DEDICATED
TO
MY PARENTS,
BROTHERS & SISTERS

DECLARATION

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

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- M. A. Mondal.

Contents

General Remarks

- ^{1}H NMR spectra were recorded on AV-200 MHz, MSL-300 MHz, AV-400 and DRX-500 MHz spectrometers using tetramethylsilane (TMS) as an internal standard. Chemical shifts have been expressed in ppm units downfield from TMS.
- ^{13}C NMR spectra were recorded on AV-50 MHz, MSL-75 MHz, and DRX-125 MHz spectrometers.
- EI Mass spectra were recorded on Finngan MAT-1020 spectrometer at 70 *eV* using a direct inlet system.
- Infrared spectra were scanned on Shimadzu IR 470 and Perkin-Elmer 683 or 1310 spectrometers with sodium chloride optics and are measured in cm^{-1}.
- Optical rotations were measured with a JASCO DIP 370 digital polarimeter.
- Melting points were recorded on Buchi 535 melting point apparatus and are uncorrected.
- All reactions were monitored by Thin Layer chromatography (TLC) carried out on 0.25 mm E-Merck silica gel plates (60F-254) with UV light, I_2 and anisaldehyde inthanol as development reagents.
- All solvents and reagents were purified and dried by according to procedures given in Vogel's Text Book of Practical Organic Chemistry.
- All reactions were carried out under Nitrogen or Argon atmosphere with dry, freshly distilled solvents under anhydrous conditions unless otherwise specified. Yields refer to chromatographically and spectroscopically homogeneous materials unless otherwise stated. All evaporations were carried out under reduced pressure on Buchi rotary evaporator below 40 °C.
- Silica gel (60-120) used for column chromatography was purchased from ACME Chemical Company, Mumbai, India.

List of abbreviations

Ac	-	Acetyl
Ac_2O	-	Acetic anhydride
AcOH	-	Acetic acid
AIBN	-	2,2'-Azobisisobutyronitrile
$H_3B{\cdot}SMe_2$	-	Borane-dimethyl sulfide complex
BnBr	-	Benzyl bromide
n-BuLi	-	*n*-Butyl lithium
m-CPBA	-	*m*-Chloroperbenzoic acid
DCC	-	Dicyclohexylcarbodiimide
DDQ	-	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DIAD	-	Diisopropyl azodicarboxylate
DIEA	-	Diisopropyl ethylamine
2,2-DMP	-	2,2-Dimethoxypropane
DMF	-	Dimethylformamide
DMSO	-	Dimethylsulfoxide
DMAP	-	4-Dimethylaminopyridine
TEA	-	Triethylamine (Et_2N)
Im	-	Imidazole
LAH	-	Lithium aluminium hydride
LiHMDS	-	Lithium hexamethyl disilazane
LDA	-	Lithium diisopropylamine
MeI	-	Methyl iodide
MsCl	-	Methanesulfonyl chloride
NaOAc	-	Sodium acetate
Pd/C	-	Palladium on Carbon
PivCl	-	Trimethylacetyl chloride

PMB-Cl	-	*p*-Methoxybenzyl chloride
Py	-	Pyridine
PPh_3 (TPP)	-	Triphenylphosphine
PPTS	-	Pyridinium *p*-toluenesulfonate
TBSCl	-	*tert*-Butyldimethylsilyl chloride
p-TSA	-	*p*-Toluenesulfonic acid
TBAF	-	Tetra-*n*-butylammonium fluoride
TBAI	-	Tetra-*n*-butylammonium iodide
Tf_2O	-	Trifluoromethanesulphonic anhydride

Abstract

The thesis entitled "**Studies Toward the Total Synthesis of Aspercyclide A-C Macrocidin A and 4-*epi*-Stagonolide B by Employing Ring Closing Metathesis reaction**" consists of four chapters. Chapter 1 describes recent advancements of RCM in the synthesis of cyclic natural products ranging from small, medium and large ring size. Chapter 2 divided into two sections; Section I represents ring closing metathesis approach toward the total synthesis of Aspercyclide A, B and C, and section II deals with an asymmetric strategy towards the total synthesis of Aspercyclide C. Chapter 3 describes construction of central core of Macrocidin A. Lastly, the Chapter 4 highlights synthetic studies toward the total synthesis of 4-*epi*-stagonolide B.

Chapter 1: Recent Advancements of RCM Reaction in the Synthesis of Cyclic Natural Products

Ring closing metathesis (RCM) is an extremely powerful method for transforming acyclic dienes into unsaturated cyclic systems in presence of transition metal carbene complexes. Although, the term metathesis is known from early 19^{th} century, the method was inappropriate in cyclization process due to the ill defined, multi component catalyst systems used in the past which had limited functional group tolerance. The present chapter describes the recent advancements of RCM and applications thereof in the total synthesis of cyclic natural products. It is noticeable from this review that the increasing popularity of RCM can be attributed to the development of molybdenum and ruthenium complexes as initiators. Extreme popularity of these catalysts is due to their soaring efficiency in promoting RCM, wide range of functional group tolerance and simplicity in experimentation without recourse to rigorously controlled conditions. The positive impact of RCM on retrosynthetic disconnection has been exemplified over the last two decades by a plethora of elegant publications to the synthesis of complex natural products and designed molecules of theoretical as well as pharmaceutical importance. Hence, the use of RCM is by no means restricted in choosing diolefins as substrates. This chapter covered almost all ring sizes, ranging from small, medium to large with typical examples available in current literatures. Although the formation of almost all ring

size by using RCM are virtually possible, the synthesis of medium size rings, particularly 9 and 11-membered are limited due to high ring strain rendering the process in a different way such as polymerization. The effect of strain in the synthesis of medium size rings is briefly discussed. Synthesis of large rings (12 and onward) requires experimentally demanding conditions such as higher catalyst loading, dilution and elevated temperature. In separate examples, the influence of protecting groups and their relative orientation on the outcome of RCM has been discussed. Despite the fact that the method quickly emerged as one of the most powerful tools for cyclization *via* carbon-carbon, some critical issues such as effect of conformational constrain on the geometry of newly formed double bond are yet to be resolved.

Chapter 2: Studies Toward the Total synthesis of Aspercyclide A, B and C

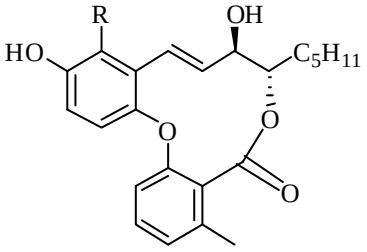
Immunoglobin E binds with high affinity IgE receptors present on mast cell and basofil that causes release of inflammatory compounds leading to the allergic diseases. Small molecule that can bind with these receptors inhibits the interactions with Immunoglobin E. Such interactions can prevent the release of inflammatory compounds from cell. This type of molecule can be used as effective drug for the treatment of allergic disorder such as asthma, allergic rhinitis and other forms of atopy. Bioassay guided fractionation and screening of *Aspergillus* sp. lead to the isolation of three natural products named aspercyclide A, B and C as highly efficient binding inhibitors of IgE receptor. All are 11-membered macrolactones with an integrated biaryl ether moiety. Combination of important biological activity, and interesting structural framework, aspercyclides are interesting targets for total synthesis. We have selected aspercyclides as our synthetic targets to continue our endeavor and longstanding interest in integrating RCM with chiron approach.

Chapter 2; Section I: Ring Closing Metathesis Approach Toward the Total Synthesis of Aspercyclide A, B and C

As a part of our interest we first undertook aspercyclide C as synthetic target. Using RCM as key macrocyclization method, the structural analysis of aspercyclide C revealed that the ribose acetonide **7**, commercially available *o*-vanillin and the idodobenzoate derivative **8** would be the ideal starting materials as presented in

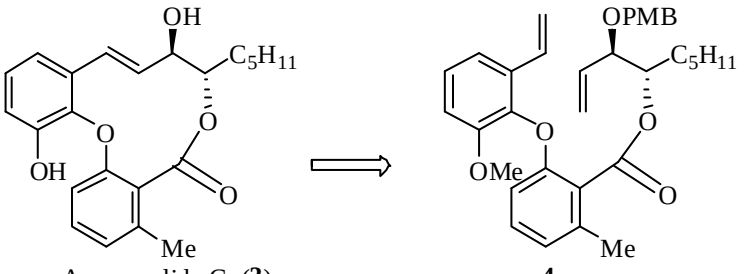
scheme 1. Keeping in mind the final deprotection of aromatic methyl group, PMB ether was a choice of protecting group in compound **5**.

Scheme 1: *Retrosynthetic disconnection of aspercyclide C*

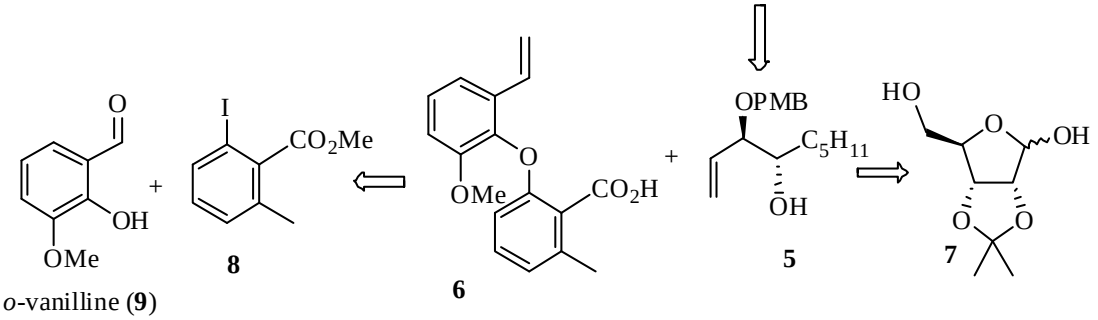


Aspercyclide A (**1**) R = –CHO

Aspercyclide B (**2**) R = $–CH_2OH$



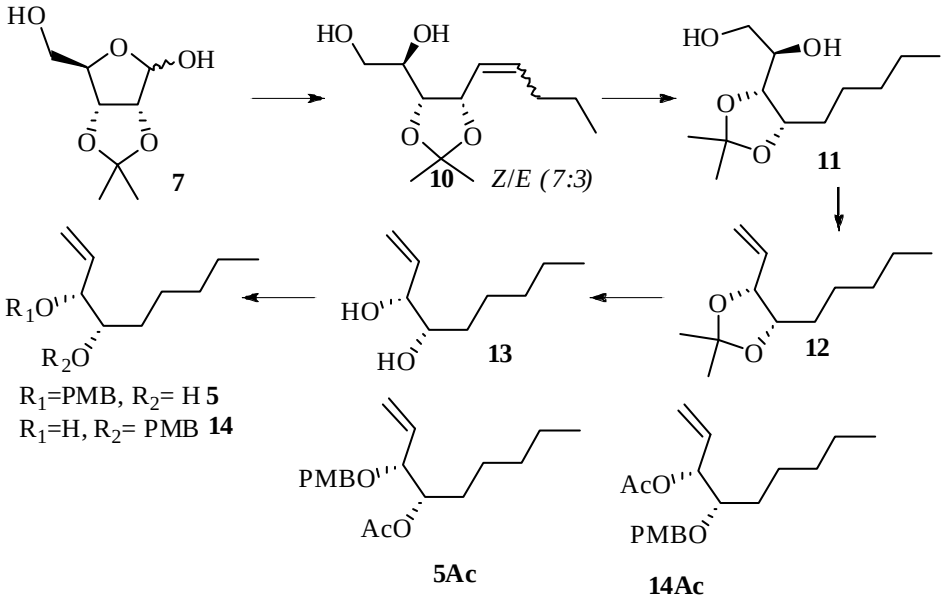
Aspercyclide C (**3**) **4**



o-vanilline (**9**) **8** **6** **5** **7**

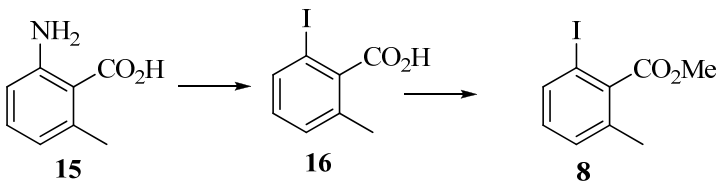
The synthesis started with 4 carbon Wittig homologation of 2,3-*O*-isopropylideneribofuranoside **7** followed by hydrogenation of resulting *cis/trans* mixture of olefins provided the diol **11** (Scheme 2). The diol was subjected to a sequence of reactions; mesylation and subsequent Zn dust mediated reductive elimination in the presence of sodium iodide to afford the acetonide-olefin **12**. Acetonide deprotection of **12** was carried out under acidic conditions. Selective PMB protection of allylic hydroxyl of diol **13** was attempted with PMBCl using sodium hydride as base. Poor selectivity in the PMB protection has been manifested due to the insignificant reactivity differences between the secondary hydroxyl groups of **13**. The position of PMB ether in **5** and **14** was determined unambiguously with the help of ^{1}H NMR analysis of corresponding acetates **5Ac** and **14Ac**.

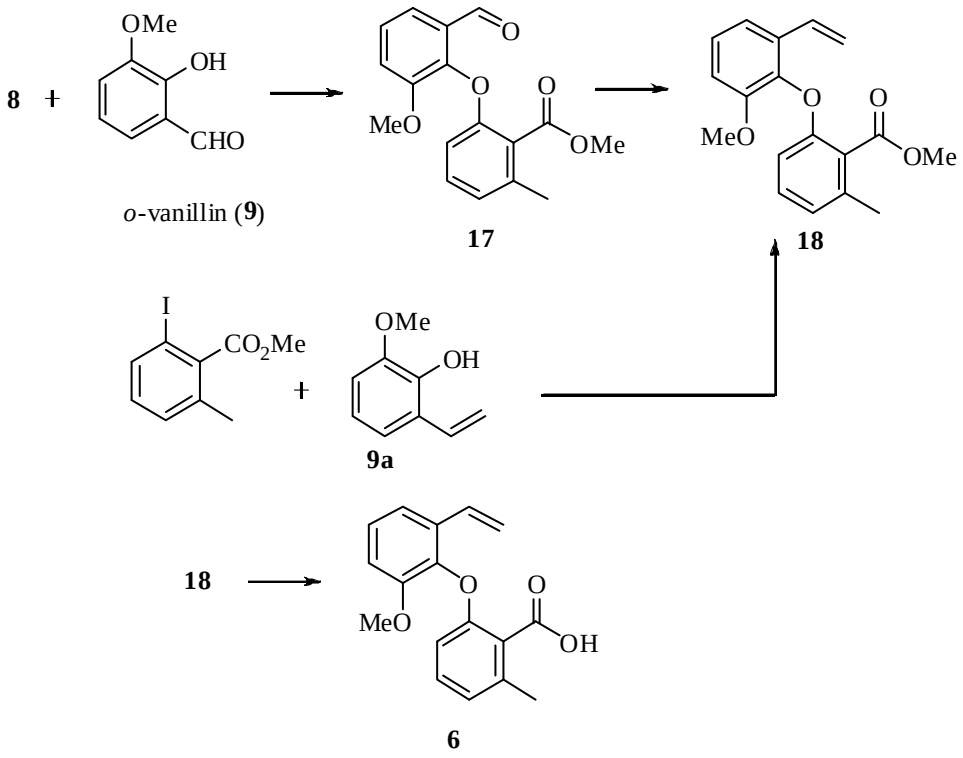
Scheme 2: *Synthesis of fragment* **5**.



The synthesis of the densely functionalized diaryl ether containing carboxylic acid **6** commenced from commercially available material **15.** The anthranilic acid derivative **15** was treated with sodium nitrite and subsequent displacement of diazo group with iodide gave the benzoic acid derivative **16**(Scheme 3). Considering the labile nature of aromatic iodide, the masking of acid functionality as methyl ester was performed under neutral conditions using an ethereal solution of diazomethane. Eventually, the coupling of iodo compound **8** and the *o*-vanillin (**9**) was conducted by following copper oxide mediated Ullmann protocol. Comparative study, in order to improve the overall efficiency in terms of yield revealed that the coupling reaction was more facile with *o*-vanillin in comparison to the similar substrate **9a**. This is presumably due to the initial chelation of copper oxide with bidentate *o*-vanillin. Saponification of compound **18** under harsh conditions gave the acid **6**.

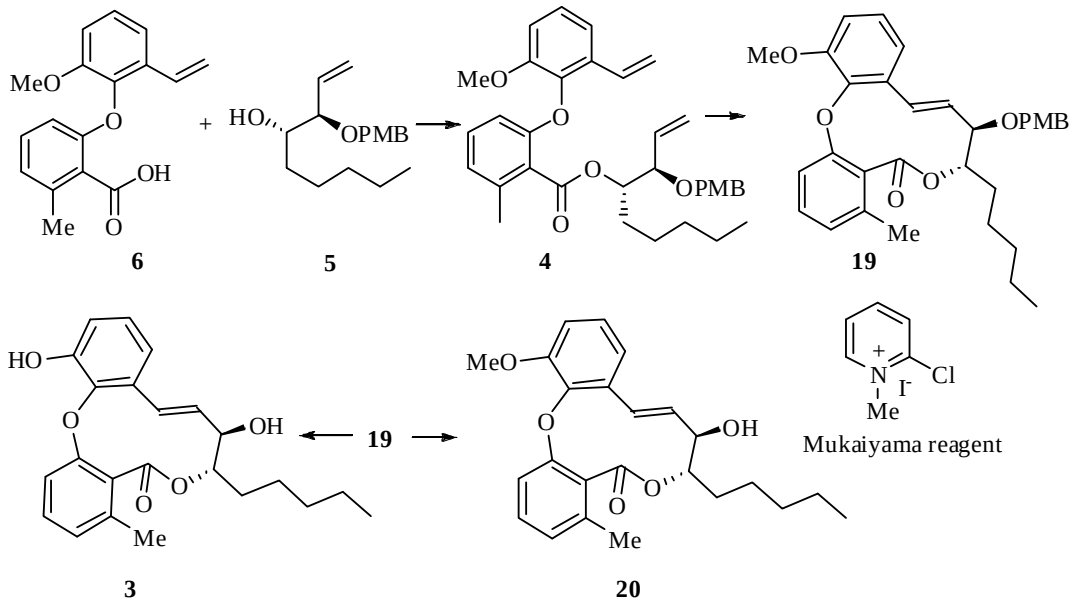
Scheme 3: *Synthesis of the acid fragment* **6**.





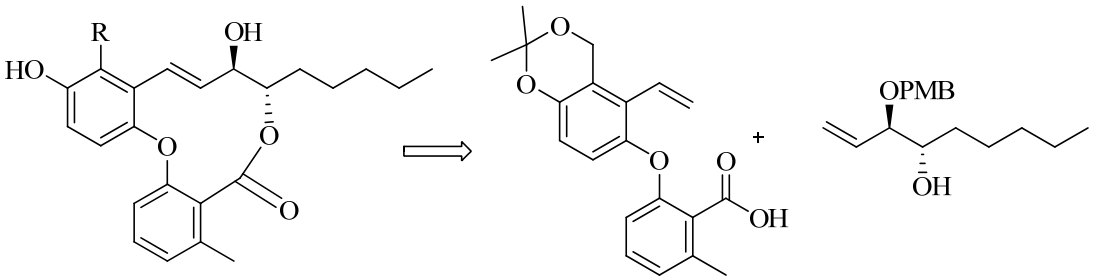
Though our initial efforts in coupling the fragments **5** and **6** using standard reagents like DCC, EDCI and Yamaguchi conditions were not fruitful, nevertheless it has been achieved successfully using Mukaiyama reagent with slight modification (Scheme 4). At the end, the projected RCM reaction on compound **4** to build 11-membered lactone was carried out by adding Grubbs 2nd gen. ruthenium complex dissolved in toluene to a dilute solution of compound **4** in toluene at 120 ^{o}C over a period of 1 h and the compound **19** was isolated exclusively in good yield. The global deprotection of PMB as well as aromatic methyl group was carried out in presence of boron tribromide. Unfortunately, at low temperature (–78 ^{o}C) only the PMB deprotected compound **20** was isolated as sole product. Spectral and analytical data were in agreement with the structure **20** which was further substantiated by *X*-ray diffraction study. Effort to do the same at higher temperature led to a complex mixture, from that required product of sufficient purity could not be separated. As the deprotection of methyl ether in **20** is already reported by Fürstner and co-workers, we have concluded this as a formal synthesis of aspercyclide C.

Scheme 4.



After having fruitful result of RCM in the cyclization of aspercyclide C, we shifted our interest to the more challenging analogues aspercyclide A and B. Applying similar flexible disconnection approach, the fragmented parts **21** and **5** would be the choice of interest for aspercyclide A and B (Scheme 5). Coupling of **21** and **5** followed by RCM and final deprotection would give aspercyclide B (**2**). Subsequently simple functional group manipulations would give another isomer A (**1**).

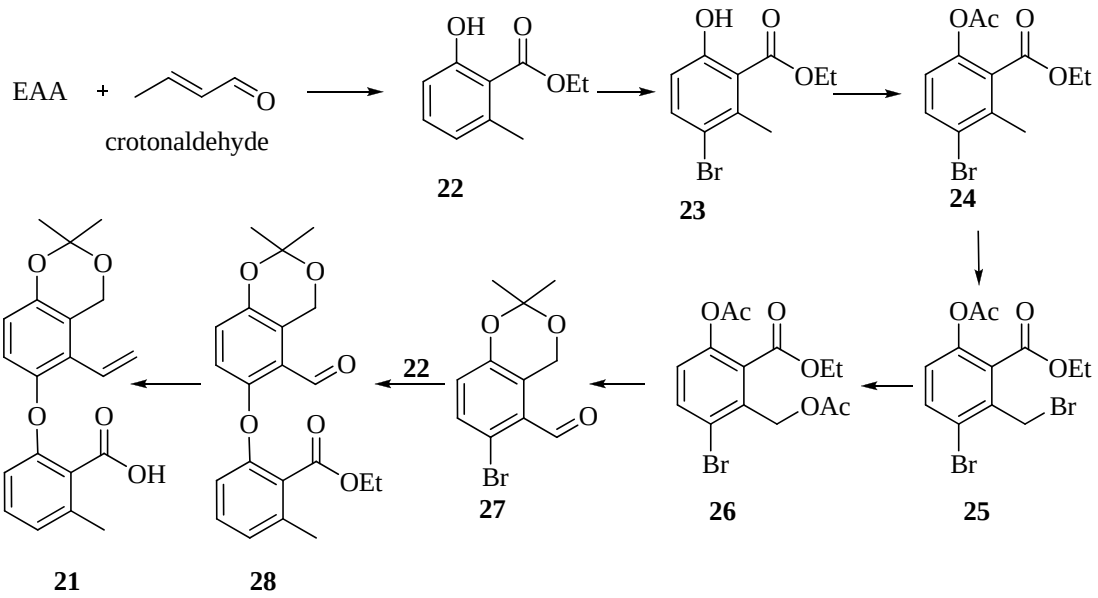
Scheme 5.



Scheme 6 describes the synthesis of acid fragment **21**, an advanced intermediate in our strategy. The building block **23** was prepared from EAA and crotonaldehyde following reported procedure. The intermediate **23** was subjected to a series of reactions, namely, nuclear bromination, masking of phenolic hydroxyl and finally side chain bromination to give **25**. Displacement of bromide with acetate followed by removal of protecting groups under reductive condition (using LAH) and

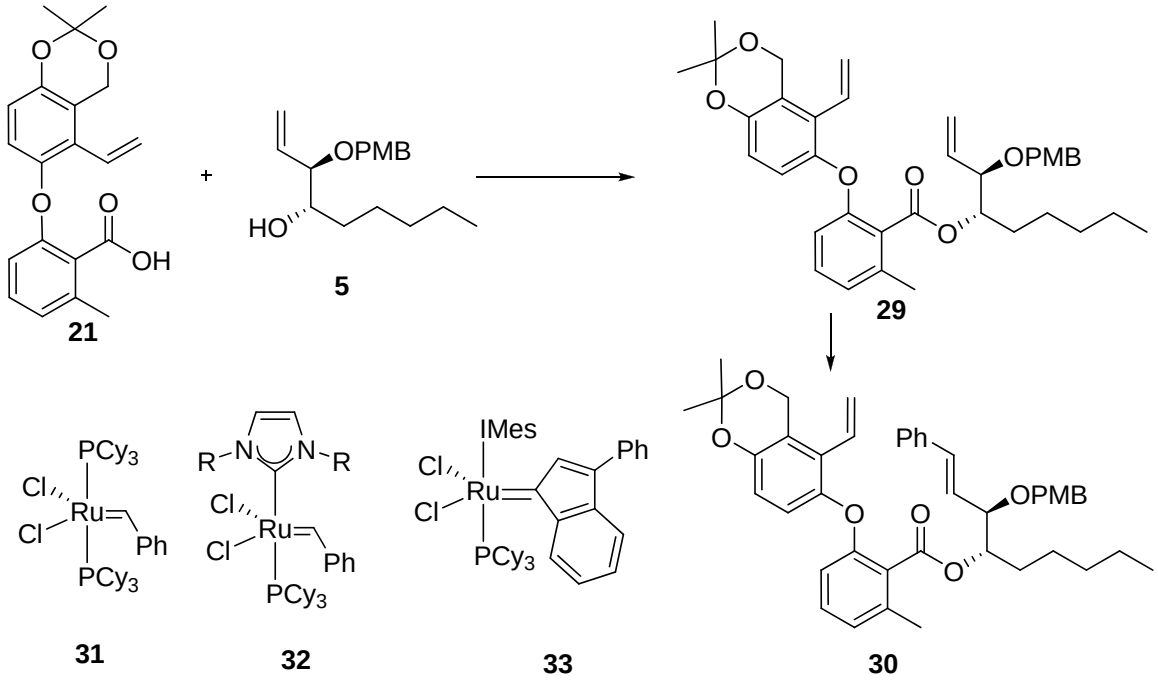
subsequent IBX oxidation after acetonide protection led to the one of the key fragment **27**. Finally, Ullmann coupling of **27** with **22** gave the biaryl adehyde **28** which in turn subjected to one carbon Wittig homologation and saponification to complete the synthesis of the acid fragment **21**. Structure of **21** was verified by rigorous analysis by NMR, IR spectra and finally single crystal *X*-ray diffraction study.

Scheme 6: *Synthesis of the fragment* **21**.



As in the previous case, the coupling of **21** and **5** was achieved by using Mukaiyama reagent and standard reaction condition. The key reaction RCM of the fully elaborated diene was studied by using catalyst **31**, **32** and **33** under different solvents and reaction temperatures and was found to be unsuccessful. With the catalyst **31**, starting material was recovered after 3 days while use of catalyst **32** and **33** gave copmplex reaction mixture after long reaction time but use of stoichiometric amount of **32** produced the cross product **30** under reflux condition in toluene. The compound **30** was characterized fully and the newly formed double bond was found to be *trans* (Scheme 7).

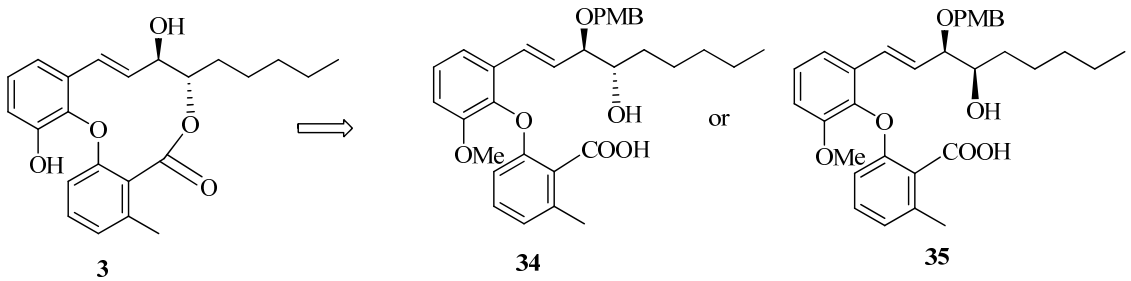
Scheme 7.



Chapter 2; Section II: Regioselective Dihydroxylation Approach Toward the Total Synthesis of Aspercyclide C

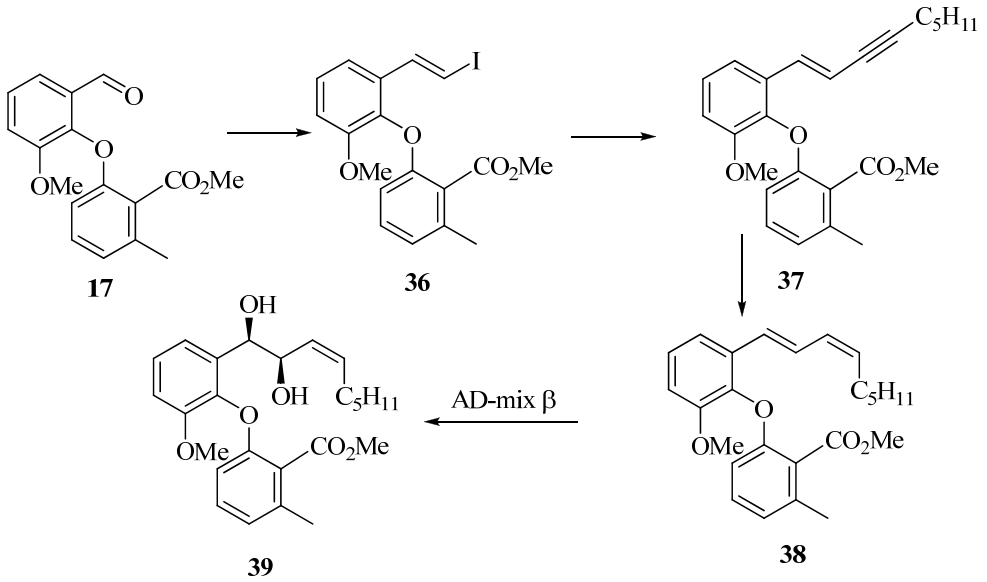
Inappropriate results of RCM in the macrocyclization of the compound **29** promoted us to think an alternative strategy and asymmetric dihydroxylation for 1,2 *anti* diol present in the ring and lactonisation for macrocyclization were adopted. Keeping the macrolactonization as key step, we have selected the crucial intermediate **34** and **35** in our initial choice as both **34** as well as **35** could produce the macrocyclic skeleton. The major difference would be the stereochemical requirements; **34** require retention while **35** should occur through inversion of configuration during lactonization (Scheme 8).

Scheme 8.



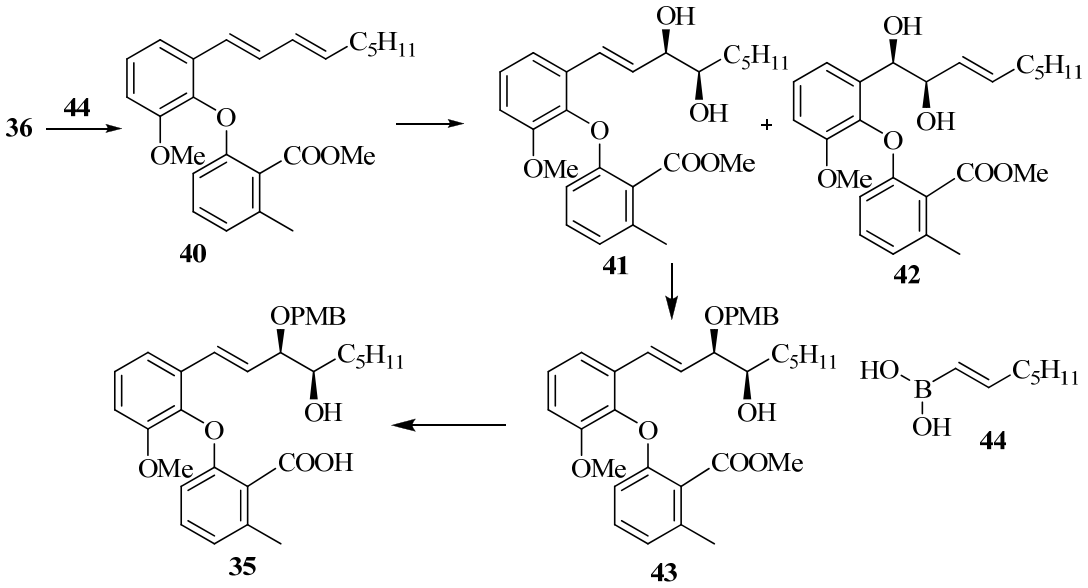
Synthesis of stereochemically important intermediate **34** was commenced with the well characterized biaryl ether containing aldehyde **17**. Accordingly, it was converted to vinyl iodide by employing Takai olefination condition and the resulting mixture was crystallized to separate the required *trans* isomer (**36**) as crystalline solid which in turn coupled with 1-heptyne under Sonogashira condition. The stereoselective partial reduction of triple bond of (**37**) was achieved by using activated Zn dust in methanol and only the *E,Z* isomer **38** was detected. Unfortunately, the AD reaction using commercially available AD-mix β gave the unrequired regioselectivity and only compound **39** was detected under controlled conditions.

Scheme 9.



Because of despairing regioselectivity in dihydroxylation of the conjugated diene **38**, we concentrated on the intermediate **35**. To make the dihydroxylation precursor **40**, the same vinyl iodide **36** was utilized and coupled with 1-heptenyl bronic acid (**44**) under Suzuki protocol to give the conjugated *E,E* diene (**40**) selectively. The dihydroxylation of **40** gave required diol **41** as major product along with isomeric compound **42**. Selective protection of allyl hydroxyl group followed by saponification gave the required intermediate **35** which was confirmed on the basis of informations obtained from spectroscopic and analytical data. Unfortunately, all attempts to cyclise the intermediate **35** under Mitsunobu conditions met with failure result. Even the intermolecular Mitsunobu reactions on **43** were found to be incompatible using benzoic as well as *p*-nitro benzoic acid as nucleophilic part under various reaction conditions (Scheme 10).

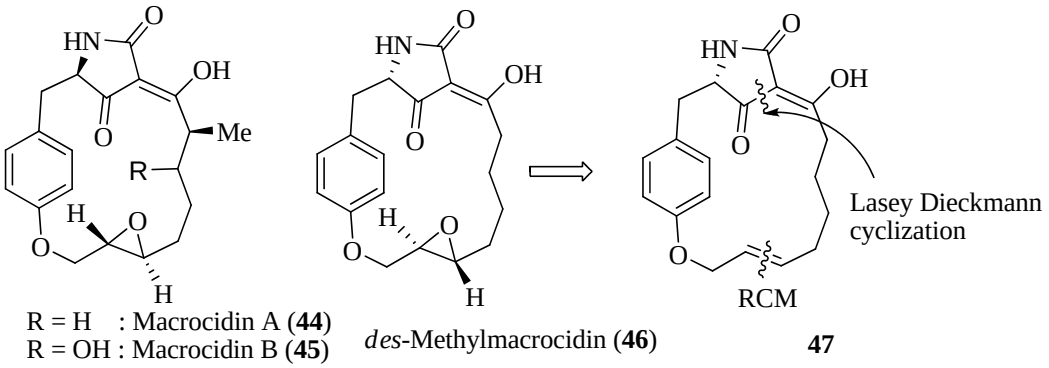
Scheme 10.



Chapter 3: Studies Toward the Total Synthesis of Macrocidin A

Macrocidins A (**44**) and B (**45**) isolated from the genus *Phoma macrostoma* showed promising cytotoxic activity against broad leaf plants with unique mode of action. The macrocidins were charecterised by their unique macrocyclic tetramic acid spanned by a *p*-substituted aromatic ring. The unique structure and promising bioactivity made the macrocidins as attractive target for total synthesis. For initial study we selected the simplified compound *des*-methylmacrocidin (**46**). We proceeded in this direction *via* a Lacey-Dieckmann cyclization and RCM and its reverse sequence. Major difference in both paths would be in the sequences of formation of structural elements, namely, 18-membered cyclic amide tetramic acid (Scheme 11).

Scheme 11.



R = H : Macrocidin A (**44**)
R = OH : Macrocidin B (**45**)

des-Methylmacrocidin (**46**)

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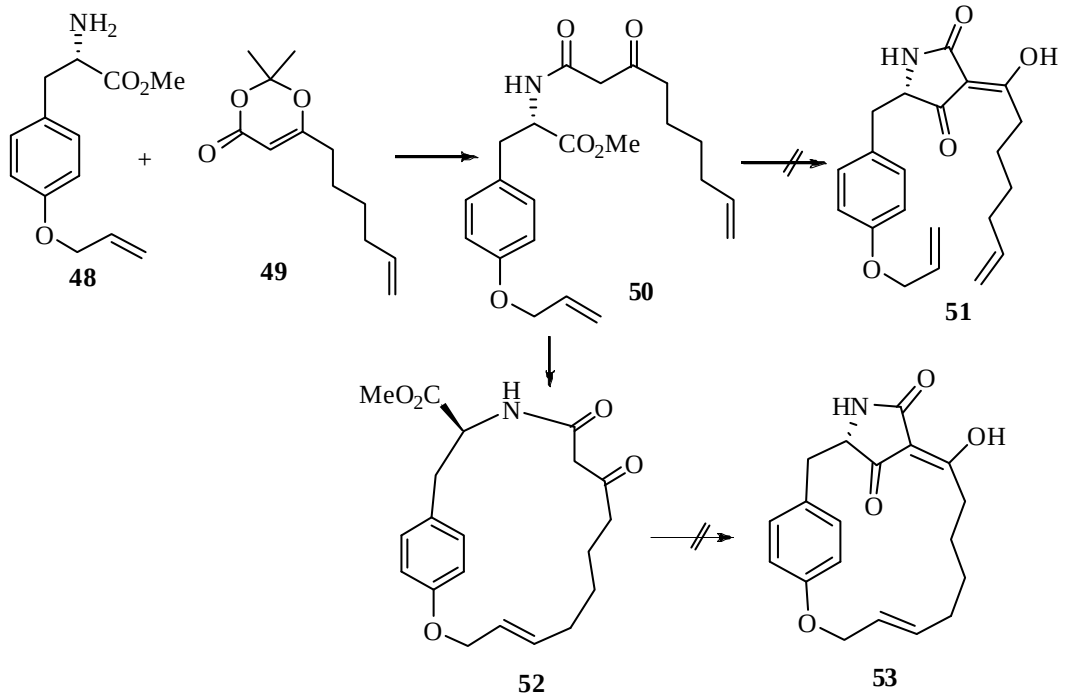
Methyl *O*-allyl-L-tyrosinate (**48**) (prepared from L-tyrosine) and 1,3-dioxin-4-one (**49**) were heated under reflux conditions in toluene in a Dean–Stark apparatus with continual removal of water to give the β-ketoamide **50**. Efforts to transform **50** into the corresponding tetramic acid derivative **51** were unsuccessful. The same observation was noted with the macrocycle **52** derived by the RCM reaction of **50** with Grubbs' 1st gen. catalyst.

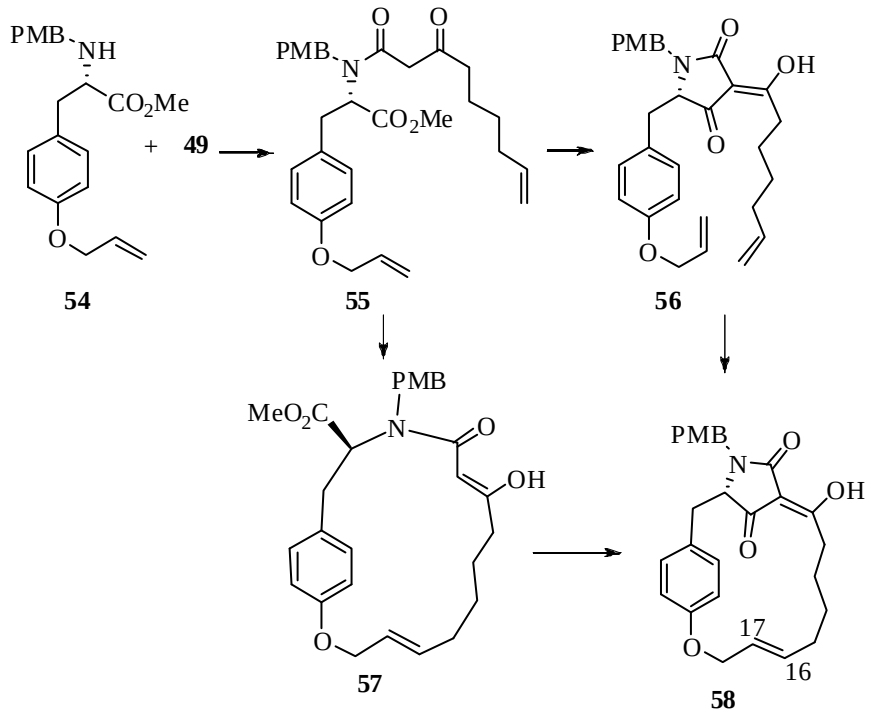
Scheme 12.



However, the Lacey–Dieckmann cyclization of the corresponding *N*-PMB derivative **55** in the presence of KO^{t}Bu was successful in giving rise to the tetramic acid derivative **56** (Scheme 13). Sequential study of crucial RCM of substrates **55** and **56** revealed that latter compound was a poor substrate for RCM. Thus the sequence; RCM followed by Lacey–Dieckmann cyclization was found to be a better choice for constructing the macrolide **58**. Structure of compound **58** was thoroughly investigated with the help NMR, IR, elemental analysis and finally by single crystal *X*-ray diffraction study. Finally, the installation of epoxide functionality at C16-C17 *trans* double bond was found to be futile. The fact, rapid degradation of **58** under oxidative condition rather than the epoxidation of less reactive double bond of the compound **58** suggested that the epoxide group should be installed from its appropriate precursors

without using any oxidizing agent. Presently work in this direction is going on in our laboratory.

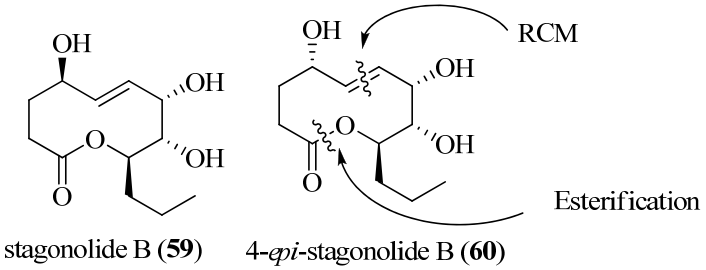
Scheme 13.



Chapter 4: Studies Toward the Total Synthesis of 4-*epi*-Stagonolide B

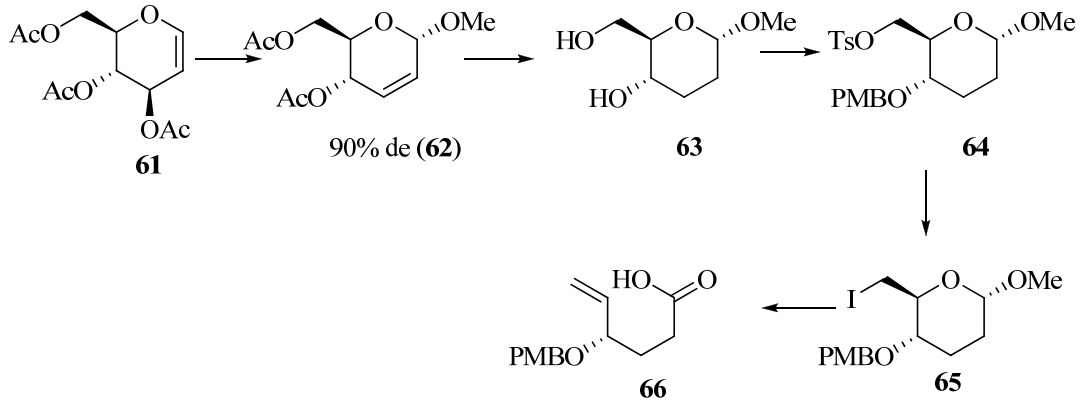
Stagonolide B (**59**) is an alkyl substituted nonenolide, isolated in 2008 from the solid culture of *Stagonospora cirsii*, and reported to be a potent mycoherbicide. The gross structure and relative configuration was determined by extensive 2D NMR study. As a part of our interest in synthesis of macrolides using RCM, we selected stagonolide B (**59**) as well as its C4 epimer **60** as our prime targets to investigate the effects of functional groups and its orientations adjacent to the participating double bonds (Scheme 14).

Scheme 14.



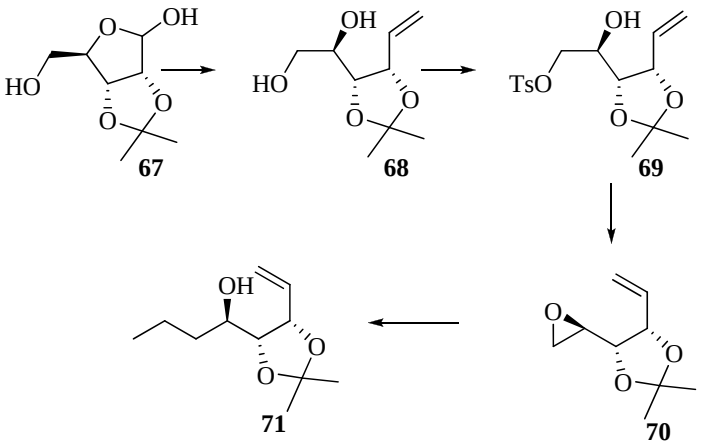
Careful structural analysis of **60** revealed that the *tri-O*-acetyl D-glucal can be used as starting material for the construction of left hand side of **60** while highly oxygenated portion can be achieved from D-ribose. Deoxygenation at C3 of D *tri-O*-acetyl D-glucal was achieved using Ferrier rearrangement protocol using methanol as glycosyl acceptor in presence of boron trifluoride followed by hydrogenation and deacetylation to give **63** (Scheme 15). The C4 and C6 hydroxy groups of **63** were protected as PMB ether and tosic acid ester respectively by using the advantage of different reactivity between them towards tosyl chloride. Finally the Vasella-Bernet fragmentation of **65** and subsequent oxidation of intermediate aldehyde afforded the acid fragment **66**.

Scheme 15.



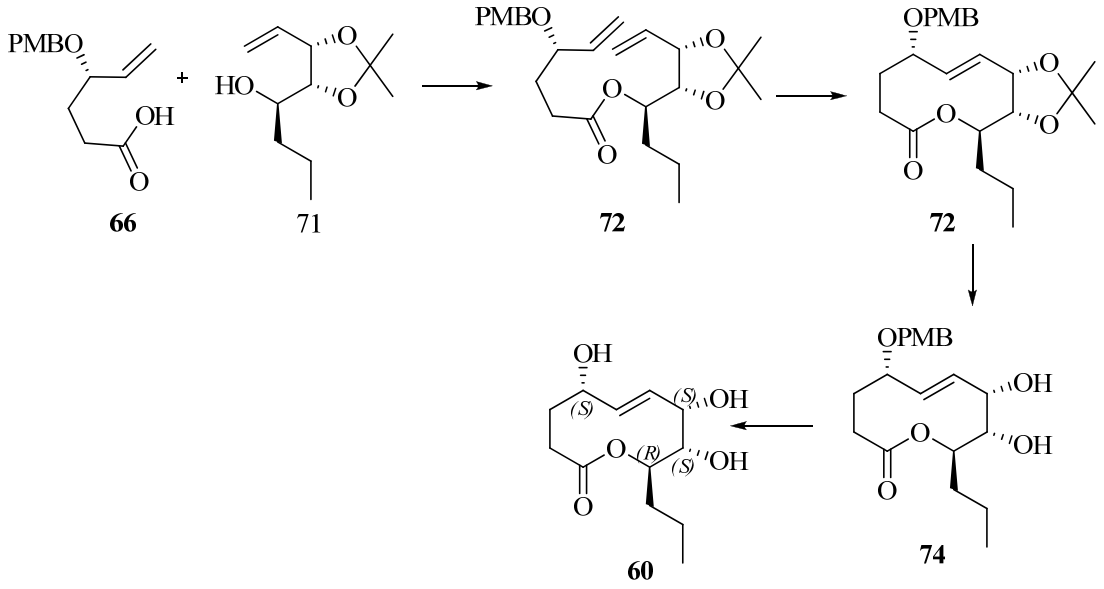
The right hand side alcohol part of **60** was synthesized from D-ribose. One carbon Wittig homologation, mono tosylation and base treatment were performed to get the epoxide **70** which intern, was opened by ethyl Grignard from less hindered side and afforded the alcohol **71**.

Scheme 16.



The RCM precursor **72** was obtained by coupling of **71** with **66** using Yamaguchi protocol. Interestingly, the diene **72** smoothly converted to *trans* alkene **73** exclusively in presence of Grubbs' 2nd gen. catalyst at 80 ^{o}C in toluene (Scheme 17). Finally, the compound was treated with 10 % TFA solution in DCM to give the compound **74** resulting from partial deprotection of acetonide. To complete the synthesis of 4-*epi*-stagonolide, compound **73** or **74** was treated separately with neat TFA at 0 ^{o}C for 1 h which gave the desired target which, isolated as crystalline solid material. Structure of **60** was confirmed by NMR IR mass and elemental analysis. The relative stereochemistry was assigned on the basis of COSY and NOESY spectra which were further substantiated by crystallographic studies. As we started from D-glucose and D-ribose, the absolute configurations of **60** were assigned to be 4*S*, 7*S*, 8*S* and 9*R*.

Scheme 17.



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

Chapter 1

Recent Advancements of RCM Reaction in the Synthesis of Cyclic Natural Products

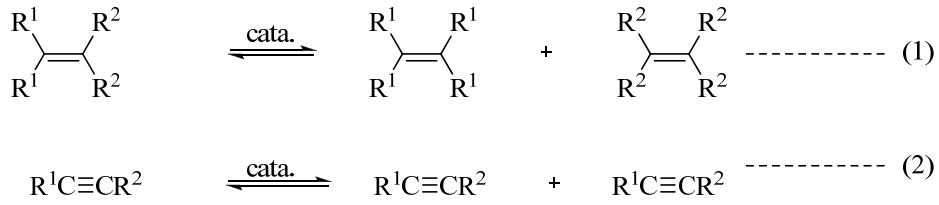
Introduction

Huge structural complexity observed in natural secondary metabolites and their pronounced biological activities make a unique challenging ground for synthetic chemists to prove the efficiency and generality of existing synthetic methodologies. With the advancement of analytical techniques and spectroscopic methods, frequent identification of complex natural products is presently quite an easy task and provide a tough platform to think synthetic community for developing new methods that can meet the requirements when multi functional, complex natural product is a synthetic target. Presently, among the novel synthetic methods, the olefin metathesis[1] and its application in the synthesis of cyclic compounds (RCM) are great concerned in this context. Although metathesis has been traced long back[2], only last few decades it became an attractive tool in the field of polymer science, medicinal chemistry and in organic synthesis when well defined catalysts systems were developed. Because of tremendous success and simplicity from the practical point of view metathesis occupied a central position among the other methods. With the continuation of our long standing interest in the application of RCM in target oriented natural product synthesis,[3] we selected to pursue the construction of aspercyclides (A, B & C), macrocidins and 4-*epi*-stagonolide by employing RCM as the key reaction. Before going to detail description of our synthetic plan and results, a review about the recent development of RCM and its application in construction of various ring size has been presented.

Olefin Metathesis

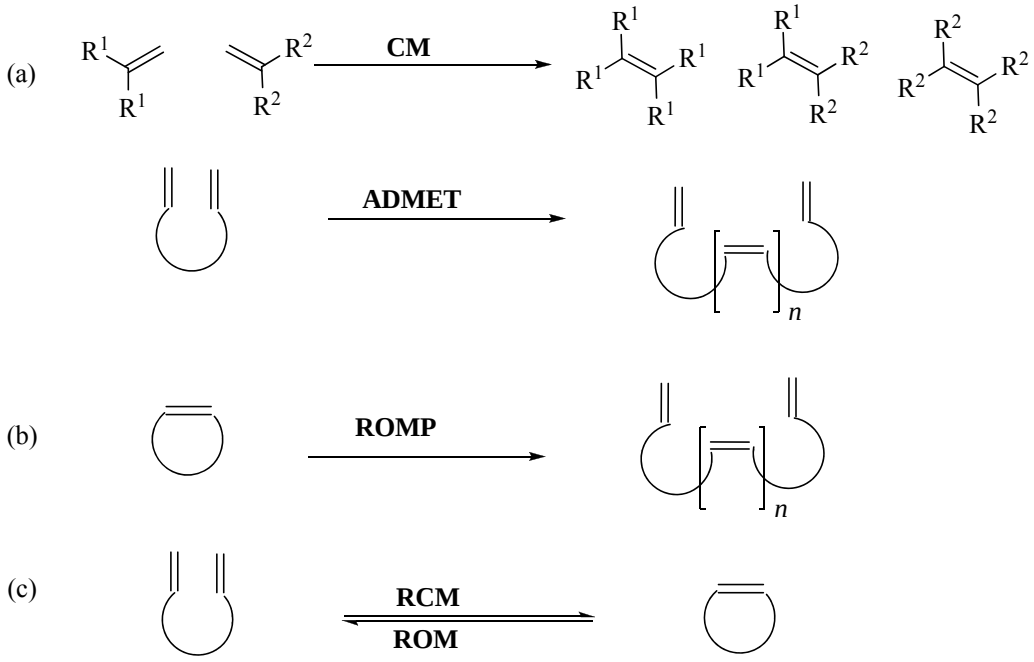
The etymology of the word metathesis comes from the Greek language that means transposition. Thus, metathesis is invoked when, for instance, two carbenes of an olefin can be exchanged to give, if they are different, another recombination leading to the two symmetrical olefins [eqn. (1)] or the two carbynes of an alkyne to give the two symmetrical alkynes [eqn. (2)]. Although the name metathesis was given for the first time to this reaction by Calderon in 1967[2b,2c], the first observation of the metathesis of propene at high temperature was reported in 1931.

Scheme 1.



Olefin metathesis is a unique carbon skeleton redistribution in which unsaturated carbon-carbon bonds are rearranged in the presence of metal carbene complexes. With the development of efficient catalysts, this reaction has emerged as a powerful tool for the formation of C-C bonds in chemistry. The number of applications of this reaction has dramatically increased in the past few years. Of particular significance, this type metathesis utilizes no additional reagents beyond a catalytic amount of metal carbene and the only other product from the reaction is, in most cases, a volatile olefin such as ethylene. The broad applicability of olefin metathesis has attracted attention from both academic and industrial scientists. The generalities of this reaction in organic, medicinal, polymer and materials chemistry has been extended to such an extent that it has now become a familiar tool for the specialists of all these fields.

Scheme 2: *Different types of olefin metathesis reactions.*

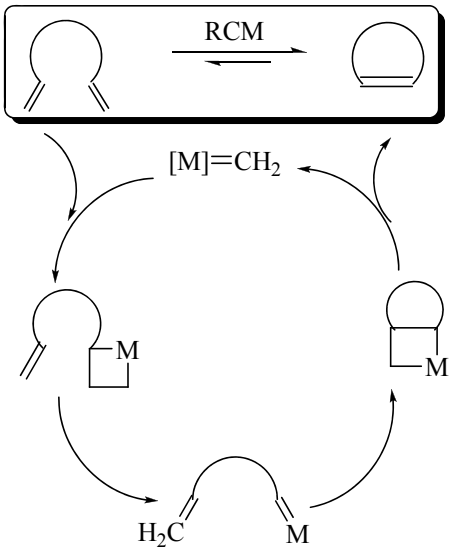


Olefin metathesis can be utilized in three closely related types of reactions (Scheme 2): (a) acyclic cross metathesis (CM) when carried out on diolefins results in polymers (Acyclic Diene Metathesis ADMET); (b) ring-opening metathesis polymerization (ROMP); and type (c), ring-closing metathesis (RCM). In this brief introduction, important and recent advances to ring-closing metathesis (RCM) reactions specially dealing with total synthesis of natural products with medium to large ring size organic molecules will be presented.

Mechanism Ring Closing Metathesis

The widely accepted mechanism (Y. Chauvin)[4] of metathesis reactions consists of a sequence of formal [2+2] cycloaddition/cycloreversion involving alkene (Figure 1), metal carbenes and metallacyclobutane intermediate. Since all individual steps of the catalytic cycle are reversible, an equilibrium mixture of olefin is obtained. Therefore, it is necessary to shift equilibrium in one direction to make the metathesis reaction productive in preparative terms. In ring closing metathesis, as shown in catalytic cycle, the forward process is entropically driven because RCM cuts one substrate molecule into two products and moreover, most of the cases one product is volatile and desired cycloalkene accommodate in the reaction mixture. Another important factor for productive RCM is the high dilution which is necessary to avoid ADMET.

Figure 1: *Catalytic cycle of ring closing metathesis.*



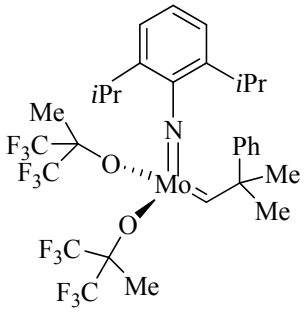
Catalyst development

The number of catalyst systems that initiate olefin metathesis is very large.[5] However, most early work in olefin metathesis was done using ill-defined multicomponent catalyst systems.[6] It is only in recent years that well-defined single component metal carbene complexes have been prepared and utilized in olefin metathesis. Although a number of titanium and tungsten catalysts have been developed for metathesis and related reactions, the well-defined molybdenum and ruthenium alkylidene complexes have seen the most applications. Unlike the earlier olefin metathesis catalysts these highly active, long-lived catalyst systems do not require Lewis acidic co-catalysts or promoters.

Molybdenum-Based Catalyst

One of the most important catalyst systems developed by Schrock and co-workers is the alkoxy imido molybdenum complex **1** (Figure 2).[7] One of the major advantages of this system is it's high reactivity toward a broad range of substrates with many steric or electronic variations. The alkoxides in the [Mo] system can be readily altered to adjust their activities. Critical drawbacks of this Mo-based carbene complex are, however, its moderate to poor functional group tolerance, high sensitivity to air, moisture or even to trace impurities present in solvents, thermal instability on storage and expense of preparation.

Figure 2: *Schrock's tetracoordinated molybdenum alkylidene complexes.*

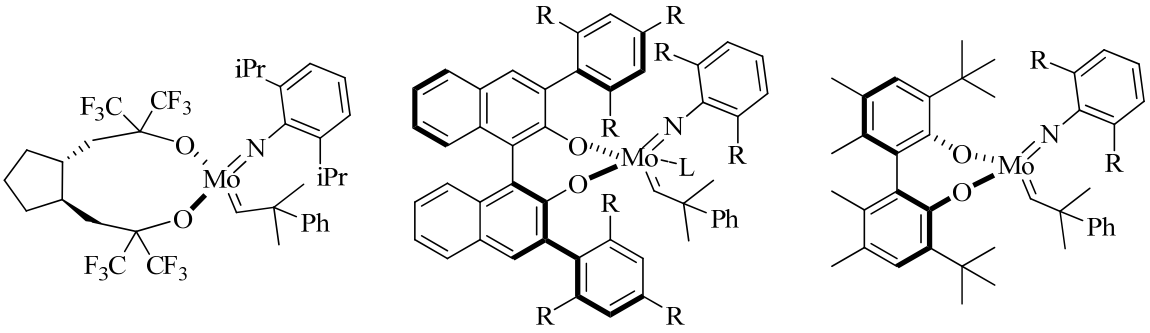


1

In addition to the pronounced reactivity, the efficiency of the complex can be tuned by using various alkoxy groups to the ligand sphere of the molybdenum center, including chiral scaffolds. This may lead to the asymmetric ring closing metathesis (ARCM) or asymmetric ring opening/cross metathesis cascades. This has been achieved with the help of catalyst **2** which contains an elaborated cyclic chiral mimic

of the OCMe(CF_3) unit.[8] Recently, excellent level of asymmetric induction has been accomplished with the molybdenum complexes **3** and **4** (Figure 3).[9]

Figure 3: *Chiral molybdenum catalyst for ARCM.*

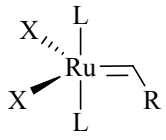


2 **3** **4**

Ruthenium Based Catalysts

The real breakthroughs were introduced by Grubbs' after discovering the ruthenim catalyst of type **5** (Figure 4) and sudden enhancement of interest in this transformation.[10] Although their activity is usually lower than the Schrock's molybdenum alkylidene complexes **1**, the spectacular tolerance of these late transition metal complexes toward an array of functional groups and the ease of handling caused by stability against oxygen, water, and minor impurity present in the solvent render them exceedingly practical tools and explain their unrivaled popularity in the organic and the polymer chemist community.

Figure 4: *1st Generation ruthenium phosphine complexes.*



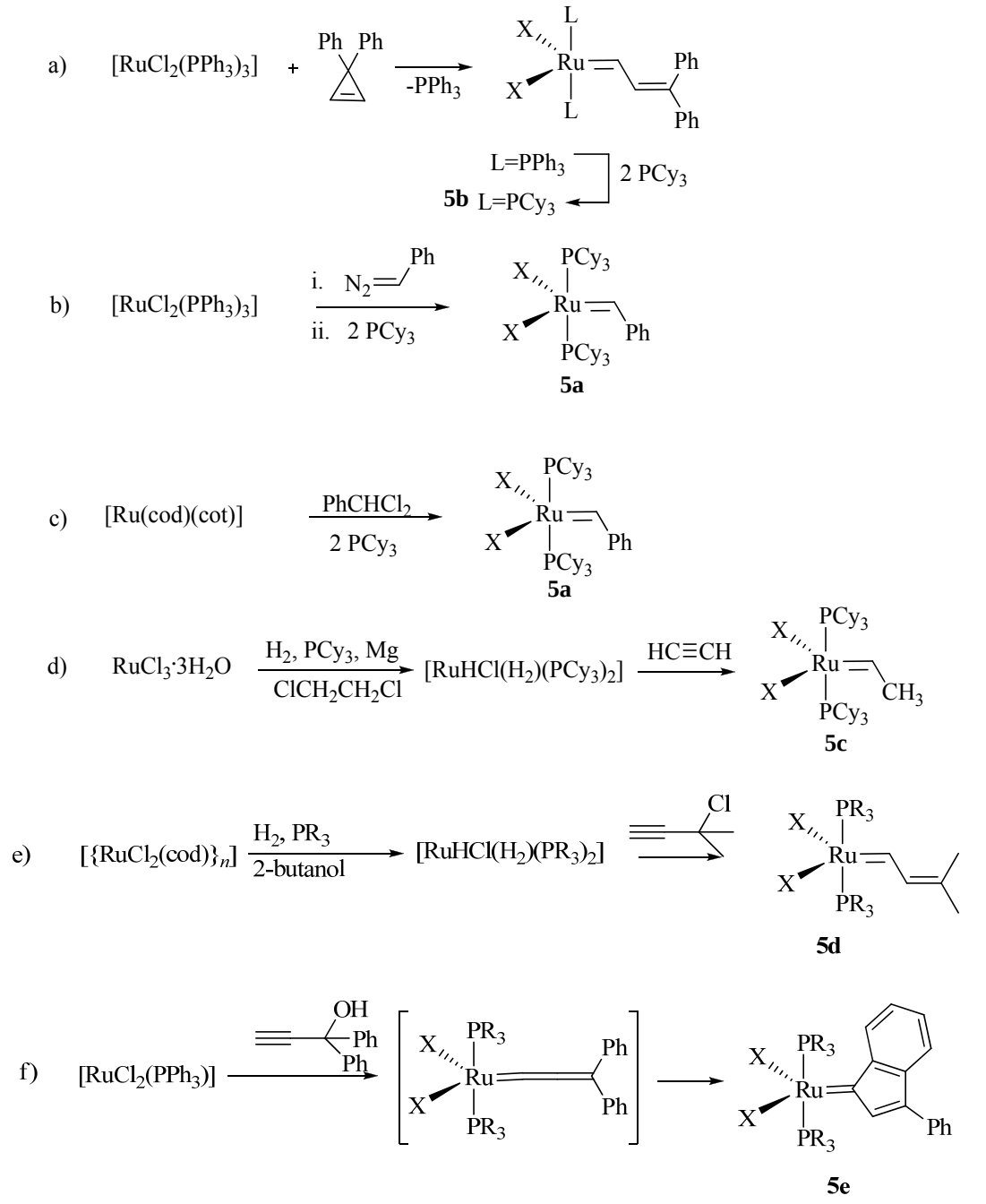
5

X=Cl, Br, CF_3COO
L= PR'_3

5b (Scheme 3) is the oldest member of the catalyst type **5** and it found less popularity in application because of its cumbersome preparation process. This catalyst is formed by Ru(II) induced rearrangement of diphenylcyclopropene.[10a,b] Since the alkyl group R at carbene unit of **5** itself, howeher, is irrelevant in many catalytic cycles several

carbene sources other than diphenyl carbene have been investigated to develop more entries into this family of ruthenium carbene complexes. Most important entries are presented in scheme 3. Significant improvement was found when diazoalkene are used as carbene sources and final ligand displacement revealed a stable, active catalyst system **5a** which is now commercially available.[11]

Scheme 3: *Synthesis of 1st generation ruthenium-phophine complexs.*

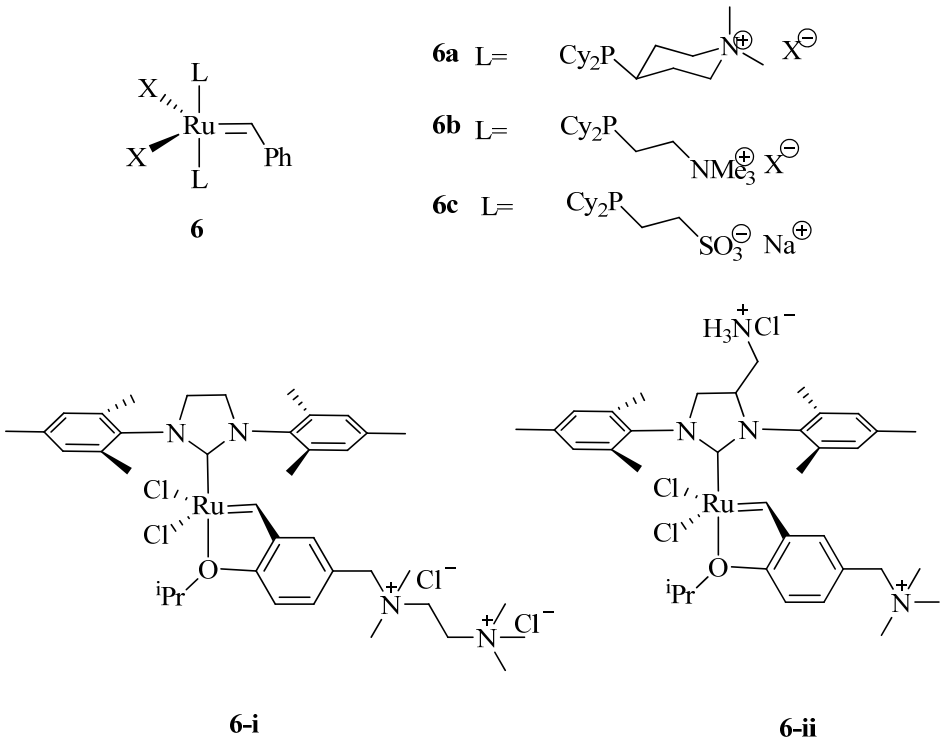


Other practical process that can be performed in industrial relevant scale either use of *gem*-dihalides,[12] alkynes,[13] or propargyl chlorides.[14] Treatment of diphenyl

propargyl alcohol with commercially available ruthenium complex $[RuCl_2(PPh_3)_3]$ lead to complex **5e.** Practical examples indicate that the catalyst **5e** is as good as or even slightly better than the standard phenyl carbene complex **5a**.[15]

The presence of electron withdrawing anionic chlorine was found to be optimal and electron donating phosphine ligands (*e.g* PCy_3) with higher cone angle were most effective. Only few other aliphatic designed members with quaternary ammonium sulfonate are most remarkable ligands.[16] Such catalysts can be used for metathesis of unprotected substrates in aqueous medium (Figure 5). Hoveyda complexes **6-i** and **6-ii** also modified to make them useful in RCM in presence of water as co-solvent and revealed that they are reasonably active for RCM but poor catalyst for cross-metathesis under that conditions.[17]

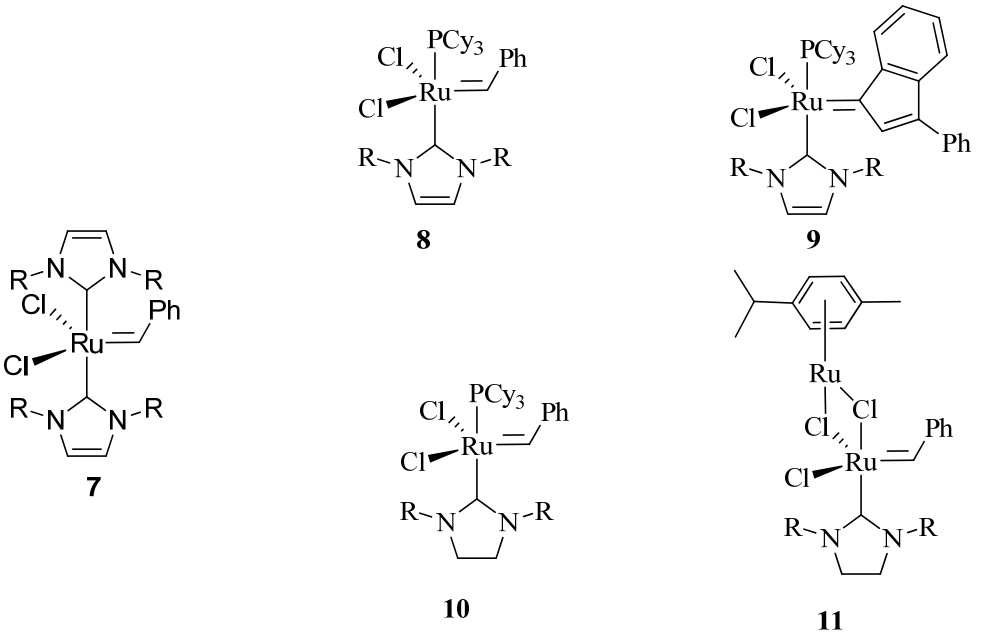
Figure 5: *Water soluble ruthenium complexes.*



Detailed mechanistic studies allow the rationalization of phosphine ligands. The bulky electron donating characters of phosphine ligand are decisive to stabilize the intermediate formed after reversible dissociation of one of the ligand to accommodate olefin and then it converts to metallocyclobutane (Figure 1). Therefore, with increased basic properties and the bulkiness of ligands should enhance the life time of the relevant intermediate formed by dissociative mechanism and overall reactivity. *N*-heterocyclic carbenes (NHC) fulfills all these requirements.[18] Herrmann

and co-workers were the first to report *N*-heterocyclic carbene containing complex in the context of metathesis.[19]Complex **7** (Figure 6), in which both PCy_3 are displaced by *N,N*-disubstituted 2,3-dihydro-1*H* imidazole-2-ylidene units, however is stable but do not show improved acivity profile. This is expected mechanistically, because the sticky NHC ligand renders the dissociative pathway less favoured and, therefore low concentration of catalytically active ruthenium template in solution.

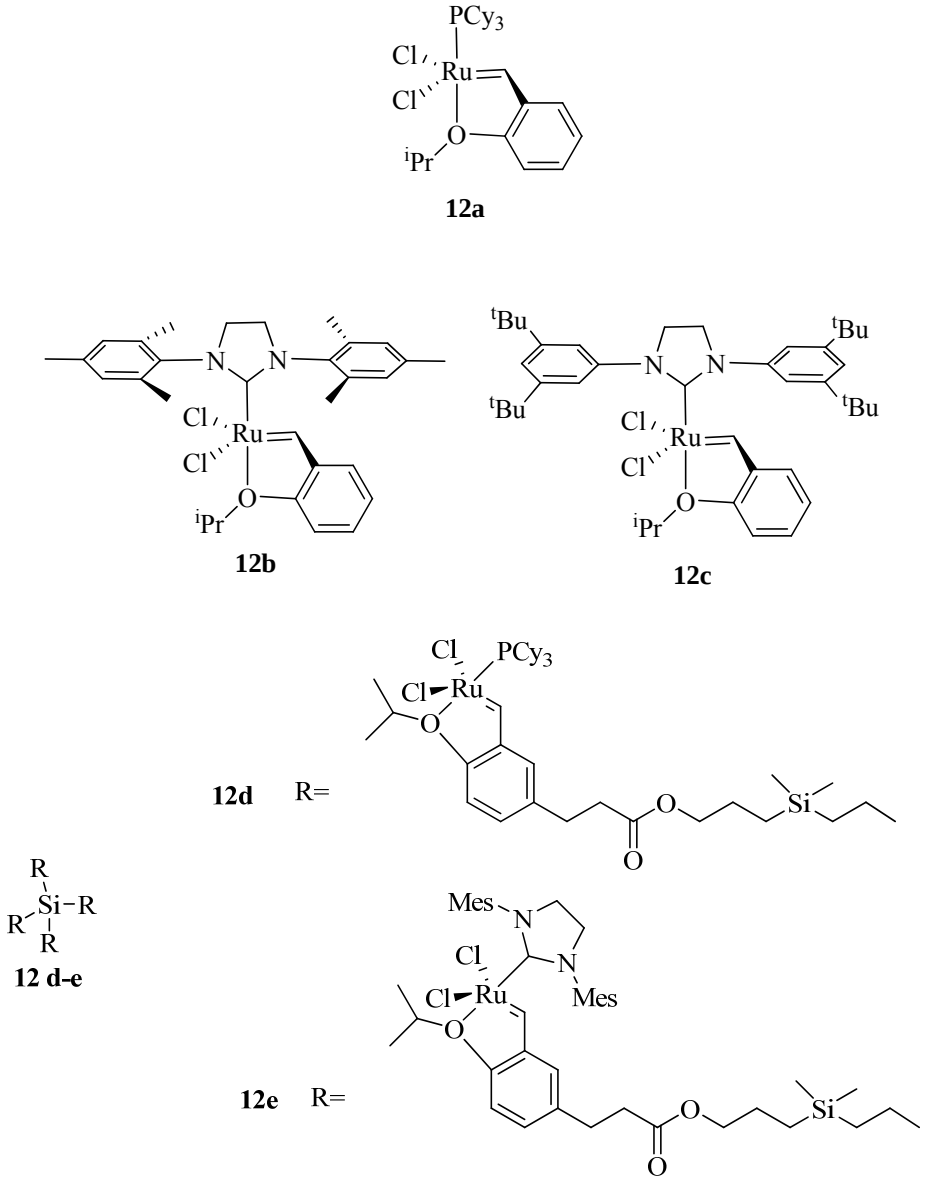
Figure 6: *Ruthenium NHC-phosphine complexes.*



R= mesityl

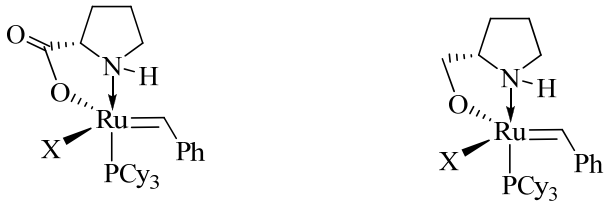
The use of kinetically inert, electron donating *N*-heterocyclic carbene ligand, in combination with coordinately labile ligand PCy_3 on the other hand, should result in the desired synergistic effect. This idea was independently pursued by three different groups which have almost simultaneously reported on the preparation and the catalytic properties of complexes **8-11**[20] (Figure 6). Bonding of the mesityl containing NHC is stronger than PCy_3 and acts as merely σ donor with no acceptor properties. The substitutents on mesityl ring also crucial which helps to restrict rotation through C-N bond for steric reason.

Figure 7: *Hoveyda catalysts.*



Several new class of highly active and recyclable Ru-based metathesis catalysts **12a-d** are reported by Hoveyda and co workers[21] (Figure 7). These complexes, both monomeric (**12b**) and dendrimeric (**12e**), promote metathesis reactions in a highly efficient manner. Unlike the first generation recoverable Ru-based complexes (**12a** and **12d**), **12b** and **12e** effect the efficient formation of trisubstituted alkenes through catalytic RCM. Tetrasubstituted olefins can be catalytically accessed too, but less efficiently than trisubstituted olefins. The related dendrimeric systems are recyclable and as active as their corresponding monomers but offer the added advantage of being more readily isolable.

Figure 8.



13a **13b**

The asymmetric bidented *N,O*-prolinate ruthenium benzylidene complexes (Figure 8) was found to be active catalyst and exhibits a wide range of functional group tolerance in metathesis at ambient temperature and it was designed to introduce chirality to the product formed in olefin metathesis reaction.[22] The electron-withdrawing carboxylic acid functionality on proline is crucial as it was observed that alkoxy analogue **13b** is very low active compare to that of **13a**. Pre-catalyst **13a** and **13b** exhibited poor efficiency in desymmetrization because of favoured dissociation of nitrogen center over phosphine during catalytic cycle where the remaining monodented carboxylic acid gives no chirality.

There are several modifications identified on both the 1st & 2nd Ru-precatalyst[23] as well on Hovayeda coplexes[24] and their activity is significantly higher than that of parent Grubbs' catalyst **5a** and **8**. Moreover, in some cases, their activities come closer to or even exceeded the Schrock molybdenum complex **1**. However, due to the exceeding thermal stability and resistance to oxygen and moisture as well as the compatibility to many functional groups of the Ru-precatalysts **5a**, **8, 9** and **10** gained extreme popularity in synthetic chemistry and polymer science and they are commercially available.

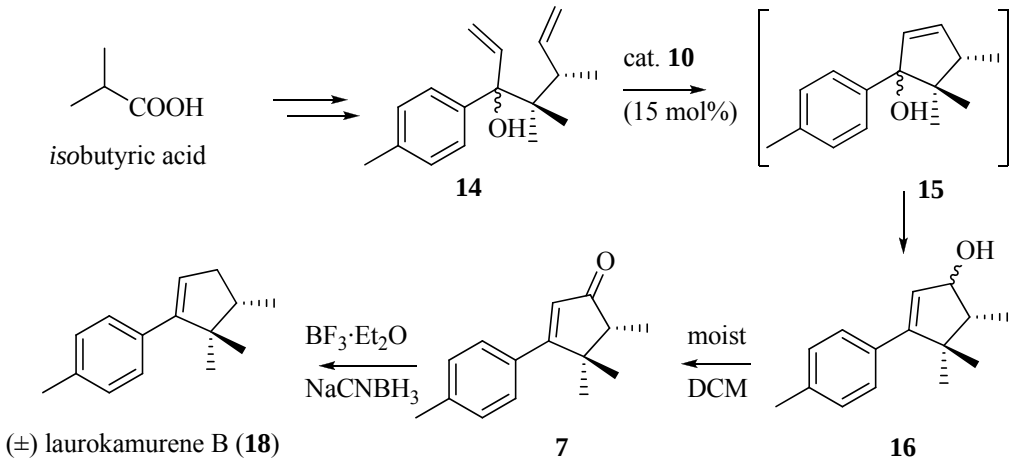
Application of ring closing metathesis reaction

Although the first example was reported in 1980 by Tsuji,[25] catalytic ring-closing metathesis (RCM) has only recently emerged as an effective strategy in organic synthesis with development of well defined catalyst system and has been extensively employed in the preparation of a wide variety of complex molecules with multiple functionalities ranging from small, medium to large rings successfully.

Synthesis of small rings (5 & 6) carbocycles and heterocycles

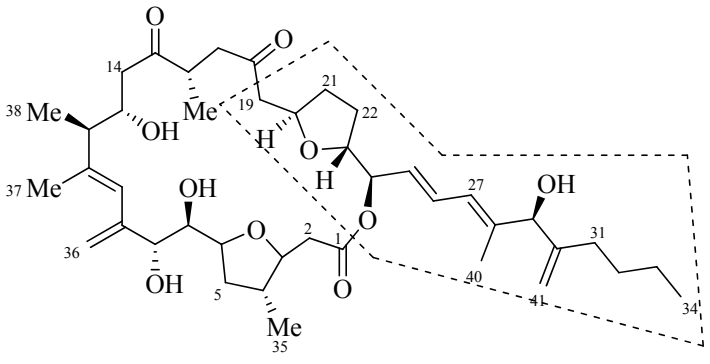
The modern use of olefin metathesis can be tracked to the series of papers [26] that demonstrated the high yielding closure of diolefins to provide 5, 6 and 7 membered rings with a diverse functionality and double bond substitution.

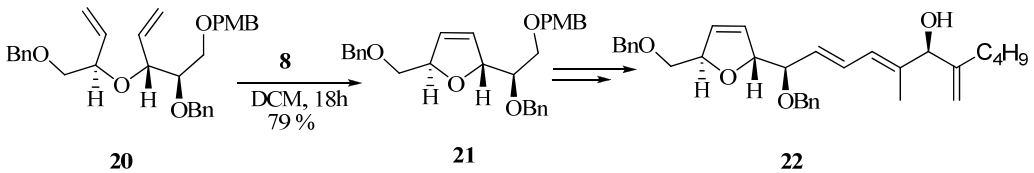
Scheme 4.



RCM has been proposed as an efficient tools for concise strategy in the synthesis of (±) laurokamurene B (**18**)[27] (Scheme 4). After a sequence of reactions, the RCM precursor prepared from isobutyric acid and successfully cyclised to 5 member carbocycle **15** using 2nd gen. catalyst which was detected as epimeric mixture of rearranged product **16** and finally in a straight forward way the total synthesis was completed.

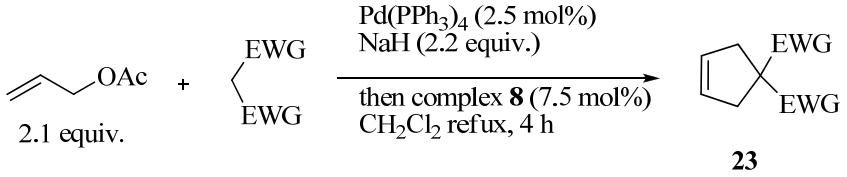
Scheme 5.





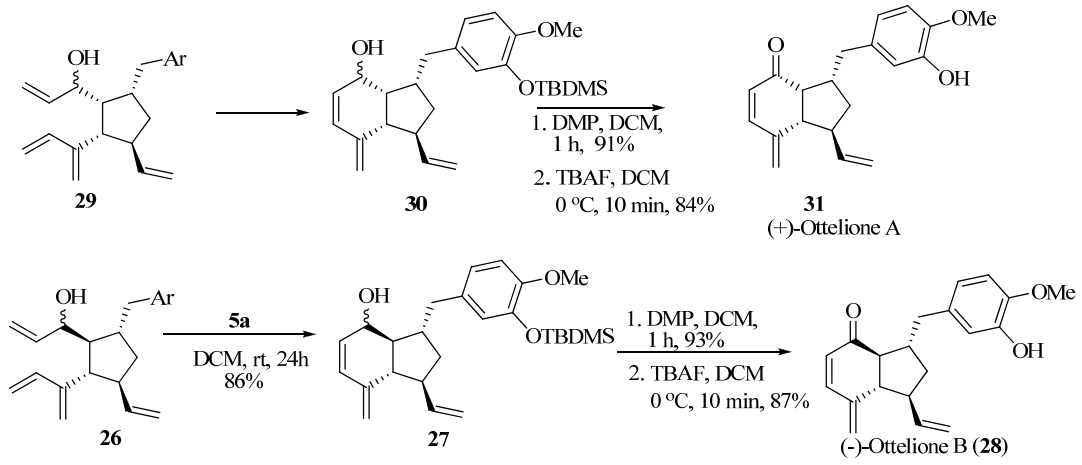
With the use of 2nd gen catalyst **8**, the efficiency of RCM in five member ring formation is so high that the use of RCM in the beginning of a multi-step, convergent synthetic strategy is quite reasonable. Thus the synthesis of C19-C34 fragment of Amphidinolide C (**6**) (Scheme 5) was accomplished by our group[28] with the help of unique tool, RCM with 12% overall yield in 10 steps.

Scheme 6.



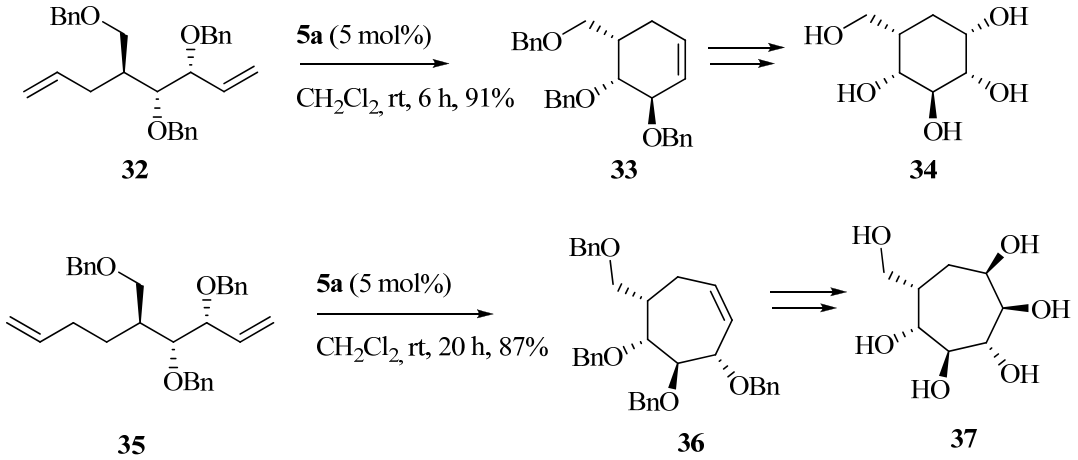
Excellency in compatibility of metathesis catalyst with other reagents also proved by the work of Guillaume Prestat *et al.*[29] In a domino sequence of reaction (Scheme 6), alkylation/ring-closing-metathesis was performed concomitantly using Pd catalyst and ruthenium complex **8**. It has been observed that Grubbs' catalysts can act as precatalysts for allylic alkylation.

Scheme 7.



The powerful antitumor agents ottelione A (**31**) and B (**27**) were synthesized in racemic as well as in optically pure form by selective ring closing metathesis[30] (Scheme 7). The presence of an additional double bond in the starting material **26** and **29** did not interfere to precede the RCM in desired manner. Both the catalysts **5a** and **8** are almost equally efficient for cyclizing the intermediate **29** and **26**. Moreover, the intermediate **28** has a strained, *trans* fused [4,3,0] bicyclic ring which is difficult to achieve by other means.

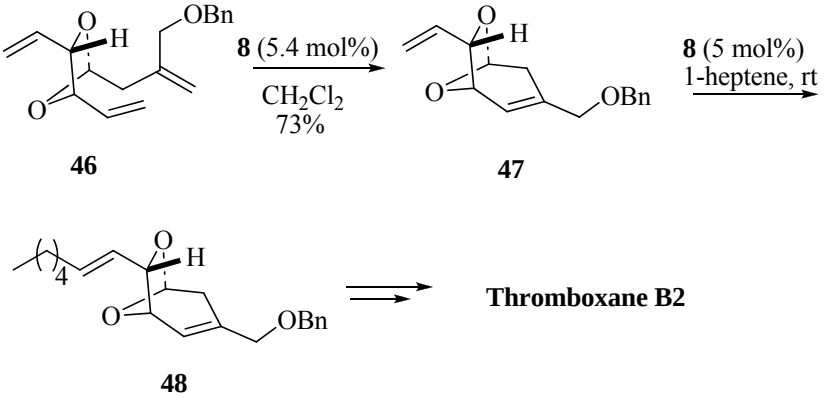
Scheme 8.



RCM was utilized for the synthesis of carba-sugar (**34** & **37**). The key RCM reaction was facile when the catalyst **5a** was used and afforded the pseudo-glycol in excellent yield[31] (Scheme 8). Similarly, the seven member carba-sugar **37** has been synthesized using the same catalyst **5a**. Comparative studies indicate that six member ring formation is easier than that of seven member analogue.

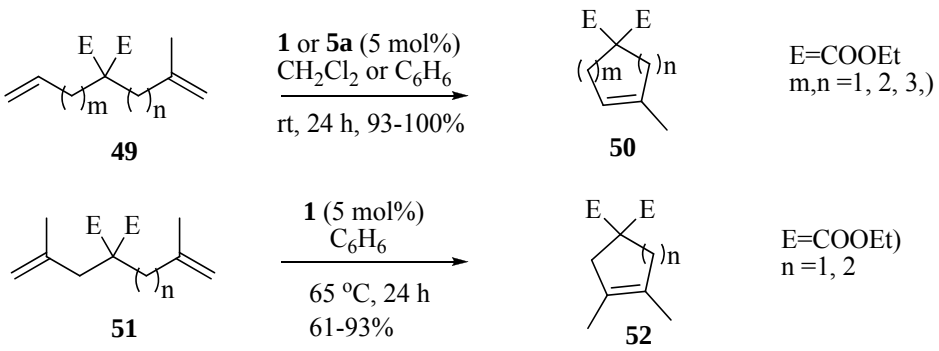
Cyclic ketals are also stable under metathesis conditions as illustrated in the synthesis of thromboxane B_2 (Scheme 9).[32] The C_2 symmetric acetal (**46**) was cyclised using the complex **8** without affecting other double bond revealed that the *gem*-disubstituted double bond containing diene are also good substrates for RCM to prepare *tri* and *tetra* substituted cyclic olefins. Cross metathesis of intermediate **47** with 1-heptene lead to the crucial intermediate **48** which was advanced sequentially to complete the total synthesis of thromboxane B_2.

Scheme 9.



Systematic studies on the RCM of dienes containing various *gem*-disubstituted olefins to yield *tri* or *tetra* substituted cyclic alkenes have been disclosed[33] by Grubbs *et al*. (Scheme 10). Cyclization of mono *gem*-substituted dienes **49** afforded trisubstituted cyclic olefins **50** in excellent yield with both Mo-catalyst **1** and Ru-catalyst **5a**. However, no 8-membered cyclic olefins (m + n = 5) were formed with either (**1 & 5a**) catalysts mainly because dimer formation was found to be predominant even under high dilution conditions. *tetra*-Substituted cyclic olefins **52** were efficiently obtained from the corresponding substituted dienes **51** only with the Mo-catalyst **1**. Differences in reactivity and functional group tolerance between the Mo-catalyst **1** and the Ru-complex **5a** were observed in attempts of RCM with dienes having different steric and electronic properties.

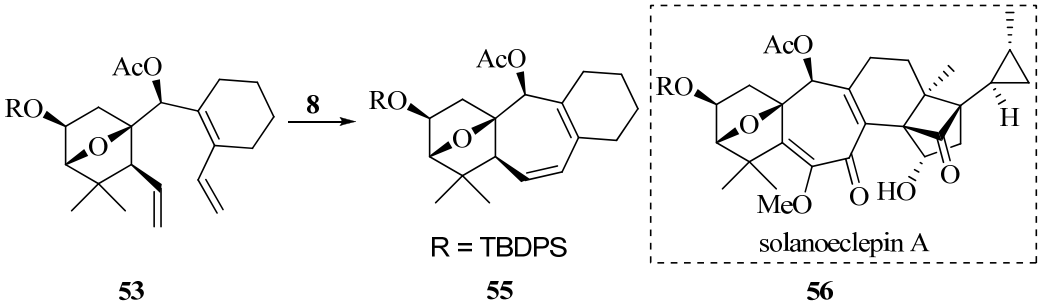
Scheme 10.



Use of RCM in synthesis of mediunm size ring (7-11)

The importance of medium-sized rings in organic chemistry is exemplified by their presence in the structural core of a large number of biologically important natural products.[34] Although synthetic approaches to five- and six-membered ring systems are common *via* cyclization and cycloaddition reactions, seven- and eight-membered ring formations are not as abundant. Cyclization strategies to medium sized rings are often inhibited due to entropic factors and transannular interactions. In general, the number of methods for preparing medium-sized carbocycles by cyclization or cycloaddition reactions from acyclic substrates is relatively small. With the discovery of well-defined catalyst system, the RCM reaction has become common transform for retrosynthetic disconnection in medium to large ring natural products.

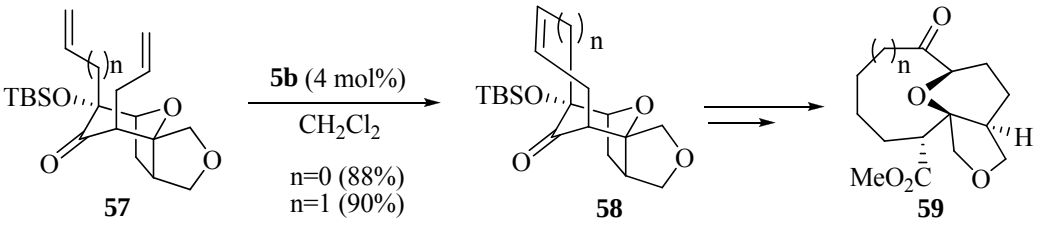
Scheme 11.



53 **55** **56**

For example, the tetracyclic left-hand substructure of solanoeclepin A[35] was synthesized from highly hindered densely functionalized intermediate **53** (Scheme 11). Use of catalytic amount of **5a** gave poor conversion whereas more stable complex **8**, only 15 mol % was required for complete conversion with in 16 h in refluxing toluene.

Scheme 12.

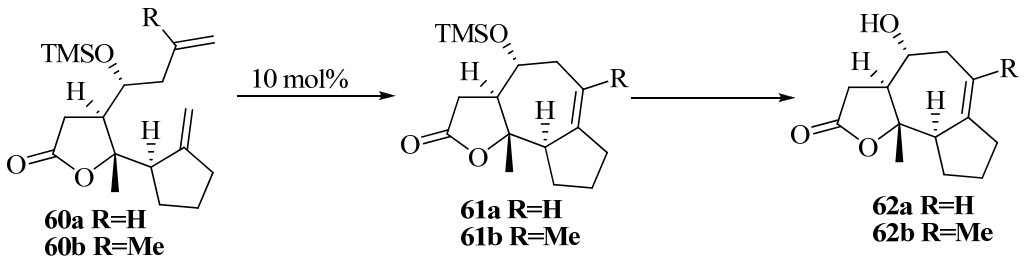


57 **58** **59**

Diene **57** was subjected to ring-closing metathesis with Grubbs' catalyst **5b** to give tetracycles **58** (Scheme 12)[36] which has been advanced to **59** by oxidative ring expansion leading to **59** (n = 0) and 10-membered (n = 1) carbocycles, commonly found in a variety of naturally occurring terpenoids.

In another example, Reiser *et al*. have shown the challenging catalytic RCM of diene **60b** to afford **61b** by employing Ru catalyst **12b** (Scheme 13). Phosphine complex **10** was a poor catalyst of choice. Whereas both the complexes **12b** and **10** exhibited similar activity with the substrate **60a** to produce **61a** in low yield.[37]

Scheme 13.



60a R=H
60b R=Me

61a R=H
61b R=Me

62a R=H
62b R=Me

Direct construction of eight membered rings from acyclic precursors is still challenging, mainly because of unfavourable entropy and enthalpy factors that produce after ring formation. This also reflecting in nature where abundance of eight member rings are very low compare to other ring size. With the discover of ruthenium and molybdenum carbene complexes having higher activity and wide range of functional group tolerance, these problems were addressed to an appreciable extent when RCM was used as new synthetic tools to construct this uncommon ring containing compounds.

It has been observed that formation of cyclooctanoid by RCM from acyclic diene as an extension of five, six and seven membered ring formatiom from acylic diene was failed.[38] Only dimeric products were observed from intermolecular metathesis reactions, even when the reactions were performed at high dilution or under control addition of catalyst or substrate. Similar difficulties were documented by Mori[39]*et al*. From the results of systematic studies on cyclooctanoid synthesis, it has become clear that one of the key factors for successful synthesis of eight membered rings is conformational constrain. This was achieved easily with substrate having pre-existing ring which helps to keep the diene in close proximity. Thus the *trans* di-substituted cylcohexane **63** was smoothly converted to trans fused, [6,4,0] bicyclic compound **65** (Scheme 14) in presence of (**5b**) whereas the cis isomer (**64**) is poor substrate for RCM (Table 1). The major side reaction was dimerization through CM.[38]

Scheme 14.

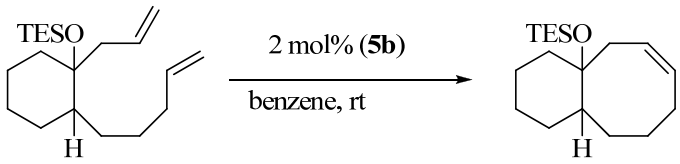
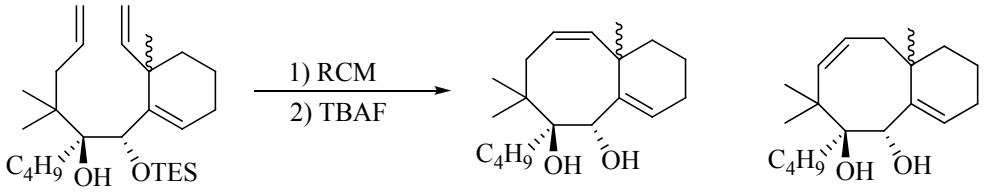


Table 1

Substrate	Time(h)	Yield(%)
63 : *Trans*	4	57 (*trans* **65**)
64 : *cis*	20	33 (*cis* **66**)

The effect of conformational constrain has been clearly demonstrated by the work of Steven P. Nolan and co-workers.[40]

Scheme 15.



67 **68-α** **68-β** **69-α** **69-β**

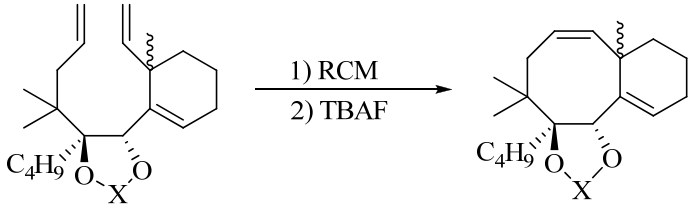
Table 2

catalyst	Yield **68** (%)	Yield **69** (%)
5a	6*	7*
8	27**	0

* only β isomer, ** only α isomer

In the case of more sterically demanding substrate **67** only one isomer appeared to be reactive, and desilylated cyclised products (**68-β**) were obtained in low yield (6%) along with 7% of cyclooctene **69-β** where the double bond had migrated to the C10-C11 position after eight days when catalyst **5a** was used (Scheme 15, Table 2). This kind of isomerization is well documented in literature.[41] It has been proposed that the isomerisation is due to prolonged exposer of products to ruthenium complex. Both products **68-β** and **69-β** have the β-configuration at C8-C21. In the case of copmplex **8** the yield was slightly better but the exciting feature, the stereochemical outcome of the cyclization was reverse.

Scheme 16.



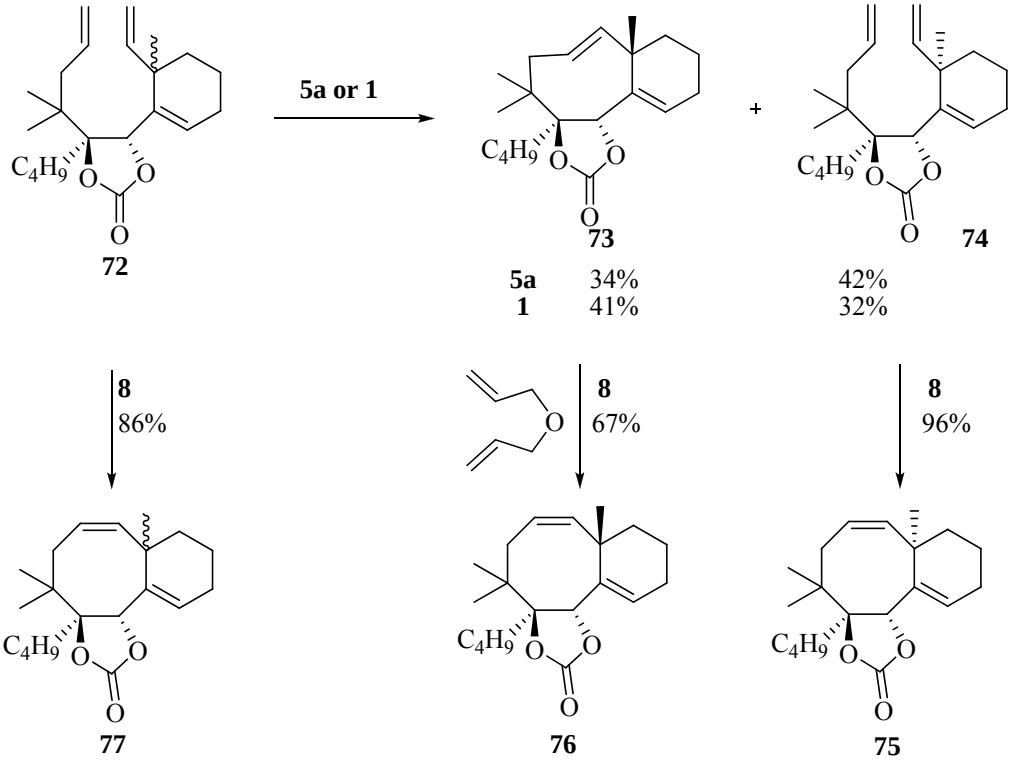
70 **71**

Table 3

X	catalyst	time	Yield (%)
Si(*t*-Bu)$_2$	**1**	3d	96
Si(*t*-Bu)$_2$	**5a**	8d	0
Si(*t*-Bu)$_2$	**8**	20h	91
C(Me)$_2$	**1**	3d	93
C(Me)$_2$	**5a**	8d	0
C(Me)$_2$	**8**	15h	86

Alternatively, both stereoisomers reacted smoothly when cyclic groups, such as silylene or acetonide, were used to protect the diol moiety (Scheme 16). The expected bicyclo- [6.4.0] dodecenes were isolated in very good yields when molybdenum carbene **1** or ruthenium carbene **8** were used. The presence of the cyclic protecting group induced a favorable proximity of the two olefins to undergo a successful RCM.

Scheme 17.

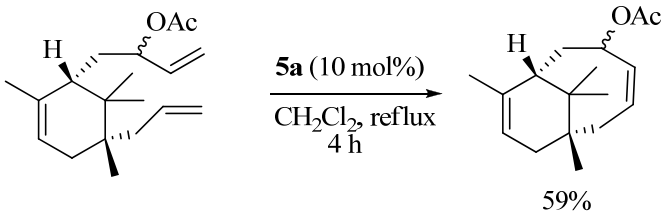


Quite unexpectedly, in the case of the corresponding cyclic carbonate, only one diastereomer cyclized in the presence of catalysts **1** and **5a**. This reaction led to the selective formation of the *trans*-cyclooctene, which was isolated in yields of 34–41%, depending on the catalyst, (Scheme 17)[42] and α (**74**) diastereomers were recovered almost quantitatively. Surprisingly, the catalyst **8** reacted differently with the same substrate (Scheme 17) where both diastereomers (1:1) of **23** converted to an epimeric mixture (1:1) of *cis*-cyclooctanoid **77**.

A possible explanation for this result is that the reaction does not proceed to complete thermodynamic equilibrium under these conditions in case of catalyst **1** and **5a**. This has been proved by independent experiments; reactions of α isomer **74** which produced only *cis* α-**75** and the *trans*-β-**74** were isomerized to *cis* β-**76** with the

complex **8.** Presumably, the isomearization underwent through a ring-closing/ring-opening process, effectively proving that RCM with this catalyst proceeds under thermodynamic control. A specific complexation of the catalyst to the carbonyl moiety was invoked on the basis of the exclusive formation of the *cis*-cyclooctene when the metathesis was performed in the presence of titanium isopropoxide.[43]

Scheme 18



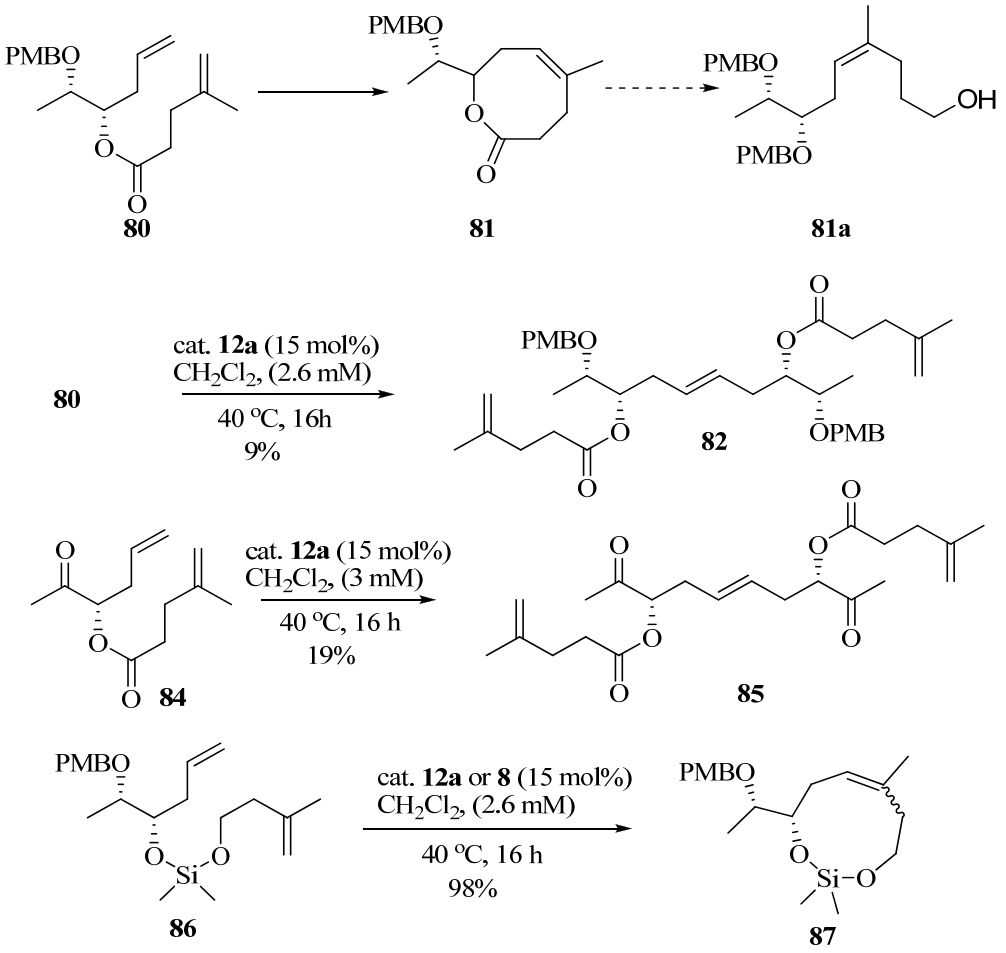
78 **79**

1,3-Cyclohexanes were also considered as possible precursors for the construction of taxoidic A,B ring fragments. The RCM of appropriately functionalized substrates was reported as an efficient method for the formation of the central bridged bicycle [5.3.1] undecene element found in some natural compounds[44] (Scheme 18). Interestingly, for steric reasons, only the optically pure isomer leading to the naturally occurring configuration underwent a smooth cyclization in the presence of 3 mol% of carbene **8** in refluxing CH_2Cl_2.

Natural products having medium size ring (**8-11**) are very less especially nine membered lactones are categorized as rare species of organic molecules and few limited compounds have been isolated up to date. On going from eight membered to nine membered ring, conformational strain reduces to some extent, and significant difference observes when one of the ring members is second row element. Thus, an interesting challenge has been solved by Mülzer *et al*. in the total synthesis of epothilone B where RCM was proposed as key step for synthesis of crucial intermediate **81a**. Both the intermediates **81** and **84** were expected to give eight membered lactones. In both the cases, dimeric products through head to head cross-metathesis were isolated. In this case, RCM was unable to overcome the energy barrier in the transition state and therefore silicon tethering methods were adopted. As silicon atom has more polarisable soft d-orbital of bigger size and larger in atomic size, it can adopt bond distortion. Accordingly, the RCM of **86** proceeded smoothly and gave 9-membered ring almost quantitatively as a mixture of *Z/E* (5/1). A

significant reduction in yield was observed when catalyst was added at once instead of slow addition through syringe pump over 16 h. [45]

Scheme 19.



Systematic studies of substituent effects on RCM in the formation of nine member lactones (Scheme 20) were disclosed recently by Rosario Hernández-Galán and co workers.[46] The closure of the nonanolactone ring precursor of the botcinolide skeleton by RCM presents a double challenge. RCM reactions of the seven diene-esters (**88-94**) were performed using standard reaction conditions. It was observed that RCM were not compatible with the TBS containing substrates due to steric reason. It was noted, however, the RCM reaction were facile with vinylic, allylic and homoallylic methyl groups and with the presence of allylic and homoallylic oxygen functions. Nevertheless, these substituens have a dramatic effect on the stereochemical output. All the diene esters (**88, 89, 90 & 93**) that underwent cyclization rendered only one isomer, in sharp contrast with less functionalized diene

(**94**) which underwent cyclization to give a statistical mixture (1:1) of *cis* and *trans* isomers.

