Divergent Synthesis of Spirocyclic Small Molecules and Synthetic Studies on Crassifosides

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BY

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SEPTEMBER 2007

Dedicated
To
My Parents, Brother,
Sister, Brother-in-law

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CERTIFICATE

This is to certify that the work presented in this thesis entitled "**Divergent Synthesis of Spirocyclic Small Molecules and Synthetic Studies on Crassifosides**" submitted by **Mr. Sushil Kumar Maurya**, has been carried out by the candidate at National Chemical Laboratory, Pune, under my supervision. Such materials as obtained from other sources have been duly acknowledged in the thesis. This work is original and has not been submitted for any other degree or diploma of this or any other university.

Dr M. K Gurjar
(Research Guide)

DECLARATION

I here by declare that the research work presented in this thesis was carried out by me at the National Chemical Laboratory, Pune, India, under the supervision of Dr. M. K. Gurjar, Head and Deputy Director, Division of Organic Chemistry: Technology, National Chemical Laboratory, Pune-411 008, submitted for the degree of Doctor of Philosophy in Chemistry to the University of Pune. This work is original and has not been submitted in part or full by me for any other degree or diploma of this or any other university.

Sushil Kumar Maurya

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Sushil Maurya

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General Remarks

1. IR spectra were recorded as chloroform solution, on a Schimadzu FT-IR spectrophotometer, using NaCl optics. IR bands are expressed in frequency (cm^{-1}).
2. Nuclear Magnetic Resonance spectra were recorded on Bruker AV 200 (200 MHz for ^{1}H and 50 MHz for ^{13}C NMR) or Bruker MSL300 (300 MHz for ^{1}H and 75 MHz for ^{13}C NMR) or Bruker AV 400 (400 MHz for ^{1}H and 100 MHz for ^{13}C NMR) spectrometers or Bruker DRX 500 (500 MHz for ^{1}H and 125 MHz for ^{13}C NMR). Chemical shifts (δ) are quoted in ppm and are referenced to tetramethylsilane (internal).
3. Mass spectra were recorded on Applied Biosystems API QSTAR Pulsar Mass Spectrometer (Electro spray ionization, direct infusuin method, solvents used acetonitrile/methanol)
4. Elemental analysis was carried out on Thermo Finnigan Flash EA 1112 series analyzer.
5. Optical rotations were measure on a JASCO-181 digital polarimeter, using D line (589.3μ).
6. All reactions were monitored by thin-layer chromatography (TLC) using pre-coated silica plates (Merck F_{254}, 0.25 mm thickness) and compounds were visualized by UV, I_2 and Anisaldehyde reagent.
7. All evaporations were carried out under reduced pressure using Buchi rotary evaporator below 50 °C.
8. All solvents and reagents were purified and dried by following the procedures given in the book “Purification of Laboratory Chemicals” by Armarego and Perrin (3^{rd} edition).
9. Silica gel (60-120, 100-200, 230-400 Mesh) used for column chromatography was purchased from Spectrochem company.
10. Compound names were written based on Chemical Abstract entries.

Abbreviations

Ac	Acetyl/Acetate
Ac_2O	Acetic anhydride
ACN	Acetonitrile
Ar	Aryl
aq	Aqueous
Bn	Benzyl
Bz	Benzoyl
DCM	Dichloromethane
$(DHQ)_2PHAL$	Hydroquinine 1,4-phthalazinediyl diether
$(DHQD)_2PHAL$	Hydroquinine 1,4-phthalazinediyl diether
DMAP	Dimethylaminopyridine
DMF	*N,N*-dimethylformamide
DMSO	Dimethyl sulfoxide
Et_3N	Triethyl amine
g	Gram
h	Hour
HCl	Hydrochloric acid
H_2O	Water
H_2SO_4	Sulfuric acid
Hz	Hertz
Im	Imidazole
J	Coupling constant
M	Molar
Me	Methyl
mL	Milliliter
mol	Mol
mmol	Millimole
MsCl	Methanesulphonyl chloride
Ms	Methanesulphonyl
$(NH_4)_2CO_3$	Ammonium Carbonate

NH_4Cl	Ammonium chloride
PTSA	*p*ara-toluene sulfonic acid
Ph	Phenyl
PMB	*para*-Methoxy benzyl
Prop	Propargyl
Py	Pyridine
rt	Room temperature
TBAI	Tetrabutylammonium Iodide
TBAF	Tetrabutylammonium fluoride
TBDPS	*tert*-Butyldiphenylsilyl
TBS	*tert*-Butyldimethylsilyl
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMS	Trimethylsilyl
TEA	Triethyl amine
TsOH	*para*-Toluene sulfonic acid
TsCl	*para*-Toluene sulfonic chloride
Ts	*para*-Toluene sulfonyl

Abstract

The thesis entitled "Divergent Synthesis of Spirocyclic Small Molecules and Synthetic Studies on Crassifosides". The first chapter highlights divergent synthesis of spirocyclic small molecules and the second chapter deals with the synthetic studies on Crassifosides.

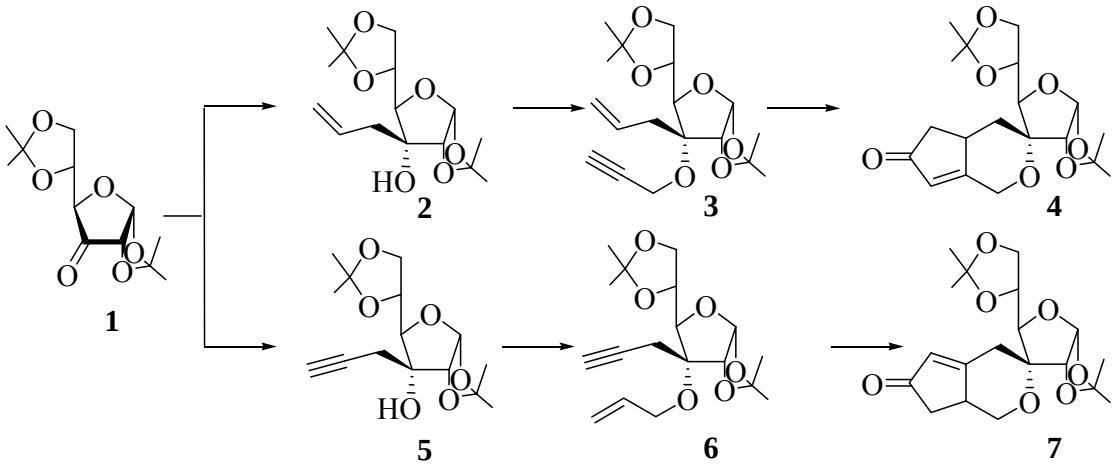
Chapter 1: Divergent synthesis of spirocyclic small molecules

The efficient, simultaneous synthesis of structurally diverse compounds, known as "Diversity Oriented Synthesis" (DOS), is not obvious and remains as a challenge to synthetic chemists. DOS involves the deliberate, simultaneous and efficient synthesis of more than one target compound in a diversity-driven approach to answer a complex biological problem. Synthesis of collection of small molecules is important for chemical *genetics* studies, hence plays major role in drug discovery process. Many natural products possess spirocyclic moieties and the inhibition of the protein function was often found to be due to the inherent conformational rigidity of the spirocycles.

In our synthetic endure, we have successfully utilized Pauson-Khand reaction (PKR) using different enynes derived from easily accessible pentofuranosyl and hexopyranosyl sugars and enone obtained was further subjected to Michael addition reaction using various thiols as nucleophile.

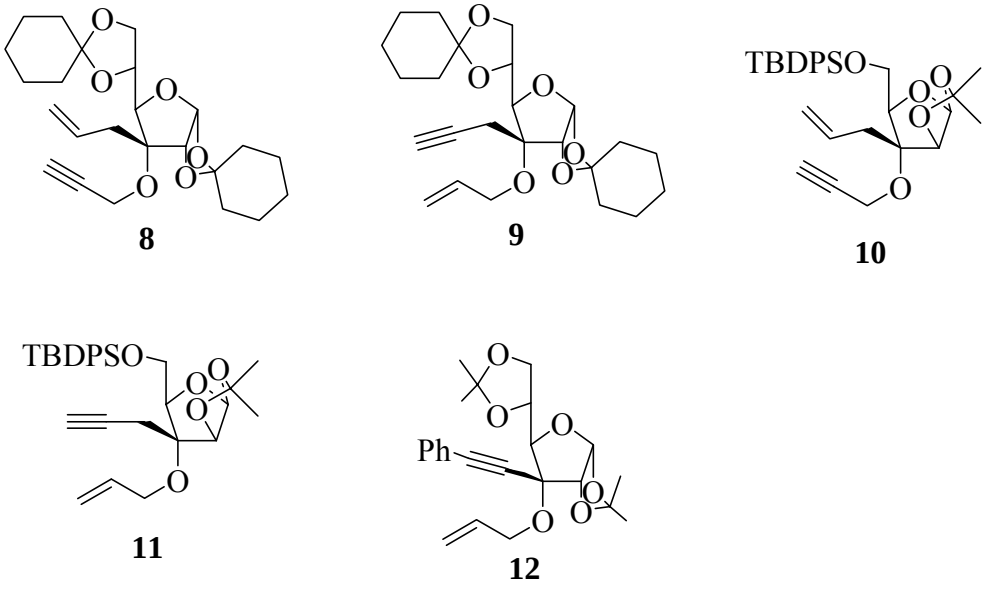
The strategy utilized for the synthesis of cyclopentenone was based on intramolecular PKR reaction of the suitably-substituted enyne. To begin our investigation, easily available 1,2:5,6-di-*O*-isopropylidene-α-D-glucofurano-3-ulose **1** was treated with allylzincbromide in tetrahydrofuran to yield the 3-*C*-allyl derivative **2**, which was alkylated using NaH, propargyl bromide and *N*-tetrabutylammonium iodide in DMF to provide required PKR precursor **3**. Enyne **3** was then treated with $Co_2(CO)_8$ for 3 h under nitrogen atmosphere in order to yield the $Co_2(CO)_6$-alkyne complex which was passed through a pad of silica gel and then dissolved in acetonitrile-dimethoxyethane (4:1), heated to 85 ^oC for 3 h to afford the spiroannulated cyclopentenone **4** a single diastereomer in excellent yield (Scheme1).

Scheme1



We then checked the efficiency of the methodology on a panel of substrates utilizing various pentose and hexose derived enynes. All the substrates (**3**,**6**,**8**,**9**,**10,11** and **12**) for the Pauson-Khand reaction were synthesized from the corresponding ketones *via* a Barbier reaction and *O*-alkylation strategy. It is worth mentioning that in all cases single diastereomeric spiroannulated products was obtained.

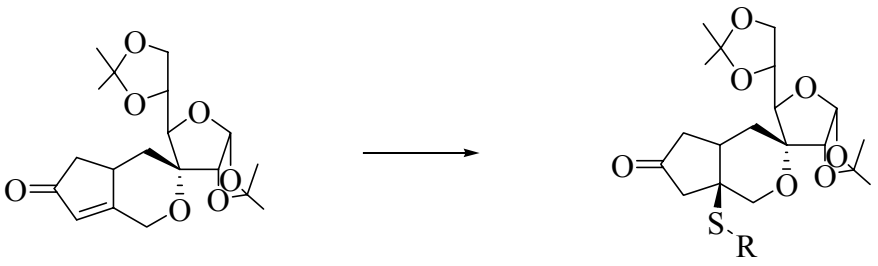
Enynes for PKR



In continuation of DOS for the synthesis of small molecules, we checked the efficiency of the Michael addition reaction on enone **4** utilizing different thiols as nucleophiles and toluene as solvent at the 70 ^{o}C in the presence of catalytic amount of DMAP. It is important to note that Michael addition reaction resulted in the formation of a single diastereomer due to conformational rigidity of the polycyclic

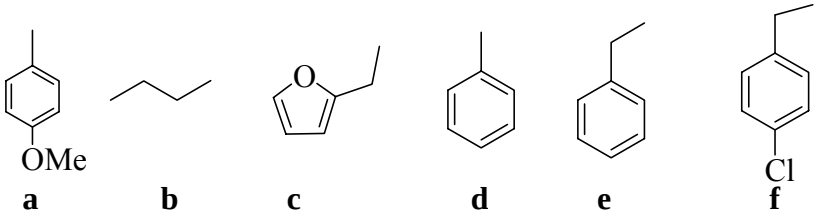
moiety whose stereochemistry was assigned by single crystal X-ray crystallography (Scheme 2).

Scheme 2



4 **13- 18**

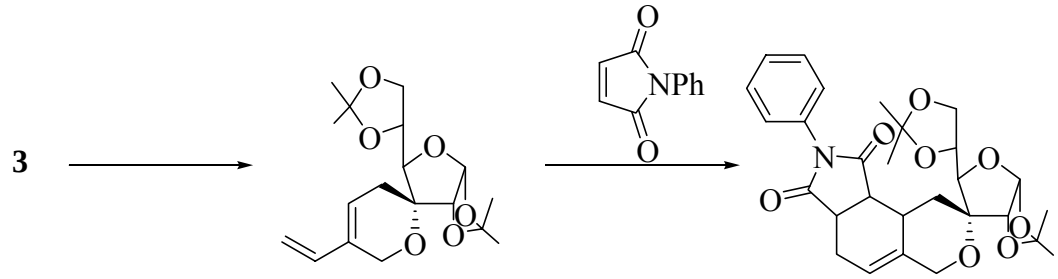
Nucleophile R =



a **b** **c** **d** **e** **f**

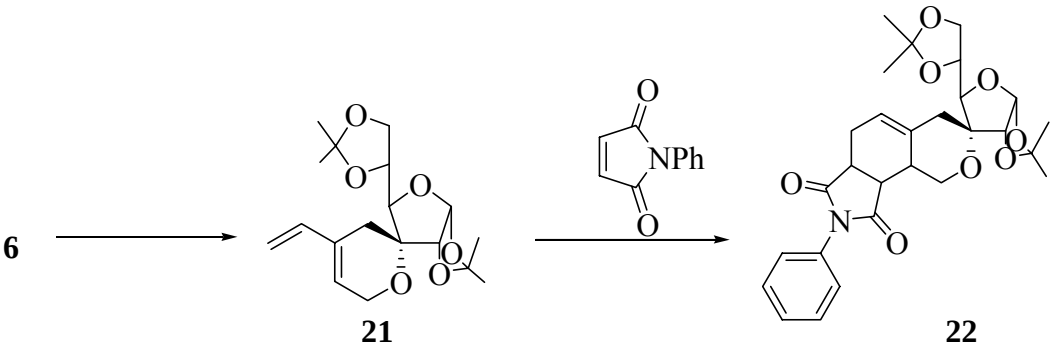
Extending our DOS approach, enynes synthesized during the above endeavor were subjected to enyne metathesis and Diels-Alder reaction sequence for the synthesis of more complex small molecules (Scheme 3).

Scheme 3



19 **20**

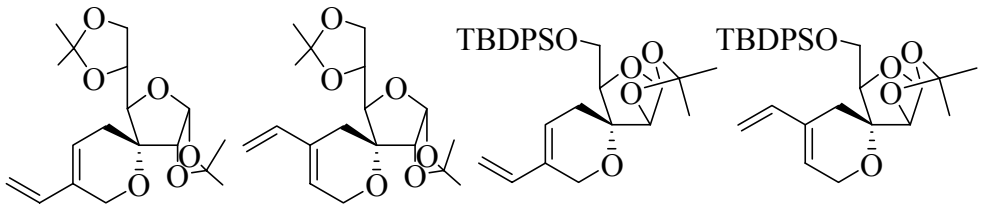
Two Products



21 **22**

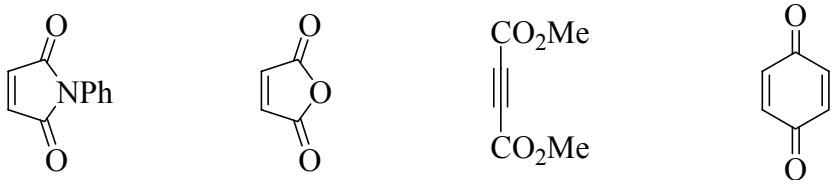
Single Product

Dienes



19 **21** **23** **24**

Dienophiles

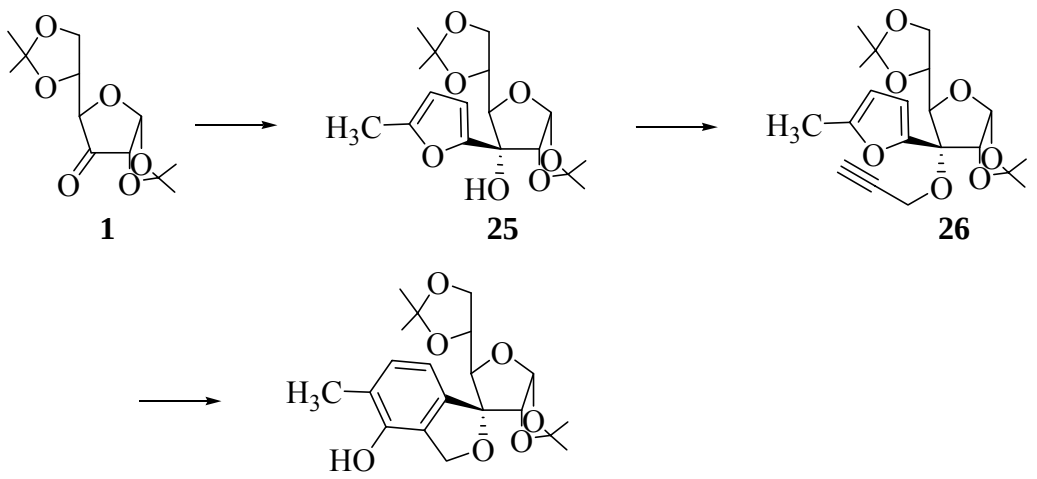


For example the diene (**19** and **21)** obtained after enyne metathesis was utilized as a substrate for the thermal Diels-Alder reaction using four-different dienophiles. It is worth mentioning that diene **19** resulted in the formation of two DA adducts while diene **21** gave only one DA adduct as the product (Scheme 3).

IMDA reaction

As a part of our programme dedicated towards exploration of carbohydrate based DOS pathways for spirocycles, we embarked on utilization of Au (III) mediated phenol synthesis for the spiroannulation on carbohydrate scaffolds. We synthesized dihydroisobenzofurans from furanylated propargyl ethers exploiting alkynophilicity of gold. To commence our studies, easily available 1,2:5,6-di-*O*-isopropylidene-α-D-glucofurano-3-ulose (**1**) was converted to corresponding 3-*C*-(2-methylfuranyl)-D-allose using 2-methylfuryl lithium in THF. Resulting *tertiary* hydroxyl group was alkylated using propargyl bromide to afford propargyl ether (**26**). Having the methylfuranylated propargyl ether moiety attached to the carbohydrate template, the intramolecular Diels-Alder (IMDA) reaction and subsequent *C*-*O* bond cleavage was effected in the presence of catalytic amount of $AuCl_3$ in acetonitrile for 10 min to afford spiroannulated dihydroisobenzofuran derivative **27** (Scheme 4).

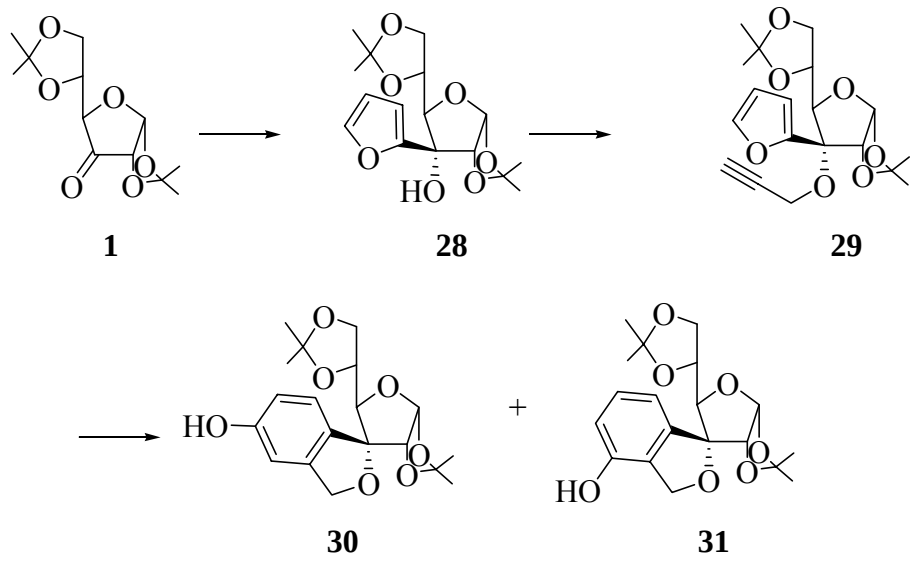
Scheme 4



1 **25** **26** **27**

We next performed the spiroannulation protocol on furanylated propargyl ether **29** and observed formation of two regioisomeric spiroannulated derivatives **30** and **31** in 1:1 ratio (Scheme 5).

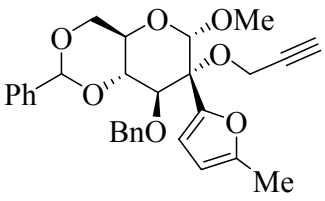
Scheme 5



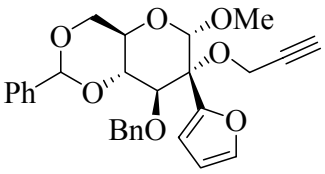
1 **28** **29** **30** **31**

Having optimized conditions in hand, we thought to explore spiroannulation protocol on diverse set of substrates derived from pentofuranosides (**34, 35**), hexofuranosides (**36, 37**) and hexopyranosides (**32, 33**).

Substrate for IMDA



32



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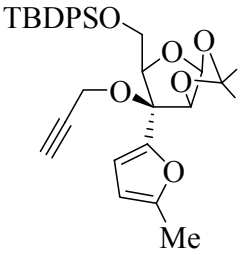

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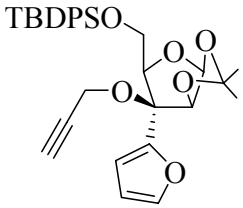
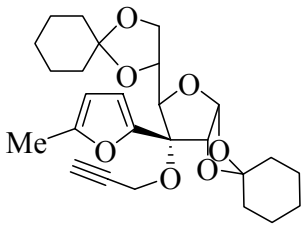
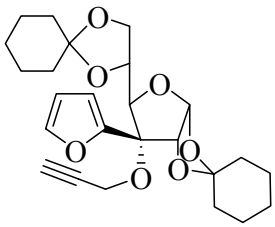


35



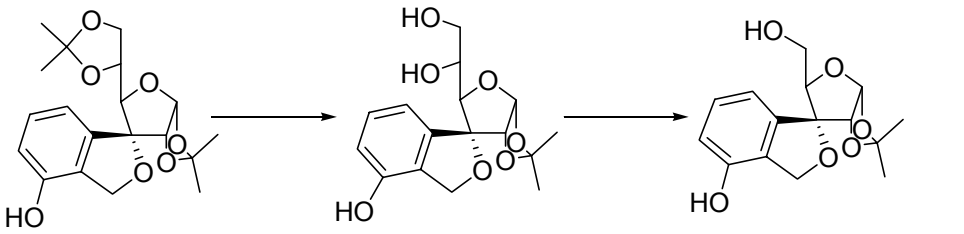
36



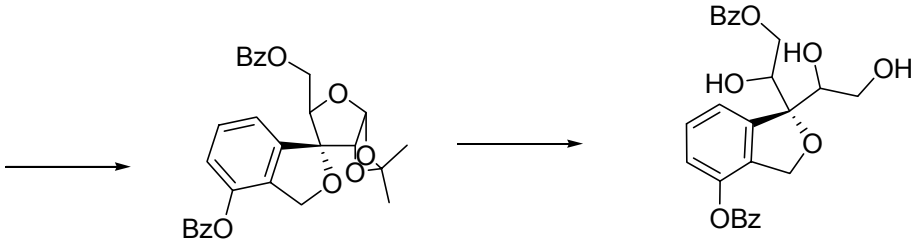
37

PKC-α belonging to the protein kinase C (PKC) family of enzymes plays dominant role in intracellular signal transduction of a variety of cellular events such as proliferation, differentiation and apoptosis. In a recent protein docking study, Sodeoka group found that chiral isobenzofuranone derivatives bind to the PKC-α. We envisaged that introduction of a spirocyclic moiety would enhance the biological activity of the PKC-α inhibitor as spirocyclic moiety occurs in many natural products and its presence was shown to inhibit many important proteins in the cellular context because of the increased conformational rigidity. Continuing our DOS approach on carbohydrate scaffolds we achieved formal total synthesis of PKC-α inhibitor starting from the substrate in which stereochemistry was fixed at early stage. To begin our synthetic endure, dihydroisobenzofuran derivative **31** was subjected to acid catalyzed regioselective deprotection of 5,6-isopropylidine and the resulting diol **38** was subjected to oxidative cleavage using $NaIO_4$ in DCM followed by reduction of resulting aldehyde to alcohol **39** using $NaBH_4$ in MeOH. The *primary* and *phenolic* hydroxyl group of **39** was then protected as benzoate ester and undergo strong acid treatment for the cleavage of lone 1,2-isopropylidine group. The masked aldehyde group of resulting lactol was reduced using $NaBH_4$ in MeOH which results in the formation of triol **41** (Scheme 6).

Scheme 6



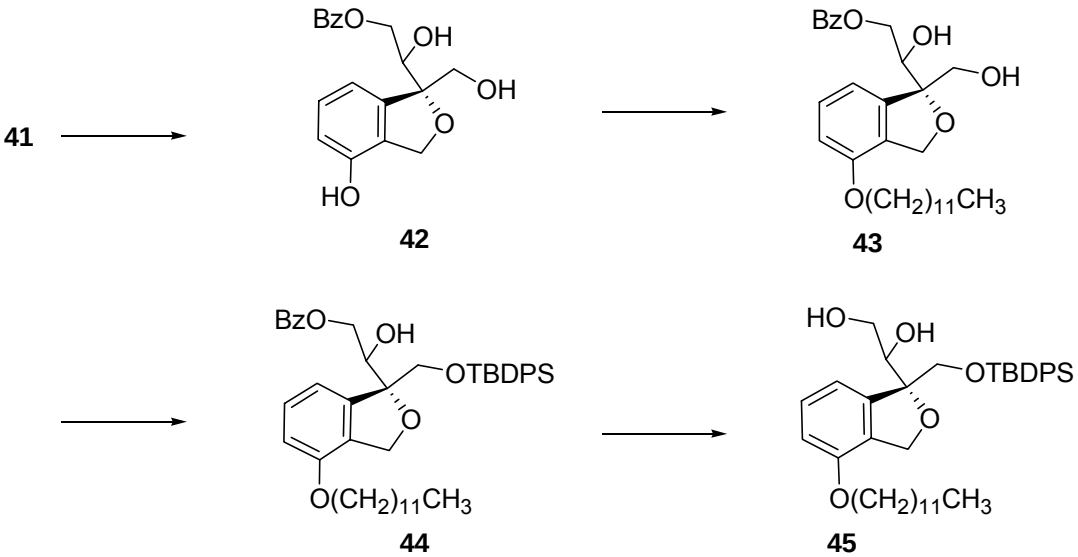
31 **38** **39**



40 **41**

Triol **41** was further subjected to oxidative cleavage and $NaBH_4$ reduction to get diol **42**. Fortunately at this step the phenolic benzoate ester was hydrolyzed selectively and resulting *phenolic* OH group was alkylated using dodecyl bromide and K_2CO_3 in acetone to obtain diol **43**. The *primary* hydroxyl group of diol **43** was protected as silyl ether **44** using TBDPSCl followed by benzoate ester hydrolysis of **44** to get diol **45** (Scheme 7).

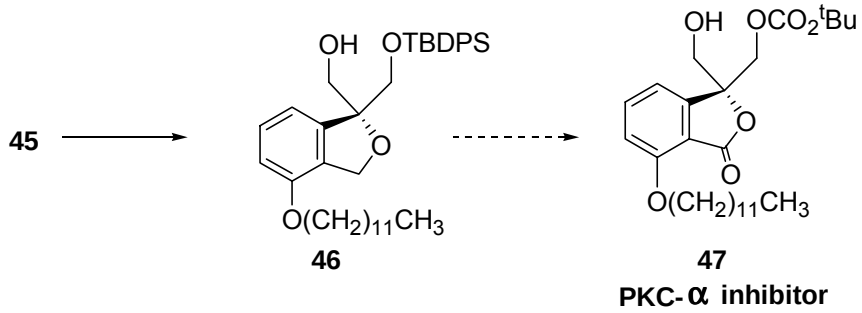
Scheme 7



42 **43** **44** **45**

Oxidative cleavage of the diol **45** using $NaIO_4$ and $NaBH_4$ mediated reduction of the resulting aldehyde results in the formation of alcohol **46** (Scheme 8).

Scheme 8



Chapter 2: Synthetic studies on Crassifosides

A glucosyl-fused unusual phenolic compound crassifoside F (**1**) was isolated from the rhizome of *Curculigo crassifolia* and exhibited the ACE inhibitor (angiotensin-converting enzyme) activities and It's isolation, structural elucidation and stereochemistry were reported by Zhou et. al. confirming its gross structure and all the stereocentres. Because of its unique structural features, notable biological activity and limited availability, the crassifoside group of molecules represents attractive targets for total synthesis. Herein, we have envisioned the first studies on the synthesis of highly oxygenated core (**2**) of crassifoside F starting from D-glucose and vanillin (Figure 1).

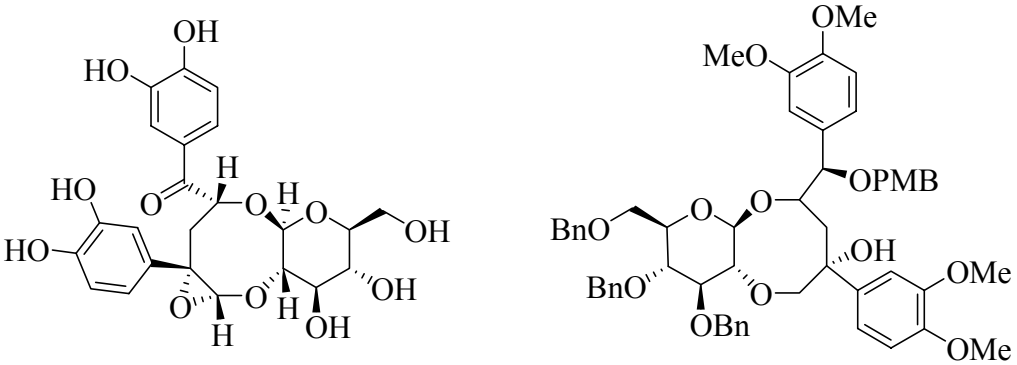


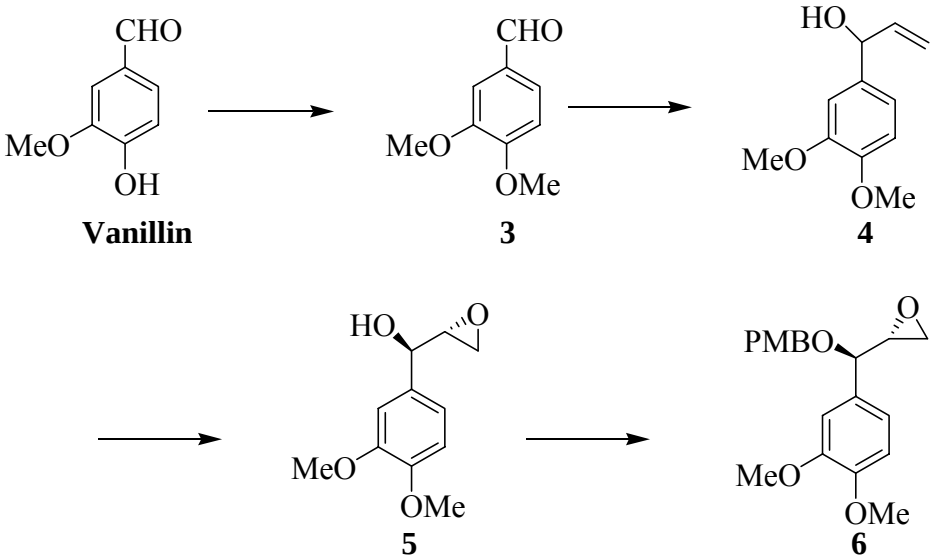
Figure 1

Our synthetic strategy for the total synthesis of crassifoside F (**1**) relies on the ring closing metathesis (RCM) reaction of diene **17** followed by epoxidation of the

resulting alkene as the key step. In the forward sense, the construction of diene **17** for RCM reaction requires sterioselective β-glycosidation of D-glucose derived orthoester **14** as glycosyl donor and alcohol **11** as aglycone followed by alkylation of *secondary* hydroxyl group at C-2 of sugar as vinyl ether. Glycosyl acceptor part would be synthesized by employing the sequential opening of suitably protected terminal epoxide **6** with lithiated anion of dithiane **7**. Epoxide **6** would arise from Sharpless asymmetric epoxidation of suitably substituted vinyl compound and the dithiane **7** in other words could be prepared from vanillin.

The first target of synthesis was to synthesize glycosyl acceptor part **11,** which was started with the 3-methoxy-4-hydroxybenzaldehyde (vanillin) following a reaction sequence. First methyl ether protection of lone *phenolic* hydroxyl group of vanillin using methyl iodide followed by vinyl Grignard of the resulting aldehyde **3** gave the racemic mixture of required allylic alcohol **4** for the kinetic resolution by Sharpless Asymmetric Epoxidation (SAE). The SAE of **4** results in the desired epoxide **5** whose free hydroxyl group was then protected as *p*-methoxy benzyl ether and resulting compound **6** was further used for the synthesis of aglycone **11 (**Scheme 8).

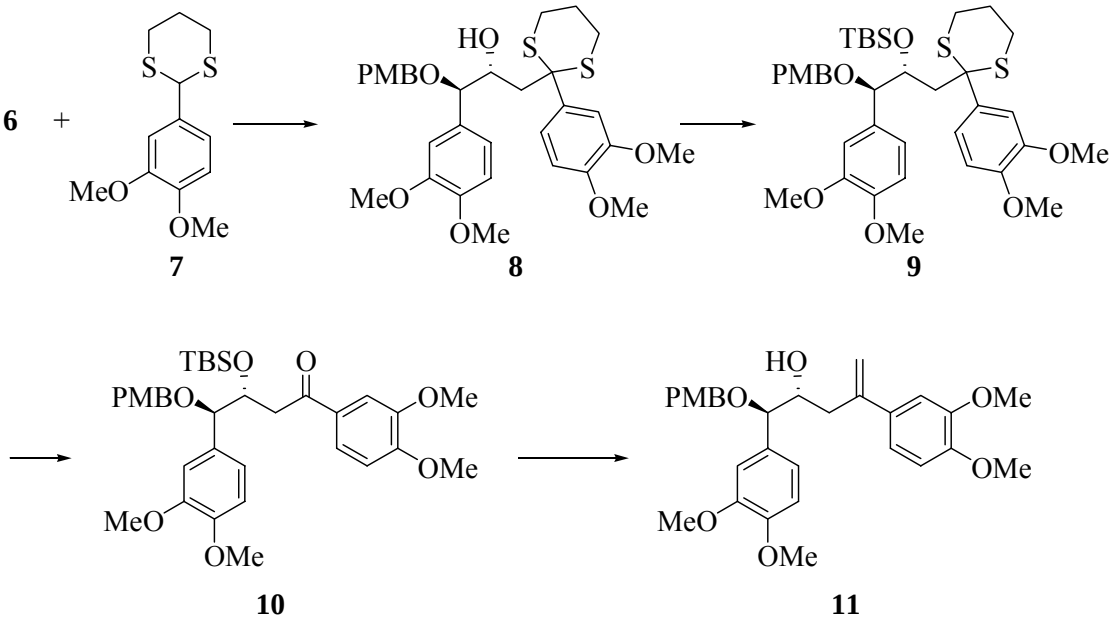
Scheme 8



As we could secure the dithiane **7** with an excellent yield from the aldehyde **3** and the epoxide **6** was already in hand, our attention was then turned towards their union. Generation of the lithiated anion of the dithiane to open the epoxide was attempted using *n*-BuLi. Resulting *secondary* hydroxyl group of coupled product **8**

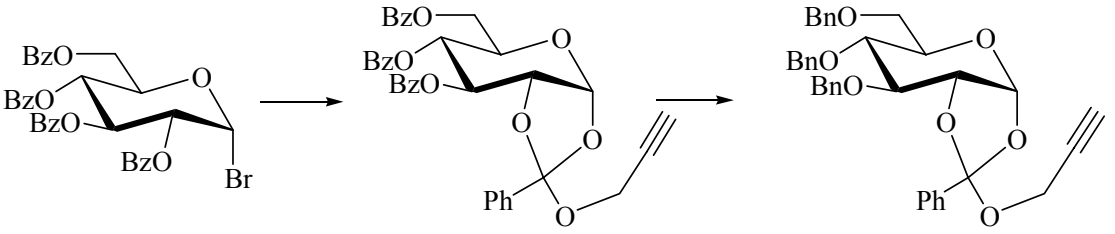
was protected as silyl ether using TBSOTf followed by deprotection of dithiane group of **9** to obtained ketone **10** which was subsequently treated for *1-C* Wittig reaction to obtain alkene and subsequent deprotection of TBS ether resulted in the required aglycone **11** for the glycosidation reaction (Scheme 9).

Scheme 9



After having aglycone **11** in our hand, next, concern was preparation of glycosyl donor **14**. To continue our synthetic endeavor, 3,4,6-tri-*O*-benzoyl propargyl orthoester **13** was prepared by a known procedure from 2,3,4,6-tetra-*O*-benzoyl glucosyl bromide **12** using propargyl alcohol and 2,6-lutidine and benzoate group of which was hydrolyzed using NaOMe in THF followed by benzylation of all free hydroxyl group which resulted in the formation of glycosyl donor **14** (Scheme 10).

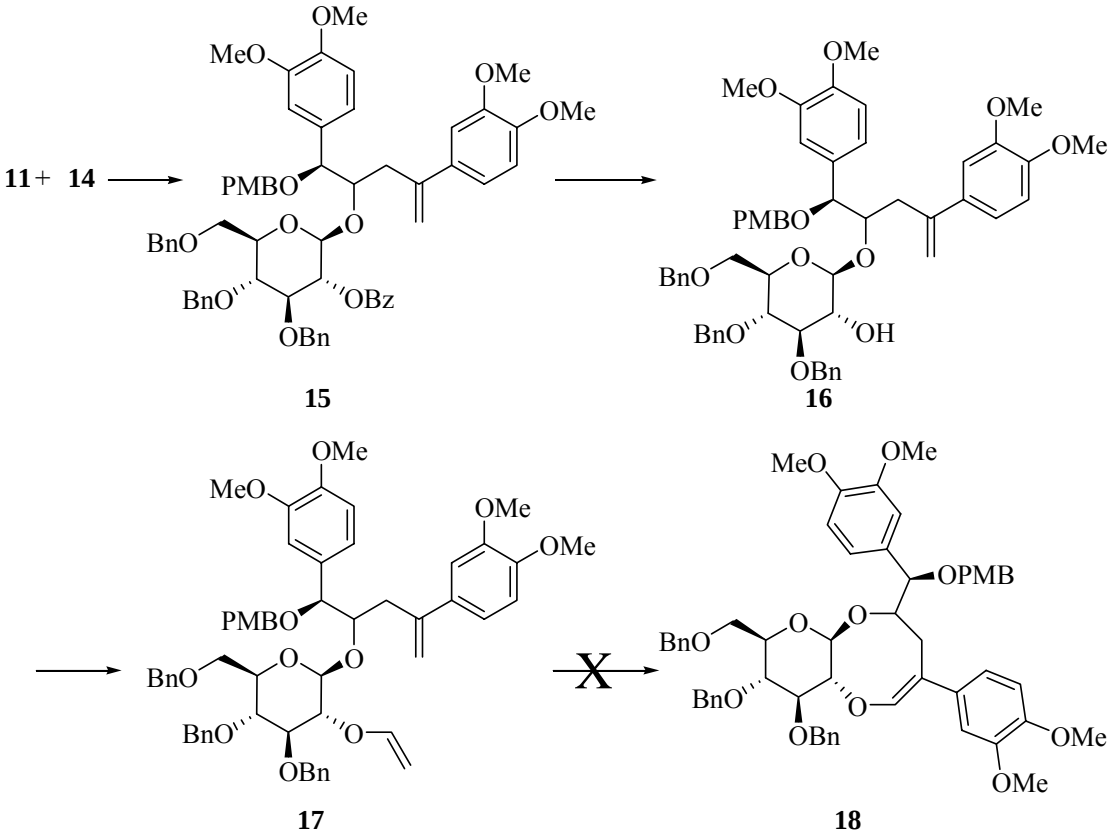
Scheme 10



Having glycosyl acceptor and donor in hand, our next target was to synthesize 8-membered core of crassifoside F. We were successful in glycosidation using propargyl glucoorthoester as glycosyl donor and $AuBr_3$ as promoter. Next, hydrolysis of benzoate ester of glucoside **15** followed by alkylation of *secondary* hydroxyl group

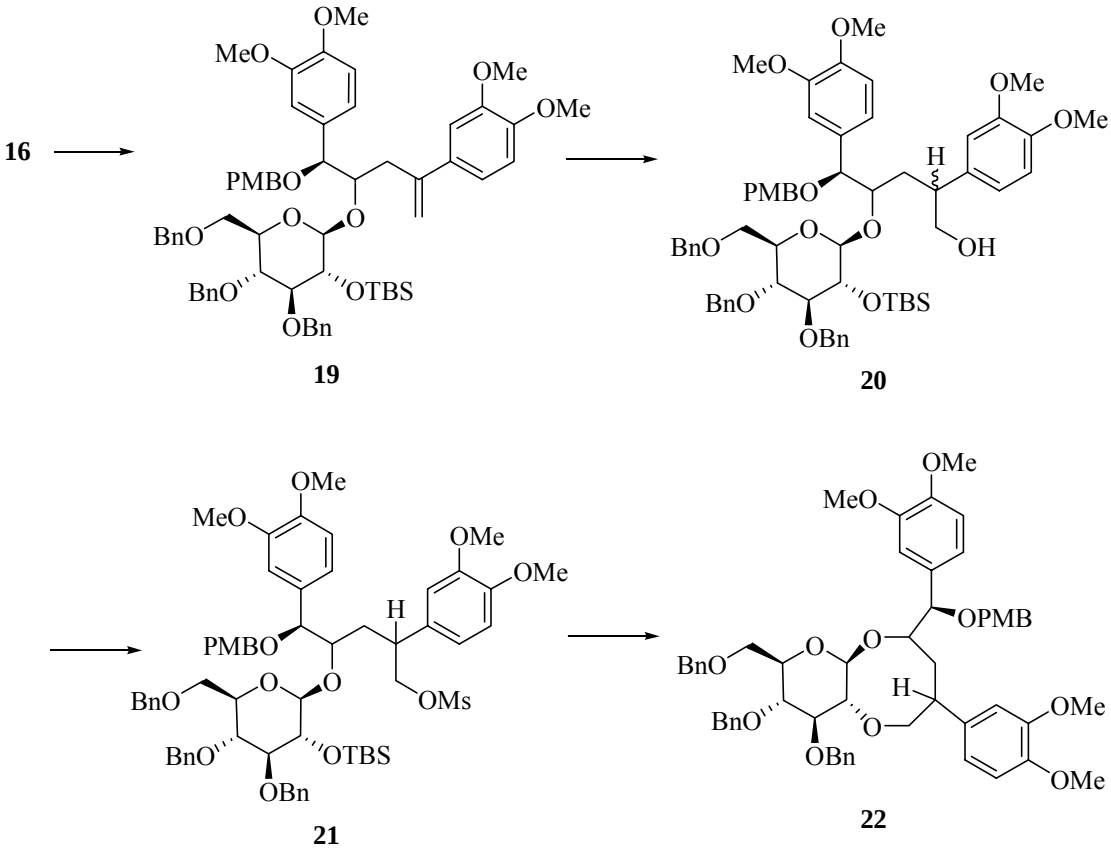
of **15** as vinylether to obtained diene **17** gave ring-closing metathesis (RCM) precursor. Several attempts towards the cyclisation of diene **17** using Grubbs' 1st and 2nd generation catalysts were unsuccessful (Scheme 11).

Scheme 11



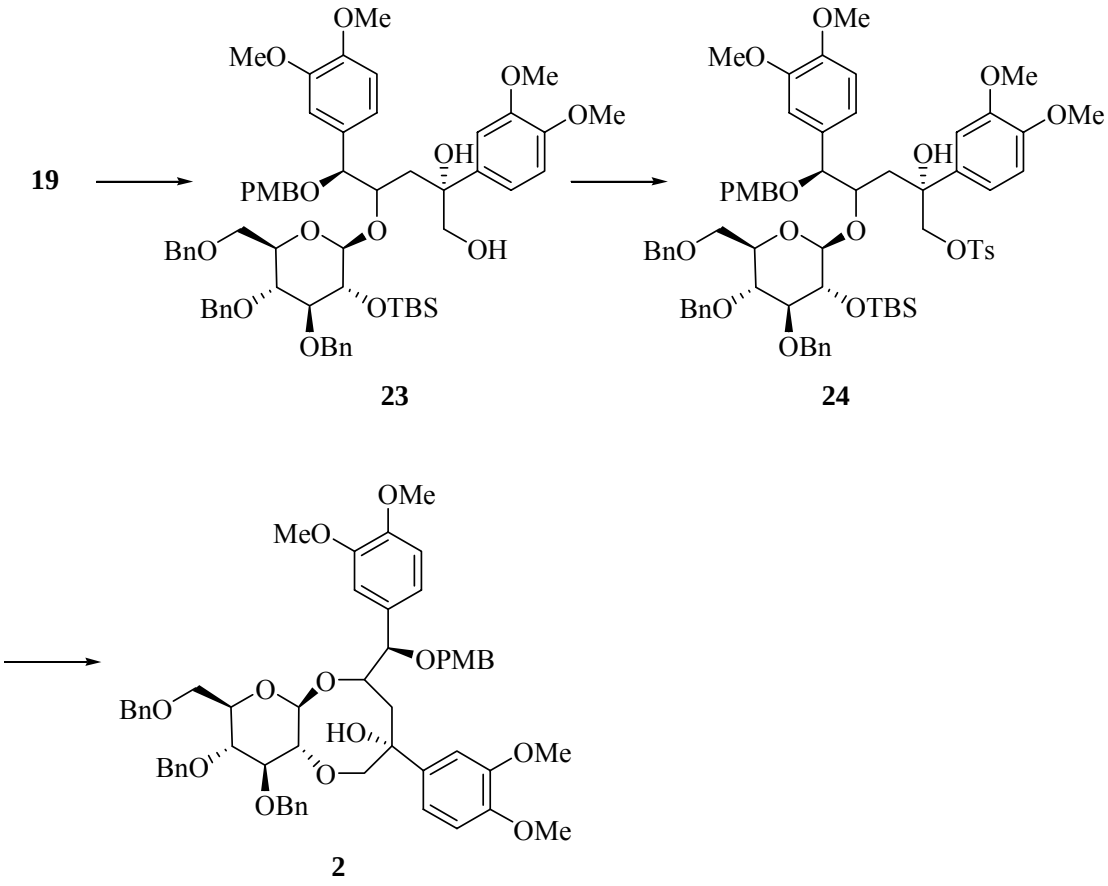
After several hardships in driving RCM reaction, the synthetic endure was altered as an S_N2 displacement of an appropriate tosylate or mesylate. Accordingly, the lone *secondary* hydroxyl group of glucoside **16** was protected as silyl ether using TBSOTf and 2,6-lutidine and the resulting alkene **19** was subjected to hydroboration reaction using $BH_3.SMe_2$ which results in the alcohol **20** as the product in inseparable 3:7 diastereomeric ratio. The lone hydroxyl group of **20** was converted mesylate ester **21** using MsCl in pyridine and both the isomers were separated by column chromatography. Then the mesylate ester **21** was treated with TBAF in anhydrous THF which resulted in the cyclic product **22**. Though ^{13}C NMR spectrum of compound **22** was well correlated with the desired product but newly generated chiral carbon and carbon attached to that appeared as pairs of doublets (Scheme 12).

Scheme 12



Then once again we thought of changing our strategy, to commence our altered synthetic endeavor, the alkene **19** was subjected to asymmetric dihydroxylation (AD) using AD-mix-α in *t*-butanol and water resulted in the diol **23**. The *primary* hydroxyl group of diol **23** was then converted to tosylate using TsCl in pyridine. Then the tosylate ester **24** was treated with $n\text{-}Bu_4N^+F^-$ in anhydrous THF for the deprotection of the silyl group which resulted in the cyclic product **2** (Scheme 13).

Scheme 13



In conclusion, eight membered cyclic core of crassifoside F has been synthesized in highly stereoselective manner exploiting salient features of Sharpless asymmetric kinetic resolution and Sharpless asymmetric dihydroxylation reaction. In addition, we developed a novel stereocontrolled protocol for the synthesis of novel glucoside crassifoside F.

Note: Compound numbers in the abstract are different from those in the thesis

Chapter 1: Divergent Synthesis of Spirocyclic Small Molecules

1.1 Introduction

Modern methods for stereoselective organic synthesis have increased the efficiency with which small molecules can be prepared. The stereloselective organic synthesis always has been very challenging and lots of attention paid to this area especially in the last few decades and have witnessed the drastic advancement. The art of organic synthesis which is better known as Target Oriented Synthesis give access to the compounds having biological and pharmaceutical importance. Target for the synthesis varies from different natural products isolated from different plant sources, microorganisms or fermentation sources and possess interesting biological properties.[1] Many of the elements which one can look for the selection of target for the synthesis are basic skeleton, chiral centers, and last but not least biological properties.

The first total synthesis of any naturally occurring compounds which is reported in literature is equilenin, which was synthesized by the Bachmann, Cole, and Wilds and appeared in literature in 1932.[2] The equilenin possesses a tetracyclic core and was considered to be very challenging for the total synthesis that time and its total synthesis was a milestone in the era of total synthesis. After the historic first total synthesis of equilenin, in 1960s and 1970s much attention was paid to the total synthesis of different antibiotics because of their importance in human life.[3] With the advancement of new characterization techniques particularly UV, IR, and most dramatically NMR and MS, which make possible quantum level thinking and gave access to the complex molecules such as non aromatic steroids containing minimally six stereogenic center with extra provision to generate further stereogenicity or long chain poly ether ciguatoxin and many more by synthetic means. The discovery of retrosynthetic analysis by Corey in 70s while the synthesis of longifolene, added new dimensions to the art of total synthesis.[4]

Target-oriented synthesis (TOS) generally depends on retrosynthetic analysis and synthetic endure starts with a structurally simple compound called synthons and will be transformed in to a structurally complex architecture. The reactions that joining together two different building blocks called fragment-coupling reactions are of great importance and the reactions which generate structural complexity are also of considerable value and

used widely in target-oriented synthesis. Tandem reactions, which are also called as "domino" or "cascade" reactions, form several covalent bonds in one sequence without isolating the intermediates and produce complex polycyclic architectures and sometime reduce the number of steps while planning a synthetic strategy and hence are of considerable importance. Retrosynthetic analysis plays vital role while planning synthetic strategy for target-oriented synthesis. Targets are often a single natural product, drug or "drug like" compound libraries with common structural features and predetermined biological properties.

The developments of new synthetic methodologies are of utmost importance in target-oriented synthesis and particularly last 25 years have witnessed revolutionary advances in the form of new, enabling reactions. Many of these developments including cross-coupling processes,[5a] trans metal driven cyclizations,[5b] olefin metathesis,[5c] as well as enantiospecific oxidations[5d] and reductions.[5e] The development of chiral auxiliaries[5f] for the control of relative stereochemistry, which then translates to absolute stereochemistry, was certainly among the major advances. Development of asymmetric reactions such as Sharpless asymmetric epoxidation and chiral catalyst such as $(DHQ)_2PHAL$ etc. were again found to be very helpful. Development of solid phase synthesis enables a synthetic chemist to synthesize long chain peptide, compound libraries of natural products or natural products analogs oligosaccharides and bioconjugates with minimal efforts. Though nature is considered as the best chemist and can synthesize any molecule with different size and awesome numbers of chiral centers just starting with the simple substrates such as acetic acid or hexoses, but nature does not have advantage of some C-C bond formation reaction such as ring-closing metathesis reaction which enable a chemist to synthesize large ring compounds very easily. Even with all of the advances, TOS is a fickle science of limited predictive capacity. However with considerable advancement of the art of organic synthesis, both in the development of novel methodologies and in the total organic synthesis are bridging the gap between the isolation and structural elucidation of natural products from the plants and various other sources and discoveries of new drugs. The stunning records of successes from equilenin to ciguatoxin suggest that no natural product structure is inaccessible to total synthesis (Fig 1).

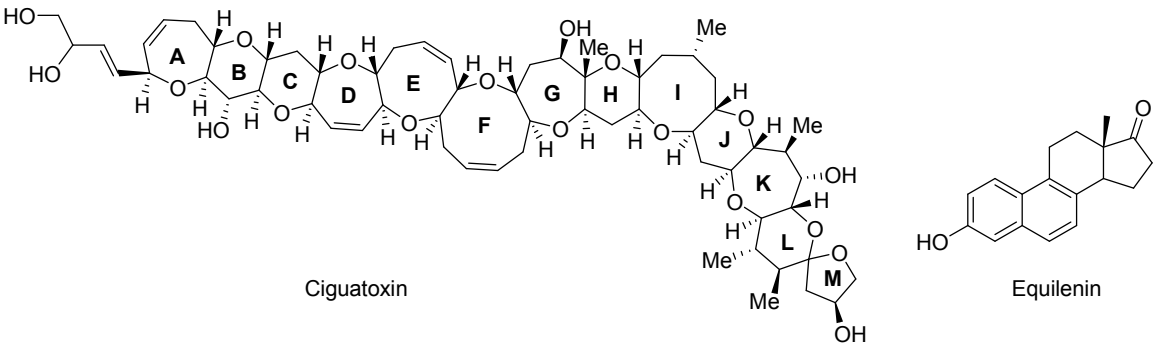


Figure 1

Combinatorial Organic Synthesis (*COS*)

Historically, the main source of biologically active compounds used in drug discovery programs has been natural products, isolated from plant, animal or fermentation sources, additionally natural products are small molecules from the nature synthesized by biosynthetic pathways and show high degree of structural diversity, but they are often mixtures and making it very difficult to identify natural active constitutes, generally abundance of natural products is very low and development of methodologies to synthesize natural products are often very costly and natural products are sometime structurally very complex so its very difficult to synthesize analogues. These complications of target oriented synthesis lead to the discovery of an algorithm in organic synthesis called combinatorial organic synthesis (COS).

Combinatorial chemistry is one of the important new methodologies developed by academics and researchers to reduce the time and costs associated with producing effective and competitive new drugs. Combinatorial chemistry allows synthesis of vast number of compounds indeed millions of compounds within a short time period. The collection of compounds synthesized (libraries) are either natural products like compounds or drugs or "drugs like" compound libraries which can be screened in bulk to get lead or a hit molecule(s). Since nature produces large number of diverse compounds with different functional groups and awesome number of chiral centers, therefore it is very important to design a COS strategy in such a way that, compounds libraries can give access to the highly diverse skeletons. The field represents an area at the interface of chemistry and biology and plays a major role in drug discovery process. The last decade

has seen a rigorous advancement in the area of combinatorial organic synthesis after its discovery in early 90s not only manually but also by automated means such as robotic while combinatorial chemistry can be explained simply, its application can take a variety of forms, each requiring a complex combination of classical organic synthesis techniques, rational drug design strategies, robotics, and scientific information management.

Approaches to Combinatorial Chemistry

As with traditional drug design, combinatorial chemistry relies on organic synthesis methodologies. The difference is that, instead of synthesizing a single compound, combinatorial chemistry exploits automation and miniaturization to synthesize large libraries of compounds. But because collection of libraries does not produce active compounds independently, so it is also required to find out a straightforward way which leads to the active components within these enormous populations. Thus, combinatorial organic synthesis (COS) is not random, but systematic and repetitive, using sets of chemical "building blocks" to form a diverse set of molecular entities (Fig. 2).[6]

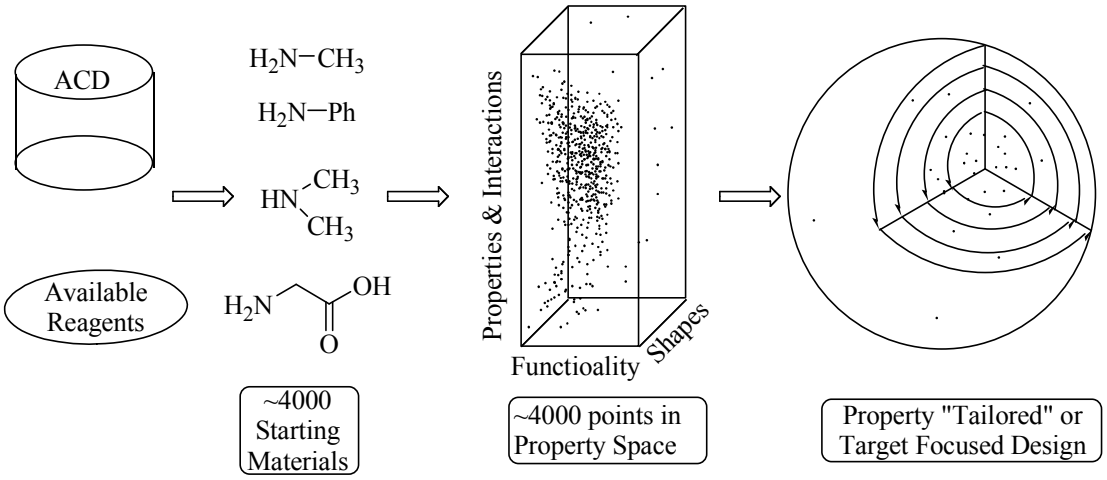


Figure 2: *Schematic illustration of designing a "tailored" combinatorial library. Candidate reagents are selected, properties are computed, candidates are assigned to bins, and a small number of substituents are selected which maximize diversity while matching a desired profile of key pharmaceutical properties.*

Scientists have developed several different COS strategies, with a focus to design the libraries in such way that it results in the maximum lead or hits. "Natural products like" or "drug like" libraries fix well in the above said criterion and give the maximum possibilities of getting a hit or lead because of predetermined properties of basic skeletons. The libraries synthesized are evaluated individually or collectively using various screening techniques such as florescence microscopy, colorimetric assays etc.

There are three common approaches to COS. During arrayed, spatially addressable synthesis, building blocks are reacted systematically in individual reaction wells or positions to form separated "discrete molecules." Active compounds are identified by their location on the grid. This method has been applied in R&D scale as well as in bulk. The second technique, known as encoded mixture synthesis, uses nucleotide, peptide, or other types of more inert chemical tags to identify each compound. In the third approach, a series of compound mixtures were synthesized combinatorially, each time fixing some specific structural feature which can be pre-selected and then assayed as a mixture and the most active combination is pursued. Again same strategy could be repeated by varying some features such as basic skeleton, functional groups, ring size in order to get distinct structures with potential properties and can be synthesized as a bulk and screened. Scientists working with peptides, for example, can use deconvolution to optimize, or locate, the most active peptide sequence from millions of possibilities. Thus combinatorial chemistry is a technologically advanced way of finding a needle in a haystack. The whole idea is to remove the presumption and instead, to create and test as many compounds or mixtures as possible--logically and systematically--to obtain a viable set of active leads.

Diversity-Oriented Syntheses (DOS)

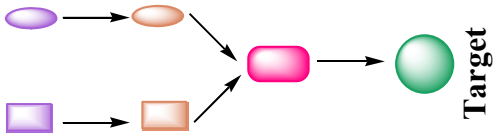
Already having TOS which gives access to the small molecules natural products by synthetic means and COS which provide access to the libraries of natural products like compounds, still there is demand to develop new methods which can give access for the collection of structurally diverse small molecules. Though Combinatorial Chemistry allows for the synthesis of vast numbers of compounds; indeed, millions of compounds but the problem with combinatorial chemistry so far is that the compounds having a

limited structural diversity which is due to the similar building blocks and starting scaffolds. In order to achieve structural diversity, the building blocks, the stereochemistry, the functional group and most importantly the molecular framework must be varied. The small molecules have been used to explore many facts of biology for a long time and generation of libraries of pure structurally-diverse compounds is key to the discovery of new medicines and to the elucidation of biological pathways through chemical genetics. Traditional genetic approaches have studied biological systems by the generation of random mutations which are then screened in search of a specific cellular or organismal phenotype. In analogy to the genetic approach, large random collections of small molecules can be utilized to shed light on the roles of specific proteins in many biological pathways.

During the last few decades, there has been a great push for the development of novel synthetic methodologies that lead to complex natural products, natural product-like molecules, and simpler analogues of natural products in an efficient manner. Tremendous progress has been made in asymmetric synthesis for the development of stereo- and enantioselective reactions. The origin of diversity-oriented synthesis dealing with organic synthesis emerged during the last few years and was largely due to the extensive time period required for the identification and synthesis of drug-like candidates and novel materials and because of their limited availability. Diversity-oriented synthesis (DOS) is an important aspect of combinatorial chemistry. Multicomponent reactions and cycloaddition reactions are commonly used in DOS to construct complex library scaffolds with distinct skeletal, substitution and stereochemistry variations. Over the past few years, we have observed the impact of diversity-oriented synthesis in the development of high-throughput synthesis of focused libraries and in chemical genetics. It is anticipated that the next era will involve diversity-based synthesis of natural product like compounds to explore their applications in emerging genomics and proteomicsrelated research activities.[7]

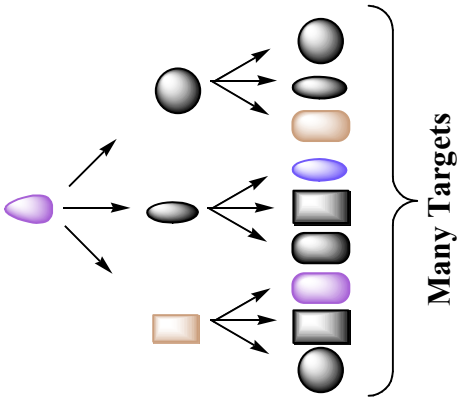
Target-Oriented Synthesis: Convergent

- Complexity-generating reactions
- Fragment-coupling reactions
- Retrosynthetic Analysis



Diversity-Oriented Synthesis: Divergent

- Complexity-generating reactions
- Multicomponent-coupling reactions
- Branching pathways
- Forward synthetic analysis



The success of the field of *Chemical Genetics* is based on the principle that small molecules may be used to perturb, and hence to interrogate, complex biological mechanisms[8] and complex structures are likely to interact with targets more selectively than flat and simple molecules therefore, structural complexity is desirable for cells selectivity. The complexity of biological systems arises from the combinations of interactions possible between macromolecules (especially proteins); these interactions are often regulated by post-translational modifications, which may be difficult to probe using a classical genetic approach alone. Dissecting biology is an immense challenge for the next decade and beyond: the functions of all proteins identified from the genome must be determined, the *in vivo* relevance of post-translation states and interaction targets recognised, and the effects on cellular physiology established. The use of small molecule probes in *Chemical Genetics* confers a number of advantages over more conventional approaches: (1) the effects of small molecules are rapid, reversible and conditional; (2) activity may be tuned by varying the ligand(s) concentration; (3) the many functions of individual proteins may often be teased apart[9] and (4) more than one small molecule effector may be used in combination to study the interplay between proteins.[10] The

approach is particularly useful for investigating tightly coordinated, dynamic biological mechanisms, especially when classical genetics may render the organism inviable.[11]

Library Designing

A key challenge in Chemical Genetics is the design and synthesis of libraries which span large tracts of biologically-relevant chemical space.[12] Natural products necessarily reside in such chemical space, since they bind to both their biosynthetic enzymes and target macromolecules; indeed, some natural products, such as trichostatin,[13a] wortmannin[13b] and brefeldin A,[13c] have been directly exploited as valuable tools in chemical genetic studies (Fig. 3).

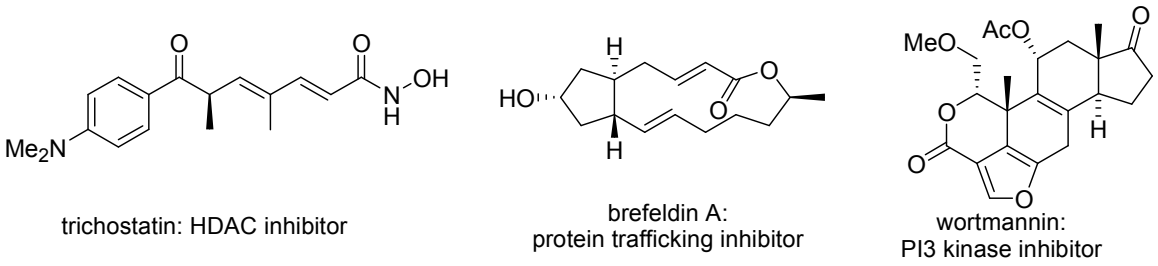


Figure 3: Few natural products as tools in chemical genetic

Unfortunately, natural products are not available in pure form and are usually screened as mixtures of many compounds, leaving problem of the purification and identification of active component and the natural product extract accessibility is limited. The natural product may be so complex structurally, such as Vancomycin (Fig. 4), that to develop methodologies for the making analogues and to optimize activity is fearsome synthetic challenge and lastly, chemical space such as space occupied by the natural products, synthetic compounds, combinatorial libraries is so large but the chemistry space encompassed by natural products (and drug-like compounds) is unlikely to be the only region which shows properties of biological and therapeutic interest, and may not be very productive region. Chemical Genetics has spawned the field of diversity-oriented synthesis (DOS),[14] in which diverse molecules are assembled simultaneously and deliberately in up to *ca.* five synthetic steps, especially when coupled with an economical and efficient technology platform, offers the means to synthesize a collection of molecules. The diversity of DOS libraries may derive from the high substitutional,

stereochemical and – ideally – scaffold diversity of its members. Ultimately, the value of a DOS library must be counted in terms of *functional* diversity, that is, the ability of library members to perturb selectively the function of unrelated proteins.

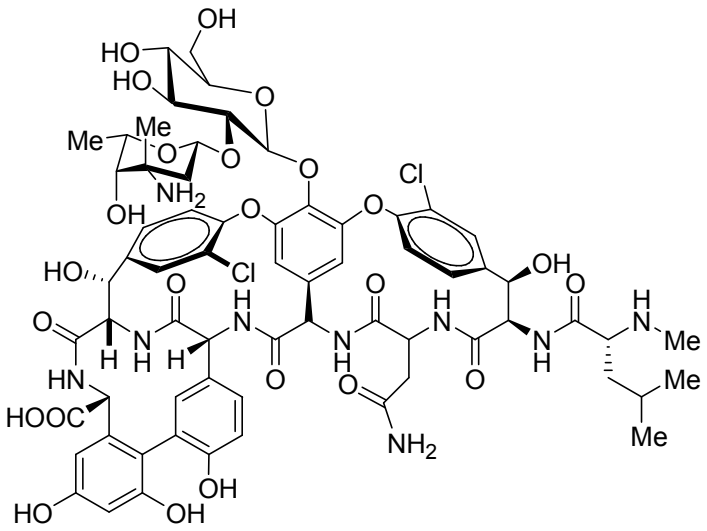


Figure 4: Vancomycin: Antibiotic

Synthetic drugs are often based on nitrogen-containing heteroaromatic scaffolds that have appropriate size and hydrogen bonding capacity to bind in the active site pockets of biological targets such as enzymes and some protein-coupled receptors. Some of these synthetic scaffolds have been identified as 'privileged' structures in that they have empirically demonstrated ability to bind multiple classes of protein targets such as HR22C16 and its analogues (Fig. 5).[15c]

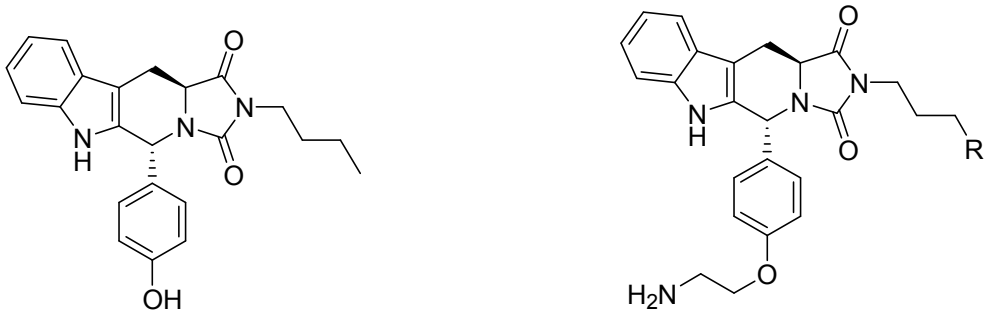


Figure 5: HR22C16: A synthetic Chemical Genetic Tool

On the other hand natural products show much greater structural diversity and complexity than synthetic drugs and generally contain a greater proportion of oxygen than nitrogen heteroatoms and a significant number of stereogenic centers. Few natural product families (e.g. alkaloids, carbohydrates etc.) are libraries of pre-validated, functionally diverse structures; these families are "privileged"[15] since individual compounds selectively modulate unrelated protein targets. Further, ligands based on specific natural product scaffolds with a predetermined properties have been shown to bind selectively to proteins with similar folds.[12b] In particular, natural product-like libraries will be in great demand because of the limited abundance of that over synthetic one and complementing the available natural products that are utilized for modulating (that is, activating or inactivating) protein function(s). It is well known that several, small-molecule, complex natural products meddle with protein-protein, carbohydrate-protein, and DNA-protein interactions. For example, in the area of protein-protein interactions, it is generally thought that the size and the rigidity of the structural elements within a small molecule tend to provide better binding/interfering agents. This is largely due to flat surfaces that are involved in most protein-protein interactions, although this may not be valid for the active sites for individual enzymes. Unsurprisingly, therefore, natural products have provided an inspiration for library design over 'drug-like' libraries and, hence the discovery of tools such as secramine[16a] and haptamide B (Fig. 6).[16b]

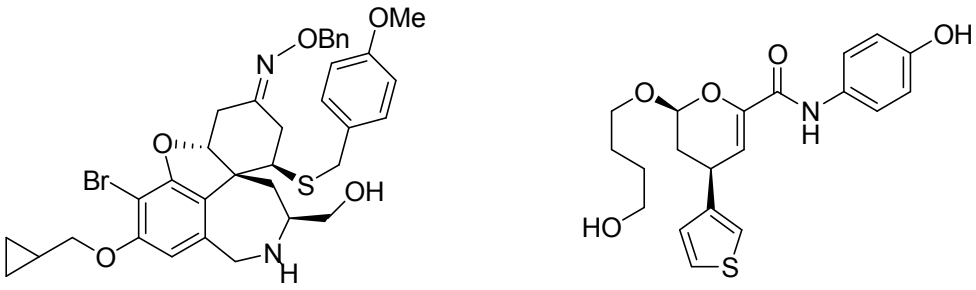


Figure 6: Natural Products as Chemical Genetic Tool

For this reason, it has been thought to design libraries of natural-products like oxygen-rich small molecules using carbohydrates scaffolds or simple sugars as synthons.

Amazingly this cheap and easily available class of compounds render available all the considerable points specified above for the libraries designing. The goal of achieving diversity in library design can be simplified by considering three distinct diversity elements: appendages, stereochemistry and skeletons.[14a]

Appendages Diversity

The simplest diversity-generating process is the central feature of combinatorial chemistry and involves the use of coupling reactions to attach different appendages to a common molecular skeleton. The efforts began with a complexity-generating reaction to yield a single, complex molecular skeleton having several attachment points followed by a series of diversity-generating appending processes to attach all possible combination of building blocks to this common skeleton. The complexity generating reactions such as Diels-Alder reaction, multicomponent reaction or oxidative cyclization reaction are very important. This one-synthesis/one-skeleton approach has proven to be general and highly efficient but impact has been limited may be because of compounds having a common molecular skeleton and display similar chemical properties in three dimensional chemical space.

Stereochemical Diversity

Stereochemical diversity increases the number of relative orientations of potential macromolecule-interacting sites in small molecules. It can best be achieved by using stereo-specific reactions that proceed with enantio- or diastereoselectivity. The corresponding transforms for these types of processes are well-known in the context of retrosynthetic planning. Since DOS involve transformation of a collection of substrates into a collection of products, it is critical that the processes used to generate new stereogenic centers both in selective and in general. The collective transformation of chiral substrates into products having increased stereochemical diversity requires powerful reagents that can override substrate favoritism and deliver diastereomeric products with very high selectivity.

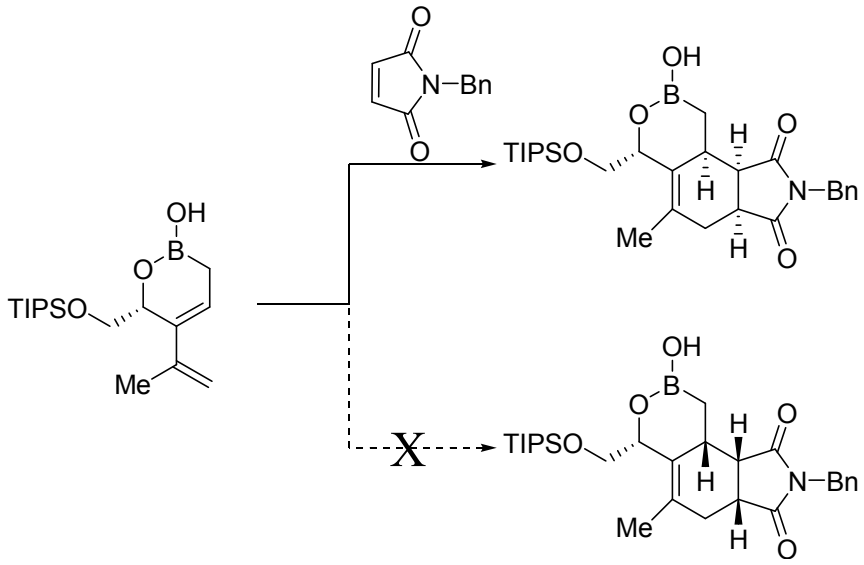


Figure 7: Substrate Controlled Stereoselectivity

For example the diastereoselective intermolecular Diels-Alder reaction was used to transform the chiral dialkenylboronic acid into cycloadduct with the selective formation of three stereogenic centers (Fig. 7). Since the diastereoselectivity of this transformation is under a powerful substrate control (steric factor due to TIPS-hydroxymethyl group) it may prove challenging to generate the opposite diasteromer.

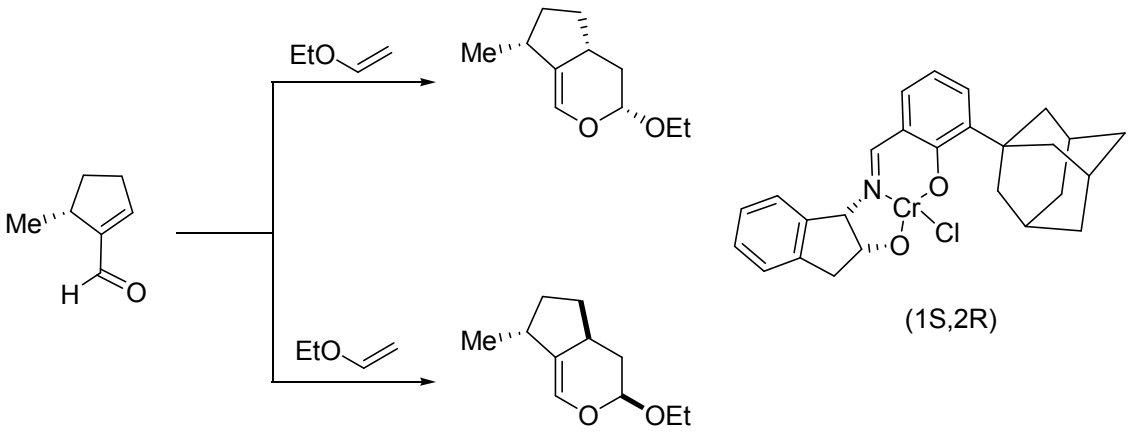


Figure 8: Catalyst Controlled Stereoselectivity

The transformation of enal in to dihydropyran cycloadduct (Fig. 8) is reagent controlled stereochemical transformation which allows access of both the isomers by using different chiral catalysts. The discovery of these types of powerful reagents is

critical to achieving stereochemical diversity in DOS. While the catalysts which are capable of controlling the face selectivity of one coupling partners, the development of double-diastereoselective reagents that can dominate the face selectivity of both the coupling partners, for example, to achieve *exo* versus *endo* selectivity in the Diels-Alder reaction, would be highly valuable.

Skeletal Diversity

DOS pathways that yield collections of products with many distinct molecular skeletons are particularly effective at achieving a diverse display of chemical functionality in three dimensional chemical spaces. There are, at present, two different strategies for planning DOS pathways that generate skeletal diversity. The first strategy involves using different reagents to transform a common substrate with the potential for diverse reactivity into a collection of products having distinct molecular skeletons (Fig. 9). In this case, diverse skeletons of small molecules can be accessed combinatorially by transforming a collection of substrates having different appendages that pre-encode

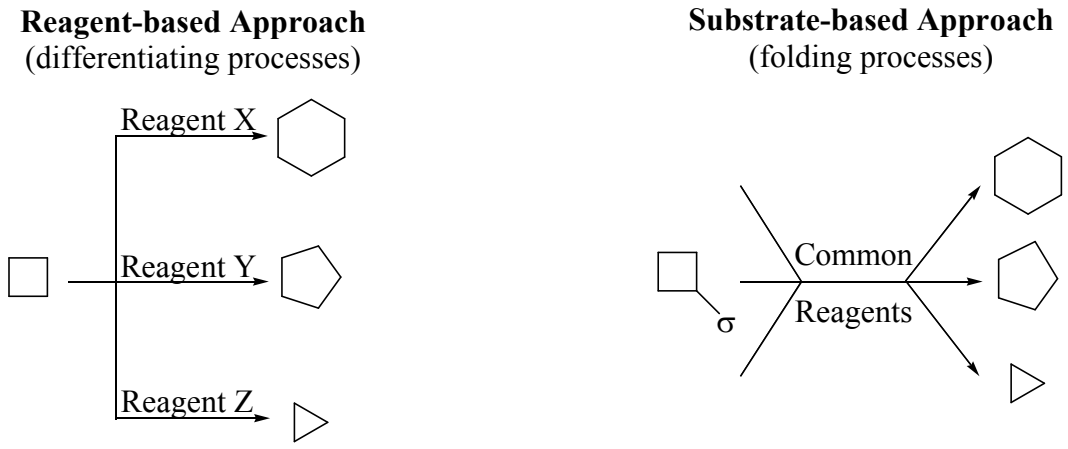


Figure 9: Two general approaches to generate skeletal diversity

skeletal information into a collection of products having distinct molecular skeletons using common reaction conditions thus, these substrate-based skeletal diversity-generating transformations are referred to as folding processes in forward-synthetic analysis. An advantage of this approach is that sets of chemical information can be

identified that act in combination, that is, a set of pre-encoded chemical informations of all combinations of distinct skeletal outcomes.

An attractive feature of folding process approach is that skeletal diversity can be pre-encoded into substrates combinatorially, thus making it possible to generate a complete matrix of molecular skeletons in an efficient manner and products having distinct diverse molecular skeletons. Since strategy allow maintaining relative structural similarity in the early stages of a synthesis and give new skeletons later on, can facilitate the generation of functionalized skeletons that might be otherwise difficult to access in DOS, especially those having building blocks coupled via carbon-carbon bonds at stereogenic quaternary carbon centers. This strategy can provide access to a collection of compounds potentially representing all possible combinations of building block, stereochemical, and skeletal diversity elements.

Screening of the Library: "Lead compounds"

Compounds having biological activity can be identified by screening diverse collections of compounds (i.e., libraries of compounds) produced through either molecular biological or synthetic chemical techniques. Such screening methods include methods wherein each member of the library is tagged with a unique identifier tag to facilitate identification of compounds having biological activity or where the library comprises a plurality of compounds synthesized at specific locations on the surface of a solid substrate wherein a receptor is appropriately labeled to identify binding to the compound, e.g., fluorescent or radioactive labels. Central to these methods is the screening of a multiplicity of compounds in the library and the ability to identify the structures of the compounds which have a requisite biological activity. Preferably, in order to facilitate synthesis and identification, the compounds in the library are typically formed on solid supports wherein the compound is covalently attached to the support via a cleavable or non-cleavable linking support. In this regard, libraries of diverse compounds are prepared and then screened to identify "lead compounds" having good binding affinity to the receptor. Pharmaceutical drug discovery relies heavily on studies of structure-activity relationships wherein the structure of "lead compounds" is typically altered to determine the effect of the alteration on activity. Modification of the structure

of the lead compounds permits evaluation of the effect of the structural alteration on activity. Thus libraries of compounds derived from a lead compound can be created by including derivatives of the lead compound and repeating the screening procedures. Preferably, the compounds are synthesized *in situ* on the solid support so that the support can be tagged to identify the synthetic steps employed and/or the derivative incorporated onto the support. However, relatively simple synthetic methods to produce a diverse collection of such derivatives on the supports are often not available (Fig. 10).

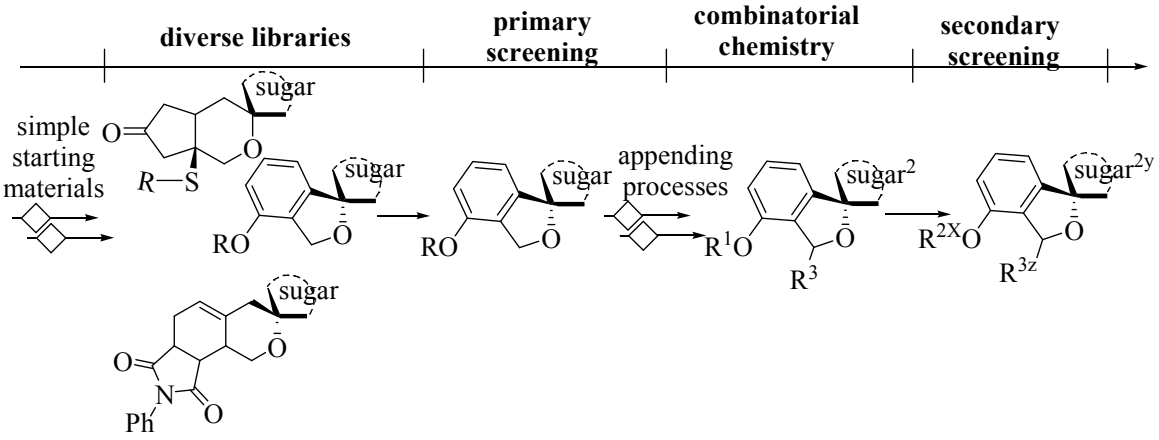
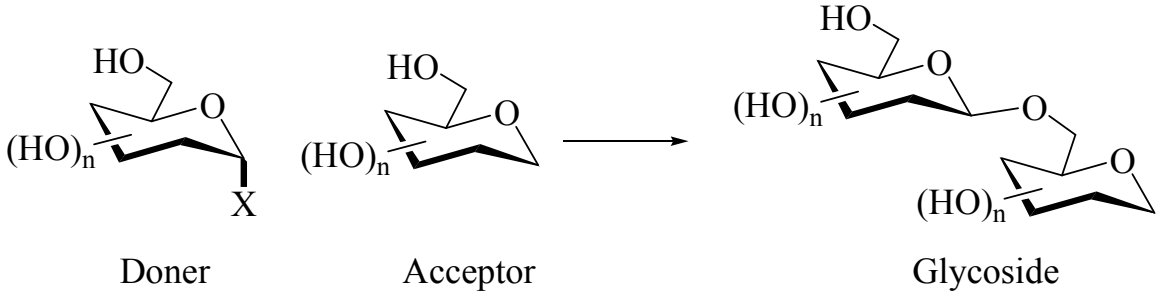


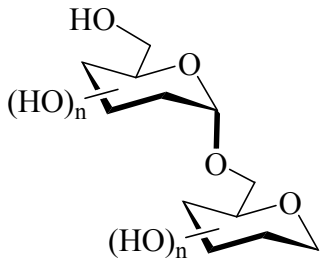
Figure 10

Structural diversity of Carbohydrates

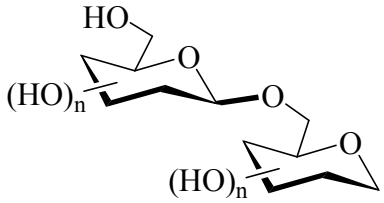
Carbohydrates contain lots of linkable hydroxyls unlike proteins or nucleic acids. However, not all of the hydroxyl groups make linkages. Sugar donor's reducing terminals (usually C_1 or anomeric positions of 6-carbon sugar) make acetal form by binding to non-reducing hydroxyls of sugar acceptor.



For instance, each monomer of 6-carbon sugars such as glucose, galactose, and mannose has a reducing terminal and four non-reducing hydroxyls. Therefore, there are four ways for two equal monomers to bind and carbohydrates can form α- & β-stereoisomers. Addition to this, sugars also have furanose form as well and there are more ways.



α -Linkage



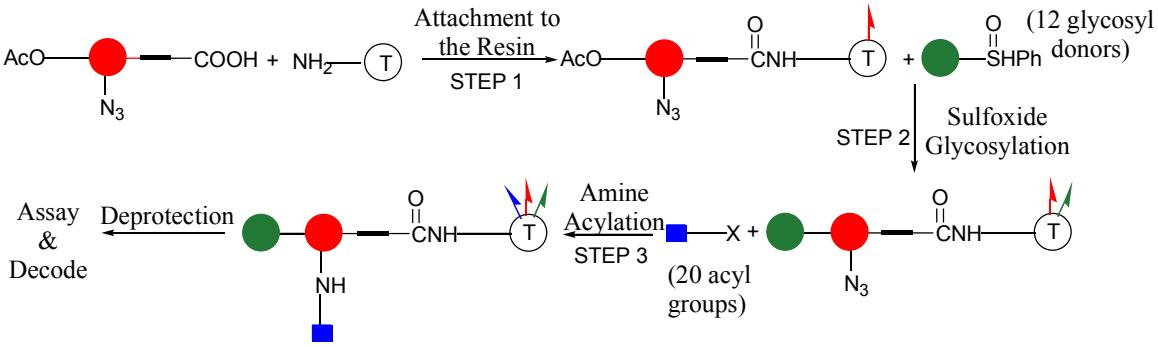
β-Linkage

Having four chiral centers with extra provision at anomeric carbon along with many hydroxyl groups and several determined reactions and pathways to achieve complex structures in the form a polycyclic oxygen rich compounds libraries, sugars are the ideal templates for a promising and exciting synthesis towards novel drug discovery through DOS.

Carbohydrate Library Synthesis

Carbohydrate library was started much later than protein or nucleic acid libraries. First of all, it was thought that proteins mainly controlled most of the important actives in living cells and carbohydrates were only for partial structures and energy storages which take part only in some biological processes. However, after recently carbohydrate series signal transduction molecules like inositol and various functions of carbohydrates are found, carbohydrate became the new library candidate.

The first library was reported by Daniel Kahne.[17] His library was library of simple carbohydrate structures with various substitutes. To be precise, even though it was a carbohydrate library, it was a small molecule type library which is different from natural carbohydrate structures (Fig. 11).



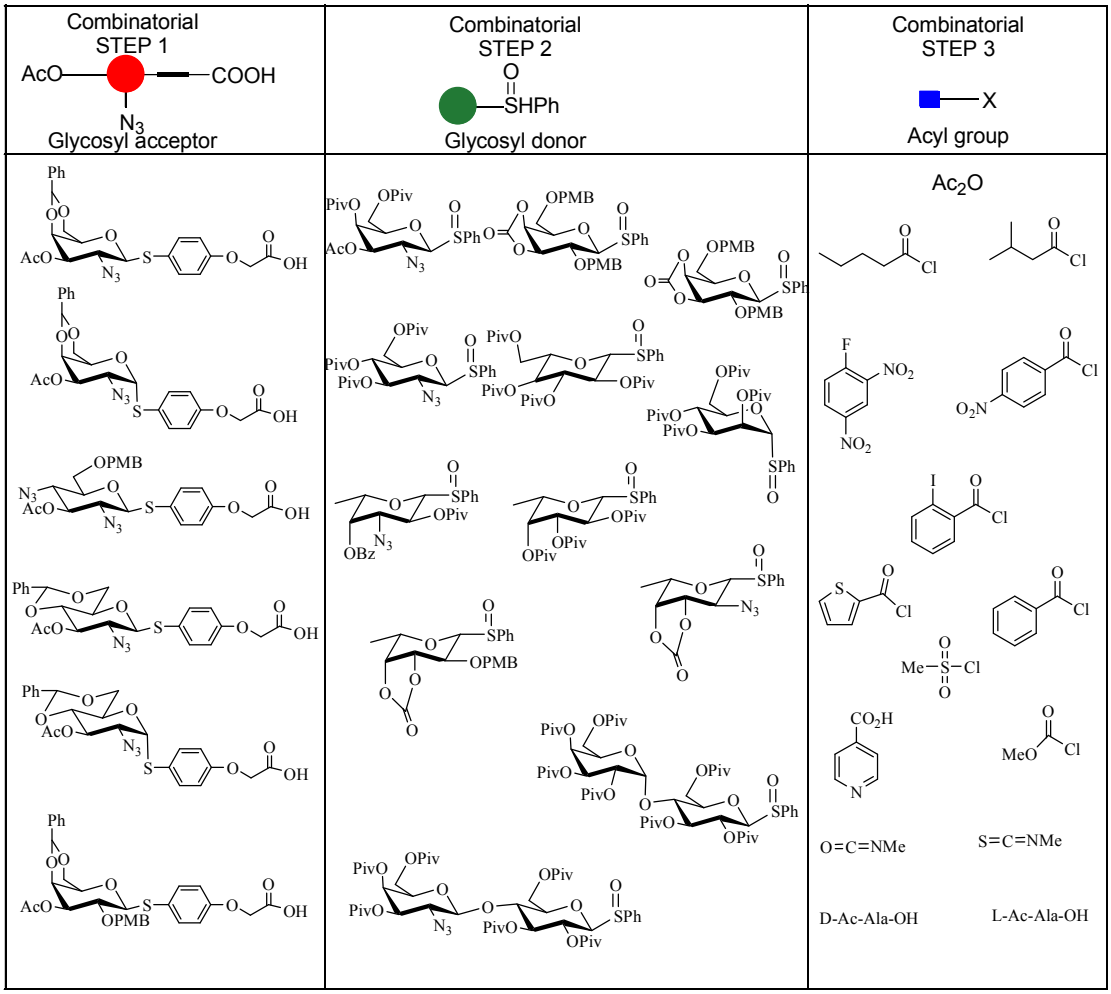


Figure 11: Kahne's solid phase carbohydrate library

Wong at Scripps Research Institute propelled a research to synthesize oligomers by doing several steps of glycoside reactions at once without filtration step. He examined reactivity of hundreds of carbohydrates from glycoside reaction, and then built database of the reaction rates. As solid phase peptide synthesis, Samuel Danishefsky at Columbia

University has worked on solid phase synthesis of carbohydrate oligomers. He suggested possibility of automated system to synthesize carbohydrate oligomers by developing glycals as sugar donors, and Seeberger at MIT built an automated synthesizer which enables solid phase carbohydrate oligomer synthesis. Even though it is limited to synthesize only 10 or less oligomers due to low yields, it is an epochal method to bring revolutionary development to this field.

As it is evident from the above account, there is not much development in DOS library derived from carbohydrates. The libraries which are reported in literature are either disaccharide libraries eg Khane's approach or oligomers libraries eg. Wong, Danishefsky and Seeberger's approach, but to the best of our knowledge there is no report for the carbohydrate derived spirocyclic DOS library.

Accordingly, in order to develop new DOS libraries to search lead compounds of therapeutic importance, it would be highly desirable to be able to generate very large libraries of diverse spirocyclic derivatives. This work is directed to general synthetic methods for generating large libraries of diverse spirocyclic compounds using various complexities generating reaction utilizing carbohydrate scaffolds.

1.2 Present Work

The target oriented synthesis (TOS) is primarily based on nature to discover small-molecules with useful, macromolecule-perturbing properties. Natural molecules can be identified in screens of extracts mixtures, isolated, and then structurally characterized by using various spectroscopic techniques and after identification, can be target for chemical synthesis. The target is often known to have useful perturbing functions. But natural products precise in small region of chemical space and often not most fertile region for discovering small-molecules that transform macromolecular function in useful ways. Given the extraordinary potential for such small molecules to promote the understanding and betterment of human health, it is required that organic chemist begins to answer this question. The one aim of diversity-oriented synthesis is to meet this challenge. The efficient, simultaneous synthesis of structurally diverse compounds, known as "Diversity-Oriented Synthesis" (DOS), is not obvious and remains as a challenge to synthetic chemists. DOS involves the planned, simultaneous and efficient synthesis of more than one target compound in a diversity-driven approach to answer a complex biological problem. Diversity-oriented synthesis (DOS), which aims to yield skeletally and stereochemically diverse products having high appending potential, may prove to be an effective means of exploring biology and medicine with chemistry.

Many natural products possess spirocyclic moieties and the inhibition of the protein function was often found to be due to the inherent conformational rigidity of the spirocycles in the conformation of peptides, carbohydrates etc. As a result, the synthesis of libraries having *spiro* moieties has attracted a lot of attention in recent times. One of the preferred methods to prepare the *spiro* unit exploits a ring closing metathesis reaction using Grubbs-catalysts. Several groups have investigated spirocyclisation by metathesis and have synthesized *spiro*- compounds comprising peptides, carbohydrates and barbituric acids as their core scaffolds. Since carbohydrates are especially given the importance, in organic chemistry, in terms of addressing critical questions in life sciences this work is directed towards the divergent synthesis of spirocyclic, oxygen-rich and chirally homogeneous small molecules with an emphasis on molecular targets of

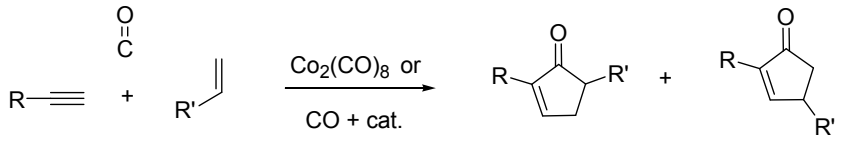
therapeutic potential utilizing sugar scaffolds as the precursor using range of complexity generation reaction such as Pauson-khand, Michael addition, Grubb's metathesis, Diels-Alder, and Hashmi's protocol for phenol synthesis.

Pauson-Khand Reaction

To begin synthetic endeavor to synthesize libraries of spirocyclic molecules we selected the Pauson–Khand reaction (PKR). Pauson–Khand reaction is formally a 2+2+1 cycloaddition involving a suitably substituted alkyne, an alkene and carbon monoxide moieties to form a cyclopentenone, was first discovered in the early seventies (Fig. 12).[18] Earlier cycloaddition was performed thermally using stoichiometric amount of $Co_2(CO)_8$. Although this reaction represented a dramatic increase in molecular complexity in proceeding from starting material to product, but have some limited applications into the synthesis of complex molecules because of steric and stereoelectronic effects. For instance, unless strained olefins were used, the efficiency of the cycloaddition was typically low. Moreover, the use of unsymmetrical alkenes led to mixtures of cyclopentenone regioisomers and the conditions required to effect this process (high temperatures and long reaction times) many times led to decomposition of starting materials and/or products. In 1981, Schore expanded the synthetic utility of this reaction considerably by attaching the alkene to the alkyne via a carbon tether and demonstrating the first intramolecular P-K cycloaddition, the reaction was carried out regioselectively with respect to the olefin and strained olefins were no longer required.[19] In the early nineties, Schreiber and Jeong independently reported the promotion of the P-K reaction at room temperature using *N*-methylmorpholine-*N*-oxide and trimethylamine *N*-oxide, respectively.[20] Two major milestones in the Pauson–Khand reaction are the carbon monoxide free protocol using stoichiometric $Co_2(CO)_8$ and cleavage of the resulting $Co_2(CO)_6$–alkyne complex using NMO and acetonitrile–dimethoxyethane. The intramolecular version of the PKR has been exploited in several ways to synthesize cyclopentenones by coupling of an alkene and an alkyne. The Pauson–Khand reaction was tested on various substrates but the use of this reaction in carbohydrate chemistry was initiated only a few years ago,[21] but the synthesis of *spiro* compounds utilizing carbohydrates as starting materials by using Pauson-khand reaction was not reported. It

has been thought to develop a methodology in our laboratory to synthesize spirocyclic small molecules using Pauson-Khand reaction from carbohydrate scaffolds.[22]

Pauson-Khand Reaction



Mechanism

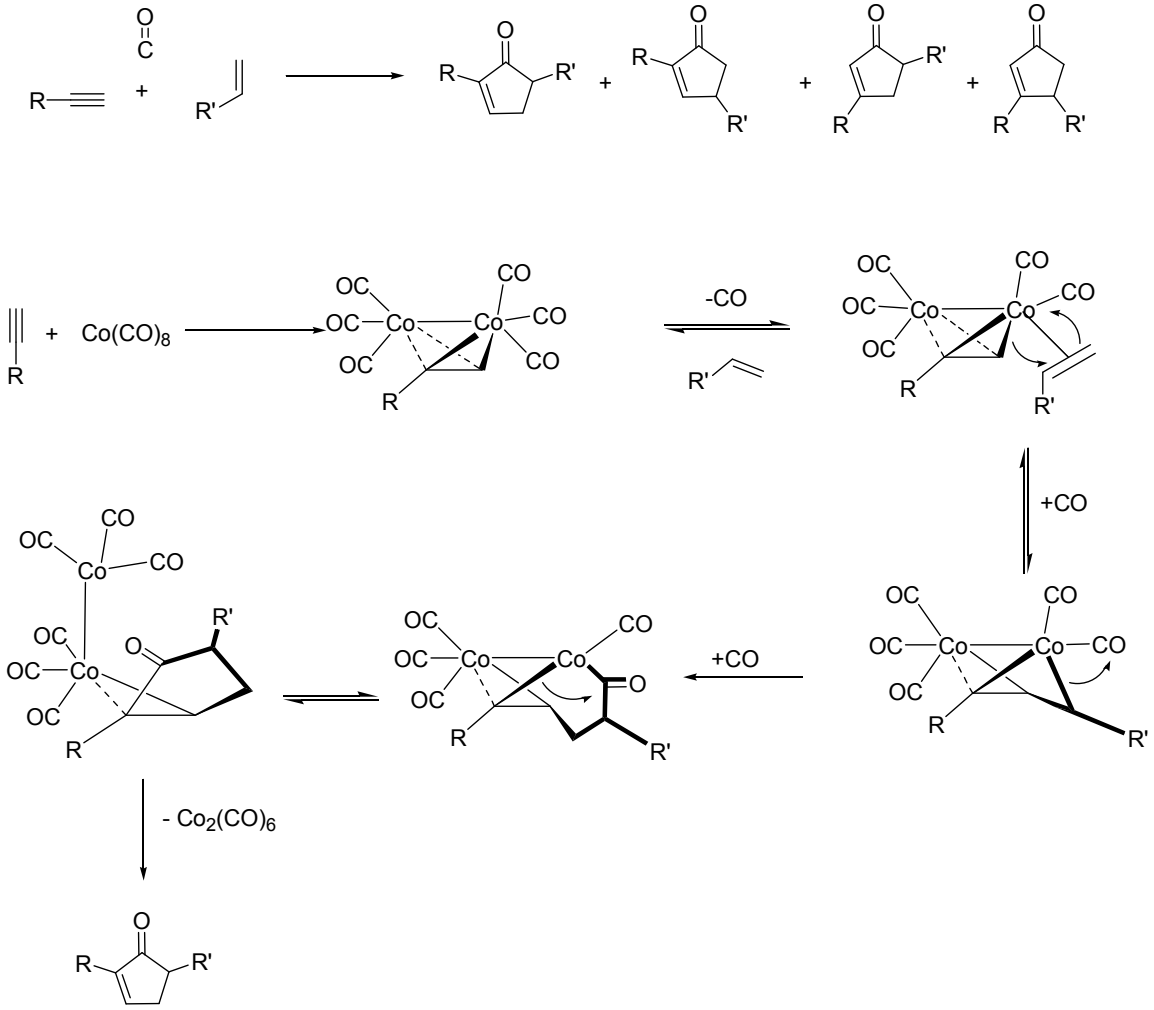


Figure 12: General scheme and mechanism of Pauson-Khand reaction

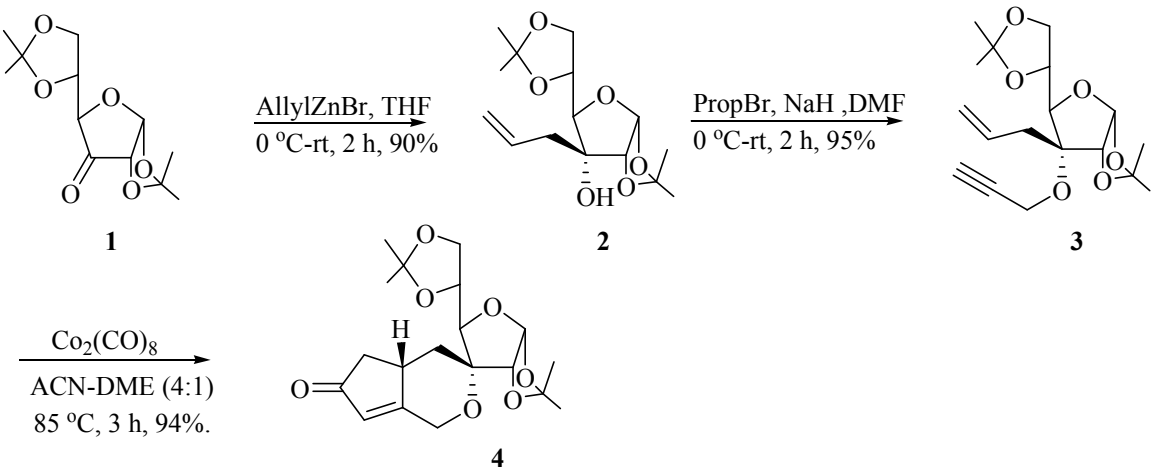
To start our investigation for synthesis, our approach required enyne precursors for the PKR were synthesized by standard methods. Accordingly, commercially

available di-acetone glucofuranose was oxidized to obtain 1,2:5,6-di-*O*-isopropylidene- α -D-glucofurano-3-ulose **1** which was subjected to Barbier Reaction. In order to continue our synthetic endavour, ketone **1** was treated with allylzinc bromide in tetrahydrofuran at 0 ^{o}C and then at room temperature for 2 h to yield the 3-*C*-allyl derivative **2**, that was subsequently *O*-alkylated using propargyl bromide, NaH and catalytic *N*-tetrabutylammonium iodide in DMF at 0 ^{o}C to room temperature to provide the required enyne **3**. In the ^{1}H NMR spectrum of enyne **3** the anomeric proton was observed at δ 5.57 ppm as a doublet, and the allylic methine occurred at δ 6.02 ppm as a multiplet and the acetylenic proton appeared at δ 2.42 ppm as a triplet. The other proton resonances of **3** were in accordance with the assigned structure. In the ^{13}C NMR spectrum, the resonances corresponding to the anomeric carbon at δ 102.9 ppm and the olefinic carbons at δ 132.2 and 118.9 ppm were observed with all the other signals in complete agreement with the assigned structure.

Enyne **3** was then treated with $Co_2(CO)_8$ in anhydrous DCM at room temperature for 3 h under nitrogen atmosphere in order to yield the $Co_2(CO)_6$-alkyne complex which was passed through a pad of silica gel and then dissolved in acetonitrile-dimethoxyethane (4:1), heated to 85 ^{o}C for 3 h to afford the spiroannulated cyclopentenone **4** in excellent yield (Scheme1). The structure of cyclopentenone was confirmed by ^{1}H, ^{13}C and DEPT NMR. In the ^{1}H NMR spectrum of compound **4**, resonances corresponding to the allylic and propargylic protons disappeared and a new singlet attributed to the olefinic proton was apparent at δ 6.02 ppm. In addition, the anomeric proton was observed at δ 5.78 ppm as a doublet, whilst two methylene groups of the spirocyclic moiety were observed at δ 2.69 and 2.13 ppm as double doublets integrating for one proton each and a multiplet for two protons at δ 1.85 ppm. The presence of an α,β-unsaturated enone group in compound **4** was evident from the ^{13}C NMR spectrum wherein the diagnostic resonances of the carbonyl group and olefinic carbons were noticed at δ 206.9, 174.9 and 127.7 ppm, respectively. The anomeric carbon was present at δ 103.8 ppm whilst all the other resonances were in complete agreement with the assigned structure. The DEPT spectrum unambiguously confirmed the presence of four –CH_2- groups at δ 67.3, 63.9, 41.8 and 34.3 ppm. In addition, the structure was established by means of mass spectral and elemental analysis data. It was rewarding to observe that the spiroannulation resulted in

the formation of a single diastereomer. The formation of a single diastereomer can be rationalized based on steric factors as the $Co_2(CO)_6$–alkyne is disposed in a highly hindered fashion and thus the participation of the alkene during carbonyl insertion was unidirectional (Scheme 1).

Scheme 1

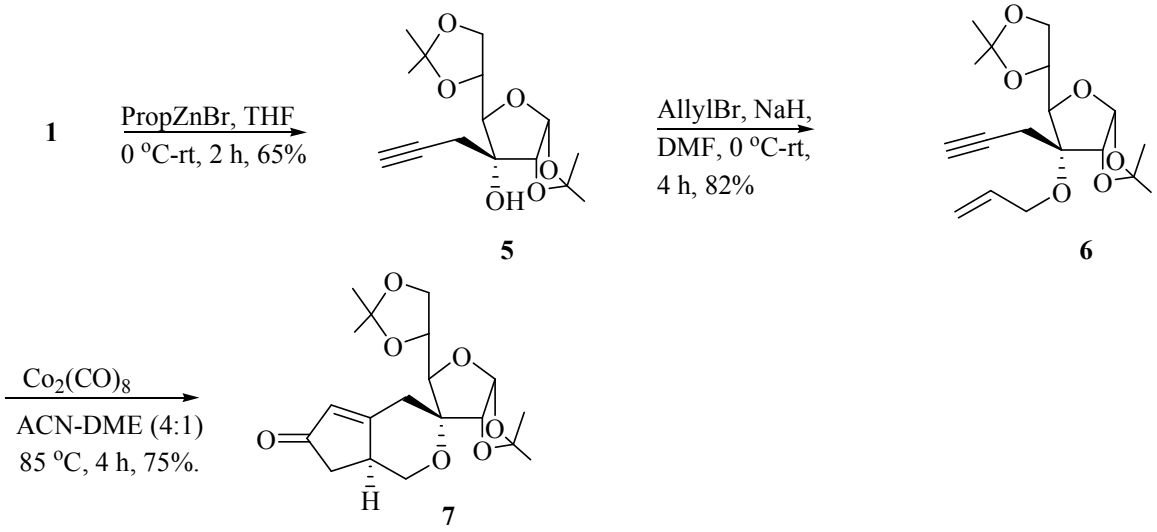


1 **2** **3** **4**

After successful formation of enone **4** as the PKR product we thought of checking efficiency of the reaction on various substrates. Interestingly, we applied sequence of reactions on 3-ulose **1** comprising a Barbier reaction followed by alkylation of the resulting tertiary alcohol. For the series, compound **1** was treated with propargylzinc bromide in tetrahydrofuran at 0 °C and then at room temperature for 2 h to yield the 3-*C*-propargyl derivative **5**, which was subsequently *O*-alkylated using allyl bromide, NaH and *N*- tetrabutylammonium iodide in DMF at 0 °C to room temperature to provide the required enyne **6**. In the ^{1}H NMR spectrum of enyne **6**, the anomeric proton was observed at δ 5.76 ppm as a doublet, and the allylic methine occurred at δ 5.94 ppm as a multiplet and the acetylenic –CH- appeared at δ 2.11 ppm as a triplet. The other proton resonances of **6** were in accordance with the assigned structure. In the ^{13}C NMR spectrum, the resonances corresponding to the anomeric carbon at δ 104.1 ppm and the olefinic carbons at δ 135.1 and 115.6 ppm were observed with all the other signals in complete agreement with the assigned structure. Enyne **6** was then treated with $Co_2(CO)_8$ in anhydrous DCM at room temperature for 3 h under nitrogen atmosphere in order to yield the $Co_2(CO)_6$-alkyne complex which was passed through a pad of silica gel and then dissolved in acetonitrile-dimethoxyethane (4:1), heated to 85 °C for 3 h to afford the

spiroannulated cyclopentenone **7** in excellent yield (Scheme 2). The structure of cyclopentenone was confirmed by ^{1}H, ^{13}C and DEPT NMR. In the ^{1}H NMR spectrum of compound **7**, resonances corresponding to the allylic and propargylic protons disappeared and a new singlet attributed to the olefinic proton was apparent at δ 6.06 ppm. In addition, the anomeric proton was observed at δ 5.74 ppm as a doublet, whilst two methylene groups of the spirocyclic moiety were observed as doublet at δ 2.93 and as double doublets at δ 1.96 ppm integrating for one proton each and two doublets at δ 2.57 ppm and δ 2.47 ppm integrating for one proton each. The presence of an α,β-unsaturated enone group in compound **7** was evident from the ^{13}C NMR spectrum wherein the diagnostic resonances of the carbonyl group and olefinic carbons were noticed at δ 207.3, 177.0 and 129.7 ppm, respectively. The anomeric carbon was present at δ 103.7 ppm whilst all the other resonances were in complete agreement with the assigned structure. The DEPT spectrum unambiguously confirmed the presence of four $-CH_2$-groups at δ 69.9, 67.5, 37.2 and 33.2 ppm. In addition, the structure was established by means of mass spectral and elemental analysis data. Gratifyingly, this reaction also resulted in the formation of single diastereomer only (Scheme 2).

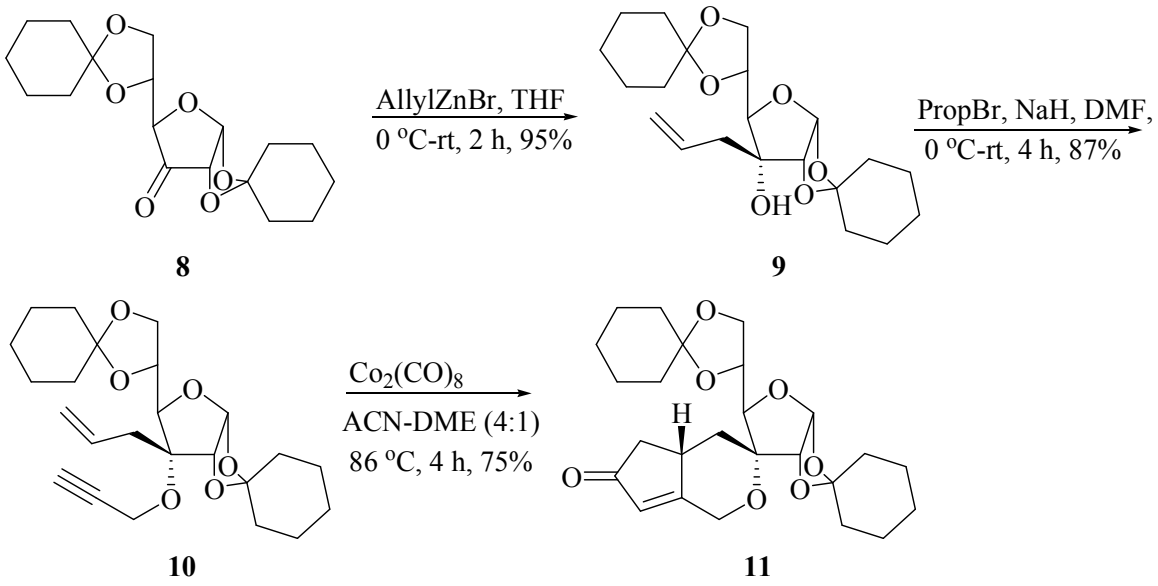
Scheme 2



After successful completion, we thought of checking the efficiency of the reaction on more sterically demanding substrates. To begin our study 1,2:5,6-di-*O*-

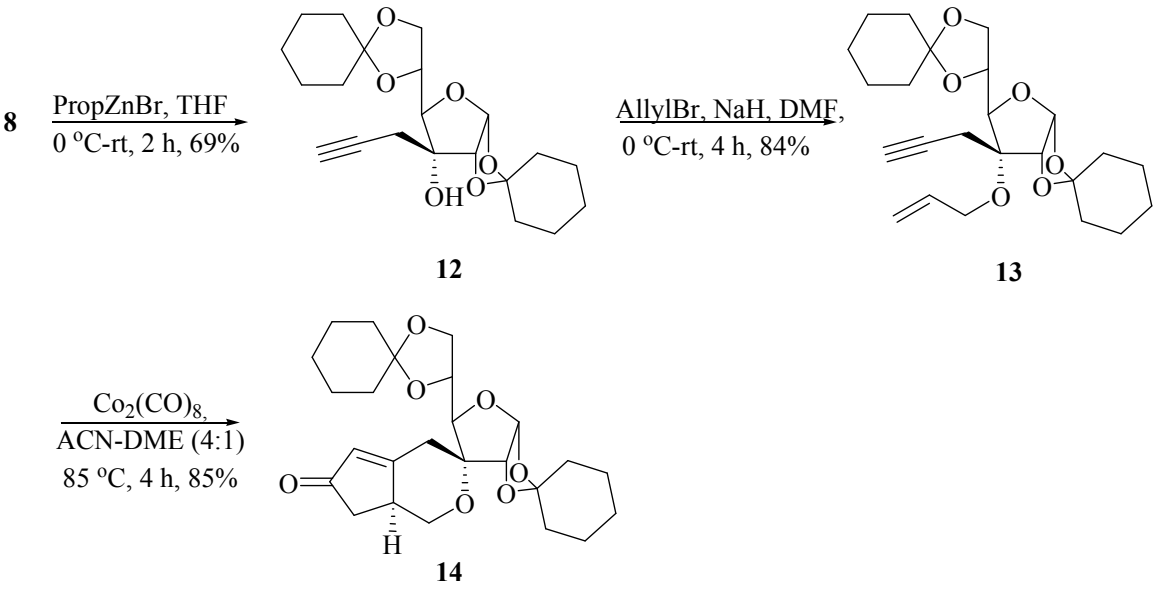
cyclohexlylidene glucofuranose was oxidised to obtain 1,2:5,6-di-*O*-cyclohexylidene- α -D-glucofurano-3-ulose **8**. Subsequently, compound **8** was treated with allylzinc bromide in tetrahydrofuran at 0 ^{o}C and then at room temperature for 2 h to yield the 3-*C*-allyl derivative **9**, which was subsequently *O*-alkylated using NaH, propargyl bromide and *N*-tetrabutylammonium iodide in DMF at 0 ^{o}C to room temperature to provide the required enyne **10**. In the ^{1}H NMR spectrum of enyne **10** the anomeric proton was observed at δ 5.58 ppm as a doublet, and the allylic methine proton occurred at δ 6.03 ppm as a multiplet and the acetylenic -CH- appeared at δ 2.40 ppm as a triplet with other proton resonances in the complete agreement with the assigned structure. In the ^{13}C NMR spectrum, the resonances corresponding to the anomeric carbon at δ 102.8 ppm and the olefinic carbons at δ 132.6 and 118.6 ppm were observed with all the other signals in complete agreement with the assigned structure. Enyne **10** was then treated with $Co_2(CO)_8$ in anhydrous DCM at room temperature for 3 h under nitrogen atmosphere in order to yield the $Co_2(CO)_6$-alkyne complex which was passed through a pad of silica gel and then dissolved in acetonitrile-dimethoxyethane (4:1), heated to 85 ^{o}C for 3 h to afford the spiroannulated cyclopentenone **11** in excellent yield. The structure of cyclopentenone was confirmed by NMR spectroscopy. In the ^{1}H NMR spectrum of compound **11**, resonances corresponding to the allylic and propargylic protons disappeared and a new singlet attributed to the olefinic proton was apparent at δ 6.01 ppm. In addition, the anomeric proton was observed at δ 5.79 ppm as a doublet, with all other resonances were in accordance to the assigned structure. The presence of an α,β-unsaturated enone group in compound **11** was evident from the ^{13}C NMR spectrum wherein the diagnostic resonances of the carbonyl group and olefinic carbons were noticed at δ 207.0 ppm and δ 175.6, 127.7 ppm, respectively. The anomeric carbon was present at δ 103.6 ppm with all the other resonances were in complete agreement with the assigned structure. The DEPT spectrum unambiguously confirmed the presence of all $-CH_2-$ groups. In addition, the structure was established by means of mass spectral and elemental analysis data (Scheme 3).

