Studies Toward the Total Synthesis of (+)-Stagonolide D, Mangiferaelactone, Cytospolide E and Sinenside A

Thesis Submitted to the AcSIR for the Award of
The Degree of
DOCTOR OF PHILOSOPHY
In Chemical Sciences

By

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UNDER THE GUIDANCE OF
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Certificate

This is to certify that the work incorporated in this Ph.D. thesis entitled ***Studies Toward the Total Synthesis of (+)-Stagonolide D, Mangiferaelactone, Cytospolide E and Sinenside A*** submitted by Mr. ***Pareshkumar M. Vadhadiya*** to Academy of Scientific and Innovative Research (AcSIR) in fulfillment of the requirements for the award of the Degree of ***Doctor Of Philosophy***, embodies original research work under my supervision. We further certify that this work has not been submitted to any other University or Institution in part or full for the award of any degree or diploma. Research material obtained from other sources has been duly acknowledged in the thesis. Any text, illustration, table etc., used in the thesis from other sources, have been duly cited and acknowledged.

Pareshkumar M. Vadhadiya
(Student)

Dr. C. V. Ramana
(Supervisor)

DECLARATION

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

Organic Chemistry Division
CSIR-National Chemical Laboratory
Pune – 411008
April–2015 **(Pareshkumar M. Vadhadiya)**

Dedicated To...

My Beloved Parents

&

Rev. Dadaji

(Pandurangshashtri Athavale,

Founder,- Swadhyay Parivar)

Acknowledgements

A research thesis is an inspiring experience, of knowledge enhancement, more importantly of realising that individual effort is actually an outcome of the support of many. That is probably why thesis writers feel the urge to write acknowledgements!

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Finally, I am immensely thankful to Rev. Dadaji (Founder, Swadhyaya Parivar) – he has been my pillar of inspiration in my life and while I write these heartfelt acknowledgements, I feel all the more grateful to God for all that He has given me and I have used directly and indirectly for this research.

Pareshkumar M. Vadhadiya

DEFINITIONS AND ABREVIATIONS

Ac	–	Acetyl
Ac_2O	–	Acetic anhydride
aq.	–	Aqueous
Bn	–	Benzyl
BnBr	–	Benzyl bromide
$NaIO_4$	–	Sodium periodate
DCM	–	Dichloro methane
DCE	–	1,2-Dichloro ethane
n-BuLi	–	*n*-Butyl lithium
Cat.	–	Catalytic/catalyst
TsCl	–	Tosyl chloride
Conc.	–	Concentrated
MCPBA	–	*meta*-Chloroperbenzoic acid
DMF	–	*N,N*-Dimethylformamide
DMAP	–	*N,N'*-Dimethylaminopyridine
DMSO	–	Dimethyl sulfoxide
Et_2O	–	Diethyl ether
EtOAc	–	Ethyl acetate
Et_3N	–	Triethylamine
Im	–	Imidazole
LAH	–	Lithium aluminium hydride
Ms/Mesyl	–	Methanesulfonyl
Me	–	Methyl
CSA	–	Camphorsulfonic acid
NOESY	–	Nuclear overhauser effect spectroscopy
Pd/C	–	Palladium on Carbon
TBSCl	–	tert-Butyldimethylsilyl chloride
TBAF	–	Tetra-n-butylammonium fluoride
$NaClO_2$	–	Sodium chlorite
NaH_2PO_4	–	Sodium dihydrogen phosphate
PMBCl	–	Para-Methoxy benzyl chloride

$(COCl)_2$	–	Oxalyl chloride
PhMgBr	–	Phenyl magnesium bromide
CuCN	–	Copper cyanide
DCC	–	*N,N'*-Dicyclohexylcarbodiimide
EDCI	–	1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
DDQ	–	2,3-Dichlro-5,6-dicyanobenzoquinone
TFA	–	Trifloroacetic acid
NH_4Cl	–	Ammonium chloride
DIPEA	–	Diisopropylethyl amine
COSY	–	Correlation spectroscopy

Abbreviations used for NMR spectral informations:

br	Broad	q	Quartet	dd	doublet of doublet
d	Doublet	s	Singlet	dt	doublet of triplet
m	Multiplet	t	Triplet	ddd	doublet of doublet of doublet

GENERAL REMARKS

- 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 reactions are monitored by Thin Layer Chromatography (TLC) carried out on 0.25 mm E-Merck silica gel plates (60F–254) with UV light, I_2, and anisaldehyde in ethanol as developing agents.
- All evaporations were carried out under reduced pressure on Buchi rotary evaporator below 45 °C unless otherwise specified.
- Silica gel (60–120), (100–200), and (230–400) mesh were used for column chromatography.
- The melting points are uncorrected and the temperatures are in the degree centigrade scale.
- 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}.
- ^{1}H NMR spectra were recorded on AV–200 MHz, AV–400 MHz, JEOL AL-400 (400 MHz) and DRX–500 MHz spectrometer using tetramethylsilane (TMS) as an internal standard. Chemical shifts have been expressed in ppm units downfield from TMS.
- ^{13}C NMR spectra were recorded on AV–50 MHz, AV–100 MHz, JEOL AL-100 (100 MHz) and DRX–125 MHz spectrometer.
- Mass spectroscopy was carried out on PI QStar Pulsar (Hybrid Quadrupole-TOF LC/MS/MS) and High-resolution mass spectra (HRMS) were recorded on a Thermo Scientific Q-Exactive, Accela 1250 pump and also EI Mass spectra were recorded on Finngan MAT–1020 spectrometer at 70 *eV* using a direct inlet system.

CONTENTS

ABSTRACT

Name of the Candidate	Pareshkumar M. Vadhadiya
Degree, Enrolment No. and Date	Ph. D in Chemical Sciences (10CC11J26049); January 2011
Title of the Thesis	Studies Toward the Total Synthesis of (+)-Stagonolide D, Mangiferaelactone, Cytospolide E and Sinenside A
Research Supervisor	Dr. C. V. Ramana (AcSIR, CSIR-NCL, Pune)

ABSTRACT

The thesis entitled "***Studies Toward the Total Synthesis of (+)-Stagonolide D, Mangiferaelactone, Cytospolide E and Sinenside A***" consist of two chapters. The first chapter is divided in to three sections A–C describing respectively the total synthesis of (+)-Stagonolide D, Mangiferaelactone and Cytospolide E. The second chapter describes the total synthesis of Sinenside A.

Chapter I:

Section-I: The total synthesis of (+)-Stagonolide D

The medium sized 10-membered lactones constitute the structural aspect of many biologically active natural products, commonly known as nonenolides or dacanolides. These were found to contain diverse biological behaviors including cytotoxic, phytotoxic, antimalarial, antifungal, antibacterial, and antimicrofilament in addition to some inhibitory effects against fish embryo larval development, AChE, and calmodulin-dependent cAMP phosphodiesterase. In 2008, Evidente *et. al* isolated five new nonenolides from the solid cultures of *Stagonosporta cirsii* and named them as Stagonolides B–F. These Stagonolides showed phytotoxic activities against *C. arvense*. As a part of an ongoing program on the total synthesis of nonenolide employing ring closing metathesis (RCM) as the key reaction, especially in the context of understanding influence of the allylic substituents on the outcome of the RCM, the total synthesis of Stagonolide D has been undertaken.

As shown in retrosynthetic analysis of Stagonolide D, the installation of the epoxide unit was identified as the final step in the total synthesis and a tandem TBS deprotection and simultaneous epoxide formation from the mesylate **2** has been planned in this context. The penultimate intermediate **2** could be realized from the macrolide **3** through selective TBS protection of allylic –OH groups and the subsequent mesylation of the remaining –OH group.

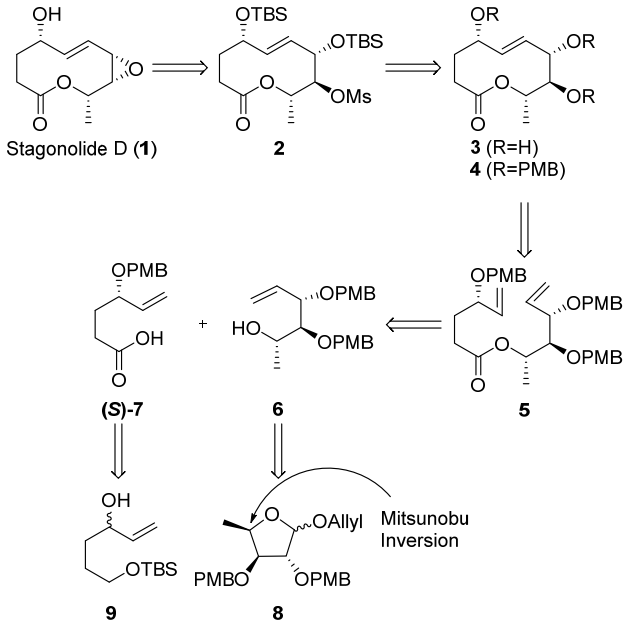
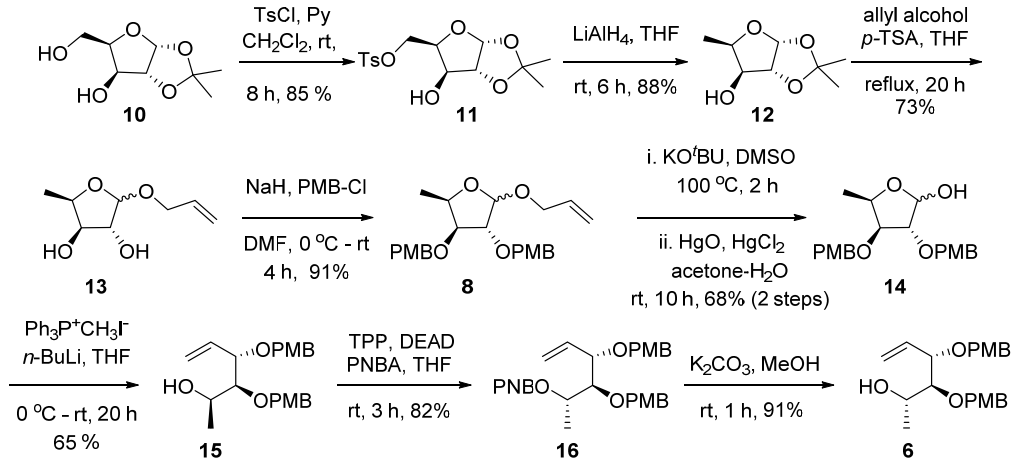


Figure 1. *Retrosynthetic analysis for Stagonolide D* (**1**)

The intermediate macrolide **3** could be accessed from the corresponding PMB protected macrolide **4** which, in turn, was planned by a RCM of the diene ester **5**. The alcohol **6** and acid (*S*)-**7** were identified as the key coupling partners for the synthesis of **5**. After a stereochemical comparison, D-xylose has been selected as a starting point for the chiral pool synthesis of the alcohol fragment **6**. The synthesis of the enantiomeric acid (*S*)-**7** has been earlier reported from our laboratory through the enzymatic resolution of the allyl alcohol **9**.

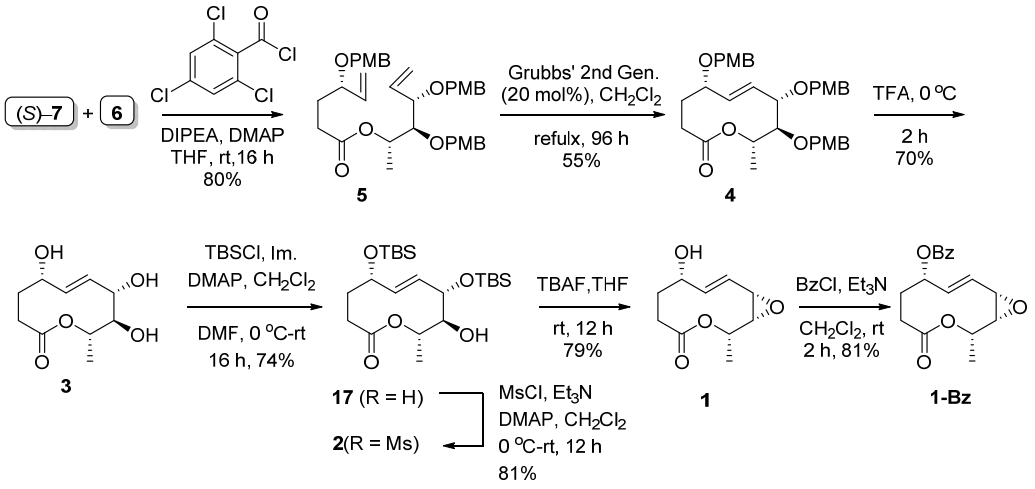


Scheme 1. *Synthesis of alcohol fragment* **6**

We began our synthesis with the preparation of the alcohol **6** from the known xylose-1,2-acetonide **10** (Scheme 1). The 5-deoxy-xylofuranose **12** was prepared as reported earlier

from **10** and then subjected for hydrolysis of the 1,2-acetonide in the presence of allylic alcohol and cat. *p*-TSA giving the anomeric mixture of allyl xylofuranosides **13**. The protection of the free hydroxyl groups in **13** as their PMB ethers resulted in **8**. Subsequently, compound **8** was subjected for deallylation followed by one carbon Witting homologation to afford the alcohol **15**. Alcohol **15** upon Mitsunobu inversion employing *p*-nitrobenzoic acid as a nucleophile gave **16** which, upon base mediated ester hydrolysis, resulted in the synthesis of the key alcohol fragment **6**. The acid (*S*)-**7** has been synthesized by following the procedures that have been established earlier in our group.

The RCM precursor **5** was obtained by the coupling of acid (*S*)-**7** and alcohol **6** using the Yamaguchi reagent. The RCM of diene ester **5** was examined under various reaction conditions and complete consumption of diene ester **5** was observed after treatment with Grubbs' second generation catalyst in CH_2Cl_2 for four days, affording the RCM product **4** in moderate yield. The deprotection PMB group in macrolide **4** was carried out using TFA to yield the macrolide **3** as a white solid. Next, the selective TBS protection of both the allylic –OH groups was carried out by using TBSCl, imidazole in dichloromethane and DMF h to procure the di-*O*-TBS derivative **17** in 74% yield. The treatment of **17** with methanesulphonyl chloride in the presence of triethyl amine in dichloromethane gave the penultimate mesylate **2**. Simultaneous cleavage of the two TBS groups followed by epoxide formation was performed with TBAF in THF at rt yielding compound **1**.

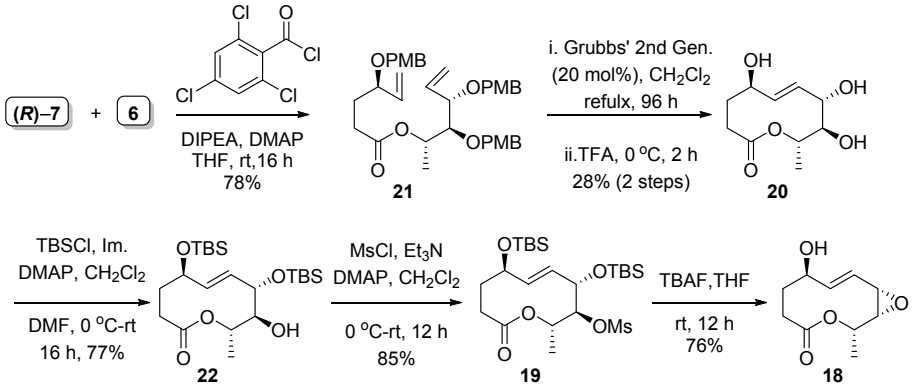


Scheme 2. *Total synthesis of putative structure of Stagonolide D* (**1**)

The NMR data of compound **1** was characterized by the presence of two sets of peaks in a ratio of 2:1, indicating the occurence of two closely related compounds which were established as the two different conformers of compound **1** in solution. However, the data of

both the compounds was found to be different from those reported for natural Stagonolide D thus warranting structural revision of Stagonolide D.

Total synthesis of (+)-Stagonolide D:



Scheme 3. *Total Synthesis of (+) - Stagonolide D*

As an alternative structural possibility, we prepared compound **18**, a stereoisomer of **1** by considering the fact that the spectral data of synthetic **1** and the data reported for the naturally occurring Stagonolide D were found to be different mainly in the region of olefin and H-C(4). As described in Scheme 3, the acid (*R*)-**7** and the alcohol **6** were connected as above by means of the Yamaguchi procedure to yield ester **21**. As expected, the RCM of diene **21** was sluggish and also the separation of the resulting lactone was found to be tedious. Therefore the crude metathesis reaction mixture was used directly for the PMB deprotection with TFA to yield the triol **20** in 28% yield over two steps. Moving forward in this direction, the allylic hydroxyl groups were protected as their TBS ethers, followed by mesylation of the remaining -OH group of the resulting compound **22** to obtain mesylate **19**, which upon treatment with TBAF at rt in THF gave compound **18**. Compound **18** was also found to be existing as a 10:1 mixture of two equilibrating conformational isomers. Gratifyingly, the spectral data of major conformer was found to be in agrement with the data reported for natural roduct. Some of the peaks corresponding to the minor conformer could be seen in the ^{1}H and 2D NMR spectra of the natural product which were ignored by the isolated group being considered as impurities. The opposite sign of the specific rotation of synthetic Stagonolide (**18**) [+76.8 (*c* 0.2, $CHCl_3$)] and natural stagonolide [–82.0 (*c* 0.2, $CHCl_3$)] revealed that it was the *anti*-pode of the natural Stagonolide D.

To conclude, the total synthesis of the putative structure of Stagonolide D and of the unnatural enantiomer (+)-Stagonolide D has been accomplished, thus revising its proposed relative configuration and also determining its absolute configuration as (4*S*,7*R*,8*R*,9*S*). The

key nonenolide unit has been constructed by employing ring closing metathesis and the oxirane ring has been formed by a concomitant *O*-TBS-deprotection and ring closure.

Section-II: The total synthesis of Mangiferaelactone

Mangiferaelactone (**23**) was isolated in 2014 from a solid culture of the endophytic fungus *Pestalotiopsis manguiferae* that was grown on a small shrub common in the central region of Panama. Mangiferaelactone showed a minimum inhibitory concentration (MIC) of 1.6863 mg/mL against *Listeria monocytogenes*, and 0.5529 mg/mL against *Bacillus cereus*. Mangiferaelactone is the optical antipode of the natural product Xyolide. Xyolide was isolated from the Amazonian endophytes *Xylaria feejeensis* in 2013. Encouraged by our previous successful implementation of ring closing metathesis (RCM) in the total syntheses of Multiplolide A, Stagonolide B and (+)- Stagonolide D, we were interested in exploring the RCM approach for the synthesis of Mangiferaelactone (**23**), as it possess a favourable *syn*-arrangement of the allylic substituents for RCM.

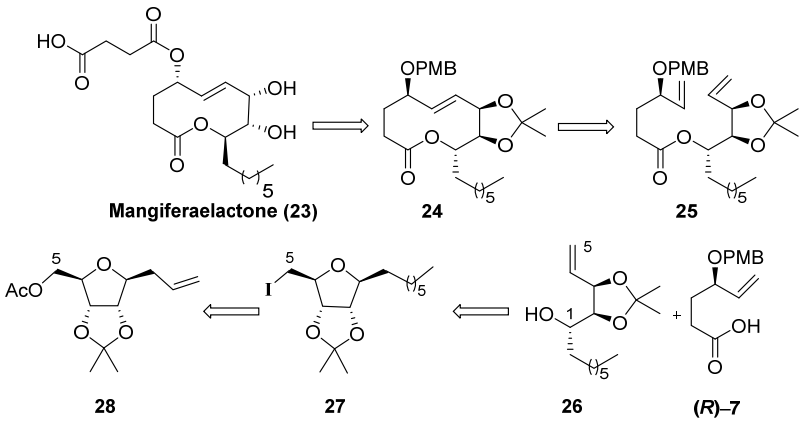
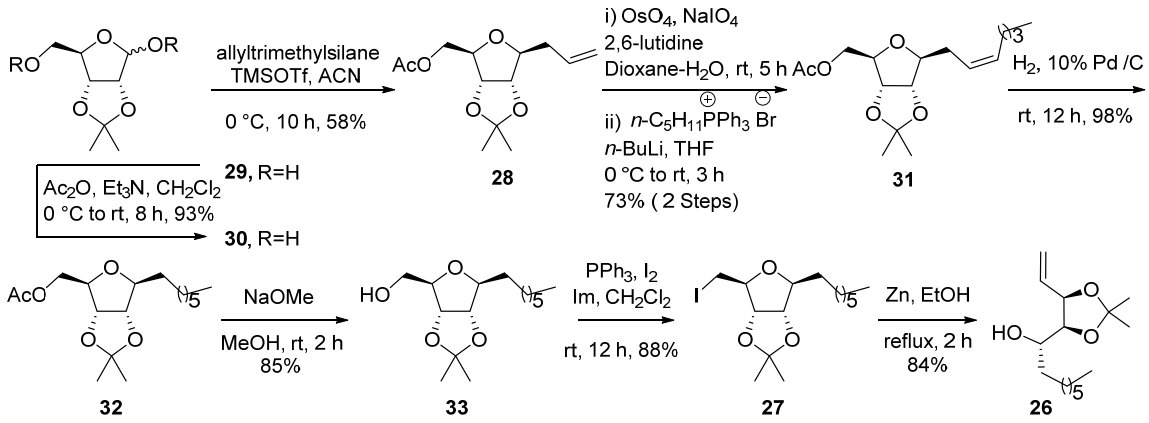


Figure 2. *Retrosynthetic analysis for Mangiferaelactone* (**23**)

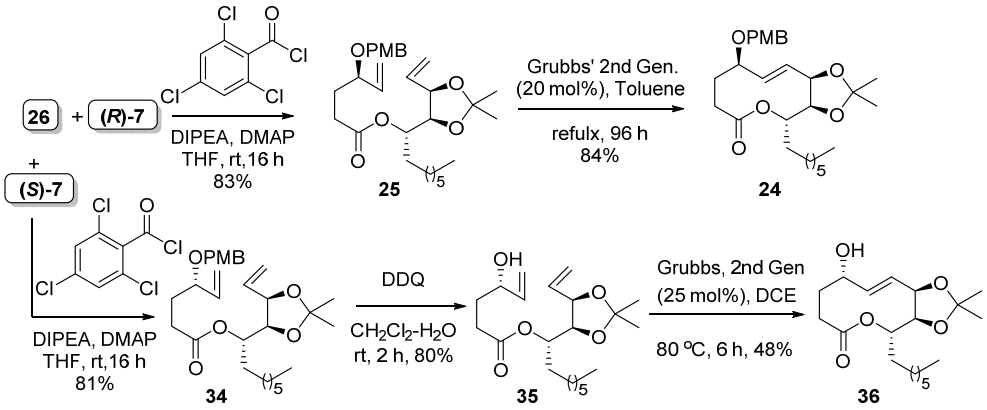
As outlined in our retrosynthesis, it was envisaged that the succinic acid moiety introduced at the penultimate step followed by acetonide deprotection would give the target molecule. The construction of the central nonenolide core was planned from the known acid (*R*)-**7** and alcohol **26**. The synthesis of alcohol **26** was planned from the Bernet-Vasella fragmentation of the iodo derivative of *β*-^{n}heptyl *C*-riboside **27** which, in turn, can be accessed from the *C*-allyl ribofuranoside **28** through Wittig homologation followed by simple functional group transformations.

Scheme 4 saliently describes the synthesis of the key alcohol fragment. Conversion of the known D-ribose monoacetonide **29** to *C*-allylribofuranoside **28** was achieved on the basis of methodology from literature reports. Subsequent oxidative cleavage of the double bond in



Scheme 4. *Synthesis of alcohol fragment **24***

compound **28** by $OsO_4/NaIO_4$ in the presence of 2,6-lutidine followed by 5-carbon Wittig homologation of the intermediate aldehyde gave exclusively the *Z*-isomer **31** in 73% yield over two steps. The hydrogenation of the double bond in compound **31** employing 10% Pd/C and subsequent deacetylation of the resulting compound **32** with NaOMe in methanol gave the alcohol **33**. The key iodo derivative **27** was prepared by treating **33** with iodine in the presence of PPh_3 and imidazole in CH_2Cl_2 at room temperature. Finally, the fragmentation of compound **27**was carried out with Zn in refluxing ethanol to afford the alcohol fragment **26**.

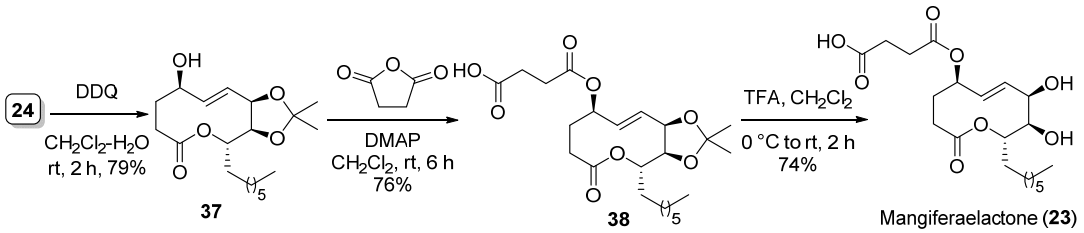


Scheme 5. *RCM of two different diene ester*

Next, the esterification of carboxylic acid (*R*)-**7** with alcohol **26** under the Yamaguchi conditions gave the diene ester **25**. As expected, with the second-generation Grubbs catalyst the RCM of **25** proceeded smoothly and provided the 10-membered lactone **24** as a single *E*-stereoisomer in very good yield. To verify our hypothesis about the role of relative stereochemistry of allylic substituents on the RCM outcome, the diene ester **34** was prepared by coupling the acid (*S*)-**7** and alcohol **26**. As expected, the RCM of the fully protected diene ester **34** was found to mainly yield the oligomeric products. To probe further in this direction, the PMB protecting group of **34** was deprotected with DDQ. As expected the ring closing

metathesis of the resulting diene ester **35** was sluggish with the second generation Grubbs' catalyst at reflux temperature in 1,2-dichloroethane finally providing the nonenolide **36**.

After having examined the feasibility of the RCM with both the diastereomers, next we proceeded for completing the total synthesis of the natural product. The deprotection of the PMB group in compound **24** was carried out by using DDQ and the free –OH group in the resulting hydroxylactone **37** was subjected for esterification with succinic anhydride in the presence of DMAP in CH_2Cl_2 to afford **38**. To this end, the deprotection of the acetonide group in compound **38** with TFA in CH_2Cl_2 provided the target Mangiferaelactone (**23**) in very good yields. The spectral data of **23** was in accordance with the data reported and the observed optical rotation [−2.1 (c 1.0, MeOH)] confirmed the assigned absolute configuration.



Scheme 6. *Total synthesis of Mangiferaelactone **(22)***

In conclusion, the first total synthesis of Mangiferaelactone (**23**) confirming its absolute configuration has been completed. The central nonenolide ring was constructed using ring closing metathesis and Yamaguchi esterification. The key alcohol fragment was synthesized by the Bernet–Vasella fragmentation of a *C*-ribofuranoside.

Section-III: Studies towards the total synthesis of Cytospolide E

The bioassay-guided fractionation of secondary metabolites from a crude acetone extract of *Cytospora sp*., an endophytic fungus from *Ilex canariensis* shrub has let to isolation of a new set of nonanolides namely cytospolides (Cytospolides A–E). Cytospolides A–E have an unprecedented 15-carbon skeleton with a unique C-2 methyl group. During the initial bioassay tests, these C2 epimers illustrated different cytotoxic properties against a A549 cell line, suggesting a probable stereochemical influence of the C2 methyl group in the growth inhibition of tumor cells (zero activity for Cytospolide A–D to IC_{50} = 7.09 μg/mL for Cytospolide E).

The retrosynthetic analysis for Cytospolide E (**39**) is depicted in Figure 3**.** Cytospolide E (**39**) could be obtained from the diene ester **40** by the ring closing metathesis (RCM) which, in turn, could be derived from the Yamaguchi esterification of an alcohol **41** and an

acid **42**. The synthesis of alcohol **41** was planned from D-glyceraldehye and acid **42** could be accessed by means of the asymmetric Evans Aldol reaction of acrolein.

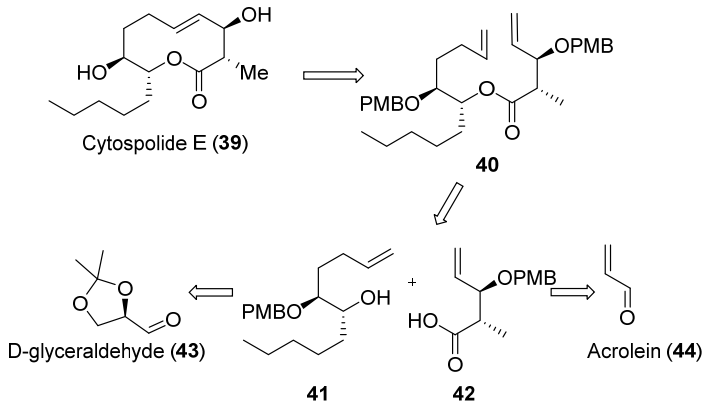
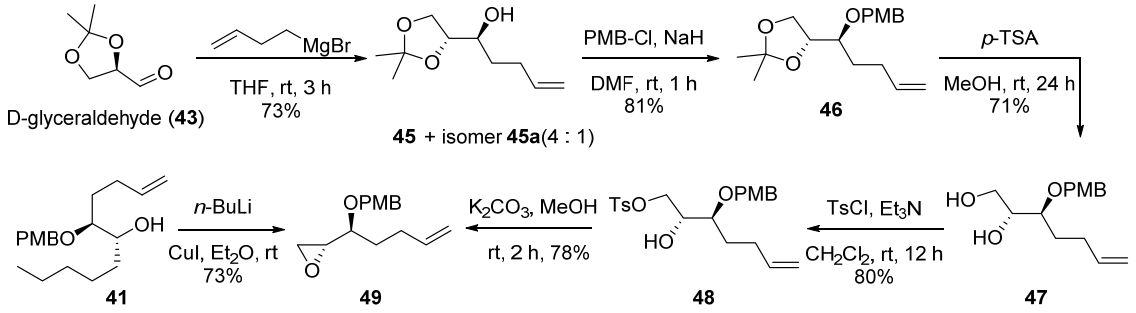


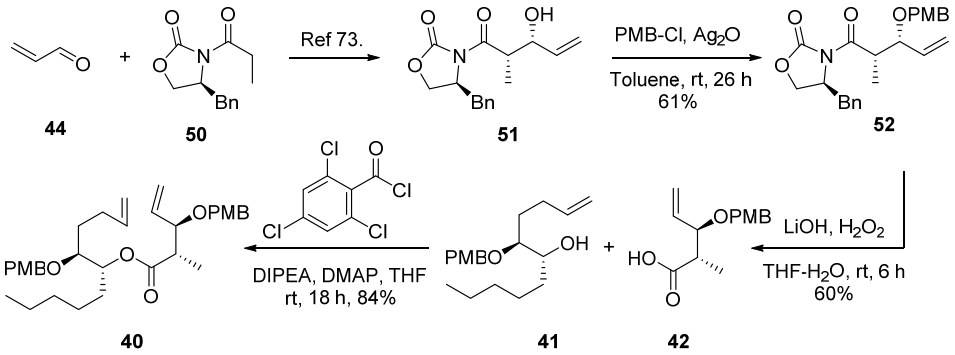
Figure 3. *Retrosynthetic disconnections for Cytospolide E (**39**)*

Our synthetic effort for the alcohol **41** originated from the Grignard addition of but-3-enylmagnesium bromide to D-glyceraldehyde to give a mixture of separable diastereomers **45** and **45a** in a 4:1 ratio with 78% yield. The free hydroxyl group of the required anti-alcohol **45** was protected as its PMB ether followed by the deprotection of acetonide group in resulting compound **46** in the presence of catalytic *p*-TSA in methanol to give the diol **47** in 71% yield. The primary hydroxyl group of diol **47** was selectively tosylated by treating with *p*-TsCl, and triethylamine in CH_2Cl_2 and the resulting tosylate **48** was used for the oxirane formation using K_2CO_3 in methanol to furnish the epoxide **49**. Finally, the regioselective opening of the epoxide **49** was carried out using *n*-butyl lithium in presence of CuI and the required alcohol fragment **41** was obtained in 73% yield.



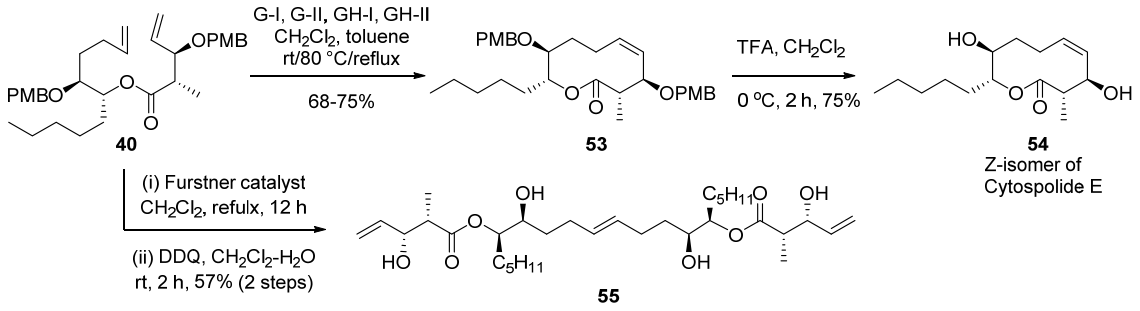
Scheme 7. *Synthesis of alcohol fragment **41***

The synthesis of acid fragment **42** is illustrated in Scheme 8. Acrolein was subjected to asymmetric aldol reaction using the known Evans oxazolidinone **50** in the presence of $TiCl_4$, DIPEA to produce the *syn*-aldol product **51** in 73% yield. The protection of the free hydroxy group in compound **51** as a PMB ether followed by hydrolysis of oxazolidinone under basic conditions gave the requisite acid **42**.



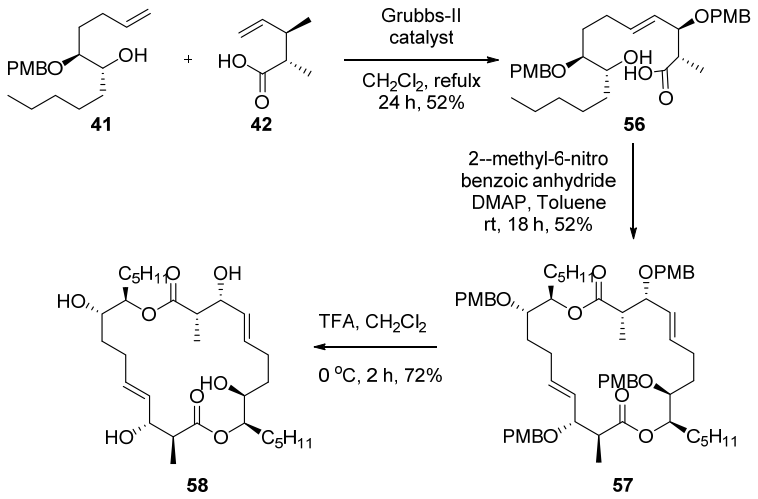
Scheme 8. *Synthesis of Diene ester **40***

The required diene ester **40** was prepared in 84% yields by coupling alcohol **41** and acid **42** under Yamaguchi esterification conditions. The RCM of **40** with the Grubbs' second generation catalyst in CH_2Cl_2 at reflux temperature for 3 h gave the RCM product **53** with the Z geometry of the newly forming double bond in 73% yield. Other attempts for the ring-closing metathesis of diene **40** by employing CH_2Cl_2 or toluene as the solvent at different temperatures in combination with Grubbs' first generation catalyst (Ru-I) or Grubbs' second generation catalyst (Ru-II) or Hoveyda–Grubbs' catalyst led to the formation of lactone **53** bearing a *cis*-geometry at the newly created double bond. Finally, the deprotection of PMB ethers of compound **53** using TFA in CH_2Cl_2 at 0 °C gave the Z-isomer of Cytospolide E (**54**) in 70% yield.



Scheme 9. *Attempted RCM of diene ester **40***

Fürstner has earlier suggested that the use of a less reactive rutheniumindenylidene complex should avoid equilibration of the products initially formed and lead to kinetically more stable *E*-products. Surprisingly, when the RCM of **40** was attempted using a catalytic amount of the rutheniumindenylidene complex with CH_2Cl_2 as solvent under reflux conditions afforded a complex mixture amongst which the dimer **55** was isolated as a major component after the deprotection of PMB using DDQ.



Scheme 10. *Cross metathesis approach for Cytospolide E*

The failure in the synthesis of the natural Cytospolide E with RCM led us to think in reverse direction of the ring closure. For that, we decided on a cross metathesis reaction at the beginning and an intramolecular esterification was planned at the later stage. According to the speculation, the cross metathesis between the alcohol **41** and the acid **42** was proceeded smoothly in the presence of Grubbs second generation catalyst to give exclusively alkene **56** having a *trans* geometry. The lactonization of the seco acid **56** employingYamaguchi, Corey-Nicolaou lactonization methods or with other coupling reagents such as DCC and EDCI resulted in a complex reaction mixture. However, the Shiina lactonization using 2-methyl-6-nitrobenzoic anhydride in the presence of DMAP proceeded smoothly to give a 20-membered macrolide **57** in 68% yield. Finally, the resultant 20-membered macrolide **57** was subjected to PMB deprotection with TFA in dichloromethane to produce the compound **58** in 72% yields.

In conclusion, the total synthesis of the Z-isomer of Cytospolide E was achieved by using RCM and a 20-membered macrolactone was obtained while aiming to synthesize the natural product. D-mannitol was used as a chiral pool starting material for the building of the alcohol fragment and Evan's aldol reaction was employed for the acid fragments.

Chapter II: The total synthesis of Sinenside A

In 2012, Ning Li and co-workers isolated two novel norlignan glucosides, namely Sinensides A (**59**) and B along with six known norlignan glucosides from the ethanolic extract of the *Curculigo sinensis* plant. In a preliminary screening, the norlignan glucosides Sinensides A (**59**) and B showed strong 1,1-diphenyl-2-picrylhydrazyl (DPPH) free radical scavenging activity with IC_{50} values comparable to that of the positive control ascorbic acid (IC_{50} = 45.84 μM).

As outlined in our retrosynthesis, it was envisaged that the *β*-glucoside link present in **59** should be installed at an early stage. The desired tricyclic core of sinenside A (**59**) would be constructed from the aldehyde *via* intramolecular acetalization and an olefin unit represents a surrogate for this aldehyde group. The orthoester **60** and *3°*-alcohols **61** were selected as partners for the key glycosidation reaction, which was expected to give rise to exclusive *β*-anomeric selectivity.

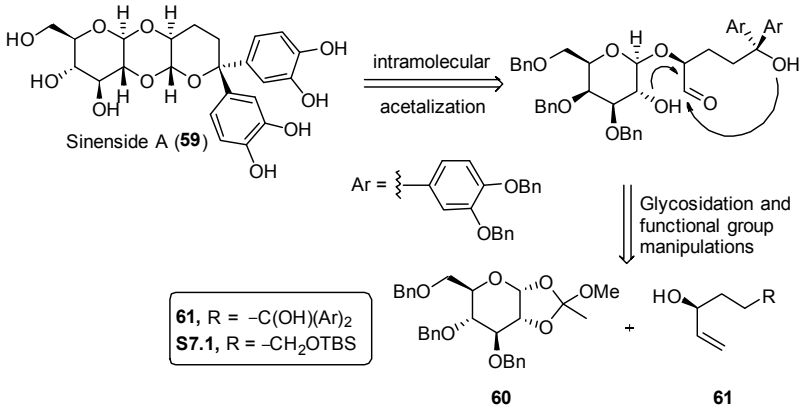
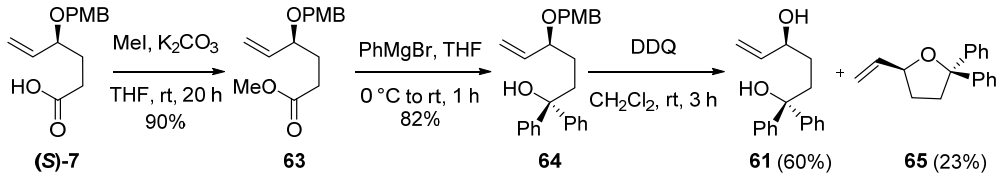


Figure 4. *Our key retrosynthetic disconnections for Sinenside A*

Synthesis of the central core of Sinenside A:

According to the retrosynthetic strategy as depicted in Figure 3, the model studies for the synthesis of the central core of Sinenside A started with the preparation of glycosyl acceptors **61**. The reaction of previously synthesized acid (***S***)-**7** with excess of K_2CO_3 and MeI in dry THF gave ester **63** in 90% yield. The nucleophilic addition of the ester **63** with the phenyl magnesium bromide in THF at rt furnished the alcohol **64**. To access the glycosyl acceptor **61**, the PMB group of compound **64** was removed using DDQ in CH_2Cl_2-water (18:1) to afford **61** (in 60% yield) along with cyclic ether **65** (in 23% yield).

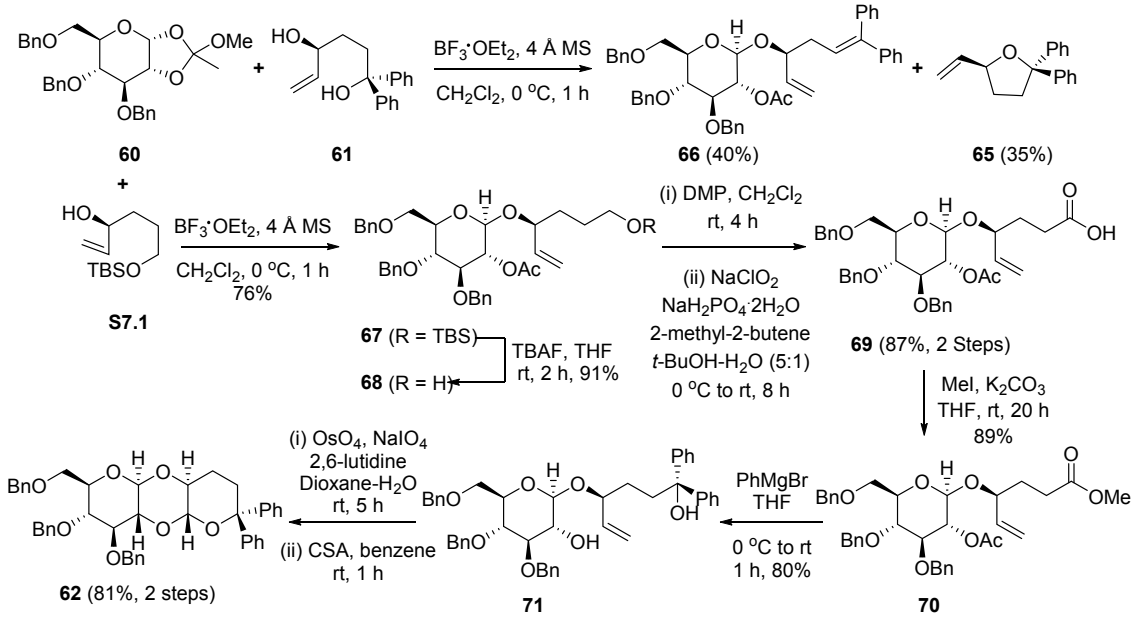


Scheme 11. *Synthesis of glycosyl acceptor **61***

The synthesis of acceptor **S7.1** has been earlier reported from our laboratory from commercially available 4-pentenol in the context of the total synthesis of Stagonolide B and the glycosyl donor **60** was prepared from glucose following a literature procedure.

Glycosidation reaction with two different acceptors:

After having the glycosyl donor and both the acceptors in hand, our attention next turned to the key glycosidation reaction. The glycosidation of **61** with orthoester **60** using $BF_3{\cdot}Et_2O$ (0.15 equiv.) in dichloromethane in the presence of 4Å molecular sieves gave the *β*-glucoside **66** along with the cyclized ether **65**. In order to avoid acid-catalyzed undesired cyclization and elimination of the sensitive tertiary hydroxy group, it was next decided to use the simple allylic alcohol **S7.1** as an acceptor. The glycosidation of **S7.1** with orthoester **60** proceeded smoothly and provided exclusively the *β*-glucoside **67** in 76% yield. The deprotection of TBS ether in compound **67** using TBAF in THF followed by the oxidation with Dess–Martin periodinane gave the aldehyde which was further oxidized to the corresponding acid **69** by treating with $NaClO_2$ and $NaH_2PO_4.H_2O$ in the presence 2-methyl-2-butene in *t*-BuOH and H_2O. Subsequent methylation of acid **69** with MeI in the presence of K_2CO_3 in dry THF gave the ester **70**.

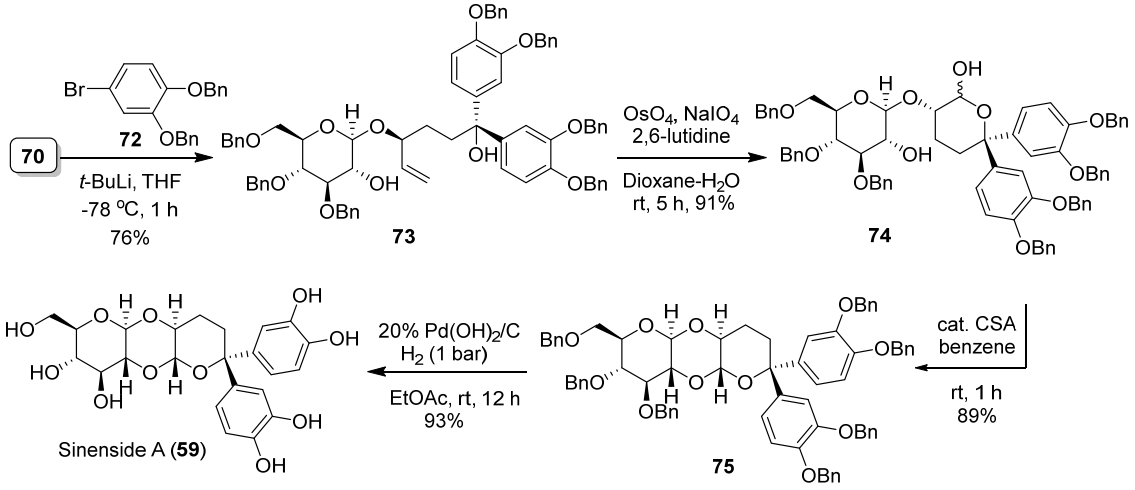


Scheme 12. *Synthesis of core structure of Sinenside A*

The Grignard reaction of the key ester **70** with excess phenyl magnesium bromide provided the diol **71** which, upon the oxidative cleavage of the double bond using $OsO_4/NaIO_4$ in the presence of 2,6-lutidine followed by intramolecular acetalization of intermediate aldehyde employing a catalytic amount of CSA in benzene at room temperature, afforded the requisite Sinenside A analogue **62**.

Total synthesis of Sinenside A:

After the synthesis of the complete core of Sinsenide A we focused our attention on the total synthesis of Sinenside A. The direct preparation of the Mg-based Grignard reagent using 3,4-bis(benzyloxy)bromobenzene **72** was found to be a problem. Alternatively, employing ^{t}BuLi for halogen-metal exchange, the diaryl addition to ester **70** could be successfully conducted to obtain the diol **73** in 76% yield. Next, diol **73** was subjected to the oxidative olefin cleavage to afford an inseparable anomeric mixture of lactols **74** which, upon treatment catalytic amount of CSA in benzene gave the tricyclic compound **75** in 89% yield. To this end, employing 20% $Pd(OH)_2/C$ in EtOAc, the exclusive hydrogenolysis of the benzyl ethers in **75** could be carried out successfully to afford the natural product Sinenside A (**59**) in quantitative yield. The spectral and analytical data of synthetic **59** were in full agreement and the specific rotation measured [–20.5 (*c* = 0.2 in MeOH)] was close to the values reported for the natural product [–15.6 (*c* = 0.11 in MeOH)].



Scheme 9. *Total synthesis of Sinenside A (**59**)*

Conclusion:

In conclusion, the first total synthesis of Sinenside A has been completed in 9 steps from readily accessible starting materials. The key step involves an intramolecular acetalization that directly affords the target parent tricyclic ring system. The approach adopted is divergent in nature and should be usable for the preparation of various analogs of sinenside A, along with the other norlignans of the same family.

INTRODUCTION

Natural product chemistry has achieved huge progress in the past few years as almost one third of current drugs are natural products or their derivatives (or mimics). Among them, macrocycles containing natural products placed themeselves in a special position in drug discovery as they possess a wide range of biological properties such as antitumor, antibiotic, antifungal etc.[1] The macrocyclic structure having one or more ester linkages are normally termed as macrolides (or macrocyclic ring lactone). These are the secondary metabolites that include the spiro-macrolide, macrodiolide, macrotetrolide etc.[2] Drugs like Zearalenone, Nonactin, Mevinolin (lovastatin), Erythromycin A, FK 506, Nystatin, Rapamycin, Avermectin and Amphotericin B are the popular examples in this regard.[3]

The medium sized 10-membered lactones constitute the structural aspect of many biologically active natural products, commonly known as nonenolides or dacanolides.[2b,4] The investigation on nonenolide was actually traced in 1942 when the Jasmine ketolactone was isolated as a component of the essential oil of *Jasminum grandif lorum*. However, its structure was completely elucidated in 1964.[5] Likewise, the isolation of diplodialide A as a steroid hydroxylase inhibitor from *Diplodiapinea* brought attention in 1975 as the second clue regarding this.[6] Over the last four decades, a rise in the number of articles in the literature reveals a great deal of advances of the nonenolide family from a variety of microorganisms. Most of the nonenolide metabolites are now being isolated from fungi, bacteria and marine organisms, whereas a few have been isolated from several marine invertebrates and plants. These were found to contain diverse biological behaviors including cytotoxic, phytotoxic, antimalarial, antifungal, antibacterial, and antimicrofilament in addition to some inhibitory effects against fish embryo larval development, AChE, and calmodulin-dependent cAMP phosphodiesterase. On the basis of their structures, these have been classified into monocyclic, aliphatic bicyclic and aromatic bicyclic 10-membered ring lactones.

I. Monocyclic 10-membered ring lactones

The largest fraction of the nonenolide family belongs to monocyclic 10-membered ring lactones which are again classified into two sub-groups such as polyketalides and oxylipins depending upon their biosynthesis.

Polyketides:

The carbon skeleton of this class of natural products was biosynthesized *via* the polyketide pathway from eight acetate building blocks. Diplodialides that exhibit methyl

(usually located at C-9) and oxygen substituents on the lactone ring are the first described group of monocyclic 10-membered ring lactones (Figure S1.1). The Diplodialides A-D were isolated in 1975 by Ishida and Wada from the plant pathogenic fungus *Diplodia pinea*. Diplodialide A showed inhibitory activity against steroid hydroxylase.[6,7] In 1976, the simplest 10-membered lactones, Phoracantholides I and J were isolated from the metasternal gland secretion of the eucalypt longicorn *Phoracantha synonyma* (Figure S1.1).[8]

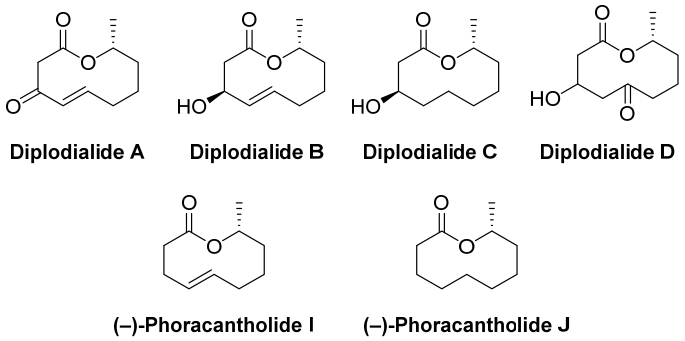


Figure S1.1. *Structures of Diplodialides A–D and Phoracantholides I–J*

In the early 1990s, from different strains of *Penicillium* species diverse nonenolides, namely Decarestrictines, have been isolated. Decarestrictines showed promising inhibition of cholesterol biosynthesis in both *in vivo* and *in vitro* studies.[9] The whole family of Decarestrictine seems to arise from a common pentaketide precursor that underwent subsequent modifications affording other members of the family. These decanolides feature a distribution of double bond and oxygen substituents in the form of hydroxy, epoxy and keto groups in different combinations across the ring. Decarestrictine D is the most potent

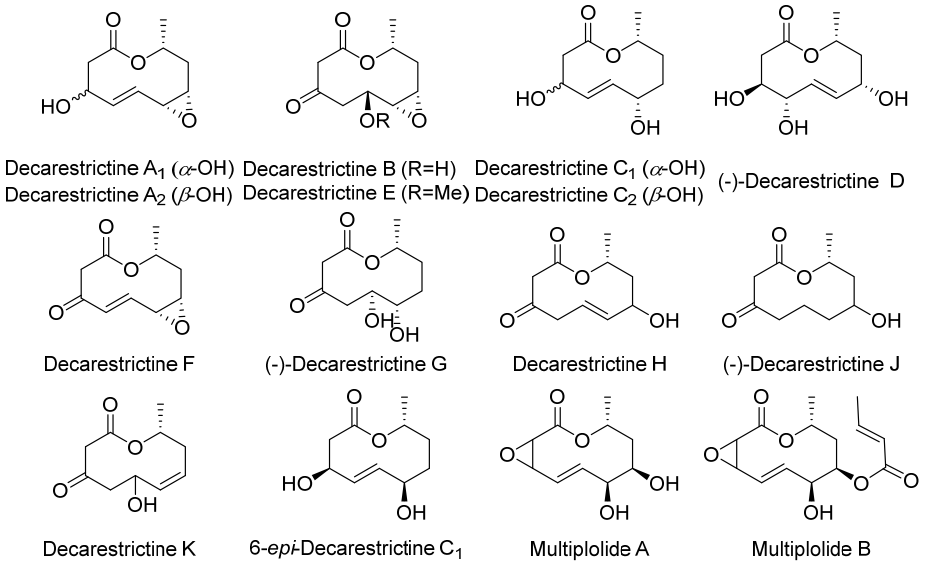
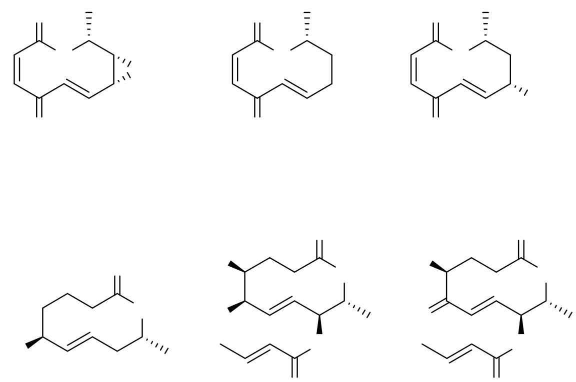


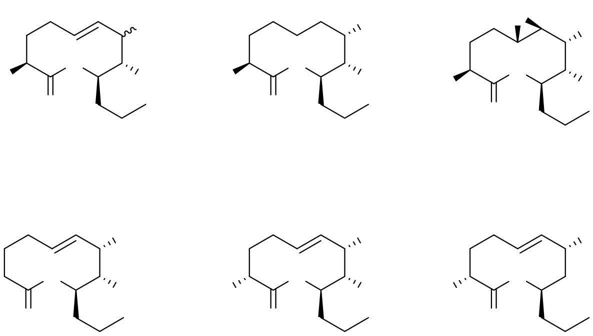
Figure S1.2. *Structurally related nonenolides Decarestricines (A1–K) & Multiplolides (A–B)*

PROHFXOH LQ WKLV IDPLO\ ZKLFK ZKHV FLDQQGDHGSLHDQQG HQ XFNDO KLRVH
VFOHURWLXP RI Polyporus tuberaster IXQJXV ZDV DOVR QDPHG $G&DV WXFNR
HSLPHU RI 'HFDUHVWULFWLQH & LQ Cordyceps militaris WKH IXQJXV
H[KLELWHG DQWLPDODULDO Plasmodium falciparum Y LWK H[WUDFWLRQ
L H 0XOWLSOROLGHV $ Xylaria multiplex L VRODWHG IURP UHODWHG
'HFDUHVWULFWLQH IDPLO\ )LJXUH 6



)LJXUH 6 Structures of Pyrenolides A–C and Aspinolides I–J

7KH XQVDWXUDWHG NHWR ODFWRQHV 3\UHQROLGHV $
Pyrenophora teres E\ 1XNLQD 7KH KLJKO\ IXQFWLRQDOL]HG 3\UHQROL
GHWHFWHG LQ WKH Ascochyta hyalospora ZKLFK H[KLELWV WKH JU
LQKLELWLRQ DQG PRUSKRJHQLF DFWLYLW\ $VSLQROLGHV ZHUH
UHSRUWHG WR EH IURP Aspergillus ochraceus FXOWXUH)LJXUH 6



)LJXUH 6 Structurally related nonenonolides Pinolidoxins, Herbarumins and Staganolides

,Q (YDQV et al. LVRODWHG WKH epi-3LQROLGR[LQ 'LK\GURSLQRO
DQG (SR[\SLQROLGR[LQ Ascochyta pinodes IURP WKH SRS\O JURXS DW WKH & SR
WKH FRPPRQ VWUXFWXUDO IHDWXUH LQ WKHVH PROHFXOHV

In 2011, Ling Li and Wen Zhang *et al.* reported the isolation of Cytospolides A–E (Figure S1.6), a nonenolides with an unprecedented 15-carbon skeleton and C2 methyl group from the endophytic fungus *Cytospora sp.*[19] The inversion of the absolute configuration at C2 from (*2R*) of Cytospolide D to (*2S*) of Cytospolide E led to an unexpected enhancement in cytotoxic activity which, to some extent, indicated a pivotal role of the C2 centre in the growth inhibition process. Further investigation on the trace compounds of the crude extract from the same fungus has resulted in the isolation of additional members of this family, namely Cytospolides F−Q.[20]

In 2012, Hiep *et al* isolated the new polyhydroxylated macrolides, Seimatopolide A and B from the fungus *Seimatosporium discosioides*, whose structures were established on the basis of 1D and 2D NMR spectroscopic analysis, and their absolute configurations were determined by the application of the modified Mosher's method.[21] These Seimatopolides are shown to activate the γ-sub type peroxysome prolifirator-activated receptors (PPAR-γ), which is an apparent crucial process in the regulation of type 2 diabetes. A comparison of the specific optical rotations and assigned configurations of Seimatopolide A and B isolated from natural sources with synthetic molecules suggested that the originally assigned (*3R, 6R, 7R, 9S*) and (*3R, 6R, 9S*)-configurations of Seimatopolides A and B should be corrected to (*3S, 6S, 7S, 9R*) and (*3S, 6S, 9R*) respectively[22] (Figure S1.7). Similarly, Xyolide, a new secondary metabolite from the Amazonian endophytic fungus *Xylaria fejeenis* was isolated by Handelsman[23] (Figure S1.7). The lowest concentration of Xyolide with a detectable activity against *Pythium ultimum* was 425 μM. The optical antipode of Xyolide is also another natural product which was isolated from a solid culture of the endophytic fungus *Pestalotiopsis manguiferae* by Luis Cubilla-Rios, named as Mangiferaelactone (Figure S1.7). Mangiferaelactone showed a minimum inhibitory concentration (MIC) of 1.6863 mg/mL against Listeria monocytogenes, and 0.5529 mg/mL against Bacillus cereus.[24]

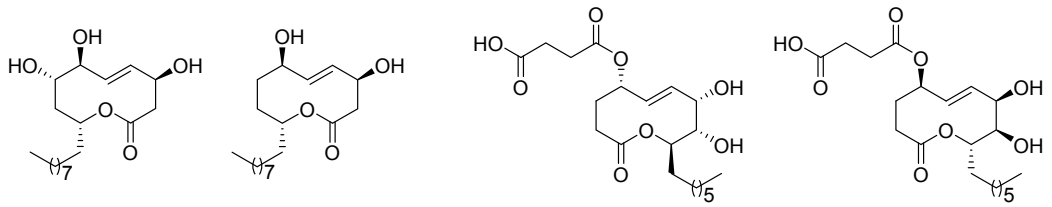
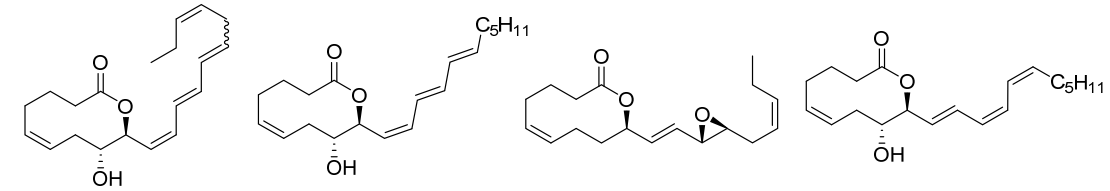


Figure S1.7. *Structure of polyhydroxy macrolide Seimatopolides, Xyolide and Mangiferaelactone*

Oxylipins:

In general, oxylipins are oxygenated fatty acid metabolites. One of the most biologically important groups of oxylipins in mammalian systems is the eicosanoid and these eicosanoids are potent modulators of immune responses and also play an important role in host physiological processes.[25] Didemnilactones A and B, and Neodidemnilactone consist of a 10-membered lactone associated with a hydrophilic side chain at the C9 carbon (Figure S1.8) were isolated in the early 1990s by Niwa.[26] These eicosanoid lactones were found in the colonial marine tunicate *Didemnum moseleyi* and showed moderate inhibitory activity against lipoxygenase.

In 1997, an 18-carbon epoxy lactone was isolated from the cyanobacterium *Aphanizomenon flos-aquae*.[27] This compound was shown to be an inhibitor of fish development and later isolated from the blue-green alga *Gloeotrichia* sp. collected in Montana's lakes[28] and was named as Mueggelone (Figure S1.8). Ascidiatrienolide was isolated in 1989 from the colonial marine ascidian *Didemnum candidum* (Figure S1.8). Initially, the structures were wrongly assigned as 9-membered lactones.[29] But later, the structure of ascidiatrienolide A was revised to a 10-membered lactone. In reality, it is an isomer of neodidemnilactone.



trans (-)-Didemnilactone A
cis (-)-Didemnilactone B
(-)-Neodidemnilactone
(+)-Mueggelone
(-)-Ascidiatrienolide

Figure S1.8. *Eicosanoid Decanolactones*

II. Bicyclic 10-membered lactones

A relatively less number of structurally complex nonenolides with additional rings has been isolated. The jasmine keto lactone and the nonenolide SCH 642305, which was isolated in 2003 from *Penicillium verrucosum*,[30] are example of aliphatic bicyclic 10-membered lactones whereas Sporostatin and Xestodecalactones A–C are the aromatic bicyclic 10-membered lactones. Sporostatin was isolated from *Sporormiella* sp. and was shown to be an inhibitor of cyclic adenosine 3,5'-monophosphate phosphodiesterase and a specific inhibitor of the epidermal growth factor (EGF) receptor tyrosine kinase.[31] Xestodecalactones A–C were isolated from the fungus *Penicillium cf. montanense* and also from the marine sponge

Xestospongia exigua. Xestodecalactone B was found to be active against *Candida albicans*[32] (Figure S1.9).

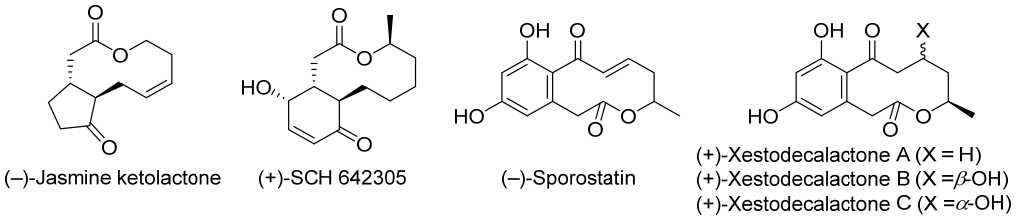


Figure S1.9. *Structurally of Bicyciic 10-membered lactone*

Various strategies for the construction of 10-membered lactones:

The wide variety of bioactivity and the fascinating functional diversity of these medium-sized ring secondary metabolites in nonenolide analogues has led to considerable awareness of their synthesis during the last two decades.[33] However, the synthesis of 10-membered lactones remains a great challenge among the macrolides. The destabilized nonbonding interactions, transannular interactions and unfavorable entropic factors are the major hurdles to overcome in the journey of synthesis. Nevertheless, many approaches have been put forward in the literature. Those are basically categorized by three main strategies:

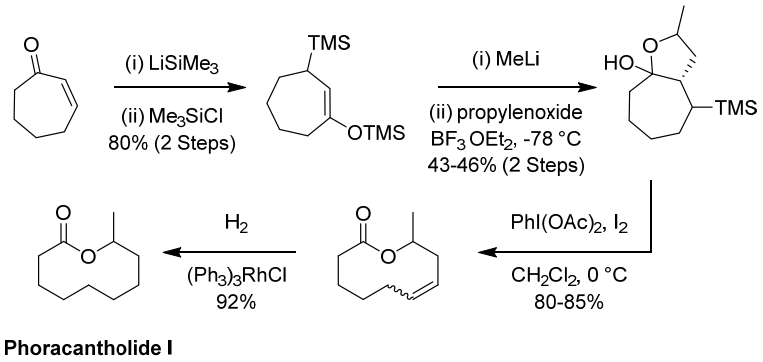
A. Ring expansion

B. Ring contraction

C. Intramolecular ring closure

A. Ring expansion Strategy

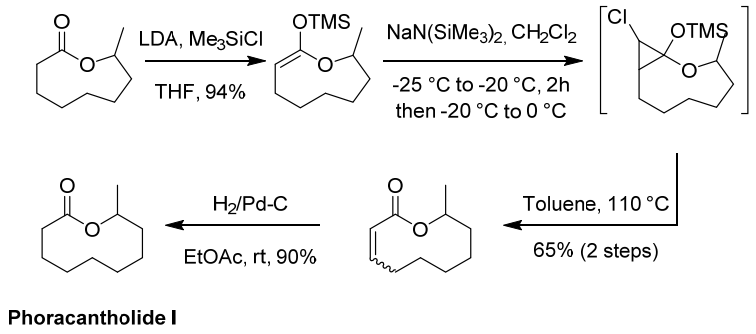
Ring expansion can be achieved by the cleavage of a C–C bond of a suitable starting material, cleavage of internal bonds in polycyclic systems, and also by the Baeyer-Villiger oxidation reaction.[2a,33a]



Scheme S1.1. *Total synthesis of (±)-Phoracantholide I by Posner et al*

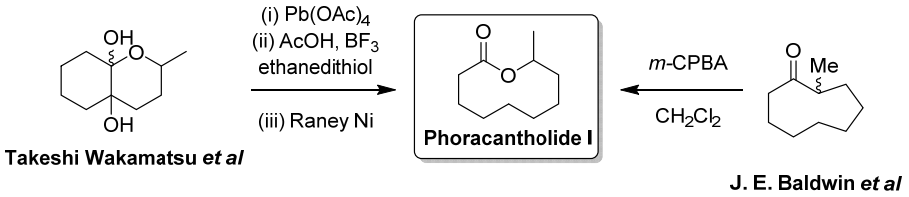
A ring expansion approach to the total synthesis of Phoracantholide I was developed by Posner et al.[34] They used the reaction of cycloheptenone with lithium trimethylsilane and

propylene epoxide to afford the intermediate hemiketal, which was then oxidized with iodosobenzene diacetate and iodine to give 10-membered homoallylic lactones as a 1:1 mixture of geometrical isomers. The reduction of the double bond in 10-membered homoallylic lactols led to (±)-Phoracantholide I (Scheme S1.1).



Scheme S1.2. *Total synthesis of (±)-Phoracantholide I by Fouque and Rousseau*

Similarly, Fouque and Rousseau also reported another effective ring expansion method comprising the silylenol ether addition of chlorocarbene to give a bicyclic intermediate, which rearranged into the E/Z-mixture of unsaturated lactones after heating in toluene. The hydrogenation of lactone gave the racemic (±)-Phoracantholide I (Scheme S1.2).[35]



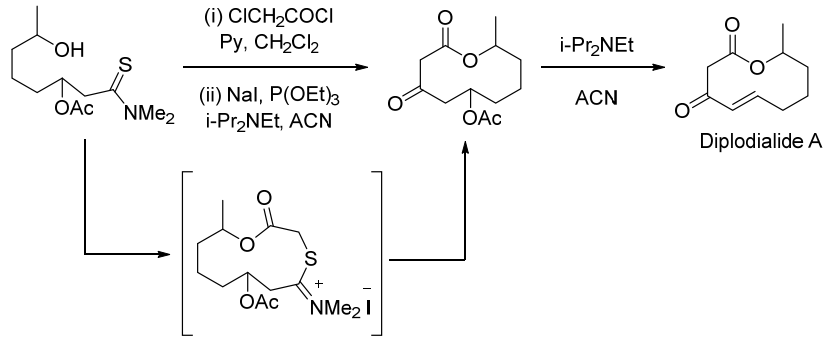
Scheme S1.3. *Ring expansion strategy for the total synthesis of (±)-phoracantholide I*

Another ring expansion method for the 10-membered lactone through oxidative cleavage of the bicyclic glycol with lead tetraacetate was reported by Takeshi Wakamatsu in the total synthesis of Phoracantholide I.[36] The reaction involves the ring opening of bicyclic glycols with lead tetraacetate in benzene and subsequent thiolactonization of the intermediate keto lactone followed by desulfurization with Raney nickel to afford the Phoracantholide I. Baldwin has also described racemic synthesis of Phoracantholide I via the ring expansion through Baeyer-Villiger oxidation of the cyclic ketone (Scheme S1.3). [37]

B. Ring contraction strategy

A report on the synthesis of macrolides through ring contraction is relatively rare due to the problem of finding suitable large-ring precursors. In 1979, Ireland and Brown

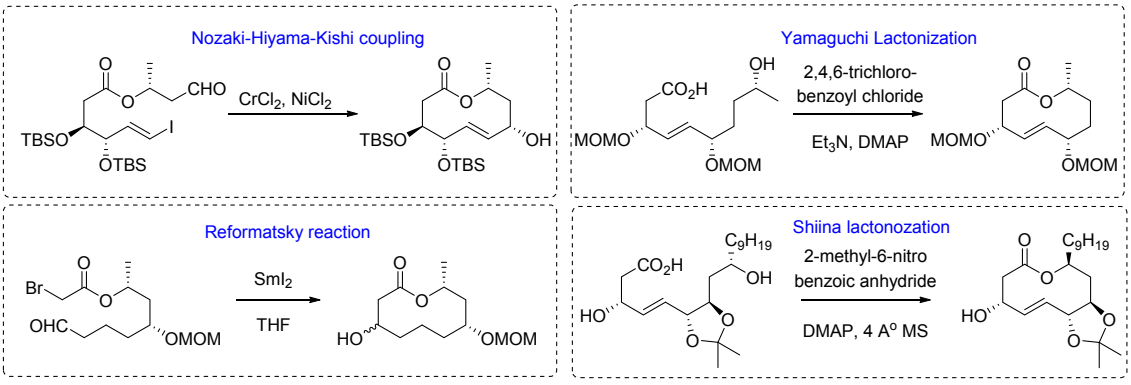
described the sulfide contraction methodology for the synthesis of Diplodialide A.[38] The key ω-hydroxy thioamide intermediate was prepared from the corresponding aldehyde in a four steps sequence. Next, the ω-hydroxy thioamide was esterified with chloroacetyl chloride, which underwent Eschenmoser sulfide contraction. Subsequent acetate elimination afforded the Diplodialide A in moderate yields (Scheme S1.4).



Scheme S1.4. *Ring contraction strategy to construct Diplodialide Askeleton*

C. Intramolecular ring closure

The most general route to macrolides is intramolecular ring closure even though the cyclization of long chain precursors is disfavored due to entropic and enthalpic reasons. The disfavored entropic factor is associated with the formation of a more rigid ring structure whereas the enthalpy factor is created by steric interactions which lead to the torsional or Pitzer stain, bond angle deformation or Baeyer strain, stereo-electronic effect and transannular interaction.[39] The commonly employed cyclization methods for the intramolecular ring closure in nonenolide synthesis are Nozaki-Hiyama-Kishi coupling [(–)-Decarestrictine D by Pilli and Victor],[40] intramolecular Reformatesky reaction (Decarestrictine J by Takayuki),[41] lactonization by Yamaguchi esterification (Decarestrictine C_2 by Arai)[42] and the Corey-Nicolou or Shiina lactonization methods [(+)-Seimatopolide A by Kavirayani R. Prasad] (Scheme S1.5).[43]



Scheme S1.5. *Intramolecular ring closure strategy to construct nonenolide skeleton*

However, these methods are not much efficient and in most of the cases difficulties arise due to the complexity in the preparation of the required intermediates for the macrocyclization. Similarly, demanding experimental conditions are not suitable when multifunctional and complex natural products are the synthetic targets. Therefore, significantly more efforts have been put forward toward the development of alternative strategies for the synthesis of medium sized ring systems.[44] Incidentally, a metathesis reaction was discovered by Grubbs at the end of the 20th century which has turned out to be a valuable tool, especially for the synthesis of these nonenolides. The beauty of this method is that two same or different alkenes having diverse functionality on there skeleton can be added to form a new alkene in the presence of a transition metal catalyst (Ru, Mo-based). This reaction can also be carried out in a intermolecular or intramolecular way. When this reaction occurs in intermolecular fashion, it is described as cross metathesis and it is called ring closing metathesis (RCM) when it is intramolecular in nature. At the beginning of the 21st century, its application has entered in the field of the synthesis of medicinal compounds and has gained popularity extensively in the field of synthetic organic chemistry. Based on this, a number of total syntheses of various sized rings has been documented recently. In addition; the effect of protecting groups, the nature of the catalyst, and the size of the ring on the outcome of the cyclization have been investigated systematically.[45]

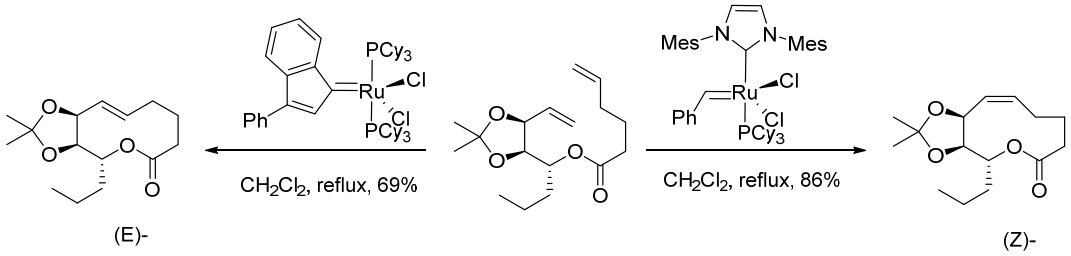
Herbarumin I, II and III, Pinolidoxin, Decarerestrictine C_1, C_2, D, J and O, Putaminoxin E, Aspinolide B, Achaetolide, Seimatopolides A and B, Stagonolide A, B and C, Nonenolide, Microcarpalide, Cephalosporolide B, C etc are various nonenolide classes of natural products were synthesized by employing RCM as the key reaction.[45b] Since the focus of this part of the thesis is going to be mainly on the substituent effects on the outcome of RCM, the following description will be restricted mainly to those total synthesis where this has been addresed.

Construction of the nonenolides employing Ring Closing Metathesis (RCM) and the effect of allylic substituents on the outcome:

The redistribution of fragments of olefins by the breakage and regeneration of the carbon-carbon double bond in the presence of metal carbene complexes is known as olefin metathesis. After acceptance of the mechanism proposed by Chauvin and the development of well defined single component ruthenium and molybdenum alkylidene catalysts, the alkene-metathesis reaction has developed into one of the most powerful carbon–carbon bond-

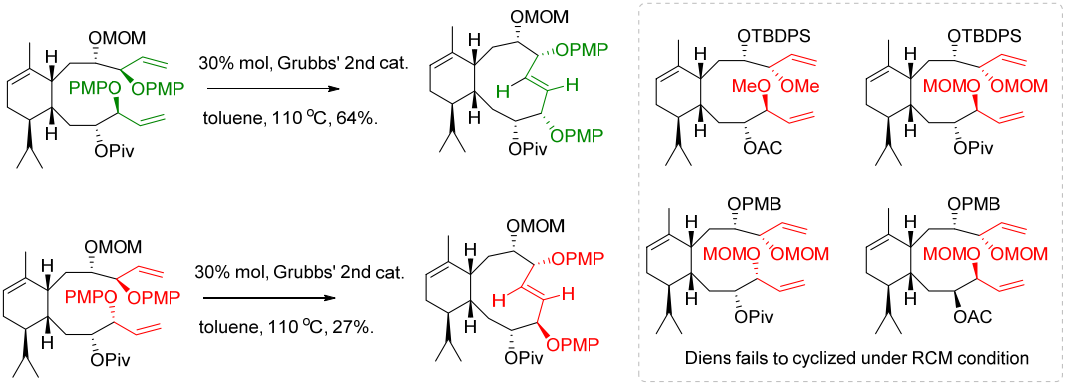
forming reactions currently available to the synthetic chemist and has enabled the synthesis of rings of different sizes. Since the first construction of a 10-membered lactone by Fürstner in 1997,[46] RCM has emerged as an attractive reaction as it provides a convergent approach to the total synthesis of nonenolide (most of the nonenolides contain a carbon–carbon double bond).[45] There are a number of factors that influence the success of a ring-closure reaction during olefin metathesis. The factors are mainly the nature of the catalyst, substituents effect on the substrate, and steric crowding around the newly forming ring-olefin.

The first total syntheses of the phytotoxic agents such as Herbarumin I, Herbarumin II, and Pinolidoxin using RCM as a key step to construct the macrolactone ring was described by Furstner.[47] They did semi-empirical calculations to find a reliable and general method for controlling the geometry of the newly formed double bond which shows that the *Z*-isomer is about 3.5 kcal mol^{-1} more stable than the *E*-isomer. Hence, conducting the RCM of the diene under the conditions of thermodynamic control would be expected to give *Z*-alkenes. This prediction then suggests that the RCM catalysts that equilibrate the products should not be employed for the synthesis of *E*-alkenes. Accordingly, the results were concurrent with the hypothesis in such a way that the RCM of the diene delivered the *E*-configured olefin on exposure to the ruthenium indenylidene complex, whereas the *Z*-configured product was obtained with the ruthenium-NHC catalyst (Scheme S1.6).



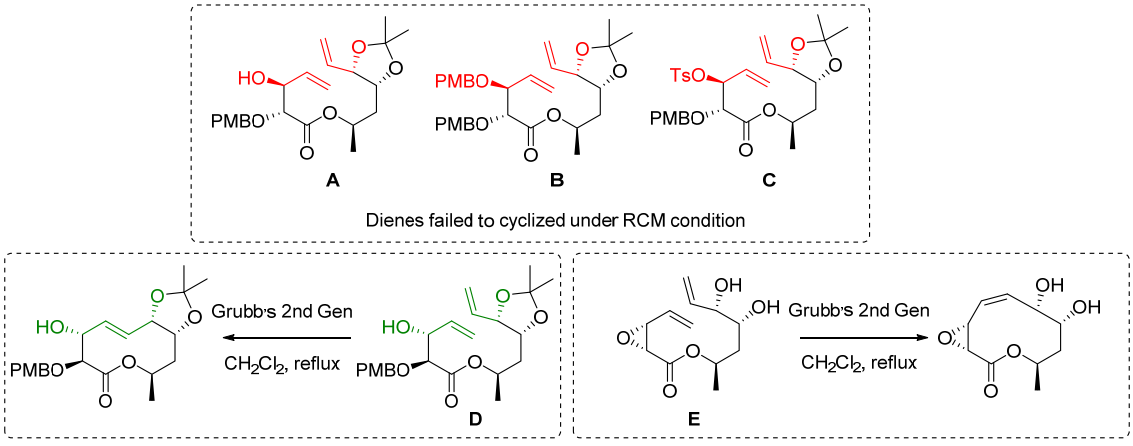
Scheme S1.6. *Fürstner Synthesis of Herbarumins*

Gennerai and co-workers have investigated the RCM reaction of a number of similar types of densely functionalized diene bearing protected and/or free alcohol functionalities at both the allylic and the homoallylic positions in the total synthesis of Eleutherobin.[48] It has been observed that the RCM reaction is substrate and protective group specific. Specifically, the RCM reaction using Grubbs 2nd generation catalyst of a densely functionalized diene bearing two allylic alcohols protected as *p*-methoxyphenyl (PMP) with both 1,4-*cis* or *trans*-configuration provided 10-membered carbocycles in good and poor yields respectively. On the other hand, dienes having two allylic alcohols either capped with MOM or methyl ether protecting groups led to the formation of oligomers (Scheme S1.7).



Scheme S1.7. *Dependence of RCM based 10-membered carbocycle construction on protecting groups and the stereochemistry of the allylic hydroxyl groups*

Gennari also investigated the stereochemical outcome of the RCM reaction with the help of DFT calculations and proposed that the *trans*-ruthenacyclobutane intermediates are thermodynamically more stable than the corresponding *cis*-isomers which ultimately lead to the formation of the less stable of *E*-olefin (which are thermodynamically unstable compared to their *Z*-isomers) under kinetically controlled conditions. After the formation of the 10-membered carbocycle with the *E*-geometry, the newly formed double bond, was flanked by two bulky –OPMP groups, is sterically too hindered to react again with the ruthenium–methylidene complex by means of [2+2] cycloaddition and cyclo-reversion thus arresting the equilibrium between the ring-closed and ring opened products and inhibiting the thermodynamic controlled product.



Scheme S1.8. *Substrate specific outcome of RCM*

Dealing with the total synthesis of Multiploide A,[49] we have noticed a substrate specific RCM reaction. Among the four similar substrates (**A–D**) employed, only one of the substrates **D** having a 1,4-*cis*-diol configuration provided the desired 10-membered

macrolactone. The other three substrates **A–C** having a 1,4-*trans*-diol configuration led to the formation of oligomers whereas the epoxy substrate **E** resulted in the undesired double bond stereochemistry (Scheme S1.8).

This idea has prompted us to examine the available RCM based nonenolides construction having the 2-ene-1,4-diol unit. We were intrigued by the fact that in most of the cases they dealt mainly with the RCM of the substrates leading to *syn*-1,4-diol configured nonenolides.[50] It is quite surprising that though several natural nonenolides having a 1,4-*trans*-diol configuration have been reported, but none of them has been concerned with the synthesis through the RCM.[51] The reported synthesis of these nonenolides (Decarestrictine C2, and Decarestrictine D) has mostly employed either a macrolactonization or an intramolecular Nozaki–Hiyama–Kishi coupling (Aspinolide B and Decarestrictine D) for the construction of the central core (Figure S1.10).[40-42]

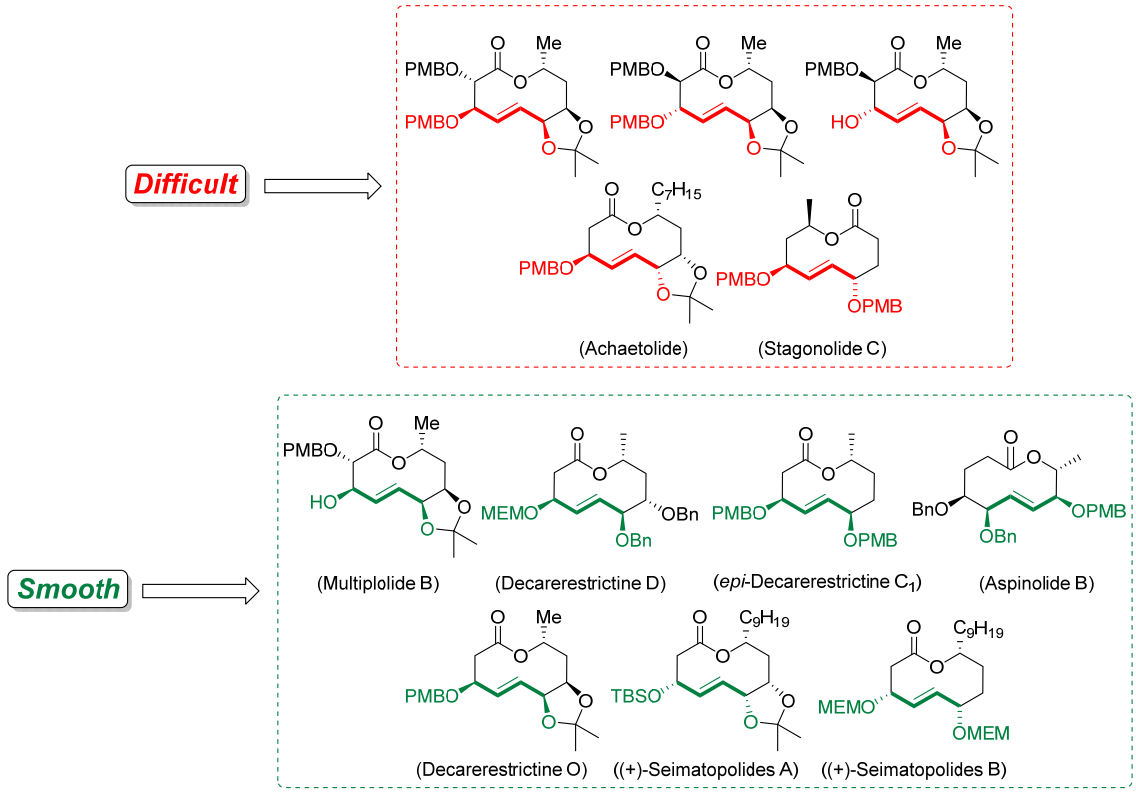
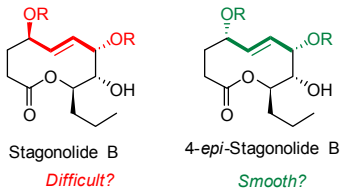


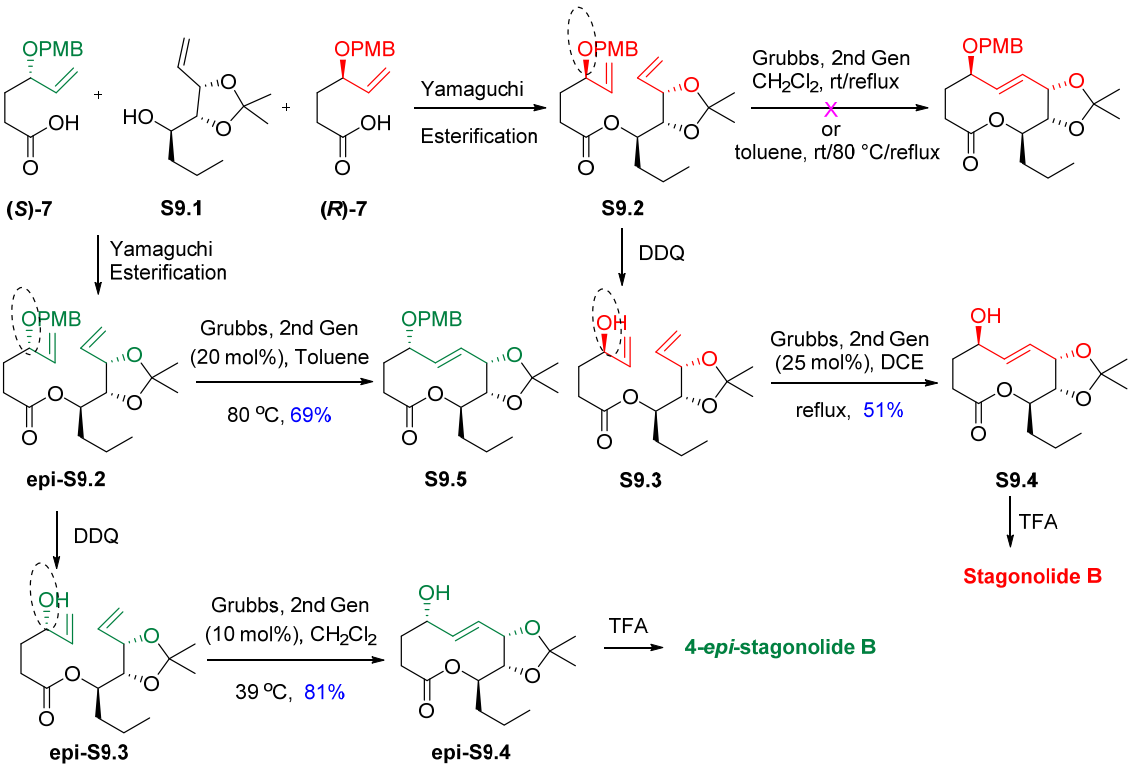
Figure S1.10. *The relative stereochemistry of the allylic hydroxy groups and the anticipated output of RCM*

Although these limited examples provide clues as to when the RCM could be a difficult proposition, in order to gain a complete examination of the stereochemical outcome of the RCM in nonenolide synthesis, our group has come up with the total synthesis of the Stagonolide B and 4-*epi*-Stagonolide B in 2010.[52] To check the influence of the relative

stereochemistry of allylic hydroxy groups and their protecting groups on the efficiency of the RCM, a tentative synthesis of both the nonenolodes has been studied.



The RCM precursor **S9.2** was collected by the coupling of the acid (*R*)-**7** and the alcohol **S9.1** under Yamaguchi condition. A number of catalysts for the metathesis have been screened on the substrate **S9.2**, but each was found to not be easy. In this context, we opted to deprotect the PMB ether to afford the diene **S9.3**. After examining the various reaction parameters, the RCM of **S9.3** was conducted successfully using 25 mol% of Grubbs' 2nd generation catalyst in DCE. Finally, the acetonide deprotection of **S9.4** with TFA gave the Stagonolide B.



Scheme S1.9. *Total Synthesis of Stagonolide B and 4-epi-Stagonolide B*

Similarly, the coupling of alcohol **S9.1** was carried out with acid (*S*)-*7* to obtain the ***epi-* S9.2**. Now, the RCM was planned to be carried out in two sets of conditions, viz. in the presence and the absence of the PMB group. The selective PMB deprotection of ***epi-* S9.2** in the presence of DDQ led to the formation of ***epi-* S9.3**. Unlike the previous substrate **S9.2**, the

RCM of ***epi-* S9.2** preceded efficiently at 80 °C in toluene leading to **S9.5** in 84% yield. Likewise, the RCM of *epi*- **S9.3** occurred smoothly in CH_2Cl_2 at reflux temperature to yield *E*/*Z* nonenolides in a 11:1 ratio. However, carrying the same reaction in toluene at 80 °C resulted in an increase of the *Z*-isomer (Z/E = 7:1) (Scheme 6). The compound *epi*- **S9.4** was then treated with neat TFA to obtain the 4-*epi*-stagonolide B.

The results of the RCM of the diene **S9.2** and *epi*- **S9.2** is quite amazing at this point. This may be due to the conformational restrictions during the formation of the ruthenacyclobutane.[47,48] We believe that the complications in the construction of the stagonolide B (with a 1,4-*trans*-diol configuration) is due to the steric hindrance exhibited on both the faces during the formation of the ruthenacyclobutane (Figure S1.11b). With a 1,4-*cis*-diol configuration (with *epi*-**S9.2**), such steric crowding is absent as both these allylic groups lie on the same face (Figure S1.11a). A strain free transition state is also probable by a simple rotation around the C−C bond leading to dimerization (Figure S1.11c).

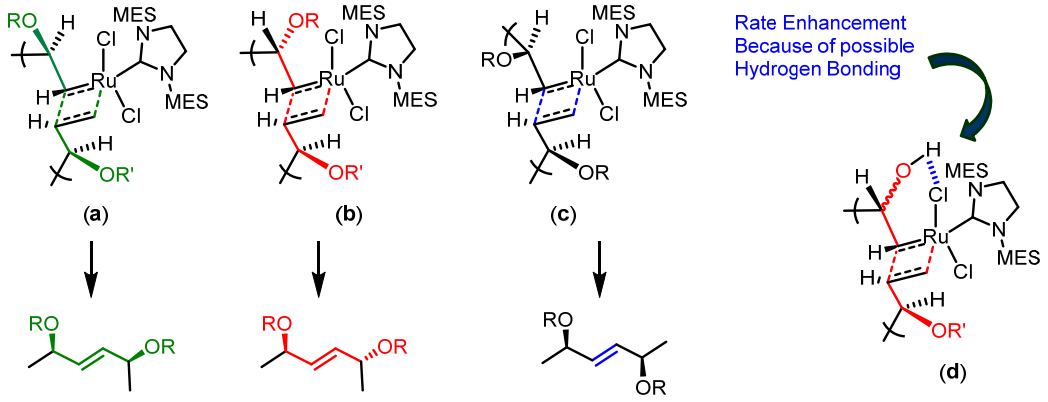


Figure S1.11. *The possible transition state of trans-ruthena-cyclobutane derivatives resulting macrolides with (a) 1,4-cis-diol (b) 1,4-trans-diol macrolides, and (c) self dimerization (d) Co-operative O–H...Cl–Ru hydrogen bonding*

The feasibility of RCM with **S9.3** (one free allylic hydroxy group) could be explained by anticipating a co-operative O–H...Cl–Ru hydrogen bonding[53c] (Figure 12d). However, the acceleration of RCM with free allylic hydroxyl groups in a regio- and stereoselective way is well documented.[53,54] This hypothesis could also be explained from the fact that the RCM of *epi*- **S9.3** occurred at 39 °C in CH_2Cl_2 whereas its PMB ether required 80 °C.

In continuation, we selected Stagonolide D, Mangiferaelactone and Cytospolide E as the synthetic targets to address the issue of how the relative orientation of the allylic substituents influences the outcome of the ring closing metathesis.

CHAPTER I; SECTION I

Total synthesis of (+)-Stagonolide D

RESULT AND DISCUSSION

Stagonospora cirsii Davis, a fungal pathogen isolated from *Cirsium arvense* (commonly called *Canada thistle*) and proposed as a potential mycoherbicide of this perennial noxious weed, produced phytotoxic metabolites both in liquid and solid cultures. In 2007 Berestetskiy *et al* isolated Stagonolide A, the main phytotoxic metabolite with interesting phytotoxic properties from the liquid culture of *Stagonospora cirsii*.[17] Furthermore when Evidente *et al* grew the same fungus on a solid medium, it led to isolation of new five nonenolides, named as Stagonolides B–F, considering their origin and structural similarity with that of Stagonolide A.[18] The relative stereochemistry and the connectivity of the free hydroxyl groups in Stagonolides B–F has been proposed by comparing their spectral data with the spectral data of Herbarumins. Inspired by our earlier observation of the influence of the allylic substituents on the outcome of the RCM in nonenolide synthesis,[49,52] we initiated a program to synthesize Stagonolide D with a 2*E*-ene-1,4-*cis*-diol unit, which is a facile system to be constructed through the RCM approach. Our retrosynthetic strategy for Stagonolide D is depicted in Figure 1.

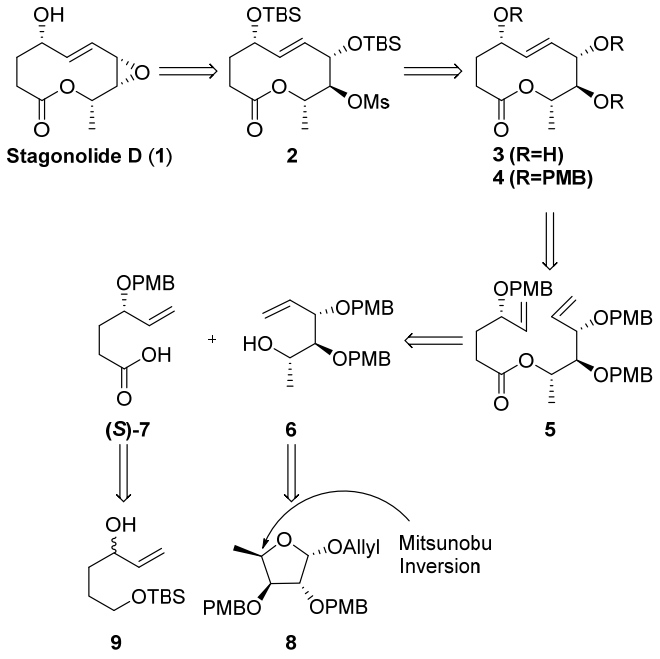
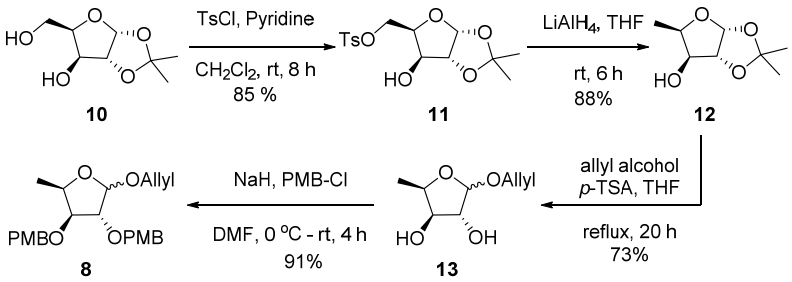


Figure 1. *Retrosynthetic analysis for Stagonolide D* (**1**)

The installation of the epoxide unit was the final event in the total synthesis, which was planned through a tandem TBS deprotection and concomitant epoxide formation from the mesylate **2**. The penultimate intermediate **2** could be realized from the macrolide **3** through selective TBS protection of allylic –OH groups and the subsequent mesylation of the remaining –OH group. The macrolide **3** with a 2*E*-ene-1,4-diol unit having a 1,4-*cis*-diol

configuration was opted as a key intermediate founded upon the earlier observations, which reveal that the construction of nonenolides with such a configuration by RCM is a facile process.[48-52] The intermediate macrolide **3** could be accessed from the corresponding PMB protected macrolide **4** which, in turn, was planned to be obtained by a RCM of the diene ester **5**. The acid (*S*)-**7** and the alcohol **6** were identified as the key coupling partners for the synthesis of the diene ester **5**. After a stereochemical comparison, D-xylose has been selected as a starting point for the chiral pool synthesis of the alcohol fragment **6**. The synthesis of the enantiomeric acid (*S*)-**7** has been earlier reported from our laboratory through the enzymatic resolution of the allyl alcohol **9**.[52] The allylic-OH of the acid (*S*)-**7** and alcohol **6** were planned to be protected as PMB ethers as a safe handle to change the steric nature of the adjacent functional groups that have been shown to influence on the outcome of the RCM (Figure 1).

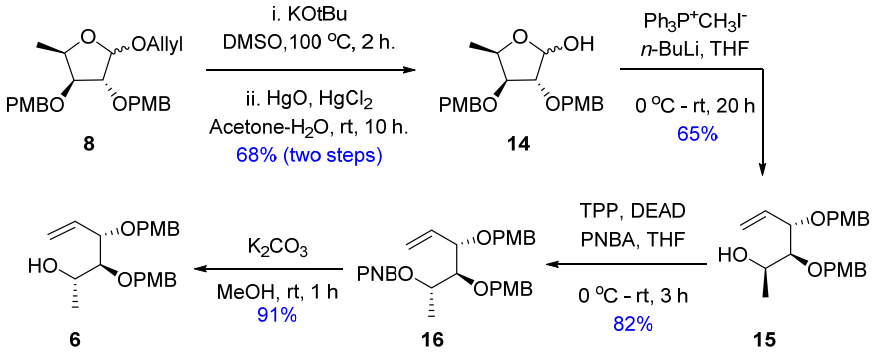
Synthesis of the alcohol fragment 6:



Scheme 1. *Synthesis of compound **8***

The total synthesis of *Stagonolide D* (**1**) commenced with the synthesis of the alcohol **6** from the chiral pool starting precursor xylose-1,2-acetonide **10** (Scheme 1). Following the known procedures,[55] xylose-1,2-acetonide was transformed to the 5-deoxy-xylose derivative **12** by selective monotosylation of the C5–OH group using TsCl and Et_3N in CH_2Cl_2 followed by deoxygenation resulting compound **11** with LAH in THF. The spectral and analytical data of compound **12** was in good agreement with the reported data.[55] The hydrolysis of the 1,2-acetonide group of **12** in the presence of allylic alcohol and cat. *p*-TSA in THF under refluxed condition gave the anomeric mixture of allyl 5-deoxy-α/β-D-xylofuranosides **13** in 73% yield. In the ^{1}H NMR spectrum of compound **13**, the allylic protons –CH and =CH_2 resonate at δ 5.16–5.30 (m, 2H) and 5.86 (ddt, J = 5.4, 10.6, 17.1 Hz, 1H) ppm respectively, whereas the appearance of anomeric proton at δ 4.92 (s, 1H, major), 5.10 (d, J = 4.1 Hz, 1H, minor) ppm suggested the formation of the requisite anomeric mixture of allyl xylofuranosides **13**. In the ^{13}C NMR spectrum of compound **13**, the peaks

appearing at δ 117.7 (t), 133.6 (d, major), 133.7 (d, minor) ppm indicate the presence of the allyl group, while anomeric carbons of major and minor isomer resonated at δ 106.1 (d, major) and 99.5 (d, minor) ppm as doublets respectively. After successfully characterizing compounds **13**, the protection of the free hydroxyl groups as PMB ethers was carried out using PMB-Cl and NaH in DMF resulting in compound **8** in 91% yields. The structure of compound **8** was well supported by ^{1}H, ^{13}C NMR spectrum and elemental analysis.



Scheme 2: Synthesis of alcohol fragment **6**

The next task was introduction of the double bond, which requires the replacing of the allyl protecting group. Compound **8** was therefore subjected for deallylation using a two step sequence, first isomerization of the double bond by KO^{t}Bu in DMSO at 100 °C followed by treatment of the resulting isomerized product with mercuric oxide and mercuric chloride in acetone-water to give inseparable anomeric mixture of lactols **14** in 68% yield. The signals due to the allyl group were seen to disappear in the ^{1}H and ^{13}C NMR of lactols **14**. Further, in the ^{1}H NMR of lactols **14**, the anomeric proton of both the epimers were seen to resonate at δ 5.19 (s, 0.5 H), 5.41 (br s, 0.5H) ppm indicating a 1:1 mixture of both epimers. Similarly in the ^{13}C NMR of Lactols **14**, the anomeric carbon of both the epimers were seen to resonate at δ 95.4 (d) and 100.9 (d) ppm. All other signals in both the NMR and mass peak at 397.1653 ([M+Na]$^{+}$) in mass the spectrum of lactos **14** are in good agreement with the proposed constitution. Next, one carbon Witting homologation of the resulting lactols **14** using triphenylphosphonium bromide and *n*-BuLi in THF gave the key alcohol **15** in 65% yields. In the ^{1}H NMR spectrum of compound **15**, the signals corresponding to anomeric protons were seen to disappear and the appearance of signals at δ 5.32–5.41 (m, 2H) and 5.89 (ddd, J = 7.4, 9.9, 17.6, Hz, 1H) ppm correspond to terminal olefinic protons and internal olefinic proton (=CH$_2$ and –CH) respectively. In the ^{13}C NMR spectrum of compound **15**, a newly generated triplet and doublet peaks at δ 118.9 (t) and 135.5 (d) ppm confirmed the presence of a

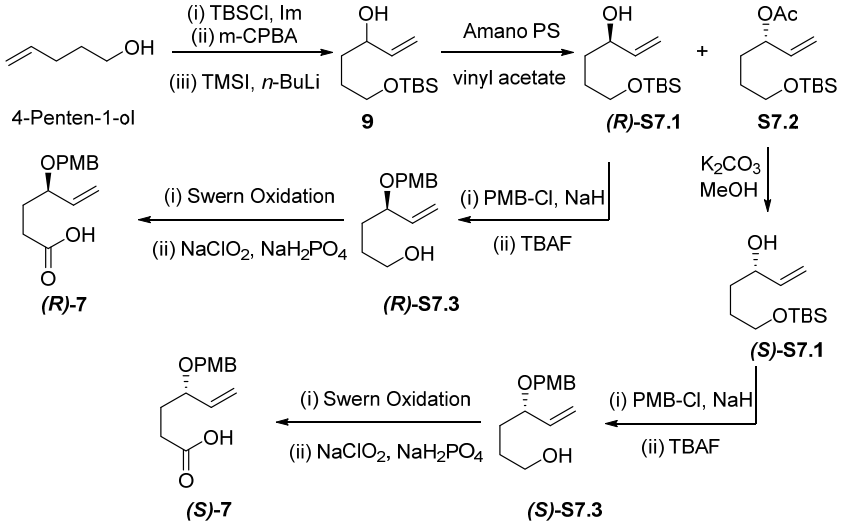
terminal olefin unit in the compound **15**. Furthermore, the presence of a strong peak in the HRMS spectra at m/z 162.0913 confirmed the constitution of the compound **15** (Scheme 2).

To access the key alcohol **6** for the synthesis of diene ester **5**, the configuration at the C5 center had to be inverted. The Mitsunobu inverstion of alcohol **15** carried out by using DEAD, TPP and *p*-nitrobenzoic acid as the nucleophile to afford the corresponding nitrobenzoate **16** in 82% yield.[56] In the ^{1}H NMR spectrum of compound **16**, new four protons in the aromatic region resonated at δ 7.97 (d, J = 9.0 Hz, 2H), 8.20 (d, J = 9.0 Hz, 2H) ppm as doublet, confirming the presence of the benzoate group, whereas the corresponding ester attached proton resonated at 5.22 (dq, J = 4.4, 6.4 Hz, 1H) ppm. In the ^{13}C NMR spectrum of compound **16**, the quaternary carbon of the carbonyl ester resonated at δ 163.7 ppm as a singlet. The characteristic C=O stretching in benzoate **16** was observed at 1722 cm^{-1} in the IR spectrum. The presence of strong peaks at 544.1903 ([M+Na]$^{+}$) in the HRMS spectra confirmed the compound **16**. The hydrolysis of nitrobenzoate ester **16** with K_2CO_3 in MeOH secured the required alcohol **6** in 91% yield having physical data different from that of the starting alcohol **15** at the inverting center. For example, in the ^{1}H NMR spectrum of compound **6**, protons of the methyl group (-CH_3) and proton attached to carbon (-CH) adjacent to the methyl group resonated at δ 1.35 (d, J = 6.3 Hz, 3H) and 3.20 (dd, J = 4.2, 5.4 Hz 1H) ppm respectively, whereas it appeared at δ 1.09 (d, J = 6.4 Hz, 3H) and 3.34 (dd, J = 5.0, 6.1 Hz 1H) ppm respectively in alcohol **15**. Similarly in the ^{13}C NMR spectrum of compound **5**, the corresponding quartet (-CH_3) resonated at δ 19.0 (q) and 67.2 (d) ppm respectively, while in compound **15** it was found at δ 19.9 (q) and 67.2 (d) ppm respectively. In the IR spectrum of compound **6**, the O–H stretching was observed at 3467 cm^{-1}. In the mass spectrum, the peaks corresponding to m/z 395.1834 (100%, [M+Na]$^{+}$), were found in accordance with the assigned structure of compound **6**.

