rotation $[\alpha]_D^{25}$	+9.25 (c 0.75, $CHCl_3$)
IR (CHCl3) ν	: 3450, 3305, 3030, 2923, 2400, 1720, 1453, 1218, 1088, 768, 698 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 1.95 (t, *J* = 2.66 Hz, 1H), 2.355 (dt, *J* = 6.93, 2.66 Hz, 2H), 2.60 (d, *J* = 7.58 Hz, 1H), 3.59-3.69 (m, 2H), 3.71-3.84 (m, 2H), 3.88 (brs, 2H), 4.44 (s, 2H), 4.54-4.66 (m, 3H), 4.70-4.87 (m, 3H), 7.29-7.38 (m, 20H).
^{13}C NMR ($CDCl_3$, 100 MHz)	: δ 23.95 (t), 69.52 (d), 69.83 (t), 70.40 (t), 72.72 (t), 73.23 (t), 74.62 (t), 75.14 (t), 76.91 (d), 79.25 (d), 79.44 (d), 81.02 (s), 127.63 (t), 127.70 (t), 127.75 (t), 127.80 (t), 128.13 (t), 128.29 (t), 128.34 (t), 128.51 (t), 137.93

	(s), 138.06 (s), 138.10 (s), 138.14 (s).
Elemental Analysis	Calcd.: C, 78.52; H, 6.96
	Found: C, 78.58; H, 6.90
ESI-MS (m/z)	573.73 $(M+23)^+$

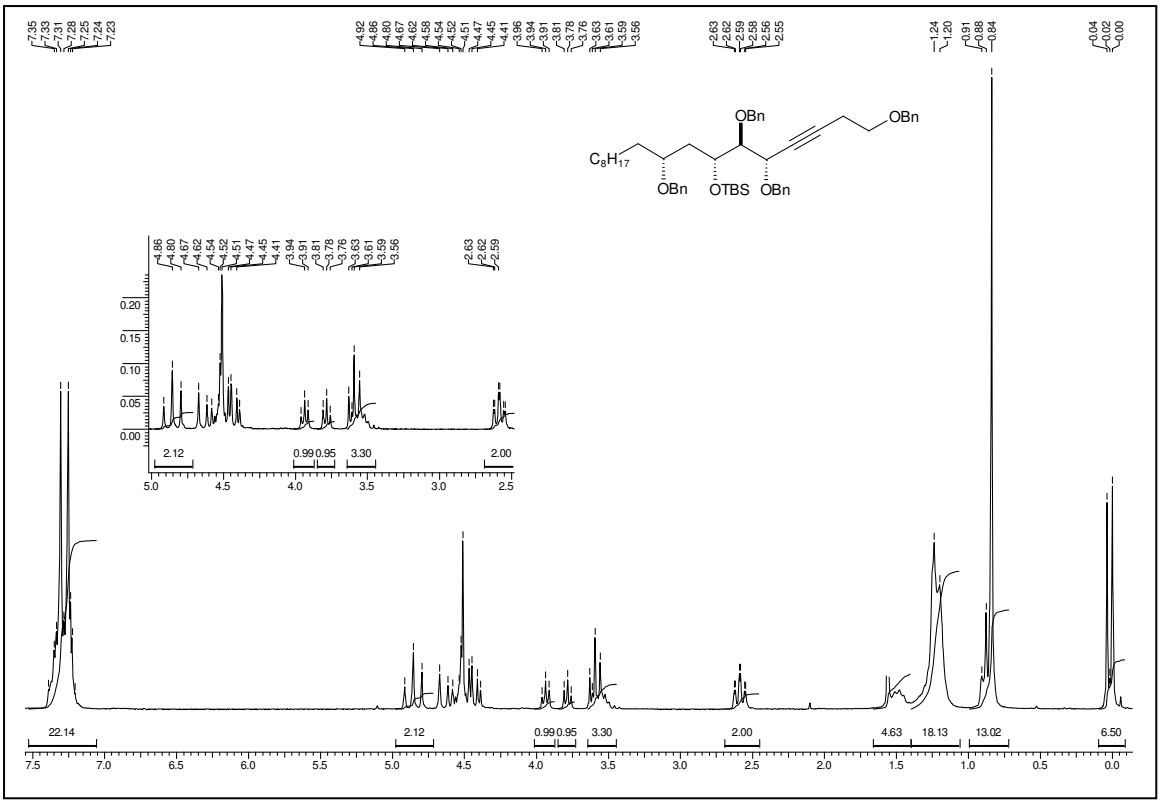
Spectral data



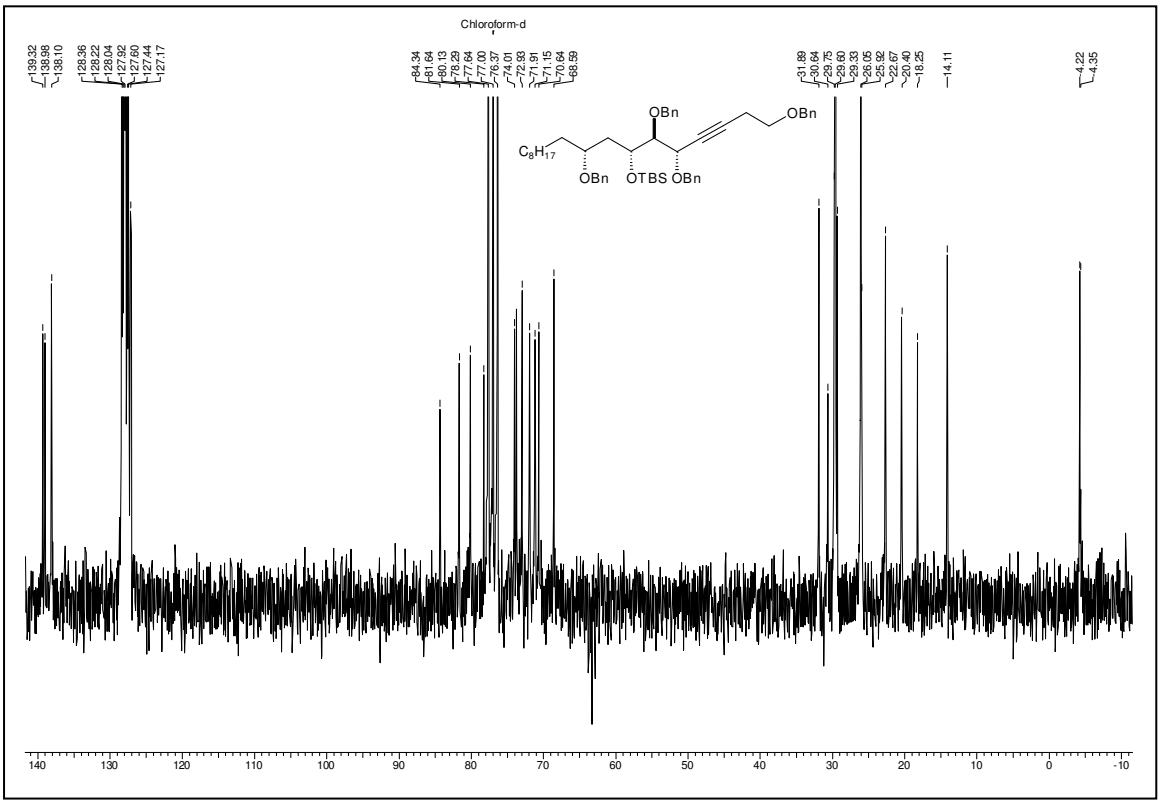
^{1}H NMR spectrum of compound 34 in $CDCl_3$



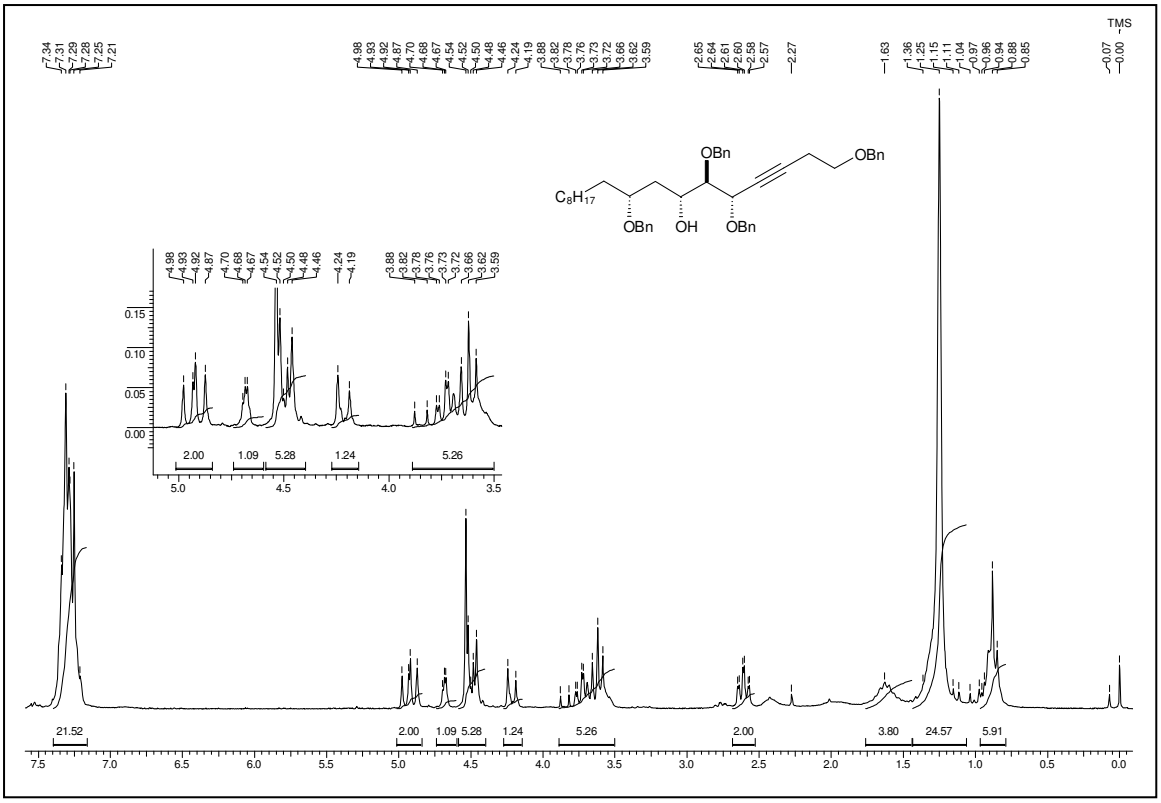
^{13}C NMR spectrum of compound 34 in $CDCl_3$



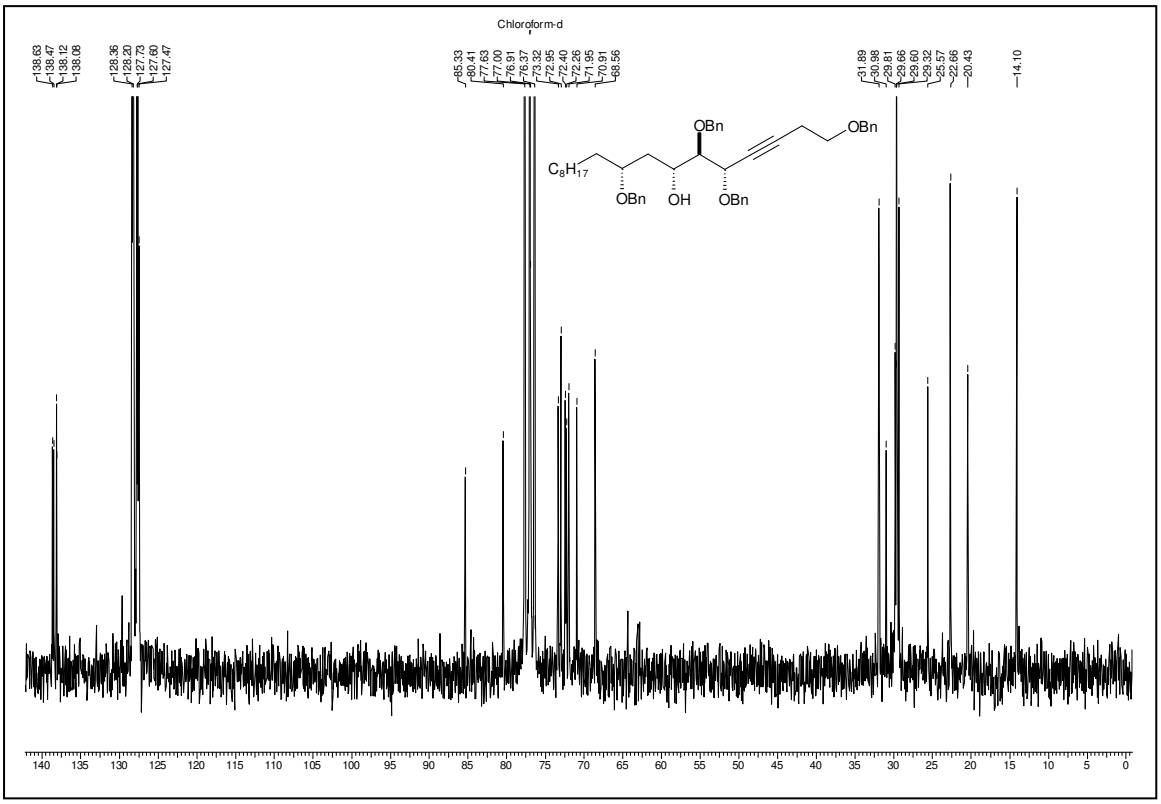
^{1}H NMR spectrum of compound 37 in $CDCl_3$



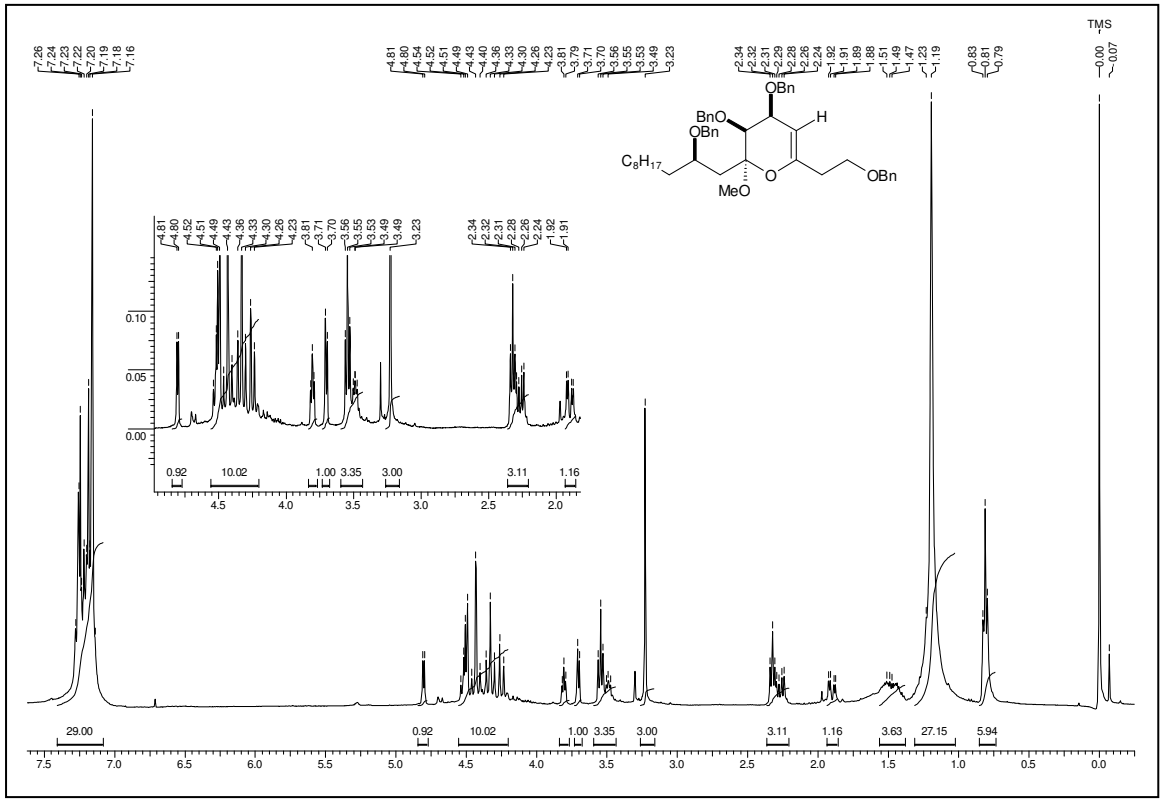
^{13}C NMR spectrum of compound 37 in $CDCl_3$



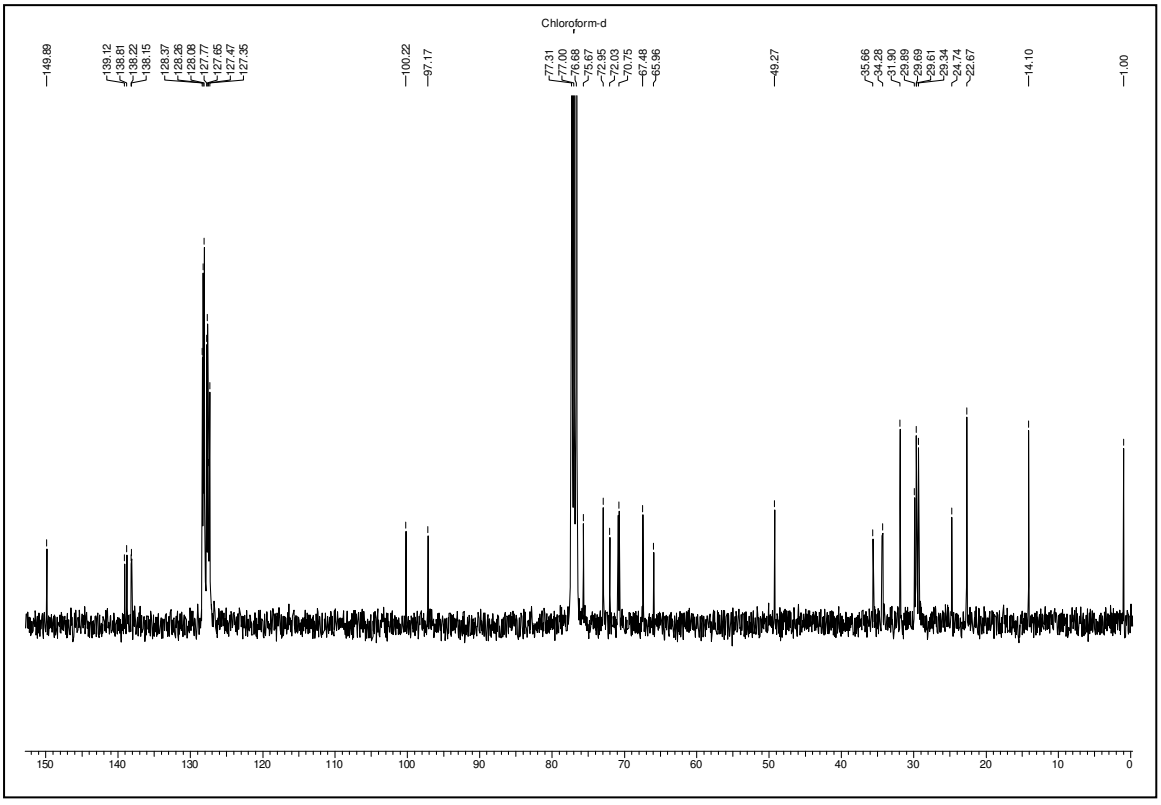
^{1}H NMR spectrum of compound 38 in $CDCl_3$



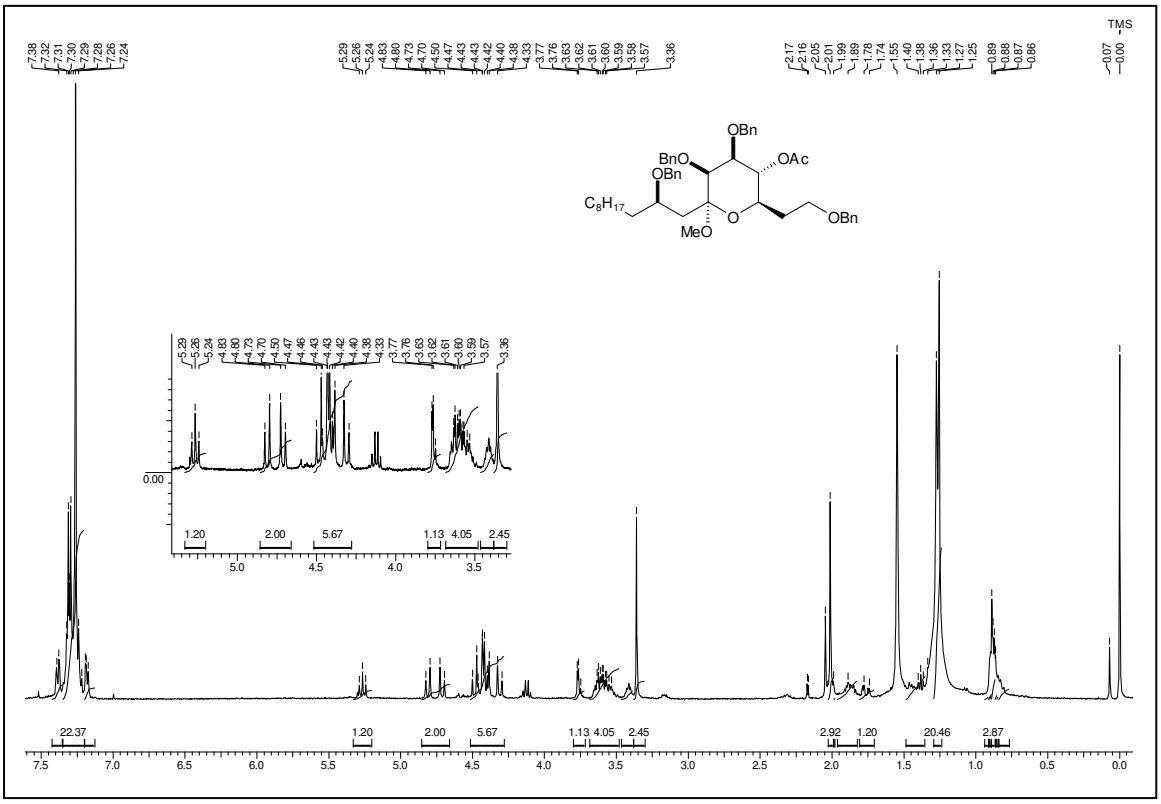
^{13}C NMR spectrum of compound 38 in $CDCl_3$



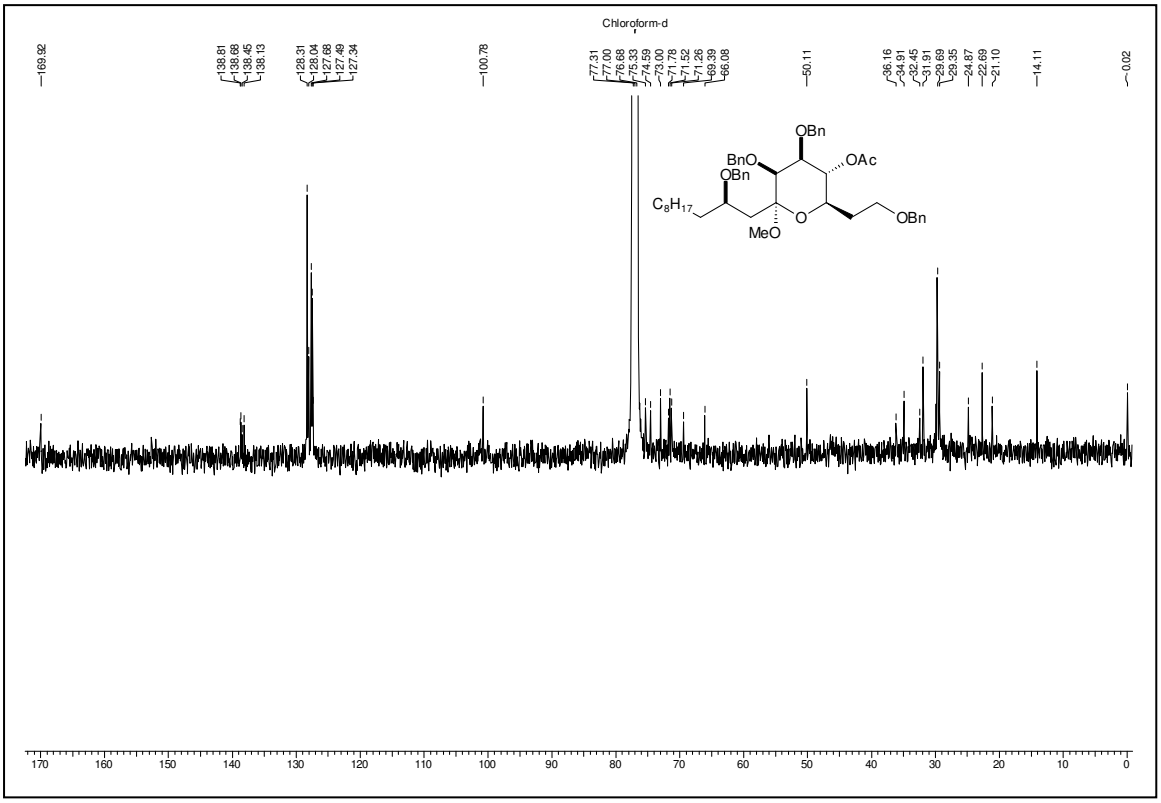
^{1}H NMR spectrum of compound 4 in $CDCl_3$



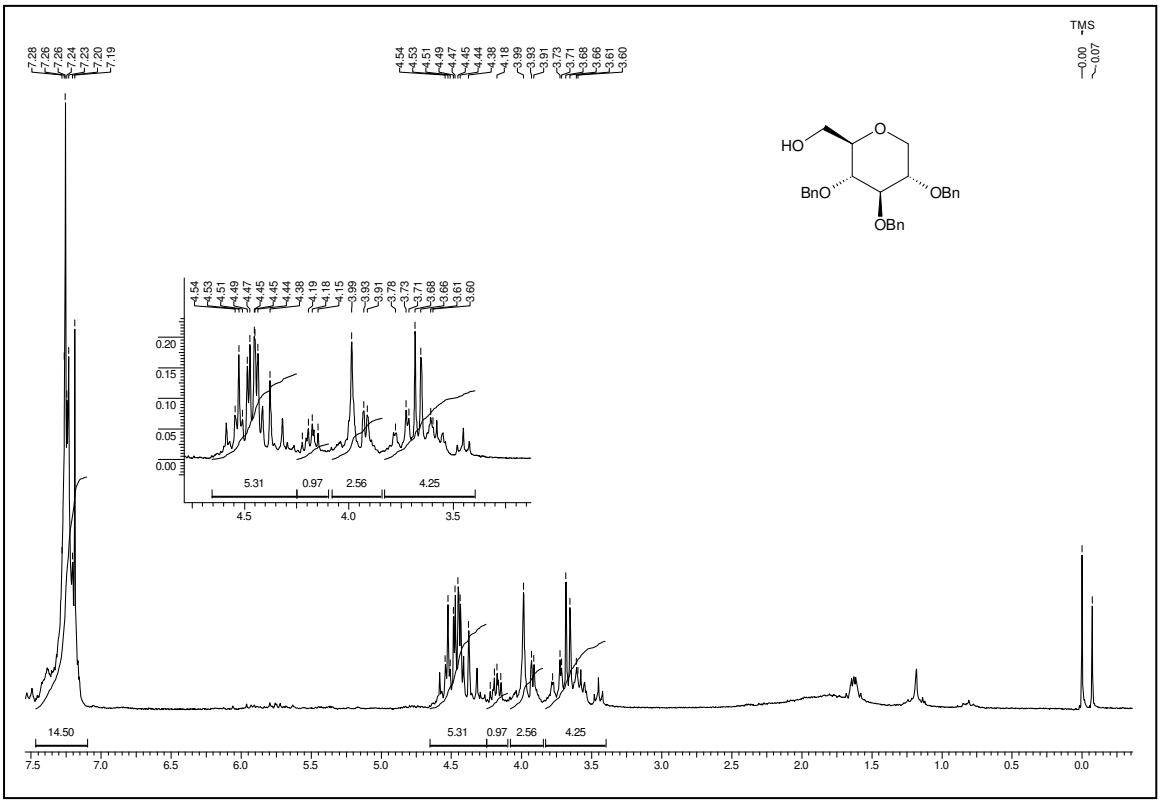
^{13}C NMR spectrum of compound 4 in $CDCl_3$



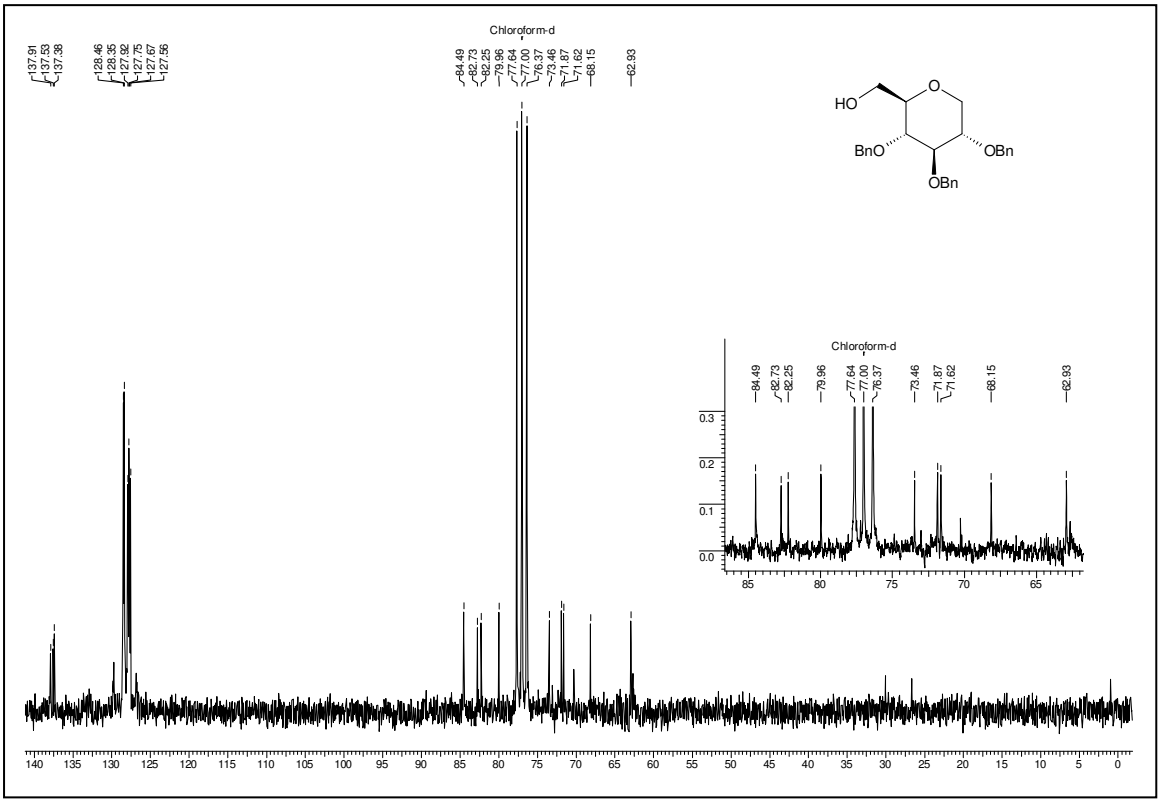
^{1}H NMR spectrum of compound 40 in $CDCl_3$



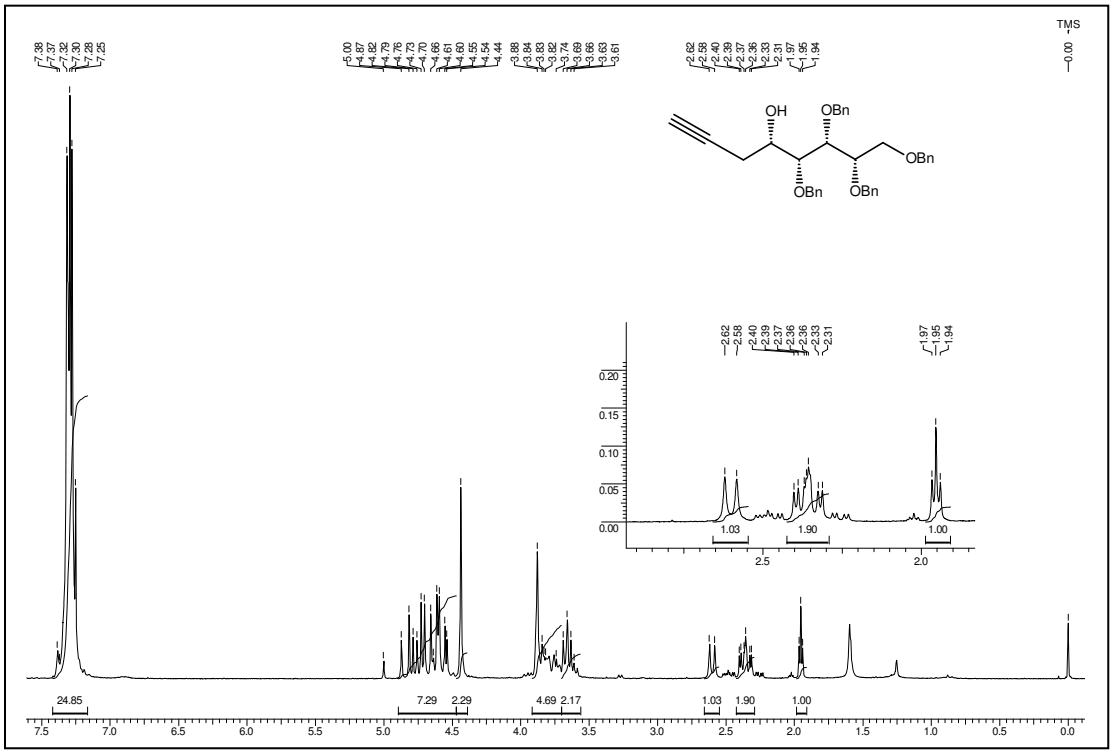
^{13}C NMR spectrum of compound 40 in $CDCl_3$



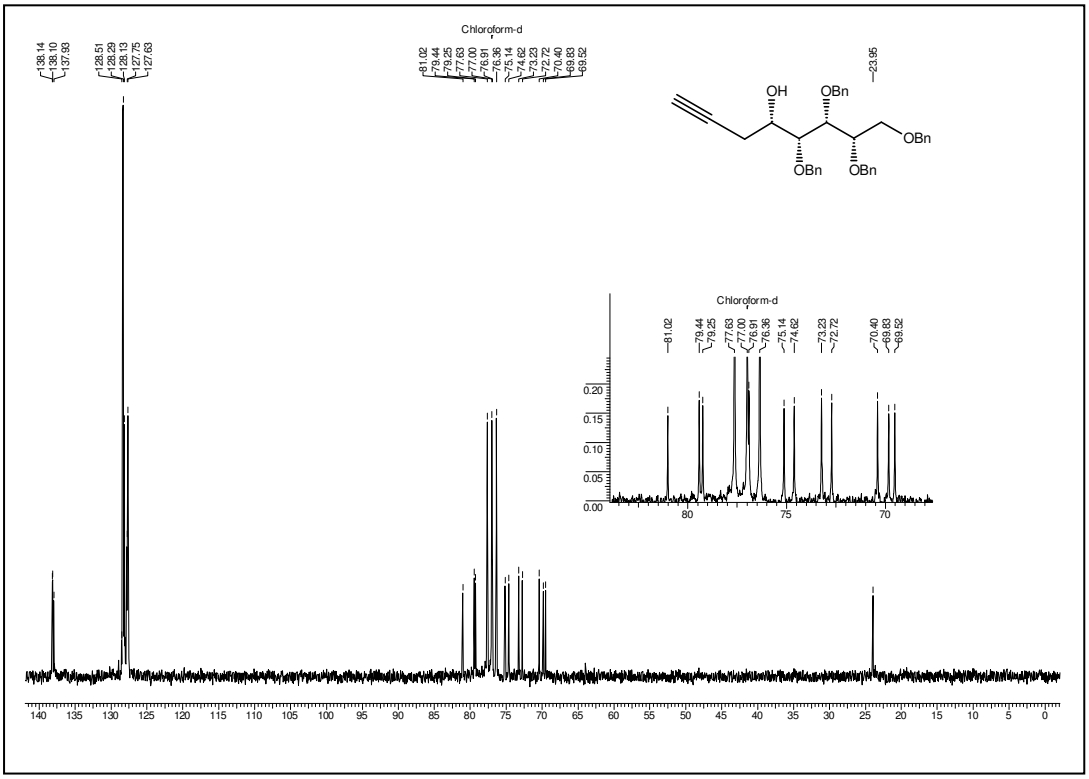
^{1}H NMR spectrum of compound 31 in $CDCl_3$



^{13}C NMR spectrum of compound 31 in $CDCl_3$



^{1}H NMR spectrum of compound 41 in $CDCl_3$



^{13}C NMR spectrum of compound 41 in $CDCl_3$

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Chapter II

Enantioselective total synthesis of (+)-bruguierol A, synthetic studies toward (+)-bruguierol C and synthesis of pyridine fused bicyclo[3.2.1]octane systems.

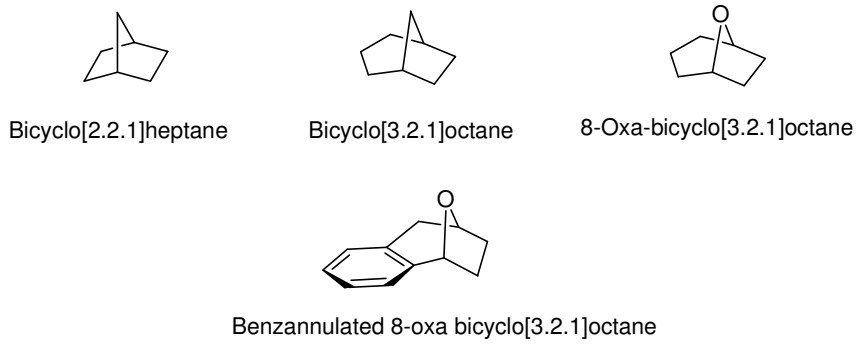
Introduction

Introduction

Carbon-carbon bond formation is one of the most useful and fundamental reactions in synthetic organic chemistry, particularly in the synthesis of complex natural products with biological activity. Development of novel synthetic methodologies and their application to synthesis of natural products is of paramount importance. The design and reduction to practice of new synthetic methodologies is an extremely important aspect of modern synthetic organic chemistry. New synthetic methodologies rely on extending the scope and utility of well-known transformations. Modern synthetic chemists indulge themselves in sketching new synthetic methods and applying them in particularly in the fields of medicinal and agricultural chemistry for the synthesis of biologically active compounds both naturally occurring and designed molecules.

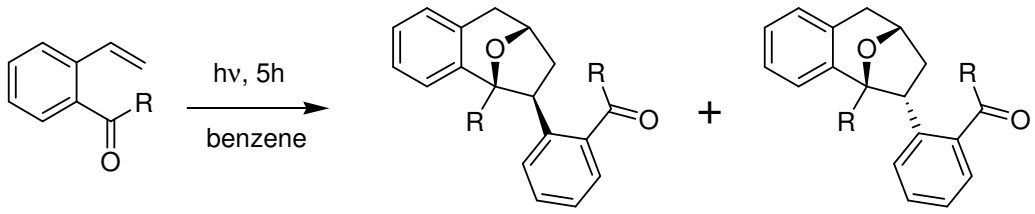
Chemistry of bridged bicyclic ethers was not studied much due to the risk factors associated such as higher ring strain and difficulty in accessing them. Bicyclic and tricyclic alkanes and their oxa and aza analogues form an interesting class of organic compounds due to their higher strain energies and greater reactivity. A wide variety of natural products and designed molecules represent these kinds of systems. The simplest of among these is norborane or bicylco[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.[1] 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. Our initial foray in this area are stimulated by the recently isolated natural products bruguierols A-C (**1-3, Figure 1**) which portrayed this new 3,4-benzannulated-8-oxa-bicyclo[3.2.1]octane structural skeleton in natural product chemistry.[2] Currently, the most general methods to access the aromatic fused [2.2.1]- and [3.2.1] bicyclic systems are by [3+4] cycloadditions[3] and annulations.[4]

Figure 1.



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.[5] Irradiation of *o*-acyl styrenes afforded a pair of stereoisomers of photodimerized benzo-fused oxygen-bridged compounds, 8-oxabicyclo[3.2.1]octane derivatives.

Scheme 1: Photodimerization of *o*-acyl styrenes



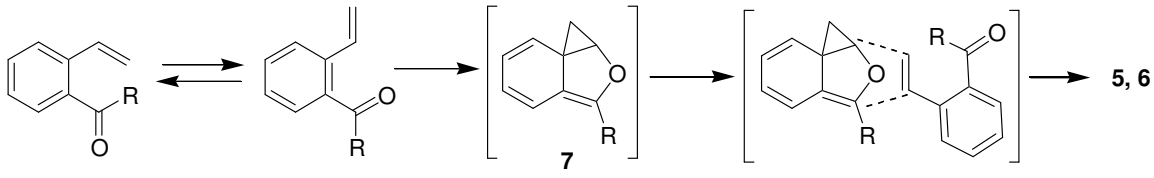
4a: R = CH_3
4b: R = Ph

5a: R = CH_3 : 32%
5b: R = Ph : 27%

6a: R = CH_3 : 32%
6b: R =Ph : 27%

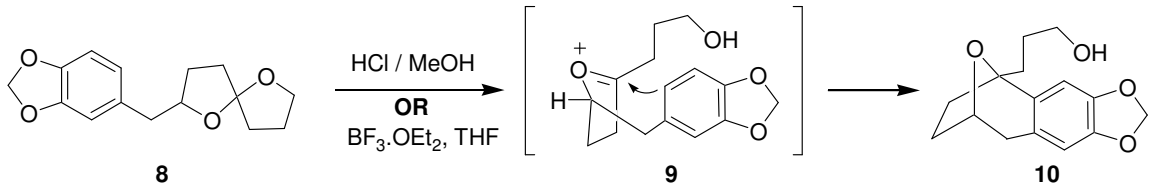
The formation of bicyclic system was explained as follows (**Scheme 2**). When the acyl group is an acetyl and a benzoyl, oxatricyclotriene intermediate **7** was exclusively generated, and subsequently underwent addition with a vinyl moiety gave 8-oxabicyclo[3.2.1]octanes **5, 6.** The selective addition of vinyl moiety was explained by a steric factor associated with acyl group.

Scheme 2:



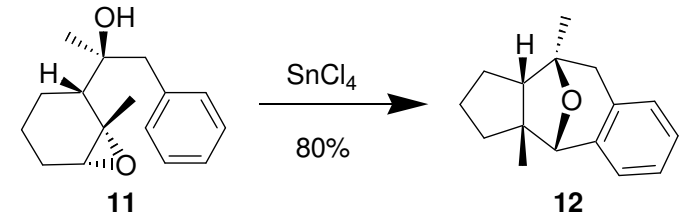
Fan and co-workers reported first examples of Friedel-Crafts alkylation using spiro-ketals as alkylating agents and accessed benzene fused 8-oxa bicyclo[3.2.1]octane system.[6] Slightly more than one equivalent of $BF_3.OEt_2$ in THF at refluxing temperature were found to be the most satisfactory conditions to achieve the desired cyclization. The formation of bicyclic system was satisfactorily explained through an oxonium intermediate **9** (scheme 3), which immediately undergoes cyclization to **10**. 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 et al, developed a novel general approach to bridged bicyclic ethers by $SnCl_4$-catalysed tandem cyclisation involving 3,4-epoxy alcohols.[7a]

Scheme 4: **Cyclization of epoxy alcohol**

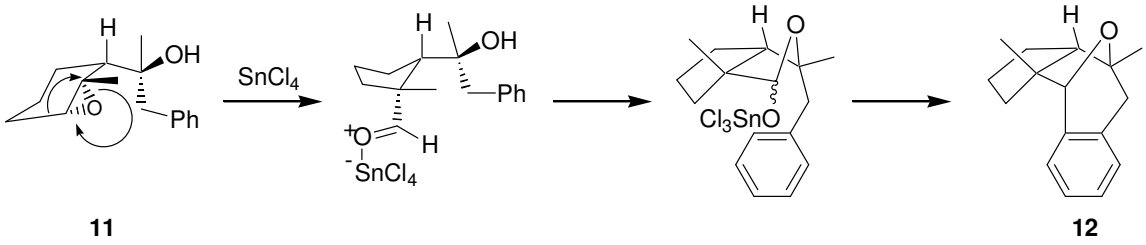


3,4-epoxy alcohol bis-fused 8-oxa bicyclo[3.2.1]octane

The above cyclizations can be understood in terms of the following sequence of events: First, epoxide ring opening and ring contraction take place, mediated by the Lewis acid (Scheme 5). 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.

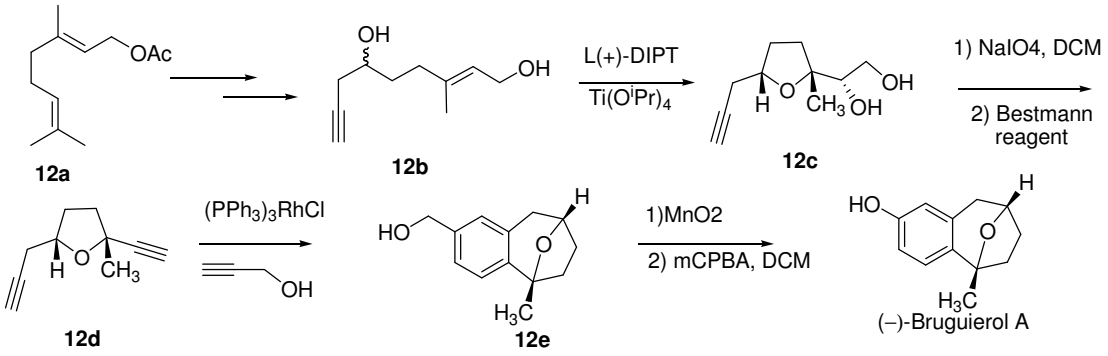
Scheme 5: Possible mechanism for the formation of 12



Our approach towards aromatic fused 8-oxa bicyclo[3.2.1]octane systems is by [2+2+2] cross alkyne cycltotrimerization. Exploration of this methodology can be utilized for the synthesis of Bruguierols.

Recently from our lab synthesis of antipode of bruguierol A was reported[7b] based on [2+2+2] cross cyclotrimerization (**Scheme 6**).

Scheme 6:



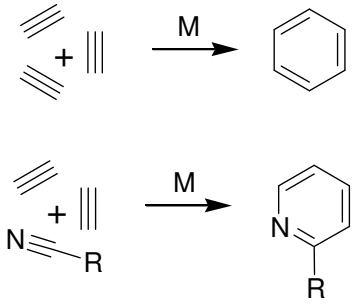
Geranyl acetate **12a** was converted to **12b** through FGI which on SAE with L(+)-DIPT and $Ti(OiPr)_4$ delivered THF derivative **12c**. Oxidative cleavage followed by Ohira-Bestmann reaction furnished **12d**. [2+2+2] cross cyclotrimerization of 12d was performed using Wilkinsons catalyst to provide **12e** which on oxidation, Baeyer-Villiger oxidation followed by hydrolysis delivered the antipode of bruguierol A.

[2+2+2] Cyclotrimerization: A brief history

Cyclizations of unsaturated molecules are intensively studied reactions since they potentially afford a variety of substituted benzenes, heterocyclic and polycyclic compounds of paramount importance in chemical synthetic methods. The simplest examples are the one-step formation of the C-C bonds of benzene by acetylene trimerization, which was first reported by Reppe[8] and the cycloaddition of nitriles

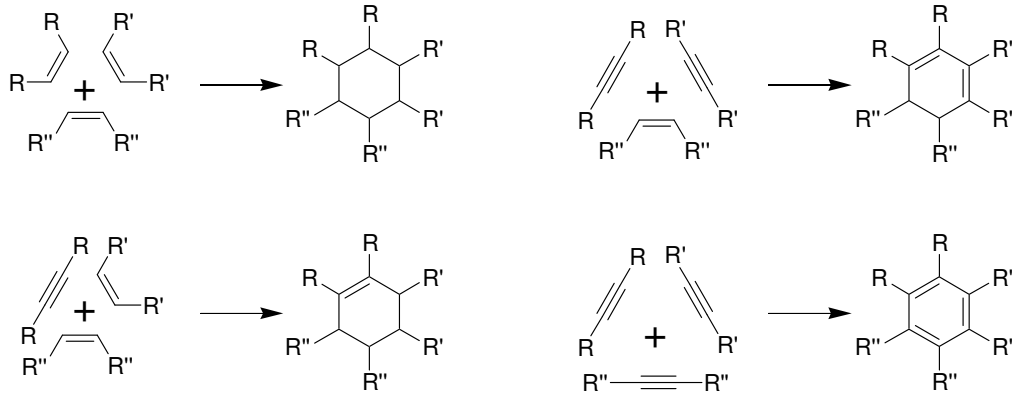
with 2 equiv of acetylene, which is a versatile and effective method for the synthesis of 2-alkyl pyridine.

Scheme 7: Cyclotrimerization of acetylene



The advantage of these [2+2+2] cycloaddition is that they are atom economical, and three new bonds would be constructed in a single operational step. A large change in molecular complexity, up to six chiral centers could be generated from completely achiral starting material.