Scheme 3



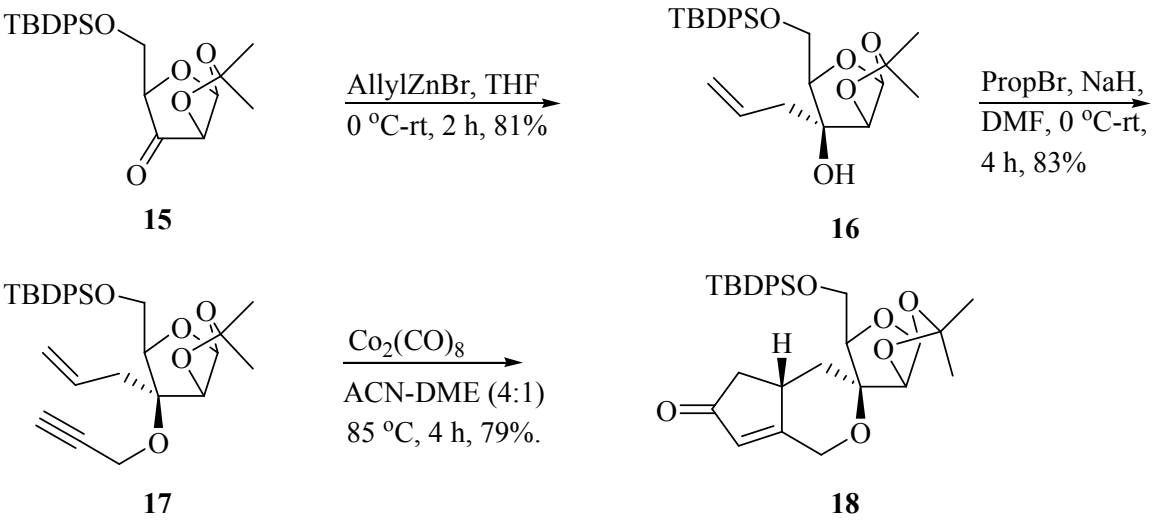
Next, we tried the reverse sequence of the reaction on the ketone **8** using propargylzinc bromide followed by alkylation of resulting *tertiary* alcohol **12** using NaH, allyl bromide and *n*-$Bu_4N^+I^-$ in anhydrous DMF at 0 °C to room temperature to obtain required enyne **13** which was subsequently treated with $Co_2(CO)_8$ in DCM and the resulting metal-alkyne complex was heated to 80 °C in the mixture of acetonitrile-dimetoxyethane to get PK-cycloadduct **14** (Scheme 4). The product was confirmed by NMR spectroscopy and elemental analysis.

Scheme 4



To generate collection of diverse scaffolds, we thought of utilizing pentose sugar as starting material for the Pauson-Khand reaction, for the series known 1,2-*O*-isoprpylidene-5-*O*-*t*-butyl-di-phenylsilyl-arbinofuranose was converted to ketone **15.** The ketone was then subjected to Barbier reaction using allylzinc bromide and *tertiary* hydroxyl group of **16** was *O*-alkylated using propargyl bromide, NaH and tetra *n*-$Bu_4N^+I^-$ in DMF in order to get enyne **17**. The enyne obtained was subjected to PKR which results in the formation of cyclopentenone **18** (Scheme 5)**.**

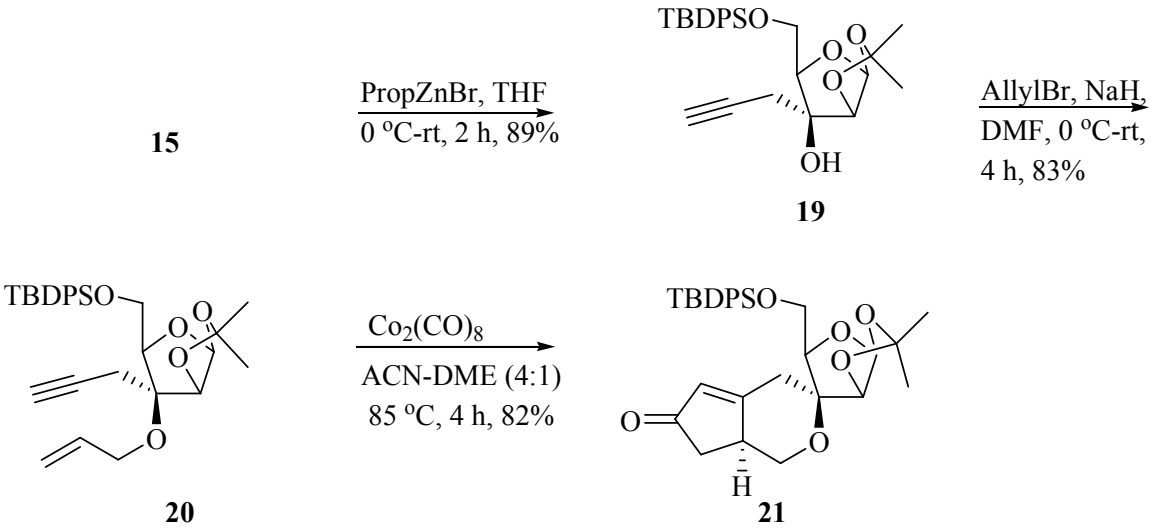
Scheme 5



15 **16** **17** **18**

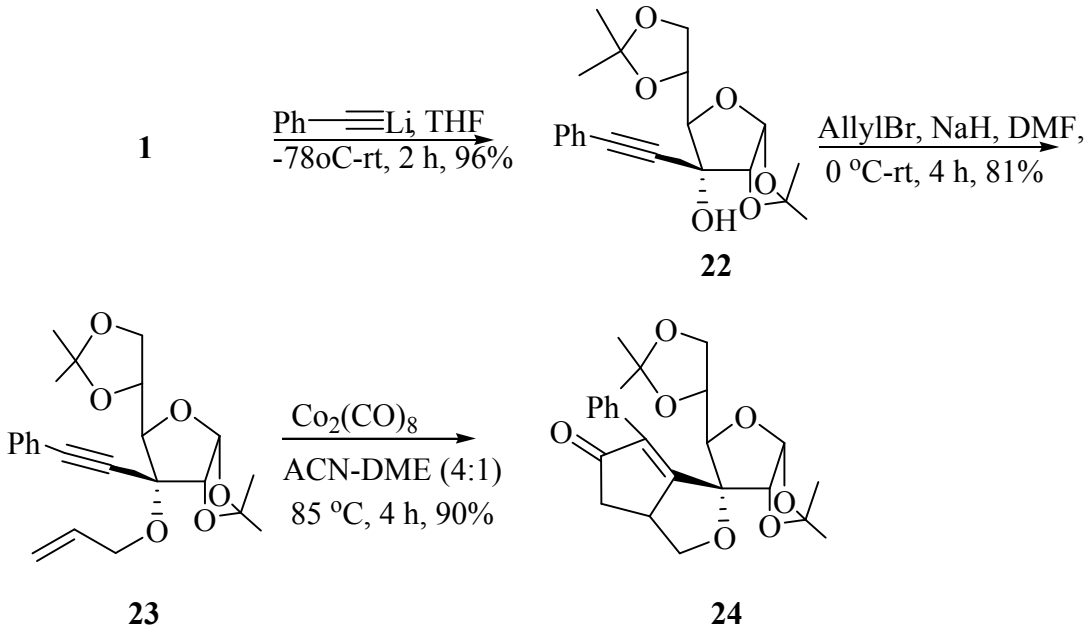
In order to get other set of diverse scaffolds the ketone **15** was subjected to Barbier reaction followed by *O*-alkylation of *tertiary* hydroxyl group of **19** to obtain enyne **20** which was further subjected to PKR following our standard procedure to furnish cyclopetenone **21**. All cyclopentenone and their precursors enyne gave satisfactory ^1H and ^{13}C NMR spectra in addition to elemental and mass analysis (Scheme 6).

Scheme 6



To generate further diversity, we envisioned to replace methyne -CH- with some substituents, hence we used phenyl acetylene as alkyne source. The generation of lithiated phenyl acetylene was carried out using *n*-BuLi in THF at -78 ^{o}C and lithiated anion was quenched with ketone **1** resulted in the formation of **22**. The *tertiary* OH group of **22** was alkylated using allyl bromide which resulted in the formation of enyne **23**. In the ^{1}H NMR spectrum of enyne **23**, the anomeric proton was observed at δ 5.88 ppm as a doublet, and the allylic methine occurred at δ 6.01 ppm as a multiplet with other proton resonances in the complete agreement with the assigned structure. In the ^{13}C NMR spectrum, the resonances corresponding to the anomeric carbon at δ 104.4 ppm and the olefinic carbons at δ 134.5 and 116.4 ppm were observed with all the other signals in complete agreement with the assigned structure. The enyne **23** was then subjected to PKR using our standard protocol which resulted in the formation of cyclopentenone **24**. The structure of cyclopentenone **24** was confirmed by ^{1}H, ^{13}C and DEPT NMR. It was observed from the experiment that alkyne accommodates well phenyl or aryl substitution in place of acetylenic –CH- for PKR and went smoothly which open the possibility for the further diversification by various substitutions to increase the diversity of the library (Scheme 7).

Scheme 7

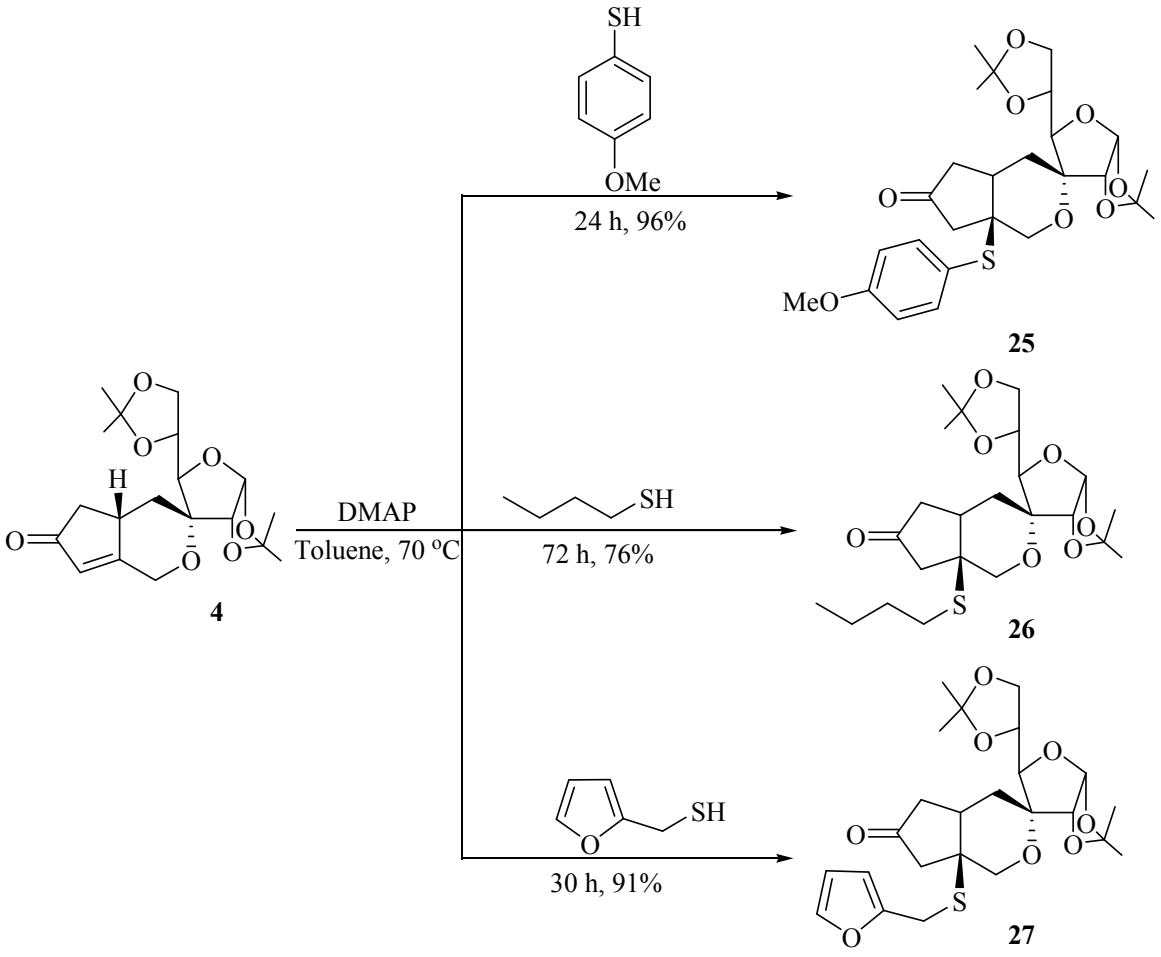


Second generation diverse scaffolds: Michael addition

The Michael addition of a thiol to α,β-unsaturated carbonyl compounds is a fundamental reaction in organic chemistry.[23] From the perspective of asymmetric synthesis, this reaction essentially consists of an *asymmetric 1,4-addition* and an *asymmetric protonation*. Excellent diastereoselective and enantioselective Michael additions of thiols to α,β -unsaturated carbonyl compounds have been extensively studied.[24] In continuation of DOS for the synthesis of small molecules, we have examined the thiolate addition reaction on to the previously synthesized cyclopetenone derivatives to generate second generation diverse scaffolds. For the purpose we treated cyclopentenone **4** with different thiols as nucleophiles and toluene as solvent at 70 ^{o}C in the presence of catalytic amount of DMAP. In a typical experiment, the 4-methoxy phenylthiol and cyclopentenone **4** were heated in toluene in presence of catalytic amount of DMAP which resulted in the formation of Michael adduct **25** as a single diastereomer. In the ^{1}H NMR spectrum of adduct **25** the anomeric proton was observed at δ 5.63 ppm as a doublet, and methyl group of -OMe occurred at δ 3.81 ppm as a singlet with other proton resonances in complete agreement with the assigned structure. In the ^{13}C NMR spectrum, the resonances corresponding to the anomeric carbon at δ 103.8 ppm with the

disappearance of α,β- unsaturated -CH- signal and appearance of one new signal of -CH_2- group at δ 44.5 ppm in the DEPT NMR spectrum with all the other signals in complete agreement with the assigned structure. The stereochemistry of adduct was confirmed by single crystal X-ray structure was found to be **β** in orientation (Fig. 13). It is important to note that Michael addition reaction using butane thiol resulted in the formation of a single diastereomer **26** while the treatment of enone **4** with furfural thiol gave Michael adduct **27** (Scheme 8).

Scheme 8



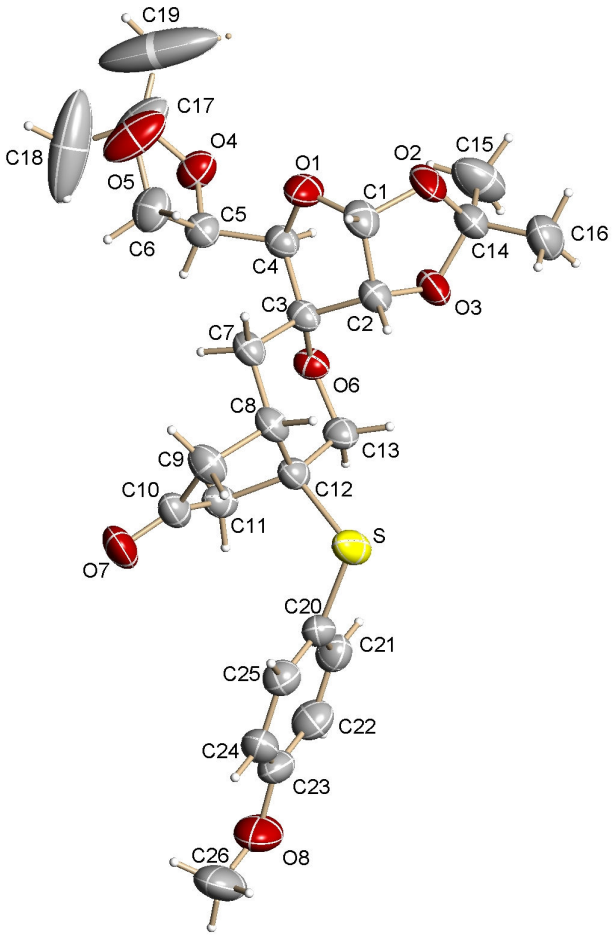


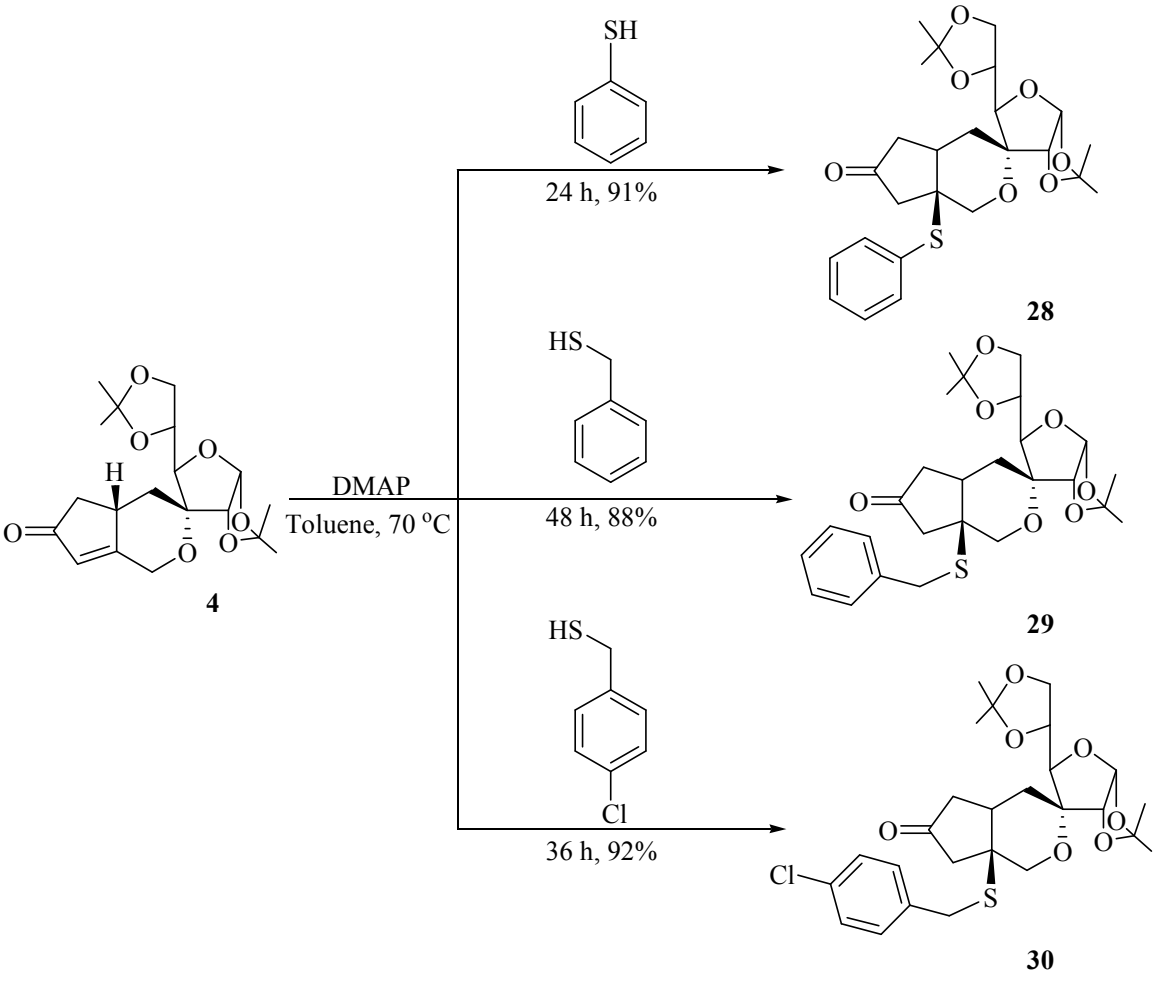
Figure 13: ORTEP diagram of the compound **25**

Crystal Data: Single crystals of the complex were grown by slow evaporation of the solution in DCM. Colourless rectangular crystal of approximate size 0.36 x 0.15 x 0.06 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. C_{26} H_{34} O_8S, M = 506.59 Crystals belong to Monoclinic, space group $P2_1$, a = 14.6269(10) b = 6.0653(4) c = 16.2203(11) Å, Beta 116.140(1) deg., V = 1291.83(15) $Å^3$, Z = 2, D_c = 1.302 mg m^{-3}, T = 293(2) K, 12621 reflections measured, 4550 unique [I>2σ(I)], R value R1 = 0.0414, wR2 = 0.1027. All the data were corrected for Lorentzian, polarisation and absorption effects. SHELX-97 (ShelxTL)[23b] 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.

Next the Michael addition reaction was performed using phenylthiol (**4→ 28**), benzylthiol (**4→ 29)** and 4-Chlorobenzylthiol (**4→ 30**). It is worth mentioning here that all Michael addition reactions resulted in the formation of single adducts with excellent yield (Scheme 9).

Scheme 9

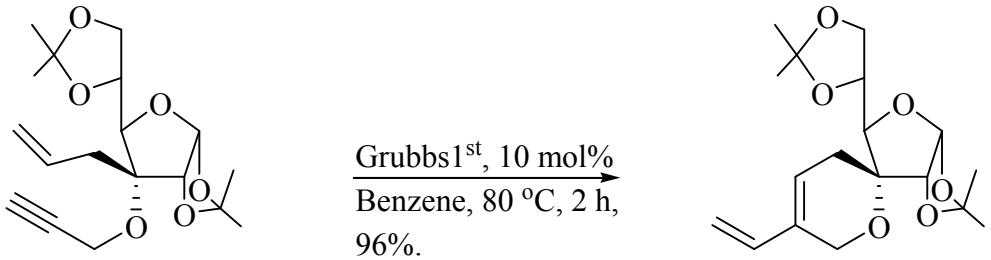


Enyne Metathesis

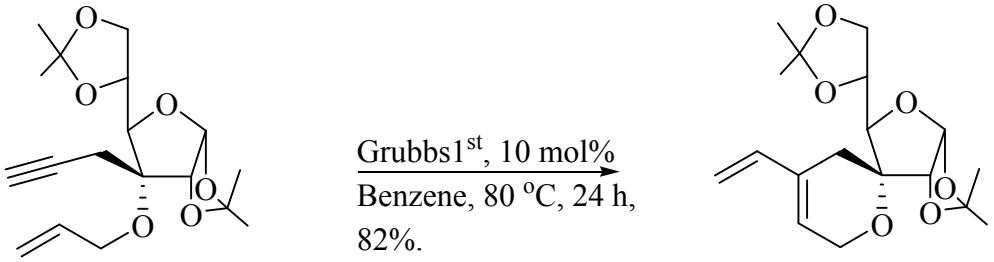
In view of the fact that main target of a DOS library is to generate collections of diverse small molecules utilizing same precursor(s) using various complexities

generating reactions/reagents. It has been thought to develop a new methodology by using Grubb's metathesis reaction utilizing enynes previously used for the Pauson-Khand reaction to generate more diverse structures. In order to begin our synthetic endeavor, enyne **3** was treated with Grubbs' 1st generation catalyst at 90 ^{o}C in benzene under nitrogen atmosphere to yield spirocyclic diene **31** in 90% yield. The structure of diene **31** was confirmed by ^{1}H, ^{13}C and DEPT NMR. In the ^{1}H NMR spectrum of compound **31**, resonances corresponding to the allylic and propargylic protons of enyne disappeared and a new signal attributed to the olefinic proton was apparent at δ 6.28 ppm as a quartet. In addition, the anomeric proton was observed at δ 5.66 ppm as a doublet, whilst terminal -CH_2- group of alkene was found at δ 4.97 and 5.01 ppm as two doublets integrating one proton each and internal alkene –CH- at δ 5.83 ppm as broad singlet integrating for one proton. In the ^{13}C NMR spectrum of **31**, the anomeric carbon occurs at δ 103.5 ppm and the DEPT spectrum unambiguously confirmed the presence external -CH_2- group at δ 111.7 ppm whilst internal methine –CH- at δ 135.3 and 122.2 ppm with all other –CH_2- resonance according to assigned structure. In addition, the structure was established by means of mass spectral and elemental analysis data. Similarly the enyne **6** was subjected to enyne metathesis which resulted in the formation of diene **32** in 82 % yield. In the ^{1}H NMR spectrum of compound **32**, resonances corresponding to the allylic and propargylic protons of enyne disappeared and a new signal attributed to the olefinic proton was apparent at δ 6.43 ppm as quartet. In addition, the anomeric proton was observed at δ 5.68 ppm as a doublet, whilst terminal -CH_2- group of alkene was found at δ 5.04 and 5.14 ppm as two doublets integrating one proton each and internal alkene –CH- at δ 5.85 ppm as broad singlet integrating for one proton. In the ^{13}C NMR spectrum of **32**, the anomeric carbon occurs at δ 103.6 and in the DEPT spectrum unambiguously confirmed the presence external -CH_2- group at δ 11.5 ppm whilst internal methine –CH- at δ 137.9 and 127.1 ppm with all other –CH_2- resonance according to assigned structure. In addition, the structure was established by means of mass spectral and elemental analysis data (Scheme 10).

Scheme 10



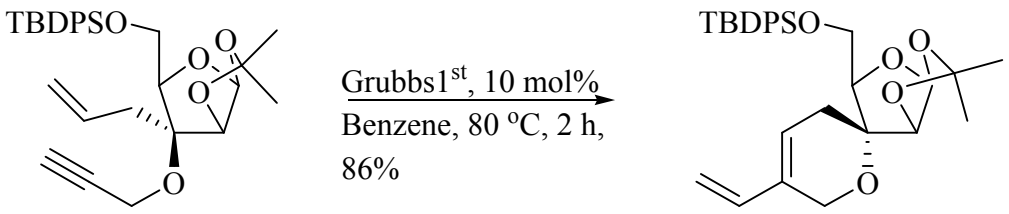
3 **31**



6 **32**

To make further diverse compounds arabinose derived enyne **17** was subjected to enyne metathesis reaction following our standard protocol which resulted in the formation of diene **33**. In the ^{1}H NMR spectrum of diene **33**, resonances corresponding to the allylic and propargylic protons of enyne disappeared and a new signal attributed to the olefinic proton was apparent at δ 6.24 ppm as a quartet. In addition, the anomeric proton was observed at δ 5.72 ppm as a doublet, whilst terminal -CH_2- group of alkene was found at δ 4.93 and 5.00 ppm as two doublets integrating one proton each and internal alkene –CH- at δ 5.73 ppm as broad singlet integrating for one proton. In the ^{13}C NMR spectra of **32** the anomeric carbon occurs at δ 103.9 ppm and the DEPT spectrum unambiguously confirmed the presence external -CH_2- group at δ 111.7 ppm with all other resonances according to assigned structure. In addition, the structure was established by means of mass spectral and elemental analysis data (Scheme 11).

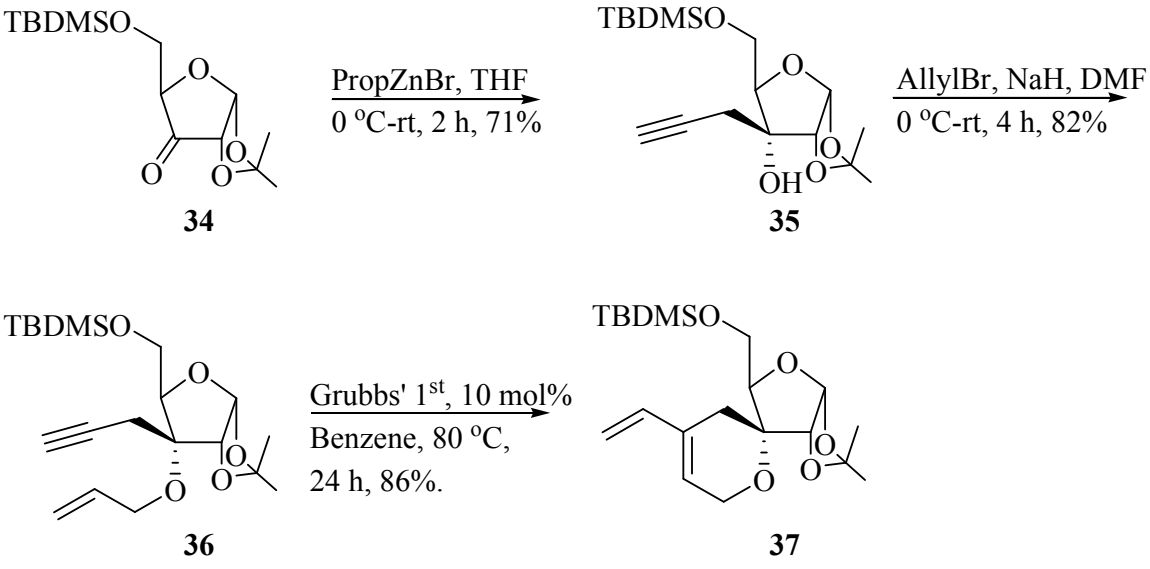
Scheme 11



17 **33**

Next, ketone **34** derived from xylose was subjected to Zn mediated Barbier reaction using propargylzinc bromide in THF and resulted *tertiary* hydroxyl group of **35** was alkylated as allyl ether to obtain enyne **36**. In the ^{1}H NMR spectrum of enyne **36** the anomeric proton was observed at δ 5.77 ppm as a doublet, and the allylic methine occurred at δ 5.96 ppm as a multiplet and the acetylenic –CH- appeared at δ 2.10 ppm as a triplet. The other proton resonances of **36** were in accordance with the assigned structure. In the ^{13}C NMR spectrum, the resonances corresponding to the anomeric carbon at δ 103.9 ppm and the olefinic carbons at δ 135.0 and 115.9 ppm were observed with all the other signals in complete agreement with the assigned structure. The enyne **36** was then subjected to enyne metathesis reaction in order to obtain diene **37**. In the ^{1}H NMR spectrum of compound **37**, resonances corresponding to the olefinic proton were apparent at δ 6.41 ppm as quartet. In addition, the anomeric proton was observed at δ 5.74 ppm as a doublet, whilst terminal -CH_2- group of alkene was found at δ 5.04 and 5.13 ppm as two doublets integrating one proton each and internal alkene –CH- at δ 5.81 ppm as broad singlet integrating for one proton. In the ^{13}C NMR spectra of **37** the anomeric carbon occurs at δ 104.0 ppm and in the DEPT spectrum unambiguously confirmed the presence external -CH_2- group at δ 111.6 ppm whilst internal –CH- at δ 137.8 and 126.6 ppm with all other –CH_2- resonance according to assigned structure. The structure was further confirmed by elemental and mass analysis (Scheme 12).

Scheme 12



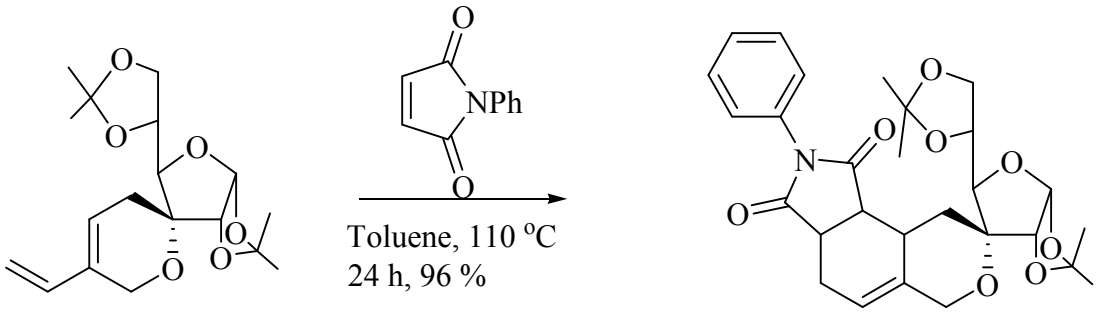
34 **35** **36** **37**

Second generation diverse scaffolds: Diels-Alder reaction

After successful preparation of different dienes, our attention turned towards the generation of further diverse scaffolds by using Diels-Alder reaction (the widespread utility of the reaction rests not only on its ability to form ubiquitous six-membered ring compounds and molecules otherwise difficultly accessible e.g. bridged bicyclic compounds, but also on its remarkable stereospecificity) utilizing different dienophiles.[25] In order to get a standard protocol, we tried different Lewis acid but most of them resulted either in the decomposition of the starting materials or deprotection of various protecting groups such as isopropylidene. After several hardships to drive Diels-Alder reaction, finally we succeeded thermally. In order to begin our investigations the diene **31** and *N*-phenylmalimide were heated to 110 ^{o}C in toluene to get Diels-Alder adduct **38** (**A** and **B**). The reaction resulted in the formation of two products in the ratio of 3:7. In the ^{1}H NMR spectrum of compound **38 A**, the resonance corresponding to the external and internal olefinic protons of diene **31** were disappeared and new signal corresponding to internal methine was apparent at δ 5.77 ppm as broad singlet integrating for one proton. In addition, the anomeric proton was observed at δ 5.65 ppm as a doublet, and the resonance corresponding to the protons attached to the three newly generated chiral carbons, one appeared at δ 2.98 ppm as multiplet whilst remaining two apparent at δ 3.30 ppm as multiplets overlapping each other with the additional five proton resonances in aromatic region apparent as multiplets with the other resonances according to the assigned structure. In the ^{13}C NMR spectra of **38 A** the anomeric carbon occurs at δ 102.7 ppm and two carbon corresponding to carbonyl groups were apparent at δ 176.9 and 178.4 ppm. The methine carbon resonance was observed at δ 119.0 ppm and the DEPT NMR spectrum unambiguously confirmed the presence of all -CH_2- groups. Compound **38 A** gave satisfactory elemental and mass spectral analysis. In the ^{1}H NMR spectrum of other diastereomer **38 B**, the resonance corresponding to the external and internal olefinic protons of diene **31** were disappeared and new signal corresponding to internal methine was apparent at δ 5.77 ppm as broad singlet integrating for one proton. In addition, the anomeric proton was observed at δ 5.69 ppm as a doublet, and the resonance corresponding to the protons attached to the three newly generated chiral carbon, one appeared at δ 2.70 ppm as a muliplet whilst remaining two protons apparent

at δ 3.30 ppm as double doublets overlapping to each other with the additional five proton resonance in aromatic region apparent as multiplets with the other resonance according to the assigned structure. In the ^{13}C NMR spectra of **38 B** the anomeric carbon occurs at δ 102.8 ppm and two carbons corresponding to carbonyl groups were apparent at δ 176.9 and 178.4 ppm. The methine carbon resonances were observed at δ 118.9 ppm and the DEPT spectrum unambiguously confirmed the presence all -CH_2- groups. All attempts to assign the stereochemistry of both the products were unsuccessful by 2D NMR spectroscopy due to the resonances corresponding to the protons attached to the newly generated chiral carbons were overlapping with those of main skeleton in the ^1H NMR spectrum and we were unable to grow crystals of the compounds as such for single crystal X-ray analysis (Scheme 13).

Scheme13



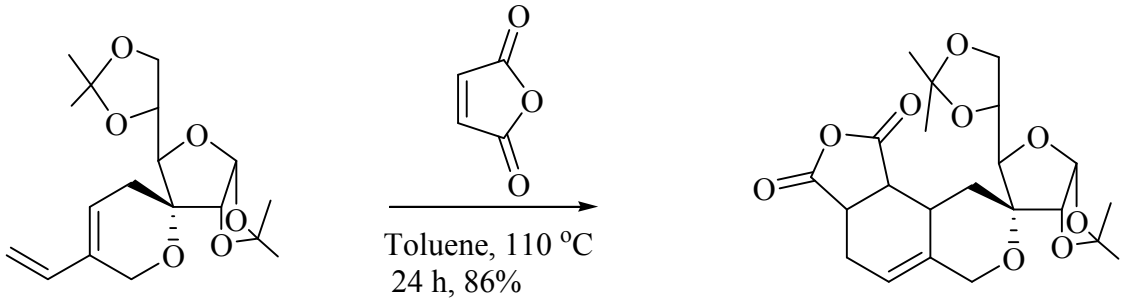
31 **38**

Two Products

Since our aim was to develop library of a diverse compounds so next we thought of utilizing various dienes and dienophiles to generate additional diverse scaffolds accordingly, we treated diene **31** with maleic anhydride in toluene at 110 °C which resulted in the formation of Diels-Alder adduct **39** in two diastereomer in 3:7 ratio. In the ^1H NMR spectrum of compound **39 A**, the signal corresponding to internal methine was apparent at δ 5.77 ppm as broad singlet integrating for one proton. In addition, the anomeric proton was observed at δ 5.67 ppm as a doublet, with the disappearance of the resonance corresponding to the external and internal methine proton of the diene **31**. In the ^{13}C NMR spectra of **39 A** the anomeric carbon occurs at δ 102.7 ppm and the resonance corresponding to carbonyl groups were apparent at δ 171.6 and 173.6 ppm

confirming the formation of DA adduct. All other resonances in the ^{13}C and DEPT NMR spectra were according to the assigned structure. In addition the structure was also confirmed by elemental and mass analysis. All attempts to get pure spectrum of compound **39 B** were unsuccessful due to degradation/rearrangement of DA-adduct while column chromatography (Scheme 14).

Scheme 14

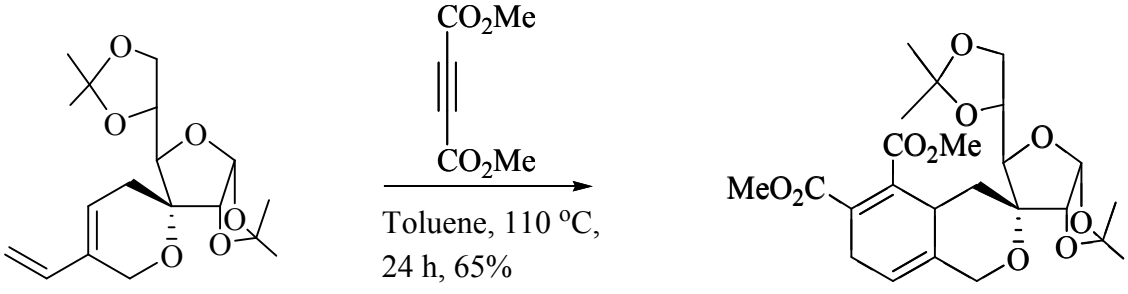


31 **39**

Two Products

Next, diene **31** was treated with dimethylacetylene dicarboxylate in toluene at 110 ^{o}C which resulted in the formation of inseparable diastereomeric mixture of DA-adduct **40** in 3:7 ratios (by ^{1}H NMR). The ^{1}H NMR of mixture of compounds showed the presence of anomeric proton resonances at δ 5.55 and 5.74 ppm in addition to all other resonances corresponding to two diastereomers. The ^{13}C NMR showed presence of one pair for every resonance signals corresponding to both diastereomers. Further structure was confirmed by mass spectroscopy (Scheme 15).

Scheme 15

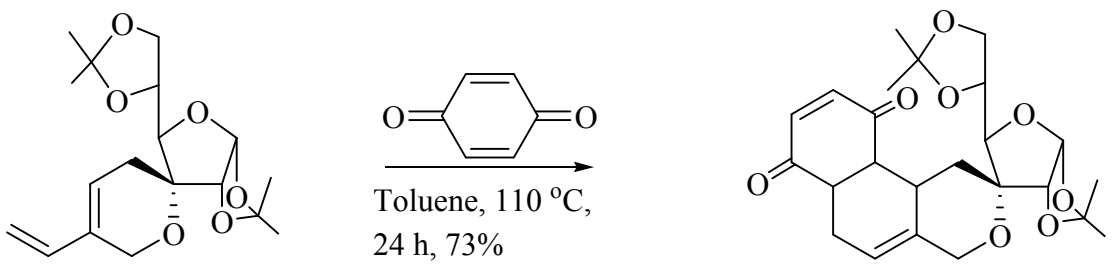


31 **40**

Inseprable mixture
of two Products

The treatment of diene **31** with 1, 4-benzoquenone resulted in the formation of inseparable diastereomeric mixture of Diels-Alder adduct **41** (Scheme 16).

Scheme 16



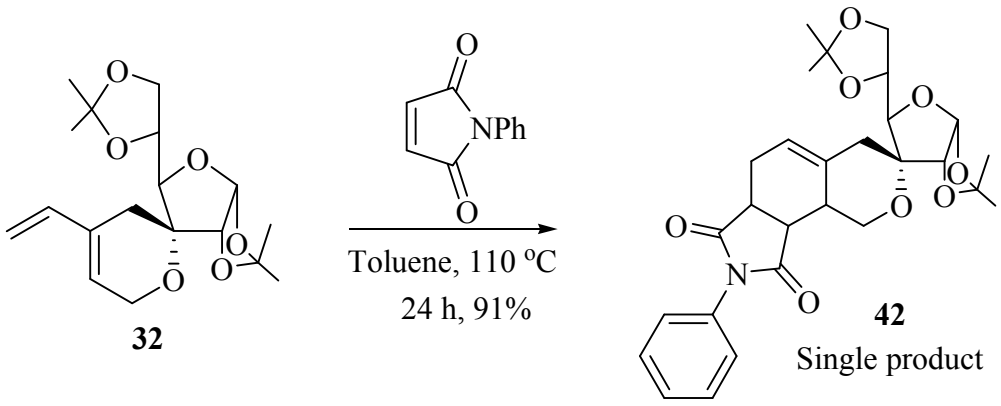
31 **41**

Inseprable mixture
of two Products

In order to generate further diverse compounds of different skeletons, the diene **32** was subjected to Diels-Alder reaction utilizing various dienophiles. To continue our synthetic endure the diene **32** was treated with *N*-phenyl maleimide in toluene at 110 ^{o}C. We were surprised to see that diene **32** resulted in the formation of only one diastereomer of possible two Diels-Alder adducts. The structure of the adduct **42** was confirmed by the ^{1}H, ^{13}C NMR and elemental and mass spectral analysis. In the ^{1}H NMR of **42,** the resonance corresponding to the external and internal olefin protons of diene **32** were disappeared and new signal corresponding to internal methine was apparent at δ 5.88 ppm as double doublet integrating for one proton. In addition, the anomeric proton was observed at δ 5.62 ppm as a doublet, and the resonances corresponding to the protons attached to the three newly generated chiral carbon, one appeared at δ 2.70 ppm as a muliplet whilst remaining two protons apparent at δ 3.30 ppm as double doublets overlapping to each other with the additional five proton resonances in aromatic region apparent as multiplets and other resonances according to the assigned structure. In the ^{13}C NMR spectrum of **42,** the anomeric carbon occurs at δ 103.0 ppm and two carbons corresponding to carbonyl groups were apparent at δ 175.9 and 178.4 ppm. The methine carbon resonance was observed at δ 122.5 ppm and the DEPT NMR spectrum unambiguously confirmed the presence all -CH_2- groups. In addition the structure was confirmed by elemental and mass analysis. Once again all attempts to assign the stereochemistry of the diasteromer **42** were unsuccessful by 2D NMR spectroscopy due

to the overlapping of the resonance corresponding to the protons attached to the newly generated chiral carbons and we could not grow crystals of the compound as such for single crystal X-ray analysis (Scheme 17).

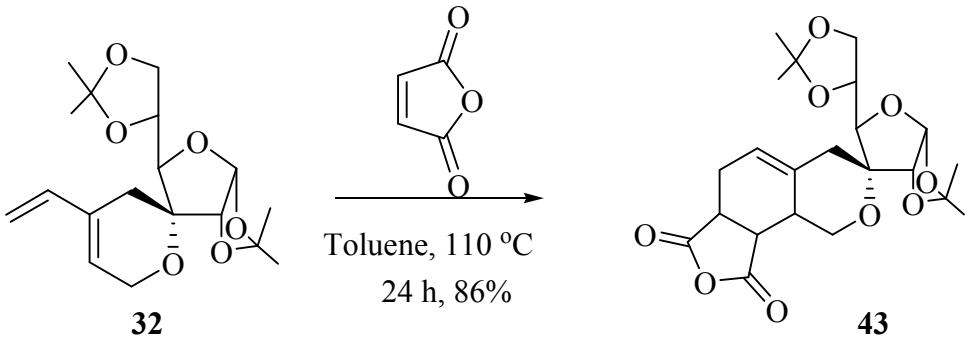
Scheme 17



32 **42**
Single product

The diene **32** was then treated with maleic anhydride in toluene which resulted in the formation of single Diels-Alder adduct **43**. In the ^{1}H NMR spectrum of **43**, the anomeric proton was apparent at δ 5.63 as doublet whilst internal methine proton resonance was apparent at δ 5.88 ppm as double doublet integrating for one proton. In the ^{13}C NMR spectrum, the anomeric carbon resonance was apparent at δ 103.0 ppm and resonances corresponding to two carbonyl groups were apparent at δ 170.9 and 173.8 ppm in addition resonance corresponding to internal olefin carbon was apparent at δ 122.7 ppm. All other resonances were according to assigned structure and DEPT NMR spectrum unambiguously confirmed presence of all $-CH_2-$ groups. Structure was also confirmed by elemental and mass analysis. We were unable to grow crystals of the DA-adduct **43** for the single crystal X-ray analysis in order to assign the stereochemistry of the product (Scheme 18).

Scheme 18

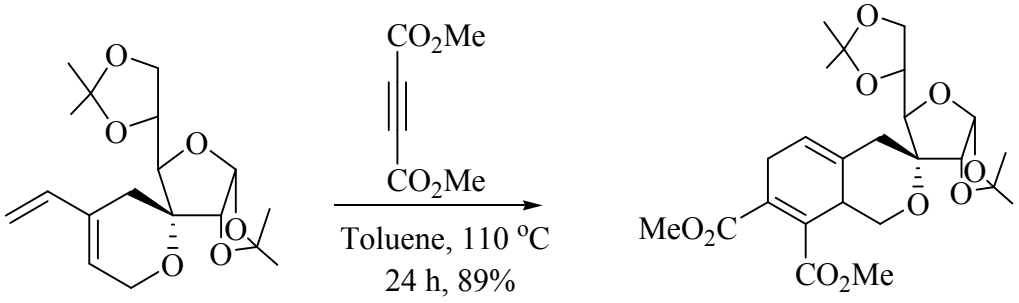


32 **43**

Single product

Continuing our synthetic endure dedicated towards the carbohydrate- based DOS library, the diene **32** was then treated with dimethylacetylene dimethylcarboxylate. The reaction went neatly giving excellent yield of only one diastereomeric adduct. In the ^{1}H NMR spectrum of adduct **44**, resonances corresponding to anomeric proton were apparent at δ 5.60 ppm as doublet integrating for one proton whilst resonance corresponding to the internal olefin proton was apparent at δ 5.54 ppm as a broad singlet integrating for one proton. In addition the resonances corresponding to two methyl groups of diester were apparent at δ 3.76 and 3.77 ppm as two singlets integrating for six protons collectively with all other proton resonances according to the assigned structure. In the ^{13}C NMR spectra of compound **44**, the resonances corresponding to anomeric carbon were apparent at δ 101.3 ppm and two ester carbonyls at δ 167.6 and 167.9 ppm whilst resonances corresponding to olefin –CH- were apparent at δ 116.9 ppm with all other resonances according to the assigned structure. The DEPT NMR spectrum unambiguously confirmed presence of $–CH_2-$ groups at δ 67.2, 66.6, 36.5 and 26.1 ppm (Scheme 19).

Scheme 19

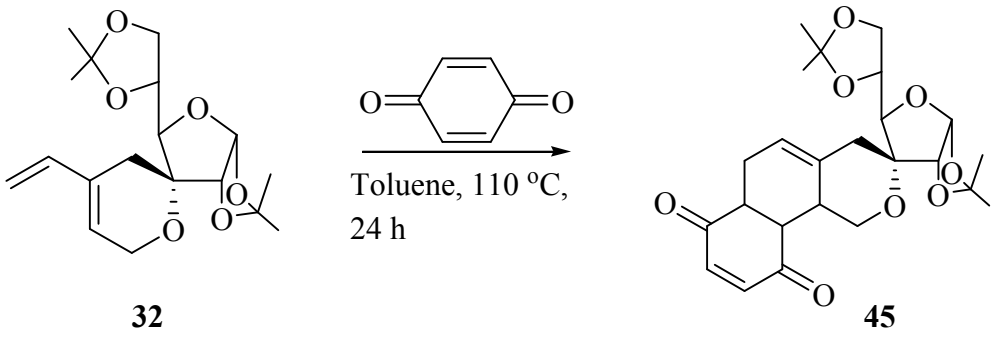


32 **44**

Single product

Treatment of diene **32** with 1, 4-benzoquinone resulted in the formation of an unidentified product. Though in ^{1}H NMR spectra all resonances corresponding to ispropylidene was apparent as four singlets but other resonances were not according to assigned structure of adduct **45**. The resonances corresponding to methine were absent in aliphatic region whilst resonances of sugar protons were also missing from the proper chemical shift region. In the ^{13}C NMR spectrum**,** the resonances corresponding to anomeric carbon were apparent at δ 103.6 ppm and two carbonyl groups at δ 184.9 and 186.9 ppm but the resonances corresponding to newly formed chiral carbon were absent in aliphatic region and were ambiguous to the assigned structure. Though DEPT NMR spectrum confirmed presence of four $-CH_2-$ group at δ 67.7, 65.6, 31.5 and 29.7 ppm respectively but all other resonances were not satisfactory according to assigned structure of adduct **45** (Scheme 20).

Scheme 20



32 **45**

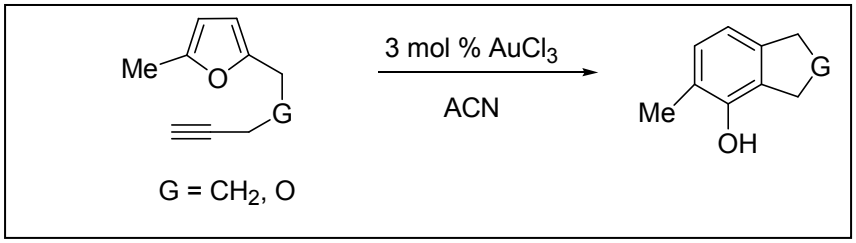
Unidentified product

Hashmi's protocol for phenol synthesis: IMDA reaction

It is widely recognized that Diels-Alder reactions are the most useful pericyclic reactions for the construction of six-membered functionalized carbocyclic compounds. The potency of Diels-Alder reactions is validated especially in cases of structurally complex natural products synthesis.[24] The usefulness of Diels-Alder reactions is further demonstrated in cases of their intramolecular versions, that is, intramolecular Diels-Alder (IMDA) reactions. The dienic reactivity of five-membered heteroaromatic compounds such as furans, thiophenes and pyrroles is well-documented in the literature.[25] The resulting heteroatom-bridged norbornenes or norbornadienes are valuable precursors to functionalized cyclohexenes. Furans, in particular, take part in inter- and intramolecular Diels-Alder reactions with a variety of dienophiles such as alkenes, alkynes (including

benzynes) and allenes.[27] The intramolecular Diels-Alder reaction of furan diene (IMDAF) is particularly attractive as two or more rings can be constructed in a single step with high regio- and stereocontrol, providing a convenient entry into polycyclic targets including natural products.[28] However, the paucity of general and convenient methods for the synthesis of IMDAF precursors and the scarcity of structural diversity in the IMDAF products curtailed the scope and potential of the IMDAF reaction as a strategy of choice for synthetic chemists. Recently, Hashmi's group developed Au (III) catalyzed synthesis of arene by using suitably substituted furans and alkynes (Fig. 14).[29]

IMDA Reaction



Mechanism

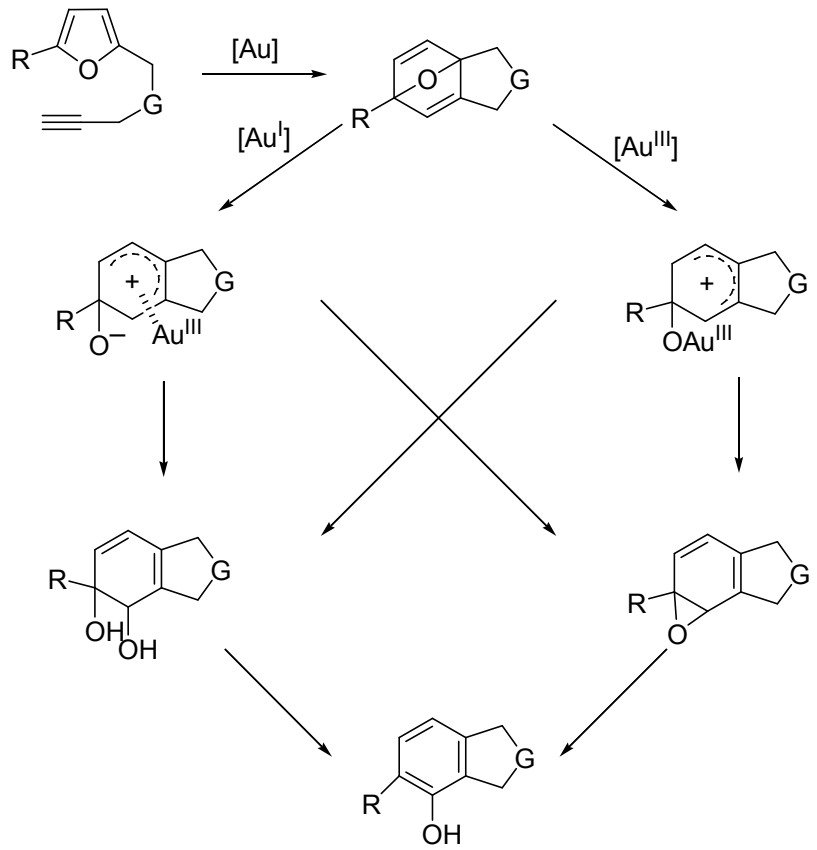


Figure 14: General scheme and mechanism for IMDA reaction

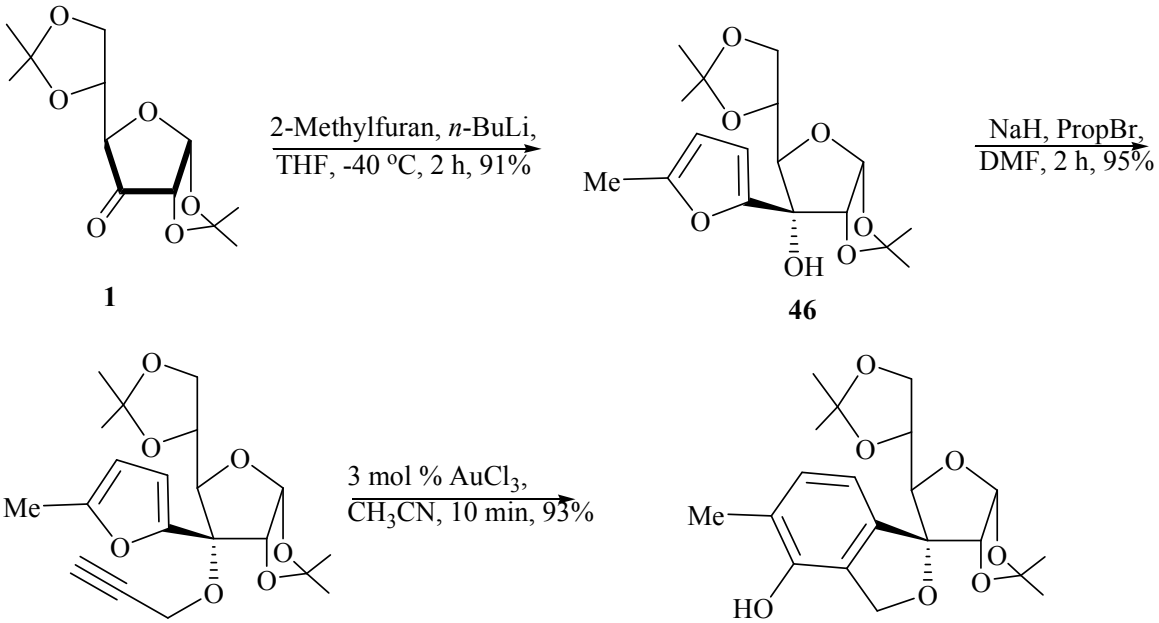
As a part of our programme dedicated to the exploration of carbohydrate based diversity oriented synthesis pathways for spirocycles,[22] we investigated the use of Au (III) mediated phenol synthesis for spiroannulation on carbohydrate scaffolds.[30]

Dihydroisobenzofurans can be synthesized from furfuryl propargyl ethers exploiting the alkynophilicity of gold. To begin our investigation, 1,2:5,6-di-*O*-isopropylidene-α-D-glucofurano-3-ulose **1** was converted to the corresponding 3-*C*-(5-methylfuranyl)-D-allose using 5-methylfuryl-2-lithium in THF generated at -40 ^{o}C for 1 h in 91 % yield. The ^{1}H NMR spectra of the resulting compound **46** showed presence of a resonance corresponding to furan -CH_3 at δ 2.28 ppm as doublet integrating for three protons. The resonances corresponding to anomeric proton were apparent at δ 6.00 ppm as doublet integrating for one proton whilst resonances corresponding to two protons of methyl furan moiety were apparent at δ 5.98 and 6.25 ppm as one double doublet and one doublet respectively integrating for one proton each along with all other resonances according to the assigned structures. In the ^{13}C NMR spectrum of compound **46**, resonance corresponding to anomeric carbon apparent at δ 101.6 and furan -CH_3 at δ 13.42 ppm respectively along with all other resonances according to assigned structure. In addition the structure was confirmed by DEPT NMR, elemental and mass analysis without any ambiguity. Resulting, *tertiary* hydroxyl group of **46** was alkylated to propargyl ether **47** using propargyl bromide and NaH in DMF at 0 ^{o}C–rt. The ^{1}H NMR spectrum of compound **47** showed presence of anomeric proton at δ 4.71 ppm as doublet and acetylenic proton at δ 2.43 ppm as triplet in addition to resonances corresponding to furan -CH_3 was apparent at δ 2.30 ppm along with all other resonances according to assigned structure. In the ^{13}C NMR spectrum of the compound **47,** the resonances corresponding to anomeric carbon as apparent at δ 104.6 ppm, and furan -CH_3 at δ 13.4 ppm along with all other resonances well matched to compound **47**.

With the furfuryl and propargyl ether moieties attached to the carbohydrate template, the compound **47** was subjected to intramolecular Diels–Alder (IMDA) reaction and subsequent C–O bond cleavage in the presence of a catalytic amount of $AuCl_3$ in acetonitrile for 10 min to afford spiroannulated dihydroisobenzofuran derivative **48** in 93% yield. Formation of isobenzofuran derivative **48** was confirmed by ^{1}H NMR

spectrum wherein the resonances corresponding to acetylenic proton disappeared and one broad singlet corresponding to the proton of phenolic hydroxyl group apparent at δ 5.23 ppm in addition to three protons corresponding to aromatic ring at δ 5.92, 6.56 and 7.03 ppm each as doublet integrating for one proton each along with a singlet corresponding to tolueic -CH_3 integrating for three protons and all other resonances as in accordance with the structure. Further confirmation of **48** came from the ^{13}C NMR, elemental and mass spectroscopic analysis. For example, in the ^{13}C NMR, characteristic carbon of tolueic methyl was apparent at δ 15.0 ppm and anomeric carbon at δ 103.5 ppm along with rest of the spectrum in complete agreement with the assigned structure. The DEPT NMR spectrum confirmed presence of all –CH_2- groups (Scheme 21).

Scheme 21

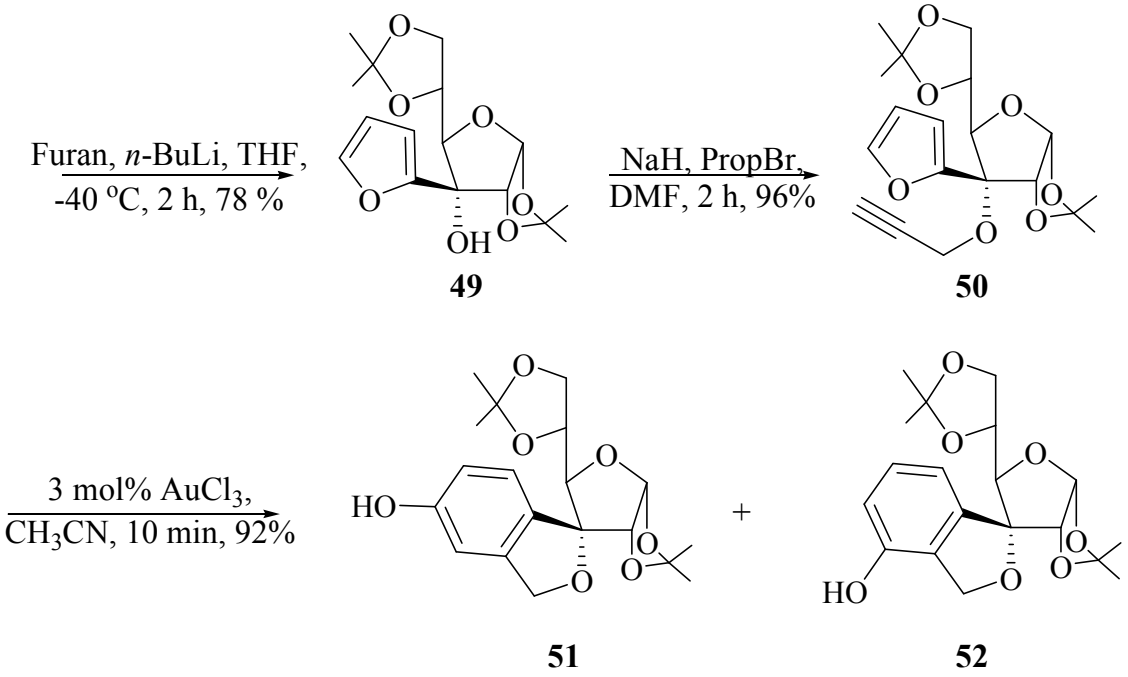


1 **46** **47** **48**

After successfully spiroannulation of **47** we thought of utilizing furan as diene for IMDA reaction. To begin our investigation the ketone **1** was converted to a reported compound 3-*C*-furanyl-D-allose[31] **49** using lithiated furan in THF at -40 °C and *tertiary* hydroxyl group of **49** then alkylated using propargyl bromide and NaH in DMF which resulted in the formation of furfuryl propargyl ether **50**. The formation of **50** was confirmed by ^1H NMR in which acetylenic proton was apparent at δ 2.44 ppm as triplet and anomeric proton at δ 4.75 ppm along with rest of the spectrum in complete agreement with the assigned structure in addition by ^{13}C & DEPT NMR, elemental and

mass analysis unambiguously confirmed the structure assigned. We next performed the current spiroannulation protocol on furfuryl propargyl ether **50** and observed the formation of two regioisomeric spiroannulated derivatives **51** and **52** in a 1:1 ratio, which were easily separated by silica gel column chromatography with a combined yield of 92 %. The structure of each of the regioisomer was established by ^{1}H, ^{13}C, DEPT NMR, elemental and mass analysis. In the ^{1}H NMR spectrum of **51** the resonances corresponding to acetylenic proton disappeared and formation of one mutiplet at δ 6.65-6.74 ppm integrating for two protons and a doublet at δ 6.92 ppm integrating for one proton corresponding to aromatic ring and characteristic broad singlet corresponding to proton of phenolic hydroxyl group at δ 6.11 ppm confirmed the spiroannulation. Whilst ^{13}C NMR spectrum was in complete agreement with the assigned structure. In the ^{1}H NMR spectrum of **52** the presence of two characteristic resonances at δ 6.30 and 6.61 ppm as two doublets and δ 7.03 ppm as triplet integrating for one proton each and one broad singlet corresponding to proton of phenolic hydroxyl at δ 6.57 ppm unambiguously confirmed the structure of **52** along with ^{13}C & DEPT NMR, elemental and mass analysis (Scheme 22).

Scheme 22



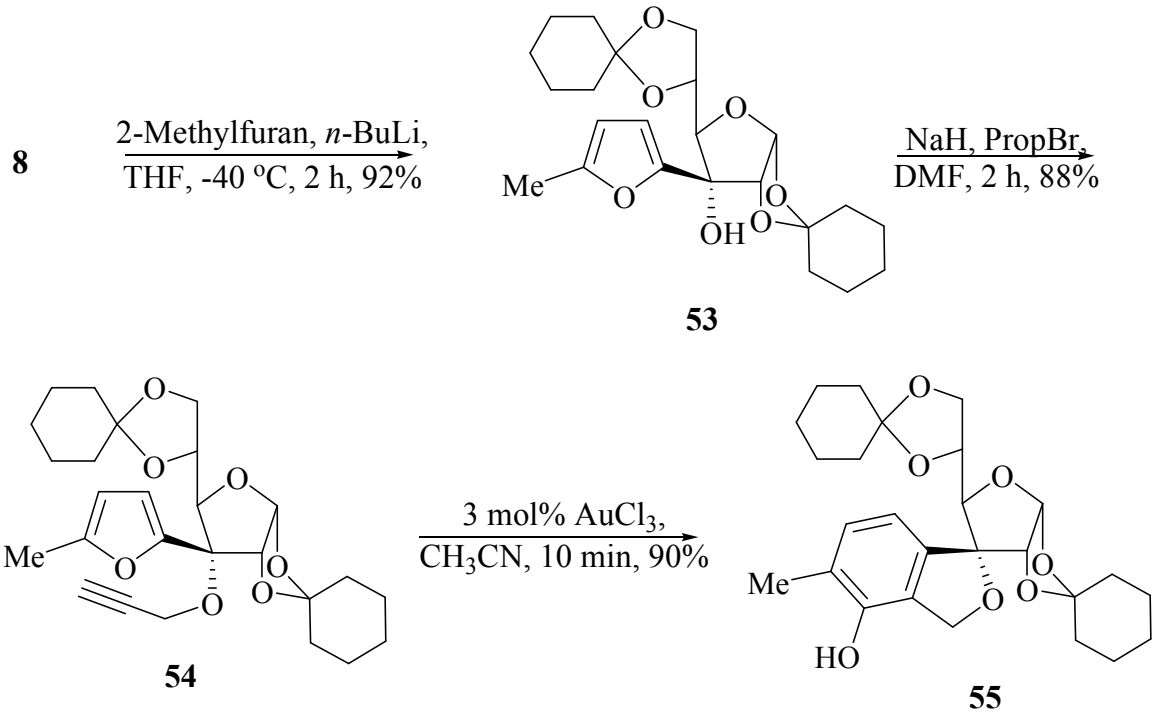
49 **50**

51 **52**

However, with optimized conditions in hand, we decided to explore this spiroannulation protocol on a diverse set of substrates derived from pentofuranosides,

hexofuranosides and hexopyranosides. To begin our synthetic endure, sterically demanding ketone **8** was treated with lithiated methyl furan which resulted in the formation of **53.** Next, the *tertiary* hydroxyl group of **53** was alkylated using propargyl bromide and NaH in DMF which resulted in the formation of methyl furfuryl propargyl derivative **54**. Structure of **54** was established by ^{1}H and ^{13}C NMR, mass and elemental analysis. In ^{1}H NMR spectra of **54**, the resonances corresponding to acetylenic proton was apparent at δ 2.42 ppm as triplet and corresponding to $-CH_3$ of furan at δ 2.28 ppm integrating for three protons in addition rest of spectrum as per the assigned structure. While ^{13}C and DEPT NMR also matched perfectly with the assigned structure. Next, the compound **54** subjected to spiroannulation resulted in the formation of isobenzofuran derivative **55** in 90% yield. The structure was established by the ^{1}H NMR spectrum in which resonance corresponding to acetylenic proton disappeared and a new resonance apparent for tolueic $-CH_3$ at δ 2.19 ppm as singlet integrating for three protons and for anomeric proton as doublet at δ 5.93 ppm with other resonances as expected. In addition structure was established by ^{13}C, DEPT NMR, elemental and mass analysis (Scheme 23).

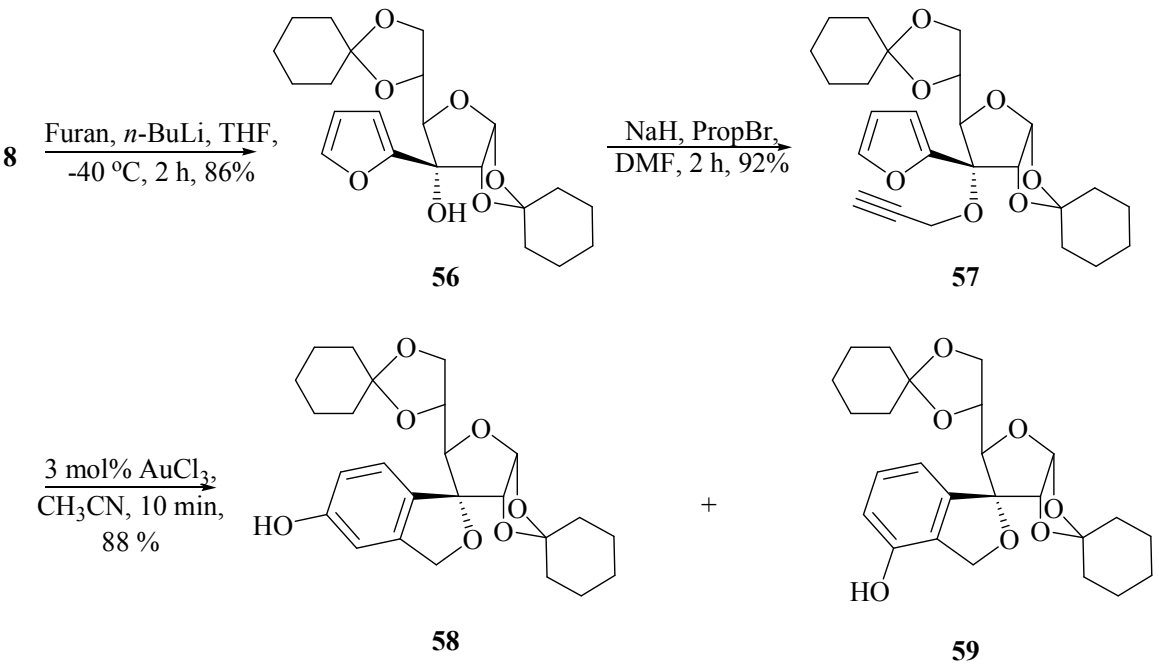
Scheme 23



Next, the ketone **8** was treated with lithiated furan which resulted in the formation of compound **56.** *Tertiary* hydroxyl group of **56** was then alkylated using propargyl

bromide and NaH in DMF resulting in the formation of furfuryl propargyl ether derivative **57**. Compound **57** was then spiroannulated by using our standard protocol which resulted in the formation of two regioisomers **58** and **59** in the ratio of 1:1. The ^{1}H, ^{13}C, DEPT NMR, elemental and mass analysis for the regioisomers **58** and **59** were found to be satisfactory (Scheme 24).

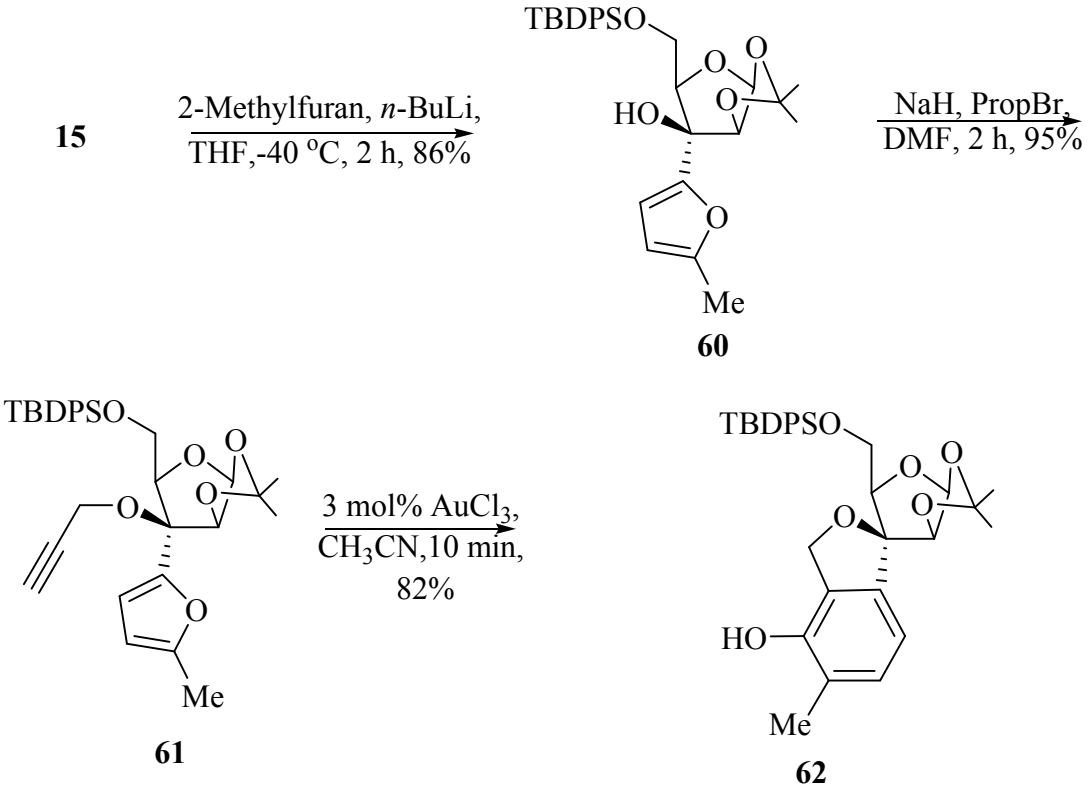
Scheme 24



To continue our DOS study for making a library of diverse scaffolds, next we thought of utilizing arabinose derived pentofuranoside derivative to check feasibility of IMDA reaction. In the sequence, the ketone **15** was treated with lithiated methyl furan to afford *C-3* methyl furan **60**. *Tertiary* hydroxyl group of **60** was then alkylated using propargyl bromide and NaH in DMF. In the ^{1}H NMR spectrum of the compound **61** acetylenic proton resonance apparent at δ 2.38 ppm as triplet and -CH_3 group of methylfuran at δ 2.15 ppm as doublet integrating for three protons and rest of the spectrum as expected. Next the resulting methyl furfuryl propargyl ether **61** was subjected to standard spiroannulation protocol which resulted in the formation of isobenzofuran derivative **62** in 82 % yield. In the ^{1}H NMR spectrum of the **62** resonance present at δ 5.92 ppm as doublet corresponding to anomeric proton whilst resonance corresponding to tolueic -CH_3 were apparent at δ 2.25 ppm as singlet integrating for three protons along with the rest of the spectrum in well correlation with assigned structure.

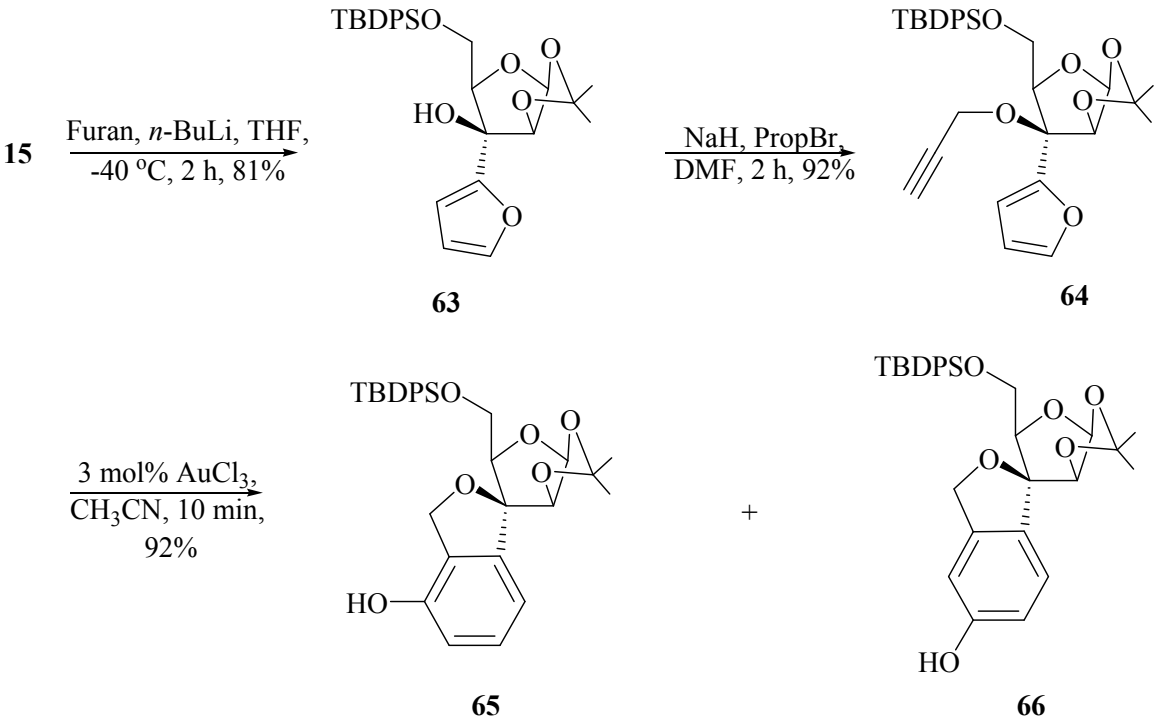
The ^{13}C NMR spectrum showed presence of a resonance corresponding to anomeric carbon at δ 103.6 ppm whilst methyl group of aromatic ring at δ 15.1 ppm. DEPT NMR unambiguously confirmed the presence of all -CH_2- group according to assigned structure (Scheme 25).

Scheme 25



In a similar fashion, the ketone **15** was treated with lithiated furan to obtain **63** and *tertiary* hydroxyl group of **63** was then alkylated using propargyl bromide and NaH in DMF which resulted in the formation of required furfuryl propargyl ether **64**. In the ^1H NMR spectrum of compound **64**, anomeric proton resonances apparent at δ 6.01 ppm as doublet and acetylenic proton at δ 2.40 ppm as triplet integrating for one proton each along with rest of the spectrum in complete agreement with the assigned structure. ^{13}C & DEPT NMR, elemental and mass analyes also were according to assigned structure. Compound **64** was then subjected to spiroannulation protocol which resulted in the formation of two regioisomeric isobenzofuran annulated compounds **65** and **66** in 1:1 ratios. The structures of each of the regioisomers were established by NMR and mass spectroscopic analysis (Scheme 26).

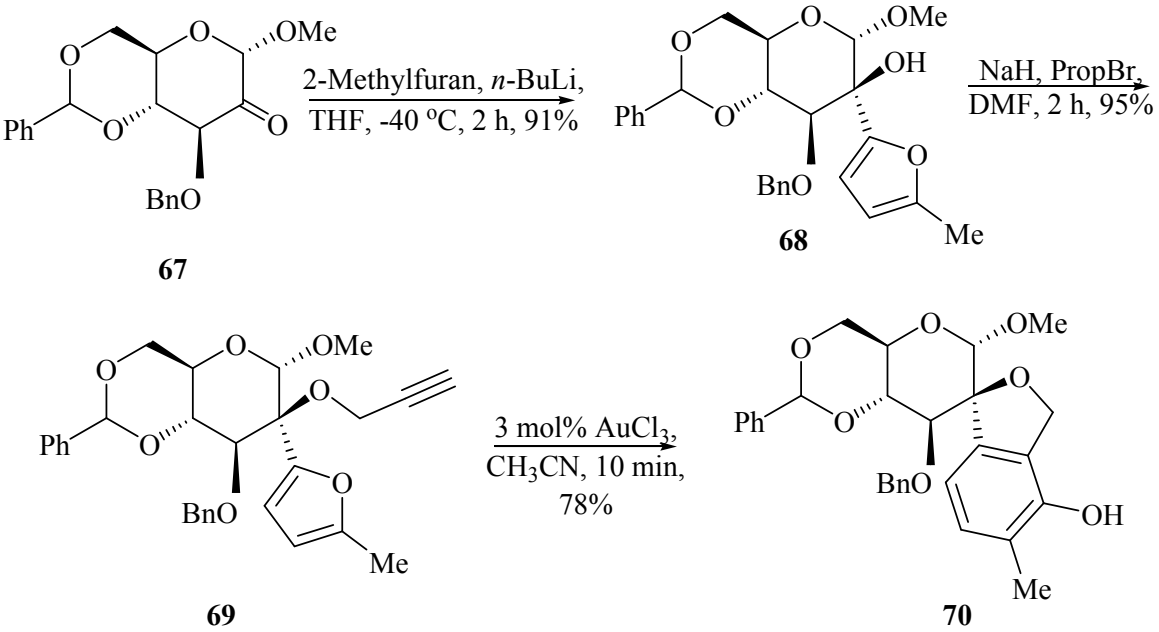
Scheme 26



Our next endeavor was directed towards DOS studies utilizing glucose derived hexopyranosides for the preparation of more diverse scaffolds. To begin our investigation the known ketone **67** prepared from D-glucose in five steps[32] was treated with lithiated methyl furan at -40 °C which resulted in the formation of methyl-3-*O*-benzyl-4,6-*O*-benzylidene-2-*C*-(2-methylfuranyl)-α-D-mannopyranoside **68** (major) in excellent yield. The *tertiary* hydroxyl group of **68** was alkylated using propargyl bromide and NaH in DMF which resulted in the formation of methyl furfuryl propargyl ether **69**. The ^{1}H NMR spectrum of **69** revealed a singlet for anomeric proton at δ 5.37 ppm while benzylidene proton at δ 5.49 ppm, whilst acetylenic proton resonance at δ 2.34 ppm as triplet. The ^{13}C NMR spectrum of **69** showed characteristic anomeric carbon at δ 100.2 ppm and benzylidene carbon at δ 101.3 ppm with the presence of methyl group of furfuryl at δ 13.7 ppm. The DEPT NMR spectral study unambiguously proved presence of three –CH2- groups at δ 53.1, 69.0 and 75.6 ppm. The furfuryl propargyl ether was then subjected to spiroannulation which resulted in the formation of isobenzofuran derivative **70** as single product. Disappearance of acetylenic proton of **69** at δ 2.34 ppm and furfuryl protons at δ 5.99 and 6.75 ppm, and up field shifting of methyl group from δ 2.32 to 2.20 ppm with appearance of protons in aromatic region confirmed the formation

of isobenzofuran derivative **70** whilst rest of the spectrum including ^{13}C and DEPT NMR were in complete agreement with the assigned structure (Scheme 27).

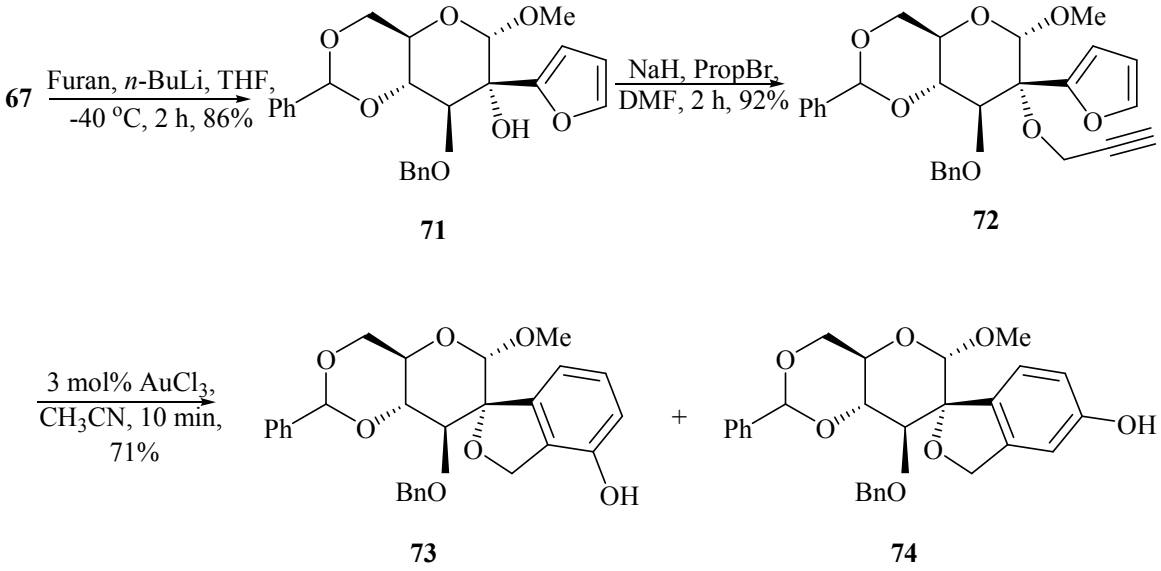
Scheme 27



Furthermore, ketone **67** was reacted with lithiated furan in THF at -40 ^0C which was resulted in the formation of C-2 furfuryl derivative **71**. In the ^1H NMR spectrum of **71**, anomeric proton was found at δ 4.72 ppm and bezylidene proton at δ 5.63 ppm as two singlets. Other signals were in concurrence with compound **71**. To convert compound **71** into propargyl ether derivative **72**, it was treated with propargyl bromide and NaH in DMF. The ^1H NMR spectrum of **72** clearly showed presence of acetylenic proton at δ 2.41 ppm as triplet whilst all other resonances according to furanyl proargyl ether **72**. The spiroannulation of the compound **72** was affected using $AuCl_3$ which resulted in the formation of regioisomers **73** and **74** in 1:1 ratio. Both the regioisomers were separated by silica gel column chromatography and identified by ^1H, ^{13}C and DEPT NMR, in the ^1H NMR of **73** disappearance of signals corresponding to acetylenic proton of **72** and furan protons and appearance of new signal in aromatic region along with one broad signal corresponding to phenolic hydroxyl group at δ 5.43 ppm clearly showed spiroannulation of **72** to isobenzofuran derivatives. In ^1H NMR spectrum of the **74** resonances corresponding to the phenolic hydroxyl proton was apparent at δ 5.50 ppm as

broad singlet whilst anomeric proton at δ 5.25 ppm and benzylidene proton at δ 5.66 ppm as two singlets integrating for one proton each along with all other resonances according to the assigned structure **74.** The structural authenticity of both the isomers was further confirmed by ^{13}C and DEPT NMR, elemental and mass analysis (Scheme 28).

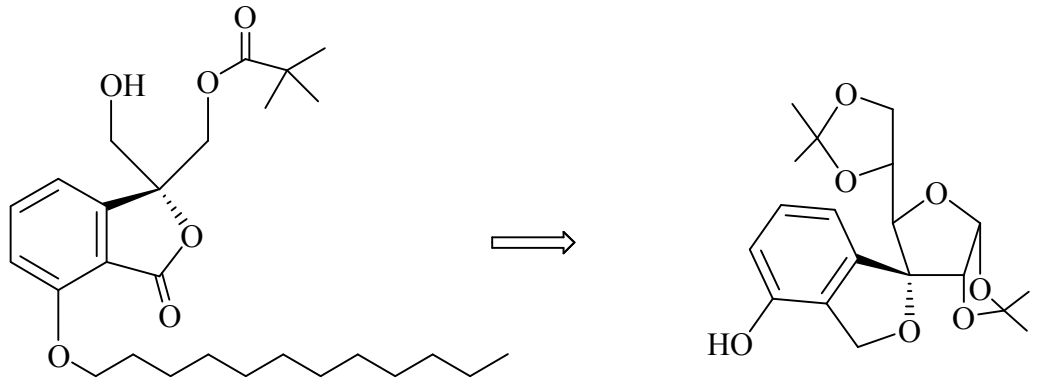
Scheme 28



Formal Synthesis of PKC-α Inhibitor

Protein kinase C (PKC) isozymes play important roles in intracellular signal transduction of a variety of cellular events, such as proliferation, differentiation, and apoptosis.[33] The isozymes are divided into three classes, conventional PKCs (α, βI/βII, γ), novel PKCs (δ, ε, η, θ) and atypical PKCs (ζ, ι /λ). It is now believed that each isozyme participates in different signaling pathways, and, in some cases, the same enzyme triggers different cell responses depending on the stimulus, though the precise molecular mechanisms of activation and the biological roles of each isozyme remains to be clarified. A recent protein docking study by Sodeoka revealed that chiral isobenzofuranone derivative **75** (Figure 13) binds to PKC-α.[34] We envisaged that introduction of a spirocyclic moiety would enhance the biological activity of the PKC-α inhibitor as the spirocyclic moiety occurs in many natural products and its presence has been shown to inhibit many important proteins in the cellular context because of the increased conformational rigidity.[35] One of compound skeleton synthesized during DOS

matched well with known PKC-α inhibitor. We thought of furnishing formal synthesis of PKC-α inhibitor.



75

PKC-α Inhibitor

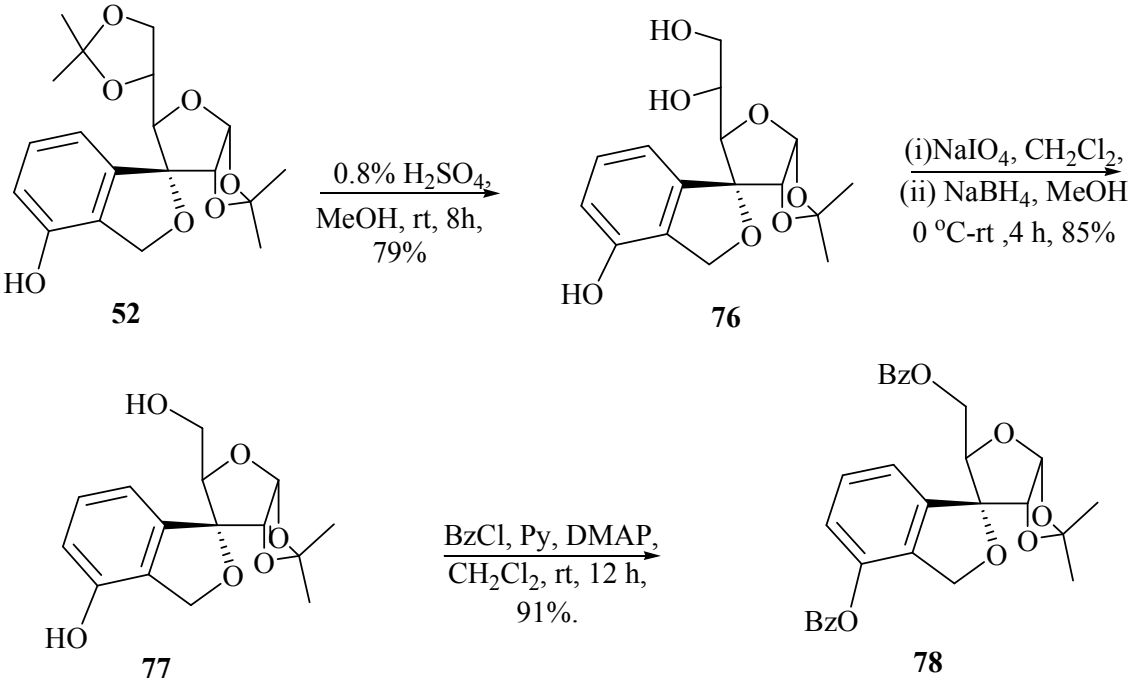
52

Figure 13

To begin the synthetic endure, dihydroisobenzofuran derivative **52** was subjected to acid catalyzed regioselective deprotection of 5,6-isopropylidine using 0.8 % H_2SO_4 and methanol which resulted in the formation of diol **76.** The ^{1}H NMR spectrum clearly showed absence of two singlets corresponding to isopropylidene group. Further, the structure was confirmed by the ^{13}C NMR which showed absence of three carbon resonances corresponding to isopropylidene group. Next, diol **76** was subjected to oxidative cleavage using $NaIO_4$ in DCM followed by reduction of resulting aldehyde to alcohol **77** using $NaBH_4$ in methanol. In ^{1}H NMR of the compound **77** the resonance of anomeric proton apparent at δ 6.01 ppm whilst two -CH_3 groups of 1,2-isopropylidene at δ1.34 and 1.60 ppm along with rest of the spectral values in complete agreement with that of the assigned structure **77**. In ^{13}C NMR spectrum, resonances due to the carbon of methyl groups of isopropylidene were apparent at δ 27.6 and 27.9 ppm whilst DEPT spectrum clearly showed presence of two -CH_2- groups. Next the hydroxyl group of compound **77** was protected as benzoate esters using benzoyl chloride and triethyl amine in DCM which resulted in diester **78**. Benzoate ester protection was chosen because of its stability towards the strong acid compared to other protecting groups. The ^{1}H NMR clearly showed the presence of multiplets in aromatic region corresponding to benzoate groups wherein all other resonances according to assigned structure **78**. Whilst in the ^{13}C

NMR spectrum, presence of two carbonyl groups at δ 163.8 and 166.1 ppm unambiguously confirmed **78** (Scheme 29).

Scheme 29

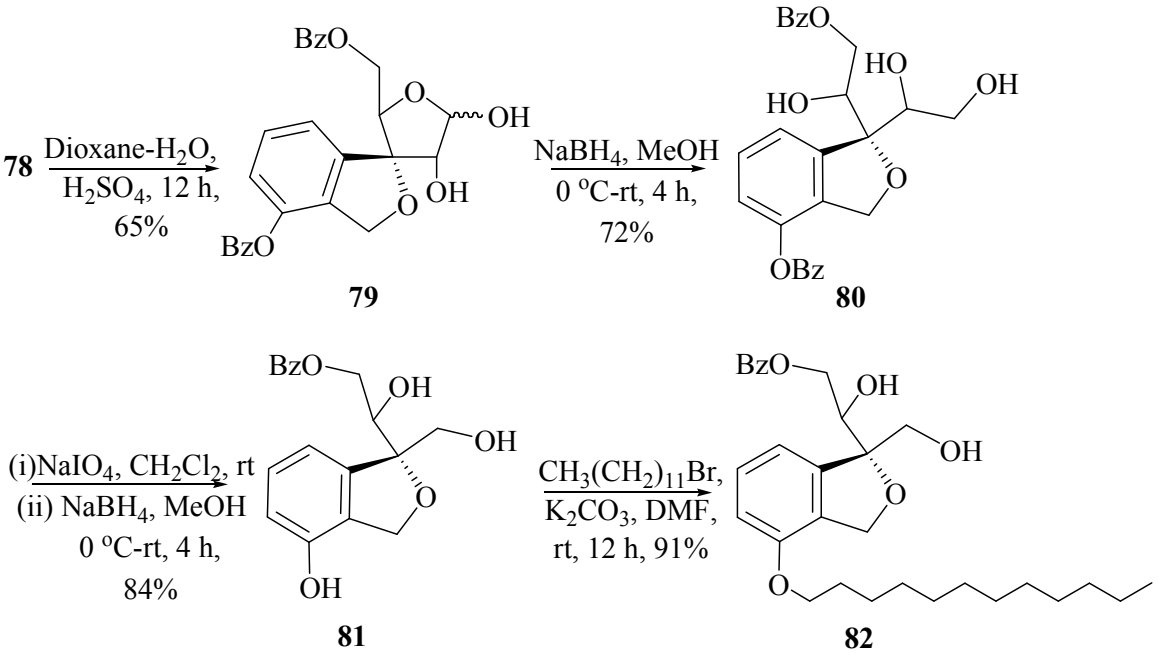


52 **76** **77** **78**

Accordingly, lone isopropylidene group of diester **78** was deprotected by treatment with strong acid in dioxane and water which resulted in the formation of lactol **79**. The masked aldehyde group of lactol was reduced by using $NaBH_4$ in methanol which resulted in the formation of triol **80**. Absence of isopropylidene group in the ^1H NMR spectrum of **80** clearly confirmed the formation of triol which was further confirmed by ^{13}C and DEPT NMR spectroscopic studies. The triol **80** was again subjected to oxidative cleavage using $NaIO_4$ in DCM followed by the reduction of the resulting aldehyde which resulted in the formation of triol **81**. At this stage we observed selective deprotection of phenolic benzoate ester as well. ^1H, ^{13}C and DEPT NMR spectrum were in complete agreement with the assigned structure of the compound **81**. The phenolic hydroxyl group of **81** was then alkylated using dodecyl bromide and K_2CO_3 in DMF which resulted in the formation of alkyl ether **82**. The *O*-alkylated derivative **82** showed a triplet at δ 0.89 ppm and a singlet at δ 1.28 ppm due to long alkyl chain in ^1H NMR spectrum. Further the structure was confirmed by DEPT spectrum where in all –

CH_2- groups corresponding to long alkyl chain were apparent unambiguously (Scheme 30).

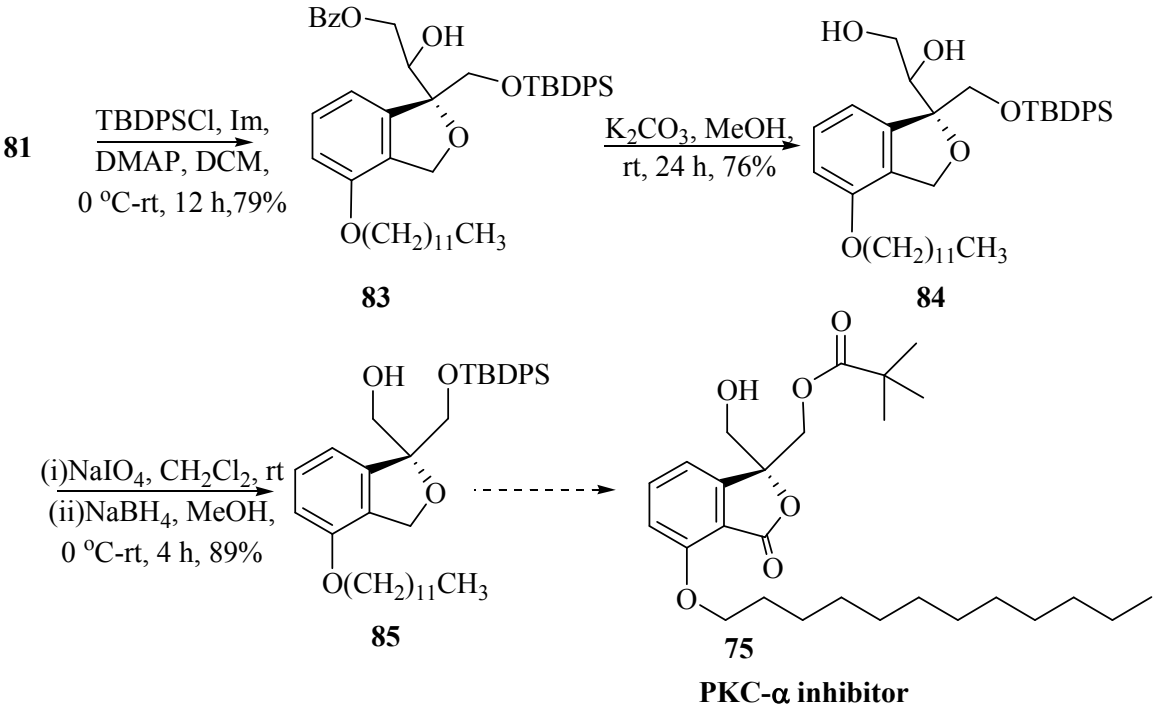
Scheme 30



Our next concern was to protect *primary* hydroxyl group of diol **82.** We decided to convert *primary* hydroxyl group to TBDPS ether because of its stability and its selectivity towards the *primary* alcohols over the *secondary* alcohols. Thus accordingly, diol **82** was treated with TBDPS-Cl and imidazole in DCM which resulted in the formation of silyl ether **83**. The ^{1}H NMR spectrum clearly showed presence of *t*-butyl group at δ 1.01 ppm whilst in the ^{13}C NMR resonances corresponding to t-butyl group at δ 26.7 ppm and carbonyl group at δ 167.0 ppm along with other resonances. The benzoate ester of **83** was deprotected using K_2CO_3 in methanol which resulted in the formation of diol **84**. The ^{1}H NMR spectrum clearly showed absence of aromatic protons and disappearance of carbonyl group in the ^{13}C NMR spectrum further confirmed debenzoylation. Diol **84** was then subjected to oxidative cleavage using $NaIO_4$ in DCM followed by $NaBH_4$ in methanol reduction of resulting aldehyde which resulted in the formation of alcohol **85**. In the ^{1}H NMR spectrum of **85** the resonance corresponding to *t*-butyl group apparent at δ 1.01 ppm, terminal methyl group of alkyl chain at δ 0.88 ppm and alkyl –CH_2- groups at δ 1.26 ppm with all resonances according to assigned structure of **85**. The ^{13}C NMR spectrum of **85** showed presence of *t*-butyl group at δ 26.7 ppm and

methyl group of alkyl chain at δ 14.1 ppm whilst DEPT NMR spectrum confirmed presence of all requisite -CH_2- groups unambiguously. In addition the structure was confirmed by elemental and mass spectral analysis. The compound **85** can be easily converted to known PKC-α inhibitor **75** by oxidizing benzylic -CH_2 group followed by known protection deprotection sequences (Scheme 31).

Scheme 31



Conclusion

A particularly relevant aspect of this research was the development of a DOS approach for the synthesis of skeletally diverse carbohydrate-derived molecules. The challenging problem of varying molecular scaffold was solved using complementary transition metal-catalysed (Au, Co, Ru) reactions. Hence, carbohydrate-derived enynes could be transformed into alternative spirocyclic molecules with varied molecular skeletons for the synthesis of a library of diverse spirocyclic oxygen-rich small molecules. The Molecular framework of some of the library members matched that of known biologically-active small molecules including a PKC-α inhibitor.

1.3 Experimental Section

General experimental procedure for Barbier reaction:

A flame dried two neck round bottom flask fit with reflux condenser and N_2 outlet was charged with Zn powder (4.0 eq) and was added anhydrous THF and catalytic amount of dibromoethane and reaction mixture was refluxed to 70 ^oC for 10 min and then cooled to 0 ^oC. To this, was added alkylhalide (allyl/propragyl bromide, 2.0 eq) drop wise over 10 min, stirred at room temperature for 30 min, and again cooled to 0 ^oC, and a solution of ketone (1.0 eq) in anhydrous THF was added drop wise over 10 min. The resulting solution was stirred for 30 min at room temperature and after completion of the reaction (TLC monitored), the reaction mixture was again cooled to 0 ^oC and quenched with saturated aq. NH_4Cl solution. The reaction mixture was diluted with water, extracted with ethyl acetate and combined organic layers were dried over anhydrous Na_2SO_4, concentrated *in vacuo* and purified by column chromatography using ethyl acetate/petroleum ether as mobile phase.

General experimental procedure for *O*-alkylation:

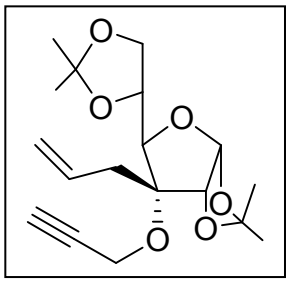
To a solution of *tertiary*-alcohol (1 eq) in anhydrous DMF cooled to 0 ^oC was added NaH (2.0 eq) and stirred at room temperature for 30 min. The resulting dark brown solution was cooled to 0 ^oC and was added *n*-$Bu_4N^+I^-$ followed by addition of alkyl halide (1.2 eq) and stirred for respective time periods. The excess NaH was quenched by the addition of methanol. After completion of the reaction (TLC monitored), the resulting solution was diluted with excess water and extracted with ethyl acetate. The combined organic layers were washed with saturated aq. NaCl solution, dried over anhydrous Na_2SO_4, concentrated *in vacuo* and purified by silica gel column chromatography using light peteroleum-ethyl acetate as mobile phase to afford enyne.

General experimental procedure for Pauson-Khand reaction:

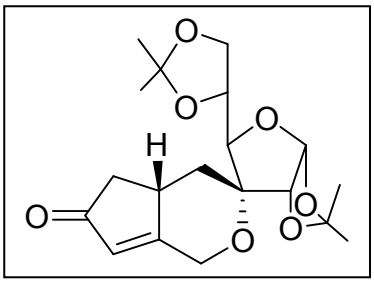
To a solution of enyne (1.0 eq) in anhydrous CH_2Cl_2 under N_2 atmosphere was added dicobalt octacarbonyl (Strem Chemicals) (1.5 eq) at room temperature and the resulting reddish brown solution was stirred for the specified time. At the end of the reaction (TLC monitored), the reaction mixture was concentrated *in vacuo* and the residue was passed through a bed of silica gel to obtain the alkyne–$Co_2(CO)_6$ complex

which was then dissolved in acetonitrile (40 mL per 100 mg of complex) and dimethoxyethane (10 mL per 100 mg of complex) and kept at 85 ^{o}C for 1–5 h. The reaction mixture was cooled to room temperature and then filtered through a pad of silica gel–celite, the filtrate was concentrated *in vacuo* and the resulting residue was purified by silica gel column chromatography.

1,2:5,6-Bis-*O*-(1-methylethylidene)-3-*C*-2-propenyl-3-*O*-2-propynyl-α-D-allofuranose (3): $[\alpha]_D$ +58.77 (*c* 1.75, $CHCl_3$); IR ($CHCl_3$): 3276 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 1.33, 1.37, 1.45, 1.59 (4s, 12H), 2.29 (dd, 1H, *J* = 7.8, 15.16 Hz), 2.42 (t, 1H, *J* = 2.40 Hz), 2.73 (dd, 1H, *J* = 6.19, 15.16 Hz), 3.94 (m, 1H), 4.12 (m, 3H), 4.47 (m, 3H), 5.15 (d, 1H, *J* = 7.96 Hz), 5.22 (s, 1H), 5.57 (d, 1H, *J* = 3.54 Hz), 6.02 (m, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 25.3, 26.4, 26.4, 26.9, 35.1, 53.7, 68.2, 72.5, 73.7, 80.7, 81.1, 83.0, 83.8, 102.9, 109.7, 112.8, 118.9, 132.2; CHN Anal. Calcd for $C_{18}H_{26}O_6$: C, 63.89, H, 7.74; Found: C, 63.63, H, 8.07

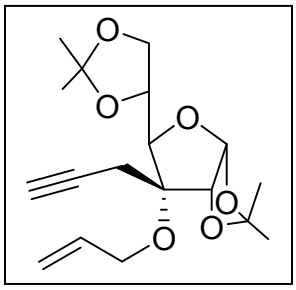


(3R,3'aR,4aS,5'R,6'aR),5'-[(4R)-2,2-Dimethyl-1,3-dioxolan-4-yl]-3'a,4a,5,6'a-tetra-hydro-2',2'-dimethyl-spiro[cyclopenta[c]pyran-3(1H),6'(5'H)-furo[2,3-d][1,3]dioxol]-6(4H)-one (4): $[\alpha]_D$ +11.72 (*c* 1.0, $CHCl_3$); IR ($CHCl_3$,): 1709, 1634 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.33, 1.38, 1.42, 1.62 (4s, 12H), 1.85 (m, 2H), 2.13 (dd, 1H, *J* = 2.93, 18.58 Hz), 2.69 (dd, 1H, *J* = 6.60, 18.58 Hz), 3.15 (m, 1H), 3.94 (m, 1H), 4.05 (m, 3H), 4.63 (ABq, 2H, *J* = 14.65 Hz), 4.73 (d, 1H, *J* = 3.66 Hz), 5.78 (d, 1H, *J* = 3.66 Hz), 6.02 (s, 1H), ^{13}C NMR ($CDCl_3$, 50 MHz): δ 25.3, 26.5, 26.6, 26.8, 34.3, 35.2, 41.8, 63.9, 67.2, 73.2, 79.7, 81.2, 81.4, 103.8, 109.6, 113.1, 127.7, 174.9, 206.9; CHN Anal. Calcd for $C_{19}H_{26}O_7$: C, 62.28, H, 7.15; Found: C, 61.8, H, 7.35; ESI Mass: 389.23 (M + Na).

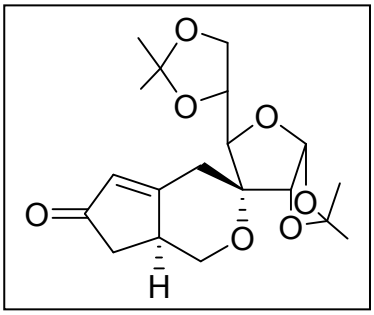


1,2:5,6-Bis-*O*-(1-methylethylidene)-3-*O*-2-propenyl-3-*C*-2-propynyl-α-D-allofuranose (6): $[\alpha]_D$ +43.03 (*c* 1.75, $CHCl_3$); IR ($CHCl_3$): 3308 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 1.35, 1.36, 1.43, 1.58 (4s, 12H), 2.11 (t, 1H, *J* = 2.65 Hz), 2.56 (dd, 1H, *J* = 2.65, 17.18 Hz), 2.77 (dd, 1H, *J* = 2.66, 17.31 Hz), 4.20 (m, 6H), 4.68 (d, 1H, *J* = 3.79

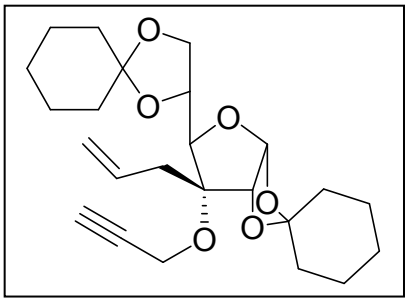
Hz), 5.13 (qd, 1H, *J* = 1.52, 3.16 Hz), 5.32 (qd, 1H, *J* = 1.77, 3.42 Hz), 5.76 (d, 1H, *J* = 3.79 Hz), 5.92 (m, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 21.6, 25.3, 26.6, 26.7, 26.9, 66.6, 67.6, 71.9, 73.3, 79.1, 81.6, 82.5, 83.5, 104.1, 109.5, 112.7, 115.6, 135.1; CHN Anal. Calcd for $C_{18}H_{26}O_6$: C, 63.89, H, 7.74; Found: C, 63.42, H, 7.87

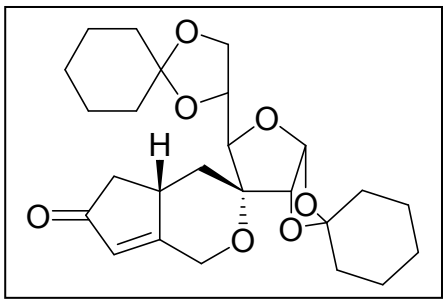


(3R, 3'aR, 5'R, 6'aR,7aS)-5'-[(4R)-2,2-Dimethyl-1,3-dioxolan-4-yl]-3'a,6'a,7,7a-tetrahydro-2',2'-dimethyl-spiro[cyclopenta[c]pyran-3(1H),6'(5'H)-furo[2,3-d][1,3]dioxol]-6(4H)-one (7): $[\alpha]_D$ -50.57 (*c* 1.05, $CHCl_3$); IR ($CHCl_3$): 1708, 1627 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.32, 1.37, 1.46, 1.58 (4s, 12H), 1.96 (dd, 1H, *J* = 2.15, 18.95 Hz), 2.53 (dd, 2H, *J* = 4.55, 18.57 Hz), 2.93 (d, 1H, *J* = 13.39 Hz), 3.13 (m, 1H), 3.41 (t, 1H, *J* = 11.24 Hz), 3.92–4.28 (m, 5H), 4.31 (d, 1H, *J* = 3.79 Hz), 5.74 (d, 1H, *J* = 3.79 Hz), 6.06 (s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 25.3, 26.6, 26.6, 26.8, 33.2, 37.2, 40.7, 67.4, 69.9, 73.5, 79.4, 80.7, 83.1, 103.7, 109.8, 113.1, 129.6, 177.0, 207.3; CHN Anal. Calcd for $C_{19}H_{26}O_7$: C, 62.28; H, 7.15; Found: C, 61.93; H, 7.55; ESI Mass: 389.25 (M + Na).