Synthesis of the acid fragment (*S*)-7:

The acid (*S*)-**7** has been synthesized by using the same procedure developed in our lab in the context of the total synthesis of staganolide B.[52] The commercially available 4-pentene-1-ol was converted into the racemic alcohol by a series of functional group transformations *via* TBS protection, epoxidation, and one carbon extension to afford the key racemic allyl alcohol **9** which was resolved later by enzymatic kinetic resolution to afford the alcohol (*R*)-**S7.1** and acetate (*S*)-**S7.2**.[57] The absolute configuration of the alcohol (*R*)- **S7.2** was then established by using the Mosher method. The hydroxyl group of (*R*)- **S7.1** was protected as its PMB ether. Likewise, the silyl deprotection of the primary alcohol followed by the

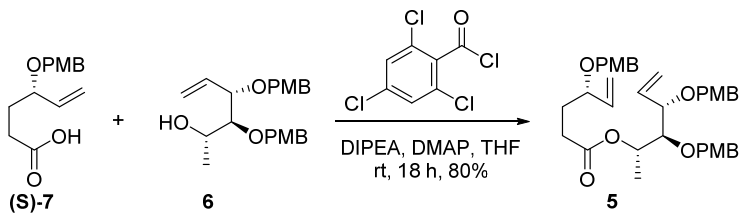
oxidation of the resulting alcohol (*R*)- **S7.3** to acid fragment (*R*)- **7** was carried out by Swern and Pinnick oxidation**.** The acetate (*S*)-**S7.2** was subjected for the deacetylation and the resulting (*S*)-**S7.1** was subsequently used for the synthesis of the enantiomer (*S*)- **7** by employing the same sequence of reactions (Scheme 3).



Scheme 3. *Synthesis of Acid fragments*

Coupling of alcohol 6 and acid (*S*)-7:

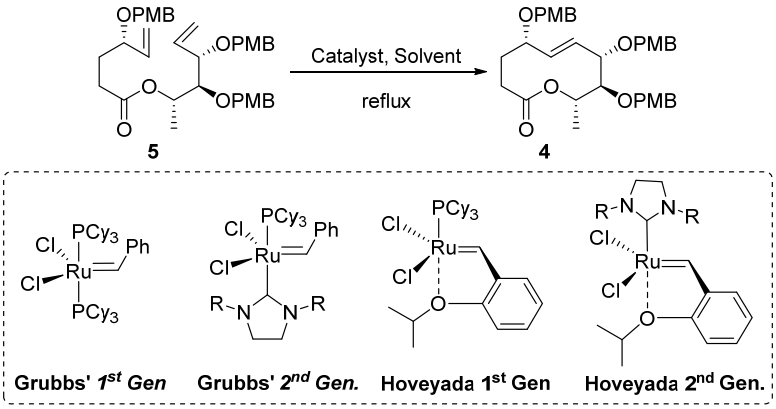
After having both crucial intermediates (*S*)**-7** and **6** in hand, the next task was completing the key macrolide construction. The coupling of these two key fragments was performed under Yamaguchi esterification method considering its widespread application in the synthesis of highly functionalized esters and macrolactones under mild conditions.[58] Following the literature reported procedure of the Yamaguchi esterification method, the first step involves the formation of a mixed anhydride of the Yamaguchi reagent (2,4,6-trichlorobenzoyl chloride) with the carboxylic acid (*S*)-**7** in the presence of Hünig's base. Subsequently the alcoholysis of in situ prepared intermediate mixed anhydride with alcohol **6** in the presence of a stoichiometric amount of DMAP afforded the desired diene-ester **5** in 80% yield (Scheme 4).



Scheme 4. *Synthesis of diene-ester **5***

In the ^{1}H NMR spectrum of diene **5**, the six olefinic protons of the two olefin moiety resonated at δ 5.17–5.34 (4H) and 5.62–5.91 (2H) ppm as a multiplet, whereas the characteristic proton of acyloxy –CH was appeared at δ 4.99 ppm as a doublet of quartet with coupling constant 3.8 and 6.5 Hz. In the ^{13}C NMR spectrum of diene **5**, the four peaks appeared at δ 117.5, 119 as triplets and 135.2 (d), 138.3 (d) ppm as doublets corresponding to the $=CH_2$ and =CH olefinic carbons respectively, while the ester carbonyl carbon resonated at δ 172.5 ppm as a singlet. All other protons and carbons in the NMR spectra appeared with their respective chemical shifts, thereby confirming the structure of ester **5**. The presence of a strong peak at [627.2935 ($[M+Na]^{+}$)] in the HRMS confirmed the structure **5**.

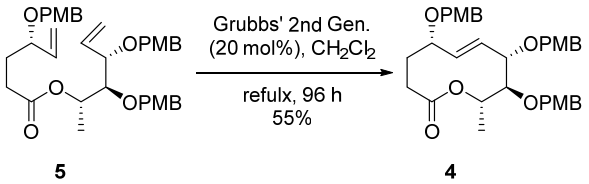
Table1. Attempted reaction conditions for RCM approach of diene ester **5**



Sr. No.	Catalyst	Solvent	Product
1	1St Generation Grubbs Catalyst	CH_2Cl_2	No reaction
		DCE	No Reaction
		Toluene	No Reaction
2	2nd Generation Grubbs Catalyst	**CH_2Cl_2**	**55%**
		DCE	No Reaction
		Toluene	**15-20%**
3	1st Generation Hoveyda-Grubbs Catalyst	CH_2Cl_2	No Reaction
		DCE	No Reaction
		Toluene	No Reaction
4	2nd Generation Hoveyda-Grubbs Catalyst	CH_2Cl_2	No Reaction
		DCE	No Reaction
		Toluene	No Reaction

After successfully synthesizing the diene ester **4**, our next target was its ring closing metathesis reaction to get the corresponding PMB protected macrolide **4**. In that context, initially we attempted the ring closing metathesis using the Grubbs' 1st & 2nd generation catalysts as well as with the Hoveyada 1st & 2nd generation catalysts in various solvents such

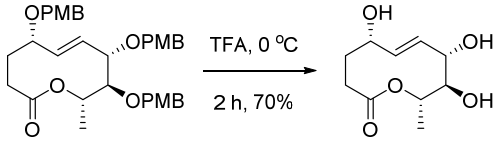
as dichloroethane (DCE), benzene and toluene (Table 1). However the RCM reaction with Grubbs' 1st and Hoveyada 1st & 2nd Generation catalyst were resulted in the formation of an undetectable products mixture (Table 1, entries 1, 3 and 4), whilst the 5-10% formation of required products was found with Grubbs' 2nd generation catalyst in toluene (Table 1, entry 2).



5 **4**

Scheme 5. *Synthesis of diene-ester **4***

To overcome this, we performed the RCM reaction of the diene ester **5** using Grubbs' 2nd generation catalysts with dichloromethane (DCM) instead of toluene with prolonged heating (96 h) at 40 °C. Under these conditions, the resulting RCM product **4** was obtained in 55% yield (Scheme 5). The structure of macrolide **4** was confirmed with the help of NMR and mass spectra. In the ^{1}H NMR spectrum of compound **4**, the disappearances of terminal olefinic protons (=CH_2) was observed, whereas new peaks generated at δ 5.39 (dd, J = 3.0, 15.9 Hz, 1H) and 5.89 (ddd, J = 1.2, 10.1, 15.9 Hz, 1H) ppm correspond to newly formed olefinic proton and the large coupling constant 15.9 Hz confirmed the *trans* geometry of the newly formed C–C double bond. Similarly, in the ^{13}C NMR spectrum of compound **4**, two olefinic carbons and the carbonyl carbon of the ester linkage were seen to resonate at 129.6 (d), 130.4 (d) and 175.2 (s) ppm respectively. Furthermore the strong peak observed at 599.2638 ($[M+Na]^{+}$) in the HRMS spectrum confirmed the compound **4**.



4 **3**

Scheme 6. *Synthesis of macrolide **3***

Having the synthesized PMB protected intermediated macrolide **4**, our next target was the selective deprotection of the allylic PMB group. In this regard, our earlier attempt of selective deprotection of the allylic PMB group using DDQ was found to be unsuccessful. Consequently, we performed the global deprotection of **4** by employing TFA to obtain the macrolide **3** as a white solid in 70% yield (Scheme 6).

The structure of triol **3** was established with the help of NMR and mass spectra as well as single crystal *X*-ray analysis. In the ^{1}H and ^{13}C NMR spectrum of compound **3**, the disappearance of benzylic and aromatic protons and carbons was observed. The structure of **3** was further confirmed by the HRMS spectrum, where a strong mass peak was observed at 217.1063 ($[M+H]^{+}$) as well as through the single crystal *X*-ray diffraction data (Figure 2).

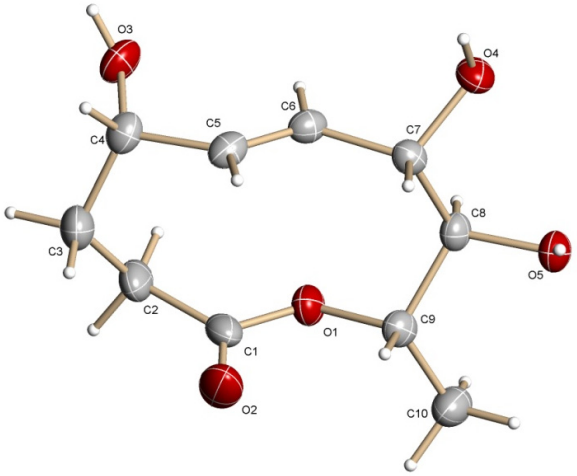
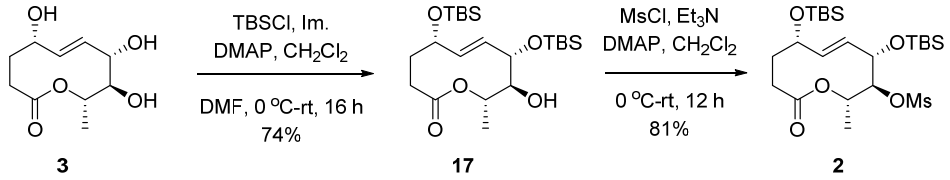


Figure 2: *ORTEP diagram of the compound **3** (Ellipsoids are drawn at 50% probability)*

After successfully synthesizing the key triol intermediate **3**, our next concern was the installation of the oxirane ring. In that direction, we attempted the selective TBS protection of both the allylic –OH groups using TBSCl (4 eq., addition at 0 °C) and imidazole in dichloromethane and DMF as solvent (1:1) at room temperature for 8 h which provided the required di-*O*-TBS derivative **17** in 74% yield (Scheme 7).[59]



Scheme 7. *Synthesis of penultimate mesylate **2***

In the ^{1}H NMR spectrum of compound **17**, the twelve protons corresponding to the four methyl groups attached to silicon resonated at δ 0.01(3H), 0.02 (3H), 0.03 (3H) and 0.05 (3H) ppm as singlets, whereas the protons corresponding to the *t*-butyl unit were seen at δ 0.86 (3H) and 0.91(3H) ppm as singlets thus confirming the presence of two –OTBS groups in the compound. ^{13}C NMR was also in agreement with the ^{1}H NMR spectrum. In the ^{13}C NMR spectrum of the compound **17**, the four methyl carbons attached to silicon atom appeared at δ –5.1 (q), –5.0 (q), –4.7 (q), –3.6 (q) ppm as quartets and the six methyl groups

of *t*-butyl unit resonated at δ 25.8 (q, 3C), 25.8 (q, 3C) ppm as quartets and the quaternary carbon of these two TBS groups appeared separately at δ 18.0 (s), 18.2 (s) ppm as singlets. Additionally, the presence of a mass peak at 467.2601 ($[M+Na]^+$) in the HRMS spectra confirmed the compound **17**.

After successfully characterizing the compound **17**, it was further treated with methanesulphonyl chloride in the presence of triethyl amine in CH_2Cl_2 to give the penultimate mesylate **2** in 81% yield (Scheme 7). The constitution of the mesylate was established with the help of ^{1}H NMR, COSY and NOESY data analysis. For example, in the ^{1}H NMR spectrum of **2**, three protons corresponding to the methyl group of the mesyl were seen to resonate at δ 3.08 (s, 3H) and C8–H attached to the mesyloxy group appeared at δ 4.4 ppm as a broad doublet of doublet with coupling constants J = 9.0, 9.6 Hz. The same C8–H in compound **18** was found to resonate at δ 3.32 (br.dd, J = 8.8, 9.6 Hz) ppm which is indicative of mesylation at C8-OH. Similarly, in the ^{13}CNMR spectrum of compound **2**, the methyl carbon of the mesyl group and carbon attached to the mesyl group were seen to resonate at 39.3 (q) and 84.2 (d) ppm respectively. Furthemore, the observed cross peak between the CH_3 of the mesyl group and C8–H in the NOESY of compound **2** also supported the assigned structure of **2** as shown in Figure 3.

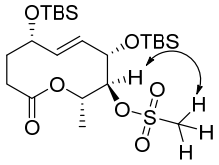
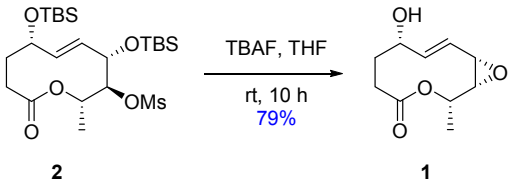


Figure 3. *nOe interactions of the mesylate (2)*

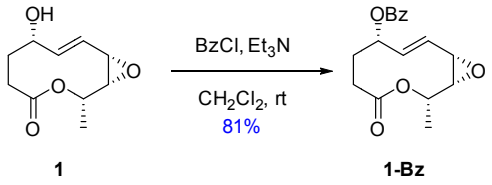
Synthesis of the Putative Structure of Stagonolide D:

Having the penultimate intermediate mesylate **2** in hand, our next job was the deprotection of TBS and subsequent epoxide formation to obtain the natural product. The cleavage of the two TBS groups of compound **2** followed by epoxide formation was performed using TBAF in THF at room temperature to yield the compound **1** in 79% yield (Scheme 8).



Scheme 8. *Synthesis of putative structure of stagonolide D (1)*

The NMR spectrum of compound **1** was characterized by the presence of two sets of peaks in a ratio of 2:1 indicating the occurrence of two closely related compounds. Surprisingly, the spectral data of these two compounds is comparable but not identical to that of the data reported for the natural Stagonolide D. Furthermore, when the ^{1}H NMR of the synthetic compound **1** was recorded at various temperatures (-50 to + 50 ºC) in $CDCl_3$, we observed that the major:minor ratio was not substantially temperature dependent.[16a]



Scheme 9. *Synthesis Benzoate **1-Bz***

In this regard, to further verify the possibility of two different components instead of equilibrating conformers in synthetic compound **1**, the corresponding benzoate **1-Bz** was made using BzCl and Et_3N in CH_2Cl_2 81% yield (Scheme 9). The NMR of **1-Bz** was also characterized by the presence of two sets of peaks. The presence of the benzoate group was confirmed by the appearance of an additional signal corresponding to four protons in the aromatic region of ^{1}HNMR and a signal corresponding to carbonyl and aromatic carbons of the benzoate group in the ^{13}CNMR of compound **1-Bz**. When we subjected benzoate **1-Bz** for HPLC analysis under different conditions and on different columns (Figure 4), however on the entire occasions only one compound with >97% purity was detected. This clearly evidenced that both the components in compound **1** and **1-Bz** represent the same constitution and configuration and presumably are conformational isomers.

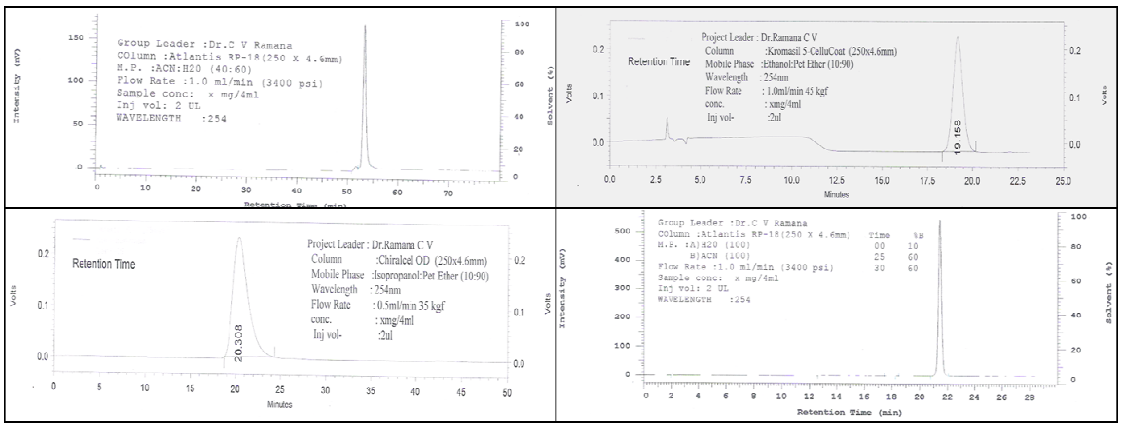


Figure 4: *HPLC Chromatograms of compound **1-Bz** under various conditions*

Further, the structures of major and the minor conformers of **1** were examined with the help of ^{1}H NMR, COSY and NOESY data. In the ^{1}H NMR of spectrum of **1**, H-C(9) of

the major isomer was found to resonate at 5.33 (dq, J = 2.7, 6.8 Hz) and that of the minor isomer at 5.27 (dq, J = 1.6, 6.8 Hz) ppm, which clearly indicates that the C9-O forms the ester linkage. This is quite important in the context of a recent report by Marco and co-workers that revised the nonelide structure of Stagonolide G to a γ-lactone structure.[60] The carbonyl band at 1731 cm^{-1} in the IR spectrum of compound **1** is also diagnostic of a ten membered lactone (in Stagonolide G it was observed at 1765 cm^{-1}). The H–C7 and H–C8 of the major isomer appeared at δ 3.69 (*t*, J = 4.2 Hz) and 3.03 (dd, J = 2.7, 4.3 Hz) ppm respectively, whereas the same for the minor isomer resonated at δ 3.53 (dt, J = 1.4, 4.3 Hz) and 2.90 (dd, J = 1.6, 4.3 Hz) ppm respectively. The observed small value of the coupling constant between H–C8 and H–C9 $J_{8,9}$ = 1.6 and 2.7 Hz in both the conformers indicated that these two protons are *cis*- to each other. Furthermore, the *cis*-stereochemistry of the oxirane ring and the C10-methyl was supported by NOE correlations present between H-C9 and H-C(8) (Figure 5). Thus, this extensive spectral data analysis indicated that these two compounds are equilibrating conformational isomers having the proposed structure of **1**, thus warranting structural revision of Stagonolide D.

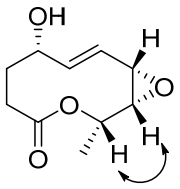
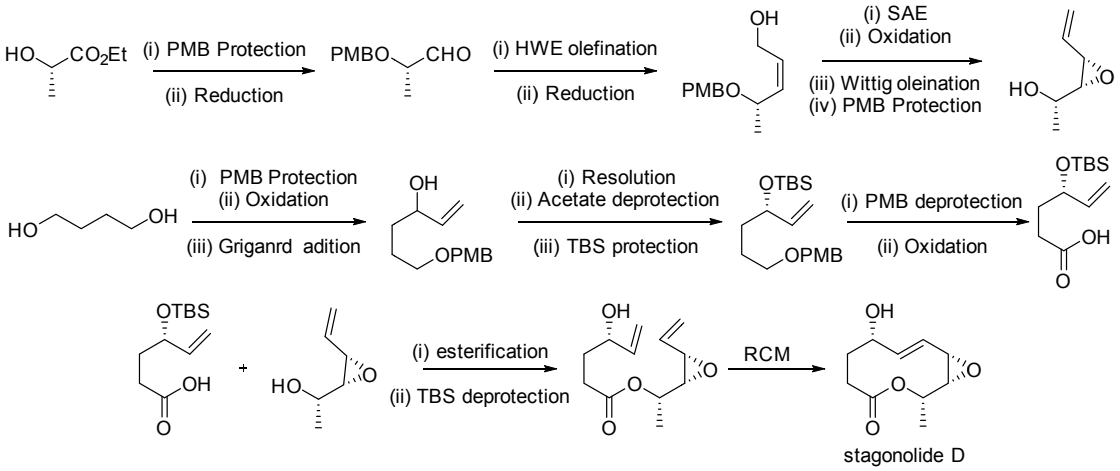


Figure 5. *nOe interactions of the putative structure of stagonolide D (**1**)*

When we were at this stage, Nanda and co-workers reported the synthesis of Stagonolide D and confirmed its given structure using RCM as the key reaction to construct the macrolide core.[61] The acid fragment was prepared from 1,4-butanediol applying metal enzyme combined DKR as a key step. The alcohol fragment was prepared by Sharpless asymmetric epoxidation of *Z*-allylic alcohol, which, in turn, was prepared from (*S*)-ethyl lactate by adopting a cis-selective HWE olefination. Finally, the two fragments were coupled using the EDCI reagent followed by removal of protecting group followed by ring closing metathesis to access the Stagonolide D (Scheme 10).



Scheme 10. *Nanda's synthesis of Stagonolide D.*

However, the ^{1}H and ^{13}C NMR spectra of synthetic Stagonolide D provided in the supporting information corresponds neither with the natural Stagonolide D nor with the data of compound **1**. For example, in the ^{1}HNMR spectrum of the natural product, the allylic proton attached to epoxide bearing carbon H-C7 was seen to resonate at δ 3.65 (dd, J = 3.9, 4.8 Hz, 1H) ppm, whereas it is below δ 3.5 ppm in the ^{1}HNMR of Stagonolide D synthesized by Nanda and coworker and was mentioned as δ 3.58. (dd, J = 1.6, 4.8 Hz, 1H) ppm in the manuscript (Figure 6).

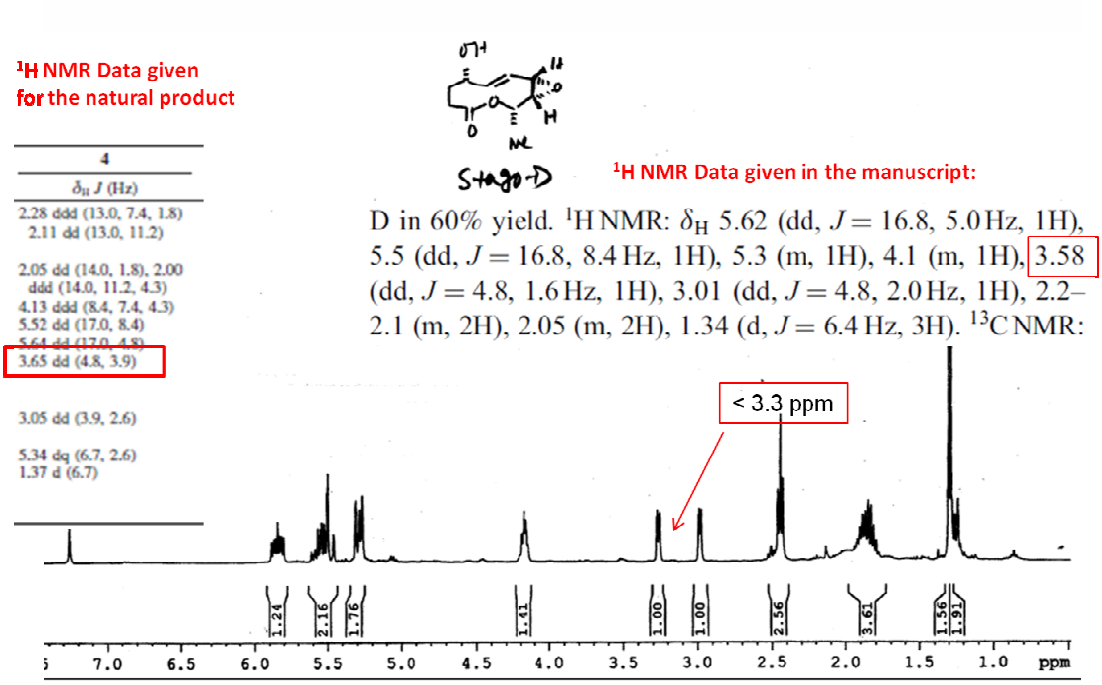


Figure 6. *^{1}H NMR of Stagonolide synthesized by nanda et al*

The comparison of the spectral data of the synthesized compound **1** and the data reported for the naturally occurring Stagonolide D revealed that the differences noticed are mainly in the region of olefin and H–C4.

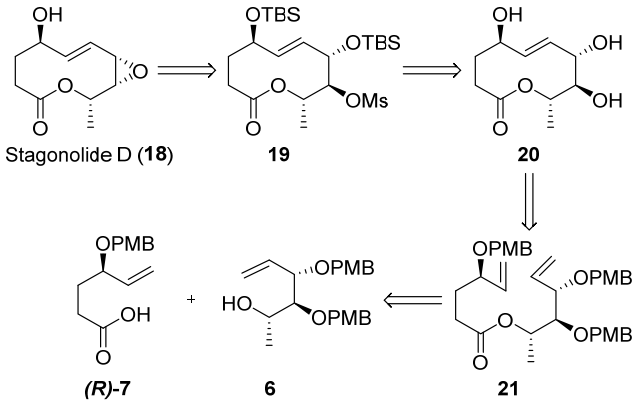
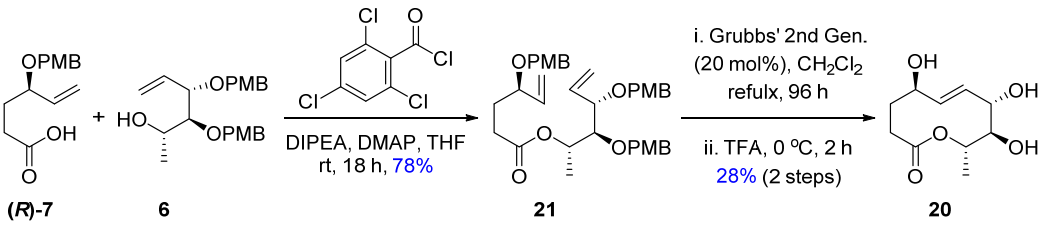


Figure 7. *Retrosynthetic analysis for (+)- Stagonolide D (**18**)*

Therefore we intend to synthesize the compound **18** as an alternative structural possibility in the same way as the latter. The detailed retro synthesis strategy has been given in Figure **7**. Compound **18** could be obtained through sequential chemical transformations as described above for the synthesis of compound **1** from alcohol **6** and **(*R*)-7** acid instead of **(*S*)-7** acid.

The synthesis of the planned isomer **18** begins with the preparation of acid (***R*)-7** using previously established synthetic routes in contest of the total synthesis of Stagonolide B. Next the coupling of alcohol **6** with (***R*)-7** acid was carried out under the Yamaguchi procedure as described previously yielding the ester **21** in 78% yield (Scheme 11).

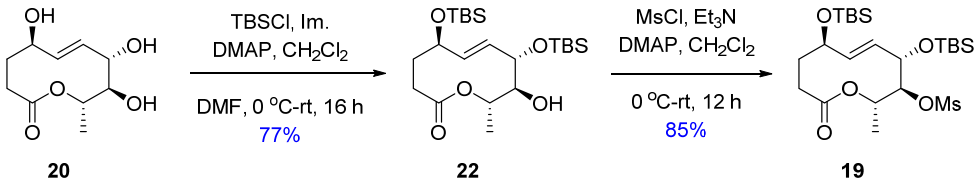


Scheme 11. *Synthesis of triol (**20**)*

Compound **21** was fully characterized with the help of NMR and Mass spectra. In the ^{1}H NMR spectrum of ester **21**, the six olefinic protons of two the olefin moiety were seen to resonate at 5.17–5.34 (m, 4H), 5.69 (ddd, J = 7.6, 11.0, 16.4 Hz, 1H) and 5.83 (ddd, J = 8.1, 10.6, 16.9 Hz, 1H) ppm, whereas the characteristic proton of acyloxy –CH appeared at δ 4.99 (dq, J = 3.8, 6.4 Hz, 1H) ppm. In the ^{13}C NMR spectrum of ester **21**, the four peaks appeared at δ 117.6 (t), 119.1 (t) ppm as a triplet and 135.2 (d), 138.3 (d) ppm as a doublet

corresponding to the terminal and internal carbon of the two olefinic moietes respectively, while the ester carbonyl carbons resonate at δ 172.5 (s) ppm as a singlet. Additionally, the presence of a mass peak at 627.2948 ($[M+Na]^+$) in the HRMS spectra confirmed the compound **21**.

After confirming the structure of compound **21**, it was further subjected for the RCM under the previously optimized condition. The RCM of diene **21** was sluggish and also the separation of the resulting lactone from the crude reaction mixture was found to be tedious. In this context, the crude RCM reaction mixture was directly subjected for global PMB deprotection by employing TFA to obtain the triol **20** in 28% l yield over two steps (Scheme 11). The structure of triol **20** was confirmed with the help of NMR and Mass spectrum. In the ^{1}H NMR spectrum of compound **20**, the disappearance of signal corresponding to PMB groups was observed. The new signals at δ 5.33 (dd, J = 9.1, 15.6 Hz, 1H) and 5.63 (dd, J = 9.6, 15.6 Hz, 1H) ppm corresponding to newly formed olefinic proton were seen. The large coupling constant 15.6 Hz confirmed the *trans* geometry of the newly formed double bond. Furthermore, the strong peak observed at 239.0871 ($[M+Na]^+$) in the HRMS spectrum confirmed the constitution of compound **20**.



20 **22** **19**

Scheme 12. *Synthesis of mesylate (**20**)*

Having the triol **20** in hand, the next step was selective protection of the allylic hydroxyl groups as their TBS ethers under the previously used reaction conditions to obtain the di-TBS compound **22** in 77% yield (Scheme 12). The structure of compound **22** was established with the help of NMR and Mass spectrum. In the ^{1}H NMR spectrum of compound **22**, the sharp singlets at δ 0.02 (s, 3H), 0.03 (s, 3H), 0.05 (s, 3H), 0.08 (s, 3H) ppm corresponding to four methyl groups attached to silicon and at δ 0.85 (s, 9H), 0.87 (s, 9H) ppm corresponding to methyls of tertiary butyl group were seen. Similarly in the ^{13}C NMR spectrum of compound **22**, the carbons of methyls attached to silicon and methyls of tertiary butyl groups appeared at δ –4.8 (q), –4.8 (q), –4.6 (q), –3.6 (q) and 25.7 (q, 3C), 25.8 (q, 3C) ppm respectively and quaternary carbons of tertiary butyl groups were seen to resonate at δ 18.0 (s), 18.1 (s) ppm. Additionally, the presence of a mass peak at 467.2603 ($[M+Na]^+$) in the HRMS spectra confirmed the compound **22**. Mesylation of the remaining -OH group of

di-TBS compound **22** using mesyl chloride, triethyl amine and catalytic DMAP in dichloromethane gave the mesylate compound **19** in 85% yield. In the ^{1}H NMR spectrum of compound **19**, a sharp singlet was noticed due to the methyl group of sulphonate at δ 3.07 (s, 3H) ppm. The regioselectivity of mesylation was confirmed by the appearance of signal due to the proton H–C8 attached to mesyloxy at δ 4.39 (dd, J = 8.7, 9.8 Hz, 1H), whereas the same H–C8 in compound **22** was found to resonate at δ 3.28 (dd, J = 8.6, 9.4 Hz, 1H). Similarly, in the ^{13}C NMR spectrum of compound **19**, the methyl carbon of mesyl group and carbon attached to the mesyl group were seen to resonate at 39.3 (q) and 84.1 (d) respectively. Furthemore, the observed cross peak between the H_3C of mesyl group and C8–H in the NOESY of compound **19** was in support of the assigned structure of **19** (Figure 8).

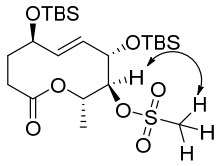
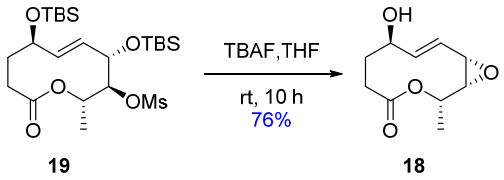


Figure 8. *nOe interactions of the mesylate (**19**)*

The mesylate **19** was advanced for the oxirane formation employing TBAF at room temperature in THF, which gave compound **18** in 76% yields. Compound **18** was also found to be existing as a 10:1 mixture of two equilibrating conformational isomers.[19,20] The spectral data of the major conformer of the compound **18** was in agreement with the data reported for the natural product. Some of the peaks corresponding to the minor conformer could be seen in the ^{1}H and 2D NMR spectra of the natural product as shown in Figure 9. The isolated group ignored the minor conformer by considering the corresponding peaks in the spectra as resulting from the impurities. The opposite sign of the specific rotation of the synthetic Stagonolide (**18**) [+76.8 (*c* 0.2, $CHCl_3$)] for **18** and the natural stagonolide [–82.0 (*c* 0.2, $CHCl_3$)] revealed that it was the *anti*-pode of the natural Stagonolide D.



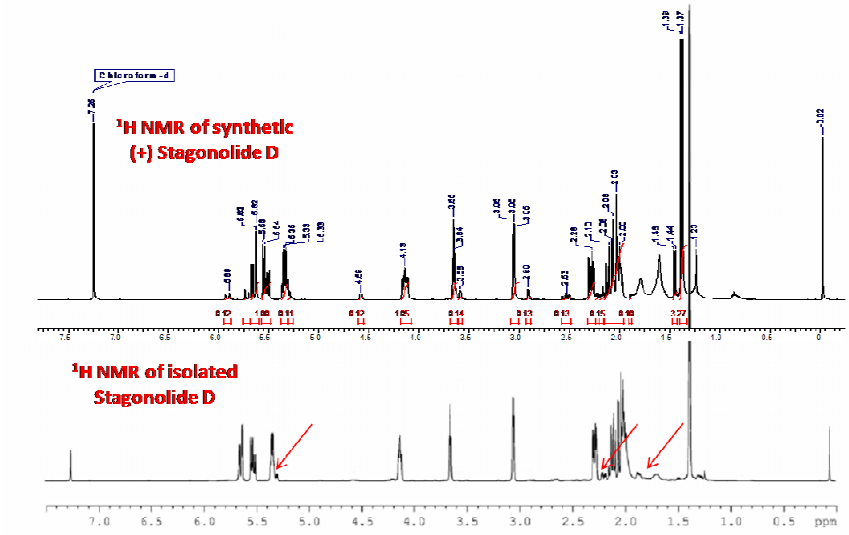
Scheme 12. *Synthesis of (+)- Stagonolide D (**18**)*

Conclusion:

- The total synthesis of the putative structure of Stagonolide D and of the unnatural enantiomer (+)-Stagonolide D has been completed. The key nonenolide unit has been

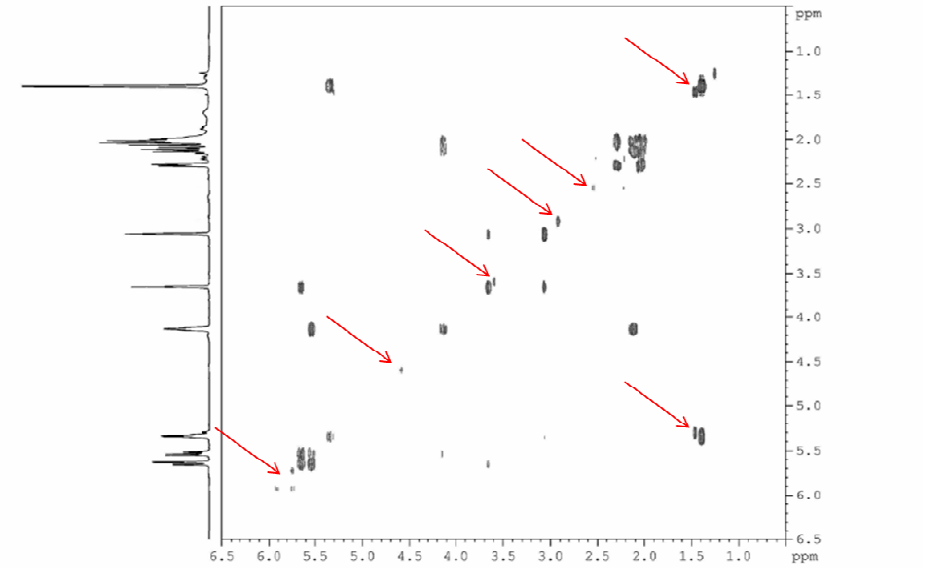
constructed by employing ring closing metathesis and the oxirane ring has been formed by a concomitant *O*-TBS-deprotection and displacement of a -OMs placed next to it.

- Revision of its relative and absolute configuration was established by synthesizing optical antipode of Stagonolide D.
- Proved beyond doubt that the compound synthesized by Nanda and Coworkers may be some uncharacterized diastereomer of the Stagonolide D
- Proposed that the natural Stagonolide D exists as mixture of two equilibrating conformers, with the minor conformer having been ignored by the isolation group.



^{1}H NMR spectrum of stagonolide D, isolated from *S. cirsii* solid culture, recorded at 600 MHz

Peaks corresponding to the minor conformer



. COSY spectrum of stagonolide D, isolated from *S. cirsii* solid culture, recorded at 600 MHz

Peaks corresponding to the minor conformer

Figure 9: *^{1}HNMR and cosy spectrum of isolated Stagonolide D*

A comparative study of both ^{1}H & ^{13}C coupling constants (*J*) and/or chemical shifts for natural Stagonolide D and synthetic **1** and **18** is given in Tables 2 and 3.

Table 2. Comparative *d* and *J* (Hz) of synthetic **1**, **18** and natural product

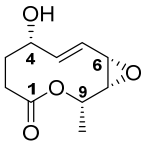
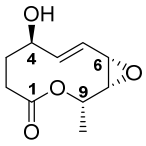
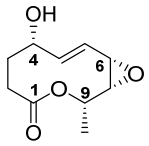
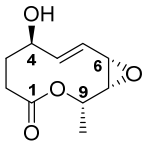
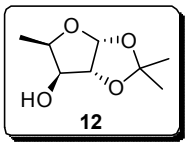
Entry				**Natural Product**		
		1 (Minor)	**1 (Major)**		**18 (Major)**	**18 (Minor)**
1	H–C(4)	4.20 (dt, *J* =4.7, 8.3 Hz)	4.54 (brs)	4.13 (ddd, *J* = 4.3, 7.4, 8.4 Hz)	4.13 (ddd, *J* = 4.4, 8.3,10.5 Hz)	4.58 (brs)
2	H–C(5)	5.53 (dd, *J* = 1.1, 16.0 Hz)	5.68 (ddd, *J* = 1.1, 3.2, 17.1 Hz)	5.52 (dd, *J* = 8.4, 17.0 Hz)	5.52 (ddd, *J* = 0.9, 8.3, 17.0 Hz)	5.72 (td, *J* = 1.7, 16.0, Hz)
3	H–C(6)	5.75 (ddd, *J* =1.1, 8.7, 16.0 Hz)	5.94 (ddd, *J* =1.1, 4.8, 17.1 Hz)	5.64 (dd, *J* = 4.8, 17.0 Hz)	5.65 (dd, *J* = 4.9, 17.0 Hz)	5.91 (ddd, *J* = 1.2, 3.2,16.0 Hz)
4	H–C(7)	3.53 (dt, *J* = 1.4, 4.2 Hz)	3.69 (t, *J* = 4.6 Hz)	3.65 (dd, *J* = 3.9, 4.8 Hz)	3.65 (brt, *J* = 4.6 Hz)	3.58 (ddd, *J* = 1.8, 3.2,4.6 Hz)
5	H–C(8)	2.90 (dd, *J* =1.6, 4.3 Hz)	3.03 (dd, *J* = 2.7,4.8 Hz)	3.05 (dd, *J* = 2.6, 3.8, Hz)	3.05 (dd, *J* = 2.6, 4.1 Hz)	2.91 (dd, *J* =1.7, 4.3 Hz)
6	H–C(9)	5.27 (dq, *J* = 1.5, 6.8 Hz)	5.33 (dq, *J* = 2.7, 6.8 Hz)	5.34 (dq, *J* = 2.6, 6.7 Hz)	5.35 (dq, *J* = 2.6, 6.8 Hz)	5.29(dq, *J* = 1.5, 6.7 Hz)
7	Me–C(9)	1.46 (d, *J* = 6.8 Hz)	1.40 (d, *J* = 6.8 Hz)	1.37 (d, *J* = 6.7 Hz)	1.38 (d, *J* = 6.8 Hz)	1.45 (d, *J* = 6.8 Hz)

Table 3. Comparative ^{13}C chemical shifts of synthetic **1**, **18** and natural product

Sr. No.	^{13}C NMR			Natural Product		
		Minor	**Major**		**Major**	**Minor**
1	C–1	172.1	174.6	173.5	173.5	172.7
2	C–2	31.7	27.7	31.2	31.2	28.7
3	C–3	32.5	33.4	35.0	35.0	29.7
4	C–4	72.7	68.1	75.1	75.1	68.1
5	C–5	135.3	134.0	134.2	134.1	134.7
6	C–6	120.6	126.2	128.1	128.2	118.2
7	C–7	56.8	55.9	55.4	55.4	56.3
8	C–8	57.3	57.6	58.2	58.2	57.7
9	C–9	65.1	66.2	65.7	65.7	66.1
10	C–10	16.2	17.7	16.2	16.2	17.7

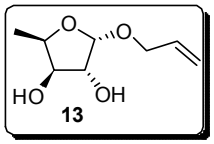
EXPERIMENTAL

***1,2-O-Isopropylidene-5-deoxy-α-D-xylofuranose* (12):**



Compound **12** was prepared according to the literature procedure (yield 80%, 0.2 mol scale); MP: 122 - 123 °C [Lit. 66 - 67 ºC]; $[\alpha]_D^{25}$ −14.9 (*c* 1.0, $CHCl_3$) [Lit. $[\alpha]_D^{25}$ −15.6 (*c* 2.0, $CHCl_3$)]; IR ($CHCl_3$) *v*: 3459, 2989, 2938, 1645, 1385, 1166, 1075, 901, 820, 729 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.28 (d, *J* = 6.4 Hz, 3H), 1.29 (s, 3H), 1.48 (s, 3H), 1.81 (s, 1H), 3.98 (d, *J* = 2.5 Hz, 1H), 4.3 (dq, *J* = 2.6, 6.5 Hz, 1H), 4.51 (d, *J* = 3.9 Hz, 1H), 5.87 (d, *J* = 3.9 Hz, 1H); ^{13}C NMR (50.32 MHz, $CDCl_3$): δ 12.7 (q), 26.0 (q), 26.5 (q), 76.0 (d), 76.2 (d), 85.4 (d), 104.3 (d), 111.3 (s) ppm; ESI–MS: 197.25 (70% $[M+Na]^+$).

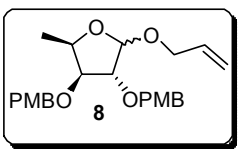
***Allyl 5-deoxy-α/β-D-xylofuranossides* (13)**:



To a solution of **12** (10.0 g, 57.4 mmol) in anhydrous THF (100 mL) was added *p*-TSA (2.0 g, 17.2 mmol) and allyl alcohol (25 mL, 344.4 mmol) and the reaction mixture was refluxed for 20 h. After completion of the reaction, the reaction mixture was neutralized with aqueous $NaHCO_3$ solution and extracted with EtOAc (3×100 mL). The organic layer was dried over sodium sulphate and evaporated under reduced pressure. The crude product was purified by silica gel chromatography (40→50% EtOAc in pet ether) to afford **13** (7.3 g, 73%) as yellow oil.

R_f 0.3 (40% EtOAc in pet ether); IR (neat) *v*: 3419, 2935, 1646, 1423, 1337, 1124, 1045, 767 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.22 (d, *J* = 6.5 Hz, 3H, Minor), 1.30 (d, *J* = 6.6 Hz, 3H, Major), 2.68 (br s, 2H), 3.85–4.07 (m, 2H), 4.09–4.27 (m, 2H), 4.31–4.34 (m, 1H, Minor), 4.45 (dq, *J* = 4.3, 6.6 Hz, 1H, Major), 4.92 (s, 1H, Major), 5.10 (d, *J* = 4.1 Hz, 1H, Minor), 5.16–5.30 (m, 2H), 5.86 (ddt, *J* = 5.4, 10.6, 17.1 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.2 (q, Minor), 15.3 (q, Major), 68.1 (t, Major), 69.1 (t, Minor), 75.0 (d, Minor), 77.0 (d, Major), 77.7 (d, Minor), 78.8 (d, Minor), 79.1 (d, Major), 80.1 (d, Major), 99.5 (d, Minor), 106.1 (d, Major), 117.7 (t), 133.6 (d, Major), 133.7 (d, Minor) ppm; ESI-MS: 197.12 (100%, $[M+Na]^+$); HRMS: 197.0790 ($[M+Na]^+$) calculated, 197.0797 ($[M+Na]^+$) observed.

***Allyl 2,3-di-O-(p-methoxybenzyl)-α/β-D-xylofuranossides* (8)**:

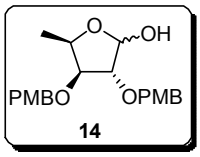


To a cooled solution of **13** (10.0 g, 57.4 mmol) in anhydrous DMF (80 mL), NaH (60% dispersion in mineral oil, 5.3 g, 132.0 mmol) was added slowly and stirred for 5 min. Then PMB-Cl (16 ml, 121 mmol) was added and stirring was continued at

room temperature for 4 h. The reaction mixture was quenched with aq. Na_2SO_4 and the aqueous layer was extracted with EtOAc (2×100 mL). The combined organic layer was washed with brine (100 mL) and concentrated under reduced pressure. The purification of residue by silica gel column chromatography (7% EtOAc in pet ether) gave **8** (21.6 g, 91%) as yellow oil.

R_f 0.4 (10% EtOAc in pet ether); IR (neat) *v*: 3075, 2934, 2837, 2059, 1613, 1514, 1249, 1174, 1035, 929, 821, 757, 518 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.21 (d, *J* = 6.4 Hz, 3H, Minor), 1.29 (d, *J* = 6.6 Hz, 3H, Major), 3.81 (s, 6H), 3.89 (dd, *J* = 3.5, 5.8 Hz, 1H), 3.97–4.16 (m, 2H), 4.20–4.39 (m, 2H), 4.44–4.56 (m, 4H), 4.92 (d, *J* = 4.3 Hz, 1H, Minor), 4.97 (d, *J* = 2.0 Hz, 1H, Major), 5.18 (ddt, *J* = 1.4, 3.0, 10.5 Hz, 1H), 5.29 (ddt, *J* = 1.6, 3.2, 17.2 Hz, 1H), 5.92 (ddt, *J* = 5.05, 10.6, 17.1 Hz, 1H), 6.87 (d, *J* = 8.7 Hz, 2H), 6.88 (d, *J* = 8.7 Hz, 2H), 7.25 (d, *J* = 8.5 Hz 4H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 15.5 (q, Minor), 16.1 (q, Major), 55.2 (q, 2C), 68.3 (t, Minor), 68.7 (t, Major), 71.5 (t, Major), 71.7 (t, Major), 71.8 (t, Minor), 72.0 (t, Minor), 73.4 (d, Minor), 76.7 (d, Major), 81.9 (d, Minor), 82.3 (d, Major), 83.9 (d, Minor), 87.2 (d, Major), 98.2 (d, Minor), 106.1 (d, Major), 113.7 (d, 2C), 113.8 (d, 2C), 117.0 (t, Major), 117.4 (t, Minor), 129.3 (d, 2C), 129.4 (d, 2C), 129.8 (s), 130.1 (s), 134.4 (d), 159.2 (s), 159.3 (s) ppm; ESI-MS: 437.33 (100%, $[M+Na]^+$); HRMS: 437.1940 ($[M+Na]^+$) calculated, 437.1924 ($[M+Na]^+$) observed.

2,3-Di-O-(p-methoxybenzyl)-α/β-D-xylofuranosides (**14**):

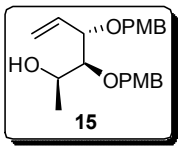


14

A suspension of **8** (9 g, 21.7 mmol), potassium tert-butoxide (6.1 g, 54.2 mmol) in DMSO (80 mL) was heated at 100 °C for 2 h. The reaction mixture was diluted with brine (50 mL) and extracted with EtOAc (2×50 mL). The combined organic layer was washed with water (2×50 mL), brine (50 mL), dried over sodium sulphate and concentrated. The resulting product (8.8 g, 21.2 mmol) was taken in acetone:water mixture (9:1, 75 mL), cooled at 0 °C and treated with yellow mercuric oxide (5.9 g, 27.6 mmol) and mercuric chloride (6.3 g, 23.4 mmol) was added over a period of 30 minutes and the stirring was continued for 10 h at room temperature. The contents were filtered through celite and the filtrate was concentrated. The residue was partioned between water and EtOAc and the organic layer was washed with saturated potassium iodide solution (2×50 mL), brine (50 mL) dried over sodium sulphate, and concentrated. Purification of the crude on silica gel column chromatography (20→25% EtOAc in pet ether) gave **14** (5.6 g, 68%) as yellow oil.

R_f 0.3 (25% EtOAc in pet ether); IR (neat) *v*: 3444, 2934, 2059, 1614, 1514, 1463, 1249, 1034, 820, 756, 584 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.23 (d, *J* = 6.4 Hz, 1.5H), 1.33 (d, *J* = 6.6 Hz, 1.5H), 3.72–3.77 (m, 1H), 3.81 (br s, 6H), 3.90–3.94 (m, 1H), 4.30 (dq, *J* = 4.3, 6.5 1H), 4.40 (d, *J* = 11.6 Hz, 1H), 4.41 (d, *J* = 11.2 Hz, 1H), 4.49–4.58 (m, 2H), 5.19 (s, 0.5 H), 5.41 (br s, 0.5H), 6.87 (d, *J* = 8.7 Hz, 2H), 6.89 (d, *J* = 8.7 Hz, 2H), 7.20 (d, *J* = 8.7 Hz, 2H), 7.24 (d, *J* = 8.8 Hz 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.3 (q), 15.3 (q), 55.2 (q, 4C), 71.4 (t), 71.5 (t), 71.8 (t), 72.7 (t), 74.4 (d), 77.7 (d), 80.8 (d), 81.6 (d), 81.8 (d), 84.8 (d), 95.4 (d), 100.9 (d), 113.7 (d, 2C), 113.8 (d, 4C), 113.9 (d, 2C), 128.8 (s), 129.1 (d, 2C), 129.2 (s), 129.2 (d, 2C), 129.4 (d, 2C), 129.4 (s), 129.6 (d, 2C), 129.8 (s), 159.2 (s), 159.3 (s), 159.4 (s), 159.5 (s), ppm; ESI-MS: 397.21 (65%, $[M+Na]^+$); HRMS: 397.1627 ($[M+Na]^+$) calculated, 397.1653 ($[M+Na]^+$) observed.

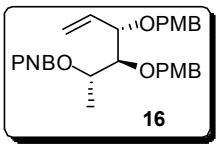
***(2R,3S,4S)-3,4-Bis((4-methoxybenzyl)oxy)hex-5-en-2-ol* (15):**



To a solution of methyltriphenylphosphorane ylide [generated by the action of *n*–butyl lithium (12.7 mL, 20.3 mmol) with $Ph_3P^+CH_3Br^-$ (7.63 g, 21.4 mmol) in anhydrous THF (50 mL) at 0 °C] was added **14** (2.0 g, 5.34 mmol) in THF (10 mL) at 0 °C and stirring was continued at rt for 20 h. The reaction mixture was quenched with saturated ammonium chloride (50 mL) and filtered. The organic layer was separated and aqueous layer extracted with EtOAc (3×75 mL). The combined organic layer was washed with brine (100 mL), dried over sodium sulphate and concentrated. The purification of residue by silica gel column chromatography (12→15% EtOAc in pet ether) gave **15** (1.3 g, 65%) as yellow oil.

R_f 0.5 (25% EtOAc in pet ether); $[\alpha]_D^{25}$ +5.2 (*c* 1.0, $CHCl_3$); IR (neat) *v*: 3435, 2934, 1611, 1512, 1248, 1035, 821, 765 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.09 (d, *J* = 6.4 Hz, 3H), 2.30 (d, *J* = 5.3 Hz, 1H), 3.20 (dd, *J* = 4.2, 5.4 Hz 1H), 3.79 (s, 6H), 3.84–3.93 (m, 1H), 4.01 (dd, *J* = 5.7, 7.6 Hz, 1H), 4.31 (d, *J* = 11.5 Hz, 1H), 4.50 (d, *J* = 10.9 Hz, 1H), 4.59 (d, *J* = 11.6 Hz, 1H), 4.80 (d, *J* = 10.9 Hz, 1H), 5.32–5.41 (m, 2H) 5.89 (ddd, *J* = 7.4, 9.9, 17.6, Hz, 1H), 6.87 (d, *J* = 8.6 Hz, 4H), 7.25 (d, *J* = 8.6 Hz, 4H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 19.9 (q), 55.2 (q, 2C), 67.2 (d), 70.2 (t), 74.8 (t), 81.2 (d), 84.8 (d), 113.7 (d, 2C), 113.7 (d, 2C), 118.9 (t), 129.5 (d, 2C), 129.8 (d, 2C), 130.3 (s), 130.4 (s), 135.5 (d), 159.1 (s), 159.3 (s) ppm; ESI-MS: 395.22 (100%, $[M+Na]^+$); HRMS: 395.1834 ($[M+Na]^+$) calculated, 395.1831 ($[M+Na]^+$) observed.

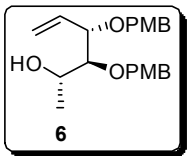
***(2S,3S,4S)–3,4-Bis(4-methoxybenzyloxy)hex-5-en-2-yl 4-nitrobenzoate* (16):**



To a solution of alcohol **15** (1.5 g, 4.0 mmol), *p*-nitrobenzoic acid (740 mg, 4.43 mmol), TPP (2.11 g, 8.1 mmol), in THF (10 mL) at 0 °C was added DEAD (1.27 mL, 8.1 mmol). Stirring was continued at 0 °C for 1 h and then at room temperature for next 2 h. After completion of the reaction, THF was removed, crude was dissolved in EtOAc (100 mL) and washed with aqueous sodium bicarbonate (30 ml), water (50 mL), dried (Na_2SO_4) and concentrated. The purification of residue by silica gel column chromatography (8→10% EtOAc in pet ether) afforded **16** (1.73 g, 82%) as yellow oil.

R_f 0.6 (15% EtOAc in pet ether); $[\alpha]_D^{25}$ –3.3 (*c* 1.0, $CHCl_3$); IR (neat) *v*: 2937, 1722, 1613, 1545, 1463, 1276, 1248, 1102, 1035, 822, 757, 720 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.38 (d, *J* = 6.4 Hz, 3H), 3.72 (m, 1H), 3.73 (s, 3H), 3.77 (s, 3H), 3.91 (dd, *J* = 5.7, 8.0 Hz, 1H), 4.29 (d, *J* = 11.4 Hz, 1H), 4.56 (d, *J* = 11.4 Hz, 1H), 4.62 (d, *J* = 11.4 Hz, 1H), 4.75 (d, *J* = 11.4 Hz, 1H), 5.22 (dq, *J* = 4.4, 6.4 Hz, 1H), 5.31–5.41 (m, 2H), 5.90 (ddd, *J* = 7.8, 10.7, 16.8 Hz, 1H), 6.76 (d, *J* = 8.7 Hz, 2H), 6.80 (d, *J* = 8.7 Hz, 2H), 7.20 (d, *J* = 8.6 Hz, 2H), 7.26 (d, *J* = 8.7 Hz, 2H), 7.97 (d, *J* = 9.0 Hz, 2H), 8.20 (d, *J* = 9.0 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 15.1 (q), 55.1 (q), 55.1 (q), 70.1 (t), 72.4 (d), 74.5 (t), 81.0 (d), 82.2 (d), 113.6 (d, 2C), 113.7 (d, 2C), 119.4 (t), 123.3 (d, 2C), 129.6 (d, 2C), 129.7 (d, 2C), 130.1 (s), 130.5 (s), 130.6 (d, 2C), 135.1 (d), 135.8 (s), 150.3 (s), 159.1 (s), 159.2 (s), 163.7 (s) ppm; ESI-MS: 544.36 (30%, $[M+Na]^+$); HRMS: 544.1947 ($[M+Na]^+$) calculated, 544.1903 ($[M+Na]^+$) observed.

***(2S,3S,4S)-3,4-Bis(4-methoxybenzyloxy)hex-5-en-2-ol* (6):**

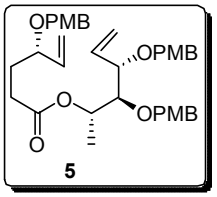


To a solution of **16** (1.7 g, 3.26 mmol), in methanol (15 mL) was added K_2CO_3 (0.9 g, 6.5 mmol) and the reaction mixture was stirred at rt for 1 h. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (12→15 % EtOAc in pet ether) to afford **6** (1.1 g, 91%) as yellow oil.

R_f 0.3 (15% EtOAc in pet ether); $[\alpha]_D^{25}$ +12.9 (*c* 1.0, $CHCl_3$); IR (neat) *v*: 3467, 2933, 1613, 1464, 1249, 1035, 933, 822, 758, cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.35 (d, *J* = 6.3 Hz, 3H), 2.81 (d, *J* = 5.7 Hz, 1H), 3.34 (dd, *J* = 5.0, 6.1 Hz 1H), 3.80 (s, 3H), 3.81 (s, 3H), 3.87 (dd, *J* = 6.2, 12.2 Hz, 1H), 4.01 (dd, *J* = 5.0, 7.3 Hz, 1H), 4.31 (d, *J* = 11.5 Hz, 1H), 4.52 (d, *J* = 11.4 Hz, 1H), 4.58 (d, *J* = 11.7 Hz, 1H), 4.66 (d, *J* = 11.2 Hz, 1H), 5.29– 5.39 (m, 1H), 5.91 (ddd, *J* = 7.4,

10.9, 18.3 Hz, 1H), 6.84 (d, *J* = 8.7 Hz, 2H), 6.86 (d, *J* = 8.7 Hz, 2H), 7.22 (d, *J* = 8.7 Hz, 2H), 7.23 (d, *J* = 8.7 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 19.0 (q), 55.2 (q, 2C), 67.3 (d), 70.2 (d), 73.5 (d), 80.6 (d), 83.1 (d), 113.7 (d, 2C), 113.8 (d, 2C), 119.1 (t), 129.6 (d, 2C), 129.6 (d, 2C), 129.8 (s), 130.4 (s), 134.6 (d), 159.2 (s), 159.3 (s) ppm; ESI-MS: 395.22 (100%, $[M+Na]^+$); HRMS: 395.1834 ($[M+Na]^+$) calculated, 395.1873 ($[M+Na]^+$) observed.

(S)-((2S,3S,4S)-3,4-Bis(4-methoxybenzyloxy)hex-5-en-2-yl)4-(4-methoxybenzyloxy)hex-5-enoate (**5**):

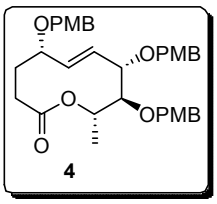


5

To a solution of acid (*S*)-**7** (0.8 g, 3.2 mmol), in THF (13 mL) were added 2,4,6-trichlorobenzoyl chloride (0.6 mL, 3.84 mmol) and *N*,*N*-diisopropyl ethyl amine (3.2 mL, 18.4 mmol) and the contents were stirred for 2 h at rt. After completion of mixed anhydride formation as indicated by TLC, DMAP (0.78 g, 6.4 mmol) and a solution of **6** (1.19 g, 3.2 mmol) in THF (5 mL) were added and stirring was continued at rt for 16 h. The reaction mixture was quenched with water and extracted with EtOAc (3×30 mL). The combined organic phase was washed with saturated $NaHCO_3$ solution (10 mL), water (20 mL), dried (Na_2SO_4) and evaporated under reduced pressure. The crude product was purified by silica gel column chromatography (9→10 % EtOAc in pet ether) to afford **5** (1.55 g, 80%) as yellow oil.

R_f 0.5 (20% EtOAc in pet ether); $[\alpha]_D^{25}$ −12.5 (*c* 1.0, $CHCl_3$); IR (neat) *v*: 2934, 1731, 1614, 1586, 1463, 1249, 1173, 931, 771 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.20 (d, *J* = 6.5, 3H), 1.75–1.88 (m, 2H), 2.24–2.32 (m, 2H), 3.55 (dd, *J* = 3.8, 6.2 Hz, 1H), 3.68–3.82 (m, 2H), 3.78 (s, 3H), 3.79 (s, 6H), 4.25 (d, *J* = 11.4 Hz, 1H), 4.28 (d, *J* = 11.4 Hz, 1H), 4.50 (d, *J* = 11.4 Hz, 1H), 4.53 (d, *J* = 11.4 Hz, 1H), 4.60 (d, *J* = 11.2 Hz, 1H), 4.67 (d, *J* = 11.2 Hz, 1H), 4.99 (dq, *J* = 3.8, 6.5 Hz, 1H), 5.17–5.34 (m, 4H), 5.62–5.91 (m, 2H), 6.84 (d, *J* = 8.7 Hz, 3H), 6.85 (d, *J* = 8.7 Hz, 3H), 7.23 (d, *J* = 8.7 Hz, 3H), 7.27 (d, *J* = 8.7 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.7 (q), 30.3 (t), 30.4 (t), 55.2 (q, 3C), 69.8 (t), 70.1 (t), 71.0 (d), 74.5 (t), 78.9 (d), 81.4 (d), 82.6 (d), 113.6 (d, 2C), 113.6 (d, 2C), 113.7 (d, 2C), 117.5 (t), 119.1 (t), 129.3 (d, 2C), 129.4 (d, 2C), 129.6 (d, 2C), 130.3 (s), 130.5 (s), 130.7 (s), 135.2 (d), 138.3 (d), 159.0 (s), 159.0 (s), 159.1 (s), 172.5 (s) ppm; ESI-MS: 627.81 (100%, $[M+Na]^+$); HRMS: 627.2934 ($[M+Na]^+$) calculated, 627.2935 ($[M+Na]^+$) observed.

(5S,8S,9S,10S,E)-5,8,9-Tris(4-methoxybenzyloxy)-10-methyl-3,4,5,8,9,10-hexahydro-2H-oxecin-2-one (**4**):

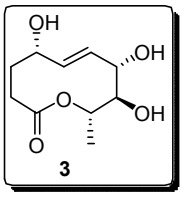


4

To a solution of **5** (50 mg, 82 μmol) in dry dichloromethane (20 mL), 2nd gen. Grubbs' catalyst (13.5 mg, 13 μmol) was added and the mixture was degassed under argon atmosphere thoroughly. The reaction mixture was refluxed for 96 h and the solvent was removed under reduced pressure. The residue was purified by column chromatography (12→15% EtOAc in pet ether) to afford **4** (26 mg, 55%) as a white amorphous solid.

R_f 0.45 (20% EtOAc in pet ether); MP: 96 °C; $[\alpha]_D^{25}$ +10.8 (*c* 1.4, $CHCl_3$); IR ($CHCl_3$) *v*: 3444, 3019, 1723, 1613, 1514, 1456, 1302, 1216, 1074, 1037, 754, 668 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.28 (d, *J* = 6.4 Hz, 3H), 1.99–2.02 (m, 2H), 2.04–2.09 (m, 1H), 2.46 (ddd, *J* = 4.6, 10.1, 14.4 Hz, 1H), 3.41 (t, *J* = 9.2 Hz, 1H), 3.79 (s, 3H), 3.81 (s, 3H), 3.82 (s, 3H), 3.84 (t, *J* = 9.1 Hz, 1H), 4.13 (dd, *J* = 4.3, 6.2 Hz, 1H), 4.34 (d, *J* = 11.3 Hz, 1H), 4.36 (d, *J* = 11.3 Hz, 1H), 4.55 (d, *J* = 11.3 Hz, 1H), 4.56 (d, *J* = 10.1 Hz, 1H), 4.57 (d, *J* = 11.3 Hz, 1H), 4.93 (d, *J* = 10.1 Hz, 1H), 4.96 (dq, *J* = 3.6, 6.4 Hz, 1H), 5.39 (dd, *J* = 3.0, 15.9 Hz, 1H), 5.89 (ddd, *J* = 1.2, 10.1, 15.9 Hz, 1H), 6.84 (d, *J* = 8.8 Hz, 2H), 6.86 (d, *J* = 8.8 Hz, 2H), 6.90 (d, *J* = 8.8 Hz, 2H), 7.25 (d, *J* = 8.5 Hz, 2H), 7.26 (d, *J* = 8.5 Hz, 2H), 7.28 (d, *J* = 8.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 18.4 (q), 28.8 (t), 30.4 (t), 55.3 (q), 55.3 (q), 55.3 (q), 69.4 (d), 69.6 (t), 70.4 (t), 74.8 (d), 75.5 (t), 82.5 (d), 84.7 (d), 113.7 (d, 2C), 113.7 (d, 2C), 113.8 (d, 2C), 129.1 (d, 2C), 129.4 (d, 2C), 129.6 (d), 129.8 (d, 2C), 130.4 (d), 130.6 (s), 130.7 (s, 2C), 159.0 (s), 159.2 (s), 159.2 (s), 175.2(s) ppm; ESI-MS: 599.57 (100%, $[M+Na]^+$); HRMS: 599.2621 ($[M+Na]^+$) calculated, 599.2638 ($[M+Na]^+$) observed.

(5S,8S,9R,10S,E)-5,8,9-Trihydroxy-10-methyl-3,4,5,8,9,10-hexahydro-2H-oxecin-2-one (**3**):



3

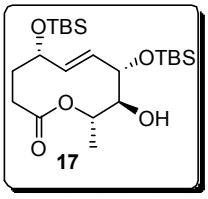
A solution of **4** (100 mg, 0.17 mmol) in TFA (2 mL) was stirred at 0 °C for 2 h. The reaction mixture was concentrated under reduced pressure and the residue was purified by column chromatography (70→100% EtOAc in pet ether) to afford **3** (26 mg, 70%) as a white crystalline solid.

R_f 0.2 (80% EtOAc in pet ether); MP: 186 °C; $[\alpha]_D^{25}$ −7.6 (*c* 0.3, MeOH); IR (MeOH) *v*: 3368, 2947, 2836, 1655, 1456, 1412, 1115, 1026 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.28 (d, *J* = 6.4 Hz, 3H), 1.84–1.89 (m, 1H), 1.98–2.01 (m, 1H), 2.04 (ddd, *J* = 2.4, 5.9, 12.9 Hz,1H), 2.44 (dt, *J*

= 2.1, 13.7 Hz, 1H), 3.22 (t, *J* = 9.2 Hz,1H), 3.73 (t, *J* = 9.4 Hz,1H), 4.42 (m, 1H), 4.85 (dq, *J* = 6.4, 9.6 Hz, 1H), 5.50 (dd, *J* = 2.7, 15.7 Hz, 1H), 5.85 (ddd, *J* = 1.6, 9.9, 15.7 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 18.5 (q), 29.0 (t), 33.0 (t), 68.9 (d), 71.4 (d), 77.2 (d), 78.2 (d), 130.7 (d), 133.4 (d), 177.1 (s) ppm; HRMS: 217.1076 ($[M+H]^+$) calculated, 217.1063 ($[M+H]^+$) observed.

Crystal Data: Single crystals of the compound were grown by slow evaporation of the solution in methanol. Colourless crystal of approximate size 0.23 x 0.09 x 0.02 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 frames = 2424, Oscillation / frame -0.3º, exposure / frame = 5.0 sec / frame, maximum detector swing angle = –30.0º, beam center = (260.2, 252.5), in plane spot width = 1.24, SAINT integration, range = 1.72 to 25.0º, completeness to of 25.0 º is 99.9 %. SADABS correction applied, $C_{10}H_{16}O_5$, *M* = 216.23. Crystals belong to Monoclinic, space group $P2_1$, a = 7.5846(7), b = 5.8330(5) Å, c = 11.817(1) Å, beta= 90.213(2)°, *V* = 522.80(8) Å^3, *Z* = 2, D_c = 1.374 g /cc, μ (MoK) = 0.110 mm^{-1}, *T* = 100(2) K, 5084 reflections measured, 1828 unique [I>2σ(I)], R value 0.0305, wR2 = 0.0697. All the data were corrected for Lorentzian, polarisation and absorption effects. SHELX-97 (ShelxTL) 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. Largest diff. peak and hole 0.159 and -0.125 e. Å $^{-3}$. Data collection and refinement parameters are listed in Table 1 (Supporting Information)

(5S,8S,9S,10S,E)–5,8–Bis(tert–butyldimethylsilyloxy)–9–hydroxy–10–methyl–3,4,5,8,9,10–hexahydro–2H–oxecin–2–one (**17**):

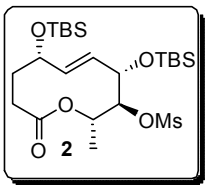


At 0 °C, a solution of **3** (30 mg, 0.14 mmol), imidazole (47 mg, 0.69 mmol) and DMAP (4 mg, 0.03 mmol) in CH_2Cl_2-DMF (0.5 ml each) was treated with TBS-Cl (84 mg, 0.55 mmol) and the contents were stirred at rt for 16 h. The excess of TBS-Cl was quenched with water (5 mL) and the reaction mixture was extracted with CH_2Cl_2 (3×10 mL). The organic layer was dried (Na_2SO_4) and concentrated at reduced pressure. The residue was purified by column chromatography (4→5% EtOAc in pet ether) to afford **17** (46 mg, 74%) as yellow oil.

R_f 0.6 (10% EtOAc in pet ether); $[\alpha]_D^{25}$ +6.1 (*c* 0.6, $CHCl_3$); IR ($CHCl_3$) *v*: 2928, 2856, 1732, 1622, 1541, 1463, 1385, 1254, 1071, 1049, 836 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.01 (s,

3H), 0.03 (s, 3H), 0.04 (s, 3H), 0.05 (s, 3H), 0.86 (s, 9H), 0.91 (s, 9H), 1.31 (d, J = 6.4 Hz, 3H), 1.71–1.76 (m, 1H), 1.99–2.06 (m, 2H), 2.43 (dt, J = 1.5, 13.6 Hz, 1H), 2.91 (s, 1H), 3.32 (dd, J = 8.8, 9.5 Hz, 1H), 3.84 (t, J = 9.2 Hz, 1H), 4.43 (m, 1H), 4.97 (dq, J = 6.4, 9.4 Hz, 1H), 5.47 (dd, J = 2.5, 15.4 Hz, 1H), 5.81 (ddd, J = 1.6, 9.8, 15.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ –5.1 (q), –5.0 (q), –4.7 (q), –3.6 (q), 18.0 (s), 18.2 (s), 18.2 (q), 25.8 (q, 3C), 25.8 (q, 3C), 28.0 (t), 33.1 (t), 68.8 (d), 69.6 (d), 76.0 (d), 78.6 (d), 130.2 (d), 133.1 (d), 175.4 (s) ppm; ESI-MS: 467.35 (33%, $[M+Na]^+$); HRMS: 467.2625 ($[M+Na]^+$) calculated, 467.2601 ($[M+Na]^+$) observed.

(2S,3S,4S,7S,E)-4,7-Bis(tert-butyldimethylsilyloxy)-2-methyl-10-oxo-3,4,7,8,9,10-hexahydro-2H-oxecin-3-yl methanesulfonate (**2**):

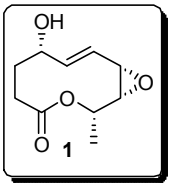


At 0 ºC, a solution of **17** (25 mg, 0.06 mmol), triethylamine (20 μL, 0.14 mmol) and DMAP (Cat.), was treated with methanesulphonyl chloride (10 μL, 0.13 mmol) and the reaction mixture was warmed to rt and stirred for 12 h. The reaction was portioned between water and CH_2Cl_2 and the aqueous layer was extracted with CH_2Cl_2 (3×10 mL). Combined organic layer was dried over sodium sulphate and concentrated. Purification of the resulting crude by column chromatography (7→8% EtOAc in pet ether) gave **2** (24 mg, 81%) as yellow oil.

R_f 0.3 (10% EtOAc in pet ether); $[\alpha]_D^{25}$ +18.8 (c 1.0, $CHCl_3$); IR ($CHCl_3$) ν: 2928, 2857, 1732, 1635, 1463, 1371, 1257, 1178, 1072, 961, 835, 775, 523 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.02 (s, 3H), 0.03 (s, 3H), 0.04 (s, 6H), 0.86 (s, 9H), 0.92 (s, 9H), 1.37 (d, J = 6.5 Hz, 3H), 1.74–1.76 (m, 1H), 1.95 (tt, J = 2.2, 13.2 Hz, 1H), 2.04 (ddd, J = 2.1, 6.1, 13.5 Hz, 1H), 2.46 (dt, J =1.5, 13.2 Hz, 1H), 3.08 (s, 3H), 4.12 (t, J = 9.2 Hz, 1H), 4.44 (br dd, J = 9.0, 9.6 Hz, 2H), 5.01 (dq, J = 6.9, 9.6 Hz, 1H), 5.42 (dd, J = 2.3, 15.4 Hz, 1H), 5.82 (ddd, J = 1.5, 9.8, 15.3 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ –5.0 (q), –5.0 (q), –3.8 (q), –3.3 (q), 18.1 (s), 18.3 (s), 18.5 (q), 25.8 (q, 3C), 26.2 (q, 3C), 27.9 (t), 32.6 (t), 39.3 (q), 68.5 (d), 68.5 (d), 76.1 (d), 84.2 (d), 130.2 (d), 132.4 (d), 175.3 (s) ppm; ESI-MS: 545.96 (100%, $[M+Na]^+$); HRMS: 545.2400 ($[M+Na]^+$) calculated, 545.2408 ($[M+Na]^+$) observed.

(1R,2S,7S,10S,E)-7-Hydroxy-2-methyl-3,11-dioxabicyclo[8.1.0]undec-8-en-4-one (**1**):

To a solution of **2** (30 mg, 0.06 mmol) in dry THF (1 mL), 1M solution of TBAF in THF (172 μL, 0.17 mmol) was added at 0 ºC and the contents were stirred at rt for 10 h. To this, was added

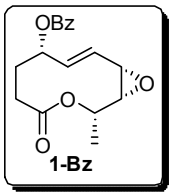


satd. ammonium chloride (3 mL) and the aqueous layer was extracted with EtOAc (3×10 mL). The combined organic layer was dried over sodium sulphate and concentrated. The residue was purified on silica gel column (40% EtOAc in pet ether) to afford **1** (9 mg, 79%) as yellow oil. R_f 0.4 (60% EtOAc in pet ether); $[\alpha]_D^{25}$ +9.1 (*c* 0.2, $CHCl_3$); IR ($CHCl_3$) *v*: = 3336, 2924, 1733, 1602, 1542, 1456, 1270, 1121 cm^{-1}; HRMS: 221.0790 ([M+Na]$^+$) calculated, 221.0748 ([M+Na]$^+$) observed.

Spectral data of major conformer: ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.40 (d, *J* = 6.8 Hz, 3H), 1.89–2.07 (m, 2H,), 2.14–2.26 (m, 1H,), 2.49 (t, *J* = 14.0 Hz, 1H,), 3.03 (dd, *J* = 2.7, 4.1 Hz, 1H), 3.69 (t, *J* = 4.6 Hz, 1H), 4.54 (br s, 1H), 5.33 (dq, *J* = 2.7, 6.8 Hz, 1H), 5.68 (ddd, *J* = 1.1, 3.2, 17.1 Hz, 1H), 5.94 (ddd, *J* =1.1, 4.8, 17.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.3 (q), 27.7 (t), 33.4 (t), 55.9 (d), 57.3 (d), 65.1 (d), 68.1 (d), 126.2 (d), 134.0 (d), 174.6 (s) ppm.

Spectral data of minor conformer: ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.46 (d, *J* = 6.8 Hz, 3H), 1.89–2.07 (m, 2H, merged with major conformer peak), 2.14–2.26 (m, 1H, merged with major conformer peak), 2.44–2.53 (m, 1H, merged with major conformer peak), 2.90 (dd, *J* =1.6, 4.3 Hz, 1H), 3.53 (dt, *J* = 1.4, 4.3 Hz, 1H), 4.20 (dt, *J* =4.7, 8.3 Hz, 1H), 5.27 (dq, *J* = 1.5, 6.8 Hz, 1H), 5.53 (dd, *J* = 1.1, 16.0 Hz, 1H), 5.75 (ddd, *J* = 1.1, 8.7, 15,9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 17.7 (q), 31.7 (t), 32.5 (t), 55.8 (d), 57.6 (d), 66.2 (d), 72.7 (d), 120.6 (d), 135.3 (d), 172.1 (s) ppm.

(1R,2S,7S,10S,E)-2-Methyl-4-oxo-3,11 dioxabicyclo[8.1.0]undec-8-en-7-yl-4-nitrobenzoate (**1-Bz**):



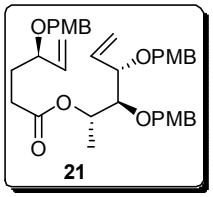
At 0 °C, a solution of *p*-nitro benzoic acid (11 mg, 65 μmol) and DMF (Cat.) in CH_2Cl_2 (1 mL) was added oxalyl chloride (4 μL, 60 μmol) dropwise and the content were stirred at rt for 6 h. The exess of oxalyl chloride was removed under argon atmosphere. The crude product dissolved in dry CH_2Cl_2, cooled to 0 °C and treated with a solution of Et_3N (14 μL, 100 μmol) and alcohol **1** (10 mg, 50 μmol) in CH_2Cl_2 (0.5 mL) and the reaction mixture was stirred at rt for 10 h. To this, was added water (3 mL) and the aqueous layer was extracted with CH_2Cl_2 (3×10 mL). The combined organic layer was dried over sodium sulphate and concentrated. The crude product was purified on silica gel column (20→22% EtOAc in light pet) to afford **1-Bz** (14 mg, 81%) as yellow oil.

R_f 0.5 (40% EtOAc in pet ether); $[\alpha]_D^{25}$ +27.9 (*c* 0.7, $CHCl_3$); IR ($CHCl_3$) *v*: 3418, 2917, 2851, 1732, 1635, 1613, 1528, 1273, 1116, 1039, 718, 625 cm^{-1}; HRMS: 370.0903 ($[M+Na]^+$) calculated, 370.0947 ($[M+Na]^+$) observed.

Spectral data of major conformer: ^1H NMR (400 MHz, $CDCl_3$): δ 1.43 (d, *J* = 6.8 Hz, 3H), 2.21–2.30 (m, 2H), 2.37–2.49 (m, 2H), 3.05 (dd, *J* = 2.5, 4.1 Hz, 1H), 3.69 (tt, *J* = 1.3, 4.6 Hz, 1H), 5.42 (dq, *J* = 2.4, 6.8 Hz, 1H), 5.67 (br s, 1H), 5.74 (dd, *J* = 1.3, 17.2 Hz, 1H), 5.86 (dd, *J* = 4.6, 17.1 Hz, 1H). 8.24 (d, *J* = 8.9 Hz, 2H), 8.30 (d, *J* = 8.9 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.4 (q), 28.9 (t), 31.5 (t), 55.5 (d), 57.5 (d), 65.3 (d), 75.9 (d), 123.0 (d, 2C), 127.5 (d), 128.9 (d), 130.8 (d, 2C), 130.8 (s), 135.3 (s), 163.8 (s), 173.8 (s) ppm.

Spectral data of minor conformer: ^1H NMR (400 MHz, $CDCl_3$): δ 1.49 (d, *J* = 6.8 Hz, 3H), 2.11–2.20 (m, 2H), 2.30–2.36 (m, 1H), 2.52–2.58 (m, 1H), 2.94 (dd, *J* =1.4, 4.3 Hz, 1H), 3.58 (br d, *J* = 4.2 Hz, 1H), 5.34 (dq, *J* = 1.3, 6.8 Hz, 1H), 5.48 (dt, *J* = 4.2, 8.2 Hz, 1H), 5.74 (dd, *J* = 1.1, 17.1 Hz, 1H), 5.90 (dd, *J* = 4.1, 17.0 Hz, 1H), 8.20 (d, *J* = 8.8 Hz, 2H), 8.28 (d, *J* = 8.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 17.1 (q), 30.2 (t), 31.4 (t), 55.7 (d), 57.7 (d), 62.2 (d), 75.7 (d), 122.7 (d), 123.6 (d, 2C), 130.7 (d, 2C), 130.8 (d), 130.8 (s), 135.5 (s), 163.3 (s), 171.9 (s) ppm.

(R)-((2S,3S,4S)-3,4-Bis(4-methoxybenzyloxy)hex-5-en-2-yl) 4-(4-methoxybenzyloxy)hex-5-enoate (21):

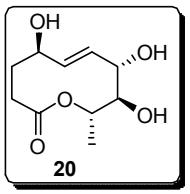


21

To a solution of acid (*R*)-**7** (1.0 g, 4.0 mmol) in THF (15 mL) 2,4,6-trichlorobenzoyl chloride (0.7 mL, 4.79 mmol) and *N*,*N*-diisopropyl ethyl amine (4 mL, 22.9 mmol) were added dropwise and stirred at room temp for 2 h. Subsequently, a solution of alcohol **6** (1.5 g, 4.0 mmol) and DMAP (0.976 g, 8.0 mmol) in dry THF (5 mL) was added dropwise. The reaction mixture was then stirred at rt for 16 h. The reaction mixture was quenched with water and extracted with EtOAc (3×30 mL). The combined organic phase was washed with saturated $NaHCO_3$ solution (10 mL), water (20 mL), dried (Na_2SO_4) and evaporated under reduced pressure. The crude product was purified by silica gel column chromatography (9→10 % EtOAc in pet ether) to afford **21** (1.89 g, 78%) as yellow oil. R_f 0.5 (20% EtOAc in pet ether); $[\alpha]_D^{25}$ +3.8 (*c* 1.0, $CHCl_3$); IR (neat) *v*: 3445, 2934, 1731, 1613, 1464, 1302, 1248, 1173, 931, 821, 770 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.20 (d, *J* = 6.4 Hz, 3H), 1.75–1.97 (m, 2H), 2.11–2.43 (m, 2H), 3.56 (dd, *J* = 3.7, 6.2 Hz, 1H), 3.68–3.75 (m, 1H), 3.78 (s, 3H), 3.79 (s, 6H), 3.82–3.92 (m, 1H), 4.24 (d, *J* = 11.3 Hz, 1H), 4.28 (d, *J* = 11.4

Hz, 1H), 4.51 (d, *J* = 11.4 Hz, 1H), 4.53 (d, *J* = 11.3 Hz, 1H), 4.61 (d, *J* = 11.3 Hz, 1H), 4.67 (d, *J* = 11.2 Hz, 1H), 4.99 (dq, *J* = 3.8, 6.4 Hz, 1H), 5.17–5.34 (m, 4H), 5.69 (ddd, *J* = 7.6, 11.0, 16.4 Hz, 1H), 5.83 (ddd, *J* = 8.1, 10.6, 16.9 Hz, 1H), 6.82–6.86 (m, 6H), 7.21–7.29 (m, 6H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.7 (q), 30.3 (t), 30.5 (t), 55.2 (q, 3C), 69.8 (t), 70.1 (t), 71.0 (d), 74.6 (t), 79.1 (d), 81.5 (d), 82.6 (d), 113.6 (d, 2C), 113.6 (d, 2C), 113.7 (d, 2C), 117.6 (t), 119.1 (t), 129.3 (d, 2C), 129.4 (d, 2C), 129.6 (d, 2C), 130.3 (s), 130.5 (s), 130.7 (s), 135.2 (d), 138.3 (d), 159.0 (s), 159.0 (s), 159.1 (s), 172.5 (s) ppm; ESI-MS: 627.68 (100%, $[M+Na]^+$); HRMS: 627.2934 ($[M+Na]^+$) calculated, 627.2948 ($[M+Na]^+$) observed.

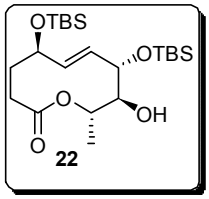
(5R,8S,9R,10S,E)-5,8,9-Trihydroxy-10-methyl-3,4,5,8,9,10-hexahydro-2H-oxecin-2-one (20):



A degassed solution of diene **21** (100 mg, 0.16 mmol) and Grubbs' 2nd gen. catalyst (27 mg, 0.03 mmol) in dichloromethane (30 mL) was heated under reflux under argon for 96 h and concentrated. The residue was purified by column chromatography (12–15% EtOAc in pet ether) giving impure macrolide. The above macrolide was suspended at 0 °C in TFA (2 mL) and stirred for 2 h. The reaction mixture was concentrated under reduced pressure and the residue was purified by column chromatography (70→100% EtOAc in pet ether) to obtain **20** (10 mg, 28%) as yellow viscous liquid.

R_f 0.2 (85% EtOAc in pet ether); $[\alpha]_D^{25}$ −20.9 (*c* 0.5, MeOH); IR (MeOH) *v*: 3367, 2945, 2833, 1657, 1449, 1114, 1027 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.27 (d, *J* = 6.4 Hz, 3H), 1.75–1.85 (m, 1H), 1.91–1.98 (m, 1H), 2.05 (dt, *J* = 1.8, 13.6 Hz, 1H), 2.29 (ddd, *J* = 2.4, 6.3, 13.8 Hz, 1H), 3.21(t, *J* = 9.1 Hz, 1H), 3.67 (t, *J* = 9.1 Hz, 1H), 4.02 (ddd, *J* = 4.9, 9.9, 14.2 Hz, 1H), 4.84 (dq, *J* = 6.4, 9.7 Hz, 1H), 5.33 (dd, *J* = 9.1, 15.6 Hz, 1H), 5.63 (dd, *J* = 9.6, 15.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.4 (q), 32.3 (t), 33.8 (t), 71.4 (d), 75.3 (d), 77.5 (d), 77.8 (d), 133.5 (d), 133.9 (d), 176.0 (s) ppm; HRMS: 239.0895 ($[M+Na]^+$) calculated, 239.0871 ($[M+Na]^+$) observed.

(5R,8S,9S,10S,E)-5,8-Bis(tert-butyldimethylsilyloxy)-9-hydroxy-10-methyl-3,4,5,8,9,10-hexahydro-2H-oxecin-2-one (**22**):

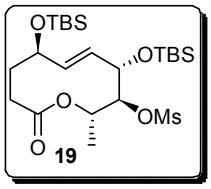


A solution of triol **20** (25 mg, 0.12 mmol) in anhydrous CH_2Cl_2-DMF (0.5 mL, each) was cooled to 0 °C, imidazole (40 mg, 0.58 mmol) and DMAP (3 mg,

0.02 mmol) followed by TBS-Cl (70 mg, 0.46 mmol) were added and stirring was continued at rt for 16 h. The excess of TBS-Cl was quenched with water (5 mL) and the reaction mixture was extracted with CH_2Cl_2 (3×10 mL). The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by column chromatography (4→5% EtOAc in pet ether) to afford **22** (40 mg, 77%) as yellow oil.

R_f 0.6 (10% EtOAc in pet ether); $[\alpha]_D^{25}$ –12.4 (*c* = 0.5 in $CHCl_3$); IR ($CHCl_3$) *v*: 2956, 2858, 1738, 1471, 1251, 1053, 836, 666, 559 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 0.02 (s, 3H), 0.03 (s, 3H), 0.05 (s, 3H), 0.08 (s, 3H), 0.85 (s, 9H), 0.87 (s, 9H), 1.30 (d, *J* = 6.4 Hz, 3H), 1.81–1.87 (m, 1H), 1.90–2.03 (m, 2H), 2.21–2.32 (m, 1H), 2.82 (s, 1H), 3.28 (dd, *J* = 8.6, 9.4 Hz, 1H), 3.78 (t, *J* = 8.6 Hz, 1H), 3.99 (dt, *J* = 5.4,9.1 *Hz,* 1H), 4.95 (dq, *J* = 6.4, 9.5 Hz, 1H), 5.41 (dd, *J* = 8.3, 15.7 Hz, 1H), 5.48 (dd, *J* = 8.6, 15.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ –4.8 (q), –4.8 (q), –4.6 (q), –3.6 (q), 18.0 (s), 18.1 (s), 18.1 (q), 25.7 (q, 3C), 25.8 (q, 3C), 31.4 (t), 34.00 (t), 69.5 (d), 75.1 (d), 76.4 (d), 78.3(d), 131.1 (d), 134.8 (d), 173.8 (s) ppm; ESI-MS: 467.34 (100%, $[M+Na]^+$); HRMS: 467.2625 ($[M+Na]^+$) calculated, 467.2603 ($[M+Na]^+$) observed.

(2S,3S,4S,7R,E)-4,7-Bis(tert-butyldimethylsilyloxy)-2-methyl-10-oxo-3,4,7,8,9,10 hexahydro-2H-oxecin-3-yl methanesulfonate (**19**):

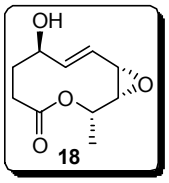


To a solution of alcohol **22** (20 mg, 0.05 mmol), in dichloromethane (1 mL) was added triethylamine (15 μL, 0.11 mmol) and DMAP (Cat.). The content was cooled to 0 °C and treated with methanesulfonyl chloride (8 μL, 0.10 mmol).The reaction mixture was warmed to rt and stirred for 6 h. The reaction was portioned between water and CH_2Cl_2 and the aqueous layer was extracted with CH_2Cl_2 (3×10 mL). Combined organic layer was dried over sodium sulphate and concentrated. Purification of the resulting crude by column chromatography (7→8% EtOAc in pet ether) afforded **19** (20 mg, 85%) as yellow oil.

R_f 0.3 (10% EtOAc in pet ether); $[\alpha]_D^{25}$ –7.6 (*c* 1.4, $CHCl_3$); IR ($CHCl_3$) *v*: 3020, 2401, 1733, 1603, 1427, 1216, 1109, 929, 770, 669 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 0.02 (s, 3H), 0.04 (s, 3H), 0.06 (s, 3H), 0.07 (s, 3H), 0.85 (s, 9H), 0.87 (s, 9H), 1.36 (d, *J* = 6.6 Hz, 3H), 1.82–1.91 (m, 2H), 1.98 (dt, *J* = 2.6, 12.7 Hz, 1H), 2.26–2.36 (m, 1H), 3.07 (s, 3H), 4.01 (ddd, *J* = 5.5, 8.2, 9.5 Hz, 1H), 4.07 (dd, *J* = 8.1, 8.7 Hz, 1H), 4.39 (dd, *J* = 8.7, 9.8 Hz, 1H), 4.98 (dq, *J* = 6.6, 9.8 Hz, 1H), 5.37 (dd, *J* = 8.1, 15.9 Hz, 1H), 5.45 (dd, *J* = 8.8, 15.9 Hz, 1H); ^{13}C NMR (100 MHz,

$CDCl_3$): δ –4.7 (q), –4.7 (q), –3.9 (q), –3.2 (q), 18.0 (s), 18.2 (s), 18.4 (q), 25.6 (q, 3C), 26.1 (q, 3C), 31.2 (t), 33.5 (t), 39.3 (q), 68.5 (d), 75.1 (d), 75.8 (d), 84.1 (d), 130.6 (d), 134.2 (d), 173.8 (s) ppm; ESI-MS: 545.33 (100%, $[M+Na]^+$); HRMS: 545.2400 ($[M+Na]^+$) calculated, 545.2408 ($[M+Na]^+$) observed.

(1R,2S,7R,10S,8E)-7-Hydroxy-2-methyl-3,11-dioxabicyclo[8.1.0]undec-8-en-4-one (**18**):

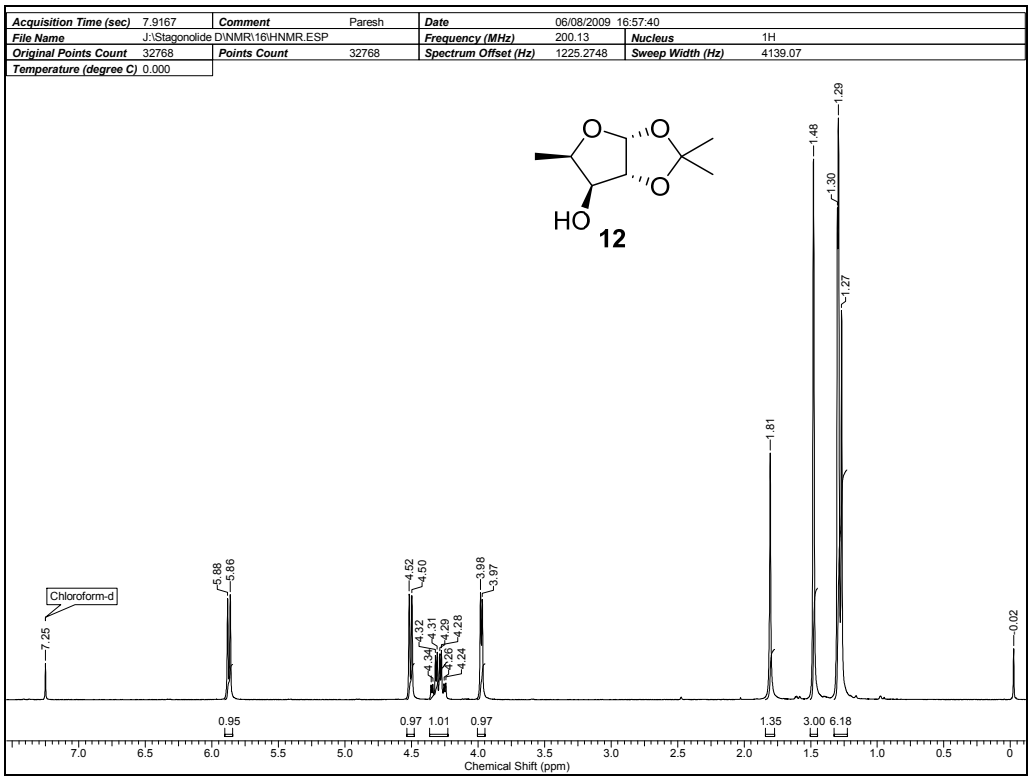


At 0 ºC, a solution of **19** (20 mg, 0.04 mmol) in dry THF (1 mL), was treated with 1M solution of TBAF in THF (114 μL, 0.12 mmol) and the contents were stirred at rt for 10 h. To this, was added satd. ammonium chloride (3 mL) and the aqueous layer was extracted with EtOAc (3×10 mL). The combined organic layer was dried over sodium sulphate and concentrated. The residue was purified on silica gel column (40→45% EtOAc in light pet) to afford **18** (6 mg, 76%) as a white crystalline solid. R_f 0.4 (60% EtOAc in pet ether); MP: 79 °C; $[\alpha]_D^{25}$ +75.2 (*c* 0.2, MeOH); IR ($CHCl_3$) *v*: 3435, 2925, 2851, 1731, 1635, 1456, 1384, 1089, 728 cm^{-1}; HRMS: 199.0970 $[M+H]^+$; calculated, 199.0961 ($[M+H]^+$) observed.

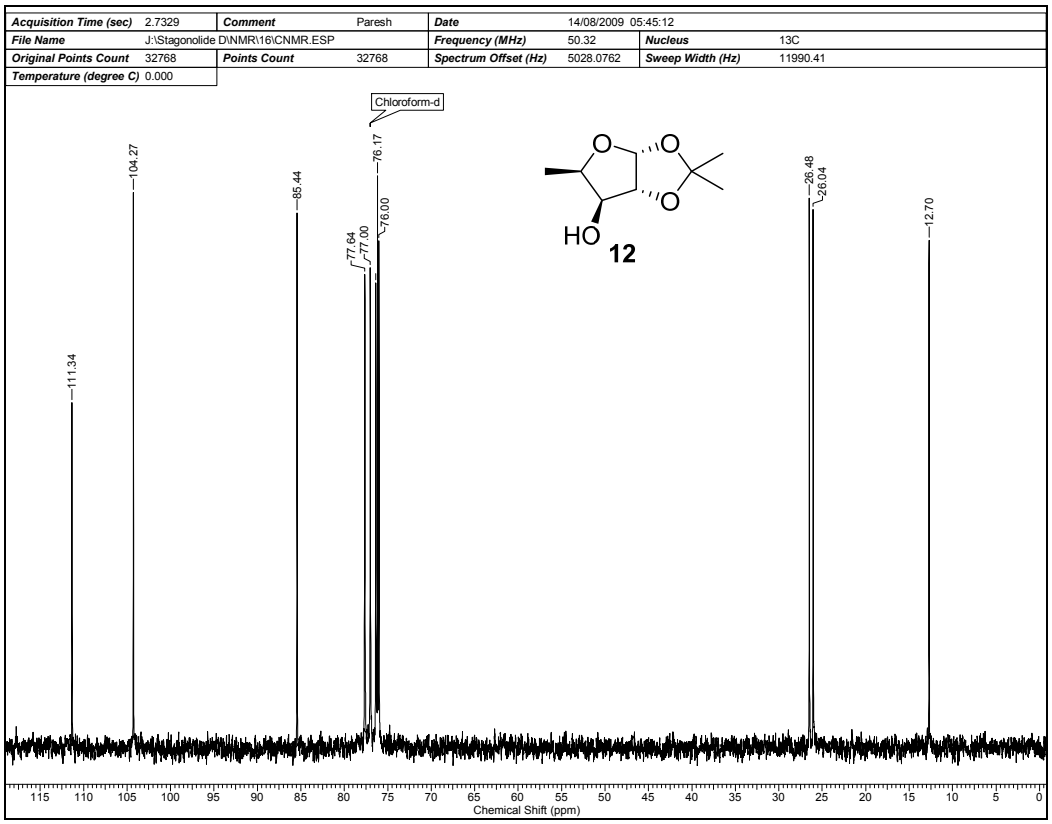
Spectral data of major conformer. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.38 (d, *J* = 6.8 Hz, 3H), 1.98–2.14 (m, 3H), 2.28 (ddd, *J* = 1.9, 8.3, 14.2 Hz, 1H), 3.05 (dd, *J* =2.6, 4.1 Hz, 1H), 3.65 (br t, *J* = 4.6 Hz, 1H), 4.13 (ddd, *J* = 4.4, 8.3, 10.5 Hz, 1H), 5.35 (dq, *J* = 2.7, 6.8 Hz, 1H), 5.52 (ddd, *J* = 0.9, 8.3, 17.0 Hz, 1H), 5.65 (dd, *J* = 4.9, 17.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.2 (q), 31.2 (t), 35.0 (t), 55.4 (d), 58.2 (d), 65.7 (d), 75.1 (d), 128.2 (d), 134.1 (d), 173.5 (s) ppm.

Spectral data of minor conformer. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.45 (d, *J* = 6.8 Hz, 3H), 1.84–1.90 (m, 1H), 2.16–2.19 (m, 1H), 2.22 (dd, *J* = 3.9, 5.2 Hz, 1H), 2.54 (ddd, *J* = 3.8, 12.6, 16.0 Hz, 1H), 2.91 (dd, *J* =1.7, 4.3 Hz, 1H), 3.58 (ddd, *J* = 1.8, 3.2, 4.6 Hz, 1H), 4.58 (br s, 1H), 5.29 (dq, *J* = 1.5, 6.7 Hz, 1H), 5.72 (td, *J* = 1.7, 16.0 Hz, 1H), 5.91 (ddd, *J* = 1.2, 3.2, 16.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 17.7 (q), 28.7 (t), 29.7 (t), 56.3 (d), 57.7 (d), 66.1 (d), 68.1 (d), 118.2 (d), 134.7 (d), 172.7 (s) ppm.