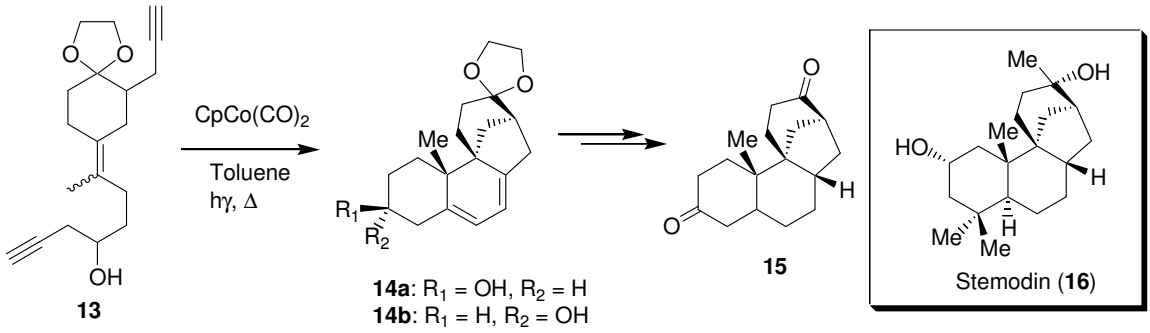
Scheme 8: Prototypical [2+2+2] cycloadditions



The transition metal catalysed [2+2+2] alkyne cyclotrimerization[9] has received continuous attention, as it is a straightforward route to substituted benzenes. The utility of this reaction is exemplified in the synthesis of a variety of complex natural products consisting aromatic rings,[10] dendritic ensembles,[11] and of cyclophanes [12] with variable sizes. Recent progress in this context includes the development of water-soluble catalysts,[13] and a variety of chiral ligands for the asymmetric version[14] of this transformation. Various transition metals (e.g. Ni, Rh, Co, Pd, Cr, Fe, Ru, and Ta) as well as the Ziegler type catalysts have been recognized to promote inter- and intramolecular versions of cyclotrimerization.

Our interest i.e., synthesis of bicyclic systems by cyclotrimerization has been attempted earlier by Albeit, Vollhardt and co-workers, and they have shown the feasibility of intramolecular [2+2+2] cycloaddition of enediynes for the synthesis of highly strained [3.2.1]bicyclooctane system.[15]

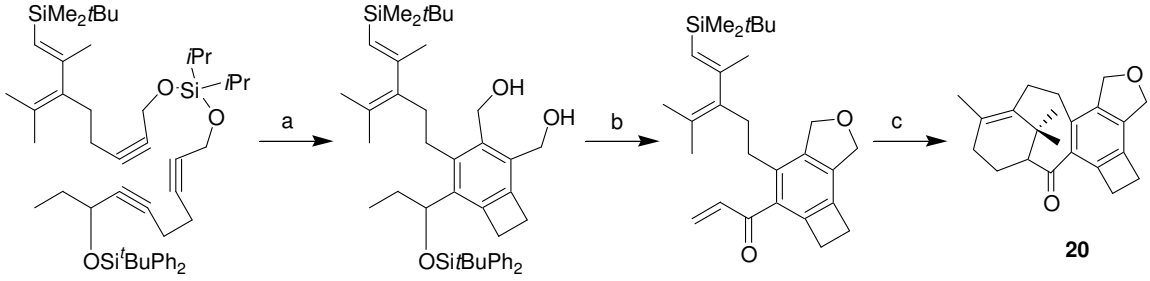
Scheme 8: Synthesis of Stemodin framework



The stereoselective assembly of **14** 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.

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 9: Synthesis of taxoid core



Reagents and conditions: (a) (i) 5 mol% $CpCo(CO)_2$, xylenes, Δ, hγ; (ii) nBu_4NF, THF, -78 °C to 0 °C; (b) (i) *n*BuLi, THF, –78 °C, TsCl, –78 °C to r.t.; (ii) nBu_4NF (1.2 equiv.), THF, reflux; (iii) IBX, DMSO, r.t.; (iv) NaHMDS, THF, –40 °C, PhSeCl, –40 °C to r.t.; (v) $NaIO_4$, $NaHCO_3$, $MeOH/H_2O$; (c) $BF_3{\cdot}Et_2O$ (5 equiv.), $CHCl_3$, –50 °C.

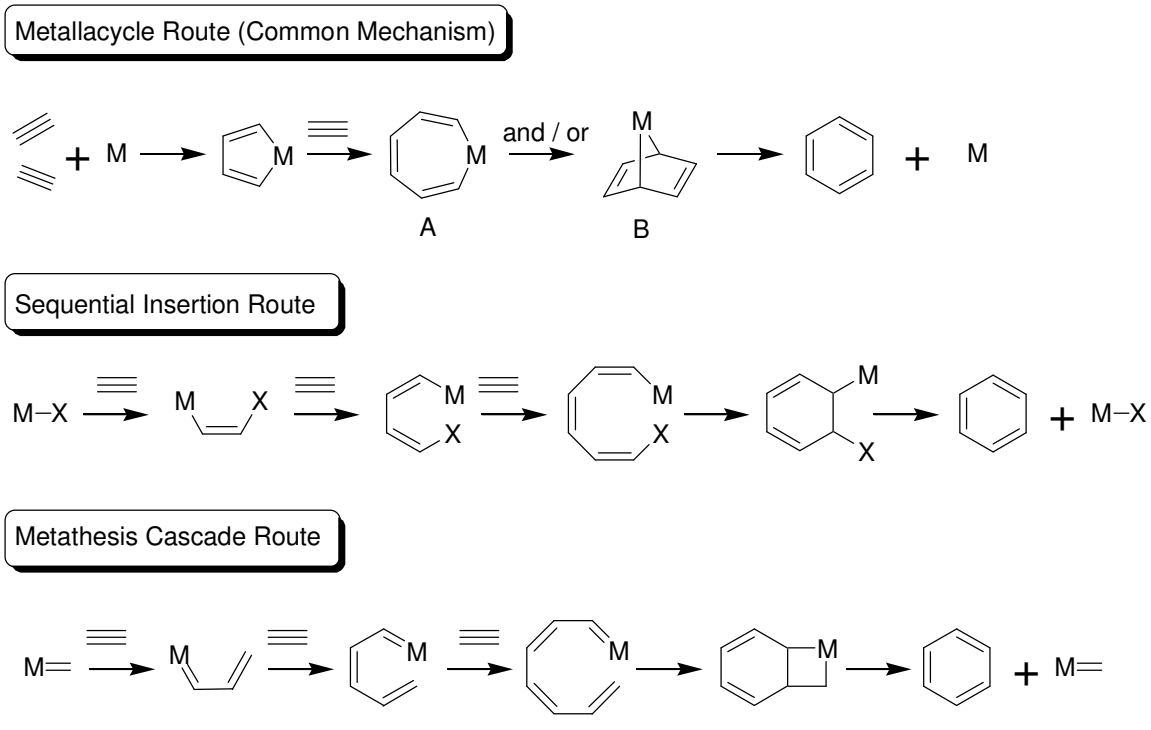
Exposure of silaketal **17** to 5 mol% of $CpCo(CO)_2$ in boiling xylenes under irradiation led to the corresponding benzocyclobutene, which after opening of the silaketal afforded the diol **18.** Monotosylation of **18** followed by

selenation/oxidation/elimination sequence accomplished the tricyclic compound **19**. The latter was treated with 5 equiv. of $BF_3.OEt_2$ in chloroform afforded the desired cycloadduct, the taxoid core **20**.

Mechanism of [2+2+2] alkyne cyclotrimerization

The mechanism of alkyne cyclotrimerization[17] and cyclic cooligomerization (cyclizations involving two alkyne and one alkene)[18] are reviewed thoroughly, but still a generality from these has not been achieved. Transition metal catalyzed alkyne cyclotrimerizations can be broadly divided in to three categories on the basis of their reaction mechanisms (scheme 9).[17b] The most widely accepted mechanism is so-called the "common mechanism". 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 operates in cyclotrimerizations catalyzed by transition-metal hydrides or halides[19].

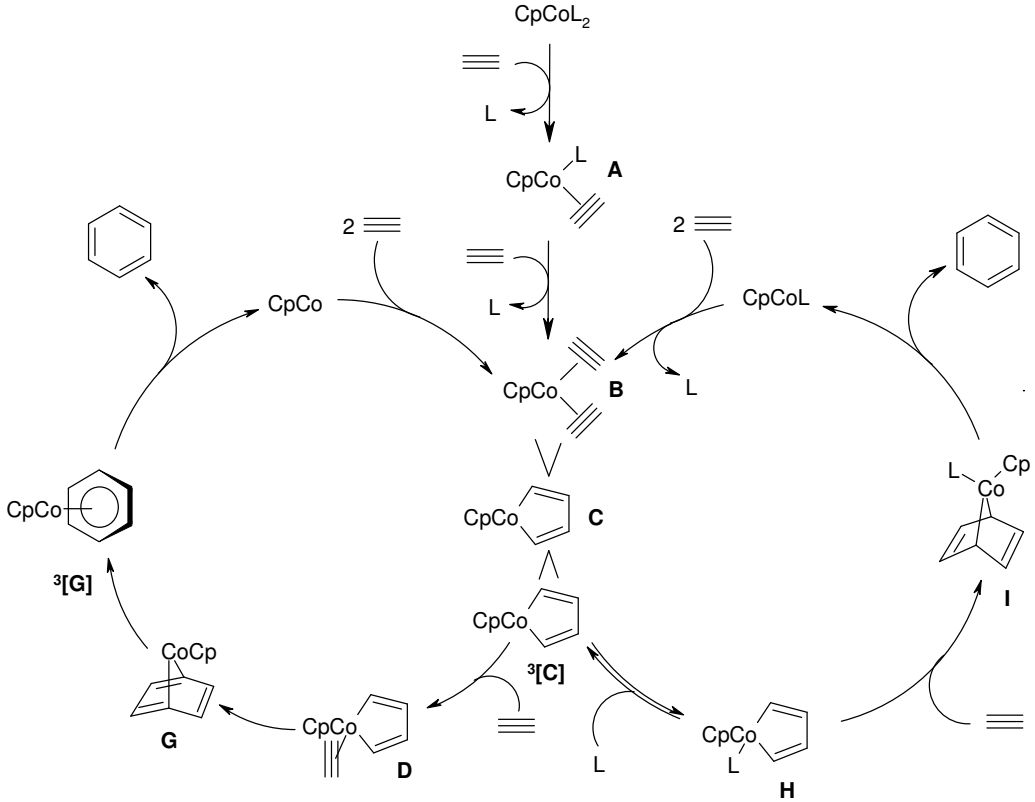
Scheme 10: Possible mechanisms of alkyne cyclotrimerization



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.[2] Aubert and co-workers recently studied mechanism of the $CpCo(L_2)$-catalyzed cyclotrimerization of acetylene on the basis of DFT computations, and proposed a parallel mechanism (Scheme 10).[21] 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}[**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 $CpCo(PR_3)_2$ or $CpCo(CO)_2$, 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}[**C**] reacts with the alkyne to give **D**, which subsequently transforms into the CpCo(η^4-arene) complex **G** via intramolecular metal-assisted [4 + 2] cycloaddition. A spin change transforms **G** into the 20-electron sandwich complex ^{3}[**G**], which dissociates to arene.

Scheme 11: Two-state mechanism for the Co-catalyzed ethyne cyclotrimerization



Chapter II

Section I

Enantioselective total synthesis of (+)-bruguierol A and synthetic studies toward (+)-bruguierol C

Among marine plants, mangroves represent a unique ecological system which can be found on tropical and sub-tropical lines. Due to necessary physiological adaptations, they are considered to harbour a variable secondary metabolism, thus being a rich source for natural products.[22] Five new aromatic compounds (**Figure 1**, **1-5**) were obtained by the phytochemical investigation of the stem of large leafed evergreen mangrove *Bruguiera gymnorrhiza,* which belongs to the *Rhizophoraceae* family, collected from the coast of Xiamen in the south china by Sattler and co-workers, of which bruguierols A-C (**1-3**), with the **benzannulated-8-oxa bicyclo[3.2.1]octane**

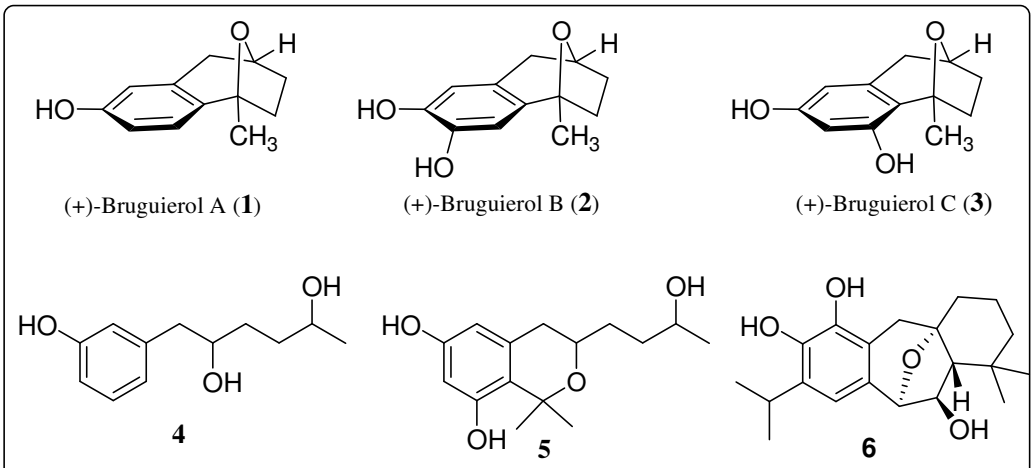


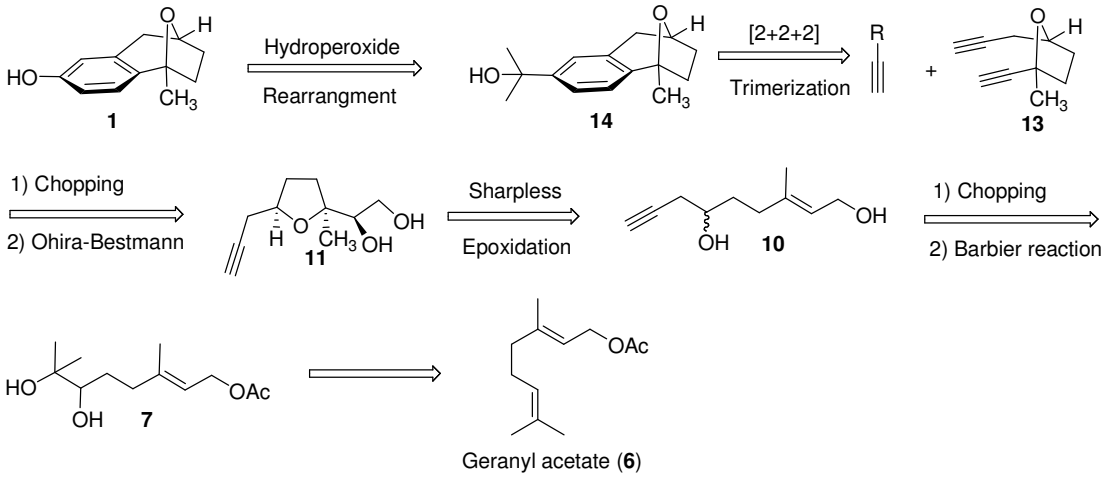
Figure 1: Five new aromatic compounds (**1-5**) from *Bruguiera gymnorrhiza*

structure, represent a new class of molecular skeleton in natural product chemistry. Only the icetexane diterpenoids, e.g., 5,6-dihydro-6α-hydroxysalviasperanol **6**, shows some structural similarities. Among them bruguierol C showed moderate activity against Gram-positive and Gram-negative bacteria including mycobacteria and resistant strains (MICs 12.5 μg/ml). Intrigued by its molecular structure and moderate biological activity, we embarked on the synthesis of (+)-bruguierol A.

These compounds (**1-3**) are not derived from the terpene biosynthetic pathway. Due to the oxidation level mismatch they also seem unrelated to catechin-type metabolites like theaflavin and purpurogallin which are branching of the shikimate-pathway.[23] **Scheme 1** shows our basic synthetic plan in an antithetic way for (+)-bruguierol A which relied on the hydroperoxide rearrangement of tertiary alcohol **14** and the Sharpless asymmetric epoxidation (SAE) of allylic alcohol **10**. Tertiary alcohol was envisaged its construction, with the consideration that the cyclotrimerization reaction would build the A and B rings of the tricyclic core, from

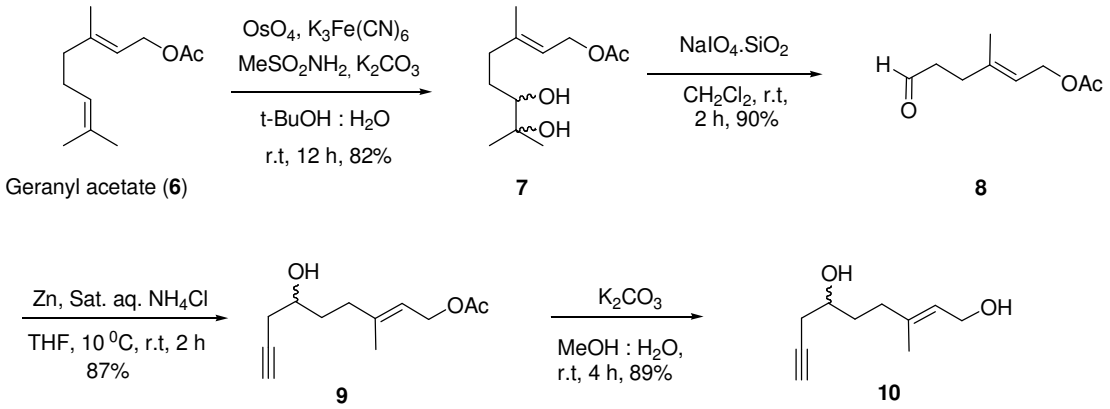
diyne **13** and dimethyl propargyl alcohol by [2+2+2] cross cyclotrimerization . The diyne **13** could be generated from the diol **11**. Aceess to this diol was to be gained from allylic alohol derivative **10** by Sharpless epoxidation which in turn could be obtained from commercially available terpene geraniol through geranyl acetate **6**.

Scheme 1: Retrosynthetic analysis



Our synthesis began with the regioselective dihydroxylation of electron rich double bond of geranyl acetate **6** with OsO_4 and NMO in t-BuOH:H_2O to furnish the diol **7** which upon $NaIO_4$ assisted oxidative cleavage resulted to the previously known aldehyde **8**.[24] Propargylation of the aldehyde **8** under the Barbier reaction conditins[25] was accomplished with zinc, propargyl bromide and sat. aq. NH_4Cl in THF at 0 ^{0}C to provide the racemic homopropargylic alcohol **9** in 87% yield. The structure of the compound is in full agreement with its spectral data. For example in the ^{1}H NMR disappearance of aldehydic proton, resonance of acetylenic proton as a triplet at 2.04 ppm and the diastereotopic propargylic $\underline{CH_2}$ protons were resonated as *ddd* at 2.32 and 2.44 ppm. In ^{13}C NMR two alkyne carbons were seen at 70.52 and 80.66 ppm respectively while the propargylic CH_2 at 27.1 ppm. All the other analytical data is in full agreement with the proposed structure. Base mediated trans-esterification of the acetate functionality of **9** was accomplished with K_2CO_3 in MeOH : H_2O to afford the racemic allylic alcohol **10** in 90% yield (**Scheme 2**). Lack of acetate stretching frequency due to OAc group in IR spectrum and disappearance of acetate carbonyl resonance peak in ^{13}C NMR was the pinpoint of the conversion. A highest peak at 191.3 $(M+Na)^+$ in EIS-MS was an added support.

Scheme 2: Preparation of allylic alcohol **10**

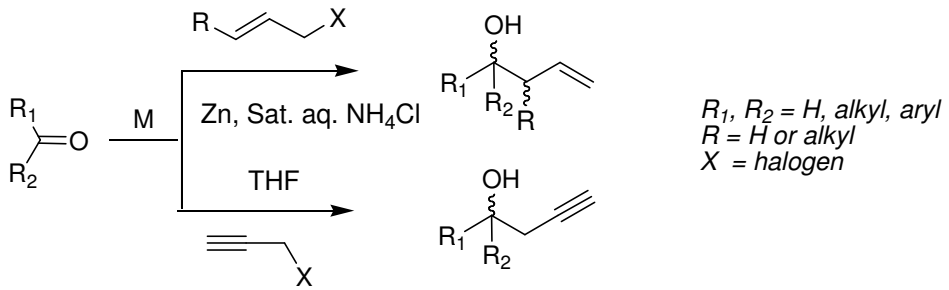


Geranyl acetate (**6**) **7** **8** **9** **10**

Short account of Barbier reaction[25]

*The reaction between an allyl or propargyl halide and a carbonyl group (aldehyde or a ketone) in the presence of metals like zinc, aluminium, indium, tin, samarium etc., or their salts is termed as Barbier reaction (**Scheme 3**). 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 the procedure part of green chemistry. The Barbier reaction is named after Victor Grignard's PhD supervisor Philippe Barbier.*

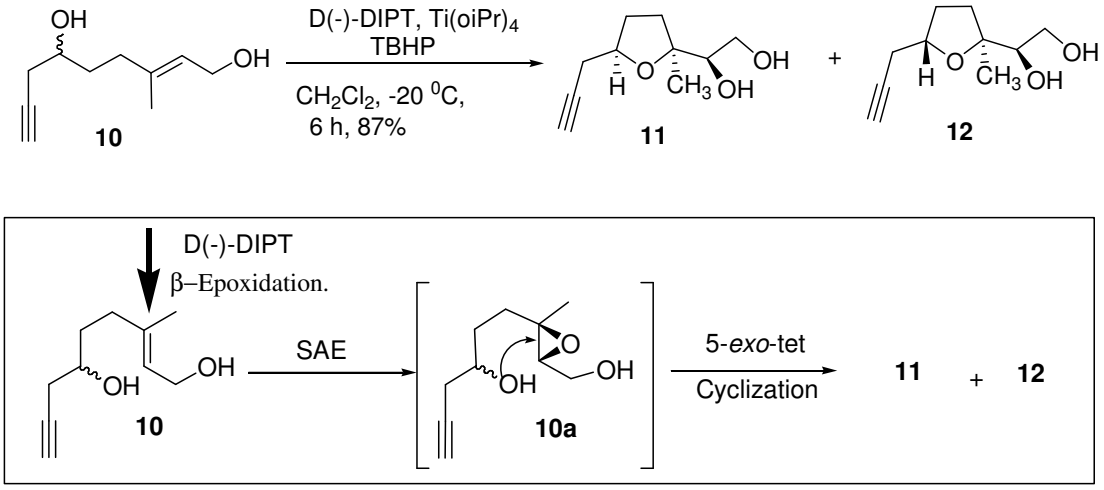
Scheme 3: General Barbier reaction



The next endeavour in the synthesis is the kinetic resolution of allylic alcohols **10** using Sharpless Asymmetric Epoxidation[26] (SAE) in advance of cyclotrimerization. In

this direction SAE of **10** was conducted at -20 ^{0}C in stoichiometric fashion in CH_2Cl_2 with t-butyl hydroperoxide as *oxo* donor and Ti(O^iPr)$_4$+D(-)-DIPT as chiral adjuvant to furnish the kinetically resoluted cis and trans tetrahydro furans **11** and **12** in 86% yield with 92% ee (**Scheme 4**).

Scheme 4: SAE of allylic alcohols **10** (kinetic resolution)



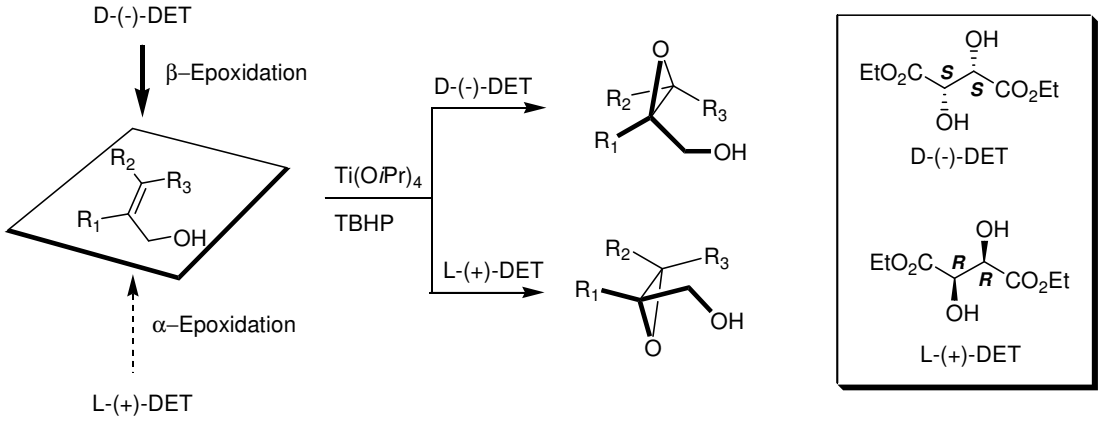
The mechanism of SAE is shown in **Scheme 4**. Epoxidation takes place from the β-face of the allylic alcohol leading to the epoxy-alcohol **10a** which undergoes preferentially 5-exo-tet cyclization to form the cis and trans THF derivatives. The preferential 5-exo-tet cyclization could be attributed to the higher stability of the insipient carbocation leading to the THF derivatives instead of THP derivatives.

Sharpless Asymmetric Epoxidation[26] (SAE)

*Since its discovery in 1981 it was by far the best asymmetric reaction known. Sharpless Asymmetric Epoxidation (SAE) is one of the central tranformations used for the enantioselective epoxidation of prochiral allylic alcohols in organic synthesis for which the scientific community awarded the Nobel Prize in chemistry in 2001. When a prochiral Z- or E-allylic alcohol is treated with a 10 membered fluxional complex (two titanium atoms bridged by two tartarate ligands) formed by the equimolar reaction of dialkyl tartate and titanium tetraisopropoxide at -20 ^{0}C in DCM followed by treatment with allylic alcohol and t-butyl hydroperoxide leading to the formation of 10 membered dissymmetric complex which delivers the epoxidation stereoselectively. D(-)-DIPT or DET delivers the epoxidation from the β-face of the allylic alcohol while the L(-)-DIPT or DET delivers from the α-face (**Figure 2**). Easy*

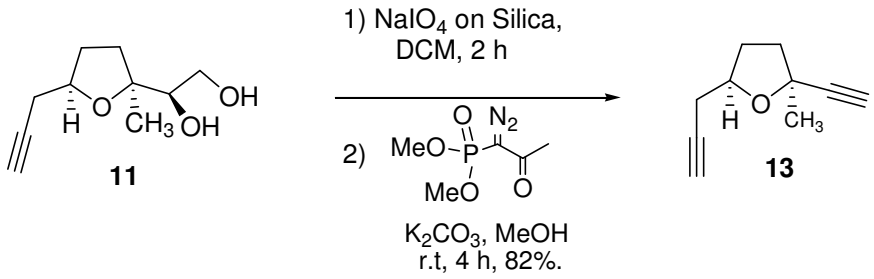
availability of reagents involved, and high enantiomeric (or diastereomeric) excess obtained in the reaction made the Sharpless asymmetric epoxidation to find wide spread application in the introduction of chirality in the complex target molecules. The easy and precise prediction of stereochemical outcome irrespective of the substitution pattern on the allylic alcohol further emphasized the reaction applications.

Figure 2: *Pneumonic of Sharpless Asymmetric Epoxidation (SAE).*



After successfully performing the SAE our next target was the synthesis of key diyne **13**. For that the diol functionality of requisite cis diastereomeric THF derivative **11** was oxidatively cleaved with $NaIO_4$ on silica to the somewhat volatile aldehyde which with out purification was quickly subjected to Ohira-Bestmann reaction conditions[27] with $CH_3COC(N_2)P(O)(OMe)_2$ and K_2CO_3 in MeOH at rt for 30 min to afford the volatile diyne **13** (with typical terpene aroma) in 82% yield (**Scheme 5**).

Scheme 5: Synthesis of diyne **13**

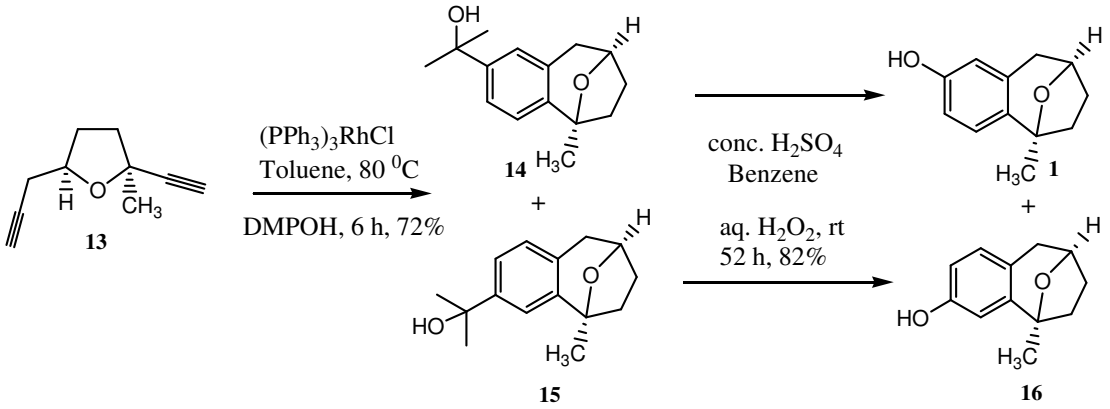


The structure of the diyne **13** was substantiated for its structure from ^{1}H NMR, ^{13}C NMR, IR and mass spectral data. For example in ^{1}H NMR resonance of two alkyne protons at 1.95 (singlet) and 2.39 ppm (triplet) while ^{13}C NMR showed four alkyne carbons at 69.68, 70.93, 80.85 and 87.86 ppm respectively. Terminal alkyne CH

asymmetric stretching frequencies were seen at 3306 and 3302 cm^{-1} in IR spectrum. A peak at m/z 171.09 $(M+Na)^+$ in EIS-Ms spectrum is an additional support.

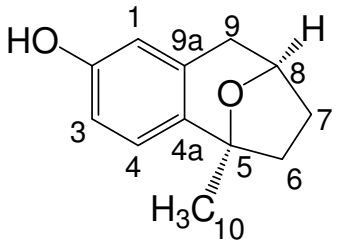
With the fully elaborated diyne framework of **13** in place, the penultimate step of cyclotrimerization of diyne **13** with dimethyl propargyl alcohol (DMPOH) was attempted with various metal catalysts in different solvents with a range of temperatures, but the reaction of diyne **13** with 5 mol% of Wilkinson's catalyst in refluxing EtOH at 80 ^0C was found to be the ideal reaction condition to deliver a 1:1 inseperable regiomeric alcohols **14** and **15** in 72% yield (**Scheme 6**). The structure of the compounds was unambiguously confirmed from its spectral data. For example, in ^1H NMR terminal alkyne protons were no more, resonance of three aromatic protons between 7.04 to 7.4 ppm and two gem dimethyls of dimethyl propargyl alcohol part as a singlet at 1.56 ppm while the ^{13}C NMR showed six aromatic carbons (118-142 ppm) and gem dimethyls at 27.0 ppm. A peak in mass spectrum at m/z 191.18 $[M+1]^+$ and 213.18 $[M+Na]^+$ is an added support.

Scheme 6: -



After successfully performing the key cyclotrimerization, our final step in the synthetic direction is the hydroperoxide rearrangement.[29] For that compounds **14** and **15** were exposed to conc. H_2SO_4 and aq. H_2O_2 in benzene at rt for 52h to furnish a 1:1 column separable (+)-bruguierol A (**1**) and its regiomer **16** in 82% of yield. The structure of the synthetic bruguierol (**1**) is in excellent agreement with that of the natural product (**Table 1**).

Table 1: NMR comparision of (+)-Bruguierol A



Carbon N0	Natural Product		Synthetic Sample	
	δ_H	δ_C	δ_H	δ_C
1	6.52	115.6	6.53	115.6
2	--	154.4	--	154.1
3	6.58	112.9	6.59	112.8
4	6.99	123.9	7.01	124.0
4a	--	136.2	--	136.5
5	--	80.4	--	80.3
6	1.84	42.9	1.85	42.9
	1.95		1.98	
7	2.25	30.4	2.24	30.4
	1.74		1.71	
8	4.69	74.2	4.70	74.2
9	3.30	37.5	3.30	37.5
	2.44		2.45	
9a	--	133.5	--	133.6
10	1.68	22.8	1.69	22.8

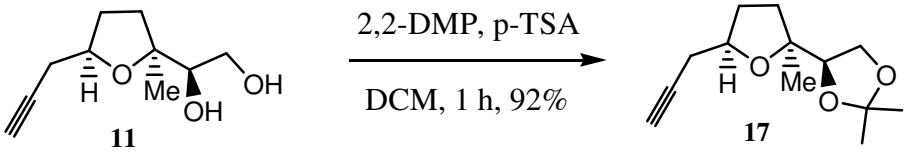
The optical rotation of synthetic sample **1** {$[\alpha]_D$ +16.1 (*c* 0.3, $CHCl_3$)} was similar to reported value {$[\alpha]_D$ +14.4 (*c* 0.3, $CHCl_3$)} with the same sign which confirmed the absolute stereochemistry of (+)-bruguierol A as (5*R*, 8*S*).

Synthetic studies toward (+)-bruguierol C

After succesfully applying the [2+2+2] cross cyclotrimerization for the synthesis of (+)-bruguierol A we next focused our attention on its higher hydroxy analogue (+)-bruguierol C. In the synthetic direction diol functionality of **11** was converted to its isopropylidene ketal upon exposure to 2,2 dimethoxy propane and cat. p-TSA in DCM to afford the isopropylidene ketal **17** in 92% yield (**Scheme 7**). Lack of hydroxy stretching frequencies in IR, resonance of two gem dimethyls of ketal as two singlets

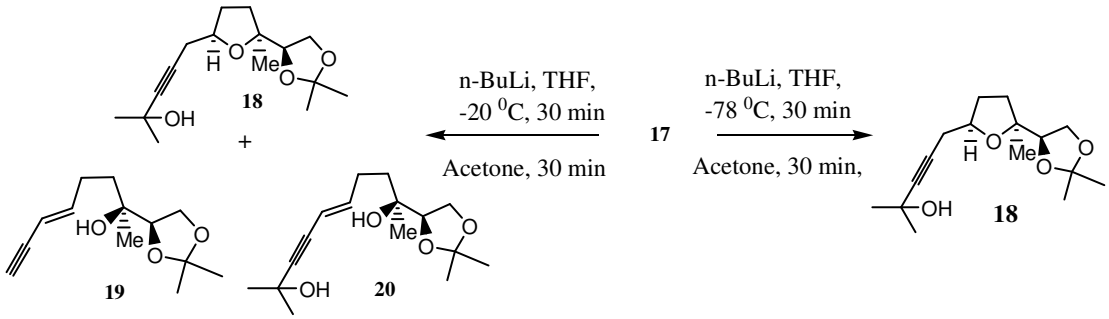
at 1.31 and 1.40 ppm in ^{1}H NMR and at 23.3 and 24.8 ppm in ^{13}C NMR were the indicative of the product.

Scheme 7: -



Our next step in the synthesis is nucleophilic addition of lituium acetylide of **17** with acetone. For that compound **17** was treated with n-BuLi at -20 ^{0}C in THF for 30 min followed by the addition of freshly distilled acetone resulted the required tertiary alcohol **18** along with the undesired THF ring opened products (enynes) **19** and **20** (**Scheme 8**). The structure of the products **19** and **20** were unambiguously confirmed by their spectral studies. For example in ^{1}H NMR of **20** (trans : cis ~5:1), two trans oriented olefinic protons were seen at 5.50 (dt, J = 15.92, 1.51 Hz) and 6.11 ppm (dt, J = 15.92, 6.94 Hz) and two gem dimethyls at 1.51 ppm. ^{13}C NMR indicated the two olefinic carbons at 109.3 and 144.23 ppm respectively. A mass peak in EIS-MS spectrum at m/z 283.8 $(M+1)^{+}$ is an additional support. As for the product **19** is concerned its ^{1}H NMR showed an alkyne CH at 2.775 ppm (d. J = 2.15 Hz) along with two trans olefinic protons at 5.475 (dd, J = 15.92, 1.65 Hz) and 6.24 ppm (dt, J = 15.92, 6.94 Hz).

Scheme 8: -

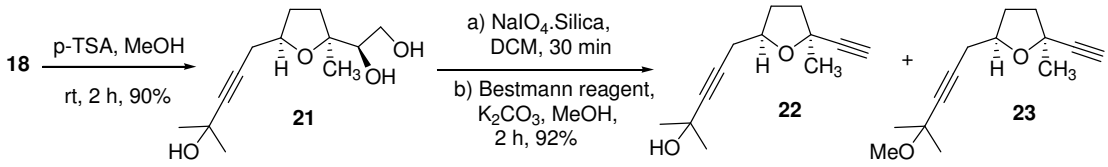


Required product **18** was obtained by performing the above said reaction at -78 ^{0}C under the same set of reaction conditions (**Scheme 8**). The product **18** structure was confirmed by its spectral data. The ^{1}H NMR spectrum of **18** revealed the presence of two gem dimethyls at 1.47 ppm and absence of terminal alkyne CH.

The observation of two singlets at 76.68 and 86.86 ppm due to two internal alkynes and two quartets at 30.5 and 31.6 ppm due to two gem dimethyls in ^{13}C NMR, was the charecteristic features of the product. Other analytical data is in agreement with the proposed structure.

Unmasking of the isopropylidene ketal of **18** was accomplished with p-TSA in MeOH to provide the diol **19** in 90% yield (**Scheme 9**). This deprotection was supported by the ^{1}H NMR spectrum by the disappearance of peaks due to isopropylidene group. The ^{13}C NMR, IR and EIS-MS [(M+23) at (*m*/*z*) 265.8] spectral studies also supported the structure.

Scheme 9: -



$NaIO_4$ aided cleavage of the diol functionality of **19** in DCM furnished the aldehyde which with out purification rapidly subjected to Ohira-Bestmann reaction conditions with $CH_3COC(N_2)P(O)(OMe)_2$ and K_2CO_3 in MeOH at rt for 30 min to afford the diyne **22** in 92% yield along with the methylated product **23** which was minimized by reducing the reaction time. The salient features of structure **22** were clearly corroborated from the spectral data in ^{1}H NMR, ^{13}C NMR, IR and EIS-MS. In ^{1}H NMR spectrum a singlet at 2.45, due to terminal alkyne CH, was observed while the ^{13}C NMR demonstrated the presence of four alkyne carbons at 70.87, 8.35, 78.59 and 86.56 ppm respectively. EIS-MS spectrum featured with a peak at m/z 229.4 $(M+23)^{+}$. Thus, this crucial transformation uneventfully framed the main skeleton with appropriate substitution and required stereochemistry for key cyclotrimerization. Thus cyclotrimerization of diyne **22** with dimethyl propargyl alcohol (DMPOH) with various catalysts in different solvents with a range of temperatures, could not deliver the required product **24** (**Table 2**) as the competitive self dimerization products of starting dialkyne (**26** and **27)** and DMPOH (**25)** were the isolated products (**Scheme 10**). The structure of the dimerised product **25** was esatblished with the help of spectral data. In ^{1}H NMR, two olefinic protons with trans coupling constant (J =16.04 Hz) were resonated at 5.72 and 6.23 ppm and two sets of gem dimethyl signals at 1.31

Scheme 10:

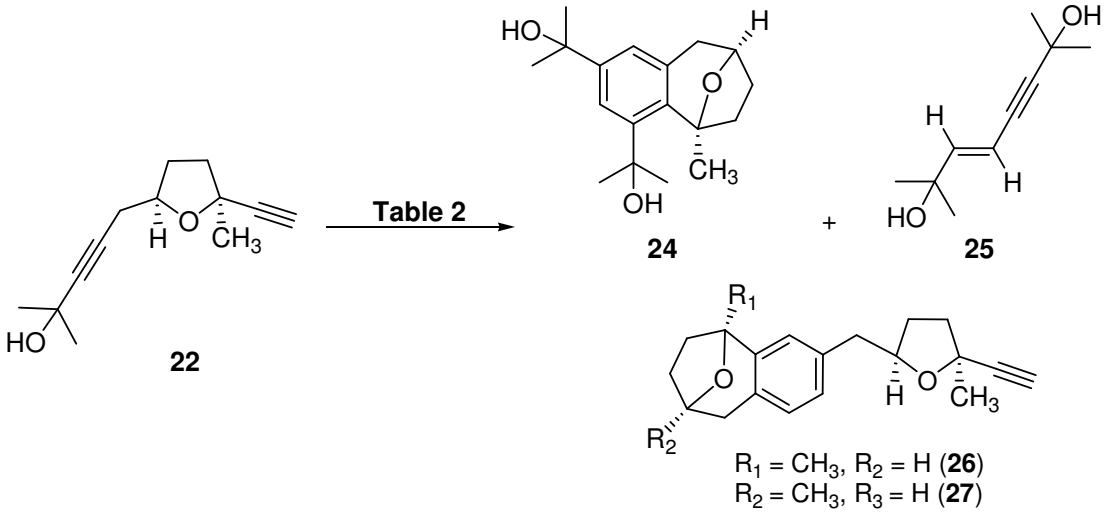


Table 2: Various cyclotrimerization conditions

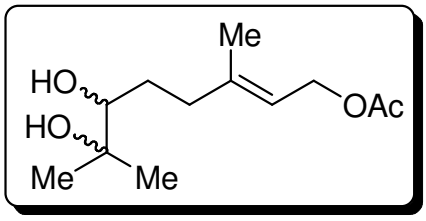
S. No	Catalyst	Solvent	Temp.	Time	Observation
1.	$Ni(cod)_2$ / PPh_3	THF / Toluene	rt-reflux	10 h	**22** + **25**
2.	$Mo(CO)_6$	THF / Toluene	reflux	12 h	**22**
3.	$Rh(PPh_3)_3Cl$	Toluene-ethanol	80 °C	3 h	**22** + **25**
4.	$CoCl_2.6H_2O$ / Zn	THF	reflux	15 h	**22**
5.	$CpCo(CO)_2$	Xylene	140 °C	5 h	**22**

and 1.51 ppm respectively. ^{13}C NMR indicated the presence of two lefinic carbons at 106.2 and 150.5 ppm and two internal alkyne carbons at 80.13 and 94.4 ppm respectively. A highest mass peak at m/z 191.08 in EIS-MS is an additional support.

At this stage the reasons for the failure of cyclotrimerization was not clear, but the high steric hinderance at the diyne site may be the cause of failure. Further studies are in progress in our laboratory.

Experimental

(E)-6, 7-dihydroxy-3, 7-dimethyloct-2-enyl acetate (7):



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 tertroxide (5.1 mL of 0.02 M soln in toluene, 0.102 mmol), geranyl acetate (10.0 g, 51 mmol) and 200 mL of 1:1 *t*-butanol-water was stirred at room temperature 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 dichloromethane, washed with 200 mL of 2 M KOH, dried over sodium sulfate, filtered and concentrated. Chromatographic purification (1:1 petroleum ether/ethyl acetate) gave diol **7** (9.62 g, 82%) as colorless oil.

Yield : 82%

Mol. Formula :$C_{12}H_{22}O_4$

IR ($CHCl_3$) $\tilde{\nu}$: 3441, 3019, 2977, 2932, 1726, 1368, 1239 cm^{-1}.

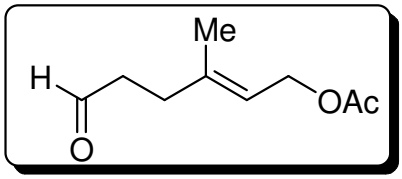
^{1}H NMR ($CDCl_3$, 200 MHz) : δ 1.15 (s, 3H), 1.20 (s, 3H), 1.36-1.64 (m, 2H), 1.72 (s, 3H), 2.05 (s, 3H), 2.10-2.40 (m, 2H), 2.48 (br s, 2H), 3.32 (dd, *J* = 10.2, 2.2 Hz, 1H), 4.58 (d, *J* = 7.0 Hz, 2H), 5.38 (qt, *J* = 7.0, 1.3 Hz, 1H) ppm.

^{13}C 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 (*m/z*) : 253.41 $[M+Na]^+$.

Elemental Analysis Calcd.: C, 62.58; H, 9.63.
Found: C, 62.39; H, 9.48.

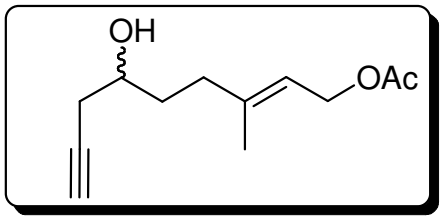
(E)-3-methyl-6-oxohex-2-enyl acetate (8):



To a vigorously stirred suspension of silica gel-supported $NaIO_4$ (80 g) in dichloromethane (300 mL) was added a solution of the diol **7** (9.0 g, 39.1 mmol) in dichloromethane (100 mL). The reaction mixture was stirred at room temperature for 30 min, filtered through sintered glass funnel and the silica gel was thoroughly washed with dichloromethane (3 X 100 mL). Combined filtrates were concentrated under reduced pressure to gave aldehyde **8** (5.98 g, 90%) as a colorless oil, which was directly taken for the next step without further purification.

Yield	:90%
Mol. Formula	:$C_9H_{14}O_3$
IR (Neat) $\tilde{\nu}$	3452, 2937, 2858, 1736, 1671, 1445, 1025 cm^{-1}.
^{1}H 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).
^{13}C 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).
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-ynylacetate (9):-



To a vigorously stirring heterogeneous solution of aldehyde **8** (10.0 g, 58.82 mmol), propargyl bromide (15.72 ml, 176.4 mmol) and activated zinc powder (11.5 g, 176.4 mmol) in THF (100 mL) at -10 ^{0}c was added sat. aq. ammonium chloride solution (20 ml) slowly dropwise over a period of 15 min and stirred for 30 min. The reaction mixture was filtered through a pad of celite and washed with ethyl acetate (100 mL). The filtrate was concentrated in vacuo and the residue was purified

by column chromatography to yield 10.75g (87%) of homopropargyl alcohol **9** as a colourless oil.

Yield : 87 %

Mol. Formula : $C_{12}H_{18}O_3$

IR (CHCl3) ν : 3451, 3021, 2977, 2932, 1726, 1364, 1236 cm^{-1}.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 1.66-1.61 (m, 1H), 1.71-1.67 (m, 1H), 1.73 (br S, 3H), 2.00 (br s, 1H), 2.05 (s, 3H), 2.125 (br d, 8.21 Hz, 1H), 2.21 (br d, 7.58 Hz, 1H), 2.325 (16.68, 6.32, 2.65 Hz, 1H), 2.40 (ddd, 16.68, 5.18, 2.65 Hz, 1H), 3.80-3.68 (m, 1H), 4.57 (d, 7.06 Hz, 2H), 5.42-5.33 (m, 1H).

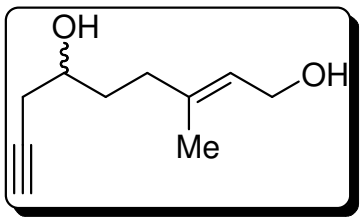
^{13}C NMR ($CDCl_3$, 50 MHz) : δ 16.11 (t), 20.63 (t), 27.07 (q), 33.61 (d), 35.13 (d), 60.96 (d), 68.97 (t), 70.52 (d), 80.66 (s), 118.41 (d), 141.35 (s), 170.70 (s).

Elemental Analysis Calcd.: C, 68.54; H, 8.634

Found: C, 68.72; H, 8.56

ESI-MS (m/z) : 233.4 $(M+Na)^+$

(E)-3-methylnon-2-en-8-yne-1,6-diol (10):



To a solution of **9** (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 aqueous layer was extracted with ethyl acetate (50 mL). The combined organic layer was dried over Na_2SO_4, filtered and concentrated in vacuo. The crude product was purified by column chromatography (2:1 petroleum ether/ethyl acetate) to afford **10** (7.7 g, 90%) as colorless oil.

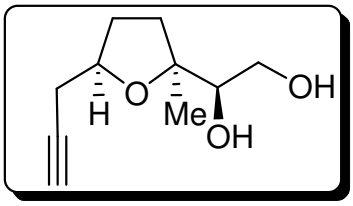
Mol. Formula : $C_{10}H_{16}O_2$

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

^{1}H NMR : δ 1.68 (s, 3H), 1.59-1.74 (m, 2H), 2.04 (t, J = 2.7 Hz,

($CDCl_3$, 200 MHz)	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
($CDCl_3$, 50 MHz)	(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 (11):

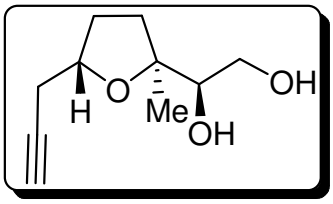


To a suspension of activated molecular sieves 4Å (2 g) in dry dichloromethane (100 mL) was added diisopropyl-*D*-tartarate (11.7 g, 49.9 mmol) and cooled to –20 ^{0}C. To this titanium tetraisopropoxide (11.82 g, 41.6 mmol) was added followed by drop wise introduction of *t*-butyl hydroperoxide solution (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 **10** (7 g, 41.6 mmol) in dry dichloromethane (30 mL) was added slowly over a period of 20 min and stirring was continued for an additional 6 h at –20 ^{0}C. The mixture was quenched by adding 10% aqueous tartaric acid solution at –20 ^{0}C and stirred at room temperature for 4 h. Organic layer was separated and the aqueous layer was washed with dichloromethane (2 X 75 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated. Flash column chromatography purification (3:2 petroleum ether/ethyl acetate) gave *syn*-diol **11** (3.45 g, 45%) and anti-diol **12** (3.45 g, 45%) as colorless oils.

