SYNTHETIC STUDIES TOWARD MANZACIDINS, PONDAPLIN AND SOME APPLICATIONS OF CYCLOPROPYLMETHYL RADICALS

A THESIS

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BY

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DIVISION OF ORGANIC CHEMISTRY: TECHNOLOGY

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OCTOBER 2006

DECLARATION

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

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CERTIFICATE

The research work presented in thesis entitled "**Synthetic studies toward Manzacidins, Pondaplin and some applications of cyclopropylmethyl radicals**" has been carried out under my supervision and is a bonafide work of **Mr. K. Sankar**. This work is original and has not been submitted for any other degree or diploma of this or any other University.

Pune-8
October 2006

(Dr. M. K. Gurjar)
Research Guide

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K. Sankar

ABBREVIATIONS

AIBN	Azaisobutyronitrile
Bn	Benzyl
DMAP	*N,N'*-Dimethylaminopyridine
DMSO	Dimethyl sulfoxide
EtOAc	Ethyl acetate
Im	Imidazole
MeI	Methyl iodide
Py	Pyridine
TEA	Triethyl Amine
TBDMSCl	*tert*-Butyldimethylchlorosilane
TBDPSCl	*tert*-Butyldiphenylchlorosilane
p-TSA	*para*-Toluenesulfonic acid
TBTH	Tri n-butyltin hydride
Boc	*tert*-Butoxy carbonyl
$(Boc)_2O$	Di-*tert*-butyl dicarbonate
DBU	1,8-Diazabicyclo [5.4.0]undec-7-ene
DIBAL-H	Diisobutylaluminium hydride
DMP	Dess-Martin periodinane
Me	Methyl
Et	Ethyl
Ph	Phenyl
*m*CPBA	*meta*-Chloroperbenzoic acid
EtOH	Ethanol
MeOH	Methanol
Pd/C	Palladium on carbon
PMB	*para*-Methoxy benzyl
TBAF	Tetra-n-butylammonium fluoride
THF	Tetrahydrofuran
DEAD	Diethyl azodicarboxylate

DMF	*N,N'*-Dimethylformamide
BH_3·DMS	Boron dimethylsulfide complex
DCC	Dicyclohexylcarbodiimide
PDC	Pyridinium dichromate
Me_3SOI	Trimethyl sulfoxonium iodide
Cy	Cyclohexyl
Mes	Mesityl

GENERAL REMARKS

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

Contents

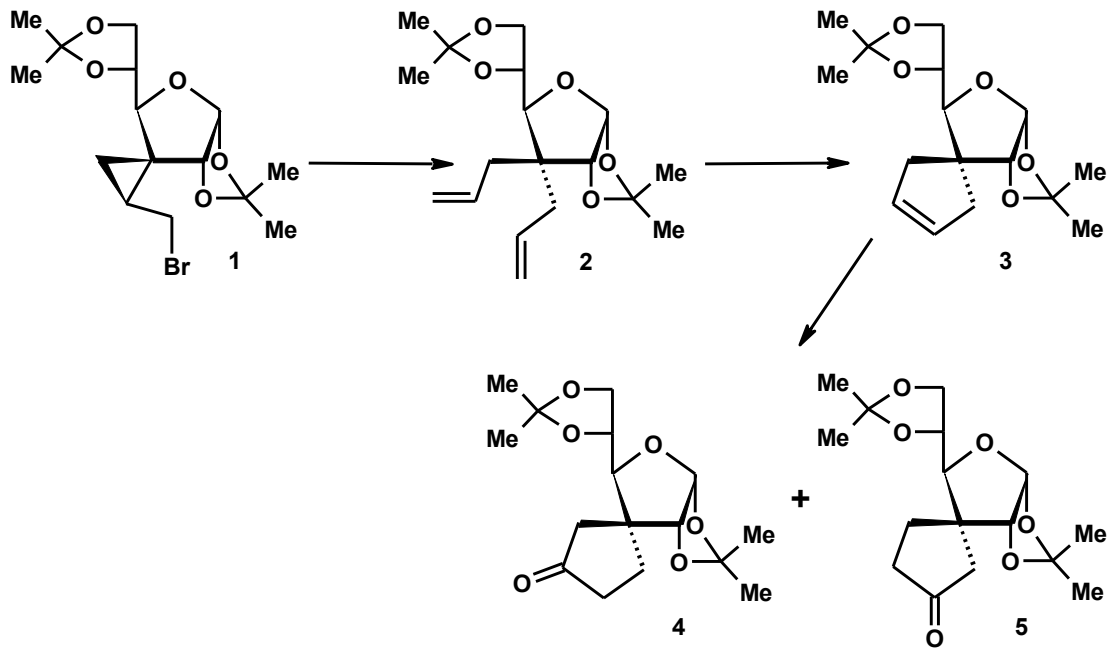
ABSTRACT

The thesis entitled "**Synthetic studies toward Manzacidins, Pondaplin and some applications of cyclopropylmethyl radicals**" is divided into three chapters. The first chapter describes the synthesis of spirocarbocycles using radical mediated *gem*-diallylation followed by RCM strategy and a synthesis of bicyclic carbohydrate derivative using cyclopropylmethyl radical chemistry. The second chapter deals with the synthetic studies on manzacidins B, a bromopyrrole alkaloid. The last chapter describes the synthetic efforts toward pondaplin, a 13-membered macrolide.

Chapter-1: Part I: synthesis of carbohydrate based spirocycles using cyclopropylmethyl radicals

Since many natural products have been characterized as possessing spirolinkages, synthesis of spirocyclic compounds has attracted considerable attention. A novel methodology has been developed in our group for *gem*-diallylation by trapping the homoallyl radical generated in situ, with allyltri-*n*-butylstannane. This *gem*-diallyl (**2**) system underwent ring closing olefin metathesis reaction with Grubbs catalyst to give spirocyclopentene derivative **3**. Hydroboration followed by oxidation of compound **3** gave

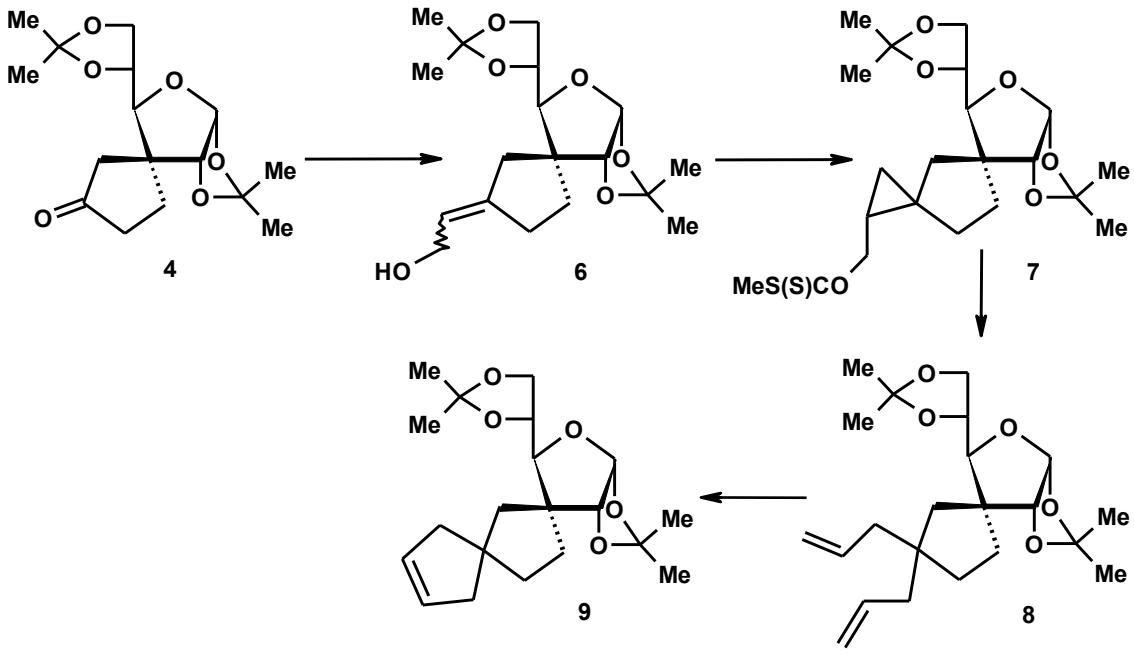
Scheme 1



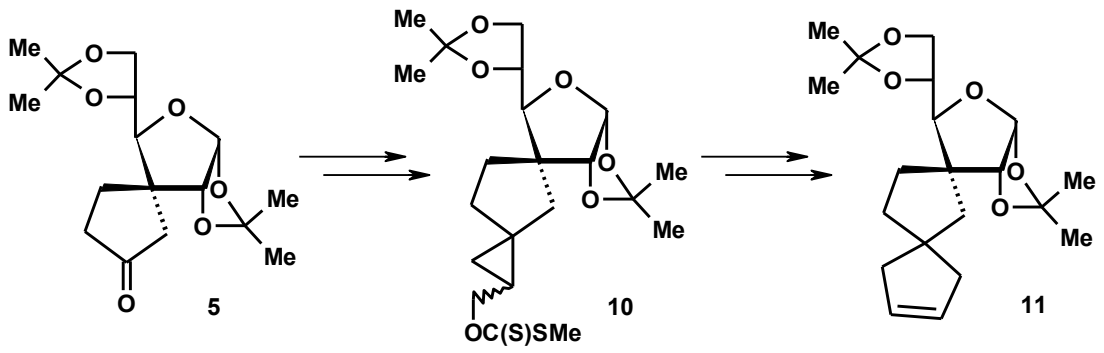
a mixture of alcohols, which were oxidized under Swern oxidation conditions to give the spiro ketones **4** and **5**.

To extend the application of this strategy for the synthesis of polycyclic spirocompounds, we targeted two novel bis-spirocyclic compounds **9** and **11** by following an iterative approach of this method from spiroketones **4** and **5**. Accordingly, compound **4** was subjected to a sequence of reactions, Wittig olefination, DIBAL-H reduction, Simmons-Smith cyclopropanation and treatment with NaH, CS_2 and MeI in THF to get the xanthate **7**. The radical allylation on xanthate **7** gave the diallyl derivative **8,** which on RCM furnished the bis-spiro compound **9**. Similarly, compound **5** was converted to the bis-spirocyclic derivative **11** by following the same sequence of reactions.

Scheme 2



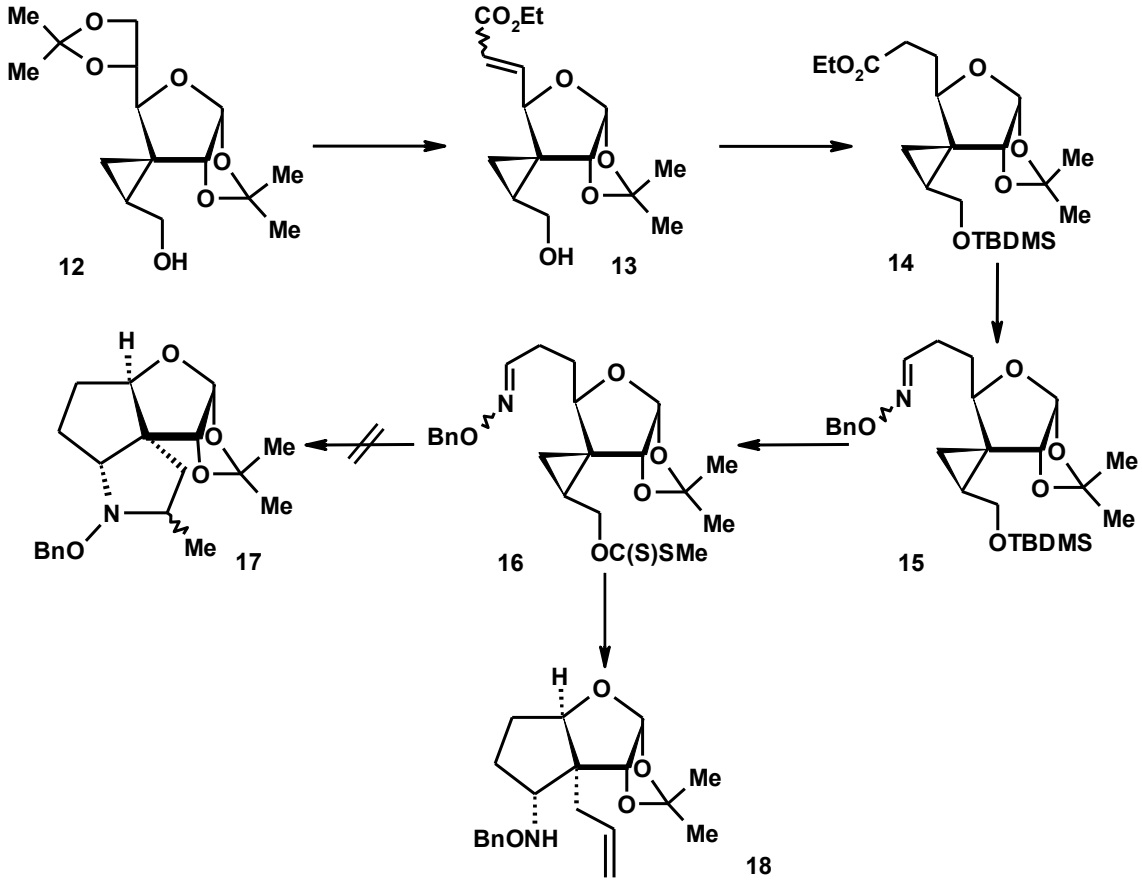
Scheme 3



Chapter-1: Part II: Synthesis of aminocarbocycle from carbohydrate based cyclopropylmethyl radical

Angularly fused triquinane natural products have attracted intense attention of synthetic organic chemists as challenging targets. Structural complexity associated with significant biological activity has necessitated development of various approaches for their synthesis. Among them, the radical cascade reactions are by far the most elegant and efficient approaches.

Scheme 4



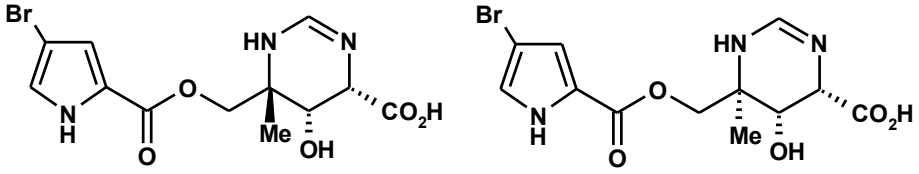
Carbohydrate based triquinanes have been synthesized from our group using intramolecular radical cascade by a homoallyl radical generated by the rearrangement of cyclopropylmethyl radical. By following that strategy, we attempted to synthesis *N*-heterocyclic triquinanes. Accordingly, compound **12** was converted to the saturated ester **14** in four steps. This ester on reduction with DIBAL-H gave an aldehyde, which on treatment with $BnONH_2.HCl$ yielded a mixture of *O*-benzyl oximes **15**. After removing the silyl group, the alcohol obtained was converted to the xanthate derivative **16**. This

xanthate **16** on treatment with *n*-Bu_3SnH and AIBN gave the tricyclic compound **18**. Although the stereochemistry of the newly formed amine and allyl groups were *syn*, which was necessary for further cyclization, it failed to produce the expected tetracyclic compound **17**.

Chapter-2: Studies toward the synthesis of Manzacidin B

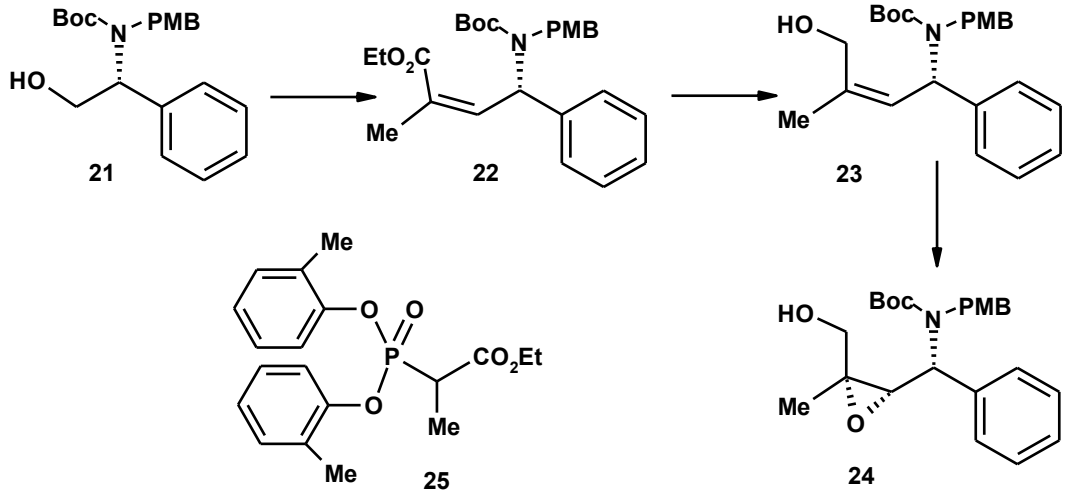
Bromopyrrole alkaloids comprise a large and varied class of marine natural products possessing interesting and potentially useful pharmacological activities as α-adrenoreceptor blockers, seretonin antagonists and actomyocin ATPase activators. Manzacidins possess unique structures consisting of an ester linked bromopyrrole carboxylic acid and a tetrahydropyrimidine ring. Although manzacidins exhibit similar biological activities to those of other bromopyrrole alkaloids, only preliminary tests have been carried out, due to the scarcity of these compounds. Because of their interesting biological properties, limited availability in nature and novel structural features, we started the synthesis of these molecules, particularly manzacidin B (**20**).

Figure 1



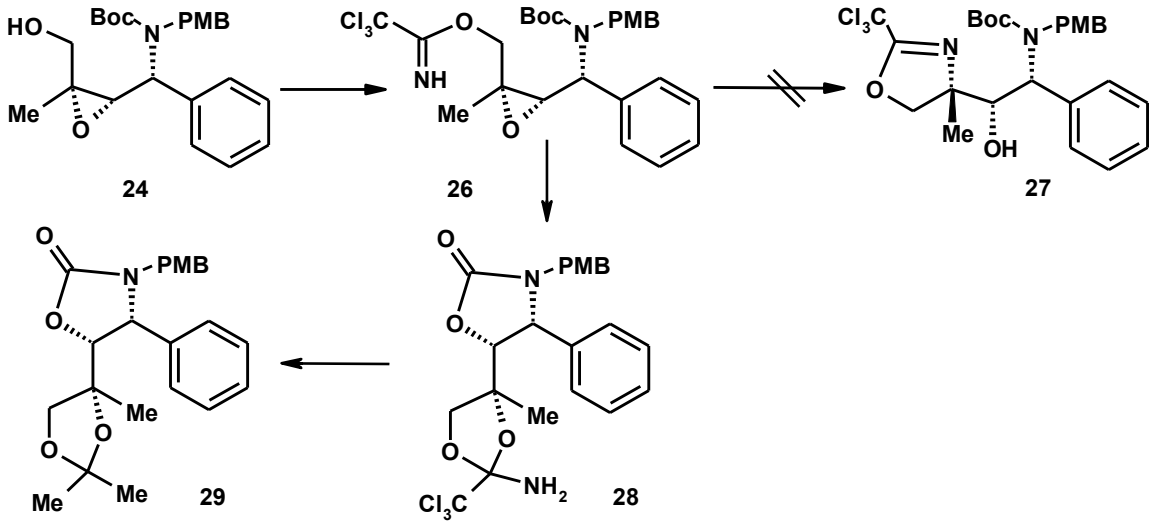
19 Manzacidin B (proposed) **20** Manzacidin B (revised)

Scheme 5



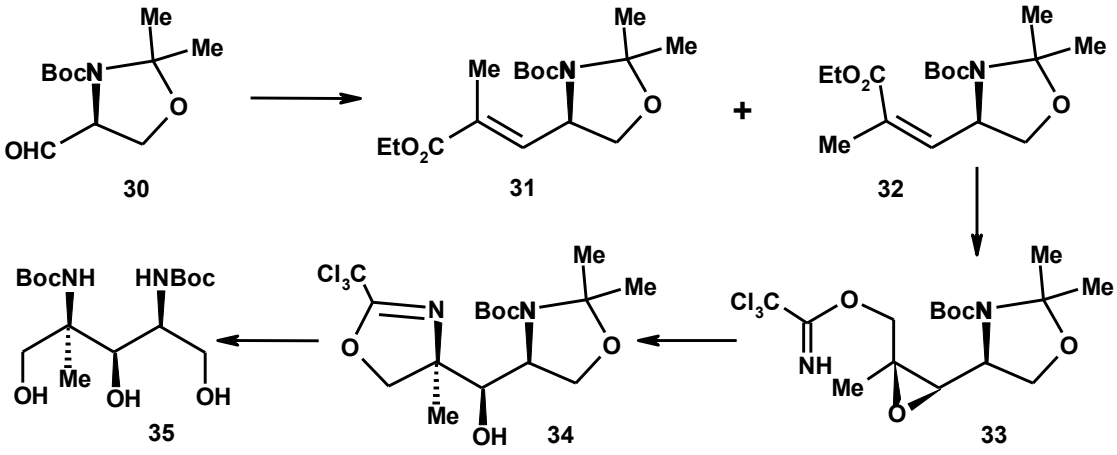
Our studies toward the synthesis of manzacidin B was started with the oxidation of protected phenylglycinol **21** followed by a stereoselective olefination with the phosphonate **23** and NaH at –78 ^{o}C to afford the *Z*-α,β-unsaturated ester **22** exclusively. Allylic alcohol **23** obtained by reduction of the ester **22** with DIBAL-H, was subjected to the stereoselective epoxidation with *m*-CPBA to give the epoxy alcohol **24** as a single product through the co-operative effect of the *N*-Boc and hydroxyl group with the peracid. This epoxy alcohol on exposure with Cl_3CCN and DBU produced the imidate **26** in quantitative yield, which on subsequent treatment with $BF_3.OEt_2$ in CH_2Cl_2 yielded an unusual orthoamide **28** instead of the desired oxazoline **27**. This orthoamide on hydrolysis with dil. HCl gave a diol, which was converted to its acetonide derivative and characterized by single crystal X-ray crystallographic analysis.

Scheme 6

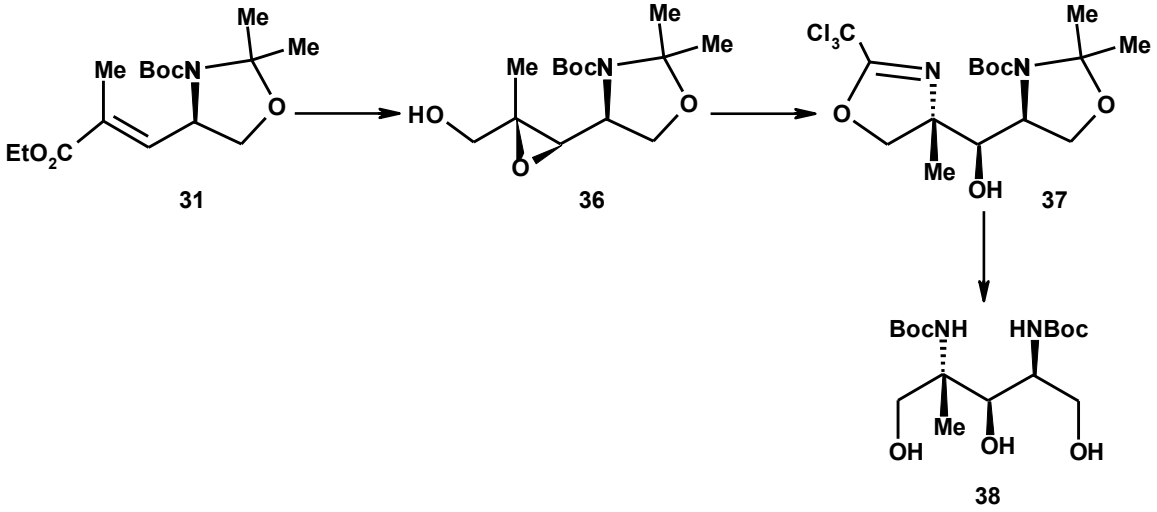


With this unexpected mode of cyclization, we have slightly modified the substrate in order to prevent the reaction of *t*-butyl carbamate with the epoxide through a conformational change. Thus, the same sequence of reactions was carried out with Garner aldehyde **30** to get the imidate **33**. As we expected, this imidate on treatment with $SnCl_4$ led to the required oxazoline **34** exclusively. After acid hydrolysis, both the amines were protected as their *N*-Boc derivative to afford the triol **35**, which was having all the chiral centers present in manzacidin B. In the mean time a synthesis of manzacidin B with revision of stereochemistry at C-9 was reported. To get the correct stereochemistry, we have synthesized the required diastereomer **38** from the *E*-α,β-unsaturated ester **31**.

Scheme 7



Scheme 8

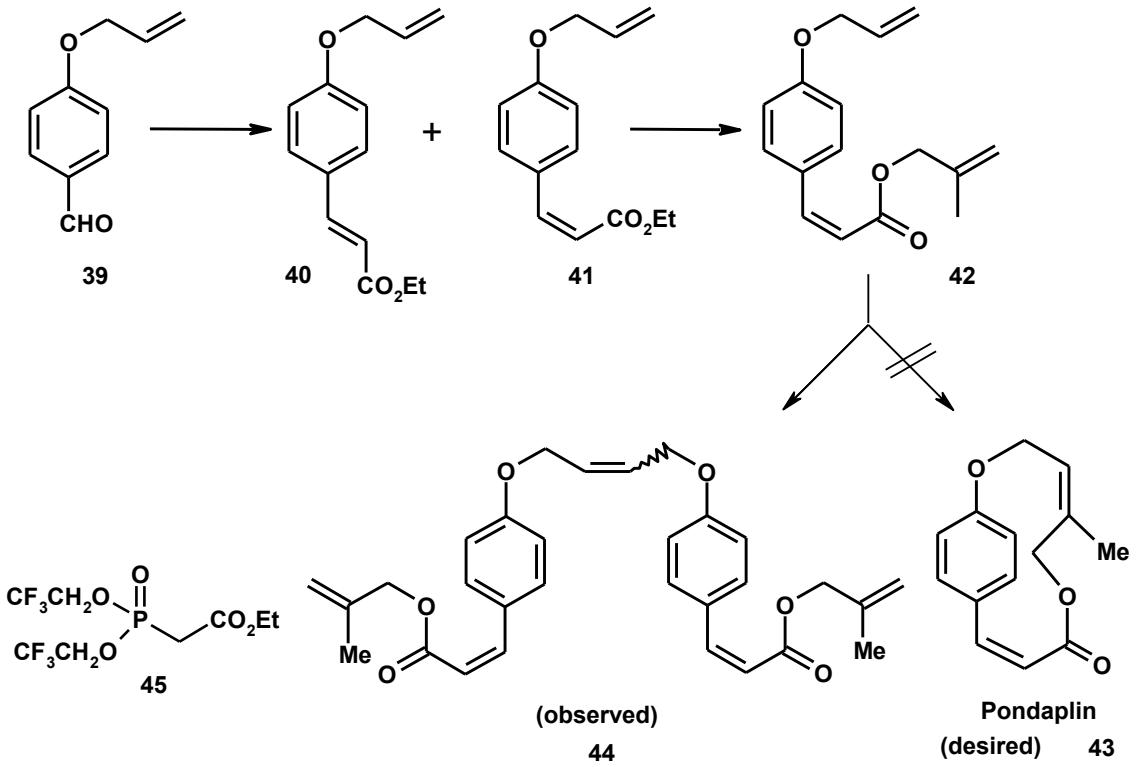


Having successfully synthesized the triol **38** with protected diamines, currently studies are directed towards the completion of the synthesis.

Chapter-3: Studies toward the synthesis of Pondaplin

Pondaplin **43**, a cyclic prenylated phenylpropanoid isolated from *Annona glabra L.*(Annonaceae), is the only example of a [9]-paracyclophane natural product. It shows moderate cytotoxicity among six human solid tumor cell lines. Five sp^2 centers in its tether confer a strong rigidity to this thirteen-membred macrolide. All these structural features and its biological activity made it an attractive target for its total synthesis.

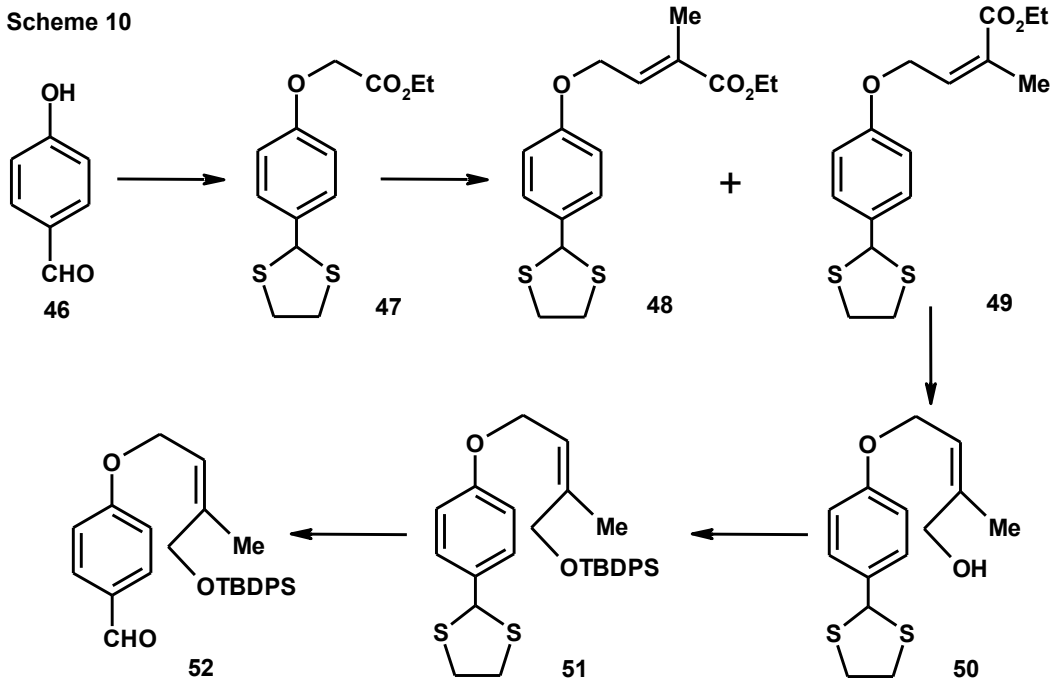
Scheme 9



Wittig-Horner olefination of aldehyde **39** with the phosphonate **45** at –78 ^{o}C produced the *Z*-α,β-unsaturated ester **41** as the major product. After transesterification with methallyl alcohol, the triene **42** obtained was subjected to the ring closing olefin metathesis reaction with Grubbs catalyst. Even under very high dilution, we could isolate only the dimer at the monosubstituted olefin (**44**).

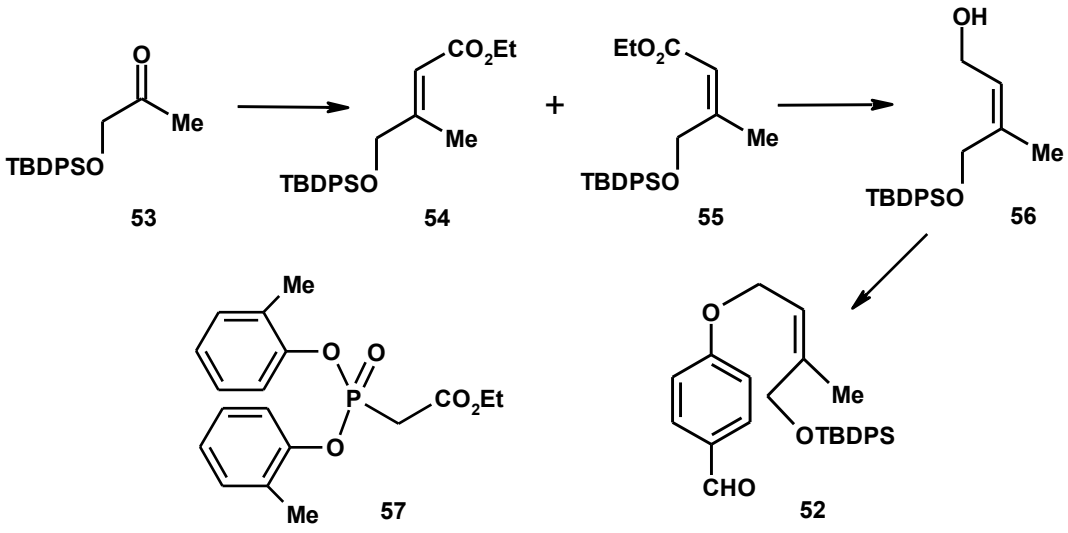
With the failure of RCM strategy, macrolactonization was considered as an alternative route to pondaplin. Thus, 4-hydroxybenzaldehyde was converted to the dithioacetal derivative **47** by alkylation with ethylbromoacetate followed by protection of the aldehyde using $BF_3.OEt_2$ and ethane-1,2-dithiol. This ester was then reduced to the aldehyde with DIBAL-H at –78 ^{o}C in toluene and was subjected to the Wittig-Horner olefination with the phosphonate **25** and NaH in THF at –78 ^{o}C to get the *Z*-α,β-unsaturated ester **49** as the major product. This ester was reduced to the corresponding allylic alcohol **50** using DIBAL-H and protected as TBDPS ether **51**. Cleavage of the dithioacetal with $HgCl_2$ and HgO yielded the aldehyde **52**.

Scheme 10



Simultaneously, we have made this aldehyde in a short method in which the trisubstituted olefin **56** was made first and coupled with the 4-hydroxybenzaldehyde. In this strategy, protected hydroxyacetone **53** was treated with the phosphonate **57** at low temperature to generate the trisubstituted *Z*-α,β-unsaturated ester **55** along with the minor *E*-isomer **56**. This ester was reduced with DIBAL-H and etherified with 4-hydroxybenzaldehyde under mitsunobu conditions to get the aldehyde **52**.

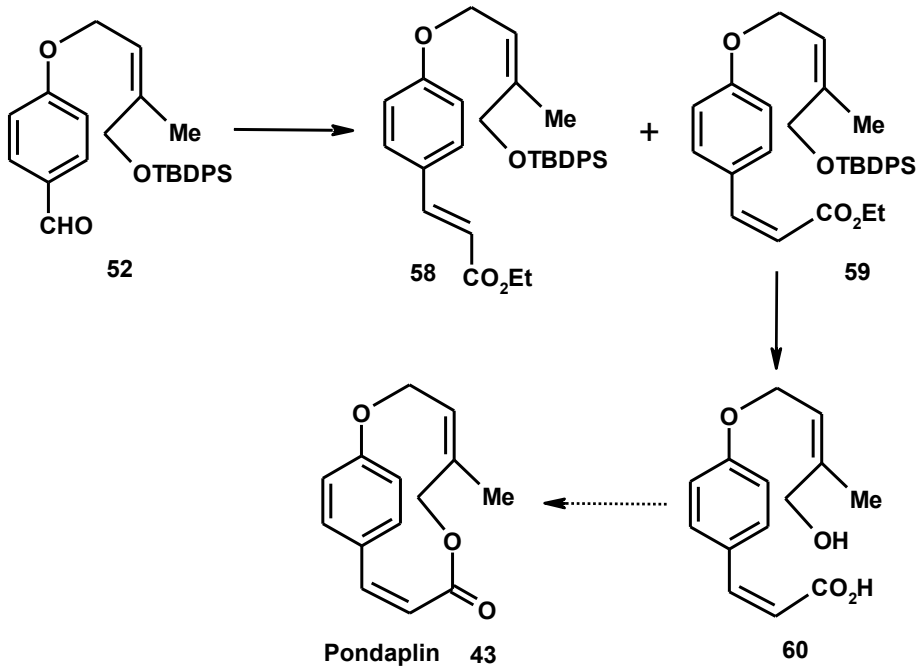
Scheme 11



Aldehyde **52** underwent Wittig-Horner olefination with the phosphonate **45** to give the *cis*-α,β-unsaturated ester (**62**) as a major product. Deprotection of this silyl ether with

TBAF followed by hydrolysis of the ester with LiOH furnished the required secoacid (**63**). Under several conditions tried for macrolactonization, we were unable to isolate the natural product, pondaplin.

Scheme 12



CHAPTER-1

Synthesis of spiro and fused polycyclic carbohydrates using cyclopropylmethyl radicals

Cyclopropylmethyl radicals

Both the basic understanding and the synthetic utilization of radical processes have increased dramatically in the last few decades.[1] One of the most powerful methods in today's synthetic arsenal is radical cyclization and/or radical rearrangement-cyclization. From the literature, it is evident that the cyclopropyl ring can undergo several kinds of ring opening reactions like electrophilic, nucleophilic and radical ring opening.[2-4] Carbon-carbon bond cleavages of strained ring systems like cyclopropane triggered by cyclopropylmethyl radical have been studied as a method for preparing alkenyl compounds[5] (Figure **1**).

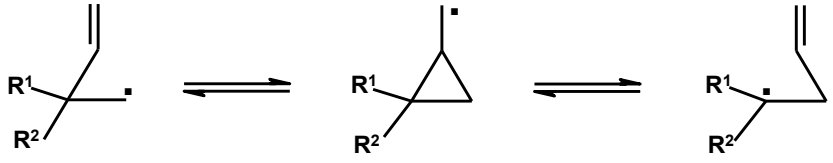


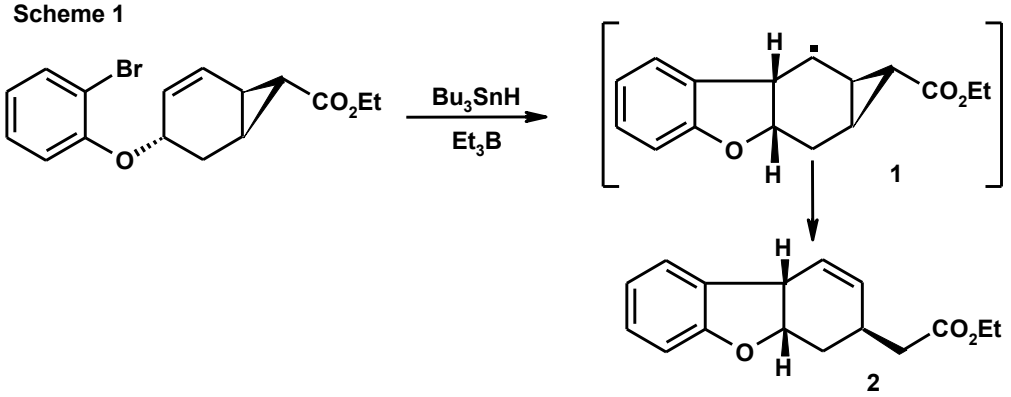
Figure 1

The rapidity of the ring opening of cyclopropylmethyl radical has resulted in the widespread use of cyclopropane rings as a probe of reaction mechanism both in chemical and enzyme catalysed reactions. Formation of ring-opened products from substrates containing the cyclopropylmethyl group has been widely used as an indication that a particular reaction proceeds via a radical intermediate.[4,6] For example, cyclopropanes having different substituents were used to study the mechanism and rate of biological reactions[5b] like hydroxylation of alkanes with cytochrome P 450, inhibition of monoamine oxidase by cyclopropylamines, hydrogen transfer reactions by nicotinamide co-enzymes, penicillin biosynthesis, biosynthesis of ethylene from 1-amino cyclopropanecarboxylates and dephosphorylation of organophosphates by *Escherichia coli*.

Similarly, evidence for the radical intermediates in dissolving-metal reduction of carbonyl compounds[7] and some photochemical reactions like Norrish type I and type II processes,[8] Paterno-Buchi reaction[9] and [2+2] cycloaddition of alkenes to enones[10] have been found by using cyclopropane compounds.

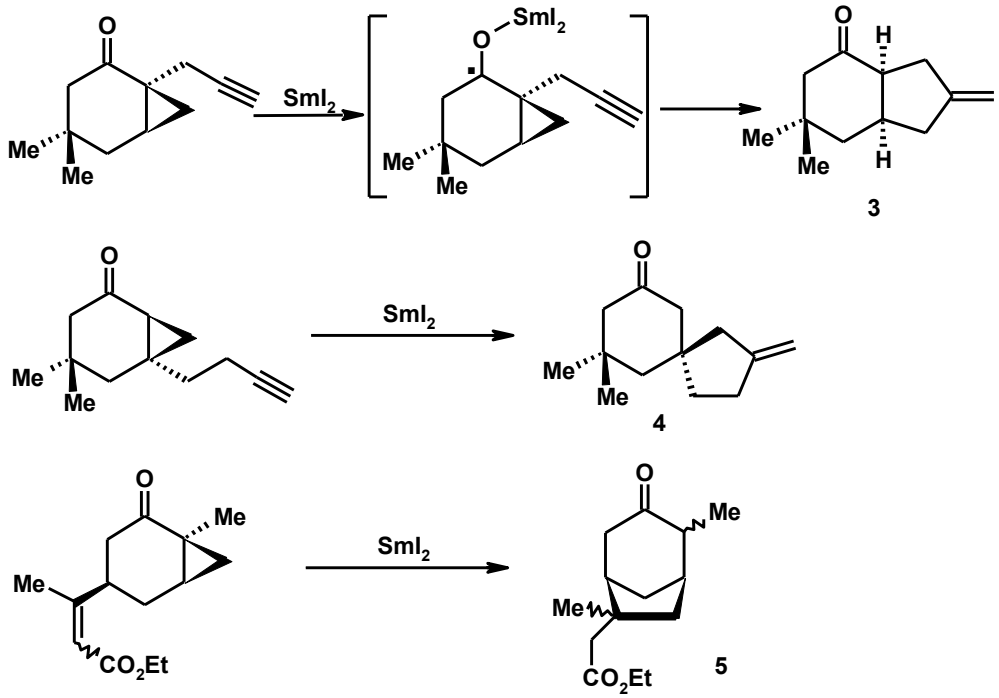
While extensive work on cyclopropylcarbinyl radicals has focused mainly on kinetic studies only a few examples of reactions from the synthetic point of view have thus far been reported. A tandem radical ring closing-radical ring opening strategy has been developed by Clive and co-workers for the synthesis of several benzofuran derivatives (**2**) for the evaluation of inhibitors of leukotriene biosynthesis, through the intermediate of cyclopropylmethyl radical **1** (Scheme **1**).[11]

Scheme 1



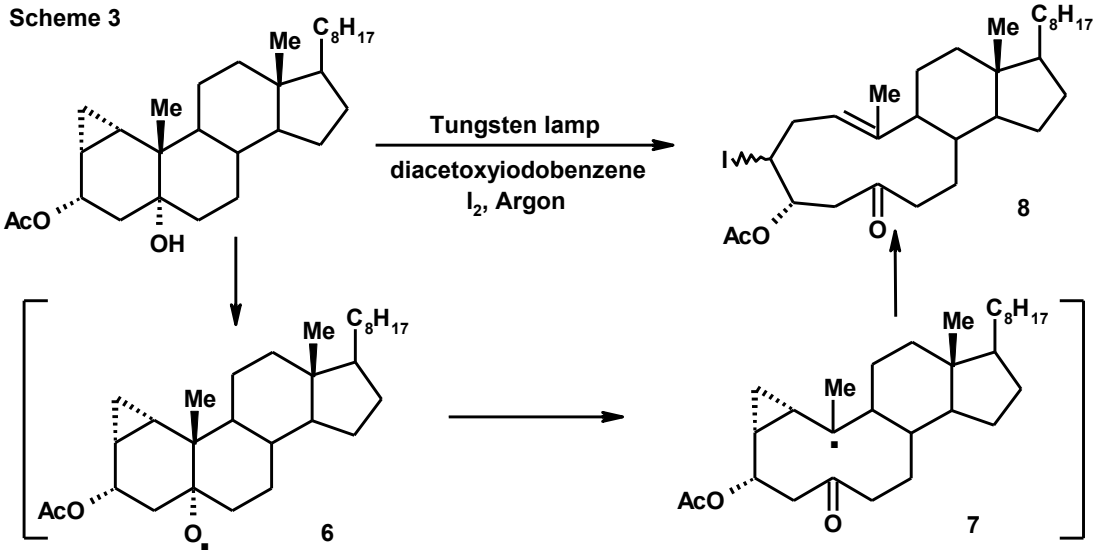
Batey *et al*. developed a general method for the synthesis of fused (**3**), spiro (**4**) and bridged (**5**) bicyclic ring systems from fused cyclopropyl ketones. Here the exoselective cyclopropylcarbinyl-allylcarbinyl radical rearrangement was triggered by single electron transfer from SmI_2 (Scheme **2**).[12]

Scheme 2



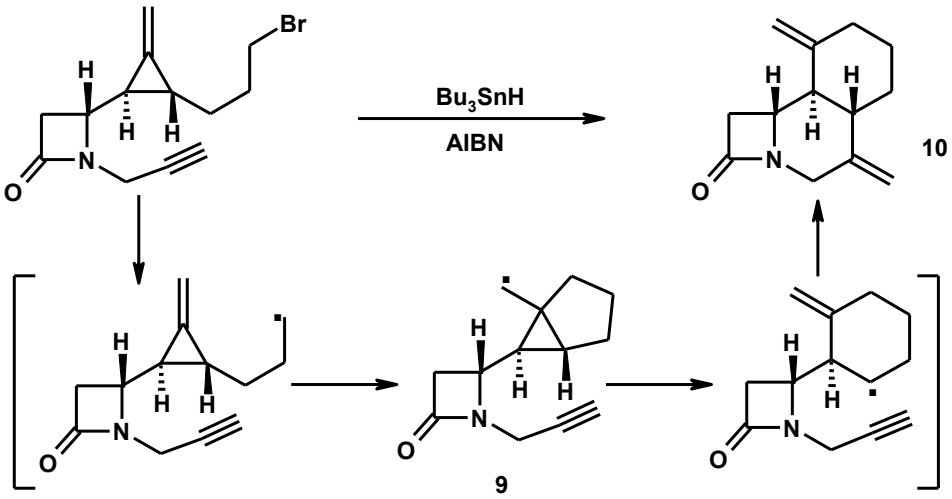
Suarez *et al.* developed a tandem β-fragmentation-cyclopropylcarbinyl radical rearrangement for the synthesis of 11-membered rings by photolysis of steroidal alcohols using (diacetoxyiodo)benzene and iodine, in which the initially formed alkoxy radical **6** rearranged to the ring expanded iododerivative **8** through the cyclopropylcarbinyl radical intermediate **7** (Scheme **3**).[13]

Scheme 3



A new method for generation of cyclopropylcarbinyl radical **9**, has been developed by intramolecular cyclization of a radical on exomethylene cyclopropane by Penfold *et al*. They have applied this strategy for the synthesis of tricyclic β-lactam **10** (Scheme **4**).[14]

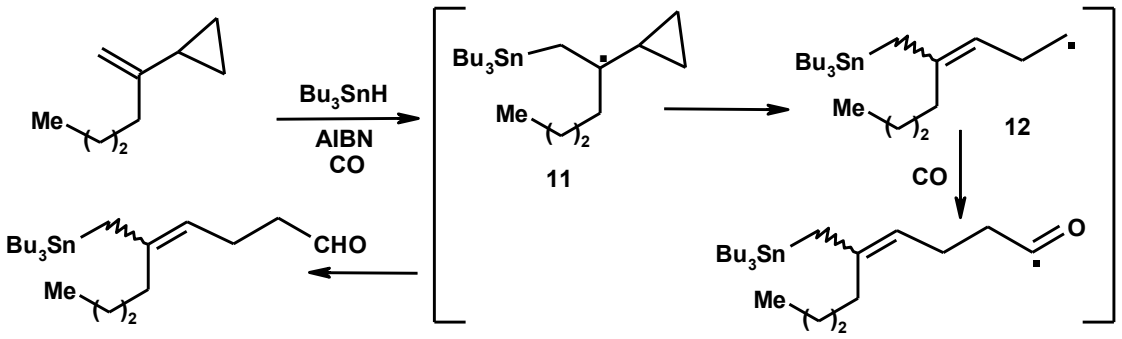
Scheme 4



Stannyl radical addition to vinyl cyclopropane generates cyclopropylmethyl radical **11**, which undergo the rearrangement to give allylcarbinyl radical **12**. Ryu and co-workers

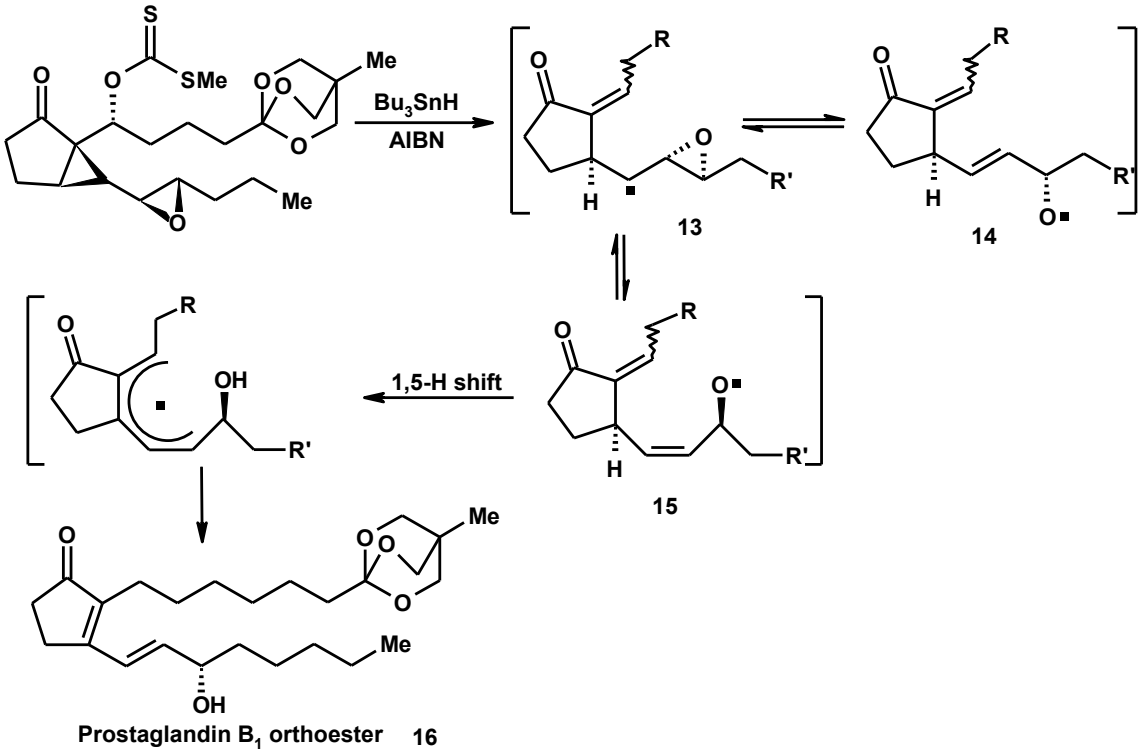
utilized this strategy for the stannylformylation of vinyl cyclopropanes by trapping the rearranged radical with carbon monoxide (Scheme **5**).[15]

Scheme 5



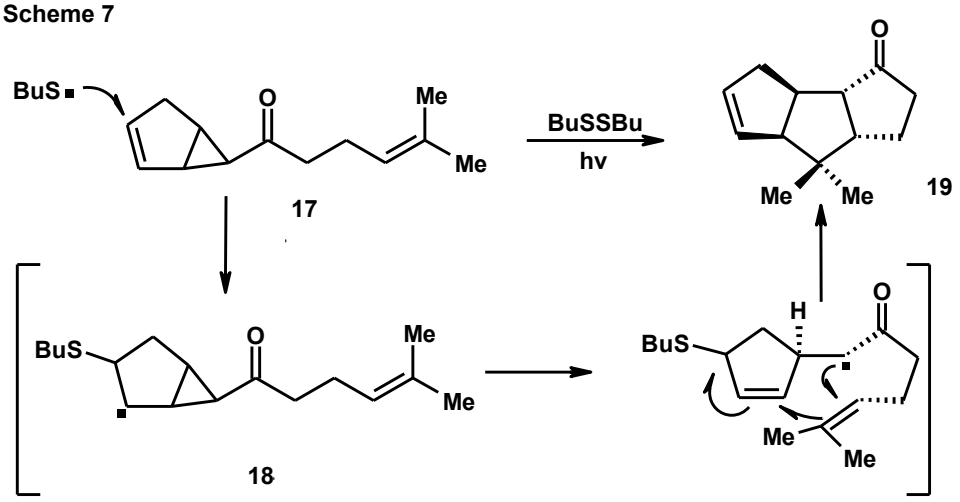
Ziegler *et al.* developed a sequential radical fragmentation of cyclopropylcarbinyl/oxirnylcarbinyl system for the synthesis of prostaglandin B_1. Here the initially formed radical preferentially ruptures the cyclopropane bond overlapping with the carbonyl group to provide the oxiranylcarbinyl radical **13** which was in rapid equilibrium with *E*- and *Z*-allyloxyl radicals **14** and **15** respectively. The *Z*-allyloxy radical **15** underwent intramolecular 1,5-H abstraction to provide the prostaglandin B_1 orthoester **16** (Scheme **6**).[16]

Scheme 6



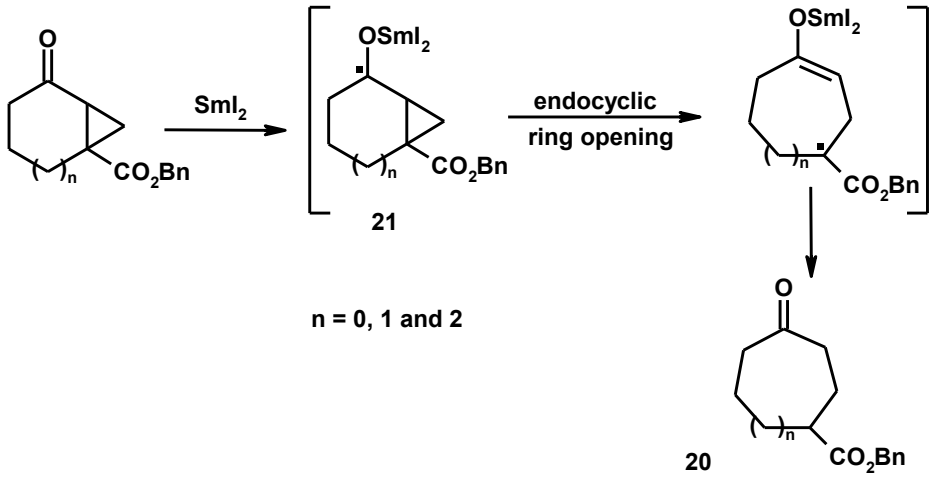
Initiation of radical cyclizations by fragmentation of a strained cyclopropyl ring system **17** beginning with the addition of a sulfur centered radical (generated by photolysis of alkyl disulfide) to an alkene was studied by Jung *et al.* for the synthesis of linear triquinanes **19** through the radical intermediate **18** using suitably placed intramolecular radical acceptor (Scheme **7**).[17]