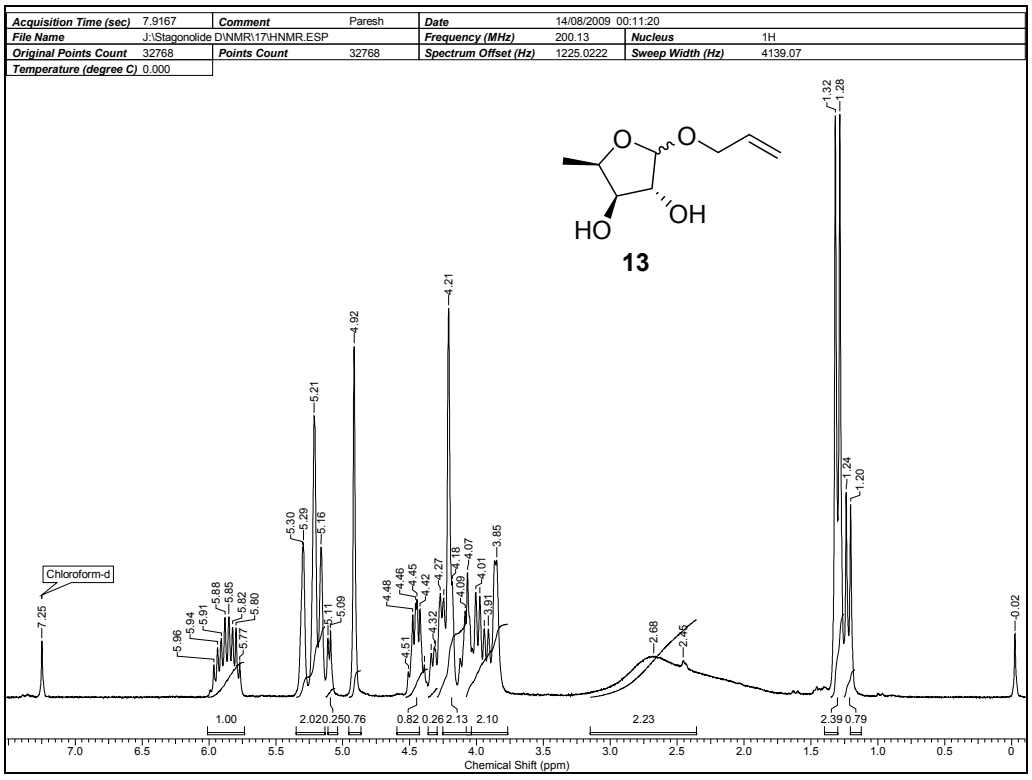
SPECTRA



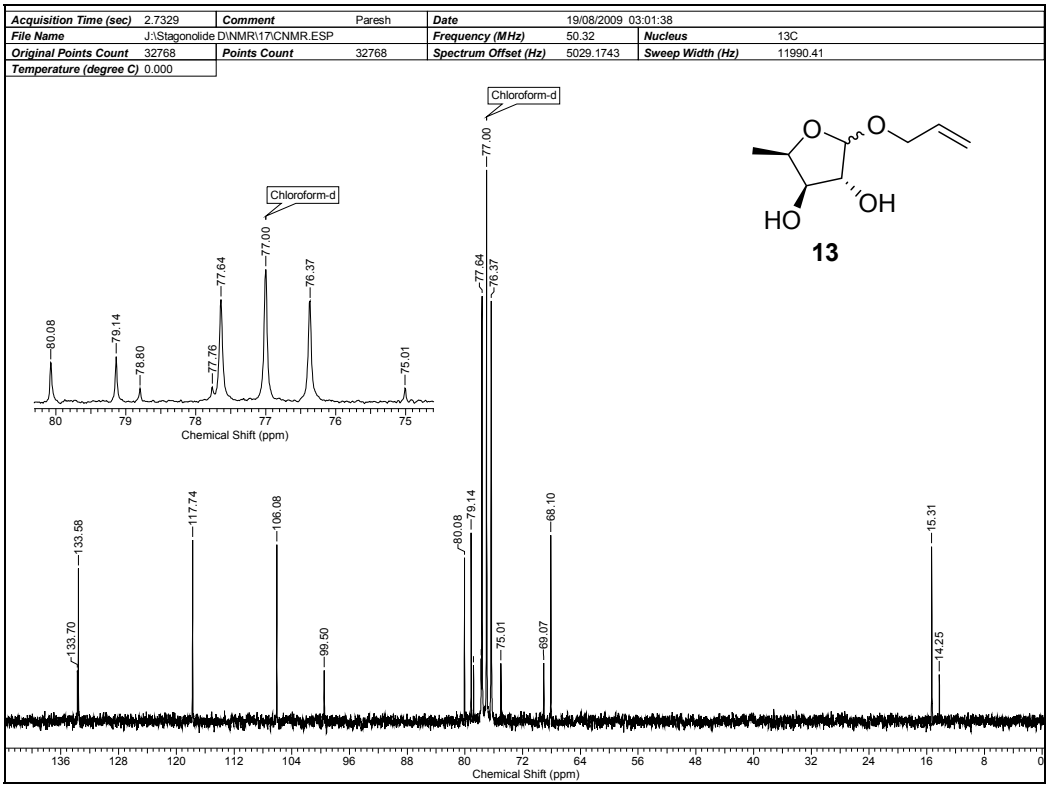
^{1}H NMR Spectrum of 12 in $CDCl_3$



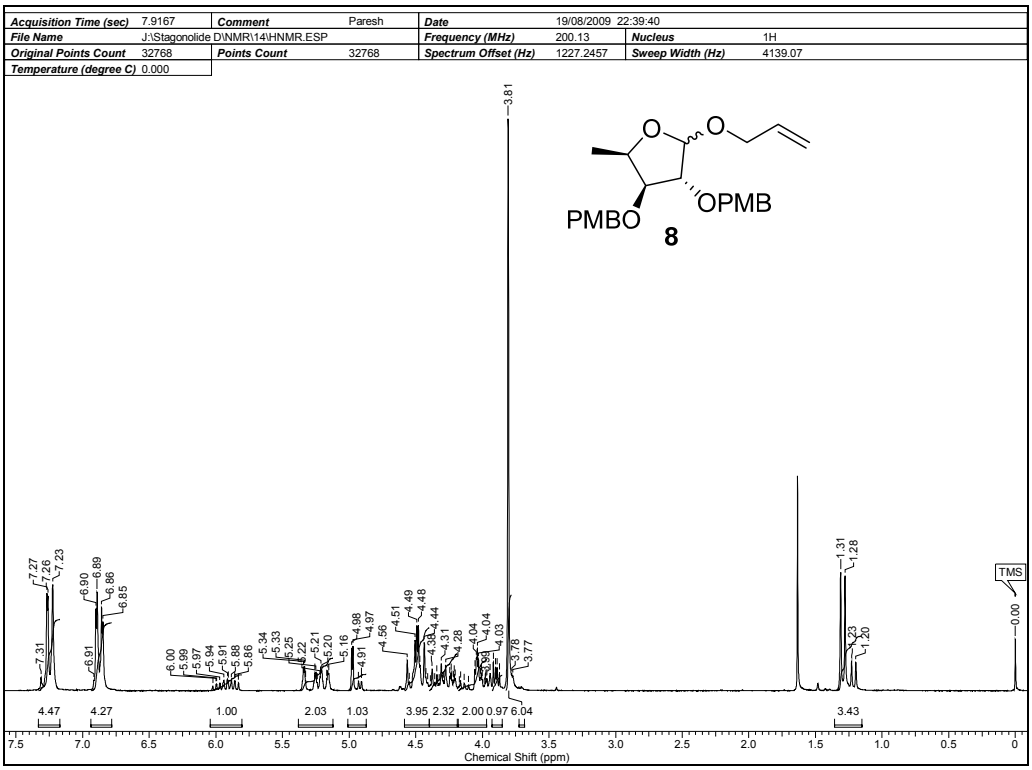
^{13}C NMR Spectrum of 12 in $CDCl_3$



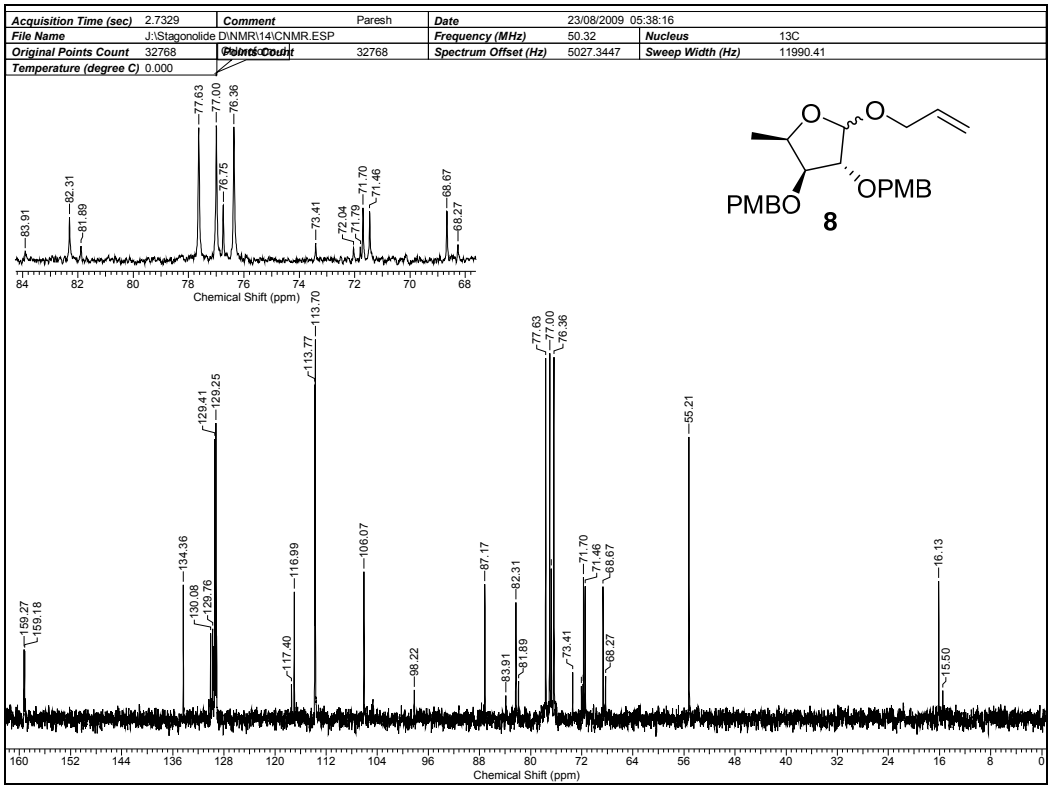
^{1}H NMR Spectrum of 13 in $CDCl_3$



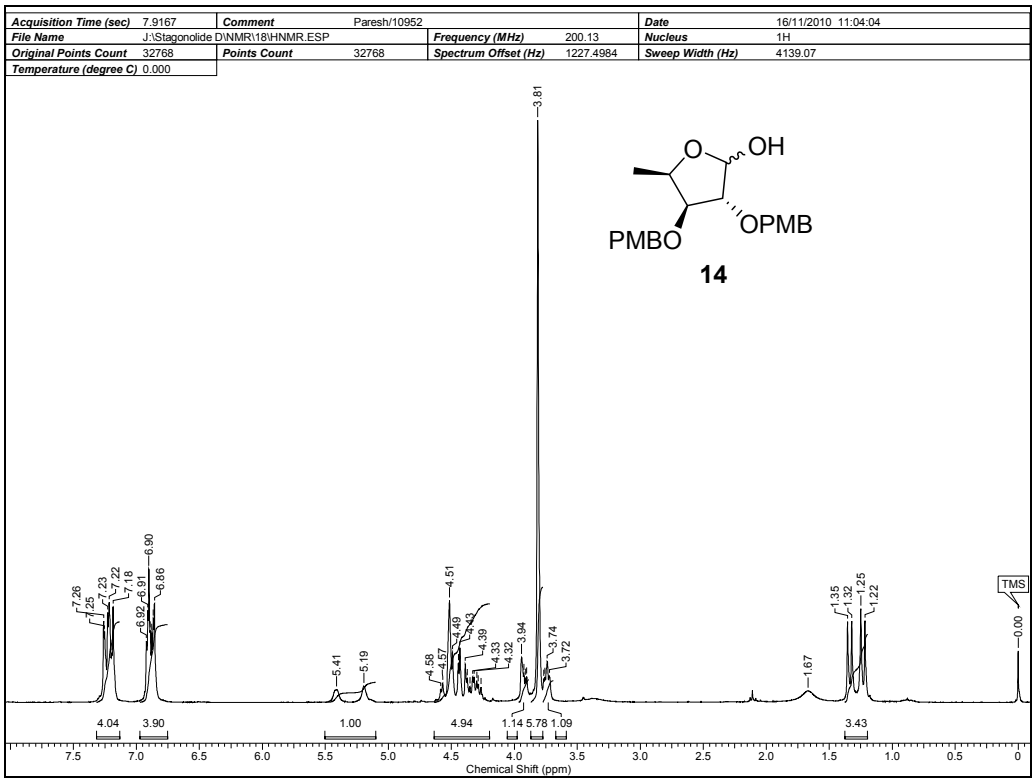
^{13}C NMR Spectrum of 13 in $CDCl_3$



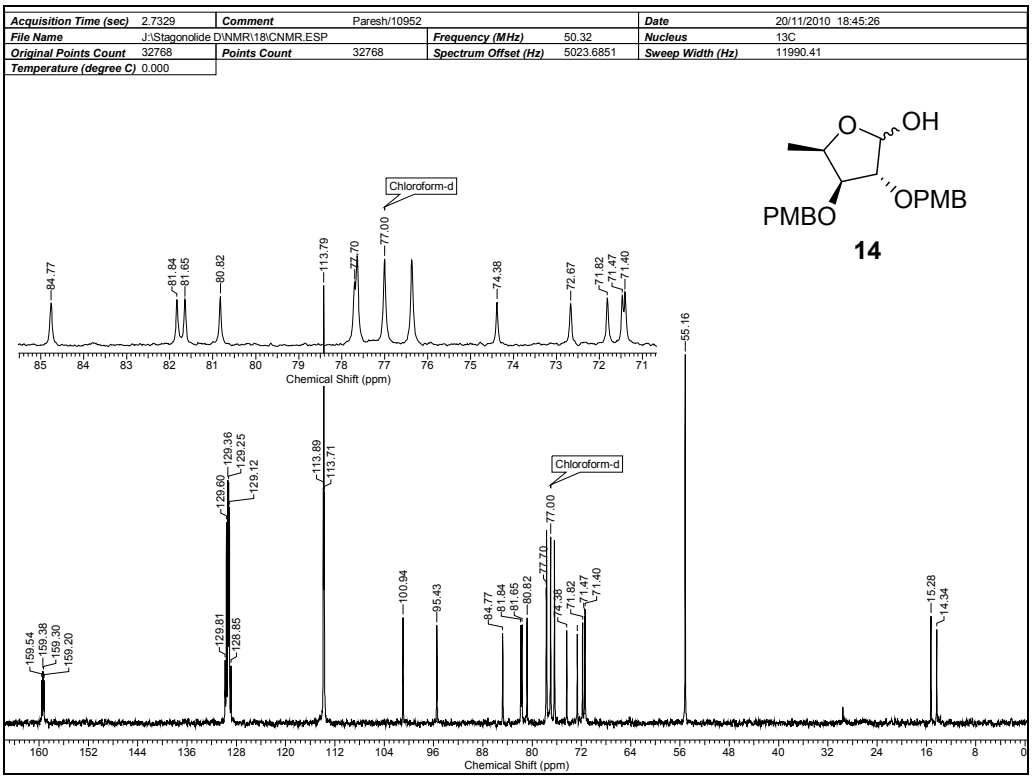
^{1}H NMR Spectrum of 8 in $CDCl_3$



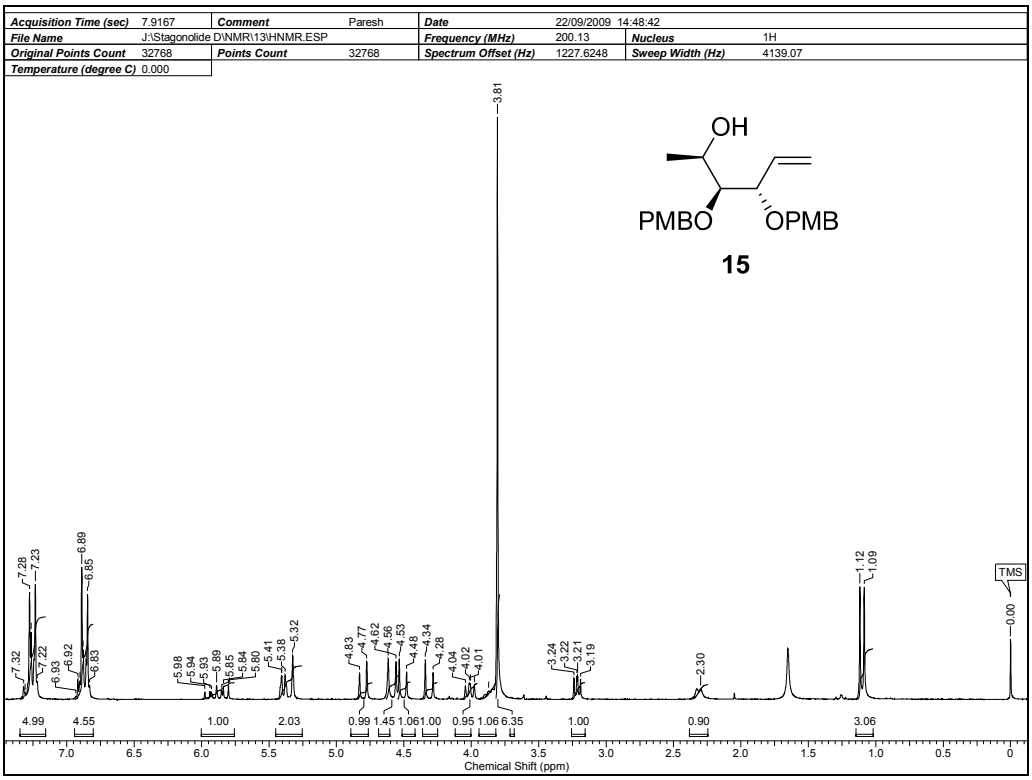
^{13}C NMR Spectrum of 8 in $CDCl_3$



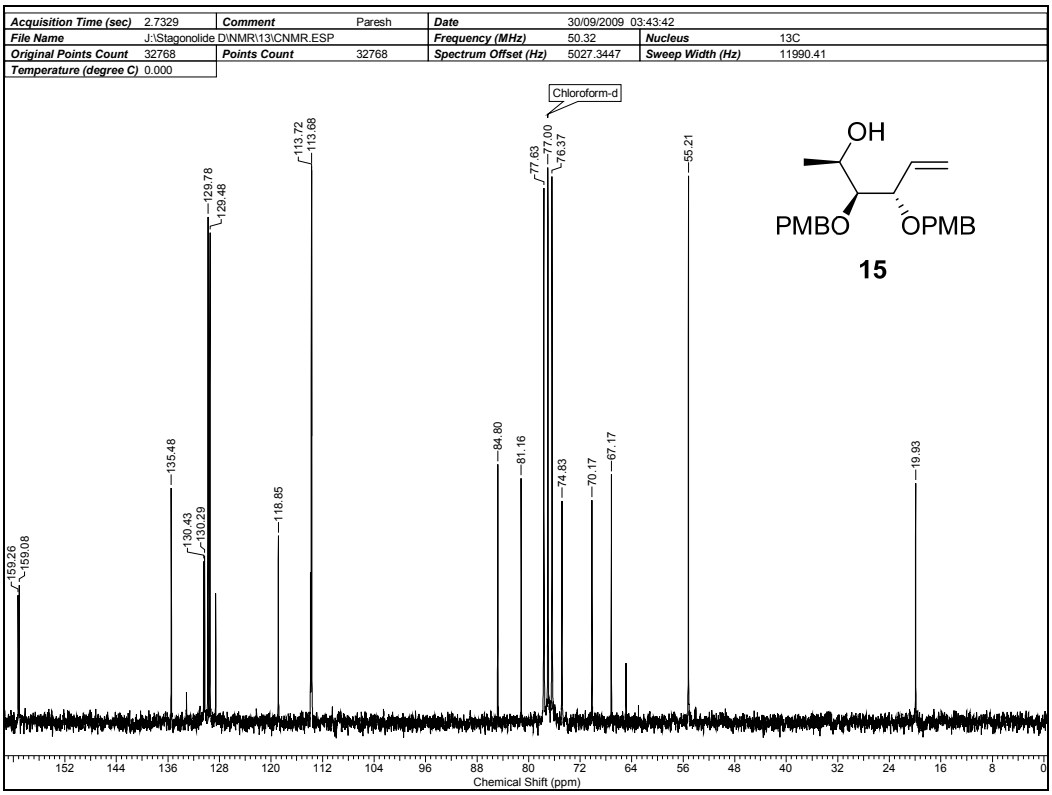
^{1}H NMR Spectrum of 14 in $CDCl_3$



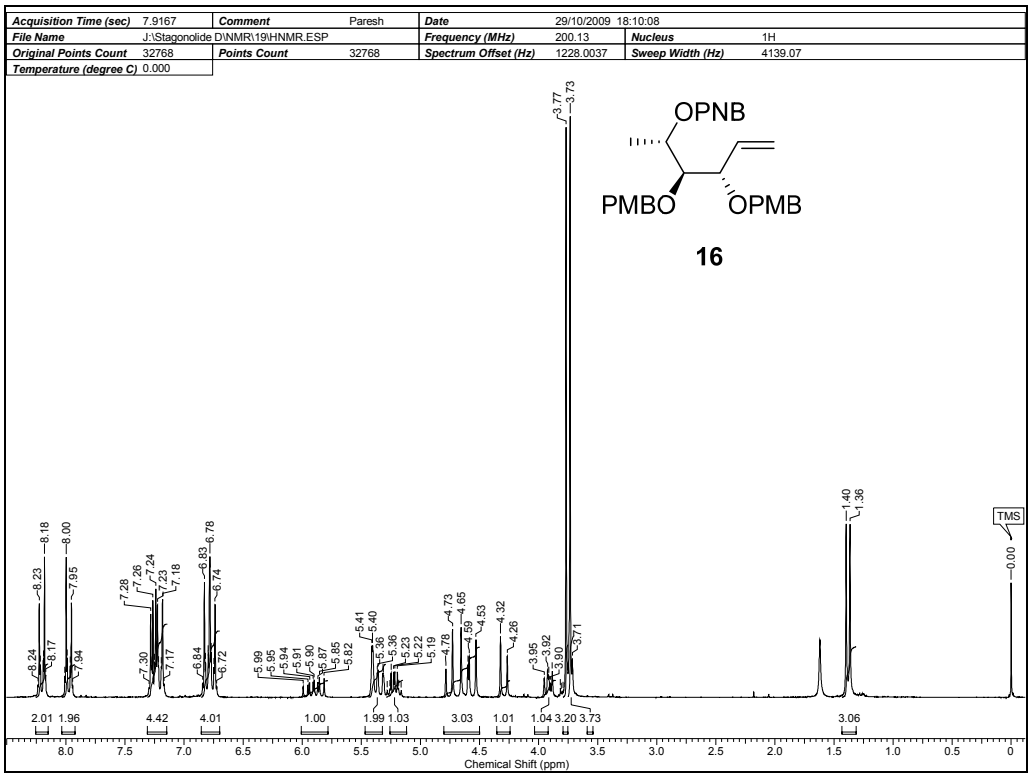
^{13}C NMR Spectrum of 14 in $CDCl_3$



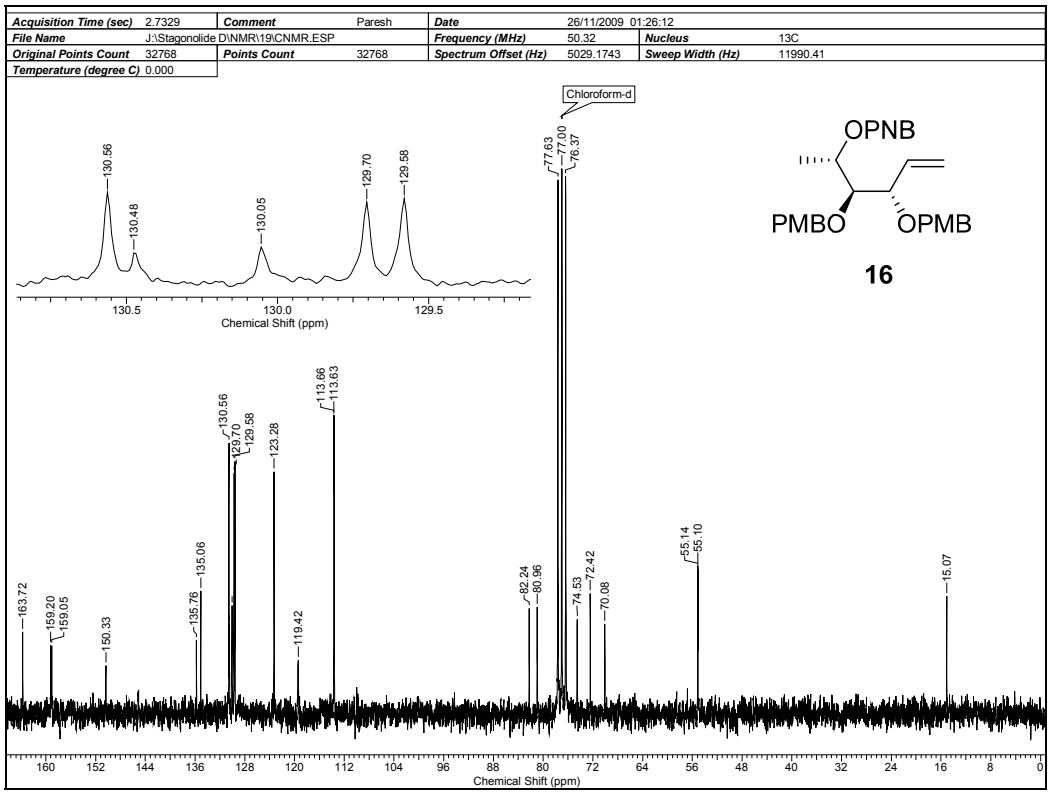
^{1}H NMR Spectrum of 15 in $CDCl_3$



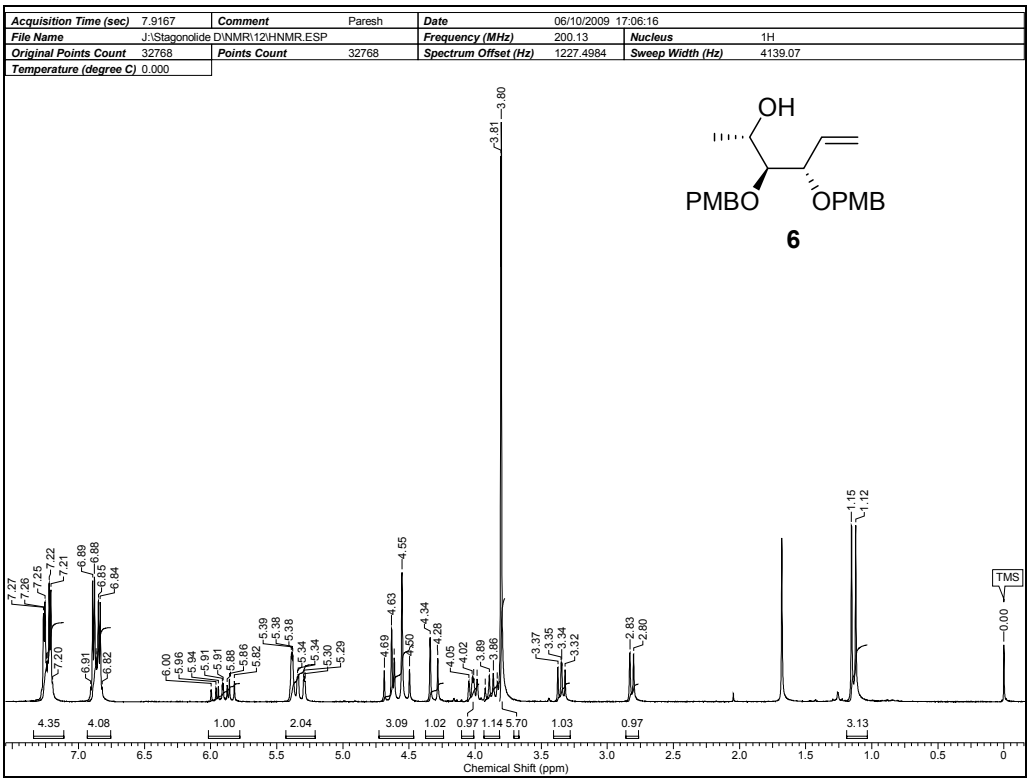
^{13}C NMR Spectrum of 15 in $CDCl_3$



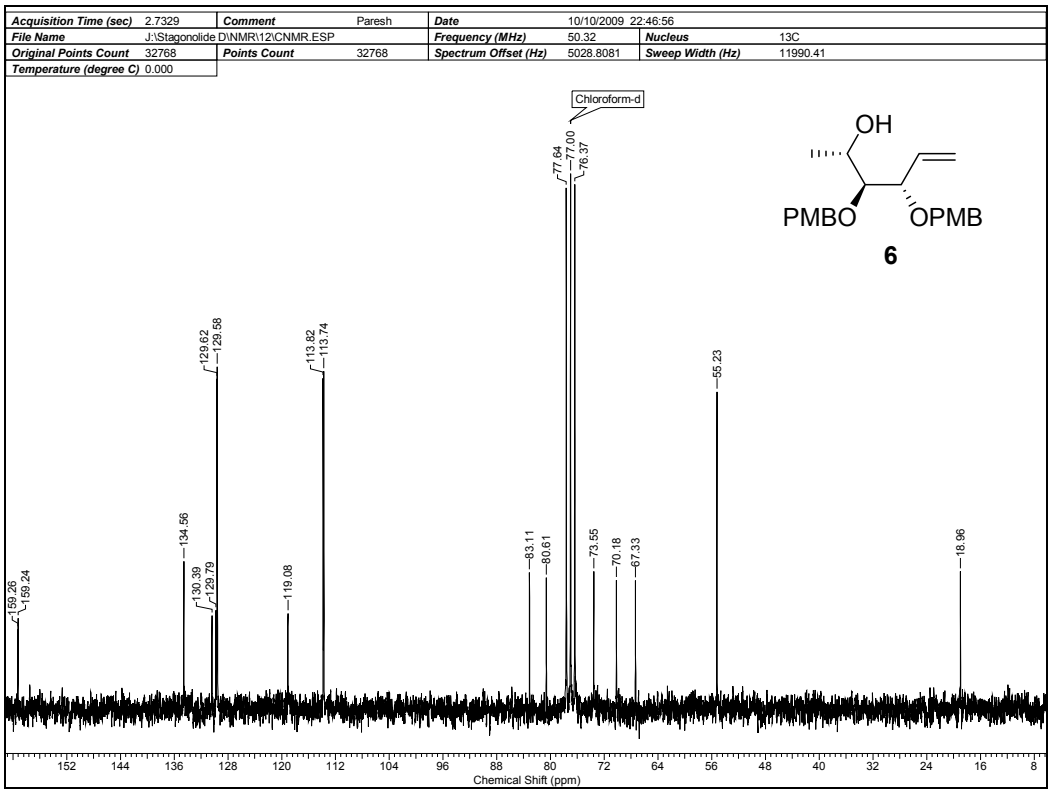
^{1}H NMR Spectrum of 16 in $CDCl_3$



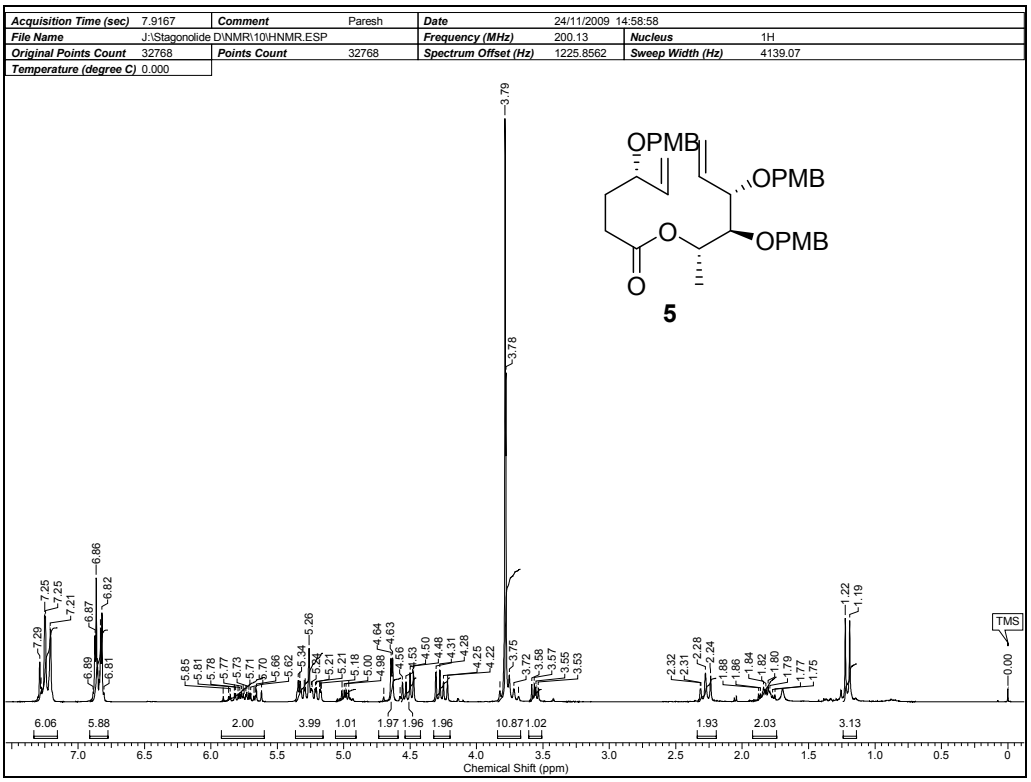
^{13}C NMR Spectrum of 16 in $CDCl_3$



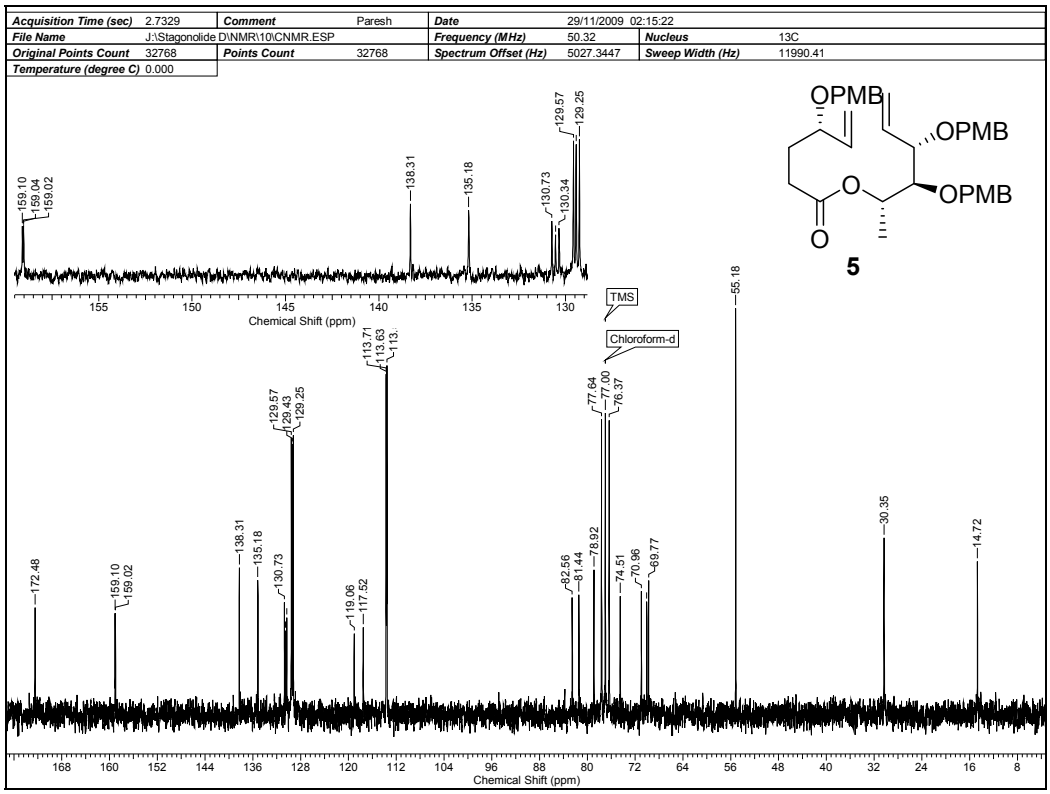
^{1}H NMR Spectrum of 6 in $CDCl_3$



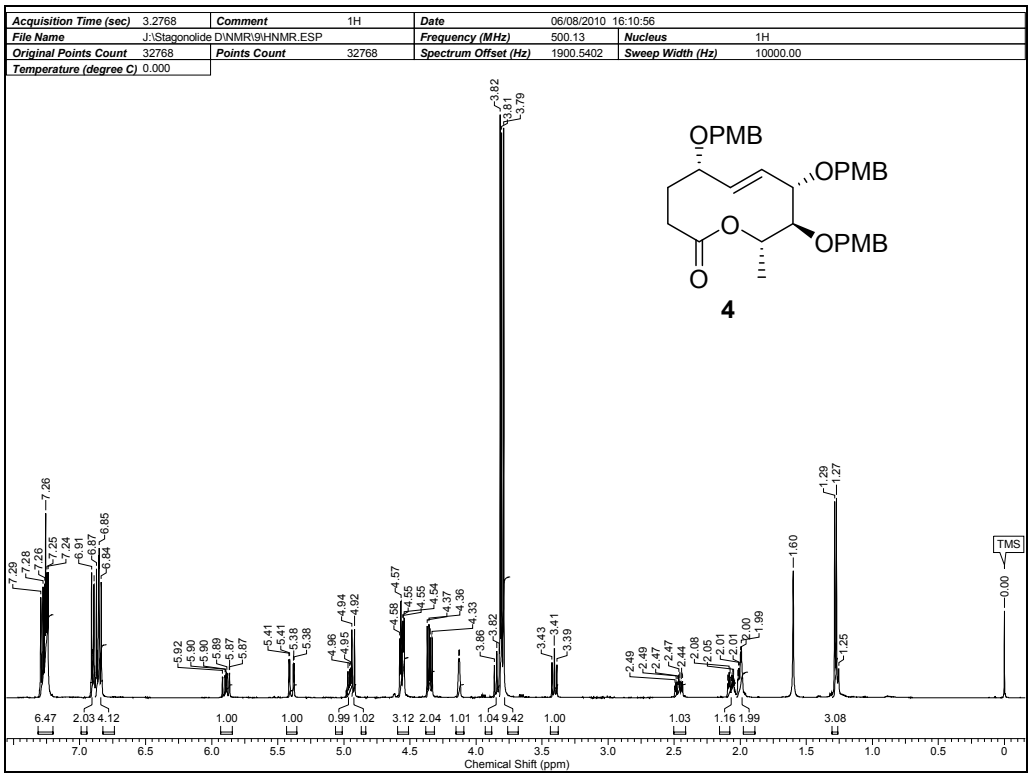
^{13}C NMR Spectrum of 6 in $CDCl_3$



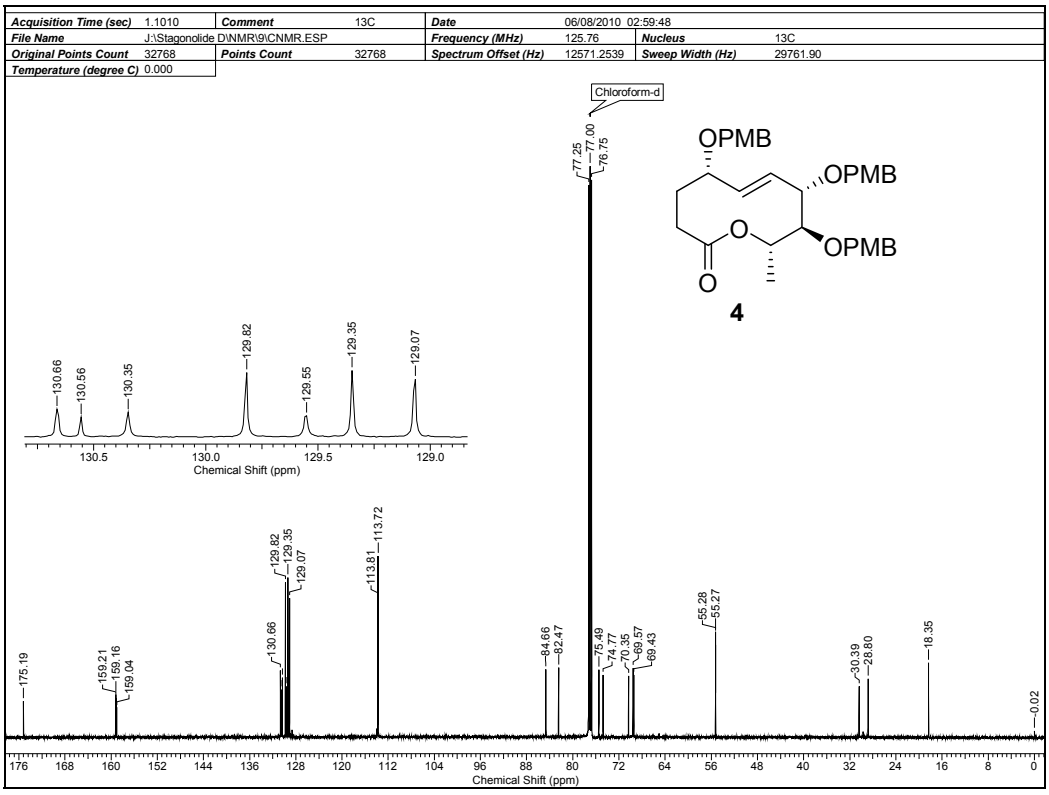
^{1}H NMR Spectrum of 5 in $CDCl_3$



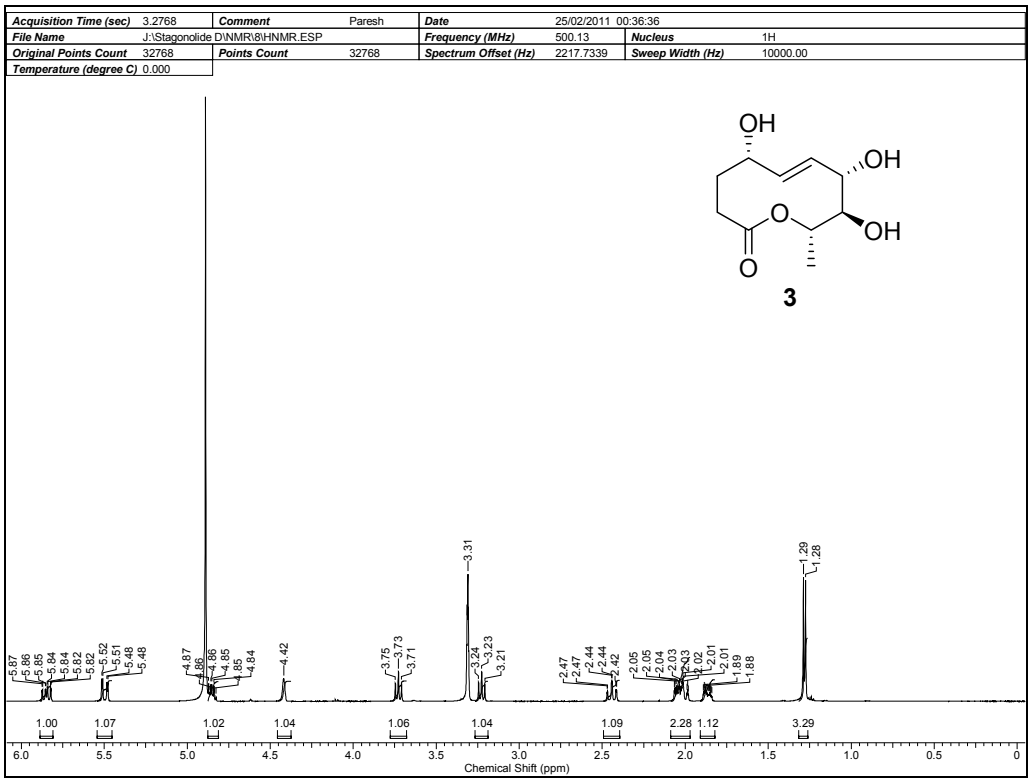
^{13}C NMR Spectrum of 5 in $CDCl_3$



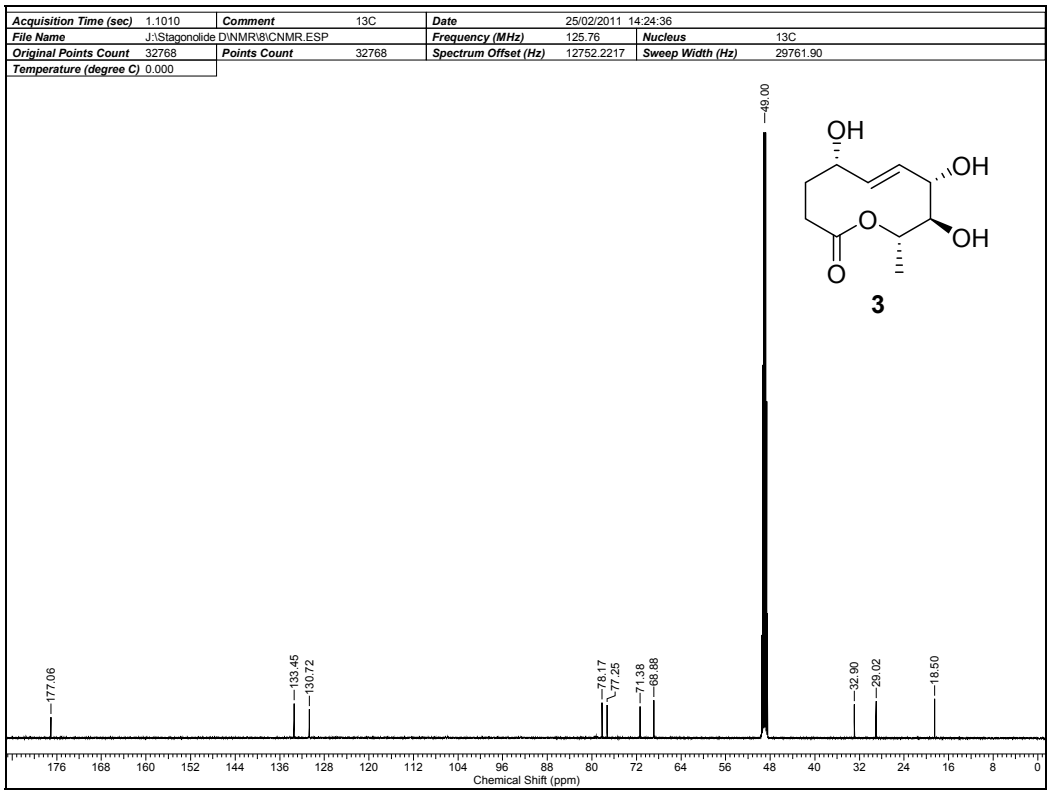
^{1}H NMR Spectrum of 4 in $CDCl_3$



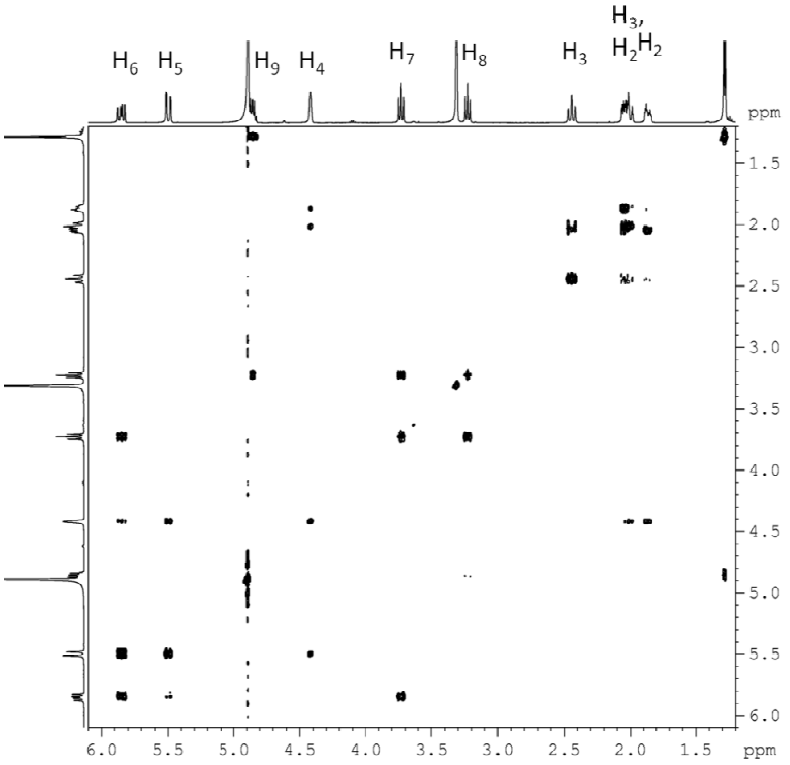
^{13}C NMR Spectrum of 4 in $CDCl_3$



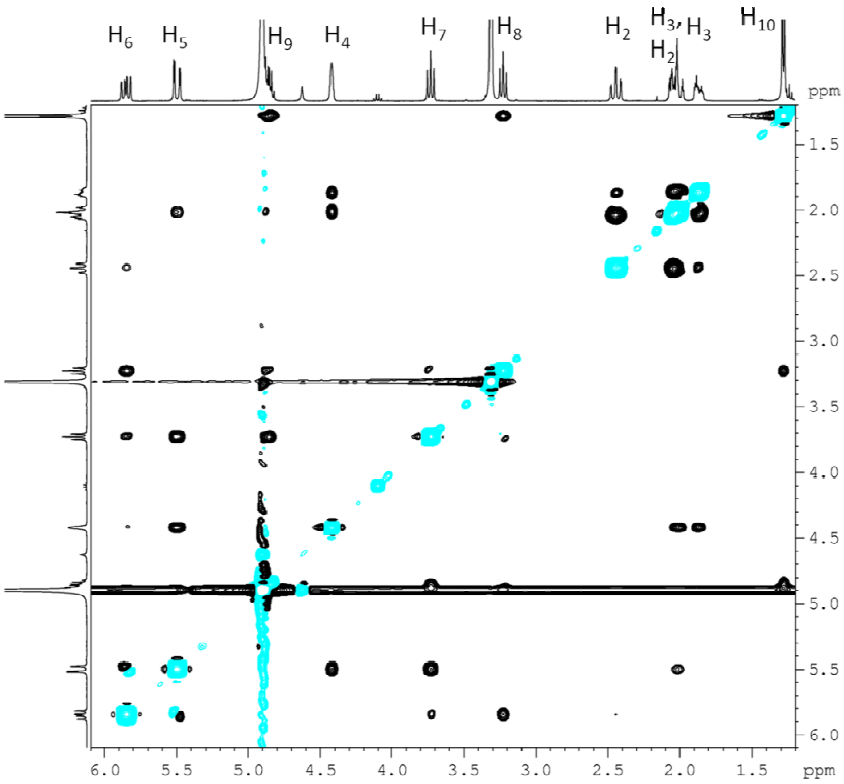
^{1}H NMR Spectrum of 3 in CD_3OD



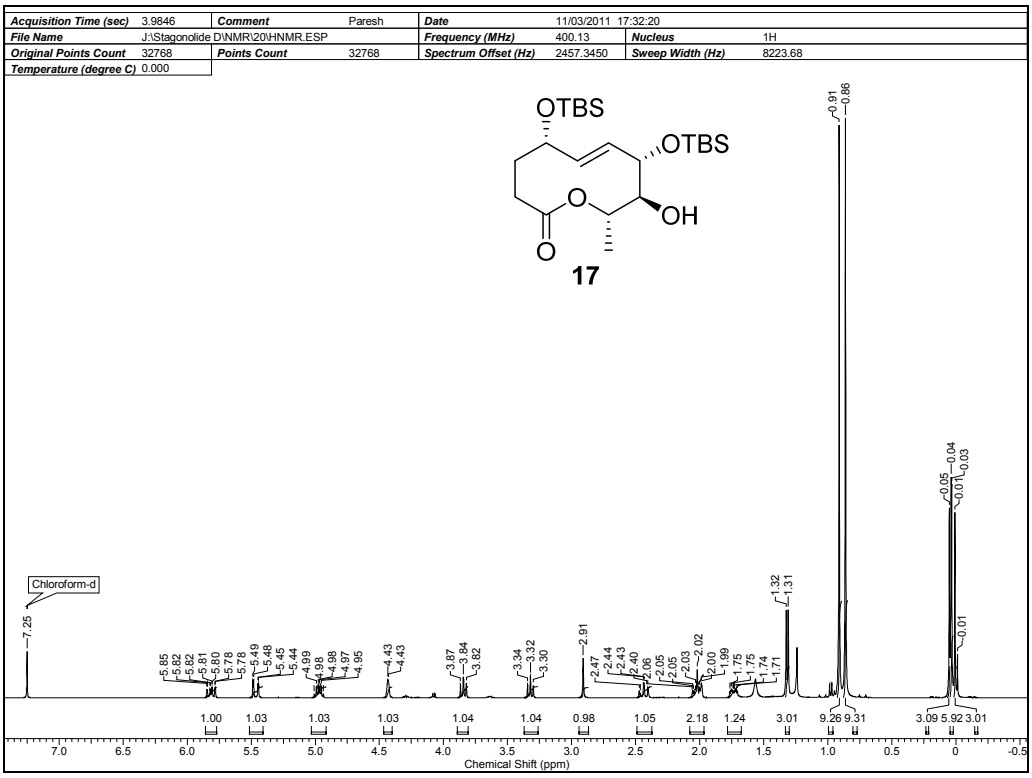
^{13}C NMR Spectrum of 3 in CD_3OD



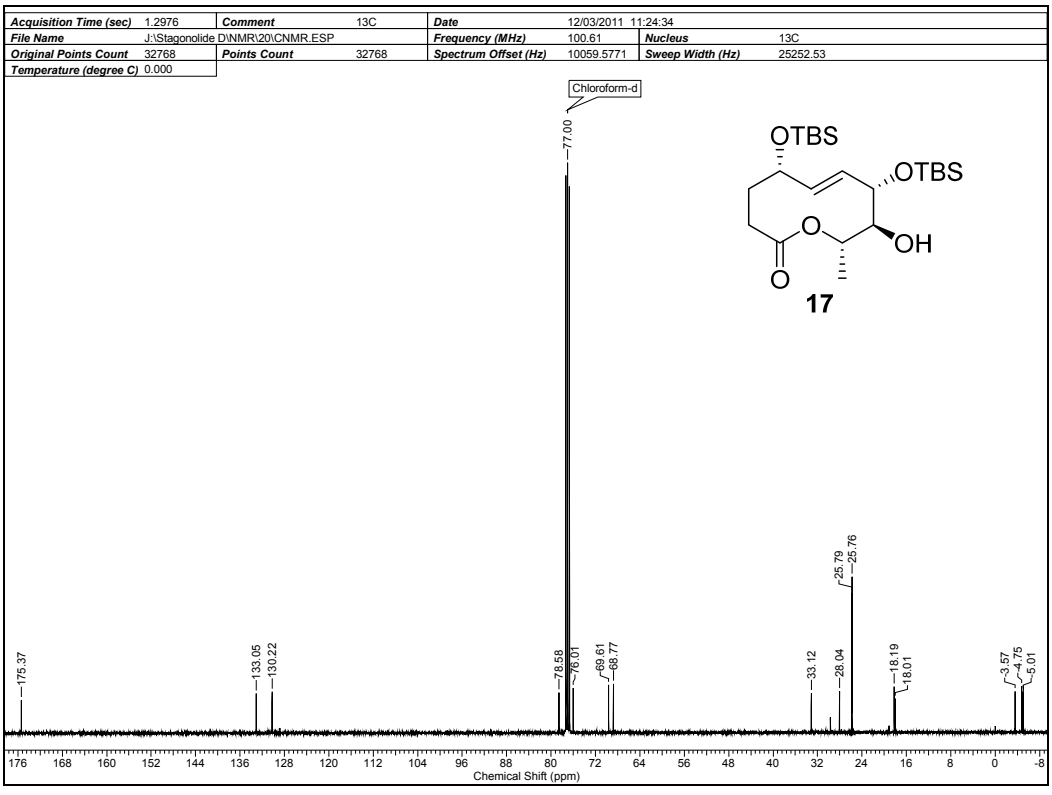
COSY Spectrum of 3 in CD_3OD



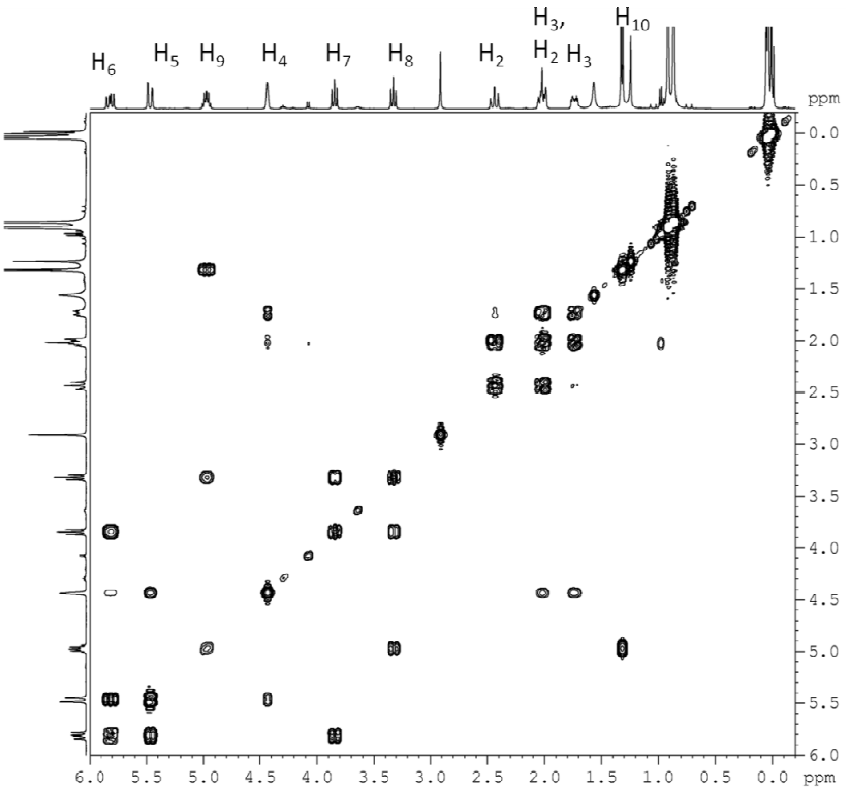
NOESY Spectrum of 3 in CD_3OD



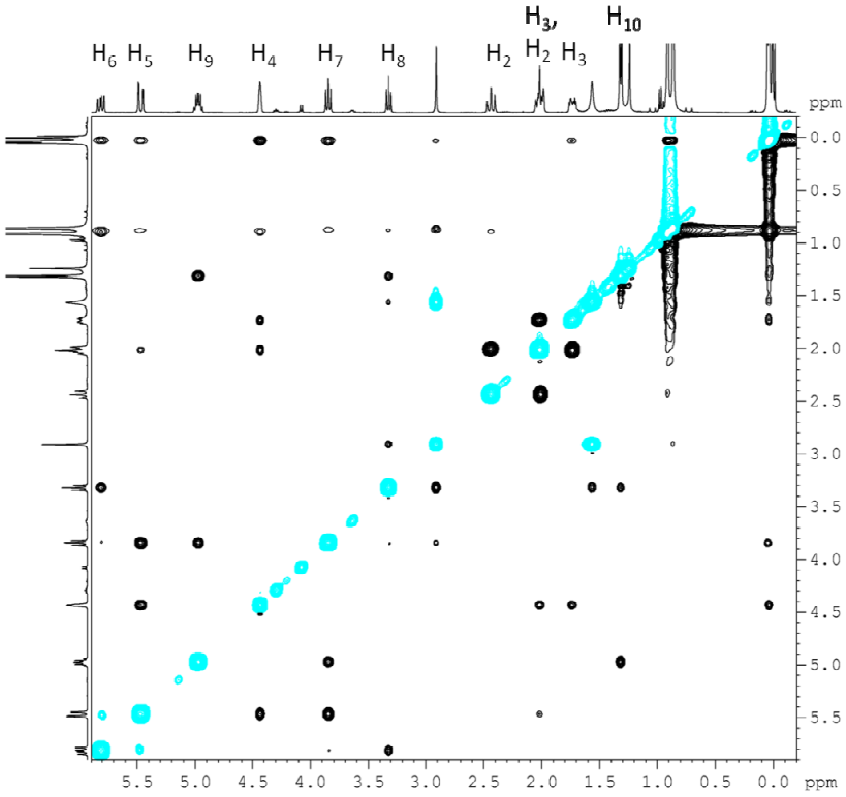
^{1}H NMR Spectrum of 17 in $CDCl_3$



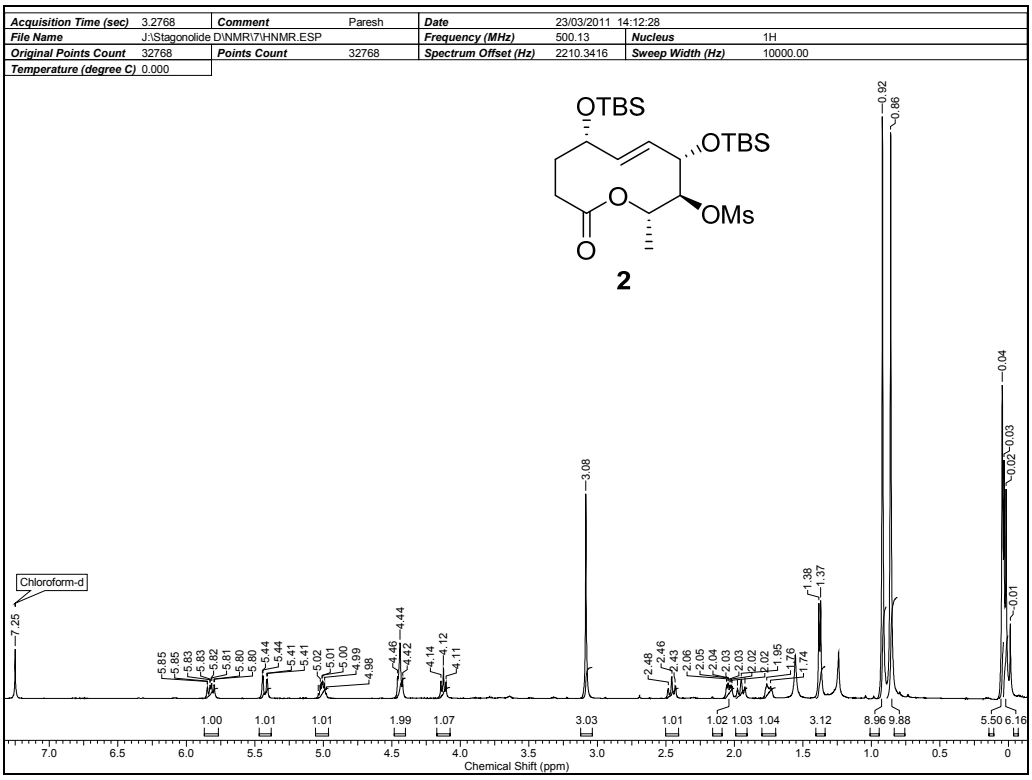
^{13}C NMR Spectrum of 17 in $CDCl_3$



COSY Spectrum of 17 in $CDCl_3$



NOESY Spectrum of 17 in $CDCl_3$



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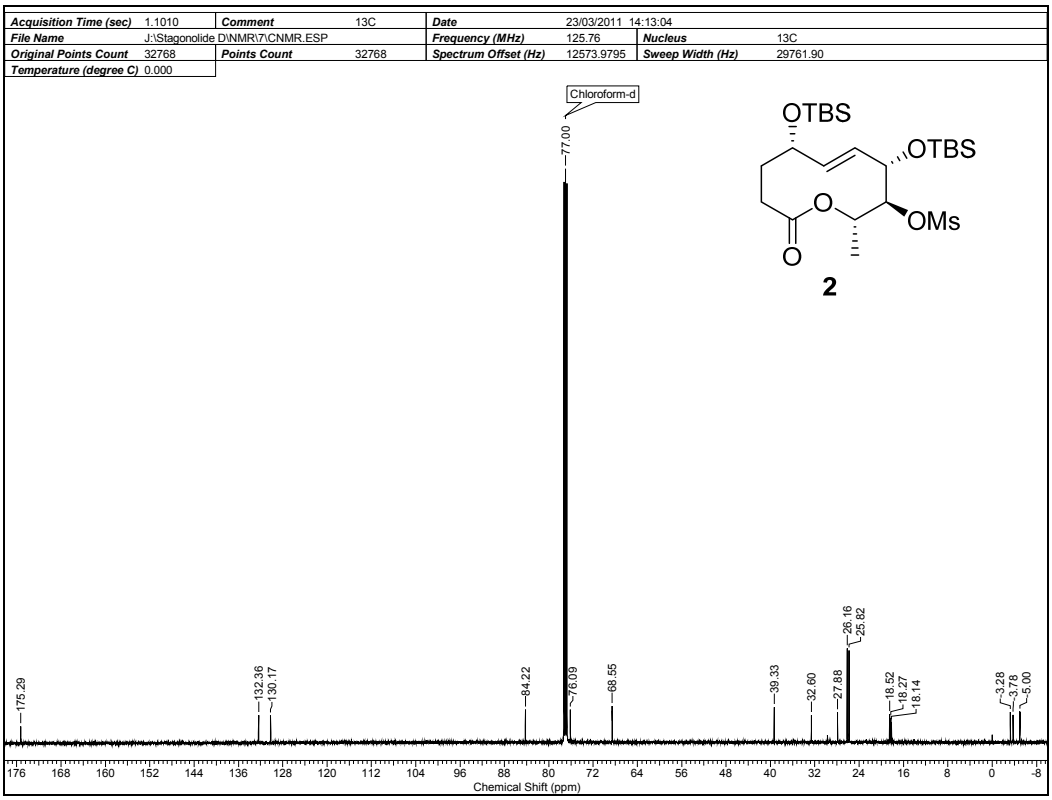

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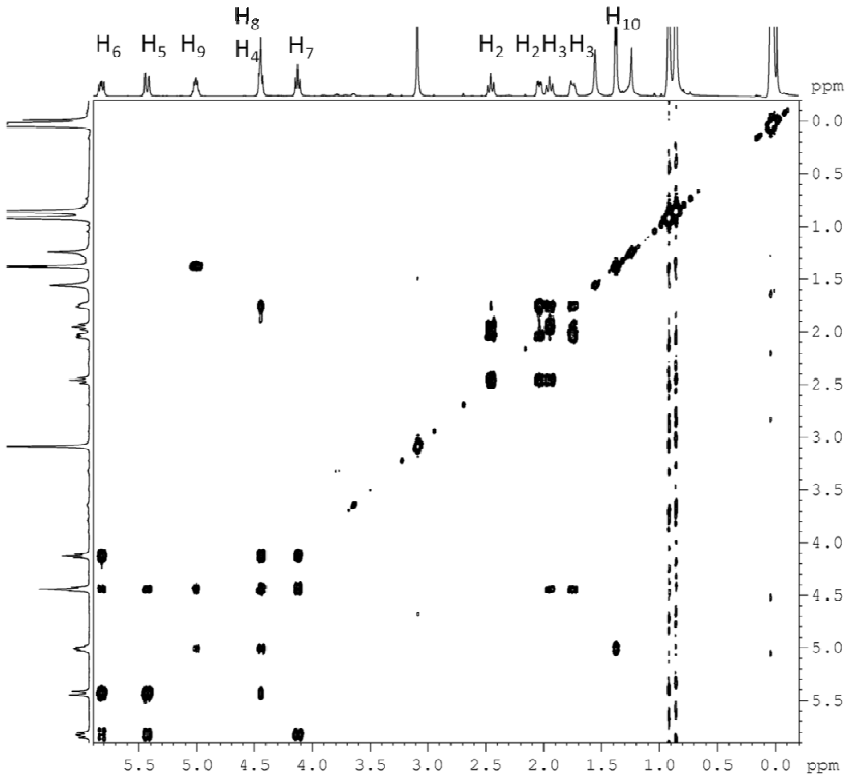

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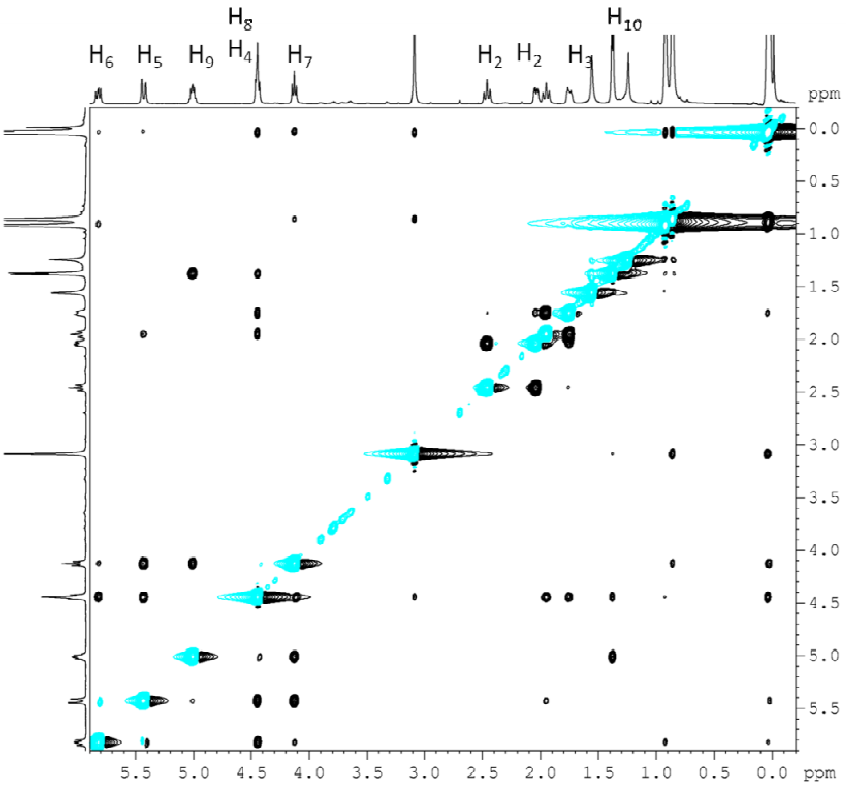

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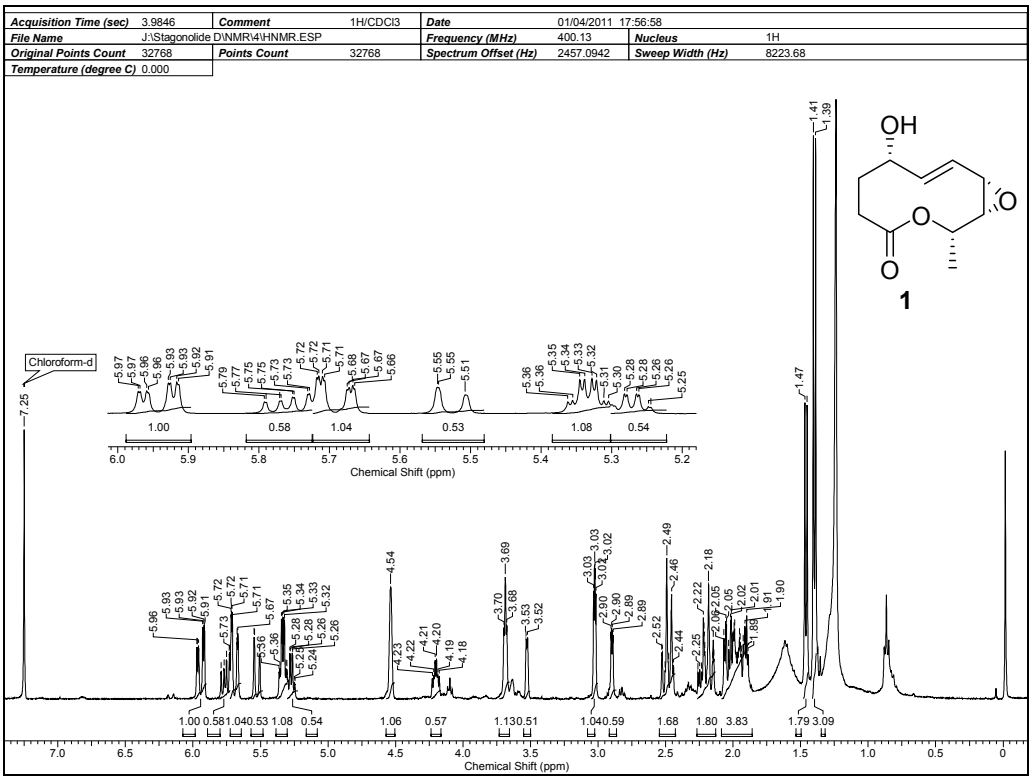

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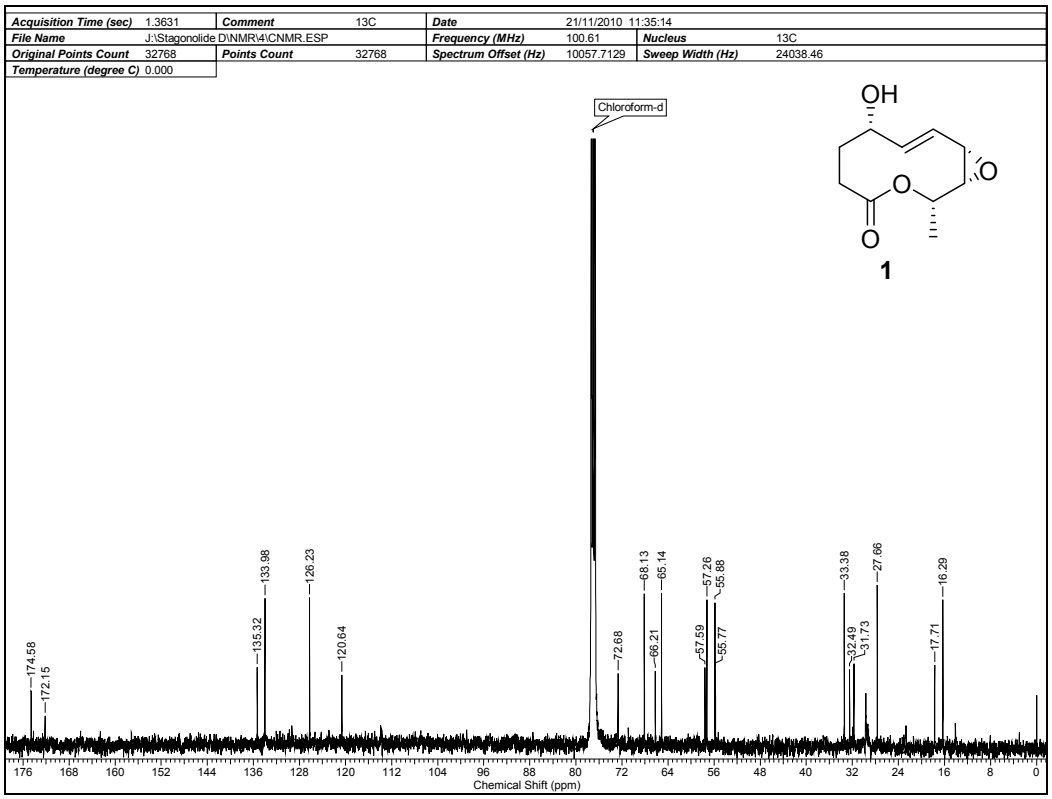

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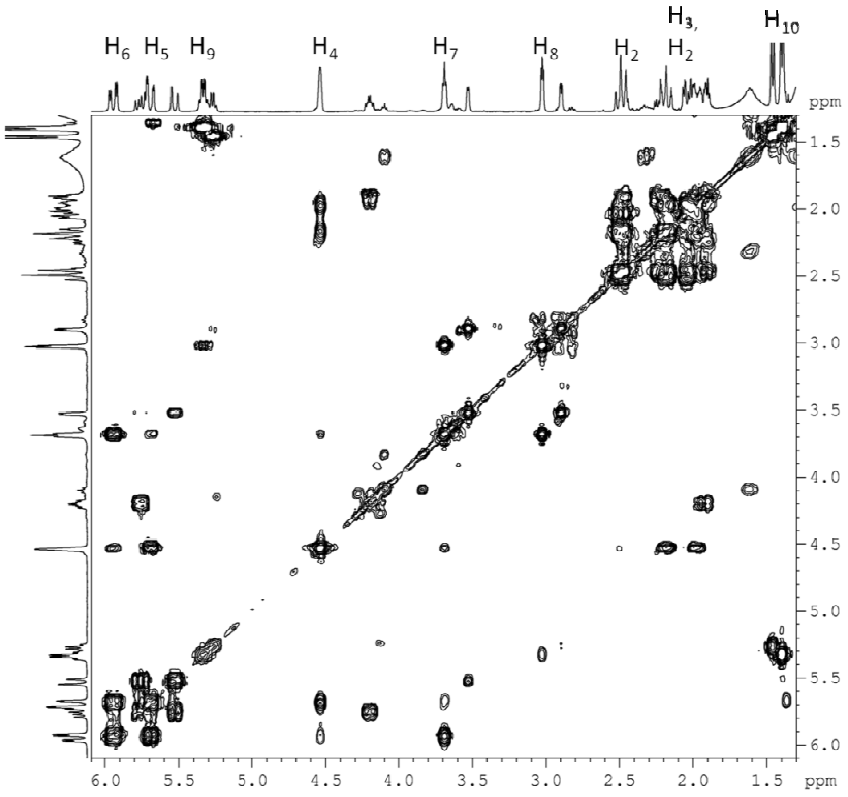

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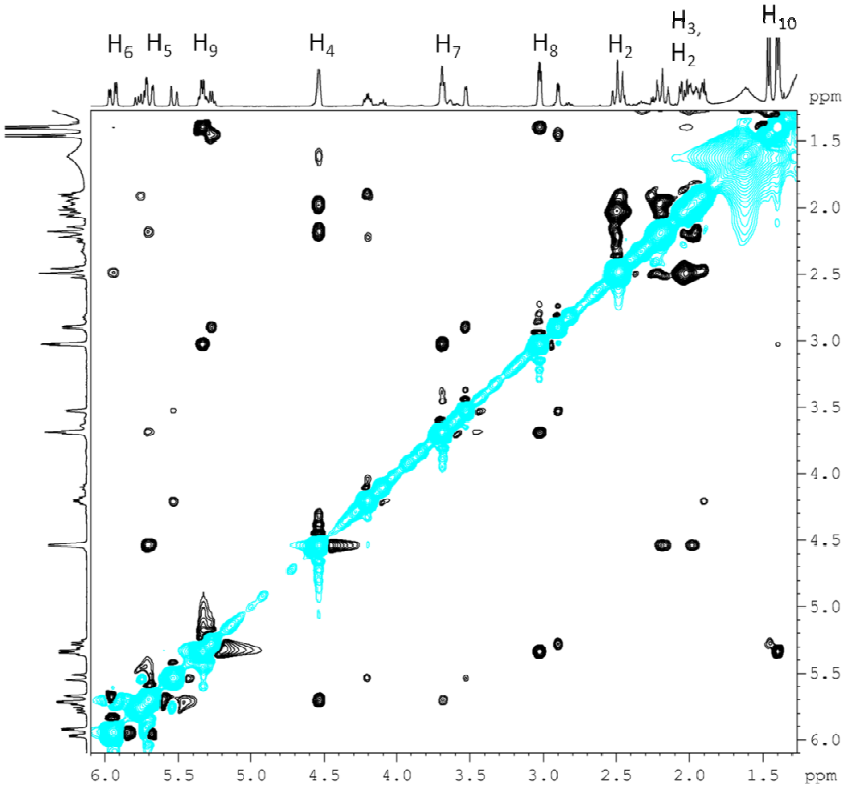
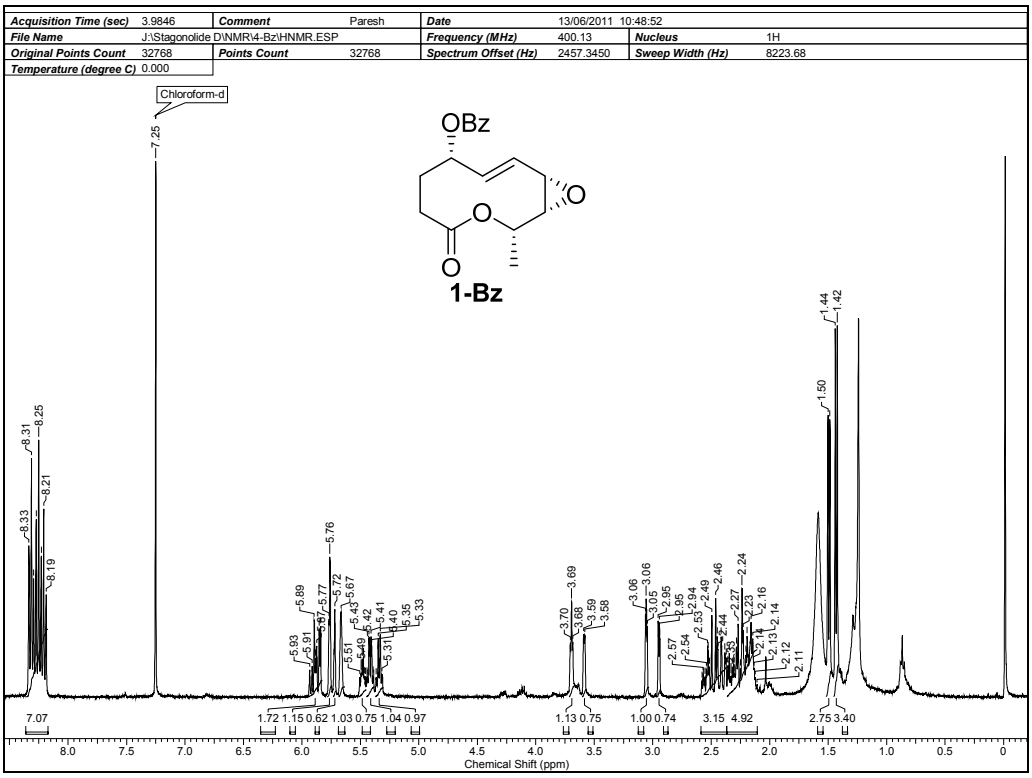


NOESY Spectrum of 1 in $CDCl_3$



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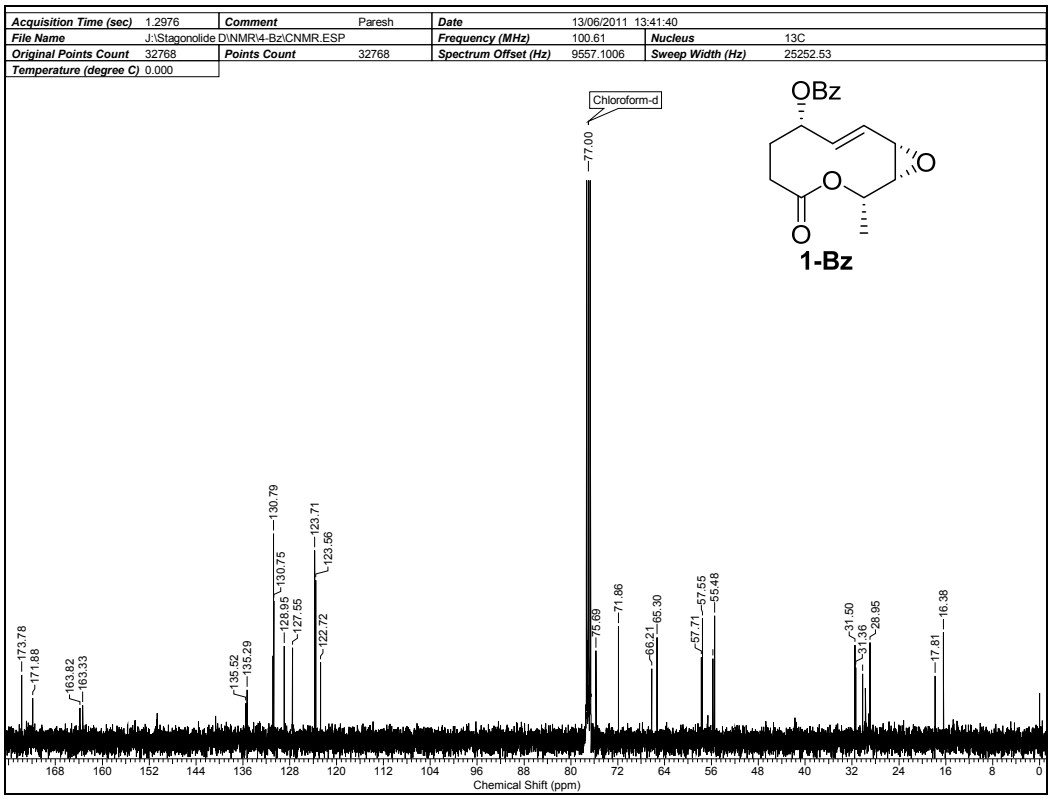
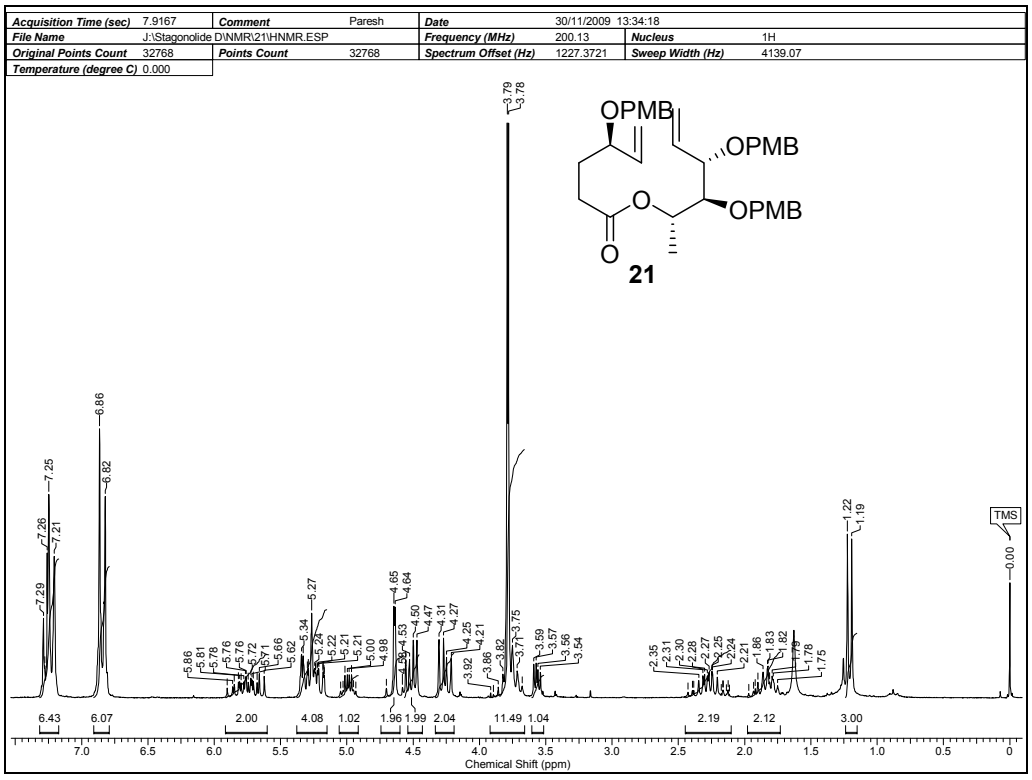


^{13}C NMR Spectrum of 1-Bz in $CDCl_3$



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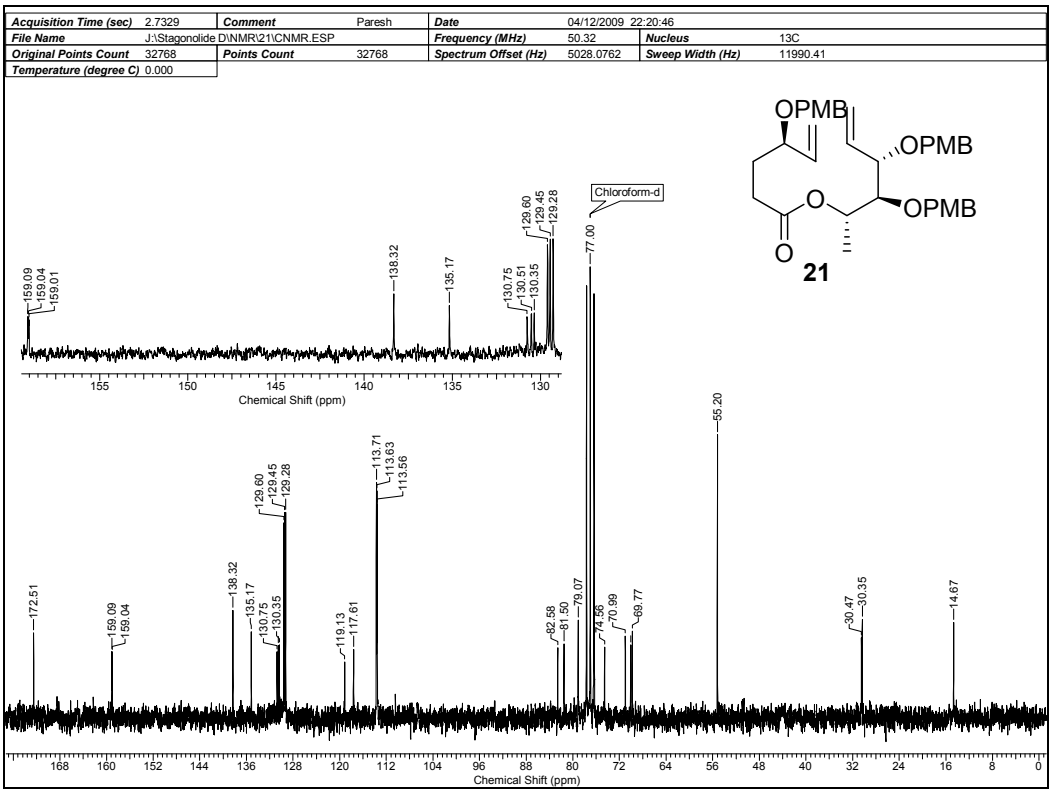
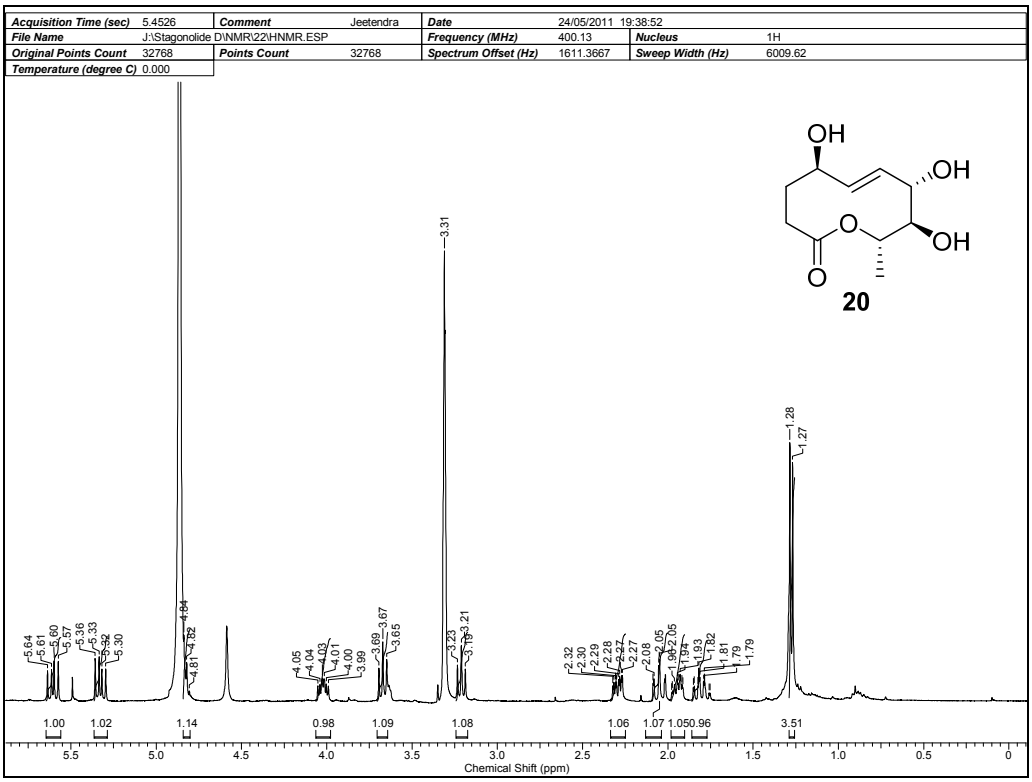


^{13}C NMR Spectrum of 21 in $CDCl_3$



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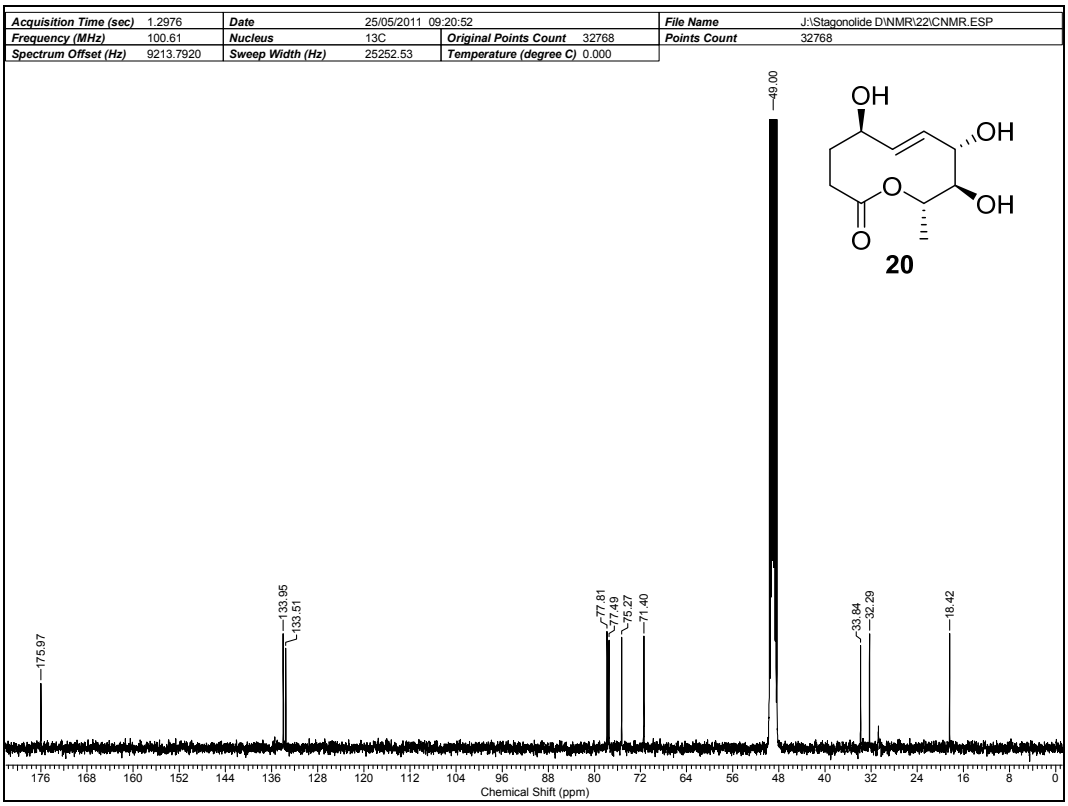
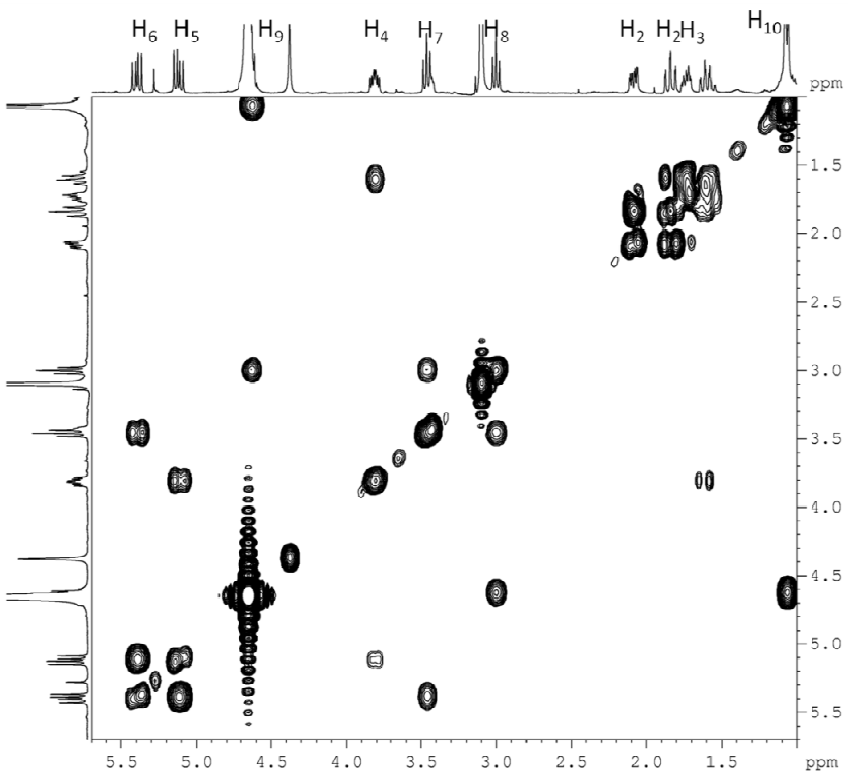
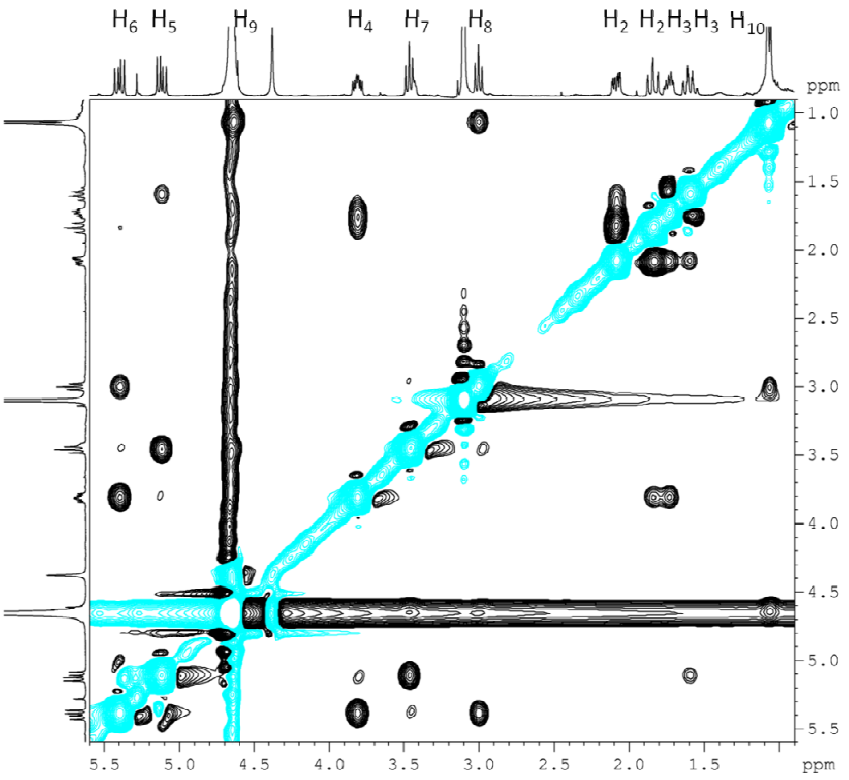


^{13}C NMR Spectrum of 20 in CD_3OD



COSY Spectrum of 20 in CD_3OD



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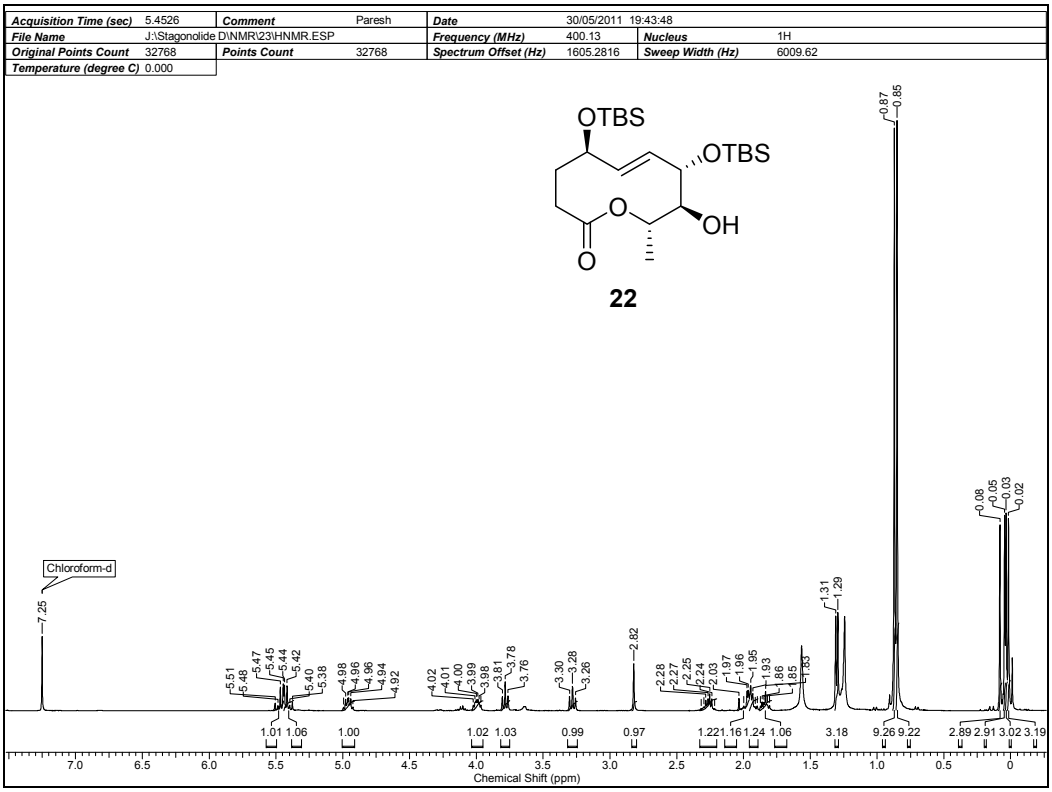
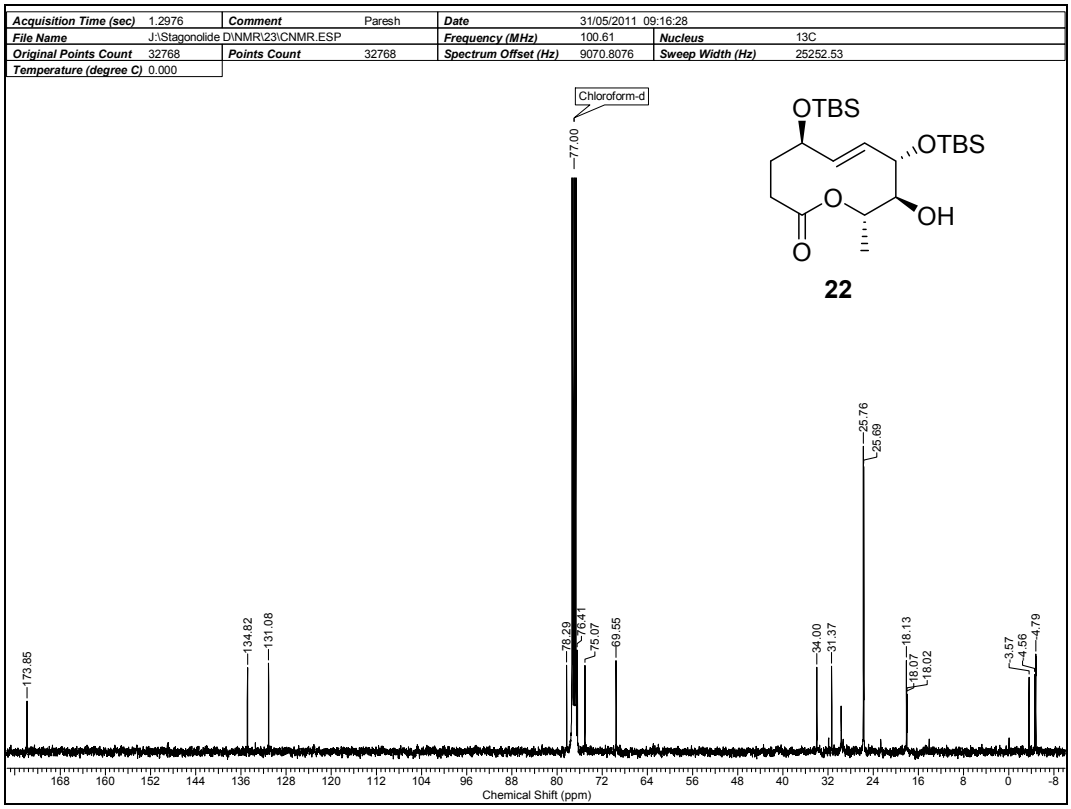
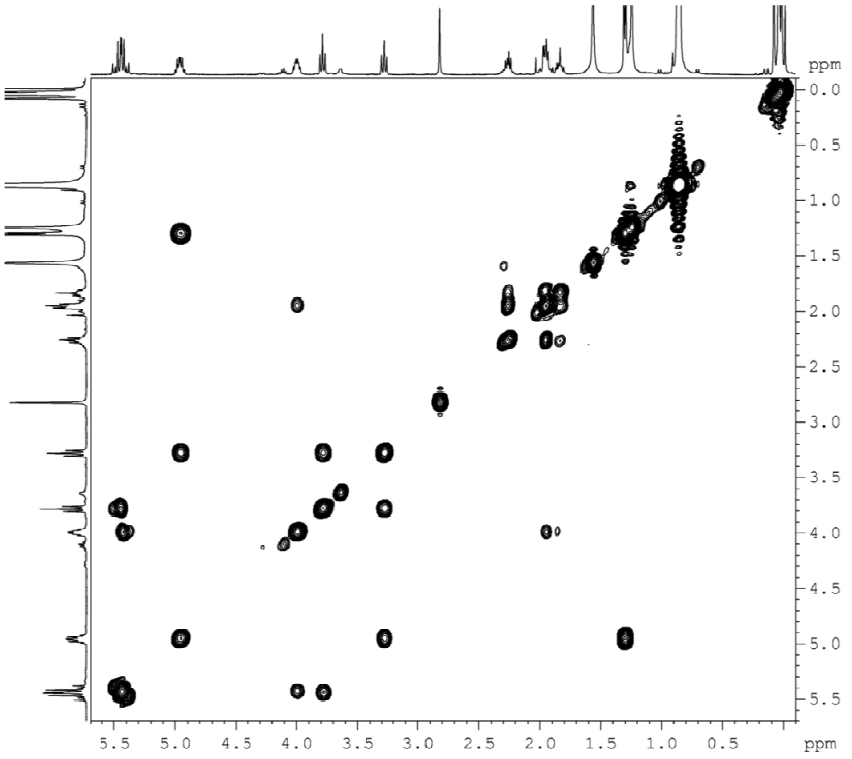