Mol. Formula	: $C_{10}H_{16}O_3$
$[\alpha]_D^{25}$	: –5.9 (*c* 1.9, $CHCl_3$)
IR (Neat) $\tilde{\nu}$	: 3417, 2973, 2119, 1956, 1454 cm^{-1}.
^{1}H NMR	: δ 1.15 (s, 3H), 1.45-1.59 (m, 1H), 1.76-1.90 (m, 1H), 2.00

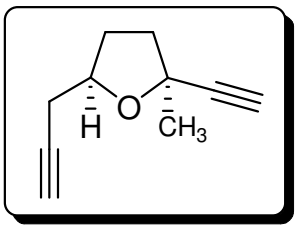
($CDCl_3$, 200 MHz)	(t, *J* = 2.6 Hz, 1H), 2.04-2.21 (m, 2H), 2.38 (ddd, *J* = 16.8, 4.4, 2.6 Hz, 1H), 2.51 (ddd, *J* = 16.8, 5.6, 2.6 Hz, 1H), 2.73 (br s, 2H), 3.51 (dd, *J* = 11.7, 8.0 Hz, 1H), 3.63-3.71 (m, 2H), 4.04-4.16 (m, 1H) ppm.
^{13}C NMR	: δ 22.73 (q), 24.80 (t), 30.51 (t), 32.21 (t), 62.89 (t), 70.43
($CDCl_3$, 50 MHz)	(d), 75.14 (d), 76.69 (d), 80.73 (s), 85.28 (s) ppm.
ESI-MS (*m/z*)	185.29 $[M+1]^+$, 207.29 $[M+Na]^+$.
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 (12):



Mol. Formula	: $C_{10}H_{16}O_3$
$[\alpha]_D^{25}$	: +16.9 (*c* 2.1, $CHCl_3$).
IR (Neat) $\tilde{\nu}$	: 3411, 2972, 2118, 1956, 1453 cm^{-1}.
^{1}H NMR	: δ 1.18 (s, 3H), 1.57-1.66 (m, 1H), 1.74-1.91 (m, 1H), 1.99
($CDCl_3$, 200 MHz)	(t, *J* = 2.6 Hz, 1H), 2.02-2.15 (m, 2H), 2.41-2.46 (m, 2H), 2.74 (br s, 2H), 3.49 (dd, *J* = 12.1, 8.9 Hz, 1H), 3.64-3.73 (m, 2H), 4.02-4.15 (m, 1H) ppm.
^{13}C NMR	: δ 23.69 (q), 25.57 (t), 30.90 (t), 32.67 (t), 63.05 (t), 69.91
($CDCl_3$, 50 MHz)	(d), 76.75 (d), 78.05 (d), 80.75 (s), 84.95 (s) ppm.
ESI-MS (*m/z*)	: 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-ethynyl-2-methyl-5-(prop-2-ynyl)tetrahydrofuran (13):

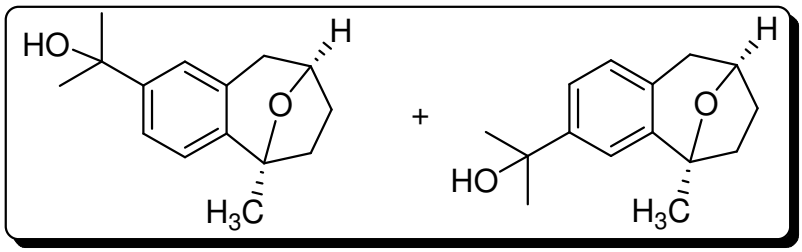


To a vigorously stirred suspension of silica gel-supported $NaIO_4$ (27 g) in dichloromethane (75 mL) was added a solution of the diol **11** (2.5 g, 13.58 mmol) in dichloromethane (20 mL) and stirred at r.t. for 2 h. After completion, the reaction mixture was filtered through sintered glass funnel and the silica gel was thoroughly washed with dichloromethane (3 X 25 mL). Combined filtrate was concentrated under reduced pressure to yield crude 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 room temperature for 4 h. Diluted with water (10 mL) and diethyl ether (20 mL). The organic phase was separated and aqueous layer extracted with ether (2 X 10 mL). The combined organic layer was washed with water, dried over sodium sulfate, filtered and concentrated in vacuo. Purification of the crude by column chromatography (4:1 petroleum ether/ethyl acetate) afforded **13** (1.65 g, 82%) as colorless oil.

Yield	: 82%
Mol. Formula	: $C_{10}H_{12}O$
$[\alpha]_D^{25}$	: +61.7 (*c* 1.8, $CHCl_3$).
IR (Neat) $\tilde{\nu}$	: 3303, 2982, 2120, 1957, 1443 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 1.53 (s, 3H), 1.79-1.93 (m, 1H), 1.95 (t, *J* = 2.6 Hz, 1H), 2.00-2.09 (m, 1H), 2.16-2.33 (m, 2H), 2.39 (s, 1H), 2.45 (ddd, *J* = 16.5, 7.8, 2.6 Hz, 1H), 2.63 (ddd, *J* = 16.5, 5.6, 2.6 Hz, 1H), 4.13-4.27 (m, 1H) ppm.
^{13}C 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 (*m/z*)	: 149.18 $[M+1]^+$.
Elemental Analysis	Calcd.: C, 81.04; H, 8.16

Found: C, 80.96; H, 8.1.

Spectral data of compounds 14 and 15:



A solution of dimethyl propargyl alcohol (0.33 mL, 3.37 mmol)) in EtOH (10 mL) was added to a refluxing solution of diyne **13** (0.05 g, 0.337 mmol) and wilkinson's catalyst (0.015 g, 0.01685 mmol) in EtOH (10 mL) through a dropping funnel over a period of 6h. EtOH was removed and the crude was chromatographed on silicagel using ethyl acetate and hexane (1:4) as an eluent to yield 1:1 regiomeric mixture of alcohols **14** and **15** (0.056 g, 72%) as colourless oil.

Yield : 72%

Mol. Formula : $C_{15}H_{20}O_2$

$[\alpha]_D^{25}$: +12.28 (*c* 0.8, $CHCl_3$).

IR (Neat) $\tilde{\nu}$: 3453, 2982, 2120, 1957, 1443, 756, 692 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz) : δ 1.56 (s, 6H), 1.57 (s, 6H), 1.70 (m, 1H), 1.72 (s, 3H), 1.75 (s, 3H), 1.86 (m, 4H), 2.05 (dd, 9.29, 2.25, Hz, 1H), 2.03 (m, 1H), 2.055 (dd, 9.28, 2.51 Hz, 1H), 2.30 (m, 1H) 2.23 (m, 1H), 2.49 (d, 6.77 Hz, 1H), 2.53 (d, 6.78 Hz, 1H), 3.33 (dd, 14.64, 6.27 Hz, 1H), 3.35 (dd 14.35, 6.02 Hz, 1H), 4.74 (brt, 6.27, 6.02 Hz, 2H), 7.04 (d, 8-03 Hz, 1H), 7.12 (d, 8.03 Hz, 1H), 7.19 (br S, 1H), 7.24 (dd, 7.78, 2.0 Hz, 1H), 7.25 (dd, 8.03, 2.25 Hz, 1H), 7.315 (d, 1.76 Hz, 1H)).

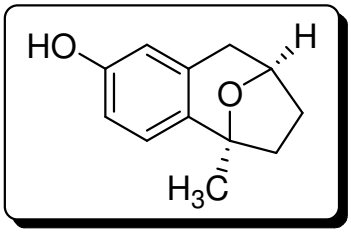
^{13}C NMR ($CDCl_3$, 100 MHz) : δ 22.68 (q), 22.79 (q), 30.50 (t), 30.54 (t), 31.64 (t), 31.71 (t), 31.85 (t), 37.01 (t), 37.52 (t), 42.86 (t), 42.92 (t), 72.29 (d), 72.48 (d), 74.37 (d), 80.35 (s), 80.69 (s), 118.61 (d), 122.01 (d), 122.52 (d), 122.78 (d), 125.31 (d), 129.05 (d), 130.30 (s), 131.74 (s), 142.38 (s), 143.80 (s), 146.83 (s), 147.42 (s)

ESI-MS (*m/z*) : 255.32 $[M+23]^+$.

Elemental Analysis Calcd.: C, 77.55; H, 8.68

Found: C, 77.72; H, 8.73.

(+)-Bruguierol A (1):



A solution of a mixture of tertiary alcohols **14/15**(0.002 g, 0.086 mmol) in benzene (5 mL) was cooled to 0 ^{0}C, to this was added aq. hydrogen peroxide (5 mL) and a drop of conc. sulphuric acid and stirred at r.t. for 52h.Two layers were separated and aq layer was extracted into ethyl acetate. Organic layer was washed with sat sodium bicarbonate, dried over sodium sulphate, evaporated under reduced pressure and purified by flash column chromatography using 10% ethyl acetate in hexane to give (+)-Bruguierol A (0.0065 g) and its regiomer (0.0065 g) with overall yield of 84%.

Yield : 42%

Mol. Formula : $C_{12}H_{14}O_2$

M. P. : 134-137 °C.

$[\alpha]_D^{25}$: +16.13 (*c* 0.45, $CHCl_3$).

IR (Neat) $\tilde{\nu}$: 3395, 3020, 2982, 2120, 1957, 1443, 750, 695 cm^{-1}.

^{1}H 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, *J* = 16.5 Hz, 1H), 3.30 (dd, *J* = 16.5, 5.1 Hz, 1H), 4.68-4.72 (m, 1H), 4.75 (br s, 1H), 6.53 (d, *J* = 2.5 Hz, 1H), 6.59 (dd, *J* = 8.4, 2.5 Hz, 1H), 7.01 (d, *J* = 8.4 Hz, 1H).

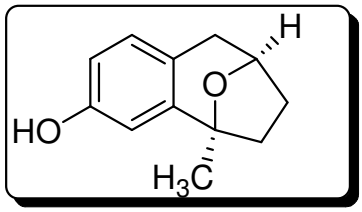
^{13}C NMR ($CDCl_3$, 100 MHz) : δ 22.85 (q), 30.47 (t), 37.55 (t), 42.95 (t), 74.20 (d), 80.34 (s), 112.86 (d), 115.67 (d), 124.01 (d), 133.69 (s), 136.55 (s), 154.17 (s).

ESI-MS (*m/z*) : 191.18 $[M+1]^+$.

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

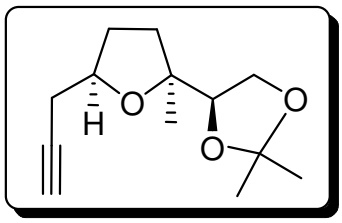
Found: C, 75.59; H, 7.33.

Regiomer of (+)-bruguierol A (16)



Yield	: 42%
Mol. Formula	: $C_{12}H_{14}O_2$
M. P.	: 160-162 °C
$[\alpha]_D^{25}$	: +16.13 (*c* 0.5, $CHCl_3$).
IR (Neat) $\tilde{\nu}$	: 3395, 3020, 2982, 2120, 1957, 1443, 750, 695 cm^{-1}.
^{1}H NMR ($CDCl_3$, 400 MHz)	: δ 1.64-1.75 (m, 1H), 1.69 (s, 3H), 1.80-1.88 (m, 1H), 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).
^{13}C NMR ($CDCl_3$, 100 MHz)	: δ 22.60 (q), 30.39 (t), 36.47 (t), 42.78 (t), 74.56 (d), 80.47 (s), 109.77 (d), 113.73 (d), 123.69 (s), 130.33 (d), 145.20 (s), 153.71 (s).
ESI-MS (*m/z*)	: 191.18 $[M+1]^+$, 213.19 18 $[M+23]^+$.
Elemental Analysis	Calcd.: C, 75.76; H, 7.42. Found: C, 75.53; H, 7.51.

(R)-4-((2S, 5R)-tetrahydro-2-methyl-5- (prop-2-ynyl) furan-2-yl)-2,2-dimethyl-1, 3-dioxolane (17): -

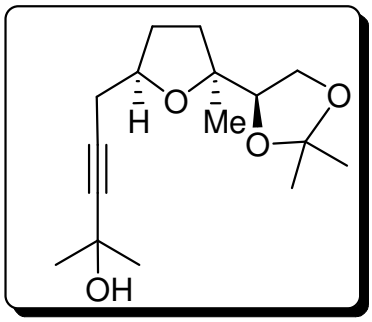


2,2 dimethoxy propane (0.66 ml, 5.427 mmol) and p-TSA (cat.) were added to a stirred solution of the diol **11** (1 g, 5.427 mmol) in DCM (15 ml) at rt and stirred for 1h. Neutralised with triethyl amine, solvent was evaporated in rota and the residue

was purified by column chromatography (ethyl acetate/hexane 2:8) to yield the product **17** (1.12 g, 92%) as colourless oil.

Yield	: 92%
Mol. Formula	: $C_{13}H_{20}O_3$:
$[\alpha]_D^{25}$	: +11.93 (*c* 1.0, $CHCl_3$).
IR (Neat) $\tilde{\nu}$	: 3309, 2984, 2886, 1456, 1380, 1372, 1215, 1071, 856, 757 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 1.16 (s, 3H), 1.31 (s, 3H), 1.40 (s, 3H), 1.60-1.73 (m, 1H), 1.75-1.87 (m, 1H), 1.915 (t, *J* = 2.68 Hz, 1H), 1.99-2.05 (m, 1H), 2.05-2.13 (m, 1H), 2.315 (ddd, *J* = 16.68, 6.95, 2.95 Hz, 1H), 2.44 (ddd, *J* = 16.68, 4.93, 2.95 Hz, 1H), 3.80 (dd, *J* = 6.31,5.43 Hz, 1H), 3.93-4.02 (m, 2H), 4.04-4.16 (m, 1H).
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ 23.32 (q), 24.86 (q), 25.60 (t), 26.25 (q), 30.87 (t), 33.29 (t), 65.98 (t), 69.71 (s), 77.95 (d), 80.75 (d), 80.94 (s), 83.82 (s), 109.34 (s).
ESI-MS (*m/z*)	: 247.8 $[M+23]^+$.
Elemental Analysis	Calcd.: C, 69.61, H, 8.99.
	Found: C, 69.03, H, 8.56.

5-((2R, 5S)-tetrahydro-5-methyl-5-(2,2-dimethyl-1,3-dioxolan-4-yl)furan-2-yl)-2-methylpent-3-yn-2-ol (18):-

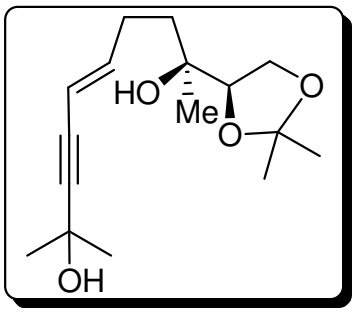


BuLi (5 ml, 9.363 mmol of 2.3 M in hexane) was added to a -78 ^{0}c cooled solution of alkyne **17** (1.4 g, 6.242 mmol) in THF (50 ml) and stirred for 30 min. Freshly distilled acetone (2 ml, 12.848 mmol) was added and stirred for 30 min and the reaction was quenched with sat. aq. NH_4Cl, two layers were separated and the aq. layer was extracted into ethyl acetate, dried over Na_2SO_4, volatiles were removed and the crude

was purified by column chromatography (ethyl acetate/hexane 3:7) to deliver the tertiary alcohol **18** (1.23 g, 70%) as a colourless oil.

Yield	: 70%
Mol. Formula	: $C_{16}H_{26}O_4$
$[\alpha]_D^{25}$	: +23.4 (*c* 1.0, $CHCl_3$).
IR (Neat) $\tilde{\nu}$	: 3440, 2984, 2983, 1731, 1456, 1373, 1216, 1070, 855, 756 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 1.16 (s, 3H), 1.31 (s, 3H), 1.40 (s, 3H), 1.47 (s, 6H), 1.59-1.72 (m, 1H), 1.75-1.89 (m, 1H), 1.94-1.99 (m, 1H), 2.00-2.04 (m, 1H), 2.05-2.11 (m, 1H), 2.385 (d, *J* = 1.26 Hz, 1H), 2.41 (s, 1H), 3.75-3.86 (m, 1H), 3.95-4.12 (m, 3H).
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ 21.94 (q), 25.07 (q), 25.10 (t), 26.33 (q), 30.53 (t), 31.65 (q), 31.70 (q), 34.85 (t), 65.80 (s), 65.79 (t), 76.80 (d), 80.30 (d), 83.64 (s), 86.36 (s), 109.35 (s).
ESI-MS (*m/z*)	: 283.8 $[M+1]^+$.
Elemental Analysis	Calcd.: C, 68.06, H, 9.28.
	Found: C, 68.03, H, 9.36.

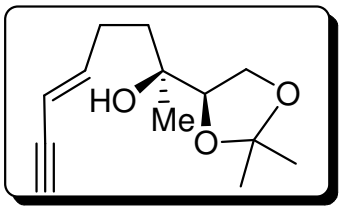
2-Ethynyl-5-(4-methoxy-4-methyl-pent-2-ynyl)-2-methyl-tetrahydro-furan (20):-



Yield	15%
Mol. Formula	: $C_{16}H_{26}O_4$
$[\alpha]_D^{25}$	: +42.1 (*c* 1.0, $CHCl_3$).
IR (Neat) $\tilde{\nu}$	: 3440, 2984, 2983, 1731, 1456, 1373, 1216, 1070, 855, 756 cm^{-1}.

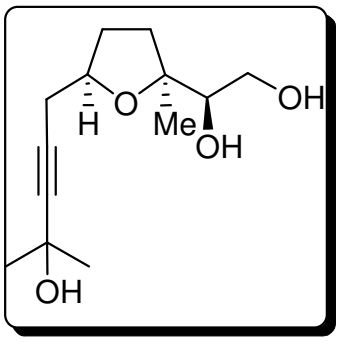
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 1.20 (s, 3H), 1.35 (s, 3H), 1.41 (s, 3H), 1.51 (s, 6H), 1.80-2.28 (m, 4H), 3.82-3.95 (m, 3H), 5.50 (dd, *J* = 15.92, 1.65 Hz), 6.10 (dt, *J* = 15.92, 6.94 Hz).
ESI-MS (*m/z*)	: 283.2 $[M+1]^+$.
Elemental Analysis	Calcd.: C, 68.06, H, 9.28.
	Found: C, 68.12, H, 9.33.

(S,E)-2-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)oct-5-en-7-yn-2-ol (19):



Yield	: 15%
Mol. Formula	: $C_{13}H_{20}O_3$
$[\alpha]_D^{25}$	: +31.93 (*c* 1.0, $CHCl_3$).
IR (Neat) $\tilde{\nu}$	: 3309, 2984, 2886, 1456, 1380, 1372, 1215, 1071, 856, 757 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 1.20 (s, 3H), 1.35 (s, 3H), 1.41(s, 3H), 1.39-1.58 (m, 2H), 1.87 (br s, 1H), 1.28-2.41 (m, 1H), 2.78 (d, *J* = 2.15 Hz, 1H), 3.83-3.98 (m, 3H), 5.48 (dt, *J* = 16.12, 1.90 Hz, 1H), 6.23 (dt, *J* = 16.12, 6.95 Hz, 1H).
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ 23.54 (q), 25.22 (q), 26.29 (q), 26.85 (t), 36.06 (t), 64.74 (t), 71.54 (S), 76.00 (d), 81.57 (d), 82.23 (S), 108.84 (d), 109.16 (S), 146.17 (d).
ESI-MS (*m/z*)	: 247.8 $[M+23]^+$.
Elemental Analysis	Calcd.: C, 69.61, H, 8.99.
	Found: C, 69.03, H, 8.56.

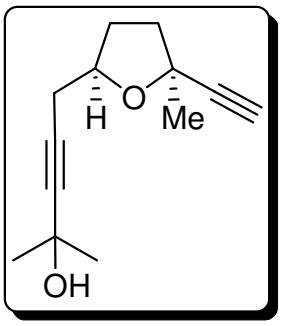
1-((2S, 5R)-tetrahydro-5- (4-hydroxy-4-methylpent-2-ynyl)-2-methylfuran-2-yl)ethane-1,2-diol (21):



To a stirred solution of acetonide derivative **18** (0.83 g, 2.93 mmol) in MeOH (10 ml) was added p-TSA (cat.) and stirred for 2h, neutralized with NEt_3, solvent was removed and the crude was purified by column chromatography (ethyl acetate/hexane 7:3) to obtain the diol **21** (0.77 g, 90%) as a thick colourless oil

Yield	: 90%
Mol. Formula	: $C_{13}H_{22}O_4$
$[\alpha]_D^{25}$	: +31.93 (*c* 1.0, $CHCl_3$).
IR (Neat) $\tilde{\nu}$	: 3420, 2974, 2881, 1454, 1377, 1216, 1089, 855, 757 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	: 1.19 (s, 3H), 1.47 (s, 6H), 1.51-1.64 (m, 1H), 1.91-2.03 (m, 2H), 2.12-2.25 (m, 1H), 2.36 (dd, *J* = 16.93, 2.91Hz, 1H), 2.655 (dd, *J* = 16.93, 4.80Hz, 1H), 3.33 (brs, 2H), 3.595 (dd, *J* = 10.23, 6.21Hz, 1H), 3.70-3.83 (m, 2H), 4.06-4.19 (m, 1H).
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ 21.77 (q), 24.96 (t), 25.26 (q), 26.29 (q), 30.78 (t), 34.76 (t), 65.84 (s), 69.71 (d), 76.83 (d), 80.26 (d), 80.99 (s), 83.78 (s), 109.21 (s).
ESI-MS (*m/z*)	: 265.8 $[M+23]^+$.
Elemental Analysis	Calcd.: C, 64.44, H, 9.15. Found: C, 64.62, H, 9.26.

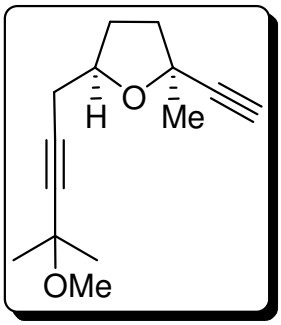
5-((2R, 5S)-5-ethynyl-tetrahydro-5-methylfuran-2-yl)-2-methylpent-3-yn-2-ol (22)



To a vigorously stirred solution of Diol **21** (0.7 g, 2.87 mmol) in DCM (5 ml) was added $NaIO_4$ on silica and stirred for 30 min and filtered through a scyntered funnel and the solvent was removed, to this crude aldhyde in MeOH (5 ml) was added phosphonate (1.09 g, 5.72 mmol) and K_2CO_3 (1.19 g, 8.58 mmol) and stirred for 2h, MeOH was removed on rota and the residue was extracted into ethyl acetate and water, combined organics were dried over Na_2SO_4, evaporated to dryness and the crude was chromatographed on silica (ethyl acetate/hexane 1.5 : 8.5) to deliver the dialkyne **22** (0.548 g, 92%) as a colourless oil.

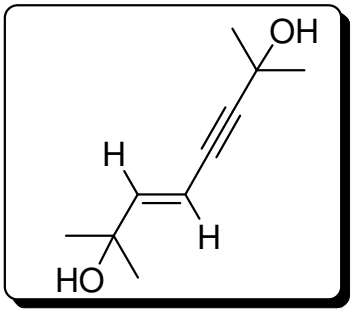
Yield	: 90%
Mol. Formula	: $C_{13}H_{22}O_4$
$[\alpha]_D^{25}$	: +69.74 (*c* 1.0, $CHCl_3$).
IR (Neat) $\tilde{\nu}$	: 3415, 3306, 2982, 1457, 1373, 1218, 1092, 757 cm^{-1}.
^{1}H NMR ($CDCl_3$, 400 MHz)	: δ 1.27 (s, 3H), 1.52 (s, 3H), 1.55 (s, 3H), 1.86-1.93 (m, 2H), 2.03-2.12 (m, 1H), 2.17-2.24 (m, 1H), 2.29-2.34 (m, 1H), 2.45 (s, 1H), 2.52 (dd, *J* = 16.31, 7.78 Hz, 1H), 2.63 (dd, *J* = 16.31, 5.01 Hz, 1H), 4.16-4.22 (m, 1H).
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ 25.90 (t), 27.99 (q), 31.49 (t), 31.53 (q), 40.51 (t), 65.03 (s), 70.87 (d), 76.24 (s), 78.35 (d), 78.59 (s), 86.56 (s), 87.83 (s).
ESI-MS (*m/z*)	: 229.43 $[M+23]^+$.
Elemental Analysis	Calcd.: C, 75.69, H, 8.80. Found: C, 75.8, H, 8.92.

(2S, 5R)-2-ethynyl-tetrahydro-5-(4-methoxy-4-methylpent-2-ynyl)-2-methylfuran (23)



Yield	: 22%
Mol. Formula	: $C_{14}H_{20}O_2$
$[\alpha]_D^{25}$	: +76.64 (*c* 1.3, $CHCl_3$).
IR (Neat) $\tilde{\nu}$	: 3306, 2985, 2936, 1361, 1216, 1073, 757 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 1.19 (s, 3H), 1.40 (s, 6H), 1.58-1.67 (m, 1H), 1.77-1.94 (m, 1H), 1.97-2.17 (m, 1H), 2.36-2.59 (m, 2H), 3.32 (s, 3H), 3.46-3.57 (m, 1H), 3.63-3.74 (m, 2H), 4.00-4.12 (m, 1H).
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ 26.01 (t), 27.98 (q), 28.44 (q), 31.64 (t), 40.51 (t), 51.38 (q), 70.46 (s), 70.81 (q), 76.19 (s), 78.38 (d), 80.64 (s), 83.35 (s), 87.78 (s).
ESI-MS (*m/z*)	: 243.02 $[M+23]^+$.
Elemental Analysis	Calcd.: C, 76.33, H, 9.15. Found: C, 76.5, H, 9.21.

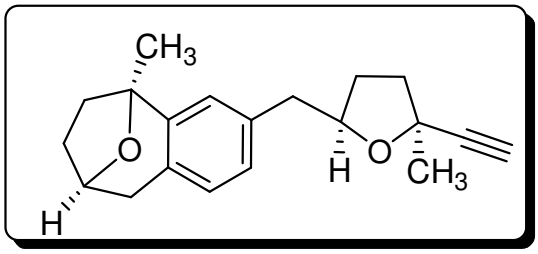
(E)-2,7-dimethyloct-3-en-5-yne-2, 7-diol (25)



Yield	: 66%
Mol. Formula	: $C_{10}H_{16}O_2$
M. P.	: 102-104 ^{0}C

IR (Neat) $\tilde{\nu}$	: 3397, 3019, 2400, 1215, 758, 669. cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 1.31 (s, 6H), 1.52 (s, 6H), 5.72 (d, *J* = 16.04 Hz, 1H), 6.23 (d, *J* = 16.04 Hz, 1H).
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ 29.38 (q), 31.36 (q), 65.44 (s), 70.94 (s), 80.13 (s), 94.39 (s), 106.27 (q), 150.52 (d).
ESI-MS (*m/z*)	: 191.08 $[M+23]^+$.
Elemental Analysis	Calcd.: C, 71.39, H, 9.59 Found: C, 71.52, H, 9.41.

Spectral data of compounds 26/27

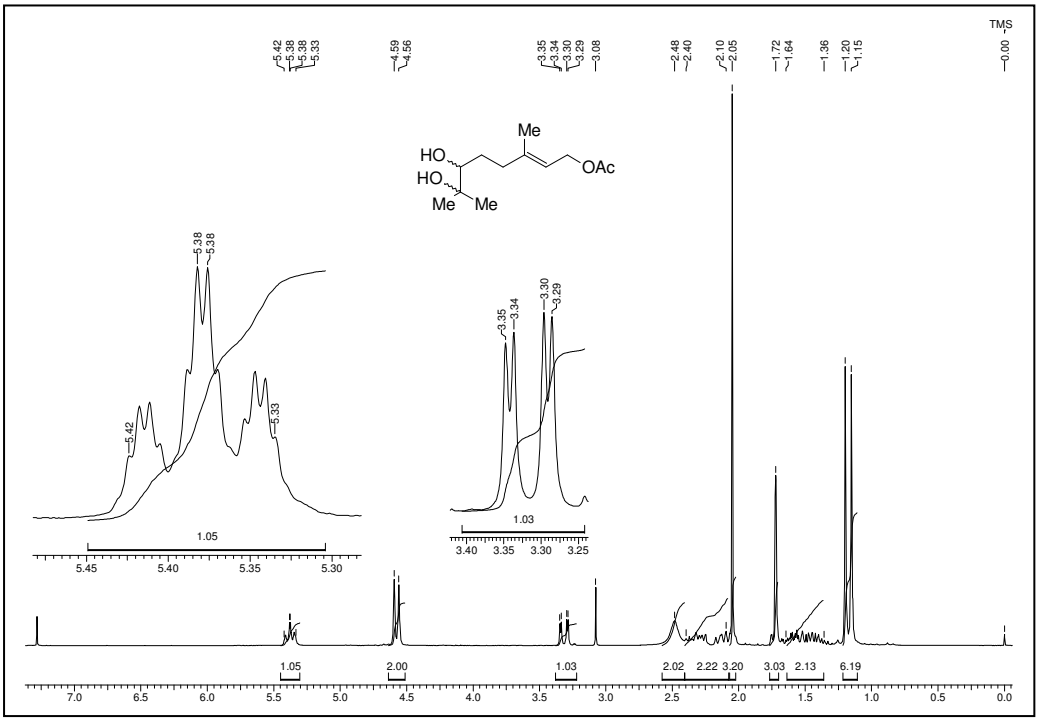


Yield	: 45%
Mol. Formula	: $C_{20}H_{24}O_2$
$[\alpha]_D^{25}$	+16.94 (*c* 1.0, $CHCl_3$).
IR (Neat) $\tilde{\nu}$	: 3302, 2987, 2936, 1361, 1216, 1073, 756, 690 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 1.41 (s, 3H), 1.62 (br s, 2H), 1.71 (s, 3H), 1.80-2.03 (m, 3H), 2.20-2.28 (m, 2H), 2.44 (d, J = 1.39 Hz, 1H), 2.53 (br s, 2H), 2.66-2.78 (m, 1H), 3.03-3.13 (m, 1H), 3.23-3.39 (m, 1H), 4.16-4.30 (m, 1H), 4.69-4.77 (m, 1H), 6.64-7.09 (m, 3H).
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ 22.72, 28.16, 30.49, 31.92, 37.01, 37.30, 40.69, 42.47, 42.72, 42.89, 70.55, 74.35, 74.40, 75.71, 80.36, 80.45, 81.15, 81.21, 88.30, 122.65, 123.68, 126.93, 127.47, 129.23, 129.99, 131.78, 136.93, 141.80.
ESI-MS (*m/z*)	: 297.19 $[M+1]^+$, 319.18 $[M+23]^+$.

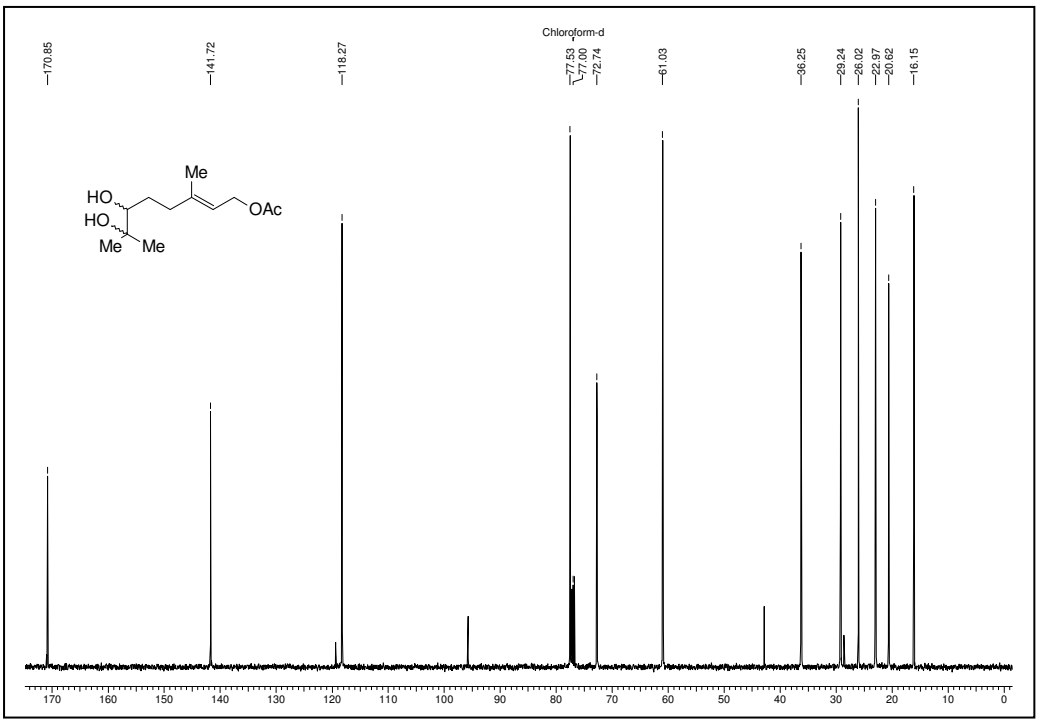
Elemental Analysis : Calcd.: C, 81.04, H, 8.15.

: Found: C, 82.12, H, 8.21.