Scheme 20: *Effect of substituents on RCM in the synthesis of nonanolactones.*

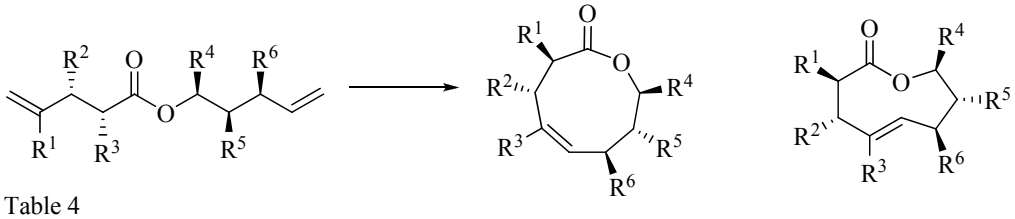
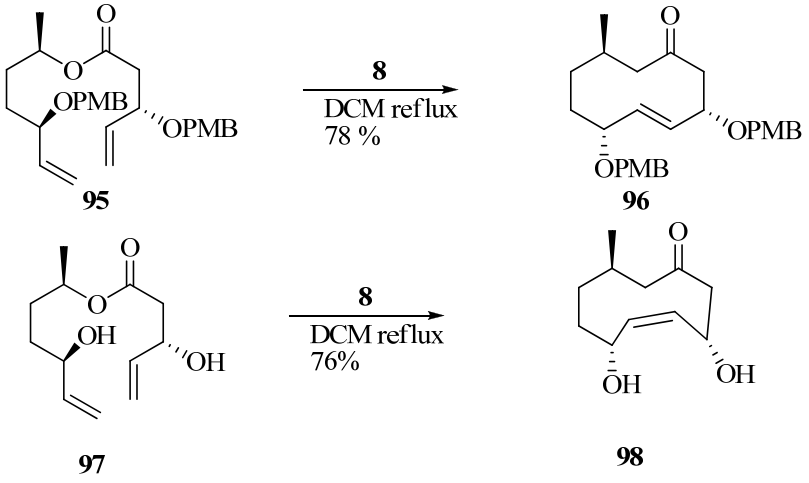


Table 4

Entry	Este	Yield (%)	Product
1	**88**	62	(*E*)-**88a :** R^1=R^3=Me; R^2=R^4=R^5=R^6 =H
2	**89**	58	(*Z*)-**89a :** R^1=R^3=Me; R^2= OAc; R^4=R^5=R^6 =H
3	**90**	46	(*Z*)-**90a :** R^1=R^3=Me; R^2= OBn; R^4=R^5=R^6 =H
4	**91**	n.r	(Z)-**91a :** R^1=R^3=Me; R^2= OTBDMS; R^4=R^5=R^6 =H
5	**92**	n.r	(Z)-**92a :** R^1=R^2=R^3=H; R^5= OTBDMS; R^4=R^6 =Me
6	**93**	71	(Z)-**93a :** R^1=R^2=R^3=H; R^5= OH; R^4=R^6 =Me
7	**94**	83	(*E:Z*=1:1)**:** R^1=R^2=R^4=R^5=R^6 =H; R^3=Me

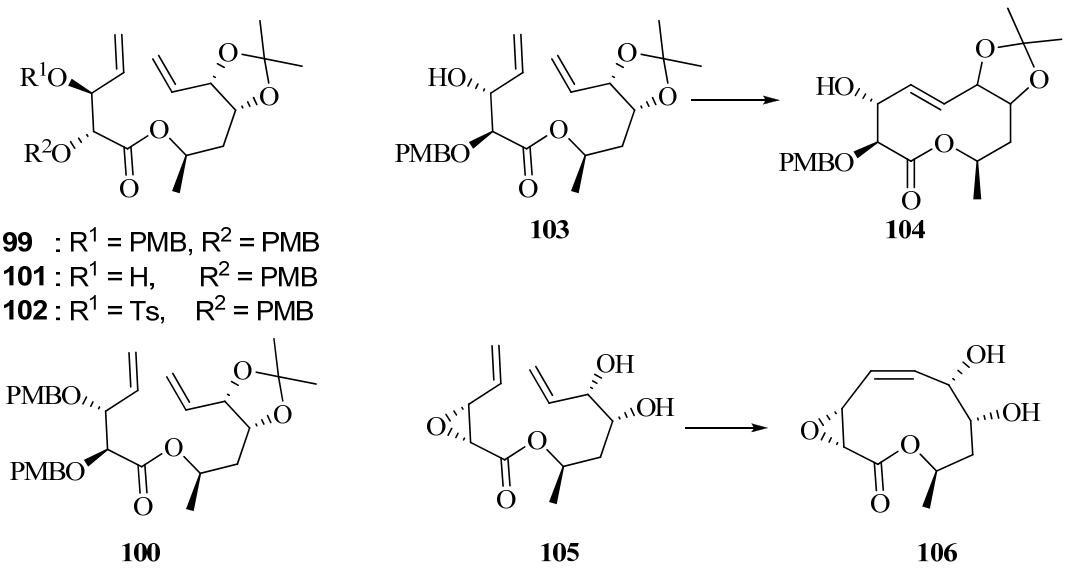
Although, it is an well established fact that the access of all ring sizes ≥5 are virtually possible, the problem of stereoselectivity limits the process for the ring size >7 as they easily adopt both the geometry *E* and *Z*. This effect becomes prominent in the case of 10-member ring. Experimental evidences revealed that the stereochemical outcome is purely thermodynamic phenomena and the second generation ruthenium catalysts (**8-11**) are more effective in this concern. Sometimes functional groups play crucial role in determining stereochemical output. Thus the RCM of PMB protected diene **95** afforded *trans* isomer whereas the diol **97** smoothly cyclised to *cis* cyclic diol **98** exclusively under same conditions[47] (Scheme 21).

Scheme 21.



A set of interesting results regarding the effect of functional groups around the participating double bonds and their stereochemistry disclosed recently from our group during total synthesis of multiplolide A.[3a] It has been observed that dienes **99**, **100**, **101** & **102** are poor substrates for RCM presumably due to the presence of bulky protecting groups. Surprisingly, a smooth conversion was observed in the case of **103** though the similar substrate **101** was inactive under same conditions. The effect of stereochemistry is still unknown. Highly functional group tolerance of Grubbs' catalyst revealed from the ring closure of the diene **105**, containing a labile functional group and free hydroxyl group. However, the stereochemical outcome was purely *cis* because of geometrical constrain imposed by oxiran group.

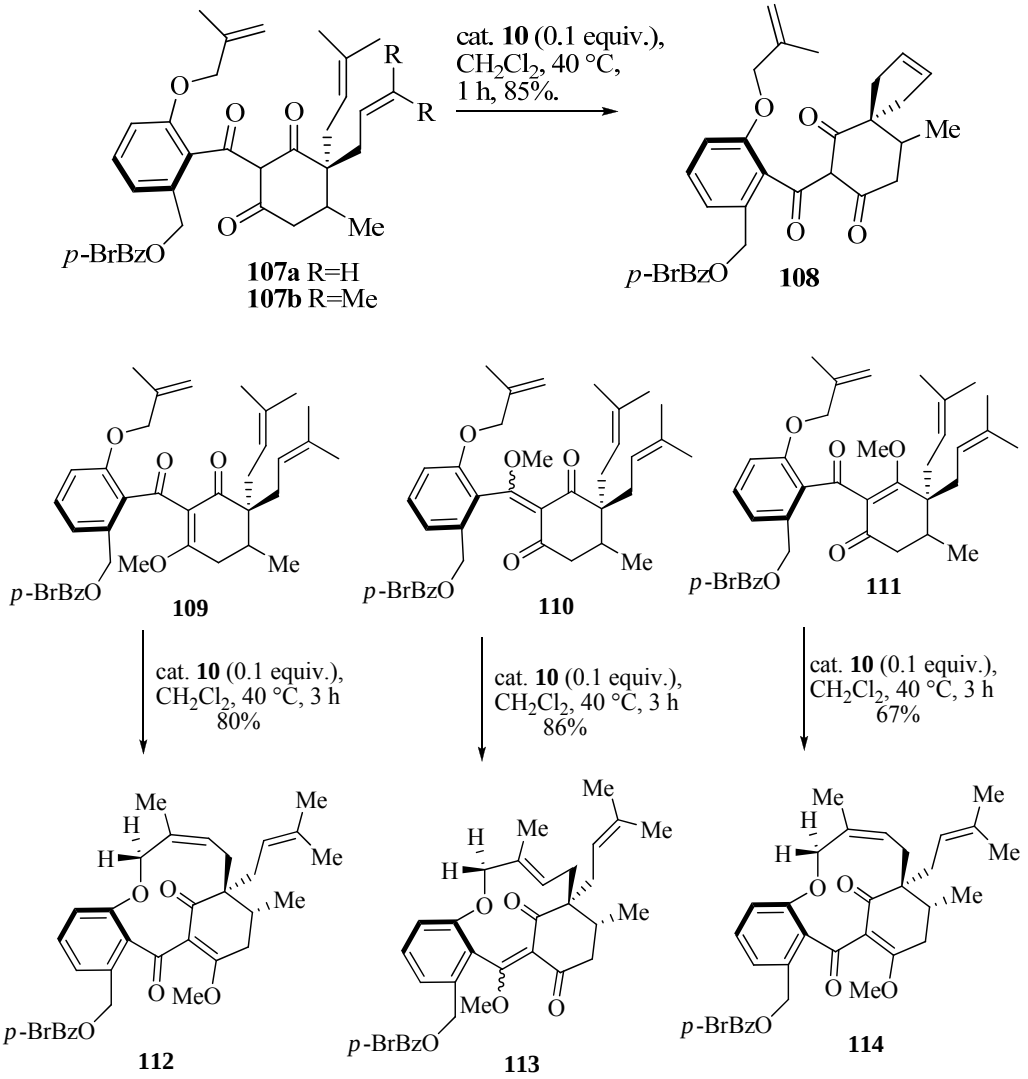
Scheme 21.



Application to eleven member carbo and heterocycles are rare and some times very low yielding. Moreover, *E/Z* isomerization which is common in metathesis becomes prominent due to flexibility of the ring and consequently both the isomers accommodate easily. One of the notable examples in this concern is the total synthesis of coleophomones B & C where olefin metathesis had proved itself a practicable ring-closing tool on a testing ground of the tricky 11-member highly strained and congested macrocycle coleophomone skeleton because so many other methods have already been failed[48] (Scheme 22). Initial study of RCM on unprotected tricarbonyl compound **107a** using catalyst **10** revealed that it rapidly converted to **108** as the only product of the reaction (in 85% yield), in preference to the desired macrocycle whereas very low activity were observed in case of fully substituted diene **107b**. One

of the possible explanations for very modest yield was the lack of stability due to the presence of unprotected tricarbonyl motif as structural unit. Interestingly, protection of one of the carbonyl to avoid unusual perturbation made ring closing very facile. Moreover the geometry of the double bond formed depends on placement of methyl ether. Thus ring closer of **109** and **111** produced *Z*-isomer but in the case of **110** it was *E* and hence ring closing metathesis proved to be an ultimate tool to access both the isomers coleophomones (B and C). These are the rare piece of examples where both the double bonds involved in RCM are highly branched.

Scheme 22: *Stereospecific key olefin Metathesis of regioisomeric vinylogous esters* **107**, **109**, *and* **110**.

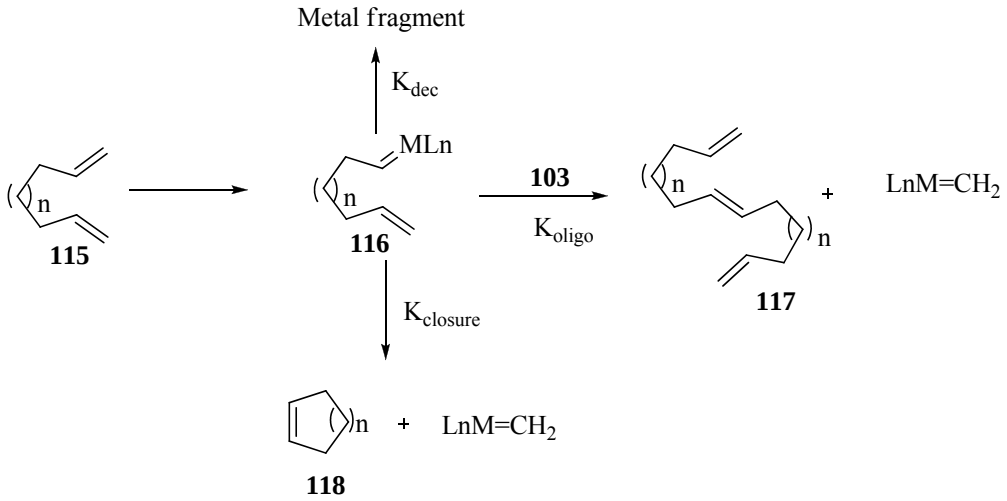


Macrocyclization Using RCM (> 11)

One of the major considerations for RCM in the synthesis of highly flexible large (>11) ring systems is the conformational predisposition of starting material for favorable intramolecular cyclization. However, it has been demonstrated that macrocyclization metathesis is highly efficient not only with substrates having suitable restrictions but also with substrates devoid of any rigorous conformational constraints by modification of the reaction conditions (usually by slow addition). Therefore, RCM is becoming recognized as one of the most straightforward and reliable methods for the formation of large ring systems and compares favorably to all current synthetic alternatives.

The key competing reactions are shown below (Scheme 23). The ratio of cyclic products **118** to oligomers **117** is determined by the ratio of $k_{closure}$ / k_{oligo}[**115**]. As the rate of closure decreases due to ring size and conformational effects, the competing reactions interfere with the desired reaction. The rate of oligomerization can be decreased by lowering the concentration of the diene or using slow addition of the substrate. Higher temperatures also favour ring closure. However, both of these factors, low concentrations and high temperature, which favor closure, also allow catalyst decomposition to start to compete with the desired reaction. As a result, closure of larger rings usually requires higher catalyst loading.

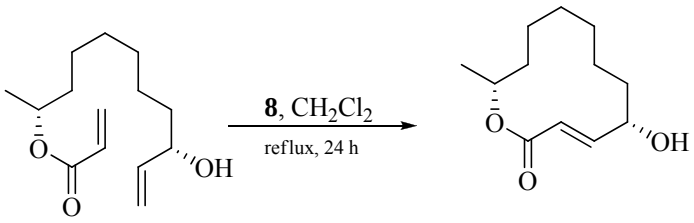
Scheme 23.



Recent discloser of RCM strategy for the synthesis of 11-*epi*-patulolide C is one such elegant example. Though the yield of cyclization was low (45%), the stereochemistry of the double bond was purely *E*[49] (Scheme 24). This result is in

sharp contrast to the statistical distribution of *cis/trans* isomer and indicate that the ring closer is purely thermodynamic controlled at least in this case.

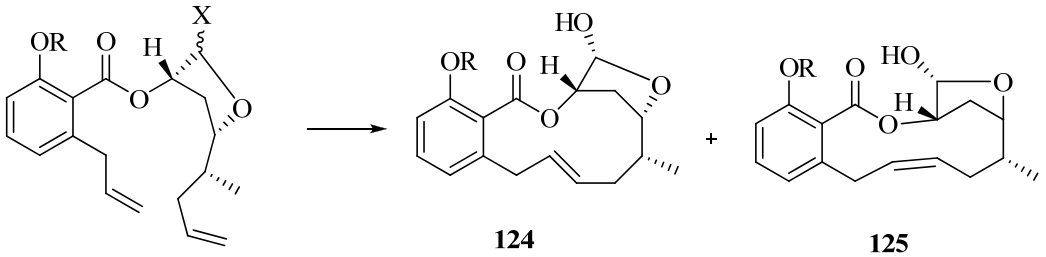
Scheme 24.



119 **120**

Another interesting result in synthesis of 12 member ring[50] were reported by Georg *et al*. Surprisingly, RCM reaction of lactone **121** failed to give any of the desired products. Whereas the RCM reaction of lactol **122** afforded desired product with *cis* isomer as major (Scheme 25; Table 5). But, when the phenolic hydroxyl was protected as TBDPS (**123**) ether, the stereochemical out come were almost reverse.

Scheme 25.



124 **125**

121 : R=H, X=O
122 : R=H, X=OH
123 : R=TBDPS, X=OH

Table 5

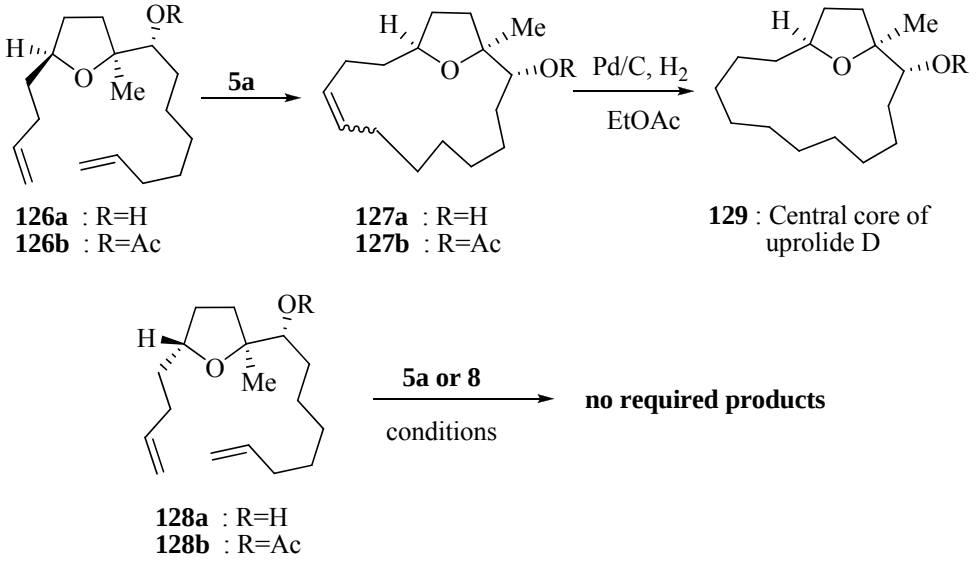
substrate	catalyst	Yield (%)	**124(%)**	**125 (%)**
121	**5a**	nr	-	-
122	**5a**	60	15	85
123	**5a**	60	70	30

It has been proposed that the introduction of the sterically demanding TBDPS protecting group apparently promotes a conformational change in the transition state of the RCM reaction that favors the formation of the *E*-alkene.

A simple and efficient strategy was established in our group for quick access of the central core uprolides D and E.[3b] The critical RCM reaction of **126a** with the catalyst **5a** was unsatisfactory and only traces of the macrocyclic derivative **127a** were isolated. Whereas corresponding acetate **126b** reacted with same catalyst and

produced the 13-membered macrocyclic derivative **115b** as an inseparable, statistical (1:1) mixture of *E/Z* in 67% yield.

Scheme 26.



However, RCM of *anti*-configured furan **128a** and its acetate **128b** was found to be problematic using either the **5a** or **8** Grubbs' catalysts under the various conditions (Scheme 26). This is presumably, due to the *trans* orientation of the participating double diene which make them unavailable for ring closing.

Scheme 27.

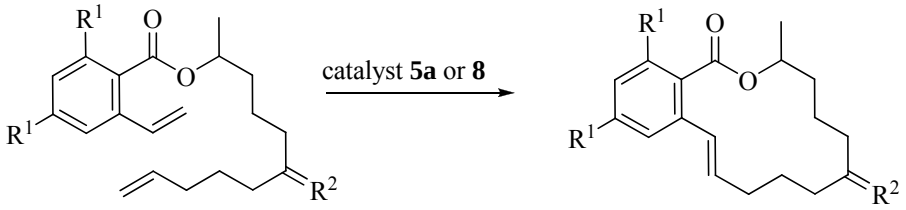


Table 6

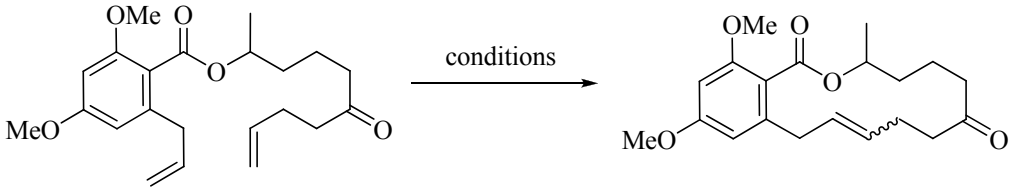
substrate	products	Yield (%)	Time (h)
130 : R^1 = H, R^2= H, H	**130a** : R^1 = H, R^2 = H, H	75	23
131 : R^1 = OMe, R^2=H, H	**131a** : R^1 = OMe, R^2 = H, H	93	15
132 : R^1 = OMe, R^2=O	**132a** : R^1 = OMe, R^2 = O	91	15
133 : R^1 = OMe, R^2 = OCH_2CH_2O	**131a** : R^1 = OMe, R^2 = OCH_2CH_2O	91	4

Note : all reactions are carried out at 80 ^oC using 5 mol% of complex **8**

With the development of new catalyst systems with greater reactivity make the transformation more effective, reliable and economical than the old methods for macrolactonisation which is clearly manifested by the work of Fürstner and co-

workers. In a short synthesis of 14-membered macrolide (*S*)-(−)-zearalenone,[51] it has been observed that the **5a** catalyst was unable to cyclise the diens **130-133** (Scheme 27). This has been achieved with the help of highly active second generation Ru-complex containing *N*-heterocyclic carbene ligand. Interestingly, presence of methoxy group on aromatic ring enhanced feasibility of RCM and further rate enhancement offered when keto functionality of the substrate **132** protected as cyclic ketal. Surprisingly, only (*E*)-isomer of the macrocyclic cycloalkene is formed in all cases (**130-133)** although one carbon shifting of double bond away from aromatic ring, **134** (Scheme 28) became good substrate for RCM for both the complex **5a** and **8** as well as it gave a mixture of a *cis* and *trans* isomers. The exclusive formation of *trans* isomer in these styrene systems is unknown.

Scheme 28.



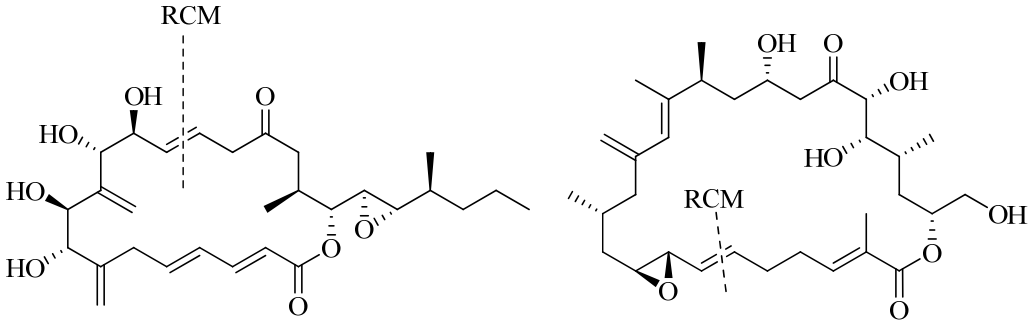
134 **135**

Table 7

Catalyst	Yield (%)	(E/Z) ratio
5a	73	2.4/1
8	85	8/1

The ratio *E/Z* (Table7) is indirect proof of higher isomerizing tendency of **8** to give thermodynamically favored *E*-configured macrocyclic lactone.

Scheme 29.

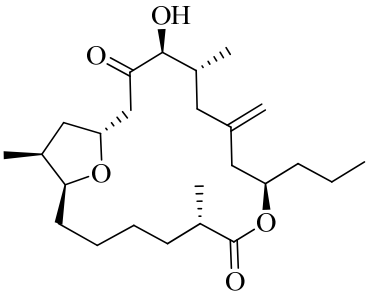


Kobayashi's proposed structure of Amphidinolide-A

136

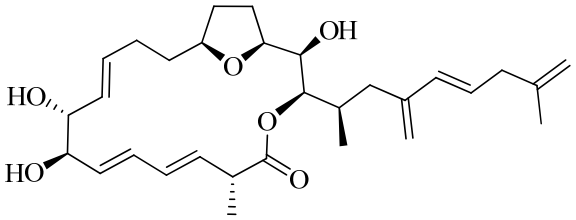
Amphidinolide H1

137



Amphidinolide T1

139



Amphidinolide E

140

Among the other powerful applications of RCM in macocylization, the synthesis of flexible and densely functionalized amphidinolides are noteworthy. In this context the successful synthesis of amphidinolide A[52a], amphidinolide H[52b], amphidinolide T[52c], amphidinolide E[52d], amphidinolide Y[52e] and amphidinolide W[52f] are remarkable (Scheme 29).

Ring closing metathesis is one of mildest processes for cyclisation through carbon-carbon bond formation. It become an well known tool in the synthetic community due to its simplicity from the practical point of view and extraordinary potential for transforming acyclic diene into unsaturated cyclic systems by using newly developed ruthenium and molybdenum carbene complexes. Discovery of these highly active catalysts has addressed some of the early issues such as functional tolerance reactivity towards olefin and discovered numerous aspects of the metathesis chemistry. Although the method is widely applicable and plethora of reports is available in this area, there is no rule for catalyst selection. Moreover, slight variation in the substrates gives different results on stereochemical output as well as the reactivity. However, it is quite reasonable to expect realistic solutions of above mentioned matters from its current progress in this area, through either selective catalyst development or optimized reaction conditions including choice of proper substrates.

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Chapter 2

Studies Toward the Total synthesis of Aspercyclide A, B and C

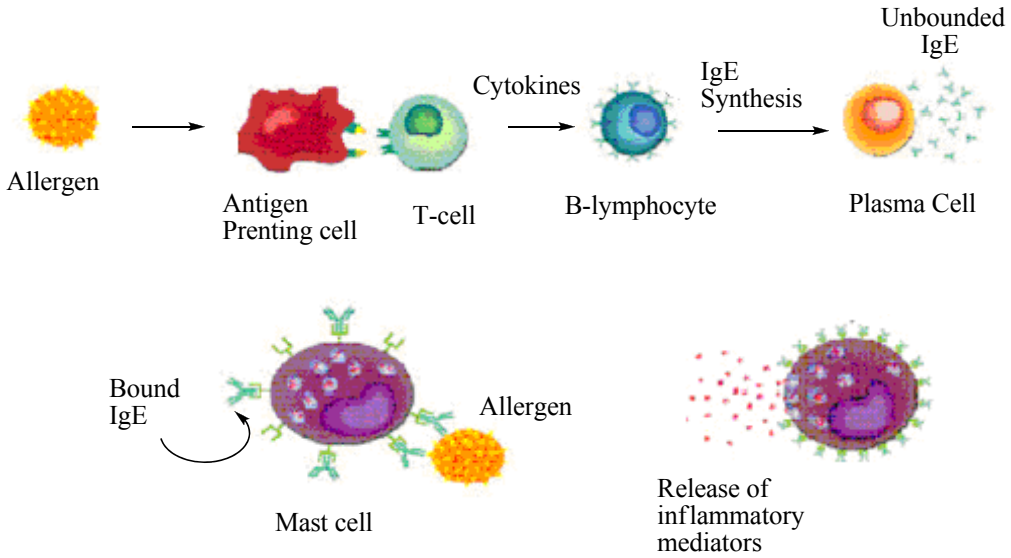
Chapter 2; Section I

Ring Closing Metathesis Approach Toward the Total Synthesis of Aspercyclide A, B and C

Introduction

Helminth infections and allergic diseases are due to high level antigen specific antibody IgE as well as the total IgE, though its presence is only in mammalians with lowest concentration compared to other isotypes Immunoglobulin IgA, IgD, IgG and IgM[1]. IgE may involve in disease in three ways; firstly IgE bound to receptors on the antigen-presenting cells, such as low-affinity IgE receptors (CD23) on B cells and to high-affinity IgE receptors (Fc_eRI) on Langerhans' cells and monocytes, can enhance antigen internalization and presentation to T cells, resulting in continuous activation of the immune system.[2] Second, IgE may mediate killing of the invading helminth and host cell damage by acting as a ligand for antibody-dependent cell-mediated cytotoxicity (ADCC) by macrophages and other immune cells.[3] But the central features of IgE are an anaphylactic and immediate hypersensitivity due to the IgE dependent activation of inflammatory cells. When an allergic individual is re-exposed to an allergen, cross-linking to IgE bound on the mast cells may occur (Figure 1).

Figure 1: *Immuno responses to allergen.*



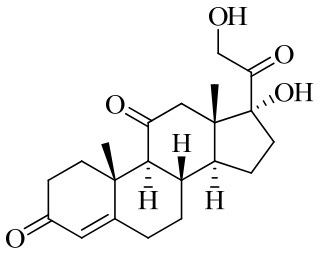
As a result, mast cells release chemical mediators such as histamine, prostaglandins and leukotrienes (Figure1). These chemical mediators can cause inflammatory responses in the body. These inflammatory responses have been linked to asthma signs and symptoms such as bronchial constriction, coughing and wheezing which causes chronic allergic inflammations. Therefore, IgE is an important therapeutic

target for the treatment of allergic disorders and small molecules that bind to the high-affinity IgE receptor prevent IgE binding and release of inflammatory compounds, thus preventing symptoms associated with allergic diseases. Consequently such molecules that target the high-affinity receptor and block IgE binding may be efficient in treating asthma.

Treatment of allergy

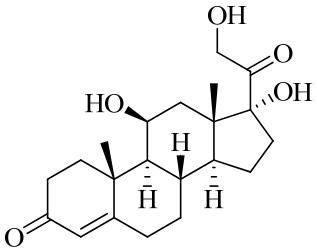
Traditionally treatment and management of allergies (atopy) involved simply avoiding the allergen in question or otherwise reducing exposure. While avoidance may help to reduce symptoms and avoid life-threatening anaphylaxis, it is difficult to achieve for those with pollen or similar air-borne allergies. Several small molecule receptor antagonists for a number of inflammatory mediators have been developed to block the action of allergic mediators, or to prevent activation of cells and degranulation processes. These include antihistamines[4], for example cortisone, dexamethasone, hydrocortisone, epinephrine (adrenaline), theophylline and cromolyn sodium. Anti-leukotrienes, such as montelukast[5a] (singulair) or zafirlukast[5b] (accolate), are commonly used for treatment of atopic syndroms. Anti-cholinergics, decongestants, mast cell stabilizers, and other compounds thought to impair eosinophil chemotaxis, are also commonly used. These drugs help to alleviate the symptoms of allergy, and are imperative in the recovery of acute anaphylaxis, but play a little role in chronic treatment of allergic disorders.

Figure 2: *Anti-inflammatory drugs.*



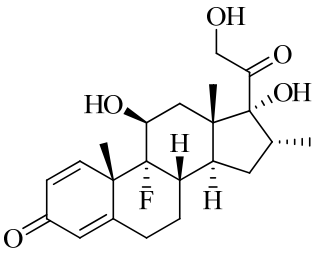
Cortisone

1



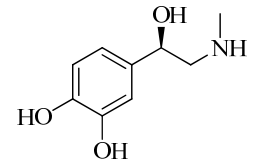
Cortisol

2



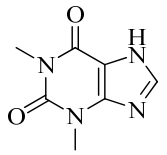
Dexamethasone

3



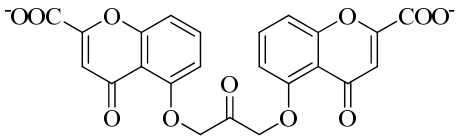
Epinephrine (adrenaline)

4



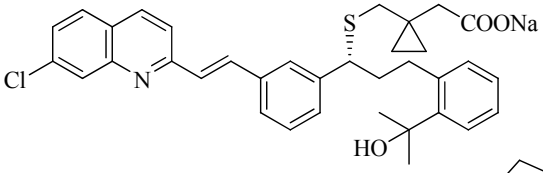
Theophylline

5



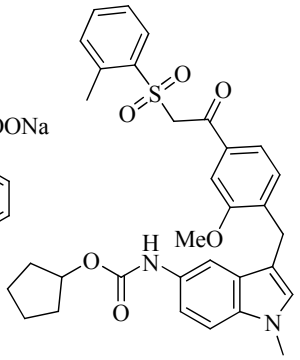
Cromoglicate

6



montelukast sodium

7



Zafirlukast

8

Drugs like anti-histamines, anti-leucotrienes trap the inflammatory chemicals that released in the late stages of inflammation and make airway muscle smooth and can not stop the process of releasing the same. Therefore, these treatments are fairly broad in their action, play little role in chronic treatment of allergic disorders and have so many unpleasant side effects. They may also inhibit important protective responses in the immune systems.

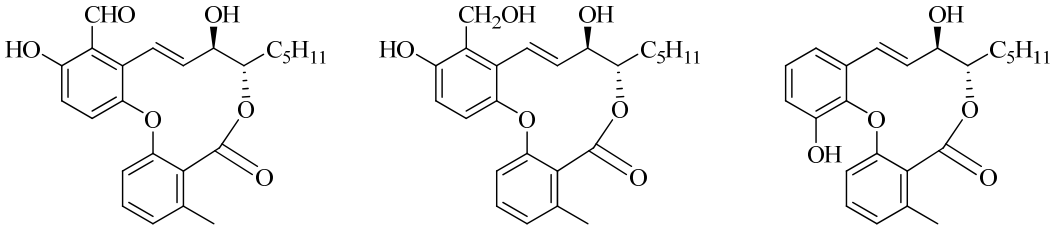
Another effective way of the treatment of hypersensitivity of type-I is blocking of the inflammatory mediator IgE or the receptor present on the inflammatory cells. Although the allergic mediator IgE has been discovered long back, structure of IgE and its interaction with receptors opened recently.[6] As a result, new generation of drugs (such as omalizumab, a monoclonal antibody) on the basis of interaction of IgE with receptor FcεRI came into play. These drugs recognize IgE not bound to its receptor and are used to neutralize existing IgE and reduction in surface bound IgE on FcεRI-bearing cells limits the degree of release of mediators of the allergic response. Due to the lack of sufficient information on the long-term effectiveness and side effects of the drug, omalizumab treatment is not yet very common, and can be expensive. Moreover, recent research suggested that IgE have significant role in immune system for finding cancer cells and use of this drug may increase the chance of contracting malignancy of different types specially cancer.[7]

It may be possible to design treatments cheaper than monoclonal antibodies (for instance, small molecule drugs) that target the high-affinity receptor and block IgE binding and thus effective in treating asthma, allergic rhinitis, and other forms of atopy. While anti-IgE antibodies have been developed as potent IgE antagonists, the search for small molecule antagonists has not been successful except for the discovery of β-hairpin[8a] and zeta (IC_{50} = 0.032lM) peptides.[8b] Therefore continuous searching of potent antagonist for inflammatory mediators with reduced side effect and greater efficiency is currently a potential ground in the field of drug discovery.

Isolation of new small molecule antagonists Aspercyclides

For many years, traditional pharmacognosy was focused on the medicinally important natural sources. In this context secondary metabolite from microorganisms have been attracted many natural product chemists. Screening of natural product extracts of microbial origin using a Myeloma α1/α2-IgE receptor binding ELISA assay led to the identification of a fungal extract with the requisite activity and bioassay-guided fractionation of the extract led to the isolation of three novel compounds named aspercyclide A (**9**), B (**10**), and C (**11**).[9] Aspercyclide A inhibited the IgE binding to its receptor by an IC_{50} value of 200μM. whereas other two compounds were much less active (IC_{50} > 200μM) suggesting that the aldehyde group of aspercyclide-A plays a prominent role in the binding activity. These are the first isolated small molecules which show inhibitory activities of such protein-protein interaction. Therefore, such small molecule antagonists like aspercyclides which can mimic the action of edogenous ligands, are very important to establish clinical significance of IgE-binding activity and developed a potential ground for the further improvement of newer anti-allergic drugs with more specific in their action.

Figure 3.



Aspercyclide A — **9**

Aspercyclide B — **10**

Aspercyclide C — **11**

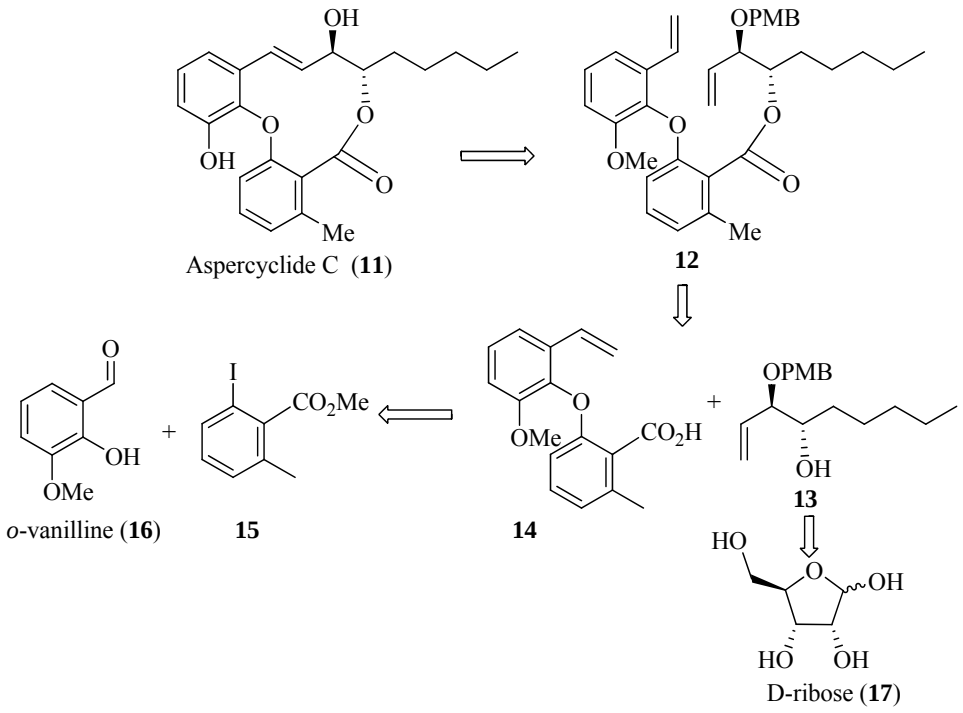
In view of growing pharmaceuticals as well as clinical importance of aspercyclides, it is necessary to synthesize in laboratory for further study in order to develop simple molecules with better reactivity. Besides their immense significance on pharmacological as well as clinical ground, aspercyclides are also challenging synthetic target due to the presence of highly strained 11-member lactone and complex molecular architecture. We intend to synthesize aspercyclides (**9**, **10** & **11**) using a common strategy applicable for all isomers using the advantage of ring closing metathesis as key cyclization method.

Present work

Retrosynthetic disconnection

Aspercyclide C (**11**), being a simplest member among the others of this family was a choice for initial studies to execute our strategy. Detailed analysis of aspercyclide C indicated that it has macro-lactones of 11-membered with densely functionalized biaryl ether moiety as an integral part. Featuring RCM[10] as the key macrocycle building reaction, **11** was disconnected into two key intermediates **13** and **14** through diene **12**. After stereochemical comparison, the D-ribose (**17**) having required two contiguous stereocenters at C2 and C3 was selected as a starting point for key coupling partner **13**. A PMB protection of allyic-OH present in **13** was decided on anticipating a global deprotection at the end of the synthesis. Ullmann coupling of *o*-vanillin (**16**) and iodobenzoate (**15**) followed by one carbon Wittig homologation and saponification should provide the requisite biaryl acid unit **14**. A brief retrosynthetic analysis is depicted in figure 4.

Figure 4: *Retrosynthetic analysis of aspercyclide C.*



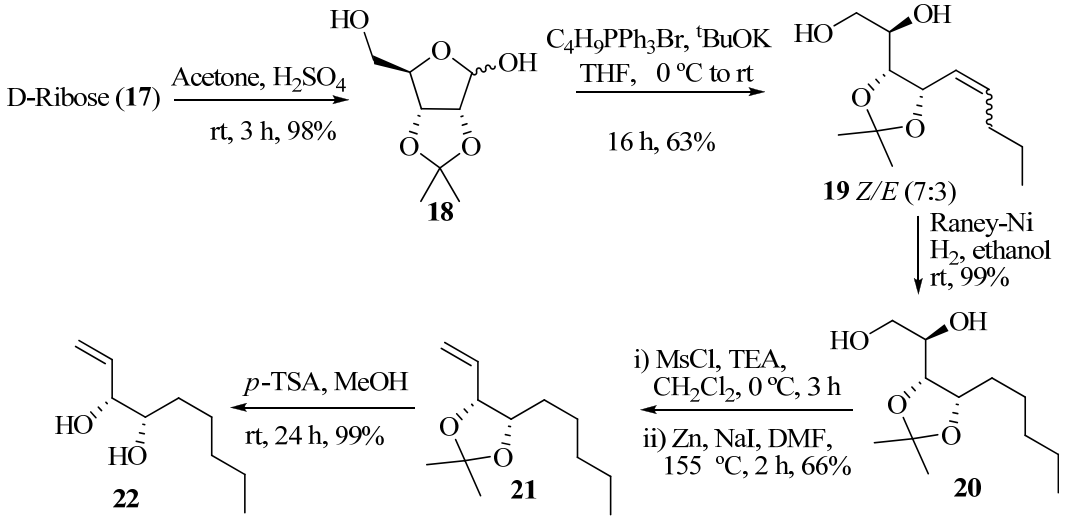
Synthesis of the alcohol fragment 13

According to the proposed scheme, D-ribose (**17**) was converted to monoacetonide **18** following reported procedure[11] and product obtained was an

anomeric mixture. After substantial optimization using a variety of bases, the 4-carbon Wittig homologation of ribose acetonide **18** was found to be facile with ^{t}BuOK and provided 7:3 *Z*/*E* mixture (on the basis of ^{1}H NMR) of olefins (**19**) in favour of *cis* isomer. Prolonged reaction time was required to get complete conversion. Hydrogenation of the resulted olefin using Raney-Ni in ethanol afforded the diol **20** which was fully characterized by its spectroscopic data analysis. In ^{1}H NMR spectrum, the characteristic singlets of three proton each at δ 1.33 and 1.40 were observed due to the acetonide methyl groups and a clean triplet at δ 0.90 (*J* = 6.5 Hz, 3H) was assigned to the terminal methyl group of the side chain. Other signals in both the spectra were according to the assigned structure **20**.

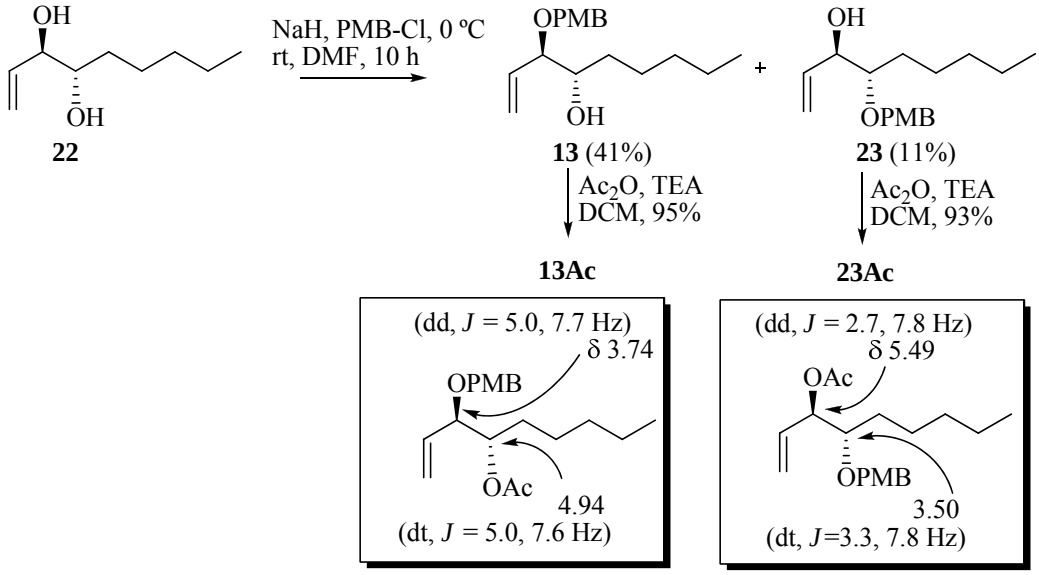
Treatment of the diol **20** with MsCl in the presence of excess TEA in dichloromethane followed by Zn-mediated elimination[12] of resulted crude dimesylate gave the olefin **21**. Presence of olefinic signals at δ 5.16-5.30 clearly indicated the formation of required compound **21**. The labile acetonide was subjected to acid catalyzed hydrolysis to afford the diol **22** in 61% over the three steps (Scheme 1). Compound **22** was fully characterized. The terminal olefinic protons resonated at δ 5.27 (*J* = 1.4, 10.4 Hz) and 5.33 (*J* = 1.3, 17.1 Hz) with splitting pattern doublet of a triplet. A clear triplet with coupling constant 6.4 Hz at δ 0.98 equivalent of three protons was attributed to the terminal methyl group of the aliphatic chain present in compound **22**. Internal olefinic proton resonated at δ 5.92 as a fine ddd (*J* = 6.4, 10.4, 17.1 Hz). Other peaks in both NMR spectra and the result of elemental analysis were in excellent agreement with the structure of **22**.

Scheme1: *Synthesis of diol* **22**.



Allylic-OH protection of diol **22** was achieved using PMB-Cl and NaH in DMF. The regioselectivity was poor, resulted with a mixture of the key coupling partner **13** along with other regiomer **23**. Both isomers were separable by column chromatography and position of the protecting group in **13** and **23** were determined unambiguously with the help of spectral and analytical data of the corresponding acetates **13Ac** and **23Ac**, respectively. Because of anisotopic effect, shifting of resonating frequency of acetoxy C-H proton was observed towards downfield in both the cases when it was protected as acetate. ^{1}H NMR of compound **13Ac** was showing a signal at δ 4.94 as a triplet of a doublet (J = 5.0, 7.6 Hz) which was assigned to be acetoxy C-H proton. But acetoxy C-H proton of **23Ac** appeared at δ 5.49 as doublet of a doublet. From these observations, position of the acetate was established and hence the free hydroxyl present in **13** and **23**.

Scheme 2: *Synthesis and determination of the position of PMB of* **13**.

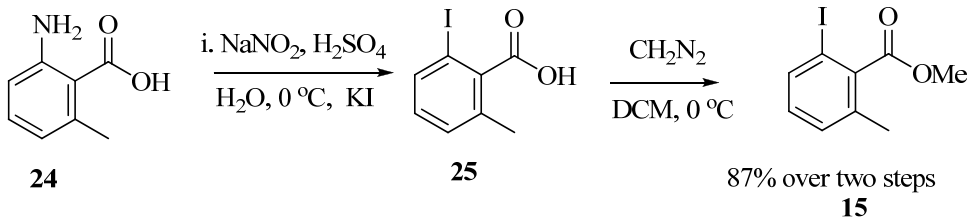


Synthesis of the fragment 14

Once the synthesis of the crucial intermediate **13** completed, we shifted our attention to the synthesis of biaryl ether containing acid **14**. Proposed synthesis commenced with commercially available materials *o*-vanillin (**16**) and 2-amino-6-methyl benzoic acid (**24**). Diazotization of the amine **24** followed by *in situ* replacement with iodide gave iodobenzoic acid derivative **25**. The previously synthesised[13] carboxylic acid was protected as its methyl ester using diazomethane. Compound **15** was obtained as light yellow liquid and structure was confirmed on the

basis of ^{1}H NMR, ^{13}C NMR, IR, elemental analysis and mass spectrometric analysis. For instance, the methyl group of ester resonated at δ 3.95 as a sharp singlet while the ring methyl appeared at δ 2.35 as singlet.

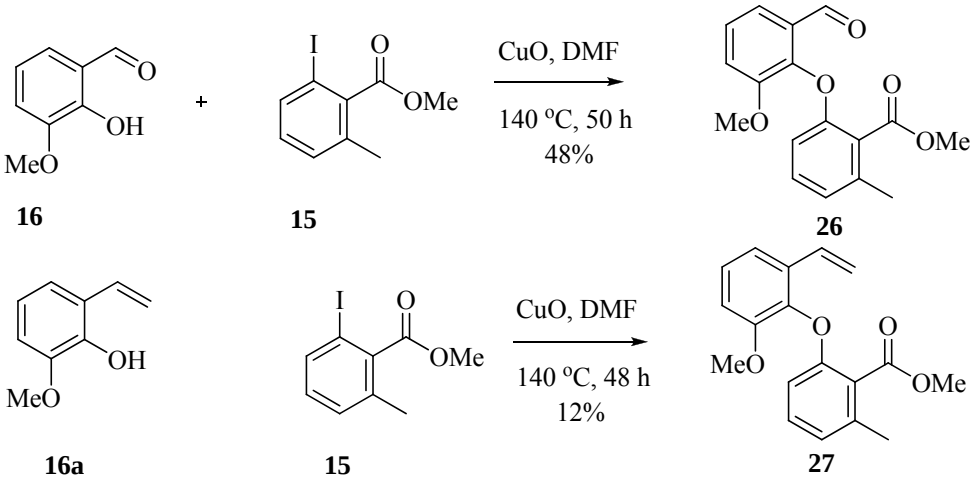
Scheme 3.



24 **25** 87% over two steps **15**

Our initial observation on copper mediated Ullmann coupling[14] between **16a** and **15** were unsatisfactory and only poor yield (12%) of required compound **27** was detected using copper oxide in DMF at 150 °C. Interestingly, when *o*-vanillin was used instead of **16a** as nucleophilic counterpart in Ullmann coupling, a smooth conversion was observed with moderate yield (48%) of the biaryl aldehyde **26** by using same condition. This is presumably, due to the initial chelation[15] of copper (II) with bidentated *o*-vanillin. The structure of compound **26** was fully analyzed by ^{1}H and ^{13}C NMR spectroscopic and elemental analysis. For example, in its ^{1}H NMR spectrum, three singlets of three protons each appeared at δ 2.37, 3.78 and 3.94 were assigned to aromatic methyl, aromatic methoxy and ester methyl respectively. One clear doublet at δ 10.30 with small coupling constant (J = 0.8 Hz, long range coupling with aromatic ring proton) attributed to the aldehyde proton, while rest of the spectrum was in complete agreement with the assigned structure.

Scheme 4.

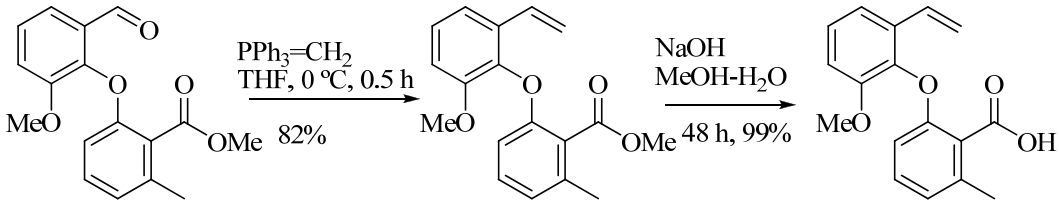


16 **15** **26**

16a **15** **27**

Turning to the requisite biarylether **14**, one carbon homologation of **26** using methyltriphenylphosphonium iodide and *n*-BuLi in THF at −78 °C resulted in the formation of the alkene **27**. The later compound **27** was then subjected to the hydrolysis using NaOH in MeOH-H_2O to obtain the second coupling partner **14 (**Scheme 5**)**. Presence of absorption frequency at 1740 & 3343 cm^{-1} in IR spectrum and disappearance of signal due to methoxy ester in ^1H NMR were clear indication of carboxylic functionality present in **14**. The carboxylic acid carbonyl appeared at δ 169.9 in ^{13}C NMR spectrum. In the ^1H NMR, two singlets at δ 2.54 & 3.77 of three protons each due to aromatic methyl and methoxy group other peaks were according to the assigned structure **14**. The structure of **14** was further confirmed by mass spectroscopy and elemental analysis.

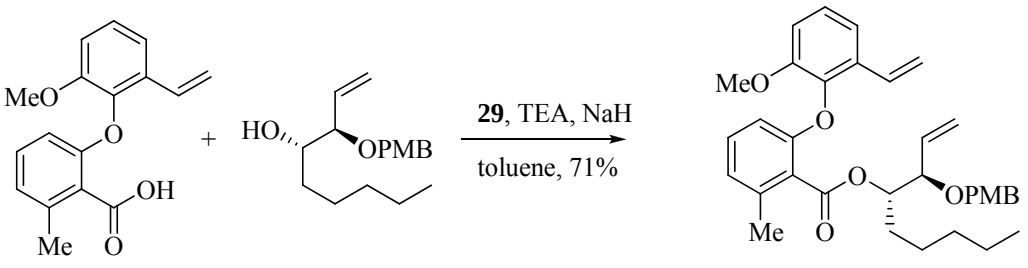
Scheme 5.



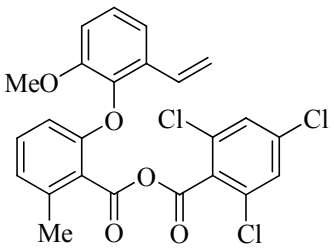
26 **27** **14**

Having synthesized the two coupling partners **13** and **14**, we proceeded further with their coupling followed by ring closing metathesis. There are several observations regarding the coupling of **13** and **14** that deserve mention. Coupling using standard reagents like DCC[16], EDCI[17] met with failure results. In case of Yamaguchi reagent, [18] we obtained only the mixed anhydride **28** in quantitative yields after prolong refluxing time and conditions.

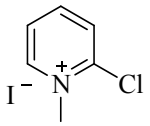
Scheme 6.



13 **14** **12**



28

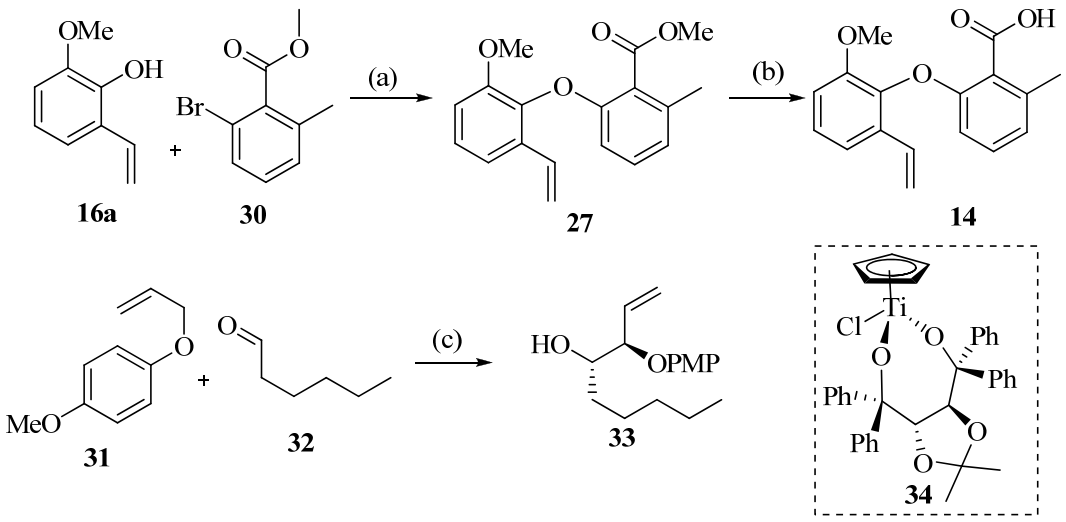


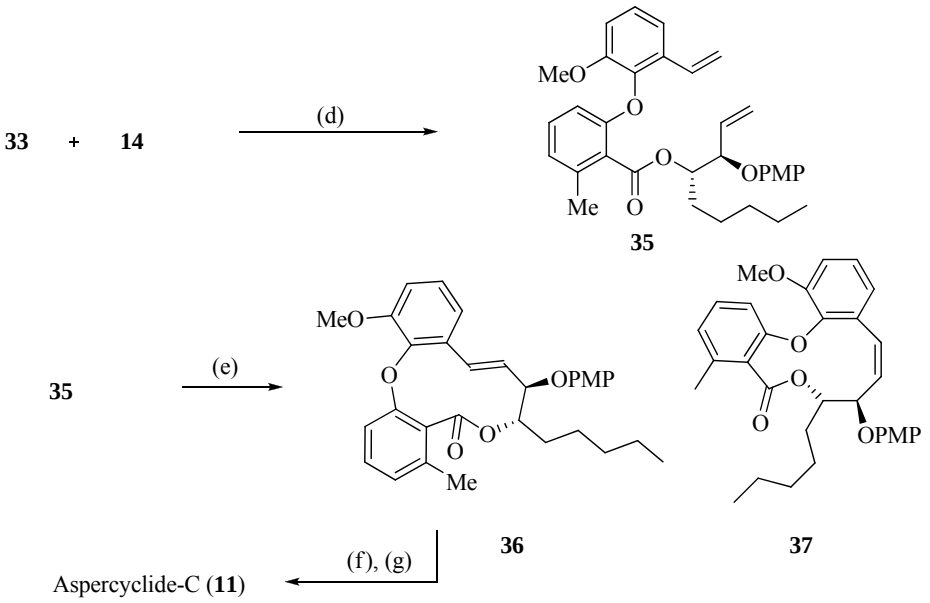
Mukaiyama reagents

29

When we were at this stage, a remarkable concise asymmetric synthesis of aspercyclide-C was published by Fürstner and co-workers[19] using RCM as cyclizing method. The hydroxy fragment **33** was prepared from allyl aryl ether **31** and hexanal **32** via *anti*-selective Duthaler–Hafner oxy-allylation[20] reaction (Scheme 7) using chiral titanium complex **34**, while the acid fragment **14** was prepared from **16a** and aromatic bromo compound **30** *via* CuO-mediated Ullmann coupling.[14] Finally, the two fragments were coupled using Mukaiyama[21] reagent followed by ring closing metathesis to access the target molecule **36**. Both *trans* (**36**) and *cis* (**37**) isomers were isolated in ratio of 5:1 in favour of *trans* geometry. Finally, synthesis was completed in a sequence of two steps for deprotection of PMP and aromatic methoxy group. It has been observed that the final deprotection which was expected to be very simple turned out to be difficult and only modest yield was isolated.

Scheme 7: *Fürstner's synthesis of aspercyclide C.*

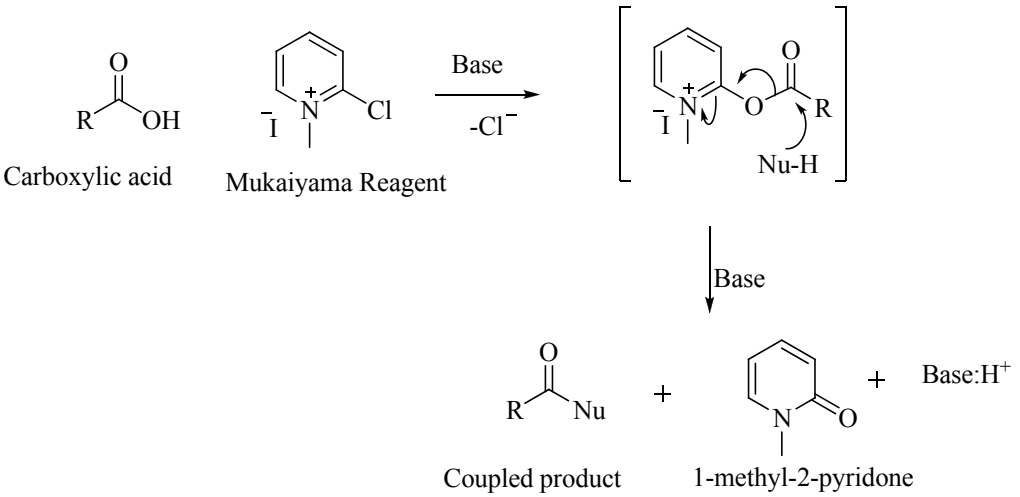




Reagents and conditions: (a) CuO, K_2CO_3, pyridine, 130 ^oC, 55%; (b) aq. NaOH, MeOH, then aq. HCl quant; (c) *sec*-BuLi, then complex **34**, hexanal, THF/Et_2O, −78 ^oC, 69%; (d) *N*-methy l-2-chloropyridinium iodide, Et_3N, MeCN, reflux, 82%; (e) Grubbs' 2nd gen. cat**.,** toluene, 69 % (f) CAN, MeCN/H_2O, 0 ^oC, 67%; (g) BBr_3, CH_2Cl_2, -78 ^oC to 0 ^oC, 40%.

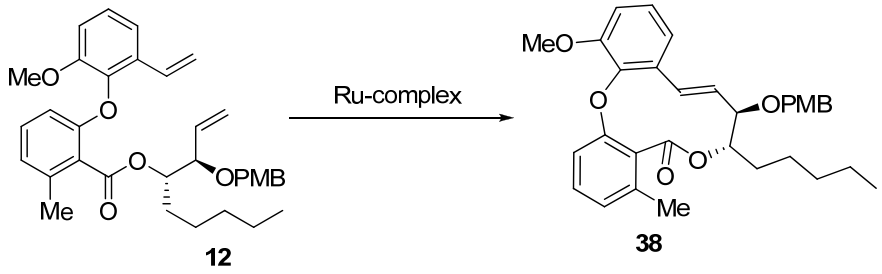
In continuation of our endeavour, initial experiments to couple **13** and **14** under the conditions reported by Fürstner and co-workers using Mukiyama reagent[21] **29** met with poor yields. Notably, when 1 eq. NaH was added after initial salt formation, the reaction proceeded smoothly and provided the key diene ester **12** in 71% yield (Scheme 6). The TEA was found to be inefficient to complete the reaction. The effect of NaH at the last step is quite easy to predict from the mechanism of the reaction. Mechanism consists initial and rapid displacement of active chloride attached at 2-position of the pyridinium salt (**29**) with carboxylate group. The second step involves an addition elimination sequence at carbonyl carbon on the salt formed in the 1st step resulting in a nucleophilic displacement of pyridine nucleus as *N*-methy-2-pyridone (Scheme 8). The reagent can be used as an activator for inter or intra molecular coupling of acid-alcohol as well as acid-amine functionality. Depending upon the reactivity of substrate, wide range of solvent and temperature ranging from rt to refluxing condition can be used. Moreover, it can be used for sterically hindered substrate which is most attractive aspect in terms of practical point of view.

Scheme 8: *Mechanism of Mukaiyama reagent mediated carboxylic acid activation.*



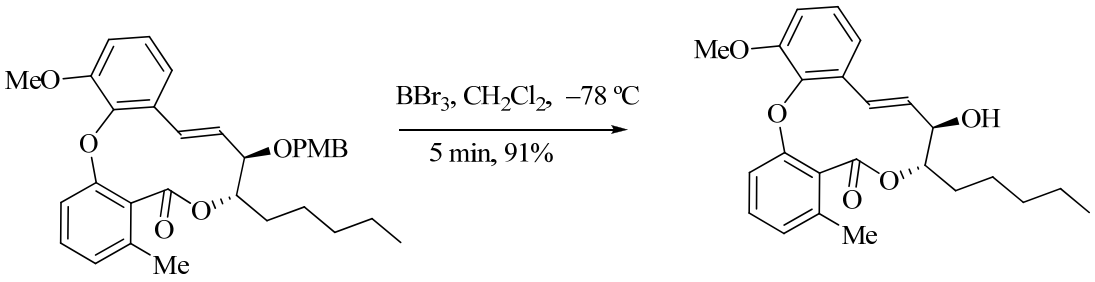
Considering the observations of Fürstner and co-workers,[19] the RCM of **12** was carried out in toluene at 120 °C by adding the Grubbs' 2nd gen. catalyst using a syringe pump over 1 h. Under this modified conditions, we observed exclusively *E*-configured macrocyclic lactone **38**.

Scheme 9: *Ring closing metathesis.*



Disappearance of signals corresponding to the terminal olefinic proton in ^{1}H NMR confirmed the completion of the ring closing reaction. The *E*-configuration of the newly formed internal olefin was assigned from the large coupling constant (16.0 Hz) noticed in the ^{1}H NMR spectrum of **38**. The acyloxy C-H proton resonated at δ 5.29 as doublet of a triplet (J = 2.4, 9.6 Hz), providing a clear indication of lactone functionality present in **38.** Appearance of an absorption in IR at 1735 cm^{-1} was an additional support in favour of lactone in **38**. Mass and analytical data of compound **38** were in favour of assigned structure.

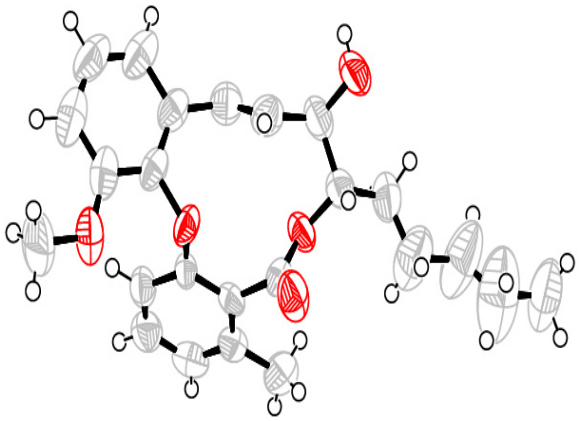
Scheme 10.



38 **39**

As intended, the final removal of aryl *O*-methyl and PMB protecting groups was attempted using excess BBr_3. Our initial observation of disappearance of compound **38** (monitored by TLC) within 5 min after addition of BBr_3 at –78 °C, prompted to quench the reaction and this led us to isolate **39** in 91% yield resulting in the selective PMB deprotection alone[22]. The spectral and analytical data of compound **39** were in excellent agreement with the assigned structure. The structure was further substantiated by a single crystal *X*-ray structure (Scheme 5). Except the value of optical rotation which was quite high, ^{1}H NMR, ^{13}C NMR and IR data exactly matched with the reported data.[19]

Figure 5: *ORTEP diagram of compound* **39.**

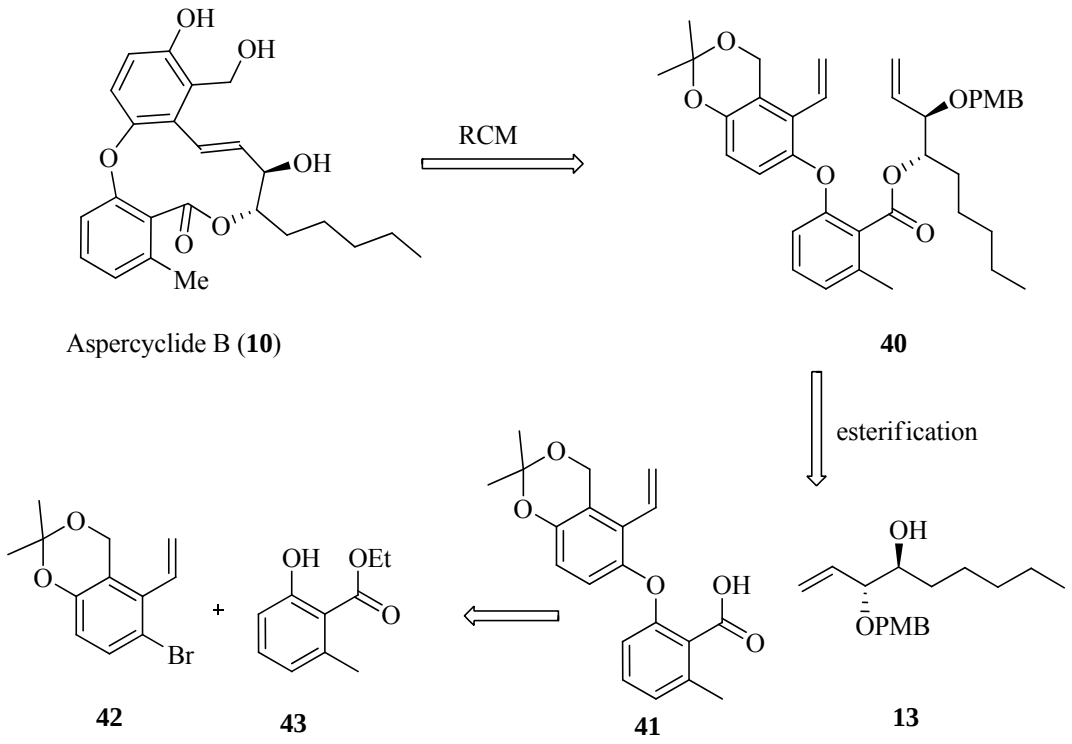


At this end to reach complete deprotection, the reaction mixture warmed to the 0 °C over 7 h but a very complex mixture was obtained from which isolation of **10** was found to be futile. Successful synthesis of the advanced intermediate **13** followed by RCM of **12** and subsequent deprotection of PMB ether represented a formal synthesis of aspercyclide C, as Fürstner reported the conversion of **39** to aspercyclide C using boron trifluoride.

Studies towards the total synthesis of Aspercyclide A and B

After successful ring closing of aspercyclide C ring system we shifted our efforts to apply similar strategy for accessing aspercyclide A & B. Keeping in mind ring closing metathesis as key cyclization step, aspercyclide B (**10**) could be disconnected into densely functionalized diaryl ether containing aromatic acid **41** and an aliphatic alcohol **13** which is used for the synthesis of aspercyclide C. Considering the similarity in substitution pattern of aromatic parts in acid **41,** it could be disconnected to a simple and common starting material **43** which is known in literature.[23]

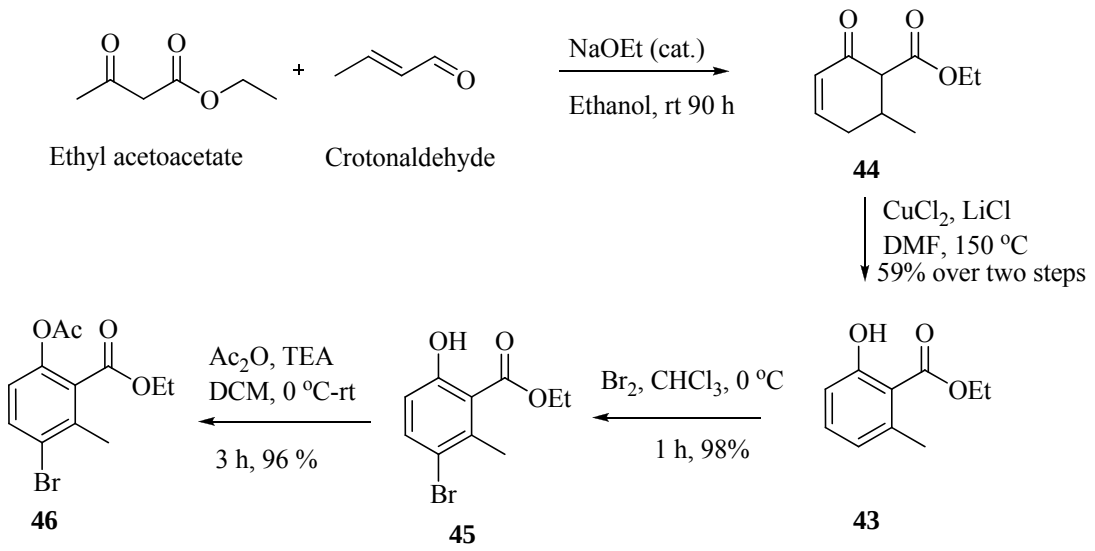
Figure 6: *Retrosynthetic analysis of aspercyclide B.*



Synthesis of the aromatic acid fragment 42

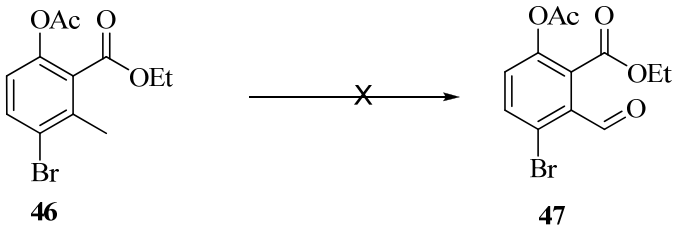
Starting material **43** was synthesized from commercially available, inexpensive ethyl acetoacetate (EAA) and crotonaldehyde following the reported procedure[23] with slight modification. The initial condensation of EAA and crotonaldehyde was performed in presence of catalytic sodium ethoxide in ethanol at ambient temperature. Resulted cyclohexenone derivative **44** was oxidized with copper (II) chloride to get our building block **43**. The spectroscopic and analytical data were exactly matched with reported one.

Scheme 11.



The selective nuclear bromination of **43** was achieved with molecular bromine at 0 ^{o}C in chloroform, and the compound **45** was only isolated product in excellent yield which was used directly for the next step without further column purification. The *para* orientation of the bromine atom with respect to the phenolic OH at aromatic ring was evident from ^{1}H NMR, showing a shielded aromatic C-H peak at δ 6.75 as a doublet with *ortho* coupling (J = 8.9 Hz). The shielding is due to the free phenolic hydroxyl functionality. The next step according to our proposed scheme was the oxofuntionalization at the methyl group attached to the aromatic ring of **45 (**Scheme 11). This could be achieved by direct oxidation of the aromatic methyl group which was well documented in literature.[24] For that purpose the phenolic hydroxyl group of **45** was acetylated to avoid unwanted ring oxidation under oxidative conditions. All attempted conditions to get **47** (Scheme 12) directly from **46** met with failure results which led us to look for a viable alternative.

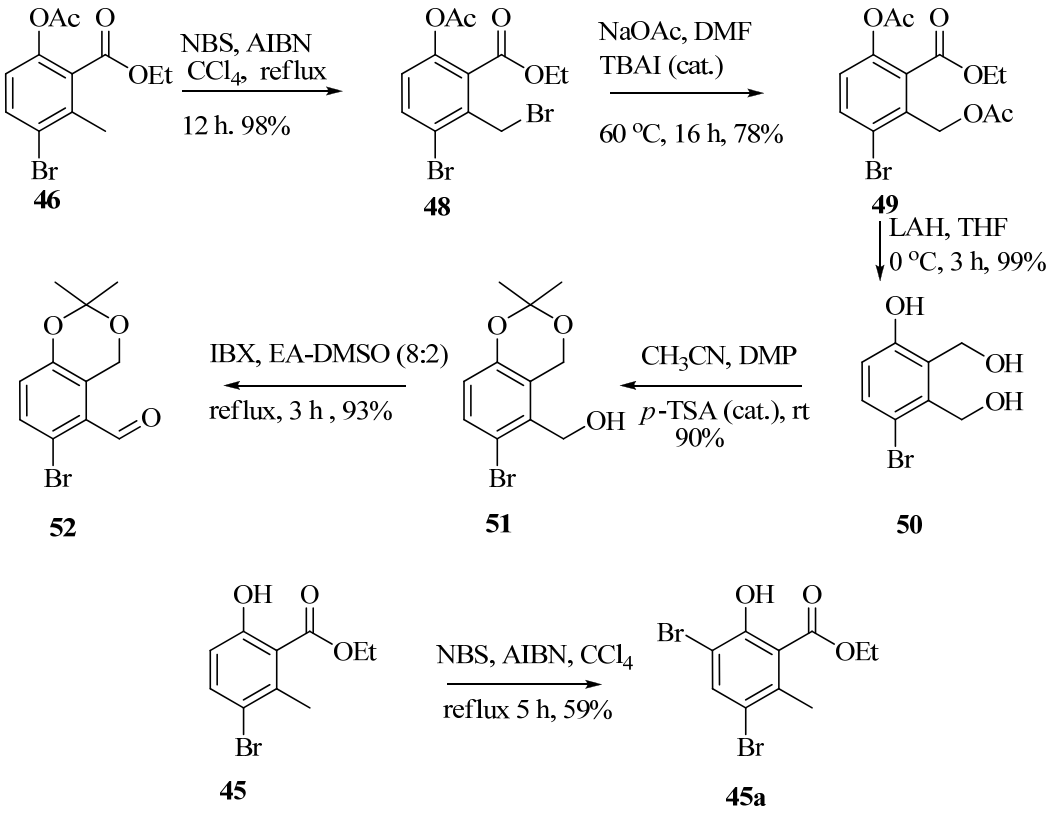
Scheme 12.



An alternative route has been followed to avoid oxidative cleavage of electron rich aromatic ring. The aromatic methyl group of **46** was brominated under free

radical condition using AIBN as radical initiator and NBS as slow generator of molecular bromine to get **48**.[25] The results were in contrast when the substrate **45** was exposed under same condition; only nuclear bromination occurred resulting in the formation of **45a**. The compound **48** isolated as a crystalline solid with excellent yield and characterized fully. Disappearance of signals due to aromatic methyl group and a sharp singlet at δ 4.72 in ^{1}H NMR spectrum indicated the formation of **48**. To reach our target, the benzylic bromide of **48** was displaced with acetoxy group under standard conditions using sodium acetate in DMF in presence of catalytic amount of TBAI. Considering the target acid **41**, the acetates were removed using LAH with simultaneous reduction of the ester group of **49**. The phenolic hydroxyl and one of the benzylic hydroxyl groups of **50** was protected as ketal with acetone. Finally, IBX[26] oxidation of free benzylic hydroxyl group of **51** afforded one of the key intermediates **52**. The ^{1}H NMR of **52** showed that the aldehyde proton resonated at δ 10.43 and the isopropylidene methyls resonated at δ 1.53. In ^{13}C NMR, aldehyde carbon appeared at 194.5 ppm and a strong absorption due to carbonyl stretching frequency at 1686 cm^{-1} in IR noticed.

Scheme 13.



Synthesis of fragment 41

The next step of the synthetic sequence was the copper catalyzed Ullmann reaction which was optimized in our previous synthesis of aspercyclide C, using CuO in DMF at 130 ^{o}C that gave the diaryl aldehyde **53** with moderate yield**.** The reduced yield of this conversion was due to an unavoidable dehalogenation[27] of the aldehyde **52**. The structures of both **53** and **54** were verified by spectral data analysis. One carbon Wittig homologation followed by saponification of **53** afforded the acid fragment **41** which was confirmed by NMR study and finally, single crystal *X*-ray diffraction analysis.

Scheme 14.

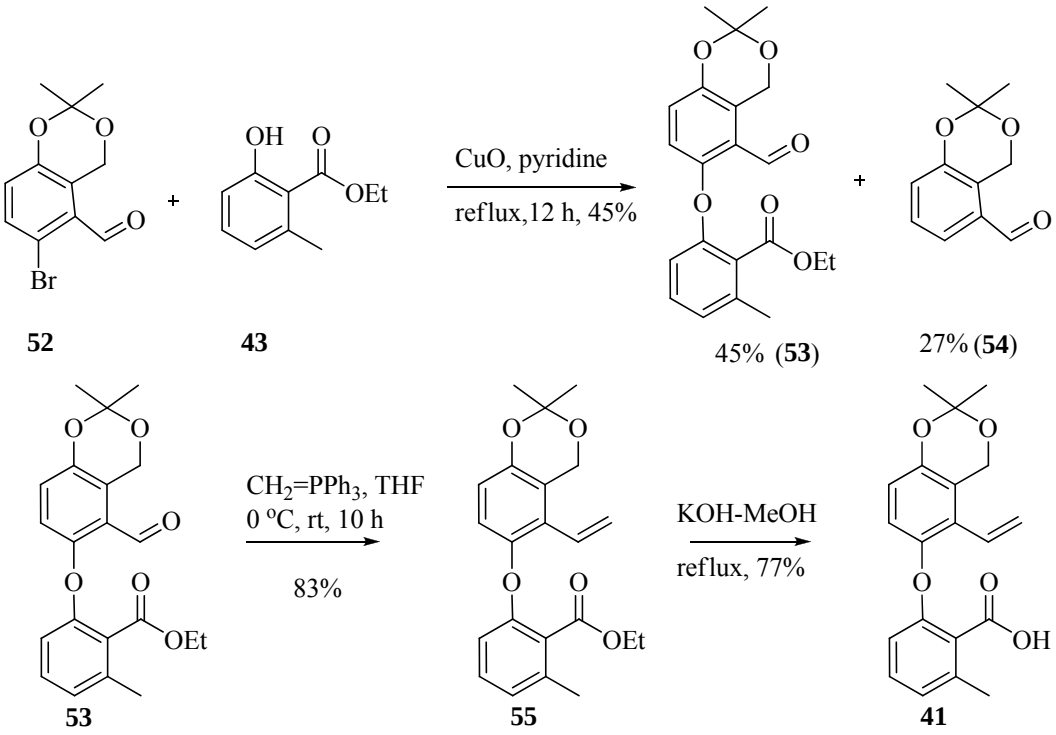
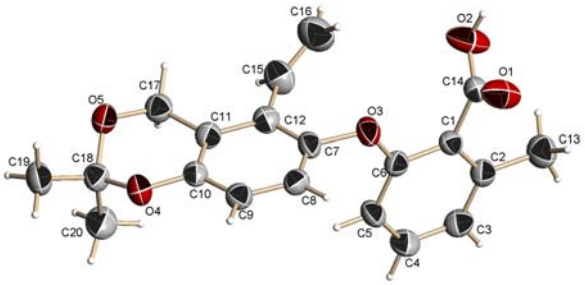


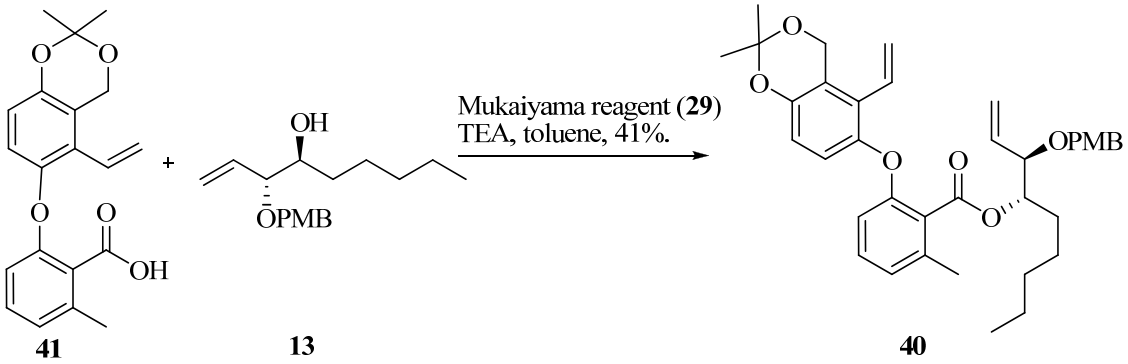
Figure 7: *ORTEP diagram of* **41**.



Coupling of fragments 13 & 41 and ring closing metathesis

In order to make the RCM precursor **40**, compound **13** and **41** were coupled under same condition optimized for the synthesis of aspercyclide C. Notably, the use of strong base such as sodium hydride was found to be ineffective to get improved yield of **40**. Compound **40** was fully analyzed with the help of analytical data NMR and IR spectroscopy and all were according to the assigned structure of **40**.

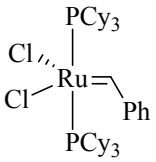
Scheme 15.



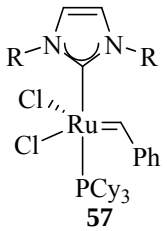
41 **13** **40**

After achieving the synthesis of diene **40** successfully, the feasibility of RCM was checked. Unfortunately, the compound **40** failed to cyclize under standard reaction conditions and with various catalysts. With ruthenium complex **56**, starting material was recovered after 3 days under reflux conditions whereas with catalyst **57** no required product was found. However, in presence of stoichiometric quantity of catalyst **57** in toluene as a solvent under reflux conditions, only the compound **59** was isolated. The stereochemistry of the newly formed double bond was assigned to be *trans* on the basis of spectroscopic data analysis as in ^{1}H NMR spectrum of 59 showing a clean doublet of a doublet at δ 6.21 (J = 8.0, 16.0 Hz) and a doublet at δ 6.58 (J = 16.0 Hz). The terminal olefinic methylene protons of **59** resonated at δ 121.0 in ^{13}C NMR. Other peaks in both the spectra were according to the structure **59**. The stretching frequency of ester carbonyl functionality appeared at 1727 cm^{-1}. Presence of a signal in ESI-MS at *m/z* 699.0 further supported the assigned structure of **59**. Treatment of compound **59** with the catalyst **58** for 3 days under reflux condition in toluene led to a complex interacting mixture from which no reasonable product was isolated.

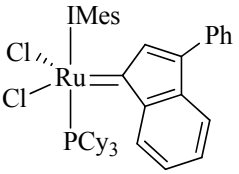
Scheme 16.



56



57

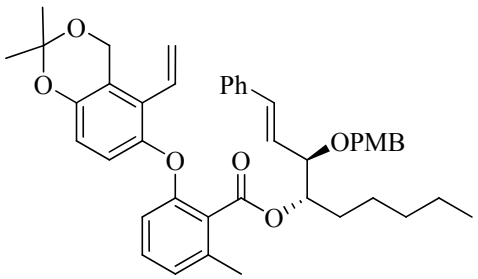


58

40

57 (1 eqv.)

toluene, reflux

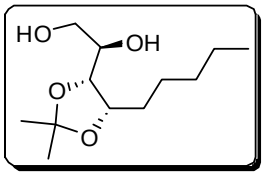


59

In summary, we have developed a simple strategy for the total synthesis of aspercyclide-C using a chiral pool approach and ring closing metathesis as the key reaction. Further application of the key intermediate alcohol **13** towards the synthesis of other aspercyclides was also investigated. We have made the crucial intermediate **40** from very simple, inexpensive, easily available starting materials EAA and crotonaldehyde in a straight forward way, although the key step, RCM was found to be inapt for macrocyclization in the synthesis of aspercyclides B.

Experimental

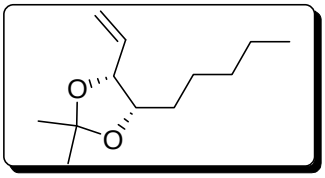
(*R*)-1-((4*R*,5*S*)-2,2-Dimethyl-5-pentyl-1,3-dioxolan-4-yl)ethane-1,2-diol (20)



To an ice-cooled, vigorously stirred suspension of solid butyl triphenylphosphonium bromide (53.7 g, 134 mmol) in THF (130 mL) was added potassium ^{t}butoxide (15.56 g, 139 mmol) by portions and stirring was continued at 0 °C for 30 min and another 2 h at room temperature. To this, a solution of ribose acetonide **18** (8.0 g, 42 mmol) in THF (20 mL) was added at 0 °C and stirring was continued at rt for 16 h. The reaction mixture was cooled to 0 °C and quenched with water (100 mL) and the layers were separated. The aqueous layer was extracted with ethyl acetate (150 x 3 mL) and the combined extracts were washed with brine and dried. Concentration in vacuum followed by chromatographic purification yielded 6.1 g (63%) of a mixture of 11*Z* and 11*E* in a ratio of 7:3 (based on ^{1}H NMR) as colorless oil. The double bond was reduced using Raney Nickel at rt under balloon pressure to afford **20** (6.08 g, 26.2 mmol) as colorless syrup.

Mol. Formula	: $C_{12}H_{24}O_4$
$[\alpha]_D^{25}$	: −7.1 (*c* = 1.0, $CHCl_3$)
^{1}H NMR (200 MHz, $CDCl_3$)	: δ 0.90 (t, *J* = 6.5 Hz, 3H), 1.24-1.42 (m, 4H), 1.33(s,3H), 1.40 (s, 3H), 1.45-1.76 (m, 4H), 2.07 (bs, 1 H), 2.33 (bs, 1H), 3.68-3.83 (m, 3H), 3.92 (dd, *J* = 5.8, 8.2 Hz, 1H), 4.17(ddd, *J* = 3.6, 5.6, 9.6 Hz, 1H) ppm.
^{13}C NMR ($CDCl_3$)	δ 14.1 (q), 22.7 (t), 25.6 (q), 26.3 (t), 28.2 (q), 29.4 (t), 31.9 (t), 64.7 (t), 69.7 (d), 77.6 (d), 78.0 (d), 108.0 (s) ppm.
Elemental Analysis	Calcd.: C, 62.04; H, 10.41 % Found: C, 62.13; H, 10.38 %

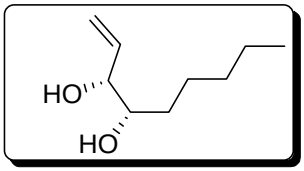
(4*S*,5*R*)-2,2-Dimethyl-4-pentyl-5-vinyl-1,3-dioxolane (21)



Triethyl amine (28.6 ml, 206.8 mmol) and subsequently mesyl chloride (5.38 mL, 69.0 mmol) were added to a solution of **20** (8.0 g, 34.5 mmol) in dry CH_2Cl_2 (100 mL) at 0 °C. After being stirred for 3 h at the same temperature, the reaction mixture was quenched with cold water and extracted with ethyl acetate. The combined extract was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The crude material obtained was taken in 100 mL dry DMF solution, sodium iodide (25.5 g, 170 mmol) and zinc dust (11.27 g, 170 mmol) were added and the contents were heated to reflux under nitrogen atmosphere for two hours. The reaction mixture was allowed to cool to rt and water (100 mL) was added and stirring continued for over night. Solid materials were removed by filtration and the filtrate was extracted with ethyl acetate (3 x 100 mL). Organic extracts were collected, washed with water, brine, dried and concentrated under reduced pressure. The crude material was then purified by column chromatography to obtain **21** (4.5g, 22.7 mmol, 66%) as colorless liquid.

Mol. Formula	: $C_{12}H_{22}O_2$
$[\alpha]_D^{25}$	: −0.9 (*c* = 1.0, CH_3OH)
^{1}H NMR (200 MHz, $CDCl_3$)	: δ 0.87 (t, *J* = 6.5 Hz, 3H), 1.24-1.51 (m, 8H), 1.33 (s, 3H), 1.45 (s, 3H), 4.10 (dt, *J* =6.0, 6.4 Hz, 1H), 4.43 (dd, *J* = 6.4, 7.7 Hz, 1H), 5.16-5.30 (m, 2H), 5.78 (ddd, *J* = 7.7, 10.1, 17.6 Hz, 1H) ppm.
^{13}C NMR ($CDCl_3$)	δ 14.1 (q), 22.6 (t), 25.7 (q), 25.9 (t), 28.3 (q), 30.4 (t), 31.9 (t), 78.3 (d), 79.9 (d), 108.0 (s), 117.9 (t), 134.7 (d) ppm.
Elemental Analysis	Calcd.: C, 72.68; H, 11.18 % Found: C, 72.52; H, 11.03%

(3*R*,4*S*)-Non-1-ene-3,4-diol (22)



To a stirred solution of **21** (4.0 g, 20.2 mmol) in moist methanol (150 mL) was added a solution of *p*-TSA (300 mg, 1.6 mmol). After being stirred for 24 h at rt, the reaction mixture was quenched with saturated solution of $NaHCO_3$ (aq.) and concentrated under reduced pressure and extracted with ethyl acetate. The combined organic extract was washed with brine, dried and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to afford **22** (3.16 g, 99%) as colorless oil.

Mol. Formula : $C_9H_{18}O_2$

$[\alpha]_D^{25}$: +2.4 (*c* = 1.4, $CHCl_3$)

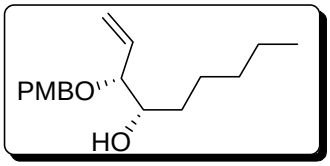
^{1}H NMR (200 MHz, $CDCl_3$) : δ 0.89 (t, *J* = 6.4 Hz, 3H), 1.23-157 (m, 8H), 2.04 (bs, 2H), 3.68 (dt, *J* = 3.6, 6.3 Hz, 1H), 4.09 (ddt, *J* = 1.4, 3.6, 6.4 Hz, 1H), 5.27 (dt, *J* = 1.4, 10.4 Hz, 1H), 5.33 (dt, *J* = 1.3, 17.1 Hz, 1H), 5.92 (ddd, *J* = 6.4, 10.4, 17.1 Hz, 1H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$) : δ 14.1 (q), 22.6 (t), 25.6 (t), 31.8 (t, 2C), 74.2 (d), 76.0 (d), 117.4 (t), 136.1 (d) ppm.

ESI-MS (*m/z*) : 181.2 $[M+Na]^+$.

Elemental Analysis Calcd.: C, 68.31; H, 11.47 %
Found: C, 68.50; H, 11.64 %

(3*R*,4*S*)-3-(4-Methoxybenzyloxy)non-1-en-4-ol (13)



To an ice cold solution of **22** (1.0 g, 6.3 mmol) in dry DMF (10 mL) was added NaH (261 mg, 6.5 mmol, 60% suspension in oil) and stirred at 0 °C for 30 min. To this, *p*-methoxy benzyl chloride (990 mg, 6.3 mmol) was added at 0 °C and the stirring was continued for additional 10 h at rt. The crude reaction mixture was poured in ice cold water and extracted with ethyl acetate. The combined organic extract was washed with brine, dried over Na_2SO_4, and concentrated in vacuum. Purification by

flash silica gel column chromatography gave **13** (721 mg, 41%) as colorless oil along with isomeric compound **23** (193 mg, 11%).

Mol. Formula : $C_{17}H_{26}O_3$

$[\alpha]_D^{25}$: −38.8 (*c* = 1.35, $CHCl_3$).

IR ($CHCl_3$) υ : 1037, 1067, 1216, 1249, 1465, 1513, 1585, 1613, 3448 cm^{-1}.

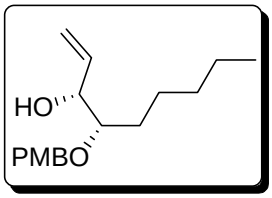
^{1}H NMR (200 MHz, $CDCl_3$) : δ 0.86 (t, *J* = 6.5 Hz, 3H), 1.21-1.34 (m, 5H), 1.35-1.47 (m, 3H), 2.12 (bs, 1H), 3.65-3.72 (m, 2H), 3.79 (s, 3H), 4.30 (d, *J* = 11.5 Hz, 1H), 4.56 (d, *J* = 11.5 Hz, 1H), 5.28 (dd, *J* = 1.8, 17.1 Hz, 1H), 5.38 (dd, *J* = 1.8, 10.4 Hz, 1H), 5.84 (ddd, *J* = 7.8, 10.4, 17.1 Hz, 1H), 6.87 (d, *J* = 8.7 Hz, 2H), 7.24 (d, *J* = 8.7 Hz, 2H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$) : δ 14.0 (q), 22.5 (t), 25.3 (t), 31.8 (t), 32.1 (t), 55.2 (q), 69.9 (t), 73.2 (d), 83.2 (d), 113.8 (d), 119.9 (t), 129.3 (d), 130.3 (s), 134.6 (d), 159.2 (s) ppm.

ESI-MS (*m/z*) : 278.9 $[M+H]^+$, 301.9 $[M+Na]^+$.

Elemental Analysis Calcd.: C, 73.34; H, 9.41 %
Found: C, 73.13; H, 9.45 %

(3*R*,4*S*)-4-(4-Methoxybenzyloxy)non-1-en-3-ol (23)



Mol. Formula : $C_{17}H_{26}O_3$

$[\alpha]_D^{25}$: −6.5 (*c* = 1.2, $CHCl_3$).

IR ($CHCl_3$) υ : 924, 1036, 1085, 1248, 1302, 1465, 1513, 1612, 2859, 2932, 3448 (b) cm^{-1}.

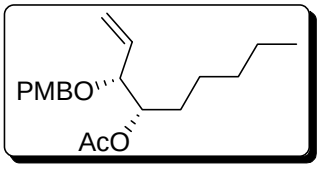
^{1}H NMR (200 MHz, $CDCl_3$) : δ 0.87 (t, *J* = 6.2 Hz, 3H), 1.25-1.58 (m, 8H), 2.15 (bs, 1H), 3.40 (dt, *J* = 3.5, 7.9 Hz, 1H), 3.79 (s, 3H), 4.26 (dd, *J* = 3.5, 5.9 Hz, 1H), 4.52-4.59 (m, 2H), 5.16-5.22 (m, 1H), 5.24-5.33 (m, 1H), 5.85 (ddd, *J* = 5.9, 10.4, 16.8 Hz, 1H), 6.86 (d, *J* = 8.4 Hz, 2H), 7.25 (d, *J* = 8.4 Hz, 2H) ppm.

^{13}C NMR : δ 14.1 (q), 22.6 (t), 25.4 (t), 29.2 (t), 31.9 (t), 55.1 (q), 71.8

(125 MHz, $CDCl_3$) (t), 73.4 (d), 81.7 (d), 113.8 (d), 116.3 (t), 129.4 (d), 130.5 (s), 136.8 (d), 159.3 (s) ppm.

Elemental Analysis Calcd.: C, 73.34; H, 9.41 %
Found: C, 73.21; H, 9.38 %

(3*R*,4*S*)-3-(4-Methoxybenzyloxy)non-1-en-4-yl acetate (13Ac)



Triethyl amine (0.15 mL, 1.1 mmol) and acetic anhydride (0.06 mL, 5 mmol) were added successively to an ice-cooled solution of **13** (100 mg, 0.3 mmol) in CH_2Cl_2 (3 mL) and the solution was stirred at rt for 5h at rt. The reaction mixture was quenched with aq. $NaHCO_3$ and extracted with EtOAc. The combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated under vacuum. The crude reaction mixture was purified by silica gel column chromatography to yield **13Ac** (109 mg, 95%) as colorless oil.

Mol. Formula : $C_{19}H_{28}O_4$

$[\alpha]_D^{25}$: −51.0 (*c* = 1.3, $CHCl_3$)

IR ($CHCl_3$) υ : 758, 1036, 1070, 1247, 1514, 1374, 1514, 1735 cm^{-1}.

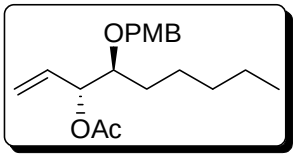
^{1}H NMR (200 MHz, $CDCl_3$) : δ 0.87 (t, *J* = 6.2 Hz, 3H), 1.20-1.35 (m, 6H), 1.50-1.65 (m, 2 H), 2.01 (s, 3H), 3.74 (dd, *J* = 5.0, 7.7 Hz, 1H), 3.80 (s, 3H), 4.30 (d, *J* = 11.7 Hz, 1H), 4.53 (d, *J* = 11.7 Hz, 1H), 4.94 (dt, *J* = 5.0, 7.6 Hz, 1H), 5.20-5.33 (m, 2H), (ddd, *J* = 0.9, 1.9, 17.0 Hz, 1H), 6.85 (d, *J* = 8.6 Hz, 2H), 7.22 (d, *J* = 8.6 Hz, 2H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$) : δ 14.1 (q), 21.1 (q), 22.6 (t), 25.1 (t), 29.7 (t), 31.7 (t), 55.1 (q), 69.9 (t), 74.8 (d), 80.8 (d), 113.7 (d), 119.3 (t), 129.3 (d), 130.3 (s), 135.3 (d), 159.1 (s), 170.4 (s) ppm.

ESI-MS (*m/z*) : 321.3 $[M+H]^+$, 343.3 $[M+Na]^+$.

Elemental Analysis Calcd.: C, 71.22; H, 8.81 %
Found: C, 71.01; H, 8.53 %

(3*R*,4*S*)-4-(4-Methoxybenzyloxy)non-1-en-3-yl acetate (23Ac)



This compound was prepared by following same procedure as for **13Ac** and isolated in 93% yield as colourless solid.

Mol. Formula : $C_{19}H_{28}O_4$

$[\alpha]_D^{25}$: −22.7 (*c* = 1.1, $CHCl_3$).

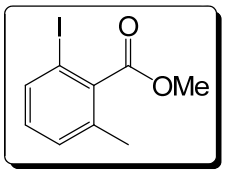
IR ($CHCl_3$) υ : 822, 1035, 1092, 1173, 1244, 1302, 1371, 1514, 1613, 1741, 2860, 2933 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$) : δ 0.91 (t, *J* = 6.2 Hz, 3H), 1.27-1.34 (m, 4H), 1.43-1.56 (m, 4H), 2.13 (s, 3H), 3.50 (dt, *J* = 3.3, 7.8Hz, 1H), 3.84 (s, 3 H), 4.47 (d, *J* = 11.1Hz, 1H), 4.68 (d, , *J* = 11.1Hz, 1H), 5.28-5.37 (m, 2H), 5.49 (dd, *J* = 2.7, 7.8 Hz, 1H), 5.91 (ddd, *J* = 6.4, 10.5, 17.1 Hz, 1H), 6.89 (d, *J* = 8.2 Hz, 2H), 7.29 (d, *J* = 8.2 Hz, 2H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$) : δ 4.1 (q), 21.2 (q), 22.6 (t), 25.4 (t), 30.5 (t), 31.7 (t), 55.2 (q), 72.0 (t), 75.8 (d), 79.7 (d), 113.7 (d), 118.3 (t), 129.6 (d), 130.5 (s), 133.0 (d), 159.2 (s), 170.0 (s) ppm.

Elemental Analysis Calcd.: C, 71.22; H, 8.81 %
Found: C, 71.06; H, 8.68 %

Methyl 2-iodo-6-methylbenzoate (15)



A solution of $NaNO_2$ (2.33 g, 33.8 mmol) in 10 mL of water was added to a solution of 2-amino-6-methylbenzoic acid (**24**) (5 g, 33.1 mmol) in 50 mL water containing 15 mL concentrated H_2SO_4 at 0 ^oC slowly over 10 min and the mixture was stirred for additional one and half hour at the same temperature. Then to this ice cold diazotized solution potassium iodide (8.7 g, 52.4 mmol) was added at a time and the mixture was heated to boil for 15 minutes. It was cooled to rt. and extracted with ethyl acetate. The organic layers were collected and washed with 10 % aq. $Na_2S_2O_3$

solution and finally with fresh water, dried on anhydride sodium sulphate and concentrated to get compound **25**.

Thus crude material obtained was dissolved in DCM and to it an ethereal solution of diazomethane were added potion wise and the reaction was monitored by TLC. After completion of esterification, volatiles were removed and crude materials were purified by column chromatography, and afforded analytically pure compound **15** (7.5 g, 82 %).

Mol. Formula : $C_9H_9IO_2$

IR ($CHCl_3$) υ : 566, 690, 730, 772, 820, 954, 1067, 1099, 1144, 1179, 1189, 1244, 1276, 1444, 1560, 1587, 1752 cm^{-1}.

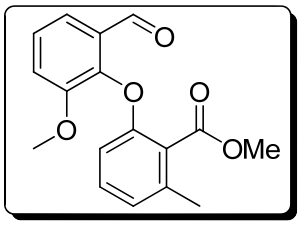
^{1}H NMR (200 MHz, $CDCl_3$) : δ 2.32 (s, 3H), 3.95 (s, 3H), 6.98 (dd, *J* = 7.7, 7.8 Hz, 1H), 7.17 (d, *J* = 7.7 Hz, 1H), 7.64 (d, *J* = 7.8 Hz, 1H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$) : δ 19.9 (q), 52.5 (q), 91.8 (s), 129.60(d), 130.6 (d), 136.3 (d), 136.5 (s), 140.1 (s), 169.4 (s) ppm.

ESI-MS (*m/z*) : 277.0 $[M+H]^+$, 299.0 $[M+Na]^+$.

Elemental Analysis Calcd.: C, 39.16; H, 3.29; I, 45.97 %
Found: C, 39.11; H, 3.30; I, 45.83 %

Methyl 2-(2-formyl-6-methoxyphenoxy)-6-methylbenzoate (26)



Iodo derivative **15** (1.5 g, 5.4 mmol), *o*-vanillin **16** (826 mg, 5.4 mmol) and copper (II) oxide (427 mg, 5.4 mmol) were taken in dry DMF (10 mL) and stirred under nitrogen atmosphere for 50 h at 140 °C. The reaction mixture was cooled to room temperature, diluted with ethyl acetate and the solids were removed by filtration on *celite* pad. The combined filtrate was washed with water, brine, dried over sodium sulfate and concentrated under reduced pressure. Chromatographic purification of the resulting crude material over silica gel afforded **26** (783 mg, 48%) as white solid (mp 76 ^oC).

Mol. Formula : $C_{17}H_{16}O_5$

IR ($CHCl_3$) υ : 668, 758, 1075, 1115, 1215, 1252, 1274, 1393, 1441, 1462,

1483, 1589, 1697, 1730, 2855, 2928, 3020 cm^{-1}.

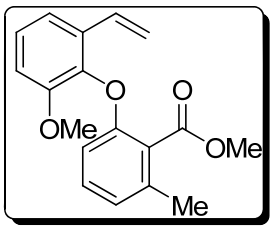
^{1}H NMR (200 MHz, $CDCl_3$): δ 2.37 (s, 3H), 3.78 (s, 3H), 3.94 (s, 3H), 6.31 (d, *J* = 8.3 Hz, 1H), 6.87 (dt, *J* = 7.71, 0.8 Hz, 1H), 7.10 (t, *J* = 8 Hz, 1H), 7.20 (dd, *J* = 8.2, 1.8 Hz, 1H), 7.30 (dt, *J* = 0.8, 8.0 Hz, 1H), 7.53 (dd, *J* = 1.9, 7.6 Hz, 1H), 10.30 (d, *J* = 0.8 Hz, 1H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ 19.4 (q), 52.1 (q), 56.2 (q), 111.2 (d), 118.5 (d), 119.3 (d), 123.31 (s), 124.0 (d), 126.0 (d), 130.1 (d),130.4 (s), 137.2 (s), 146.1 (s), 152.7 (s), 155.6 (s), 167.8 (s), 189.2 (d) ppm.

ESI-MS (*m/z*): 299.8 $[M]^+$, 317.2 $[M+NH_4]^+$.

Elemental Analysis Calcd.: C, 67.99; H, 5.37 %
Found: C, 67.83; H, 5.19 %

Methyl 2-(2-methoxy-6-vinyl-phenoxy)-6-methylbenzoate (27)



To a stirred suspension of methyltriphenylphosphonium iodide (3.24 g, 8.01 mmol) in dry THF (30 mL) at 0 °C was added *n*-BuLi (5 mL, 1.6 M) and stirred for 30 min at 0 °C. After complete generation of ylide, a solution of aldehyde **26** (1.85 g, 6.16 mmol) in THF (10 mL) was added and stirred for another 30 minutes at same temperature. Afterward the reaction was quenched with ice. Water was added and the mixture was extracted with ethyl acetate. Column purification of the crude product afforded 1.51 g (82%) of **27,** a yellow liquid.

Mol. Formula: $C_{18}H_{18}O_4$

IR ($CHCl_3$) υ: 758, 1215, 1586, 1728 cm^{-1}.

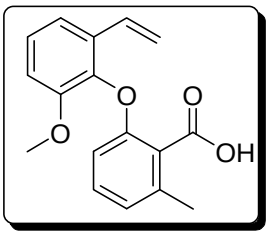
^{1}H NMR ($CDCl_3$, 200 MHz): δ 2.36 (s, 3H), 3.73 (s, 3H), 3.95 (s, 3H), 5.25 (dd, *J* = 1.2, 10.9 Hz, 1H), 5.74 (dd, *J* = 1.2, 17.6 Hz, 1H), 6.23 (d, *J* = 8.3 Hz, 1H), 6.77-6.89 (m, 2H), 6.70-7.19 (m, 4H) ppm.

^{13}C NMR ($CDCl_3$, 50 MHz): δ19.3 (q),52.1 (q), 56.0 (q), 110.7 (d),112.0 (d),116.1 (t), 117.8 (d), 123.0 (d), 125.7 (d), 129.9 (d), 130.4 (d), 132.3 (s), 136.6 (s, 2C), 140.3 (s), 152.7 (s), 1 55.3 (s),168.4 (s) ppm.

ESI-MS (*m/z*): 299.3 $[M+H]^+$, 321.9 $[M+Na]^+$.

Elemental Analysis Calcd.: C, 72.47; H, 6.08 %
Found: C, 72.36; H, 6.09 %

2-(2-Methoxy-6-vinyl-phenoxy)-6-methyl-benzoic acid (14)



A solution of ester **27** (2.46 g, 8.25 mmol) in MeOH-H_2O (6:4) (100 ml) mixture was treated with 10% aqueous NaOH and heated to reflux for 48 h. Methanol was then removed under reduced pressure, acidified with 3N aq. HCl and extracted with ethyl acetate. The combined organic extract was dried (Na_2SO_4) and concentrated under reduced pressure. Column purification of crude product afforded the compound **14** (2.30 g, 99%) as white solid m.p. 95-96 ^oC.

Mol. Formula : $C_{17}H_{16}O_4$

IR ($CHCl_3$) υ : 1067, 1215, 1461, 1705, 1740, 3368 cm^{-1}.

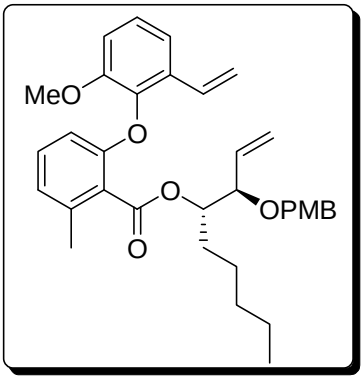
^{1}H NMR (200 MHz, $CDCl_3$) : δ 2.54 (s, 3H), 3.77 (s, 3H), 5.33 (d, *J* = 11.1 Hz, 1H), 5.83 (d, *J* = 17.5 Hz, 1H), 6.39 (d, *J* = 8.3 Hz, 1H), 6.83-6.97 (m, 3H), 7.08-7.29 (m, 3H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$) : δ 20.3 (q), 56.0 (q), 111.7 (d), 111.8 (d), 116.7 (t), 118.1 (d), 121.9 (s), 124.4 (d), 125.9 (d), 130.2 (d), 130.8 (d), 132.7 (s), 138.8 (s), 140.6 (s), 151.9 (s), 155.9 (s), 169.9(s) ppm.

ESI-MS (*m/z*) : 285.1 $[M+H]^+$, 301.1 $[M+NH_4]^+$, 307.1 $[M+Na]^+$.

Elemental Analysis Calcd.: C, 71.82; H, 5.67 %
Found: C, 71.69; H, 5.61 %

(3*R*,4*S*)-3-(4-Methoxybenzyloxy)non-1-en-4-yl 2-(2-methoxy-6-vinylphenoxy)-6-methylbenzoate (12)



To a mixture of acid **14** (332 mg, 1.17 mmol), alcohol **13** (293 mg, 105 mmol) and triethyl amine (0.5 ml, 3.61mmol) in toluene (2 ml) was added solid 1-methyl-2-chloropyridinium chloride (320 mg, 1.26 mmol) under nitrogen atmosphere and the resulting mixture was refluxed for 1 h. The suspension of pyridinium salt became clear as reaction proceeded. Subsequently it was cooled to 0 °C and NaH (54 mg, 1.35 mmol; 60% dispersion in oil) was added and stirring was continued for 2 h at room temperature. The reaction mixture was quenched with water and extracted with ethyl acetate. The combined organic extract was washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography to get **12** (451 mg, 71%) as light yellow liquid.

Mol. Formula : $C_{34}H_{40}O_6$

$[\alpha]_D^{25}$: −43.9 (*c* = 0.9, $CHCl_3$).