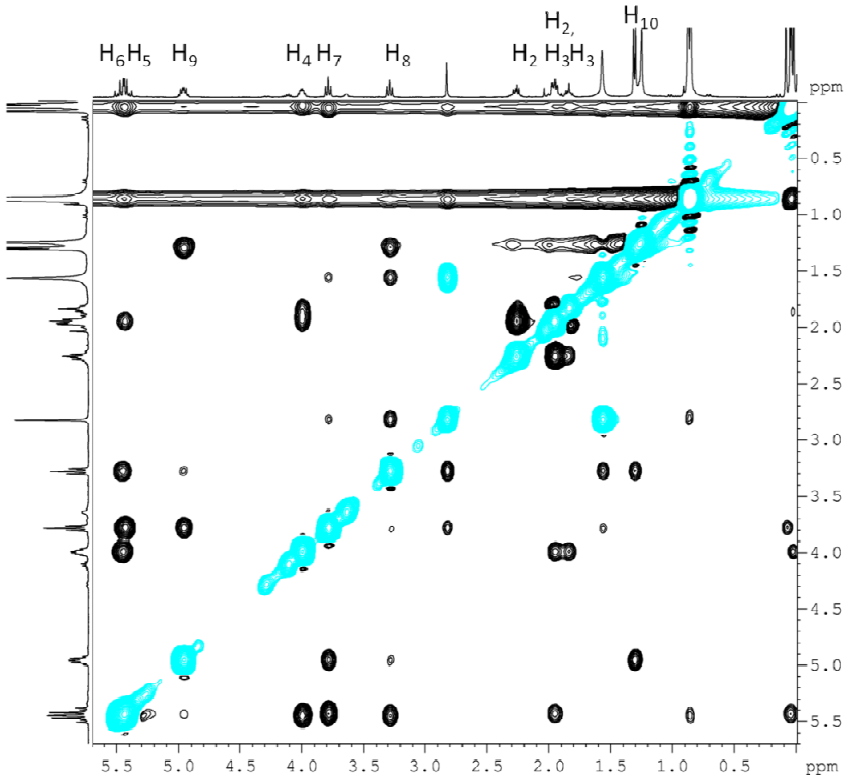
^{1}H NMR Spectrum of 22 in $CDCl_3$



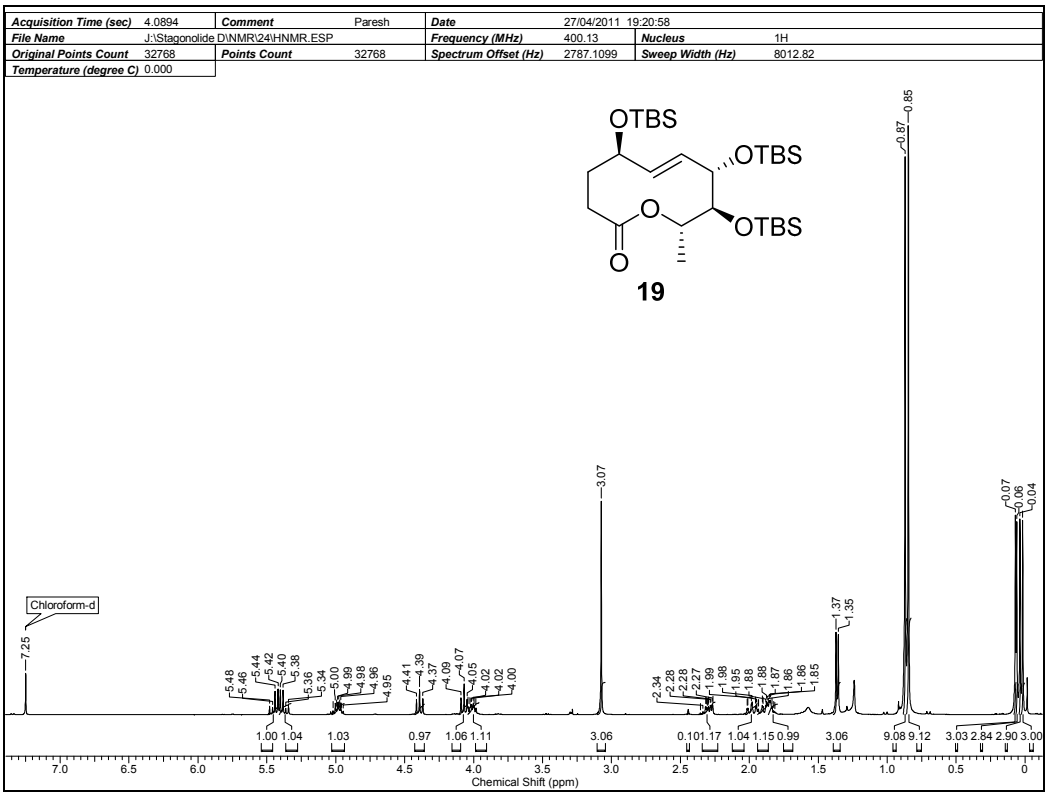
^{13}C NMR Spectrum of 22 in $CDCl_3$



COSY Spectrum of 22 in $CDCl_3$



NOESY Spectrum of 22 in $CDCl_3$



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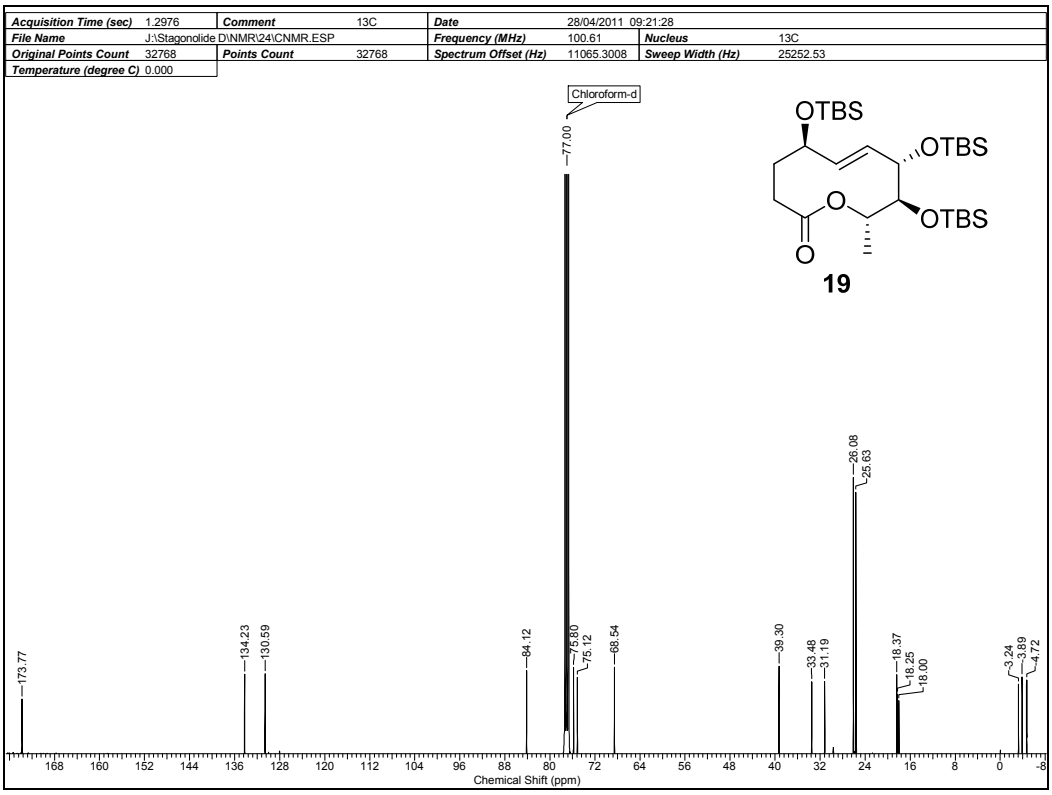
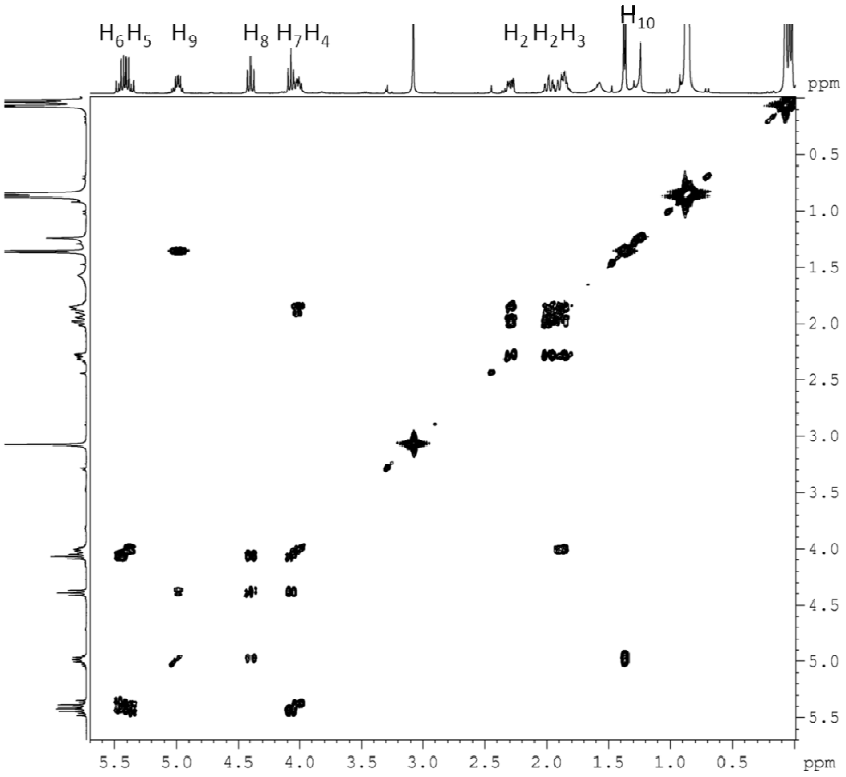
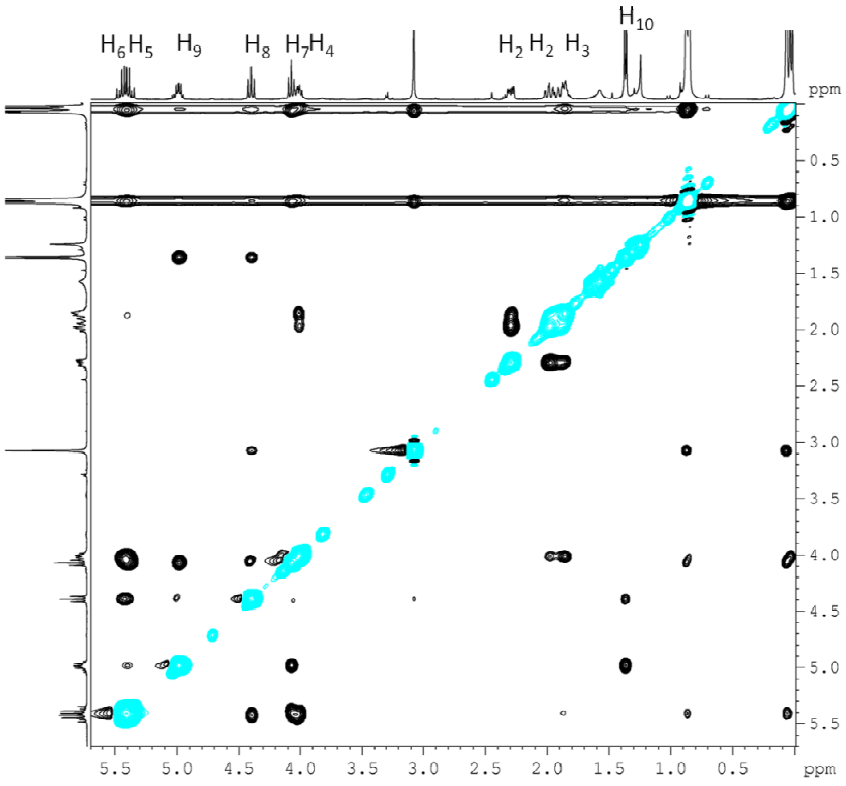


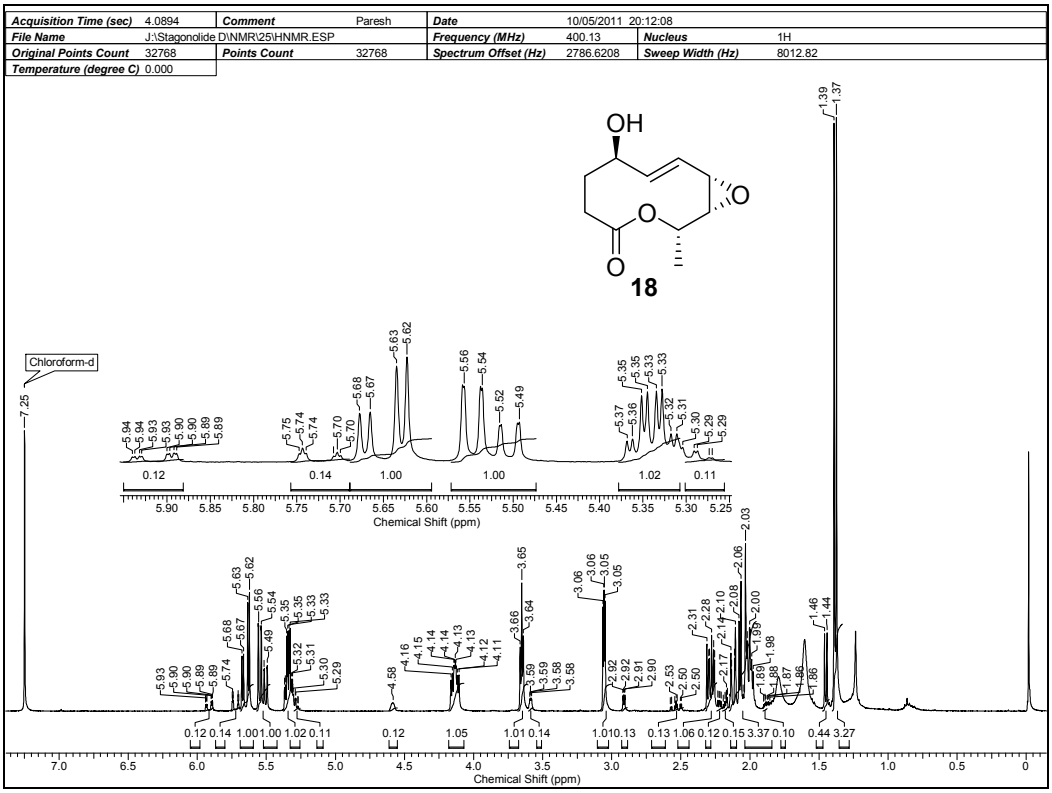
^{13}C NMR Spectrum of 19 in $CDCl_3$



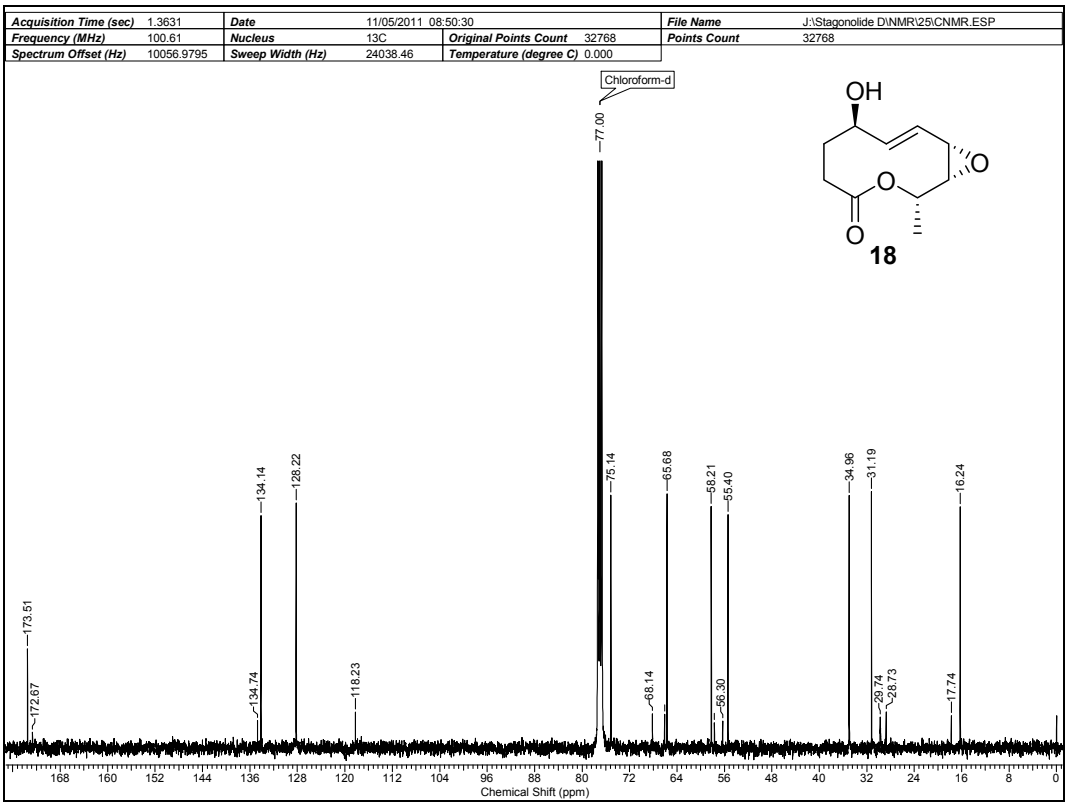
COSY Spectrum of 19 in $CDCl_3$



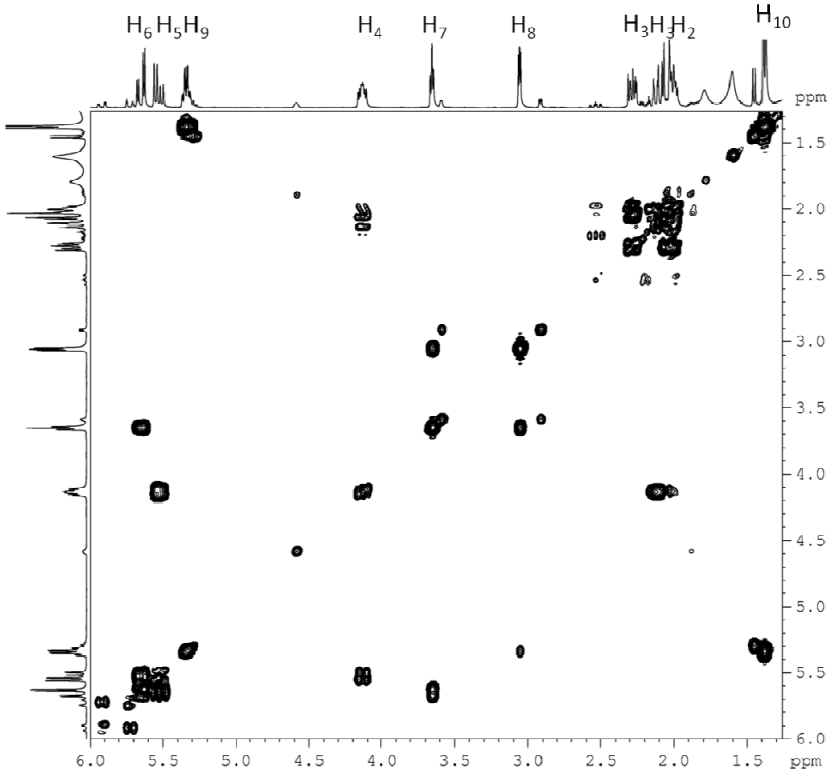
NOESY Spectrum of 19 in $CDCl_3$



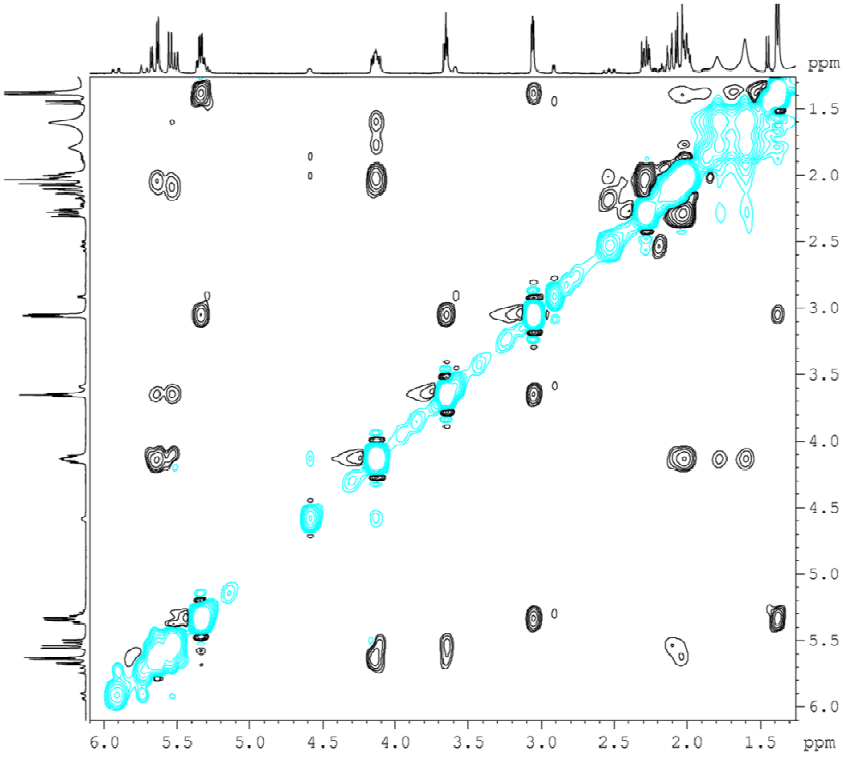
^{1}H NMR Spectrum of 18 in $CDCl_3$



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



COSY Spectrum of 18 in $CDCl_3$



NOESY Spectrum of 18 in $CDCl_3$

CHAPTER I; SECTION II

Total synthesis of Mangiferaelactone

RESULT AND DISCUSSION

Endophytic fungi are a rich source of unique biologically active and structurally diverse natural products. The majority of natural products isolated from endophytic microorganisms have antimicrobial activities, which have been implicated in protecting the host plant against phytopathogenic microorganisms. In 2014, Luis Cubilla-Rios and co-workers reported the isolation of Mangiferaelactone (**23**) from a solid culture of the endophytic fungus *Pestalotiopsis manguiferae* that was grown on a small shrub common in the central region of Panama.[24] Mangiferaelactone showed a minimum inhibitory concentration (MIC) of 1.6863 mg/mL against *Listeria monocytogenes*, and 0.5529 mg/mL against *Bacillus cereus*. The complete constitution of mangiferaelactone was elucidated with the help of extensive NMR and mass spectral analysis and the absolute configuration was established as 4*R*,7*R*,8*R*,9*S* by vibrational circular dichroism (VCD) studies. In continuation of our interest, we were interested in exploring the RCM approach for the synthesis of **23**, considering the fact that it disposes a favourable *syn*-arrangement of the allylic substituents (Figure 10), and to confirm its absolute configuration.

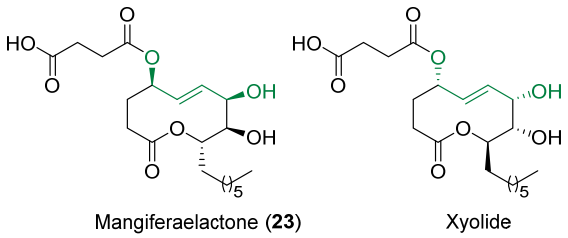


Figure 10. *Strucrure of Mangiferealactone and Xyolide*

Mangiferaelactone is the optical antipode of the natural product Xyolide. Xyolide was isolated by Handelsman *et al* from the Amazonian endophytes Xylaria feejeensis in 2013. The structure was elucidated with the help of 1D and 2D NMR methods and the absolute configuration was determined by exciton-coupled circular dichroism. The MIC of xyolide against P. ultimum was 425 μM. The first total synthesis of xyolide was reported by Subba Reddy *et al* using Steglich esterification, and ring closing metathesis as key steps for making the nonenolide skeletal.[62] At the same time, Mohapatra *et al* also achieved the total synthesis of xyolide using the same RCM reaction as a key reaction.[63] After that, Nanda *et al* described the asymmetric total synthesis of Xyolide and employed the cross metathesis reaction and Shiina lactonization method for the construction of the central core of macrolide.[64] Subha Reddy and Samik Nanda used the same starting material n-nonanal for the synthesis of the alcohol fragment where as D-(–)-ribose was taken as the starting material for the alcohol fragment synthesis by Mohapatra (Figure 11).

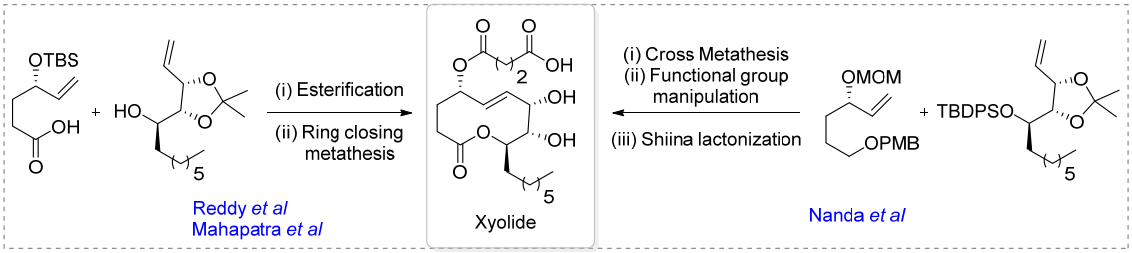


Figure 11. *Reported synthesis of xyolide*

Our key retrosynthetic disconnections are outlined in Figure 12. The planned total synthesis of Mangiferaelactone involves the introduction of the succinic acid moiety at the penultimate stage.[62-65] The construction of the central nonenolide core was planned from two fragments that resulted after the disconnection of the central ring using the RCM transformation. We have earlier reported practical procedures for the synthesis of either of the enantiomers of the acid fragment (*R*)-**7**.[52] As shown in figure 12, considering the *pseudo*-symmetry present in the ribose, we devised an enantio-divergent approach that relies on the Bernet-Vasella fragmentation of the iodo derivative of *β*-^{n}heptyl *C*-riboside **27**.[66] The synthesis of the key intermediate **27** has been planned from the *C*-allyl ribofuranoside **28** through Wittig homologation followed by simple functional group transformations.

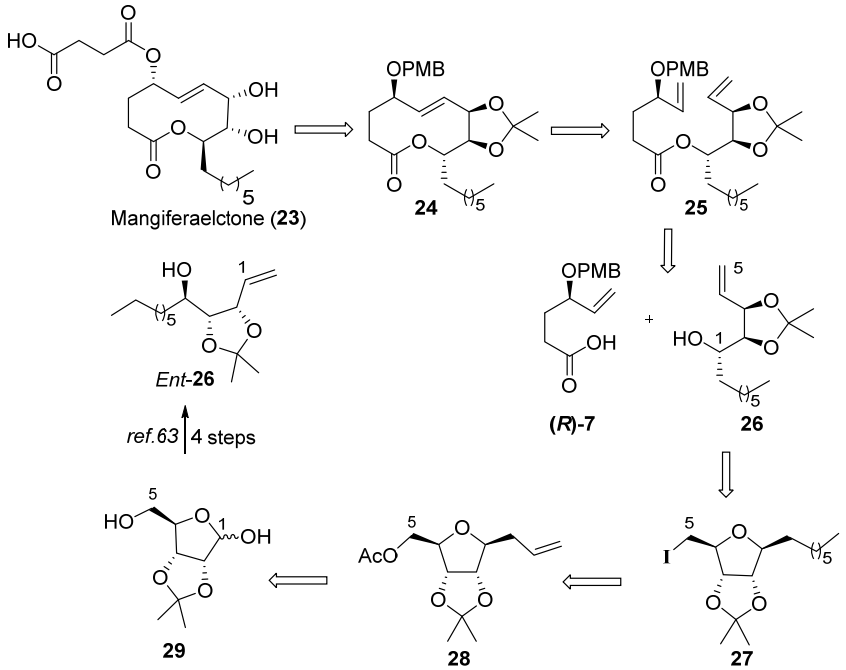
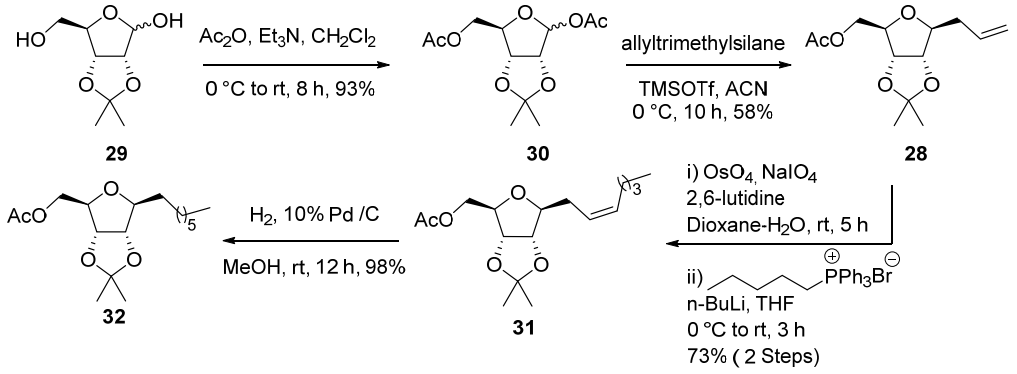


Figure 12. *Retrosynthetic analysis for Mangiferaelactone (**23**)*

Synthesis of the alcohol fragment 26:

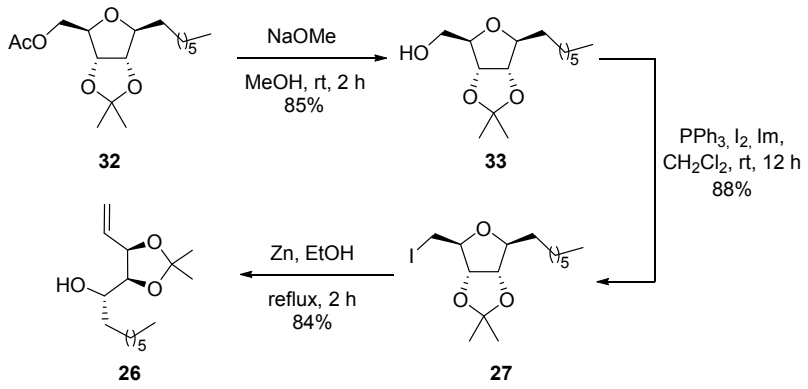
The synthesis of the alcohol fragment **26** was started with the preparation of the *C*-allyl ribofuranoside **28** following the established literature procedures.[47b] Acetylation of D-ribose monoacetonide **29** using triethyl amine and acetic anhydride afforded compound **30** in 93% yield. The treatment of diacetate **30** with allyltrimethylsilane and TMSOTf in acetonitrile gave the desired *C*-glycoside **28** in 58% yield together with a trace amount of the corresponding *α*-anomer (α:*β* ≈ 1:10). The spectroscopic and analytical data of compound **28** are in good agreement with the reported data (Scheme 13).



Scheme 13. *Synthesis of Acetate **32***

Subsequent oxidative cleavage of the double bond in compound **28** by $OsO_4/NaIO_4$ in the presence of 2,6-lutidine[67] followed by 5-carbon Wittig homologation of the intermediate aldehyde gave exclusively the *Z*-isomer **31** in 73% yield over two steps. The structure of **31** was fully established with the help of spectral and analytical data. In the ^{1}H NMR spectrum of compound **31**, the presence of a triplet at *δ* 0.90 (*J* = 6.7, 3H) ppm belong to a terminal methyl group of long chain as well as the appearance of peaks at *δ* 1.26-1.41 (m, 4H), 2.02-2.09 (m, 2H), 2.20-2.47 (m, 2H) ppm corresponding to the long chain protons confirmed the presence of the side chain, while the newly formed olefinic protons resonated at *δ* 5.33-5.46 ppm and 5.49-5.62 ppm as a multiplet having the largest coupling constant of about *J* = 12.4 Hz which clearly indicated the presence of internal olefin with *cis* geometry and most importantly the terminal olefin proton seen to disappear. In the ^{13}C NMR spectrum of compound **31**, the characteristic olefinic carbons appeared at *δ* 123.4 and 133.1 ppm as doublet, whereas the carbon of the methyl and methelylene group of the long chain carbon resonated at *δ* 13.9 ppm as a quartet and at *δ* 22.3, 27.1, 31.2, 31.6 ppm as triplets respectively. Additionally, the mass peak at 507.2317 in the HRMS spectrum satisfied the expected constitution of compound **31**. The hydrogenation of the double bond of compound

31 was carried out using 10% Pd/C in MeOH under H_2 (balloon) atmosphere gave the reduced product **32** in quantitative yield. In the ^{1}H NMR spectrum of compound **32**, the disappearance of the olefinic protons was observed, and the appearance of four more protons in the aliphatic long chain region suggested the reduction of the double bond in compound **32**. Later, this was confirmed by both ^{13}C NMR and HRMS (Scheme 13).



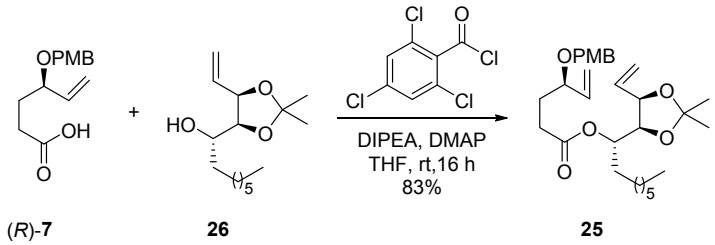
Scheme 14. *Synthesis of alcohol fragment **4***

In order to obtain precursor **27** for Bernet-Vasella fragmentation, the acetate protection group in compound **32** has to be removed. Thus, deacetylation of the compound **32** was carried out using catalytic NaOMe in methanol to obtain the alcohol **33** in 85% yields. In the ^{1}H NMR spectrum of **33**, the methyl signals corresponding to the acetyl group disappeared and the highest mass peak observed at *m/z* 210.3 (100%, $[M+Na]^+$) supported the assigned structure of **33**. The hydroxyl group of **33** is then converted into the corresponding iodide **27** by treatment of compound **33** with iodine in the presence of PPh_3 and imidazole in CH_2Cl_2 at room temperature.[68] The presence of the iodo group in compound **27** was well supported by the spectral and analytical data. In the ^{1}H NMR spectrum of the iodo derivative **27**, protons of the methylene attached to iodine group resonated relatively up field at δ 3.26-3.34 ppm as a multiplet and in the ^{13}C NMR spectrum of compound **27**, carbon attached to iodine resonated as a triplet at δ 7.3 ppm due to iodine which confirmed the assigned constitution. The presence of a strong peak at m/z 383.1078 (100%, $[M + Na]^+$) in the ESI-HRMS spectrum supported the structure of **27**. After successful synthesis of the iodo derivative **27,** the next step was the Vasella-Bernet fragmentation and it was achieved by treating the iodo derivative **27** with activated zinc dust in moist ethanol under refluxing conditions to deliver the olefin **26** in 84% yield. The structure of olefin **26** was established with the help of spectral and mass analysis. In the ^{1}H NMR spectrum of compound **26**, the new two olefinic protons appeared at δ 5.32 (dd, J = 1.1, 10.5 Hz, 1H), 5.43 (dd, J = 1.1, 16.9 Hz, 1H) ppm corresponding to the terminal carbon, while the internal proton appeared at δ

6.00-6.09 ppm as a multiplet. In the ^{13}C NMR spectrum of compound **26**, the olefinic carbons appeared at δ 118.5 and 134.7 ppm as triplet and doublet respectively. Furthermore, the mass peak at 279.1927 in the HRMS spectrum confirmed the compound **26** (Scheme 14).

Coupling of alcohol 26 and acid (*R*)-S9.1:

Having both the coupling partners (*R*)**-7** and **26** in hand, we proceeded further with their coupling followed by ring closing metathesis. In this direction, the coupling of the alcohol **26** with the available acid (*R*)-**7** was carried out by following the Yamaguchi protocol to afford the diene ester **25** in 83% yields.[58] The spectral and analytical data of **25** were in well agreement with the proposed structure. In the ^{1}H NMR spectrum of compound **25**, four terminal alkene protons resonated at δ 5.19-5.34 ppm and two internal alkene protons resonated at δ 5.68-5.84 ppm as multiplets. On the other hand, the charectiristic acyloxy -CH was seen to appear at δ 4.90 ppm as a doublet of triplet with coupling constatnt J = 3.4, 7.6 Hz. In the ^{13}C NMR spectrum of compound **25**, the four carbons corresponding to the two olefinic units resonated at 117.7 (t), 118.4 (t), 133.2 (d), and 138.3 (d) ppm. Further coupling was evidenced from the appearing of signals corresponding to the alcohol moiety and acid moiety together in the ^{1}H and ^{13}C NMR spectrum (Scheme 15).

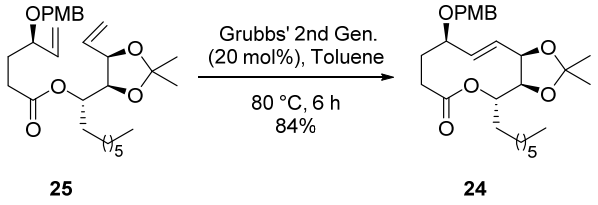


(*R*)-**7** **26** **25**

Scheme 15. *Synthesis of Diene ester **25***

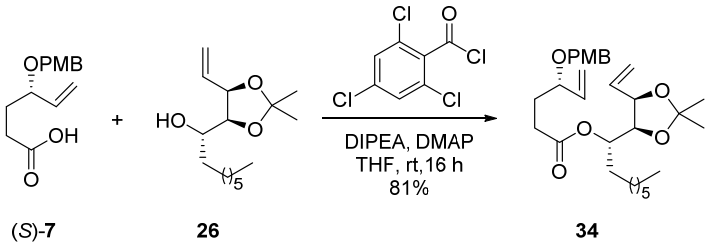
After fully establishing the structure of compound **25**, it was subjected for the RCM reaction using catalytic amounts of the second-generation Grubbs catalyst in toluene at 80 °C to obtain the desired lactone (*E*)-**24** as the major product in 84% yield. The constitution of compound **24** was established with help of NMR and HRMS. In the ^{1}H NMR spectrums of compound **24**, the signals corresponding to the newly formed olefinic protons were appeared at δ 5.68 (dd, J = 8.8, 15.9 Hz, 1H) and 5.85 (dd, J = 3.0, 15.9 Hz, 1H) ppm. The large coupling constant (J = 15.9 Hz) confirmed the *E*-configuration of the newly formed internal olefin. The characteristic acyloxy C-H proton resonated at δ 4.95 ppm as broad triplet with coupling constant J = 9.3 Hz providing a clear indication of lactone functionality present in **24**. In the ^{13}C NMR of compound **24**, olefinic carbons and the carbonyl carbon were seen to

resonate at δ 127.4 (d), 128.7 (d) and 174.9 (s) ppm respectively. Furthermore, the HRMS spectrum of compound **24** was in favor of the assigned structure (Scheme 16).



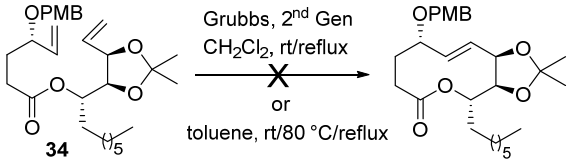
Scheme 16. *Synthesis of macrolide **24***

Next, to verify our hypothesis about the role of the relative stereochemistry of allylic substituents on the RCM outcome, the diene ester **34** was prepared by coupling the acid (*S*)-**7** and alcohol **26** under similar Yamaguchi conditions as previously used for the preparation of diene **25** to procure diene **34** in 81% yield. Compound **34** has shown data similar to that of compound **25**. For example, in the ^{1}HNMR of compound **34**, terminal olefinic protons were seen to resonate at δ 5.19-5.34 (m, 4H) ppm and internal protons at δ 5.68-5.83 (m, 2H) ppm. The acyloxy -CH proton was noticed at δ 4.90 (dt, J = 3.5, 7.9 Hz, 1H) ppm. Similarly in the ^{13}CNMR spectrum of compound **34**, signals at δ 117.7 (t), 118.4 (t) ppm corresponding to terminal olefin carbons and signals at 133.2 (d), 138.3 (d) ppm corresponding to the internal olefin carbons and a signal at δ 172.5 (s) ppm correponding to carbonyl carbon of ester group were noticed (Scheme 17).



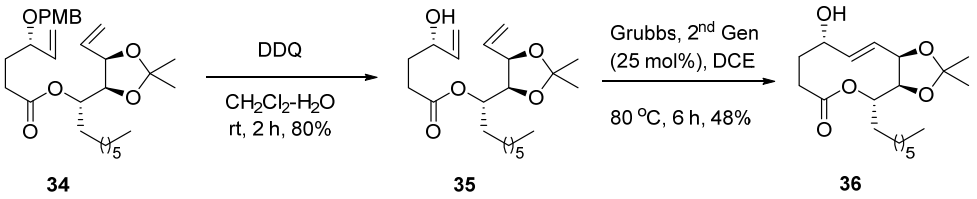
Scheme 17. *Synthesis of diene ester **34***

As expected, when the RCM of the fully protected diene ester **34** was performed under the previously employed conditions using second-generation Grubbs catalyst in CH_2Cl_2/reflux or toluene at 80 °C/reflux it was found to mainly yield the oligomeric products (Scheme 18).



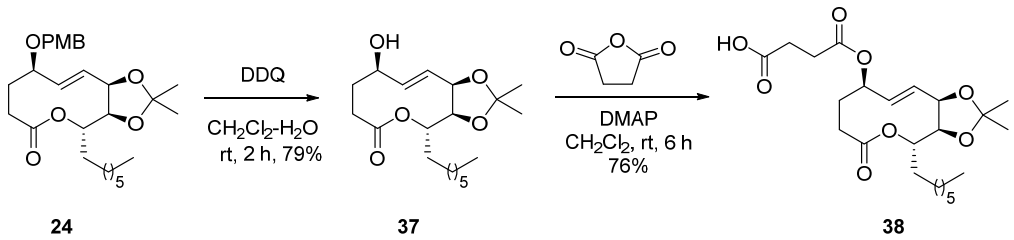
Scheme 18. *Failed RCM of diene ester **34***

To probe further in this direction, the PMB protecting group of compound **34** was deprotected with DDQ in the CH_2Cl_2-H_2O mixture at room temperature to obtain compound **35** in 80% yield. In the ^1H and ^{13}C NMR spectrum of **35**, the signals corresponding to the PMB group were seen to disappear as well as the presence of strong mass peak at m/z 363.2124 (100%, $[M+Na]^+$) in the HRMS spectrum confirmed the structure of **35**. After successfully characterizing the compound **35**, the RCM reaction of **35** was carried out using 2nd-generation Grubbs catalyst in DCE at 80 °C and the macrolide **36** was isolated in moderate yields.[48] In the ^{1}HNMR spectrum of compound **36**, the appearance of signals at δ 5.66 (dd, J = 6.9, 15.5 Hz, 1H), 5.81 (dd, J = 6.3, 15.5 Hz, 1H) ppm indicated the presence of internal olefin having a *trans* double bond. Similarly, in the ^{13}C NMR spectrum of compound **36**, the olefinic carbons were seen to resonate at δ 125.7 (d), 135.6 (d) ppm and carbonyl carbon at δ 172.2 (s) ppm. Additionally, the presence of a strong peak in the HRMS spectrum of compound **36** at 363.2136 confirmed the assigned constitution (Scheme **19**).



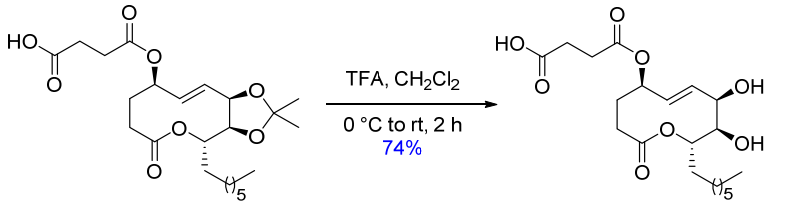
Scheme 19. *RCM of diene ester **35***

After having examined the feasibility of the RCM with both the diastereomers, next we proceeded for completing the total synthesis of the natural product. In this regard, the removal of PMB protecting groups of compound **24** was attempted using DDQ in dichloromethane-water (18:1) as a solvent which led us to isolate hydroxylactone **37** in 79% yield. In the ^1H and ^{13}C NMR spectrum of **37**, the signals corresponding to the PMB group were seen to disappear. Furthermore, the presence of a sharp mass peak at m/z 363.2124 (100%, $[M+Na]^+$) in the HRMS spectra are in good agrement with the assigned structure of **37** (Scheme 20).



Scheme 20. *Synthesis of macrolide **38***

As intended, the free –OH group in the hydroxylactone **37** was subjected for esterification with succinic anhydride in the presence of DMAP in CH_2Cl_2 to afford **38**.[62-65] In the ^1H NMR spectrum of **38**, the proton corresponding to the succinic acid moiety appeared at δ 2.58-2.68 (m, 4H) ppm, while the corresponding ester attached proton resonated at δ 5.19-5.25 ppm as a multiplet. In the ^{13}C NMR spectrum of **38**, carbonyl carbons of succinic acid moiety appeared at δ 170.6, 171.3 ppm as singlets and the carbonyl carbon of lactone appeared at δ 174.7 ppm as a singlet. In the ESI-HRMS of **38**, the characteristic peak at *m/z* 463.2278 (100%, $[M+Na]^+$) supported the assigned constitution of **38** (Scheme 20).



38 Mangiferaelactone (**23**)

Scheme 21. *Total synthesis of Mangiferaelactone (**23**)*

To this end, the deprotection of the acetonide group in compound **38** with TFA in CH_2Cl_2 at 0 °C to room temperature in 2 h provided the target Mangiferaelactone (**23**) in very good yields. The spectral data of synthetic **23** was in accordance with the data reported (Table 4) and the observed optical rotation [−2.1 (c 1.0, MeOH)] confirmed the assigned absolute configuration.[24]

Conclusion:

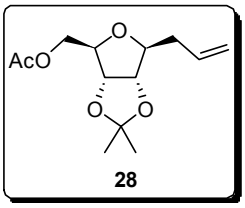
In conclusion, the first total synthesis of Mangiferaelactone (**23**) confirming its absolute configuration has been completed. The central nonenolide ring was constructed using ring closing metathesis and Yamaguchi esterification. The key alcohol fragment was synthesized by the Bernet–Vasella fragmentation of a *C*-ribofuranoside.

Table 4: *Comparative δ and J values of synthetic and natural Mangiferealactone:*

Position	Natural Mangiferaelactone		Synthetic Mangiferaelactone	
	^{1}H NMR	**^{13}C NMR**	**^{1}H NMR**	**^{13}C NMR**
1		175.9 (qC)		175.9 (qC)
2	2.32 (ddd, *J* = 2.3, 6.1, 13.9 Hz, 1H) 2.09 (dt, *J* = 2.0, 13.9 Hz, 1H)	32.3 (CH_2)	2.32 (ddd, *J* = 2.2, 6.1, 13.9 Hz, 1H) 2.09 (dt, *J* = 1.9, 13.9 Hz, 1H)	32.3 (CH_2)
3	1.98 (m, 1H), 1.92 (m, 1H)	30.9 (CH_2)	1.96-2.01 (m,1H) 1.91 (dt, *J* = 2.2, 13.2, 1H)	30.9 (CH_2)
4	5.17 (dt, *J* = 4.9, 10.3 Hz, 1H)	78.3 (CH)	5.17 (dt, *J* = 4.7, 10.3 Hz, 1H)	78.3 (CH)
5	5.49 (ddd, *J* = 2.2, 10.3, 15.6 Hz, 1H)	123.9 (CH)	5.49 (ddd, *J* = 2.2, 9.5, 15.5 Hz, 1H)	123.8 (CH)
6	5.92 (dd, *J* = 2.2, 15.6 Hz, 1H)	136.1 (CH)	5.92 (dd, *J* = 2.1, 15.7 Hz, 1H)	136.1 (CH)
7	4.40 (br d, 1H)	73.6 (CH)	4.40 (br d, *J* = 2.1 Hz, 1H)	73.6 (CH)
8	3.53 (dd, *J* = 2.4, 9.7 Hz, 1H)	74.7 (CH)	3.53 (dd, *J* = 2.4, 9.7 Hz, 1H)	74.6 (CH)
9	5.13 (dt, *J* = 2.6, 9.7 Hz, 1H)	72.3 (CH)	5.13 (dt, *J* = 2.6, 9.5 Hz, 1H)	72.2 (CH)
10	1.84 (m, 1H) 1.48 (m, 1H)	32.9 (CH_2)	1.82-1.87 (m, 1H) 1.47-1.49 (m, 1H)	32.9 (CH_2)
11	1.25–1.36 (m, 2H)	25.8 (CH_2)	1.25–1.36 (m, 2H)	25.8 (CH_2)
12	1.25–1.36 (m, 2H)	30.8 (CH_2)	1.25–1.36 (m, 2H)	30.8 (CH_2)
13	1.25–1.36 (m, 2H)	30.8 (CH_2)	1.25–1.36 (m, 2H)	30.8 (CH_2)
14	1.25–1.36 (m, 2H)	33.2 (CH_2)	1.25–1.36 (m, 2H)	33.1 (CH_2)
15	1.25–1.36 (m, 2H)	23.9 (CH_2)	1.25–1.36 (m, 2H)	23.8 (CH_2)
16	0.89 (t, *J* = 7.0 Hz, 3H)	14.6 (CH_3)	0.89 (t, *J* = 6.9 Hz, 3H)	14.6 (CH_3)
17		173.6 (qC)		173.5 (qC)
18	2.50–2.60 (br s, 2H)	30.5 (CH_2)	2.56 (s, 2H)	30.5 (CH_2)
19	2.50–2.60 (br s, 2H)	30.5 (CH_2)	2.56 (s, 2H)	30.5 (CH_2)
20		175.9 (qC)		175.9 (qC)

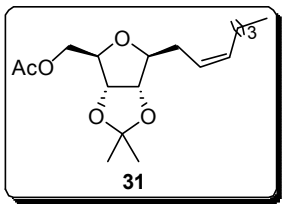
EXPERIMENTAL

***Allyl* (28):**



Compound **28** was prepared according to the literature procedure. $[\alpha]_D^{25}$ 12.8 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.32 (s, 3H), 1.51 (s, 3H), 2.08(s, 3H), 2.36 (t, *J* = 6.7 Hz, 2H), 3.94-4.03 (m, 1H), 4.04-4.13 (m, 2H), 4.26 (dd, *J* = 5.7, 10.4 Hz, 1H), 4.37 (dd, *J* = 4.2, 6.8 Hz, 1H), 4.47 (dd, *J* = 3.9, 6.8 Hz, 1H), 5.09-5.18 (m, 2H), 5.70-5.91 (m, 1H) ; ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.7 (q), 25.3 (q), 27.2 (q), 37.6 (t), 64.2 (t), 81.5 (d), 81.7 (d), 83.5 (d), 83.7 (d), 114.5 (s), 117.8 (t), 133.1 (d), 170.5 (s) ppm; HRMS (ESI+) calcd for $C_{13}H_{20}O_5Na$ 279.1203; Found 279.1202.

***Acetate* (31):**



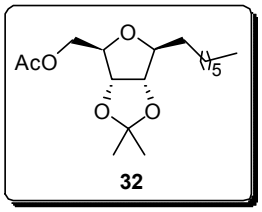
At 0 °C, $NaIO_4$ (13.4 g, 62.4 mmol) was added to a solution of alkene **28** (4 g, 15.6 mmol), 2,6-lutidine (3.62 mL, 31.2 mmol) and OsO_4 (6.24 ml 50 mM in toluene, 0.312 mmol) in 1,4-dioxane-water mixture (3:1, 100 mL) and the stirring was continued for 5 h at rt. After completion of the reaction, the reaction mixture was quenched with water and aqueous layer extracted with CH_2Cl_2 (2×100 mL). The combined organic layer was washed with water (100 mL), dried (Na_2SO_4) and concentrated the resulting crude lactol was used directly for next step.

To a solution of pentyltriphenylphosphorane ylide [generated by the action of *n*–butyl lithium (11.6 mL, 18.6 mmol) with $Ph_3P^+C_5H_{11}Br^-$ (8.86 g, 21.5 mmol) in anhydrous THF (100 mL) at 0 °C] was added to above crude aldehyde (3.70 g, 14.33 mmol) in THF (10 mL) at 0 °C and stirring was continued at rt for 20 h. The reaction mixture was quenched with saturated ammonium chloride (50 mL) and filtered. The organic layer was separated and aqueous layer extracted with EtOAc (3×75 mL). The combined organic layer was washed with brine (100 mL), dried over sodium sulphate and concentrated. The purification of residue by silica gel column chromatography (15→20% EtOAc in pet ether) gave **31** (3.4 g, 73%) as yellow oil.

$[\alpha]_D^{25}$ 17.2.0 (*c* 0.9, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.90 (t, *J* = 7.2 Hz, 3H), 1.26-1.41 (m, 4H), 1.34 (s, 3H), 1.54 (s, 3H), 2.00-2.09 (m, 2H), 2.10 (s, 3H), 2.20-2.47 (m, 2H), 3.97 (dt, *J* = 4.4, 10.7 Hz, 1H), 4.05-4.15 (m, 2H), 4.23-4.31 (m, 2H), 4.37 (dd, *J* = 4.4, 6.7 Hz, 1H), 4.49 (dd, *J* = 4.2, 6.8 Hz, 1H), 5.33-5.46 (m, 1H), 5.49-5.62 (m, 1H) ; ^{13}C NMR (50 MHz, $CDCl_3$): δ 13.9 (q), 20.8 (q), 22.3 (t), 25.4 (q), 27.1 (t), 27.3 (q), 31.2 (t), 31.6 (t), 64.4 (t), 81.5 (d), 81.9 (d),

84.1 (d), 84.2 (d), 114.6 (s), 123.4 (d), 133.1 (d), 170.7 (s) ppm; HRMS (ESI+) calcd for $C_{17}H_{28}O_5Na$ 335.1829; Found 335.1814.

***Acetate* (32):**

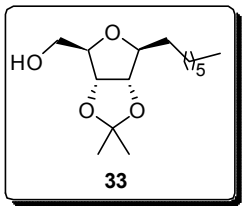


32

To a solution of **31** (3 g, 10.5 mmol) in MeOH (20 mL) was added 10% Pd/C (Catalytic) and the reaction mixture was stirred at rt under H_2 atmosphere (baloon) for 12 h. After disappearance of starting material on TLC, reaction mixture was filtered through Celite pad and the Celite pad was washed repeatedly with methanol. Combined filtrate was evaporated under reduced pressure to afford acetate derivative **32** (3 g, 98%) as yellow syrup.

$[\alpha]_D^{25}$ −5.6 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.88 (t, *J* = 6.8 Hz, 3H), 1.24-1.32 (m, 8H), 1.34 (s, 3H), 1.38-1.45 (m, 2H), 1.53 (s, 3H), 1.55-1.69 (m, 2H), 2.09 (s, 3H), 3.88 (dt, *J* = 4.5, 11.2 Hz, 1H), 4.05-4.13 (m, 2H), 4.26 (dd, *J* = 3.3, 10.9 Hz, 1H), 4.32 (dd, *J* = 4.5, 6.8 Hz, 1H), 4.48 (dd, *J* = 4.2, 6.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.0 (q), 20.8 (q), 22.6 (t), 25.3 (t), 25.5 (q), 27.4 (q), 29.1 (t), 29.5 (t), 31.7 (t), 33.7 (t), 64.5 (t), 81.5 (d), 82.0 (d), 84.7 (d), 84.8 (d), 114.6 (s), 170.7 (s) ppm; HRMS (ESI+) calcd for $C_{17}H_{30}O_5Na$ 337.1985; Found 337.1981.

***Alcohol* (33):**

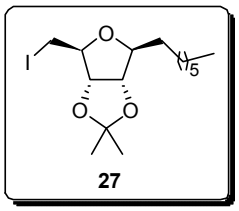


33

To a solution of acetate derivative **32** (2 g, 6.4 mmol) in Methanol (20 mL) was added NaOMe (70 mg, 1.3 mmol) and the suspension was stirred at rt for 2 h. After completion of reaction, reaction mixture was directly concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (25→30% EtOAc in petroleum ether) to afford the alcohol **33** (1.5 g, 85%) as a light yellow oil.

$[\alpha]_D^{25}$ −23.9 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.86 (t, *J* = 6.6 Hz, 3H), 1.22-1.30 (m, 8H), 1.32 (s, 3H), 1.34-1.41 (m, 2H), 1.51 (s, 3H), 1.54-1.60 (m, 2H), 3.64 (dd, *J* = 4.3, 11.7 Hz, 1H), 3.79 (dd, *J* = 3.4, 12.1 Hz, 1H), 3.83 (dd, *J* = 6.7, 11.9 Hz, 1H), 4.93 (q, *J* = 4.3 Hz, 1H), 4.25 (dd, *J* = 5.0, 7.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.0 (q), 22.6 (t), 25.4 (q), 25.5 (t), 27.3 (q), 29.1 (t), 29.5 (t), 31.7 (t), 33.6 (t), 62.7 (t), 81.3 (d), 83.9 (d), 84.5 (d), 85.0 (d), 114.6 (s) ppm; HRMS (ESI+) calcd for $C_{15}H_{28}O_4Na$ 295.1880; Found 295.1876.

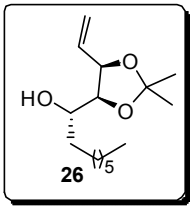
***Iodo* (27):**



To a solution of alcohol derivative **33** (1.4 g, 5.14 mmol) in CH_2Cl_2 (20 mL) was added imidazole (1.05 g, 15.42 mmol), PPh_3 (1.75 g, 6.68 mmol) and iodine (1.7 g, 6.68 mmol) and the suspension was stirred at rt for 12 h. The reaction mixture was quenched with water (25 mL) and filtered. The organic layer was separated and aqueous layer extracted with CH_2Cl_2 (3×25 mL). The combined organic layer was washed with brine (20 mL), dried over sodium sulphate and concentrated. The purification of residue by silica gel column chromatography (7→10% EtOAc in pet ether) gave **27** (1.73 g, 88%) as yellow oil.

$[\alpha]_D^{25}$ −33.1 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.88 (t, *J* = 6.8 Hz, 3H), 1.28-1.30 (m, 8H), 1.35 (s, 3H), 1.38-1.47 (m, 2H), 1.54 (s, 3H), 1.57-1.69 (m, 2H), 3.26-3.34 (m, 2H), 3.88 (dd, *J* = 4.8, 9.6 Hz, 1H), 3.92 (dd, *J* = 6.4, 11.4 Hz, 1H), 4.36 (dd, *J* = 4.1, 6.7 Hz, 1H), 4.43 (dd, *J* = 4.0, 6.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ -7.3 (t), 14.1 (q), 22.6 (t), 25.4 (t), 25.5 (q), 27.3 (q), 29.1 (t), 29.5 (t), 31.7 (t), 33.8 (t), 82.4 (d), 84.8 (d), 85.0 (d), 85.2 (d), 114.6 (s) ppm; HRMS (ESI+) calcd for $C_{15}H_{28}O_3INa$ 383.1078; Found 383.1078.

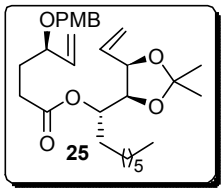
(*S*)-1-((4*S*,5*R*)-2,2-Dimethyl-5-vinyl-1,3-dioxolan-4-yl)octan-1-ol (26):



To a solution of iodo derivative **27** (1.7 g, 4.45 mmol) in ethanol (50 mL) was added activated zinc dust (1.45 g, 22.24 mmol) and the suspension was heated to reflux for 2 h. After cooling to rt the suspension was filtered through the pad of Celite and the filtrate was concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (12→14% EtOAc in petroleum ether) to afford the alcohol **26** (960 mg, 84%) as a light yellow oil.

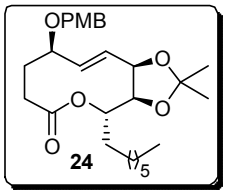
$[\alpha]_D^{25}$ −10.0 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.89 (t, *J* = 7.2 Hz, 3H), 1.28-1.35 (m, 8H), 1.38 (s, 3H), 1.40-1.47 (m, 1H), 1.48 (s, 3H), 1.51-1.83 (m, 1H), 1.68-1.75 (m, 2H), 3.66 (tt, *J* = 3.4, 8.4 Hz, 1H), 3.98 (dt, *J* = 0.9, 7.3 Hz, 1H), 4.65 (br t, *J* = 7.0 Hz, 1H), 5.32 (dd, *J* = 1.1, 10.5 Hz, 1H), 5.43 (dd, *J* = 1.1, 16.9 Hz, 1H), 6.00-6.09 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.1 (q), 22.6 (t), 25.2 (t), 25.3 (q), 27.8 (q), 29.3 (t), 29.6 (t), 31.8 (t), 33.7 (t), 70.0 (d), 78.9 (d), 80.7 (d), 108.7 (s), 118.5 (t), 134.7 (d) ppm; HRMS (ESI+) calcd for $C_{15}H_{28}O_3Na$ 279.1931; Found 279.1927.

(*S*)-1-((4*S*,5*R*)-2,2-Dimethyl-5-vinyl-1,3-dioxolan-4-yl)octyl (*R*)-4-((4-methoxybenzyl)oxy)hex-5-enoat (25):



To a solution of acid (*R*)-**7** (500 mg, 2.0 mmol) in dry THF (10 mL), 2,4,6-trichlorobenzyl chloride (0.37 mL, 2.40 mmol) followed by *N,N*-diisopropylethylamine (2 mL, 11.49 mmol) were added and the mixture was stirred for 2 h at ambient temperature. After completion of mixed anhydride formation as indicated by TLC, DMAP (488 mg, 4.0 mmol) and a solution of alcohol **26** (512 mg, 2.0 mmol) in THF (5 mL) was introduced and the contents were stirred for 16 h at rt. The reaction mixture was quenched with cold water and extracted with ethyl acetate. The combined organic phase was washed with aq. $NaHCO_3$ solution and water, dried (Na_2SO_4) and evaporated under reduced pressure. The crude product was purified by silica gel column chromatography (8→10% EtOAc in petroleum ether) to procure diene **25** (810 mg, 83%) as a light yellow oil. $[\alpha]_D^{25}$ −40.2 (*c* 1.7, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.88 (t, *J* = 7.1 Hz, 3H), 1.26-1.31 (m, 10H), 1.37 (s, 3H), 1.48 (s, 3H), 1.62-1.77 (m, 2H), 1.80-1.96 (m, 2H), 2.25-2.44 (m, 2H), 3.76 (dd, *J* = 7.4, 13.3 Hz 1H), 3.81 (s 3H), 4.17 (t, *J* = 6.8 Hz, 1H), 4.27 (d, *J* = 11.5 Hz, 1H), 4.52 (d, *J* = 11.4 Hz, 1H), 4.59 (t, *J* = 7.1 Hz, 1H), 4.90 (dt, *J* = 3.4, 7.6 Hz, 1H), 5.19-5.34 (m, 4H), 5.68-5.84 (m, 2H), 6.88 (d, *J* = 8.5 Hz, 2H), 7.25 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.1 (q), 22.6 (t), 24.6 (t), 25.2 (q), 27.5 (q), 29.2 (t), 29.5 (t), 30.4 (t, 2C), 31.2 (t), 31.8 (t), 55.3 (q), 69.8 (t), 71.9 (d), 78.4 (d), 78.8 (d), 79.1 (d), 108.8 (s), 113.7 (d, 2C), 117.7 (t), 118.4 (t), 129.3 (d, 2C), 130.6 (s), 133.2 (d), 138.3 (d), 159.1 (s), 172.5 (s) ppm; HRMS (ESI+) calcd for $C_{29}H_{44}O_6Na$ 511.3030; Found 511.3030.

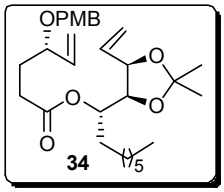
(3a*S*,4*S*,9*R*,11a*R*,*E*)-4-Heptyl-9-((4-methoxybenzyl)oxy)-2,2-dimethyl-3a,4,7,8,9,11a-hexahydro-6H-[1,3]dioxolo[4,5-c]oxecin-6-one (24):



To a solution of diene **25** (100 mg, 0.20 mmol) in dry toluene (25 mL), 2nd gen. Grubbs' catalyst (17 mg, 0.02 mmol) was added and the mixture was degassed under an argon atmosphere thoroughly. The reaction mixture was heated at 80 ˚C for 6 h and the solvent was removed under reduced pressure. The residue was purified by column chromatography (10 →12% EtOAc in petroleum ether) giving macrolide **24** (79 mg, 84%) as a colorless liquid.

$[\alpha]_D^{25}$ −82.0 (*c* 0.8, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.87 (t, *J* = 7.0 Hz, 3H), 1.25-1.33 (m, 10H), 1.41 (s, 3H), 1.45-1.50 (m, 1H), 1.57 (s, 3H), 1.79 (d, *J* = 7.5 Hz, 1H), 1.95-2.17 (m, 3H), 2.33 (dd, *J* = 6.6, 13.9 Hz, 1H), 3.81 (s, 3H), 3.84 (dd, *J* = 5.1, 9.5 Hz, 1H), 3.97 (dd, *J* = 4.4, 10.1 Hz, 1H), 4.29 (d, *J* = 11.4 Hz, 1H), 4.58 (d, *J* = 11.6 Hz 1H), 4.72-4.74 (m, 1H), 4.95 (br t, *J* = 9.3 Hz, 1H), 5.68 (dd, *J* = 8.8, 15.9 Hz, 1H), 5.85 (dd, *J* = 3.0, 15.9 Hz, 1H), 6.87 (d, *J* = 6.8 Hz, 2H), 7.25 (d, *J* = 7.1 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.1 (q), 22.6 (t), 24.5 (t), 26.3 (q), 28.5 (q), 29.1 (t), 29.4 (t), 31.4 (t), 31.8 (t, 2C), 32.0 (t), 55.3 (q), 69.8 (t), 70.8 (d), 75.9 (d), 78.5 (d), 81.6 (d), 109.3 (s), 113.7 (d, 2C), 127.4 (d), 128.7 (d), 129.3 (d, 2C), 130.5 (s), 159.1 (s), 174.9 (s) ppm; HRMS (ESI+) calcd for $C_{27}H_{40}O_6Na$ 483.2717; Found 483.2695.

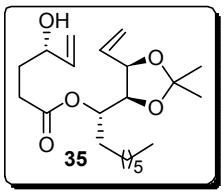
(S)-1-((4*S*,5*R*)-2,2-Dimethyl-5-vinyl-1,3-dioxolan-4-yl)octyl (*S*)-4-((4-methoxybenzyl)oxy)hex-5-enoate (34):



A solution of the acid (*S*)-**7** (600 mg, 2.4 mmol)**,** *N,N*-diisopropylethylamine (2.40 mL, 13.78 mmol) and 2,4,6-trichlorobenzyl chloride (0.45 mL, 2.88 mmol) in THF (10 mL) was stirred at room temperature for 2 h. After completion of mixed anhydride formation as indicated by TLC, DMAP (585 mg, 4.8 mmol) and a solution of alcohol **26** (614 mg, 2.4 mmol) in THF (5 mL) was introduced and the reaction mixture was stirred for 16 h at rt. The reaction mixture was quenched with cold water and extracted with ethyl acetate. The combined organic phase was washed with aq. $NaHCO_3$ solution and water, dried (Na_2SO_4) and evaporated under reduced pressure. The crude product was purified by silica gel column chromatography (8→10% EtOAc in petroleum ether) to procure diene **34** (952 mg, 81%) as a light yellow oil.

$[\alpha]_D^{25}$ −22.4 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.87 (t, *J* = 7.3 Hz, 3H), 1.25-1.27 (m, 10H), 1.37 (s, 3H), 1.48 (s, 3H), 1.52-1.72 (m, 2H), 1.80-1.91 (m, 2H), 2.32-2.37 (m, 2H), 3.76 (dd, *J* = 6.9, 13.5 Hz 1H), 3.81 (s 3H), 4.17 (t, *J* = 7.2 Hz, 1H), 4.27 (d, *J* = 11.4 Hz, 1H), 4.51 (d, *J* = 11.4 Hz, 1H), 4.59 (t, *J* = 6.7 Hz, 1H), 4.90 (dt, *J* = 3.5, 7.9 Hz, 1H), 5.19-5.34 (m, 4H), 5.68-5.83 (m, 2H), 6.88 (d, *J* = 8.3 Hz, 2H), 7.24 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.1 (q), 22.6 (t), 24.6 (t), 25.2 (q), 27.5 (q), 29.2 (t), 29.5 (t), 30.4 (t, 2C), 31.2 (t), 31.8 (t), 55.2 (q), 69.8 (t), 71.9 (d), 78.4 (d), 78.8 (d), 79.1 (d), 108.7 (s), 113.7 (d, 2C), 117.7 (t), 118.4 (t), 129.3 (d, 2C), 130.5 (s), 133.2 (d), 138.3 (d), 159.1 (s), 172.5 (s) ppm; HRMS (ESI+) calcd for $C_{29}H_{44}O_6Na$ 511.3030; Found 511.3022.

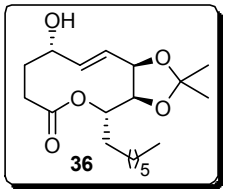
(*S*)-1-((4*S*,5*R*)-2,2-Dimethyl-5-vinyl-1,3-dioxolan-4-yl)octyl (*S*)-4-hydroxyhex-5-enoate (35):



A solution of **34** (400 mg, 0.82 mmol) and DDQ (538 mg, 2.37 mmol) in CH_2Cl_2-water (10 mL, 18:1) was stirred for 2 h at room temperature. To this was added aqueous sodium bicarbonate solution, and the contents were partitioned between water and CH_2Cl_2. The aqueous layer was extracted with CH_2Cl_2, and the combined organic layer was dried over Na_2SO_4 and concentrated. The residue was purified by silica gel chromatography (28 →30% EtOAc in petroleum ether) to give compoumd **35** (240 mg, 80%) as a yellow oil.

$[\alpha]_D^{25}$ −8.6 (*c* 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.88 (t, *J* = 7.1 Hz, 3H), 1.25-1.28 (m, 10H), 1.37 (s, 3H), 1.48 (s, 3H), 1.56-1.71 (m, 2H), 1.75-1.93 (m, 2H), 2.32-2.43 (m, 2H), 4.13-4.17 (m, 1H), 4.19 (t, *J* = 6.7 Hz, 1H), 4.61 (t, *J* = 6.9 Hz, 1H), 4.92 (dt, *J* = 3.4, 7.7 Hz, 1H), 5.13-5.36 (m, 4H), 5.76-5.90 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.1 (q), 22.6 (t), 24.6 (t), 25.2 (q), 27.5 (q), 29.1 (t), 29.5 (t), 30.3 (t), 31.1 (t), 31.5 (t), 31.8 (t), 72.1 (d, 2C), 78.3 (d), 78.8 (d), 108.8 (s), 115.1 (t), 118.5 (t), 133.2 (d), 140.3 (d), 172.9 (s) ppm; HRMS (ESI+) calcd for $C_{21}H_{36}O_5Na$ 391.2455; Found 391.2446.

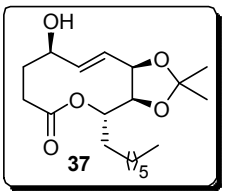
(3a*S*,4*S*,9*S*,11a*R*,*E*)-4-Heptyl-9-hydroxy-2,2-dimethyl-3a,4,7,8,9,11a-hexahydro-6H-[1,3]dioxolo[4,5-c]oxecin-6-one (36):



A degassed solution of **35** (0.050 mg, 0.13 mmol) and Grubbs' second-generation catalyst (28 mg, 0.03 mmol) in dry 1,2-dichloroethane (20 mL) was heated under reflux under argon for 24 h. After completion of reaction as indicated by TLC, the solvent was removed under reduced pressure. The residue was purified by column chromatography (32 →34% EtOAc in petroleum ether) giving macrolide **36** (22 mg, 48%) as a colorless liquid.

$[\alpha]_D^{25}$ −1.4 (*c* 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.88 (t, *J* = 6.8 Hz, 3H), 1.25-1.33 (m, 10H), 1.38 (s, 3H), 1.47 (s, 3H), 1.54-1.56 (m, 1H), 1.75-1.83 (m, 3H), 2.33-2.50 (m, 2H), 4.14 (dd, *J* = 6.1, 9.7 Hz, 1H), 4.16-4.20 (m, 1H), 4.62 (t, *J* = 6.4 Hz, 1H), 4.90-4.95 (m, 1H), 5.66 (dd, *J* = 6.9, 15.5 Hz, 1H), 5.81 (dd, *J* = 6.3, 15.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.1 (q), 22.6 (t), 24.1 (t), 25.4 (q), 27.9 (q), 29.2 (t), 29.6 (t), 29.7 (t), 30.7 (t), 31.8 (t), 31.9 (t), 70.4 (d), 71.1 (d), 77.8 (2C, d), 108.7 (s), 125.7 (d), 135.6 (d), 172.2 (s) ppm; HRMS (ESI+) calcd for $C_{19}H_{32}O_5Na$ 363.2142; Found 363.2136.

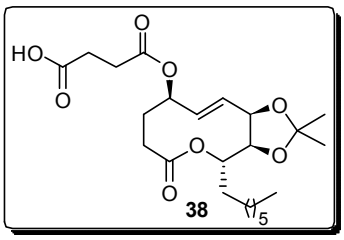
(3a*S*,4S,9*R*,11a*R*,*E*)-4-Heptyl-9-hydroxy-2,2-dimethyl-3a,4,7,8,9,11a-hexahydro-6H-[1,3]dioxolo[4,5-c]oxecin-6-one (37)



To a solution of compound **24** (200 mg, 0.434 mmol) in CH_2Cl_2–H_2O (10 mL, 18 : 1), DDQ (285 mg, 1.26 mmol) was added and stirred for 2 h at rt. The reaction mixture was quenched with aqueous $NaHCO_3$ solution and partitioned between water and CH_2Cl_2. The aqueous layer was extracted with CH_2Cl_2 and the combined organic layer was dried (Na_2SO_4) and concentrated. The residue was purified by silica gel chromatography (30 →32% EtOAc in petroleum ether) to procure compoumd **37** (117 mg, 79%) as a colorless oil.

$[\alpha]_D^{25}$ −72.8 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.88 (t, *J* = 7.1 Hz, 3H), 1.25-1.31 (m, 10H), 1.39 (s, 3H), 1.43-1.48 (m, 1H), 1.55 (s, 3H), 1.79 (dq, *J* = 2.7, 8.4 Hz, 1H), 2.02-2.09 (m, 3H), 2.33-2.37 (m, 1H), 3.97 (dd, *J* = 4.7, 10.0 Hz, 1H), 4.15-4.20 (m, 1H), 4.70 (br s, 1H), 4.93 (dt, *J* = 2.7, 9.8 Hz, 1H), 5.67 (ddd, *J* = 1.7, 8.7, 16.0 Hz, 1H), 5.83 (dd, *J* = 3.3, 15.9 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 14.1 (q), 22.6 (t), 24.5 (t), 26.2 (q), 28.4 (q), 29.1 (t), 29.4 (t), 31.2 (t), 31.8 (t), 32.0 (t), 33.6 (t), 71.0 (d), 75.5 (d), 75.8 (d), 78.6 (d), 109.4 (s), 126.7 (d), 128.1 (d), 174.9 (s) ppm; HRMS (ESI+) calcd for $C_{19}H_{32}O_5Na$ 363.2142; Found 363.2124.

4-(((3a*S*,4*S*,9*R*,11a*R*,*E*)-4-Heptyl-2,2-dimethyl-6-oxo-3a,6,7,8,9,11a-hexahydro-4H-[1,3]dioxolo[4,5-c]oxecin-9-yl)oxy)-4-oxobutanoic acid (38):

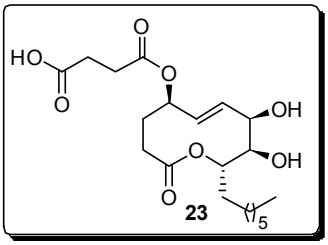


A solution of **37** (30 mg, 88.12 µmol), DMAP (10.8 mg, 88.12 µmol) in CH_2Cl_2 (3 ml) was treated with Succinic anhydride (17.3 mg, 176.2 µmol), and the contents were stirred at rt for 6 h. The reaction mixture was poured into a mixture of EtOAc and the phosphate buffer (pH 3.6) with vigorous stirring. The layers were separated, and the aqueous layer was extracted with EtOAc two times. The organic layer was dried (Na_2SO_4) and concentrated at reduced pressure. The residue was purified by column chromatography (3→4% MeOH in CH_2Cl_2) to afford **38** (29.5 mg, 76%) as a yellow oil.

$[\alpha]_D^{25}$ −73.6 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.87 (t, *J* = 7.0 Hz, 3H), 1.25-1.31 (m, 10H), 1.37 (s, 3H), 1.45-1.49 (m, 1H), 1.54 (s, 3H), 1.75-1.83 (m, 1H), 2.05-2.10 (m, 3H), 2.35-2.38 (m, 1H), 2.58-2.68 (m, 4H), 3.99 (dd, *J* = 4.7, 10.0 Hz, 1H), 4.68-4.70 (m, 1H), 4.92 (dt, *J* = 2.9, 9.3 Hz, 1H), 5.19-5.25 (m, 1H), 5.63 (ddd, *J* = 1.7, 8.9, 16.2 Hz, 1H), 5.92 (dd, *J* =

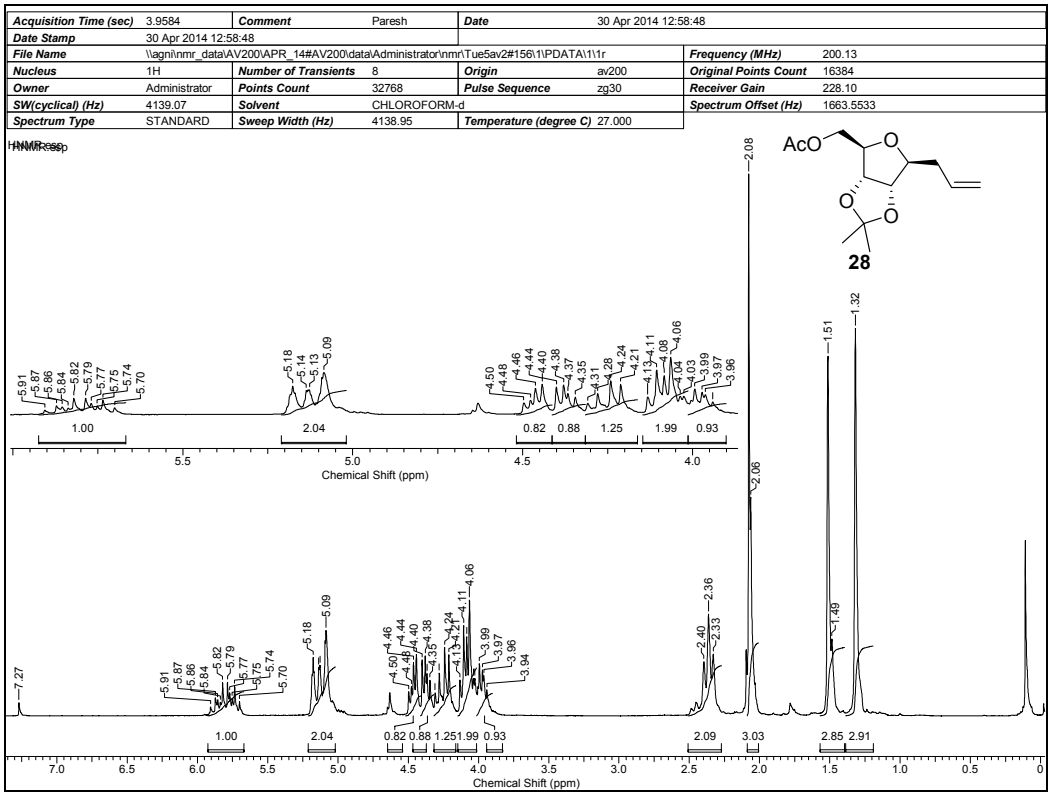
3.4, 15.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.1 (q), 22.6 (t), 24.5 (t), 26.2 (q), 28.4 (q), 28.5 (t), 29.0 (t), 29.1 (t), 29.4 (t), 30.6 (t), 30.9 (t), 31.8 (t), 31.9 (t), 71.1 (d), 75.5 (d), 77.2 (d), 78.5 (d), 109.4 (s), 123.8 (d), 128.3 (d), 170.6 (s), 171.3 (s), 174.7 (s) ppm; HRMS (ESI+) calcd for $C_{23}H_{36}O_8Na$ 463.2302; Found 463.2278.

Mangiferealactone (**23**):

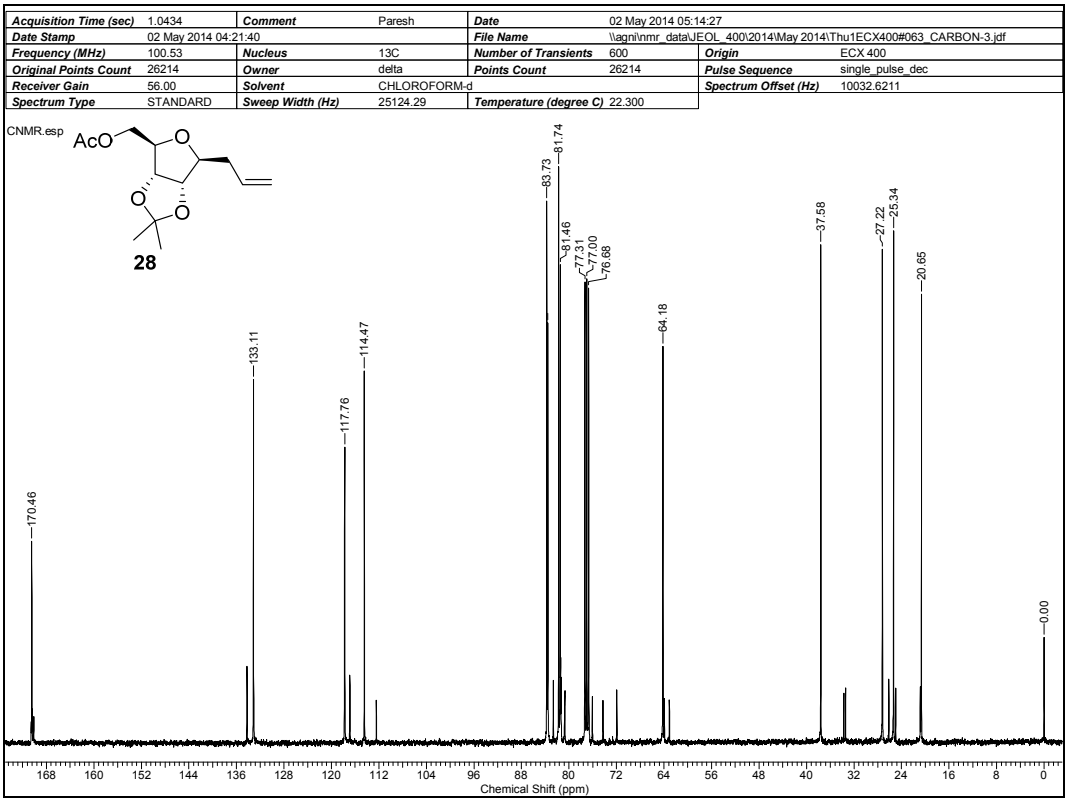


To an ice cooed solution of **38** (20 mg, 45.40 µmol) in dry CH_2Cl_2 (2 mL) was added TFA (10 µL) and stirred for 2h at rt. The reaction mixture was concentrated under reduced pressure, and the resulting residue was purified on silica gel column (8→10% MeOH in CH_2Cl_2) to furnish Mangiferaelactone (**23**) (13.5 mg, 74%) as a yellowish-cream solid. $[\alpha]_D^{25}$ −2.1 (*c* 1.0, MeOH); ^{1}H NMR (500 MHz, CD_3OD): δ 0.89 (t, *J* = 6.9 Hz, 3H), 1.25-1.36 (m, 10H), 1.47-1.49 (m, 1H), 1.82-1.87 (m, 1H), 1.91 (dt, *J* = 2.2, 13.2, 1H), 1.96-2.01 (m, 1H), 2.09 (dt, *J* = 1.9, 13.9 Hz, 1H), 2.32 (ddd, *J* = 2.2, 6.1, 13.9 Hz, 1H), 2.56 (s, 4H), 3.53 (dd, *J* = 2.4, 9.7 Hz, 1H), 4.40 (br d, *J* = 2.1 Hz, 1H), 5.13 (dt, *J* = 2.6, 9.5 Hz, 1H), 5.17 (dt, *J* = 4.7, 10.3 Hz, 1H), 5.49 (ddd, *J* = 2.2, 9.5, 15.5 Hz, 1H), 5.92 (dd, *J* = 2.1, 15.7 Hz, 1H); ^{13}C NMR (125 MHz, CD_3OD): δ 14.6 (q), 23.8 (t), 25.8 (t), 30.5 (t, 2C), 30.8 (t, 2C), 30.9 (t), 32.3 (t), 32.9 (t), 33.1 (t), 72.2 (d), 73.6 (d), 74.6 (d), 78.3 (d), 123.8 (d), 136.1 (d), 173.5 (s), 175.9 (s, 2C) ppm; HRMS (ESI+) calcd for $C_{20}H_{32}O_8Na$ 423.1989; Found 423.1983.

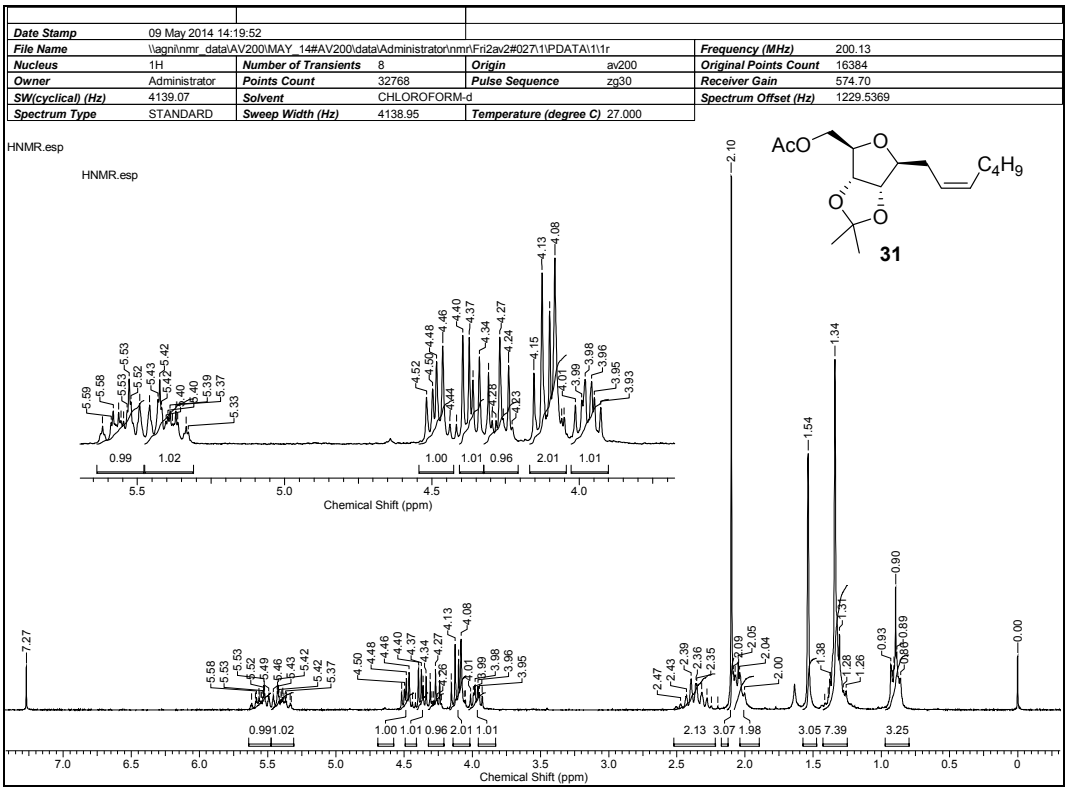
SPECTRA



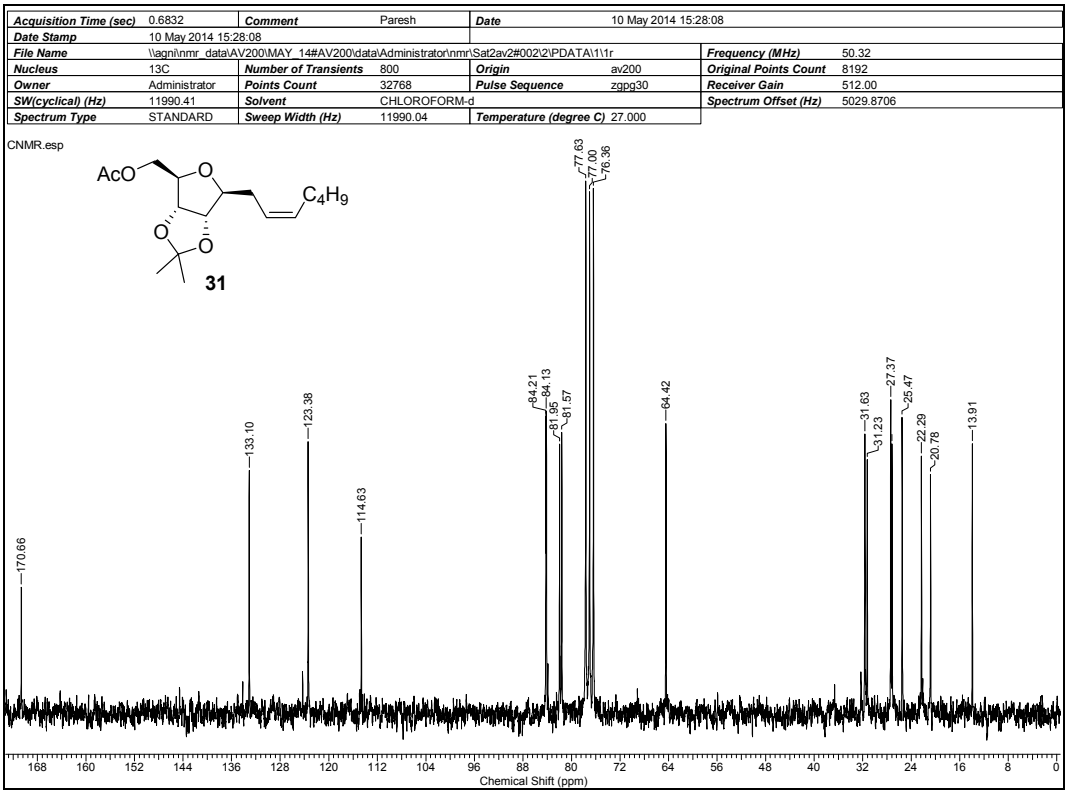
^{1}H NMR Spectrum of 28 in $CDCl_3$



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

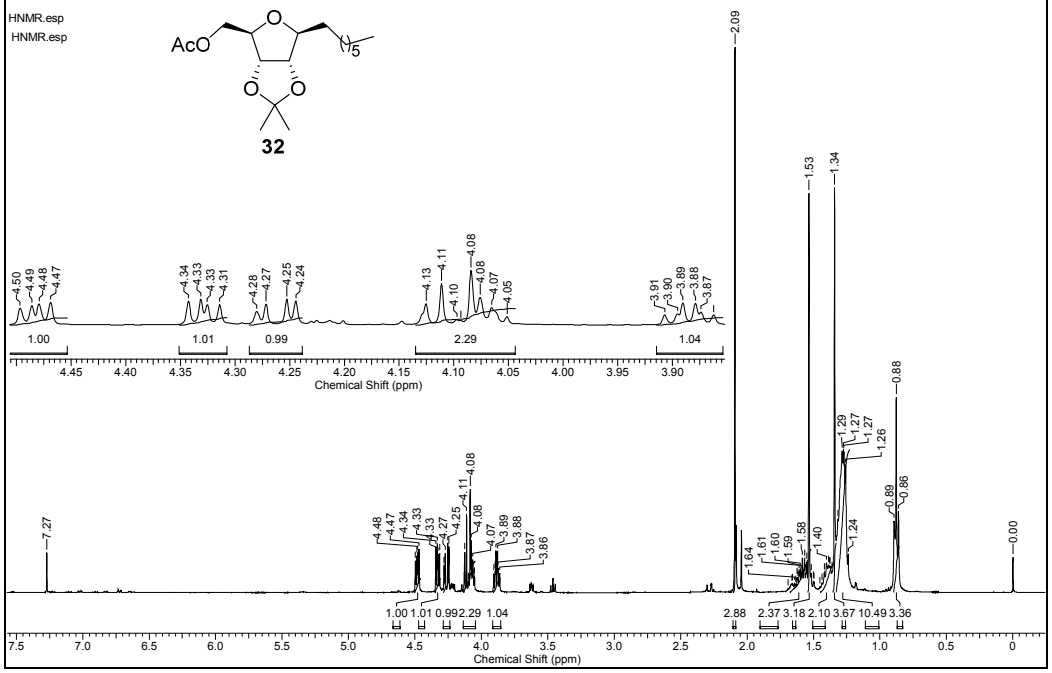


^{1}H NMR Spectrum of 31 in $CDCl_3$



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

Date Stamp	11 May 2014 10:20:56			***File Name***	\\agni\nmr_data\AV400\May_14_400\Sun3av400#002\1\PDATA\1\1r		
Frequency (MHz)	400.13	***Nucleus***	1H	***Number of Transients***	64	***Origin***	spect
Original Points Count	16384	***Owner***	Administrator	***Points Count***	32768	***Pulse Sequence***	zg30
Receiver Gain	114.00	***SW(cyclical) (Hz)***	8012.82	***Solvent***	CHLOROFORM-d		
Spectrum Offset (Hz)	2795.6045	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	8012.58	***Temperature (degree C)***	24.500



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

Acquisition Time (sec)	0.6488	***Comment***	13C	***Date***	11 May 2014 11:07:52		
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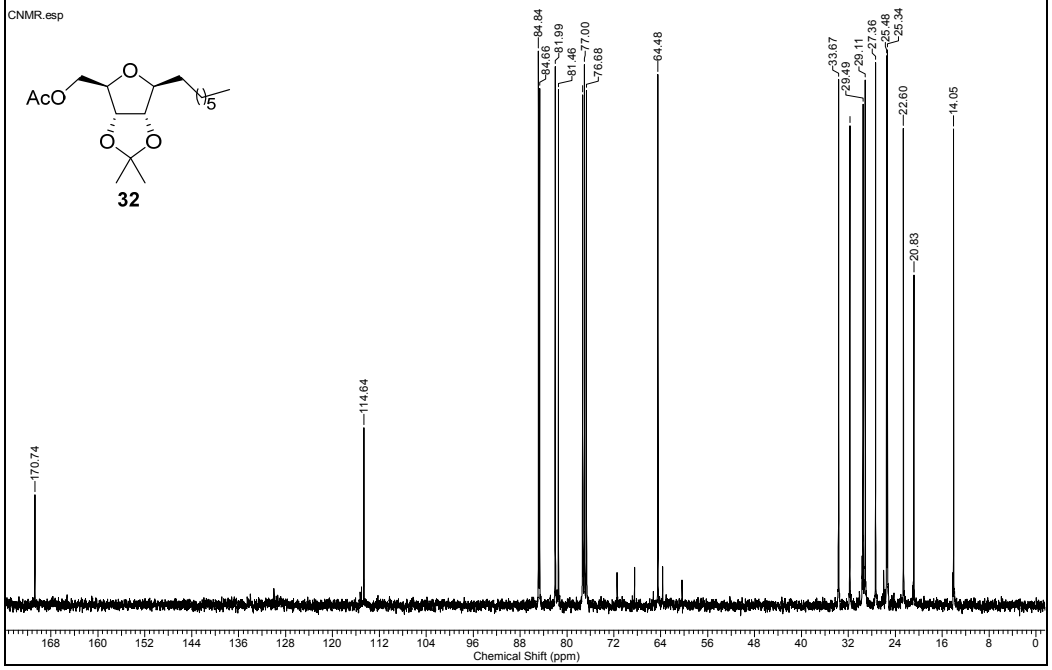
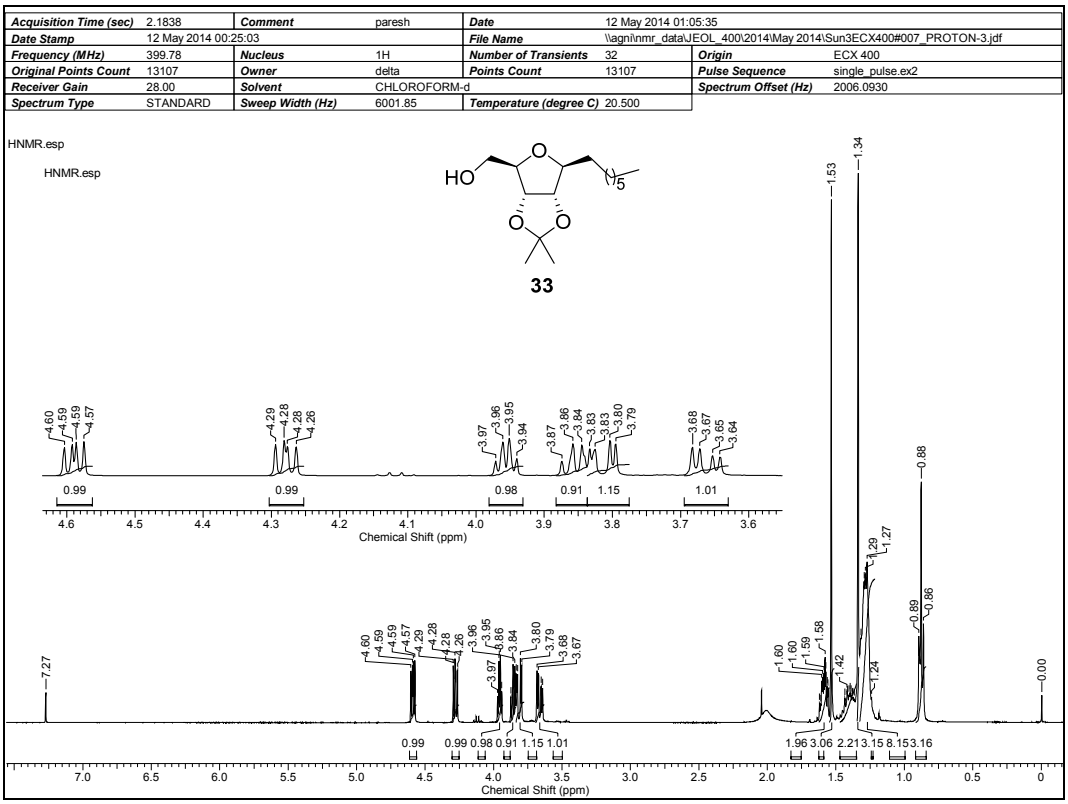
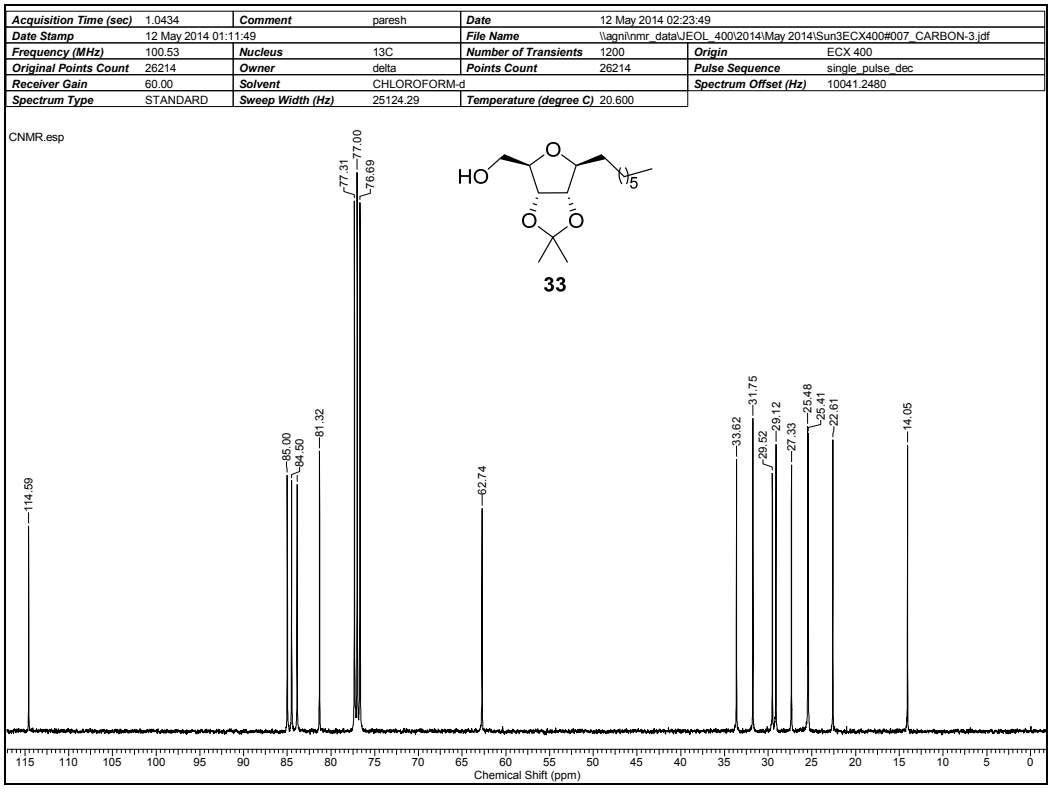
Frequency (MHz)	100.61	***Nucleus***	13C	***Number of Transients***	897	***Origin***	spect
Original Points Count	16384	***Owner***	root	***Points Count***	32768	***Pulse Sequence***	zgpg
Receiver Gain	2050.00	***SW(cyclical) (Hz)***	25252.53	***Solvent***	CHLOROFORM-d		
Spectrum Offset (Hz)	9634.8799	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	25251.75	***Temperature (degree C)***	25.100