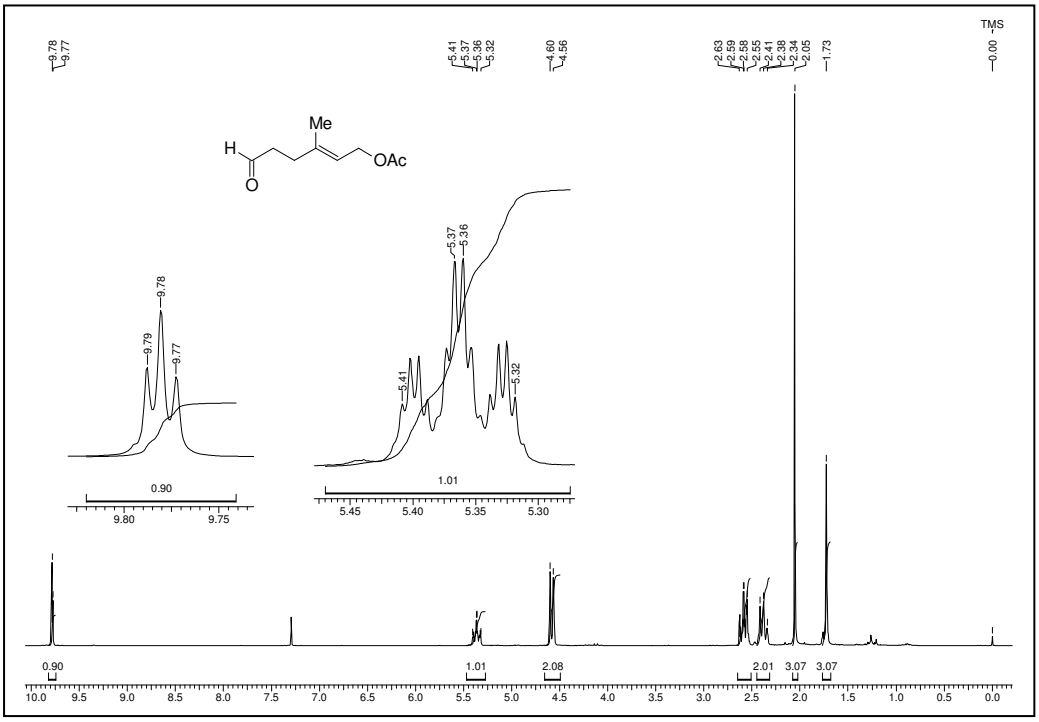
Spectral data



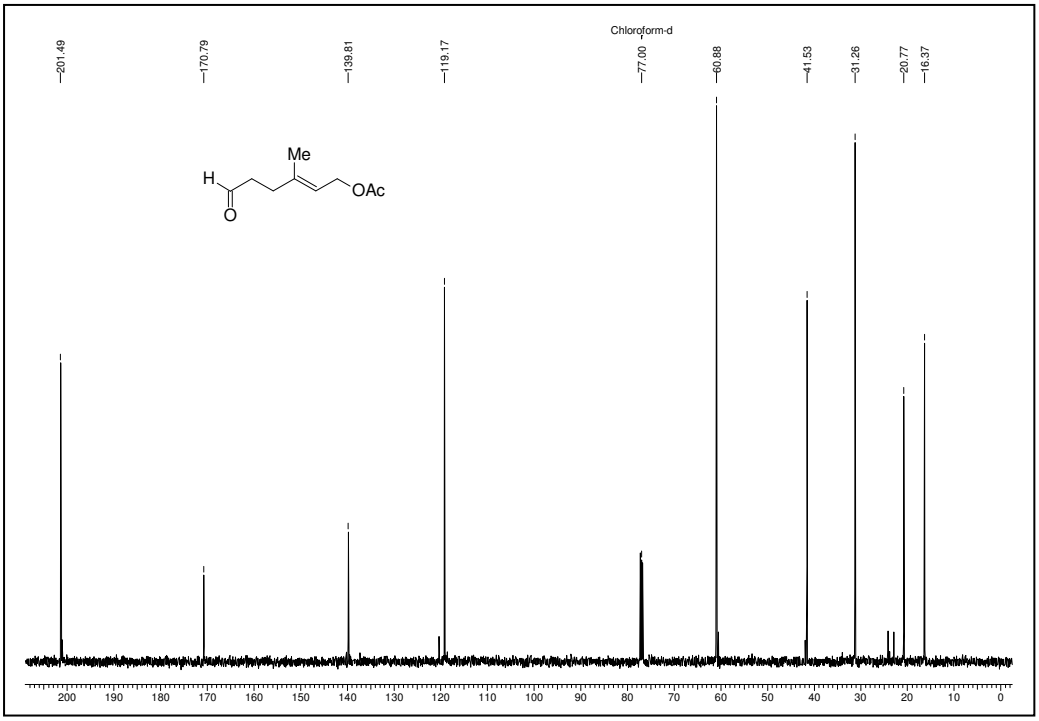
^{1}H-NMR Spectrum of 7 in $CDCl_3$



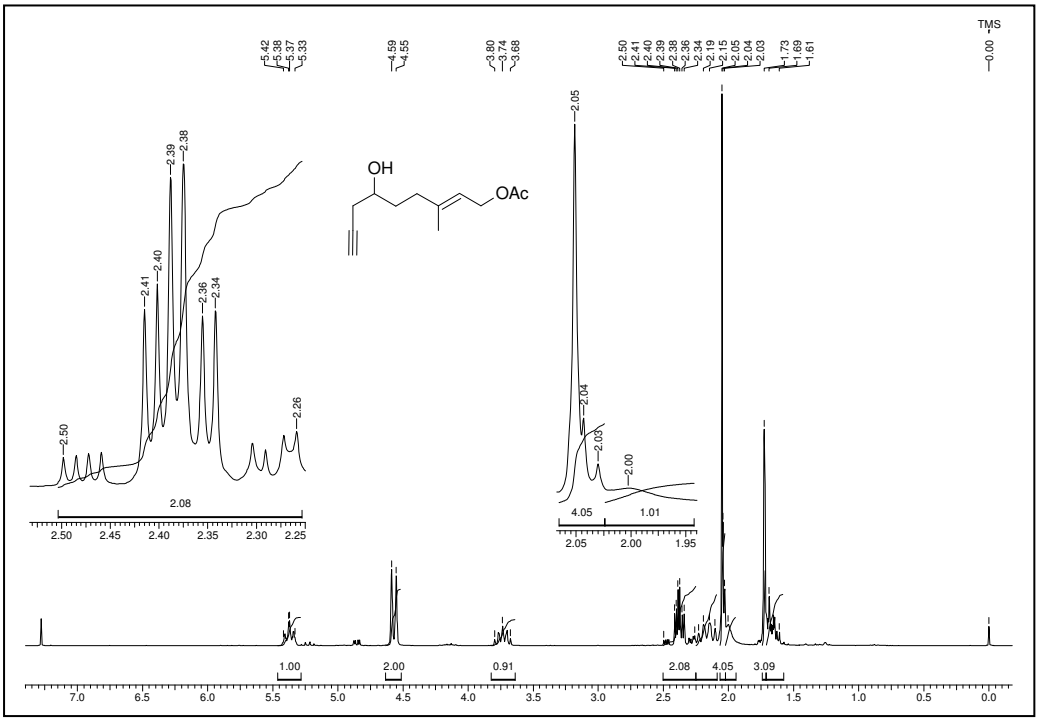
^{13}C-NMR Spectrum of 7 in $CDCl_3$



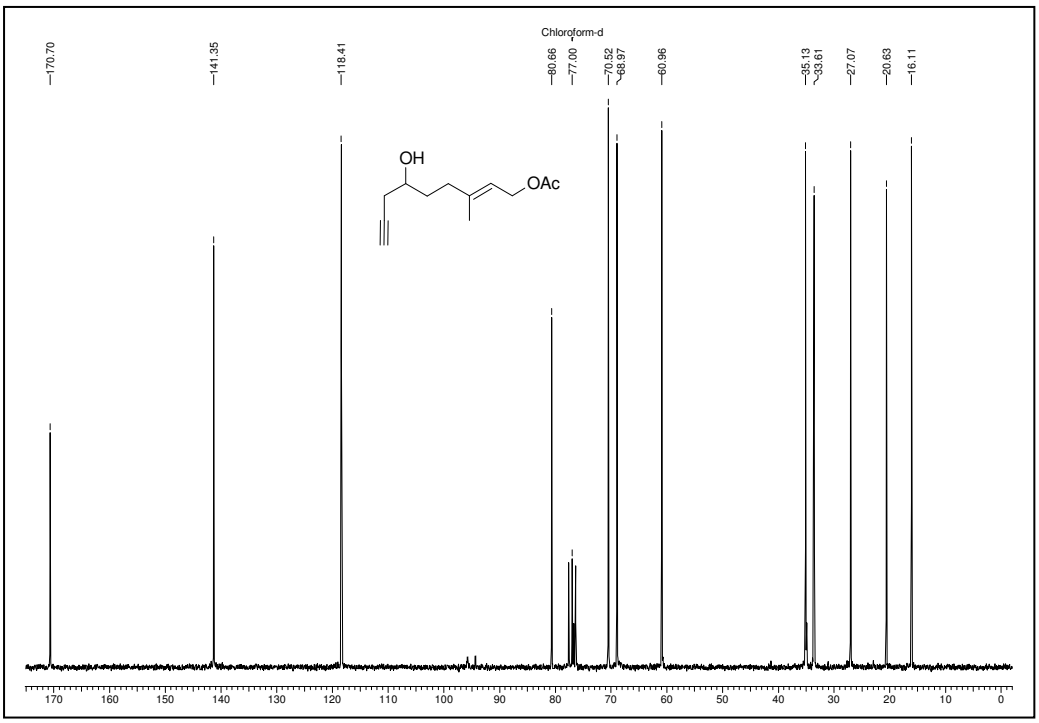
^{1}H-NMR Spectrum of 8 in $CDCl_3$



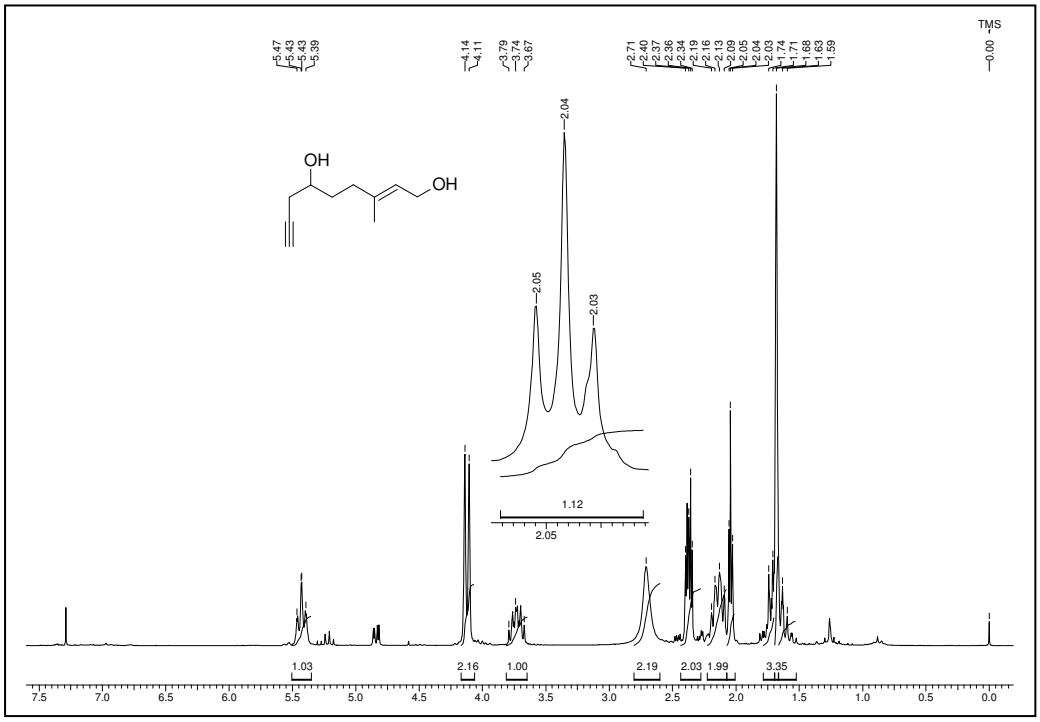
^{13}C-NMR Spectrum of 8 in $CDCl_3$



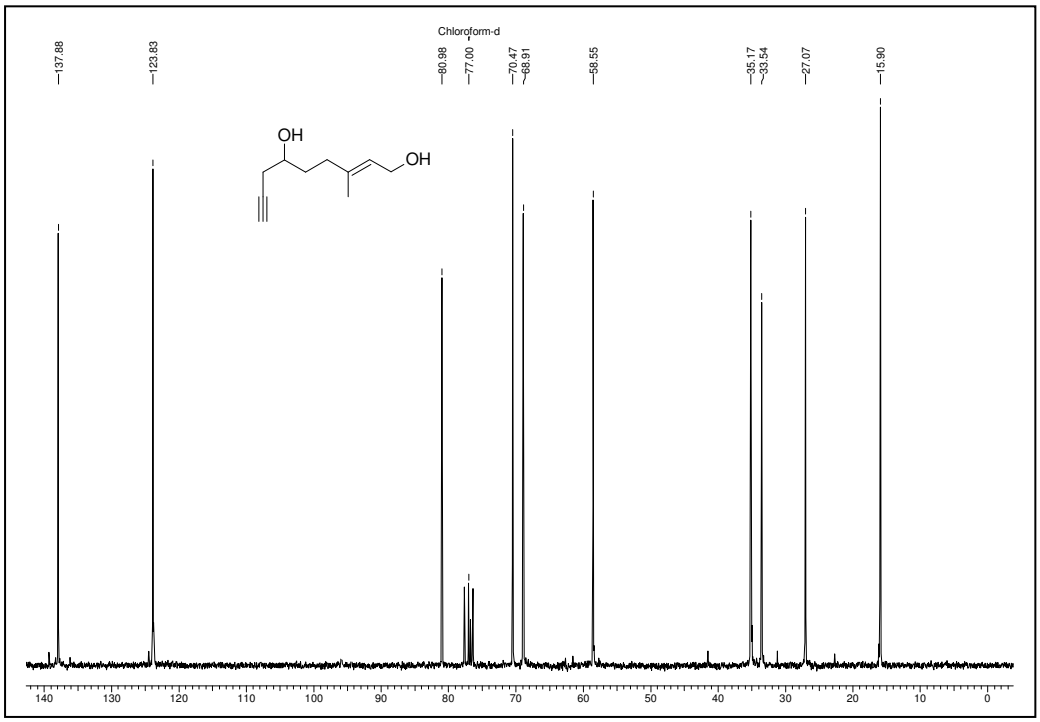
^{1}H-NMR Spectrum of 9 in $CDCl_3$



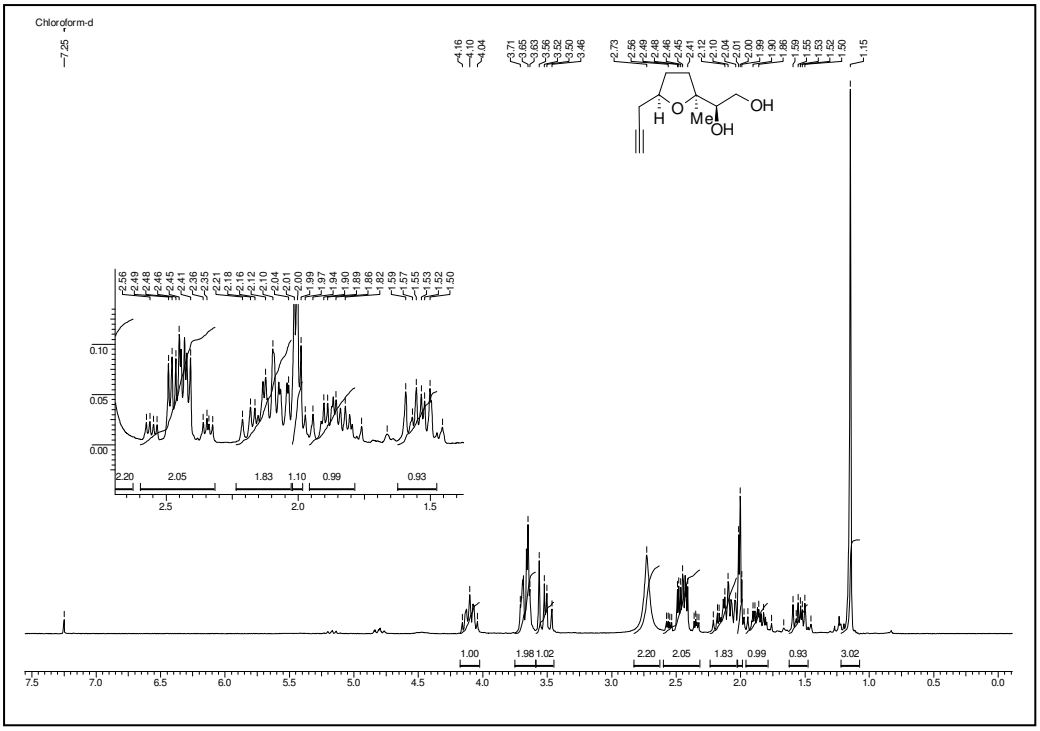
^{13}C-NMR Spectrum of 9 in $CDCl_3$



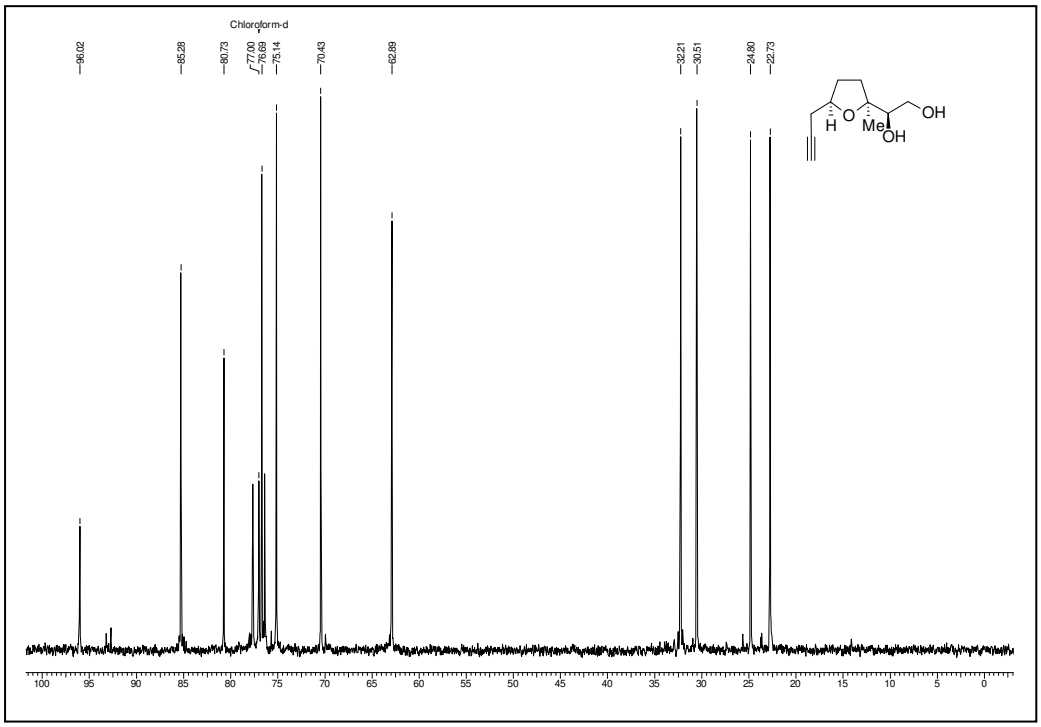
^{1}H-NMR Spectrum of 10 in $CDCl_3$



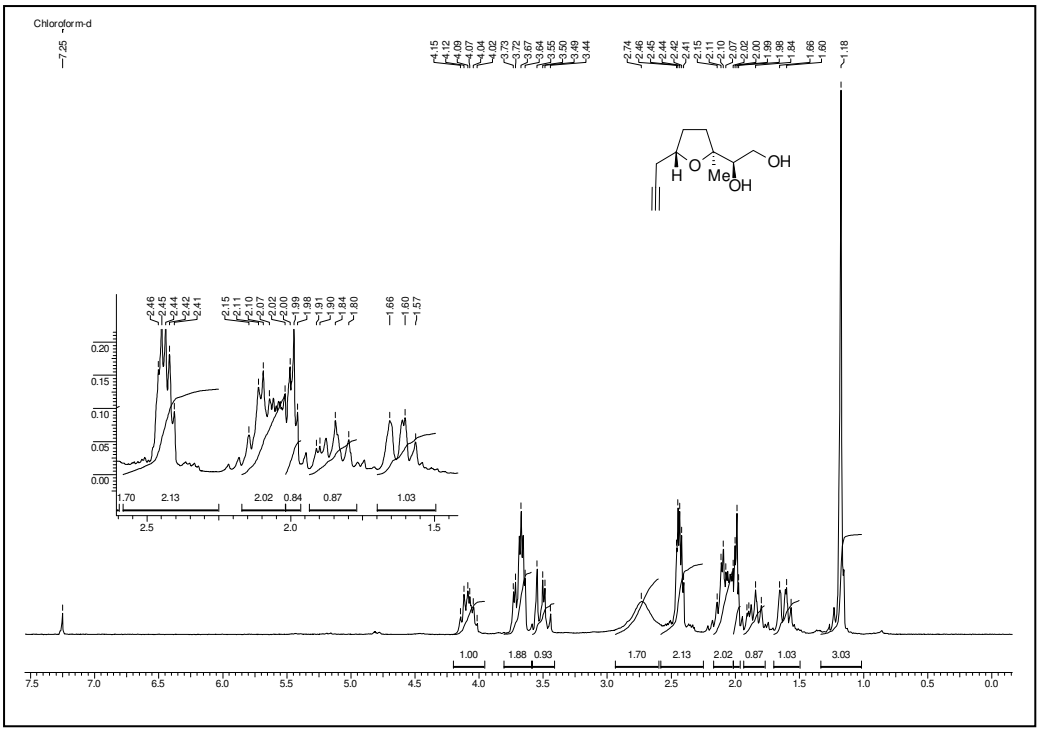
^{13}C-NMR Spectrum of 10 in $CDCl_3$



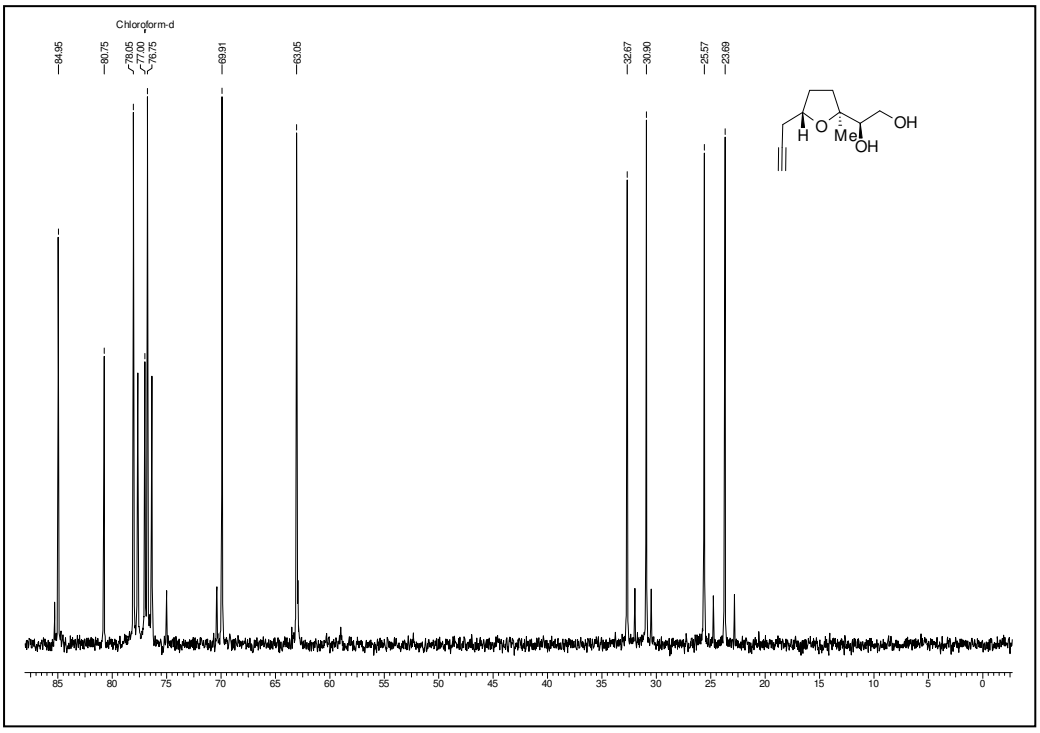
^{1}H-NMR Spectrum of 11 in $CDCl_3$



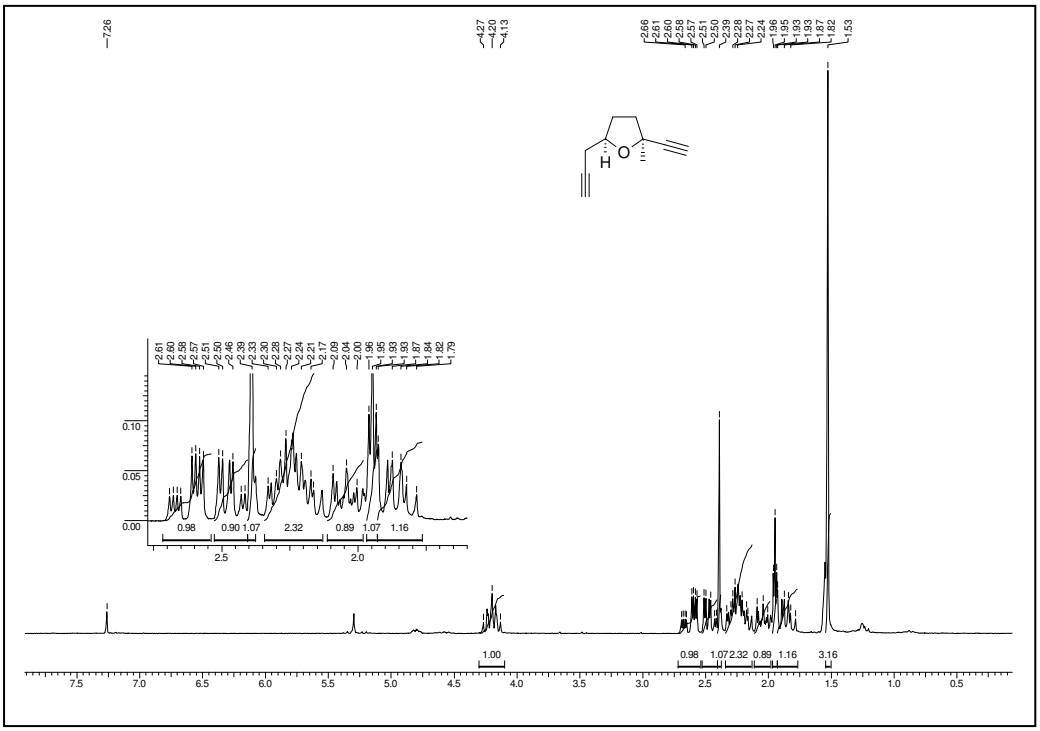
^{13}C-NMR Spectrum of 11 in $CDCl_3$



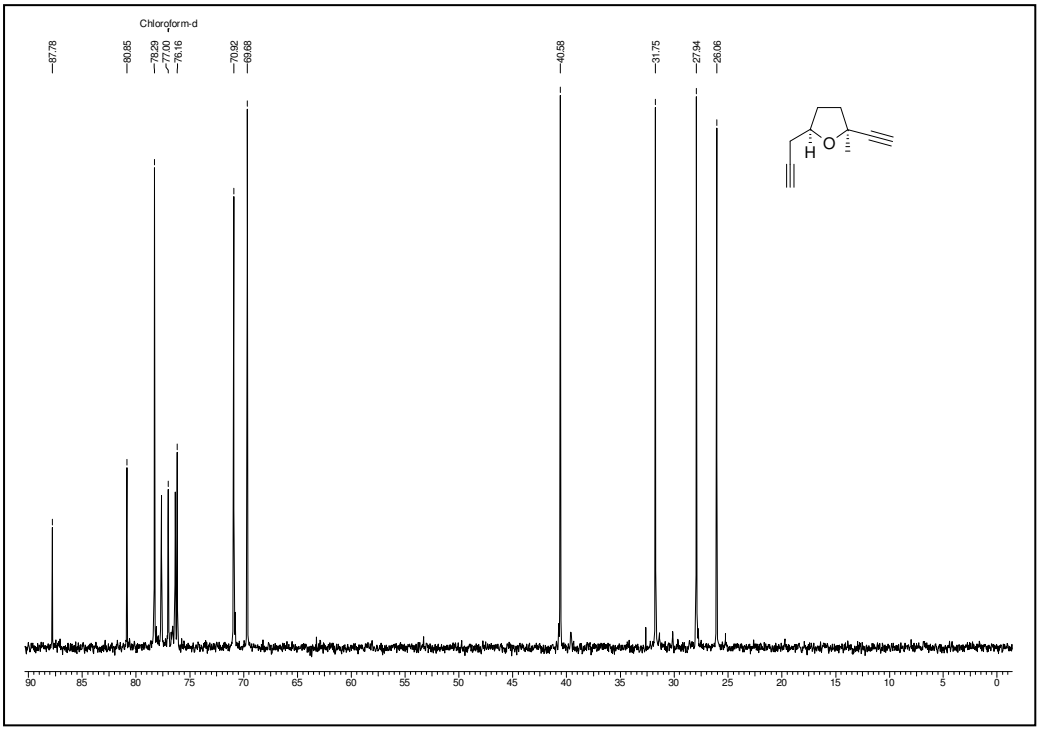
^{1}H-NMR Spectrum of 12 in $CDCl_3$



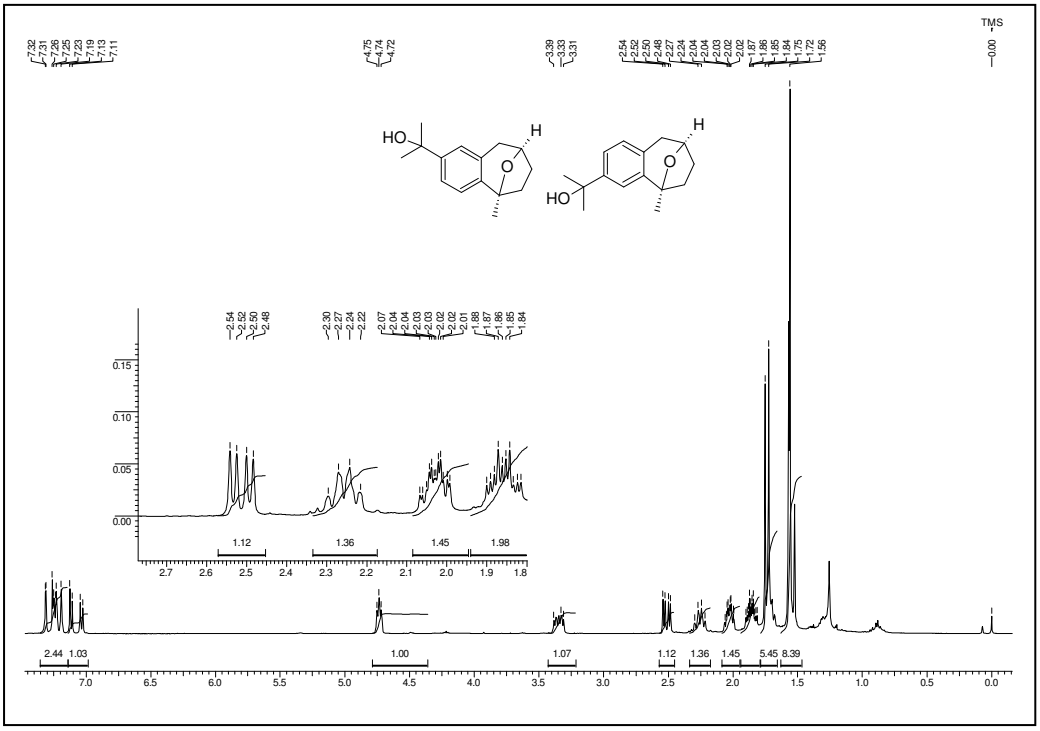
^{13}C-NMR Spectrum of 12 in $CDCl_3$



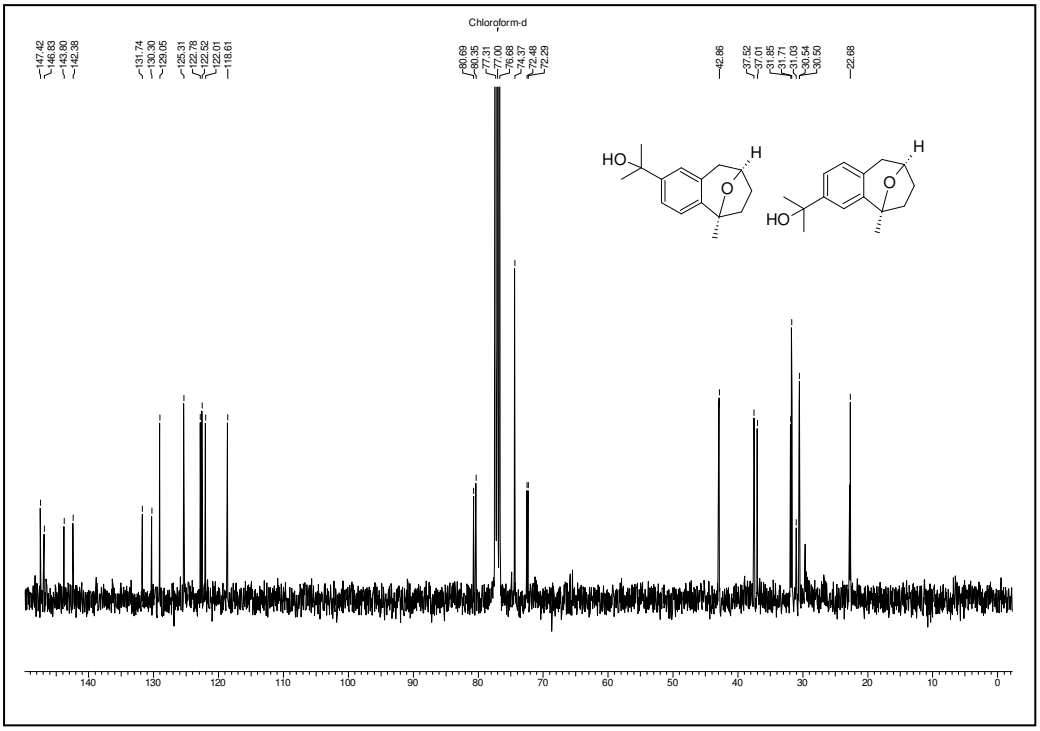
^{1}H-NMR Spectrum of 13 in $CDCl_3$



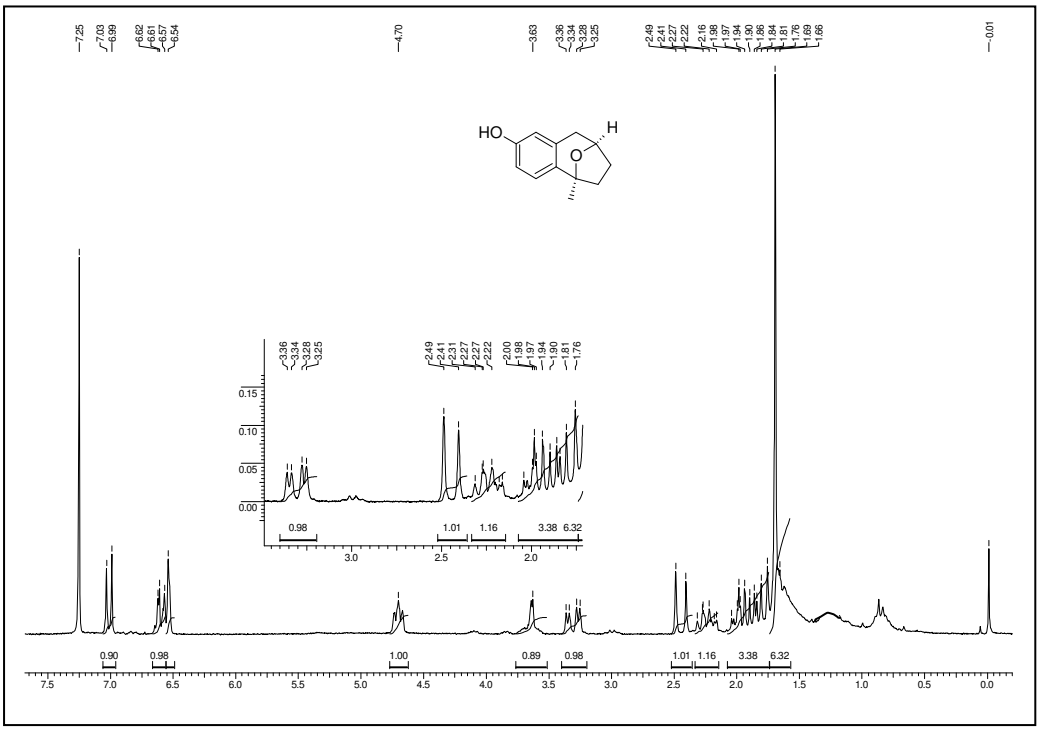
^{13}C-NMR Spectrum of 13 in $CDCl_3$



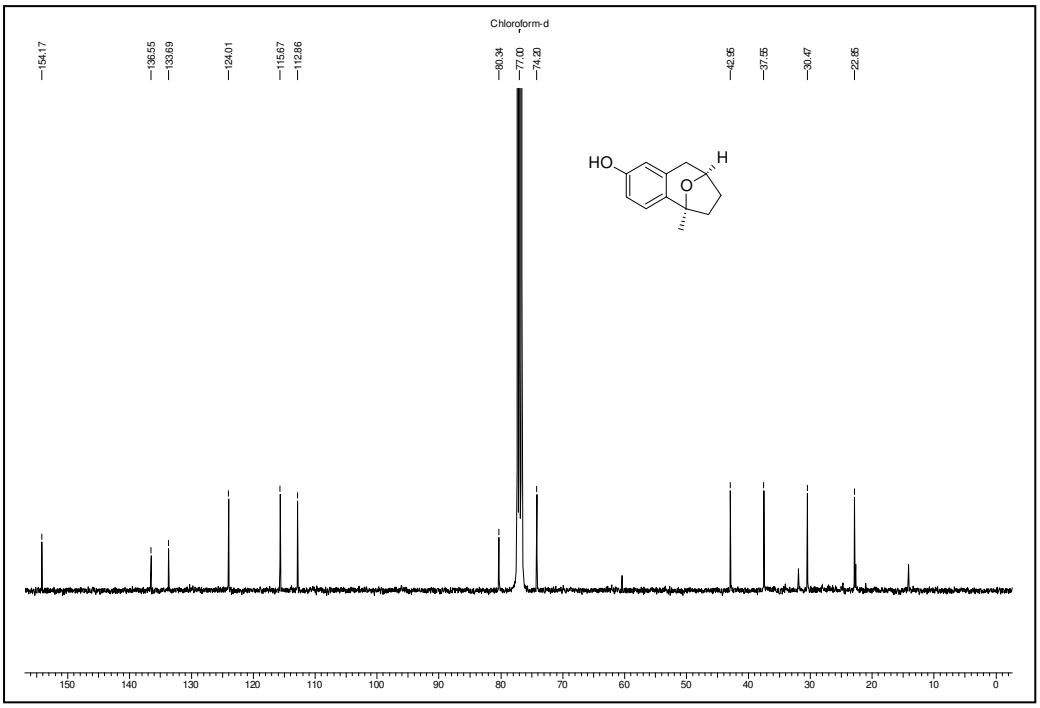
^{1}H-NMR Spectrum of 14/15 in $CDCl_3$



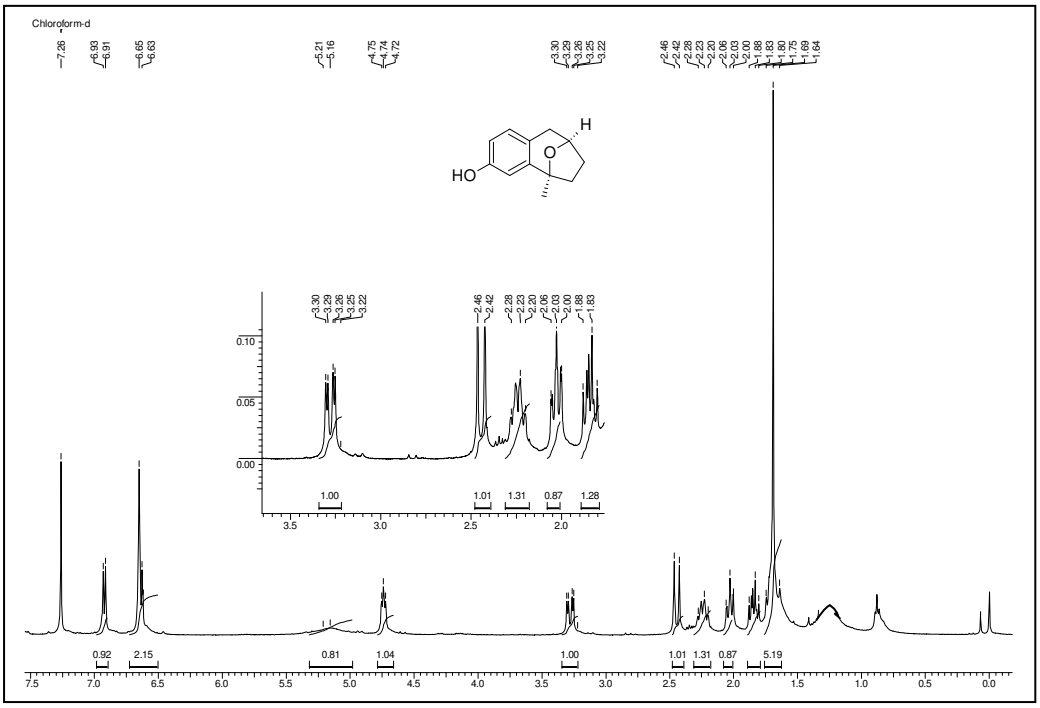
^{13}C-NMR Spectrum of 14/15 in $CDCl_3$