Scheme 7



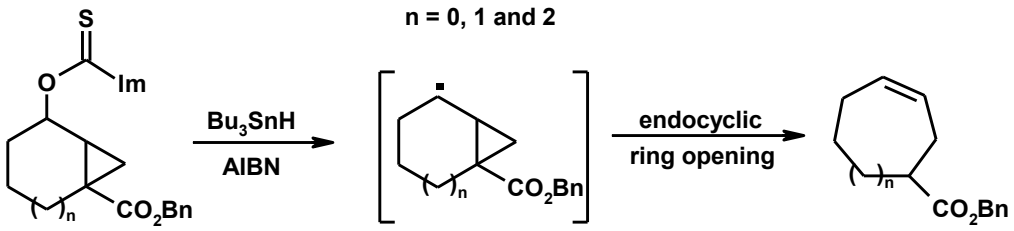
Lee *et al*. described a procedure for thermodynamically favored endoselective cyclopropane ring opening in fused bicyclic ketones for the synthesis of ring expanded ketones **20** using SmI_2 through the intermediate **21** (Scheme **8**).[18]

Scheme 8



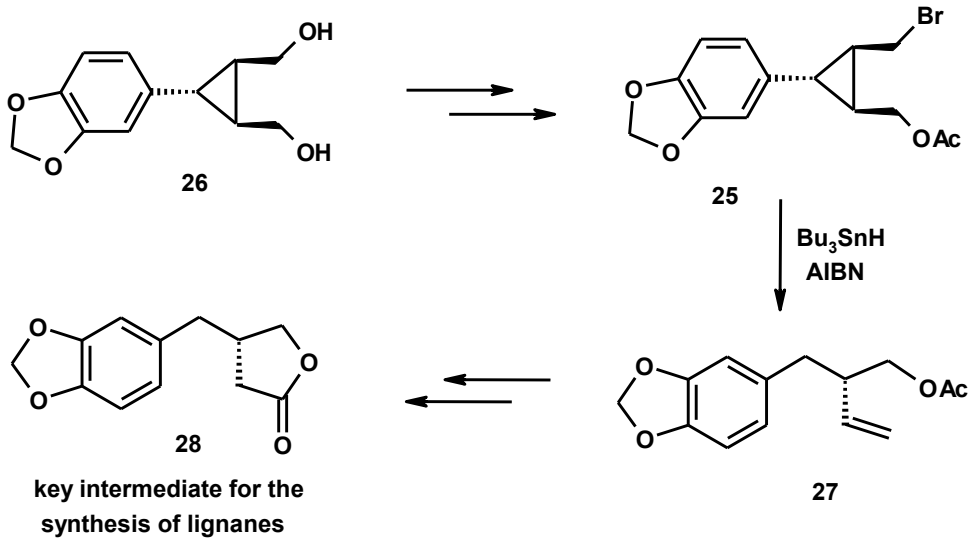
Similarly Lee and co-workers also used bicyclic cyclopropylcarbinyl thiocarbamates **22** as precursor for cyclopropylcarbinyl radicals **23**, which underwent the rearrangement to provide the ring expanded olefins **24** with the ring size of 6 to 8 (Scheme **9**).[19]

Scheme 9



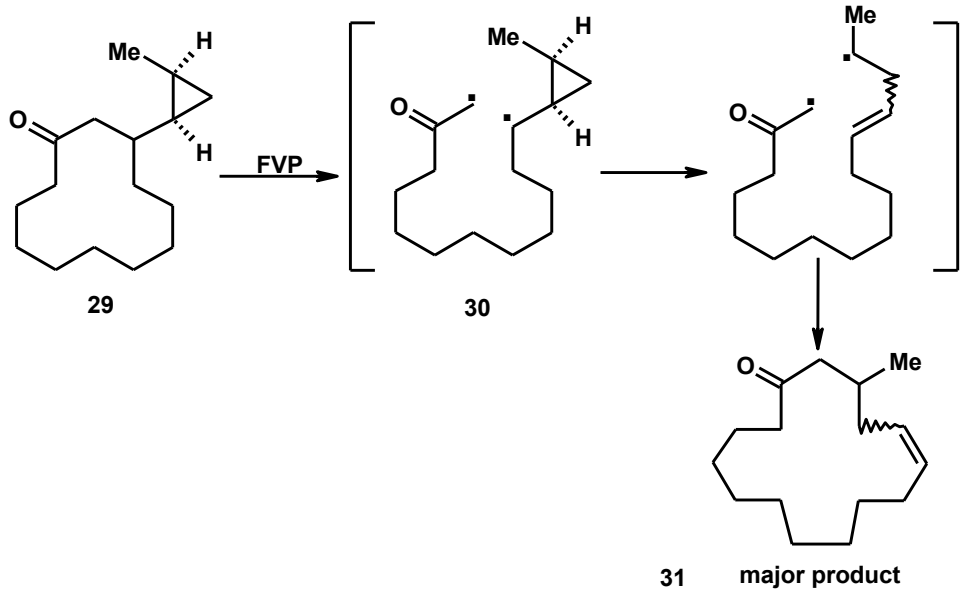
Takekawa *et al*. achieved a regeioselective cleavage of C-C bond of optically active cyclopropanes initiated by cyclopropylcarbinyl radicals and enantioselective synthesis of suitably functionalized alkenes that would serve as versatile chiral building blocks for the construction of a wide variety of biologically active compounds. Here the optically active bromide **25** obtained from meso-diol **26** by enzymatic desymmetrization, was converted to enantiopure homoallylic acetate **27** using the cyclopropylcarbinyl-homoallylic radical rearrangement. This acetate was converted to a key intermediate **28** for the synthesis of biologically active lignanes (Scheme **10**).[20]

Scheme 10



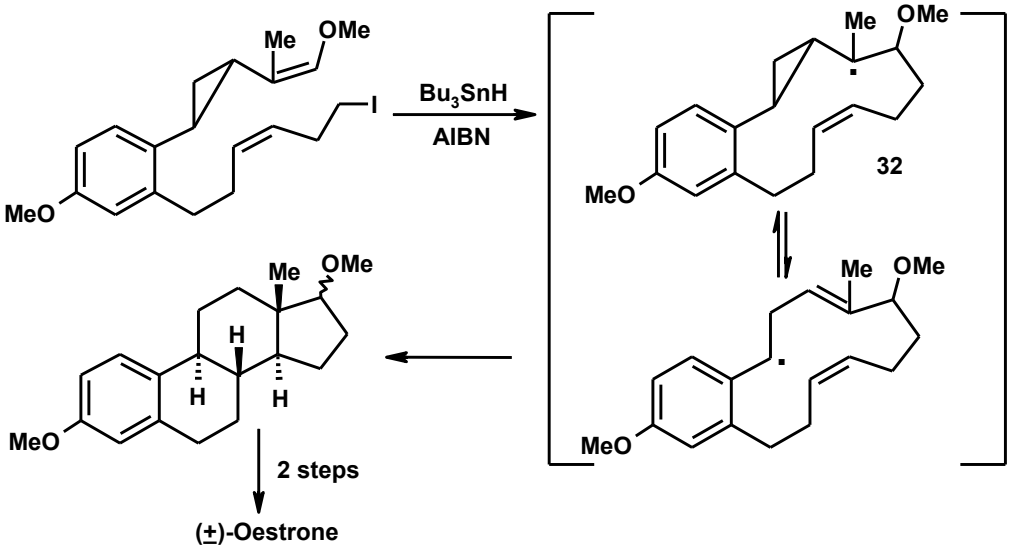
Recently Ruedi *et al.* developed a three-carbon ring expansion strategy for the synthesis of *rac*-muscone **31** from inexpensive C-12 starting materials, in which cyclopropyl ketone **29** cleaved homoletically under flash vacuum pyrolysis. Cyclopropylmethyl radical **30** has been proposed as an intermediate in this rearrangement (Scheme **11**).[21]

Scheme 11



Pattenden and co-workers have disclosed a new total synthesis of rac-oestrone recently, in which three carbocycles were formed in a single step through a radical cascade. Cyclopropylmethyl radical **32** was an intermediate in that synthesis (Scheme **12**).[22]

Scheme 12



Radical mediated *gem*-diallylation

Introduction of *gem*-diallyl functionality in a molecule is usually achieved either by direct base mediated diallylation using allyl halides[23] or by Pd-catalyzed allylation using allyl acetates.[24] But these methods are limited only to compounds having active methylene groups. To overcome this problem a new method has been developed in our laboratory

(Gurjar *et al.*)[25] in which a aldehyde/ketone carbonyl group was converted to *gem*-diallyl group. Key transformation in this strategy was trapping the allylcarbinyl radical **33** (formed by the rearrangement of cyclopropylcarbinyl radical **34**) with allyltri-n-butyltin (Keck allylation)[26] as given in figure **2**.

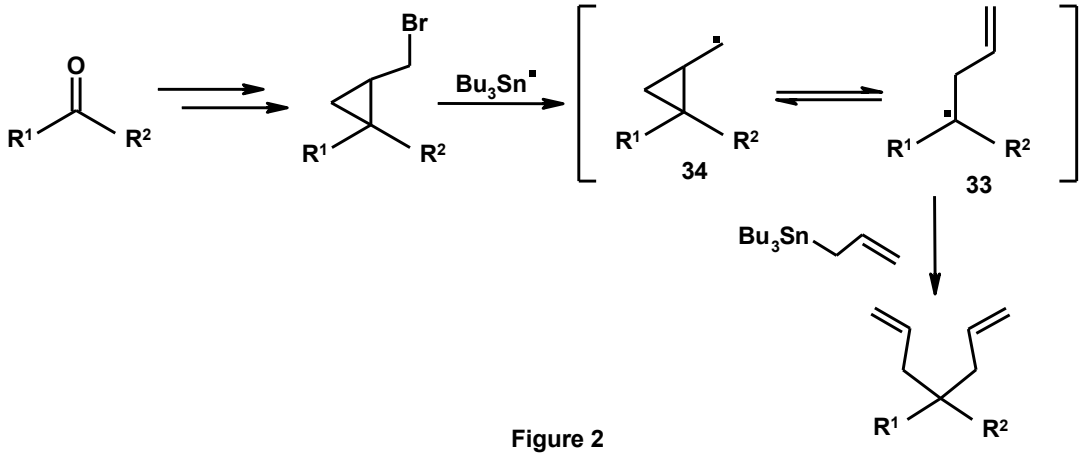
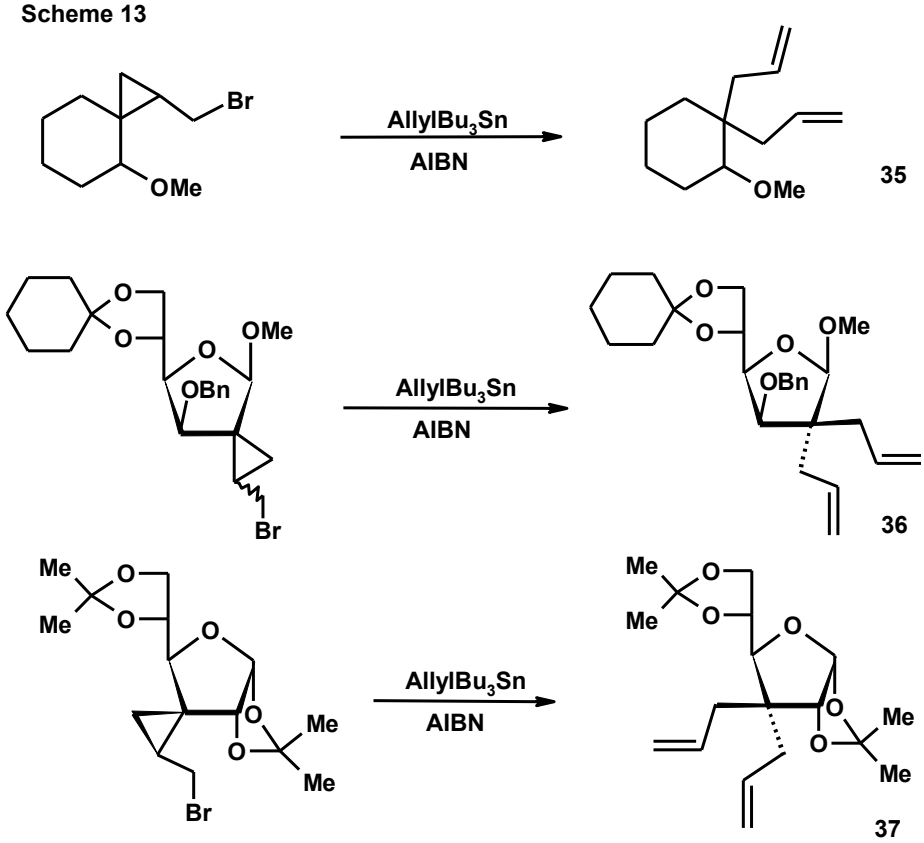
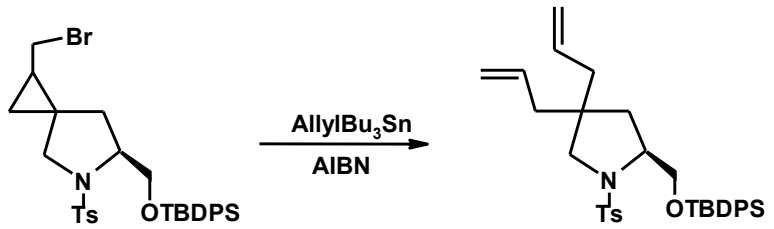


Figure 2

This *gem*-diallylation method has been successfully used in aliphatic (**35**), carbohydrate (**36**, **37**) and amino acid (**38**) systems as given below (Scheme **13**).[25, 27]

Scheme 13

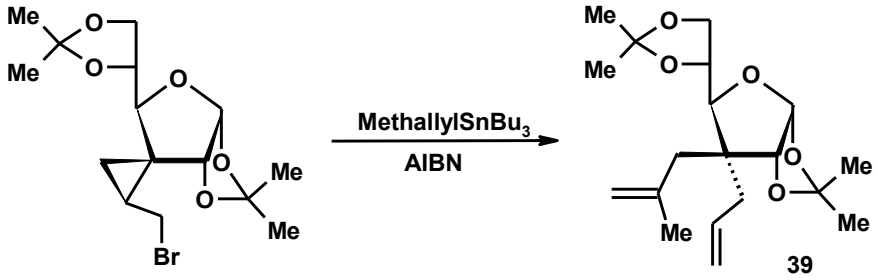




38

Similarly, methallyltri-n-butyltin was used to generate differentially substituted *gem*-diallyl system **39** as a single diastereomer. Exclusive formation of the compound **39** was a result of steric hindrance from the 1,2-*O*-isopropylidene group for the approach of methallyl tin reagent (Scheme **14**).[27]

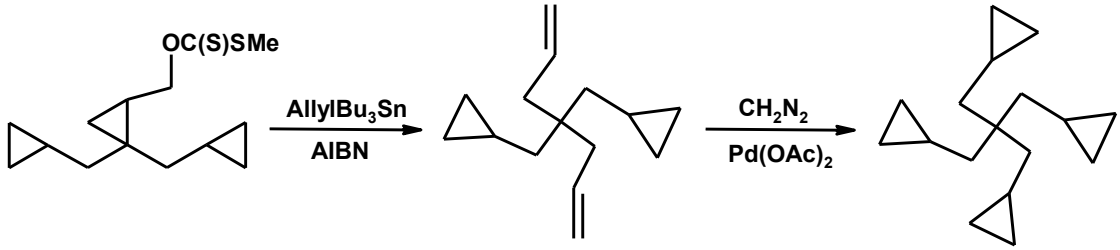
Scheme 14



39

By using this radical mediated *gem*-diallylation strategy an expedient synthesis of tetrakis(cyclopropylmethyl)methane **41**, a symmetric molecule was achieved for its conformational studies in solid and solution phase (Scheme **15**).[28]

Scheme 15

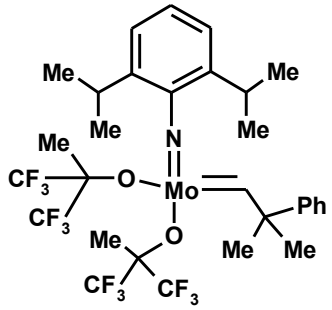


40 41

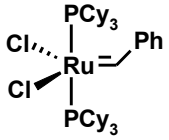
Spirocycles by *gem*-diallylation/RCM strategy

Molecules containing spirocycles find innumerable applications particularly in peptides,[29] nucleosides[30] and carbohydrates.[31] Synthesis of spirocycles was difficult until the advent of novel catalysts (Figure **3**) by Schrock[32] (**42**) and Grubbs[33] (**43** and **44**) used in ring closing olefin metathesis (RCM) though there are a number of methods available like, intramolecular alkylation, cycloaddition and rearrangements.[34] The RCM based approaches have made the introduction of a spiro group in the structural framework of an organic

molecule an easy proposition.[35] For instance, *gem*-diallyl containing substrates undergo RCM to produce spirocyclopentenyl derivatives.[36]

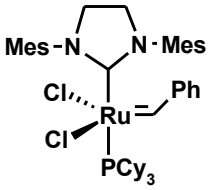


Schrock's catalyst 42



Grubbs 1st generation catalyst

43



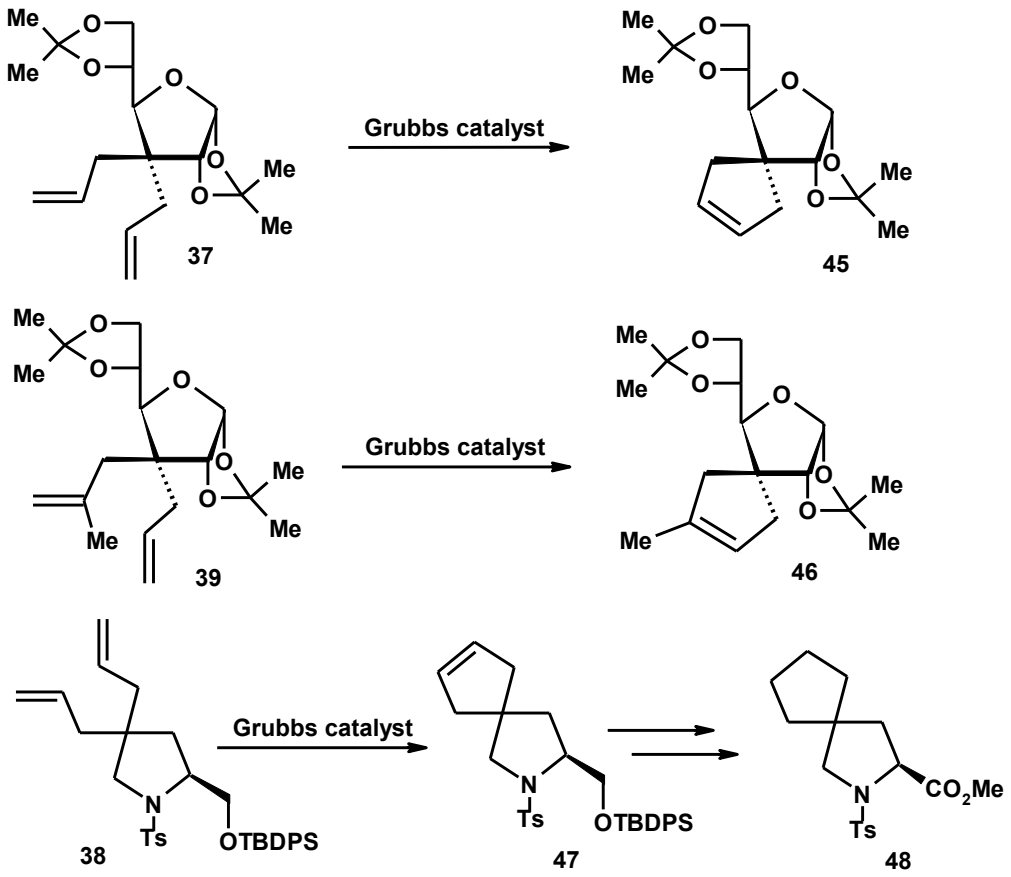
Grubbs 2nd generation catalyst

44

Figure 3

A new strategy has been developed in our laboratory by the combination of radical mediated *gem*-diallylation and RCM to synthesis spirocyclopentenyl derivatives. Accordingly, carbohydrates and amino acids having diallyl functionality were cyclised by RCM to generate spirocyclopentenyl derivatives **45**, **46** and **47** (Scheme **16**).[27]

Scheme 16

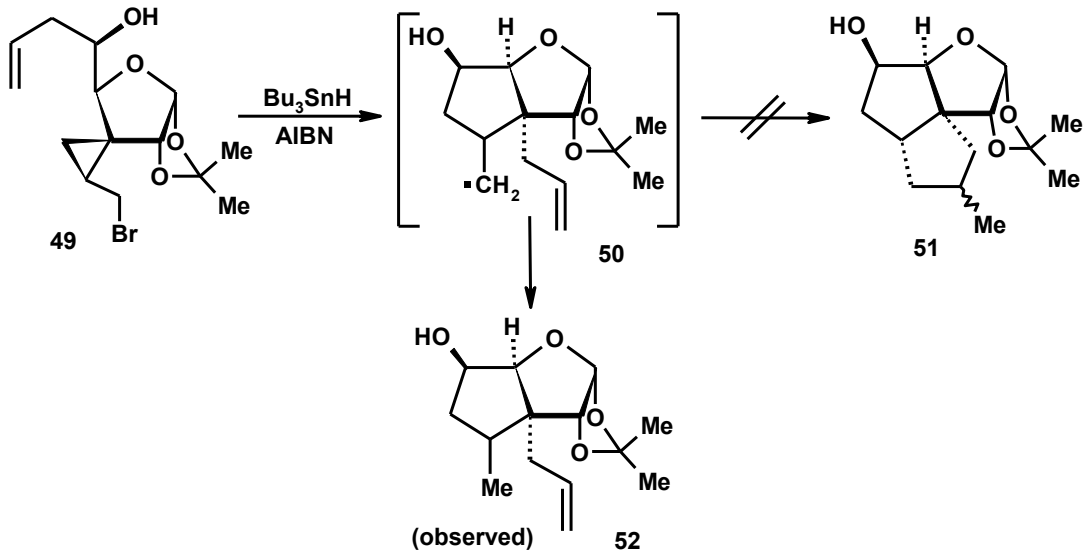


Triquinanes from cyclopropylcarbinyl radicals

Angularly fused triquinanes have attracted intense attention of synthetic organic chemists as challenging targets.[37] Structural complexity associated with significant biological activity has necessitated development of many approaches for their synthesis.[38] Among them, radical cascade reactions are by far the most elegant and efficient approaches as significantly demonstrated by the work of Curran and others.[39] Fraser-Reid[40] and co-workers have performed some novel transformations mediated by serial radical cyclization on carbohydrate substrates to synthesize naturally occurring triquinanes.

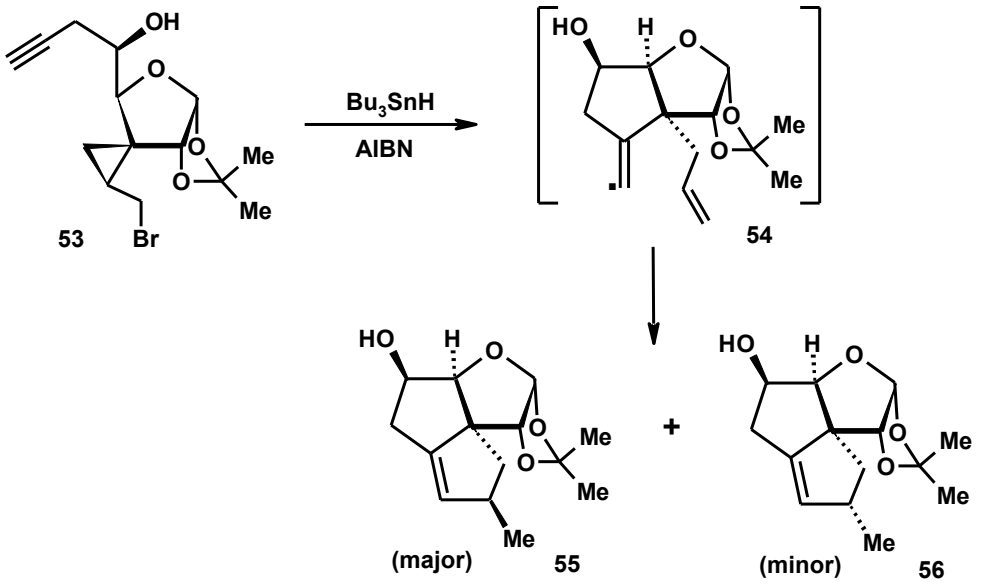
A novel approach has been disclosed for the synthesis of carbohydrate based oxa- and dioxa-triquinanes from our group using a radical cascade initiated by the cyclopropylcarbinyl radical. In this approach the olefin initially formed from the rearrangement of cyclopropylcarbinyl radical acts as an intramolecular radical acceptor to complete the radical cascade with the formation of triquinanes.[41] Substrate **49** on treatment with Bu_3SnH produced a fused bicyclic compound **52** instead of the expected angularly fused tricyclic compound **51**. This premature termination of radical cascade could be attributed to the poor reactivity of the methyl radical **50** (Scheme **17**).

Scheme 17



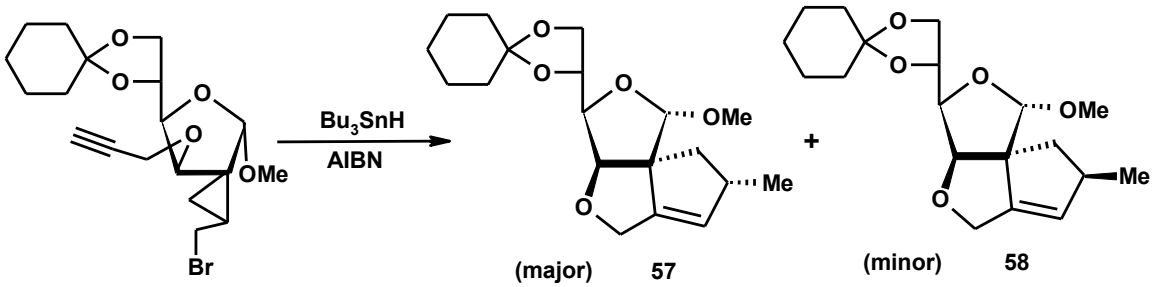
In order to circumvent this problem a homopropargyl alcohol substrate **53** was used to generate the desired triquinanes (**55** and **56**) as a mixture of epimers at the newly formed methyl center (Scheme **18**).

Scheme 18



Similarly dioxa-triquinanes were also synthesized by following the same strategy, as a mixture of epimers, **57** and **58** (Scheme **19**).

Scheme 19



Present Work

Part I: synthesis of carbohydrate based spirocycles using cyclopropylmethyl radicals

In continuation of our work in carbohydrate based cyclopropylmethyl radical chemistry, [25,28,41] we were interested in the synthesis of enantiomerically pure spirocyclic ring systems **59** and **60,** with defined quaternary carbon centers and the bis-spirocyclic ring systems **61** and **62** using the *gem*-diallylation/RCM strategy.[27] Since compounds **59** and **60** could be further elaborated to natural as well as designed molecules with suitable modifications, especially by opening of the furanose ring, these spirocycles are considered as chiral building-blocks for the synthesis of enantiomerically pure carbocyclic spirocompounds (Figure **4**).

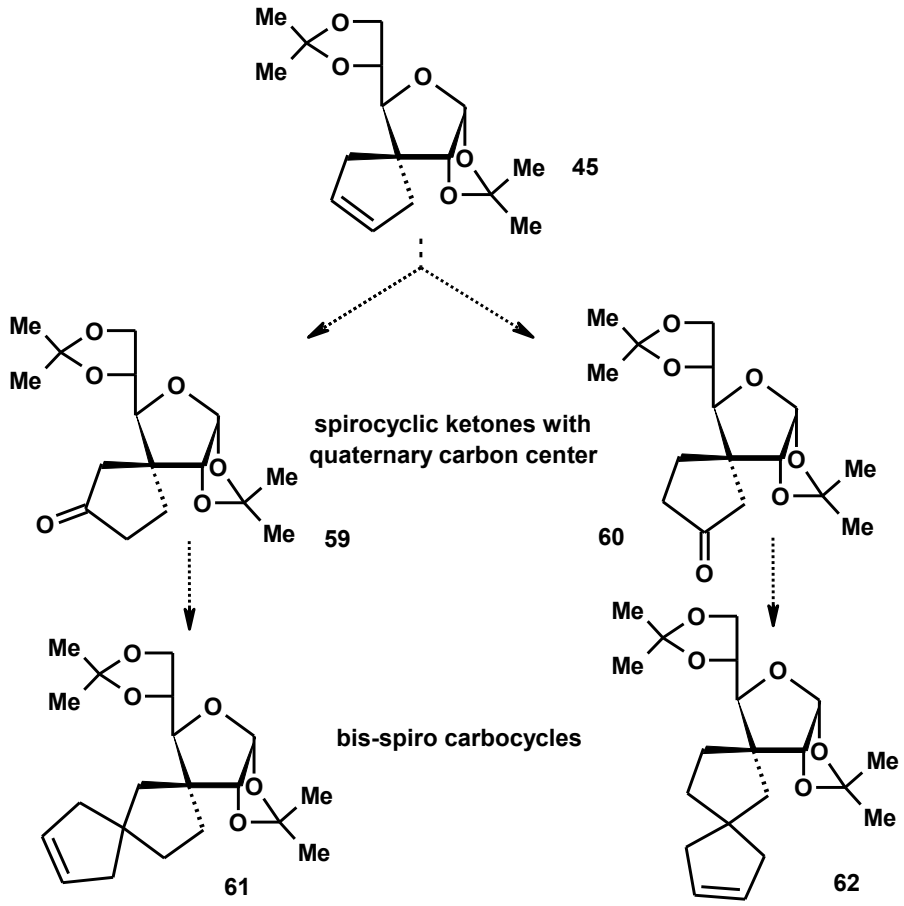
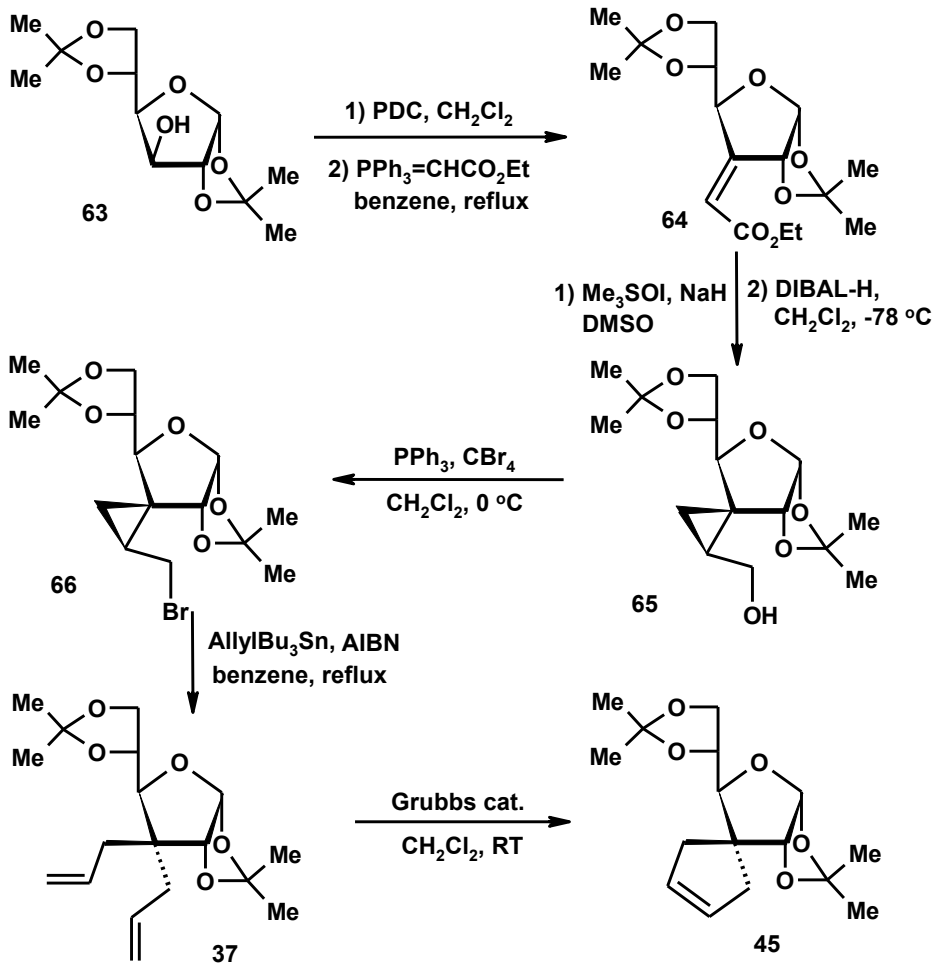


Figure 4 : synthetic plan

We started the synthesis of spiroketones **59** and **60** from the spirocyclopentenyl derivative **45**, which was made by the procedure reported from our laboratory using radical mediated *gem*-diallylation followed by RCM methodology.[25] Accordingly, 1,2:5,6-di-*O*-

isopropylidene-α-D-glucofuranose **63** was subjected to PDC oxidation followed by Wittig olefination with the ylide PPh_3=$CHCO_2Et$ in refluxing benzene to get the conjugated ester **64**. This ester on cyclopropanation using dimethylsulfoxonium methylide (generated in situ from Me_3SOI and NaH) followed by reduction with DIBAL-H gave the corresponding cyclopropylmethyl alcohol **65**. The bromide **66** obtained from the alcohol **65** using PPh_3/CBr_4 was subjected to the radical mediated *gem*-diallylation with allyltri-n-butyltin to get the diallyl compound **37**. Ring closing olefin metathesis of compound **37** gave the spirocyclopentenyl derivative **45** (Scheme **20**).

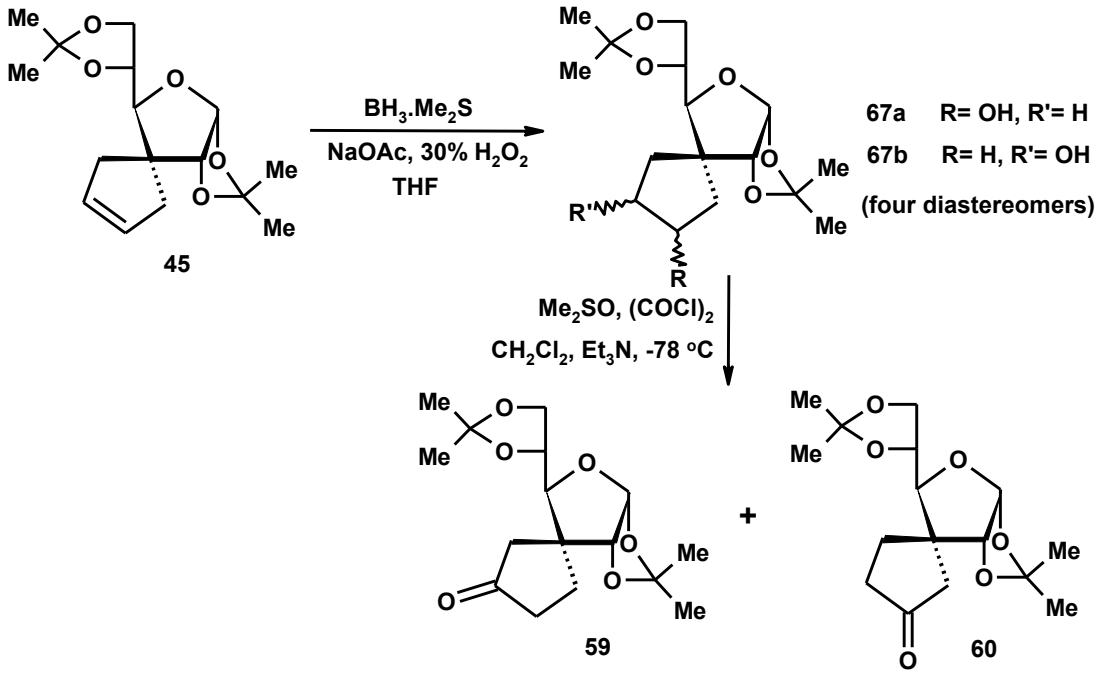
Scheme 20



Hydroboration/oxidation of the olefin to get the spirocyclopentyl alcohol followed by oxidation of hydroxyl groups to the ketones was considered for the synthesis of the spiroketones **59** and **60** from compound **45**. Accordingly, hydroboration of compound **45** using $BH_3.SMe_2$ in THF followed by oxidative workup with H_2O_2 and NaOAc gave a

mixture of alcohols **67** (four diastereomers). Although the ^{1}H NMR spectrum of compound **67** was complex, we did observe the absence of resonances due to olefinic protons. This mixture of alcohols on treatment with oxalyl chloride, DMSO and Et_3N in CH_2Cl_2 at –78 °C (Swern condition),[42] furnished a mixture of ketones **59** and **60** which were separated by silica gel column chromatography, in a ratio of 9:11 (Scheme **21**).

Scheme 21



In the ^{1}H NMR spectrum of compound **59,** isolated methylene protons (H-a and H-b) in the carbocycle were observed as two doublets at 1.95 and 2.50 ppm with J =17.8 Hz whereas in compound **60,** the same (H-b' and H-c') were observed at 2.54 ppm as an ABq. Absolute stereochemistry at the newly formed quaternary carbon centers was established by NOESY experiments. In the compound **59,** NOE was observed between H-2 and H-a as well as H-4 and H-c. This proved that the newly formed quaternary carbon have (*S*)-configuration. Similarly NOE between H-2 and H-a' as well as H-4 and H-b' clearly indicated that the C-4 carbon have (*R*)-configuration in compound **60** (Figure **5**). In ^{13}C NMR spectrum, resonance due to the carbonyl carbons were observed at 216.2 and 215.8 ppm for compounds **59** and **60** respectively. The mass spectrum [m/z 297 for $(M\text{-}CH_3)^+$ for both the ketones] and elemental analysis supported the structure of these compounds. Spectroscopic and analytical data of compound **59** matched with the literature report by

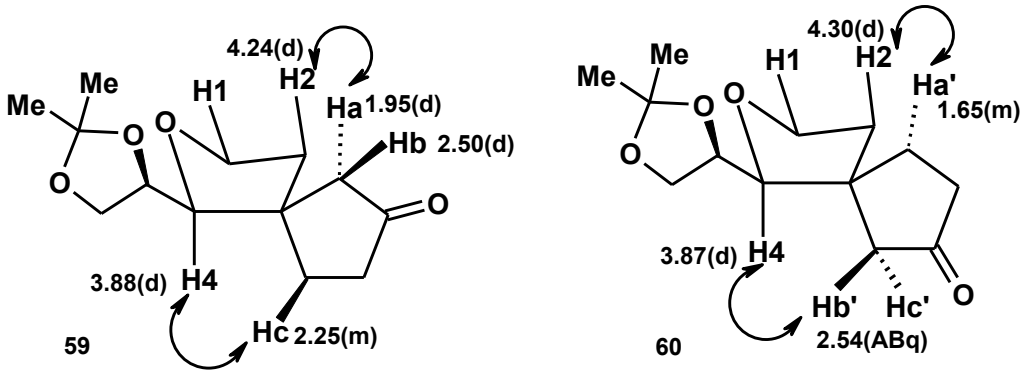


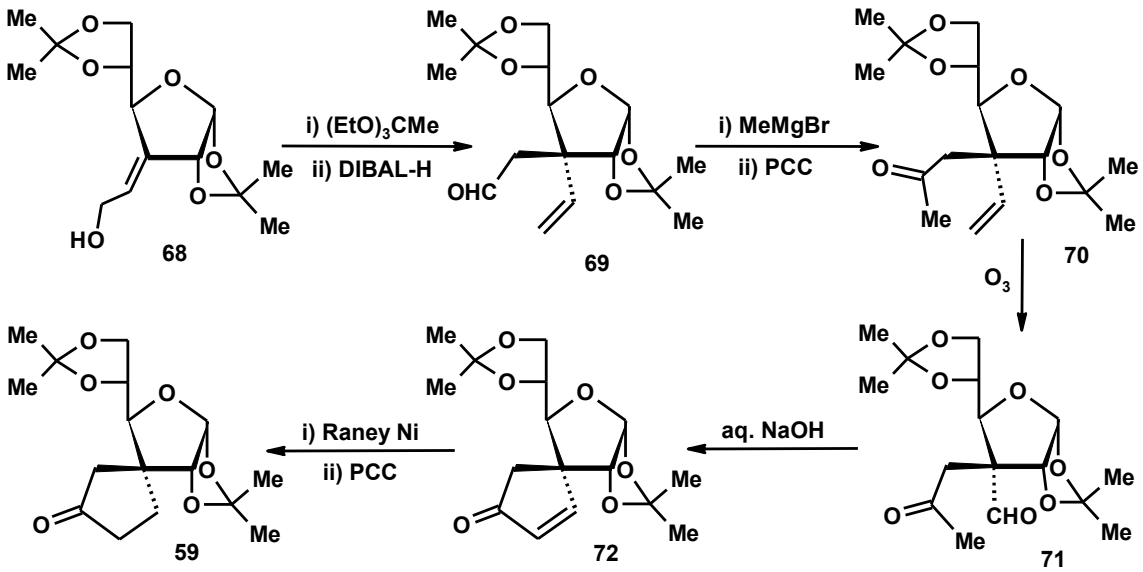
Figure 5: NOE studies

Tadano *et al.*[31a] We proceeded further with these ketones separately, for the synthesis of bis-spirocyclic compounds **61** and **62**, without any attempt to improve the selectivity in favor of a particular ketone**.**

Tadano's approach for the synthesis of ketone 59

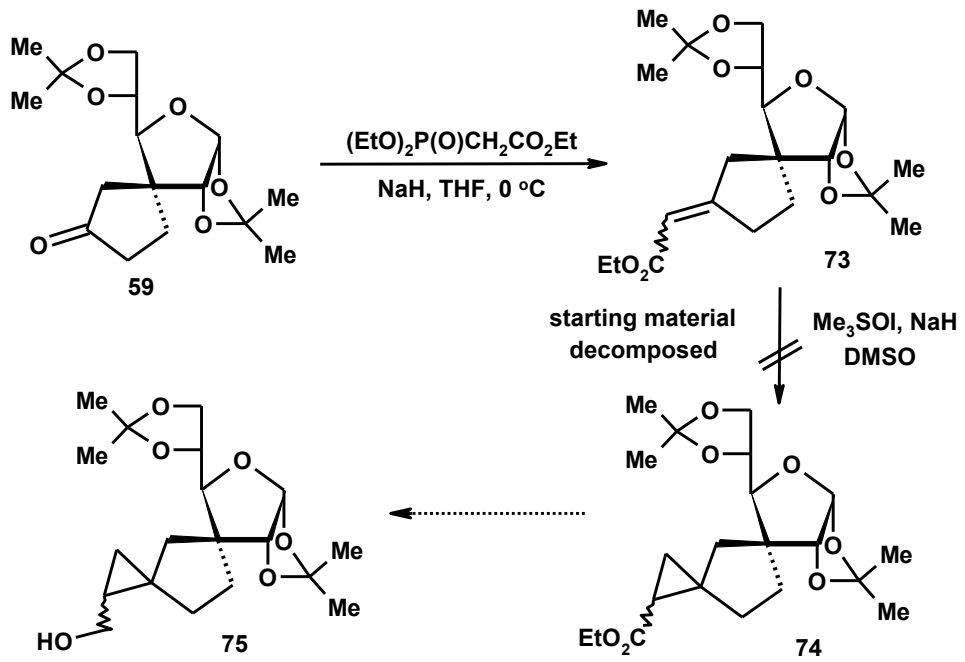
Tadano *et al.*[31a] have reported a stereoselective synthesis of ketone **59** from the allylic alcohol **68** using claisen orthoester rearrangement to generate the quaternary carbon center. The olefinic ester obtained was elaborated to the target ketone **59** through intramolecular aldol reaction (Scheme **22**).

Scheme 22



Having synthesized the spiroketones, we next turned our attention for the synthesis of bis-spirocyclic compounds **61** and **62** using *gem*-diallylation protocol followed by RCM methodology. For this endeavor, we started the synthesis of cyclopropylmethyl alcohol **75**, which was required to execute the radical mediated diallylation. To synthesize compound **75,** we adapted the Corey-Chaykovsky[43] method of cyclopropanation. Accordingly, the ketone **59** on treatment with triethyl phosphonoacetate and NaH in THF (Wittig-Horner olefination) produced a mixture of α, β-unsaturated esters **73.** The ^{1}H NMR spectrum of compound **73** showed a singlet at 5.76 ppm for olefinic proton. The signal due to H-1 was observed as two doublets at 5.63 ppm, which clearly indicated that compound **73** was a mixture of *E*- and *Z*- isomers. In the ^{13}C NMR spectrum, the peaks at 165.8 and 166.1 ppm were assigned for the ester carbonyl and a signal at 165.0 ppm for the olefinic quaternary carbon. When we attempted for the cyclopropanation on compound **73** with dimethylsulfoxonium methylide (generated in situ from Me_3SOI and NaH in DMSO),[43] the starting material decomposed under the reaction conditions (Scheme **23**).

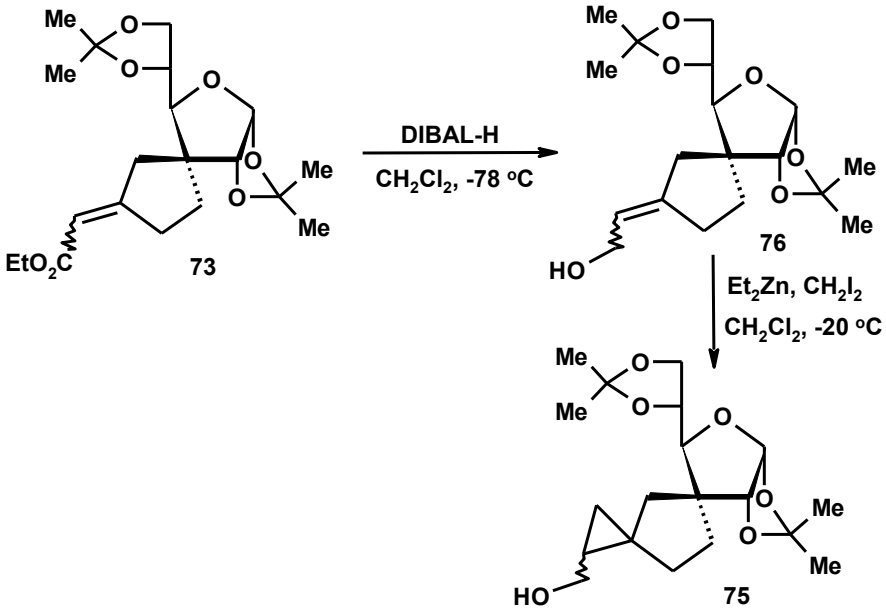
Scheme 23



The Simmons-Smith reaction was considered as an alternative method to achieve this cyclopropanation. The allylic alcohol **76** required for this transformation was obtained by reduction of **73** with DIBAL-H in CH_2Cl_2 at –78 °C. In the ^{1}H NMR spectrum of compound **76**, hydroxyl methylene protons were located at 3.85-4.17 ppm along with other furanose ring protons as a multiplet and the olefinic protons were observed at 5.58 ppm.

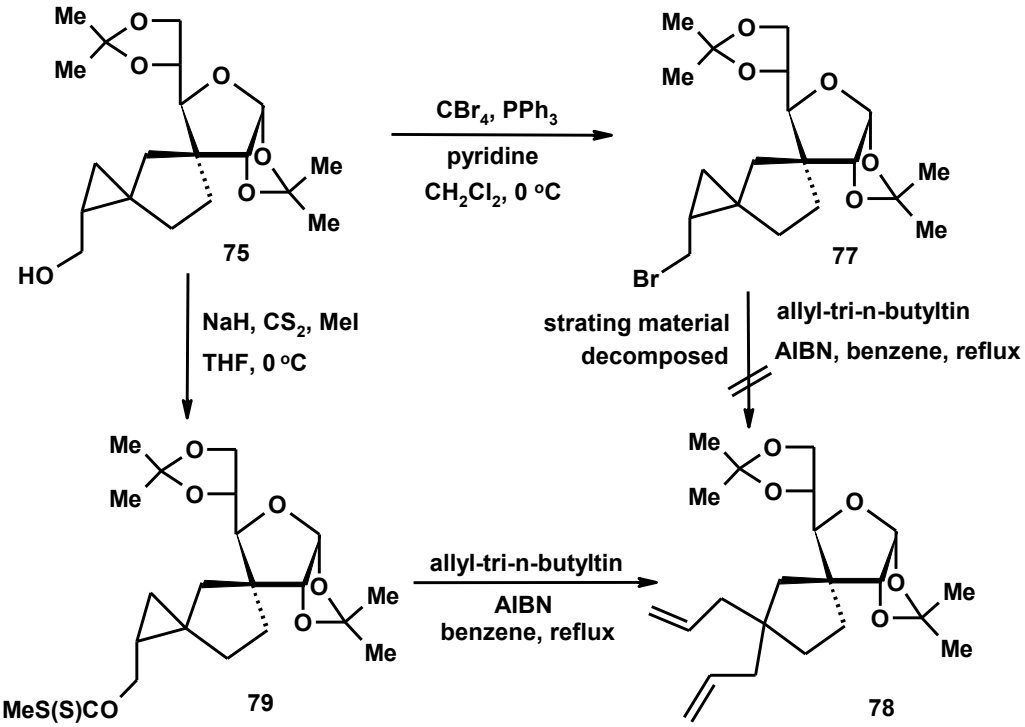
Mass spectrum (m/z 340 for M^+) and elemental analysis of compound **76** were also supportive of this structure. Cyclopropanation of this mixture of allylic alcohols **76** was accomplished by treatment with Et_2Zn and CH_2I_2 in CH_2Cl_2 at –20 °C (modified Simmons-Smith condition)[44] to get the cyclopropylmethyl alcohols **75**, which were found to be a mixture of four isomers arising from the two new chiral centers in cyclopropane ring. In the ^1H NMR spectrum of compound **75**, we observed resonances due to the cyclopropane protons in the upfield region with the absence of olefinic proton signals (Scheme **24**).

Scheme 24



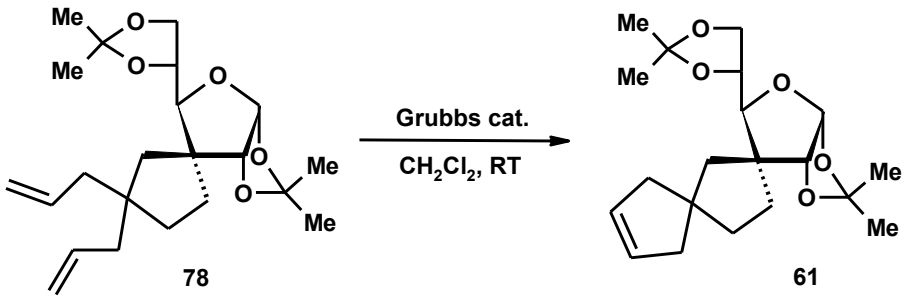
Mixture of cyclopropylmethyl alcohols **75** was converted to bromo derivatives **77** using PPh_3 and CBr_4 in CH_2Cl_2 at 0 °C and was subjected for radical mediated *gem*-diallylation under standard reaction conditions (allyltri-n-butyltin and AIBN in benzene at 80 °C). At this temperature, the cyclopropylmethyl bromo derivative decomposed and we were unable to isolate the desired diallyl compound **78**. With this unexpected thermal instability of the bromo compound as a radical precursor, we went for the xanthate derivative **79**, which was believed to be a stable radical precursor in this case. Accordingly, treatment of the alkoxide generated from alcohol **75** using NaH in THF at 0 °C with CS_2 and MeI provided compound **79**. This transformation was confirmed from spectral and elemental analysis. When this xanthate was subjected to radical mediated *gem*-diallylation reaction, diallyl derivative **78** formed as a single product. The ^1H NMR spectrum of compound **78** showed multiplets at 5.73 and 5.03 ppm integrating for two and four protons

Scheme 25



respectively for the allylic olefin protons. The ^{13}C NMR spectrum of compound **78** showed characteristic signals for the olefinic carbons at 135.4 and 117.4 ppm. Rest of the signals in ^{1}H and ^{13}C NMR spectra were in complete agreement with the assigned structure and elemental analysis of this compound was satisfactory (Scheme **25**).

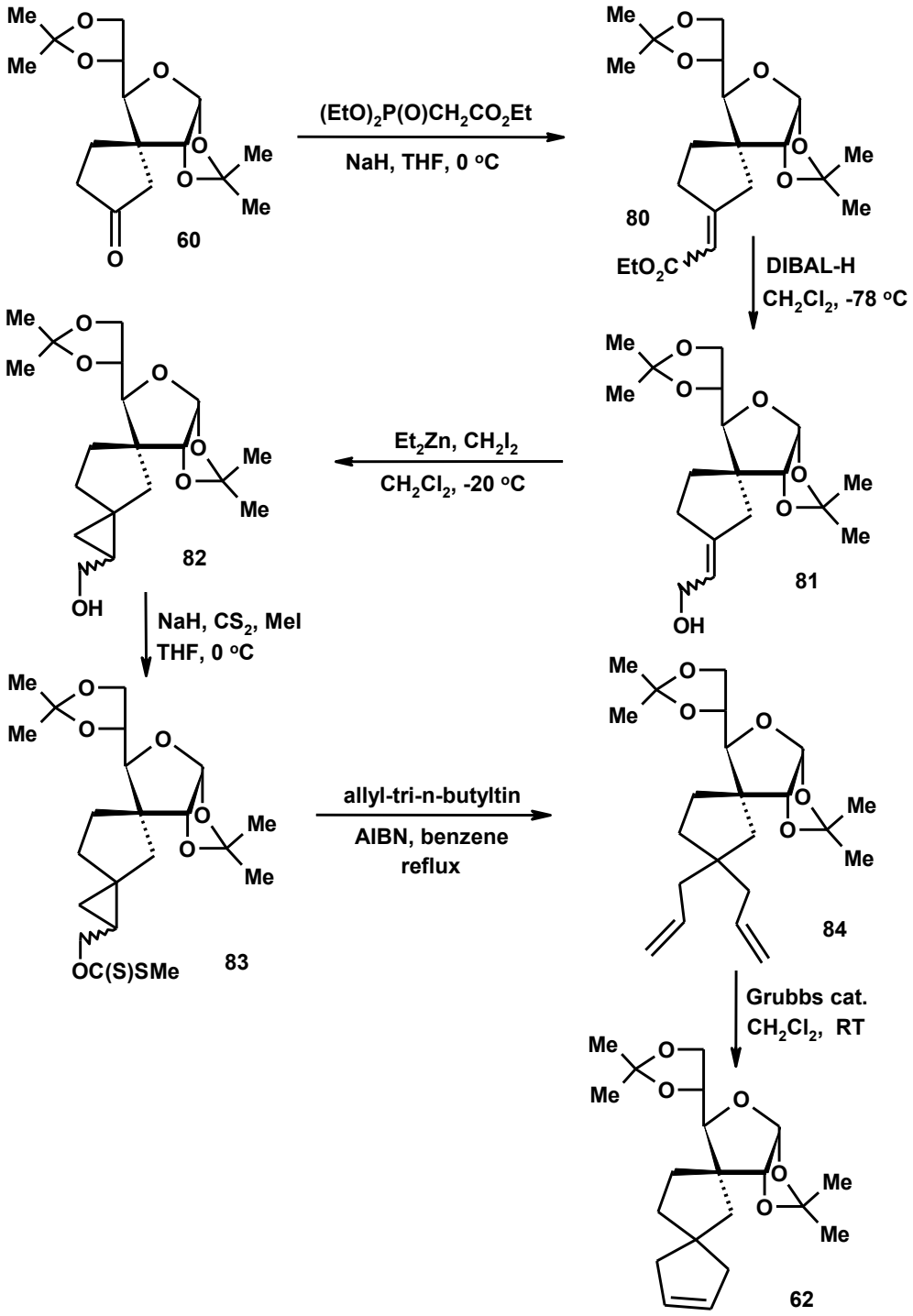
Scheme 26



Compound **78** on treatment with Grubbs 1st generation catalyst in CH_2Cl_2 at room temperature gave the desired bis-spirocyclic derivative **61** in 88 % isolated yield. Absence of resonance due to terminal olefinic protons in ^{1}H NMR spectrum confirmed the structure. Signals due to the internal disubstituted olefinic carbons in ^{13}C NMR spectrum were noticed at 129.5 and 130.0 ppm. Elemental analysis for this compound was satisfactory (Scheme **26**).