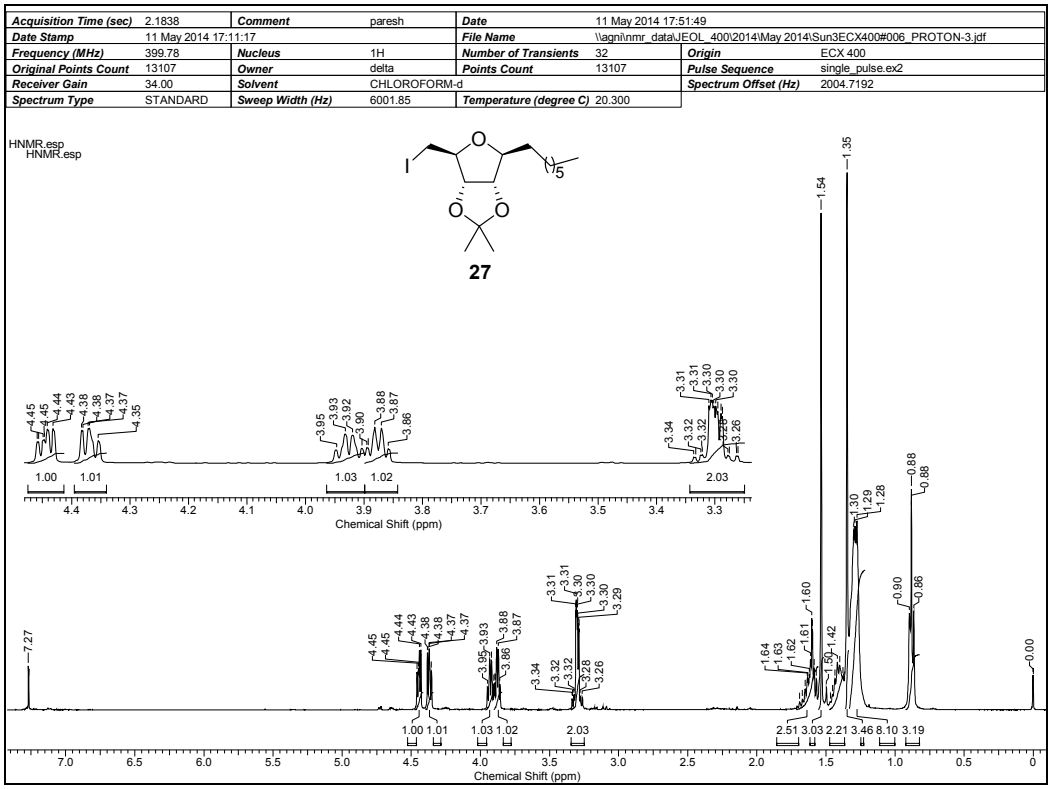
^{13}C NMR Spectrum of 32 in $CDCl_3$



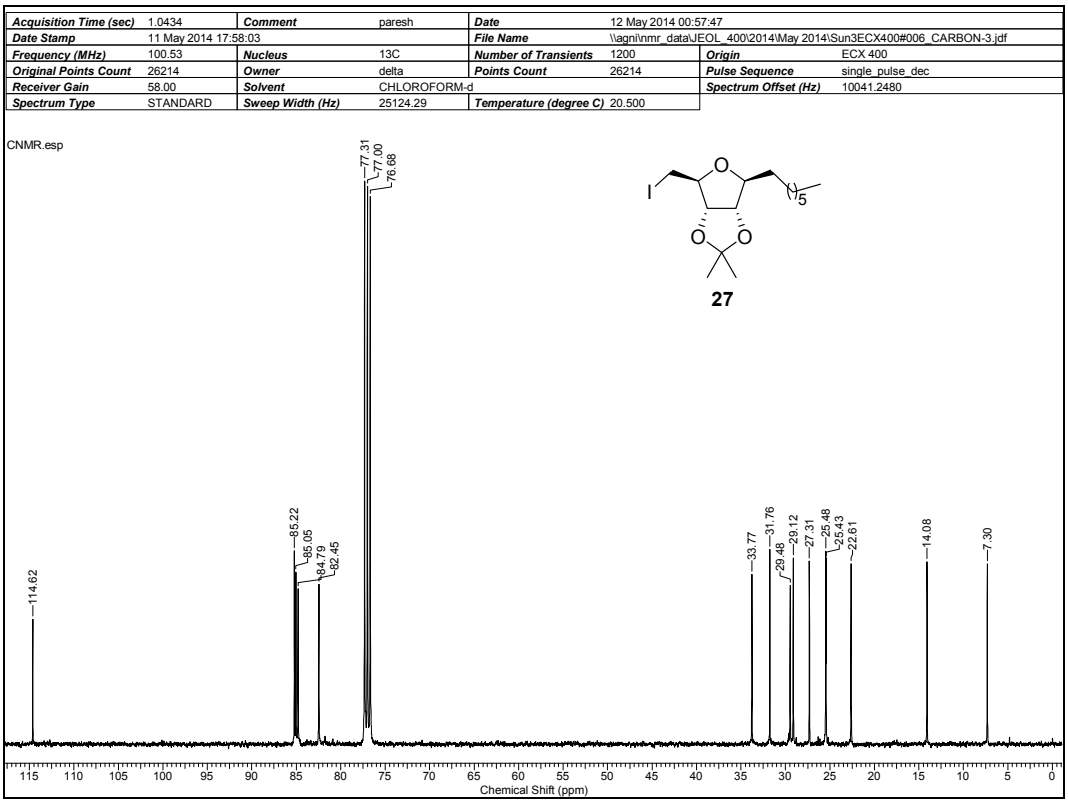
^{1}H NMR Spectrum of 33 in $CDCl_3$



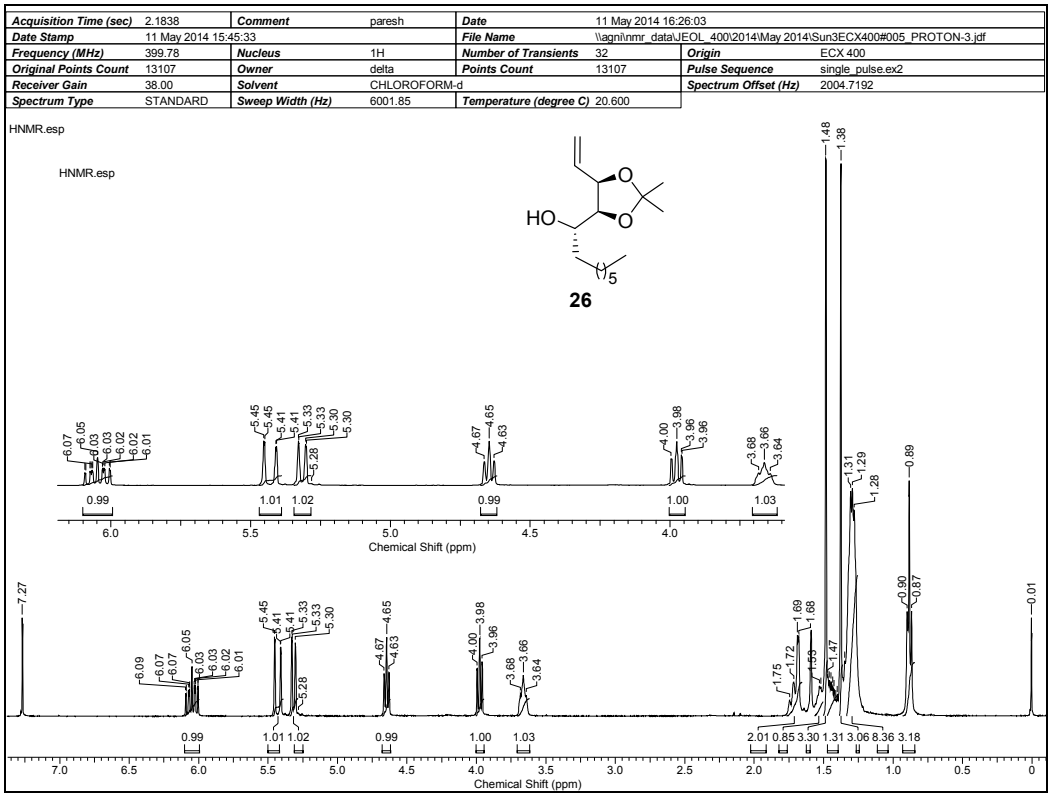
^{13}C NMR Spectrum of 33 in $CDCl_3$



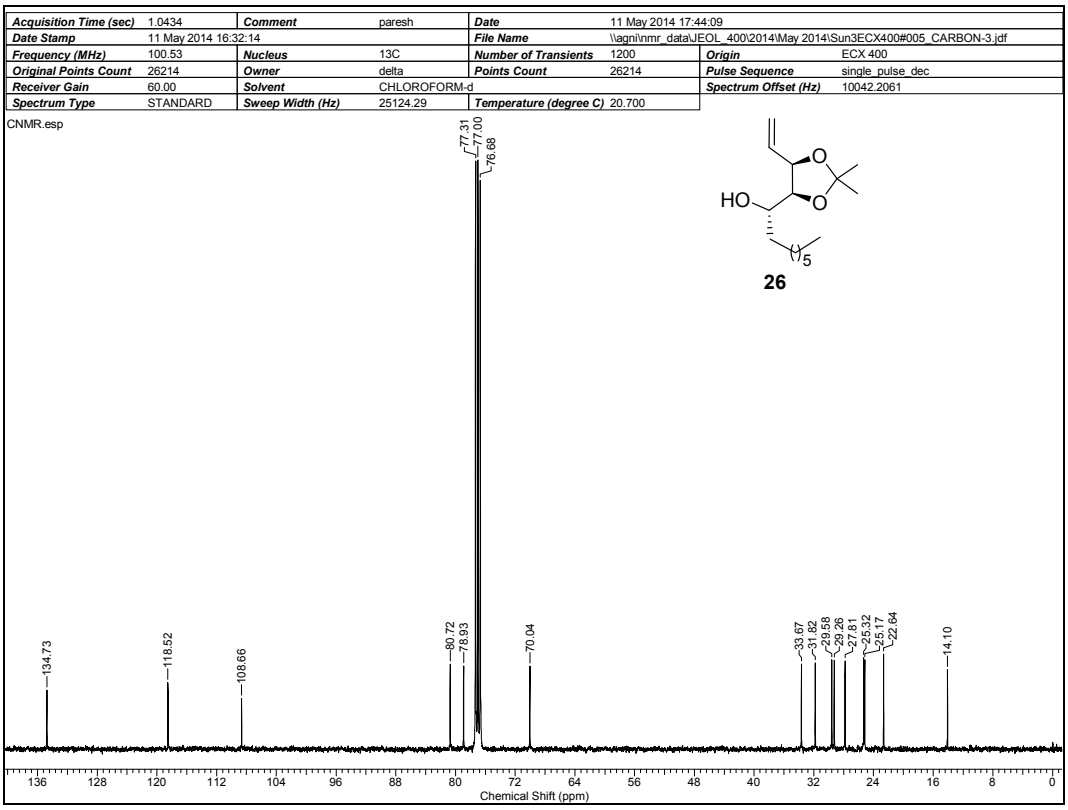
^{1}H NMR Spectrum of 27 in $CDCl_3$



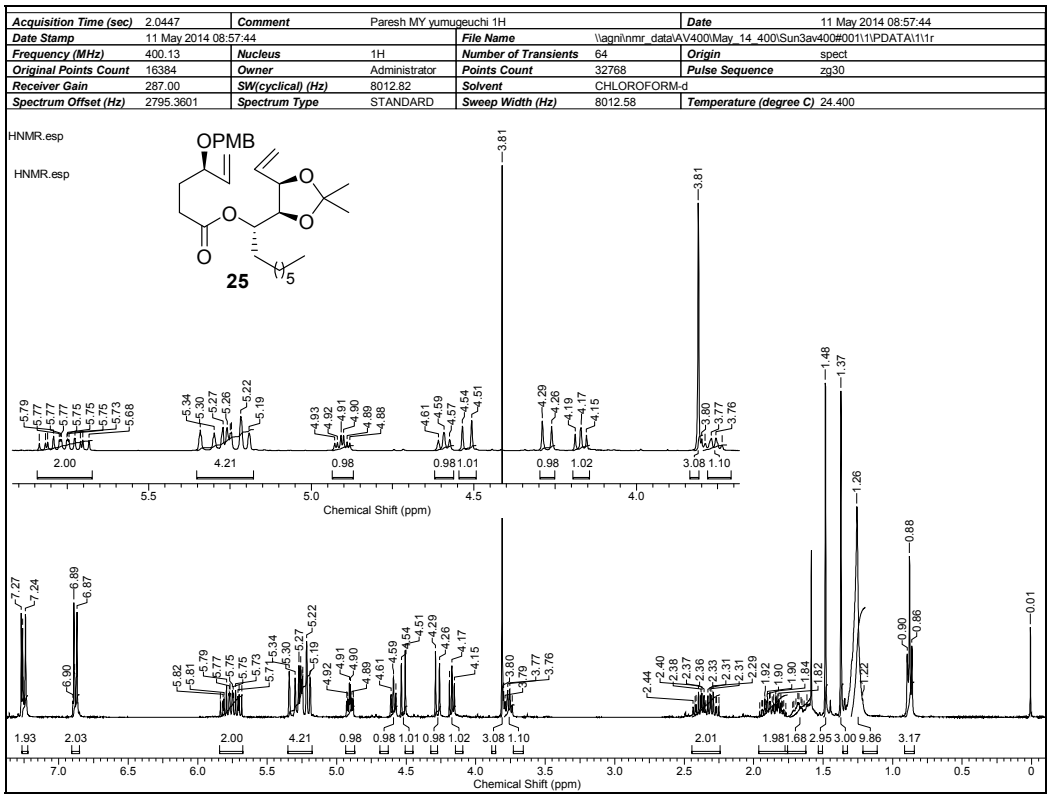
^{13}C NMR Spectrum of 27 in $CDCl_3$



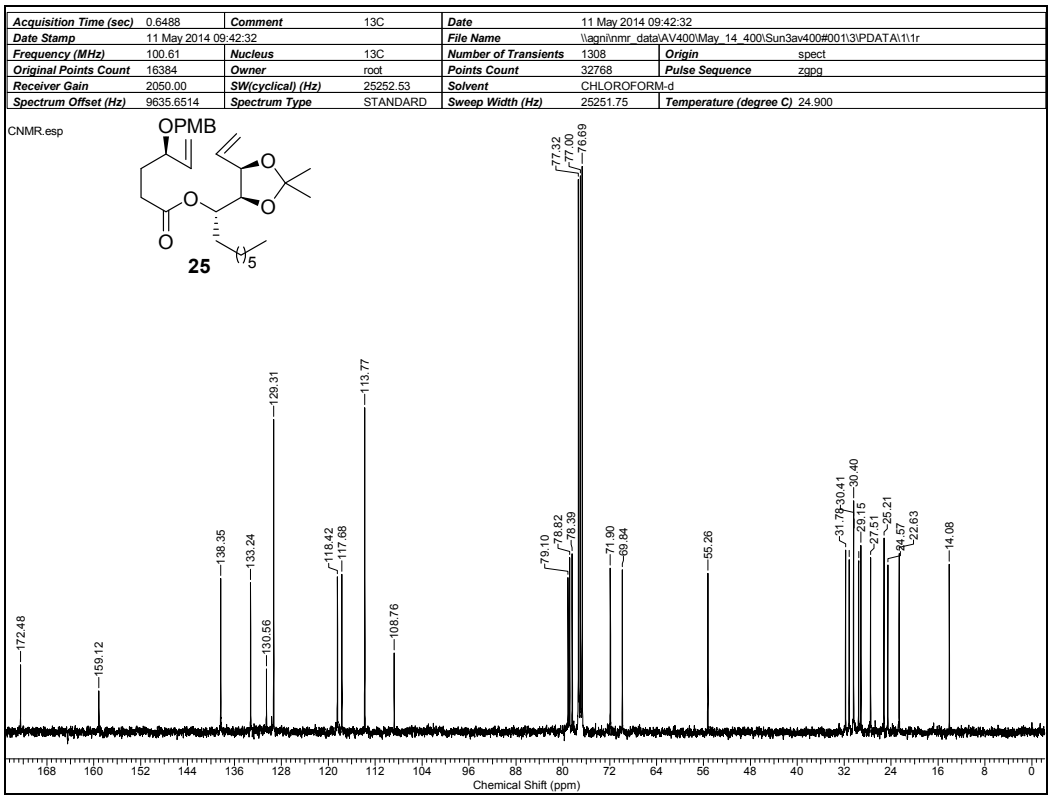
^{1}H NMR Spectrum of 26 in $CDCl_3$



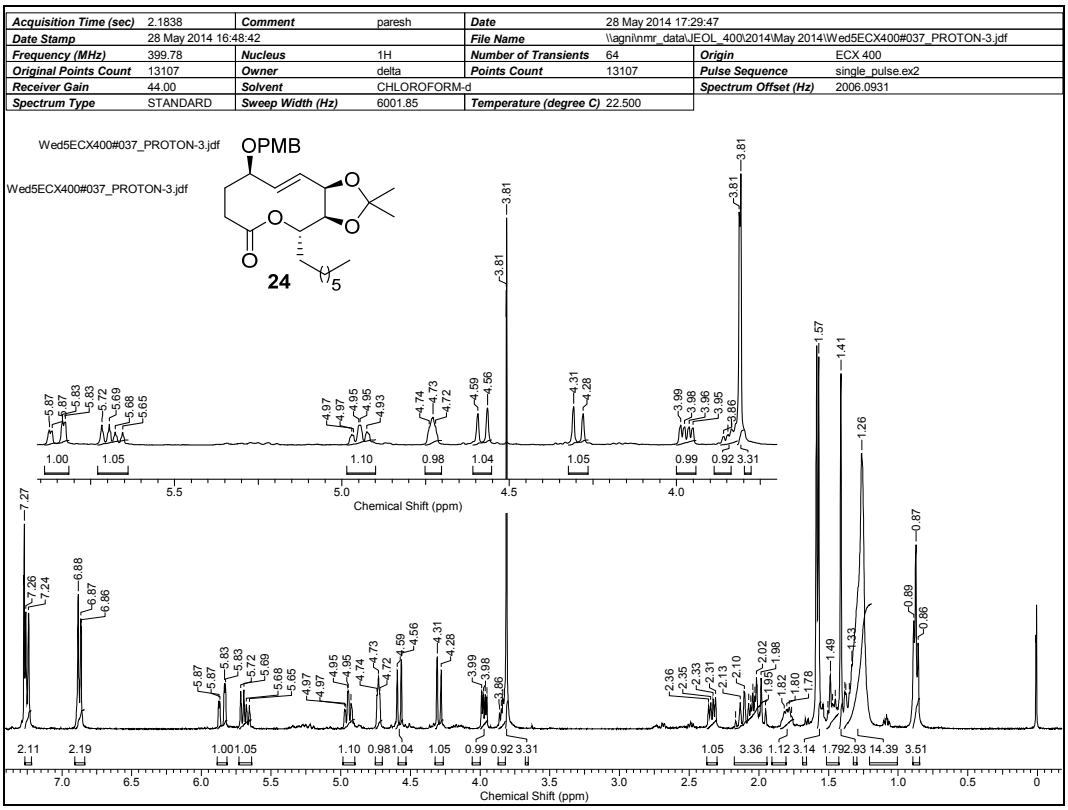
^{13}C NMR Spectrum of 26 in $CDCl_3$



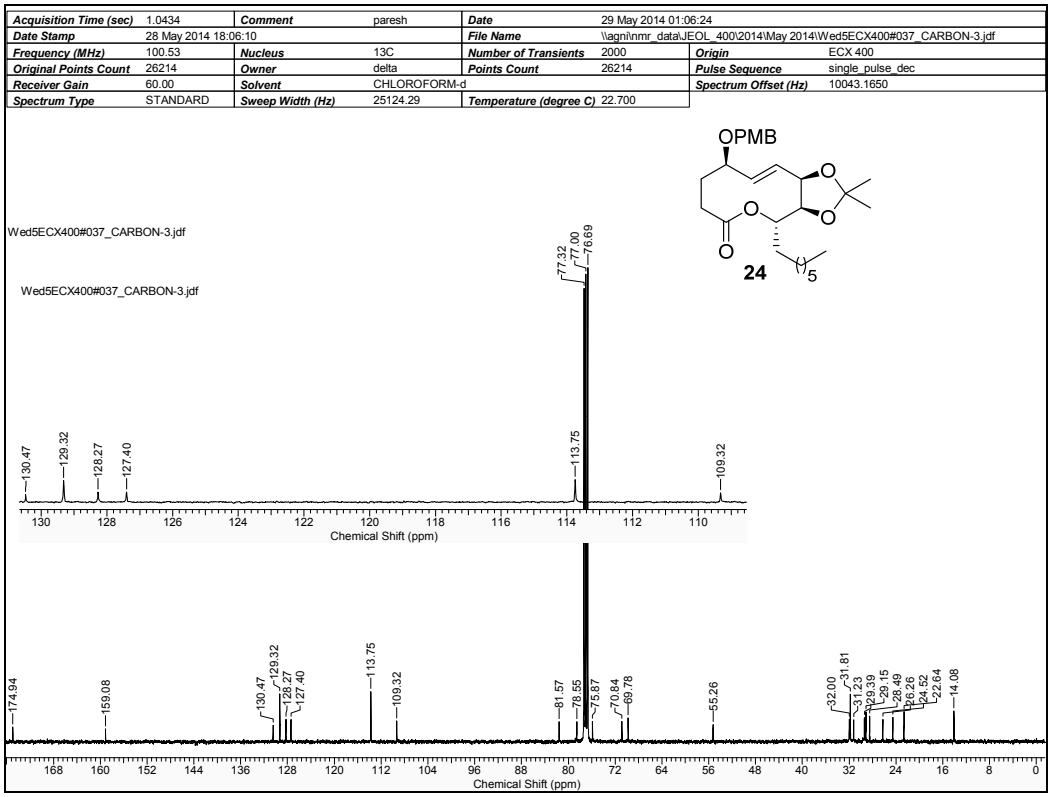
^{1}H NMR Spectrum of 25 in $CDCl_3$



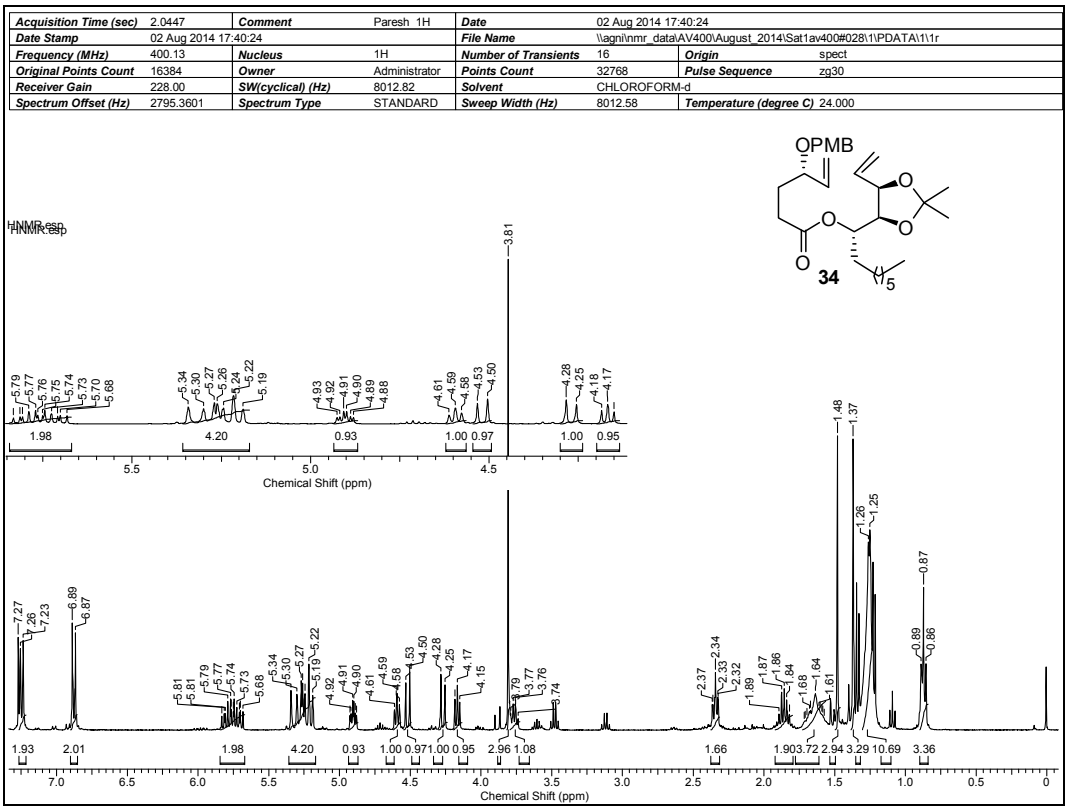
^{13}C NMR Spectrum of 25 in $CDCl_3$



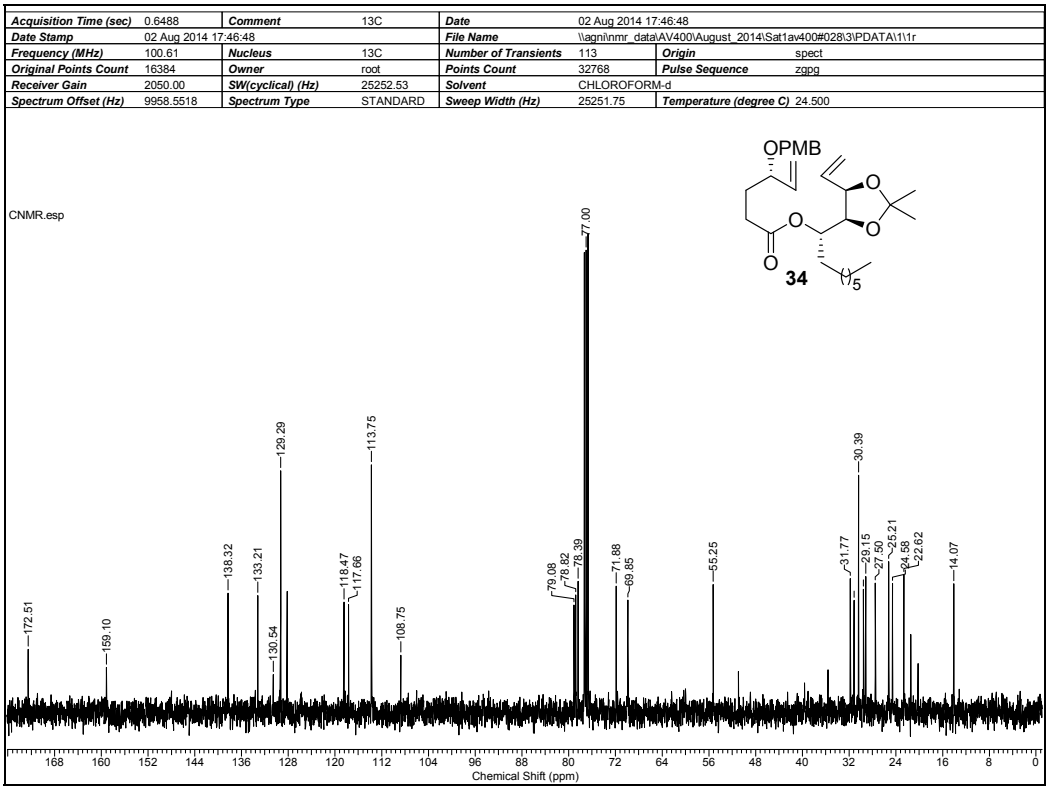
^{1}H NMR Spectrum of 24 in $CDCl_3$



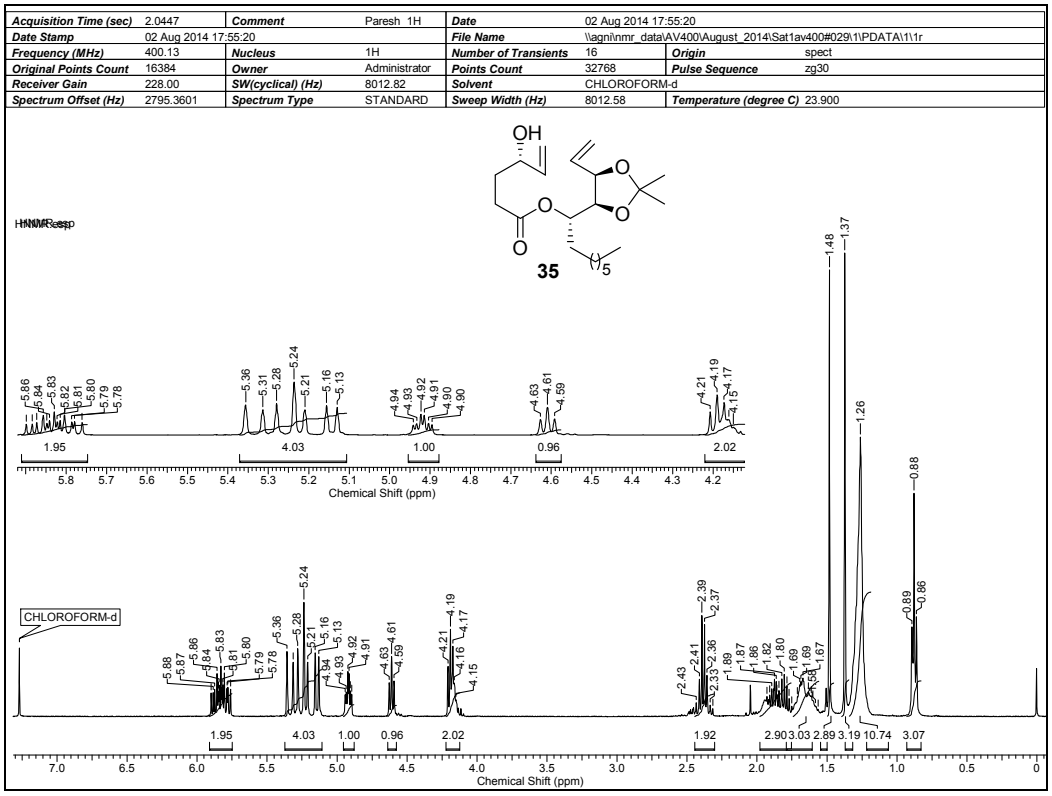
^{13}C NMR Spectrum of 24 in $CDCl_3$



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



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



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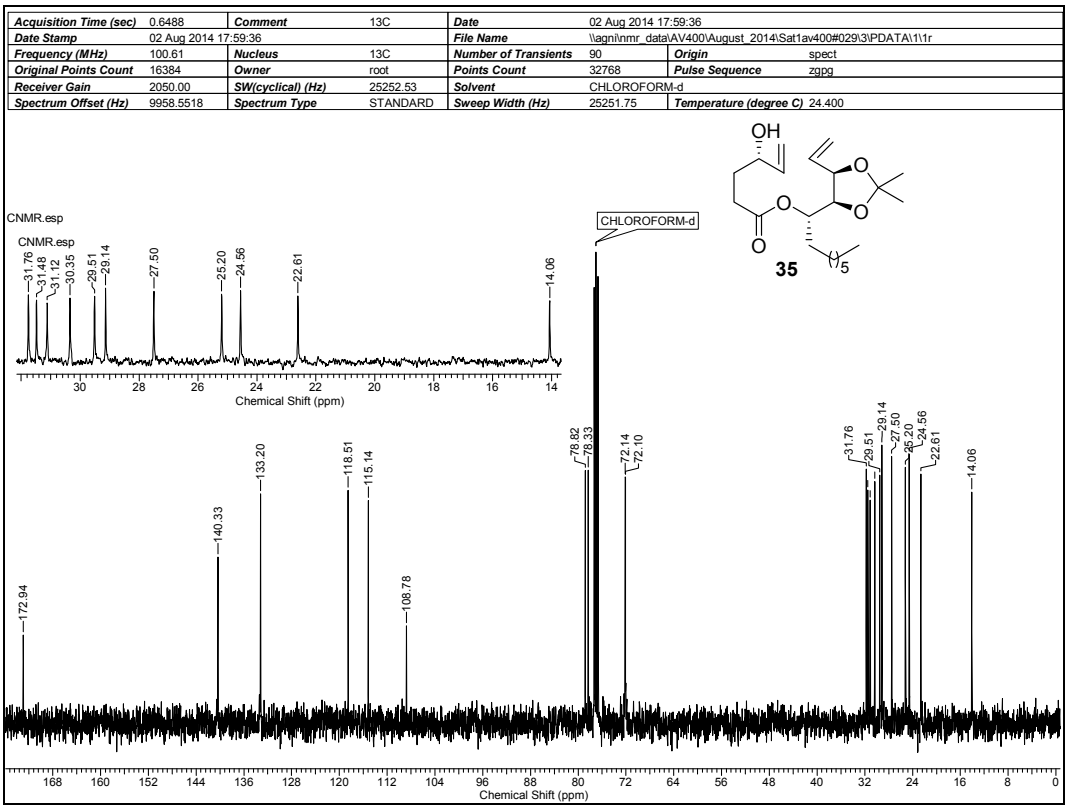
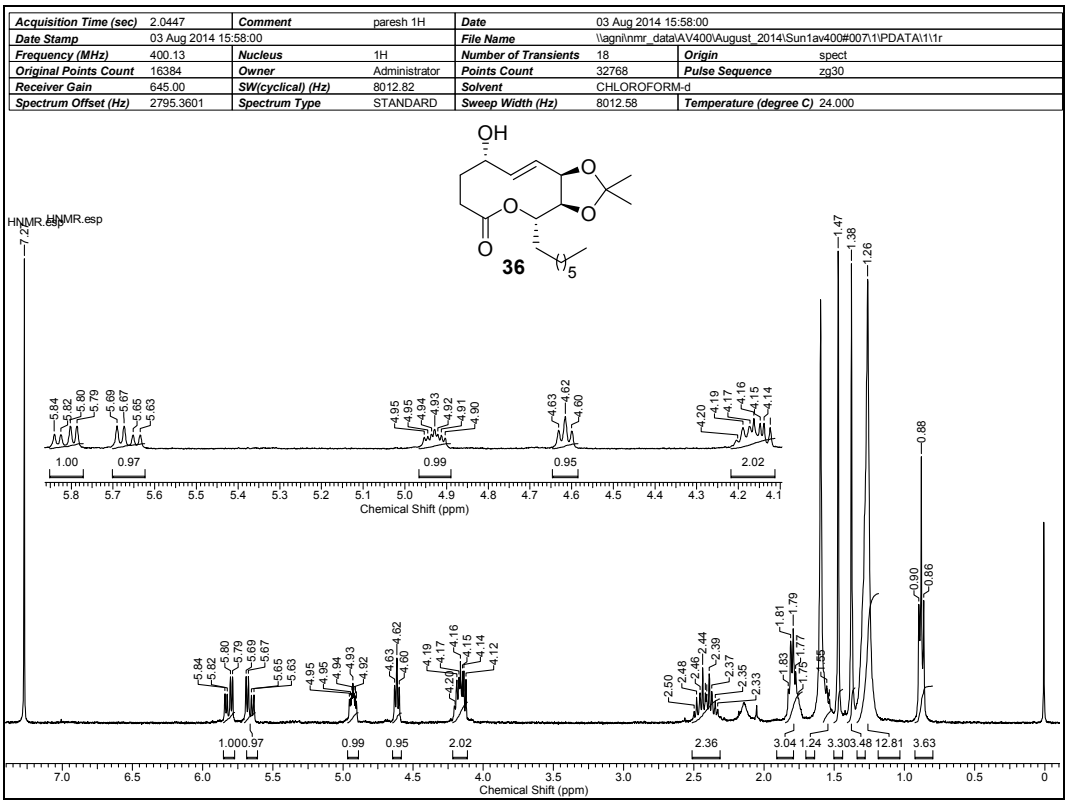
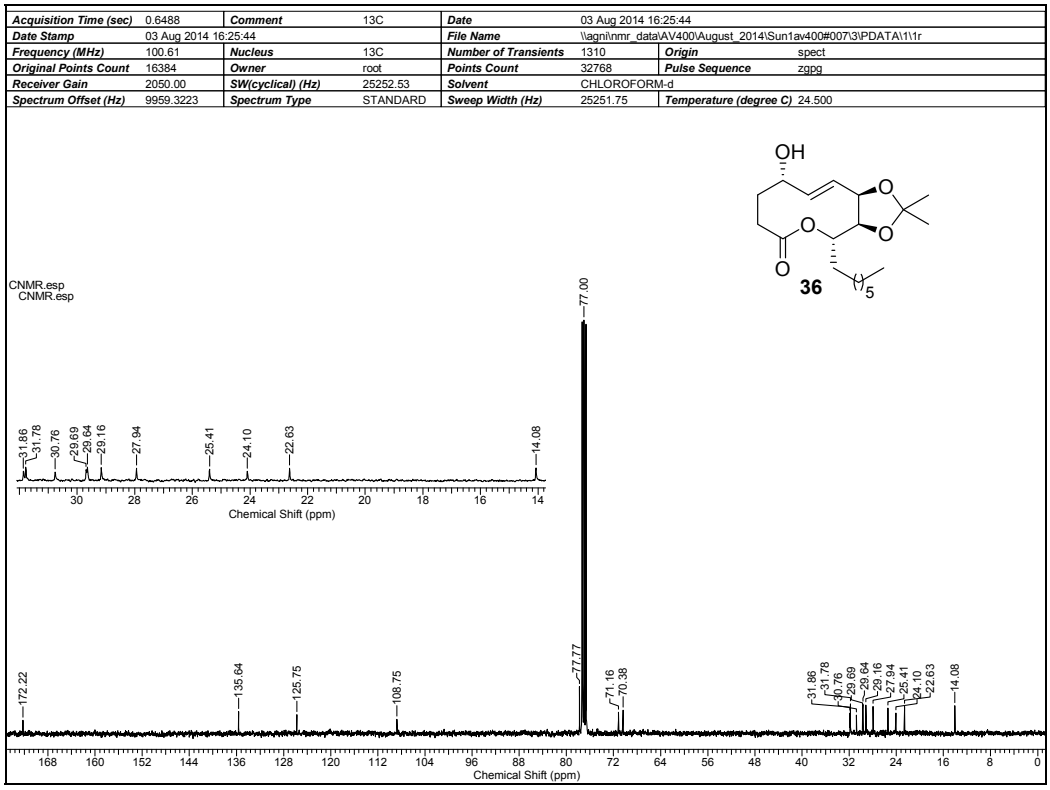


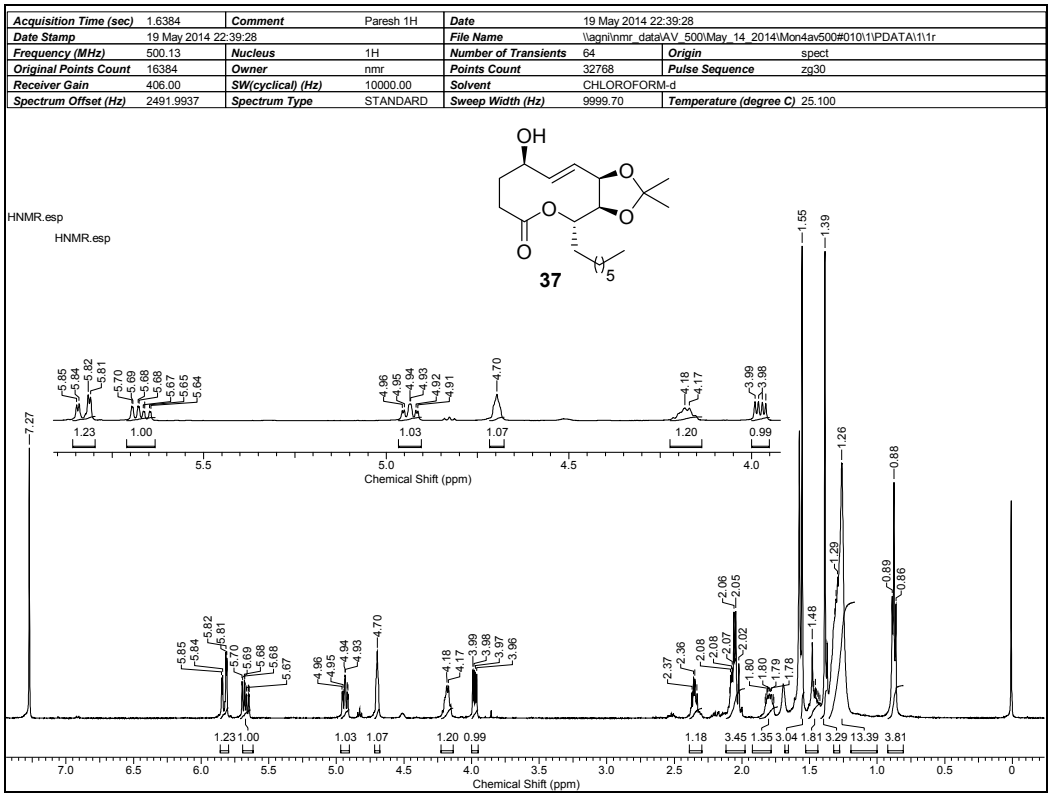
^{13}C NMR Spectrum of 35 in $CDCl_3$



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



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



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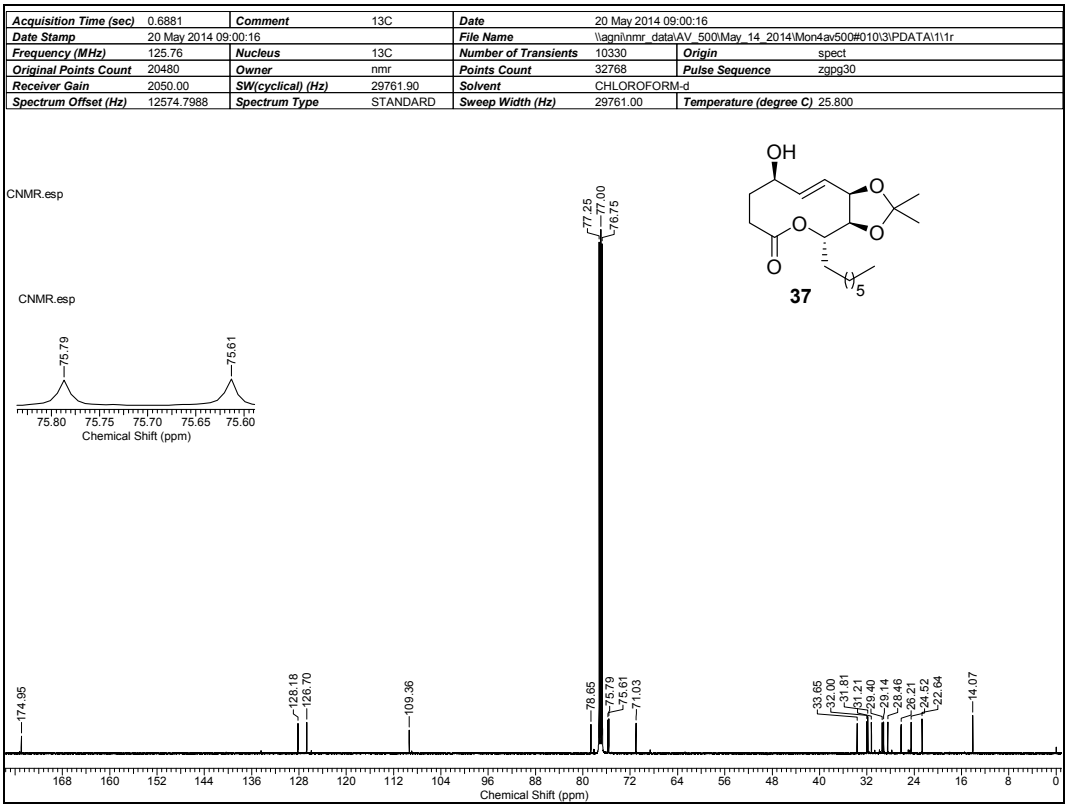
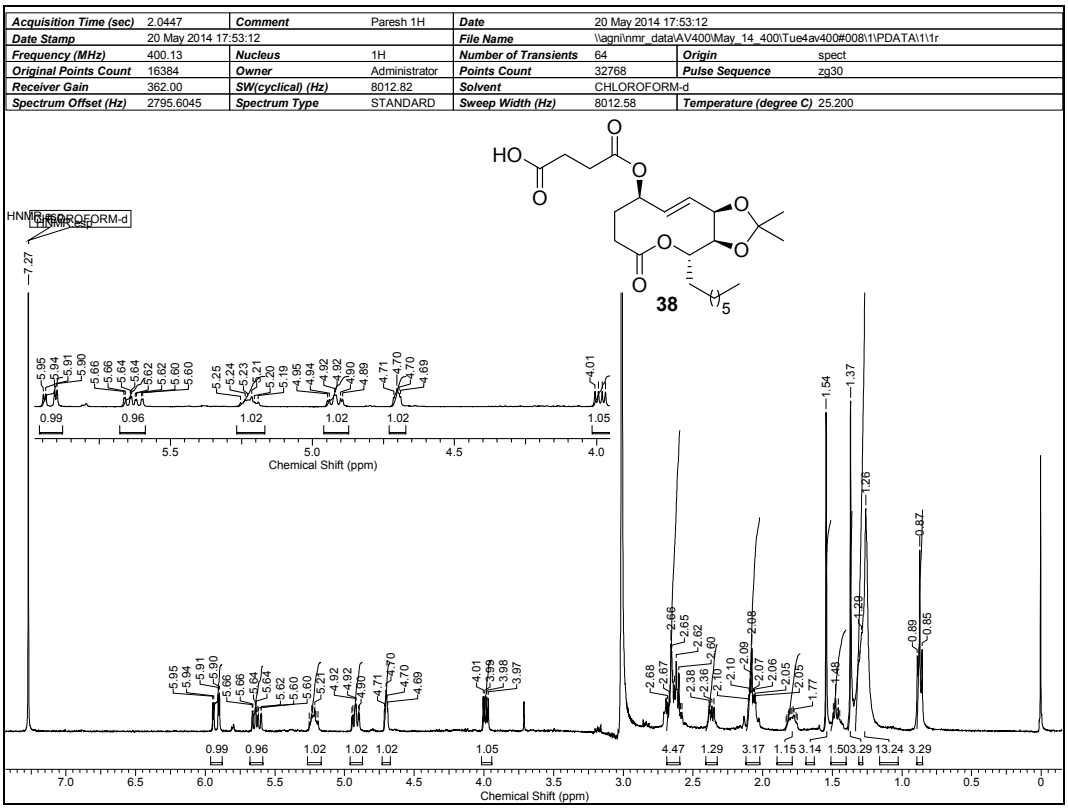
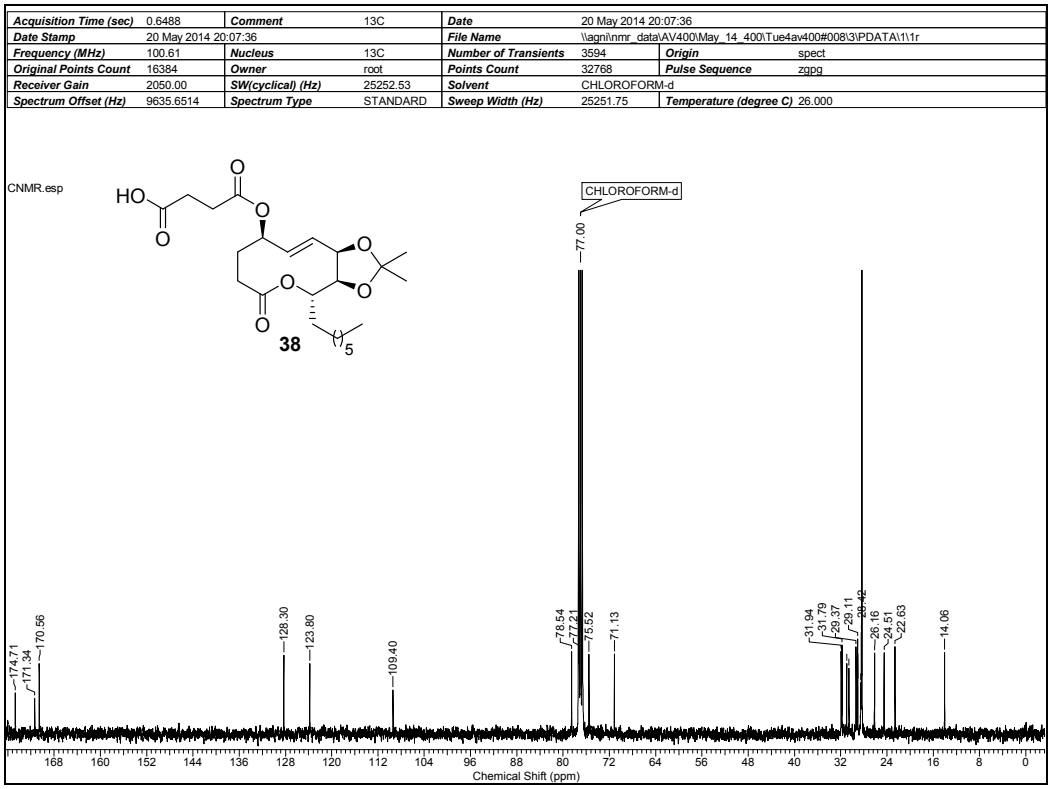


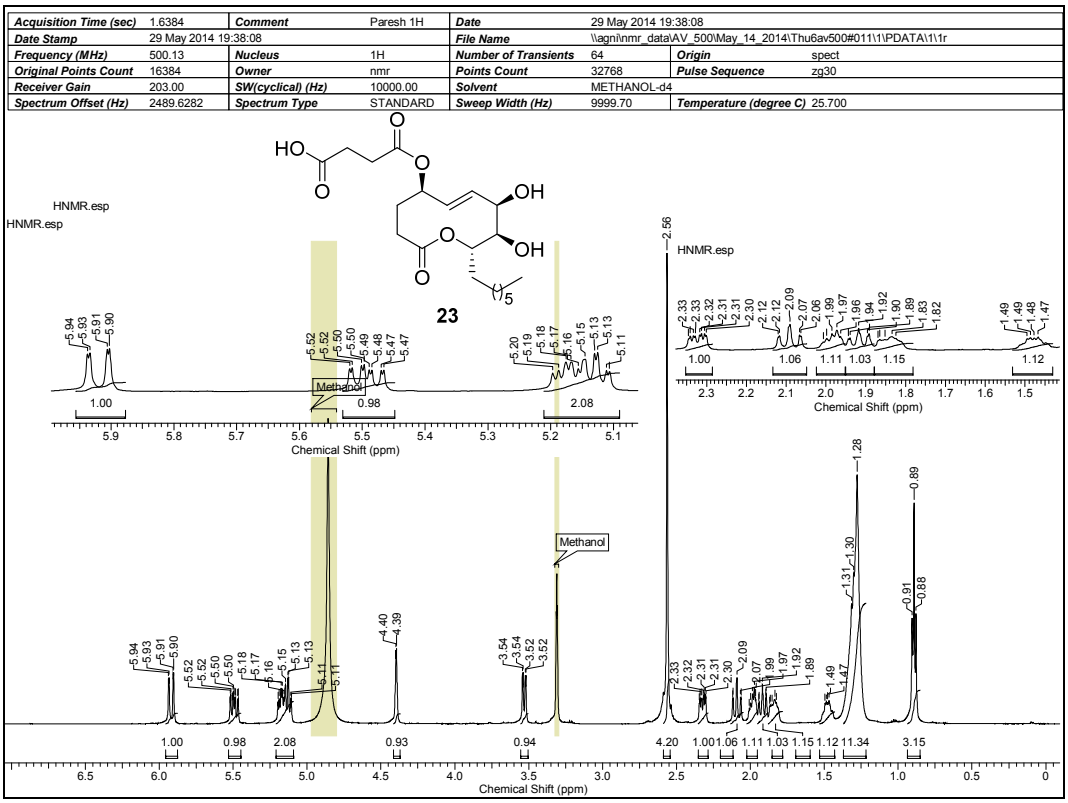
^{13}C NMR Spectrum of 37 in $CDCl_3$



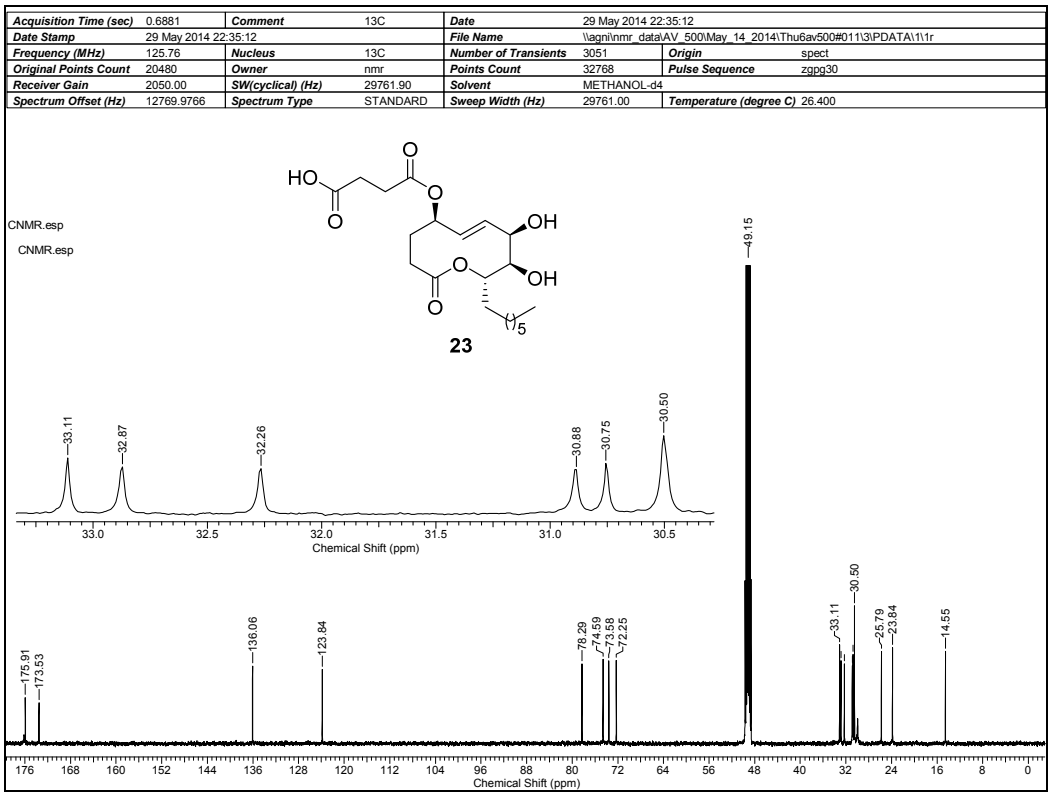
^{1}H NMR Spectrum of 38 in $CDCl_3$



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



^{1}H NMR Spectrum of 23 in CD_3OD



^{13}C NMR Spectrum of 23 in CD_3OD

CHAPTER I; SECTION III

Studies towards the total synthesis of Cytospolide E

RESULT AND DISCUSSION

Nonenolides are extremely important because of their extraordinary cytotoxic potential towards the cancerous cells. They also show a broad spectrum of bioactivities such as antifungal, antibacterial, antimicrofilament, and antimalarial activities.[45b] All the nonenolides are constructed with an even number of carbon atoms having a C-9 alkyl attachment. In 2011, Zhang and co-workers reported the isolation of five new nonenolides from the fungus *Cytospora sp.* obtained from the acetone extraction of *Ilex canariensis* shrub and name Cytospolides A–E.[19] Cyctospolides are characterized with an unprecedented fifteen carbon atom skeleton having a C2 methyl group which was rarely observed in this class of natural products. The structural interpretations and absolute configurations were determined with the help of spectroscopic techniques, single-crystal XRD together with the time dependent (TD)-DFT calculations of the CD spectra. These cytospolides in general exist as a mixture of conformers which was confirmed by the soft pulse transfer NMR technique and DFT calculations. The Cytospolides A–D have a similar absolute configuration and vary only on the presence of acetate group(s) and its position. The Cytospolide E is a C2 epimer of cytospolide D. During the initial bioassay tests, these C2 epimers illustrated different cytotoxic properties against the A549 cell line, suggesting a probable stereochemical influence of the C2 methyl group in the growth inhibition of tumor cells (zero activity for cytospolide A–D to IC_{50} = 7.09 μg/mL for cytospolide E).

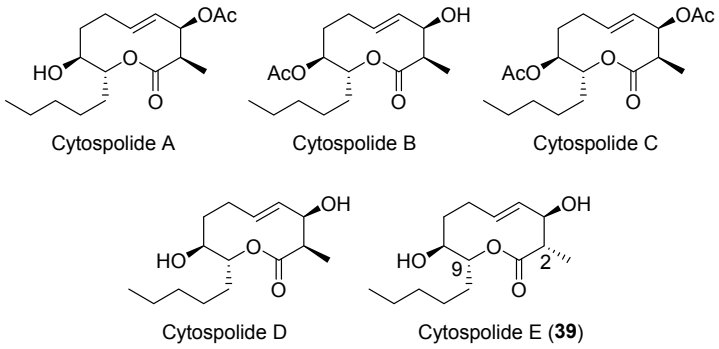


Figure 13. *Strucrure of Cytospolide A-E*

Hence, with the extension of our curiosity in the synthesis of nonanolides using ring closing metathesis as a key step and inspired by the hypothesis of enhanced cytotoxic activity of the inverse methyl group in Cytospolide E, we have initiated a program to synthesize the Cytospolide E. In this section, we present our efforts towards the synthesis of naturally occurring Cytospolide E (**43**) beginning from cheaply available starting materials.

We have completed the total synthesis of Z isomer of cytospolide E and we were at the final stage for the total synthesis of natural E isomer of Cytospolide E. Afterwards there were about three synthetic efforts that had been put forward toward the synthesis of cytospolide D and E in the literature. Yadav *et al* have described the *Z*-isomer of Cytospolide E[69] whereas Kamal synthesized both the E and Z-isomers of Cytospolide D,[70] and Nanda emphasized the chemo-enzymatic asymmetric synthesis of Z-isomer of Cytospolides D, E and their stereoisomers.[71] It is interesting to note that one common reaction employed by all the authors is the metathesis reaction for the construction of the alkene at the penultimate stage of the total synthesis.

Retrosynthetic analysis for Cytospolide E (**39**) is depicted in Figure 14**.** Cytospolide E (**39**) could be obtained from the diene ester **40** by the ring closing metathesis (RCM) which in turn, could be derived from the Yamaguchi esterification of an alcohol **41** and an acid having the *α*-configured C-2 methyl group **42**. A series of simple transformations will be followed for the synthesis of alcohol **41** from D-glyceraldehye **43** and acid **42** could be accessed by means of the asymmetric Evans aldol reaction of acrolein **44**.

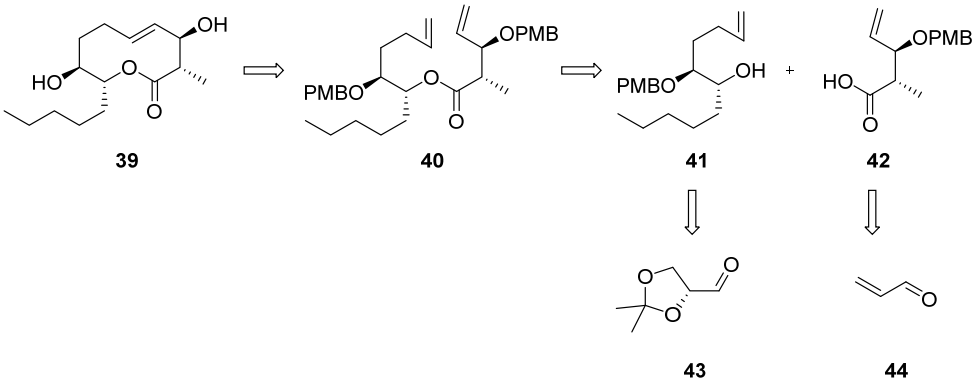
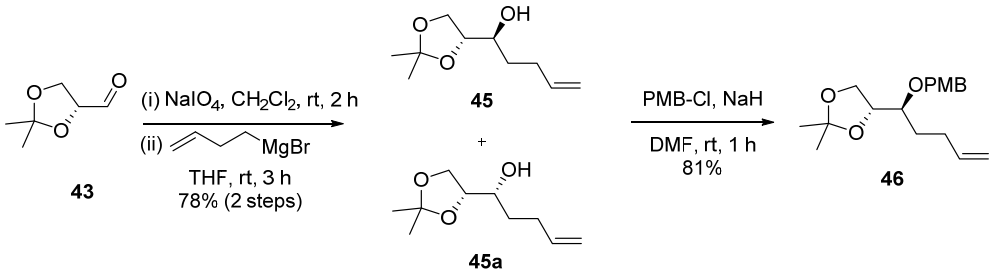


Figure 14: *Retrosynthetic disconnection for Cytospolide E (43)*

Synthesis of alcohol fragment 45:

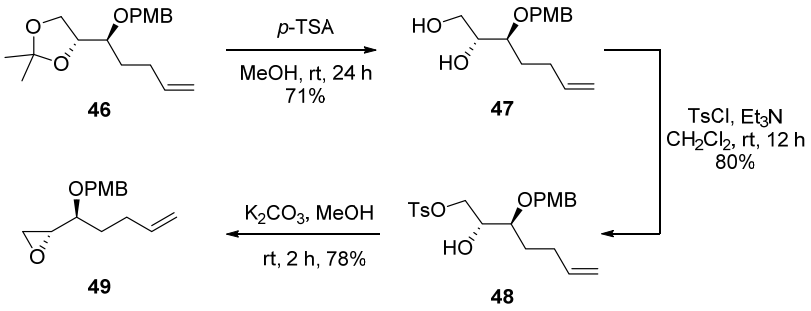
The journey of synthesis of alcohol **41** was begun with the Grignard addition of homoallylic magnesium bromide to D-glyceraldehyde **43** (prepared freshly by means of periodate cleavage of D-mannitol 1,2:5,6-diacetonide) to give a mixture of separable diastereomers **45** and **45a** in a 4:1 ratio with 78% yield.[72] In the ^{1}H NMR spectrum of compound of both the diastereomers, the *syn* isomer shows three separable multiplets in the region of *δ* 3.44–4.03 ppm and the *anti* isomer shows a complex multiplet in the region of *δ* 3.73–4.05 ppm. All other signals in both the spectra are in good agreement with the assigned constitution (Scheme 22).

The free hydroxyl group of the required *anti* alcohol **45** was protected as their PMB ether using *p*-methoxy benzyl chloride (PMBCl) and NaH in *N,N*-dimethylformamide to afford compound **46** in 81% yield. Compound **46** was characterized with the help of NMR and mass spectra. In the ^{1}H NMR spectrum of compound **46**, the diastereotopic benzylic protons were seen to resonate at δ 4.50 & 4.59 ppm as a doublet with very high geminal coupling J = 11.2 Hz, whereas the sharp singlets appeared at δ 3.79 ppm corresponding to the methoxy of the PMB group. In the ^{13}C NMR spectrum of compound **46**, methine and quaternary carbons of the aromatic ring were seen to resonate at δ 113.6 (d, 2C), 129.2 (d, 2C), 130.4 (s), 159.0 (s) ppm respectively whereas the methoxy carbon and benzylic carbon appeared at 55.0 (q) and 66.0 (t) ppm respectively (Scheme 22).



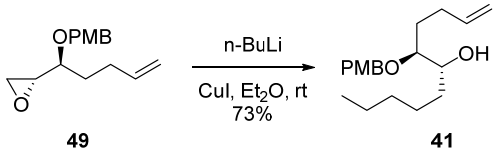
Scheme 22. *Synthesis of compound **50***

Next, the deprotection of the acetonide group in compound **46** was achieved in the presence of catalytic *p*-TSA in methanol to afford diol **47** in 71% yields. In the ^{1}H NMR spectrum of compound **47**, the two singlets corresponding to the two methyls of acetonide group were seen to disappear. Similarly in the ^{13}C NMR spectrum of **47**, peaks corresponding to the quaternary carbon and two methyl carbons of the acetonide group were seen to disappear.Additionally, in the HRMS spectrum, the presence of a strong peak at m\z 289.1409 confirmed the compound **47**. Next the tosylation of the primary hydroxyl of compound **47** was carried out using tosyl chloride and triethyl amine in dichloromethane to afford the tosyl derivative **48** in 80% yield. The formation of the mono-tosyl compound was confirmed by spectral and analytical data. For instance, in the ^{1}H NMR spectrum of **48**, sharp singlets appeared at δ 2.43 ppm corresponding to the methyl group attached with the sulphonate, while two doublets generated at δ 7.34 and 7.78 ppm with a coupling constant J = 8.0 Hz are due to the *para*-disubstituted symmetric aromatic ring protons of the tosyl group. Similarly, the presence of the tosyl group was confirmed by the appearance of signals at 21.6 (q), 128.0 (d, 2C), 129.9 (d, 2C), 132.6 (s), 145.0 (s) ppm due to the tosyl group. The HRMS-ESI spectrum of compound **48** showed the signals of *m*/*z* 764.5 ($[M + Na]^{+}$), which further supported the assigned structure (Scheme 23).



Scheme 23. *Synthesis of epoxide **53***

After characterising the mono tosyl compound **48**, it was further transformed to the required epoxide **49** by treating with potassium carbonate in methanol. The volatile epoxide **49** was isolated in 78% yield as colourless oil. In the ^{1}H NMR spectrum of **49**, the epoxide methylene (-CH_2) protons appeared at δ 2.71 (dd, J = 2.6, 5.3 Hz) and 2.78 (dd, J = 3.9, 5.2 Hz) ppm. The internal methine (-CH) proton resonated at δ 2.91 (ddd, J = 2.6, 3.9, 6.4 Hz) ppm and, most importantly, the protons corresponding to the tosyl group were seen to disappear. In the ^{13}C NMR spectrum of **49**, the signals of the oxirane ring carbons were found to be relatively up field at δ 45.5 (CH_2) and 53.3 (CH) ppm as a triplet and doublet respectively (Scheme 23).

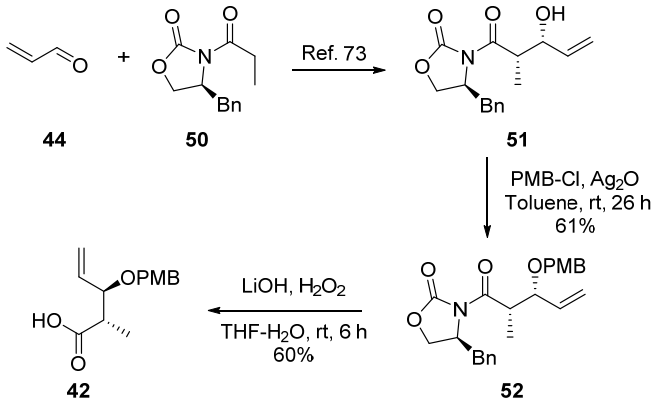


Scheme 24. *Synthesis of alcohol fragment **41***

Our next task was to open the epoxide with a four carbon Grignard reagent. Finally, the regioselective opening of the epoxide **49** was carried out using *n*-butyl lithium in the presence of CuI and the required alcohol fragment **41** was obtained in 73% yield (Scheme 24). The structure of compound **41** was established with the help of NMR and mass spectra analysis. The disappearance of signals due to protons attached to the epoxide carbons and the appearance of a triplet at δ 0.89 (J = 6.7 Hz) due to the terminal methyl group of the aliphatic long chain in the^{1}H NMR spectrum of compound **41** clearly indicated butyl incorporation. Similarly, in the ^{13}C NMR spectrum of compound **41**, the appearance of a signal at δ 13.9 (q), 22.5 (t), 25.7 (t), 27.7 (t) ppm accounted for the butyl chain and a signal at 71.4 (d) ppm due to the carbon attached to the hydroxyl group were seen. The presence of a strong peak of at *m/z* 223.1 $[M+Na]^{+}$in the ESI-HRMS mass spectrum of **41** provided additional support to the assigned constitution of compound **41**.

Synthesis of acid fragment 42:

The synthesis of the acid fragment **42** was started by means of the asymmetric aldol reaction between acrolein **44** and imide **50** using known procedures. Thus, Evans' *syn*-aldolisation was carried out by using $TiCl_4$ and diisopropylethyl amine to give an allyl alcohol **51** in 73% yields.[73] The spectroscopic and analytical data of compound **51** are in agreement with reported data**.** The free hydroxyl group of the allyl alcohol was protected as PMB ether employing mild reaction conditions (using silver oxide and PMB-Cl in toluene for 26 h) in order to prevent epimerization at the α-position of the amide and hydrolysis of the chiral auxiliary. The reaction was sluggish and the product **52** was isolated in 61% yield with respect to the recovered starting material. The presence of the PMB group was confirmed by the appearance of a signal corresponding to the PMB group in both ^{1}H and ^{13}C NMR of compound **52**. The oxazolidinone thereafter was hydrolyzed under basic conditions to provide the requisite acid **42**. In ^{1}H NMR of acid **42**, the olefinic protons were seen to resonate at δ 5.26-5.37 (m, 2H) and 5.79 (ddd, J = 7.7, 10.6, 16.9 Hz, 1H) ppm, and the C-H proton attached to OPMB and methyl proton appeared at δ 4.01 (dd, J = 5.8, 7.7, 1H) ppm and 1.20 (d, J = 7.1 Hz, 3H) ppm respectively. Similarly, in the ^{13}C NMR of compound **42**, the carbonyl carbon was seen to resonate at δ 178.6 (s) ppm, whereas it was at δ 174.3 ppm in imide **52**. Additionally, HRMS provided extra support to the assigned constitution of compound **42** (Scheme 25).

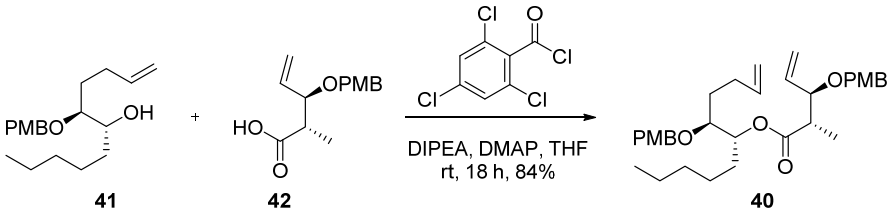


Scheme 25. *Synthesis of acid fragment **42***

Coupling of alcohol 41 and acid fragment 42:

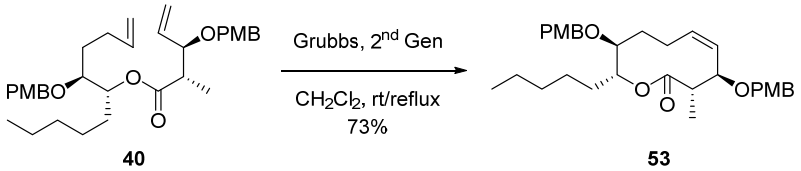
With both intermediates **41** and **42** in hand, our next task was their coupling. Accordingly, Yamaguchi esterification of the olefinic acid fragment **42** with the olefinic alcohol fragment **41** at ambient temperature provided the diene ester **40** in 84% yield[58] (Scheme 26). In the ^{1}H NMR spectrum of diene **40**, the signal corresponds to the olefin

region at δ 4.94–5.02 (m, 2H), 5.25–5.29 (m, 2H) and 5.73–5.84 (m, 2H) ppm, confirming the presence of two olefin moieties, whereas the characteristic acyloxy CH was seen to appear at δ 5.08 ppm as a triplet of doublet with a coupling constant J = 3.4, 9.4 Hz. In the ^{13}C NMR spectrum of diene ester **40**, the carbons of the terminal olefin methylenes (=CH_2) and internal olefin methine carbons were seen to appear at δ 114.8, 118.7 and 136.4 (d), 138.4 (d) ppm respectively whereas the carbonyl carbon was appeared at δ 173.9 ppm. All other protons and carbons in the NMR spectra appeared with their respective chemical shifts, thereby confirming the structure of ester **40**. The structure of **40** was further supported by HRMS.



Scheme 26. *Synthesis of diene ester **40***

This set the stage for the crucial macrolactonization *via* ring-closing metathesis. Treatment of **40** with the Grubbs' second generation catalyst in CH_2Cl_2 at reflux temperature for 3 h gave the RCM product **53** with Z geometry of the newly forming double bond in 73% yield (Scheme 27). The structure of **53** was ascertained by its NMR spectrum. In the ^{1}H NMR spectrum of **53**, two olefinic protons were seen to resonate at δ 5.26 (t, J = 9.9 Hz, 1H) and 5.75 (dt, J = 3.4, 11.5 Hz) ppm as well as the terminal olefinic protons were seen to disappear. The low value of the coupling constant J = 9.9 Hz and 11.5 Hz clearly reveals the Z geometry of the newly formed olefin. In the ^{13}C NMR spectrum of **53**, the two new carbons peaks appeared at δ 128.2 and 135.6 ppm as a doublet corresponding to the newly formed internal olefin moiety. Furthermore, in the HRMS spectrum, the presence of a strong peak at 533.2866 ([M+Na]$^+$, 100%) confirmed the compound **53**.

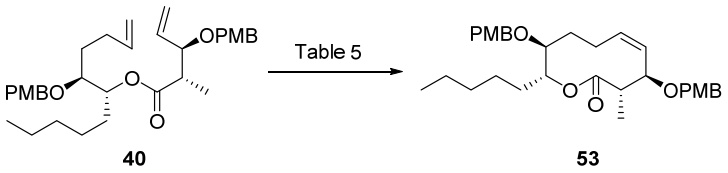


Scheme 27. *Synthesis of macrolide **53***

Other attempts for the ring-closing metathesis of diene ester **40** by employing CH_2Cl_2 or toluene as the solvent at different temperatures in combination with Grubbs' firstgeneration catalyst (Ru-I) or Grubbs' second generation catalyst (Ru-II) or Hoveyda–

Grubbs' catalyst led to the formation of lactone **53** bearing a *cis*-geometry at the newly created double bond. These results are summarized in Table 5.

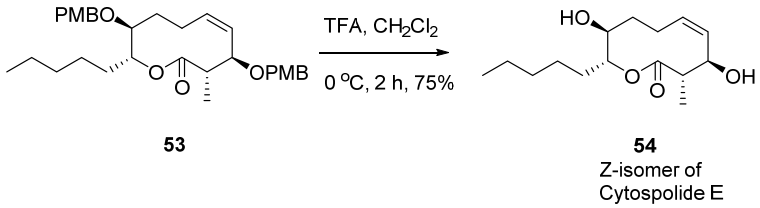
Table 5. *RCM of Diene ester **40***



40 **53**

Sr. No.	Catalyst	Solvent	Product
1	Grubbs-I Catalyst	CH_2Cl_2, Toluene	Z- isomer
2	Grubbs-II Catalyst	CH_2Cl_2, Toluene	Z- isomer
3	1st Generation Hoveyda-Grubbs Catalyst	CH_2Cl_2, Toluene	Z- isomer
4	2nd Generation Hoveyda-Grubbs Catalyst	CH_2Cl_2, Toluene	Z- isomer

Finally, the deprotection of PMB ethers of compound **53** using TFA in CH_2Cl_2 at 0 °C gave the Z-isomer of Cytospolide E **54** in 75% yield (Scheme 58). The structure of compound **54** was fully characterized with the help of NMR and mass spectra. In the ^{1}H NMR spectrum of compound **54**, the olefinic protons were seen to resonate at δ 5.35 (dt, J = 1.5, 10.9 Hz, 1H), 5.73 (dt, J = 3.5, 11.2 Hz, 1H) ppm, whereas protons on carbon attached to the hydroxy group appeared at δ 3.79 (brs, 1H), 4.62 (t, J = 9.5 Hz, 1H) ppm. Similarly, in the ^{13}C NMR of compound **54,** ester carbonyl appeared at δ 174.7 (s) ppm**.** The signal corresponding to the PMB groups were seen to disappear in the ^{1}H and ^{13}C NMR of compound **54**. The structure of **54** was further supported by the presence of a peak at *m/z* 848.3 ($[M+Na]^+$) in the ESI-HRMS spectrum of compound **54**.



53 **54**
Z-isomer of
Cytospolide E

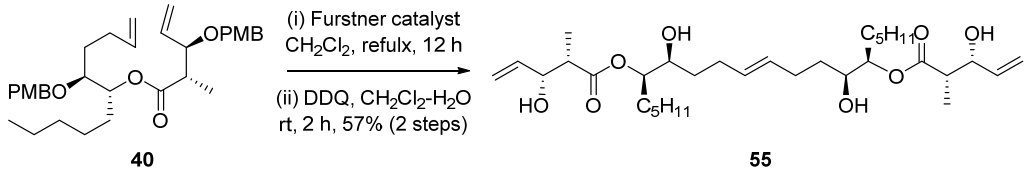
Scheme 28. *Synthesis of Z-isomer of Cytospolide E (**54**)*

The unexpected formation of the *Z*-isomer may be attributed to the fact that the *Z*-isomer is thermodynamically more stable than the *E*-isomer. This result is in agreement with observations noticed by Gennari that less densely functionalized diene with lack of functionality at the allylic position or at only one allylic position resulted in the exclusive

formation of the *Z*-isomer of the ten-membered carbocycles in the RCM reactions as a result of thermodynamic control.[48]

As suggested by Fürstner, the Grubbs catalysts, due to their higher overall activity, are able to isomerize the cycloalkenes formed during the course of the reaction and hence enrich the mixture in the thermodynamically favored product. Thus to avoid equilibration of the products initially formed, the less reactive rutheniumindenylidene complex should be used.[47]

Surprisingly, when the RCM of **40** was attempted using catalytic amount of the rutheniumindenylidene complex with CH_2Cl_2 as solvent under reflux conditions and purification of the metathesis product was found to be difficult, we subsequently subjected it for PMB deprotection treatment with DDQ. Surprisingly, the homo metathesis product **55** was obtained as the major product (Scheme 29). The structure of homo metathesis product **55** was established with the help of spectral and mass analysis. In ^{1}H NMR spectrum of **55**, two terminal and internal olefinic protons of the terminal olefin moiety were seen to resonate at δ 5.32 (br d, J = 17.4 Hz, 2H), 5.20 (br d, J = 10.4 Hz, 2H) and 5.81-5.90 ppm as a multiplate respectively. Similarly in the ^{13}C NMR spectrum terminal olefinic carbon were seen to resonate at δ 116.3 (t, 2C) and 137.5 (d, 2C) ppm. The structure of **55** was further supported by the presence of a peak at *m/z* 591.3 ($[M+Na]^+$) in the ESI-HRMS spectrum of compound **55**.



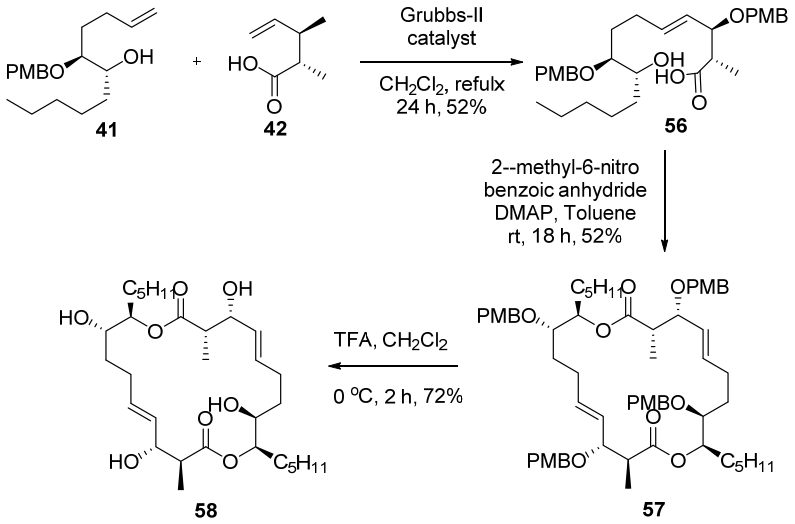
40 **55**

Scheme 29. *Homo metathesis of diene ester (**40**)*

The failure in the synthesis of the natural Cytospolide E (by following Yamaguchi esterification and the RCM strategy) led us to think in the reverse direction for the ring closure. For that, we intended on a cross metathesis reaction at the beginning and an intramolecular esterification was planned at the later stage.

According to speculation, the cross metathesis in between the alcohol **41** and the acid **42** was proceeded smoothly in the presence of Grubbs 2nd generation catalyst under reflux condition in CH_2Cl_2 for 24 h to give exclusively alkene **56** having a *trans* geometry in 52% yield (Scheme 30).[74] The formation of the *trans* alkene **56** was ascertained by its spectral and analytical data. In the ^{1}H NMR spectrum of **56**, the terminal olefinic protons were seen to disappear and internal olefinic protons were seen to resonate at δ 5.36 (dd, J = 8.8, 15.5 Hz, 1H) and 5.67 (td, J = 6.9, 15.3 Hz, 1H) ppm. The *trans* geometry of alkene was confirmed

from its large coupling constant of 15.3 Hz. The two methyl groups corresonding to the aliphatic long chain and attached to the α-carbon of carbonyl were located at δ 0.89 (t, J= 6.4 Hz, 3H) and 1.16 (d, J= 7.0 Hz, 3H) ppm. In the ^{13}C NMR spectrum of **56**, the carbonyl carbon was observed at δ 176.7 ppm as a singlet, the benzylic carbons of the two PMB groups were located at δ 69.8 & 71.5 ppm as a triplet and the methine carbon attached to methyl appeared at δ 44.6 ppm as a doublet. Additionally, in the HRMS spectrum, the presence of a strong peak at m\z 551.2972 confirmed the compound **56**.



Scheme 30. *Synthesis of 20-membered macrolide (**58**)*

After having the fully characterized seco acid **56** in hand, the next task was the lactonization to prepare the macrolide core. Attempted lactonization of seco acid **56** using Yamaguchi lactonization, Corey-Nicolaou lactonization methods or other coupling reagents such as DCC, EDCI resulted in a complex reaction mixture. However, the Shiina lactonization[75] using 2-methyl-6-nitro benzoic anhydride in the presence of DMAP proceeded smoothly to give a 20-membered macrolide **57** in 52% yield instead of the required 10-membered nonenolide (Scheme 30). The structure of **57** was confirmed by NMR as well as HRMS. The ^{1}H NMR and ^{13}CNMR of compound **57** were found to be similar to the expected ten membered lactone. For example, in the ^{1}H NMR spectrum of compound **57**, the olefinic protons were seen to resonate at δ 5.50 (dd, J = 8.7, 15.7 Hz, 2H), 5.62 (td, J = 5.6, 15.2 Hz, 2H) ppm and acyloxy proton at δ 4.99-5.00 (m, 2H) ppm. In the ^{13}C NMR spectrum, the olefinic carbons and carbonyl carbon were located at δ 128.2 (d, 2C), 135.5 (d, 2C), and 173.3 (s, 2C) ppm respectively. However in the HRMS, the presence of a strong peak at 1043.5865 ([M+Na]$^{+}$, 100%) confirmed the presence of a 20 membered macrolide structure

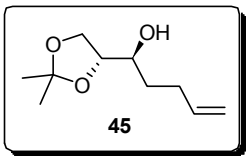
in **57**. Finally, global deprotection of the PMB groups in macrolide **57** was carried out using TFA in dichloromethane at 0 °C to gave a 20-membered macrolide **58** in 72% yield. In the HRMS spectrum of compound **58**, the presence of a strong peak at 563.3550 ($[M+Na]^+$,) confirmed assigned structure of **58** and the NMR Specrum of compound **58** was characterized by the presence of two sets of signals indicating mixture of two equilibrating conformational isomers. However, the lack of sufficient quantity, especially in its pure form, was the major hurdle in comprehensively assigning its structure. Work in the direction of synthesizing natural Cytospolide E is under progress.

Conclusion:

In conclusion, the total synthesis of the Z-isomer of Cytospolide E was achieved by using RCM and a 20-membered macrolactone was obtained while aiming to synthesize the natural product. D-mannitol was used as a chiral pool starting material for the building of the alcohol fragment and Evan's aldol reaction was employed for the acid fragments.

EXPERIMENTAL

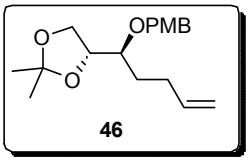
(S)-1-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)pent-4-en-1-ol **(45):**



A suspension of Mg (3.7 g, 153.7 mmol) and catalytic iodine in dry THF (150 mL) was treated with butenyl bromide (11.7 mL, 115.7 mmol) and the contents were stirred at rt for 1 h. To this, a solution of the aldehyde **43** (10 g, 76.8 mmol) in THF (50 mL) was added drop wise at 0 °C and the mixture was stirred for another 1 h at rt. The reaction mixture was quenched saturated ammonium chloride (200 mL) and extracted with ethyl acetate (2×200 mL). The combined organic extract was dried (Na_2SO_4), concentrated and the resulting crude residue was purified by silica gel column chromatography (10→12% EtOAc in pet ether) afforded **45** (9 g, 63%) and **45a** (2 g, 15%) as a colorless oil.

$[\alpha]_D^{25}$ 17.3 (*c* 1.0, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.34 (s, 3H), 1.40 (s, 3H), 1.42-1.65 (m, 2H), 2.03-2.16 (m, 3H), 3.75 (dt, *J* = 3.9, 7.9 Hz, 1H), 3.84-4.05 (m, 3H), 4.94-5.08 (m, 2H), 5.71-5.91 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 25.2 (q), 26.4 (q), 29.8 (t), 31.8 (t), 64.7 (t), 70.2 (d), 78.6 (d), 108.9 (s), 115.0 (t), 137.9 (d) ppm; HRMS (ESI+) calcd for $C_{10}H_{18}O_3Na$ 209.1148; Found 209.1147.

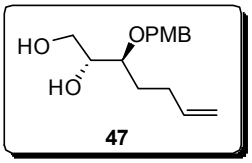
(R)-4-((S)-1-((4-methoxybenzyl)oxy)pent-4-en-1-yl)-2,2-dimethyl-1,3-dioxolane **(46):**



To a cooled solution of **45** (8 g, 42.9 mmol) in anhydrous DMF (80 mL) were added NaH (60% dispersion in mineral oil, 2.1 g, 51.5 mmol) followed by PMB-Cl (6.4 ml, 47.2 mmol) and the contents stirred at rt for 4 h. The reaction mixture was quenched with aq. Na_2SO_4 (200 mL) and the aqueous layer was extracted with EtOAc (2×200 mL). The combined organic layer was washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (5-8% EtOAc in petroleum ether) to procure **46** (10.7 g, 81%) as as a yellow oil.

$[\alpha]_D^{25}$ 3.8 (*c* 1.0, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.35 (s, 3H), 1.42 (s, 3H), 1.57-1.68 (m, 2H), 2.10-2.26 (m, 2H), 3.54 (q, *J* = 5.2 Hz, 1H), 3.79 (s, 3H), 3.87 (t, *J* = 6.4 Hz, 1H), 4.10-4.13 (m, 2H), 4.50 (d, *J* = 11.2 Hz, 1H), 4.59 (d, *J* = 11.1 Hz, 1H), 4.93-5.07 (m, 2H), 5.71-5.91 (m, 1H), 6.85-6.89 (m, 2H), 7.24-7.29 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 25.1 (q), 26.4 (q), 29.0 (t), 30.3 (t), 55.0 (q), 66.0 (t), 72.3 (t), 77.7 (d), 77.8 (d), 108.8 (s), 113.6 (d, 2C), 114.6 (t), 129.2 (d, 2C), 130.4 (s), 138.2 (d), 159.0 (s) ppm; HRMS (ESI+) calcd for $C_{18}H_{26}O_4Na$ 329.1723; Found 329.1720.

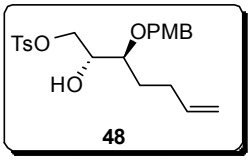
***(2R,3S)-3-((4-methoxybenzyl)oxy)hept-6-ene-1,2-diol* (47):**



At 0 °C *p*-TSA (500 mg, 2.94 mmol) was added to a solution of **46** (9 g, 29.4 mmol) in dry MeOH (80 mL) and the contents was stirred at same temperature for 10 h. After completion, the reaction mixture was neutralized with $NaHCO_3$ and directly concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (60-70% EtOAc in petroleum ether) to procure **47** (5.55 g, 71%) as as a yellow oil.

$[\alpha]_D^{25}$ 3.0 (*c* 1.0, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.65-1.83 (m, 2H), 2.08-2.23 (m, 2H), 3.44-3.76 (m, 4H), 3.80 (s, 3H), 4.47 (d, *J* = 11.0 Hz, 1H), 4.55 (d, *J* = 10.9 Hz, 1H), 4.96-5.08 (m, 2H), 5.70-5.91 (m, 1H), 6.87 (d, *J* = 8.8 Hz, 2H), 7.23-7.27 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 29.3 (t), 29.5 (t), 55.1 (q), 63.3 (t), 72.0 (t), 72.7 (d), 79.5 (d), 113.7 (d, 2C), 114.8 (t), 129.4 (d, 2C), 130.1 (s), 138.2 (d), 159.1 (s) ppm; HRMS (ESI+) calcd for $C_{15}H_{22}O_4Na$ 289.1410; Found 289.1409.

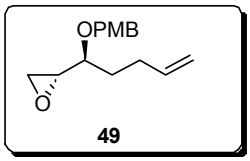
***(2R,3S)-2-hydroxy-3-((4-methoxybenzyl)oxy)hept-6-en-1-yl 4-methylbenzenesulfonate* (48):**



At 0 ºC, a solution of **47** (5 g, 18.8 mmol), triethylamine (3.1 mL, 22.5 mmol) and DMAP (Cat.) in Dry CH_2Cl_2 (50 mL) was treated with *p*-Toluenesulfonyl chloride (4 g, 20.6 mmol) and stirred at rt for 12 h. The reaction was portioned between water (100 ml) and CH_2Cl_2 (100 mL) and the aqueous layer was extracted with CH_2Cl_2 (100 mL). Combined organic layer was dried (Na_2SO_4) and concentrated. Purification of the crude product by column chromatography (30→35% EtOAc in petroleum ether) gave **48** (6.3 g, 80%) as yellow oil.

$[\alpha]_D^{25}$ 3.0 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.52-1.61 (m, 1H), 1.63-1.71 (m, 1H), 2.02-2.11 (m, 1H), 2.13-2.22 (m, 1H), 2.43 (s, 3H), 3.45-3.49 (m, 1H), 3.79 (s, 3H), 3.86-3.90 (m, 1H), 4.08 (dd, *J* = 6.3, 10.6 Hz, 1H), 4.15 (dd, *J* = 3.6, 10.6 Hz, 1H), 4.40 (d, *J* = 10.9 Hz, 1H), 4.46 (d, *J* = 10.9 Hz, 1H), 4.94-5.02 (m, 2H), 5.71-5.81 (m, 1H), 6.85 (d, *J* = 8.6 Hz, 2H), 7.17 (d, *J* = 8.6 Hz, 2H), 7.33 (d, *J* = 8.2 Hz, 2H), 7.78 (d, *J* = 8.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.6 (q), 29.0 (t), 29.2 (t), 55.2 (q), 70.8 (d), 71.3 (t), 72.1 (t), 78.0 (d), 113.8 (d, 2C), 115.0 (t), 128.0 (d, 2C), 129.5 (d, 2C), 129.9 (d, 2C), 130.1 (s), 132.6 (s), 138.1 (d), 145.0 (s), 159.3 (s) ppm; HRMS (ESI+) calcd for $C_{22}H_{28}O_6SNa$ 443.1499; Found 443.1493.

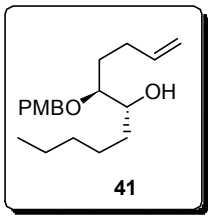
***(R)-2-((S)-1-((4-methoxybenzyl)oxy)pent-4-en-1-yl)oxirane* (49):**



To a solution of **48** (3 g, 7.13 mmol), in methanol (20 mL) was added K_2CO_3 (2.96 g, 21.4 mmol) at rt and stirred for 1 h. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (8→10 % EtOAc in petroleum ether) to afford **49** (1.39 g, 78%) as colorless oil.

$[\alpha]_D^{25}$ −2.3 (*c* 1.0, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.65-1.76 (m, 2H), 2.04-2.37 (m, 2H), 2.71 (dd, *J* = 2.7, 5.3 Hz, 1H), 2.78 (dd, *J* = 4.0, 5.2 Hz, 1H), 2.89-2.95 (m, 1H), 3.25 (q, *J* = 5.6 Hz, 1H), 3.79 (s, 3H), 4.41 (d, *J* = 11.2 Hz, 1H), 4.59 (d, *J* = 11.2 Hz, 1H), 4.94-5.06 (m, 2H), 5.70-5.90 (m, 1H), 6.87 (d, *J* = 8.8 Hz, 2H), 7.25 (d, *J* = 8.5 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 29.3 (t), 31.9 (t), 45.5 (t), 53.3 (d), 55.1 (q), 71.9 (t), 77.0 (d), 113.6 (d, 2C), 114.8 (t), 129.2 (d, 2C), 130.5 (s), 138.1 (d), 159.1 (s) ppm; HRMS (ESI+) calcd for $C_{15}H_{20}O_3Na$ 271.1305; Found 271.1320.

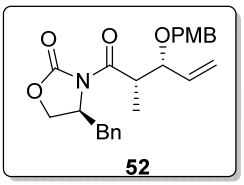
***(5S,6R)-5-((4-methoxybenzyl)oxy)undec-1-en-6-ol* (41):**



At 0 °C, a suspension of CuI (1.15 g, 6.0 mmol) in dry ether (20 mL) was treated with a solution of *n*-butyl lithium (7.5 mL, 12.08 mmol, 1.6 M solution in Hexane) and the contents were stirred at 0 °C for 20 min. To this, a solution of the epoxide **49** (1 g, 4.03 mmol) in dry ether (5 mL) was introduced and the mixture was stirred for another 1 h at 0 °C. The reaction mixture was quenched with cold water (50 ml) and extracted with ethyl acetate (2×50 mL). The combined organic extract was dried (Na_2SO_4), concentrated and the resulting crude product was purified by silica gel column chromatography (12→15 % EtOAc in petroleum ether) to afford **41** (900 mg, 73%) as yellow oil.

$[\alpha]_D^{25}$ −9.2 (*c* 1.0, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.89 (t, *J* = 6.7 Hz, 3H), 1.30-1.80 (m, 9H), 1.98-2.36 (m, 3H), 3.35 (td, *J* = 3.5, 9.0 Hz, 1H), 3.81 (s, 3H), 3.81-2.84 (m, 1H), 4.45 (d, *J* = 11.0 Hz, 1H), 4.55 (d, *J* = 11.0 Hz, 1H), 4.94-5.06 (m, 2H), 5.70-5.90 (m, 1H), 6.88 (d, *J* = 8.7 Hz, 2H), 7.27 (d, *J* = 6.8 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 13.9 (q), 22.5 (t), 25.7 (t), 27.7 (t), 29.8 (t), 31.8 (t), 32.0 (t), 55.1 (q), 71.3 (t), 71.4 (d), 81.0 (d), 113.7 (d, 2C), 114.6 (t), 129.3 (d, 2C), 130.4 (s), 138.5 (d), 159.1 (s) ppm; HRMS (ESI+) calcd for $C_{19}H_{30}O_3Na$ 329.2087; Found 329.2081.

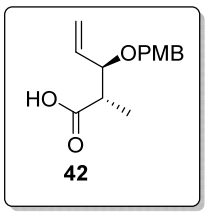
***(S)-4-benzyl-3-((2S,3R)-3-((4-methoxybenzyl)oxy)-2-methylpent-4-enoyl)oxazolidin-2-one* (52)**:



52

To a solution of alcohol **51** (2 g, 6.91 mmol) in toluene (20 mL) was added PMBCl (1.9 mL, 13.82 mmol) followed by Ag_2O (3.2 g, 13.82 mmol) at rt. Then the reaction mixture was stirred at room temperature for 26 h and rection mixture was filtered over celite, concentrated under reduced pressure. The resulting crude product was purified by the column chromatography (230–400 silica gel, 10% EtOAc in pet ether) to give **52** (600 mg, 61%) as a colorless oil along with recovered starting material 700 mg. $[\alpha]_D^{25}$ −25.7 (*c* 2.0, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.24 (d, *J* = 6.8 Hz, 3H), 2.71 (dd, *J* = 13.3, 9.7 Hz, 1H), 3.25 (dd, *J* = 13.3, 3.2 Hz, 1H), 3.77 (s, 3H), 3.88–4.12 (m, 4H), 4.25 (d, *J* = 11.7 Hz, 1H), 4.37–4.51 (m, 1H), 4.55 (d, *J* = 11.7 Hz, 1H), 5.24–5.33 (m, 2H), 5.5.83 (ddd, *J* = 16.1, 9.0, 7.3 Hz, 1H), 6.84 (d, *J* = 8.7 Hz, 2H), 7.16–7.37 (m, 7H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ 12.5 (q), 37.7 (t), 42.2 (d), 55.2 (q), 55.5 (d), 65.8 (t), 69.8 (t), 80.2 (d), 113.6 (d, 2C), 118.8 (t), 127.2 (d), 128.9 (d, 2C), 129.4 (d, 2C), 129.5 (d, 2C), 130.3 (s), 135.3 (s), 136.0 (d), 153.1 (s), 159.0 (s), 174.3 (s) ppm; HRMS (ESI+) calcd for $C_{24}H_{27}O_5NNa$ 432.1781; Found 432.1777; HRMS (ESI+) calcd for $C_{24}H_{27}O_5$ NNa 432.1781; Found 432.1777.

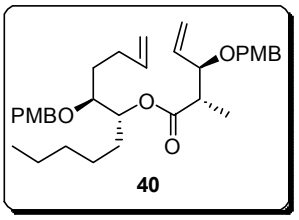
(2S,3R)-3-((4-methoxybenzyl)oxy)-2-methylpent-4-enoic acid (42):



42

To a solution oxazolidinone **52** (450 mg, 1.1 mmol) in THF:H_2O (4:1 mL) was added LiOH.H_2O (92 mg, 2.2 mmol) followed by 30% H_2O_2 in water (149 mg, 0.5 ml, 4.4 mmol) at 0 ^{o}C. The reaction mixture was stirred at rt for 3 h. After completion of reaction, the reaction mixture was neutralized with 2N HCl and the aqueous layer was washed with CH_2Cl_2 (3×20 mL), concentrated, and purified by column chromatography (100-200 silica gel, 4% MeOH in CH_2Cl_2) to give of acid **42** (165 mg, 60%). $[\alpha]_D^{25}$ −43.2 (*c* 1.0, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.20 (d, *J* = 7.1 Hz, 3H), 2.69 (quintet, *J* = 6.9 Hz, 1H), 3.80 (s, 3H), 4.01 (dd, *J* = 7.6, 5.9 Hz, 1H), 4.32 (d, *J* = 11.4 Hz, 1H), 4.58 (d, *J* = 11.4, 1H), 5.27–5.37 (m, 2H), 5.79 (ddd, *J* = 16.9, 10.6, 7.8 Hz, 1H), 6.86 (d, *J* = 8.7 Hz, 2H), 7.23 (d, *J* = 8.7 Hz, 2H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ 12.1 (q), 44.5 (d), 55.2 (q), 70.2 (t), 80.5 (d), 113.8 (d, 2C), 119.7 (t), 129.4 (d, 2C), 129.8 (s), 135.1 (d), 159.2 (s), 178.6 (s) ppm; HRMS (ESI+) calcd for $C_{14}H_{18}O_4$ Na 273.1097; Found 273.1094.

***(5S,6R)-5-((4-methoxybenzyl)oxy)undec-1-en-6-yl (2S,3R)-3-((4-methoxybenzyl)oxy)-2-methylpent-4-enoate* (40):**

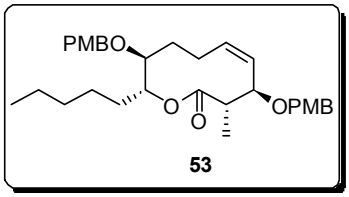


40

To a solution of acid **42** (500 mg, 2.0 mmol) in dry THF (10 mL), 2,4,6-trichlorobenzyl chloride (0.37 mL, 2.40 mmol) followed by *N,N*-diisopropylethylamine (2 mL, 11.49 mmol) were added and the mixture was stirred for 2 h at ambient temperature. After completion of mixed anhydride formation as indicated by TLC, DMAP (488 mg, 4.0 mmol) and a solution of alcohol **41** (612 mg, 2.0 mmol) in THF (5 mL) was introduced and the contents were stirred for 16 h at rt. The reaction mixture was quenched with cold water (20 mL) and extracted with ethyl acetate (2×30 mL). The combined organic phase was washed with aq. $NaHCO_3$ solution and water, dried (Na_2SO_4) and evaporated under reduced pressure. The crude product was purified by silica gel column chromatography (8→10% EtOAc in petroleum ether) to procure diene **40** (900 mg, 84%) as a light yellow oil.

$[\alpha]_D^{25}$ −8.0 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.85 (t, *J* = 6.6 Hz, 3H), 1.20 (d, *J* = 7.0 Hz, 3H), 1.22-1.25 (m, 2H), 1.47-1.79 (m, 8H), 2.01-2.08 (m, 1H), 2.17-2.25 (m, 1H), 2.63 (quin, *J* = 7.0 Hz, 1H), 3.41 (td, *J* = 3.2, 8.9 Hz, 1H), 3.78 (s, 3H), 3.78 (s, 3H), 3.97 (t, *J* = 7.2 Hz, 1H), 4.27 (d, *J* = 11.2 Hz, 1H), 4.31 (d, *J* = 10.8 Hz, 1H), 4.50 (d, *J* = 11.3 Hz, 1H), 4.58 (d, *J* = 11.0 Hz, 1H), 4.93-5.00 (m, 2H), 5.06 (td, *J* = 3.3, 9.3 Hz, 1H), 5.24-5.28 (m, 2H), 5.72-5.83 (m, 2H), 6.83-6.85 (m, 4H), 7.20-7.26 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 13.0 (q), 14.0 (q), 22.5 (t), 25.4 (t), 29.5 (t), 29.8 (t), 30.0 (t), 31.6 (t), 45.4 (d), 55.2 (q), 55.2 (q), 70.2 (t), 71.8 (t), 74.8 (d), 79.3 (d), 81.2 (d), 113.7 (d, 2C), 113.7 (d, 2C), 114.8 (t), 118.7 (t), 129.2 (d, 2C), 129.5 (d, 2C), 130.5 (s), 130.7 (s), 136.4 (d), 138.4 (d), 159.0 (s), 159.1 (s), 173.9 (s) ppm; HRMS (ESI+) calcd for $C_{33}H_{47}O_6$ 539.3367; Found 539.3378.

***(3S,4R,9S,10R,Z)-4,9-bis((4-methoxybenzyl)oxy)-3-methyl-10-pentyl-3,4,7,8,9,10-hexahydro-2H-oxecin-2-one* (53):**



53

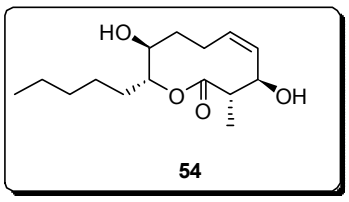
To a solution of diene **40** (100 mg, 0.18 mmol) in dry CH_2Cl_2 (30 mL), 2nd gen. Grubbs' catalyst (31 mg, 0.04 mmol) was added and the mixture was degassed under an argon atmosphere thoroughly.

The reaction mixture was heated at 40 ˚C for 6 h and the solvent was removed under reduced pressure. The residue was purified by column chromatography (10 →12% EtOAc in petroleum ether) giving macrolide **53** (69 mg, 73%) as a colorless liquid.

$[\alpha]_D^{25}$ 7.2 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.85 (t, *J* = 6.9 Hz, 3H), 1.25-1.28 (m, 5H), 1.30 (d, *J* = 6.9 Hz, 3H), 1.45-1.55 (m, 4H), 2.01-2.08 (m, 2H), 2.34-2.39 (m, 1H), 2.53-2.60 (m, 1H), 3.30 (dt, *J* = 2.2, 7.2 Hz, 1H), 3.79 (s, 3H), 3.80 (s, 3H), 4.20-4.27 (m, 2H), 4.44 (s, 2H), 4.52 (d, *J* = 11.8 Hz, 1H), 4.99-5.02 (m, 1H), 5.25 (t, *J* = 10.1 Hz, 1H), 5.73 (dt, *J* = 3.6, 11.8 Hz, 1H), 6.85-6.88 (m, 4H), 7.20-7.23 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 13.9 (q), 15.3 (q), 22.5 (t), 24.6 (t), 24.7 (t), 30.2 (t), 31.5 (t), 31.6 (t), 47.7 (d), 55.3 (q), 55.3 (q), 70.1 (t), 70.5 (t), 75.0 (d, 2C), 79.9 (d), 113.7 (d, 2C), 113.7 (d, 2C), 128.2 (d), 129.1 (d, 2C), 129.5 (d, 2C), 130.6 (s, 2C), 135.6 (d), 159.1 (s), 159.1 (s), 172.8 (s) ppm; HRMS (ESI+) calcd for $C_{31}H_{42}O_6Na$ 533.2874; Found 533.2866.

***(3S,4R,9S,10R,Z)-4,9-dihydroxy-3-methyl-10-pentyl-3,4,7,8,9,10-hexahydro-2H-oxecin-2-one* (54):**

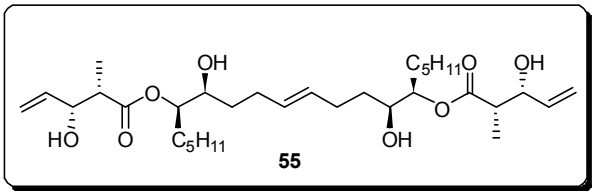
To an ice cooed solution of **53** (50 mg, 97.91 µmol) in dry CH_2Cl_2 (2 mL) was added TFA (15 µL) and stirred for 2h at 0 °C. The reaction mixture was concentrated under reduced pressure, and the resulting residue was purified on silica gel column (30 →35% EtOAc in petroleum ether) to furnish **54** (20.0 mg, 75%) as a white solid.



54

$[\alpha]_D^{25}$ 15.2 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.87 (t, *J* = 6.5 Hz, 3H), 1.29-1.36 (m, 6H), 1.38 (d, *J* = 6.7 Hz, 3H), 1.55-1.62 (m, 2H), 1.76-1.85 (m, 1H), 1.92-2.03 (m, 2H), 2.47-2.55 (m, 1H), 2.73 (dq, *J* = 3.7, 12.2 Hz, 1H), 3.79 (brs, 1H), 4.62 (t, *J* = 9.5 Hz, 1H), , 5.11 (td, *J* = 3.7, 8.3 Hz, 1H), 5.35 (dt, *J* = 1.5, 10.9 Hz, 1H), 5.73 (dt, *J* = 3.5, 11.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.9 (q), 14.9 (q), 22.4 (t), 25.2 (t), 25.3 (t), 30.9 (t), 31.3 (t), 31.4 (t), 49.1 (d), 69.5 (d), 74.3 (d), 77.7 (d), 129.9 (d), 133.9 (d,), 174.7 (s) ppm; HRMS (ESI+) calcd for $C_{15}H_{26}O_4Na$ 293.1723; Found 293.1722.

***(6R,7S,14S,15R,E)-7,14-dihydroxyicos-10-ene-6,15-diyl (2S,2'S,3R,3'R)-bis(3-hydroxy-2-methylpent-4-enoate)* (55):**

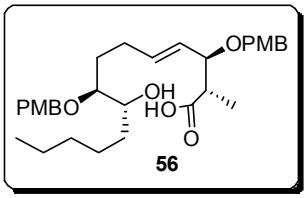


55

To a solution of diene **40** (100 mg, 0.18 mmol) in dry CH_2Cl_2 (30 mL), furstner' catalyst (18 mg, 0.02 mmol) was added and the mixture was degassed under an argon atmosphere thoroughly. The reaction mixture was heated at 40 ˚C for 12 h and the solvent was removed under reduced pressure. A solution of resulting crude CM product (70 mg, 0.07 mmol) and DDQ (76 mg, 0.33 mmol) in CH_2Cl_2-water (3 mL, 18:1) was stirred for 3 h at room temperature. To this was added aqueous sodium bicarbonate solution (5 ml), and the contents were partitioned between water and CH_2Cl_2. The aqueous layer was extracted with CH_2Cl_2 (5 ml), and the combined organic layer was dried over Na_2SO_4 and concentrated. The residue was purified by silica gel chromatography (60 →70% EtOAc in petroleum ether) to give **55** (30 mg, 57%) as yellow syrup

$[\alpha]_D^{25}$ 28.6 (*c* 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.87 (t, *J* = 6.7 Hz, 6H), 1.15 (d, *J* = 7.1 Hz, 6H), 1.24-1.26 (m, 14H), 1.44-1.52 (m, 6H), 2.16-2.34 (m, 4H), 2.62-2.68 (m, 2H), 3.64-3.72 (m, 2H), 4.47 (s, 2H), 4.88-4.93 (m, 2H), 5.20 (d, *J* = 10.5 Hz, 2H), 5.32 (d, *J* = 17.2 Hz 2H), 5.39 (t, *J* = 5.0 Hz, 1.2H), 5.46 (t, *J* = 3.8 Hz, 0.4H), 5.81-5.90 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.0 (q, 2C), 22.5 (t, 2C, Major), 22.6 (t, 2C, Minor), 23.4 (t, 2C), 25.2 (t, 2C), 28.9 (t, 2C), 29.7 (t, 2C), 31.3 (t, 2C), 31.6 (t, 2C), 36.8 (q, 2C, Minor), 36.8 (q, 2C, Major), 45.2 (d, 2C, Minor), 45.3 (d, 2C, Major), 71.9 (d, 2C, Major), 72.5 (d, 2C, Minor), 73.2 (d, 2C, Minor), 73.3 (d, 2C, Major), 77.9 (d, 2C), 116.3 (t, 2C, Major), 116.4 (t, 2C, Minor), 129.9 (d, 2C, Major), 130.0 (d, 2C, Minor), 137.5 (d, 2C, Major), 138.5 (d, 2C, Minor), 175.2 (s) ppm; HRMS (ESI+) calcd for $C_{38}H_{56}O_8Na$ 591.3867; Found 591.3865.

***(2S,3R,8S,9R,E)-9-hydroxy-3,8-bis((4-methoxybenzyl)oxy)-2-methyltetradec-4-enoic acid* (56):**



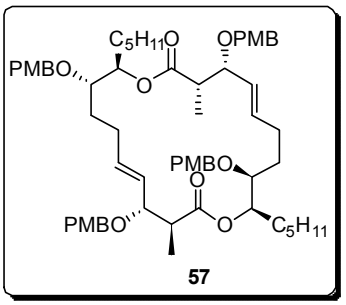
56

A degassed solution of acid **42** (50 mg, 0.2 mmol), alcohol **41** (122 mg, 0.4 mmol) and Grubbs' 2nd gen. catalyst (33 mg, 0.04 mmol) in dichloromethane (30 mL) was heated under reflux under argon for 96 h and concentrated. The residue was purified by column chromatography (4–5% MeOH in CH_2Cl_2) to afford **56** (55 mg, 52%) as yellow oil.

$[\alpha]_D^{25}$ −20.8 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.89 (t, *J* = 6.9 Hz, 3H), 1.16 (d, *J* = 7.2 Hz, 3H), 1.29-1.35 (m, 5H), 1.36-1.55 (m, 4H), 1.63-1.75 (m, 1H), 2.04-2.17 (m, 1H), 2.21-2.29 (m, 1H), 2.67 (quin, *J* = 6.3 Hz, 1H), 3.34 (td, *J* = 3.7, 8.6 Hz, 1H), 3.73-3.79 (m, 1H), 3.79 (s, 6H), 3.89 (dd, *J* = 6.1, 8.3 Hz, 1H), 4.29 (d, *J* = 11.4 Hz, 1H), 4.44 (d, *J* = 11.2 Hz, 1H), 4.54 (d, *J* = 11.6 Hz, 2H), 5.36 (dd, *J* = 8.8, 15.4 Hz, 1H), 5.67 (td, *J* = 6.8, 15.4 Hz, 1H), 6.85-6.89 (m, 4H), 7.21 (d, *J* = 8.4 Hz, 2H), 7.26 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 12.5 (q), 14.0 (q), 22.6 (t), 25.9 (t), 28.0 (t), 28.4 (t), 31.8 (t, 2C), 44.6 (d), 55.2 (q, 2C), 69.8 (t), 71.4 (d), 71.5 (t), 80.5 (d), 81.0 (d), 113.8 (d, 2C), 113.8 (d, 2C), 126.9 (d), 129.4 (d, 2C), 129.5 (d, 2C), 129.7 (s), 130.3 (s), 136.7 (d), 159.2 (s), 159.3 (s), 176.9 (s) ppm; HRMS (ESI+) calcd for $C_{31}H_{44}O_7Na$ 551.2979; Found 551.2972.

***(3S,4R,5E,9S,10R,13S,14R,15E,19S,20R)-4,9,14,19-tetrakis((4-methoxybenzyl)oxy)-3,13-dimethyl-10,20-dipentyl-1,11-dioxacycloicosa-5,15-diene-2,12-dione* (57):**

A solution of seco acid **56** (40 mg, 75.6 µmol) in dry toluene (20 mL), was added to the stirred solution of molecular sieves (4A°, 1g), DMAP (27 mg, 0.22 mmol) and 2-Methyl-6-Nitrobenzoic anhydride (20 mg, 0.06 mmol) in dry toluene (20 ml) using syringe pump (0.8 ml/h). After the addition was complete it was stirred for another 6 h at rt. The rection mix was diluted with ethyl acetate and was filtered. The organic phase was washed with sat. $NaHCO_3$, brine, dried and concentrated. The residue was purified by column chromatography (20 →25% EtOAc in petroleum ether) giving **57** (20 mg, 52%) as a yellow liquid.