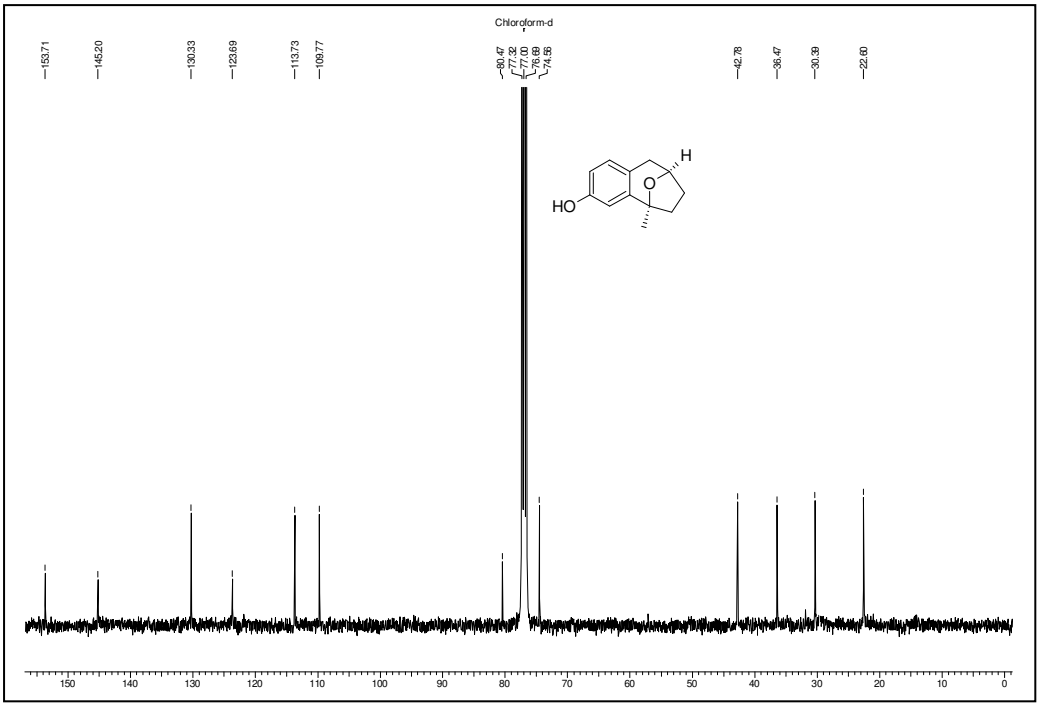
^{1}H-NMR Spectrum of 1 in $CDCl_3$



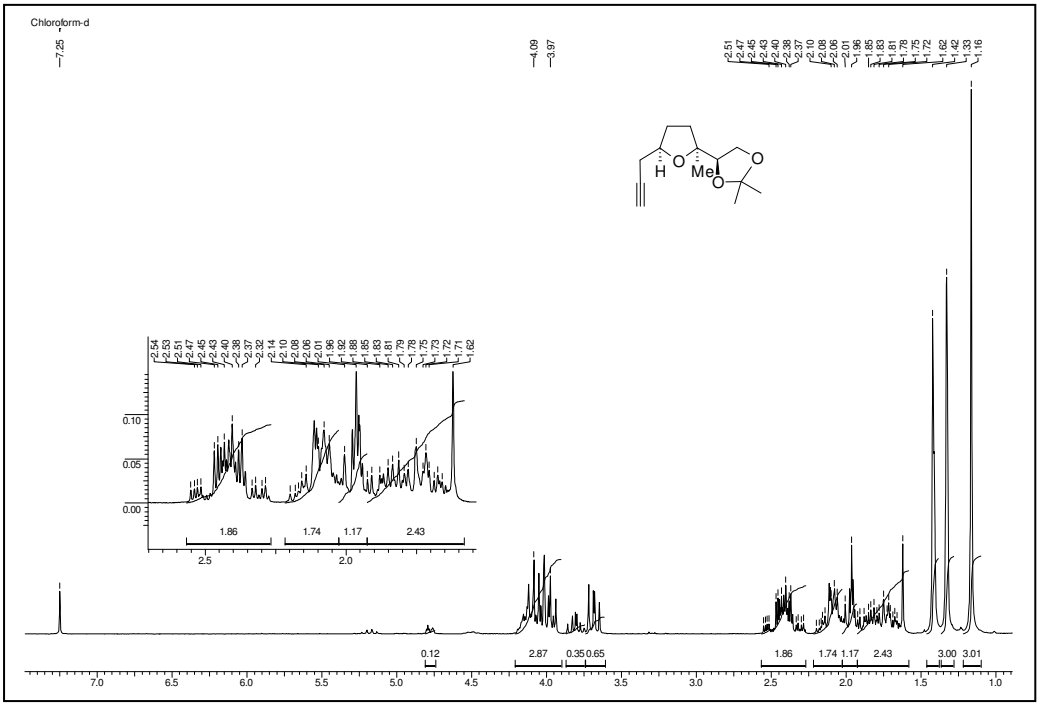
^{13}C-NMR Spectrum of 1 in $CDCl_3$



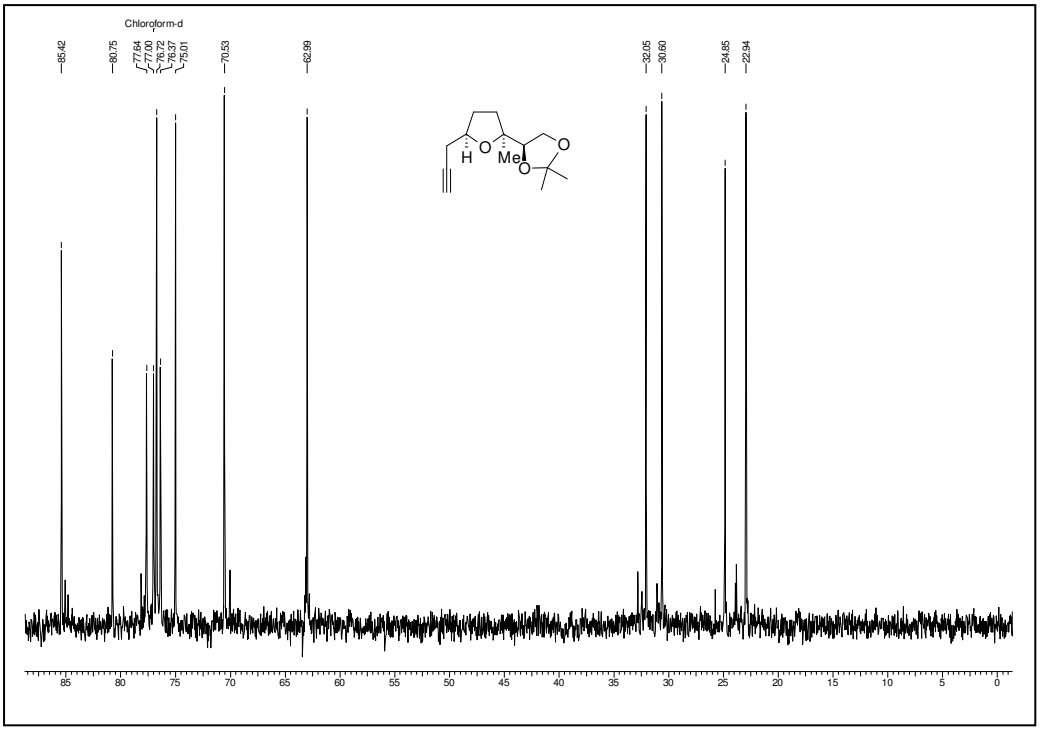
^{1}H-NMR Spectrum of 16 in $CDCl_3$



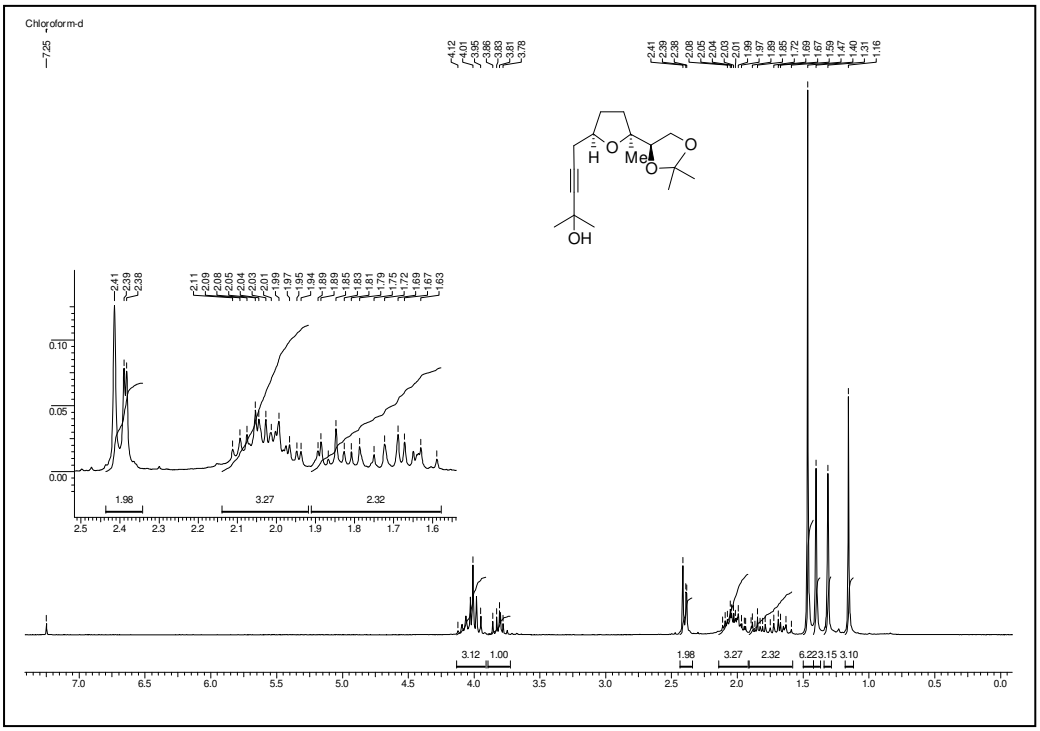
^{13}C-NMR Spectrum of 16 in $CDCl_3$



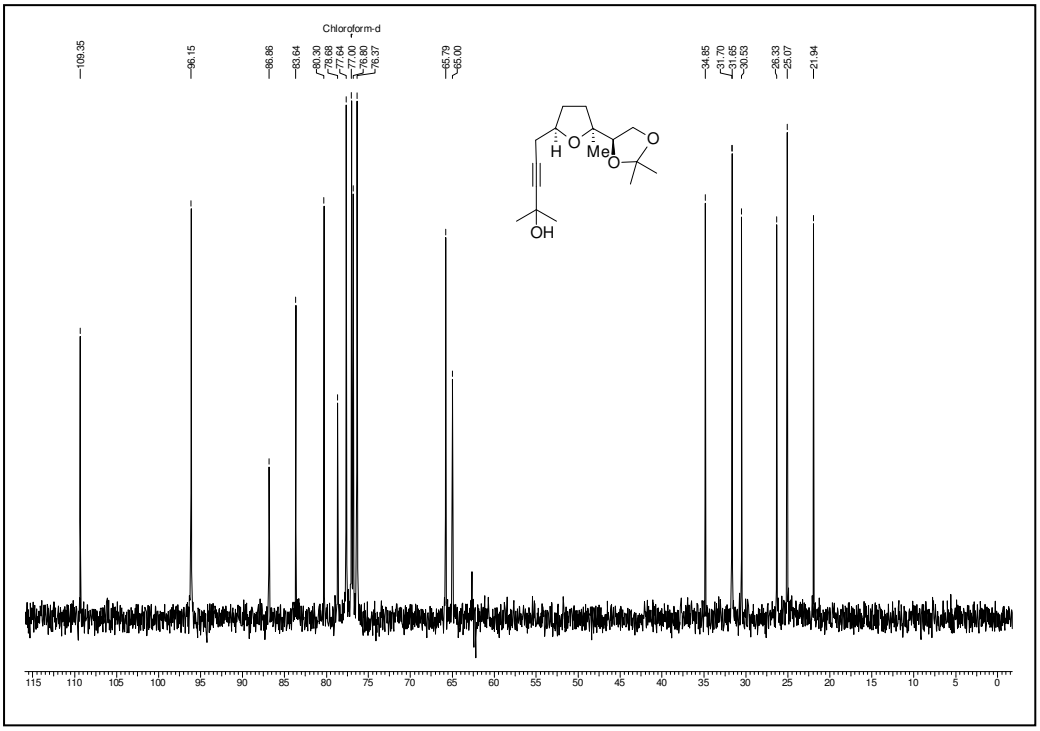
^{1}H-NMR Spectrum of 17 in $CDCl_3$



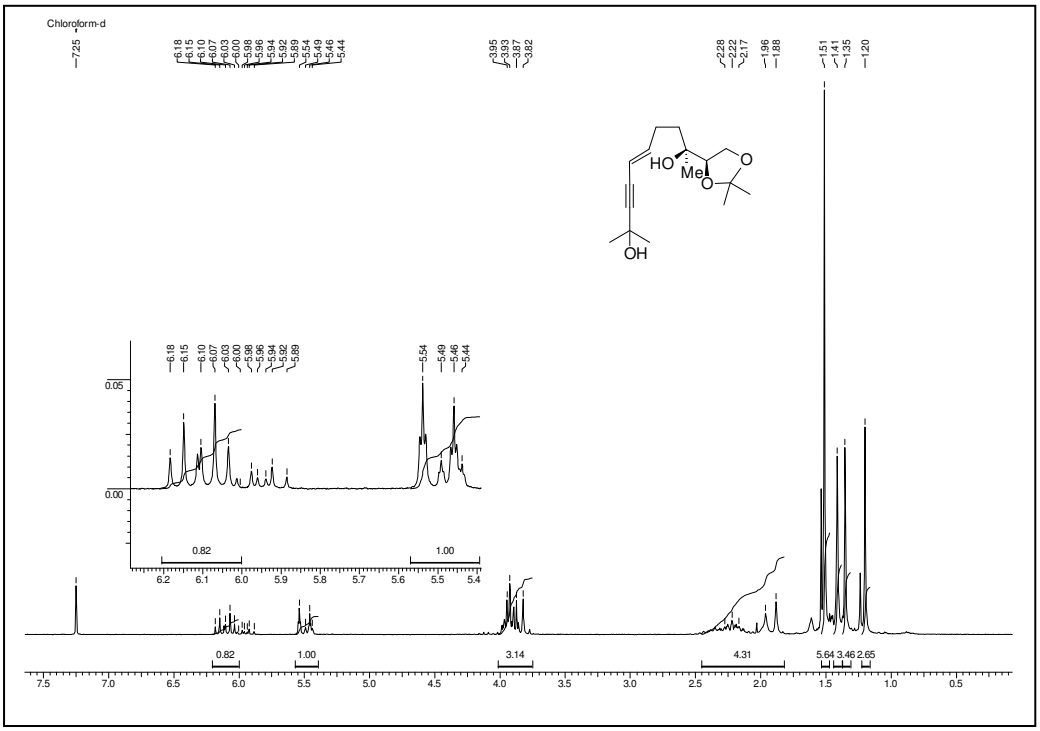
^{13}C-NMR Spectrum of 17 in $CDCl_3$



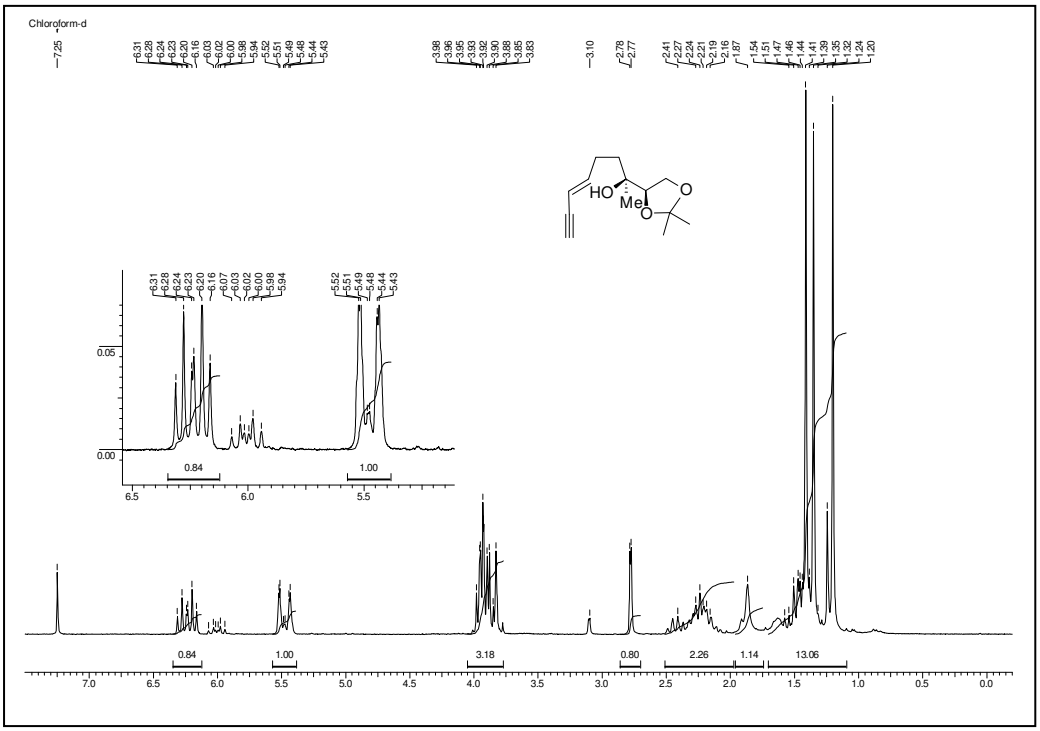
^{1}H-NMR Spectrum of 18 in $CDCl_3$



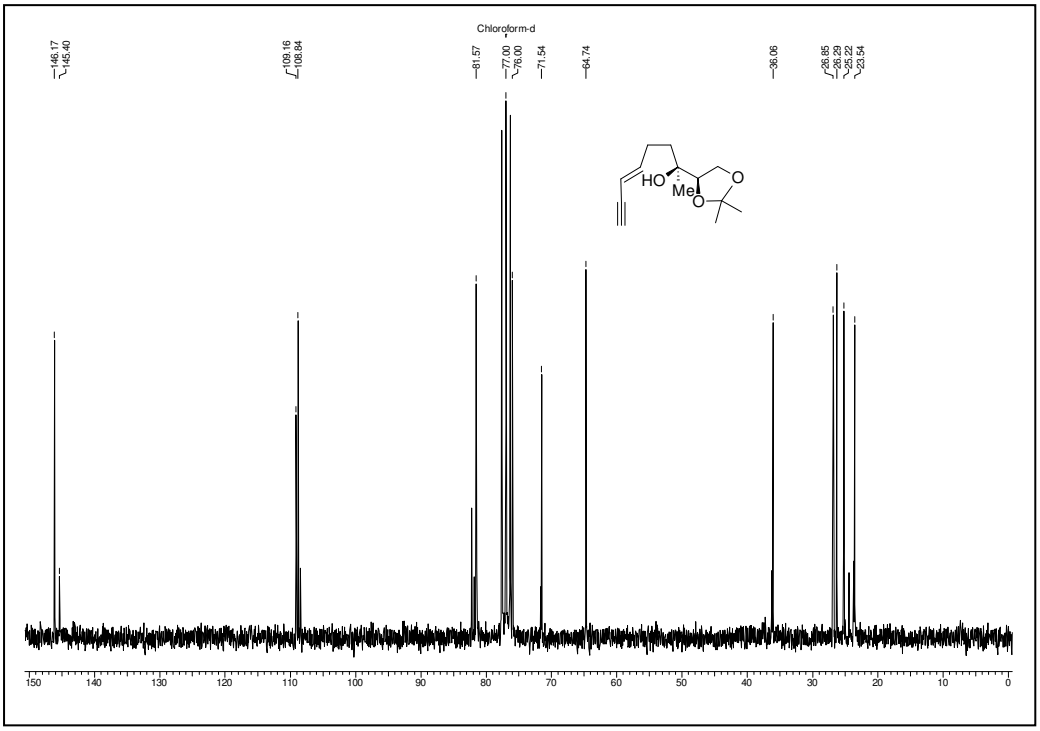
^{13}C-NMR Spectrum of 18 in $CDCl_3$



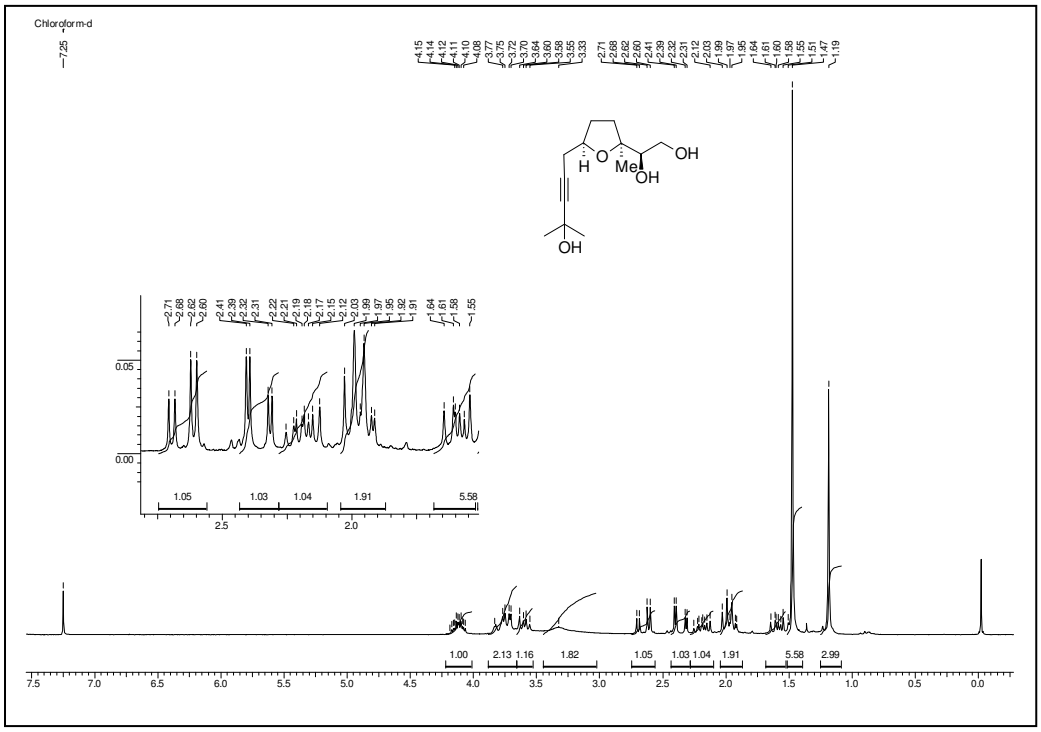
^{1}H-NMR Spectrum of 20 in $CDCl_3$



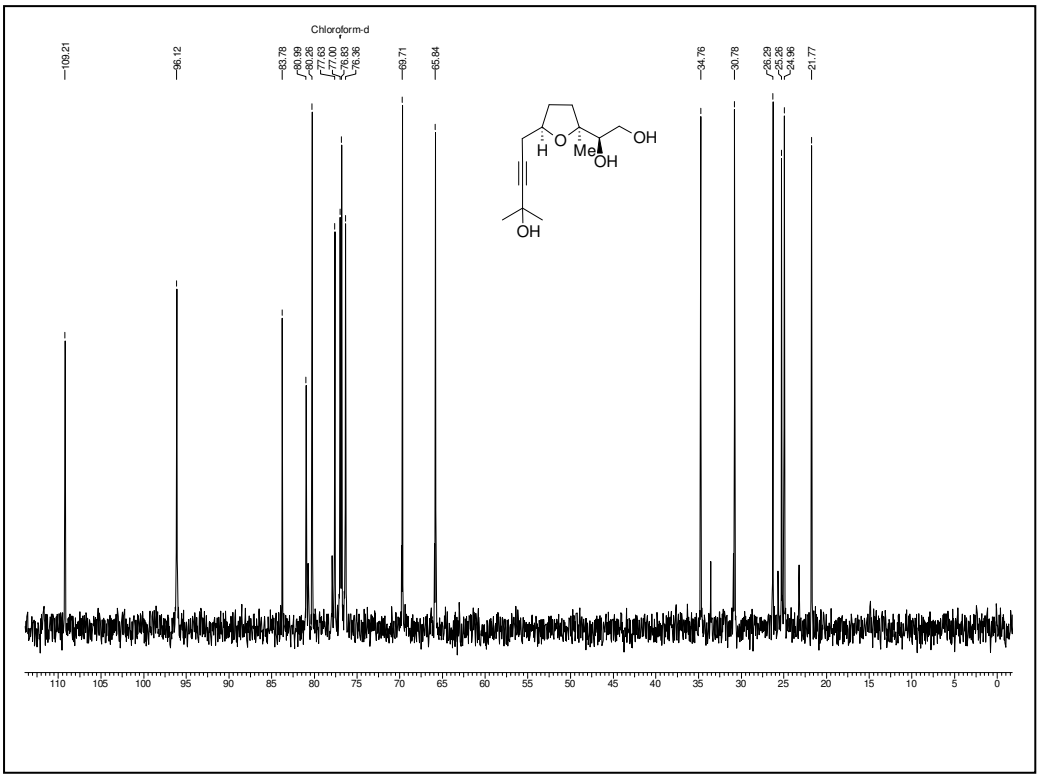
^{1}H-NMR Spectrum of 19 in $CDCl_3$



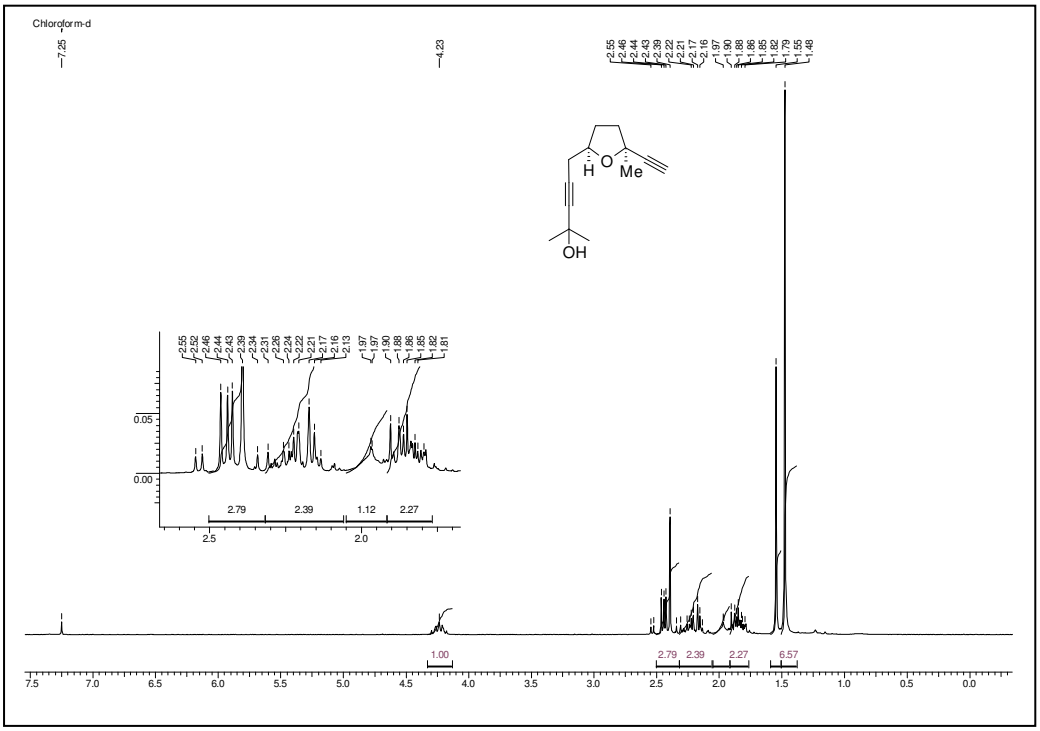
^{13}C-NMR Spectrum of 19 in $CDCl_3$



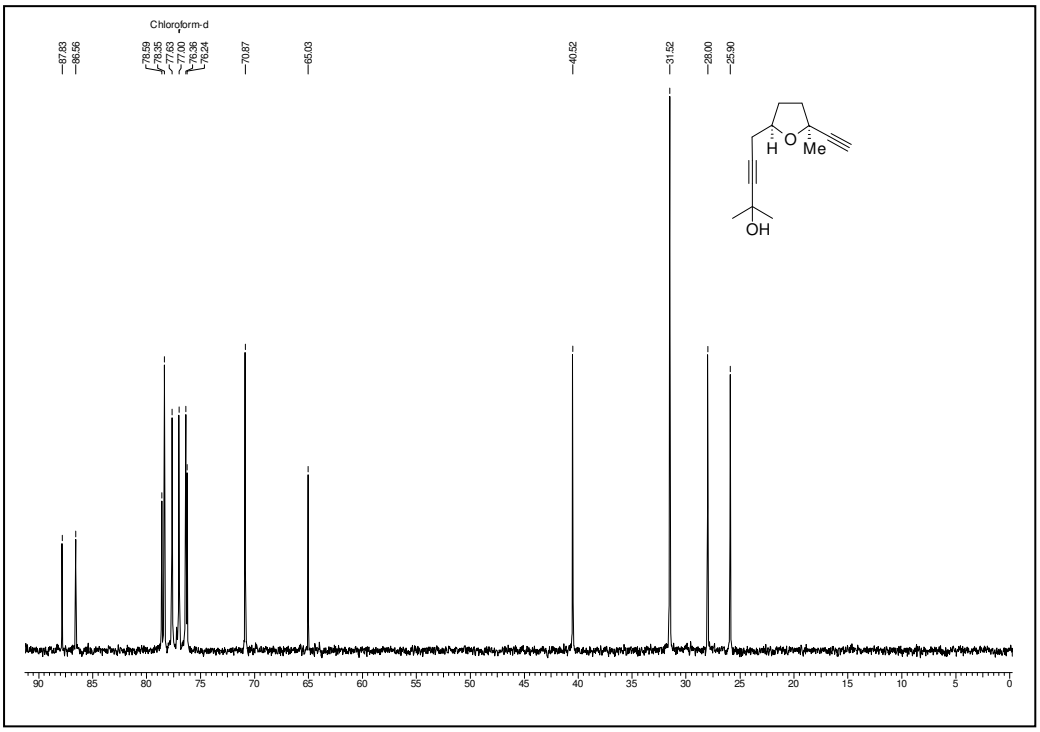
^{1}H-NMR Spectrum of 21 in $CDCl_3$



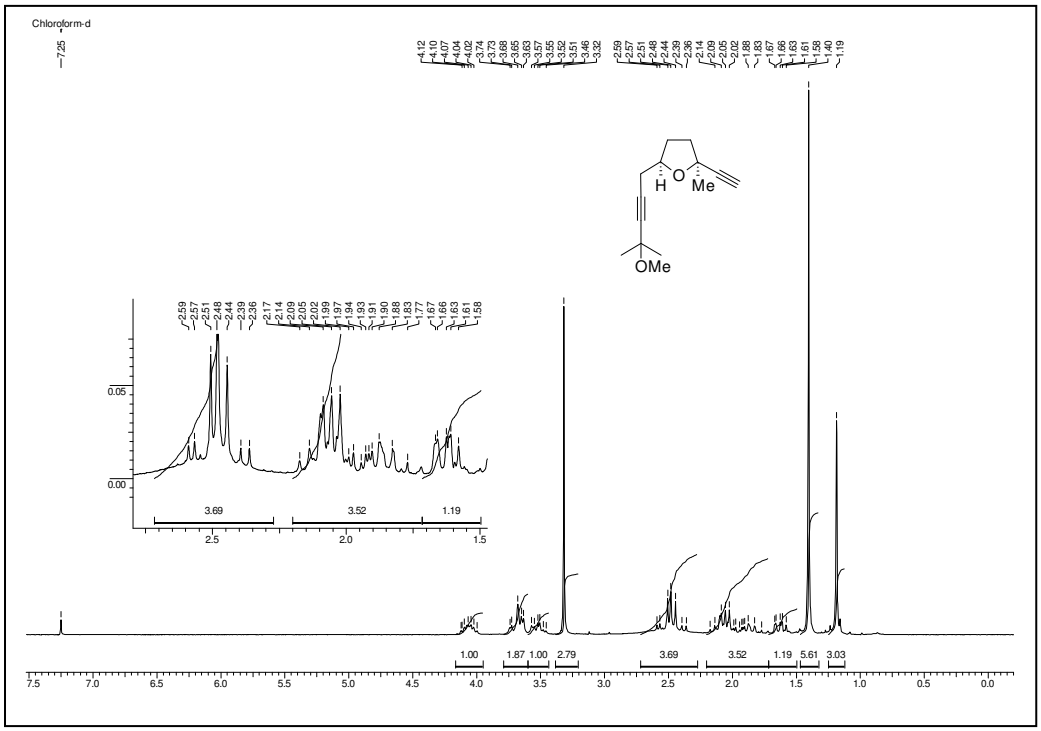
^{13}C-NMR Spectrum of 21 in $CDCl_3$



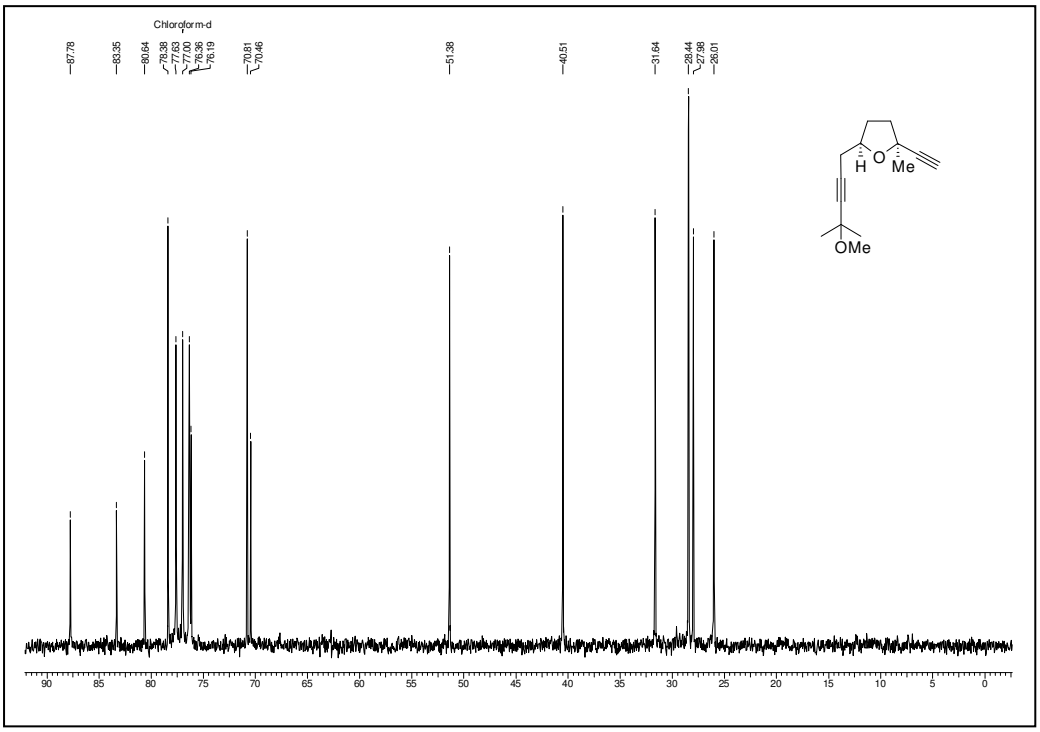
^{1}H-NMR Spectrum of 22 in $CDCl_3$



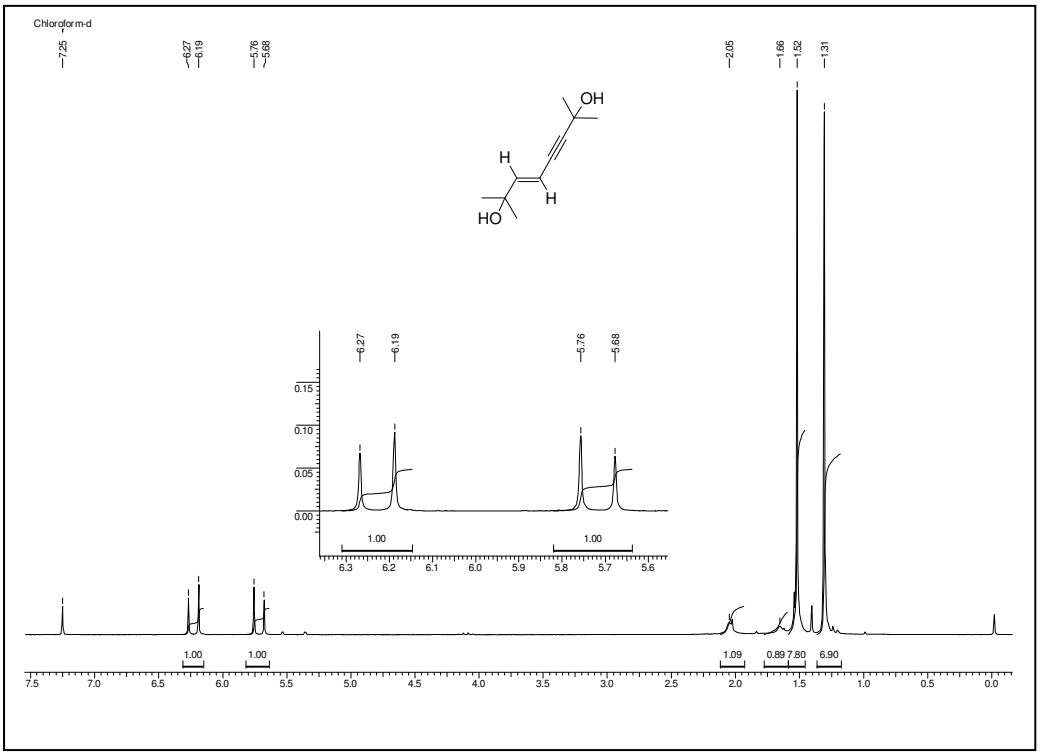
^{13}C-NMR Spectrum of 22 in $CDCl_3$



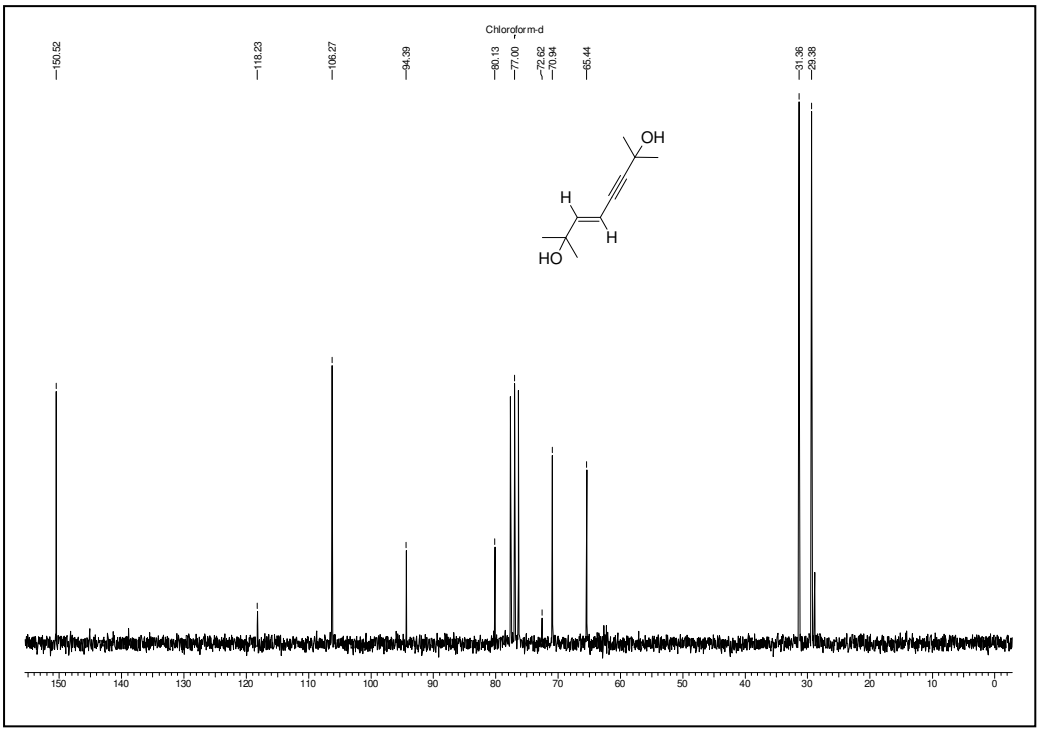
^{1}H-NMR Spectrum of 23 in $CDCl_3$



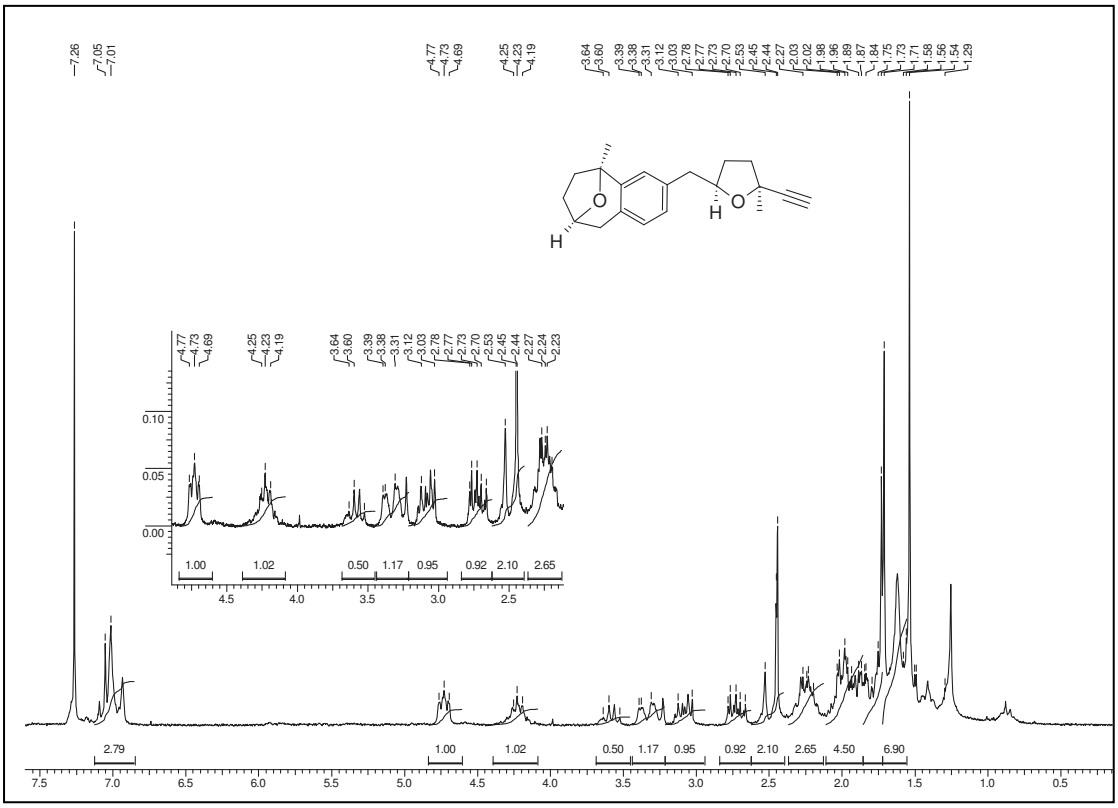
^{13}C-NMR Spectrum of 23 in $CDCl_3$



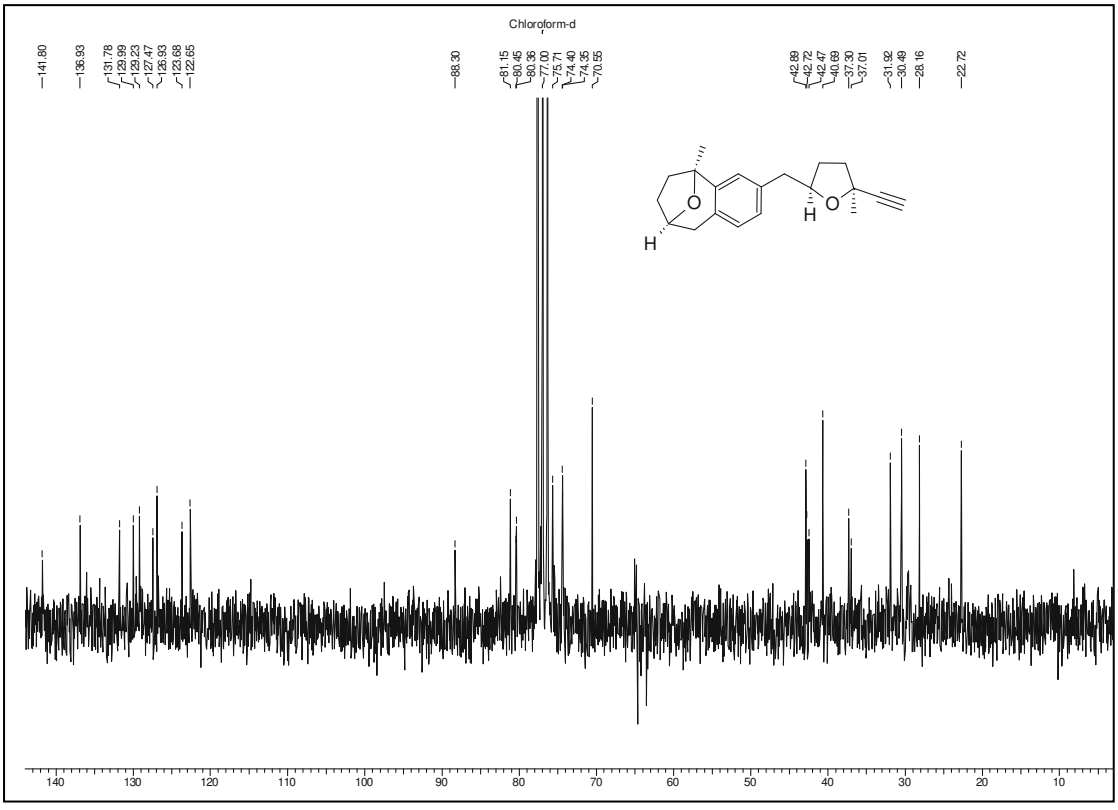
^{1}H-NMR Spectrum of 25 in $CDCl_3$



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



^{1}H-NMR Spectrum of 26/27 in $CDCl_3$



^{13}C-NMR Spectrum of 26/27 in $CDCl_3$

Chapter II

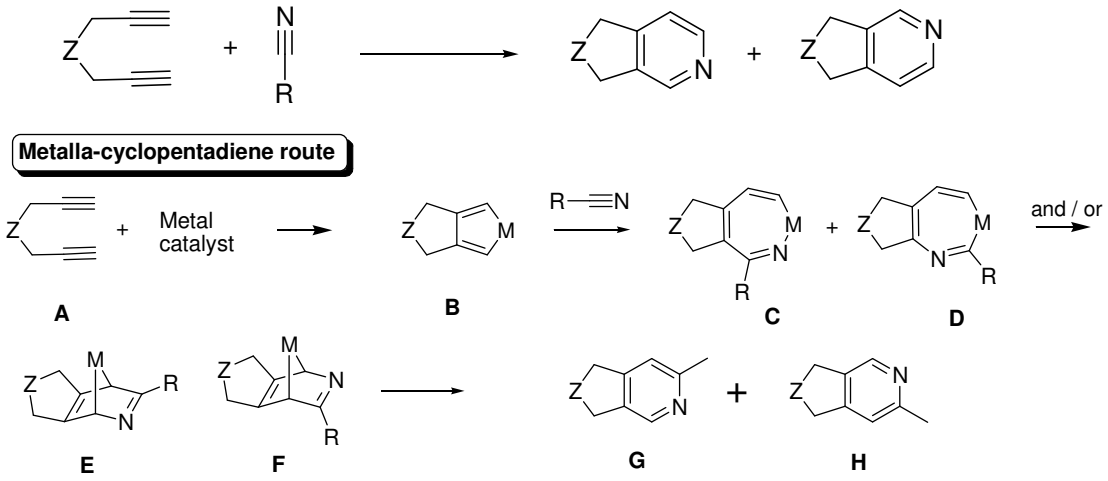
Section II

Synthesis of pyridine fused bicyclo[3.2.1]octane systems by employing [2+2+2] cross cyclotrimerization.

Pyridine rings are found in many biologically relevant structures including compounds with antiviral (HIV),[28] antimicrobial,[29] anticancer,[30] and protein kinase inhibition activity. Catalyst systems applied in cyclotrimerizations towards pyridine synthesis are mainly based on cobalt and recent developments have led to mild reaction conditions applicable to organic synthesis.[31] The [2+2+2] cyclotrimerization reaction is an efficient tool for the construction of carbo- and heterocyclic Structures.[32] Traditionally, the most commonly used catalyst systems are based on cobalt and rhodium. These catalysts, in conjunction with a partially intramolecular reaction using tethered alkynes, have led to several practical applications of the [2+2+2] cyclotrimerization in the construction of fused pyridine and benzene molecules, including several total syntheses.[33]

Generally synthesis of pyridines using [2+2+2]cyclotrimerization involves a reaction between a α,ω-diyne with the corresponding nitriles (**Scheme 1**).

Scheme 1:

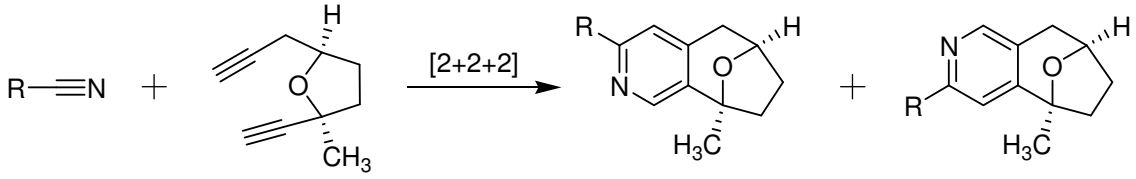


The mechanism of cyclotrimerization is shown in **Scheme 1** which involves the oxidative addition of metal catalyst to form the metallacyclopentadiene (**B**) which reacts with alkyl/aryl nitrile to form a regiomeric mixture of **C** and **D** or **E** and **F** which on reductive elimination of the catalyst delivers a 1:1 mixture of regiomeric mixture of substituted pyridenes **G** and **H**. This chemistry affords substantial molecular complexity in a single step, with excellent atom-economy.[34]

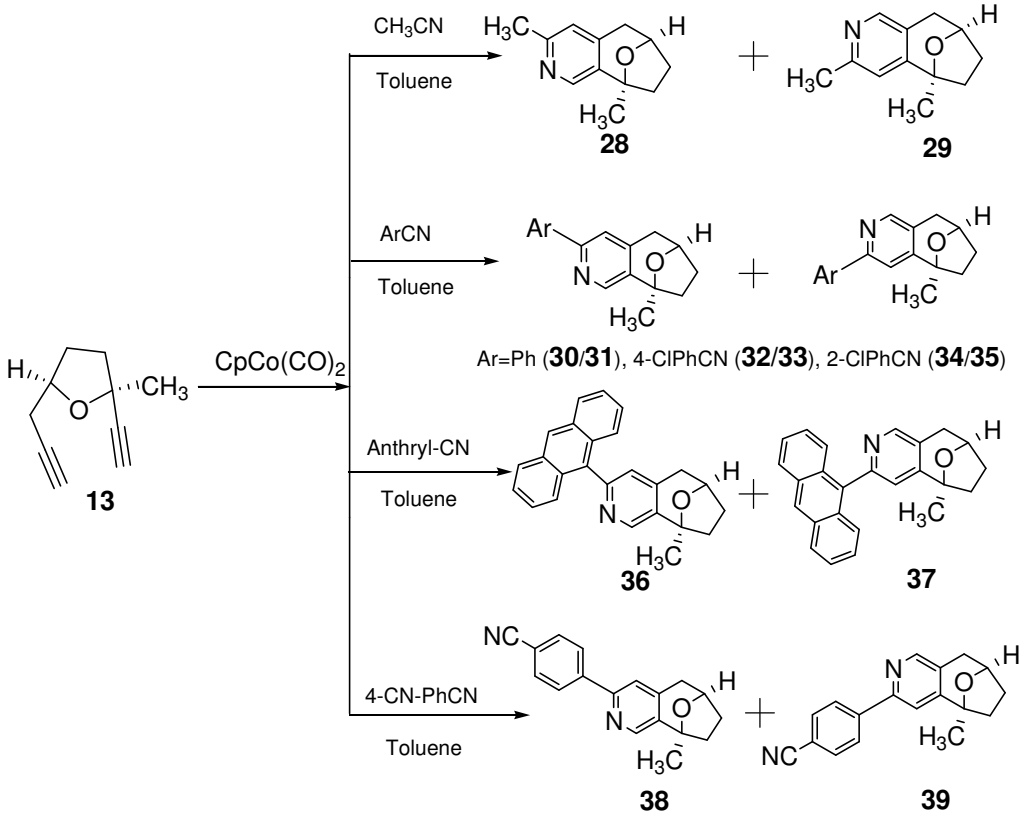
After being established the feasibility of [2+2+2] alkyne cyclotrimerization for the synthesis of highly strained benzannulated 8-oxa bicyclo[3.2.1]octane systems and

successfully applying to the first total synthesis of (+) bruguierol A, we later directed to synthesize different pyridine fused bicyclic systems. The dialkyne **20** was expected to accomplish pyridines treating with different nitriles (**Scheme 2**).

Scheme 2: pyridine fused 8-oxa bicyclo[3.2.1]octane systems



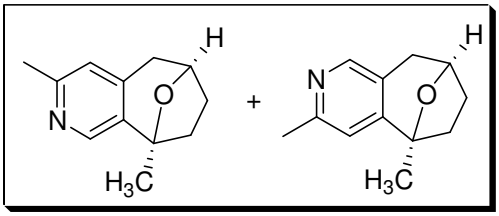
Reports from literature reveals that cobalt catalysts are efficient to bring about this type of cycloaddition for pyridine synthesis[35]. Different nitriles are treated with dialkyne **13** using 5 mol% of $CpCo(CO)_2$ in refluxing toluene temperature gave regiomeric pyridines in equal ratio (**Scheme 2**). Initially the reaction conditions were standardized with acetonitrile and it was found that $CpCo(CO)_2$ (5 mol%, 1.5 M solution in xylene) in refluxing toluene for 6 h gave the regiomeric inseparable pyridines **28/29** in 64% yield. The products were extensively studied by spectral and analytical data. The ^{1}H-NMR spectrum showed the aromatic proton α to the pyridine nitrogen at 8.21 and 8.29 ppm as two separate singlets. The other aromatic proton was resonated at 6.89 and 6.92 ppm as two doublets. The methyl group α to the pyridine nitrogen resonated at 2.48 and 2.51 ppm as two singlets. The two C-benzylic protons appeared at 3.28 and 2.51 ppm. The ring junction quaternary methyl was resanoated at 1.70 and 1.77 ppm as two singlets. Further the ^{13}C-NMR studies reveal the presence of equal ratio of regiomeric pyridines. IR and mass spectral studies are in full agreement with the assigned structure.



Later we subjected different nitriles like banzonitrile, 4-chloro benzyl cyanide, 2-chloro benzyl cyanide, anthryl nitrile and 4-cyanobenzonitrile for cycloadditon and the regiomeric pyridines **30/31**, **32/33**, **34/35,36/37** and **38/39** were obtained in good yields. All the products were characterized by spectral and analytical data. It was found that the regiomeric pyridines **30/31** and **32/33** were separable by simple chromatography and was characterized.

Experimental

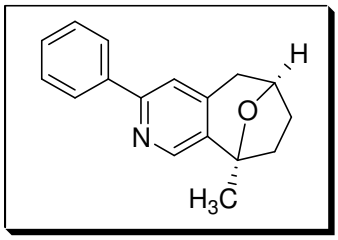
Cyclotrimerisation with Acetonitrile (28/29):-



To a stirred solution of dialkyne **13** (0.1 g, 0.67 mmol) in dry toluene (20 mL) was added acetonitrile (1mL) followed by $CpCo(CO)_2$ (1.25 M solution in p-xylene, 10 mol%) and the reaction mixture was heated to 80-90 ^{0}c for 8 h. volatiles were evaporated under vacuo and the crude obtained was purified by column chromatography (3:7 ethyl acetate/petroleum ether) gave **28/29** (0.076 g, 60%) as colorless oil.

Yield	: 60%
Mol. Formula	: $C_{12}H_{15}NO$
$[\alpha]_D^{25}$	: +61.7 (*c* 1.8, $CHCl_3$).
IR (Neat) $\tilde{\nu}$	: 3019, 2972, 1464, 1215, 759, 669 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 1.47 (s, 3H), 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, J = 16.4, Hz, 1H), 3.37 (dd, J = 16.4, 5.3 Hz, 1H), 4.72-4.76 (m, 1H), 6.77 (s, 1H), 6.84 (s, 1H).
^{13}C NMR ($CDCl_3$, 50 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).
ESI-MS (*m/z*)	: 190.34 $[M+1]^+$.
Elemental Analysis	Calcd.: C, 76.16; H, 7.99; N, 7.40. Found: C, 76.21; H, 8.04; N, 7.29.

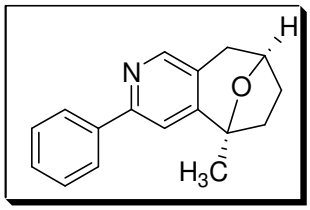
Cyclotrimerisation with benzonitrile (Top spot, 30):-



To a stirred solution of dialkyne **13** (0.1 g, 0.67 mmol) in dry toluene (20 mL) was added benzonitrile (0.5 mL) followed by $CpCo(CO)_2$ (1.25 M solution in p-xylene, 10 mol%) and the reaction mixture was heated to 80-90 ^{0}c for 8 h. volatiles were evaporated under vacuo and the crude obtained was purified by column chromatography (3:7 ethyl acetate/petroleum ether) gave a 1:1 seperable mixture of **30** (0.042 g, 25%) and **31** (0.042 g, 25%) as colorless oils.

Yield	: 25%
Mol. Formula	: $C_{17}H_{17}NO$
$[\alpha]_D^{25}$	: +43.6 (*c* 1.2, $CHCl_3$).
IR (Neat) $\tilde{\nu}$	: 3019, 2972, 1464, 1215, 759, 669 cm-1.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 1.74 (brs, 1H), 1.82 (s, 3H), 1.92-2.14 (m, 2H), 2.26-2.42 (m, 1H), 2.58 (d, *J* = 17.18 Hz, 1H), 3.375 (dd, *J* = 17.18, 5.05 Hz, 1H), 4.75-4.81 (m, 1H), 7.39-7.45 (m, 4H), 7.945 (d, *J* = 6.82 Hz, 2H), 8.49 (s, 1H).
^{13}C NMR ($CDCl_3$, 100 MHz)	: δ 22.14 (q), 30.53 (d), 37.04 (d), 42.93 (d), 73.90 (d), 79.27 (s), 120.91 (d), 126.70 (d), 128.66 (d), 128.70 (d), 138.21 (s), 139.22 (s), 142.36 (s), 144.14 (d), 155.73 (s).
ESI-MS (*m/z*)	: 252.46 $[M+1]^+$.
Elemental Analysis	Calcd.: C, 81.24; H, 6.82; N, 5.57.
	Found: C, 81.4; H, 6.92; N, 5.70.

Bottom spot (31):



Yield : 25%

Mol. Formula : $C_{17}H_{17}NO$

$[\alpha]_D^{25}$: +38.9 (*c* 1.5, $CHCl_3$).

IR ($CHCl_3$) ν : 3019, 2972, 1464, 1215, 759, 669 cm^{-1}.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 1.72 (brs, 1H), 1.79 (s, 3H), 1.90-2.14 (m, 2H), 2.14-2.41 (m, 1H), 2.585 (d, *J* = 16.67 Hz, 1H), 3.355 (dd, *J* = 16.67, 5.05 Hz, 1H), 4.75-4.81-4.87 (m, 1H), 7.40-7.52 (m, 4H), 7.92-7.97 (m, 2H), 8.41 (s, 1H).

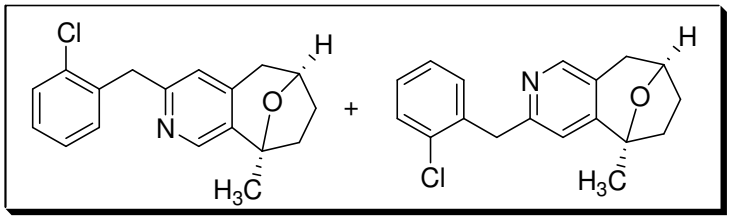
^{13}C NMR ($CDCl_3$, 50 MHz) : δ 22.14 (q), 30.53 (d), 37.04 (d), 42.93 (d), 73.90 (d), 79.27 (s), 120.91 (d), 126.70 (d), 128.66 (d), 128.70 (d), 138.21 (s), 139.22 (s), 142.36 (s), 144.14 (d), 155.73 (s).

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

: Found: C, 81.4; H, 6.92; N, 5.70.

ESI-MS (m/z) : 252.46 $(M+1)^+$

Cyclotrimerisation with 2-chloroBenzonitrile (34/35) :-



To a stirred solution of dialkyne **13** (0.1 g, 0.67 mmol) in dry toluene (20 mL) was added 2-chloro benzonitrile (0.5 mL) followed by $CpCo(CO)_2$ (1.25 M solution in p-xylene, 10 mol%) and the reaction mixture was heated to 80-90 ^{0}c for 8 h. volatiles were evaporated under vacuo and the crude obtained was purified by column chromatography (3:7 ethyl acetate/petroleum ether) gave a mixture of **34** and **35** (0.101 g, 50%) as colorless oils.

Yield : 50% (Bottom spot)

Mol. Formula : $C_{18}H_{18}ClNO$

$[\alpha]_D$: +53.4 (*c* 0.8, $CHCl_3$).

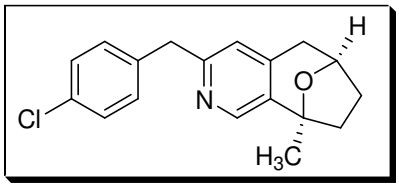
IR (Neat) $\tilde{\nu}$: 3018, 2928, 1605, 1215, 756, 668 cm^{-1}.

^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 1.70 (s, 1H), 1.79 (s, 3H), 1.80-1.90 (m, 1H), 1.92-2.03 (m, 1H), 2.10-2.30 (m, 1H), 2.38 (d, *J* = 17.43 Hz, 1H), 3.18 (dd, *J* = 17.43, 5.31 Hz, 1H), 4.18 (s, 2H), 4.62-4.69 (m, 1H), 6.77 (s, 1H), 7.12-7.17 (m, 2H), 7.30-7.35 (m, 2H), 8.30 (s, 1H).
^{13}C NMR ($CDCl_3$, 100 MHz)	: δ 22.16 (q), 30.51 (t), 36.89 (t), 42.81 (t), 73.80 (d), 79.19 (s), 123.64 (d), 127.03 (d), 128.11 (s), 129.59 (s), 131.50 (s), 143.02 (d), 157.05 (s).
ESI-MS (*m/z*)	: 300.92 $[M+1]^+$.
Elemental Analysis	: Calcd.: C, 72.11; H, 6.05; N, 4.67.
	: Found: C, 72.32; H, 6.12; N, 4.80.

Cyclotrimerisation with 4-chloroBenzonitrile:-

To a stirred solution of dialkyne **13** (0.1 g, 0.67 mmol) in dry toluene (20 mL) was added 4-chloro benzonitrile (0.5 mL) followed by $CpCo(CO)_2$ (1.25 M solution in p-xylene, 10 mol%) and the reaction mixture was heated to 80-90 ^{0}c for 8 h. volatiles were evaporated under vacuo and the crude obtained was purified by column chromatography (3:7 ethyl acetate/petroleum ether) gave a 1:1 separable mixture of **32** (0.050 g, 25%) and **33** (0.050 g, 25%) as colorless oils.

Top spot (32):



Yield	: 50%
Mol. Formula	: $C_{18}H_{18}ClNO$
$[\alpha]_D^{25}$	:+49.4 (*c* 1.1, $CHCl_3$)
IR ($CHCl_3$) ν	: 3018, 2928, 2856, 1605, 1215, 756, 668 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 1.60−1.68 (m, 1H), 1.74 (s, 3H), 1.83-1.91 (m, 1H), 1.98-2.03 (m, 1H), 2.23-2.32 (m, 1H), 2.42 (d, *J* = 17.32 Hz, 1H), 3.23 (dd, *J* = 17.32, 5.28 Hz, 1H), 4.03 (s, 2H), 4.68-4.72 (m, 1H), 6.79 (s, 1H), 7.17 (d, *J* =

8.53 Hz, 2H), 7.255 (d, *J* = 4.27 Hz, 2H), 8.31 (s, 1H).

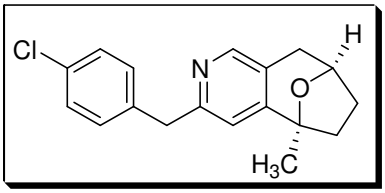
^{13}C NMR ($CDCl_3$, 50 MHz) : δ 22.19 (q), 30.50 (t), 36.81 (t), 42.86 (t), 43.53 (t), 73.80 (d), 79.18 (s), 123.25 (d), 128.66 (d), 130.43 (d), 132.22 (s), 137.55 (s), 137.97 (s), 142.42 (s), 143.84 (d), 158.42 (s).

Elemental Analysis : Calcd.: C, 72.11; H, 6.05; Cl, 11.83; N, 4.67

: Found: C, 72.19; H, 6.14; Cl, 11.48; N, 4.49

ESI-MS (m/z) : 300.86 $(M+1)^+$

Bottom spot (33):



Yield : 50%

Mol. Formula : $C_{18}H_{18}ClNO$

$[\alpha]_D^{25}$: +44.8 (*c* 1.2, $CHCl_3$).

IR ($CHCl_3$) ν : 3018, 2928, 2856, 1605, 1215, 756, 668 cm^{-1}.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 1.64 (s, 3H), δ 1.66–1.71 (m, 1H), 1.81-1.87 (m, 1H), 1.93-1.99 (m, 1H), 2.23-2.33 (m, 1H), 2.49 (d, *J* = 16.32 Hz, 1H), 3.23 (dd, *J* = 16.32, 5.02 Hz, 1H), 4.05 (s, 2H), 4.75-4.78 (m, 1H), 6.86 (s, 1H), 7.17 (d, *J* = 8.28 Hz, 2H), 7.255 (d, *J* = 5.27 Hz, 2H), 8.24 (s, 1H).

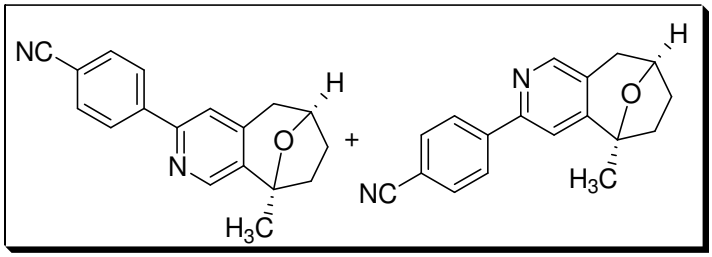
^{13}C NMR ($CDCl_3$, 50 MHz) : δ 21.79 (q), 30.39 (t), 33.97 (t), 42.55 (t), 43.70 (t), 74.27 (d), 79.87 (s), 116.61 (d), 125.42 (s), 128.63 (d), 130.28 (d), 130.86 (d), 132.15 (s), 138.18 (s), 150.16 (d), 152.93 (s), 157.96 (s).

Elemental Analysis : Calcd.: C, 72.11; H, 6.05; Cl, 11.83; N, 4.67

: Found: C, 72.21; H, 6.12; Cl, 11.48; N, 4.52

ESI-MS (m/z) : 300.86 $(M+1)^+$

Cyclotrimerisation with 4-CyanoBenzonitrile (36/37):-



To a stirred solution of dialkyne **13** (0.1 g, 0.67 mmol) in dry toluene (20 mL) was added 4-cyano benzonitrile (0.5 mL) followed by $CpCo(CO)_2$ (1.25 M solution in p-xylene, 10 mol%) and the reaction mixture was heated to 80-90 ^{0}c for 8 h. volatiles were evaporated under vacuo and the crude obtained was purified by column chromatography (3:7 ethyl acetate/petroleum ether) gave (0.084g, 45%) as colourless oil.

Yield : 50%

Mol. Formula : $C_{18}H_{16}N_2O$

$[\alpha]_D^{25}$: +61.7 (*c* 1.8, $CHCl_3$).

IR ($CHCl_3$) ν : 3019, 2927, 2229, 1605, 1215, 757, 668 cm^{-1}.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 1.73, 1.76 (s, 3H), δ 1.56–1.81 (m, 2H), 1.85-2.07 (m, 1H), 2.18-2.32 (m, 1H), 2.54(d, *J* = 17.18 Hz, 1H), 3.31 (dd, *J* = 17.18, 5.02 Hz, 1H), 4.69-4.82 (m, 1H), 7.43 (s, 1H), 7.68 (d, *J* = 8.28 Hz, 2H), 8.01 (d, *J* = 8.23 Hz, 2H), 8.37, 8.45 (s, 1H).

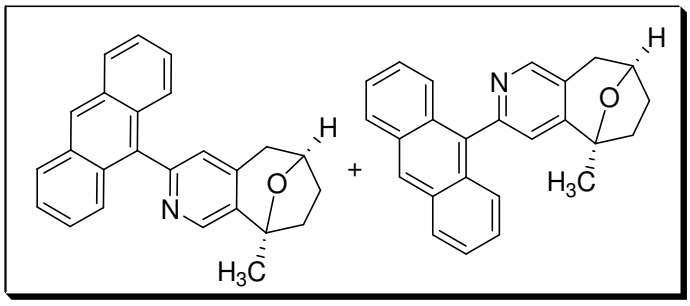
^{13}C NMR ($CDCl_3$, 50 MHz) : δ 14.11 (q), 22.67 (t), 31.90 (t), 37.03 (t), 73.82 (d), 79.26 (s), 80.00 (s), 114.66 (s), 121.42 (d), 127.28 (d), 132.51 (d), 144.55 (s), 150.79 (s), 161.44 (s).

Elemental Analysis : Calcd.: C, 78.24; H, 5.84; N 10.14

: Found: C, 78.32; H, 5.94; N 10.27

ESI-MS (m/z) : 277.4 $(M+1)^+$

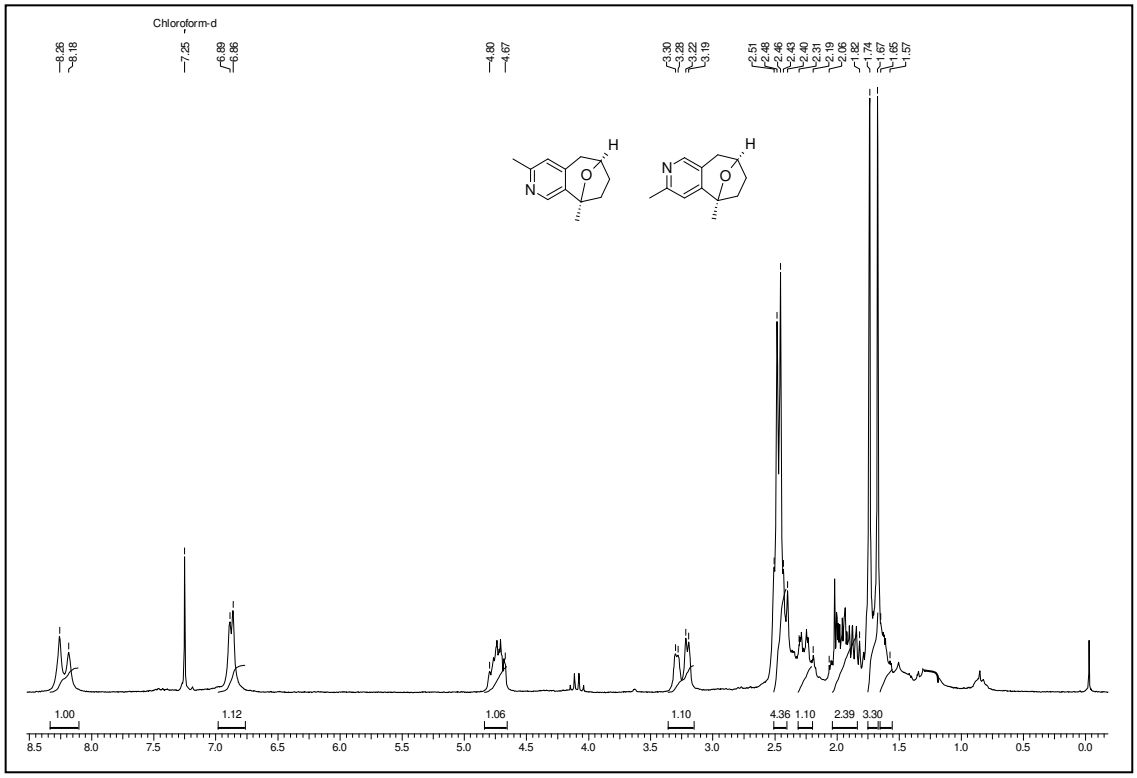
Cyclotrimerisation with 9-Anthrylnitrile (38/39) :-



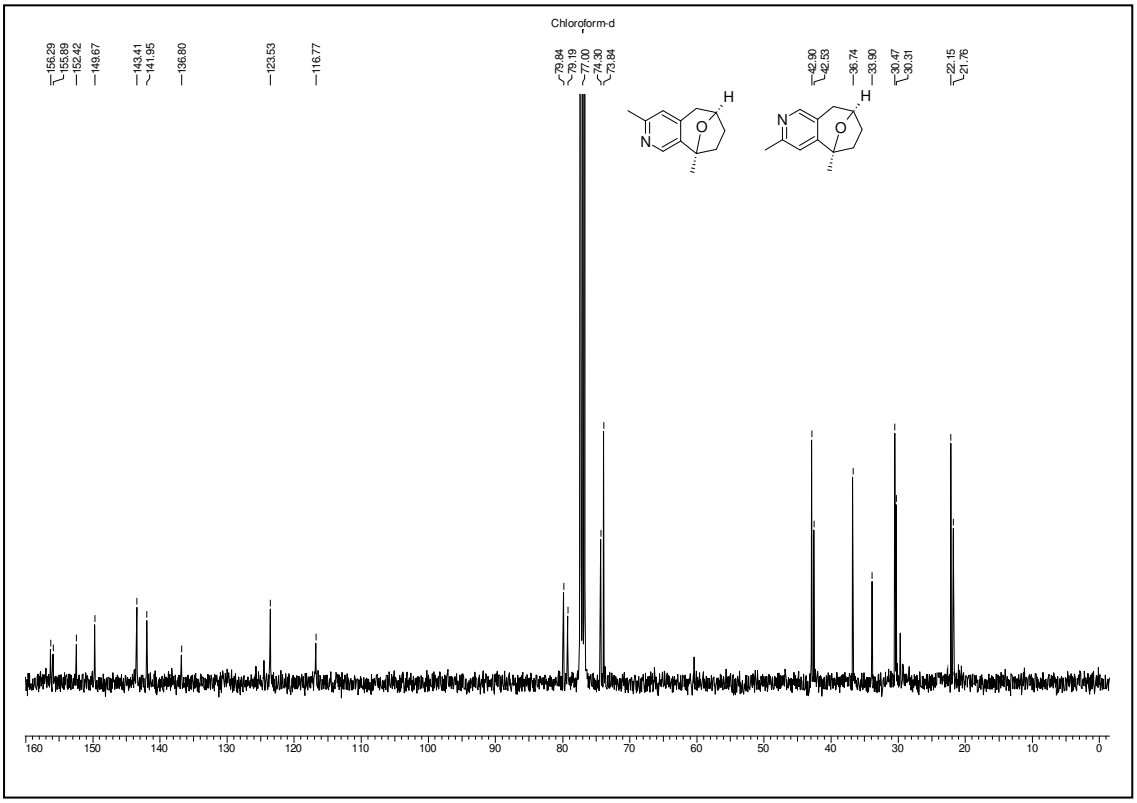
To a stirred solution of dialkyne **13** (0.1 g, 0.67 mmol) in dry toluene (20 mL) was added 9-anthryl nitrile (0.5 g) followed by $CpCo(CO)_2$ (1.25 M solution in p-xylene, 10 mol%) and the reaction mixture was heated to 80-90 ^{0}c for 8 h. volatiles were evaporated under vacuo and the crude obtained was purified by column chromatography (3:7 ethyl acetate/petroleum ether) gave (0.118 g, 50%) as colourless oil.