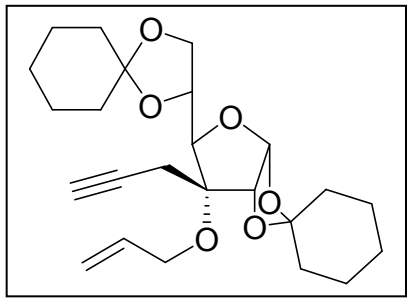
1,2:5,6-Di-*O*-cyclohexylidene-3-*C*-2-propenyl-3-*O*-2-propynyl-α-D-allofuranose (10): $[\alpha]_D$ +57.27 (*c* 0.96, $CHCl_3$); IR ($CHCl_3$): 3309, 2939 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.58 (m, 20H), 2.30 (dd, 1H, *J* = 7.83, 14.90 Hz), 2.40 (t, 1H, *J* = 2.40 Hz), 2.71 (dd, 1H, *J* = 6.31, 14.98 Hz), 3.86 (m, 1H), 4.11 (m, 3H), 4.43 (d, 1H, *J* = 3.66 Hz), 4.50 (dd, 2H, *J* = 2.40, 4.55 Hz), 5.13 (dd, 1H, *J* = 1.77, 8.59 Hz), 5.20 (s, 1H), 5.58 (d, 1H, *J* = 3.66 Hz), 6.03 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 23.6, 23.9, 24.0, 24.0, 24.9, 25.2, 34.8, 35.7, 36.0, 36.1, 36.6, 53.8, 68.0, 72.4, 73.4, 80.8, 82.6, 83.9, 102.8, 110.3, 113.5, 118.6, 132.6; CHN Anal. Calcd for $C_{25}H_{34}O_6$: C, 68.87; H, 8.19; Found: C, 68.57; H, 8.23



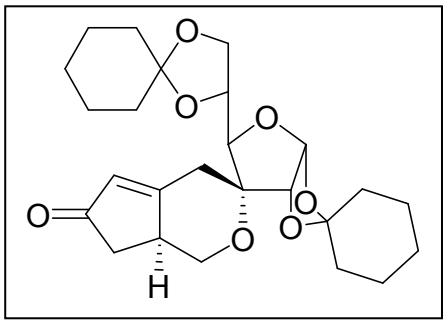


(3'aR, 3''R, 4''aS, 5'R, 6'aR)-5'-(2R)-1,4-Dioxaspiro[4.5]dec-2-yl-3'a,4''a,5'',6'a-tetrahydro-dispiro[cyclohexane-1,2'-furo[2,3-d][1,3]dioxole-6'(5'H),3''(1''H)-cyclo- penta[c]pyran]-6''(4''H)-one (11): $[\alpha]_D$ +9.77 (*c* 1.05, $CHCl_3$); IR ($CHCl_3$): 1707, 1634 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 1.29 (m, 22H), 2.12 (dd, 1H, *J* = 2.56, 18.21 Hz), 2.69 (dd, 1H, *J* = 5.37, 18.37 Hz), 3.13 (m, 1H), 3.90 (m, 1H), 4.03 (m, 3H), 4.63 (ABq, 2H, *J* = 14.20 Hz), 4.70 (d, 1H, *J* = 3.92 Hz), 5.79 (d, 1H, *J* = 3.92 Hz), 6.01 (s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 23.6, 23.8, 23.9, 24.8, 25.0, 34.5, 34.8, 35.2, 36.1, 36.2, 36.2, 41.8, 63.8, 67.1, 72.9, 79.4, 81.4, 103.6, 110.1, 113.7, 127.5, 175.4, 207.0; CHN Anal. Calcd for $C_{25}H_{34}O_7$: C, 67.24, H, 7.67; Found: C, 67.51, H, 7.15

1,2:5,6-Di-*O*-cyclohexylidene-3-*O*-2-propenyl-3-*C*-2-propynyl-α-D-allofuranose (13): $[\alpha]_D$ +48.93 (*c* 1.40, $CHCl_3$); IR ($CHCl_3$): 3308, 2938 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 1.61 (m, 20H), 2.10 (t, 1H, *J* = 2.78, 5.56 Hz), 2.67 (dq, 2H, *J* = 2.78, 17.18 Hz) 3.94 (q, 1H, *J* = 5.18, 8.09 Hz), 4.13 (m, 3H), 4.31 (m, 2H), 4.66 (d, 1H, *J* = 3.79 Hz), 5.11 (qd, 1H, *J* = 1.51, 3.41 Hz), 5.32 (qd, 1H, *J* = 1.77, 3.67 Hz), 5.76 (d, 1H, *J* = 3.79 Hz), 5.93 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 21.8, 23.7, 23.9, 24.0, 24.0, 25.0, 25.2, 34.9, 36.2, 36.3, 36.6, 66.9, 67.6, 71.8, 73.1, 79.3, 81.8, 82.2, 83.4, 104.0, 113.4, 115.4, 135.3; CHN Anal. Calcd for $C_{24}H_{34}O_6$: C, 68.87, H, 8.19; Found: C, 68.57, H, 8.29

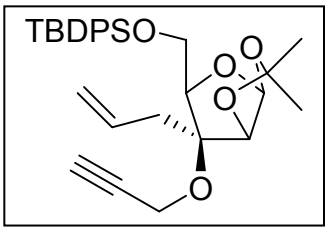


(3'aR,3''R,5'R,6'aR,7''aS)-5'-(2R)-1,4-Dioxaspiro[4.5]dec-2-yl-3'a,6'a,7'',7''a-tetra-hydro-dispiro[cyclohexane-1,2'-furo[2,3-d][1,3]dioxole-6'(5'H),3''(1''H)-cyclopenta [c]pyran]-6''(4''H)-one (14): $[\alpha]_D$ -28.11 (*c* 1.70, $CHCl_3$); IR ($CHCl_3$): 1706 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 1.6 (m, 20H), 1.97 (dd, 1H, *J* = 2.14, 18.94 Hz), 2.51 (d, 1H, *J* = 13.55 Hz), 2.52 (q, 1H, *J* = 5.22, 18.94 Hz), 3.04 (m, 2H), 3.42 (m, 1H, *J* = 11.36), 4.07 (m, 5H), 4.28 (d, 1H, *J* =3.90 Hz), 5.75

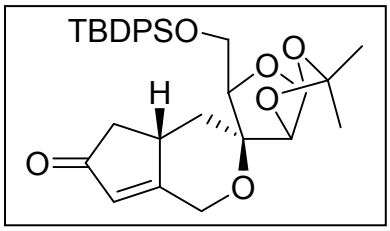


(d, 1H, *J* = 3.90 Hz), 6.05 (s, 1H), ^{13}C NMR ($CDCl_3$, 75 MHz): δ 23.7, 24.0, 24.0, 24.0, 24.9, 25.2, 33.4, 35.0, 36.3, 36.3, 36.4, 37.2, 40.9, 67.5, 69.9, 73.5, 79.3, 81.1, 83.2, 103.6, 110.3, 113.8, 129.6, 177.1, 207.1; CHN Anal. Calcd for $C_{25}H_{34}O_7$: C, 64.24, H, 7.67; Found: C, 64.69, H, 7.69

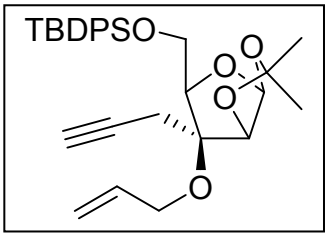
5-*O*-[(1,1-Dimethylethyl)diphenylsilyl]-1,2-*O*-(1-methylethylidene)-3-*C*-2-propenyl-3-*O*-2-propynyl- β-D-arabinofuranose (17): $[\alpha]_D$ -14.43 (*c* 1.10, $CHCl_3$); IR ($CHCl_3$): 3308, 2931 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.06, 1.33, 1.58 (3s, 15H), 2.35 (dq, 2H, *J* = 7.46, 14.92 Hz), 2.39 (t, 1H, *J* = 2.46 Hz), 3.86 (m, 2H), 4.32 (m, 4H), 5.01 (m, 1H), 5.07 (s, 1H), 5.63 (d, 1H, *J* = 3.69 Hz), 5.86 (m, 1H), 7.4 (m, 6H), 7.71 (m, 4H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 18.9, 26.5, 26.8, 53.6, 62.3, 73.9, 80.5, 81.2, 82.4, 83.7, 103.5, 112.6, 118.5, 127.6, 129.6, 132.4, 135.2, 133.3, 134.8, 135.1, 135.6, 135.7; CHN Anal. Calcd for $C_{30}H_{38}O_5Si$: C, 71.11, H, 7.56; Found: C, 70.29, H, 7.20



(3R, 3'aS, 4aS, 5'R, 6'aS)- 5'-[[[(1,1-Dimethylethyl)diphenylsilyl]oxy]methyl]-3'a,4a,5,6'a-tetrahydro-2',2'-dimethyl-spiro[cyclopenta[c]pyran-3(1H),6'(5'H)-furo [2,3-d] [1,3]dioxol]-6(4H)-one (18): $[\alpha]_D$ -4.08 (*c* 1.25, $CHCl_3$); IR ($CHCl_3$): 1709 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.02, 1.39 (2s, 12H), 1.53 (m, 1H), 1.63, (s, 3H), 1.90 (m, 2H), 2.61 (q, 1H, *J* = 6.66, 18.91 Hz), 3.02 (bs, 1H), 3.79 (m, 2H), 4.18 (t, 1H, *J* = 5.11 Hz), 4.56 (m, 2H), 4.69 (d, 1H, *J* = 3.94 Hz), 5.84 (d, 1H, *J* = 3.94 Hz), 5.98 (s, 1H), 7.37 (m, 6H), 7.68 (m, 4H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 19.2, 26.7, 34.5, 35.2, 41.8, 61.7, 63.9, 79.2, 81.0, 81.3, 104.2, 113.0, 127.7, 129.7, 133.1, 133.2, 134.8, 135.6, 174.8, 207.0; CHN Anal. Calcd for $C_{31}H_{38}O_6Si$: C, 69.63, H, 7.16; Found: C, 69.23, H, 7.43

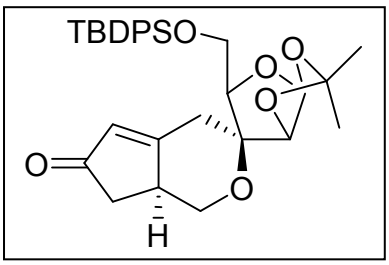


5-*O*-[(1,1-Dimethylethyl)diphenylsilyl]-1,2-*O*-(1-methylethylidene)-3-*O*-2-propenyl-3-*C*-2-propynyl- β-D-arabinofuranose (20): $[\alpha]_D$ -34.49 (*c* 1.55, $CHCl_3$); IR ($CHCl_3$): 3308 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.05, 1.36, 1.57 (3s, 15H), 2.01 (t, 1H, *J* = 2.51), 2.49 (dq, 2H, *J* = 2.88, 17.43 Hz), 3.87 (m, 2H), 4.23 (m, 3H), 4.63 (d, 1H, *J* = 3.89 Hz), 5.18 (m, 2H), 5.79 (d, 1H, *J* = 3.88 Hz),

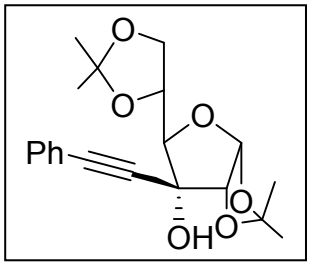


5.92 (m, 1H), 7.37 (m, 6H), 7.69 (m, 4H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 19.2, 21.6, 26.8, 62.1, 66.9, 71.9, 79.4, 81.5, 81.7, 83.0, 104.0, 112.6, 116.0, 127.6, 127.6, 129.6, 133.3, 133.3, 135.0, 135.7; CHN Anal. Calcd for $C_{30}H_{38}O_5Si$: C, 71.11, H, 7.56; Found: C, 70.69, H, 7.12

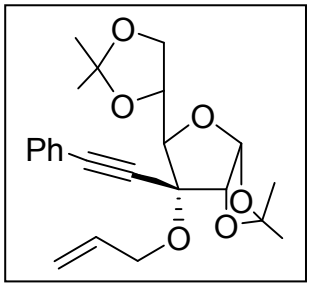
(3R, 3'aS, 5'R, 6'aS, 7aS)-5'-[[[(1,1-Dimethylethyl)diphenylsilyl]oxy]methyl]-3'a, 6'a,7,7a-tetrahydro-2',2'-dimethyl-spiro[cyclopenta[c]pyran-3(1H),6'(5'H)-furo[2,3-d][1,3]dioxol]-6(4H)-one (21): $[\alpha]_D$ +32.25 (*c* 1.10, $CHCl_3$); IR ($CHCl_3$): 1707 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.06, 1.33, 1.58 (3s, 15H), 1.95 (dd, 1H, *J* = 2.27, 18.95 Hz), 2.47 (d, 1H, *J* = 14.40 Hz), 2.5 (q, 1H, *J* = 6.70, 18.44 Hz), 2.75 (d, 1H, *J* = 13.89 Hz), 2.96 (m, 1H), 3.40 (t, 1H, *J* = 11.12 Hz), 3.92 (d, 2H, *J* = 5.18 Hz), 4.22 (t, 2H, *J* = 5.31 Hz), 4.27 (d, 1H, *J* = 3.90 Hz), 5.79 (d, 1H, *J* = 3.79 Hz), 6.02 (s, 1H), 7.40 (m, 6H), 7.70 (m, 4H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 19.2, 26.6, 26.7, 33.1, 37.2, 40.8, 61.9, 69.9, 79.0, 80.3, 82.8, 103.9, 112.9, 127.7, 129.7, 129.7, 133.1, 135.6, 177.0, 207.2; CHN Anal. Calcd for $C_{31}H_{38}O_6Si$: C, 69.63, H, 7.16; Found: C, 69.19, H, 7.29



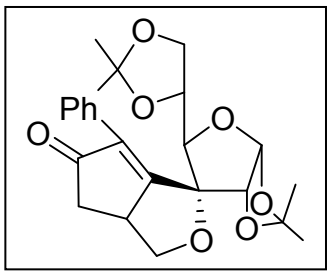
1,2:5,6-Bis-*O*-(1-methylethylidene)-3-*C*-(phenylethynyl)- α-D-allofuranose (22): ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.39, 1.48, 1.63 (3s, 12H), 3.17 (s, 1H), 3.98 (d, 1H, *J* = 7.58 Hz), 4.14 (dq, 2H, *J* = 6.07, 8.72, 14.78 Hz), 4.51 (m, 1H), 4.70 (d, 1H, *J* = 3.53 Hz), 5.89 (d, 1H, *J* = 3.54 Hz), 7.34 (m, 3H), 7.46 (m, 2H).



1,2:5,6-Bis-*O*-(1-methylethylidene)-3-*C*-(phenylethynyl)-3-*O*-2-propenyl- α-D-allofuranose (23): $[\alpha]_D$ +26.06 (*c* 1.66, $CHCl_3$); IR ($CHCl_3$): 2927 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.37, 1.46, 1.60 (3s, 12H), 4.17 (m, 3H), 4.29 (d, 1H, *J* = 4.80 Hz), 4.45 (m, 2H), 4.68 (d, 1H, *J* = 3.66 Hz), 5.18 (qd, 1H, *J* = 1.39, 3.28 Hz), 5.36 (qd, 1H, *J* = 1.77, 3.53 Hz), 5.88 (d, 1H, *J* = 3.53 Hz), 6.01 (m, 1H), 7.34 (m, 3H), 7.45 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 25.3, 26.4, 26.8, 26.9, 65.6, 67.4, 74.7, 81.2, 81.7, 83.3, 84.5, 90.6, 104.4, 108.7, 113.5,



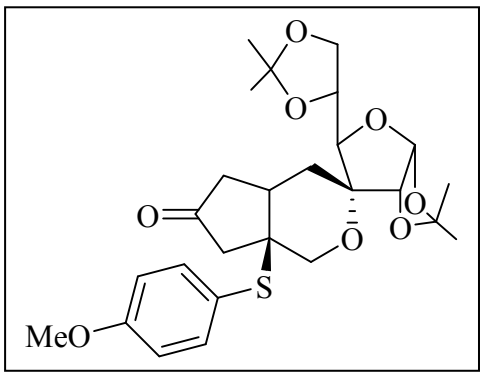
116.3, 121.5, 128.4, 129.0, 131.7, 134.7; CHN Anal. Calcd for $C_{23}H_{28}O_6$: C, 68.98, H, 7.05; Found: C, 68.39, H, 6.91



(1R,3aS,3'aR,5'R,6'aR)-5'-[(4R)-2,2-Dimethyl-1,3-dioxolan-4-yl]-3a,3'a,4,6'a-tetra- hydro-2',2'-dimethyl-6-phenyl-spiro[1H-cyclopenta[c]furan-1,6'(5'H)-furo[2,3-d][1,3]dioxol]-5(3H)-one (24): $[\alpha]_D$ +30.37 (*c* 1.35, $CHCl_3$); IR ($CHCl_3$): 1712 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 1.13, 1.37, 1.47, 1.55 (s, 12H), 2.33 (dd, 1H, *J* = 3.67, 18.06 Hz), 2.86 (dd, 1H, *J* = 6.57, 18.06 Hz), 3.50 (dd, 1H, *J* = 7.83, 10.74 Hz), 3.91 (m, 1H), 4.12 (m, 5H), 4.45 (t, 1H, *J* = 7.96 Hz), 4.59 (d, 1H, *J* = 3.92), 7.27 (m, 2H), 7.39 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 25.4, 26.3, 26.5, 39.7, 49.2, 67.8, 71.3, 74.5, 80.9, 82.8, 88.0, 104.4, 110.0, 112.6, 128.0, 129.0, 129.6, 129.9, 139.5, 176.2, 207.0; CHN Anal. Calcd for $C_{24}H_{28}O_7$: C, 67.28, H, 6.59; Found: C, 67.01; H, 6.39

General experimental procedure for Michael Addition of Thiols:

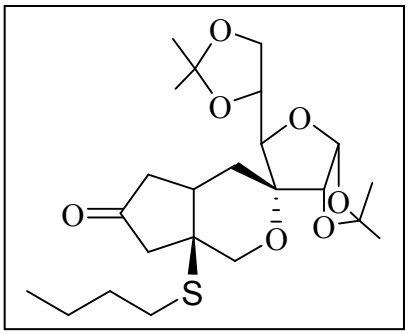
To a solution of cyclopentenone (1.0 eq) in anhydrous toluene under a N_2 atmosphere was added thiol (1.2 eq) and a catalytic amount of DMAP at room temperature and the resulting solution was stirred at 70 ^oC for the specified time. At the end of the reaction (TLC monitored), the reaction mixture was concentrated *in vacuo*, adsorbed over silica gel and purified by silica gel column chromatography using light petroleum and ethyl acetate as mobile phase.



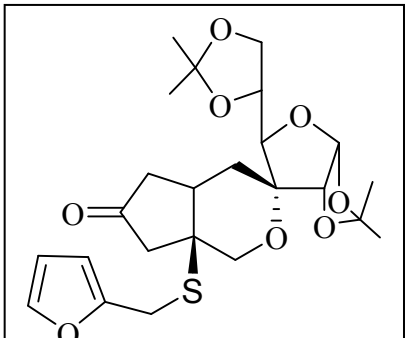
Compound 25: $[\alpha]_D$ -22.39 (*c* 1.54, $CHCl_3$); IR ($CHCl_3$): 1743 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 1.27, 1.31, 1.35 (3s, 9H), 1.50 (m, 1H), 1.59 (s, 3H), 1.78 (m, 1H), 2.01 (d, 1H, *J* = 18.44 Hz) 2.14 (d, 1H, *J* = 18.95 Hz), 2.36 (m, 1H), 2.87 (d, 1H, *J* = 18.95 Hz), 3.05 (dd, 1H, *J* = 7.07, 18.44 Hz), 3.81 (s, 3H), 3.98 (m, 6H), 4.29 (d, 1H, *J* = 3.66 Hz), 5.63 (d, 1H, *J* = 3.79 Hz), 6.86 (m, 2H), 7.40 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 25.2, 26.3, 26.5, 26.8, 29.8, 33.9, 43.2, 44.5, 52.8, 55.2, 67.6, 68.4, 73.5, 79.1, 81.0,

81.2, 103.8, 109.4, 112.9, 114.6, 120.2, 138.8, 161.0, 215.1; CHNS Anal. Calcd for $C_{26}H_{34}O_8$: C, 61.64, H, 6.76, S, 6.33; Found: C, 61.24, H, 6.27, S, 6.77

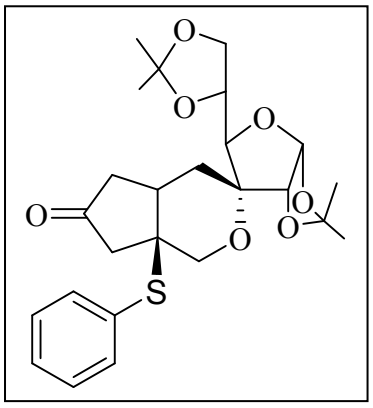
Compound 26: $[\alpha]_D$ -4.60 (*c* 0.82, $CHCl_3$); IR ($CHCl_3$): 1742 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 0.95 (t, 3H, *J* = 7.08 Hz), 1.30, 1.39 (2s, 9H), 1.42 (m, 5H), 1.61 (s, 3H), 1.87 (m, 1H), 1.99 (d, 1H, *J* = 18.31 Hz), 2.28 (d, 1H, *J* = 18.70 Hz), 2.48 (m, 3H), 2.96 (m, 2H), 3.97 (m, 6H), 4.62 (d, 1H, *J* = 3.79 Hz), 5.73 (d, 1H, *J* = 3.79 Hz); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 13.6, 22.1, 22.3, 26.6, 26.9, 27.5, 29.6, 31.9, 34.9, 43.3, 44.7, 49.9, 67.7, 68.6, 73.6, 79.3, 81.1, 81.2, 103.9, 109.6, 113.1, 215.6; CHNS Anal. Calcd for $C_{23}H_{36}O_7S$: C, 60.50; H, 7.95; S, 7.00; Found: C, 60.10; H, 7.52; S, 7.15



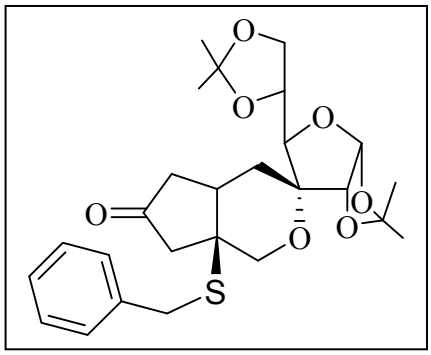
Compound 27: $[\alpha]_D$ +2.37 (*c* 1.80, $CHCl_3$); IR ($CHCl_3$): 1744 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 1.29, 1.38 (2s, 9H), 1.50 (dd, 1H, *J* = 6.19, 14.27 Hz), 1.60 (s, 3H), 1.86 (m, 1H), 1.96 (d, 1H, *J* = 18.31 Hz), 2.26 (d, 1H, *J* = 18.95 Hz), 2.38 (m, 2H), 2.97 (m, 2H), 3.76 (s, 2H), 3.97 (m, 5H), 4.58 (d, 1H, *J* = 3.79 Hz), 5.72 (d, 1H, *J* = 3.66 Hz), 6.16 (d, 1H, *J* = 3.29 Hz), 6.32 (dd, 1H, *J* = 1.90, 3.16 Hz), 7.37 (dd, 1H, *J* = 0.88, 1.89 Hz); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 25.1, 25.2, 26.5, 26.6, 26.9, 29.9, 34.6, 43.0, 44.6, 50.7, 67.7, 68.1, 73.5, 79.2, 81.0, 81.1, 103.9, 107.7, 109.5, 110.7, 113.1, 142.2, 150.7, 215.2; CHNS Anal. Calcd for $C_{24}H_{32}O_8S$: C, 59.98, H, 6.71, S, 6.67; Found C, 58.21, H, 6.37, S, 7.01



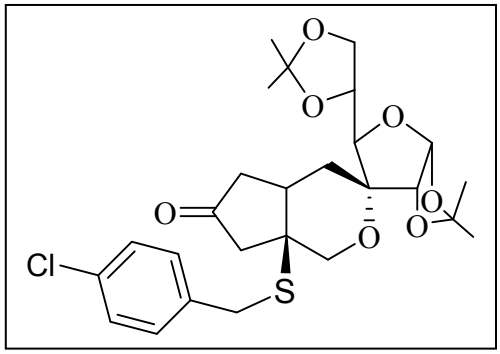
Compound 28: $[\alpha]_D$ -26.78 (*c* 1.50, $CHCl_3$); IR ($CHCl_3$): 1744 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 1.29, 1.30, 1.35 (3s, 9H), 1.47 (dd, 1H, *J* = 6.19, 14.27 Hz), 1.59 (s, 3H), 1.79 (m, 1H), 2.02 (d, 1H, *J* = 18.45 Hz), 2.16 (d, 1H, *J* = 18.95 Hz), 2.38 (m, 1H), 2.90 (d, 1H, *J* = 18.95 Hz), 3.07 (dd, 1H, *J* = 7.07, 18.44 Hz), 3.96 (m, 6H); 4.26 (d, 1H, *J* = 3.66 Hz), 5.62 (d, 1H, *J* = 3.78 Hz), 7.42 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 25.2, 26.3, 26.5, 26.8, 29.7,



34.0, 43.3, 44.5, 52.9, 67.5, 68.3, 73.4, 78.9, 81.0, 103.7, 109.5, 112.9, 129.1, 129.3, 129.7, 137.3, 215.2; CHNS Anal. Calcd for $C_{25}H_{32}O_7S$: C, 63.00, H, 6.77, S, 6.73; Found: C, 62.62, H, 6.47, S, 6.83



Compound 29: $[\alpha]_D$ -6.81 (*c* 1.46, $CHCl_3$); IR ($CHCl_3$): 1744 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 1.29, 1.38 (2s, 9H), 1.47 (dd, 1H, *J* = 6.19, 14.40 Hz), 1.60 (s, 3H), 1.79 (m, 1H), 1.97 (d, 1H, *J* = 18.32 Hz), 2.26 (d, 1H, *J* = 18.60 Hz), 2.44 (m, 1H), 2.85 (m, 6H), 3.96 (m, 6H), 4.16 (d, 1H, *J* = 3.78 Hz), 5.72 (d, 1H, *J* = 3.78 Hz), 7.25 (m, 5H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 25.2, 26.5, 26.6, 26.8, 29.4, 29.5, 34,8, 36.3, 43.2, 44.6, 50.3, 67.7, 68.4, 73.5, 79.3, 81.0, 81.2, 103.9, 109.5, 113.1, 126.6, 128.3, 128.5, 139.7, 215.3; CHNS Anal. Calcd for $C_{27}H_{36}O_7S$: C, 64.26, H, 7.16, S, 6.39; Found: C, 63.69, H, 6.69, S, 6.44

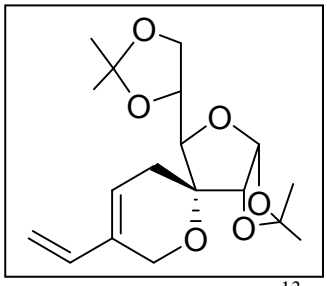


Compound 30: $[\alpha]_D$ -3.23 (*c* 2.12, $CHCl_3$); IR ($CHCl_3$): 1744 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 1.29, 1.38, 1.39 (3s, 9H), 1.48 (dd, 1H, *J* = 6.06, 14.27 Hz), 1.60 (s, 3H), 1.80 (m, 1H), 1.99 (d, 1H, *J* = 18.19 Hz), 2.29 (d, 1H, *J* = 18.70 Hz), 2.44 (m, 1H), 2.96 (m, 2H); 3.86 (m, 8H), 4.54 (d, 1H, *J* = 3.66 Hz), 5.72 (d, 1H, *J* = 3.79 Hz), 7.27 (m, 4H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 25.2, 26.5, 26.6, 26.8, 29.5, 32.1, 34.6, 43.2, 44.5, 51.0, 67.7, 68.3, 73.4, 79.2, 80.9, 81.1, 103.9, 109.5, 113.1, 128.8, 129.9, 133.2, 135.7, 214.9; CHNS Anal. Calcd for $C_{26}H_{33}O_7ClS$: C, 59.48, H, 6.33, Cl, 6.75, S, 6.11; Found: C, 58.83, H, 5.99, Cl, 6.55, S 6.06

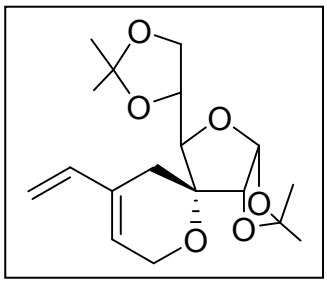
General experimental procedure for enyne-metathesis reaction:

To a solution of enyne (1.0 eq) in anhydrous benzene under a N_2 atmosphere was added Grubbs' 1st generation catalyst (Aldrich Chemicals) (0.10 eq) (10 mol %) at room temperature and the resulting reddish brown solution was stirred for the specified time at 80 ^oC. At the end of the reaction (TLC monitored), the reaction mixture was

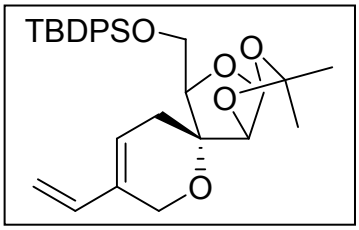
concentrated *in vacuo*, adsorbed over silica gel and was purified by silica-gel column chromatography using light petroleum and ethyl acetate as solvents.



Compound 31: $[\alpha]_D$ +133.10 (*c* 1.40, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): δ 1.33, 1.35, 1.45, 1.61 (4s, 12H), 3.31 (d, 1H, *J* = 5.13, 19.06 Hz), 2.64 (d, 1H, *J* = 18.11 Hz), 3.95 (dd, 1H, *J* = 5.86, 8.06 Hz), 4.12 (m, 3H), 4.36 (d, 1H, *J* = 3.66 Hz), 4.52 (m, 2H), 4.97 (d, 1H, *J* = 13.19 Hz), 5.01 (d, 1H, *J* = 6.60 Hz), 5.66 (d, 1H, *J* = 3.66 Hz), 5.83 (bs, 1H), 6.28 (q, 1H, *J* = 10.99, 18.32 Hz); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 25.2, 26.5, 26.6, 26.8, 26.9, 63.1, 67.3, 73.5, 80.0, 80.9, 82.0, 103.5, 109.5, 111.7, 113.0, 122.2, 135.3, 135.6; CHN Anal. Calcd for $C_{18}H_{26}O_6$: C, 63.89, H, 7.74; Found: C, 63.59, H, 7.64

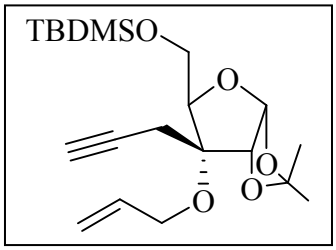


Compound 32: $[\alpha]_D$ -114.37 (*c* 1.10, $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz): δ 1.32, 1.36, 1.45, 1.61 (4s, 12H), 1.91 (d, 1H, *J* = 16.67 Hz), 2.54 (d, 1H, *J* = 16.55 Hz), 4.12 (m, 5H), 4.30 (d, 1H, *J* = 3.79 Hz), 4.46 (d, 1H, *J* = 14.53 Hz), 5.04 (d, 1H, *J* = 10.74 Hz), 5.14 (d. 1H, *J* = 17.56 Hz), 5.68 (d, 1H, *J* = 3.79 Hz), 5.85 (bs, 1H), 6.43 (q, 1H, *J* = 10.74, 17.56 Hz); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 25.2, 25.3, 26.5, 26.9, 63.6, 67.3, 73.4, 80.1, 80.9, 81.9, 103.6, 109.6, 111.5, 112.9, 127.1, 130.6, 137.9; CHN Anal. Calcd for $C_{18}H_{26}O_8$: C, 68.89, H, 7.74; Found: C, 68.51, H, 7.53

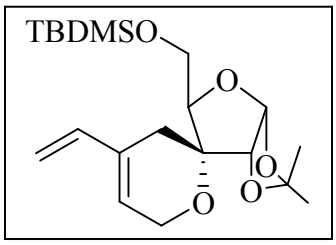


Compound 33: $[\alpha]_D$ -97.91 (*c* 1.15, $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz): δ 1.04, 1.34, 1.62 (3s, 15H), 1.72 (ddd, 1H, *J* = 1.64, 5.56, 18.62 Hz), 2.39 (dd, 1H, *J* = 1.77, 18.32 Hz), 2.82 (d, 1H, *J* = 2.02 Hz), 3.84 (s, 1H), 4.25 (d, 1H, *J* = 4.42 Hz), 4.29 (d, 1H, *J* = 3.67 Hz), 4.36 (d, 1H, *J* = 16.91 Hz), 4.54 (d, 1H, *J* = 16.91 Hz), 4.93 (d, 1H, *J* = 12.38 Hz), 5.00 (d, 1H, *J* = 5.56 Hz), 5.72 (d, 1H, *J* = 3.66 Hz), 5.73 (bs, 1H), 6.24 (q, 1H, *J* = 11.12, 17.81 Hz), 7.37 (m, 6H), 7.71 (m, 4H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 19.15, 29.50, 26.69, 26.83, 62.6, 62.8, 79.4,

81.2, 81.5, 103.9, 111.7, 112.8, 122.6, 127.6, 129.5, 133.3, 134.7, 135.2, 135.6; CHN Anal. Calcd for $C_{30}H_{38}O_5Si$: C, 71.11, H, 7.56; Found: C, 68.51, H, 7.53



Compound 36: $[\alpha]_D$ +41.91 (*c* 1.20, $CHCL_3$); ^1H NMR ($CDCl_3$, 300 MHz): δ 0.07, 0.89, 1.35, 1.58 (4s, 21H), 2.10 (t, 1H, *J* = 2.78 Hz), 2.47 (dd, 1H, *J* = 2.78, 17.56 Hz), 2.60 (dd, 1H, *J* = 2.78, 17.56 Hz), 3.86 (m, 2H), 4.12 (q, 1H, *J* = 3.66, 6.44 Hz), 4.28 (m, 2H), 4.61 (d, 1H, *J* = 3.91 Hz), 5.14 (qd, 1H, *J* = 1.51, 3.03 Hz), 5.30 (qd, 1H, *J* = 1.64, 3.29 Hz), 5.77 (d, 1H, *J* = 3.79 Hz), 5.96 (m, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ -5.5, -5.4, 13.4, 21.4, 25.8, 26.6, 26.7, 61.3, 66.8, 71.8, 79.4, 81.6, 81.7, 82.9, 103.9, 112.5, 115.9, 135.0; CHN Anal. Calcd for $C_{20}H_{34}O_5Si$: C, 62.79, H, 8.96, Si, 7.34; Found C, 62.51, H, 8.45

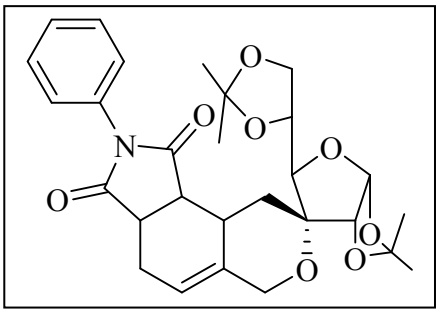


Compound 37: $[\alpha]_D$ +93.91 (*c* 1.30, $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz) δ 0.08, 0.90, 1.32, 1.60 (4s, 21H), 1.87 (d, 1H, *J* = 16.93 Hz), 2.36 (d, 1H, *J* = 16.92 Hz), 3.85 (m, 2H), 4.12 (q, 1H, *J* = 3.41, 5.94 Hz), 4.25 (d, 1H, *J* = 3.79 Hz), 4.38 (ABq, 2H, *J* = 17.94 Hz), 5.04 (d, 1H, *J* = 10.87 Hz), 5.13 (d, 1H, *J* = 17.56 Hz), 5.74 (d, 1H, *J* = 3.79 Hz), 5.81 (bs, 1H), 6.41 (q, 1H, *J* = 0.74, 17.56 Hz); ^{13}C ($CDCl_3$, 50 MHz) δ -5.3, 18.3, 25.1, 25.8, 26.6, 26.8, 61.7, 63.4, 79.6, 81.4, 81.5, 104.0, 111.6, 112.7, 126.7, 131.0, 137.8; CHN Anal. Calcd for $C_{20}H_{34}O_5Si$: C, 62.79, H 8.90, Si, 7.34; Found: C, 62.49, H, 8.58

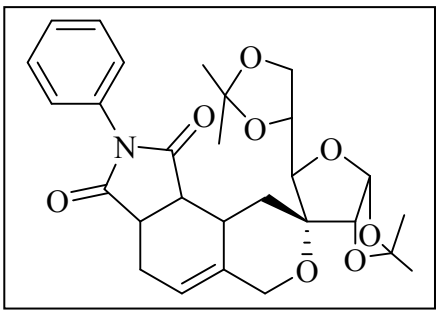
General experimental procedure for Intermolecular Diels-Alder reaction:

A single neck round bottom flask fit with a reflux condenser charged with a solution of diene (1.0 eq) in anhydrous toluene under a N_2 atmosphere. To this solution was added dienophile (1.2 eq) at room temperature and the resulting reaction mixture was stirred for the specified time at 110 ^oC. At the end of the reaction (TLC monitored), the reaction mixture was concentrated *in vacuo*, adsorbed over silica gel and was purified by silica gel column chromatography.

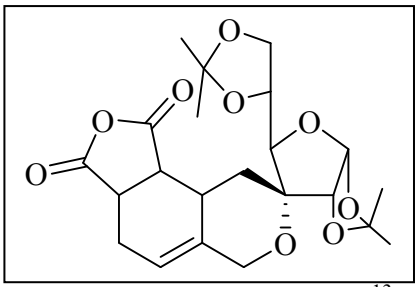
Compound 38 (A): $[\alpha]_D$ -6.65 (*c* 1.00, $CHCl_3$); IR ($CHCl_3$): 1708 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.32, 1.34, 1.37, 1.60 (4s, 12H), 2.15 (dd, 1H, *J* = 5.52, 14.55 Hz), 2.26 (m, 1H), 2.40 (t, 1H, *J* = 14.31 Hz), 2.88 (q, 1H, *J* = 7.02, 15.31 Hz), 2.92 (m, 1H), 3.30 (m, 2H), 3.91 (m, 1H), 3.97 (d, 1H, *J* = 8.03 Hz), 4.12 (m, 4H), 4.35 (d, 1H, *J* = 3.26 Hz), 5.65 (d, 1H, *J* = 3.26 Hz), 5.77 (bs, 1H), 7.19 (m, 2H) 7.38 (m, 1H), 7.45 (m, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 24.1, 25.6, 25.7, 26.3, 26.3, 26.5, 27.0, 30.3, 39.7, 42.5, 64.8, 68.4, 73.5, 79.9, 82.0, 84.6, 102.7, 109.5, 113.2, 118.9, 126.3, 128.6, 129.0, 131.6, 138.8, 176.9, 178.4; ESI Mass: 534.58 (M + Na)



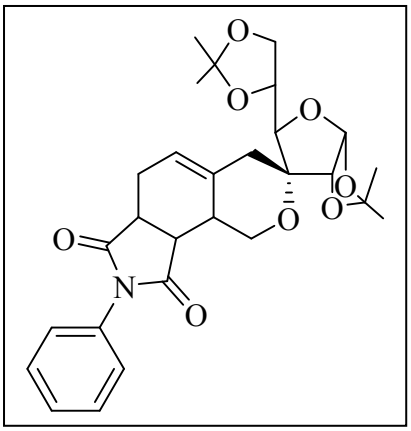
Compound 38 (B): $[\alpha]_D$ +36.61 (*c* 1.30, $CHCl_3$); IR ($CHCl_3$): 1711 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.33, 1.35, 1.43, 1.61 (4s, 12H), 1.72 (d 1H, *J* = 3.90, 14.05 Hz), 2.30 (d, 1H, *J* = 15.02 Hz), 2.7 (m, 1H), 2.81 (t, 1H, *J* = 14. 05 Hz), 2.90 (q, 1H, *J* = 7.02, 15.61 Hz), 3..33 (dd, 2H, *J* = 2.15, 4.88 Hz), 3.94 (m, 1H), 4.01 (d, 1H, *J* = 8.39 Hz), 4.06 (d, 1H, *J* = 13.66 Hz), 4.12 (m, 2H), 4.45 (d, 1H, *J* = 3.52 Hz), 4.51 (d, 1H, *J* = 13.46 Hz), 5.69 (d, 1H, *J* = 3.52 Hz), 5.77 (bs, 1H), 7.19 (m, 2H), 7.38 (m, 1H), 7.44 (m, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 24.1, 25.8, 26.4, 26.6, 27.1, 30.4, 39.8, 42.6, 64.9, 68.5, 73.6, 80.0, 82.1, 84.7, 102.8, 109.6, 113.2, 118.9, 126.4, 128.7, 129.1, 131.7, 138.9, 176.9, 178.4; ESI Mass: 534.83 (M + Na)



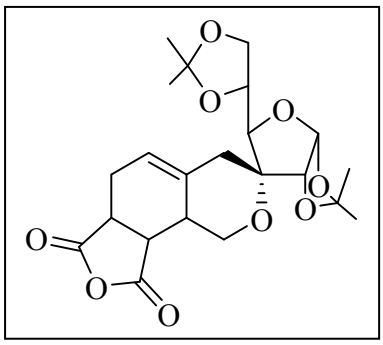
Compound 39 (A): $[\alpha]_D$ +17.38 (*c* 1.30, $CHCl_3$); IR ($CHCl_3$): 1779 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 1.29, 1.36, 1.36, 1.60 (4s, 12H), 2.11 (s, 1H), 2.16 (d, 1H, *J* = 3.79 Hz), 2.26 (m, 1H), 2.79 (dd, 1H, *J* = 6.82, 15.66 Hz), 3.46 (m, 1H), 3.44 (m, 2H), 4.01 (m, 4H), 4.18 (bs, 2H), 4.37 (d, 1H, *J* = 3.42 Hz), 5.87 (d, 1H, *J* = 3.29 Hz), 5.77 (bs, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 23.7, 25.7, 25.8, 26.4, 26.5, 27.0, 29.5, 40.1, 43.3, 64.8, 73.5,



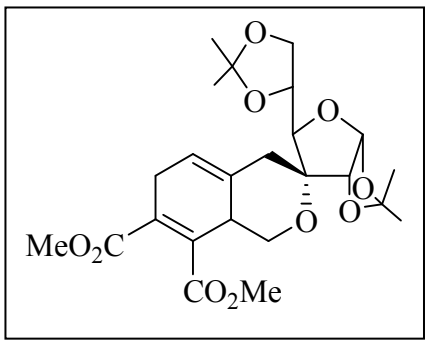
79.9, 82.0, 84.6, 102.7, 109.7, 113.4, 119.1, 138.9, 171.6, 173.6; ESI Mass: 437.62 (M + H)



Compound 42: $[\alpha]_D$ -13.41 (*c* 1.30, $CHCl_3$); IR ($CHCl_3$): 1711 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.33, 1.47, 1.61 (3s, 12H), 1.98 (d, 1H, *J* = 15.06 Hz), 2.30 (m, 1H), 2.76 (m, 1H), 2.60 (ddd, 1H, *J* = 1.26, 7.28, 15.56 Hz), 2.51 (td, 1H, *J* = 1.50, 3.51, 15.06 Hz), 3.32 (m, 2H), 3.94 (m, 1H), 3.99 (m, 2H), 4.10 (m, 3H), 4.63 (t, 1H, *J* = 11.79 Hz), 5.62 (d, 1H, *J* = 3.52 Hz), 5.88 (dd, 1H, *J* = 3.02, 6.78 Hz), 7.19 (m, 2H), 7.38 (m, 1H), 7.44 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 24.6, 25.3, 26.4, 26.5, 27.0, 29.9, 37.2, 40.5, 41.0, 62.2, 68.4, 73.7, 81.0, 81.5, 83.5, 103.0, 109.7, 113.1, 122.5, 126.3, 128.6, 129.0, 131.8, 136.0, 175.9, 178.4; ESI Mass: 534.94 (M + Na)



Compound 43: $[\alpha]_D$ +6.62 (*c* 1.0, $CHCl_3$); IR ($CHCl_3$): 2989, 1850, 1780, 1715 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 1.32, 1.37, 1.48. 1.60 (4s, 12H), 1.99 (d, 1H, *J* = 15.41 Hz), 2.29 (td, 1H, *J* = 3.28, 6.19, 15.79 Hz), 2.69 (m, 1H), 2.82 (dd, 1H, *J* = 7.83, 15.92 Hz), 2.97 (d, 1H, *J* = 15.04 Hz), 3.46 (m, 2H), 4.05 (m, 6H), 4.56 (t, 1H, *J* = 11.74 Hz), 5.63 (d, 1H, *J* = 3.41 Hz), 5.91 (dd, 1H, *J* = 2.91, 6.44 Hz); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 24.4, 25.3, 26.3, 26.5, 26.5, 27.0, 29.9, 36.4, 41.1, 41.5, 61.7, 68.5, 73.6, 81.1, 81.5, 83.5, 103.0, 109.8, 113.2, 122.7, 136.5, 170.9, 173.8; ESI Mass: 437.82 (M + H)



Compound 44: $[\alpha]_D$ + 40.08 (*c* 1.60, $CHCl_3$); IR ($CHCl_3$): 1724 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 1.27, 1.34, 1.36, 1.59 (4s, 12H), 2.19 (d, 1H, *J* = 13.39 Hz), 2.54 (d, 1H, *J* = 13.89 Hz), 3.01 (m, 2H), 3.35 (m, 1H), 3.76, 3.77 (2s, 6H), 4.02 (m, 6H), 4.25 (d, 1H, *J* = 3.67 Hz), 5.54 (bs, 1H), 5.60 (d, 1H, *J* = 3.41 Hz); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 25.7, 26.3, 27.0, 28.1, 36.5,

36.6, 52.1, 52.3, 67.2, 69.6, 71.4, 81.2, 83.8, 87.7, 101.3, 109.5, 113.2, 116.9, 129.5, 132.1, 133.1, 167.6, 167.9; ESI Mass: 503.62 (M + Na)

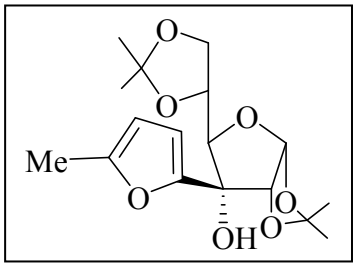
General Experimental procedure for furan addition:

To a solution of furan (1.1 eq) in anhydrous THF cooled at -40 ^{o}C was added *n*-BuLi (1.1 eq., 1.6 M solution in hexane) and the solution was stirred for 45 min at the same temperature, to this ketone (1.0 eq) dissolved in anhydrous THF was added drop wise and reaction mixture was again stirred for additional 30 min. After completion (TLC monitored), reaction mixture was quenched with saturated aq. NH_4Cl solution and diluted with ethyl acetate. The resulting solution was extracted three times with ethyl acetate, pooled organic layers were washed with brine, dried over anhydrous Na_2SO_4, concentrated under vacuo and purified by silica gel column chromatography using ethyl acetate and petroleum ether as mobile phase.

General experimental procedure for Spiroannulation:

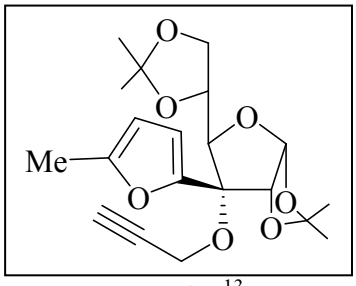
To a solution of furfuranylated propargyl ether (1.0 eq) in anhydrous acetonitrile was added $AuCl_3$ (0.03eq, 3 mol %) in 1 mL of acetonitrile under an argon atmosphere and the resulting mixture stirred at room temperature for 10 min. The reaction mixture was concentrated *in vacuo* and purified by silica gel column chromatography using ethyl acetate and light petroleum as the mobile phase to yield spiroannulated product.

1,2:5,6-Bis-*O*-(1-methylethylidene)-3-*C*-(5-methyl-2-furanyl)- α-D-allofuranose (46):

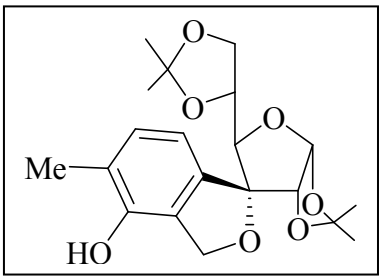


$[\alpha]_D$ +17.71 (*c* 0.85, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.30, 1.40, 1.43, 1.63 (4s, 12H), 2.28 (d, 3H, *J* = 0.75 Hz), 3.15 (bs, 1H), 3.54 (dd, 1H, *J* = 6.32, 8.47 Hz), 3.67 (dd, 1H, *J* = 5.94, 8.47 Hz), 3.97 (q, 1H, *J* = 5.87, 12.00 Hz), 4.15 (d, 1H, *J* = 5.55 Hz), 4.58 (d, 1H, *J* = 3.54 Hz), 5.98 (dd, 1H, *J* = 6.25 Hz), 6.00 (d, 1H, *J* = 3.66 Hz), 6.25 (d, 1H, *J* = 6.25 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 13.4, 25.1, 26.4, 26.5, 26.7, 65.3, 74.1, 78.7, 82.3, 82.3, 82.6, 101.6, 106.4, 108.1, 108.9, 113.1, 150.2, 152.1; CHN Anal. Calcd. for $C_{17}H_{24}O_7$: C, 59.99, H, 7.11; Found: C, 59.55, H, 7.23; ESI Mass: 363..03 (M + Na).

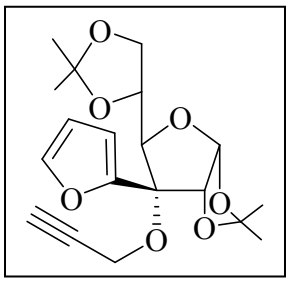
1,2:5,6-Bis-*O*-(1-methylethylidene)-3-*C*-(5-methyl-2-furanyl)-3-*O*-2-propynyl- α-D-allofuranose (47): $[\alpha]_D^{25}$ +59.3 (*c* 1.15, $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz): δ 1.29, 1.39, 1.41, 1.63 (4s, 12H), 2.30 (d, 3H, *J* = 0.63 Hz), 2.43 (t, 1H, *J* = 2.40 Hz), 3.32 (dd, 2H, *J* = 1.15, 6.07 Hz), 4.18 (dq, 2H, *J* = 2.45, 14.65 Hz), 4.22 (m, 1H), 4.45 (d, 1H, *J* = 3.00 Hz), 4.71 (d, 1H, *J* = 3.89 Hz), 5.98 (d, 1H, *J* = 3.54 Hz), 6.01 (m, 1H), 6.29 (d, 1H, *J* = 3.16 Hz); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 13.4, 24.8, 26.2, 26.6, 26.7, 26.8, 53.9, 63.5, 74.1, 79.6, 80.6, 82.1, 83.4, 104.6, 106.6, 108.3, 110.6, 113.0, 147.4, 152.9; CHN Anal. Calcd. for $C_{20}H_{26}O_7$: C, 63.48; H, 6.93; Found: C, 63.37; H, 7.09; ESI Mass: 401.06 (M + Na).



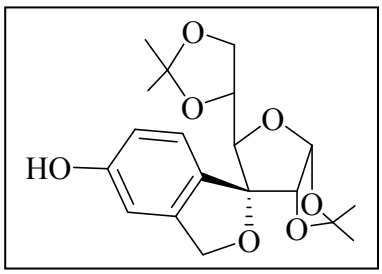
(1'R,3aR,5R,6aR)-5-[(4R)-2,2-Dimethyl-1,3-dioxolan-4-yl]-3a,6a-dihydro-2,2,5'-trimethyl-spiro[furo[2,3-d]-1,3-dioxole-6(5H),1'(3'H)-isobenzofuran]-4'-ol (48): $[\alpha]_D$ +13.4 (*c* 1.05, $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz): δ 1.19, 1.36, 1.45, 1.67 (4s, 12H), 2.08 (d, 3H, *J* = 2.03 Hz), 3.71 (m, 2H), 3.98 (dd, 1H, *J* = 4.02, 8.36 Hz), 4.30 (d, 1H, *J* = 8.09 Hz), 4.36 (d, 1H, *J* = 3.52 Hz), 5.19 (d, 2H, *J* = 2.18 Hz), 5.23 (bs, 1H), 5.92 (d, 1H, *J* = 3.52 Hz), 6.56 (d, 1H, *J* = 7.62 Hz), 7.03 (d, 1H, *J* = 7.42 Hz); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 15.0, 25.5, 26.3, 26.7, 26.9, 67.3, 71.7, 74.1, 79.1, 84.4, 94.1, 103.5, 109.4, 112.9, 113.4, 123.4, 126.6, 130.7, 137.2, 148.6; CHN Anal. Calcd. for $C_{20}H_{26}O_7$: C, 63.48; H, 6.93; Found: C, 63.07; H, 6.80; ESI Mass: 401.08 (M + Na).



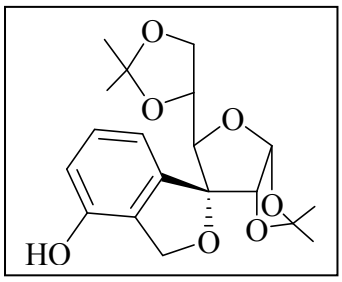
3-*C*-2-Furanyl-1,2:5,6-bis-*O*-(1-methylethylidene)-3-*O*-2-propynyl- α-D-allofuranose (50): $[\alpha]_D$ +69.7 (*c* 1.20, $CHCl_3$); IR ($CHCl_3$): 3308 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 1.28, 1.39, 1.40, 1.64 (4s, 12H), 2.44 (t, 1H, *J* = 2.52 Hz), 3.29 (d, 1H, *J* = 1.43 Hz), 3.33 (d, 1H, *J* = 0.77 Hz), 4.21 (dq, 2H, *J* = 2.49, 14.51 Hz), 4.12 (m, 1H), 4.45 (d, 1H, *J* = 3.41 Hz), 4.74 (d, 1H, *J* = 3.80 Hz), 6.00 (d, 1H, *J* = 3.67 Hz), 6.45 (d, 2H, *J* = 1.32 Hz), 7.47 (t, 1H, *J* = 1.40 Hz); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 25.1, 26.4, 26.8, 26.9, 54.3, 63.8, 74.1, 74.2, 79.6, 80.9, 82.0,



83.8, 104.8, 108.5, 109.8, 110.8, 113.3, 143.1, 149.9; CHN Anal. Calcd for $C_{19}H_{24}O_7$: C, 62.63, H, 6.64; Found: C, 62.47; H, 6.78 ESI Mass: 387.06 (M + Na).

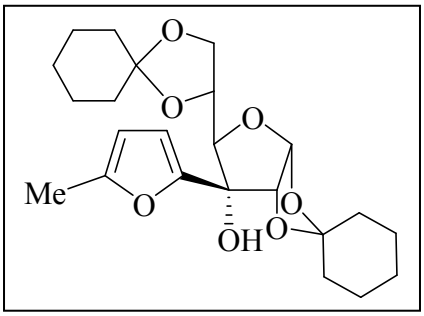
(1'R,3aR,5R,6aR)-5-[(4R)-2,2-Dimethyl-1,3-dioxolan-4-yl]-3a,6a-dihydro-2,2-dimethyl-spiro[furo[2,3-d]-1,3-dioxole-6(5H),1'(3'H)-isobenzofuran]-5'-ol (51): 

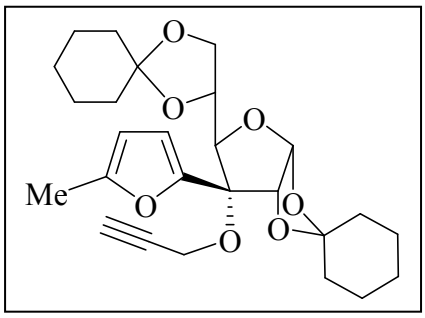
$[\alpha]_D$ +9.1 (*c* 1.40, $CHCl_3$); IR ($CHCl_3$): 3401 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 1.17, 1.36, 1.41, 1.67 (4s, 12H), 3.64 (m, 1H), 3.78 (dd, 1H, *J* = 5.85, 8.40 Hz), 3.94 (dd, 1H, *J* = 4.93, 8.48 Hz), 4.30 (d, 1H, *J* = 7.84 Hz), 4.37 (d, 1H, *J* = 3.52 Hz), 5.12 (m, 2H), 5.94 (d, 1H, *J* = 3.57 Hz), 6.11 (bs, 1H), 6.68 (s, 1H), 6.71 (dd, 1H, *J* = 2.28, 8.58 Hz), 6.92 (d, 1H, *J* = 8.53 Hz); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 25.4, 26.3, 26.6, 26.9, 67.2, 73.3, 73.9, 79.3, 84.3, 93.3, 103.5, 108.4, 109.3, 113.4, 114.8, 122.3, 129.0, 142.2, 156.9; CHN Anal. Calcd for $C_{19}H_{24}O_7$: C, 62.63, H, 6.64; Found: C, 62.39, H, 6.67; ESI Mass: 387.06 (M + Na).

(1'R,3aR,5R,6aR)-5-[(4R)-2,2-Dimethyl-1,3-dioxolan-4-yl]-3a,6a-dihydro-2,2-dimethyl-spiro[furo[2,3-d]-1,3-dioxole-6(5H),1'(3'H)-isobenzofuran]-4'-ol (52): 

$[\alpha]_D$ +18.6 (*c* 1.40, $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz): δ 1.23, 1.36, 1.48, 1.68 (4s, 12H), 3.78-3.95 (m, 2H), 4.06 (m, 1H), 4.33 (d, 1H, *J* = 8.29 Hz), 4.37 (d, 1H, *J* = 3.53 Hz), 5.22 (m, 2H), 5.93 (d, 1H, *J* = 3.60 Hz), 6.30 (d, 1H, *J* = 7.68 Hz), 6.57 (bs, 1H), 6.61 (d, 1H, *J* = 7.45 Hz), 7.03 (t, 1H, *J* = 7.71 Hz); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 25.3, 26.3, 26.7, 26.9, 67.5, 71.8, 73.9, 79.0, 84.3, 94.2, 103.5, 107.8, 112.9, 113.5, 114.8, 126.6, 129.2, 139.3, 150.8; CHN Anal. Calcd. for $C_{19}H_{24}O_7$: C, 62.63, H, 6.64; Found: C, 62.57, H, 6.89; ESI Mass: 387.06 (M + Na).

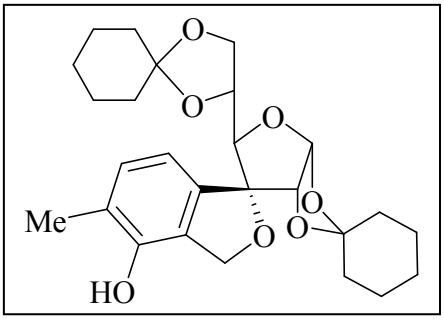
1,2:5,6-Di-*O*-cyclohexylidene-3-*C*-(5-methyl-2-furanyl)-α-D-allofuranose (53): ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.30-1.89 (m, 20H), 2.27 (d, 3H, *J* = 0.76 Hz), 2.48 (dd, 1H, *J* = 6.32, 8.34 Hz), 3.20 (bs, 1H), 3.64 (dd, 1H, *J* = 6.07, 8.47 Hz), 3.95 (q, 1H, *J* = 5.94, 11.88 Hz), 4.13 (d, 1H, *J* = 1.01, 5.56 Hz), 4.57 (d, 1H, *J* = 3.66 Hz), 5.96 (dd, 1H, *J* = 1.01, 3.16 Hz), 6.01 (d, 1H, *J* = 8.97 Hz), 6.24 (d, 1H, *J* = 3.16 Hz)





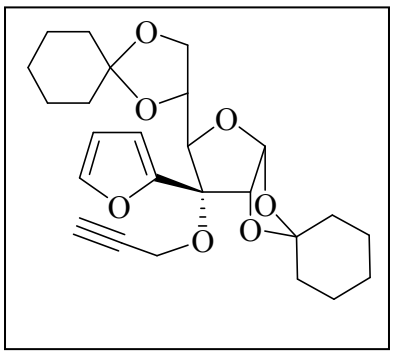
1,2:5,6-Di-*O*-cyclohexylidene-3-*C*-(5-methyl-2-furanyl)-3-*O*-2-propynyl- α-D-allo- furanose (54): $[\alpha]_D$ +50.31 (*c* 1.15, $CHCl_3$); IR($CHCl_3$): 3308, 2938 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.36-1.91 (m, 20H), 2.28 (d, 3H, *J* = 0.68 Hz), 2.42 (t, 1H, *J* = 2.52 Hz), 3.34 (d, 2H, *J* = 6.31 Hz), 4.12 (dd, 1H, *J* = 2.52, 14.52 Hz), 4.17 (dt, 1H, *J* = 3.41, 6.32 Hz), 4.32 (dd, 1H, *J* = 2.40, 14.52 Hz), 4.45 (d, 1H, *J* = 3.28 Hz), 4.70 (d, 1H, *J* = 3.79 Hz), 5.99 (m , 2H), 6.30 (d, 1H, *J* = 3.16 Hz); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 13.4, 23.7, 23.8, 23.9, 24.9, 25.2, 34.4, 35.8, 36.2, 36.3, 54.0, 63.5, 73.8, 79.8, 80.3, 82.2, 83.7, 104.5, 106.7, 108.9, 110.5, 113.7, 147.8, 152.9; CHN Anal. Calcd. for $C_{26}H_{34}O_7$: C, 68.10, H, 7.47; Found: C, 67.91, H, 7.23; ESI Mass: 481.18 (M + Na).

(1''R,3'aR,5'R,6'aR)-5'-[(2R)-1,4-Dioxaspiro [4.5] dec-2-yl]-3'a,6'a-dihydro-5''-methyl-dispiro [cyclo hexane-1,2'-furo[2,3-d][1,3]dioxole-6'(5'H),1''(3'' H) -isobenzofuran]-4''-ol (55): $[\alpha]_D$ +3.91 (*c* 1.45, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.34-1.93 (m, 20H), 2.19 (s, 3H), 3.58 (m, 1H), 3.80 (dd, 1H, *J* = 5.81, 8.34 Hz), 3.88 (dd, 1H, *J* = 5.81, 8.34 Hz), 4.26 (d, 1H, *J* = 8.34 Hz), 4.38 (d, 1H, *J* = 3.54 Hz), 5.06 (bs, 1H), 5.23 (q, 2H, *J* = 11.87, 17.18 Hz), 5.93 (d, 1H, *J* = 3.54 Hz), 6.56 (d, 1H, *J* = 7.45 Hz), 7.04 (d, 1H, *J* = 7.58 Hz); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 15.1,



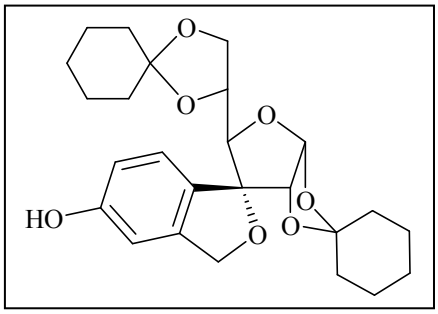
23.5, 23.7, 23.8, 24.0, 24.9, 25.0, 34.7, 35.9, 36.2, 36.3, 67.3, 71.8, 73.5, 79.5, 83.8, 94.3, 103.2, 109.9, 113.1, 114.0, 123.4, 126.6, 130.6, 137.4, 148.5; CHN Anal. Calcd. for $C_{26}H_{34}O_7$: C, 68.10, H, 7.47; Found: C, 67.86, H, 7.19; ESI Mass: 481.19 (M + Na).

1,2:5,6-Di-*O*-cyclohexylidene-3-*C*-2-furanyl-3-*O*-2-propynyl- α-D-allofuranose (57):



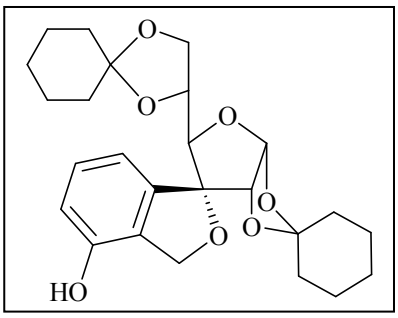
$[\alpha]_D$ +48.94 (*c* 1.05, $CHCl_3$); IR ($CHCl_3$): 3308, 2939 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 1.36-1.91 (m, 20H), 2.43 (t, 1H, *J* = 2.40 Hz), 3.33 (m, 2H), 4.07 (m, 1H), 4.12 (dd, 1H, *J* = 2.40, 14.44 Hz), 4.35 (d, 1H, *J* = 2.40, 14.44 Hz), 4.45 (d, 1H, *J* = 3.66 Hz), 4.73 (d, 1H, *J* = 3.67 Hz), 6.01 (d, 1H, *J* = 3.66 Hz), 6.45 (m, 2H), 7.45 (dd, 1H, *J* = 1.01, 1.64 Hz); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 23.8, 23.9, 24.0, 24.9, 25.2, 34.6, 35.9, 36.3, 36.4, 54.2, 63.8, 73.8, 74.0, 79.7, 80.5, 82.1, 84.2, 104.6, 109.1, 109.7, 110.8, 113.9, 143.0, 150.1; CHN Anal. Calcd. for $C_{25}H_{32}O_7$: C, 67.55, H, 7.26; Found: C, 67.25, H, 7.08; ESI Mass: 467.16 (M + Na).

(1''R,3'aR,5'R,6'aR)-5'-(2R)-1,4-Dioxaspiro [4.5] dec-2-yl-3'a,6'a-dihydro-dispiro [cyclohexane-1,2'-furo[2,3-d][1,3]dioxole-6'(5'H),1''(3''H)-isobenzo furan]-5''-ol (58):



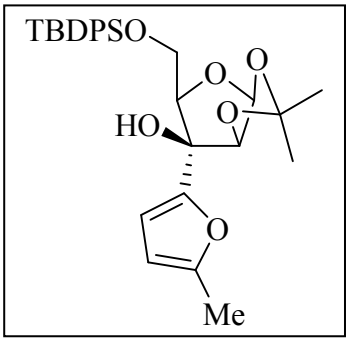
$[\alpha]_D$ +48.94 (*c* 1.05, $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz): δ1.33-1.92 (m, 20H), 3.54, (m, 1H), 3.83 (s, 1H), 3.87 (d, 1H, *J* = 1.01 Hz), 4.25 (d, 1H, *J* = 8.34 Hz), 4.38 (d, 1H, *J* = 3.53 Hz), 5.11 (d, 1H, *J* = 1.25 Hz), 5.24 (d, 1H, *J* = 12.13 Hz), 5.82 (bs, 1H), 5.95 (d, 1H, *J* = 3.53 Hz), 6.73 (m, 2H), 6.93 (d, 1H, *J* = 8.46 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 23.4, 23.7, 23.8, 24.0, 24.8, 25.0, 34.7, 35.9, 36.2, 36.3, 67.3, 73.3, 73.4, 79.6, 83.3, 93.5, 103.2, 108.2, 109.9, 114.1, 114.7, 122.2, 129.0, 142.2, 156.9; CHN Anal. Calcd for $C_{25}H_{32}O_7$: C, 67.55, H, 7.26; Found C, 67.31, H, 7.39; ESI Mass: 467.16 (M + Na).

(1''R,3'aR,5'R,6'aR)-5'-[(2R)-1,4-Dioxaspiro[4.5]dec-2-yl]-3'a,6'a-dihydro-, dispiro [cyclohexane-1,2'-furo[2,3-d][1,3]dioxole-6'(5'H),1''(3''H)-isobenzofuran]-4''-ol (59):

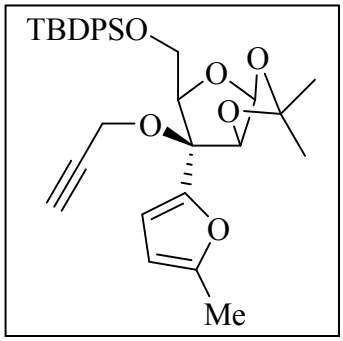


$[\alpha]_D$ -23.77 (*c* 0.85, $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz): δ 1.37-1.93 (m, 20), 3.66 (td, 1H, *J* = 5.81, 14.15 Hz), 3.93 (dd, 1H, *J* = 5.81, 12.76 Hz), 4.28 (d, 1H, *J* = 8.46 Hz), 4.39 (d, 1H, *J* = 3.53 Hz), 5.24 (q, 2H, *J* = 12.00, 19.96 Hz) 5.94 (d, 1H, *J* = 3.54 Hz), 6.01 (s, 1H), 6.52 (d, 1H, *J* = 7.83 Hz), 6.63 (d, 1H, *J* = 7.45 Hz), 7.09 (t, 1H, *J* = 7.84, 15.54 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 23.5, 23.7, 23.8, 24.0, 24.9, 25.0, 34.6, 35.9, 36.2, 36.3, 67.4, 72.0, 73.3, 79.5, 83.7, 94.4, 103.2, 110.3, 112.9, 114.1, 114.8, 126.6, 129.2, 139.4, 150.8; CHN Anal. Calcd. for $C_{25}H_{32}O_7$: C, 67.55, H, 7.26; Found: C, 67.39, H, 7.12; ESI Mass: 467.10 (M + Na).

5-*O*-[(1,1-Dimethylethyl)diphenylsilyl]-1,2-*O*-(1-methylethylidene)-3-*C*-(5-methyl-2-furanyl)-β-D-lyxofuranose (60): $[\alpha]_D$ +38.70 (*c* 1.05, $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz): δ 1.03, 1.40, 1.63 (3s, 15H), 2.20 (d, 3H, *J* = 0.63 Hz), 3.03 (s, 1H), 3.55 (dd, 1H, *J* = 6.57, 10.99 Hz), 3.66 (dd, 1H, *J* = 5.30, 10.99 Hz), 4.24 (dd, 1H, *J* = 5.31, 6.44 Hz), 4.56 (d, 1H, *J* = 3.67 Hz), 5.90 (dd, 1H, *J* = 3.10, 3.16 Hz), 6.01 (d, 1H, *J* = 3.79 Hz), 6.16 (d, 1H, *J* = 3.16 Hz), 7.38 (m, 6H), 7.61 (m, 4H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 13.5, 19.1, 26.7, 26.8, 63.1, 78.6, 83.0, 83.2, 104.7, 106.1, 107.9, 113.1, 127.6, 129.6, 133.1, 133.3, 135.6, 150.3, 152.0; CHN Anal. Calcd for $C_{29}H_{32}O_6Si$: C, 68.47, H, 7.13; Found: C, 68.17, H, 7.19; ESI Mass: 531.19 (M + Na).

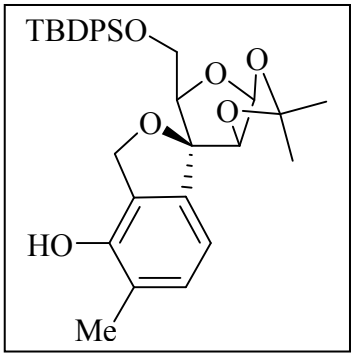


5-*O*-[(1,1-Dimethylethyl)diphenylsilyl]-1,2-*O*-(1-methylethylidene)-3-*C*-(5-methyl-2-furanyl)-3-*O*-2-propynyl- β-D-lyxofuranose (61): $[\alpha]_D$ +20.70 (*c* 1.45, $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz): δ 1.03, 1.41, 1.65 (3s, 15H), 2.15 (d, 3H, *J* = 0.63 Hz), 2.38 (t, 1H, *J* = 2.52 Hz), 3.43 (dd, 1H, *J* = 7.20, 11.37 Hz), 3.83 (dd, 1H, *J* = 3.41, 11.24 Hz), 4.02 (dd, 1H, *J* = 2.53, 14.66 Hz), 4.22 (dd, 1H, *J* = 2.40, 14.65 Hz), 4.48 (q, 1H, *J* = 3.54, 7.08 Hz), 4.76 (d, 1H, *J* = 3.79 Hz), 5.88 (dd, 1H, *J* = 1.01, 3.16 Hz),

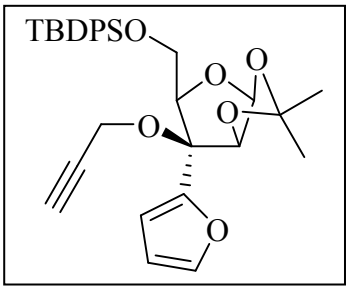


5.96 (d, 1H, *J* = 3.67 Hz), 6.19 (d, 1H, *J* = 3.16 Hz), 7.36 (m, 6H), 7.66 (m, 4H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 13.5, 19.2, 26.8, 26.9, 27.0, 53.9, 63.7, 73.8, 80.0, 81.1, 83.3, 83.6, 104.9, 106.3, 110.7, 113.2, 127.4, 127.5, 129.3, 129.4, 133.6, 133.8, 135.7, 135.8, 147.6, 152.8; CHN Anal. Calcd for $C_{32}H_{38}O_6Si$: C, 70.30, H, 7.01; Found: C, 70.11, H, 7.31; ESI Mass: 569.34 (M + Na).

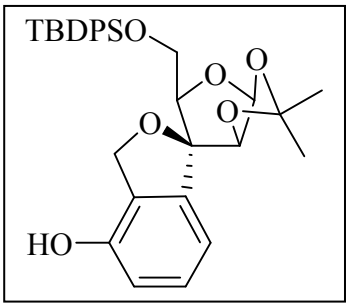
(1'S,3aS,5R,6aS)-5-[[[(1,1-Dimethylethyl)diphenylsilyl]oxy]methyl]-3a,6a-dihydro-2,2,5'-trimethyl-Spiro[furo[2,3-d]-1,3-dioxole-6(5H),1'(3'H)-isobenzofuran]-4'-ol (62): $[\alpha]_D$ +19.78 (*c* 1.35, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 0.97, 1.35, 1.67 (3s, 15H), 2.25 (s, 3H), 3.39 (dd, 1H, *J* = 5.44, 10.99 Hz), 3.60 (dd, 1H, *J* = 6.44, 10.99 Hz), 4.31 (d, 1H, *J* = 3.53 Hz), 4.55 (t, 1H, *J* = 6.06 Hz), 4.87 (s, 1H), 5.09 (m, 2H), 5.92 (d, 1H, *J* = 3.54 Hz), 6.55 (d, 1H, *J* = 7.58 Hz), 7.01 (d, 1H, *J* = 7.58 Hz), 7.30 (m, 6H), 7.45 (m, 2H), 7.58 (m, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 15.1, 19.1, 26.4, 26.7, 26.9, 62.8, 71.4, 80.0, 84.0, 94.0, 103.6, 113.3, 113.7, 123.3, 125.9, 127.5, 127.6, 129.4, 129.5, 130.9, 133.2, 133.4, 135.5, 135.6, 137.2, 148.3; CHN Anal. Calcd for $C_{32}H_{38}O_6Si$: C, 70.30, H, 7.01; Found: C, 69.91, H, 6.89; ESI Mass: 569.20 (M + Na).



5-*O*-[(1,1-Dimethylethyl)diphenylsilyl]-3-*C*-2-furanyl-1,2-*O*-(1-methylethylidene)-3-*O*-2-propynyl-β-D-lyxofuranose (64): $[\alpha]_D$ -30.45 (*c* 1.45, $CHCl_3$); IR ($CHCl_3$): 3308, 2932 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.02, 1.44, 1.65 (3s, 15H), 2.40 (t, 1H, *J* = 2.52 Hz), 3.40 (dd, 1H, *J* = 6.95, 11.24 Hz), 3.75 (dd, 1H, *J* = 3.92, 11.24 Hz), 4.03 (dd, 1H, *J* = 2.52, 14.53 Hz), 4.26 (dd, 1H, *J* = 2.40, 14.53 Hz), 4.49 (dd, 1H, *J* = 3.92, 6.82 Hz), 4.78 (d, 1H, *J* = 3.66 Hz), 6.01 (d, 1H, *J* = 3.79 Hz), 6.32 (m, 2H), 7.30-7.41 (m, 7H), 7.65 (m, 4H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 19.2, 26.8, 26.9, 27.0, 54.2, 63.4, 73.9, 79.8, 81.2, 83.9, 104.9, 109.6, 110.3, 113.3, 127.5, 127.6, 129.4, 133.5, 133.7, 135.6, 135.7, 142.9, 149.9; CHN Anal. Calcd for $C_{31}H_{36}O_6Si$: C, 69.90, H, 6.81; Found: C, 69.39, H, 6.68; ESI Mass: 555.18 (M + Na).

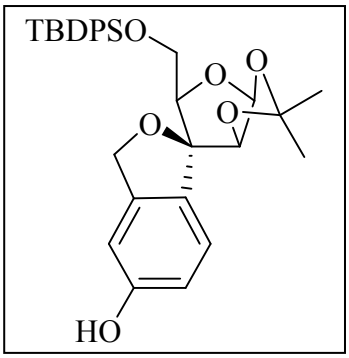


(1'S,3aS,5R,6aS)-5-[[[(1,1-Dimethylethyl)diphenylsilyl]oxy]methyl]-3a,6a-dihydro-2,2-dimethyl-spiro[furo[2,3-d]-1,3-dioxole-6(5H),1'(3'H)-isobenzofuran]-4'-ol (65):



$[\alpha]_D$ -14.83 (*c* 1.35, $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz): δ 0.97, 1.35, 1.66 (3s, 15H), 3.40 (dd, 1H, *J* = 5.43, 10.99 Hz), 3.59 (dd, 1H, *J* = 6.45, 10.99 Hz), 4.33 (d, 1H, *J* = 3.54 Hz), 4.56 (t, 1H, *J* = 6.19 Hz), 5.11 (m, 2H), 5.56 (bs, 1H), 5.95 (d, 1H, *J* = 3.54 Hz) 6.68 (q, 2H, *J* = 7.45, 18.06 Hz), 7.10 (t, 1H, *J* = 7.70 Hz), 7.24-7.39 (m, 6H), 7.45 (m, 2H), 7.58 (m, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 19.1, 26.4, 26.7, 26.9, 62.7, 71.5, 80.0, 83.9, 94.1, 103.7, 113.4, 113.9, 115.1, 126.0, 127.5, 127.6, 129.5, 129.6, 133.2, 133.4, 135.5, 135.6, 139.6, 150.3; CHN Anal. Calcd for $C_{31}H_{36}O_6Si$: C, 69.90, H, 6.81; Found: C, 69.34, H, 6.69; ESI Mass: 555.18 (M + Na).

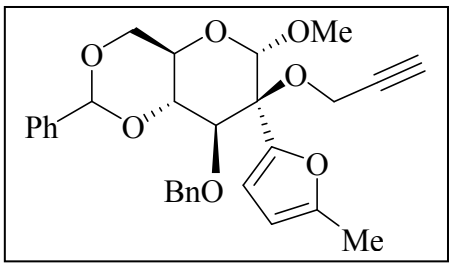
(1'S,3aS,5R,6aS)-5-[[[(1,1-Dimethylethyl) diphenylsilyl] oxy]methyl]-3a,6a-dihydro-2,2-dimethyl-spiro[furo[2,3-d]-1,3-dioxole-6(5H),1'(3'H)-isobenzofuran]-5'-ol (66):



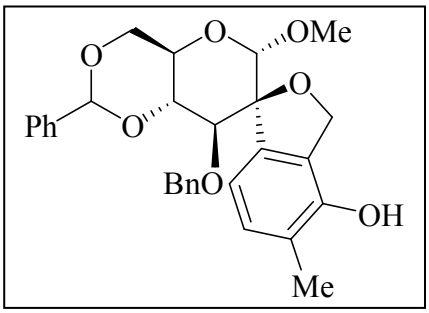
$[\alpha]_D$ -6.69 (*c* 1.20, $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz): δ 0.97, 1.36, 1.67 (3s, 15H), 3.36 (dd, 1H, *J* = 5.81, 10.99 Hz), 3.59 (dd, 1H, *J* = 6.19, 10.87 Hz), 4.31 (d, 1H, *J* = 3.54 Hz), 4.54 (t, 1H, *J* = 6.07 Hz), 5.04 (q, 2H, *J* = 12.64, 18.45 Hz), 5.48 (bs, 1H) 5.92 (d, 1H, *J* = 3.66 Hz), 6.64 (d, 1H, *J* = 1.77 Hz), 6.71 (dd, 1H, *J* = 2.27, 8.21 Hz), 6.92 (d, 1H, *J* = 8.21 Hz), 7.29-7.39 (m, 6H), 7.43 (m, 2H), 7.58 (m, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 19.0, 26.4, 26.7, 26.9, 62.7, 73.0, 79.8, 84.0, 93.2, 103.5, 108.2, 113.4, 115.1, 122.7, 127.5, 127.6, 129.1, 129.4, 129.6, 133.1, 133.3, 135.4, 135.6, 141.7, 156.6; CHN Anal. Calcd for $C_{31}H_{36}O_6Si$: C, 69.90, H, 6.81; Found: C, 69.54, H, 7.01; ESI Mass: 555.18 (M + Na).

Methyl 2-*C*-(5-methyl-2-furanyl)-3-*O*-(phenyl methyl)-4,6-*O*-[(R)-phenylmethylene]-2-*O*-2-prop ynyl-α-D-mannopyranoside (69): $[\alpha]_D$ -14.20 (*c* 1.20, $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz): δ 2.32 (s, 3H), 2.34 (t, 1H, *J* = 2.53 Hz), 3.52 (s, 3H), 3.70 (t, 1H, *J* =

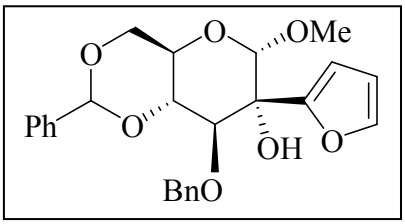
10.11 Hz), 3.78 (t, 1H, *J* = 9.60 Hz), 3.95 (m, 2H), 4.21 (m, 2H), 4.35 (d, 1H, *J* = 9.60 Hz), 4,94 (s, 2H), 5.37 (s, 1H), 5.49 (s, 1H), 5.98 (d, 1H, *J* = 3.04 Hz), 6.75 (d, 1H, *J* = 3.16 Hz), 7.24-7.49 (m, 10H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 13.7, 53.0, 55.2, 63.5, 68.9, 73.1, 75.6, 80.3, 80.5, 80.7, 80.9, 100.2, 101.3, 106.6, 115.0, 126.0, 127.3, 127.6, 128.1, 128.8, 137.4, 138.9, 147.5, 152.4; CHN Anal. Cacld for $C_{29}H_{30}O_7$: C, 71.00, H, 6.16; Found: C, 70.59, H, 6.34; ESI Mass: 513.15 (M + Na).

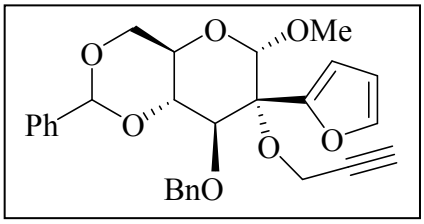


(1S,2'R,4'aR,6'S,8'S,8'aR)-4',4'a,8',8'a-Tetrahydro-6'-methoxy-5-methyl-2'-phenyl-8'-(phenylmethoxy)-spiro[isobenzofuran-1(3H),7'(6'H)-pyrano[3,2-d][1,3]dioxin]-4-ol (70): $[\alpha]_D$ -36.35 (*c* 1.10, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 2.20 (s, 3H), 3.43 (s, 3H), 3.89-4.11 (m, 3H), 4.29 (d, 1H, *J* = 9.60 Hz), 4.40 (d, 1H, *J* = 7.45 Hz), 4.60 (s, 1H), 4.79 (q, 2H, *J* = 12.13, 17.81 Hz), 5.01 (bs, 1H), 5.13 (ABq, 2H, *J* = 11.87 Hz), 5.59 (s, 1H), 7.02 (q, 2H, *J* = 7.70, 9.86 Hz), 7.19 (s, 4H), 7.36 (m, 4H), 7.45 (m, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 15.0, 55.2, 63.1, 69.1, 71.9, 75.2, 80.5, 90.9, 101.4, 103.5, 115.4, 123.3, 126.0, 127.2, 127.5, 127.7, 128.0, 128.1, 128.8, 130.3, 137.4, 138.3, 138.8, 148.0; CHN Anal. Calcd for $C_{29}H_{30}O_7$: C, 71.00, H, 6.16; Found: C, 70.61, H, 6.19; ESI Mass: 513.10 (M + Na).

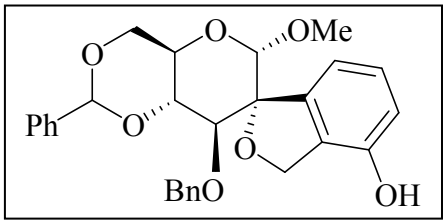


Methyl 2-*C*-2-furanyl-3-*O*-(phenylmethyl)-4,6-*O*-[(R)-phenylmethylene]- α-D-glucopyranoside (71): ^{1}H NMR ($CDCl_3$, 200 MHz): δ 3.13 (s, 1H), 3.44 (s, 3H), 3.54 (m, 2H), 3.90 (d, 1H *J* = 9.79 Hz), 4.15 (t, 1H, *J* = 9.39 Hz), 4.38 (d, 1H, *J* = 11.75 Hz), 4.39 (dq, 1H, *J* = 4.59, 10.19 Hz), 4.52 (d, 1H, *J* = 11.39 Hz), 4.72 (s, 1H), 5.63 (s, 1H), 6.41 (dd, 1H, *J* = 1.90, 3.28 Hz), 6.52 (dd, 1H, *J* = 0.88, 3.28 Hz), 7.04 (m, 2H), 7.21 (m, 3H), 7.38 (m, 5H), 7.49 (m, 2H).

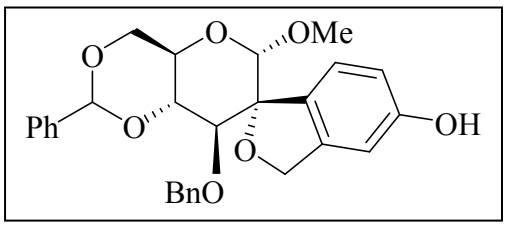


Methyl 2-*C*-2-furanyl-3-*O*-(phenylmethyl)-4,6-*O*-[(R)-phenylmethylene]-2-*O*-2-propynyl- α-D-glucopyranoside (72): 

$[\alpha]_D$ -21.34 (*c* 0.90, $CHCl_3$); IR ($CHCl_3$): 3307, 2930, 2871 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 2.41 (t, 1H, *J* = 2.40 Hz), 3.45 (s, 3H), 3.49 (m, 1H), 3.97 (t, 2H, *J* = 9.73 Hz), 4.29 (t, 1H, *J* = 9.60 Hz), 4.38 (dd, 1H, *J* = 4.92, 10.35 Hz), 4.50 (t, 2H, *J* = 2.91 Hz), 4.51 (d, 1H, *J* = 10.87 Hz) 4.61 (s, 1H), 4.73 (d, 1H , *J* = 11.34 Hz), 5.85 (s, 1H), 6.44 (dd, 1H, *J* = 1.77, 3.28 Hz), 6.58 (dd, 1H, *J* = 0.88, 3.22 Hz), 7.10 (m, 2H), 7.22 (m, 3H), 7.38 (m, 4H), 7.49 (m, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 55.5, 58.0, 67.8, 68.6, 73.5, 74.9, 79.3, 80.8, 81.1, 101.4, 104.5, 110.2, 110.7, 126.0, 127.3, 127.8, 128.0, 128.2, 128.8, 137.5, 138.1, 142.0, 150.0; CHN Anal. Calcd for $C_{28}H_{28}O_7$: C, 70.57, H, 5.92; Found: C, 70.19, H, 5.62; ESI Mass: 499.08 (M + Na).

(1R,2'R,4'aR,6'S,8'S,8'aR)-4',4'a,8',8'a-Tetrahydro-6'-methoxy-2'-phenyl-8'-(phenyl -methoxy)-spiro[isobenzofuran-1(3H),7'(6'H)-pyrano [3,2-d][1,3]dioxin]-4-ol (73): 

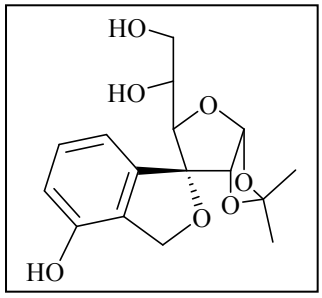
$[\alpha]_D$ +1.56 (*c* 0.80, $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz): δ 3.38 (s, 3H), 3.56 (ddd, 1H, *J* = 5.05, 9.85, 14.53 Hz), 3.79 (d, 1H, *J* = 9.72 Hz), 3.97 (t, 1H, *J* = 10.23 Hz), 4.23 (t, 1H, *J* = 9.60 Hz), 4.32 (d, 1H, *J* = 11.62 Hz), 4.41 (q, 1H, *J* = 5.06, 10.49 Hz), 4.52 (s, 1H), 4.59 (d, 1H, *J* = 11.62 Hz), 5.19 (s, 2H), 5.43 (bs, 1H), 5.65 (s, 1H), 6.76 (m, 5H), 7.14 (m, 3H), 7.39 (m, 3H), 7.52 (m, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 57.8, 68.9, 68.6, 74.7, 74.8, 80.1, 80.8, 90.8, 101.4, 104.9, 108.2, 114.7, 120.9, 126.0, 127.5, 128.0, 128.1, 128.2, 128.8, 129.5, 137.6, 137.7, 143.3, 156.4; CHN Anal. Calcd for $C_{28}H_{28}O_7$: C, 70.57, H, 5.92; Found: C, 70.15, H, 5.64; ESI Mass: 499.10 (M + Na).

(1R,2'R,4'aR,6'S,8'S,8'aR)-4',4'a,8',8'a-Tetrahydro-6'-methoxy-2'-phenyl-8'-(phenyl -methoxy)-spiro[isobenzofuran-1(3H),7'(6'H)-pyrano[3,2-d][1,3]dioxin]-5-ol (74): 

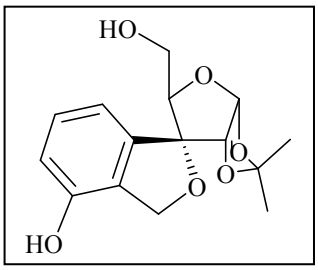
$[\alpha]_D$ -18.08 (*c* 1.30, $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz): δ 3.39 (s, 3H), 3.57 (ddd, 1H, *J* = 4.90,

9.85, 14.52 Hz), 3.83 (d, 1H, *J* = 9.60 Hz), 3.98 (t, 1H, *J* = 10.23 Hz), 4.25 (t, 1H, *J* = 9.60 Hz), 4.30 (d, 1H, *J* = 11.62 Hz), 4.41 (dd, 1H, *J* = 4.93, 10.49 Hz), 4.56 (s, 1H), 4.57 (d, 1H, *J* = 11.62 Hz), 5.25 (s, 2H), 5.50 (bs, 1H) 5.66 (s, 1H), 6.50 (d, 1H, *J* = 7.33 Hz) 6.70 (d, 1H, *J* = 7.58 Hz), 6.83 (dd, 2H, *J* = 1.65, 7.08 Hz), 7.12 (m, 4H), 7.39 (m, 3H), 7.52 (m, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 57.8, 66.9, 68.6, 73.2, 74.8, 79.9, 80.8, 91.7, 101.4, 104.7,112.3, 115.2, 126.0, 127.4, 127.7, 128.0, 128.1, 128.2, 128.3, 129.2, 137.5, 137.6, 139.9, 150.3; CHN Anal. Calcd for $C_{28}H_{28}O_7$: C, 70.57, H, 5.92; Found: C, 70.39, H, 5.71; ESI Mass: 499.08 (M + Na).

Formal synthesis of the PKC-α Inhibitor

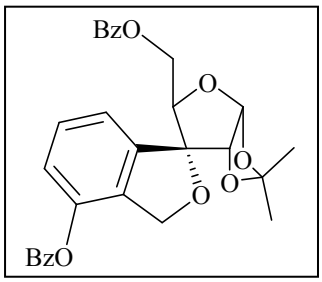


Compound 76: To a solution of **52** (1.80g, 4.93 mmol) in 50 mL methanol at room temperature was added 5 mL of 0.8 % aq H_2SO_4 solution and reaction mixture was stirred for 8 h and after complete disappearance of **52** (TLC monitored), the reaction mixture was quenched with saturated aq. $NaHCO_3$ and extracted with ethyl acetate (3 × 50 mL). The pooled organic layers were dried over anhydrous Na_2SO_4, concentrated *in vacuo* and crude residue was purified by silica-gel column chromatography using 2:3 ethyl acetate and light petroleum as mobile phase to afford the diol **76** in (1.26g, 79 %) as pale yellow syrup. $[\alpha]_D$ +83.56 (*c* 1.10, CH_3OH); IR ($CHCl_3$): 3425 cm^{-1}; ^{1}H NMR (CD_3OD, 200 MHz): δ 1.34, 1.59 (2s, 6H), 3.17 (m, 1H), 3.48 (dd, 1H, *J* = 5.94, 11.50 Hz), 3.62 (dd, 1H, *J* = 2.91, 11.50 Hz), 4.16 (d, 1H, *J* = 9.22 Hz), 4.34 (d, 1H, *J* = 3.66 Hz), 5.04 (d, 1H, *J* = 11.75 Hz), 5.17 (d, 1H, *J* = 11.75 Hz), 5.96 (d, 1H, *J* = 3.67 Hz), 6.64 (d, 1H, *J* = 7.45 Hz), 6.73 (d, 1H, *J* = 8.09 Hz) 7.15 (t, 1H, *J* = 7.58 Hz); ^{13}C NMR (CD_3OD, 100 MHz): δ 27.5, 27.9, 66.6, 72.8, 73.4, 80.2, 86.5, 96.9, 105.7, 114.5, 115.1, 116.8, 128.4, 131.3, 141.9, 154.0; ESI Mass: 347.81 (M + Na).



Compound 77: To a solution of diol **76** (1.20g, 3.70 mmol) in anhydrous 40 mL of DCM was added $NaIO_4$ (1.58g, 7.38 mmol) adsorbed over silica gel and the reaction mixture was stirred at ambient temperature for 1 h. After the complete disappearance of the diol, the reaction mixture was filtered

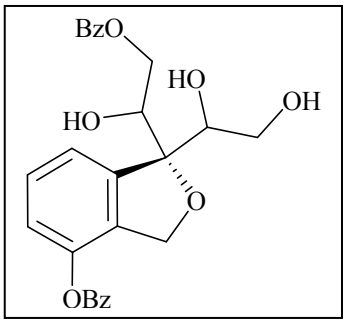
through sintered funnel and concentrated *in vacuo*. The residue obtained was dissolved in 40 mL anhydrous methanol and cooled to 0 ^{o}C. To this was added $NaBH_4$ (0.169g, 4.40 mmol) portionwise and reaction mixture was stirred for additional 3 h at room temperature. After completion of the reaction (TLC monitored) the reaction mixture was concentrated *in vacuo*, dissolved in water (50 mL) and extracted with ethyl acetate (3 × 50 mL), pooled organic layers were dried over anhydrous Na_2SO_4, concentrated *in vacuo* and residue was purified by silica gel column chromatography using 2:3 ethyl acetate and light petroleum as mobile phase to afford alcohol **77** (0.926g, 85 %) as pale yellow syrup. $[\alpha]_D$ +31.83 (*c* 1.10, CH_3OH); IR ($CHCl_3$): 3401 cm^{-1}; ^{1}H NMR (CD_3OD, 200 MHz): δ 1.34, 1.60 (2s, 6H), 3.28 (m, 2H), 4.31 (d, 1H, *J* = 3.77 Hz), 4.35 (dd, 1H, *J* = 4.92, 6.44 Hz), 5.08 (q, 2H, *J* = 12.26, 16.05 Hz), 6.01 (d, 1H, *J* = 3.67 Hz), 6.71 (q, 2H, *J* = 7.45, 13.01 Hz), 7.16 (t, 1H, *J* = 7.83 Hz); ^{13}C NMR (CD_3OD, 50 MHz): δ 27.6, 27.9, 63.2, 73.4, 82.8, 85.6, 95.7, 106.4, 114.6, 115.2, 116.9, 127.4, 131.6, 141.2, 154.1; ESI Mass: 317.06 (M + Na).



Compound 78: To a solution of **77** (0.880g, 2.99 mmol) in 20 mL of anhydrous CH_2Cl_2 cooled at 0 ^{o}C was added pyridine (1.418 mL, 17.94 mmol) and catalytic amount of DMAP. The reaction mixture was allowed to stir for 10 minutes followed by addition of benzoyl chloride (1.39 mL, 11.96 mmol) dropwise and the reaction mixture was warmed to room temperature and stirred for 12 h. After complete consumption of the starting material, the reaction mixture was diluted with cold water (50 mL) to quench excess of benzoyl chloride at 0 ^{o}C. The mixture was extracted with ethyl acetate (3 × 50 mL) and pooled organic layers were washed with saturated aq. brine solution (50 mL), dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue obtained was purified by silica gel column chromatography using 1:4 ethyl acetate and light petroleum as mobile phase to obtain dibenzoate ester **78** (1.36g, 91 %) as white syrup. $[\alpha]_D$ +28.11 (*c* 1.55, CH_3OH); IR ($CHCl_3$): 1736, 1722 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.40, 1.72 (2s, 6H), 4.20 (m, 2H), 4.46 (d, 1H, *J* = 3.54 Hz) 4.79 (dd, 1H, *J* = 4.42, 6.95 Hz), 5.20 (s, 2H), 6.08 (d, 1H, *J* = 3.54 Hz), 7.22 (m, 2H), 7.37-7.71 (m, 7H), 8.00- 8.19 (m, 4H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 26.3, 26.8, 63.3, 71.9, 77.2, 83.1, 93.8, 104.0, 113.7, 119.3,

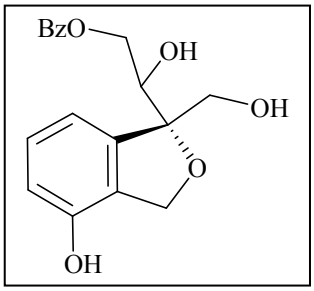
122.4, 128.2, 128.4, 128.7, 129.7, 130.0, 130.1, 130.2, 132.0, 132.9, 133.9, 139.2, 145.4, 163.8, 166.1; ESI Mass: 525.43 (M + Na).

Compound 80: Di-benzoate ester **78** (1.25g, 2.48 mmol) was dissolved in dioxane-water 1:1 (50 mL) and to this was added a catalytic amount of H_2SO_4 and reaction mixture was heated to 80 ^oC for 12 h. After complete disappearance of the compound **78** (checked by TLC), excess acid was quenched with saturated aq. $NaHCO_3$, reaction mixture was diluted with water (50 mL) and extracted with ethyl acetate (3 × 50 mL), washed with brine solution, concentrated *in vacuo* and residue was purified by silica gel column chromatography using 6:4 ethyl acetate and petroleum ether as mobile phase to afford lactol **79** (0.743g, 65 %) as thick syrup.

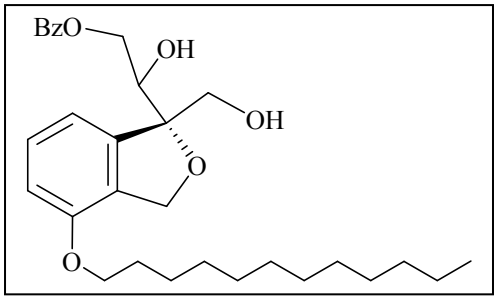


To a solution of diol (0.720g, 1.56 mmol) in 10 mL of methanol cooled at 0 ^oC was added $NaBH_4$ (0.118g, 3.11 mmol) portionwise and reaction mixture was stirred at ambient temperature for 4 h. After completion, reaction mixture was concentrated *in vacuo,* diluted with 50 mL of water and extracted with ethyl acetate (3 × 30 mL), the pooled organic layers were dried over anhydrous Na_2SO_4, concentrated *in vacuo* and residue was purified by silica gel column chromatography using 7:1 ethyl acetate and light petroleum as mobile phase to afford triol **80** (0.538g, 72 %) as thick syrup. $[\alpha]_D$ +41.12 (*c* 1.10, CH_3OH); IR ($CHCl_3$): 3435, 1736, 1719 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 3.68 (dd, 1H, *J* = 5.06, 11.12 Hz), 3.84 (dd, 1H, *J* = 3.53, 11.37 Hz), 4.16 (q, 2H, *J* = 8.09, 12.38 Hz), 4.48 (d, 1H, *J* = 1.89 Hz), 4.50 (dd, 1H, *J* = 2.15, 16.04 Hz), 5.15 (d, 2H, *J* = 1.77 Hz), 7.19 (dd, 1H, *J* = 0.78, 7.83 Hz), 7.38 (q, 3H, *J* = 7.58, 14.65 Hz), 7.54 (m, 4H), 7.64 (m, 1H), 7.94 (td, 2H, *J* = 1.13, 8.08 Hz), 8.17 (td, 2H, *J* = 1.51, 8.46 Hz); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 62.3, 66.7, 72.0, 73.8, 75.3, 91.5, 121.5, 121.7, 128.3, 128.7, 129.5, 129.7, 130.2, 132.2, 133.2, 133.9, 140.3, 144.9, 164.0, 167.5; ESI Mass: 487.86 (M + Na).

Compound 81: To a solution of triol **80** (0.5g, 1.07 mmol) in 20 mL of anhydrous DCM was added $NaIO_4$ (0.458g, 2.15 mmol) adsorbed over silica gel and reaction mixture was stirred at ambient temperature for 1 h, after complete disappearance of the diol (TLC monitored), the reaction mixture was filtered through sintered funnel and concentrated *in vacuo*. The residue obtained was dissolved in 20 mL anhydrous methanol and cooled to 0 ^oC. To this was added $NaBH_4$ (0.049g, 1.28 mmol) and the reaction mixture was stirred for additional 3 h at room temperature. After completion of the reaction (TLC monitored), the reaction mixture was concentrated *in vacuo*, dissolved in 50 mL water and extracted with ethyl acetate (3 × 30 mL), dried over anhydrous Na_2SO_4, concentrated i*n vacuo* and residue was purified by silca gel column chromatography using 1:1 ethyl acetate and light petroleum as mobile phase to afford alcohol **81** (0.297g, 84 %) as thick syrup. $[\alpha]_D$ +39.94 (*c* 0.85, CH_3OH); IR ($CHCl_3$): 3328, 2854, 1697 cm^{-1}; ^1H NMR (CD_3OD, 200 MHz): δ 3.76 (d, 1H, *J* = 11.62 Hz), 3.94 (d, 1H, *J* = 11.62 Hz), 4.03 (dt, 1H, *J* = 3.54, 10.61 Hz), 4.37 (dt, 2H, *J* = 2.53, 10.87 Hz), 5.10 (s, 2H) 6.69 (dd, 1H, *J* = 0.64, 7.84 Hz), 6.93 (d, 1H, *J* = 7.07 Hz), 7.12 (t, 1H, *J* = 7.84 Hz), 7.42 (t, 2H, *J* = 7.20 Hz), 7.57 (td, 1H, *J* = 1.39, 8.72 Hz), 7.93 (td, 2H, *J* = 1.52, 8.21 Hz); ^{13}C NMR (CD_3OD, 50 MHz): δ 67.9, 68.5, 73.2, 73.4, 93.9, 116.1, 116.4, 128.4, 130.3, 130.9, 131.5, 132.2, 135.0, 143.0, 153.6, 169.1; ESI Mass: 353.26 (M + Na).

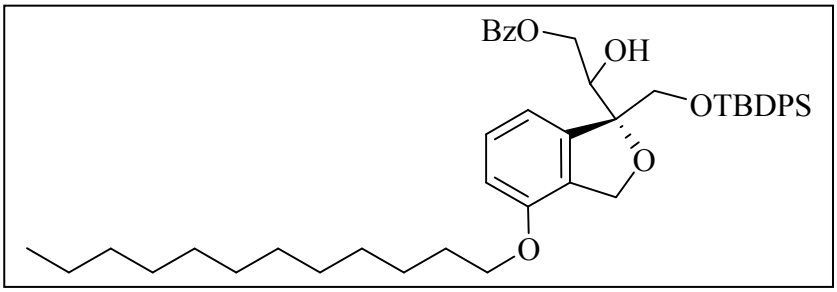


Compound 82: To the solution of triol **81** (0.250g, 0.76 mmol) in 20 mL of anhydrous DMF was added freshly activated K_2CO_3 (0.419g, 3.02 mmol) and stirred for 10 min. To this solution was added dodecyl bromide (0.378g, 1.52 mmol) and reaction mixture was stirred for 12 h at room temperature. After disappearance of the starting material (by TLC) reaction mixture was diluted with water (40 mL) and extracted with ethyl acetate (3 × 20 mL), pooled organic layers were dried over anhydrous Na_2SO_4, concentrated *in vacuo* and residue was purified by silica gel column chromatography using 3:7 ethyl



acetate and petroleum ether to afford compound **82** (0.349g, 92 %) as syrup. $[\alpha]_D$ +35.26 (*c* 0.90, $CHCl_3$); IR ($CHCl_3$): 3444, 2928, 1718 cm^{-1}; ^1H NMR (CD_3OD, 200 MHz): δ 0.89 (t, 3H, *J* = 6.57 Hz), 1.28 (s, 18H), 1.76 (m, 2H), 3.77 (d, 1H, *J* = 11.74 Hz), 3.97 (t, 2H, *J* = 5.61 Hz), 4.00 (d, 1H, *J* = 11.59 Hz), 4.09 (q, 1H, *J* = 8.53, 11.87 Hz), 4.41 (m, 2H), 5.13 (s, 2H), 6.79 (d, 1H, *J* = 7.96 Hz), 7.03 (d, 1H, *J* = 7.45 Hz), 7.24 (t, 1H, *J* = 7.83 Hz), 7.41 (t, 2H, *J* = 7.20 Hz), 7.56 (tt, 1H, *J* = 1.26, 8.54 Hz), 7.88 (d, 1H, *J* = 1.52 Hz) 7.92 (s, 1H); ^{13}C NMR (CD_3OD, 50 MHz): δ 12.9, 21.9, 25.3, 28.4, 28.6, 28.8, 28.9, 31.2, 65.2, 65.9, 67.2, 70.4, 70.7, 91.0, 110.0, 114.4, 127.1, 127.5, 128.6, 128.8, 129.2, 132.3, 139.8, 152.8, 166.5; ESI Mass: 521.28 (M + Na).

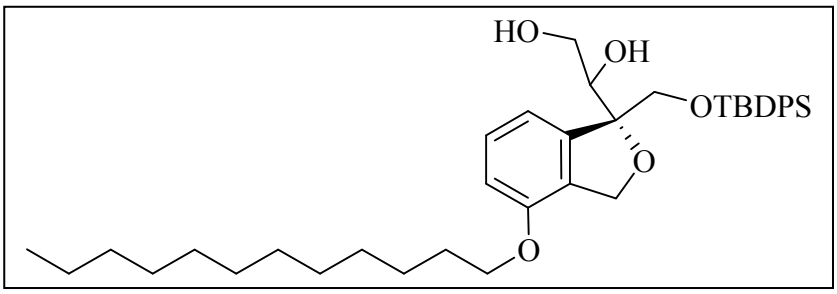
Compound 83: To a solution diol **82** (0.320g, 0.64 mmol) in 10 mL of anhydrous CH_2Cl_2 at 0 ^oC was added imidazole



(0.087g, 1.28 mmol) and solution was stirred for 10 min. To this solution was added TBDPSCl (0.197 mL, 0.77 mmol) drop wise and the reaction mixture was stirred for 12 h at room temperature. After completion (TLC monitored), the reaction mixture was diluted with 20 mL of water and extracted with ethyl acetate (3 × 20 mL). The pooled organic layers were washed with brine solution and dried over anhydrous Na_2SO_4, concentrated *in vacuo* and residue was purified by silica gel column chromatography using 1:9 ethyl acetate and petroleum ether to afford silyl ether **83** (0.372g, 79 %) as thick syrup. $[\alpha]_D$ +20.53 (*c* 0.90, $CHCl_3$); IR ($CHCl_3$): 3466, 2929, 1718 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 0.87 (t, 3H, *J* = 6.70 Hz), 1.01 (s, 9H), 1.27 (s, 18H), 1.74 (m, 2H), 2.90 (bs, 1H), 3.87 (d, 1H, *J* = 10.48 Hz), 3.94 (t, 2H, *J* = 6.45 Hz), 4.03 (d, 1H, *J* = 10.48 Hz), 4.25 (dd, 1H, *J* = 7.45, 11.50 Hz), 4.51 (m, 2H), 5.06 (d, 1H, *J* = 7.83 Hz), 5.16 (d, 1H, *J* = 12.50 Hz), 6.73 (d, 1H, *J* = 7.83 Hz), 7.00 (d, 1H, *J* = 7.33 Hz), 7.19 (t, 1H, *J* = 7.83 Hz), 7.29-7.42 (m, 9H), 7.63 (m, 4H), 7.91 (td, 2H, *J* = 1.52, 8.59 Hz); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 14.1, 19.2, 22.7, 26.0, 26.7, 29.2, 29.3, 29.4, 29.5, 29.6, 29.6, 29.7, 31.9, 66.7, 67.9, 68.0, 71.7, 72.7, 91.3, 110.6, 115.1, 127.7, 128.2, 129.1, 129.6, 129.6,

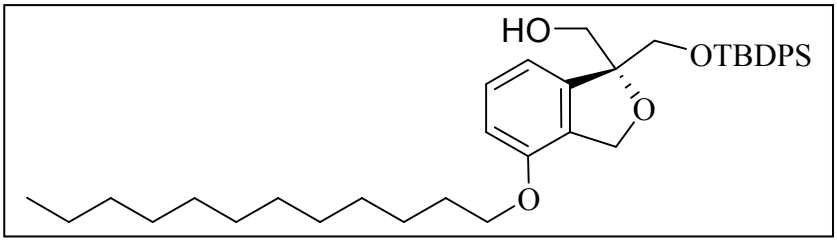
129.7, 129.9, 132.9, 133.3, 135.6, 135.7, 140.6, 153.5, 167.0; ESI Mass: 759.36 (M + Na).

Compound 84: To a solution of **83** (0.270g, 0.37 mmol) in 10 mL of methanol was added oven dried K_2CO_3 (0.505g, 3.70 mmol),



the reaction mixture was stirred for 24 h at room temperature. After complete disappearance of starting material (TLC monitored), the reaction mixture was diluted with 50 mL of water and extracted with ethyl acetate (3 × 20 mL). The pooled organic layers were washed with brine solution and dried over anhydrous Na_2SO_4, concentrated *in vacuo* and residue obtained was purified by silica gel column chromatography using 3:7 ethyl acetate and light petroleum to afford compound **84** (0.178g, 75 %) as syrup. $[\alpha]_D$ -5.10 (*c* 0.80, $CHCl_3$); IR ($CHCl_3$): 3450 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 0.88 (t, 3H, *J* = 6.70 Hz), 1.00 (s, 9H), 1.26 (bs, 18H), 1.76 (m, 2H), 2.24 (bs, 2H), 3.69 (m, 2H), 3.79 (d, 1H, *J* = 10.49 Hz), 3.90 (d, 1H, *J* = 10.48 Hz), 3.98 (t, 2H, *J* = 6.57 Hz), 4.21 (dd, 1H, *J* = 3.91, 5.93 Hz), 5.08 (q, 2H, *J* = 12.50, 18.69 Hz), 6.77 (d, 1H, *J* = 7.96 Hz), 6.94 (d, 1H, *J* = 7.33 Hz), 7.24 (t, 1H, *J* = 7.83 Hz), 7.30- 7.44 (m, 6H), 7.54-7.63 (m, 4H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 14.1, 19.1, 22.7, 26.0, 26.7, 29.2, 29.3, 29.4, 29.5, 29.6, 29.7, 31.9, 63.2, 67.6, 68.0, 71.9, 73.4, 92.5, 110.6, 114.7, 127.7, 127.8, 129.2, 129.7, 129.8, 132.7, 133.0, 135.5, 135.7, 141.3, 153.5; ESI Mass: 655.81 (M + Na).

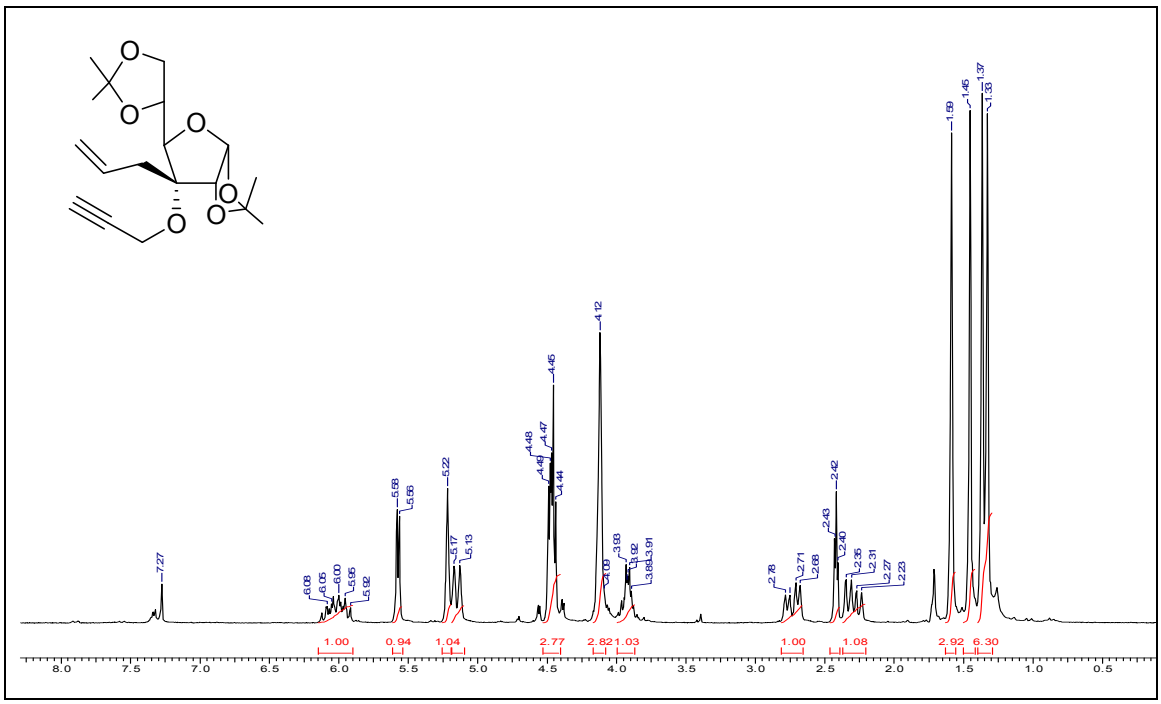
Compound 85: To a solution of diol **80** (0.120g, 0.19 mmol) in 10 mL of anhydrous DCM was added



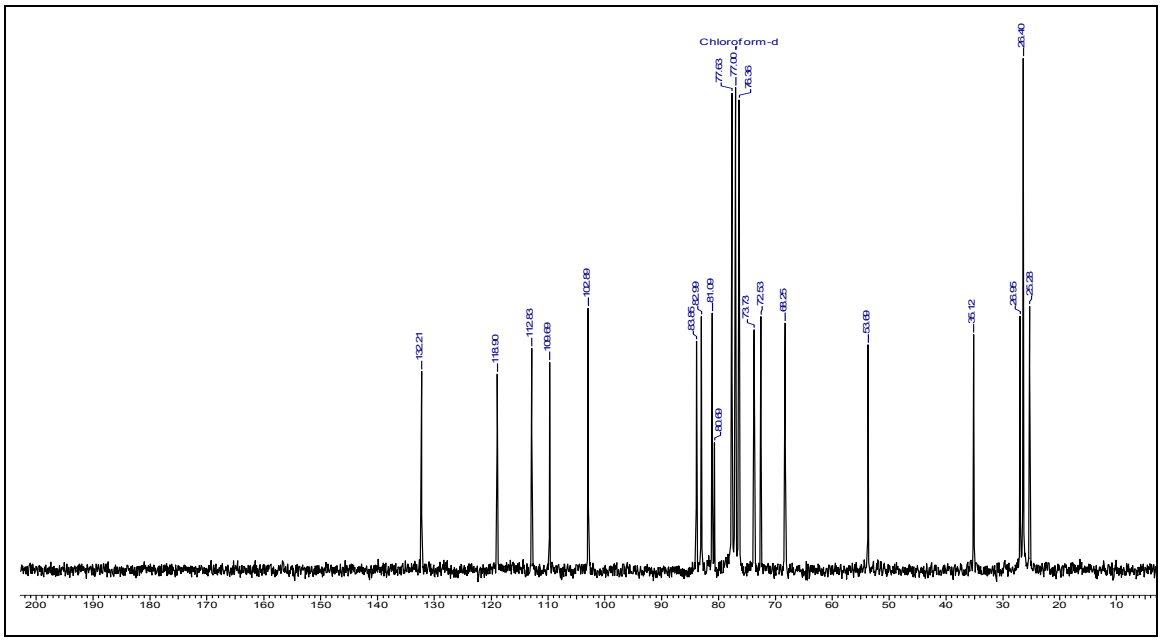
$NaIO_4$ (0.081g, 0.379 mmol) adsorbed over silica gel and reaction mixture was stirred at ambient temperature for 1 h. After the complete disappearance of the diol, the reaction mixture was filtered through sintered funnel and concentrated *in vacuo*. The residue

obtained was dissolved in 10 mL of anhydrous methanol and cooled to 0 ^{o}C. To this was added $NaBH_4$ (0.009g, 0.23 mmol), and reaction mixture was stirred for additional 3 h at room temperature. After completion of the reaction (TLC monitored), the reaction mixture was concentrated *in vacuo*, dissolved in 20 mL of water and extracted with ethyl acetate (3 × 20 mL), dried over anhydrous Na_2SO_4, concentrated *in vacuo* and residue was purified by silica gel column chromatography using 1:1 ethyl acetate and light petroleum as mobile phase to afford alcohol **81** (0.102g, 84 %) as sticky syrup. $[\alpha]_D$ -1.66 (*c* 1.05, $CHCl_3$); IR ($CHCl_3$): 3417, 2929 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 0.88 (t, 3H, *J* = 6.69 Hz), 1.01 (s, 9H), 1.26 (s, 18H), 1.76 (m, 2H), 1.90 (bs, 1H), 3.82 (s, 2H), 3.90 (t, 2H, *J* = 11.62 Hz), 3.99 (t, 2H, *J* = 6.32 Hz), 5.11 (q, 2H, *J* = 12.51, 15.59 Hz), 6.78 (d, 1H, *J* = 8.08 Hz), 6.86 (d, 1H, *J* = 7.32 Hz), 7.24 (t, 1H, *J* = 7.83 Hz), 7.30-7.44 (m, 6H), 7.56- 7.64 (m, 4H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 14.1, 19.2, 22.7, 26.0, 26.7, 29.2, 29.3, 29.4, 29.5, 29.6, 29.7, 31.9, 65.8, 67.0, 68.0, 71.5, 91.4, 101.6, 114.2, 127.6, 128.2, 129.1, 129.6, 129.7, 133.0, 133.3, 135.6, 135.7, 141.8, 153.6; ESI Mass: 625.64 (M + Na).