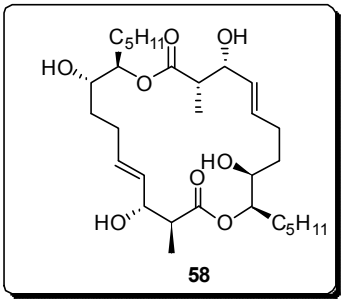
57

$[\alpha]_D^{25}$ 13.9 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.85 (t, *J* = 7.3 Hz, 6H), 1.19 (d, *J* = 6.7 Hz, 6H), 1.25-1.32 (m, 16H), 1.40-1.46 (m, 2H), 1.65-1.72 (m, 2H), 1.95-2.02 (m, 2H), 2.24-2.31 (m, 2H), 2.71 (quin, *J* = 7.4 Hz, 2H), 3.36-3.38 (m, 2H), 3.71 (t, *J* = 7.8 Hz, 2H), 3.77 (s, 6H), 3.77 (s, 6H), 4.21 (d, *J* = 11.3 Hz, 2H), 4.34 (d, *J* = 10.8 Hz, 2H), 4.48 (d, *J* = 11.1 Hz, 2H), 4.54 (d, *J* = 10.9 Hz, 2H), 4.99-5.00 (m, 2H), 5.50 (dd, *J* = 8.7, 15.7 Hz, 2H), 5.62 (td, *J* = 5.6, 15.2 Hz, 2H), 6.82-6.85 (m, 8H), 7.21 (d, *J* = 8.1 Hz, 8H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.0 (q, 2C), 14.1 (q, 2C), 22.5 (t, 2C), 25.3 (t, 2C), 28.0 (t, 2C), 29.3 (t, 2C), 30.3 (t, 2C), 31.7 (t, 2C), 46.0 (d, 2C), 55.2 (q, 4C), 69.3 (t, 2C), 71.3 (t, 2C), 74.2 (d, 2C), 78.7 (d, 2C), 81.2 (d, 2C), 113.7 (d, 4C), 113.7 (d, 4C), 128.2 (d, 2C), 129.2 (d, 4C), 129.4 (d, 4C), 130.4 (s, 2C),

130.6 (s, 2C), 135.5 (d, 2C), 159.0 (s, 2C), 159.2 (s, 2C), 173.3 (s, 2C) ppm; HRMS (ESI+) calcd for $C_{62}H_{84}O_{12}Na$ 1043.5855; Found 1043.5865.

(3S,4R,5E,9S,10R,13S,14R,15E,19S,20R)-4,9,14,19-tetrahydroxy-3,13-dimethyl-10,20-dipentyl-1,11-dioxacycloicosa-5,15-diene-2,12-dione **(58):**

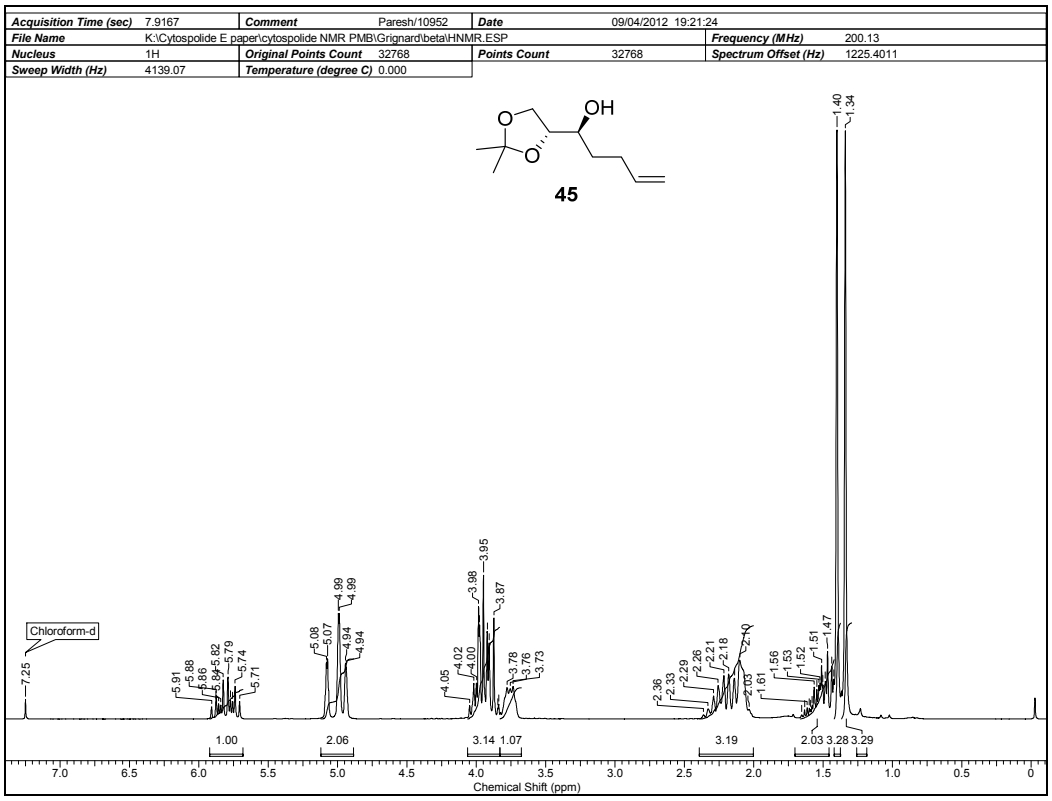
To an ice cooed solution of **57** (20 mg, 19.58 μmol) in dry CH_2Cl_2 (2 mL) was added TFA (10 μL) and stirred for 2h at rt. The reaction mixture was concentrated under reduced pressure, and the resulting residue was purified on silica gel column (3→4% MeOH in CH_2Cl_2) to furnish macrolide **58** (7.6 mg, 72%) as a white-cream solid.



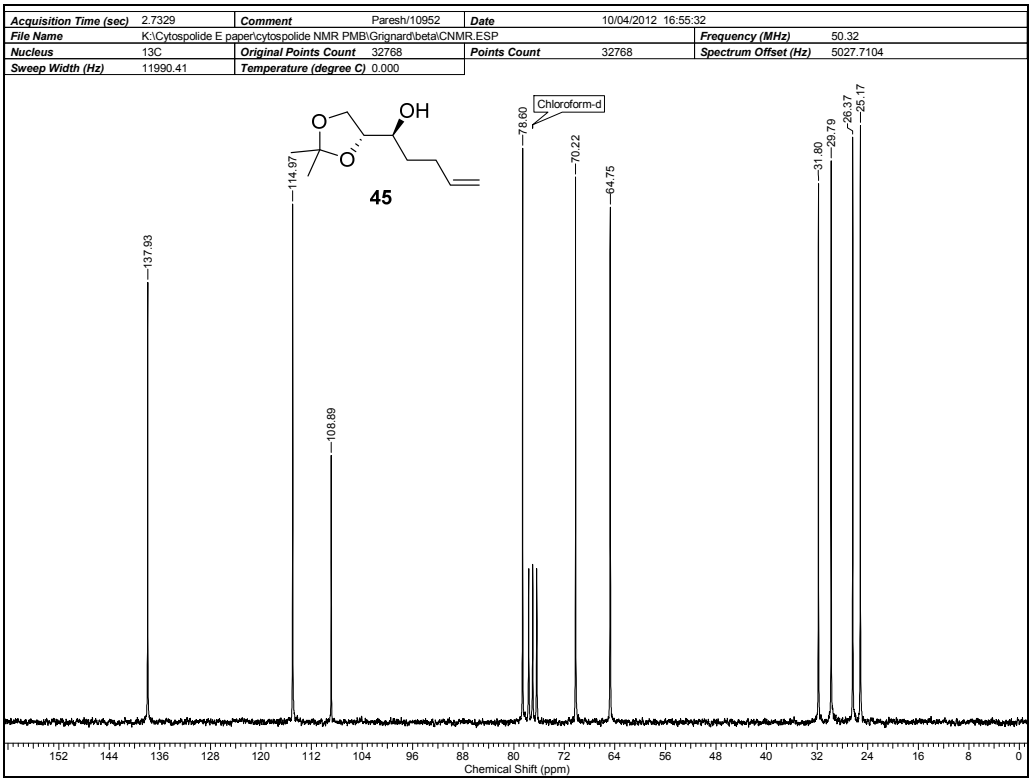
58

$[\alpha]_D^{25}$ 26.3 (*c* 0.3, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.85 (t, *J* = 7.3 Hz, 6H), 1.18-1.32 (m, 22H), 1.57-1.69 (m, 4H), 2.00-2.03 (m, 4H), 2.76-2.92 (m, 2H), 3.40-3.45 (m, 1H, Minor), 3.62-3.67 (m, 2H, Major), 4.08-4.13 (m, 2H), 4.87-4.96 (m, 2H), 4.96-5.0 (m, 1H, Minor), 5.59-5.66 (m, 2H), 5.77-5.85 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.5 (q, 2C, Minor), 13.8 (q, 2C, Major), 14.0 (q, 2C, Minor), 14.1 (q, 2C, Major), 22.4 (t, 2C, Minor), 22.7 (t, 2C, Major), 25.3 (t, 2C, Minor), 25.6 (t, 2C, Major), 28.1 (t, 2C, Minor), 28.5 (t, 2C, Major), 28.9 (t, 2C, Minor), 29.4 (t, 2C, Major), 30.1 (t, 2C, Minor), 30.4 (t, 2C, Major), 31.4 (t, 2C, Minor), 31.5 (t, 2C, Major), 45.6 (d, 2C, Minor), 46.7 (d, 2C, Major), 72.5 (d, 2C, Minor), 73.1 (d, 2C, Major), 73.9 (d, 2C, Minor), 74.4 (d, 2C, Major), 75.8 (d, 2C, Minor), 77.9 (d, 2C, Major), 129.2 (d, 2C, Major), 130.5 (d, 2C, Minor), 130.8 (d, 2C, Major), 131.6 (d, 2C, Minor), 174.5 (s, 2C, Major), 174.7 (s, 2C, Minor) ppm; HRMS (ESI+) calcd for $C_{30}H_{52}O_8Na$ 563.3554; Found 563.3550.

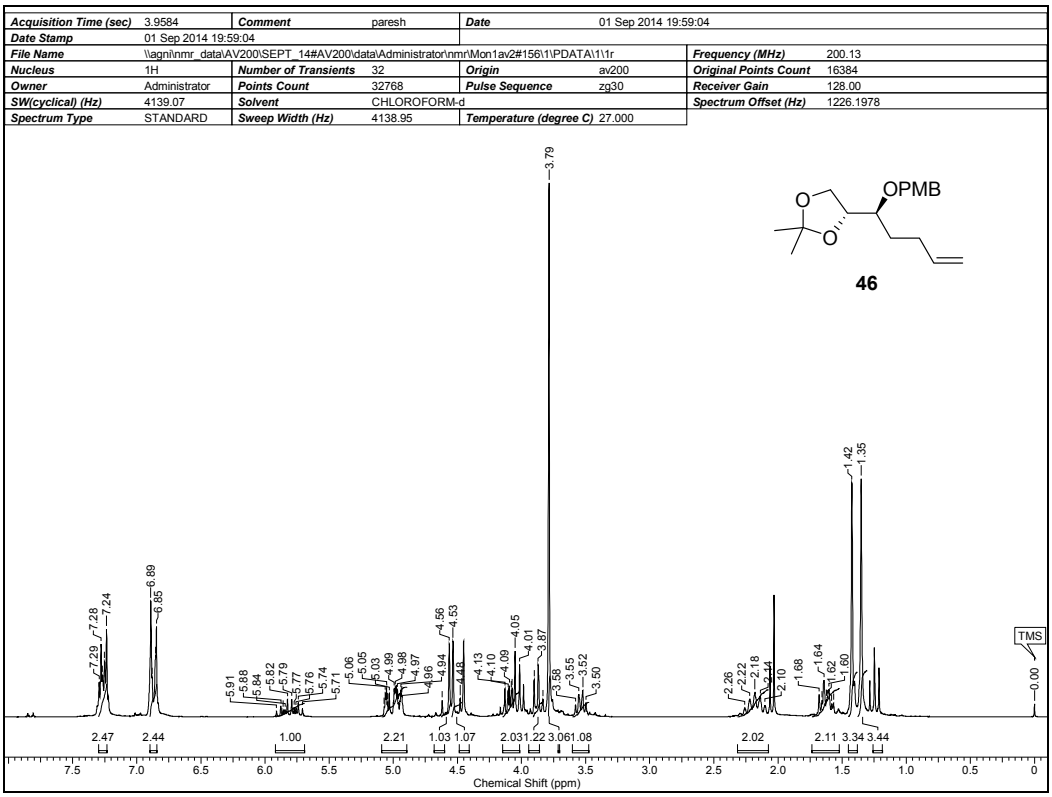
SPECTRA



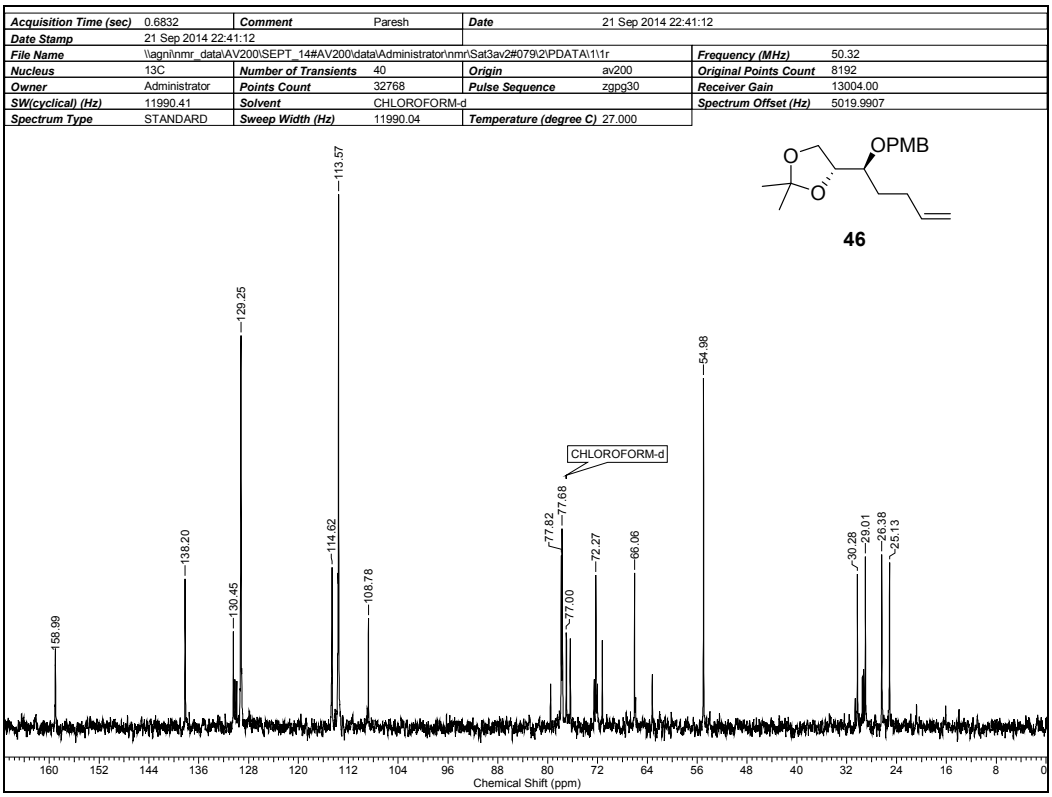
^{1}H NMR Spectrum of 45 in $CDCl_3$



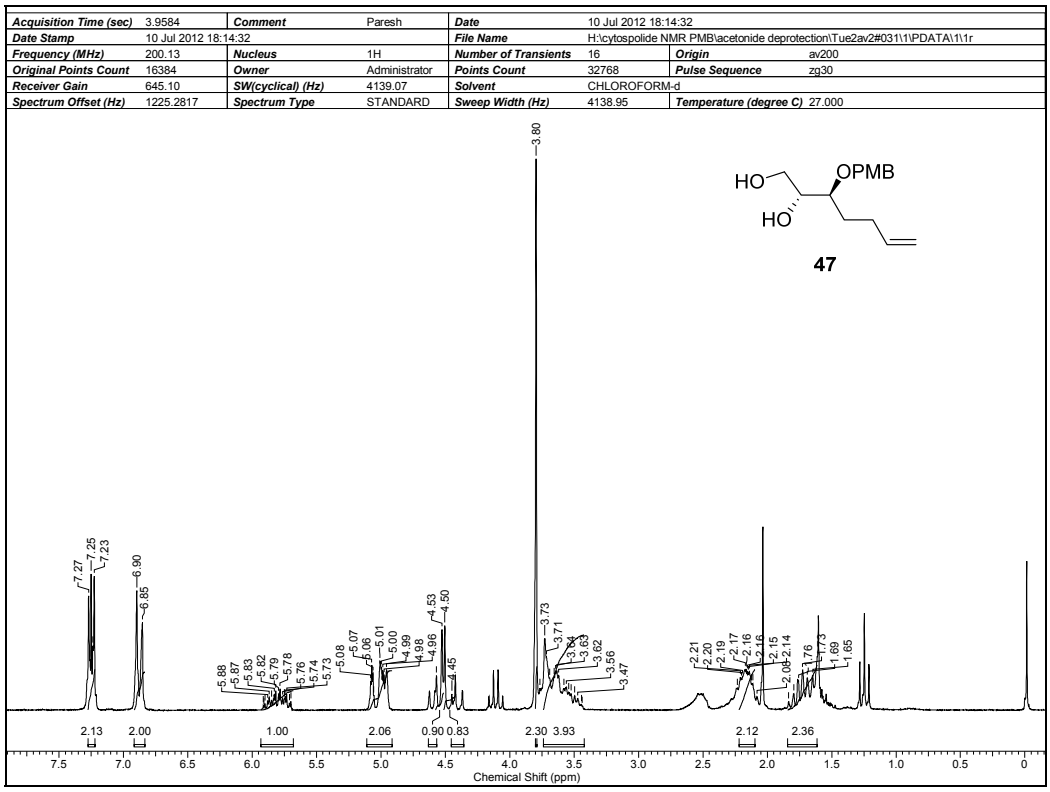
^{13}C NMR Spectrum of 45 in $CDCl_3$



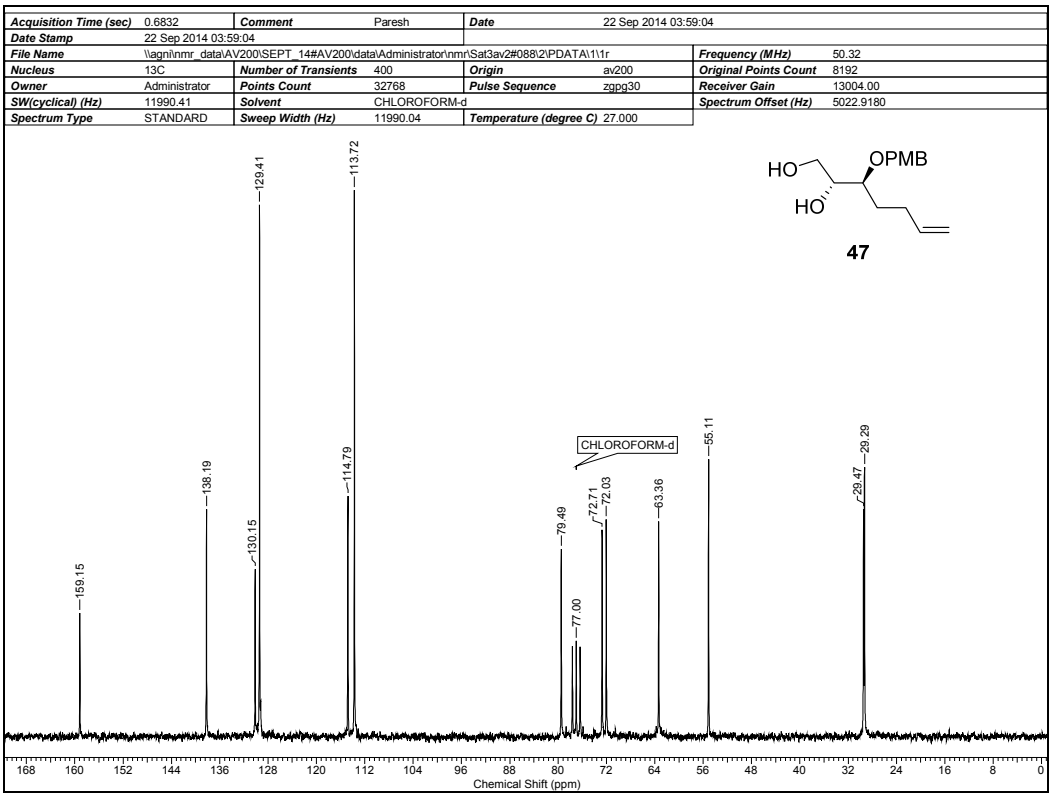
^{1}H NMR Spectrum of 46 in $CDCl_3$



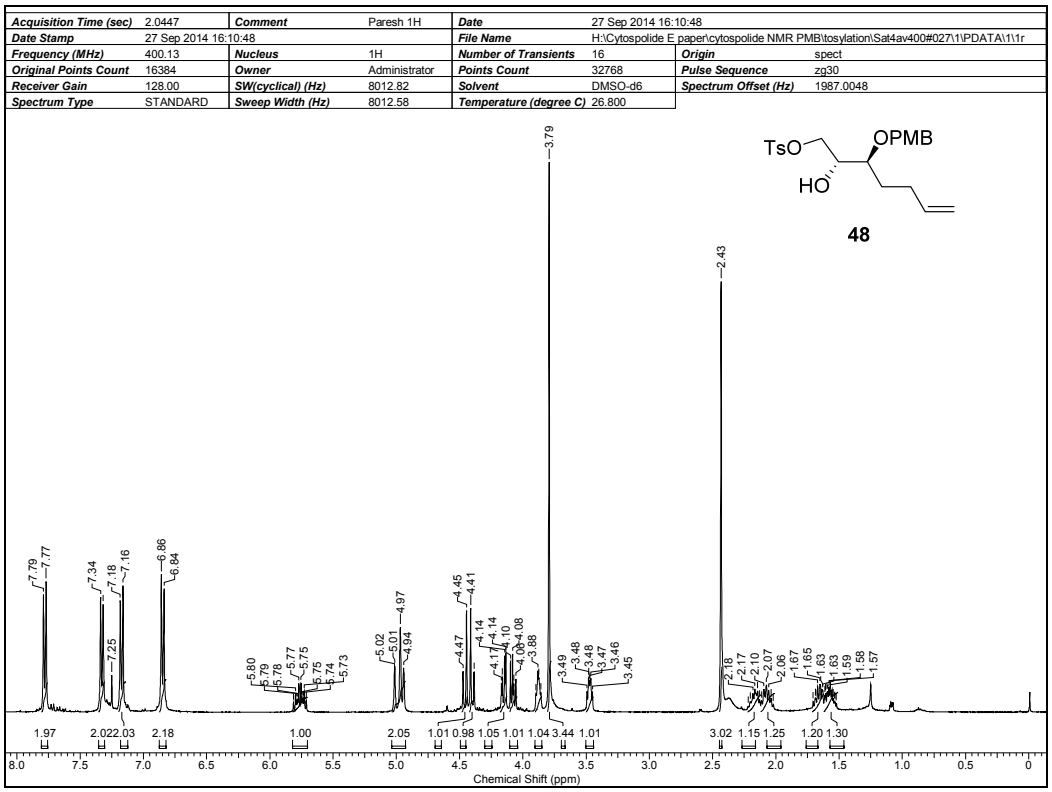
^{13}C NMR Spectrum of 46 in $CDCl_3$



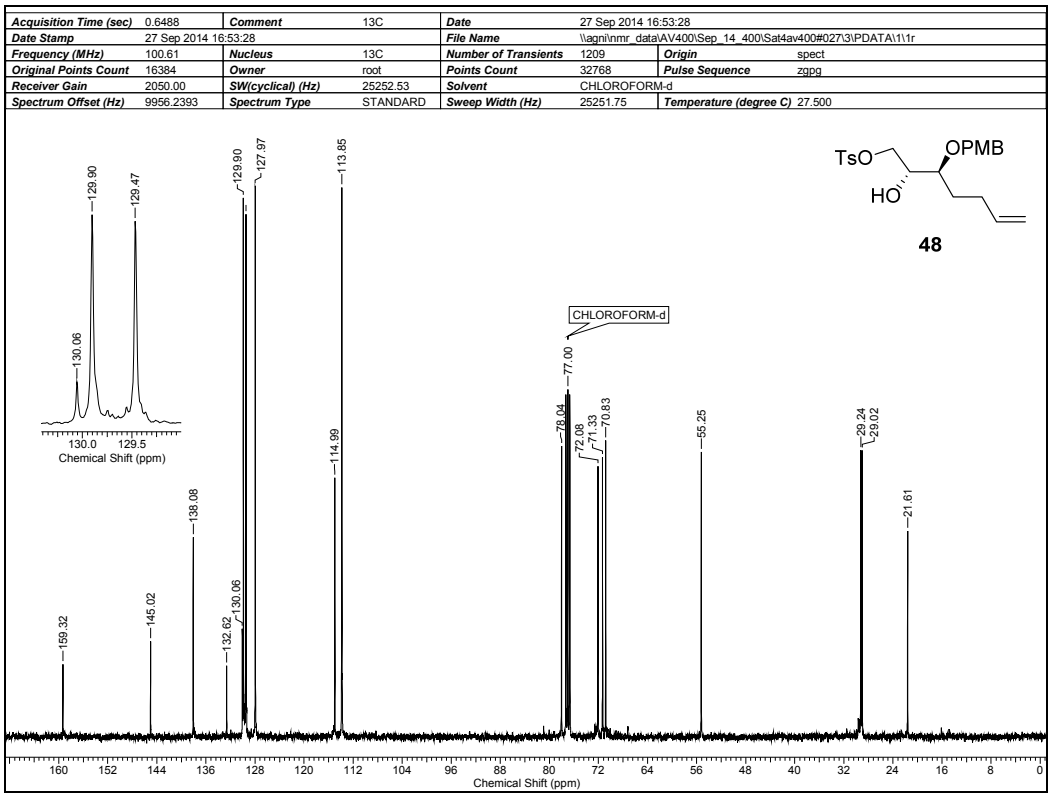
^{1}H NMR Spectrum of 47 in $CDCl_3$



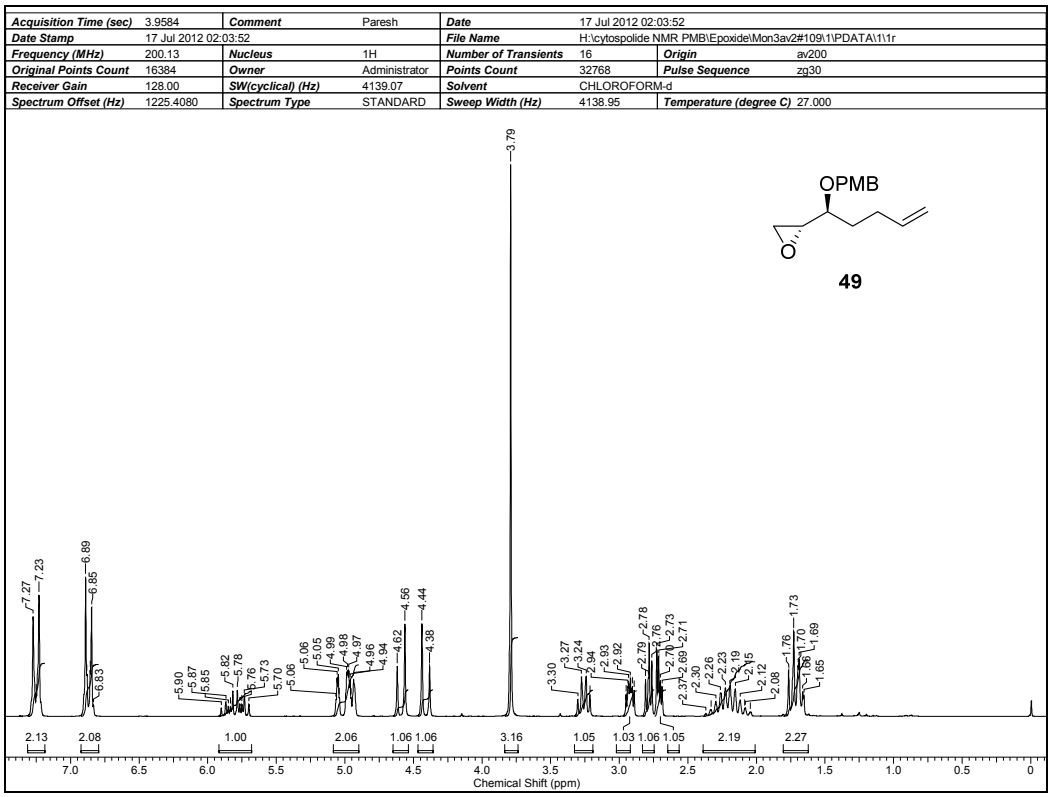
^{13}C NMR Spectrum of 47 in $CDCl_3$



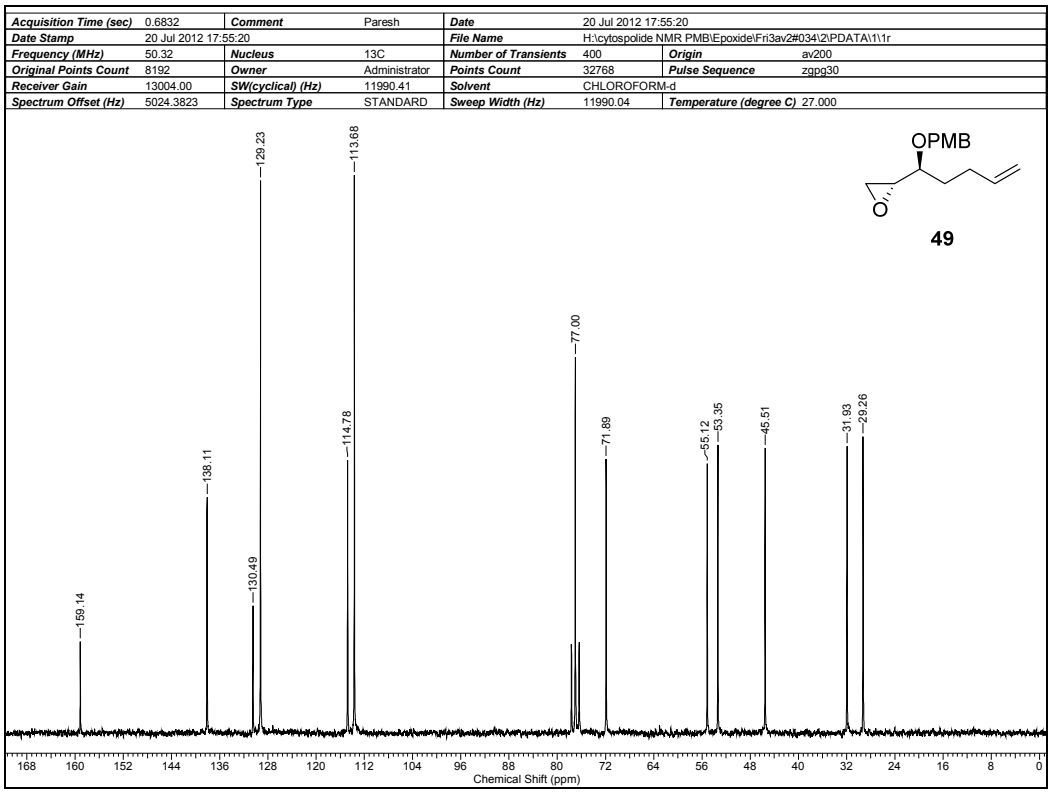
^{1}H NMR Spectrum of 48 in $CDCl_3$



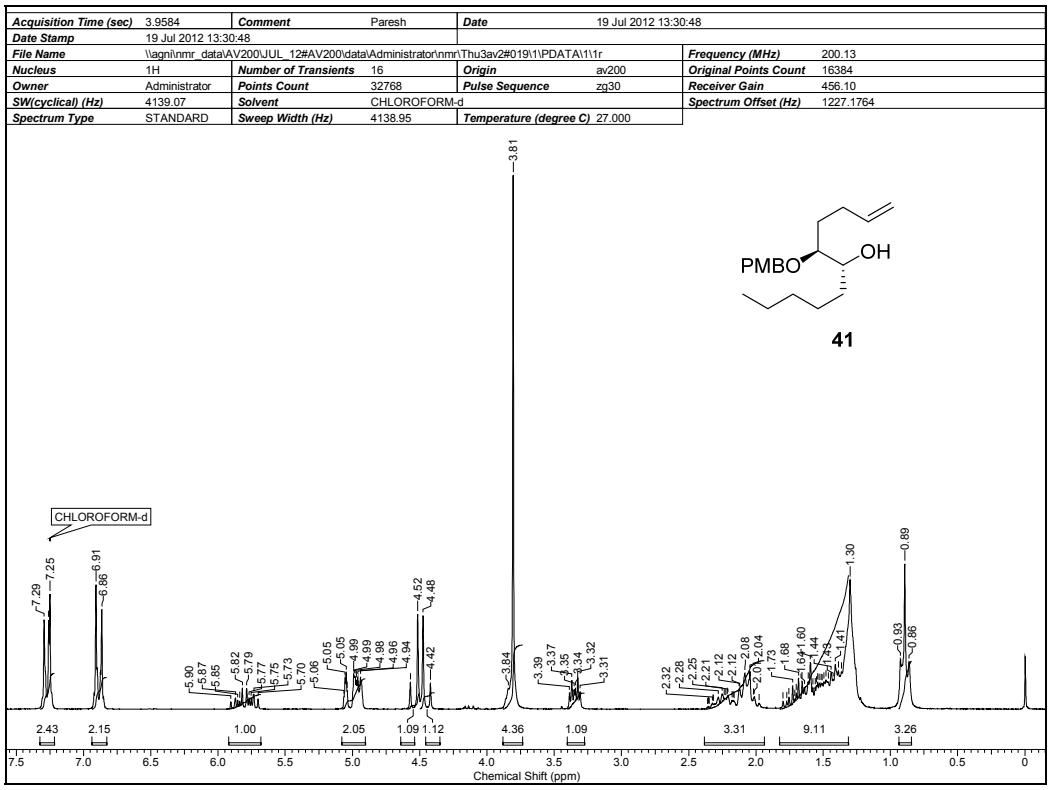
^{13}C NMR Spectrum of 48 in $CDCl_3$



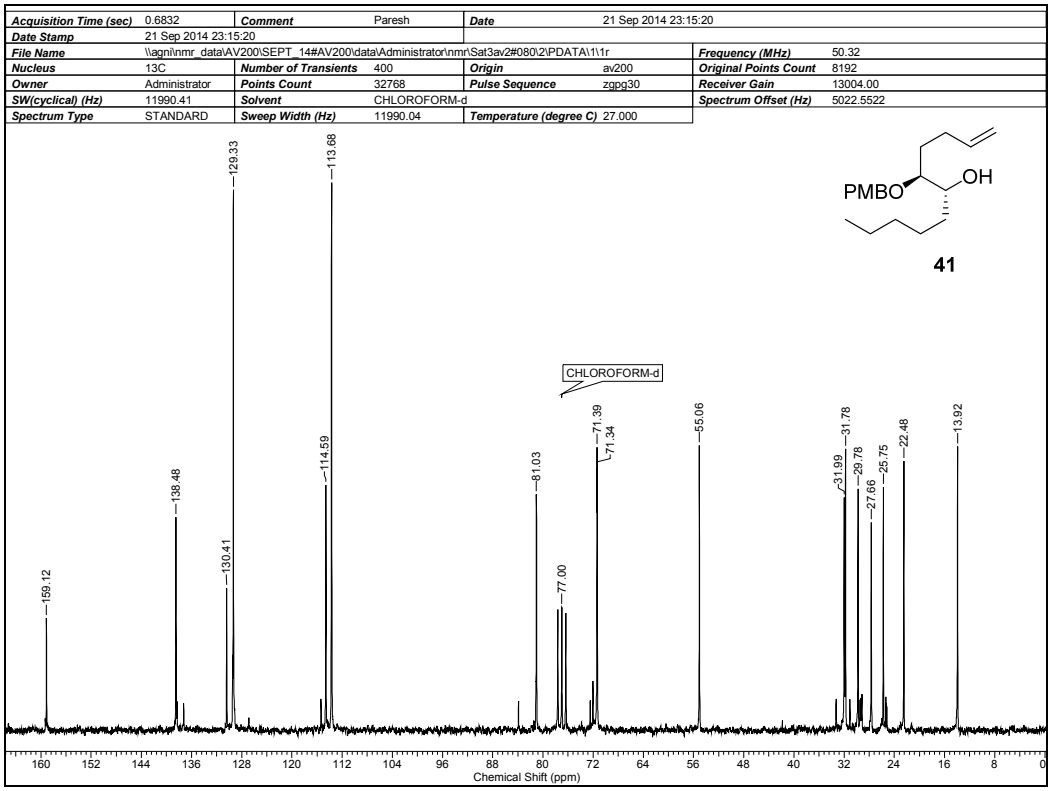
^{1}H NMR Spectrum of 49 in $CDCl_3$



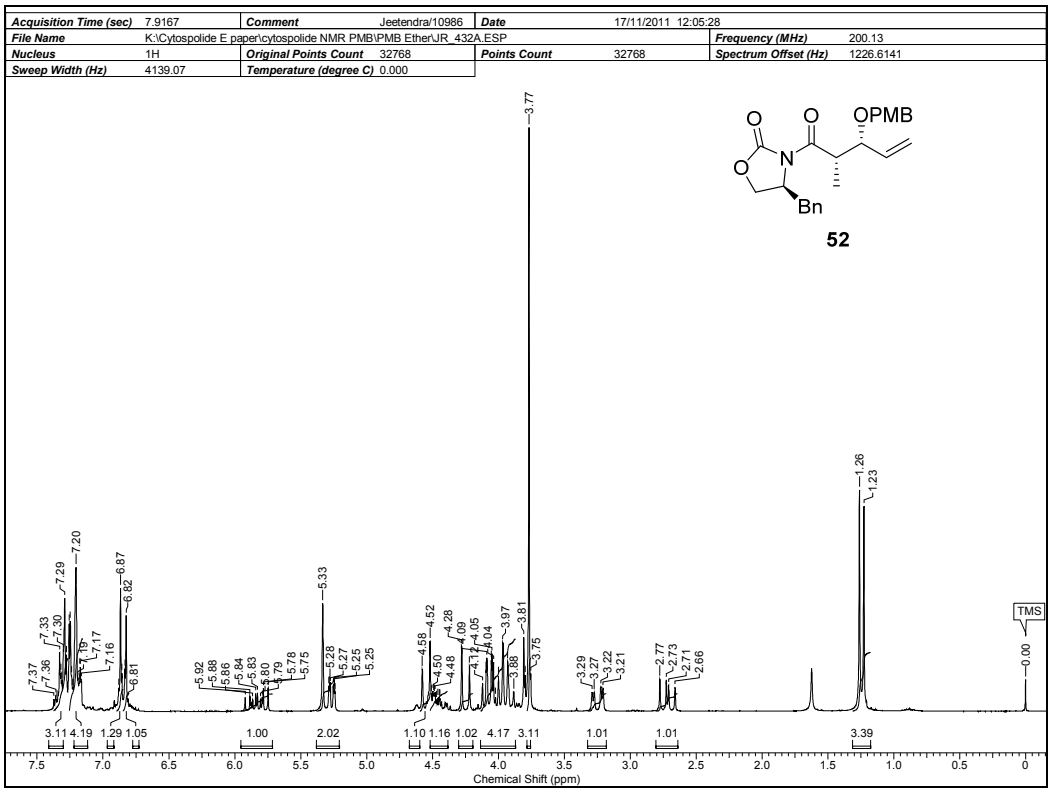
^{13}C NMR Spectrum of 49 in $CDCl_3$



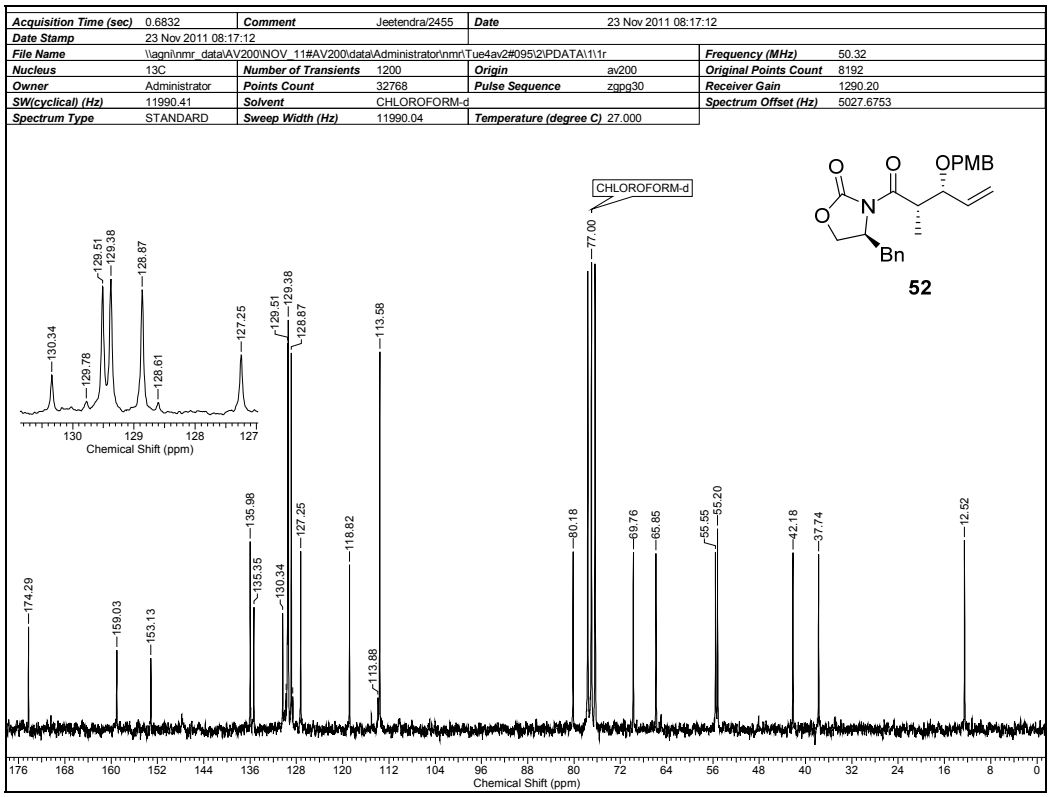
^{1}H NMR Spectrum of 41 in $CDCl_3$



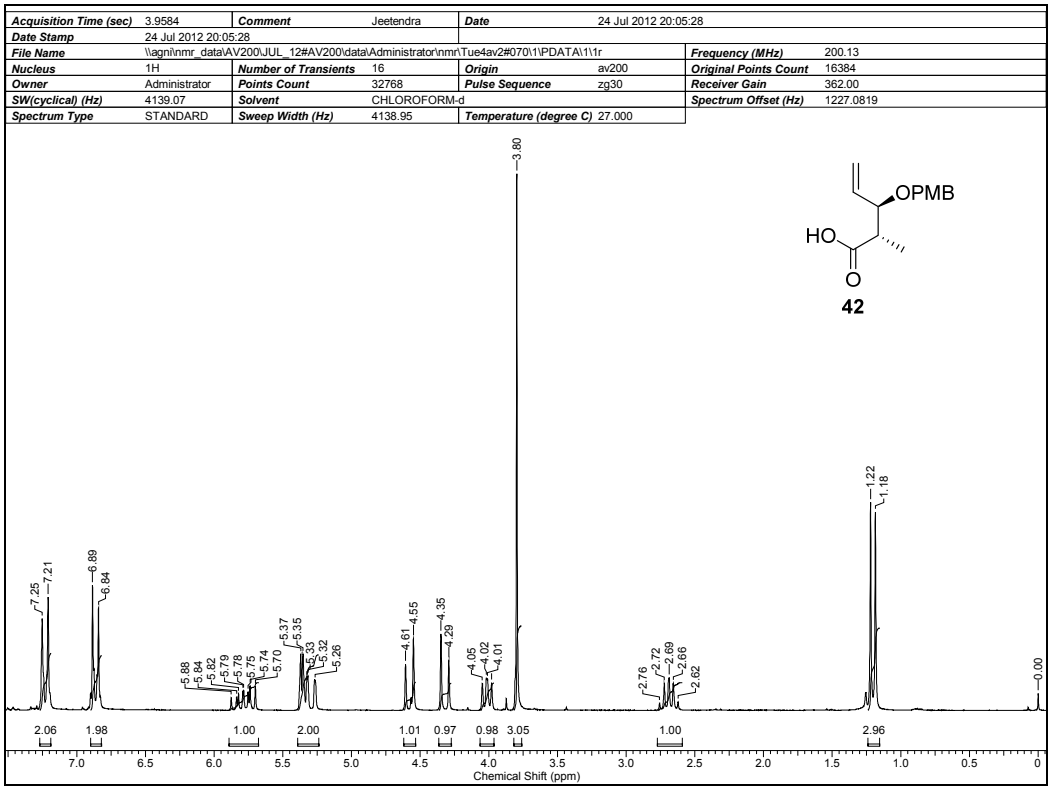
^{13}C NMR Spectrum of 41 in $CDCl_3$



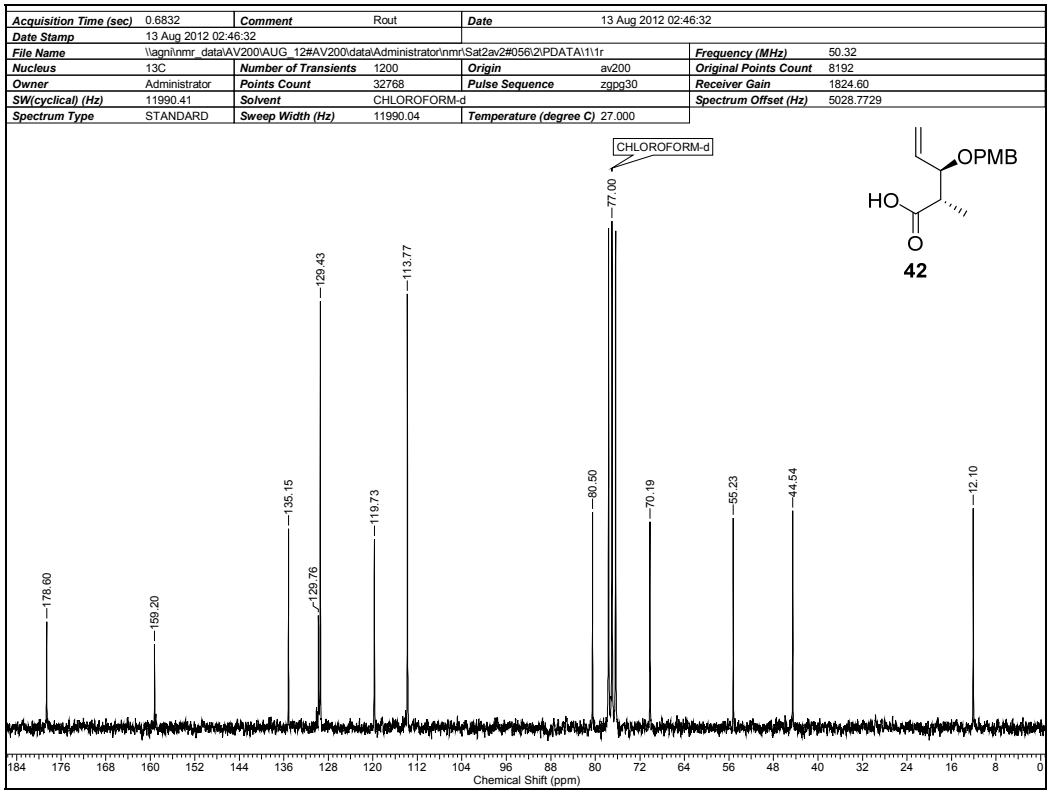
^{1}H NMR Spectrum of 52 in $CDCl_3$



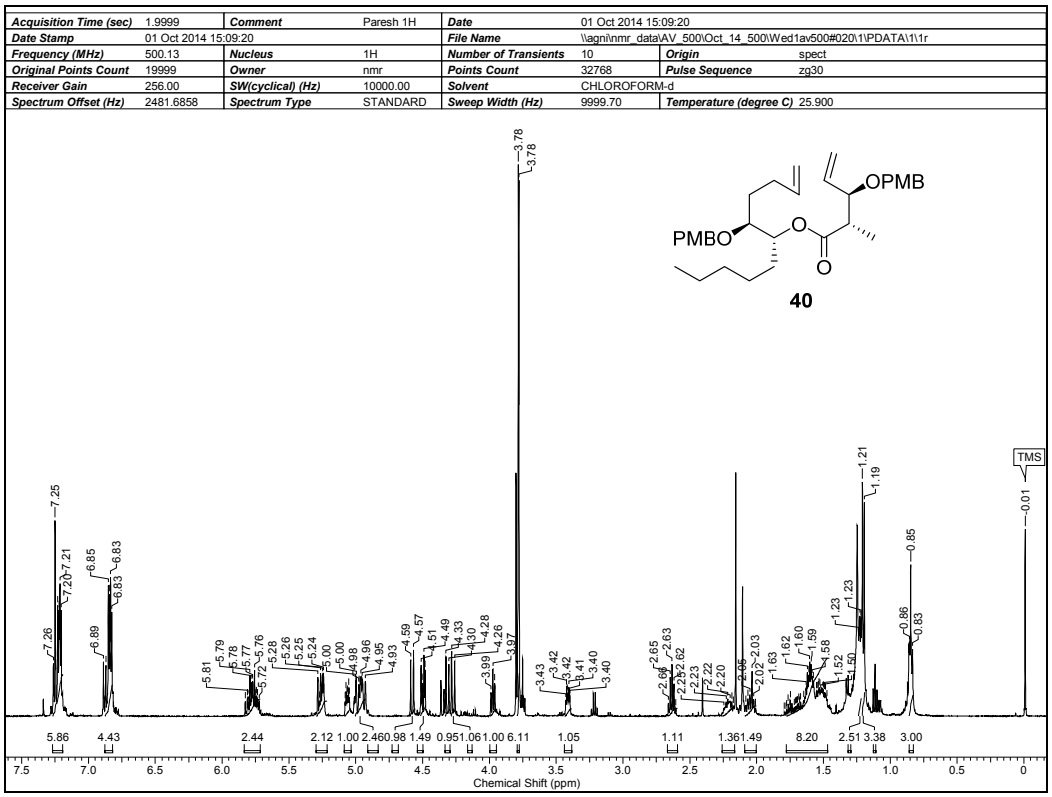
^{13}C NMR Spectrum of 52 in $CDCl_3$



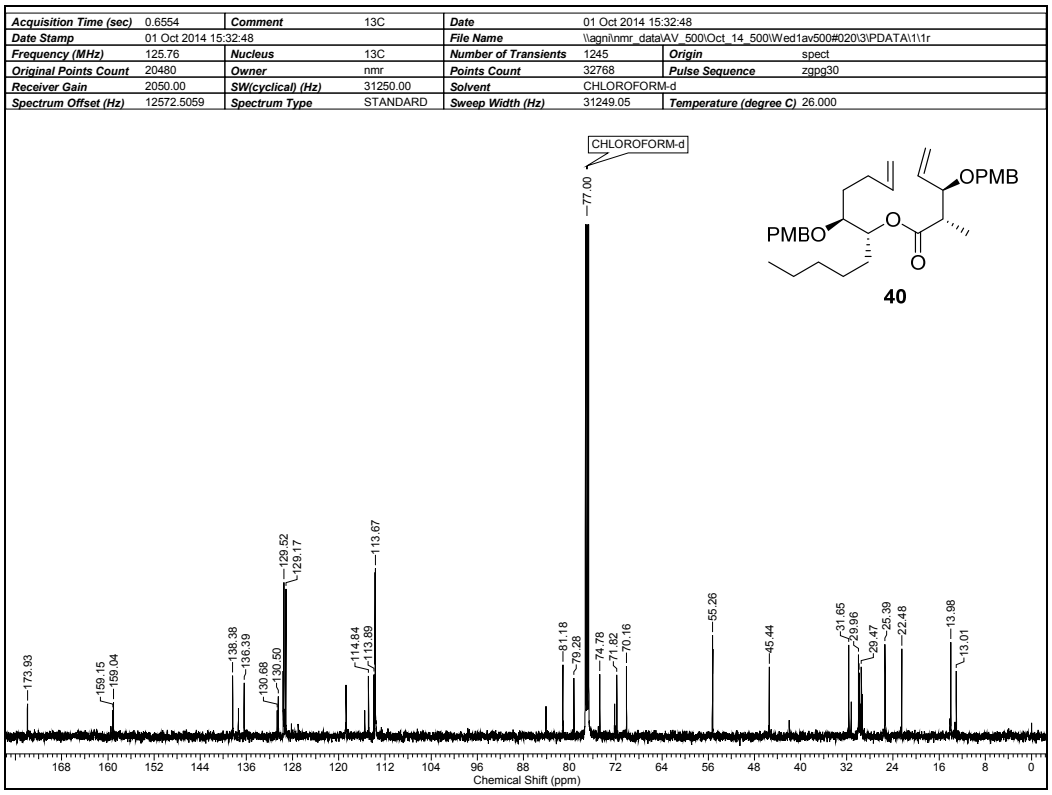
^{1}H NMR Spectrum of 42 in $CDCl_3$



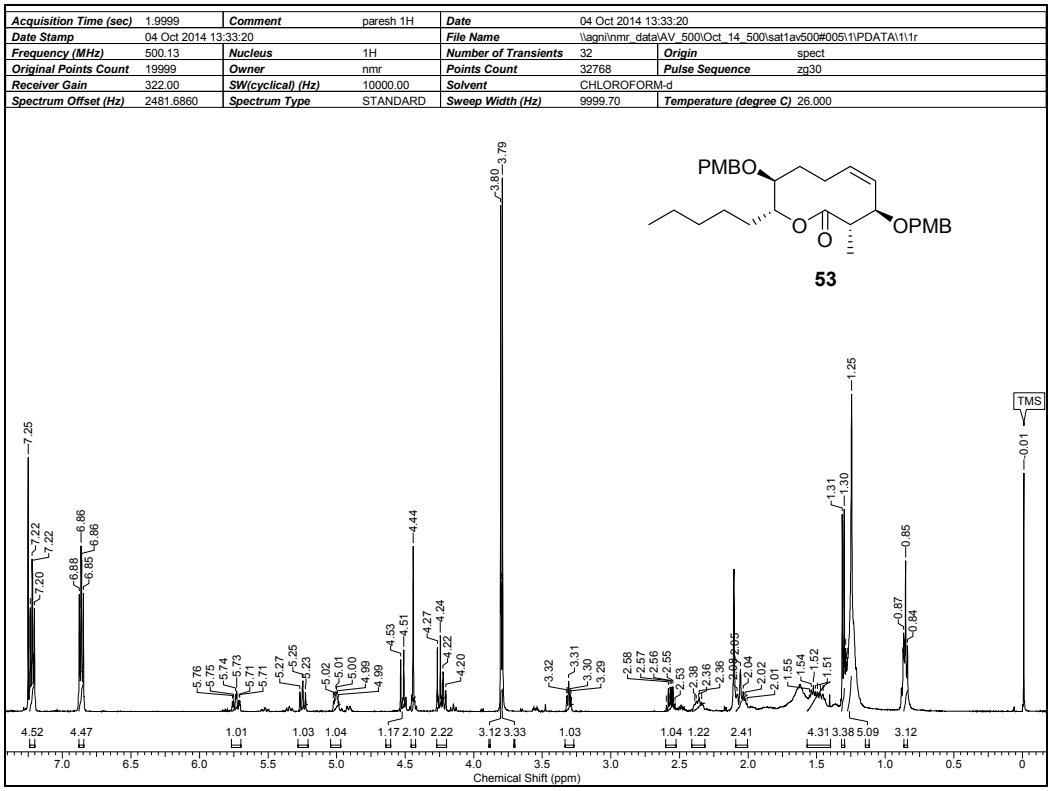
^{13}C NMR Spectrum of 42 in $CDCl_3$



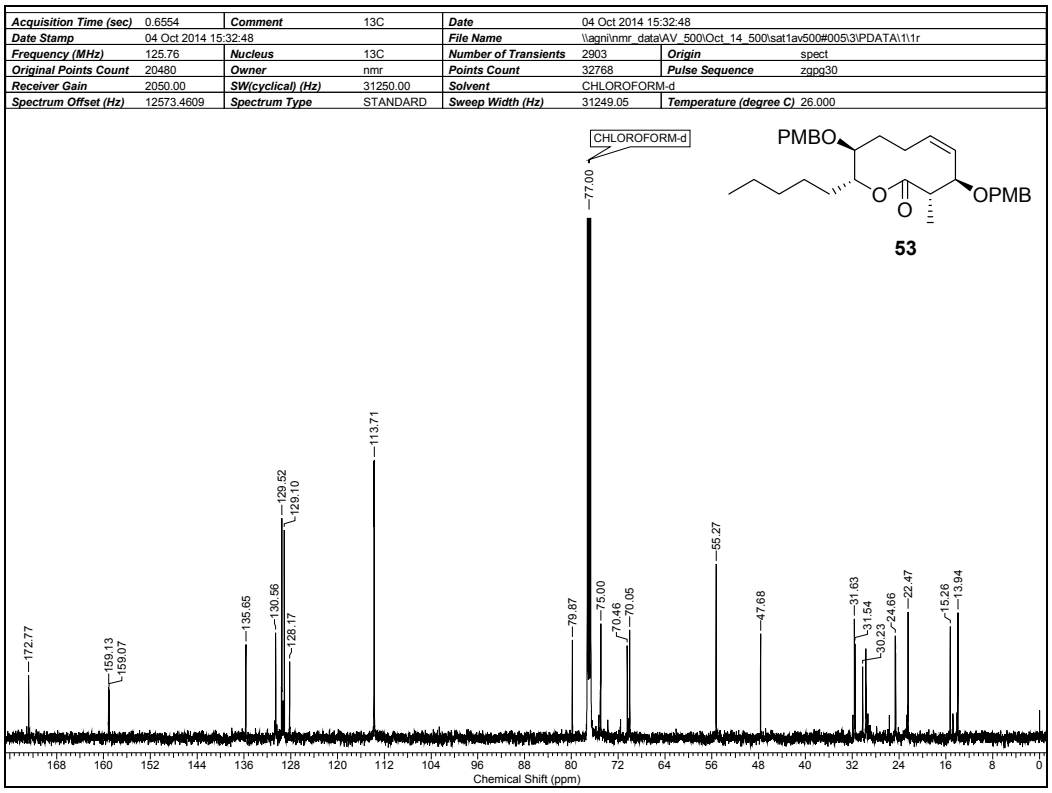
^{1}H NMR Spectrum of 40 in $CDCl_3$



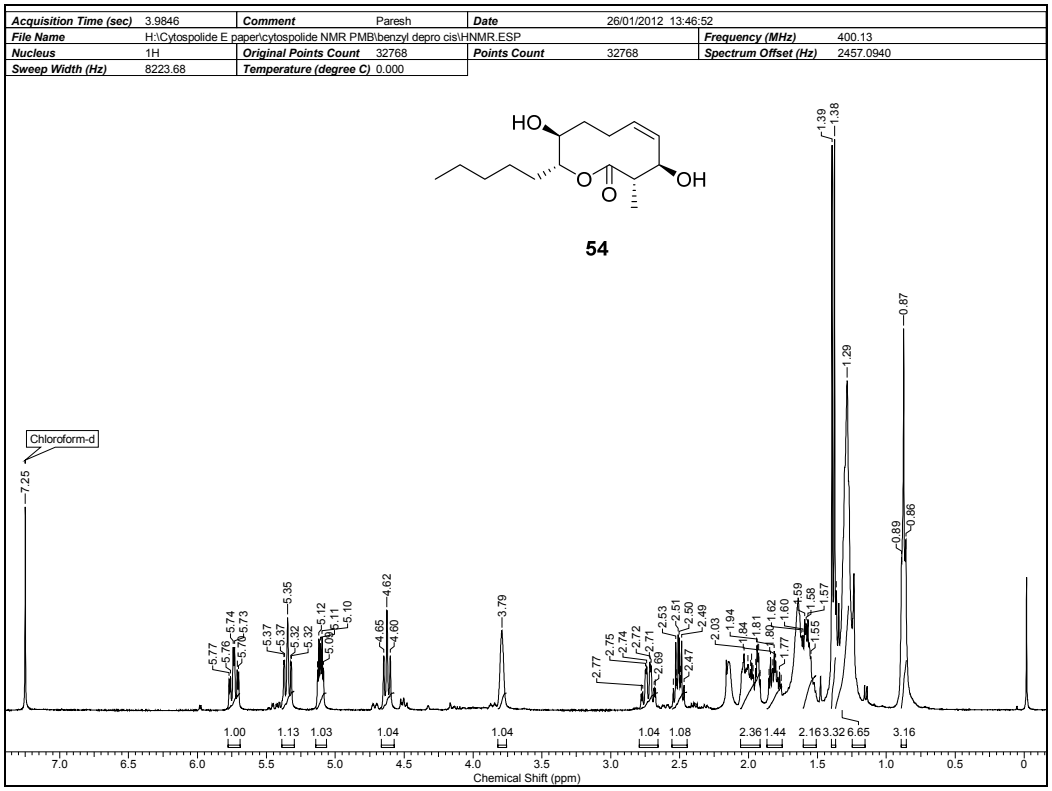
^{13}C NMR Spectrum of 40 in $CDCl_3$



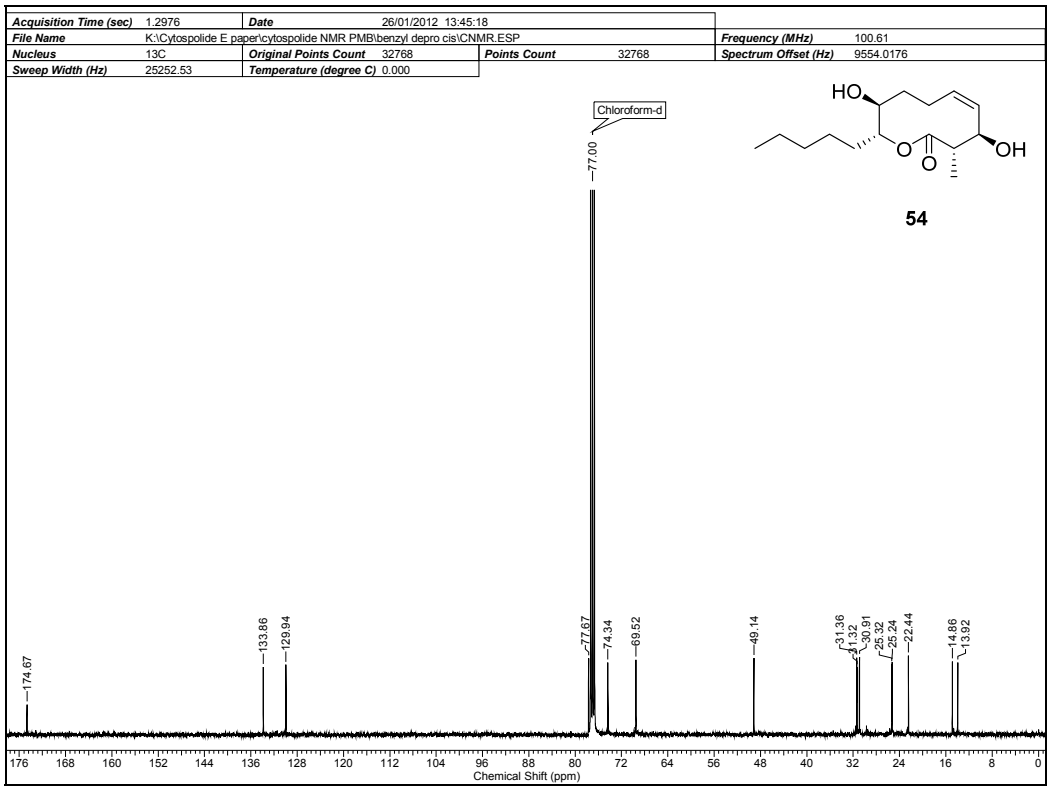
^{1}H NMR Spectrum of 53 in $CDCl_3$



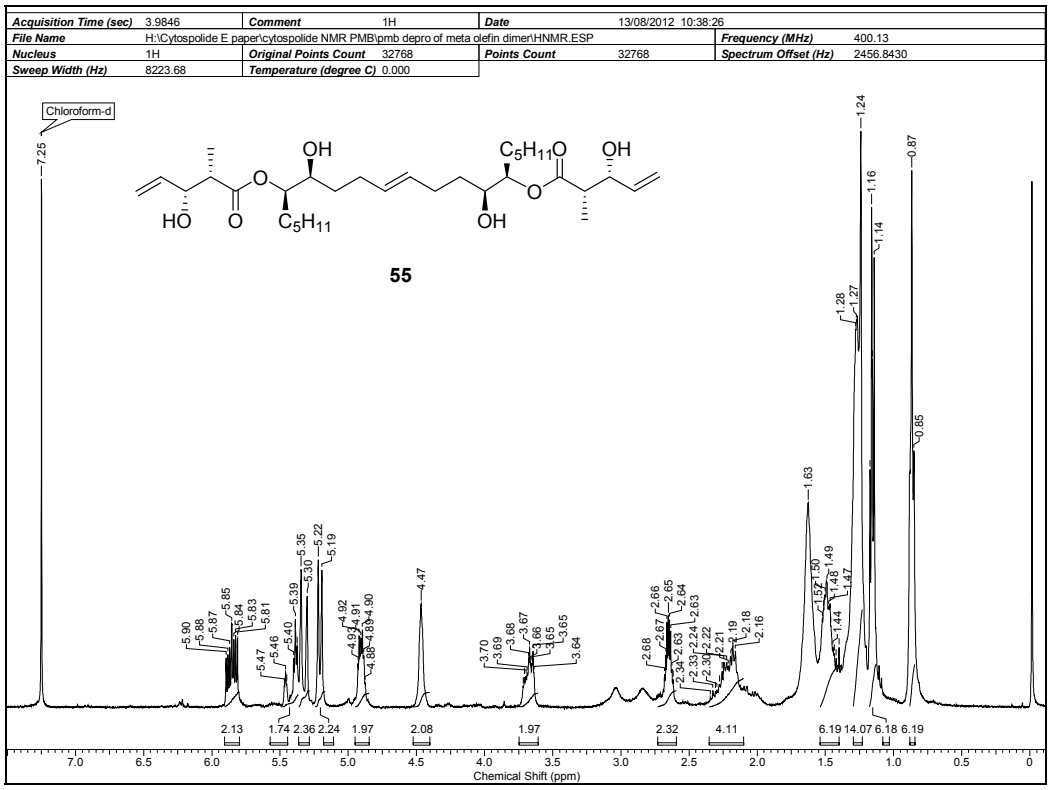
^{13}C NMR Spectrum of 53 in $CDCl_3$



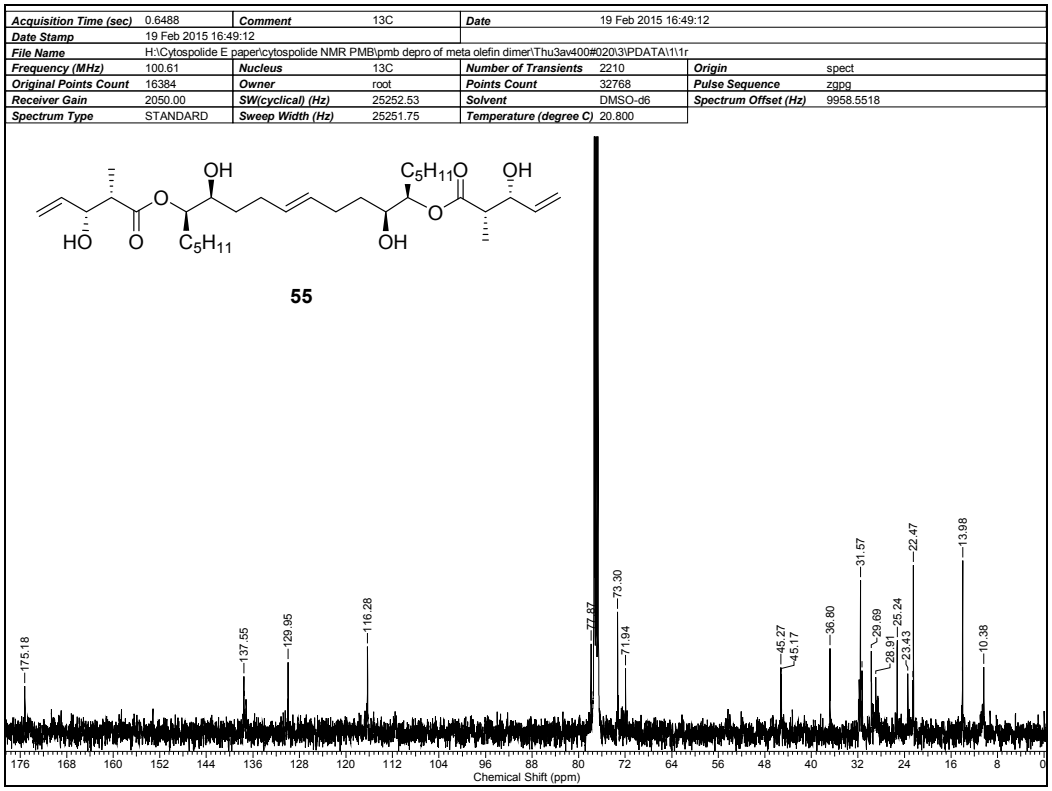
^{1}H NMR Spectrum of 54 in $CDCl_3$



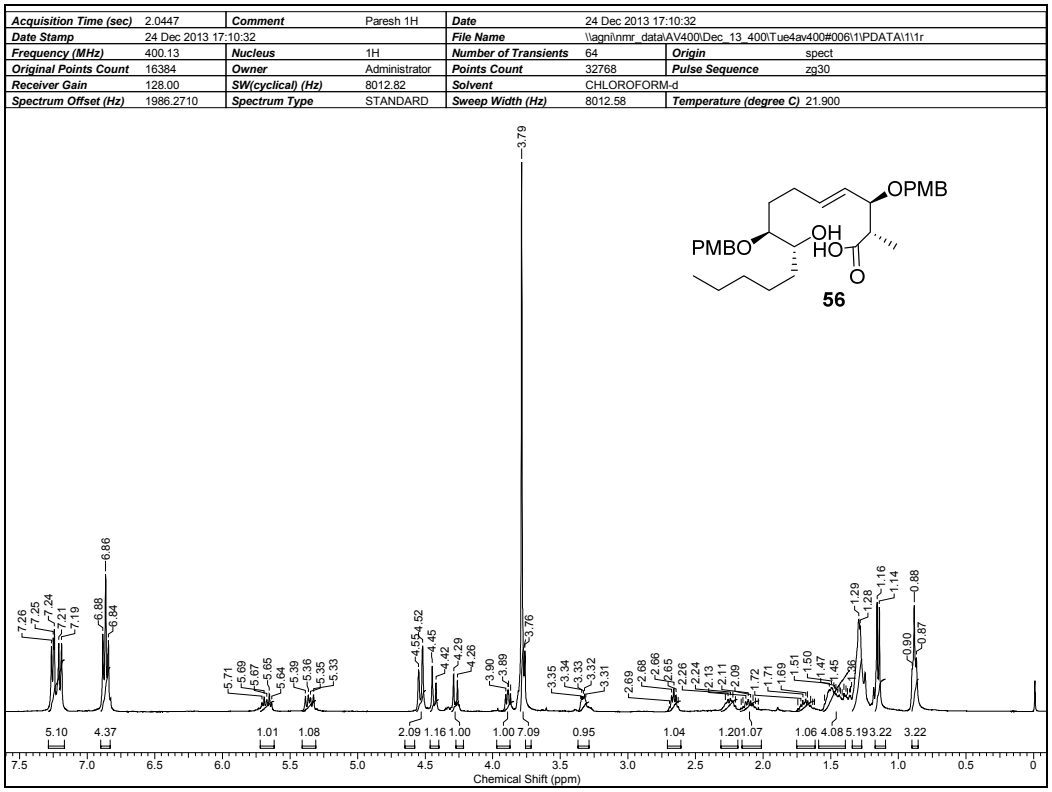
^{13}C NMR Spectrum of 54 in $CDCl_3$



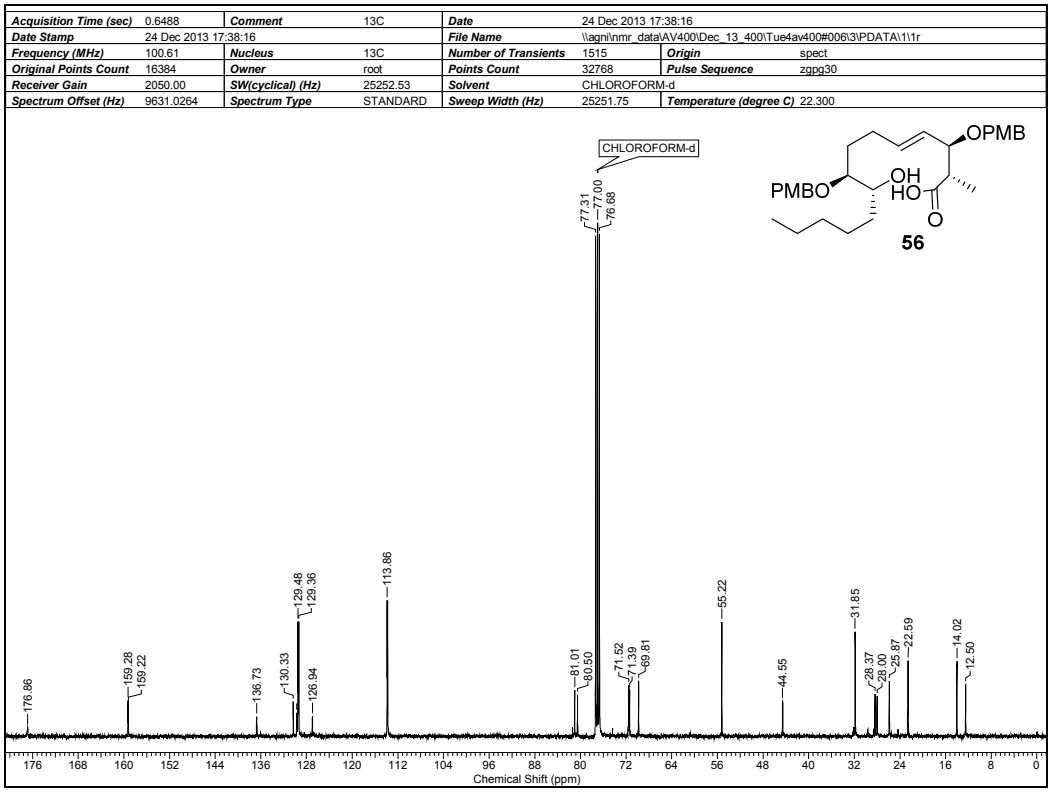
^{1}H NMR Spectrum of 55 in $CDCl_3$



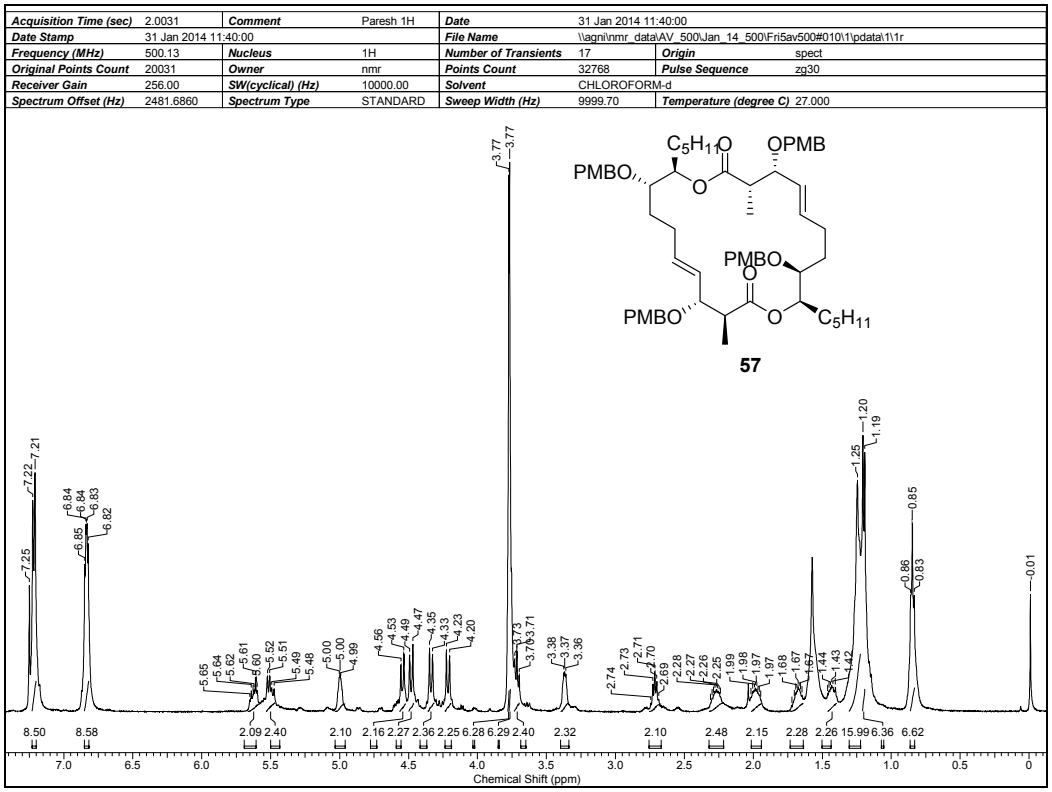
^{13}C NMR Spectrum of 55 in $CDCl_3$



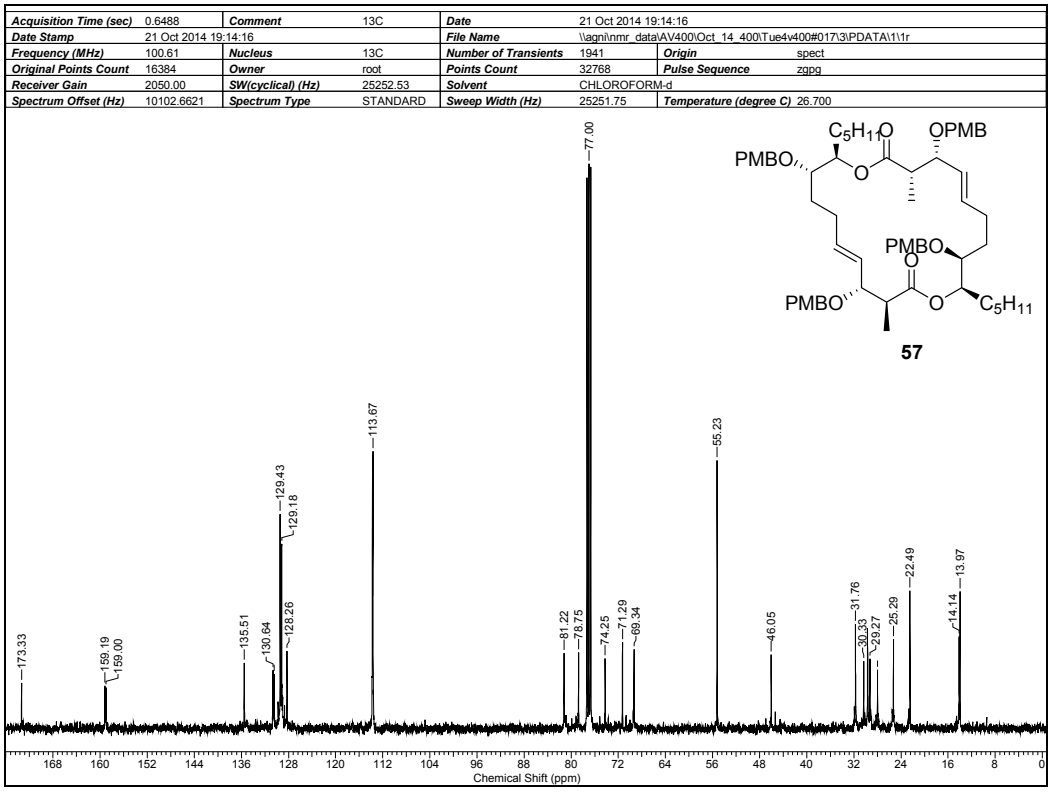
^{1}H NMR Spectrum of 56 in $CDCl_3$



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

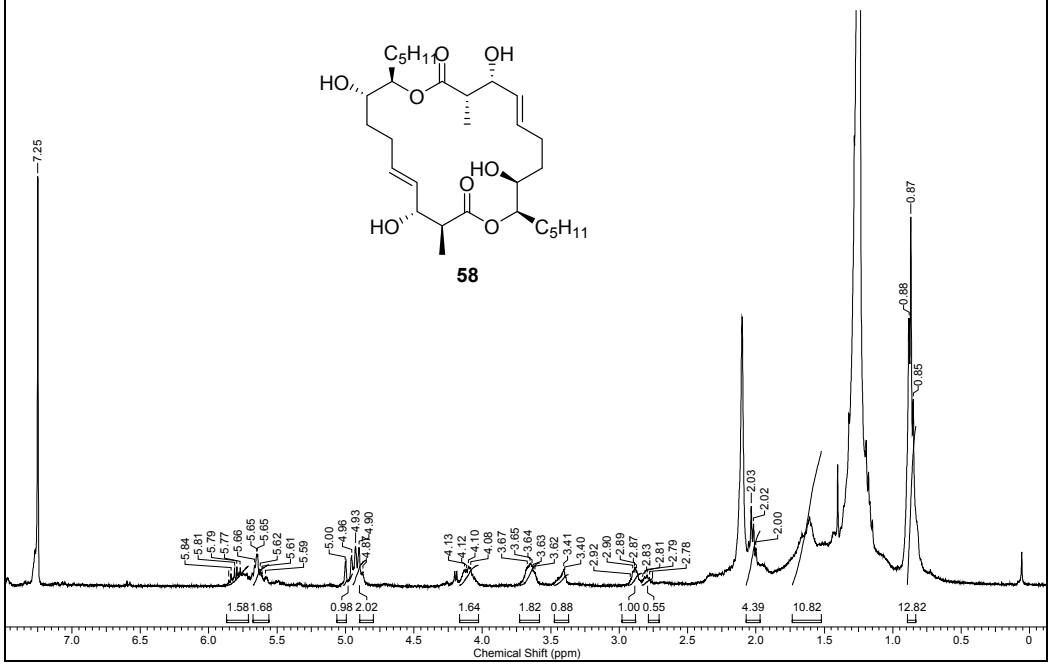


^{1}H NMR Spectrum of 57 in $CDCl_3$



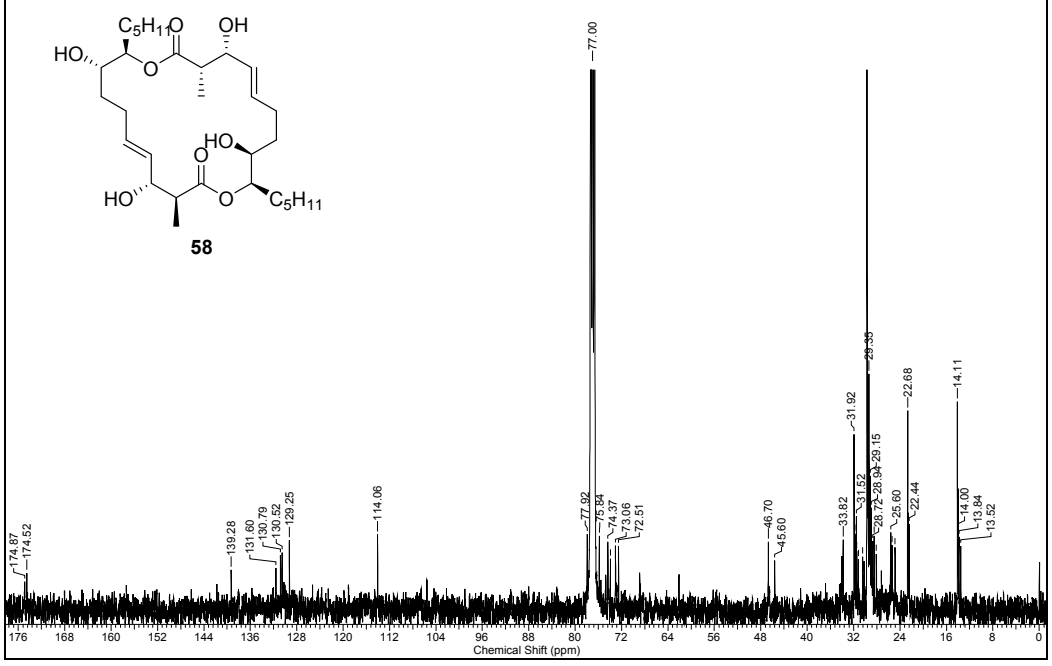
^{13}C NMR Spectrum of 57 in $CDCl_3$

Acquisition Time (sec)	2.0447	***Comment***	paresh 1H	***Date***	04 Nov 2014 11:37:44		
Date Stamp	04 Nov 2014 11:37:44						
File Name	H:\Cytospolide E paper\cytospolide NMR PMB\PMB deprotection after shiina\Tue2av400#012\1\PDATA\1\1r					***Frequency (MHz)***	400.13
Nucleus	1H	***Number of Transients***	16	***Origin***	spect	***Original Points Count***	16384
Owner	Administrator	***Points Count***	32768	***Pulse Sequence***	zg30	***Receiver Gain***	322.00
SW(cyclical) (Hz)	8012.82	***Solvent***	CHLOROFORM-d			***Spectrum Offset (Hz)***	2387.3035
Spectrum Type	STANDARD	***Sweep Width (Hz)***	8012.58	***Temperature (degree C)***	24.000		



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

Acquisition Time (sec)	0.6488	***Comment***	13C	***Date***	17 Feb 2015 08:57:44		
Date Stamp	17 Feb 2015 08:57:44						
File Name	H:\Cytospolide E paper\cytospolide NMR PMB\PMB deprotection after shiina\Mon3av400#027\3\PDATA\1\1r						
Frequency (MHz)	100.61	***Nucleus***	13C	***Number of Transients***	20921	***Origin***	spect
Original Points Count	16384	***Owner***	root	***Points Count***	32768	***Pulse Sequence***	zgpg
Receiver Gain	2050.00	***SW(cyclical) (Hz)***	25252.53	***Solvent***	DMSO-d6	***Spectrum Offset (Hz)***	9959.3223
Spectrum Type	STANDARD	***Sweep Width (Hz)***	25251.75	***Temperature (degree C)***	25.000		



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

REFERENCES

1. Gradillas, A.; Paez-Castells, J. *Angew. Chem. Int. Ed.* **2006**, *45*, 6086-6101.
2. (a) Nicolaou, K. C. *Tetrahedron* **1977**, *33*, 683-710. (b) Back, T. G. *Tetrahedron* **1977**, *33*, 3041-3059. (c) Roxburgh, C.J. *Tetrahedron,* **1995**, *51*, 9767-9822.
3. (a) Davies, H. G.; Green, R. H. *Nat. Prod. Rep.* **1986**, *3*, 87-121. (b)Tanaka, H.; Kuroda, A.; Marusawa, H.; Hatanaka, H.; Kino, T.; Goto, T.; Hashimoto, M.; Taga, T. *J. Am. Chem. Soc.* **1987**, *109*, 5031-5033. (c) Baker, R.; Swain, C. J. *Chem. Brit.* **1989**, *25*, 692-696. (d) Schreiber, S. L. *Science* **1991**, *251*, 283-287. (e) Rosen, M. K.; Schreiber, S. L. *Angew. Chem., Int. Ed. Engl* **1992**, *31*, 384-400. (f) Gerlitz, M.; Hammann, P.; Thiericke, R.; Rohr, J. *J. Org. Chem.* **1992**, *57*, 4030-4033. (g) Drose, S.; Bindseil, K. U.; Bowman, E. J.; Siebers, A.; Zeeck, A.; Altendorf, K. *Biochem.* **1993**, *32*, 3902-3906. (h) Bedorf, N.; Schomburg, D.; Gerth, K.; Reichenbach, H.; Hofle, G. *Liebigs Ann. Chem.* **1993**, 1017-1021. (i) Grabley, S.; Thiericke, R.; Wink, J.; Henne, P.; Philipps, S.; Wessels, P.; Zeeck, A. *J. Nat. Prod.* **1994**, *57*, 541-544. (j) Abel, S.; Faber, D.; Huter, O.; Giese, B. *Angew. Chem., Int. Ed.* **1994**, *33*, 2466-2468. (k) Gerth, K.; Bedorf, N.; Irschik, H.; Hofle, G.; Reichenbach, H. *J. Antibiot.* **1994**, *47*, 23-31. (l) Ikeda, H.; Omura, S. *J, Antibiot.* **1995**, *48*, 549-562.
4. (a) Roxburgh, C. J. *Tetrahedron* **1993**, *49*, 10749-10784. (b) Rousseau, G. *Tetrahedron* **1995**, *51*, 2777-2849. (c) Drager, G.; Kirschning, A.; Thiericke, R.; Zerlin, M. *Nat. Prod. Rep.* **1996**, *13*, 365-375.
5. (a) Naves, Y. R.; Grampoloff, A. V. *Helv. Chim. Acta* **1942**, *25*, 1500-1514. (b) Demole, E.; Willhalm, B.; Stoll, M. *Helv. Chim. Acta* **1964**, *47*, 1152.
6. Ishida, T.; Wada, K. *J. Chem. Soc., Chem. Comm.* **1975**, 209-210.
7. (a) Wada, K.; Ishida, T. *J. Chem. Soc., Chem. Comm.* **1976**, 340-341. (b) Wada, K.; Ishida, T. *J. Chem.Soc., Perkin Trans. 1* **1979**, 1154-1158.
8. Moore, B. P.; Brown, W. V. *Aust. J. Chem.* **1976**, *29*, 1365-1374.
9. (a) Grabley, S.; Granzer, E.; Hutter, K.; Ludwig, D.; Mayer, M.; Thiericke, R.; Till, G.; Wink, J.; Philips, S.; Zeeck, A. *J. Antibiot.* **1992**, *45*, 56-65. (b) Gohrt, A.; Zeeck, A.; Hutter, K.; Kirsch, R.; Kluge, H.; Thiericke, R. *J. Antibiot.* **1992**, *45*, 66-73. (c) Grabley, S.; Hammann, P.; Hutter, K.; Kirsch, R.; Kluge, H.; Thiericke, R.; Mayer, M.; Zeeck, A. *J. Antibiot.* **1992**, *45*, 1176-1181.

10. Ayer, W. A.; Sun, M.; Browne, L. M.; Brinen, L. S.; Clardy, J. *J. Nat. Prod.* **1992**, *55*, 649-653.
11. Rukachaisirikul, V.; Pramjit, S.; Pakawatchai, C.; Isaka, M.; Supothina, S. *J. Nat. Prod.* **2004**, *67*, 1953-1955.
12. Boonphong, S.; Kittakoop, P.; Isaka, M.; Pittayakhajonwut, D.; Tanticharoen, M.; Thebtaranonth, Y. *J. Nat. Prod.* **2001**, *64*, 965-967.
13. (a) Nukina, M.; Ikeda, M.; Sassa, T. *Agric. Biol. Chem.* **1980**, *44*, 2761-2762. (b) Venkatasubbaiah, P.; Chilton, W. S. *J. Nat. Prod.* **1992**, *55*, 461-467.
14. Asaoka, M.; Naito, S.; Takei, H. *Tetrahedron Lett.* **1985**, *26*, 2103-2106.
15. Evidente, A.; Lanzetta, R.; Capasso, R.; Vurro, M.; Bottalico, A. *Phytochemistry* **1993**, *34*, 999-1003.
16. (a) Rivero-Cruz, J. F.; Garcia-Aguirre, G.; Cerda-Garcia-Rojas, C. M.; Mata, R. *Tetrahedron* **2000**, *56*, 5337-5344. (b) Rivero-Cruz, J. F.; Macias, M.; Cerda-Garcia-Rojas, C. M.; Mata, R. *J. Nat. Prod.* **2003**, *66*, 511-514.
17. (a) Yuzikhin, O.; Mitina, G.; Berestetskiy, A. *J. Agric. Food Chem.* **2007**, *55*, 7707-7711.
18. (a) Evidente, A.; Cimmino, A.; Berestetskiy, A.; Mitina, G.; Andolfi, A.; Motta, A. *J. Nat. Prod.* **2008**, *71*, 31-34. (b) Evidente, A.; Cimmino, A.; Berestetskiy, A.; Andolfi, A.; Motta, A. *J. Nat. Prod.* **2008**, *71*, 1897-1901.
19. Lu, S.; Kurtán, T.; Yang, G.; Sun, P.; Mándi, A.; Krohn, K.; Draeger, S.; Schulz, B.; Yi, Y.; Li, L.; Zhang, W. *Eur. J. Org. Chem.* **2011**, 5452–5459.
20. Lu, S.; Sun, P.; Li, T. J.; Kurtan, T.; Mandi, A.; Antus, S.; Krohn, K.; Draeger, S.; Schulz, B.; Yi, Y. H.; Li, L.; Zhang, W. *J. Org. Chem.* **2011**, *76*, 9699-9710.
21. (a) Hiep, N. T; Choi, Y.-h; Kim, N.; Hong, S. S; Hong, S.-B; Hwang, B. Y; Lee, H.-J; Lee, S.-J; Jang, D. S; Lee, D. *J. Nat. Prod.* **2012**, *75*, 784−788. (b) Hiep, N. T; Choi, Y.-H; Kim, N.; Hong, S. S; Hong, S.-B; Hwang, B. Y; Lee, H. -J; Lee, S.-J; Jang, D. S; Lee, D. *J. Nat. Prod.* **2012**, *75*, 2045−2046.
22. (a) Reddy, C. R; Rao, N. N; Reddy, M. D. *Eur. J. Org. Chem*. **2012**, 4910−4913. (b) Schmidt, B.; Kunz, O.; Petersen, M. H. *J. Org. Chem*. **2012**, *77*, 10897−10906.
23. Baraban, E. G.; Morin, J. B.; Phillips, G. M.; Phillips, A. J.; Strobel, S. A.; Handelsman, J. *Tetrahedron Lett.* **2013,** *54*, 4058-4060.

24. Ortega, H. E.; Shen, Y. Y.; TenDyke, K.; Rios, N.; Cubilla-Rios, L. *Tetrahedron Lett.* **2014,** *55*, 2642-2645.
25. Funk, C. D. *Science* **2001**, *294*, 1871-1875.
26. (a) Niwa, H.; Inagaki, H.; Yamada, K. *Tetrahedron Lett.* **1991**, *32*, 5127-5128. (b) Niwa, H.; Watanabe, M.; Inagaki, H.; Yamada, K. *Tetrahedron* **1994**, *50*, 7385-7400.
27. Papendorf, O.; Konig, G. M.; Wright, A. D.; Chorus, I.; Oberemm, A. *J. Nat. Prod.* **1997**, *60*, 1298-1300.
28. Stierle, D. B.; Stierle, A. A.; Bugni, T.; Loewen, G. *J. Nat. Prod.* **1998**, *61*, 251-252.
29. Lindquist, N.; Fenical, W. *Tetrahedron Lett.* **1989**, *30*, 2735-2738.
30. Chu, M.; Mierzwa, R.; Xu, L.; He, L.; Terracciano, J.; Patel, M.; Gullo, V.; Black, T.; Zhao, W.; Chan, T.-M.; McPhail, A. T. *J. Nat. Prod.* **2003**, *66*, 1527-1530.
31. Kinoshita, K.; Sasaki, T.; Awata, M.; Takada, M.; Yaginuma, S. *J. Antibiot.* **1997**, *50*, 961-964.
32. Edrada, R. A.; Heubes, M.; Brauers, G.; Wray, V.; Berg, A.; Grafe, U.; Wohlfarth, M.; Muhlbacher, J.; Schaumann, K.; Sudarsono; Bringmann, G.; Proksch, P. *J. Nat. Prod.* **2002**, *65*, 1598-1604.
33. (a) Back, T. G. *Tetrahedron* **1977**, *33*, 3041-3059. (b) Roxburgh, C. J. *Tetrahedron* **1993**, *49*, 10749-10784.
34. Hatcher, M. A.; Borstnik, K.; Posner, G. H. *Tetrahedron Lett.* **2003**, *44*, 5407-5409.
35. Fouque, E.; Rousseau, G. *Synthesis* **1989**, *1989*, 661-666.
36. Wakamatsu, T.; Akasaka, K.; Ban, Y. *Tetrahedron Lett.* **1977**, *18*, 2755-2758.
37. Baldwin, J. E.; Adlington, R. M.; Singh, R. *Tetrahedron* **1992**, *48*, 3385-3412.
38. Ireland, R. E.; Brown, F. R. *J. Org. Chem.* **1980**, *45*, 1868-1880.
39. (a) Ruggli, P. *Liebigs Ann. Chem.* **1917**, *412*, 1-13. (b) Huisgen, R.; Ott, H. *Tetrahedron* **1959**, *6*, 253-267 (c) Dunitz, J. D. *Pure Appl. Chem.* **1971**, *25*, 495-508. (d) Illuminati, G.; Mandolini, L. *Acc. Chem. Res* **1981**, *14*, 95-102. (e) Wiberg, K. B.; Waldron, R. F. *J. Am. Chem. Soc.* **1991**, *113*, 7697-7705. (f) Wiberg, K. B.; Waldron, R. F.; Schulte, G.; Saunders, M. *J. Am. Chem. Soc.* **1991**, *113*, 971-977.
40. Pilli, R. A.; Victor, M. M. *Tetrahedron Lett.* **1998**, *39*, 4421-4424.
41. Yamada, S.; Tanaka, A.; Oritani, T. *Biosci., Biotechnol., Biochem.* **1995**, *59*, 1657 -1660.
42. Arai, M.; Morita, N.; Aoyagi, S.; Kibayashi, C. *Tetrahedron Lett.* **2000**, *41*, 1199-1203.

43. Prasad, K. R.; Revu, O. *J. Org. Chem.* **2014**, *79*, 1461-1466.

44. (a) Petasis, N. A.; Patane, M. A. *Tetrahedron* **1992**, *48*, 5757-5821. (b) Mehta, G.; Singh, V. *Chem. Rev.* **1999**, *99*, 881-930. (c) Minnaard, A. J.; Wijnberg, J. B. P. A.; de Groot, A. *Tetrahedron* **1999**, *55*, 2115-2146. (d) Rousseau, G. *Tetrahedron* **1995**, *51*, 2777-2849. (e) Crimmins, M. T.; Emmitte, K. A. *J. Am. Chem. Soc.* **2001**, *123*, 1533-1534. (f) Evans, P. A.; Holmes, B. *Tetrahedron* **1991**, *47*, 9131-9166.

45. For some recent reviews see: (a) Riatto, V. B.; Pilli, R. A.; Victor, M. M. *Tetrahedron* **2008**, *64*, 2279-2300. (b) Ferraz, H. M. C.; Bombonato, F. I.; Longo Jr., L. S. *Synthesis* **2007**, 3261-3285. (c) Gradillas, A.; Paez-Castells, J. *Angew. Chem. Int. Ed.* **2006**, *45*, 6086-6101.(d) Deiters, A.; Martin, S. F. *Chem. Rev.* **2004**, *104*, 2199-2238. (f) Riatto V. B.; Pilli R. A.; Victor M. M. *Tetrahedron* **2008**, *64*, 2279-2300.

46. Fürstner A.; Thomas M.; *Synlett* **1997**, 1010-1012.

47. (a) Fürstner A. Radkowski K. *Chem. Commun.* **2001**, 671-672. (b) Furstner A.; Radkowski K.; Wirtz C.; Goddard R.; Lehmann C. W.; Mynott R. *J. Am. Chem. Soc.* **2002**, *124*, 7061-7069.

48. (a) Caggiano, L.; Castoldi, D.; Beumer, R.; Bayon, P.; Tesler, J.; Gennari, C. *Tetrahedron Lett.* **2003**, *44*, 7913-7919. (b) Castoldi, D.; Caggiano, L.; Panigada, L.; Sharon, O.; Costa, A. M.; Gennari, C. *Chem. Eur. J.* **2006**, *12*, 51-62. (c) Gennari, C.; Castoldi, D.; Sharon, O. *Pure Appl. Chem.* **2007**, *79*, 173-180.

49. Ramana, C. V.; Khaladkar, T. P.; Chatterjee, S.; Gurjar, M. K. *J. Org. Chem.* **2008**, *73*, 3817-3822.

50. For 2*E*-ene-1,4-*cis*-disubstituted noneolide construction using RCM see: (a) Ghosh, S.; Rao, R. V. *Tetrahedron Lett.* **2007**, *48*, 6937-6940. (b) Guptali, P.; Kumar, P. *Eur. J. Org. Chem.* **2008**, 1195-1202. (c) Liu, J.; Zhang, L.; He, J. M.; He, L.; Ma, B. W.; Pan, X. F.; She, X. G. *Tetrahedron: Asymmetry* **2008**, *19*, 906-911. (d) Krishna, P. R.; Rao, T. J. *Tetrahedron Lett.* **2010**, *51*, 4017-4019.

51. For 2*E*-ene-1,4-*trans*- disubstituted noneolide construction using RCM see: (a) Srihari, P.; Kumaraswamy, B.; Somaiah, R.; Yadav, J. S. *Synthesis* **2009**, 1039-1045. (b) Jana, N.; Mahapatra, T.; Nanda, S. *Tetrahedron: Asymmetry* **2009**, *20*, 2622-2628. (c) Mohapatra, D. K.; Dash, U.; Naidu, P. R.; Yadav, J. S. *Synlett* **2009**, 2129-2132. (d) Das, T.; Bhuniya, R.; Nanda, S. *Tetrahedron: Asymmetry* **2010**, *21*, 2206-2211. (e) Chandrasekhar, S.; Balaji, S.

V.; Rajesh, G. *Tetrahedron Lett.* **2010**, *51*, 5164-5166. (f) Srihari, P.; Kumaraswamy, B.; Shankar, P.; Ravishashidhar, V.; Yadav, J. S. *Tetrahedron Lett.* **2010**, *51*, 6174-6176.

52. Giri, A. G.; Mondal, M. A.; Puranik, V. G.; Ramana, C. V. *Org. Biomol. Chem.* **2010**, *8*, 398-406.
53. (a) Schuster, M.; Blechert, S. *Angew. Chem., Int. Ed.* **1997**, *36*, 2036-2056. (b) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413-4450. (c) Fürstner, A.; *Angew. Chem. Int. Ed.* **2000**, *39*, 3012-3043. (d) Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res* **2001**, *34*, 18-29.
54. Selected reports that deal with the proximal substituent effects on the construction of medium rings by RCM: a) Hoye, T. R.; Zhao, H. *Org. Lett.* **1999**, *1*, 1123-1125. b) RamiÌrez-FernaÌndez , J.; Collado, I. G.; HernaÌndez-Galán, R., *Synlett* **2008**, 339-342. c) Ghosh, S.; Ghosh, S.; Sarkar, N. *J. Chem. Sci.* **2006**, *118*, 223-235. d) Mitchell, L.; Parkinson, J. A.; Percy, J. M. Singh K. *J. Org. Chem.* **2008**, *73*, 2389-2395. e) Imahori T.; Ojima H.; Yoshimura Y.; Takahata H. *Chem. Eur. J.* **2008**, *14*, 10762-10771. f) Imahori T.; Ojima H.; Tateyama H.; Mihara Y.; Takahata H. *Tetrahedron Lett.* **2008**, *49*, 265-268.
55. (a) Hildebrandt, B.; Nakamura, Y.; and Ogawa, S. *Carbohydr. Res* **1991**, *214*, 87-93. (b) Rao, A. V. R.; Murthy, V. S.; Sharma, G. V. M. *Tetrahedron Lett.* **1995**, *36*, 139-142.
56. (a) Mitsunobu.O; Yamada, M. *Bull. Chem. Soc. Jpn* **1967**, *40*, 2380-2382. (b) Mitsunobu, O. *Synthesis* **1981**, 1-28.
57. Enders, D.; Nguyen, D. *Synthesis* **2000**, 2092–2098.
58. Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; and Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989–1993.
59. (a) Hicks, J. D.; Huh, C. W.; Legg, A. D.; Roush, W. R. *Org. Lett.* **2007**, *9*, 5621-5624. (b) Bose, D.; Fernandez, E.; Pietruszka, J. *J. Org. Chem.* **2011**, *76*, 3463-3469.
60. Angulo-Pachon, C. A.; Diaz-Oltra, S.; Murga, J.; Carda, M.; Marco, J. A. *Org. Lett.* **2010**, *12*, 5752-5755.
61. Mahapatra, T.; Das, T.; Nanda, S. *Bull. Chem. Soc. Jpn.* **2011**, *84*, 511-519.
62. Reddy, B. V. S.; Reddy, P. S.; Reddy, B. P.; Yadav, J. S.; Al Ghamdi, A. A. *Tetrahedron Lett.* **2013**, *54*, 5758-5760.
63. Mohapatra, D. K.; Reddy, D. P.; Karhale, D. S.; Yadav, J. S. *Synlett* **2013**, *24*, 2679-2682.
64. Rej, R. K.; Jana, A.; Nanda, S. *Tetrahedron* **2014**, *70*, 2634-2642.
65. Kobayashi, Y.; Okui, H. *J. Org. Chem.* **2000**, 65, 612-615.