IR ($CHCl_3$) υ : 767, 823, 929, 995, 1035, 1035, 1072, 1251, 1273, 1302, 1461, 1513, 1585, 1612, 1729, 2859, 2931, 2955 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$) : δ 0.71 (t, *J* = 6.5 Hz, 3H), 0.99-1.24 (m, 6H), 1.31-1.51 (m, 1H), 1.63-1.73 (m, 1H), 2.32 (s, 3H), 3.67 (s, 3H), 3.78 (s, 3H), 3.97 (dd, *J* = 4.3, 7.4 Hz, 1H), 4.38 (d, *J* = 11.5 Hz, 1H), 4.51 (d, *J* = 11.5 Hz, 1H), 5.19 (dd, *J* = 11.0, 1.1 Hz, 1H), 5.26-5.39 (m, 3H), 5.72 (dd, *J* = 17.6, 1.3 Hz, 1H), 5.88 (ddd, *J* = 7.5, 10.0, 17.6 Hz, 1H), 6.21 (d, *J* = 8.3 Hz, 1H), 6.76-6.89 (m, 5H), 6.94-7.23 (m, 5H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$) : δ 13.9 (q), 19.4 (q), 22.4 (t), 24.9 (t), 29.8 (t), 31.7 (t), 55.2 (q), 56.0 (q), 70.2 (t), 76.1 (d), 81.3 (d), 110.5 (d), 111.9 (d), 113.5 (d), 115.9 (d), 117.7 (d), 119.3 (t), 123.0 (d), 123.6 (s), 125.6 (d), 129.2 (d), 129.7 (d), 130.50 (d), 130.54 (s), 132.3 (s), 135.1 (d), 136.8 (s), 140.2 (s), 152.8 (s), 155.2 (s), 158.9

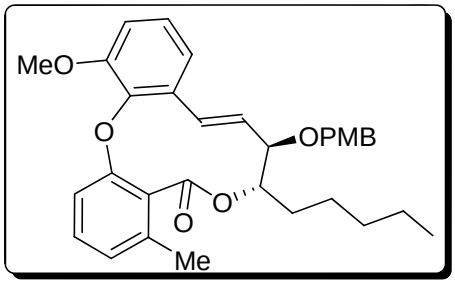
(s), 167.7 (s) ppm.

ESI-MS (*m/z*) : 545.5 $[M+H]^+$, 567.4 $[M+Na]^+$.

Elemental Analysis Calcd.: C, 74.97; H, 7.40 %

Found: C, 74.79; H, 7.28 %

(7*S*,8*R*,*E*)-14-Methoxy-8-(4-methoxy benzyloxy)-4-methyl-7-pentyl-7,8-dihydro-5H-dibenzo[b,j][1,5] dioxacycloundecin-5-one (38)



A solution of diene **12** (40 mg, 73.4 μmol) in toluene (30 ml) was degassed thoroughly under argon atmosphere and heated to 120 °C. To this Grubb's 2nd gen. Catalyst (12 mg, 14.6 μmol) in toluene (10 mL) was added via syringe pump over 1 h. After complete addition the reaction mixture was stirred at same temperature for additional 2 h. The volatiles were removed and purified by flash column chromatography to procure **38** (27 mg, 71%) as yellow oil.

Mol. Formula : $C_{32}H_{36}O_6$

$[\alpha]_D^{25}$: +148.7 (*c* = 0.4, $CHCl_3$).

IR ($CHCl_3$) υ : 757, 1081, 1251, 1460, 1514, 1585, 1610, 1735 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) : δ 0.91 (t, *J* = 7 Hz, 3H), 1.29-1.54 (m, 6H), 1.55-1.62 (m, 1H), 1.99-2.05 (m, 1H), 2.33 (s, 3H), 3.74 (t, *J* = 9.6 Hz, 1H), 3.80 (s, 3H), 3.91 (s, 3H), 4.32 (d, *J* = 11.5 Hz, 1H), 4.58 (d, *J* = 11.5 Hz, 1H), 5.29 (dt, *J* = 2.4, 9.6 Hz, 1H), 5.95 (dd, *J* = 9.6, 16.0 Hz, 1H), 6.26 (d, *J* = 16.0 Hz, 1H), 6.55 (d, *J* = 8.3 Hz, 1H), 6.78 (d, *J* = 7.6 Hz, 1H), 6.80 (d, *J* = 7.6 Hz, 1H), 6.84 (t, distorted *J* = 2 Hz, 1H), 6.86 (t, distorted *J* = 2.5 Hz, 1H), 6.93 (d, *J* = 1.2, 8.3 Hz, 1H), 7.06 (t, *J* = 7.9 Hz, 1H), 7.12 (t, *J* = 7.9 Hz, 1H), 7.21 (t, distorted, *J* = 2.2 Hz, 1H), 7.23 (t, distorted, *J* = 2.2 Hz, 1H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$) : δ 14.1 (q), 19.4 (q), 22.6 (t), 25.3 (t), 31.7 (t), 32.0 (t), 55.2 (q), 56.1 (q), 70.5 (t), 75.7 (d), 82.9 (d), 111.7 (d), 113.8 (d), 114.3 (d), 121.7 (d), 123.7 (d), 125.4 (d), 126.8 (s), 129.4 (d),

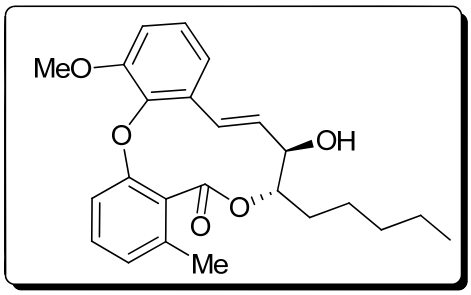
129.6 (d), 129.6 (d), 130.2 (s), 133.8 (s), 134.7 (s), 136.9 (d), 143.2 (s), 153.9 (s), 154.1 (s), 159.3 (s), 167.5 (s) ppm.

ESI-MS (*m/z*) : 539.1 $[M+Na]^+$, 555.1 $[M+K]^+$.

Elemental Analysis Calcd.: C, 74.39; H, 7.02.%

Found: C, 74.13; H, 7.28%

(7*S*,8*R*,*E*)-8-Hydroxy-14-methoxy-4-methyl-7-pentyl-7,8-dihydro-5H-dibenzo [b,j][1,5]dioxacycloundecin-5-one (39)



To a solution of **38** (25 mg, 48.4 μmol) in CH_2Cl_2 (2 mL) was added 1M solution of BBr_3 (0.5 ml, 6.67 mmol) at –78 °C. After being stirred for 5 min at the same temperature, the reaction mixture was quenched with water and extracted with CH_2Cl_2. The combined organic extract was washed with brine, dried (Na_2SO_4) and concentrated under vacuum. Crystallization of the resulting white solid in methanol afforded **39** (19 mg, 92%) as transparent needles (mp 240-241^oC).

Mol. Formula : $C_{24}H_{28}O_5$

$[\alpha]_D^{25}$: +330.5 (*c* = 0.8, DCM)

IR ($CHCl_3$) υ : 759, 1080, 1215, 1461, 1584, 1601, 1722, 3445 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) : δ 0.93 (t, *J* = 6.6 Hz, 3H), 1.26-1.45 (m, 4H), 1.50-1.60 (m, 1H), 1.63-1.73 (m, 2H), 2.03-2.10 (m, 1H), 2.35 (s, 3H), 3.90 (s, 3H), 4.03 (t, *J* = 9.0 Hz, 1H), 5.19 (t, *J* = 9.2 Hz, 1H), 5.99 (dd, *J* = 9.2, 15.6 Hz, 1H), 6.27 (d, *J* = 15.6 Hz, 1H), 6.57 (d, *J* = 8.3 Hz, 1H), 6.73 (d, *J* = 7.53 Hz, 1H), 6.82 (d, *J* = 7.5 Hz, 1H), 6.91 (d, *J* = 8.0 Hz, 1H), 7.07 (d, *J* = 8.3 Hz, 1H), 7.11 (d, *J* = 8.3 Hz, 1H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) : δ 14.1 (q), 19.4 (q), 22.6 (t), 25.4 (t), 31.7 (t), 31.8 (t), 56.1 (d), 77.0 (d), 77.2 (d), 111.8 (d), 114.4 (d), 121.6 (d), 123.8 (d), 125.5 (d), 126.7 (s), 128.0 (d), 129.7 (d), 133.6 (s), 134.7 (s), 137.8 (d), 143.2 (s), 153.8 (s), 154.1 (s), 167.7(s) ppm.

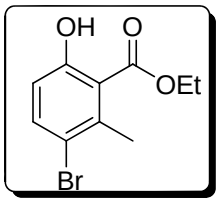
ESI-MS (*m/z*) : 397.2 $[M+H]^+$, 419.2 $[M+Na]^+$.

Elemental Analysis Calcd.: C, 72.70; H, 7.12 %
Found: C, 72.82; H, 7.36 %

Crystal data for 39.

Empirical formula	$C_{24}H_{28}O_5$
Formula weight	396.46
Temperature	293(2) K
Wavelength	0.71073 A
Crystal system, space group	Orthorhombic, P212121
Unit cell dimensions	a = 7.7202(7) Å
	b = 7.9040(7) Å
	c = 34.803(3) Å
Volume	2123.7(3) A^3
Z, Calculated density	4, 1.240 Mg/m^3
Absorption coefficient	0.086 mm^{-1}
F(000)	848
Crystal size	0.45 x 0.09 x 0.05 mm
Theta range for data collection	2.34 to 23.50º
Limiting indices	-8<=h<=8, -8<=k<=8, -39<=l<=39
Reflections collected / unique	17310 / 3144 [R(int) = 0.1139]
Completeness to theta = 23.50	99.9 %
Max. and min. transmission	0.9957 and 0.9625
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3144 / 0 / 266
Goodness-of-fit on F^2	1.077
Final R indices [I>2sigma(I)]	R1 = 0.0811, wR2 = 0.1605
R indices (all data)	R1 = 0.1142, wR2 = 0.1764
Absolute structure parameter	-2(3)
Largest diff. peak and hole	0.183 and -0.202 $e.A^{-3}$

Ethyl 3-bromo-6-hydroxy-2-methylbenzoate (45)



An ice-cold bromine solution (21.0 mL, 408 mmol) in $CHCl_3$ was added to a solution of 2-hydroxy-6-methyl-benzoic acid ethyl ester **(43)** (66.8 g, 371 mmol) in chloroform (300 mL) over 30 minutes at 0 ^oC slowly with vigorous stirring. After complete addition of bromine solution, the reaction mixture was quenched with water 300 mL and partitioned by separation funnel. The organic layer was washed with 200 mL of 5% aqueous sodium thiosulfate and finally with water. The organic layer was collected and dried over anhydrous sodium sulfate. Removal of volatiles under reduced pressure yielded (94.1 g, 98 %) **45** as light brown liquid. The brominated product was sufficiently pure to take it for next acylation reaction and the analytical samples were made by purification with flash column chromatography.

Mol. Formula : $C_{10}H_{11}BrO_3$

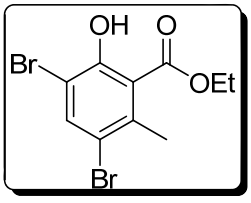
IR ($CHCl_3$) υ : 800, 823, 861, 1016, 1100, 1215, 1278, 1309, 1332, 1372, 1395, 1455, 1595, 1663, 2982, 3356 (b) cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$) : δ 1.44 (t, *J* = 7.0 Hz, 3H), 2.64 (s, 3H), 4.45 (q, *J* = 7.0 Hz, 2H), 6.75 (d, *J* = 8.9 Hz, 1H), 7.54 (d, *J* = 8.9 Hz, 1H), 10.88 (s, 1H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) : δ 14.1 (q), 22.9 (q), 62.1 (t), 114.7 (s), 116.1 (s), 116.9 (d), 137.9 (d), 139.4 (s), 161.2 (s), 170.7 (s) ppm.

Elemental Analysis Calcd.: C, 46.36; H, 4.28; Br, 30.84 %
Found: C, 46.29; H, 4.11; Br, 30.56 %

Ethyl 3,5-dibromo-2-hydroxy-6-methylbenzoate (45a)



The brominated product **45** (1.158 g, 4.47mmol) was taken in dry CCl_4 (20 mL) and to this solution recrystallized NBS (1.035g, 5.81 mmol) was added followed by AIBN (cat. 100 mg) and heated to reflux for 5 h. Then the reaction mixture was cooled to room temperature and solid byproducts were removed by filtration on *celite*

pad. The resulting mixture was extracted with ethyl acetate. Whole organic extracts were collected, dried over sodium sulfate and evaporated under reduced pressure. Thus, the crude mixture obtained was purified by column chromatography using silica gel as solid support and a mixture of petroleum ether and ethyl acetate as mobile to get **45a** as yellow solid (0.894g, 59 %).

Mol. Formula : $C_{10}H_{10}Br_2O_3$

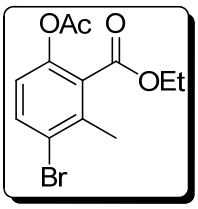
IR ($CHCl_3$) υ : 733, 862, 908, 1015, 1208, 1274, 1328, 1373, 1399, 1559, 1582, 1666, 2985, 3368 (b) cm^{-1}

^{1}H NMR (200 MHz, $CDCl_3$) : δ 1.44 (t, *J* = 7.2 Hz, 3H), 2.59 (s, 3H), 4.48 (q, *J* = 7.2 Hz, 2H), 7.87 (s, 1H), 11.29 (s, 1H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$) : δ 14.0 (q), 22.8 (q), 62.7 (t), 109.3 (s), 115.8 (s), 116.0 (s), 138.9 (s), 140.0 (d), 157.2 (s), 170.2 (s) ppm.

Elemental Analysis Calcd.: C, 35.54; H, 2.98; Br, 47.28 %
Found: C, 35.35; H, 2.81; Br, 47.03 %

Ethyl 6-acetoxy-3-bromo-2-methylbenzoate (46)



To a stirring solution of phenol **45** (89.2 g, 0.344 mmol) in dry DCM (250 mL) at 0 ^oC under nitrogen atmosphere acetic anhydride (42.2 g, 0.447 mmol) was charged via syringe to the mixture and stirred for 15 min. After that triethyl amine (143 mL, 10.32 mmol) was added slowly at the same temperature for over a period of 20 min. After complete addition of acetic anhydride, *N,N*-dimethyl 4-aminopyridine (200 mg) was added and the mixture was stirred for 6 h on ice bath. The progress of reaction was monitored by TLC. After completion of reaction, water was added and organic layer was separated. The organic layer was then washed with brine, collected and dried over anhydrous sulfate. Thus the crude material obtained after removal of volatiles under reduced pressure was purified by column chromatography. Compound **46** was obtained as light yellow liquid (99.5 g, 96%).

Mol. Formula : $C_{12}H_{13}BrO_4$

IR ($CHCl_3$) υ : 813, 861, 885, 1015, 1033, 1096, 1137, 1198, 1262, 1368, 1459, 1557,1729, 1770 (b) cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$) : δ 1.37 (t, *J* = 7.0 Hz, 3H), 2.26 (s, 3H), 2.41 (s, 3H), 4.38 (q, *J* = 7.0 Hz, 2H), 6.87 (d, *J* = 8.7 Hz, 1H), 7.58 (d, *J* = 8.7 Hz, 1H) ppm.

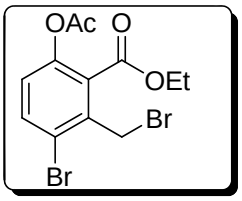
^{13}C NMR (50 MHz, $CDCl_3$) : δ 14.1 (q), 20.5 (q), 20.7 (q), 61.7 (t), 121.8 (d), 122.5 (s), 128.8 (s), 134.1 (d), 136.7 (s), 146.8 (s), 165.9 (s), 168.6 (s) ppm.

ESI-MS (*m/z*) : 323.1$[M+Na]^+$, 325.1 $[M+Na+2]^+$.

Elemental Analysis Calcd.: C, 47.86; H, 4.35; Br, 26.53 %

Found: C, 47.69; H, 4.28; Br, 26.41 %

Ethyl 6-acetoxy-3-bromo-2-(bromomethyl)benzoate (48)



To a stirred solution of acetate **46** (41.8g, 139 mmol) in carbon tetrachloride (700 mL), recrystallized NBS (37.1 g, 208 mmol) was added and degassed under argon atmosphere thoroughly. Then AIBN (cat. 2g) was added and degassed again thoroughly under same condition with vigorous stirring and the mixture was heated to reflux for 10 h. Initial heavy precipitate of NBS was floating on carbon tetrachloride indicating the completion of reaction. On cooling the reaction mixture on ice bath solid byproducts and excess of NBS were precipitated out and filtered off through *celite* pad. The filtrate was collected and concentrated under reduced pressure. The crude product thus obtained was purified by column chromatography using silica gel and ethyl acetate petroleum ether as eluent. The purified dibromo compound **48** (51.2 g, 97 %) was isolated as crystalline solid (m.p 66-67 ^oC).

Mol. Formula : $C_{12}H_{12}Br_2O_4$

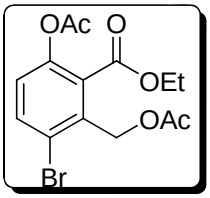
IR ($CHCl_3$) υ : 861, 1079, 1264, 1368, 1397, 1560, 1668, 1770 (b) cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$) : δ 1.42 (t, *J* = 7.0 Hz, 3H), 2.28 (s, 3H), 4.44 (q, *J* = 7.0 Hz, 2H), 4.72 (s, 2H), 7.02 (d, *J* = 8.8 Hz, 1H), 7.65 (d, *J* = 8.8 Hz, 1H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$) : δ: 14.1 (q), 20.7 (q), 29.2 (t), 62.2 (t), 122.3 (s), 124.7 (d), 128.7 (s), 135.3 (d), 136.0 (s), 147.5 (s), 164.7 (s), 168.3 (s) ppm.

Elemental Analysis Calcd.: C, 37.93; H, 3.18; Br, 42.05 %
Found: C, 37.75; H, 3.03; Br, 42.00 %

Ethyl 6-acetoxy-2-(acetoxymethyl)-3-bromobenzoate (49)



A mixture of dibromo compound **48** (39 g, 103 mmol), sodium acetate (42.2g, 514 mmol), TBAI (2.0 g), and 100 mL of dry DMF was heated for 16 h. The mixture was diluted with ethyl acetate and the solid byproducts were filtered off. The filtrate was washed thoroughly with fresh water. Combined organic layer was dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude material thus obtained was purified by flash column chromatography to get the diacetate **49** as light yellow liquid (28.6 g, 78 %).

Mol. Formula : $C_{14}H_{15}BrO_6$

IR ($CHCl_3$) υ : 706, 756, 822, 884, 1030, 1098, 1195, 1265, 1368, 1454, 1591, 1733, 1735, 1766 cm^{-1}.

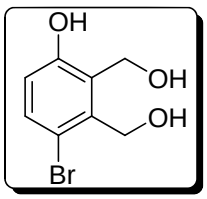
^{1}H NMR (200 MHz, $CDCl_3$) : δ 1.36 (t, *J* = 7.1 Hz, 3H), 2.06 (s, 3H), 2.28 (s, 3H), 4.35 (q, *J* = 7.1 Hz, 2H), 5.31 (s, 2H), 7.05 (d, *J* = 8.7 Hz, 1H), 7.66 (d, *J* = 8.7Hz, 1H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$) : δ 14.0 (q), 20.51 (q), 20.6 (q), 62.0 (t), 63.5 (t), 122.2 (s), 124.6 (d), 129.3 (s), 134.1 (d), 134.9 (s), 147.4 (s), 164.8 (s), 168.5 (s), 170.2 (s) ppm.

ESI-MS (*m/z*) : 381.2 $[M+Na]^+$, 383.2 $[M+Na+2]^+$.

Elemental Analysis Calcd.: C, 46.82; H, 4.21; Br, 22.25 %
Found: C, 46.69; H, 4.11; Br, 22.19 %

4-Bromo-2,3-bis(hydroxymethyl)phenol (50)



To a solution of diacetate **49** (14.21 g, 39.5 mmol) in THF (150 mL) LAH (9.02 g, 237 mmol) was added portion wise over a period of 30 min at 0 ^oC. After

complete addition the mixture was stirred for 3 h at the same temperature. The excess reagent was quenched with 9 mL water followed by 9 ml of 20% sodium hydroxide solution and finally 18 mL of water. After acification with 5% aqueous sulfuric acid the mixture was extracted with ethyl acetate. The organic extracts were concentrated to get the triol **50** as colourless solid (9.12 g, 99%) with mp 119-121 ^{o}C. The triol obtained was used without further purification for next steps.

Mol. Formula : $C_8H_9BrO_3$

IR ($CHCl_3$) υ : 648, 734, 817, 910, 976, 1220, 1285, 1374, 1457, 1580, 3396 (b) cm^{-1}.

^{1}H NMR (200 MHz, CD_3OD+$CDCl_3$) : δ 4.72 (s, 2H), 4.75 (s, 2H), 6.59 (d, *J* = 8.7 Hz, 1H), 7.22 (d, *J* = 8.7 Hz, 1H) ppm.

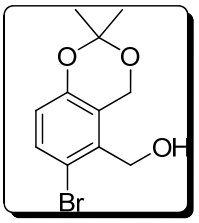
^{13}C NMR (50 MHz, $CDCl_3$) : δ 57.3 (t), 61.5 (t), 114.4 (s), 117.2 (d), 127.7 (s), 132.6 (d), 138.3 (s), 155.3 (s) ppm.

ESI-MS (*m/z*) : 255.1 $[M+Na]^+$, 257.1 $[M+Na+2]^+$.

Elemental Analysis Calcd.: C, 41.23; H, 3.89; Br, 34.28 %

Found: C, 41.09; H, 3.75; Br, 34.13 %

(6-Bromo-2,2-dimethyl-4H-benzo[d][1,3]dioxin-5-yl)methanol (51)



The triol **50** (9.12 g, 39.2 mmol) was dissolved in dry acetonitrile. To this solution 2,2-dimethoxy propane (14.4 mL, 117.5 mmol) was added followed by catalytic amount of *p*-toluenesulphonic acid. The mixture was stirred for 3 h at room temperature. On progress of reaction it became light brown. After that the mixture was quenched with triethyl amine. Then, acetonitrile was removed under reduced pressure and purified by column chromatography using silica gel and a mixture of ethyl acetate/ petroleum ether, afforded the compound **51** (9.62 g, 90%) as a thick liquid.

Mol. Formula : $C_{11}H_{13}BrO_3$

IR ($CHCl_3$) υ : 712, 733, 793, 813, 870, 910, 1005, 1044, 1062, 1120, 1143, 1205, 1247, 1270, 1297, 1357, 1375, 1385, 1455,

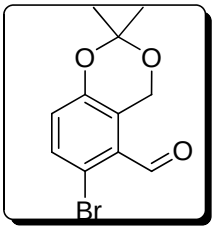
1579, 3429 (b) cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$) : δ 1.52 (s, 6H), 2.20 (bs, 1H), 4.65 (bs, 2H), 4.99 (s, 2H), 6.68 (d, *J* = 8.7 Hz, 1H), 7.35 (d, *J* = 8.7 Hz, 1H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$) : δ 24.5 (q), 59.5 (d), 61.2 (d), 99.2 (s), 114.9 (s), 118.8 (d), 120.7 (s), 131.9 (d), 134.7 (s), 150.9 (s) ppm.

Elemental Analysis Calcd.: C, 48.37; H, 4.80; Br, 29.26 %
Found: C, 48.21; H, 4.63; Br, 29.11 %

6-Bromo-2,2-dimethyl-4H-benzo[d][1,3]dioxine-5-carbaldehyde (52)



Alcohol **51** (8.51 g, 31.1 mmol) and IBX (13.0 g, 46.6 mmol) was taken in a mixture of DMF and ethyl aceate (1:2; 50 mL) and the mixture was stirred for 3 h. Then it was diluted with ethyl acetate and the solids were removed by filtration through *celite* pad. The filtrate was washed with water, dried and concentrated under reduced pressure. On chromatographic purification crude material afforded the required aldehyde **52** (7.84 g, 28.9 mmol) in 93 % yield.

Mol. Formula : $C_{11}H_{11}BrO_3$

IR ($CHCl_3$) υ : 682, 733, 797, 823, 850, 879, 909, 1044, 1059, 1143, 1295, 1273, 1295, 1375, 1386, 1399, 1452, 1686 (b) cm^{-1}.

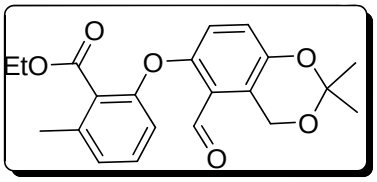
^{1}H NMR (200 MHz, $CDCl_3$) : δ 1.53 (s, 6H), 5.16 (s, 2H), 6.94 (d, *J* = 8.8 Hz, 1H), 7.49 (d, *J*= 8.8 Hz, 1H), 10.43 (s, 1H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$) : δ 24.5 (q), 61.0 (t), 99.4 (s), 119.3 (s), 123.7 (s), 124.1 (d), 129.0 (s), 133.1 (d), 151.5 (s), 194.5 (d) ppm.

ESI-MS (*m/z*) : 309.1 $[M+K]^+$, 311.1 $[M+K+2]^+$.

Elemental Analysis Calcd.: C, 48.73; H, 4.09; Br, 29.47 %
Found: C, 48.59; H, 4.01; Br, 29.33 %

Ethyl 2-(5-formyl-2,2-dimethyl-4H-benzo[d][1,3]dioxin-6-yloxy)-6-methylbenzoate (53)



A mixture of aldehyde **52** (3.574 g, 13.2 mmol), phenol **43** (2.373 g, 13.2 mmol) and copper oxide (0.63 g, 7.9 mmol) in pyridine (20 mL) was refluxed for 24 h. Then the reaction mixture was cooled and diluted with ethyl acetate. Solids were removed by filtration through a *celite* pad and the filtrate was concentrated under reduced pressure. Flashed column chromatographic purification gave the pure diaryl aldehyde **53** (2.099 g, 43%) along with dehalogenated product **54** (683 mg, 27 %).

Mol. Formula : $C_{21}H_{22}O_6$

IR ($CHCl_3$) υ : 733, 778, 801, 872, 913, 984, 1035, 1076, 1110, 1146, 1204 , 1240, 1255, 1274, 1375, 1385, 1403, 1682, 1730 (b) cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$) : δ 1.28 (t, *J* = 7.2 Hz, 3H), 1.54 (s, 6H), 2.39 (s, 3H), 4.33 (q, *J* = 7.2 Hz, 2H), 5.19 (s, 2H), 6.68 (d, *J* = 8.2 Hz, 1H), 6.86 (d, *J* = 9.0 Hz, 1H), 6.70 (d, *J* = 7.7 Hz, 1H), 7.02 (d, *J* = 9.0 Hz, 1H), 7.24 (dd, *J* = 7.7, 8.2 Hz, 1H), 10.49 (s, 1H) ppm.

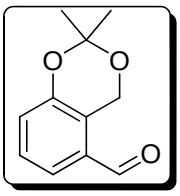
^{13}C NMR (50 MHz, $CDCl_3$) : δ 14.1 (q), 19.3 (q), 24.5 (q, 2C), 61.3 (t, 2C), 99.0 (s), 115.5 (d), 119.4 (d), 121.7 (s), 123.1 (s), 124.5 (d), 125.6 (d), 126.1 (s), 130.5 (d), 137.7 (s), 147.6 (s), 154.2 (s), 154.3 (s), 167.1 (s), 191.3 (d) ppm.

ESI-MS (*m/z*) : 393.4 $[M+Na]^+$.

Elemental Analysis Calcd.: C, 68.10; H, 5.99 %

Found: C, 67.83; H, 5.85 %

2,2-Dimethyl-4H-benzo[d][1,3]dioxine-5-carbaldehyde (54)



Compound **54** was isolated as a by product in Ullmann coupling reaction between **52** and **43** in presence of copper oxide.

Mol. Formula : $C_{11}H_{12}O_3$

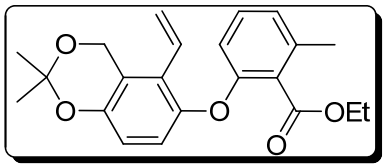
IR ($CHCl_3$) υ : δ 671, 692, 733, 787, 874, 909, 1047, 1080, 1143, 1207, 12 78, 1314, 1357, 1375, 1386, 1397, 1460, 1584, 1692 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$) : δ 1.55 (s, 6H), 5.22 (s, 2H), 7.09 (dd, *J* = 3.0, 7.4 Hz, 1H), 7.38-7.41 (m, 2H), 10.00 (s, 1H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$) : 24.6 (q), 60.9 (t), 99.2 (s), 120.9 (s), 123.2 (d), 127.8 (d), 128.0 (d), 132.7 (s), 152.0 (s), 193.4 (d) ppm.

Elemental Analysis Calcd.: C, 68.74; H, 6.29 %
Found: C, 68.68; H, 6.17 %

Ethyl 2-(2,2-dimethyl-5-vinyl-4H-benzo[d][1,3]dioxin-6-yloxy)-6-methylbenzoate (55)



To a suspension of methyltriphenylphosphonium iodide (1.551 g, 3.84 mmol) in dry THF (10 mL) *n*-butyl lithium (2.4 mL, 1.6 M) was added at 0 ^oC. The mixture was continuously stirred for 30 minutes for complete generation of ylide. Then ylide solution was transfer via cannula to the aldehyde (**53**) (0.948 g, 2.56 mmol) in THF (5 mL) and the whole mixture was stirred for 5 h at rt. After completion of reaction, it was quenched with water and extracted with ethyl acetate. The organic extract was collected, dried and concentrated. Column purification of resulting material afforded compound **55** (782 mg, 83 %) as light yellow viscous liquid.

Mol. Formula : $C_{22}H_{24}O_5$

IR ($CHCl_3$) υ : 648, 733, 909, 971, 1075, 1110, 1146, 1204, 1254, 1274, 1 374, 1385, 1461, 1589, 1727 (b) cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$) : δ 1.33 (t, *J* = 7.0 Hz, 3H), 1.56 (s, 6H), 2.36 (s, 3H), 4.37 (q, *J* = 7.0 Hz, 2H), 4.90 (s, 2H), 5.47 (dd, *J* = 1.5, 11.8, Hz, 1H), 5.60 (dd, *J* = 11.5, 17.9 Hz, 1H), 6.47 (d, *J* = 8.3 Hz, 1H), 6.55 (dd, *J* = 11.8, 17.9 Hz, 1H), 6.72 (d, *J* = 8.8 Hz, 1H), 6.85 (d, *J* = 8.8 Hz, 1H), 6.86 (d, *J* = 7.6 Hz, 1H), 7.12 (t, *J* = 7.9 Hz, 1H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$) : δ 14.2 (q), 19.2 (q), 24.6 (q), 60.4 (t), 61.2 (t), 98.8 (s), 113.4 (d), 117.0 (d), 118.2 (s), 120.7 (d), 121.1 (t), 123.9 (d),

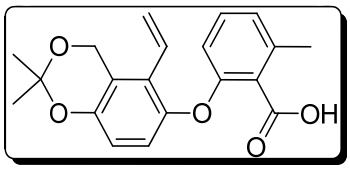
125.0 (s), 126.9 (s), 128.5 (d), 130.1 (d), 136.9 (s), 146.8 (s), 147.8 (s), 155.1 (s), 167.8 (s) ppm.

ESI-MS (*m/z*) : 369.3 $[M+H]^+$.

Elemental Analysis Calcd.: C, 71.72; H, 6.57 %

Found: C, 71.51; H, 6.44 %

2-(2,2-Dimethyl-5-vinyl-4H-benzo[d][1,3]dioxin-6-yloxy)-6-methylbenzoic acid (41)



Ester **55** (713 mg, 1.93 mmol) was treated with 10 % KOH in methanol (20 mL) at refluxing condition for 24 h. After removing methanol, the mixture was diluted with water and acidified with saturated aqueous ammonium chloride solution followed by extraction with ethyl acetate. The organic extracts were collected, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product thus obtained was purified by flash column chromatography to get pure acid **41** (507 mg, 77%) as colourless crystalline solid (m.p. 78 ^oC).

Mol. Formula : $C_{20}H_{20}O_5$

IR ($CHCl_3$) υ : 798, 828, 1032, 1076, 1141, 12421279, 1384,1458, 1586,1696, 3350 (b) cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$) : δ 1.56 (s, 6H), 2.47 (s, 3H), 4.89 (s, 2H), 5.47 (dd, *J* =1.3, 11.9 Hz, 1H), 5.58 (dd, *J* = 1.3, 17.8 Hz, 1H), 6.48 (d, *J* = 8.7 Hz, 1H), 6.52 (dd, *J* = 11.9, 17.8 Hz, 1H), 6.74 (d, *J* = 9.0 Hz, 1H), 6.88 (d, *J* = 8.8 Hz, 1H), 6.90 (d, *J* = 7.5 Hz, 1H), 7.16 (t, *J* = 8.0 Hz, 1H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$) : δ 20.1 (q), 24.6 (q), 60.4 (t), 98.9 (s), 113.2 (d), 117.2 (d), 118.4 (s), 121.1 (d), 121.5 (t), 122.7 (s), 124.3 (d), 127.4 (s), 128.3 (d), 130.9 (d), 138.3 (s), 146.2 (s), 148.2 (s), 155.8 (s), 171.4 (s) ppm.

ESI-MS (*m/z*) : 341.2 $[M+H]^+$, 363.2 $[M+Na]^+$

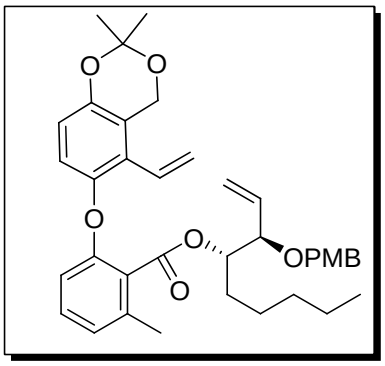
Elemental Analysis Calcd.: C, 70.57; H, 5.92 %

Found: C, 70.42; H, 5.81 %

Crystal data for 41.

Empirical formula	$C_{20}H_{20}O_5$
Formula weight	340.36
Temperature	295(2) K
Wavelength	0.71073 A
Crystal system, space group	Triclinic, P-1
Unit cell dimensions	a = 8.411(2) Å α = 85.072(4) deg.
	b = 9.978(2) Å α= 82.874(4) deg.
	c = 10.418(2) Å γ = 77.872(4) deg.
Volume	846.6(3) $Å^3$
Z, Calculated density	2, 1.335 Mg/m^3
Absorption coefficient	0.096 mm^{-1}
F(000)	360
Crystal size	0.13 x 0.10 x 0.08 mm
Theta range for data collection	1.97 to 25.00 º
Limiting indices	-9<=h<=9, -11<=k<=11, -12<=l<=12
Reflections collected / unique	9052 / 2965 [R(int) = 0.0282]
Completeness to theta = 25.00	99.8 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9924 and 0.9874
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2965 / 0 / 229
Goodness-of-fit on F^2	1.190
Final R indices [I>2sigma(I)]	R1 = 0.0647, wR2 = 0.1286
R indices (all data)	R1 = 0.0878, wR2 = 0.1381
Largest diff. peak and hole	0.212 and -0.170 $e.Å^{-3}$

(3*R*,4*S*)-3-(4-Methoxybenzyloxy)non-1-en-4-yl 2-(2,2-dimethyl-5-vinyl-4H-benzo[d][1,3]dioxin-6-yloxy)-6-methylbenzoate (40)



To a mixture of acid **41** (180 mg, 0.529 mmol) and alcohol **13** (220 mg, 0.793 mmol) in toluene (5 mL) triethyl amine (1 mL) was added followed by Mukaiyama reagent (**29**) (202 mg, 0.793 mmol) under argon atmosphere and the mixture was stirred for 10 h at 100 ^{o}C. Then the reaction mixture cooled to rt and the volatiles were removed. The crude mixture was subjected to flash column chromatography to get pure ester **40** (130 mg, 41%).

Mol. Formula : $C_{37}H_{44}O_7$

$[\alpha]_D^{25}$: –24.2 (*c* = 0.90, $CHCl_3$)

IR ($CHCl_3$) υ : 667, 824, 971, 1036, 1074, 1172, 1216, 1251, 1384, 1461, 1513, 1612, 1727, 2858, 2926

^{1}H NMR (500 MHz, $CDCl_3$) : δ 0.76 (t, *J*= 7.0 Hz, 3H), 1.05-1.17 (m, 4H), 1.21-1.42 (m, 2H), 1.55 (s, 6H), 1.60-1.67 (m, 2H), 2.31 (s, 3H), 3.79 (s, 3H), 3.92 (dd, *J*= 4.3, 7.5 Hz, 1H), 4.34 (d, *J*= 11.4 Hz, 1H), 4.51(d, *J*= 11.4 Hz, 1H), 4.88 (s, 2H), 5.24-5.36 (m, 3H), 5.41 (dd, *J*= 11.8, 1.4 Hz, 1H), 5.54 (dd, *J*= 1.4, 17.9 Hz, 1H), 5.84 (ddd, *J*= 7.4, 9.7, 17.4 Hz, 1H), 6.42 (d, *J*= 8.9 Hz, 1H), 6.52 (dd, *J*= 11.7, 17.9Hz, 1H), 6.69(d, *J*= 8.8 Hz, 1H), 6.78-6.91 (m, 4H), 7.10 (t, *J*= 8.0 Hz, 1H), 2.20 (d, *J*= 8.6 Hz, 2H) ppm.

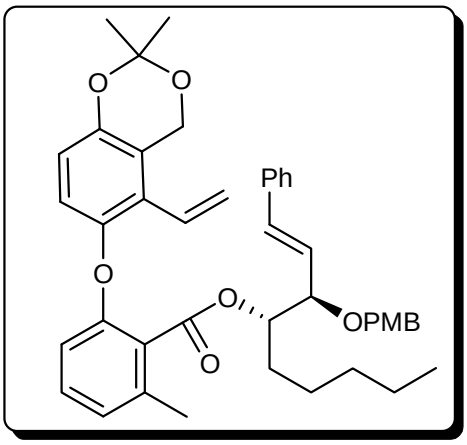
^{13}C NMR (125 MHz, $CDCl_3$) : δ 13.9 (q), 19.4 (q), 22.4 (t), 24.6 (q), 24.6 (q), 24.9 (t), 29.8 (t), 31.7 (t), 55.2 (q), 60.4 (t), 70.1 (t), 76.1 (d), 81.2 (d), 98.8 (s), 113.1 (d), 113.6 (d), 117.1 (d), 118.2 (s), 119.4 (t), 121.0 (d), 121.0 (t), 123.7 (d), 125.2 (s), 127.1 (s), 128.5 (d), 129.1 (d), 129.9 (d), 130.5 (s), 135.0 (d), 137.0 (s), 146.8 (s), 147.9 (s), 155.2 (s), 159.0 (s), 167.5 (s) ppm.

ESI-MS (*m/z*) : 601.6 $[M+H]^+$, 623.5 $[M+Na]^+$.

Elemental Analysis Calcd.: C, 73.97; H, 7.38 %

Found: C, 73.63; H, 7.39 %

(*E*,3*R*,4*S*)-3-(4-Methoxybenzyloxy)-1-phenylnon-1-en-4-yl 2-(2,2-dimethyl-5-vinyl-4H-benzo[d][1,3]dioxin-6-yloxy)-6-methylbenzoate (59)



To a stirred solution of starting ester **40** (40 mg, 0.066 mmol) in 50 mL dry toluene Grubbs' 2nd generation catalyst (1 eqv.) was loaded and degassed thoroughly under argon atmosphere and the mixture heated at 120 °C for 24 h. Then toluene was removed under reduced pressure and flash column purification of the crude product gave pure cross coupled product **59** (28 mg, 63%).

Mol. Formula : $C_{43}H_{48}O_7$

$[\alpha]_D^{25}$: –15.4 (*c* = 0.70, $CHCl_3$)

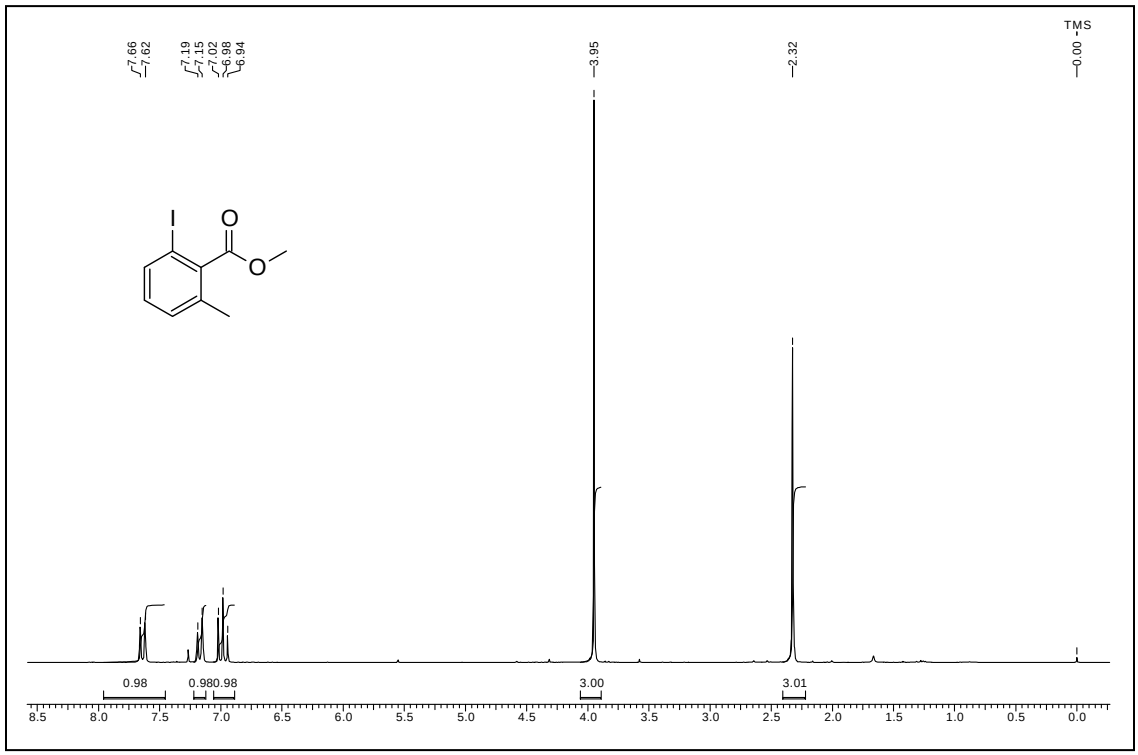
IR ($CHCl_3$) υ : 667, 695, 826, 875, 970, 1036, 1073, 1111, 1145, 1173, 1254, 1375, 1385, 1461, 1513, 1585, 1611, 1727 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) : δ 0.76 (t, *J*= 6.0 Hz, 3H), 1.09-1.23 (m, 4H), 1.28-1.36 (m, 1H), 1.37-1.48 (m, 1H), 1.55 (s, 6H), 1.66-1.71 (m, 2H), 2.25 (s, 3H), 3.79 (s, 3H), 4.08 (dd, *J*= 4.7, 7.8 Hz, 1H), 4.39 (d, *J*= 11.5 Hz, 1H), 4.55 (d, *J*= 11.5 Hz, 1H), 4.85 (s, 2H), 5.36-5.42 (m, 2H), 5.53 (dd, *J*= 1.3, 17.7 hz, 1H), 6.21 (dd, *J*= 8.0, 16.0 Hz, 1H), 6.41 (d, *J*= 8.2 Hz, 1H), 6.48 (dd, *J*= 11.7, 17.7 Hz, 1H), 6.58 (d, *J*= 16.0 Hz, 1H), 6.67 (d, *J*= 8.7 Hz, 1H), 6.78-6.84 (m, 4H), 7.08 (t, *J*= 8.0 Hz, 1H), 7.21-7.25 (m, 7H) ppm.

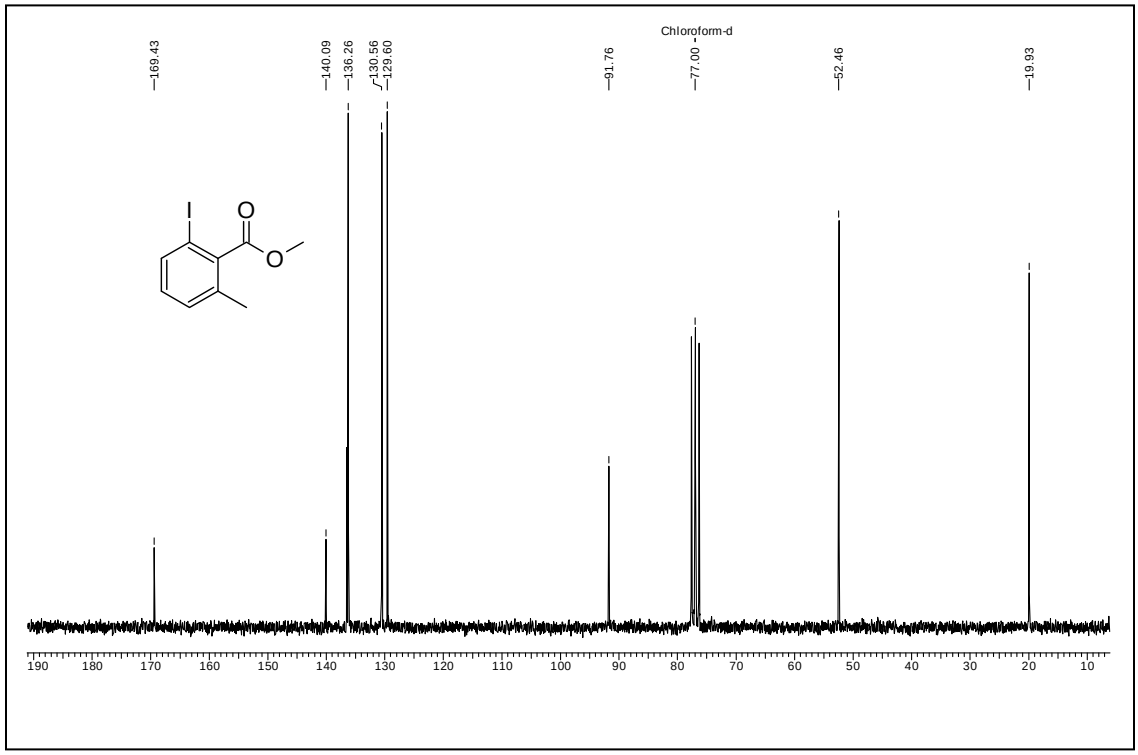
^{13}C NMR (125 MHz, $CDCl_3$) : δ 13.9 (q), 19.3 (q), 22.5 (t), 24.60 (q), 24.65 (q), 24.9 (t), 30.2 (t), 31.7 (t), 55.2 (q), 60.4 (t), 70.1 (t), 76.3 (d), 80.9 (d), 98.8 (s), 112.9 (d), 113.6 (d), 117.1 (d), 118.2 (s), 121.0 (t), 121.2 (d), 123.7 (d), 125.1 (s), 126.4 (d), 126.6 (d), 127.2 (s), 127.8 (d), 128.46 (d), 128.50 (d), 129.2 (d), 129.9 (d), 130.5

	(s), 134.5 (d), 136.4 (s), 137.1 (s), 146.7 (s), 147.9 (s), 155.3 (s), 159.0 (s), 167.6 (s) ppm.
ESI-MS (*m/z*)	: 699.0 $[M+Na]^+$.
Elemental Analysis	Calcd.: C, 76.30; H, 7.15 %
	Found: C, 76.16; H, 7.16 %