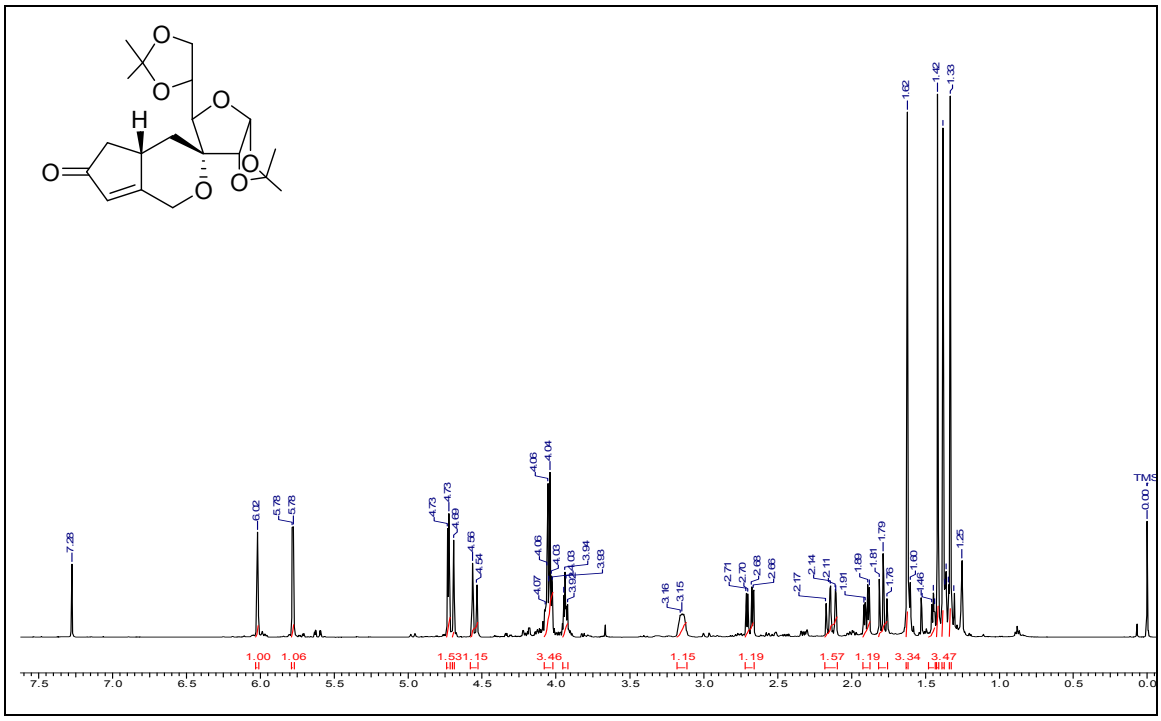
1.4 Spectra



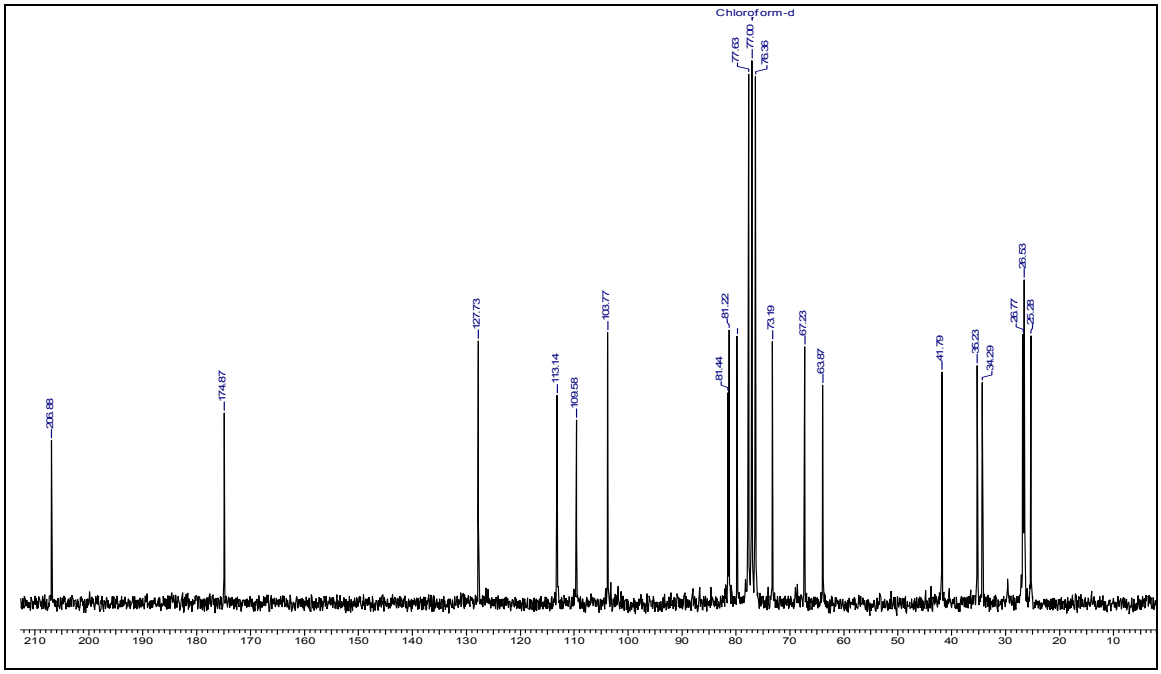
^{1}H NMR spectrum of compound 3 in $CDCl_3$



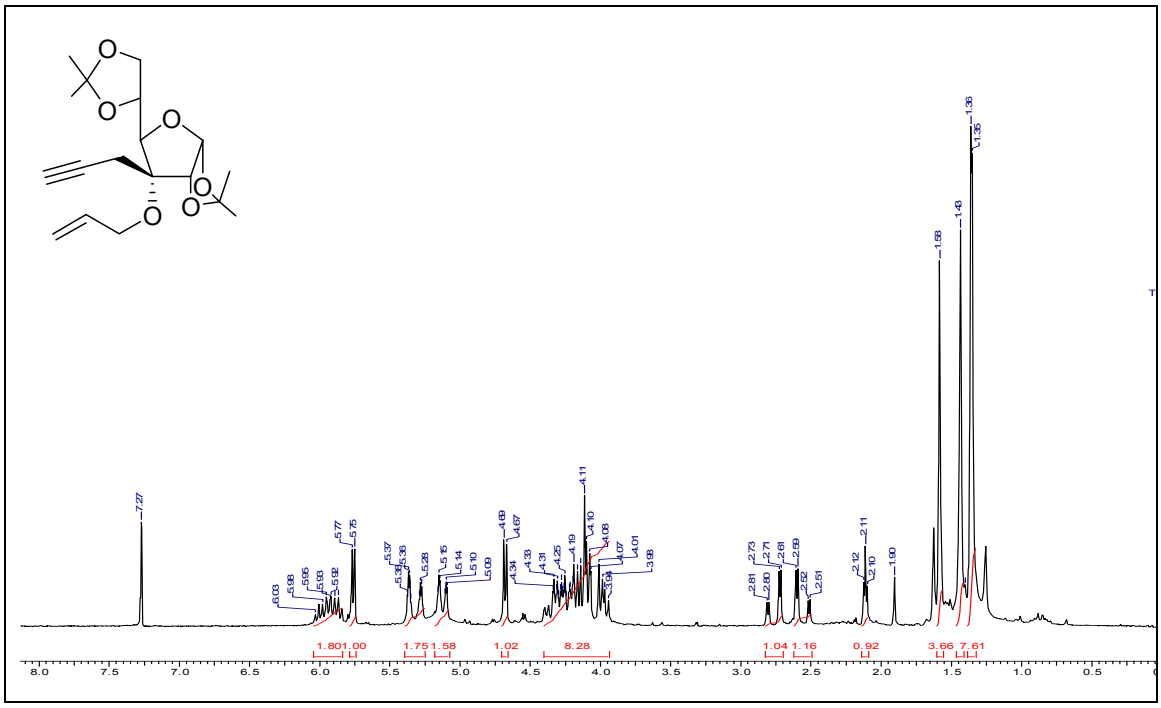
^{13}C NMR spectrum of compound 3 in $CDCl_3$



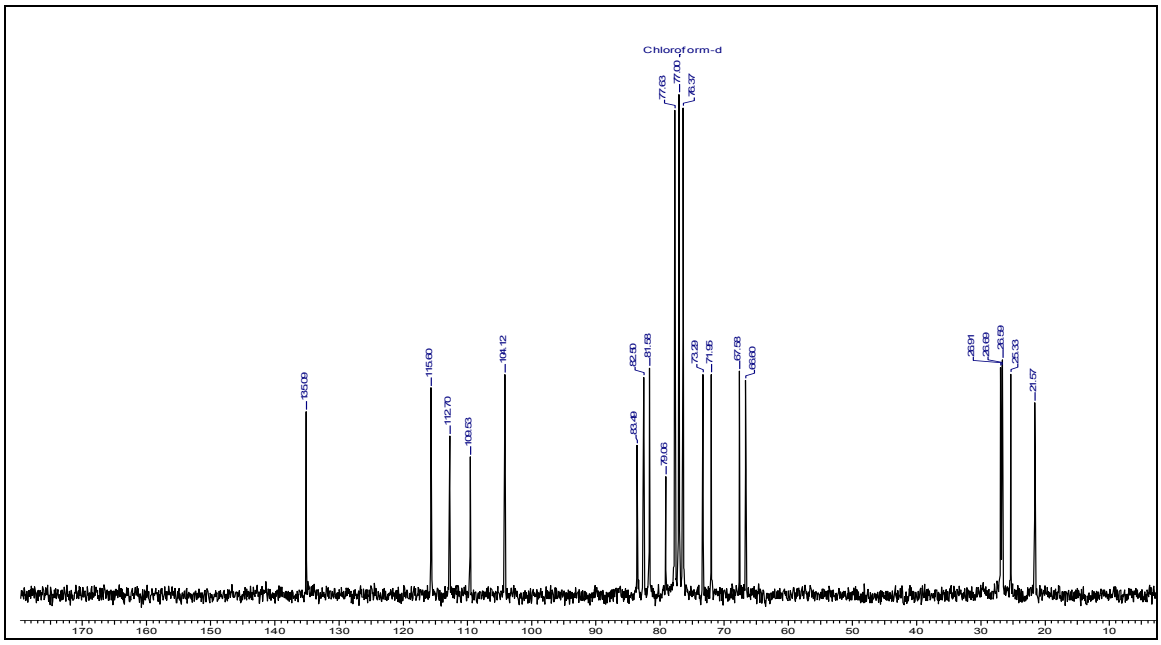
^{1}H NMR spectrum of compound 4 in $CDCl_3$



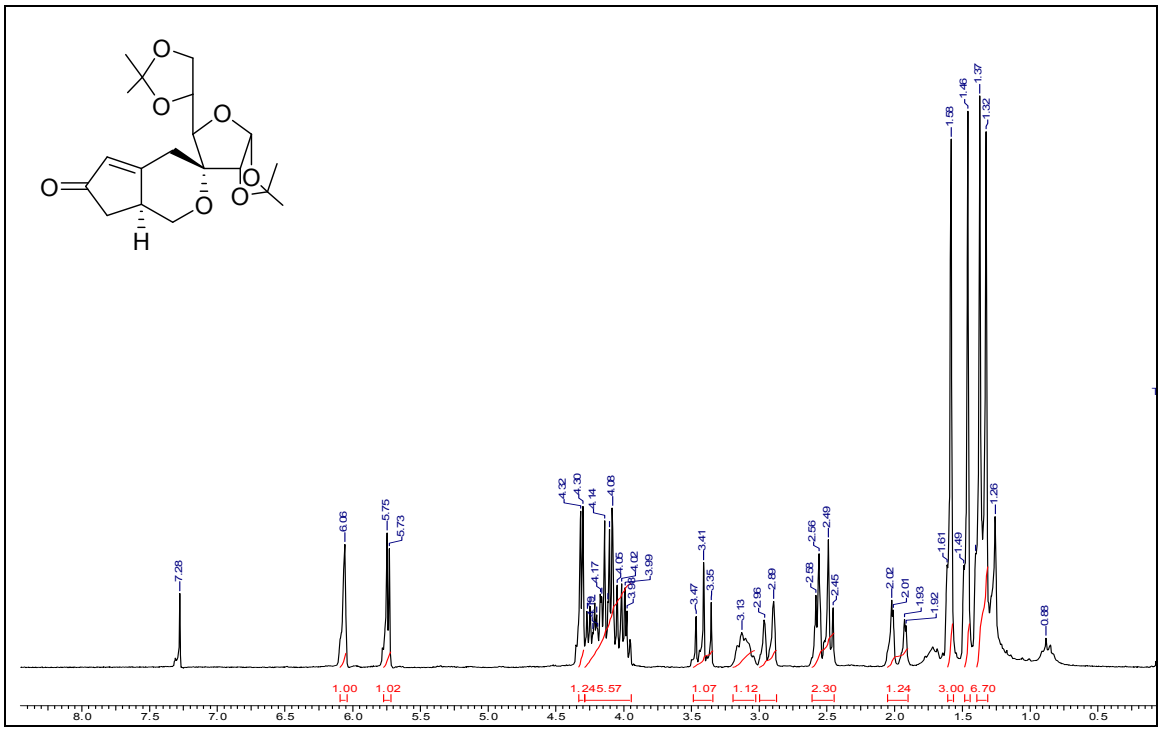
^{13}C NMR spectrum of compound 4 in $CDCl_3$



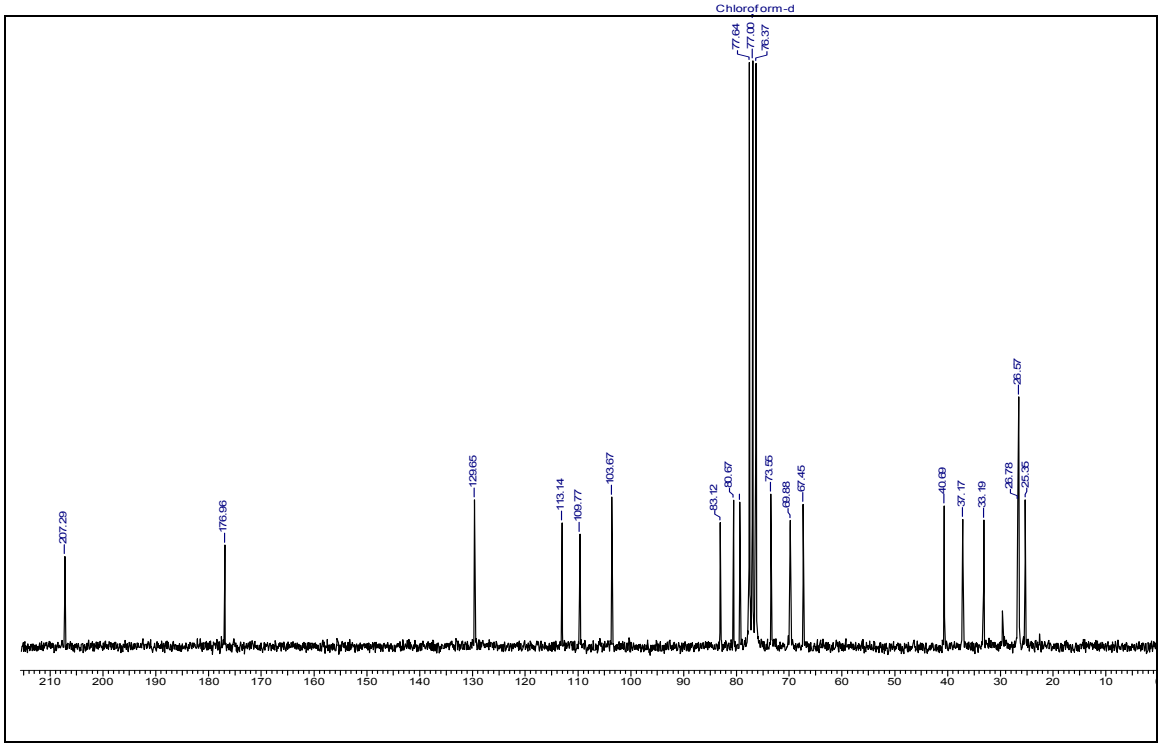
^{1}H NMR spectrum of compound 6 in $CDCl_3$



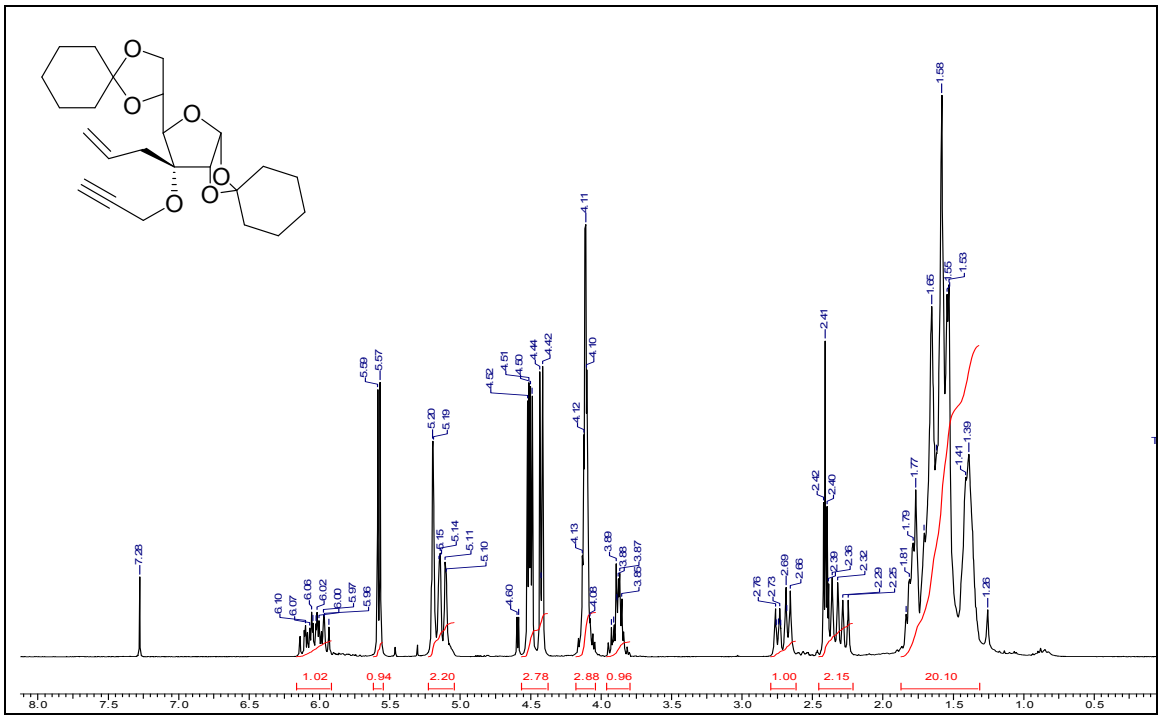
^{13}C NMR spectrum of compound 6 in $CDCl_3$



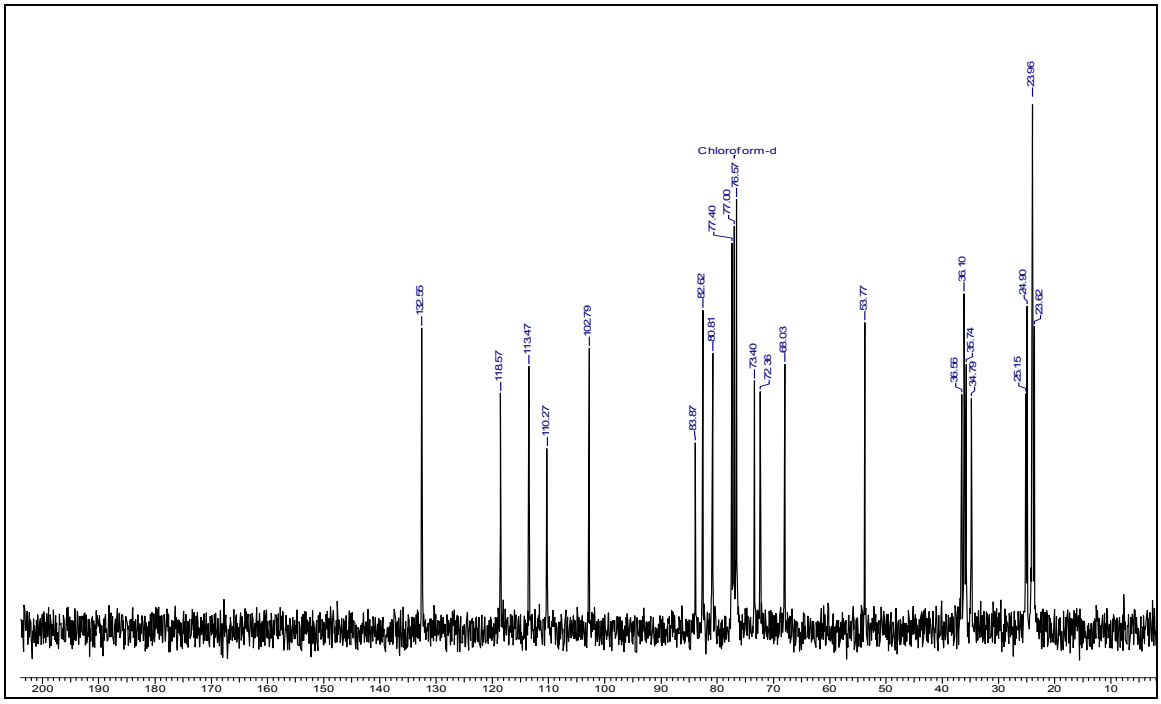
^{1}H NMR spectrum of compound 7 in $CDCl_3$



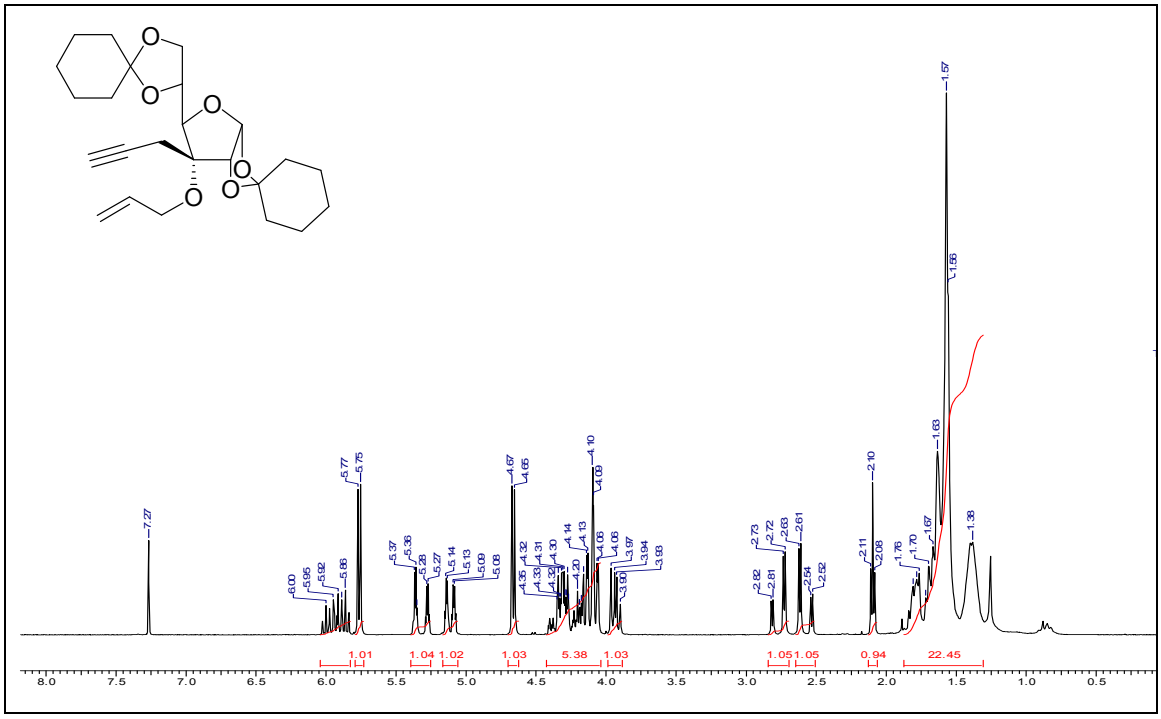
^{13}C NMR spectrum of compound 7 in $CDCl_3$



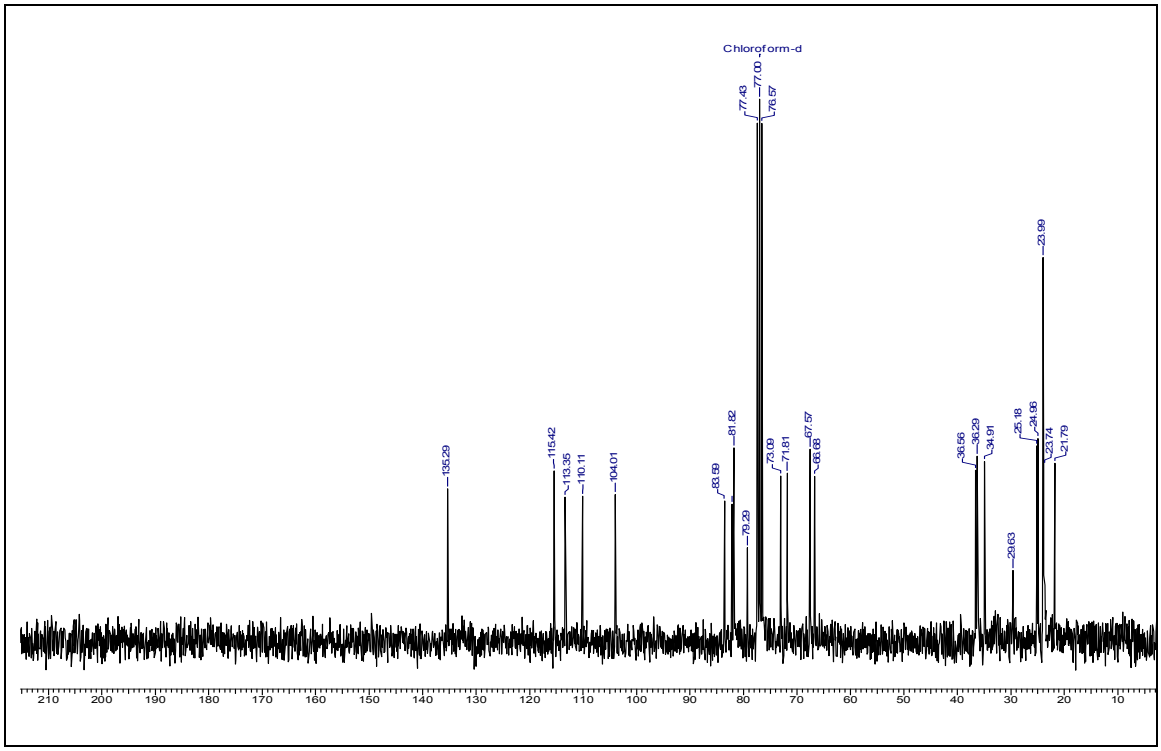
^{1}H NMR spectrum of compound 10 in $CDCl_3$



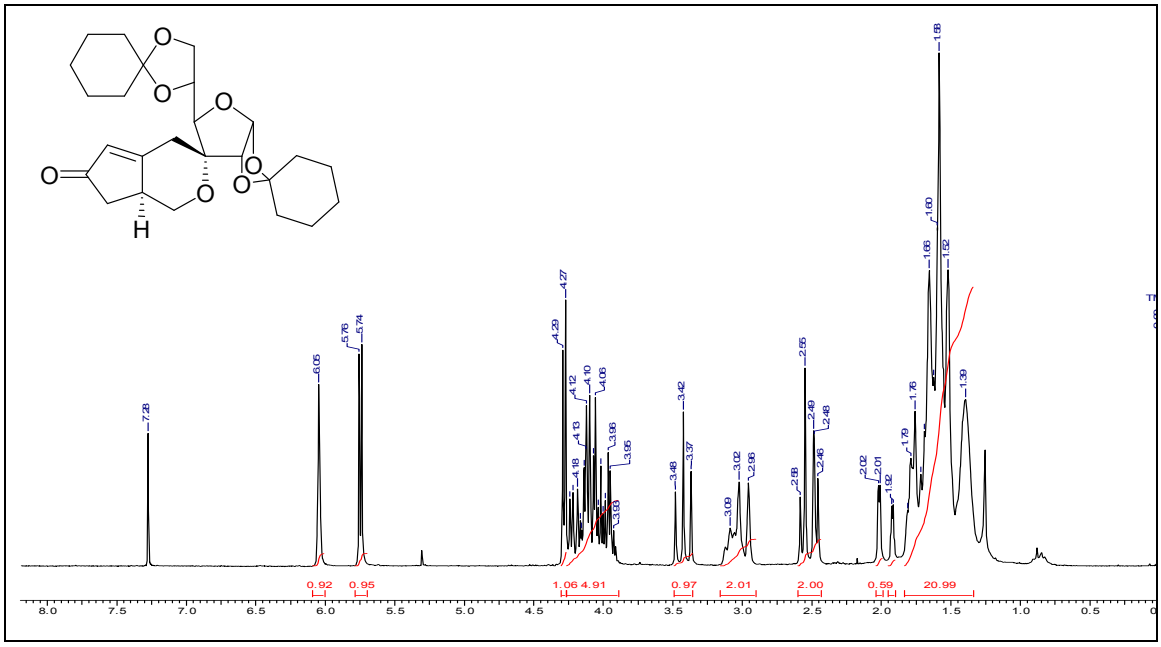
^{13}C NMR spectrum of compound 10 in $CDCl_3$



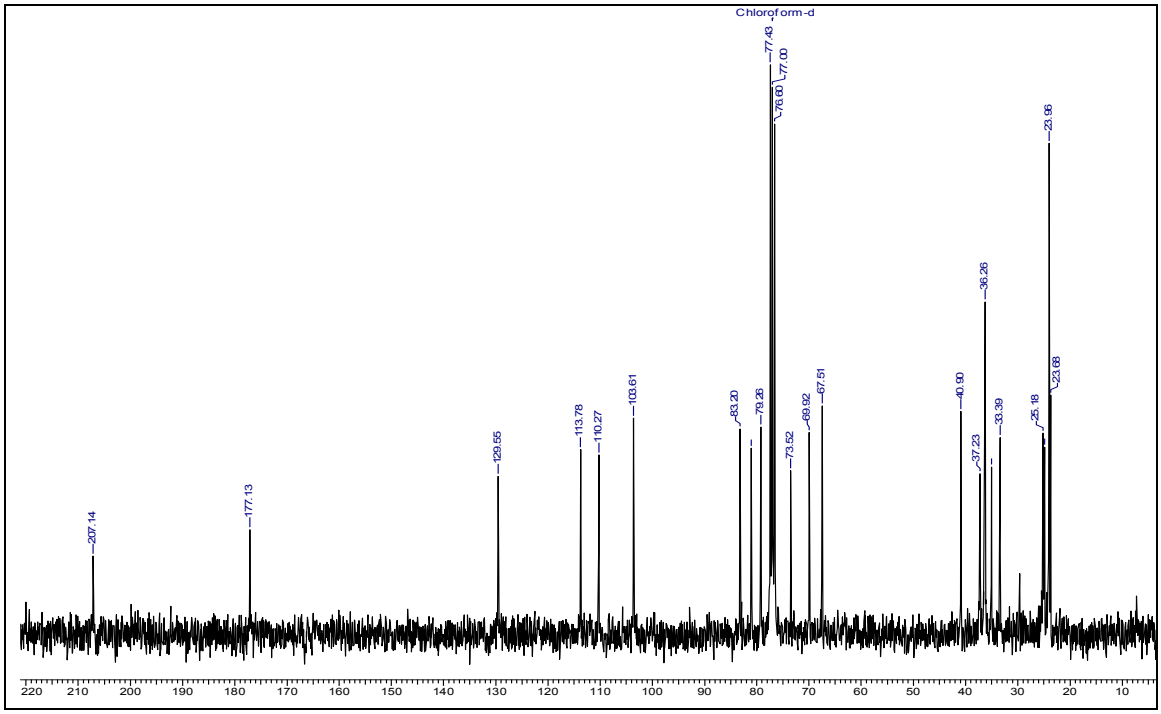
^{1}H NMR spectrum of compound 13 in $CDCl_3$



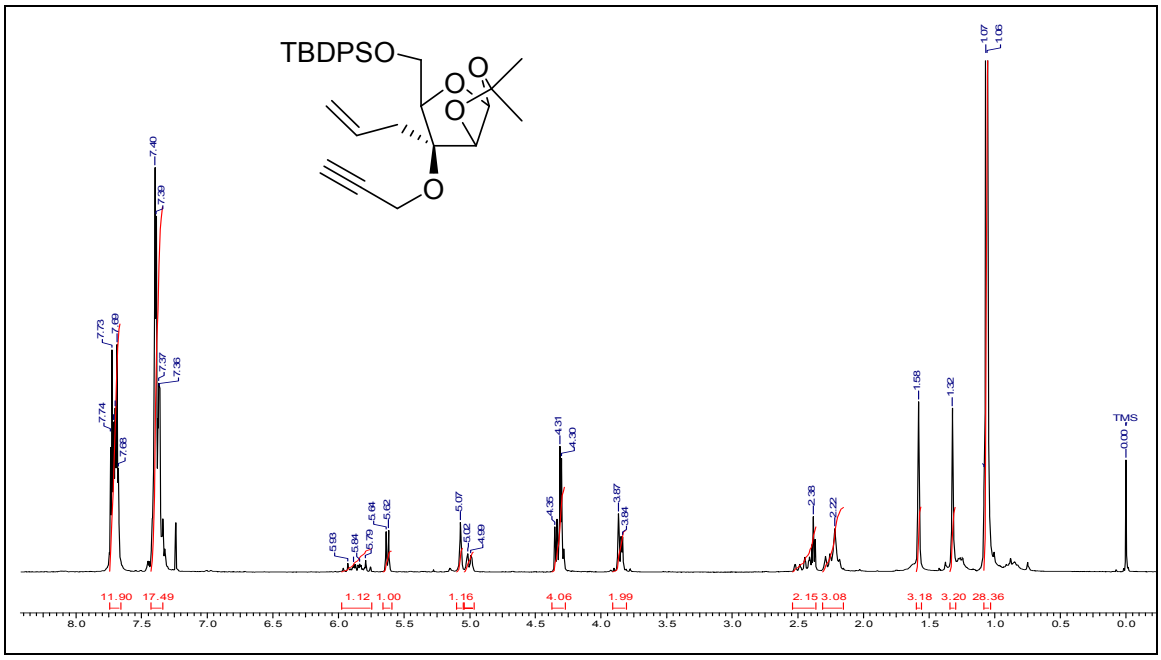
^{13}C NMR spectrum of compound 13 in $CDCl_3$



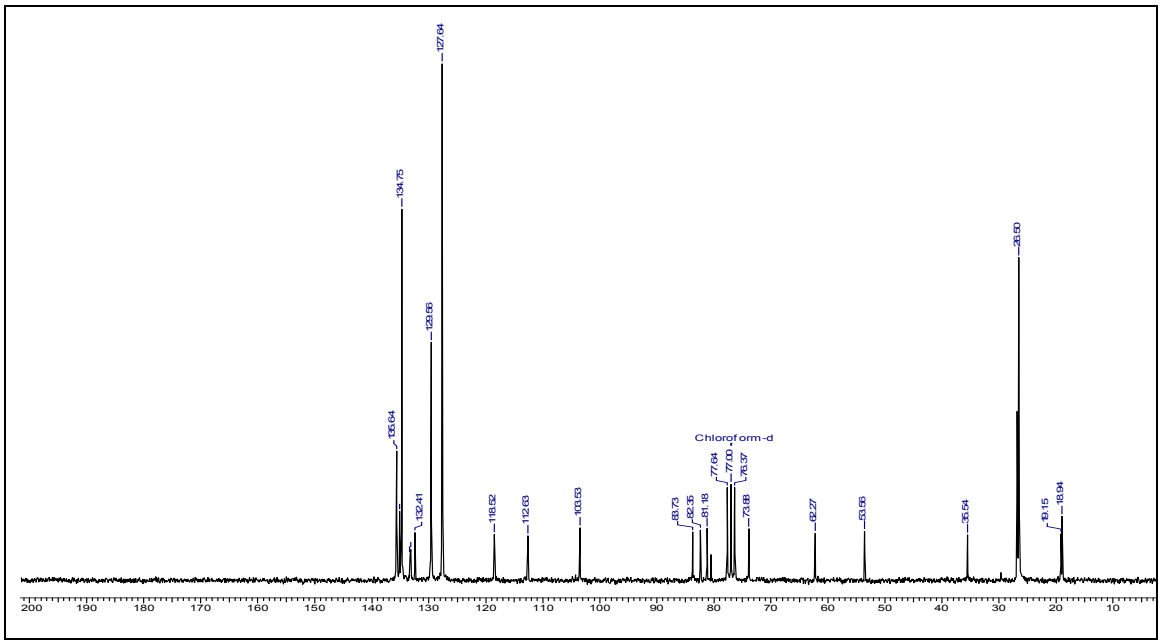
^{1}H NMR spectrum of compound 14 in $CDCl_3$



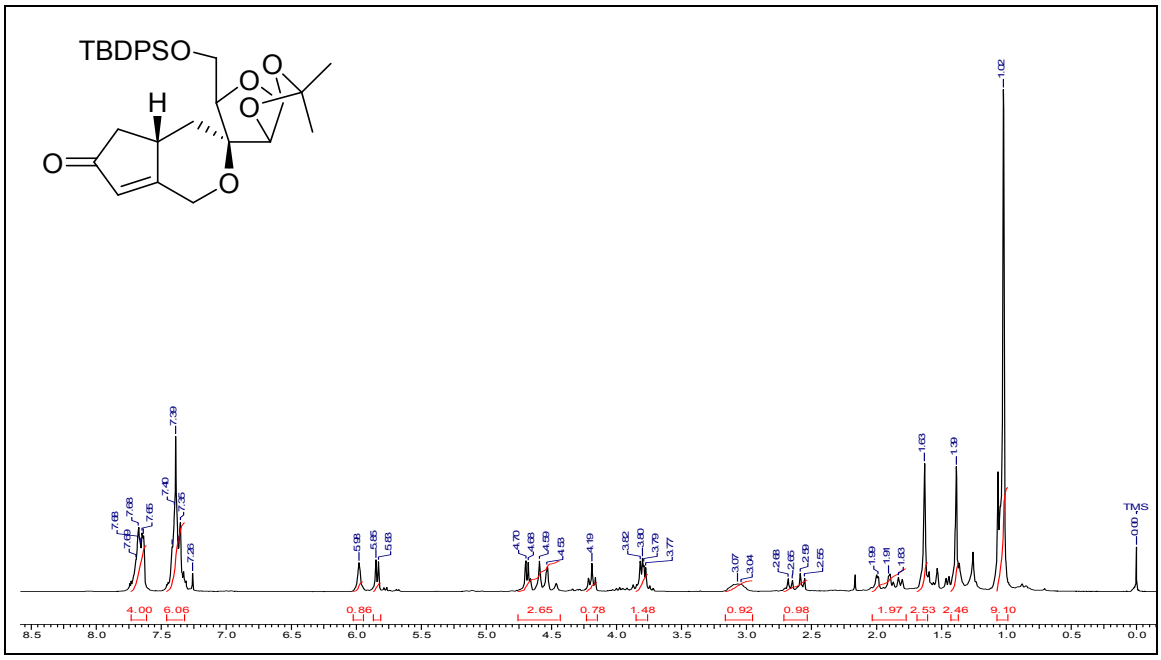
^{13}C NMR spectrum of compound 14 in $CDCl_3$



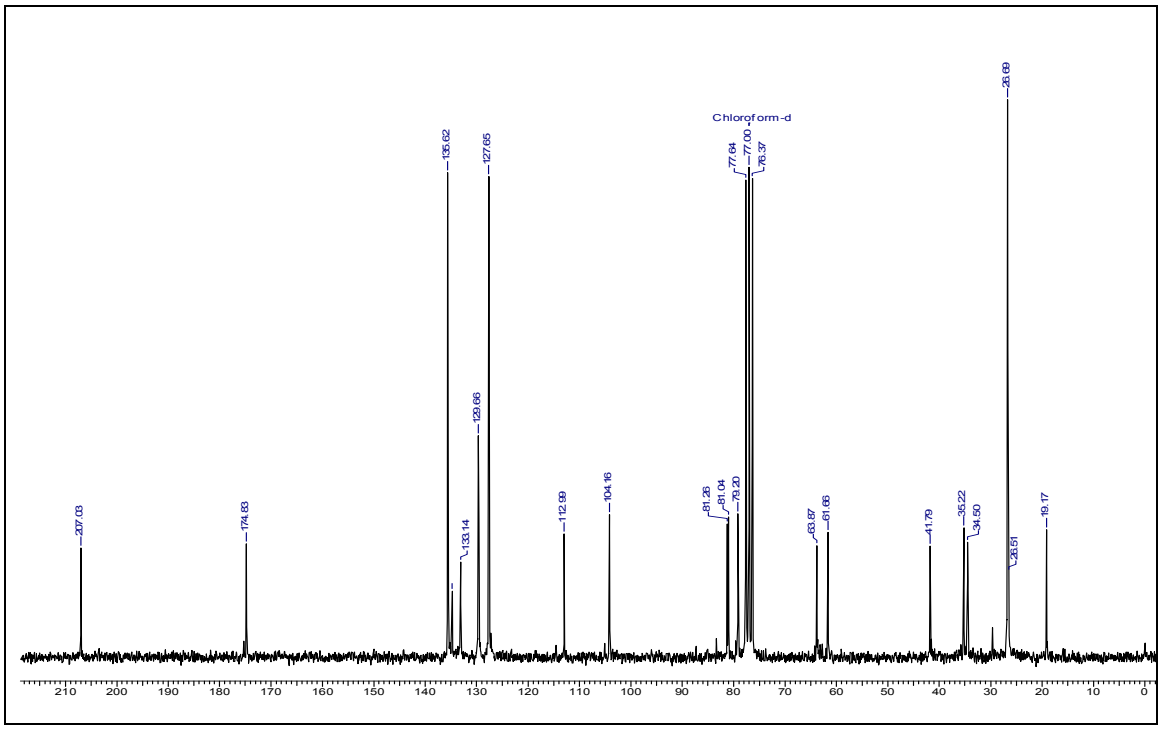
^{1}H NMR spectrum of compound 17 in $CDCl_3$



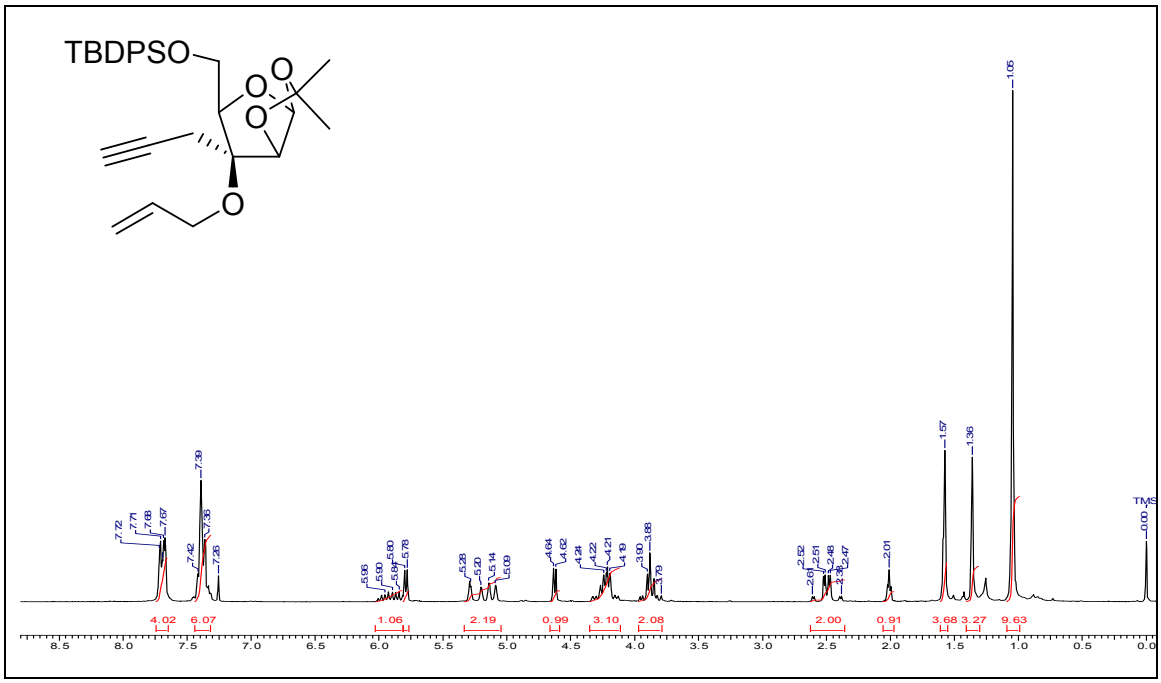
^{13}C NMR spectrum of compound 17 in $CDCl_3$



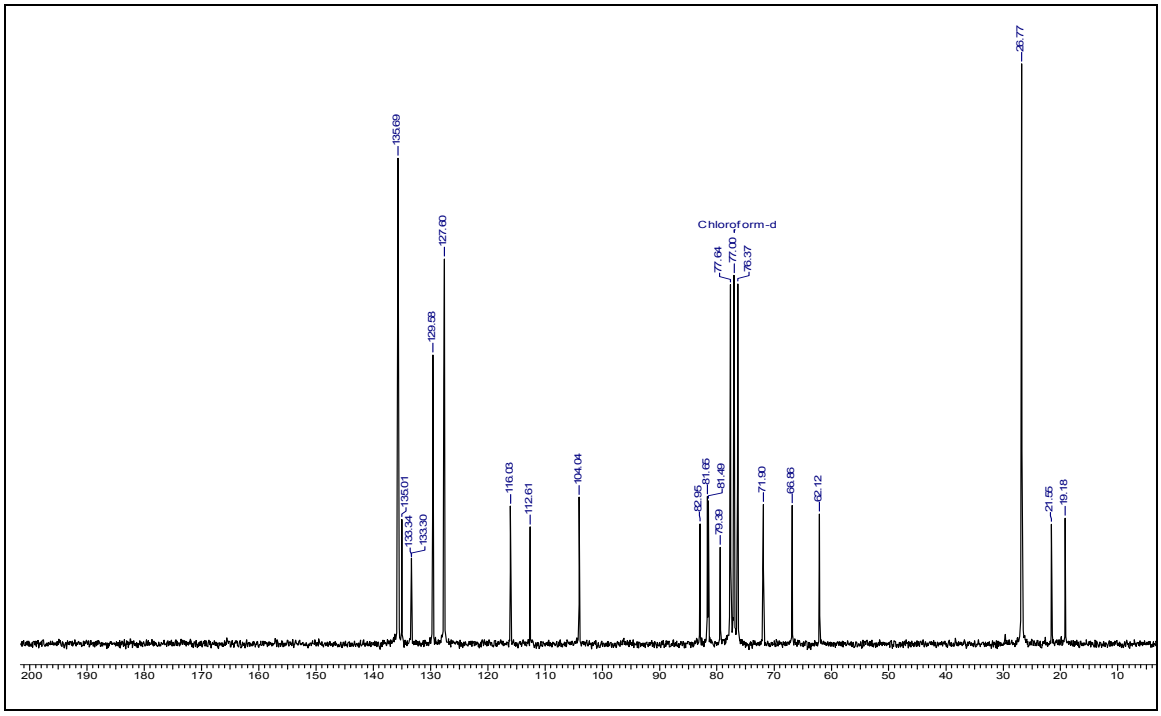
^{1}H NMR spectrum of compound 18 in $CDCl_3$



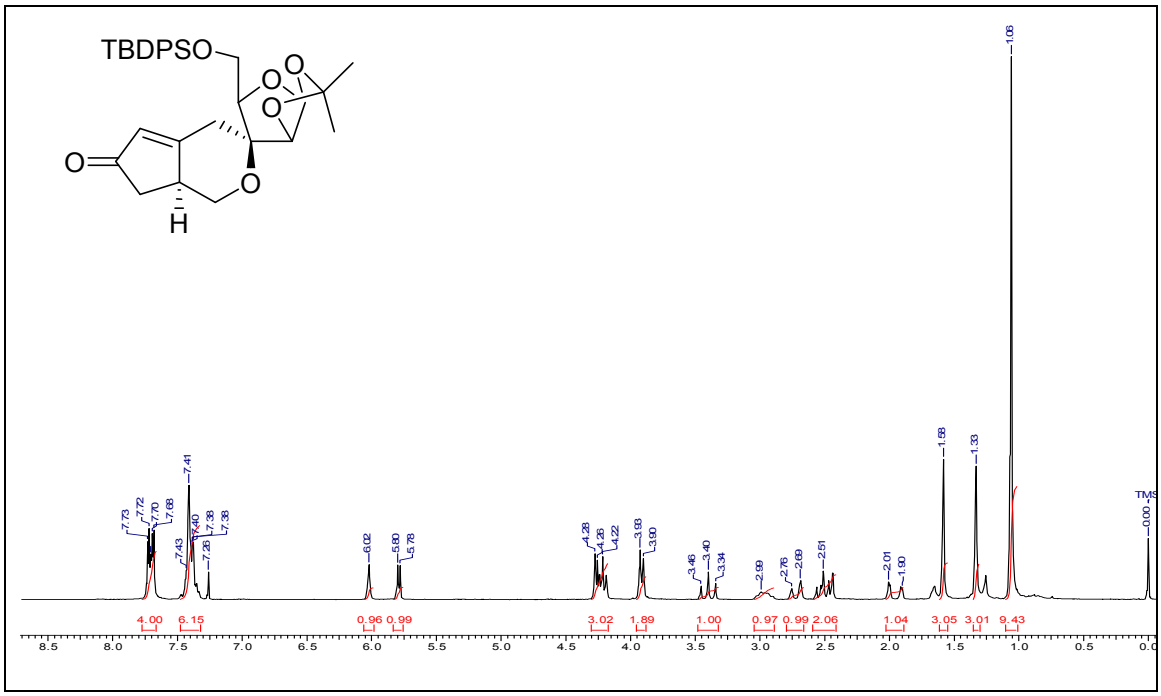
^{13}C NMR spectrum of compound 18 in $CDCl_3$



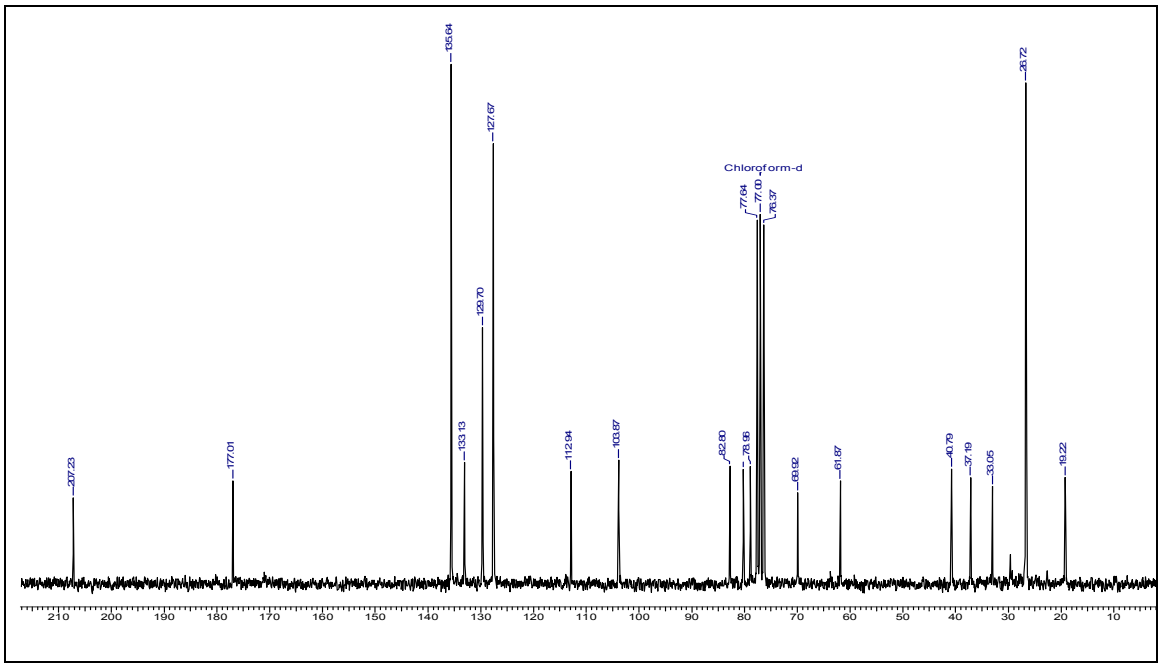
^{1}H NMR spectrum of compound 20 in $CDCl_3$



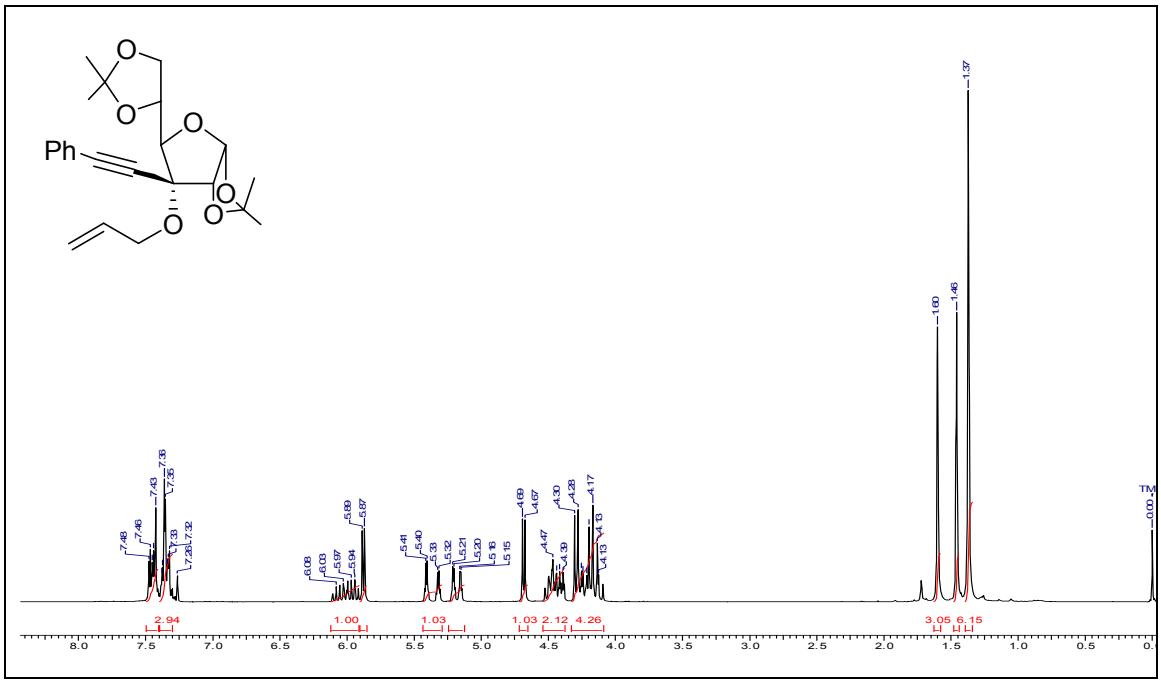
^{13}C NMR spectrum of compound 20 in $CDCl_3$



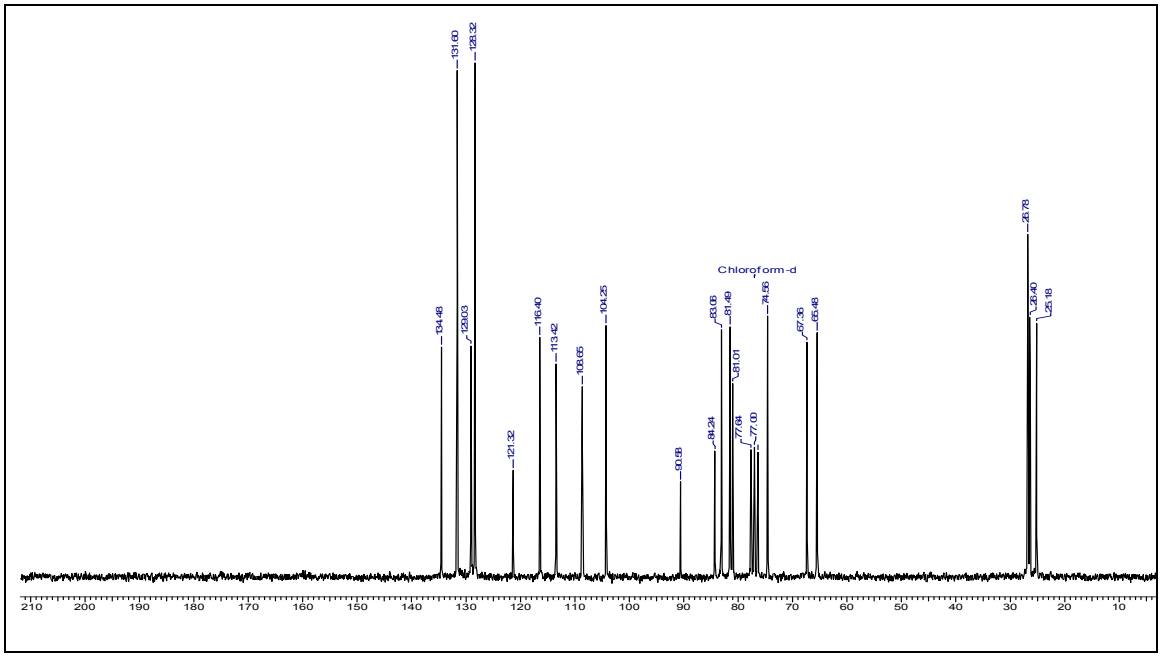
^{1}H NMR spectrum of compound 21 in $CDCl_3$



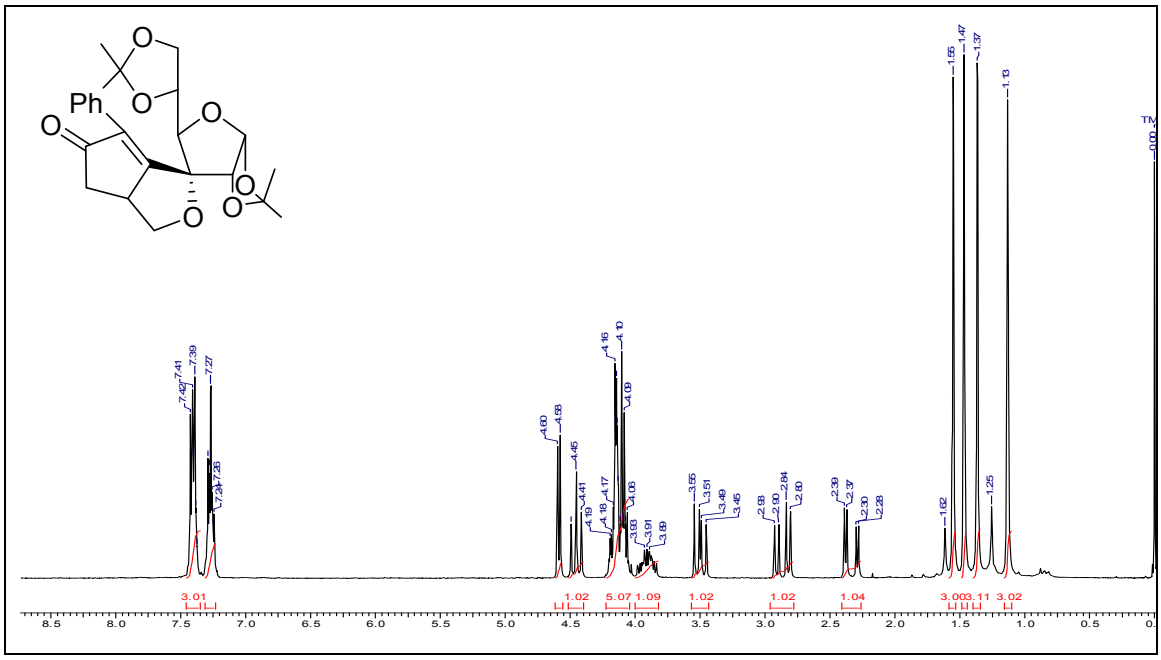
^{13}C NMR spectrum of compound 21 in $CDCl_3$



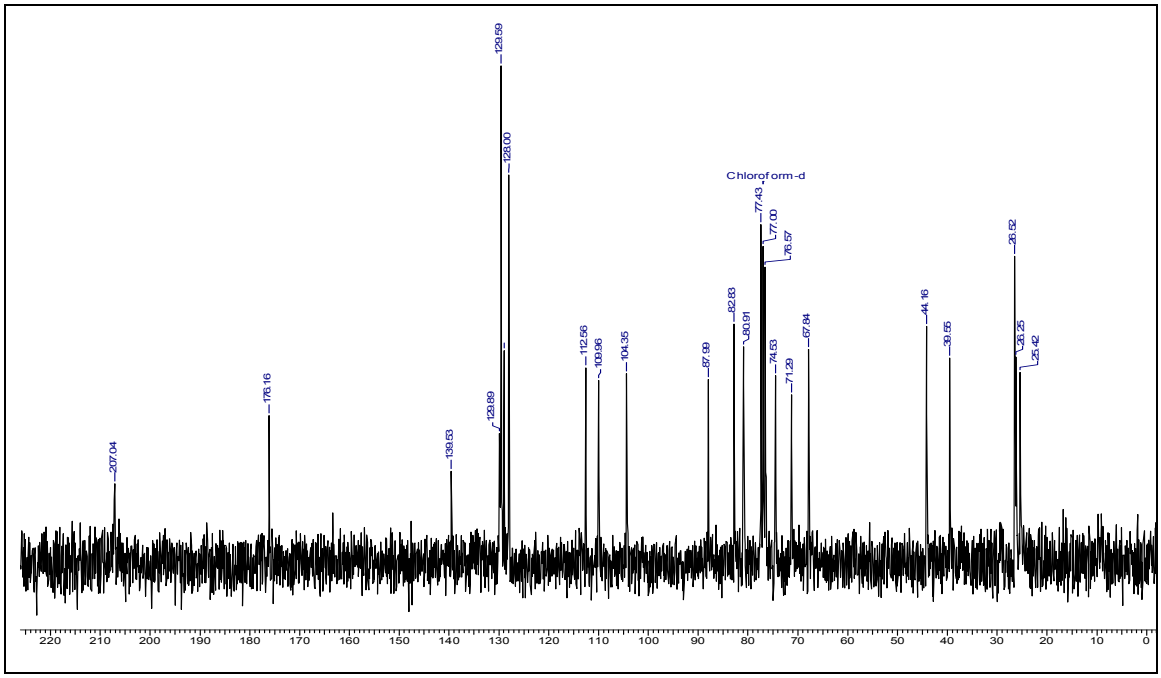
^{1}H NMR spectrum of compound 23 in $CDCl_3$



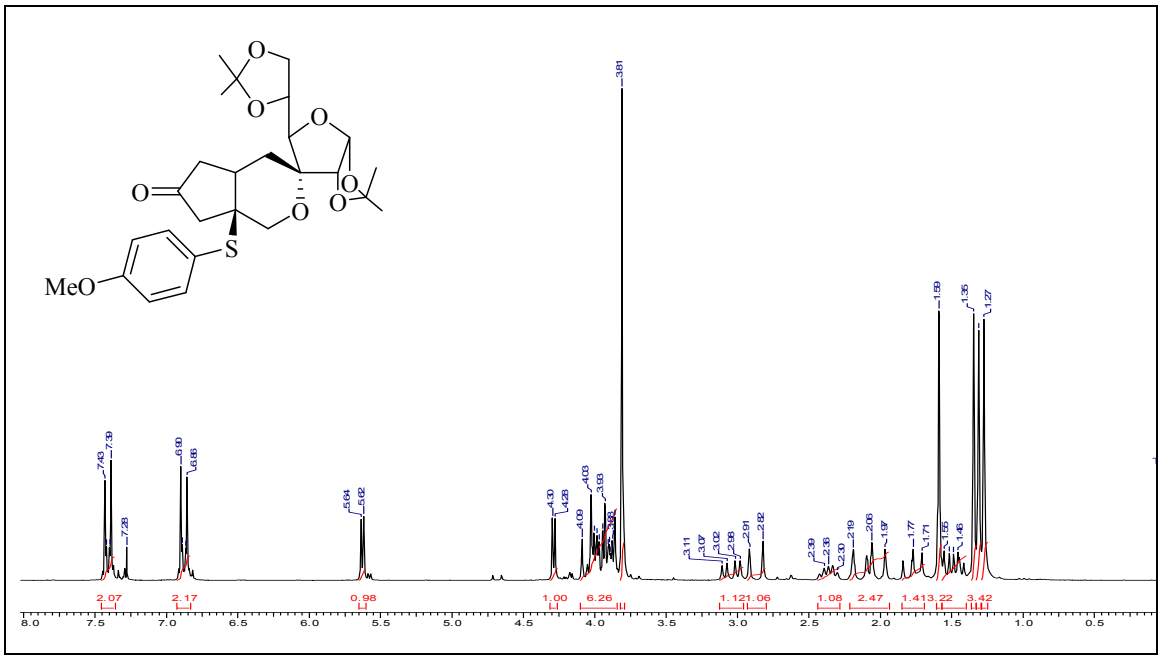
^{13}C spectrum of compound 23 in $CDCl_3$



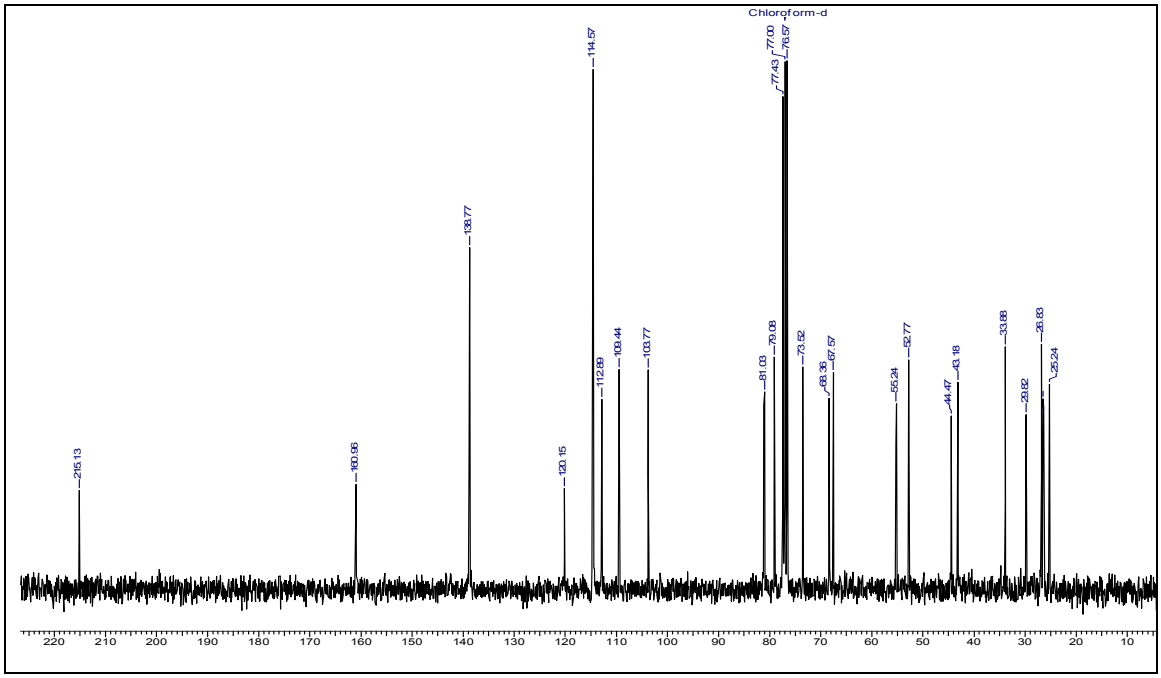
^{1}H NMR spectrum of compound 24 in $CDCl_3$



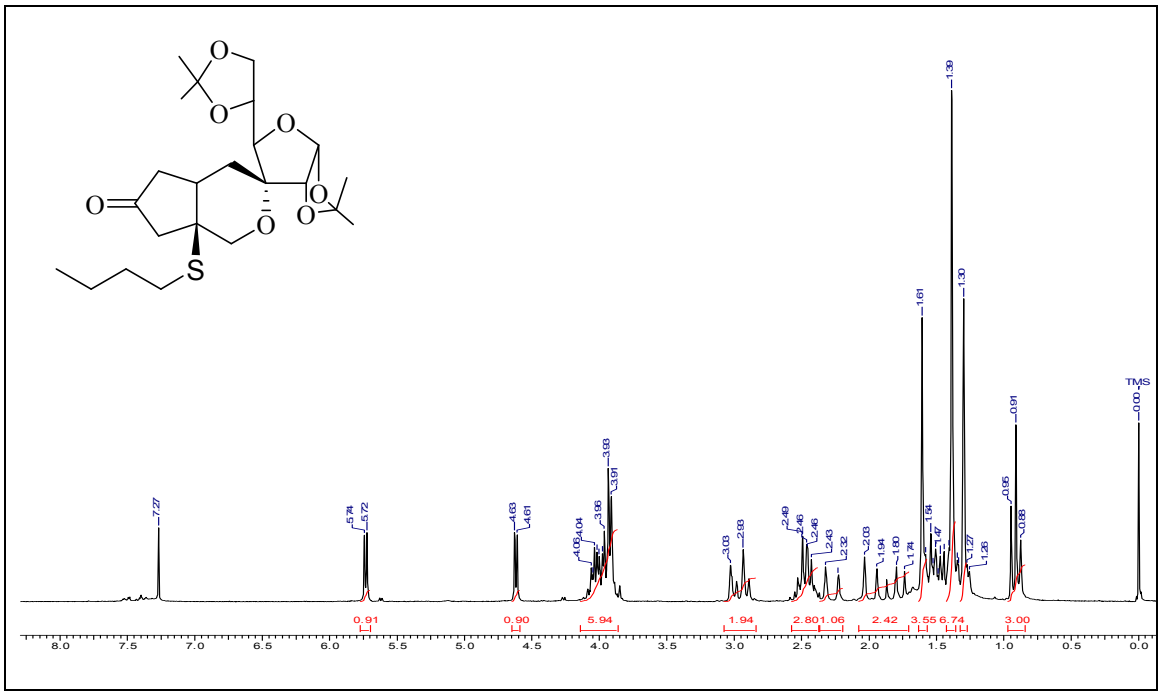
^{13}C NMR spectrum of compound 24 in $CDCl_3$



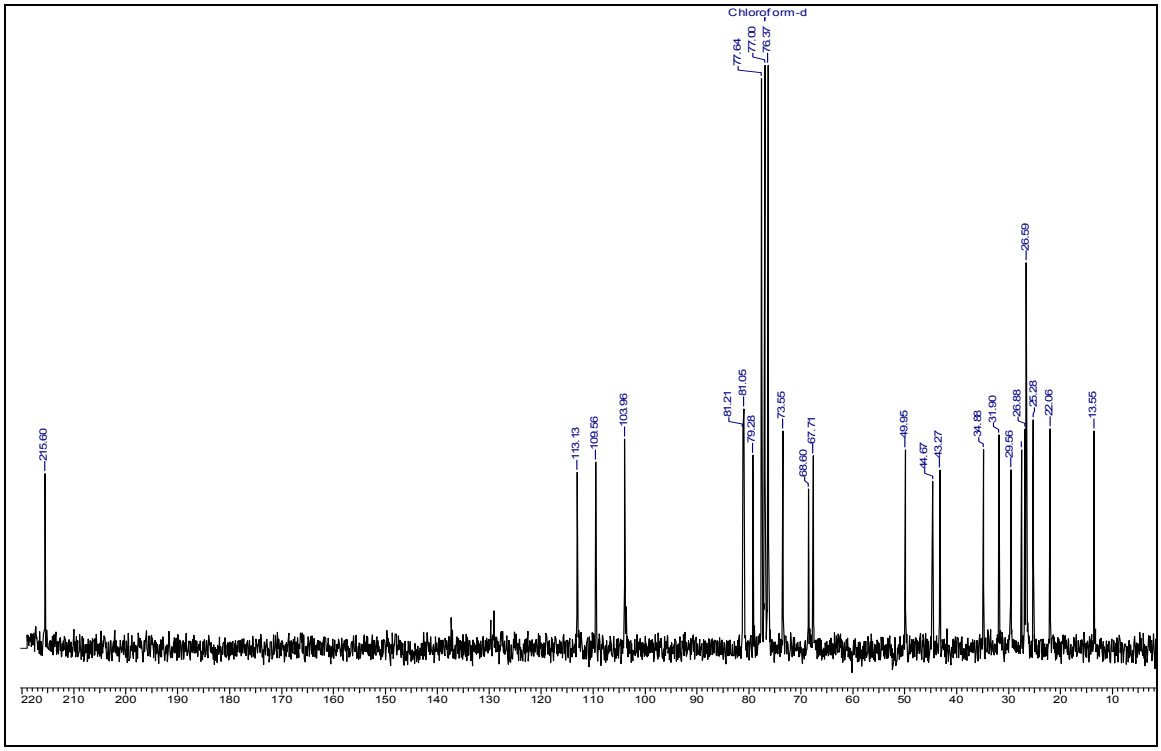
^{1}H NMR spectrum of compound 25 in $CDCl_3$



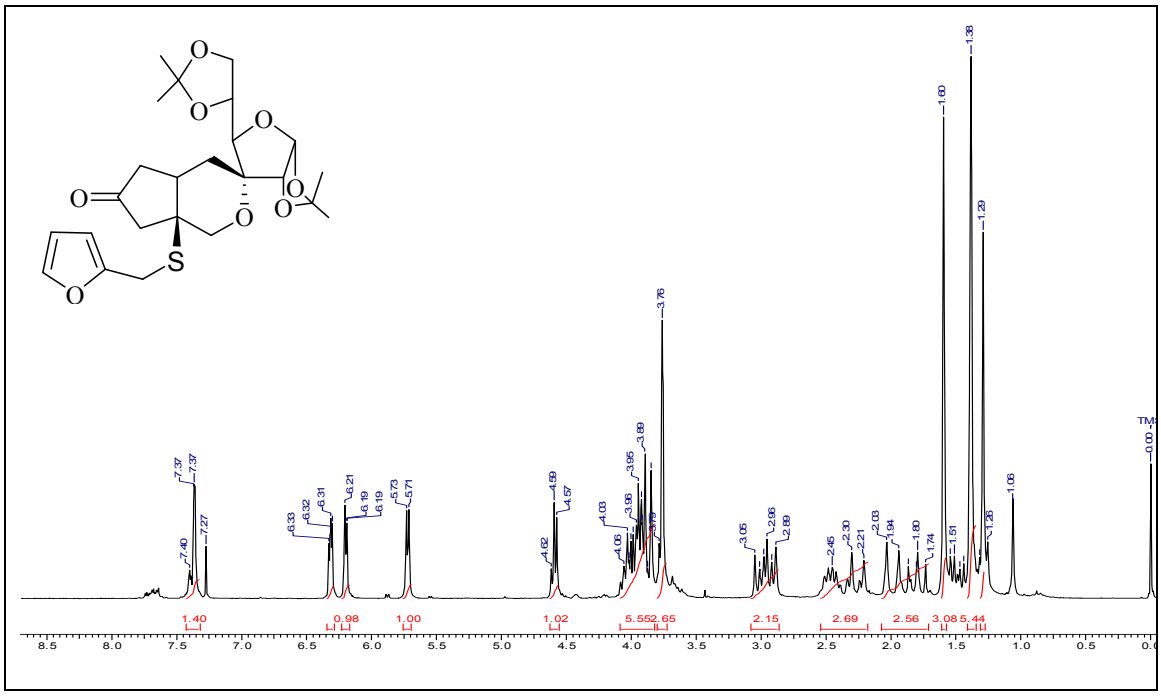
^{13}C NMR spectrum of compound 25 in $CDCl_3$



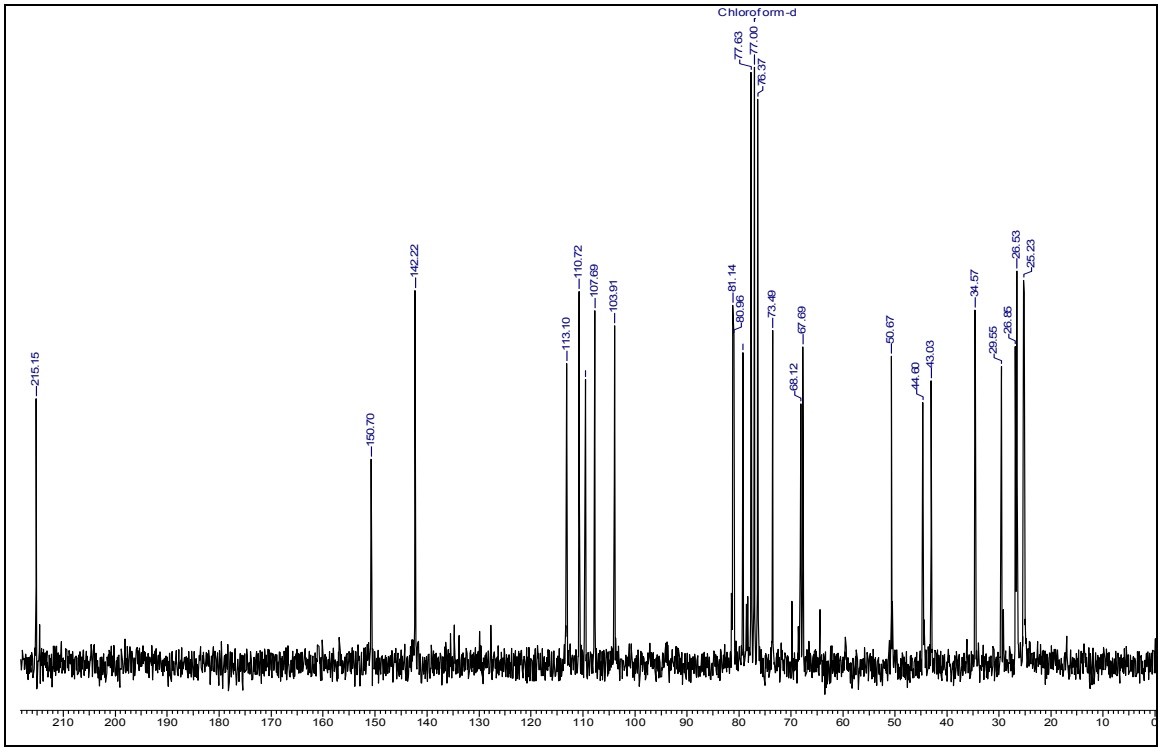
^{1}H NMR spectrum of compound 26 in $CDCl_3$



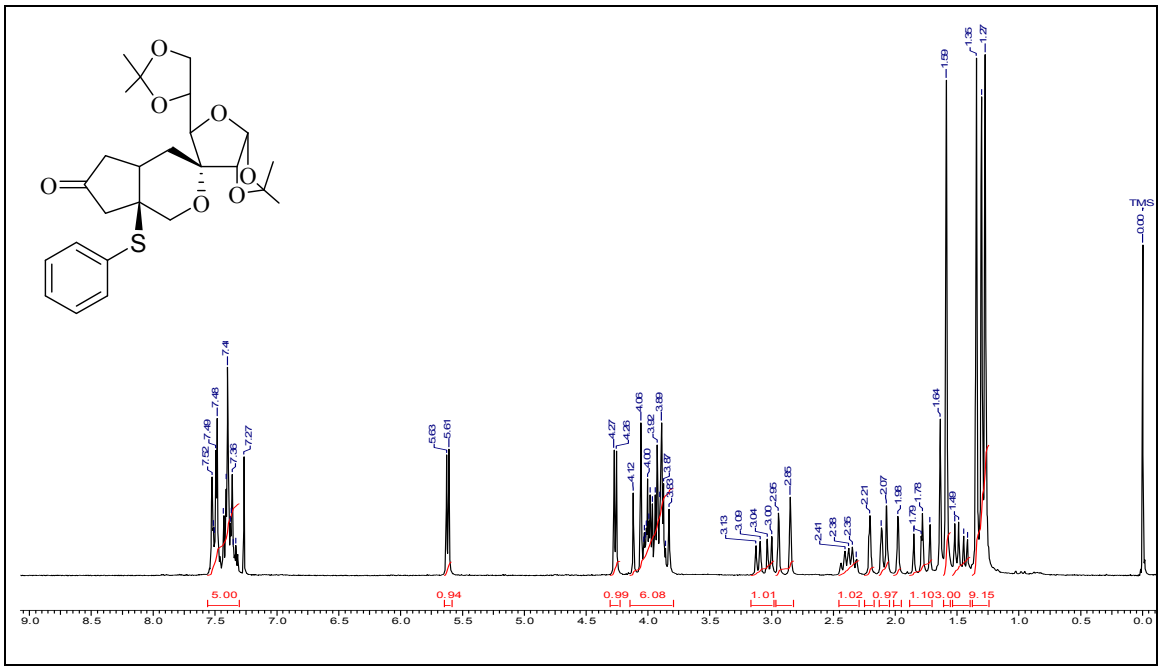
^{13}C NMR spectrum of compound 26 in $CDCl_3$



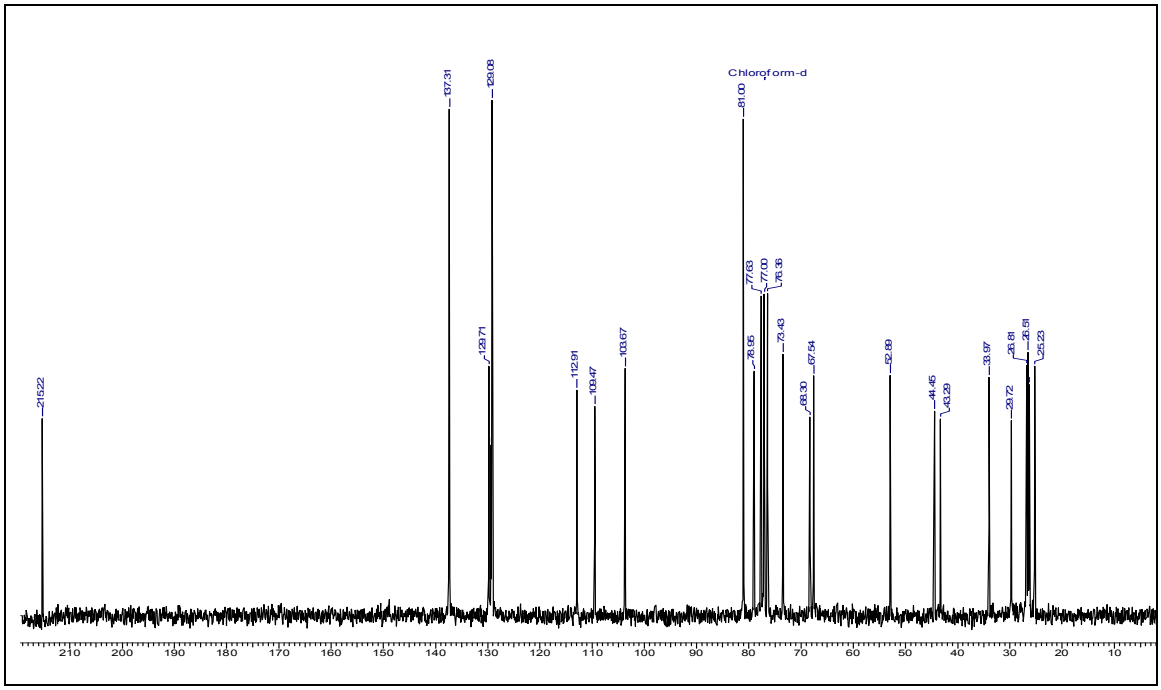
^{1}H NMR spectrum of compound 27 in $CDCl_3$



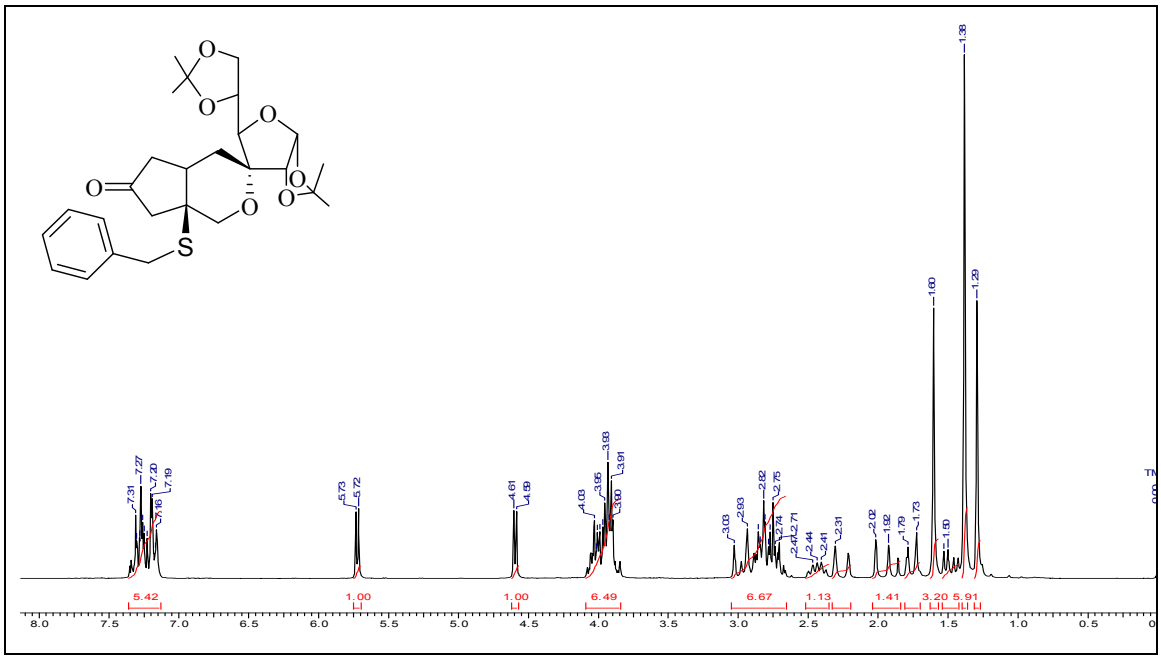
^{13}C NMR spectrum of compound 27 in $CDCl_3$



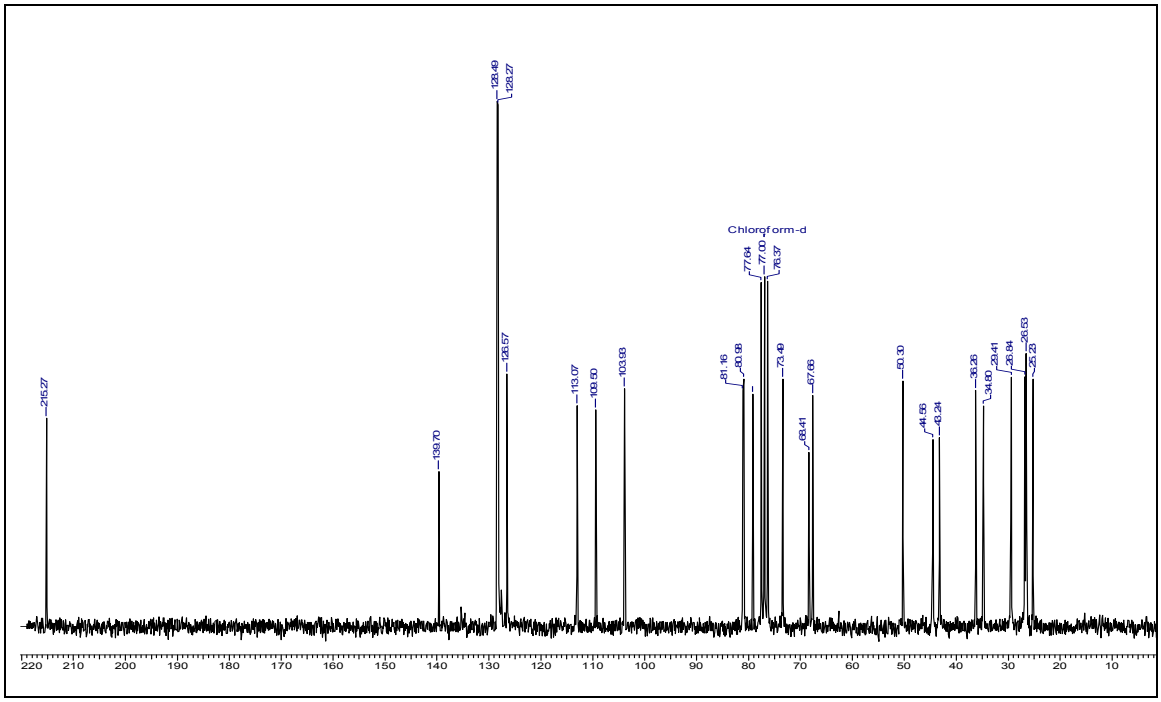
^{1}H NMR spectrum of compound 28 in $CDCl_3$



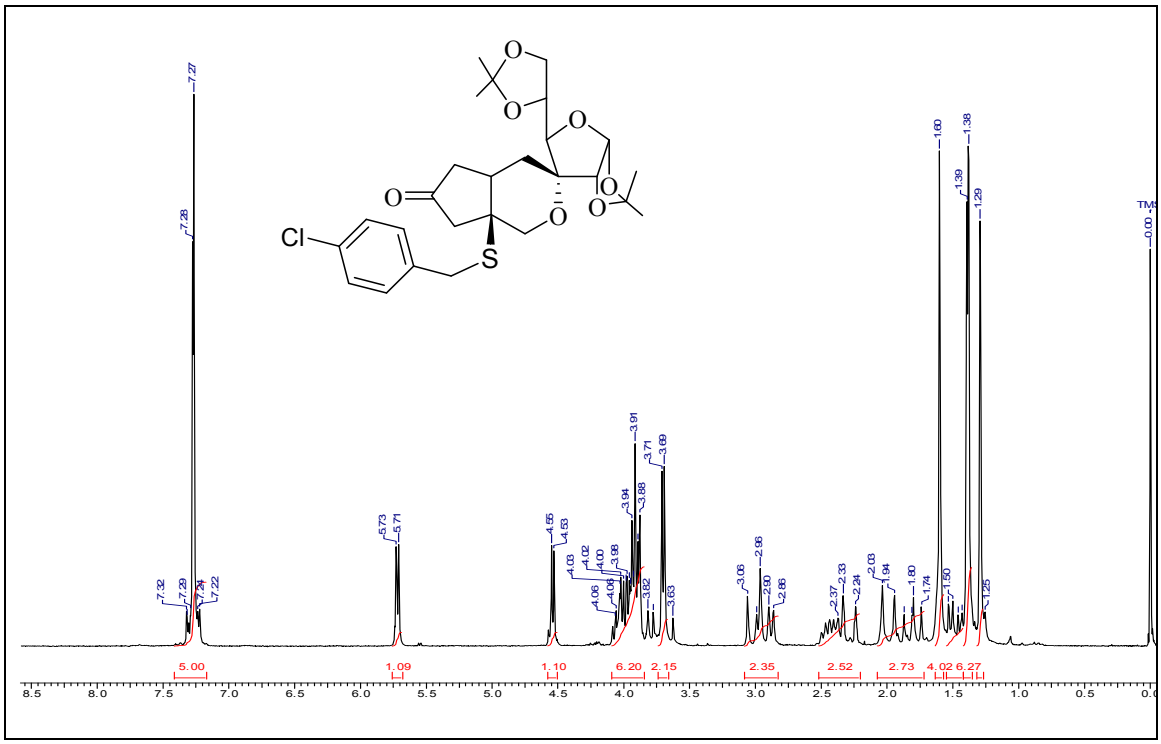
^{13}C NMR spectrum of compound 28 in $CDCl_3$



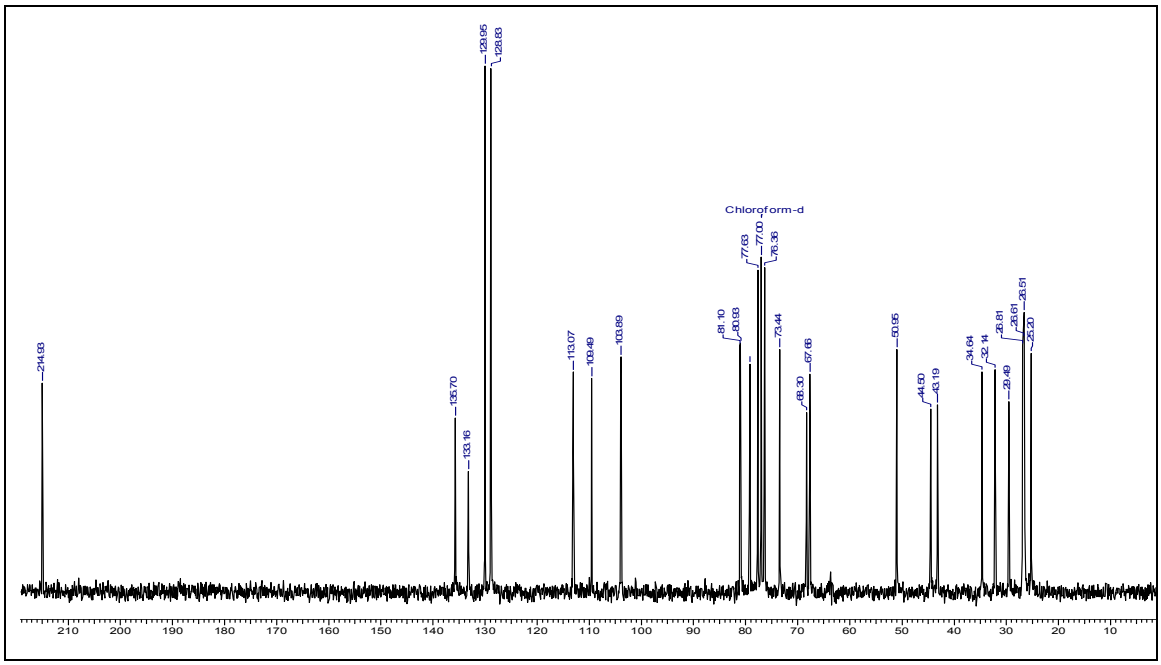
^{1}H NMR spectrum of compound 29 in $CDCl_3$



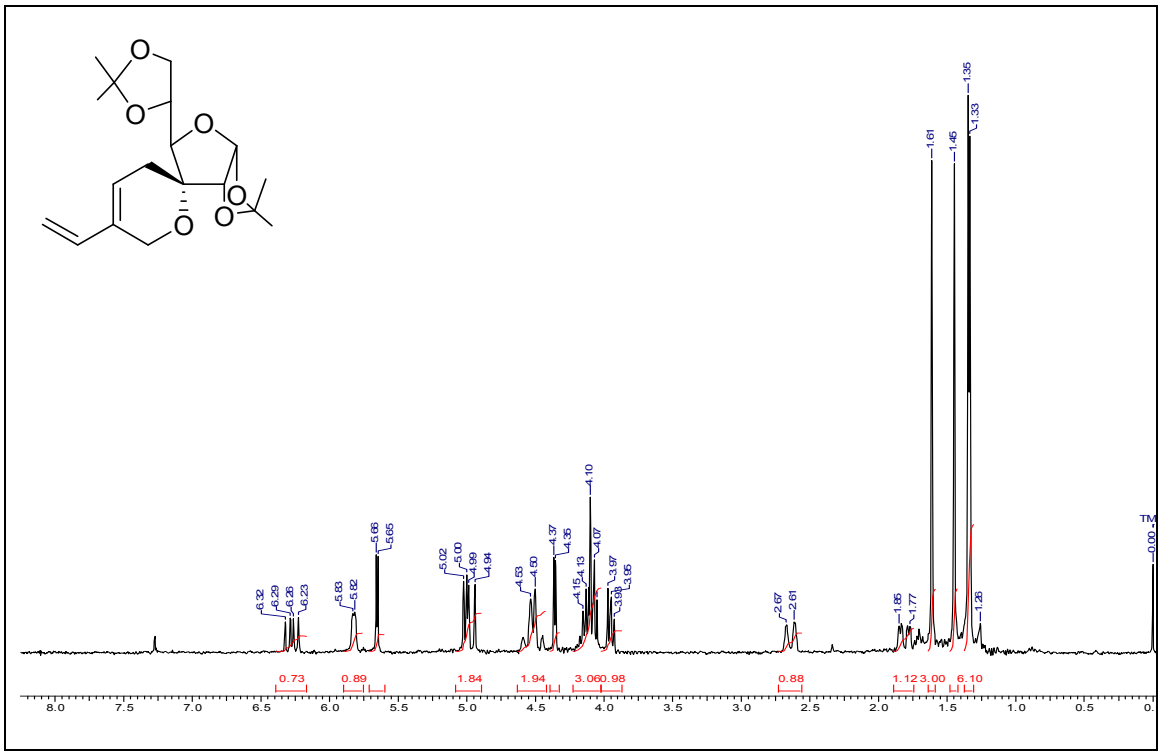
^{13}C NMR spectrum of compound 29 in $CDCl_3$



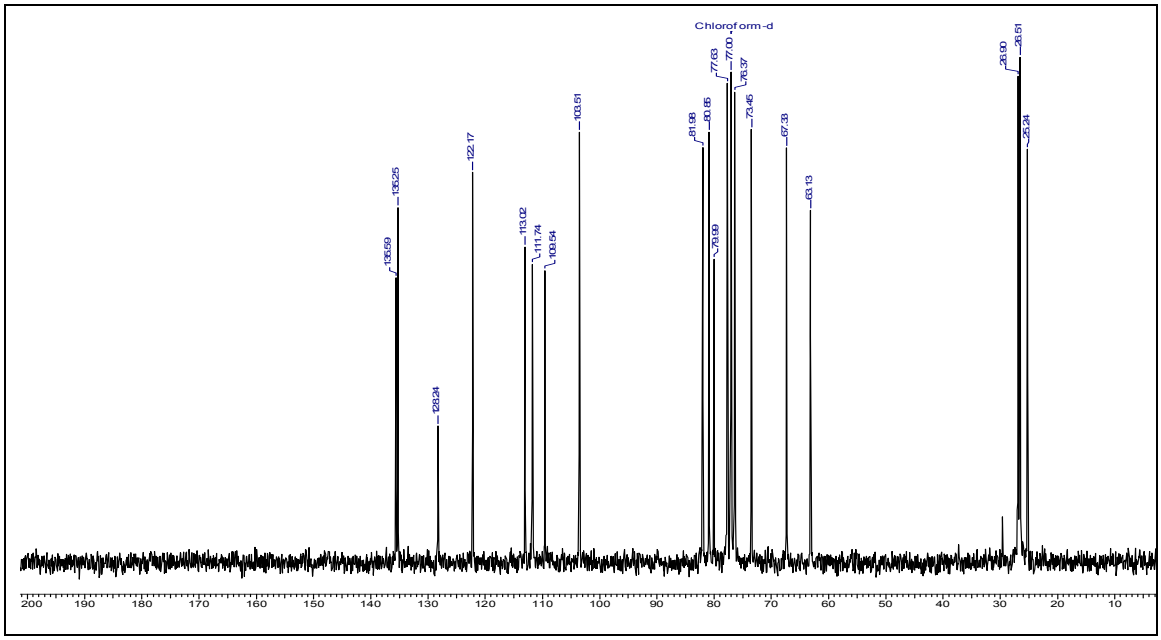
^{1}H NMR spectrum of compound 30 in $CDCl_3$



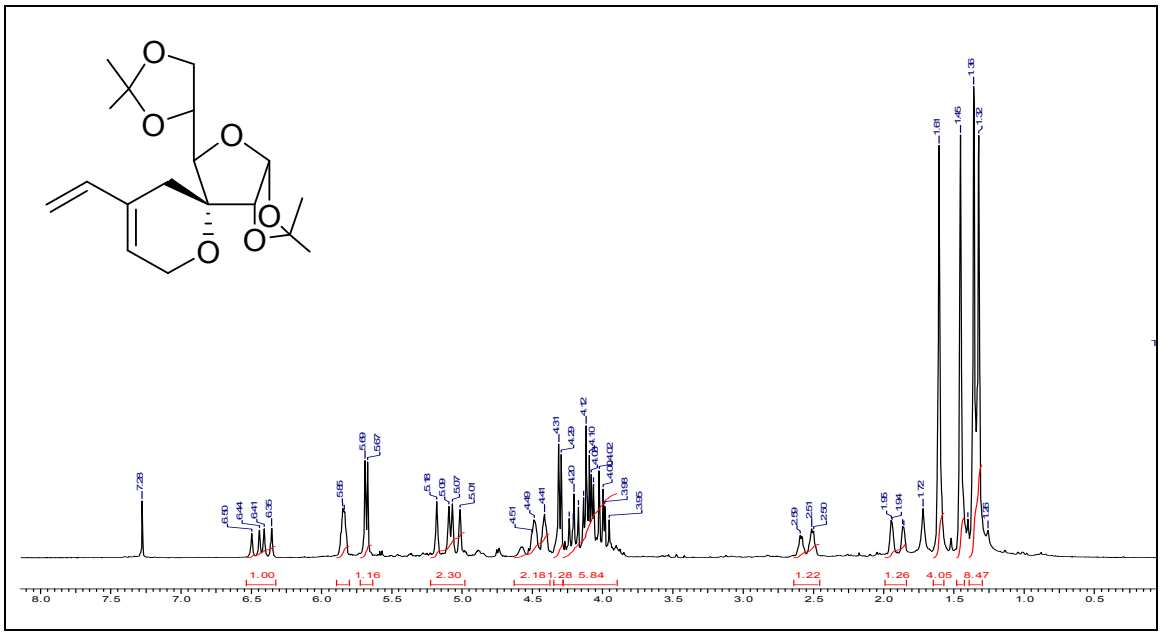
^{13}C NMR spectrum of compound 30 in $CDCl_3$



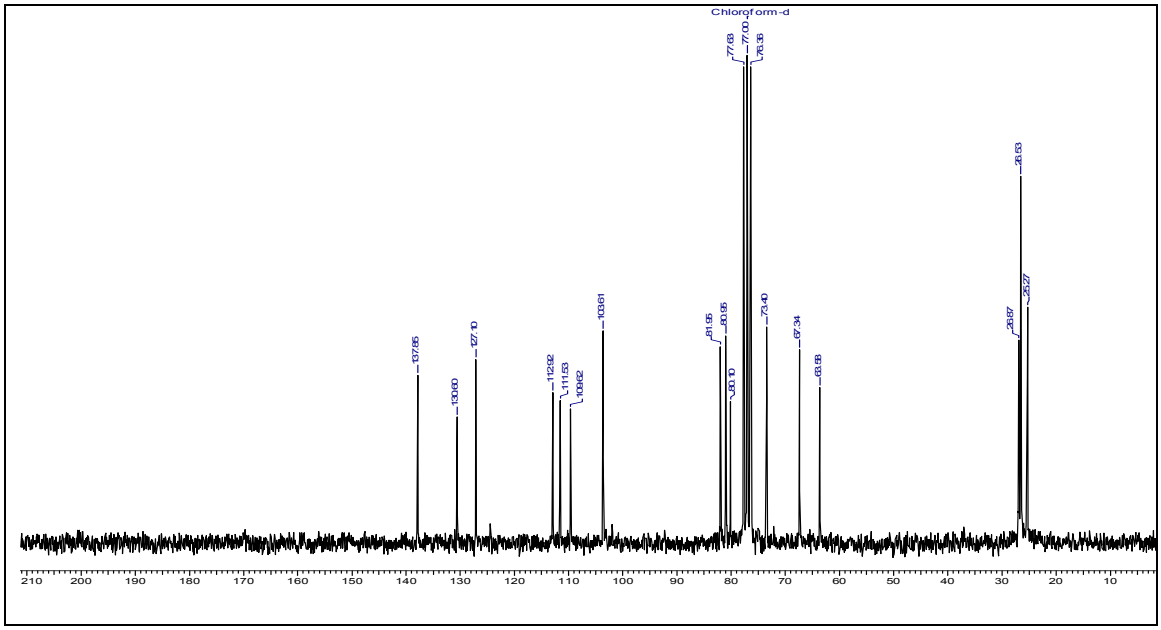
^{1}H NMR spectrum of compound 31 in $CDCl_3$



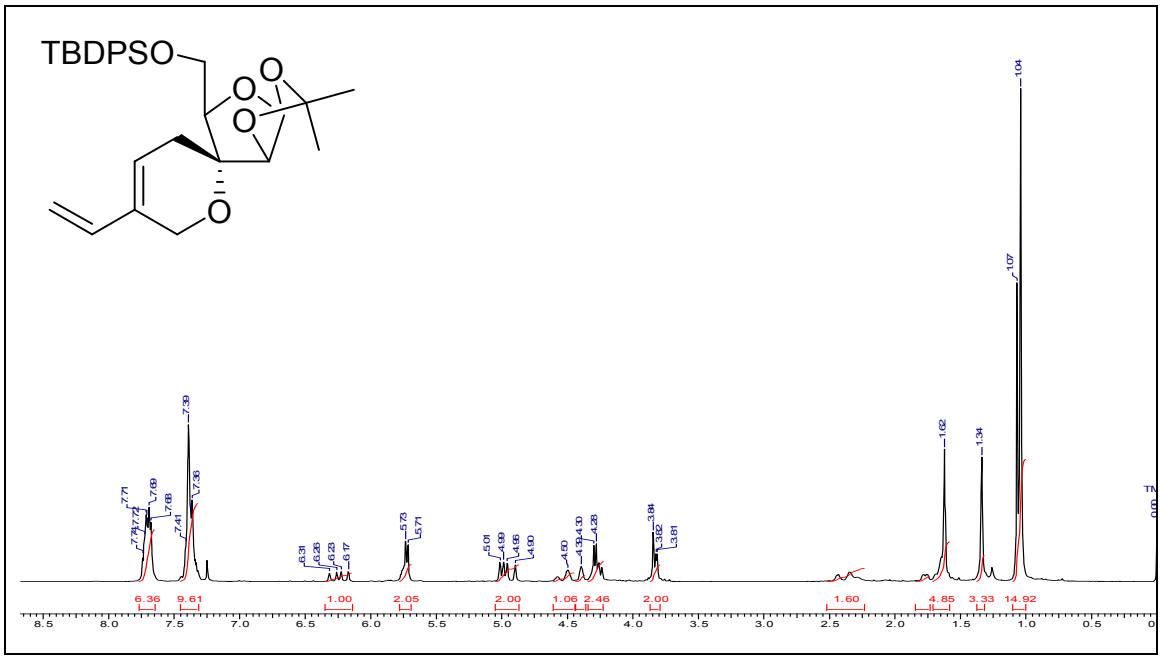
^{13}C NMR spectrum of compound 31 in $CDCl_3$



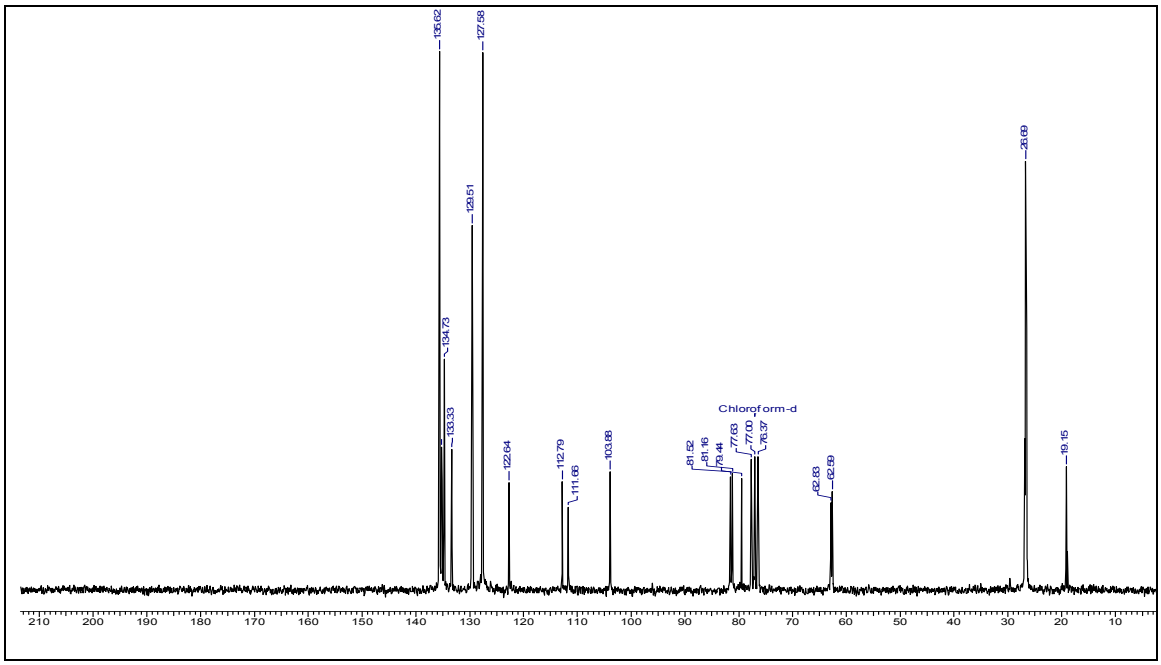
^{1}H NMR spectrum of compound 32 in $CDCl_3$



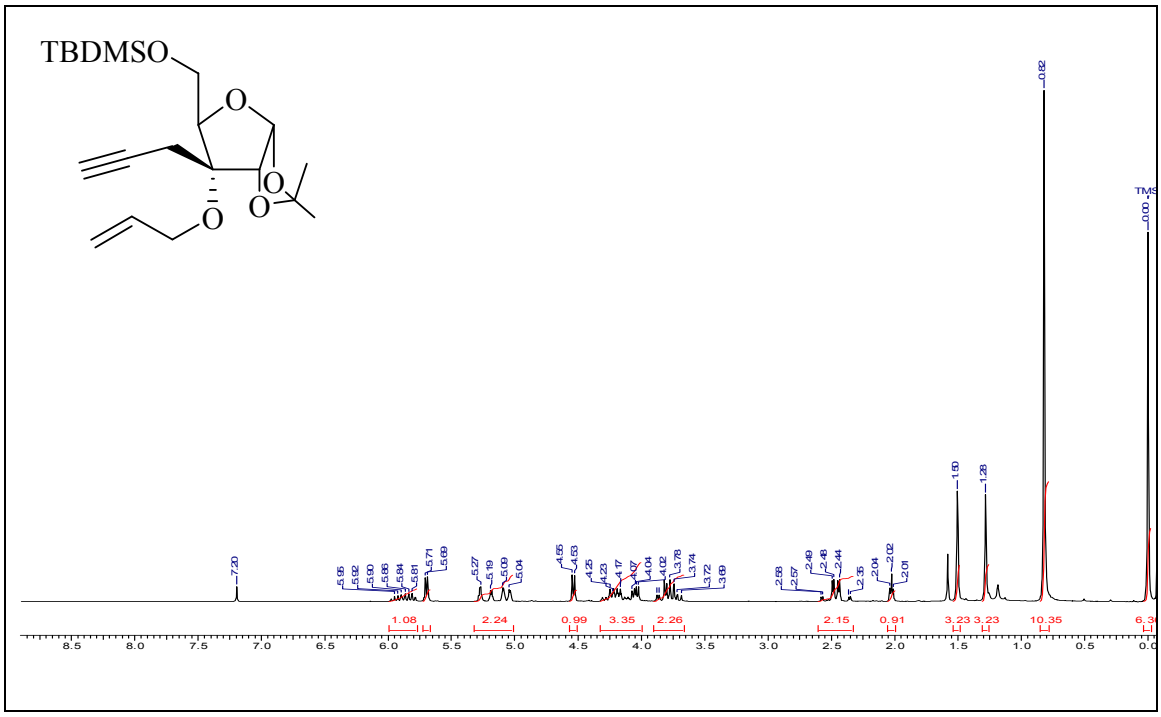
^{13}C NMR spectrum of compound 32 in $CDCl_3$



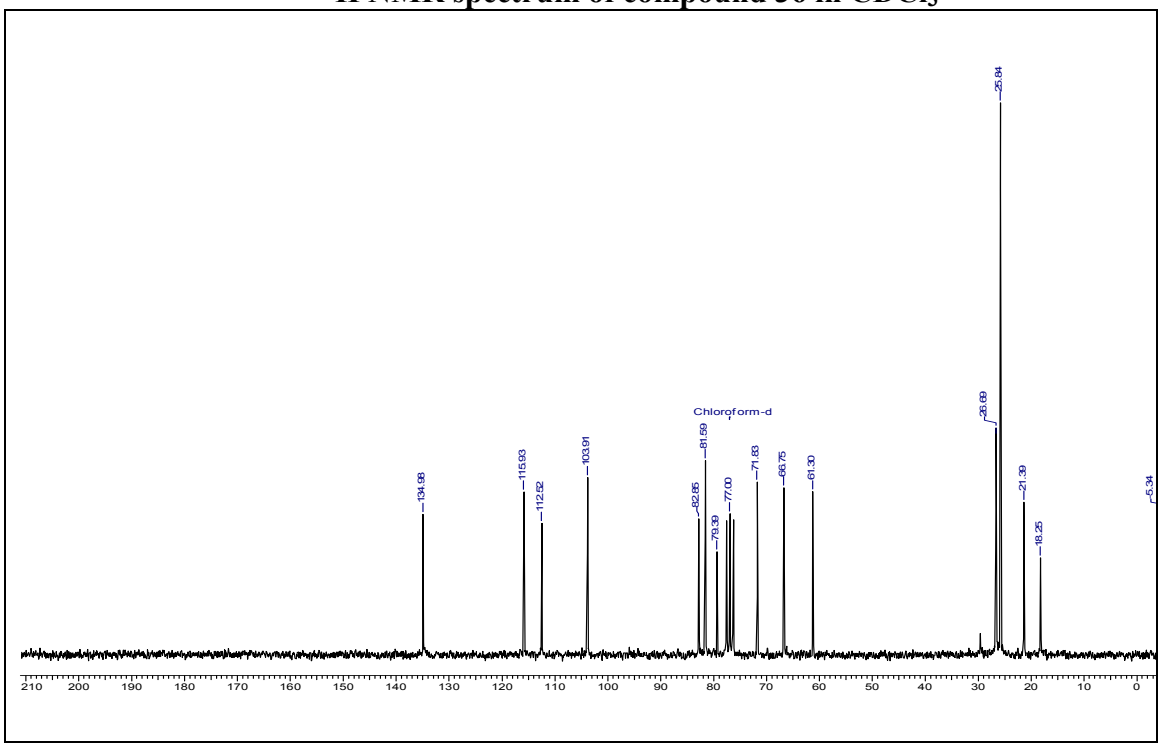
^{1}H NMR spectrum of compound 33 in $CDCl_3$