66. Bernet, B.; Vasella, A. *Helv. Chim. Acta.* **1979**, 62, 1990-2016.
67. Yu, W. S.; Mei, Y.; Kang, Y.; Hua, Z. M.; Jin, Z. D. *Org. Lett.* **2004**, *6*, 3217-3219.
68. (a) Garegg, P. J.; Samuelsson, B. *J. Chem. Soc., Perkin Trans 1* **1980**, 2866-2869. (b) Bennett, S. M.; Kouya Biboutou, R.; Zhou, Z.; Pion, R. *Tetrahedron* **1998**, *54*, 4761-4786. (c) Jackowski, O.; Chretien, F. o.; Didierjean, C.; Chapleur, Y. *Carbohydra. Res.* **2012**, *356*, 93-103.
69. Yadav, J. S.; Pandurangam, T.; Kumar, A. S.; Reddy, P. A. N.; Prasad, A. R.; Reddy, B. V. S.; Rajendraprasad, K.; Kunwar, A. C. *Tetrahedron Lett.* **2012**, *53*, 6048-6050.
70. Kamal, A.; Balakrishna, M.; Reddy, P. V.; Rahim, A. *Tetrahedron Asymmetry* **2014**, *25*, 148-155.
71. Rej, R. K.; Nanda, S. *Eur. J. Org. Chem.* **2014**, 860-871.
72. (a) Chattopadhyay, A.; Mamdapur, V. R. *J. Org. Chem.* **1995**, *60*, 585-587. (b) Chattopadhyay, A.; Vichare, P.; Dhotare, B. *Tetrahedron Lett.* **2007**, *48*, 2871-2873. (c) Chattopadhyay, A. *J. Org. Chem.* **1996**, *61*, 6104-6107.
73. Evans, D. A.; Weber, A. E. *J. Am. Chem. Soc.* **1986**, *108*, 6757-6761.
74. Chatterjee, A. K.; Choi, T. L.; Sanders, D. P.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 11360-11370.
75. Shiina, I.; Kubota, M.; Oshiumi, H.; Hashizume, M. *J. Org. Chem.* **2004**, *69*, 1822-1830.

CHAPTER II:

Total synthesis of Sinenside A

INTRODUCTION

A large number of secondary metabolites often referred to as “natural products,” are produced by plants, fungi, and bacteriabut utilized in the reproductive and defensive processes of both plants and animals.[1] From a medicinal point of view, these provide a rich source of bioactive agents such as antitumor, antibacterial, anti-insecticidal, anthelmintic, antinematodal and immuno suppressive.[2] The phenylpropanoid derivatives are a class of natural products comprised of a huge collection of secondary metabolites formed from L-phenylalanine and/or L-tyrosine *via* the Shikimate pathway. Lignin, lignans, norlignans, flavonoids, coumarins, quinones, stilbenes, catechin, aurones, and neoflavonoids are just a few of the many different types of phenylpropanoid derivatives produced from the enzymatic conversion of L-phenylalanine into the key intermediate *p*-coumaroyl-CoA.[3] Among them, the lignans and norlignans constitute abundant classes of phenylpropanoid natural products. The word "lignan" was first introduced and defined by Haworth as a 8,8'-linked phenylpropanoid dimer.[4] Later, some researchers have tried to redefine it but that consequently produced a lot of confusion. Nowadays, the original proposed definition by Haworth is frequently employed to refer to such kind of compounds. Similarly, the term "norlignan" was coined by Kai as "nor-lignan" for diphenylpentane derivatives, Sugiresinol and Hydroxysugiresinol.[5] The intention of adding the prefix "nor" was to address the intermediates that are actually the derivatives of the parent “lignan” molecules with a loss of a carbon atom. Later, Hatam and Whiting described that Sequirins also belongs to this group.[6] The word "norlignan" is now significantly used for identifying the natural phenolic compounds with a diphenylpentane carbon skeleton (C6-C5-C6). The typical carbon framework of a norlignan possesses a 7,8'-linked diphenylpentane core.[7]

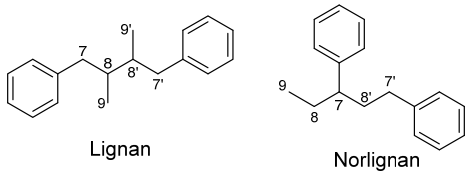


Figure S2.1. *Typical carbon framework of lignan and norlignan*

The chemical structures of norlignan are apparently composed of phenylpropane (C6-C3) and phenylethane (C6-C2) units. Based on the linkage position between the two units, the chemical structures are classified into three groups[7]:

(1) C7-C8′ linkage type

(2) C8-C8′ linkage type

(3) C9-C8′ linkage type

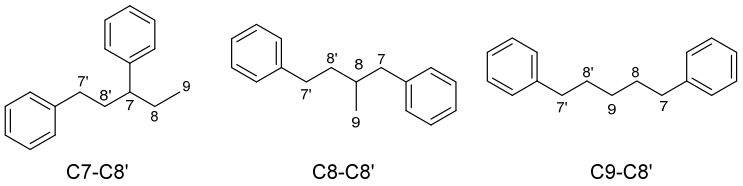


Figure S2.2. *Basic skeletons of norlignan*

Norlignans are found in many coniferous trees (especially in the heartwood) and some monocotyledonous plants.[7]

Norlignans from conifers:

Many norlignans have been found in the heartwood of coniferous trees.[8] Taxodiaceae, Cupressaceae, and Araucariaceae are good sources of typical conifer norlignans. Sugiresinol (Sequirin A) was the first member of this class and is a constituent of *Agathis austrazis* and *Sequoia sempervirens* Don, which also yielded Sequirin B and Sequirin C.[3a,6,9] Heartwood of *Sequoiadendron giganteum* Lindl provided the Sequirins E, F and G.[3a,10] Agatharesinol is present in *Agathisaustralis* and *Athrotaxis selaginoides*.[3a,11] Other norlignans with related structures are Metasequirin A, Hydroxymetasequirin A and Metasequirin B which have been isolated from the heartwood of *Metasequoia glyptostroboides*[3a,12] whereas Yateresinol has been isolated from the heartwood of *Libocedrus yateensis*[3a,13] (Figure S2.3).

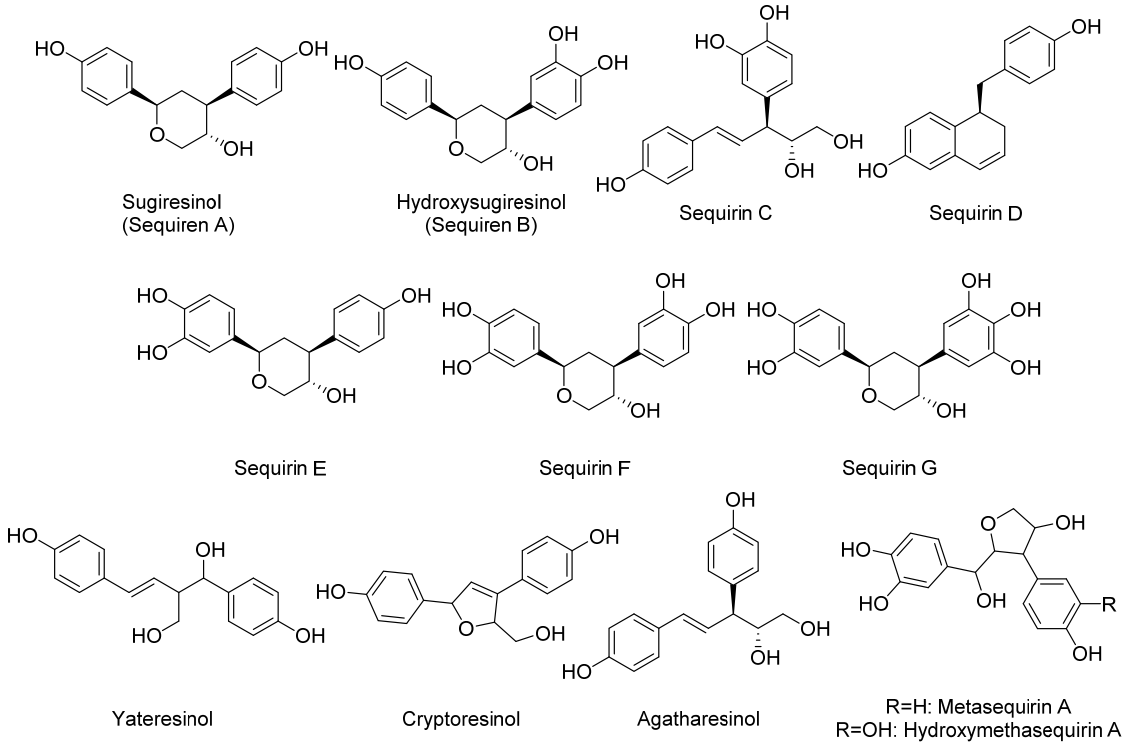


Figure S2.3. *Chemical structures of norlignans from conifers*

Norlignans from monocotyledons:

Some monocotyledonous species such as "Liliaceae and Hypoxidaceae" produce norlignans with a C7-C8′ linkage. Specifically, the genus *Curculigo* (Hypoxidaceae) comprises of about 20 species which are perennial herbs growing in the tropic and subtropic zones of Asia, Africa, South America and Australia. It is a rich source of phenolic compounds and norlignans with the functions of antiarrhythmia, antiosteoporosis, antioxidant, ACE inhibitionetc. In ancient times, various species of *Curculigo* were used as folk medicines to treat child pneumonia in China.[14] In 1996, Lee and co-workers isolated Curcapitosideas a novel glucosyl-fused phenanthropyran from the rhizome of *Curculigo capitulates*.[15] In 2010, Li and co-workers isolated Capituloside, Capituloside B, Crassifoside I and Sinensigenin C from the same rhizomes.[16] Later, two new phenolic glycosides namely Crassifoside C and Crassifoside D obtained from the ethanolic extraction of the rhizomes of *Curculigo crassifolia* have been added to this family by Li and co-workers[17] (Figure S2.4).

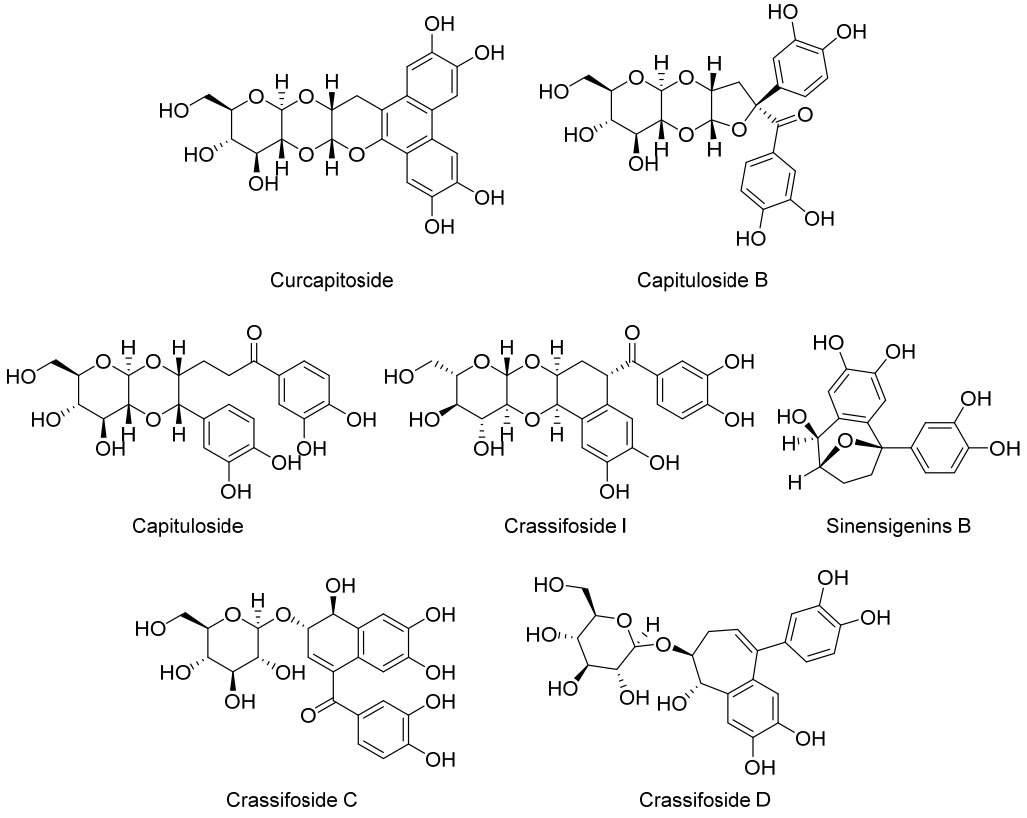


Figure S2.4. *Chemical structures of norlignans from Curculigo capitulata and Curculigo crassifolia*

Similarly, two novel skeleton-rearranged norlignans, Breviscaside A and Breviscapin B have been isolated from the rhizomes of *Curculigo breviscapa*[18] whereas Sinensigenins A

and B were obtainrd from the rhizomes of *Curculigo sinensis*[19] by Ning Li in 2010 (Figure S2.5). The structures were established on the basis of spectral evidence and comparisons with literature data.

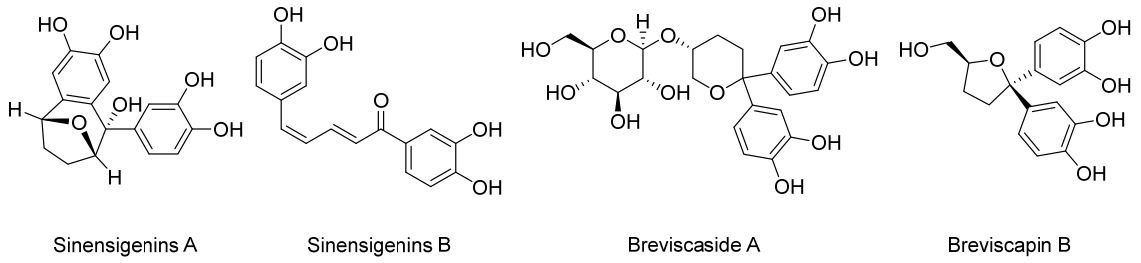


Figure S2.5. *Chemical structures of norlignans from Curculigo breviscapa and Curculigo sinensis*

Norlignans from other plant sources:

Several norlignans were also derived from the sources other than conifers and monocots. Three glycosylated norlignans, Pueroside A, Pueroside B and Sophoraside A were isolated from *Pueraria lobata* and *Sophora japonica*.[20] The hydroxylation at the 6-position and the C9-lactonization are the unique features in this family when compared with those norlignans from conifers and monocotyledons. Daphneolone, which is a C9-C8′ type norlignan, was isolated from *Daphne odora*[21] (Figure S2.6).

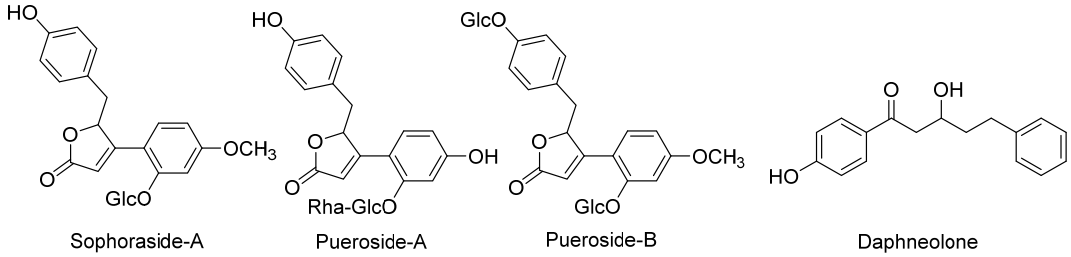


Figure S2.6. *Chemical structures of norlignans from other than conifers and monocots*

Pharmaceutical importance of norlignans:

Norlignans have been reported with diverse biological activities such as antifungal, antiprotozoal and estrogen-like activities and with an inhibitory effect on the cyclic AMP phosphodiesterase. From a pharmacological point of view, these compounds have a long and fascinating history beginning with their use as folk remedies by many different cultures.[22] For example, the Hypoxis species (Hypoxidaceae) are herbaceous plants occurring mainly in the Southern hemisphere. The rhizomes of these species have been used for the treatment of urinary diseases and prostate hypertrophy and internal cancer. Hypoxoside, a norlignan glucoside was found to be the main constituent of the rhizomes of several *Hypoxis spp* .In recent years, screening against animal models has revealed that Hypoxoside was able to

reduce the response to chemical pain stimuli, such as in the formalin and in the writhing test, whereas it did not change the pain response in the hot plate or in the tail tlick, test indicating that Hypoxoside exerts analgesic effects. The intraperitoneal administration of Hypoxosideat doses of 1, 5, 10 and 20 mg/kg did not induce gross behaviour alalterations or locomotor impairment.[23] Similarly, Crassifoside E and Crassifoside F isolated from the rhizomes of *Curculigo crassifolia* displayed ACE inhibitory activity (angiotensin-converting enzyme) with an IC_{50} value of 10 and 8.5 µg/mL respectively.[24] Norlignans Butylnysicosides and Nyasicoside were isolated from the *n*-BuOH soluble fraction of the rhizomes of *Curculigo capitulata* and possessed potent anti-arrhythmia activity[25] (Figure S2.7).

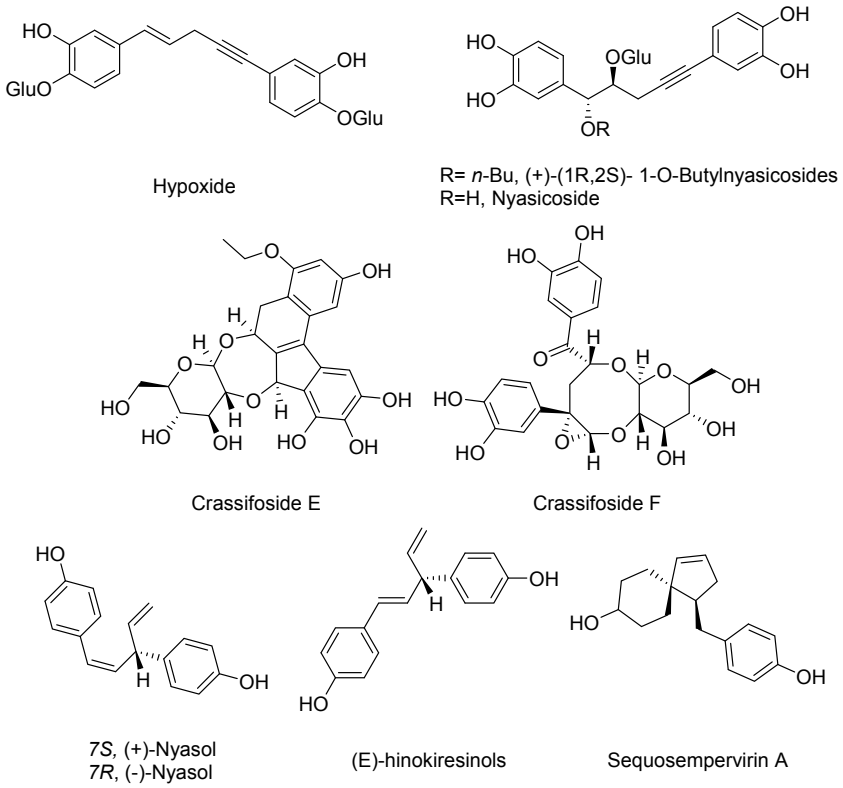


Figure S2.7. *Chemical structures of some biologically important norlignans* .

(±)-Nyasol was isolated from the methanol extract of *Anemarrhena asphodeloides* rhizomes. Nyasol effectively inhibited mycelial growth of various fungi *Colletotrichum orbiculare*, *P. capsici, Pythium ultimum, R. solani,* and *Cladosporium cucumerinum* in a range of 1–50µg/ml, but did not affect the growth of bacteria and yeast. Nyasol was also reported to possess antifungal activity and inhibit testosterone 5α-reductase. Furthermore, Nyasol was found to exhibit antioxidant and anti-atherogenic activities. On the other hand, (–)-Nyasol has been reported to suppress neuro-inflammatory response through the inhibition of nitric oxide (NO), prostaglandin E_2 (PGE_2), tumor necrosis factor (TNF)-α, and interleukin

(IL)-1β. (–)-Nyasol inhibits the production of NO and PGE_2 by suppressing the expression of inducible nitric oxide synthase (*i*NOS) and cyclooxygenase-2 (COX-2). (*E*)-Hinokiresinol (geometrical isomer of (–)-Nyasol) - the phytoalexins of *Cryptomeria japonica* is another important nor-lignan with potential antifungal activity and estrogen-like activity, and inhibits cyclic AMP phosphodiesterase.[26] Sequosempervirin A, the first naturally occurring norlignan containing one spirocyclewas isolated from the branches and leaves of *Sequoia sempervirens*a species of the taxodiaceae family, and exhibited useful bioactivity[27] (Figure S2.7).

Isolation, biological activity and structural features of Sinenside A:

In 2012, Li and co-workers isolated two novel norlignan glucosides, namely Sinenside A and Sinenside B along with six known compounds that include Crassifoside D and Capituloside from the ethanolic extracts of *Curculigo sinensis* plants.[28] In the preliminary study, these norlignan glucosides showed a strong 1,1-diphenyl-2-picrylhydrazyl (DPPH) free radical scavenging activity and displayed potent antioxidant activity. The DPPH anti-oxidant activity of all the norlignan glycosides with IC_{50} value were found to be comparable to that of the positive control ascorbic acid (IC_{50} = 45.84 µM). A critical examination of the structures of these norlignans indicated that all these norlignan glucosides are created through novel rearrangements (Figure S2.8).

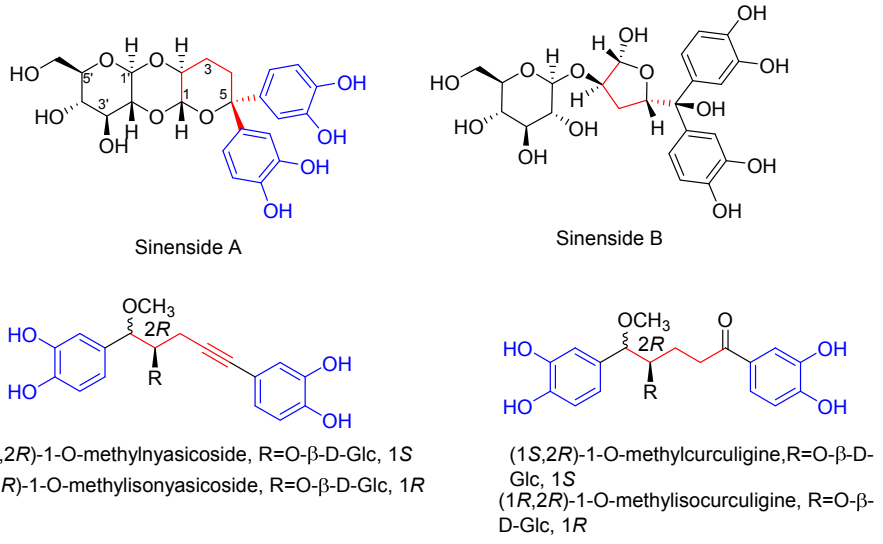


Figure S2.8. *Chemical structures of norlignans from Curculigo sinensis*

Among these novel norlignan glucosides, Sinenside A has attracted our attention because of its novel structural architecture. The central skeleton of Sinenside A (**1**) is characterized by a unique cyclic disaccharide (or saccharide dianhydride) in which two

pyranose residues are fused with a challenging 1,2-*trans*-configuration and a *gem*-diaryl (with free phenolic–OH groups) unit present on one of the tetrahydropyran moiety.[29]

Saccharide dianhydrides isolated from acid hydrolysis:

Cyclic disaccharides (also called saccharide dianhydrides) have been known for a long time. These saccharide dianhydrides have been isolated as part of a complex mixture when the corresponding monomers were treated with acids, anhydrous HF or during the hydrolysis of polysaccharide. Linear polysaccharides have usually served as the precursors of the cyclic oligosaccharides. However, the natural, semi-synthetic, enzymatically produced cyclic disaccharides are quite limited.[30]

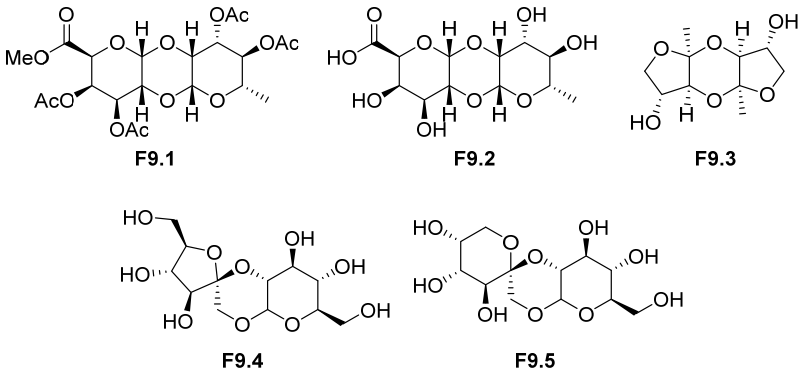


Figure S2.9. *Structures of the dianhydrides*

For example, Fujiwara and co-workers reported the isolation of 1,2':1',2-dianhydride of 3,4-di-O-acetyl- *β*-L-rhamnopyranose and methyl 3,4-di-O-acetyl-α-D-galactopyranuronate from the residues resulting from the acid hydrolysis of the water-soluble polysaccharide of wobaku wood by successive treatment with methanolic hydrogen chloride and acetic anhydride-pyridine.[31] It was also reported that the dialdose dianhydride **F9.1** was obtained by the treatment of methanolic hydrogen chloride of the disaccharide fraction containing 2-O-(α-D-galactopyranosyluronic acid)-L-rhamnopyranose from the acid hydrolyzate of the water-soluble polysaccharide of *Phellodendron umurense* Rupr. Similarly 1,2':2,1'-dianhydride of α-D-galactopyranuronic acid and β-L-rhamnopyranose **F9.2** was obtained by the partial hydrolysis of the hetero polysaccharide complex from the roots of the marshmallow*(Aithaea officinalis* L.) and by treatment of cell walls isolated from carrot, cotton, tobacco, and tomato with anhydrous hydrogen fluoride (HF).[32] The formation of di-*β*-1-deoxy-D-xylulofuranose 2,3':3,2'-dianhydride **F9.3** by acid hydrolysis of β-1-deoxy-D-xylulofuranose was described by Spenser's group.[33] Similarly, the conversion of trehalulose into a mixture of *α*-D-glucopyranose/*β*-D-fructofuranose- and *α*-D-glucopyranose/*β*-D-

fructopyranose-1,1':2,2' dianhydrides (**F9.4** and **F9.5** respectively) by dissolution in pyridinium poly(hydrogen fluoride) or in pure HF at low sugar dilution was reported by Defaye and co-workers (Figure S2.9). [34]

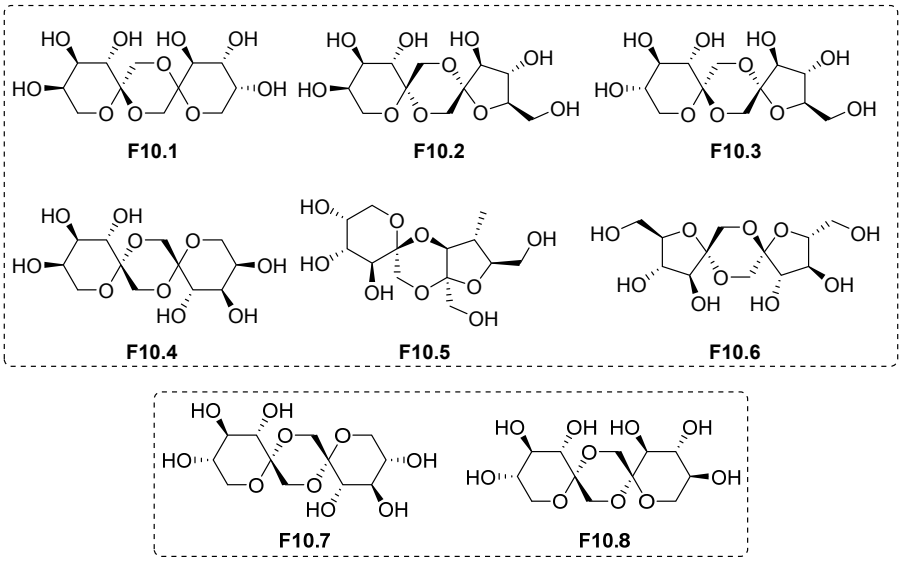
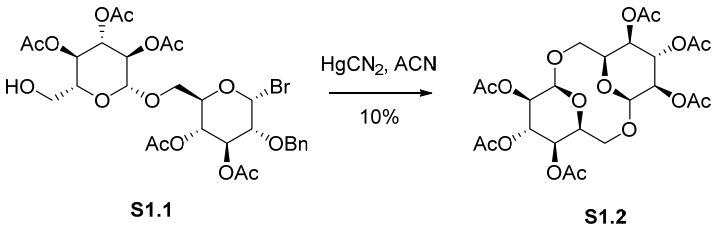


Figure S2.10. *Structures of the cyclic di-D-fructose anhydrides and cyclic di-L-sorbose anhydrides*

The treatment of inulin or D-fructose with strong acids afforded disaccharide dianhydrides **F10.1-F10.6** with combinations of D-fructofuranose and D-fructopyranose residues linked by α- or *β*-(1→2)-glycosidic bonds, i.e., they possess dispiro structures. The only exception within this series is compound **F10.5** which incorporates both *α*-(1→2) and *β*-(2→3)-linkages.[35] Likewise, treatment of L-sorbose with concentrated HCl or anhydrous HF afforded the disaccharides **F10.7** and **F10.8**, composed of (1→2)-linked α- or *β*-L-sorbopyranose residues (Figure S2.10). [36]

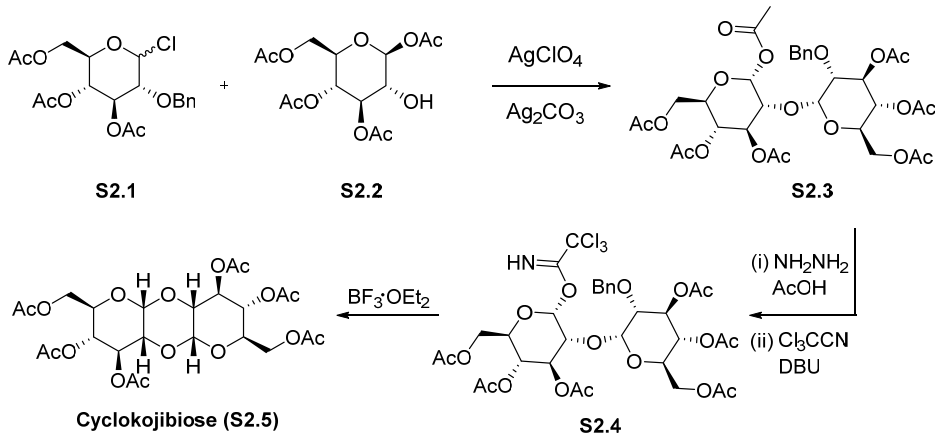
Saccharide dianhydrides by intramolecular glycosylation:

There are very limited reports on the controlled synthesis of saccharide dianhydrides. In the synthesis of cyclodextrins and other cyclooligosaccharides, the role of intramolecular glycosylation is very important. There are very few reports known that were discovered serendipitously for the synthesis of cyclodisaccharides.[37] In connection with the syntheses of cyclic or linear oligomers of β-(1→6)-glucans, Didierg and co-workers reported the intermolecular glycosidation of **S1.1** under standard glycosylation conditions giving a mixture of the expected oligomers and the unexpected cyclic disaccharide **S1.2** in 10% yield (Scheme S2.1).[38]



Scheme S2.1. *Synthesis of 1,6-dianhydried derivative **S1.2***

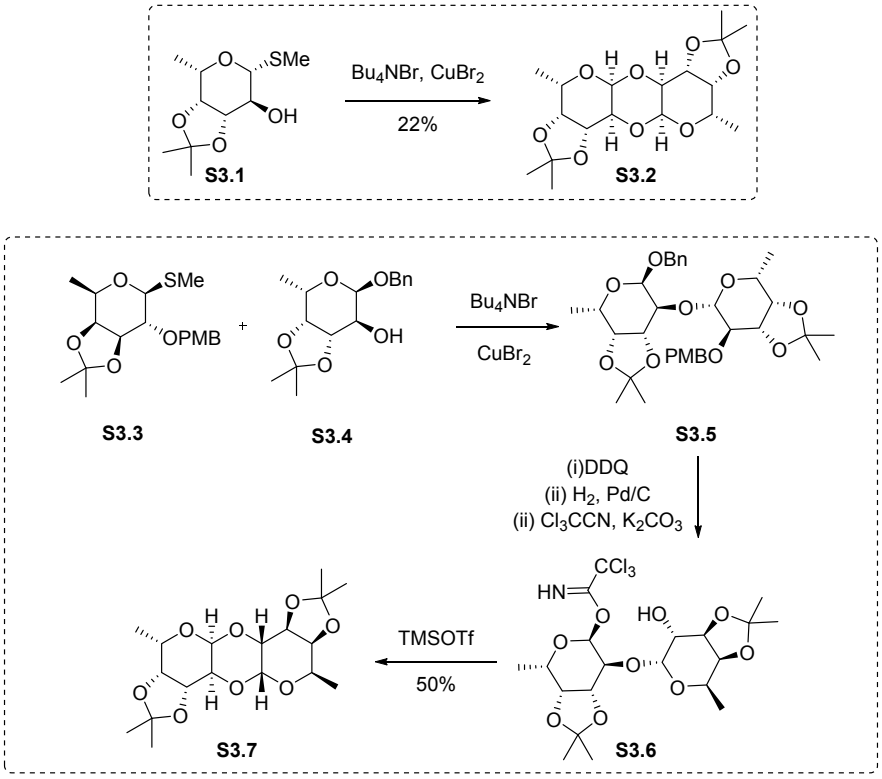
The second example in this regard is the serendipitous synthesis of *cyclo-α-(1 →*2)-glucobiose (cyclokojibiose) by Pozsgay.[39] The protected kojibiose derivative **16** was obtained by the condensation of chloride **S2.1** with alcohol **S2.2** promoted by $AgClO_4/Ag_2CO_3$. The regioselective deacetylation of **S2.3** afforded the hemiacetal which was converted to theimidate **S2.4** under standard conditions. A Glc α (1→2)-Glc trichloroacetimidate derivative **S2.4** was treated with BF_3OEt_2 to yield cyclo-α(1→2) glucobioside (cyclokojibiose) **S2.5** in high yield. Here, the neighboring 2'-*O*-benzyl oxygen proved itself as a good nucleophile with the deprotection of the benzyl group. X-ray studies explained the reason behind the formation of the unexpected result. The glucopyranoside in both rings possesses slightly distorted $^4C_1$ conformations and the central 1,4-dioxane ring has a boat conformation with the anomeric carbon in the bow positions.



Scheme S2.2. *Synthesis of Cyclokojibiose*

A similar cyclodisaccharide was prepared by Theime's group during their journey towards the synthesis of a fucose hexasaccharide.[40] It has been observed that when L-fucose thioglycoside **S3.1** was subjected for glycosidation employing $Bu_4NBr/CuBr_2$ as activators, the cyclo-α-(1→2)-L-fucobioside **S3.2** was isolated in modest yields along with some oligosaccharides. They also investigated the synthesis of an achiral molecule having a centre of inversion from the corresponding D- and L-fucose derivative. Using halide activation glycosylation, the donor D-fucose derivative **S3.3** and acceptor L-fucose derivative **S3.4** gave

the corresponding α-linked disaccharide **S3.5**. For elimination of traces of the β-linked isomer and due to problems with catalytic hydrogenation directly after the thioglycoside mediated glycosylation, the removal of the two benzyl groups was carried out in two steps. The 2'-position was deprotected with DDQ followed by the 1-position in catalytic hydrogenation conditions. The disaccharide was activated by making it as a trichloroacetamidate in the presence of a mild base (K_2CO_3). Thus 2'-*O*-unprotected D-Fucα(1→2)-L-Fuc trichloroacetimidate **S3.6** was used for intramolecular glycosylation with TMSOTf to yield a cyclodisaccharide **S3.7** which is optically inactive despite having 10 contiguous stereogenic centers.



Scheme S2.3. *Synthesis of difucopyranose dianhydrides*

In all the synthesis of dianhydrides, in general, the products resulted in a *cis*-1,2-diol configuration in both the pyranosyl residues. In contrast, the Sinenside A holds a *trans*-vicinal diol configuration on the sugar pyranose unit that adds another challenge in its synthesis. The details of our efforts in this direction will be discussed in the next part of this chapter.

RESULT AND DISCUSSION

Norlignans are a class of natural phenolic compounds a with diphenylpentane carbon skeleton (C6–C5–C6) and are found mainly among conifers, monocotyledonous plants and insome Leguminosae trees as well. The plant *Curculigo sinensis*is a perennial herb growing mainly in the Yunnan region of China and has been relatively less explored in the context of identifying the bioactive chemical components. In 2012, Li and co-workers reported isolation of several norlignan glucosides from the ethanolic extract of the rhizomes of *C. sinensis*. Amongst the eight norlignans isolated, two of them, namely Sinensides A (**59**) and B are new and, most importantly, are skeletally-rearranged.[28] The structural details of thesetwo compounds have been established with the help of extensive spectroscopic data analysis, including UV, IR, HRESI-MS, and hydrolysis experiments. Sinensides A and B have been identified as norlignan glucosides having the same Ph–C_5–Ph skeleton. A preliminary biological screeningrevealed that Sinensides A and B displayed potent antioxidant and radical scavenging activity. In view of their impressive biological profile, and novel structures, we decided to undertake the total synthesis of Sinenside A (**59**). The structure of Sinenside A has been characterized as glucoside a fused norlignan. The central skeleton of Sinenside A is characterized by a unique cyclic disaccharide (or saccharide dianhydride) in which two pyranose residues are fused with a challenging 1,2-*trans*-configuration and a *gem*-diaryl (with free phenolic–OH groups) unit present on one of the tetrahydropyran moiety.

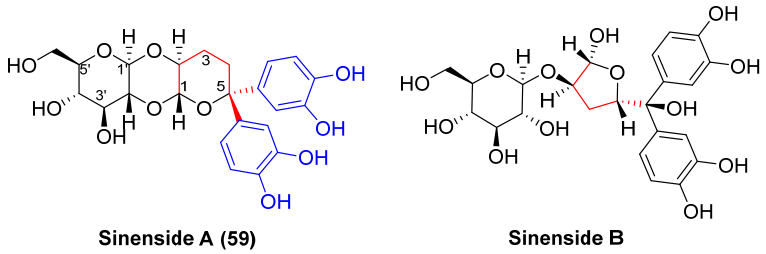


Figure 1. *Structures of Sinenside A and B isolated from Curculigo sinensis plant*

Retrosynthetic analysis:

As mentioned in the introductory part, reports on the synthesis of saccharide dianhydrides employing intramolecular glycosidation are limited. In addition, an examination of the structures of all the saccharide dianhydrides synthesized so far revealed that they are having the 1,2-*cis* configuration and that the 1,2-*trans*-configuration present in Sinenside A is a challenging task that needed a critical consideration while designing the retrosynthetic strategy. As outlined in the retrosynthesis depicted in Scheme 1, it was envisaged that the *β*-glucoside link present in **59** should be installed at an early stage. Keeping this in mind, we intended to construct the tricyclic core of Sinenside A (**59**) from the intermediate aldehyde

via intramolecular acetalization. We have selected an olefin as a surrogate for this aldehyde group. The orthoester **60** and the 3°-alcohol **61** were selected as partners for the key glycosidation reaction, which was expected to give rise to exclusive *β*-anomeric selectivity.[41]

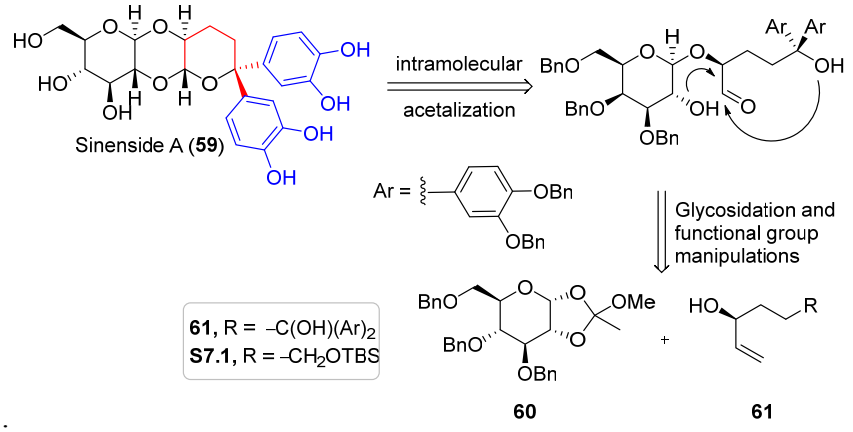


Figure 2. *Our key retrosynthetic disconnections for Sinenside A (**63**)*

Although the key intermediates and a proper retrosynthetic strategy was designed for Sinenside A, in order to validate the key intramolecular acetalization we initially opted for the construction of the central core with a simple phenyl moiety.

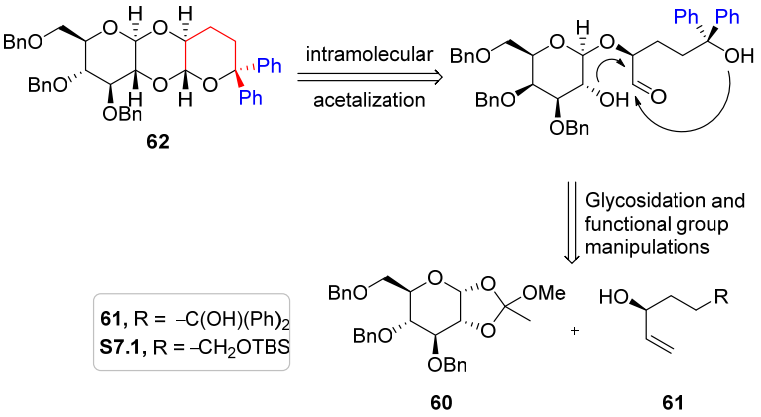
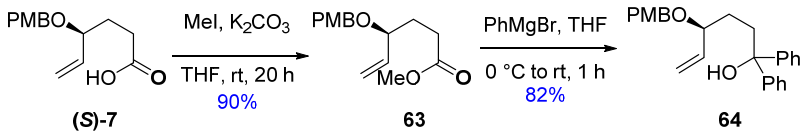


Figure 3. *Retrosynthetic strategy of the central core of Sinenside A(**62**)*

Synthesis of the central core of Sinenside A:

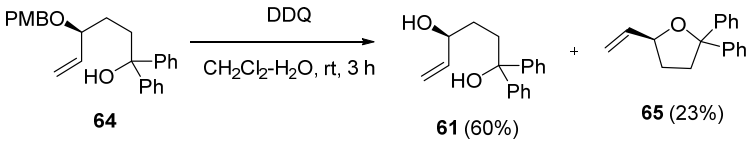
According to the retrosynthetic strategy as depicted in Figure 3, the model studies for the synthesis of the central core of Sinenside A started with the preparation of the glycosyl acceptor **61**. The reaction of the previously synthesized acid (*S*)-**7** with excess of K_2CO_3 and MeI in dry THF gave ester **63** in 90% yields. In the ^{1}H NMR spectrum of **63**, the methyl proton of the ester group was seen to resonate at δ 3.79 (s, 3H) ppm, whereas in the ^{13}C NMR spectrum, the corresponding carbon appeared at δ 51.5 ppm as a quartet. The nucleophilic

addition of the ester **63** with the phenyl magnesium bromide in THF at rt furnished the alcohol **64**. The expected addition of two phenyl groups was confirmed by the presence of ten extra protons in the aromatic region of the ^{1}H NMR spectrum of compound **64** (Scheme 1).



Scheme 1. *Synthesis of tertiary alcohol **64***

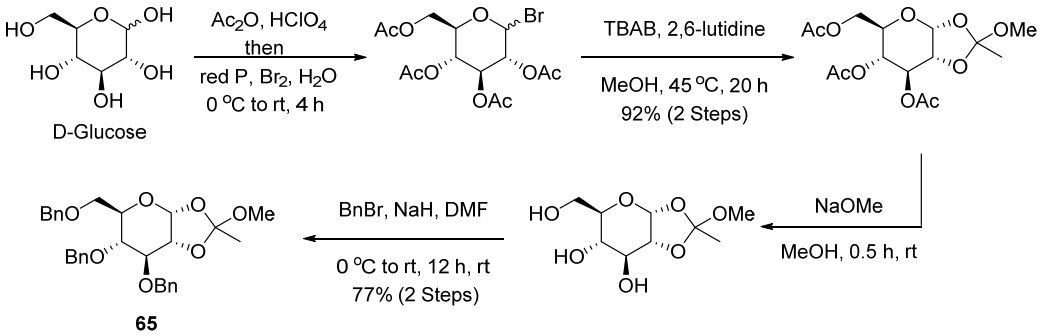
To access the glycosyl acceptor **61**, the PMB group present in compound **64** was deprotected employing DDQ in CH_2Cl_2-water (18:1). Under these conditions, the required alcohol **61** was isolated in 60% yield along with another compound that was obtained in substantial amounts and which later was identified as the cyclic ether **65**. The compound **61** and **65** were fully characterized with the help of spectral and analytical data. A comparison of the spectral data of both **61** with **65** has indeed clearly revealed that **65** contain a furan unit. Some of the characteristic signals that clearly differentiate a open chain structure from the furan structure are the ^{13}C signals of the oxygen bearing carbons. In case of **61**, these two carbons appeared at δ 73.0 (d) and 77.8 (s) ppm, whereas the same carbons in compound **65** were found to resonate at δ 80.0 (d) and 88.4 (s) ppm respectively. In addition to this, in compound **61**, the four protons of the central methylene unit have appeared separately as two multiplets at δ 1.46-1.58 (m, 2H), 2.38 (t, J = 7.6 Hz, 2H) ppm. On the other hand, the same four protons in compound **65** were seen to resonate at sufficient chemical shift differences [δ1.72-1.89 (m, 1H), 2.04-2.21 (m, 1H), 2.53-2.77 (m, 2H) ppm] which indicated that they are diastereotopic. Also, in the ^{1}H NMR of compound **61**, a broad singlet noticed at 3.02 ppm integrating for 2H has been assigned for the two -OH protons. Additionally, the characteristic peaks at 291.1351 $(M+Na)^{+}$ in the ESI-HRMS of compound **61** confirmed the assigned constitution. Similarly, the characteristic peaks at 273.1250 $(M+Na)^{+}$ in the ESI-HRMS of compound **65** confirmed the assigned constitution (Scheme 2).



Scheme 2. *Synthesis of glycosyl acceptor **61***

The synthesis of acceptor (*S*)-**S7.1** has been earlier reported from our laboratory from commercially available 4-pentenol in the context of the total synthesis of Stagonolide B as

discussed in Chapter 1. The glycosyl donor **60** was prepared from D-glucose following a literature procedure. 1,2,3,4,6-Penta-*O*-acetyl-D-glucopyranose was obtained by conventional *O*-acetylation of D-glucose which was converted to glucosyl bromide using Br_2 and red Phosphrous. This glycosyl bromide was directly subjected for the cyclization employing 2,6-lutidine in the presence of tetrabutyl ammonium bromide in methanol to afford triacetyl orthoester. The acetyl groups were hydrolyzed employing sodium methoxide and the resulting free hydroxy groups were benzylated to give orthoester **60** (Scheme 3).[42]

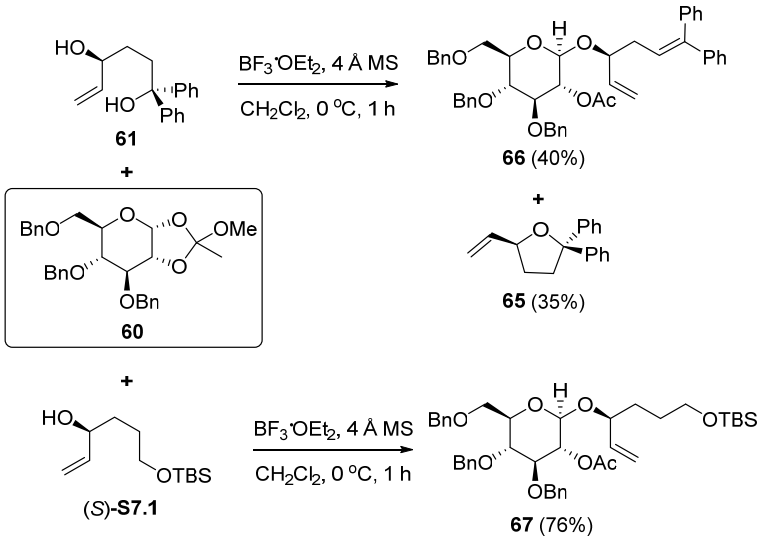


Scheme 3. *Synthesis of glycosyl donor **60***

Glycosidation reaction with two different acceptors

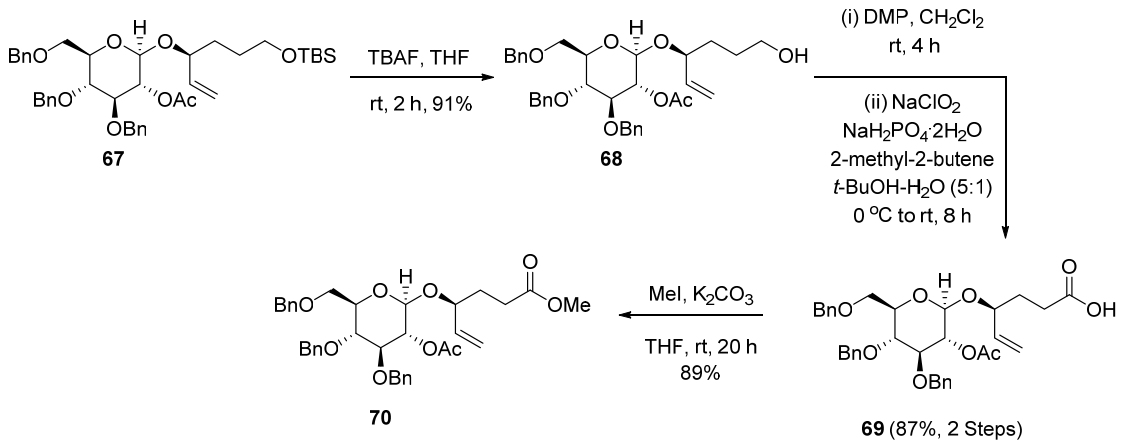
After having glycosyl donor **60** and both the acceptors **61** and (*S*)**-S7.1** in hand, our attention next turned to the key glycosidation reaction. A successful glycosidation with **61** was expected to provide the complete carbon framework of Sinenside A quickly. Considering this, initially, the glycosidation of orthoester **60** has been attempted with **61** using $BF_3 \cdot Et_2O$ (0.15 equiv.) in dichloromethane in the presence of 4Å molecular sieves. This reaction has led to isolation of a new compound **66** along with the previously characterized furan **65**.[43] The detailed spectral data analysis of this new compound **66** has led to realization that the expected *β*-glucosidation with the 2°-alcohol of **61** has indeed occurred, However, the spectator *3*°-OH has eliminated resulting in the formation of a trisubstituted olefin. For example in the ^{1}HNMR spectrum of compound **66**, the anomeric proton was seen to resonated at δ 4.40 as a doublet with coupling constant 7.9 Hz and the next the anomeric one, resonated at 5.03 (t, J = 8.1 Hz, 1H) ppm, which is indicative of a *β*-glucoside linkage. The protons associated with the previously present terminal olefin were seen to resonate at δ 5.17-5.21 (m, 2H), 5.54-5.63 (m, 1H) ppm along with a new signal at δ 6.12 (t, J = 7.0 Hz, 1H) ppm integrating for one proton. This has been assigned for the newly formed internal olefin as a result of elimination of the tertiary hydroxyl group. To support this, the signals corresponding to one of the methylene-CH_2 were seen to disappear and there were only two

multiplets in the aliphatic region at δ 2.33-2.40, 2.43-2.50 ppm integrating each for one proton. In the ^{13}C NMR spectrum of compound **66**, carbon corresponding to internal olefin were seen to resonated at δ 124.7 (d) and 139.9 (s) ppm where as that of terminal olefin at δ 117.7 (t) and 137.3 (d) ppm. The anomeric carbon and ester carbonyl appeared at δ 98.0 (d) and 169.4 (s) ppm respectively. The structure of **66** was further supported by the presence of a peak at 747.3286 in ESI-HRMS (Scheme 4).



Scheme 4. *Optimization of glycosidation reaction*

In order to avoid acid-catalyzed undesired cyclization and elimination of the sensitive tertiary hydroxy group, it was next decided to use the simple allylic alcohol (*S*)**-S7.1** as an acceptor. The glycosidation of (*S*)**-S7.1** with orthoester **60** proceeded smoothly and provided exclusively the *β*-glucoside **67** in 76% yield. The glycoside product **67** was completely characterized by the physical and spectroscopic techniques. The appearance of a doublet at δ 4.39 ppm with a coupling constant J = 8.1 Hz (the characteristic value of *β*-glucoside) corresponding to an anomeric proton, *t*-butyldimethyl silyl protons at δ 0.03 (s, 6H), 0.88 (s, 9H) and a phenyl proton of the benzyl group at δ 7.19 (d, J = 1.3, 7.1 Hz, 2H), 7.25-7.29 (m, 7H), 7.31-7.39 (m, 6H) ppm in the ^{1}H NMR spectrum of **67** were initial indications for the synthesis of *β*-glucoside **67**. Similarly, the presence of an anomeric carbon at δ 98.0 (d) ppm, olefinic carbons at δ 117.3 (t), 137.9 (d) ppm and a carbonyl carbon of acetate at δ 169.3 (s) ppm in the ^{13}C NMR spectrum of compound **67** confirmed the assigned *β*-glucoside structure of **67**. Furthermore, HRMS supported the expected structure (Scheme 4).

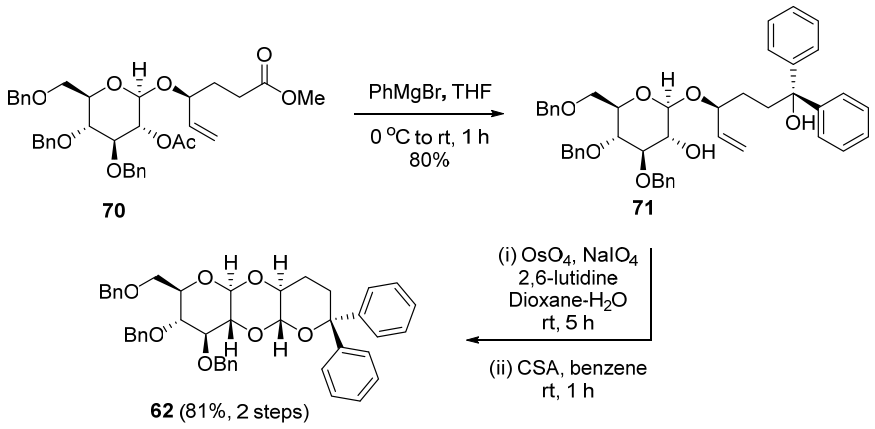


Scheme 5. *Synthesis of ester **70***

Having the *β*-glucoside derivative **67** in hand, our next task was TBS deprotection and oxidation of the resulting primary hydroxyl group. Thus, the treatment of compound **67** with TBAF in THF at rt afforded the alcohol **68** in 91% yield. Next, the oxidation of the primary hydroxyl group of compound **68** using Dess–Martin periodinane in CH_2Cl_2 gave the aldehyde which was further oxidized to the corresponding acid **69** by treating with $NaClO_2$ and $NaH_2PO_4.H_2O$ in the presence 2-methyl-2-butene in *t*-BuOH and H_2O.[44] The spectral and analytical data of acid **69** were in accordance with the proposed structure. Subsequent methylation of acid **69** with MeI in the presence of K_2CO_3 in dry THF gave the ester **70**.[45] The formation of methyl ester was confirmed by spectral and analytical data. For instance, in the ^{1}H NMR spectrum of compound **70**, two sharp singlets at δ 1.95 (s, 3H) and 3.62 (s, 3H) ppm corresponding to the methyl groups of acetate and of the ester, appeared. Similarly, in the ^{13}C NMR spectrum of **70**, the carbonyl carbon of acetate and ester groups were seen to resonate at δ 169.4 (s) and 173.9 (s) ppm respectively. Other peaks in both the spectra were in agreement with the assigned structure. In the ESI-HRMS spectrum, the characteristic mass peak at *m/z* 641.2724 ([M+Na]+) confirmed the proposed constitution of **70** (Scheme 5).

In proceeding with our synthesis toward the central core of Sinenside A, it was first necessary to introduce the aromatic moieties. In this pursuit, the Grignard reaction of the key ester **70** with excess phenyl magnesium bromide has been executed to prepare the diol **71** in 80% yield. The structure of **71** was supported by ^{1}H NMR and mass spectra. For example, in the ^{1}H NMR spectrum of **71**, the methyl signals corresponding to the methyl ester and acetate group were seen to disappear and ten extra protons in the aromatic region were present which indicated the expected addition of two phenyl rings along with the removal of the acetate protecting group. Similarly in the ^{13}C NMR spectrum of compound **71**, the signal

corresponding to the carbonyl carbon of the acetate group and the methyl ester were disappeared and new signal at δ 78.0 (s) ppm corresponding to the quaternary carbon attached to the tertiary hydroxyl group was noticed. In the mass spectrum, the characteristic mass peak at *m/z* 723.3287($[M+Na]^+$) confirmed the proposed constitution of **71** (Scheme 6).



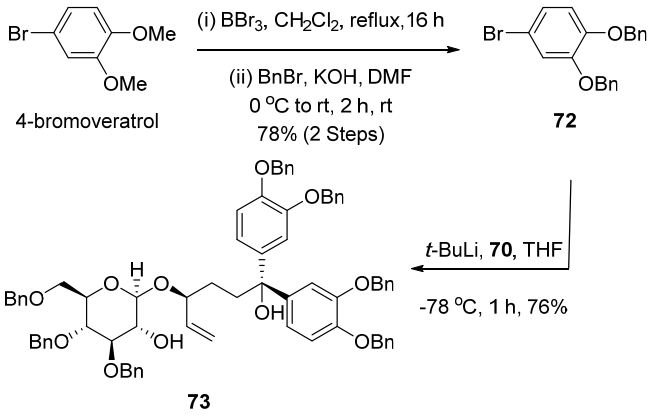
Scheme 6. *Synthesis of core structure of Sinenside A*

After having made the diol **71**, we next investigated the oxidative cleavage of the double bond and proposed intramolecular acetalization of the resulting aldehyde. Thus, the oxidative cleavage of the double bond in compound **71** was carried out using $OsO_4/NaIO_4$ in the presence of 2,6-lutidine.[46] The intermediate aldehyde thus obtained was immediately subjected for the intramolecular acetalization employing a catalytic amount of CSA in benzene at room temperature to exclusively obtain **62** in 81% yields over two steps.[47] Part of the NMR spectroscopic data of **62** was comparable with that of the natural product Sinenside A. For example, in the ^{1}HNMR of compound **62**, the signal corresponding to the C1–H and C2–H appeared at δ 4.69 (s, 1H) and 4.23 (t, J = 8.9 Hz, 1H) ppm whereas they were present at δ 4.72 (s, 1H) and 3.77–3.79 (m, 1H) ppm in Sinenside A respectively. The chemical shift and coupling constants of these two signals indicated a *trans*-diaxial relation between these two protons. Similarly, in the ^{13}C NMR spectrum, the anomeric carbon of the glucose residue and the newly formed acetal carbon were seen to resonate at δ 98.3 (d) and 90.1 (d) ppm whereas in the natural Sinenside A, they were observed respectively at δ 99.8 (d) and 91.9 (d) ppm (Scheme 6).

Total synthesis of Sinenside A:

After the successful synthesis of the complete core, we next focused our attention on the total synthesis of Sinenside A. For that it was first necessary to prepare the required catechol moiety and its coupling with the ester **70**. The requisite coupling partner 3,4-

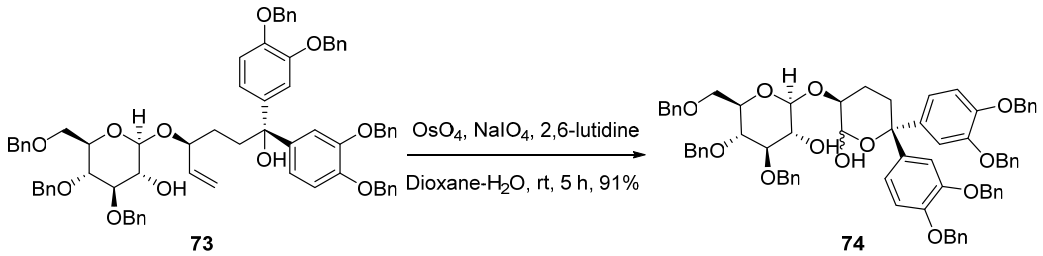
bis(benzyloxy)bromobenzene **72** was prepared by following the established procedures from 4-bromo veratrol. The hydrolysis of the methyl ether with BBr_3 in CH_2Cl_2 resulted in 4-bromo-catechol which upon treatment with BnBr in the presence of K_2CO_3 in DMF resulted in the formation of 3,4-bis(benzyloxy)bromobenzene **72** in 78% yield in 2 steps. The spectroscopic and analytical data of **72** were in good agreement with the reported data (Scheme 7).[48]



Scheme 7. *Synthesis of Diol 73*

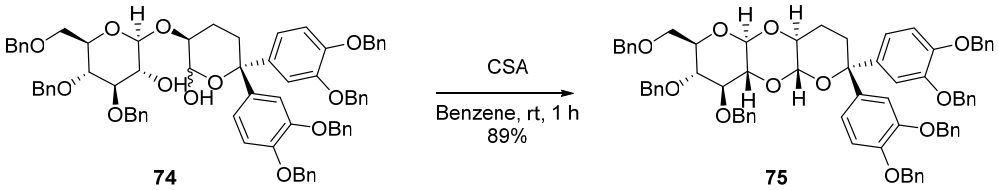
The next task was the generation of the Grignard reagent from **72** and the addition of this to the ester **70**. However, the direct preparation of the Mg-based Grignard reagent using 3,4-bis(benzyloxy)bromobenzene **72** was found to be a problem.[48] Alternatively, employing ^{t}BuLi for halogen-metal exchange, the diaryl addition to ester **70** could be successfully conducted to obtain the diol **73** in 76% yields.[49] In the ^{1}HNMR spectrum of **73**, the protons of the two catechol rings were seen to resonate at δ 6.78-7.82 (m, 2H), 6.83-6.88 (m, 2H) and 6.92-6.96 (m, 2H) ppm. In ^{13}C NMR spectrum of **73**, six methine and six quaternary carbon of two catechol aromatic ring were seen to resonate at δ 113.9 (d), 114.0 (d), 114.1 (d), 114.2 (d), 119.0 (d), 119.1 (d) ppm and at δ 140.3 (s), 141.0 (s), 147.7 (s), 147.8 (s), 148.2 (s, 2C) ppm respectively. Similarly, the quaternary carbon attached to the tertiary hydroxyl group appeared at δ 77.5 (s) ppm. Furthermore, the disappearance of the signal corresponding to the acetate group and the methyl ester group and the appearance of a signal corresponding to four more benzyl groups indicated the expected addition of two required diaryl units along with the removal of the acetate protecting group. In HRMS the presence of a strong peak at 1147.4968 ($[M+Na]^+$) confirmed the constitution of compound **73** (Scheme 7).

Next, the diol **73** was subjected for the oxidative olefin cleavage by employing the previously established reaction conditions "OsO_4/$NaIO_4$/2,6-lutidine" to afford an inseparable anomeric mixture of lactols **74** in 91% yield (Scheme 8).



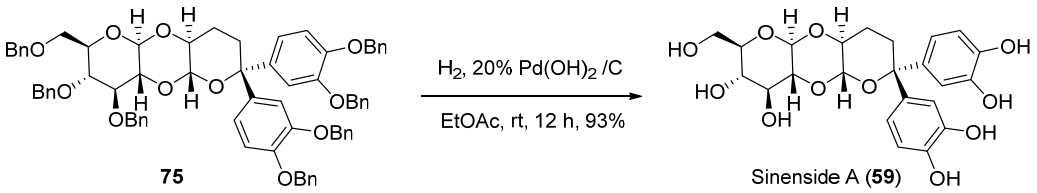
Scheme 8. *Synthesis of Lactols 74*

In the ^{13}CNMR spectrum of compound **74**, the disappearance of the olefinic carbons at δ 117.8 (t),137.7 (d) ppm present in **73**, and the appearance of a two signals for the C1 center at δ 91.3 (d) and 94.2 (d) ppm indicated the formation of lactols. Further shifting of signal corresponding to quaternary carbon attached to tertiary hydroxyl in compound **73** from δ 77.5 (s) to at δ 81.1 (s) and 81.2 (s) ppm in compound **74** and the presence of five different signals in the region δ 1.63-2.43 ppm corresponding to two -CH_2 in the ^{1}H NMR of compound **74** revealed that the tertiary hydroxyl group had taken part in hemiacetal formation. Other peaks in both the spectra and HRMS were in agreement with the assigned structure.



Scheme 9. *Synthesis of tricyclic compound 75*

Our next concern was the intramolecular acetalization of lactols **74** that was carried out by treatment of lactols **74** with a catalytic amount of CSA in benzene at rt. Under these conditions, the desired tricyclic compound **75** was obtained in 89% yield. The structure of compound **75** is comparable with the previously synthesized analog **62** and was further established with the help of spectral and analytical data. For example, in the ^{1}H NMR of compound **75**, the C1–H, C2–H and anomeric proton of the glucose moiety appeared at δ4.55 (s, 1H), 4.16 (t, J = 8.7 Hz, 1H) and 4.43 (d, J = 7.9 Hz, 1H) ppm respectively. Similarly, in the ^{13}C NMR spectrum, the quaternary carbon attached to the two catechol moiety, and the newly formed acetal carbon and anomeric carbon of glucose residue were seen to resonate at δ 81.3 (s), 90.1 (d) and 98.2 (d) ppm respectively. Additionally, HRMS provided the additional support for the proposed structure (Scheme 9).



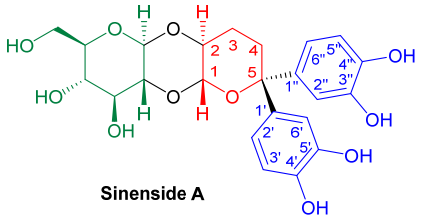
Scheme 10. *Total synthesis of Sinenside A (**59**)*

Having the complete skeleton in hand, now the stage was set to complete thetotal synthesis of Sinenside A by removing the benzyl protecting group. When we subjected compound **75** for hydrogenolysis of the benzyl ethers using 10% Pd-C in methanol at 1 bar pressure of H_2 gas, we observed the partial hydrogenolysis of the O–C(Ar)$_2$ bond as well. To find the appropriate conditions, we systematically varied the catalyst/solvents and it was observed that when employing 20% Pd(OH)$_2$/C in EtOAc, the exclusive hydrogenolysis of the benzyl ethers in **75** proceeded smoothly at 1 bar within 12 h and afforded the natural product Sinenside A (**59**) in quantitative yield. The spectral and analytical data of synthetic **59** were in full agreement (Table 6) and the specific rotation measured [–20.5 (*c* = 0.2 in MeOH)] was close to the values reported for the natural product [–15.6 (*c* = 0.11 in MeOH)].

Conclusion:

In conclusion, the first total synthesis of Sinenside A has been completed in 9 steps from readily accessible starting materials. The key step involves an intramolecular acetalization that directly affords the target parent tricyclic ring system. The approach adopted is divergent in nature and should be usable for the preparation of various analogs of Sinenside A, along with other norlignans of the same family.

Table 6. Comparative δ and J values of synthetic and natural Sinenside A:

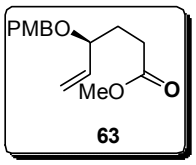


Sinenside A

Position	Natural Product		Synthetic Sinenside A	
	^{1}H NMR	^{13}C NMR	^{1}H NMR	^{13}C NMR
Pyran Unit				
1	4.72 (s, 1H)	91.9 (d)	4.72 (s, 1H)	91.9 (d)
2	3.77–3.79 (m, 1H)	72.0 (d)	3.79-3.80 (m, 1H)	71.9 (d)
3	1.95–2.04 (m, 2H)	26.9 (t)	1.95-2.08 (m, 2H)	26.9 (t)
4	2.28–2.32 (m, 1H) 2.15 (td, J = 3.8, 13.5 Hz, 1H)	30.4 (t)	2.29-2.32 (m, 1H) 2.15 (td, J = 2.9, 13.2 Hz, 1H)	30.4 (t)
5		83.2 (s)		83.2 (s)
Aromatic				
1'		142.3 (s)		142.3 (s)
2'	6.85 (s, 1H)	114.1 (d)	6.85 (s, 1H)	114.0 (d)
3'		145.6 (s)		145.6 (s)
4'		144.9 (s)		144.9 (s)
5'	6.65 (d, J = 8.3 Hz, 1H)	115.6 (d)	6.63 (d, J = 8.2 Hz, 1H)	115.6 (d)
6'	6.59 (d, J = 8.3 Hz, 1H)	118.1 (d)	6.59 (d, J = 8.8 Hz, 1H)	118.0 (d)
1"		134.2 (s)		134.1 (s)
2"	6.95 (s, 1H)	116.1 (d)	6.94 (s, 1H)	116.1 (d)
3"		146.8 (s)		146.8 (s)
4"		145.8 (s)		145.7 (s)
5"	6.81–6.84 (overlap)	116.3 (d)	6.83-6.84 (m, 1H)	116.2 (d)
6"	6.81–6.84 (overlap)	120.2 (d)	6.83-6.84 (m, 1H)	120.1 (d)
Glucose unit				
1	4.52 (d, J = 7.9 Hz, 1H)	99.8 (d)	4.53 (d, J = 7.9 Hz, 1H)	99.8 (d)
2	3.91 (t, J = 8.3, 8.9 Hz, 1H)	73.6 (d)	3.91 (t, J = 8.4 Hz, 1H)	73.6 (d)
3	3.53–3.57 (m, 1H)	75.2 (d)	3.53-3.57 (m, 1H)	75.2 (d)
4	3.53–3.57 (m, 1H)	72.1 (d)	3.53-3.57 (m, 1H)	72.0 (d)
5	3.48–3.56 (m, 1H)	80.1 (d)	3.48-3.57 (m, 1H)	80.1 (d)
6	3.95 (d, J = 11.7 Hz, 1H) 3.80 (dd, J = 5.0, 12.6 Hz, 1H)	62.6 (t)	3.95 (d, J = 11.8 Hz, 1H) 3.81 (dd, J = 4.6, 12.1 Hz, 1H)	62.5 (t)

EXPERIMENTAL

***Methyl (S)-4-((4-methoxybenzyl)oxy)hex-5-enoate* (68):**

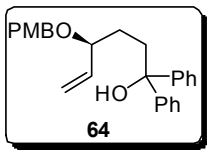


63

To a solution of acid (*S*)-**7** (500 mg, 2.00 mmol) in THF (5 mL) was added K_2CO_3 (360 mg, 2.60 mmol) followed by MeI (0.16 mL, 2.60 mmol) and the reaction mixture was stirred for 20 h at rt. The reaction mixture was concentrated under reduced pressure and the residue was purified by column chromatography (10→12% EtOAc in petroleum ether) to afford **63** (475 mg, 90%) as a colorless syrup.

R_f 0.4 (20% EtOAc in petroleum ether); $[\alpha]_D^{25}$ – 24.9 (*c* = 1.0 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.81-1.95 (m, 2H), 2.36 (dt, *J* = 4.4, 7.6 Hz, 2H), 3.62 (s, 3H), 3.74 (q, *J* = 7.8 Hz, 1H), 3.79 (s, 3H), 4.25 (d, *J* = 11.3 Hz, 1H), 4.50 (d, *J* = 11.3 Hz, 1H), 5.20-5.25 (m, 2H), 5.72 (ddd, *J* = 7.6, 11.0, 16.4 Hz, 1H), 6.86 (d, *J* = 8.5 Hz, 2H), 7.23 (d, *J* = 8.5 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 30.0 (t), 30.4 (t), 51.5 (q), 55.2 (q), 69.8 (t), 78.9 (d), 113.7 (d, 2C), 117.6 (t), 129.3 (d, 2C), 130.5 (s), 138.3 (d), 159.1 (s), 174.0 (s) ppm; HRMS (ESI+) calculated for $C_{15}H_{20}O_4Na$ 287.1259; Found 287.1251.

***(S)-4-((4-Methoxybenzyl)oxy)-1,1-diphenylhex-5-en-1-ol* (69):**



64

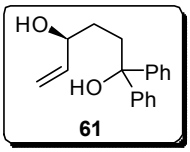
A suspension of Mg (142 mg, 6.05 mmol) and catalytic iodine in dry THF (10 mL) was treated with bromobenzene (0.5 mL, 4.54 mmol) and the contents were stirred at rt for 1 h. To this, a solution of the ester **63** (400 mg, 1.51 mmol) in THF (5 mL) was added dropwise at 0 °C and the mixture was stirred for another 1 h at rt. The reaction mixture was quenched with saturated ammonium chloride (20 mL) and extracted with ethyl acetate (2×30 mL). The combined organic extract was dried (Na_2SO_4), concentrated and the resulting crude residue was purified by silica gel column chromatography (15→17% EtOAc in petroleum ether) afforded **64** (480 mg, 82%) as a yellow syrup.

R_f 0.3 (20% EtOAc in petroleum ether); $[\alpha]_D^{25}$ –18.5 (*c* = 1.0 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.65-1.75 (m, 2H), 2.44 (dt, *J* = 3.2, 7.6 Hz, 2H), 3.81 (q, *J* = 7.3 Hz, 1H), 3.85 (s, 3H), 4.34 (d, *J* = 11.4 Hz, 1H), 4.59 (d, *J* = 11.4 Hz, 1H), 5.26-5.30 (m, 2H), 5.77 (ddd, *J* = 7.6, 11.2, 16.5 Hz, 1H), 6.95 (d, *J* = 8.5 Hz, 2H), 7.27 (d, *J* = 7.1 Hz, 2H), 7.33 (d, *J* = 8.0 Hz, 3H), 7.37 (d, *J* = 7.3 Hz, 3H), 7.48 (d, *J* = 7.6 Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 29.8 (t), 37.5 (t), 55.1 (q), 69.7 (t), 77.6 (s), 80.0 (d), 113.6 (d, 2C), 117.2 (t), 126.0 (d, 2C), 126.1 (d, 2C), 126.5 (d, 2C), 127.9 (d, 4C), 129.4 (d, 2C), 130.2 (s), 138.4 (d), 147.0 (s), 147.4 (s) 159.0 (s) ppm; HRMS (ESI+) calculated for $C_{26}H_{28}O_3Na$ 411.1936; Found 411.1927.

Deprotection of PMB ether in 64:

A solution of **64** (300 mg, 0.77 mmol) and DDQ (210 mg, 0.92 mmol) in CH_2Cl_2-water (8 mL, 18:1) was stirred for 3 h at rt. To this was added aq. $NaHCO_3$ solution (20 mL), and the contents were partitioned between water and CH_2Cl_2 (30 mL). The aqueous layer was extracted with CH_2Cl_2 (50 mL), and the combined organic layer was dried over Na_2SO_4 and concentrated. The residue was purified by silica gel chromatography (28 →30% EtOAc in petroleum ether) to give **61** (125 mg, 60%) as yellow syrup along with cyclic ether **65** (45 mg, 23%).

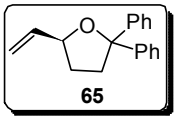
***Characterization data of* 61:**



61

R_f 0.5 (50% EtOAc in petroleum ether); $[\alpha]_D^{25}$ + 1.1 (*c* = 1.0 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.46-1.58 (m, 2H), 2.38 (t, *J* = 7.6 Hz, 2H), 3.02 (s, 2H), 4.06 (q, *J* = 5.7 Hz, 1H), 5.03 (dt, *J* = 1.3, 10.5 Hz, 1H), 5.14 (dt, *J* = 1.3, 17.1 Hz, 1H), 5.71-5.79 (m, 1H), 7.16-7.20 (m, 2H), 7.24-7.28 (m, 4H), 7.37-7.39 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 31.1 (t), 37.4 (t), 73.0 (d), 77.8 (s), 114.7 (t), 126.0 (d, 2C), 126.1 (d, 2C), 126.6 (d), 126.7 (d), 128.0 (d, 4C), 140.9 (d), 146.9 (s), 147.1 (s) ppm; HRMS (ESI+) calculated for $C_{18}H_{20}O_2Na$ 291.1361; Found 291.1351.

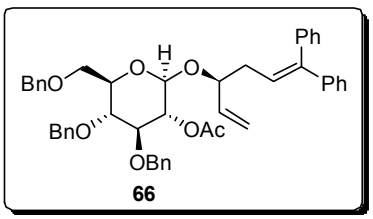
***Characterization data of (S)-2,2-Diphenyl-5-vinyltetrahydrofuran* (65):**



65

R_f 0.5 (5% EtOAc in petroleum ether); $[\alpha]_D^{25}$ + 10.1 (*c* = 1.0 in $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.72-1.89 (m, 1H), 2.04-2.21 (m, 1H), 2.53-2.77 (m, 2H), 4.62 (q, *J* = 6.8 Hz, 1H), 5.14 (br d, *J* = 10.2 Hz, 1H), 5.32 (br d, *J* = 17.1 Hz, 1H), 5.99 (ddd, *J* = 6.8, 10.2, 17.1 Hz, 1H), 7.21-7.36 (m, 6H), 7.48-7.51 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 31.8 (t), 38.4 (t), 80.0 (d), 88.4 (s), 115.3 (t), 125.7 (d, 4C), 126.5 (d, 2C), 127.9 (d, 2C), 128.0 (d, 2C), 139.3 (d), 146.4 (s), 146.8 (s) ppm; HRMS (ESI+) calculated for $C_{18}H_{18}ONa$ 273.1255; Found 273.1250.

Glycosidation with acceptor 61:



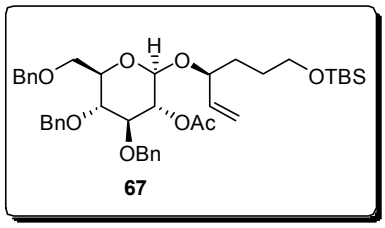
66

At 0 °C, a vigorously stirred suspension of alcohol **61** (100 mg, 0.37 mmol), orthoester **60** (377 mg, 0.74 mmol) and 300 mg 4Å molecular sieves in CH_2Cl_2 (10 mL) was treated with $BF_3{\cdot}OEt_2$ (0.05 mmol, 0.1 mL of a 0.8 M stock solution in CH_2Cl_2) and stirring was continued at 0 °C for 1h. The contents were filtered through Celite pad and the Celite pad was washed with CH_2Cl_2

(50 mL). The combined filtrate was washed with aqueous sodium bicarbonate (20 ml), water (30 mL), dried (Na_2SO_4) and concentrated. The purification of residue by silica gel column chromatography (10→15% EtOAc in petroleum ether) gave **66** (109 mg, 40%) as colourless syrup along with cyclic ether **65** (33 mg, 35%).

R_f 0.3 (10% EtOAc in petroleum ether); $[\alpha]_D^{25}$ –22.5 (*c* = 1.0 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.92 (s, 3H), 2.33-2.40 (m, 1H), 2.43-2.50 (m, 1H), 3.41-3.45 (m, 1H), 3.61-3.72 (m, 4H), 4.22 (q, *J* = 6.8 Hz, 1H), 4.40 (d, *J* = 7.9 Hz, 1H), 4.50 (d, *J* = 12.4 Hz, 1H), 4.53 (d, *J* = 11.1 Hz, 1H), 4.58 (d, *J* = 11.9 Hz, 1H), 4.65 (d, *J* = 11.3 Hz, 1H), 4.77 (d, *J* = 11.1 Hz, 2H), 5.03 (t, *J* = 8.1 Hz, 1H), 5.17-5.21 (m, 2H), 5.54-5.63 (m, 1H), 6.12 (t, *J* = 7.0 Hz, 1H), 7.15 (d, *J* = 8.6 Hz, 3H), 7.18-7.20 (m, 6H), 7.25-7.27 (m, 5H), 7.27-7.31 (m, 9H), 7.34 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.9 (q), 35.7 (t), 68.8 (t), 73.2 (d), 73.4 (t), 74.9 (t, 2C), 75.0 (d), 78.0 (t), 78.8 (d), 83.0 (d), 98.0 (d), 117.7 (t), 124.7 (d), 126.9 (d), 127.2 (d, 2C), 127.5 (d), 127.6 (d, 3C), 127.8 (d, 3C), 127.9 (d, 4C), 128.1 (d, 2C), 128.3 (d, 2C), 128.4 (d, 5C), 129.9 (d, 2C), 137.3 (d), 137.9 (s), 138.1 (s), 138.2 (s), 139.9 (s), 142.6 (s), 143.1 (s), 169.4 (s) ppm; HRMS (ESI+) calculated for $C_{47}H_{48}O_7Na$ 747.3298; Found 747.3286.

Glycosidation with acceptor (*S*)**-S7.1:**



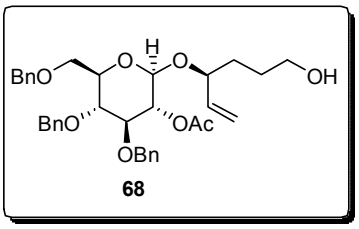
67

A suspension of alcohol (*S*)**-S7.1** (300 mg, 1.30 mmol), orthoester **60** (1.32 g, 2.60 mmol) and 800 mg 4Å molecular sieve in CH_2Cl_2 (20 mL) was cooled to 0 °C and treated with $BF_3{\cdot}OEt_2$ (0.19 mmol, 0.2 mL of a 0.8 M stock solution in CH_2Cl_2) and stirred at 0 °C. The contents were filtered through Celite and the Celite pad was rinsed with CH_2Cl_2 (100 ml). The filtrate was washed with aqueous sodium bicarbonate (40 ml), water (50 mL), dried (Na_2SO_4) and concentrated. The purification of residue by silica gel column chromatography (4→6% EtOAc in petroleum ether) gave **67** (700 mg, 76%) as colourless syrup.

R_f 0.4 (10% EtOAc in petroleum ether); $[\alpha]_D^{25}$ + 3.2 (*c* = 1.0 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.03 (s, 6H), 0.88 (s, 9H), 1.52-1.64 (m, 4H), 1.96 (s, 3H), 3.43 (br td, *J* = 2.5, 9.0 Hz, 1H), 3.56-3.61 (m, 2H), 3.66 (t, *J* = 8.8 Hz, 2H), 3.70-3.74 (m, 2H), 4.09-4.16 (m, 1H), 4.39 (d, *J* = 8.1 Hz, 1H), 4.56 (d, *J* = 12.1 Hz, 1H), 4.57 (d, *J* = 10.7 Hz, 1H), 4.61-4.69 (m, 2H), 4.77 (d, *J* = 11.3 Hz, 1H), 4.78 (dd, *J* = 10.8 Hz, 1H), 5.00 (d, *J* = 8.1 Hz, 1H), 5.15-5.19 (m, 2H), 5.55-5.63 (m, 1H), 7.19 (d, *J* = 1.3, 7.1 Hz, 2H), 7.25-7.29 (m, 7H), 7.31-7.39 (m, 6H); ^{13}C NMR (125

MHz, $CDCl_3$): δ –5.3 (q, 2C), 18.3 (s), 20.9 (q), 25.9 (q, 3C), 28.2 (t), 31.6 (t), 62.9 (t), 68.8 (t), 73.2 (d), 73.4 (t), 74.9 (t, 2C), 75.0 (d), 78.1 (d), 78.7 (d), 83.1 (d), 98.0 (d), 117.3 (t), 127.5 (d), 127.6 (d, 3C), 127.8 (d, 2C), 127.9 (d, 2C), 128.3 (d, 3C), 129.4 (d, 4C), 137.9 (d), 138.0 (s), 138.2 (s, 2C), 169.3 (s) ppm; HRMS (ESI+) calculated for $C_{41}H_{56}O_8NaSi$ 727.3637; Found 727.3635.

Alcohol (68):

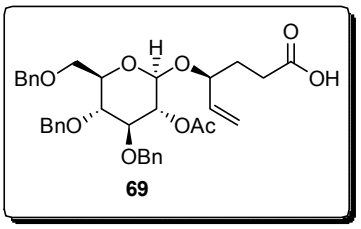


68

To a cooled solution of **67** (1 g, 1.42 mmol) in dry THF (20 mL) was added TBAF (445 mg, 1.70 mmol) and the contents were stirred at rt for 2 h. To this, was added saturated ammonium chloride (50 mL) and the aqueous layer was extracted with EtOAc (2×100 mL). The combined organic layer was dried (Na_2SO_4) and concentrated. The residue was purified by silica gel column chromatography (40→45% EtOAc in petroleum ether) to afford **68** (765 mg, 91%) as colourless syrup.

R_f 0.3 (40% EtOAc in petroleum ether); $[\alpha]_D^{25}$ +1.7 (c = 1.2 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.60-1.70 (m, 4H), 1.95 (s, 3H), 3.45 (ddd, J = 2.2, 4.9, 9.5 Hz, 1H), 3.63-3.65 (m, 3H), 3.66 (dd, J = 4.8, 11.4 Hz, 2H), 3.72 (dd, J = 2.2, 10.9 Hz, 1H), 4.21-4.23 (m, 1H), 4.39 (d, J = 8.1 Hz, 1H), 4.55 (d, J = 11.9 Hz, 2H), 4.61 (d, J = 12.2 Hz, 1H), 4.65 (d, J = 11.3 Hz, 1H), 4.77 (d, J = 11.5 Hz, 1H), 4.78 (d, J = 10.8 Hz, 1H), 4.97-5.02 (m, 1H), 5.15-5.19 (m, 2H), 5.56-5.65 (m, 1H), 7.17 (dd, J = 1.8, 6.7 Hz, 2H), 7.25-7.29 (m, 8H), 7.31-7.34 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.9 (q), 28.1 (t), 31.7 (t), 62.6 (t), 68.8 (t), 73.3 (d), 73.4 (t), 74.9 (d), 74.9 (t, 2C), 78.0 (d), 78.9 (d), 83.0 (d), 98.3 (d), 117.0 (t), 127.6 (d), 127.7 (d, 4C), 127.8 (d, 4C), 128.0 (d, 3C), 128.4 (d, 3C) 137.7 (d), 137.9 (s), 138.1 (s), 138.2 (s), 169.5 (s) ppm; HRMS (ESI+) calculated for $C_{35}H_{42}O_8Na$ 613.2772; Found 613.2770.

Acid (**69**):



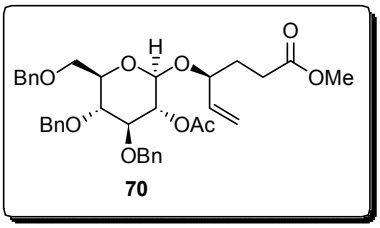
69

Dess-Martin periodinane (970 mg, 2.29 mmol) was added portion wise to a stirred solution of **68** (900 mg, 1.52 mmol) in dry CH_2Cl_2 (15 mL) at 0 °C and stirring was continued at rt for 4 h. The reaction mixture was diluted with sat. $Na_2S_3O_4$ (30 mL) and sat. $NaHCO_3$ (30 mL) and extracted with CH_2Cl_2 (2×100 mL). The combined organic layer was washed with water (2×50 mL) dried over sodium sulphate and concentrated. The resulting crude

product (825 mg, 1.4 mmol) was taken in *t*-butanol:water mixture (5:1, 10 mL), cooled to 0 °C and treated with $NaH_2PO_4 \cdot 2H_2O$ (655 mg, 4.20 mmol), $NaClO_2$ (380 mg, 4.20 mmol) followed by 2-methyl-2-butene (1.5 mL, 14.01 mmol) and the stirring was continued for 8 h at rt. The reaction mixture was diluted with water (100 mL) and extracted with ethyl acetate (2×100 mL). The organic extract was dried (Na_2SO_4) and concentrated. The crude product was purified by silica gel column chromatography (50→60% ethyl acetate in petroleum ether) to obtain acid **69** (800 mg, 87%) as a colorless syrup.

R_f 0.3 (50% EtOAc in petroleum ether); $[\alpha]_D^{25}$ –3.9 (*c* = 1.0 in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.81-1.90 (m, 2H), 1.95 (s, 3H), 2.46 (t, *J* = 7.1 Hz, 2H), 3.42 (br d, *J* = 8.9 Hz, 1H), 3.63 (t, *J* = 8.8 Hz, 1H), 3.66 (d, *J* = 9.1 Hz, 1H), 3.69-3.72 (m, 2H), 4.16 (br q, *J* = 6.8 Hz, 1H), 4.36 (d, *J* = 8.0 Hz, 1H), 4.53 (d, *J* = 11.8 Hz, 1H), 4.56 (d, *J* = 10.8 Hz, 1H), 4.62 (d, *J* = 12.1 Hz, 1H), 4.65 (d, *J* = 11.6 Hz, 1H), 4.77 (d, *J* = 11.2 Hz, 2H), 4.99 (t, *J* = 8.5 Hz, 1H), 5.17-5.21 (m, 2H), 5.57-5.64 (m, 1H), 7.18 (d, *J* = 7.0 Hz, 2H), 7.25-7.29 (m, 7H), 7.31-7.33 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 20.9 (q), 29.7 (t), 30.2 (t), 68.8 (t), 73.2 (d), 73.5 (t), 74.9 (t, 2C), 75.0 (d), 77.8 (d), 78.0 (d), 83.0 (d), 98.2 (d), 117.4 (t), 127.6 (d), 127.7 (d, 4C), 127.8 (d, 3C), 128.0 (d, 3C), 128.4 (d, 4C) 137.1 (d), 137.9 (s), 138.1 (s), 138.2 (s), 169.5 (s, 2C) ppm; HRMS (ESI+) calculated for $C_{35}H_{40}O_9Na$ 627.2565; Found 627.2562.

Methyl ester (**70**):



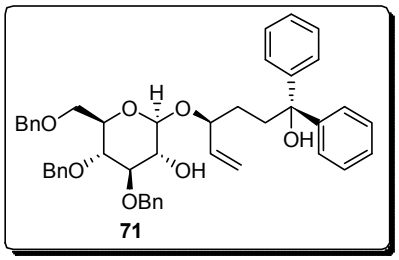
70

K_2CO_3 (237 mg, 1.72 mmol) and MeI (0.12 mL, 1.72 mmol) were sequentially added to carboxylic acid **69** (800 mg, 1.32 mmol) in THF (8 mL) and the reaction mixture was stirred for 20 h. After completion of the reaction, the reaction mixture was concentrated under reduced pressure and the residue was purified by column chromatography (20→25% EtOAc in petroleum ether) to afford **70** (730 mg, 89%) as a yellow syrup.

R_f 0.5 (35% EtOAc in petroleum ether); $[\alpha]_D^{25}$ –3.1 (*c* = 1.0 in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.82-1.89 (m, 2H), 1.95 (s, 3H), 2.42 (dt, *J* = 3.7, 8.0 Hz, 2H), 3.42 (td, *J* = 3.3, 6.6 Hz, 1H), 3.62 (s, 3H), 3.63 (d, *J* = 9.7 Hz, 1H), 3.67-3.71 (m, 3H), 4.16 (q, *J* = 6.8 Hz, 1H), 4.36 (d, *J* = 8.1 Hz, 1H), 4.55 (d, *J* = 12.3 Hz, 1H), 4.57 (d, *J* = 11.4 Hz, 1H), 4.63 (d, *J* = 12.5 Hz, 1H), 4.65 (d, *J* = 11.8 Hz, 1H), 4.77 (d, *J* = 11.3 Hz, 1H), 4.78 (d, *J* = 10.8 Hz, 1H), 4.98 (t, *J* = 8.5 Hz, 1H), 5.18-5.21 (m, 2H), 5.60 (ddd, *J* = 7.0, 10.3, 17.4 Hz, 1H), 7.19 (dd, *J* = 1.7, 7.6 Hz,

2H), 7.27-7.29 (m, 7H), 7.30-7.34 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 20.9 (q), 29.5 (t), 30.2 (t), 51.4 (q), 68.8 (t), 73.2 (d), 73.5 (t,), 74.9 (t, 2C), 75.1 (d), 77.8 (d), 78.0 (d), 83.0 (d), 98.2 (d), 117.4 (t), 127.6 (d, 3C), 127.7 (d), 127.8 (d, 3C), 128.0 (d, 2C), 128.3 (d, 2C), 128.4 (d, 4C), 137.2 (d), 138.0 (s), 138.2 (s, 2C), 169.4 (s), 173.9 (s) ppm; HRMS (ESI+) calculated for $C_{36}H_{42}O_9Na$ 641.2721; Found 641.2724.

Diol (**71**):

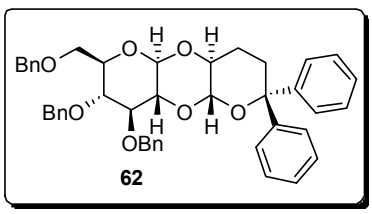


71

A suspension of Mg (55 mg, 2.26 mmol) and catalytic iodine in dry THF (5 mL) was treated with bromobenzene (0.2 mL, 1.94 mmol) and the contents were stirred at rt for 1 h. To this, a solution of the ester **70** (200 mg, 0.32 mmol) in THF (3 mL) was added dropwise at 0 °C and the mixture was stirred for another 1 h at rt. The reaction mixture was quenched with saturated ammonium chloride (20 mL) and extracted with ethyl acetate (2×40 mL). The combined organic extract was dried (Na_2SO_4), concentrated and the resulting crude residue was purified by silica gel column chromatography (20→25% EtOAc in petroleum ether) afforded **71** (182 mg, 80%) as a colorless oil.

R_f 0.3 (25% EtOAc in petroleum ether); $[\alpha]_D^{25}$ –3.0 (*c* = 1.0 in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.59-1.64 (m, 2H), 2.43 (t, *J* = 6.9 Hz, 2H), 3.44-3.45 (m, 1H), 3.53-3.57 (m, 3H), 3.60 (dd, *J* = 5.0, 11.4 Hz, 1H), 3.68 (dd, *J* = 1.3, 10.6 Hz, 1H), 4.32 (q, *J* = 6.9 Hz, 2H), 4.43 (d, *J* = 12.2 Hz, 1H), 4.47 (d, *J* = 12.2 Hz, 1H), 4.51 (d, *J* = 11.0 Hz, 1H), 4.80 (d, *J* = 10.7 Hz, 1H), 4.81 (d, *J* = 11.3 Hz, 1H), 4.91 (d, *J* = 11.3 Hz, 1H), 5.16-5.23 (m, 2H), 5.60-5.67 (m, 1H), 7.14 (dd, *J* = 2.2, 7.2 Hz, 2H), 7.16-7.19 (m, 2H), 7.23-7.31 (m, 14H), 7.32-7.36 (m, 3H), 7.39-7.41 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 29.8 (t), 36.5 (t), 68.8 (t), 73.3 (t), 74.6 (d), 74.9 (t), 75.0 (d), 75.1 (t), 77.6 (d), 78.0 (s), 79.4 (d), 84.6 (d), 99.8 (d), 117.8 (t), 126.1 (d, 5C), 126.6 (d), 126.7 (d), 127.6 (d), 127.7 (d), 127.8 (d, 3C), 127.9 (d), 128.0 (d, 3C), 128.1 (d, 3C), 128.4 (d, 5C), 128.4 (d), 137.7 (d), 138.0 (s, 2C), 138.6 (s), 146.8 (s), 147.6 (s), ppm; HRMS (ESI+) calculated for $C_{45}H_{48}O_7Na$ 723.3292; Found 723.3287.

Tricyclic compound (**62**):



62

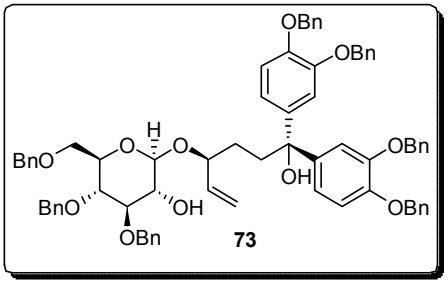
At 0 °C, $NaIO_4$ (61 mg, 0.28 mmol) was added to a solution of alkene **71** (50 mg, 0.07 mmol), 2,6-lutidine (0.02 mL, 0.14 mmol) and OsO_4 (0.03 ml 50 mM in toluene, 0.001 mmol) in 1,4-dioxane-water mixture (3:1, 3

mL) and the stirring was continued for 5 h at rt. After completion of the reaction, the reaction mixture was quenched with water and aqueous layer extracted with CH_2Cl_2 (2×15 mL). The combined organic layer was washed with water (10 mL), dried (Na_2SO_4) and concentrated the resulting crude lactol was used directly for next step.

A solution of above crude lactol (45 mg, 0.06 mmol) in benzene (2 mL) and camphorsulfonic acid (3 mg, 0.01 mmol) was stirred at rt for 1 h. After the completion of the reaction as indicated by TLC, the reaction mixture was quenched sat.$NaHCO_3$ (2 mL) and the aqueous layer was extracted with EtOAc (2×5 mL). The combined organic layer was washed with water (5 mL), dried (Na_2SO_4) and concentrated. The resulting crude product was purified by silica gel column chromatography (15→20% EtOAc in petroleum ether) to yield **62** (40 mg, 81%) as a yellow syrup. In the ^{1}H NMR spectra of purified **62**, the presence of some minor signals that might be attributable to 2,2'-trans diastereomer of **62** are found. Attempts to isolate this minor compound for a comprehensive characterization are unsuccessful.

R_f 0.5 (40% EtOAc in petroleum ether); $[\alpha]_D^{25}$ +2.9 (*c* = 0.7 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.91-1.98 (m, 1H), 2.04-2.09 (m, 1H), 2.34 (td, *J* = 4.6, 13.1 Hz, 1H), 2.42-2.46 (m, 1H), 3.63 (dt, *J* = 2.8, 9.2 Hz, 1H), 3.72-3.75 (m, 4H), 3.80 (t, *J* = 9.3 Hz, 1H), 4.24 (t, *J* = 8.2 Hz, 1H), 4.45 (d, *J* = 8.2 Hz, 1H), 4.51 (d, *J* = 12.1 Hz, 1H), 4.52 (d, *J* = 10.7 Hz, 1H), 4.61 (d, *J* = 12.1 Hz, 1H), 4.69 (s, 1H), 4.77 (d, *J* = 11.4 Hz, 1H), 4.88 (d, *J* = 10.7 Hz, 1H), 5.04 (d, *J* = 11.0 Hz, 1H), 7.14-7.18 (m, 5H), 7.27-7.40 (m, 15H), 7.48-7.51 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 25.4 (t), 28.2 (t), 68.7 (t), 70.6 (d), 73.3 (d), 73.6 (t), 74.6 (t), 75.3 (t), 76.7 (d), 77.2 (d), 81.6 (s), 82.2 (d), 90.1 (d), 98.3 (d), 124.8 (d, 3C), 126.6 (d), 127.1 (d, 3C), 127.3 (d), 127.6 (d), 127.7 (d), 128.0 (d, 7C), 128.1 (d), 128.4 (d, 5C), 128.9 (d, 2C), 137.9 (s), 138.1 (s), 138.8 (s), 141.3 (s), 147.7 (s) ppm; HRMS (ESI+) calculated for $C_{44}H_{44}O_7Na$ 707.2979; Found 707.2974.

Diol (**73**):



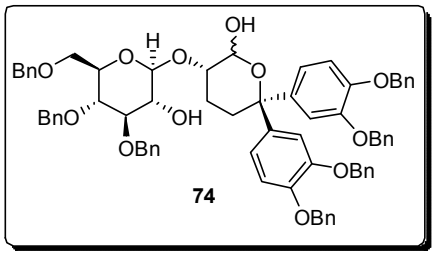
73

To a stirred solution of bromo compound **72** (2.15 g, 5.82 mmol) in THF (30 mL) was added *t*-BuLi (4.0 mL, 6.01 mmol, 1.5 M solution in pentane) at −78 °C and stirred for 15 min at the same temperature and then treated with a solution of ester **70** (600 mg, 0.97 mmol) in THF (5 mL). The resulting mixture was allowed to stir vigorously at −78 °C for 1 h before it

was quenched by adding saturated ammonium chloride (50 mL). The contents were extracted with EtOAc (2×100 mL) and the combined organic layer was washed with brine (50 mL), dried (Na_2SO_4) and concentrated. The crude was purified by silica gel column chromatography (30→35% EtOAc in petroleum ether) to afford **73** (834 mg, 76%) as a yellow oil.

R_f 0.5 (60% EtOAc in petroleum ether); $[\alpha]_D^{25}$ –12.5 (c = 2.0 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.53 (q, J = 7.2 Hz, 2H), 2.26 (t, J = 7.4 Hz, 2H), 2.31 (br s, 1H), 2.65 (br s, 1H), 3.45-3.46 (m, 1H), 3.53-3.63 (m, 4H), 3.68 (dd, J = 1.5, 10.6 Hz, 1H), 4.28 (q, J = 6.9 Hz, 1H), 4.32 (d, J = 6.8 Hz, 1H), 4.41 (d, J = 12.2 Hz, 1H), 4.46 (d, J = 12.2 Hz, 1H), 4.51 (d, J = 10.7 Hz, 1H), 4.81 (d, J = 10.7 Hz, 1H), 4.82 (d, J = 11.1 Hz, 1H), 4.93 (d, J = 11.1 Hz, 1H), 5.04 (s, 2H), 5.07 (d, J = 12.1 Hz, 2H), 5.11 (s, 2H), 5.13 (d, J = 11.6 Hz, 2H), 5.17-5.23 (m, 2H), 5.61 (ddd, J = 7.4, 10.3, 17.4 Hz, 1H), 6.78-7.82 (m, 2H), 6.83-6.88 (m, 2H), 6.92-6.96 (m, 2H), 7.15 (dd, J = 1.5, 5.7 Hz, 2H), 7.24-7.39 (m, 27H), 7.44 (dd, J = 1.5, 5.7 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 29.8 (t), 36.6 (t), 68.9 (t), 71.2 (t, 4C), 73.3 (t), 74.6 (d), 74.9 (t), 75.0 (d), 75.1 (t), 77.5 (s), 77.6 (d), 79.2 (d), 84.6 (d), 99.7 (d), 113.9 (d), 114.0 (d), 114.1 (d), 114.2 (d), 117.8 (t), 119.0 (d), 119.1 (d), 127.2 (d, 5C), 127.4 (d), 127.5 (d, 6C), 127.6 (d, 2C), 127.7 (d, 7C), 127.8 (d, 2C), 127.9 (d, 2C), 128.3 (d, 5C), 128.4 (d, 5C), 137.3 (s, 2C), 137.4 (s, 2C), 137.7 (d), 138.0 (s, 2C), 138.7 (s), 140.3 (s), 141.0 (s), 147.7 (s), 147.8 (s), 148.2 (s, 2C) ppm; HRMS (ESI+) calculated for $C_{73}H_{72}O_{11}Na$ 1147.4957; Found 1147.4968.

Lactols (**74**):

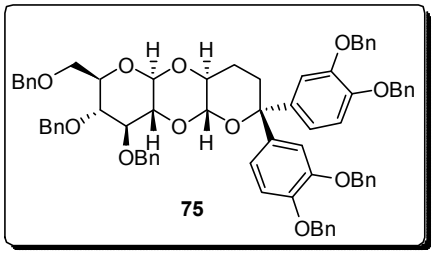


74

A suspension of alkene **73** (100 mg, 0.09 mmol), 2,6-lutidine (0.02 mL, 0.17 mmol) and OsO_4 (0.04 mL of a 50 mM in toluene, 0.002 mmol) in dioxane-water mixture (3:1, 4 mL), at 0 °C was treated with $NaIO_4$ (76 mg, 0.35 mmol) and the stirring was continued for additional 5 h at rt. After completion of the reaction, the reaction mixture was quenched with water (15 ml) and the aqueous layer was extracted with CH_2Cl_2 (2×20 mL). The combined organic layer was washed with water (15 mL), dried over sodium sulphate and concentrated. The purification of residue by silica gel column chromatography (40→50% EtOAc in petroleum ether) gave lactols **74** (91 mg, 91%) as yellow oil.

R_f 0.5 (70% EtOAc in petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.68 (quin, J = 12.8 Hz, 1H), 1.84 (td, J = 3.3, 14.2 Hz, 0.5H), 2.03-2.07 (m, 1H), 2.12-2.19 (m, 1H), 2.44 (dt, J = 3.8, 14.2 Hz, 0.5H), 3.43-3.47 (m, 1H), 3.52-3.60 (m, 3H), 3.62-3.72 (m, 2H), 4.37 (d, J = 7.8 Hz, 0.5 H), 4.46-4.52 (m, 2H), 4.53-4.55 (m, 1.5 H), 4.57-4.61 (m, 1H), 4.81 (d, J = 10.3 Hz, 1H), 4.82 (d, J = 11.1 Hz, 1H), 4.90-4.94 (m, 1H), 5.03-5.09 (m, 6H), 5.11-5.17 (m, 3H), 6.63-6.68 (m, 0.9H), 6.72-6.77 (m, 1H), 6.81 (br s, 0.4H), 6.84 (dd, J = 2.0, 5.5 Hz, 1.3 H), 6.87-6.90 (m, 2H), 6.98 (s, 0.4H), 7.15-7.20 (m, 2H), 7.26-7.42 (m, 31H), 7.45-7.49 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 26.9 (t), 27.6 (t), 28.9 (t), 34.7 (t), 68.7 (t), 68.9 (t), 70.8 (t), 71.1 (t, 2C), 71.2 (t, 5C), 71.3 (t), 73.4 (t, 2C), 74.5 (d), 74.9 (t), 75.0 (t, 2C), 75.0 (d), 75.1 (d), 76.5 (d), 77.4 (d, 2C), 77.7 (d), 79.6 (d), 81.1 (s), 81.2 (s), 84.6 (d), 84.8 (d), 91.3 (d), 94.2 (d), 103.6 (d), 104.6 (d), 112.9 (d), 113.1 (d), 114.2 (d, 3C), 114.3 (d), 114.4 (d) 114.6 (d), 118.3 (d), 118.4 (d), 119.8 (d), 120.1 (d), 127.2 (d, 4C), 127.3 (d, 7C), 127.5 (d, 7C), 127.6 (d, 3C), 127.7 (d, 10C), 127.8 (d, 8C), 127.9 (d, 6C), 128.3 (d, 4C), 128.4 (d, 12C), 128.5 (d, 3C), 128.6 (d, 4C), 128.8 (d, 2C), 134.4 (s), 134.6 (s), 137.2 (s, 2C), 137.3 (s, 2C), 137.4 (s, 3C), 137.5 (s), 137.9 (s, 2C), 138.1 (s, 3C), 138.5 (s), 138.6 (s), 140.9 (s), 148.1 (s, 2C), 148.2 (s, 4C), 148.7 (s, 2C) ppm; HRMS (ESI+) calculated for $C_{72}H_{70}O_{12}Na$ 1149.4759; Found 1149.4758.