Yield	: 50%
Mol. Formula	: $C_{25}H_{21}NO$
$[\alpha]_D^{25}$	: +53.6 (*c* 1.1, $CHCl_3$).
IR ($CHCl_3$) ν	: 3019, 2957, 2927, 1708, 1215, 757, 668 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 1.47−1.68 (m, 1H), 1.87 (s, 3H), 1.91-2.11 (m, 1H), 2.178-2.38 (m, 2H), 2.56(d, *J* = 17.43 Hz, 1H), 3.38 (dd, *J* = 17.43, 5.56 Hz, 1H), 4.75-4.83 (m, 1H), 7.29-7.58 (m, 7H), 7.98 (d, *J* = 8.21 Hz, 2H), 8.46 (s, 1H), 8.37, 8.63 (s, 1H).
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ 14.10 (q), 22.66 (t), 29.33 (t), 31.89 (t), 74.45 (d), 80.05 (s), 124.99 (d), 125.11 (d), 126.42 (d), 127.44 (d), 128.37 (d), 128.51 (d), 129.09 (d), 129.68 (s), 130.16 (s), 141.32 (s), 147.12 (s), 161.39 (s).
Elemental Analysis	: Calcd.: C, 85.44; H, 6.02; N, 3.99. :Found: C, 85.38; H, 5.94; N, 3.77.
ESI-MS (m/z)	: 352.5 $[M+1]^+$.

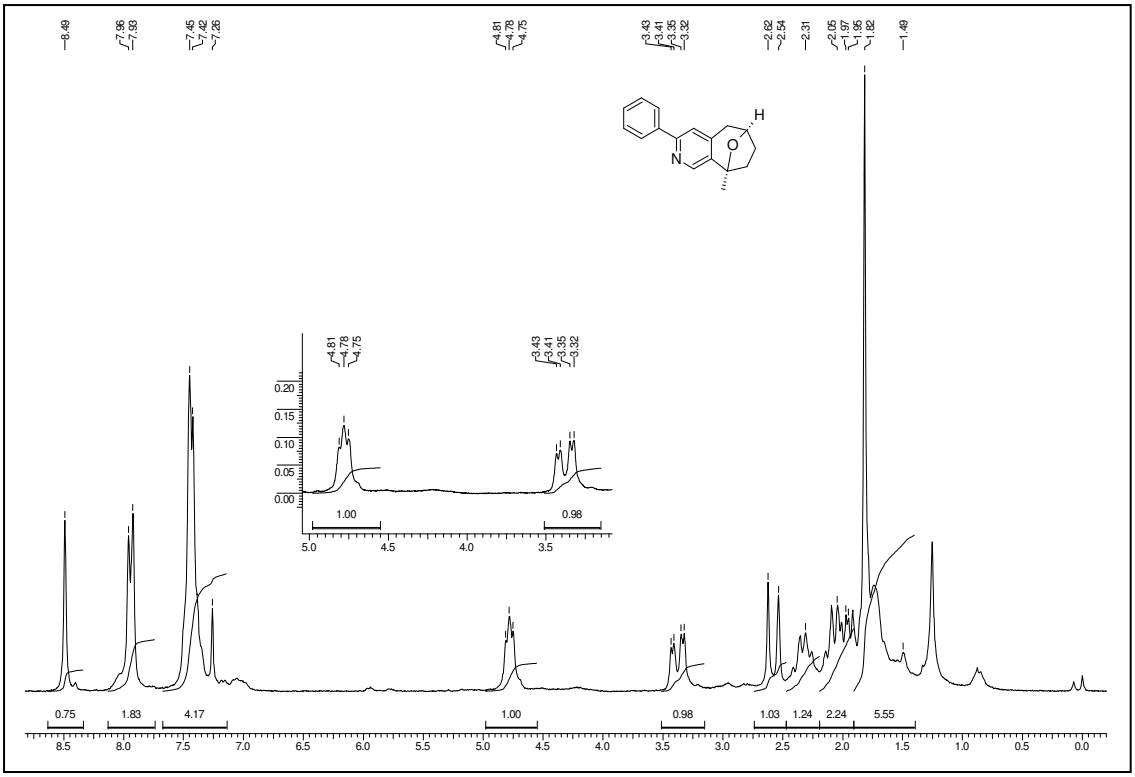
Spectral data



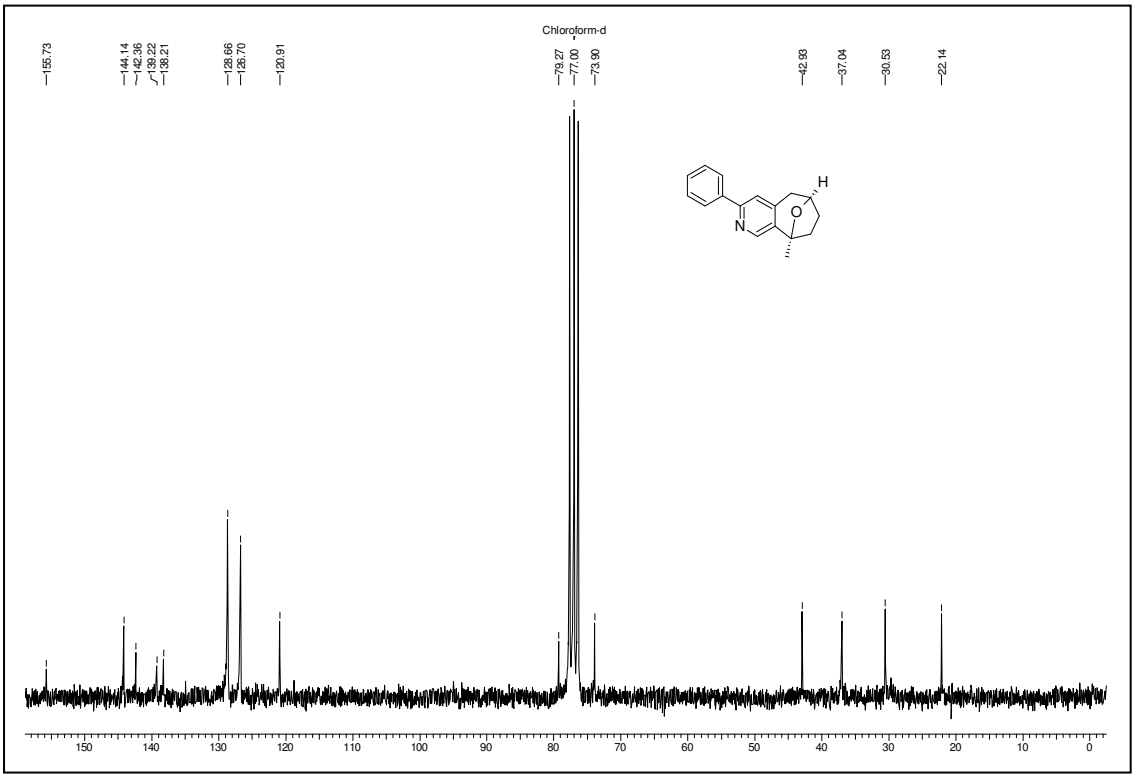
^{1}H NMR of compound 28/29 in $CDCl_3$



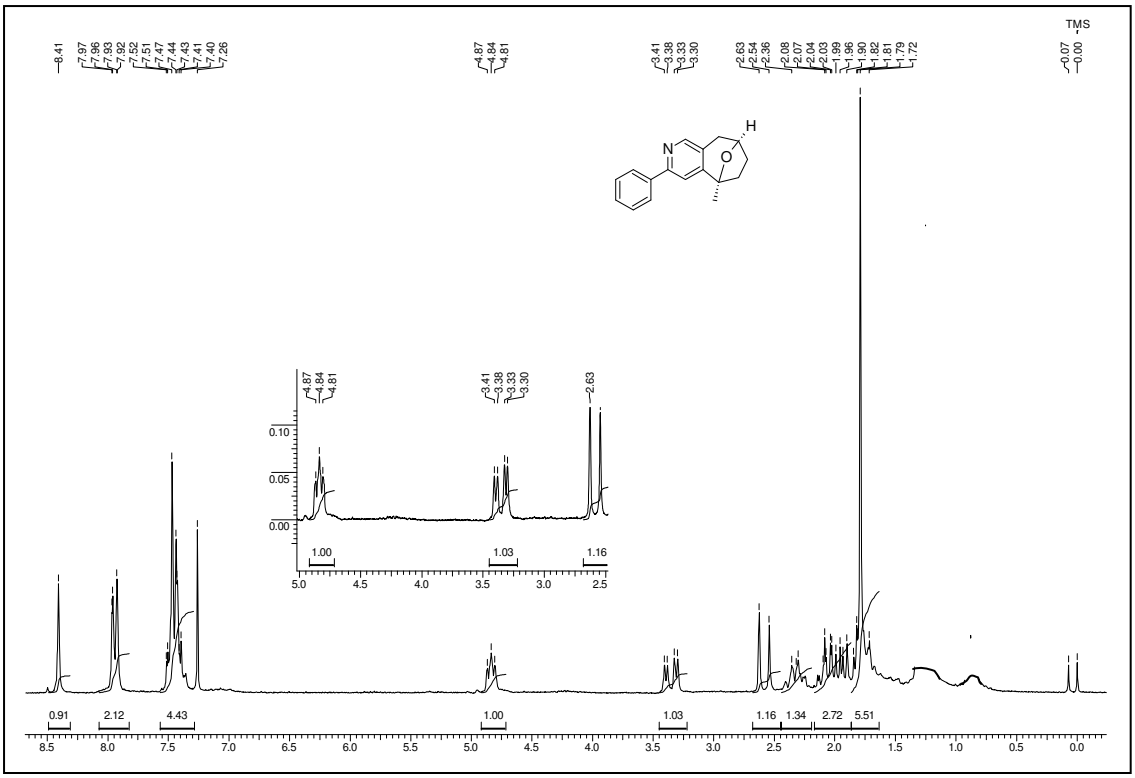
^{13}C NMR of compound 28/29 in $CDCl_3$



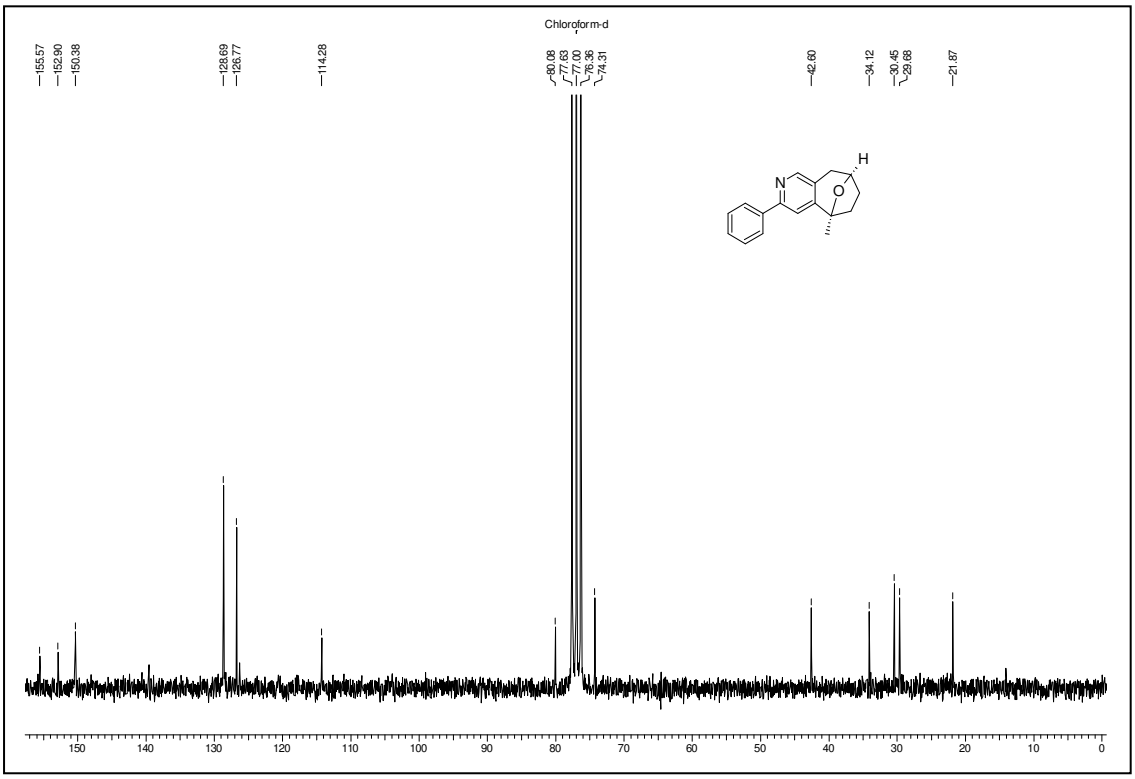
^{1}H NMR of compound 30 in $CDCl_3$



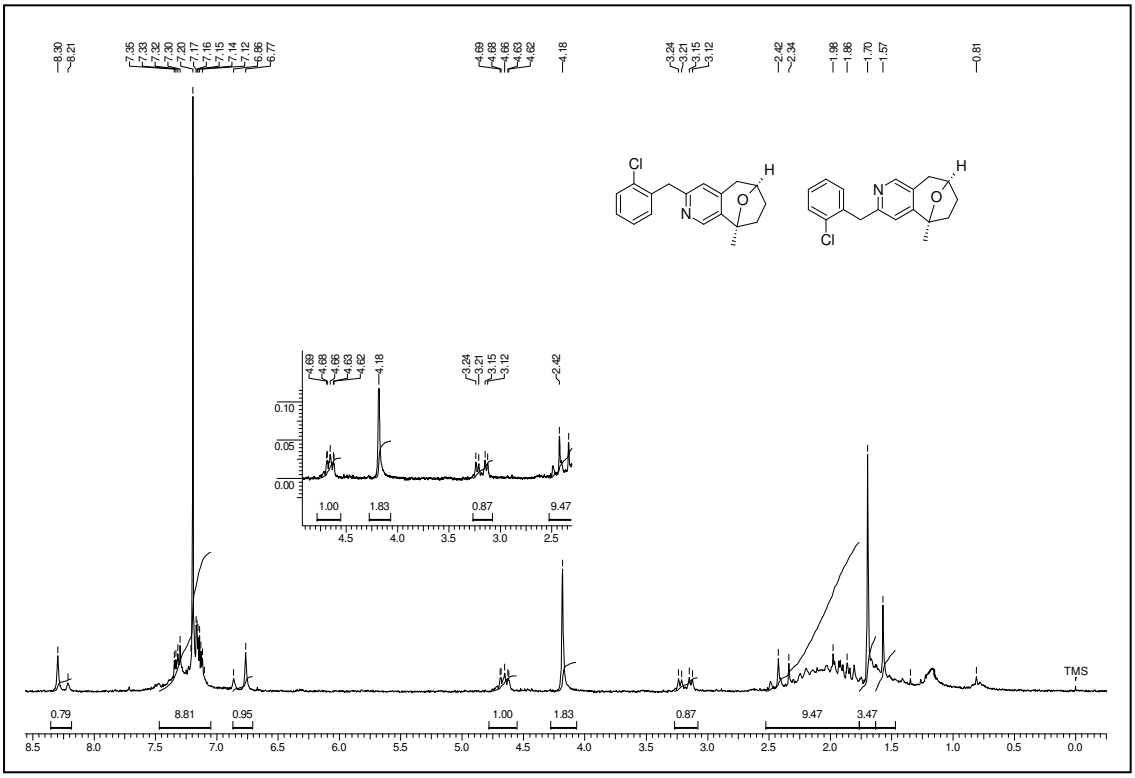
^{13}C NMR of compound 30 in $CDCl_3$



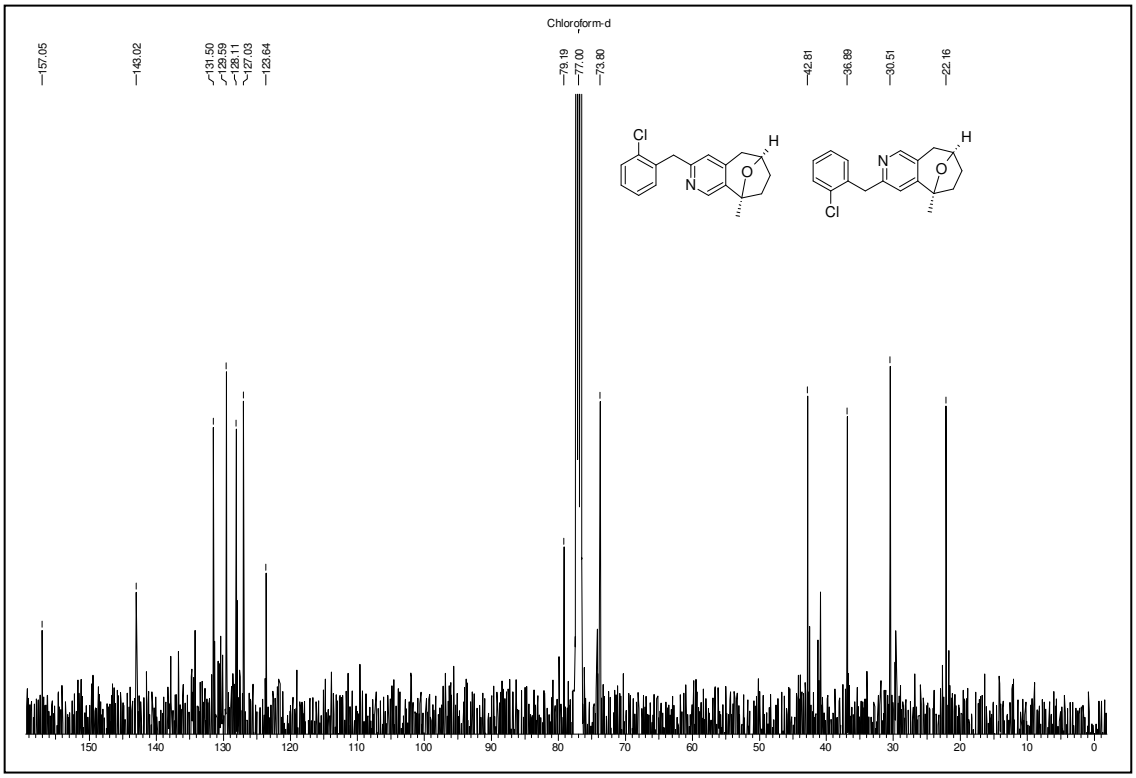
^{1}H NMR of compound 31 in $CDCl_3$



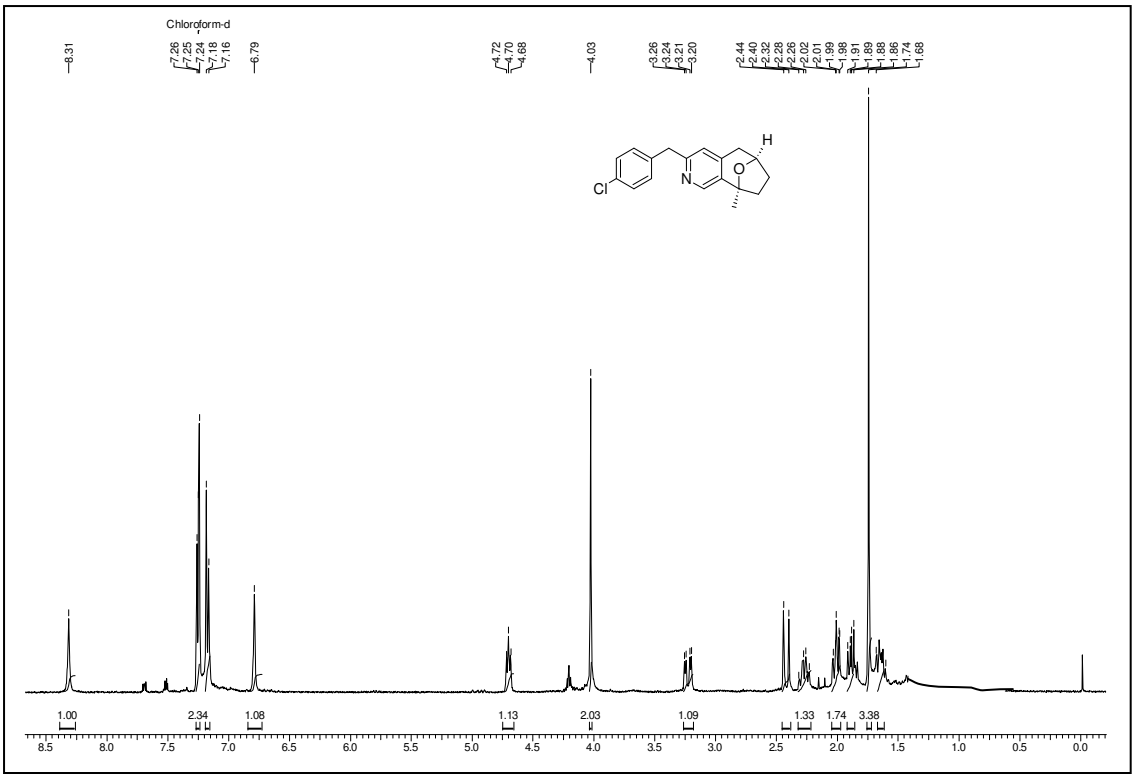
^{13}C NMR of compound 31 in $CDCl_3$



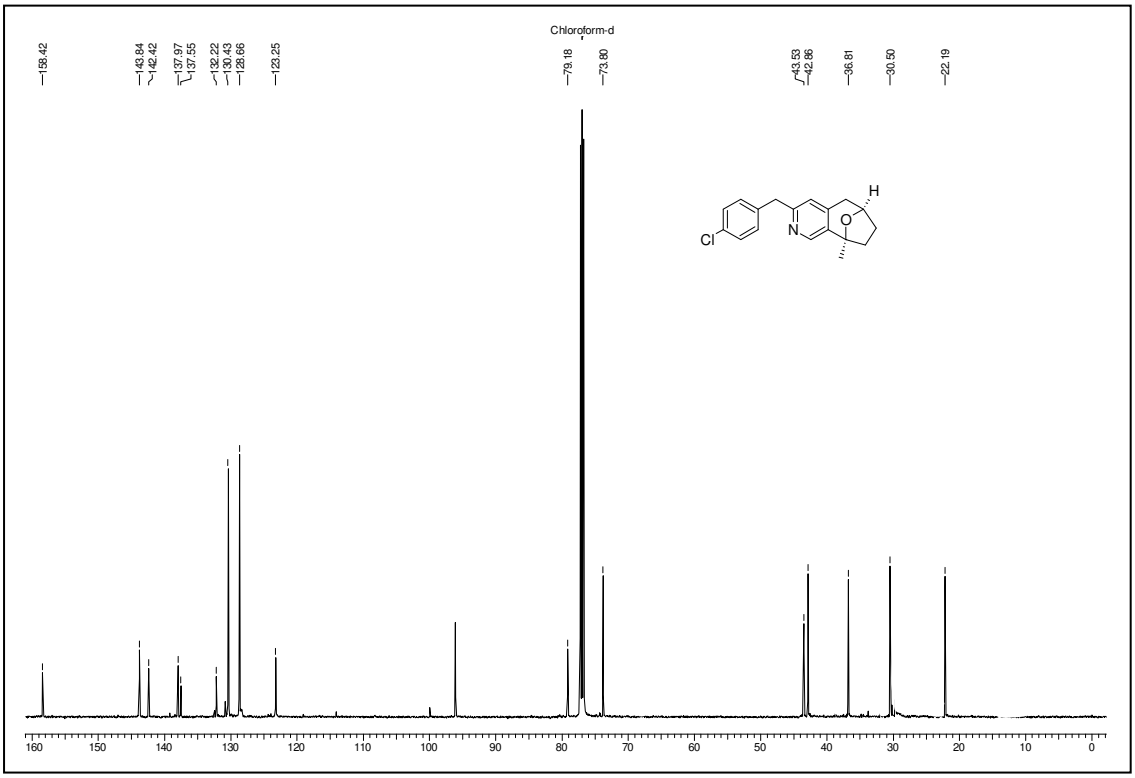
^{1}H NMR of compound 34/35 in $CDCl_3$



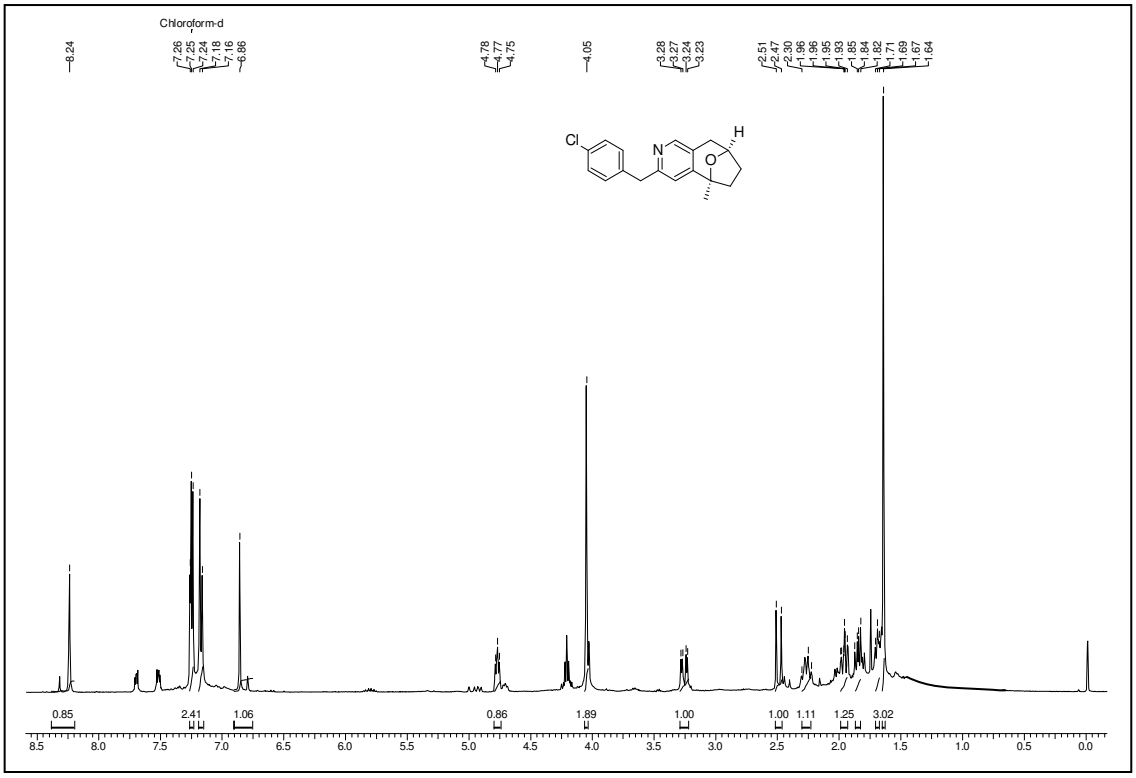
^{13}C NMR of compound 34/35 in $CDCl_3$



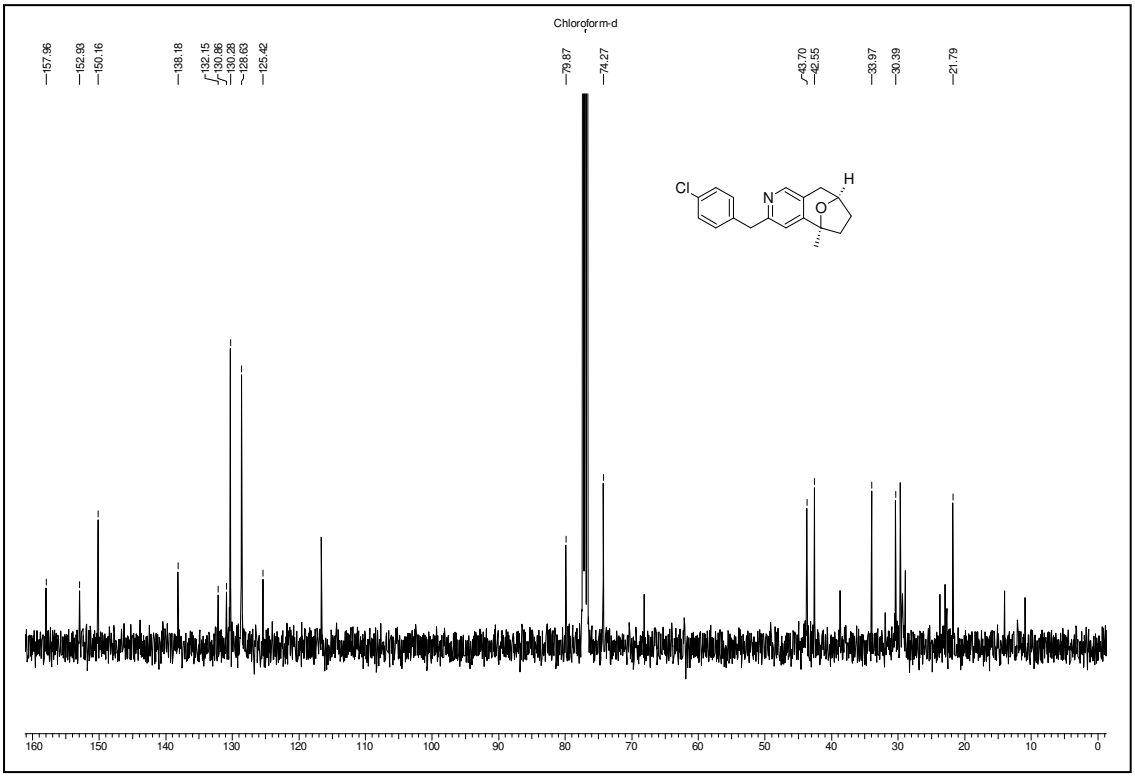
^{1}H NMR of compound 32 in $CDCl_3$



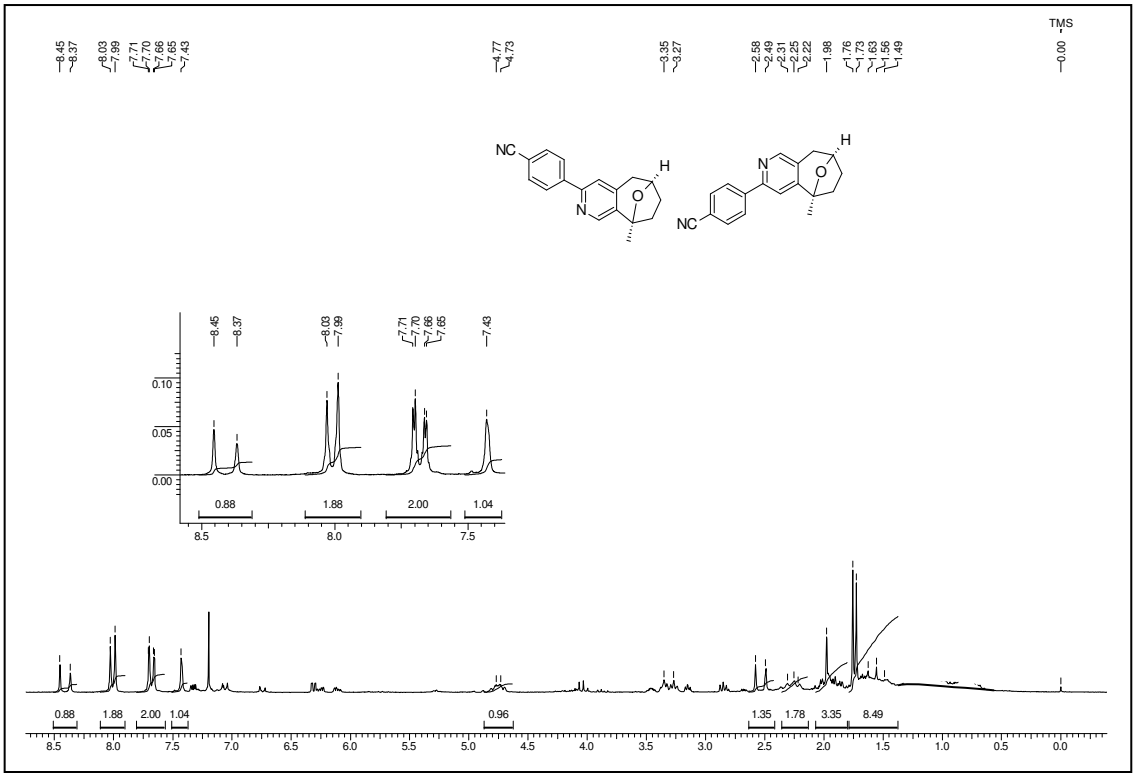
^{13}C NMR of compound 32 in $CDCl_3$



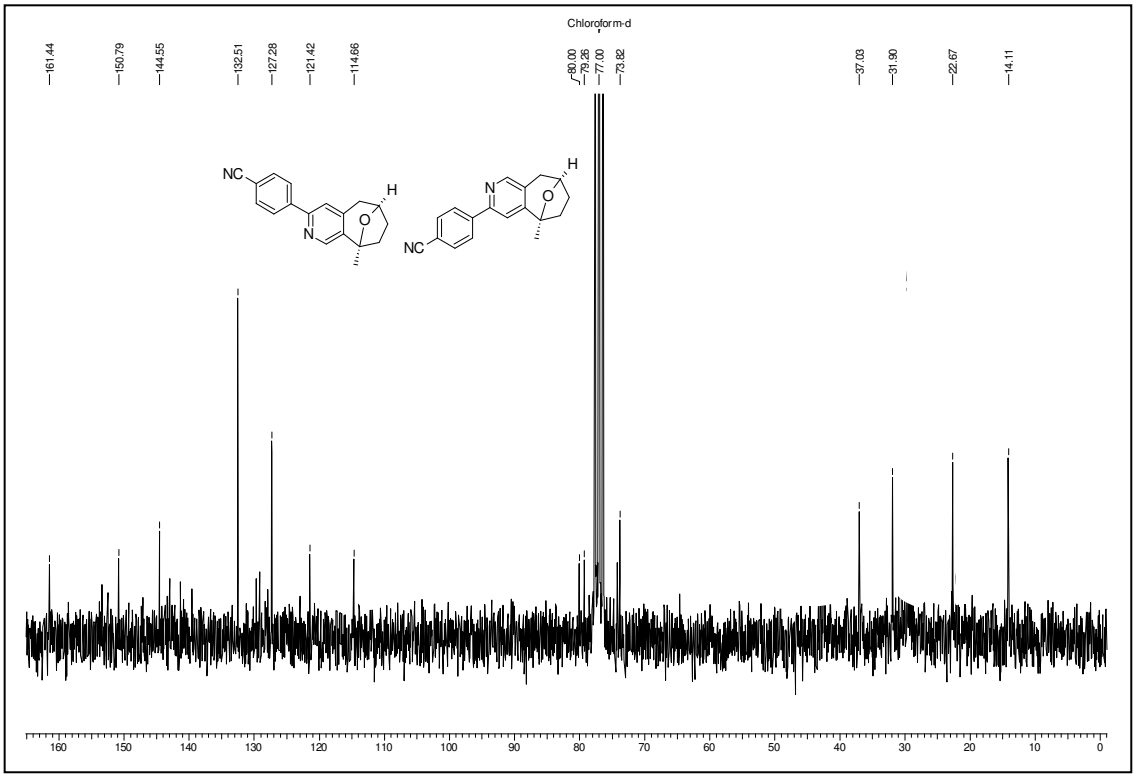
^{1}H NMR of compound 33 in $CDCl_3$



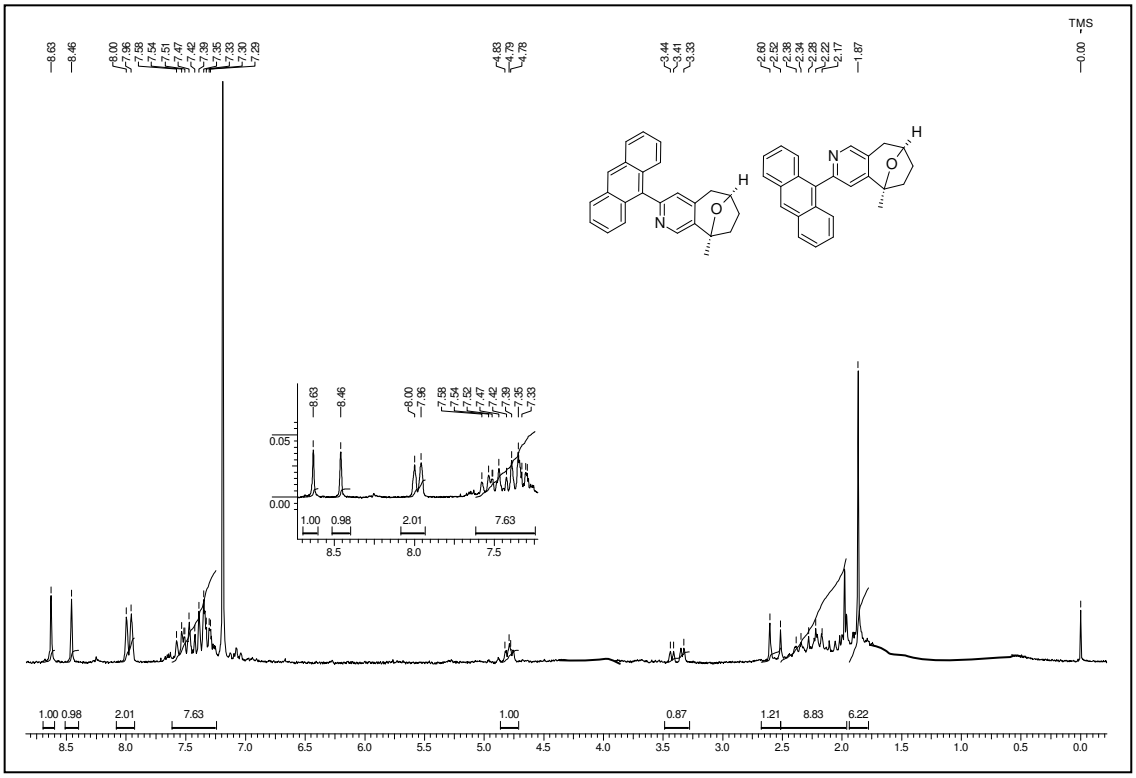
^{13}C NMR of compound 33 in $CDCl_3$



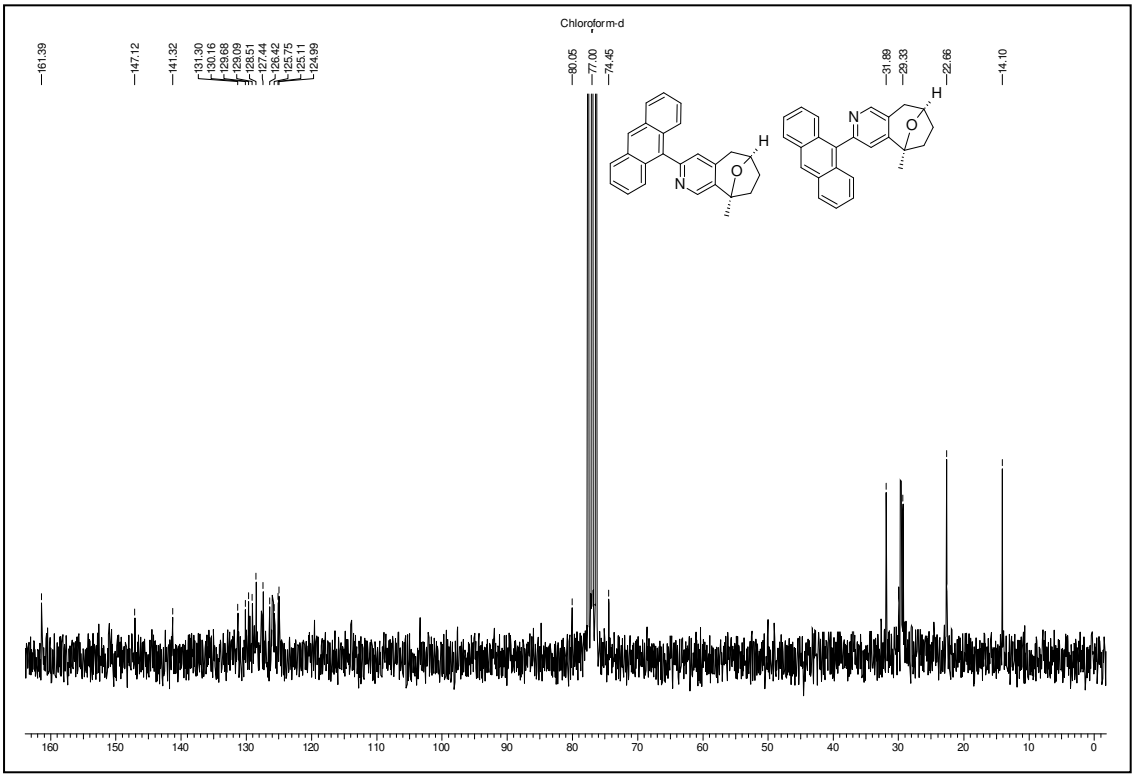
^{1}H NMR of compound 36/37 in $CDCl_3$



^{13}C NMR of compound 36/37 in $CDCl_3$



^{1}H NMR of compound 38/39 in $CDCl_3$



^{13}C NMR of compound 38/39 in $CDCl_3$

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Chapter III

Double Suzuki approach for the Synthesis of some 10-diarylmethylidene 1, 8-dichloanthraquinones

Introduction

Introduction

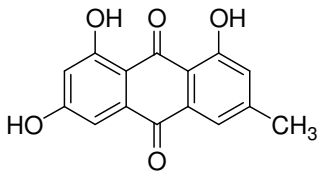
Each natural product shows some sort of biological activity i. e. antibacterial or anticancer or antiviral etc, but the major problem is the isolation of these compounds in sufficient quantities. Although synthesis is an alternative, this also does not provide, in majority of the cases, in sufficient quantities. To circumvent these problems scientists started designing the compounds which was inspired by the natural compounds. Designing should be in such a way that it should satisfy the following conditions.

1) Minimum perturbation of the basic chromophore of the natural product.
2) Easy to synthesize with minimum number of steps in major quantities.
3) Designing should be such that to provide a library of compounds.

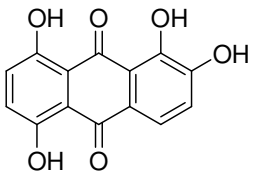
One of the biggest advantages of this process is we can make a library of compounds with minimal structural changes to fine tune the required biological activity.

In this regard, we paid attention on the anthraquinone substituted ligands as they showed several biological activities against many diseases. Anthraquinoes inhibit tau aggregation and dissolved Alzheimer's[2] paired helical filaments *in vitro* and *in cells*[1]. Several compounds from the family of anthraquinones including emodin, daunorubicin, adriamycin (**Figure 1**) and others were able to inhibit PHF (paired helical filaments) with IC_{50} values of 1-5 μM and to disassemble preformed PHFs at DC_{50} values of 2-4 μM.

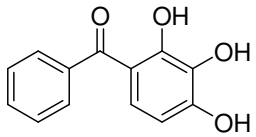
Figure 1:



Emodin (**1**)



PHF016 (**2**)



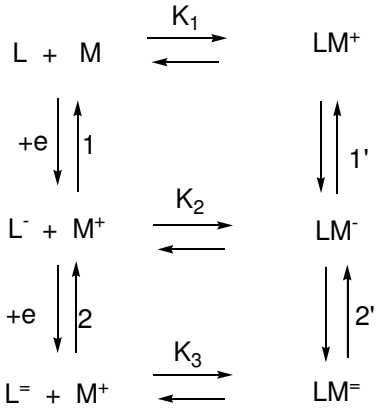
PHF005 (**3**)

The above compounds (**1**-**3**) are able to inhibit the transition from soluble to aggregated K19 protein, but they differ in their efficiency. Using fixed protein concentrations of K19 at 10 μM and tested the compounds in a concentration range from 10 pM to 200 μM and determined IC_{50} values. Inhibitory effects begin to appear at ~0.1 μM (ratio of Protein to compound = 100) and each nearly complete inhibition

at 100 μM compound (ratio of protein to compound = 0.1).

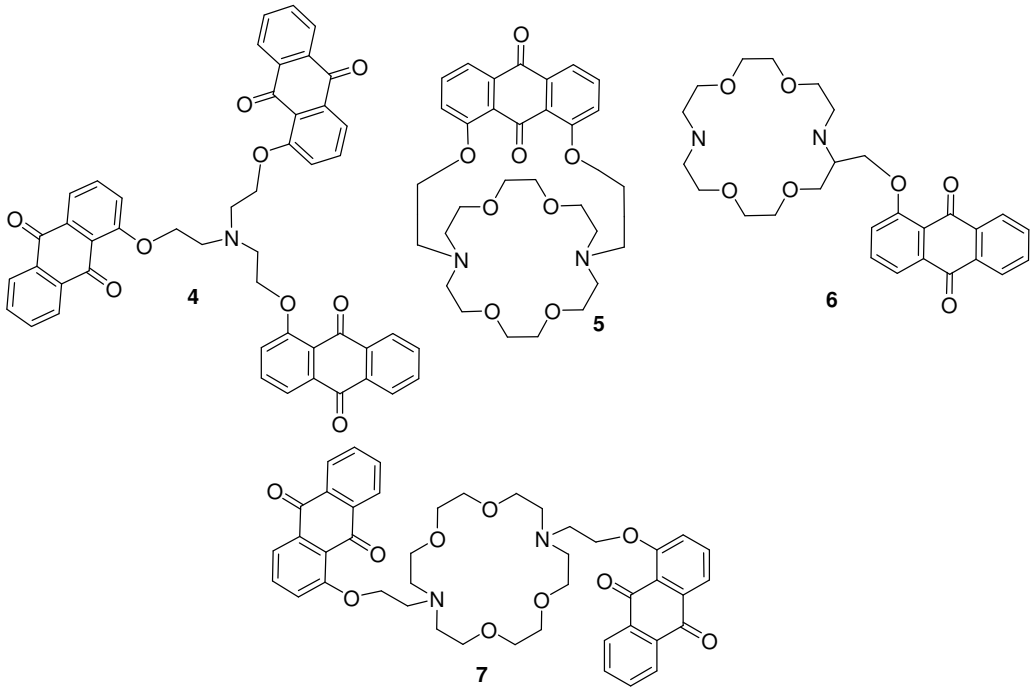
Anthraquinone substituted ligands (podants, crown ethers and cryptands) have been used as electrochemically switched systems capable of enhanced cation binding and enhanced transport across model membranes. The principle behind this phenomenon is coupling of the redox processes of the quinones to the cation binding equilibria.

Scheme 1



Scheme 1 shows the reduction properties of the anthraquinone ligands. The electrochemical processess 1 and 2 correspond to the reduction steps of the free ligand while the 1' and 2' shows the reduction steps of ligand-cation binding equilibria. The

Figure 2:

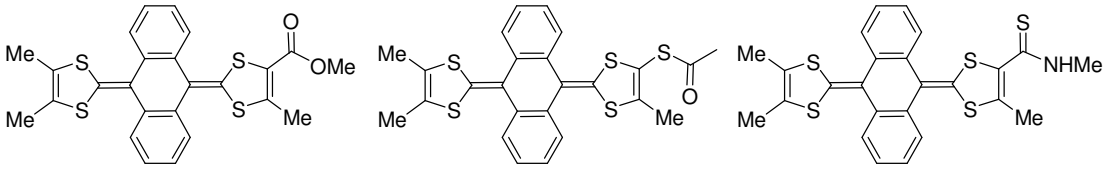


binding enhancements K2/K1 and K3/K2 are typically $\leq 10^3$ [2,4] and have been used to enhance cation binding transport rates across model liquid membranes. Since the reduced states of anthraquinone group are stable in aqueous media at neutral pH, these anthraquinone-containing ligands are potentially useful as cation-, electron-, and proton-transporting systems across membranous materials.

As shown in **Figure 2**, compounds **4-7** which are the derivatives of anthraquinones and cryptands/crown ethers are practically tested and proven cation binding and transport enhancers across the biological membranes.

Anthrquinones of the *Rubiaceace* family exhibit some interesting biological activities such as antimalarial, antifungal, hypotensive, analgesic, antimalarial, antioxidant, antileukemic and mutagenic functions[5].