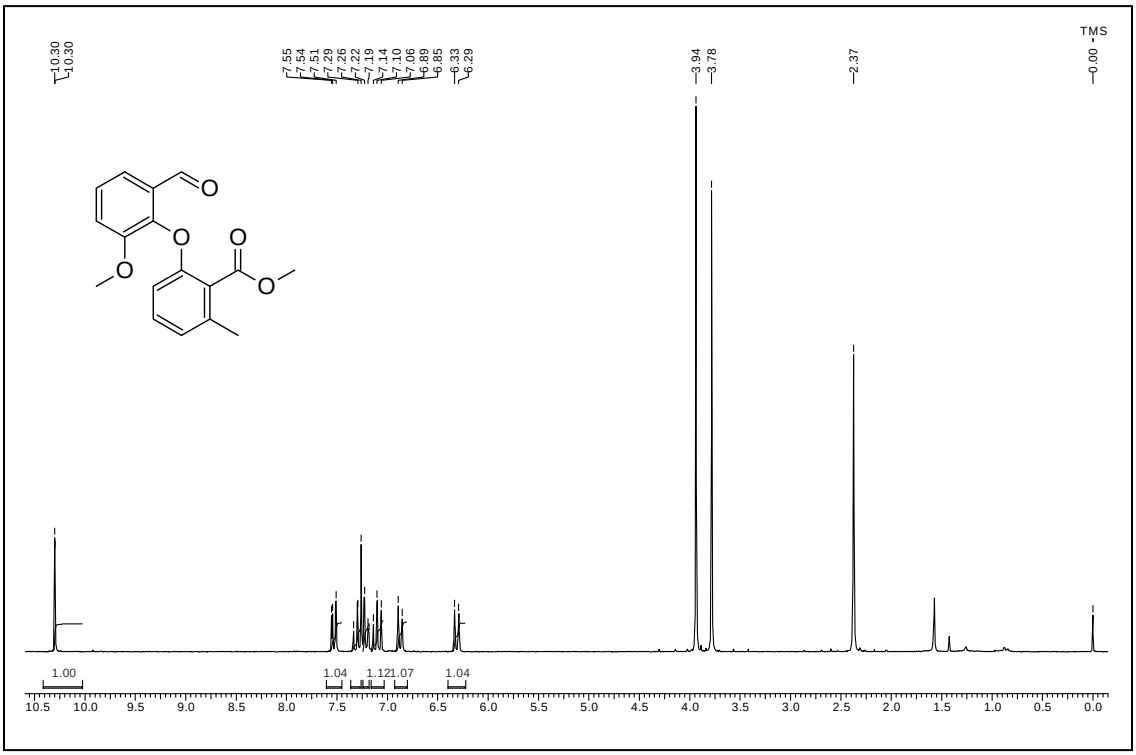
Spectra



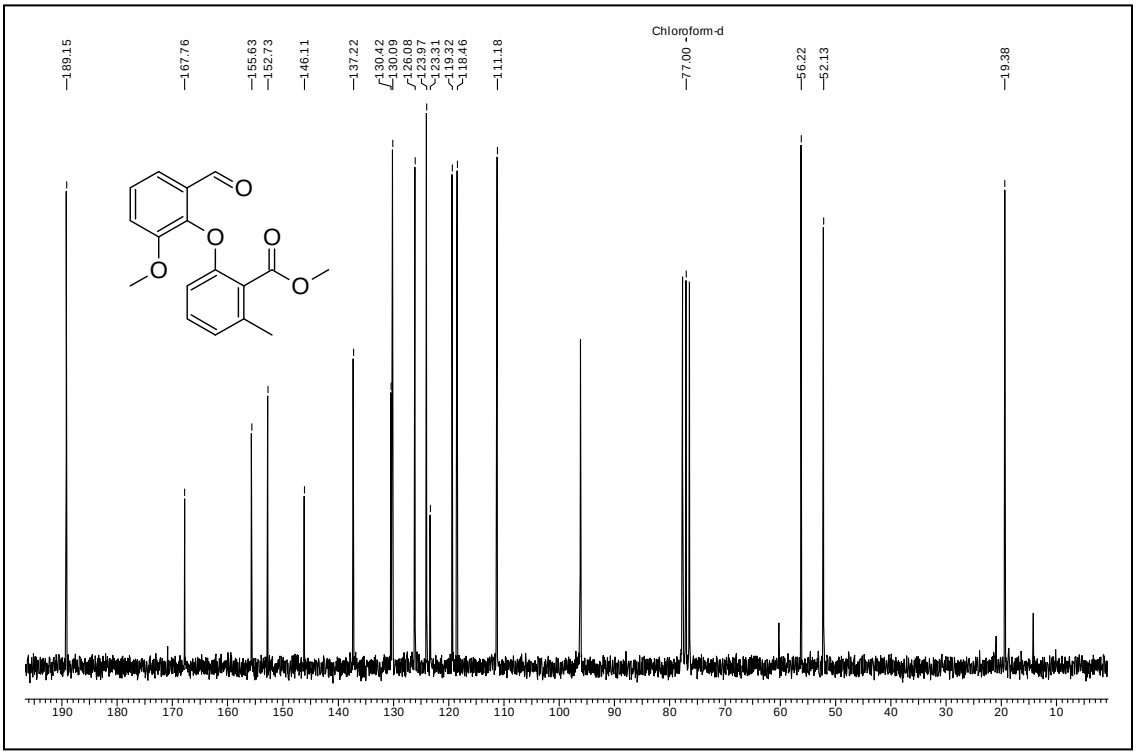
^{1}H NMR Spectrum of 15 in $CDCl_3$



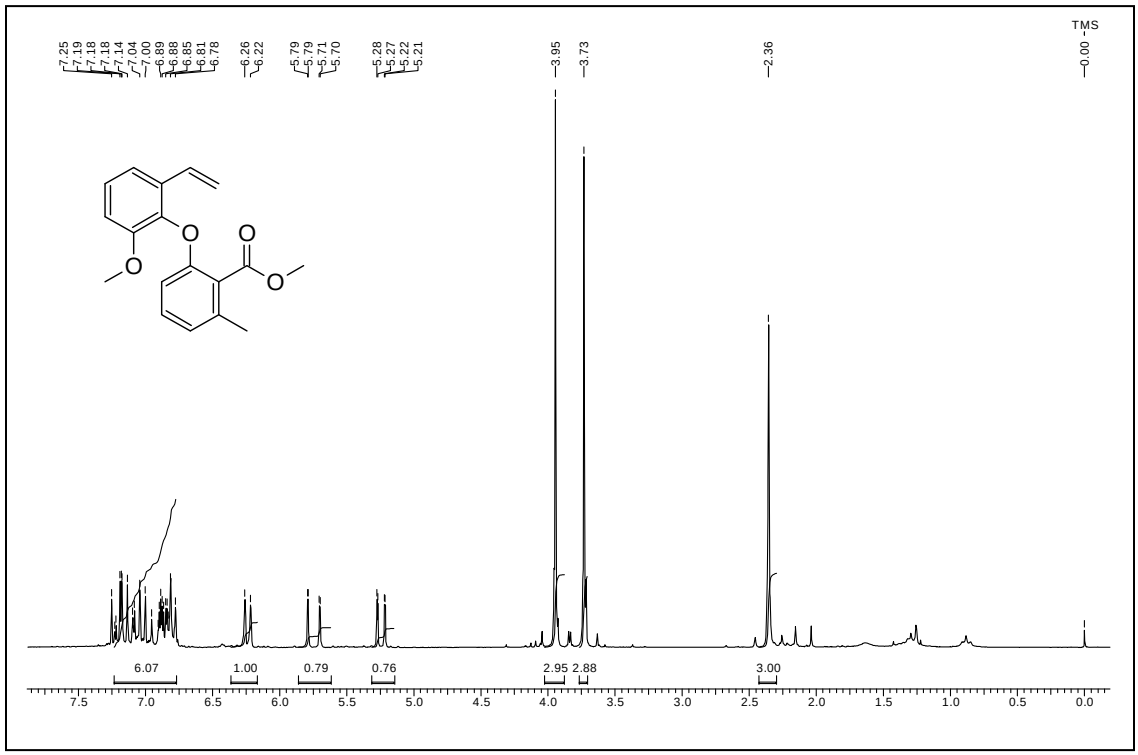
^{13}C NMR Spectrum of 15 in $CDCl_3$



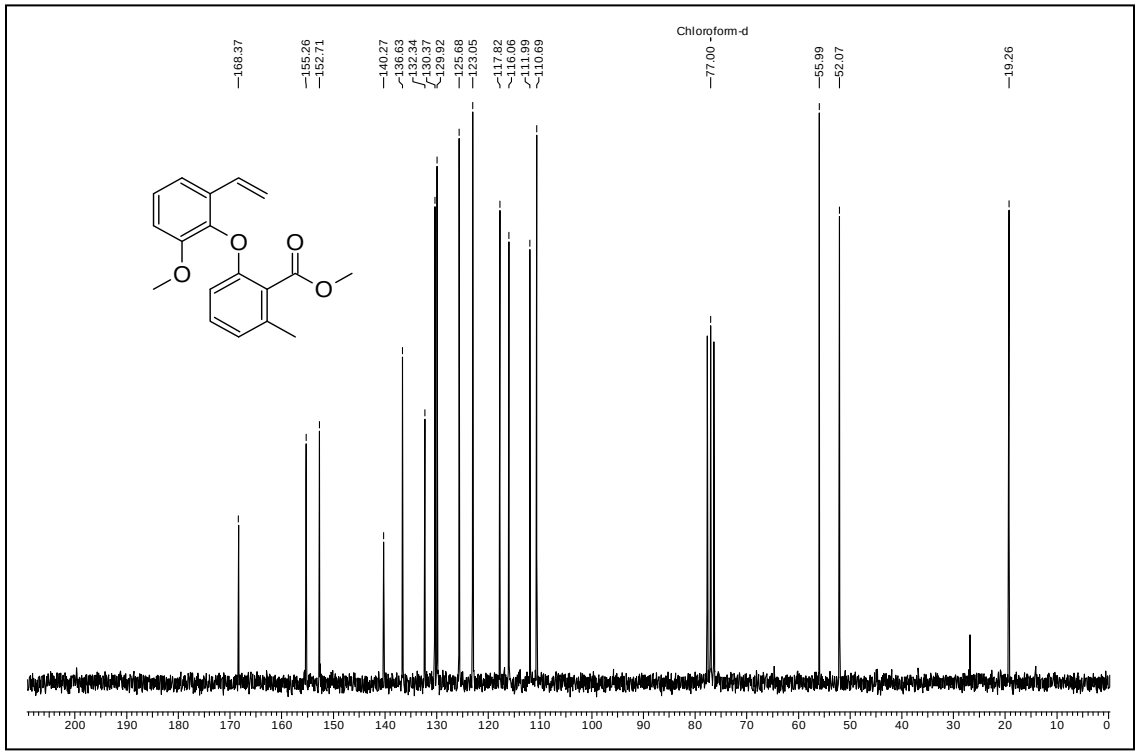
^{1}H NMR Spectrum of 26 in $CDCl_3$



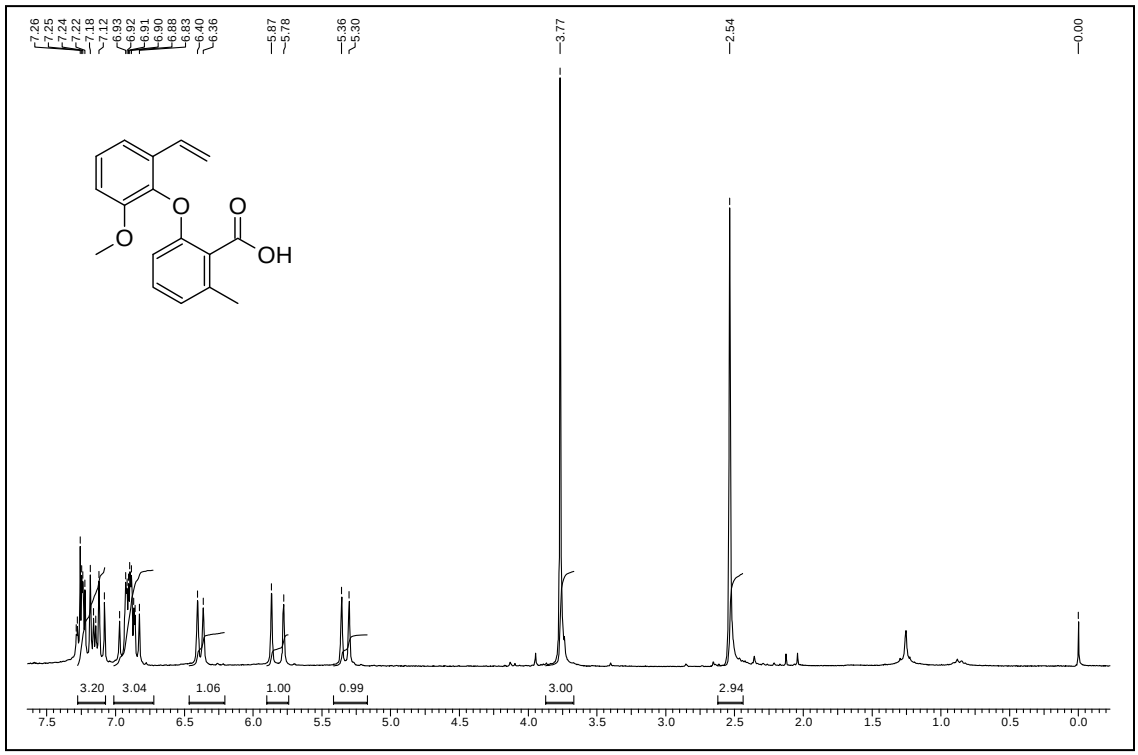
^{13}C NMR Spectrum of 26 in $CDCl_3$



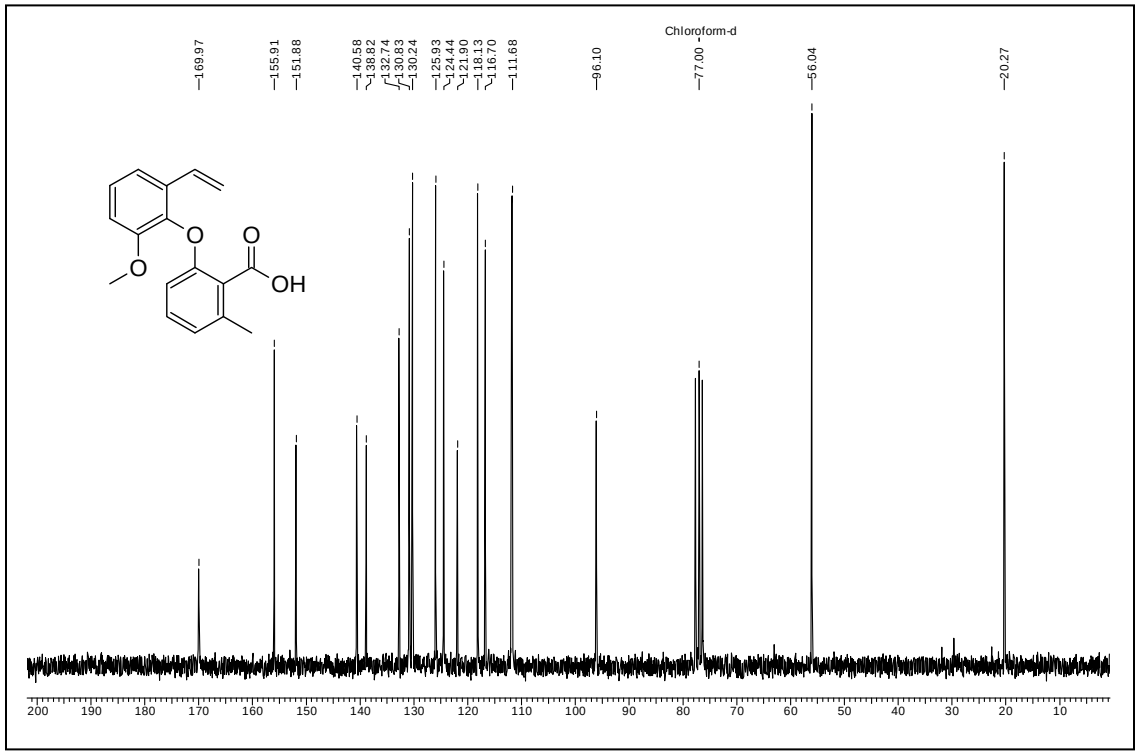
^{1}H NMR Spectrum of 27 in $CDCl_3$



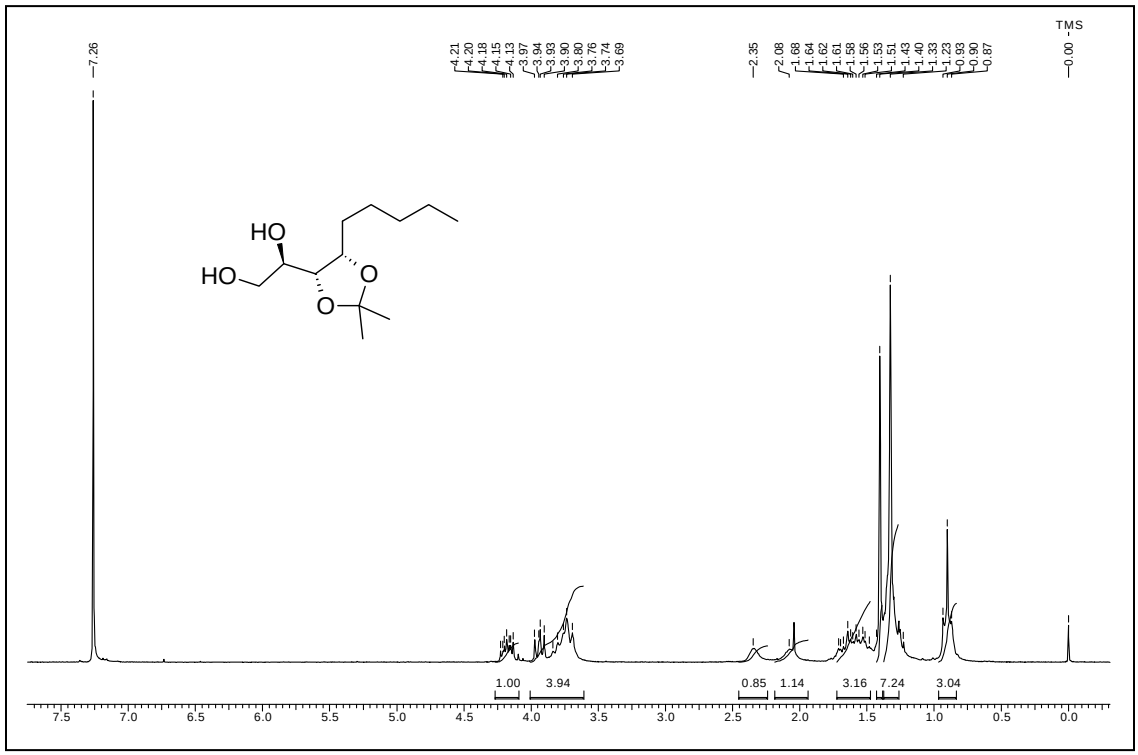
^{13}C NMR Spectrum of 27 in $CDCl_3$



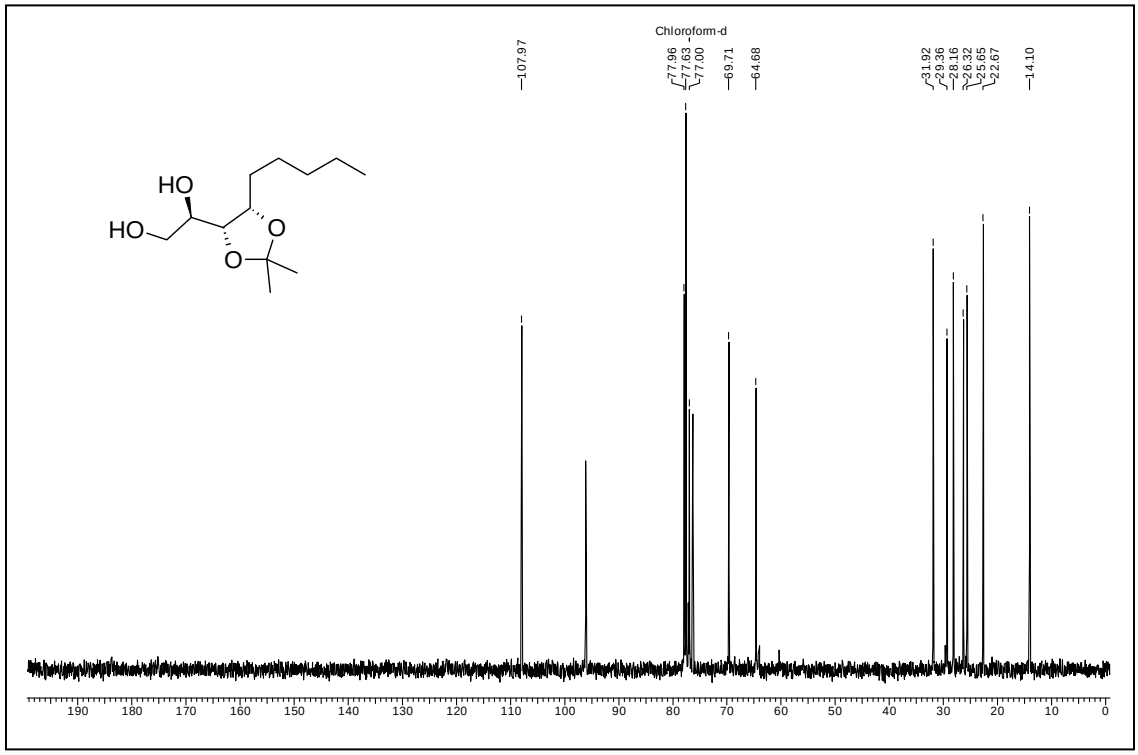
^{1}H NMR Spectrum of 14 in $CDCl_3$



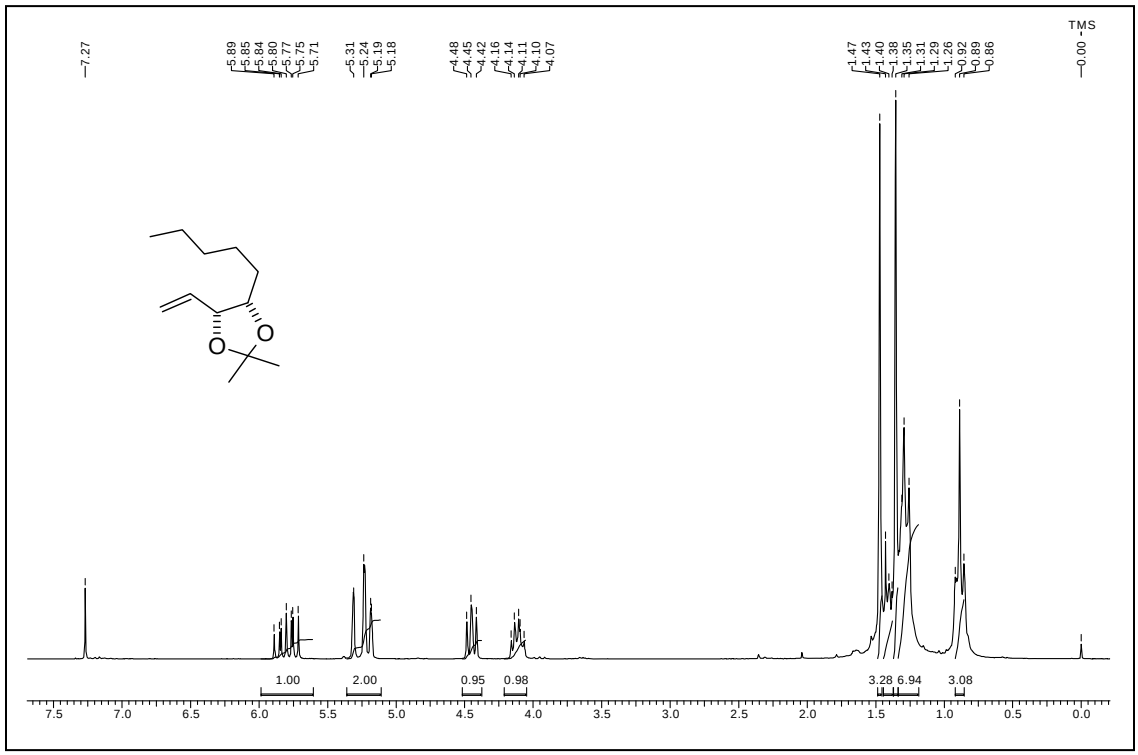
^{13}C NMR Spectrum of 14 in $CDCl_3$



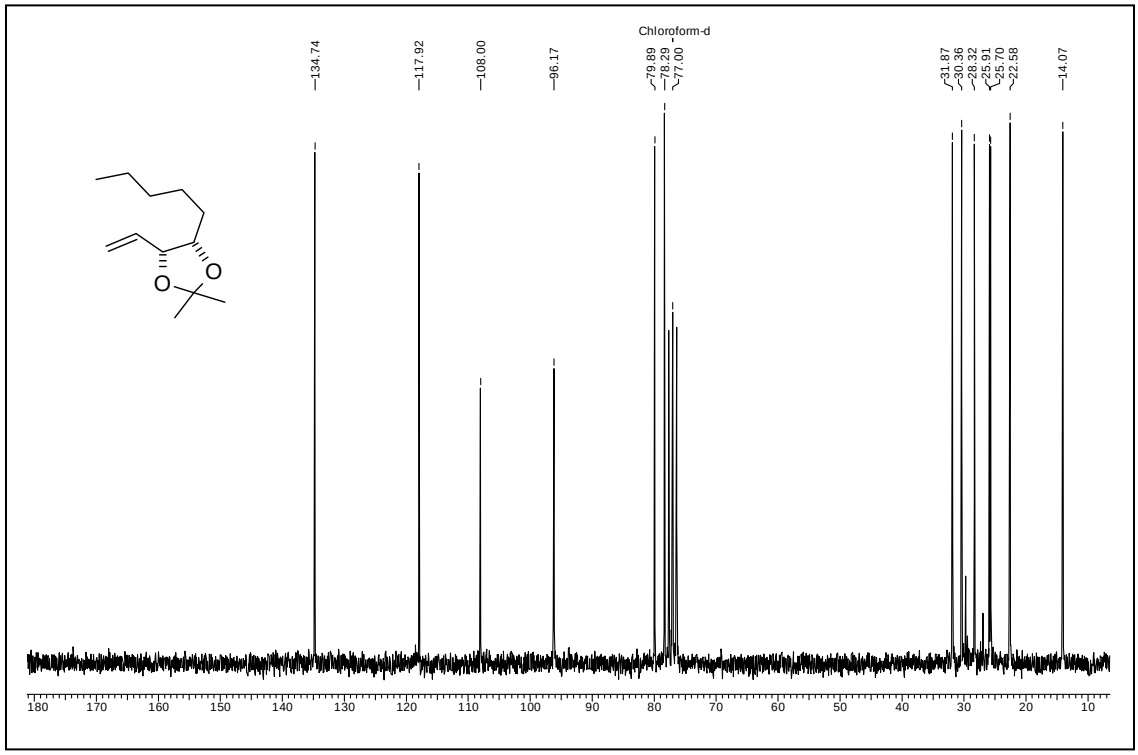
^{1}H NMR Spectrum of 20 in $CDCl_3$



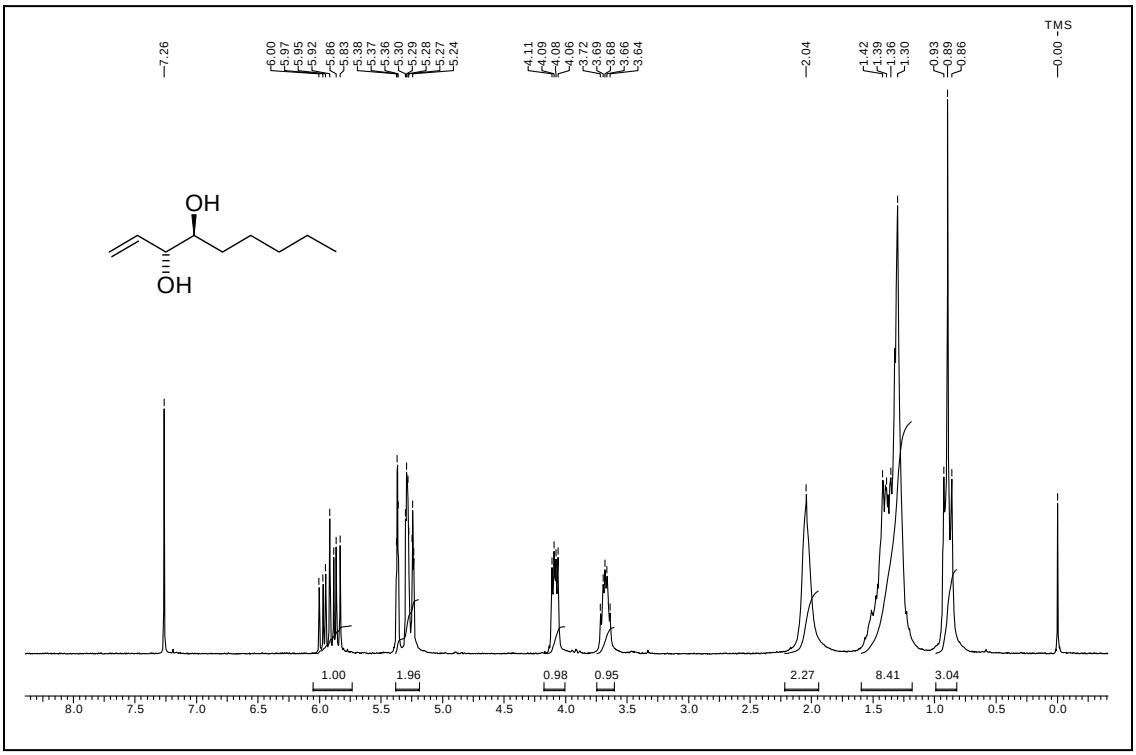
^{13}C NMR Spectrum of 20 in $CDCl_3$



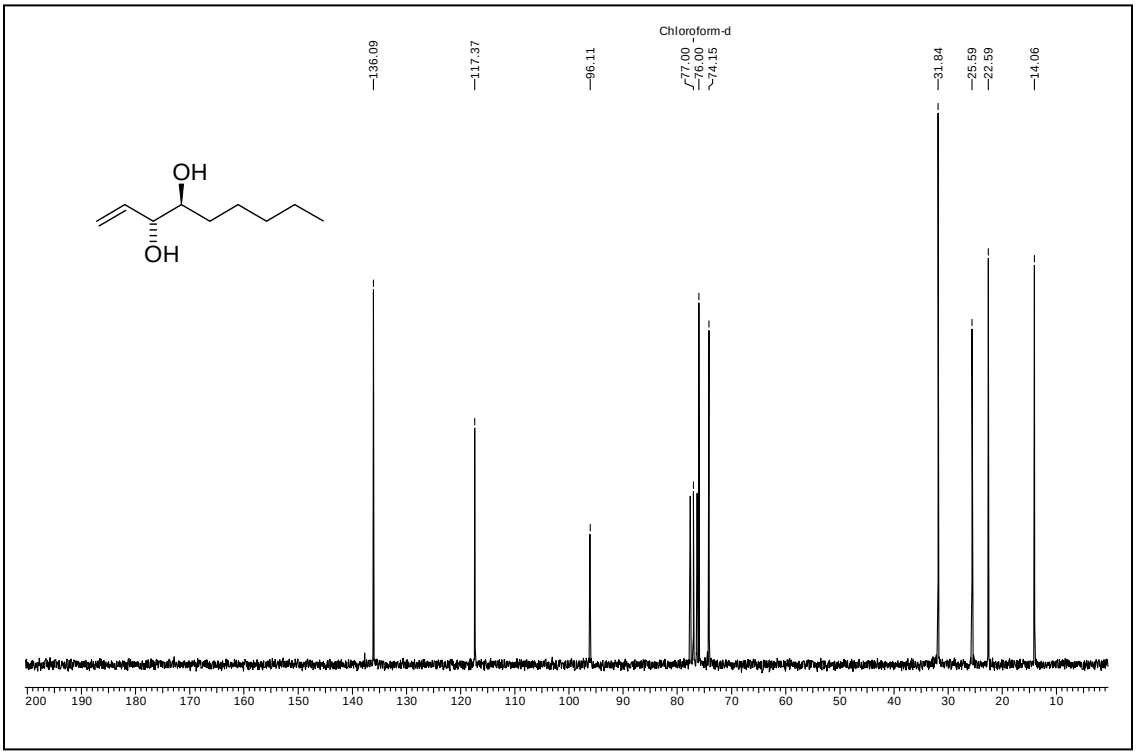
^{1}H NMR Spectrum of 21 in $CDCl_3$



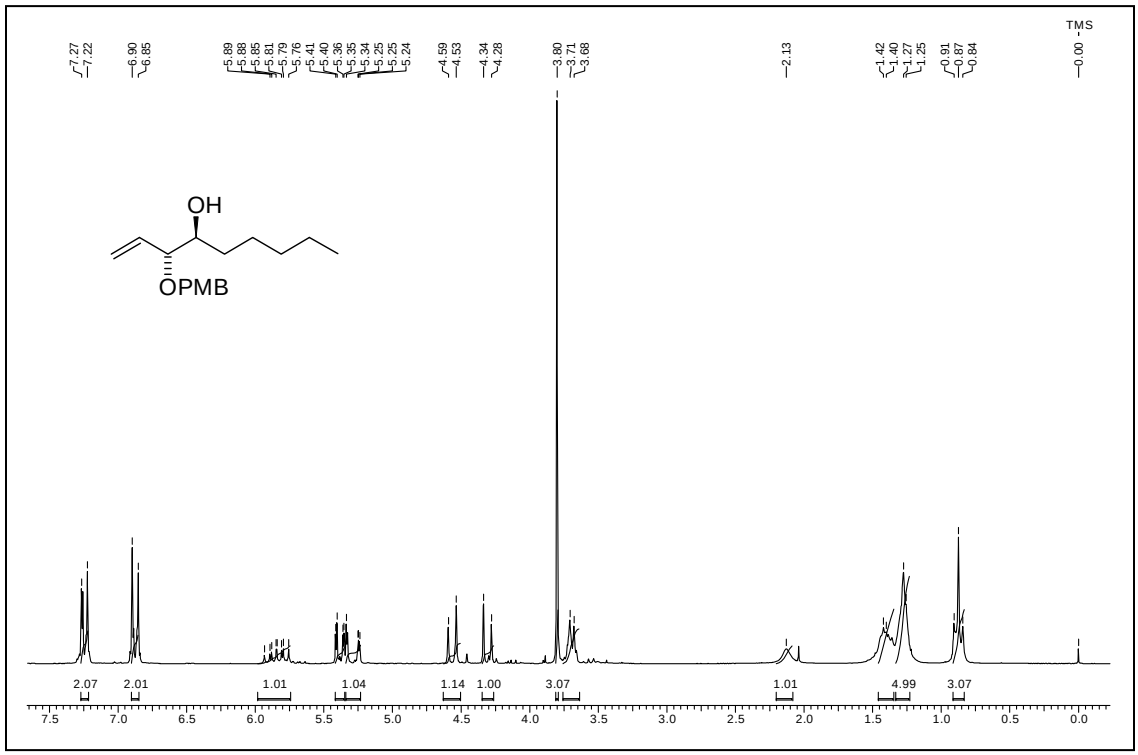
^{13}C NMR Spectrum of 21 in $CDCl_3$



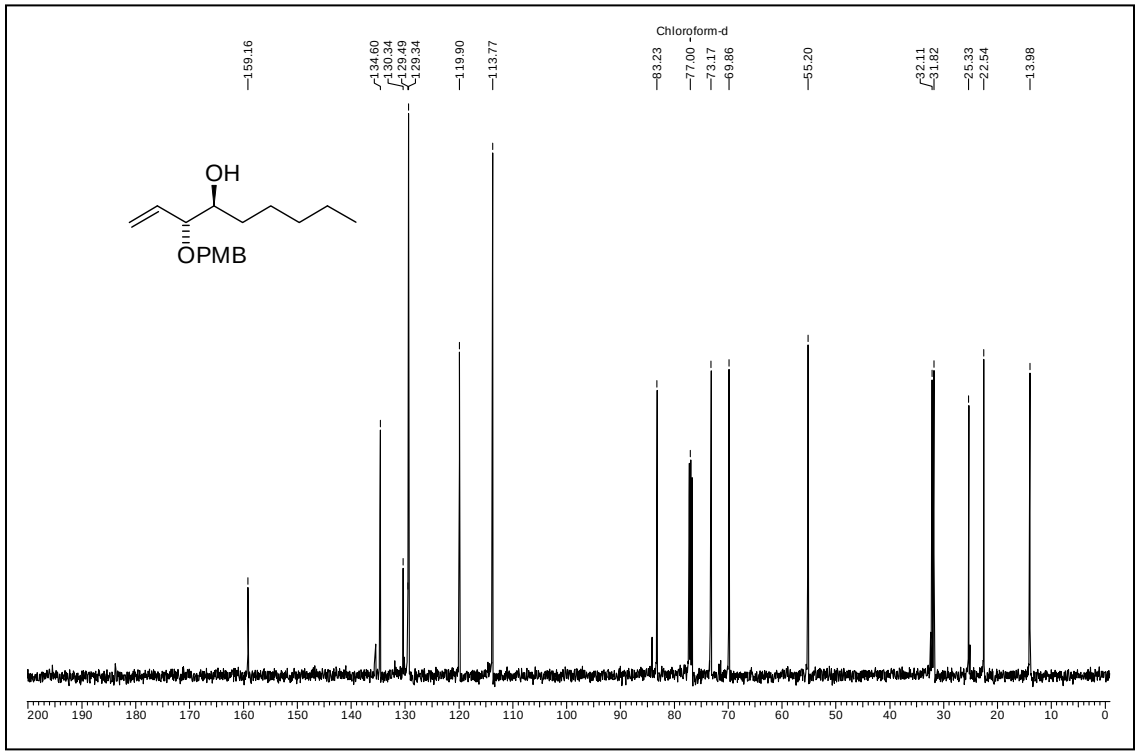
^{1}H NMR Spectrum of 22 in $CDCl_3$



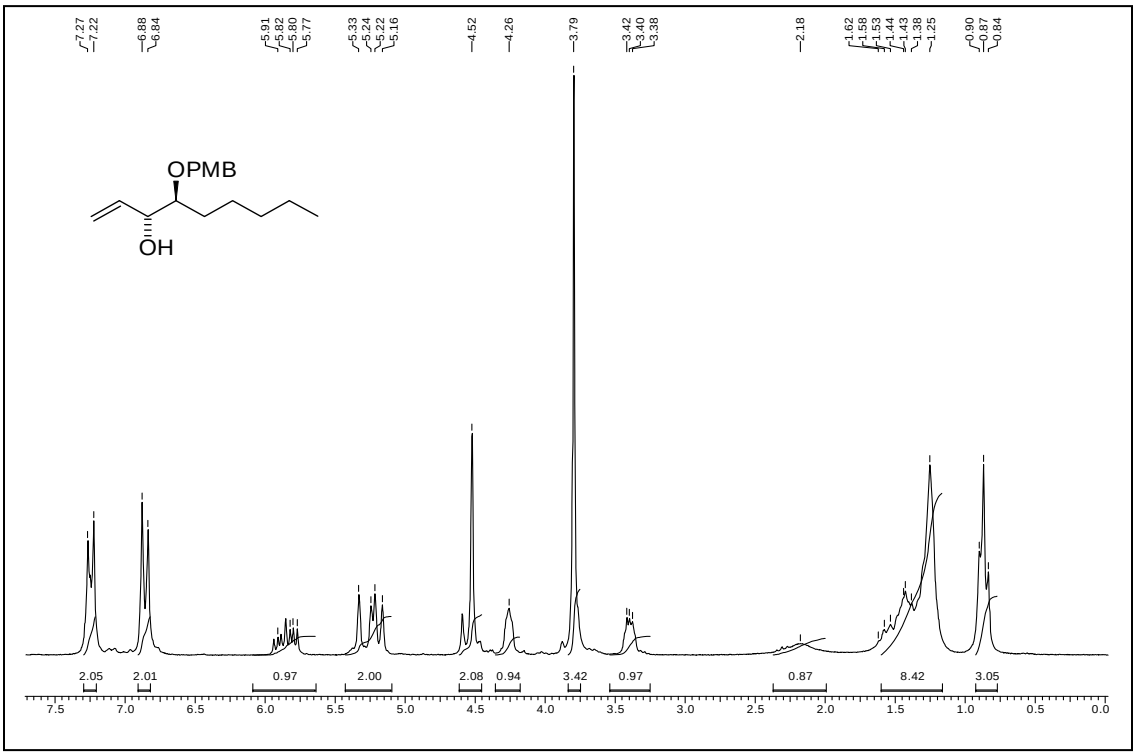
^{13}C NMR Spectrum of 22 in $CDCl_3$



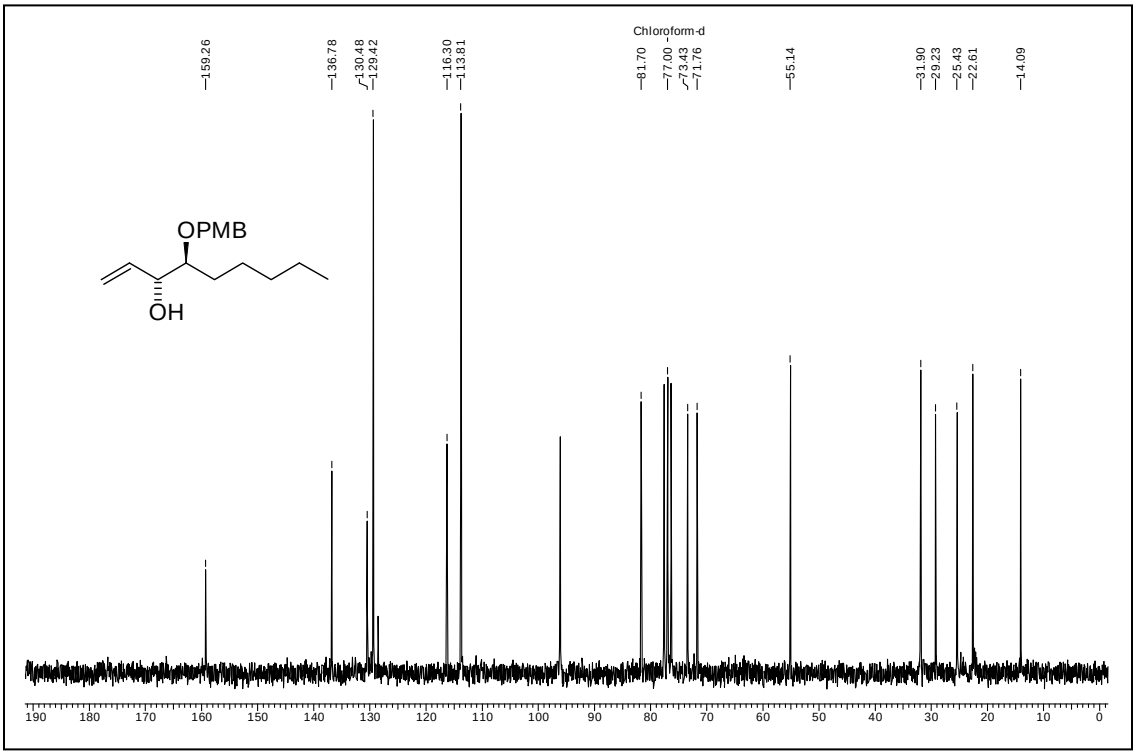
^{1}H NMR Spectrum of 13 in $CDCl_3$



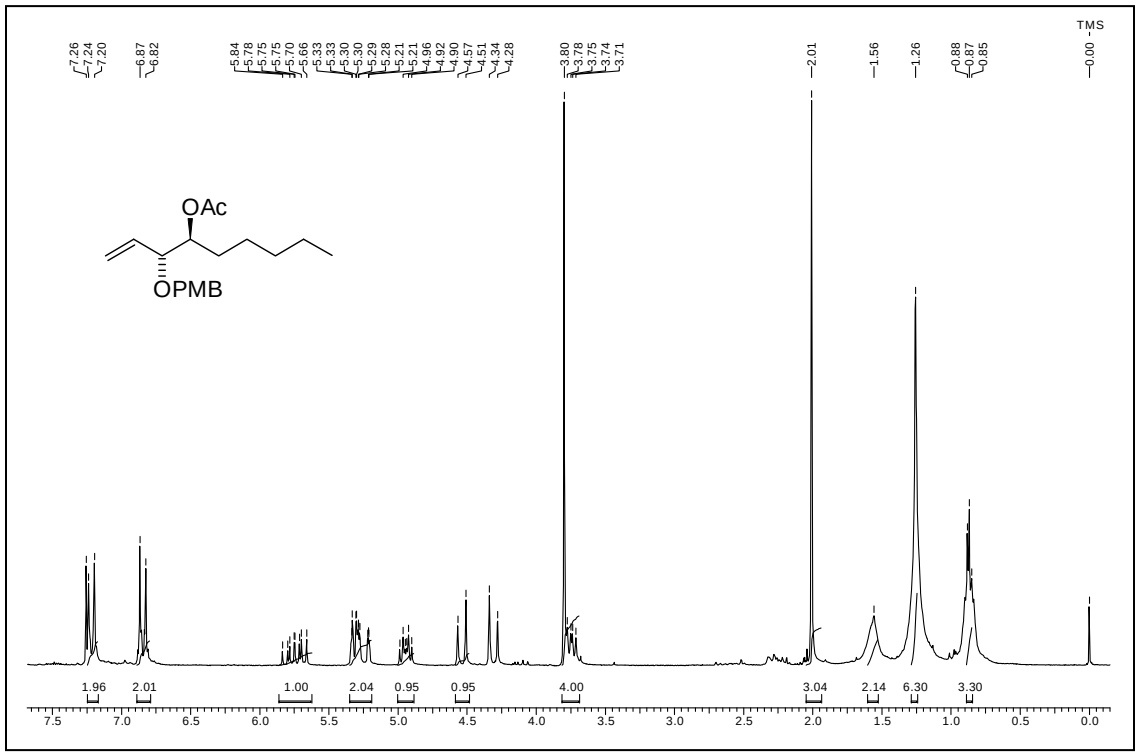
^{13}C NMR Spectrum of 13 in $CDCl_3$



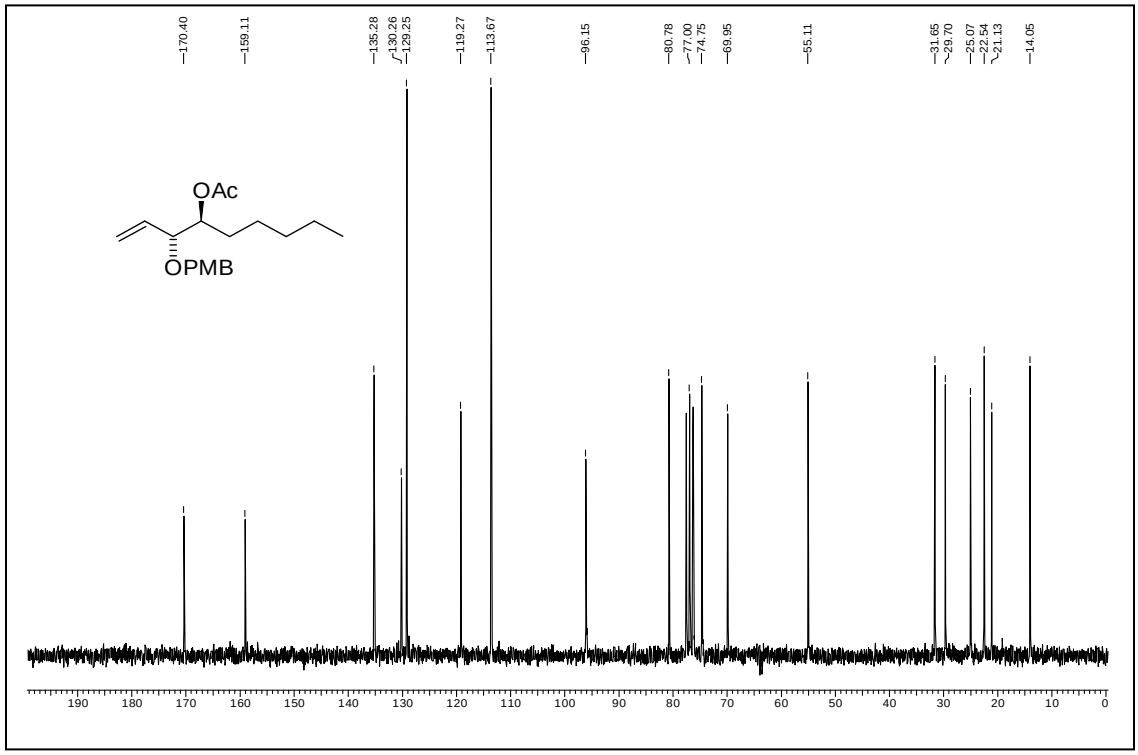
^{1}H NMR Spectrum of 23 in $CDCl_3$



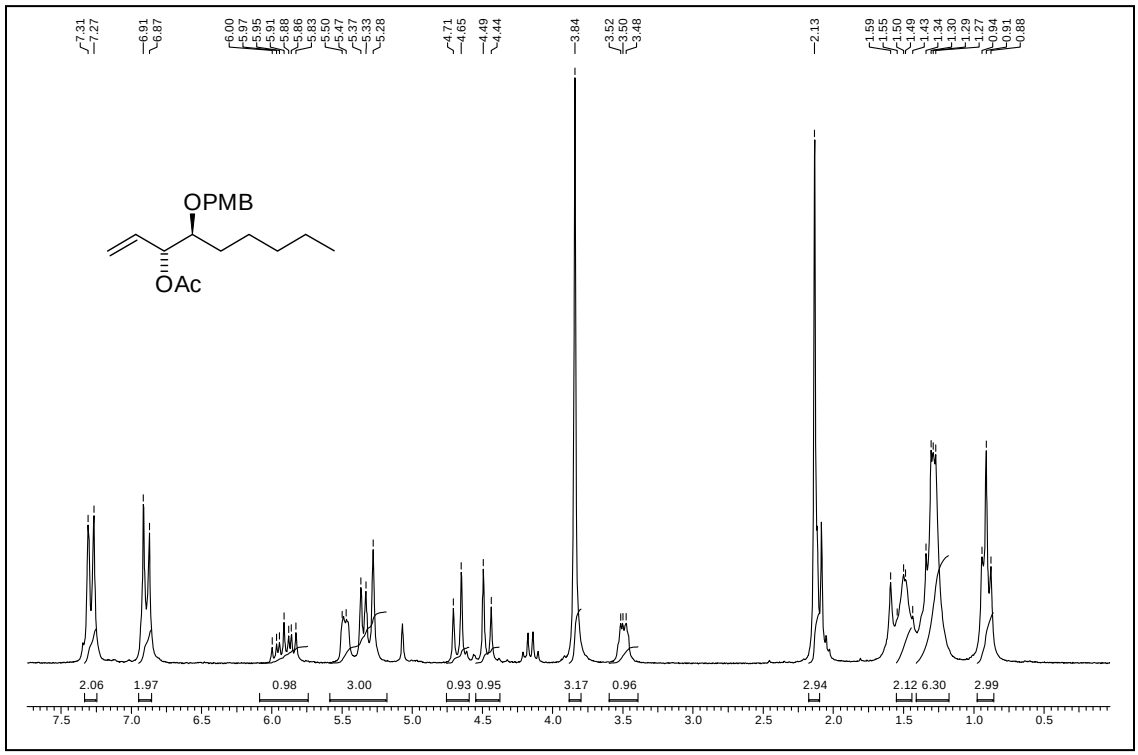
^{13}C NMR Spectrum of 23 in $CDCl_3$



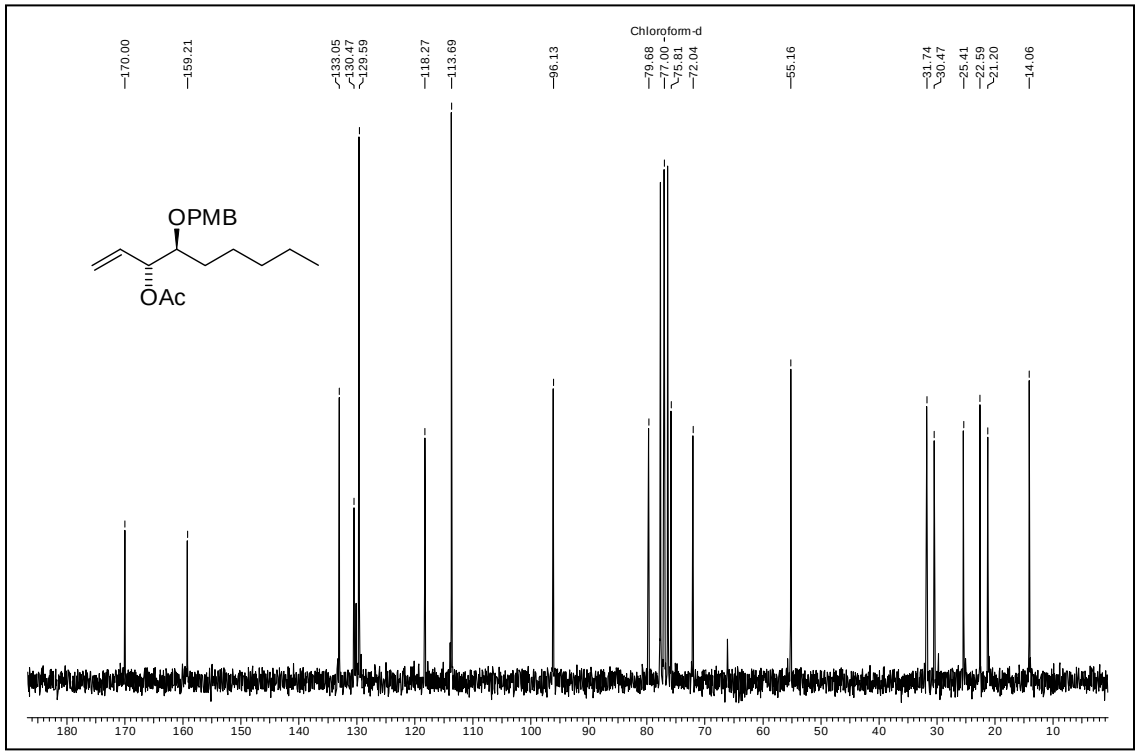
^{1}H NMR Spectrum of 13Ac in $CDCl_3$



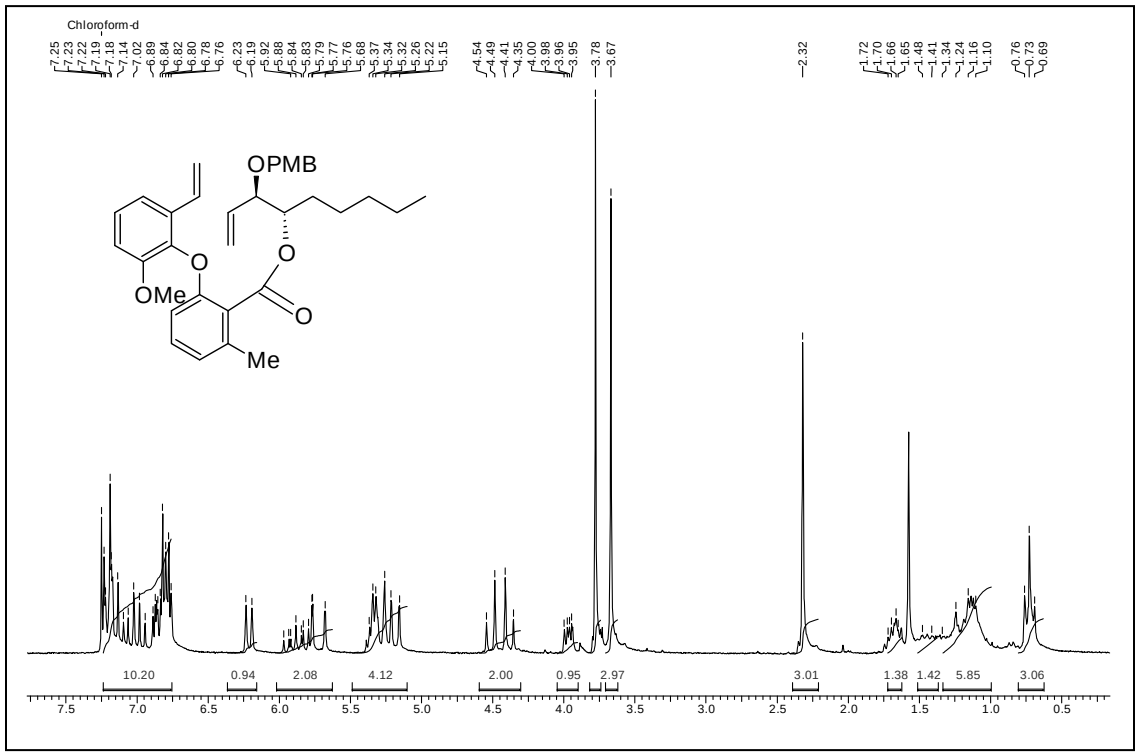
^{13}C NMR Spectrum of 13Ac in $CDCl_3$



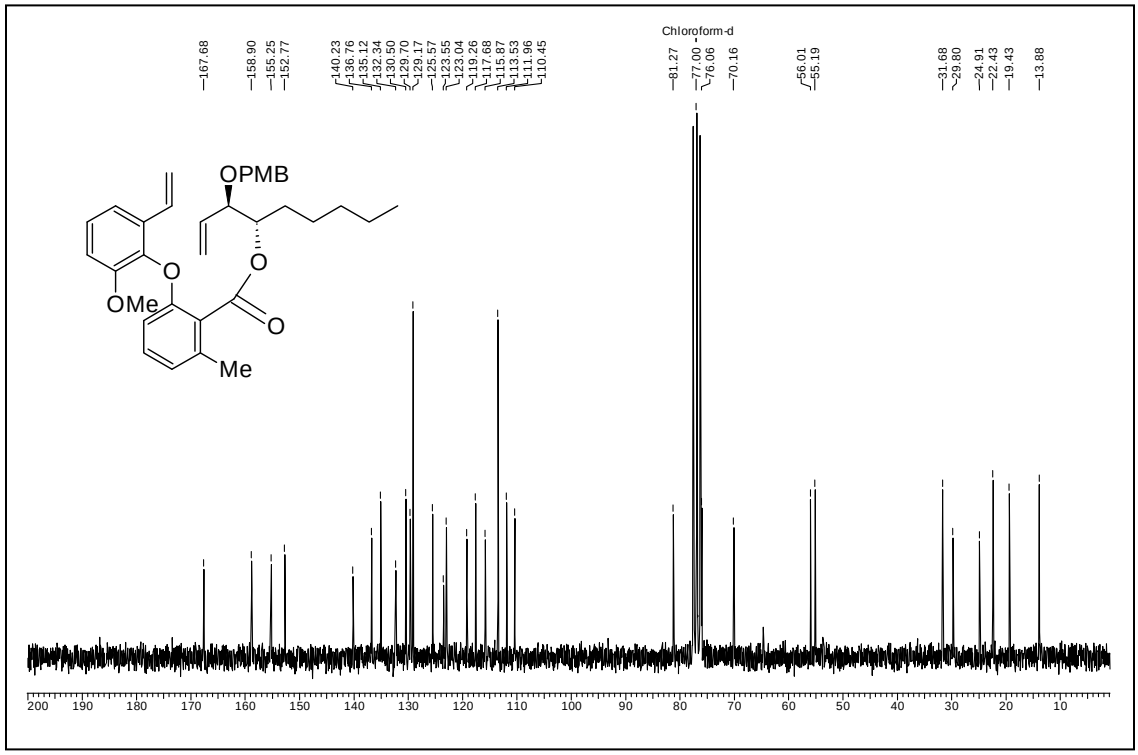
^{1}H NMR Spectrum of 23Ac in $CDCl_3$



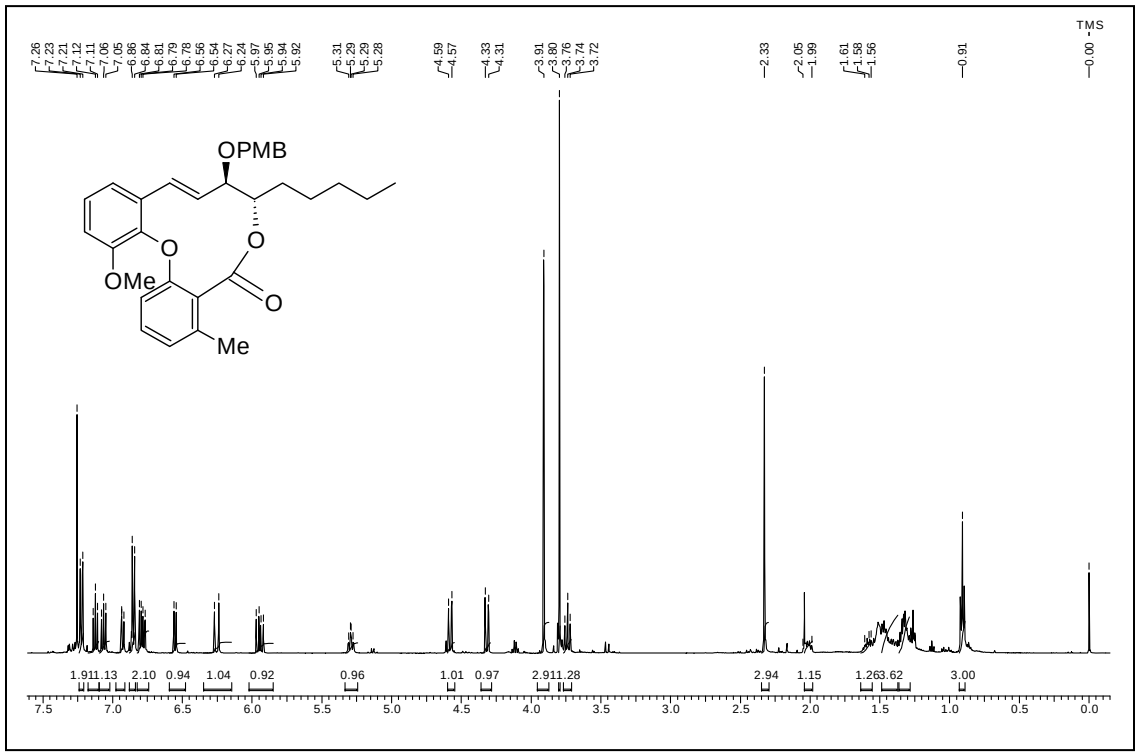
^{13}C NMR Spectrum of 23Ac in $CDCl_3$



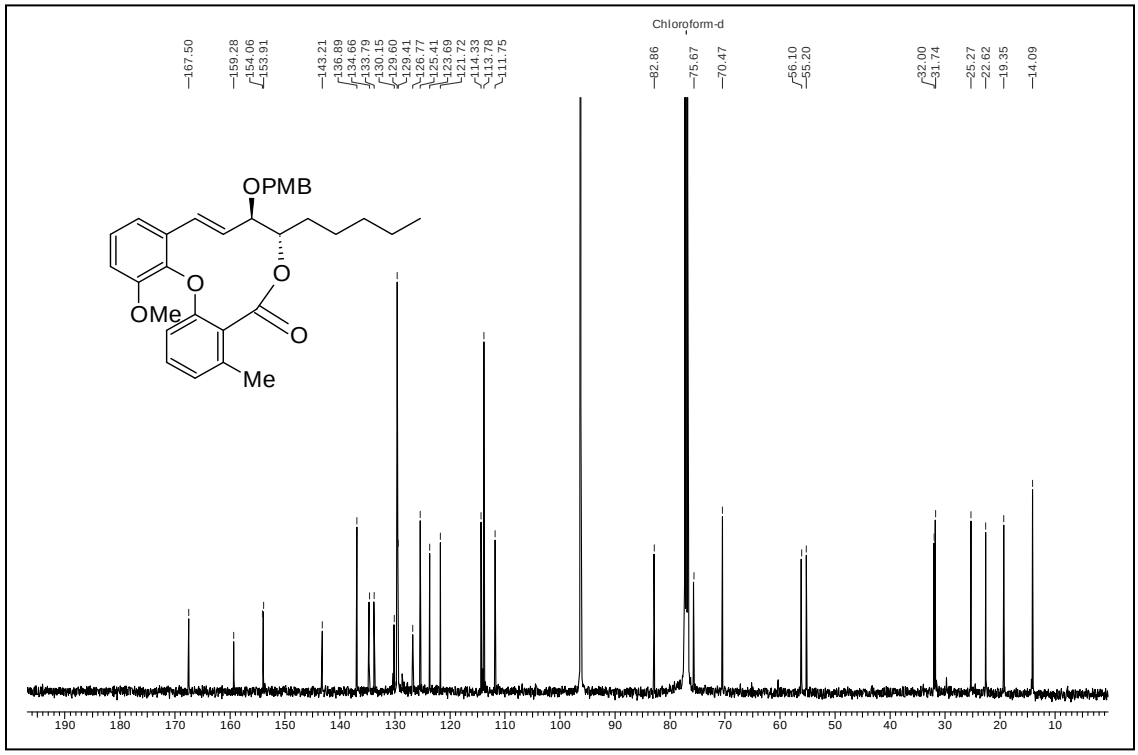
^{1}H NMR Spectrum of 12 in $CDCl_3$



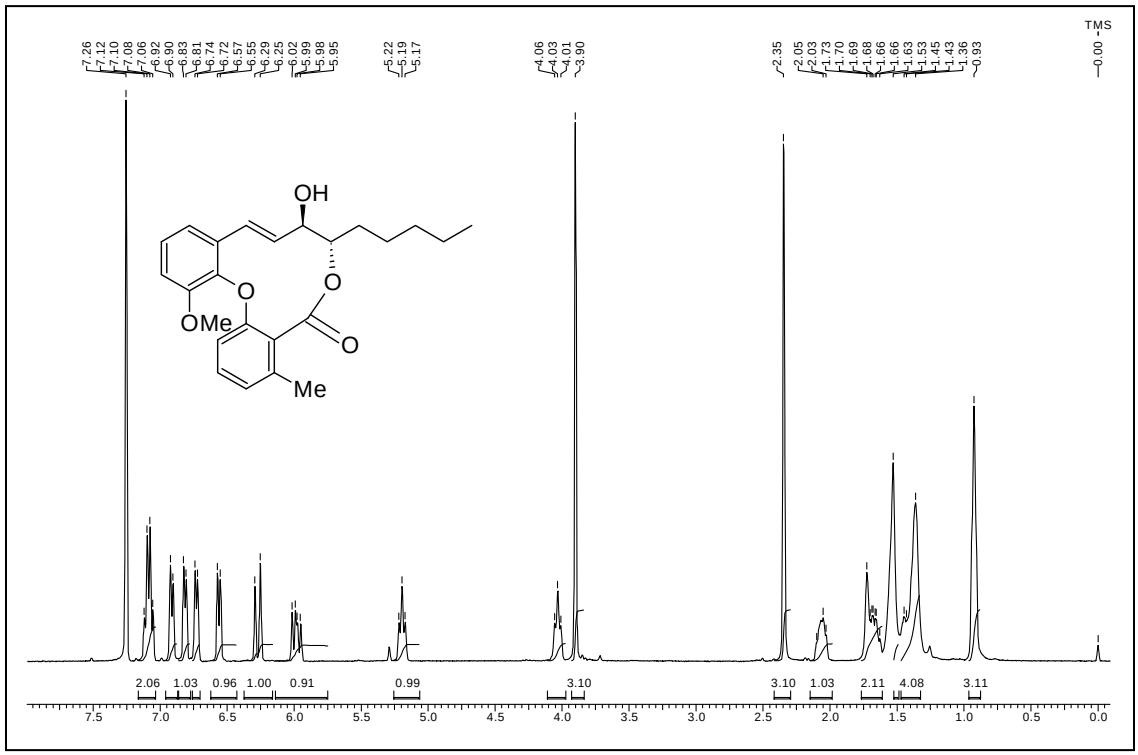
^{13}C NMR Spectrum of 12 in $CDCl_3$



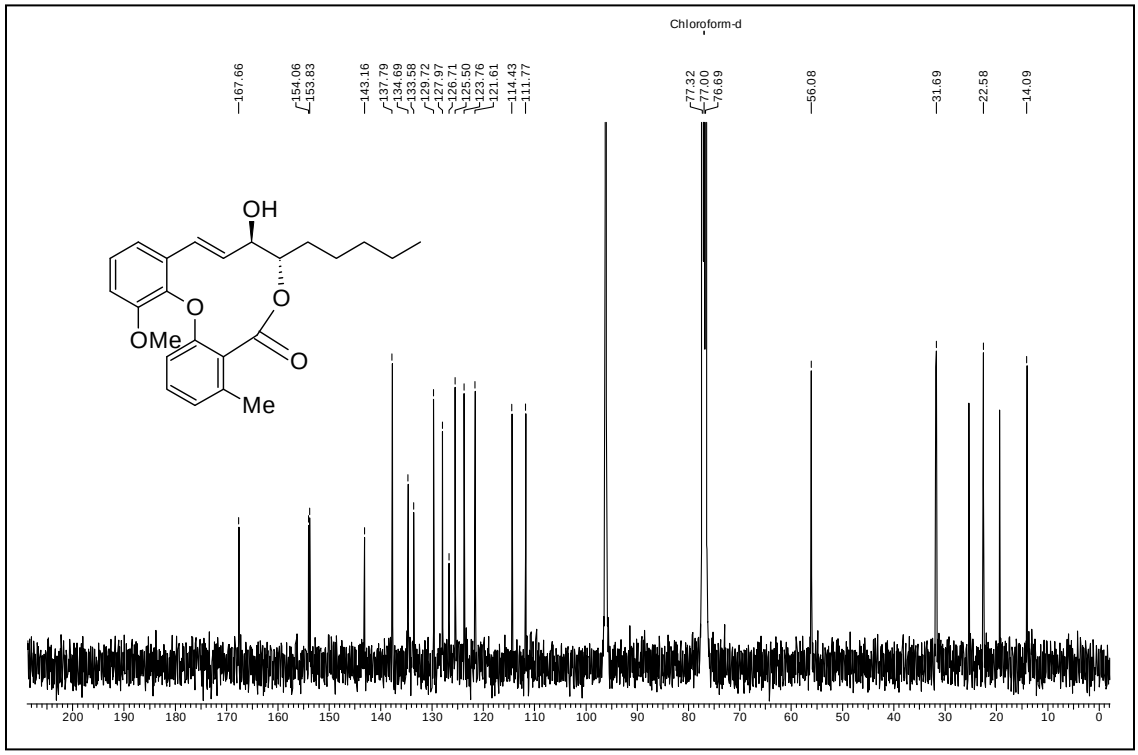
^{1}H NMR Spectrum of 38 in $CDCl_3$



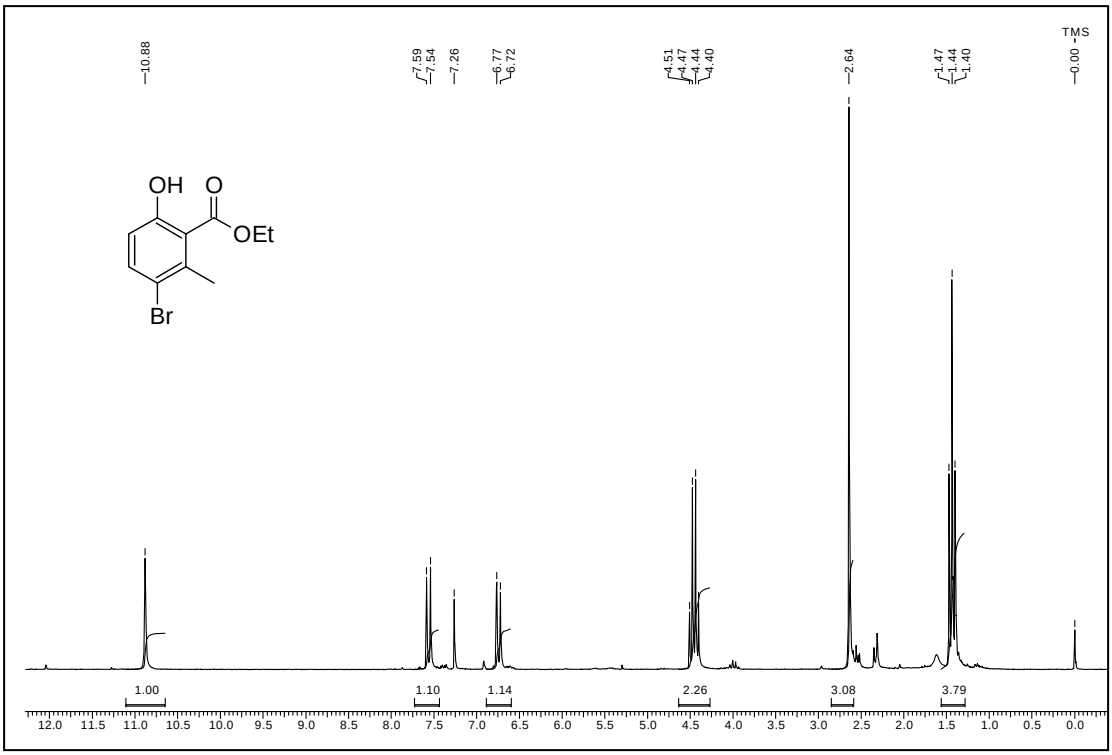
^{13}C NMR Spectrum of 38 in $CDCl_3$



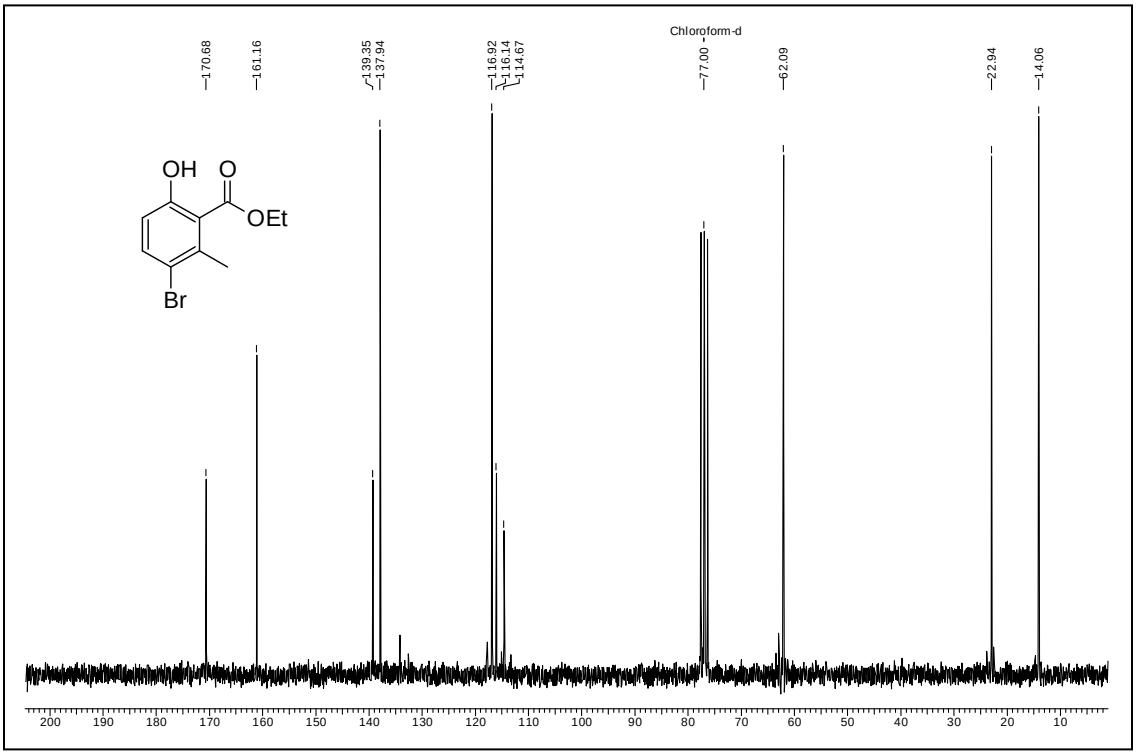
^{1}H NMR Spectrum of 39 in $CDCl_3$



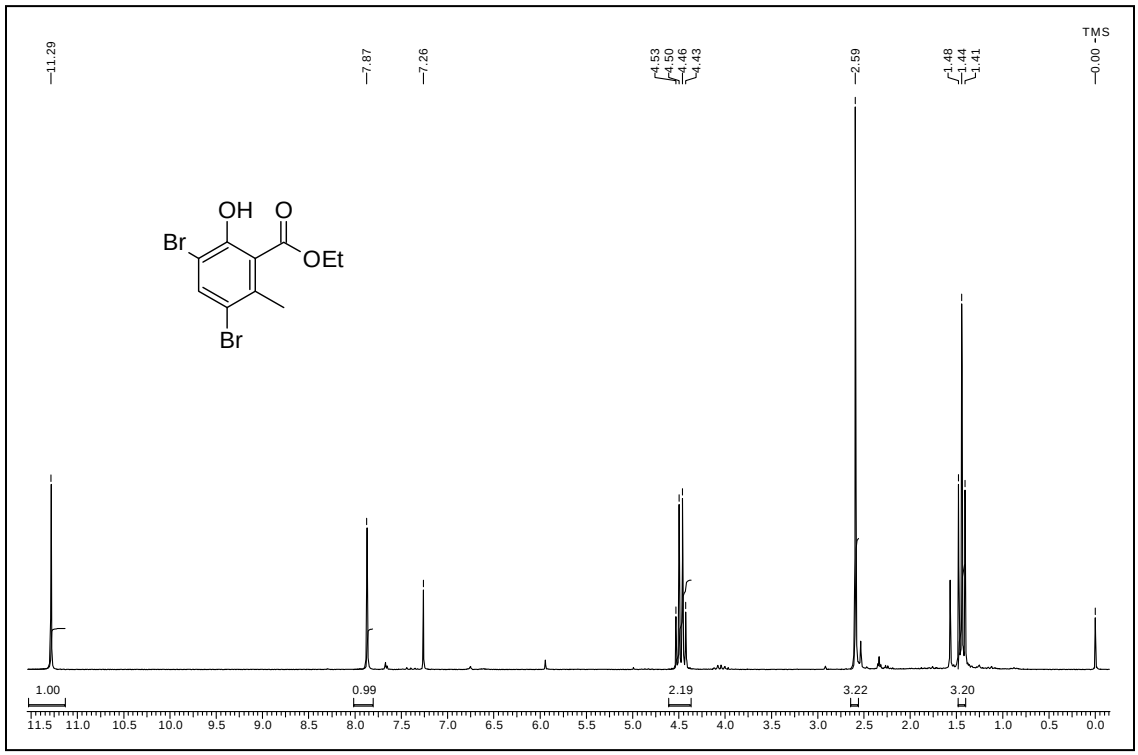
^{13}C NMR Spectrum of 39 in $CDCl_3$



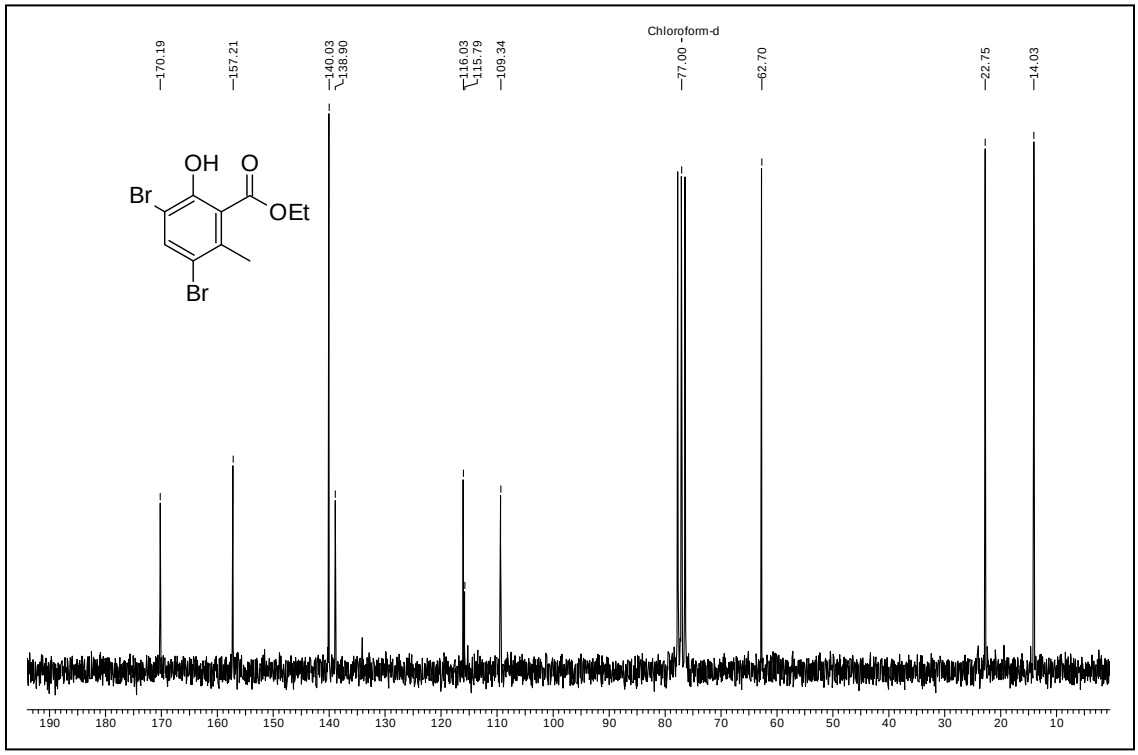
^{1}H NMR Spectrum of 45 in $CDCl_3$



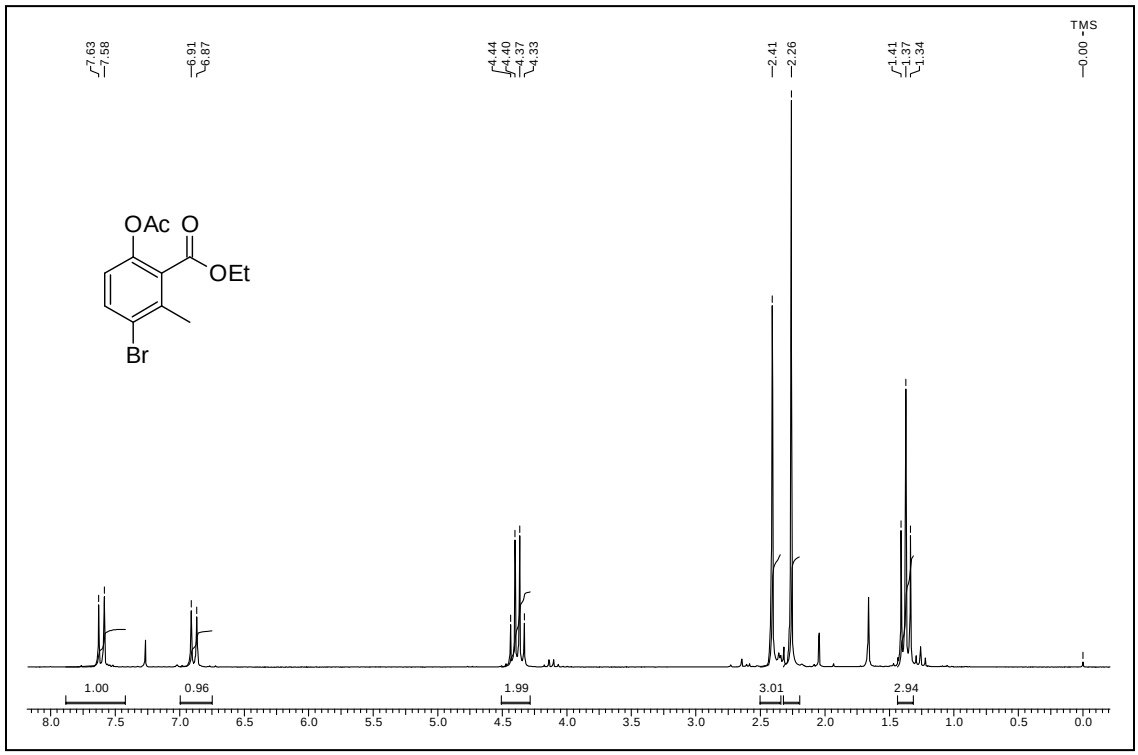
^{13}C NMR Spectrum of 45 in $CDCl_3$



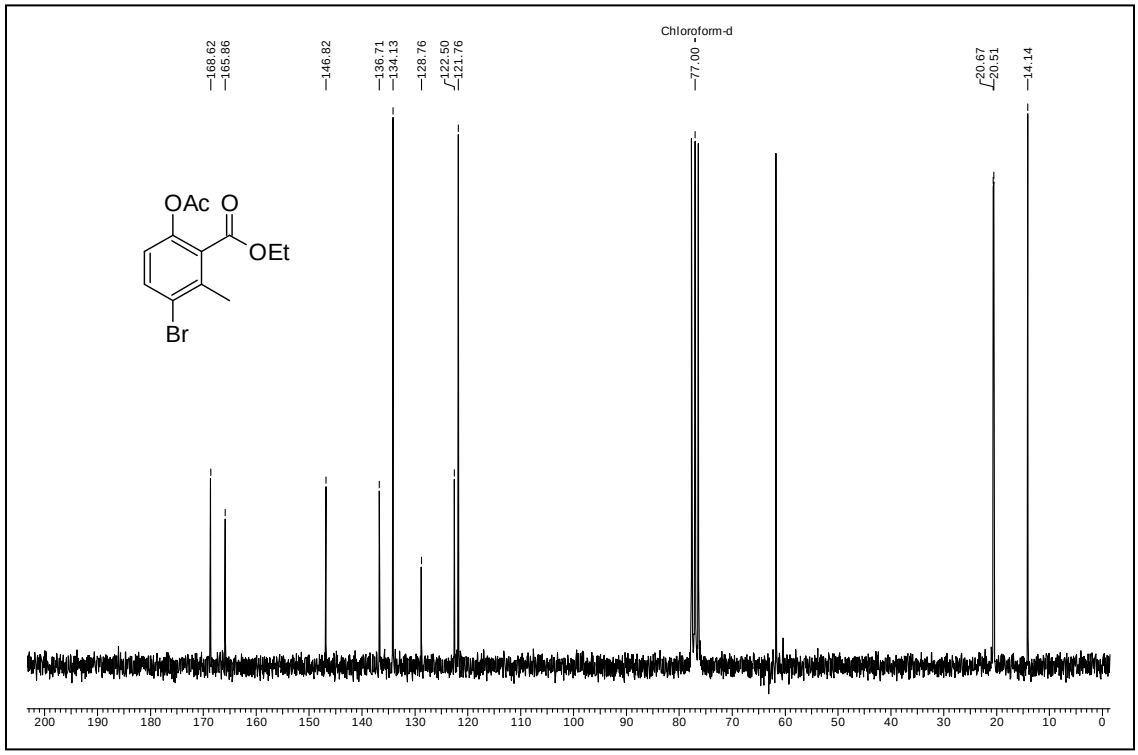
^{1}H NMR Spectrum of 45a in $CDCl_3$



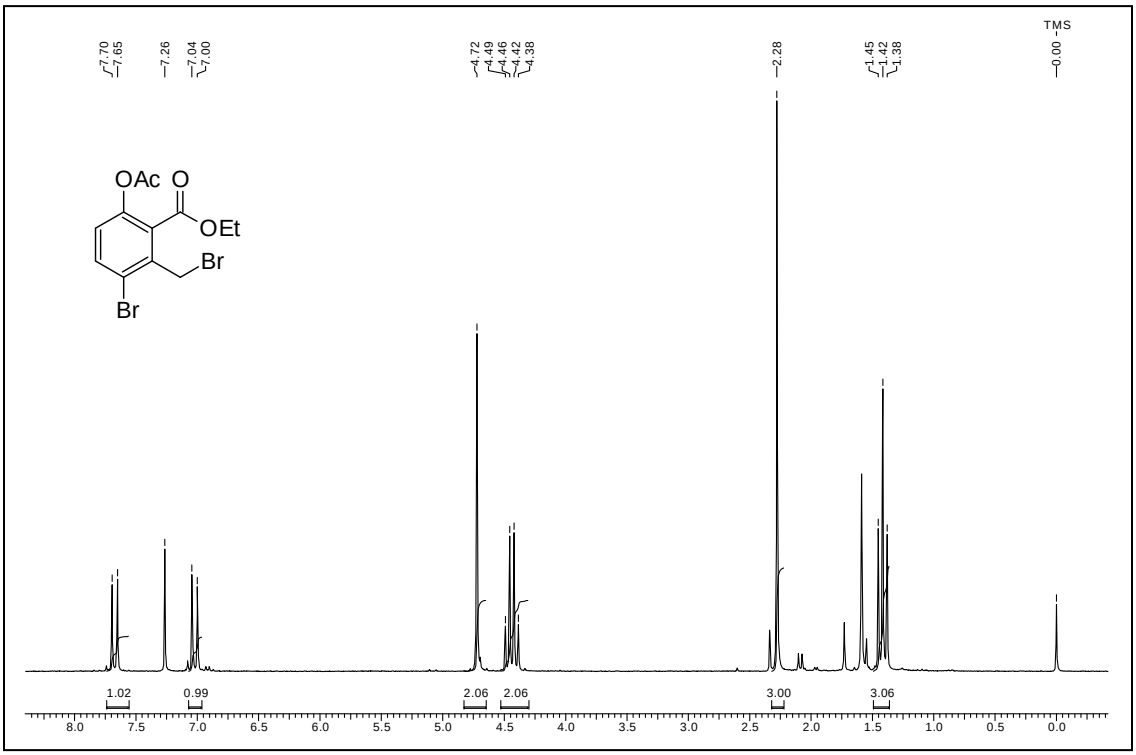
^{13}C NMR Spectrum of 45a in $CDCl_3$



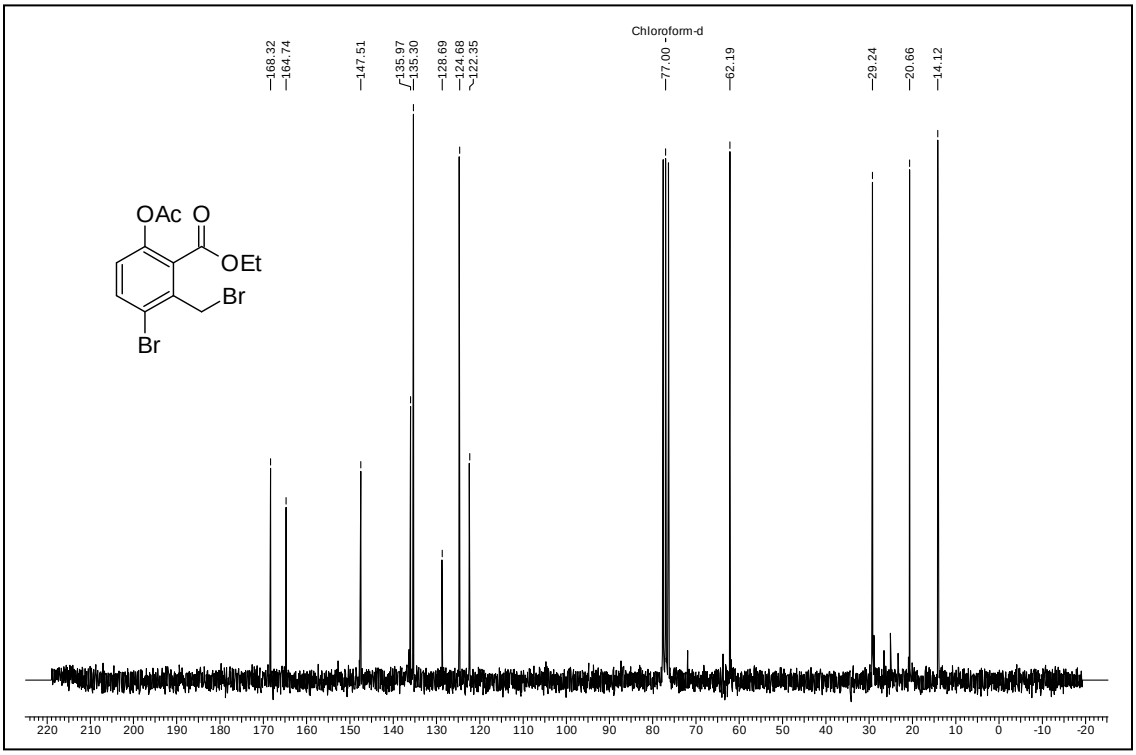
^{1}H NMR Spectrum of 46 in $CDCl_3$



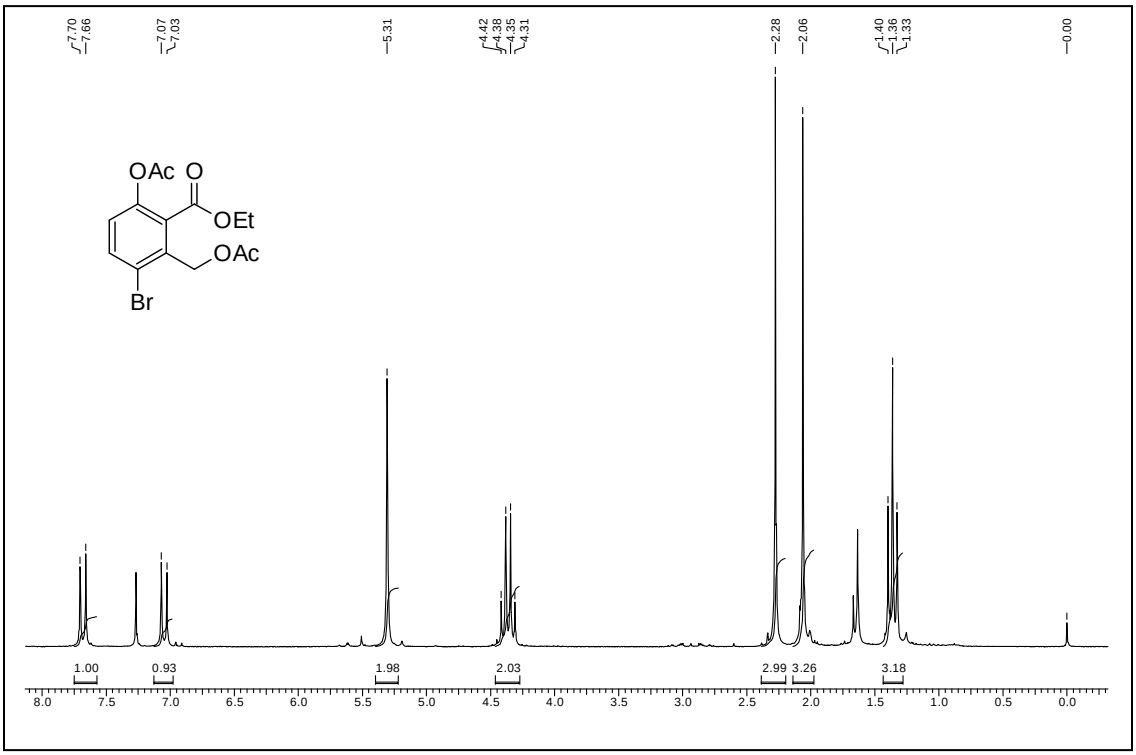
^{13}C NMR Spectrum of 46 in $CDCl_3$



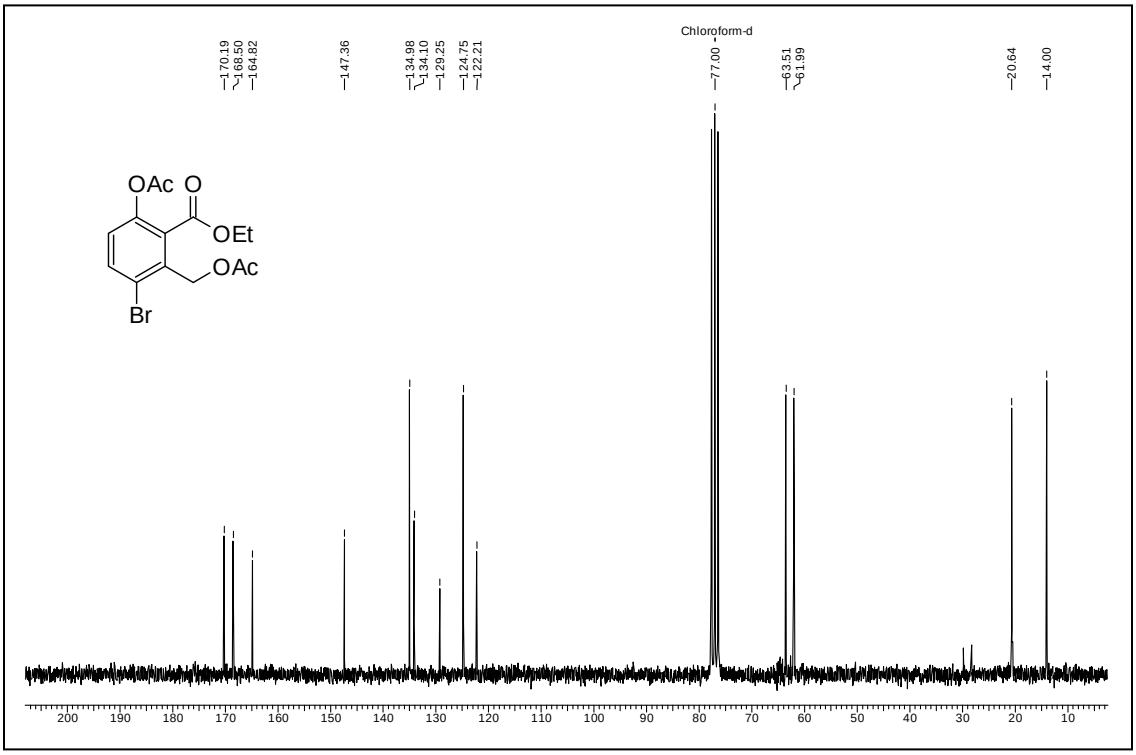
^{1}H NMR Spectrum of 48 in $CDCl_3$



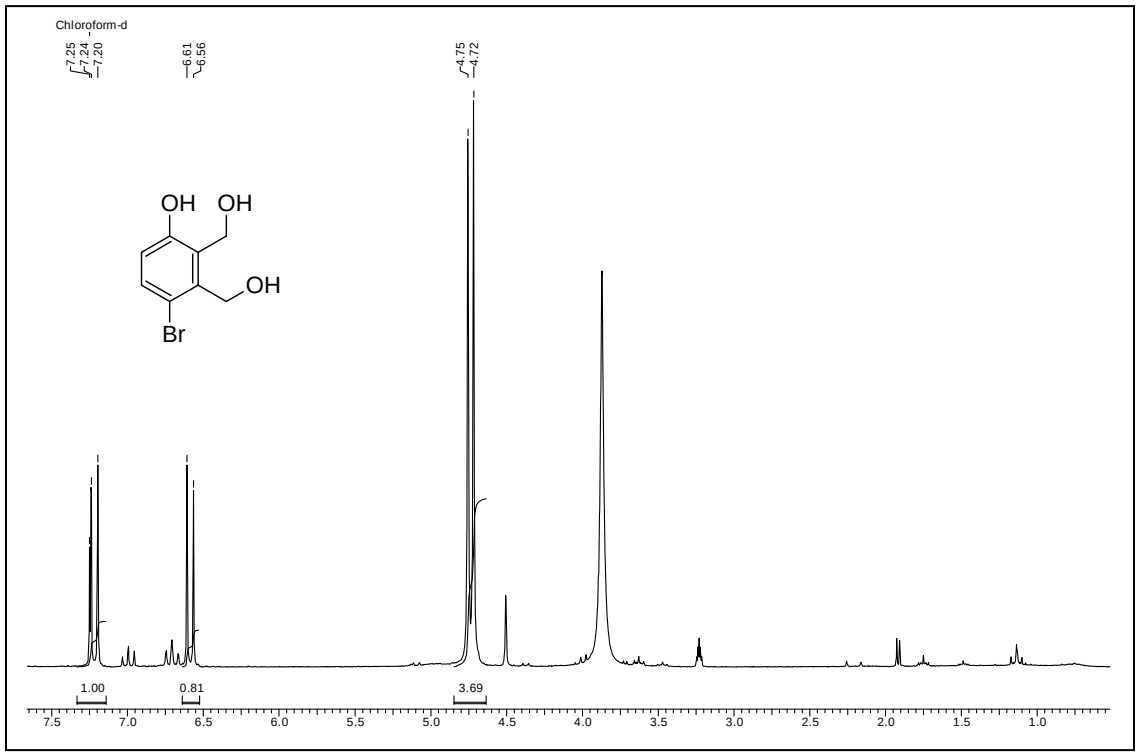
^{13}C NMR Spectrum of 48 in $CDCl_3$



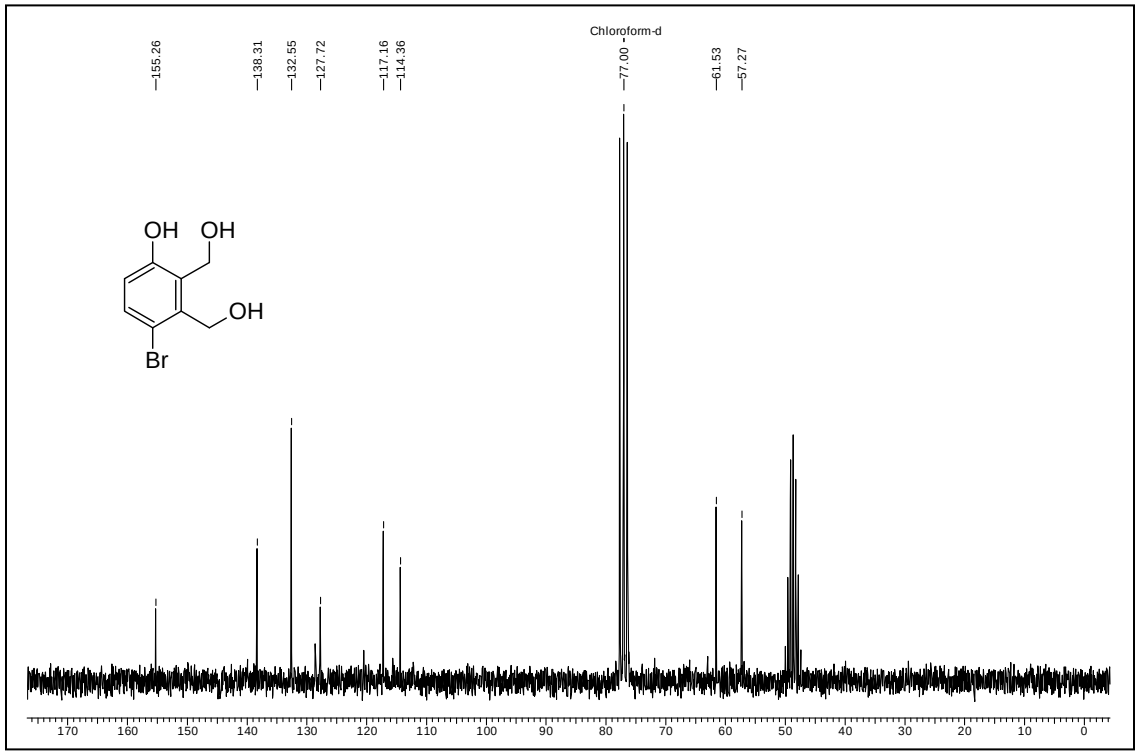
^{1}H NMR Spectrum of 49 in $CDCl_3$



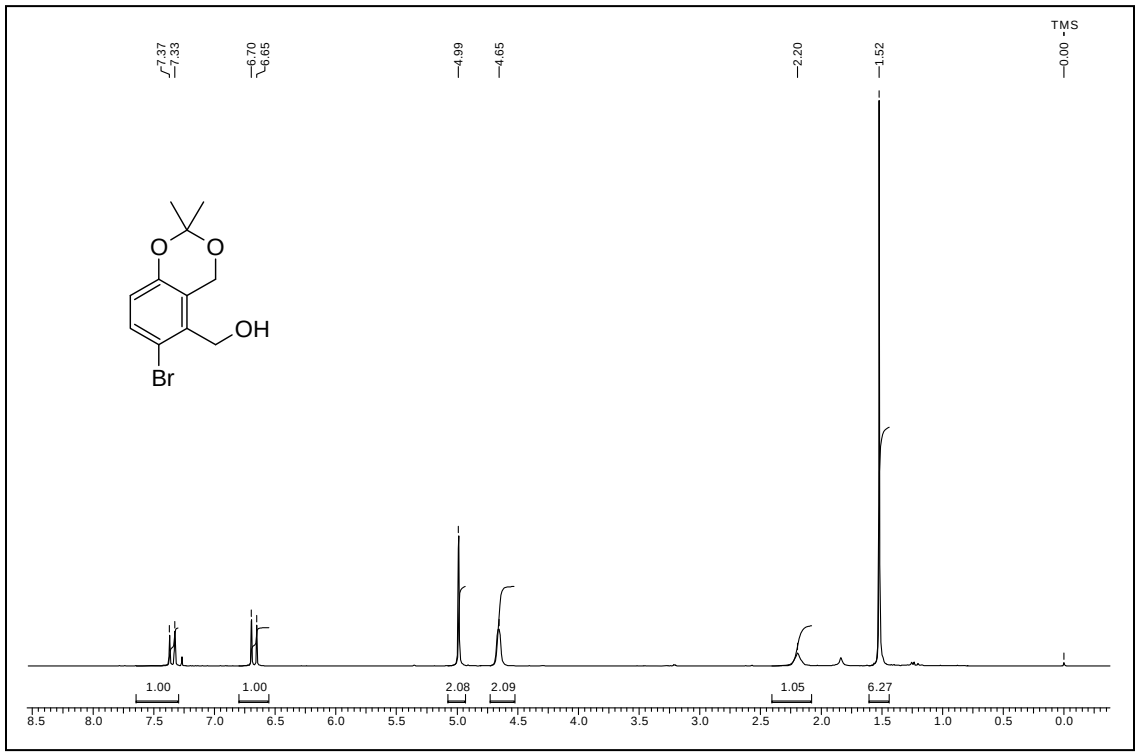
^{13}C NMR Spectrum of 49 in $CDCl_3$



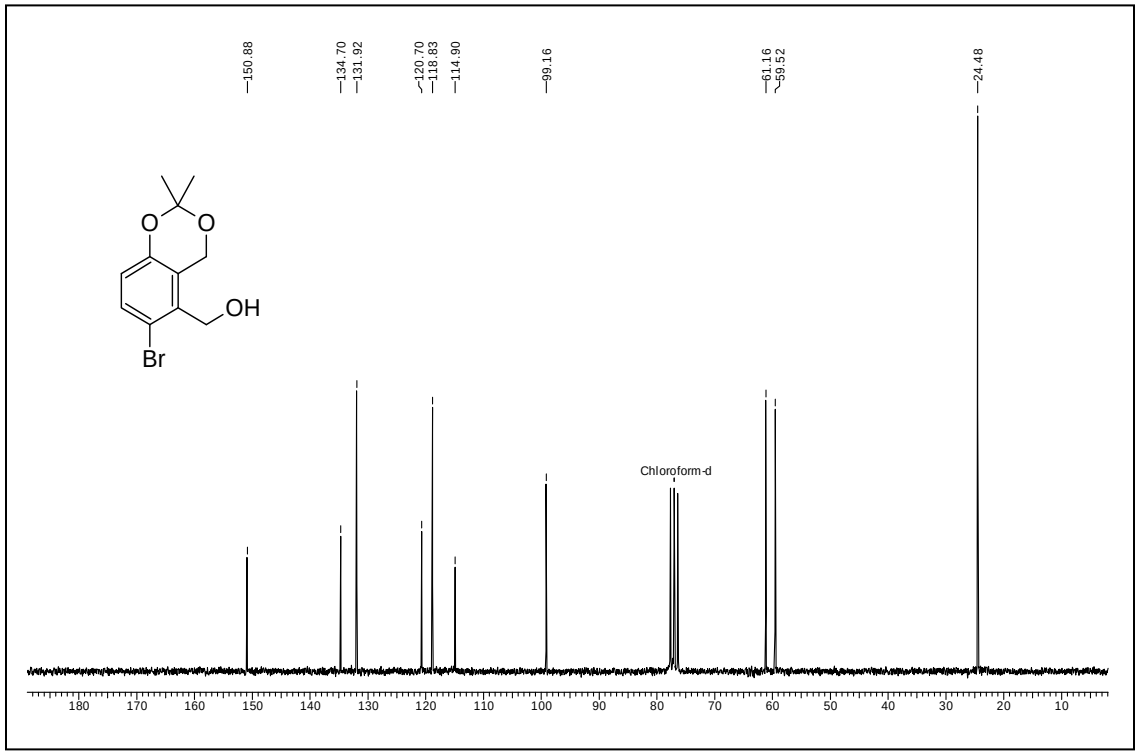
^{1}H NMR Spectrum of 50 in $CD_3OD+CDCl_3$



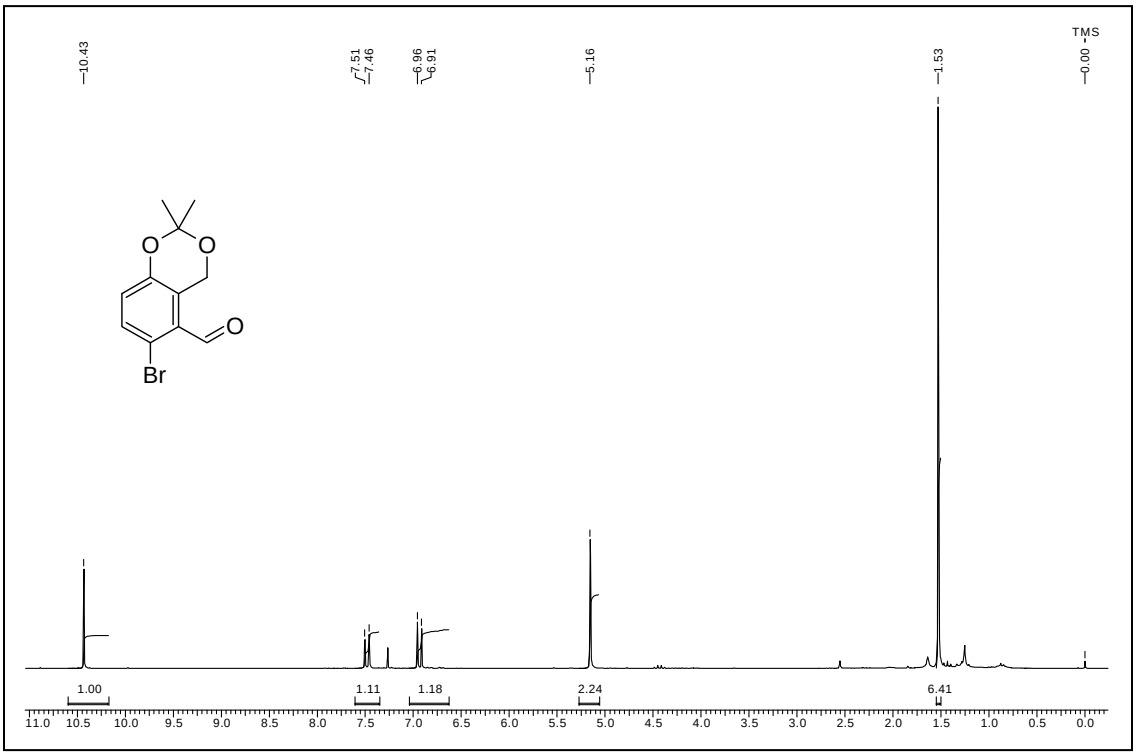
^{13}C NMR Spectrum of 50 in $CD_3OD+CDCl_3$



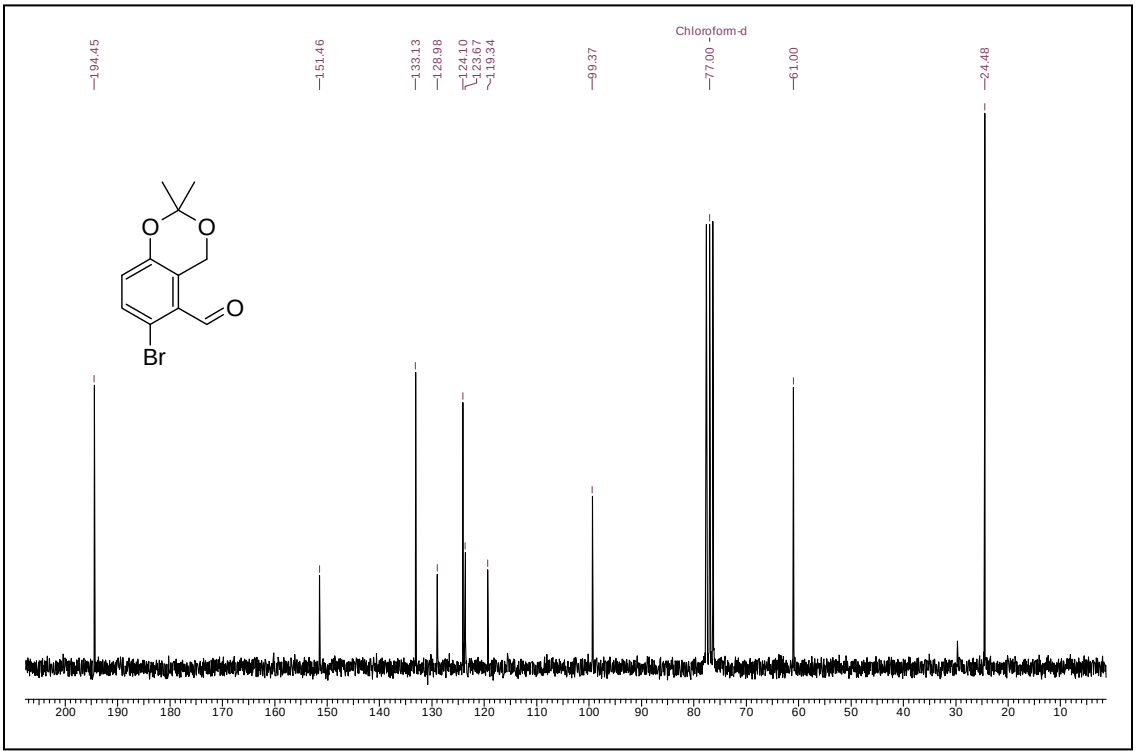
^{1}H NMR Spectrum of 51 in $CDCl_3$



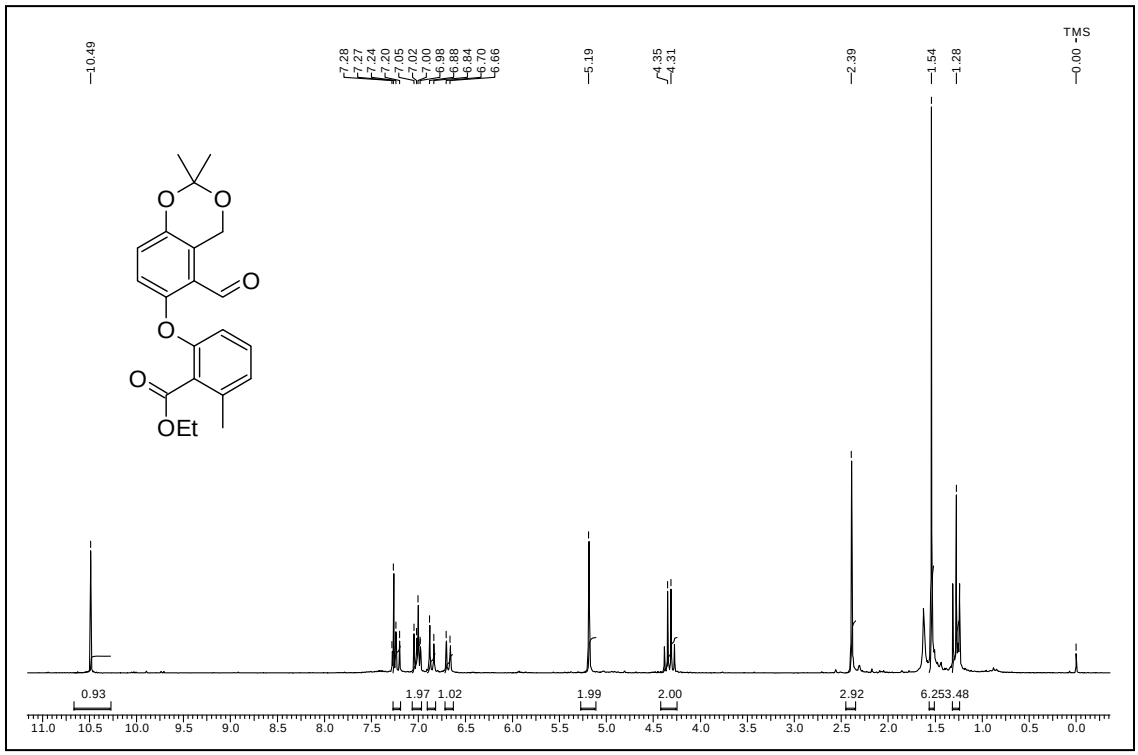
^{13}C NMR Spectrum of 51 in $CDCl_3$



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



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



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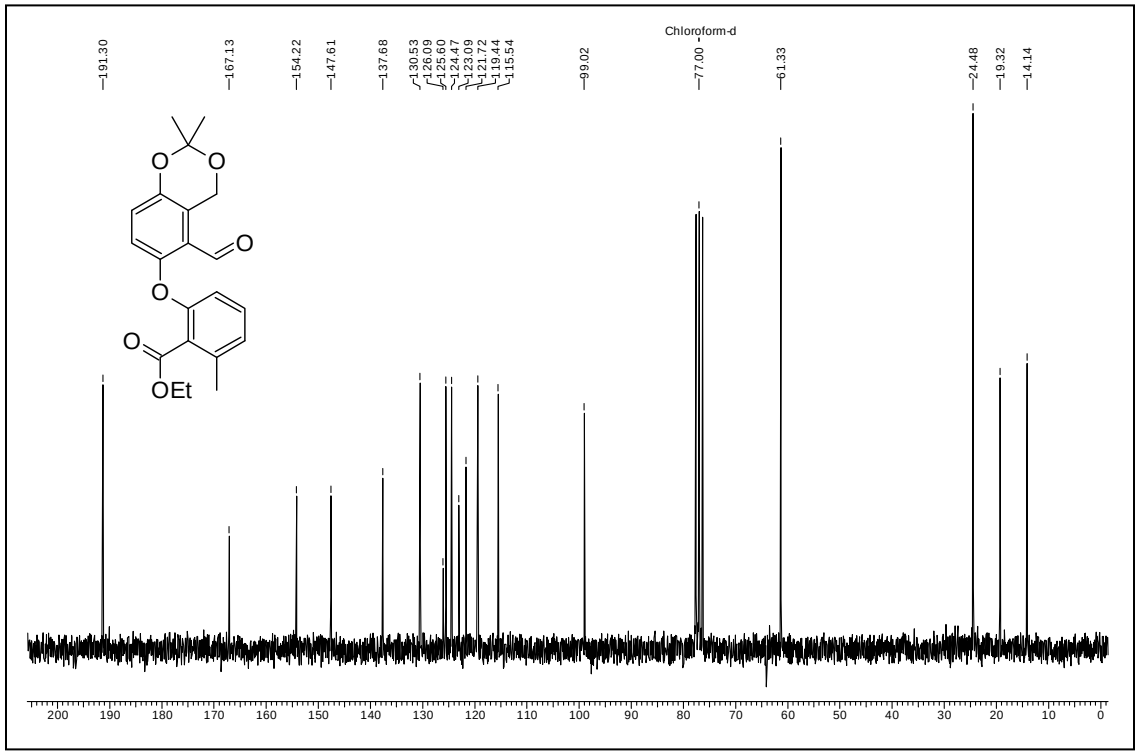
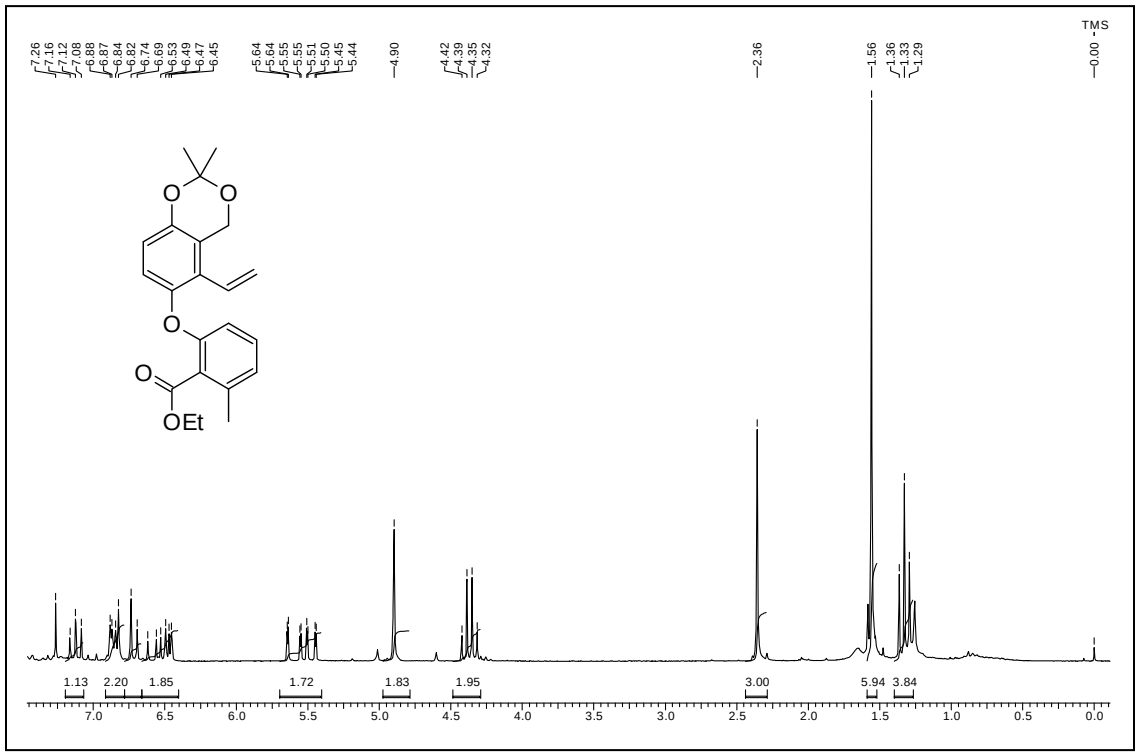
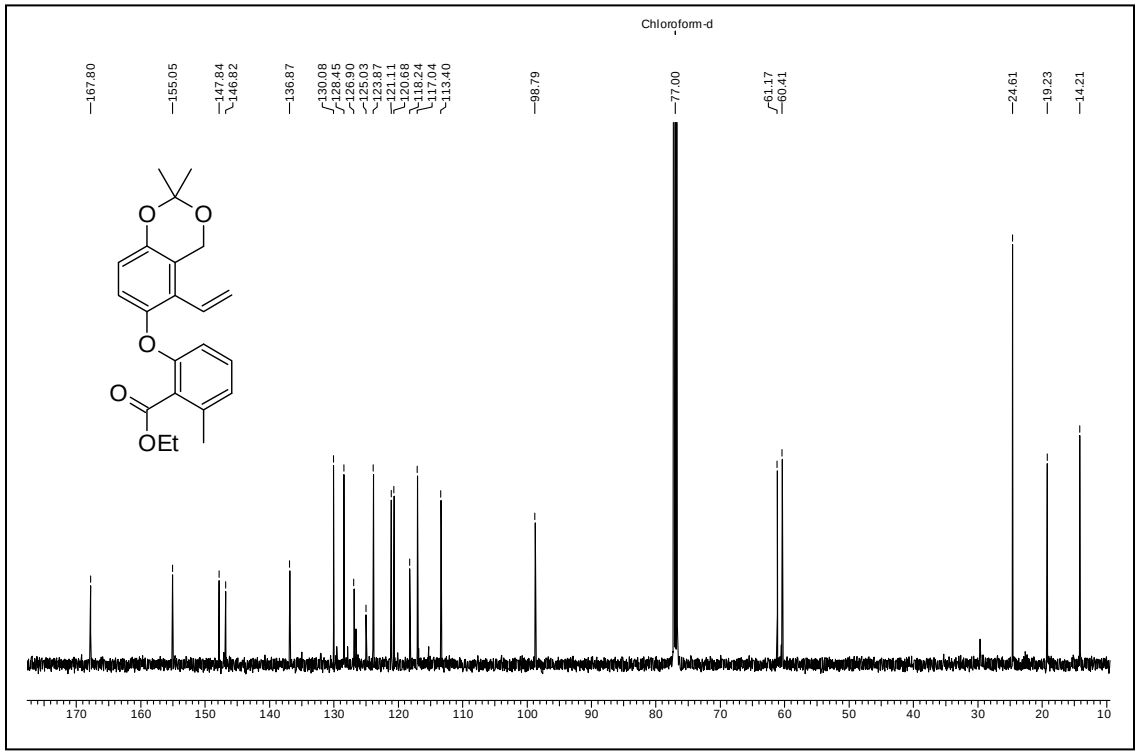


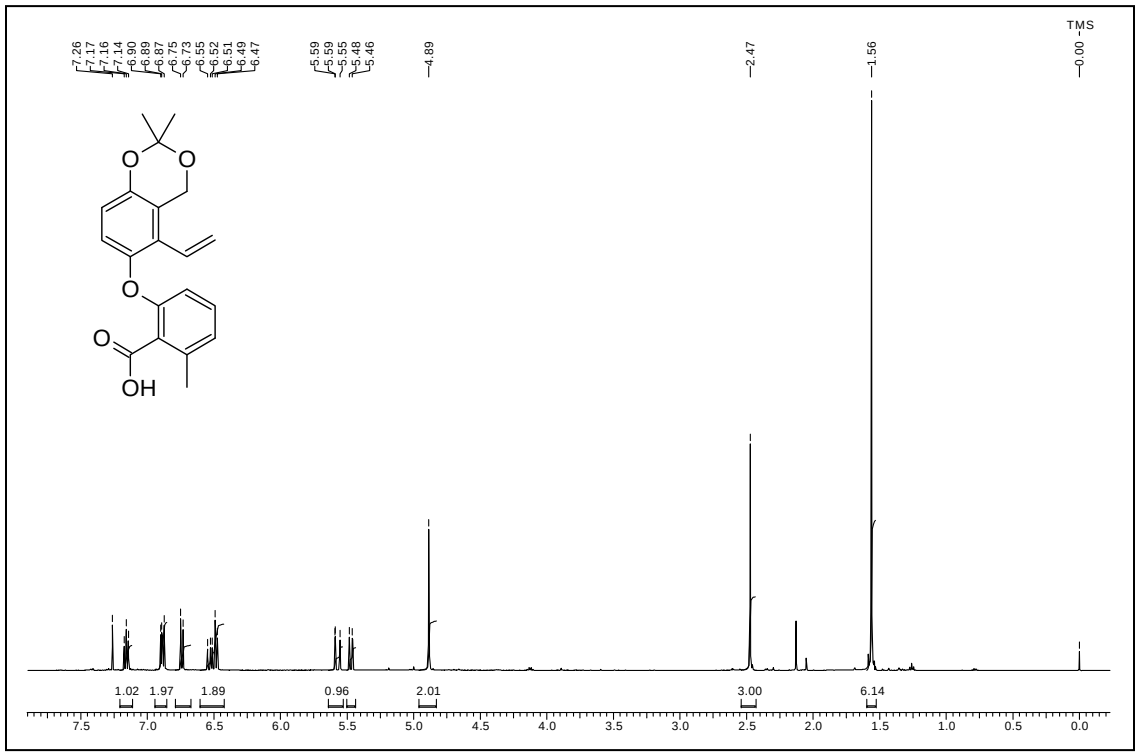
^{13}C NMR Spectrum of 53 in $CDCl_3$



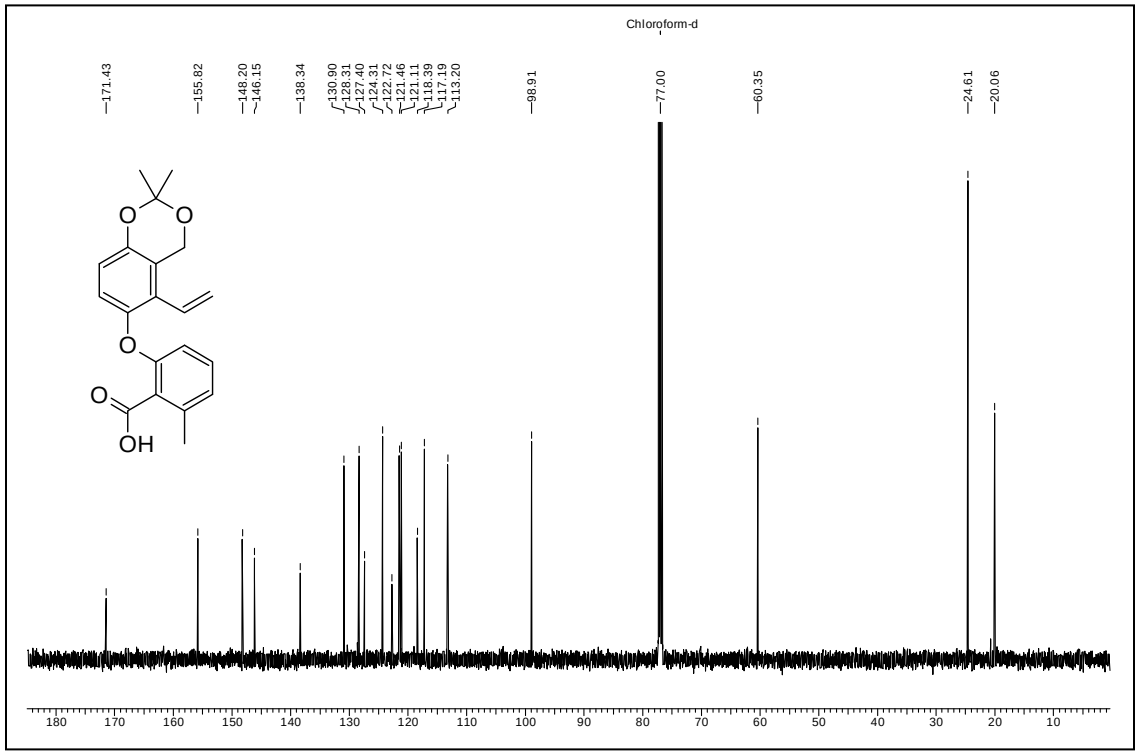
^{1}H NMR Spectrum of 55 in $CDCl_3$



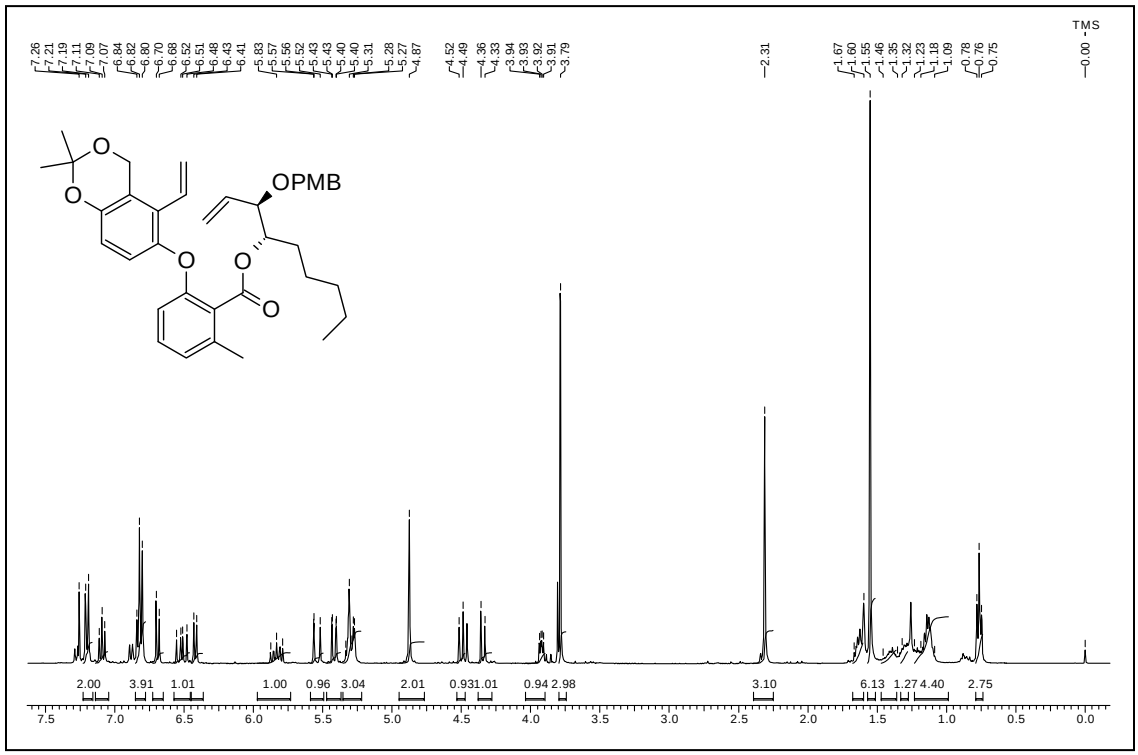
^{13}C NMR Spectrum of 55 in $CDCl_3$



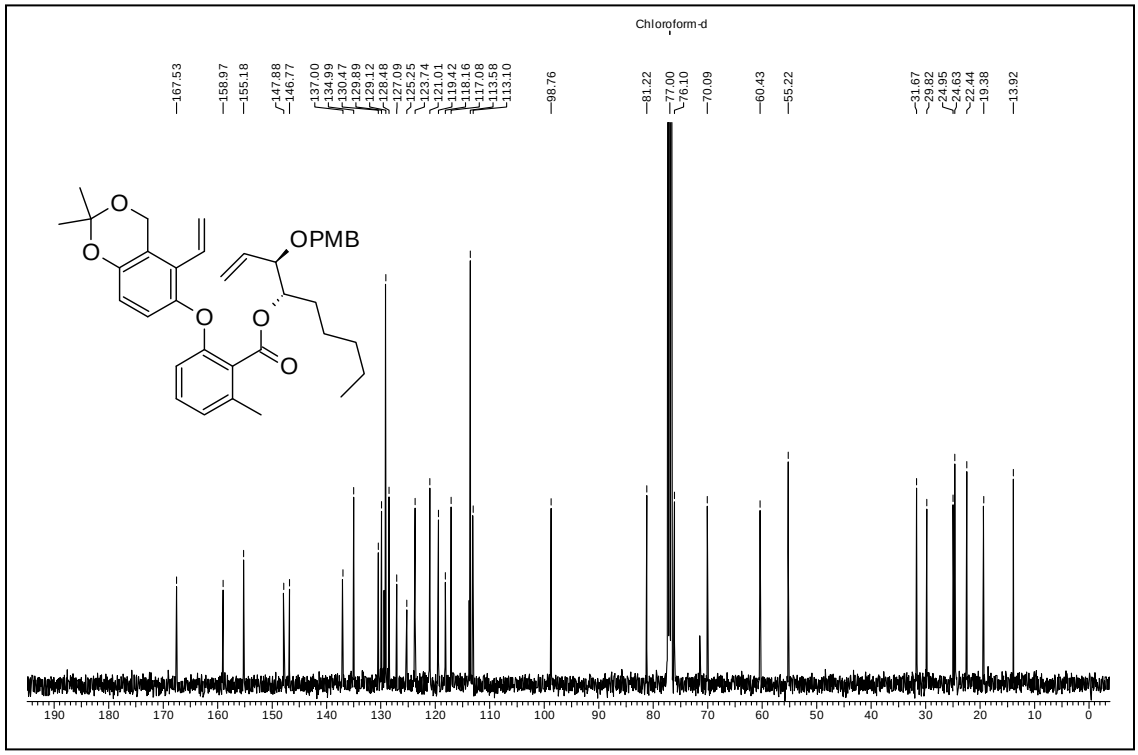
^{1}H NMR Spectrum of 41 in $CDCl_3$



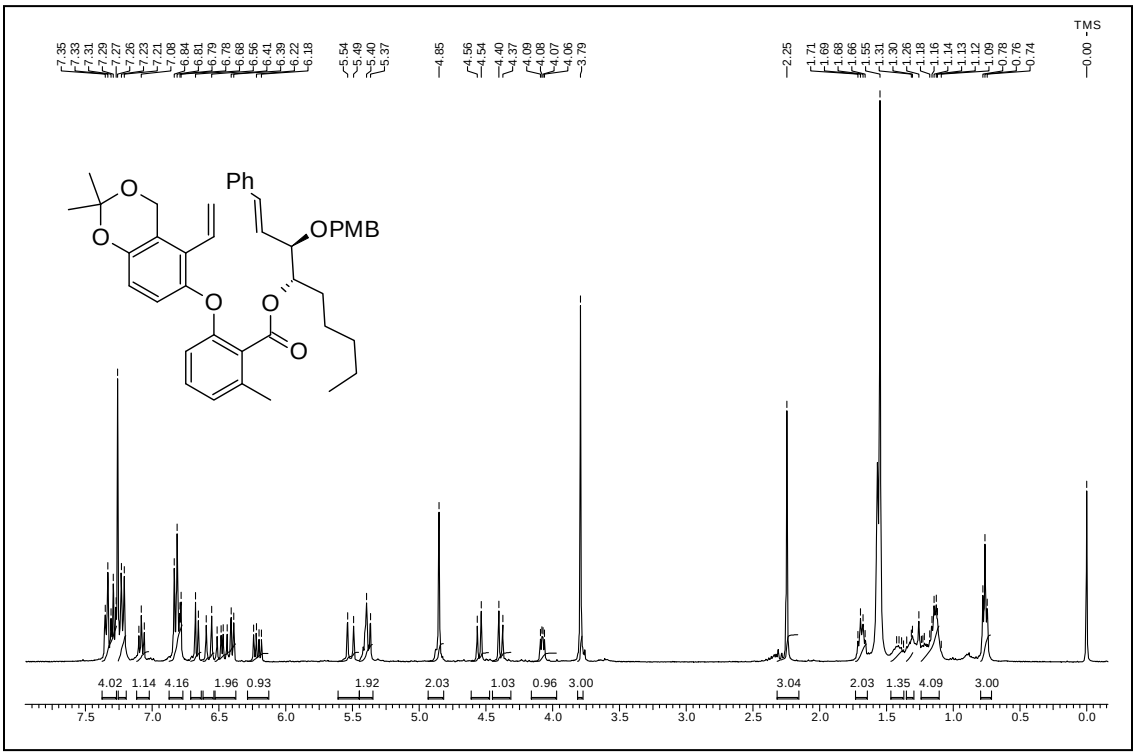
^{13}C NMR Spectrum of 41 in $CDCl_3$



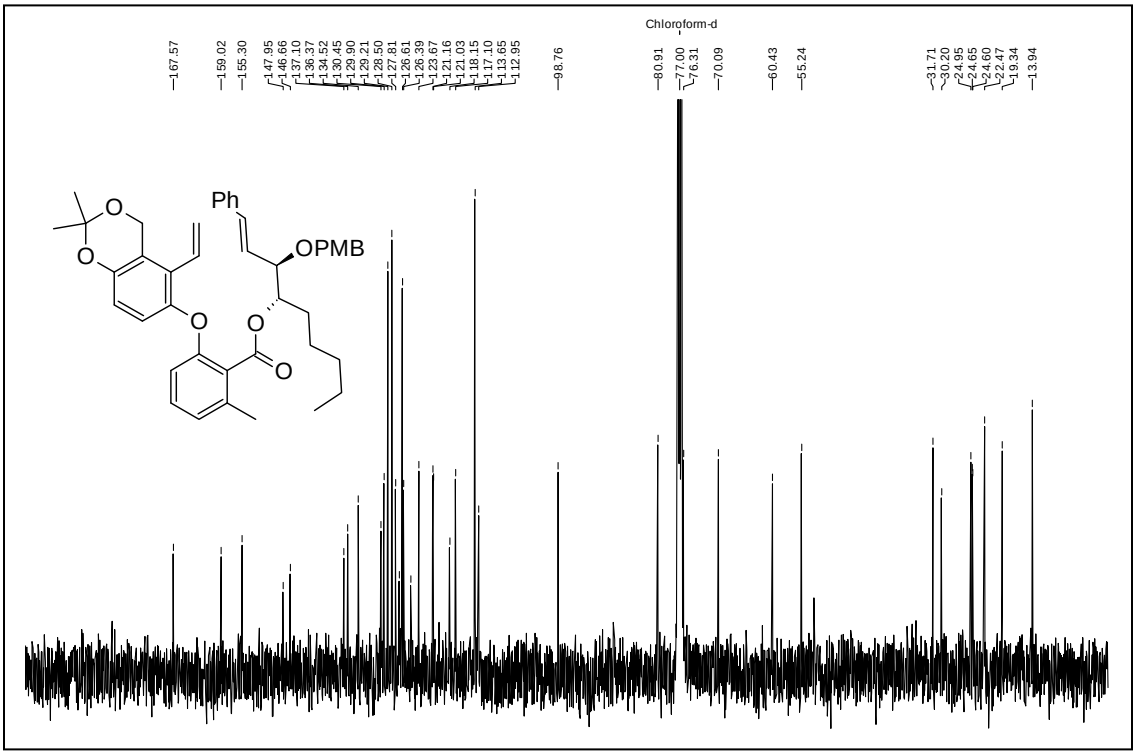
^{1}H NMR Spectrum of 40 in $CDCl_3$



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



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



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

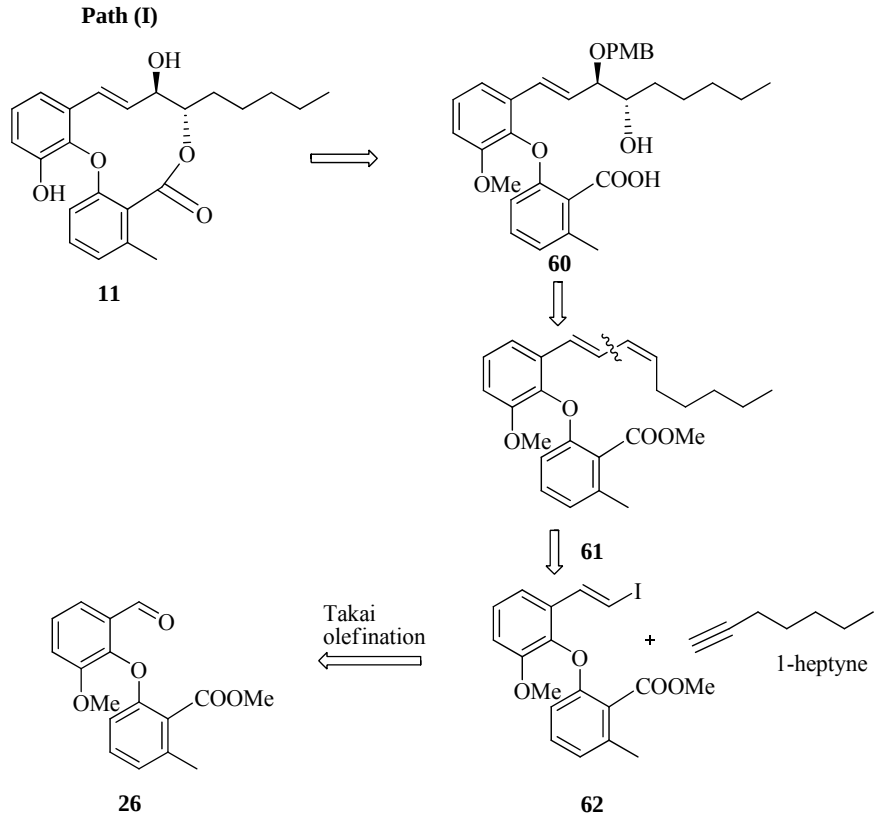
Chapter 2; Section II

Regioselective Dihydroxylation Approach Toward the Total Synthesis of Aspercyclide C

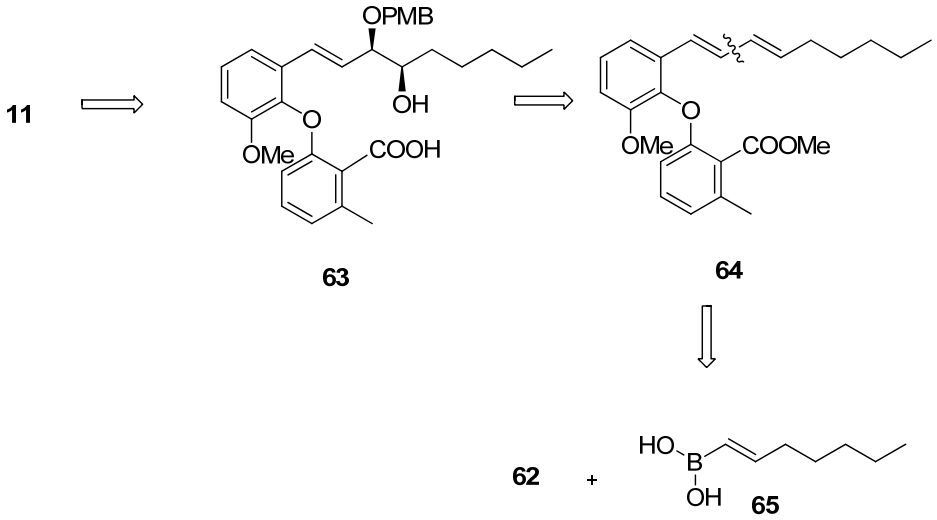
Present Work

Having failed with the ring closing metathesis in cyclisation of the intermediate **40**, we switched our attention to macrolactonization as an alternative approach for the cyclistion of the basic skeleton of aspercyclide B. To check the applicability of the strategy we have chosen initially aspercylide C, as the simplest member as the target. Keeping the lactonization as a key step, aspercyclide C was disconnected and the key intermediate **60** and **63** were found to be decisive. We have intended to furnish the decisive chiral intermediates **60** and **63** by means of regioselective asymmetric dihydroxylation (AD).[28] Therefore, both diene **61** and **64** were selected. The same vinyl iodide **62** could be used for synthesis of both the dienes. Critical differences between the path (I) and (II) were in the lactonization step. Lactonization of **60** should proceed with retention of configuration whereas in the case of **63** the same should be with inversion of the participating hydroxyl center and final deprotection could give aspercyclide C. Major issue in both the routes could be the regioselectivity during AD reaction.[29]

Figure 8. *Retrosynthetic analysis of aspercyclide C.*



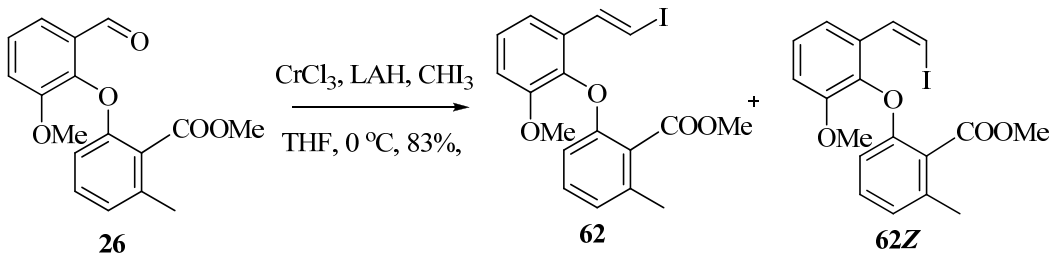
Path (II)



Synthesis of the diene 61

Our synthetic sequence commenced with previously used aldehyde **26** (Section I). Thus, the aldehyde **26** was converted to vinyl iodide **62** by using *in situ* generated chromium (II) chloride, and using iodoform (Takai olefination)[30] in very good yield (83%) and product obtained was a mixture of geometrical isomers namely, *trans* (**62**) and *cis* (**62Z**) (13:4). The pure *trans* isomer **62** was separated by crystallization in 5% ethyl acetate and petroleum ether as mixed solvent and it was characterized fully with the help of analytical and spectroscopic data. For instance, in ^{1}H NMR the olefinic protons were seen as a doublet at δ 7.00 and 7.59 as a doublet with coupling constant 15.0 Hz, thereby confirming the *trans* orientation of the newly formed double bond. The ester carbonyl carbon resonated at δ 168.2 in ^{13}C NMR.

Sheme 17: *Takai olefination.*



After getting the pure *trans* isomer **62** the next concern was to extend the chain length with extended conjugation keeping stereochemistry of the double bond intact. From our retrosynthetic disconnection, it is clear that Sonogashira reaction will

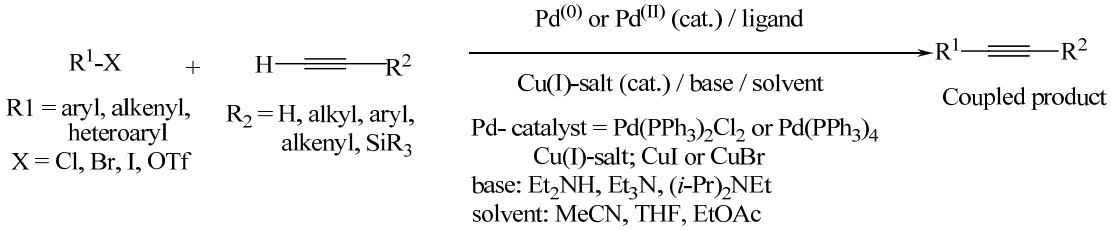
be the method of choice. Therefore a brief account on Sonogashira reaction is discussed here.

Sonogashira coupling and Mechanism

In 1975, K. Sonogashira and co-workers reported that symmetrically substituted alkynes could be prepared under mild conditions by reacting acetylene gas with aryl iodides or vinyl bromides in the presence of catalytic amounts of $Pd(PPh_3)_2Cl_2$ *and cuprous iodide (CuI). During the same year the research groups both R. F. Heck and L. Cassar independently disclosed similar Pd-catalyzed processes, but they did not use copper co-catalysis, and the reaction conditions were harsh.*[31e,f] *The copper-palladium catalysed coupling of terminal alkynes with aryl and vinyl halides to give enynes is known as the 'Sonogashira coupling' and can be considered as catalytic version of the Castro-Stephens coupling. The general features of the reaction are: 1) the coupling can usually be conducted at or slightly above room temperature, and this is the major advantage over the forcing conditions required for the alternative Castro-Stephenes coupling; 2) the handling of the shock-sensitive/explosive copper acetylides is avoided by the use of a catalytic amounts of copper(I) salt; 3) the copper(I) salt can be commercially available CuI or CuBr and usually applied in 0.5 -5 mol % with respect to the halide or alkyne; 4) the best palladium catalyst are* $Pd(PPh_3)_2Cl_2$ *or* $Pd(PPh_3)_4$*; 5) the solvents and the reagents do not need to be rigorously dried. However, a thorough deoxygenation is essential to maintain the activity of the Pd-catalyst; 6) often the base serves as the solvent but occasionally a co-solvent is used; 7) the reaction works well on both very small and large scale (>100 g); 8) the coupling is stereospecific; the stereochemical information of the substrates is preserved in the products; 9) the order of the reactivity for the aryl and vinyl halides is I ~ OTf > Br >> Cl; 10) the difference between the reaction rates of iodides and bromides allows selective coupling with the iodides in the presence of bromides; 11) almost all functional groups are tolerated on the aromatic and vinyl halide substrates. However, alkynes with conjugated electron-withdrawing groups ((*R^2*= COOMe) give Michael addition products and propargylic substrates with electron-withdrawing groups ((*R^2*= COOMe or* NH_2*) tend to rearrange to allenes*

under the reaction conditions; 12) the exceptional functional group tolerance of the process makes it feasible to use this coupling for complex substrates in the late stages of a total synthesis. The coupling of sp^2-C halides with sp-C metal derivatives is also possible by using other reactions such as the Negishi-, Stille-, Suzuki-, and Kumada cross-couplings. In terms of functional group tolerance, the Negishi cross-coupling is the best alternative to the Sonogashira reaction. There are certain limitations on the Sonogashira coupling: 1) aryl halides and bulky substrates that are not very reactive require higher reaction temperature; and 2) at higher temperatures terminal alkynes undergo side reactions.

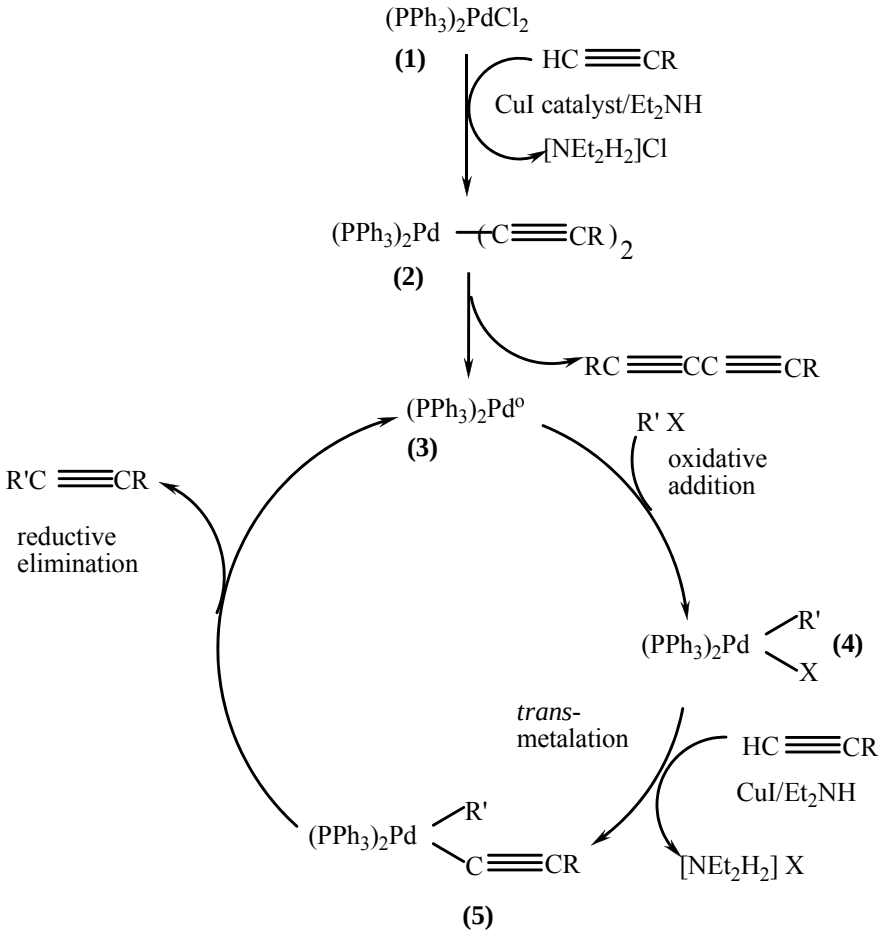
Scheme18.



Mechanism:

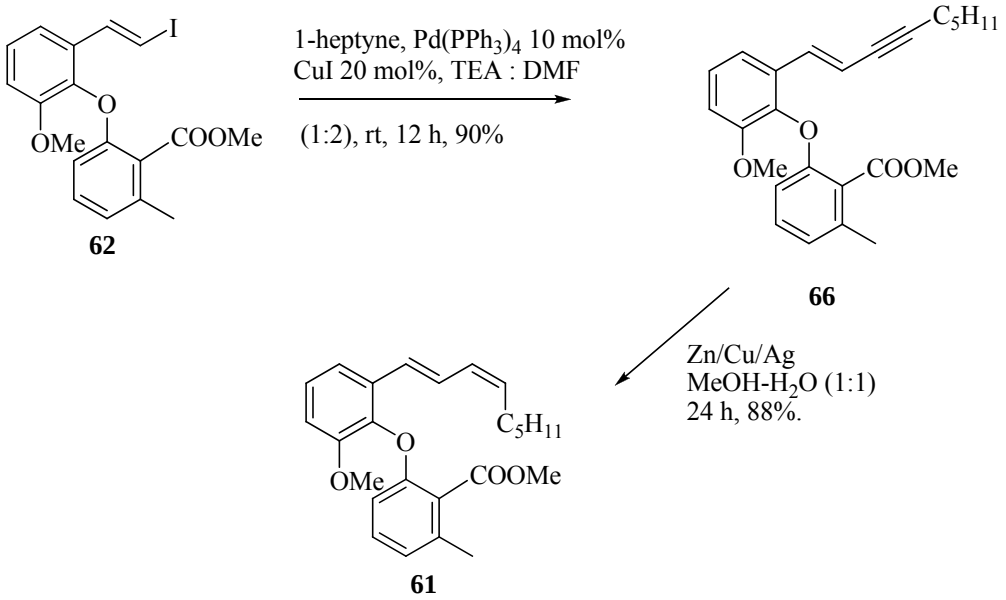
*Although the detailed mechanism of the reaction is yet to be clarified, it seems likely that the substitution occurs through an initial formation of bis-(triphenylphosphine)dialkynylpalladium (II) (**2**), which gives a catalytic species, bis-(triphenylphosphine)dialkynylpalladium (0) (**3**), through a reductive elimination of 1,4-diphenylbutadiyne. Subsequent oxidative addition of vinyl halide to (**3**), followed by an alkynylation of the adduct (**4**), gives vinyl-alkynyl derivative of palladium (**5**), which easily regenerates the original bis-(triphenylphosphine)dialkynylpalladium (0) (**3**) through the reductive elimination of the substitution products. The alkynylation of the starting catalyst (**1**) or an oxidative adduct (**4**) in the catalytic cycle in scheme 1 is catalyzed by cuprous iodide in the presence of diethylamine.*

Figure 9 : *Catalytic cycle of Sonogashira reaction.*



Considering the above discussion, the projected Sonogashira[31] coupling of **62** with 1-heptyne was performed by using 10 mol% $Pd(PPh_3)_4$ in presence of cuprous iodide (20 mol%) and a smooth conversion was observed (Scheme 19). The retention of *trans* geometry of the double bond in **66** was evident from ^{1}H NMR which have shown a large coupling constant (16.3 Hz) between the olefin protons appeared at δ 6.22 as doublet of a triplet. The partial reduction of triple bond of **66** using activated zinc in methanol gave exclusive *E, Z* diene **61** in 88% yield (Scheme 19).[32] The stereochemistry of the newly formed double bond of **61** was assigned on the basis of ^{1}H NMR in which a characteristic peak at δ 5.49 (dt, J = 7.7, 10.7 Hz, 1H) and 6.01 (t, J = 10.7 Hz) were assigned to the newly formed double bond protons.

Scheme 19.

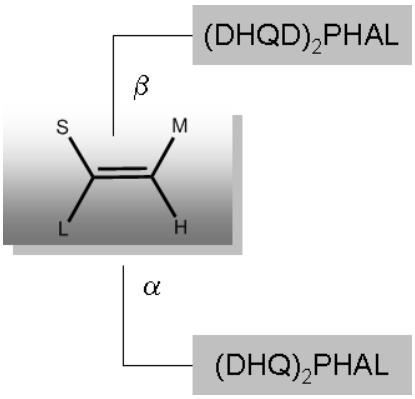


Regioselective asymmetric dihydroxylation of conjugated diene

Dihydroxylation of double bond in stereo-specific manner by osmium tetraoxide is one of the powerful transformations in organic synthesis developed in last few decades. Though the reaction was known from long back the major breakthrough came out when Criegee noticed substantial rate acceleration in presence of Pyridine. On the basis of this observation catalytic process was developed using other cheaper co-oxidant and the reaction became more economic. Later on, with the advent of i) use of two phase conditions with $K_3Fe(CN)_6$ as reoxidant; ii) $MeSO_2NH_2$ for rate acceleration and iii) second generation ligands (phthalazine and diphenylpyrimidine, with two independent cinchona alkaloid units) by Sharpless et al., catalytic AD came into focus. The enantioselectivity in the AD reaction is due to the enzyme-like binding pocket present in the dimeric cinchona alkaloid ligands. The Cinchona alkaloid backbone is ideally suited for providing high ligand acceleration and enantioselectivity. The reaction rates are influenced by the nature of O-9 substituent of the Cinchona alkaloid. With certain aromatic olefins, especially large rate accelerations observed due the stabilization of the transition state through π staking interaction between aromatic ring and aromatic floor of the phthalazine ring. Although this kind of stabilization is operative even in monomeric first generation ligand, it is most effective in the dimeric second-generation ligands due to the

presence of a binding pocket. Thus the almost perfect match between the phthalazine ligands and aromatic olefins with respect to rates and enantioselectivities can be readily explained by a especially good transition state stabilization resulting from offset-parallel interactions between the aromatic substituent of the olefin and the phthalazine floor of the ligand, as well as favorable edge-to-face interactions with the methoxyquinoline ring.

Figure 10: ***Mnemonic diagram*** *(S = small group, L = large group, M = medium group, H = proton).*



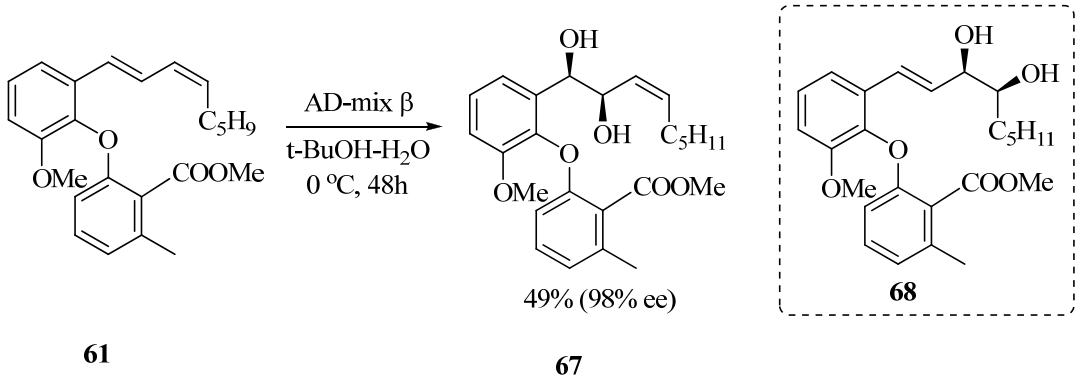
The above observations have led to a revised mnemonic device for predicting the enantiofacial selectivity in the reaction. An olefin positioned accordingly will be attacked either from the top face (β face) in the case of dihdroquinidine derivatives or from the bottom face (α face) in the case of dihydroquinine derived ligands.

Regioselectivity: *The regio-selectivity of AD reaction of conjugated diene depends on the eletronic nature and the steric property of the individual double bonds. Kinetic studies with olefin having isolated double bond found that trans-1, 2 di-substituted and tri substituted olefins have greater tendency to be oxidized compared to cis-1,2 disubstituted and terminal olefins.*[28,29] *Diene conjugated with aromatic ring are spatially important because they give excellent enantioselectivity and very good regioselectivity in dihydroxylation reaction. Supposed interactions between the substituents on aromatic rings and olefins, staking interactions between the phthalazine ring of the ligand used commonly for asymmetric dihydroxylation and aromatic ring attached to olefin are attractive issues from the mechanistic point of view. Another important factor regarding the selectivity is the size of the substituents attached to the aromatic ring. In our present case both double bonds are disubstituted*

having conjugation with aromatic ring. One of our aims was to find out which factors are important in this particular substrate.

Asymmetric dihydroxylation of the diene[28,29] **61** with commercial AD-mix β reagent afforded only compound **67** with 98% *ee* [measured by Chiral cell OD-H (250x4.6 mm) mobile phase IPA/PE 8.5:91.5, flow rate 0.5 ml/min, λ_{max} 254 nm, conc. 2.8 mg/3.0mL]. Compound **68** was not observed even in trace amounts. This was a clear indication that only *trans* double bond fitted to the catalyst pocket and the ligand acceleration effect was so strong that the reaction proceeded through a path involving *trans* double bond only. This factor is overwhelming the others such as steric and electronic interactions and disturbing the extended conjugation with aromatic rings. The stereochemistry was assigned on the basis of mnemonic device proposed by Sharpless.[29]

Scheme 20. *Asymetric dihydroxylation of the E, Z diene* **61**.



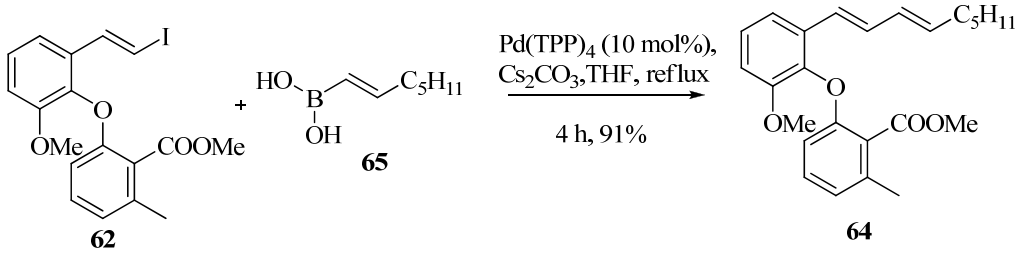
61 **67**

Synthesis of *E, E* conjugated diene 64 and AD reaction

After having the undesired regioselectivity in the dihydroxylation, we shifted our attention to path (II) (as shown in Figure 8). In order to synthesize the compound **64**, we adopted Suzuki[33] coupling for the same. Compound **64** was synthesized by coupling of vinyl iodide **62** and the vinyl boronic acid **65** in presence of catalytic $Pd(PPh_3)_4$. Cs_2CO_3 was found to be optimal for the Suzuki coupling. Other bases such as NaOMe met with unwanted side reactions which gave the deiodination product **27**. Presence of a triplet at δ 0.88 (J = 6.6, 3H) along with others expected signals in their respective positions in proton NMR was a clear indication of the presence of the side chain with terminal methyl group. In ^{1}H NMR the newly formed double bond

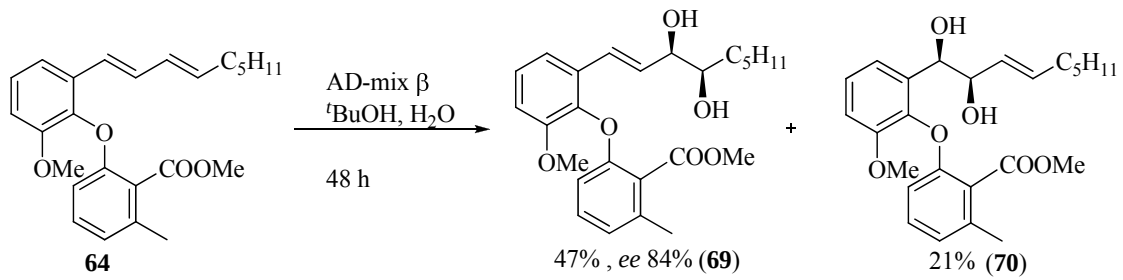
resonated at δ 5.80 (dt, *J* = 7.0, 15.1 Hz) and 6.16 (ddt, *J* = 1.2, 9.6, 15.1 Hz). Stretching frequency of ester carbonyl appeared at 1725 cm^{-1} in IR region. The structure was further substantiated with the help of ^{13}C NMR and mass spectral data analysis.

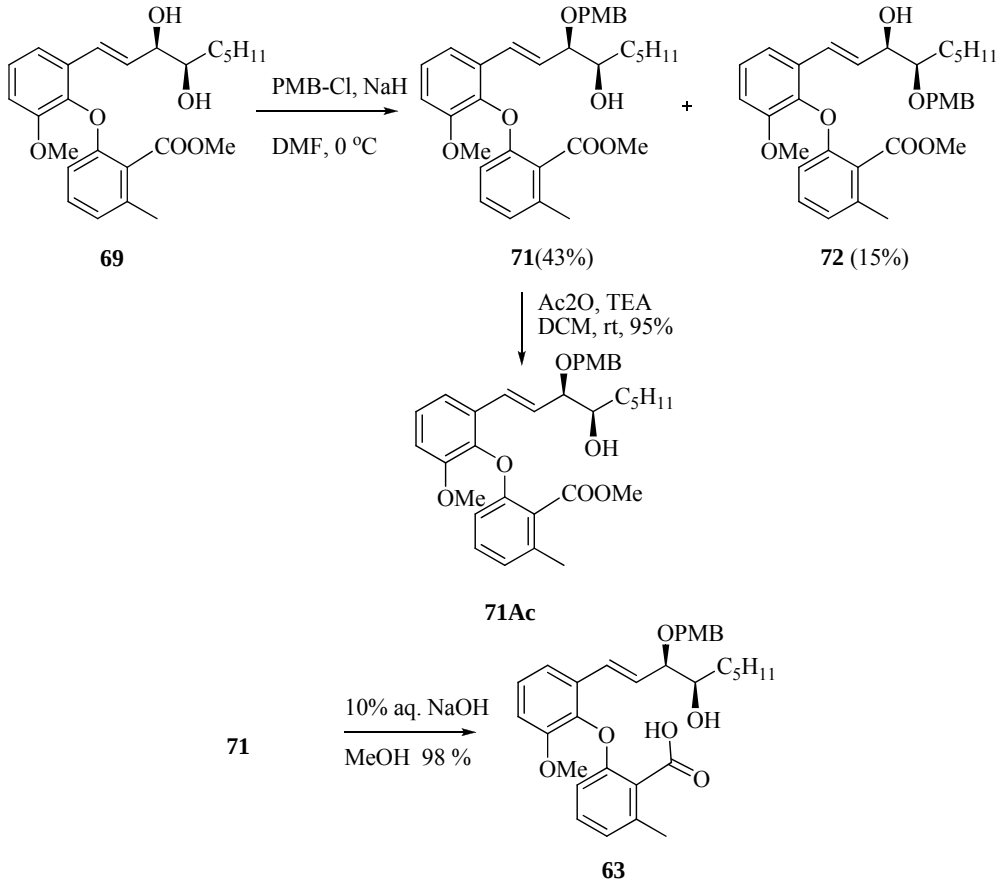
Scheme 21.



The dihydroxylation of **64** led to required diol **69** in 74% yield [84% ee, Measured by HPLC; Chiral cell OJ-H (250x4.6 mm) mobile phase IPA/PE 2.5 : 97.5, flow rate 0.7ml/min,λ_{max} 220 nm, conc. 2.8 mg/3.0 ml] along with regioisomeric diol **70** using standard protocol of AD-reaction. The products were easily and unambiguously confirmed by the ^{1}H, ^{13}C NMR and mass spectroscopic data. In the ^{1}H NMR spectrum of **69**, the two methine protons attached to hydroxy groups were located at δ 3.43 and δ 3.97. One of the conjugated olefin proton of **69** resonated at δ 6.19 as doublet of a doublet (*J* = 6.5, 16.0 Hz). The characteristic triplet at δ 0.85 (*J* = 7.0 Hz.) was attributed to the terminal methyl group of side chain. The ^{13}C NMR and elemental analysis further supported the assigned structure of **69**. The position of hydroxyl group in the isomeric diol **70** was confirmed on the basis of proton NMR. The hydroxyl attached methine peaks appeared at δ 4.10 and 4.60. Moreover, presence of the signals corresponding to isolated olefinic protons in ^{1}H NMR at δ 5.31 (dd, *J* = 7.5, 15.5 Hz), 5.49 (dt, *J* = 6.5, 15.5 Hz) further supported the assigned structure of **70**.

Scheme 22.

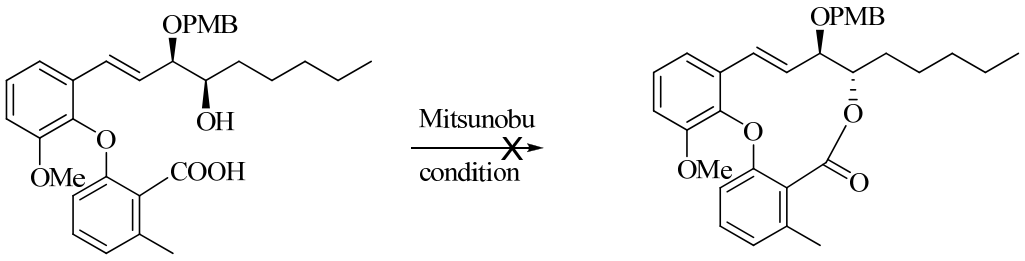




After obtaining the complete structural framework, the next attempt was lactonization with inversion of configuration of the alkoxy center. In order to do the same, the allylic hydroxyl was protected as PMB ether to get **71** by using NaH and PMB-Cl. Under that condition **71** was isolated in 43% yield along with regioisomer **72** as minor product (15%). Position of PMB ether in **71** was determined by NMR analysis of corresponding acetate **71Ac**. Finally, saponification of **71** afforded the crucial intermediate **63.** Compound **63** was analyzed completely and fully corroborated with the assigned structure.

After successful synthesis of **63**, the crucial lactonisation under Misunobu conditions[34] was carried out in different solvents (THF, toluene, dioane) using DEAD or DIAD in combination with triphenylphosphine from room temperature to reflux conditions. But unfortunately all attempted endeavors met with failure results.

Scheme 23.



63 **38**

As the one pot protocol i.e. lactonization with inversion of configuration was unsuccessful, we tried usual intermolecular Mitsunobu inversion of the free hydroxyl, and simple lactonisation (Scheme 24) to complete the synthesis of Aspercyclide C. Unfortunately the Mitsunobu inversion was unsuccessful with benzoic acid as well as with *p*-nitrobenzic acid as nucleophile under commonly used reaction conditions.

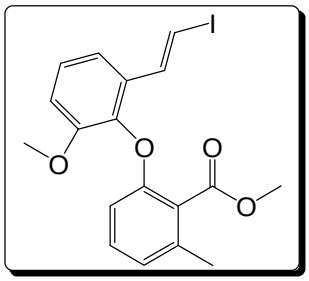
Scheme 24.