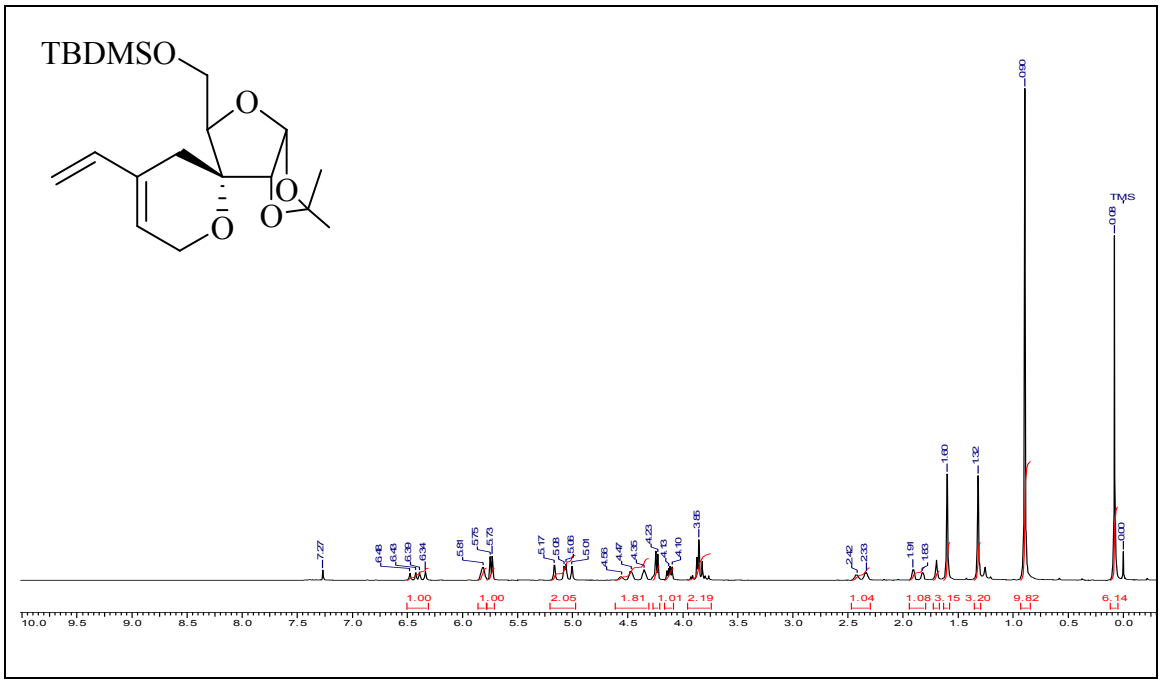
^{13}C NMR spectrum of compound 33 in $CDCl_3$



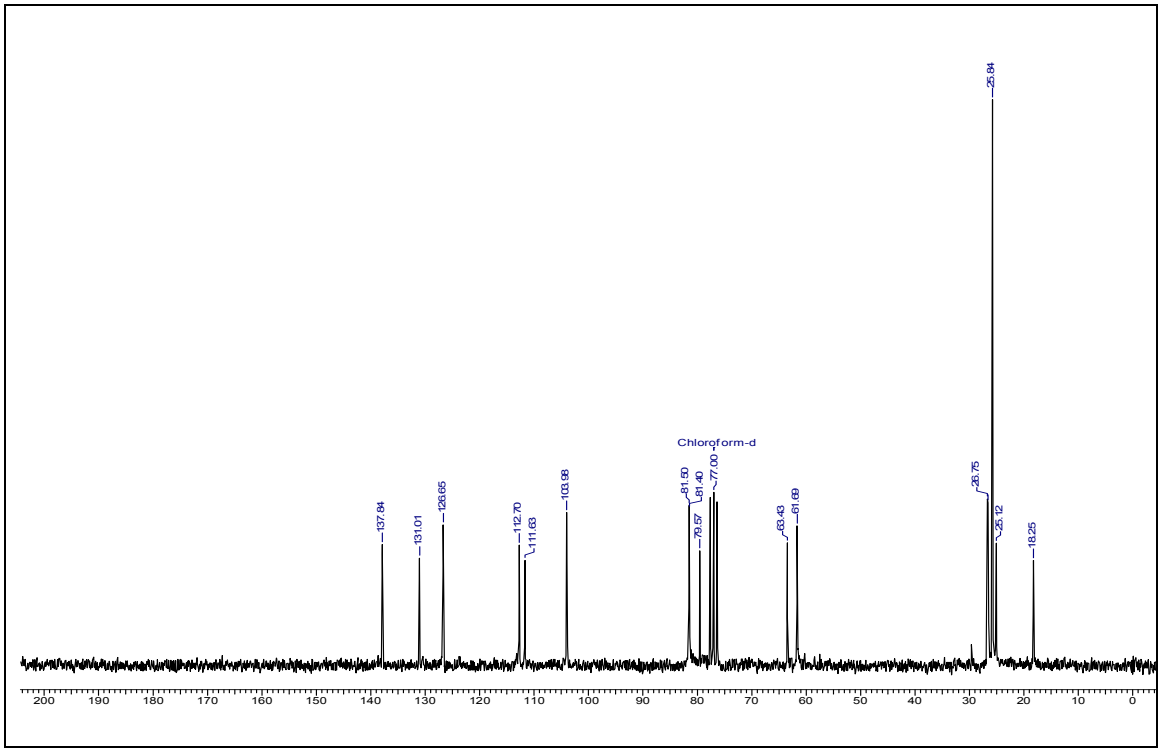
^{1}H NMR spectrum of compound 36 in $CDCl_3$



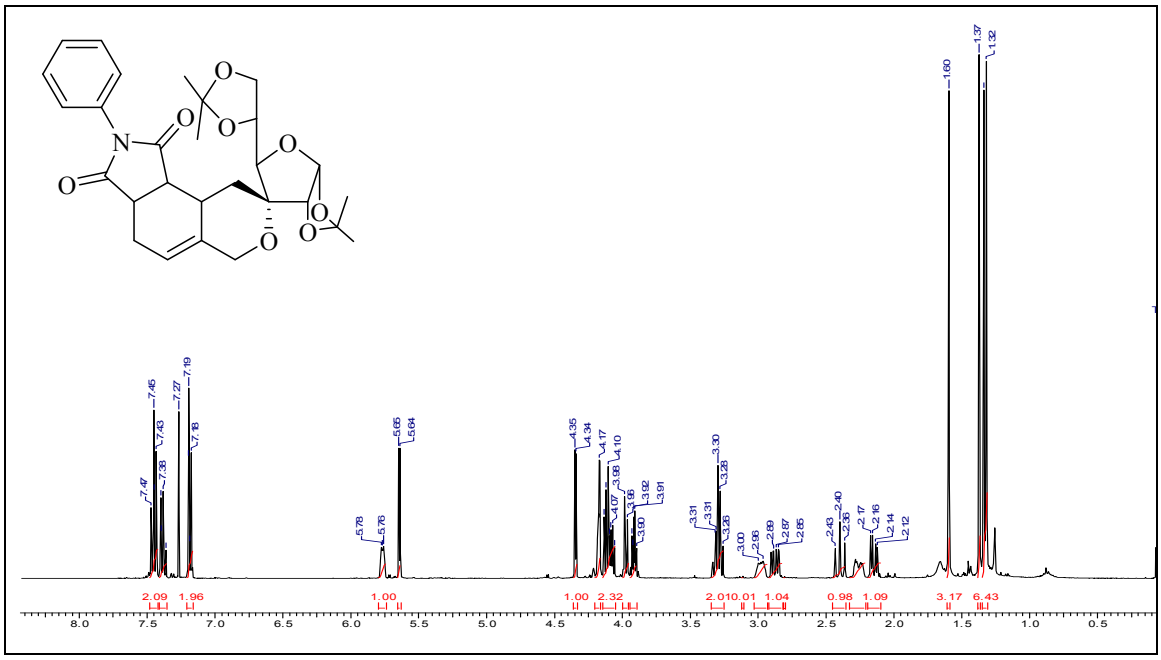
^{13}C NMR spectrum of compound 36 in $CDCl_3$



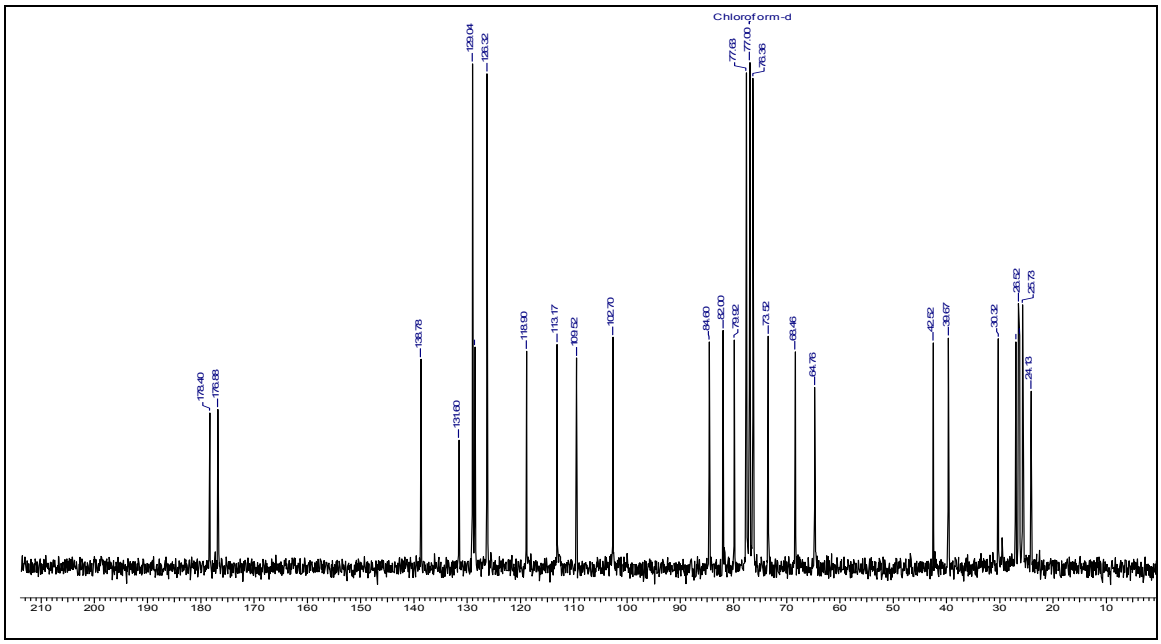
^{1}H NMR spectrum of compound 37 in $CDCl_3$



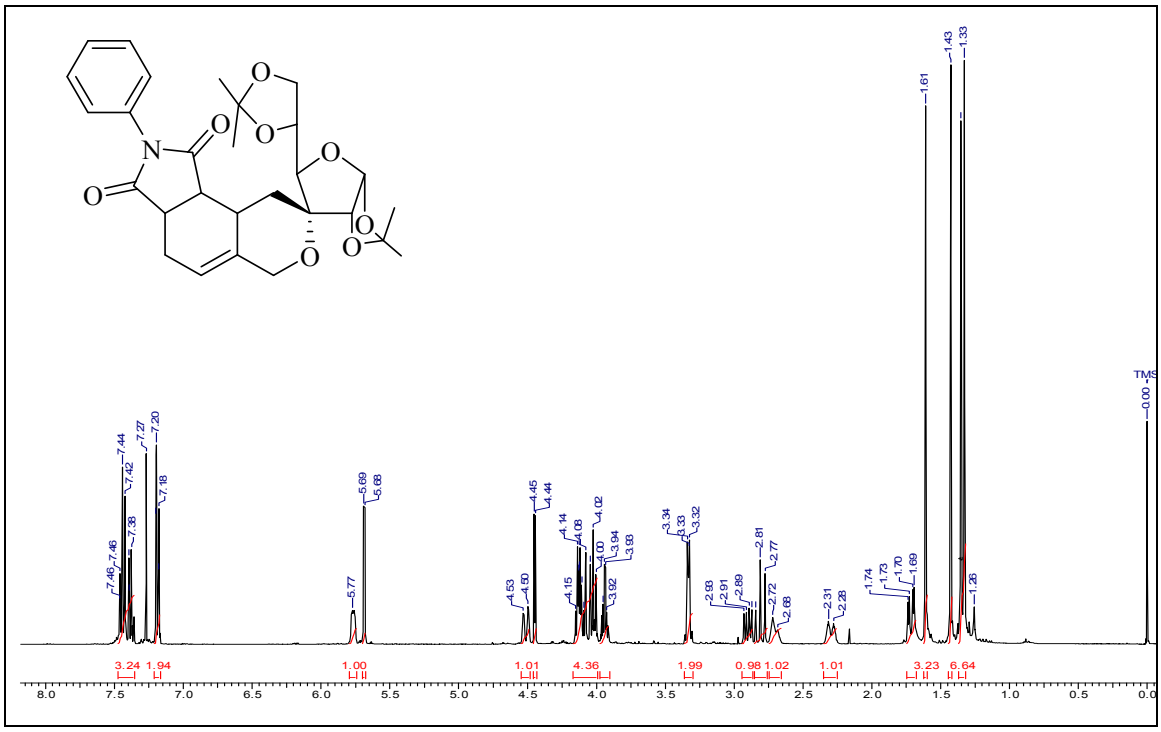
^{13}C NMR spectrum of compound 37 in $CDCl_3$



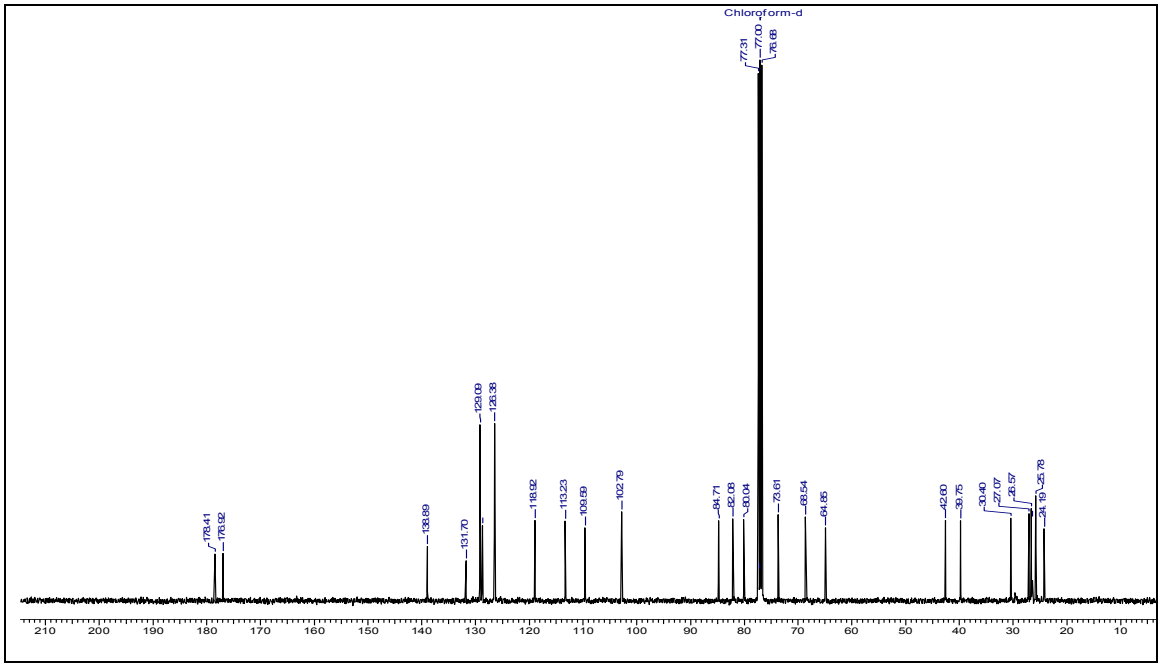
^{1}H NMR spectrum of compound 38 A in $CDCl_3$



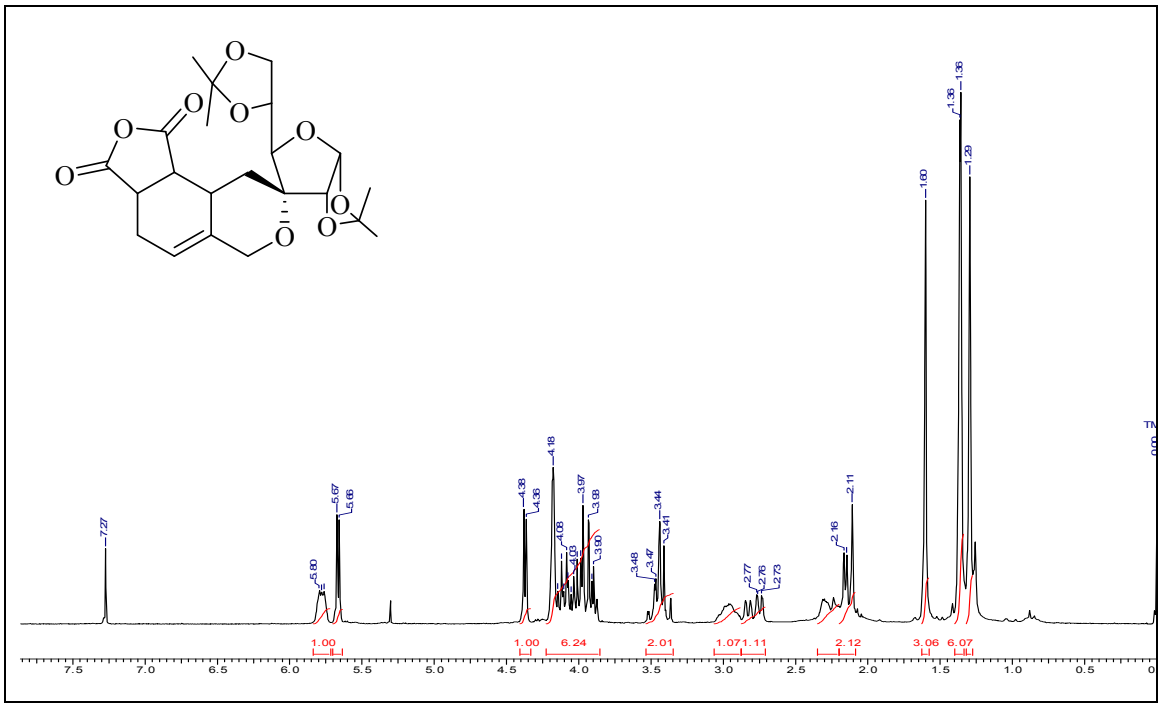
^{13}C NMR spectrum of compound 38 A in $CDCl_3$



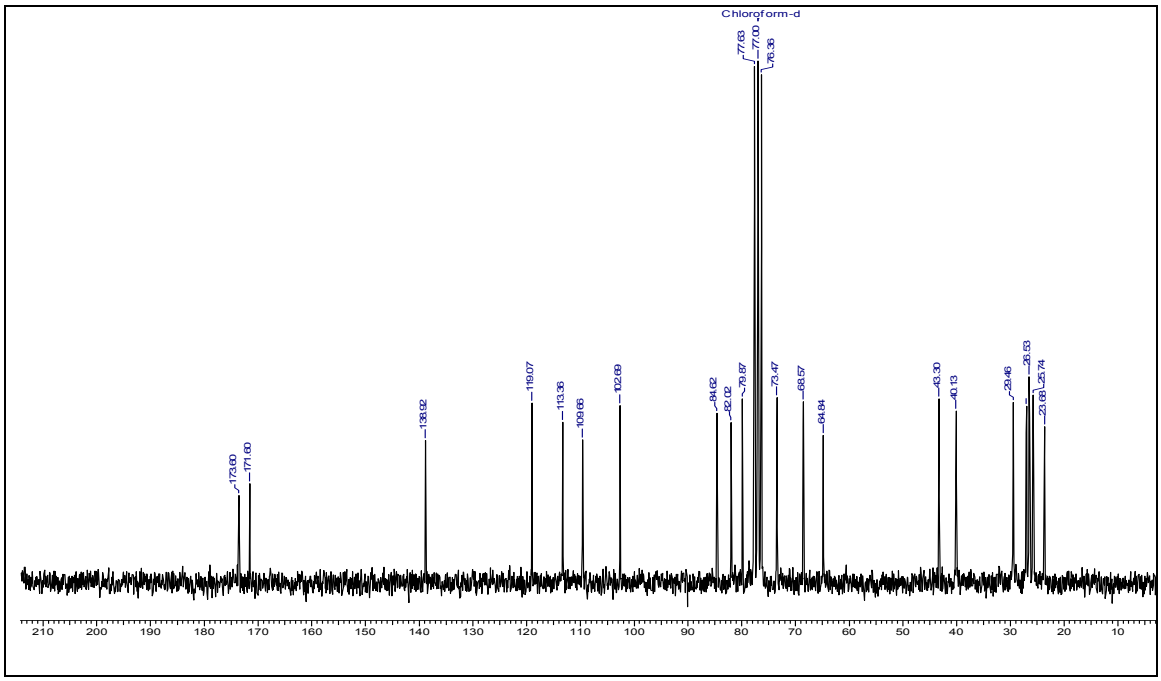
^{1}H NMR spectrum of compound 38 B in $CDCl_3$



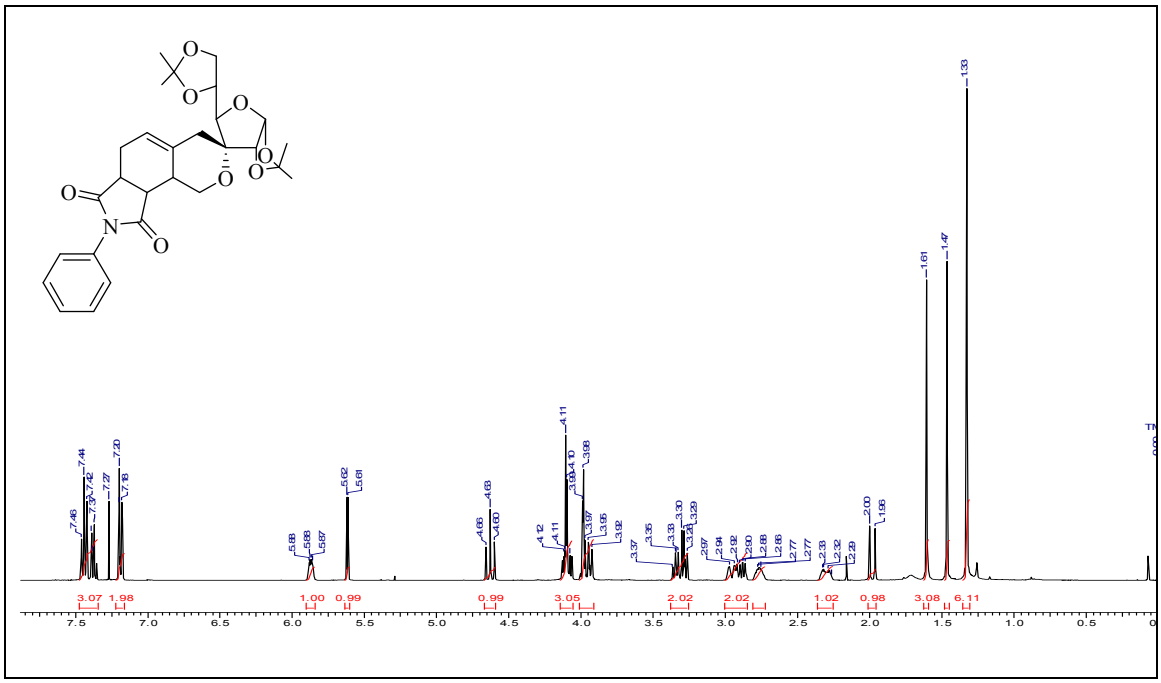
^{13}C NMR spectrum of compound 38 B in $CDCl_3$



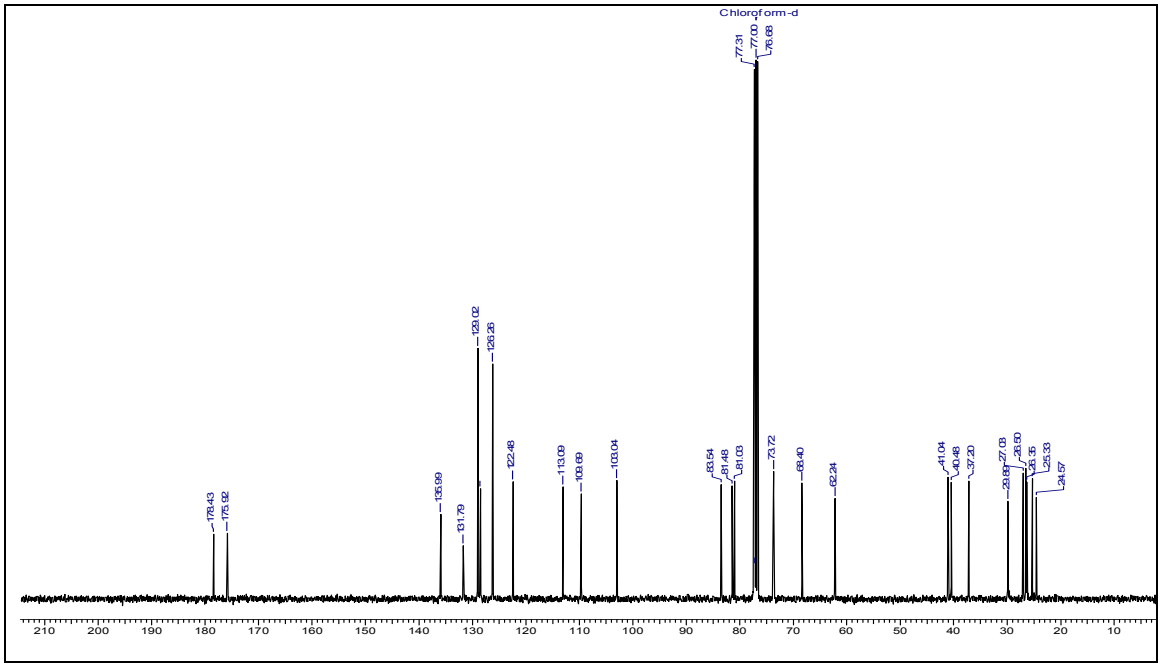
^{1}H NMR spectrum of compound 39 A in $CDCl_3$



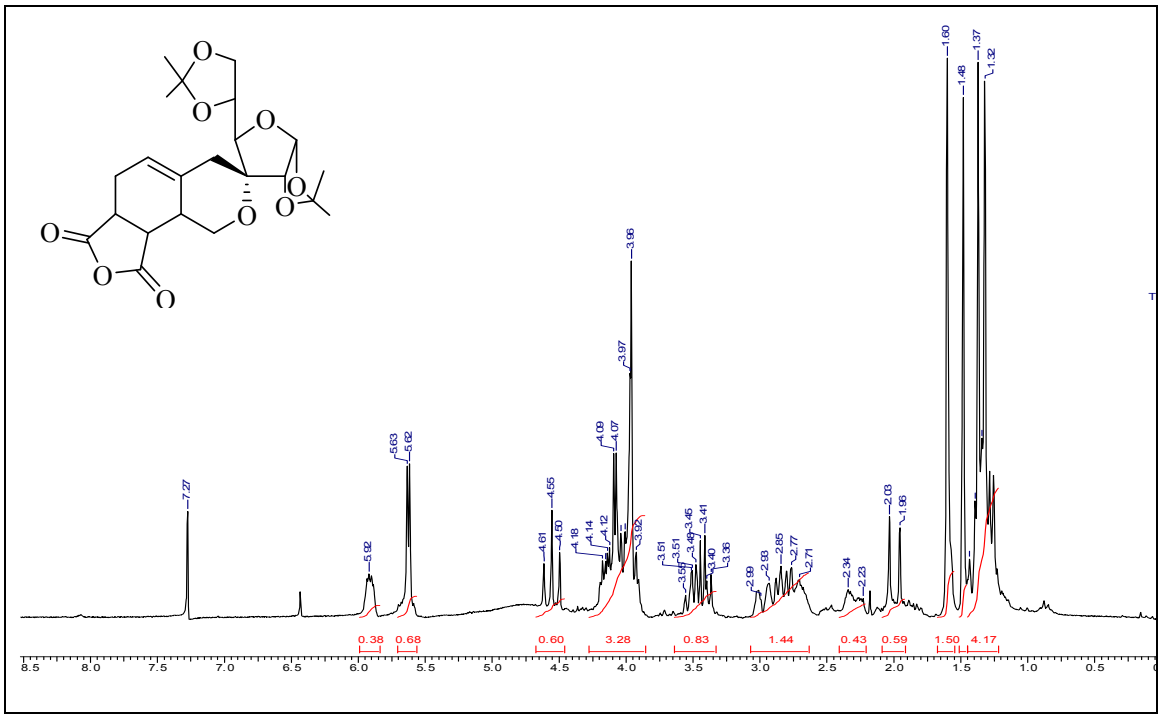
^{13}C NMR spectrum of compound 39 A in $CDCl_3$



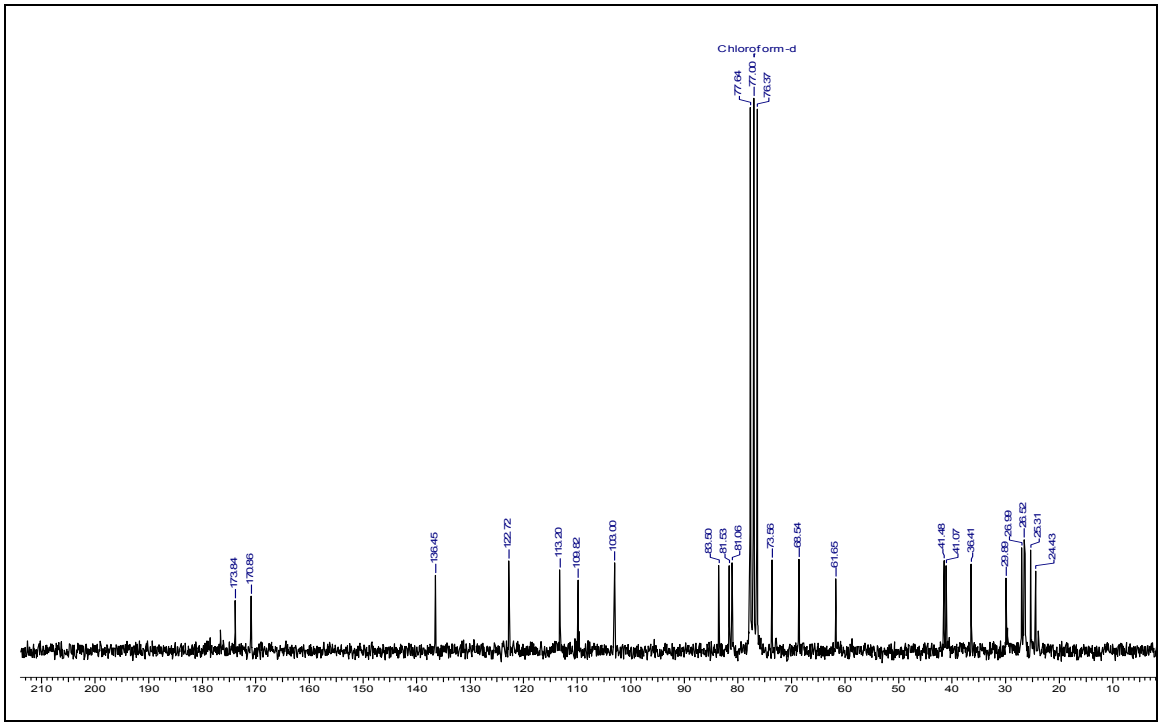
^{1}H NMR spectrum of compound 42 in $CDCl_3$



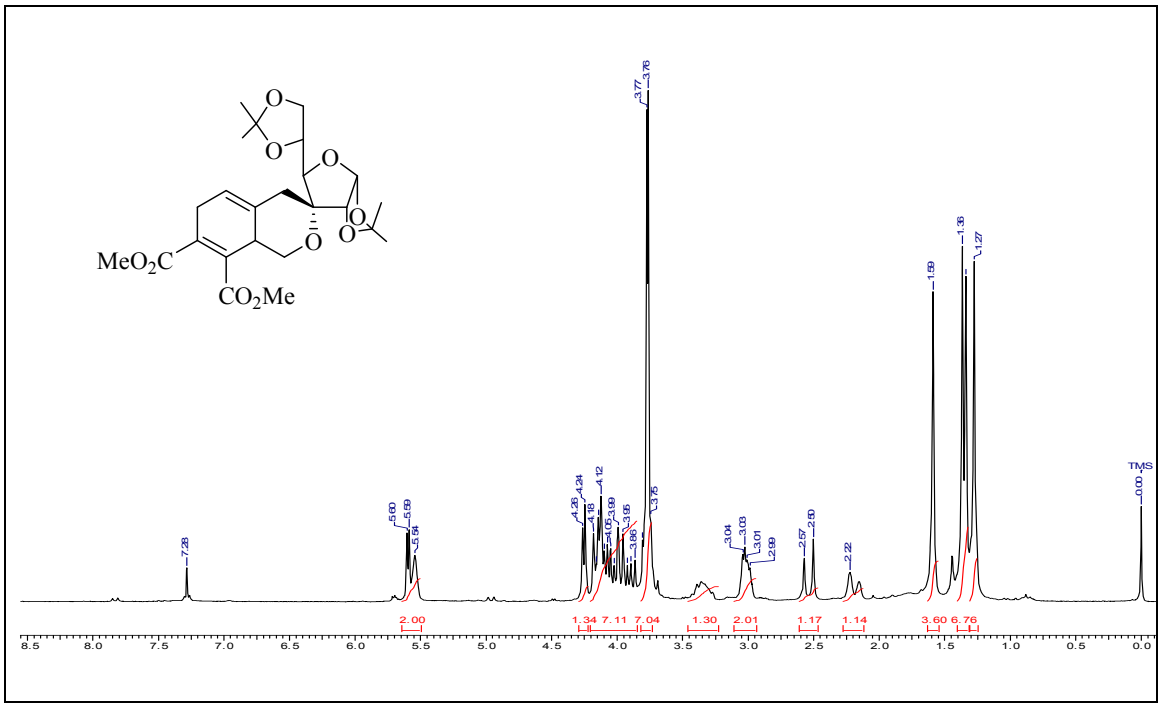
^{13}C NMR spectrum of compound 42 in $CDCl_3$



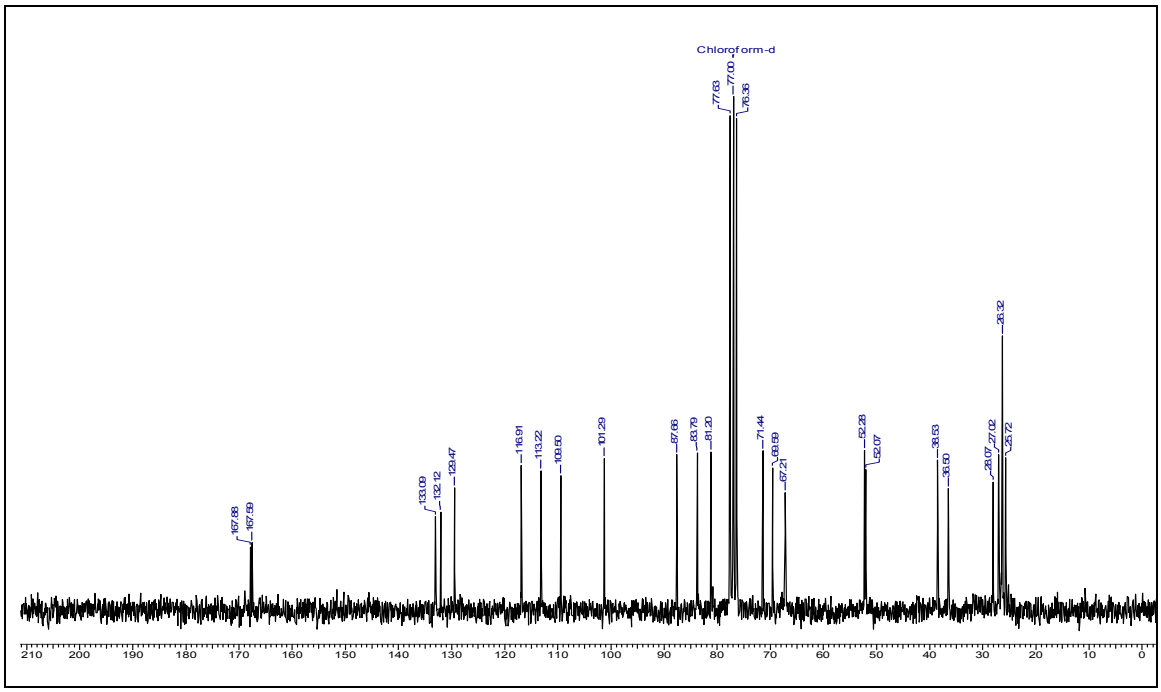
^{1}H NMR spectrum of compound 43 in $CDCl_3$



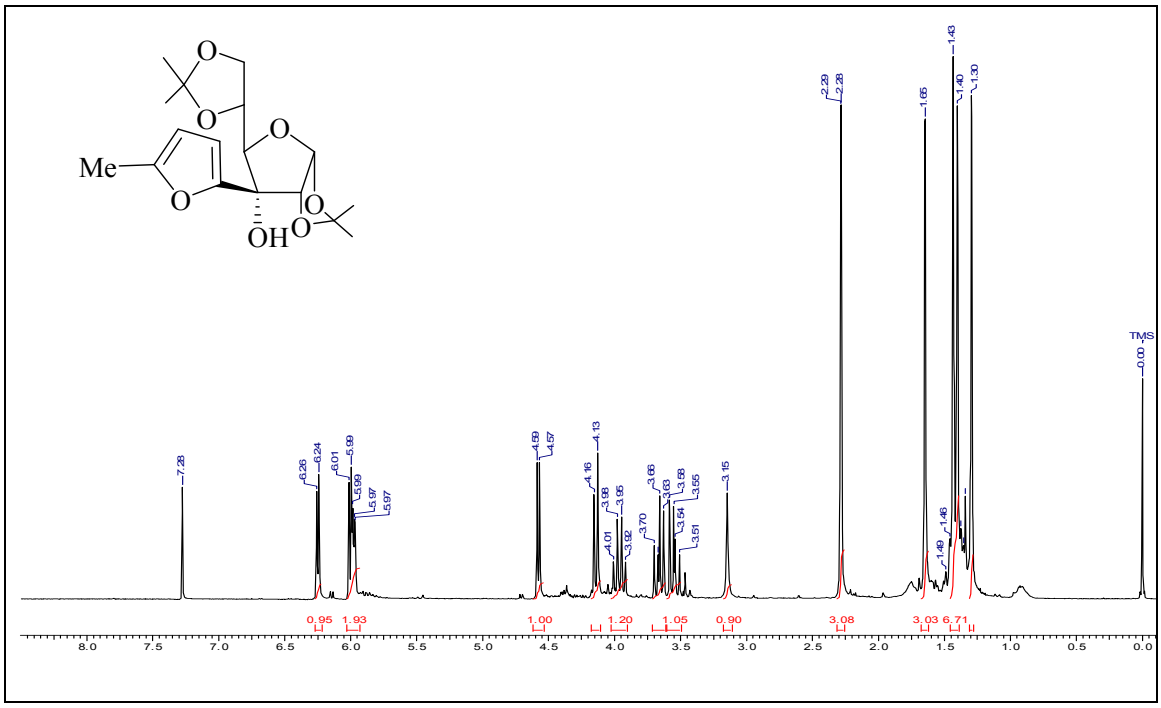
^{13}C NMR spectrum of compound 43 in $CDCl_3$



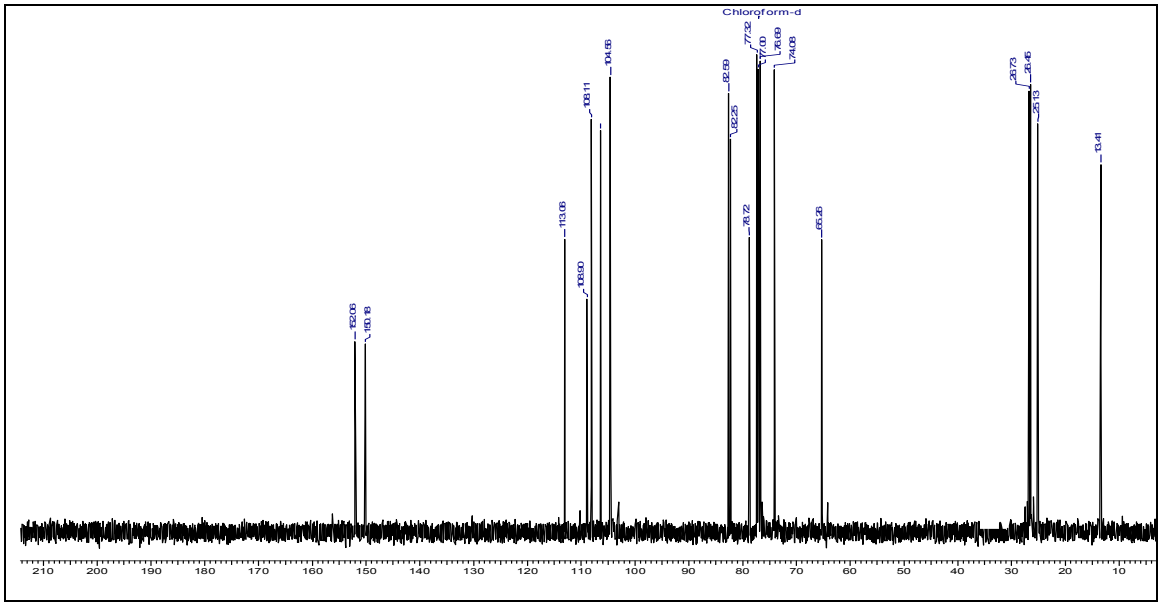
^{1}H NMR spectrum of compound 44 in $CDCl_3$



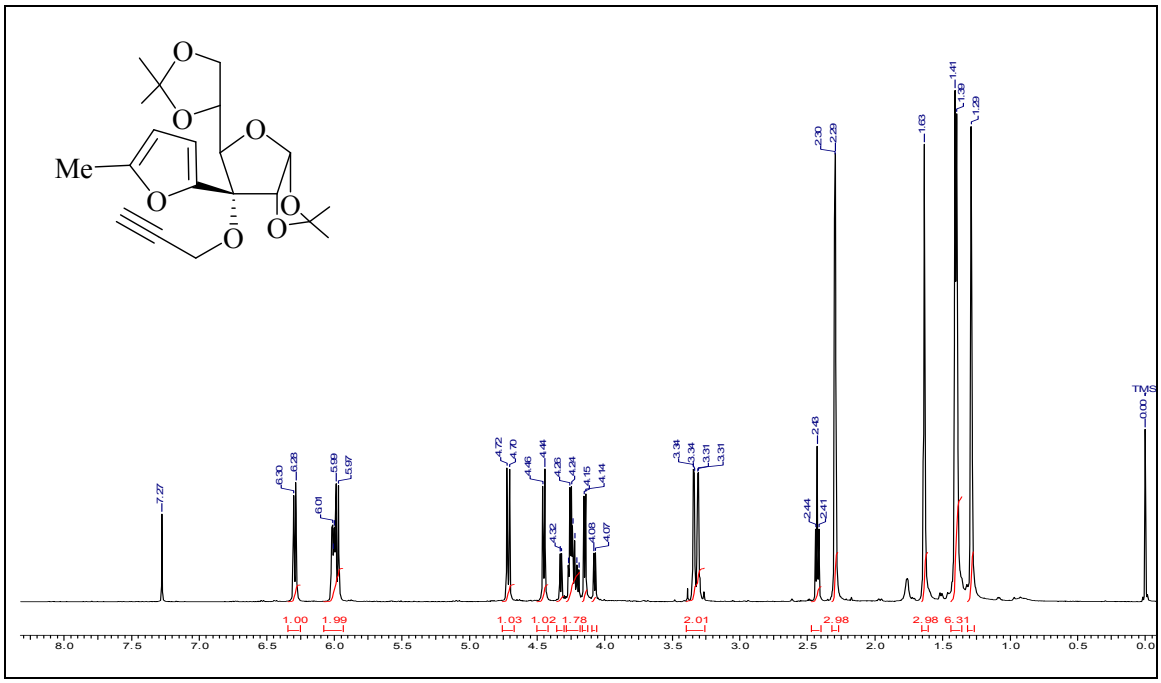
^{13}C spectrum of compound 44 in $CDCl_3$



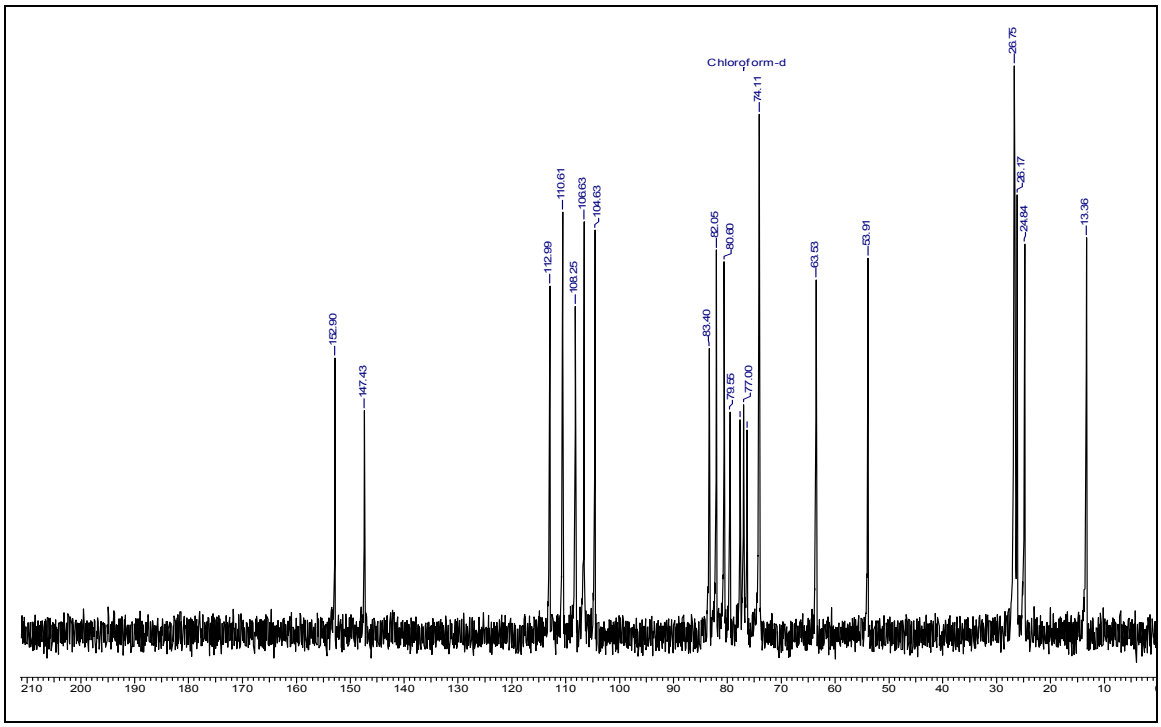
^{1}H NMR spectrum of compound 46 in $CDCl_3$



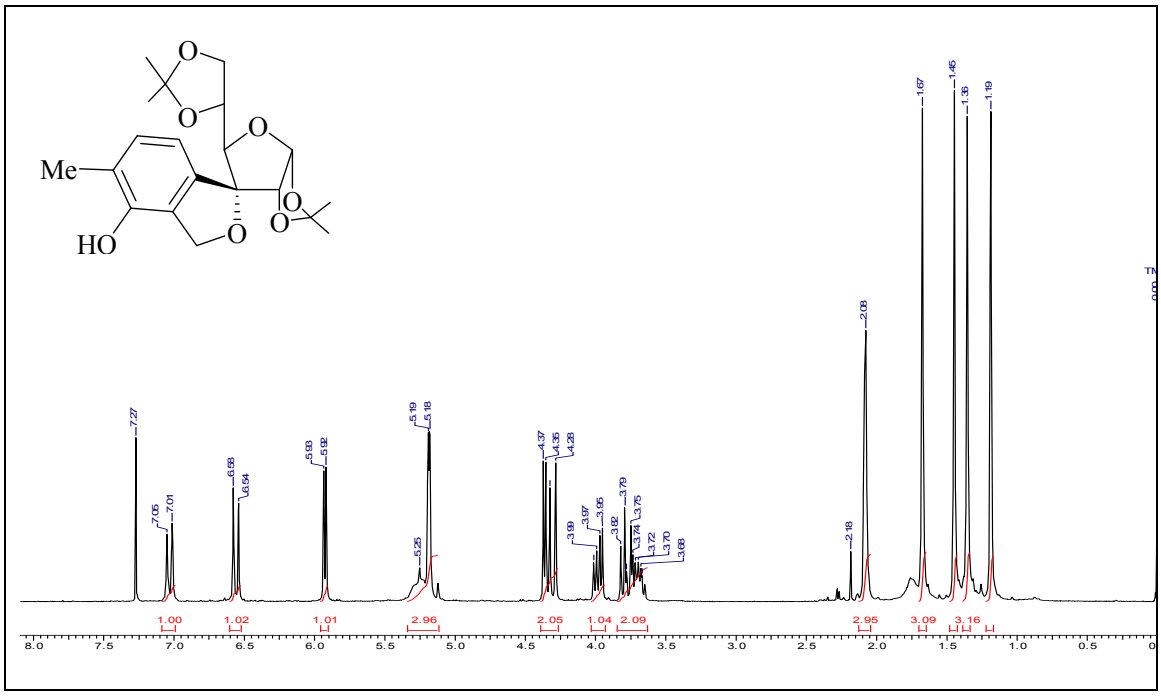
^{13}C NMR spectrum of compound 46 in $CDCl_3$



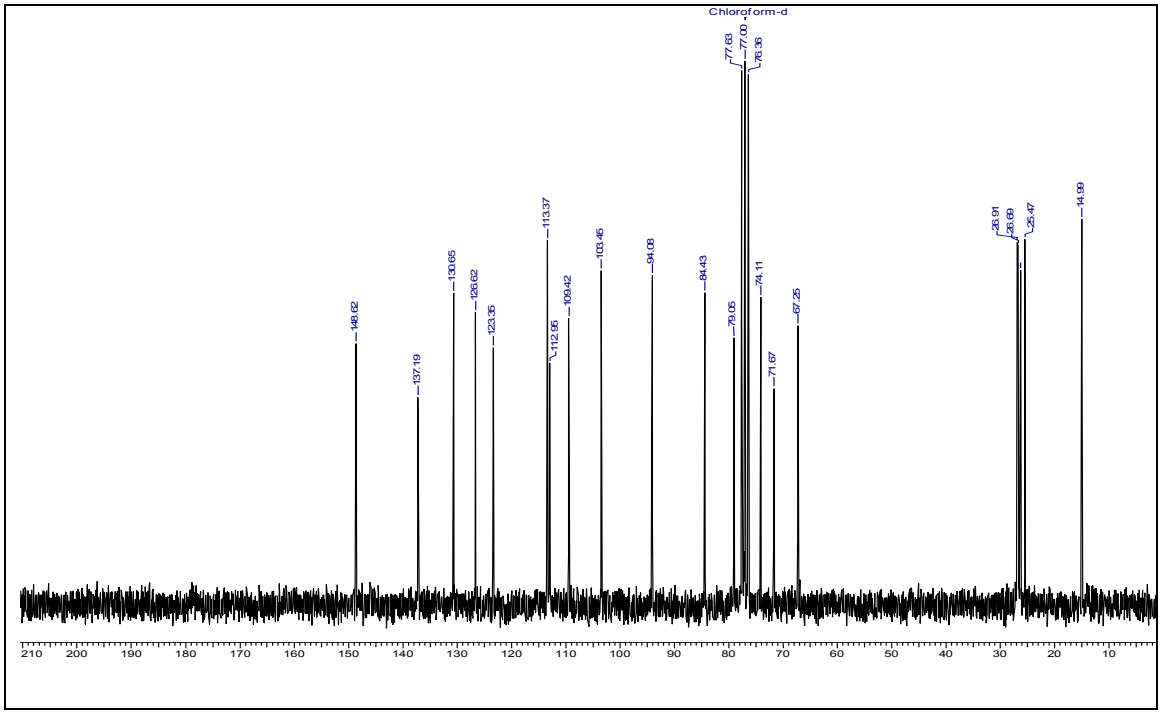
^{1}H NMR spectrum of compound 47 in $CDCl_3$



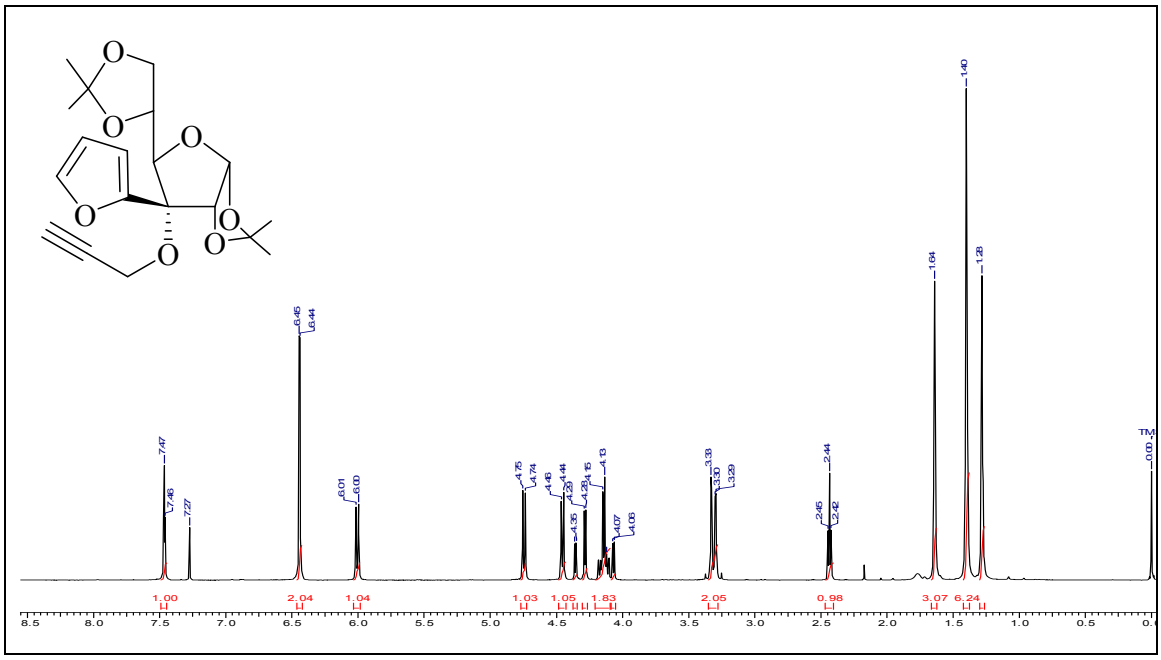
^{13}C NMR spectrum of compound 47 in $CDCl_3$



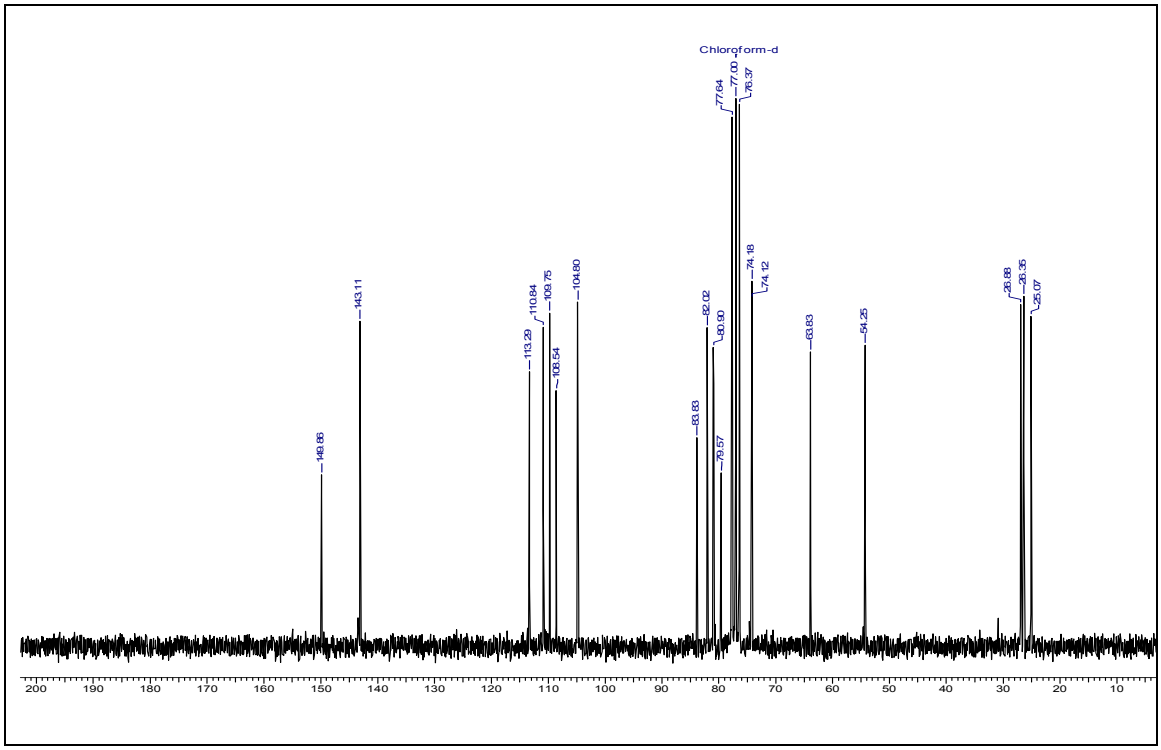
^{1}H NMR spectrum of compound 48 in $CDCl_3$



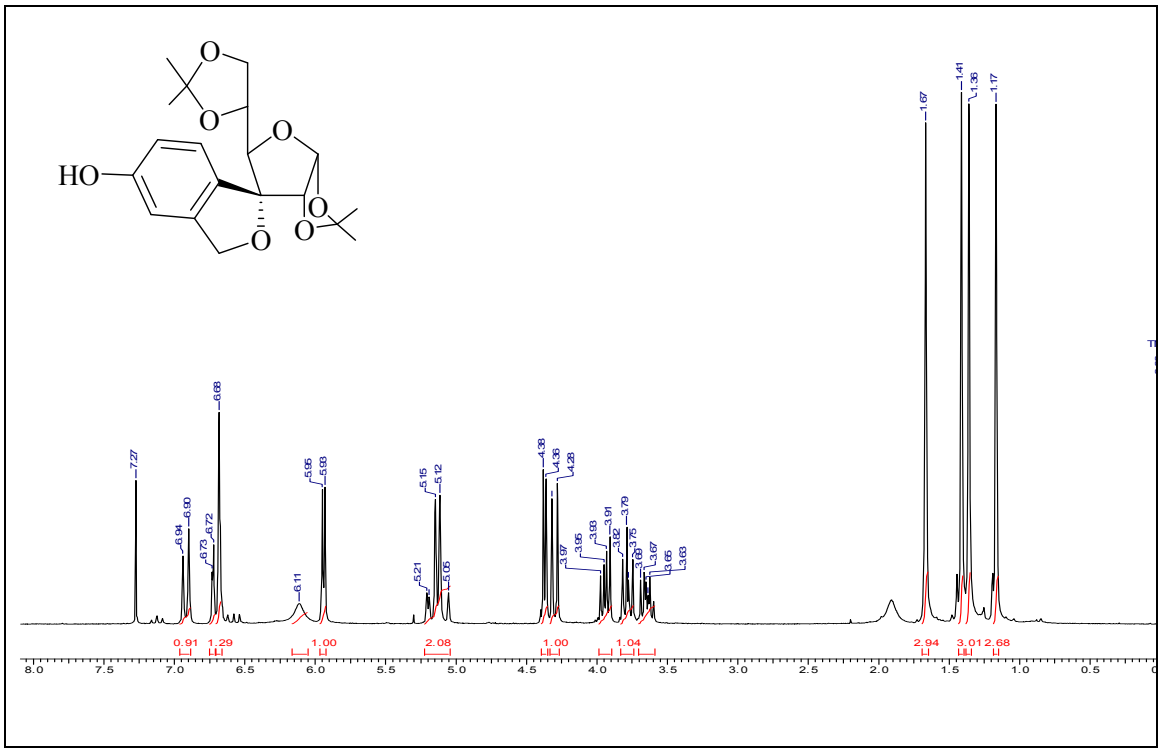
^{13}C NMR spectrum of compound 48 in $CDCl_3$



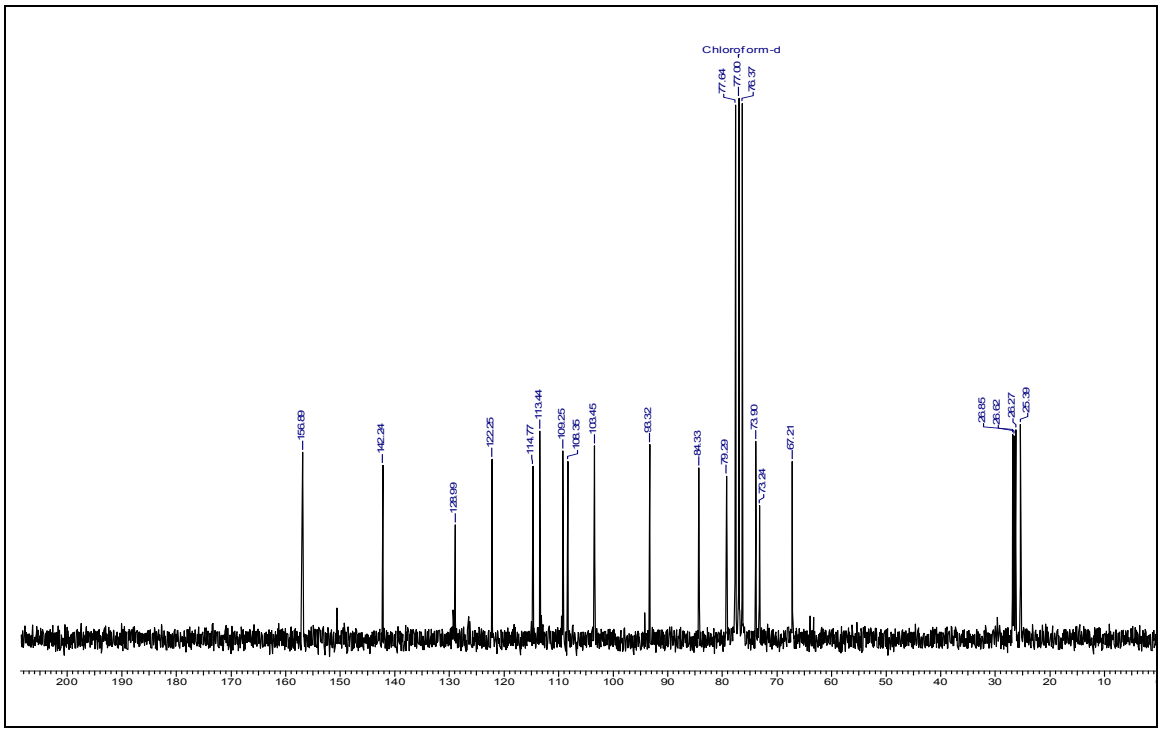
^{1}H NMR spectrum of compound 50 in $CDCl_3$



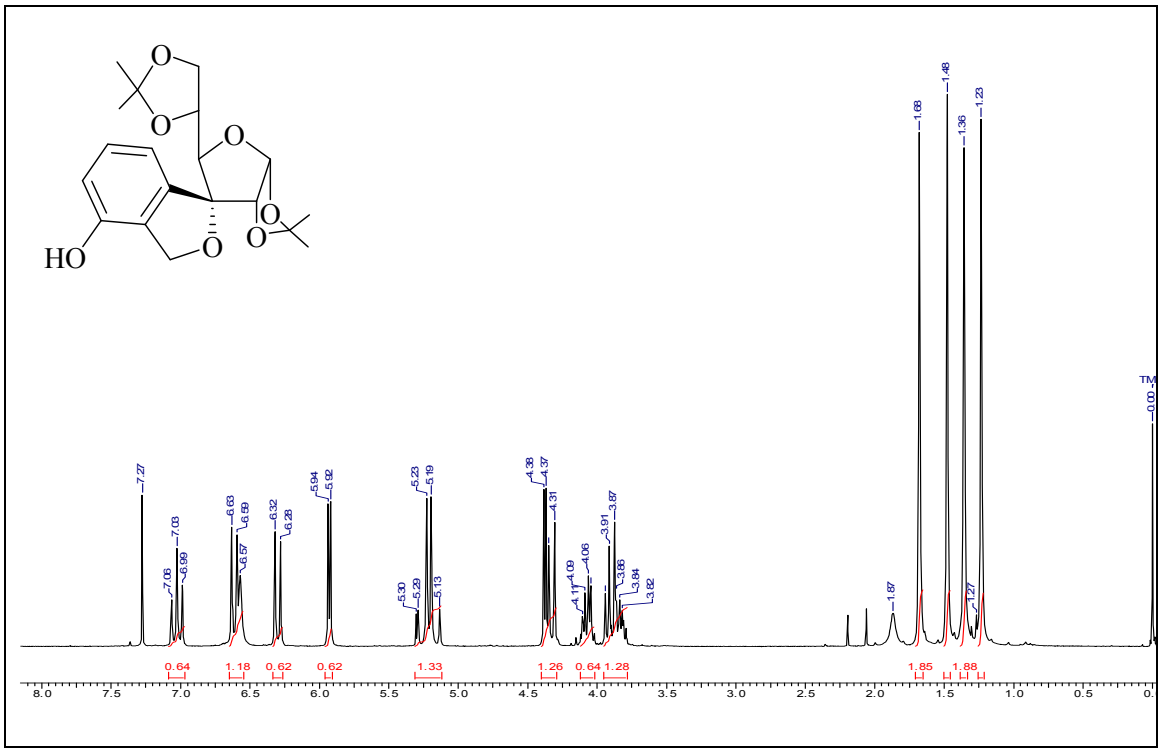
^{13}C NMR spectrum of compound 50 in $CDCl_3$



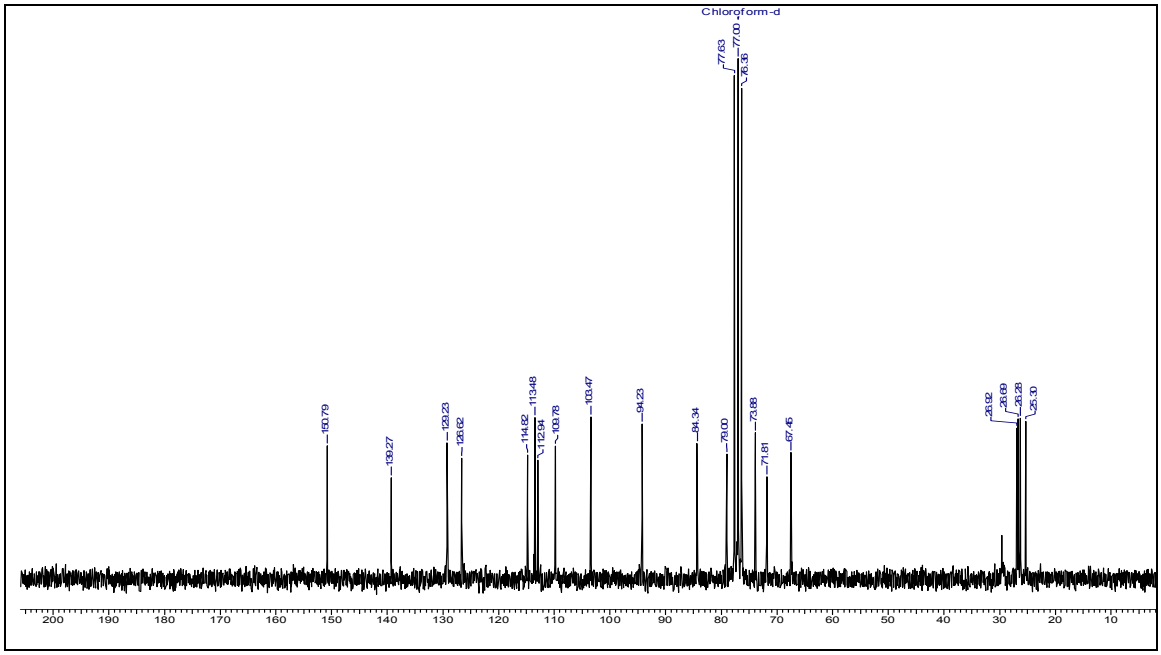
^{1}H NMR spectrum of compound 51 in $CDCl_3$



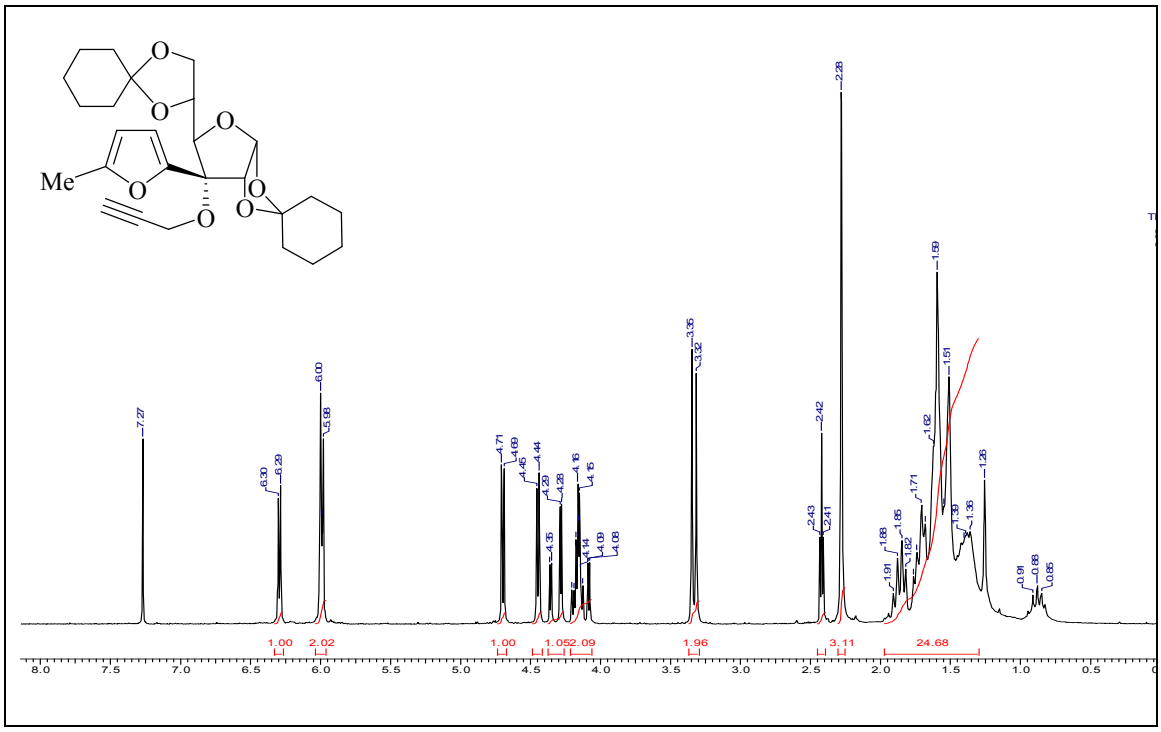
^{13}C NMR spectrum of compound 51 in $CDCl_3$



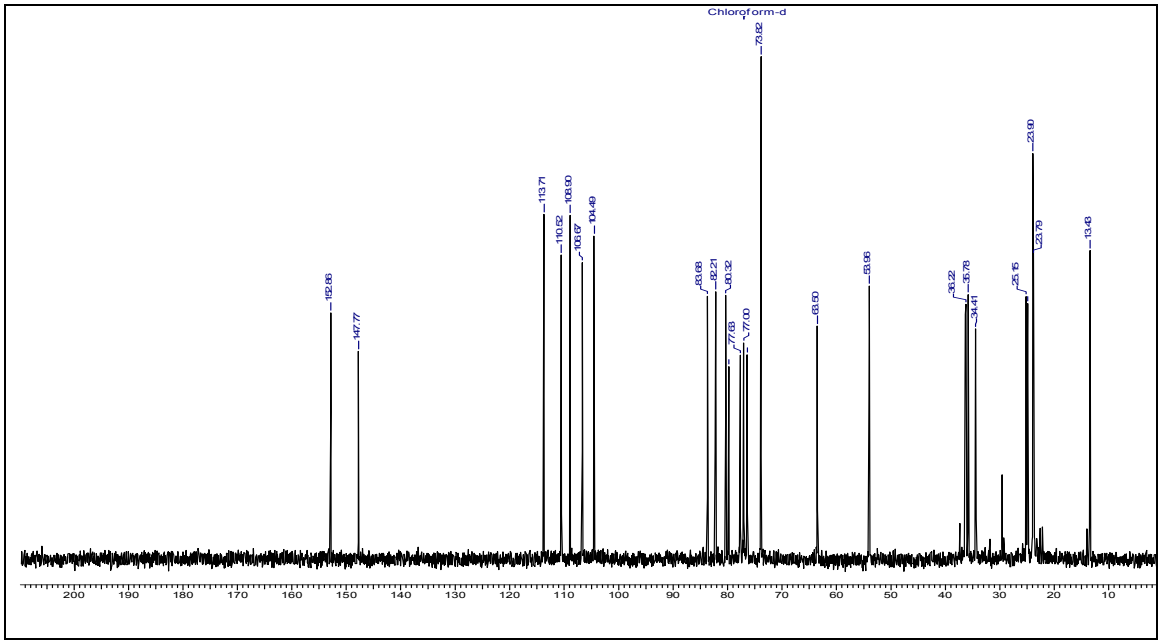
^{1}H NMR spectrum of compound 52 in $CDCl_3$



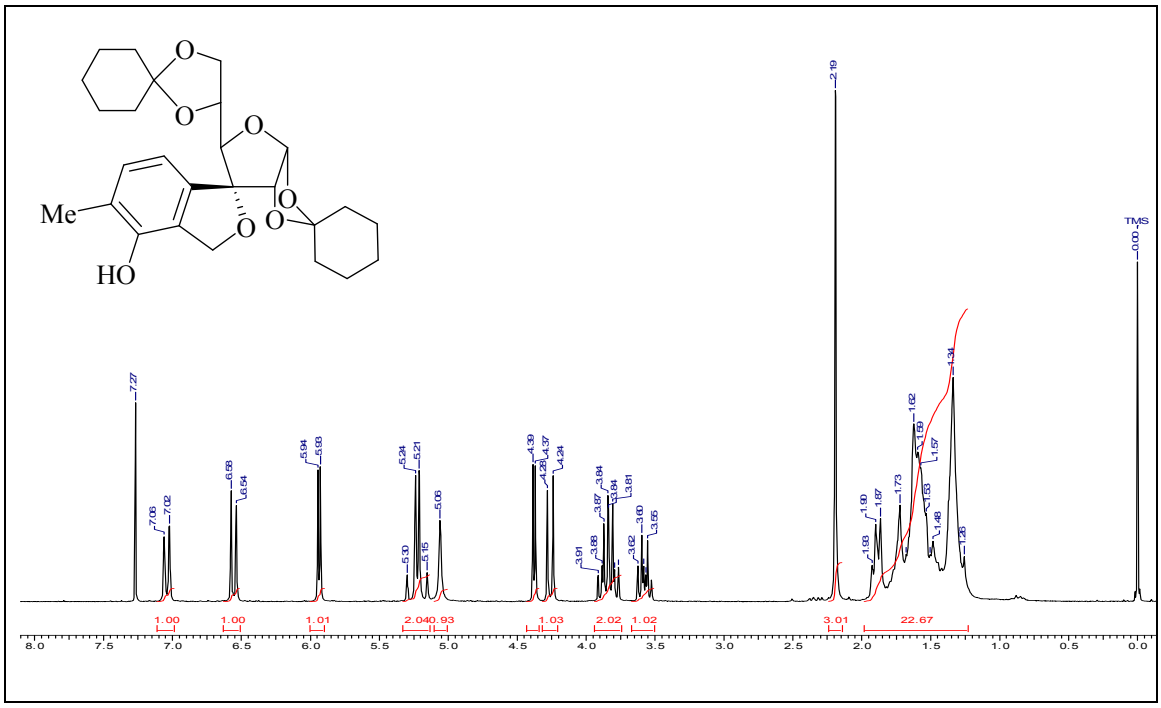
^{13}C NMR spectrum of compound 52 in $CDCl_3$



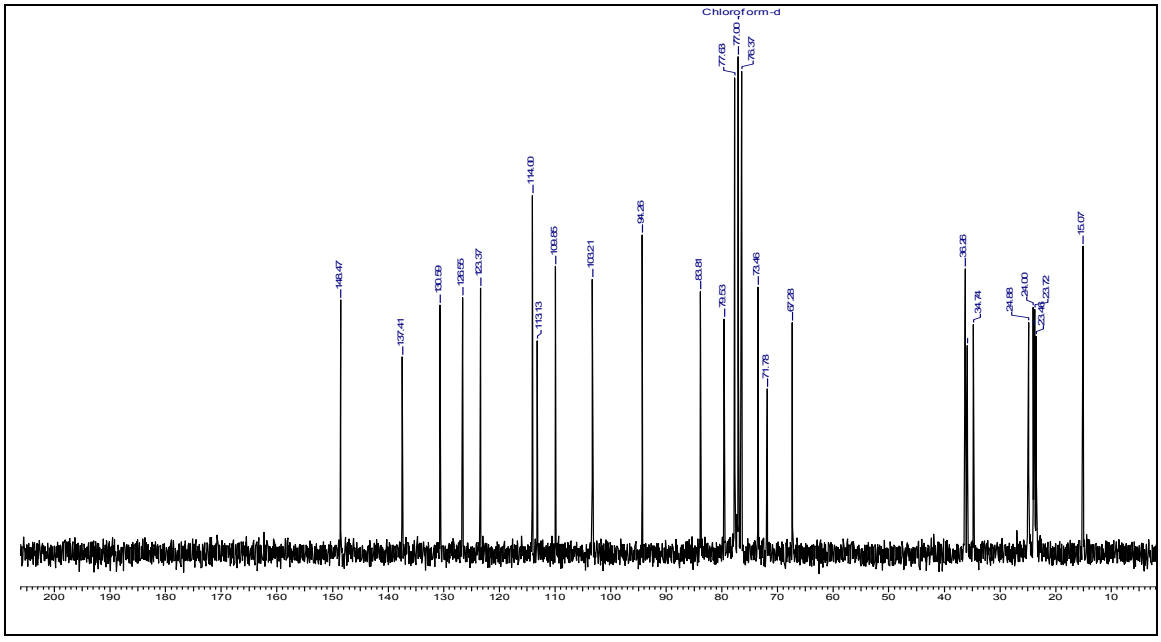
^{1}H NMR spectrum of compound 54 in $CDCl_3$



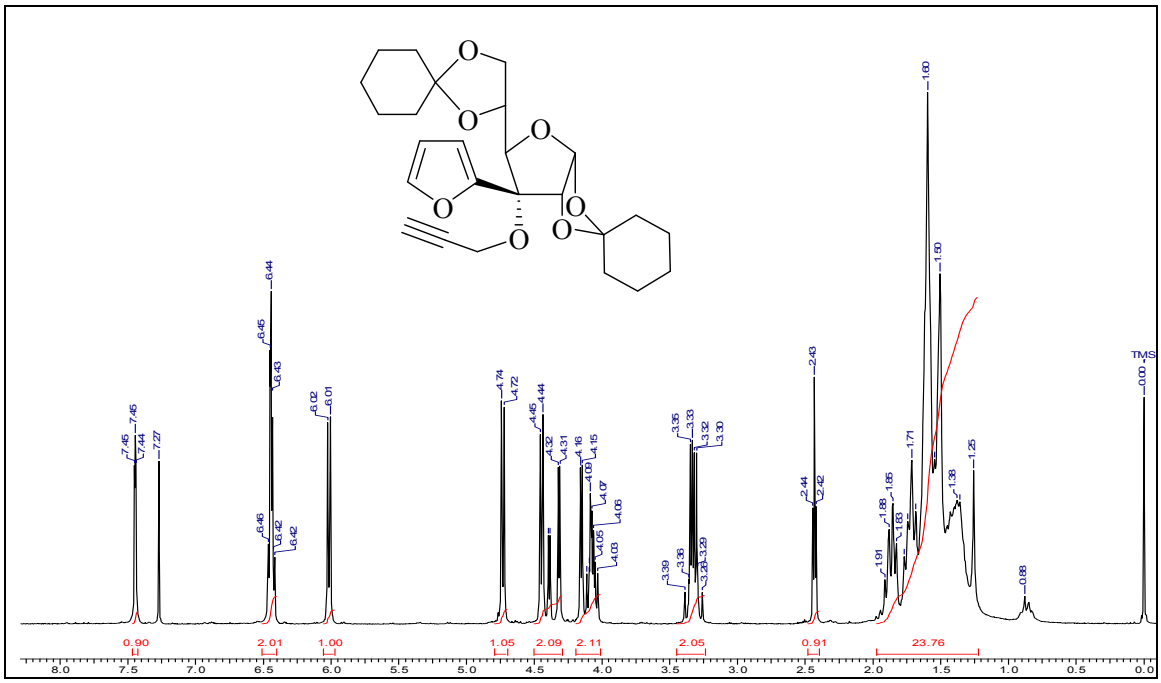
^{13}C NMR spectrum of compound 54 in $CDCl_3$



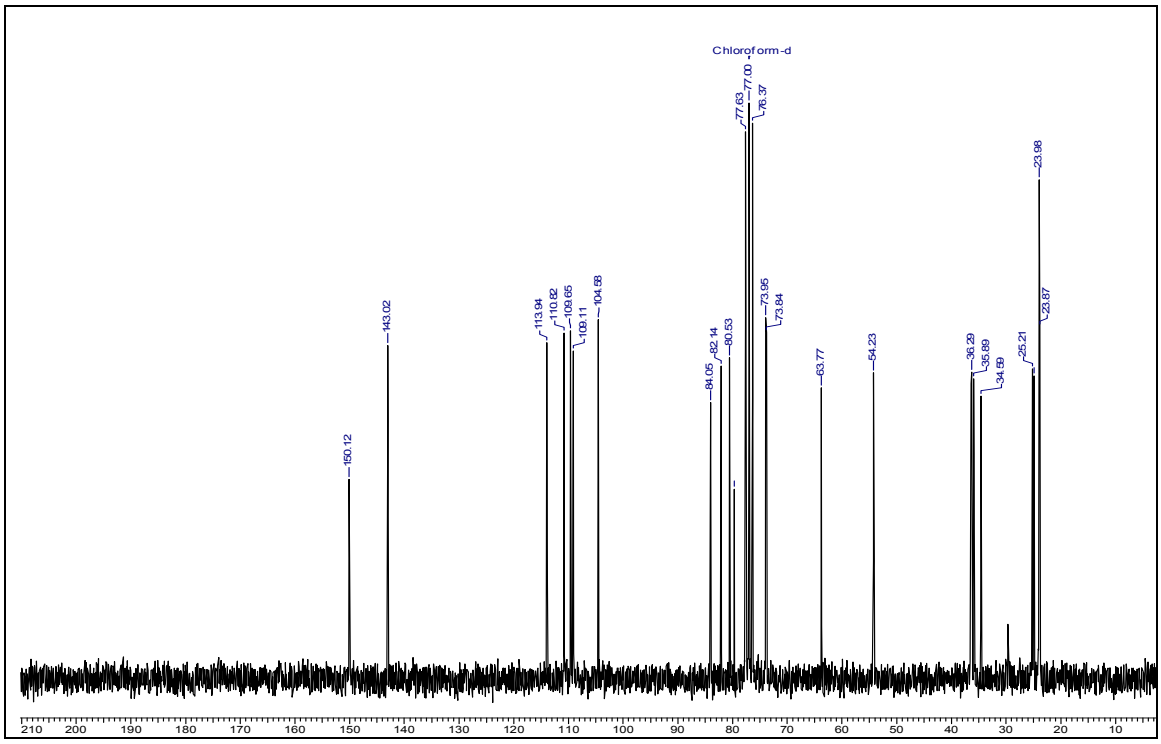
^{1}H NMR spectrum of compound 55 in $CDCl_3$



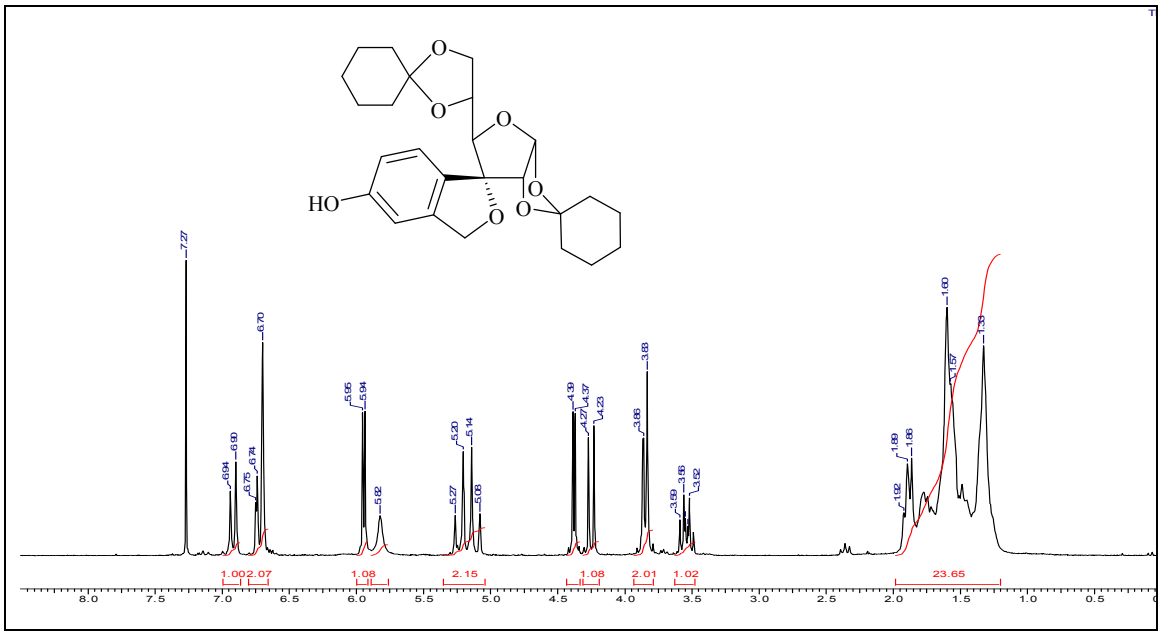
^{13}C NMR spectrum of compound 55 in $CDCl_3$



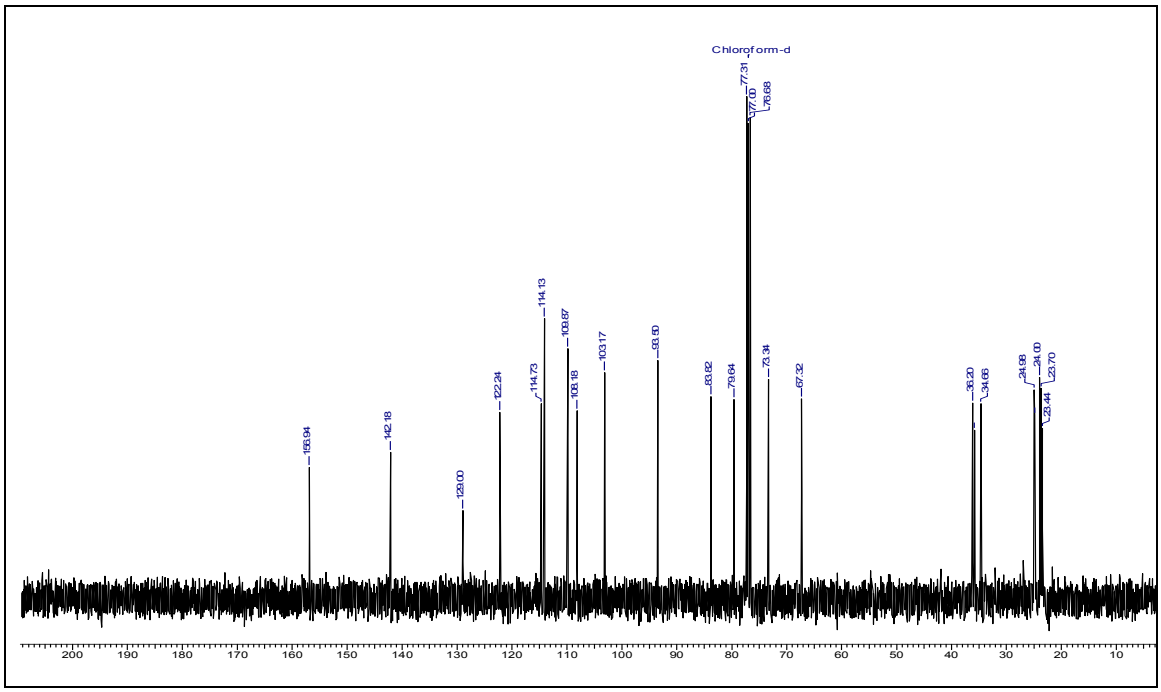
^{1}H NMR spectrum of compound 57 in $CDCl_3$



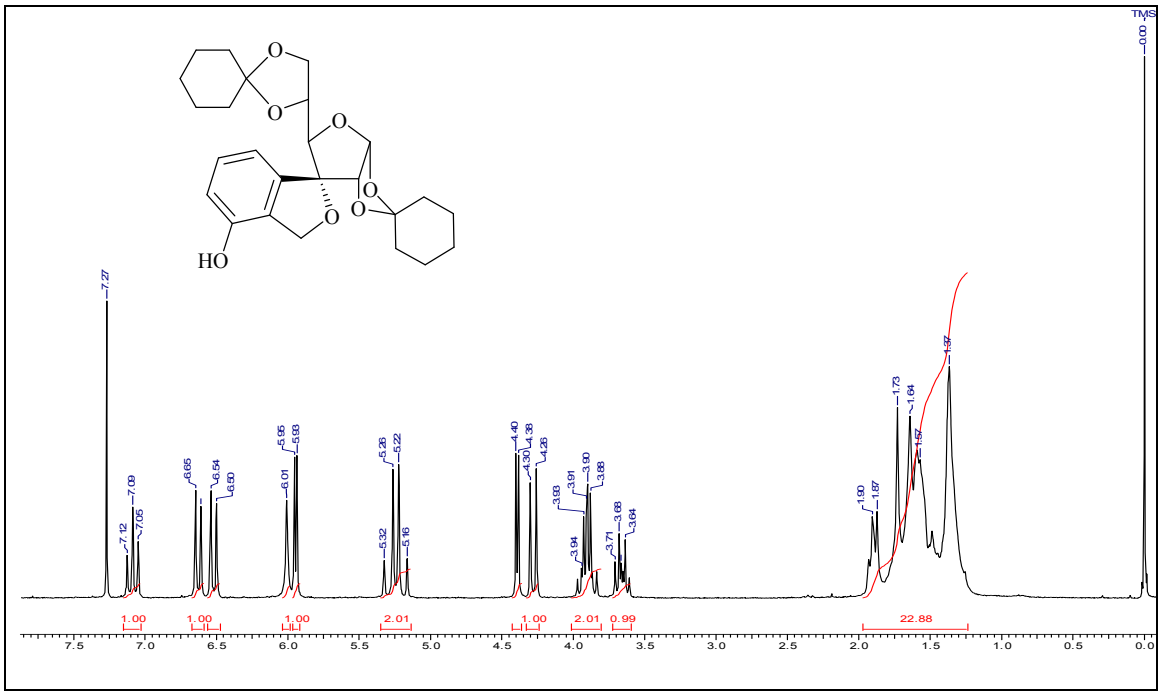
^{13}C NMR spectrum of compound 57 in $CDCl_3$



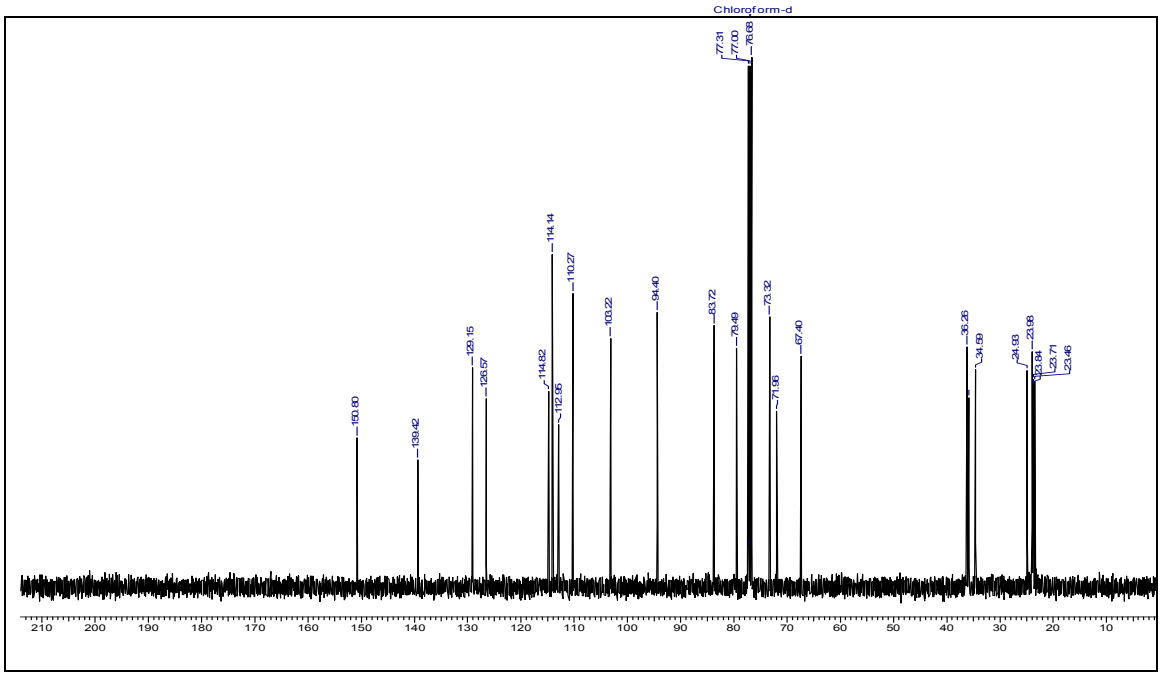
^{1}H NMR spectrum of compound 58 in $CDCl_3$



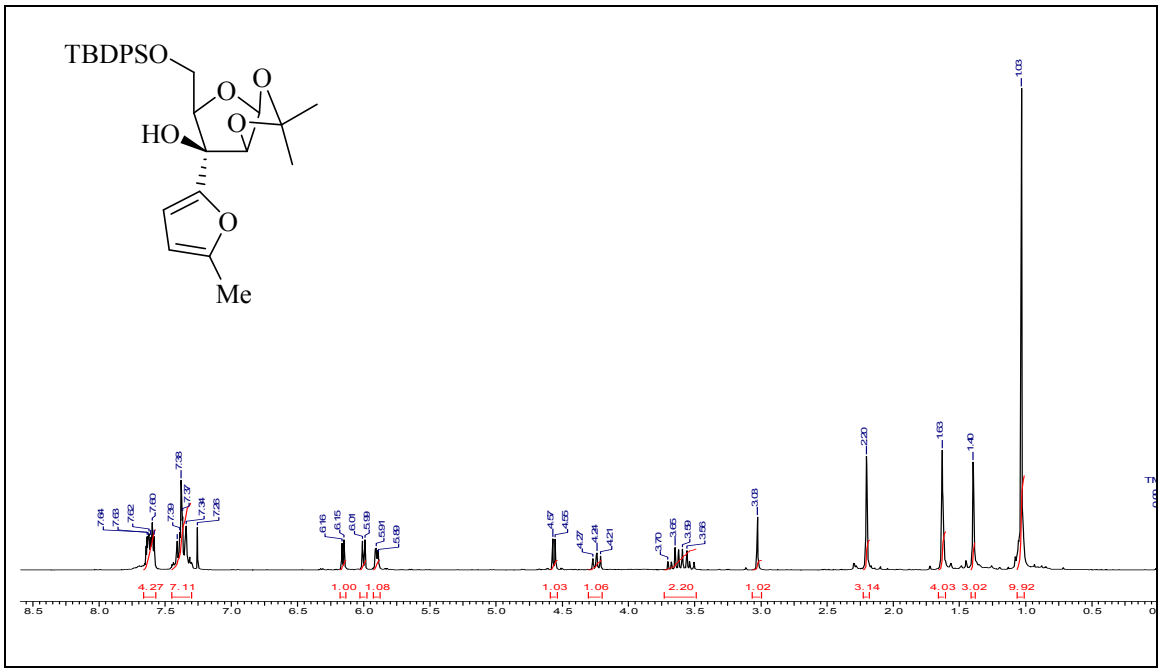
^{13}C NMR spectrum of compound 58 in $CDCl_3$



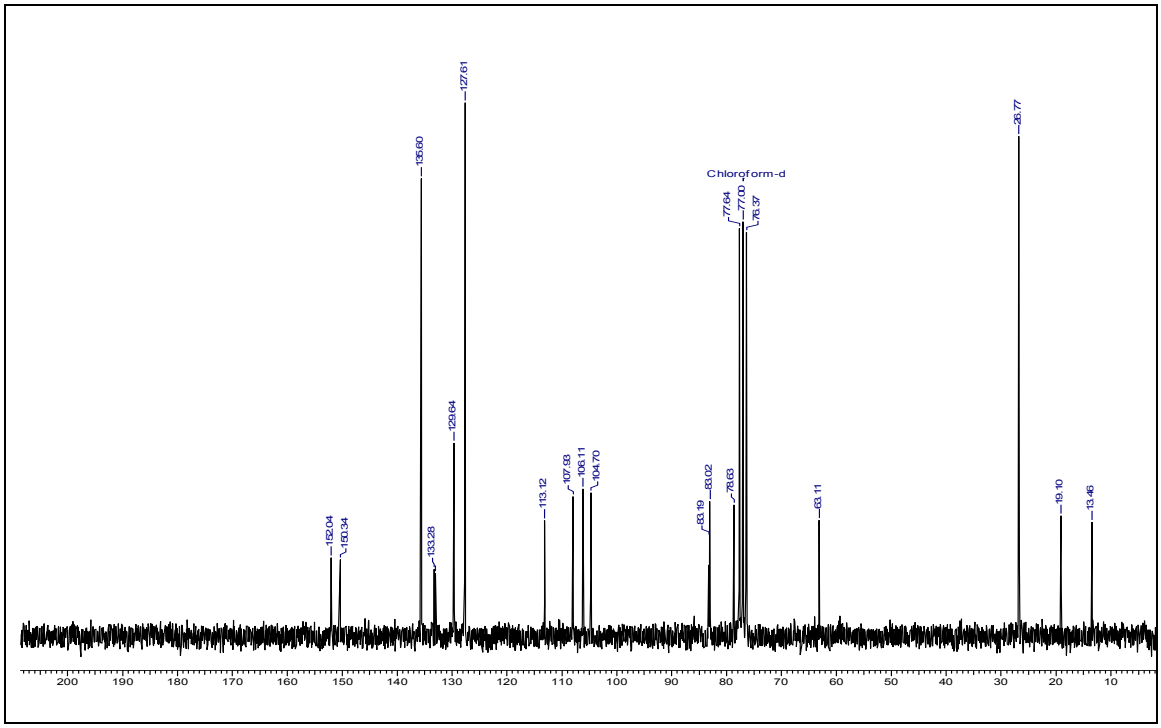
^{1}H NMR spectrum of compound 59 in $CDCl_3$



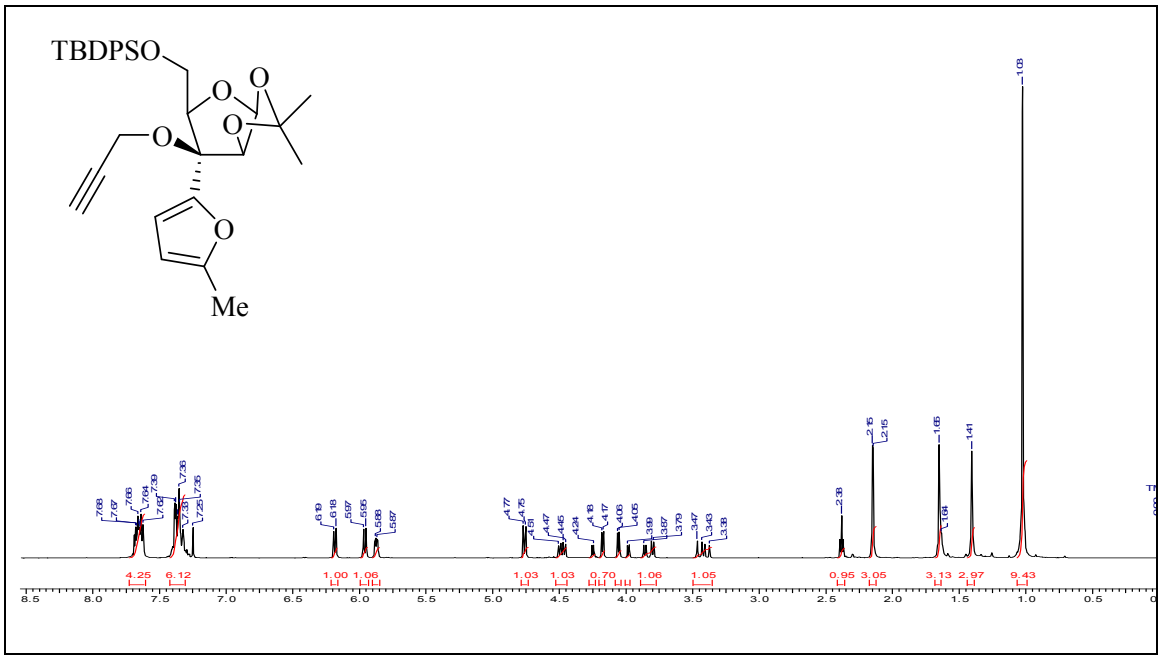
^{13}C NMR spectrum of compound 59 in $CDCl_3$



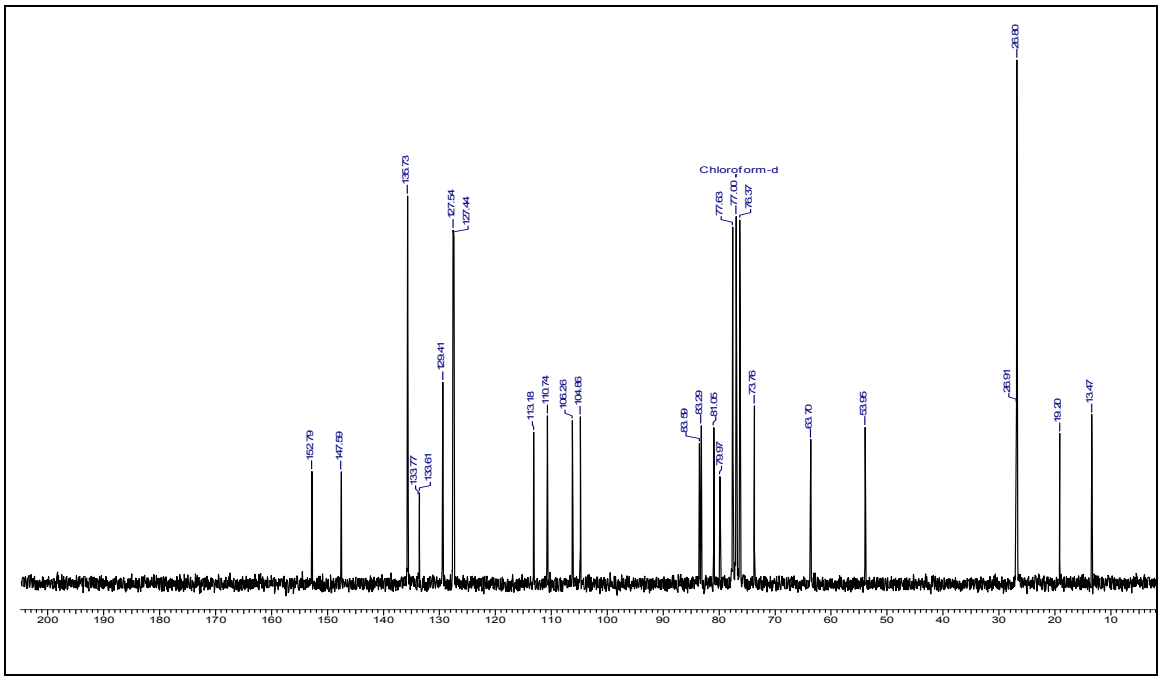
^{1}H NMR spectrum of compound 60 in $CDCl_3$



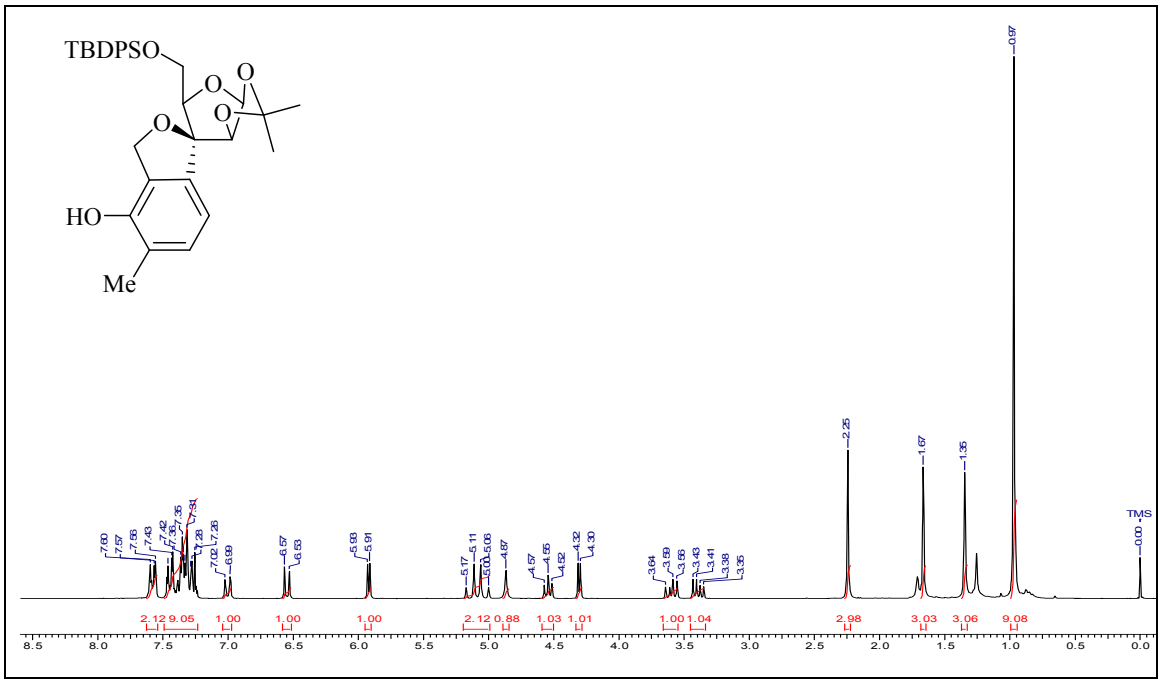
^{13}C NMR spectrum of compound 60 in $CDCl_3$



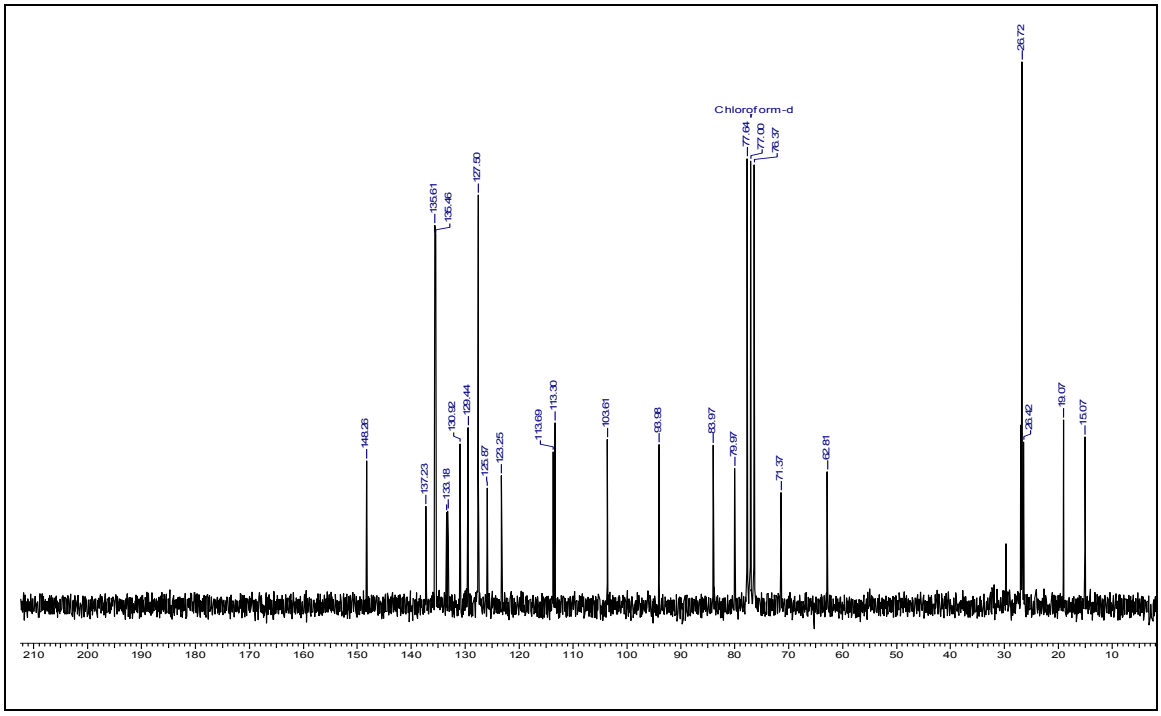
^{1}H NMR spectrum of compound 61 in $CDCl_3$



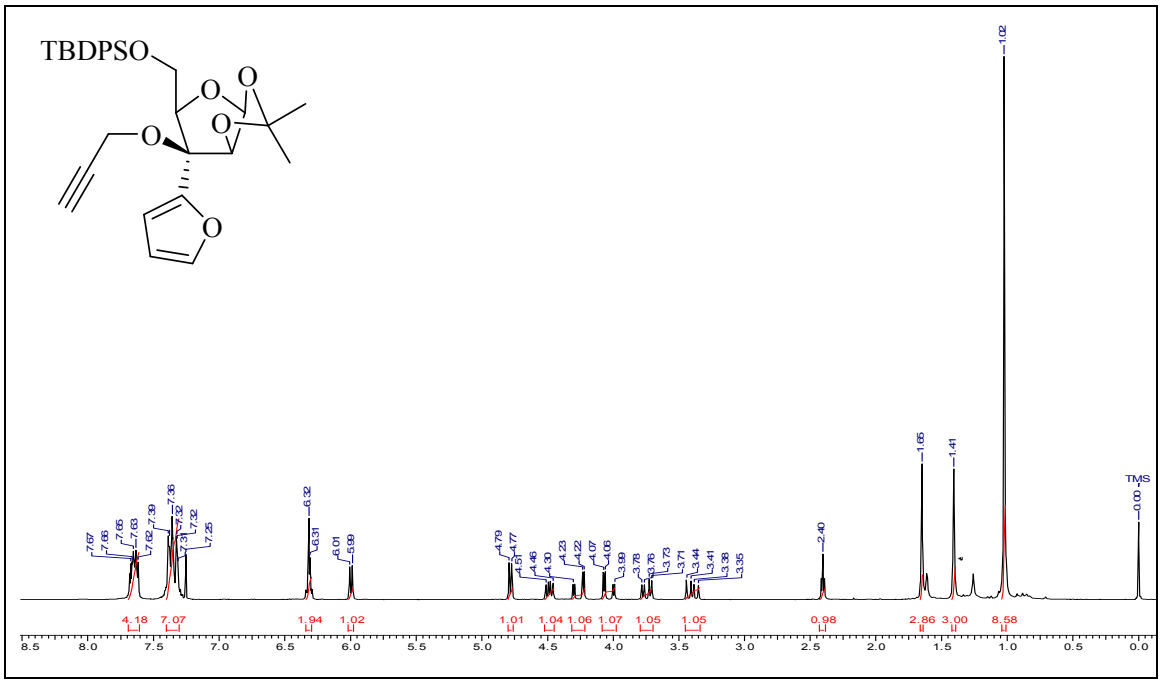
^{13}C NMR spectrum of compound 61 in $CDCl_3$



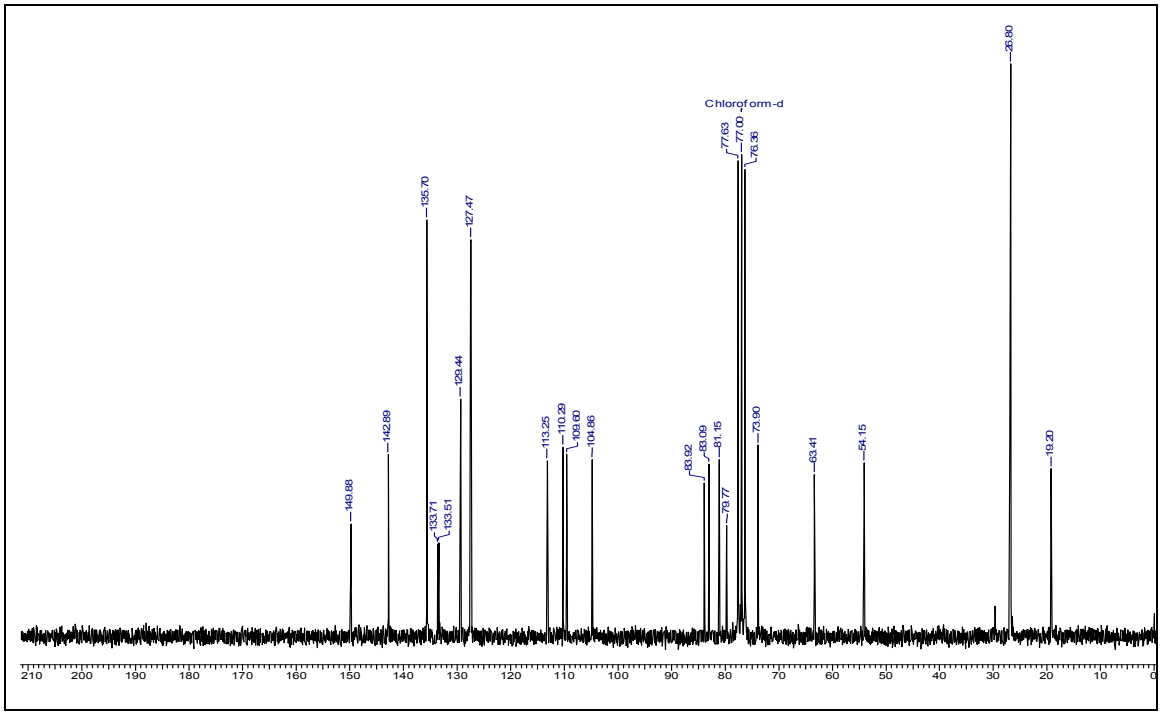
^{1}H NMR spectrum of compound 62 in $CDCl_3$



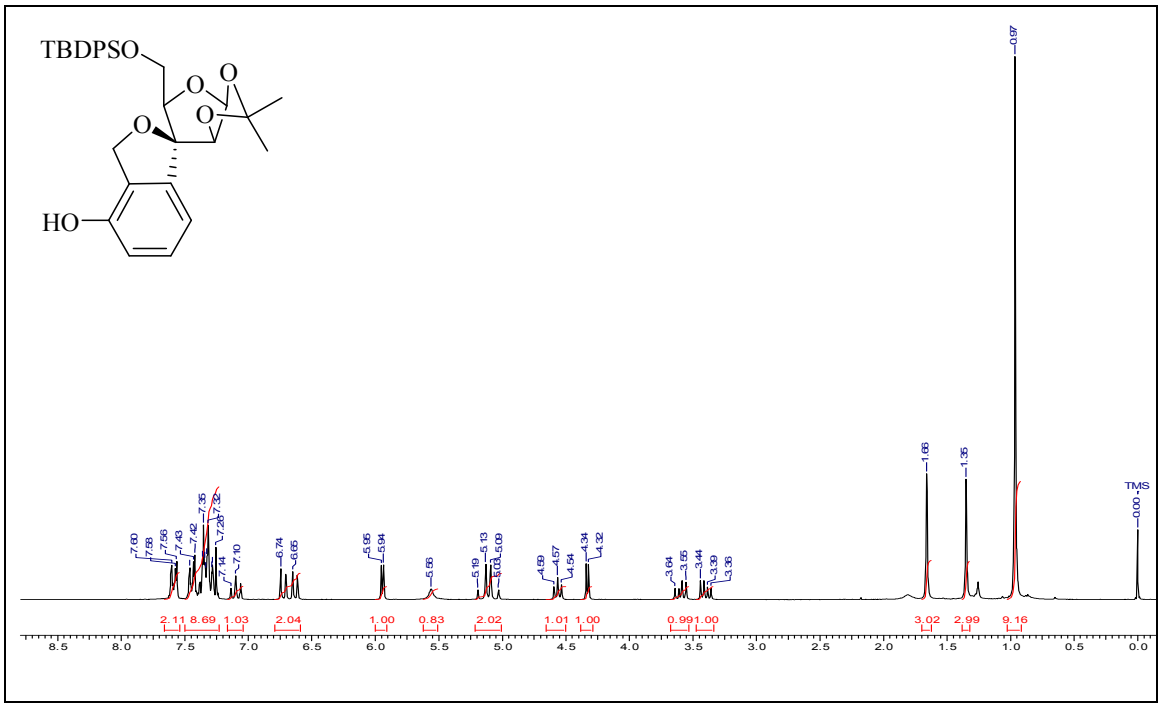
^{13}C NMR spectrum of compound 62 in $CDCl_3$