Figure 3:

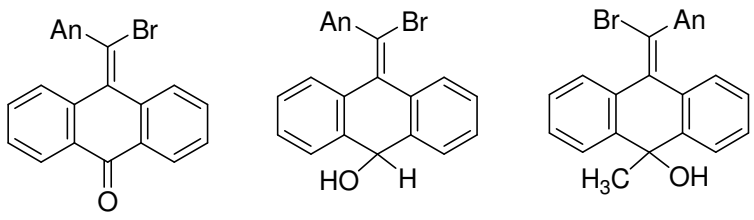


8 **9** **10**

Another class of anthraquinone substituted compounds that are the building blocks for supramolecular and organic material chemistry[7] (**8**-**10**) are terathiafulvalene derivatives[6] (**Figure 3**) which possess extended Π-extended conjugation. Especially in materials chemistry the usage of these derivatives have been increasing day by day. The basic property and the principle, responsible for this, is the extensive conjugation of these derivatives in which electronic conductance and other related properties are enhanced.

Some classes of anthraquinone related compounds (**11-13**, **Scheme 2**) are studied extensively for the 1,4-, 1,10-, and 1,2- eliminations and 1,7 rearrangments.[8]

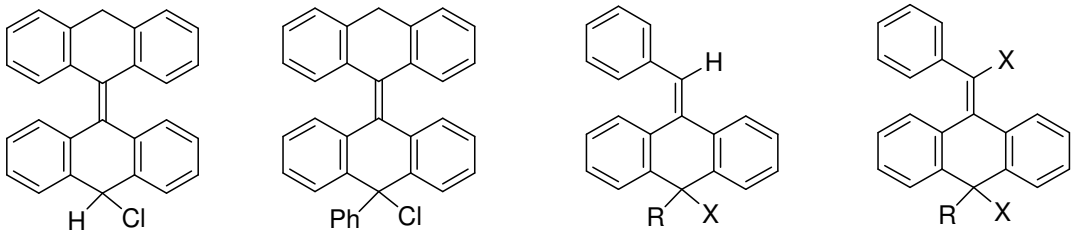
Scheme 2



11 **12** **13**

Some other derivatives (**14-24, Scheme 3**) have been studied for the nucleophilic (LAH, $NaBH_4$, NaN_3, NaSCN, NaSPh, KOH, MeOH, MeMgI, NaOMe, PhMgBr etc.) Substitution at the ring position.[9]

Scheme 3



14 **15** R = OH, Cl, Br (**16**, **17**, **18**) X = Me, Ph, p-OMe (**19**-**21**) X = OH, Cl, Br (**22**, **23**, **24**)

Although there are many literature reports on these anthraquinone derivatives (as above said reports and much more) a little has been focused on it synthesis. Inspired by these biological activities coupled with the lack of synthetic methods for the substituted anthraquinones, we undertook this challenge and designed a basic skeleton (**Figure 3**) so as to satisfy the above conditions.

Figure 3:

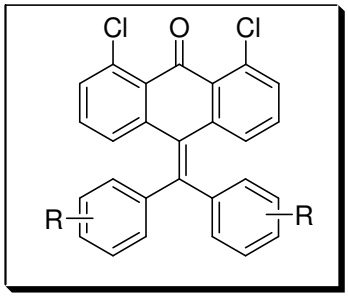


Figure 3 shows our design of the basic skeleton which reveals the following features

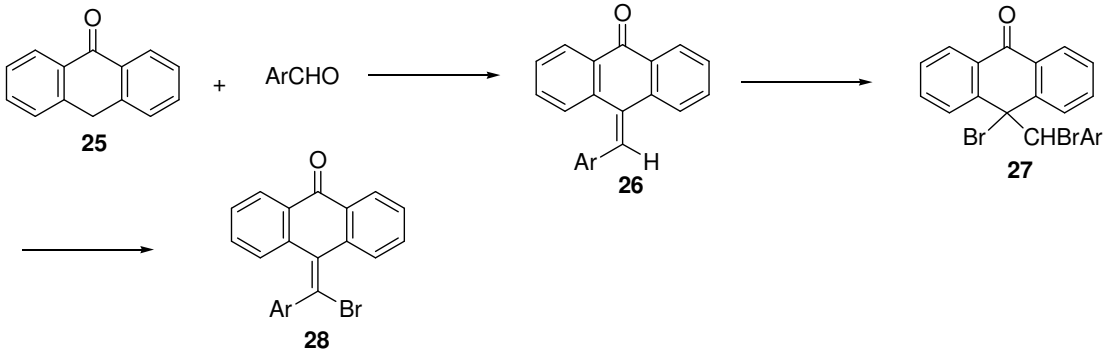
1) The structure has the basic anthraquinone chromophore.
2) Two additional substituted aromatic rings were attached to enhance its receptor binding as well as other non-covalent interactions
3) Two chloro groups on C_1 and C_8 which are meant for replacement with the required polar group (like alkoxy, crown ethers, sugars and cryptands) to increase its solubiblity properties as well as these chloro groups provide two additional binding sites for the receptors.

4) We designed so as to synthesize very easily with the commercially available starting materials with minimum number of steps.
5) R groups on the aromatic ring are ranges from non polar (like Me, Ph etc) to polar groups (like NO_2, OAc etc) which alters the physical properties.

Literature reports :

Although there are no reports on the synthesis of exact compounds, few reports are there on the synthesis of related compounds.[8]

Scheme 4



Anthrone **25** was condensed with the respective aldehyde in the presence of a base like pyridine to furnish the monoaryl methylidene anthraquinones (**Scheme 4**) in moderate to good yields. Although this reaction works well for the aldehydes, ketones reacts sluggishly With the substituted anthraquinones due to steric strain which means preparation of diaryl methylidene anthraquinones by this method is very difficult.

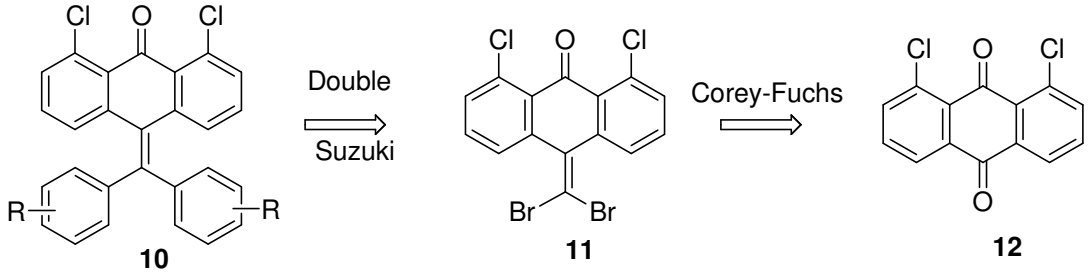
Present work

Present work

Due to lack of literature reports for the synthesis of these compounds coupled with their biological properties, here in we report the synthesis of diarylmethylidene 1, 8-dichloro anthraquinones.

Retrosynthetic analysis :

Scheme 5



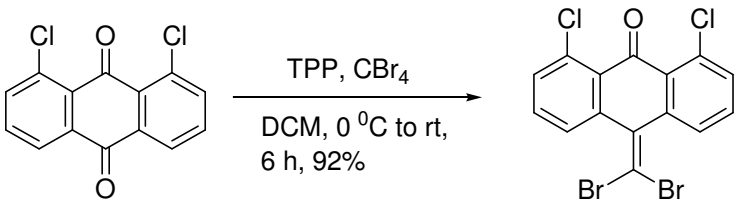
10 **11** **12**

Antithetic analysis is shown in **Scheme 5**. A double Suzuki retron of **10** would reveal the dibromo derivative **11** which could be easily accessed from commercially available 1, 8-dichloro anthraquinone **12** by regioselective Corey-Fuchs dibromo olefination.

Present work:

Our synthesis began with commercially available 1, 8-dichloro anthraquinone **12** which was subjected to Corey-Fuchs reaction conditions[10] with TPP and CBr_4 in DCM for 6h to furnish the dibromolefine **11** in 92% of yield. The product structure was confirmed by its spectral data.

Scheme 6

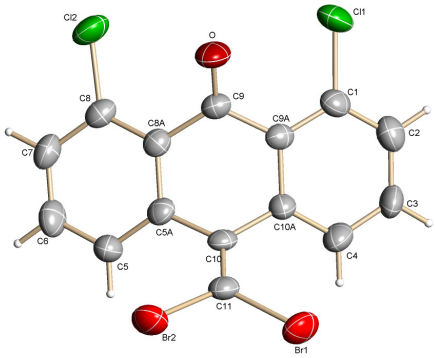


12 **11**

For example in ^{13}C NMR one of the carbonyl carbons was disappeared and two olefinic carbons were seen at 126.57 and 95.6 ppm respectively. The carbon attached two bromo atoms was resonated upfield at 95.6 ppm which is the characteristic of

dibromo derivative. Three peaks in EIS-MS spectrum with an intensity ratio of 1:2:1 at m/z 432.8, 434. 8 and 436.7 respectively, which is an additional support of the product. The problem of its regioselectivity was solved from its single crystal x-ray structure (**Figure 4**) which showed that dibromoolefination has taken place at C_{10} of the 1, 8-dichloro anthraquinone, as was anticipated.

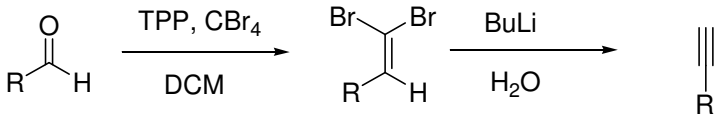
Figure 4: ORTEP diagram of dibromo compound



A brief overview of Corey-Fuchs reaction[10]

*The **Corey-Fuchs reaction** is a series of chemical reactions designed to transform an aldehyde into an alkyne (**Scheme 7**). The reaction is named after its discoverers, American chemists Elias James Corey and Philip L. Fuchs.*

Scheme 7

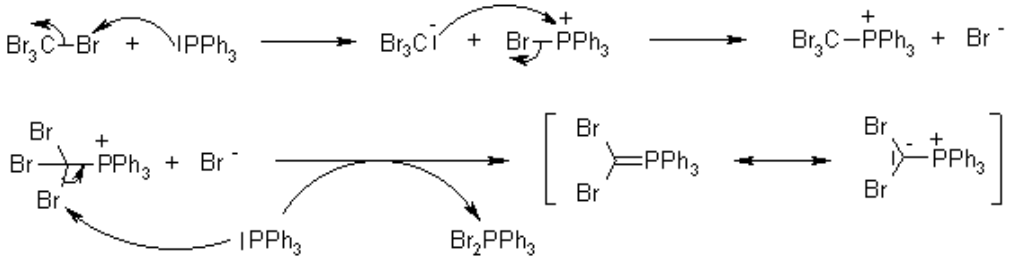


*This two step methodology allows the preparation of terminal alkynes by one-carbon homologation of an aldehyde. The first step is comparable to a **Wittig Reaction**, and leads to a dibromoalkene. Treatment with a lithium base (BuLi, LDA) generates a bromoalkyne intermediate via dehydrohalogenation, which undergoes metal-halogen exchange under the reaction conditions and yields the terminal alkyne upon work-up. A modification of the Corey-Fuchs Reaction involves the reaction of the intermediate alkynyllithium with an electrophile prior to aqueous work-up, giving a chain*

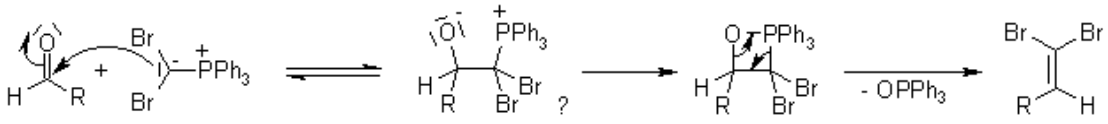
extension product:

Mechanism:

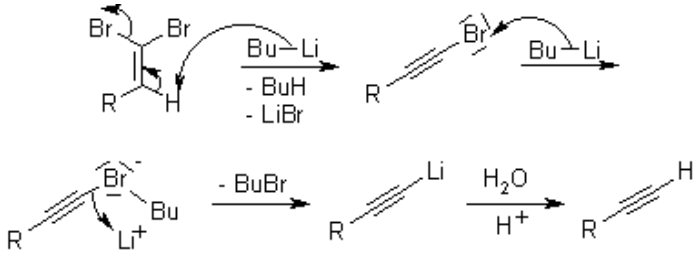
The Corey-Fuchs reaction is based on a special case of the Wittig Reaction, where the phosphorus ylide is formed from dibromocarbene. This carbene is generated in situ from the reaction of Triphenylphosphine and carbon tetrabromide. In the formation of the ylide from CBr_4, two equivalents of triphenylphosphine are used. One equivalent forms the ylide while the other acts as reducing agent and bromine scavenger. Triphenylphosphine then attacks the nascent carbene to form the reactive ylide. This ylide undergoes a Wittig Reaction when exposed to an aldehyde.



The addition of the ylide to the aldehyde



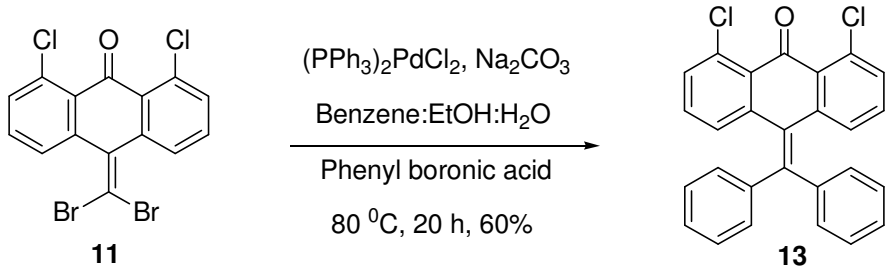
Reaction of the dibromoalkene with BuLi



Deprotonation of the weakly acidic olefinic proton with butyllithium gives rise to a lithio-olefinic species which can undergo a beta-elimination to produce the

bromoalkyne. Further treatment with butyllithium allows for a lithium-halogen exchange and the intermediate can be quenched with an electrophile, such as water or an alkyl halide, transforming the bromoalkyne to the terminal acetylene, or the internal alkyne, respectively.

Scheme 8



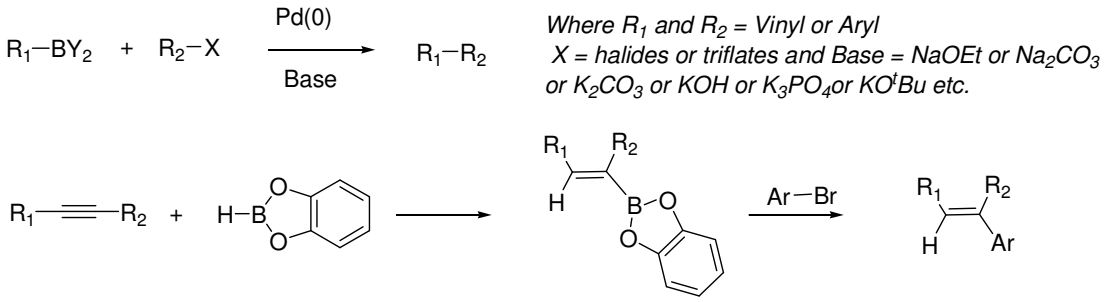
11 **13**

After having the dibromo derivative in hand, our next concern was the double Suzuki coupling reaction[11], which was developed in our laboratory, with the various aryl boronic acids. Our initial attempts to optimize the reaction conditions were carried out with simple phenylboronic acid. After a careful examination of various reaction conditions, such as reaction temperature, reaction time, base, solvent and amount of phenylboronic acid, we concluded that the best results for the intended double-Suzuki reaction were achieved by using a suspension of benzene-ethanol-water as a solvent, Na_2CO_3 as a base, conducting the reaction at 70–80 °C and addition of catalyst $Pd(PPh_3)_2Cl_2$ (7.5 mol%) and phenylboronic acid (1.5 eq) twice to the reaction mixture in 10 h interval (**Scheme 8**) to furnish product **13** in 60% yield.

A brief overview of Suzuki (Miyaura-Suzuki) coupling

*The **Suzuki reaction** is the organic reaction of an aryl- or vinyl-boronic acid with an aryl- or vinyl-halide catalyzed by a palladium(0) complex.[12, 13] It is widely used to synthesize poly-olefins, styrenes, and substituted biphenyls (**Scheme 9**). Since first bieng published in 1979, the Suzuki coupling of a boronic acid with a halide or triflate has developed into one of the most important cross coupling reactions, totalling about a quarter of all current palldium-catalysed cross coupling*

Scheme 9

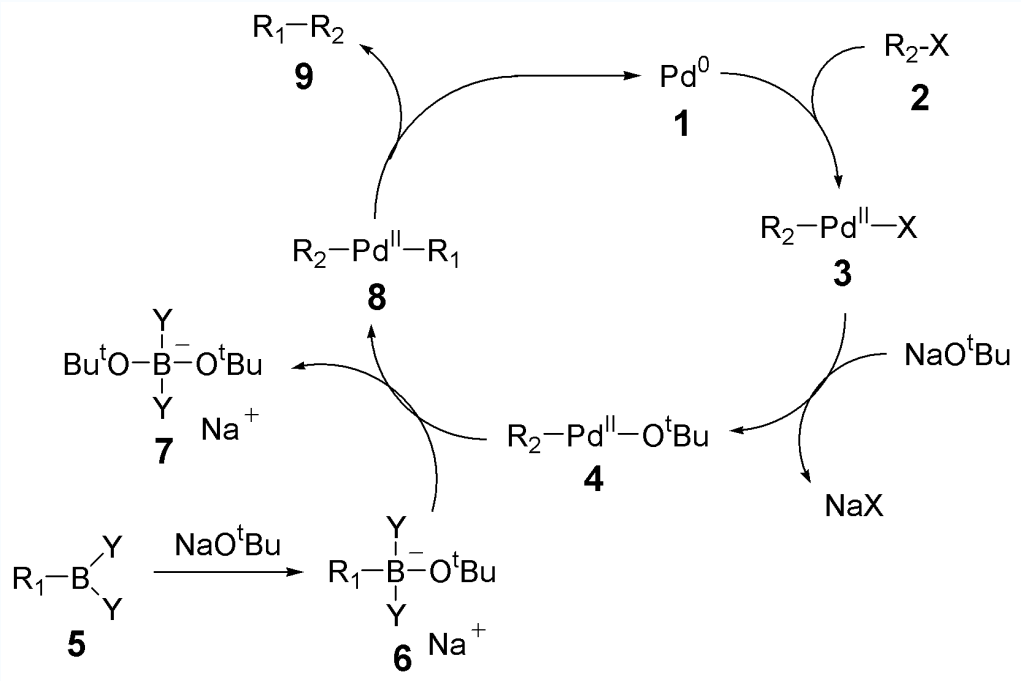


reactions. The original version consisted of hydroboration of an alkyne with catecholborane, followed by palladium(0)-catalysed coupling of resuling vinyl boronate with an aromatic iodide or bromide. The hydroboration is generally regioselective for the less hindered position and addition of boron and hydrogen occurs cis stereospecifically. The reaction relies on a palladium catalyst such as tetrakis(triphenylphosphine)palladium(0) to effect part of the transformation. The palladium catalyst (more strictly a pre-catalyst) is 4-coordinate, and usually involves phosphine supporting groups.

Relative reactivity: R_2-I > R_2-OTf > R_2-Br >> R_2-Cl

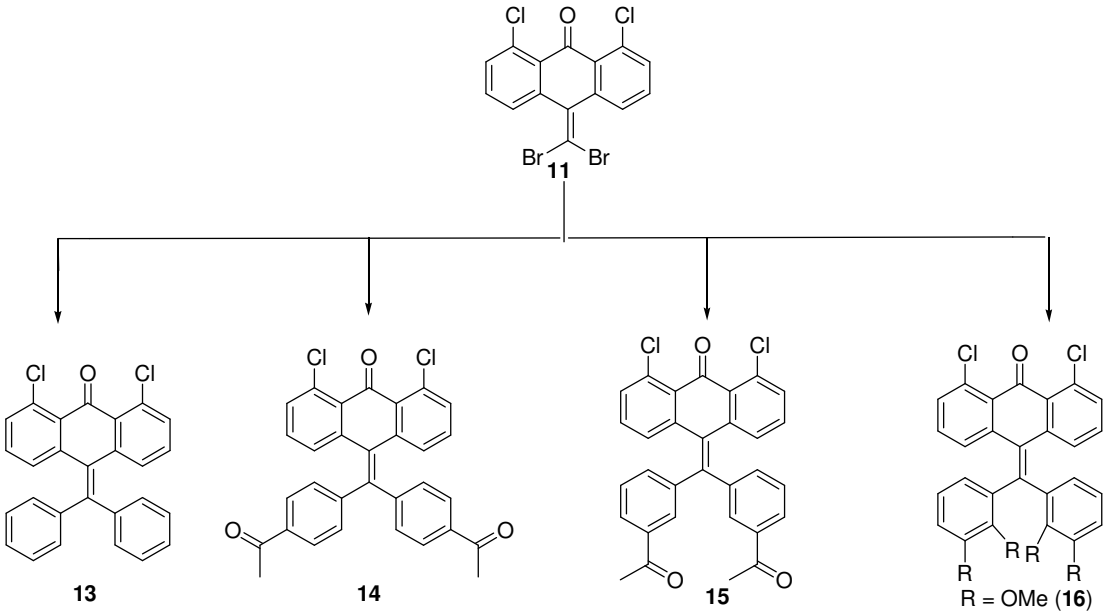
The mechanism of the Suzuki reaction is best viewed from the perspective of the palladium catalyst. The first step is the oxidative addition of palladium to the halide ***2*** *to form the organo-palladium species* ***3****. Oxidative addition proceeds with retention of stereochemistry with vinyl halides, while giving inversion of stereochemistry with allylic and benzylic halides. The oxidative addition initially forms the cis-palladium complex, which rapidly isomerizes to the trans-complex. Reaction with base gives intermediate* ***4****, which via transmetallation[14] with the boron-ate complex* ***6*** *forms the organopalladium species* ***8****. Reductive elimination of the desired product* ***9*** *restores the original palladium catalyst* ***1.*** *The important difference between Stille and the Suzuki is the transmetallation step, which explains the need for an additional base, usually sodium or potassium ethoxide or hydroxide, in the Suzuki coupling. The base accelerates the transmetallation step leading to the borate directly presumable via a more nucleophilic 'ate 'complex. As in the Stille coupling, the geometry of the both the unsaturated compounds is preserved during the coupling so this is an excellent*

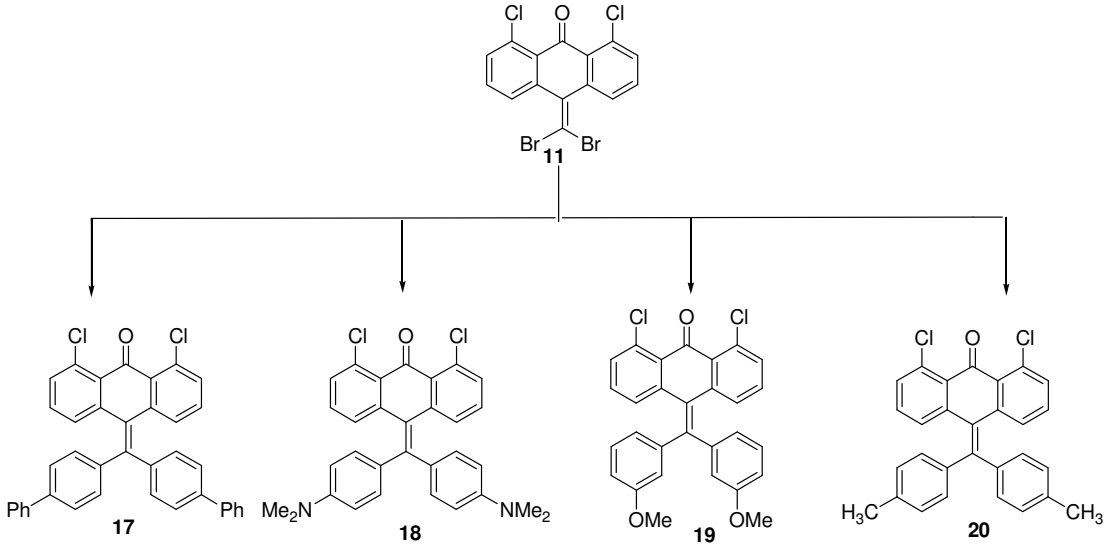
Mechanism:



method for stereospecific diene synthesis.[15] After the establishment of standard experimental procedure for the intended double Suzuki reaction, later we performed the same reaction with the substituted aryl

Scheme 10



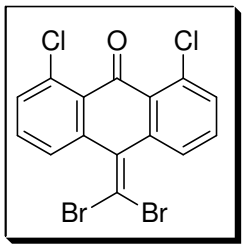


S.No	Boronic acid	Yield (%)	M.P
1	Phenyl boronic acid	60%	235-238
2	4-biphenyl boronic acid	68%	110.4-112
3	4-methyl Phenyl boronic acid	70%	266-268
4	3-methoxy Phenyl boronic acid	71%	232.5-235
5	2,3-dimethoxy Phenyl boronic acid	52%	178.8-181
6	4-NMe_2 Phenyl boronic acid	73%	219.8-222
7	3-acetyl Phenyl boronic acid	85%	282-284
8	4-acetyl Phenyl boronic acid	82%	290.8-292

boronic acids (both electron rich and electron deficient) and the Products thus obtained were purified by column chromatography to furnish the pure compounds and characterised by all the spectral data (^{1}H NMR, ^{13}C NMR, mass and IR spectral data) (**Scheme 10**).

Experimental

9-(dibromomethylene)-4,5-dichloroanthracen-10(9H)-one (11):



To an ice cold solution of CBr_4 (1 g, 1.803 mmol) and anthraquinone **12** in DCM (20 ml) was added TPP (3.78 g, 14.43 mmol) and stirred for 10 min, warmed to room temperature, stirred for 6h. Diluted with pet ether, filtered over celite washed with ether and purified by column chromatography using ethyl acetate/hexane (1:10) as an eluent to yield the dibromo compound **11** as light yellow crystalline solid.

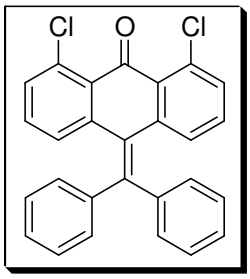
Crystal Data: Single crystals of the compound were grown by slow evaporation of the solution mixture in Benzene and DCM. Colourless crystal of approximate size 0.30 x 0.16 x 0.12 mm, was used for data collection on *Bruker SMART APEX* CCD diffractometer using Mo K_α radiation with fine focus tube with 50kV and 30mA. θ range 2.67 to 25.00 º, SADABS correction applied , C15 H6 Br2 Cl2 O, *M* = 432.92. Crystals belong to Triclinic, P-1, *a* = 7.6891(8), *b* = 7.6891(7), *c* = 12.1921(9) Å, *V* = 714.34(11) $Å^3$, *Z* = 4, D_c = 2.013 mg m^{-3}, *T* = 293(2) K, 3725 reflections measured, 1458 unique [I>2σ(I)], R value 0.0332, wR2 = 0.0656. SHELX-97 (ShelxTL)[ref] was used for structure solution and full matrix least squares refinement on F^2. Hydrogen atoms were included in the refinement as per the riding model.

Yield	: 92 %
Mol. Formula	: $C_{15}H_6Br_2Cl_2O$.
Melting Point	: 238-239 ^{0}C
IR ($CHCl_3$) ṽ	: 3019, 2972.85, 2972.67, 1683.95, 1584.5, 1569.2, 1448.52, 1421.58, 1282.54, 1215.81, 1130.72, 921.61, 822.31, 755.49, 698.88, 669.10 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 7.38 (t, 8.08, 7.23 Hz, 2H); 7.455 (dd, *J* = 8.09, 1.64 Hz, 2H), 7.855 (dd, *J* =7.23, 1.64 Hz, 2H).
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ 95.11 (s), 126.57 (d), 130.86 (d), 131.30 (d), 131.46 (s), 132.10 (s), 135.67 (s), 138.68 (s), 183.37(s).
Elemental Analysis	Calcd.: C, 41.62; H, 1.40

Found: C, 42.8; H, 1.21

ESI-MS (m/z) : 432.6 $(M)^+$

10-Benzhydrylidene-1,8-dichloro-10H-anthracen-9-one (13) :-



To a solution of compound **2** (0.5 g, 1.155 mmol) in benzene (40 ml), $(PPh_3)_2PdCl_2$ (0.881 g, 0.155 mmol), Na_2CO_3 (0.306 g, 2.8875 mmol), 3-acetyl phenylboronicacid (0.285 g, 1.7325 mmol), EtOH (2 ml) and distilled water (2 ml) were added at once, degassed under argon for 5 min, heated to 80 ^{0}C and stirred for 10h. The reaction mixture was cooled to rt catalyst (0.081 g, 0.155 mmol) and boronic acid (0.285 g, 1.7325 mmol) were added, heated to 80 ^{0}C and stirred for 10h. Solvent was removed, filtered over celite and extracted into ethyl acetate, purified by column chromatography (230-400 mesh) using EtOAc/hexane (2:8) as an eluent to deliver compound 1**3** as yellow solid.

Yield : 92 %

Mol. Formula : $C_{27}H_{16}Cl_2O$

Melting Point : 235-238 ^{0}C

IR ($CHCl_3$) $\tilde{\nu}$: 3019.74, 1685.30, 1450.45, 1215.93, 1141.45, 757.59, 668.77 cm^{-1}.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 6.94 (t, J = 7.83, 7.46 Hz, 2H), 7.005 (dd, J = 7.84, 1.65 Hz, 2H), 7.19-7.28 (m, 12H).

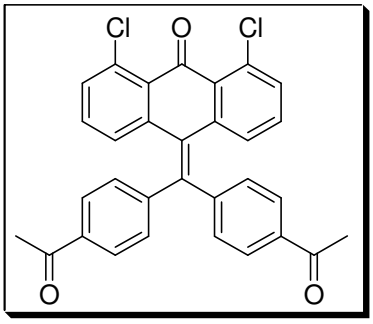
^{13}C NMR ($CDCl_3$, 50 MHz) : δ 184.72 (s), 146.68 (s), 141.52 (s), 140.18 (s), 132.41 (s), 132.37 (s), 131.70 (d), 130.86 (d), 130.27 (d), 130.86 (s), 129.77 (d), 128.95 (d). 128.56 (d), 127.31 (d), 127.36 (d).

Elemental Analysis Calcd.: C, 75.89; H, 3.77

Found: C, 75.34; H, 3.92

ESI-MS (m/z) : 428.37 $(M+1)^+$

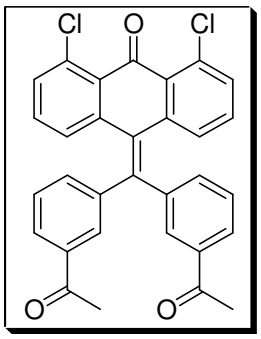
10-[Bis-(4-acetyl-phenyl)-methylene]-1,8-dichloro-10H-anthracene-9-one (14) :-



To a solution of compound **11** (0.5 g, 1.155 mmol) in benzene (40 ml), $(PPh_3)_2PdCl_2$ (0.081 g, 0.155 mmol), Na_2CO_3 (0.306 g, 2.8875 mmol), 4-acetyl phenyl boronicacid (0.285 g, 1.7325 mmol), EtOH (2 ml) and distilled water (2 ml) were added at once, degassed under argon for 5 min, heated to 80 ^{0}C and stirred for 10h. The reaction mixture was cooled to rt catalyst (0.081 g, 0.155 mmol) and boronic acid (0.285 g, 1.7325 mmol) were added, heated to 80 ^{0}C and stirred for 10h. Solvent was removed, filtered over celite and extracted into ethyl acetate, purified by column chromatography (230-400 mesh) using EtOAc/hexane (2:8) as an eluent to furnish compound **14** as yellow solid.

Yield	: 82 %
Mol. Formula	: $C_{31}H_{20}Cl_2O_3$
Melting Point	: 290.8-292 ^{0}C
IR ($CHCl_3$) ṽ	: 2924.16, 1685.41, 1585.97, 1461.88, 1376.98, 1266.90, 1119.98, 928.81, 696.23cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 2.56 (s, 6H), 6.985 (dd, J = 7.96, 7.83, 2H), 6.975 (d, *J* =5.44 Hz, 2H), 7.29 (dd, *J* = 5.43, 3.46, Hz, 2H), 7.35 (d, *J* = 8.5Hz, 4H), 7.865 (d, *J* = 8.6 Hz, 4H).
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ 26.53(q), 127.03(d), 128.73(d), 129.32(d), 130.43(d), 130.66(d), 131.60(s), 132.16(s) 132.23(s), 136.01(s), 139.24(s), 143.93(s), 145.52(s), 184.22(s), 197.28(s).
Elemental Analysis	Calcd.: C, 72.81; H, 3.94 Found: C, 73.34; H, 4.06
ESI-MS (m/z)	: 512.02 $(M+1)^+$

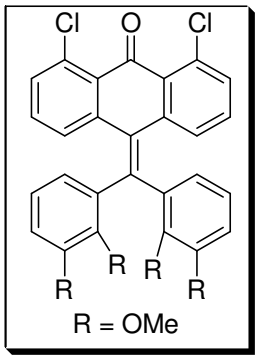
10-[Bis-(3-acetyl-phenyl)-methylene]-1,8-dichloro-10H-anthracene-9-one (15) :-



To a solution of compound **11** (0.500 g, 1.155 mmol) in benzene (40 ml), $(PPh_3)_2PdCl_2$ (0.081 g, 0.155 mmol), Na_2CO_3 (0.306 g, 2.8875 mmol), 3-acetyl phenylboronicacid (0.285 g, 1.7325 mmol), EtOH (2 ml) and distilled water (2 ml) were added at once, degassed under argon for 5 min, heated to 80 ^{0}C and stirred for 10h. The reaction mixture was cooled to rt catalyst (0.081 g, 0.155 mmol) and boronic acid (0.285 g, 1.7325 mmol) were added, heated to 80 ^{0}C and stirred for 10h.Solvent was removed, filtered over celite and extracted into ethyl acetate, purified by column chromatography (230-400 mesh) using EtOAc/hexane (2:8) as an eluent to provide compound **15** as yellow solid.

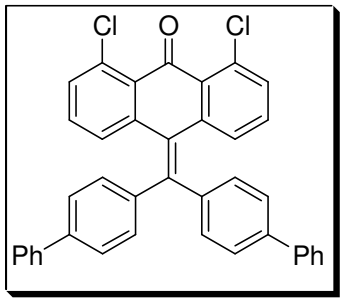
Yield	: 85 %
Mol. Formula	: $C_{31}H_{20}Cl_2O_3$
Melting Point	: 282-284 ^{0}C
IR ($CHCl_3$) $\tilde{\nu}$	: 3019.50, 1685.66, 1585.70, 1451.09, 1421.11, 1358.50, 1282.63, 1215.86, 756.38, 668.57 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 2.52 (s, 6H), 6.955 (dd, J = 7.96,7.83 Hz, 2H), 6.945 (d, J =6.06 Hz, 2H), 7.285 (dd, J = 6.06, 2.90 Hz, 2 H), 7.34-7.39 (m, 4H), 7.78-7.83 (m, 4H), 7.90 (m, 2H).
^{13}C NMR ($CDCl_3$, 50 MHz)	:δ 26.67(q), 127.21(d), 127.68(d), 128.63(d), 129.15(d), 130.35(d), 130.56(d), 131.66(s), 132.22(s), 132.40(s), 133.78(d), 137.41(s), 139.48(s), 141.49(s), 143.92(s), 184.26(s), 197.45(s).
Elemental Analysis	Calcd.: C, 72.81; H, 3.94 Found: C, 73.12; H, 3.87
ESI-MS (m/z)	: 512.2 $(M+1)^+$

10-[Bis- (2,3-dimethoxy-phenyl)-methylene]-1,8-dichloro-10H-anthracen-9-one (16) :-



Yield	: 52 %
Mol. Formula	: $C_{31}H_{24}Cl_2O_5$
Melting Point	: 235-238 ^{0}C
IR ($CHCl_3$) ṽ	: 2931.19, 1685.75, 1585.92, 1474.02, 1449.97, 1282.34, 1257.39, 1226.20, 1073.41, 1006.00, 756.89, 694.45, 665.93 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 3.64 (s, 6H), 3.7764 (s, 6H), 6.75 (dd, *J* =7.95, 1.38 Hz, 2H), 6.89 (t, *J* =7.96, 7.70 Hz, 2H), 6.99 (t, *J* =8.09, 7.70 Hz, 4H), 7.22 (s, 2H), 7.26 (s, 2H).
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ 55.61 (q), 60.19 (q), 111.96 (d), 123.12 (d), 123.40 (d), 126.26 (d), 129.62 (d), 130.34 (d), 131.39 (s), 132.15 (s), 132.29 (s), 135.09 (s), 140.37 (s), 140.51 (s), 145.96 (s), 152.42 (s), 184.62 (s).
Elemental Analysis	Calcd.: C, 68.02; H, 4. 24 Found: C, 68.62; H, 4.37
ESI-MS (m/z)	: 570.36 $(M+23)^+$

10-(Bis-biphenyl-4-yl-methylene)-1,8-dichloro-10H-anthracen-9-one (17) :-



Yield : 73 %

Mol. Formula : $C_{39}H_{24}Cl_2O$

Melting Point : 232.5-235 ^{0}C

IR ($CHCl_3$) ṽ : 3019.65, 1686.45, 1586.05, 1486.41, 1450.38, 1215.70, 1141.45, 757.56, 669.00 cm^{-1}.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 6.89 (t, *J* =7.96, 7.83 Hz, 2H), 7.025 (dd, *J* = 7.95, 1.14 Hz, 2H), 7.17-7.23 (m, 4H), 7.25-7.30 (m, 6H), 7.34-7.38 (m, 5H), 7.42-7.50 (m, 5H).

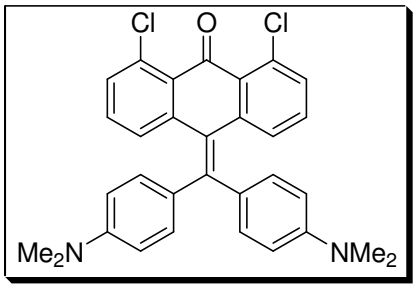
^{13}C NMR ($CDCl_3$, 50 MHz) : δ 126.90 (d), 127.20 (d), 127.36 (d), 127.54 (d), 128.80 (d), 129.53 (d), 129.86 (d), 130.34 (s), 130.43 (d), 131.78 (s), 132.37 (s), 140.09 (s), 140.12 (s), 140.18 (s), 140.38 (s), 145.96 (s), 184.76 (s) (s), 141.46 (s), 148.54 (s), 149.42 (s), 185.24 (s).

Elemental Analysis Calcd.: C, 80.83; H, 4.17

Found: C, 81.34; H, 4.27

ESI-MS (m/z) : 579.6 $(M)^+$

10-[Bis-(4-dimethylamino-phenyl)-methylene]-1,8-dichloro-10H-anthracen-9-one (18) :-



Yield : 73 %

Mol. Formula : $C_{31}H_{26}Cl_2N_2O$.

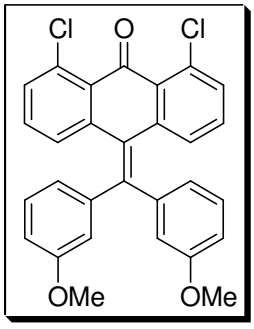
Melting Point : 292-294 ^{0}C

IR ($CHCl_3$) ṽ : 3019.61, 1685.01, 1607.45, 1586.02, 1519.20, 1448.79. 1357.43, 1216.14, 756.47, 668.35 cm^{-1}.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 2.91 (s, 12H), 6.56 (d, *J* = 8.84 Hz, 4H), 6.995 (d, *J* = 8.97 Hz, 4H), 6.94-7.03 (m, 2H), 7.165 (dd, *J* = 7.96, 1.03 Hz, 2H), 7.225 (dd, *J* = 7.84, 1.01 Hz, 2H).

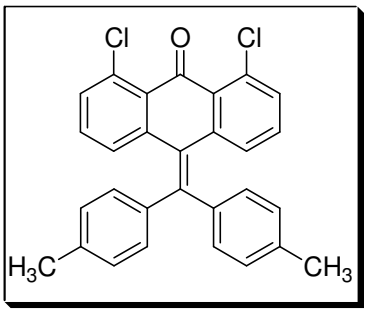
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ 40.26 (q), 111.85 (d), 127.32 (d), 128.84 (d), 130.08 (d), 130.57 (d), 131.17 (s), 132.10 (s), 141.46 (s), 148.54 (s), 149.42 (s), 185.24 (s).
Elemental Analysis	Calcd.: C, 68.02; H, 4. 24 Found: C, 68.62; H, 4.37
ESI-MS (m/z)	: 514.2 $(M+1)^+$

10-[Bis- (3-Methoxy-phenyl)-methylene]-1,8-dichloro-10H-anthracene-9-one (19).



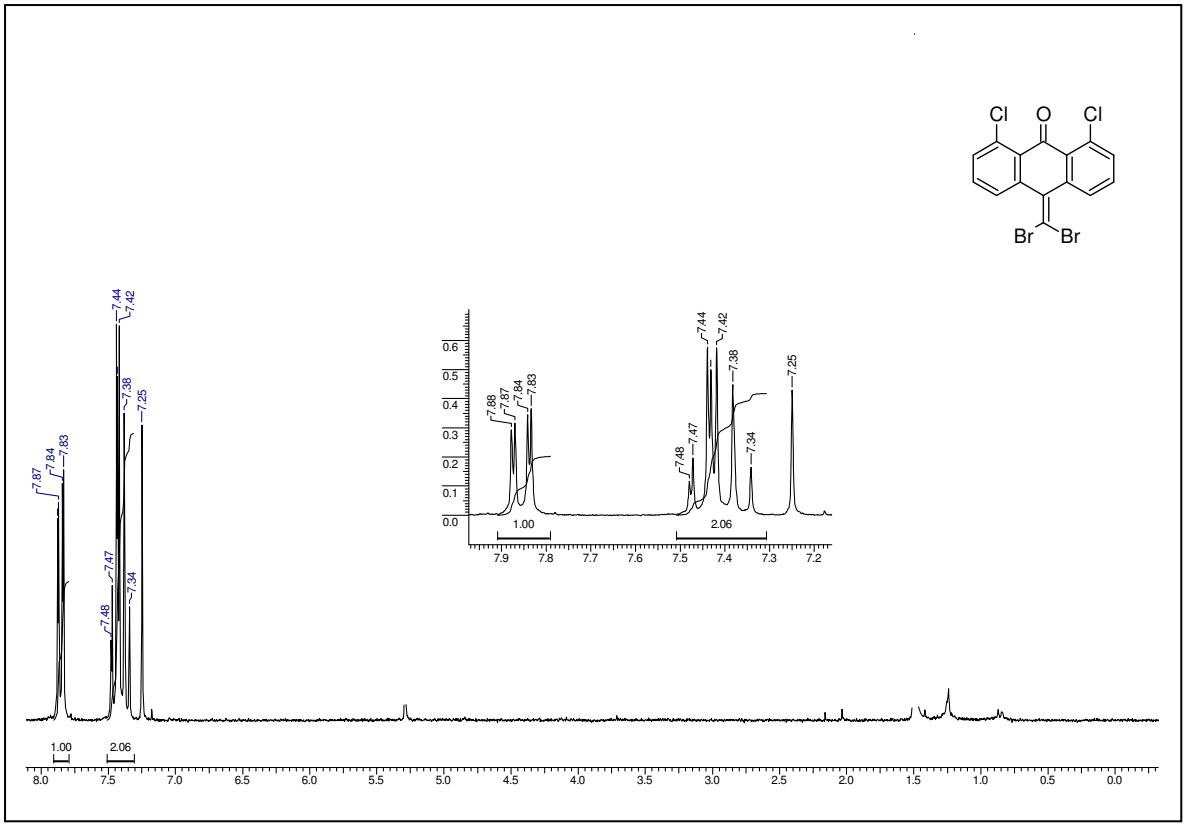
Yield	: 70 %
Mol. Formula	: $C_{29}H_{20}Cl_2O_3$
Melting Point	: 232.5 – 235 ^{0}C
IR ($CHCl_3$) ṽ	: 2924.16, 1685.41, 1585.97, 1461.88, 1376.98, 1266.90, 1119.98, 928.81, 696.23 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 3.70 (s, 6H), 6.71-6.76 (m, 4H), 6.815 (dt, *J* =7.73, 1.26 Hz, 2H), 6.97 (t, *J* = 7.83 Hz, 2H), 7.085 (dd, , *J* =7.83, 1.26 Hz, 2H), 7.165 (dd, , *J* =8.84, 7.85Hz, 2H), 7.27 (dd, , *J* = 7.71, 1.26 Hz, 2H).
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ 55.23 (q), 112.71 (d), 114.69 (d), 121.52 (s), 127.19 (d), 129.64 (d), 129.85 (d), 129.96 (s), 130.06 (d), 130.40 (d), 131.70 (s), 132.24 (s), 140.12 (s), 142.68 (s), 159.58 (s), 184.71 (s).
Elemental Analysis	Calcd.: C, 71.47; H, 4.14 Found: C, 72.32; H, 4.31
ESI-MS (m/z)	: 512.06 $(M+1)^+$

10-[Bis-(4-methylphenyl)-methylene]-1,8-dichloro-10H-anthracene-9-one (20) :-

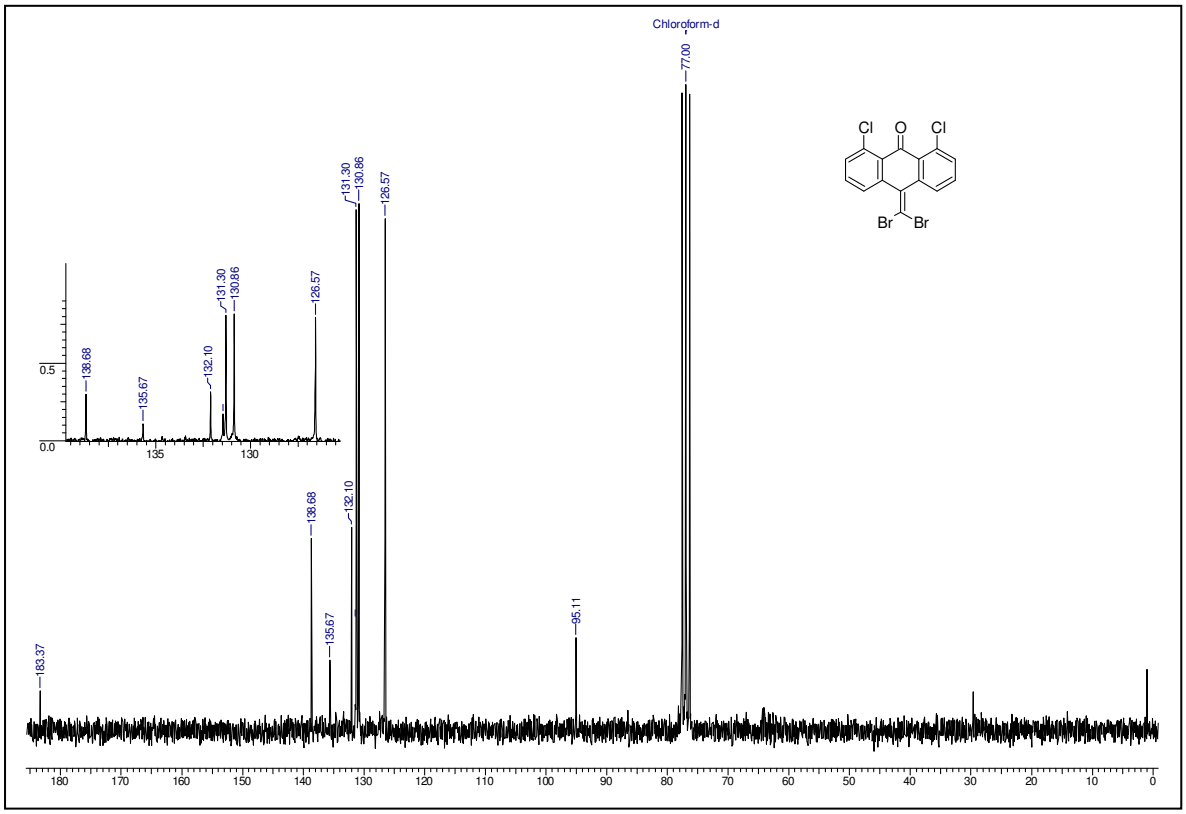


Yield	: 70 %
Mol. Formula	: $C_{29}H_{20}Cl_2O$
Melting Point	: 266 – 268 ^{0}C
IR ($CHCl_3$) $\tilde{\nu}$	: 3019.91, 1686.46, 1586.58, 1508.06, 1450.36, 1215.78, 759.05, 669.03 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 2.28 (s, 6H), 6.965 (t, *J* =7.8 3, 7.71 Hz, 2H), 7.255 (dd, *J* =7.58, 1.52 Hz, 2H), 7.02-7.11 (m, 10H).
^{13}C NMR ($CDCl_3$, 50 MHz)	:δ 21.14 (q), 127.36 (d), 128.84 (d), 129.22 (d), 129.53 (s), 129.57 (d), 130.28 (d), 131.56 (s), 132.34 (s), 137.07 (s), 138.82 (s), 140.47 (s), 146.99 (s), 184.90 (s).
Elemental Analysis	Calcd.: C, 76.49; H, 4.43 Found: C, 76.12; H, 4.62
ESI-MS (m/z)	: 478.04 $(M+23)^+$