71

Conclusion: In context of the failure of RCM in case of aspercyclide A and B, we have investigated an alternative asymmetric regioselective dihydroxylation route for aspercyclide skeleton and successfully synthesized the skeleton of aspercyclide-C by asymmetric means, though the crucial lactonisation of the intermediate **63** (Scheme 23) was not facile. Comparative study of dihydroxylation of the conjugated diene **61** revealed that dihydroxylation occurred preferentially at *trans* double bond keeping *cis* double bond intact under biphasic condition using AD-mix β.

Experimental

Methyl 2-(2-((*E*)-2-iodovinyl)-6-methoxyphenoxy)-6-methylbenzoate (62)



To a suspension of anhydrous $CrCl_3$ (15.43 g, 97.43 mmol) in dry THF (120 mL), LAH (0.55 g, 14.61 mmol) was added portion wise at 0 ^oC over 20 min and the slurry was stirred for 2 h at rt. After complete reduction it was cooled to 0 ^oC again, and a mixture of iodoform (7.67 g, 19.48 mmol) and aldehyde **26** (2.92 g, 9.74 mmol) in THF (20 mL) was added to it. The mixture was stirred for another 1h at same temperature. It was then quenched with cold water and extracted with diethyl ether. The combined ether layer was collected, dried, concentrated and the crude product was purified by silica gel column chromatography to afford the titled compound **62** (2.98 g, 72%) which was assigned to be a mixture of *trans* and *cis* (13:4) isomers by ^1H NMR spectrum. The *trans* isomer was separated out by crystallization in ethyl acetate / Pet. Ether mixed solvent to get **62** as solid (m. p. 66-67 ^oC).

Mol. Formula : $C_{18}H_{17}IO_4$

IR ($CHCl_3$) υ : 928, 951, 1074, 1114, 1253, 1275, 1438, 1462, 1477, 1584, 1600, 1728 cm^{-1}.

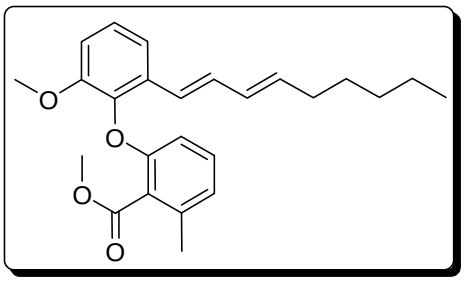
^1H NMR (200 MHz, $CDCl_3$) : δ 2.37 (s, 3H), 3.72 (s, 3H), 3.97 (s, 3H), 6.26 (d, *J* = 8.1Hz, 1H), 6.84 (d, *J* = 7.8 Hz, 1H), 6.90 (dd, *J* = 1.5, 7.9 Hz, 1H), 7.00 (d, *J* = 15.0 Hz, 1H), 6.99-7.20 (m, 3H), 7.59 (d, *J* = 15.0 Hz, 1H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$) : δ 19.3 (q), 52.2 (q), 56.0 (q), 80.2 (d), 110.8 (d), 112.5 (d), 118.6 (d), 123.2 (s), 123.4 (d), 125.8 (d), 129.9 (d), 132.1 (s), 136.9 (s), 139.1 (d), 139.8 (s), 152.7 (s), 154.8 (s), 168.2 (s) ppm.

ESI-MS (*m/z*) : 425.1 $[M+H]^+$, 448.2 $[M+Na]^+$.

Elemental Analysis Calcd.: C, 50.96; H, 4.04; I, 29.91 %
Found: C, 50.87; H, 4.05; I, 29.85 %

Methyl 2-(2-methoxy-6-((1*E*,3*E*)-nona-1,3-dienyl)phenoxy)-6-methylbenzoate (64)



To a mixture of vinyl iodide **62** (2.00 g, 4.7 mmol), (*E*)-hept-1-enylboronic acid (**65**) (0.87 g, 6.13 mmol) and Cs_2CO_3 (1.84 g, 5.6 mmol) in THF (20 mL) $Pd(PPh_3)_4$ (0.544g, 10 mol%) was added and the mixture was degassed under argon atmosphere. It was then refluxed for 2 h. After cooling and diluting the mixture with water it was extracted with ethyl acetate. Crude material was then further purified by column chromatography to get pure compound **64** (1.57 g, 84 %) as liquid.

Mol. Formula : $C_{25}H_{30}O_4$

IR ($CHCl_3$) υ : 806, 1015, 1167, 1253, 1461, 1597, 1730 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$) : δ 0.88 (t, *J* = 6.6 Hz, 3H), 1.17-1.46 (m, 6H), 2.10 (q, *J* = 6.8 Hz, 2H), 2.37 (s, 3H), 3.72 (s, 3H), 3.96 (s, 3H), 5.80 (dt, *J* = 7.0, 15.1 Hz, 1H), 6.16 (ddt, *J* = 1.2, 9.6, 15.1 Hz, 1H), 6.23 (d, *J* = 8.2 Hz, 1H), 6.59-6.91 (m, 4H), 7.01-7.24 (m, 3H) ppm.

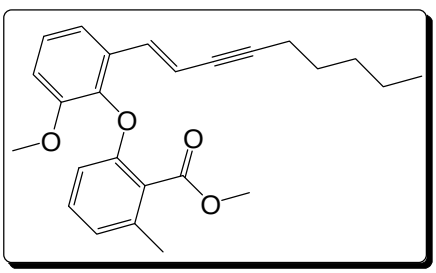
^{13}C NMR (50 MHz, $CDCl_3$) : δ 14.0 (q), 19.4 (q), 22.5 (t), 28.9 (t), 31.4 (t), 32.8 (t), 52.2 (q), 56.0 (q), 110.8 (d), 111.1 (d), 117.5 (d), 123.1 (d), 123.1 (s), 123.2 (d), 125.6 (d), 130.0 (d), 130.9 (d), 131.4 (d), 132.5 (s), 136.6 (d), 136.6 (s), 140.1 (s), 152.8 (s), 155.4 (s), 168.5 (s) ppm.

ESI-MS (*m/z*) : 417.4 $[M+Na]^+$.

Elemental Analysis Calcd.: C, 76.11; H, 7.66 %

Found: C, 76.01; H, 7.53 %

Methyl 2-(2-methoxy-6-((E)-non-1-en-3-ynyl)phenoxy)-6-methylbenzoate (66)



Starting vinyl iodide **62** (470 mg, 1.1 mmol) was dissolved in dry TEA (10 mL) and thoroughly degassed under argon atmosphere. To this solution $PdCl_2(PPh_3)_2$ (78 mg, 0.11 mmol), cuprous iodide (43 mg, 0.22 mmol) and 1-heptyne (0.6 mL, 4.4 mmol) were added and degassed again. The whole mixture was stirred for 12 h at rt. After that the mixture passed through *celite* pad and filtrate was concentrated, finally purified by silica gel column chromatography to get pure enyne **66** (380 mg, 87 %).

Mol. Formula : $C_{25}H_{28}O_4$

IR ($CHCl_3$) υ : 668, 929, 956, 1114, 1438, 1458, 1478, 1586, 1728 cm^{-1}.

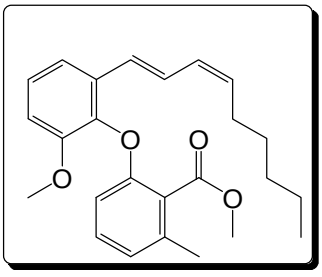
^{1}H NMR (200 MHz, $CDCl_3$) : δ 0.89 (t, *J*= Hz, 3H), 1.26-1.42 (m, 4H), 1.42-1.50 (m, 2H), 2.32 (dt, *J*= 2.2, 7.0 Hz, 2H), 2.37 (s, 3H), 3.71 (s, 3H), 3.96 (s, 3H), 6.22 (dt, *J* = 2.2, 16.3 Hz, 1H) 6.26 (d, *J*= 8.0 Hz, 1H), 6.81-6.91 (m, 2H), 7.01-7.12 (m, 4H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$) : δ 13.9 (q), 19.3 (q), 19.6 (t), 22.2 (t), 28.37 (t), 31.1 (t), 52.1 (q), 56.0 (q), 79.9 (s), 93.6 (s), 110.9 (d), 111.1 (d), 112.3 (d), 117.5 (d), 123.2 (s), 123.2 (d), 125.7 (d), 129.9 (d), 131.5 (s), 133.6 (d), 136.7 (s), 140.2 (s), 152.7 (s), 155.3 (s), 168.3 (s) ppm.

ESI-MS (*m/z*) : 393.2 $[M+H]^+$, 415.6 $[M+Na]^+$.

Elemental Analysis Calcd.: C, 76.50; H, 7.19 %
Found: C, 76.41; H, 7.20 %

Methyl 2-(2-methoxy-6-((1*E*,3*Z*)-nona-1,3-dienyl)phenoxy)-6-methylbenzoate (61)



A suspension of freshly activated Zn powder (2.2 g, 33.6 mmol) under argon with $Cu(OAc)_2 \cdot H_2O$ (168 mg, 0.84 mmol) and $AgNO_3$ (185 mg, 1.1 mmol) in MeOH/water (1:1; 20 mL) was added to a solution of the enyne **66** (330 mg, 0.84 mmol) in methanol (20 mL) at room temperature and with stirring. After 24 h heating at 50 ^oC, the reaction mixture was filtered through *Celite* pad and the subsequent aqueous workup, flash chromatography afforded the pure *E*,*Z* conjugate diene **61** (291 mg, 88 %).

Mol. Formula : $C_{25}H_{30}O_4$

IR ($CHCl_3$) υ : 757, 956, 988, 1030, 1074, 1112, 1182, 1203, 1241, 1276, 1439, 1461, 1477, 1586, 1605, 1732 cm^{-1}

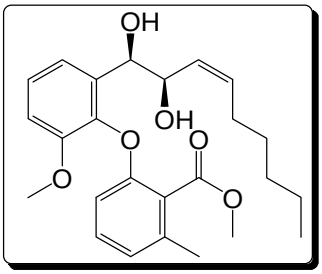
^{1}H NMR (200 MHz, $CDCl_3$) : δ 0.88 (t, *J* = 6.5 Hz, 3H), 1.26-1.46 (m, 6H), 2.18-2.29 (m, 2H), 2.36 (s, 3H), 3.73 (s, 3H), 3.95 (s, 3H), 5.49 (dt, *J* = 7.7, 10.7 Hz, 1H), 6.01 (t, *J* = 10.7 Hz, 1H), 6.28 (d, *J* = 8.3 Hz, 1H), 6.68-6.86 (m, 3H), 7.01-7.28 (m, 4H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$) : δ 14.0 (q), 19.3 (q), 22.5 (t), 27.9 (t), 29.3 (t), 31.4 (t), 52.1 (q), 56.0 (q), 110.9 (d), 111.4 (d), 117.9 (d), 123.1 (d), 123.1 (s), 125.3 (d), 125.6 (d), 126.4 (d), 129.0 (d), 129.9 (d), 132.5 (s), 133.8 (d), 136.6 (s), 140.3 (s), 152.8 (s), 155.3 (s), 168.4 (s) ppm.

ESI-MS (*m/z*) : 395.2 $[M+H]^+$.

Elemental Analysis Calcd.: C, 76.11; H, 7.66 %
Found: C, 75.91; H, 7.65 %

Methyl 2-(2-((*Z*,1*R*,2*R*)-1,2-dihydroxynon-3-enyl)-6-methoxyphenoxy)-6-methylbenzoate (67)



To a mixture of AD-mix-β (767 mg) and $MeSO_2NH_2$ (52 mg, 0.54 mmol) in ^{t}BuOH/H_2O (10 mL; 1:1), diene **61** (216 mg, 0.547 mmol) (in 5 mL *t*BuOH) was added at 0 ^{o}C and the mixture was stirred vigorously for 48 h at the same temperature. It was then quenched with Na_2SO_3 and extracted with ethyl acetate. Whole organic layer was collected, dried and concentrated under reduced pressure. Silica gel column chromatographic purification gave compound **67** (143 mg, 61 %) as colourless liquid.

Mol. Formula : $C_{25}H_{32}O_6$

$[\alpha]_D^{25}$: +9.8 (*c* = 1.2, $CHCl_3$)

IR ($CHCl_3$) υ : 759, 958, 1027, 1075, 1114, 1202, 1242, 1255, 1273, 1440, 1462, 1479, 1591, 1605, 1731, 3431 (bs) cm^{-1}.

^{1}H NMR : δ 0.81 (t, *J* = 7.0 Hz, 3H), 0.93-1.22 (m, 6H), 1.61-1.70 (m,

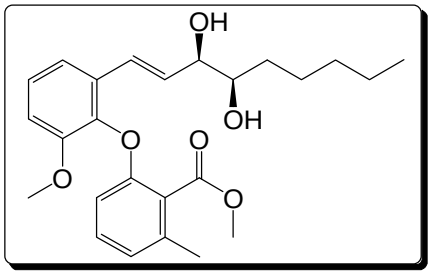
(400 MHz, $CDCl_3$) 1H), 1.77-1.84 (m, 1H), 2.35 (s, 3H), 2.65 (bs, 1H), 3.25 (bs, 1H), 3.69 (s, 3H), 3.92 (s, 3H), 4.46 (t, *J* = 8.1 Hz, 1H), 6.68 (d, *J* = 7.8 Hz, 1H), 5.30 (dd, *J* = 8.7, 11.0 Hz, 1H), 5.40 (dt, *J* = 7.3, 11.0 Hz, 1H), 6.31 (d, *J* = 8.5 Hz, 1H), 6.82 (d, *J* = 7.5 Hz, 1H), 6.89 (dd, *J* = 1.3, 8.0 Hz, 1H), 7.05 (dd, *J*= 1.3, 7.7 Hz, 1H), 7.07 (t, *J* = 8.0 Hz, 1H), 7.17 (t, *J* = 7.7 Hz, 1H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$) δ 14.0 (q), 19.5 (q), 22.5 (t), 27.7 (t), 28.9 (t), 31.3 (t), 52.2 (q), 56.0 (q), 71.2 (d), 73.2 (d), 110.9 (d), 112.3 (d), 120.6 (d), 122.5 (s), 123.4 (d), 125.9 (d), 127.2 (d), 130.1 (d), 134.8 (s), 135.2 (d), 137.0 (s), 140.4 (s), 152.2 (s), 154.9 (s), 168.5 (s) ppm.

ESI-MS (*m/z*) : 429.3 $[M+H]^+$, 451.3 $[M+Na]^+$.

Elemental Analysis Calcd.: C, 70.07; H, 7.53 %
Found: C, 69.85; H, 7.48 %

Methyl 2-(2-((*E*,3*R*,4*R*)-3,4-dihydroxynon-1-enyl)-6-methoxyphenoxy)-6-methylbenzoate (69)



The mixture of AD-mix-β (3.602 g) and $MeSO_2NH_2$ (244 mg, 2.57 mmol) in *t*BuOH/H2O (20 mL; 1:1) was stirred at room temperature for 15 min and then cooled to 0 °C. To this solution the diene **64** (1.015 g, 2.57 mmol) dissolving in 5 mL *t*BuOH was added. The reaction mixture was stirred at 0 °C for 48 h and then quenched with saturated aqueous Na_2SO_3 at room temperature. EtOAc was added to the reaction mixture, and after separation of the layers, the aqueous layer was further extracted with EtOAc twice. The combined organic layers were dried over Na_2SO_4 and concentrated under vacuum. Purification by flash column afforded diol **69** (518 mg, 47%) as a colourless oil along with the regioisomeric diol **70 (**231 mg, 21%).

Mol. Formula : $C_{25}H_{32}O_6$

$[\alpha]_D^{25}$: + 7.4 (*c* = 1.3, CH_3OH)

IR ($CHCl_3$) υ : 1075, 1115, 1439, 1461, 1520, 1587, 1726, 3469 (b) cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$) : δ 0.85 (t, *J* = 7.0 Hz, 3H), 1.12-1.42 (m, 8H), 2.33 (s, 3H), 3.41-3.45 (m, 1H), 3.74 (s, 3H), 3.93 (s, 3H), 3.97 (t, *J* = 6.5 Hz, 1H), 6.19 (dd, *J* = 6.5, 16.0 Hz, 1H), 6.24 (d, *J* = 8.5 Hz, 1H), 6.18-6.25 (m, 3 H), 7.02-7.16 (m, 3H) ppm.

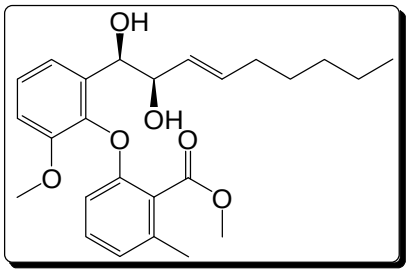
^{13}C NMR (50 MHz, $CDCl_3$) : δ14.0 (q), 19.3 (q), 22.6 (t), 25.3 (t), 31.8 (t), 32.7 (t), 52.3 (q), 56.1 (q), 74.4 (d), 76.1 (d), 111.0 (d), 111.9 (d), 119.3 (d), 123.2 (s), 123.3 (d), 125.9 (d), 126.3 (d), 130.0 (d), 131.7 (s), 132.2 (d), 136.6 (s), 140.6 (s), 152.9 (s), 155.0 (s), 168.8 (s) ppm.

ESI-MS (*m/z*) : 429.1 $[M+H]^+$, 451.0 $[M+Na]^+$.

Elemental Analysis Calcd.: C, 70.07; H, 7.53 %

Found: C, 69.81; H, 7.55 %

Methyl 2-(2-((*E*,1*R*,2*R*)-1,2-dihydroxynon-3-enyl)-6-methoxyphenoxy)-6-methylbenzoate (70)



Mol. Formula : $C_{25}H_{32}O_6$

$[\alpha]_D^{25}$: –6.83 (*c* = 1.3, $CHCl_3$)

IR ($CHCl_3$) υ : 668, 961, 1076, 1115, 1241, 1254, 1275, 1439, 1462, 1479, 1590, 1606, 1727, 2858, 2956, 3019, 3473 (bs) cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$) : δ 0.85 (t, *J* = 6.7 Hz, 3H), 1.05-1.36 (m, 6 H), 1.91 (q, *J* = 6.5 Hz, 2H), 2.37 (s, 3H), 3.72 (s, 3H), 3.94 (s, 3H), 4.06-4.17 (m, 1H), 5.60 (d, *J* = 6.8 Hz, 1H), 5.31 (dd, *J* = 7.5, 15.5 Hz, 1H), 5.49 (dt, *J* = 6.5, 15.5 Hz, 1H), 6.29 (d, *J* = 8.2 Hz, 1H), 6.83 (d, *J* = 7.6 Hz, 1H),6.91 (dd, *J* = 1.6, 8.2 Hz, 1H), 7.01 (dd, *J* = 1.4, 7.8 Hz, 1H), 7.08 (t, *J* = 7.8 Hz, 1H), 7.18 (t, *J* = 7.9 Hz, 1H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$) δ 14.0 (q), 19.6 (q), 22.5 (t), 28.7 (t), 31.2 (t), 32.2 (t), 52.1 (q), 55.8 (q), 73.6 (d), 75.8 (d), 110.8 (d), 112.0 (d), 120.8 (d),

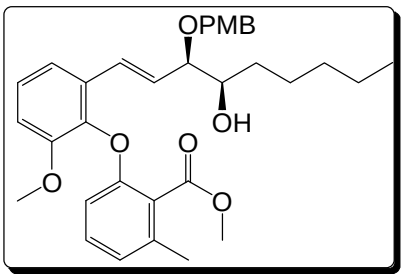
122.5 (s), 123.4 (d), 125.8 (d), 128.3 (d), 130.1 (d), 134.3 (d), 135.3 (s), 137.1 (s), 140.1 (s), 152.2 (s), 154.9 (s), 168.2 (s) ppm.

ESI-MS (*m/z*) : 429.0 $[M+H]^+$, 451.0 $[M+Na]^+$.

Elemental Analysis Calcd.: C, 70.07; H, 7.53 %

Found: C, 69.98; H, 7.61 %

Methyl 2-(2-((*E*,3*R*,4*R*)-3-(4-methoxybenzyloxy)-4-hydroxynon-1-enyl)-6-methoxyphenoxy)-6-methylbenzoate (71)



Compound **69** (952 mg, 2.22 mmol) in DMF (5 mL) was added to a stirred suspension of NaH (98 mg, 2.26 mmol, 60% in mineral oil) in DMF (7 mL) at 0 ^oC. After stirring the resulting solution at rt for 30 min, *p*-methoxy benzyl chloride (0.35 mL, 2.22 mmol) was added at 0 ^oC and strring was continued for another 1 h at same temperature. Then the reaction mixture was quenched by ice-cold water and extracted with EtOAc. The combined organic layer was washed with water, dried (Na_2SO_4) and concentrated. The residue was purified on silica gel column chromatography to obtain **71** (524 mg, 43%) as colourless liquid along with isomeric compound **72** (182 mg, 15%).

Mol. Formula : $C_{33}H_{40}O_7$

$[\alpha]_D^{25}$: –16.8 (*c* = 1.4, $CHCl_3$)

IR ($CHCl_3$) υ : 1180, 1276, 1440, 1460, 1477, 1586, 1610, 1732, 3560 (b) cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$) : δ 0.85 (t, *J* = 7.7 Hz, 3H), 1.09-1.33 (m, 8H), 2.59 (bs,1H), 2.34 (s, 3H), 3.42-3.62 (m, 2H), 3.77 (s, 3H), 3.78 (s, 3H), 3.93 (s, 3H), 4.06 (d, *J* =11.3 Hz, 1H), 4.33 (d, *J* = 11.3 Hz, 1H), 6.03 (dd, *J* = 8.3, 16.1 Hz, 1H), 6.25 (d, *J* = 8.2 Hz, 1H), 6.75-6.92 (m, 5H), 7.00-7.16 (m, 5H) ppm.

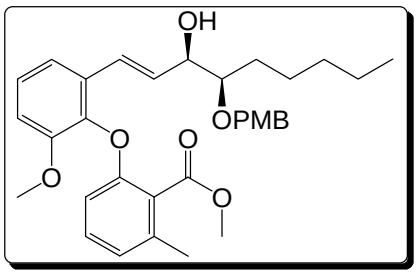
^{13}C NMR (50 MHz, $CDCl_3$) : δ 14.2 (q), 19.4 (q), 22.7 (t), 25.2 (t), 31.9 (t), 32.6 (t), 52.1 (q), 55.1 (q), 56.1 (q), 69.6 (t), 73.4 (d), 83.5 (d), 110.9 (d), 112.2 (d), 113.8 (d), 119.0 (d), 123.3 (d), 123.4 (s), 125.9 (d),

129.2 (d), 129.6 (d), 129.6 (d), 129.9 (d), 130.1 (s), 131.7 (s), 136.8 (s), 140.7 (s), 153.0 (s), 155.4 (s), 159.2 (s), 168.1 (s) ppm.

MALDI-TOF-MS (*m*/z) : 571.8 $[M+Na]^+$

Elemental Analysis Calcd.: C, 72.24; H, 7.35 %
Found: C, 72.34; H, 7.34 %

Methyl 2-(2-((*E*,3*R*,4*R*)-4-(4-methoxybenzyloxy)-3-hydroxynon-1-enyl)-6-methoxyphenoxy)-6-methylbenzoate (72)



Mol. Formula : $C_{33}H_{40}O_7$

$[\alpha]_D^{25}$: –8.3 (*c* = 0.90, $CHCl_3$)

IR ($CHCl_3$) υ : 666, 821, 976, 1034, 1075, 1113, 1178, 1204, 1251, 1275, 1440, 1461, 1512, 1586, 1610, 1731, 2858, 2931, 3004, 3440 (b) cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) : δ 0.85 (t, *J* = 7.2 Hz, 3H), 1.11-1.17 (m, 2H), 120-131 (m, 4H), 1.32-150 (m, 2H), 2.34 (s, 3H), 2.53 (bs, 1H), 3.32 (dt, *J* = 5.7, 5.9 Hz, 1H), 3.74 (s, 3H), 3.78 (s, 3H), 3.92 (s, 3 H), 4.14 (t, *J* = 5.9 Hz, 1H), 4.39 (d, *J* = 11.0 Hz, 1H), 4.46 (d, *J* = 11.0 Hz, 1H), 6.21 (dd, *J* = 5.9, 16.0 Hz, 1H), 6.24 (d, *J* =8.2 Hz, 1H), 6.76-6.78 (m, 2H), 6.81 (d, *J* = 8.2 Hz, 2H), 6.85 (dd, *J* = 1.8, 7.3 Hz, 1H), 7.01 (t, *J* = 8.0 Hz, 1H), 7.09-7.13 (m, 2H), 7.17 (d, *J* = 8.2 Hz, 2H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$) : δ14.2 (q), 19.4 (q), 22.7 (t), 25.0 (t), 30.5 (t), 32.0 (t), 52.1 (q), 55.1 (q), 56.1 (q), 72.3 (t), 74.2 (d), 82.0 (d), 111.1 (d), 111.8 (d), 113.8 (d), 119.1 (d), 123.2 (d), 123.5 (s), 125.4 (d), 125.7 (d), 129.5 (d), 129.9 (d), 130.6 (s), 132.0 (d), 132.4 (s), 136.6 (s), 140.8 (s), 152.9 (s), 155.3 (s), 159.3 (s), 168.3 (s)

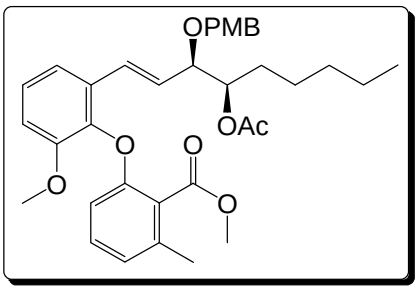
ppm.

ESI-MS (*m/z*) : 549.3 $[M+H]^+$, 571.3 $[M+Na]^+$.

Elemental Analysis Calcd.: C, 72.24; H, 7.35 %

Found: C, 72.31; H, 7.24 %

methyl 2-(2-((3*R*,4*R*,*E*)-4-acetoxy-3-(4-methoxybenzyloxy)non-1-enyl)-6-methoxyphenoxy)-6-methylbenzoate (71Ac)



A mixture of **71** (68 mg, 123 μmol), Ac_2O (26 mg, 247 μmol) and DMAP (5 mg) in DCM (3 mL) was stirred for 8 h. The reaction mixture was diluted with ethyl acetate and washed with water. The organic layer was concentrated under reduced pressure and residue was purified on silica gel column chromatography using EtOAc:light petroleum ether (1:9) as an eluent to obtain **71Ac** (69 mg, 95%).

Mol. Formula : $C_{35}H_{42}O_8$

$[\alpha]_D^{25}$: –35.6 (*c* = 1.1, $CHCl_3$)

IR ($CHCl_3$) υ : 1477, 1586, 1610, 1725, 1735, 2860, 2933, 2955, 3019 cm^{-1}.

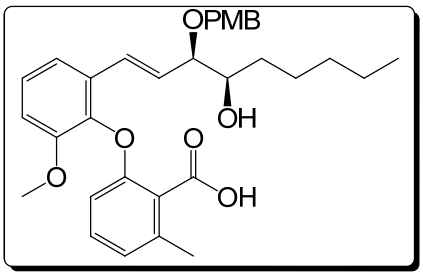
^{1}H NMR (200 MHz, $CDCl_3$) : δ 0.83 (t, *J* = 6.6 Hz, 3H), 1.02-1.26 (m, 6H), 1.36-1.50 (m, 2H), 2.00 (s, 3H), 2.35 (s, 3H), 3.69 (s, 3H), 3.79 (s, 3H), 3.81 (dd, *J* = 4.4, 5.4 Hz, 1H), 3.93 (s, 3H), 4.06 (d, *J* = 11.8 Hz, 1H), 4.40 (d, *J* = 11.8 Hz, 1H), 4.94 (dt, *J* = 5.4, 7.8 Hz, 1H), 6.04 (dd, *J* = 8.2, 16.0 Hz, 1H), 6.27 (d, *J* = 8.2 Hz, 1H), 6.71-6.93 (m, 5H), 6.95-7.23 (m, 5H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$) : δ 14.0 (q), 19.4 (q), 21.0 (q), 22.5 (t), 24.9 (t), 30.1 (t), 31.6 (t), 52.2 (q), 55.2 (q), 56.1 (q), 69.4 (t), 75.0 (d), 79.4 (d), 110.8 (d), 112.2 (d), 113.5 (d), 118.6 (d), 123.2 (s), 123.2 (d), 125.9 (d), 128.3 (d), 128.6 (d), 129.5 (d), 130.0 (d), 130.1 (s), 131.6 (s), 136.8 (s), 140.4 (s), 152.8 (s), 155.3 (s), 159.0 (s), 168.3 (s), 170.6 (s) ppm.

Elemental Analysis Calcd.: C, 71.17; H, 7.17 %

Found: C, 69.92; H, 7.01 %

2-(2-((*E*,3*R*,4*R*)-3-(4-methoxybenzyloxy)-4-hydroxynon-1-enyl)-6-methoxyphenoxy)-6-methylbenzoic acid (63)



A mixture of ester **71** (256 mg, 466 μmol) in methanol (10 mL) and 10 % aqueous solution NaOH (10 mL) was reflux for 24 h. Then methanol was removed under reduced pressure and diluted with water. The mixture was then acidified with 3 N HCl and extracted with ethyl acetate. The organic layer was collected, dried on sodium sulfate and concentrated under vacuum. The crude thus product obtained was subjected to column purification to get compound **63** (244 mg, 98%) as liquid.

Mol. Formula : $C_{32}H_{38}O_7$

$[\alpha]_D^{25}$: –17.2 (*c* = 0.7, $CHCl_3$).

IR ($CHCl_3$) υ : 733, 909, 958, 1072, 1034, 1180, 1205, 1251, 1275, 1302, 1462, 1514, 1586, 1610, 1727, 3440 (b) cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$) : δ 0.8 (t, *J* = 6.4 Hz, 3H), 1.14-1.43 (m, 8H), 2.53 (s, 3H), 3.50-3.56 (m, 1H), 3.66 (t, *J* = 7.5 Hz, 1H), 3.77 (s, 3H), 3.78 (s, 3H), 4.18 (d, *J* = 11.2 Hz, 1H), 4.45 (d, *J* = 11.2 Hz, 1H), 6.18 (dd, *J* = 8.2, 16.2 Hz, 1H), 6.40 (d, *J* = 7.9 Hz, 1H), 6.77-6.95 (m, 5H), 7.08-7.26 (m, 5H) ppm.

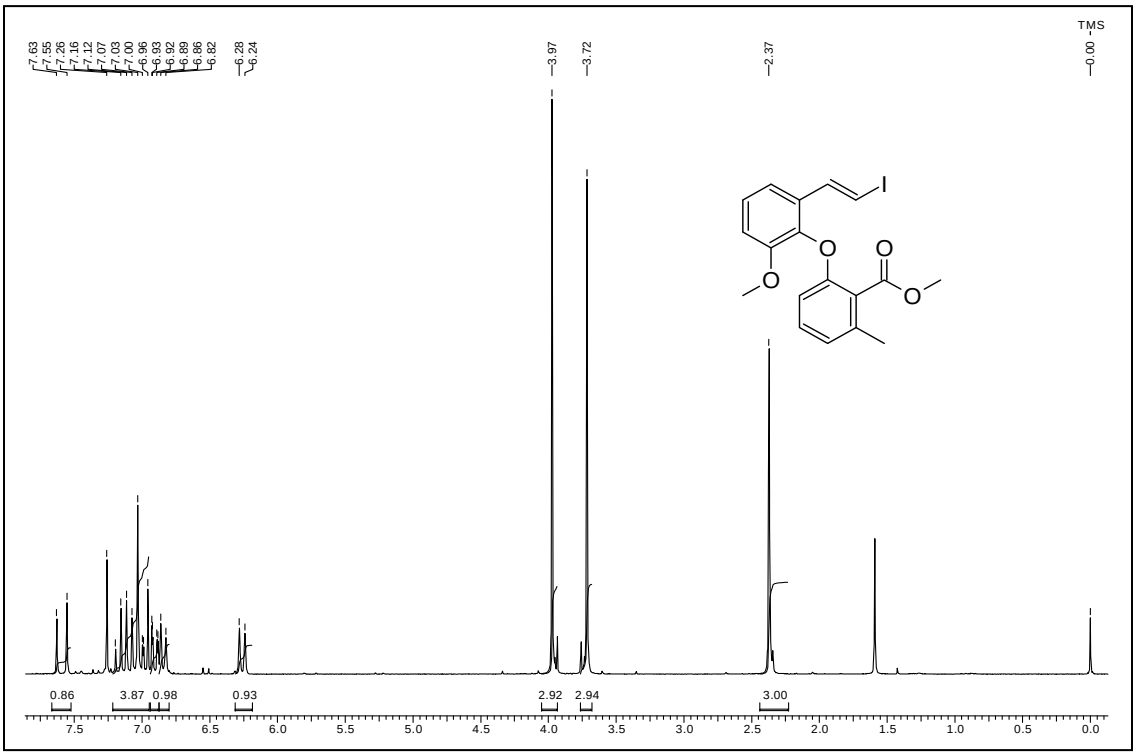
^{13}C NMR (50 MHz, $CDCl_3$) : δ 14.0 (q), 20.5 (q), 22.5 (t), 25.1 (t), 31.8 (t), 32.6 (t), 55.2 (q), 56.2 (q), 70.0 (t), 73.6 (d), 83.2 (d), 111.95 (d), 111.98 (d), 113.8 (d), 119.0 (d), 121.9 (s), 125.2 (d), 126.2 (d), 128.2 (d), 129.6 (d), 129.8 (s), 130.2 (d), 131.0 (d), 132.0 (s), 139.8 (s), 140.8 (s), 151.7 (s), 156.0 (s), 159.2 (s), 167.6 (s) ppm.

ESI-MS (*m/z*) : 535.5 $[M+H]^+$, 557.6 $[M+Na]^+$.

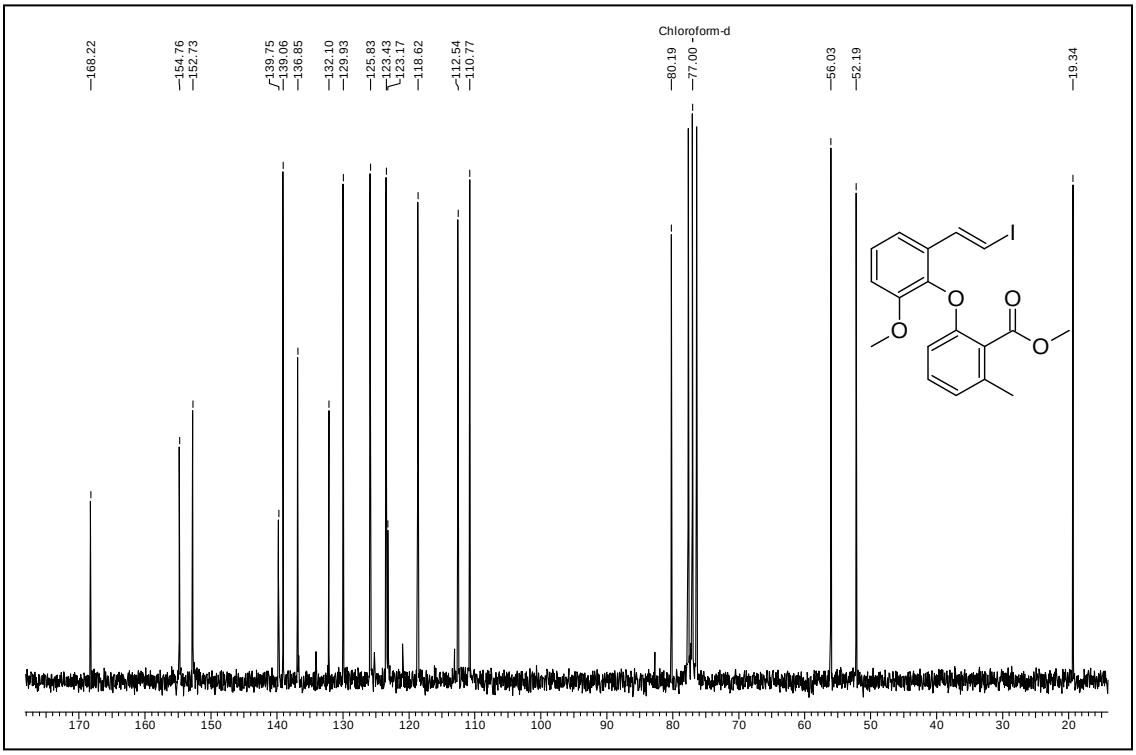
Elemental Analysis Calcd.: C, 71.89; H, 7.16 %

Found: C, 71.63; H, 7.09 %

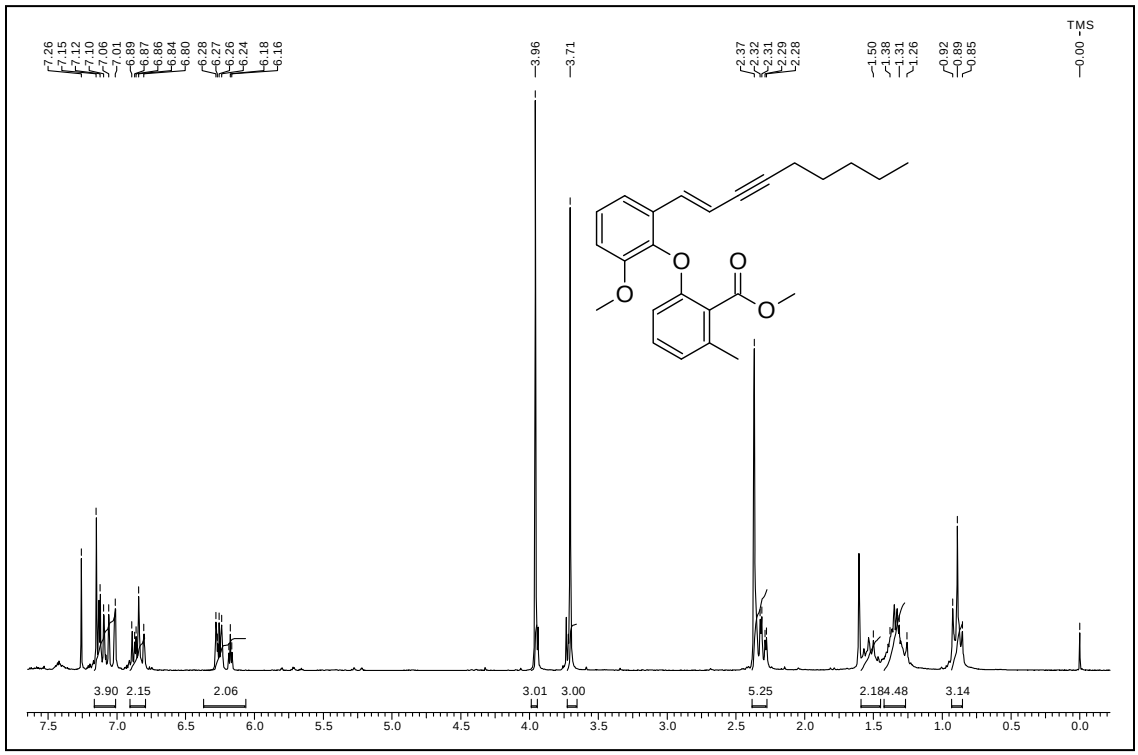
Spectra



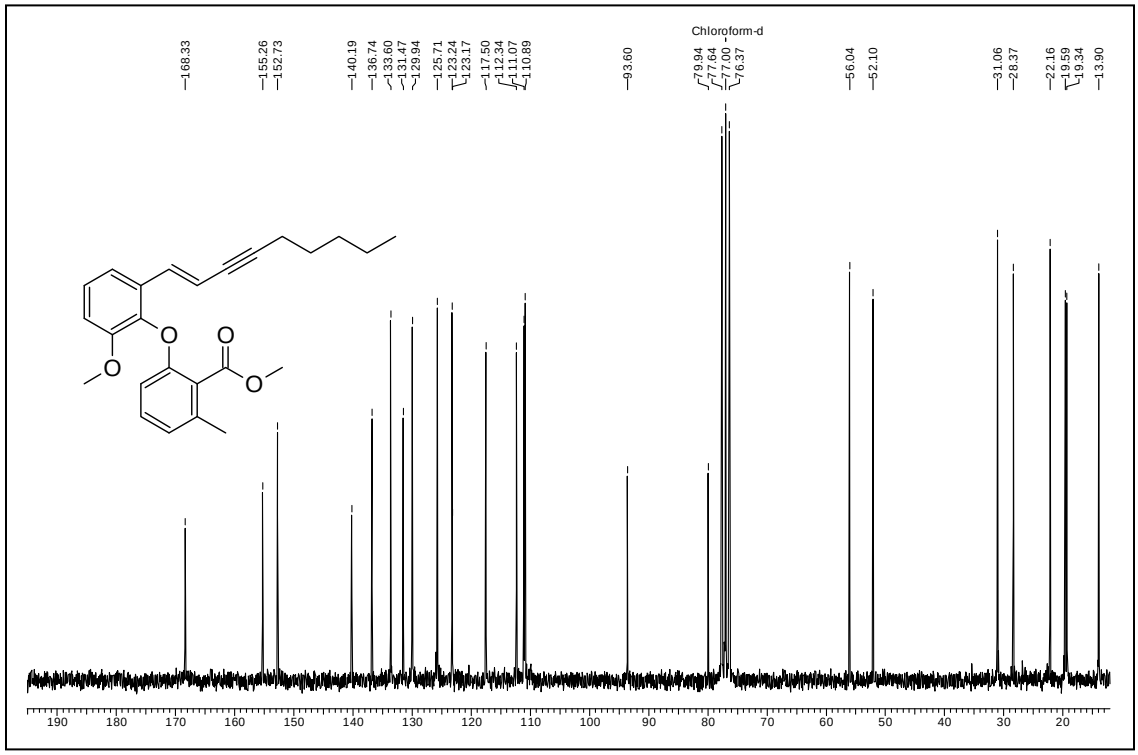
^{1}H NMR Spectrum of 62 in $CDCl_3$



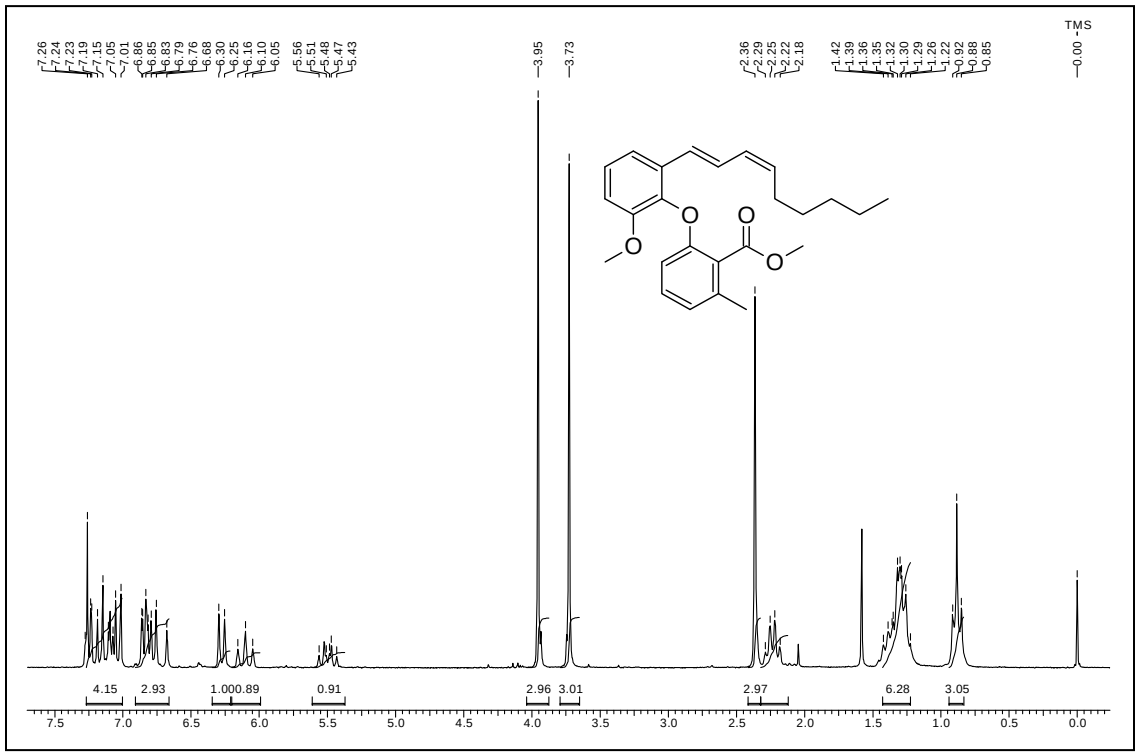
^{13}C NMR Spectrum of 62 in $CDCl_3$



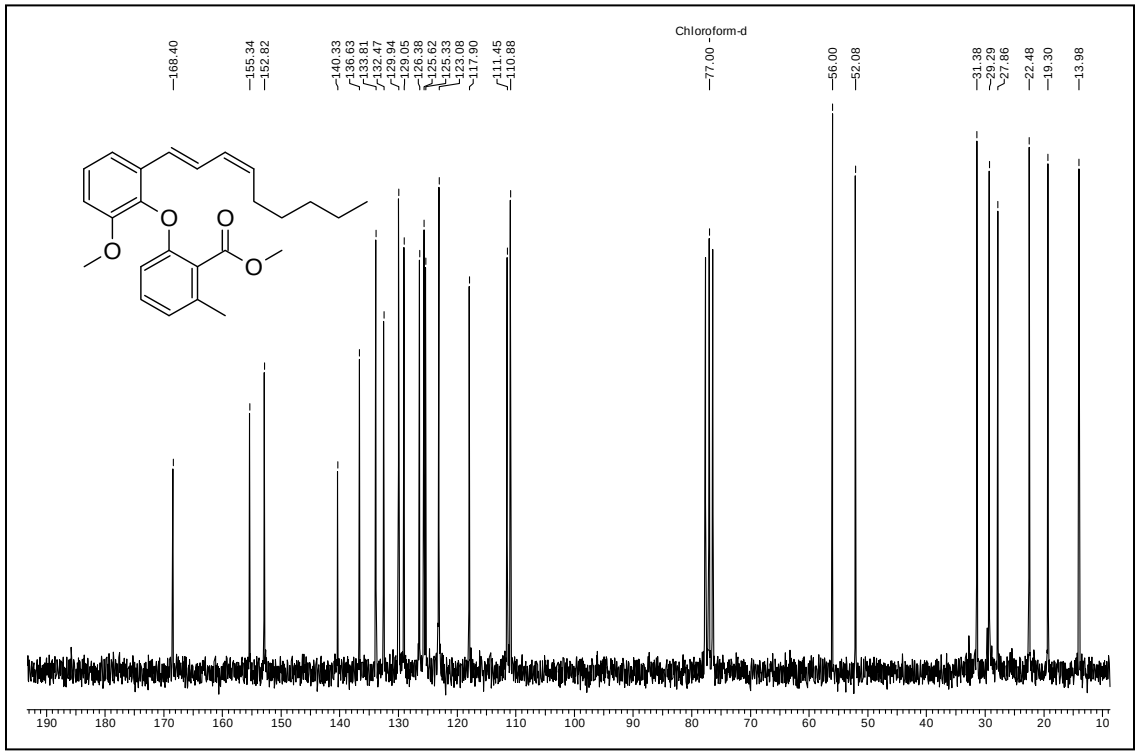
^{1}H NMR Spectrum of 66 in $CDCl_3$



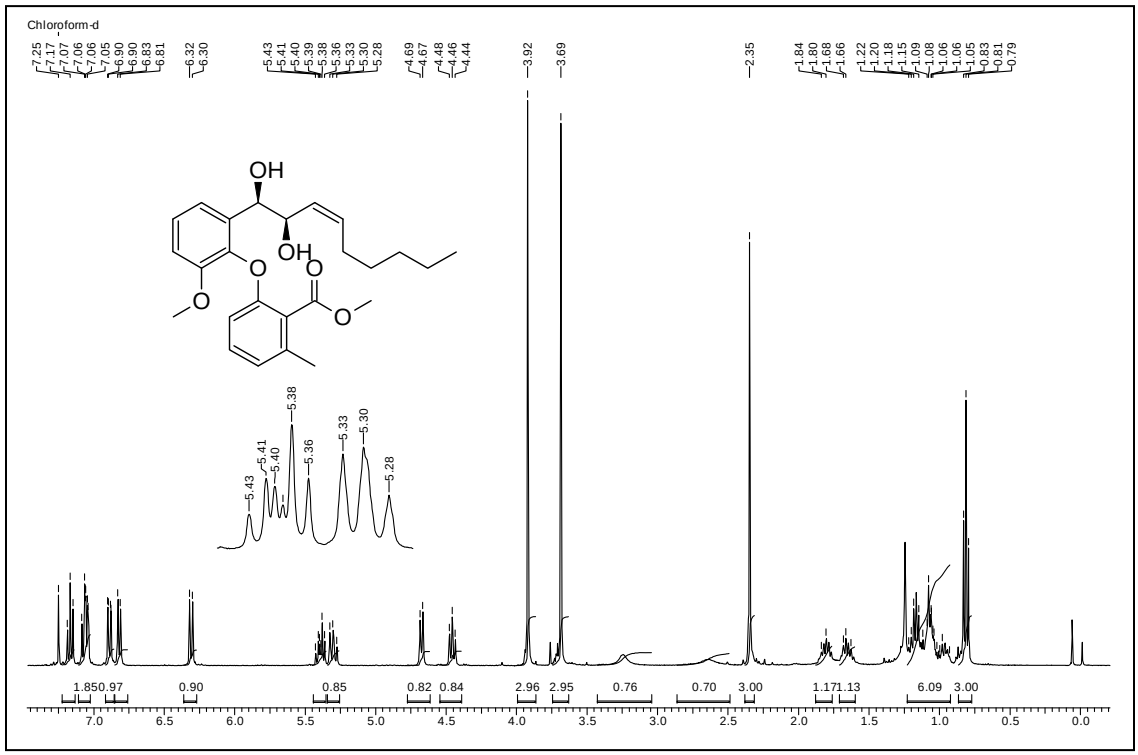
^{13}C NMR Spectrum of 66 in $CDCl_3$



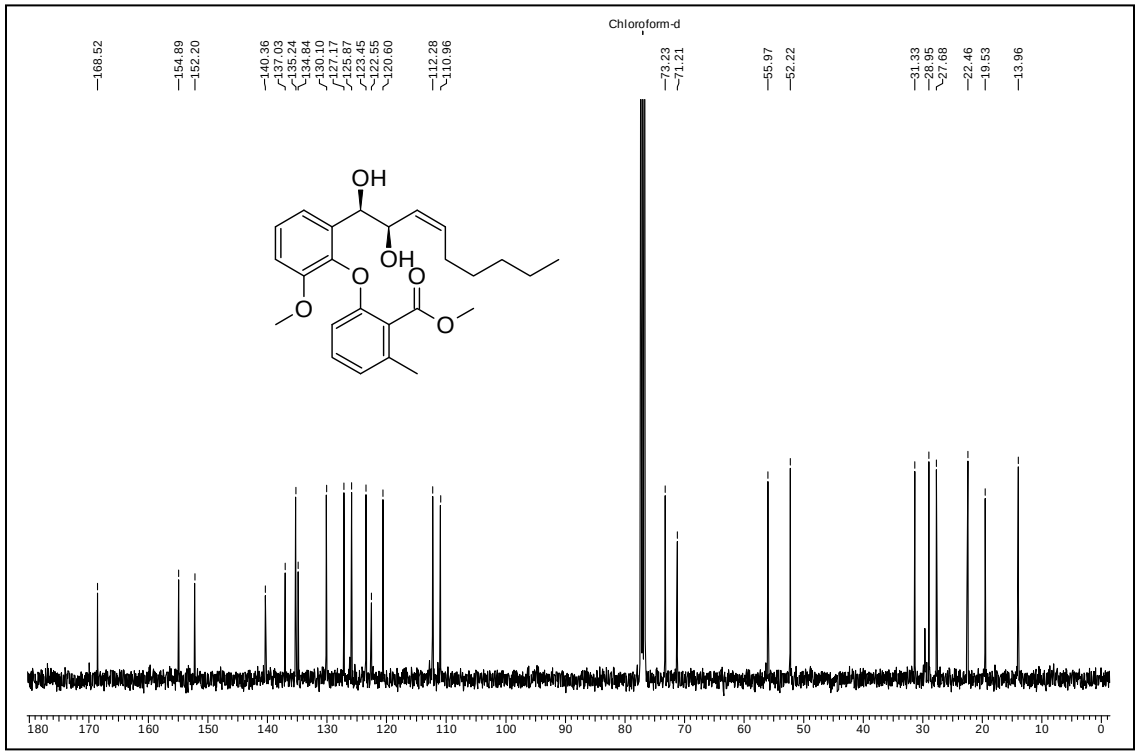
^{1}H NMR Spectrum of 61 in $CDCl_3$



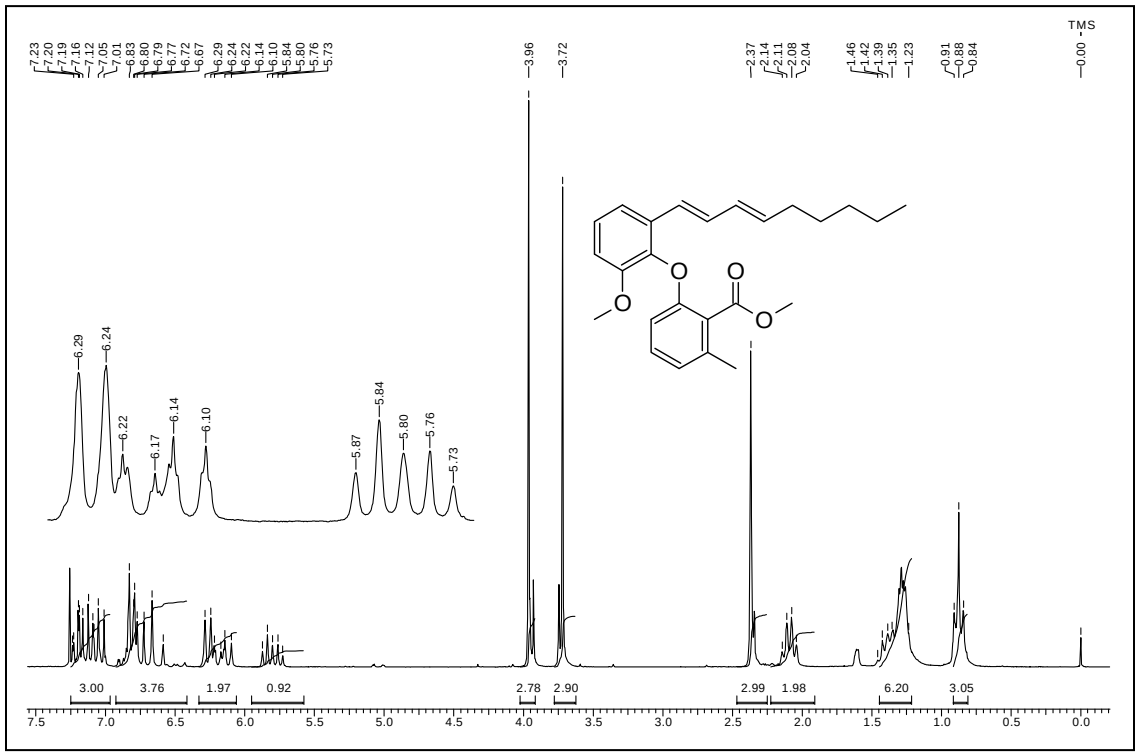
^{13}C NMR Spectrum of 61 in $CDCl_3$



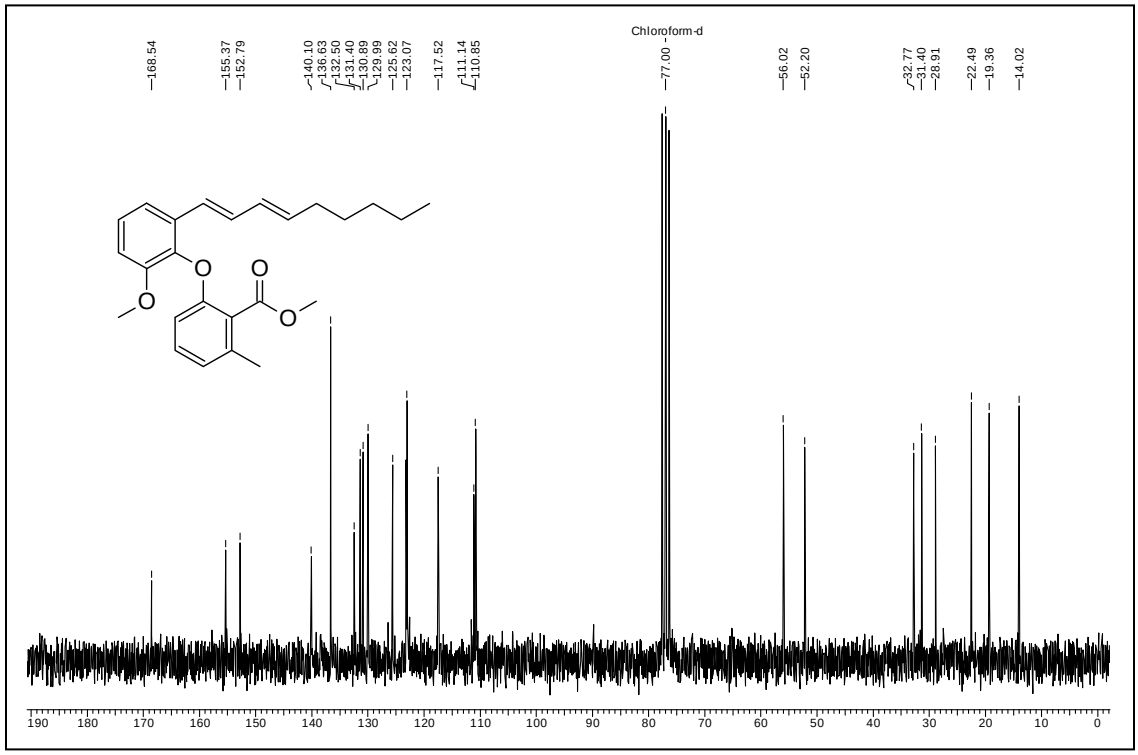
^{1}H NMR Spectrum of 67 in $CDCl_3$



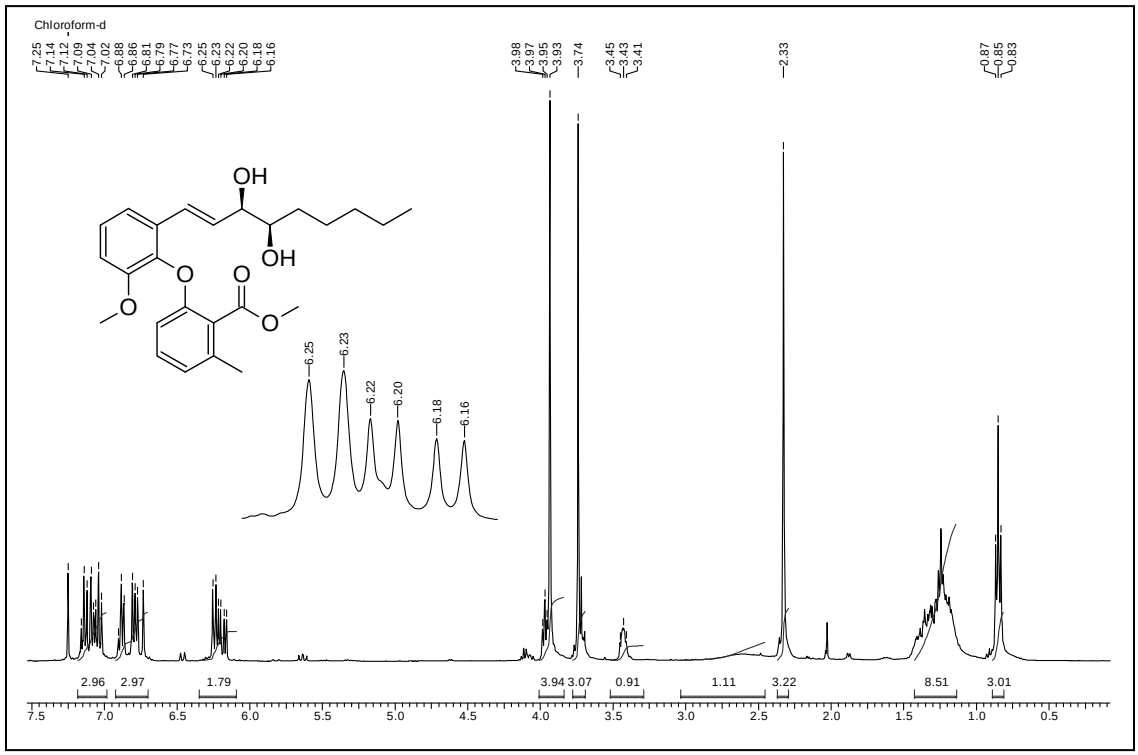
^{13}C NMR Spectrum of 67 in $CDCl_3$



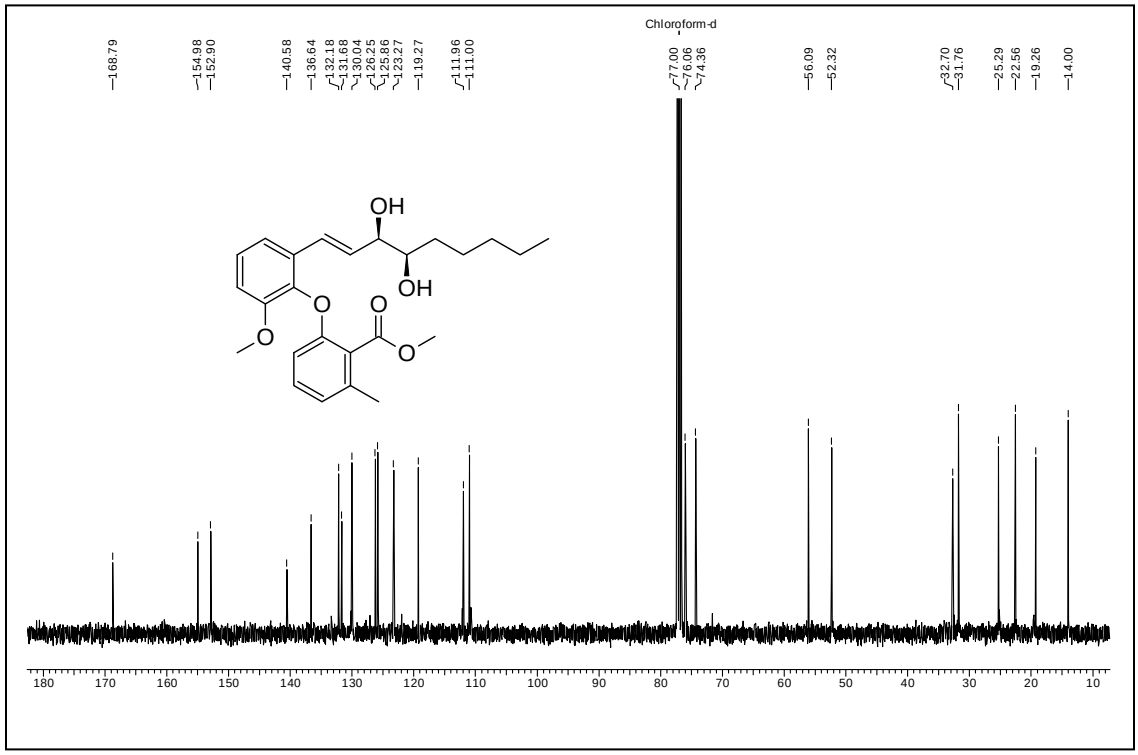
^{1}H NMR Spectrum of 64 in $CDCl_3$



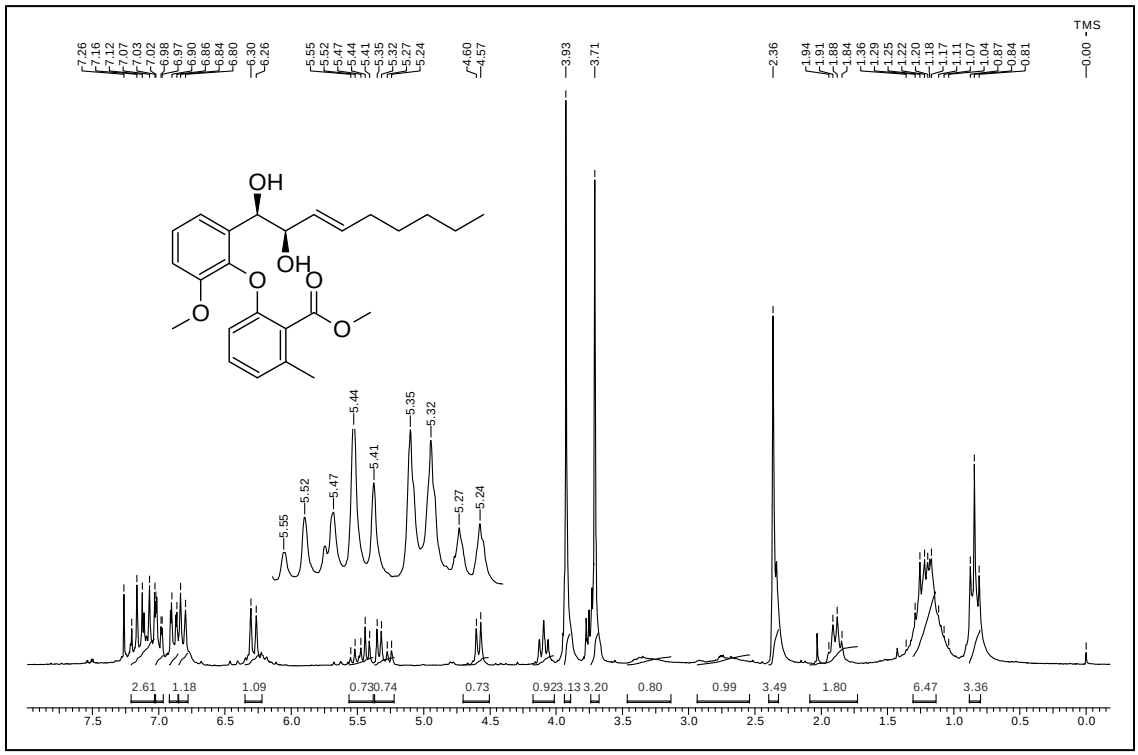
^{13}C NMR Spectrum of 64 in $CDCl_3$



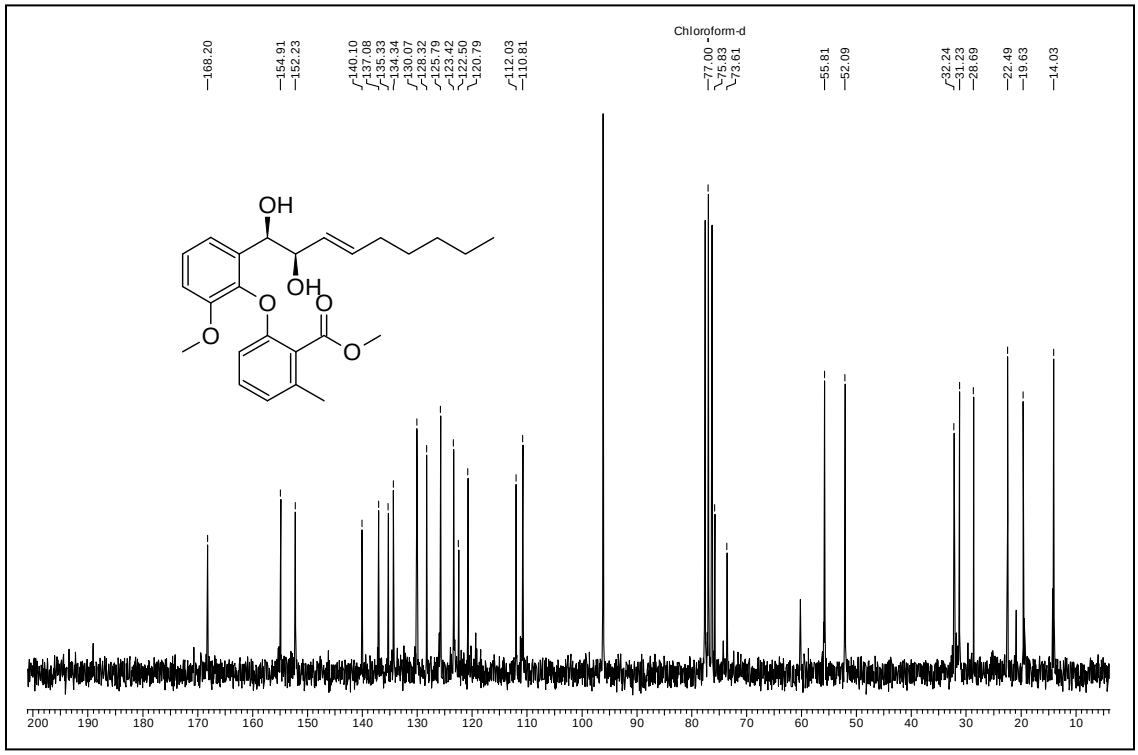
^{1}H NMR Spectrum of 69 in $CDCl_3$



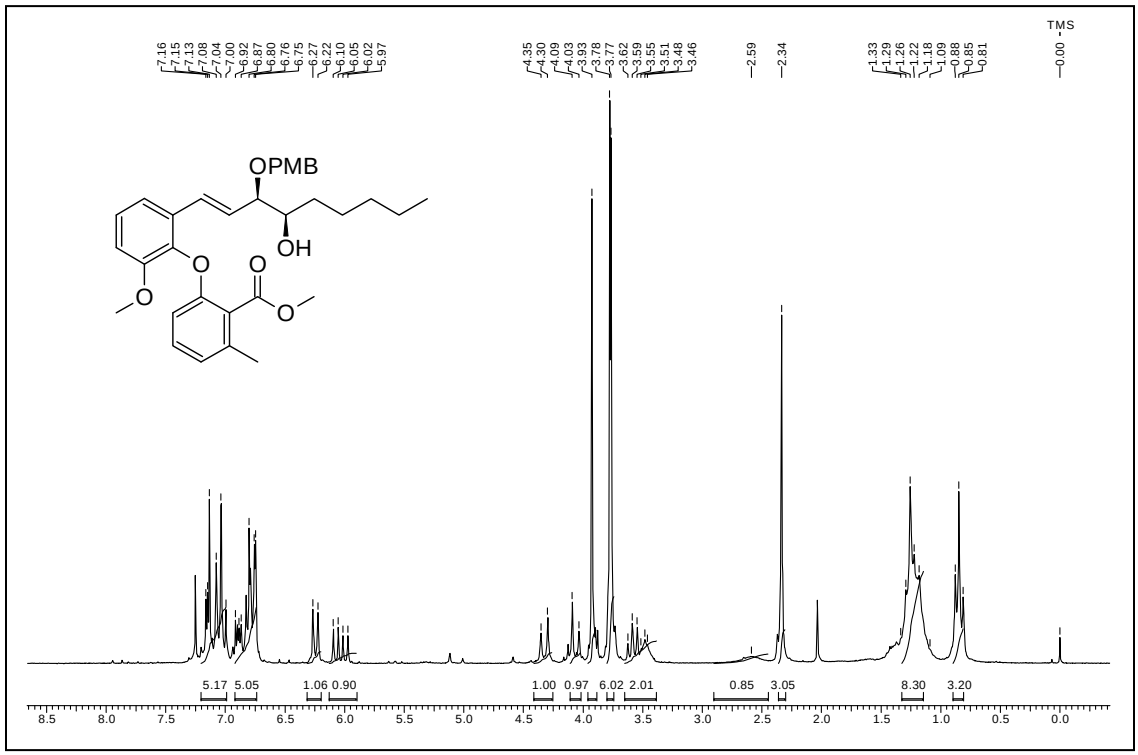
^{13}C NMR Spectrum of 69 in $CDCl_3$



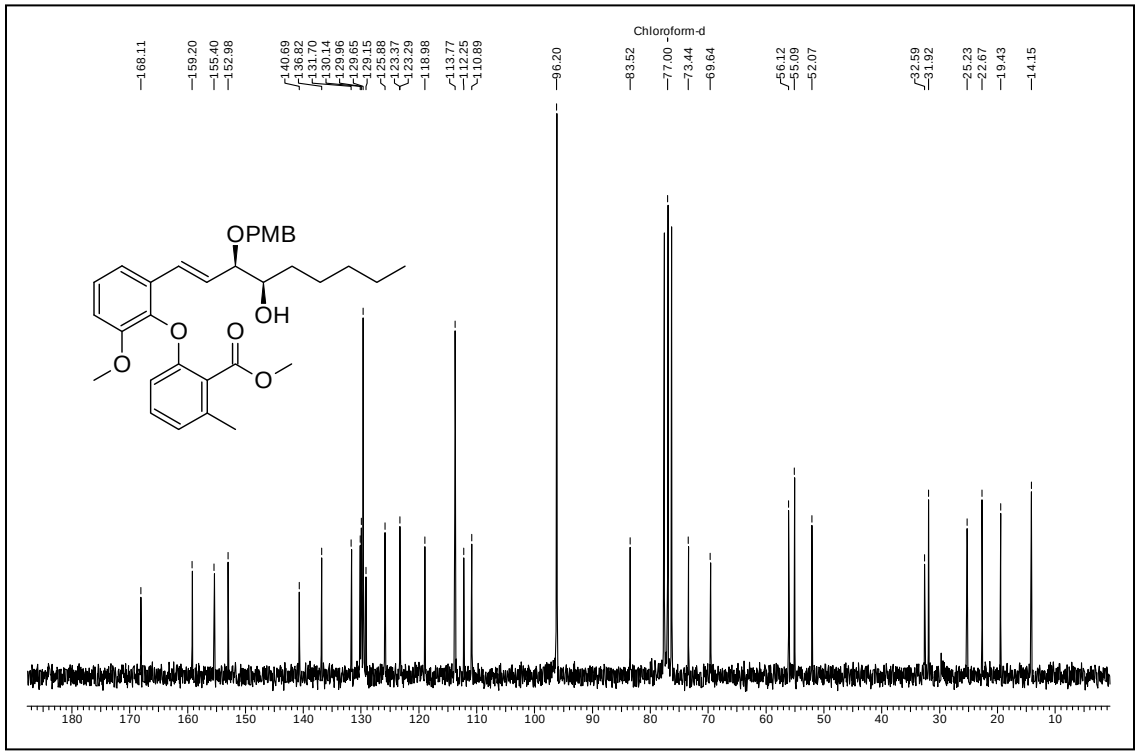
^{1}H NMR Spectrum of 70 in $CDCl_3$



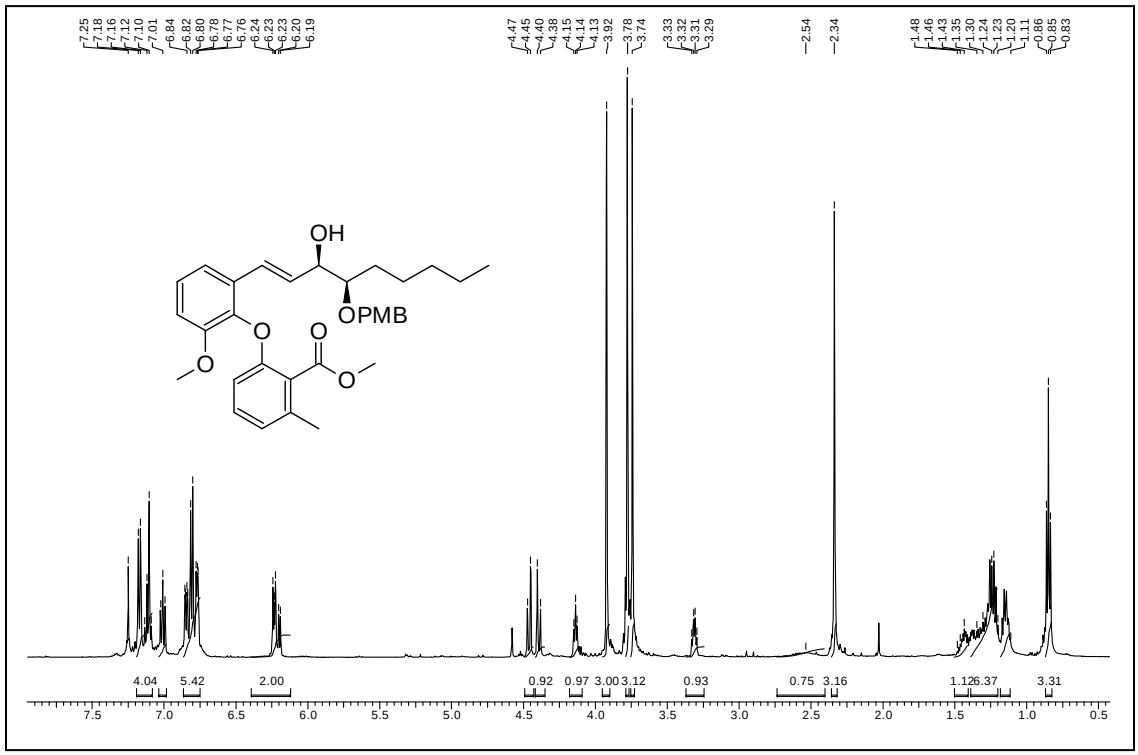
^{13}C NMR Spectrum of 70 in $CDCl_3$



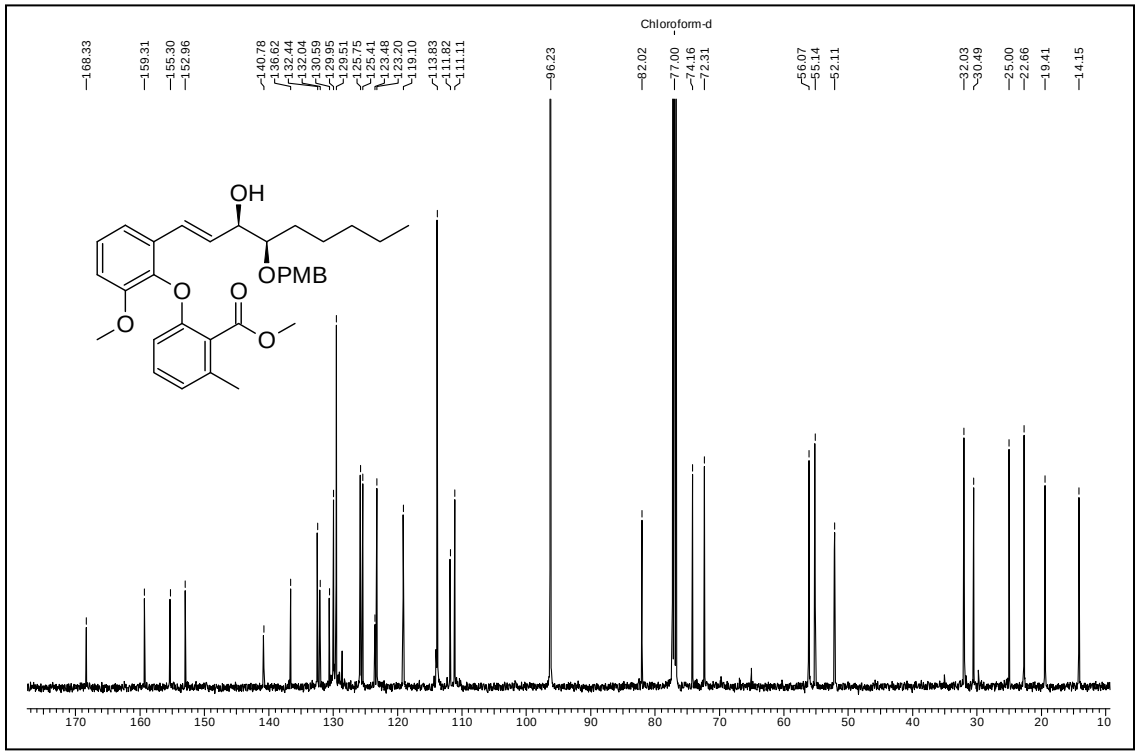
^{1}H NMR Spectrum of 71 in $CDCl_3$



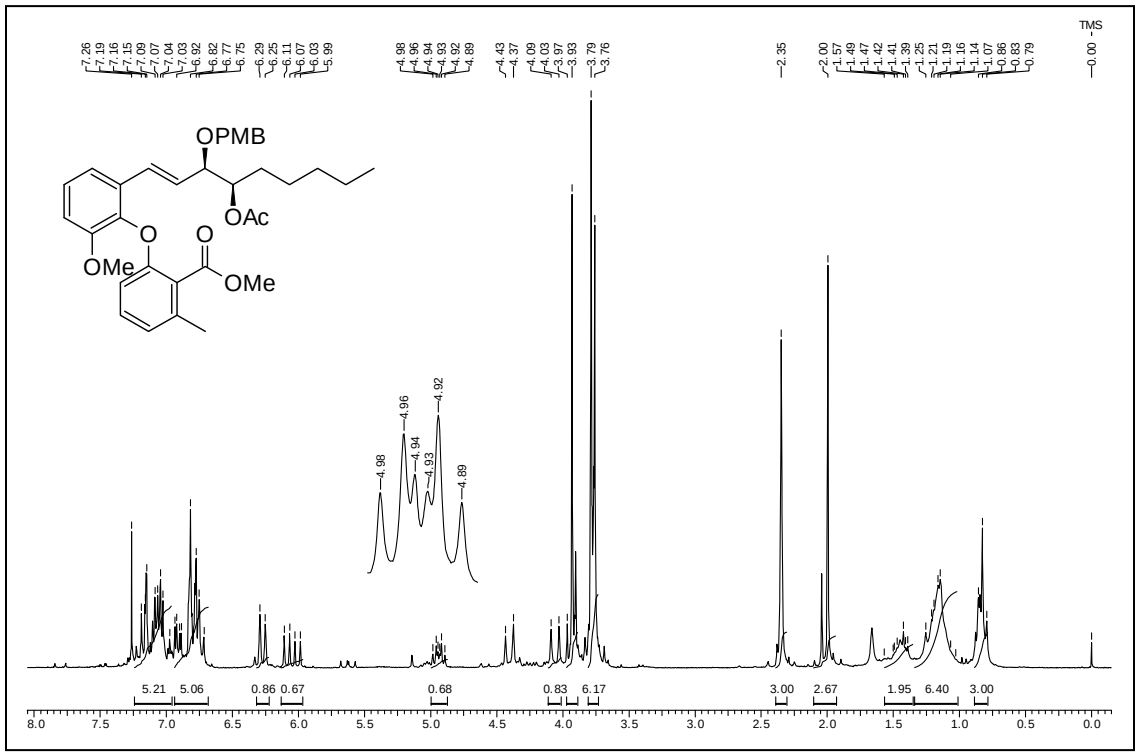
^{13}C NMR Spectrum of 71 in $CDCl_3$



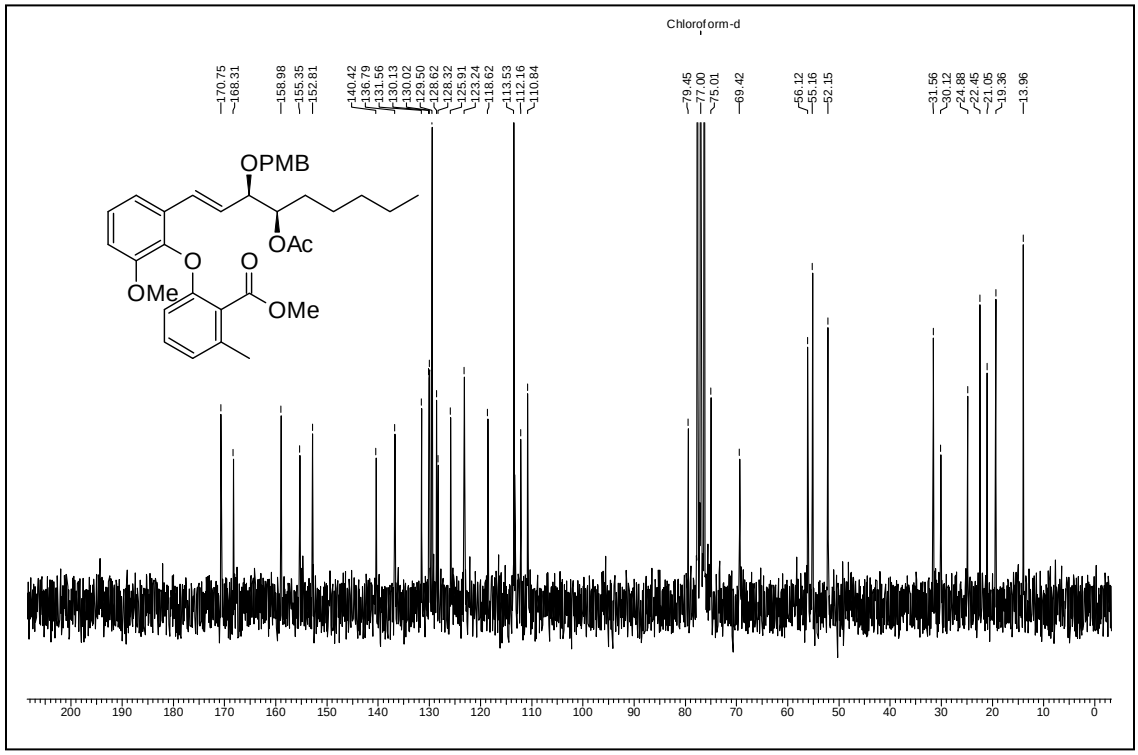
^{1}H NMR Spectrum of 72 in $CDCl_3$



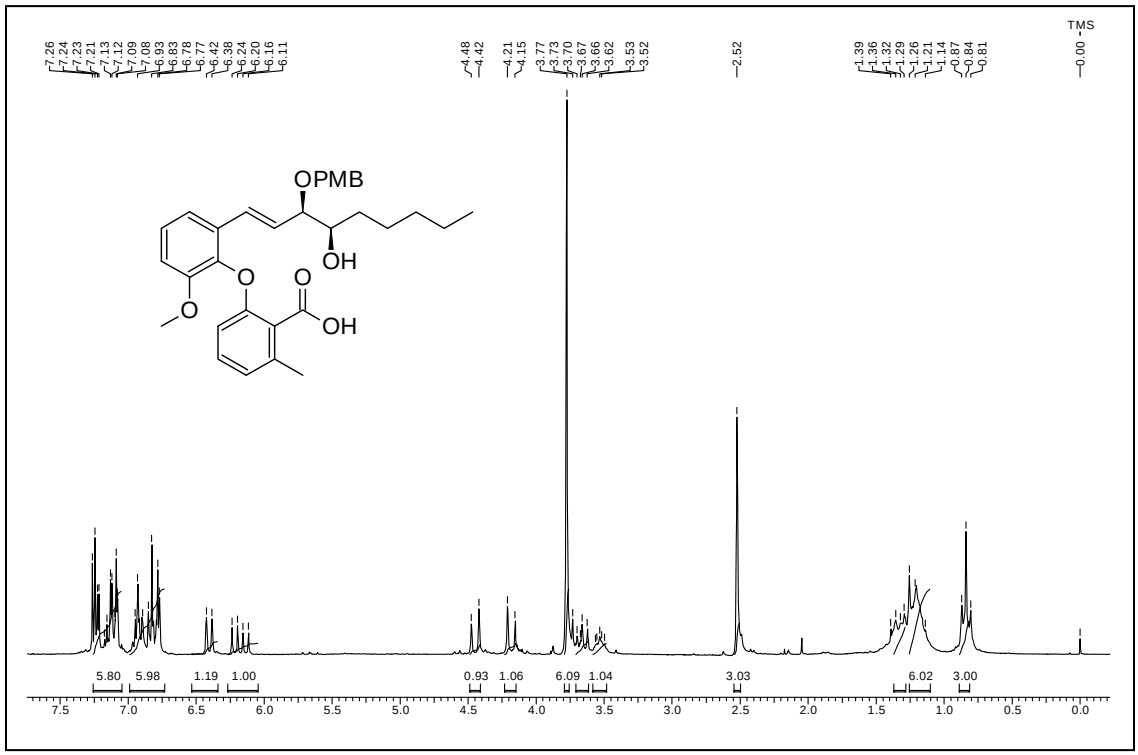
^{13}C NMR Spectrum of 72 in $CDCl_3$



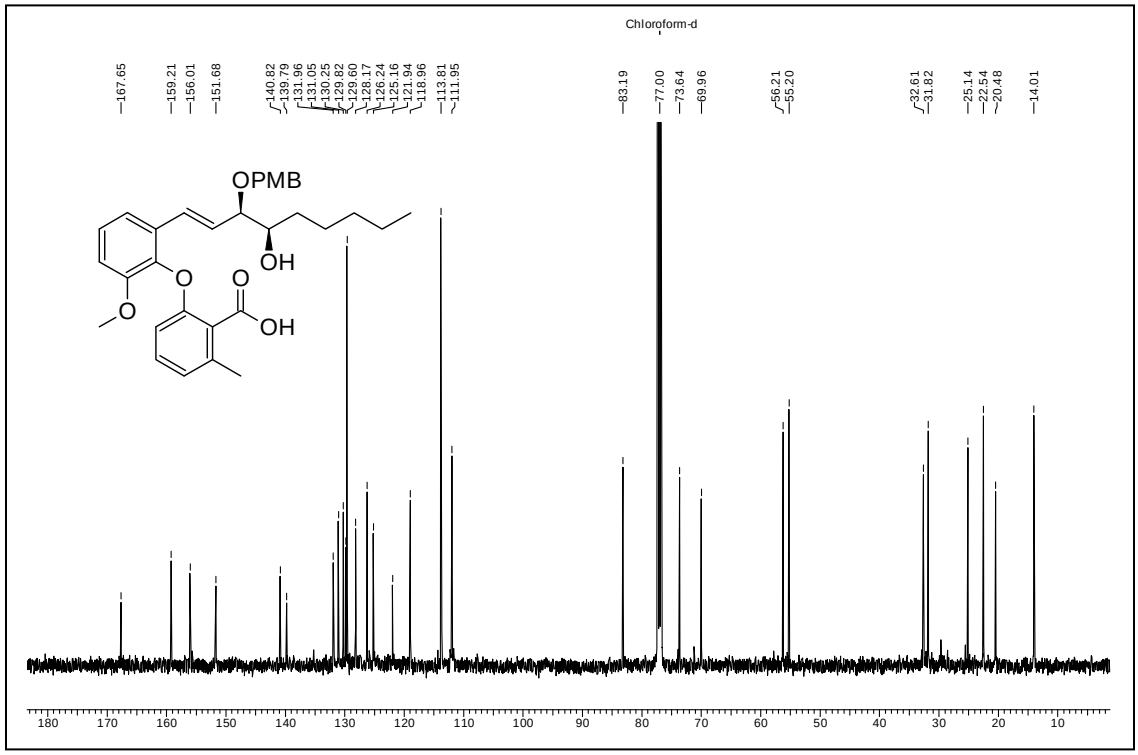
^{1}H NMR Spectrum of 71Ac in $CDCl_3$



^{13}C NMR Spectrum of 71Ac in $CDCl_3$



^{1}H NMR Spectrum of 63 in $CDCl_3$



^{13}C NMR Spectrum of 63 in $CDCl_3$

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Chapter 3

Studies Toward the Total Synthesis of Macrocidin A

Introduction

The high standard of today's agriculture can be attributed to the great advance in the agricultural science, especially use of herbicides in combination with pesticide and fungicides and highly productive seed grains.[1] Herbicides are the chemical or mixture of chemical specially designed and developed for the use in the control of weed in the field of agriculture.[2] Herbicides are especially more important in this context to protect crops, because major obstacle and serious loss in production of agricultural product come from unwanted plants called weeds. On the other hand there is an increase pressure on farmers to optimize the use of pesticide on the ground of human health and environment pollution. Because of slow degradation of pesticide after use, it pollute ground water, soil contamination whereas herbicides are environmental benign and cost-effective. Beside the impedimental effect of weeds in crop production, they can also clog essential waterway's and canals, poisons live stocks, causes dermatitis in human, induces hey fever and other respiratory problems etc.

Physiologically crops and weeds are equivalent, in that both require same resources from environment for growth and developments. When unwanted plants used up same of the resources, they are no longer available to the crop and these reasons nearly in all cases restrict crop growth and hence reduces yield. Therefore, to get enhance yield growth of unwanted plant should be prevented selectively. Traditionally, weeds are usually removed physically or mechanically by hand pulling, hoeing, cutting, digging etc. They are tedious in terms of time and man power. Use of herbicides is the most effective and popular method in weed control management. Though the science of herbicides new, its use is known from ancient time.

Classification of herbicides

Both selective and nonselective herbicides are classified according to HRAC on the basis of target site, mode of action, similarity of induced symptoms or chemical classes.[3]

- **ACCase inhibitors:** Acytyl CoA carboxylase are compounds that kill grasses. Acetyl coenzyme A carboxylase (ACCase) is part of the first step of lipid synthesis. Thus, ACCase inhibitors affect cell membrane production in the meristems of the grass plant. The ACCases of grasses are sensitive to these

herbicides, whereas the ACCases of dicot plants are not. Acryloxyphenoxy-propionate, cyclohexanedione and phenylpyrazoline are examples of such group.

- **ALS inhibitors**: The acetolactate synthase (ALS) enzyme (also known as acetohydroxyacid synthase, or AHAS) is the first step in the synthesis of the branched-chain amino acids (valine, leucine, and isoleucine). These herbicides slowly starve affected plants of these amino acids which eventually lead to inhibition of DNA synthesis. They affect grasses and dicots alike. The ALS inhibitor family includes sulfonylureas (SUs), imidazolinones (IMIs), triazolopyrimidines (TPs), pyrimidinyl oxybenzoates (POBs), and sulfonylamino carbonyl triazolinones (SCTs). ALS is a biological pathway that exists only in plants and not in animals thus making the ALS-inhibitors among the safest herbicides.
- **EPSPS inhibitors**: The enolpyruvylshikimate 3-phosphate synthase enzyme EPSPS is used in the synthesis of the amino acids tryptophan, phenylalanine and tyrosine. They affect grasses and dicots alike. Glyphosate (Roundup) is a systemic EPSPS inhibitor but inactivated by soil contact.
- **Synthetic auxin** inaugurated the era of organic herbicides. They were discovered in the 1940s after a long study of the plant growth regulator auxin. Synthetic auxins mimic this plant hormone. They have several points of action on the cell membrane, and are effective in the control of dicot plants. 2,4-dichlorophenoxyacetic acid is a synthetic auxin herbicide.
- **Photosystem II inhibitors** reduce electron flow from water to $NADPH^{2+}$ at the photochemical step in photosynthesis. They bind to the Qb site on the D1 protein, and prevent quinone from binding to this site. Therefore, this group of compounds causes electrons to accumulate on chlorophyll molecules. As a consequence, excess oxidation reactions in the cell occur, and the plant dies. The triazine herbicides (including atrazine) and urea derivatives (diuron) are photosystem II inhibitors.

Environment & Use of herbicides

Certain herbicides affect selectively metabolic pathways of plants and not found in animals.[4] These are the safest crop protection product having essentially no

effect on mammals, birds, amphibians or reptiles. Some herbicides[5]can cause a variety of health effects ranging from skin rashes to death due to their improper use and intentional or unintentional consumption. Under extreme conditions herbicides can also be transported via surface runoff to contaminate distant water sources. Most herbicides decompose rapidly in soils *via* soil microbial decomposition, hydrolysis or photolysis and some herbicides are more persistent with longer soil half-lives. However, because of the large number of herbicides in use, there is significant concern regarding health effects. Some of the herbicides in used are known to be mutagenic, carcinogenic or teratogenic.[5] However, some herbicides may also have a therapeutic use. Current research aims to use herbicides as an anti-malaria drug[6] that targets the plant-like apicoplast plastid in the malaria-causing parasite *Plasmodium falciparum*.

Necessary of newer herbicides

Most of the species contains different individual genotypes. Therefore, it is quite natural that these may differ in susceptibility to particular herbicides. If same herbicides are used consistently over a number of years, individuals within the species that has genetic resistance to the herbicide will survive and flourish after the demise of its sensitive siblings. There are several ways to avoid from herbicide resistance such as use of physical method for removing weeds, rotation of crops regularly. But the most effective way is the use newer herbicides with different mode of action and targets. Thus constant effort to discover new herbicides in the field herbicide chemistry is a growing concern.

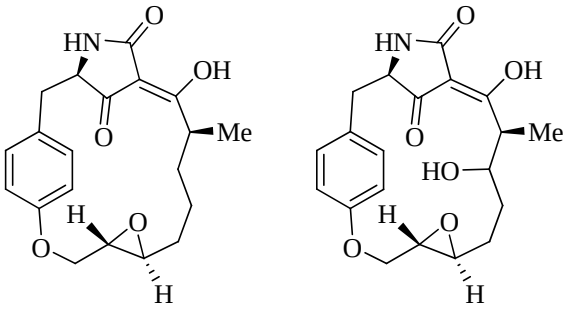
Isolation of New herbicides

Plant pathogenic microbes are known to be a vast source of wide range of unusual herbicidal metabolites associated with unique modes of action. From pathogenic fungi several class of chemical compounds including alkaloids, terpenoids, peptides, macrolides, phenolics, and numerous other classes of compounds including compounds of mixed biogenesis were isolated.[7] Some of them interestingly accelerate pathogenicity of many crop and weed pathogens.[8] Though, none of them were exhibited significant activities to be commercialized, they served as template to design synthetic compounds. In this connection the species of the genus *Phoma* is well known for plant pathogenisis.[9]

Isolation and biological bioactivity of macrocidin A and B

In 2003 P. R Graupner[10] and coworkers reported the isolation and structure determination of Macrocidins A and B.

Figure 1: *Structure of macrocidins.*



Macrocidin A (**1**) Macrocidin B (**2**)

Macrocidins were isolated from *phoma macrostoma* collected from diseased Canada thistle growing in several geographically diverse regions. Cultural extracts exhibited intense bleaching and clorosis to newly growth broadleaf plants. The UV spectra of these compounds (15% aqueous CH_3CN, λ_{max} 202, 226, 245(sh), 284 μm) were unusual and with the help of UV and LC/MS (ESI) these cultural extracts were purified. The main compounds were isolated by reversed-phase LC. To isolate macrocidins, liquid culture were fractionated in 1 g aliquots by preparative HPLC (YMC ODS-AQ 50 mm x 25 cm; particle size, 10 μm) with a gradient of 10% acetonitrile to 50% acetonitrile in 10 mM ammonium acetate. Bioassayed of each fraction of the eluents yielded macrocidine A. Repetitive isocratic chromatography of the earlier active fractions on a YMC ODS-AQ column (4.6 mm x25 cm; particle size, 5 um) using 6% acetonitrile in 10 mM ammonium acetate yielded macrocidin B. Purified samples exhibited siginificant herbicide activity. Their mode of action was remained unknown. Although, plat symptoms observed with macricidines were similar to sulcotrione and other inhibitors of hydroxyphenyl pyruvate dioxygenase (HPPD), but *in vivo* experiment were not in agreement apparent observations. Presence of acidic functionality tetramic acid rendered them Phloem mobility as it shown bleaching and stunting at the newly growing portion of susceptible plants. Therefore, macrocidins are belonging to a new chemotype with cytotoxicity and phloem mobility which are extremely rear.[11]

Structure determination macrocidin A

The gross structure of macrocidin A was elucidated by using COSY, NOESY and HMBC data analysis and both the isomers characterized by a tetramic acid moiety spanned by a *para* substituted aromatic ring. The relative stereochemistry of the *trans* epoxide was fixed on the basis of ROESY and NOE experiments. On the basis of molecular modeling and the coupling constants observed in ^{1}H NMR the relative stereochemistry of the methyl group was assigned. This was further substantiated by single crystal *X*-ray diffraction study which was full support of the structure macrocidin A. Due to the lack of sufficient sample the absolute stereochemistry was remained undetermined.

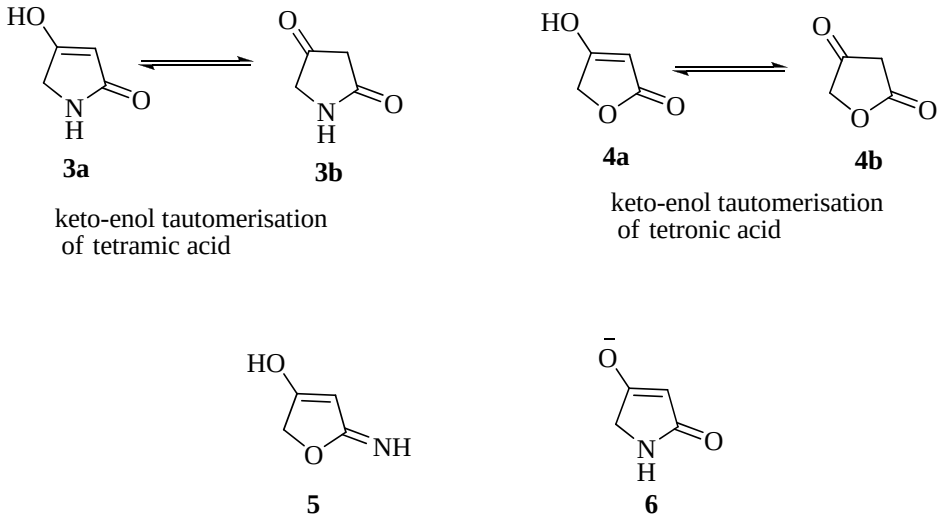
Tetramic acid

Although, the heterocyclic motif "tetramic" acid were known from early twentieth century the real breakthroughs are introduced on 1964 when a considerable numbers of natural products originating from a variety of marine and terrestrial species such as sponges, cyanobacteria, bacteria and fungi with wide range of biological activities such as potent antibiotic, antiviral and antiulcerative properties, cytotoxicity and mycotoxicity, the inhibition of tumors (in mice and humans) as well as fungicidal action. The mentioned moiety, in most cases, is present as a 3-acyl derivative or, less commonly, as a 4-*O*-alkyl ether derivative.

Physical and chemical properties of tetramic acid

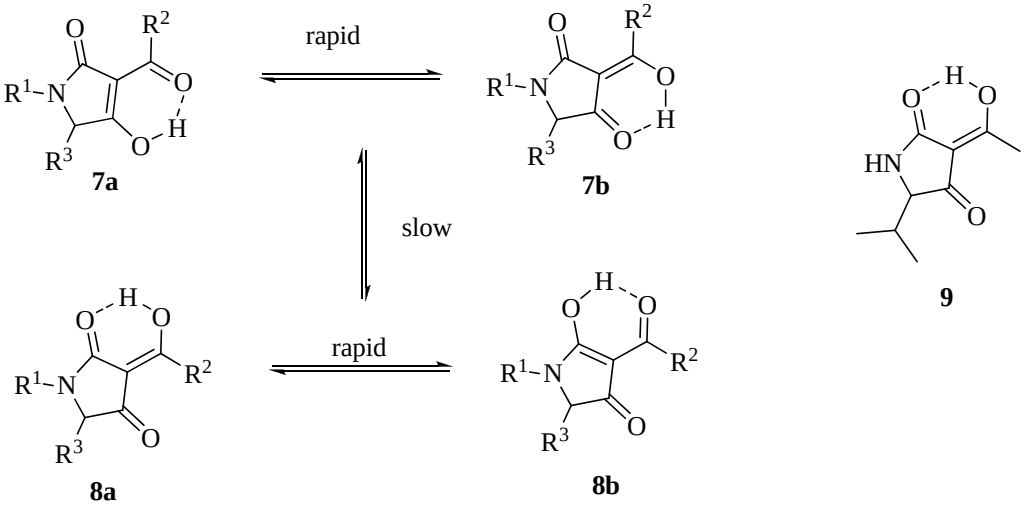
Tetramic acid traditionally has been presented as enolic tautomer of 4-hydroxy-3- pyrrolin-2-one **3a** on the basis of assumption that it would show similar properties as it structurally analogue of well know tetronic acid **4**. First synthesis of tetronic acid reported[12] in 1896 and it is strongly acidic (pKa = 3.76) in aqueous solution; exist as an equilibrating mixture keto-enol tautomers both in solution as well in solid phase. In contrast to the oxygen analogue **4**, tetramic acid **3** is less acidic and exists mainly as diketo-form in solid sate. However, in solution it maintain an equilibrium with the enolate **6** and diketo **3b** enolic tautomer **3a** being absent (Figure 2). Surprisingly the first synthesis of tetramic acid came in literature only in 1972[13]. Early attempts[14] led to the synthesis of isomeric compound 2-iminotetronic acid[15] **5**.

Figure 2.



Tetramic acids bearing acyl at 3rd position have similar acidity to the tetronic acids. Proton NMR spectra indicate the complete enolization of these systems although they are complicated by the presence of several tautomeric forms. Theoretically 3-acyl tetramic acids can exit in nine tautomeric form out of which four are detectable in solution namely two pairs of rapidly interconverting tatomers **7a**/**7b** and **8a**/**8b**. The interconversion between the pairs **7** and **8** is slow in NMR time scale because it requires C-C bond rotation.

Figure 3. *Keto-enol tautomerism of 3-acyl tetramic acid.*



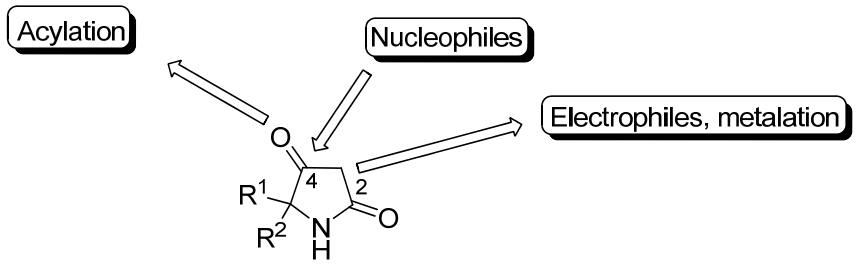
For simple 3-acyltetramic acids, Steyn[16] *et al.* found the *exo*-enol **8a** to be the prevailing tautomer in solution and in the crystalline state. For instance, the 3-acetyl-

5-isopropyltetramic acid **9** ($R^2 = CH_3$, $R^3 = {}^{i}Pr$) was shown by ^{13}C NMR spectroscopy to be a mixture of tautomers of ratio **7a**/**7b**/**8a**/**8b** = 5:15:80:0. However, certain substituents R^3 or residues other than hydrogen at the N-atom (R^1)[17] and solvent[18] may change the ratio of tautomers considerably. For instance, *N*-acylated 3-acyltetramic acids prefer the **7a** tautomer.[19]

Reaction of tetramic acids

Tetramic acid consists of a highly labile, cyclic β-ketoamide. The C3 carbon of *N*-protected tetramic acid is most active in presence of base and its nucleophilic character allows attaching various electrophilic species such as aldehydes, bromine or nitrating agents. It is also possible to add nucleophilic species (eg. hydrazine) at C2 and C4. The keto-enol tautomerism can be trapped in enolic form by acylation or alkylation on C4 oxygen atom. Acylation is also possible at C3 under certain conditions.[20]

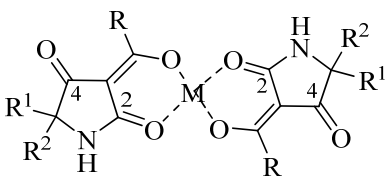
Figure 4.



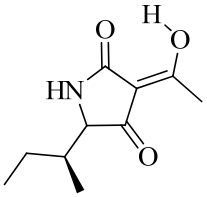
10

3-Acyl tetramic acid moiety is intrinsically a bidented ligand and can complex with alkaline earth and transition metals efficiently. Chelation occurs through the binding of the enolic oxygen of the C3-acyl group and the C4-oxygen atom.

Figure 5.



11



Tenuazoic acid **TA-H**

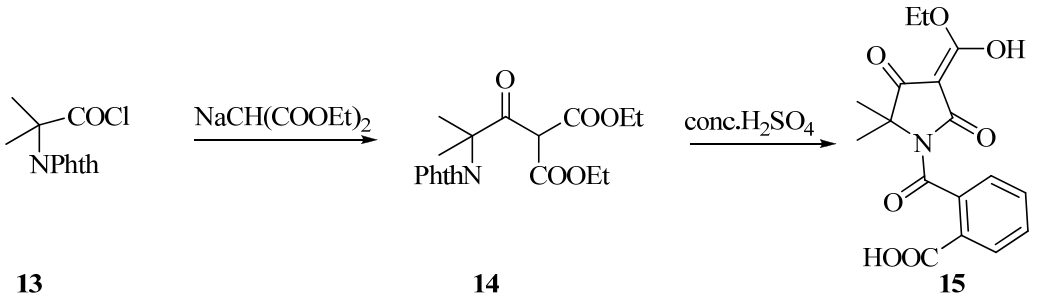
12

Metal chelation seems to be crucial for the stability of some natural tetramic acids as well as for their transport in biological tissues and across membranes. In some cases the bioactivity of tetramic and tetronic acids was shown to be dependent on metal chelation. For instance, tenuazonic acid (TA-H; **12**) was isolated as a mixture of calcium and magnesium complexes, $Ca(TA)_2$ and $Mg(TA)_2$, from *Phoma sorghina*, a fungus implicated in the aetiology of onyalai, a haematologic disorder affecting Black African populations south of the Sahara.[21] Other[22] complexes were isolated, for example, $Cu(TA)_2$, $Ni(TA)_2$ and $Fe(TA)_3$. The complex $Cu(TA)_2 \cdot H_2O$ was shown by *X*-ray single crystal structure analysis to contain the tenuazonate coordinating *via* 2-*O* and the 3-acyl oxygen atoms.[23] Binding constants for the complex $Fe(TA)_3$ and analogues thereof lie in the range of 10^{-29}.

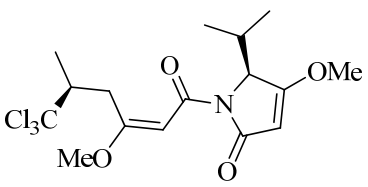
Synthetic methods of tetramic acid and it's 3-acyl derivative.

Reaction of phthalimidoisobutyryl chloride **(13)** with diethyl sodiomalonate gave **14**, which on treatment with concentrated sulfuric acid cyclized to the 3-ethoxycarbonyl tetramic acid **15** (Scheme **1)**.[24] This method is applicable only for the synthesis of racemic tetramic acids. Total synthesis of dysidin (**16**) is one of the most successful applications of similar method in the synthesis of tetramic acid natural products.