Similarly, spiroketone **60** was converted to the bis-spirocyclic derivative **62** by following the same sequence of reactions described above. Accordingly, ketone **60** was transformed into allylic alcohol **81** by Wittig-Horner olefination followed by reduction of the ester to the corresponding allylic alcohol using DIBAL-H. In the ^{1}H NMR spectrum of

Scheme 27



compound **81**, signals due to –C$\underline{H}_2$OH methylene and the olefin protons were observed at 4.10 (m) and 5.49 (m) ppm respectively. In the mass spectrum, a signal at m/z 340 for M^+ was observed. Synthesis of the diallyl derivative **84** was achieved in three steps from compound **81**. In the ^{1}H NMR spectrum of compound **84**, resonances due to the allylic olefin protons were noted at 5.73 (2H, m) and 5.01 (4H, m) ppm. Signals at 135.7, 135.9 ppm (-$\underline{C}$H=CH$_2$) and 117.0, 117.3 ppm (-CH=$\underline{C}$H$_2$) were observed in ^{13}C NMR spectrum of the *gem*-diallyl compound **84**. Finally, ring closing olefin metathesis of compound **84** gave the bis-spirocyclic compound **62** in 87 % yield. Absence of resonances due to the terminal olefinic protons revealed the formation of compound **62**. In the ^{13}C NMR spectrum, signals due to the internal olefinic carbons were noticed at 129.4 and 130.0 ppm. Elemental analyses for all these compounds were satisfactory (Scheme **27**).

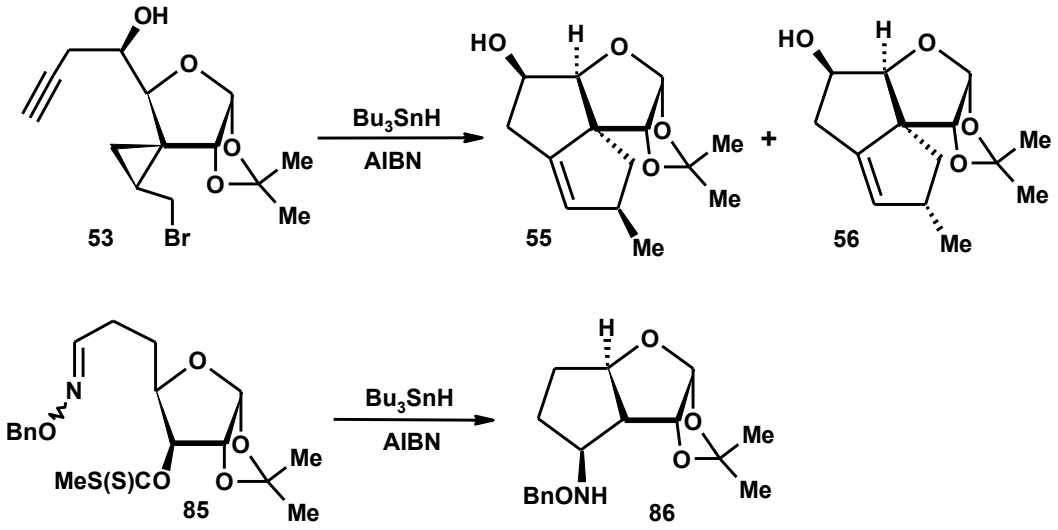
In conclusion, we have synthesized carbohydrate based novel spirocyclic ketones **59, 60** and bis-spirocyclic ring systems **61**, **62** using our radical mediated *gem*-diallylation/ring closing olefin metathesis strategy.[27] Since enantiopure carbocycles are important chiral building-blocks in natural product synthesis, these ketones should serve as synthetic precursors for spirocyclic compounds. In addition, synthesis of bis-spiro derivatives **61** and **62** shows that the diallyl followed by RCM methodology could be used for the synthesis of polycyclic spiro compounds.

Present Work

Part II: Synthesis of aminocarbocycle from carbohydrate based cyclopropylmethyl radical

Oximes are well known as radical acceptors in carbohydrate derived substrates for the synthesis of various five and six membered amino cyclitols.[45] Marco-Contelles has studied the off template diastereoselectivity in radical cyclization on furanose ring system using oxime as radical acceptor and synthesized aminocarbocycle **86** in good diastereoselectivity.[46] Carbohydrate based cyclopropylmethyl-homoallyl radical rearrangement was successfully employed for the synthesis of angularly fused oxa-triquinane ring systems **55** and **56** from these laboratories (Scheme **28**).[25,41] In continuation of our studies on carbohydrate based cyclopropylmethyl radicals,[27,28] we were interested to apply this radical cascade for the synthesis of oxaza-triquinanes by combining these two strategies.

Scheme 28



Accordingly, a substrate like **87**should undergo the radical rearrangement to give the stable tertiary radical **88**, which could further react with the suitably placed oxime in a 5-*exo*-trig fashion to generate the nitrogen centered radical **89** with the formation of two vicinal chiral centers. The main objective of this work was to study the stereochemical outcome of this step and further cyclization of the nitrogen centered radical for the synthesis of oxaza-triquinane **90** (Figure **6**).

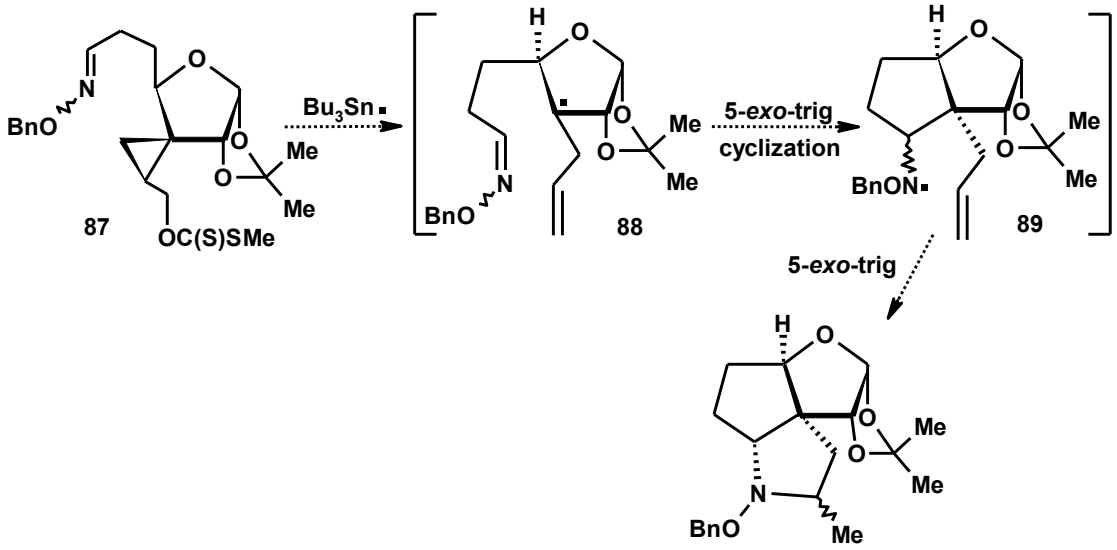
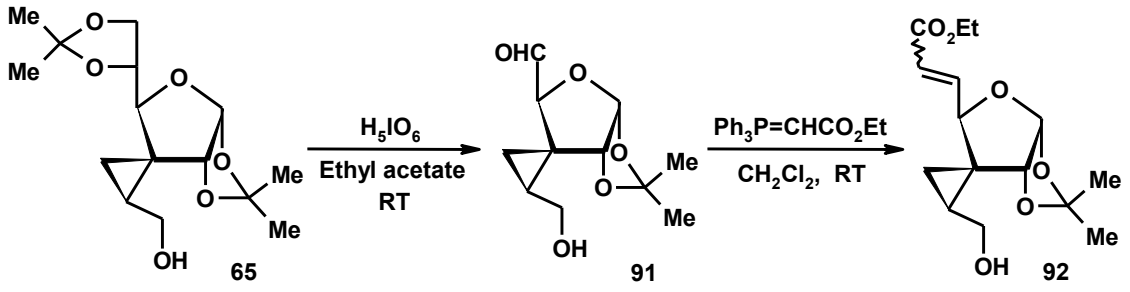


Figure 6: synthetic plan

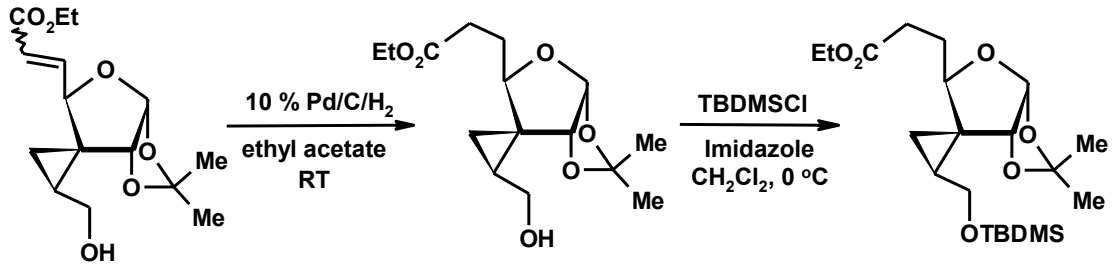
Our first target was to synthesize the radical precursor **87** in order to study the proposed radical cascade. Our synthetic endeavor started with the oxidative cleavage of the known compound **65**[47] to get the aldehyde **91** by treatment with periodic acid in ethyl acetate. The crude aldehyde obtained was used for the next step without further purification. Treatment of the aldehyde **91** with ylide PPh_3=$CHCO_2Et$ in CH_2Cl_2 at room temperature gave an inseparable mixture of α, β-unsaturated esters **92** in a ratio of 4:6. In ^{1}H NMR spectrum, signals due to ethyl protons were obsevered at 1.29 (-$CH_2C\underline{H}_3$) and 4.19 (-$C\underline{H}_2CH_3$) ppm integrating for three and two protons respectively and for olefinic protons, the resonances were at 5.76- 6.08 ppm and at 6.46 ppm as multiplets. Resonances observed in ^{13}C NMR spectrum at165.3 and164.8 ppm were assigned for the ester carbonyl carbons whereas the signals at 123.2, 123.6, 141.1 and 142.4 ppm were assigned for the olefinic carbons. IR (1718 cm^{-1} for C=O), mass spectral [m/z 283 for $(M\text{-}CH_3)^+$] and elemental analysis was in supportive of the assigned structure **92** (Scheme **29**).

Scheme 29



Compound **92** was reduced to the saturated ester **93** as a single product under hydrogen atmosphere (balloon pressure) using 10 % Pd/C in ethyl acetate. In the ^{1}H NMR spectrum, absence of signals due to the olefinic protons confirmed this transformation. Elemental analysis and mass spectrum [m/z 285 for $(M\text{-}CH_3)^+$] were as expected for the assigned structure. The free hydroxyl group in compound **93** was then protected as its silyl ether using TBDMSCl and imidazole in CH_2Cl_2 at 0 °C in 96 % yield. Presence of silyl group was confirmed from the signals observed at 0.07 (6H) and 0.90 (9H) ppm in ^{1}H NMR and at –5.5, 18.0, 25.7 ppm in the ^{13}C NMR spectra. A signal at m/z 399 for $(M\text{-}CH_3)^+$ was observed in mass spectrum of compound **94** (Scheme **30**).

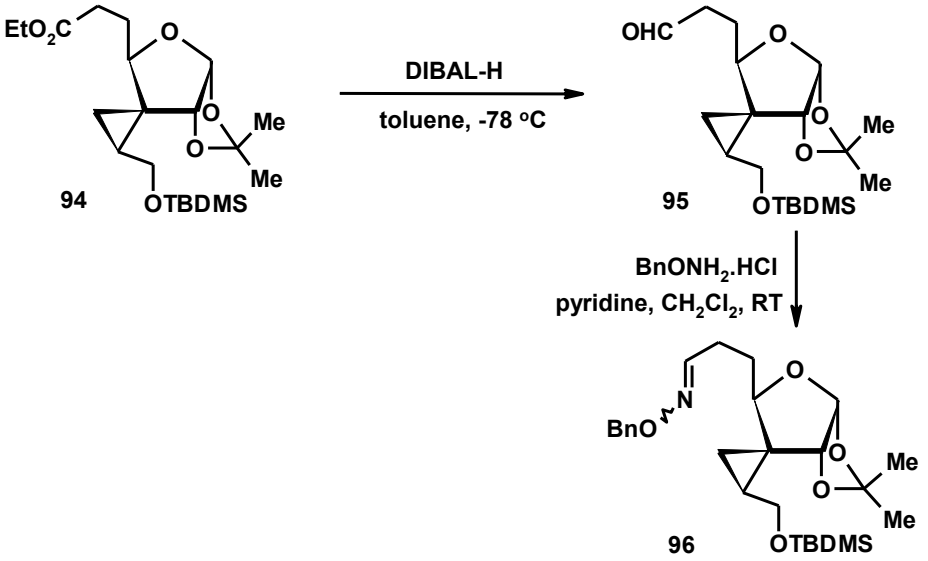
Scheme 30



92 **93** **94**

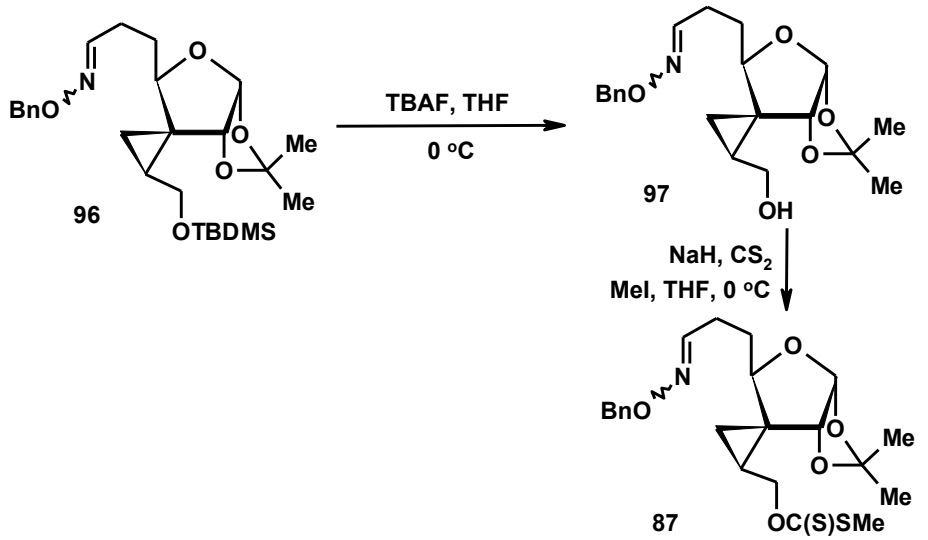
For the introduction of *O*-benzyl protected oxime in place of the carboxylic ester a two-step procedure was considered. Accordingly, ester **94** was reduced to the corresponding aldehyde **95** by treatment with DIBAL-H in toluene at –78 °C. This crude aldehyde on treatment with *O*-benzyl hydroxylamine hydrochloride and pyridine in CH_2Cl_2 at 0 °C gave a mixture of *syn* and *anti*-*O*-benzyl oxime derivative **96** in 82 % overall yield for two steps.[46] In the ^{1}H NMR spectrum, signals due to oxime protons (-C<u>H</u>=NOBn) were observed at 7.47 and 6.71 ppm as triplets whereas presence of two singlets at 5.03 and 5.09 ppm and a multiplet at 7.27-7.40 ppm confirmed the benzyl group. The signals for the oxime carbons were observed at 150.1 and 151.0 ppm in ^{13}C NMR spectrum. Mass [m/z 476 for $(M+H)^+$] and elemental analysis were in supportive of the assigned structure **96** (Scheme **31**).

Scheme 31



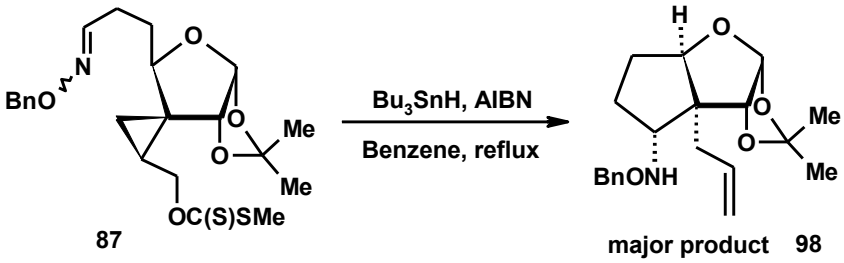
The silyl ether **96** was cleaved by TBAF in THF at 0 °C to get the free hydroxyl group in 91 % yield. Absence of signals for the silyl group in the ^{1}H NMR, ^{13}C NMR spectra and mass spectrum [m/z 362 for $(M+H)^{+}$] confirmed the formation of compound **97**. The alkoxide formed from the alcohol **97** and NaH in THF at 0 °C was treated with CS_2 and MeI to get the xanthate derivative **87**. The resonance observed at 2.58 ppm integrating for three protons was assigned for –SC<u>H</u>$_3$ protons. The down field shift of the -C<u>H</u>$_2$O- methylene protons from 3.25 and 4.04 ppm (in alcohol) to 4.49 and 4.99 ppm in ^{1}H NMR spectrum and a signal in ^{13}C NMR spectrum at 215.7 ppm (C=S) were in supportive of the assigned structure **87** (Scheme **32**).

Scheme 32



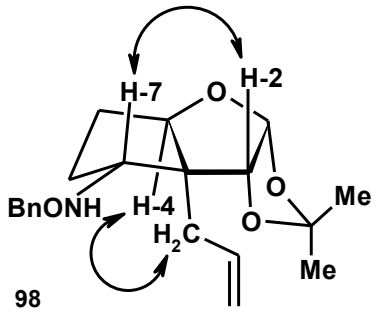
Having synthesized the radical precursor **87**, the next step was to subject this xanthate for the proposed radical cascade. Thus compound **87** on treatment with tri-n-butyltinhydride and AIBN in refluxing benzene for 8 h gave a mixture of products. Among those, the major product (compound **98**) was isolated in 23 % yield. ^{1}H NMR spectrum of compound **98** showed signals at 5.09 (C<u>H</u>$_2$=CHCH$_2$-) and 5.86 (CH$_2$=C<u>H</u>CH$_2$-) ppm which were characteristic of olefinic protons with the absence of signals for the oxime protons. A new signal at 3.41 ppm (triplet, J =7.4 Hz) was assigned for the >C<u>H</u>NHOBn proton. ^{13}C NMR spectrum clearly showed resonances for the allylic olefin carbons at 117.7 and 137.7 ppm. In mass spectrum m/z 346 for $(M+H)^+$ was observed (Scheme **33**).

Scheme 33



87 **major product 98**

Stereochemistry at the newly formed chiral centers was assigned based on NOESY experiment (Figure **7**). NOE between H-4 and the allylic methylene protons proved the stereochemistry at C-3 was (*S*) and the ring fusion was *cis*. Another NOE between H-2 and H-7 clearly indicated the stereochemistry at the carbon (C-7) having the amino functionality as (*R*)-configuration. From these studies structure of the major product was assigned as compound **98**.



98

Figure 7: NOE studies

Formation of compound **98** can be explained by the following mechanistic pathway (Figure **8**). Initially formed cyclopropylmethyl radical **99** rearranged to the more stable homoallylic tertiary radical as expected. This tertiary radical can have two different

conformations (**100** and **101**) for further (5-*exo*-trig) cyclization with the oxime. Based on steric considerations, it was clear that this *exo*-cyclization took place through the *re*-face attack (conformation **100**), where it avoids the steric hindrance between oxime and the furanose ring. It is worthy to mention here that the newly formed stereocenter at C-7 was (*R*), where as the amino carbocycle synthesized by Marco-Contelles had the (*S*) configuration.

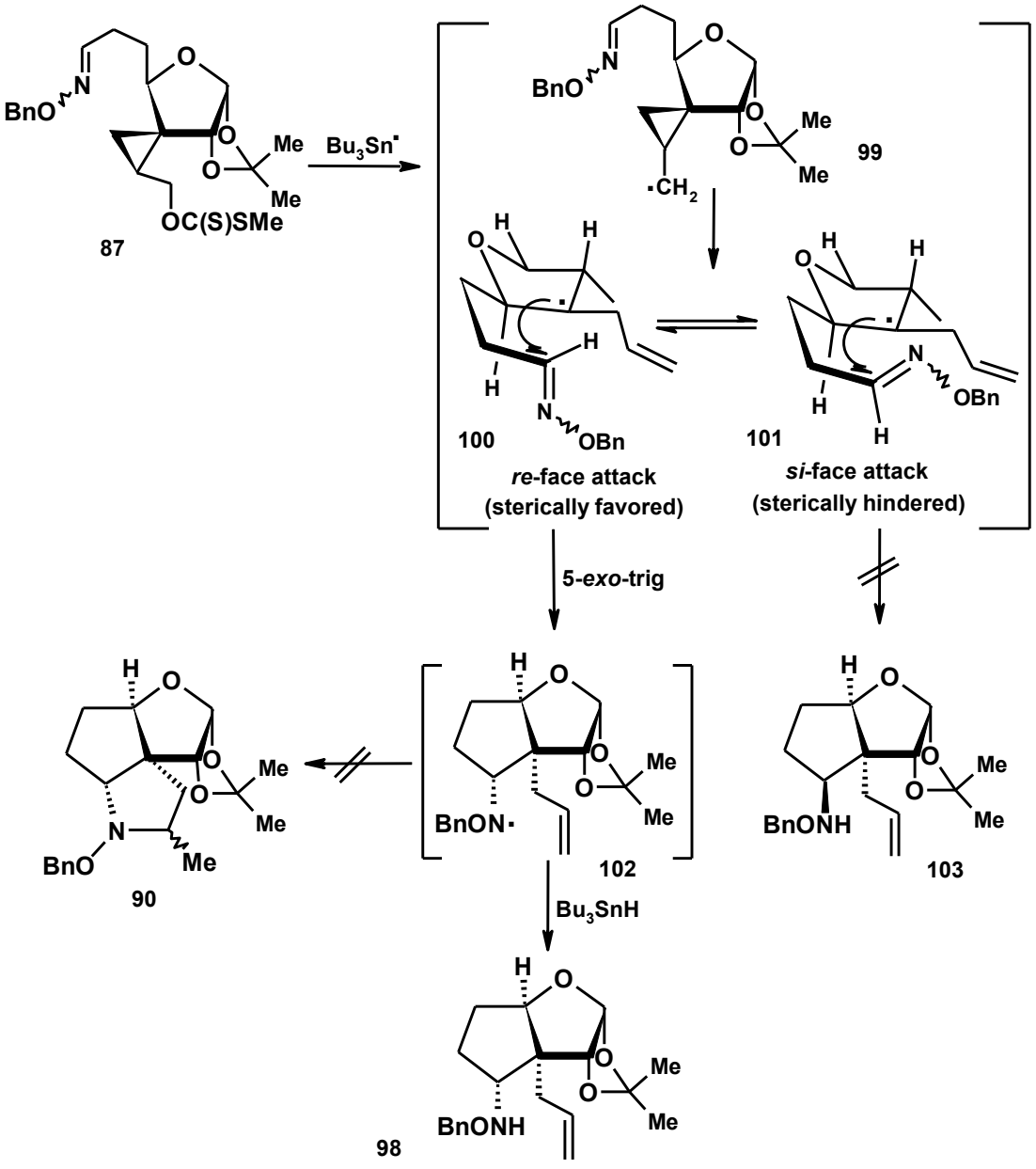


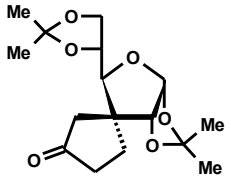
Figure 8: mechanism for the radical cascade

In conclusion, our attempted radical cascade for the synthesis of oxaza-triquinane yielded only the prematured aminocarbocycle **98**, by trapping the rearranged homoallyl radical with a suitably placed oxime in the radical precursor. Though compound **98** had the *syn* relation between the amine and olefin, which was required for further cyclization, it failed to produce the angularly fused aza-heterocycle. With the availability of reactions like, aminomercuration and iodoamination it could be possible to achieve this transformation.

(3*S*)-3-Deoxy-1,2:5,6-di-*O*-isopropylidene-3,3-*C*-(3-oxo-cyclopentane)-α-D-glucofuranose (59) and (3*R*)-3-Deoxy-1,2:5,6-di-*O*-isopropylidene-3,3-*C*-(3-oxo-cyclopentane)-α-D-glucofuranose (60):

To a solution of compound **45** (1.8 g, 6.1 mmol) in THF (10 mL) under N_2 was added $BH_3.Me_2S$ (0.6 mL, 6.7 mmol) at 0 ^oC. After 2 h, saturated aq. solution of sodium acetate and H_2O_2 (30% solution, 0.8 mL, 7.3 mmol) were added at –15 ^oC. Solvent was removed and the residue dissolved in ethyl acetate, washed with brine, dried (Na_2SO_4), and concentrated. The mixture of alcohols **67** (1.6 g) obtained after silica gel column chromatography (light petroleum and ethyl acetate -3:2) was added to a solution of $(COCl)_2$ (0.43 mL, 5.0 mmol) and Me_2SO (0.7 mL, 9.94 mmol) in CH_2Cl_2 (5 mL) under nitrogen at –78 ^oC. After stirring for 1 h at that temperature, Et_3N (2.3 mL, 16.5 mmol) was added. The reaction mixture was diluted with CH_2Cl_2, washed with water, brine, dried (Na_2SO_4) and concentrated. The crude product was purified on silica gel column with light petroleum and ethyl acetate (5:1) to afford the less polar ketone **59** followed by its diastereomer **60** (1.05 g, 56%, **59**: **60 =** 9:11) as colourless thick liquids.

Compound 59:



[α]$_D$ +89.1 (*c* 1.0, $CHCl_3$) [lit. **[α]$_D$** +73.7 (*c* 1.26, $CHCl_3$)]

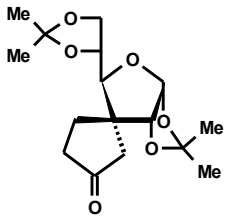
^{1}H NMR (500 MHz, $CDCl_3$): δ 1.33 (s, 6H), 1.42 (s, 3H), 1.55 (s, 3H), 1.95 (d, 1H, *J* = 17.8 Hz), 2.17-2.32 (m, 2H), 2.35- 2.47 (m, 2H), 2.50 (d, 1H, *J* = 17.8 Hz), 3.88 (d, 1H, *J* = 8.9 Hz), 3.95 (m, 2H), 4.16 (m, 1H), 4.24 (d, 1H, *J* = 3.7 Hz), 5.73 (d, 1H, *J* = 3.7 Hz).

^{13}C NMR (50 MHz, $CDCl_3$): δ 25.1, 26.4, 26.7, 26.9, 36.4, 43.0, 53.1, 68.8, 74.2, 82.2, 86.1, 104.1, 109.7, 112.2, 216.2

Anal. Calcd. for $C_{16}H_{24}O_6$ (MW. 312): C, 61.52; H, 7.74; Found C, 61.65; H, 7.46.

MS (EI) m/z: 297 $(M\text{-}CH_3)^+$

Compound 60:



$[\alpha]_D$ +32.3 (*c* 1.0, $CHCl_3$)

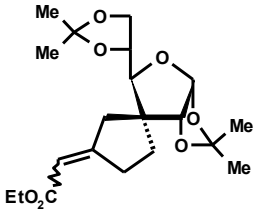
^{1}H NMR (500 MHz, $CDCl_3$): δ 1.31 (s, 6H), 1.38 (s, 3H), 1.52 (s, 3H), 1.65 (m, 1H), 2.17-2.32 (m, 2H), 2.46 (m, 1H), 2.54 (ABq, 2H, *J* = 17.5 Hz), 3.87 (d, 1H, *J* = 9.4 Hz), 3.95 (dd, 1H, *J* = 5.2, 8.6 Hz), 4.07 (ddd, 1H, *J* = 9.4, 5.2, 6.2 Hz), 4.18 (dd, 1H, *J* = 6.2, 8.6 Hz), 4.30 (d, 1H, *J* = 3.2 Hz), 5.79 (d, 1H, *J* = 3.2 Hz).

^{13}C NMR (50 MHz, $CDCl_3$): δ 24.9, 25.5, 26.1, 26.4, 26.6, 36.7, 41.8, 52.6, 68.6, 73.8, 81.8, 86.6, 103.9, 109.6, 111.9, 215.8

Anal. Calcd. for $C_{16}H_{24}O_6$ (MW. 312): C, 61.52; H, 7.74; Found C, 61.69; H, 7.56.

3 MS (EI) m/z: 297 $(M\text{-}CH_3)^+$

(3*R*)--Deoxy-1,2:5,6-di-*O*-isopropylidene-3,3-*C*-[3*E/Z*-(ethoxycarbonylmethylene)-cyclopentane]-α-D-glucofuranose (73):



Triethyl phosphonoacetate (0.25 mL, 1.3 mmol) was added to a suspension of NaH (48 mg, 1.2 mmol) in THF (5 mL) at 0 °C and stirred for 15 min at room temperature. Reaction mixture was cooled to 0 °C and a solution of aldehyde **59** (0.312 g, 1.0 mmol) in THF (5 mL) was added dropwise. After stirring for 30 min at room temperature, saturated

aq. NH_4Cl was added and the solvent removed under reduced pressure. The residue was taken in ethyl acetate, washed with water, brine, dried and concentrated. The crude product was purified on silica gel column by using light petroleum and ethyl acetate (3:2) to afford a mixture of *α,β*-unsaturated esters **73** (0.32 g, 84%) as a colourless paste.

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.22 (m, 9H), 1.31 (s, 3H), 1.43 (s, 3H), 2.02 (m, 3H) 2.55 (m, 2H), 2.95 (m, 1H), 3.84 (m, 2H), 4.04 (m, 4H), 5.63 (2d, 1H, *J* = 3.9 Hz), 5.76 (s, 1H).

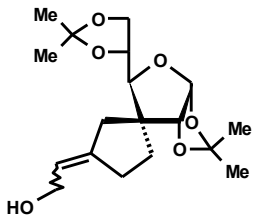
^{13}C NMR (50 MHz, $CDCl_3$): δ 14.1, 25.0, 26.2, 26.5, 26.7, 27.7, 29.4, 30.0, 32.3, 36.1, 39.1, 55.0, 56.1, 59.1, 68.5, 74.0, 74.1, 80.9, 81.2, 85.0, 85.5, 103.9, 109.1, 109.2, 111.6, 113.2, 113.4, 165.0, 165.8, 166.1

Anal. Calcd. for $C_{20}H_{30}O_7$ (MW. 382): C, 62.81; H, 7.91; Found C, 63.06; H, 8.13.
MS (EI) m/z: 382 (M^+)

Reaction of (3*R*)-3-Deoxy-1,2:5,6-di-*O*-isopropylidene-3,3-*C*-[3*E/Z*-(ethoxycarbonylmethylene)-cyclopentane]-α-D-glucofuranose (73) with trimethyl sulfoxoniun ylide

To a mixture of Me_3SOI (277 mg, 1.26 mmol) and NaH (50 mg, 1.26 mmol) was added dry DMSO (3 mL) at 10 ^oC and stirred for 15 min at room temperature. A solution of the unsaturated ester **73** (320 mg, 0.84 mmol) in DMSO (5 mL) was added to this reaction mixture and stirring continued. Under this reaction condition within 1 h, starting material was decomposed.

(3*R*)-3-Deoxy-1,2:5,6-di-*O*-isopropylidene-3,3-*C*-[3*E/Z*-(hydroxyethylidene)-cyclopentane]-α-D-glucofuranose (76):



DIBAL-H (2.0 M solution in toluene, 1.0 mL, 2.0 mmol) was added to a solution of ester **73** (0.32 g, 0.84 mmol) in CH_2Cl_2 (8 mL) at –78 ^oC. After 30 min, saturated aq. NH_4Cl was added at the same temperature and the biphasic mixture was separated, aq layer was extracted with CH_2Cl_2 (2x 10 mL), combined organic layer was washed with brine, dried and concentrated. The crude product was passed through a short bed of silica gel eluting with light petroleum and ethyl acetate (1:1) to give the corresponding allylic alcohol **76** (0.26 g, 91%).

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.30, 1.32, 1.40, 1.52 (4s, 12H), 1.88-2.07 (m, 3H), 2.29-2.60 (m, 3H), 3.85-4.17 (m, 7H), 5.58 (m, 1H), 5.70 (m, 1H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 25.2, 25.9, 26.3, 26.6, 26.8, 27.2, 27.5, 30.2, 32.6, 37.4, 55.0, 55.8, 59.9, 60.1, 68.4, 74.2, 81.1, 85.2, 85.4, 103.9, 109.2, 111.5, 121.5, 143.6

Anal. Calcd. for $C_{18}H_{28}O_6$ (MW. 340): C, 63.51; H, 8.29; Found C, 63.59; H, 8.13.
MS (EI) m/z: 340 (M^+)

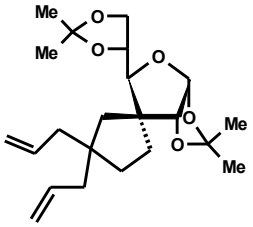
Reaction of (3*R*)-3-Deoxy-1,2:5,6-di-*O*-isopropylidene-3,3-*C*-[3*E/Z*-(bromoethylidene)-cyclopentane]-α-D-glucofuranose (77) with allyl tri-n-butyltin:

To a solution of allylic alcohol **76** (337 mg, 0.98 mmol) in dry CH_2Cl_2 (6 mL) under Ar at –20 ^oC, was added a 1.0 M solution of Et_2Zn (2.9 mL, 2.9 mmol) and CH_2I_2 (0.47 mL, 5.9 mmol). After 12 h, the reaction was quenched with ice and partitioned between CH_2Cl_2 and water. Organic layer was dried, concentrated and the residue passed through a short column of silica gel using light petroleum and ethyl acetate as eluent (1:1) to afford a mixture of cyclopropylmethyl alcohol **75** (220 mg) as a colourless paste. To a solution of this cyclopropylmethyl alcohol (220 mg, 0.62 mmol) in CH_2Cl_2 (10 mL) and pyridine (1 mL) was added CBr_4 (410 mg, 1.24 mmol) and PPh_3 (325 mg, 1.24 mmol) at 0 ^oC and stirred for 1 h. After removing solvent, the residue was purified by silica gel column chromatography using light petroleum and ethyl acetate (9:1) to give the corresponding bromide derivative **77** as a colourless paste (210 mg, 51% for two steps). A solution of this cyclopropylmethyl bromide (210 mg, 0.5 mmol), allyl tri-n-butyltin (330 mg, 1.0 mmol)

and AIBN (20 mg) in benzene (5 mL) was degassed with argon and refluxed. Within 3 h, starting material decomposed.

(3*R*)-3-Deoxy-1,2;5,6-di-*O*-isopropylidene-3,3-*C*-(3,3-*C*-diallyl-cyclopentane)-α-D-glucofuranose (78)

To a solution of cyclopropylmethyl alcohol **75** (85 mg, 0.24 mmol) in THF (4 mL) was added 19 mg of NaH (0.48 mmol) at 0 °C under nitrogen atmosphere. After stirring for 15 min, 0.06 mL (0.96 mmol) of CS_2 and 0.08 mL (1.2 mmol) of MeI were added at 15 min interval and stirring continued for 30 min. After quenching the reaction with aq NH_4Cl solution, THF was removed under reduced pressure. The residue was taken in ethyl acetate and washed with water, dried, concentrated and purified over silica gel column chromatography using light petroleum and ethyl acetate (4:1) as eluent to give the xanthate derivative **79** (90 mg). A solution of this xanthate (90 mg, 0.2 mmol), allyl tri-n-butyltin (0.13 mL, 0.4 mmol) and AIBN (5 mg) in benzene (4 mL) was degassed and refluxed under Ar for 12 h. Benzene was removed under reduced pressure, diluted with ether and stirred with an aq. solution of KF for 3 h and then filtered. The filtrate was dried over Na_2SO_4, concentrated and purified by silica gel column chromatography using light petroleum and ethyl acetate (9:1) to give the *gem*-diallyl derivative **78** (26 mg, 30% overall yield for two steps).



$[\alpha]_D$ +22.8 (*c* 1.1, $CHCl_3$)

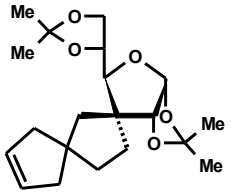
^{1}H NMR (200 MHz, $CDCl_3$): δ 0.97 (d, 1H, *J* = 14.4 Hz), 1.32, 1.34, 1.40, 1.50 (4s, 12H), 1.55-1.67 (m, 2H), 1.75 (d, 1H, *J* = 14.4 Hz), 1.83-2.03 (m, 2H), 2.15 (d, 4H, *J* = 6.4 Hz), 3.80-3.93 (m, 2H), 4.01-4.20 (m, 2H), 4.26 (d, 1H, *J* = 3.4 Hz), 4.94-5.10 (m, 4H), 5.62 (d, 1H, *J* = 3.4 Hz), 5.66-5.92 (m, 2H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 25.5, 26.5, 26.8, 27.1, 27.9, 35.5, 39.2, 43.3, 43.9, 45.7, 56.2, 69.1, 74.0, 82.8, 87.8, 104.1, 109.4, 111.9, 117.4, 135.4

Anal. Calcd. for $C_{22}H_{34}O_5$ (MW. 378): C, 69.81; H, 9.05; Found C, 70.03; H, 9.13.

(3*R*)-3-Deoxy-1,2;5,6-di-*O*-isopropylidene-3,3-*C*-[3,3-*C*-(3-cyclopentenyl)-cyclopentane)-α-D-glucofuranose (61):

A solution of *gem*-diallyl compound **78** (22 mg, 0.06 mmol) and Grubbs catalyst (4 mg) in CH_2Cl_2 (4 mL) was stirred at room temperature for 3 h. Solvent was removed under reduced pressure and the crude product purified by column chromatography on silica gel using light petroleum and ethyl acetate (9:1) to give the spiro cyclopentenyl derivative **61** (18 mg, 88%), as a colourless paste.



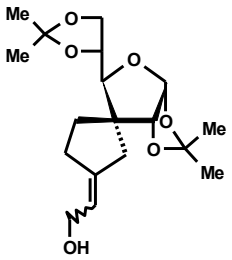
$[\alpha]_D$ +22.7 (*c* 0.5, $CHCl_3$).

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.22 (d, 1H, *J* = 15.1Hz), 1.32, 1.35, 1.41, 1.51 (4s, 12H), 1.55-1.74 (m, 2H), 1.82-2.13 (m, 3H), 2.34 (m, 4H), 3.88 (m, 2H), 4.11 (m, 2H), 4.29 (d, 1H, *J* = 3.5 Hz), 5.62 (d, 1H, *J* = 3.5 Hz), 5.65 (s, 2H)

^{13}C NMR (50 MHz, $CDCl_3$): δ 25.6, 26.6, 26.8, 27.2, 28.8, 39.5, 43.7, 47.0, 47.3, 50.3, 55.9, 69.1, 74.2, 83.1, 88.4, 104.3, 109.4, 111.8, 129.5, 130.0

Anal. Calcd. for $C_{20}H_{30}O_5$ (MW. 350): C, 68.55; H, 8.63; Found C, 68.30; H, 8.73.

(3*S*)-3-Deoxy-1,2:5,6-di-*O*-isopropylidene-3,3-*C*-[3*E/Z*-(hydroxyethylidene)-cyclopentane]-α-D-glucofuranose (81)



Ketone **60** (380 mg) was converted to a mixture of allylic alcohols **81** by following the two-step process described for compound **76**, in 70% (289 mg) overall yield.

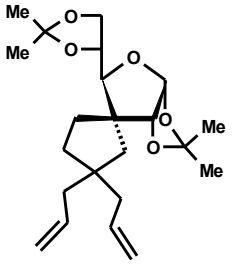
^{1}H NMR (200 MHz, $CDCl_3$): δ 1.28 (s, 3H), 1.30 (s, 3H), 1.38 (s, 3H), 1.49 (s, 3H), 1.80-2.02 (m, 2H), 2.24-2.72 (m, 4H), 3.28 (br s, 1H), 3.87 (m, 2H), 3.97-4.17 (m, 5H), 5.49 (m, 1H), 5.69 (d, 1H, J = 3.6 Hz).

^{13}C NMR (50 MHz, $CDCl_3$): δ 24.8, 25.9, 26.2, 26.4, 26.5, 27.6, 27.8, 30.9, 35.2, 54.7, 55.2, 59.5, 68.0, 73.7, 73.9, 80.6, 81.0, 84.9, 85.3, 103.7, 108.9, 111.2, 120.3, 120.5, 142.2

Anal. Calcd. for $C_{18}H_{28}O_6$ (MW. 340): C, 63.51; H, 8.29; Found C, 63.73; H, 8.36.
MS (EI) m/z: 340 (M^+)

(3*S*)-3-Deoxy-1,2;5,6-di-*O*-isopropylidene-3,3-*C*-(3,3-*C*-diallyl-cyclopentane)-α-D-glucofuranose (84):

Compound **84** was prepared from allylic alcohol **81** (26% overall yield for three steps) by following the same procedure described for compound **78**.



$[\alpha]_D$ +47.6 (*c* 1.0, $CHCl_3$)

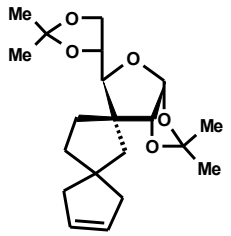
^{1}H NMR (200 MHz, $CDCl_3$): δ 1.31, 1.33, 1.39, 1.49 (4s, 12H), 1.57 (m, 3H) 1.76-1.92 (m, 3H), 2.11 (d, 4H, *J* = 7.3 Hz), 3.75-3.93 (m, 2H), 3.98- 4.17 (m, 3H), 4.98-5.08 (m, 4H), 5.63 (d, 1H, *J* = 3.4 Hz), 5.72-5.93 (m, 2H)

^{13}C NMR (50 MHz, $CDCl_3$): δ 25.7, 26.5, 26.8, 27.2, 29.0, 35.9, 38.0, 43.9, 44.1, 44.3, 55.9, 69.1, 74.2, 82.6, 87.7, 104.4, 109.4, 111.6, 117.0, 117.3, 135.7, 135.9

Anal. Calcd. for $C_{22}H_{34}O_5$ (MW. 378) : C, 69.81; H, 9.05; Found C, 69.82; H, 9.15.

(3*S*)-3-Deoxy-1,2;5,6-di-*O*-isopropylidene-3,3-*C*-[3,3-*C*-(3-cyclopentenyl)-cyclopentane]-α-D-glucofuranose (62):

Following the procedure described for compound **61**, diallyl compound **84** (30 mg, 0.08 mmol) was converted to the bis-spiroderivative **62** using Grubbs' catalyst (4 mg) in CH_2Cl_2 (5 mL) in 87% (24 mg) yield.



$[\alpha]_D$ +38.9 (*c* 0.85, $CHCl_3$)

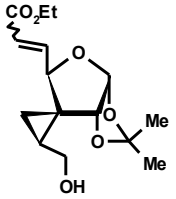
^{1}H NMR (200 MHz, $CDCl_3$): δ 1.32, 1.34, 1.40, 1.49 (4s, 12H), 1.55-1.87 (m, 4H), 1.93 (d, 1H, *J* = 14.2 Hz), 2.11 (d, 1H, *J* = 14.2 Hz), 2.20-2.41 (m, 4H), 3.79-3.94 (m, 2H), 4.04-4.20 (m, 3H), 5.63 (m, 3H)

^{13}C NMR (50 MHz, $CDCl_3$): δ 25.6, 26.5, 26.8, 27.1, 30.0, 39.9, 42.2, 46.6, 47.3, 49.0, 55.5, 69.0, 74.1, 82.9, 88.8, 104.3, 109.4, 111.6, 129.4, 130.0

Anal. Calcd. for $C_{20}H_{30}O_5$ (MW. 350): C, 68.55; H, 8.63; Found C, 68.80; H, 8.80.

Ethyl-3,5,6-trideoxy-3,3-*C*-[(*S*)-(hydroxymethyl)ethylene]-1,2-isopropylidene-α-D-*erythro*-hept-5*E/Z*-eno-1,4-furanos-7-onate (92)

Periodic acid (2.92 g, 12.8 mmol) was added to a solution of compound **65** (3.2 g, 10.7 mmol) in ethyl acetate (20 mL) and stirred for 1h at room temperature. The solid formed was filtered, washed with ethyl acetate and the combined washings were concentrated to dryness. This crude aldehyde **91** was dissolved in CH_2Cl_2 (10 mL) and stirred for 4 h with PPh_3=$CHCO_2Et$ (4.45 g, 12.8 mmol) at room temperature. After removing solvent, the crude material was chromatographed on silica gel column using light petroleum and ethyl acetate (3:2) to give a mixture of α, β-unsaturated esters **92** (1.97 g, 62% for two steps) as a colourless oil.



^{1}H NMR (200 MHz, $CDCl_3$): δ 0.42 (t, 0.4H, *J* = 5.8 Hz), 0.5 (t, 0.6H, *J* = 5.8 Hz), 0.79 (dd, 0.4H, *J* = 5.4, 8.9 Hz), 0.89 (dd, 0.6H, *J* = 5.6, 8.8 Hz), 1.29 (t, 3H, *J* = 7.1 Hz and m, 1H), 1.35 (s, 3H), 1.59 (s, 1.8H), 1.63 (s, 1.2H), 3.29 (t, 1H, *J* = 11.2 Hz), 4.04 (m, 1H), 4.19 (q, 2H, *J* = 7.1 Hz), 4.49 (d, 1H, *J* = 3.9 Hz), 4.93 (d, 0.6H, *J* = 5.6 Hz), 5.76-6.08 (m, 2.8H), 6.46 (dd, 0.6H, *J* = 5.7, 15.7 Hz).

^{13}C NMR (50 MHz, $CDCl_3$): δ 11.3, 11.9, 13.9, 18.4, 18.6, 26.1, 26.4, 26.6, 26.7, 34.0, 34.6, 60.3, 64.1, 64.3, 74.9, 78.1, 85.0, 85.3, 104.5, 104.7, 111.7, 123.2, 123.6, 141.1, 142.4, 164.8, 165.3

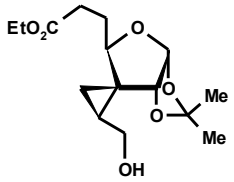
IR ($CHCl_3$, cm^{-1}): 3518, 1718, 1663, 1384, 1163 and 1045.

MS (EI) m/z: 283 $(M-CH_3)^+$

Anal. Calcd. for $C_{15}H_{22}O_6$ (MW. 298): C, 60.39; H, 7.43; Found C, 60.19; H, 7.31.

Ethyl-3,5,6-trideoxy-3,3-*C*-[(*S*)-(hydroxymethyl)ethylene]-1,2-isopropylidene-α-D-*erythro*-hepto-1,4-furanos-7-onate (93)

Unsaturated esters **92** (1.6 g, 5.4 mmol) and 10 % Pd/C (50 mg) in ethyl acetate (5 mL) was stirred for 6 h under hydrogen atmosphere (ballon pressure). After filtration through Celite, the solution was concentrated and passed through a short bed of silica gel (light petroleum and ethyl acetate, 3:2) to afford the saturated ester **93** (1.49 g, 93%) as colourless oil.



[α]$_D$ +88.8 (c 1.1, $CHCl_3$)

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.48 (t, 1H, *J* = 5.8 Hz), 1.03 (dd, 1H, *J* = 5.6, 9.0 Hz), 1.25 (t, 3H, *J* = 7.1 Hz), 1.33 (s, 3H), 1.37 (m, 3H), 1.57 (s, 3H), 2.29-2.65 (m, 2H), 3.05 (dd, 1H, *J* = 2.0, 11.7 Hz), 3.26 (ddd, 1H, *J* = 2.0, 10.3, 12.2 Hz), 4.05 (m, 1H), 4.12 (q, 2H, *J* = 7.1 Hz), 4.32 (dd, 1H, *J* = 3.9, 8.5 Hz), 4.44 (d, 1H, *J* = 4.0 Hz), 5.89 (d, 1H, *J* = 4.0 Hz).

^{13}C NMR (75 MHz, $CDCl_3$): δ 11.1, 13.5, 18.9, 24.7, 25.7, 26.0, 30.4, 33.7, 59.5, 63.7, 77.3, 85.2, 103.6, 110.5, 172.2

IR ($CHCl_3$, cm^{-1}): 3483, 1728, 1165 and 1053.

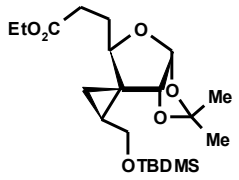
MS (EI) m/z: 285 $(M\text{-}CH_3)^+$

Anal. Calcd. for $C_{15}H_{24}O_6$ (MW. 300): C, 59.98; H, 8.05; Found C, 59.82; H, 8.21.

Ethyl-3,5,6-trideoxy-3,3-*C*-[(*S*)-(*tert*-butyldimethylsilyloxymethyl)ethylene]-1,2-isopropylidene-α-D-*erythro*-hepto-1,4-furanos-7-onate (94)

TBSCl (1.16 g, 7.7 mmol) was added to a mixture of the alcohol **93** (2.1 g, 7.0 mmol) and imidazole (570 mg, 8.4 mmol) in CH_2Cl_2 (10 mL) at 0 °C. After 1 h the solid was filtered and washed with CH_2Cl_2. Combined washings were concentrated and

chromatographed over silica gel, eluting with light petroleum and ethyl acetate (4:1) to afford the silylether **94** (2.78 g, 96%) as a colourless thick liquid.



[α]$_D$ +112.9 (c 1.3, $CHCl_3$)

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.07 (s, 6H), 0.56 (t, 1H, *J* = 5.6 Hz), 0.90 (s, 9H), 0.93 (m, 1H), 1.10 (m, 1H), 1.25 (t, 3H, *J* = 7.1 Hz), 1.27 (s, 3H), 1.32-1.43 (m, 2H), 1.50 (s, 3H), 2.25-2.65 (m, 2H), 3.54 (dd, 1H, *J* = 6.5, 10.7 Hz), 4.03 (dd, 1H, *J* = 4.2, 10.7 Hz), 4.11 (q, 2H, *J* = 7.1 Hz), 4.24 (dd, 1H, *J* = 4.2, 8.1 Hz), 4.33 (d, 1H, *J* = 3.9 Hz), 5.79 (d, 1H, *J* = 3.9 Hz).

^{13}C NMR (50 MHz, $CDCl_3$): δ –5.5, 11.1, 14.0, 18.0, 19.0, 25.2, 25.7, 26.4, 26.8, 30.9, 33.2, 59.8, 62.4, 77.6, 85.9, 104.0, 110.8, 172.5

I R ($CHCl_3$, cm^{-1}): 2956, 1729, 1471, 1166 and 1084.

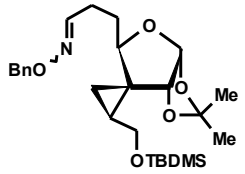
MS (EI) m/z: 399 $(M-CH_3)^+$

Anal. Calcd. for $C_{21}H_{38}O_6Si$ (MW. 414): C, 60.84; H, 9.24; Found C, 60.63; H, 9.17.

3,5,6-Trideoxy-3,3-*C*-[(*S*)-(*tert*-butyldimethylsilyloxymethyl)ethylene]-1,2-isopropylidene-7*E/Z*-(*O*-benzyloximino)-α-D-*erythro*-hepto-1,4-furanose (96)

A 2.3 M solution of DIBAL-H (1.8 mL, 4.06 mmol) was added to the ester **94** (1.4 g, 3.38 mmol) in toluene (20 mL) at –78 °C. After 1 h the reaction was quenched by the addition of 1 mL of methanol and excess of aq sodium potassium tartrate solution and stirred for 1 h at room temperature. Layers were separated and aq layer was extracted with CH_2Cl_2. Combined organic layer was dried over Na_2SO_4 and concentrated to give the crude aldehyde **95**. To a solution of this aldehyde (1.2 g) in dry CH_2Cl_2 (10 mL) was added 2 mL of pyridine and 636 mg (4.0 mmol) of *O*-benzyl hydroxylamine hydrochloride at 0 °C and stirred for 3 h at room temperature. After removing solvent under reduced pressure,

the residue was purified by silica gel column chromatography using light petroleum and ethyl acetate (6:1) to give a mixture of oximes **96** (*syn: anti*-4: 6) as a colourless thick paste in 82% (1.31 g) yield.



^{1}H NMR (200 MHz, $CDCl_3$): δ 0.07 (s, 6H), 0.55 (t, 1H, *J* = 5.5 Hz), 0.90 (s, 9H and m, 1H), 0.99-1.35 (m, 6H), 1.51 (s, 3H), 2.17-2.58 (m, 2H), 3.53 (dd, 1H, *J* = 6.7, 10.8 Hz), 4.04 (dd, 1H, *J* = 4.3, 10.8 Hz), 4.27 (m, 1H), 4.33 (d, 1H, *J* = 3.8 Hz), 5.03 (s, 1.2H), 5.09 (s, 0.8H), 5.81 (d, 1H, *J* = 3.8 Hz), 6.71 (t, 0.4H, *J* = 5.5 Hz), 7.27-7.40 (m, 5H), 7.47 (t, 0.6H, *J* = 5.8 Hz).