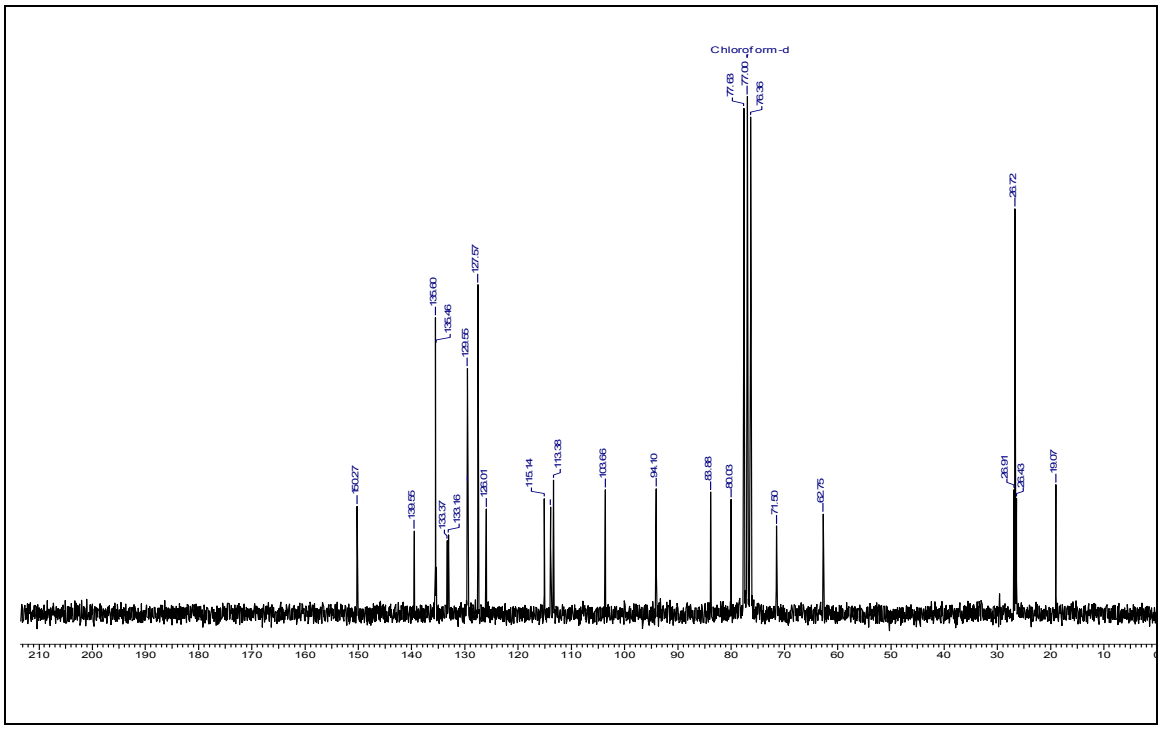
^{1}H NMR spectrum of compound 64 in $CDCl_3$



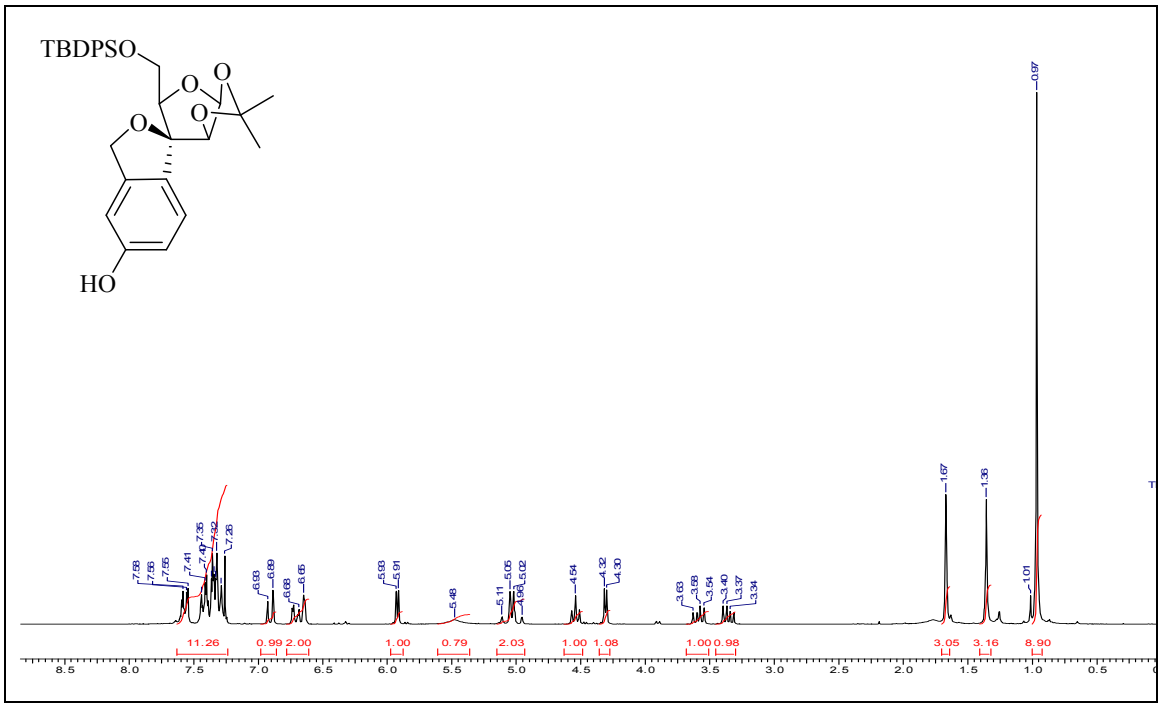
^{13}C NMR spectrum of compound 64 in $CDCl_3$



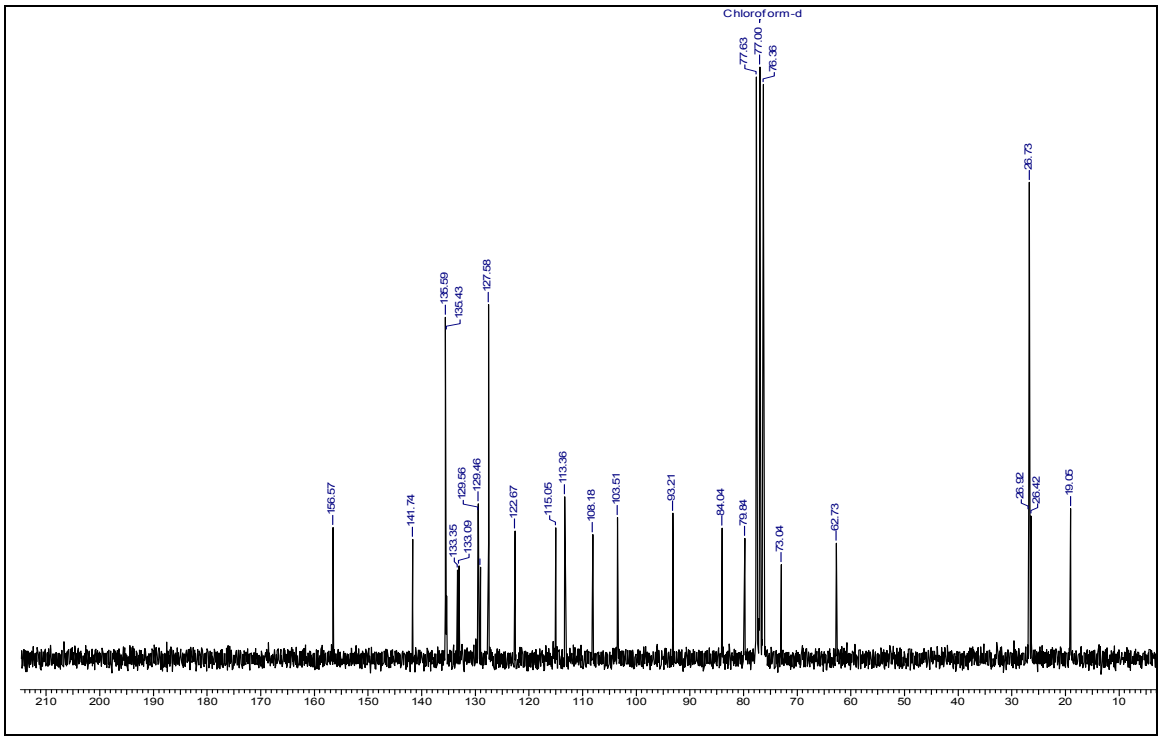
^{1}H NMR spectrum of compound 65 in $CDCl_3$



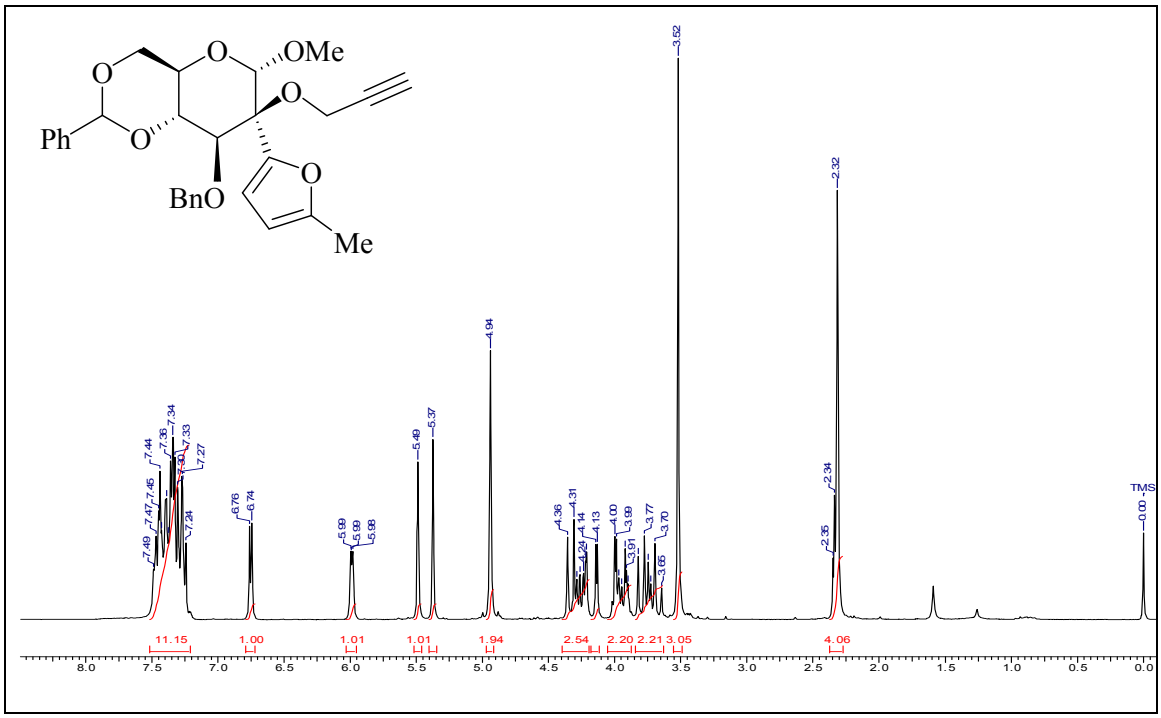
^{13}C NMR spectrum of compound 65 in $CDCl_3$



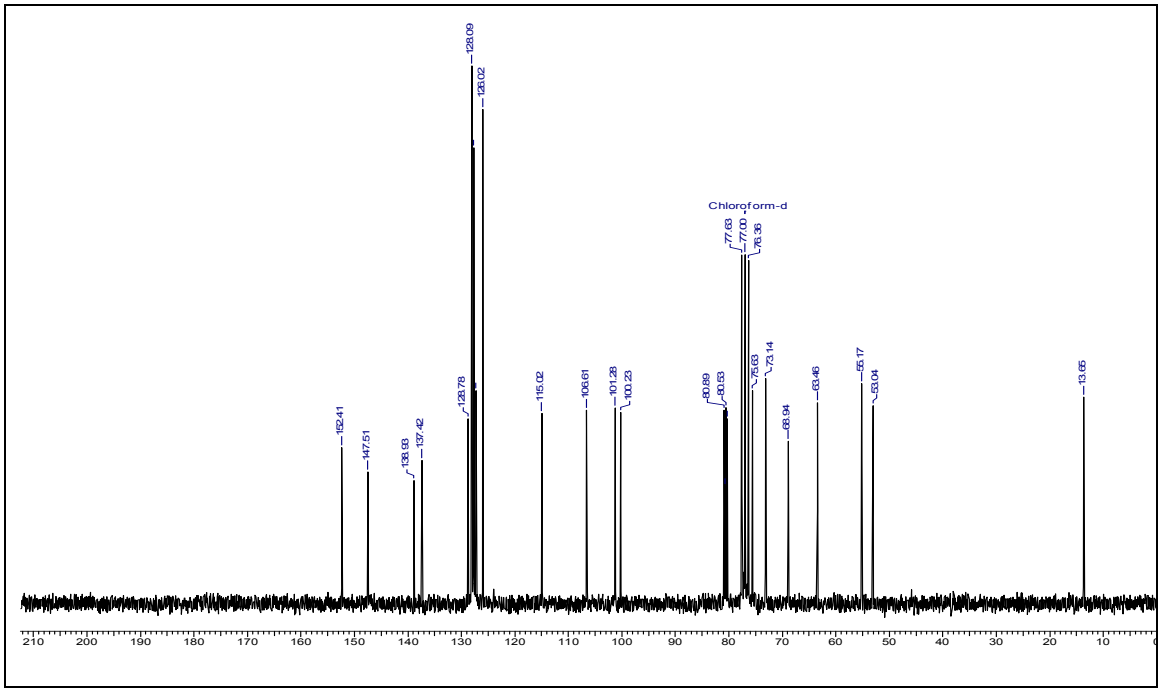
^{1}H NMR spectrum of compound 66 in $CDCl_3$



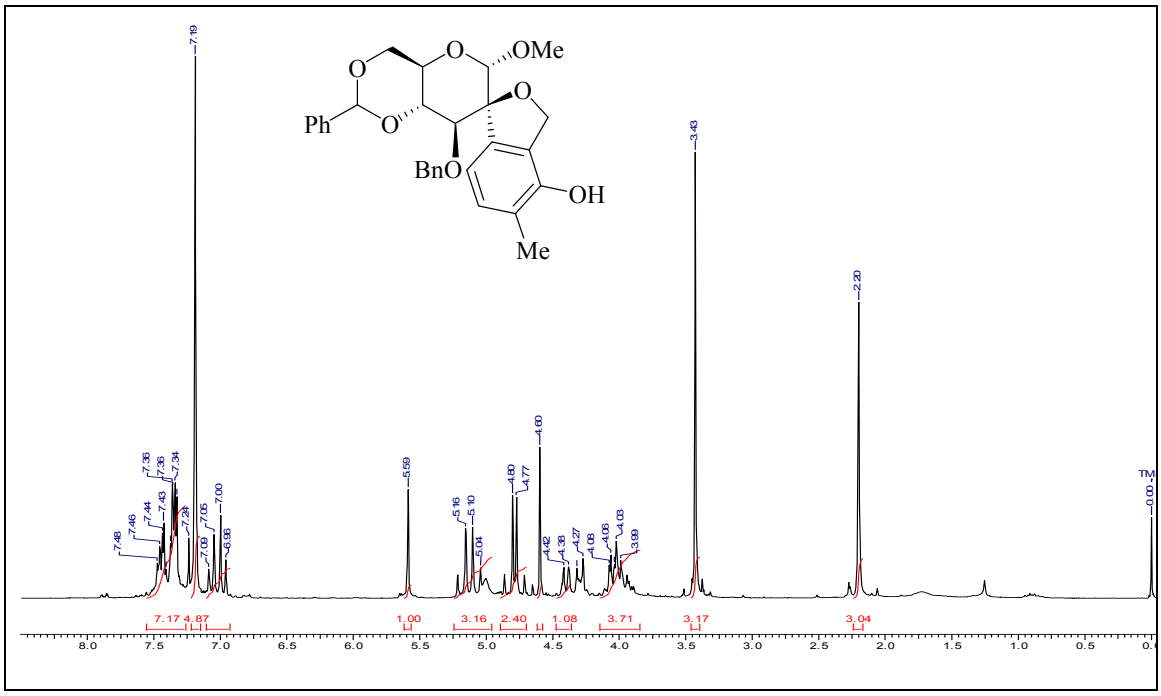
^{13}C NMR spectrum of compound 66 in $CDCl_3$



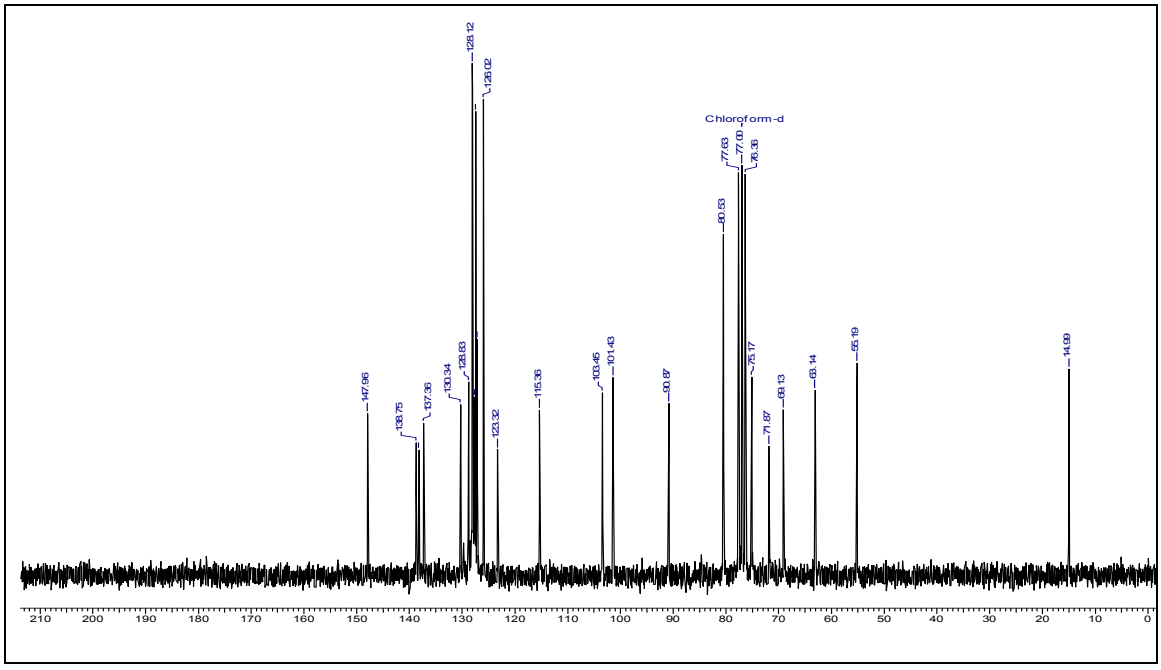
^{1}H NMR spectrum of compound 69 in $CDCl_3$



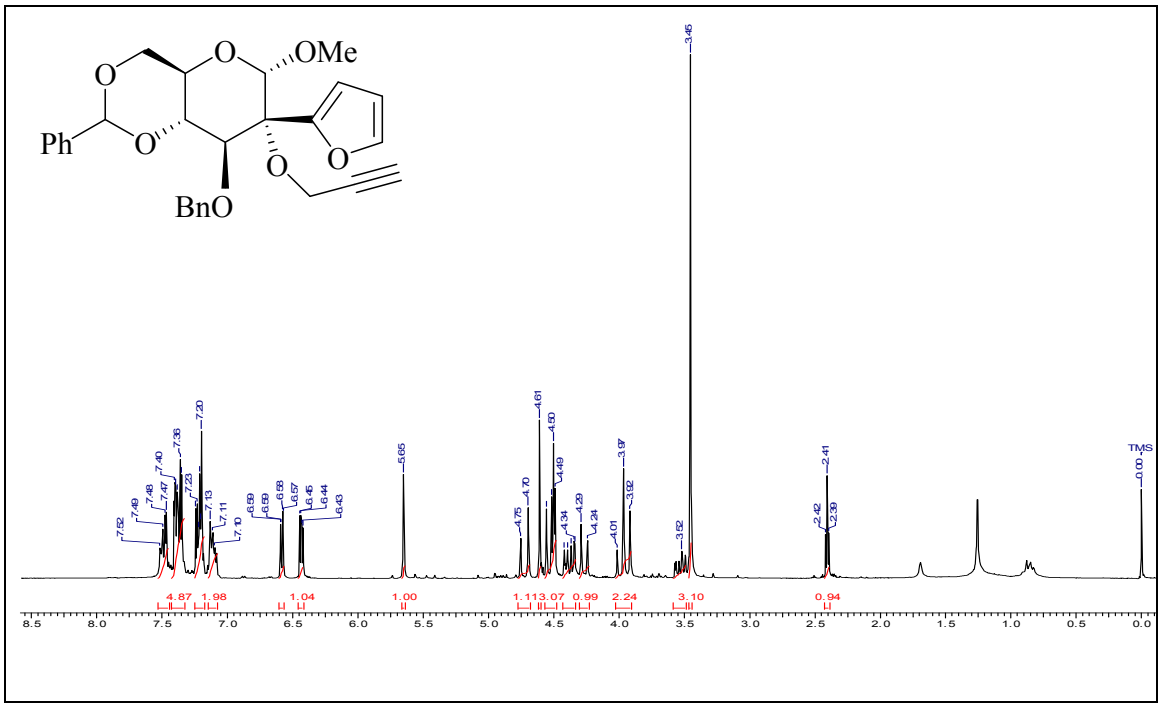
^{13}C NMR spectrum of compound 69 in $CDCl_3$



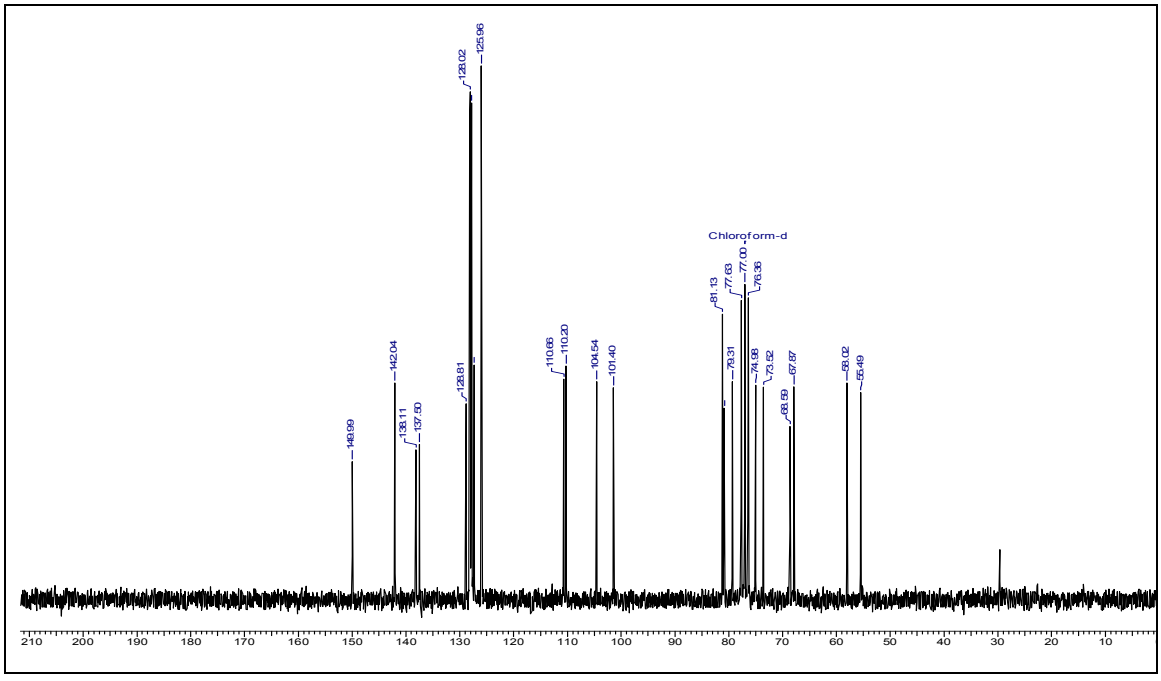
^{1}H NMR spectrum of compound 70 in $CDCl_3$



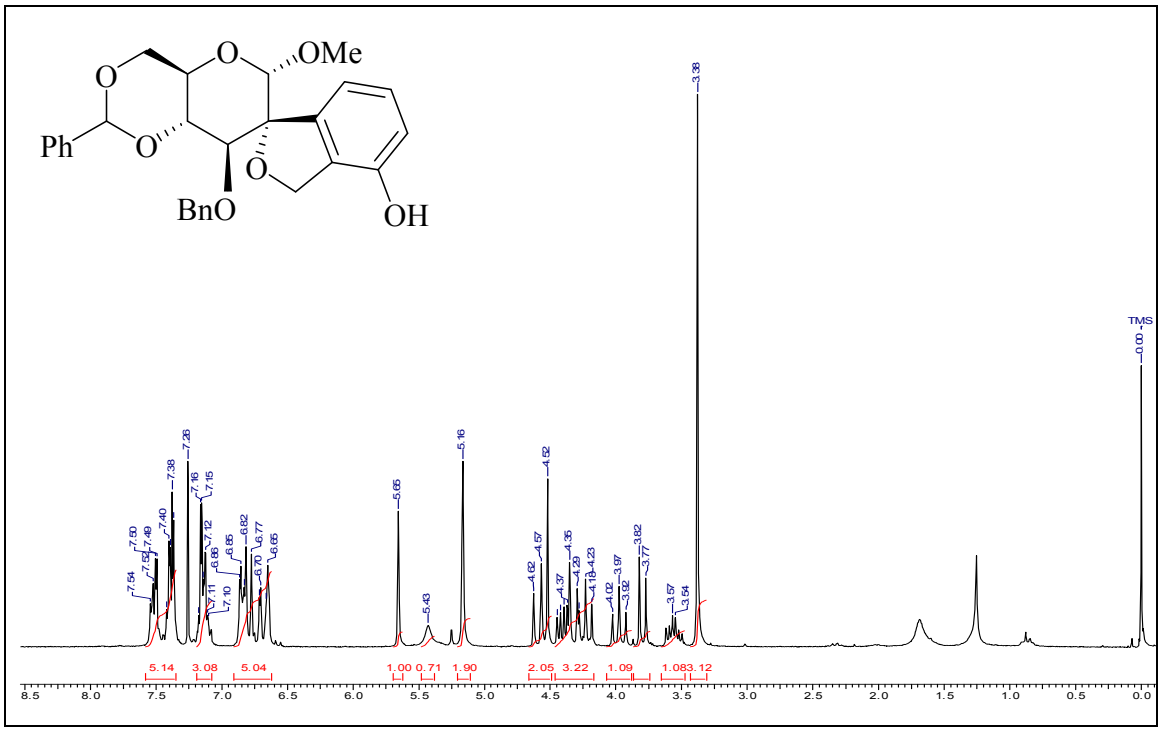
^{13}C spectrum of compound 70 in $CDCl_3$



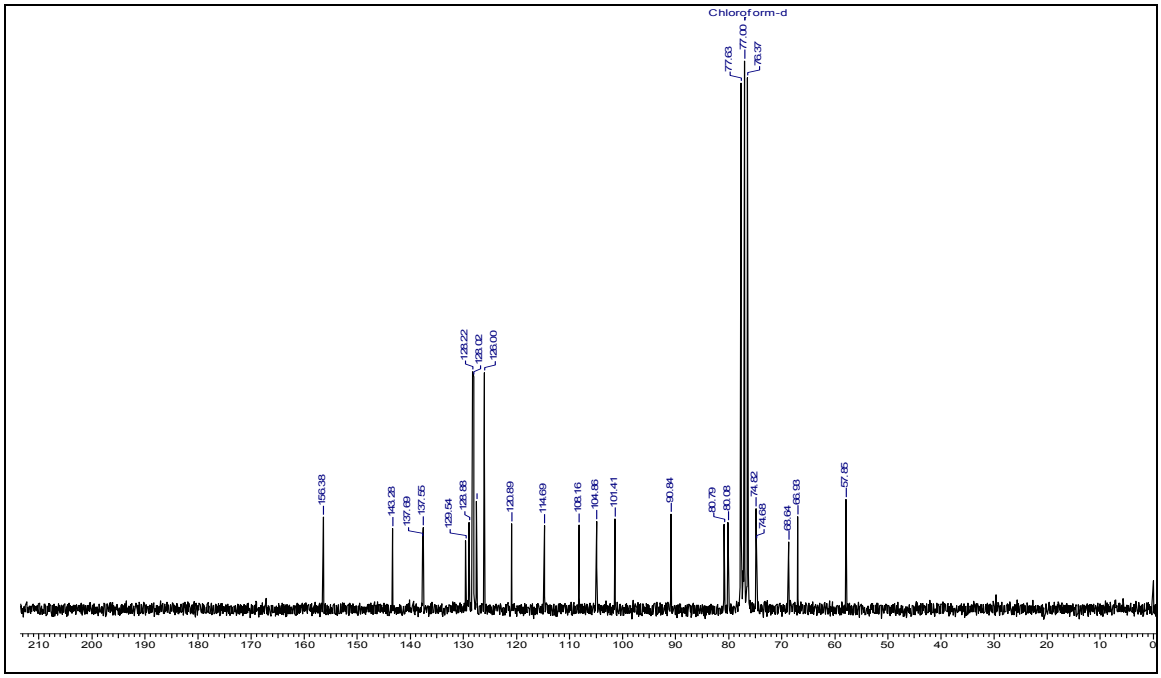
^{1}H NMR spectrum of compound 72 in $CDCl_3$



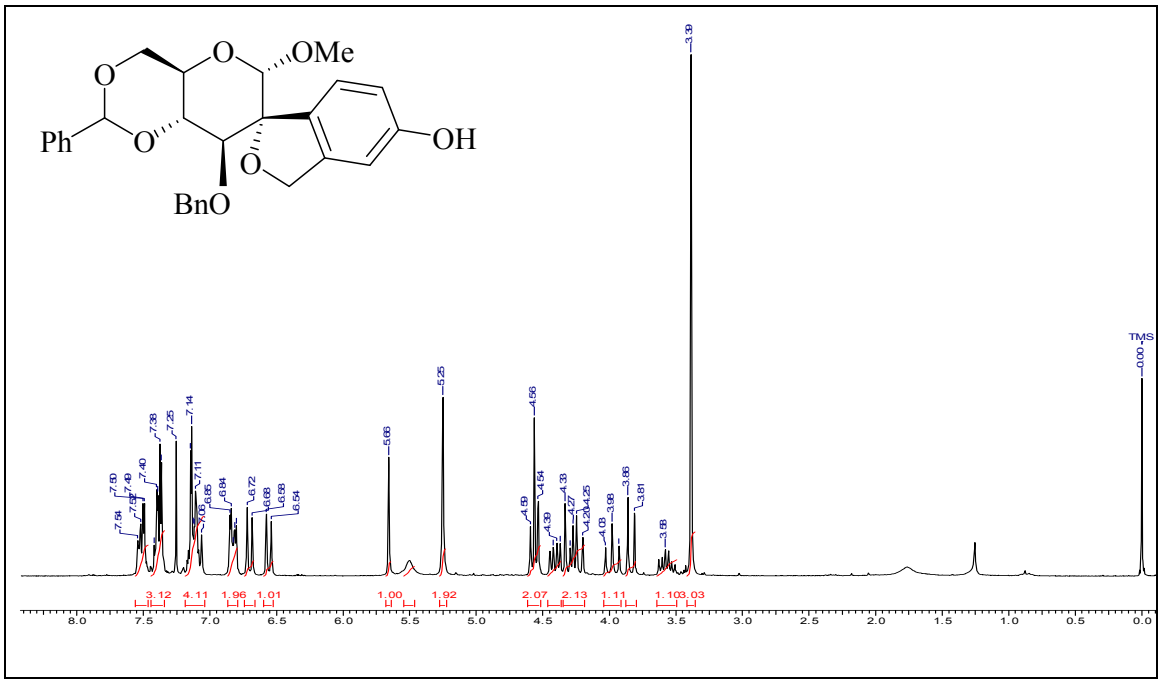
^{13}C NMR spectrum of compound 72 in $CDCl_3$



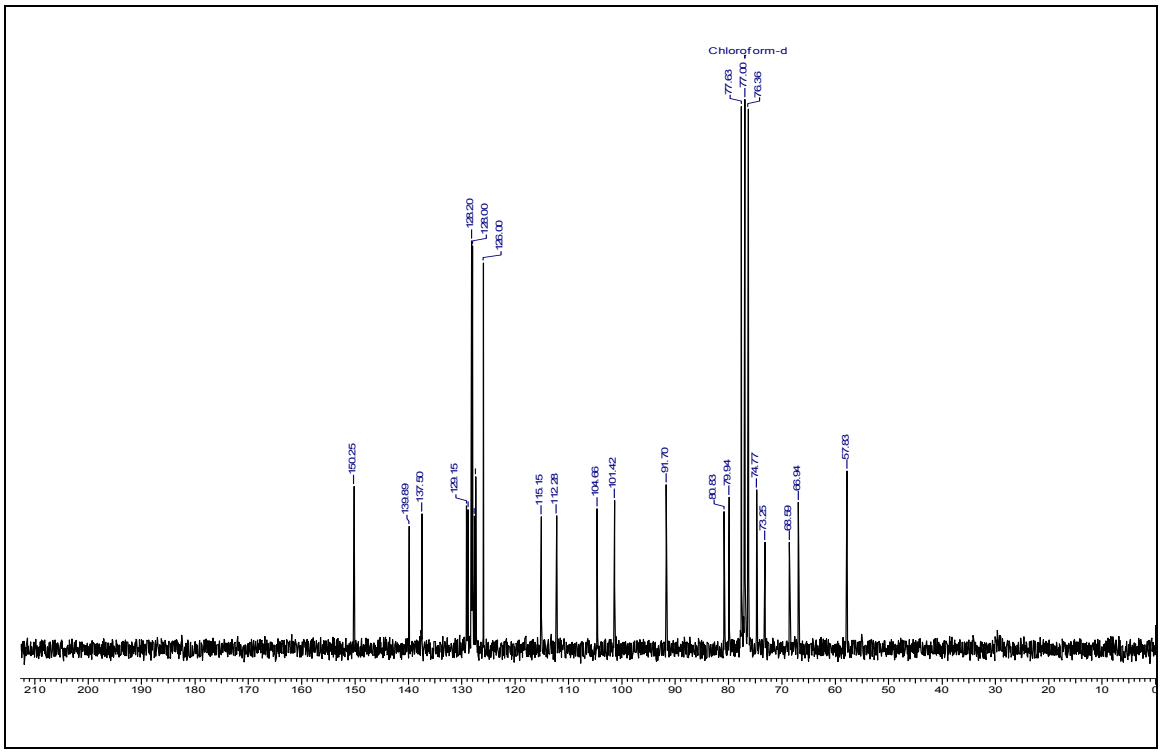
^{1}H NMR spectrum of compound 73 in $CDCl_3$



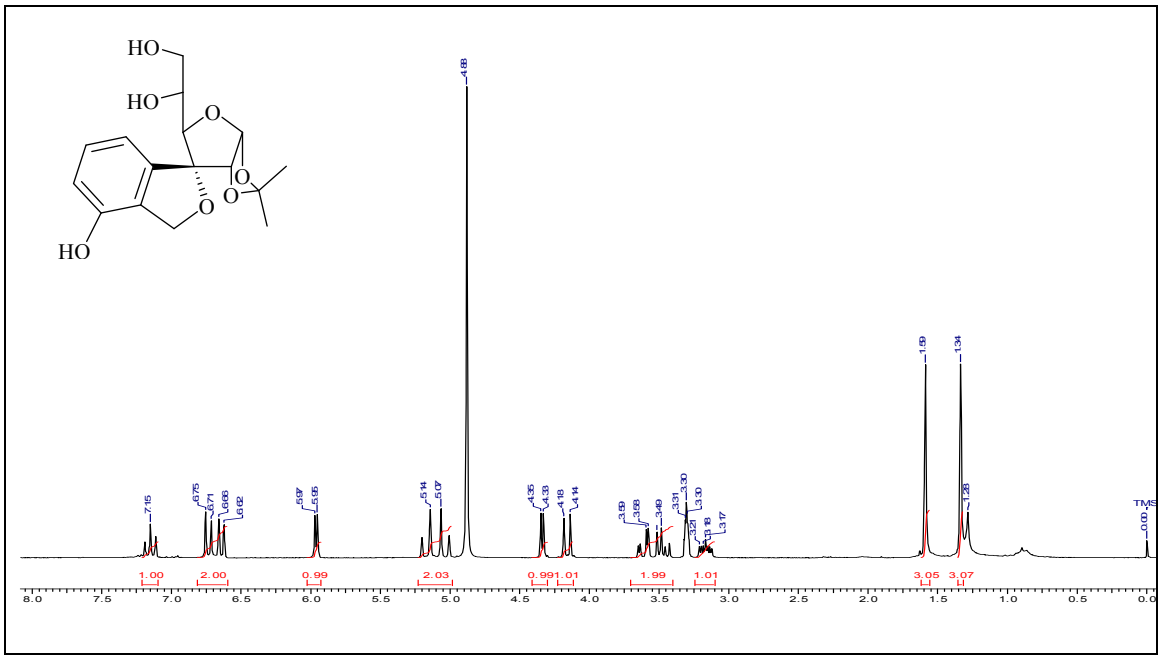
^{13}C NMR spectrum of compound 73 in $CDCl_3$



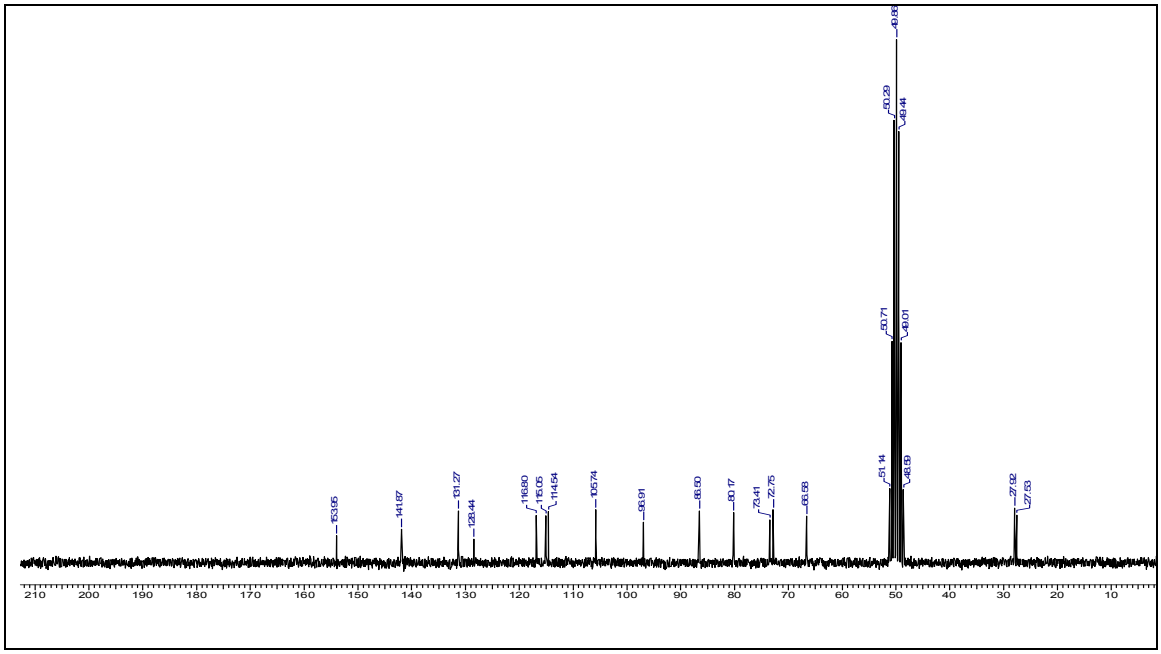
^{1}H NMR spectrum of compound 74 in $CDCl_3$



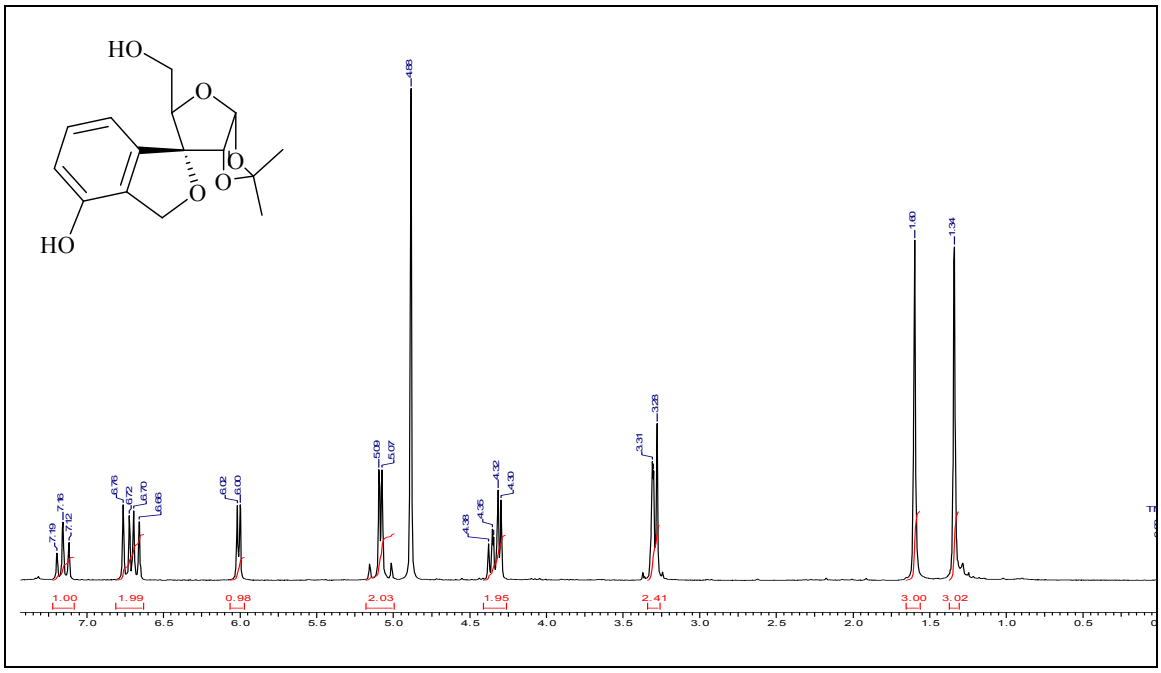
^{13}C NMR spectrum of compound 74 in $CDCl_3$



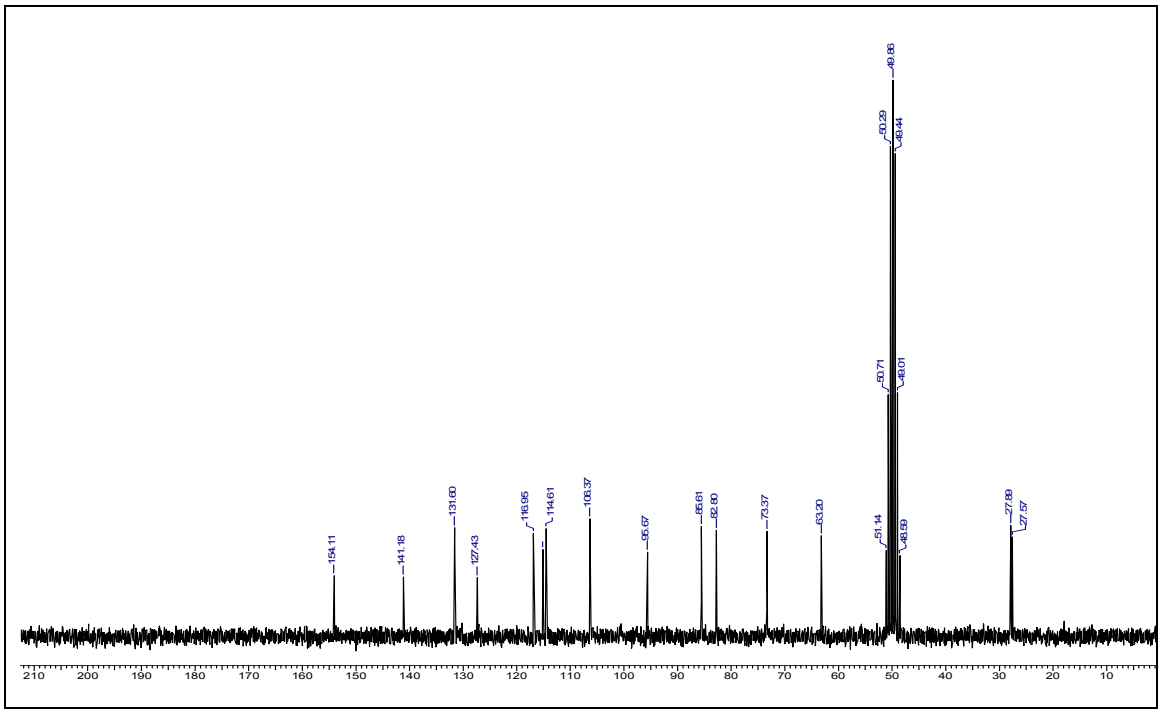
^{1}H NMR spectrum of compound 76 in CD_3OD



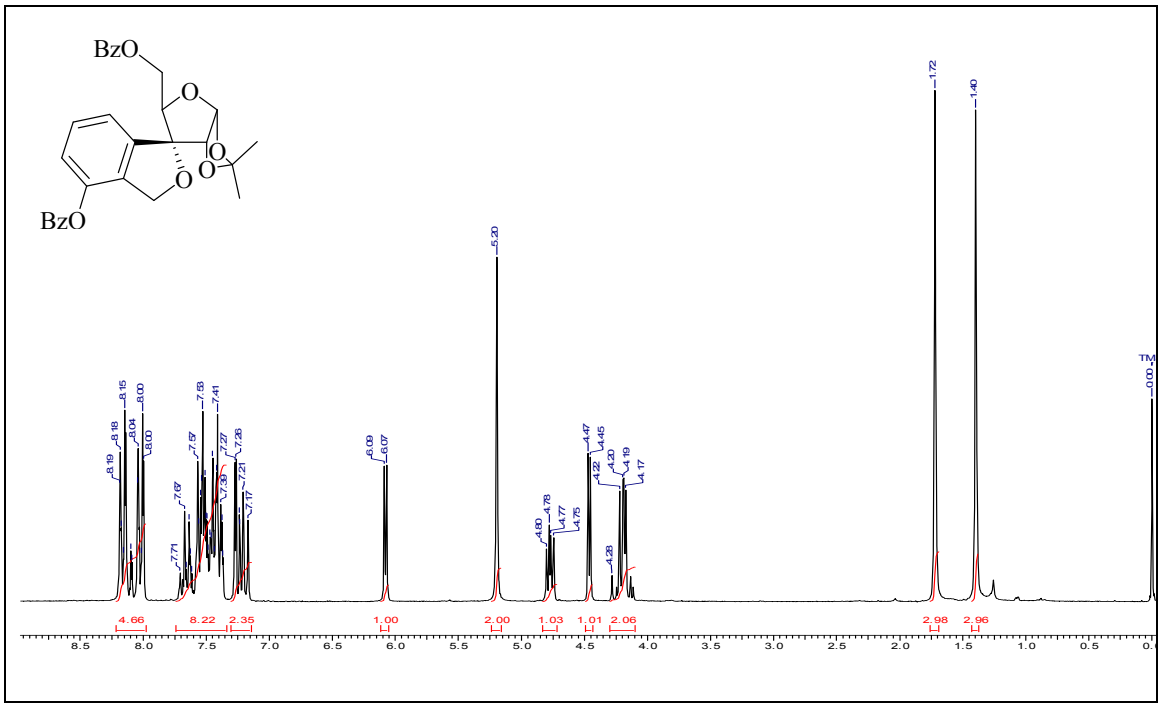
^{13}C NMR spectrum of compound 76 in CD_3OD



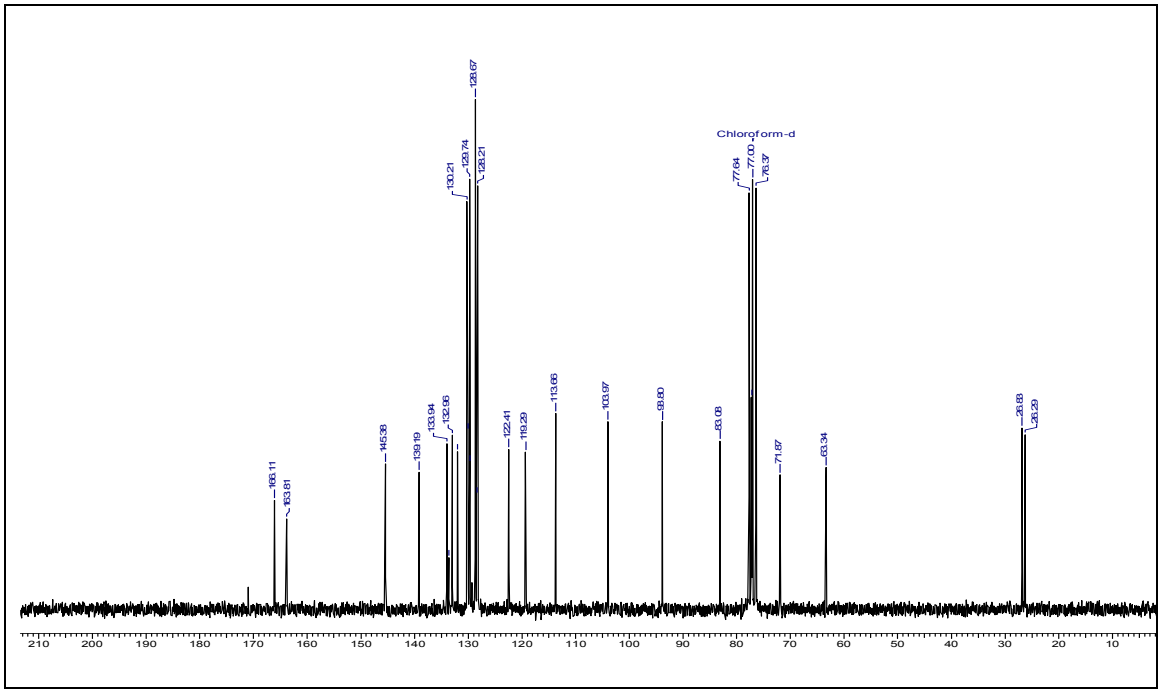
^{1}H NMR spectrum of compound 77 in CD_3OD



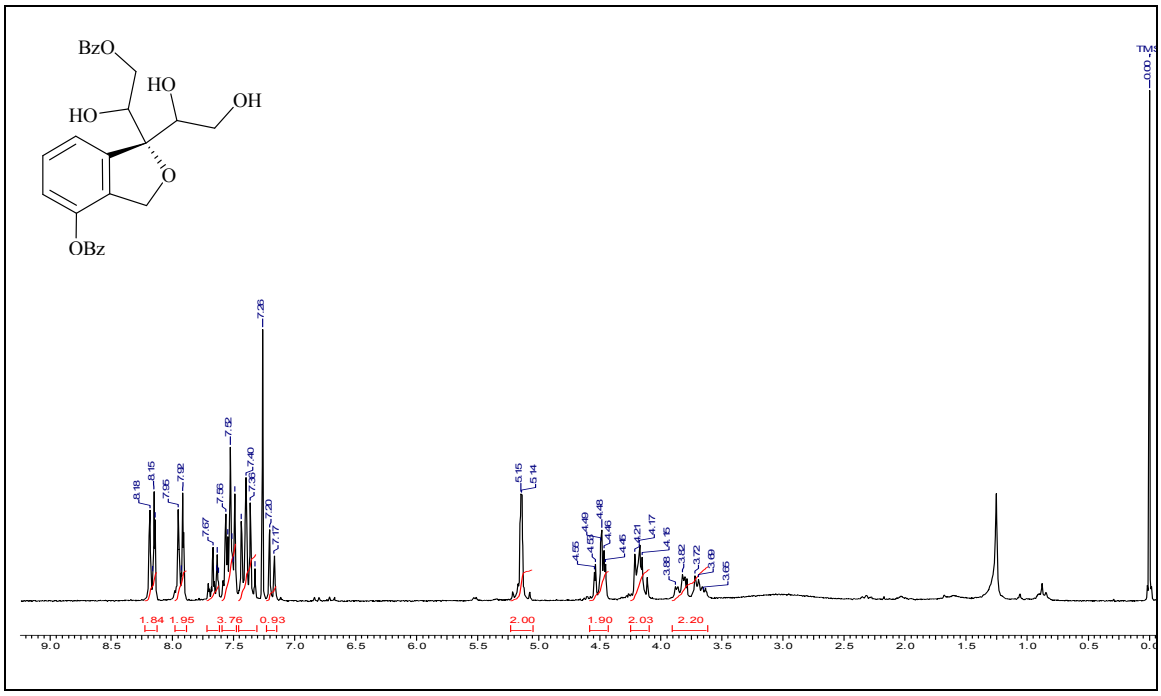
^{13}C NMR spectrum of compound 77 in CD_3OD



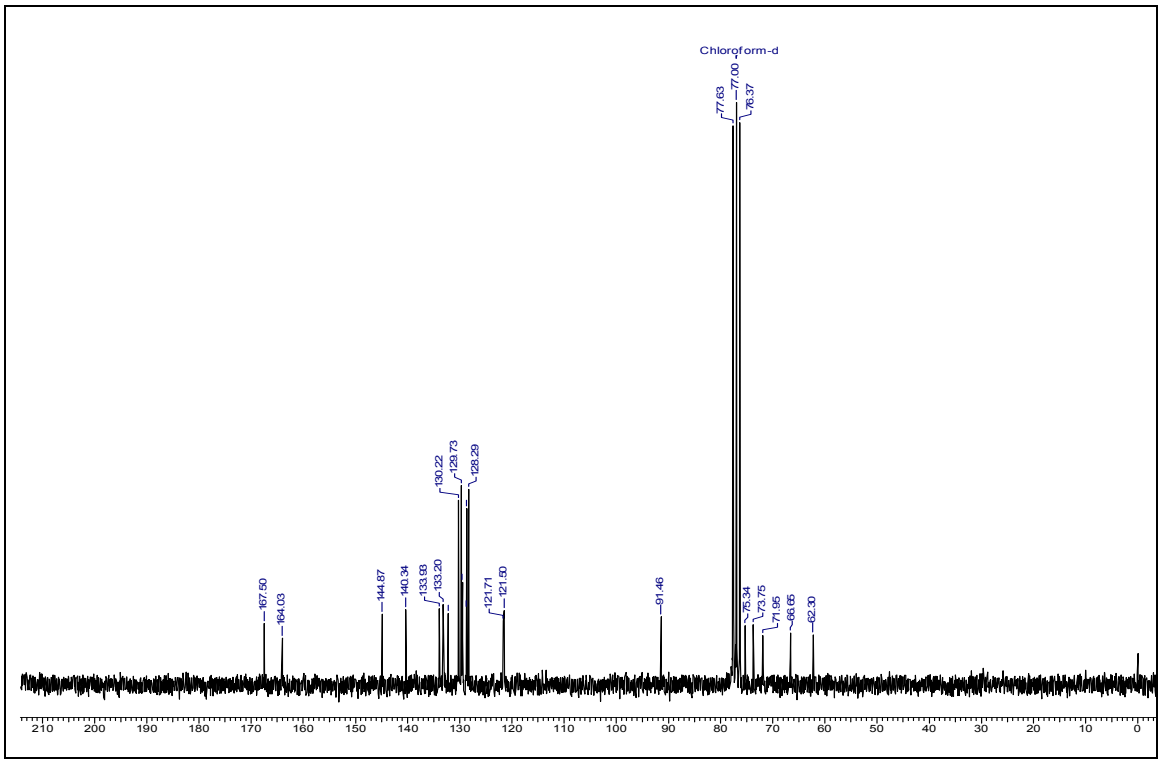
^{1}H NMR spectrum of compound 78 in $CDCl_3$



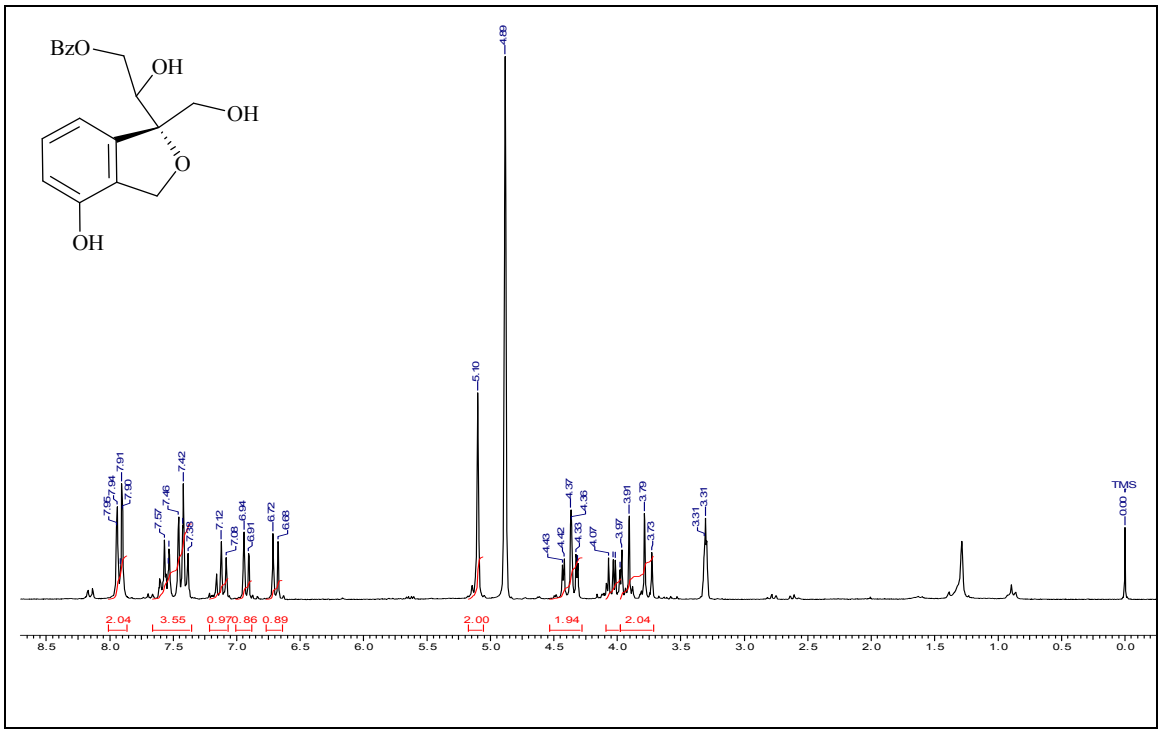
^{13}C NMR spectrum of compound 78 in $CDCl_3$



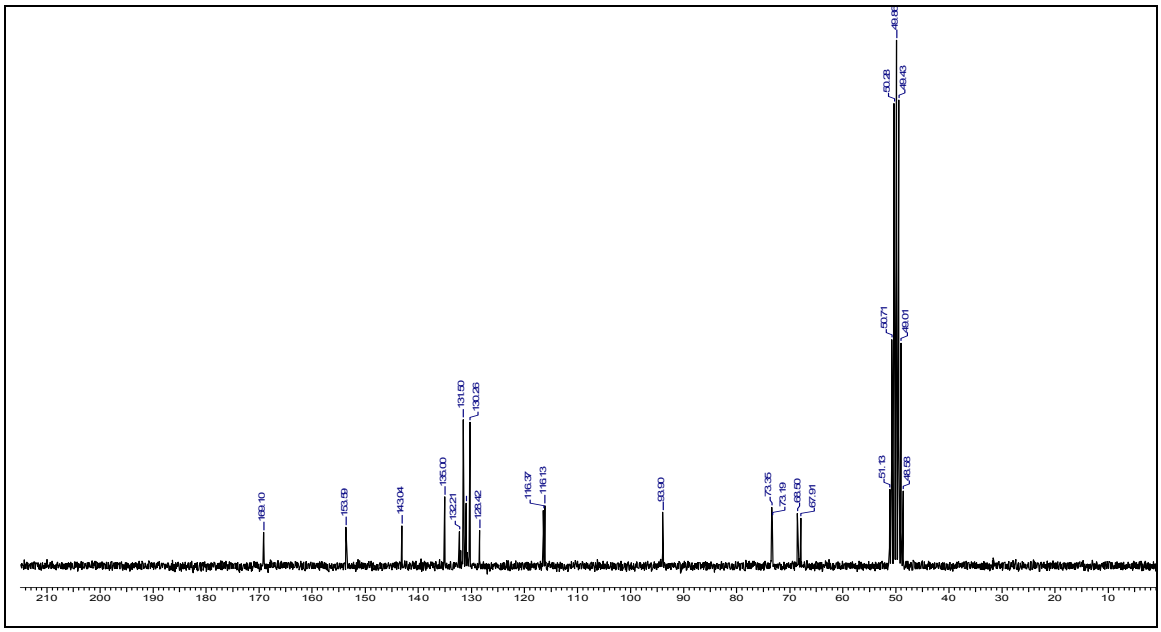
^{1}H NMR spectrum of compound 80 in $CDCl_3$



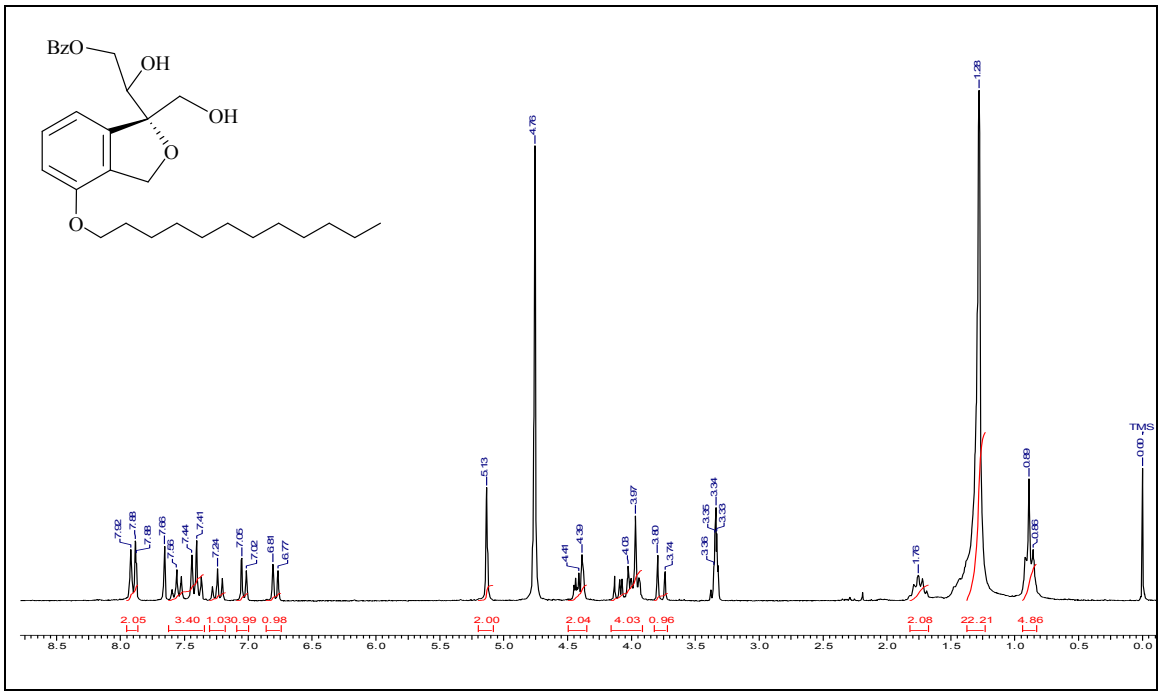
^{13}C NMR spectrum of compound 80 in $CDCl_3$



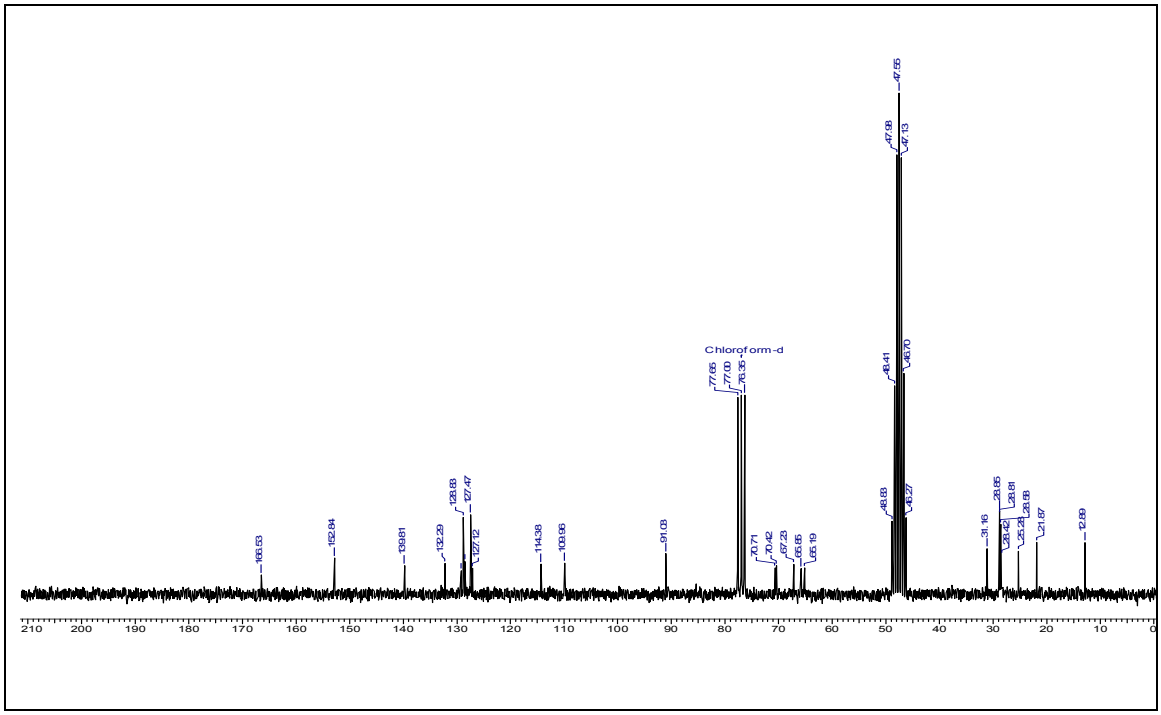
^{1}H NMR spectrum of compound 81 in CD_3OD



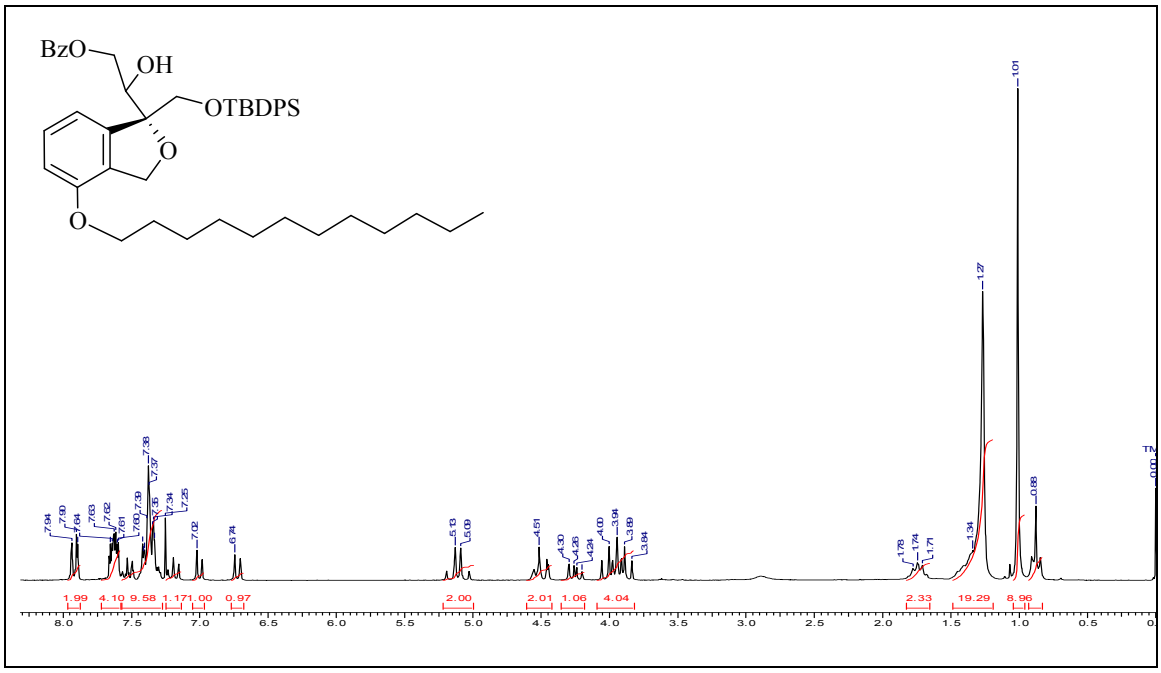
^{13}C NMR spectrum of compound 81 in CD_3OD



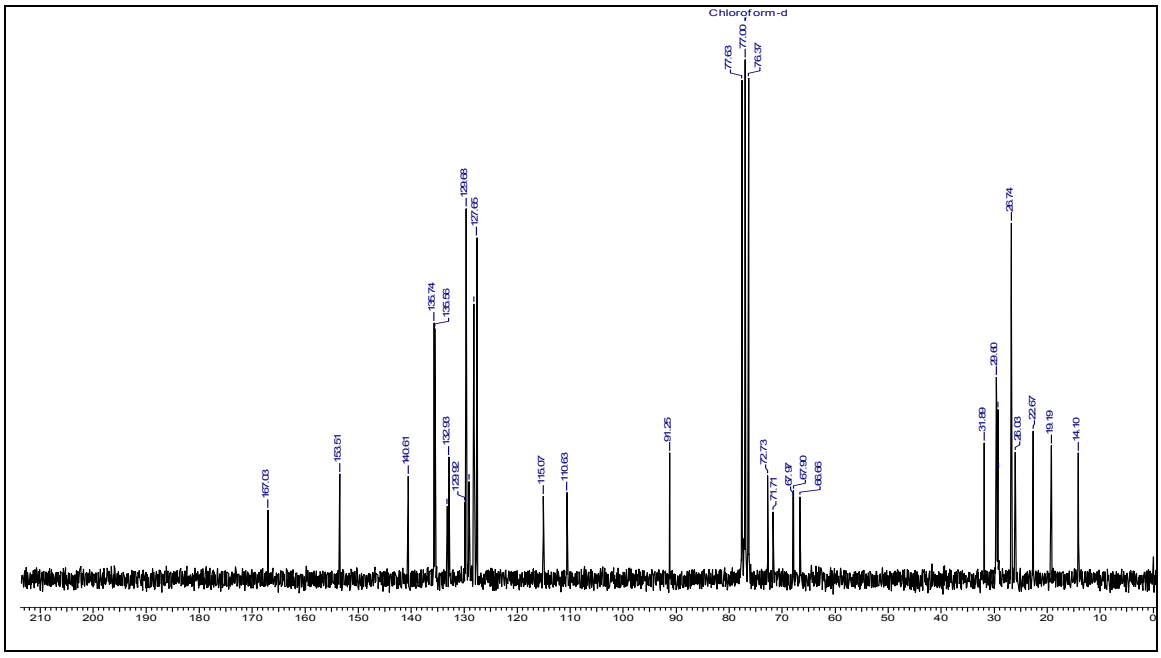
^{1}H NMR spectrum of compound 82 in CD_3OD



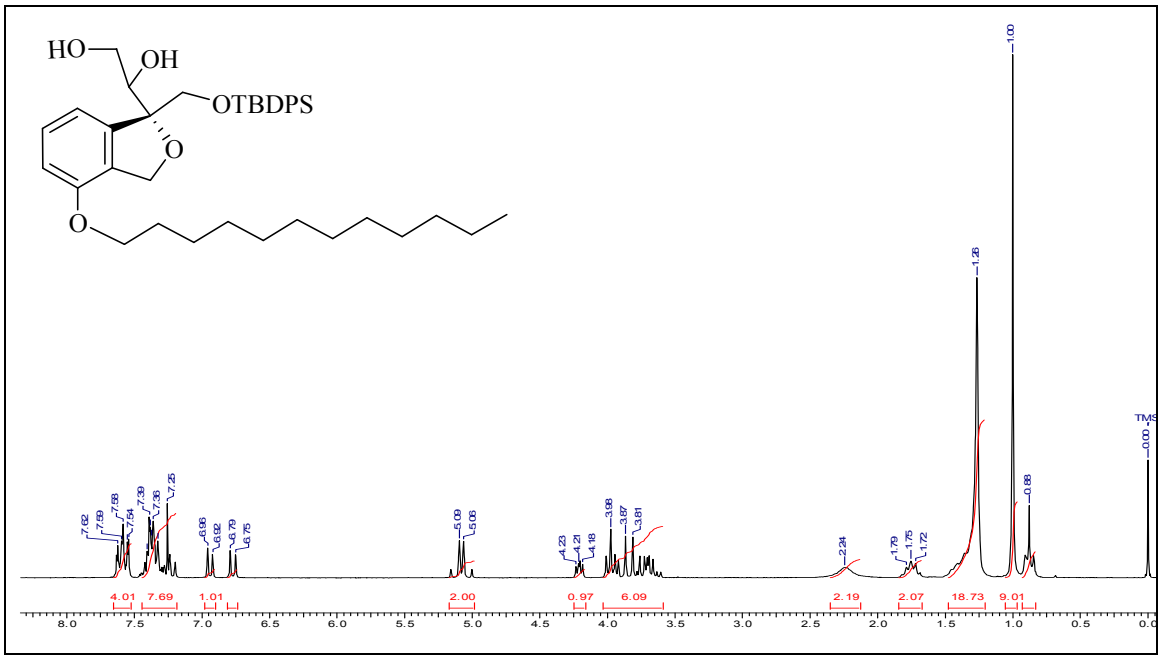
^{13}C NMR spectrum of compound 82 in CD_3OD



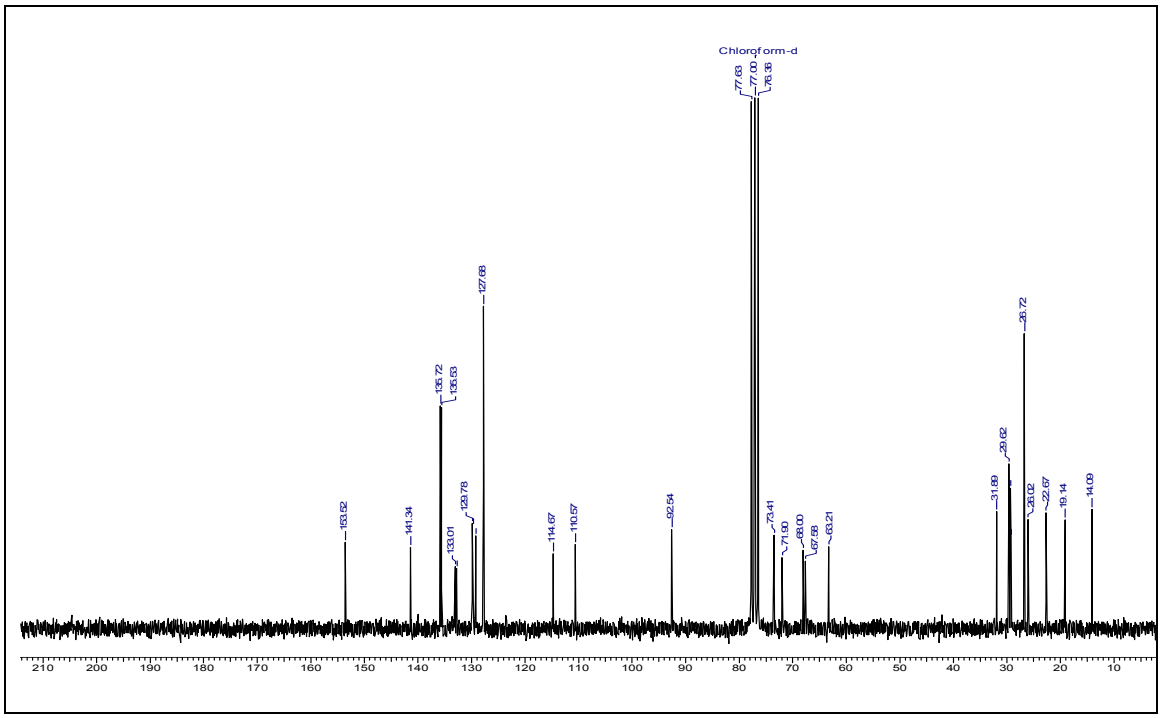
^{1}H NMR spectrum of compound 83 in $CDCl_3$



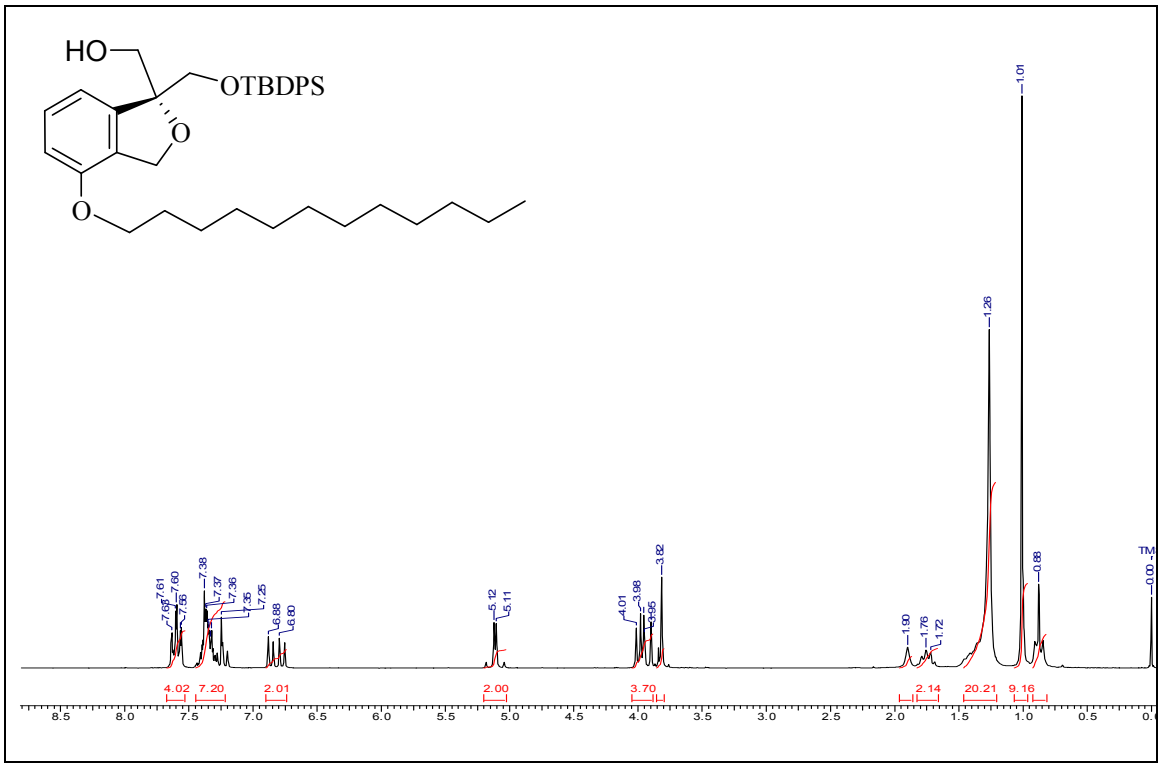
^{13}C NMR spectrum of compound 83 in $CDCl_3$



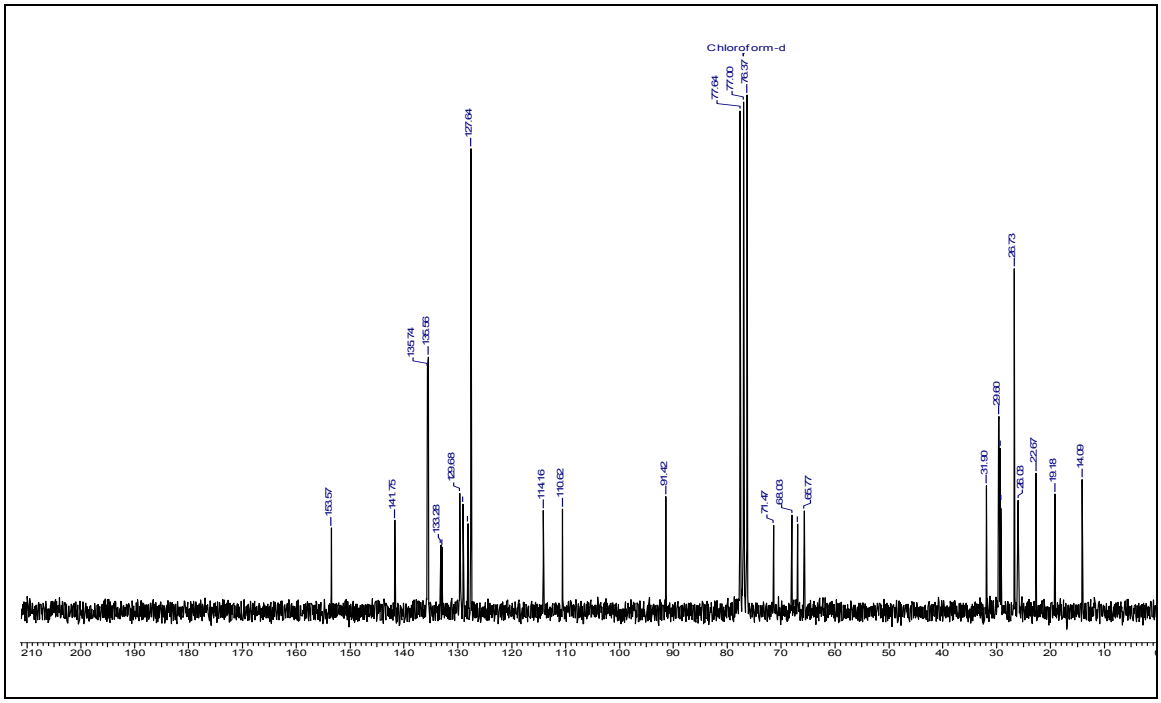
^{1}H NMR spectrum of compound 84 in $CDCl_3$



^{1}H NMR spectrum of compound 84 in $CDCl_3$



^{1}H NMR spectrum of compound 85 in $CDCl_3$



^{13}C NMR spectrum of compound 85 in $CDCl_3$

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Chapter 2: Synthetic Studies on Crassifosides

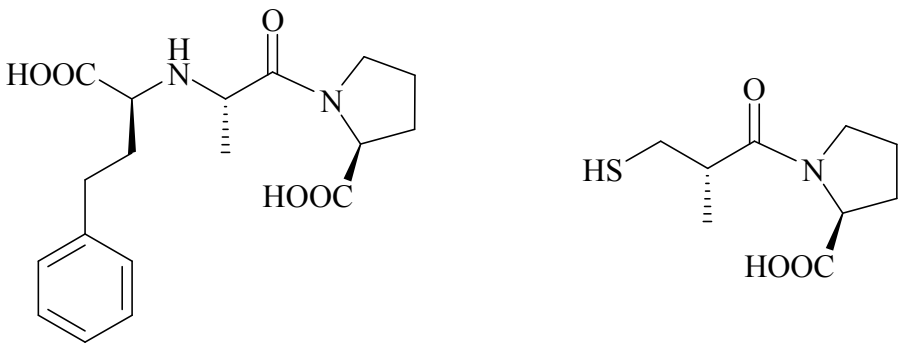
2.1 Introduction

Last half century has witnessed drastic advancement in the organic synthesis especially in the area of total synthesis. So many complex natural products have been isolated and synthesized in the laboratory. Discovery of new C-C bond formation reactions such as ring closing metathesis reinforce the art of organic synthesis and enable one to synthesize natural products of various ring sizes with different functional groups. On the other side, development of various enantioselective processes such as Diels-Alder reactions or Sharpless asymmetric reactions proved to be very fruitful to solve the problems of regioselectivity/enantioselectivity up to some extent[1]. Discovery of new methodologies played major role and enable synthetic chemist to take various challenges for synthesis. Though art of synthesis have seen many advances in last few decades especially after the Corey's discovery of retrosynthetic analysis in 70's but it always have been a fickle science.[2] Since nature is such a skillful and imaginative chemist, there are always too many interesting choices to narrow the field down to just one and targets often based on structures ranging from various families such as alkaloids, macrolides or terpenoides or on biological activity depending on the interest of the chemist but target always have the unique sum of the individual parts and make it challenging for synthesis and always offers the chemist different opportunities for discovery and invention.[3] Natural products are the main source of biologically active compounds used in drug discovery programs and has been isolated from plant, animal or fermentation sources. Plants are the major contributors and often contain a wide variety of natural products which possess wide range of biological activities such as ACE inhibitor, antioxidant properties etc.

ACE Inhibitors

Angiotensin II is a very potent chemical that causes the muscles surrounding blood vessels to contract and thereby narrows the blood vessels. The narrowing of the vessels increases the pressure within the vessels and can cause high blood pressure (hypertension).[4] Angiotensin II is formed from angiotensin I in the blood by the enzyme

angiotensin converting enzyme (ACE). As their name implies, Angiotensin-converting enzyme inhibitors (ACE inhibitors) work by inhibiting the action of the angiotensin converting enzymes, thus preventing the conversion of angiotensin I to angiotensin II. As a result, the blood vessels enlarge or dilate, and the blood pressure is reduced and makes it easier for the heart to pump blood and can improve the function of a failing heart. Hence, ACE inhibitors are a group of pharmaceuticals that are used primarily in treatment of hypertension and congestive heart failure. ACE inhibitors (i.e. Enalapril, Captopril etc.) reduce peripheral vascular resistance via blockage of the angiotensin converting enzyme (Fig. 1). This action reduces the myocardial oxygen consumption, thereby improving cardiac output and moderating left ventricular and vascular hypertrophy. ACE inhibitors are essential for treatment of congestive heart failure (CHF) due to systolic dysfunction. The most common side effect of ACE inhibitors is coughing and potential side effect called hyperkalemia – an abnormally high level of potassium in the blood.[5]



Enalapril Captopril

Figure 1

ACE inhibitors work by manipulating the *renin-angiotensin system*. This system is a self-regulating feedback loop that begins in the kideny with the production of *renin* in response to a drop in blood pressure.[6] Renin is converted into angiotensin. In turn, angiotensin is converted into angiotensin II through the action of *angiotensin converting enzymes*. Angiotensin II is a potent vasoconstrictor that causes constriction of the arteries in the body, as well as retention of water and sodium. Thus, lower levels of angiotensin II are desirable because arteries are more relaxed and open (Figure 2).

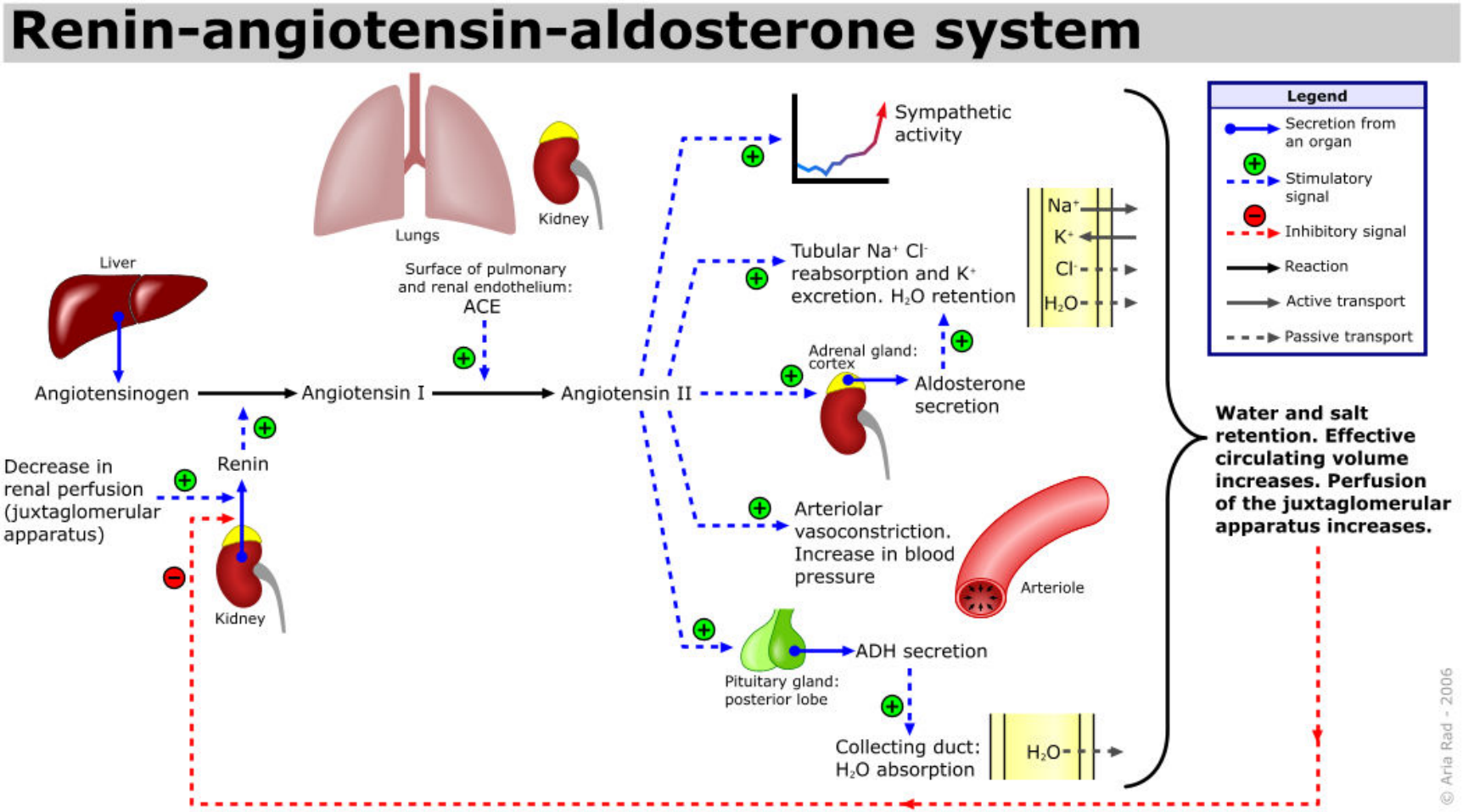

Renin-angiotensin-aldosterone system
Lungs
Kidney
Liver
Surface of pulmonary and renal endothelium:
ACE
Angiotensinogen
Angiotensin I
Angiotensin II
Renin
Decrease in renal perfusion (juxtaglomerular apparatus)
Kidney
Sympathetic activity
Tubular Na+ Cl- reabsorption and K+ excretion. H2O retention
Na+
K+
Cl-
H2O
Adrenal gland: cortex
Aldosterone secretion
Arteriolar vasoconstriction. Increase in blood pressure
Arteriole
ADH secretion
Pituitary gland: posterior lobe
Collecting duct: H2O absorption
H2O
Water and salt retention. Effective circulating volume increases. Perfusion of the juxtaglomerular apparatus increases.
Legend
Secretion from an organ
Stimulatory signal
Inhibitory signal
Reaction
Active transport
Passive transport
© Aria Rad - 2006

Figure 2

ACE inhibitors played vital role for a variety of conditions such as:

- **High Blood Pressure** (hypertension): A condition in which blood is pumped with excessive force against the artery walls. ACE inhibitors cause blood vessels to relax, or widen, reducing blood pressure and may be used alone or in combination with other antihypertensives (e.g. beta blockers, A-II blockers etc.) or diuretics.

- **Heart Failure**: A condition in which one or more of the heart's chambers is not pumping well enough to meet the body's demands, leading to fluid in the lungs and shortness of the breath. ACE inhibitors are often given in combination with β-blockers to reduce the workload on the heart and slow the progression of the heart failure.

- **Heart attack**: An event that results in permanent heart damage or death. A heart attack occurs when one of the coronary arteries becomes severely or totally blocked, usually by a blood clot. When the heart muscle does not obtain the oxygen–rich blood that it needs, it will begin to die. When given shortly after a heart attack, certain ACE inhibitors may prevent some of the damage to the heart and improve the survival rate of heart attack patients.

- **Coronary artery disease**: A condition in which one or more of the blood vessels supplying the heart muscle (coronary arteries) becomes narrowed due to a buildup of plaque (atherosclerosis).

- **Diabetes**: A metabolic condition in which the body cannot properly absorb blood sugar (glucose) because of a lack of, or inability to use, insulin. As a result, glucose levels can rise to dangerously high levels in the bloodstream, which can lead to complications such as kidney damage and increased risk of heart disease. Large studies have shown that ACE inhibitors were able to reduce the risk of developing diabetes.

Treating high blood pressure is important because the condition puts a burden on the heart and the arteries, which can lead to permanent damage over time. If untreated, high blood pressure increases the risk of heart attacks, heart failure, stroke, or kidney failure. ACE inhibitors may also be prescribed for other conditions. For example, captopril is used to treat kidney problems in people who take insulin to control diabetes. ACE inhibitors have gained wide acceptance clinically and are commonly prescribed for the treatment of hypertension and congestive heart failure (CHF).[7] Captopril and lisinopril are also given to some patients after a heart attack. Heart attacks damage and weaken the heart muscle, and the damage continues even after a person recovers from the attack. ACE inhibitors helps slow down further damage to the heart and used to treat congestive heart failure.

Polyphenolic Compounds as Antioxidant

Few plants contain compounds that have potent antioxidant activity and provide protection against diseases, including cancer and cardio- and cerebrovascular diseases in the form of fruits and vegetables and have been attributed to the various antioxidants, especially antioxidant vitamins, including ascorbic acid and α-tocopherol, contained in these fruits and vegetables.[8] However, the majority of the antioxidant activity of a fruit or vegetable may be from compounds other than vitamin C, vitamin E, or β-carotene. For example, some flavonoids that are often found in the human diet have antioxidant activities which cannot be accounted for by their vitamin C content and it was also found that some flavonoids had much stronger antioxidant activities against peroxyl radicals than vitamin E, vitamin C, and glutathione.[9]

The best-known phytochemical antioxidants are traditional nutrients, such as *β*-carotene, ascorbic acid, and α-tocopherol. However, there is growing evidence that a significant portion of the antioxidant capacity of many food plants is due to compounds other than the traditional vitamins. Epidemiological studies indicate that fruit and vegetable consumption is inversely related to cancer and coronary heart disease mortality, and some researchers have suggested that this reduction is not solely due to increased

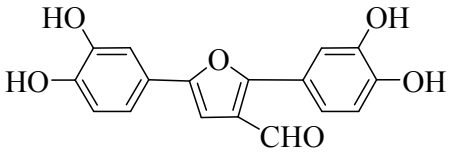
levels of vitamins and fibers.[10] Other compounds, such as polyphenolics, appear to play an important role in the overall antioxidant capacity of fruits and vegetables.

Metabolism, which is nothing but complete sets of reactions that occurs in living cells and forms basis of life like other aspects of life, involves tradeoffs. These metabolic processes always have some byproducts and oxidant byproducts of normal metabolism cause extensive damage to DNA, protein, and lipid and this damage is a major contributor to aging and to various degenerative diseases of aging such as cancer, cardiovascular disease, immune-system decline, brain dysfunction, and cataracts.[11] The functional degeneration of somatic cells during aging appears, in good part, to contribute to these diseases. The relationship between cancer and age in various mammalian species depends on the life span of the species and clear this point. That way cancer increases with about the fifth power of age in both short-lived species, such as rats, and long-lived species, such as humans. One important factor in longevity appears to be basal metabolic rate, which is about seven times higher in a rat than in a human and which could markedly affect the level of endogenous oxidants and other mutagens produced as by-products of metabolism. The level of oxidative DNA damage appears to be roughly related to metabolic rate in a number of mammalian species. It is well known that a balance diet can avoid this type of ageing diseases. Antioxidant defenses against this damage include ascorbate, tocopherol, and carotenoids. Though plants phenols have not been completely studied because of their chemical nature and wide occurrence in plants but still there has been various reports in literature that polyphenols natural products are very good antioxidants. The main source of antioxidants is some fruits such as berries, cherries, blackgraps, citrus fruits and vegetables such as aubergin, chicory, sweet potato yellow onions etc. Olive oil is one of the best sources which contain different polyphenolic compounds which possess anti oxidant properties.[12]

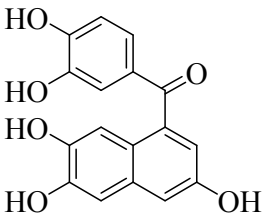
Different studies on various species of genus *Curculigo* have been reported and found rich source of several phenolic and other compounds with interesting biological properties and are well known for their use in medicine. For example, vanillin, 4-hydroxybenzaldehyde, ethyl protocatechuate, orcinol-1-*O*-β-D-glucoside, 2,6-dimethoxy-benzoic acid, β-sitosterol 3-*O*-β-D-glucoside, 2,4-dichloro-5-methoxy-3-methyl-phenol,

curlignan, and 4-ethoxy-3-hydroxy-methylphenol were isolated from the rhizome of the *Curculigo capitulate* while a cycloartenol related triterpenes curculigol A was isolated from the rhizomes of related plant *Curculigo orchioides*.[13]

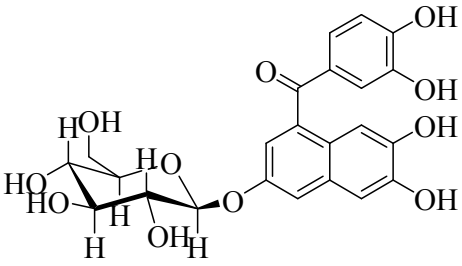
The rhizomes of *Curculigo crassifolia* are used as a folk medicine for treating child pneumonitis. The interesting massive medicinal importance of this plant led to the isolation of the different polyphenolic compounds with prominent biological activity in last few years. Report for isolation of two poly phenolic compounds crassifogenin A and B and two glycosyl-fused novel poly phenolic compounds, Crassifoside C and D from the rhizomes of *Curculigo crassifolia* has come in 2004 (Figure 3).[14]



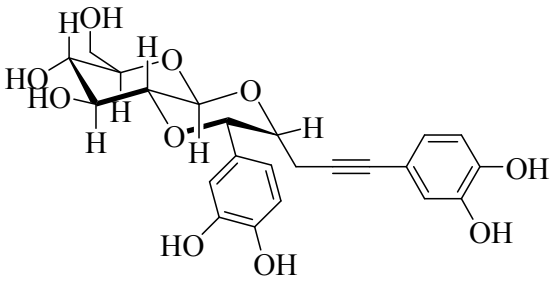
Crassifogenin A



Crassifogenin B



Crassifoside C

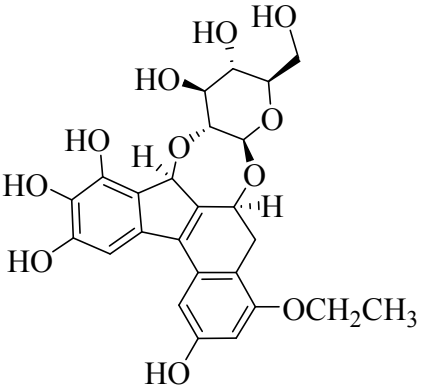


Crassifoside D

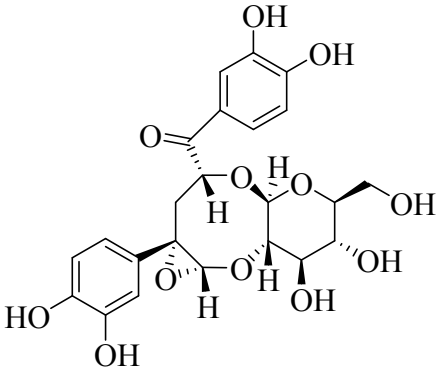
Figure 3

Continuing study on exploring the biologically active part of the rhizomes of this plant resulted in the isolation of two new glucosyl-fused polyphenolic compounds Crassifoside E and F in 2005.[15] Crassifoside E and F exhibited dose dependent ACE inhibition with an IC_{50} value of 10 and 8.5 µg/mL respectively using captopril as positive control substance with an IC_{50} value of 27.5 µg/mL (Figure 4). No report has come so far for the synthesis of this novel class of compounds. Crassifosides E represents the first

natural occurance of a glucosyl-fused 5,6-2H-benzo[4a,4b]fluorine in addition to a diox-seven-membered ring skeleton while Crassifoside F represents the first natural occurrence of a glucosyl-fused diox-eight-membered ring skeleton. The important profound biological properties and unique structural features prompted us to take up the total synthesis of Crassifoside F.



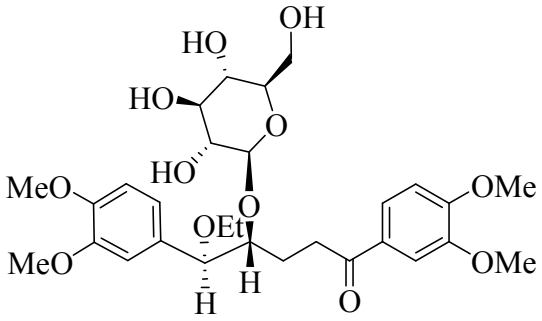
Crassifoside E



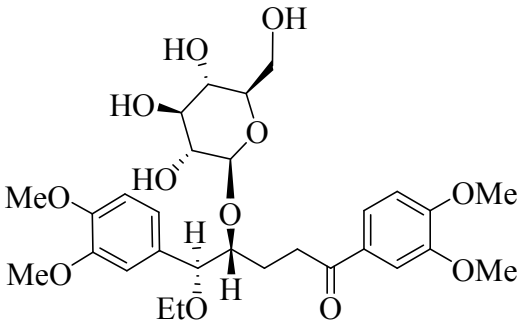
Crassifoside F

Figure 4

Very recently in 2007, a report has come for the isolation of two new polyphenolic glycosyl compounds Crassifoside G and Isocrassifoside G with novel antioxidant activity of IC_{50} 15.53 μM collectively in addition to some known phenolic compounds from the rhizomes of *Curculigo crassifolia* (Figure 5).[16]



Crassifoside G



Isocrassifoside G

Figure 5

Carbohydrates are the straight chain simple organic compounds, containing aldehydes or ketones functional group with enormous number of hydroxyl groups.

Carbohydrates are the most abundant of the four major classes of biomolecules which also include proteins, lipids and nucleic acids. Carbohydrate is especially given importance area in organic chemistry because sugars play important role in various biological processes such as glycolysis, a metabolic pathway by which a 6-carbon glucose molecule is oxidised to two molecules of pyruvic acid, and have got much attention in organic synthesis. The basic carbohydrate units are called monosaccharides such as glucose, galactose, and fructose. Monosaccharides can be linked together in almost limitless ways. Two joined monosaccharides are called disaccharides, such as sucrose and lactose. Carbohydrates containing between about three to six monosaccharide units are termed oligosaccharide; and larger than this is a polysaccharides, such as starch, glycogen which can reach many thousands of units in length. Many carbohydrates contain one or more modified monosaccharide units that have had one or more groups replaced or removed. For example, deoxyribose, a component of DNA, contains modified ribose. Glycosides are the compounds containing carbohydrates part attached to a non carbohydrate or carbohydrate part at anomeric carbon. The glycosyl part, better known as glycosyl donor, attached to a non carbohydrate or carbohydrate part known as aglycone or glycosyl acceptor and the linkage between the donor and the acceptor is known as glycosidic linkage. Depending on the orientation of the glycosidic linkage termed as α or β. Disaccharides are the simplest polysaccharides, composed of two monosaccharide units bound together by a glycosidic linkage. Various methods are well documented in literature for the formation of stereoselective glycosidic linkage. [17]

Since polyphenolic compounds are konown to play very important role as antioxidant and when these polyphenolic compounds are attached with different sugars *via* glycosidic linkage, then importance of these compounds increase tremendously. Crassifosides shows important ACE inhibitor activity, limited availability and contains unique structural features which make them attractive target for the total synthesis. Considering the important antioxidant properties of polyphenolic compounds which is well documented in literature and noted ACE inhibitor activity of Crassifosides, it has been thought to develop a novel pathway to synthesize different members of Crassifosides family. Since family provides a choice for the selection of target for the

total synthesis, **Crassifoside F** was chosen because it contains β-fused D-gucosyl units with two phenolic rings attached to an eight member cyclic core with a number of chiral centers.

2.2 Present Work

Interesting biological activity of different glucosides isolated from the *Curculigo crassifolia* and its limited biological availability prompted us to initiate a programme to develop a strategy for the total synthesis of Crassifosides F (1). As a part of the long term goal to synthesize oxygen-rich, complex and multi-cyclic compounds of profound biological activity, we contemplated upon taking of Crassifosides for the total synthesis.

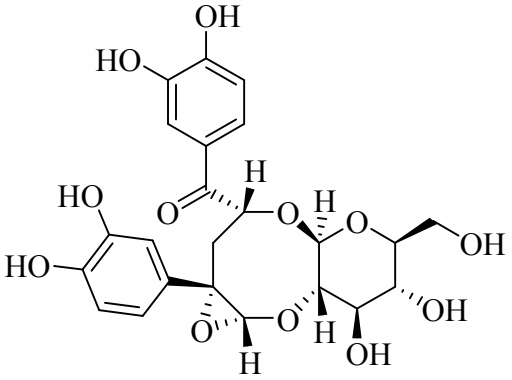
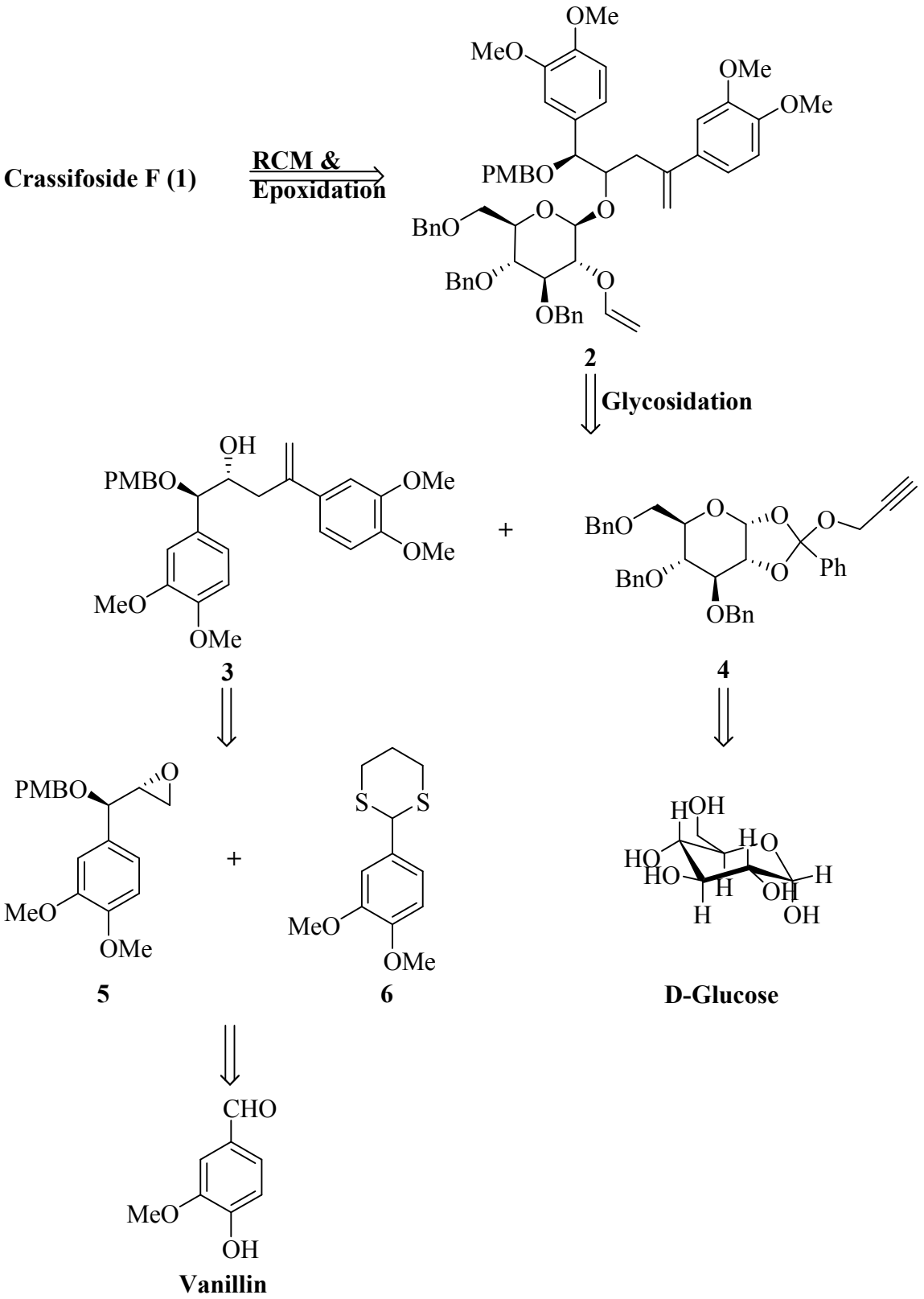


Figure 1: Crassifoside F (1)

The report on the isolation of the Crassifoside F has come in the middle of 2005 and the chemical structure with gross stereochemistry was confirmed by 2D NMR spectroscopy (Fig. 1). Soon after, we initiated our work directed towards the total synthesis of the glucosyl fused novel poly phenolic compound **1**. Our choice of Crassifoside F as a target molecule was based on its polyphenolic framework, ACE inhibitor activity and unique structure. Additionally, we viewed the synthesis of this highly oxygenated natural product as an ideal template for expanding the scope of natural products isolated from the *Curculigo crassifolia*.

Retrosynthetic Analysis of Crassifoside F

Close examination of structure of crassifoside F revealed that this unique glycosyl fused natural product contains a glucose unit attached to an aromatic part *via* a β-glycosidic linkage and hydroxyl group at *C-2* of glucose unit is attached to aromatic ring *via* an ether linkage. The crassifoside F contains an eight member ring with two



Scheme 1: Retrosynthetic Analysis of Crassifoside F (1)

epoxide could be formed from the alkene, which can be obtain from the ring closing metathesis reaction of the suitably substituted diene containing *exo* alkene on the aromatic ring and a vinyl group on the hydroxyl group of the glucose at *C-2* position of the glucoside. The selective glycosidic linkage can be achieved by *trans* glycosidation reaction using recently reported glucoorthoester which is easily available from the D-glucose in excellent yield. On the other hand, the aglycone can be made from the stereoselective opening of epoxide by a Vanillin derived dithiane. The epoxide can be prepared from the allylic alcohol by the help of Sharpless asymmetric epoxidation by kinetic resolution in order to fix the stereochemistry of the alcohol. The epoxide can be easily made from the aldehyde by Grignard reaction using vinyl bromide as the alkylating agent. Aldehyde precursor for Grignard and dithiane can be easily accessed from vanillin by protecting lone phenolic hydroxyl group (Scheme 1). We started our synthetic journey from D-glucose as it is cheap and easily available though there is some ambiguity in the reported structure and structure shown in the original paper by *Li et. al.*[15]

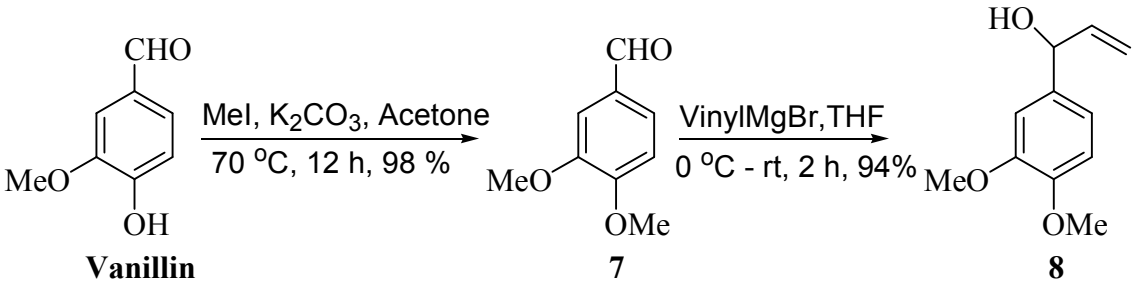
We planned our strategy in three parts (a) Synthesis of aromatic aglycone (b) Synthesis of glucoorthoester as glucosyl donor and (c) Glycosidation of aglycone in order to get oxygen rich cyclic core of Crassifoside F.

Synthesis of Aromatic Aglycone

To begin our investigation, lone phenolic hydroxyl group of vanillin was converted to the methyl ether using MeI and oven dried K_2CO_3 in anhydrous acetone at reflux temperature. The ^{1}H NMR spectrum of aldehyde **7** clearly showed the presence of two singlets at δ 3.95 and 3.98 ppm confirming the presence of two methoxy groups whilst resonances corresponding to aldehyde proton were apparent at δ 9.86 ppm as singlet. Next, the aldehyde **7** was subjected to Grignard reaction using vinylmagnesium bromide in anhydrous THF which resulted in the formation of allyl alcohol **8**. In the ^{1}H NMR spectrum of alcohol **8**, the resonances corresponding to aldehyde proton have disappeared and new resonances corresponding to the methine proton were apparent at δ 6.04 ppm as multiplets while resonances corresponding to alkene $–CH_2$- group were evident at δ 5.15 and 5.32 ppm as two doublets. In the ^{13}C NMR spectrum of alcohol **8**,

the resonances due to methine carbon were identified at δ 140.2 ppm whilst DEPT NMR clearly showed presence of resonances at δ 114.7 ppm corresponding to $–CH_2$- group. Structure of alcohol **8** was further confirmed by elemental and mass spectral analysis (Scheme 2).

Scheme 2



Vanillin **7** **8**

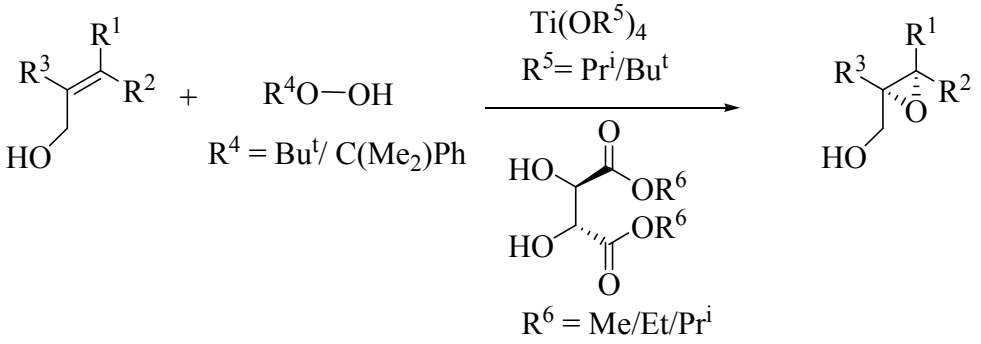
A Short Account on Sharpless Asymmetric Epoxidation Reaction

Asymmetry is ubiquitous in every part of Nature and has a great impact in many fields, not only in chemistry but also even in arts. In the pharmaceutical area and drug discovery process, asymmetry plays an important role, since both enantiomers of a determinate drug do not necessarily have the same activity. Enantioselective synthesis is defined as the transformation of an achiral substrates into only one of the two possible product enantiomers, mainly through the use of chiral catalyst, solvents, etc., and avoiding the annoying attachment and deattachment of chiral auxiliaries, typical of the related diastereoselective approaches. The last three decades have witnessed tremendous increase in the research in enantioselective synthesis and have undergone a true revolution and one process resulted in the award of the 2001 Nobel Prize in Chemistry to Professors Sharpless, Knowles and Noyori for their work on enantioselective synthesis. Titanium is seventh most abundant metal on earth and one of the cheapest transition metal, and nontoxic compare to other transition metals such as Pb, Hg, Cr, Ni, Mn etc. Its nontoxic and environment friendly nature has permitted its use in medical sciences such as sunscreens, removal of toxic metals, prostheses and its relative inertness toward redox processes and the possibility of adjusting its reactivity and selectivity by different ligands make it a preferred candidate for any enantioselective reaction, even employing stoichiometric amounts of the titanium component. In 1980 a major shift occurred with

the introduction of the enantioselective epoxidation of allylic alcohols. Without any doubt this reaction has changed the dimensions of the enantioselective synthesis.[18]

In general, the enantioselective epoxidation of allylic alcohols was accomplished by reaction of an alkyl hydroperoxide in the presence of titanium alkoxide and a chiral tartrate ester**.** The enantioselectivity depends strongly on different variables such as chiral tartrates, ratio of titanium to tartrate, ratio of catalyst (titanium-tartrate complex) to allylic alcohol etc. (Scheme 3).