Scheme 1: *Gabriel's synthesis of tetramic acid.*



13 **14** **15**

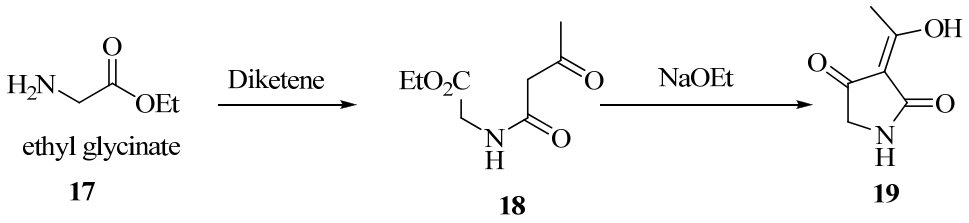


Dysidin **16**

3-Acyltetramic Acids *via* Lacey's Modified Dieckmann Cyclization

In 1954, Lacey[25] has reported a convenient two-step synthesis of 3-acyltetramic acids from readily available α-amino esters. This strategy has since became widely adopted in the construction of the tetramic acid ring and is certainly the most common method employed in the synthesis of mentioned motif. The original method involved condensation of a α-amino ester **17** with diketene to give the *N*-acetoacetyl-α-amino ester **18,** which cyclized to the 3-acyltetramic acid **19** upon exposure to sodium ethoxide

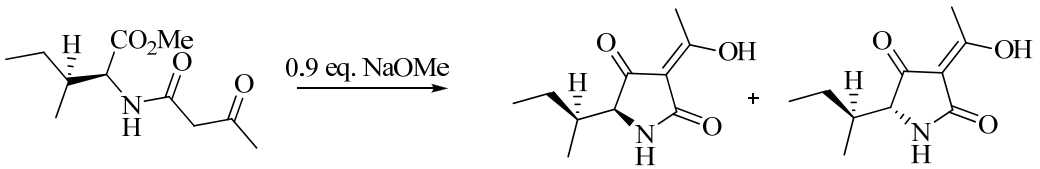
Scheme 2.



The two step strategy for the synthesis of 3-acyl tetramic acid is extremely flexible and it is possible to construct a wide range of substituent pattern by simply combining with suitable α-amino acid and diketene. The only limitation of this method is that it requires strong basic condition at the last step of the synthetic sequence. This condition may lead to the cleavage of the amide bond[26] and recemisation of the labile stereocenter at C5 position in the case of chiral 3-acyl tetramic acid synthesis. Tenuazonic acid **12** was prepared from ethyl L-isoleucinate **20** and diketene by several groups[27] with racemization of the stereogenic center at C-5. Evidences of recemisation revealed from the work of Kozikowski's group during total synthesis of α-cyclopiazonic acid. A careful study of the occurrence of racemization during Lacey-Dieckmann cyclizations revealed, first, that partial loss of stereochemical integrity was encountered under the controlled conditions used and, second, that the diastereomer ratio was dependent upon base concentration and reaction time.[28] Thus, Dieckman cyclisation of the β-keto amide **20** (Scheme 3) gave mixture of two diastereomers **21** and **22** when NaOMe was used as base at refluxing condition for 2 h. Higher base concentration and prolonged reaction time resulted complete recemization at the C5 center. The stereochemical output was according to

the stereochemistry of starting **20** and independent of the stereo-center at C6 position.[28] This was confirmed when same operation was performed on the diastereomer of **20**. In each case, the major epimer presented the same configuration as its precursor. This consistent finding implies that epimerization during the Dieckmann cyclization is not related to thermodynamic equilibrium between the two epimers **21** and **22**.

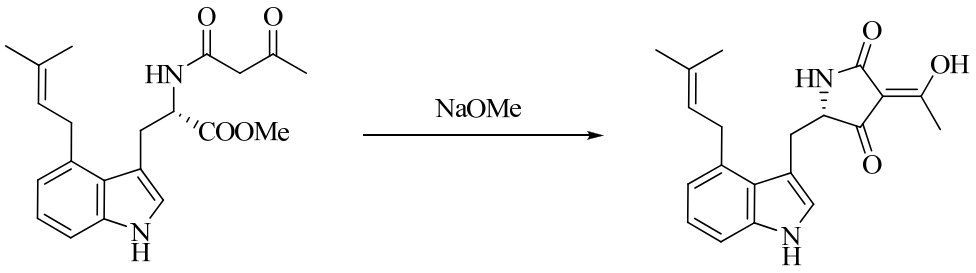
Scheme 3.



20 (5*S*, 6*S*) **21** 94.5 % (5*R*,6*R*) **22** 5.5 %

Despite the above criteria, an almost identical process has been used successfully to prepare β-cyclopiazonic[29] acid **24**, in optically pure form, through exposure of **23** to methoxide (3.6 equiv) in refluxing benzene for 10 h. The CD spectra of synthetic and natural material were identical thus demonstrating that stereochemical integrity was not lost during the base-induced ring closure. An enantioselective Lacey-Dieckmann cyclization was employed in the landmark syntheses of (+)-ikarugamycin (Boeckman,[30a] Paquette[30b]) and furthermore, the optical rotation of the synthetic material was either in excellent agreement or virtually identica1 to that of the natural samples. Several reports[31] in this concern are available in literature. Therefore recemization can be avoided by optimization of the reaction time and concentration of the base.

Scheme 4.



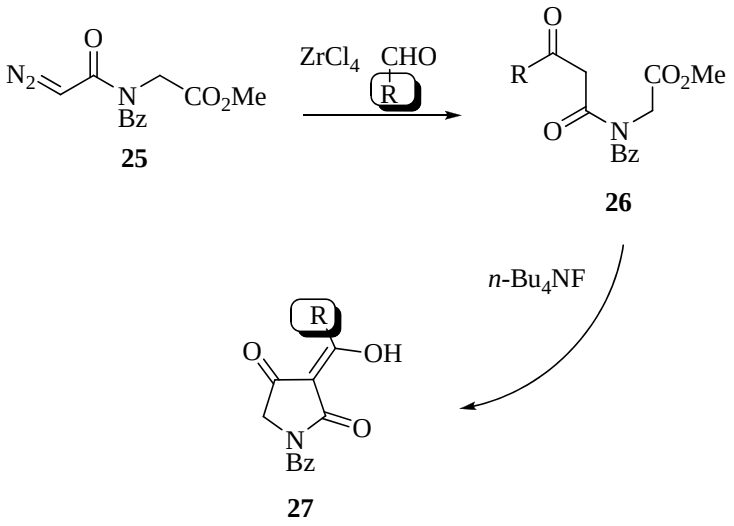
23 β-cyclopiazonic acid **24**

A number of methods recently available for the synthesis of β-ketoamide and with the combination of Dieckmann cyclization, these methods provided a significant

improvement in the synthesis of 3-acyl tetramic acid. Most useful methods are shortly described.

i) Zirconium (IV)-catalyzed [32]coupling of aldehydes and α-diazoacetamides **25** is one of the mildest methods in this regard. The products of the coupling reaction were readily cyclized to the 3-acyltetramic acids **27** by standard methods. Hence, using same precursor **25** and simply changing R group on aldehyde, an array of different tetramic acid synthesis became quite easy.

Scheme 5.



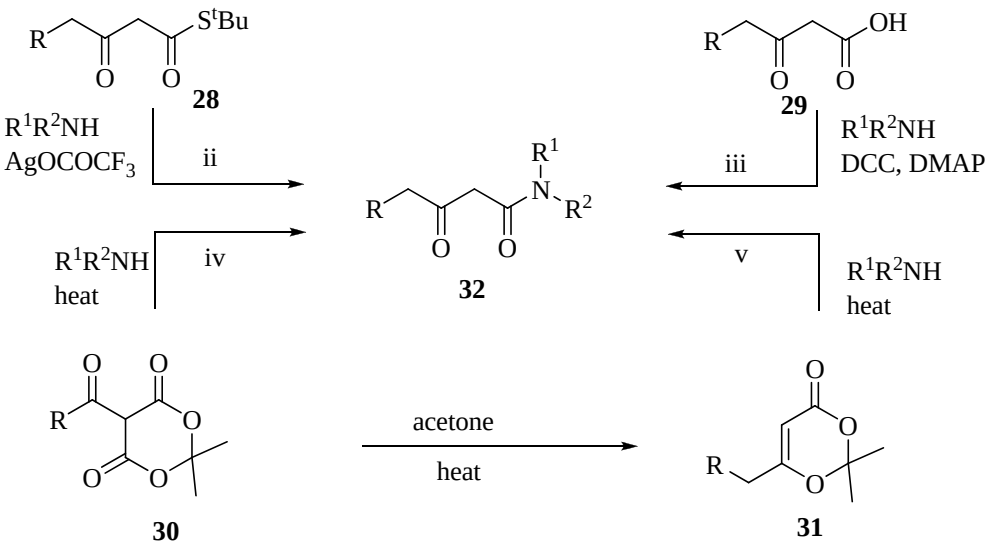
ii) Ley[33] has developed and explored the use of β- ketothioesters (Scheme 6) as the acylating agents. In this approach, the thioester is treated with silver (I) salt in presence of amine to yield β-ketoamide.

iii) Under careful conditions it is also possible to form amide bond from β-ketoacid under conventional mild condition. Decarboxylation is the prime concern in this method.[34]

iv) Acylation of Meldrum's acid derivatives followed by opening with suitable[35] base can offer acyl tetramic acid.

v) Most useful method is the coupling of dioxineone with amine. Under this condition, dioxineone is believed to proceed via a retro Diels-Alder reaction to produced acyl ketene which is trapped by amine.[36]

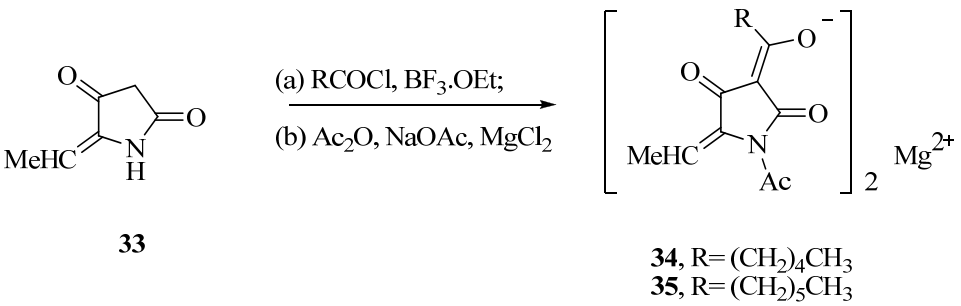
Scheme 6.



Acylation at C3 position of tetramic acid

The acylation of pyrrolidine-2,4-diones, bearing no substituent at the 3-position, was regarded as a promising alternative means of access to complex naturally occurring 3- acyl tetramic acids, first in view of the ease with which the simple heterocycle can be made (through Lacey-Dieckmann cyclization) and second, because of the appearance of an acyl substituent at C-3 in many of the natural systems. Kohl was the first to use this strategy, in the synthesis of magnesidins (**34** and **35**).[37] Acylation of 5-ethylidenepyrrolidine-2,4-dione (**33**) was achieved through reaction with the appropriate acid chloride in the presence of boron trifluoride-etherate (Scheme 7).

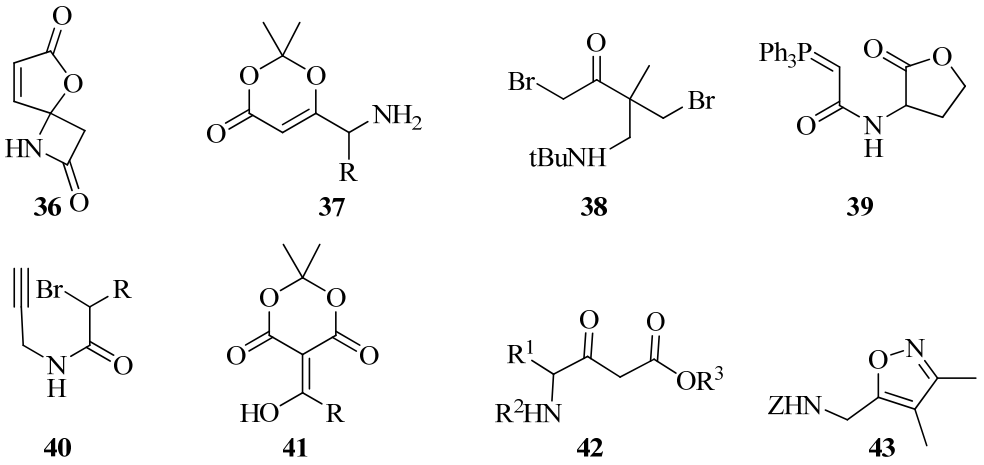
Scheme 7.



Common methods for the synthesis of tetramic acid

A number of other synthetic routes[38] to simple pyrrolidine-2,4-diones have been published over the years, namely: base-induced rearrangement of spiro β-lactams **36**, intramolecular thermal rearrangement of 6-(aminoalkyl)-1,3-diox-5-en-4-one1s **37**, fluoride ion-promoted cyclization of 4-bromobutanamides **38**, ring opening of Meldrum's acid derivatives **41** by aminoacetonitrile, intramolecular Wittig reaction of γ-acylphosphonium ylides **39**, radical cyclization of propargyl bromoamides **40**, cyclization of γ-amino-β-keto esters **42**, and the cyclization of isoxazole-4-carboxylates **43** followed by hydrogenolysis, but as none of these have received little or no attention from those working in the natural product area.

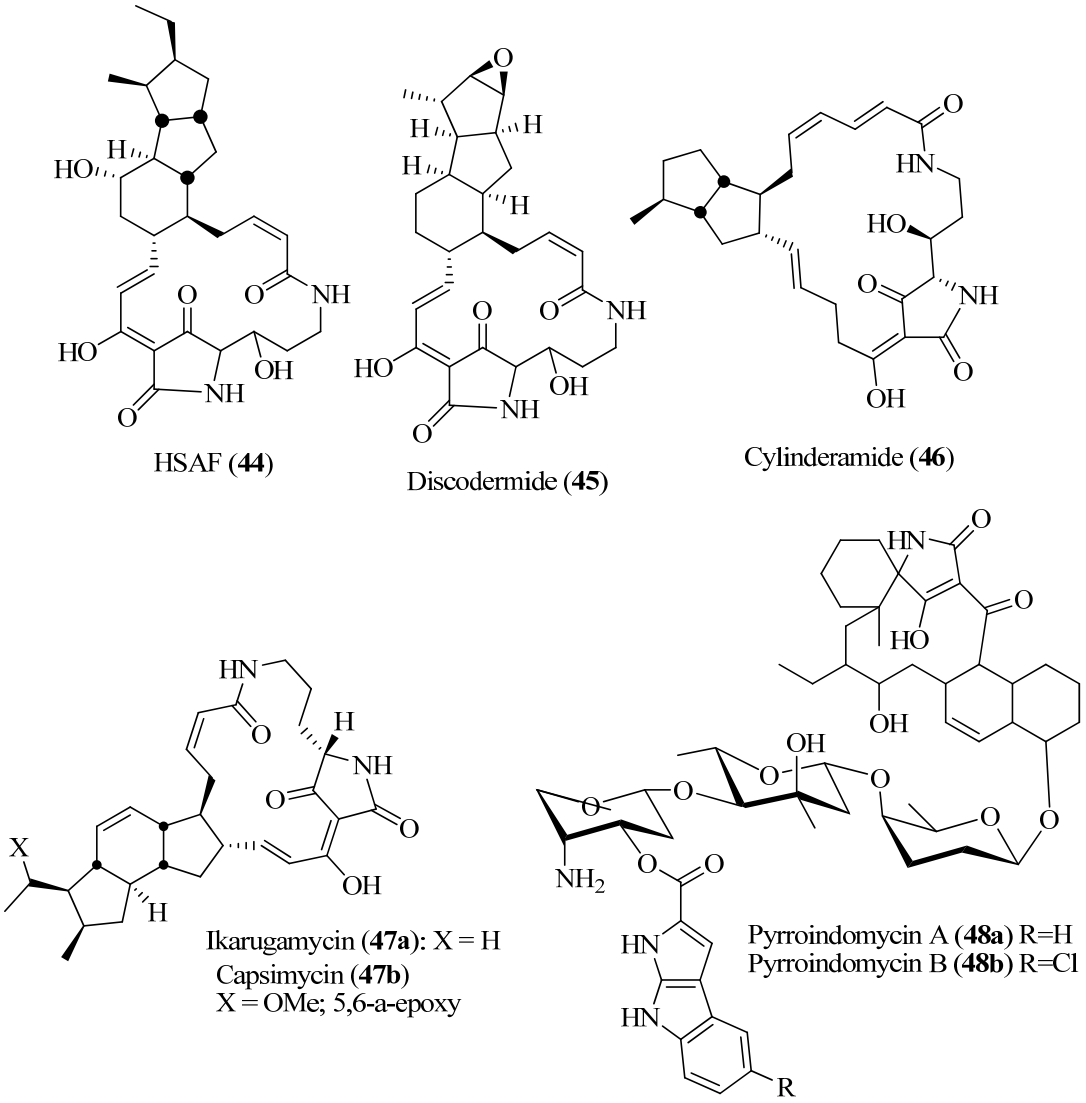
Figure 6.



Present work

Recent isolation of a huge number of macrocyclic compounds associated with acyl tetramic acid and complex structural architecture with wide range of biological activities have attracted a substantial amount of attention from synthetic chemist, and synthesis of many of them have been accomplished. Few of representative examples of macrocyclic acyl tetramic acids are depicted in figure 7. HSAF[39] (heat-stable antifungal factor; **44**), a secondary metabolite produced by the bacterium Lysobacter enzymogenes strain C3 when kept in nutritionally limited media such as 10% TSB, is highly active against a wide range of fungi by a novel and unique mode of action. Like HSAF, discodermide[40] **45** is antifungal, particularly against *Candida albicans,* and also cytotoxic. It was isolated from the Carribean deep-sea sponge *Discoderma dissoluta*. Ikarugamycin[41] **47a**, a metabolite of Streptomyces phaeochromogenes *var ikaruganensin*, is an antibiotic and antiprotozoal bearing a 5,5,6-tricyclic system on the macrolactam. The antifungal Streptomyces metabolite capsimycin[41] **47b** also features a similar structure. Cylindramide[42] (**46**) was originally isolated in 1993 by Fusetani *et al*. from the marine sponge *Halichondria Cylindrata Tanita* and *Hoshino*. It is structurally akin toaburatubolactams A and C and like these very likely of bacterial origin. It exhibited cytotoxicity against B16 melanoma cells with an IC50 of 0.8 lg/mL. Pyrroindomycins[43] A and B (**48a & 48b**) were isolated from *Streptomyces rugosporus* LL-42D005 by Ding *et al*. They are composed of an unusual pyrroloindole group linked to a deoxytrisaccharide and a tetramic acid containing moiety. Pyrroindomycins A and B exhibit good to excellent *in vitro* activity against Gram-positive bacteria such as methicillin-resistant Staphylococcus aureus strains but only poor activity against Gram-negative bacteria. Pyrroindomycin A (**48a**) is generally more active than the chlorinated derivative pyrroindomycin B (**48b**).

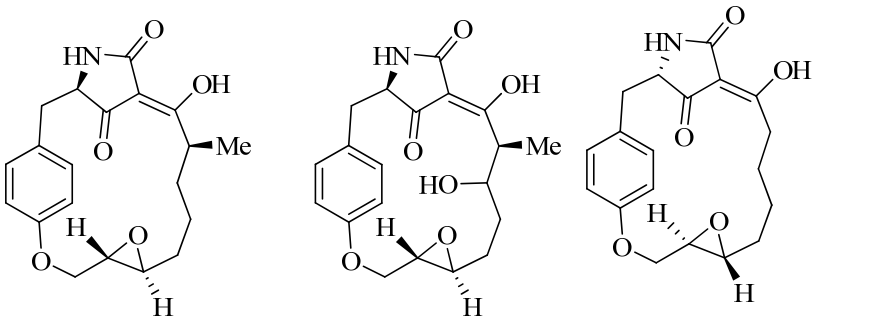
Figure 7.



Continuous effort of searching for new natural products from plant pathogenic microorganism in order to get new herbicides, led to the isolation of new macrocyclic tetramic acid macrocidin A along with it's congener macrocidin B in 2003 by Grupner *et al.* from the liquid cultures of *Phoma macrostoma* obtained from diseased Canada thistle growing in several geographically diverse regions. The novel, structurally unique macrocyclic skeleton and the relative configuration of **1** were determined by extensive 2D NMR and by a single crystal *X*-ray structure. However, the absolute configuration of both the compounds was remained unknown due to lack of sufficient sample. Macrocidins A (**1**) and B (**2**) are the first representatives of a new family of cyclic tetramic acids. Their significant biological activity in combination

with unique mode of actions, these new chemotypes may offer significant potential as a template for herbicide design. To continue our study on RCM in construction of macrocyclic molecular framework and the interesting biological profile coupled with structural parameters of macrocidins encouraged us to undertake its synthesis. For initial study, as absolute configuration was unknown, we have chosen *des*-methylmacrocidin A, the simplified form of macrocidin A without methyl center and having (*S*) configuration adjacent at nitrogen bearing carbon.

Figure 8.

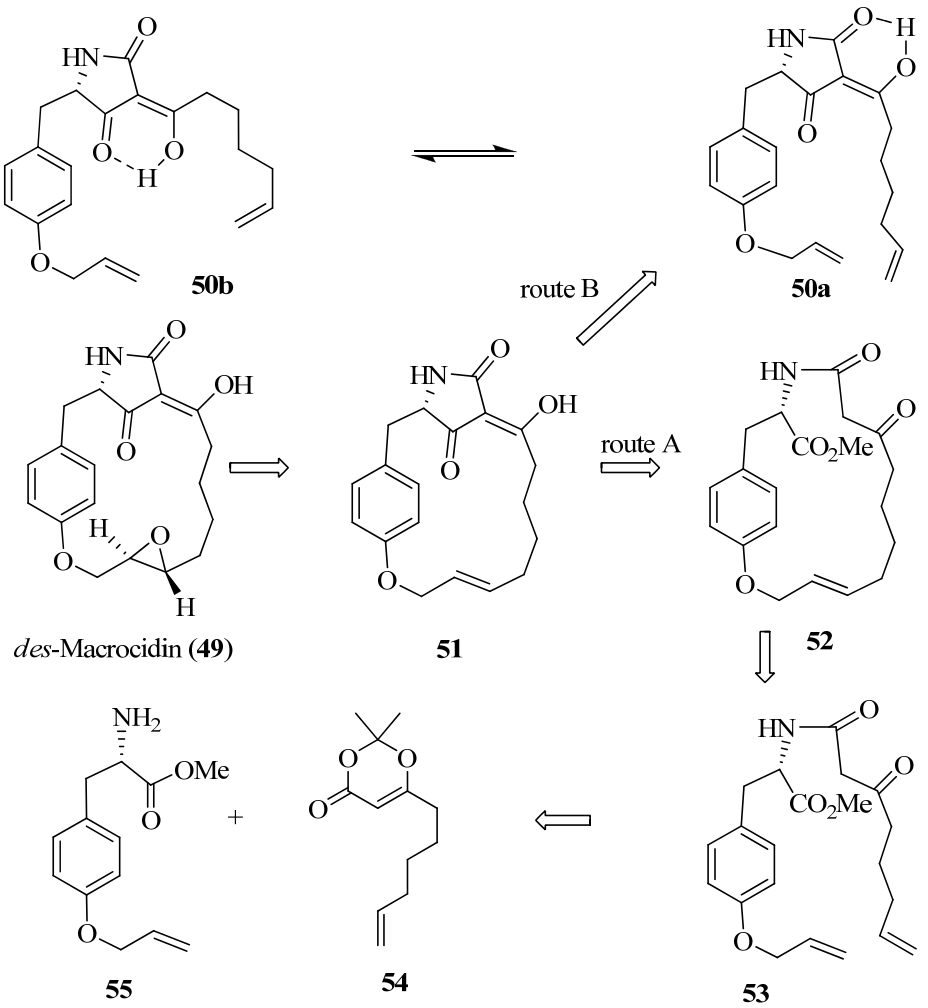


Macrocidin A (**1**) Macrocidin B (**2**) *des*-Methylmacrocidin (**49**)

Retrosynthetic analysis

The retrosynthetic analysis is represented by two strategies *viz* route-A and route-B, which differ in the order in which critical structural elements – the tetramic acid or the 18-membered macrocycle are formed. One issue in case of route-B would be the effect of the tautomeric structures **50a** and **50b**.[44] The tautomeric structure represented by **50b** could prevent the RCM reaction to take place. After macrocyclization, the epoxide present at C16-C17 of **49** could be installed easily at C16-C17 *E*-double bond. The disconnection of **53** through amide bond, we have identified the synthetic equivalents of the fragmented parts of compound **53** as the L-tyrosine derivative **58** and alkylated diketene acetone adduct **54**.

Figure 9.

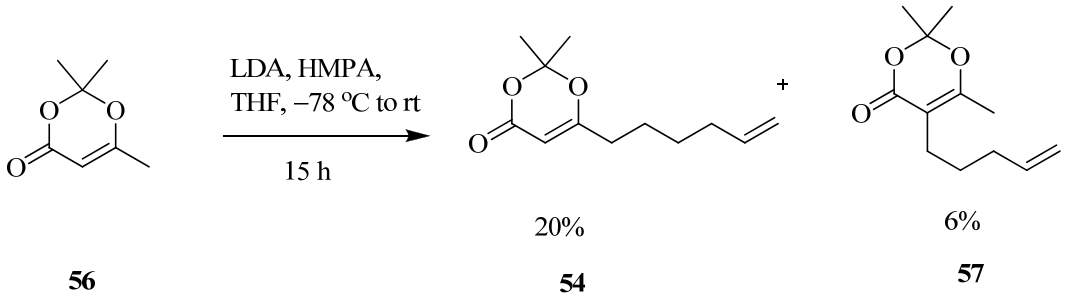


Synthesis of fragment 54 and 55

Compound **54** was made following reported procedure[45] by alkylation of diketene acetone adduct **56** at low temperature using pentenyl bromide and cryogenic solvent HMPA in combination with THF. Use of HMPA was found to be crucial as it was observed that absence of HMPA alkylation was unsuccessful. Very low conversion of starting was due to lower reactivity of pentenyl bromide. Both the isomers are column separable and characterized fully. In the ^{1}H NMR spectrum of compound **54**, the ring olefin proton resonated at δ 5.16 as singlet. Another singlet equivalent to six protons was observed at δ 1.63 due to the isopropylidene methyl groups. The lactone carbonyl carbon resonated at δ 171.5 ppm in ^{13}C NMR spectrum. Whereas in the isomeric compound **57** the ring olefin proton was absent and a singlet observed at δ 1.91 and attributed to the γ-methyl group. The structures of both the

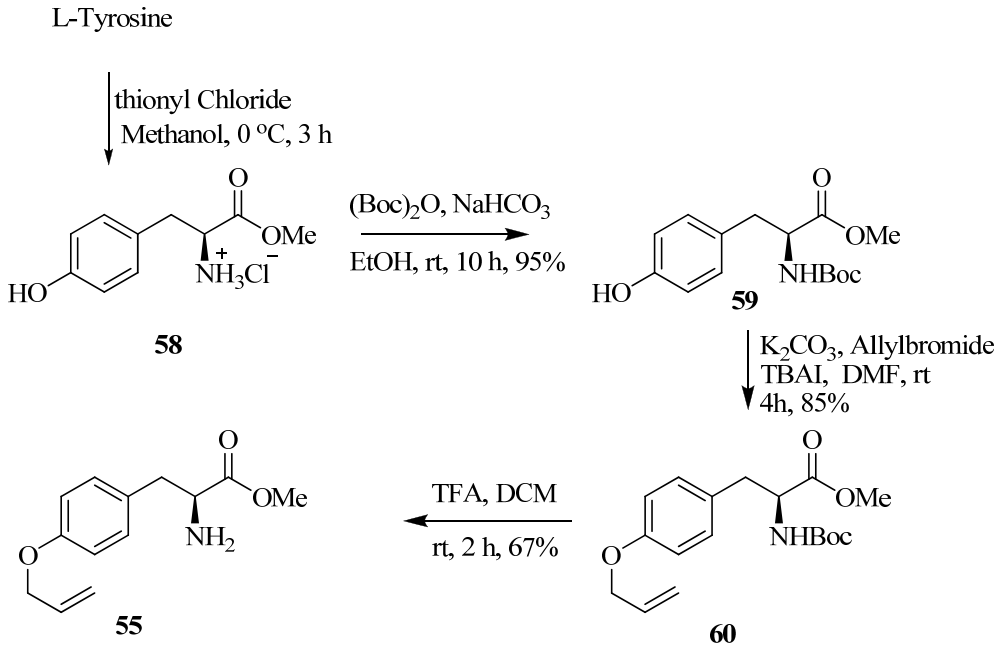
isomer were further confirmed by IR, mass and elemental analysis which were in excellent agreement with their assigned structures.

Scheme 8.



The synthesis of the fragment **55** was started from commercially available L-tyrosine. The carboxylic acid of tyrosine was masked as methyl ester under acidic condition[46] using thionyl chloride and methanol on ice bath and isolated as hydrochloride salt of methyl ester **58** quantitatively (Scheme 8). Remembering the target, we planed to make allyl aryl ether on the phenolic hydroxyl group and this was achieved after masking of amine as *tert*-butyl carbamate. The hydrochloride salt **58** was used directly for Boc protection using $(Boc)_2O$ in ethanol and $NaHCO_3$. The complex pattern in NMR spectra of carbamate protected aryl-allyl ether (**60**) clearly suggested the presence of rotational isomers due to the hindered amide bond and it was slow on NMR time scale. Finally, acid catalyzed deprotection of *tert*-butoxycarbamate afforded the fragment **55** as light yellow liquid. A strong peak (100% intensity) at *m/z* 236.10 in ESI mass spectrum indicated the presence of compound **55**. The terminal olefin CH_2 resonated at δ 5.23 (dq, J = 1.5, 10.5 Hz, 1H) and 5.38 (dq, J = 1.5, 17.3 Hz, 1H). Two separate doublet of a doublets at δ 2.79 (J = 7.6, 13.5 Hz), 3.00 (J = 5.2, 13.5 Hz) were assigned to the diastereomeric benzylic protons. A sharp singlet due to alkoxy methyl group appeared at δ 3.70. All peaks in ^{13}C were in accordance with the assigned structure of compound **55**. The stretching frequency of the ester carbonyl observed at 1737 cm^{-1}. Although we were aware of the pessimistic reactivity of the proton α to the ester group under strong basic condition, we explored the allylation using potassium carbonate in DMF at rt and on the basis of HPLC data we believed that there was no recemisation under that condition.

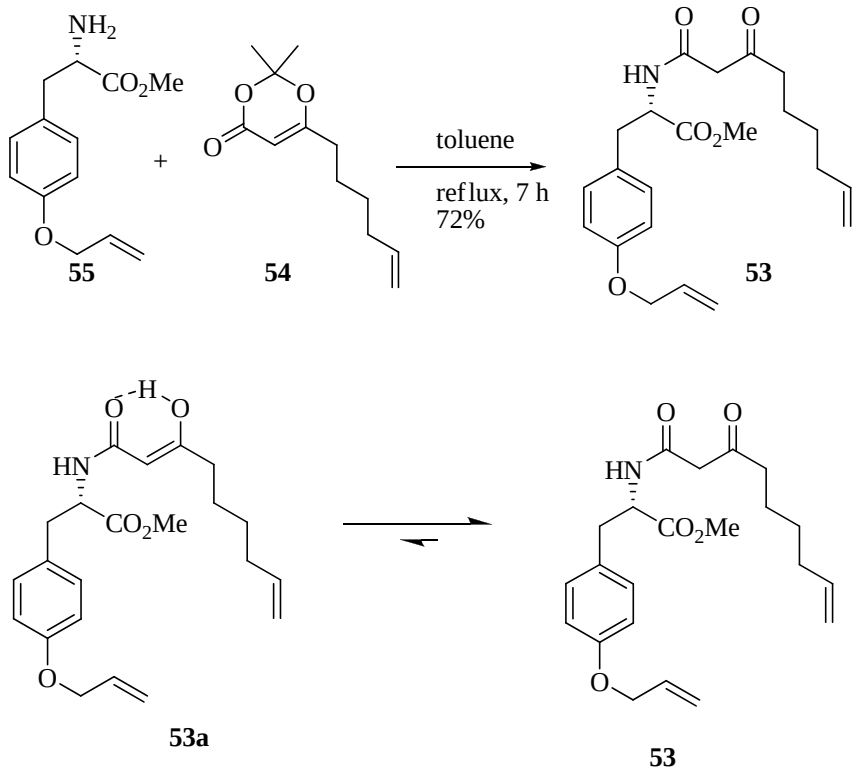
Scheme 9.



Coupling of fragments 54 and 55 and construction of the tetramic acid core

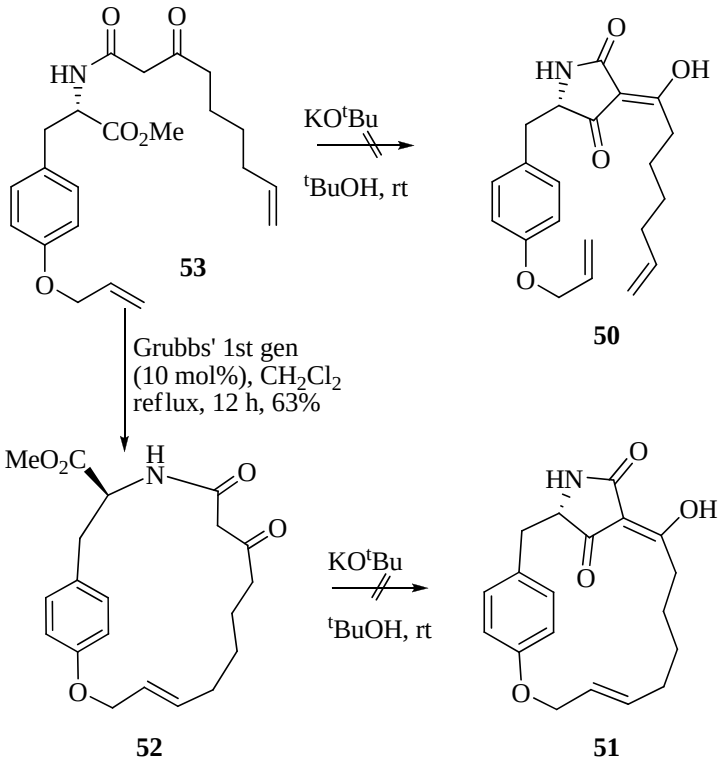
After the successful completion of synthesis of both the key intermediates **55**, and **54**, our next attention was focused on coupling of them. Considering the reactivity towards nucleophiles of the dioxin 4-one moiety present in compound **54** and the nucleophilic property of amine **55**, the coupling was attempted without any additive and by simply heating the mixture of **54** and **55** in toluene, a smooth conversion was observed and resulted in the β-keto amide **53** with very good isolated yield[47] (Scheme 10). Presence of an intense (100%) peak in ESI MS at *m/z* 388.18 and the result of elemental analysis indicated formation of compound **53**. Being associated with the labile β-keto amide functionality of compound **53**, one can expect a dynamic equilibrium between keto-enol **53** and enol form[48] **53a**, but ^{1}H NMR of **53** indicated the presence of only keto-form in solution state. The active methylene protons resonated at δ 3.33 as singlet. Existence of compound **53** in exclusive keto isomer further supported from ^{13}C NMR; the carbonyl carbon appeared at δ 205.5, ester carbonyl at δ 171.6 and the amide carbonyl at δ 165.1. Other peaks in both ^{13}C and ^{1}H NMR were according to the structure of **53**.

Scheme 10.



The next step was to furnish the tetramic acid moiety following Lacey-Dieckmann cyclisation[25] methods. All attempts to get tetramic acid under various conditions met with failure results. Under experimentally demanding conditions compound **53** undergoes decomposition. Since route B was not effective to furnish **50** we shifted our attention to path A (figure 9). Accordingly, the intermediate **53** was treated with Grubb's 1st gen. catalyst under refluxing condition in DCM and a smooth conversion to 18-membered lactum **52** occurred which was isolated as white solid. Compound obtained in this step was a single diastereomer, confirmed by ^{1}H and ^{13}C-NMR spectra. Because of structural rigidity in **52** the active methylene protons have appeared separately with high geminal coupling (14.4 Hz). In ^{1}H NMR the ester methyl protons appeared at δ 3.80 as singlet. Large coupling constant (16.6 Hz) observed between the olefin protons suggested the *trans* geometry of the newly formed double bond. Finally to reach the critical structural element tetramic acid of (**51**), next task was base induced Dieckmann cyclisation. Unfortunately, in this step same observation was found as in the case of transformation from **53** to **50**.

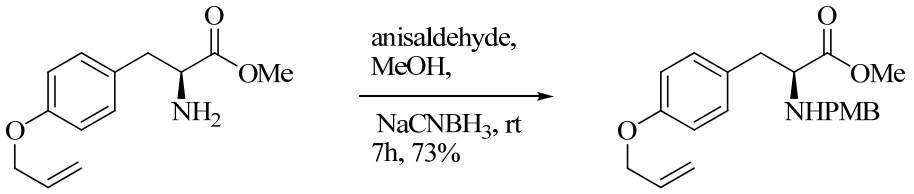
Scheme 11.



These obstacles were due to hydrolysis of the amide bond[26] under strong basic condition which is one of the major draw back of Dieckmann cyclization in the synthesis of 3-acyl tetramic acids. Literature, survey revealed that in some of the cases, the problem of amide hydrolysis has been bypassed simply by protection of amide nitrogen with suitable alkyl group which could be removed at the last stage of synthesis. Among the several protecting groups used for these purpose, 2,4-methoxy benzyl and 4-methoxy benzyl group have been found significant importance as they could be removed easily under acidic conditions without any interference of tetramer acid moiety. Being a simple, easy access and handling *p*-methoxy benzyl group was a choice of protecting group in our strategy. Accordingly, the secondary amine **55a** was prepared under reductive amination condition using anisaldehyde and sodium cyanoborohydride with good isolated yield. The, reducing agent sodium cyanoborohydride is a typical reagent for reductive amination as it is selective to the imine reduction and force the equilibrium of aldehyde-imine towards right. Other reagents like sodium borohydride increase the percentage of aldehyde reduced profile in reaction mixture. Compound **55a** was fully characterized. In ^{1}H NMR spectrum of

compound **55a**, two separate doublets at δ 3.56 with high geminal coupling (13.5 Hz) confirmed the presence of PMB group. The stretching frequency of ester carbonyl observed at 1733 cm^{-1}. All signals in ^{13}C NMR also confirmed the assigned structure of **55a**. An intense peak detected in ESI mass at *m/z* 336.18 due to the protonated molecular ion provided further proof in favour of structure **55a**.

Scheme 12.

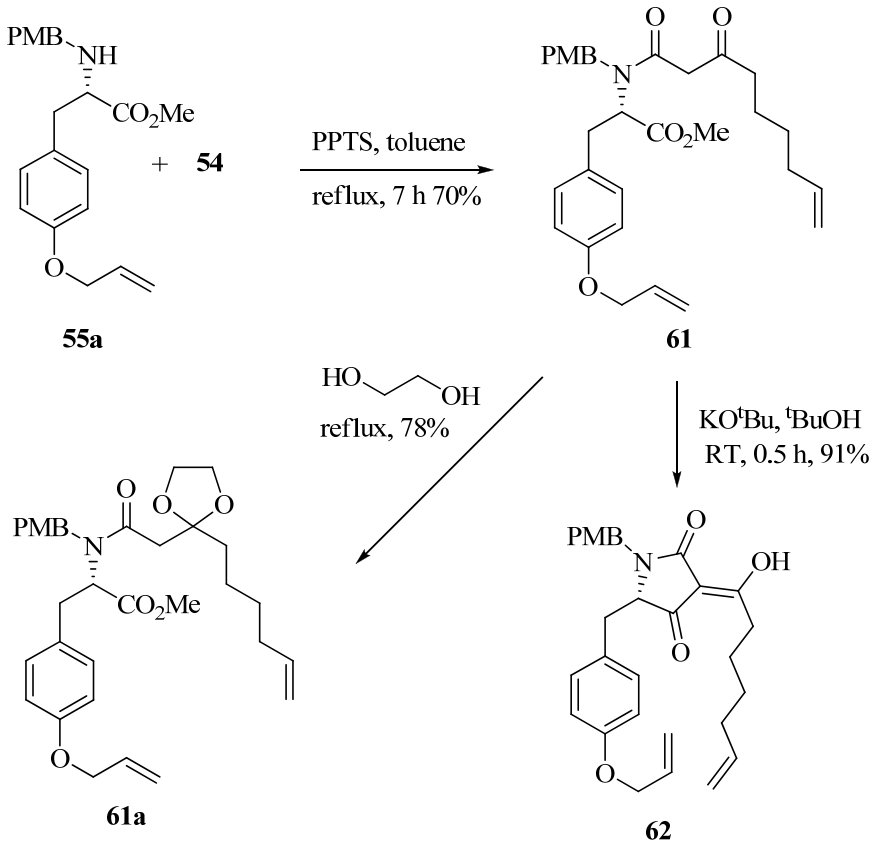


55 **55a**

After having the protected amine **55a**, the next attempt was to couple it with dioxineone derivative **54**. Coupling of **54** and **55a** furnished the protected β-keto **61** amide as yellow liquid. In this case, the coupling reaction was sluggish and could be improved by employing PPTS as acid catalyst. Prior to discussion on the proposed strategy, it is pertinent to mention some issues observed in NMR spectra of compound **61**. The mass spectra and elemental analysis indicated the formation of compound **61**. The NMR spectra were very complex. Careful analysis of ^{1}H and ^{13}C NMR indicated that equilibrium existed between the keto and enol forms of **61**. Therefore, the compound **61** was characterized after trapping of the enolisable keto group by ethelene glycol and this was achieved by azeotropic removal of water from the mixture of compound **61** and excess ethylene glycol in presence of *p*-TSA in toluene with 78% isolated yield. In ^{1}H NMR the active methylene flanked between the imide keto and carbonyl of **61a** resonated at δ 2.89 as singlet. Presence of a multiplet ranging from δ 4.89-5.46 integrating for 4 protons was assigned for the terminal double bonds. The carbonyl bearing carbon, after masking resonated at δ 110.38 in ^{13}C NMR spectrum, indicating the presence of ketal. Two sharp singlets at δ 3.61 and 3.78 were due to the ester methyl group and methoxy ether of PMB. Other spectroscopic data were in accordance with the assigned structure. The Lacey-Dieckmann cyclisation of the corresponding *N*-PMB derivative **61** (scheme 13) in the presence of $KO^{t}Bu$ successfully afforded the tetramic acid derivative **62**. The cyclisation was also performed with other base such as NaOMe and TBAF and almost

identical optical rotation was observed. These consistent results of optical rotation indicated the absence of partial recemization of the stereocentre under the basic condition used for the transformation. The compound **62** was characterized fully with the help of spectroscopic as well as analytical data. Presence of signal at *m/z* 476.2 $[M+H]^+$ 498.20 $[M+Na]^+$ and 514.19$[M+K]^+$ in ESI mass spectra indicated the formation of compound. In the ^1H NMR spectrum, signals due to the methyl ester were absent thus supporting the assigned structure of **62**. Interestingly, due to the ring formation the diastereotropic proton of PMB attached to the nitrogen appeared separately with substantial chemical shift difference [3.85 (d, *J* =14.7 Hz) 5.18 (d, *J* =14.7 Hz)]. The ring carbon of *exo*-cyclic double bond of teramic acid moiety appeared at δ 101.38 in ^{13}C NMR and this is typical characteristic of 3-acyl teramic acid moiety. Moreover, the quaternary nature (disappeared in DEPT Expt.) of this signal proved that the tetramic acid **62** was present as its enol exclusively. Other peaks appeared in both ^1H and ^{13}C NMR were according to the assigned structure.

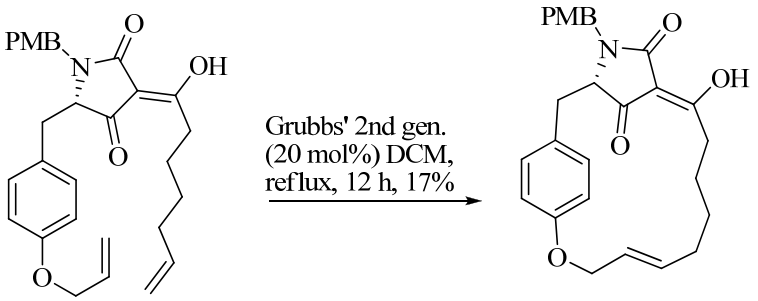
Scheme 13.



Successful synthesis of the intermediate **61** and **62** set a ground for examining the feasibility of RCM of them. It has been observed that the critical RCM reaction of

62 with 1st and 2nd generation Grubbs' catalysts under various reaction conditions was unsatisfactory and only traces of macrocyclic derivative **63** was isolated. This suggested that in tautomeric structures **50b** was favoured.

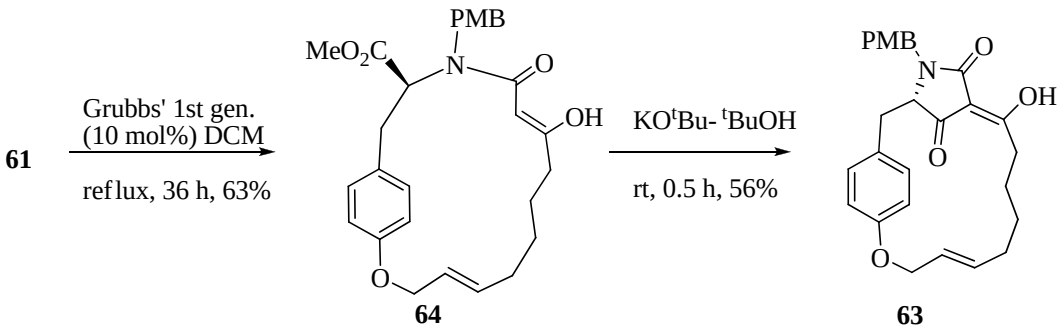
Scheme 14.



62 **63**

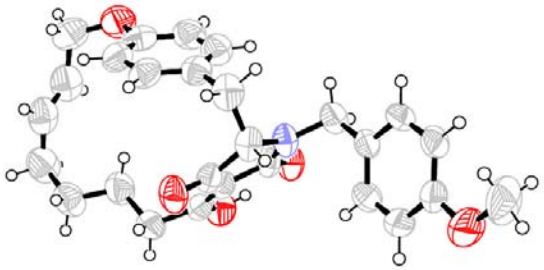
On the other hand, the RCM reaction of the ketoamide **61** with the 1st generation Grubbs' catalyst was fruitful and produced the 18-membered cyclic lactam derivative **64** in 63% yield. ESI mass spectra of **64** carrying a moderate intense signal at *m/z* 580.3 was a proof in favour of compound **64**. Due to the keto-enol tautomerism, the NMR spectra of **64** were very complex and it was further characterized fully after the next step. The Lacey-Dieckmann cyclization of **64** using KO^{t}Bu in *t*-butanol gave the core structure **63**. The spectral and analytical data of **63** were in accordance with the assigned structure. The large coupling (J = 15.6 Hz) in the ^{1}H NMR of spectrum of **63** (which exists as an equilibrating 1:3 keto-enol mixture from NMR in solution state) indicated the required *E*-configuration of the cyclic olefin. A single crystal *X*-ray structural analysis of **63** confirmed the structure (Figure 10).

Scheme 15.



64 **63**

Figure 10 : *ORTEP* structure of **63.**



Epoxidation of 63

The final endeavour to install the epoxide on the C16-C17 olefin, which looked to be straight forward, turned out difficult. Many reagents described in table 1 were utilized but the substrate **63** was unstable to these reagents and gave intractable mixtures of compounds from which no pure product could be isolated in appreciable yield.

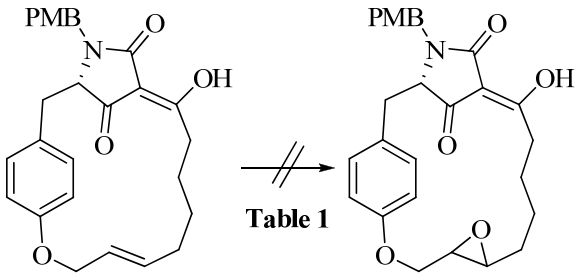


Table 1. *Attempted conditions for the epoxidation of* **63**

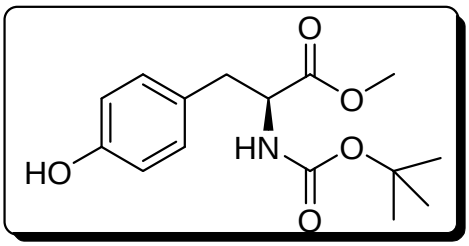
entry	Reagents and Conditions	Inference
1	*m*-CPBA, CH_2Cl_2, –78 °C	No reaction
2	MCPBA, CH_2Cl_2, rt	Decomposition
3	Oxone®, acetone, EtOAc, rt	Decomposition
4	H_2O_2, $NaHCO_3$, THF-water	Decomposition
5	H_2O_2, $NaHCO_3$, $CHCl_3$-water	Decomposition

6	H_2O_2, $NaHCO_3$, PhCN-methanol	Decomposition
7	Diisopropyl Tartarate, $Ti(O^iPr)_4$, THF, –78 °C, ^tBuOOH	Decomposition
8	$PhCO_2Ag$, I_2, Ph, reflux	No reaction

In conclusion, we have designed and executed a simple strategy for a quick access to the central core of macrocidins using Ring Closing Metathesis as a skeletal building transform and Lacey-Dieckmann cyclization as key tetramic acid construct. However, one of the projected reactions, i.e. epoxidation was found to be unsuccessful due to the susceptibility of this compound to a variety of oxidants employed. This warrants a rigorous retrosynthetic disconnection and identification of critical surrogates for the epoxidation prior to the macrocyclic construction. Work in this direction is progressing in our group.

Experimental

***tert*-Butyl (*S*)-1-(methoxycarbonyl)-2-(4-hydroxyphenyl)ethylcarbamate (59)**



To a suspension of **58** (4.16 g, 17.9 mmol) in 50 mL dry ethanol was added solid sodiumbicarbonate (4.90 g, 58.3 mmol) and the mixture was stirred for 30 min at rt. While adding bicarbonate effervescences were observed. Then Boc anhydride (4.11 g, 19.0 mmol) was added to the mixture and the mixture was stirred for 10 h. Then ethanol was removed under reduced pressure resulting thick slurry. The mixture was diluted with 50 mL water and extracted with ethyl acetate. Organic extract was collected, dried and concentrated under reduced pressure. Column chromatographic purification of the crude product afforded **59** (5.14 g, 97 %) as white solid.

Mol. Formula : $C_{15}H_{21}NO_5$

$[\alpha]_D^{25}$: +47.0 (*c* = 0.98, $CHCl_3$)

M. P. : 98-100 ^oC.

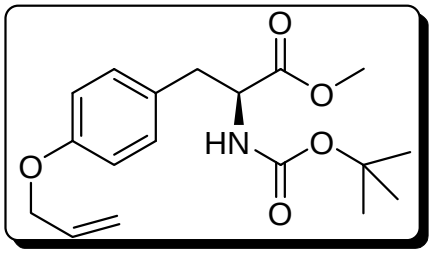
^{1}H NMR (200 MHz, $CDCl_3$) : δ 1.41 (s, 9H), 2.88-3.07 (m, 2H), 3.70 (s, 3H), 4.51 (dt, *J* = 8.0, 6.0 Hz, 1H), 4.99 (bd, *J* = 8.0 Hz, 1H), 5.87 (bs, 1H), 6.70 (d, *J* = 8.2 Hz, 2H), 6.94 (d, *J* = 8.2 Hz, 2H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$) : δ 28.2 (q), 37.4 (t), 52.2 (d), 54.6 (q), 80.3 (s), 115.5 (d), 126.9 (s), 130.2 (d), 155.4 (s), 155.4 (s), 172.7 (s) ppm.

ESI-MS (*m/z*) : 296.1 $[M+H]^+$

Elemental Analysis Calcd.: C, 61.00; H, 7.17; N, 4.74 %
Found: 60.85; H, 7.06; N, 4.73 %

***tert*-Butyl (*S*)-1-(Methoxycarbonyl)-2-(4-(allyloxy)phenyl)ethylcarbamate (60)**



To a solution of compound **59** (5.04 g, 17.0 mmol) in dry DMF (30 mL) K_2CO_3 (4.94 g, 35.7mmol), allyl bromide (2.3mL, 26.8 mmol) and TBAI (100 mg) were added under nitrogen atmosphere at rt. The mixture was stirred for 4 h at same temperature. Then 70 mL water was added and the mixture was extracted with ethyl acetate. The organic extract was washed with water, dried and concentrated under reduced pressure. Column purification of the crude mixture gave compound **60** (4.93 g, 85 %) as thick liquid.

Mol. Formula : $C_{18}H_{24}O_5$

$[\alpha]_D^{25}$: +50.4 (*c* = 0.76, $CHCl_3$)

IR ($CHCl_3$) υ : 1021, 1054, 1105, 1256, 1275, 1368, 1393, 1439, 1511, 1584, 1611, 1717, 1757 cm^{-1}.

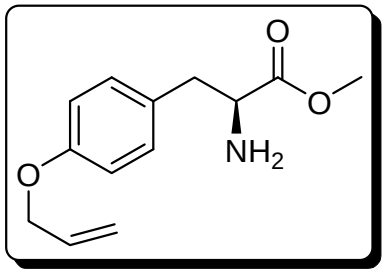
^{1}H NMR (200 MHz, $CDCl_3$) : δ 1.42 (s, 9H), 2.89-3.09 (m, 2H), 3.70 (s, 3H), 4.51 (dt, *J* = 1.4, 5.3 Hz, 2H), 4.96 (d, *J* = 7.7 Hz, 1H), 5.27 (dq, *J* = 1.4, 10.5 Hz, 1H), 5.40 (dq, *J* = 1.5, 17.2 Hz, 1H), 6.04 (ddt, *J* = 5.2, 10.5, 17.2 Hz, 1H), 6.83 (d, *J* = 8.6 Hz, 2H), 7.02 (d, *J* = 8.6 Hz, 2H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$) : δ 27.7 (q), 37.4 (t), 52.0 (q), 54.4 (d), 68.6 (t), 79.7 (s), 114.7 (d), 117.5 (t), 128.0 (s), 130.2 (d), 133.2 (d), 154.9 (s), 157.6 (s), 172.3 (s) ppm.

ESI-MS (*m/z*) : 336.1 $[M+H]^+$.

Elemental Analysis Calcd.: C, 64.46; H, 7.51; N, 4.18 %
Found: 64.31; H, 7.52; N, 4.10 %

(*S*)-Methyl 3-(4-(Allyloxy)phenyl)-2-aminopropanoate (55)



To a solution of compound **60** (4.93g, 14.7 mmol) in DCM (50) TFA (5 mL) was added slowly at 0 ^{o}C, and the whole mixture was stirred at ambient temperature for 2 h. Progress of reaction was monitored by TLC. After complete conversion the volatiles were removed under reduced pressure. The mixture thus obtained was basified with aqueous bicarbonate, extracted with chloroform and finally concentrated after drying on sodium sulfate to get compound **55** (3.25 g, 94%). The material was sufficiently pure for next reaction.

Mol. Formula : $C_{13}H_{17}NO_3$

$[\alpha]_D^{25}$: +4.3 (*c* = 1.2, $CHCl_3$)

IR ($CHCl_3$) υ : 824, 928, 1022, 1115, 1177, 1242, 1364, 1438, 1511, 1582, 1610, 1647, 1737, 3380 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$) : δ 1.52 (bs, 2H), 2.79 (dd, *J* = 7.6, 13.5 Hz, 1H), 3.00 (dd, *J* = 5.2, 13.5 Hz, 1H), 3.66 (dd, *J* = 5.3, 7.6 Hz, 1H), 3.70 (s, 3H), 4.49 (dt, *J* = 5.2, 1.5 Hz, 1H), 5.23 (dq, *J* = 1.5, 10.5 Hz, 1H), 5.38 (dq, *J* = 1.5, 17.3 Hz, 1H), 6.03 (ddt, *J* = 5.2, 10.5, 17.3 Hz, 1H), 6.82 (d, *J* = 8.4 Hz, 2H), 7.06 (d, *J* = 8.4 Hz, 2H) ppm.

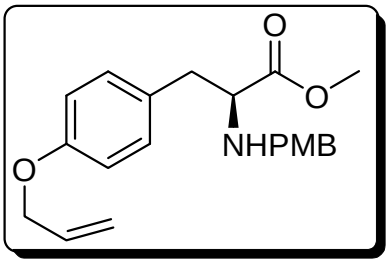
^{13}C NMR (50 MHz, $CDCl_3$) : δ 39.6 (t), 51.3 (d), 55.4 (q), 68.1 (t), 114.2 (d), 116.9 (t), 128.8 (s), 129.7 (d), 132.9 (d), 157.0 (s), 174.8 (s) ppm.

ESI-MS (*m/z*) : 236.1 $[M+H]^+$, 258.1 $[M+Na]^+$.

Elemental Analysis Calcd.: C, 66.36; H, 7.28; N, 5.95 %

Found: C, 66.31; H, 7.28; N, 5.94 %

(*S*)-Methyl 2-(4-methoxybenzylamino)-3-(4-(allyloxy)phenyl)propanoate (55a)



To a mixture of 4-methoxy benzaldehyde (1.2 mL, 9.8 mmol) and compound **55** (2.3 g, 9.8 mmol) in dry methanol (20 mL) two drops of acetic acid was added and stirred under nitrogen atmosphere at ambient temperature for 1 h. Then to this mixture sodium cyanobrohydride (1.54 g, 24.4 mmol) was added portionwise (three times with 10 min interval) at room temperature. After starring at rt for 7 h methanol was removed under reduced pressure and diluted with ethyl acetate. The mixture was then washed with aqueous bicarbonate and organic extract was collected and dried. Removal of volatile and flash column chromatographic purification gave pure secondary amine **55a** (2.536 g, 74%), as highly viscous liquid.

Mol. Formula : $C_{21}H_{25}NO_4$

$[\alpha]_D^{25}$: +2.9 (*c* = 1.3, $CHCl_3$)

IR ($CHCl_3$) υ : 740, 824, 1034, 1110, 1174, 1245, 1300, 1462, 1512, 1584, 1611, 1733, 3342 cm^{-1}.

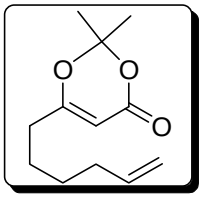
^{1}H NMR (200 MHz, $CDCl_3$) : δ 2.89 (d, *J* = 6.8 Hz, 2H), 3.48 (t, *J* = 6.8 Hz, 1H), 3.56 (d, *J* = 13.3 Hz, 1H), 6.63 (s, 3H), 3.67 (d, *J* = 13.3 Hz, 1H), 3.78 (s, 3H), 4.45 (dt, *J* = 1.5, 5.3 Hz, 2H), 5.27 (dq, *J* = 1.5, 10.5 Hz, 1H), 5.40 (dq, *J* = 1.5, 17.3 Hz, 1H), 6.05 (ddt, *J* = 5.3, 10.5, 17.3 Hz, 1H), 6.81 (d, *J* = 8.5Hz, 2H), 6.82 (d, *J* = 8.5 Hz, 2H), 7.05 (d, *J* = 8.5Hz, 2H), 7.14 (d, *J* = 8.5 Hz, 2H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$) : δ 38.5 (t), 51.1 (t), 51.1 (q), 54.7 (q), 61.7 (d), 68.3 (t), 113.4 (d), 114.2 (d), 117.0 (t), 129.0 (d), 129.1 (s), 129.8 (d), 131.3 (s), 133.1 (d), 157.1 (s), 158.4 (s), 174.6 (s) ppm.

ESI-MS (*m/z*) : 336.2 $[M+H]^+$, 378.12 $[M+Na]^+$.

Elemental Analysis Calcd.: C, 70.96; H, 7.09; N, 3.94 %
Found: C, 70.68; H, 7.10; N, 3.81 %

6-(Hex-5-enyl)-2,2-dimethyl-4H-1,3-dioxin-4-one (54)



To a mixture of isopropyl amine (2.5 mL, 17.2 mmol) HMPA (5 mL) in THF *n*-BuLi (9.3 mL, 1.6 M) was added at −78 ^{o}C and stirring was continued at same temperature for 30 min. After completion of LDA formation, a solution of 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one (**56**) (1.52 g, 10.7 mmol) in THF was introduced followed by pentenyl bromide (2 mL, 16.8 mmol). After stirring at −78 ^{o}C for 1h and at rt for 15 h the mixture was quenched with aqueous ammonium chloride solution. The mixture was then extracted with ethyl acetate. The organic extract was washed thoroughly with water, dried and concentrated under reduced pressure. Column chromatographic purification of the crude mixture afforded **54** (0.472 g, 21%) and **57** (0.134 g, 6%) as light yellow liquids.

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

IR ($CHCl_3$) υ : 666, 756, 810, 905, 1014, 1204, 1255, 1273, 1376, 1391, 1438, 1461, 1633, 1725, 2861, 2935, 3017, 3078 cm^{-1}.

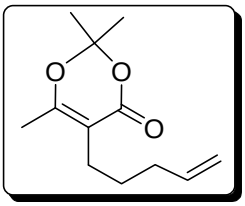
^{1}H NMR (500 MHz, $CDCl_3$) :δ 1.37-1.43 (m, 2H), 1.49-1.59 (m, 2H), 1.63 (s, 6H), 2.02 (q, *J* = 7.0 Hz, 2H), 2.17 (t, *J* = 7.0 Hz, 2H), 4.91-4.97 (m, 2H), 5.16 (s, 1H), 5.71 (ddt, *J* = 6.7, 10.4, 16.9 Hz, 1H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$) : δ 25.0 (q), 25.1 (t), 28.1 (t), 33.2 (t), 33.4 (t), 93.2 (d), 106.1 (s), 115.0 (t), 137.9 (d), 160.9 (s), 171.5 (s) ppm.

ESI-MS (*m/z*) : 211.1 $[M+H]^+$, 233.1 $[M+Na]^+$.

Elemental Analysis Calcd.: C, 68.54; H, 8.63 %
Found: 68.51; H, 8.64 %

2,2,6-Trimethyl-5-(pent-4-enyl)-4H-1,3-dioxin-4-one (57)



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

IR ($CHCl_3$) υ : 912, 1269, 1390, 1399, 1642, 1715, 2929, 3018, 3078 cm^{-1}.

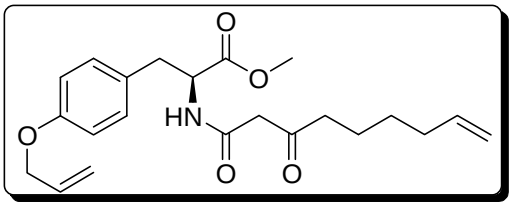
^{1}H NMR (200 MHz, $CDCl_3$) :δ 1.45-1.54 (m, 2H), 1.52 (s, 6H), 1.91 (s, 3H), 2.03 (q, *J* = 6.5 Hz, 2H), 2.18 (t, *J* = 6.5 Hz, 2H), 4.87-4.99 (m, 2H), 5.61-5.85 (m, 1H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$) : δ 17.1 (q), 24.6 (t), 24.9 (q), 28.3 (t), 33.3 (t), 104.4 (s), 105.3 (s), 114.7 (t), 138.1 (d), 161.6 (s), 162.6 (s) ppm.

ESI-MS (*m/z*) : 233.1 $[M+Na]^+$.

Elemental Analysis Calcd.: C, 68.54; H, 8.63 %
Found: C, 68.48; H, 8.52 %

3-(4-Allyloxy-phenyl)-2-(3-oxo-non-8-enoylamino)-propionic acid methyl ester (53)



A mixture of amine **55** (84 mg, 257 μmol) and the compound **54** (75 mg, 257 μmol) were taken in 5 mL dry toluene and refluxed for 7 h. Then toluene was removed under reduced pressure and the resulting light yellow liquid was subjected to column purification to get the *β*-keto amide **53** (99 mg, 72%) as yellow liquid.

Mol. Formula : $C_{22}H_{29}NO_5$

$[\alpha]_D^{25}$: +38.2 (*c* = 1.0, $CHCl_3$)

IR ($CHCl_3$) υ : 1216, 1438, 1511, 1670, 1741, 2931, 3019, 3450 cm^{-1}.

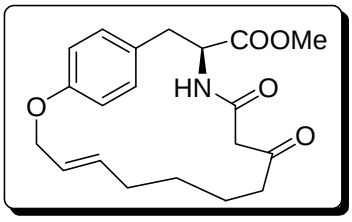
^{1}H NMR (200 MHz, $CDCl_3$) : δ 1.29-1.44 (m, 2H), 1.51-1.58 (m, 2H), 2.05 (q, *J* = 7.1 Hz, 2H), 2.49 (t, *J* = 7.1 Hz, 2H), 3.09 (dd, *J* = 6.7, 13.9 Hz, 1H), 2.99 (dd, *J* = 6.7, 14.4 Hz, 1H), 3.34 (s, 2H), 3.72 (s, 3H), 4.49 (dt, *J* = 1.4, 5.3 Hz, 2H), 4.77 (dd, *J* = 6.7, 13.8 Hz, 1H), 4.92-5.03 (m, 2H), 5.24-5.43 (m, 2H), 5.66-5.87 (m, 1H), 5.94-6.13 (m, 1H), 6.82 (d, *J* = 8.6 Hz, 2H), 7.03 (d, *J* = 8.6 Hz, 2H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) : δ 22.7 (t), 28.2 (t), 33.4 (t), 37.0 (t), 43.4 (t), 48.9 (t), 52.2 (q), 53.5 (d), 68.6 (t), 114.7 (d), 114.9 (t), 117.5 (t), 127.9 (s), 130.2 (d), 133.3 (d), 138.1 (d), 157.7 (s), 165.1 (s), 171.6 (s), 205.5 (s) ppm.

ESI-MS (*m/z*) : 388.2 $[M+H]^+$, 405.2 $[M+NH_4]^+$, 410.2 $[M+Na]^+$.

Elemental Analysis Calcd.: C, 68.20; H, 7.54; N, 3.61 %
Found: C, 67.94; H, 7.74; N, 3.49 %

10,12-Dioxo-2-oxa-13-aza-bicyclo[14.2.2]eicosa-1(19),4,16(20),17-tetraene-14-carboxylic acid methyl ester (52)



To a solution of diene **53** (60 mg, 157 μmol) in 50 mL dry DCM Grubbs' 1st gen. catalyst (10 mol%) was added under argon atmosphere at ambient temperature and the mixture was stirred for 7 h at same temperature. Then volatile were removed under reduced pressure and flash column purification gave the cyclic *β*-keto amide **52** (35 mg, 63%) as liquid.

Mol. Formula : $C_{20}H_{25}NO_5$

$[\alpha]_D^{25}$: +15.28 (*c* = 1.1, $CHCl_3$)

IR ($CHCl_3$) υ : 767, 1217, 1511, 1611, 1727, 1973, 2931, 3019, 4033 cm^{-1}.

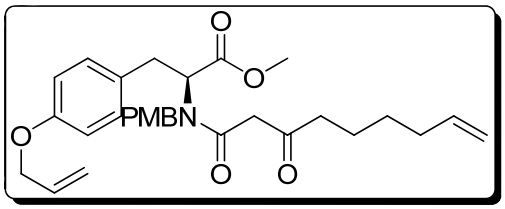
^{1}H NMR (500 MHz, $CDCl_3$) : δ 1.22–1.46 (m, 4H), 2.03 (d, *J* = 12.0 Hz, 1H), 2.04 (d, *J* = 12 Hz, 1H) 2.22 (ddd, *J* = 5.2, 9.3, 17.3 Hz, 1H), 2.40 (ddd, *J* = 5.9, 9.5, 17.3 Hz, 1H), 2.71 (dd, *J* = 10.0, 14.2 Hz, 1H), 3.18 (m, 2H), 3.35 (d, *J* = 14.5 Hz, 1H), 3.80 (s, 3H), 4.57 (dd, *J* = 5.8, 14.2 Hz, 1H), 4.62 (dd, *J* = 5.5, 14.2 Hz, 1H), 4.67 (m, 1H), 5.45 (dt, *J* = 5.3, 15.6 Hz, 1H), 5.59 (dt, *J* = 6.9, 15.6 Hz, 1H), 6.75 (d, *J* = 8.2 Hz, 2H), 6.94 (d, *J* = 8.2 Hz, 2H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$) : δ 21.7 (t), 27.5 (t), 31.0 (t), 36.9 (t), 43.6 (t), 49.6 (t), 52.4 (q), 53.3 (d), 67.4 (t), 115.9 (d), 127 (d), 127.5 (s), 129.9 (d), 134.4 (d), 156.5 (s), 164.2 (s), 171.8 (s), 206.4 (s) ppm.

ESI-MS (*m/z*) : 360.1 $[M+H]^+$, 382.1 $[M+Na]^+$.

Elemental Analysis Calcd.: C, 66.83; H, 7.01; N, 3.90 %
Found: C, 66.66; H, 7.13; N, 3.72 %

3-(4-Allyloxy-phenyl)-2-[(4-methoxy-benzyl)-(3-oxo-non-8-enoyl)-amino]-propionic acid methyl ester (61)



To a mixture of amine **55a** (1.35 g, 3.8 mmol) and **54** (0.80 g, 3.8 mmol) in toluene PPTS (0.992 g, 3.67 mmol) was added under nitrogen atmosphere and the mixture was stirred for 7 h. The crude material, obtained after removal of volatiles were purified by coloumn chromatography and afforded the PMB protected β-keto amide **61** (1.39 g, 72%) as yellow liquid.

Mol. Formula : $C_{30}H_{37}NO_6$

$[\alpha]_D^{25}$: –96.1 (*c* = 1.28, $CHCl_3$)

IR ($CHCl_3$) υ : 3440, 3019, 2953, 1740, 1643, 1613, 1512, 1247, 1216 cm^{-1}.

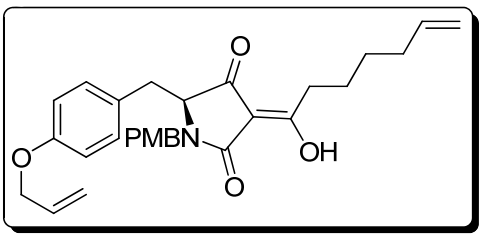
^{1}H NMR (200 MHz, $CDCl_3$) :δ 1.34-1.45 (m, 2H), 1.51-1.63 (m, 2H), 2.00-2.14 (m, 3H), 2.48-2.57 (m, 1H), 3.08-3.34 (m, 2H), 3.37&3.47 (s, 2H), 3.62 & 3.65 (s, 3H), 3.78 (d, *J* = 16.4 Hz, 1H), 3.79 (s, 3H), 4.06-4.24 (m, 1H), 4.36 (d, *J* = 16.4 Hz, 1H), 4.51-4.53 (m, 2H), 4.92-5.03 (m, 2H), 5.25-5.45 (m, 2H), 5.67-5.88 (m, 1H), 5.96-6.15 (m, 1H), 6.76-6.85 (complex pattern, 4H), 6.99-7.05 (m, 4H).

ESI-MS (*m/z*) : 508.2 $[M+H]^+$, 530.2 $[M+Na]^+$, 546.2 $[M+K]^+$.

Elemental Analysis Calcd.: C, 70.98; H, 7.35; N, 2.76 %

Found: C, 70.69; H, 7.32; N, 2.56 %

(5*S*)-5-(4-(Allyloxy)benzyl)-1-(4-methoxybenzyl)-3-(hept-6-enoyl)pyrrolidine-2,4-dione (62)

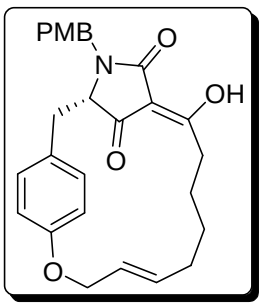


To an ice cold solution of *β*-Keto amide **61** (535 mg, 1.05 mmol) in 10 mL dry ^{t}BuOH solid ^{t}BuOK (124 mg, 1.11 mmol) was added and stirred for 30 min. Then the reaction mixture was acidified with 1 N aqueous HCl and extracted with ethyl acetate.

The organic extract was collected, dried on sodium sulfate and concentrated. Column purification of the crude product gave **62** (456 mg, 91%) as liquid.

Mol. Formula	: $C_{29}H_{33}NO_5$
$[\alpha]_D^{25}$	: −36.2 (*c* = 1.2, $CHCl_3$)
IR ($CHCl_3$) υ	: 613, 821, 920, 996, 1032, 1110, 1176, 1247, 1303, 1346, 1459, 1512, 1611, 1710, 3402 (b) cm^{-1}.
^{1}H NMR (200 MHz, $CDCl_3$)	: δ 1.33 (m, 2H), 1.53-1.68 (m, 2H), 2.05 (q, *J* = 7.0 Hz, 2H), 2.61-2.91 (m, 2H), 3.00 (dd, *J* = 4.8, 14.5 Hz, 1H), 3.08 (dd, *J*= 4.2, 14.5 Hz, 1H), 3.76 (dd, *J* = 4.2, 4.8 Hz, 1H), 3.78 (s, 3H), 3.85 (d, *J* = 14.7 Hz, 1H), 4.49 (dt, *J* = 1.5, 5.3 Hz, 2H), 4.91-5.06 (m, 2H), 5.18 (d, *J* = 14.7 Hz, 1H), 5.28 (dq, distorted, *J* = 1.5, 10.5 Hz, 1H), 5.39 (dq, distorted, *J* = 1.5, 17.2 Hz, 1H), 5.78 (ddt, *J* = 6.7, 10.1, 16.9 Hz, 1H), 6.04 (ddt, *J* = 5.2, 10.5, 17.2 Hz, 1H), 6.78 (d, *J* = 8.5 Hz, 2H), 6.82 (d, *J* = 8.5 Hz, 2H), 6.99 (d, *J* = 8.5 Hz, 2H), 7.02 (d, *J* = 8.5 Hz, 2H) ppm.
^{13}C NMR (50 MHz, $CDCl_3$)	: δ 25.3 (t), 28.2 (t), 32.3 (t), 33.2 (t), 34.4 (t), 43.0 (t), 55.2 (q), 64.4 (d), 68.7 (t), 101.4 (s), 114.1 (d), 114.6 (d), 114.7 (t), 117.6 (t), 127.3 (s), 127.4 (s), 129.5 (d), 130.4 (d), 133.1 (d), 138.2 (d), 157.5 (s), 159.3 (s), 173.3 (s), 187.5 (s), 193.8 (s) ppm.
ESI-MS (*m/z*)	: 476.2 $[M+H]^+$, 498.2 $[M+Na]^+$, 514.2 $[M+K]^+$.
Elemental Analysis	Calcd.: C, 73.24; H, 6.99; N, 2.95 % Found: C, 73.03; H, 6.85; N, 2.81 %

7-Hydroxy-4-(4-methoxy-benzyl)-15-oxa-4-aza-tricyclo[14.2.2.13,6]heneicosa-1(19),6,12,16(20),17-pentaene-5,21-dione (63)



Cyclic *β*-keto amide **64** (317 mg, 661 μmol) [prepared from the diene **61** by RCM using Grubb's 1st gen, catalyst in DCM at rt; isolated in 63% yield] was taken in

7 mL dry ^{t}BuOH and cooled to rt. To this cold solution solid ^{t}BuOK (74 mg, 661 μmol) was added and stirred for 30 min at the same temperature. Then the reaction was acidified with 1 (N) aqueous HCl and extracted with ethyl acetate. The organic extract was collected, dried on sodium sulfate, concentrated. Column purification followed by recrystallization gave crystalline material **63** (0.166 g, 56%).

Mol. Formula : $C_{27}H_{29}NO_5$

M. P. : 144 ^oC

$[\alpha]_D^{25}$: −36.2 (*c* = 1.2, $CHCl_3$)

IR ($CHCl_3$) υ : 3400, 3019, 2932, 1708, 1613, 1511, 1461, 1433, 1246, 1215, 1034, 757 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) : δ 1.04–1.13 (m, 2H), 1.15–1.23 (m, 1H), 1.26–1.34 (m, 1H), 1.89–1.94 (m, 2H), 2.02–2.07 (m, 1H), 2.97 (dd, *J* = 4.1, 14.4 Hz, 1H), 3.04 (dd, *J* = 2.7, 14.4 Hz, 1H), 3.20 (dt, *J* = 6.7, 11.6 Hz, 1H), 3.79 (s, 3H), 4.14 (d, *J* = 14.8 Hz, 1H), 4.55–4.60 (m, 3H), 5.27–5.42 (m, 1H), 5.34 (d, *J* = 14.8 Hz, 1H), 5.52 (dt, *J* = 7.4, 15.6 Hz, 1H), 6.68 (br s, 2H), 6.76–6.78 (m, 1H), 6.87 (br d, *J* = 8.0 Hz, 2H), 6.95 (br s, 1H), 7.21 (br d, *J* = 8.0 Hz, 2H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$) : δ 27.5 (t), 28.6 (t), 32.1 (t), 32.2 (t), 32.4 (t), 42.6 (t), 55.2 (q), 64.1 (d), 66.8 (t), 101.5 (s), 114.3 (d), 114.4 (d), 125.5 (d), 125.6 (s), 127.4 (s), 129.6 (d), 129.7 (d), 136.7 (d), 155.9 (s), 159.5 (s), 173.4 (s), 187.1 (s), 193.4 (s) ppm.

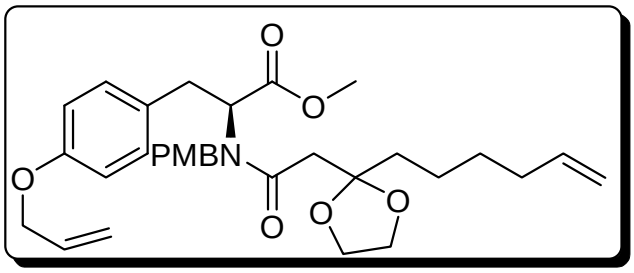
ESI-MS (*m/z*) : 448.2 $[M+H]^+$, 470.2 $[M+Na]^+$.

Elemental Analysis Calcd.: C, 72.46; H, 6.53; N, 3.13 %.
Found: C, 72.28; H, 6.45; N, 2.98 %.

Crystal Data for 63: Single crystals of the compound were grown by slow evaporation of the solution in ethyl acetate. Colourless plate of approximate size 0.54 x 0.30 x 0.08 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. Crystal to detector distance 6.05 cm, 512 x 512 pixels / frame, Quadrant data acquisition. Total scans = 5, total frames = 3030, Oscillation / frame -0.3º, exposure / frame = 20.0 sec / frame, maximum detector swing angle = –30.0º, beam center =

(260.2, 252.5), in plane spot width = 1.24, SAINT integration, θ range = 1.45 to 25.0º, completeness to θ of 24.99º is 99.8%. SADABS correction applied, $C_{27}H_{29}NO_5$, M = 447.51. Crystals belong to triclinic, space group $P2_1$, a = 10.0276 (6), b = 8.6768 (5), c = 14.0094 (8) Å, β = 96.253 (1)°, V = 1211.67 (12) Å^3, Z = 2, D_c = 1.227mg m^{-3}, μ (MoK_α) = 0.084 mm^{-1}, T = 293 (2) K, 11989 reflections measured, 4246 unique [I>2σ(I)], R value 0.0435, wR2 = 0.1164. All the data were corrected for Lorentzian, polarisation and absorption effects. SHELX-97 (ShelxTL) [G. M. Sheldrick, SHELX-97 program for crystal structure solution and refinement, University of Gottingen, Germany, 1997] 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.

3-(4-Allyloxy-phenyl)-2-[[2-(2-hex-5-enyl-[1,3]dioxolan-2-yl)-acetyl]-(4-methoxy-benzyl)-amino]-propionic acid methyl ester (61a)



To a solution of *β*-keto amide **61** (235 mg, 462 μmol) in benzene (25 mL) ethylene glycol (287 mg, 4.63 mmol) and *p*-TSA (30 mg) were added. The mixture was subjected to azeotropic distillation to remove released water. After complete conversion, volatiles were removed and column purification gave pure ketal **61a** (199 mg, 78%) as liquid.

Mol. Formula : $C_{32}H_{41}NO_7$

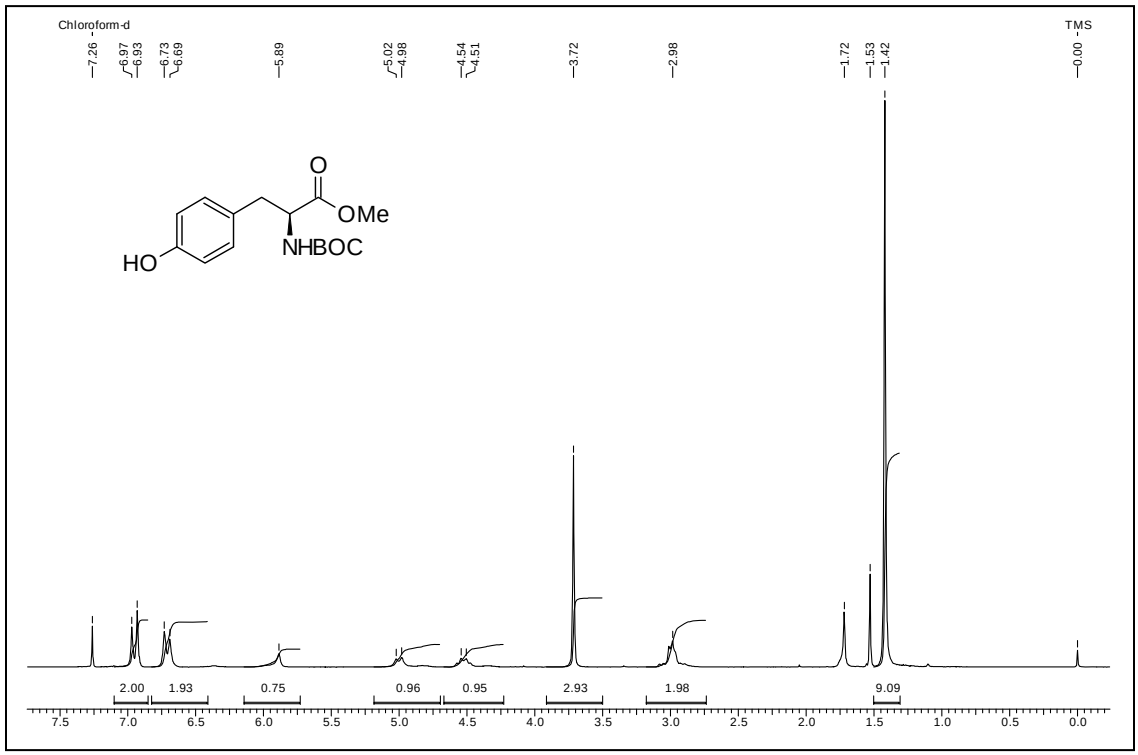
$[\alpha]_D^{25}$: –78.1 (c = 1.2, $CHCl_3$)

IR ($CHCl_3$) υ : 668, 757, 1035, 1246, 1512, 1613, 1639, 1739, 3018 cm^{-1}.

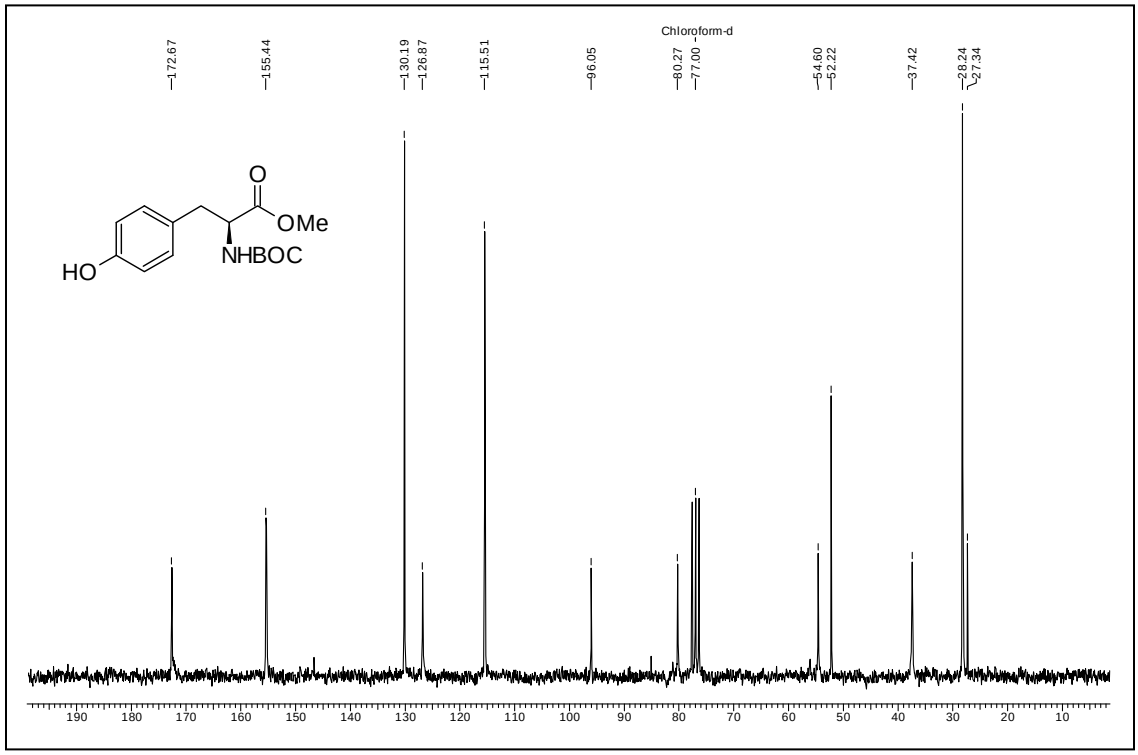
^{1}H NMR (200 MHz, $CDCl_3$) :δ 1.33-1.42 (m, 4H), 1.71-1.86 (m, 2H), 1.96-2.10 (m, 2H), 2.89 (s, 2H), 3.07 (dd, J = 8.7, 14.1 Hz, 1H), 3.27 (dd, J = 6.0, 14.1, 1H), 3.60 (s, 3H), 3.77 (s, 3H), 3.85-3.93 (m, 5H), 4.20 (dd, J = 6.0, 8.7, 1H), 4.48-58 (m, 3H), 4.86-5.02 (m, 2H), 5.27 (dq, distorted, J = 1.4, 10.4 Hz, 1H), 5.40 (dq, distorted, J = 1.5, 17.2 Hz, 1H), 5.78 (ddt, J = 6.7,10.4, 16.8 Hz, 1H), 6.05 (ddt, J = 5.2, 10.5, 17.2 Hz, 1H), 8.77 (d, J = 8.6Hz, 2H), 8.78

	(d, *J* = 8.6 Hz, 2H), 7.01 (d, *J* = 8.6 Hz, 2H), 7.04 (d, *J* = 8.6 Hz, 2H) ppm.
^{13}C NMR (100 MHz, $CDCl_3$)	: δ 23.1 (t), 28.9 (t), 33.7 (t), 34.3 (t), 37.8 (t), 41.4 (t), 51.8 (q), 51.9 (t), 55.1 (q), 60.7 (d), 64.9 (t), 65.0 (t), 68.6 (t), 110.4 (s), 113.8 (d), 114.3 (t), 114.5 (d), 117.4 (t), 128.2 (s), 128.5 (d), 130.3 (s), 130.3(d), 133.3 (d), 138.7 (d), 157.2 (s), 159.0 (s), 169.6 (s), 170.7(s) ppm.
MALDI-TOF MS (*m/z*)	: 551.7 $[M]^+$, 574.7 $[M+Na]^+$, 590.6 $[M+K]^+$.
Elemental Analysis	Calcd.: C, 69.67; H, 7.49;N, 2.54 % Found: C, 66.84; H, 7.94; N, 2.29 %