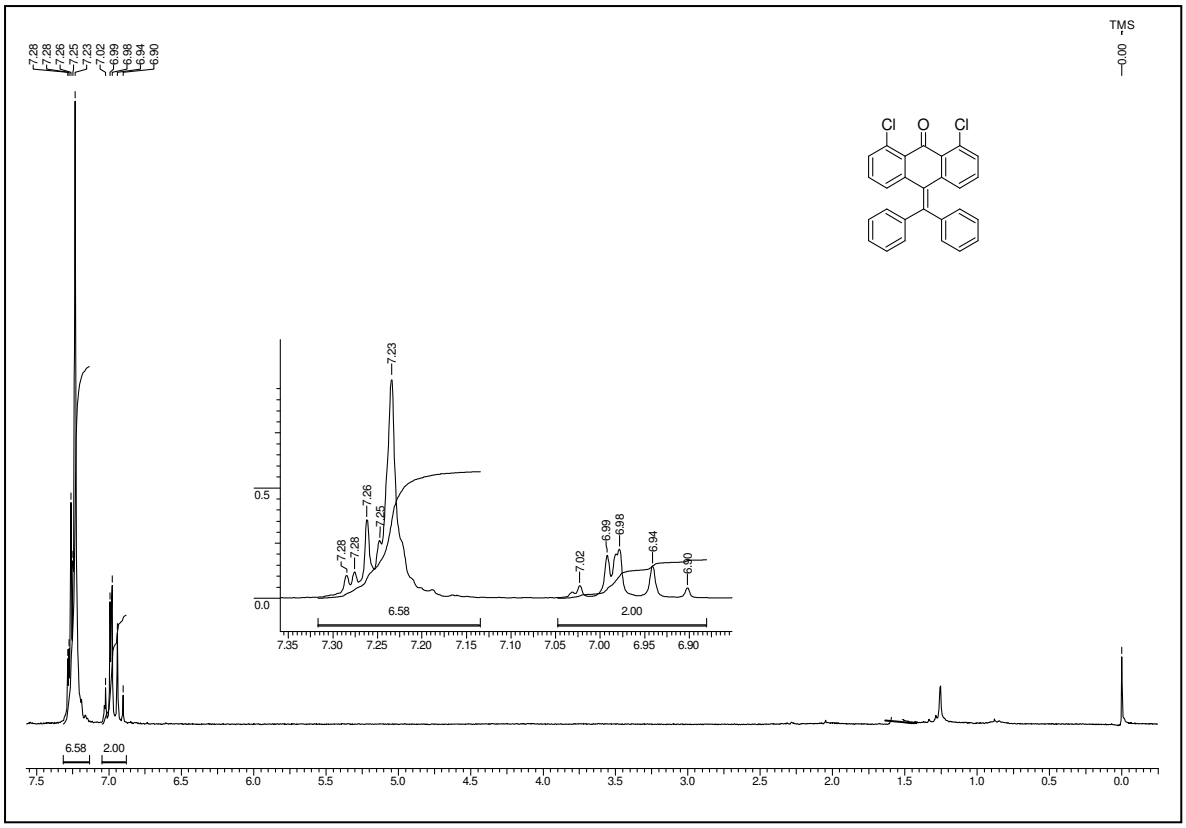
Spectral data



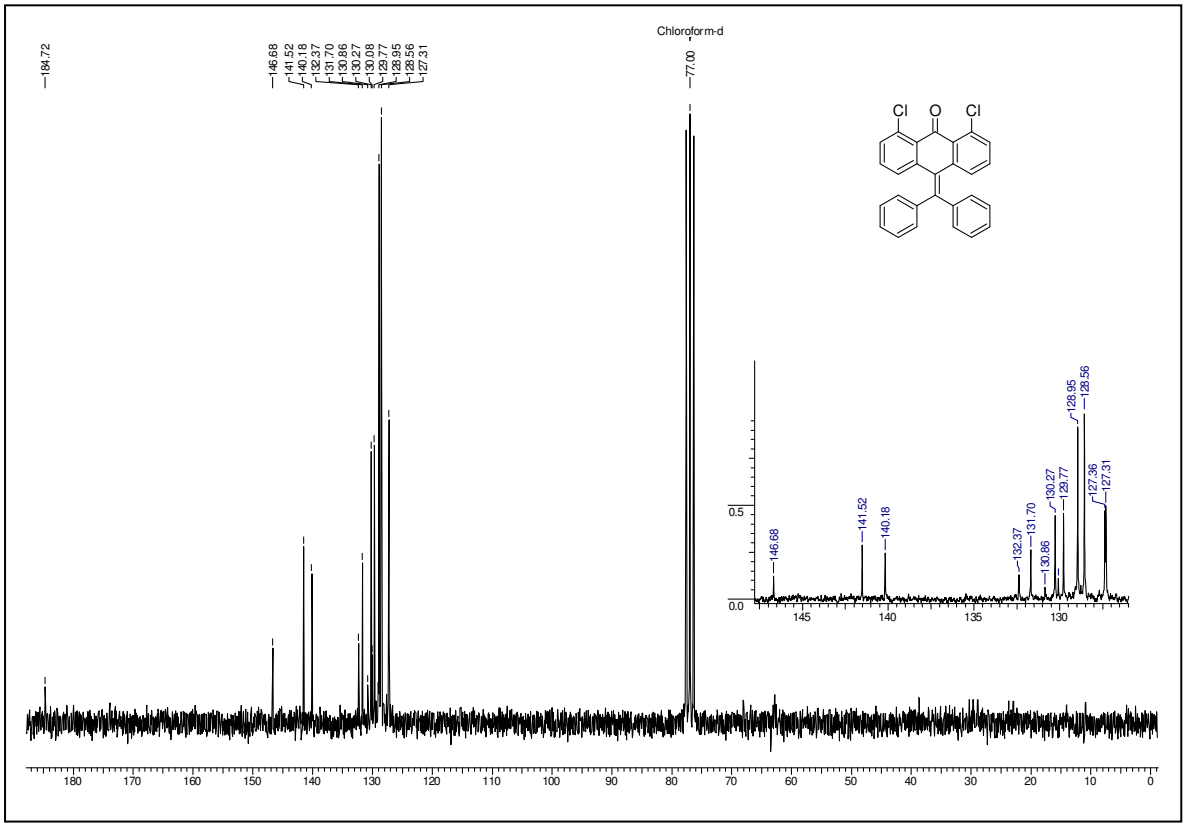
^{1}H NMR spectrum of compound 11 in $CDCl_3$



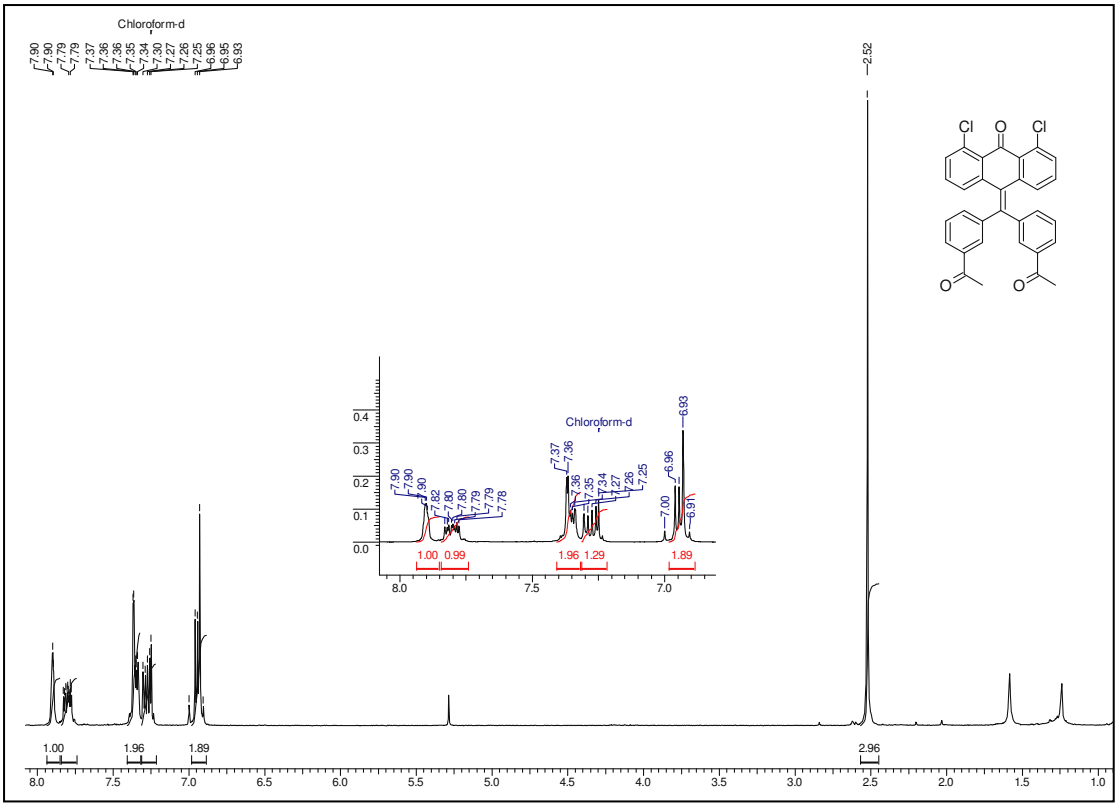
^{13}C NMR spectrum of compound 11 in $CDCl_3$



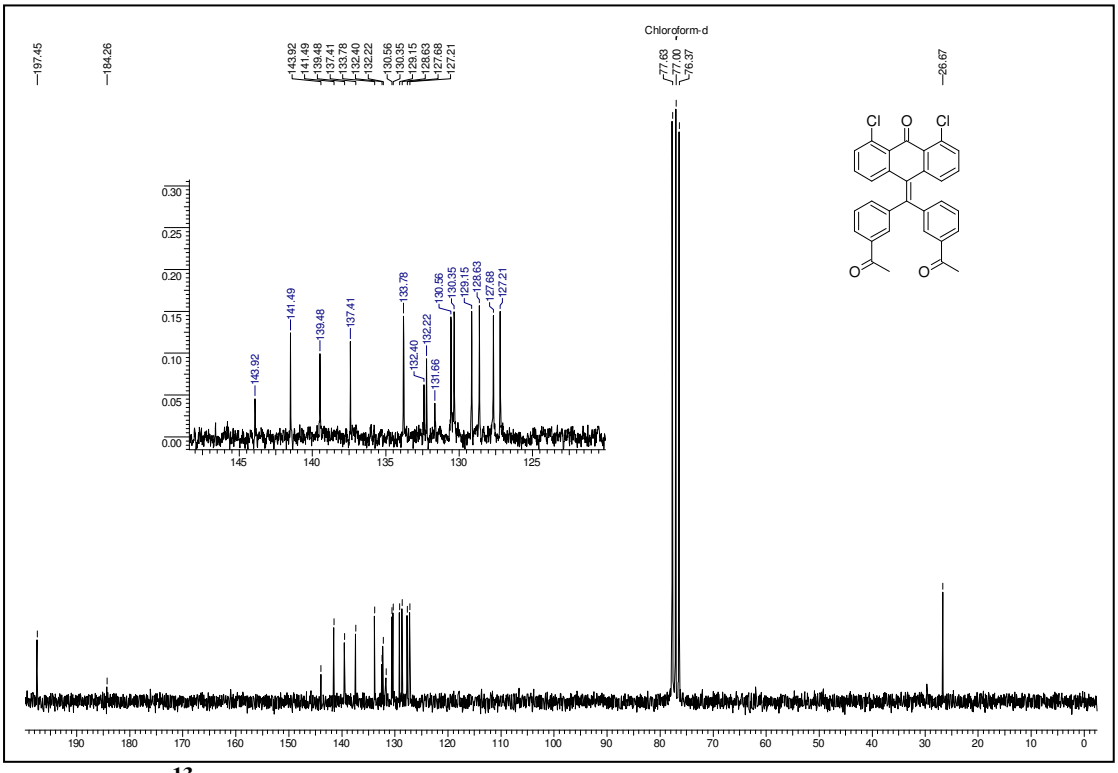
^{1}H NMR spectrum of compound 13 in $CDCl_3$



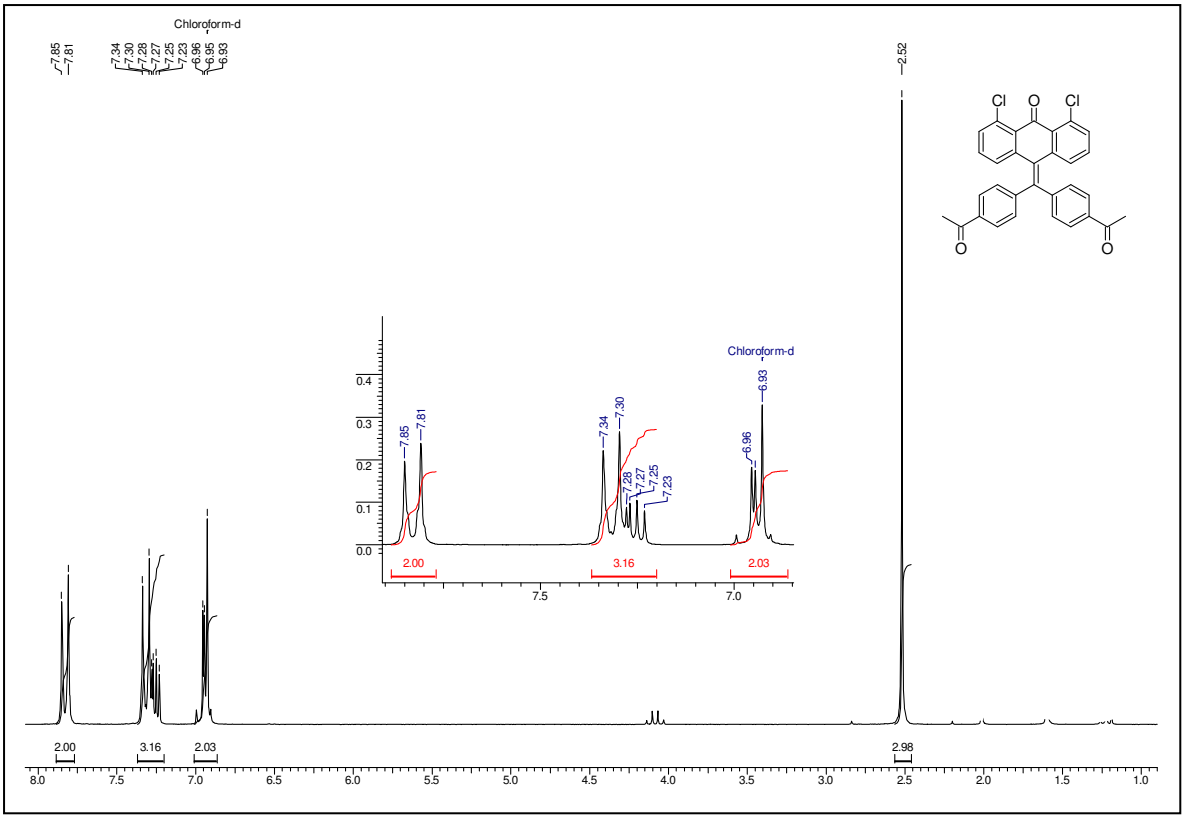
^{13}C NMR spectrum of compound 13 in $CDCl_3$



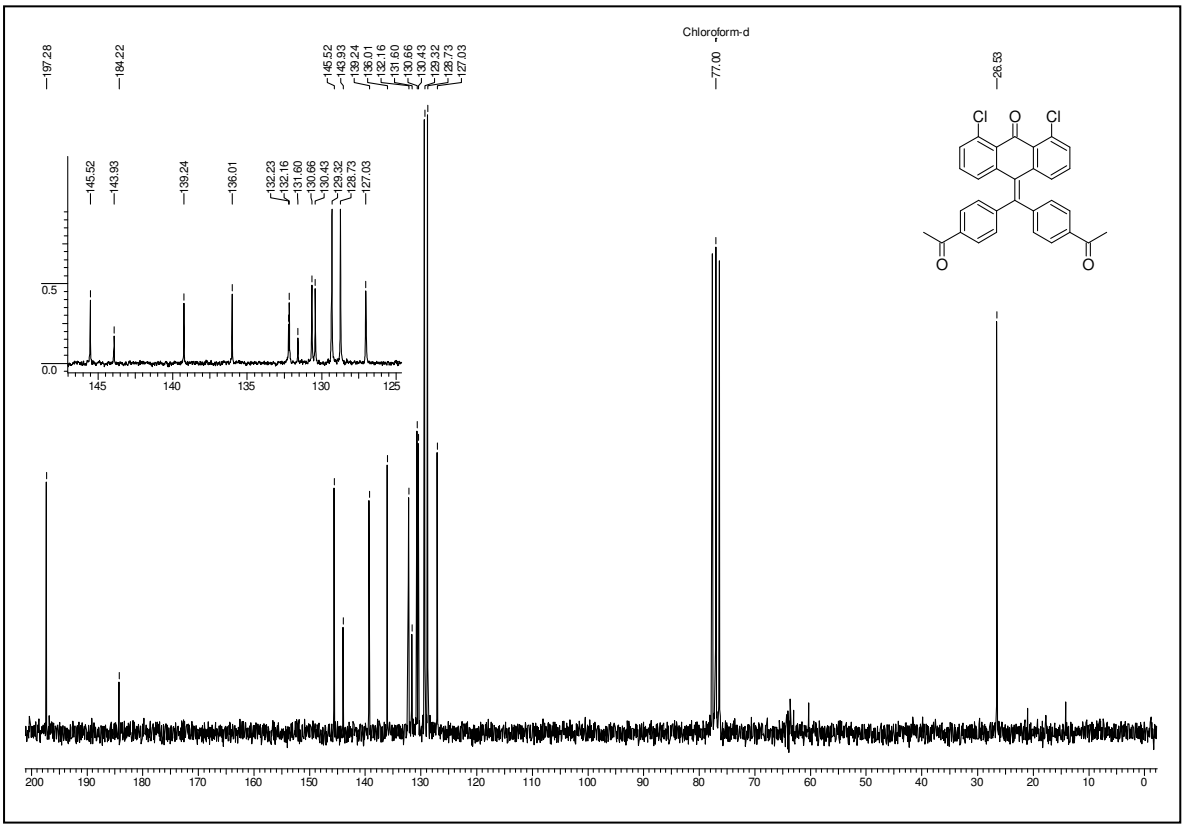
^{1}H NMR spectrum of compound 15 in $CDCl_3$



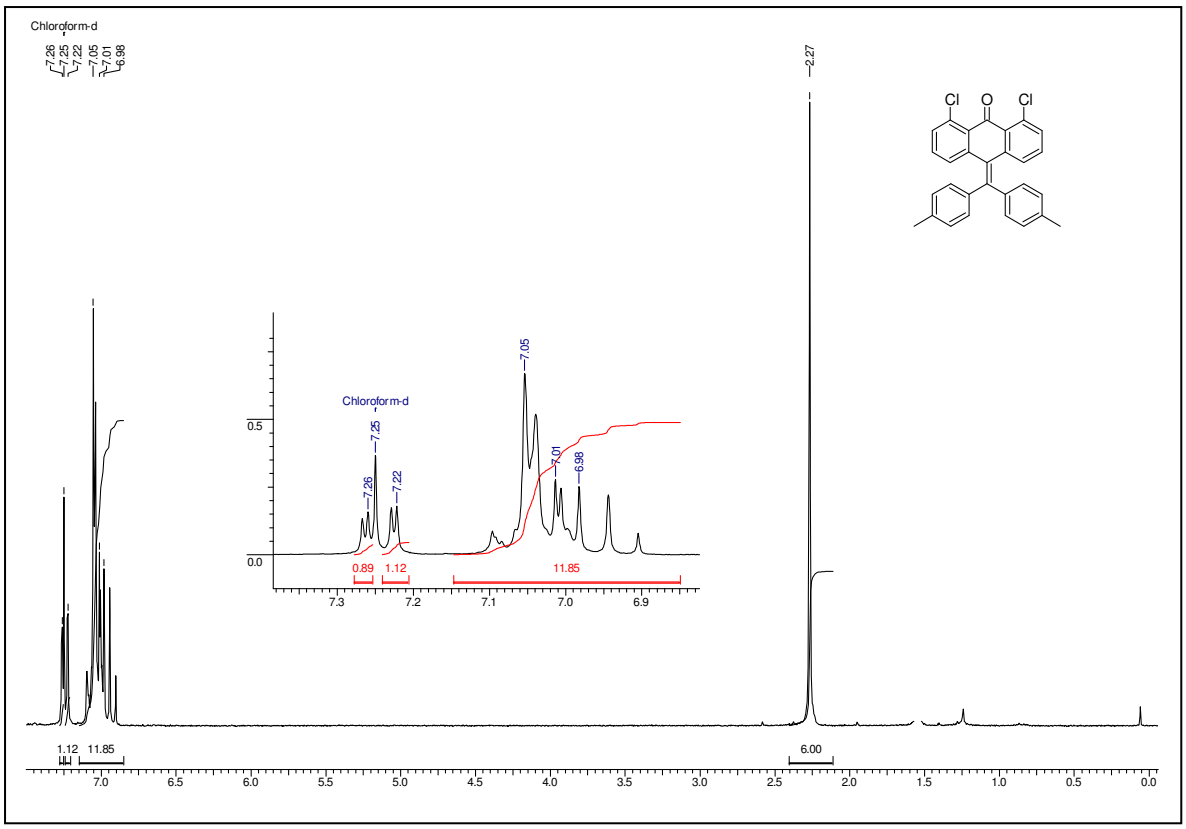
^{13}C NMR spectrum of compound 15 in $CDCl_3$



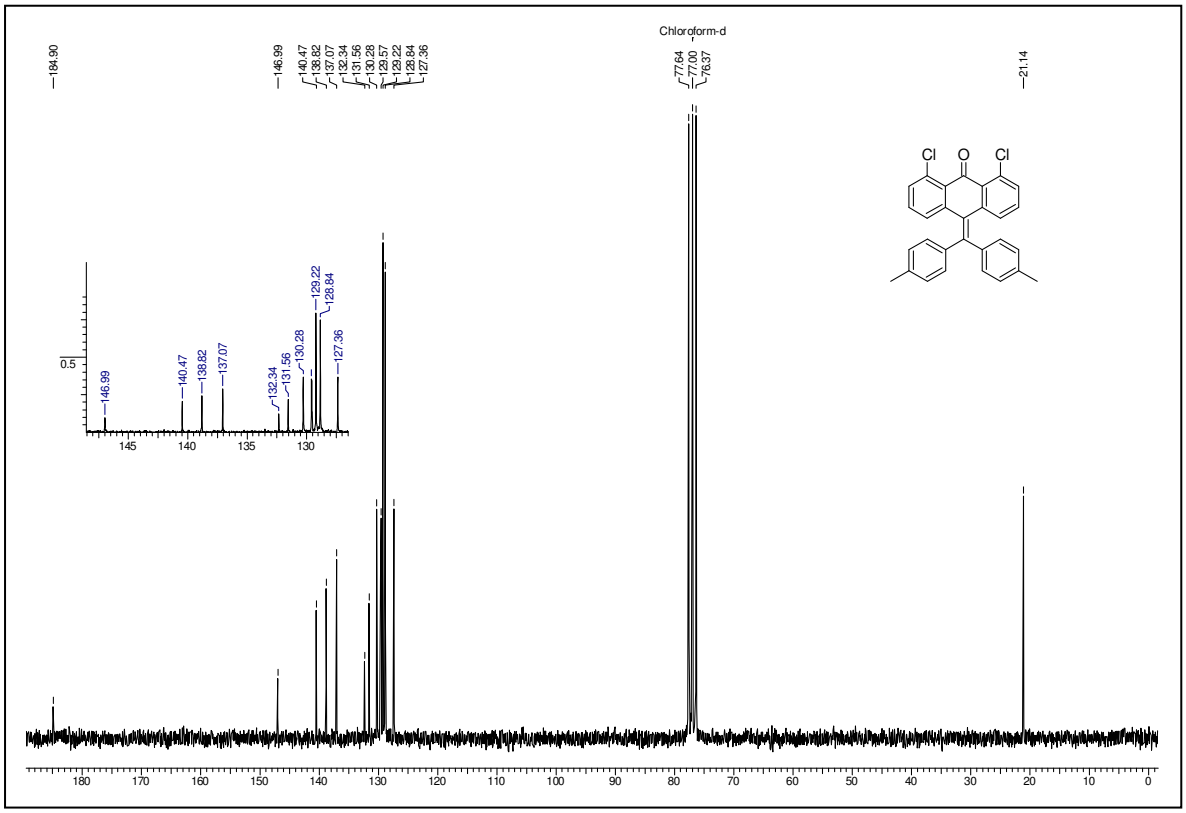
^{1}H NMR spectrum of compound 14 in $CDCl_3$



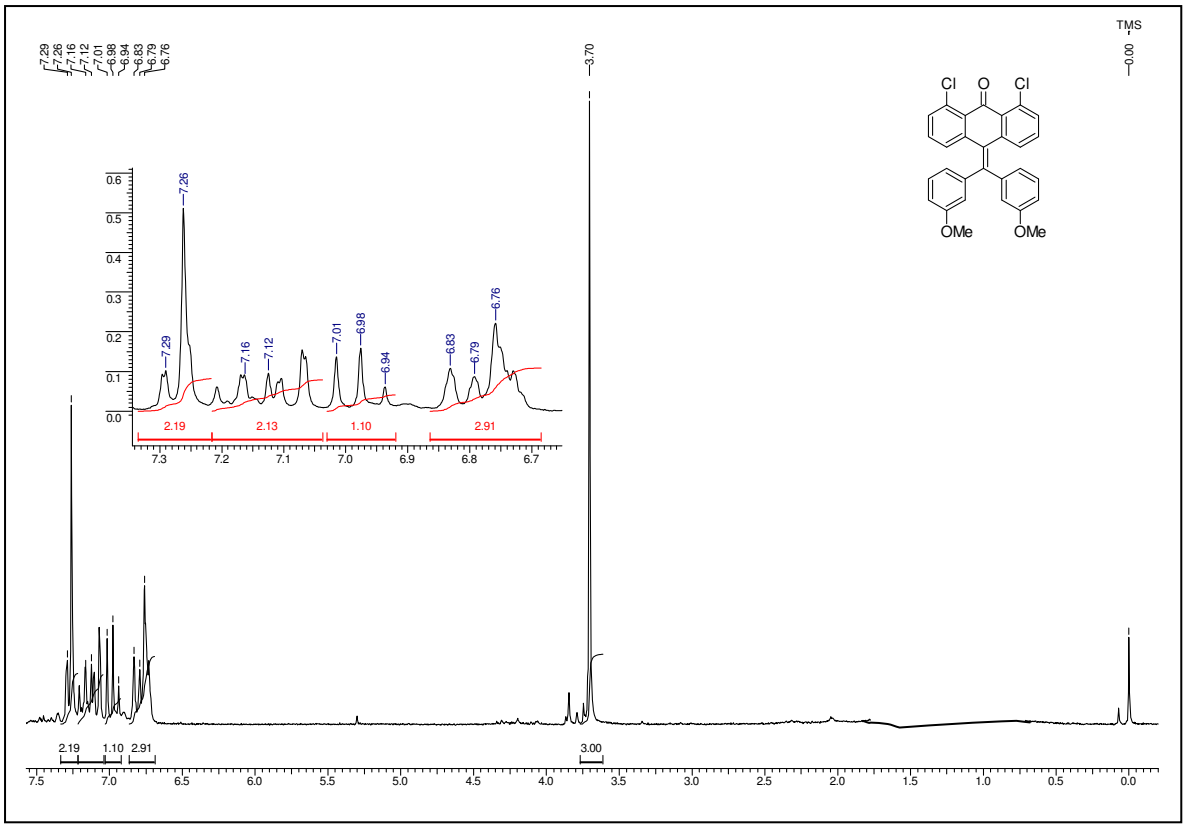
^{13}C NMR spectrum of compound 14 in $CDCl_3$



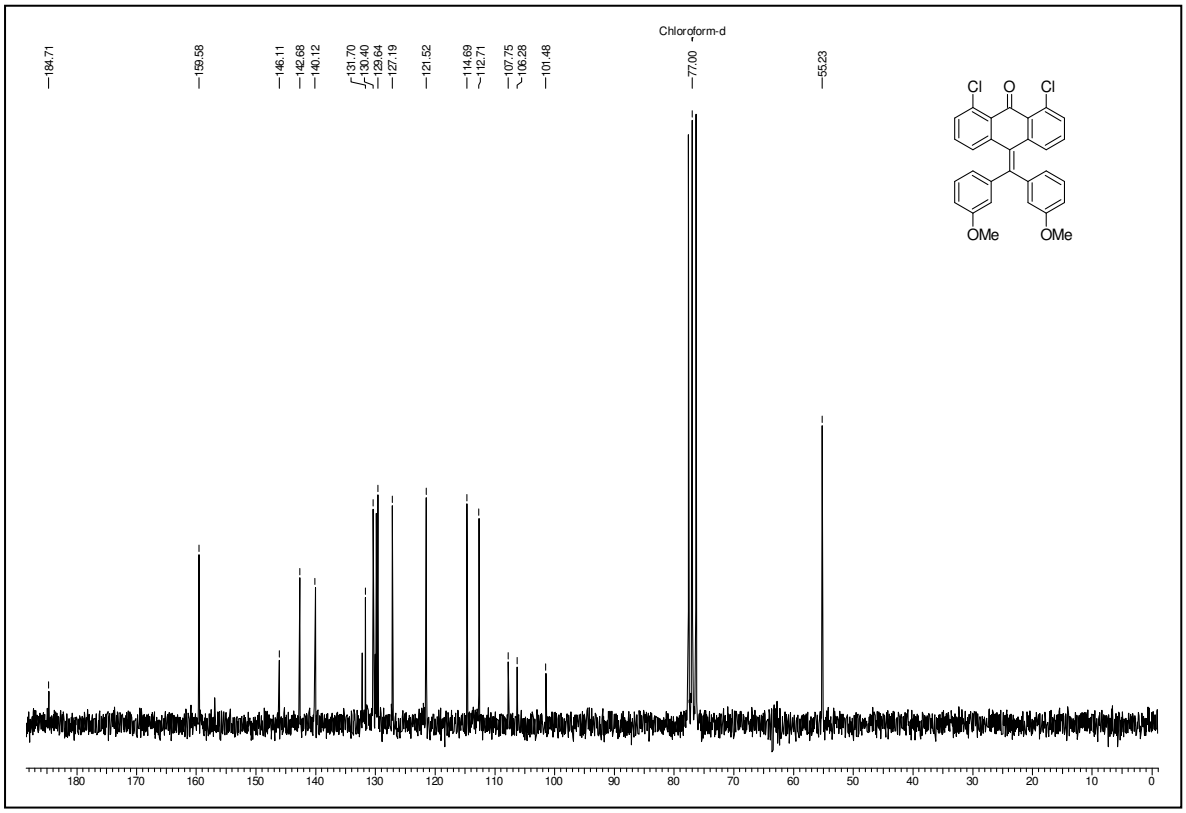
^{1}H NMR spectrum of compound 20 in $CDCl_3$



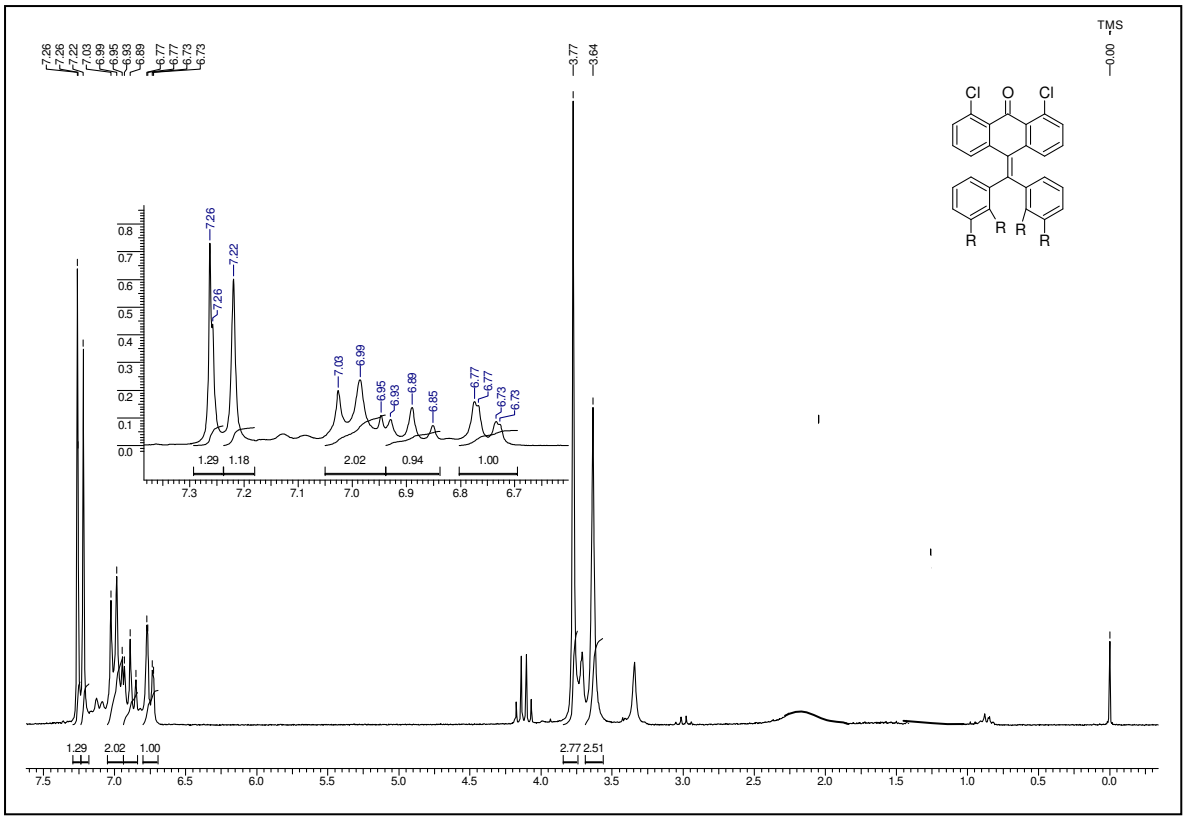
^{13}C NMR spectrum of compound 20 in $CDCl_3$



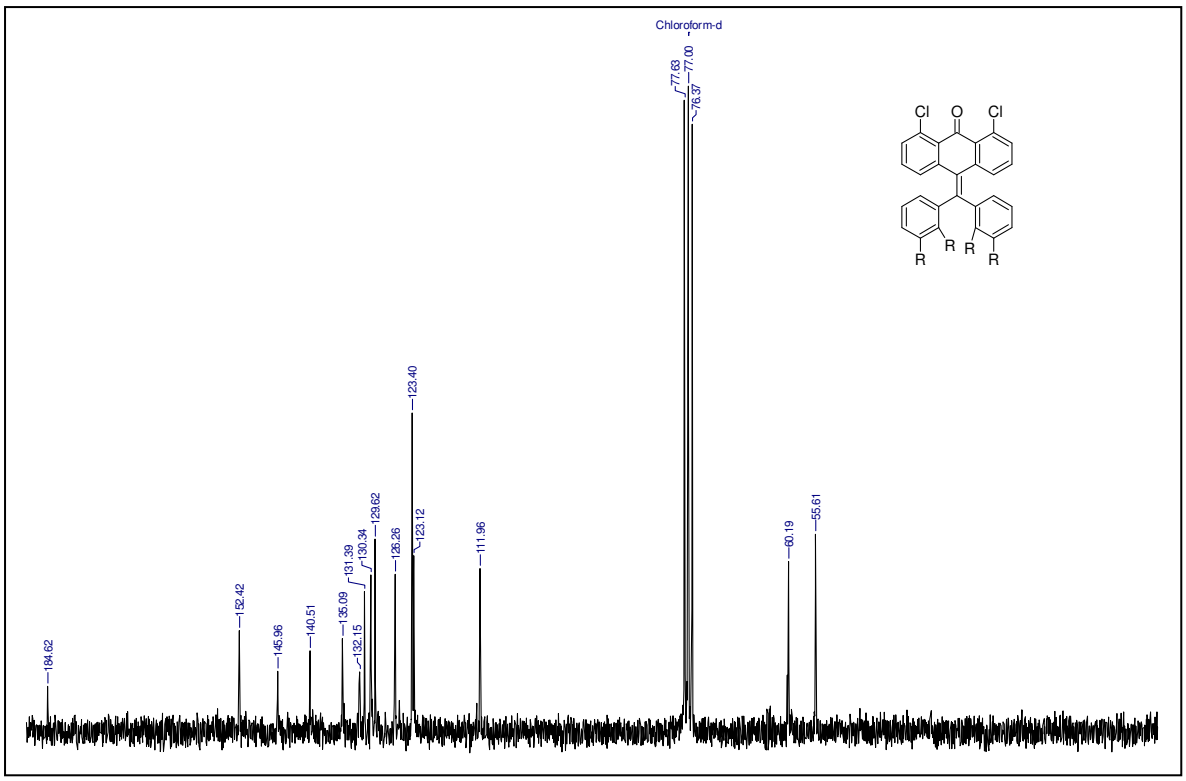
^{1}H NMR spectrum of compound 19 in $CDCl_3$



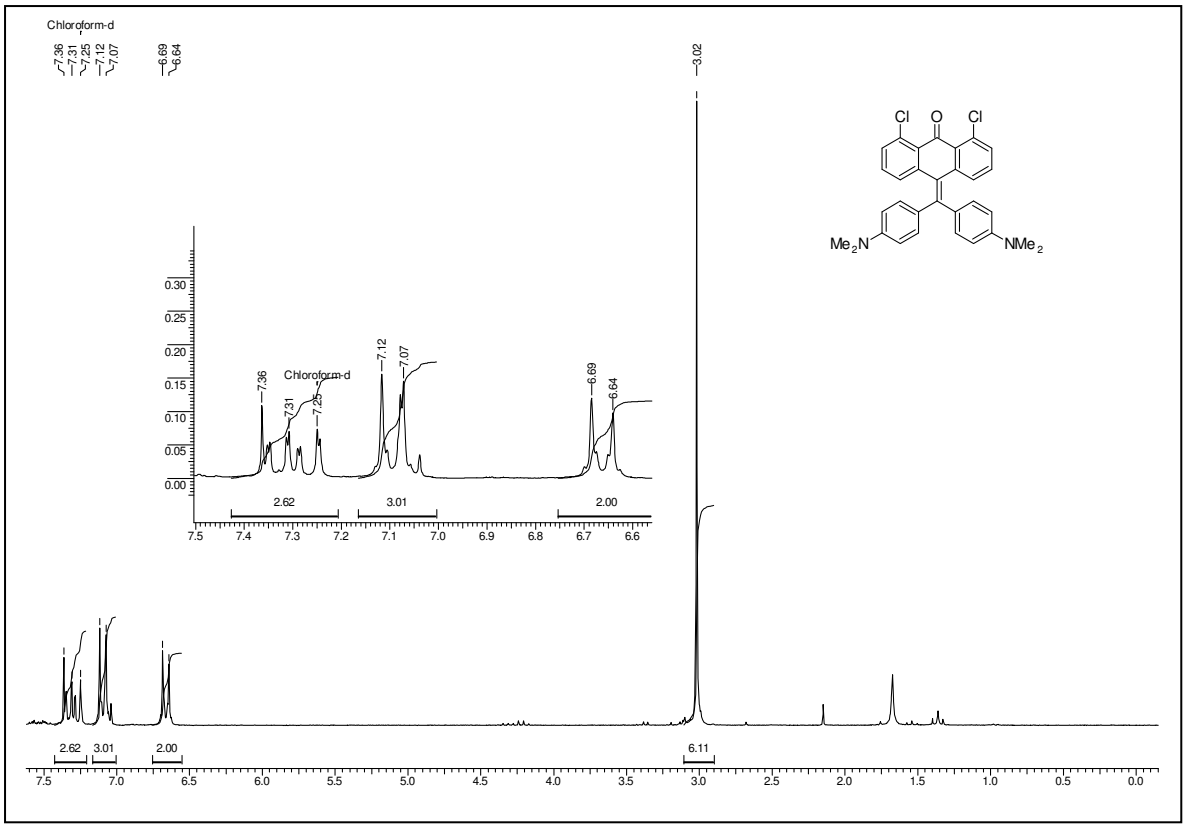
^{13}C NMR spectrum of compound 19 in $CDCl_3$



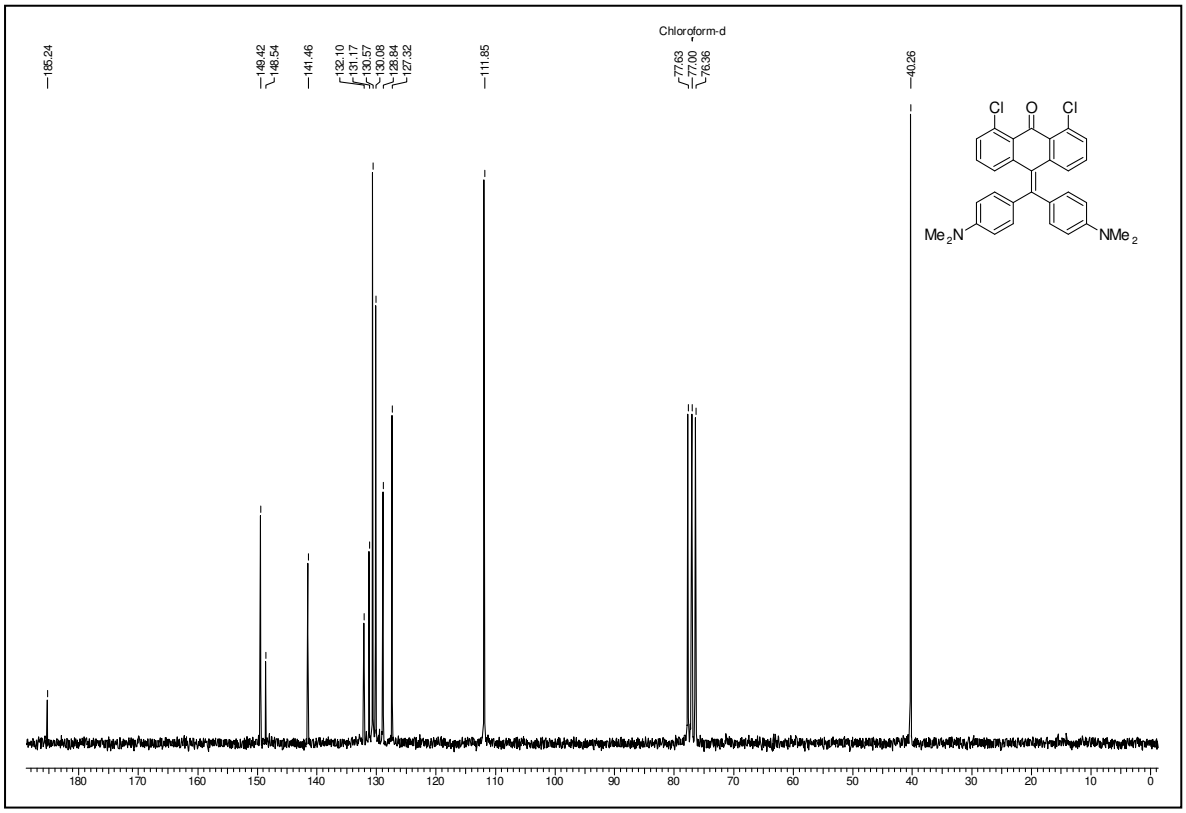
^{1}H NMR spectrum of compound 16 in $CDCl_3$



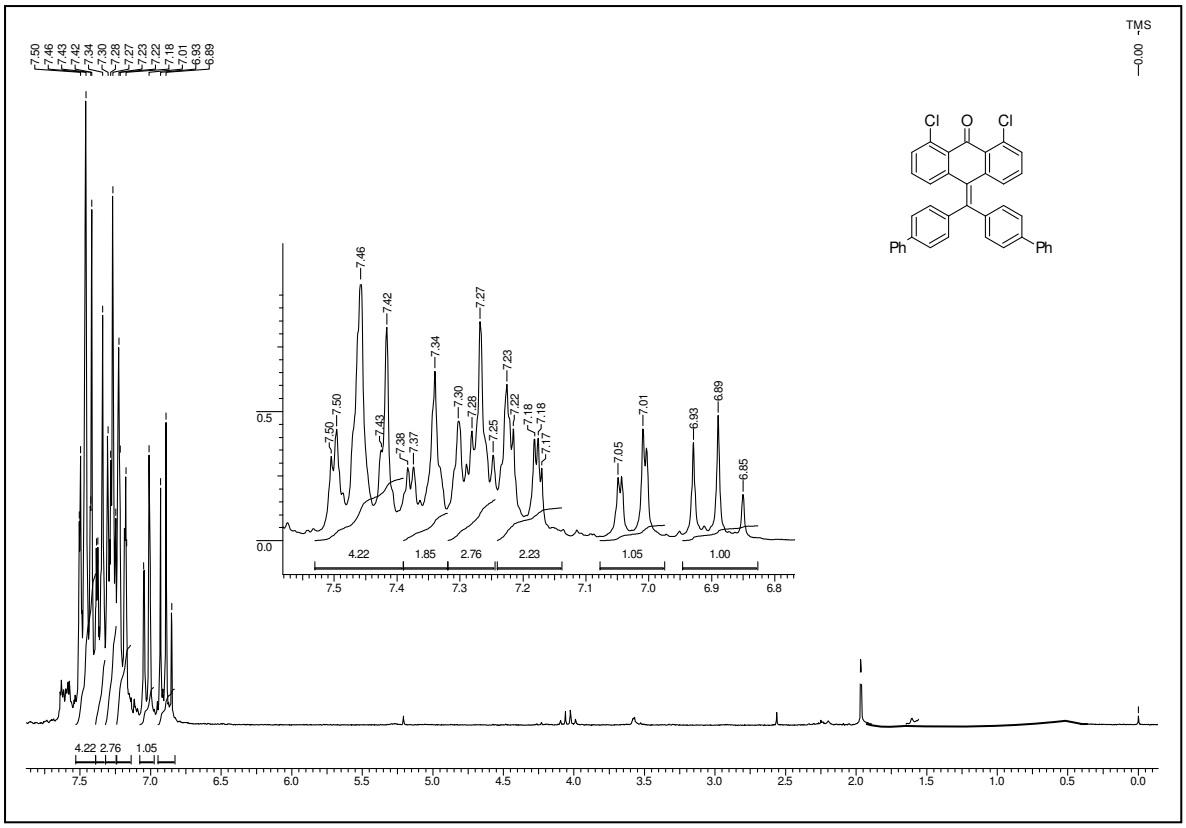
^{13}C NMR spectrum of compound 16 in $CDCl_3$



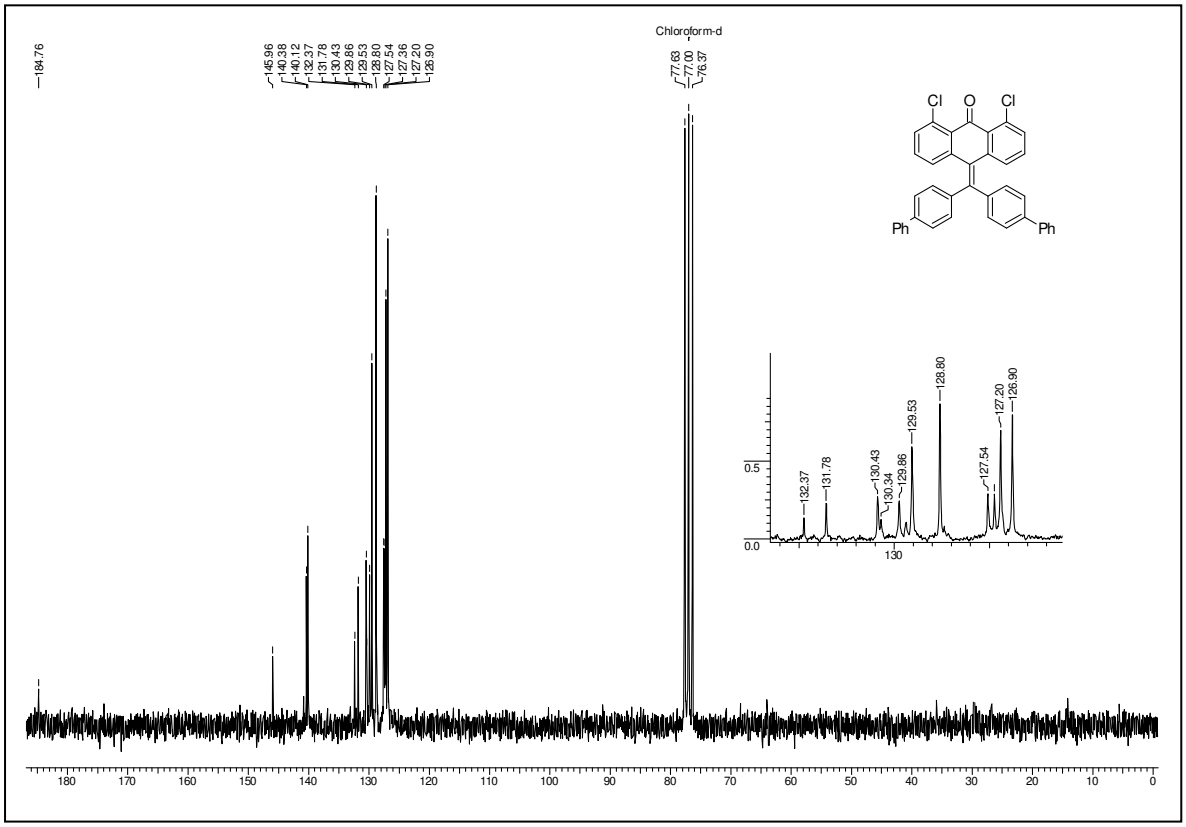
^{1}H NMR spectrum of compound 18 in $CDCl_3$



^{13}C NMR spectrum of compound 18 in $CDCl_3$



^{1}H NMR spectrum of compound 17 in $CDCl_3$



^{13}C NMR spectrum of compound 17 in $CDCl_3$

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Publications

1. Kiran C. N.; Ramana C.V.; Gurjar M. K. "A Pd mediated ω-alkynone cyclo-isomerization approach for the central Tetrahydropyran and synthesis of C_{31}-C_{48} fragment of Aflastatin A" (Manuscript under Preparation).

2. Kiran C. N.; Ramana C.V.; Gurjar M. K. "Total synthesis of natural Bruguierol A and synthetic studies toward Bruguierol C." (To be communicated).

3. Kiran C. N.; Ramana C.V.; Gurjar M. K. "Diversity Oriented synthesis of various analogs of 10-diarylmethylidene and1,8-dichloro anthraquinones and evaluation of their biological activity" (To be communicated).