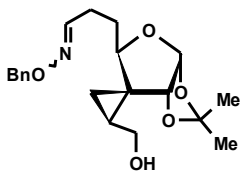
^{13}C NMR (50 MHz, $CDCl_3$): δ –5.5, 10.9, 18.0, 18.8, 23.0, 25.7, 26.2, 26.5, 26.7, 33.0, 62.4, 75.2, 75.3, 77.6, 77.8, 85.5, 103.8, 110.8, 127.3, 127.4, 127.6, 127.9, 128.0, 137.5, 137.8, 150.1, 151.0

I R ($CHCl_3$, cm^{-1}): 3066, 1471, 1454, 1253, 1165 and 1083.

MS (ESI) m/z: 476 $(M+H)^+$

Anal. Calcd. for $C_{26}H_{41}NO_5Si$ (MW. 475): C, 65.65; H, 8.69; N, 2.94; Found C, 65.78; H, 8.59; N, 3.05.

3,5,6-Trideoxy-3,3-*C*-[(*S*)-(hyroxymethyl)ethylene]-1,2-isopropylidene-7*E/Z*-(*O*-benzyloximino)-α-D-*erythro*-hepto-1,4-furanose (97)



A 1.0 M solution of TBAF (1.5 mL, 1.5 mmol) was added to the silyl ether **96** (650 mg, 1.37 mmol) in THF (5 mL) at 0 °C. After 1 h, solvent was removed under reduced pressure and purified by silica gel column chromatography using light petroleum and ethyl acetate (7:3) to afford the alcohol **97** as a colourless thick paste in 91% (450 mg) yield.

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.46 (t, 1H, *J* = 5.8 Hz), 0.96 (m, 1H), 1.24 (m, 3H), 1.33 (s, 3H), 1.56 (s, 3H), 2.18-2.56 (m, 2H), 3.04 (d, 1H, *J* = 11.2 Hz), 3.26 (t, 1H, *J* = 11.2 Hz), 4.04 (dt, 1H, *J* = 4.2, 11.2 Hz), 4.33 (2t, 1H, *J* = 2.8 Hz), 4.43 (d, 1H, *J* = 4.0 Hz), 5.02 (s, 1.2H), 5.08 (s, 0.8H), 5.88 (d, 1H, *J* = 4.0 Hz), 6.70 (t, 0.4H, *J* = 5.6 Hz), 7.28-7.37 (m, 5H), 7.46 (t, 0.6H, *J* = 5.7 Hz).

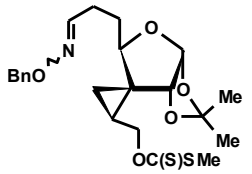
^{13}C NMR (50 MHz, $CDCl_3$): δ 11.6, 19.4, 23.0, 26.3, 26.4, 26.6, 26.8, 34.4, 64.5, 75.4, 75.6, 77.9, 78.1, 85.6, 104.0, 111.1, 127.5, 127.8, 128.0, 128.1, 137.6, 137.9, 149.9, 150.7

IR ($CHCl_3$, cm^{-1}): 3521, 1454, 1165 and 1047.

MS (ESI) m/z: 362 $(M+H)^+$

Anal. Calcd. for $C_{20}H_{27}NO_5$ (MW. 361): C, 66.46; H, 7.53; N, 3.88; Found C, 66.28; H, 7.34; N, 4.08.

3,5,6-Trideoxy-3,3-*C*-{(*S*)-[(S-methyl-dithiocarbonato)methyl]ethylene}-1,2-isopropylidene-7*E/Z*-(*O*-benzyloximino)-α-D-*erythro*-hepto-1,4-furanose (87)



To a solution of cyclopropylmethyl alcohol **97** (400 mg, 1.1 mmol) in THF (5 mL) was added NaH (88 mg, 2.2 mmol) at 0 °C under nitrogen atmosphere. After stirring for 15 min 0.27 mL (4.4 mmol) of CS_2 and 0.41 mL (6.6 mmol) of MeI were added at 15 min interval and stirring continued for 30 min. Reaction was quenched by the addition of aq NH_4Cl solution, THF was removed, and the residue was partitioned between ethyl acetate

and water. Organic layer was dried, concentrated and purified over silica gel column chromatography using light petroleum and ethyl acetate (9:1) as eluent to give a mixture of xanthate derivative **87** as pale yellow paste in 90% (449 mg) yield.

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.66 (t, 1H, *J* = 5.8 Hz), 1.07 (m, 1H), 1.14-1.45 (m, 6H), 1.52 (s, 3H), 2.19-2.55 (m, 2H), 2.58 (s, 3H), 4.31 (m, 1H), 4.34 (d, 1H, *J* = 3.9 Hz), 4.49 (dd, 1H, *J* = 8.8, 11.7 Hz), 4.99 (dd, 1H, *J* = 5.6, 11.7 Hz), 5.03 (s, 1.2H), 5.09 (s, 0.8H), 5.86 (d, 1H, *J* = 3.9 Hz), 6.72 (t, 0.4H, *J* = 5.5 Hz), 7.28-7.39 (m, 5H), 7.48 (t, 0.6H, *J* = 5.6 Hz).

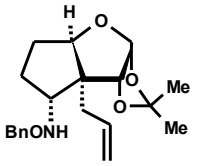
^{13}C NMR (50 MHz, $CDCl_3$): δ 13.0, 15.4, 18.9, 23.0, 26.4, 26.5, 26.6, 26.8, 34.5, 74.8, 75.4, 75.6, 77.4, 77.6, 85.5, 104.1, 111.4, 127.6, 127.8, 128.1, 128.2, 137.7, 137.9, 149.9, 150.7, 215.7

IR ($CHCl_3$, cm^{-1}): 3064, 2988, 2930, 1454, 1165 and 1064.

MS (EI) m/z: 436 $(M\text{-}CH_3)^+$

Anal. Calcd. for $C_{22}H_{29}NO_5S_2$ (MW. 451): C, 58.51; H, 6.47; N, 3.10; S, 14.20; Found C, 58.38; H, 6.20; N, 3.24; S, 14.02.

(1*S*,2*R*,6*R*,8*R*,11*R*)-1-(3-Propenyl)-11-(*O*-benzyloxyamino)-4,4-dimethyl-3,5,7-trioxatricyclo-[6.3.0.0^{2,6}]-undecane (98)



A solution of xanthate **87** (380 mg, 0.84 mmol), tri-n-butyltinhydride (490 mg, 1.69 mmol), AIBN (30 mg) in benzene (5 mL) was degassed with argon and refluxed for 8 h. After removing solvent under reduced pressure, the crude material was purified by silica gel column chromatography using light petroleum and ethyl acetate (9:1) to give the tricyclic compound **98** as a colourless thick liquid in 23% (67 mg) yield.

$[\alpha]_D$ +111.5 (c 1.1, $CHCl_3$)

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.33 (s, 3H), 1.51 (s, 3H), 1.59 (m, 1H), 1.71 (m, 1H), 1.87 (m, 2H), 2.01 (m, 1H), 2.59 (dd, 1H, *J* = 5.5, 13.6 Hz), 3.41 (t, 1H, *J* = 7.4 Hz), 4.28 (d, 1H, *J* = 3.6 Hz), 4.65 (ABq, 2H, *J* = 11.7 Hz), 4.70 (d, 1H, *J* = 3.6 Hz), 5.09 (m, 2H), 5.29 (br s, 1H), 5.71 (d, 1H, *J* = 3.6 Hz), 5.86 (m, 1H), 7.34 (m, 5H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 26.7, 27.3, 28.6, 29.5, 37.0, 58.9, 65.1, 75.8, 83.3, 89.4, 106.9, 111.1, 117.7, 127.9, 128.4, 128.5, 134.7, 137.6

MS (ESI) m/z: 346 $(M+H)^+$

Anal. Calcd. for $C_{20}H_{27}NO_4$ (MW. 345): C, 69.54; H, 7.88; N, 4.05; Found C, 69.68; H, 7.79; N, 4.19.

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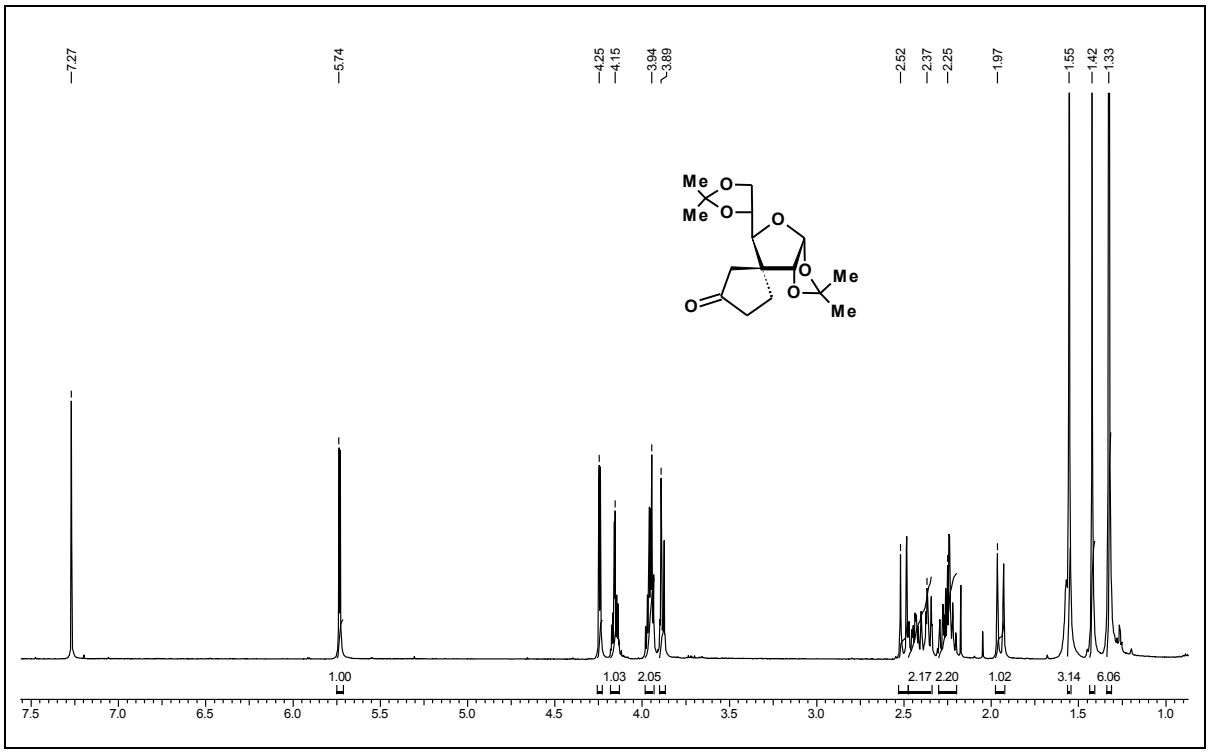
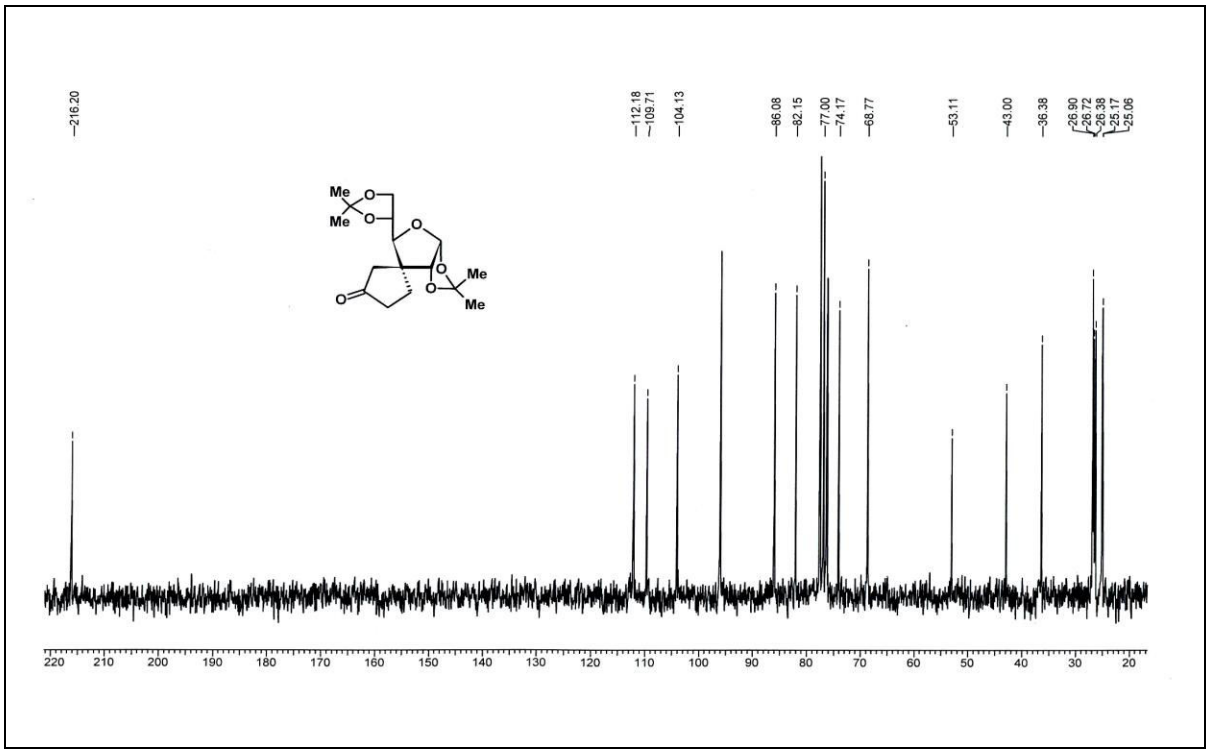
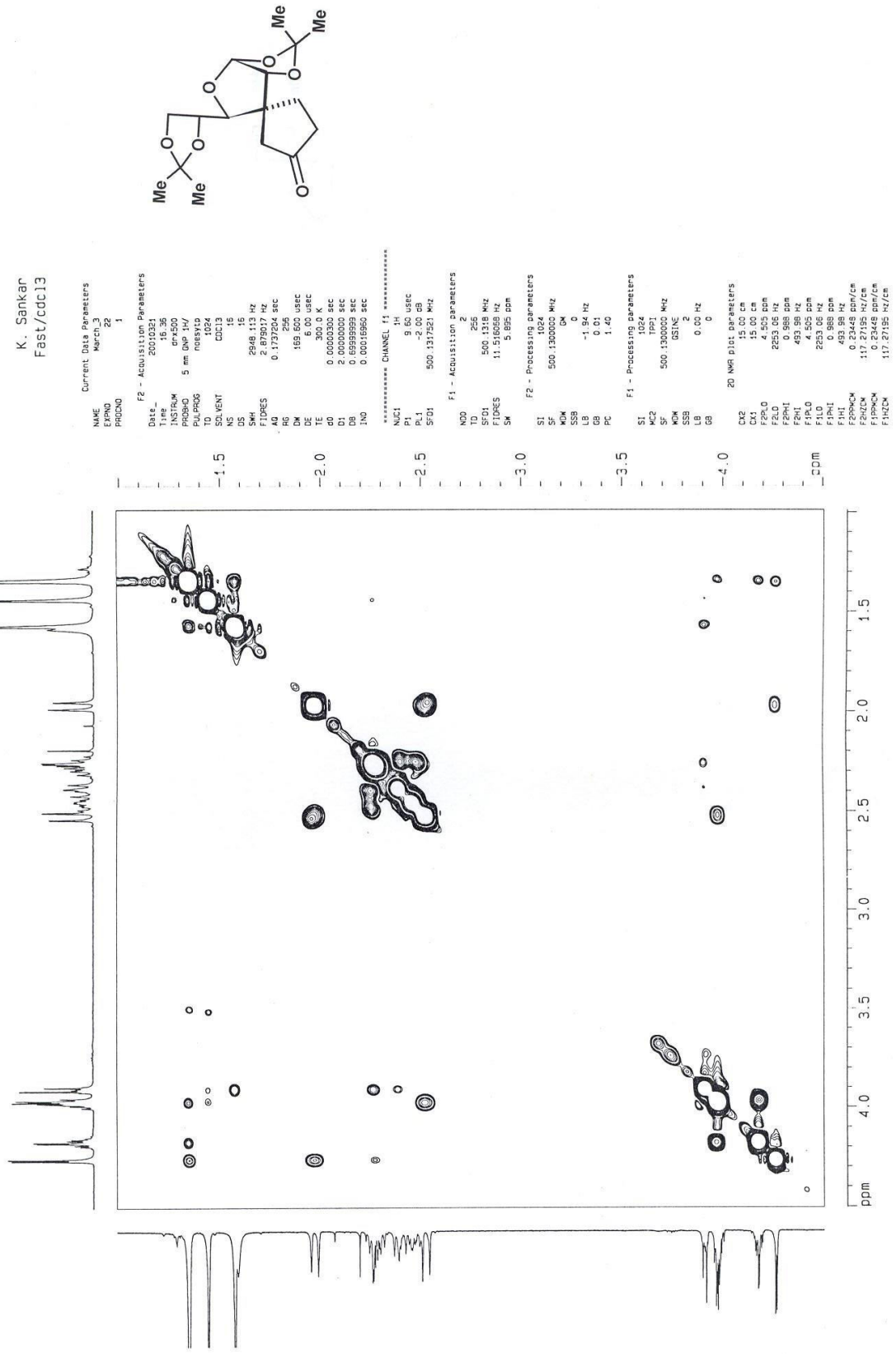


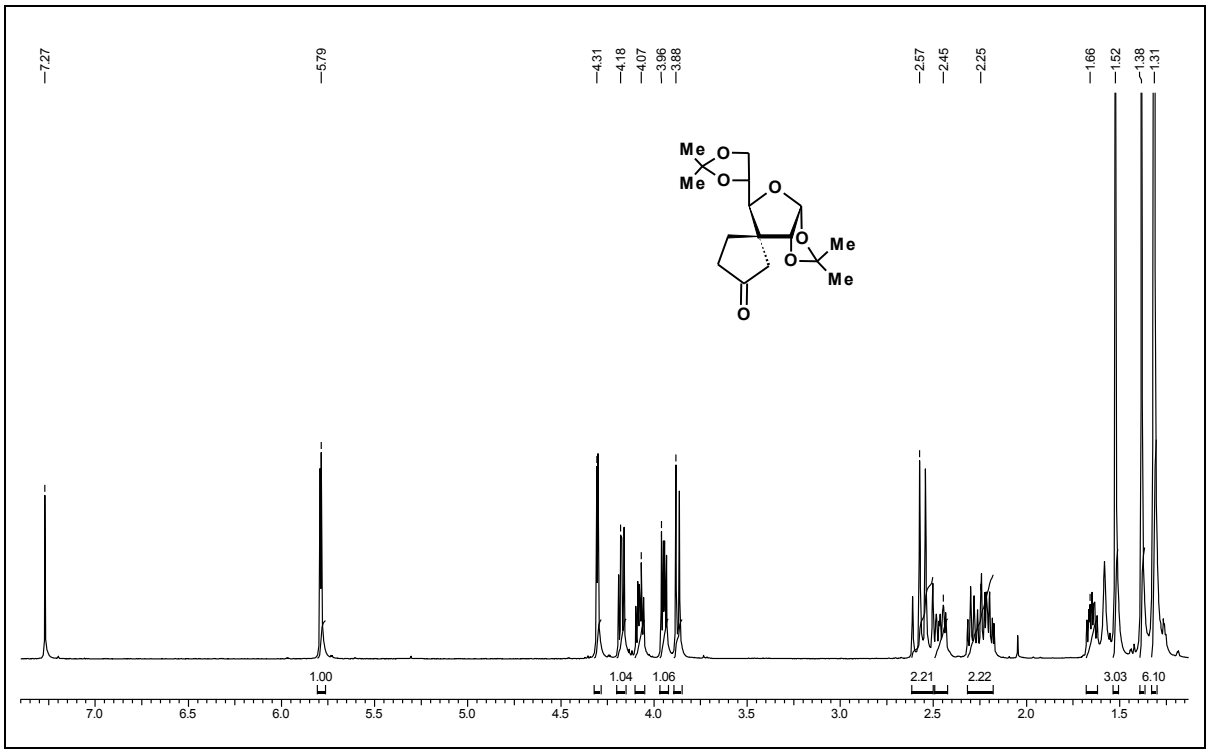
^{1}H NMR spectrum of compound 59 in $CDCl_3$



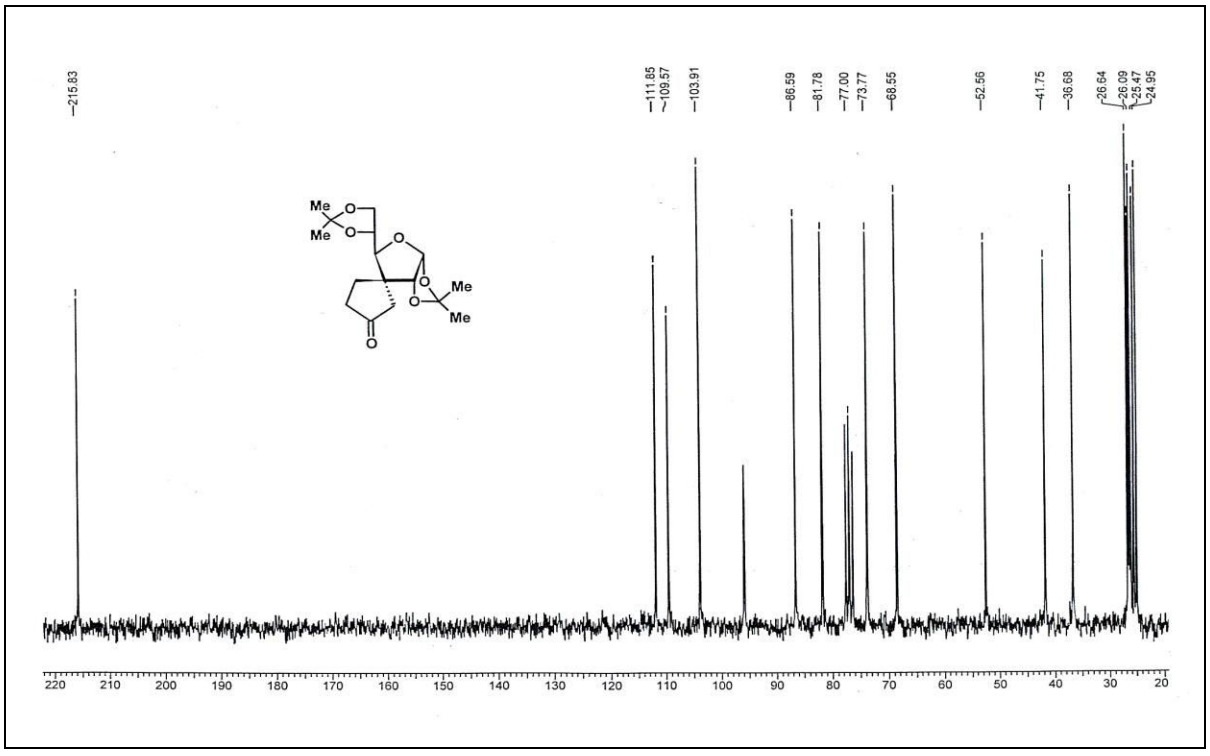
^{13}C NMR spectrum of compound 59 in $CDCl_3$



NOESY spectrum of compound 59

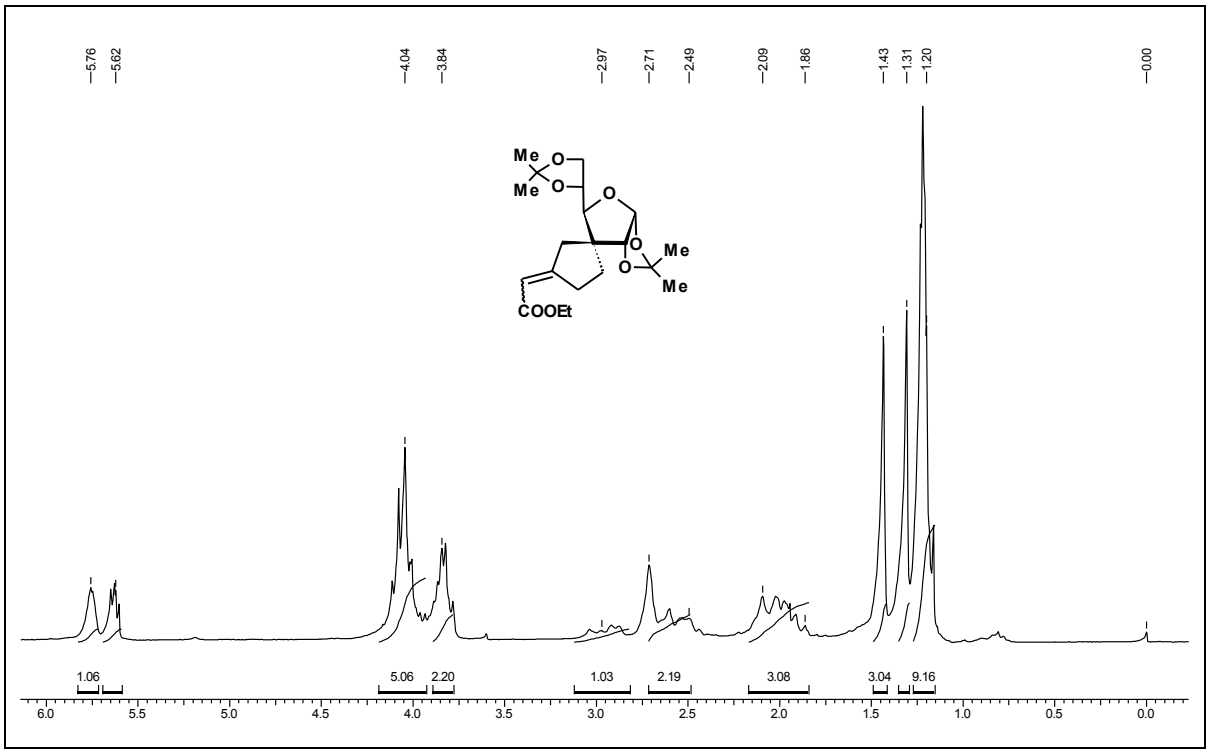


^{1}H NMR spectrum of compound 60 in $CDCl_3$

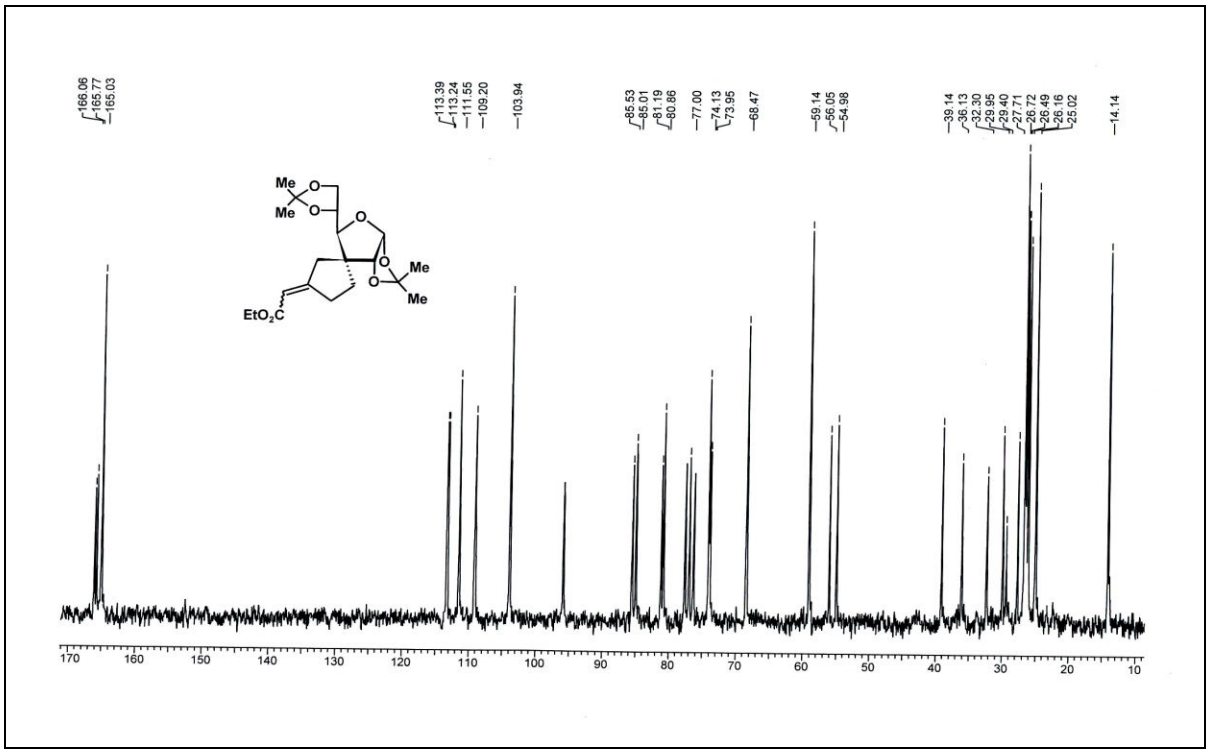


^{13}C NMR spectrum of compound 60 in $CDCl_3$

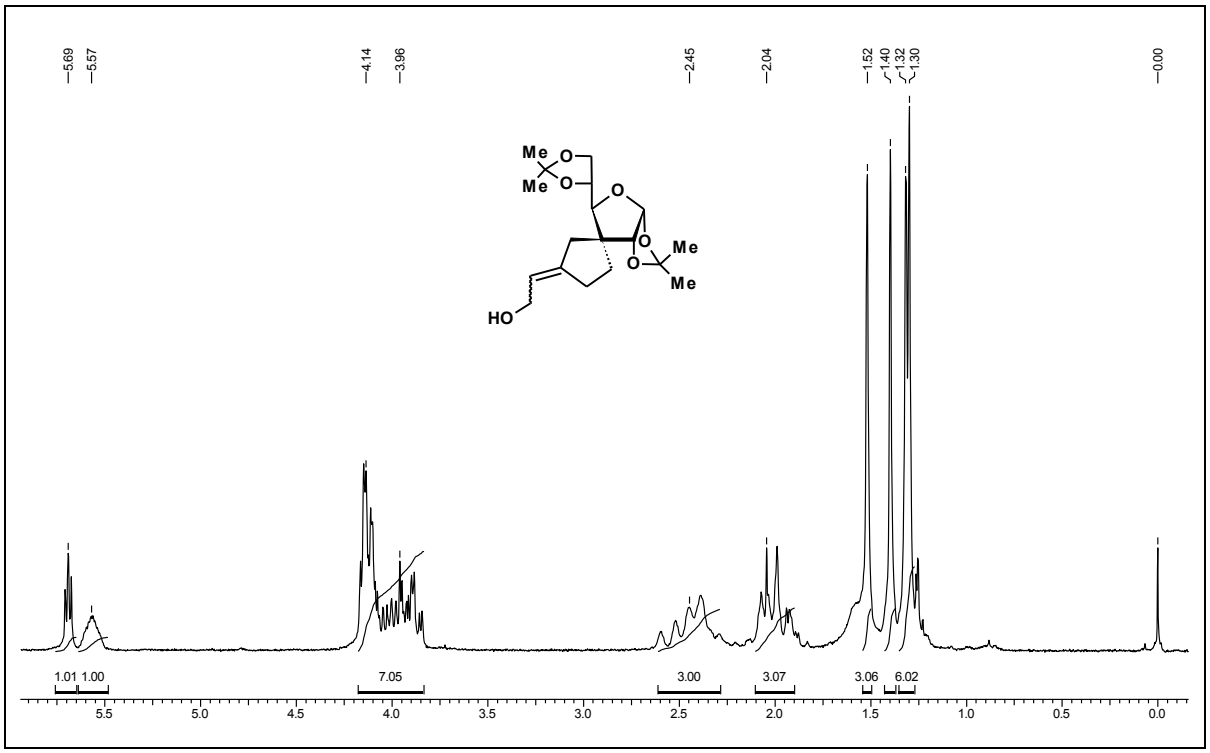
NOESY spectrum of compound 60



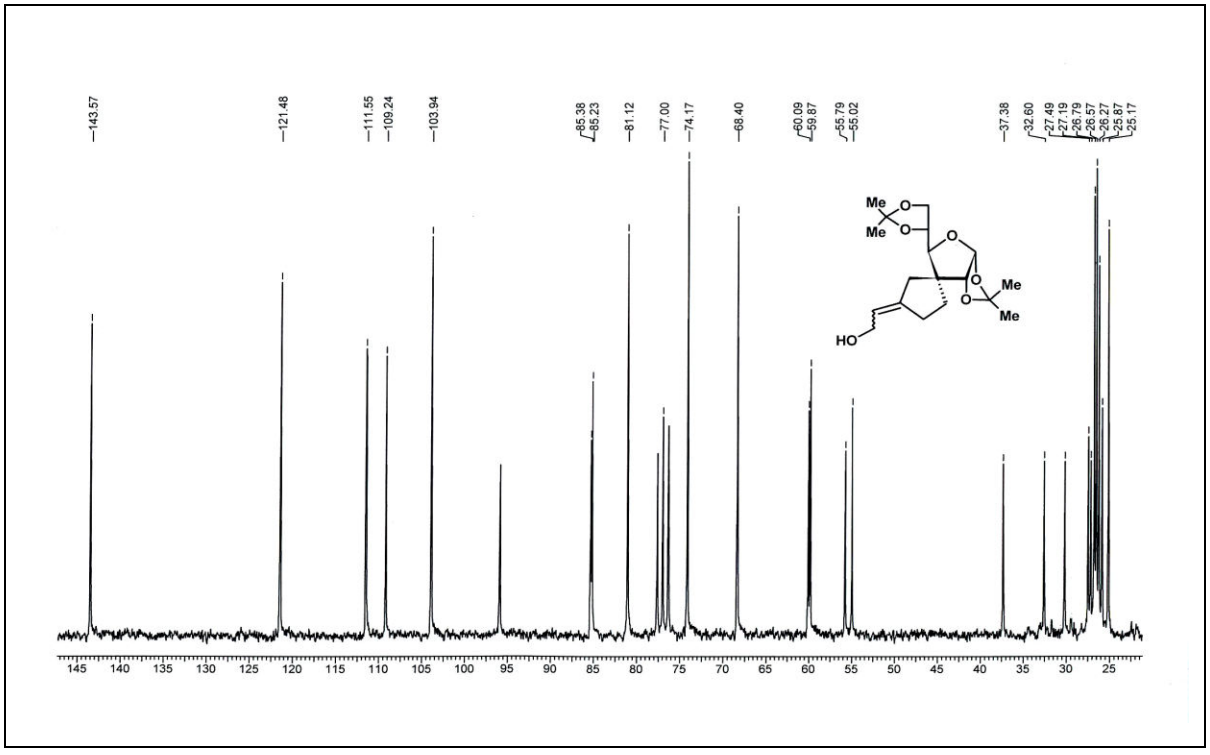
^{1}H NMR spectrum of compound 73 in $CDCl_3$



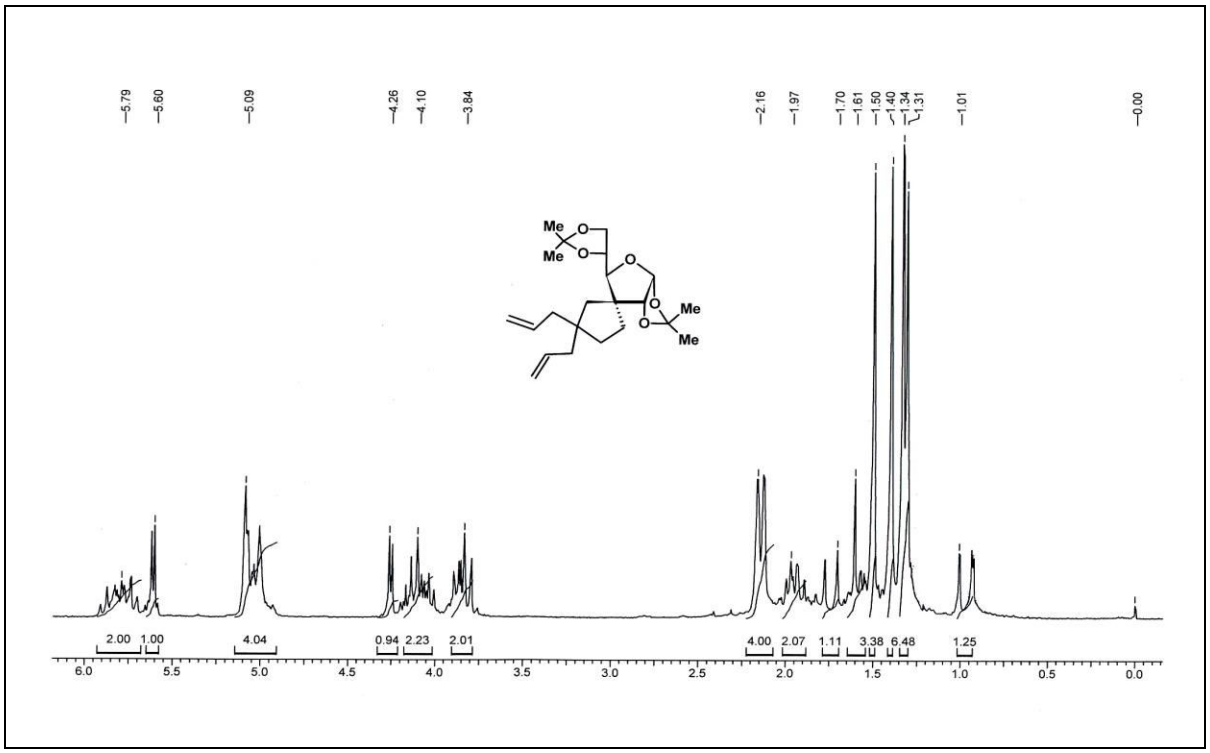
^{13}C NMR spectrum of compound 73 in $CDCl_3$



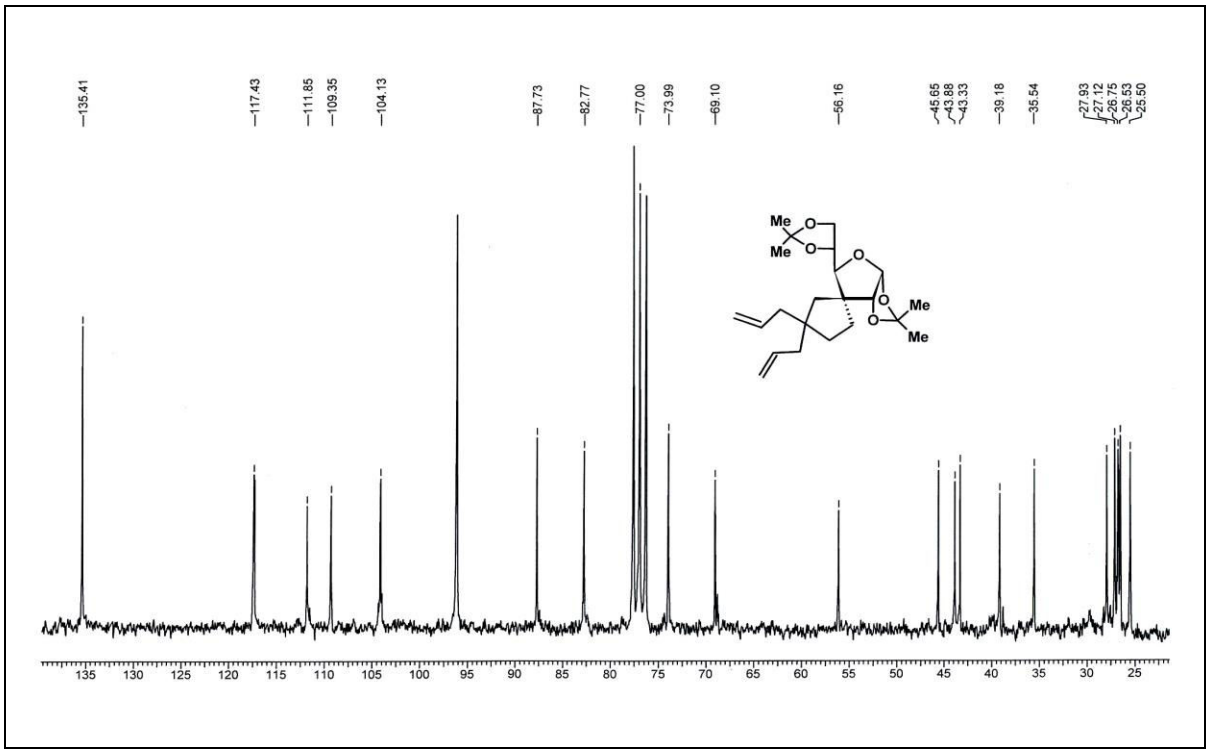
^{1}H NMR spectrum of compound 76 in $CDCl_3$



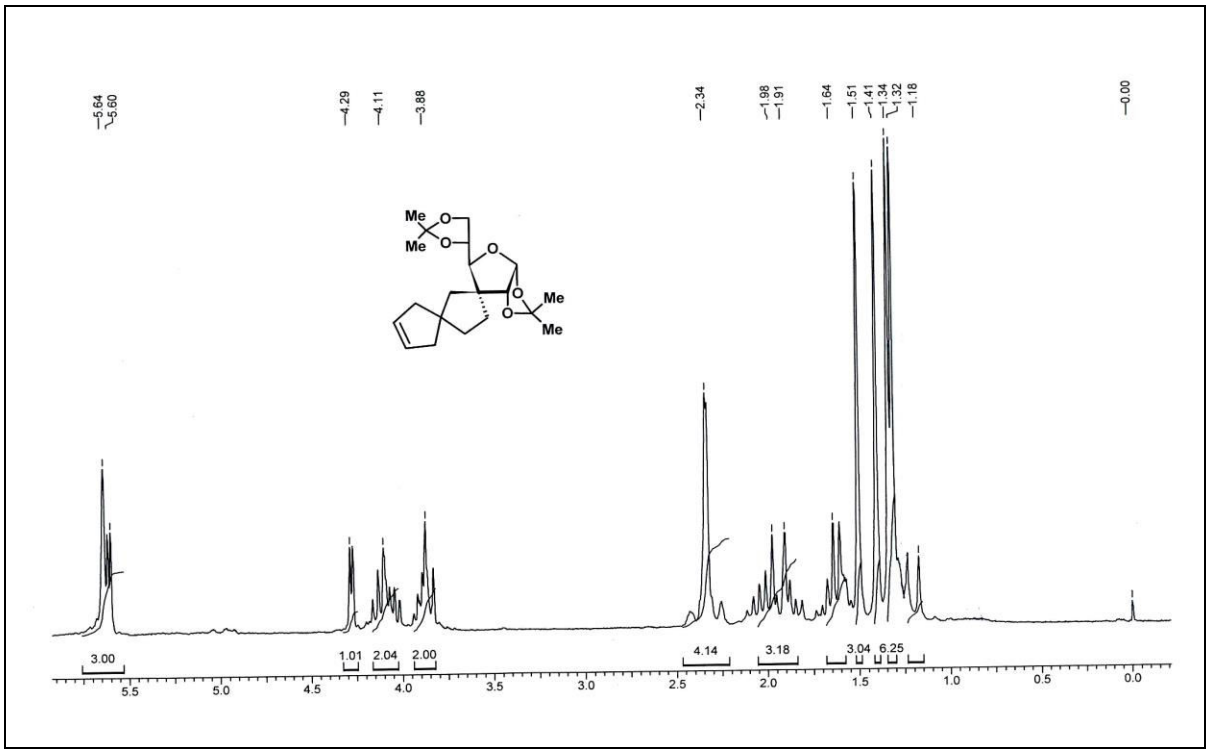
^{13}C NMR spectrum of compound 76 in $CDCl_3$



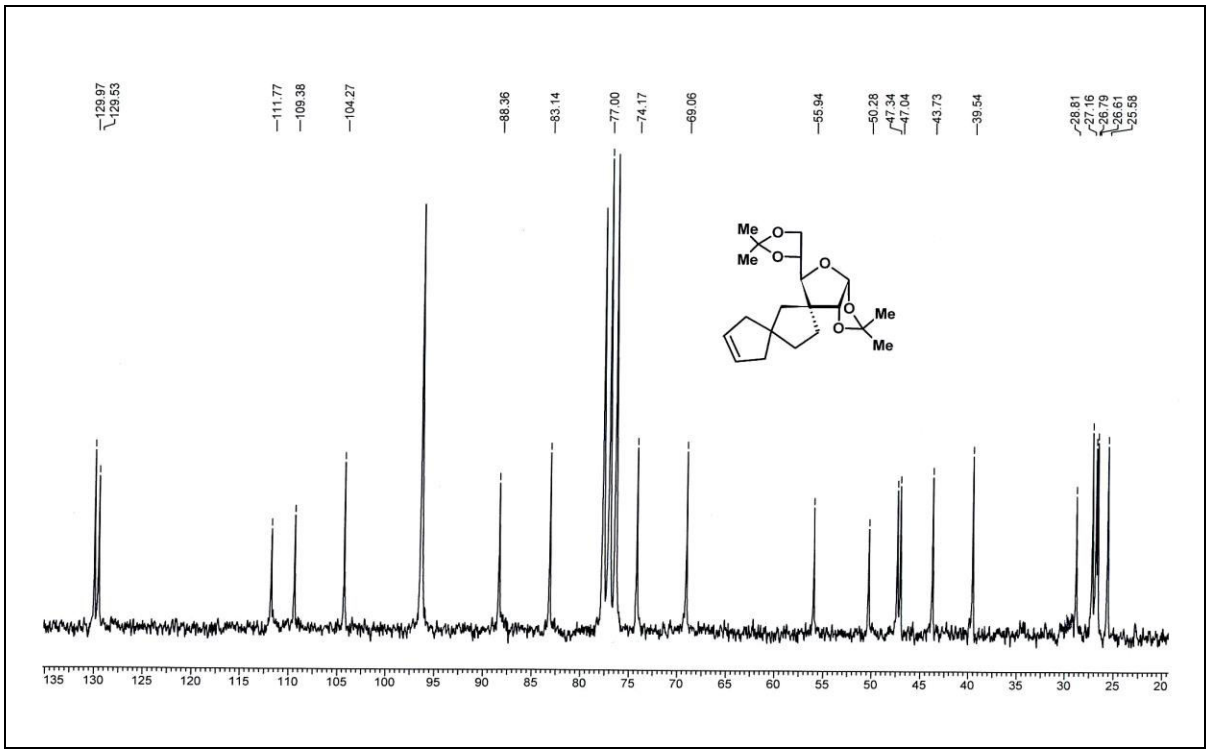
^{1}H NMR spectrum of compound 78 in $CDCl_3$



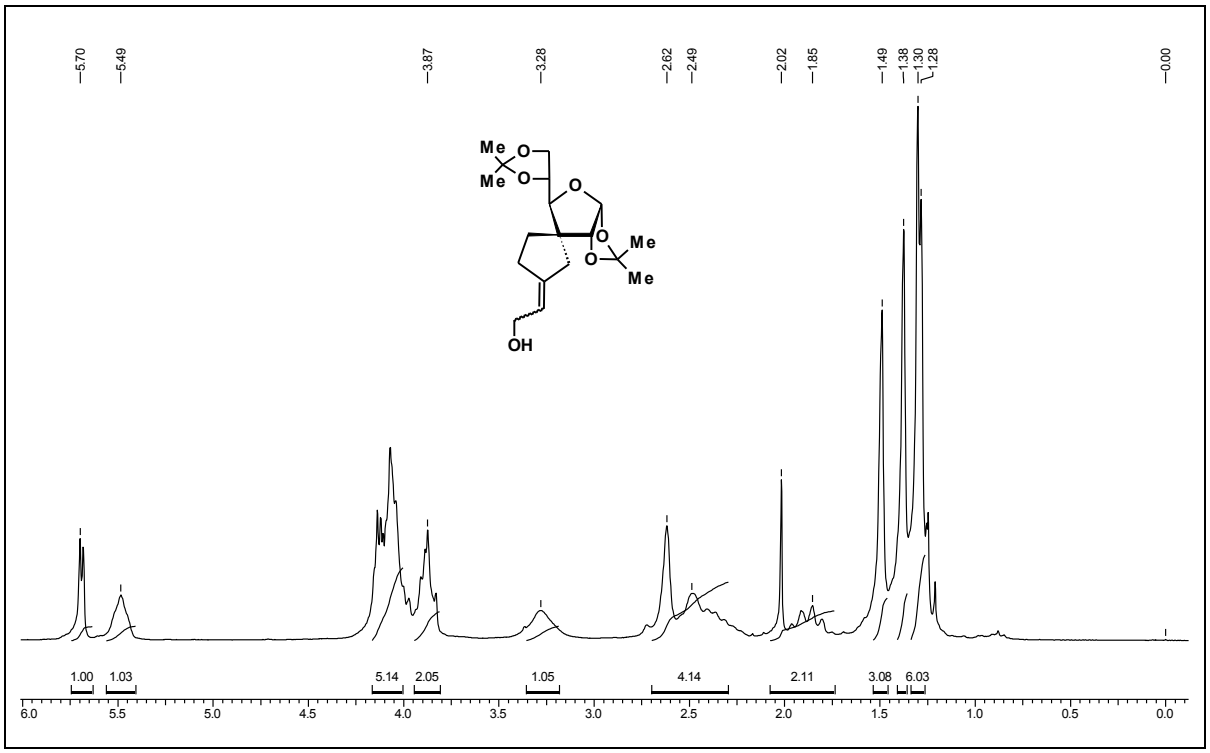
^{13}C NMR spectrum of compound 78 in $CDCl_3$



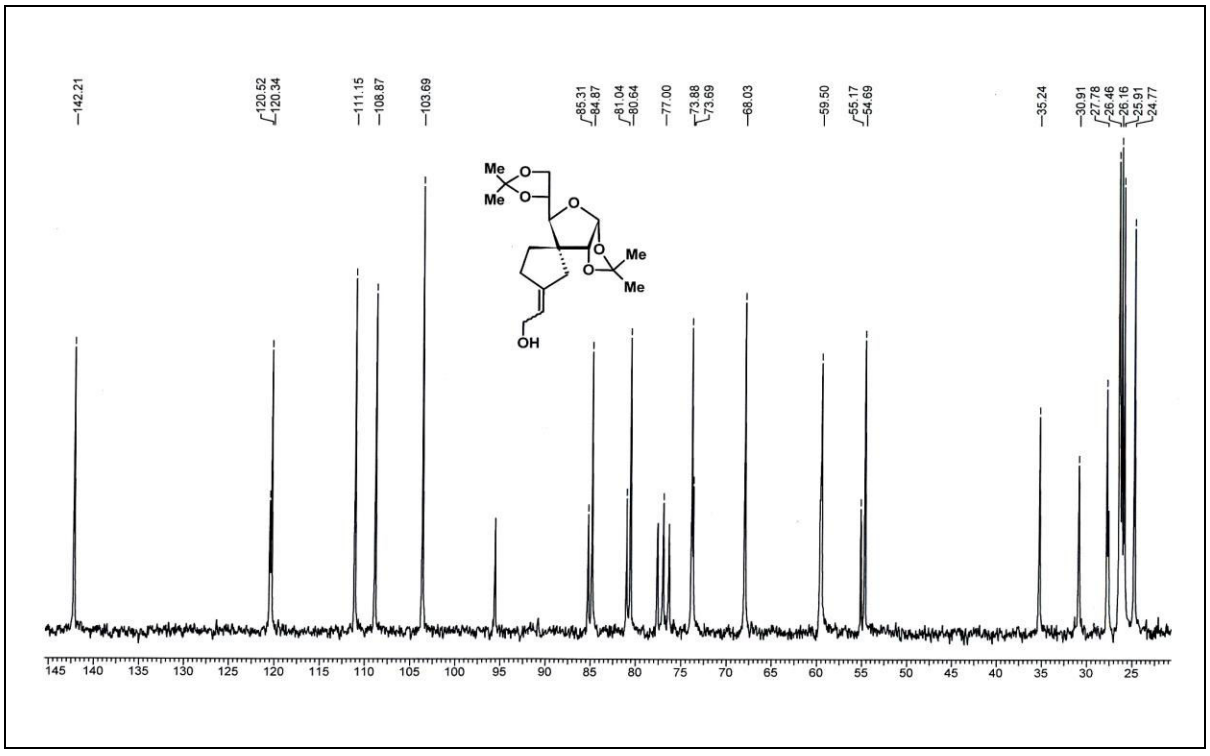
^{1}H NMR spectrum of compound 61 in $CDCl_3$



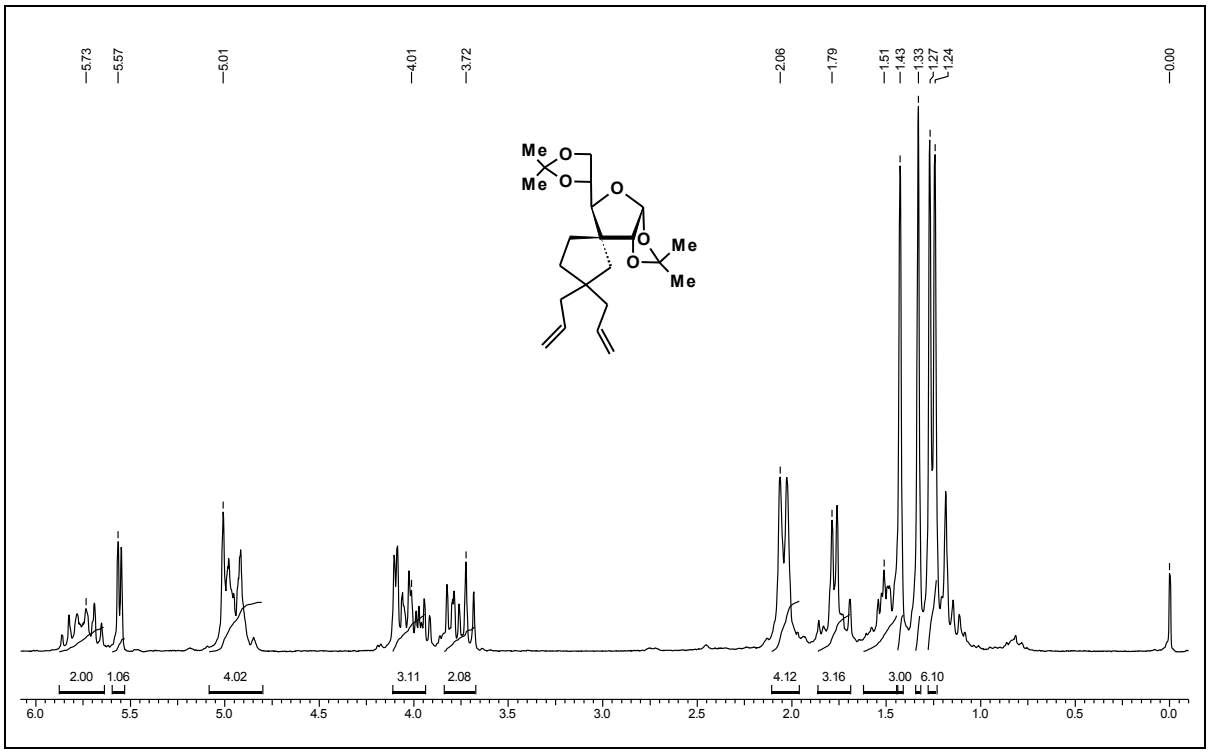
^{13}C NMR spectrum of compound 61 in $CDCl_3$