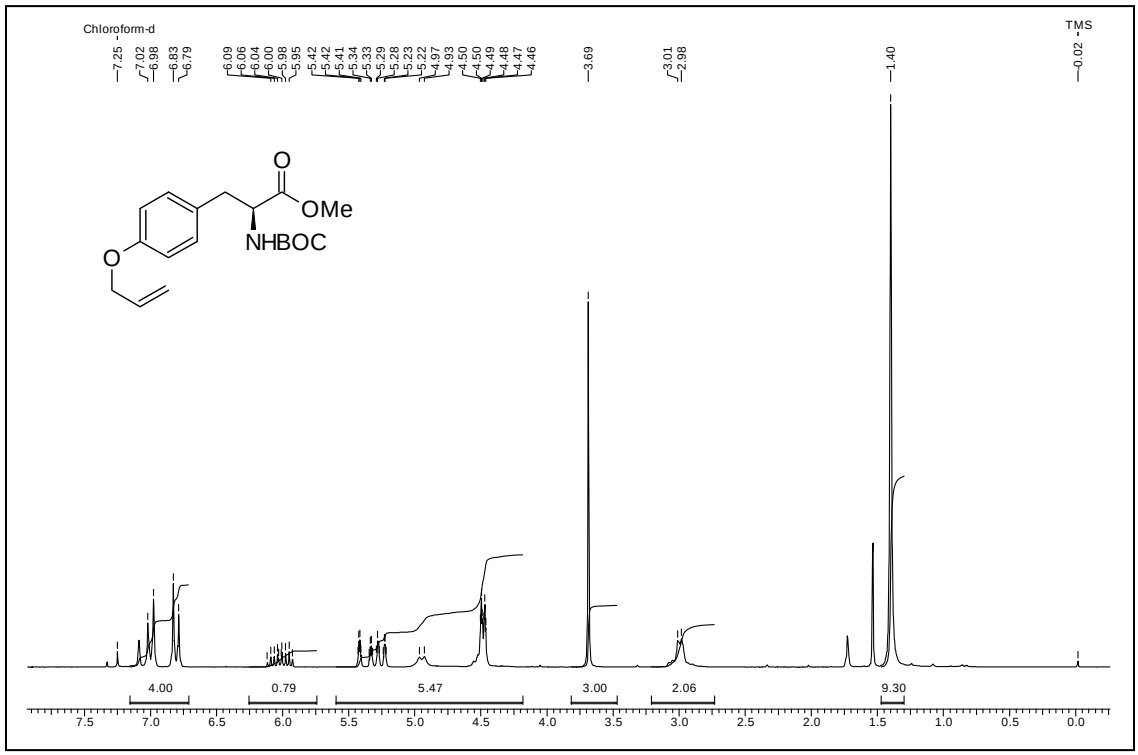
Spectra



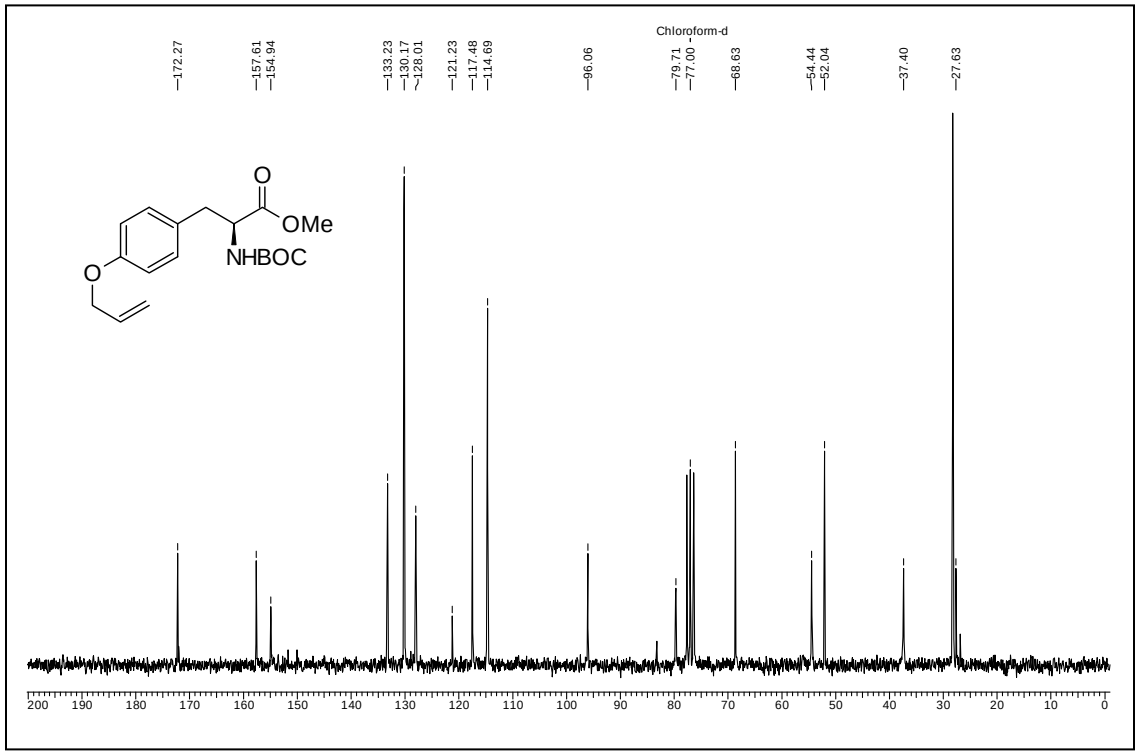
^{1}H NMR Spectrum of 59 in $CDCl_3$



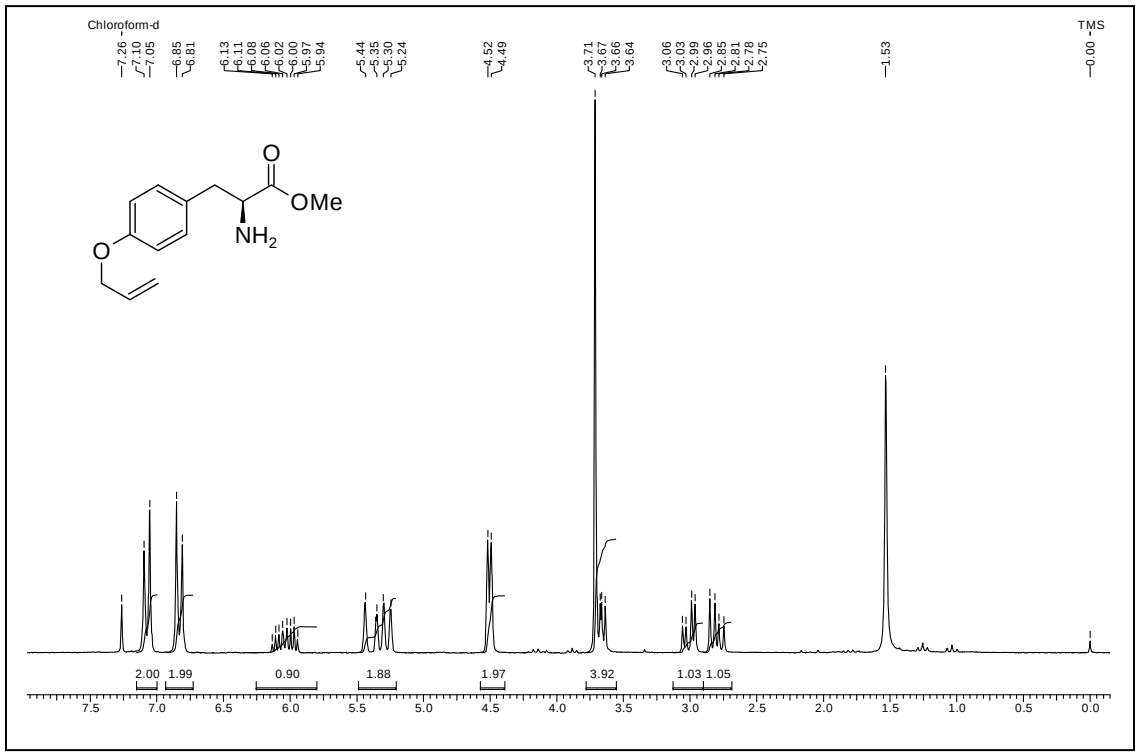
^{13}C NMR Spectrum of 59 in $CDCl_3$



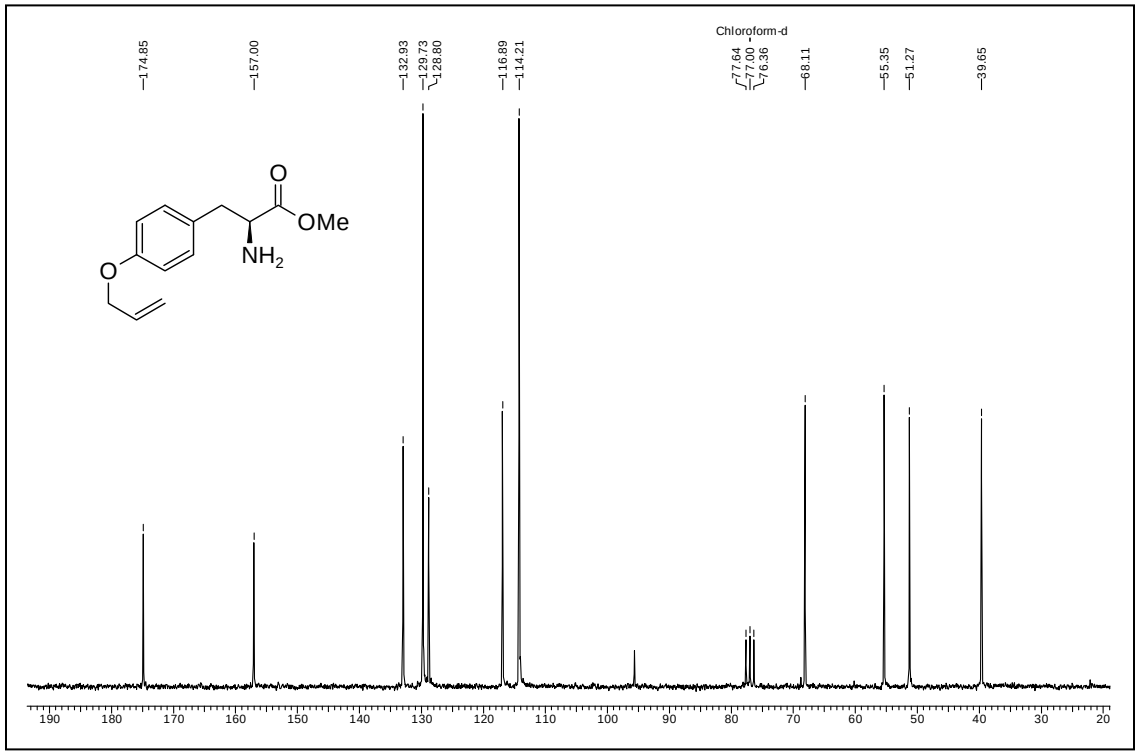
^{1}H NMR Spectrum of 60 in $CDCl_3$



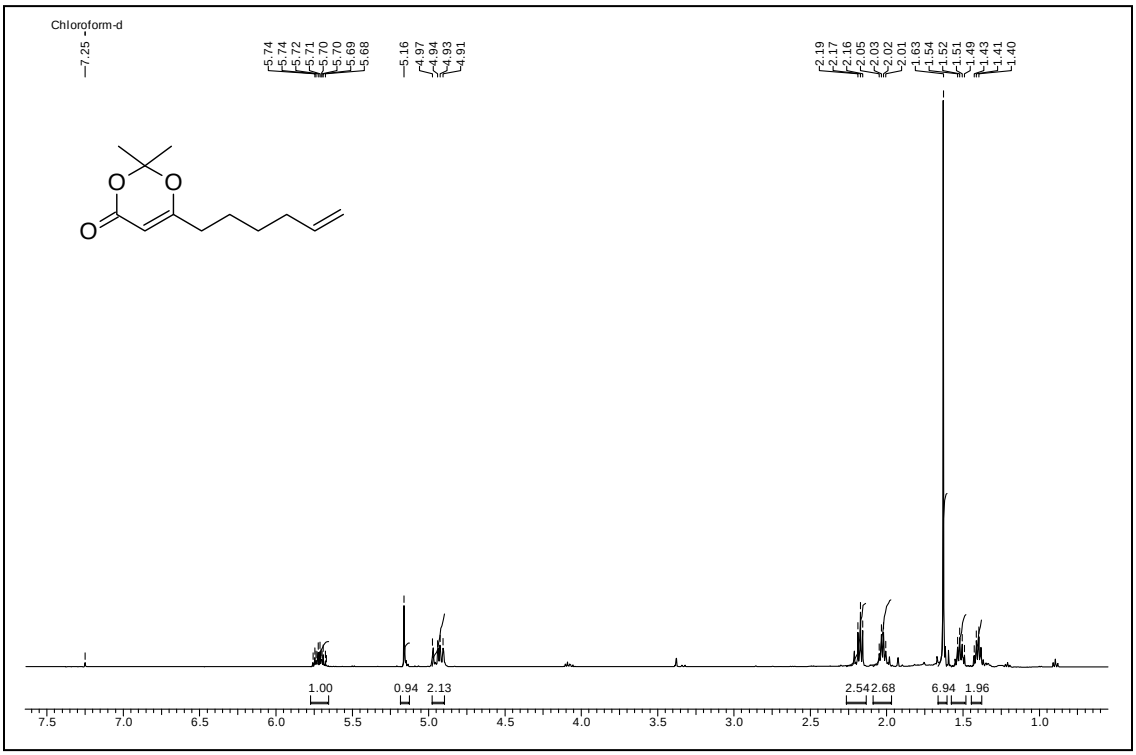
^{13}C NMR Spectrum of 60 in $CDCl_3$



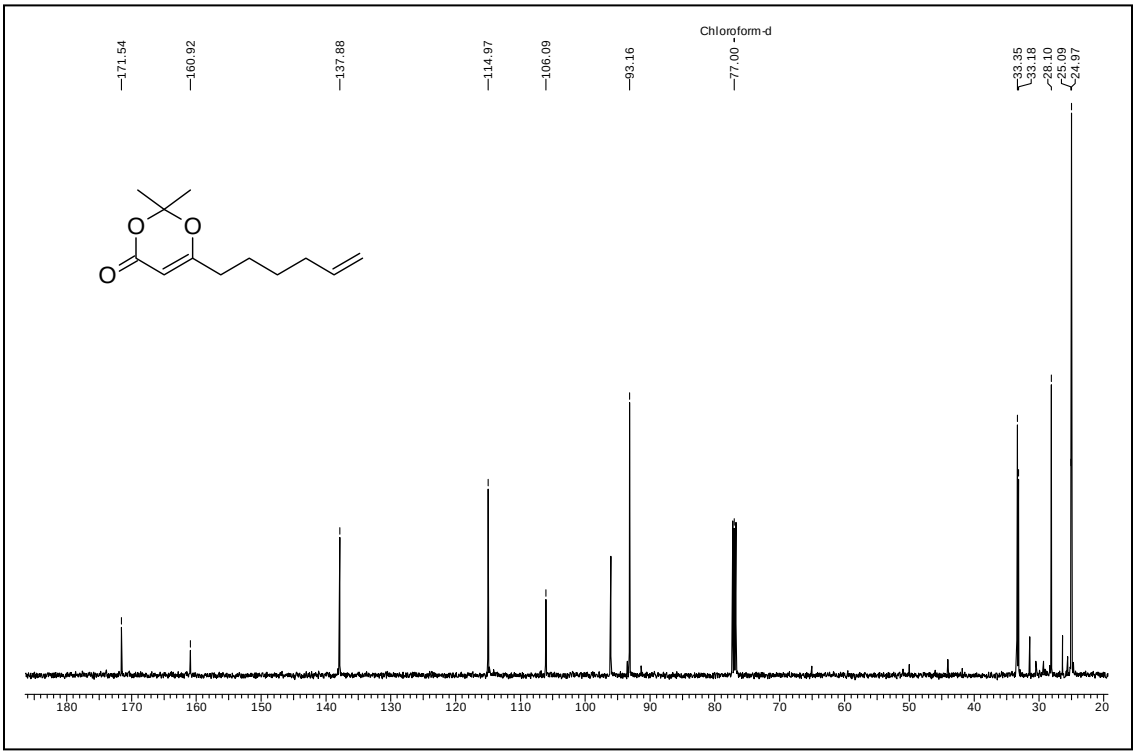
^{1}H NMR Spectrum of 55 in $CDCl_3$



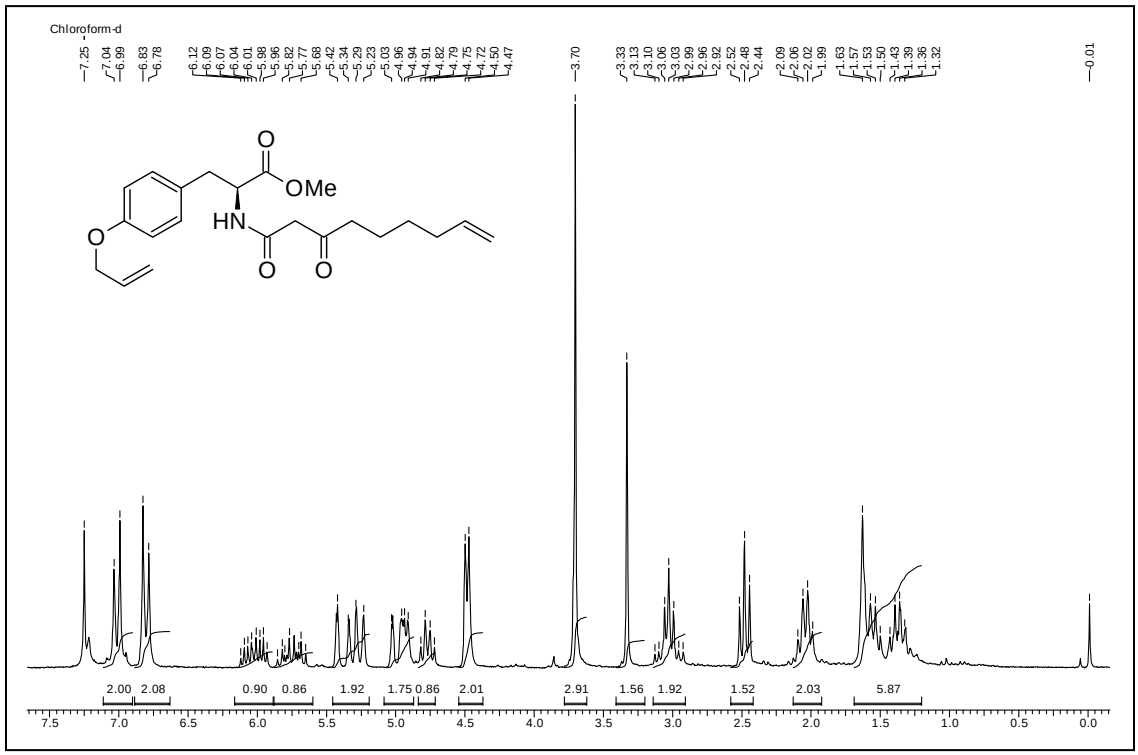
^{13}C NMR Spectrum of 55 in $CDCl_3$



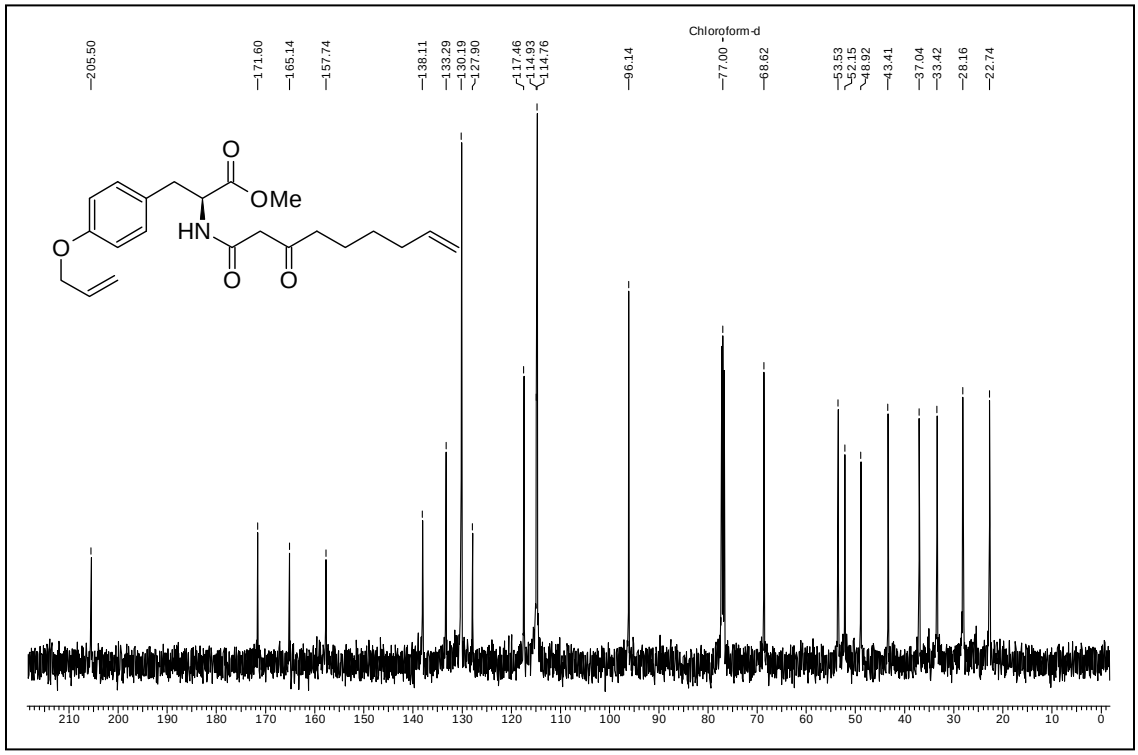
^{1}H NMR Spectrum of 54 in $CDCl_3$



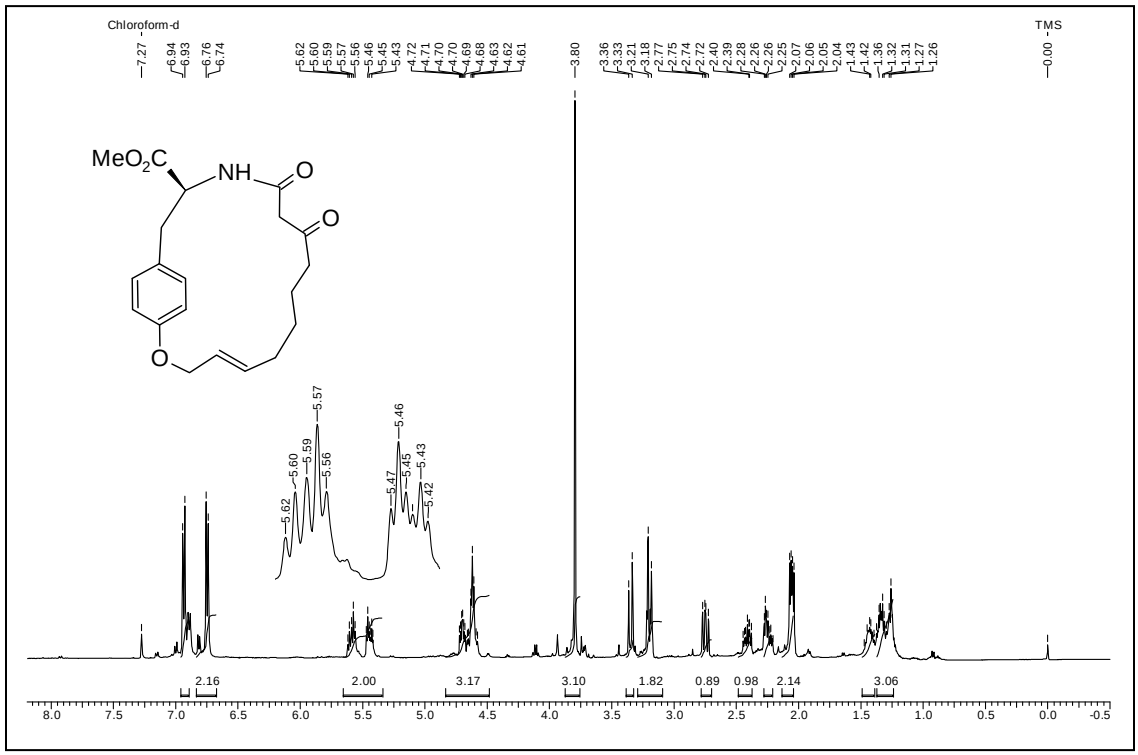
^{13}C NMR Spectrum of 54 in $CDCl_3$



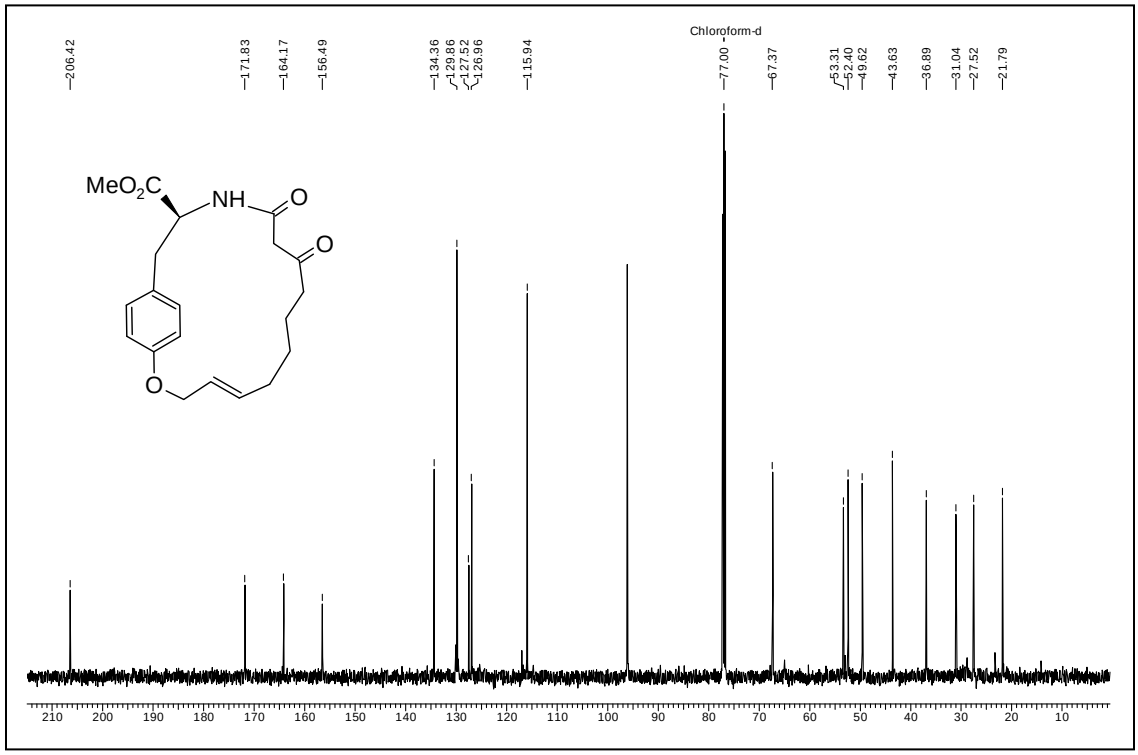
^{1}H NMR Spectrum of 53 in $CDCl_3$



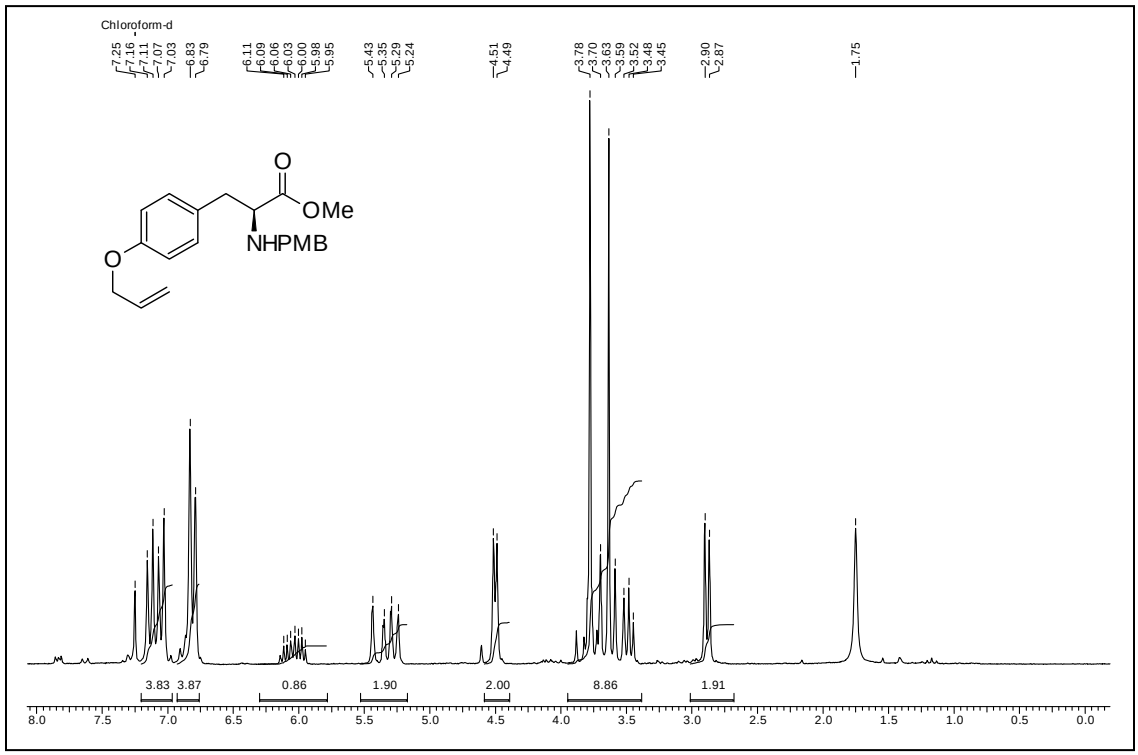
^{13}C NMR Spectrum of 53 in $CDCl_3$



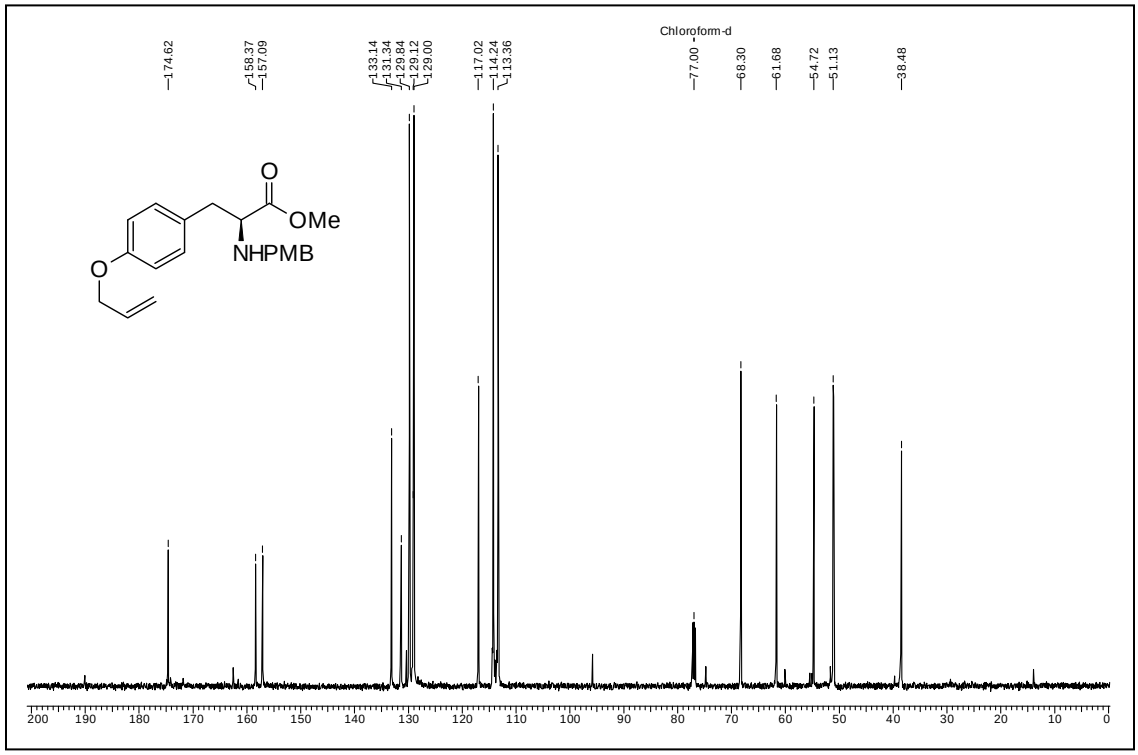
^{1}H NMR Spectrum of 52 in $CDCl_3$



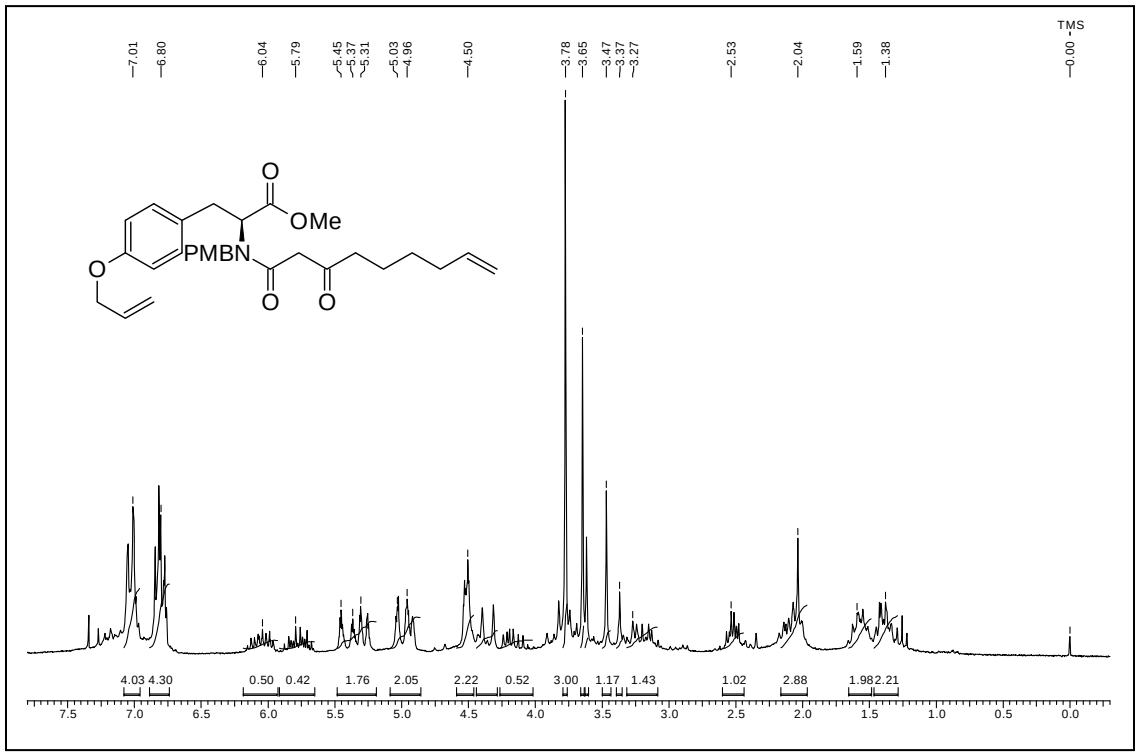
^{13}C NMR Spectrum of 52 in $CDCl_3$



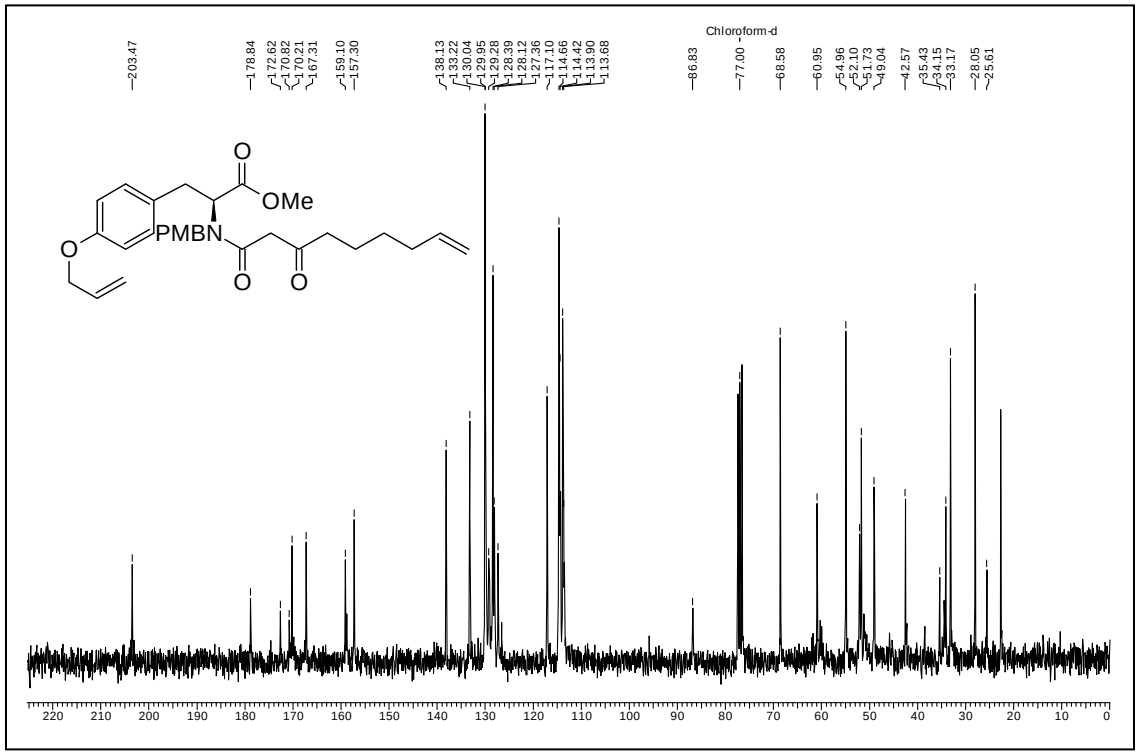
^{1}H NMR Spectrum of 55a in $CDCl_3$



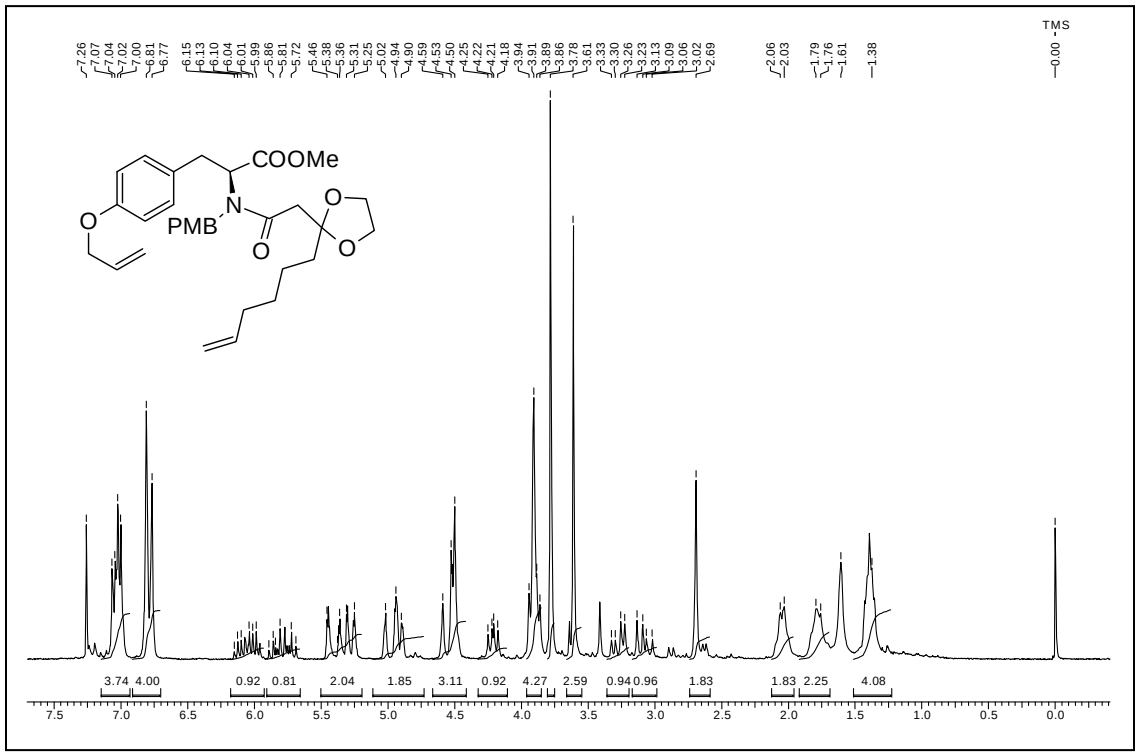
^{13}C NMR Spectrum of 55a in $CDCl_3$



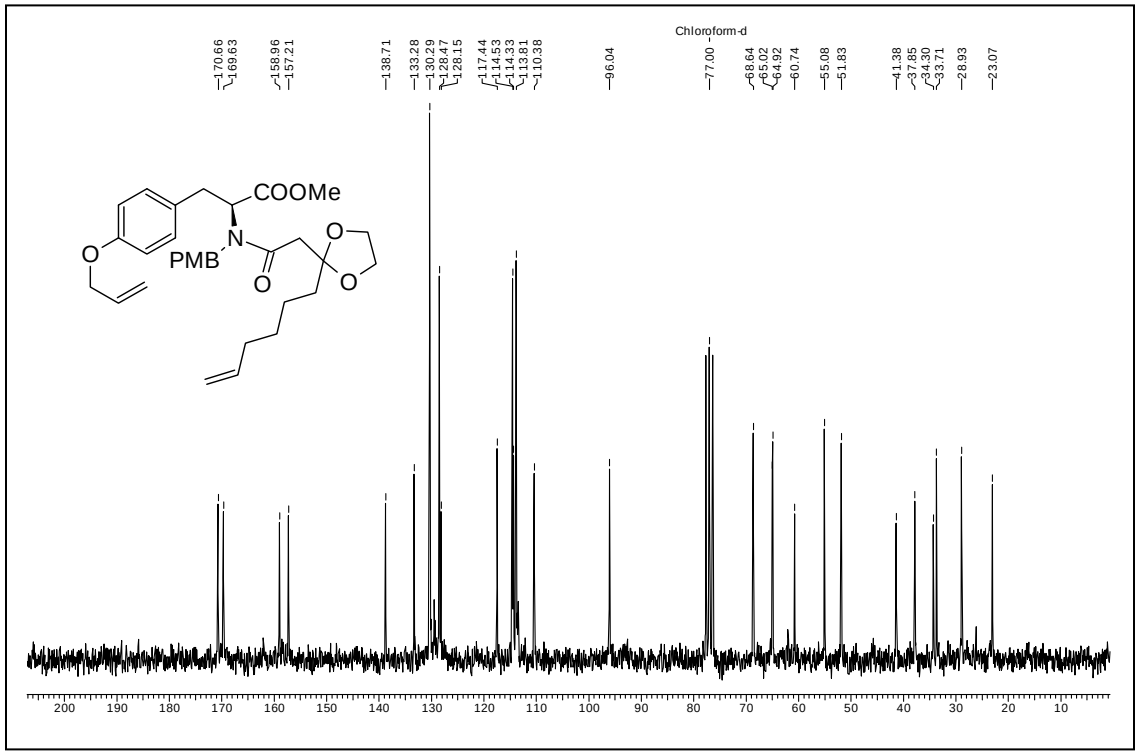
^{1}H NMR Spectrum of 61 in $CDCl_3$



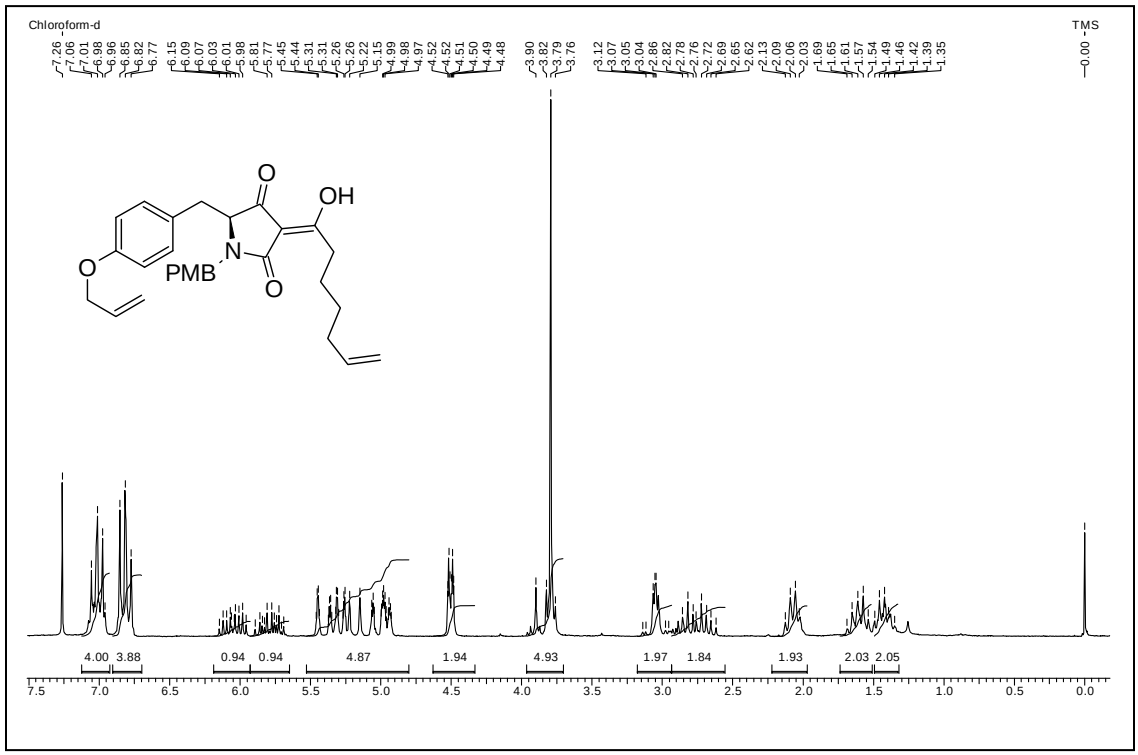
^{13}C NMR Spectrum of 61 in $CDCl_3$



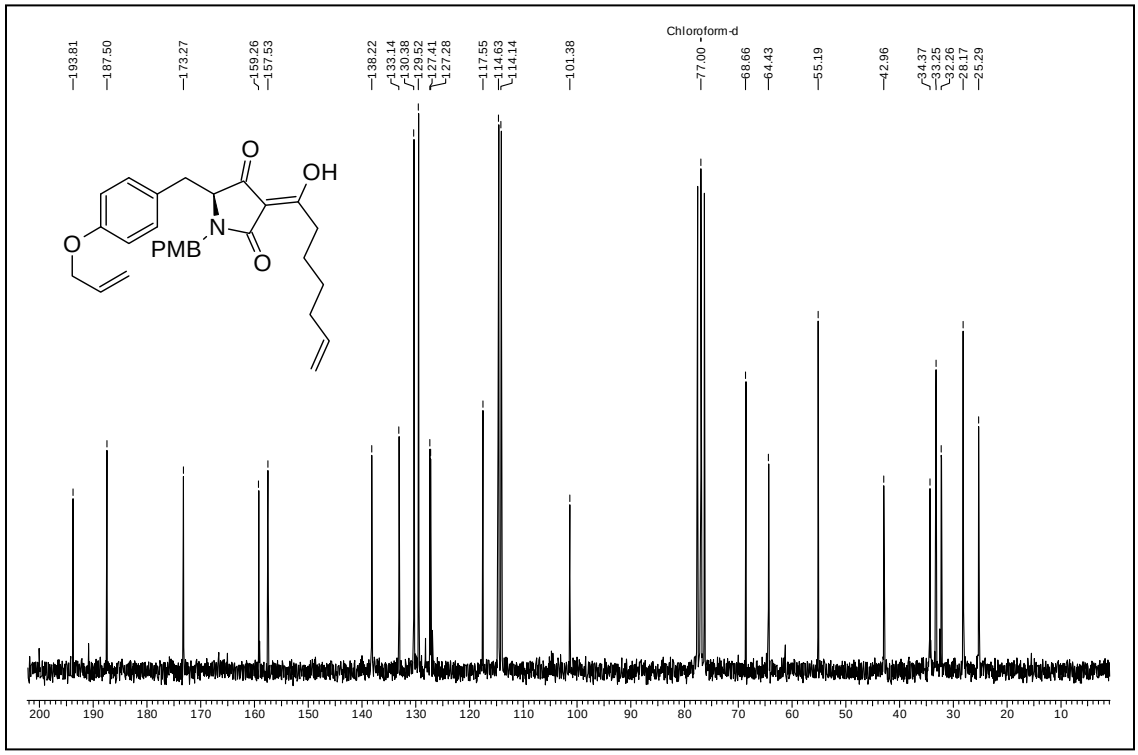
^{1}H NMR Spectrum of 61a in $CDCl_3$



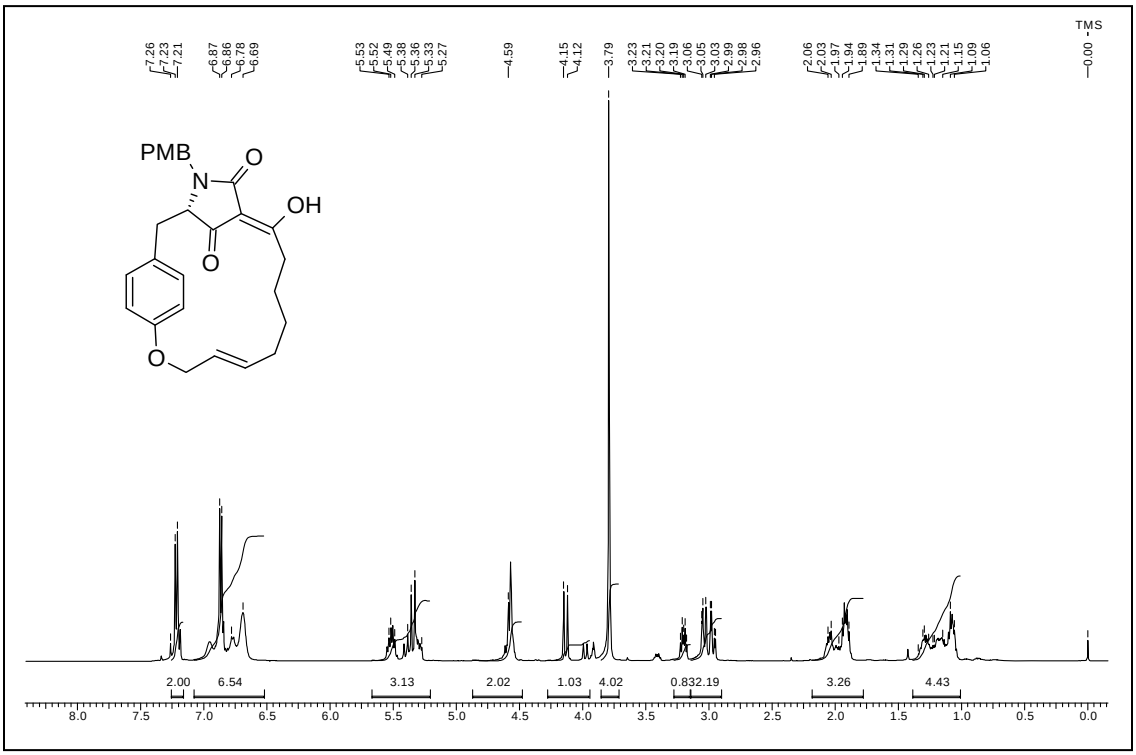
^{13}C NMR Spectrum of 61a in $CDCl_3$



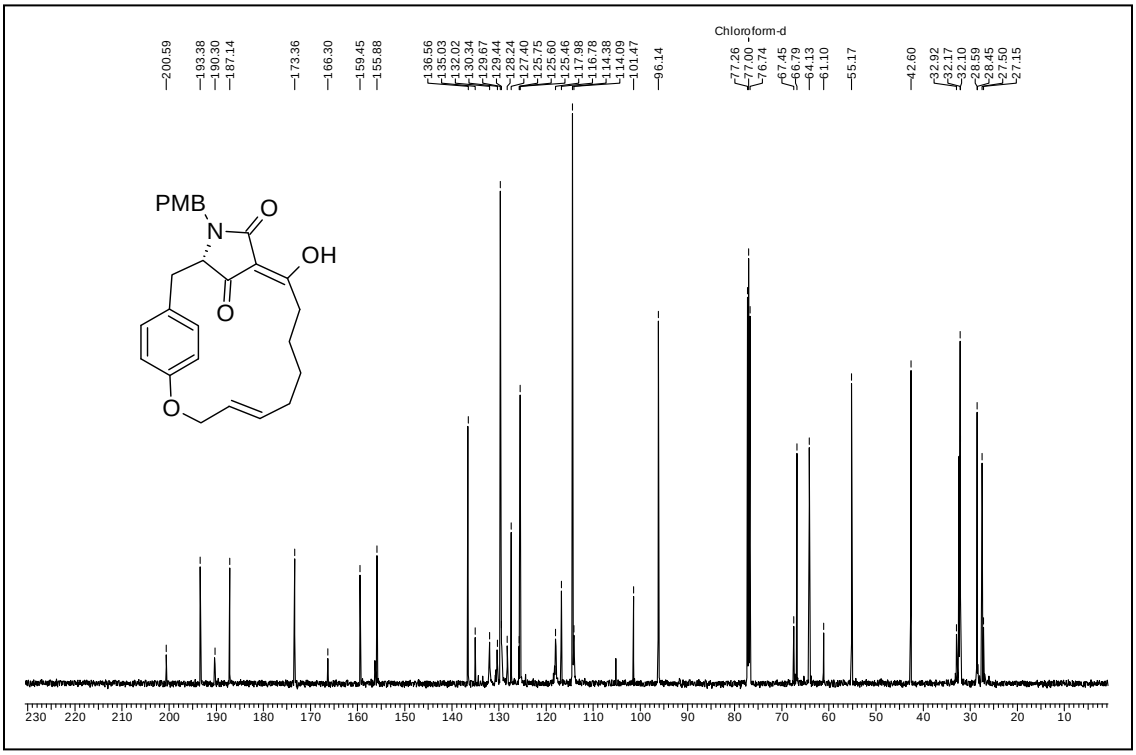
^{1}H NMR Spectrum of 62 in $CDCl_3$



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



^{1}H NMR Spectrum of 63 in $CDCl_3$



^{13}C NMR Spectrum of 63 in $CDCl_3$

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Chapter 4

Studies Toward the Total Synthesis of 4-epi-Stagonolide B

Introduction

Macrocyclic secondary metabolites containing 8-10 membered ring are a subject of continuous interest to the synthetic chemists, as they are core structure of many natural products[1] with wide range of bioactivity and they are obtained from almost all kind of sources. They were identified as monocyclic hydrocarbons, heterocyclic compounds such as ether, amine, amide, lactones etc. Construction of medium size ring is not straightforward and formation is more difficult than higher analogues.[2] These difficulties are caused by entropy[3a] as well as enthalpy.[3b] The entropic factor is disfavoured by the carbon chain becoming too long and thus the probability of a reaction taking place between the two chain termini decreases. The enthalpy factor is mainly created by steric interactions which lead to the torsional or Pitzer stain, bond angle deformation or Baeyer strain, stereoelectronic[4] effect and *trans* annular interaction[5]. The last two are particularly more important for medium size lactone rings. Simple methods used to for the synthesis of smaller size rings has been also extended for the synthesis of medium size ring[6], but they are less effective and in most of the cases difficulties arose due the complexity in preparation of required intermediate designed for the macrocyclisation and experimentally demanding conditions which were not suitable when multifunctional, complex, natural products were in synthetic target. Therefore, much more efforts have been put forward toward the development of alternative strategy for the synthesis of medium size rings systems.[7]

Monocyclic ten-membered-ring lactones

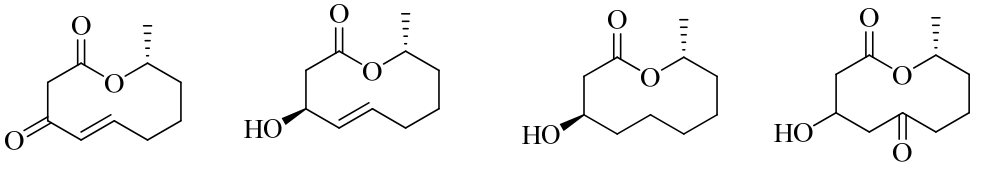
Amongst the medium size rings, ten membered especially associated with lactone functionality are widely appeared and most abundant among the medium size ring systems in nature. Over the last four decades a series of compounds have been isolated and characterized from various sources. The medium-sized lactones are secondary metabolites biosynthesized mainly by fungi, bacteria and marine organisms, with only few being produced by plants or insects. The jasmine lactone[8], isolated from the essential oil of *Jasminum grandiflorium*, was the first representative member of this family came in literature after 1942 and its structure was confirmed after twenty years later.[9] Upto 1975 it was only known natural occurring decalactone.

The common types of ten-member lactone frequently observed in nature are mono cyclic polyketalides, oxylipins, bicyclic aliphatic and aromatic. Representative examples and their source, bio-activities are presented here.

Polyketalides

Polyketalides are the most common congener of the family, ten member lactones. Diplodialides[10] are the first described group of monocyclic ten-membered-ring lactones (Figure 1). Diplodialides A, B and C were isolated in 1975, by Ishida and Wada, from the plant pathogenic fungus *Diplodia pinea*. Diplodialide A showed inhibitory activity against steroid hydroxylase. The isolation of diplodialide D, as well as the full structural elucidation of the four metabolites, was reported by the same authors, who also established the *R* configuration for the C9 center.

Figure 1.

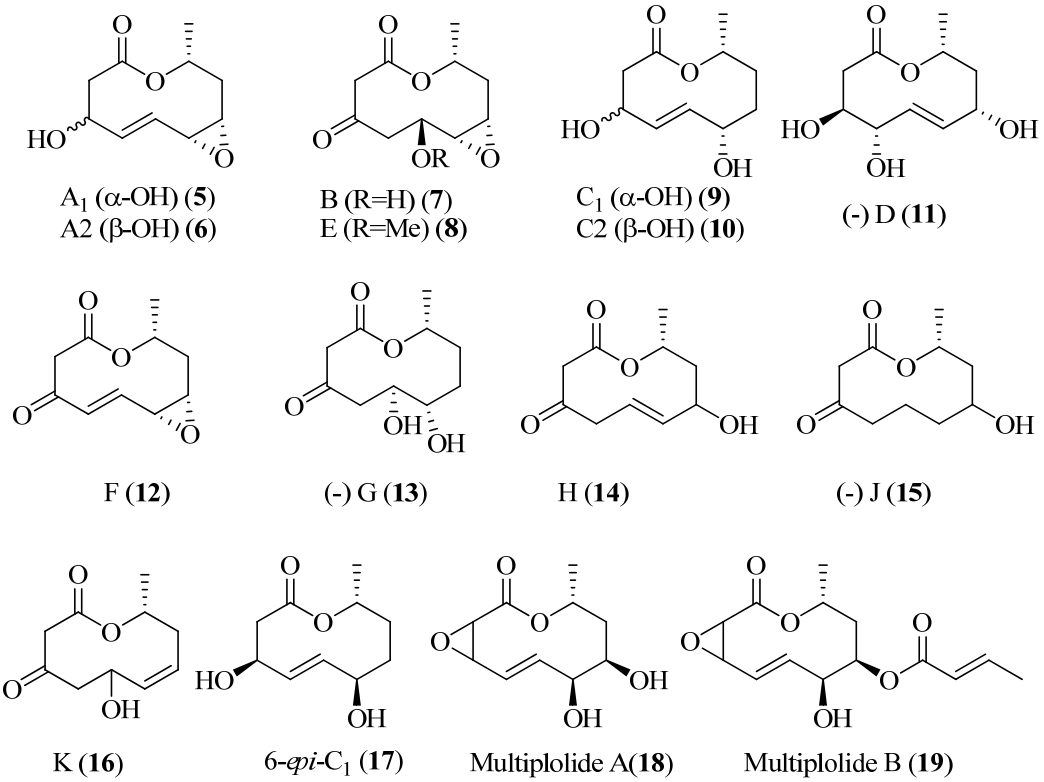


Diplodialide A (**1**) Diplodialide B (**2**) Diplodialide C (**3**) Diplodialide D (**4**)

Another series of ten member lactones were isolated from different strains of *Penicillium* species, named decarestrictines (**5-19**, Figure 2) in early 1990s and shown to be inhibitors of cholesterol biosynthesis, demonstrated by both *in vivo* and *in vitro* studies.[11] Most of them consists of a ten member skeleton with different oxofunctionality at C3 and C7. Five of them (A_1, A_2, B, E, and F) bear an epoxide function at C6–C7, eight (A_1, A_2, C_1, C_2, D, F, H, K) possess a double bond, and seven of the decarestrictines (B, E, F, G, H, J, K) are β-keto lactones. The most biologically active among these natural products, decarestrictine D (**11**), was simultaneously and independently isolated from the canadian tuckahoe (the sclerotium of the fungus *Polyporus tuberaster*) and was named tuckolide by the authors.[12]

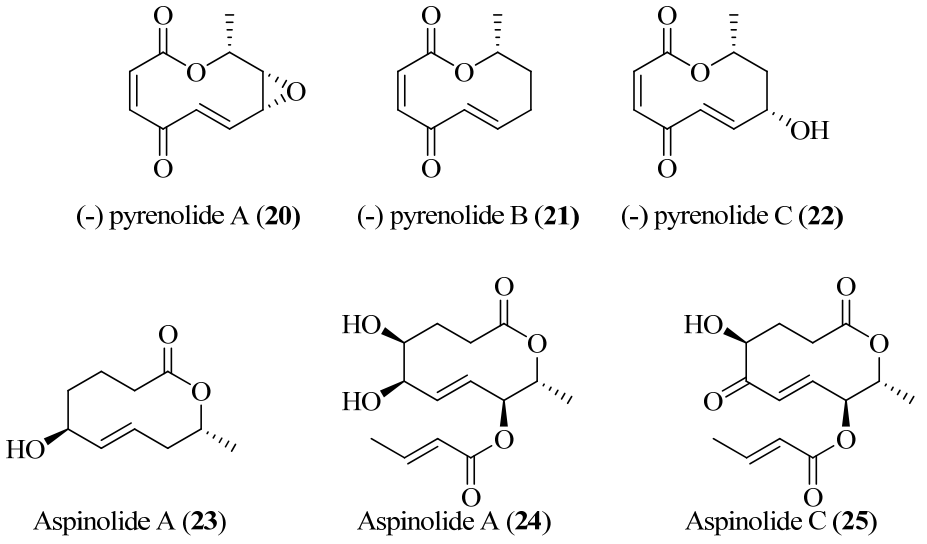
A C6-epimer of decarestrictine C_1 (**9**) was isolated in 2004 from the fungus *Cordyceps militaris* exibited antimalarial activity against *Plasmodium falciparum* K1. The epoxy lactones multiplolides A and B (**18** and **19**), isolated from *Xylaria multiplex*, are also closely related to the decarestrictine family (Figure 2).[13]

Figure 2.



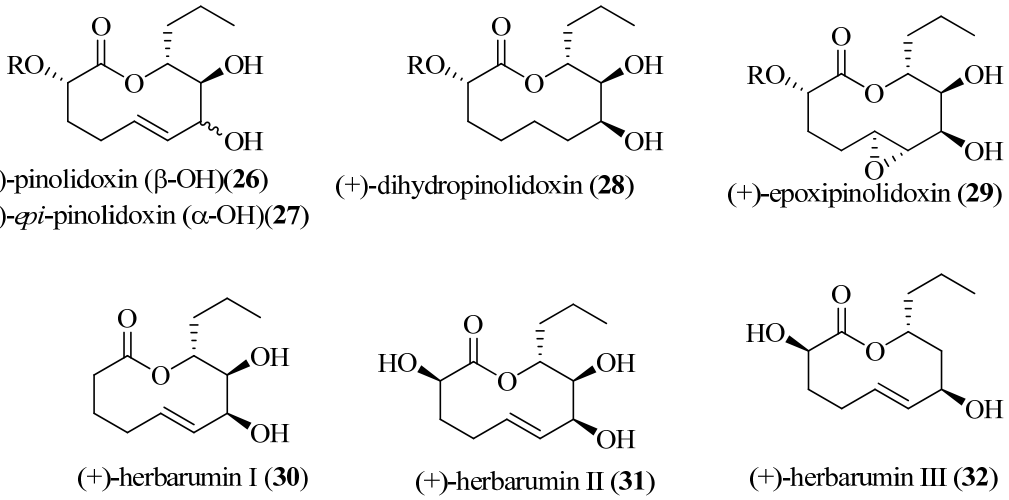
Pyrenolides A, B and C were isolated from *Pyrenophora teres*[14a,b]. Pyrenolide A (**20**) was also detected in the culture filtrates of *Ascochyta hyalospora*[14c]. These highly functionalized unsaturated keto lactones, which differ only by the pattern of oxidation at the C7 and C8 positions, exhibit growth inhibiting and morphogenic activities toward fungi. Aspinolides[15] A–C (**23-25**, Figure 3) were reported to be found in the cultures of *Aspergillus ochraceus* in 1997.

Figure 3.



In 1993, Evidente[16] *et al*. isolated pinolidoxin (**26**), a nonenolide containing an *n*-propyl group at C9, from *Ascochyta pinoda*, as well as three related compounds, namely *epi*-pinolidoxin (**27**), dihydropinolidoxin (**28**) and epoxypinolidoxin (**29**) (Figure 4). Assayed on pea and bean leaves, the first three compounds were shown to be highly toxic, whereas epoxypinolidoxin was inactive. Herbarumin I –III (**30**-**32**)[17], structurally similar to the pinolidoxin were isolated by Rivero-Cruz *et al.* from the different source *Phoma* (*P. herbarum*), and were found to interact with the bovine brain calmodulin, inhibiting the activation of the enzyme cAMP phosphodiesterase.

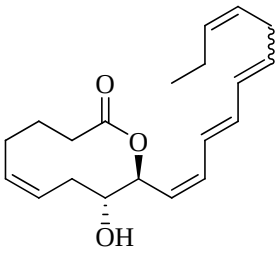
Figure 4.



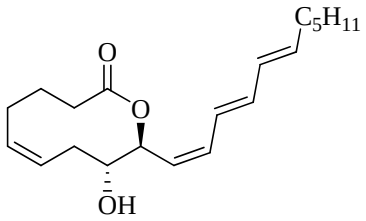
Oxylipins

In general, oxylipins are oxygenated fatty acid metabolites. One of the most biologically important groups of oxylipins in mammalian system is the ecosanoid. These eicosanoids are potent modulators of immune responses in addition to playing a role in numerous basic host physiologic processes.[18] Didemnilactones[19] A and B, and neodidemnilactone, a group of compounds consisting of ten member lactone associated with hydrophilic side chain at the C9 carbon (Figure 5) were isolated in the early 1990s by Niwa et al. These eicosanoid lactones were found in the colonial marine tunicate *Didemnum moseleyi*, and showed moderate inhibitory activity against lipoxygenase.

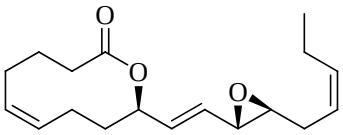
Figure 5.



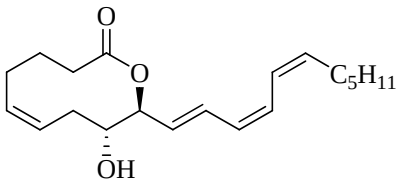
trans (-)- didemnilactone A (**33**)
cis (-)- didemnilactone B (**34**)



(-)-neodidemnilactone (**35**)



(+)-mueggelone (**36**)



(-)-ascidiatrienolide (**37**)

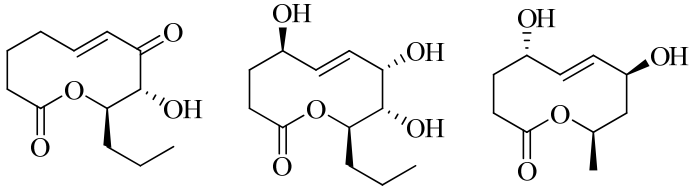
In 1997, an 18-carbon epoxy lactone (**36**) was isolated from the cyanobacterium *Aphanizomenon flos-aquae*. This compound was shown to be an inhibitor of fish development[20a], and was named mueggelone (Figure 5). In the next year, the same lactone **36** was also found in the blue-green alga *Gloeotrichia* sp.[20b], collected in Montana's lakes. Ascidiatrienolides[21a] A–C, isolated in 1989 from the colonial marine ascidian *Didemnum candidum*, was first assigned as being nine-membered-ring lactones. Some years later, however, the structure of ascidiatrienolide A (**37**) was revised to a ten-membered-ring lactone[21b] (Figure 5), isomeric in the side chain with neodidemnilactone (**35**).

Later on a number of bicyclic ten member lactones such as Sch642305[22a], xestodecalactones[22b] A–C, sporostatin[22c], apicularens[22d], nargenicin[22e], coloradocin[22f] with moderate to high complexity were isolated. They are structurally and biologically important addition to the family of nonolide. Almost all of the natural products described here are synthesized and established their structures[23]. It needs to emphasize that numbers of strategy used for macrocyclisation is rather small. These methodologies include are mainly the Corey–Nicolaou[24] and Yamaguchi lactonizations[25] as well as the RCM[26] approach of which RCM is well studied in this concern and presently it is a fascinating task in the field of organic chemistry.

Isolation and structure elucidation of Stagonolide B

Stagonolides[27a] (Figure 6) were isolated in 2007 from the pathogenic fungus *Stagonospora cirsii*, isolated from *Cirsium arvense*. Bioassay guided extraction of solid culture of *Stagonospora cirsii* led to the isolation of stagonolide B (**39**) along with other four metabolites. Interestingly, the major factor stagonolide[27b] (**38**) observed in the liquid culture were absent in solid cultural medium. Being similarity in the ^{1}H and ^{13}C NMR with the previously isolated compound stagonolide (**38**) it has been considered that all were associated with ten member lactones and hence they are named stagonolide B-E.

Figure 6: *Strucrure of Stagonolides.*

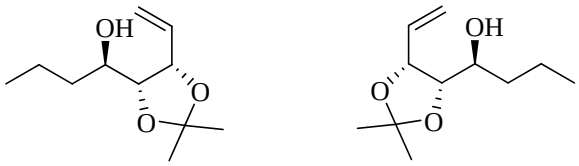


The chemical formula $C_{10}H_{14}O_4$ of stagonolide B was assigned on the basis of RHESIMS. Presence of three degree of unsaturation and lactone carbonyl absorption in IR spectra confirmed the nonenolide structure of stagonolide B. Considering the similarity in ^{1}H and ^{13}C NMR with herbarumins[17], phytotoxic metabolites with potential herbicidal activity isolated from *Phoma herbarum* the connectivity of the free hydroxyl groups were assigned and their relative orientations have been determined, as usual in the case of other natural products on the basis of extensive 2D NMR studies.

Past work on the synthesis of the triol fragment 44a and its enatiomer 44b

Considering similarity of C5-C12 fragment of stagonolide B with that of herbarumins and pinolidoxin, a brief overview regarding the synthesis of the polyhydroxy fragments **44** have been described here.

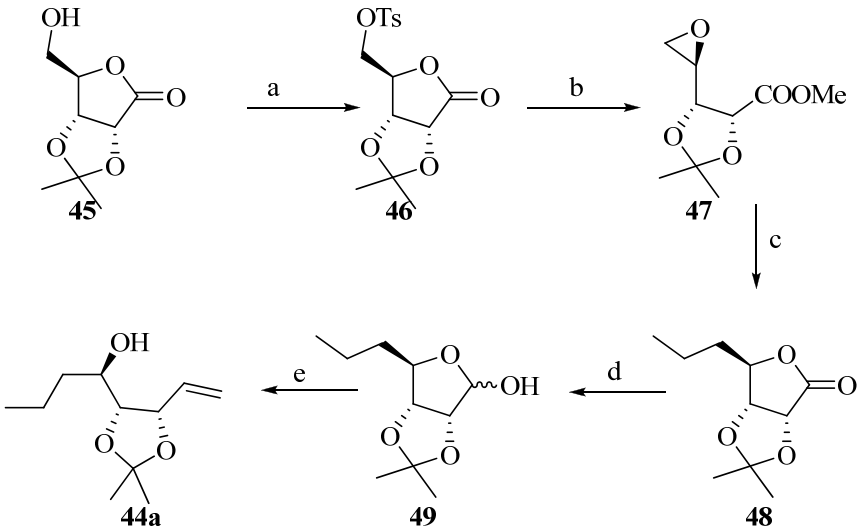
Figure 7.



44a **44b**

First communication[28] describing the synthesis of the densely functionalized fragments **44** was published by Fürstner in 2002 and has been used for the total synthesis of herbarumins. The author based their strategy on the construction of the three stereogenic centeres starting from D-ribonolactone **45** which was converted to its tosyl derivative **46** under standard condition. The lactone **46** was then converted to the epoxide **47** derivative under basic condition using NaOMe. Finally synthesis was completed with subsequent epoxide opening with ethyl grignard followed by DIBAL-H reduction and one carbon homologation. Starting from **45** the overall yield was 17%.

Scheme 1.

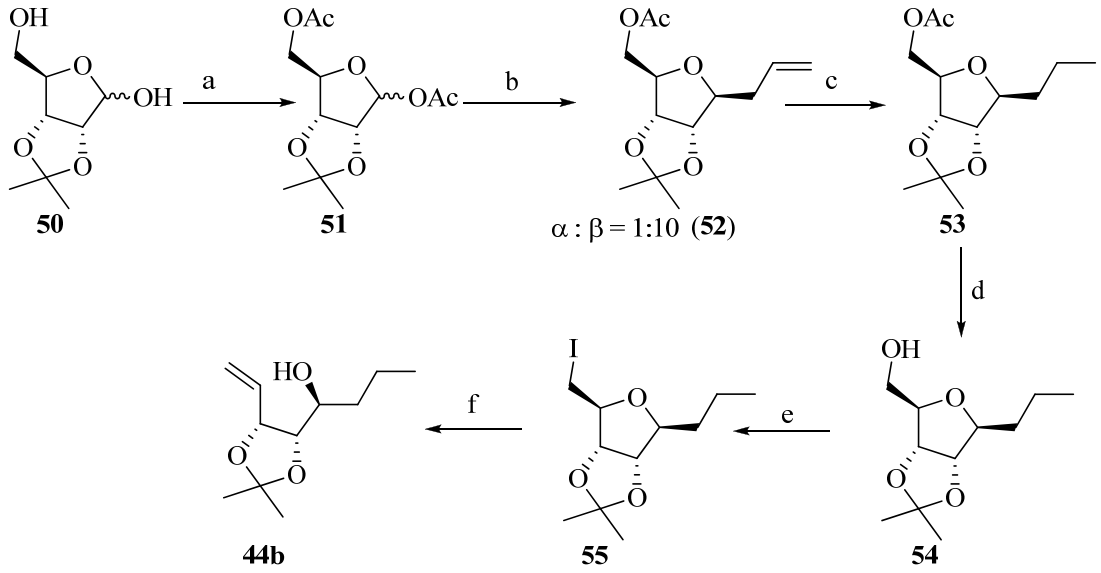


Reagent and condition: (a) Tosyl chloride, pyridine, –25 ^{o}C, 77%. b) NaOMe, THF, 0 ^{o}C to rt, 62%. c) EtMgBr, CuBr·Me_2S, THF, –78 ^{o}C- rt, 60%. d) DIBAL-H, CH_2Cl_2, –78 ^{o}C, 97%. e) $Ph_3P{=}CH_2$, quinuclidine cat., THF, reflux, 62-77%.

The same group also described a synthetic protocol for the enantiomer **44b**. Considering pseudosymmetry present in D-ribose, a *C*-glycosidation using allyl trimethylsilane of the acetate **51** was utilized which produced β isomer **52** as major product. After reducing unsaturation and removing acetate group the primary

hydroxyl group of **54** was converted to iodide **55**. Finally, the furan ring of **55** was opened under reductive β elimination condition to complete the synthesis of the fragment **44a** in overall 40% yield (Scheme 2).

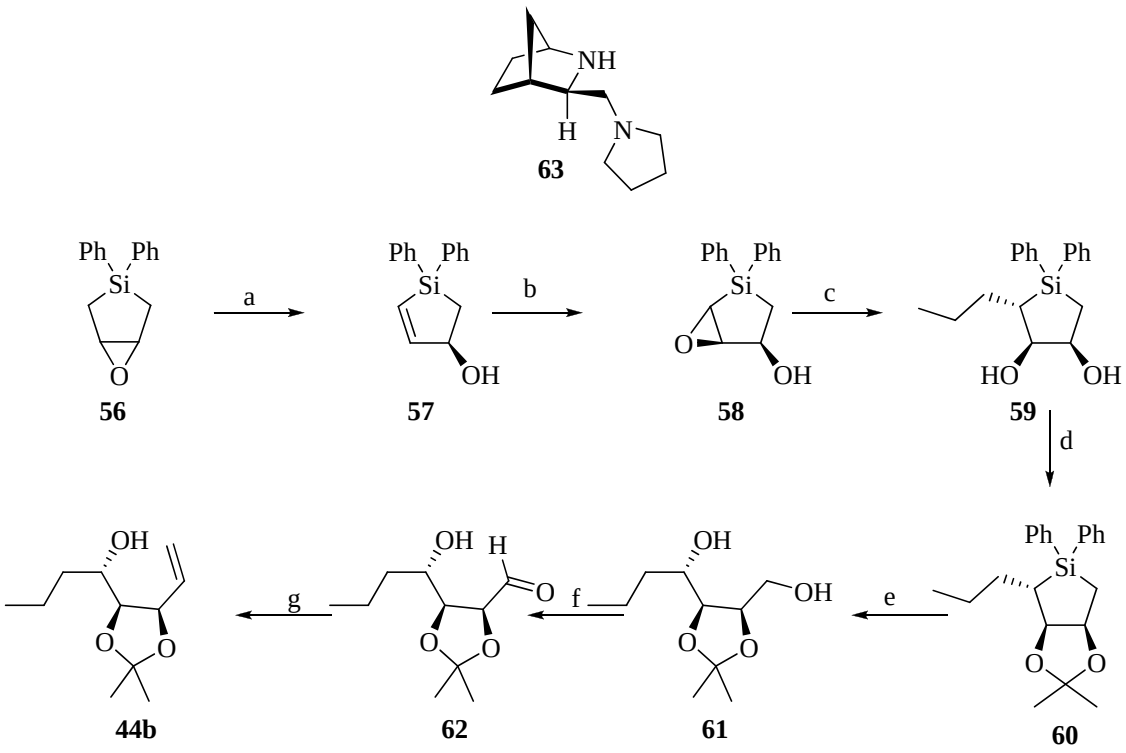
Scheme 2.



Reagent and conditions: (a) Ac_2O, py, rt, 97%. b) allyltrimethylsilane, TMSOTf (0.3 equiv), 0 °C, 63% (α.β =1:10). c) H_2, Pd/C, DCM, quant. d) NaOMe cat., MeOH, rt, 85%. e) I_2, PPh_3, imidazole, DCM, rt, 89%. f) Zn(Ag)– graphite, rt, 86%.

Although lengthy, an innovative synthesis of the fragment **44b** was published by Kozmin[29] *et al.* in 2002. Their strategy began with enantioselective isomerization of **56** using strong base LDA in presence of chiral organoligand **63** under cryogenic condition. The second hydroxyl was installed by applying a sequence of diastereoselctive epoxidation and opening with propyl grignard to afford **58**. After protection of diol **58**, silacyclic scaffold of **60** was removed under oxidative condition. Finally by a sequence of simple and straightforward way they have completed the synthesis of **44b** (Scheme 3), and utilized the same for the total synthesis of herbarumin I and pinolidoxin.

Scheme 3.



Reagents and conditions: (a) 10 mol% 63, LDA, -78, b) m-CPBA, DCM. c) *n*-PrMgBr, CuCN, d) DMP, PPTS. e) *t*-BuOOH, KH, DMF. f) i. TES-Cl, TEA, ii. Swern oxidation. g) i. $Ph_3P=CH_2$, ii. TBAF.

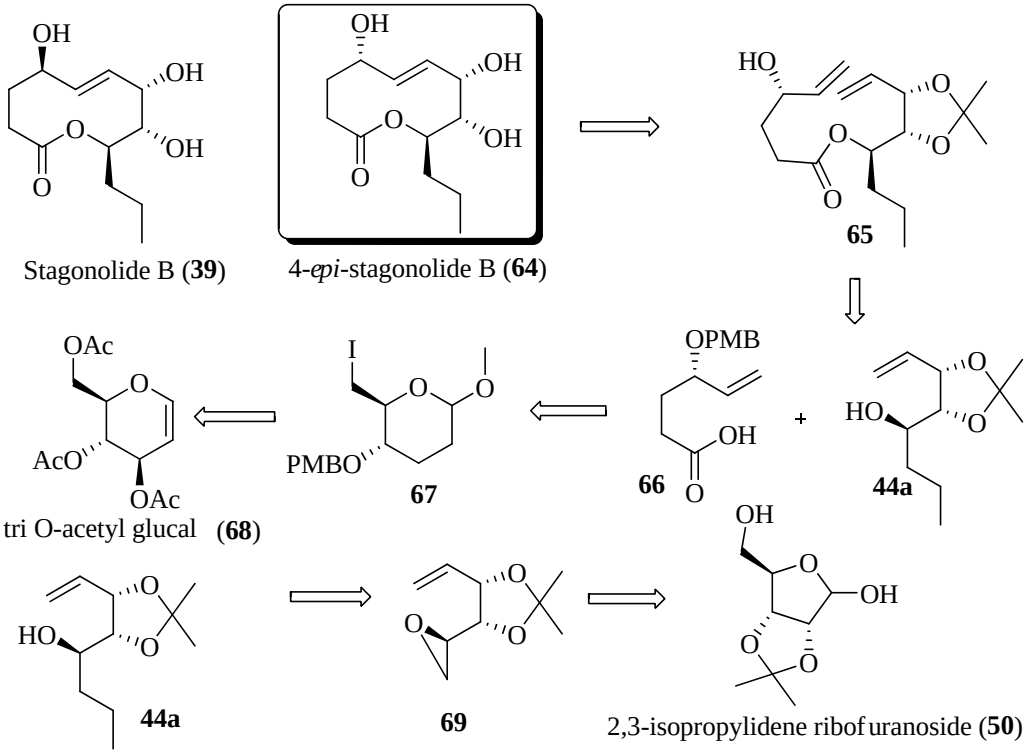
Present Work

Strategy

In continuation[30] of our investigation on RCM reaction in the synthesis of bio-active, macrocyclic natural products, we have selected stagonolide **39** as our target. Stagonolide B consists of several features including the ten member lactone containing a *trans* alkene subunits and a highly oxygenated portions attached with a hydrophobic unit C2-C3. Due to the presence of *trans* double bond at the middle of nonenolide ring, RCM was the inherent method of choice. Although RCM has quickly emerged as a powerful tool[31] for cyclising di olefin through C-C bond formation, and early promises are being realized with the development of new catalyst systems, nevertheless some critical issues such as early prediction of stereochemical out put, effect of functional groups associated with participating double bonds are yet to be solved.[32] Scrutiny of previous results in this direction revealed that extent of bias and its direction is not generalized. Therefore, presently a significant effort has been put forward in this challenging area. Taking into account the difficulty in the prediction of the stereochemical outcome of RCM reaction and the effect of stereochemistry, we have opted to explore the synthesis of both the isomer **39** and **64**. The synthesis of **64** has been described in this section. Our retrosynthetic strategy was totally based on chiral pool approach and has been designed to explore mainly two things. Firstly, exploration of RCM[26] in the synthesis of ten member lactone proceeded after coupling of the acid fragment **66** with the secondary alcohol **44a**. That strategy could serve as common method for accessing both the isomers **39** and **64** and the second issue was to find out the effect of orientation of C4 hydroxy and the protecting group on RCM reaction.

We have intended an efficient protocol for the required acid **66** having single chirogenic center protected as PMB ether starting from inexpensive readily available starting material *tri O*- acetyl glucal[33] **68**. The advanced triol fragment **44a** was planned to furnish from D-ribose after extension of two carbon unit using Grignard protocol at C5 carbon of ribose.

Figure 8: *Retorsynthetic analysis of 4-epi-stagonolideB.*

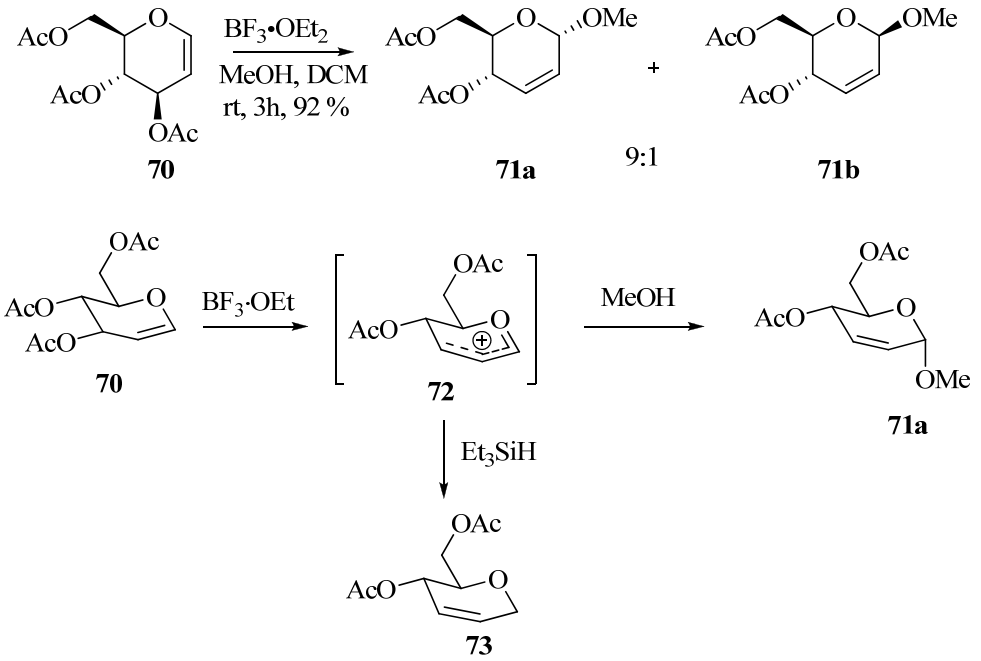


Synthesis of the acid fragment 66

According to our planned strategy, *tri O*- acetyl glucal (**68**) was treated with boron trifluride in presence of methanol 0 ^{o}C and the rearranged product obtained in 92 % yield as an anomeric mixture (α/β 9:1 from ^{1}H NMR). The products obtained in this step were characterized with the help of NMR and compared with literature data. Stereochemical output was assigned on the basis of reported results. This method, known as Ferrier rearrangement, continues to be pinnacle of chemistry of 2,3 unsaturated sugar and one of the common methods for the deoxygenation of sugar templates as it provides valuable intermediate which has been used for synthesis of many natural products and easy access of *tri O*- acetyl glucal[34] from glucose in straight forward ways. From the mechanistic point of view, it involves an SN^{1} with rearrangement of double bond. The reaction proceeds through a delocalized allyloxocarbenium ion **72**. Evidences in favour of delocalized oxocarbenium ion came from the fact that the transient intermediate **72** was trapped with various nucleophiles[35] and reduced with triethylsilane[36] to **73**. The *anti* orientation of C4 acetate with respect to C3 acetate is crucial, because it participates in anchimeric assistance to form **72**. Participation of C4 acetate proved from the fact that the *tri O*-acetyl galactal (C4 epimer of **70**) and 3,4-*di O*-acetyl-L-fucal gives only 1,2-addition

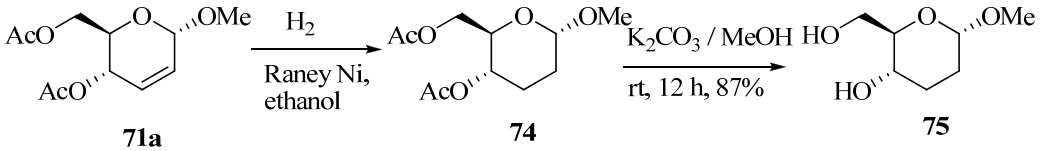
product under the same condition and because of stereoelectronic requirements the method is not applicable universally to all systems.[37]

Scheme 4.



Following, chromatographic purification of **71a**, the unsaturation was removed under hydrogenation condition using freshly prepared Raney Ni in ethanol at 60 *psi* hydrogen pressure at ambient temperature (Scheme 5). Use of palladium, supported on charcoal gave partial deacetylation products along with hydrogenation of double bond. After coloumn purification, the saturated product **74** was characterized fully. The acetates of **74** were removed under basic condition using potassium carbonate in methanol at room temperature and after removing of the solids from reaction mixture the crude product was used directly for next step. The analytical samples of **75** were prepared after coloumn purification. The spectroscopic data and analytical results were superimposed with reported results.[38a]

Scheme 5.



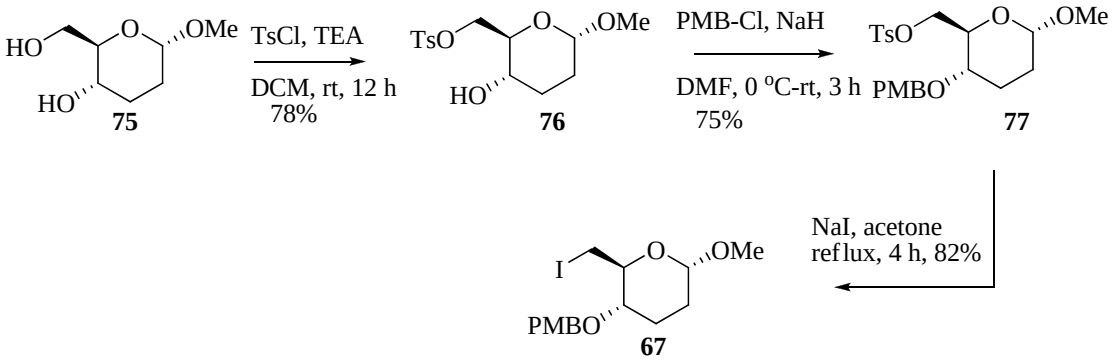
Remembering the target acid **66**, we need to protect the secondary hydroxyl, the required stereocenter at C4 position of target **64** and to do the same, the C6

primary hydroxyl was masked selectively with tosyl chloride in presence of triethyl amine in DCM at room temperature and only the expected product **76** was isolated in 78 % yield (Scheme 6). In ^{1}H NMR the presence of a sharp singlet at δ 2.45 equivalent to three protons assigned to *para* methyl group, two separate doublets with aromatic *ortho* coupling (J = 8.0 Hz) at δ 7.31 & 7.81 equivalent to two proton each and the anisotropic shift of methylene proton of C6 protons confirmed the attachment of tosyl to the compound **76**. This anisotropic shifting was also observed in ^{13}C NMR spectra of **76**. The anomeric carbon resonated at δ 97.35 in ^{13}C NMR. Other signals observed in both ^{1}H and ^{13}C NMR were exactly matching with the compound **76**. This was further supported from mass and elemental analysis. Then the secondary hydroxyl of **77** was protected as PMB ether as adopted in our strategy using PMB-Cl and sodium hydride at rt in dry DMF. The PMB protected compound **77** was isolated as white solid with 75% yield. Another possible side reaction under the same reaction condition is the formation of [4,2,0] bicyclic fused ring through intramolecular nucleophilic substitution.[38b] In the present case, it has been observed that the reaction proceeded through required path that gave only compound **77**. The *trans* fused ring formation is forbidden due to the stetreoelectronic ground and steric constrain created by the six member pyran ring. Presence of PMB group was confirmed from NMR, mass and elemental analysis. In ^{1}H NMR, the diastereotopic benzylic protons of **77** resonated at δ 4.28 & 4.49 as separate doublet associated with very high geminal coupling. Three sharp singlets carrying in ^{1}H NMR at δ 2.42, 3.27 & 3.80 with relative integration three each were assigned to the *para* methyl group of tosyl, anomeric methyl and the methoxy of PMB group respectively. Other peaks present in both the spectrum were according to the structure assigned.

Having successfully synthesized **77** with good overall yield, our subsequent effort concentrated on the crucial reductive elimination (Vasella-Bernet fragmentation). For reductive elimination in order to open pyran ring system with formation of terminal double bond, we have converted the tosyl compound **77** to the iodo **67** using sodium iodide as nucleophile under refluxing condition in dry acetone. With the progress of reaction the initial clear acetone solution became turbid and finally a thick precipitate of sodium salt of toluene sulfonic acid was observed. Simply, filtration and coloumn purification afforded the pure iodo compound **67** in 82% yield (Scheme 6). The incorporation of iodine in compound **67** was confirmed

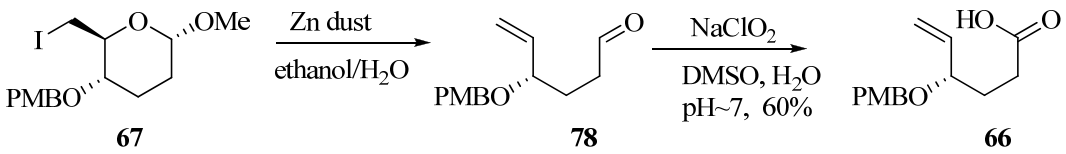
from the result of ESI mass (*m/z* 415.1[M+Na]$^+$) and elemental analysis. The ^{13}C and ^{1}H NMR were in excellent agreement in favour of structure **67**.

Scheme 6.



After successful synthesis of the crucial intermediate **67**, the next step was the Vasella-Bernet fragmentation[39] and it was achieved using activated zinc dust in moist ethanol (95%) under refluxing condition (Scheme 7). Keeping in mind the pessimistic reactivity of aliphatic aldedehyde **78**, it was oxidized by using sodium chlorite without further purification. The aliphatic acid **66** obtained as colourless liquid in 60% yield over two steps. Presence of multiplets ranging from δ 5.20-5.29 integrating of two protons and a fine ddt at δ 5.73 (*J* = 7.6, 9.5 & 17 Hz) equivalent to one proton were due to the terminal double bond present in compound **66**. Two separate doublets at δ 6.86 and 7.22 with aromatic *ortho* coupling (8.7 Hz) were due to the symmetric disubstituted aromatic ring protons of PMB ether. Corresponding olefinic carbons in ^{13}C NMR were observed at δ 117.7 add 138.1. The quaternary carbon of carboxylic acid and highly deshielded aromatic carbon attached with methoxy group appeared at δ 179.2 and 159.0 respectively.

Scheme 7.

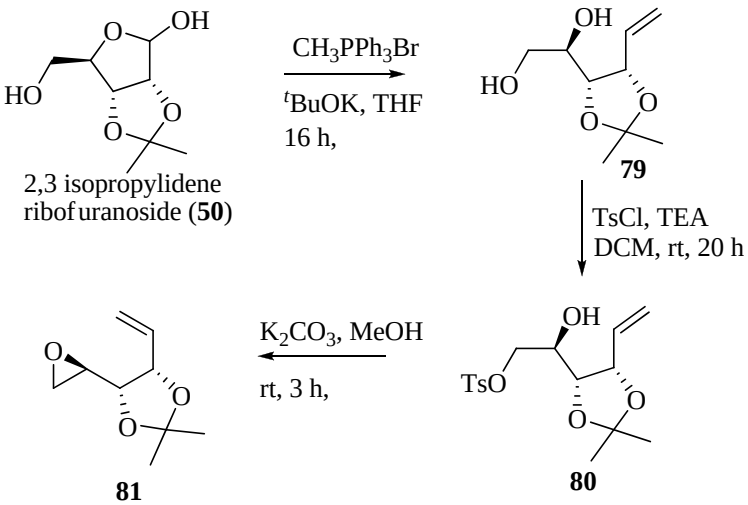


Synthesis of the polyol fragment 44a

Considering the similarity in relative stereochemistry of the alcohol fragment **44a** with that of D-ribose at C2, C3 and C4, we have chosen 2,3-isopropylidene **50** as suitable starting material for the synthesis of alcohol fragment **44a**. Following the reported procedure[40], compound **50** was treated with triphenylphosphonium bromide

in presence of ^{t}BuOK in THF for 16 h and the crude product **79** was used for the next step without column purification. The primary hydroxyl of **79** was converted to a good leaving group as tosic acid ester selectively using tosyl chloride and triethyl amine in DCM at ambient temperature. Tosyl compound **80** was isolated in 62% yield over two steps. The formation of monotosyl compound was confirmed by spectroscopic methods. For instance, in ^{1}H NMR three sharp singlets at δ 1.28, 1.37 and 2.43 were due to the isopropylidene methyls and the methyl group attached with sufonyl aromatic ring. Two separate doublets at δ 7.33 and 7.79 with coupling constant 8 Hz were due to the *para* disubstituted symmetric aromatic ring protons. This compound was further confirmed after converting it to epoxide **81** by using potassium carbonate in methanol. The volatile epoxide **81** isolated in 78% yield as colourless light oil. In ^{1}H NMR the epoxide methylene protons appeared at δ 2.66 (dd, J = 2.6, 5.0 Hz) and 2.81 (dd, J = 3.9, 5.0 Hz) the internal methyne proton resonated at δ 2.94 (ddd, J = 2.6, 3.9, 7.2 Hz). Two singlets of isopropylidene observed at δ 1.36 and 1.50. Corresponding signals due to oxirane ring were found at δ 45.7 (CH_2) and 49.7 (CH). Other peaks in both the spectra were in excellent agreement with the assigned structure.

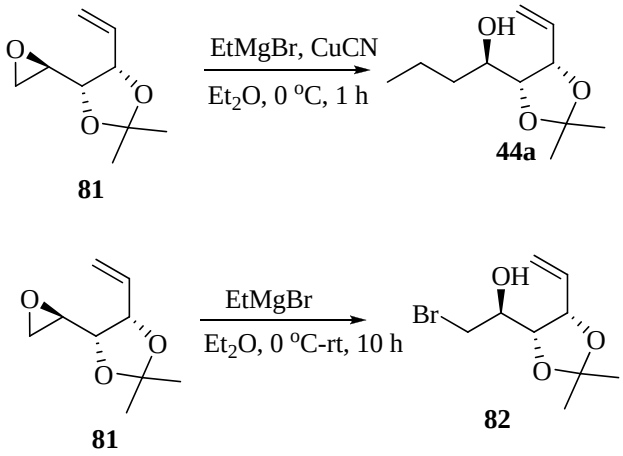
Scheme 8.



Now at this point, time has been set to extend the chain length to complete the synthesis of alcohol fragment **44a**. The high strain of epoxide ring makes them susceptible to nucleophilic reagent. In this concern the reaction of organometallic with epoxide functionality has been studied routinely. Generally, the opening of an unsymmetric oxirane ring results from less hindered side.[41] Organolithium and copper

reagent were used much more frequently. However, since Grignard reagents are an equilibrium mixture of RMgX, R_2Mg, and MgX_2, all of which can react with epoxides, their reactions with substituted epoxides are complicated by various side reactions that often lead to a mixture of products. Considering above discussed properties of grignard reagent, we have decided to use copper (I) cyanide. The addition of the epoxide **81** to a suspension of alkyl cuprate prepared separately with EtMgBr and CuCN in ether afforded the crucial alcohol fragment **44a** (Scheme 9). Under same reaction condition, without CuCN led to the exclusive formation of halohydrin **82** resulted from the opening of epoxide ring from less hindered side by bromide ion. In addition to the overall efficiency of epoxide opening reaction, use of copper cyanide force the reaction in a desired fashion. The bromohydrine **82** was characterized fully with the help of spectroscopic as well as analytical techniques and result was in favour of structure **82**. Presence of strong peak of highest *m/z* at 223.1 $[M+Na]^+$, 239.1 $[M+K]^+$ in ESI mass spectrum and presence of a triplet at δ 0.92 (J = 6.9 Hz) due to the terminal aliphatic methyl group were a clear indication of ethyl incorporation to the epoxide **81**. The terminal olefin protons of **44a** appeared at δ 5.30 (bd, J = 10.1 Hz) and 5.41 (bd, J = 17.1 Hz). A fine ddd at δ 6.03 (J = 7.7, 10.1, 17.1 Hz) were due to the internal double bond proton. Corresponding signals of olefinic carbon observed at δ 118.5 (CH_2) and 134.7 (CH). All the observed data were superimposed with the reported data of the same intermediate used for total synthesis of herbarumin I, published by Fürstner.

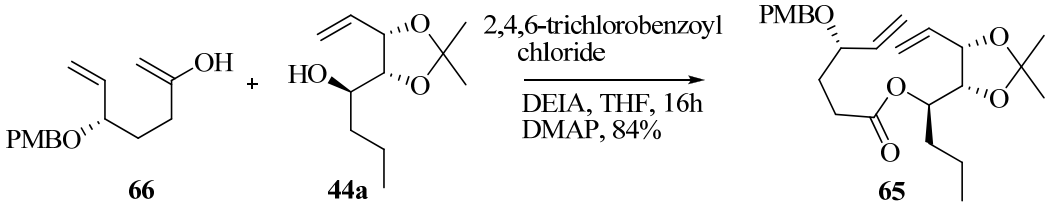
Scheme 9.



After completing the synthesis of crucial intermediates **66** and **44a**, the next task was the coupling between them. Considering the simplicity of the acid fragment

66, initially we tried with common activating reagent such as DCC and EDCI. With DCC in presence of DMAP very low conversion (20%) was observed after 3 days, while EDCI was not able to provide coupling product under standard conditions. These observations led us to shift our attention to Yamaguchi esterification[25] method, because Yamaguchi esterification allows synthesis of highly functionalized esters under mild conditions. After formation of a mixed anhydride between the Yamaguchi reagent (2,4,6-trichlorobenzoyl chloride) and the carboxylic acid **66** and the reaction of the anhydride with an alcohol in presence of a stoichiometric amount of DMAP generated the desired ester **65** in very good yield.

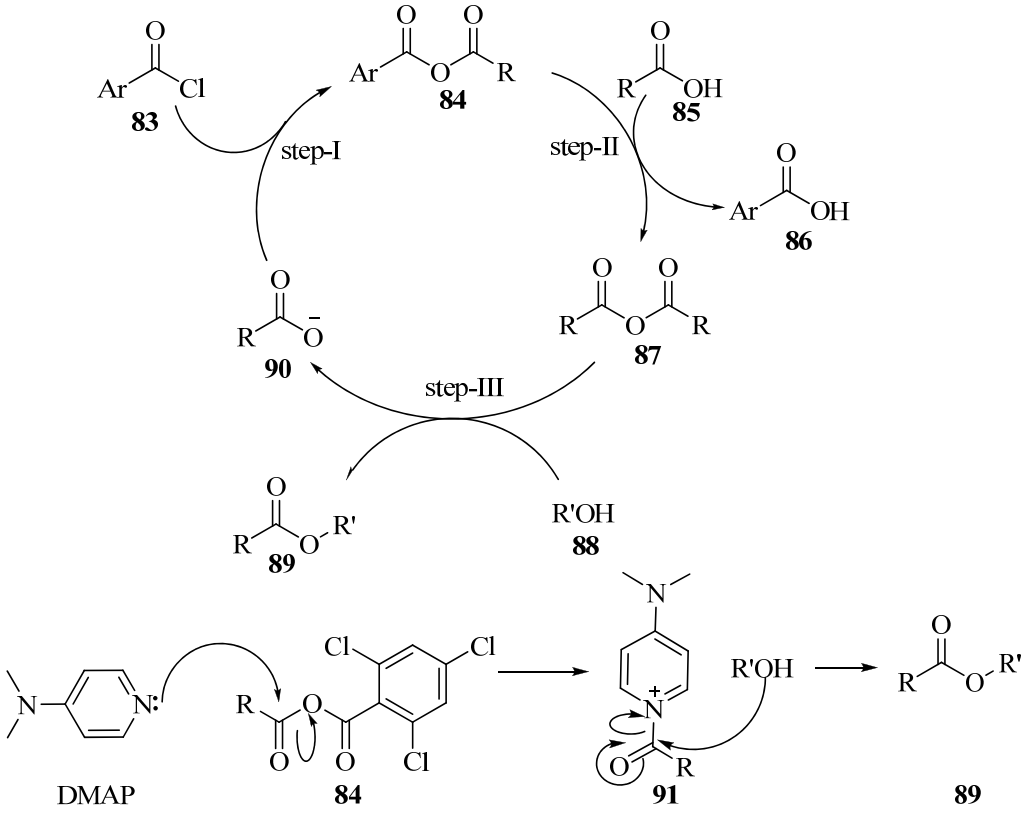
Scheme 10.



66 **44a** **65**

Mechanism of Yamaguchi reagent mediated esterification consists a sequence of steps with initial formation of mixed anhydride **84** (step-I) in presence of mild base. The next step is nucleophilic attack of carboxylic acid to form symmetric anhydride **87** which is the reactive species for desired out come of Yamaguchi esterification in case of aliphatic acid and absence of DMAP (step-III). But in presence of DMAP the picture is quite different. It participate in step-II and III as DMAP is better nucleophile than participating alcoholic OH group and increase the electrophilicity of acyl carbon, hence acts as good acyl transferring reagent in the catalytic cyclic.[42] The regioselectivity of mixed anhydrides is due to inaccessibility of the aromatic domain for steric reasons to nucleophiles. Because of mild reaction condition and simplicity from the practical point of view, the method has become a familiar tool in the field of organic synthesis and is highlighted the reaction many times in the synthesis of complex natural products.

Scheme 11:



In ^{1}H NMR spectrum of compound **65**, the characteristic four terminal olefin protons appeared as multipletes ranging from δ 5.17-5.34 while the internal protons resonated at δ 5.83-5.88 as multiplet. The alkoxy CH proton appeared at δ 4.91 (dt, *J* = 3.8, 7.4 Hz). The carbon of the terminal olefin methylenes, ester carbonyl carbons appeared in ^{13}C NMR at δ 117.6, 119.3 and 172.4 respectively. All other protons and carbons in NMR spectra appeared with their respective chemical shifts, thereby confirming the structure of ester **65**. The structure of **65** was further supported from ESI mass and elemental analysis.

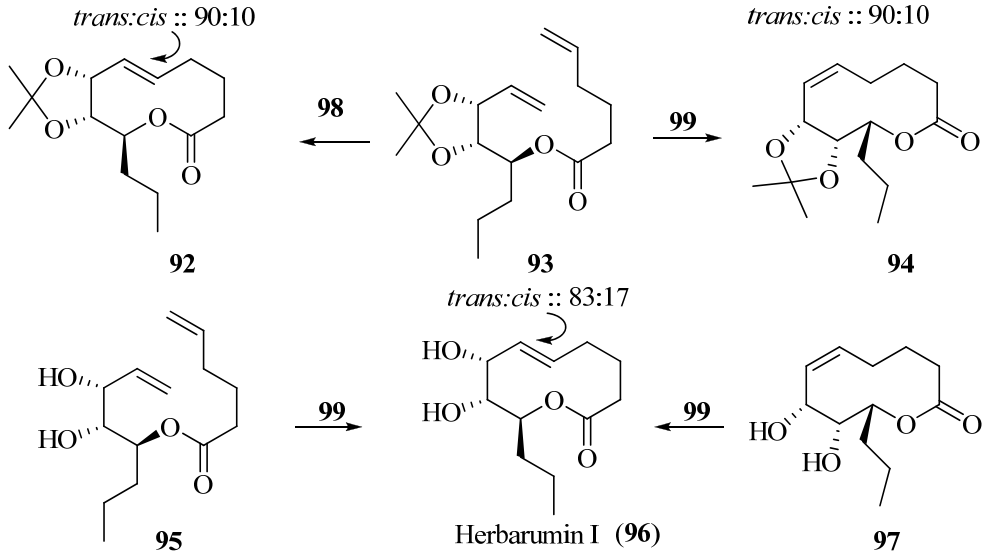
Conformational analysis and thermodynamic reversibility in RCM

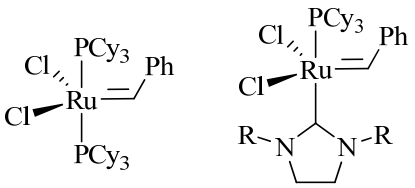
One of the serious restrictions which make the successful synthesis of ten member lactones rather limited is the thermodynamic reversibility. Ring strain force the cycloalkene for reverse process, for ring opening metathesis or ring opening metathesis polymerization. Clear-cut evidences for reversible nature of RCM published by Kozmin[29] *et al.* and solve the puzzle of stereochemical output of the newly formed double bond in the synthesis of herbarumin I (**96**). The diene **93** in presence of highly active Grubbs 2nd generation catalyst produced *cis* isomer as major

product while sterochemical orientation of double bond was *trans* when 1st generation catalyst was used. The *cis* selectivity in the case of catalyst **99** was apparent from the results based on semiempirical calculation of lowest energy conformer of *trans* and *cis* isomers. It has been revealed that lactone **92** containing *trans* double bond was higher in energy by 2.7 kcal mol^{-1}. Interestingly, removal of conformational constrain imposed by acetonide ring make the system in different order of stability. The *trans* isomer of the deprotected cycloalkene **96** is more stable by 1.2 kcal mol^{-1}. Therefore, *trans* isomer should be the RCM product under thermodynamic control condition. The prediction has been proved experimentally and it has been observed that *trans* alkene formed as major product along with 17 % *cis* isomer using Grubbs 2nd gen. catalyst. As it was expected, treatment of the diol containing *cis* alkene **97** under same conditions resulted in formation of the two isomers in the same ratio, providing unambiguous support for the reversible nature of this ring opening metathesis.

Although the conformational constrain in RCM precursor predispose the reacting center in a suitable orientation, their bias in the stereochemical output is not obvious and can not be predicted certainly. In general, there are no general and reliable methods for controlling the newly formed double bond. On the basis of higher reactivity of second generation ruthenium carbene complexes and the product stability consideration based on semiempirical calculations preliminarily help in choosing metathesis catalysts for getting required geometry.

Scheme 12.



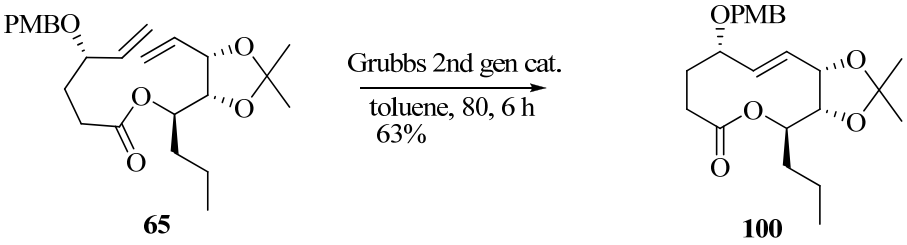


98 **99**

Ring closing metathesis of 65

Keeping in mind of the results obtained in RCM reactions in the cases of herbarumin I (**96**) and pinolidoxin (**26),**[28,29] we selected the ruthenium complex **99** as the catalyst of choice for the proposed RCM of **65**. Our initial attempt of RCM on substrate **65** using catalyst **99** in DCM or toluene at rt met with complete recovery of starting material after 12 h. Gratifyingly, treatment with second generation Grubbs catalyst in toluene at 80 ^{o}C gave the desired *trans* isomer **100** exclusively. Presence of *trans* double bond was evident from ^{1}H NMR, showing signals at δ 5.66 (ddd, *J* =1.6, 8.3, 15.9 Hz) and 5.84 (*J* =3.1, 15.9 Hz). The large coupling constant 15.9 Hz is typical value for *trans* protons of C-C double bond. The acetonide methyl groups appeared at δ 1.39 and 1.55 as sharp singlet. The benzylic methylene attached at C4 oxygen appeared as two separate doublets with high geminal coupling at δ 4.27 (*J* =11.5 Hz), 4.56 (*J* =11.5 Hz). The quaternary carbon of lactone resonated at δ 174.9 in ^{13}C NMR. Other observations were according to the assigned structure.

Scheme 13.

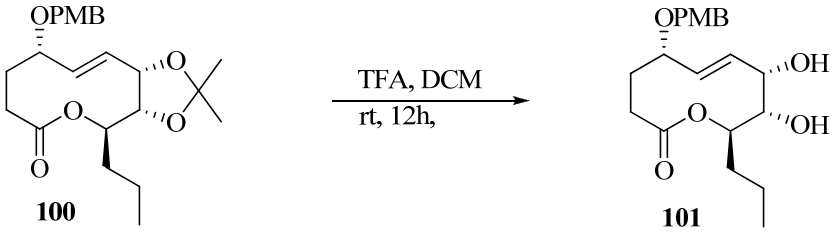


65 **100**

Finally to complete our primary target **64**, the next synthetic step was the one pot global deprotection. Considering the labile nature of both acetonide and PMB ether under acidic condition, the compound **100** was treated with 10% TFA in DCM at ambient temperature. Under above conditions, after disappearance of the starting within 12 h, (monitored by TLC) led to the isolation of compound **101**, resulting from the selective removal of acetonide of **100**. The compound **101** was confirmed by ^{1}H, ^{13}C NMR other analytical techniques. In ESI mass a strong peak at *m/z* 428.5 (100%) were due to the sodiated molecular ion peak. The stretching frequency of carbonyl

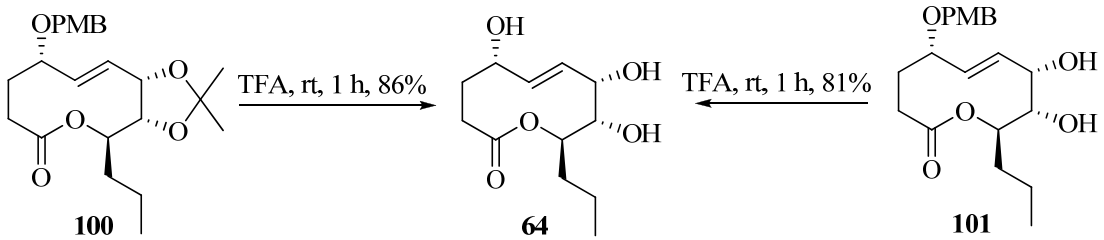
carbon of lactone observed at 1725 cm^{-1} in IR spectrum. The singlets due to the acetonide methyl group was absent in ^1H NMR. The diastereotopic methylene protons of PMB ether in ^1H NMR appeared at δ 4.28 (d, *J* =11.5 Hz) and 4.52 (d, *J* = 11.5 Hz). The symmetric disubstituted aromatic protons resonated at δ 6.68 (d, *J* = 8.5 Hz) and 7.22 (d, *J* = 8.5 Hz).

Scheme 14.

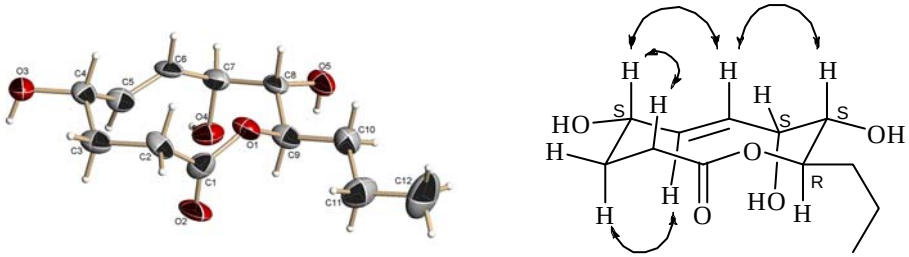


To achieve a one pot deprotection, the compound **100** was treated with neat TFA for 1 h at 0 ^oC and compound **64** obtained as crystalline solid in 86% isolated yield. As it was expected, the spectroscopic data and analytical results of **64** were significantly different from that of natural product stagonolide B (**39**). The ^1H NMR, ^{13}C NMR spectra, elemental analysis COSY and NOESY experiments confirmed the assigned structure **64**. For instance, in the ^1H NMR spectrum, the C12-Me resonated as a triplet at δ 0.91 (*J* = 7.3 Hz). The C5 olefin appeared at δ 5.49 (ddd, *J* = 2.2, 9.3, 15.7 Hz) whereas the C6 proton resonated at δ 5.77 (dd, *J* = 2.2, 15.7 Hz). The presence of a fine ddd (*J* = 4.6, 9.6, 10.4 Hz) at δ 4.05 and a dd at δ 4.38 (*J* = 2.2, 4.4 Hz) were assigned to the C4 and C7 protons. The diastereotopic protons C2 appeared separately at δ 2.27 (ddd, *J* = 2.4, 6.3, 13.7 Hz) and 2.03 (ddd, *J* = 1.9, 13.7 Hz). In ^1H NMR, the clear doublet of a triplet at δ 5.13 (J= 2.4, 9.3 Hz) was due to the C9 proton. Other resonances were fully in agreement with the assigned structure **64**. The stereochemical assignment was further supported from NOESY (Figure 9). The assignment of relative stereochemistry at C4, C7, C8 and C9 centers of (**64**) was further determined based on single crystal *X*-ray crystallographic studies. Considering the absolute stereochemistry of starting materials (**50** and **70**) and the careful examination of all the data obtained from the compound **64**, the absolute stereochemistry of **64** was assigned as shwn in figure 9. The ORTEP diagram of **64** (Figure 9) supported NOE assignment. The details of crystal data are given with other spectroscopic data in experimental section.

Scheme 15.



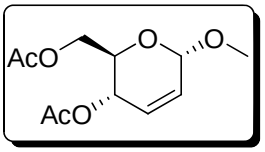
Figgure 9: *ORTEP diagram of compound* **64** *and selective NOE interactions.*



In conclusion, we have synthesized the 4-*epi*-stagonolide in a convergent and chiral pool approach starting from inexpensive, easily available D-glucal and D-ribose in a straight forward way using ring closing metathesis as the key reaction. The synthesis of natural isomer **39** is under progress in our laboratory.

Experimental

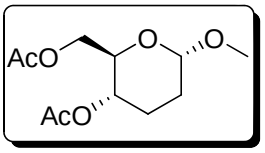
Methyl 4,6-di-*O*-acetyl-2,3-dideoxy-α-D-erythro-hex-2-enopyranoside (71a)



To a stirred solution of tri-*O* acetyl glucal **70** (10.00 g, 36.73 mmol) in dry DCM (150 mL) a mixture of methanol (7.4 mL, 183.65 mmol) and freshly distilled $BF_3 \cdot Et_2O$ (6.2 mL, 47.75 mmol) were added by syringe at 0 ^oC over 10 min and the whole mixture was stirred for another 3 h at the same temperature under dry and argon atmosphere. Then the mixture was diluted with DCM and washed with aqueous sodium bicarbonate solution followed by fresh water. The organic extract was collected and dried over anhydrous sodium sulfate. The volatiles were removed on a rotary evaporator under vacuum affording the crude product as syrup. The residue thus obtained was purified further by flash column chromatography (P.E–ethyl acetate) to afford **71a** (8.25 g, 92%) as 9:1 mixture of the α and β methyl glucosides.

Mol. Formula	: $C_{11}H_{16}O_6$
^{1}H NMR (200 MHz, $CDCl_3$)	:δ 2.06 (s, 3H), 2.08 (s, 3H), 3.42 (s, 3H), 4.04 (ddd, *J* = 2.7, 5.0, 9.3 Hz, 1H), 4.17-4.22 (m, 2H), 4.90 (t, *J* = 1.6 Hz, 1H), 5.29 (ddd, *J* = 1.6, 2.7, 9.6 Hz, 1H), 5.81-585 (m, 2H) ppm.
^{13}C NMR (50 MHz, $CDCl_3$)	: δ 20.7 (q), 20.9 (q), 55.9 (q), 62.9 (t), 65.2 (d), 66.8 (d), 95.4 (d), 127.6 (d), 129.2 (d), 170.2 (s), 170.7 (s) ppm.
Elemental Analysis	Calcd.: C, 54.09; H, 6.60 % Found: C, 53.91; H, 6.65 %

Methyl 4,6-di-*O*-acetyl-2,3-dideoxy-α-D-erythro-hexpyranoside (74)



A solution of **71a** (8.05 g, 32.95 mmol) in 40 mL of ethyl alcohol was hydrogenated in the presence of Raney-Ni for 2 h under 60 psi at rt. The catalyst was removed by filtration and the solvent was evaporated under reduced pressure. The residue was purified by flash column chromatography (P.E-ethyl acetate) to

afford **74** (7.95 g, 32.3 mmol) in 98 % yield as a 9:1 mixture (from ^{1}H NMR) of the α and β methyl glucosides.

Mol. Formula : $C_{11}H_{18}O_6$

$[\alpha]_D^{25}$: +121.6 (*c* = 1.1, $CHCl_3$)

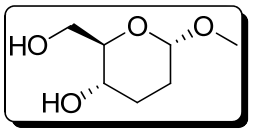
IR ($CHCl_3$) υ : 924, 958, 975, 998, 1053, 1087, 1239, 1370, 1440, 1741, 2835, 2902, 2950 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$) : δ 1.77 (m, 3H), 1.93-1.97 (m, 1H), 2.01 (s, 3H), 2.06 (s, 3H), 3.36 (s, 3H), 3.87 (ddd, *J* = 2.1, 5.1, 9.8 Hz, 1H) , 4.07 (dd, *J* = 2.0, 11.8 Hz, 1H), 4.23, (dd, *J* = 5.1, 11.8 Hz, 1H), 4.68-4.72 (m, 2H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$) : δ 20.8 (q), 21.0 (q), 23.8 (t), 28.6 (t), 54.6 (q), 63.1 (t), 67.7 (d), 68.4 (d), 97.5 (d), 170.0 (s), 170.8 (s) ppm.

Elemental Analysis Calcd.: C, 53.65; H, 7.37
Found: C, 53.41; H, 7.42

(2*R*,3*S*,6*R*)-2-(Hydroxymethyl)-6-methoxytetrahydro-2H-pyran-3-ol (75)



To a solution of diacetate **74** (7.58 g, 30.78 mmol) in methanol (50 mL), solid K_2CO_3 (25.48 g, 184.68 mmol) was added and stirred at rt for 12 h. After completion of reaction solids were filtered off and the filtrate was concentrated under reduced pressure to get pasty solid which was then diluted with water and extracted with ethyl acetate. The whole organic layer was collected, dried and concentrated to get crude diol **75**. The crude materials were further purified by coloumn chromatography using PE-ethyl acetate to get **75** as highly viscous liquid (4.34 g, 87 %).

Mol. Formula : $C_7H_{14}O_4$

$[\alpha]_D^{25}$: +119.9 (*c* = 1.0, CH_3OH)

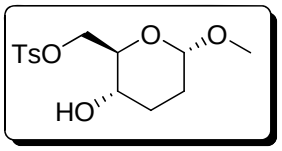
IR ($CHCl_3$) υ : 946, 976, 1001, 1047, 1128, 1208, 1371, 1443, 1651, 2940, 3410 (b) cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) : δ 1.72-1.80 (m, 2H), 1.82-1.90 (m, 2H), 2.37 (bs, 2H), 3.36 (s, 3H), 3.53 (dt, *J* = 4.0, 9.3 Hz, 1H), 3.60 (dt, *J* = 4.6, 9.9 Hz, 1H), 3.79 (dd, *J* = 4.0, 11.5 Hz, 1H), 3.83 (dd, *J* = 4.0, 11.5 Hz, 1H), 4.68 (bd, *J* = 2.7 Hz, 1H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$) : δ 26.5 (t), 28.9 (t), 54.2 (q), 62.2 (t), 66.1 (d), 72.9 (d), 97.2 (d) ppm.

Elemental Analysis Calcd.: C, 51.84; H, 8.70
Found: C, 51.65; H, 8.61

((2*R*,3*S*,6*R*)-3-Hydroxy-6-methoxytetrahydro-2H-pyran-2-yl)methyl 4-methylbenzenesulfonate (76)



To a stirred solution of diol **75** (4.23 g, 26.08 mmol) in dry DCM (90 mL), *p*-toluene sulfonyl chloride (5.96 g, 31.29 mmol) was added followed by triethyl amine (12.63 mL, 91.28 mmol) and catalytic amount of DMAP (100 mg). The mixture was stirred for overnight at rt. After complition of starting (monitored by TLC), the reaction mixture was diluted with DCM and washed with fresh water. The organic layer was collected, dried and concentrated under reduced pressure. Hence the crude product obtained was subjected to column purification to get pure mono tosyl compound **76** (6.43 g, 78%).

Mol. Formula : $C_{14}H_{20}O_6S$

$[\alpha]_D^{25}$: +65.8 (*c* = 0.6, $CHCl_3$)

IR ($CHCl_3$) υ : 730, 790, 815, 881, 947, 1055, 1097, 1130, 1175, 1189, 1359, 1448, 1598, 2835, 2902, 2941, 3522 cm^{-1}.

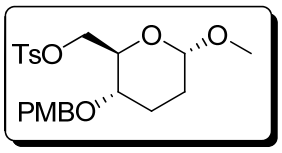
^{1}H NMR (200 MHz, $CDCl_3$) : δ 1.70-1.82 (m, 3H), 1.87-1.90 (m, 1H), 2.37 (bs, 1H), 2.45 (s, 3H), 3.29 (s, 3H), 3.58 (dt, *J* = 4.9, 9.6 Hz, 1H), 3.65 (ddd, *J* = 1.9, 4.4, 9.6 Hz, 1H), 4.21 (dd, *J* = 1.9, 11.0 Hz, 1H), 4.36 (dd, *J* = 4.4, 11.0 Hz, 1H), 4.63 (d, *J* = 2.4 Hz, 1H), 7.31 (d, *J* = 8.0 Hz, 2H), 7.81 (d, *J* = 8.0 Hz, 2H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$) : δ 21.6 (q), 27.0 (t), 28.9 (t), 54.5 (q), 65.4 (d), 69.7 (t), 71.4 (d), 97.4 (d), 127.9 (d), 129.8 (d), 132.8 (s), 144.8 (s) ppm.

ESI-MS (*m/z*) : 339.1 $[M+Na]^+$.

Elemental Analysis Calcd.: C, 53.15; H, 6.37; S, 10.14
Found: C, 52.85; H, 6.47; S, 9.83

((2*R*,3*S*,6*R*)-6-Methoxy-3-(4-methoxybenzyloxy)tetrahydro-2H-pyran-2-yl)methyl 4-methylbenzenesulfonate (77)



Sodium hydride (1.24 g, 31.10 mmol; 60% suspension in oil) was added to an ice cold solution of compound **76** (6.15 g, 19.43 mmol) in dry DMF (40 mL) under argon atmosphere. The mixture was then stirred for 30 min at the same temperature. To this solution *p*-methoxy benzyl chloride (4 mL, 29.75 mmol) was added at 0 ^{o}C and the mixture was stirred for another 3 h at rt. The reaction was monitored by TLC and after quenching with cold water it was diluted with ethyl acetate and washed with water. The organic extract was collected, dried and concentrated under reduced pressure. The crude product thus obtained was further purified by column chromatography using silica gel and ethyl acetate-P.E mixed solvent to afford compound **77** as fresh white solid (6.36 g, 75 %).

Mol. Formula : $C_{22}H_{28}O_7S$

M. P. : 76 ^{o}C

$[\alpha]_D^{25}$: + 84.1 (*c* = 0.4, $CHCl_3$)

IR ($CHCl_3$) υ : 811, 822, 884, 937, 959, 1047, 1132, 1179, 1252, 1357, 1446, 1514, 1585, 1612 cm^{-1}.

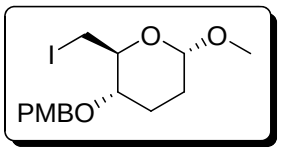
^{1}H NMR (200 MHz, $CDCl_3$) : δ 1.60-1.83 (m, 3H), 1.98-2.04 (m, 1H), 2.42 (s, 3H), 3.27 (s, 3H), 3.29-3.44 (m, 1H), 3.70-3.80 (m, 1H), 3.80 (s, 3H), 4.19 (dd, *J* = 2.1, 10.3 Hz, 1H), 4.29 (dd, *J* = 4.4, 10.3 Hz, 1H), 4.28 (d, *J* = 11.0 Hz, 1H), 4.49 (d, *J* = 11.0 Hz, 1H), 4.60 (d, *J* = 2.6 Hz, 1H), 6.85 (d, *J* = 8.6 Hz, 2H), 7.16 (d, *J* = 8.6 Hz, 2H) , 7.30 (d, *J* = 8.1 Hz, 2H), 7.79 (d, *J* = 8.1 Hz, 2H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$) δ 21.5 (q), 23.5 (t), 28.5 (t), 54.4 (q), 55.2 (q), 69.6 (t), 70.1 (t), 71.9 (d), 97.3 (d), 113.7 (d), 113.8 (d), 127.9 (d), 129.2 (d), 129.6 (d), 130.1 (s), 133.1 (s), 144.5 (s), 159.2 (s) ppm.

ESI-MS (*m/z*) : 437.3 $[M+H]^+$, 459.2 $[M+Na]^+$.

Elemental Analysis Calcd.: C, 60.53; H, 6.47; S, 7.35 %
Found: C, 60.35; H, 6.36; S, 7.01 %

(2*S*,3*S*,6*R*)-2-(Iodomethyl)-6-methoxy-3-(4-methoxybenzyloxy)tetrahydro-2H-pyran (67)



A mixture of compound **77** (5.95 g, 13.63 mmol) and sodium iodide (10.22 g, 68.15 mmol) in dry acetone (30 mL) was refluxed for 4 h. As the reaction progress, the initial clear solution became turbid and finally a heavy precipitate of sodium chloride was observed. Solids were filtered off and the filtrate was concentrated under reduced pressure. A column purification of crude material gave pure iodocompound **67** (4.38 g, 82%) as light yellow liquid**.**

Mol. Formula : $C_{15}H_{21}IO_4$

$[\alpha]_D^{25}$: +114.6 (*c* = 1.20, $CHCl_3$)

IR ($CHCl_3$) υ : 820, 943, 1056, 1095, 1128, 1249, 1302, 1371, 1440, 1313, 1586, 1612, 2834, 2899, 2934, 2995 cm^{-1}.

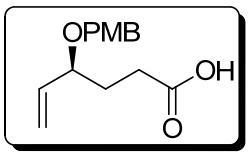
^{1}H NMR (200 MHz, $CDCl_3$) :δ 1.66-1.91 (m, 3H), 1.96-2.05 (m, 1H), 3.18-3.59 (m, 4H), 3.40 (s, 3H), 3.80 (s, 3H), 4.40 (d, *J* = 11.0 Hz, 1H), 4.59 (d, *J* = 11.0 Hz, 1H), 4.70 (d, *J* = 2.7 Hz, 1H), 6.88 (d, *J* = 8.7 Hz, 2H), 7.23 (d, *J* = 8.7 Hz, 2H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$) : δ 9.0 (t), 23.5 (t), 29.0 (t), 54.7 (q), 55.2 (q), 70.3 (t), 70.7 (d), 76.7 (d), 97.7 (d), 113.8 (d), 129.4 (d), 130.2 (s), 159.3 (s) ppm.

ESI-MS (*m/z*) : 415.1 $[M+Na]^+$.

Elemental Analysis Calcd.: C, 45.93; H, 5.40; I, 32.35 %
Found: C, 45.82; H, 5.41; I, 32.03 %

(*S*)-4-(4-Methoxybenzyloxy)hex-5-enoic acid (66)



To a solution of iodocompound **67** (2.13 g, 5.43 mmol) in ethanol (20 mL) was added freshly activated zinc dust (3.52 g, 54.3 mmol) and was refluxed for 1 h. Then solids were filtered off and the filtrate was diluted with water finally extracted with diethyl ether. The organic layer was collected, washed with fresh water and evaporated under reduced pressure to get crude aldehyde **78**.

To a solution aldehyde 78 in 10 mL DMSO sodium chlorite (2.05 g, 16.2 mmol) and phosphate buffer (10 mL, pH 7) were added and the resulting mixture was stirred at rt for 10 h. Then the reaction mixture was diluted with water and extracted with ethyl acetate. The organic extract was collected, dried and concentrated. Finally the resulting residue was purified by column chromatography to get pure acid **66** (820 mg, 60%).