Scheme 3: Sharpless Asymmetric Epoxidation



Mechanism

There are so many reports for the mechanism of SAE reaction, but after so many studies, the mechanism given in figure 2 is finally accepted. The X-ray crystallography studies revealed that the reaction goes through a bimetallic species which, after a double exchange between two isopropoxide ligands and both the hydroperoxide and the starting olefin, gave the real catalytic species denoted as complex. The hydroperoxide must occupy both the equatorial site and one of the two available axial coordination sites, with the allylic alcohol in the remaining axial site. To achieve the necessary proximity for transferring the oxygen atom to the olefin, the distal oxygen is placed in the equatorial position. The axial site on the lower face of the complex is chosen for the more sterically demanding *t*-butyl moiety, with the allylic alcohol binding to the remaining axial coordinating site. The enantioselective epoxidation takes place on this intermediate, in which olefin coordinates in an appropriate space.

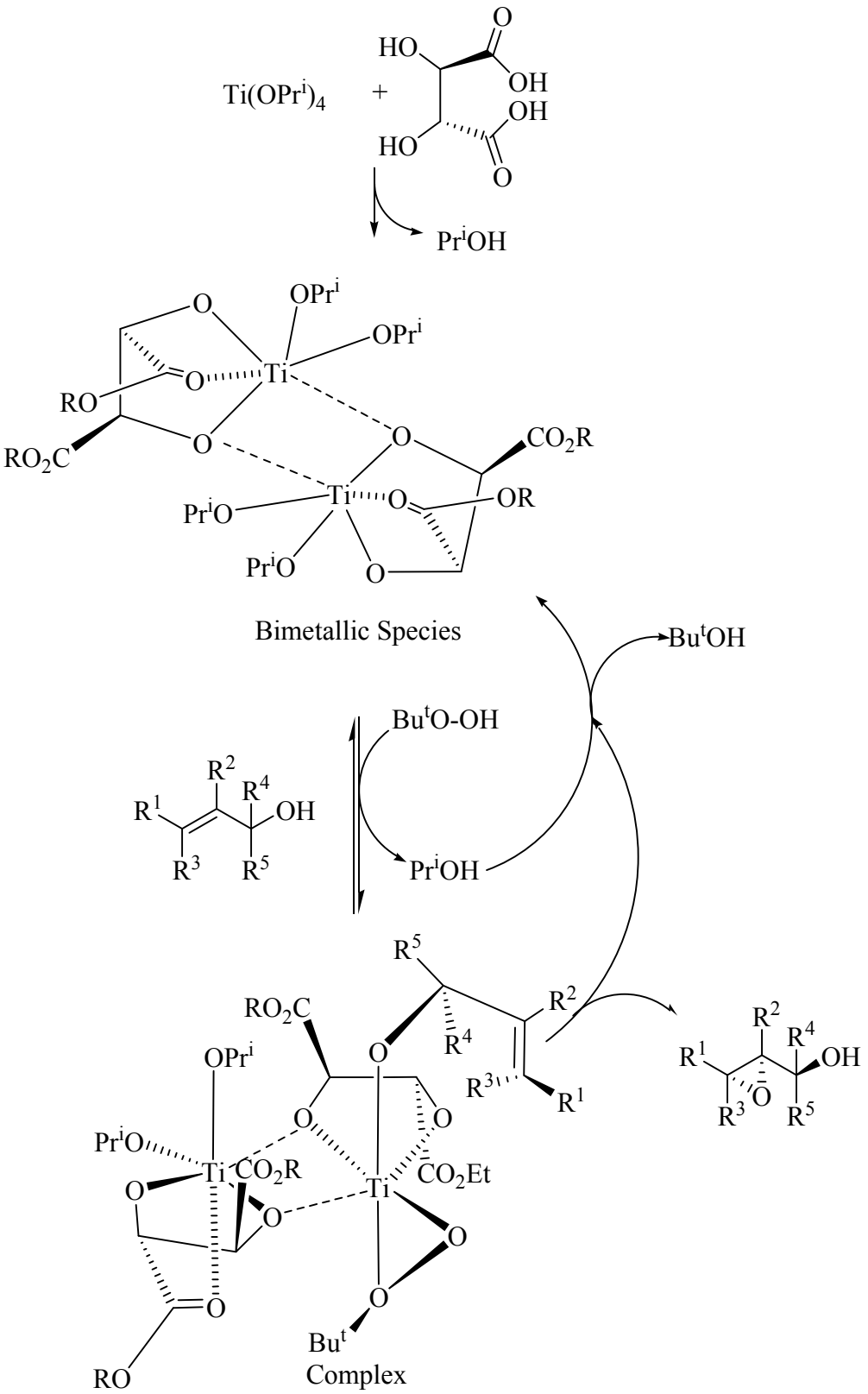
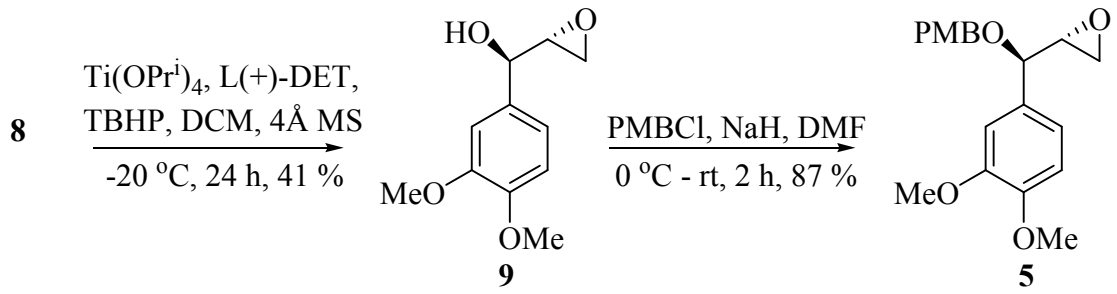


Figure 2: Proposed Catalytic Cycle for the Sharpless Epoxidation

Sharpless Asymmetric Epoxidation on 8

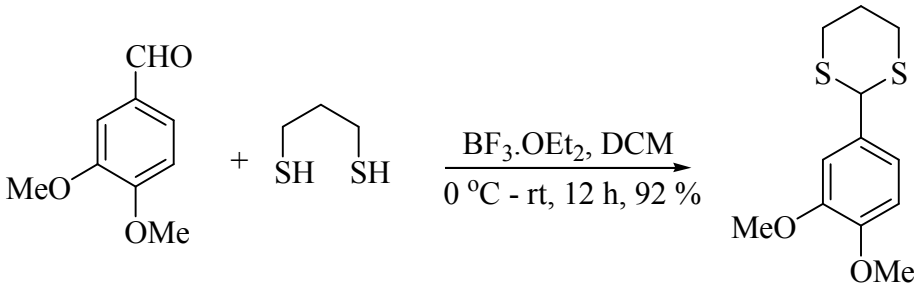
Allyl alcohol **8** was subjected to the Sharpless asymmetric kinetic resolution reaction using $Ti(OPr^i)_4$, L(+)-diethyl tartrate and *t*-butyl hydrogen peroxide in anhydrous DCM in the presence of freshly activated 4 Å MS powder to obtain epoxide **9**. The ^1H NMR spectrum of the epoxide **9** showed absence of the resonances corresponding to the methine and $–CH_2-$ group of allyl alcohol whereas new resonances attributed to epoxide $-CH_2-$ group were apparent at δ 2.79 and 2.95 ppm as two double doublets and resonances corresponding to the methine proton were apparent at δ 3.22 ppm along with other resonances according to assigned structure of epoxide **9**. The ^{13}C NMR spectrum showed absence of resonances corresponding to alkene group of allyl alcohol with the appearance of two new resonances at δ 55.0 and 43.6 ppm whilst in DEPT NMR spectrum resonances at δ 43.6 ppm confirmed the presence of $–CH_2-$ group of epoxide **9**. Next, the free hydroxyl group of epoxide **9** was protected as PMB ether using PMBCl and NaH in anhydrous DMF. In the ^1H NMR of the PMB ether **5**, the resonances at δ 3.80 and 3.89 ppm corresponds to three –OMe groups whilst resonances corresponding to benzylic $–CH_2-$ group were apparent at δ 4.31 and 4.49 ppm as two doublets along with requisite protons resonances in aromatic region. In the ^{13}C NMR spectrum, the resonances corresponding to three aromatic –OMe groups were noticed at δ 55.9 and 55.2 ppm along with the resonances at δ 159.2 ppm corresponding to *quaternary* carbon of PMB group. In the DEPT NMR spectrum, two $–CH_2-$ resonances occurred at δ 70.2 and 45.2 ppm whilst resonances corresponding to *quaternary* carbon of aromatic ring were disappeared confirming the structure of PMB protected epoxide **5**. In addition the structure was also confirmed by elemental and mass spectral analysis (Scheme 4).

Scheme 4



After successful preparation of epoxide **5** our next target was to synthesize the dithiane **6**. The treatment of aldehyde **7** with 1,3-propane dithiol in the presence of catalytic amount of the $BF_3.OEt_2$ at room temperature resulted in the formation of dithiane **6**. The ^1H NMR spectrum clearly showed the absence of the resonances corresponding to the aldehyde group and new resonances attributed to the aliphatic $–CH_2$- groups at δ 2.00 and δ 2.84 – 3.14 ppm as two multiplets clearly showed the formation of dithiane. In the ^{13}C NMR spectrum resonances corresponding to aliphatic $-CH_2-$ group of dithiane moiety were identified at δ 32.1 and 25.0 ppm which was unambiguously confirmed by the DEPT NMR spectroscopy (Scheme 5).

Scheme 5

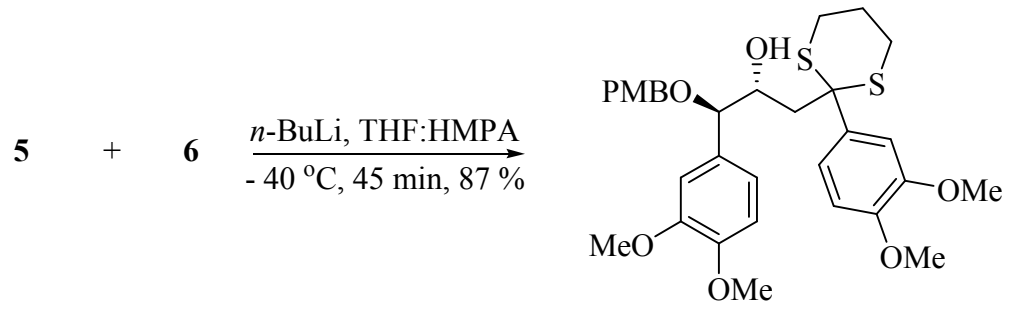


7 **6**

Having epoxide **5** and dithiane **6** in hand, our attention was then turned towards their union. In order to get the coupled product, the generation of the lithiated anion of the dithiane **6** was attempted using *n*-BuLi in THF: HMPA (10:1), - 40 °C, followed by the quenching of the anion with epoxide **5** which resulted in the formation of coupled product **10** in excellent yield. In the ^1H NMR spectrum of the **10**, the resonances corresponding to the $–CH_2$- groups of dithiane moiety observed at δ 1.94 and 2.72 ppm as two multiplets while the other $–CH_2$- group of epoxide shifted up field and noticed at δ 2.22 and 2.53 ppm as double doublets and doublet respectively integrating for one proton each with five $-OCH_3$ groups at δ 3.78, 3.80, 3.84, 3.88 ppm with all other resonances with the assigned structure of **10**. The ^{13}C NMR spectrum showed the presence of *quaternary* carbon resonances of dithiane moiety at δ 57.07 ppm along with all other resonances according to the structure **10** while the DEPT NMR spectrum clearly showed resonances corresponding to $–CH_2$- groups of dithiane moiety at δ 24.7, 27.6, 27.8, corresponding to benzylic $-CH_2-$ at δ 70.3 ppm and other resonances were apparent at δ

46.7 ppm. In addition the structure was also confirmed by elemental and mass spectral analysis.

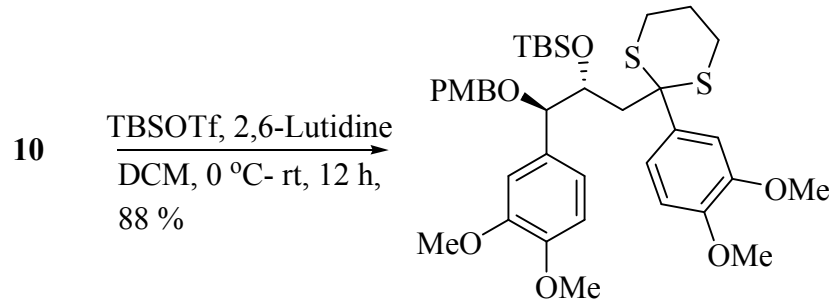
Scheme 6



10

Subsequently, the *secondary* hydroxyl group of coupling product **10** was protected as its silyl ether **11** using TBSOTf and 2,6-lutidine in anhydrous DCM. In the ^{1}H NMR spectrum of the **11**, the resonances corresponding to the *t*-butyl group were apparent at δ 0.84 ppm as singlet while the resonances corresponding to two methyl groups of silyl ether were found at δ 0.03 ppm along with all other proton resonances according to assigned structure. The ^{13}C NMR spectrum showed the resonances corresponding to carbons attached to silyl group at δ -5.0, -3.9 and 25.9 ppm along with *quaternary* carbon resonances of *t*-butyl groups at δ 18.0 ppm which were further confirmed by DEPT NMR spectrum wherein all resonances were found according to assigned structure of **11** without ambiguity (Scheme 7).

Scheme 7

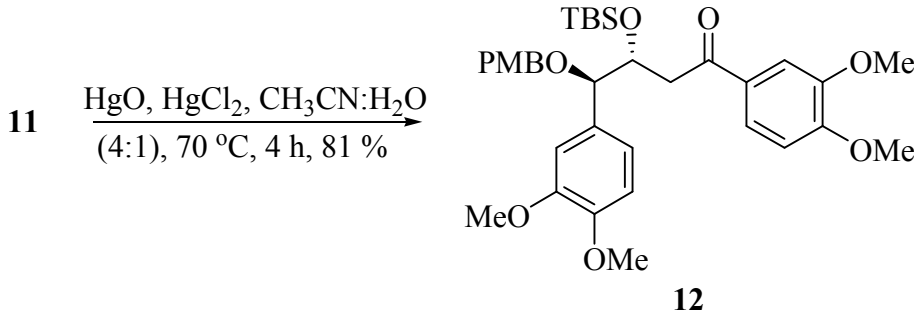


11

Our next concern was to form *exo* double bond in order to get alglycone **3**. Accordingly, the deprotection of the dithiane group was affected by treatment of silyl ether **11** with HgO (yellow) and $HgCl_2$ in acetonitrile-water (4:1) at 70 °C for 4 h which resulted in the formation of ketone **12** in 92 % yield. In the ^{1}H NMR spectrum, all

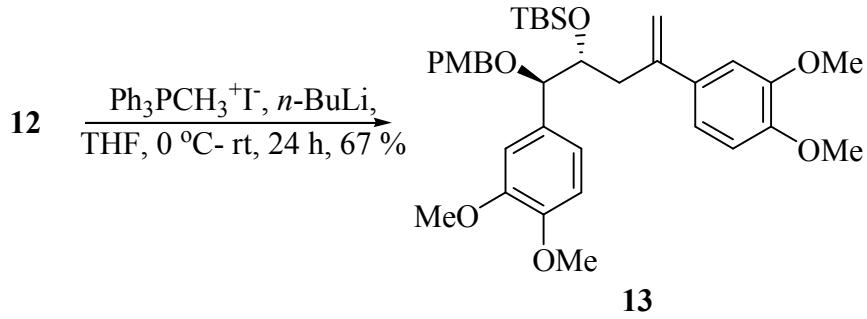
resonances corresponding to $-CH_2-$ groups of dithiane of silyl ether **11** were absent wherein ^{13}C NMR spectrum resonances at δ 197.5 ppm confirmed the presence of carbonyl group. The structure was further confirmed by DEPT NMR spectroscopy and elemental and mass analysis (Scheme 8).

Scheme 8



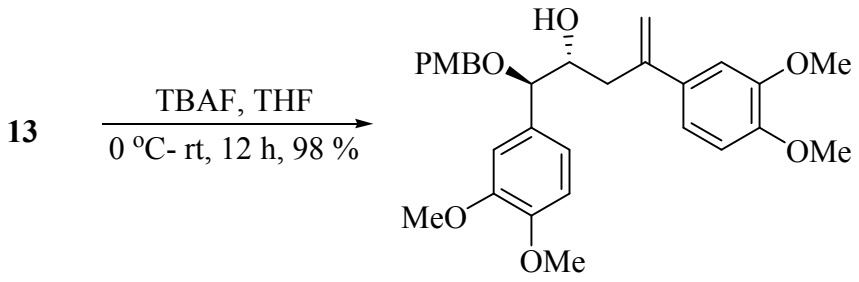
Further, the ketone **12** was subjected to one-carbon Wittig reaction using one-carbon Wittig "ylide" and *n*-BuLi in anhydrous THF which resulted in the formation of alkene **13** in 67 %. In the ^1H NMR spectrum of **13**, resonances corresponding to the newly generated *exo* $-CH_2-$ group of alkene were apparent at δ 5.06 ppm as a singlet and δ 5.29 ppm as doublet along with other resonances according to the assigned structure. In the ^{13}C NMR spectrum of the compound **13**, the resonances corresponding to carbonyl group of ketone **12** was absent and new resonances were apparent at δ 144.5 and 114.0 ppm corresponding to *quaternary* carbon and *exo* $-CH_2-$ group of alkene respectively wherein DEPT NMR spectrum showed resonances of *exo* $-CH_2-$ group at δ 114.0 ppm along with all other resonances according to assigned structure (Scheme 9).

Scheme 9



The TBS group of the alkene **13** was deprotected using tetra n-butyl ammonium fluoride solution in anhydrous THF which resulted in the formation of aglycone **5**. The structure of the aglycone was confirmed by various spectroscopic methods (Scheme 10).

Scheme 10



3

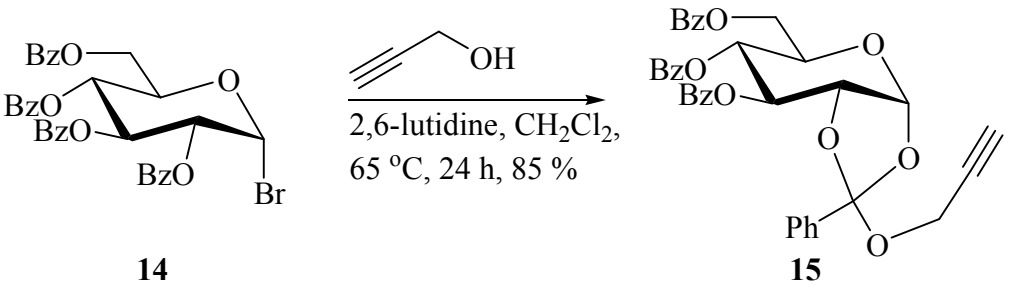
After successful preparation of aglycone **5** our next concern was to prepare glycosyl donor in order to effect the glycosylation reaction.

Synthesis of Glycosyl Donor

Stereoselective glycosidation reaction is one of the most challenging problem in carbohydrate chemistry and much effort has been devoted to develop methods for the stereoselective synthesis of glycosides. Recently, we discovered propargyl ortho ester as *trans*-glycosyl donors.[19] It has been thought to utilize the recently identified propargyl ortho ester as glycosyl donors in the total synthesis of various glycosyl natural products.

Continuing our synthetic endure towards the total synthesis of Crassifoside F, 3,4,6-tri-*O*-benzoyl propargyl orthoester **15** was prepared by a known procedure from 2,3,4,6-tetra-*O*-benzoyl glucosyl bromide **14** using propargyl alcohol and 2,6-lutidine at 65 ^{o}C for 24 h.[20] In the ^{1}H NMR spectrum of the orthoester **15**, the resonances corresponding to the acetylenic protons were noticed at δ 2.40 ppm while anomeric proton resonances were observed at δ 6.12 ppm along with all other requisite resonances. The ^{13}C NMR spectrum showed resonances at δ 97.7 ppm corresponding to the anomeric carbon whilst three benzoate ester carbonyls at δ 164.1, 165.1 and 165.9 ppm along with all other resonances according to assigned structure of **15**. The DEPT NMR spectrum unambiguously confirmed presence resonances corresponding to two –CH_2- groups at δ 52.3 and 63.8 ppm along with all other resonances (Scheme 11).

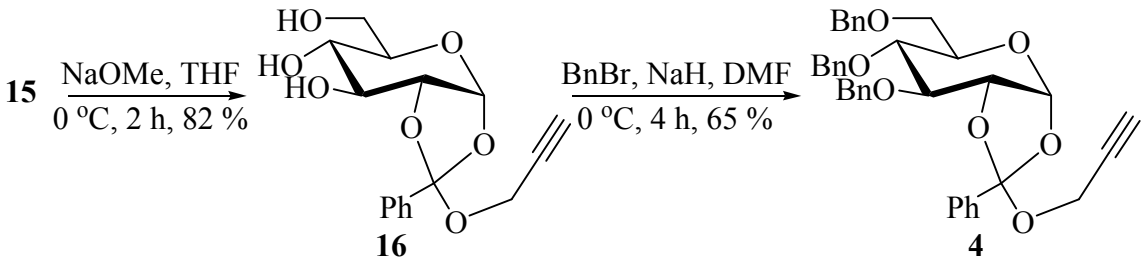
Scheme 11



14 **15**

As it is obvious from the structure of crassifoside F, it possesses an eight member ether ring fused with glucose unit at anomeric position *via* a β-glycosidic linkage and at *C-2* position as an ether *via* α-linkage. Our next concern was to manipulate the protecting group of 3,4,6-tri-*O*-benzoyl propargyl glucoorthoester **15** in such a way so we can use C-2 hydroxyl group stereoselectively. Accordingly, the benzyl protection was chosen because of its high stability towards the most of the acidic and basic conditions. The hydrolysis of benzoate ester groups of orthoester **15** was effected using NaOMe in anhydrous THF followed by per benzylation of resulting three hydroxyl groups of triol **16** using BnBr and NaH in anhydrous DMF in order to get 3,4,6-tri-*O*-benzyl propargyl glucoorthoester **4** as glycosyl donor. In the ^{1}H NMR spectrum of the compound **4**, the resonances corresponding to acetylenic proton were apparent at δ 2.36 ppm as triplet while resonances of anomeric proton were at δ 6.00 ppm with all other resonances according to **4**. The ^{13}C NMR spectrum showed presence of propargyl –CH_2- group at δ 52.0 ppm while anomeric carbon resonances were identified at δ 98.3 ppm whereas DEPT NMR spectrum showed presence of all –CH_2- groups resonances along with all other carbon resonances according to assigned structure of **4** without any ambiguity. Structure of compound **4** was further confirmed by elemental and mass spectroscopy (Scheme 12).

Scheme 12



16 **4**

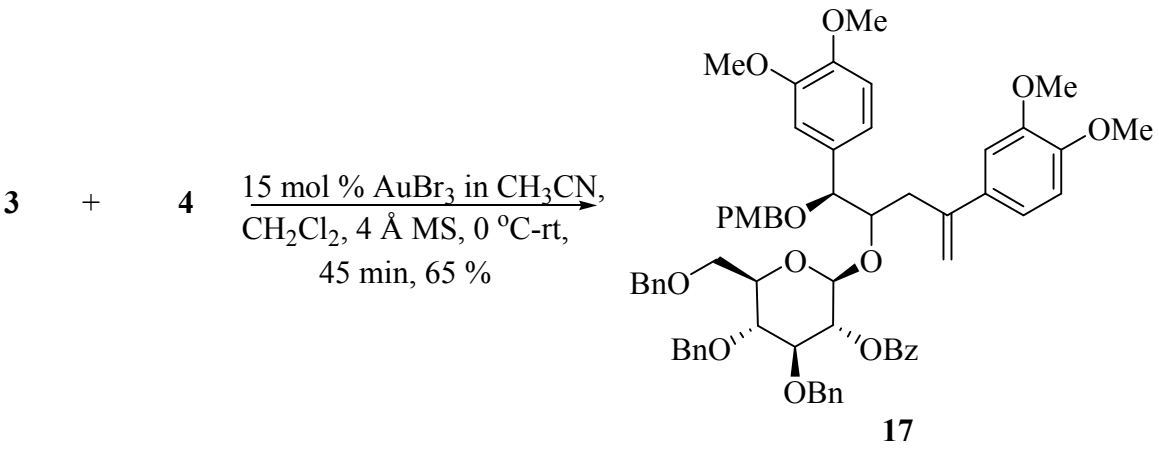
Glycosidation

Having prepared glycosyl donor and aglycone, our next attention turned towards the glycosidation reaction. Very first, we tried glycosidation reaction in acetonitrile solvent using 10-20 mol % $AuCl_3$ as promoter at room temperature in presence of 4 Å MS powder but glycosidation did not result in any desired product. When we tried the same reaction in anhydrous DCM in presence of freshly activated 4 Å MS powder using 10 mol % $AuCl_3$ by dumping method (solid addition of promoter) at room temperature, the reaction resulted in the formation glucoside **17** in very low yield *ca*~25 % along with the formation of some unidentified products whereas increase in promoter concentration to 20 mol % did not give any considerable improvement in yield and resulted in the decomposition of aglycone. To minimize formation of byproducts we thought of controlled addition of promoter dissolved in some solvent. Hence $AuCl_3$ dissolved in acetonitrile was added dropwise *via* a syringe over 5 min. Gratifyingly there was some improvement in yield *ca*~ 35 % but still the decomposition of the aglycone along with the formation of some byproducts was observed. Furthermore we checked the effect of temperature on the reaction. To begin our investigation, aglycone and glycosyl donor were dissolved in anhydrous DCM in presence of freshly activated 4 Å MS powder cooled at 0 ^oC was added 15 mol % of $AuCl_3$ dissolved in acetonitrile *via* a syringe over 5 min, and then temperature was raised to room temperature. The reaction resulted in the formation of glucoside **17** in 45 % yield with minimal decomposition of aglycone.

We then focused our attention on varying the catalyst. The Lewis acidity of $AuBr_3$ is considered to be higher than the $AuCl_3$. Thus, we used $AuBr_3$ in place of $AuCl_3$ under the optimize condition which resulted in the formation of glucoside **17** in 65 % yield with minimal decomposition of aglycone (78 % based on recovered aglycone). In ^1H NMR spectrum of the glucoside **17**, the resonances corresponding to $–CH_2-$ group of aglycone were apparent at δ 2.65 ppm whereas five –OMe groups at δ 3.55, 3.76, 3.79, 3.80, 3.82 ppm along with resonances of two benzoate protons at δ 8.02 ppm. In the ^{13}C NMR spectrum, resonances corresponding to the anomeric carbon were apparent at δ 101.5 ppm while benzoate carbonyl resonances at δ 164.3 ppm wherein DEPT NMR spectrum resonances at δ 34.2 ppm corresponding to aliphatic $–CH_2-$, four resonances at δ 69.1, 71.1, 73.2, 73.4, 74.8 ppm confirmed the presence of four benzylic $-CH_2-$ and one

glucose -CH_2- whilst resonances corresponding to *exo* –CH_2- group were apparent at δ 113.8 ppm (Scheme 13).

Scheme 13

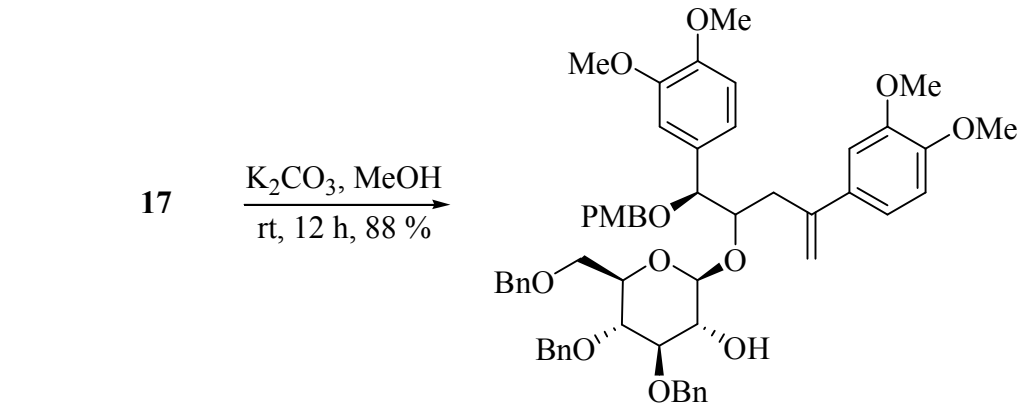


17

First Generation Strategy Based on a Ring-Closing Metathesis Reaction

Next, hydrolysis of benzoate ester group at *C-2* of glucose moiety was performed using K_2CO_3 in methanol. The ^{13}C NMR spectrum clearly showed absence of carbonyl resonances corresponding to benzoate esters. Structural authenticity was further confirmed by ^1H, DEPT NMR and elemental and mass spectral analysis (Scheme 14).

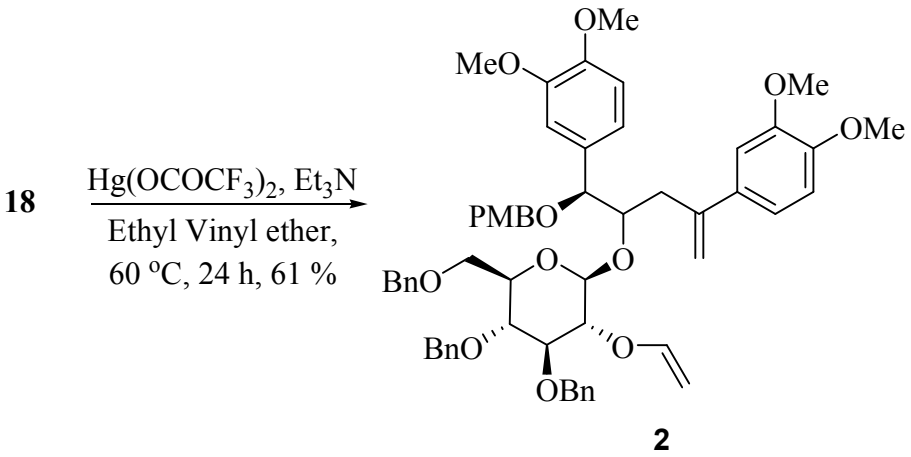
Scheme 14



18

After having glucoside **18** containing a free hydroxyl group at *C-2* position of glucose moiety, our next concern was to protect it as vinyl ether in order to get diene **2** as RCM precursor. Initial attempts to convert hydroxyl group to vinyl ether by treatment of glucoside **18** with ethyl vinyl ether using catalytic to stoichiometric amount of $Hg(OCOCF_3)_2$ at 0 ^oC to reflux temperature were unsuccessful. Next, a tube fitted with screw cap containing glucoside **18** in ethyl vinyl ether was heated with $Hg(OCOCF_3)_2$, and triethyl amine at 60 ^oC for 24 h resulted in the formation of vinyl ether in 61 % yield (32 % recovered alcohol **18**).[21] In the ^1H NMR spectrum of vinyl ether **2**, the resonances corresponding to –CH- proton were apparent at δ 6.46 ppm as double doublets whereas ^{13}C NMR spectrum showed resonances corresponding to vinyl –CH- and -CH_2- groups at δ 153.2 and 88.7 ppm respectively which was further confirmed by DEPT NMR spectroscopy (Scheme 15).

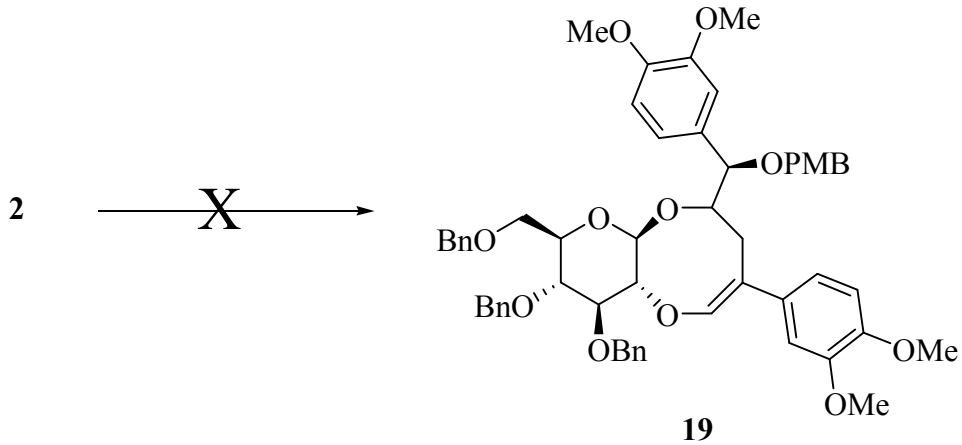
Scheme 15



2

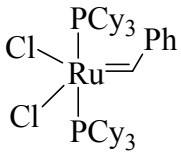
After successfully preparation of diene **2** our immediate concern was towards ring closing metathesis reaction of the diene **2**. We tried several reaction conditions using 5-20 mol % of Grubbs 1st (**A**) and 2nd (**B**) generation catalysts for the RCM reaction as listed in Scheme 16. Our efforts to promote the RCM reaction by varying temperature, time, solvent and catalyst were unsuccessful. All the attempts resulted in either no reaction or hydrolysis of the vinylic ether group.

Scheme 16



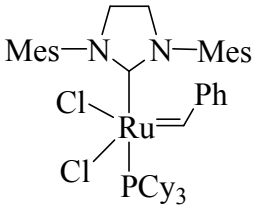
19

Catalyst	Solvent	Temperature	Results
A	DCM	rt – reflux	No-reaction
A	Benzene	rt – reflux	No-reaction
A	Toluene	rt – 90 ^{o}C	No reaction
B	DCM	rt – reflux	No reaction
B	Benzene	rt – 90 ^{o}C	No reaction
B	Toluene	rt – 85 ^{o}C	No reaction
B	Toluene	> 85 ^{o}C	Hydrolysis of vinyl ether



A

Grubbs 1st generation catalyst



B

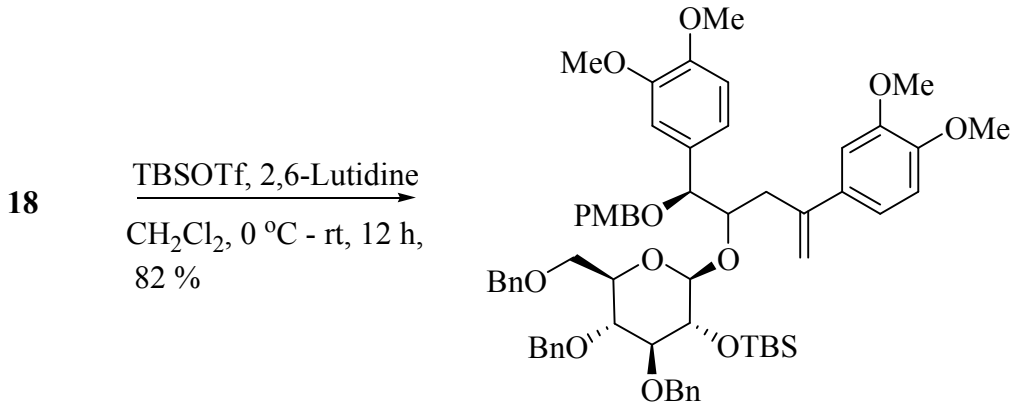
Grubbs 2nd generation catalyst

Second Generation Strategy Based on a Hydroboration Reaction

After several hardships in driving ring closing metathesis reaction, the synthetic endure was altered to an S_N2 displacement of an appropriate tosylate or mesylate to check the efficiency of cyclization to form eight member cyclic ether. Accordingly, the lone *secondary* hydroxyl group of glucoside **18** was protected as silyl ether using TBSOTf and

2,6-lutidine in anhydrous DCM. In the ^{1}H NMR of the silyl ether **20**, the resonances corresponding to *t*-butyl group were noticed at δ 0.92 ppm whilst other resonances such as δ 0.16 and 0.04 ppm corresponding to methyl groups of silyl ether were seen along with all other resonances according to assigned structure of **20**. The structure was further confirmed by ^{13}C NMR wherein *t*-butyl group resonances were apparent at δ 26.1 ppm whilst quaternary carbon at δ 18.0 ppm along with two methyl groups at δ -3.5 and -4.5 ppm whereas DEPT NMR spectrum confirmed presence of all $–CH_2-$ groups of compound **20** unambiguously (Scheme 17).

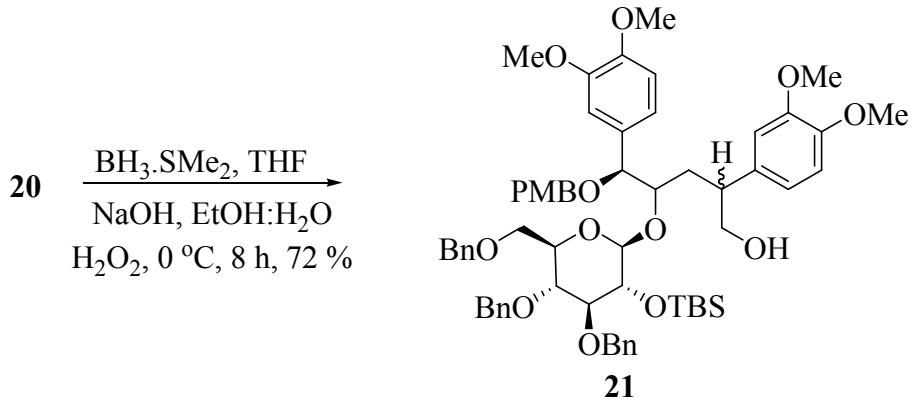
Scheme 17



20

Next, the silyl ether **20** was subjected to hydroboration reaction using $BH_3.SMe_2$ in anhydrous THF which resulted in the alcohol **70** as the product in inseparable 3:7 diastereomeric ratio. The ^{1}H NMR spectrum clearly showed the resonances corresponding to both the diastereomers according to the assigned structure of **20** whilst structure was further confirmed by ^{13}C and DEPT NMR spectroscopy (Scheme 18).

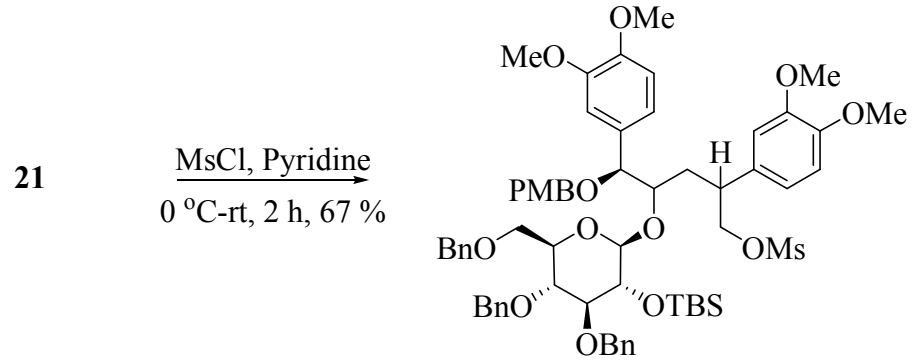
Scheme 18



21

The *primary* hydroxyl group of **20** was then converted to a mesylate ester **21** using MsCl in pyridine and both the isomers were separated by column chromatography and the major isomer was characterized and used for further synthesis. In ^{1}H NMR spectrum of **22**, resonances corresponding to characteristic $-CH_3$ group of mesyl ester were noticed at δ 2.67 ppm whereas ^{13}C NMR spectrum showed resonances at δ 41.6 ppm. Structure was further confirmed by DEPT NMR spectroscopy wherein seven resonances at δ 32.7, 68.8, 71.1, 73.4, 73.6, 74.7, 75.4 ppm confirmed presence of required $-CH_2-$ groups in addition to other resonances according to the assigned structure (Scheme 19).

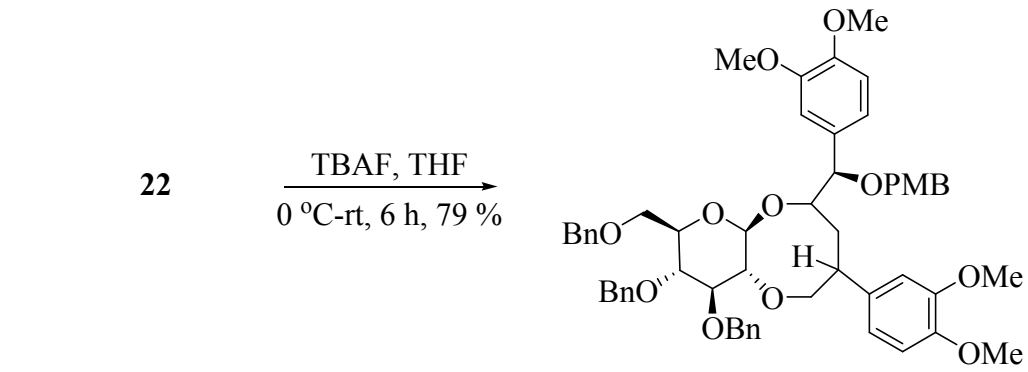
Scheme 19



22

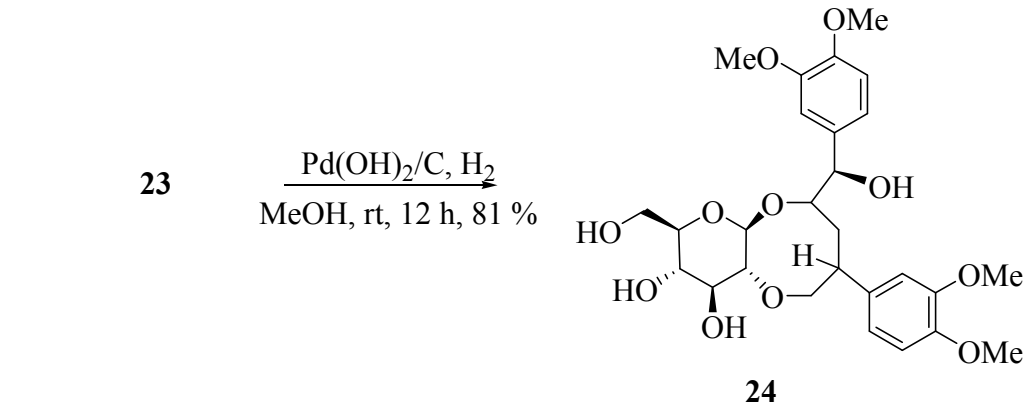
After successful preparation of mesylate **22**, our next concern was to get cyclic product *via* S_N2 reaction. Accordingly, the TBS group of mesylate **22** was deprotected using TBAF in anhydrous THF. Interestingly, the formation of cyclic ether was observed as the ^{1}H NMR spectrum of the resulting product showed the absence of the resonances from the TBS as well as mesylate groups. Whereas ^{13}C NMR spectrum of cyclic ether **23** was well correlated with assigned structure but newly generated chiral carbon *via* hydroboration at δ 42.0 and 42.2 ppm and carbons attached to that such as δ 32.7,32.8, 86.3, 88.8 and 133.5, 133.6 ppm were found to appear as pairs of doublets (Scheme 20).

Scheme 20



It has been thought that the multiplicity can be attributed to conformational strain due to the highly strained ring system because of the presence of bulky benzyl protecting groups. Next, we thought of deprotecting benzyl ethers in order to get rid from the multiplicity by relieving the strain of the cyclic ether. Accordingly, the benzyl groups were deprotected using $Pd(OH)_2/C$ in methanol which resulted in the formation of compound **24**. In ^1H NMR spectrum, resonances corresponding to four –OMe were apparent at δ 3.75, 3.79, 3.83 ppm whilst rest of the spectrum looked satisfactory whereas in ^{13}C NMR spectrum of compound **24** problem of multiplicity remained persistent (Scheme 21).

Scheme 21



Third Generation Strategy Based on a Dihydroxylation Reaction

The NMR ambiguity in hydroboration strategy once again forced us to change our strategy to asymmetric dihydroxylation reaction.

The direct reaction of the non chiral reagent with the substrate, lead to a racemate **B**, and the less-than-perfect recognition of substrate **A** while in the presence the reagent/catalyst complex, leading to variable amounts of (-) **B**, which erodes the enantiomeric purity like wise other reagent/catalyst complex leads to (+) **B** (Figure 2). These basic principles resulted in the discovery of asymmetric catalysis which are very helpful in asymmetric synthesis. The different chiral catalysts are well documented in literature.

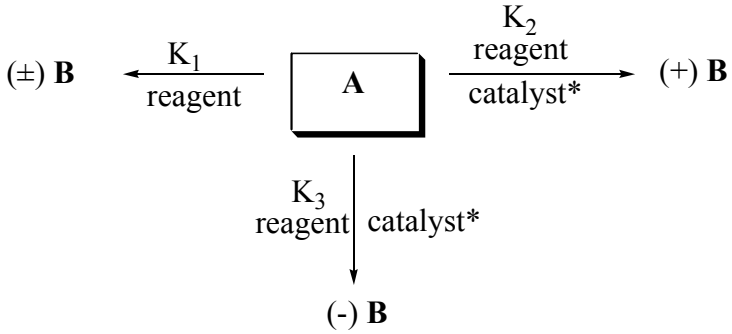


Figure 3

A Short Account on Sharpless Asymmetric Dihydroxylation Reaction

Last three decades have witnessed discovery of number of powerful asymmetric reactions which have helped dramatically in efficient and practical syntheses of biologically active compounds. Catalytic asymmetric reaction always plays a vital role in such syntheses because of their ease of introducing chirality which is a fearsome challenge in organic synthesis. Among them, asymmetric epoxidation and asymmetric dihydroxylation discovered by Sharpless are very promising. Earlier, dihydroxylation was mainly carried out by OsO_4, however, cost considerations make the stoichiometric osmylation uneconomical. Initially, the asymmetric dihydroxylation was performed using cinchona alkaloids under stoichiometric conditions but Sharpless and co-workers discovered that process become catalytic when *N*-methylmorpholine-*N*-oxide (NMO) employed as cooxidant whereas low enantioslectivity was observed which was attributed

to second catalytic cycle. The participation of the second catalytic cycle was controlled by performing the reaction under two-phase conditions with $K_3Fe(CN)_6$ as the stoichiometric reoxidant while hydrolysis of osmium, glycolate was accelerated by $MeSO_2NH_2$ and in presence of both additive time required for the reaction was much shorter even at low temperature with high enantioselectivity. The third generation ligands, bis-cinchona alkaloids with aromatic appendages especially phthalazine bis-dihydroquinidine $(DHDQ)_2PHAL$ and its dihydroquinine analogue $(DHQ)_2PHAL$ which enhanced enantioselectivity through enzyme-mimic binding cleft.[22]

The excellent reactivity of OsO_4 toward all olefins and only olefins, and its broad application ranging from tetra substituted alkenes to electron deficient and sulfur containing olefins, its higher catalytic turn over, high yield with greater enantioselectivity with optical purity have proven it a most reliable reaction for synthesis of various bioactive natural products and chiral building blocks. However observation of "noncovalent" binding effects in this reaction seems to offer exciting prospects for designing even better AD ligands as well as selective catalysts for other transformations.

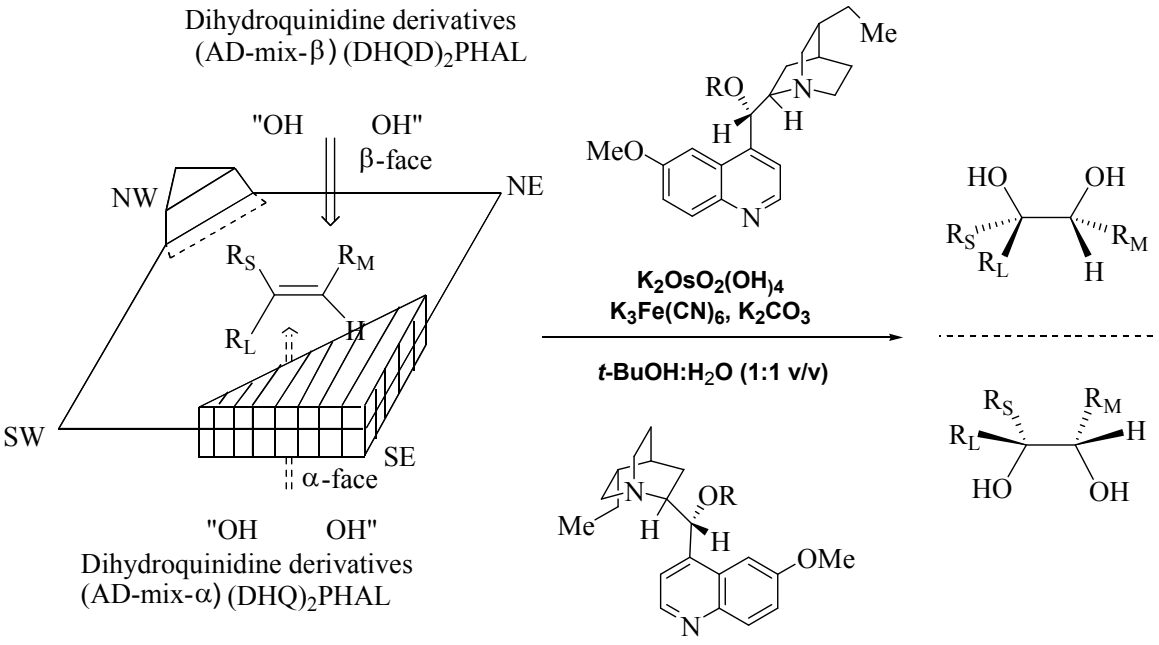
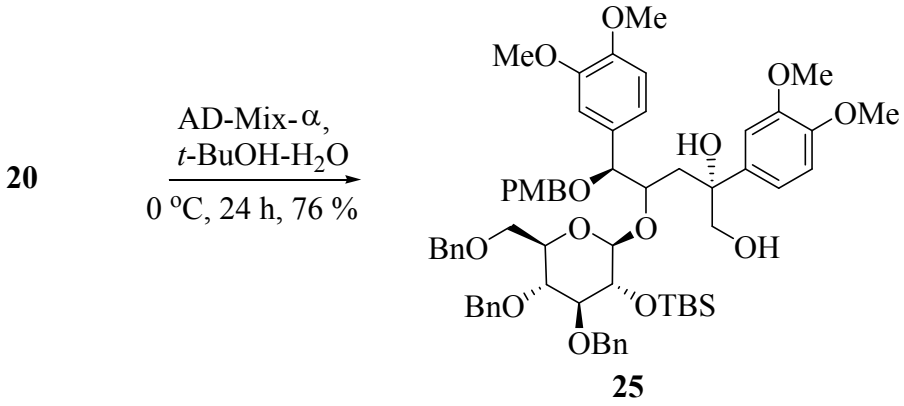


Figure 4: Mnemonic representation of olefin orientation and face selectivity in Sharpless Asymmetric Dihydroxylation

Having understood of salient features of Sharpless Asymmetric Dihydroxylation process, we wanted to check its efficiency on the compound **20** so that a diol can be obtained which can be further manipulate to the eight member cyclic compound. The alkene **20** was subjected to asymmetric dihydroxylation (AD) using AD-mix-α in *t*-butanol and water resulted in the diol **25** as a single diastereomer. In the ^{1}H NMR spectrum of the diol **25**, the $-CH_2-$ group shifted towards the shielding region due to the absence of alkene along with all other resonances according to assigned structure. ^{13}C and DEPT NMR further confirmed the structure of diol **25** unambiguously (Scheme 22).

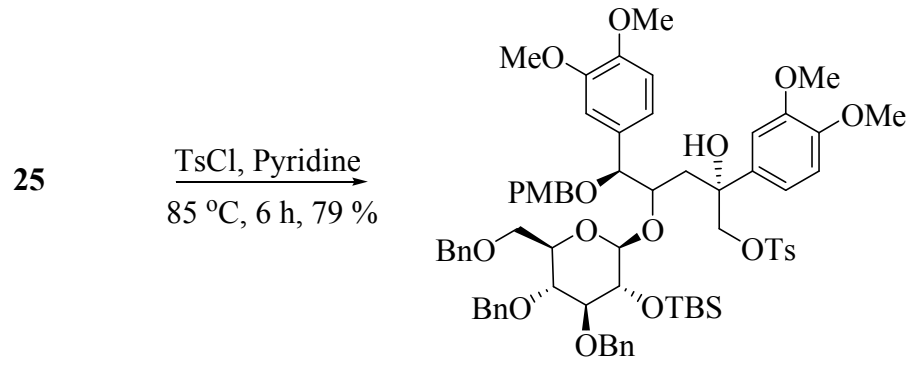
Scheme 22



25

The diol **25** was then subjected to tosylation reaction using TsCl in pyridine at 85 ^{o}C which resulted in the product **26**. Tosyl group was selected over mesyl because of its stability and selectivity towards the *primary* hydroxyl group over *tertiary* hydroxyl group. In the ^{1}H NMR spectrum of the tosylate **26**, the resonances corresponding to the characteristic tolueic $-CH_3$ were apparent at δ 2.42 ppm along with all other resonances according to assigned structure. The ^{13}C NMR spectrum showed resonances δ 21.6 ppm corresponding to tolueic methyl carbon whilst anomeric carbon resonances were apparent at δ 98.6 ppm along with all other resonances according to **26**. Structure was further confirmed by DEPT NMR spectroscopy and elemental and mass spectral analysis (Scheme 23).

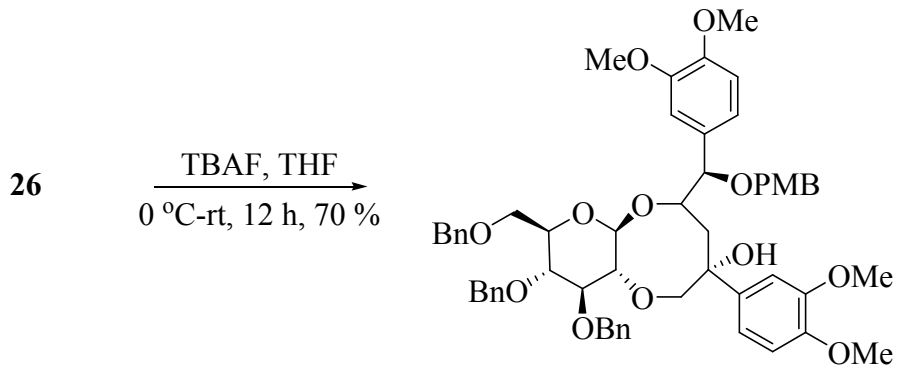
Scheme 23



26

Next, the TBS group of tosylate was deprotected using TBAF in anhydrous THF which resulted in the formation of cyclic ether **27**. In ^{1}H NMR spectrum of compound **27**, the resonances corresponding to characteristic –CH_3 of tosyl group were absent along with disappearance of the resonances corresponding to *t*-butyl and two methyl groups of silyl ether whilst new resonances corresponding to –CH_2- were apparent at δ 2.13 and 2.21 ppm as double doublets and rest of the spectrum according to assigned structure. ^{13}C NMR spectrum showed resonances at δ 39.9 ppm corresponding to –CH_2- group whilst anomeric carbon resonances were apparent at δ 101.1 ppm. The DEPT NMR spectrum unambiguously confirmed presence of seven –CH_2- groups at δ 40.0, 68.9, 70.2, 71.1, 73.5, 74.9 and 75.1 ppm along with all other required resonances. The compound **27** was further confirmed by mass spectroscopy where in a peak found at 966.58 accounting for molecular weight of cyclic ether i.e. 943.08 with Na (M + 23 for Na). It is worth mention here that we did not observe any epoxide formation while tosylation reaction or during the course of the deprotection of TBS group though presence of adjacent hydroxyl group to tosylate ester (Scheme 24).

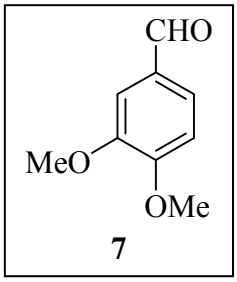
Scheme 24



Conclusion

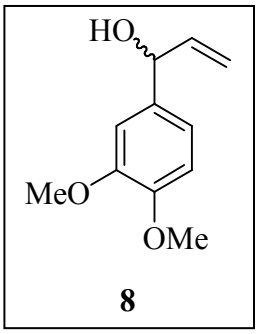
In conclusion, we have achieved the first synthesis of the highly oxygenated multicyclic framework of Crassifoside F in a highly efficient and stereocontrolled manner. We started our synthetic endure with D-glucose and showed that the synthesis of Crassifoside F using RCM approach is not very encouraging and we guess the reason behind that are (a) electron deficient styrene like diene system (b) instability of vinyl ether group at high temperature and (c) ease of formation of eight member cyclic ring using RCM reaction compared to other ring systems. The cyclic ether **27** can be easily converted to Crassifoside F by using known transformations. For example, the *tertiary* hydroxyl group can be converted to mesylate followed by elimination reaction which results in alkene followed by stereoselective epoxidation of the alkene further deprotection of PMB ether and oxidation of benzylic hydroxyl group and finally global deprotection of all protecting groups can give Crassifoside F. There is no report on the total synthesis or for synthetic studies so far on Crassifoside F, thus the current endeavor gives a straight forward strategy for the synthesis of this important bioactive natural product.

2.3 Experimental Section



7

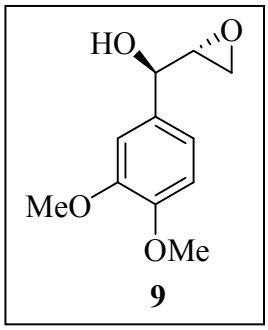
Compound 7: To a solution of vanillin (20g, 144.9 mmol) in anhydrous acetone (200 mL) was added oven dried K_2CO_3 (100g, 724.5 mmol), MeI (61.7g, 434.8 mmol) and reaction mixture was refluxed at 70 ^oC for 12 h. Then reaction mixture was cooled to room temperature, filtered through celite and concentrated *in vacuo*. The residue was diluted with water (200 mL) and extracted with ethyl acetate (3 × 100 mL) and pooled organic layers were dried over anhydrous Na_2SO_4, concentrated *in vacuo* and crude product **7** (23.8g, 98 %) obtained was used for next step without further purification. ^1H NMR ($CDCl_3$, 200 MHz): δ 3.95, 3.98 (2s, 6H), 6.99 (d, 1H, *J* = 8.21 Hz), 7.42 (d, 1H, *J* = 1.64 Hz), 7.47 (dd, 1H, *J* = 1.90, 8.21 Hz), 9.86 (s, 1H).



8

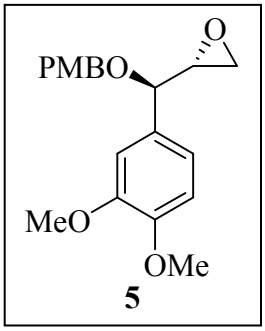
Compound 8 (Grignard reaction): A two neck round-bottom flask equipped with reflux condenser and nitrogen outlet was charged with Mg turnings (8.24g, 343.4 mmol) and dried by using flame. The flask was cooled to room temperature and to this was added anhydrous THF (60 mL) and 1,2-dibromoethane (cat. amount), and stirred for 10 min. Then the mixture was cooled to 0 ^oC, and was added vinyl bromide (38.1 mL of 6M solution in THF, 228.9 mmol) dropwise over a period of 10 min. The reaction mixture was stirred for additional 30 min at 0 ^oC and to this was added aldehyde **7** (19g, 114.5 mmol) dissolved in anhydrous THF. The reaction mixture was stirred for additional 1 h and after complete consumption of the aldehyde (TLC monitored), the reaction mixture was quenched with saturated aq. solution of NH_4Cl, extracted with ethyl acetate (3 × 100 mL), pooled organic layers were washed with saturated brine solution and dried over anhydrous Na_2SO_4, concentrated *in vacuo* and residue was purified by silica gel column chromatography using 20 % ethyl acetate and light petroleum as the mobile phase to afford alcohol **8** (21.5g, 94 %) as thick syrup. IR ($CHCl_3$): 3401, 1668 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 2.34 (bs, 1H), 3.86, 3.87 (2s, 6H), 5.14 (s, 1H), 5.15 (d, 1H, *J* = 18.32 Hz), 5.32 (d, 1H, *J* = 17.05 Hz), 6.04 (m, 1H), 6.85 (m, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 55.7, 55.8, 74.9, 109.4, 110.9,

114.7, 118.5, 135.2, 140.2, 148.4, 148.9; CHN Anal. Calcd for $C_{11}H_{14}O_3$: C, 68.02, H, 7.11; Found: C, 67.59, H, 7.22; ESI Mass: 217.14 (M + Na).



9

Compound 9 (Sharpless Asymmetric Epoxidation): A two neck round bottom flask was charged with 4Å molecular sieves powder and activated under flame for 10 min. After cooling to room temperature, was added 60 mL anhydrous DCM, $Ti(OPr^i)_4$ (30.74g, 108.24 mmol) dissolved in anhydrous DCM and L (+) diethyl tartrate (26.75g, 129.89 mmol) dissolved in anhydrous DCM and solution was cooled to -20 ^oC. To this, was added allyl alcohol **8** (21g, 108.24 mmol) dissolved in anhydrous DCM dropwise. After 10 min., *t*-BuOOH (5.84g, 64.94 mmol, 19.1 mL of 3.4M solution in toluene) was added and the resulting mixture was stirred for 24 h at -20 ^oC. Then reaction mixture was quenched with 10 % aq solution of tartaric acid (200 mL) at -20 ^oC and was allowed to warm to room temperature and stirred for additional 10 h. The reaction mixture was separated in to two distinct layers, extracted with DCM (3 × 120 mL), pooled organic layers were dried over anhydrous Na_2SO_4, concentrated *in vacuo* and purified by silica gel column chromatography using a gradient of (20→30 %) ethyl acetate and light petroleum to afford epoxide **9** (9.32g, 41 %) as a syrup. $[\alpha]_D$ +77.37 (*c* 1.20, $CHCl_3$); IR ($CHCl_3$): 3468, 2935, 1611 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 2.34 (bs, 1H), 2.79 (dd, 1H, *J* = 4.04, 5.05 Hz), 2.95 (dd, 1H, *J* = 2.78, 5.05 Hz), 3.22 (q, 1H, *J* = 3.03, 6.82 Hz), 3.88, 3.90 (2s, 6H), 4.86 (d, 1H, *J* = 2.90 Hz), 6.90 (m, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 43.6, 55.0, 55.8, 55.9, 70.7, 109.5, 111.1, 118.7, 132.0, 148.9, 149.1; CHN Anal Calcd for $C_{11}H_{14}O_4$: C, 62.85, H, 6.71; Found: C, 62.34, H 6.91; ESI Mass: 233.61 (M + Na).

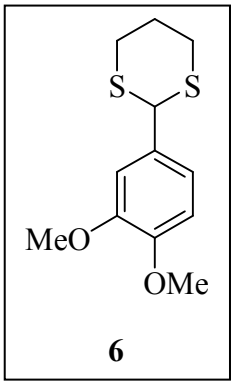


5

Compound 5: To a solution of epoxide **9** (9.1g, 43.33 mmol) in 30 mL of anhydrous DMF cooled to 0 ^oC was added NaH (2.07g, 86.66 mmol) and resulting dark brown colored solution was stirred at 0 ^oC for 30 min. To this was added *p*-methoxy benzyl chloride (8.14g, 52.00 mmol) dropwise and reaction mixture stirred for an additional 2 h. After completion of the reaction, the NaH was

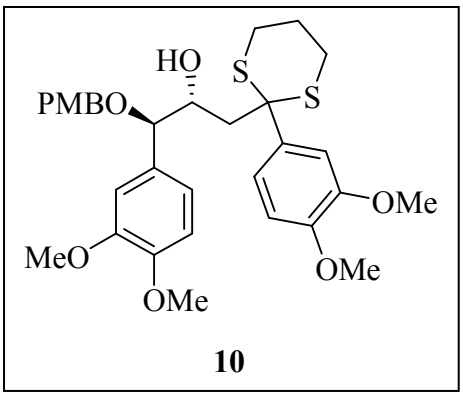
quenched by methanol (10 mL) and the reaction mixture was diluted with water (150 mL) and extracted with ethyl acetate (3 × 100 mL). The pooled organic layers were washed with brine solution and dried over anhydrous Na_2SO_4, concentrated *in vacuo* and purified by silica gel column chromatography using a gradient of (10→20 %) ethyl acetate and light petroleum as solvent to afford PMB ether **5** (12.4g, 37.69 mmol, 87 %) as a syrup. $[\alpha]_D$ +53.83 (*c* 1.10, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 2.68 (dd, 1H, *J* = 4.29, 5.30 Hz), 3.16 (m, 1H), 3.74 (m, 1H), 3.80, 3.89 (2s, 9H), 4.26 (d, 1H, *J* = 4.58 Hz), 4.31 (d, 1H, *J* = 12.11 Hz), 4.49 (d, 1H, *J* = 11.13 Hz), 6.89 (m, 5H), 7.23 (m, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 45.2, 54.4, 55.2, 55.6, 70.2, 79.4, 101.2, 110.9, 113.7, 120.0, 129.3, 130.0, 130.7, 148.9, 149.1, 159.2; CHN Anal. Calcd for $C_{19}H_{22}O_5$: C, 69.07, H, 6.71; Found: C, 68.61, H, 6.93; ESI Mass: 353.14 (M + Na).

Compound 6: To a solution of aldehyde **7** (9.0g, 54.21 mmol) in 50 mL of anhydrous DCM cooled to 0 ^oC was added 1,3-propanedithiol (6.54 mL, 65.0 mmol) and a catalytic amount of $BF_3.Et_2O$. The reaction mixture was allowed to stir at room temperature for 12 h. After completion of the reaction (TLC monitored), the reaction mixture was quenched with saturated solution of $NaHCO_3$, diluted with water and extracted with ethyl acetate (3 × 80 mL). The pooled organic layers were washed with saturated brine solution, dried over anhydrous Na_2SO_4, concentrated *in vacuo* and residue was purified by silica gel column chromatography using 20 % ethyl acetate and light petroleum to afford dithiane **6** (12.7g, 92 %) as white crystalline solid. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 2.00 (m, 2H), 2.84-3.14 (m, 4H), 3.86, 3.90 (2s, 6H), 5.13 (s, 1H), 6.82 (d, 1H, *J* = 8.85 Hz), 7.02 (m, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 25.0, 32.1, 51.1, 55.8, 110.7, 111.0, 119.9, 131.6, 148.9; CHNS Anal. Calcd for $C_{12}H_{16}O_2S_2$: C, 56.22, H, 6.29, S, 25.01; Found: C, 55.94, H, 6.32, S, 24.81; ESI Mass: 278.98 (M + Na).



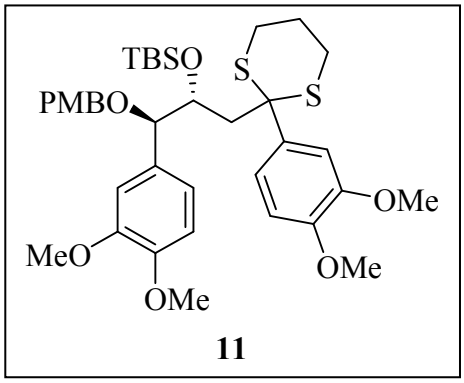
6

Compound 10: A flame dried two neck round bottom flask was charged with dithiane **6** (7.5g, 29.09 mmol) under nitrogen and was added 50 mL anhydrous THF and 5 mL of HMPA. The solution was cooled to -40 ^{o}C and to this was added *n*-BuLi (1.86g, 29.09 mmol, 18.1 mL of 1.6M in hexane) dropwise. The dark brown reaction mixture was stirred for 30 min and to this was added epoxide **5** (8g, 24.2 mmol) dissolved in 50 mL of anhydrous THF and 5 mL of HMPA dropwise. The reaction mixture was stirred for additional 45 min, then quenched with saturated solution of NH_4Cl, diluted with water (100mL) and extracted with ethyl acetate (3 × 100 mL). Pooled organic layers were washed with saturated brine solution, dried over anhydrous Na_2SO_4, concentrated *in vacuo* and residue was purified using silica gel column chromatography using a gradient of (20→30 %) ethyl acetate and light petroleum to afford coupled product **10** (12.3g, 87 %) as thick syrup. $[\alpha]_D$ +21.42 (*c* 1.10, $CHCl_3$); IR ($CHCl_3$): 3584 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.94 (m, 2H), 2.22 (dd, 1H, *J* = 8.46, 15.03 Hz), 2.33 (bs, 1H), 2.53 (d, 1H, *J* = 14.02 Hz) 2.72 (m, 4H), 3.78, 3.80, 3.84, 3.88 (4s, 15H), 4.12 (d, 1H, *J* = 5.94 Hz), 4.21 (d, 1H, *J* = 11.37 Hz), 4.42 (d, 1H, *J* = 11.37 Hz), 6.82 (m, 6H), 7.20 (d, 2H, *J* = 8.72 Hz), 7.39 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 24.7, 27.6, 27.8, 46.7, 55.2, 55.8, 57.1, 70.3, 71.8, 83.4, 110.3, 110.6, 110.7, 111.4, 113.7, 120.2, 121.1, 129.3, 130.2, 130.9, 133.9, 147.9, 148.5, 148.9, 151.1; CHN Anal. Calcd for $C_{31}H_{38}O_7S_2$: C, 63.46, H, 6.53, S, 10.93; Found: C, 63.14, H, 6.91, S, 10.21; ESI Mass: 609.35 (M + Na).



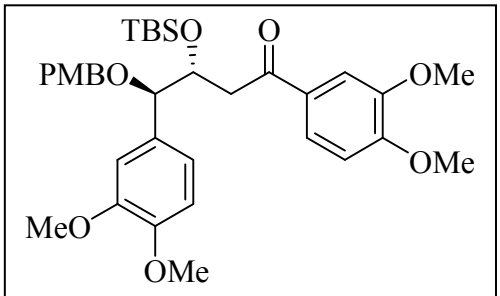
10

Compound 11: To a solution of alcohol **10** (9g, 15.3 mmol) dissolved in anhydrous DCM cooled to 0 ^{o}C was added 2,6-lutidine (3.56 mL, 30.6 mmol) and the solution was stirred at the same temperature for 10 min. To this was added TBSOTf (4.85g, 18.36 mmol) dropwise and solution was stirred at room temperature for additional 12 h. After complete consumption of the alcohol **10** (TLC monitored), the reaction mixture was



11

quenched with saturated solution of $NaHCO_3$ and diluted with water (100 mL), extracted with DCM (3 × 80 mL), pooled organic layers were washed with saturated brine solution, dried over anhydrous Na_2SO_4, concentrated *in vacuo* and residue was purified by silica gel column chromatography using a gradient of (10→20 %) ethyl acetate and light petroleum as mobile phase to afford silyl ether **11** (9.47g, 88 %) as thick syrup. $[\alpha]_D$ +6.51 (*c* 1.10, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 0.03, 0.84 (2s, 15H), 1.86 (m, 2H), 2.01 (dd, 1H, *J* = 3.03, 15.16 Hz), 2.16 (dd, 1H, *J* = 6.82, 15.04 Hz), 2.60 (m, 4H), 3.76, 3.80, 3.81, 3.84, 3.85 (5s, 15H), 4.04 (d, 1H, *J* = 11.50 Hz), 4.12 (m, 1H), 4.22 (d, 1H, *J* = 11.37 Hz), 6.58 (dd, 1H, *J* = 1.64, 8.21 Hz), 6.70-6.88 (m, 6H), 7.13 (d, 2H, *J* = 8.59 Hz) 7.36 (m, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ -5.0, -3.9, 18.0, 24.7, 25.9, 27.6, 48.6, 55.0, 55.5, 55.6, 55.7, 57.5, 70.0, 71.8, 83.5, 109.7, 110.5, 111.7, 111.9, 113.3, 121.5, 121.7, 128.8, 130.0, 130.8, 133.6, 147.7, 148.2, 148.3, 148.7, 158.7; CHNS Anal. Calcd for $C_{37}H_{52}O_7S_2Si$: C, 63.39, H, 7.48, S, 9.15, Si, 4.01; Found: C, 63.82, H, 7.59, S, 8.28; ESI Mass: 723.82 (M + Na).

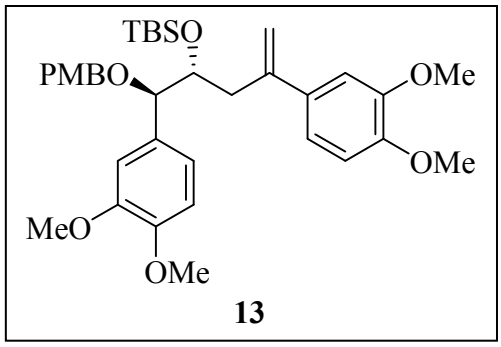


12

Compound 12: To a solution of dithiane (9.1g, 13.0 mmol) dissolved in 50 mL of acetonitrile: water (4:1) was added HgO (3.08g, 14.3 mmol) and $HgCl_2$ (8.80g, 32.5 mmol) and the reaction mixture was heated to 70 ^{o}C for 4 h. After completion of the reaction (TLC monitored), the reaction mixture was concentrated *in vacuo*, diluted with saturated $(NH_4)_2CO_3$ and extracted with ethyl acetate (3 × 80 mL). The pooled organic layers were washed with brine solution, dried over anhydrous Na_2SO_4, concentrated *in vacuo* and purified by silica gel column chromatography using 20 % ethyl acetate and light petroleum to afford ketone **12** (6.42g, 81 %) as thick syrup. $[\alpha]_D$ +50.30 (*c* 0.90, $CHCl_3$); IR ($CHCl_3$): 1731 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz): δ -0.27, -0.12, 0.72 (3s, 15H), 3.05 (dd, 1H, *J* = 6.19, 15.66 Hz), 3.17 (dd, 1H, *J* = 5.31, 15.66 Hz), 3.79, 3.87, 3.88, 3.89, 3.95 (5s, 15H) 4.16 (d, 1H, *J* = 11.25 Hz), 4.24 (d, 1H, *J* = 6.06 Hz), 4.36 (d, 1H, *J* = 11.24 Hz), 4.57 (q, 1H, *J* = 5.56, 11.37 Hz), 6.78-6.96 (m, 6H), 7.09 (d, 2H, *J* = 8.71 Hz), 7.47 (d, 1H, *J* = 1.89 Hz), 7.53 (dd, 1H, *J* = 1.89, 8.33 Hz); ^{13}C

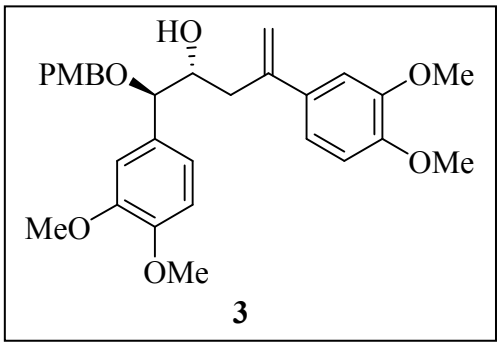
NMR ($CDCl_3$, 50 MHz): δ -5.1, -5.0, 17.9, 25.8, 43.0, 55.2, 55.8, 55.9, 56.0, 70.1, 73.2, 84.2, 109.8, 110.3, 110.6, 111.0, 113.5, 121.1, 122.9, 128.5, 129.4, 130.3, 130.9, 131.8, 148.7, 148.8, 148.9, 153.0, 158.9, 197.2; CHN Anal. Calcd for $C_{34}H_{46}O_8Si$: C, 66.86, H, 7.59, Si, 4.60; Found: C, 66.31, H, 7.91; ESI Mass: 633.78 (M + Na).

Compound 13: A two neck round bottom flask charged with Wittig "ylide" $Ph_3PCH_3^+I^-$ (16.4g, 40.6 mmol) under nitrogen outlet was added anhydrous THF (60 mL) and the solution was cooled to 0 ^oC. To this was added *n*-BuLi (2.53g, 39.58 mmol, 24.7 mL of 1.6M in hexane) drop wise over 10 min and dark brown solution was stirred at room temperature for 30 min. The reaction mixture was again cooled to 0 ^oC and was added ketone **12** (6.2g, 10.1 mmol) dissolved in anhydrous THF dropwise over a period of 15 min. The reaction mixture was stirred at room temperature for 12 h. After complete consumption of ketone (TLC monitored), reaction mixture was quenched with saturated solution of NH_4Cl, extracted with ethyl acetate (3 × 100 mL) and pooled organic layers were washed with saturated brine solution. The pooled organic layers were dried over anhydrous Na_2SO_4, concentrated *in vacuo* and residue was purified by silica gel column chromatography using a gradient of (10→20 %) ethyl acetate and light petroleum to afford alkene **13** (4.11g, 67 %) as pale yellow syrup. $[\alpha]_D$ +10.60 (*c* 0.80, $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz): δ -0.36, -0.16, 0.79 (3s, 15H), 2.58 (dd, 1H, *J* = 7.20, 14.53 Hz), 2.89 (dd, 1H, *J* = 4.04, 14.40 Hz), 3.72, 3.80, 3.86, 3.88, 3.89 (5s, 15H), 4.16 (d, 1H, *J* = 11.24 Hz), 4.20 (d, 1H, *J* = 4.92 Hz), 4.36 (d, 1H, *J* = 11.24 Hz), 5.06 (s, 1H), 5.29 (d, 1H, *J* = 1.77 Hz), 6.74-6.89 (m, 8H), 6.94 (s, 1H), 7.18 (d, 2H, *J* = 8.72 Hz); ^{13}C NMR ($CDCl_3$, 50 MHz): δ -4.9, -4.5, 18.1, 25.9, 39.7, 55.2, 55.5, 55.8, 55.9, 70.2, 74.5, 83.6, 109.6, 110.5, 110.7, 111.3, 113.6, 114.0, 118.7, 121.0, 129.3, 130.7, 131.9, 133.6, 144.5, 148.3, 148.4, 148.5, 148.7, 159.0; CHN Anal. Calcd for $C_{35}H_{48}O_7Si$: C, 69.05, H, 7.95, Si, 4.61; Found: C, 68.61, H, 7.80; ESI Mass: 631.92 (M + Na).



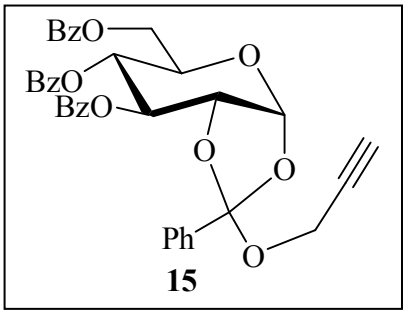
13

Aglycone 3: To a solution of alkene **13** (4.1g, 6.73 mmol) in anhydrous THF was added *n*-$Bu_4N^+F^-$ (3.52g, 13.48 mmol) and reaction mixture was stirred for 12 h at room temperature. After completion of the reaction (TLC monitored), the reaction mixture was concentrated *in vacuo* and residue was purified by silica gel column chromatography using (10→25 %) ethyl acetate and light petroleum to afford the aglycone **3** (3.26g, 98 %) as thick syrup. $[\alpha]_D$ +37.17 (*c* 1.55, $CHCl_3$); IR ($CHCl_3$): 3516 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 1.86 (s, 1H), 2.44 (dd, 1H, *J* = 9.34, 14.65 Hz), 3.01 (dd, 1H, *J* = 2.15, 14.53 Hz), 3.77, 3.80, 3.87, 3.89 (4s, 15H), 4.23 (d, 1H, *J* = 11.24 Hz), 4.26 (d, 1H, *J* = 5.68 Hz), 4.45 (d, 1H, *J* = 11.24 Hz), 5.09 (s, 1H), 5.33 (d, 1H, *J* = 1.39 Hz), 6.78 (d, 1H, *J* = 8.08 Hz), 6.85-6.94 (m, 8H), 7.23 (d, 2H, *J* = 8.72 Hz); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 38.8, 55.2, 55.6, 55.8, 70.3, 72.8, 83.4, 109.6, 110.5, 110.9, 113.5, 113.7, 118.5, 120.4, 129.4, 130.2, 130.9, 133.3, 144.7, 148.6, 148.8, 149.1, 159.2; CHN Anal. Calcd for $C_{29}H_{34}O_7$: C, 70.43, H, 6.93; Found: C, 70.12, H, 6.81; ESI Mass: 517.78 (M + Na).



3

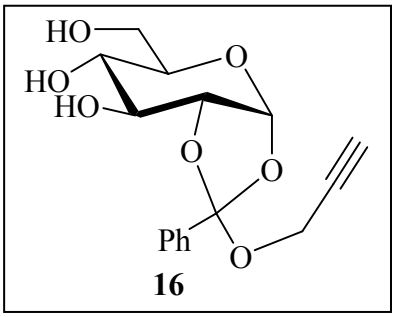
3,4,6-Tri-*O*-benzoyl-α-D-glucopyranose-1,2-(propargyl orthobenzoate) 15: To a solution of 2,3,4,6-tetra-*O*-benzoyl-α-D-glucopyranosyl bromide[20.] **14** (20.0g, 30.3 mmol) in anhydrous CH_2Cl_2 (150 mL) was added 2,6-lutidine (15 mL), propargyl alcohol (9 mL, 151.70 mmol) and *n*-$Bu_4N^+I^-$ (0.100g) under nitrogen at room temperature. The reaction mixture was refluxed at 65 ^oC for 24 h, diluted with water (100 mL) and extracted with DCM (2 × 100 mL). The combined organic layers were washed with water and brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to yield a brownish-black residue which was purified by silica gel column chromatography using ethyl acetate–petroleum ether as the mobile phase to afford the 3,4,6-Tri-*O*-benzoylgluco orthoester **15** (16.34 g, 85 %) as a white amorphous



15

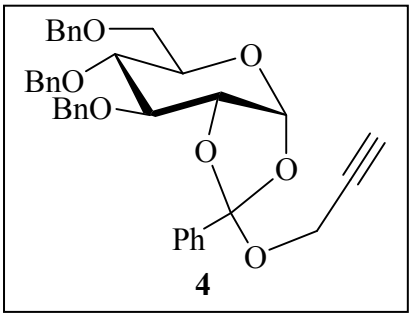
solid. $[\alpha]_D$ +3.55 (c 1.0, $CHCl_3$); IR ($CHCl_3$): 1714, 1730, 1737, 3305 cm^{-1}; ^1H (CDCl3, 200 MHz): δ 2.40 (t, 1H, *J* = 2.40 Hz), 3.99 (d, 2H, *J* = 2.28 Hz), 4.17 (m, 1H), 4.40 (dd, 1H, *J* = 4.68, 12.00 Hz), 4.56 (dd, 1H, *J* = 3.04, 12.13 Hz), 4.89 (m, 1H), 5.54 (d, 1H, *J* = 8.72 Hz), 5.79 (dd, 1H, *J* = 1.14, 2.78 Hz), 6.11 (d, 1H, *J* = 5.31 Hz), 7.21-7.65 (m, 12H), 7.80 (m, 2H), 7.95 (m, 4H), 8.09 (m, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz): 52.3, 63.9, 67.5, 68.4, 68.9, 72.0, 73.9, 79.1, 92.7, 121.1, 126.4, 128.1, 128.3, 128.4, 128.4, 128.5, 128.9, 129.0, 129.5, 129.6, 129.8, 129.9, 130.0, 132.9, 133.5, 133.6, 134.0, 164.1, 165.1, 165.9; CHN Anal. Calcd for $C_{37}H_{30}O_{10}$: C, 70.02, H, 4.76; Found: C, 70.04, H, 5.06; ESI Mass: 656.21 (M + Na).

α-D-glucopyranose-1,2-(propargyl orthobenzoate) 16: To a flask containing 3,4,6-Tri-*O*-benzoyl-α-D-glucopyranose-1,2-(propargyl orthobenzoate) **15** (10g, 15.75 mmol) dissolved in 100 mL of anhydrous THF cooled at 0 ^oC was added a solution of sodium metal dissolved in 10 mL methanol (0.400g) dropwise. After completion (TLC, 1–2 h), the reaction mixture was concentrated to dryness, water (100 mL) and ethyl acetate (100 mL) were added and the organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by column chromatography to afford triol **16** (4.16g, 82 %).



16

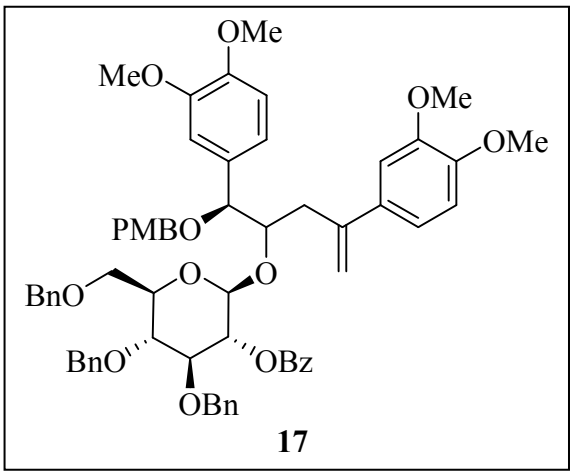
3,4,6-Tri-*O*-benzyl-α-D-glucopyranose-1,2-(propargyl orthobenzoate) 4: To a solution of triol (4.16g, 12.93 mmol) dissolved in anhydrous DMF cooled at 0 ^oC was added NaH (1.39g, 58.18 mmol) and dark brown solution was stirred for 30 min at the same temperature. To this was added benzyl bromide (1.85 mL, 15.51 mmol) and reaction mixture was stirred for additional 4 h at 0 ^oC. After completion of the reaction, excess NaH was quenched by using methanol (10 mL), diluted with water (100 mL) and extracted with ethyl acetate (3 × 100 mL). The pooled organic layers were dried over anhydrous Na_2SO_4, concentrated *in vacuo* and purified by



4

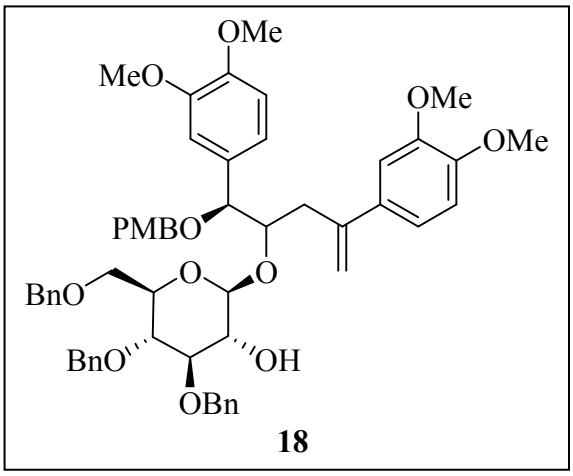
silica gel column chromatography to afford orthoester **4** (4.97g, 65 %) as syrup. $[\alpha]_D$ +53.98 (c 1.10, $CHCl_3$); IR ($CHCl_3$): 2343, 3305 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 2.36 (t, 1H, *J* = 2.40 Hz), 3.59 (d, 2H, *J* = 1.14 Hz), 3.73 (d, 2H, *J* = 1.14 Hz), 3.95 (m, 3H), 4.29-4.75 (m, 7H), 6.00 (d, 1H, *J* = 5.30 Hz), 7.13 (m, 2H), 7.23-7.36 (m, 16H), 7.65 (m, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 52.0, 69.0, 70.2, 71.9, 72.5, 73.1, 73.5, 75.1, 77.5, 79.6, 98.3, 120.3, 126.3, 126.5, 127.5, 127.7, 127.8, 127.8, 127.9, 128.0, 128.3, 128.4, 128.5, 129.6, 134.9, 137.6, 137.9, 138.1; CHN Anal. Calcd for $C_{37}H_{36}O_7$: C, 74.98, H, 6.12; Found: C, 75.06, H, 6.22; ESI Mass: 615.07 (M + Na).

Compound 17: To a round bottom flask containing 3,4,6-Tri-*O*-benzyl-α-D-gluco-pyranose-1,2-(propargyl orthobenzoate) **4** (1.31g, 2.22 mmol) and aglycone **3** (1.0g, 2.02 mmol) dissolved in DCM was added freshly activated 4 Å MS powder (0.500g). The solution was cooled to 0 ^oC and to this was added $AuBr_3$ (0.145g, 0.33 mmol) dissolved in acetonitrile dropwise. The reaction mixture was stirred for additional 30 min at room temperature, filtered through the celite, concentrated *in vacuo* and residue was purified by silica gel column chromatography using a gradient of (10→25 %) ethyl acetate and light petroleum to afford glucoside **17** (1.35g, 67 %) as thick syrup. $[\alpha]_D$ +9.34 (*c* 1.10, $CHCl_3$); IR ($CHCl_3$): 1730 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 2.65 (bs, 2H), 3.55 (s, 3H), 3.65 (m, 4H), 3.76, 3.79, 3.80, 3.82 (4s, 12H), 3.88 (m, 1H), 4.43-4.88 (m, 12H), 5.30 (t, 1H, *J* = 8.45 Hz), 6.39-6.92 (m, 8H), 7.10-7.33 (m, 18H), 7.40-7.61 (m, 3H), 8.02 (d, 2H, *J* = 7.07 Hz); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 34.2, 55.1, 55.3, 55.6, 69.2, 71.2, 73.2, 73.4, 73.9, 74.5, 74.8, 78.1, 82.4, 82.5, 82.8, 84.4, 101.5, 108.7, 109.8, 110.5, 110.6, 113.4, 113.8, 118.2, 119.3, 127.4, 127.5, 127.6, 127.7, 127.8, 127.9, 128.1, 128.2, 128.3, 129.2, 129.6, 130.1, 130.9, 132.2, 132.8, 132.9, 137.7, 137.8, 137.9, 143.8, 147.8, 148.1, 148.2, 148.6, 158.8, 164.8; CHN Anal. Calcd for $C_{63}H_{66}O_{13}$: C, 73.38, H, 6.45; Found: C, 72.61, H, 6.11; ESI Mass: 1053.90 (M + Na).



17

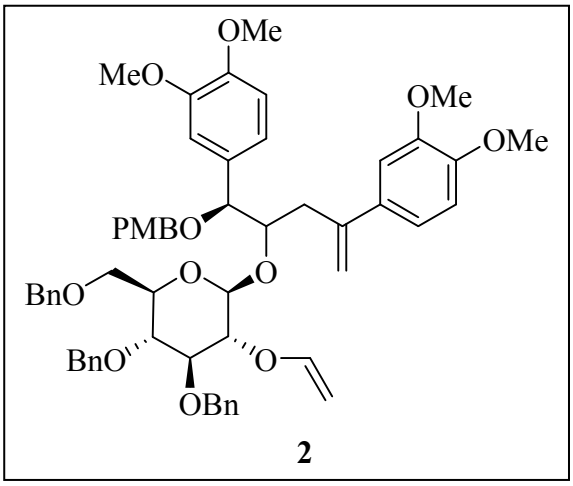
Compound 18: To the solution of glucoside **17** (1.2g, 1.16 mmol) in methanol cooled to 0 ^{o}C was added K_2CO_3 (0.322g, 2.32 mmol) and the resulting solution was stirred for 12 h at room temperature. After disappearance of the starting material (TLC monitored), the reaction mixture was concentrated *in vacuo,* diluted with water (50 mL), extracted with ethyl acetate (3 × 50 mL), pooled organic layers were dried over anhydrous Na_2SO_4, concentrated *in vacuo* and residue was purified by silica gel column chromatography using 30 % ethyl acetate and light petroleum to afford alcohol **18** (0.947g, 88 %) as a thick syrup. $[\alpha]_D$ -8.93 (*c* 1.20, $CHCl_3$); IR ($CHCl_3$): 3535 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 2.69 (dd, 1H, *J* = 9.22, 14.40 Hz), 3.37 (bs, 1H), 3.52 (dd, 1H, *J* = 1.52, 7.71 Hz), 3.60 (m, 2H), 3.66 (s, 2H), 3.72 (m, 1H), 3.77, 3.79, 3.83, 3.87, 3.92 (5s, 15H), 4.14 (d, 1H, *J* = 7.32 Hz), 4.36-4.57 (m, 4H), 4.75 (d, 1H, *J* = 11.12 Hz), 4.76 (d, 1H, *J* = 2.67 Hz), 4.85 (d, 1H, *J* = 10.87 Hz), 4.98 (d, 1H, *J* = 11.12 Hz), 5.08 (s, 1H), 5.30 (d, 1H , *J* = 1.51 Hz), 6.65-6.95 (m, 7H), 7.16-7.56 (m, 18H), 8.04 (dd, 2H, *J* = 1.14, 8.21 Hz); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 35.5, 51.9, 55.1, 55.5, 55.7, 55.8, 69.3, 71.0, 73.2, 74.6, 74.9, 75.0, 77.3, 81.5, 82.5, 84.3, 103.9, 109.2, 110.3, 110.8, 110.9, 113.5, 113.7, 118.7, 119.9, 127.4, 127.5, 127.6, 127.8, 128.2, 129.2, 129.4, 130.4, 131.1, 132.5, 132.8, 138.0, 138.1, 138.7, 145.4, 148.3, 148.5, 148.6, 148.8, 159.0; ESI Mass: 950.05 (M + Na).



18

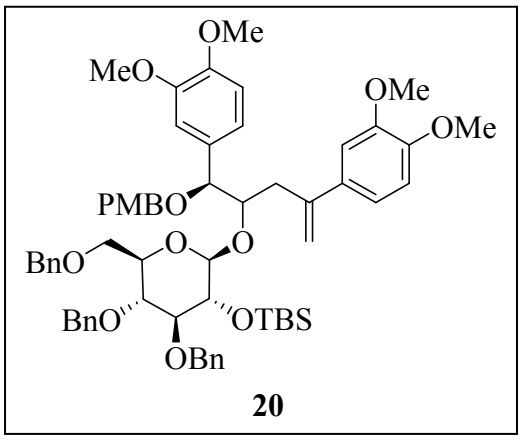
Vinyl Ether 2: To a screw tube charged with alcohol **18** (0.100g, 0.107 mmol) was added 2 mL of freshly distilled ethyl vinyl ether. To this, was added $Hg(OCOCF_3)_2$ (0.058g, 0.135 mmol) portionwise and triethyl amine (16 µL, 0.108 mmol) dropwise. The reaction vial was screw capped and heated to 60 ^{o}C for 12 h then the reaction mixture was transferred to a separating funnel and quenched by saturated aq $NaHCO_3$ (5 mL), diluted with water (10 mL), extracted with ethyl acetate (3 × 20 mL). The pooled organic

layers were washed with saturated brine solution, dried over anhydrous Na_2SO_4, concentrated *in vacuo* and purified by flash column chromatography using 20 % ethyl acetate and light petroleum to afford diene **2** (0.063g, 61%) as syrup and alcohol **18** (32 %). ^{1}H NMR ($CDCl_3$, 200 MHz): δ 2.78 (d, 2H, *J* = 5.43 Hz), 3.32 (m, 1H), 3.55-3.88 (m, 22H), 4.05 (dd, 1H, *J* = 1.26, 6.19 Hz), 4.32-4.56 (m, 6H), 4.68-4.91 (m, 4H), 5.12 (s, 1H) 5.22 (s, 1H), 6.46 (dd, 1H, *J* = 6.31, 13.77 Hz), 6.59-7.04 (m, 8H), 7.17- 7.36 (m, 17H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 34.9, 52.7, 55.2, 55.5, 55.7, 55.8, 69.1, 71.1, 73.3, 73.5, 74.4, 74.9, 75.3, 76.8, 77.2, 82.2, 83.0, 84.0, 86.9, 88.7, 102.2, 109.2, 109.4, 110.1, 110.6, 110.7, 113.5, 114.7, 117.8, 118.5, 119.6, 127.5, 127.7, 127.8, 127.9, 128.1, 128.2, 128.3, 129.1, 13.0, 131.9, 133.2, 133.9, 137.9, 138.0, 138.2, 143.8, 147.5, 148.0, 148.3, 149.4, 148.7, 153.3, 159.9



2

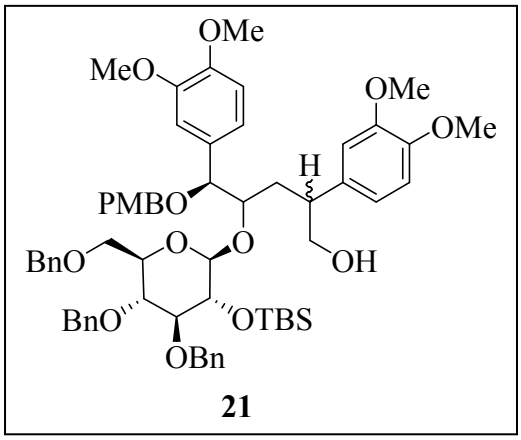
Compound 20: To a solution of alcohol **18** (0.600g, 0.64 mmol) in anhydrous DCM cooled to 0 ^{o}C was added 2,6-lutidine (151 μL, 1.29 mmol) and the reaction mixture was stirred for 10 min. To this was added TBSOTf (0.203g, 0.768 mmol) dropwise and reaction mixture was stirred for an additional 12 h at room temperature. After completion of the reaction (TLC monitored), the reaction mixture was quenched with saturated solution of $NaHCO_3$, diluted with water (20 mL) and extracted with ethyl acetate (3 × 20 mL). The pooled organic layers were washed with saturated brine solution, dried over anhydrous Na_2SO_4, concentrated *in vacuo* and purified by silica gel column chromatography using 20 % ethyl acetate and light petroleum to afford silyl ether **20** (0.546g, 82 %) as thick syrup. $[\alpha]_D$ -20.49 (*c* 1.50, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 0.05, 0.16, 0.92 (3s, 15H), 2.80 (dd, 1H, *J* = 8.21, 15.41 Hz), 3.01 (d, 1H, *J*



20

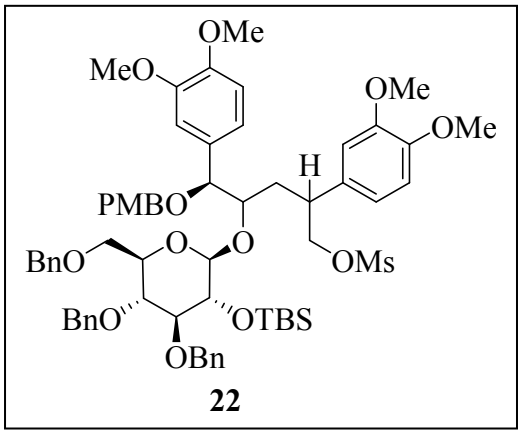
= 14.91 Hz), 3.21 (dd, 1H, *J* = 2.65, 9.35 Hz), 3.39-3.88 (m, 21H), 4.07 (t, 1H, *J* = 3.41 Hz), 4.31-4.51 (m, 5H), 4.68 (m, 2H), 4.87 (s, 2H), 5.16 (d, 1H, *J* = 12.13 Hz), 6.62 (d, 1H, *J* = 3.03 Hz), 6.66 (s, 2H), 6.86 (m, 4H), 7.08 (m, 3H), 7.27 (m, 16H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ -4.4, -3.5, 18.0, 25.9, 26.1, 35.8, 55.2, 55.5, 55.6, 55.7, 68.9, 71.0, 73.3, 74.5, 74.7, 74.9, 75.1, 78.1, 78.5, 83.7, 86.0, 101.8, 109.3, 110.3, 110.7, 113.5, 113.9, 118.6, 119.7, 126.8, 127.1, 127.4, 127.5, 127.8, 128.1, 128.3, 129.2, 130.9, 132.3, 133.4, 138.0, 138.1, 138.8, 145.4, 148.0, 148.3, 148.4, 148.6, 158.9; CHN Anal. Calcd for $C_{72}H_{76}O_{12}Si$: C, 71.51, H, 7.36, Si, 2.70; Found: C, 71.04, H, 6.91; ESI Mass: 1064.12 (M + Na).

Compound 21: To the solution of alkene **20** (0.300g, 0.29 mmol) in 10 mL of anhydrous THF cooled to 0 ^{o}C was added $BH_3.S(CH_3)_2$ (54.7 µL, 0.58 mmol) diluted with anhydrous THF (1 mL) dropwise under nitrogen atmosphere *via* a syringe. The resulted reaction mixture was stirred for 2 h at the same temperature and after complete disappearance of the alkene **20** (TLC monitored), the reaction mixture was again cooled to 0 ^{o}C and to this was added NaOH (0.047g, 1.16 mmol) dissolved in 2 mL of 2:1 mixture of ethanol and water dropwise and allowed to stir for 10 min. To this was added H_2O_2 (62.6g, 1.74 mmol) and the reaction was stirred for 6 h. The reaction mixture was diluted with water (10 mL), extracted with ethyl acetate (3 × 20 mL), pooled organic layers were dried over anhydrous Na_2SO_4, concentrated *in vacuo* and residue was purified by silica gel column chromatography using (20→30 %) ethyl acetate and light petroleum to afford alcohol **21** (0.229g, 72 %) 3:7 diastereomeric mixture as syrup.



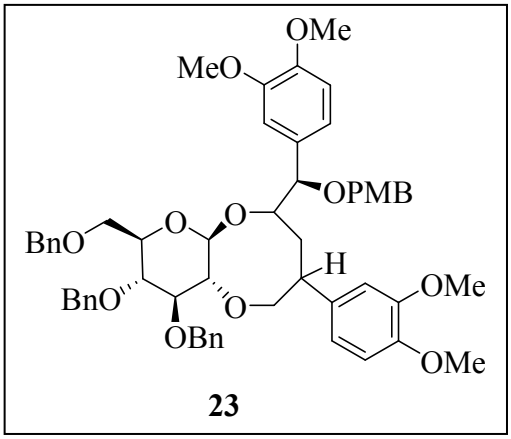
21

Compound 22: To a solution of diastereomeric mixture of alcohol **21** (0.210g, 0.20 mmol) in anhydrous pyridine cooled to 0 ^{o}C was added MsCl (31 µL, 39.6 mmol) dropwise and reaction mixture was allowed to stir at room temperature for 2 h. After completion of the reaction (TLC monitored), the reaction mixture was diluted with water (10 mL) and extracted with ethyl acetate (3 × 10 mL). The pooled organic layers were washed with brine solution, dried over anhydrous Na_2SO_4, concentrated *in vacuo* and purified by silica gel column chromatography using 25 % ethyl acetate and light petroleum to afford mesylate **22** (0.148g, 67 %) as the major isomer. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 0.03, 0.11, 0.90 (3s, 15H), 1.88 (ddd, 1H, *J* = 3.54, 9.73, 13.89 Hz), 2.29 (m, 1H), 2.67 (s, 3H), 2.83 (m, 1H), 3.08 (dd, 1H, *J* = 2.90, 9.47 Hz), 3.36-3.61 (m, 5H), 3.77, 3.79, 3.80 (3s, 15H), 4.01 (d, 1H, *J* = 6.82 Hz), 4.12 (d, 2H, *J* = 6.57 Hz), 4.38 (d, 1H, *J* = 10.99 Hz), 4.39 (d, 1H, *J* = 5.05 Hz), 4.48 (d, 2H, *J* = 11.88 Hz), 4.66 (s, 1H), 4.69 (d, 1H, *J* = 5.43 Hz), 4.86 (s, 2H), 6.46 (d, 1H, *J* = 1.77 Hz), 6.57 (dd, 1H, *J* = 1.77, 8.22 Hz), 6.72 (t, 2H, *J* = 8.71 Hz), 4.87 (m, 4H), 7.08 (m, 2H), 7.22-7.33 (m, 17H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ -4.4, -3.6, 18.1, 26.0, 32.7, 37.0, 41.6, 55.2, 55.7, 55.8, 68.8, 71.1, 73.3, 73.6, 74.6, 74.7, 74.8, 75.4, 78.2, 78.3, 83.4, 85.9, 101.2, 110.0, 110.8, 111.1, 111.5, 113.6, 119.3, 119.6, 127.0, 127.1, 127.5, 127.6, 127.7, 127.8, 128.1, 128.2, 128.3, 129.4, 130.7, 132.3, 132.8, 138.0, 138.2, 138.7, 148.0, 148.1, 148.7, 148.8, 159.0.



22

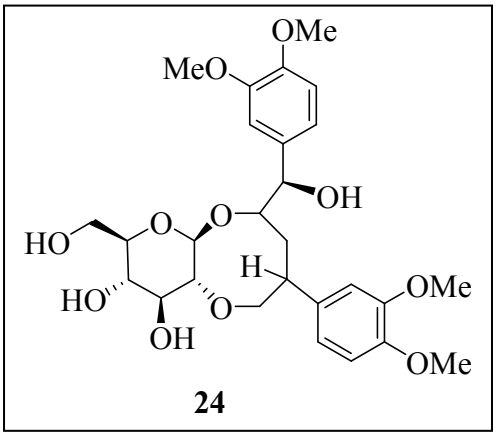
Compound 23: To a solution of mesylate **22** (0.120g, 0.11 mmol) in anhydrous THF cooled at 0 ^{o}C was added *n*-$Bu_4N^+F^-$ (0.055g, 0.21 mmol) and the solution was stirred for 6 h at room temperature. After completion of the reaction (TLC monitored), the reaction mixture was concentrated *in vacuo* and residue was purified by silica gel column chromatography



23

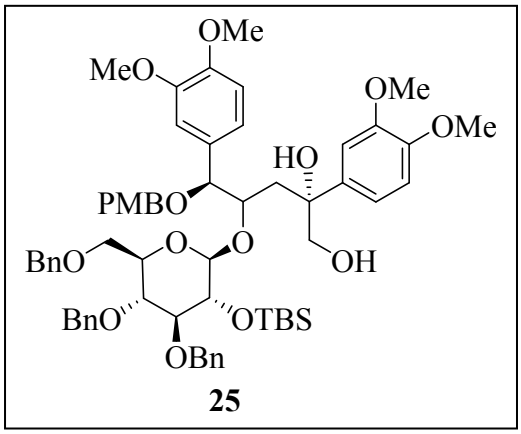
using 20 % ethyl acetate and light petroleum to afford cyclic ether **23** (0.079g, 79 %) as syrup. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.93 (m, 2H), 2.96 (m, 1H), 3.29 (s, 1H), 3.41 (m, 1H), 3.59 (m, 5H), 3.76, 3.78, 3.81, 3.83, 3.86 (5s, 15H), 4.02 (m, 1H), 4.22-4.57 (m, 8H), 4.76 (d, 1H, *J* = 11.11 Hz) 4.86 (d, 1H, *J* = 10.87 Hz), 4.93 (d, 1H, *J* = 11.11 Hz), 6.60-6.98 (m, 8H), 7.17-7.38 (m, 17H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 32.7, 42.0, 42.2, 55.1, 55.7, 55.8, 69.2, 70.7, 73.3, 73.4, 74.9, 75.1, 75.2, 77.4, 77.9, 82.2, 84.6, 86.3, 88.0, 102.2, 110.6, 110.8, 111.3, 111.5, 113.6, 113.7, 119.7, 120.5, 127.5, 127.6, 127.7, 127.9, 128.3, 129.2, 129.5, 129.9, 130.3, 133.5, 133.6, 138.0, 138.1, 138.7, 147.9, 148.6, 148.8, 148.9, 159.2.

Compound 24: To a solution of cyclic ether **23** (0.060g, 0.065 mmol) dissolved in methanol was added $Pd(OH)_2/C$ (0.010g) and reaction mixture was flushed with H_2. The reaction mixture was allowed to stir for 12 h at room temperature under hydrogen atmosphere and after complete disappearance of the starting material (TLC monitored), the reaction mixture was filtered through sintered funnel, concentrated *in vacuo* and residue was purified by silica gel column chromatography using 5 % methanol and dichloromethane to afford the alcohol **24** (0.028g, 80 %) as syrup. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.76 (t, 1H, *J* = 6.77 Hz), 2.02 (t, 1H, *J* = 6.78 Hz), 2.46 (bs, 1H), 3.11 (d, 1H, *J* = 9.04 Hz), 3.58 (s, 2H), 3.75, 3.74, 3.83 (3s, 12H), 4.17-4.40 (m, 4H), 4.55 (bs, 1H), 5.07 (s, 1H), 5.14 (bs, 1H), 5.42 (bs, 1H), 6.45 (s, 1H), 6.54 (d, 1H, *J* = 8.28 Hz), 6.75 (m, 3H), 6.90 (s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 31.9, 42.0, 42.2, 55.8, 60.8, 68.9, 73.3, 74.4, 75.8, 76.3, 77.2, 81.8, 86.1, 102.2, 109.4, 110.9, 111.4, 111.7, 118.2, 119.9, 132.2, 133.1, 133.2, 148.0, 148.2, 148.8, 148.9



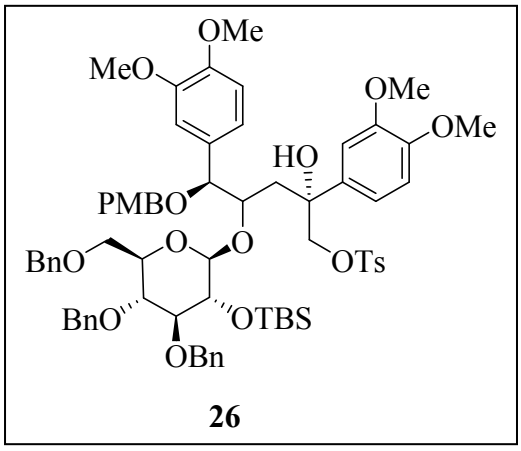
24

Compound 25: A stirred suspension of AD-mix-α (0.269g, 1.4 g/mmol, Aldrich) in *t*-BuOH-H_2O (1:1, 10 mL) was treated with alkene **20** (0.200g, 0.19 mmol) dissolved in *t*-BuOH (5mL) at 0 ^oC, and the resulting biphasic reaction mixture was stirred at room temperature for 12 h. After completion of the reaction (TLC monitored) Na_2SO_3 (0.288g, 1.5g/mmol) was added and the reaction mixture was stirred for 30 min, and diluted with ethyl acetate (10 mL). After separation of two layers, the aqueous phase was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with water (20 mL) and saturated aqueous brine solution (20 mL), dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The crude was purified by silica gel column chromatography using 50 % ethyl acetate and light petroleum to afford diol **25** (0.156g, 76 %) as a single diastereomer. $[\alpha]_D$ -5.92 (*c* 0.90, $CHCl_3$); IR ($CHCl_3$): 3415 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ -0.03, 0.05, 0.90 (3s, 15H), 2.13 (d, 2H, *J* = 14.78 Hz), 2.48 (dd, 1H, *J* = 2.15, 9.60 Hz), 2.64 (dd, 1H, *J* = 6.69, 15.15 Hz), 3.15 (m, 3H), 3.33 (t, 1H, *J* = 9.47 Hz), 3.49 (m, 3H), 3.64, 3.74, 3.81, 3.84 (4s, 15H), 4.12 (d, 1H, *J* = 11.75 Hz), 4.18 (d, 1H, *J* = 11.75 Hz), 4.19 (t, 2H, *J* = 10.86 Hz), 4.43 (d, 1H, *J* = 10.99 Hz), 4.46 (d, 1H, *J* = 10.61 Hz), 4.57 (d, 1H, *J* = 10.99 Hz), 4.77 (d, 2H, *J* = 1.14 Hz), 5.09 (bs, 1H), 6.66 (d, 1H, *J* = 8.21 Hz), 6.77-6.93 (m, 6H), 7.02 (d, 1H, *J* = 2.78 Hz), 7.06 (d, 2H, *J* = 1.64 Hz), 7.16-7.35 (m, 15H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ -4.4, -3.6, 18.1, 26.0, 42.7, 55.2, 55.5, 55.7, 55.9, 68.5, 70.5, 70.9, 73.6, 74.1, 74.2, 74.4, 75.1, 75.3, 77.2, 77.9, 83.8, 85.8, 98.6, 109.4, 110.4, 110.9, 111.0, 114.0, 117.5, 120.3, 127.0, 127.1, 127.4, 127.6, 127.8, 128.0, 128.1, 128.2, 128.7, 130.2, 131.3, 137.1, 138.3, 138.5, 138.7, 147.8, 148.5, 148.5, 148.7, 159.7; ESI Mass: 1098.72 (M + Na).