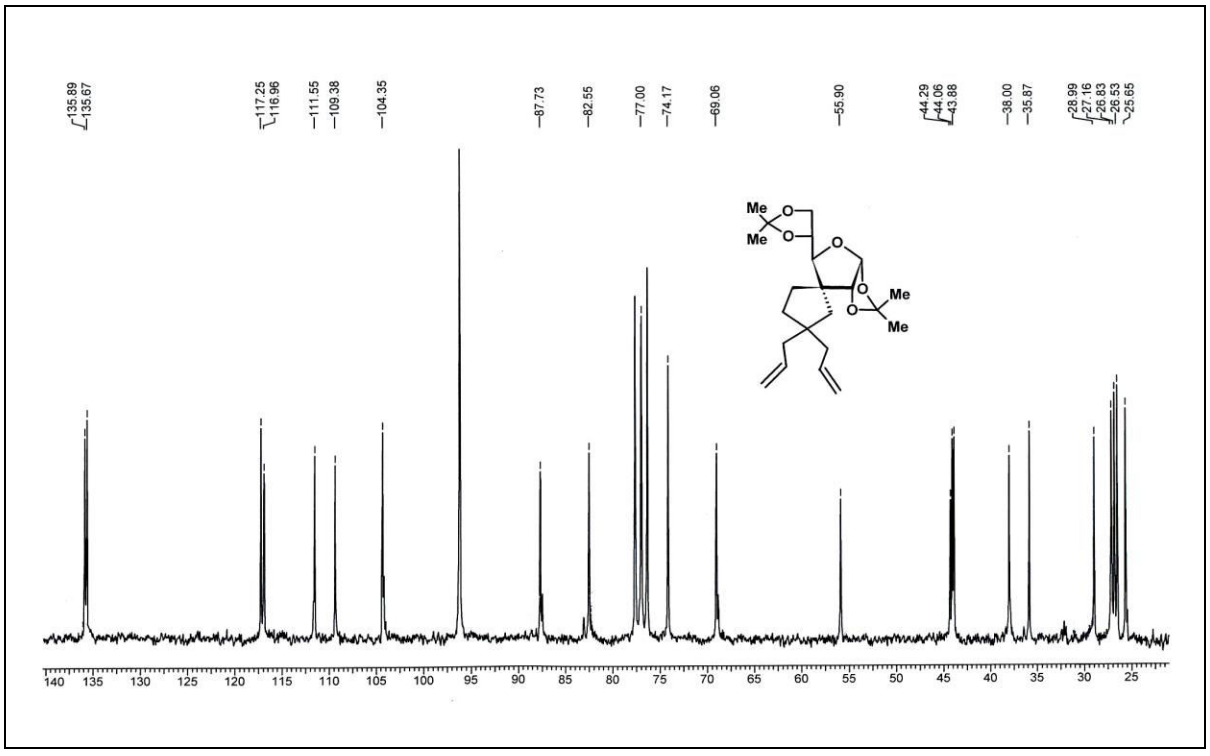
^{1}H NMR spectrum of compound 81 in $CDCl_3$



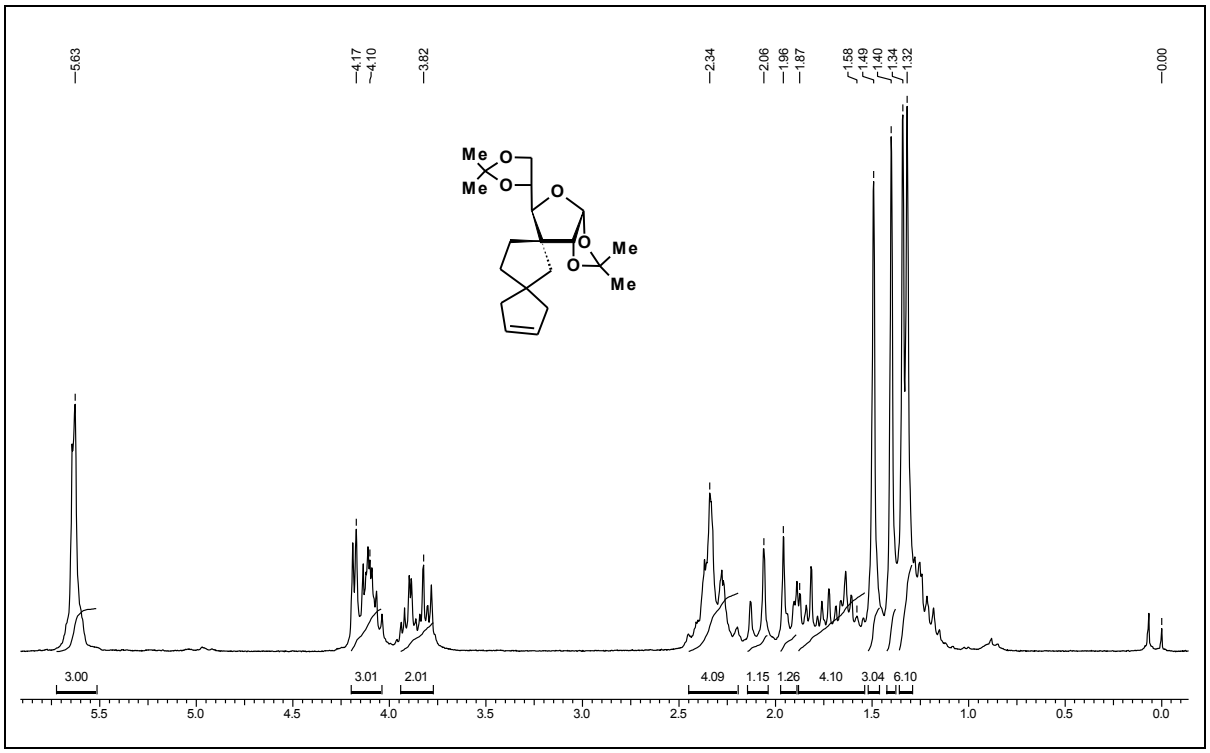
^{13}C NMR spectrum of compound 81 in $CDCl_3$



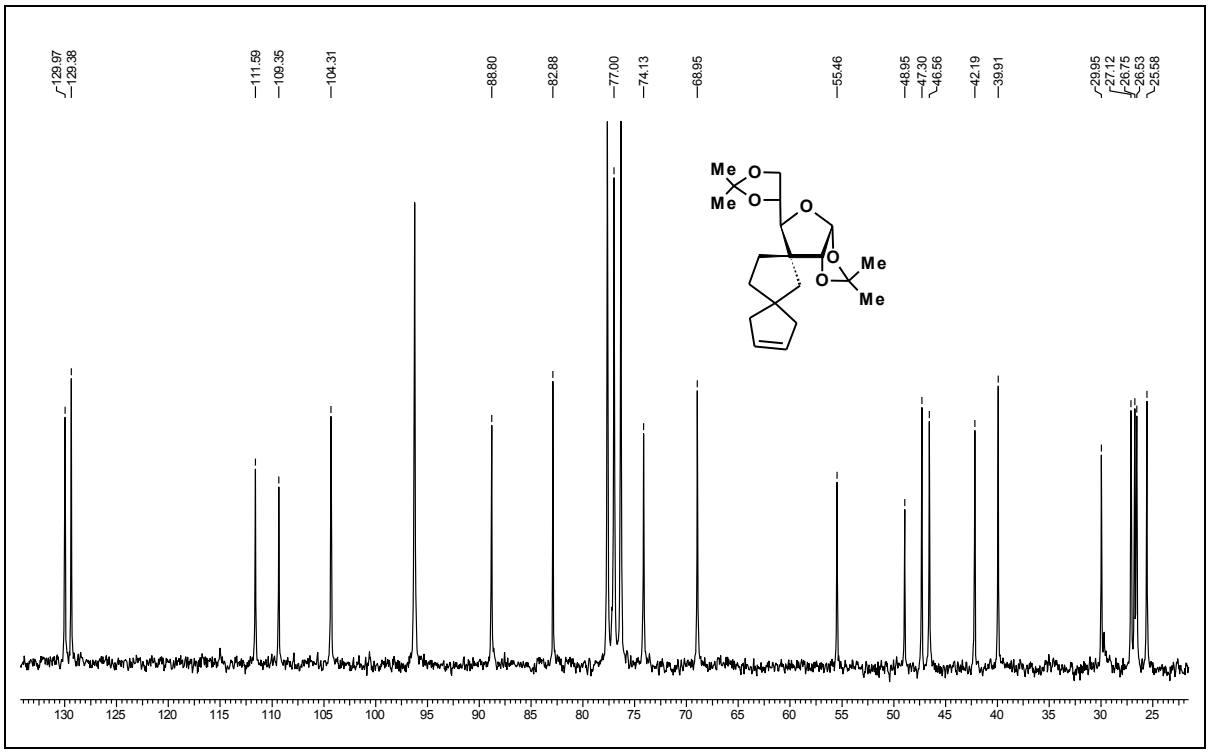
^{1}H NMR spectrum of compound 84 in $CDCl_3$



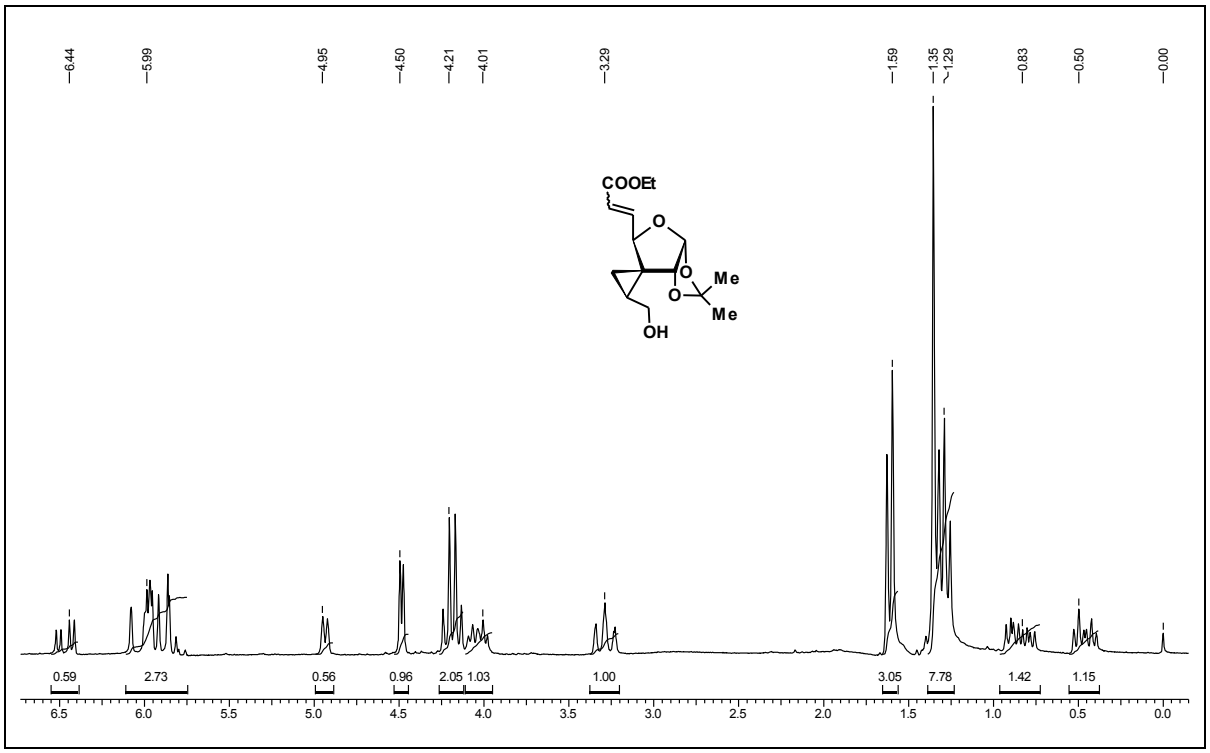
^{13}C NMR spectrum of compound 84 in $CDCl_3$



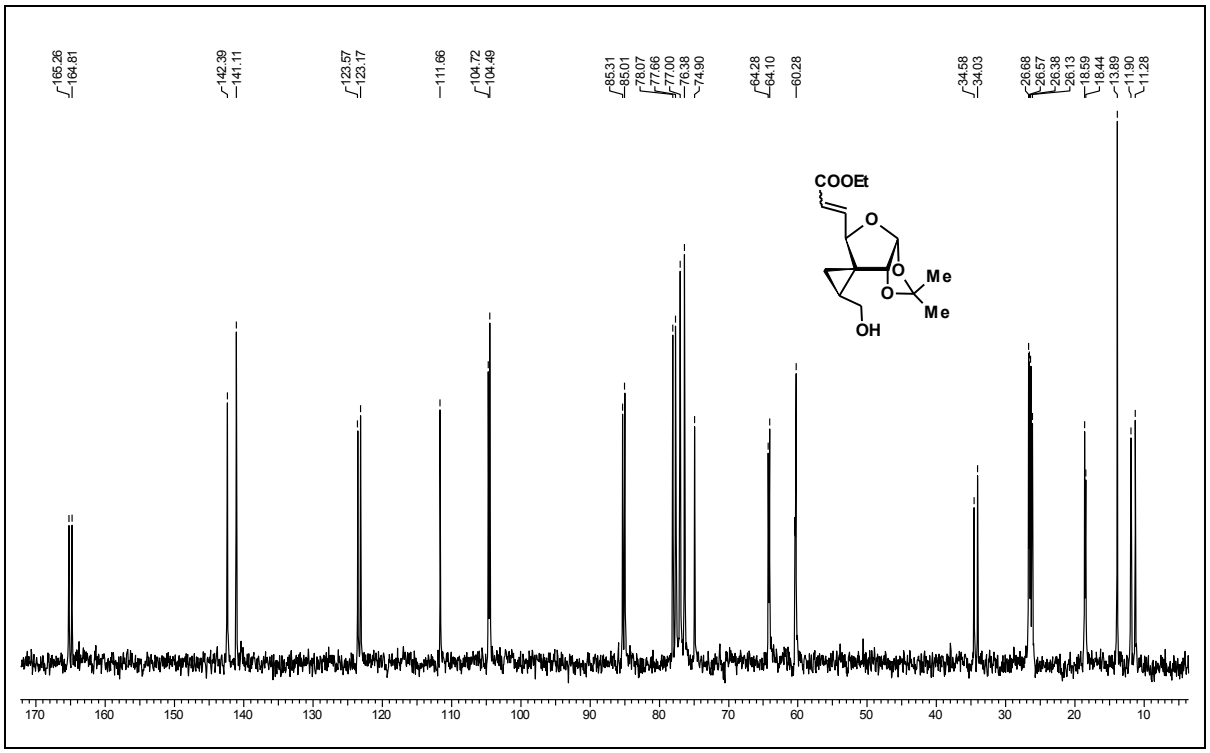
^{1}H NMR spectrum of compound 62 in $CDCl_3$



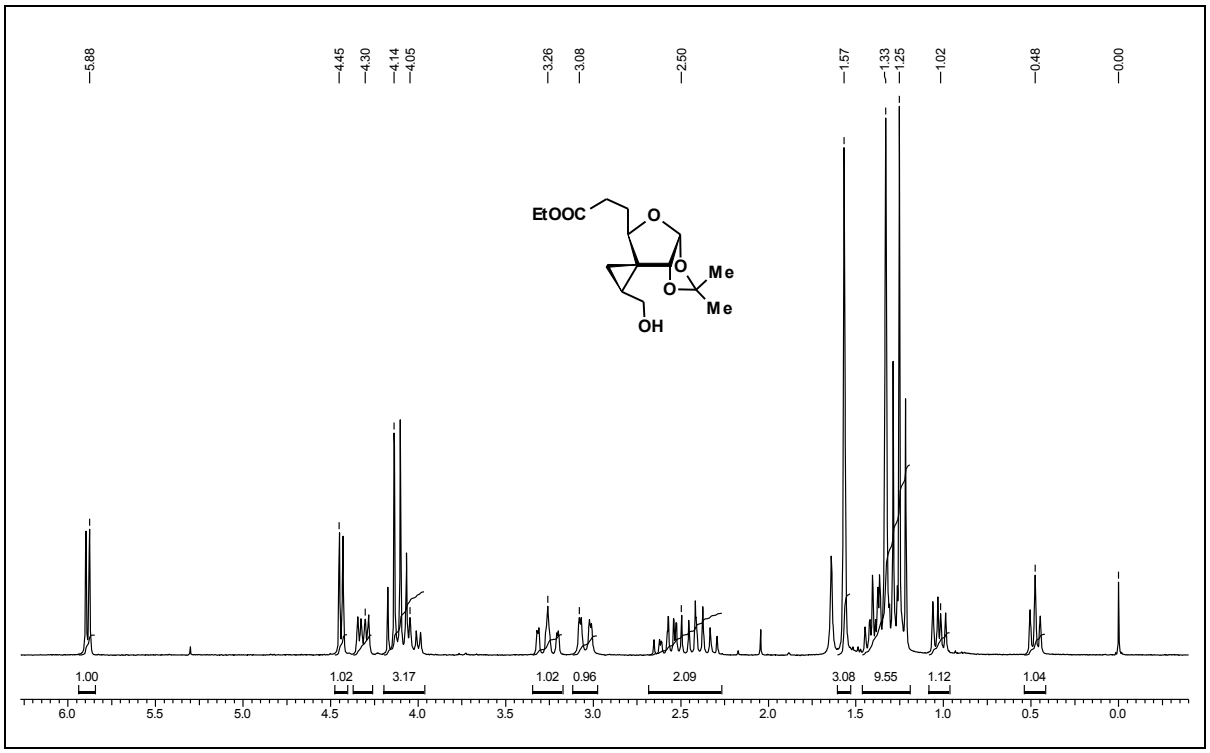
^{13}C NMR spectrum of compound 62 in $CDCl_3$



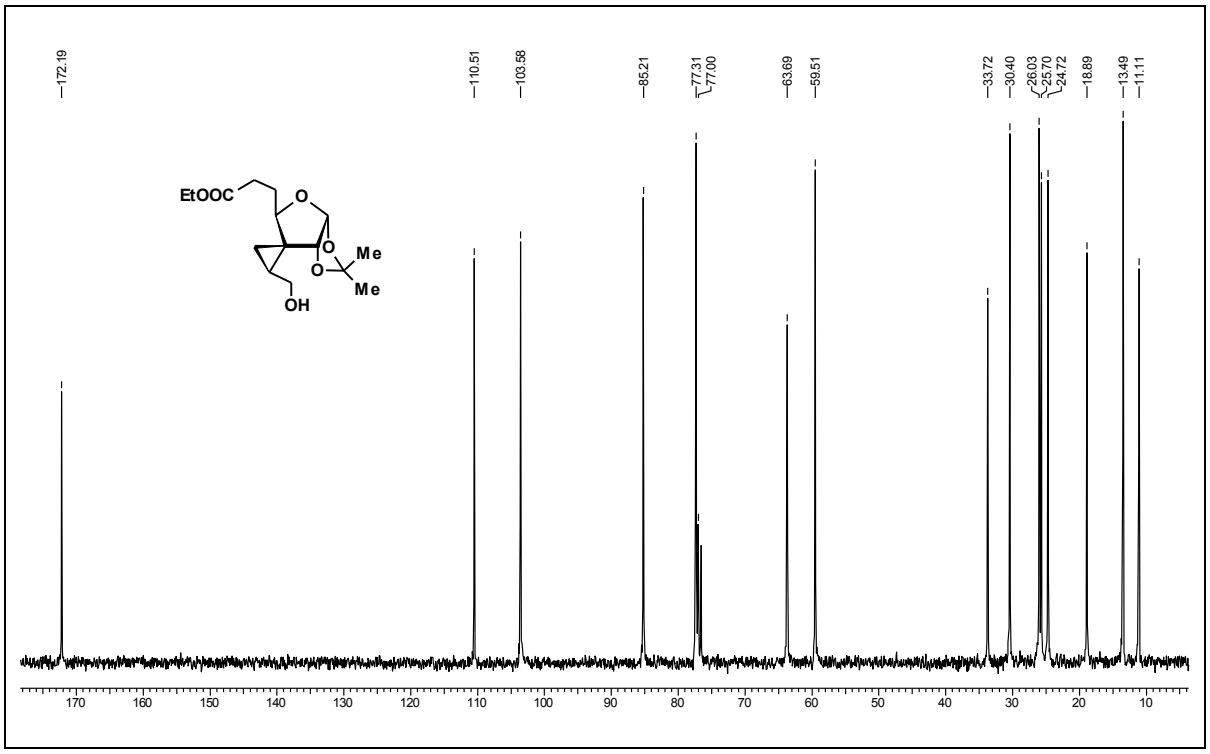
^{1}H NMR spectrum of compound 92 in $CDCl_3$



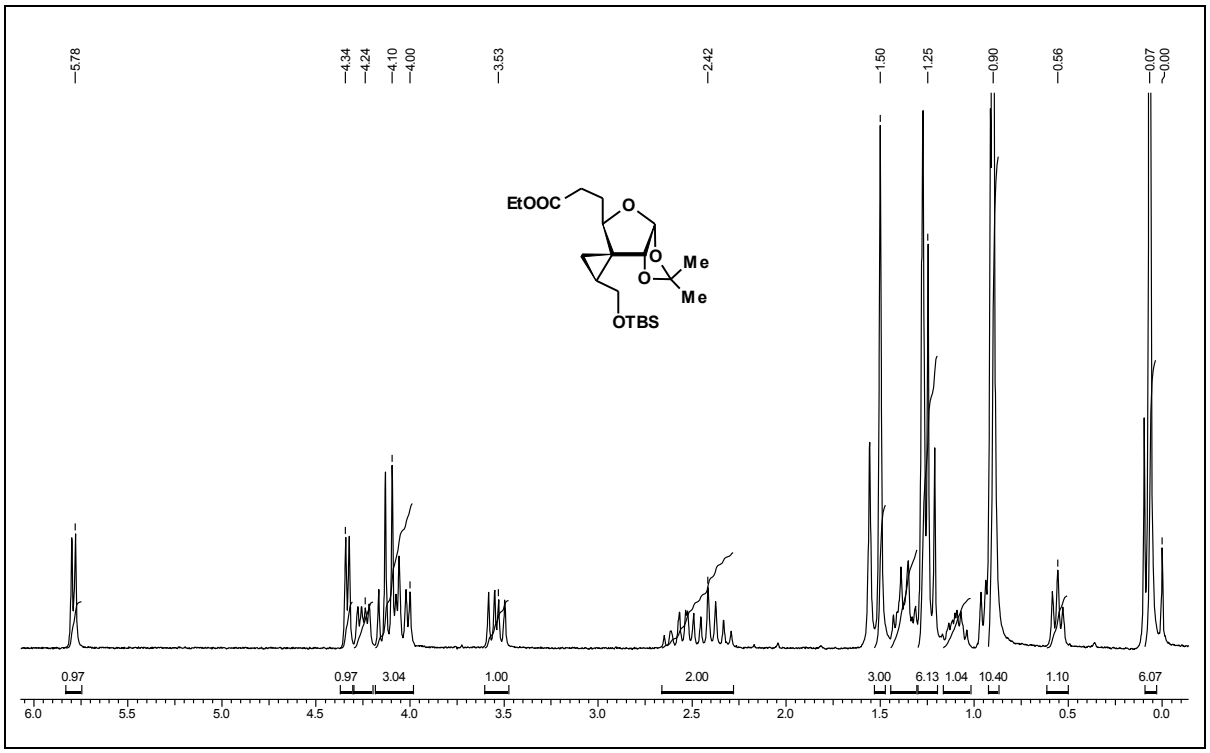
^{13}C NMR spectrum of compound 92 in $CDCl_3$



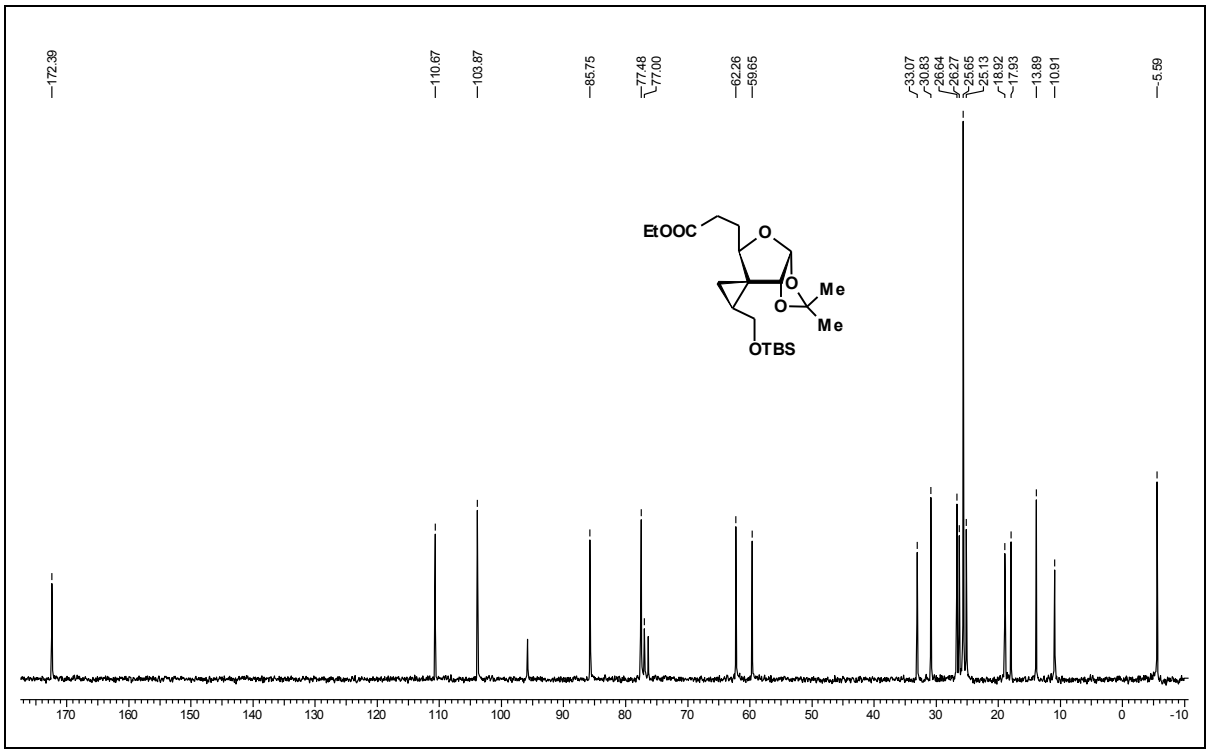
^{1}H NMR spectrum of compound 93 in $CDCl_3$



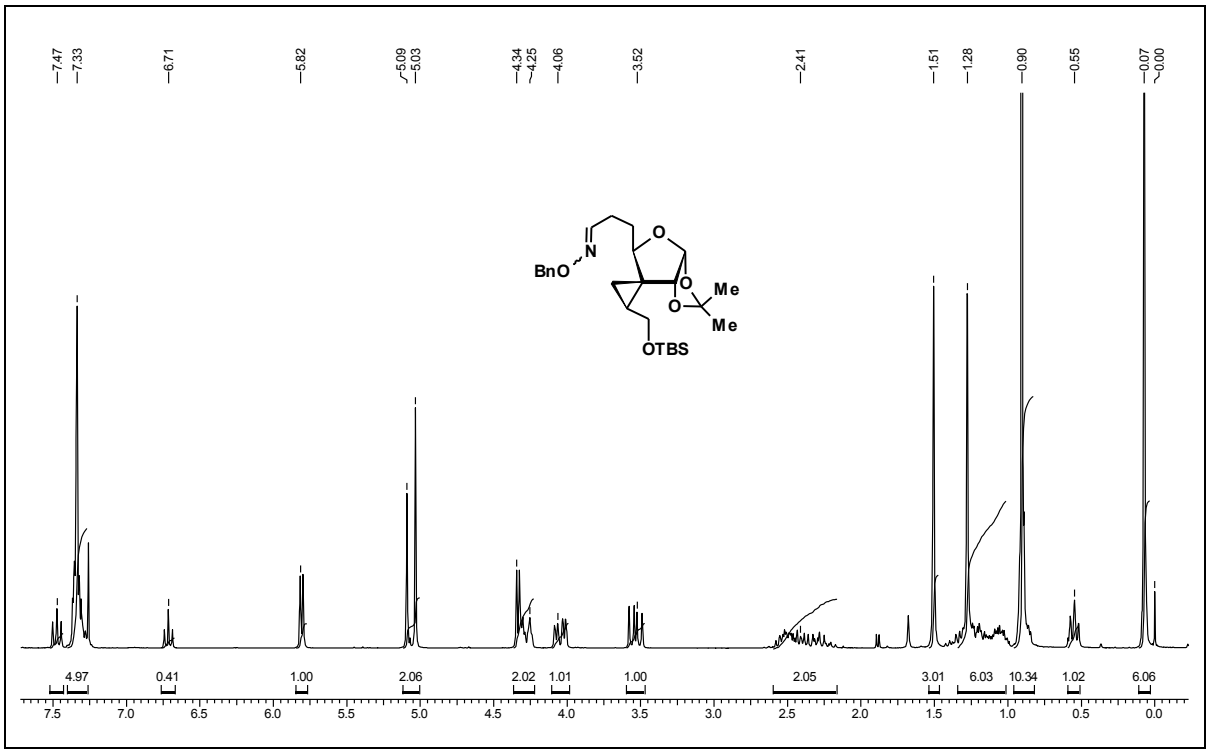
^{13}C NMR spectrum of compound 93 in $CDCl_3$



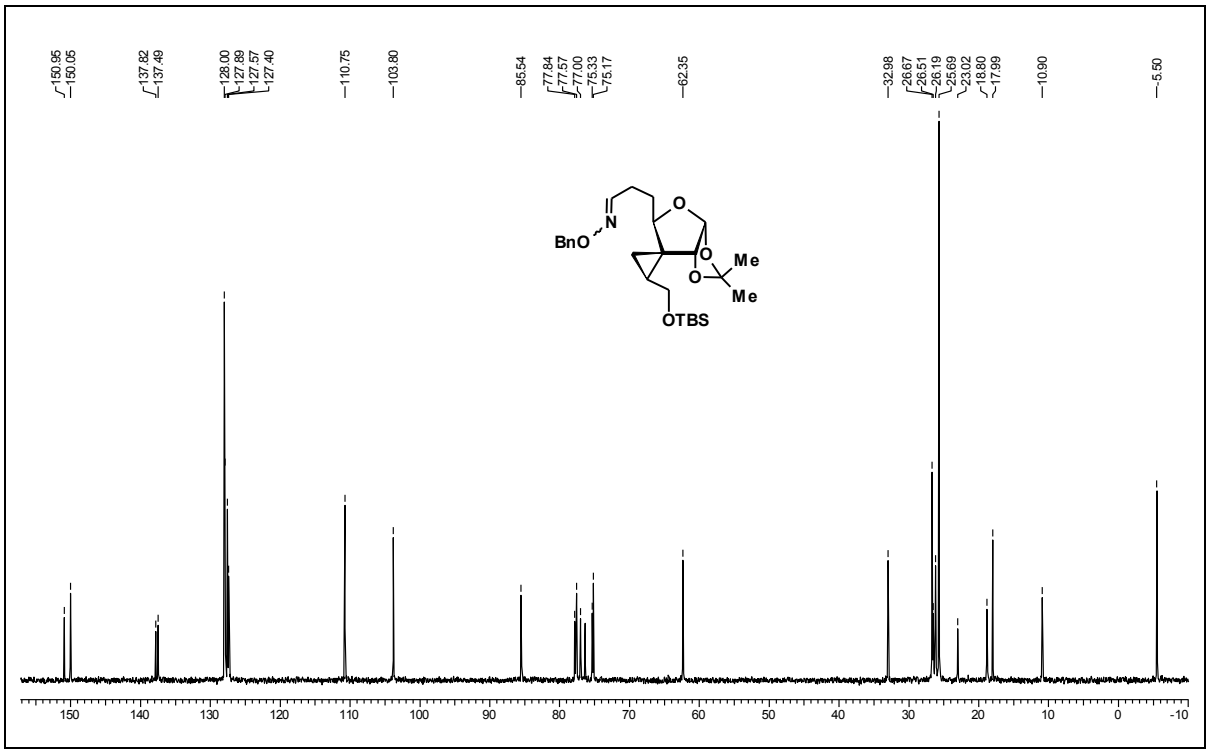
^{1}H NMR spectrum of compound 94 in $CDCl_3$



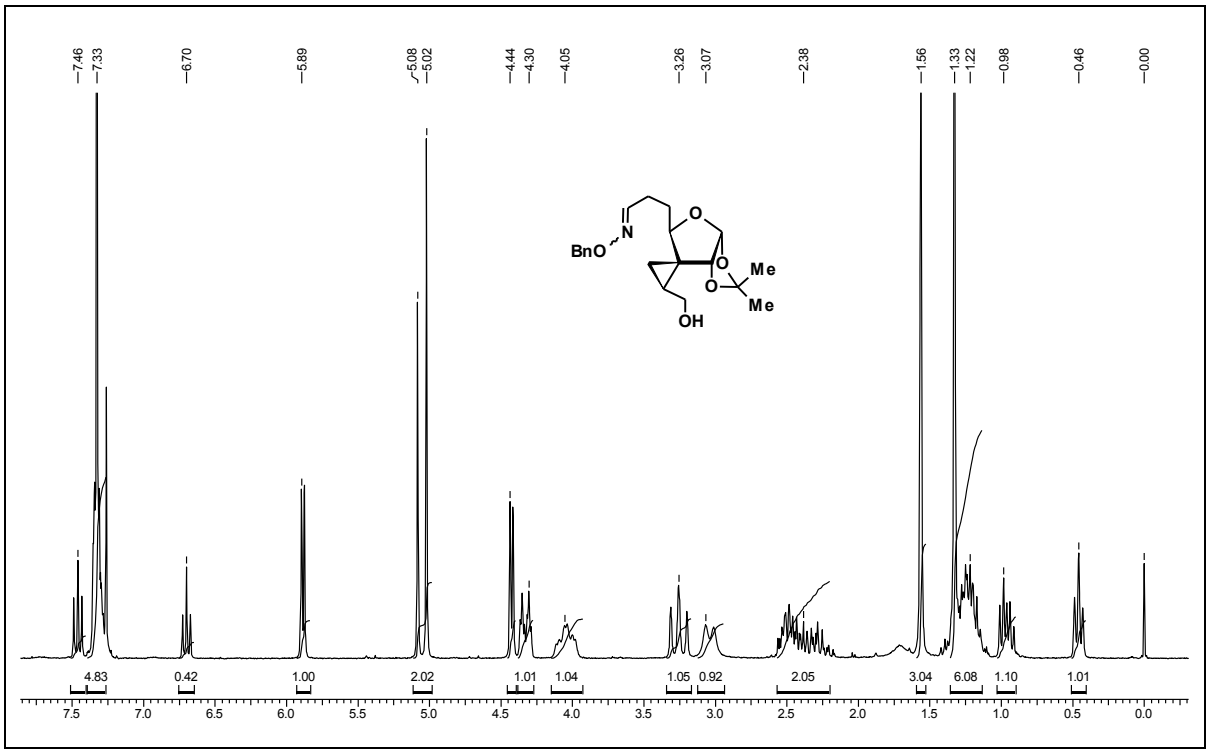
^{13}C NMR spectrum of compound 94 in $CDCl_3$



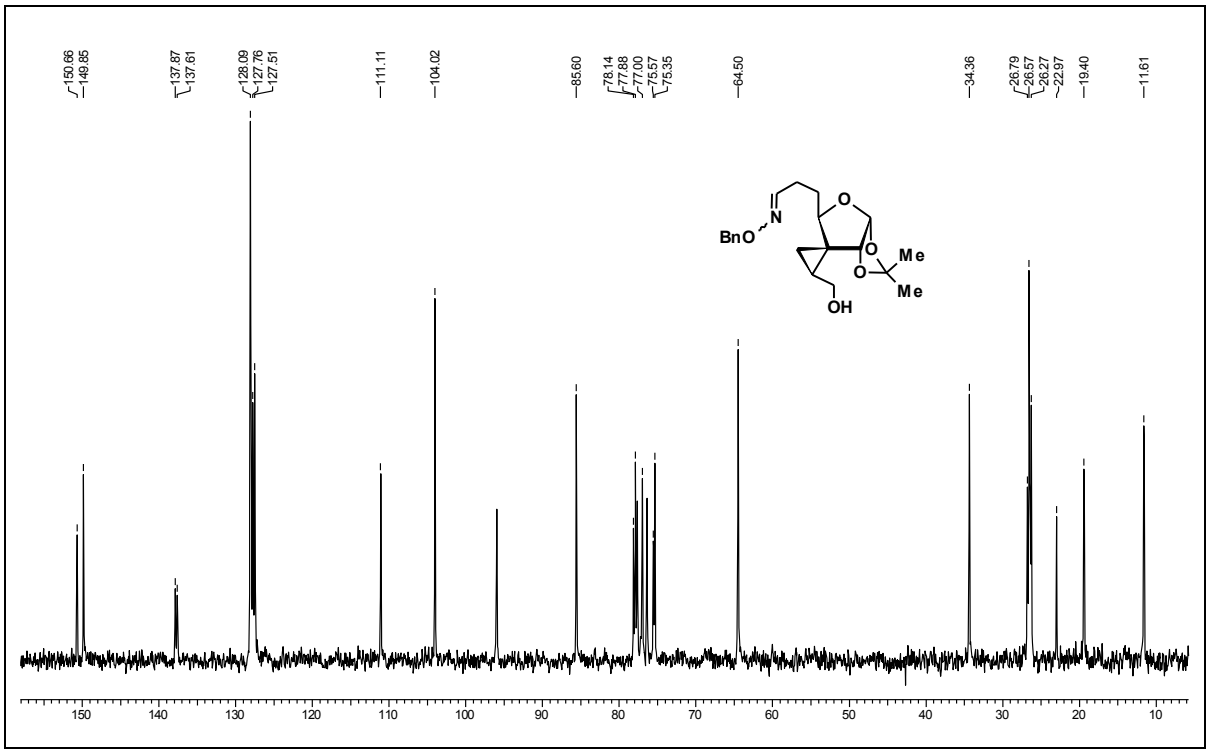
^{1}H NMR spectrum of compound 96 in $CDCl_3$



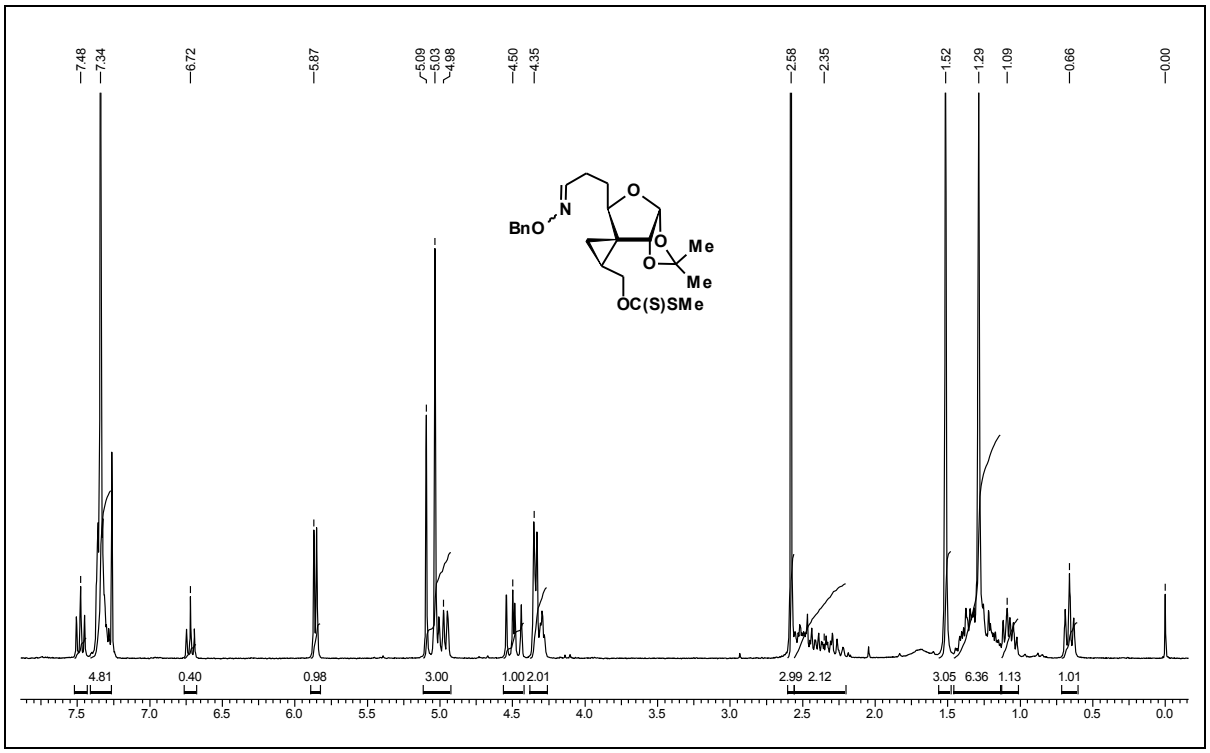
^{13}C NMR spectrum of compound 96 in $CDCl_3$



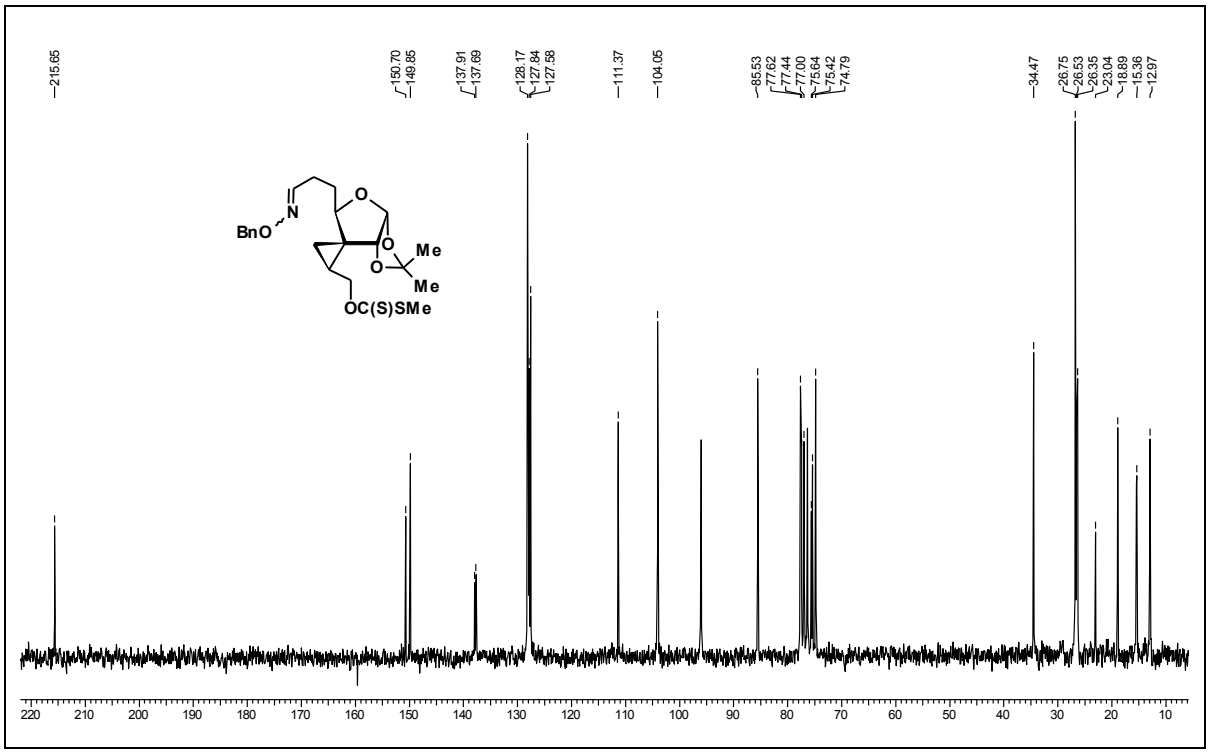
^{1}H NMR spectrum of compound 97 in $CDCl_3$



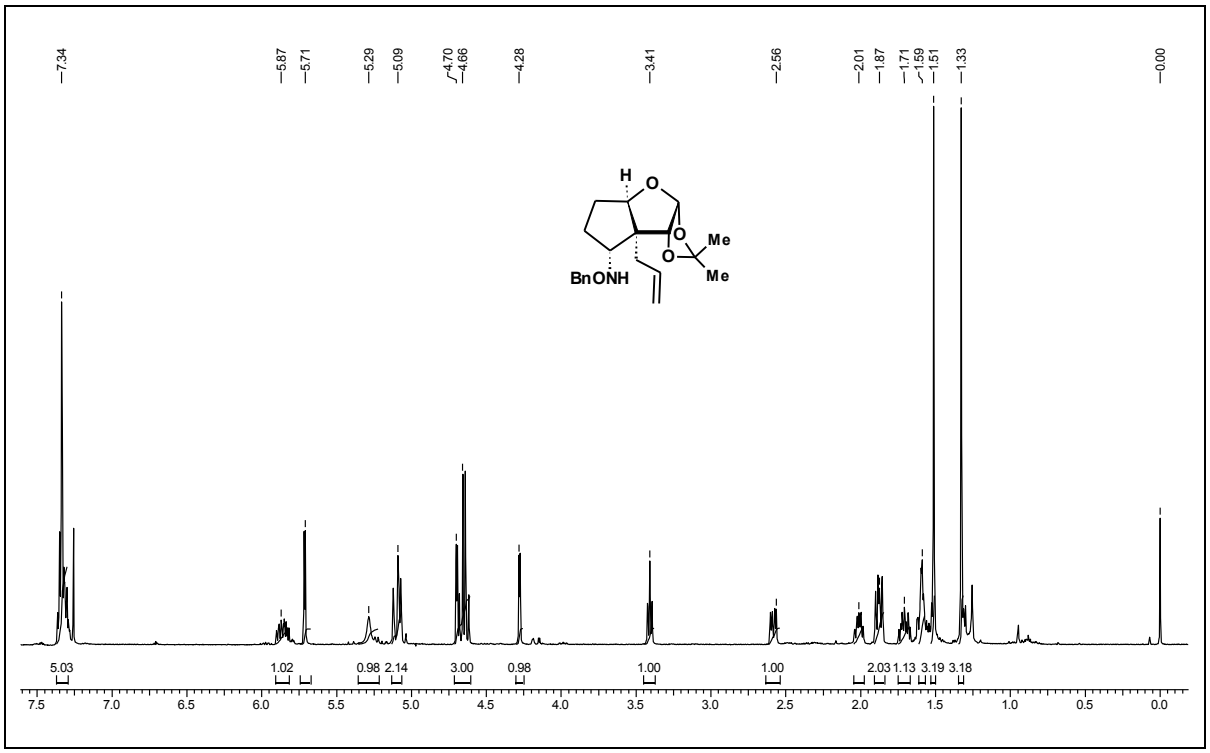
^{13}C NMR spectrum of compound 97 in $CDCl_3$



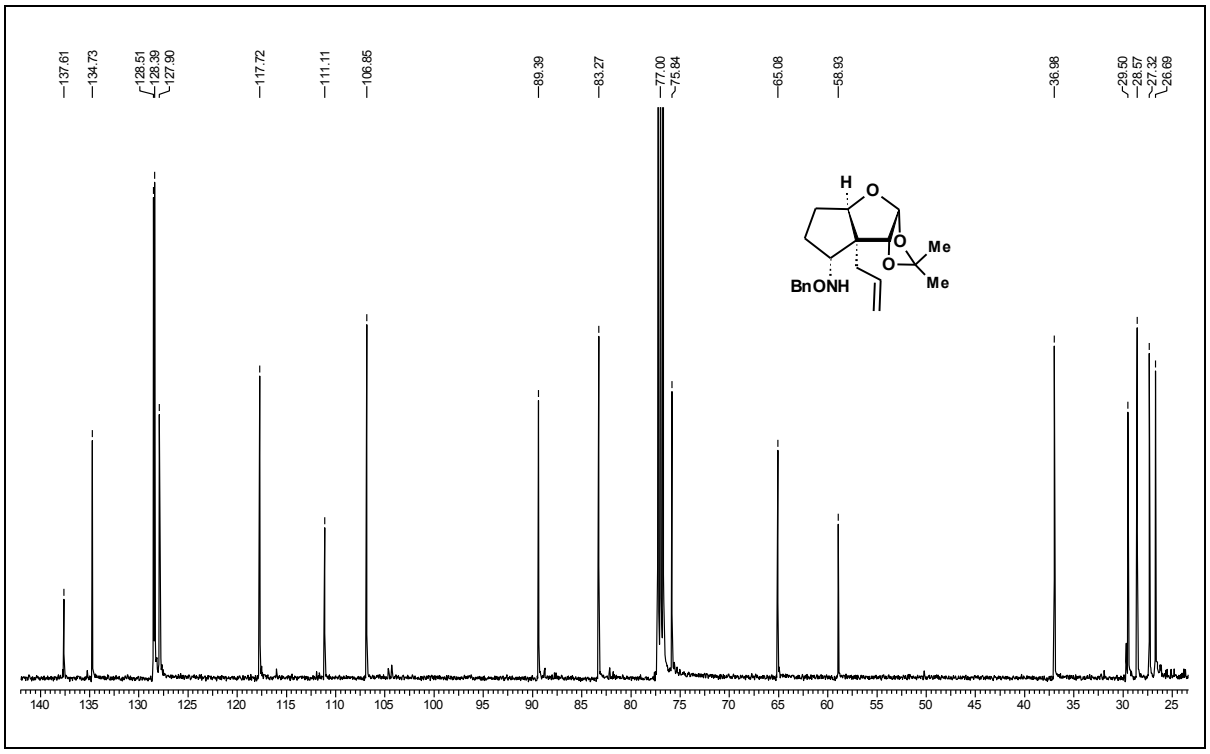
^{1}H NMR spectrum of compound 87 in $CDCl_3$



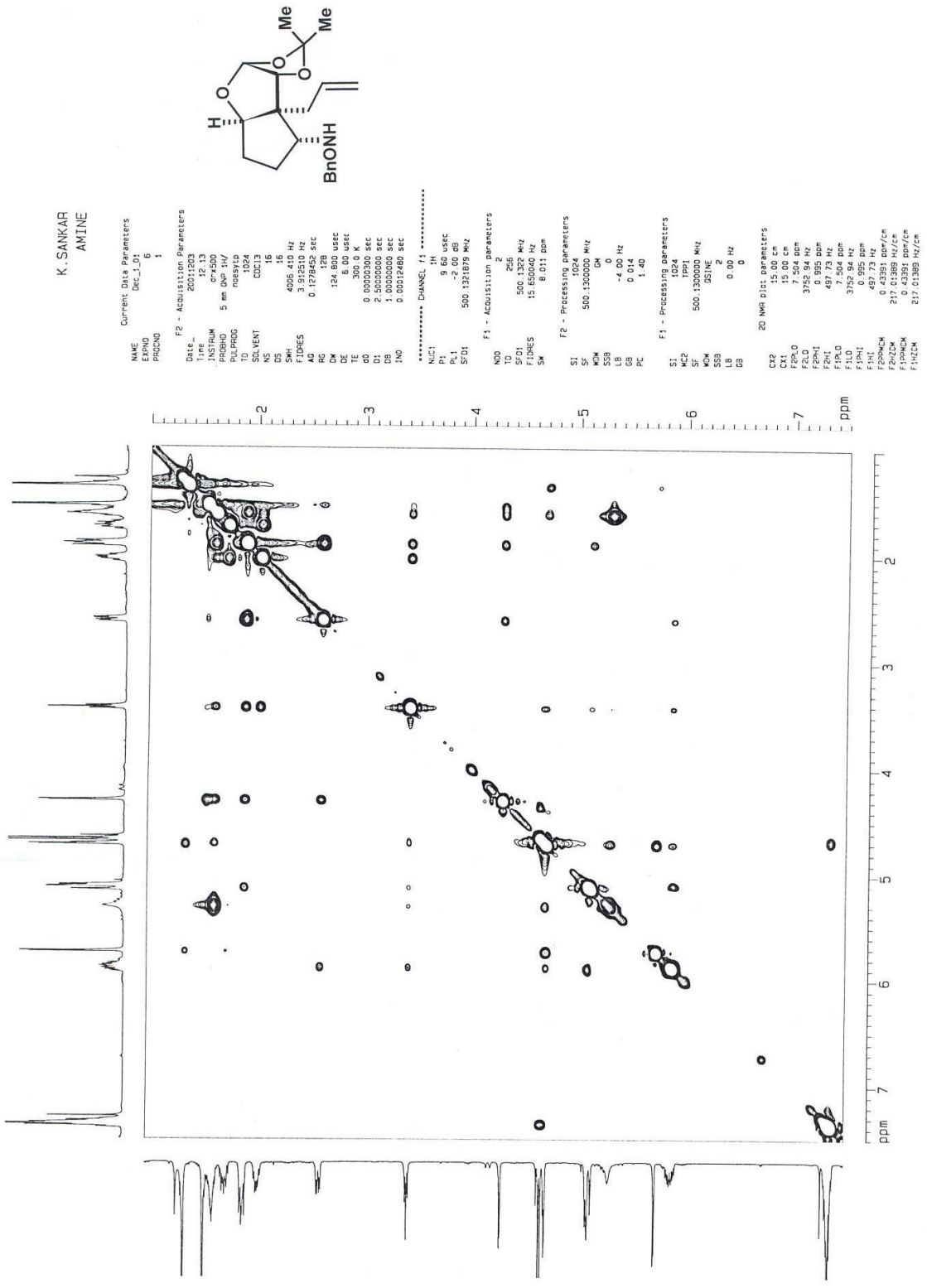
^{13}C NMR spectrum of compound 87 in $CDCl_3$



^{1}H NMR spectrum of compound 98 in $CDCl_3$



^{13}C NMR spectrum of compound 98 in $CDCl_3$



NOESY spectrum of compound 98

CHAPTER-2

Studies toward the synthesis of Manzacidin B

Bromopyrrole alkaloids

Bromopyrrole alkaloids comprise a large and varied class of marine natural products possessing interesting and potentially useful pharmacological activities as α-adrenoreceptor blockers, seretonin antagonists and actomyosin ATPase activators.[1] Some of the open chain and closed bromopyrrole-imidazole alkaloids, bromopyrrole alkaloids with tetrahydropyrimidine core and their closely related compounds are given below.