Mol. Formula : $C_{14}H_{18}O_4$

$[\alpha]_D^{25}$: –39.9 (*c* = 1.2, $CHCl_3$)

IR ($CHCl_3$) υ : 757, 821, 930, 1035, 1070, 1173, 1248, 1302, 1422, 1513, 1613, 1708, 3076 (b) cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$) : δ 1.81-1.97 (m, 2H), 2.44 (t, *J* = 7.3 Hz, 2H), 3.73-3.84 (m, 1H), 3.79 (m, 3H), 4.27 (d, *J* = 11.5 Hz, 1H), 4.53 (d, *J* = 11.5 Hz, 1H), 5.20-5.29 (m, 2H), 5.65-5.82 (m, 1H), 6.86 (d, *J* = 8.6 Hz, 2H), 7.24 (d, *J* = 8.6 Hz, 2H) ppm.

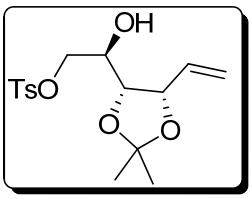
^{13}C NMR (50 MHz, $CDCl_3$) : δ 30.0 (t), 30.1 (t), 55.2 (q), 69.8 (t), 78.8 (d), 113.8 (d), 117.7 (t), 129.4 (d), 130.4 (s), 138.1 (d), 159.1 (s), 179.29 (s) ppm.

ESI-MS (*m/z*) : 273.1 $[M+H]^+$, 289.1 $[M+Na]^+$.

Elemental Analysis Calcd.: C, 67.18; H, 7.25 %

Found: C, 66.86; H, 7.17 %

(*R*)-2-((4*R*,5*S*)-2,2-Dimethyl-5-vinyl-1,3-dioxolan-4-yl)-2-hydroxyethyl 4-methylbenzenesulfonate (80)



To a stirred suspension of methyltriphenylphosphonium bromide (55.75g, 156 mmol) in dry THF (350 mL) at 0 ^oC KO^{t}Bu (19.29 g, 172 mmol) was added under argon atmosphere and stirred for 30 min. at same temperature. Then a solution of compound **50** (10.23 g, 53 mmol) dissolving in THF (30 mL) was added and stirred for 16 h. After completion of reaction (monitored by TLC), the mixture was diluted and partitioned. The aqueous layer was thoroughly washed. The organic extracts were collected dried over Na_2SO_4 and concentrated under reduced pressure. The crude material thus obtained was dissolved in dry DCM (150 mL) and treated

with TsCl (10.25 g, 53.7 mmol) in presence of TEA (22.3 mL, 161 mmol) at 0 ^{o}C for 10 h. Then reaction mixture was diluted with water and partitioned. The organic layer was washed with water, dried and concentrated under reduced pressure. the crude material thus obtained was subjected to column purification to afford **80** (11.41 g, 62%) as light yellow liquid.

Mol. Formula : $C_{16}H_{22}O_6S$

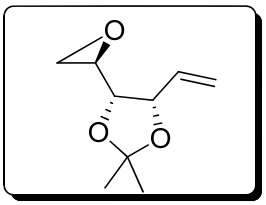
$[\alpha]_D^{25}$: +25.5 (*c* = 1.1, $CHCl_3$)

^{1}H NMR (200 MHz, $CDCl_3$) : δ 1.28 (s, 3H), 1.37 (s, 3H), 2.38 (bs, 1H), 2.43 (s, 3H), 3.76-3.87 (m, 1H), 3.99 (dd, *J* = 6.2, 8.8 Hz, 1H), 4.04 (dd, *J* = 6.6, 10.3 Hz, 1H), 4.28 (dd, *J* = 2.1, 10.3 Hz, 1H), 4.6 (t, *J* = 6.2 Hz, 1H), 5.25 (dt, *J* = 1.2, 10.3 Hz, 1H), 5.40 (dt, *J* = 1.2, 17.0 Hz, 1H), 5.91 (ddd, *J* = 6.6, 10.3, 17.0 Hz, 1H), 7.33 (d, *J* = 8.0 Hz, 2H), 7.79 (d, *J* = 8.0 Hz, 2H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$) : δ 21.5 (q), 25.1 (q), 27.4 (q), 68.0 (d), 72.2 (t), 76.9 (d), 78.1 (d), 109.0 (s), 118.1 (t), 127.9 (d), 129.8 (d), 132.5 (s), 133.0 (d), 144.9 (s) ppm.

Elemental Analysis Calcd.: C, 56.12; H, 6.48; S, 9.36 %
Found: C, 55.89 ; H, 6.51; S, 9.12 %

(4*S*,5*S*)-2,2-Dimethyl-4-((*R*)-oxiran-2-yl)-5-vinyl-1,3-dioxolane (81)



To a solution of **80** (8.52 g, 24.8 mmol) in methanol (75 mL), solid K_2CO_3 (10.32 g, 124.4 mmol) was added at rt and stirred for 12 h. After that the solid was removed by filtration and after diluting with water the filtrate was extracted with diethyl ether (3x75 mL). The organic extract was collected and the washed with fresh water, dried and concentrated at reduced pressure (bath temperature 20 ^{o}C). The residue thus obtained was purified by column chromatography to get the compound **81** (3.30 g, 19.4 mmol) as light oil in 78% yield.

Mol. Formula : $C_9H_{14}O_3$

$[\alpha]_D^{25}$: +18.8 (*c* =1.0, $CHCl_3$)

IR ($CHCl_3$) υ : 872, 1042, 1217, 1253, 1383, 1601, 2930, 2991 cm^{-1}.

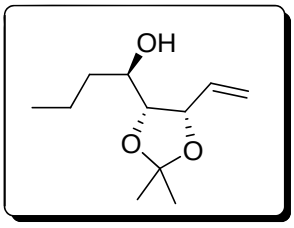
^{1}H NMR (400 MHz, $CDCl_3$) : δ 1.36 (s, 3H), 1.50 (s, 3H), 2.66 (dd, *J* = 2.6, 5.0 Hz, 1H), 2.81 (dd, *J* = 3.9, 5.0 Hz, 1H), 2.94 (ddd, *J* = 2.6, 3.9, 7.2 Hz, 1H), 3.74 (dd, *J* = 6.7, 7.2 Hz, 1H), 4.7 (dt, *J* = 1.0, 6.7 Hz, 1H), 5.34 (ddd, *J* = 1.0, 1.6, 10.2 Hz, 1H), 5.46 (ddd, *J* = 1.2, 1.6, 17.0 Hz, 1H), 5.98 (ddd, *J* = 6.7, 10.2, 17.0 Hz, 1H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$) : δ 25.1 (q), 27.6 (q), 45.7 (d), 49.7 (d), 78.6 (d), 78.9 (d), 109. (s), 118.8 (t), 132.4 (d) ppm.

ESI-MS (*m/z*) : 171.1$[M+H]^+$.

Elemental Analysis Calcd.: C, 63.51; H, 8.29 %
Found: C, 63.35; H, 8.18 %

(*R*)-1-((4*R*,5*S*)-2,2-Dimethyl-5-vinyl-1,3-dioxolan-4-yl)butan-1-ol (44a)



To a suspension of magnesium turnings (1.85 g, 76 mmol, activated by a pinch of iodine) in dry ether (30 mL) in a well equipped setup, ethyl bromide (3.42 mL, 45.6 mmol)) was added in such rate that the mixture was refluxing gently. This Grignard solution was transferred via syringe to a suspension of anhydrous CuCN (1.64 g, 18.2 mmol) in 10 mL dry ether at 0 ^oC and stirred for 20 min. at the same temperature. A dark brown, colloidal mixture was observed on addition of ethyl magnesium bromide to copper cyanide solution. To this cuprate solution, the epoxide **81** (2.59 g, 15.2 mmol, in 10 mL ether) was introduced and the mixture was stirred for another 1h at 0 ^oC. The reaction mixture was quenched with cold water and extracted with ethyl acetate. The organic extract was collected, dried and concentrated. Then the crude material was purified by column chromatography to get alcohol **44a** (2.77 g, 13.8 mmol) in 91% yield.

Mol. Formula : $C_{11}H_{20}O_3$

$[\alpha]_D^{25}$: +20.9 (*c* = 1.3, $CHCl_3$)

IR ($CHCl_3$) υ : 874, 1033, 1067, 1099, 1168, 1217, 1253, 1381, 1428, 1458, 2874, 2936, 2959, 2987, 3437 (b) cm^{-1}.

^{1}H NMR : δ 0.92 (t, *J* = 6.9 Hz, 3H), 1.31-1.72 (m, 4H), 1.35

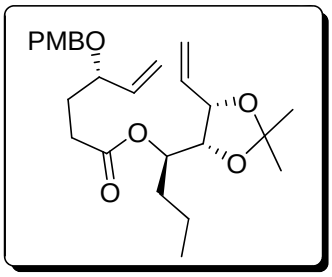
(400 MHz, $CDCl_3$) (s, 3H), 1.46 (s, 3H), 3.66 (dt, *J* = 2.1, 8.1 Hz, 1H), 3.96 (dd, *J* = 6.6, 8.1 Hz, 1H), 4.63 (dd, *J* = 7.7, 6.6 Hz, 1H), 5.30 (bd, *J* = 10.1 Hz, 1H), 5.41 (bd, *J* = 17.1 Hz, 1H), 6.03 (ddd, *J* = 7.7, 10.1, 17.1Hz, 1H) ppm.

^{13}C NMR : δ 14.0 (q), 18.3 (t), 25.3 (q), 27.8 (q), 35.8 (t), 69.7 (d), 78.9 (d), 80.7 (d), 108.6 (s), 118.5 (t), 134.7 (d) ppm.
(50 MHz, $CDCl_3$)

ESI-MS (*m/z*) : 223.1 $[M+Na]^+$, 239.1$[M+K]^+$.

Elemental Analysis Calcd.: C, 65.97; H, 10.07 %
Found: C, 65.83; H, 9.84 %

(*S*)-((*R*)-1-((4*R*,5*S*)-2,2-Dimethyl-5-vinyl-1,3-dioxolan-4-yl)butyl) 4-(4-methoxybenzyloxy)hex-5-enoate (65)



To a solution of aliphatic acid **66** (240 mg, 0.96 mmol) in dry THF (5 mL), 2,4,6-trichlorobenzoyl chloride (0.22 mL, 1.44 mmol) and by *N*,*N*-diisopropyl ethyl amine (0.83 mL, 4.8 mmol) were added and the mixture was stirred for 2 h at ambient temperature. After completion of mixed anhydride formation (as indicated by TLC) the alcohol **44a** (192 mg, 0.96 mmol, dissolved in 2 mL THF) was added and the reaction mixture was stirred for 16 h at rt. Then the reaction mixture was quenched with water and extracted with ethyl acetate. The combined organic phase was washed with saturated sodium bicarbonate solution, water, dried and evaporated under vacuum to afford the compound **65** (350 mg, 0.81 mmol, 84%) as light yellow, viscous liquid.

Mol. Formula : $C_{25}H_{36}O_6$

$[\alpha]_D^{25}$: –2.8 (*c* = 1.37, $CHCl_3$)

IR ($CHCl_3$) υ : 821, 872, 928, 1037, 1067, 1172, 1301, 1372, 1442, 1464, 1514, 1613, 1644, 1737, 2872, 2932 cm^{-1}.

^{1}H NMR : δ 0.89 (t, *J* = 7.2 Hz, 3H), 1.23-1.36 (m, 2H), 1.36 (s, 3H), 1.48 (s, 3H), 1.56-1.71 (m, 2H), 1.77-1.96 (m,
(400 MHz, $CDCl_3$)

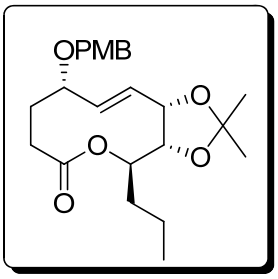
2H), 2.19-2.48 (m, 2H), 3.70-3.79 (m, 1H), 3.79 (s, 3H), 4.16 (dd, *J* = 6.4, 7.4 Hz, 1H), 4.26 (d, *J* = 11.3 Hz, 1H), 4.43 (d, *J* = 11.3 Hz, 1H), 4.54-4.62 (m, 1H), 4.91 (dt, *J* = 7.4, 3.8 Hz, 1H), 5.16-5.36 (m, 4H), 5.63-5.88 (m, 2H), 6.87 (d, *J* = 8.7 Hz, 2H), 7.24 (d, *J* = 8.7 Hz, 2H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$) : δ 14.0 (q), 17.8 (t), 25.1 (q), 27.4 (q), 30.3 (t, 2C), 33.3 (t), 55.2 (q), 69.7 (t), 71.6 (d), 78.3 (d), 78.7 (d), 79.0 (d), 108.7 (s), 113.7 (d), 117.6 (t), 118.3 (t), 129.2 (d), 130.5 (s), 133.2 (d), 138.3 (d), 159.1 (s), 172.4 (s) ppm.

ESI-MS (*m/z*) : 433.6 $[M+H]^+$, 455.2 $[M+Na]^+$.

Elemental Analysis Calcd.: C, 69.42; H, 8.39 %
Found: C, 69.31; H, 8.41 %

(3a*R*,4*R*,9*S*,11a*S*,E)-9-(4-Methoxybenzyloxy)-2,2-dimethyl-4-propyl-7,8,9,11a-tetrahydro-3aH-[1,3]dioxolo[4,5-c]oxecin-6(4H)-one (100)



To a solution of diene **65** (70 mg, 162 μmol) in dry toluene Grubbs' 2nd catalyst (14 mg, 10 mol %) was added and the mixture was degassed under argon atmosphere thoroughly. The mixture was heated at 80 ^oC for 6 h with continuous stirring. Then volatiles were removed and the residue was purified by flash column chromatography to afford **100** (41 mg, 63%) as liquid.

Mol. Formula : $C_{23}H_{32}O_6$

$[\alpha]_D^{25}$: –9.0 (*c* = 0.6, $CHCl_3$)

IR ($CHCl_3$) υ : 820, 1035, 1114, 1162, 1249, 1301, 1363, 1465, 1512, 1611, 1725, 2851, 2924, 2959, 3018, cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$) : δ 0.91 (t, *J* = 7.0 Hz, 3H), 1.21-1.34 (m, 2H), 1.39 (s, 3H), 1.51-1.68 (m, 2H), 1.55 (s, 3H), 1.71-1.76 (m, 1H), 1.94-2.08 (m, 2H), 2.26-36 (m, 1H), 3.79 (s, 3H), 3.81 (dd, *J* =4.6, 8.5 Hz, 1H), 3.95 (dd, *J* =4.6, 10.1 Hz, 1H),

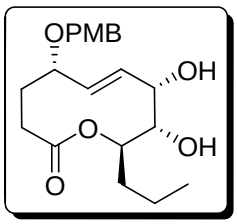
4.27 (d, *J* = 11.5 Hz, 1H), 4.56 (d, *J* = 11.5 Hz, 1H), 4.71 (ddd, *J* = 1.6, 3.0, 4.6 Hz, 1H), 4.94 (ddd, *J* = 2.6, 8.3, 10.1 Hz, 1H), 5.66 (ddd, *J* = 1.6, 8.3, 15.9 Hz, 1H), 5.84 (dd, *J* = 3.1, 15.9 Hz, 1H), 6.85 (d, *J* = 8.6 Hz, 2H), 7.23(d, *J* = 8.6 Hz, 2H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$) : δ 13.8 (q), 17.8 (t), 26.2 (q), 28.4 (q), 31.2 (t), 31.8 (t), 34.2 (t), 55.2 (q), 69.8 (t), 70.6 (d), 75.9 (d), 78.6 (d), 81. 6 (d), 109.3 (s), 113.8 (d), 127.4 (d), 128.2 (d), 129.3 (d), 130.5 (s), 159.1 (s), 174.9(s) ppm.

ESI-MS (*m/z*) : 405.5 $[M+H]^+$, 427.5 $[M+Na]^+$.

Elemental Analysis Calcd.: C, 68.29; H, 7.97 %
Found: C, 68.35; H, 7.82 %

(5*S*,8*S*,9*S*,10*R*,*E*)-8,9-Dihydroxy-5-(4-methoxybenzyloxy)-10-propyl-3,4,5,8,9,10-hexahydro-2H-oxecin-2-one (101)



To a stirred solution of **100** (35 mg, 86 μmol) in DCM (3 mL), TFA (2 mL, 10% in DCM) was added at rt and stirred for 12 h. The reaction mixture was concentrated under reduced pressure and the resulting residue was subject to column purification to get compound **101** (28 mg, 89%) as colourless liquid.

Mol. Formula : $C_{20}H_{28}O_6$

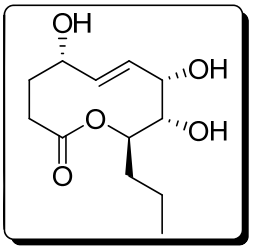
$[\alpha]_D^{25}$: –28.0 (*c* = 0.4, $CHCl_3$)

IR ($CHCl_3$) υ : 1060, 1110, 1160, 1248, 1362, 1514, 1612, 1731, 2872, 2960, 3010, 3443 (b) cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$) : δ 0.90 (t, *J* = 7.4 Hz, 3H), 1.20-1.30 (m, 2H), 1.50-1.59 (m, 1H), 1.82-1.90 (m, 1H), 1.92-2.12 (m, 3H), 2.27-2.34 (m, 1H), 3.51 (dd, *J* = 2.4, 10.0 Hz, 1H), 3.76-3.82 (m, 1H), 3.79 (s, 3H), 4.28 (d, *J* = 11.5 Hz, 1H), 4.51 (bs, 1H) 4.52 (d, *J* = 11.5 Hz, 1H), 4.94 (dt, *J* = 2.4, 9.5 Hz, 1H),5.52 (ddd, *J* = 2.2, 9.2, 16.0 Hz, 1H) 5.77 (dd, *J* = 1.5,16.0 Hz, 1H), 6.68 (d, *J* = 8.5 Hz, 2H), 7.22 (d, *J* = 8.5 Hz, 2H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$)	: δ 13.8 (q), 17.9 (t), 30.8 (t), 31.4 (t), 33.6 (t), 55.3 (q), 69.9 (t), 70.5 (d), 73.1 (d), 73.9 (d), 80.6 (d), 113.8 (d), 127.7 (d), 129.4 (d), 130.3 (s), 132.0 (d), 159.2 (s), 175.2 (s) ppm.
ESI-MS (*m/z*)	: 387.5 $[M+Na]^+$.
Elemental Analysis	Calcd.: C, 65.91; H, 7.74 %
	Found: C, 65.75; H, 7.68 %

4-*epi*-Stagonolide B (64)



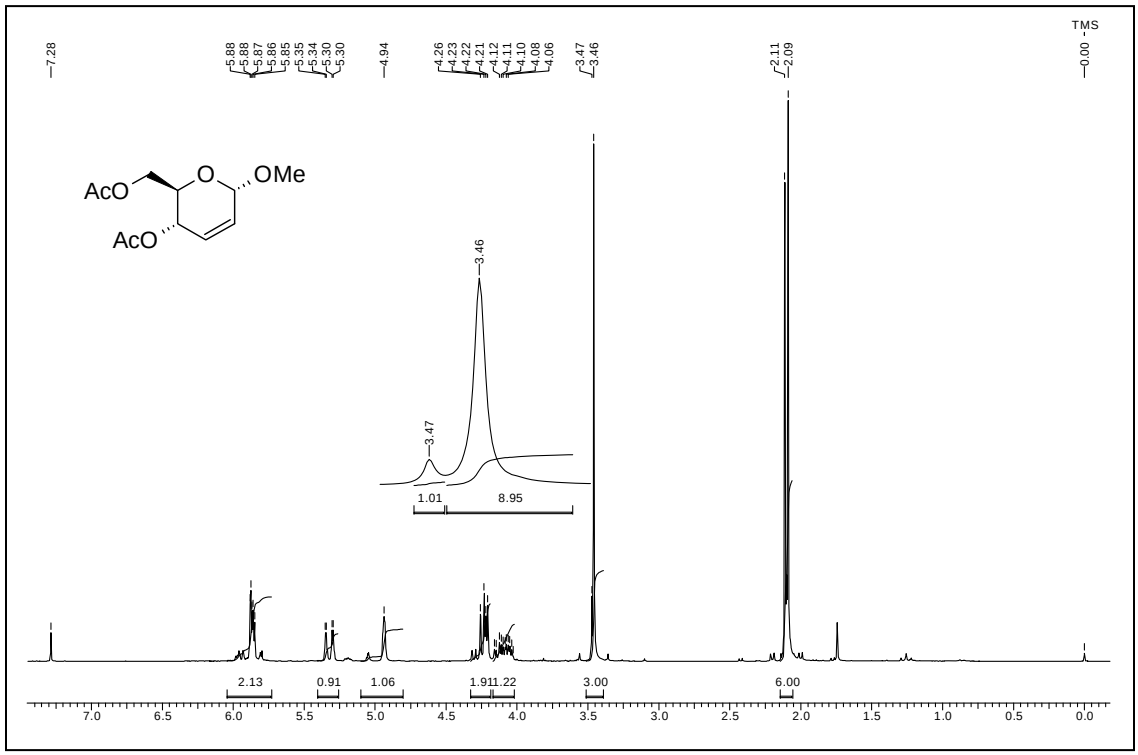
A mixture of compound **100** (21 mg, 51.9 μmol) and TFA (2 mL) was stirred at 0 ^oC for 1 h. The volatiles were removed under reduced pressure and the residue was purified by column chromatography using silica gel and ethyl acetate: P.E (80:20) to obtain the target **64** as crystalline solid (11 mg, 86%).

Mol. Formula	: $C_{12}H_{20}O_5$
Melting Point	: 185-187 ^oC
$[\alpha]_D^{25}$	: +11.3 (*c* = 0.3, CH_3OH)
^{1}H NMR (500 MHz, CD_3OD)	: δ 0.91 (t, *J* = 7.4 Hz, 3H), 1.22-1.36 (m, 2H), 1.42-1.52 (m, 1H), 1.76-1.85 (m, 2H), 1.89-1.94 (m, 1H), 2.03 (dt, *J* = 1.9, 13.5 Hz 1H), 2.26 (ddd, *J* = 1.9, 6.0, 13.5 Hz, 1H), 3.50 (dd, *J* = 2.2, 9.7 Hz, 1H), 4.06 (dt, *J* = 4.5, 10.0 Hz, 1H), 4.39 (dd, *J* = 2.6, 4.5 Hz, 1H), 5.13 (dt, *J* = 2.2, 9.5 Hz, 1H), 5.50 (dd, *J* = 9.5, 15.6 Hz, 1H), 5.77 (dd, *J* = 1.4, 15.6 Hz, 1H) ppm.
^{13}C NMR (125 MHz, $CDCl_3$)	: δ 14.4 (q), 18.9 (t), 32.5 (t), 33.9 (t), 35.1 (t), 71.9 (d), 73.6 (d), 74.6 (d), 75.9 (d), 128.2 (d), 133.5 (d), 176.3 (s) ppm
ESI-MS (*m/z*)	: 245.2 $[M+H]^+$, 267.3 $[M+Na]^+$.
Elemental Analysis	Calcd.: C, 59.00; H, 8.25 %
	Found: C, 48.85; H, 8.26 %

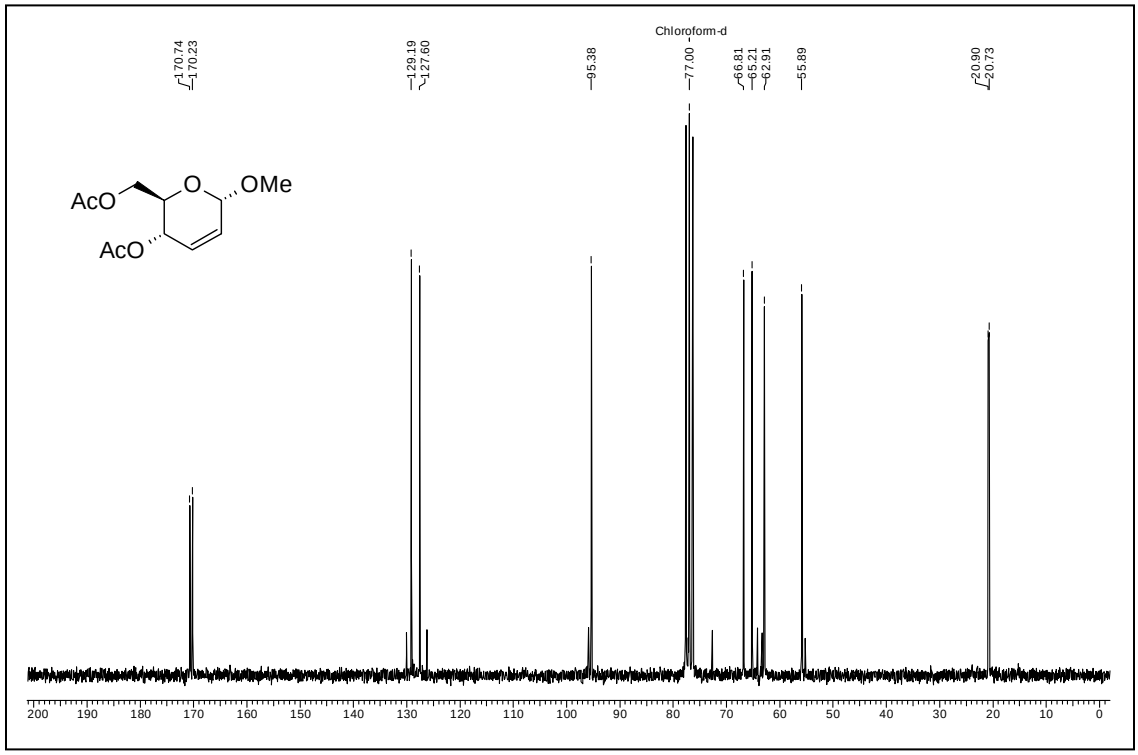
Crystal data for 64.

Empirical formula	$C_{12}H_{20}O_5$
Formula weight	244.28
Temperature	295(2) K
Wavelength	0.71073 Å
Crystal system, space group	Monoclinic, C_2
Unit cell dimensions	a = 16.861(15) Å α = 90º
	b = 4.981(4) Å β = 112.087(14)º
	c = 16.109(14) Å γ = 90º
Volume	1253.7(19) A^3
Z, Calculated density	4, 1.294 Mg/m^3
Absorption coefficient	0.100 mm^{-1}
F(000)	528
Crystal size	0.14 x 0.05 x 0.02 mm
Theta range for data collection	1.36 to 25.00º
Limiting indices	-20<=h<=19, -5<=k<=5, -15<=l<=19
Reflections collected / unique	5114 / 2177 [R(int) = 0.1106]
Completeness to theta = 25.00	99.7 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9979 and 0.9864
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2177 / 1 / 158
Goodness-of-fit on F^2	0.835
Final R indices [I>2sigma(I)]	R1 = 0.0720, wR2 = 0.1554
R indices (all data)	R1 = 0.1490, wR2 = 0.1731
Absolute structure parameter	5(3)
Largest diff. peak and hole	0.277 and -0.275 $e.A^{-3}$

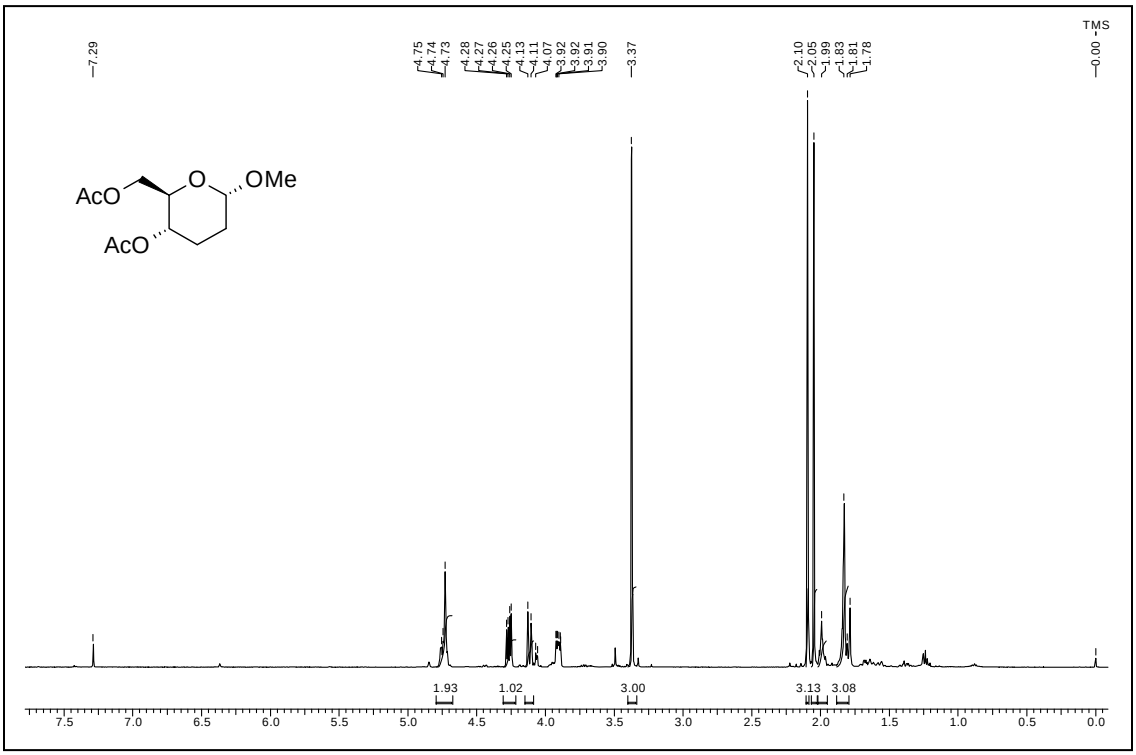
Spectra



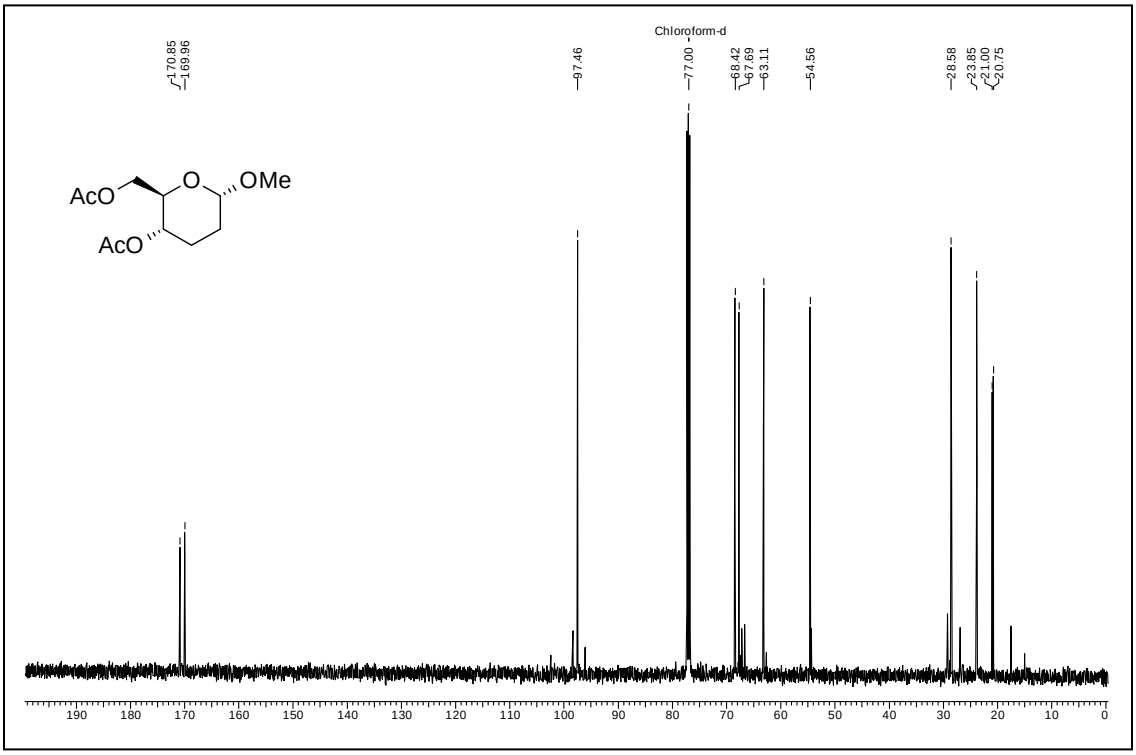
^{1}H NMR Spectrum of 71a in $CDCl_3$



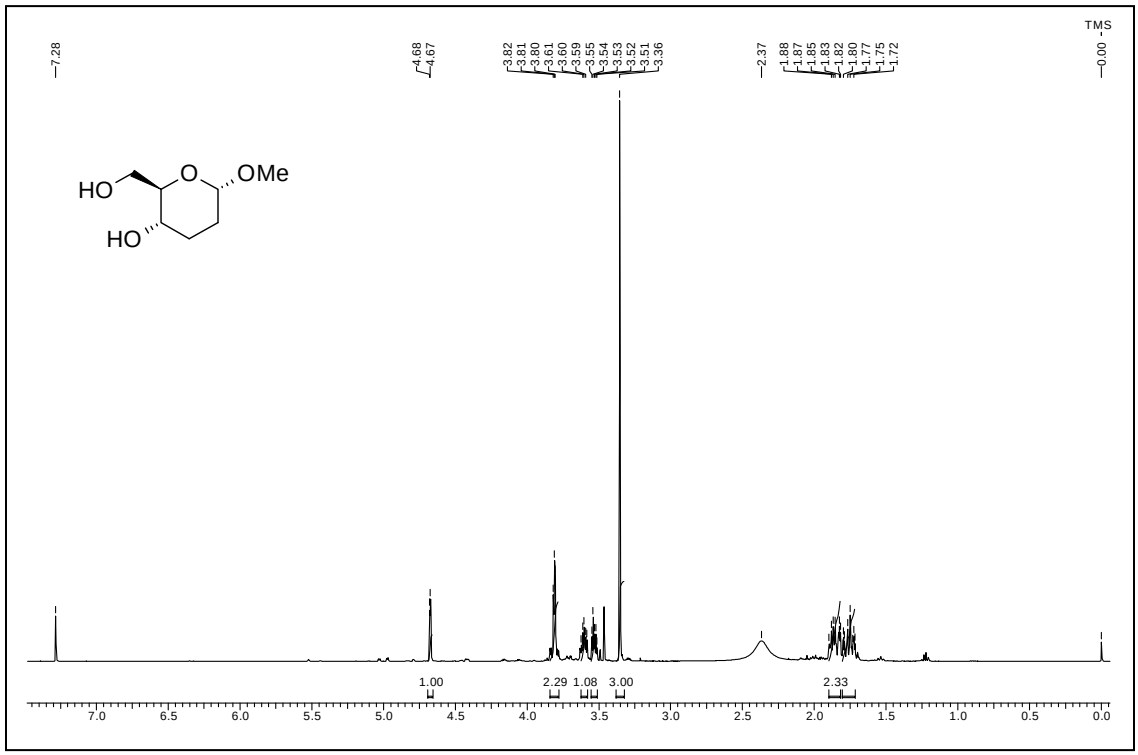
^{13}C NMR Spectrum of 71a in $CDCl_3$



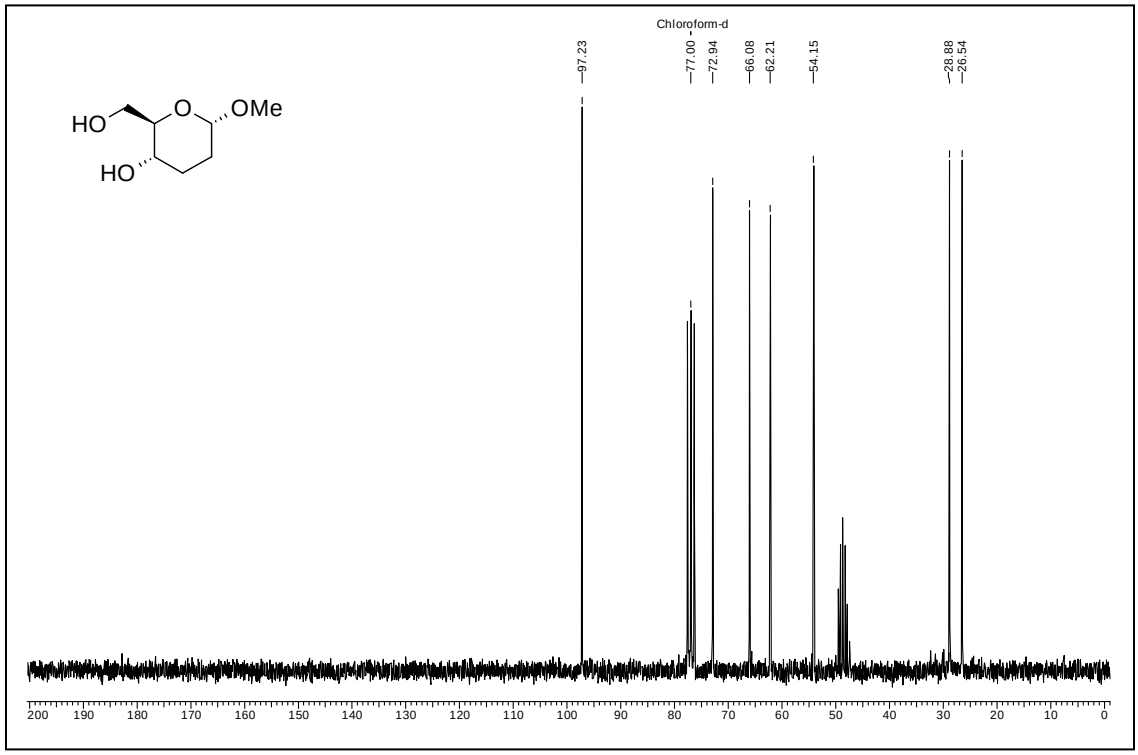
^{1}H NMR Spectrum of 74 in $CDCl_3$



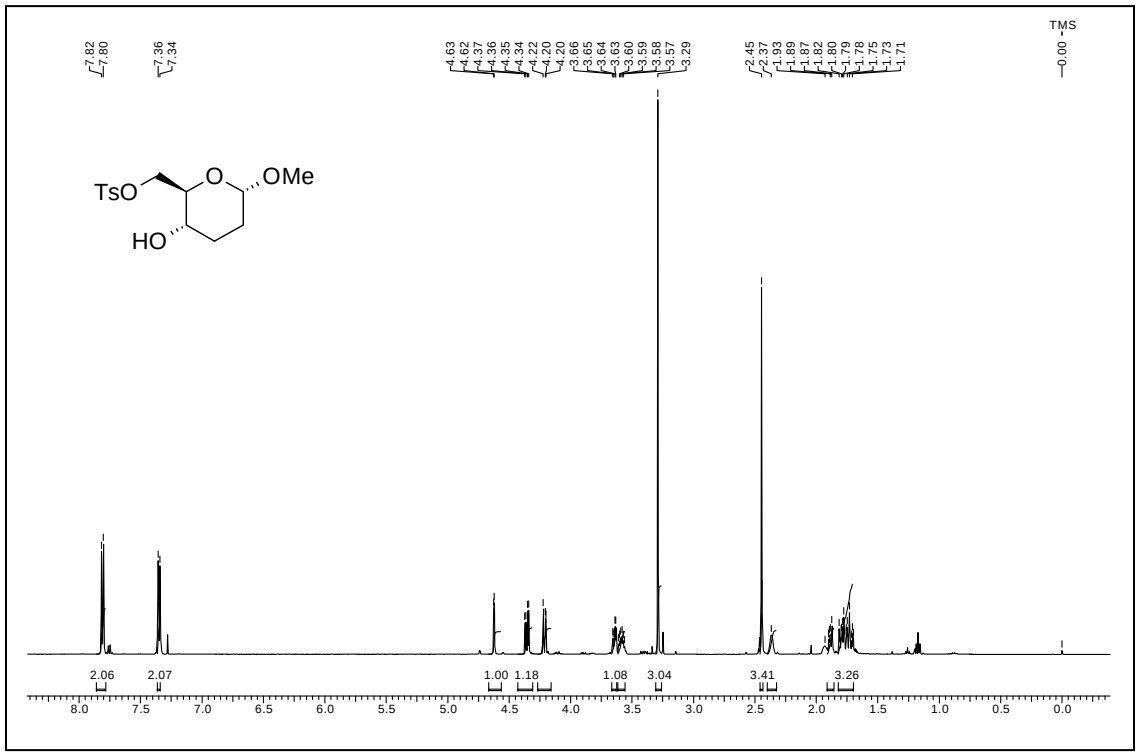
^{13}C NMR Spectrum of 74 in $CDCl_3$



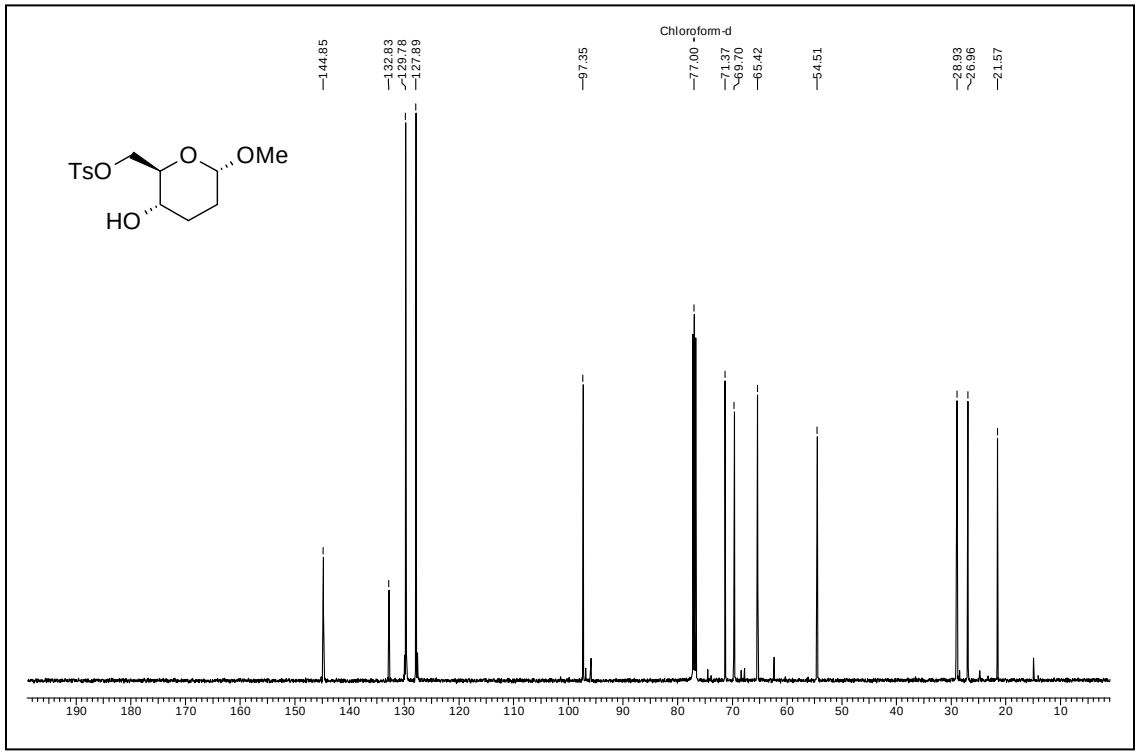
^{1}H NMR Spectrum of 75 in $CDCl_3$



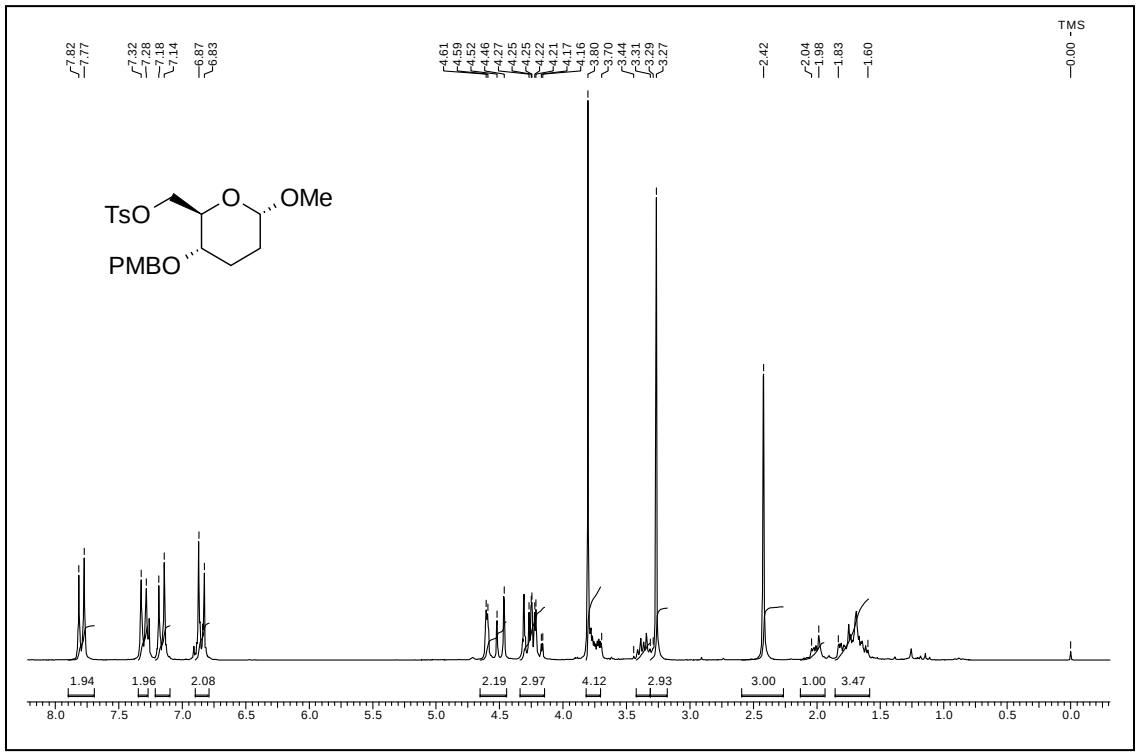
^{13}C NMR Spectrum of 75 in (CD_3OD + $CDCl_3$)



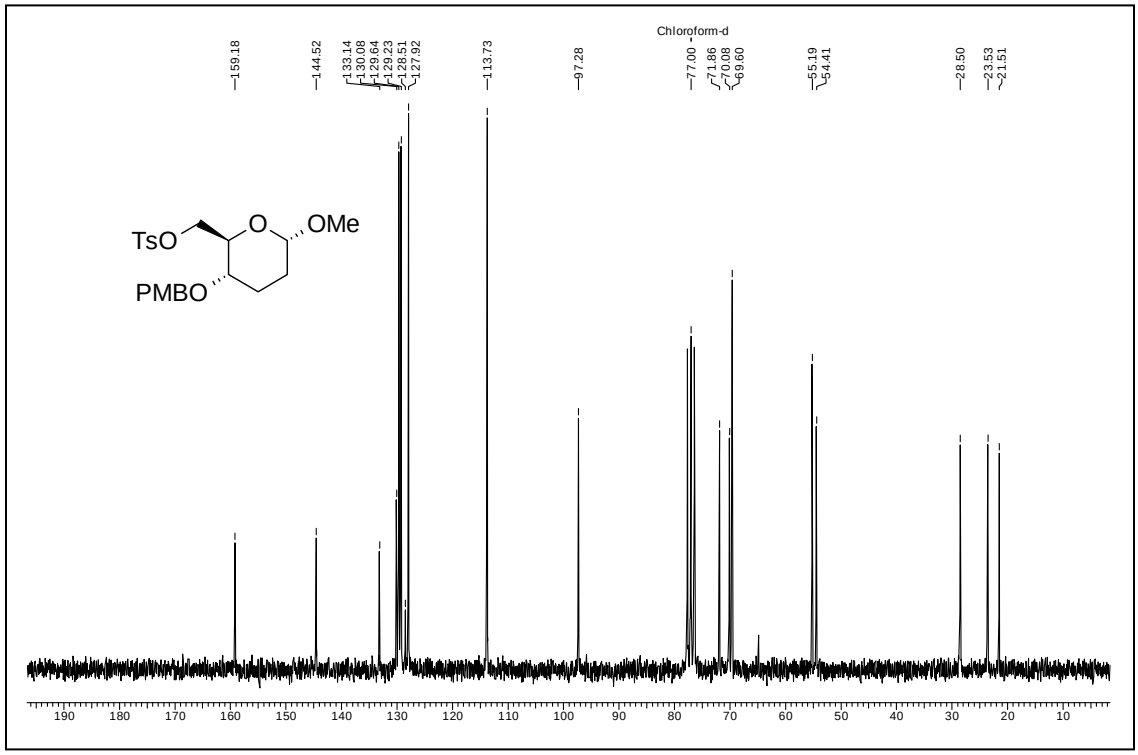
^{1}H NMR Spectrum of 76 in $CDCl_3$



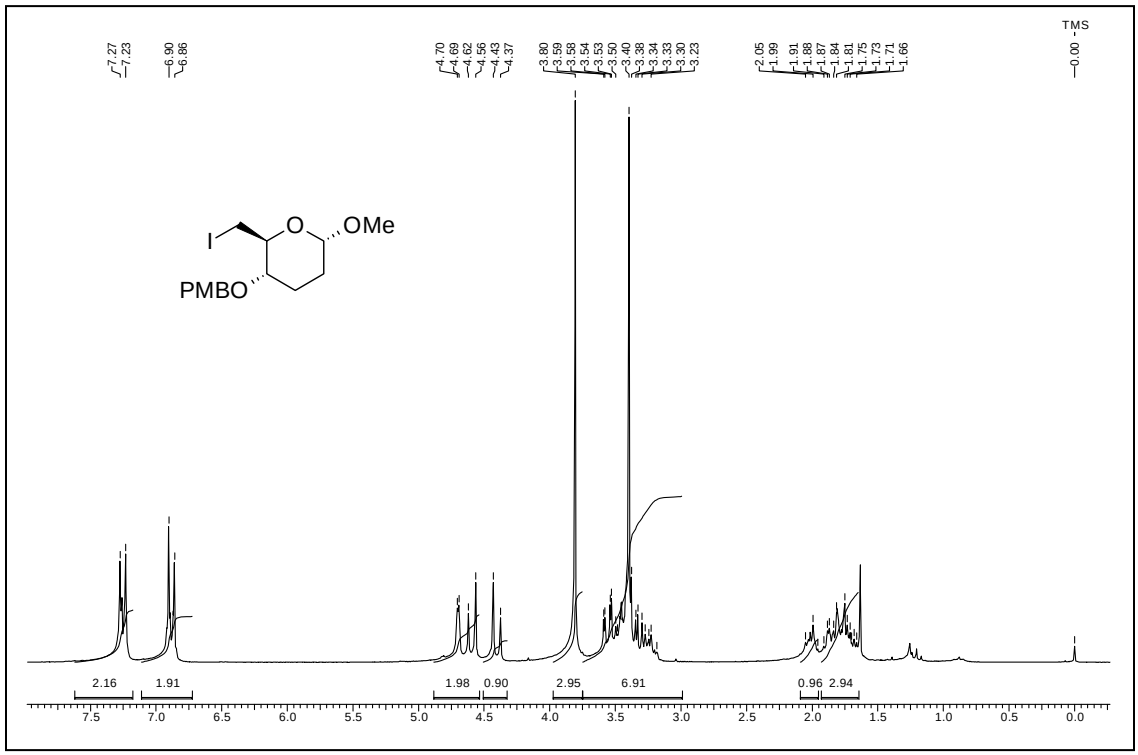
^{13}C NMR Spectrum of 76 in $CDCl_3$



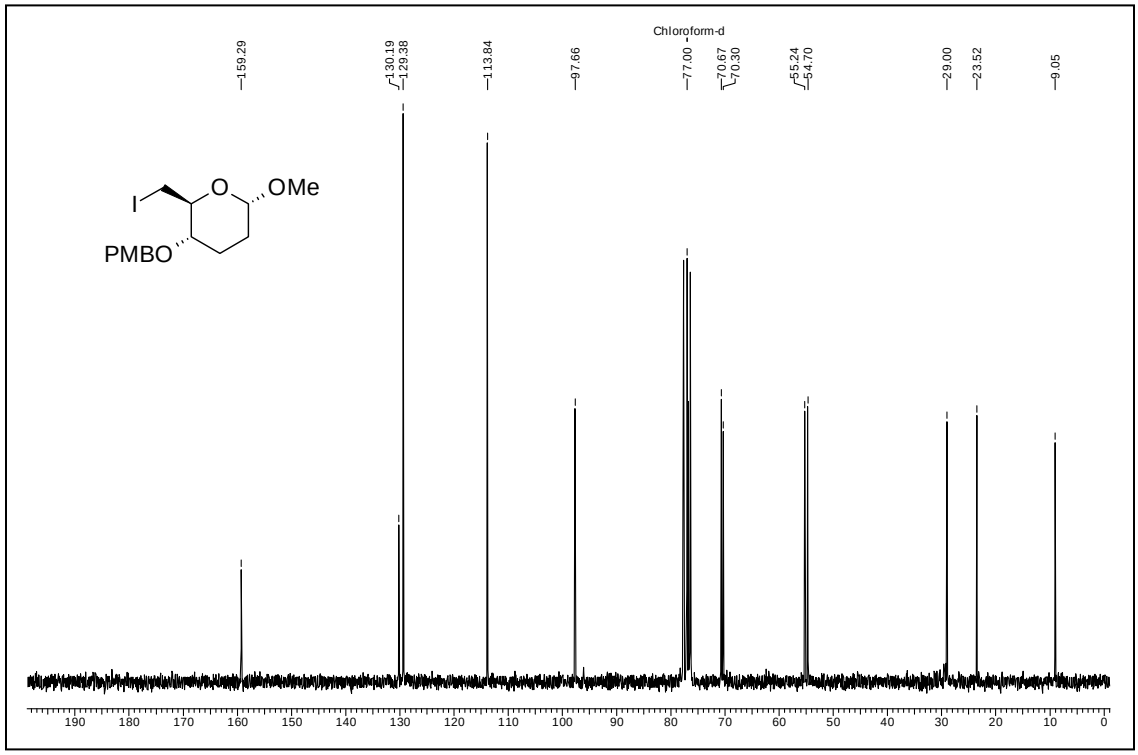
^{1}H NMR Spectrum of 77 in $CDCl_3$



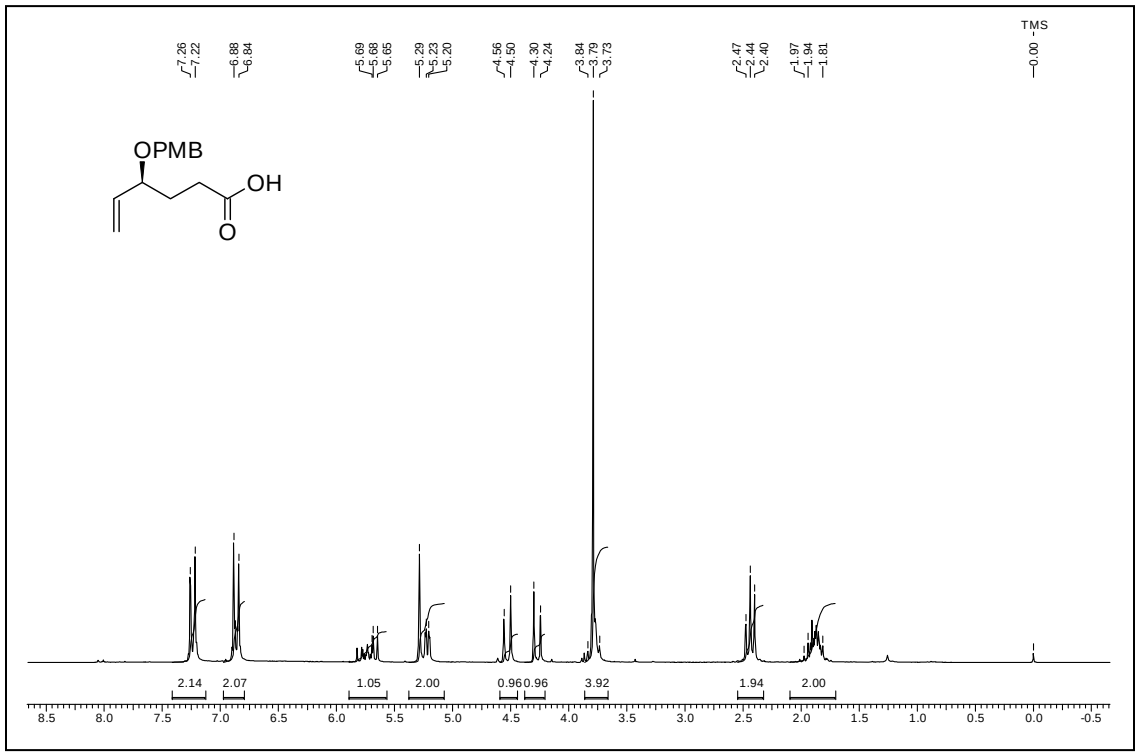
^{13}C NMR Spectrum of 77 in $CDCl_3$



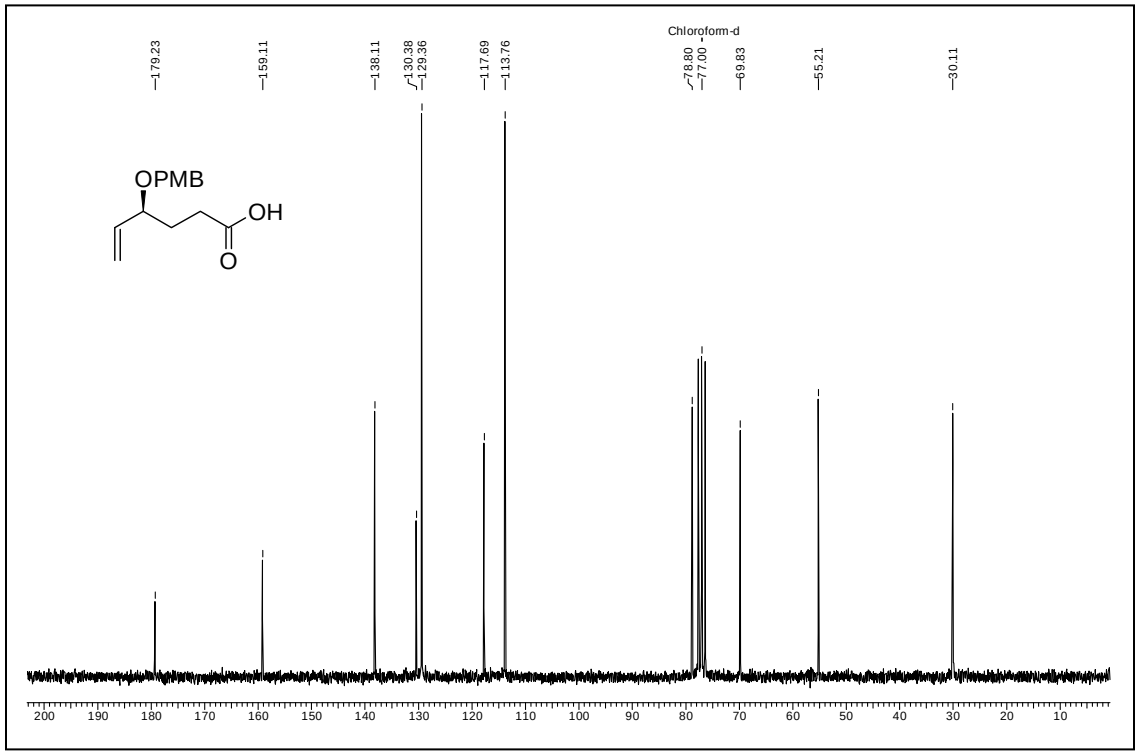
^{1}H NMR Spectrum of 67 in $CDCl_3$



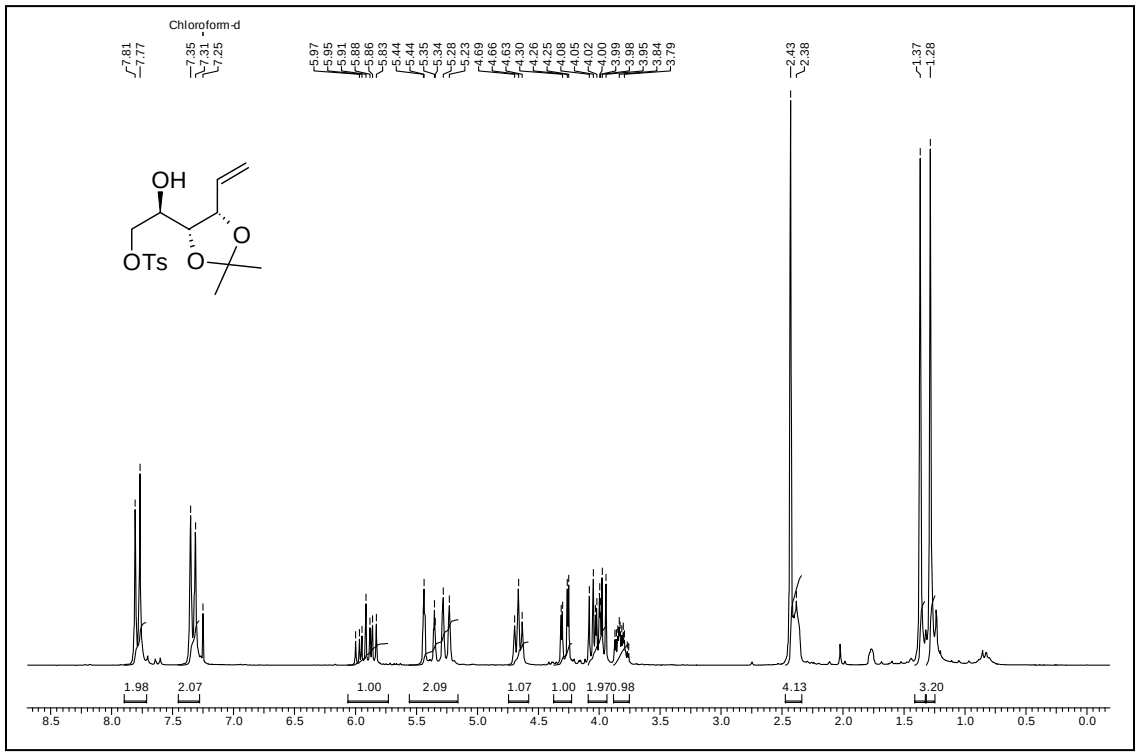
^{13}C NMR Spectrum of 67 in $CDCl_3$



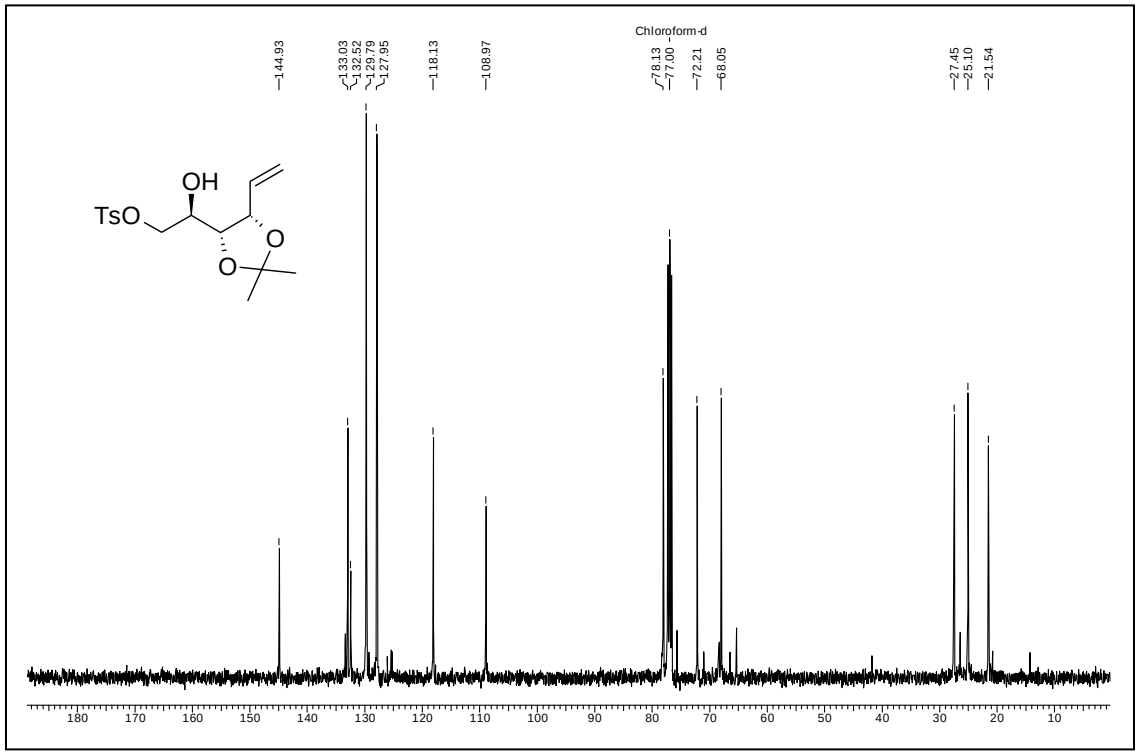
^{1}H NMR Spectrum of 66 in $CDCl_3$



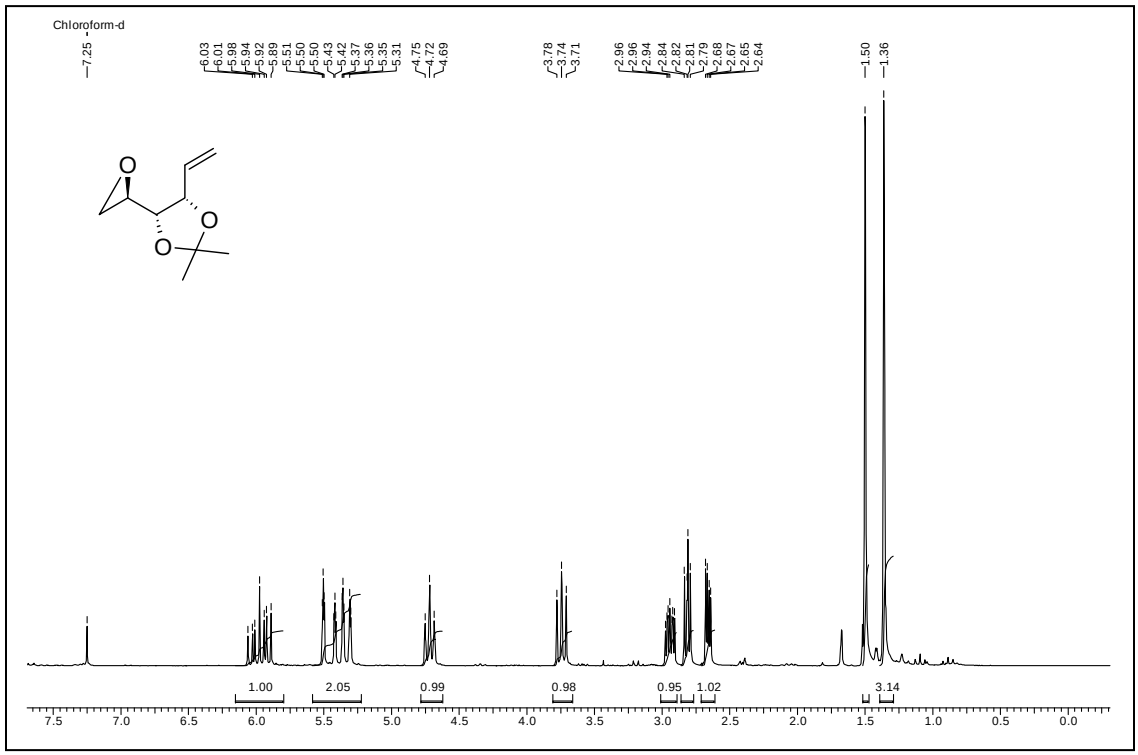
^{13}C NMR Spectrum of 66 in $CDCl_3$



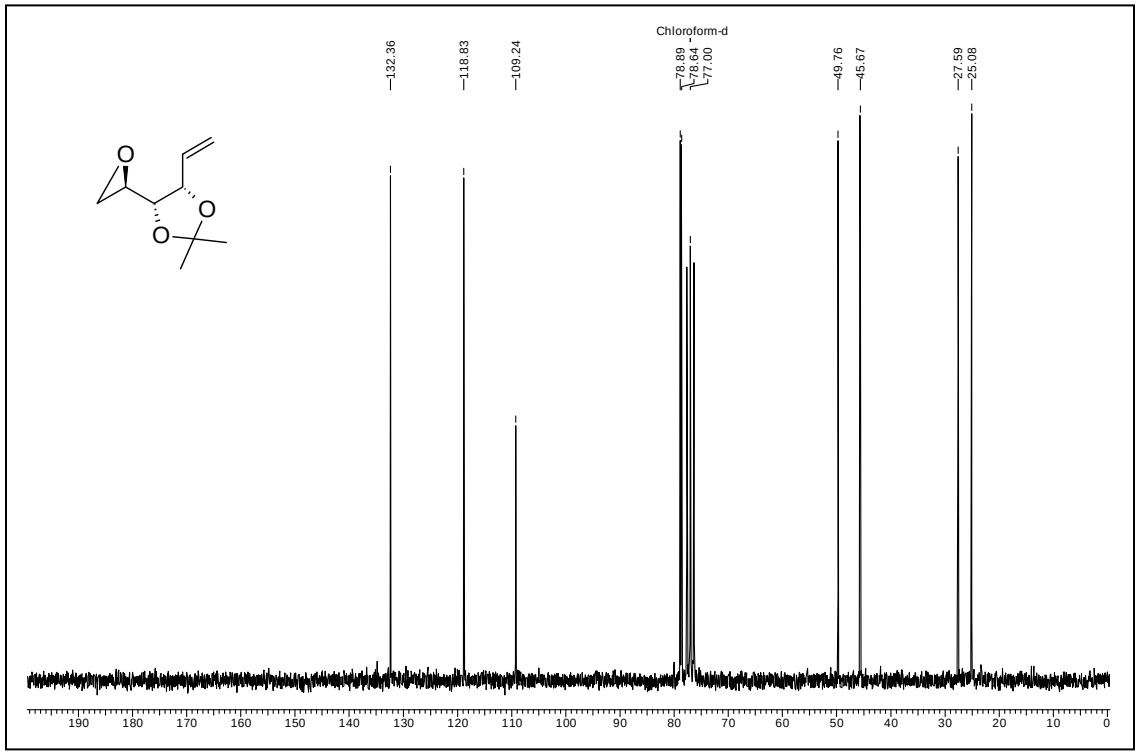
^{1}H NMR Spectrum of 80 in $CDCl_3$



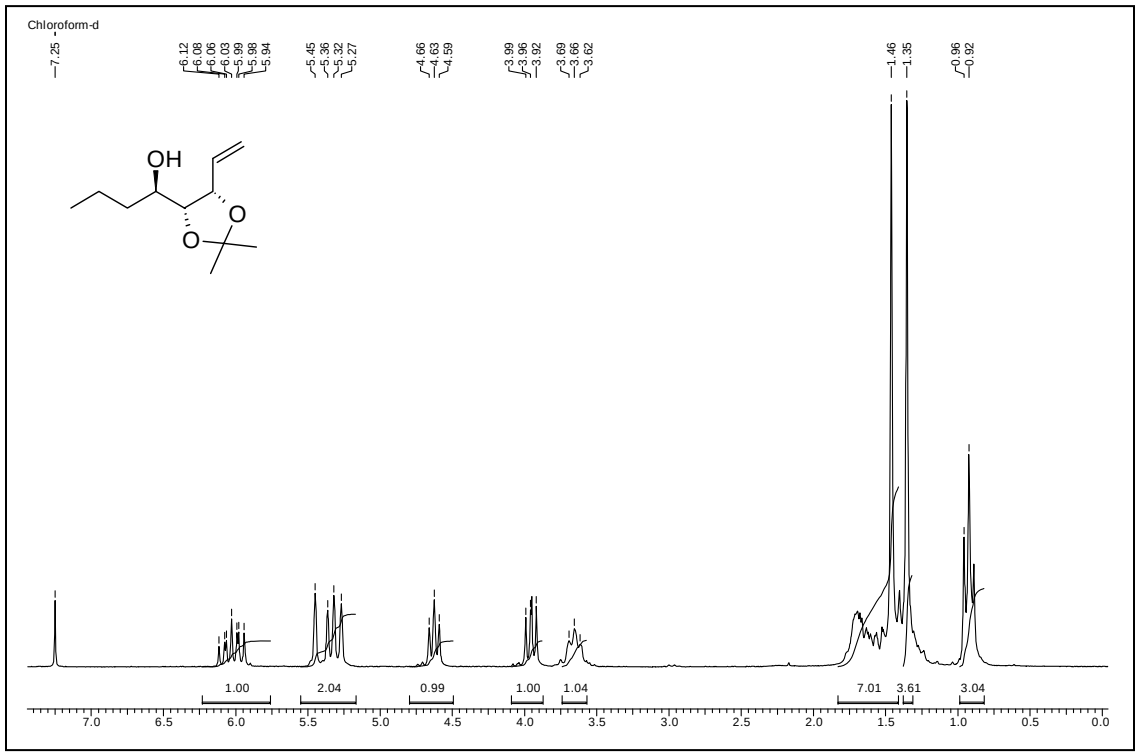
^{13}C NMR Spectrum of 80 in $CDCl_3$



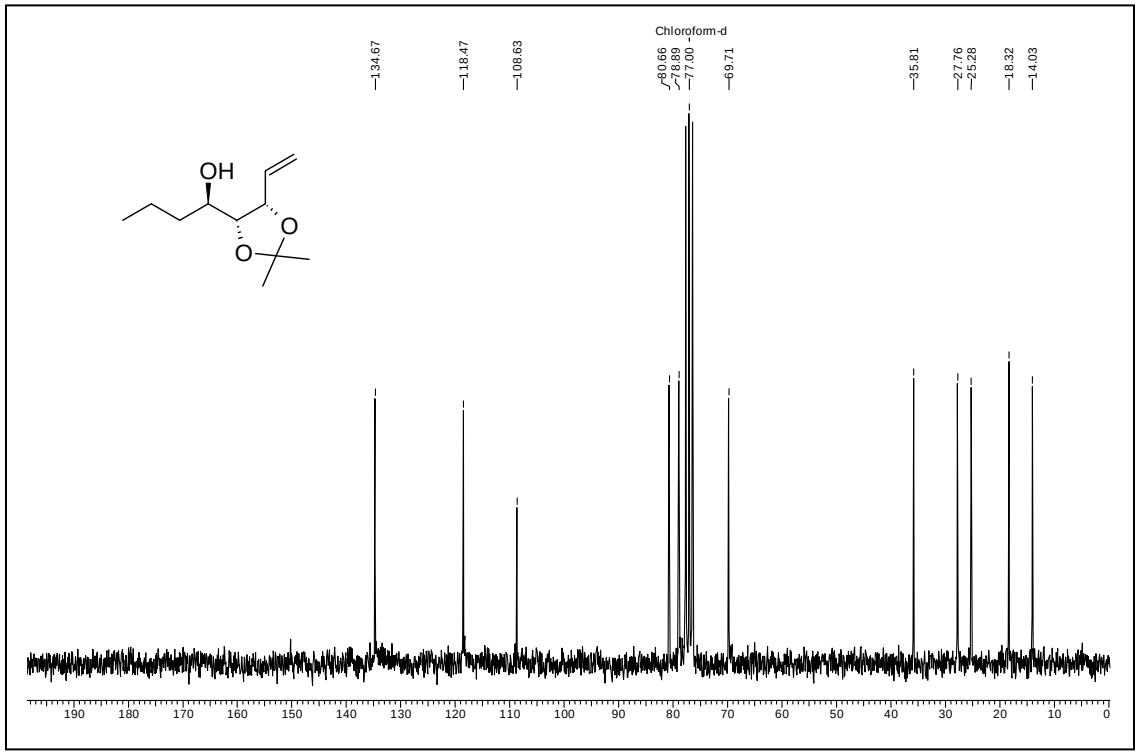
^{1}H NMR Spectrum of 81 in $CDCl_3$



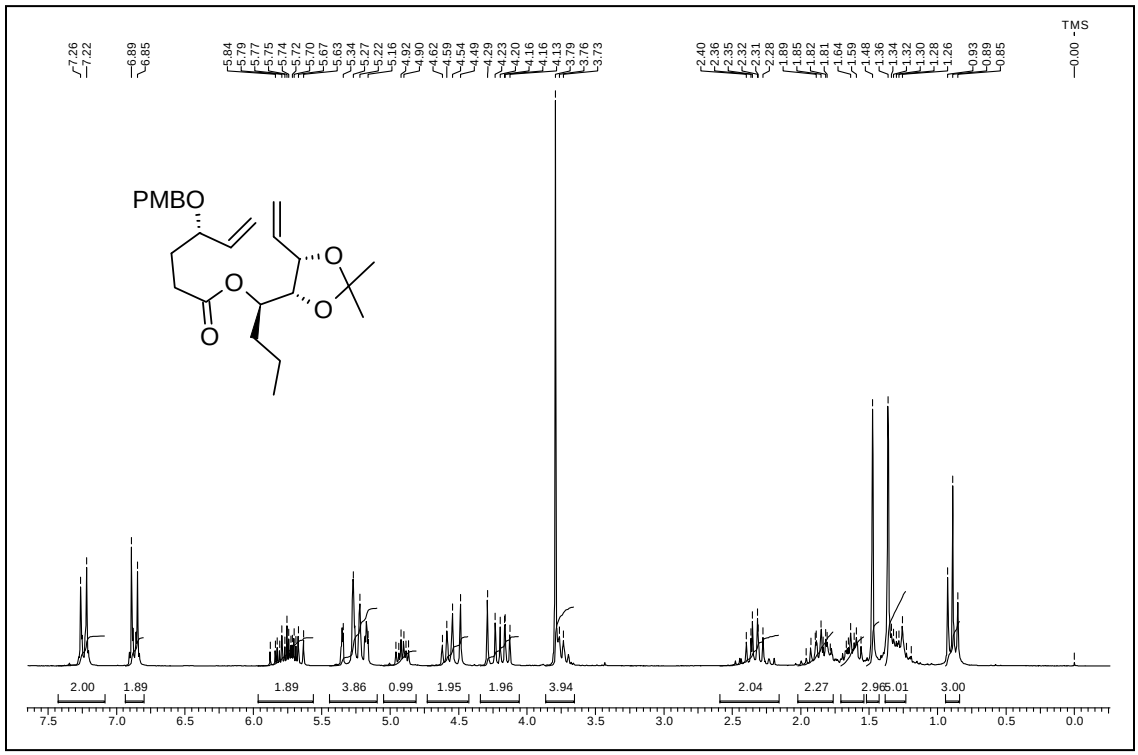
^{13}C NMR Spectrum of 81 in $CDCl_3$



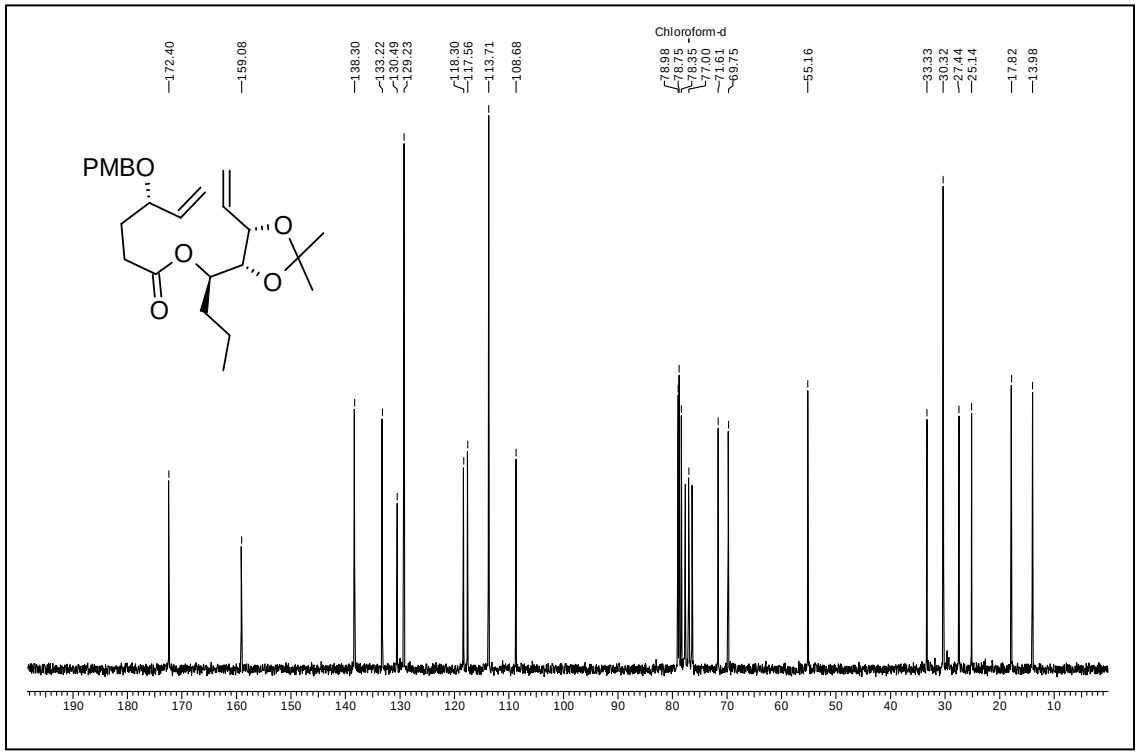
^{1}H NMR Spectrum of 44a in $CDCl_3$



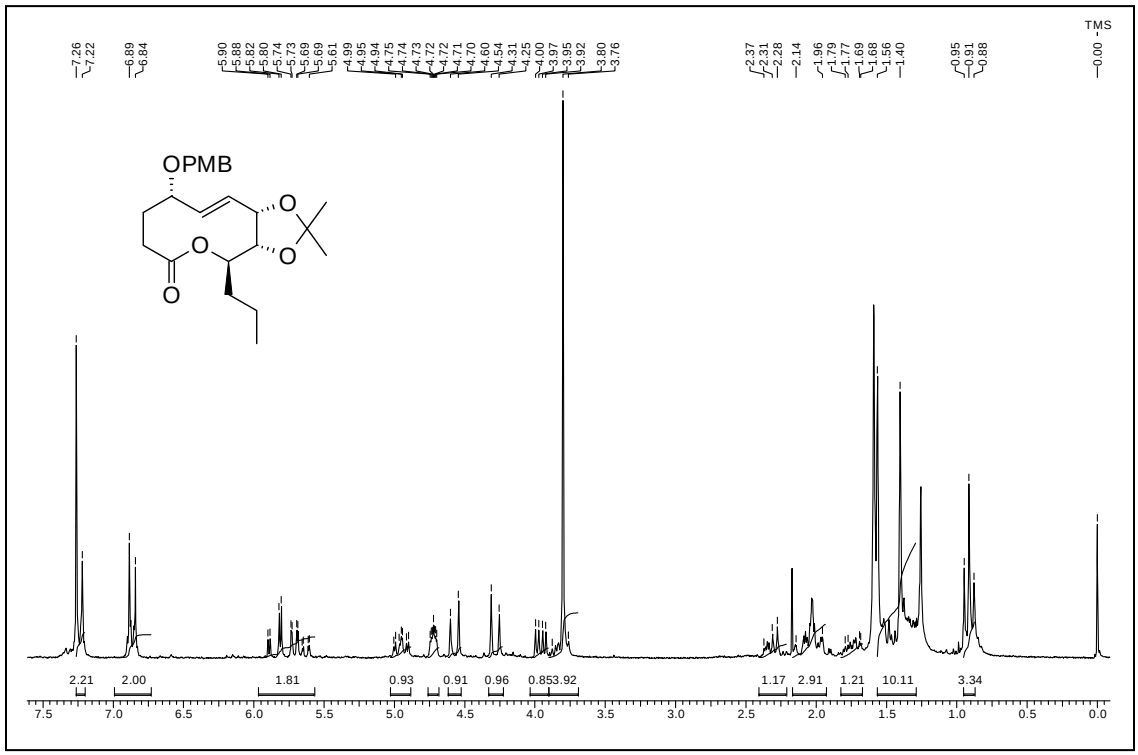
^{13}C NMR Spectrum of 44a in $CDCl_3$



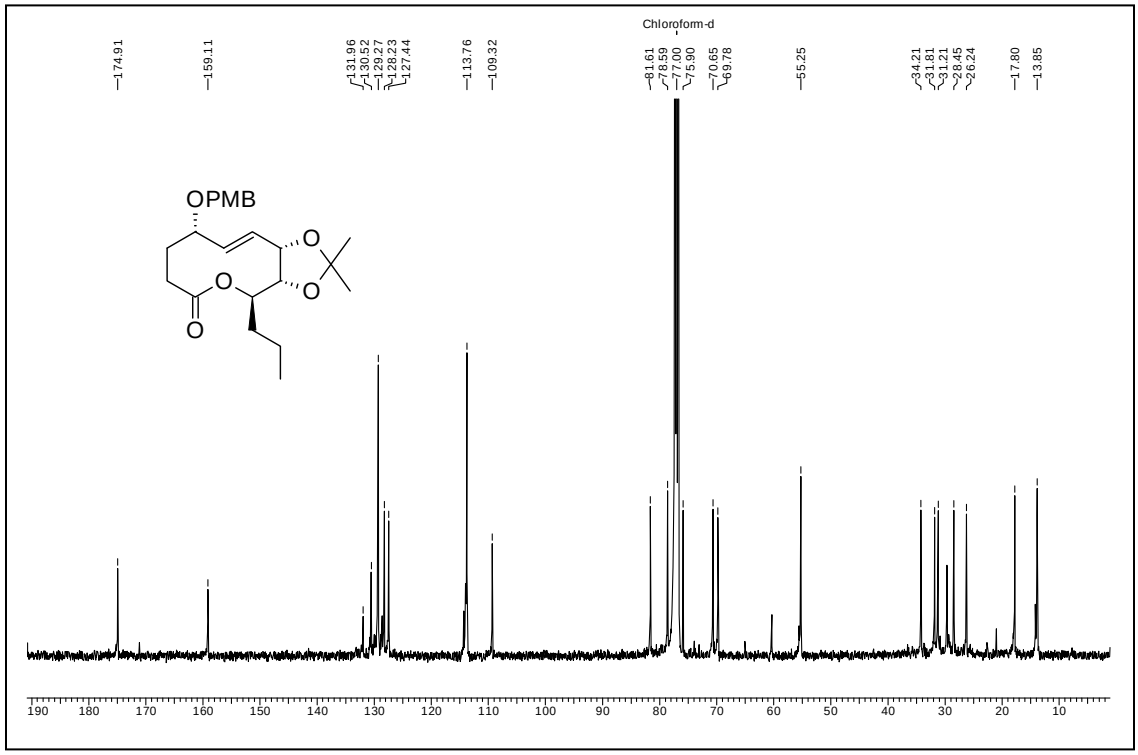
^{1}H NMR Spectrum of 65 in $CDCl_3$



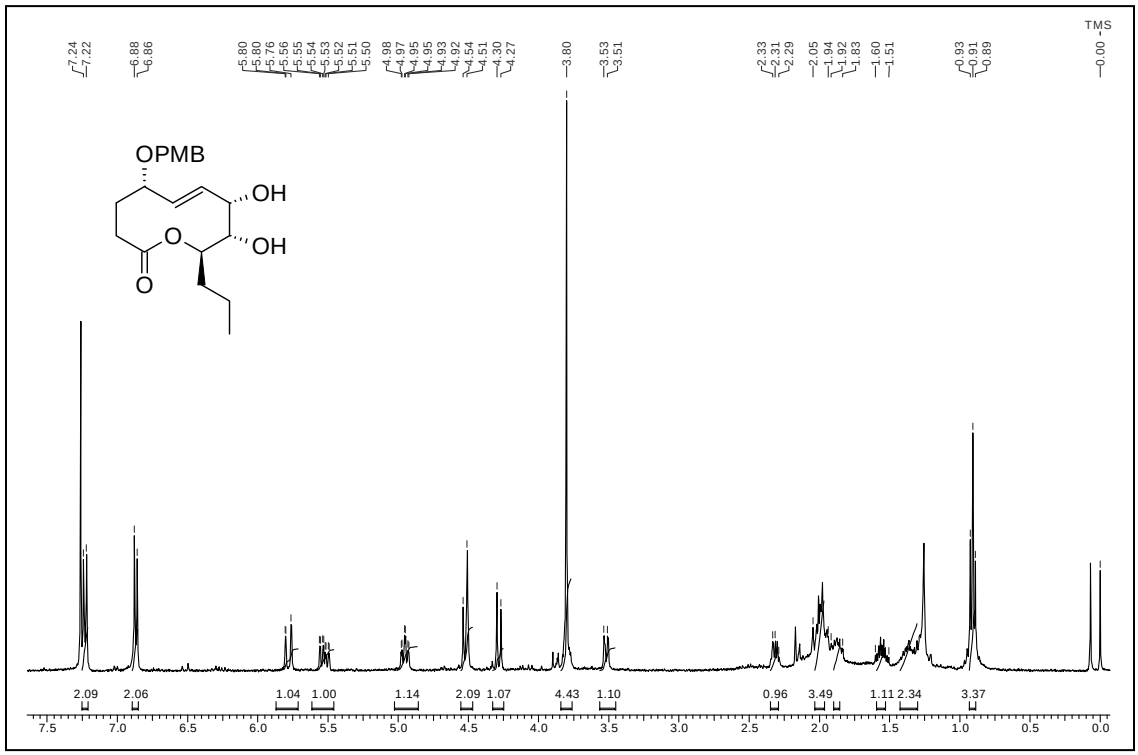
^{13}C NMR Spectrum of 65 in $CDCl_3$



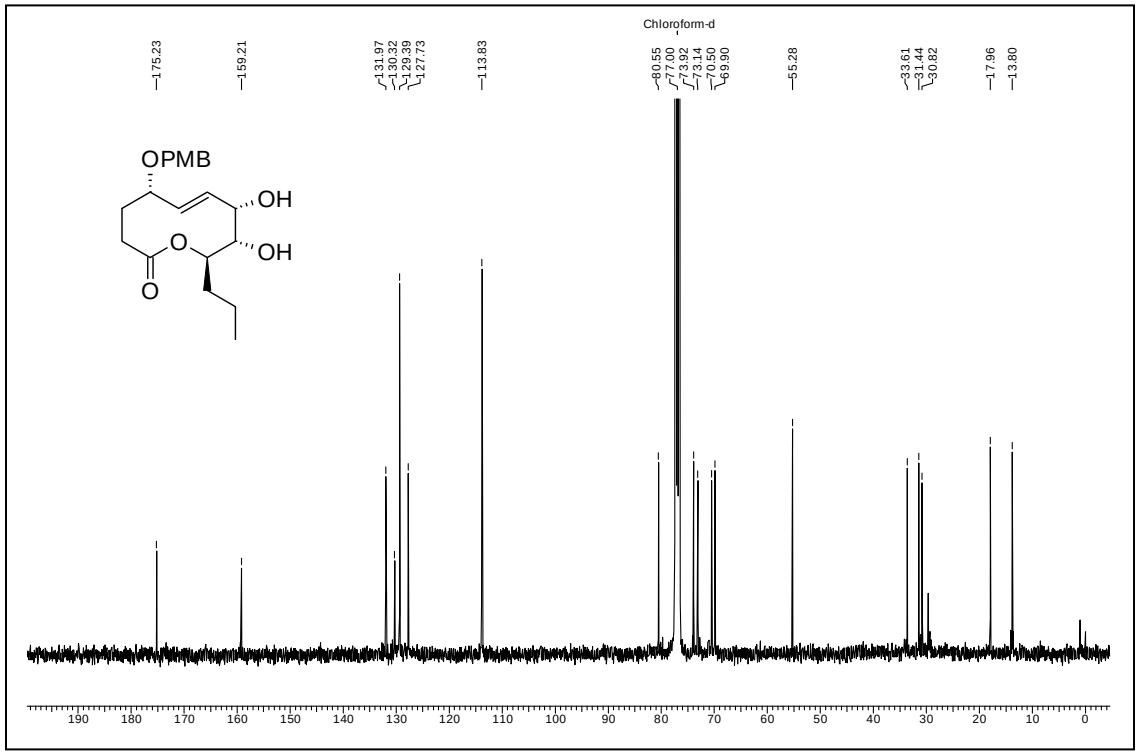
^{1}H NMR Spectrum of 100 in $CDCl_3$



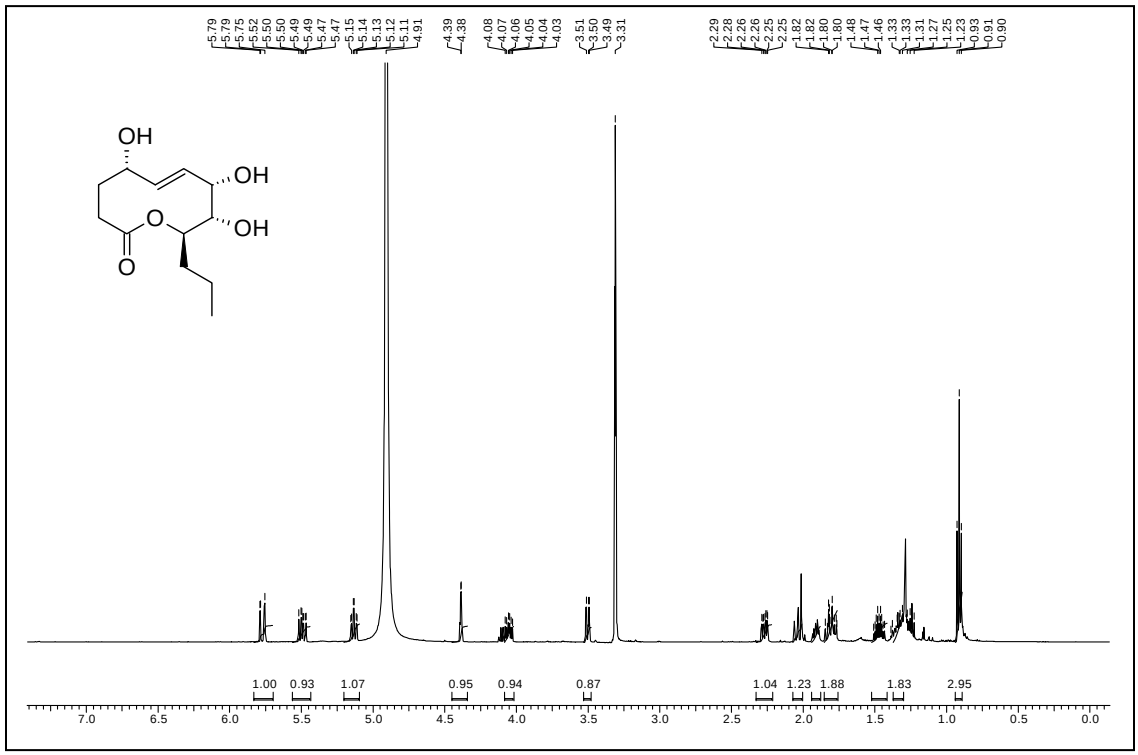
^{13}C NMR Spectrum of 100 in $CDCl_3$



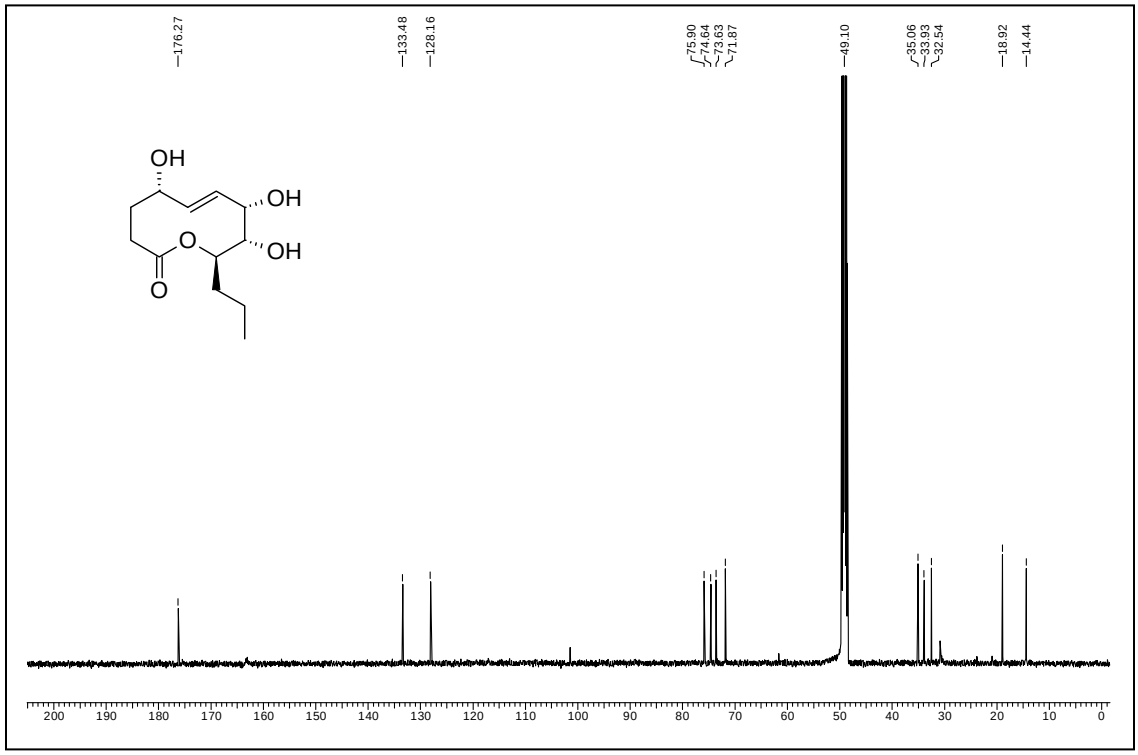
^{1}H NMR Spectrum of 101 in $CDCl_3$



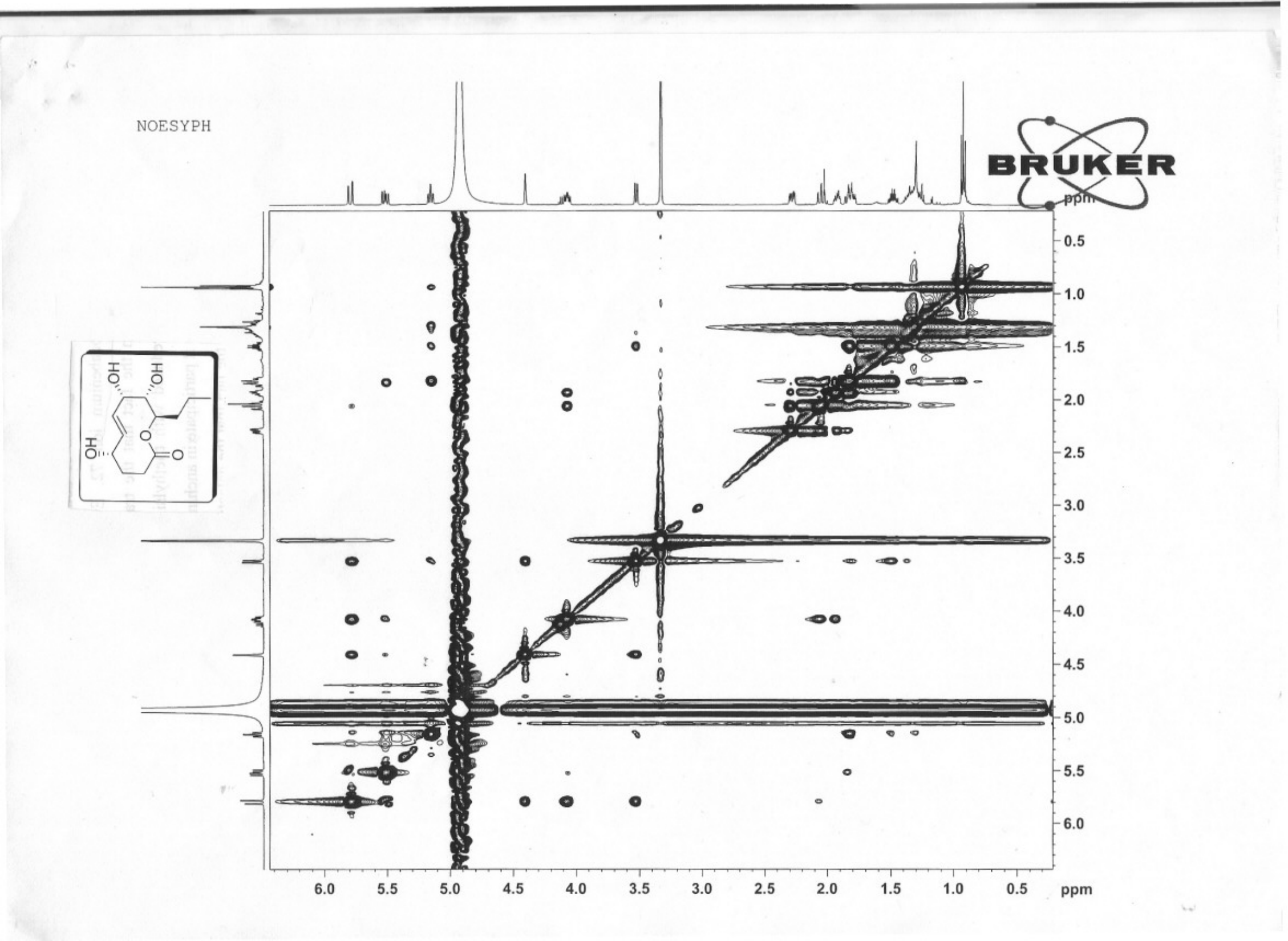
^{13}C NMR Spectrum of 101 in $CDCl_3$



^{1}H NMR Spectrum of 64 in CD_3OD



^{13}C NMR Spectrum of 64 in $CDCl_3$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BRUKER
OH
OH
OH
O
O
ppm
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1.0
1.5
2.0
2.5
3.0
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4.0
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5.0
5.5
6.0
6.0
5.5
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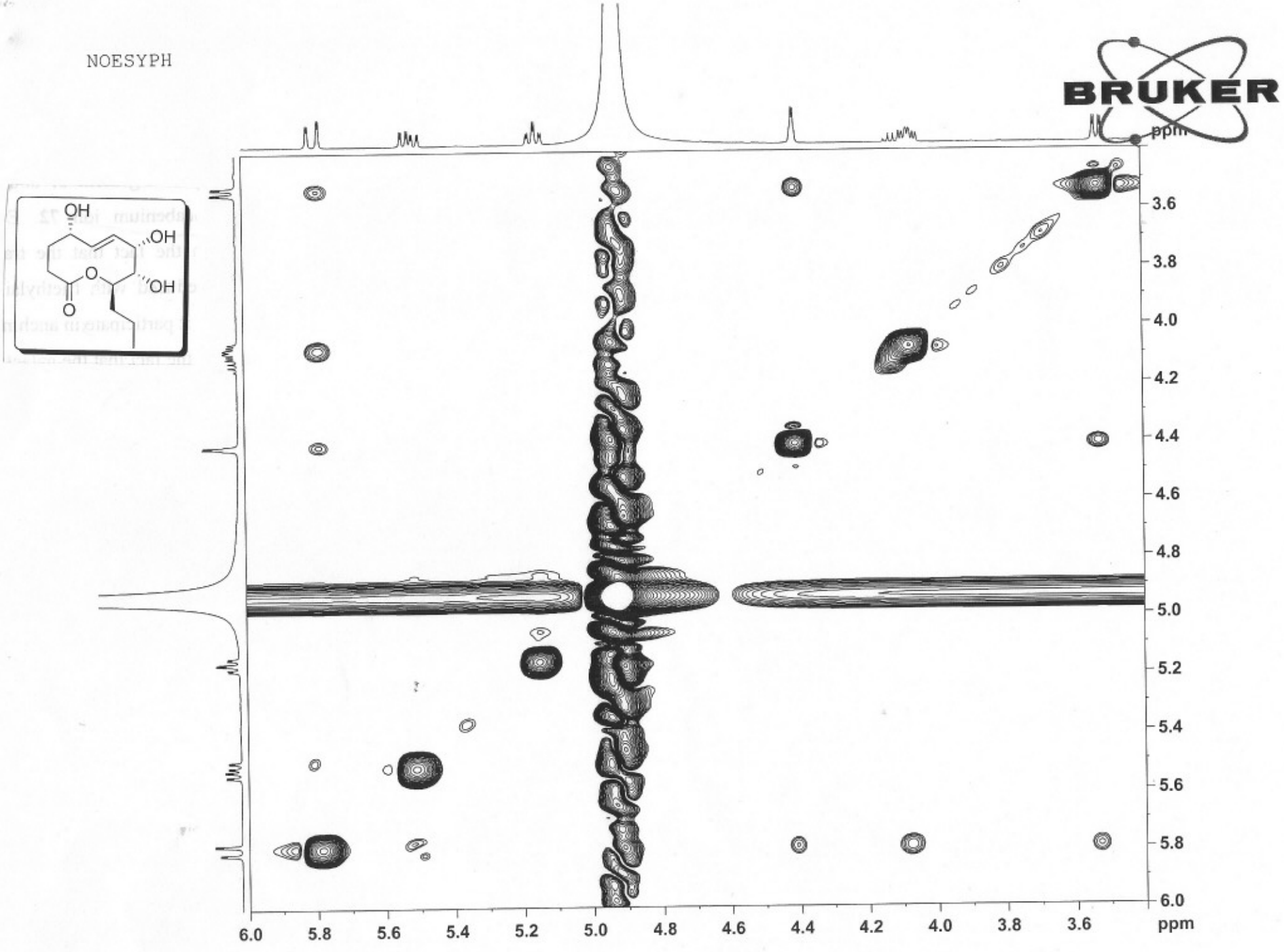
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

NOESYPH


BRUKER
ppm
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OH
OH
O
O
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4.2
4.4
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5.6
5.8
6.0
6.0
5.8
5.6
5.4
5.2
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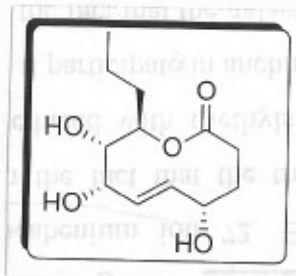
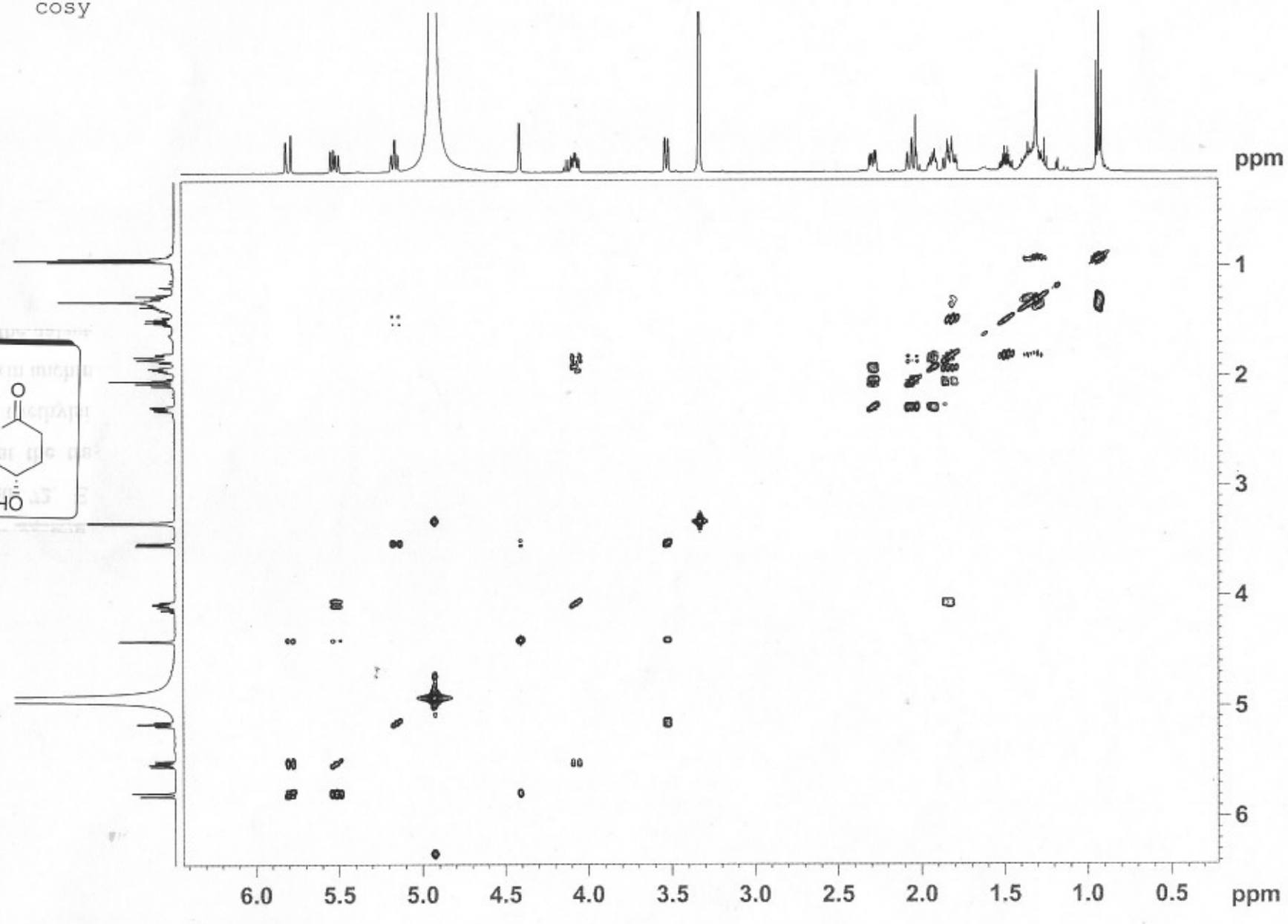
4.8
4.6
4.4
4.2
4.0
3.8
3.6
ppm

Mondal
cosy





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List of Publications

1. “Synthetic studies toward macrocidins: an RCM approach for the construction of the central cyclic core” C. V. Ramana, **Mohabul A. Mondal**, Vedavati G. Puranik and Mukund K. Gurjar. *Tetrahedron Lett.***2006**, *47*, 4061-4064.
2. “A carbohydrate based approach towards the synthesis of aspercyclide C” C. V. Ramana, **Mohabul A. Mondal**, Vedavati G. Puranik and Mukund K. Gurjar. *Tetrahedron Lett.* **2007**, *48*, 7524–7527.

Erratum