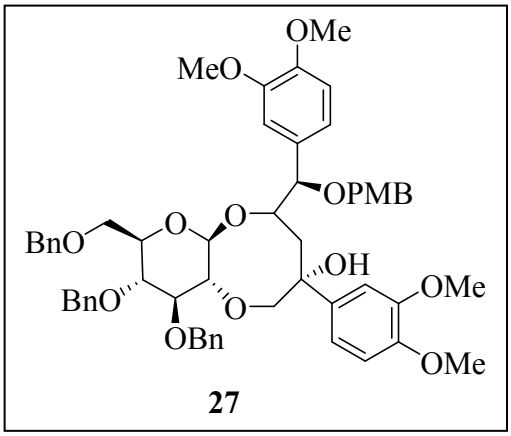
25

Compound 26: To a solution of diol **25** (0.110g, 0.102 mmol) in anhydrous pyridine was added TsCl (0.024g, 0.123 mmol) dropwise under nitrogen atmosphere and the reaction mixture was allowed to stir at 85 ^{o}C for 12 h. After completion of the reaction (TLC monitored), the reaction mixture was diluted with water (20 mL) and extracted with ethyl acetate (3 × 10 mL). The pooled organic layers were washed with brine solution, dried over anhydrous Na_2SO_4, concentrated *in vacuo* and purified by silica gel column chromatography using 30 % ethyl acetate and light petroleum to afford tosylate **26** (0.096g, 79 %) as thick syrup. $[\alpha]_D$ +2.93 (*c* 0.80, $CHCl_3$); IR ($CHCl_3$): 3417 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 0.02, 0.05, 0.90 (3s, 15H), 2.15 (d, 1H, *J* = 15.03 Hz), 2.38 (d, 1H, *J* = 5.81 Hz), 2.42 (s, 3H), 2.73 (dd, 1H, *J* = 6.57, 15.41 Hz), 3.13 (m, 3H), 3.26-3.53 (m, 4H), 3.64, 3.72, 3.79, 3.80, 3.82 (5s, 15H), 3.88 (s, 1H), 4.04-4.32 (m, 5H), 4.50 (m, 4H), 4.77 (s, 1H), 6.57-6.97 (m, 8H) 7.05 (d, 2H, *J* = 1.77 Hz), 7.15-7.34 (m, 18H), 7.71 (d, 2H, *J* = 8.33 Hz); ^{13}C NMR ($CDCl_3$, 50 MHz): δ -4.4, -3.6, 18.1, 21.6, 26.0, 42.0, 55.2, 55.5, 55.7, 55.9, 68.3, 70.8, 73.4, 73.5, 74.0, 74.3, 75.2, 75.3, 77.8, 83.0, 85.7, 98.6, 109.6, 110.4, 110.8, 110.9, 114.0, 117.9, 120.3, 126.9, 127.0, 127.1, 127.3, 127.4, 127.5, 127.7, 127.9, 128.0, 128.1, 128.2, 128.3, 128.6, 129.7, 130.5, 131.4, 132.8, 135.2, 138.3, 138.5, 138.6, 144.6, 148.2, 148.4, 148.5, 148.7, 159.6



26

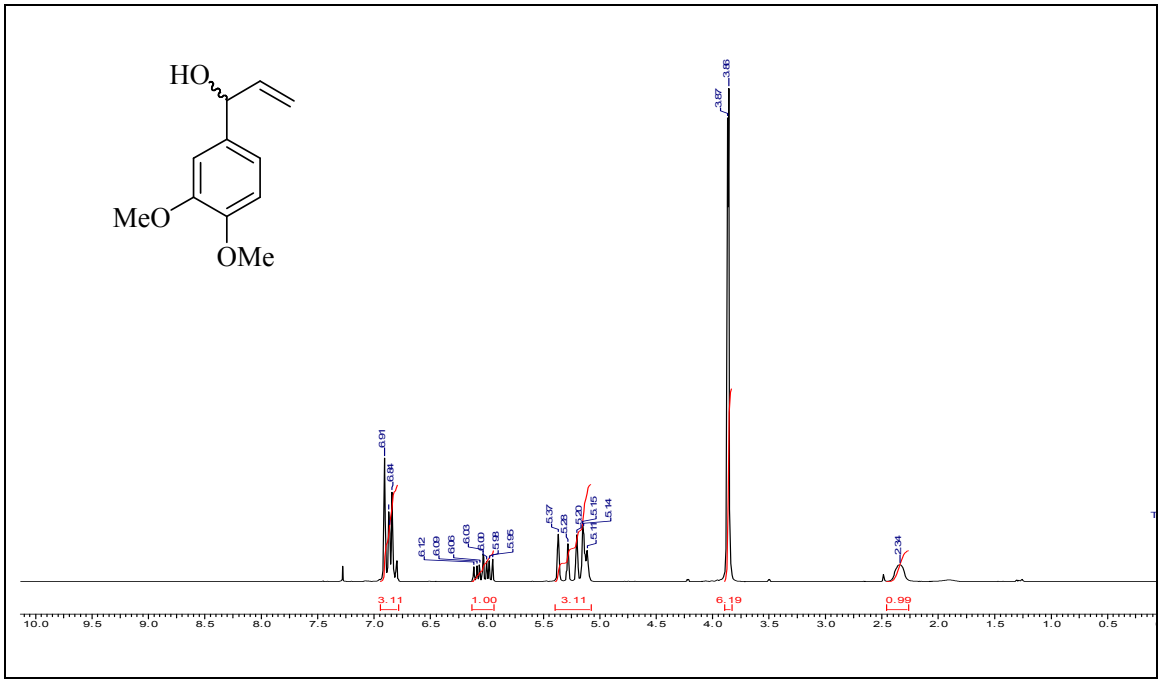
Compound 27: To a solution of tosylate **26** (0.040g, 0.032 mmol) in anhydrous THF cooled at 0 ^{o}C was added *n*-$Bu_4N^+F^-$ (0.017g, 0.065 mmol) and solution was stirred for 12 h at room temperature. After completion of the reaction (TLC monitored) the reaction mixture was concentrated *in vacuo* and residue was purified by silica gel column chromatography using 40 % ethyl acetate and light petroleum to afford



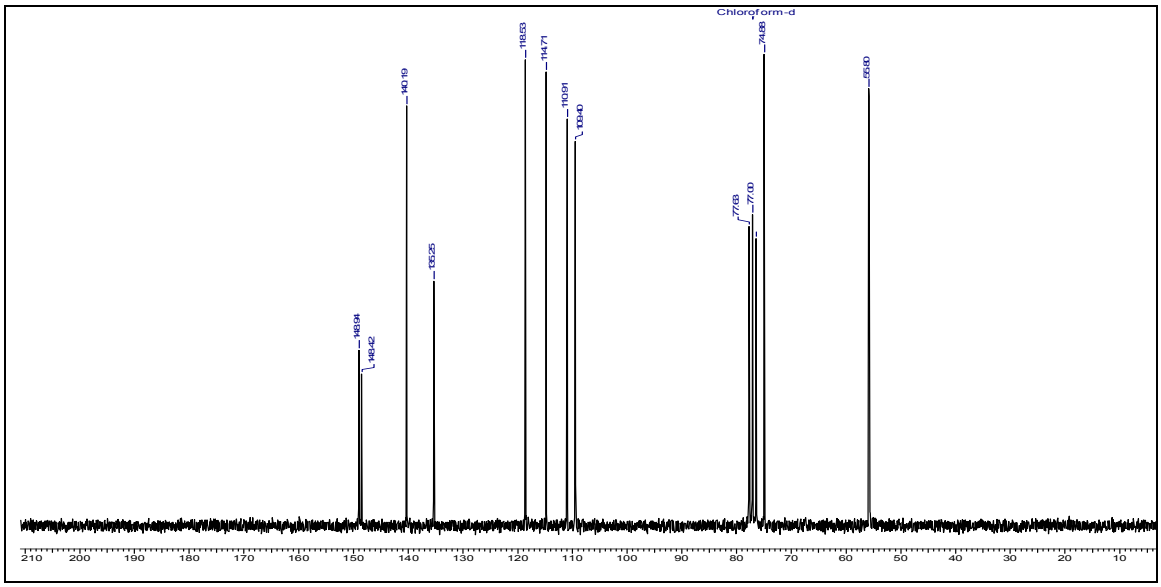
27

cyclic ether **27** (0.021g, 70 %) as syrup. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.13 (dd, 1H, *J* = 6.27, 15.31 Hz), 2.21 (dd, 1H, *J* = 4.27, 15.56 Hz), 3.21 (dd, 1H, *J* = 2.26, 9.29 Hz), 3.44-3.65 (m, 6H), 3.77, 3.80, 3.81, 3.82 (4s, 15H), 3.87 (d, 1H, *J* = 15.85 Hz), 4.21 (d, 2H, *J* = 7.03 Hz), 4.33 (dd, 2H, *J* = 4.76, 11.04 Hz), 4.41-4.58 (m, 4H), 4.79 (d, 1H, *J* = 10.79 Hz), 4.81 (s, 2H), 6.72-6.85 (m, 6H), 6.90 (d, 1H, *J* = 1.50 Hz), 7.00 (d, 1H *J* = 1.50 Hz), 7.16-7.36 (m, 18H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 40.0, 55.3, 55.8, 55.9, 56.0, 68.9, 70.2, 71.1, 73.5, 74.8, 75.1, 75.2, 75.4, 83.2, 84.7, 102.1, 109.2, 110.7, 110.8, 110.9, 113.8, 117.3, 120.3, 127.6, 127.7, 127.8, 127.9, 128.0, 128.3, 128.4, 128.5, 129.7, 137.6, 138.0, 138.1, 138.6, 148.0, 148.6, 148.8, 159.4; ESI Mass: 966.58 (M + Na).

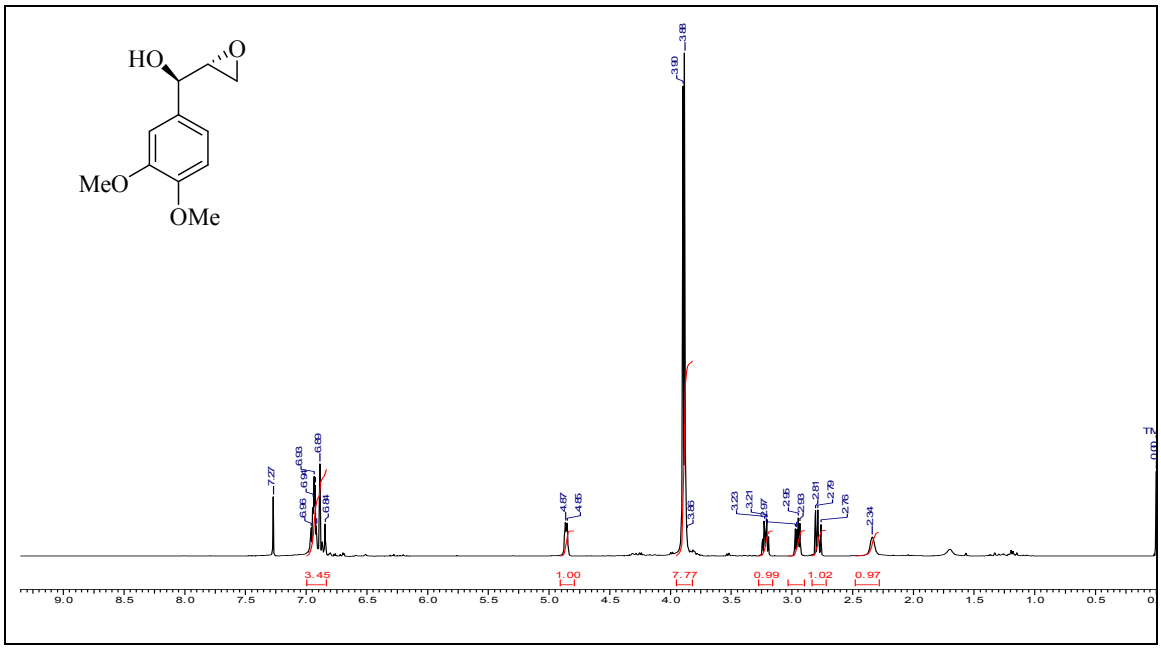
2.4 Spectra



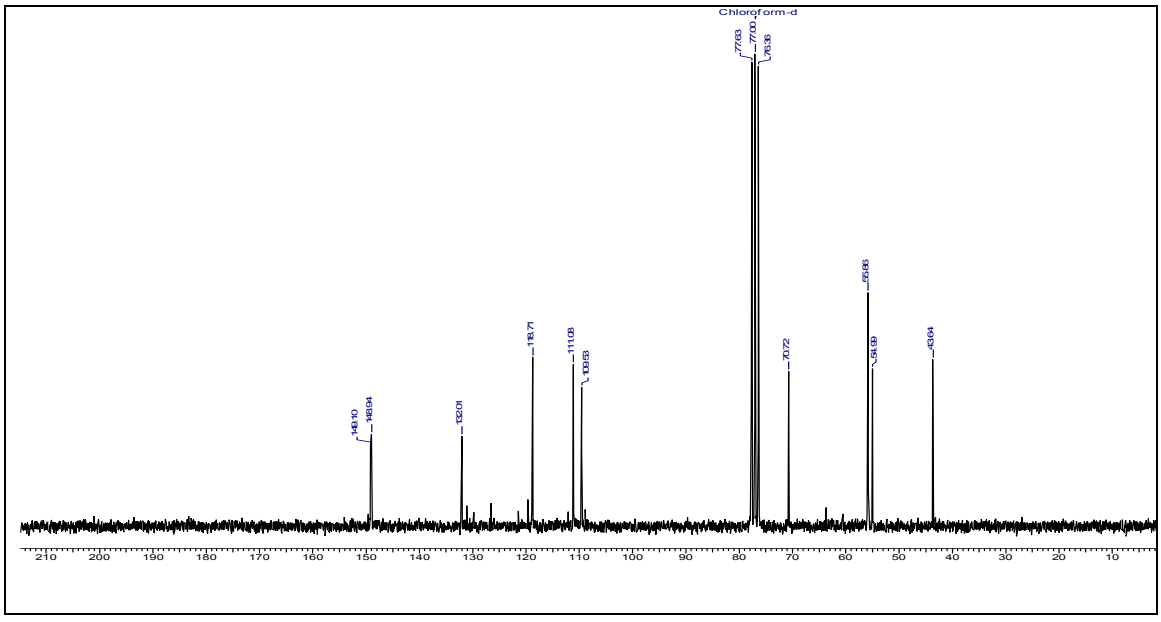
^{1}H NMR spectrum of compound 8 in $CDCl_3$



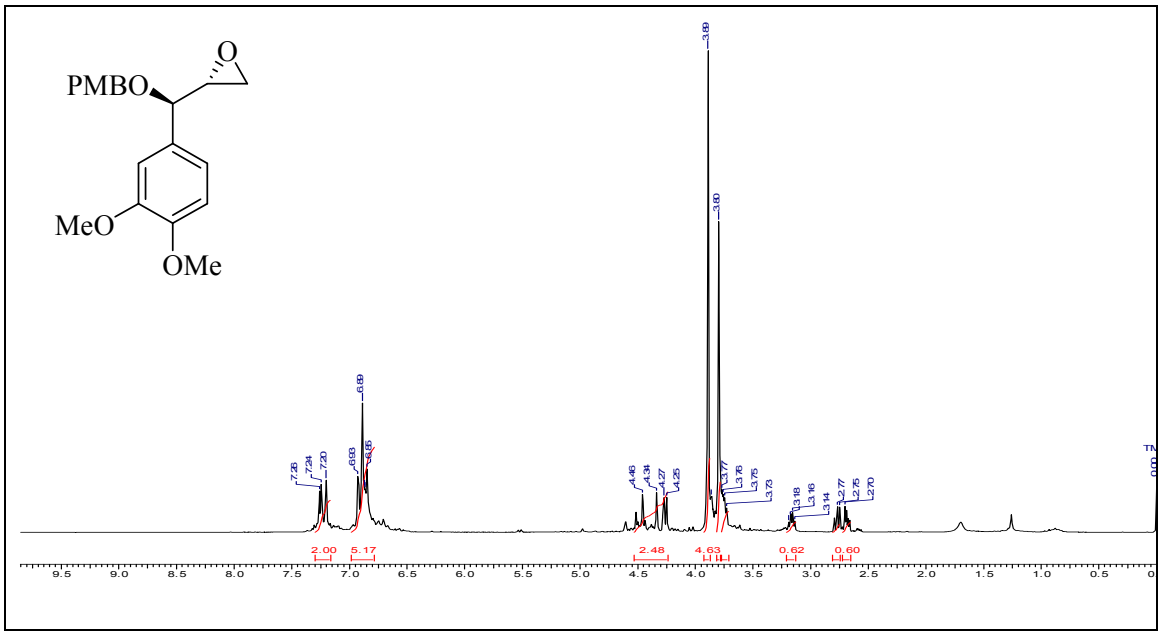
^{13}C NMR spectrum of compound 8 in $CDCl_3$



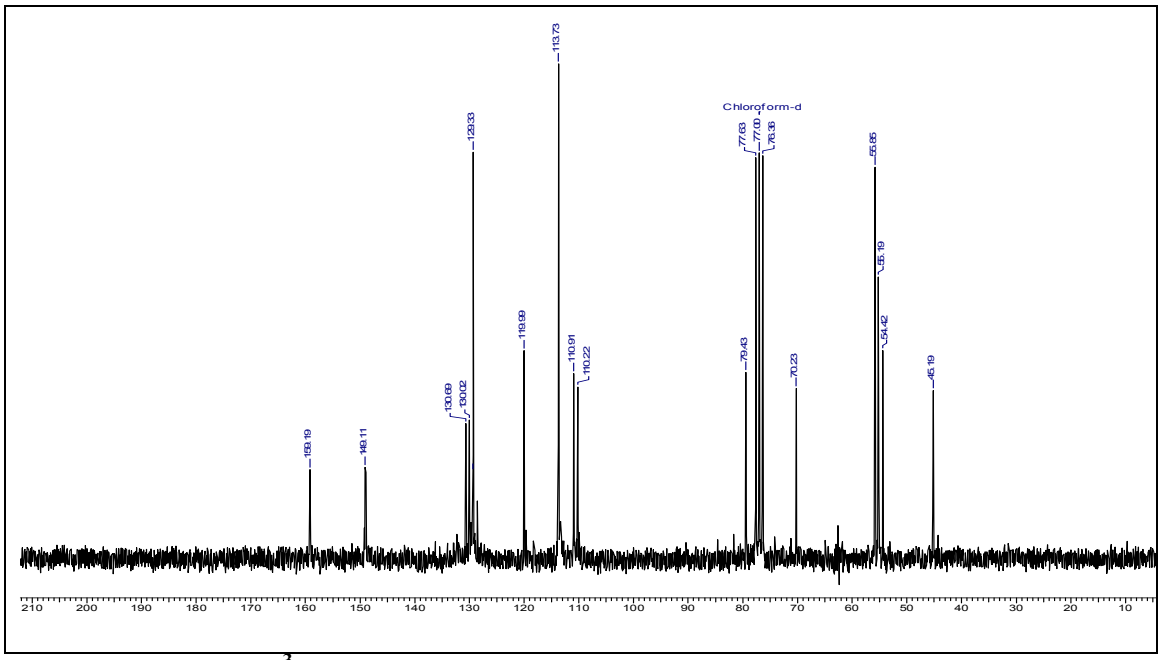
^{1}H NMR spectrum of compound 9 in $CDCl_3$



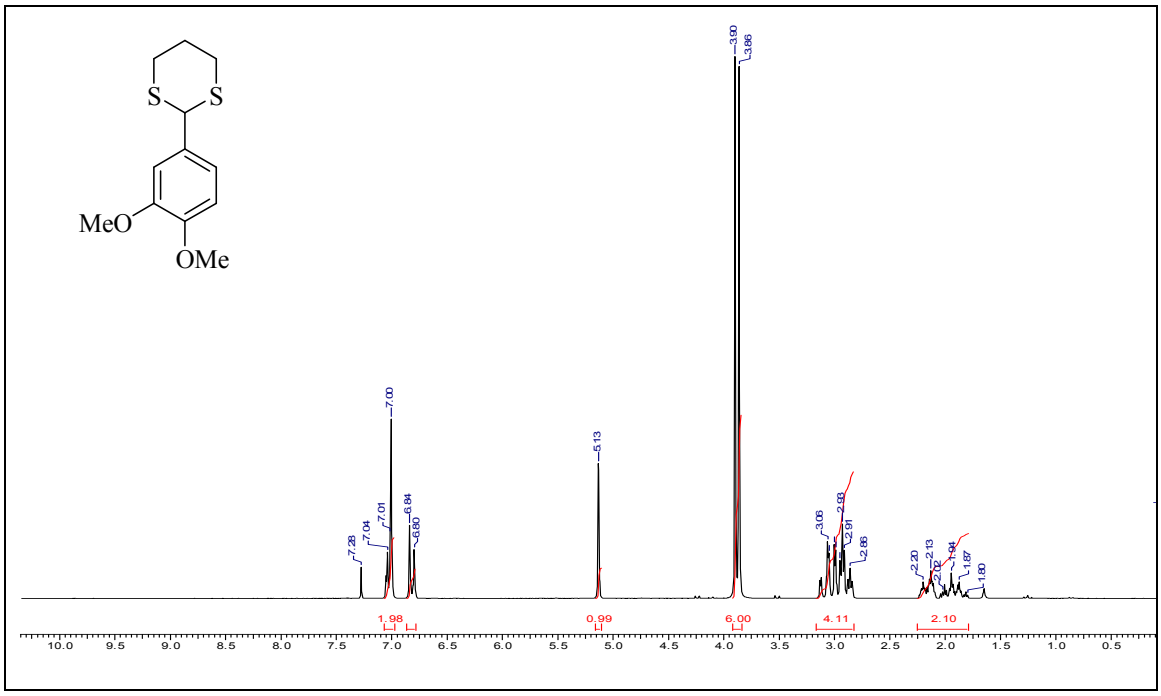
^{13}C NMR spectrum of compound 9 in $CDCl_3$



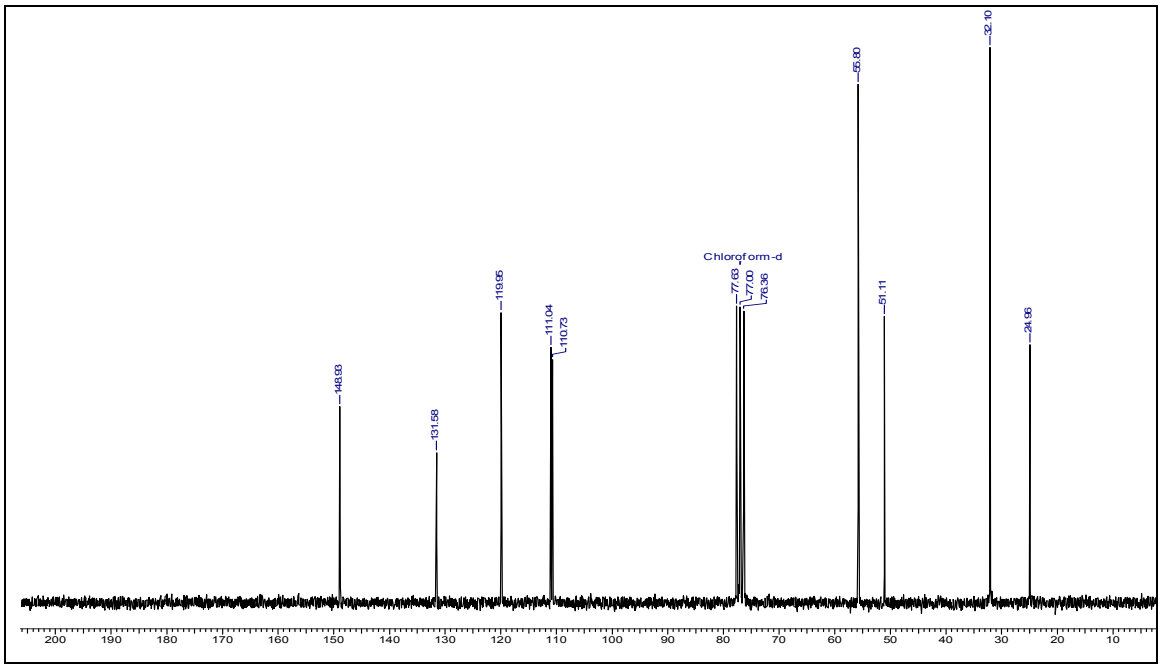
^{1}H NMR spectrum of compound 5 in $CDCl_3$



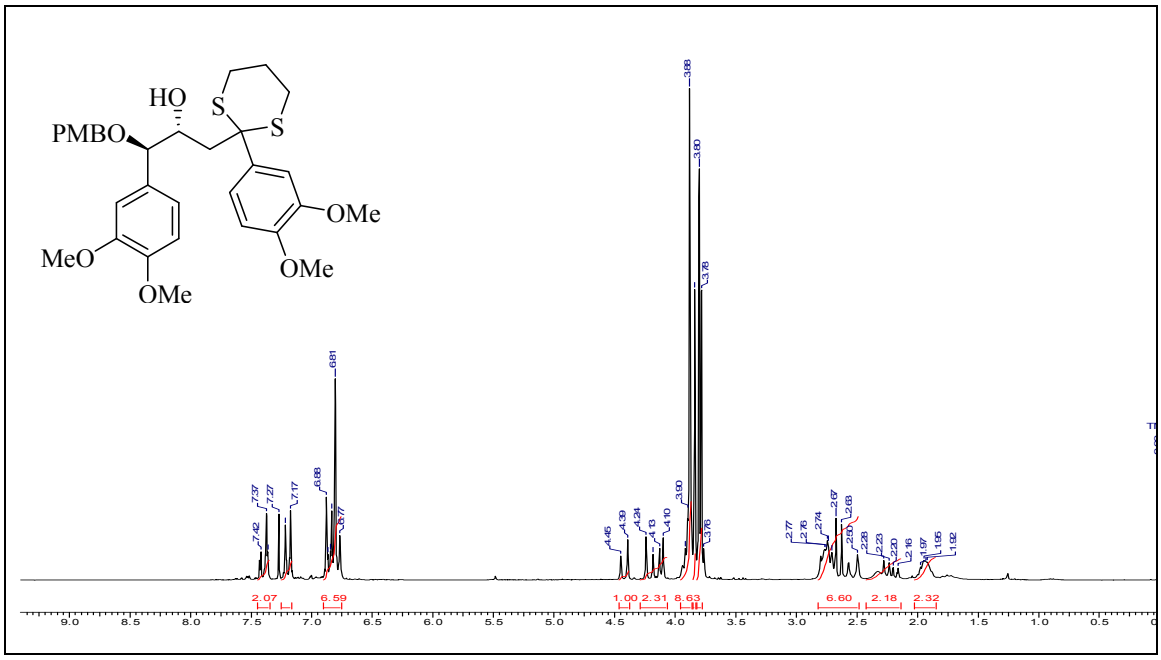
^{3}C NMR spectrum of compound 5 in $CDCl_3$



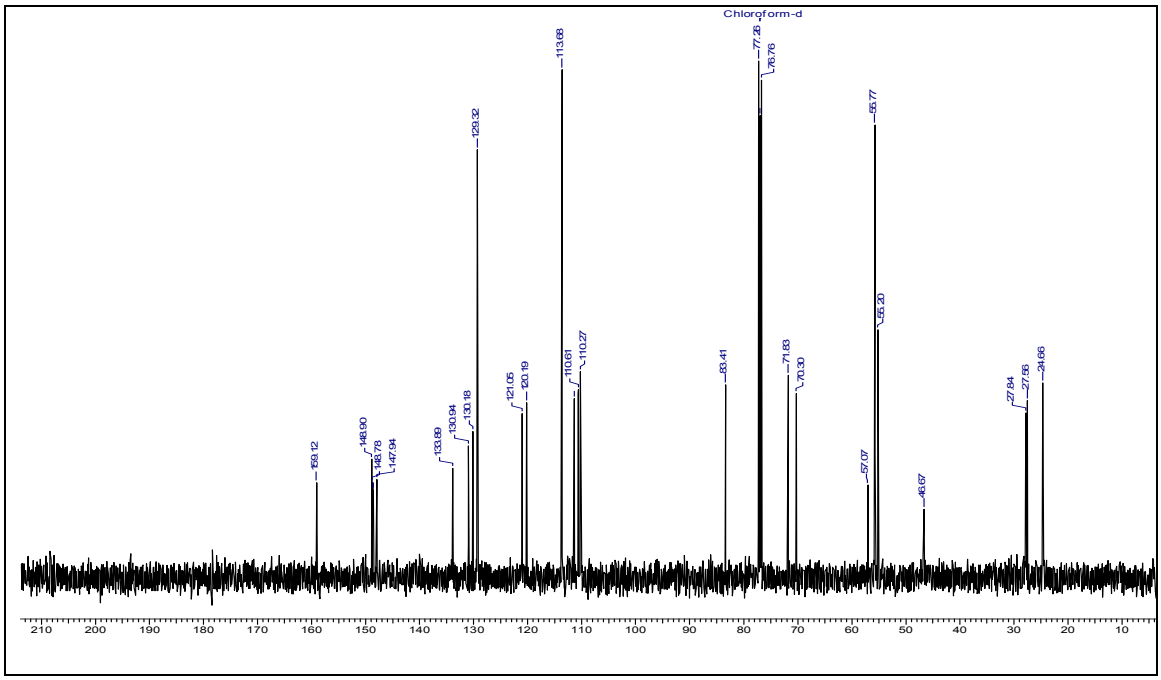
^{1}H NMR spectrum of compound 6 in $CDCl_3$



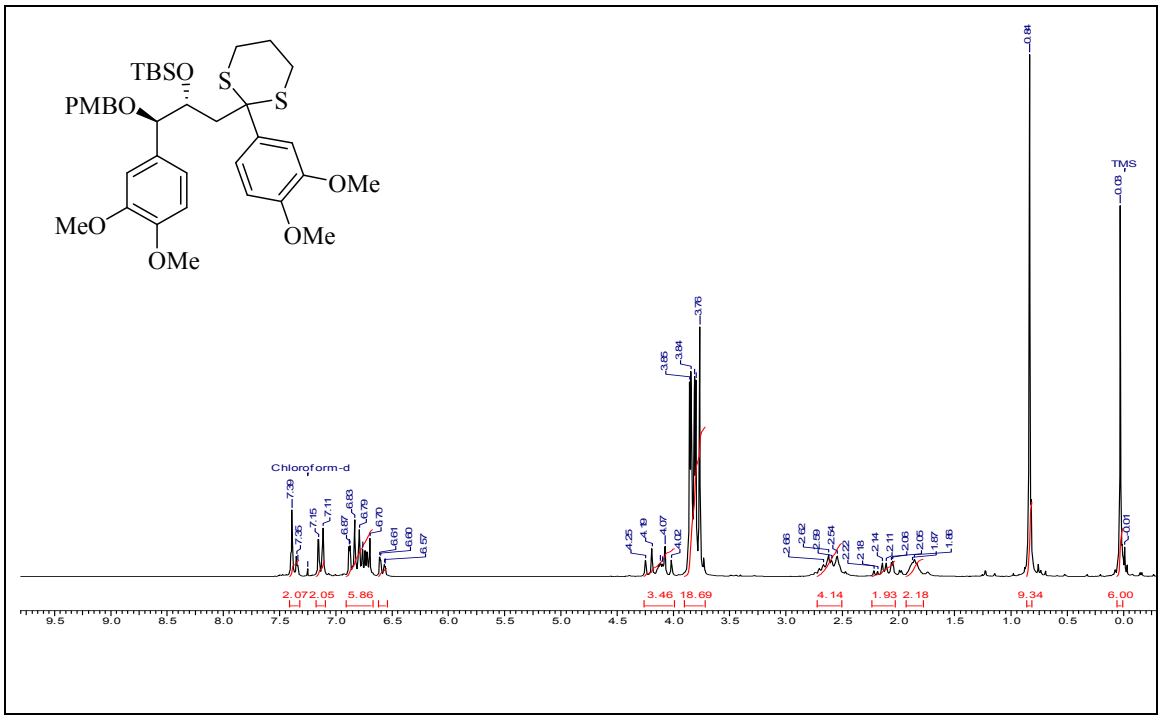
^{13}C NMR spectrum of compound 6 in $CDCl_3$



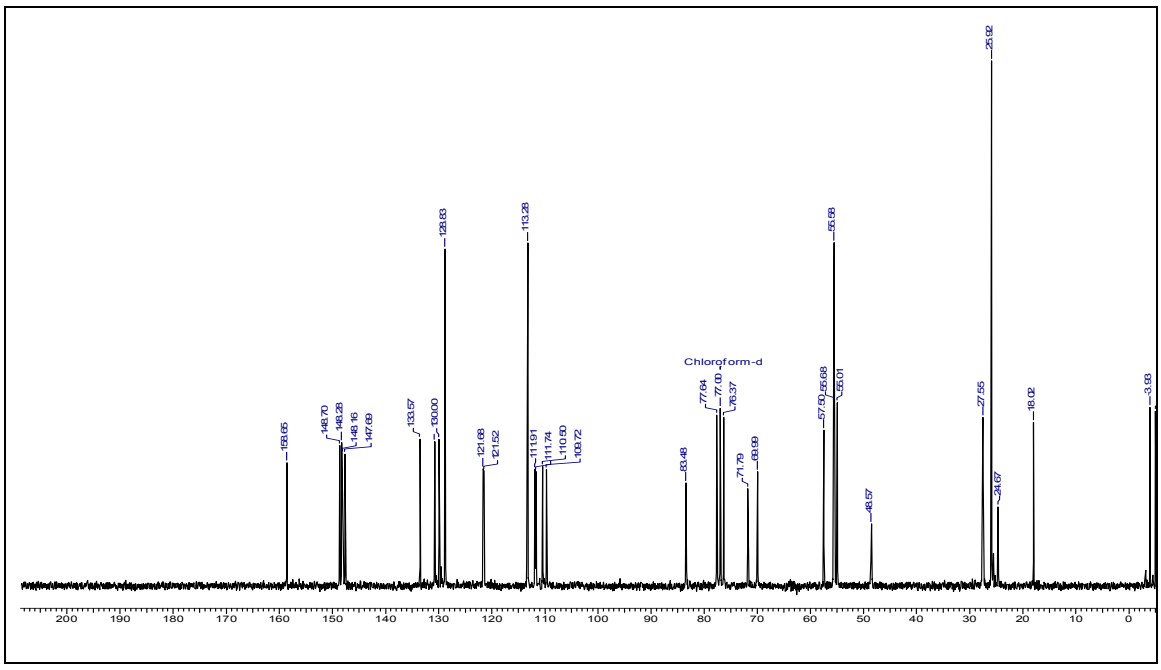
^{1}H NMR spectrum of compound 10 in $CDCl_3$



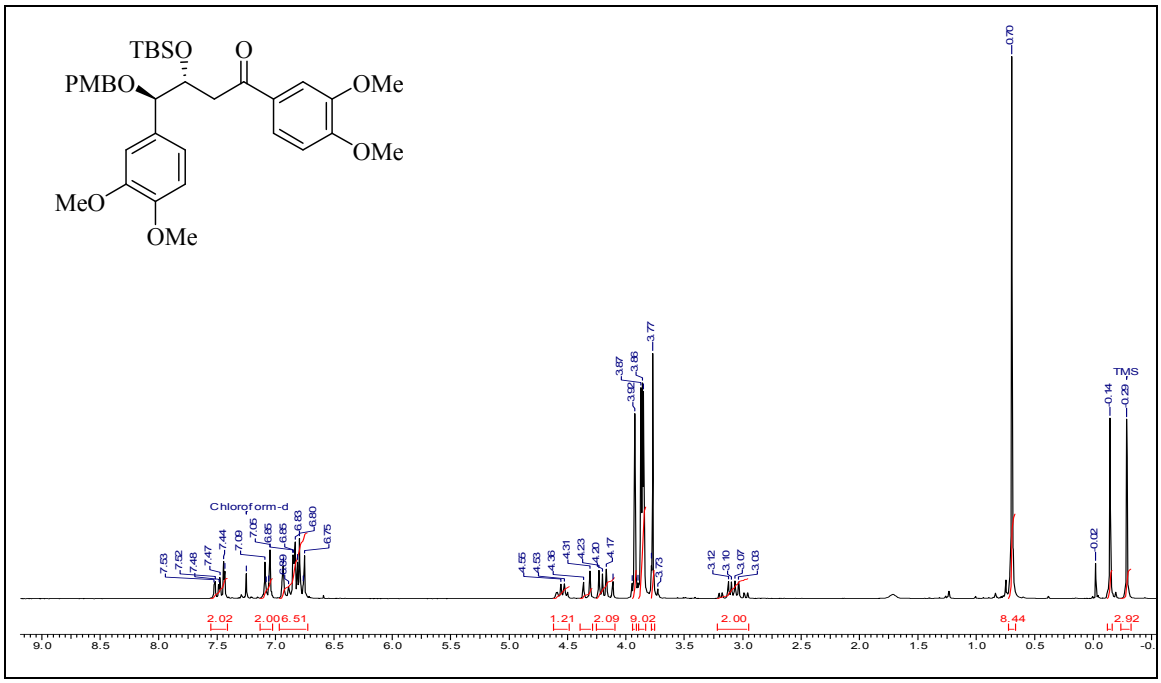
^{13}C NMR spectrum of compound 10 in $CDCl_3$



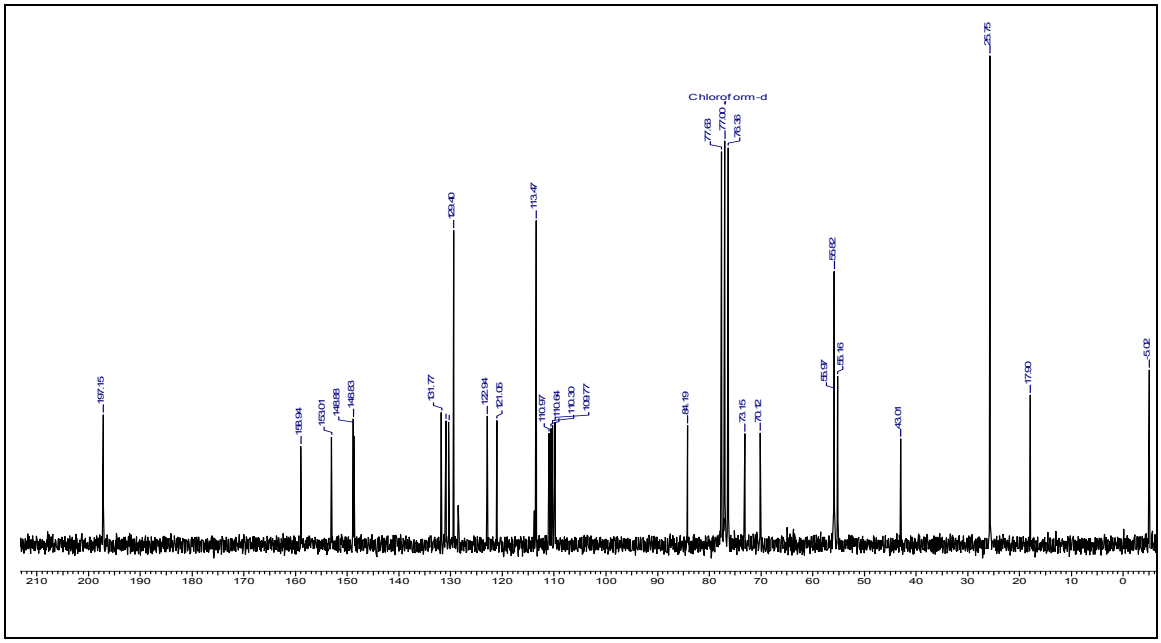
^{1}H NMR spectrum of compound 11 in $CDCl_3$



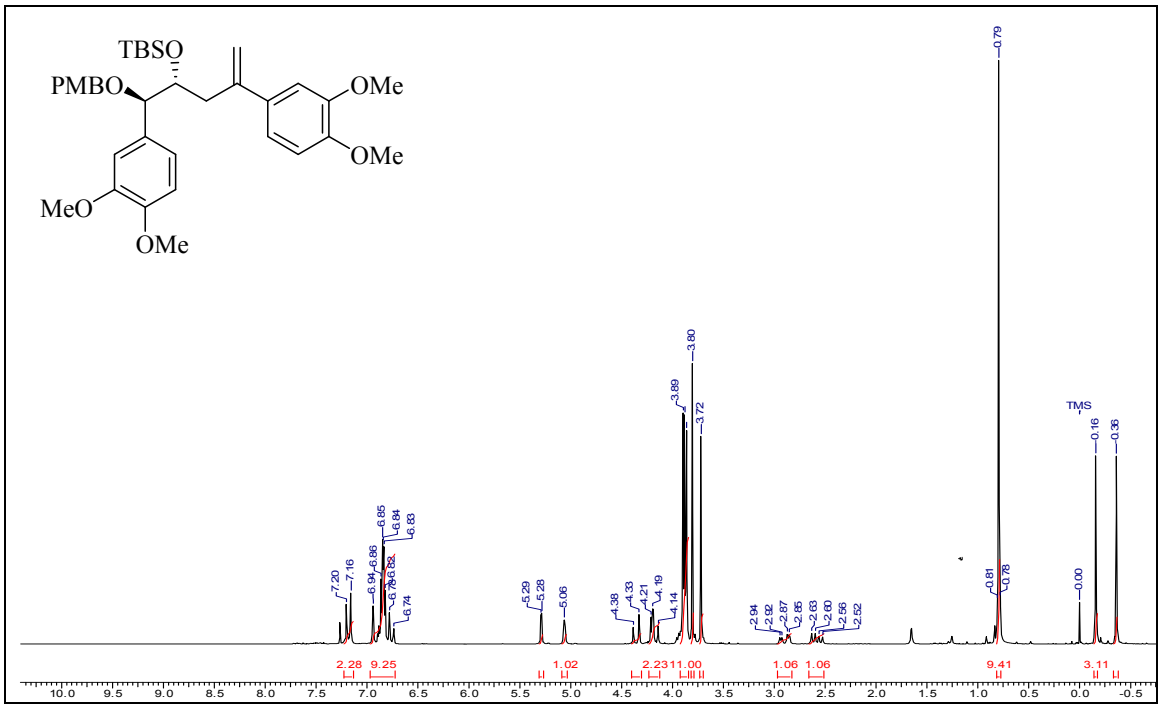
^{13}C NMR spectrum of compound 11 in $CDCl_3$



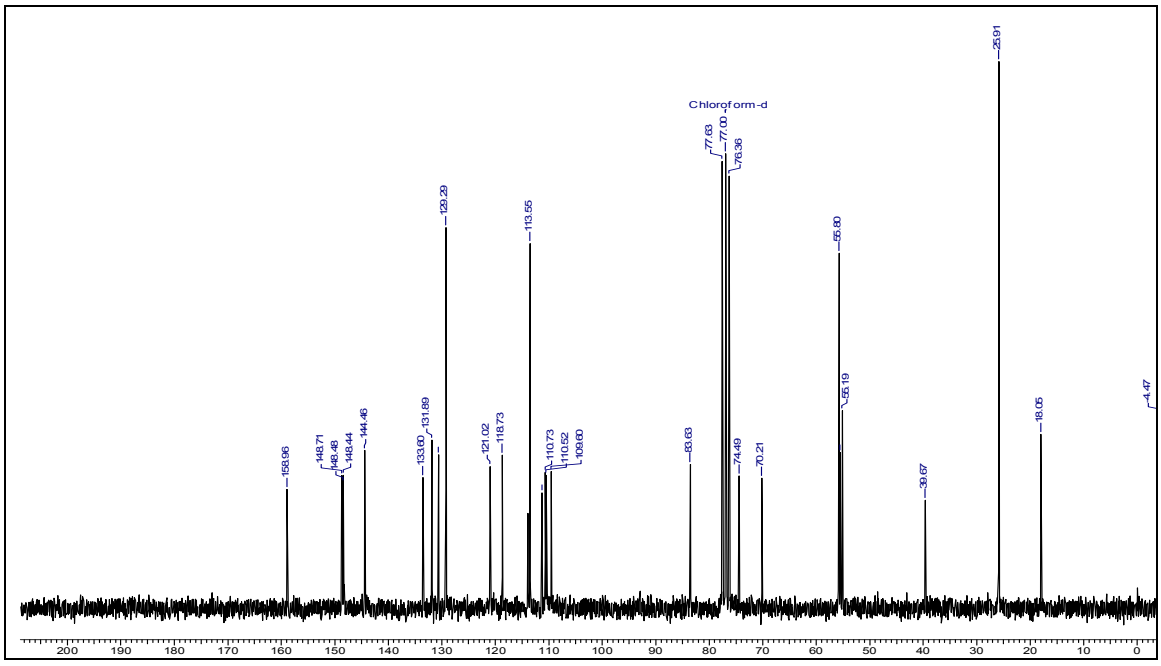
^{1}H NMR spectrum of compound 12 in $CDCl_3$



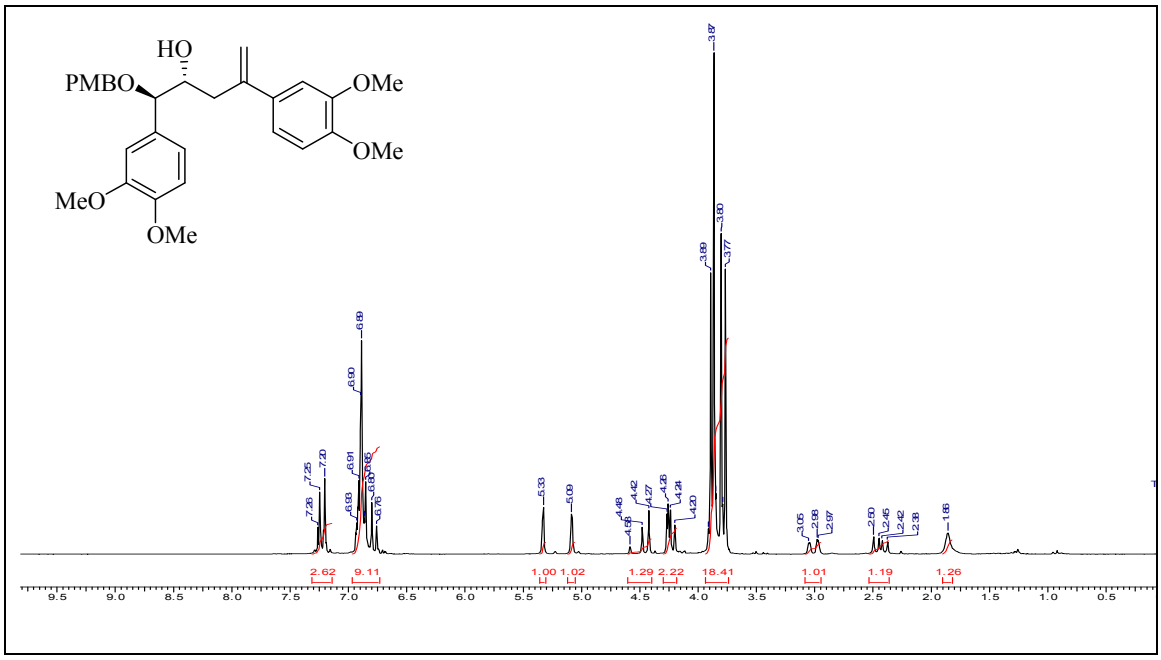
^{13}C NMR spectrum of compound 12 in $CDCl_3$



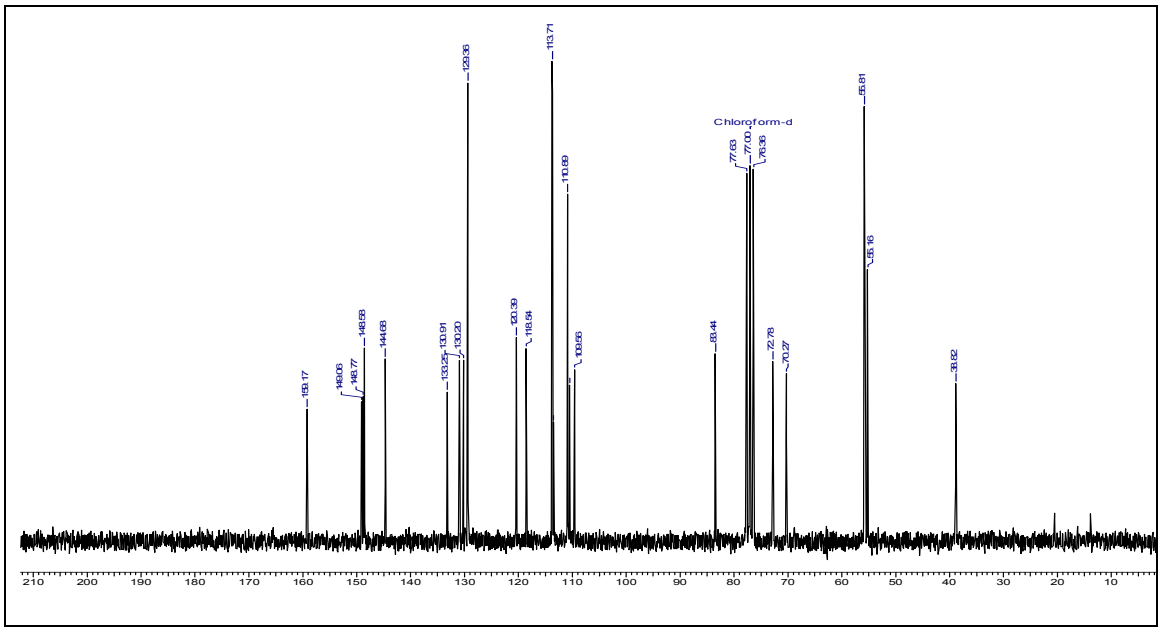
^{1}H NMR spectrum of compound 13 in $CDCl_3$



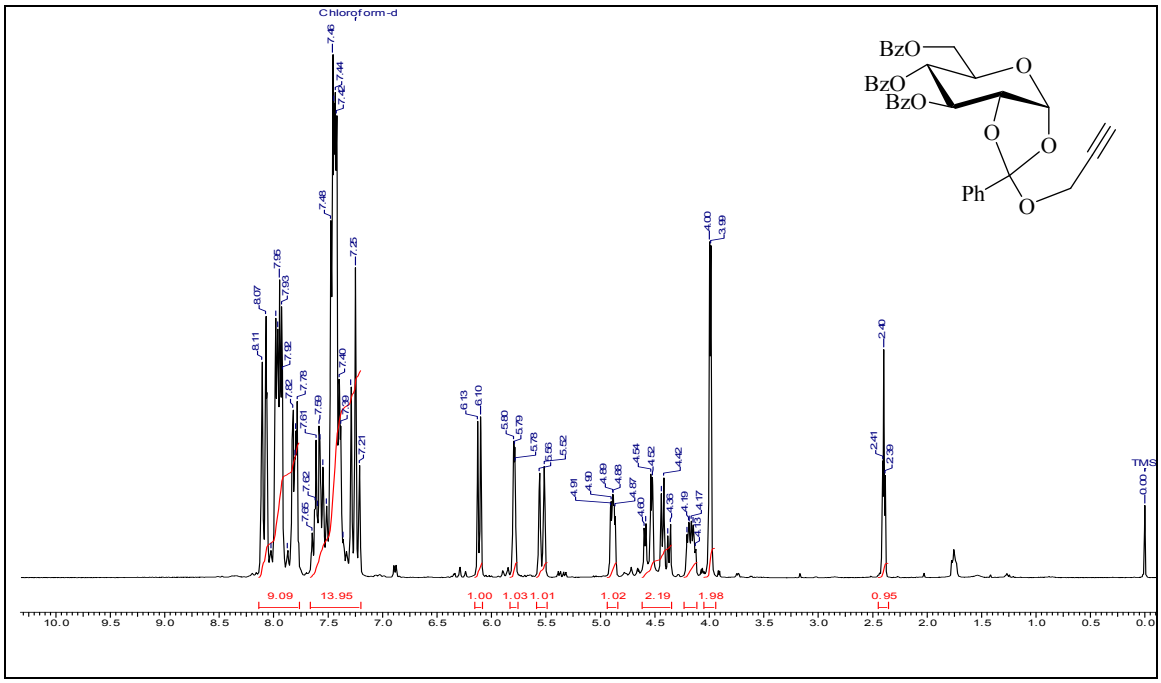
^{13}C NMR spectrum of compound 13 in $CDCl_3$



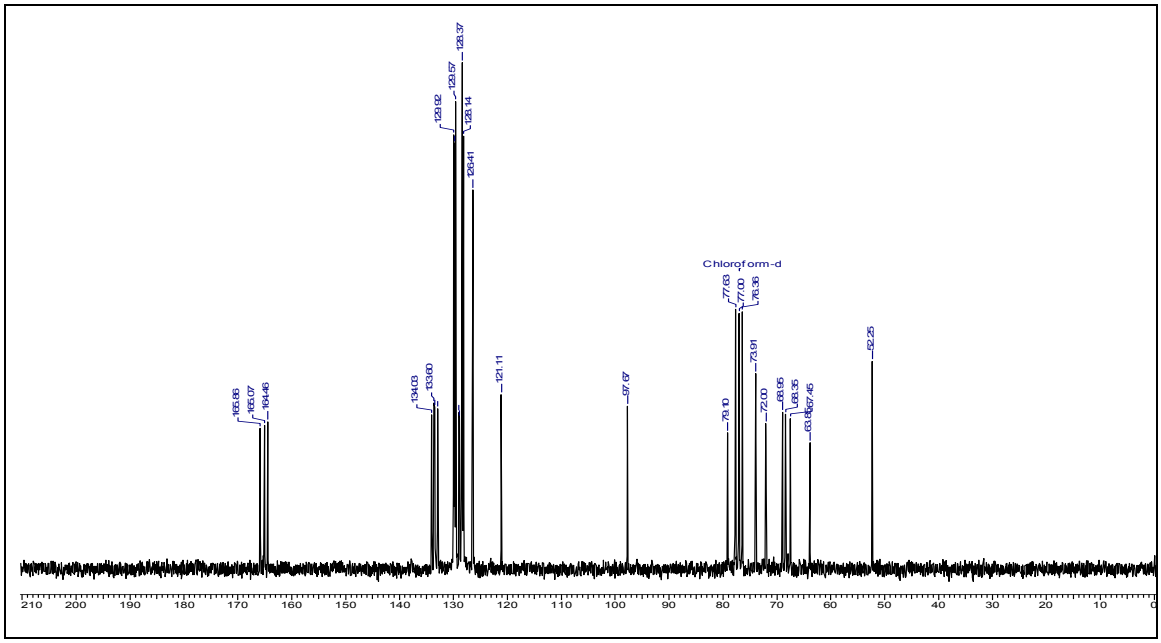
^{1}H NMR spectrum of compound 3 in $CDCl_3$



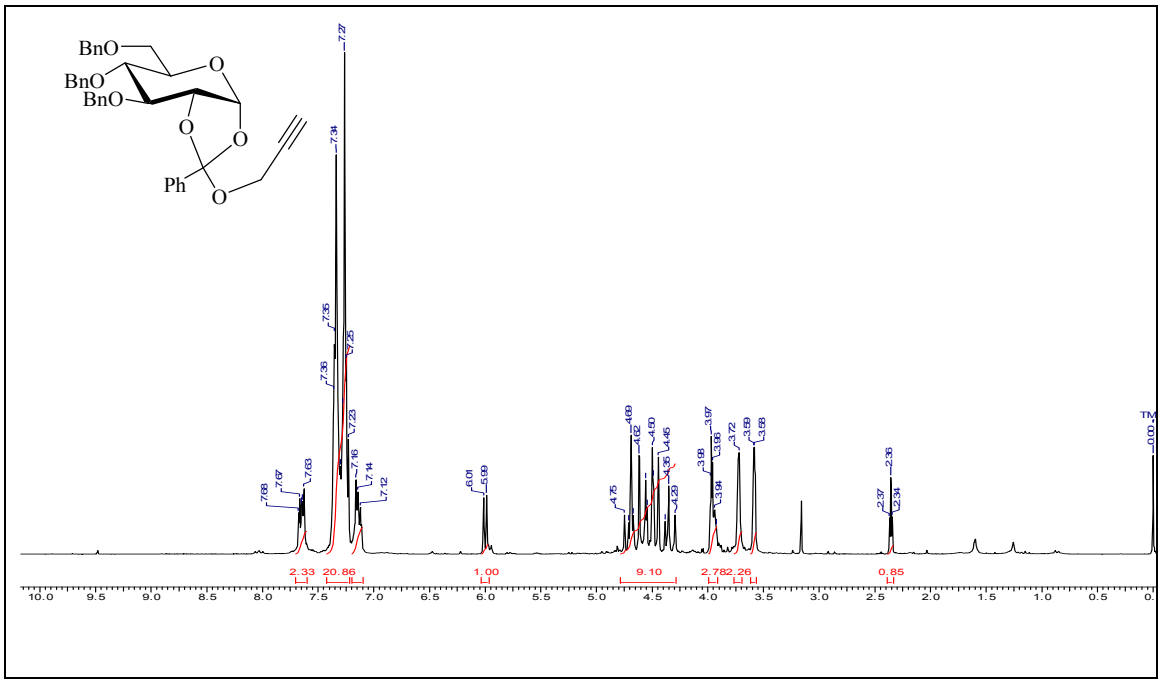
^{13}C NMR spectrum of compound 3 in $CDCl_3$



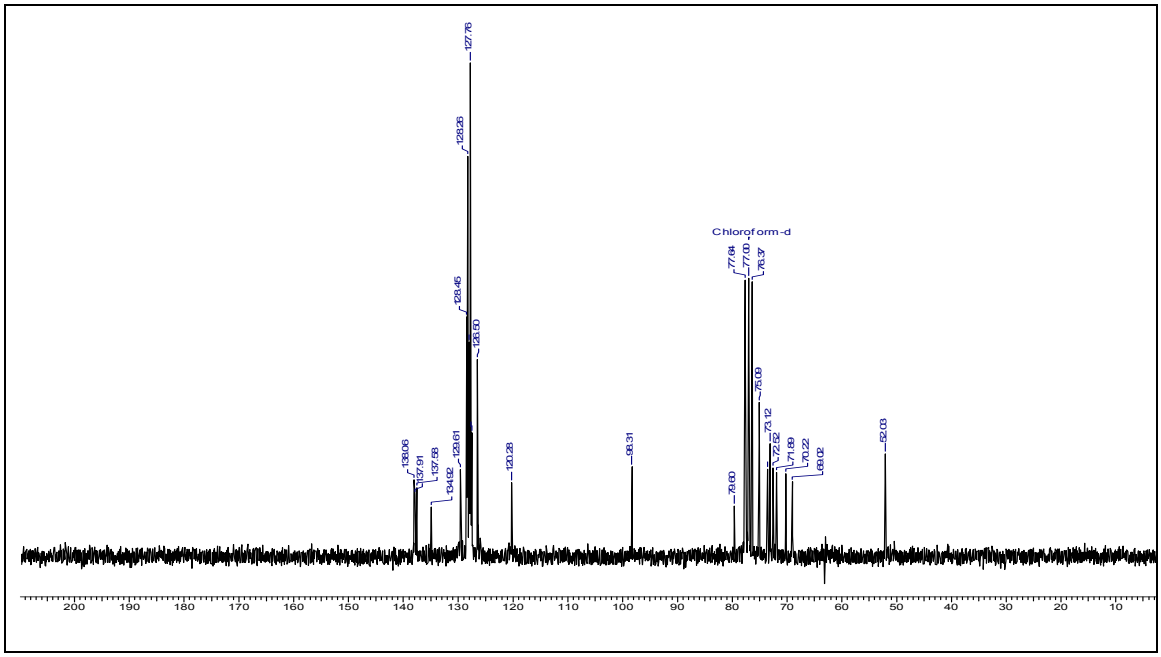
^{1}H NMR spectrum of compound 15 in $CDCl_3$



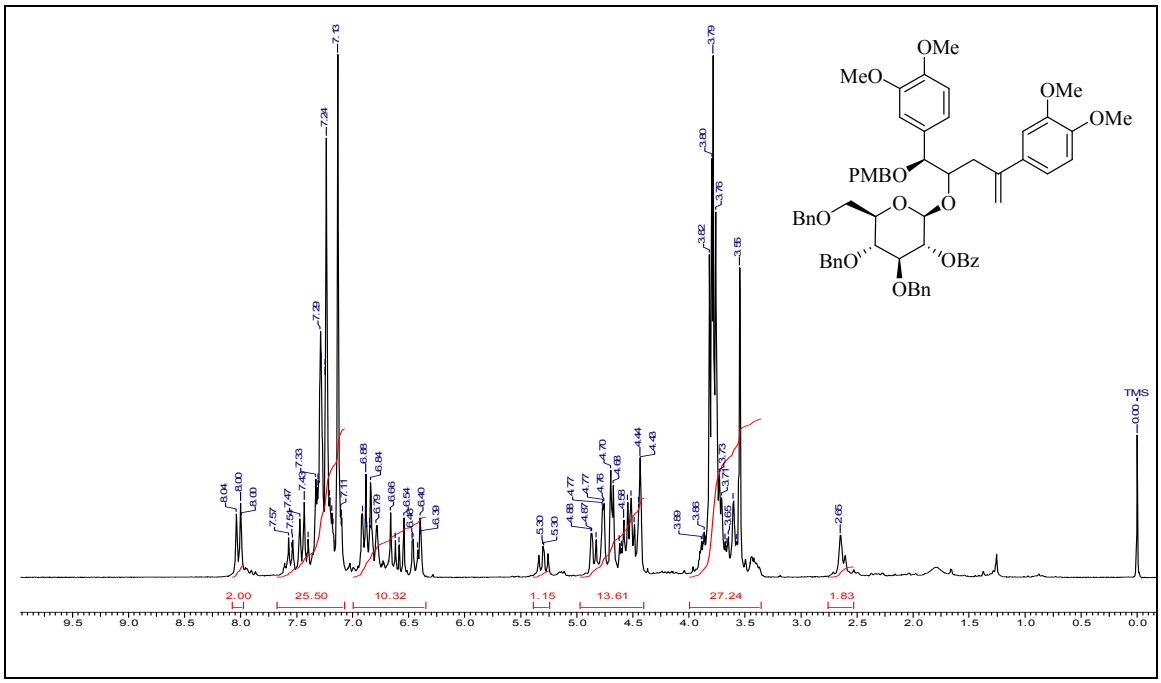
^{13}C NMR spectrum of compound 15 in $CDCl_3$



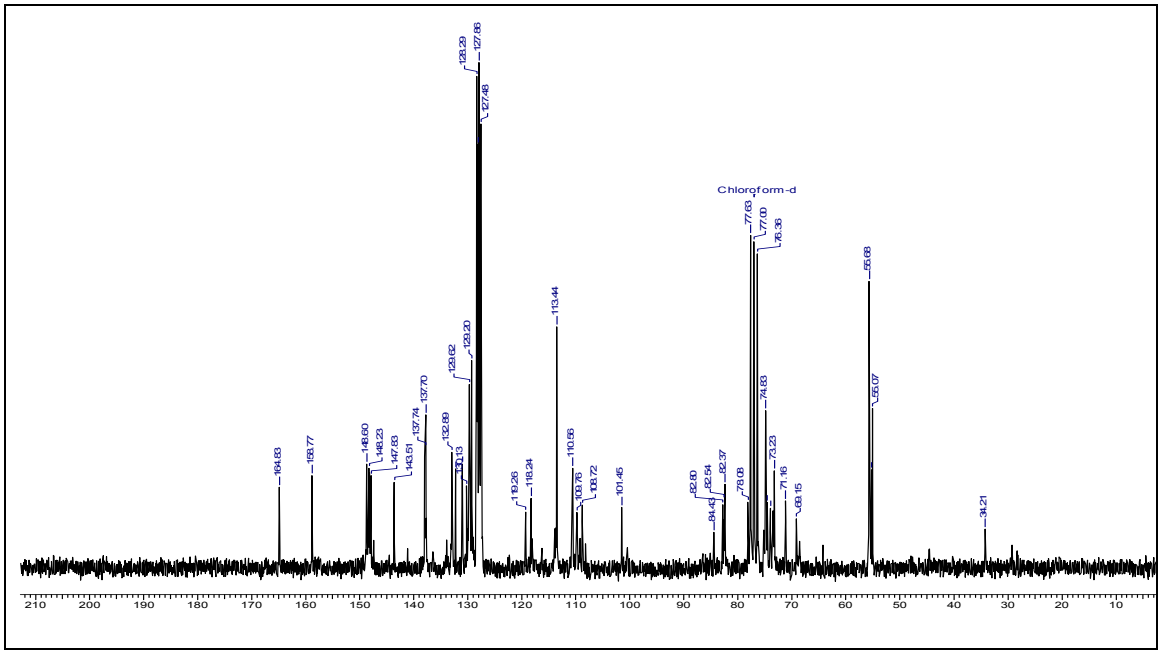
^{1}H NMR spectrum of compound 4 in $CDCl_3$



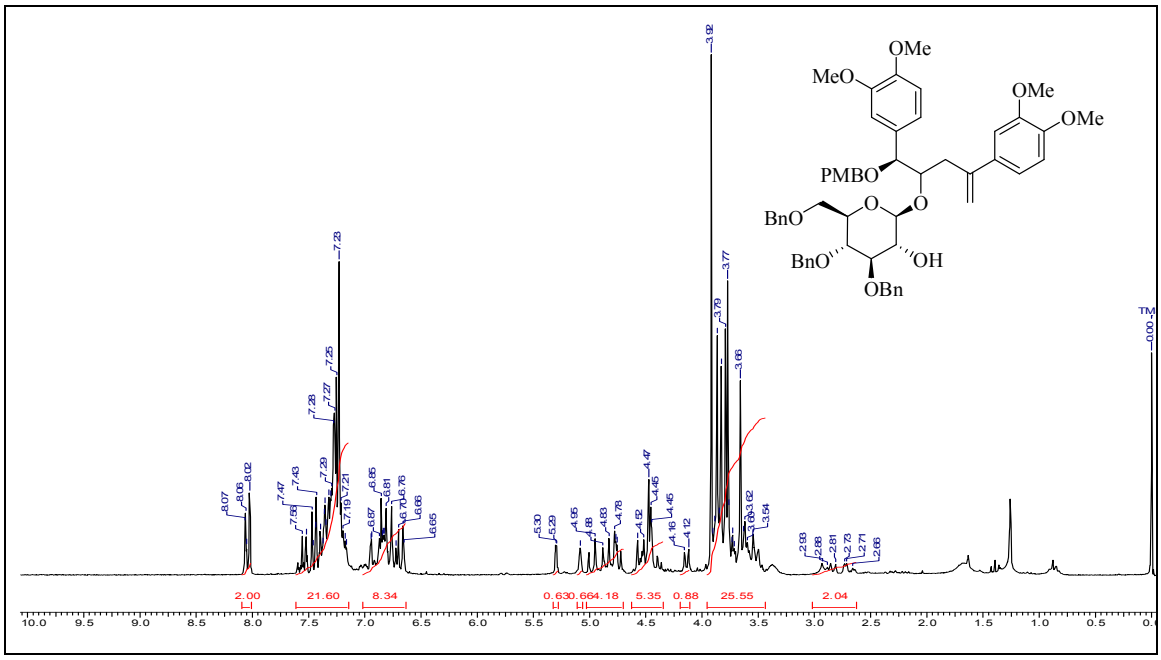
^{13}C NMR spectrum of compound 4 in $CDCl_3$



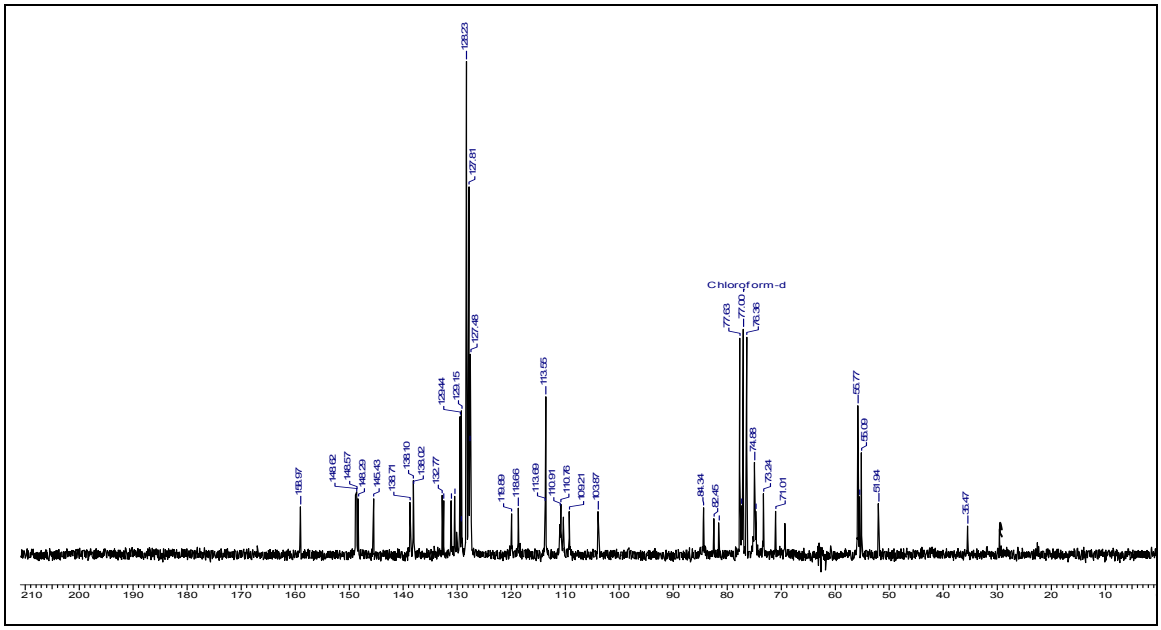
^{1}H NMR spectrum of compound 17 in $CDCl_3$



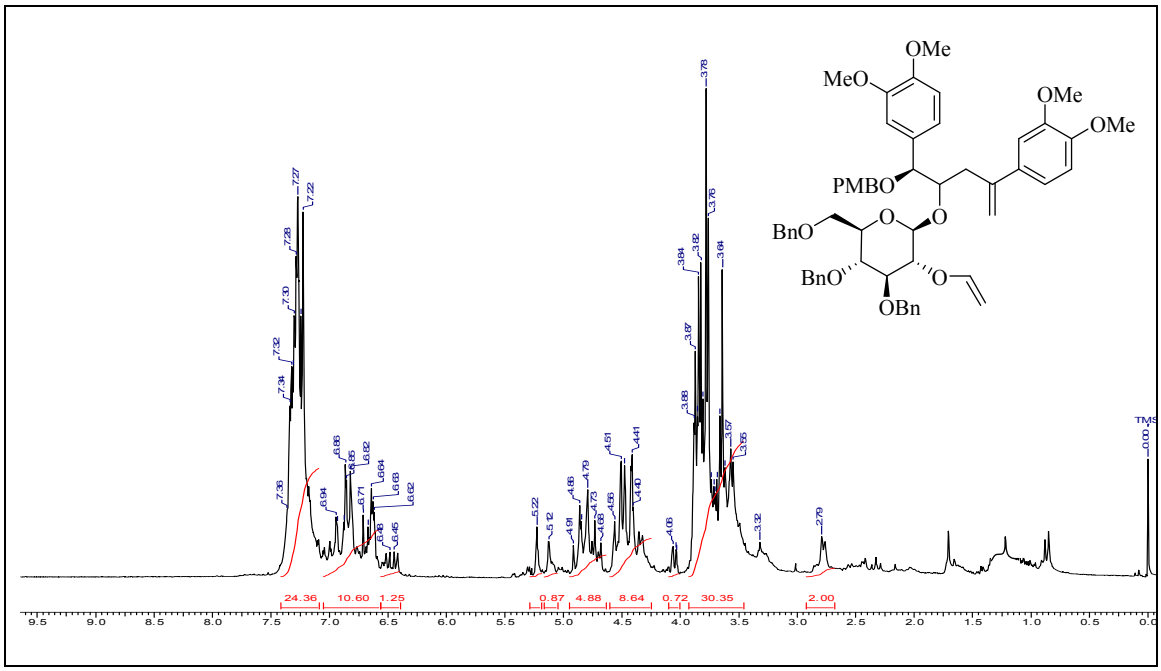
^{13}C spectrum of compound 17 in $CDCl_3$



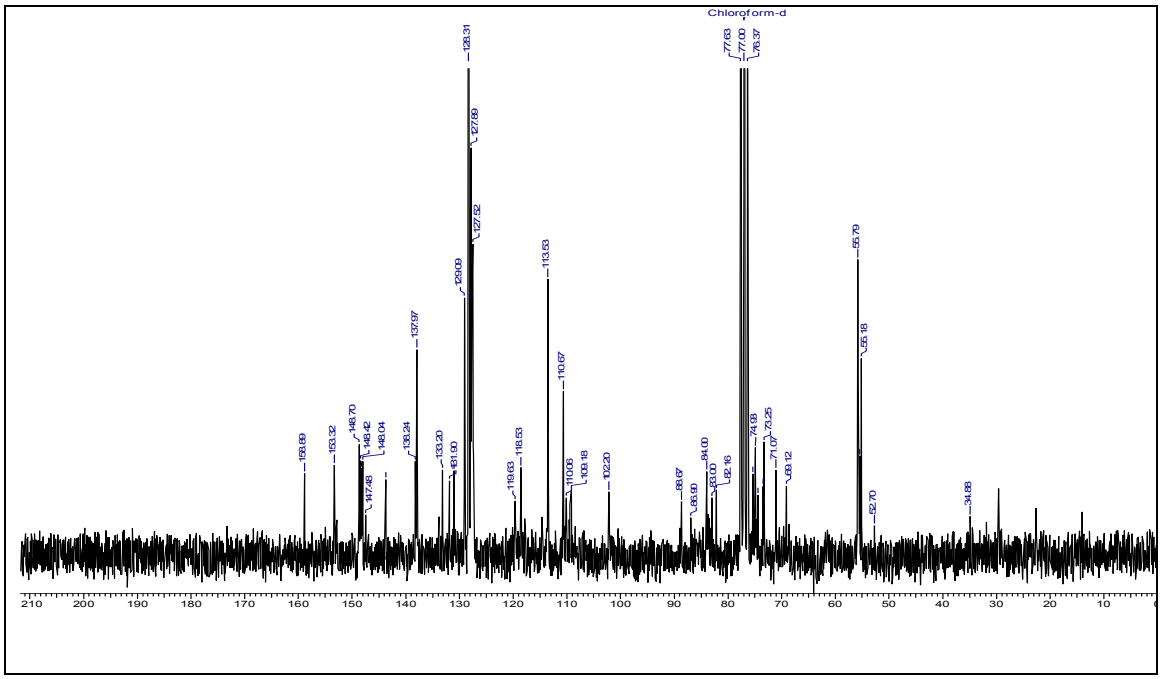
^{1}H NMR spectrum of compound 18 in $CDCl_3$



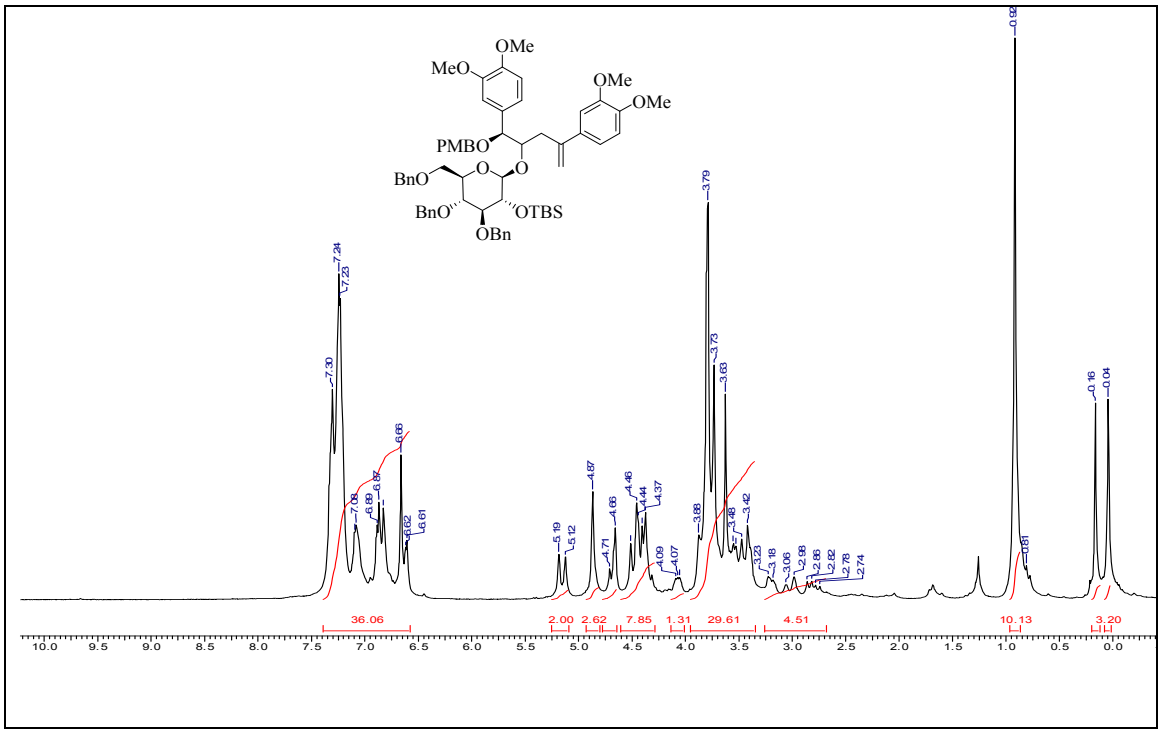
^{13}C NMR spectrum of compound 18 in $CDCl_3$



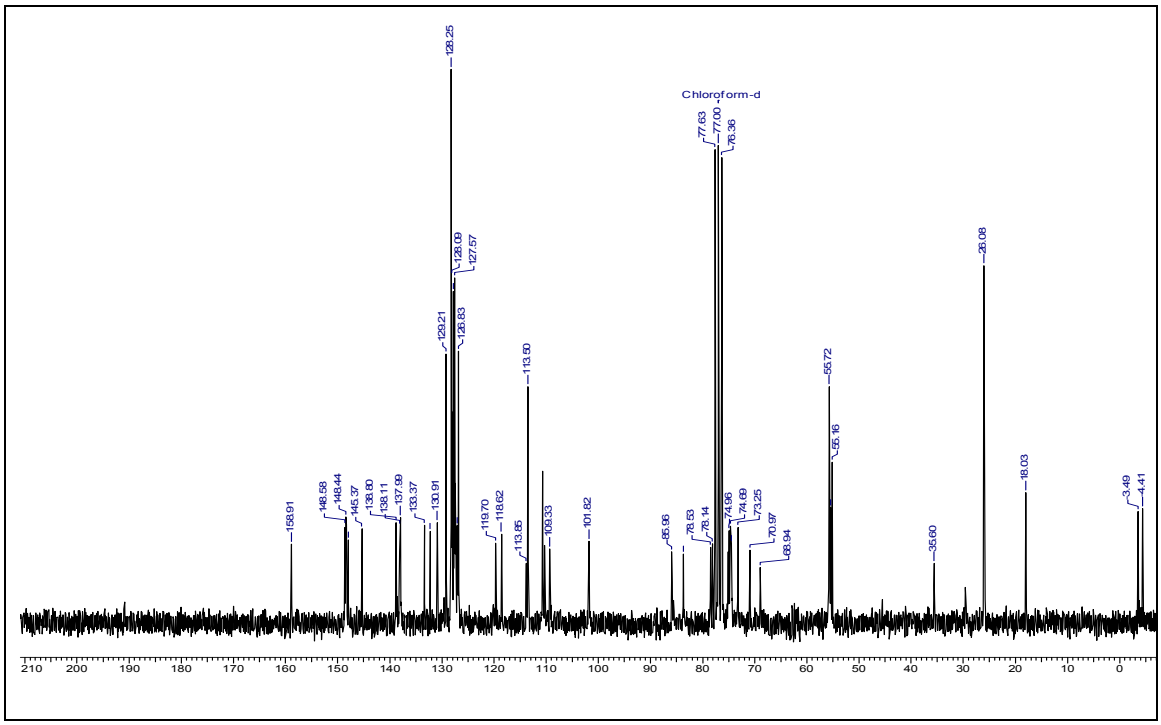
^{1}H NMR spectrum of compound 2 in $CDCl_3$



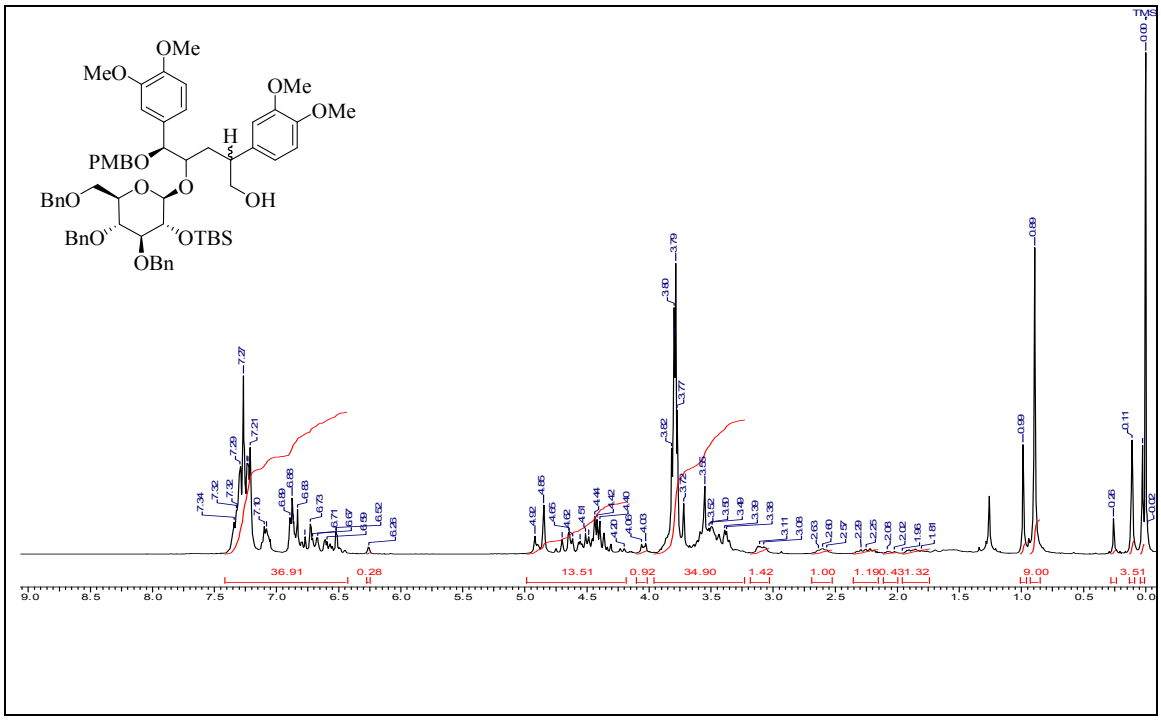
^{13}C NMR spectrum of compound 2 in $CDCl_3$



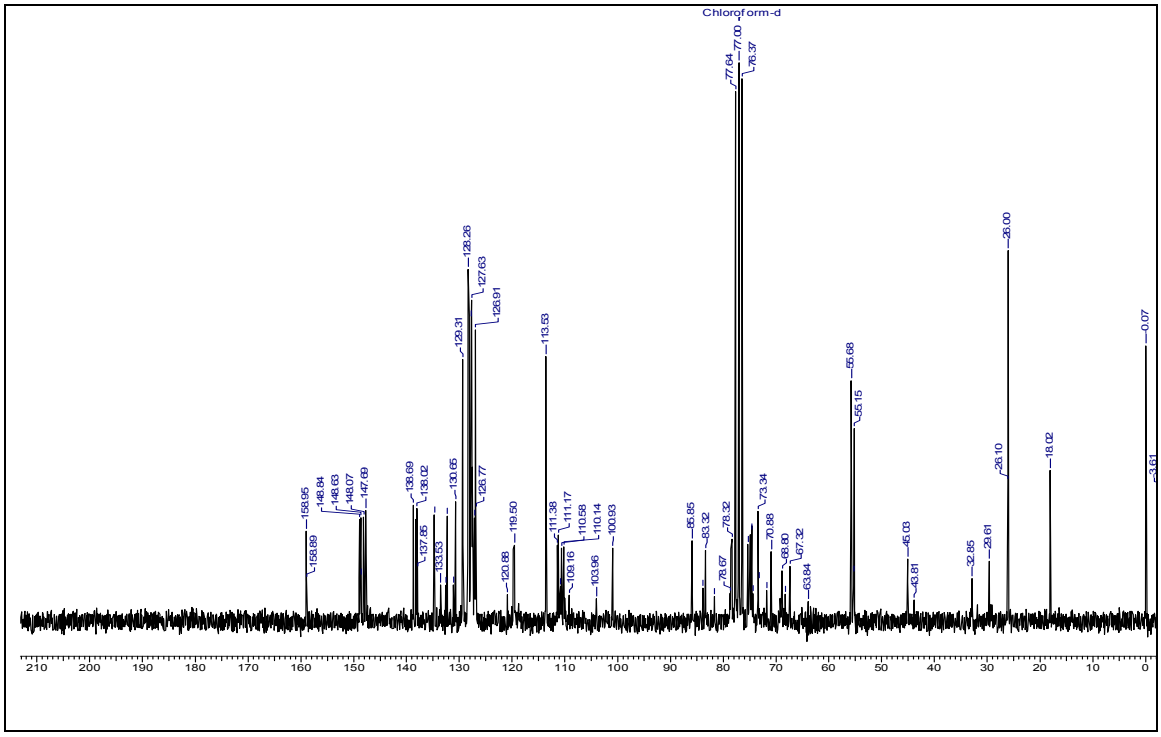
^{1}H NMR spectrum of compound 20 in $CDCl_3$



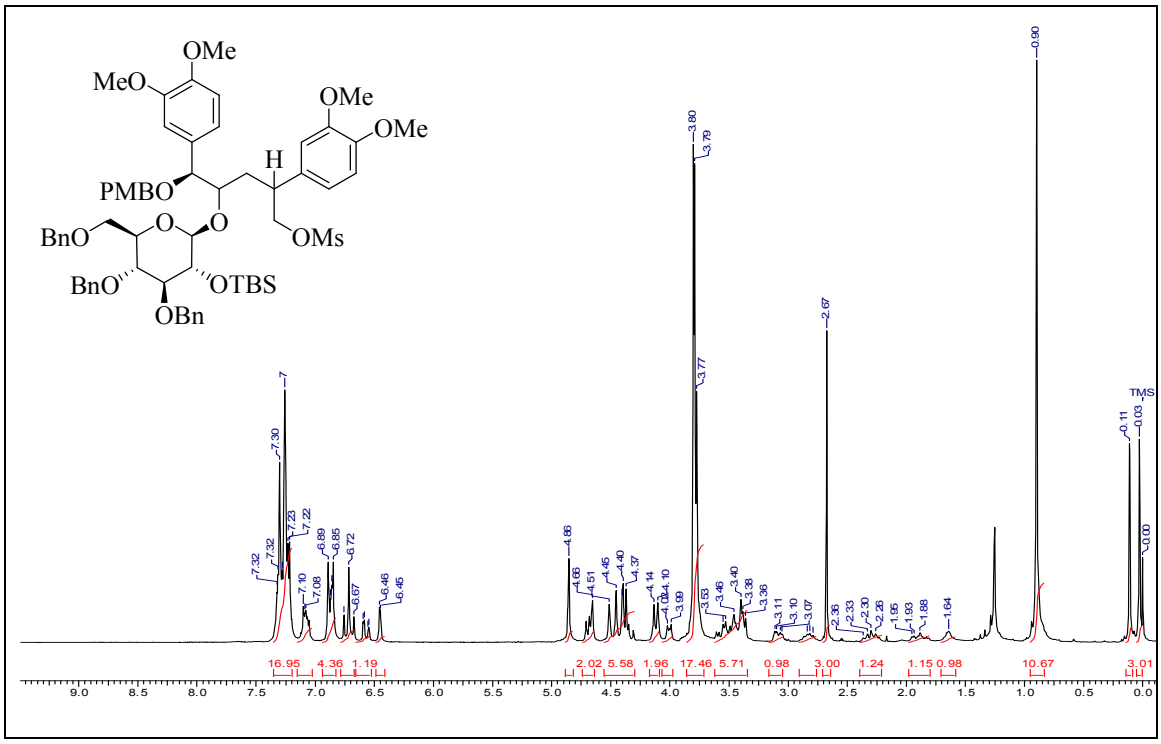
^{13}C NMR spectrum of compound 20 in $CDCl_3$



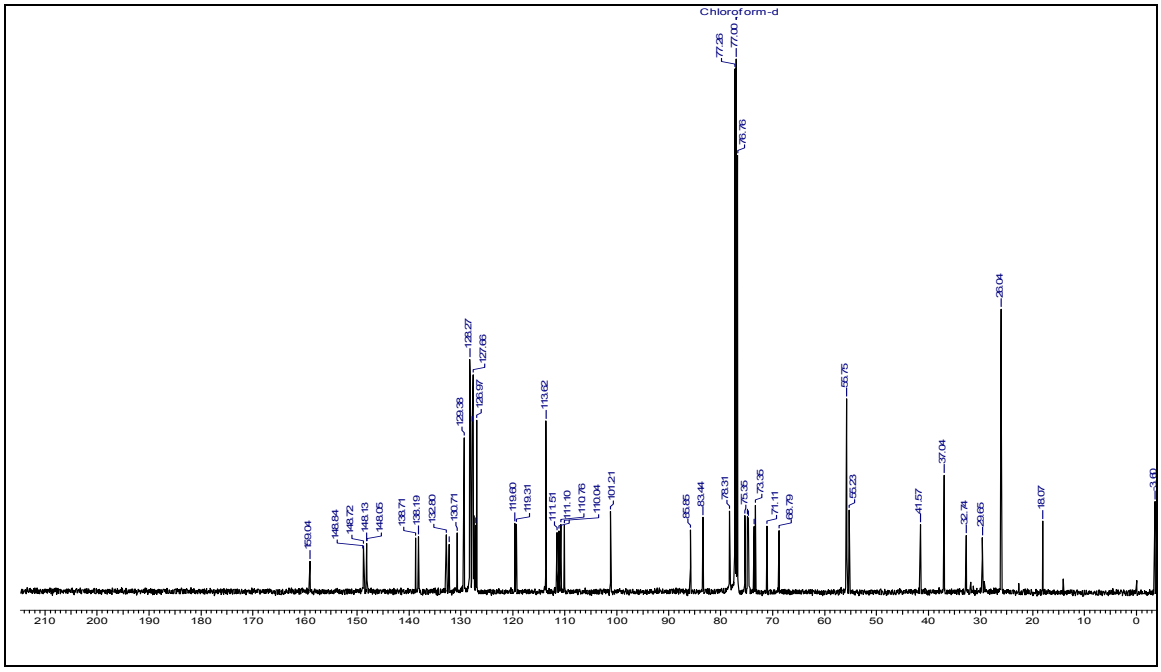
^{1}H NMR spectrum of compound 21 (diastereomeric mixture) in $CDCl_3$



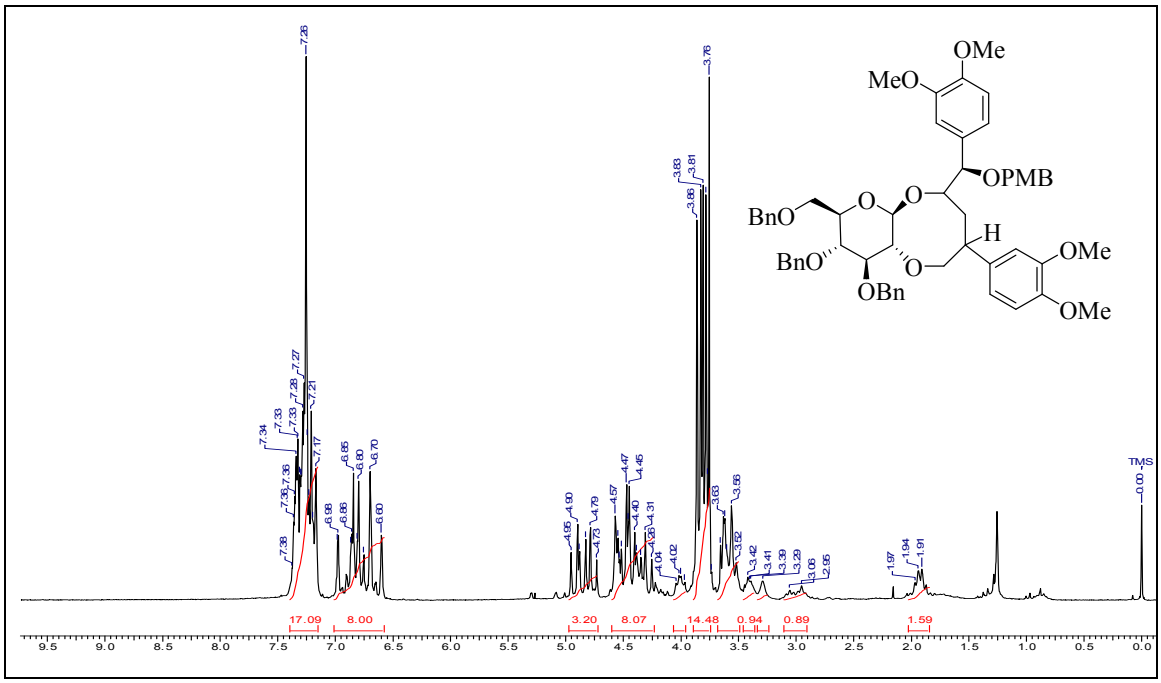
^{13}C NMR spectrum of compound 21 (diastereomeric mixture) in $CDCl_3$



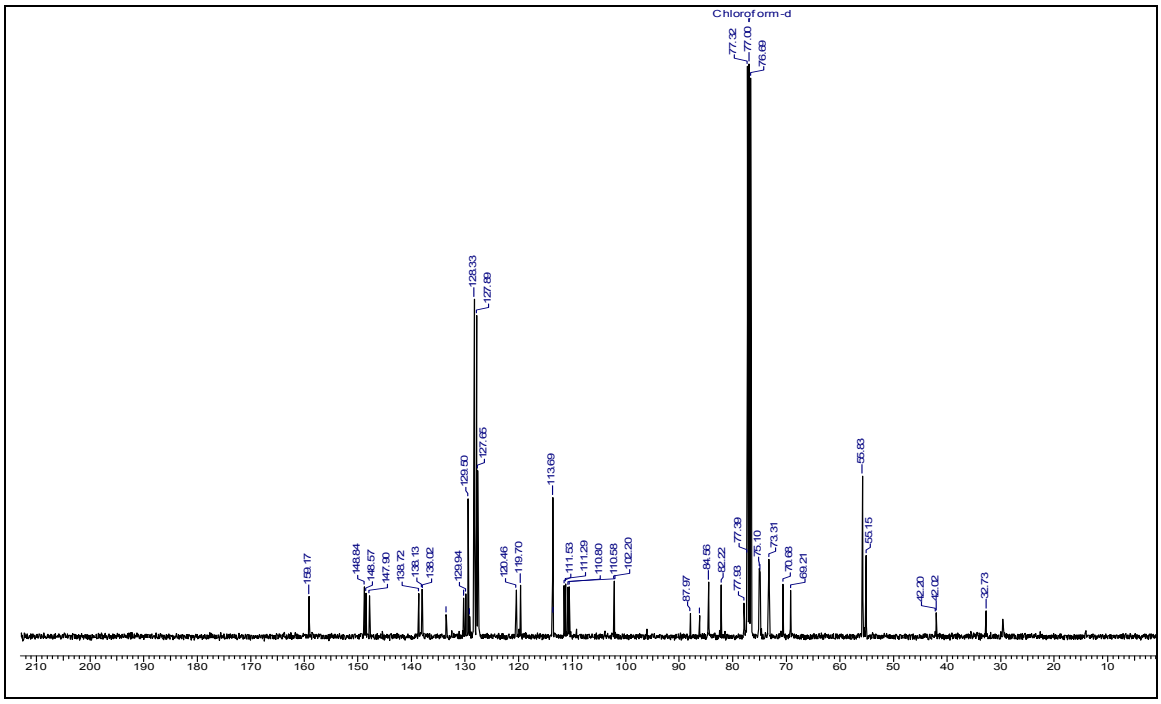
^{1}H NMR spectrum of compound 22 in $CDCl_3$



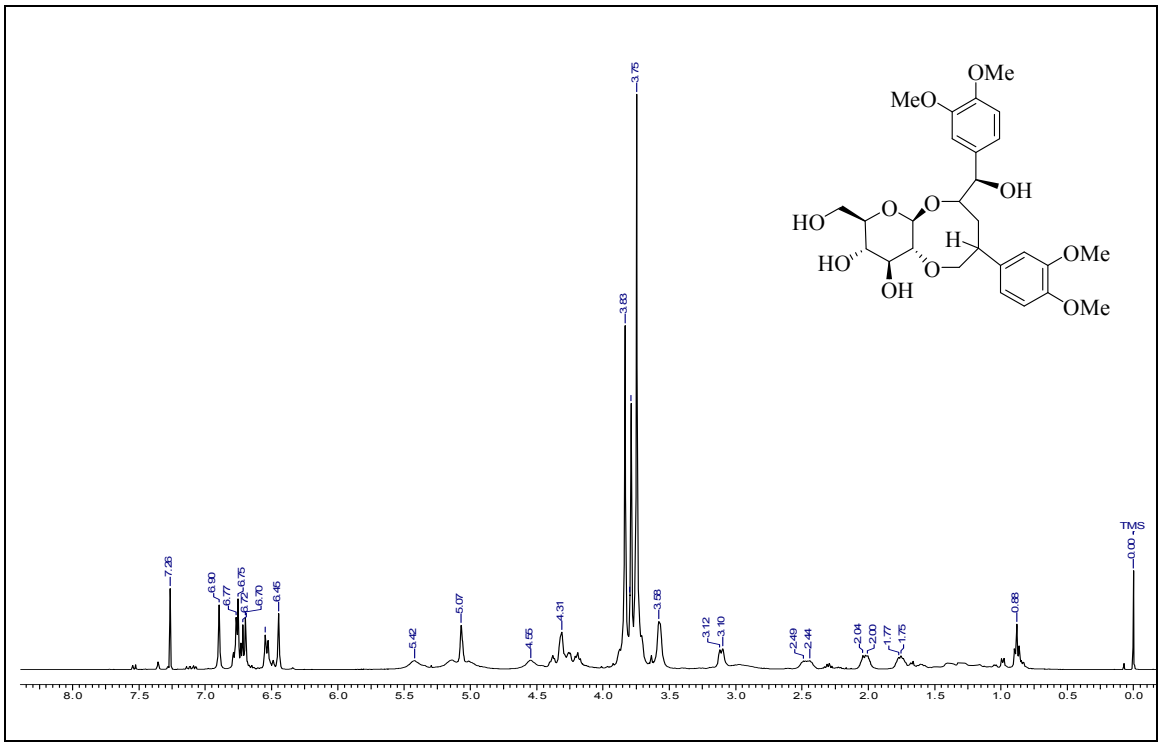
^{13}C NMR spectrum of compound 22 in $CDCl_3$



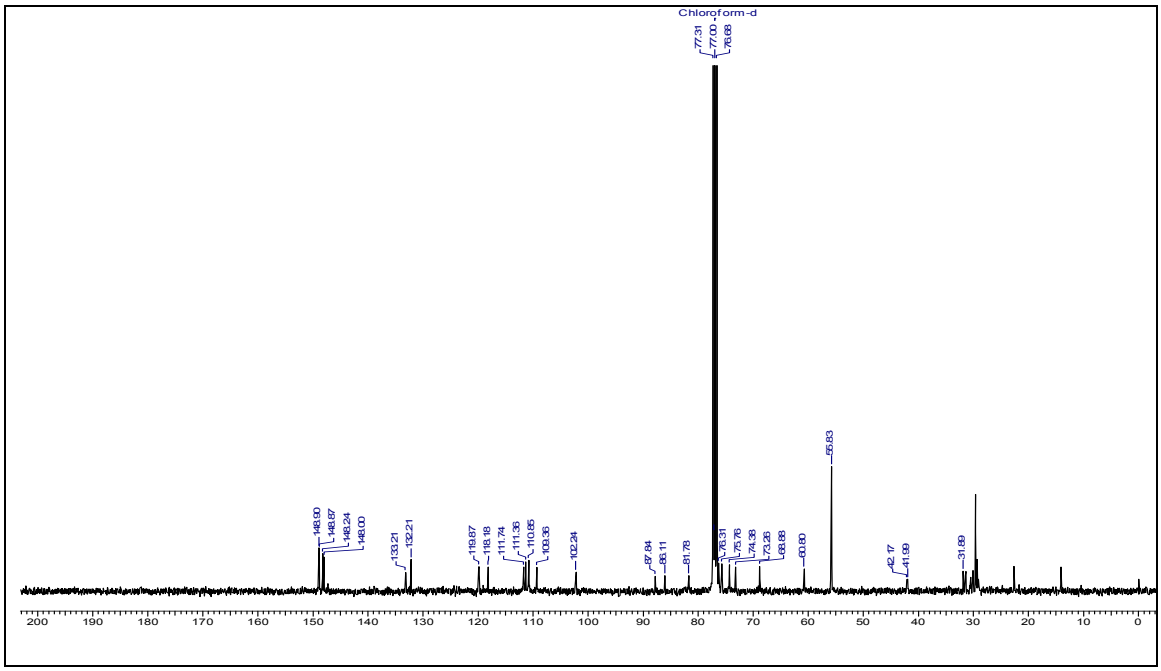
^{1}H NMR spectrum of compound 23 in $CDCl_3$



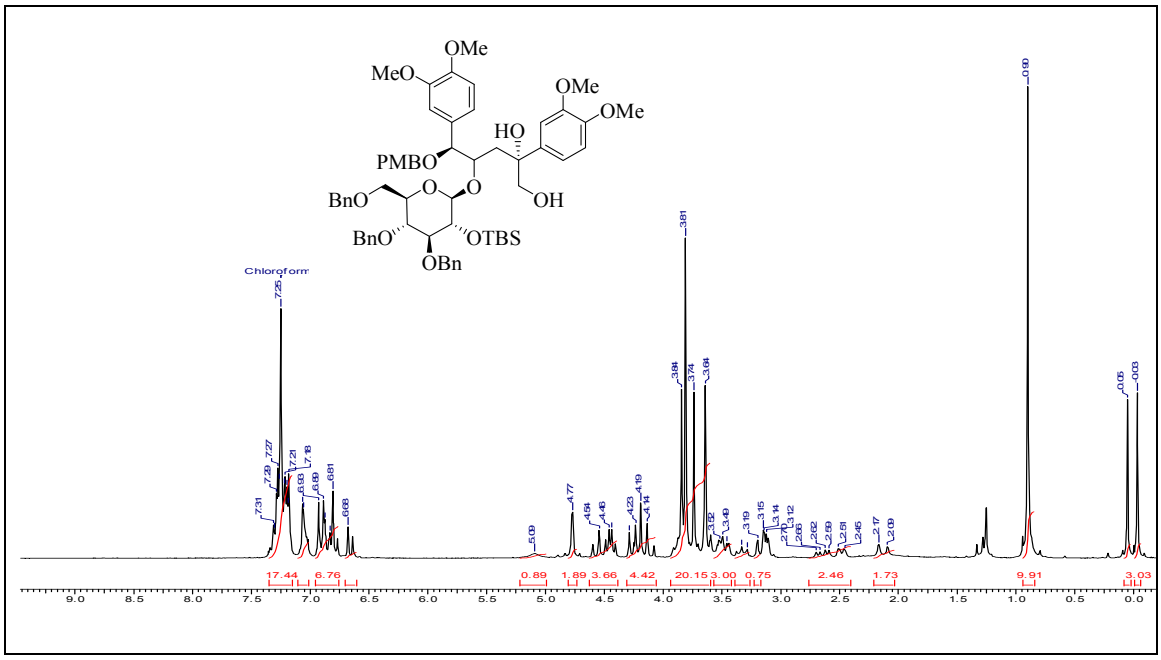
^{13}C NMR spectrum of compound 23 in $CDCl_3$



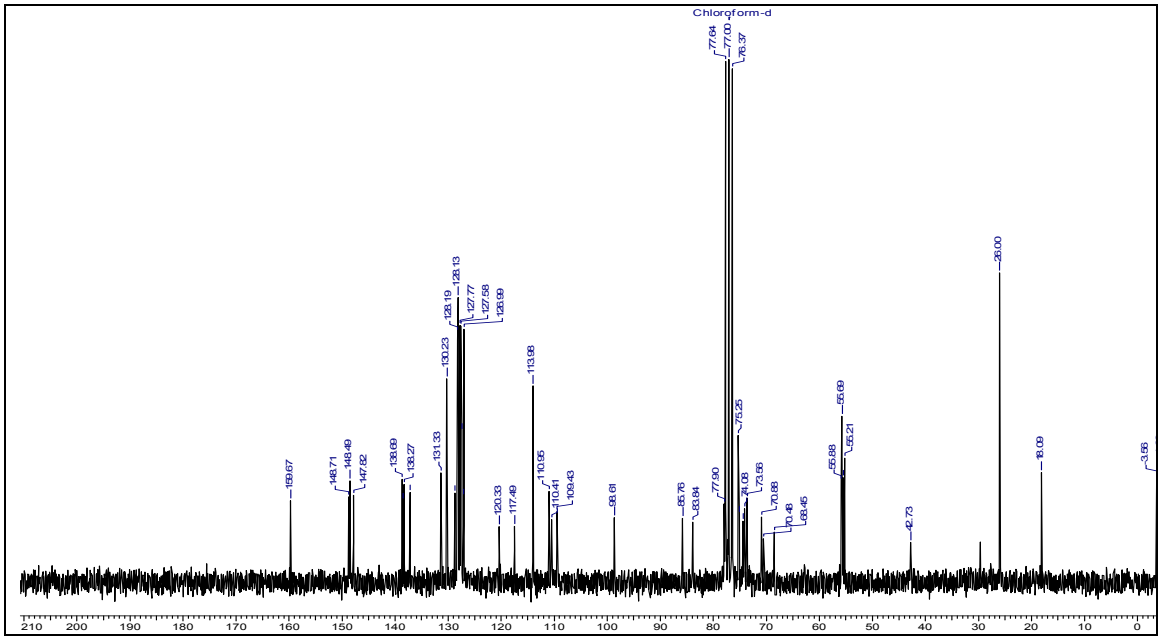
^{1}H NMR spectrum of compound 24 in $CDCl_3$



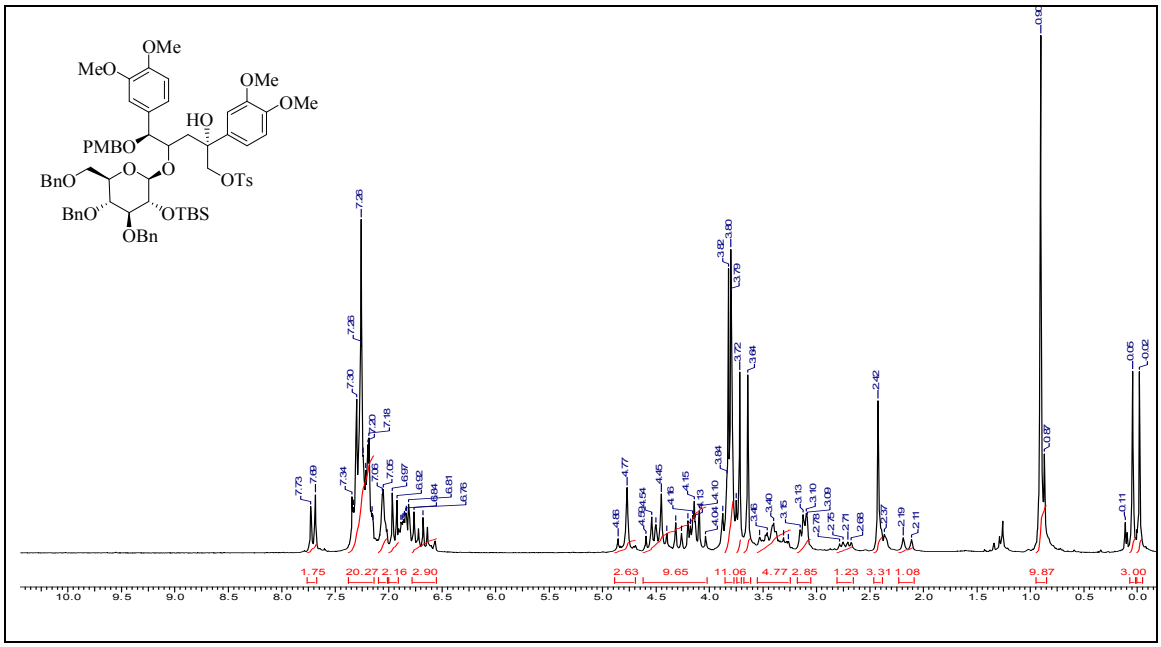
^{13}C NMR spectrum of compound 24 in $CDCl_3$



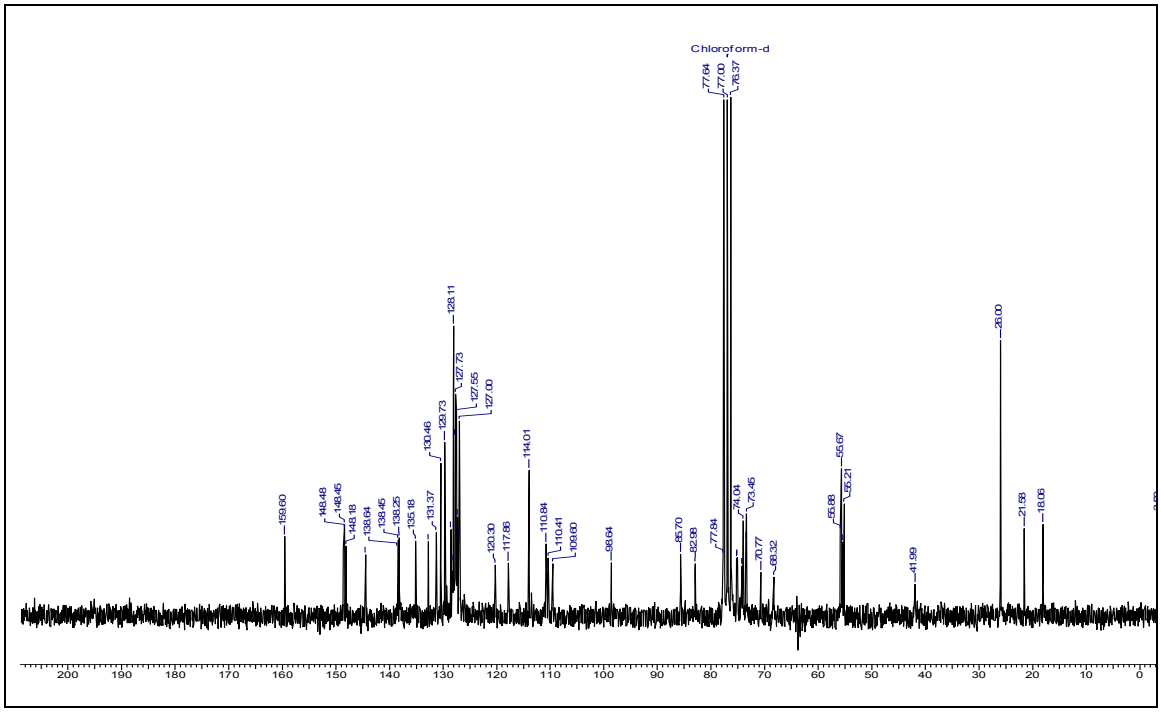
^{1}H NMR spectrum of compound 25 in $CDCl_3$



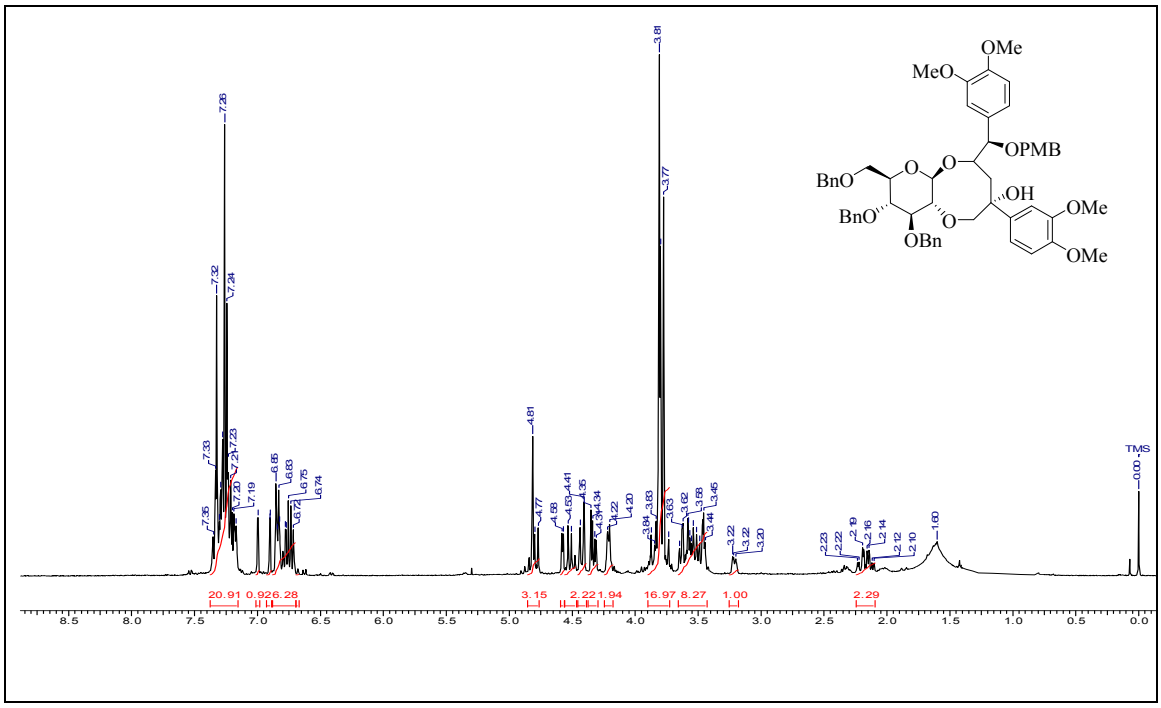
^{13}C NMR spectrum of compound 25 in $CDCl_3$



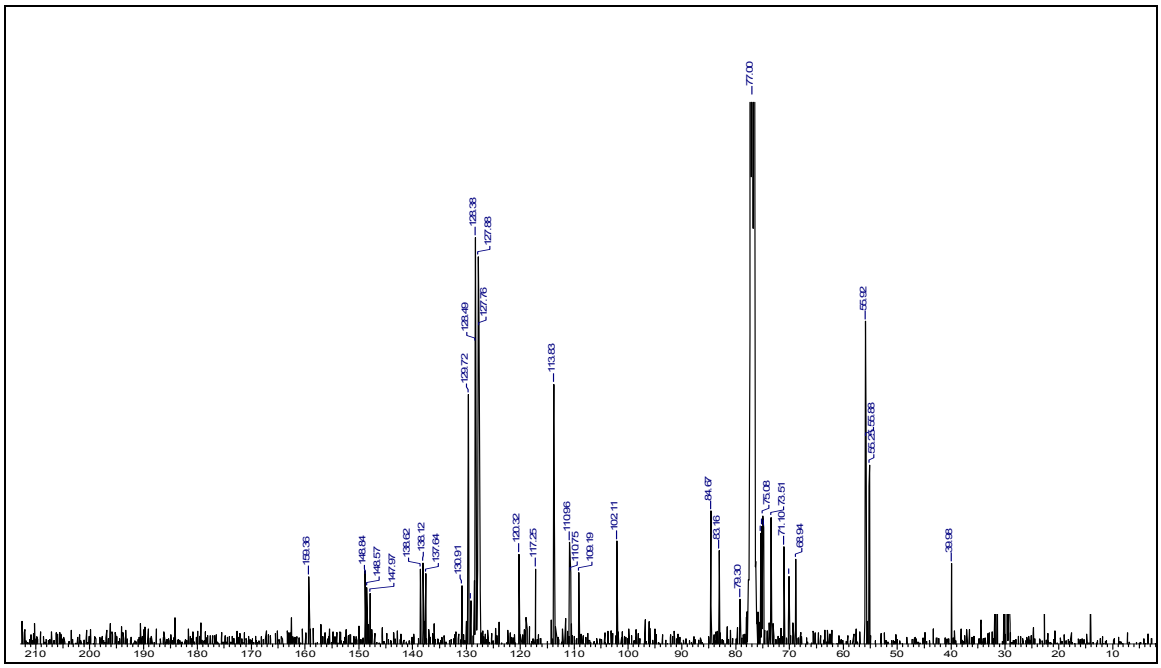
^{1}H NMR spectrum of compound 26 in $CDCl_3$



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



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



^{3}C NMR spectrum of compound 27 in $CDCl_3$

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List of Publications

1. "Synthesis of spiroannulated dihydroisobenzofuranylated monosaccharides": **Sushil K. Maurya** and Srinivas Hotha, *Tetrahedron Lett.* 2006*,* **47**, 3307.
2. "Stereoselective synthesis of spiroannulated cyclopentenones by the Pauson–Khand reaction on carbohydrate derived enynes": Srinivas Hotha, **Sushil K. Maurya** and Mukund K. Gurjar T*etrahedron Lett.* 2005, **46**, 5329.
3. "Vapor phase oxidation of 4-fluorotoluene over vanadia–titania catalyst": **Sushil K. Maurya**, Pratap Patil, Shubhangi B. Umbarkar, Mukund K. Gurjar, Mohan Dongare*,* Stephan Rudiger, Erhard Kemnitz *Journal of Molecular Molecular Catalysis A: Chemical* 2005, **234**, 51.
4. "Solid acid catalysts for fluorotoluene nitration using nitric acid": **Sushil K. Maurya**, M. K. Gurjar, K. M. Malshe, P. T. Patil, M. K. Dongare and Erhard Kemnitz *Green Chemistry* 2003, **5**, 720.
5. "Diversity oriented synthesis of spirocyclic small molecules": **Sushil K. Maurya**, Jerrin Kuriakose, Mukund K. Gurjar and Srinivas Hotha. (Manuscript under preparation)
6. "Synthetic studies towards the Crassifoside F: Synthesis of oxygen rich bicyclic core": **Sushil K. Maurya**, Muknd K. Gurjar and Srinivas Hotha. (Manuscript under preparation)