Open chain pyrrole-imidazole alkaloids

The first member of this class of compounds, oroidin (**1**) was isolated from *Agelas oroides* by Forenza *et al*. and its structure was reassigned by its synthesis by Garcia and co-workers.[2a, b] Hymenidin (**2**), a novel antagonist of serotonergic receptors, isolated from the Okinawan marine sponge *Hymeniacidon sp*. by Kobayashi and co-workers.[2c] Bromopyrrole alkaloids dispacamide (**3**) and monobromo dispacamide (**4**) were isolated by Cafieri and co-workers from the Caribbean *Agelas* species, namely *A. dispar, A. clathrodes, A. longissima, and A, conifera.* These compounds show a potent and selective antagonistic activity against histaminergic receptors as a result of tests performed *in vitro* on the guinea pig ileum[3] (Figure **1**).

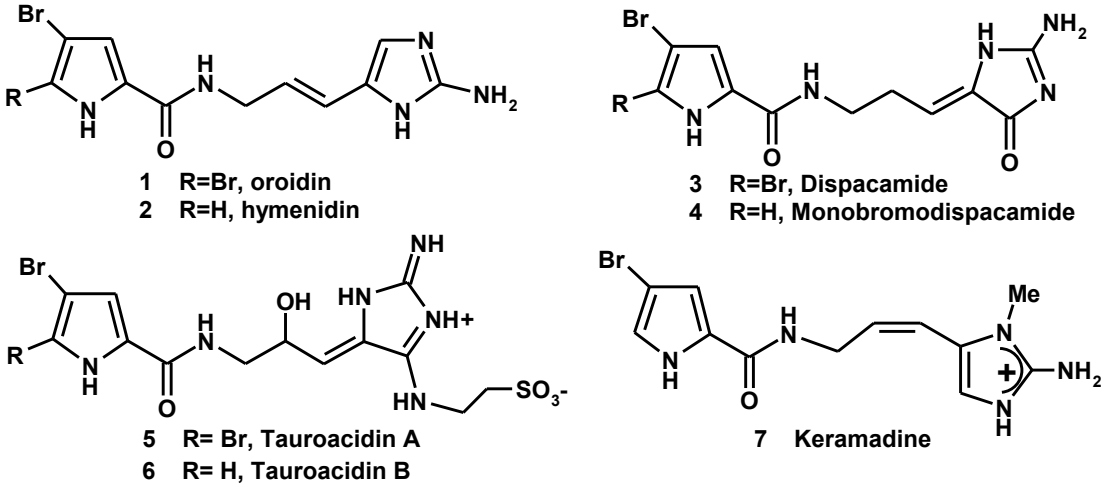


Figure 1

Jun'ichi Kobayashi *et al*. have isolated two new bromopyrrole alkaloids, tauroacidins A (**5**) and B (**6**), with tyrosine kinase inhibitory activity from an Okinawan marine sponge *Hymeniacidon* sp. and the structures were elucidated on the basis of spectral data and

chemical means.[4] Keramadine (**7**), a novel antagonist of serotonergic receptors, has been isolated from the Okinawan sea sponge *Agelas sp*. by Nakamura *et al*. Keramadine is biogenetically closely related to oroidin and sceptrin, which have been isolated from the same genus Agelas. However, the configuration of the double bond is in reverse of those in these compounds.[5]

Cyclic pyrrole-imidazole alkaloids

Sceptrin (**8**), the first dimeric pyrrole-imidazole alkaloid was isolated from *Agelas sceptrum* (Lamarck) by Faulkner and co-workers. It shows potent antiviral, antimuscarinic, antibacterial, and antihistaminic activity.[6a] Ageliferin (**9**), an antiviral agent structurally related to sceptrin, was isolated in 1989 from *Agelas conifera* by Rinehart[6b] (Figure **2**).

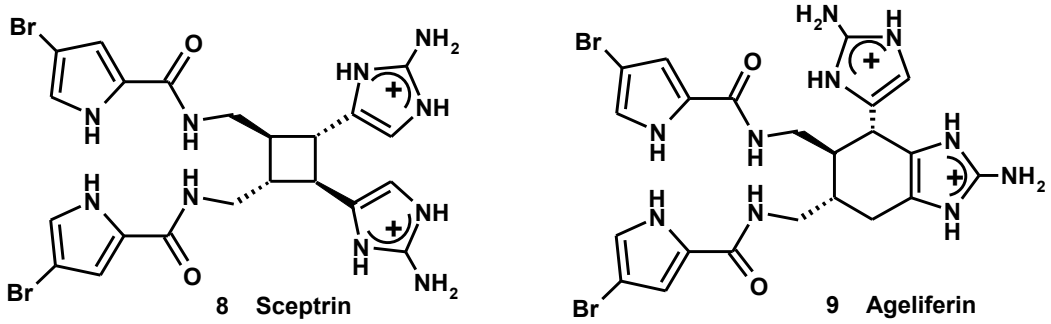


Figure 2

Slagenins A, B and C (**10**-**12**) are novel bromopyrrole alkaloids with a unique tetrahydrofuro[2,3-d]imidazolidin-2-one moiety, isolated from the Okinawan marine sponge, *Agelas nakamurai* by Kobayashi and co-workers[7] (Figure **3**).

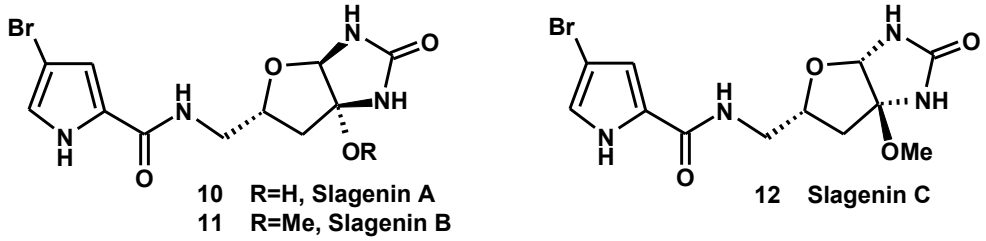


Figure 3

Cyclooroidin (**13**), isolated from the Mediterranean sponge *Agelas oroides* possesses the unprecedented N1:C9 connection.[8] Hymenialdisine (**14**), a tricyclic bromo pyrrole alkaloid, was isolated from the Okinawan marine sponge *Hymeniacidon aldis* by Kitagawa and co-workers in 1983.[9] Dibromophakellin (**15**), a guanidine alkaloid isolated as a hydrochloride salt from the marine sponge *Phakellia flabellate* by Sharma *et al*. It exhibits

a very mild antibacterial action against *B. subtilis* and *E. coli.*[10a] Dibromoagelaspongin (**16**) was isolated as its hydrochloride salt from the marine sponge *Agelas sp*.(Tanzania) and contains a guanidine moiety, possesses a different molecular skeletal structure. This compound appeared to be biogenetically related to phakellins[10b] (Figure **4**).

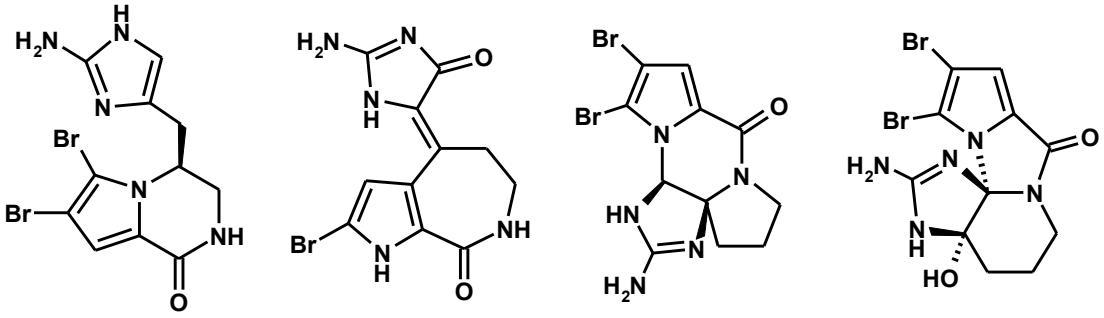


Figure 4

Agelastatin A (**17**), a tetracyclic alkaloid of the oroidin family was isolated from the axinellid sponge Agelas dendronorpha by D'Ambrosio *et al*. It shows cytotoxicity toward tumour cells.[11] Palau'amine (**18**), a hexacyclic bisguanidine alkaloid was isolated from the Sponge *Stylotella agminata* by Scheuer and co-workers in 1993 (Figure **5**). It possesses antibiotic, antifungal and immunosuppressive activity.[12]

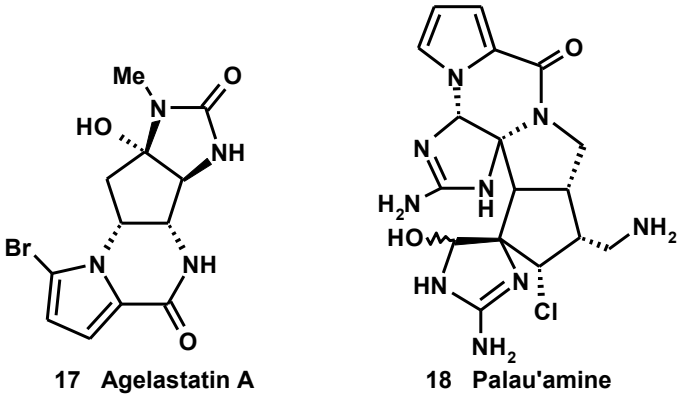


Figure 5

Bromopyrrole alkaloids with 3,4,5,6-tetrahydropyrimidine core

Manzacidins A, B and C (**19**-**21**) belonging to an unprecedented class of bromopyrrole alkaloids were isolated from the marine sponge *Hymeniacidon sp*. collected from Okinawa, Japan.[13a] Manzacidin D (**23**) was isolated from the coralline demosponge *Astrosclera willeyana* collected in Australia.[13b] N-Methyl manzacidin C (**22**) was from the marine sponge *Axinella brevistyla* in Japan.[13c] Manzacidins consists of pyrrolecarboxilic

acid and an unusual 3,4,5,6-tetrahydropyrimidine unit in which the two amino groups of the latter are attached to secondary and tertiary stereogenic carbon centers. While manzacidin A and C are diastereomeric at the C-9 position, manzacidin A and D have different substituents at the C-3 and N-14 positions (Figure **6**). In the preliminary tests, manzacidins exhibit similar biological activities like other bromopyrrole alkaloids.

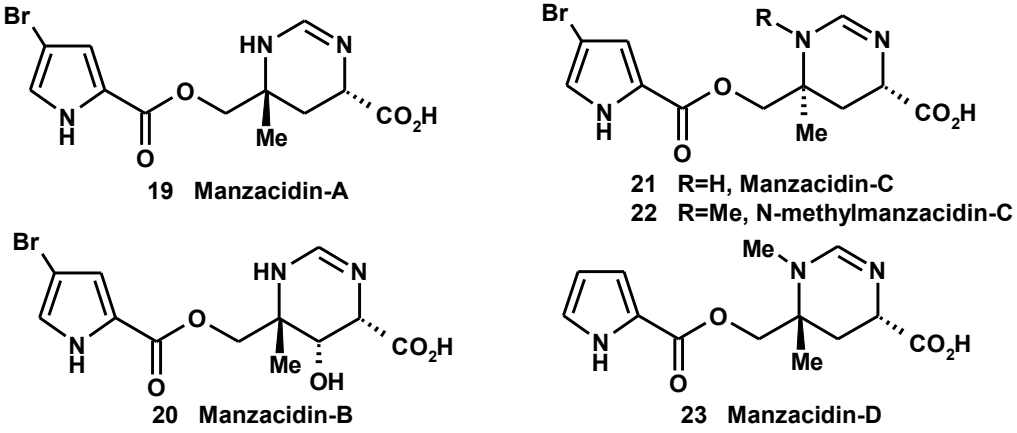


Figure 6

Alkaloids structurally related to manzacidins

Clathramides A (**24**) and B (**26**) are two novel isomeric bromopyrrole alkaloids containing the uncommon N-methylimidazolinium moiety, isolated from the Caribbean sponge *Agelas Clathrodes*.[14a] Clathramides C (**25**) and D (**27**) are N-14 nor- derivatives of clathramides A and B respectively isolated from the same source by Cafieri *et al*.[14b] These compounds show mild antifungal activity (Figure **7**).

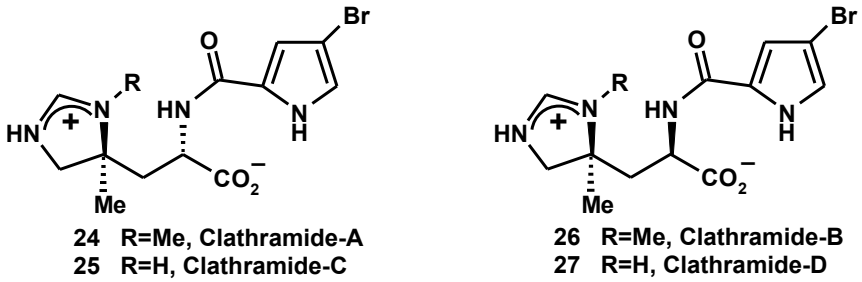


Figure 7

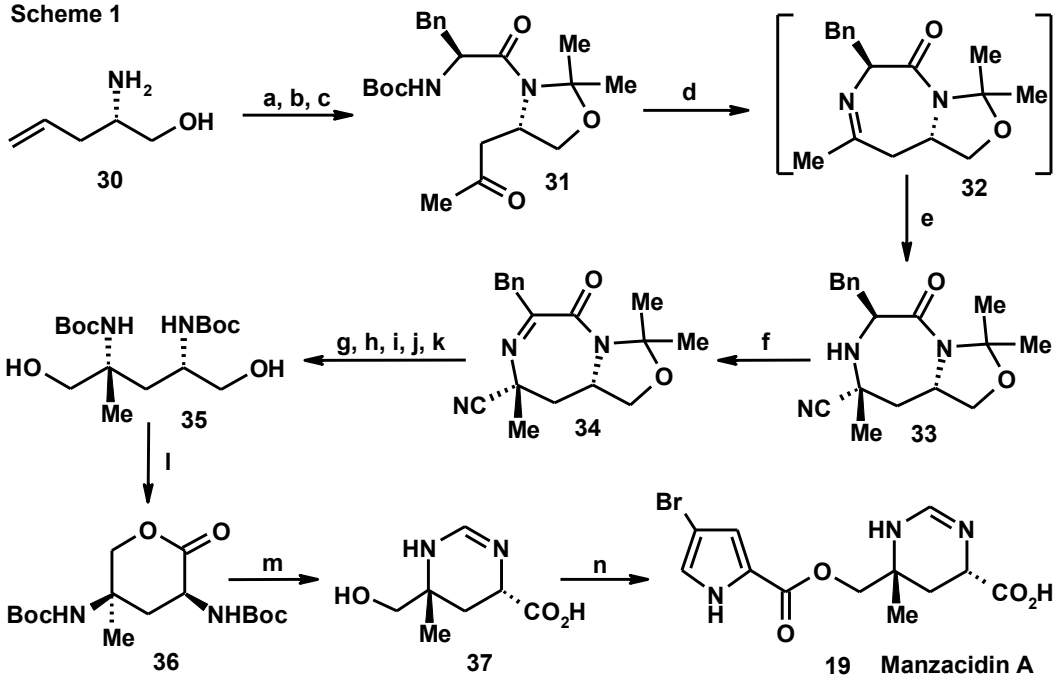
Ectoine (**28**) and hydroxyectoine (**29**) possess the 3,4,5,6-tetrahydropyrimidine moiety, which is present in all the manzacidins.[15a] Though this pyrimidine core is found in a number of chromopeptidic siderophores of fluorescent *Pseudomonsa*, compounds **28** and **29** are closely related to manzacidins (Figure **8**). These secondary aminoacids act as agonists or antagonists for the receptors of peptide molecules.[15b]

Figure 8

Synthetic approaches in manzacidins

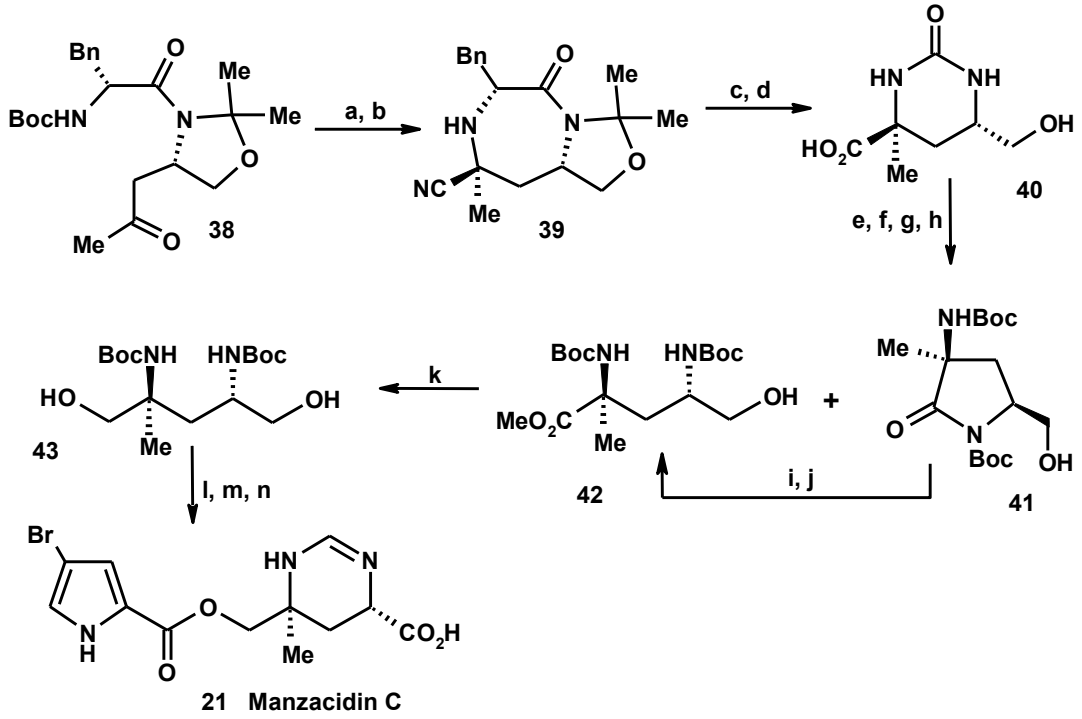
Ohfune's approach (manzacidin A and C)[16]

Ohfune *et al*. synthesized both the manzacidin A (**19**) and C (**21**) using asymmetric Strecker reaction with phenylalanine as the chiral axillary, to create the quaternary amine and assigned the absolute stereochemistry of these natural products. Phenylalanine was removed from the substrate by oxidation into the imine followed by hydrolysis in the synthesis of manzacidin A. But in the case of manzacidin C, the axillary was removed by oxidation into the corresponding hydroxylamine and was hydrolyzed (Schemes **1** and **2**).



Reagents: a) Et_3N, Boc-L-phenylalanine succinimide; b) 2,2-dimethoxypropane, p-TSA; c) $PdCl_2$, CuCl, O_2; d) TMSOTf, 2,6-lutidine; e) TMSCN, $ZnCl_2$; f) O_3, MeOH; g) conc. HCl; h) Boc_2O, $NaHCO_3$; I) $Me_4NOH.5H_2O$, $(Boc)_2O$; j) CH_2N_2; k) $LiAlH_4$; l) PDC; m) TFA, $CH(OMe)_3$, conc. HCl; n) NaH, 4-bromotrichloroacetylpyrrole.

Scheme 2

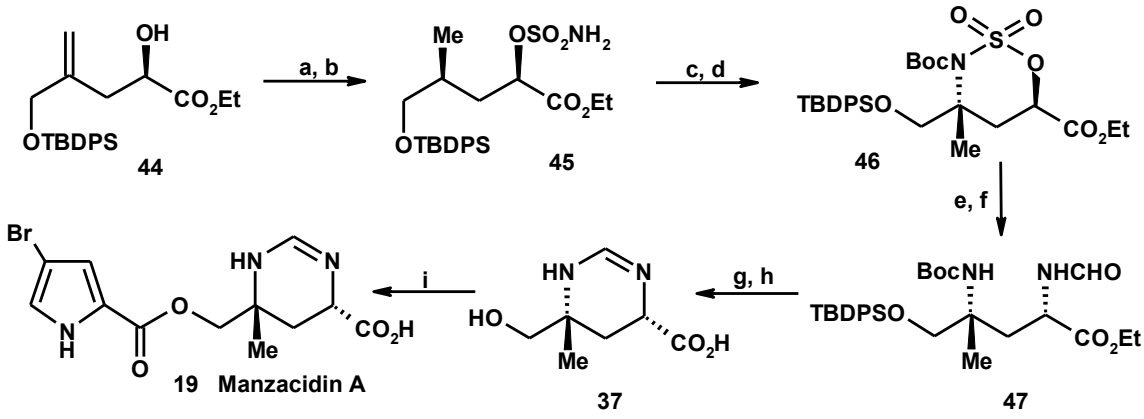


Reagents: a) TMSOTf, 2,6-lutidine; b) TMSCN, $ZnCl_2$; c) $MeReO_3$, urea-H_2O_2; d) conc. HCl; e) 10 % H_2SO_4; f) Boc_2O, $NaHCO_3$; g) $Me_4NOH.5H_2O$, Boc_2O; CH_2N_2; I) 0.3N NaOH; j) CH_2N_2; k) $LiAlH_4$; l) PDC; m) TFA, $CH(OMe)_3$, conc. HCl; n) NaH, 4-bromotrichloroacetylpyrrole.

Du Bois' approach (manzacidin A and C)[17]

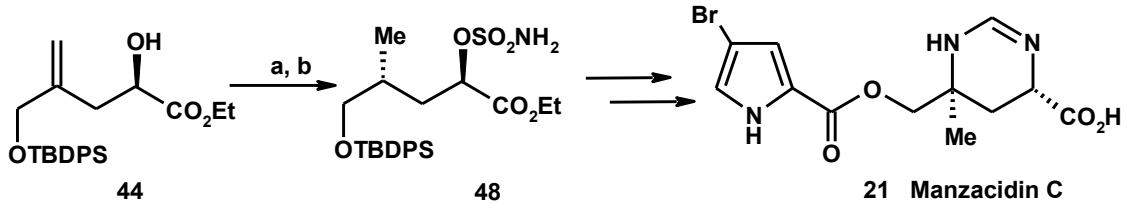
Du Bois *et al*. have synthesized both manzacidin A (**19**) and C (**21**) through a C-H insertion of nitrene reaction for the construction of the quaternary amine. Their synthesis commenced with the diastereoselective hydrogenation of the homoallylic alcohol (Schemes **3** and **4**).

Scheme 3: synthesis of manzacidin-A



Reagents: a) H_2, $Rh(cod)_2OTf$, (R)-PHANEPHOS; b) $ClSO_2NCO$, HCO_2H; c) $Rh_2(OAc)_4$, $PhI(OAc)_2$, MgO; d) Boc_2O; e) NaN_3; f) H_2, Pd/C, N-formylbenzotriazole; g) $POCl_3$, 2,6-^{t}Bu$_2$-4-MeC_5H_2N; h) 8 M HCl; i) NaH, 4-bromotrichloroacetylpyrrole.

Scheme 4: synthesis of manzacidin-C

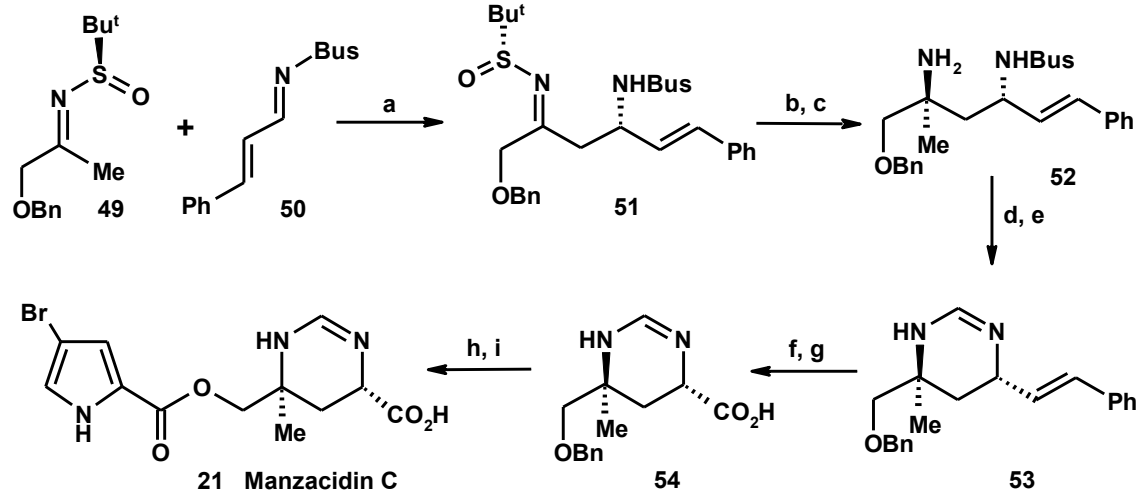


Reagents: a) H_2, Rh[((*S,S*)-Et-DUPHOS)(cod)]OTf; b) $ClSO_2NCO$, HCO_2H.

Lanter's approach (manzacidin C)[18]

A total synthesis of manzacidin C (**21**) was reported by Lanter and co-workers by asymmetric aza-Mannich reaction utilizing chiral sulfinimine anion as the nucleophile and N-sulfonyl aldimine as the electrophilic component (Scheme **5**).

Scheme 5



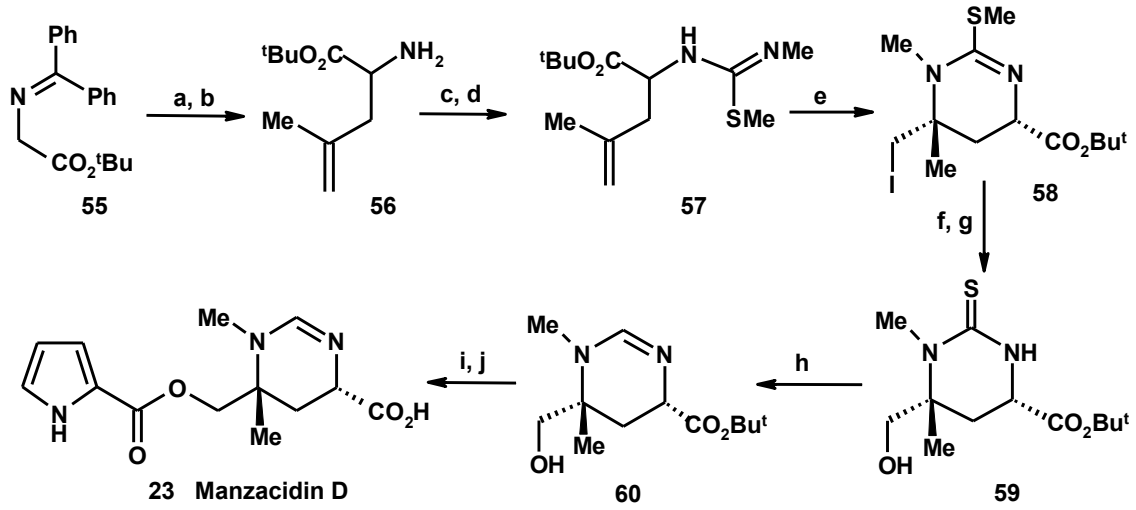
Reagents: a) LHMDS; b) MeMgBr; c) HCl/dioxane; d) $AcOCH(OMe)_2$; e) HCl/AcOH; f) O_3, MeOH; g) $NaClO_2$; h) H_2, Pd/C; I) NaH, 4-bromotrichloroacetylpyrrole.

MacKay's approach (manzacidin D)[19]

The first total synthesis of manzacidin D (**23**) was reported by MacKay and co-workers using a diastereoselective iodocyclization of an olefinic isothiourea **57** to

introduce the quaternary center. Conversion of thiourea **59** to the requisite formamidine **60** was achieved using H_2O_2.urea complex (Scheme **6**).

Scheme 6

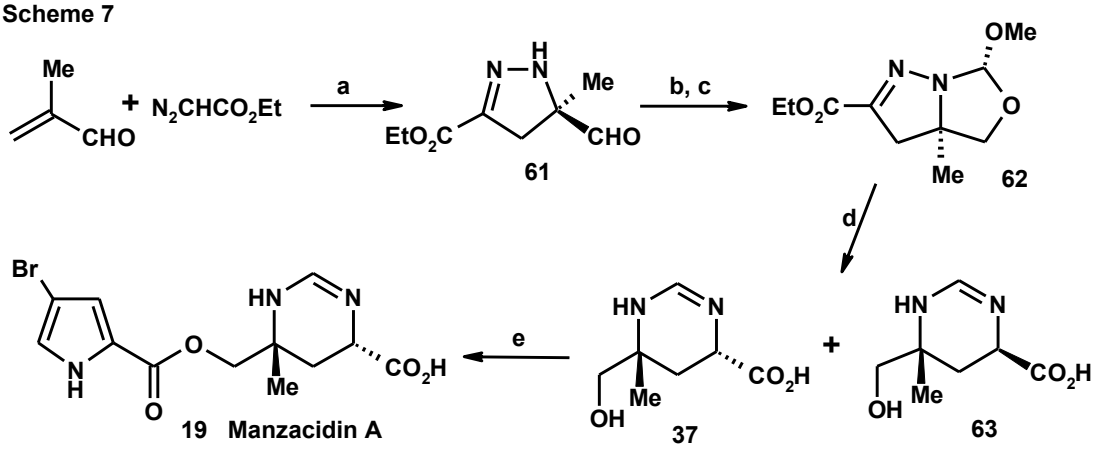


Reagents: a) NaH, methallylbromide; b) dil.HCl; c) MeNCS; d) MeI, MeCN; e) IBr; f) $AgOCOCF_3$; g) H_2S, pyridine, Et_3N; h) H_2O_2.urea; i) 4N HCl; j) NaH, trichloroacetylpyrrole.

Kano's approach (manzacidin A)[20]

Using catalytic asymmetric 1,3-dipolar cycloaddition, a short total synthesis of manzacidin A (**19**) was reported by Kano and *et al*. This natural product was achieved in just five steps in good enantioselectivity (Scheme **7**).

Scheme 7

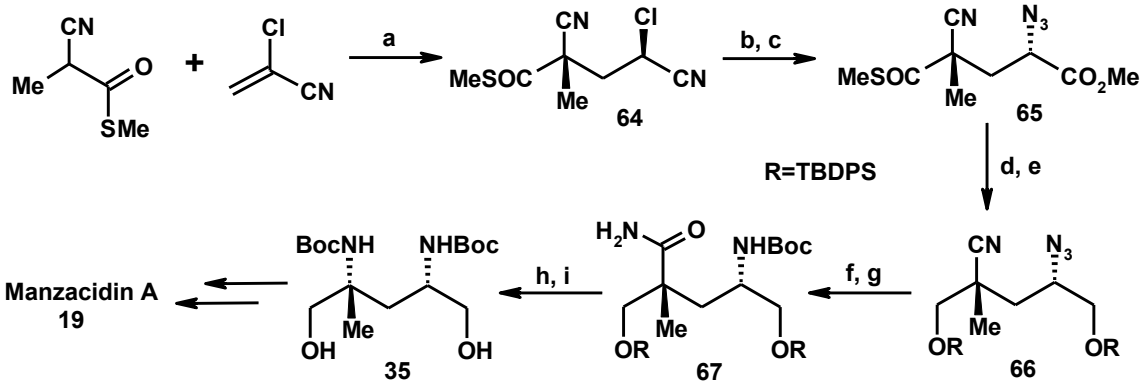


Reagents: a) Bis {((S)-binaphthoxy)(isopropoxy)titanium}oxide; b) $NaBH_4$; c) PPTS, $CH(OMe)_3$; d) Raney-Ni, H_2, $^iPrOH/H_2O$; e) NaH, 4-bromotrichloroacetylpyrrole.

Li Deng's approach (manzacidin A)[21]

A formal total synthesis of manzacidin A (**19**) has been reported by Deng and co-workers, using cinchona alkaloid catalyzed asymmetric tandem conjugate addition-protonation for the direct creation of nonadjacent stereocenters (Scheme **8**).

Scheme 8



Reagents: a) 20 mole % Quinidine-9-acetate; b) NaN_3; c) TMSCl, MeOH; d) $NaBH_4$, $Hg(OAc)_2$; e) TBDPSCl, imidazole; f) $[PtH(PMe_2OH)(PMe_2O)_2H]$; g) Pd/C, $(Boc)_2O$; h) $Pb(OAc)_4$, ^tBuOH; i) TBAF.

Bromopyrrole alkaloids manzacidin A-D and *N*-methyl manzacidin C (**19**-**23**) were isolated from marine sponges.[13] The constitution and relative stereochemistry of manzacidins were elucidated via a combination of NMR, IR and mass spectroscopic techniques. These molecules consist of a bromopyrrolecarboxylic acid and an unusual 3,4,5,6-tetrahydropyrimidine unit in which the two amino groups of the latter are attached to secondary and tertiary stereogenic carbon centers. While manzacidin A and C are diastereomeric at the C-9 position, manzacidin A and D have different substituents at the C-3 and N-14 positions. The most complex member of this class of alkaloids, manzacidin B has an additional, secondary hydroxyl group in the pyrimidine core. Bromopyrrole alkaloids are known to exhibit pharmacologically useful activities such as α-adrenoceptor blockers, antagonists of serotonergic receptor, actomyosin ATPase activators etc. Although manzacidins exhibit similar biological activities, only preliminary tests have been carried out owing to the extremely small amount of samples available from marine sources (Figure **9**).

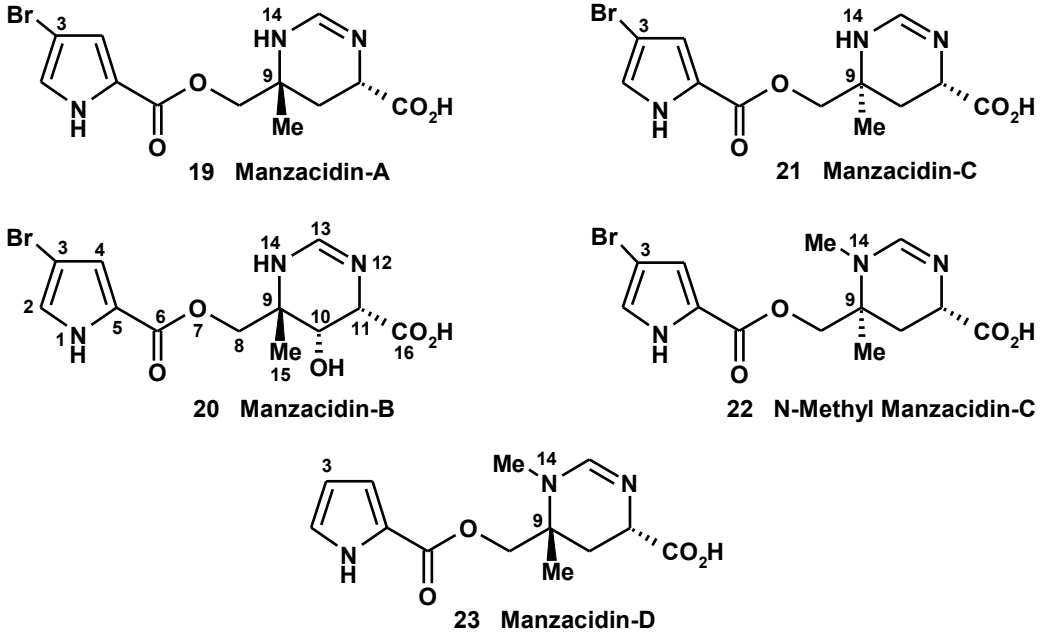


Figure 9: Manzacidins

Due to their structural complexity, natural scarcity, and biological importance, manzacidins prompted many groups to pursue their total synthesis. Enantioselective

syntheses of manzacidin A and C,[16-18,20,21] and a racemic synthesis of manzacidin D[19] have been reported. Because of their daunting molecular architecture and biological properties, we embarked on a program directed toward their total synthesis, initially targeting manzacidin B.

Synthetic strategy

In planning our approach, we hoped to develop a convergent, flexible, and stereocontrolled route that would provide the natural products as well as their analogues for further biological study. Inspection of the structural features of manzacidin B (**20**) coupled with the literature precedents revealed the ester functionality as the strategic site for disconnection to give the known bromopyrrole moiety[16] (**68**) and the highly functionalized tetrahydropyrimidine core (**69**). We planned to construct the compound **69** from the lactone **70** using trimethyl orthoformate by following a similar strategy reported by Ohfune *et al*.[16] For the synthesis of the lactone **70**, which includes all the three chiral

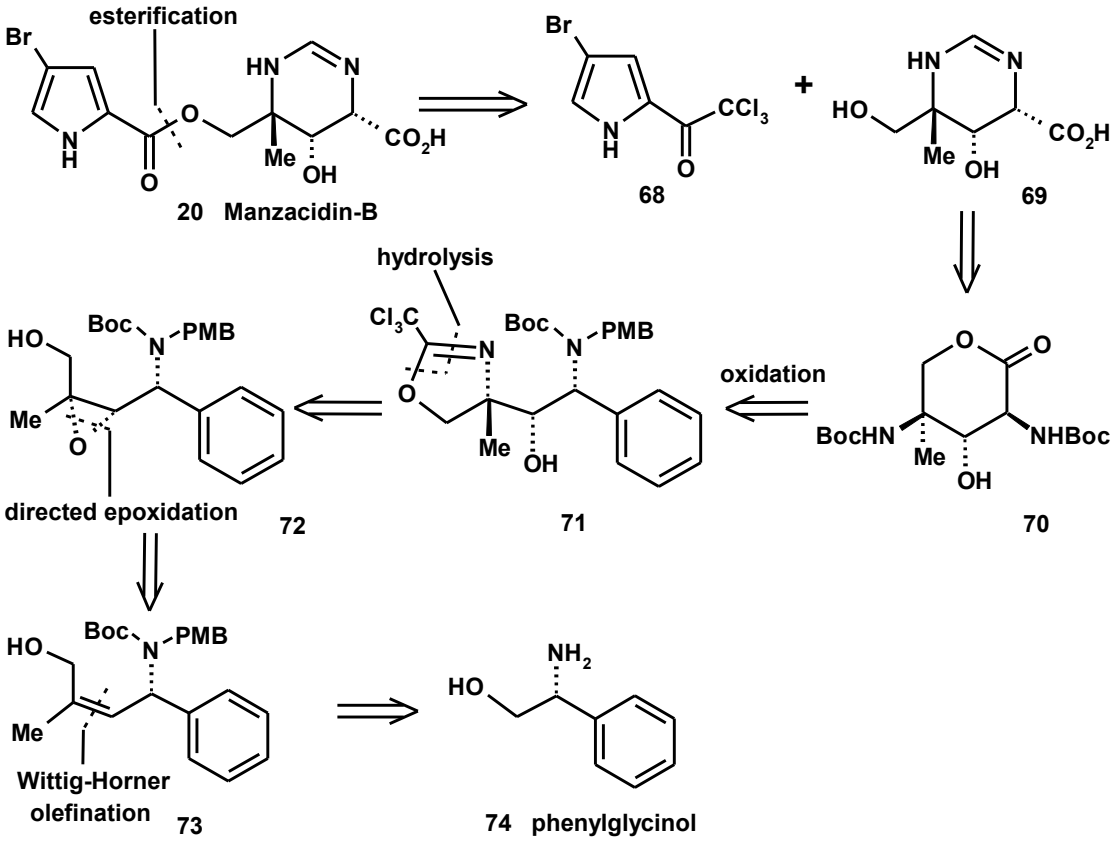
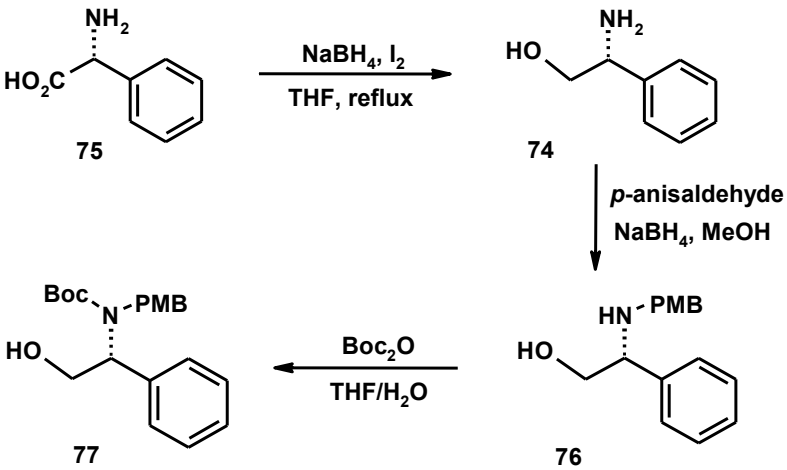


Figure 10: Synthetic strategy

centers present in the molecule, we have devised a novel strategy by the combination of a chelation controlled epoxidation[22] of the allylic alcohol **73** and an intramolecular epoxide opening with trichloroacetimidate (Hatakeyama's protocol)[23] for the introduction of the tertiary amine stereoselectively. The allylic alcohol **73** could be made from phenyl glycinol **74** by a stereoselective Wittig-Horner olefination followed by reduction of the ester (Figure **10**).

Our synthesis was started with the reduction of phenyl glycine using $NaBH_4/I_2$ in THF to get the phenyl glycinol **74** by following the known procedure.[24] The amino group in phenyl glycinol was protected by reductive amination followed by carbamate formation. The imine formed from compound **74** and *p*-anisaldehyde in methanol at 0 ^oC, was reduced with $NaBH_4$ in the same pot.[25] This secondary amine **76** was converted to the Boc derivative **77** by treatment with $(Boc)_2O$ in THF/water. In the ^1H NMR spectrum of compound **77**, a resonance due to the *tert*-butyl protons was observed at 1.44 ppm (9H, s) and the $-OC\underline{H}_3$ protons were at 3.77 ppm as a singlet. PMB methylene protons were observed at 4.18 ppm (2H, br s) and the $-C\underline{H}_2OH$ protons were at 3.98 ppm (2H, br s). The Boc-carbonyl carbon resonated at 158.1 ppm in the ^{13}C NMR spectrum. Mass spectrum [m/z 358 for $(M+H)^+$] and elemental analysis confirmed the assigned structure (Scheme **9**).

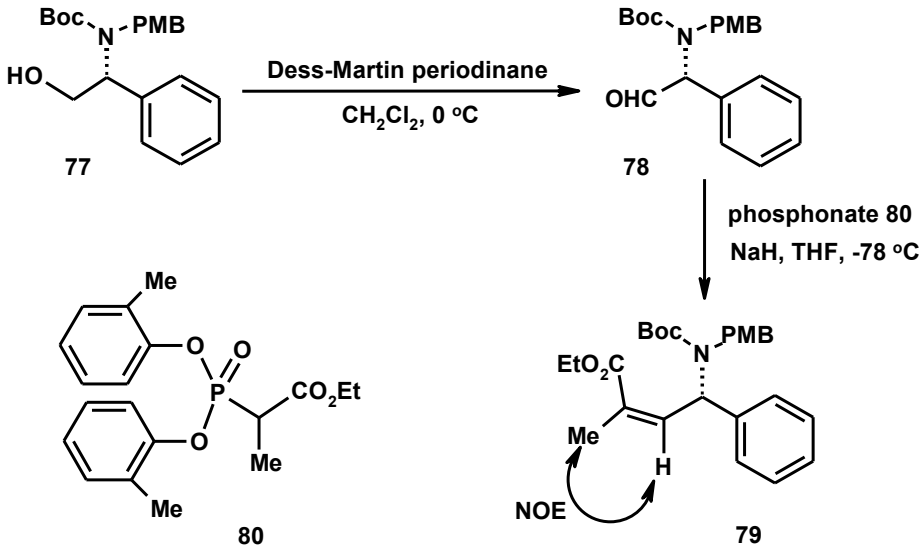
Scheme 9



For the stereoselective construction of the α,β-unsaturated *Z*-ester **79**, the alcohol **77** was first subjected to the Dess-Martin periodinane oxidation to the corresponding aldehyde **78**.[26] This aldehyde (without column purification) on treatment with the anion generated from the phosphonate **80** and NaH, at –40 ^oC for 6 h afforded the desired *Z*-unsaturated ester **79**, exclusively.[27] In the ^1H NMR spectrum of compound **79**, a signal for the olefinic

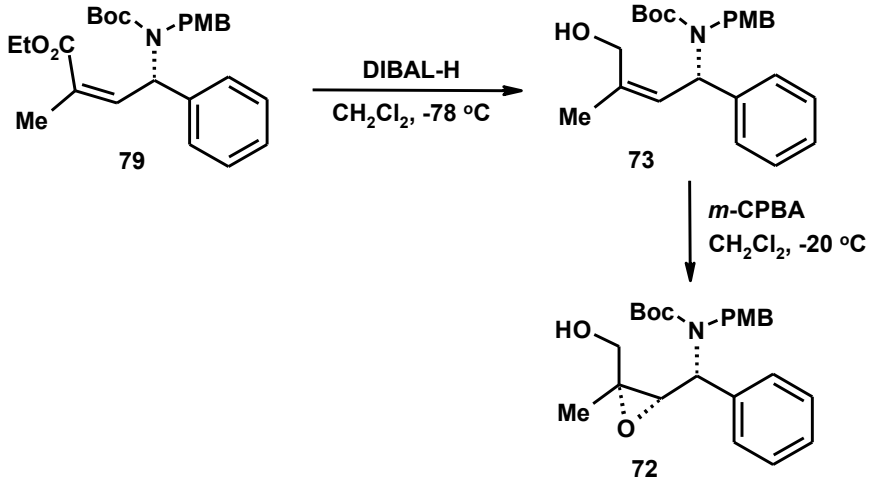
proton was observed at 6.18 ppm (1H, d, J = 9.2 Hz) and the resonance due to the allylic –$C\underline{H}_3$ was at 1.93 ppm (3H, s). The ester carbonyl carbon was observed at 166.5 ppm whereas the olefinic carbons were at 129.5 and 137.6 ppm in the ^{13}C NMR spectrum. Configuration of the olefin was confirmed from the NOE studies on compound **79**. NOE between the allylic –$C\underline{H}_3$ protons and the olefinic proton clearly indicated the *Z*-geometry of the olefin. In the mass spectrum, a signal for $(M+H)^+$ was observed at m/z 440. Though

Scheme 10



we could get the conjugated ester in good selectivity, the product was found to be optically inactive, probably due to racemization in the olefination step. Further studies were carried out with this racemic product without any attempt to get the optically pure material (Scheme **10**).

Scheme 11



The conjugated ester was reduced to the corresponding allylic alcohol **73** using DIBAL-H in CH_2Cl_2 at –78 ^oC. The allylic methylene protons of compound **73** were resonated at 4.02 and 4.05 ppm as doublets with J = 12.4 Hz and the olefinic proton was at 5.52 ppm as a doublet with J = 9.3 Hz. The mass spectrum [m/z 398 for $(M+H)^+$] and elemental analysis confirmed this transformation. For the synthesis of the *syn* epoxide **72**, we followed the chelation-controlled epoxidation reported by Kishi.[22] This transformation was accomplished by using 50 % *m*-CPBA in CH_2Cl_2 at –20 ^oC to give the desired epoxy alcohol **72**, as a single diastereomer (Scheme **11**). In the ^1H NMR spectrum of compound **72**, the epoxide proton signal appeared at 3.39 ppm as a doublet with J = 9.1 Hz. Mass spectrum [m/z 414 for $(M+H)^+$] supported the oxidized product. Stereoselectivity in this epoxidation was expected based on chelation between the allylic alcohol and carbamate in the substrate with the perbenzoicacid (co-operative effect, Figure **11**) and confirmed at a later stage.

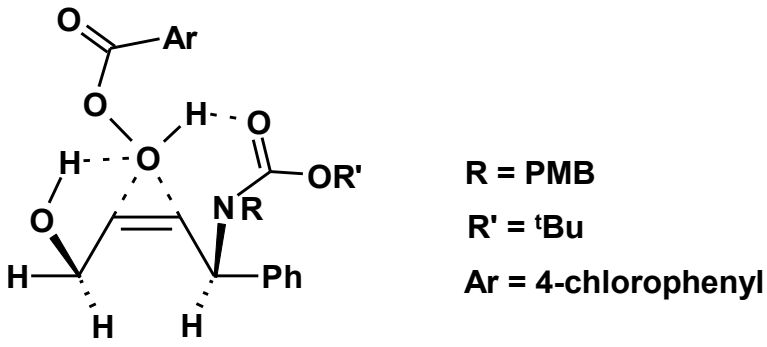
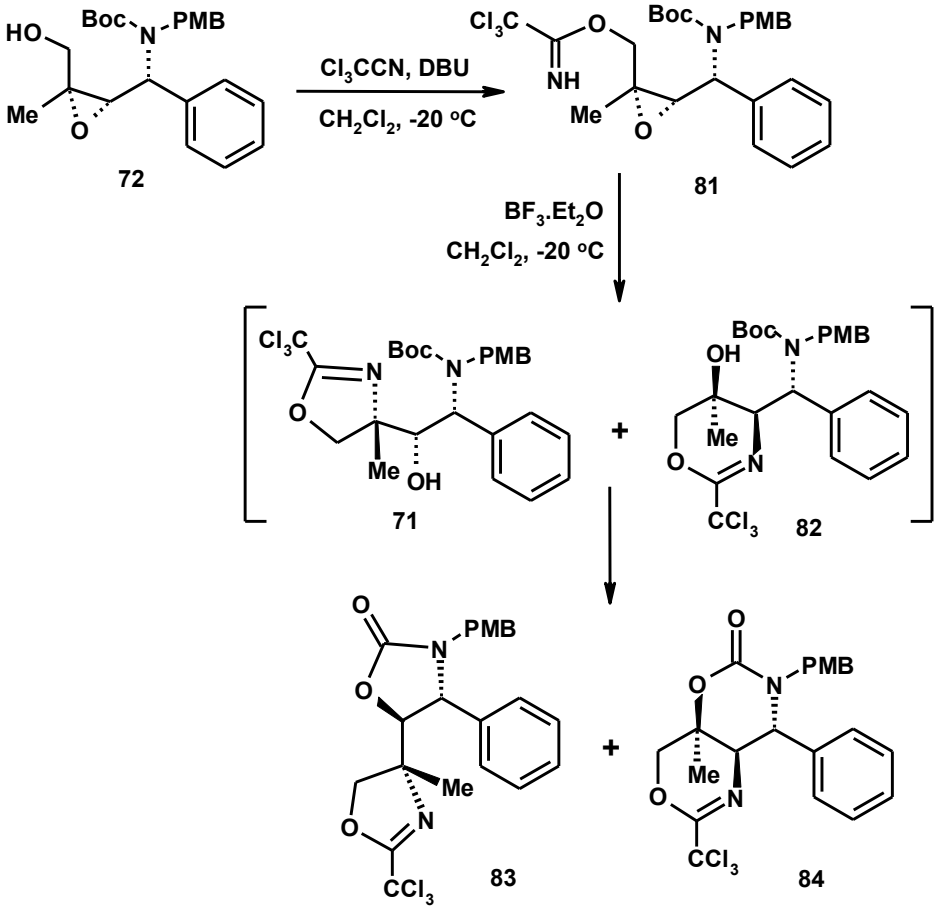


Figure 11: Chelation controlled epoxidation

To introduce the tertiary amine, we had adapted the Hetakeyama's protocol[23] using the trichloroacetimidate. Accordingly, compound **72** was treated with trichloroacetonitrile and DBU in CH_2Cl_2 at –20 ^oC to get the imidate **81**. After column purification, the imidate was subjected to the Lewis acid catalyzed epoxide opening using $BF_3.OEt_2$ in CH_2Cl_2 at –20 ^oC with the expectation to get the oxazoline derivative **71** (Scheme **12**). From the ^1H NMR spectrum, it was clear that the product formed was an inseparable mixture of two compounds in a ratio of 6:4. Absence of a signal due to the tertiary butyl group in the ^1H NMR spectrum, molecular ion at m/z 501 [which was 56 (butyl) less than the expected oxazoline] and the presence of a carbamate carbon in the ^{13}C NMR spectrum at 157.2 and 157.3 ppm indicated that the epoxide opening had taken place with the loss of *tert*-butyl group to give the compounds **83** and **84**. Formation of these compounds can be explained

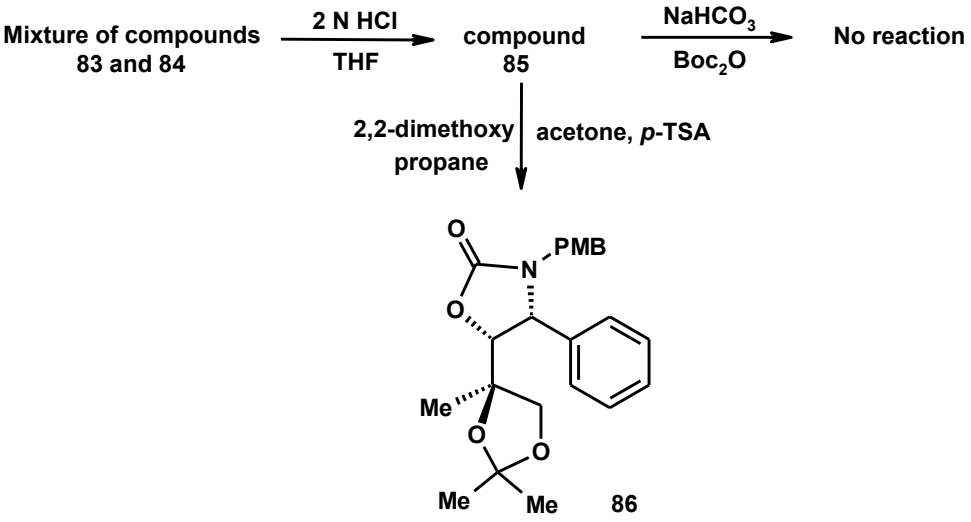
through the intermediates of **71** and **82**. Use of $SnCl_4$ instead of $BF_3.OEt_2$ also produced the same result.