Heptabenzyl sinenside A (**75**):



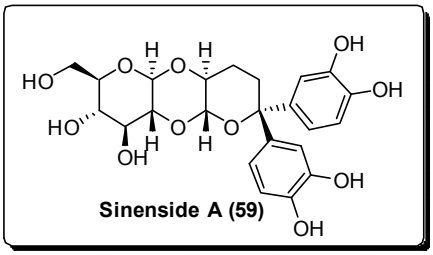
75

A solution of the lactols **74** (50 mg, 0.04 mmol) in benzene (2 mL) was treated with camphorsulfonic acid (2 mg, 0.01 mmol) stirred at rt for 1 h. To this, was added sat. $NaHCO_3$ (5 mL) and the aqueous layer was extracted with EtOAc (2×10 mL). The combined organic layer was washed with water (5 mL), dried (Na_2SO_4) and concentrated. The crude product thus obtained was purified by silica gel column chromatography (25→30% EtOAc in petroleum ether) to yield 44 mg of **75** (89%) as yellow syrup. Like in case of compound **62**, even in the ^{1}H NMR spectra of purified **75**, the presence of some minor signals that might be attributable to 2,2'-trans diastereomer of **75** are found. Attempts to isolate this minor compound for a comprehensive characterization are unsuccessful.

R_f 0.4 (35% EtOAc in petroleum ether); $[\alpha]_D^{25}$ +6.5 (c = 0.5 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.70-1.78 (m, 1H), 1.91 (dd, J = 3.0, 14.6 Hz, 1H), 2.08-2.13 (m, 1H), 2.19 (td, J =

4.0, 14.4 Hz, 1H), 3.62-3.67 (m, 2H), 3.69-3.78 (m, 4H), 4.16 (t, *J* = 8.7 Hz, 1H), 4.43 (d, *J* = 7.9 Hz, 1H), 4.50 (d, *J* = 12.3 Hz, 1H), 4.53 (d, *J* = 10.9 Hz, 1H), 4.55 (s, 1H), 4.59 (d, *J* = 12.3 Hz, 1H), 4.76 (d, *J* = 11.2 Hz, 1H), 4.88 (d, *J* = 11.1 Hz, 1H), 5.01 (s, 2H), 5.01 (d, *J* = 11.1 Hz, 1H), 5.05 (s, 2H), 5.11 (s, 2H), 5.15 (s, 2H), 6.75-6.83 (m, 3H), 6.85-6.90 (m, 2H), 6.99 (s, 1H), 7.14 (dd, *J* = 3.7, 7.3 Hz, 2H), 7.21-7.32 (m, 19H), 7.34-7.41 (m, 9H), 7.43-7.46 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 25.4 (t), 28.5 (t), 68.7 (t), 70.5 (d), 71.0 (t), 71.1 (t), 71.2 (t, 2C), 73.3 (d), 73.6 (t), 74.5 (t), 75.3 (t), 76.7 (d), 77.2 (d), 81.3 (s), 82.2 (d), 90.1 (d), 98.2 (d), 112.9 (d), 114.3 (d), 114.4 (d), 114.5 (d), 118.1 (d), 120.0 (d), 127.2 (d, 4C), 127.6 (d, 7C), 127.7 (d, 2C), 127.8 (d, 2C), 127.9 (d, 2C), 128.0 (d, 4C), 128.3 (d, 6C), 128.4 (d, 4C), 128.5 (d, 2C), 128.6 (d), 128.9 (d), 134.2 (s), 137.0 (s), 137.3 (s, 2C), 137.5 (s), 137.9 (s), 138.1 (s), 138.9 (s), 141.4 (s), 147.6 (s), 147.9 (s), 148.2 (s), 148.7 (s) ppm; HRMS (ESI+) calculated for $C_{72}H_{68}O_{11}Na$ 1131.4654; Found 1131.4659.

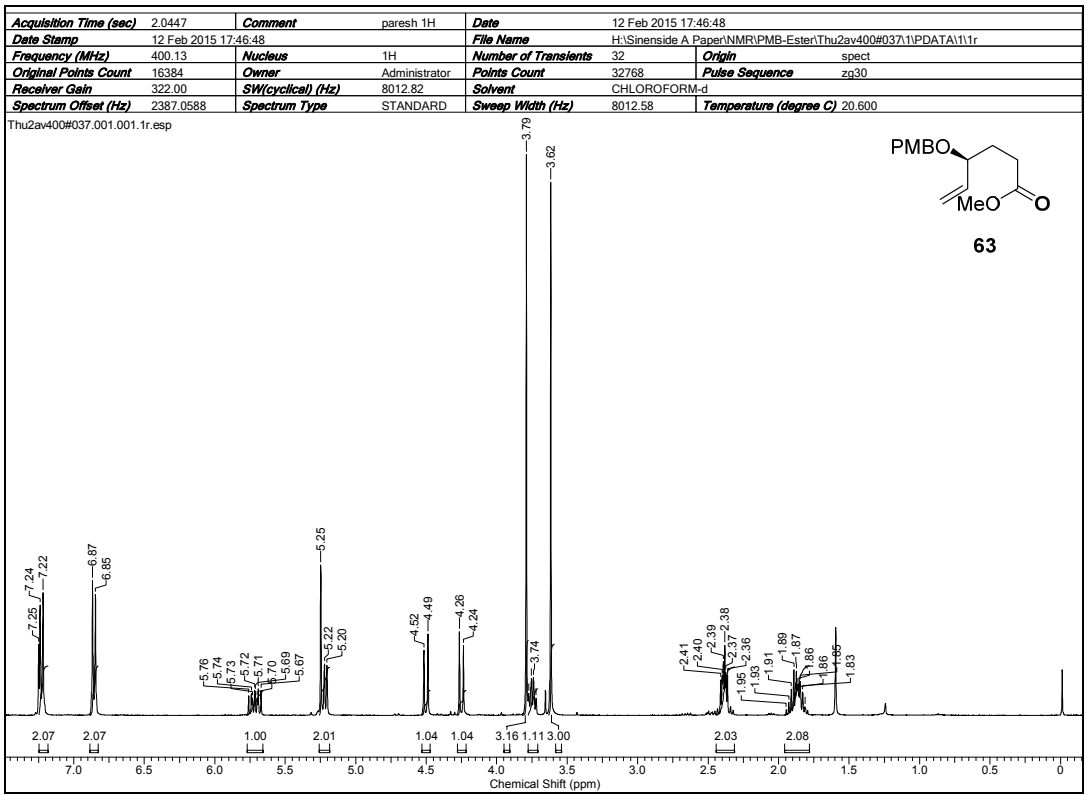
Sinenside A (**59**):



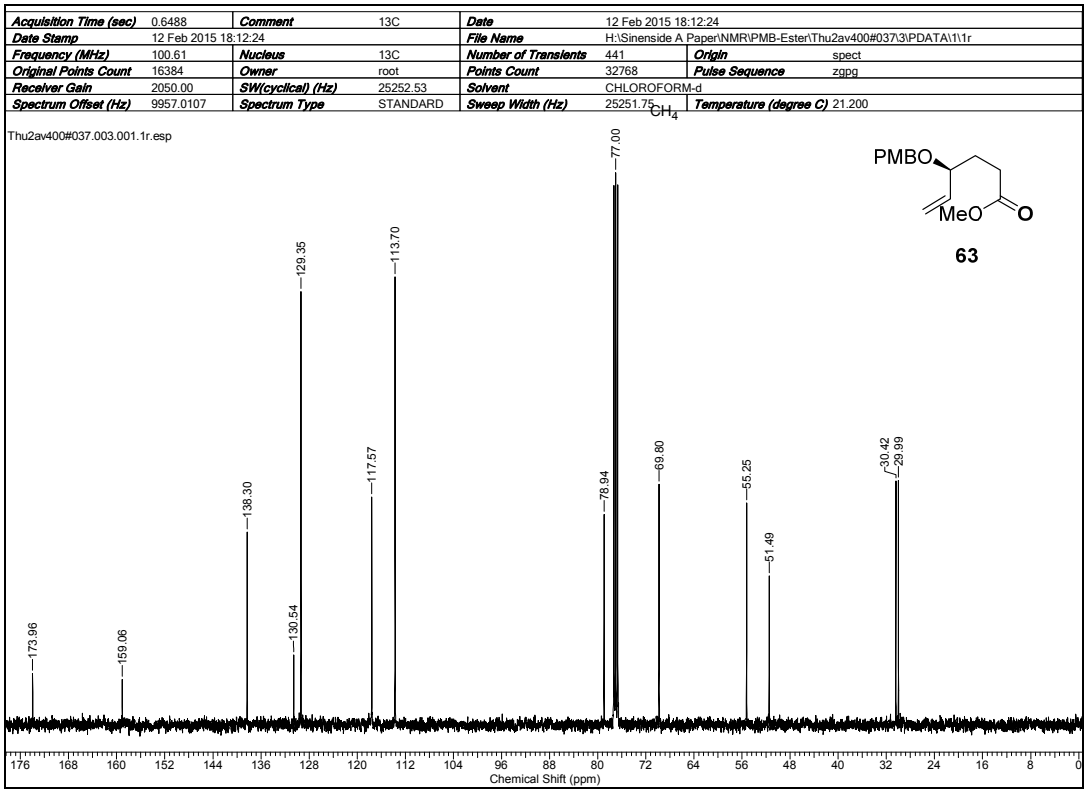
To a solution of **75** (30 mg, 0.03 mmol) in ethyl acetate (3 mL) was added 20% $Pd(OH)_2$/C (9 mg) and the reaction mixture was stirred at rt under H_2 atmosphere (baloon) for 16 h. After disappearance of starting material on TLC, reaction mixture was filtered through Celite pad and the Celite pad was washed repeatedly with methanol. Combined filtrate was evaporated under reduced pressure to afford sinenside A **(59)** (12 mg, 93%) as white solid.

$[\alpha]_D^{25}$ –20.5 (*c* = 0.2 in MeOH); ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.95-2.08 (m, 2H), 2.15 (td, *J* = 2.9, 13.2 Hz, 1H), 2.29-2.32 (m, 1H), 3.48-3.57 (m, 3H), 3.79-3.80 (m, 1H), 3.81 (dd, *J* = 4.6, 12.1 Hz, 1H), 3.91 (t, *J* = 8.4 Hz, 1H), 3.95 (d, *J* = 11.8 Hz, 1H), 4.53 (d, *J* = 7.9 Hz, 1H), 4.72 (s, 1H), 6.59 (d, *J* = 8.8 Hz, 1H), 6.63 (d, *J* = 8.2 Hz, 1H), 6.83-6.84 (m, 2H), 6.85 (s, 1H), 6.94 (s, 1H), ^{13}C NMR (125 MHz, $CDCl_3$): δ 26.9 (t), 30.4 (t), 62.5 (t), 71.9 (d), 72.0 (d), 73.6 (d), 75.2 (d), 80.1 (d), 83.2 (s), 91.9 (d), 99.8 (d), 114.0 (d), 115.6 (d), 116.1 (d), 116.2 (d), 118.0 (d), 120.1 (d), 134.1 (s), 142.3 (s), 144.9 (s), 145.6 (s), 145.7 (s), 146.8 (s) ppm; HRMS (ESI+) calculated for $C_{23}H_{26}O_{11}Na$ 501.1367; Found 501.1370.

SPECTRA



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



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

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Date Stamp	26 Jan 2015 17:31:52			***File Name***	H:\Sinenside A Paper\NMR\phenyl grignard\Mon5av400#017\1\PDATA\1\1r		
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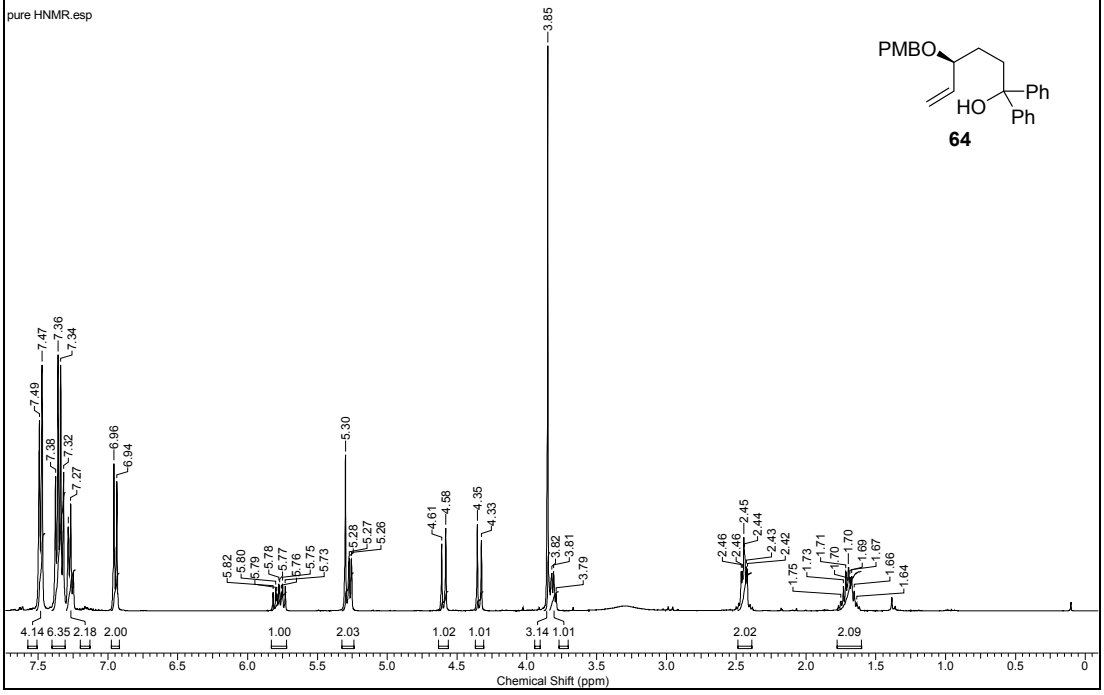
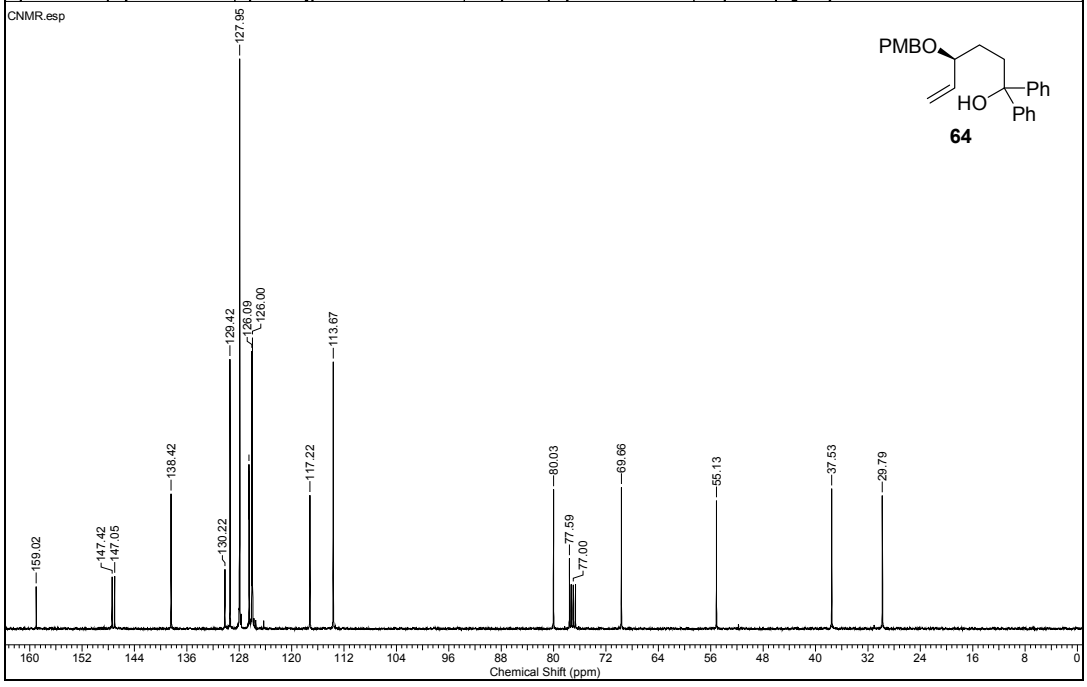
Original Points Count	16384	***Owner***	Administrator	***Points Count***	32768	***Pulse Sequence***	zg30
Receiver Gain	40.30	***SW(cyclical) (Hz)***	8012.82	***Solvent***	CHLOROFORM-d		
Spectrum Offset (Hz)	2398.3071	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	8012.58	***Temperature (degree C)***	20.300

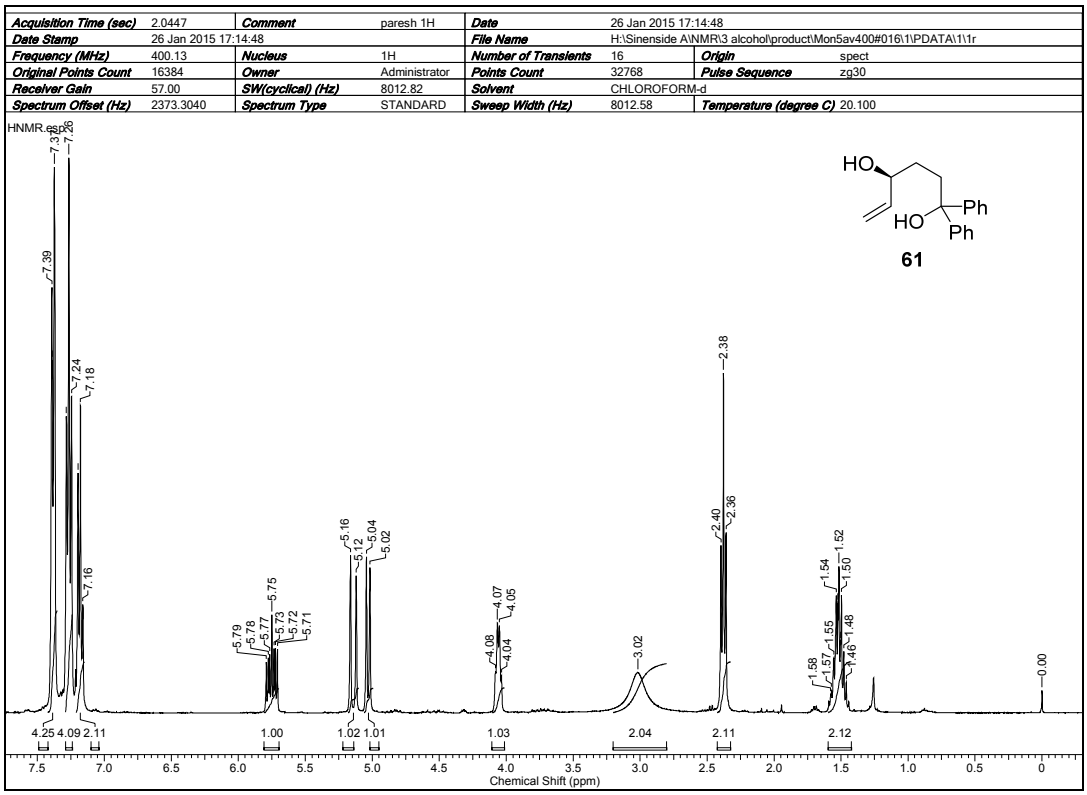


^{1}H NMR Spectrum of 64 in $CDCl_3$

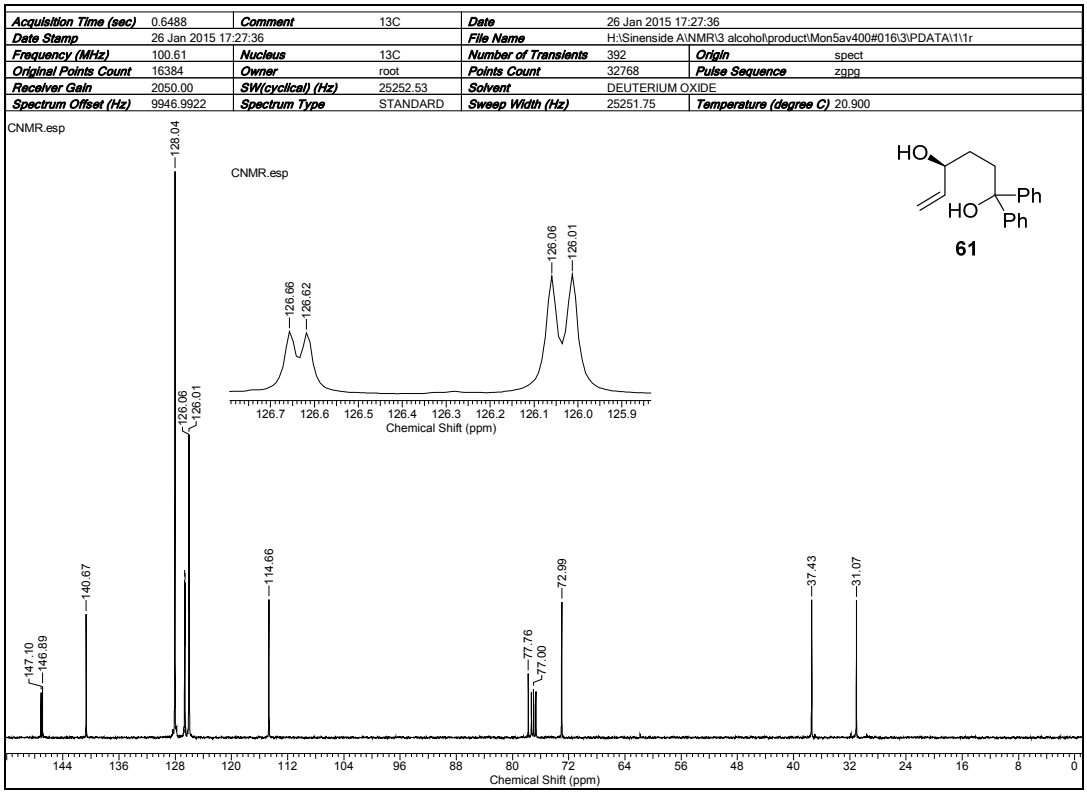
Acquisition Time (sec)	0.6488	***Comment***	13C	***Date***	26 Jan 2015 17:44:40		
Date Stamp	26 Jan 2015 17:44:40			***File Name***	H:\Sinenside A Paper\NMR\phenyl grignard\Mon5av400#017\3\PDATA\1\1r		
Frequency (MHz)	100.61	***Nucleus***	13C	***Number of Transients***	281	***Origin***	spect
Original Points Count	16384	***Owner***	root	***Points Count***	32768	***Pulse Sequence***	zgpg
Receiver Gain	2050.00	***SW(cyclical) (Hz)***	25252.53	***Solvent***	DEUTERIUM OXIDE		
Spectrum Offset (Hz)	9941.5977	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	25251.75	***Temperature (degree C)***	21.100



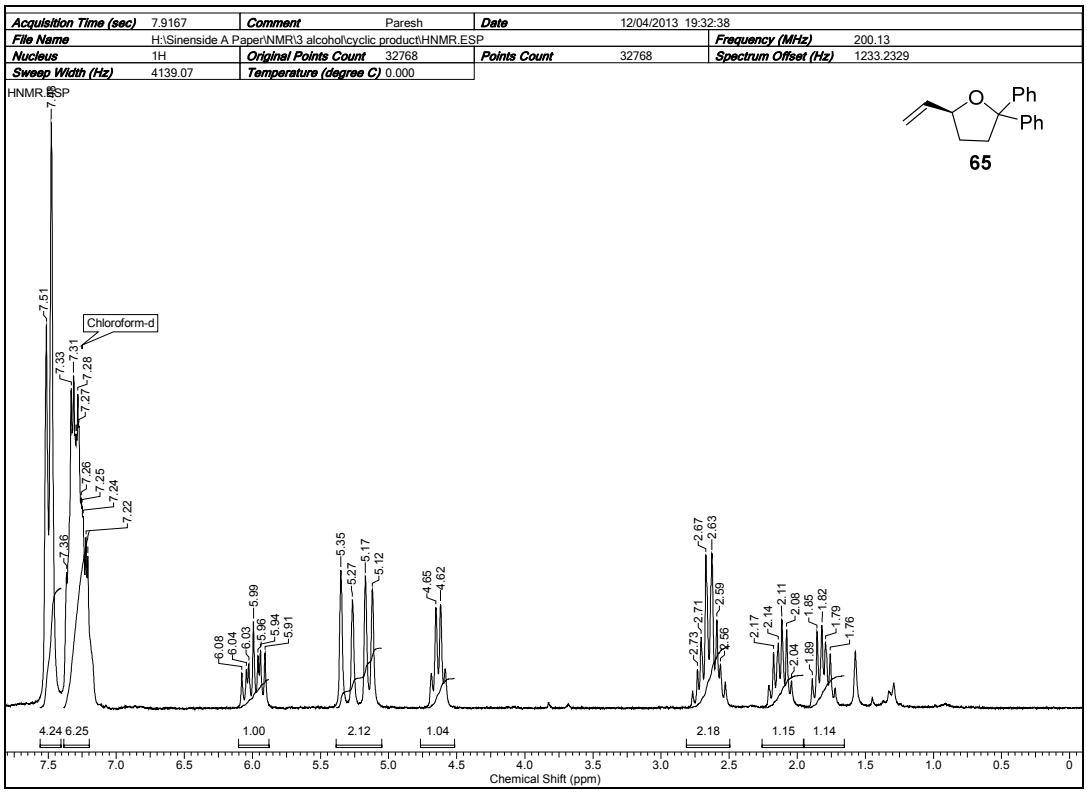
^{13}C NMR Spectrum of 64 in $CDCl_3$



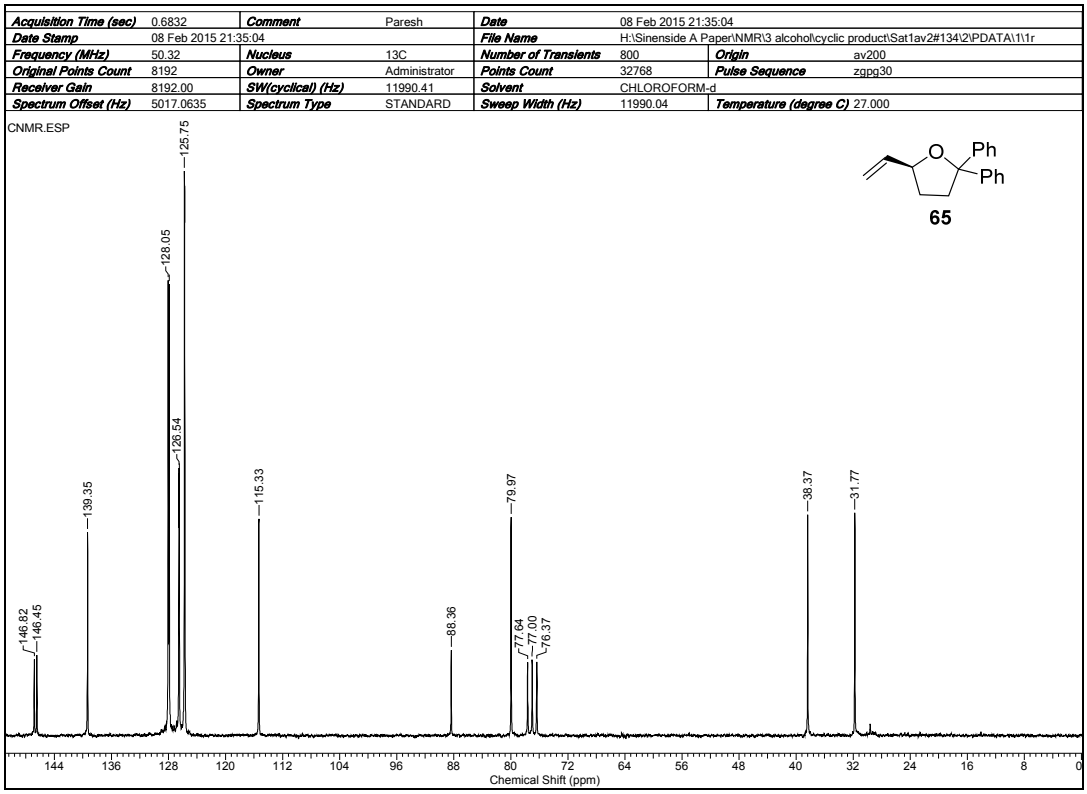
^{1}H NMR Spectrum of 61 in $CDCl_3$



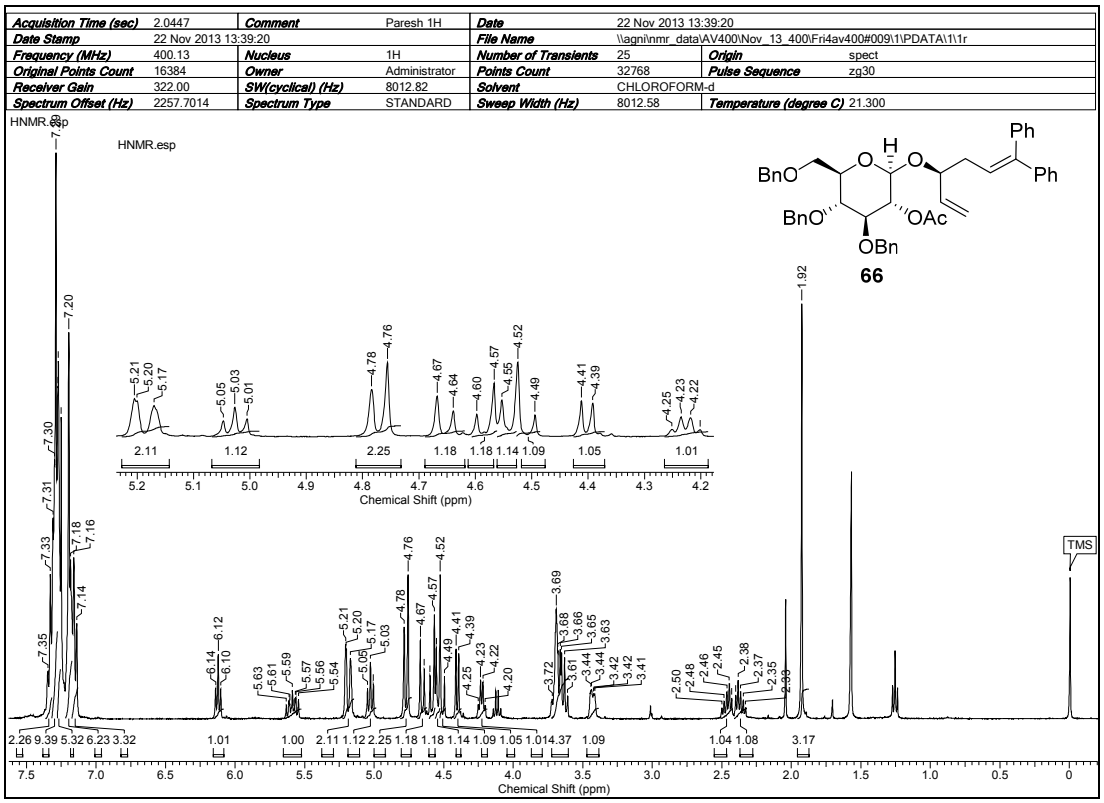
^{13}C NMR Spectrum of 61 in $CDCl_3$



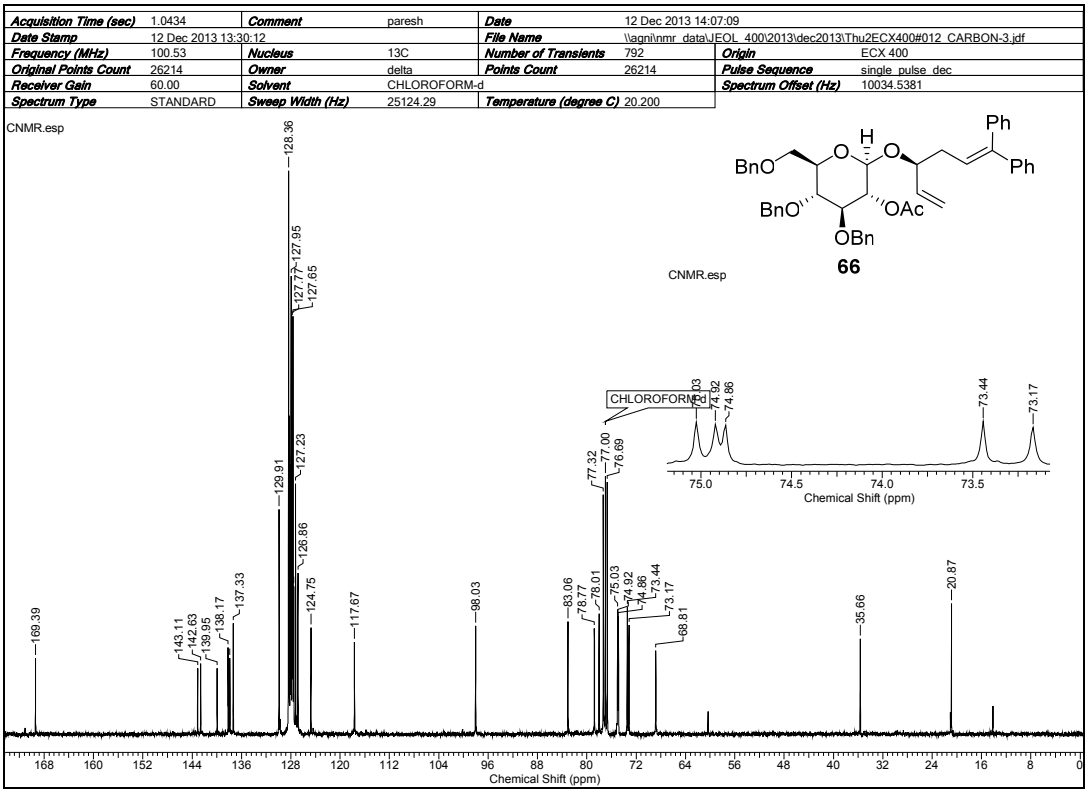
^{1}H NMR Spectrum of 65 in $CDCl_3$



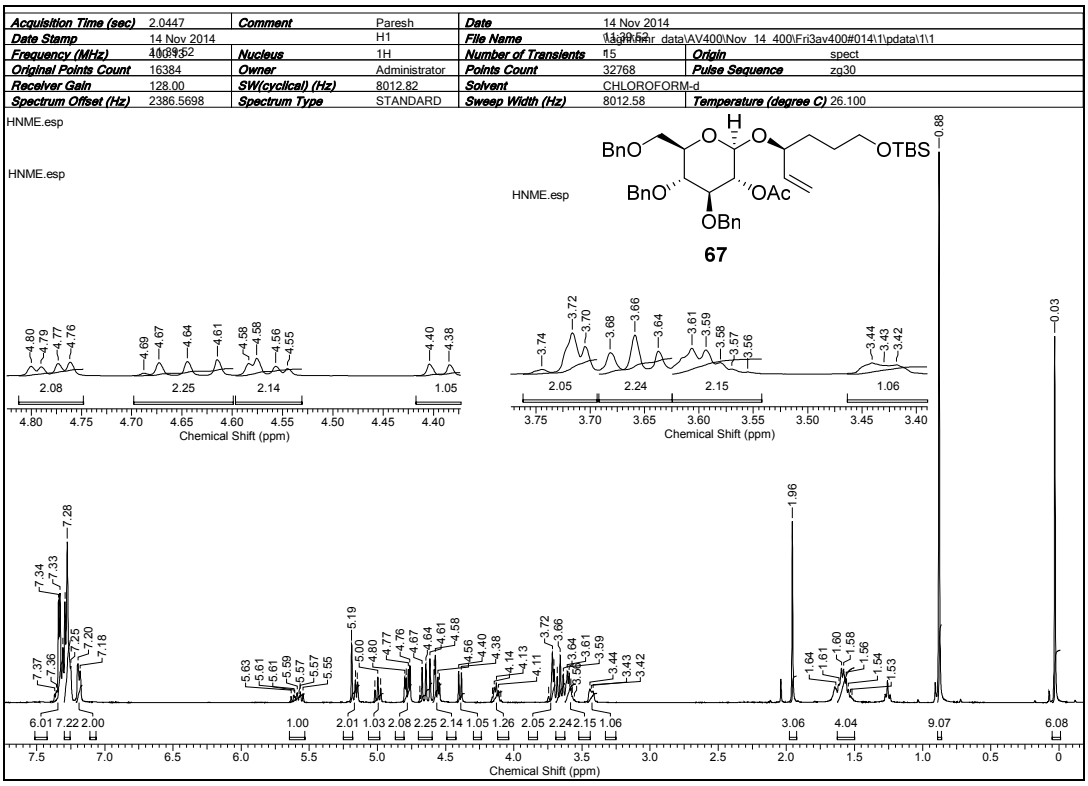
^{13}C NMR Spectrum of 65 in $CDCl_3$



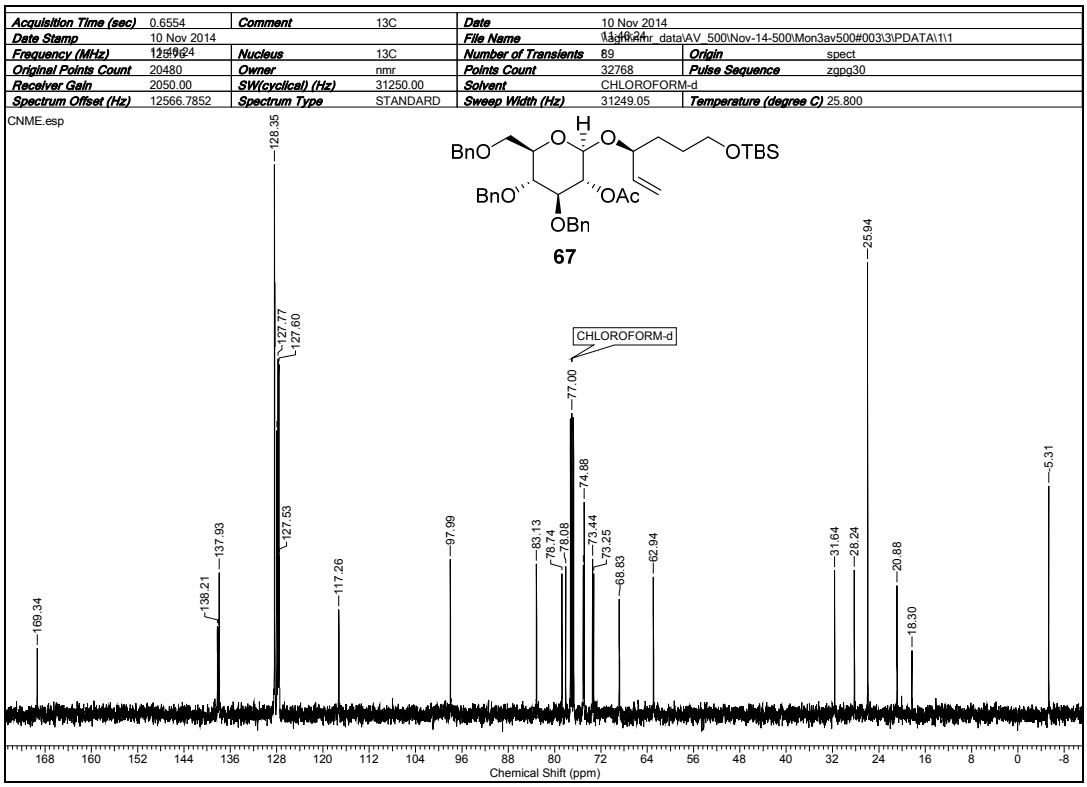
^{1}H NMR Spectrum of 66 in $CDCl_3$



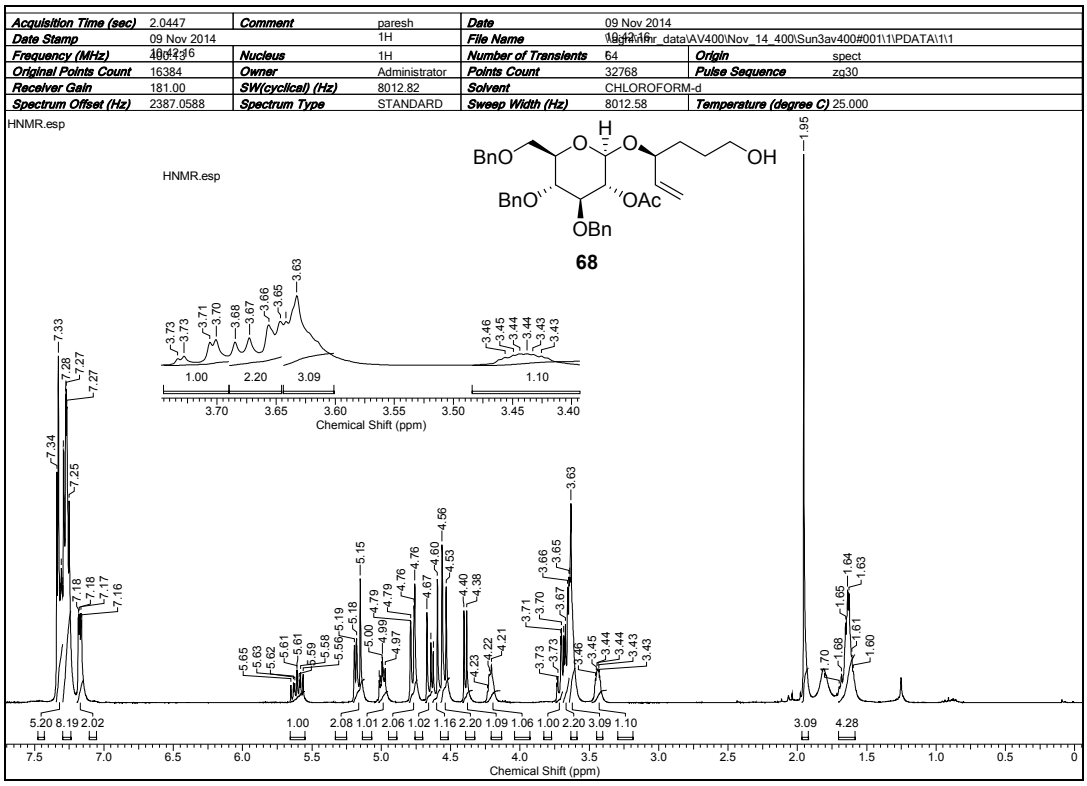
^{13}C NMR Spectrum of 66 in $CDCl_3$



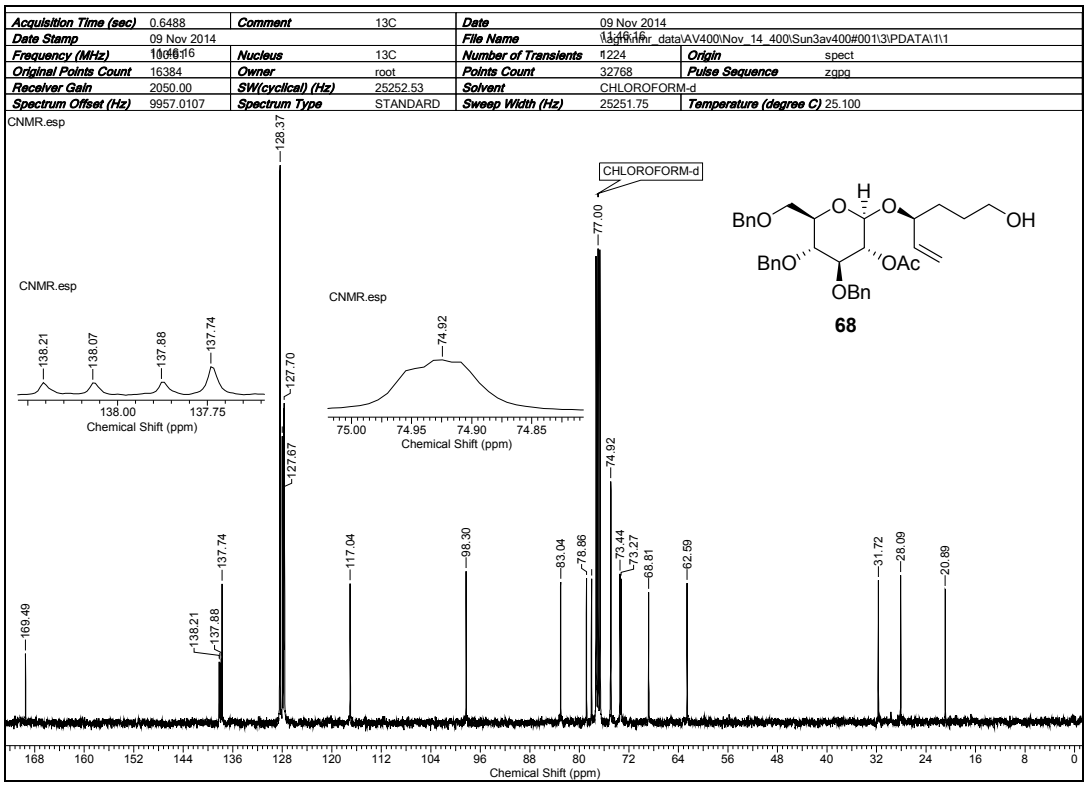
^{1}H NMR Spectrum of 67 in $CDCl_3$



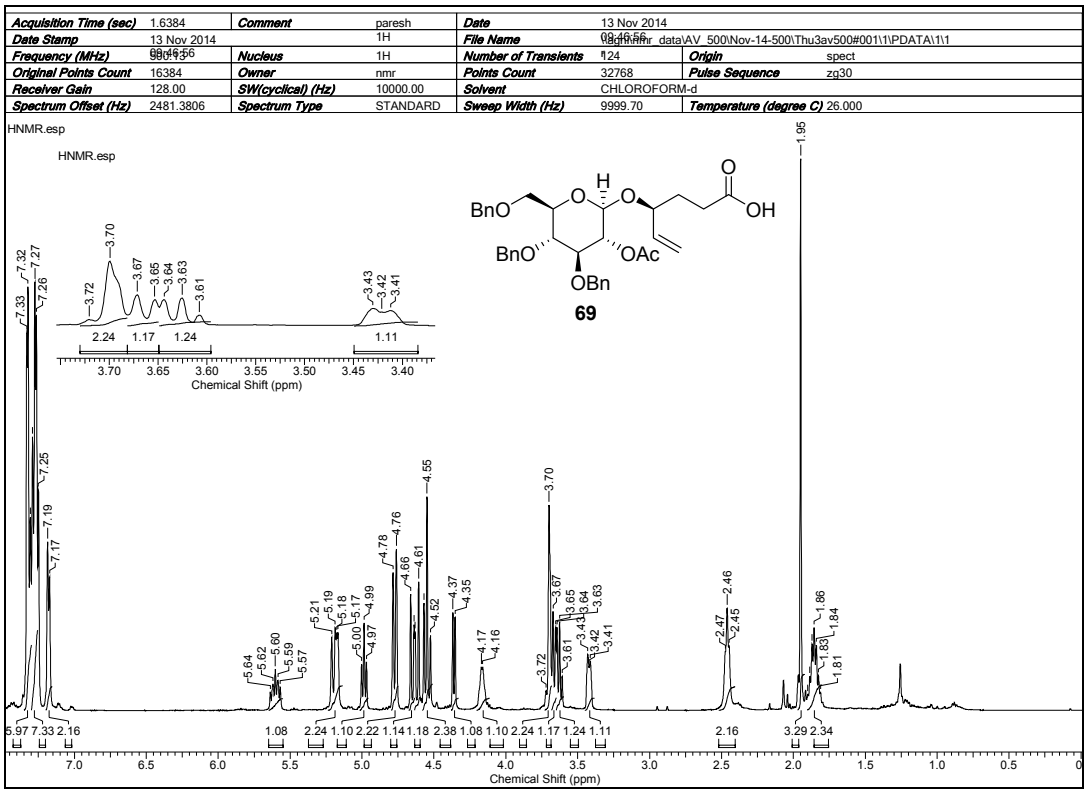
^{13}C NMR Spectrum of 67 in $CDCl_3$



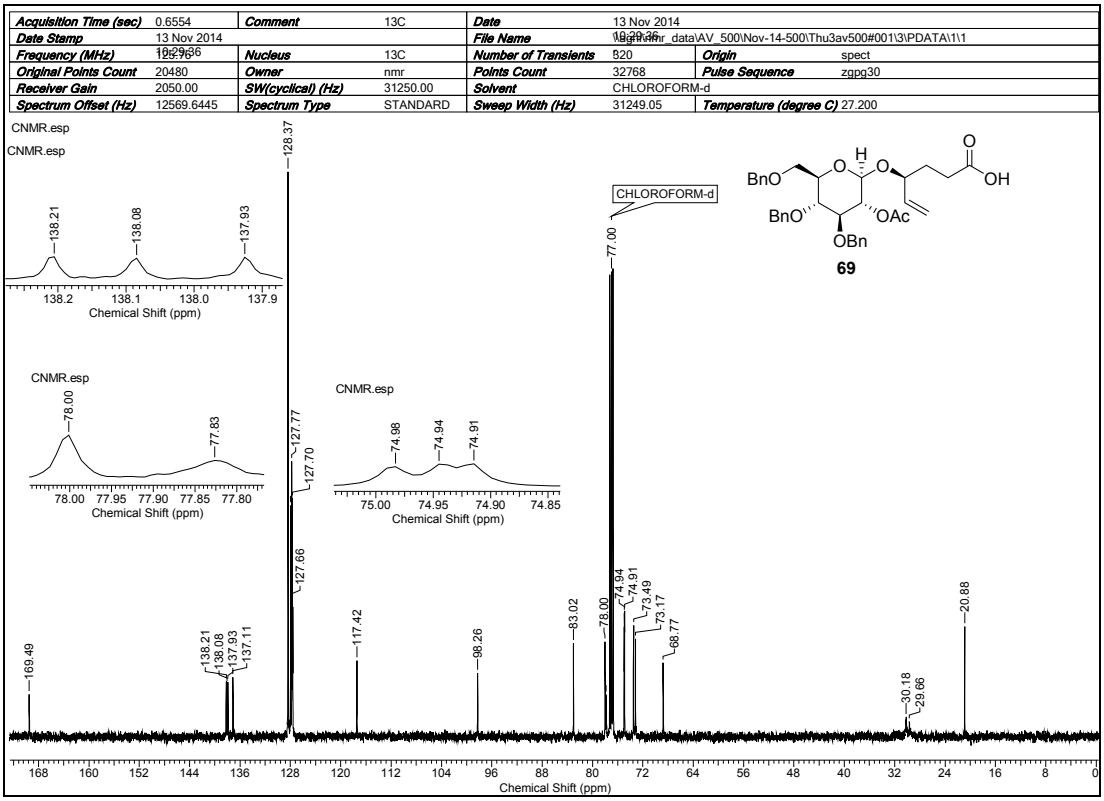
^{1}H NMR Spectrum of 68 in $CDCl_3$



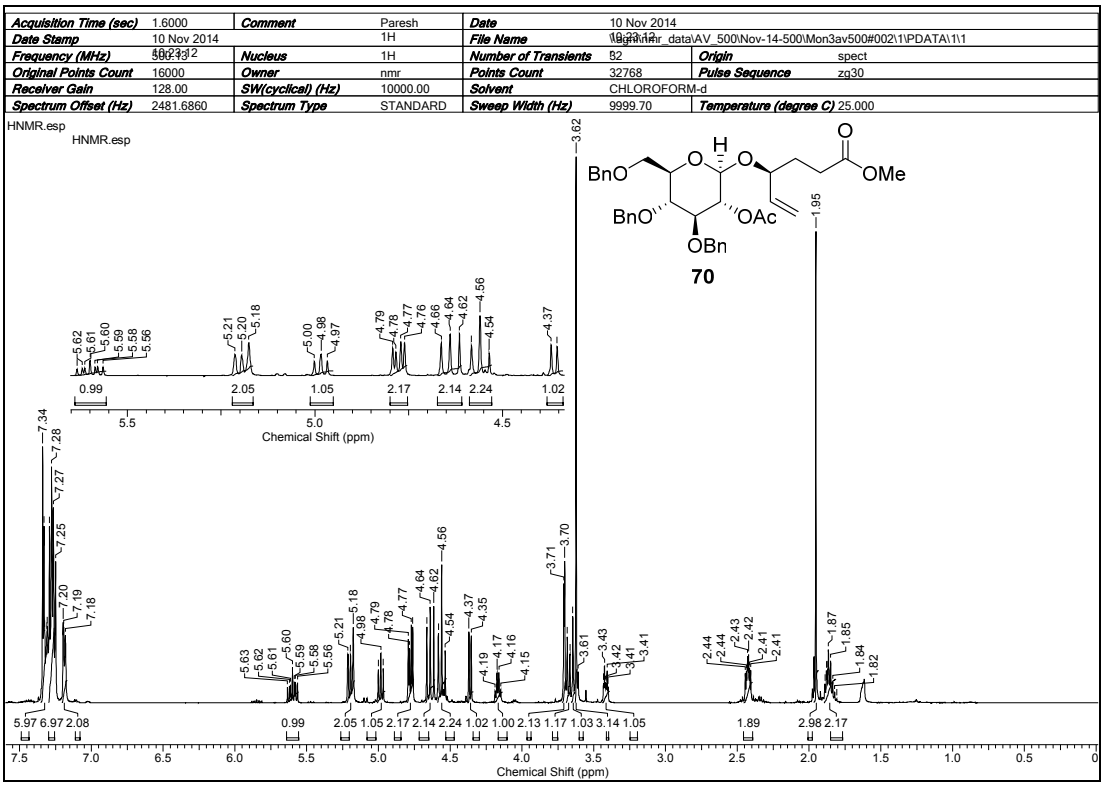
^{13}C NMR Spectrum of 68 in $CDCl_3$



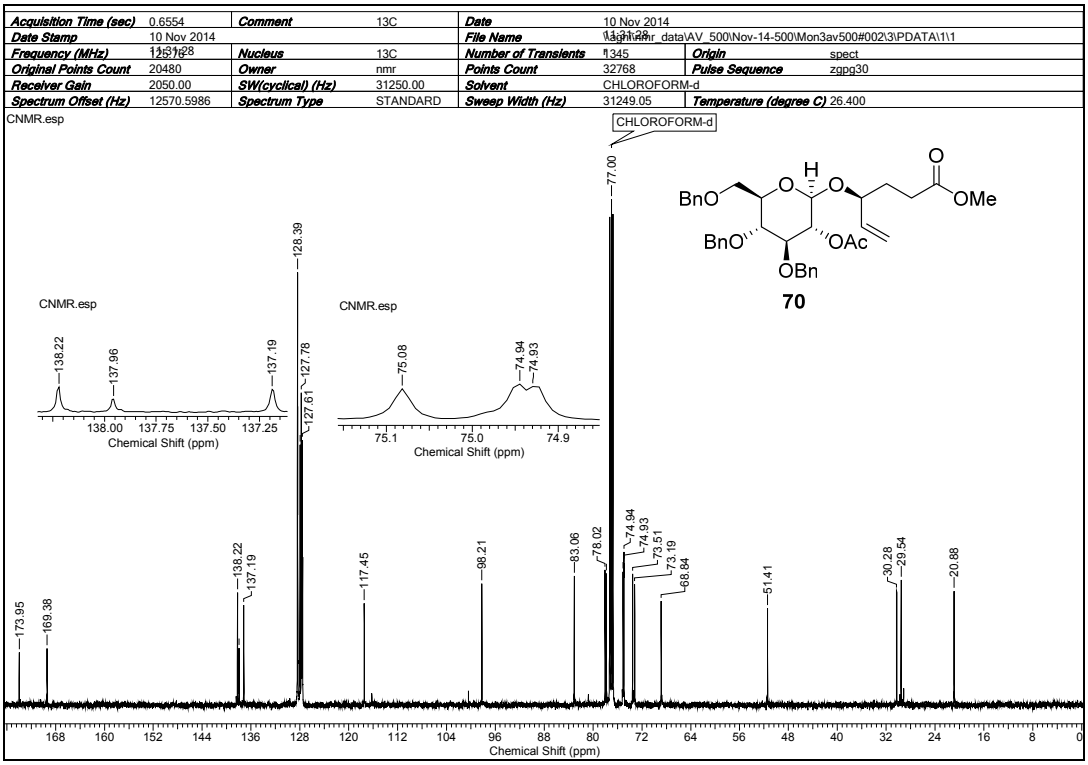
^{1}H NMR Spectrum of 69 in $CDCl_3$



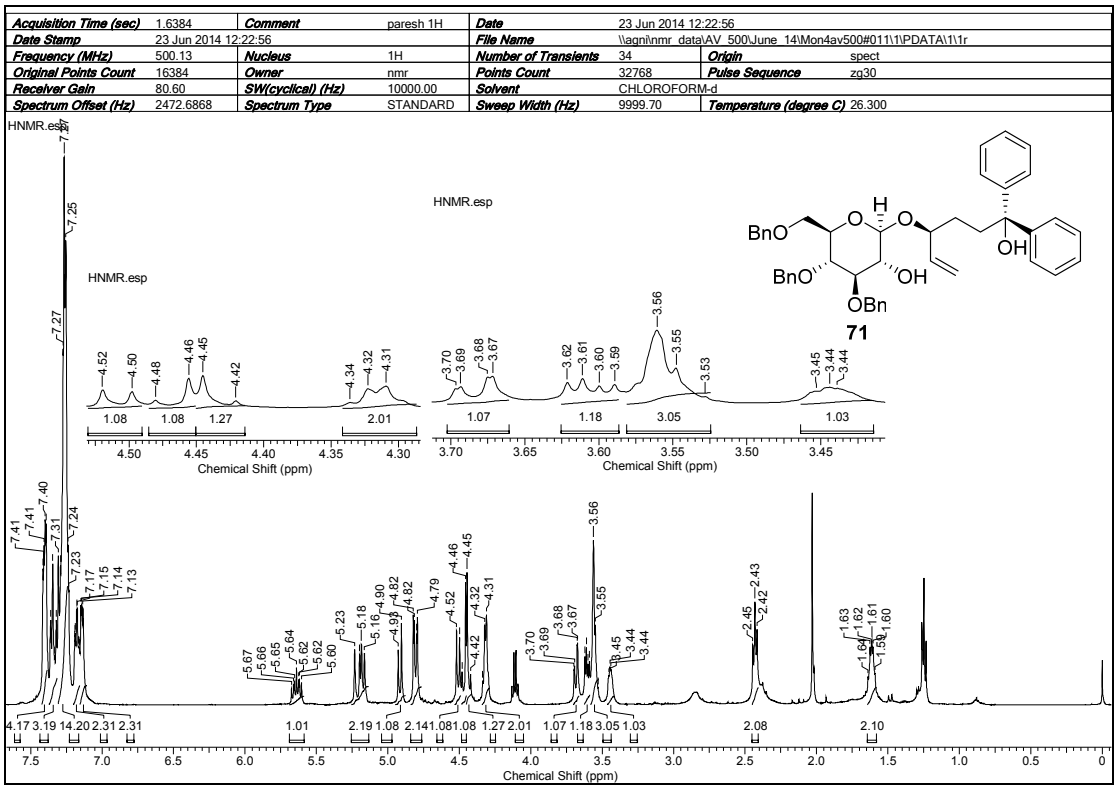
^{13}C NMR Spectrum of 69 in $CDCl_3$



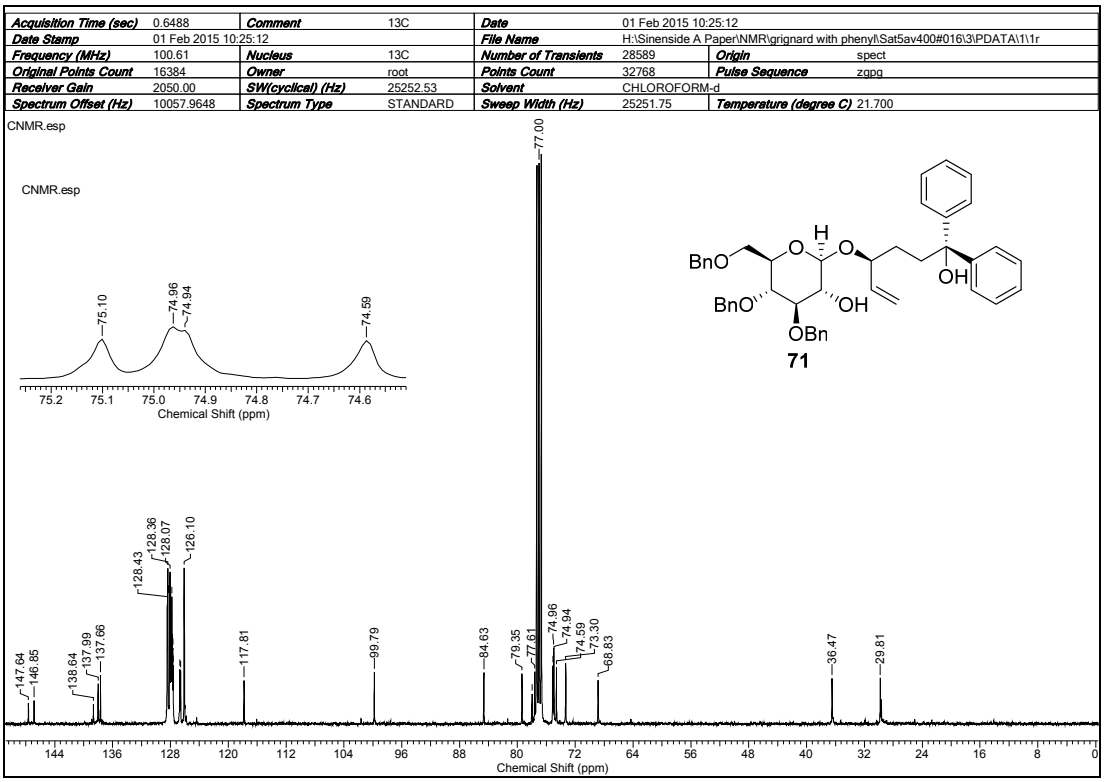
^{1}H NMR Spectrum of 70 in $CDCl_3$



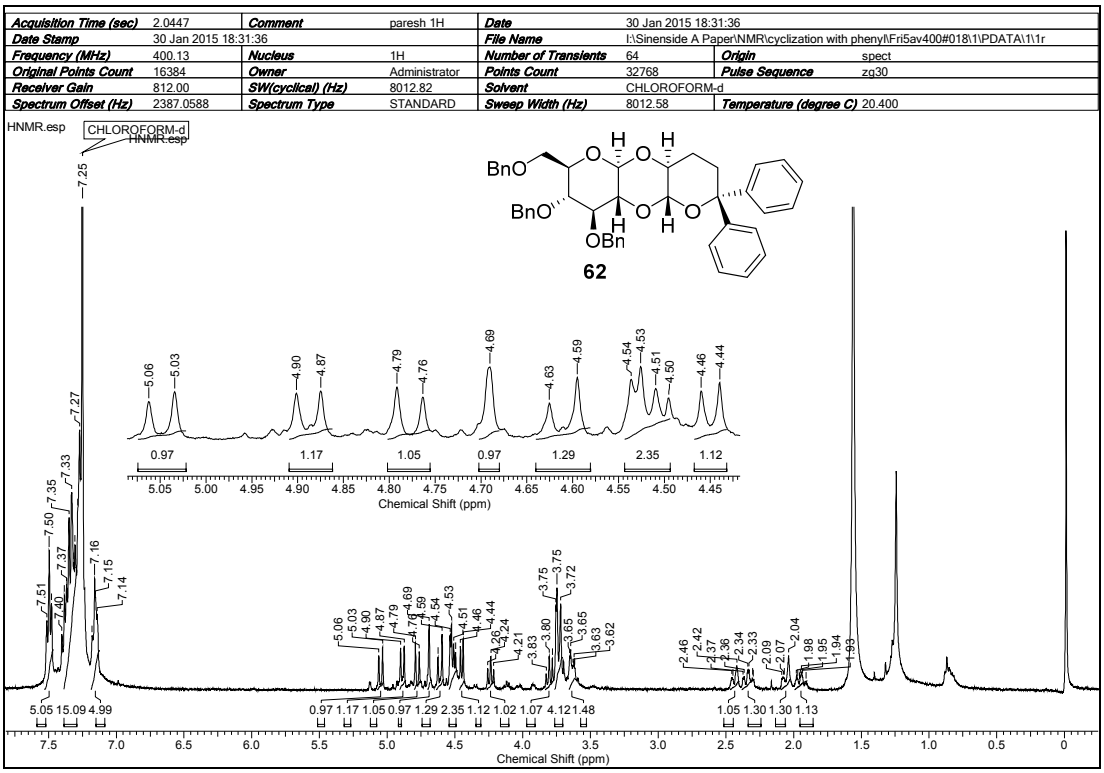
^{13}C NMR Spectrum of 70 in $CDCl_3$



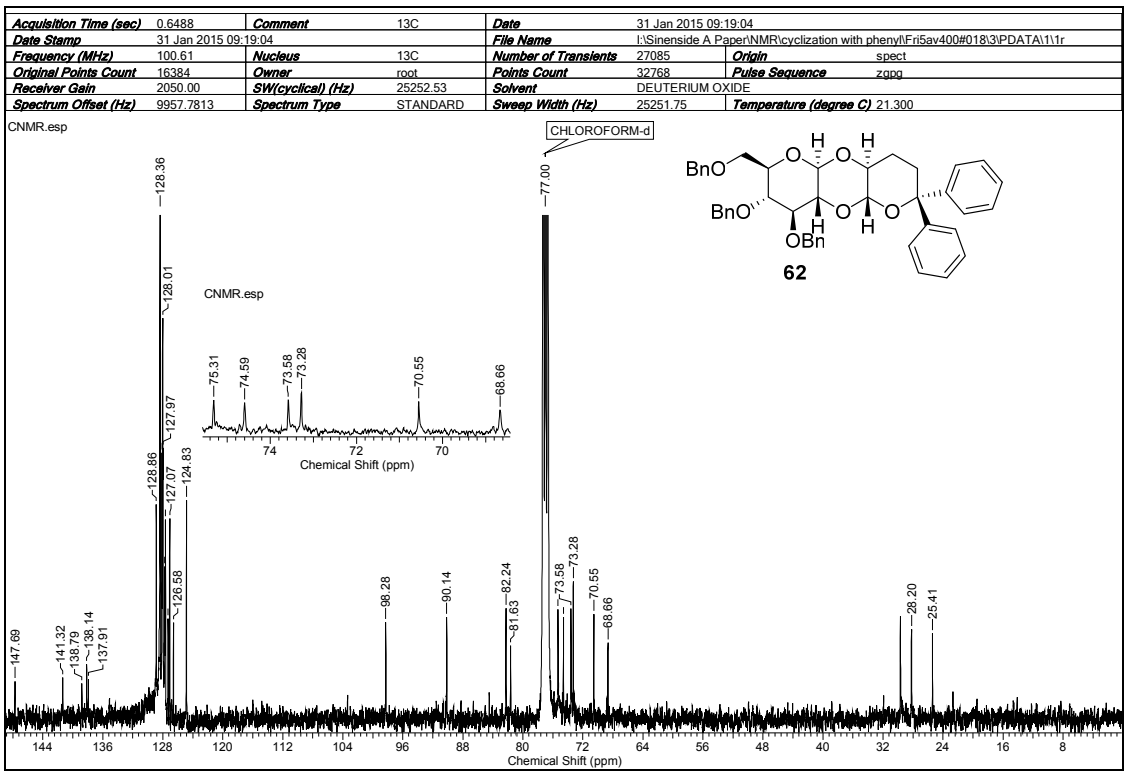
^{1}H NMR Spectrum of 71 in $CDCl_3$



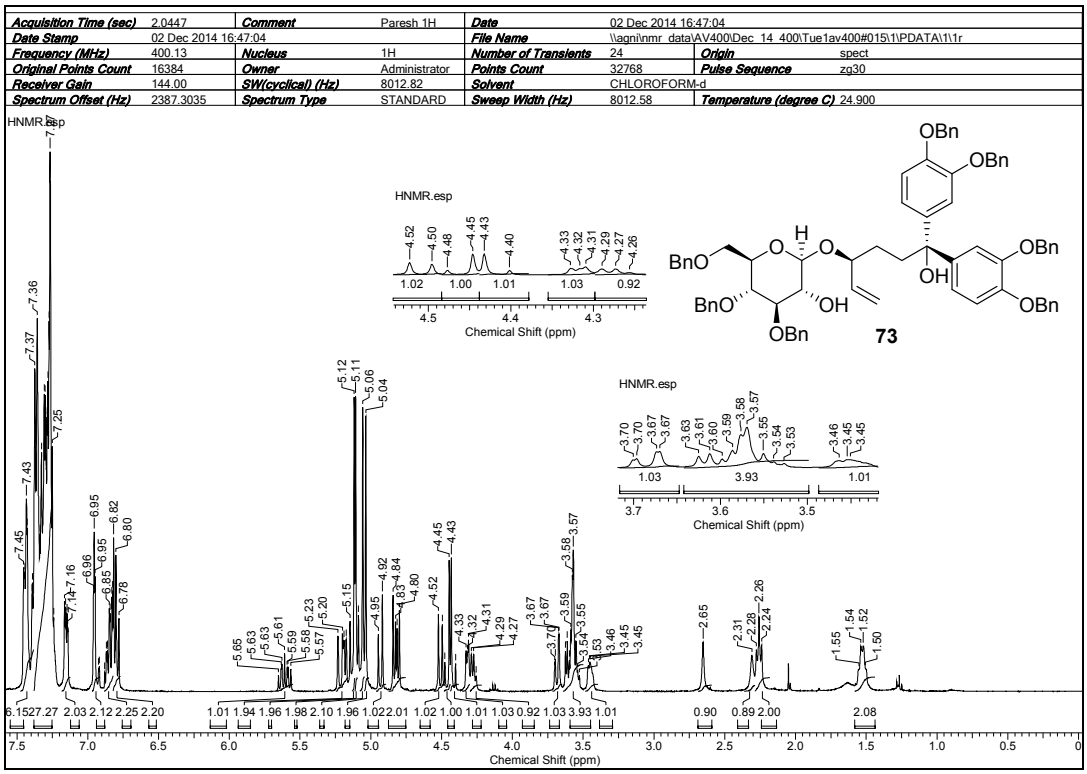
^{13}C NMR Spectrum of 71 in $CDCl_3$



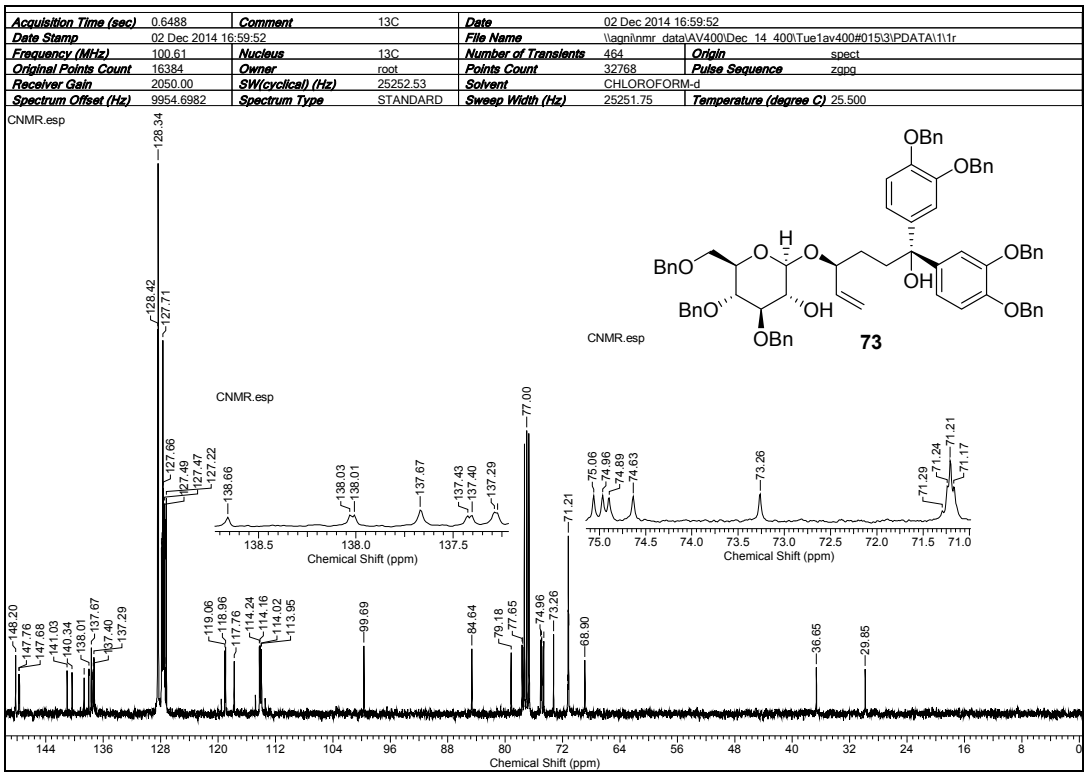
^{1}H NMR Spectrum of 62 in $CDCl_3$



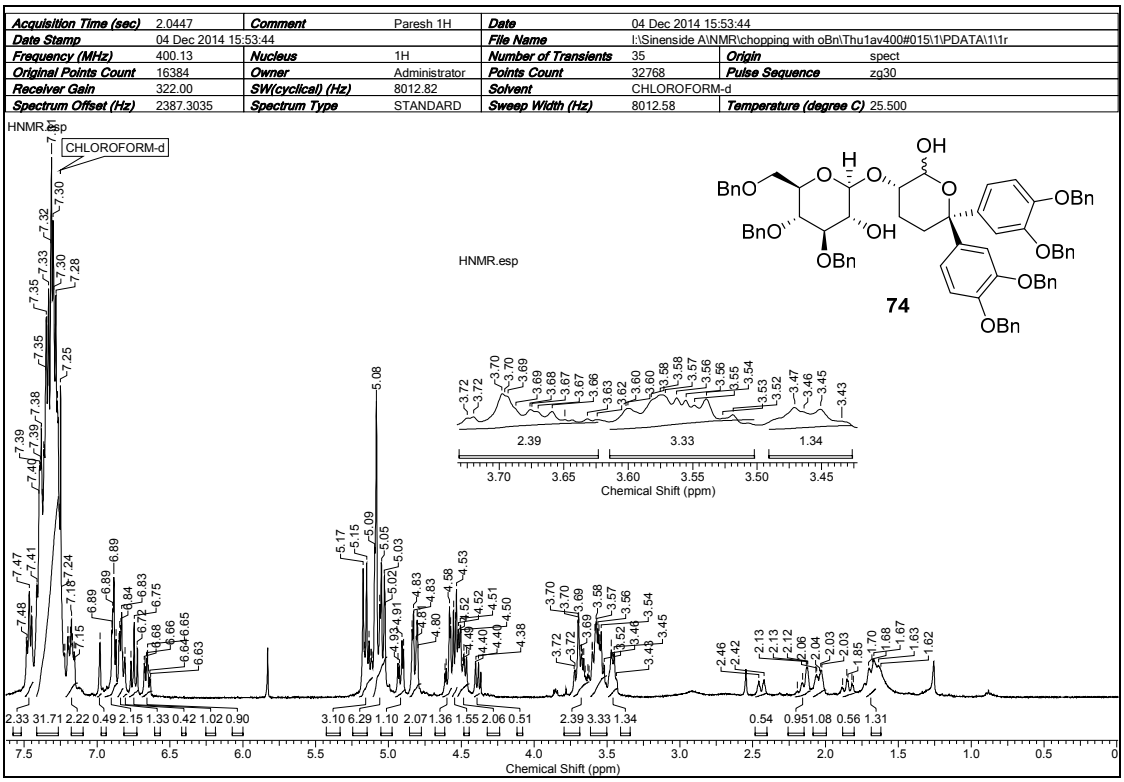
^{13}C NMR Spectrum of 62 in $CDCl_3$



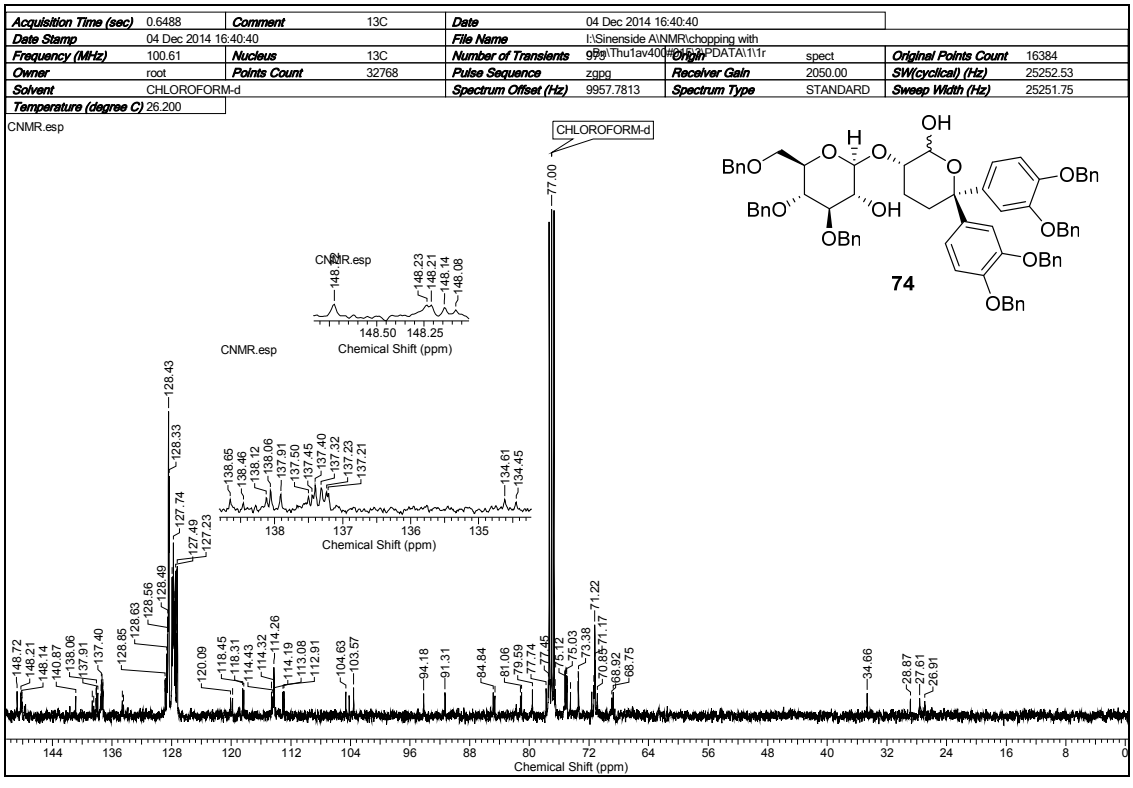
^{1}H NMR Spectrum of 73 in $CDCl_3$



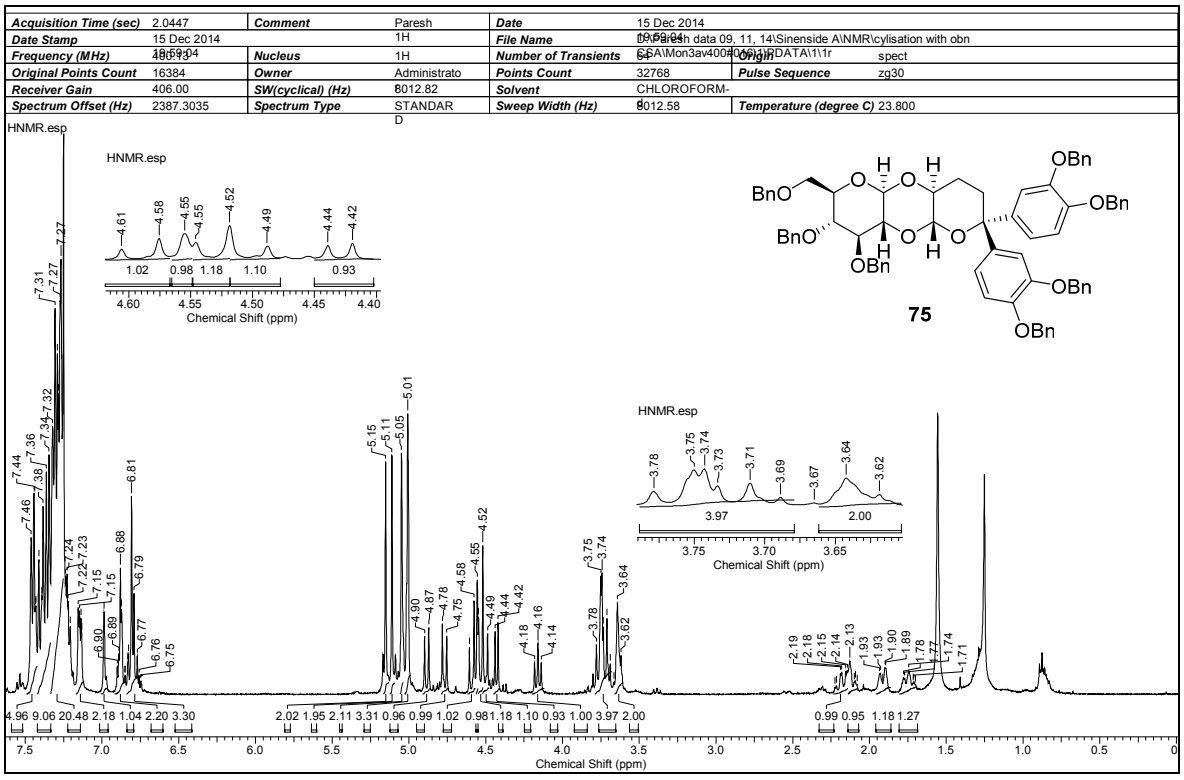
^{13}C NMR Spectrum of 73 in $CDCl_3$



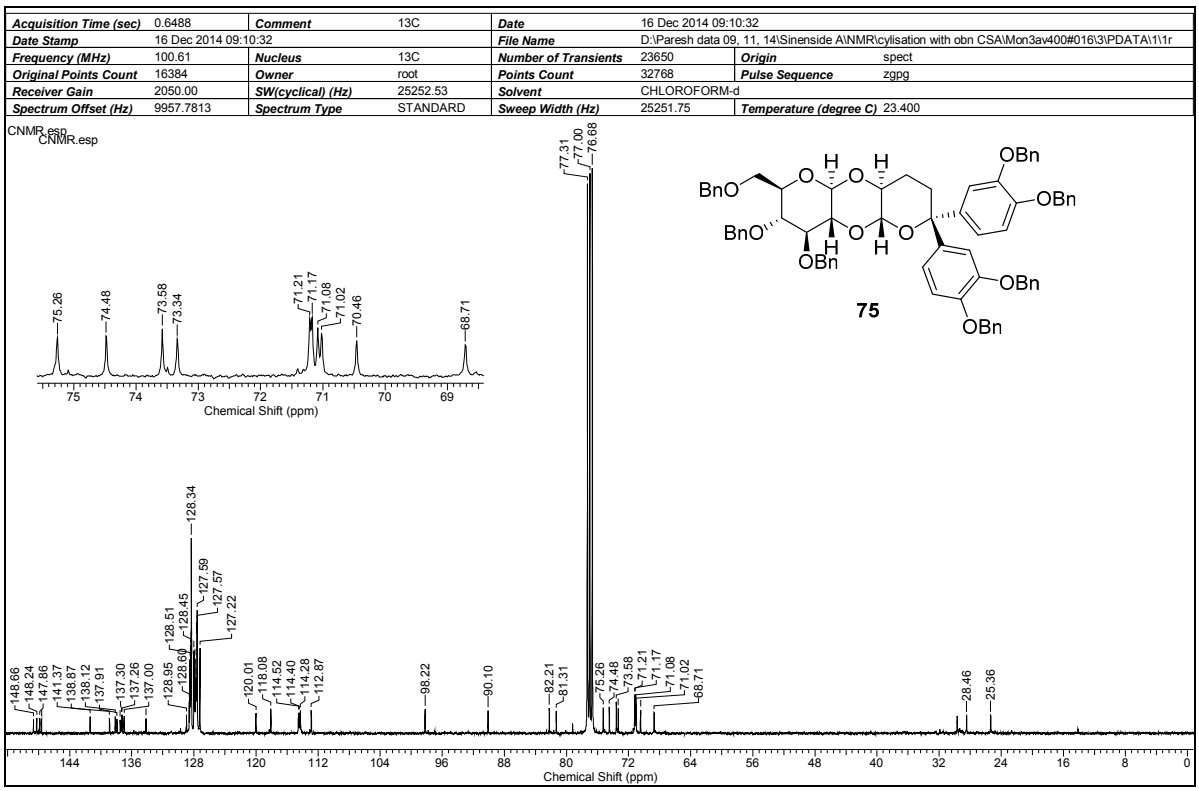
^{1}H NMR Spectrum of 74 in $CDCl_3$



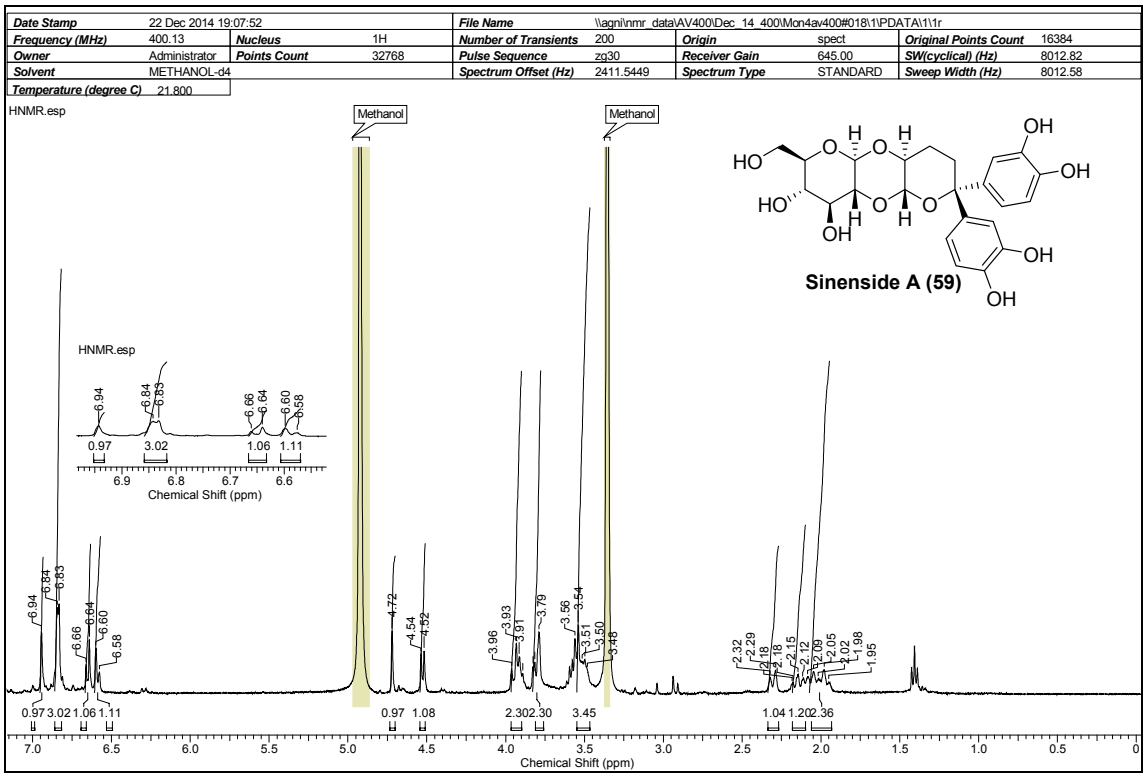
^{13}C NMR Spectrum of 74 in $CDCl_3$



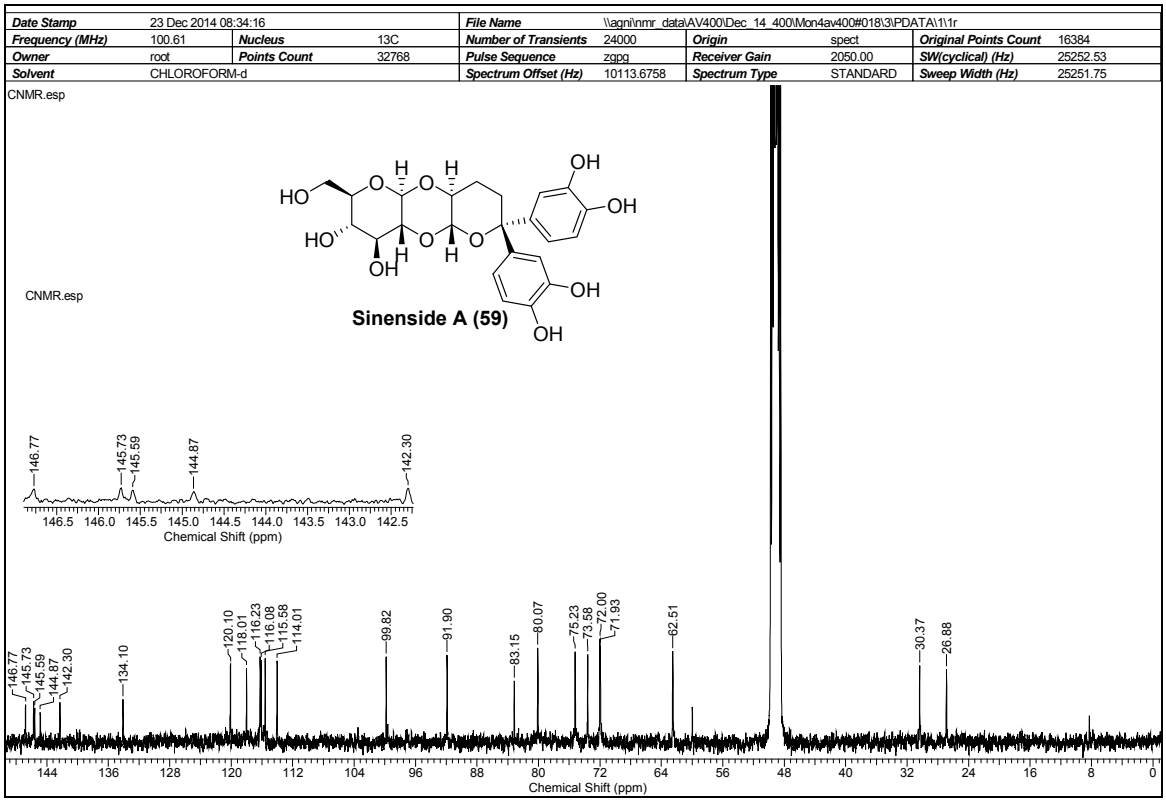
^{1}H NMR Spectrum of 75 in $CDCl_3$



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



^{1}H NMR Spectrum of 59 in CD_3OD



^{13}C NMR Spectrum of 59 in CD_3OD

REFERENCES

1. (a) Herbert, R. B., The Biosynthesis of Secondary Metabolites, 2nd ed., Chapman and Hall, New York, **1989** (b) Challis, G. L.; Hopwood, D. A. *Proc. Natl Acad Sci* **2003**, *100*, 14555-14561. (c) Miller, K. A.; Tsukamoto, S.; Williams, R. M. *Nat. Chem.* **2009**, *1*, 63-68. (d) Finefield, J. M.; Sherman, D. H.; Kreitman, M.; Williams, R. M. *Angew. Chem. Int. Ed.* **2012**, *51*, 4802-4836.
2. (a) Clardy, J.; Walsh, C. *Nature* **2004**, *432*, 829-837. (b) Gunatilaka, A. A. L. *J. Nat. Prod.* **2006**, *69*, 509-526.
3. (a) Whiting, D. A. *Nat. Prod. Rep.* **1987**, *4*, 499-525. (b) Vogt, T. *Mol. Plant* **2010**, *3*, 2-20.
4. Haworth, R. D., *J. Chem.* Soc. **1942**, 448; *Nuture (London),* **1941**, *147*, 225.
5. Kai, Y. *Mokuzai Gakkaishi* **1965**, *11*, 23
6. Hatam, N. A. R.; Whiting, D. A. *Tetrahedron Lett.* **1967**, *8*, 781-785.
7. Suzuki, S.; Umezawa, T. *J. Wood Sci.* **2007**, *53*, 273-284.
8. Castro, M. A.; Gordaliza, M.; Miguel Del Corral, J. M.; Feliciano, A. S. *Phytochemistry* **1996**, *41*, 995-1011.
9. (a) Riffer, R.; Anderson, A. B. *Phytochemistry* **1967**, *6*, 1557-1562. (b) Hatam, N. A. R.; Whiting, D. A. *J. Chem. Soc. (C)* **1969**, 1921-1932.
10. Henley-Smith, P.; Whiting, D. A. *Phytochemistry* **1976**, *15*, 1285-1287.
11. Enzell, C. R.; Thomas, B. R. *Tetrahedron Lett.* **1966**, *7*, 2395-2402.
12. (a) Enoki, A., Takahama, S., Kitao, K., *Mokuzai Gakkaishi,* **1977**, *23*, 579. (b) Enoki, A., Takahama, S., Kitao, K., *Mokuzai Gakkaishi,* **1977**, *23*, 587.
13. Erdtman, H.; Harmatha, J. *Phytochemistry* **1979**, *18*, 1495-1500.
14. (a) Chifundera, K.; Palazzino, G.; Messana, I.; Ping, L.; Galeffi, C.; Cannarsa, G. *Phytochemistry* **1994**, *35*, 1343-1348. (b) Wu, Q.; Fu, D. X.; Hou, A. J.; Lei, G. Q.; Llu, Z. J.; Chen, J. K.; Zhou, T. S. *Chem. Pharm. Bull* **2005**, *53*, 1065-1067. (c) Wang, K.-j.; Li, N.; Wang, H. *Molecules* **2008**, *13*, 1696-1701. (d) Li, N.; Zhu, C.-C.; Xiao, H.-M.; Wang, K.-J. *Fitoterapia* **2010**, *81*, 528-531. (e) Nie, Y.; Dong, X.; He, Y.; Yuan, T.; Han, T.; Rahman, K.; Qin, L.; Zhang, Q. *J Ethnopharmaco.* **2013**, *147*, 547-563.
15. Shoei-Sheng, L.; Wen-Liang, C.; Chung-Hsiung, C. *Tetrahedron Lett.* **1996**, *37*, 4405-4408.

16. (a) Li, N.; Chen, J. J.; Zhao, Y. X.; Zhou, J. *J. Asian Nat. Prod. Res.* **2005**, *7*, 189-195. (b) Di, L.; Wang, K.-J.; Zhu, C.-C.; Li, N. *Bull. Korean Chem. Soc.* **2010**, *31*, 2999-3002. (c) Wang, K.-J.; Zhu, C.-C.; Di, L.; Li, N.; Zhao, Y.-X. *Fitoterapia* **2010**, *81*, 869-872.
17. Li, N.; Chen, J.-J.; Zhou, J. *Z. Naturforsch.* **2006**, *61*, 611-614.
18. Li, N.; Zhu, C.-C.; Wang, K.-J.; Hu, J.-M. *Z. Naturforsch.* **2010**, *65*, 79-82.
19. Li, N.; Wang, T.-M.; Wang, K.-J.; Zhao, Y.-X. *Helvetica Chimica Acta* **2010**, *93*, 724-728.
20. (a) Kinjo, J.-e.; Furusawa, J.-i.; Nohara, T. *Tetrahedron Lett.* **1985**, *26*, 6101-6102. (b) Shirataki, Y.; Tagaya, Y.; Yokoe, I.; Komatsu, M. *Chem. Pharm. Bull.* **1987**, *35*, 1637-1640. (c) Nohara, T.; Kinjo, J.; Furusawa, J.; Sakai, Y.; Inoue, M.; Shirataki, Y.; Ishibashi, Y.; Yokoe, I.; Komatsu, M. *Phytochemistry* **1993**, *33*, 1207-1210.
21. Kogiso, S.; Hosozawa, S.; Wada, K.; Munakata, K. *Phytochemistry* **1974**, *13*, 2332-2334.
22. Pinarosa, A. *Stud. Nat. Prod. Chem.* **2005**, *30*, 603-634. (b) Wang, W.; Zeng, Y. H.; Osman, K.; Shinde, K.; Rahman, M.; Gibbons, S.; Mu, Q. *J. Nat. Prod.* **2010**, *73*, 1815-1820. (c) Kwon, J.; Kondaji, G.; Song, S.; Kim, C.; Lee, K.; Kim, W.-K.; Choi, Y. *Bull. Korean Chem. Soc.* **2013**, *34*, 1247-1249.
23. Nicoletti, M.; Pieretti, S.; Capasso, A.; Galeffi, C. *Phytotherapy Res.* **1996**, *10*, 398-401.
24. Li, N.; Wang, K. J.; Chen, J. J.; Zhou, J. *Tetrahedron Lett.* **2005**, *46*, 6445-6447.
25. (a) Galeffi, C.; Multari, G.; Msonthi, J. D.; Nicoletti, M.; Marinibettolo, G. B. *Tetrahedron* **1987**, *43*, 3519-3522. (b) Chang, W. L.; Su, M. J.; Lee, S. S. *J. Nat. Prod.* **1997**, *60*, 76-80.
26. (a) Muraoka, O.; Zheng, B. Z.; Fujiwara, N.; Tanabe, G. *J. Chem. Suc., Perkin Trans. 1* **1996**, 405-411 (b) Skytte, D. M.; Rasmussen, H. B.; Christensen, S. B. *Nat. Prod. Res.* **2008**, *22*, 116-123. (c) Lim, H.; Nam, J. W.; Seo, E.-K.; Kim, Y. S.; Kim, H. P. *Arch. Pharm. Res.* **2009**, *32*, 1509-1514 (d) Yamamura, M.; Suzuki, S.; Hattori, T.; Umezawa, T. *Org. Biom. Chem.* **2010**, *8*, 1106-1110. (e) Fang, Y.; Park, H. *Syn. Comm.*, **2014** *45*, 137-142.
27. (a) Zhang, Y. M.; Tan, N. H.; He, M.; Lu, Y.; Shang, S. Q.; Zheng, Q. T. *Tetrahedron Lett.* **2004**, *45*, 4319-4321. (b) Ito, Y.; Takahashi, K.; Nagase, H.; Honda, T. *Org. Lett.* **2011**, *13*, 4640-4643.
28. Li, N.; Li, S.-P.; Wang, K.-J.; Yan, G.-Q.; Zhu, Y.-Y. *Carbohydr. Res.* **2012**, *351*, 64–67.
29. (a) Lee, S. S.; Chang, W. L.; Chen, C. H. *Tetrahedron Lett.* **1996**, *37*, 4405–4408. (b) Di, L.; Wang, K.-J.; Zhu, C.-C.; Li, N. *Bull. Korean Chem. Soc.* **2010**, *31*, 2999–3002.

30. (a) Gattuso, G.; Nepogodiev, S. A.; Stoddart, J. F. *Chem. Rev.* **1998**, *98*, 1919–1958. (b) Jung, K. H.; Müller, M.; Schmidt, R. R. *Chem. Rev.* **2000**, *100*, 4423–4442.
31. (a) Fujiwara, T.; Arai, K. *Carbohydr. Res.* **1979**, *69*, 97–105. (b) Fujiwara, T.; Arai, K. *Carbohydr. Res.* **1979**, *69*, 107–115.
32. (a) Capek, P.; Uhrin, D.; Rosik, J.; Kardosova, A.; Toman, R.; Mihalov, V. *Carbohydr. Res.* **1988**, *182*, 160–165. (b) Komalavilas, P.; Mort, A. J. *Carbohydr. Res.* **1989**, *189*, 261–272.
33. Kennedy, I. A.; Hemscheidt, T.; Britten, J. F.; Spenser, I. D. *Can. J. Chem.* **1995**, *73*, 1329–1337.
34. Fernandez, J. M. G.; Defaye, J. *Tetrahedron Lett.* **1992**, *33*, 7861–7864.
35. Defaye, J.; Gadelle, A.; Pedersen, C. *Carbohydr. Res.* **1985**, *136*, 53–65.
36. (a) Wolfrom, M. L.; Hilton, H. W. *J. Am. Chem. Soc.* **1952**, *74*, 5334-5336. (b) Defaye, J.; Gadelle, A.; Pedersen, C. *Carbohydr. Res.* **1986**, *152*, 89-98. (c) Bock, K.; Pedersen, C.; Defaye, J.; Gadelle, A. *Carbohydr. Res.* **1991**, *216*, 141–148.
37. (a) Thiem, J.; Klaffke, W. *J. Chem. Soc.Chem. Commun.* **1990**, 76-78. (b) Goddat, J.; Grey, A. A.; Hricovini, M.; Grushcow, J.; Carver, J. P.; Shah, R. N. *Carbohydr. Res.* **1994**, *252*, 159-170. (c) Dondoni, A.; Marra, A.; Scherrmann, M. C.; Bertolasi, V. *Chem. Eur. J.* **2001**, *7*, 1371–1382.
38. Gagnaire, D.; Tran, V.; Vignon, M. *J. Chem. Soc. Chem. Commun.* **1976**, 6–7.
39. (a) Dubois, E. P.; Neszmelyi, A.; Lotter, H.; Pozsgay, V. *Tetrahedron Lett.* **1996**, *37*, 3627–3630. (b) Pozsgay, V.; Dubois, E. P.; Lotter, H.; Neszmelyi, A. *Carbohydr. Res.* **1997**, *303*, 165–173.
40. Ludewig, M.; Lazarevic, D.; Kopf, J.; Thiem, J. *J. Chem. Soc.,Perkin Trans. 1* **1998**, 1751–1752.
41. For selected papers on the glycosidations with ortho-ester see: (a) Boren, H. B.; Ekborg, G.; Eklind, K.; Garegg, P. J.; Pilotti, A.; Swahn, C. G. *Acta Chem. Scand* **1973**, *27*, 2639–2644. (b) Ogawa, T.; Nozaki, M.; Matsui, M. *Tetrahedron* **1980**, *36*, 2641–2648. (c) Ogawa, T.; Nakabayashi, S.; Shibata, S. *Agric. Biol. Chem.* **1983**, *47*, 1353–1356. (d) Skrydstrup, T.; Mazeas, D.; Elmouchir, M.; Doisneau, G.; Riche, C.; Chiaroni, A.; Beau, J. M. *Chem. Eur. J.* **1997**, *3*, 1342–1356. (e) Draghetti, V.; Poletti, L.; Prosperi, D.; Lay, L. *J. Carbohydr. Chem.* **2001**, *20*, 813–819 (f) Torres-Sanchez, M. I.; Zaccaria, C.; Buzzi, B.;

Miglio, G.; Lombardi, G.; Polito, L.; Russo, G.; Lay, L. *Chem. Eur. J.* **2007**, *13*, 6623–6635. (g) Danieli, E.; Proietti, D.; Brogioni, G.; Romano, M. R.; Cappelletti, E.; Tontini, M.; Berti, F.; Lay, L.; Costantino, P.; Adamo, R. *Bioorg. Med. Chem.* **2012**, *20*, 6403–6415.

42. (a) Ogawa, T.; Nozaki, M.; Matsui, M. *Tetrahedron* **1980**, *36*, 2641-2648. (b) Abe, H.; Shuto, S.; Matsuda, A. *J. Org. Chem.* **2000**, *65*, 4315-4325. (c) Vauzeilles, B.; Sinay, P. *Tetrahedron Lett.* **2001**, *42*, 7269-7272. (d) Torres-Sanchez, M. I.; Zaccaria, C.; Buzzi, B.; Miglio, G.; Lombardi, G.; Polito, L.; Russo, G.; Lay, L. *Chem. Eur. J.* **2007**, *13*, 6623-6635. (e) Tiwari, V. K.; Kumar, A.; Schmidt, R. R. *Eur. J. Org. Chem.* **2012**, 2945-2956.
43. (a) Pandey, S. K.; Ramana, C. V. *J. Org. Chem.* **2011**, *76*, 2315–2318. (b) Rout, J. K.; Ramana, C. V. *J. Org. Chem.* **2012**, *77*, 1566–1571.
44. (a) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277–7287. (b) Dalcanale, E.; Montanari, F. *J. Org. Chem.* **1986**, *51*, 567–569. (c) Wakabayashi, T.; Mori, K.; Kobayashi, S. *J. Am. Chem. Soc.* **2001**, *123*, 1372–1375.
45. Bigi, M. A.; Reed, S. A.; White, M. C. *J. Am. Chem. Soc.* **2012**, *134*, 9721–9726.
46. Yu, W. S.; Mei, Y.; Kang, Y.; Hua, Z. M.; Jin, Z. D. *Org. Lett.* **2004**, *6*, 3217–3219.
47. (a) Hsu, D.-S.; Lin, S.-C. *J. Org. Chem.* **2012**, *77*, 6139–6146. (b) Hume, P. A.; Furkert, D. P.; Brimble, M. A. *Org. Lett.* **2013**, *15*, 4588–4591.
48. Sharma, P. K.; He, M.; Romanczyk, L. J., Jr.; Schroeter, H. *J. Label. Compd. Radiopharm.* **2010**, *53*, 605–612.
49. Quideau, S.; Lebon, M.; Lamidey, A. M. *Org. Lett.* **2002**, *4*, 3975–3978.

LIST OF PUBLICATIONS

1. "The Total Synthesis and Structural Revision of Stagonolide D" **Paresh M. Vadhadiya,** Vedavati G. Puranik and C. V. Ramana*, *J. Org. Chem.* **2012,** *77,* 2169–2175.

2. "Total Synthesis of Mangiferaelactone" **Paresh M. Vadhadiya** and C. V. Ramana*, *Tetrahedron Lett.* **2014***, 55,* 6263–6265.

3. "Total Synthesis of Sinenside A" **Paresh M. Vadhadiya** and C. V. Ramana*, *Org. Lett.*, **2015**, *17*, 1724–1727.

4. "Studies towards the total synthesis of Cytospolide E" **Paresh M. Vadhadiya**, Jeetendra Kumar Rout and C. V. Ramana*, "*To be communicated*"

Erratum

Erratum

Erratum