Scheme 12



To further confirm the proposed structures, the mixture of compounds **83** and **84** was subjected to acid hydrolysis with 2 N HCl in THF. After disappearance of the starting material (TLC), the reaction mixture was treated with solid $NaHCO_3$ and Boc_2O in the same pot. To our surprise, there was no reaction in the second step and the intermediate **85** was isolated as a single compound. In the ^1H NMR spectrum of this compound, a singlet was observed at 3.33 ppm (2H) along with two doublets at 3.50 and 4.78 ppm with a coupling constant 14.7 Hz. But the elemental analysis showed presence of only one nitrogen atom in this compound. Formation of a single compound from a mixture of starting material and the elemental analysis did not help to assign the structure. Fortunately, an acetonide derivative **86** obtained from compound **85** by treatment with 2,2-dimethoxypropane and *p*-TSA gave suitable crystals for the single crystal X-ray crystallographic analysis to assign the structure and relative stereochemistry of the

Scheme 13



compound **85** (Scheme **13**). From the crystal structure analysis, it was found that an inversion at the methine carbon (>CHO-) of the oxazolidinone and the retention at the quaternary center had taken place in the Lewis acid catalyzed reaction of compound **81** (Figure **12**). From the elemental analysis it was found that compound **86** also had only one nitrogen. From the crystal structure analysis and the elemental analysis result we have assigned the structure of this compound to be **86**. In the ^{1}H NMR spectrum of this compound **86**, the acetonide methyl protons resonated at 1.25 and 1.35 ppm. The quaternary carbon of this acetonide was observed at 110.0 ppm in the ^{13}C NMR spectrum. The crystal structure showed the three chiral centers were *R,R,R* (relative stereochemistry), which in turn proved the geometry of the olefin in the Wittig olefination step and the stereochemistry of the epoxide.

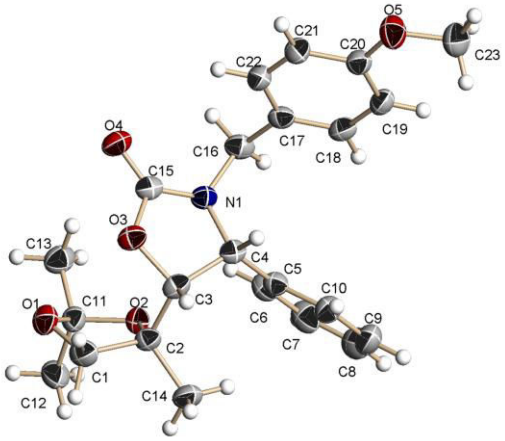
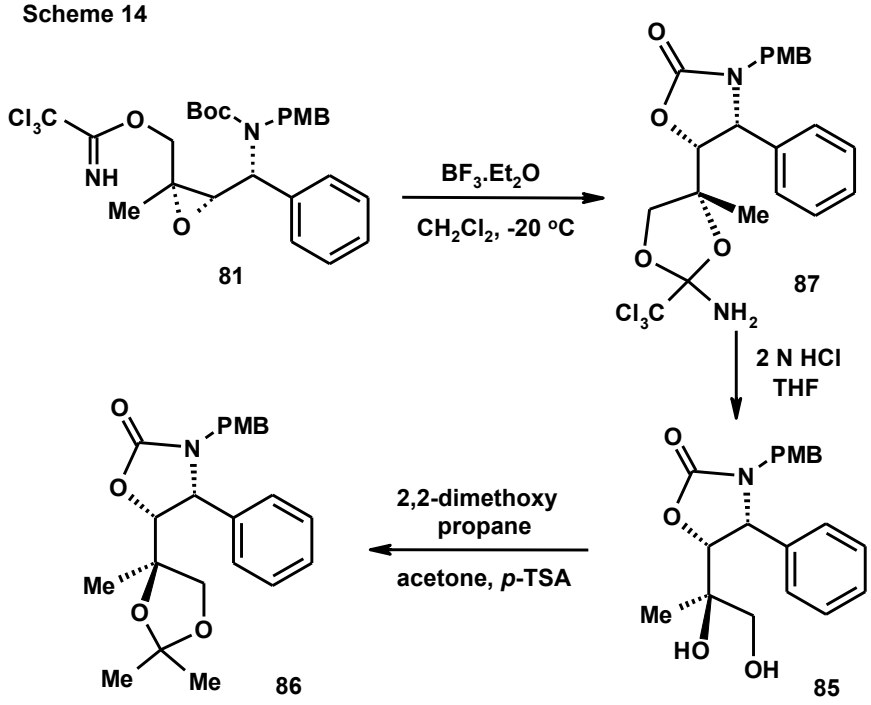


Figure 12: ORTEP diagram of compound 86

From the formation of compound **86**, we have assigned the structure of the hydrolysis product as a diol **85**. Since compound **85** was obtained as a single product in 82% yield from a 6:4 mixture of starting material, we came to a conclusion that both the starting compounds should have the diol **85** as part of their structure. From these results the product formed in the epoxide opening reaction with Lewis acid was reassigned as compound **87**. Here the epoxide opening had taken place with the tert-butoxy carbonyl group with the loss of the *tert*-butyl group to give the oxazolidinone. And the tertiary alcohol formed in this reaction cyclised with the imidate under the influence of the Lewis

Scheme 14



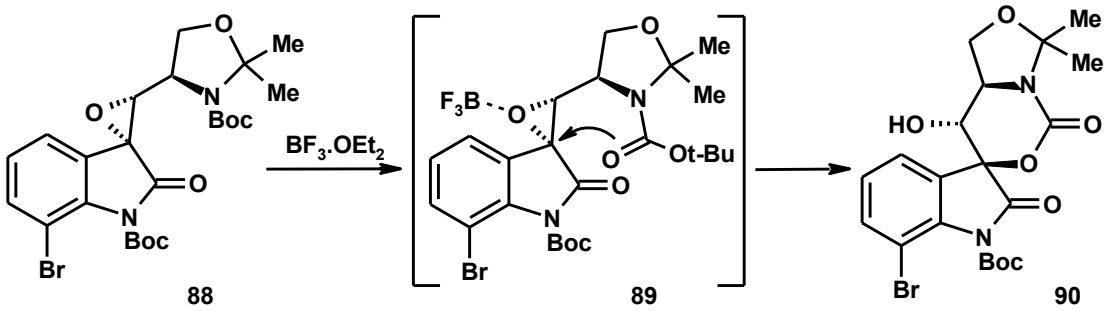
acid to form an unusual orthoamide with a quaternary carbon chiral center. This structure was confirmed from the careful analysis of the NMR spectra of compound **87**. The singlets observed at 2.39 ppm and at 2.61 ppm were assigned for the amine protons. The signal at 115.7 and 116.9 ppm were assigned for the orthoamide quaternary carbon. Formation of a mixture of products was due to the newly formed orthoamide quaternary chiral center (diastereomers, Scheme **14**).

Mechanism for the formation of the orthoamide

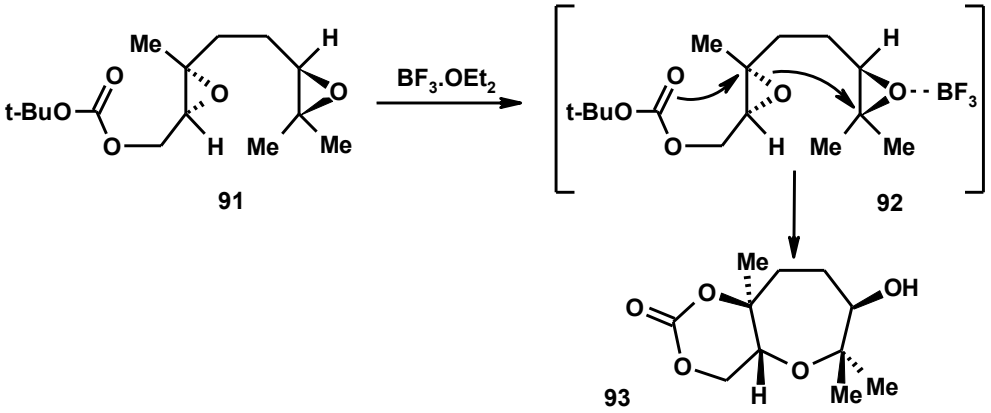
Lewis acid promoted epoxide opening with N-*tert*-butyl carbamate (**88** to **90**) was employed by Hirama and co-workers in a synthesis of TMC-A, a potent proteasome inhibitor (Scheme **15**).[28] Similarly a series of epoxide opening with a carbonate

functionality for the synthesis of trans fused polycyclic ethers (Scheme **16**), using Lewis acid also reported (**91** to **93**).[29] From these reactions it was clear that the epoxides undergo Lewis acid catalyzed ring opening and also it take part in further reactions if a suitably placed electrophile is available in the substrate.

Scheme 15

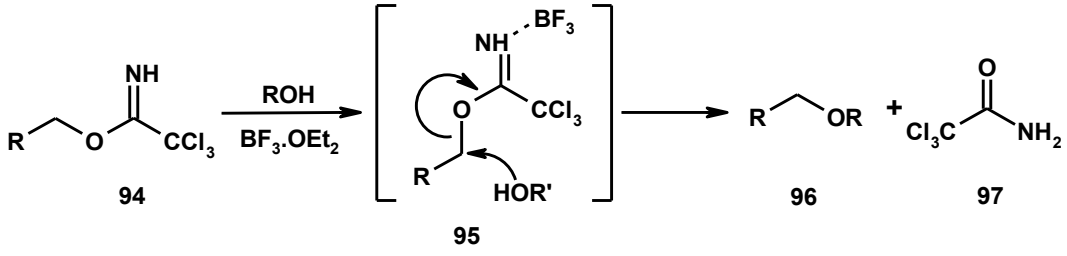


Scheme 16



Use of trichloroacetimidate is well documented in the literature as an activator in glycosidation[30a] and used in the protection of hydroxyl groups as their benzyl[30b] and *tert*-butyl ethers as well as formation of *tert*-butyl esters catalyzed by Lewis acids.[30c] In all these cases, the carbon attached with the imidate oxygen becomes electrophilic when the imidate nitrogen complexes with the Lewis acid (Scheme **17**).

Scheme 17



From these literature reports, a possible mechanism for the formation of the orthoamide has been outlined below by a combination of two distinct reactions (Figure **13**). First, the epoxide opening took place with the *tert*-butyl carbamate (as a nucleophile) to form an oxazolidinone instead of the expected trichloroacetimidate in the presence of a Lewis acid (**98**). Second, the tertiary hydroxyl group formed in the epoxide opening with the Boc group **99**, added with the trichloroacetimidate in a 1,2-fashion under the influence of the same Lewis acid to form an unusual cyclic orthoamide **87** with a stereogenic carbon

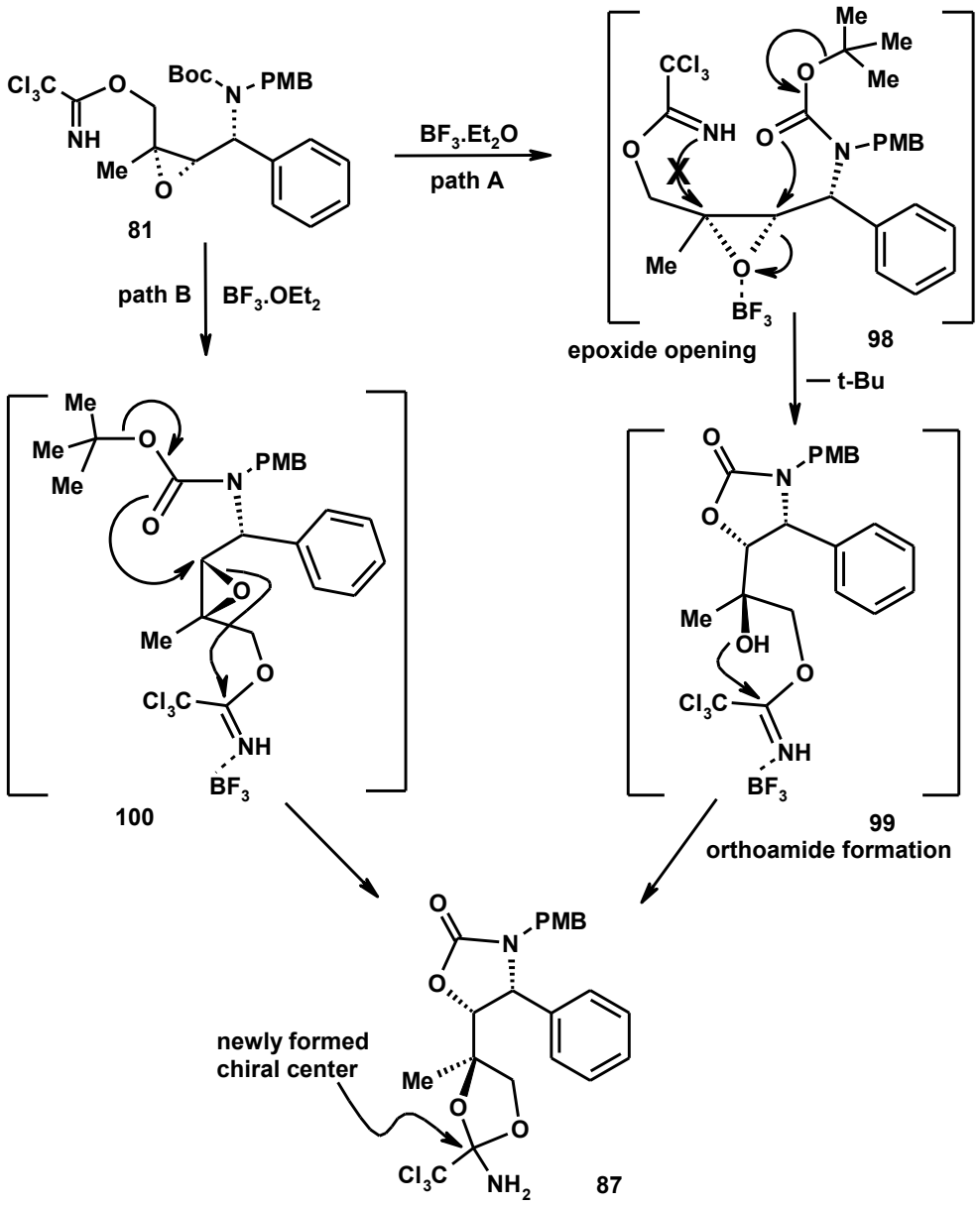
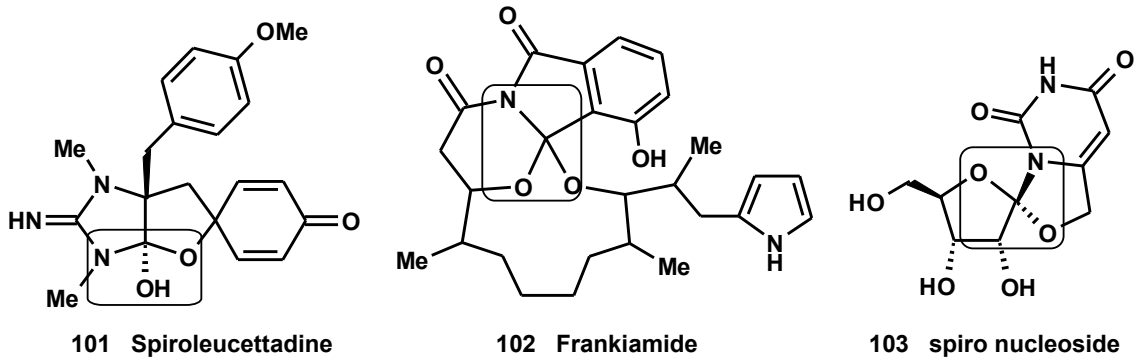


Figure 13: Proposed mechanism

center (path A). Also the simultaneous formation of both the oxazolidinone and orthoamide as given in path B (via **100**) cannot be ruled out. In both the cases, the trichloroacetimidate acts as an electrophile instead of a nucleophile. Though the epoxide opening with carbamate is well known,[28] to the best of our knowledge, formation of an orthoamide from the trichloroacetimidate (in a 1,2-addition in the presence of a Lewis acid) was a new observation.

It is pertinent to mention that there are few examples found in the literature having the orthoamide functionality as part of a molecule. For example, Spiroleucettadine (**101**)[31a] and Frankiamide (**102**)[31b] possess this orthoamide group. In addition to these molecules, synthetic analogue of spirocyclic nucleosides (**103**) also have this moiety (Figure **14**).[31c]



101 Spiroleucettadine **102 Frankiamide** **103 spiro nucleoside**

Figure 14 : Natural and designed orthoamides

Revised strategy

From the formation of the unusual orthoamide **87**, it was clear that the *tert*-butyl carbamate act as a better nucleophile than the trichloroacetimidate in the compound **81** under the reaction conditions. To overcome the chemoselectivity problem, we have devised an alternative approach in which the *tert*-butoxy carbonyl group was conformationally restricted in such a way that it could not react with the epoxide in the reactive conformation. Since the carbamate protection was necessary for the stereoselective epoxidation through the co-operative effect with the perbenzoic acid, we opted for this strategy. We believed that incorporating the Boc protected amine in a ring, like the substrate, **104** could bring the required conformational change. Though the *tert*-butoxycarbonyl group can occupy either pseudo equatorial (**105** and **106**) or axial (**107** and **108**) positions as given in conformations **A-D** (Figure **15**), the former should be favored

for the steric considerations. Similarly, the side chain having both the epoxide and the imidate can be either in a folded (**105** and **107**) or in a linear (**106** and **108**) conformations and the linear one was expected to be the more stable, again for the steric reasons.

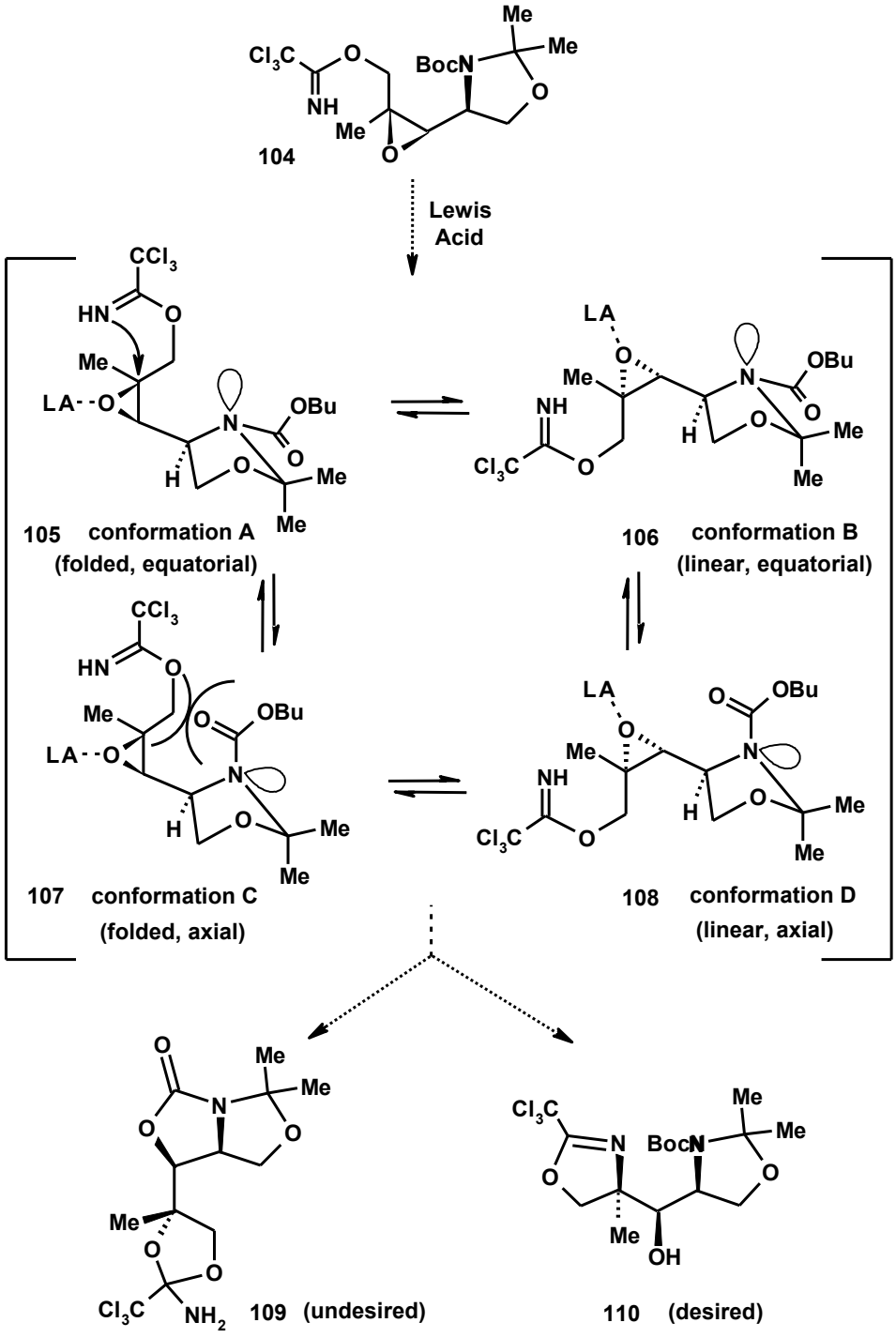


Figure 15: Conformational analysis

From this conformational analysis, it was clear that the Boc couldn't react with the epoxide unless until the molecule reaches the conformation **107** (which will not be favored due to steric congestion). But in all the conformations, the imidate could react with the epoxide to form the required oxazoline without facing any such steric hindrance. To test our hypothesis, we planed to synthesize the substrate **104** by following the same strategy described for the synthesis of the imidate **81**, from the Garner aldehyde. Since the absolute stereochemistry of the natural product was not known, the (*S*)-Garner aldehyde was selected as the starting material (Figure **16**). The oxazoline (**110**) formed could be converted to the triol (**112**) by acid hydrolysis followed by protection of the amine. This triol in turn could be converted to the lactone **111** either by direct oxidation or through selective protection/deprotection sequence.

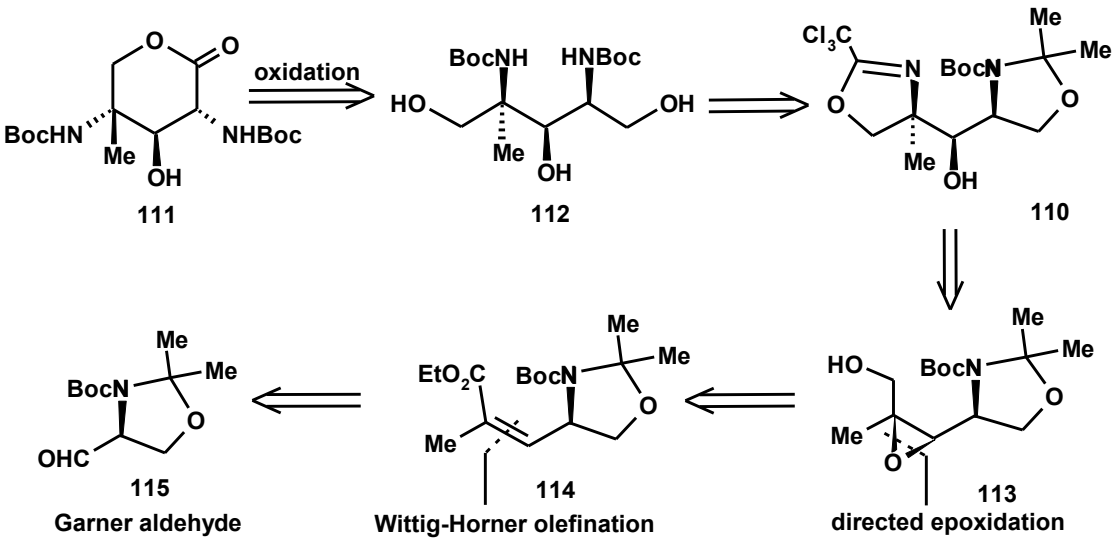
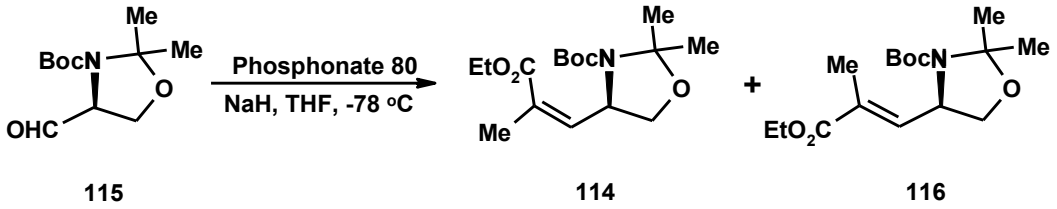


Figure 16: Revised strategy

Garner aldehyde[32] (**115**) on treatment with the phosphonate **80** and NaH at –78 ^{o}C in THF for 4 h produced a mixture of the conjugated esters in the ratio of 3.5:1 in favor of the desired *Z*-isomer (**114**).[27] In the ^{1}H NMR spectrum of the major isomer, the olefinic proton signal was observed at 6.00 ppm as a multiplet due to rotamers whereas the same for the minor isomer was a doublet at 6.63 ppm with J = 9.2 Hz. The carbonyl carbons of the ester groups were resonated at 166.0 ppm for the major isomer whereas in minor isomer it was noticed at 166.6 ppm in the ^{13}C NMR spectra. The IR spectrum (1691 and 1701 cm^{-1} for *Z* and *E* isomers respectively) and the mass spectrum [m/z 314 for $(M+H)^{+}$ in both the

Scheme 18



115 114 116

isomers] supported the formation of these compounds (Scheme **18**). The configurations of the olefins were confirmed from the NOE studies. NOE between the olefinic proton and the allylic –C<u>H</u>$_3$ protons clearly indicated the *Z*-geometry of the major isomer. In the minor isomer **116**, a NOE between the allylic –CH_3 protons and the allylic methine proton proved the *E*-geometry of the olefin (Figure **17**).

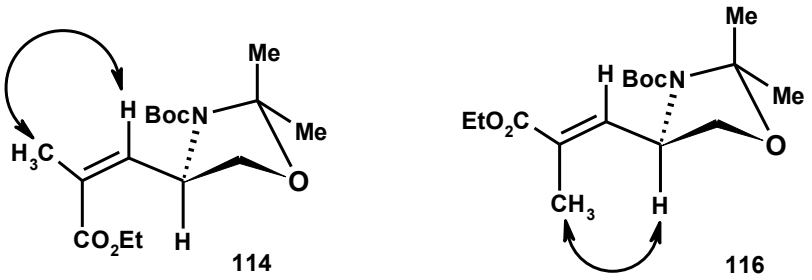
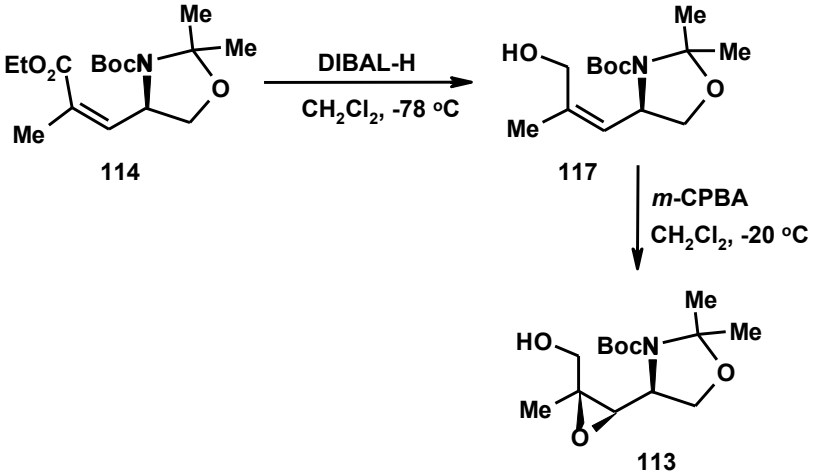


Figure 17: NOE studies

Having synthesized the required conjugated ester **114**, we next turned our attention for the construction of the *syn* epoxide **113**, which was required for the introduction of the tertiary amine chiral center. Thus, unsaturated ester **114** was reduced to the corresponding allylic alcohol **117** using DIBAL-H at –78 ^{o}C in CH_2Cl_2. In the ^{1}H NMR spectrum of

Scheme 19

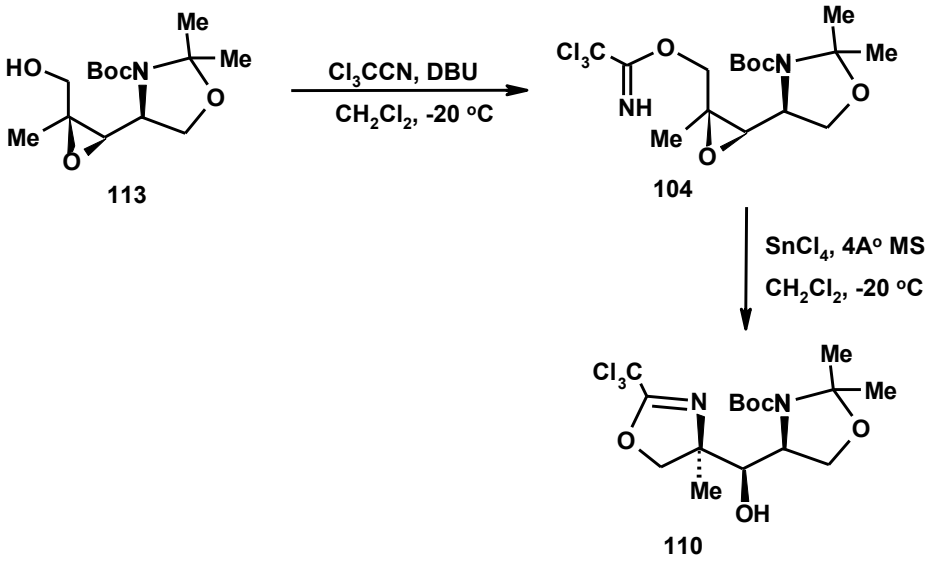


114 117 113

compound **117**, signals for the –C<u>H</u>$_2$OH protons were observed at 3.64 and 4.51 ppm as doublets with J = 12.1 Hz whereas the olefinic proton was at 5.27 ppm (d, 1H, J = 10.3 Hz). In the ^{13}C NMR spectrum, the olefinic carbons were resonated at 124.7 ppm and 137.8 ppm. Mass spectrum [m/z 272 for $(M+H)^+$] and elemental analysis confirmed this transformation. Epoxidation of this allylic alcohol with *m*-CPBA in CH_2Cl_2 at –20 ^{o}C gave the epoxy alcohol **113** as a single diastereoisomer (Scheme **19**). The epoxide proton was located at 2.80 ppm (d, 1H, J = 7.9 Hz). In the mass spectrum m/z 288 was observed for $(M+H)^+$.

The epoxy alcohol **113** was converted to the imidate **104** using trichloroacetonitrile and DBU in CH_2Cl_2 at –20 ^{o}C. When this imidate was subjected to the epoxide opening using $SnCl_4$ at –20 ^{o}C, desired oxazoline derivative **110** was isolated as a single product (Scheme **20**). In the ^{1}H NMR spectrum of the compound **110**, the oxazoline protons were observed at 4.25 and 4.99 ppm as two doublets with J = 9.0 Hz where as the C<u>H</u>OH was at 3.76 ppm (d, 1H, J = 9.8 Hz). In the ^{13}C NMR spectrum, -<u>C</u>Cl$_3$ and the <u>C</u>=N were observed at 86.2 and 161.3 ppm respectively. In the IR spectrum an absorption at 1658 cm^{-1} was observed for the C=N of the oxazoline. The mass spectrum [m/z 431 for $(M+H)^+$] and elemental analysis confirmed this structure assignment. Finally, the regioselectivity of the epoxide opening and the relative stereochemistry were confirmed from the single crystal X-ray crystallographic analysis of the compound **110** (Figure **18**).

Scheme 20



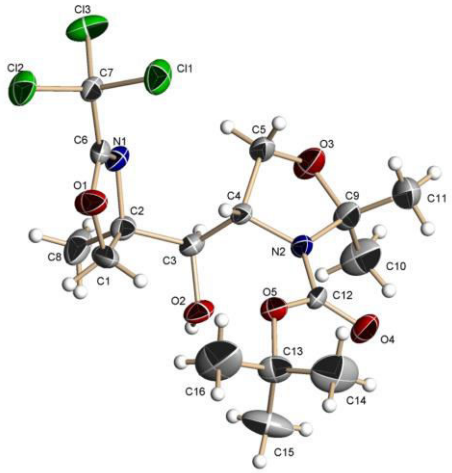


Figure 18: ORTEP diagram of compound 110

With this oxazoline formation, the synthesis of the chiral fragment present in the natural product, manzacidin B was achieved. A comparison of the structure and the reactivity of both the imidates derived from phenyl glycine and from the Garner aldehyde were shown in figure **19**. Though both the substrates (**81** and **104**) have the same electrophile (epoxide) and the nucleophiles (imidate and Boc), the complete reversal of

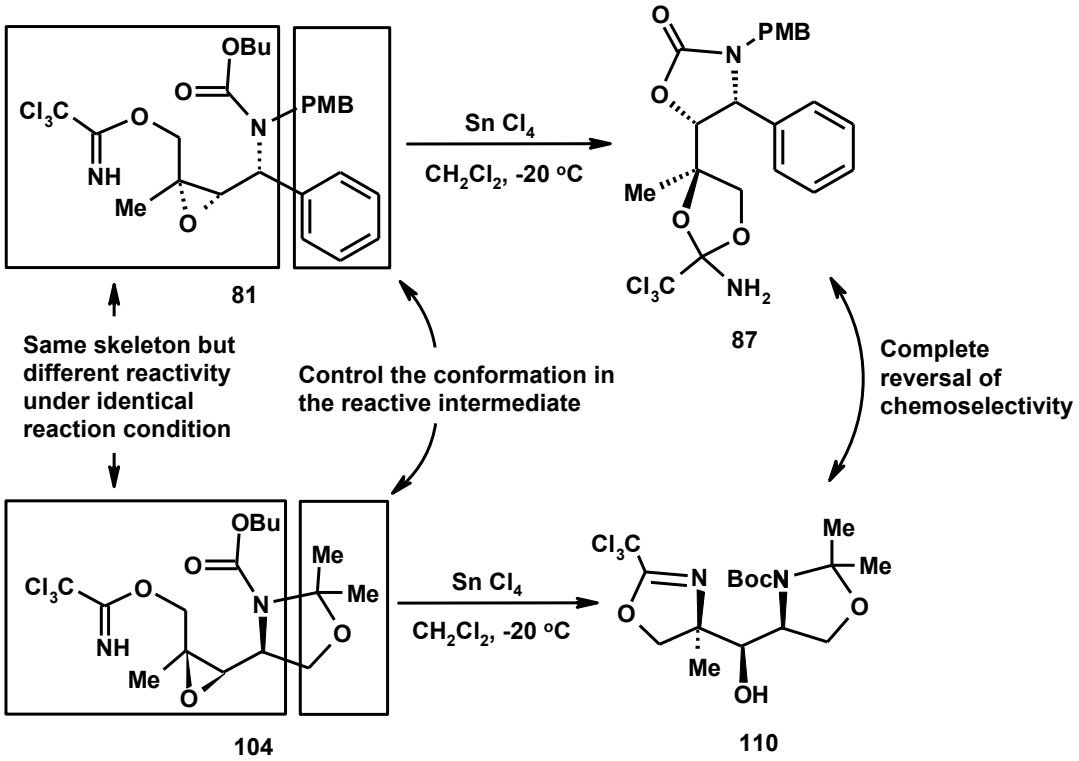
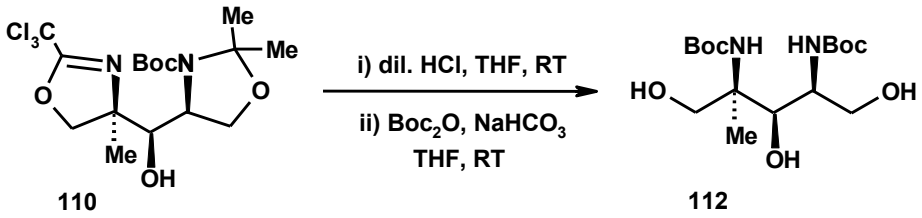


Figure 19: Effect of conformation on reactivity

chemoselectivity was achieved by bringing an overall conformational change with a slight modification in the substrate, under identical reaction conditions.

The oxazoline **110** was next converted to the triol **112** in two-steps by treatment with 2 N HCl in THF to hydrolyze the oxazoline and the acetonide followed by protection of both the amines as their Boc derivative using $(Boc)_2O$ after neutralizing the reaction mixture with $NaHCO_3$ in the same pot (Scheme **21**). In the ^1H NMR spectrum of compound **112**, the methylene protons adjacent to the tertiary amine carbon center were located at 3.67 and 3.95 ppm as doublets (J = 11.5 Hz) where as the other methylene protons resonated at 3.64 ppm (dd, 1H, J = 10.6, 6.2 Hz) and 3.74 ppm (dd, 1H, J = 10.6, 3.6 Hz). In the ^{13}C NMR spectrum, the methylene carbons were resonated at 63.7 and 65.8 ppm while the quaternary carbon having an amine was at 59.8 ppm. In the mass spectrum, m/z 365 was observed for $(M+H)^+$.

Scheme 21



After the stereoselective synthesis of the triol **112** with all the stereocenters required for the construction of manzacidin B was completed, a report appeared with the synthesis and structural revision of manzacidin B[33] (Figure **20**). This article described the revision in the stereochemistry of the C-9 chiral center of manzacidin B based on the total synthesis (details not available).

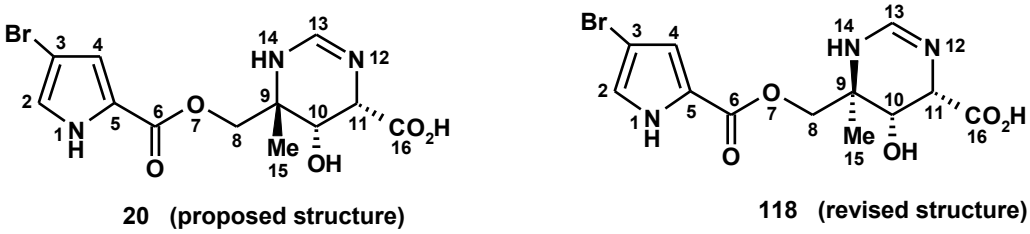
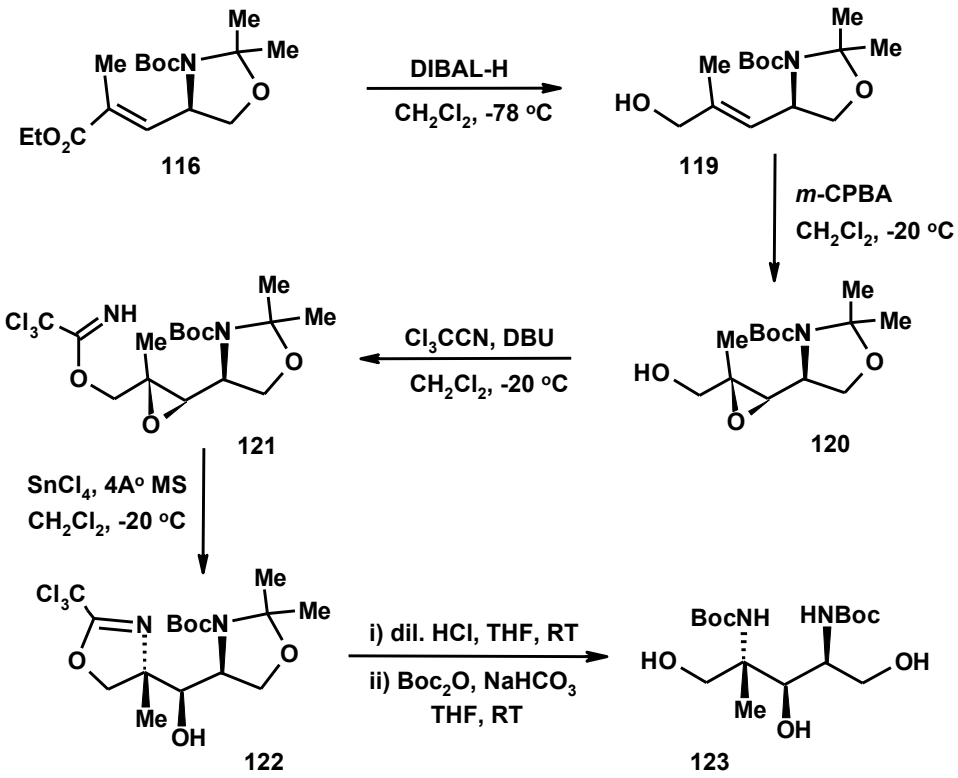


Figure 20: structure of manzacidin B

Based on this report, synthesis of the triol **112** was of no use as the stereochemistry at the C-9 carbon of triol needed revision. Therefore we directed our effort for the

synthesis of triol **123** by following the same strategy used for the synthesis of the triol **112**. In order to get the correct stereochemistry at C-9, we started the synthesis of the triol **123** from the trans isomer **116** of the Wittig-Horner reaction. Accordingly, compound **116** was reduced to the corresponding allylic alcohol **119** using DIBAL-H at –78 ^{o}C in CH_2Cl_2. In the ^{1}H NMR spectrum of the compound **119**, a signal for the –C$\underline{H_2}$OH was observed at 4.00 ppm as a singlet for two protons whereas the olefinic proton was at 5.44 ppm (d, 1H, J = 9.2 Hz). In the ^{13}C NMR spectrum, the olefinic carbons were resonated at 124.2 ppm and 135.8 and 137.1 ppm (rotamer). The mass spectrum [m/z 272 for $(M+H)^{+}$] and elemental analysis confirmed this transformation. Epoxidation of this allylic alcohol was accomplished by treatment with *m*-CPBA in CH_2Cl_2 at –20 ^{o}C. In the ^{1}H NMR spectrum

Scheme 22



of the compound **120**, the epoxide proton was located at 2.87 ppm (d, 1H, J = 7.8 Hz). In the mass spectrum m/z 288 was observed for $(M+H)^{+}$. This alcohol was converted to the trichloroacetimidate **121** using trichloroacetonitrile and DBU in CH_2Cl_2 at –20 ^{o}C. When this imidate was subjected for the epoxide opening using $SnCl_4$ at –20 ^{o}C, the desired oxazoline derivative **122** was isolated as a single product. In the ^{1}H NMR spectrum of this compound, the oxazoline protons were observed at 4.30 and 4.70 ppm as two doublets with

J = 8.9 Hz where as the CHOH was at 3.64 ppm (d, 1H, J = 9.4 Hz). In the ^{13}C NMR spectrum -CCl_3 and C=N were observed at 86.5 and 161.8 ppm respectively. In the IR spectrum, an absorption at 1654 cm^{-1} was observed for the C=N of the oxazoline. The mass spectrum [m/z 431 for $(M+H)^+$] and elemental analysis confirmed this structure assignment. Finally, the regioselectivity of the epoxide opening and the relative stereochemistry of compound **122** were confirmed from the single crystal X-ray crystallographic analysis (Figure **21**). Hydrolysis and Boc protection of the compound **122** yielded the triol **123**. In the ^{1}H NMR spectrum of the compound **123**, the methylene protons adjacent to the tertiary amine carbon center were located at 4.30 (1H, d, J = 8.9 Hz) and 4.70 (1H, d, J = 8.9 Hz) ppm where as the other methylene protons resonated at 3.99 (1H, dd, J = 5.6, 9.4 Hz) ppm and 4.35 (d, 1H, J = 9.4 Hz) ppm. In the ^{13}C NMR spectrum, the methylene carbons were resonated at 63.5 and 67.9 ppm while the quaternary carbon having an amine was at 59.1 ppm. In the mass spectrum, m/z 365 was observed for $(M+H)^+$ (Scheme **22**).

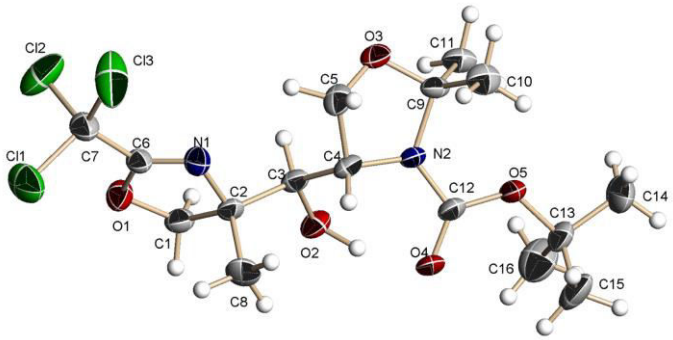
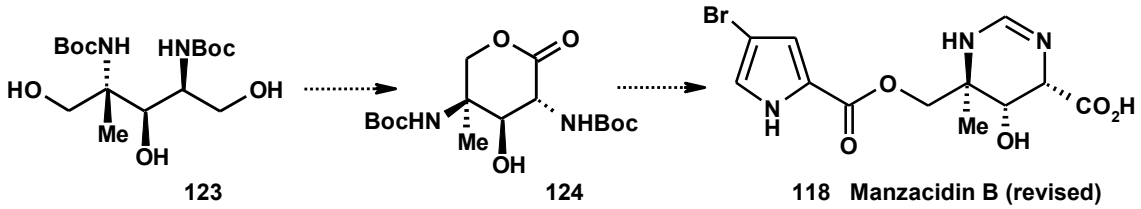


Figure 21: ORTEP diagram of compound 122

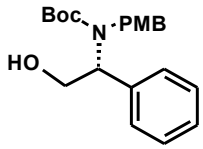
Having synthesized the triol **123** with the required stereochemistry our next concern was to synthesise the lactone **124** from the triol (Scheme **23**). Studies are directed toward the synthesis of this triol and the natural product, manzacidin B **118** (revised).

Scheme 23



In conclusion, our attempt for the Lewis acid catalyzed epoxide opening with the imidate derived from phenyl glycine yielded an undesired compound **87**, which includes a cyclic carbamate and an unusual cyclic orthoamide. To overcome this problem, a change in the overall conformation was brought in without changing the functional groups, and two diastereomers of the basic unit present (with all the chiral centers) in manzacidins were synthesized. Conversion of the triol **123** into the natural product **118** through the lactone **124** is in progress in our laboratory.

(2*R*)-2-[(*tert*-Butoxycarbonyl)(4-methoxybenzyl)amino]-2-phenylethanol (77)



To a mixture of $NaBH_4$ (12.1 g, 317.9 mmol) and D-phenyl glycine (20.0 g, 132.5 mmol) in THF (250 mL) was added a solution of iodine (33.7 g, 132.5 mmol) in THF (50 mL) dropwise at 0 °C and refluxed for 18 h. After cooling to 0 °C, methanol was added to the reaction mixture and the solvent was removed at reduced pressure. The residue was dissolved in 20% aq KOH solution (200 mL), stirred for 4 h and extracted with CH_2Cl_2 (4x100 mL). The organic layer was washed with brine, dried and concentrated to give the phenyl glycinol **74** (17.6 g) that was used in the next step without further purification. This amino alcohol was dissolved in methanol (200 mL) and *p*-anisaldehyde (17.5 g, 128.5 mmol) was added at 0 °C. After stirring for 1 h at room temperature, $NaBH_4$ (5.4 g, 141.4 mmol) was added and stirring continued for 2 h. The reaction was quenched by the addition of dilute acetic acid and the solvent was removed at reduced pressure. The residue was suspended in a 1:1 mixture of THF-water (100 mL) and Boc_2O (31.7 g, 145.2 mmol) was added. After 2 h, solvent was removed and the crude material was partitioned between CH_2Cl_2 and water. The organic layer was dried, concentrated and purified by silica gel column chromatography using light petroleum and ethyl acetate (7:3) as eluent to give the protected amino alcohol **77** (35.9 g, 76% for three steps) as a colourless thick paste.

$[\alpha]_D$ –30.6 (*c* 1.4, $CHCl_3$)

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.44 (s, 9H), 3.77 (s, 3H), 3.94 (br s, 2H), 4.18 (br s, 2H), 5.05 (t, 1H, *J* = 6.7 Hz), 6.80 (d, 2H, *J* = 8.7 Hz), 7.09-7.32 (m, 7H).

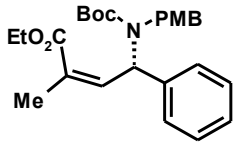
^{13}C NMR (50 MHz, $CDCl_3$): δ 27.9, 47.9, 54.5, 61.1, 62.1, 79.7, 113.2, 126.9, 127.4, 127.9, 130.9, 138.0, 156.1, 158.1

IR ($CHCl_3$, cm^{-1}): 3437, 2975, 2933, 1682, 1585, 1513, 1455, 1404, 1366, 1246, 1162, and 1036.

MS (ESI) m/z: 358 $(M+H)^+$

Anal. Calcd. for $C_{21}H_{27}NO_4$ (MW. 357): C, 70.56; H, 7.61; N, 3.92; Found C, 70.42; H, 7.65; N, 3.82.

Ethyl-(2*Z*,4*S*)-4-[(*tert*-butoxycarbonyl)(4-methoxybenzyl)amino]-2-methyl-4-phenyl-but-2-enoate (79)



Dess-Martin periodinane (5.3 g, 12.6 mmol) was added to a solution of amino alcohol **77** (3.0 g, 8.4 mmol) in CH_2Cl_2 (30 mL) and stirred at room temperature. After 30 min, diethyl ether (25 mL) was added followed by a solution of sodium thiosulphate (23 g) in 80% saturated aq $NaHCO_3$ (30 mL) and stirred for 10 min. The organic layer was separated and the aq layer was extracted with ether (20 mL). Combined organic layer was washed with water and brine. After drying over Na_2SO_4, solvent was removed at reduced pressure to give the aldehyde **78** (2.8 g) as a thick paste.

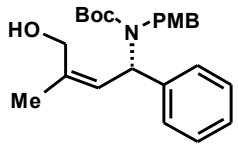
Phosphonate **80** (3.8 g, 10.5 mmol) in THF (10 mL) was added to a suspension of NaH (0.4 g, 10.1 mmol) in THF (5 mL) at 0 °C and stirred for 15 min at room temperature. The reaction mixture was cooled to –78 °C and a THF (10 mL) solution of aldehyde **78** (2.8 g) was added dropwise. After stirring for 6 h at –40 °C, the reaction was quenched by the addition of aq NH_4Cl. THF was removed at reduced pressure and the residue was partitioned between ethyl acetate and water. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated. The crude material was purified by silica gel column chromatography using light petroleum and ethyl acetate (19:1) to afford α,β-unsaturated ester **79** (2.66 g, 72% for two steps) as a colourless thick paste.

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.17 (t, 3H, *J* = 7.1 Hz), 1.31 (s, 9H), 1.93 (s, 3H), 3.78 (s, 3H), 4.09 (q, 2H, *J* = 7.1 Hz), 4.14 (d, 1H, *J* = 15.4 Hz), 4.60 (d, 1H, *J* = 15.4 Hz), 6.16 (d, 1H, *J* = 9.2 Hz), 6.38 (d, 1H, *J* = 9.2 Hz), 6.79 (d, 2H, *J* = 8.8 Hz), 7.17 (m, 7H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 13.6, 20.2, 27.8, 48.9, 54.6, 57.6, 60.0, 79.5, 113.2, 126.3, 127.7, 128.6, 129.5, 130.8, 137.6, 140.3, 155.1, 158.2, 166.5

IR ($CHCl_3$, cm^{-1}): 2978, 2931, 1711, 1691, 1512, 1452, 1366, 1247, 1163, and 1032.
MS (ESI) m/z: 440 $(M+H)^+$
Anal. Calcd. for $C_{26}H_{33}NO_5$ (MW. 439): C, 71.05; H, 7.57; N, 3.19; Found C, 71.09; H, 7.60; N, 3.21.

(2*Z*, 4*S*)-4-[(*tert*-Butoxycarbonyl)(4-methoxybenzyl)amino]-2-methyl-4-phenyl-but-2-en-1-ol (73)



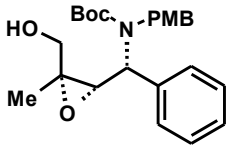
To a solution of the ester **79** (2.2 g, 5.0 mmol) in CH_2Cl_2 (20 mL) under argon at –78 °C was added a 2.0 M solution of DIBAL-H (6.0 mL, 12.0 mmol) dropwise. After stirring for 30 min, the reaction was quenched with MeOH (2 mL) and saturated aq sodium potassium tartrate and stirred for 30 min at room temperature. Organic layer was separated, dried over Na_2SO_4 and concentrated to dryness. The residue was purified by silica gel column chromatography using light petroleum and ethyl acetate (3:2) as eluent to give the allylic alcohol **73** (1.79 g, 90%) yield as a colourless thick paste.

^{1}H NMR (500 MHz, DMSO-d_6): δ 1.27 (s, 9H), 1.71 (s, 3H), 3.71 (s, 3H), 3.78 (d, 1H, *J* = 12.4 Hz), 4.02 (d, 1H, *J* = 12.4 Hz), 4.05 (d, 1H, *J* = 15.5 Hz), 4.48 (d, 1H, *J* = 15.5 Hz), 4.72 (s, 1H), 5.52 (d, 1H, *J* = 9.3 Hz), 5.85 (br s, 1H), 6.83 (d, 2H, *J* = 8.6 Hz), 7.05-7.33 (m, 7H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 21.4, 27.9, 47.3, 54.7, 55.6, 60.6, 80.0, 113.1, 123.7, 126.8, 128.0, 131.2, 139.2, 140.0, 155.9, 158.0

IR ($CHCl_3$, cm^{-1}): 3437, 2974, 2933, 1687, 1612, 1513, 1454, 1366, 1247, 1163, and 1035.
MS (ESI) m/z: 398 $(M+H)^+$
Anal. Calcd. for $C_{24}H_{31}NO_4$ (MW. 397): C, 72.52; H, 7.86; N, 3.52; Found C, 72.36; H, 7.79; N, 3.65.

(2*R*,3*S*,4*R*)-4-[(*tert*-Butoxycarbonyl)(4-methoxybenzyl)amino]-2,3-epoxy-2-methyl-4-phenyl-butan-1-ol (72)



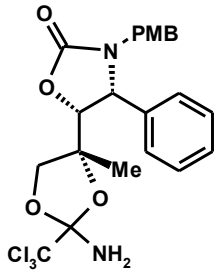
To a solution of the allylic alcohol **73** (3.6 g, 9.1 mmol) in CH_2Cl_2 (30 mL) at –20 °C was added (4.7 g, 27.2 mmol) *m*-CPBA and stirred for 40 min. After quenching the reaction with aq $NaHCO_3$, layers were separated. The aq layer was extracted with CH_2Cl_2 and the combined organic layer was dried, concentrated. Purification of this crude material by silica gel column chromatography using light petroleum and ethyl acetate (3:1) as eluent gave the epoxy alcohol **72** (2.47 g, 66% yield) as a colourless paste.

^{1}H NMR (500 MHz, DMSO-d_6, 333K): δ 1.30 (s, 9H), 1.37 (s, 3H), 3.39 (d, 1H, *J* = 9.1 Hz), 3.49 (ABq, 2H, *J* = 11.8 Hz), 3.74 (s, 3H), 4.26 (d, 1H, *J* = 15.6 Hz), 4.46 (d, 1H, *J* = 15.6 Hz), 4.91 (d, 1H, *J* = 9.1 Hz), 6.83 (d, 2H, *J* = 8.7 Hz), 7.16-7.35 (m, 7H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 19.9, 28.0, 49.0, 55.0, 58.1, 62.0, 63.1, 63.5, 80.2, 113.5, 126.5, 127.3, 128.5, 130.8, 138.1, 155.8, 158.4

IR ($CHCl_3$, cm^{-1}): 3460, 2975, 2931, 1693, 1613, 1513, 1455, 1366, 1247, 1163, and 1036.
MS (ESI) m/z: 414 $(M+H)^+$
Anal. Calcd. for $C_{24}H_{31}NO_5$ (MW. 413): C, 69.71; H, 7.56; N, 3.39; Found C, 69.52; H, 7.73; N, 3.18.

(4*R*,5*R*)-5-[(4*R*,2*R/S*)-2-Amino-2-(trichloromethyl)-4-methyl-1,3-dioxolan-4-yl]-3-(4-methoxybenzyl)-4-phenyl-2-oxazolidinone (87)



Trichloroacetonitrile (0.7 mL, 6.68 mmol) and DBU (0.1 mL, 0.6 mmol) were added to a solution of epoxy alcohol **72** (2.3 g, 5.57 mmol) in CH_2Cl_2 (10 mL) at –20 °C. After 20 min, solvent was removed at reduced pressure and passed through a short silica gel column using light petroleum and ethyl acetate (9:1) as eluent to give the imidate **81** as a colourless solid (2.96 g).

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.36 (s, 9H), 1.53 (s, 3H), 3.36 (d, 1H, *J* = 9.2 Hz), 3.77 (s, 3H), 4.19 (m, 2H), 4.32 (d, 1H, *J* = 11.0 Hz), 4.46-4.89 (m, 2H), 6.81 (d, 2H, *J* = 8.4 Hz), 7.14-7.35 (m, 7H), 8.27 (s, 1H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 20.1, 28.3, 49.3, 55.1, 58.4, 60.0, 63.4, 69.8, 80.3, 91.0, 113.8, 126.7, 127.5, 128.6, 130.9, 138.1, 155.7, 158.8, 162.1

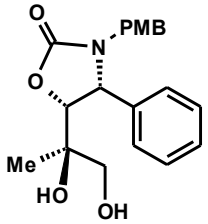
To a solution of this imidate **81** in CH_2Cl_2 (15 mL) was added $BF_3.Et_2O$ (0.3 mL, 2.3 mmol) at –20 °C. After 20 min, the reaction was quenched by addition of aq $NaHCO_3$ and the layers were separated. The aq layer was extracted with CH_2Cl_2 (2x25 mL) and the combined organic layer was dried, concentrated and purified by silica gel column chromatography (light petroleum and ethylacetate-4:1) to give compound **87** (2.42 g, 78% for two steps) as a colourless sticky solid.

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.02 (s, 1.2H), 1.17 (s, 1.8H), 2.39 (s, 1.2H), 2.61 (s, 0.8H), 3.56 (m, 1.6H), 3.68 (d, 0.4H, *J* = 8.1 Hz), 3.79 (s, 1.8H), 3.80 (s, 1.2H), 4.13 (d, 0.6H, *J* = 7.8 Hz), 4.28 (d, 0.4H, *J* = 8.1 Hz), 4.55 (d, 0.6H, *J* = 8.5 Hz), 4.59 (d, 0.4H, *J* = 8.5 Hz), 4.78 (d, 0.6H, *J* = 8.5 Hz), 4.80 (d, 0.4H, *J* = 8.5 Hz), 4.86 (d, 1H, *J* = 14.6 Hz), 6.79 (d, 1.2H, *J* = 8.6 Hz), 6.81 (d, 0.8H, *J* = 8.6 Hz), 6.97 (d, 1.2H, *J* = 8.6 Hz), 6.99 (d, 0.8H, *J* = 8.6 Hz), 7.39 (m, 5H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 20.3, 21.4, 45.2, 55.0, 60.6, 60.9, 74.8, 80.4, 81.0, 83.8, 84.3, 102.5, 103.1, 114.0, 115.7, 116.9, 127.2, 128.6, 129.3, 129.8, 133.0, 157.2, 157.3, 159.3

GCMS m/z: 501 (M^+) for both the diastereomers (MW. 501).

(4*R*,5*R*)-5-[(2*R*)-1,2-Dihydroxypropan-2-yl]-3-(4-methoxybenzyl)-4-phenyl-2-oxazolidinone (85)



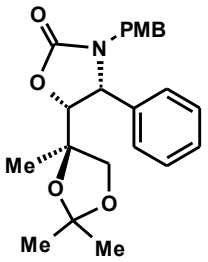
To a solution of the compound **87** (1.6 g, 3.2 mmol) in THF (10 mL) was added 2 mL of 2 N HCl at room temperature and stirred for 6 h. After neutralizing with solid $NaHCO_3$, THF was removed under reduced pressure and the residue was partitioned between CH_2Cl_2 and water. The organic layer was dried, concentrated and purified by silica gel column (light petroleum and ethyl acetate-2:3) to give diol **85** (930 mg, 82%) as a colourless thick paste.

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.78 (s, 3H), 2.83 (br s, 2H), 3.33 (s, 2H), 3.50 (d, 1H, *J* = 14.7 Hz), 3.78 (s, 3H), 4.53 (d, 1H, *J* = 7.8 Hz), 4.69 (d, 1H, *J* = 7.8 Hz), 4.78 (d, 1H, *J* = 14.7 Hz), 6.80 (d, 2H, *J* = 8.6 Hz), 6.98 (d, 2H, *J* = 8.6 Hz), 7.21 (br s, 2H), 7.37 (m, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 19.6, 45.2, 55.1, 61.3, 67.7, 72.7, 81.4, 114.1, 127.5, 128.6, 129.1, 129.7, 134.0, 158.0, 159.3

IR ($CHCl_3$, cm^{-1}): 3432, 2937, 1745, 1612, 1514, 1415, 1248, 1175, and 1039.
MS (ESI) m/z: 358 $(M+H)^+$
Anal. Calcd. for $C_{20}H_{23}NO_5$ (MW. 357): C, 67.21; H, 6.49; N, 3.92; Found C, 67.16; H, 6.35; N, 4.09.

(4*R*,5*R*)- 5-[(4*R*)-2,2,4-Trimethyl-1,3-dioxolan-4-yl]-3-(4-methoxybenzyl)-4-phenyl-2-oxazolidinone (86)



A solution of the diol **85** (0.5 g, 1.4 mmol), *p*-TSA (50 mg) and 2,2-dimethoxy propane (4 mL) in acetone (4 mL) was stirred for 6 h at room temperature. The reaction mixture was diluted with diethyl ether (20 mL) and washed with aq $NaHCO_3$ solution and brine. After drying over anhydrous Na_2SO_4, the solvent was removed under reduced pressure. The residue was chromatographed on silica gel column using light petroleum and ethyl acetate (4:1) to give the acetonide derivative **86** (0.49 g, 88%) as a colourless crystalline solid (Mp 144-146 °C).

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.83 (s, 3H), 1.25 (s, 3H), 1.35 (s, 3H), 3.38 (d, 1H, *J* = 8.5 Hz), 3.55 (d, 1H, *J* = 14.6 Hz), 3.79 (s, 3H), 3.92 (d, 1H, *J* = 8.5 Hz), 4.52 (s, 2H), 4.85 (d, 1H, *J* = 14.6 Hz), 6.81 (d, 2H, *J* = 8.6 Hz), 6.99 (d, 2H, *J* = 8.6 Hz), 7.19 (br s, 2H), 7.38 (m, 3H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 21.5, 26.1, 27.0, 45.0, 54.9, 60.9, 71.6, 80.2, 81.1, 110.0, 113.8, 127.3, 128.2, 128.8, 129.2, 129.6, 133.4, 157.5, 159.1

IR ($CHCl_3$, cm^{-1}): 2936, 1752, 1611, 1513, 1411, 1249, and 1037.

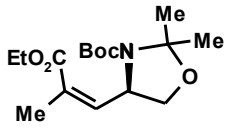
MS (ESI) m/z: 398 $(M+H)^+$

Anal. Calcd. for $C_{23}H_{27}NO_5$ (MW. 397): C, 69.50; H, 6.85; N, 3.52; Found C, 69.32; H, 6.80; N, 3.60.

Ethyl-2-methyl-3-[3-(*tert*-butoxycarbonyl)-2,2-dimethyl-(4*R*)-oxazolidinyl]-prop-(2*Z*)-enoate (114) and ethyl-2-methyl-3-[3-(*tert*-butoxycarbonyl)-2,2-dimethyl-(4*R*)-oxazolidinyl]-prop-(2*E*)-enoate (116)

Compounds **114** and **116** were made from (*S*)-Garner aldehyde **115** (5.0 g, 21.8 mmol) using the phosphonate (9.9 g, 27.3 mmol) and NaH (1.05 g, 26.2 mmol) in 86% (5.87 g) yield in the ratio 7:2 by following the procedure described for the compound **79**. The reaction mixture was stirred for 4 h at –78 °C and purified by silica gel column chromatography (light petroleum and ethyl acetate -20:1).

Compound 114



[α]$_D$ –11.9 (*c* 1.2, $CHCl_3$)

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.30 (t, 3H, *J* = 7.1 Hz), 1.38 (s, 5H), 1.50 (s, 7H), 1.62 (s, 3H), 1.92 (s, 3H), 3.74 (d, 1H, *J* = 9.0 Hz), 4.18 (t, 2H, *J* = 7.1 Hz and m, 1H), 5.10 (m, 1H), 6.00 (m, 1H).

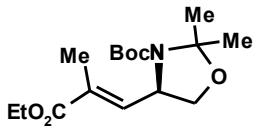
^{13}C NMR (50 MHz, $CDCl_3$): δ 13.6, 19.3, 23.2, 24.1, 25.8, 26.8, 27.7, 55.7, 56.6, 59.6, 68.3, 69.0, 78.5, 79.2, 92.9, 93.4, 126.7, 126.9, 144.1, 145.9, 151.0, 151.4, 166.0

IR ($CHCl_3$, cm^{-1}): 2982, 2934, 1691, 1392, 1368, 1106, and 1052.

MS (ESI) m/z: 314 $(M+H)^+$

Anal. Calcd. for $C_{16}H_{27}NO_5$ (MW. 313): C, 61.32; H, 8.68; N, 4.47; Found C, 61.14; H, 8.75; N, 4.36.

Compound 116



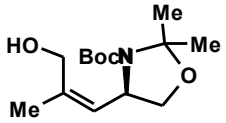
[α]$_D$ –21.1 (*c* 1.1, $CHCl_3$)

^{1}H NMR (200MHz, $CDCl_3$): δ 1.31 (t, 3H, *J* = 7.1 Hz), 1.36-1.57 (m, 12H), 1.63 (s, 3H), 1.88 (s, 3H), 3.70 (dd, 1H, *J* = 3.6, 8.9 Hz), 4.11 (dd, 1H, *J* = 6.4, 8.9 Hz), 4.21 (q, 2H, *J* = 7.1 Hz), 4.65 (m, 1H), 6.63 (d, 1H, *J* = 9.2 Hz).

^{13}C NMR (50MHz, $CDCl_3$): δ 11.8, 13.6, 23.4, 24.2, 25.5, 26.7, 27.7, 54.7, 59.8, 66.9, 79.0, 92.9, 93.6, 127.4, 128.4, 139.4, 139.9, 150.9, 166.6

IR ($CHCl_3$, cm^{-1}): 2981, 2936, 1701, 1386, 1366, 1259, 1100, and 1055.
MS (ESI) m/z: 314 $(M+H)^+$
Anal. Calcd. for $C_{16}H_{27}NO_5$ (MW. 313): C, 61.32; H, 8.68; N, 4.47; Found C, 61.23; H, 8.88; N, 4.32.

(2*Z*)-3-[3-(*tert*-Butoxycarbonyl)-2,2-dimethyl-(4*R*)-oxazolidinyl]-2-methyl-prop-2-en-1-ol (117)



Compound **114** (3.0 g, 9.6 mmol) was reduced to the corresponding allylic alcohol **117** using DIBAL-H (11.5 mL, 23.0 mmol) by following the procedure described for the compound **73** (2.31 g, 89%) as a colourless paste.
$[\alpha]_D$ –2.4 (*c* 1.5, $CHCl_3$)

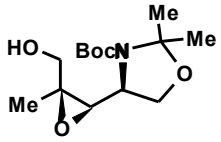
^{1}H NMR (500 MHz, $CDCl_3$): δ 1.47 (s, 9H), 1.48 (s, 3H), 1.57 (s, 3H), 1.82 (s, 3H), 3.64 (d, 1H, *J* = 12.1 Hz), 3.68 (d, 1H, *J* = 8.8 Hz), 4.03 (dd, 1H, *J* = 5.8, 8.8 Hz), 4.28 (br s, 1H), 4.51 (d, 1H, *J* = 12.1 Hz), 4.84 (dd, 1H, *J* = 5.8, 10.3 Hz), 5.27 (d, 1H, *J* = 10.3 Hz).

^{13}C NMR (50 MHz, $CDCl_3$): δ 21.4, 24.0, 26.7, 27.6, 53.8, 60.3, 67.5, 78.4, 79.5, 92.4, 124.7, 137.8, 151.3

IR ($CHCl_3$, cm^{-1}): 3436, 2979, 2936, 1697, 1675, 1395, 1366, 1249, 1111, and 1057.
MS (ESI) m/z: 272 $(M+H)^+$

Anal. Calcd. for $C_{14}H_{25}NO_4$ (MW. 271): C, 61.97; H, 9.29; N, 5.16; Found C, 62.16; H, 9.31; N, 5.02.

(2*S*,3*R*)-3-[3-(*tert*-Butoxycarbonyl)-2,2-dimethyl-(4*R*)-oxazolidinyl]-2-methyl-2,3-epoxy-propan-1-ol (113)



Compound **117** (3.0 g, 11.1 mmol) was converted to the epoxide **113** using *m*-CPBA (5.7 g, 16.6mmol) by following the procedure described for the compound **72** (2.48 g, 78%) as a colourless crystalline solid (Mp 103-104 °C).

$[\alpha]_D$ +7.2 (*c* 1.0, $CHCl_3$)

^{1}H NMR (500 MHz, DMSO-d_6, 333K): δ 1.27 (s, 3H), 1.44 (s, 9H), 1.45 (s, 3H), 1.55 (s, 3H), 2.80 (d, 1H, *J* = 7.9 Hz), 3.48 (ABq, 2H, *J* = 11.5 Hz), 3.84 (m, 2H), 4.00 (dd, 1H, *J* = 6.3, 9.1 Hz), 4.60 (br s, 1H).

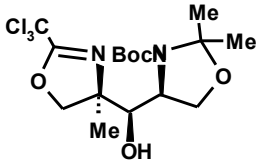
^{13}C NMR (50 MHz, $CDCl_3$): δ 19.8, 23.1, 24.3, 26.6, 27.2, 28.0, 56.2, 59.4, 59.9, 63.1, 65.8, 66.1, 79,7, 80.2, 93.7, 152.1, 152.4.

IR ($CHCl_3$, cm^{-1}): 3432, 2983, 2936, 1690, 1392, 1367, 1170, 1105, and 1056.

MS (ESI) m/z: 288 $(M+H)^+$

Anal. Calcd. for $C_{14}H_{25}NO_5$ (MW. 287): C, 58.52; H, 8.77; N, 4.87; Found C, 58.34; H, 8.59; N, 4.75.

oxazoline (110)



Trichloroacetonitrile (0.33 mL, 3.3 mmol) and DBU (0.04 mL, 0.3 mmol) were added to a solution of epoxy alcohol **113** (0.8 g, 2.8 mmol) in CH_2Cl_2 (8 mL) at –20 °C. After 20 min, solvent was removed at room temperature under reduced pressure and the residue was

purified by a short silica gel column chromatography using light petroleum and ethyl acetate (4:1) to give imidate **104** in quantitative yield as a colourless crystalline solid. To a solution of this imidate in CH_2Cl_2 (10 mL) and molecular sieves powder (1.0 g), $SnCl_4$ (0.06 mL, 0.56 mmol) was added at –20 °C. After 15 min, the reaction was quenched by the addition of aq $NaHCO_3$. After separation of the layers, the aq layer was extracted with CH_2Cl_2 (2x20 mL) and the combined organic layer was dried, concentrated and purified by silica gel column chromatography using light petroleum and ethyl acetate (4:1) as eluent to give the oxazoline **110** (980 mg, 82% for two steps) as a colourless crystalline solid (Mp 142-144 °C).

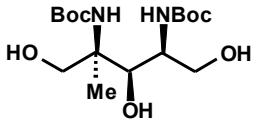
$[\alpha]_D$ –3.5 (*c* 1.1, $CHCl_3$)

^{1}H NMR (500 MHz, $CDCl_3$+D_2O): δ 1.49 (s, 3H), 1.51 (s, 9H), 1.53 (s, 3H), 1.60 (s, 3H), 3.76 (d, 1H, *J* = 9.8 Hz), 3.85 (dd, 1H, *J* = 5.4, 9.5 Hz), 3.97 (dd, 1H, *J* = 5.4, 9.8 Hz), 4.10 (d, 1H, *J* = 9.5 Hz), 4.25 (d, 1H, *J* = 9.0 Hz), 4.99 (d, 1H, *J* = 9.0 Hz).

^{13}C NMR (50 MHz, $CDCl_3$): δ 23.5, 25.9, 26.8, 28.0, 58.1, 66.0, 75.1, 77.6, 77.9, 81.2, 86.2, 93.3, 155.7, 161.3

IR ($CHCl_3$, cm^{-1}): 3406, 2983, 2936, 1694, 1658, 1405, 1368, 1249, 1167, 1110, and 1058.
MS (ESI) m/z: 431 $(M+H)^+$
Anal. Calcd. for $C_{16}H_{25}N_2Cl_3O_5$ (MW. 430): C, 44.51; H, 5.84; N, 6.49; Cl, 24.63; Found C, 44.68; H, 5.74; N, 6.47; Cl, 24.45.

(*2R,3R,4S*)-2,4-Bis(*tert*-butoxycarbonylamino)-2-methyl-pentan-1,3,5-triol (112)



To a solution of the oxazoline **110** (850 mg, 2.0 mmol) in THF (10 mL), 2 mL of 2 N HCl was added and stirred for 2 h at room temperature. After basification with Na_2CO_3, $(Boc)_2O$ (2.3 mL, 10 mmol) was added and stirring continued for 24 h. THF was removed at reduced pressure and the residue was extracted with CH_2Cl_2 (4x25 mL), dried and

concentrated. This crude material was purified by silica gel column chromatography using light petroleum and ethyl acetate (2:3) to give the triol **112** (618 mg, 86% for two steps) as a white solid (Mp 136-138 °C).

[α]$_D$ –36.7 (*c* 1.0, $CHCl_3$)

^{1}H NMR (400 MHz, $CDCl_3$+D_2O): δ 1.23 (s, 3H), 1.44 (s, 9H), 1.45 (s, 9H), 3.64 (dd, 1H, *J* = 10.6, 6.2 Hz), 3.67 (d, 1H, *J* = 11.5 Hz), 3.74 (dd, 1H, *J* = 10.6, 3.6 Hz), 3.90 (m, 1H), 3.95 (d, 1H, *J* = 11.5 Hz), 4.01 (s, 1H).

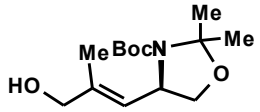
^{13}C NMR (50 MHz, Acetone-d_6 +DMSO-d_6): δ 18.9, 28.5, 51.8, 59.8, 63.7, 65.8, 71.7, 78.6, 78.9, 156.0, 156.6

IR ($CHCl_3$, cm^{-1}): 3449, 2924, 2856, 1717, 1670, 1499, 1460, 1365, 1254, and 1180.

MS (ESI) m/z: 365 $(M+H)^+$

Anal. Calcd. for $C_{16}H_{32}N_2O_7$ (MW. 364): C, 52.73; H, 8.85; N, 7.69; Found C, 52.64; H, 9.02; N, 7.52.

(2*E*)-3-[3-(*tert*-Butoxycarbonyl)-2,2-dimethyl-(4*R*)-oxazolidinyl]-2-methyl-prop-2-en-1-ol (119)



Compound **116** (2.4 g, 7.7 mmol) was reduced to the corresponding allylic alcohol **119** using a 2.0 M solution of DIBAL-H (9.2 mL, 18.4 mmol) by following the procedure described for compound **73** (1.91 g, 92%) as a colourless paste.

[α]$_D$ +26.5 (*c* 1.0, $CHCl_3$)

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.42-1.53 (m, 12H), 1.59 (s, 3H), 1.73 (s, 3H), 3.64 (dd, 1H, *J* = 3.2, 8.7 Hz), 4.00 (s, 2H), 4.05 (dd, 1H, *J* = 6.2, 8.7 Hz), 4.60 (m, 1H), 5.44 (d, 1H, *J* = 9.2 Hz).

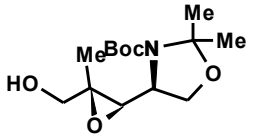
^{13}C NMR (50 MHz, $CDCl_3$): δ 13.3, 23.6, 24.8, 26.0, 26.6, 28.1, 54.7, 67.0, 68.1, 79.0, 79.6, 93.1, 93.4, 124.2, 135.8, 137.1, 151.6

IR ($CHCl_3$, cm^{-1}): 3442, 2982, 1688, 1393, 1367, and 1055.

MS (ESI) m/z: 272 $(M+H)^+$

Anal. Calcd. for $C_{14}H_{25}NO_4$ (MW. 271): C, 61.97; H, 9.29; N, 5.16; Found C, 61.88; H, 9.42; N, 5.13.

(2*R*,3*R*)-3-[3-(*tert*-Butoxycarbonyl)-2,2-dimethyl-(4*R*)-oxazolidinyl]-2-methyl-2,3-epoxy-propan-1-ol (120)



The allylic alcohol **119** (1.6 g, 5.9 mmol) was converted to the epoxy alcohol **120** (1.15 g, 68%) as a colourless crystalline solid (Mp.128-130 °C) using *m*-CPBA (3.1 g, 8.9 mmol) by following the procedure described for compound **72**.

$[\alpha]_D$ +10.0 (*c* 1.0, $CHCl_3$)

^{1}H NMR (500 MHz, DMSO-d_6, 323K): δ 1.23 (s, 3H), 1.43 (s, 9H), 1.45 (s, 3H), 1.55 (s, 3H), 2.87 (d, 1H, *J* = 7.8 Hz), 3.35 (s, 2H), 3.80 (m, 2H), 4.04 (dd, 1H, *J* = 7.2, 9.5 Hz), 4.60 (s, 1H).

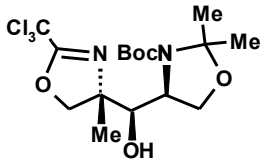
^{13}C NMR (50 MHz, $CDCl_3$): δ 14.4, 23.2, 24.5, 26.6, 26.9, 28.0, 56.9, 59.4, 61.9, 65.2, 65.5, 79.9, 93.9, 152.0

IR ($CHCl_3$, cm^{-1}): 3452, 2983, 2935, 1691, 1391, 1254, 1170, and 1059.

MS (ESI) m/z: 288 $(M+H)^+$

Anal. Calcd. for $C_{14}H_{25}NO_5$ (MW. 287): C, 58.52; H, 8.77; N, 4.87; Found C, 58.34; H, 8.92; N, 4.74.

oxazoline (122)



The epoxide **120** (1.0 g, 3.5 mmol) was converted to the oxazoline **122** (1.27 g) in 85% yield as a colourless crystalline solid (Mp. 156-158 °C) by following the procedure described for compound **110**.

$[\alpha]_D$ –95.3 (*c*1.0, $CHCl_3$)

^{1}H NMR (400 MHz, $CDCl_3$+D_2O): δ 1.42 (s, 3H), 1.51 (s, 12H), 1.61 (s, 3H), 3.64 (d, 1H, *J* = 9.4 Hz), 3.99 (dd, 1H, *J* = 5.6, 9.4 Hz), 4.27 (m, 1H), 4.30 (d, 1H, *J* = 8.9 Hz), 4.35 (d, 1H, *J* = 9.4 Hz), 4.70 (d, 1H, *J* = 8.9 Hz).

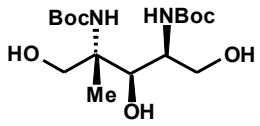
^{13}C NMR (50 MHz, $CDCl_3$): δ 19.3, 23.9, 27.0, 28.2, 58.6, 66.1, 74.9, 78.3, 81.6, 81.7, 86.5, 93.6, 155.8, 161.8

IR ($CHCl_3$, cm^{-1}): 3436, 2982, 1654, 1404, 1368, 1168, 1109, and 1055.

MS (ESI) m/z: 431 $(M+H)^+$

Anal. Calcd. for $C_{16}H_{25}N_2Cl_3O_5$ (MW. 430): C, 44.51; H, 5.84; N, 6.49; Cl, 24.63; Found C, 44.58; H, 5.96; N, 6.56; Cl, 24.81.

(*2S,3R,4S*)-2,4-Bis(*tert*-butoxycarbonylamino)-2-methyl-pentan-1,3,5-triol (123)



The oxazoline **122** (720 mg, 1.67 mmol) was converted to the triol **123** (480 mg) as a colourless crystalline solid (Mp 89-91 °C) in 79 % yield by following the procedure described for compound **112**.

$[\alpha]_D$ +12.9 (*c*1.1, $CHCl_3$)

^{1}H NMR (200 MHz, DMSO-d_6): δ 1.09 (s, 3H), 1.36 (s, 18H), 3.25 (m, 2H), 3.42 (m, 1H), 3.65 (m, 2H), 3.90 (d, 1H, *J* = 6.7 Hz), 4.58 (t, 1H, *J* = 5.5 Hz), 4.65 (t, 1H, *J* = 5.2 Hz), 5.00 (d, 1H, *J* = 6.7 Hz), 5.71 (d, 1H, *J* = 9.1 Hz), 5.82 (s, 1H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 18.1, 28.3, 50.5, 59.1, 63.5, 67.9, 68.7, 79.2, 79.9, 155.8, 157.1

IR ($CHCl_3$, cm^{-1}): 3435, 2978, 2929, 1684, 1500, 1367, 1169, and 1056.

MS (ESI) m/z: 365 $(M+H)^+$

Anal. Calcd. for $C_{16}H_{32}N_2O_7$ (MW. 364): C, 52.73; H, 8.85; N, 7.69; Found C, 52.64; H, 9.06; N, 7.69.

Table 1. Crystal data and structure refinement for Compound No. **86**.

Identification code	Compound No. **86**
Empirical formula	C23 H27 N O5
Formula weight	397.46
Temperature	297(2) K
Wavelength	0.71073 A
Crystal system, space group	Monoclinic, P2 (1)/c
Unit cell dimensions	a = 10.516(6) A alpha = 90 deg. b = 20.155(11) A beta = 117.623(9) deg.
Volume	2128(2) A^3
Z, Calculated density	4, 1.241 Mg/m^3
Absorption coefficient	0.087 mm^-1
F (000)	848
Crystal size	0.41 x 0.20 x 0.19 mm
Theta range for data collection	2.02 to 25.00 deg.
Limiting indices	-11<=h<=12, -23<=k<=23, -13<=l<=13
Reflections collected / unique	10468 / 3749 [R(int) = 0.0234]
Completeness to theta = 25.00	99.9 %
Max. and min. transmission	0.9836 and 0.9647
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3749 / 0 / 266
Goodness-of-fit on F^2	1.007
Final R indices [I>2sigma(I)]	R1 = 0.0405, wR2 = 0.1017
R indices (all data)	R1 = 0.0546, wR2 = 0.1106
Largest diff. peak and hole	0.144 and -0.137 e.A^-3

Table 2. Crystal data and structure refinement for Compound No. **110**

Identification code	Compound No. **110**
Empirical formula	C16 H25 Cl3 N2 O5
Formula weight	431.73
Temperature	297(2) K
Wavelength	0.71073 A
Crystal system, space group	ORTHORHOMBIC, P2 (1)2(1)2(1)
Unit cell dimensions	a = 11.210(6) A alpha = 90 deg.
	b = 18.823(9) A beta = 90 deg.
	c = 20.925(10) A gamma = 90 deg.
Volume	4415(4) A^3
Z, Calculated density	8, 1.299 Mg/m^3
Absorption coefficient	0.441 mm^-1
F(000)	1808
Crystal size	0.43 x 0.26 x 0.08 mm
Theta range for data collection	2.11 to 24.99 deg.
Limiting indices	-10<=h<=13, -22<=k<=22, -23<=l<=24
Reflections collected / unique	22284 / 7767 [R (int) = 0.0554]
Completeness to theta = 24.99	99.9 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9668 and 0.8336
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	7767 / 0 / 483
Goodness-of-fit on F^2	1.101
Final R indices [I>2sigma(I)]	R1 = 0.0748, wR2 = 0.1418
R indices (all data)	R1 = 0.1130, wR2 = 0.1576
Absolute structure parameter	-0.09(8)
Largest diff. peak and hole	0.304 and -0.171 e.A^-3

Table 3. Crystal data and structure refinement for Compound No. **122**.

Identification code	Compound No. **122**
Empirical formula	C16 H25 Cl3 N2 O5
Formula weight	431.73
Temperature	297(2) K
Wavelength	0.71073 A
Crystal system, space group	Monoclinic, P2(1)
Unit cell dimensions	a = 11.454(9) A alpha = 90 deg. b = 6.186(5) A beta = 105.582(12) deg. c = 15.081(12) A gamma = 90 deg.
Volume	1029.4(14) A^3
Z, Calculated density	2, 1.393 Mg/m^3
Absorption coefficient	0.473 mm^-1
F(000)	452
Crystal size	1.13 x 0.129 x 0.052 mm
Theta range for data collection	2.00 to 25.00 deg.
Limiting indices	-12<=h<=12, -2<=k<=7, -10<=l<=17
Reflections collected / unique	2597 / 2094 [R(int) = 0.0418]
Completeness to theta = 25.00	90.1 %
Absorption correction	Semi-empirical from equivalents
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2094 / 1 / 245
Goodness-of-fit on F^2	1.069
Final R indices [I>2sigma(I)]	R1 = 0.0710, wR2 = 0.1791
R indices (all data)	R1 = 0.0778, wR2 = 0.1875

Absolute structure parameter	-0.04(16)
Largest diff. peak and hole	0.544 and -0.383 e.A^-3

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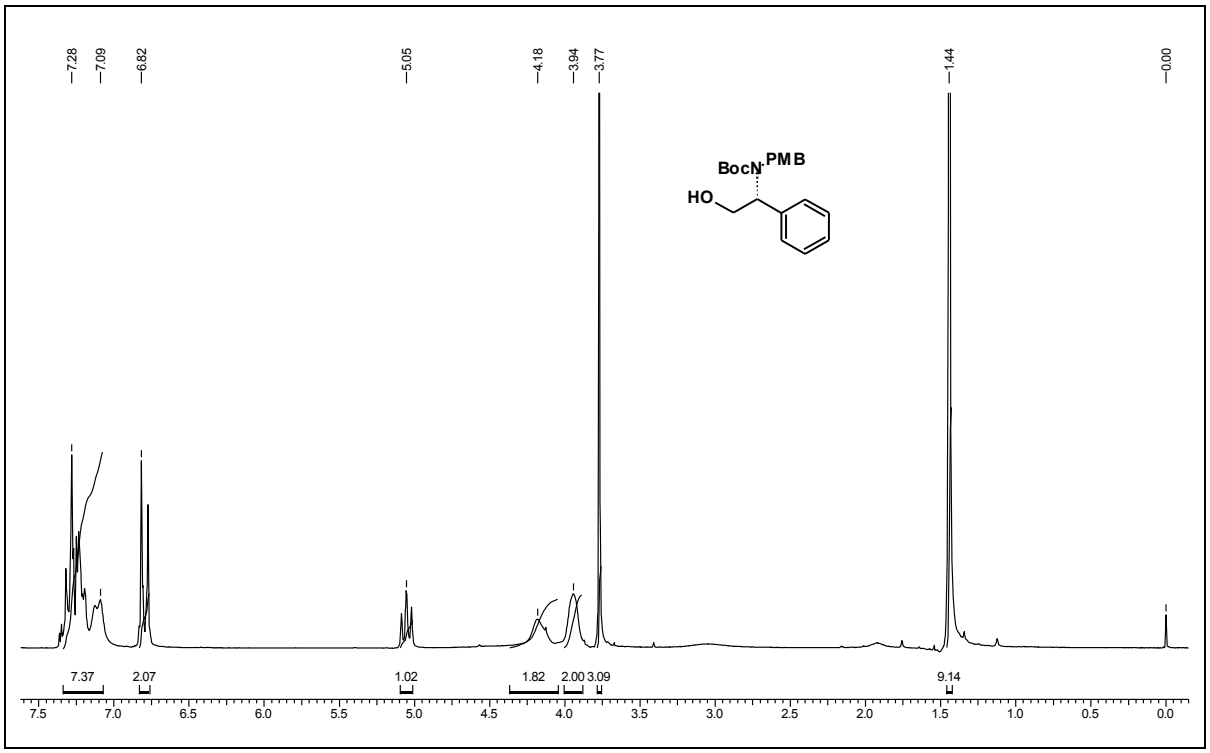
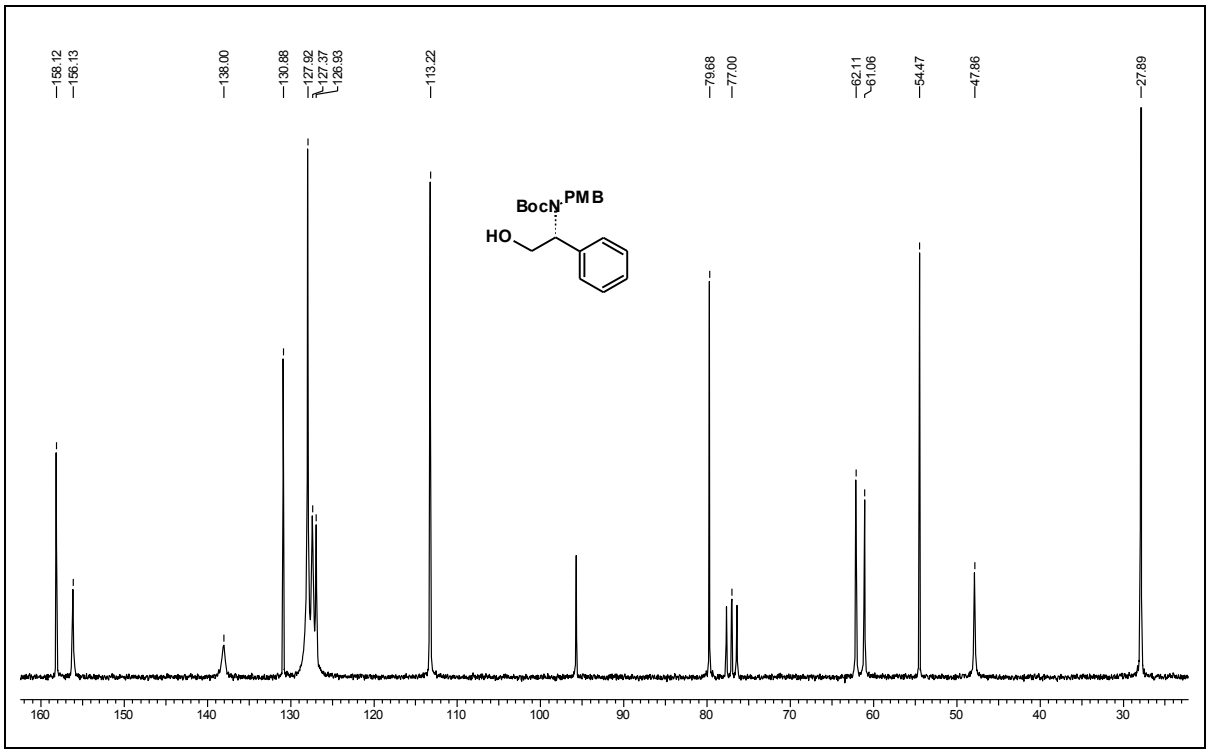
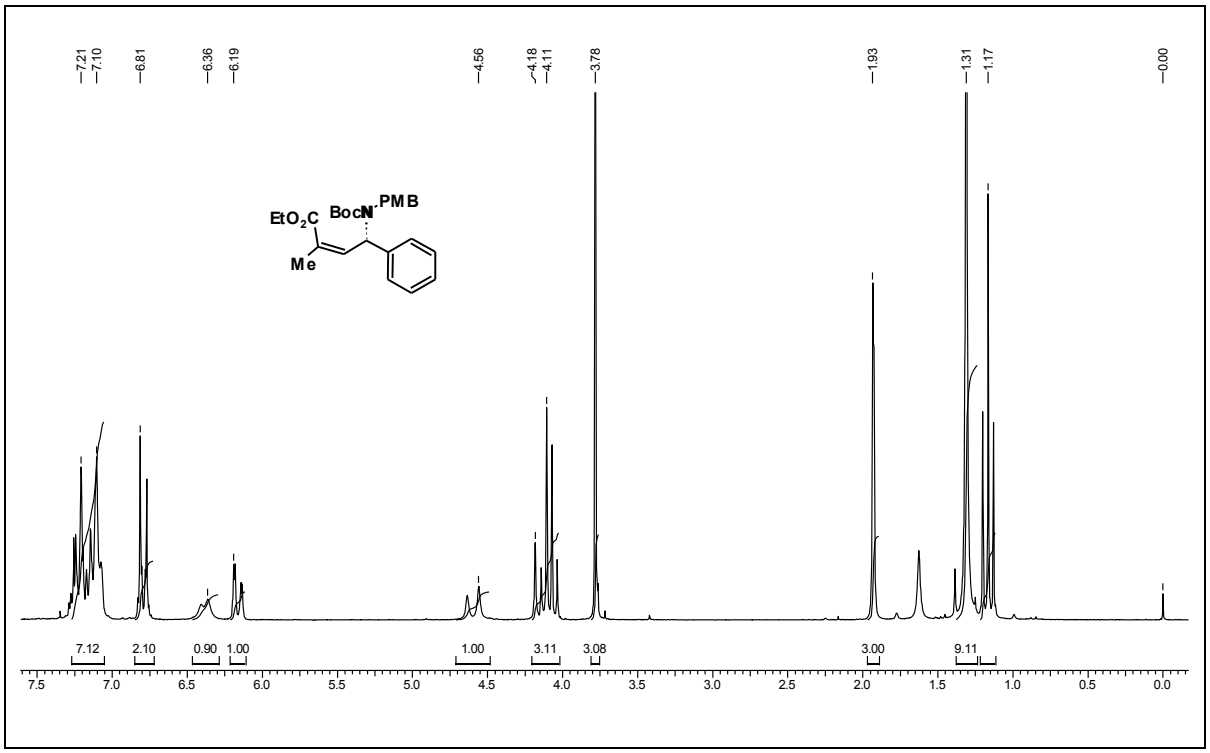


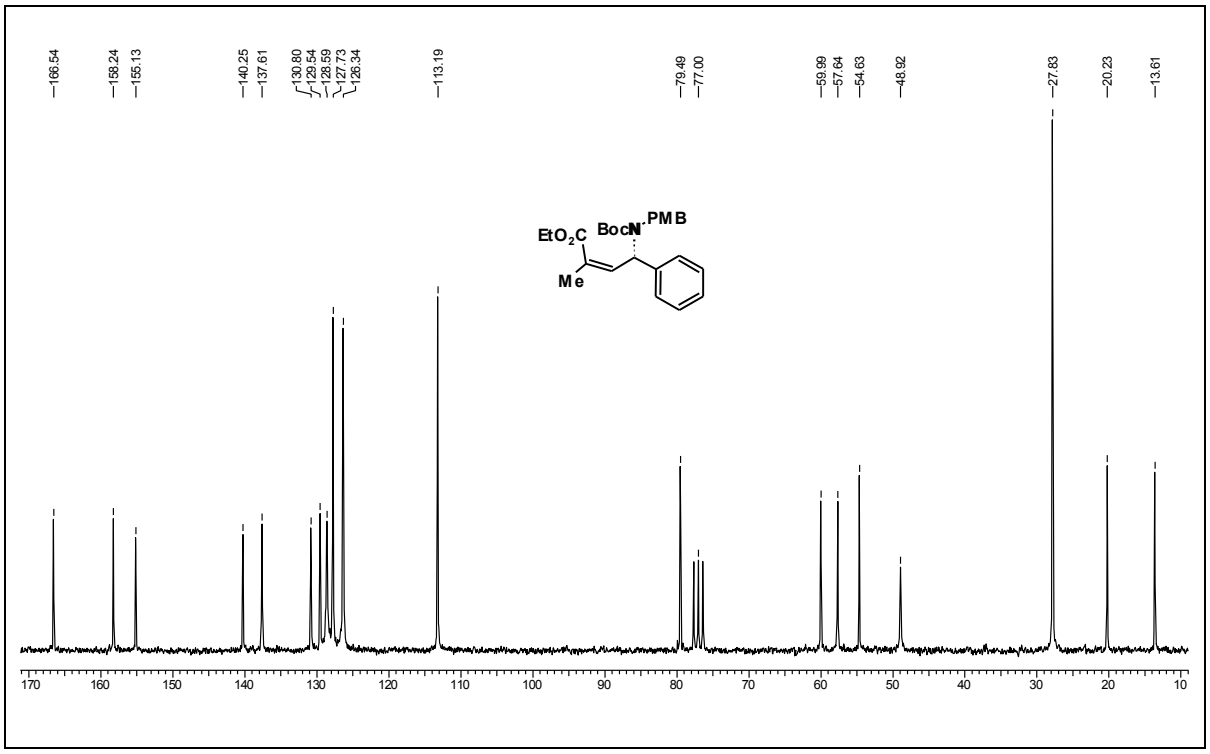
^{1}H NMR spectrum of compound 77 in $CDCl_3$



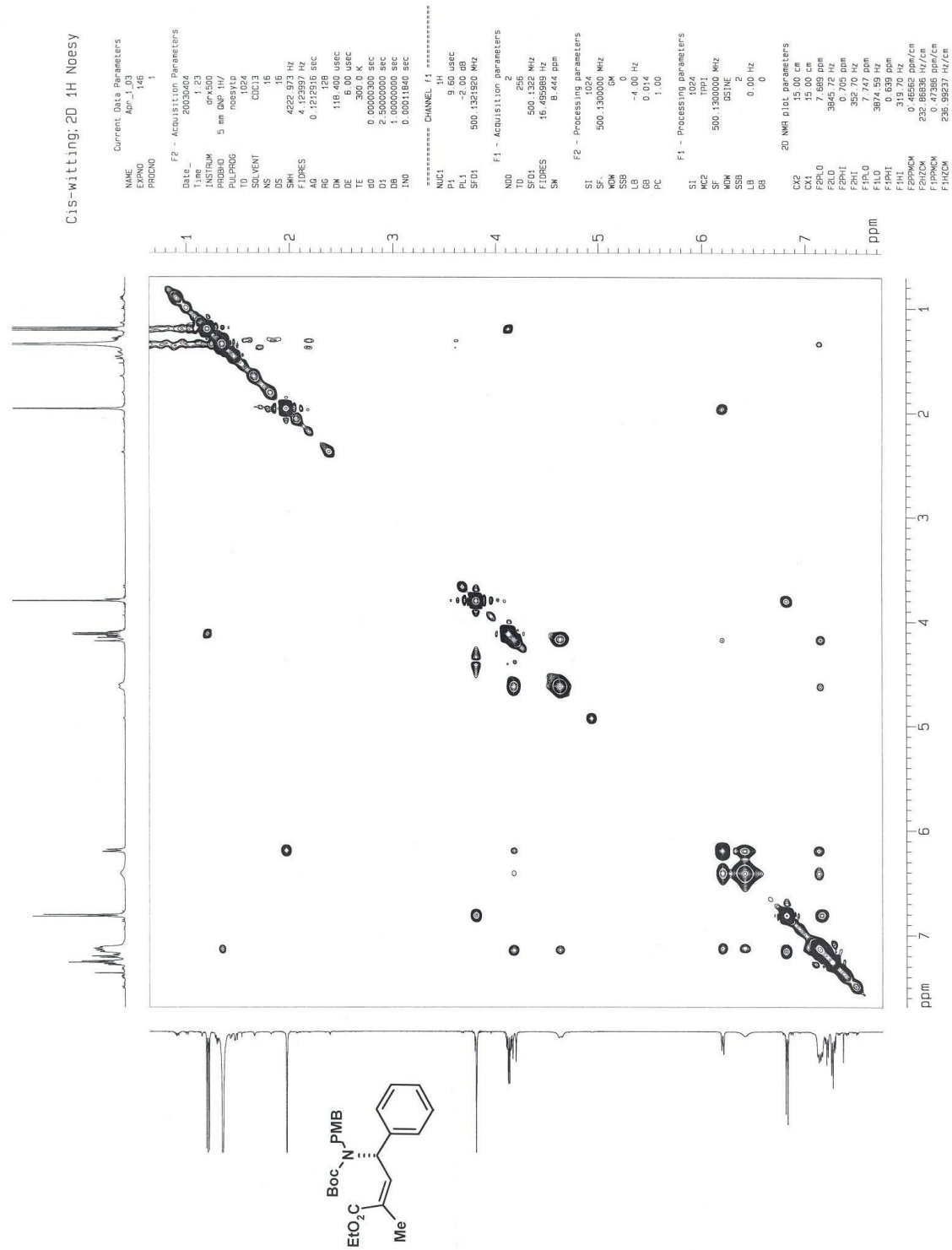
^{13}C NMR spectrum of compound 77 in $CDCl_3$



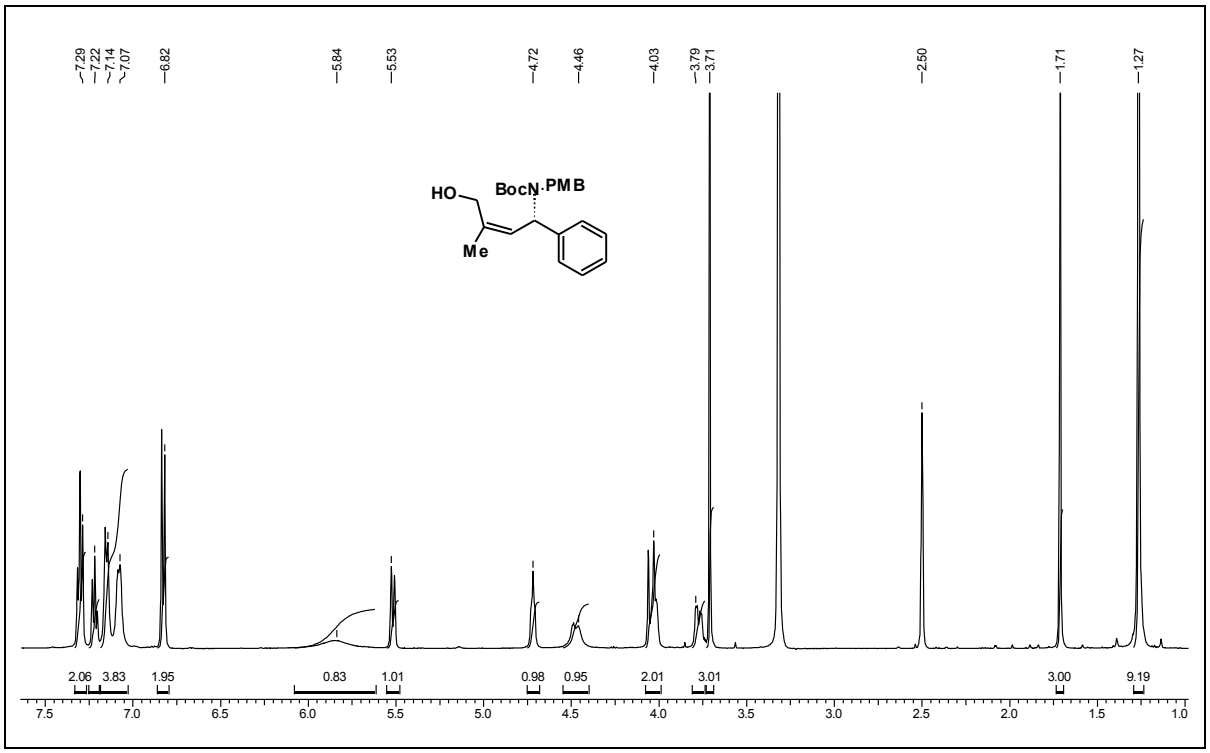
^{1}H NMR spectrum of compound 79 in $CDCl_3$



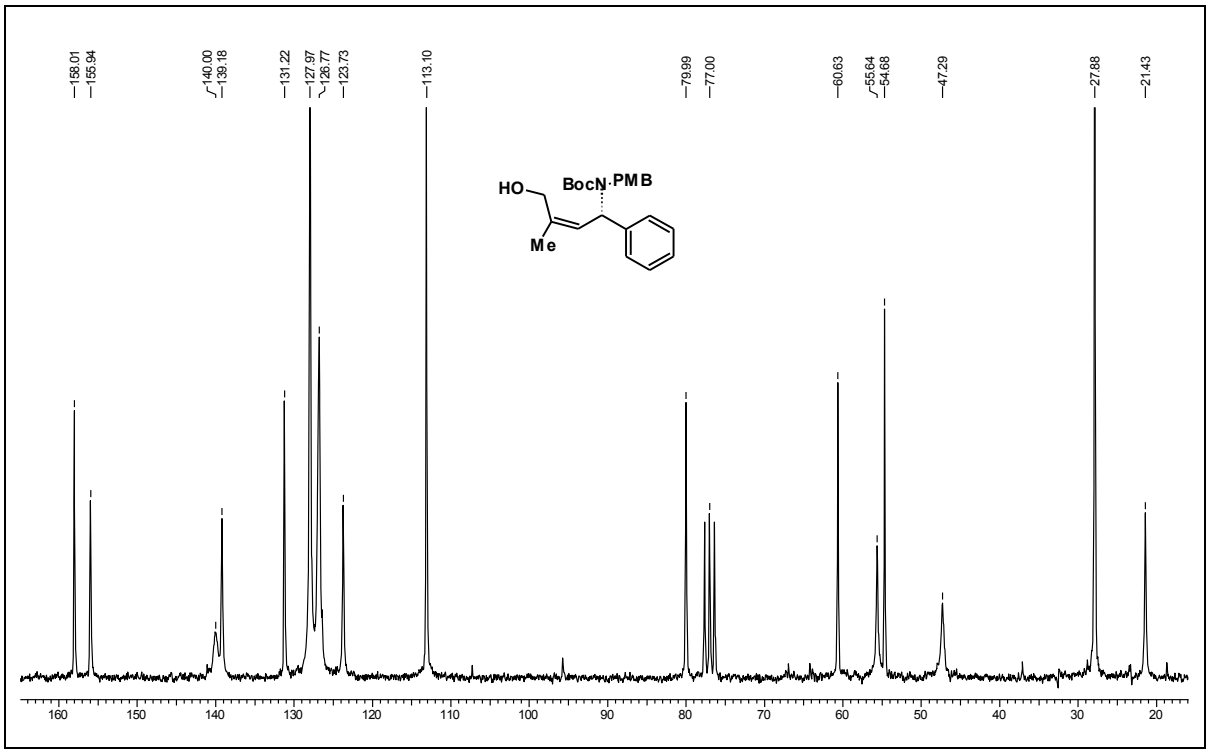
^{13}C NMR spectrum of compound 79 in $CDCl_3$



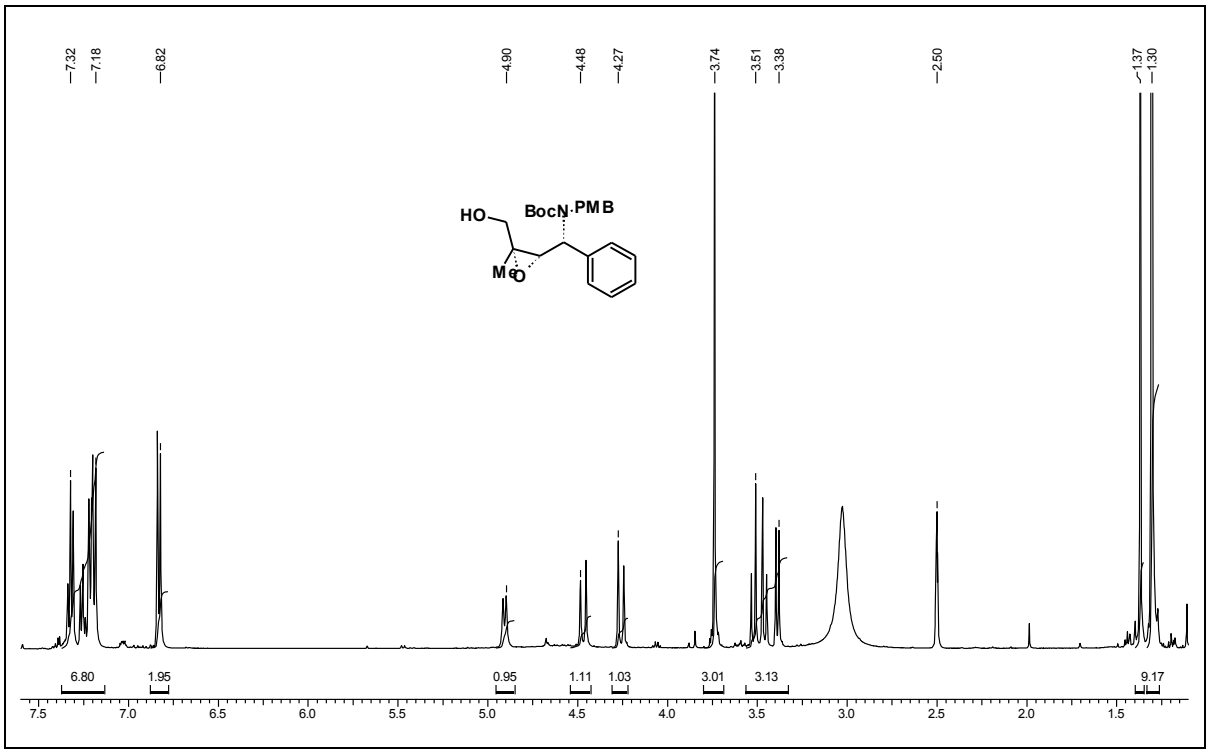
NOESY spectrum of compound 79



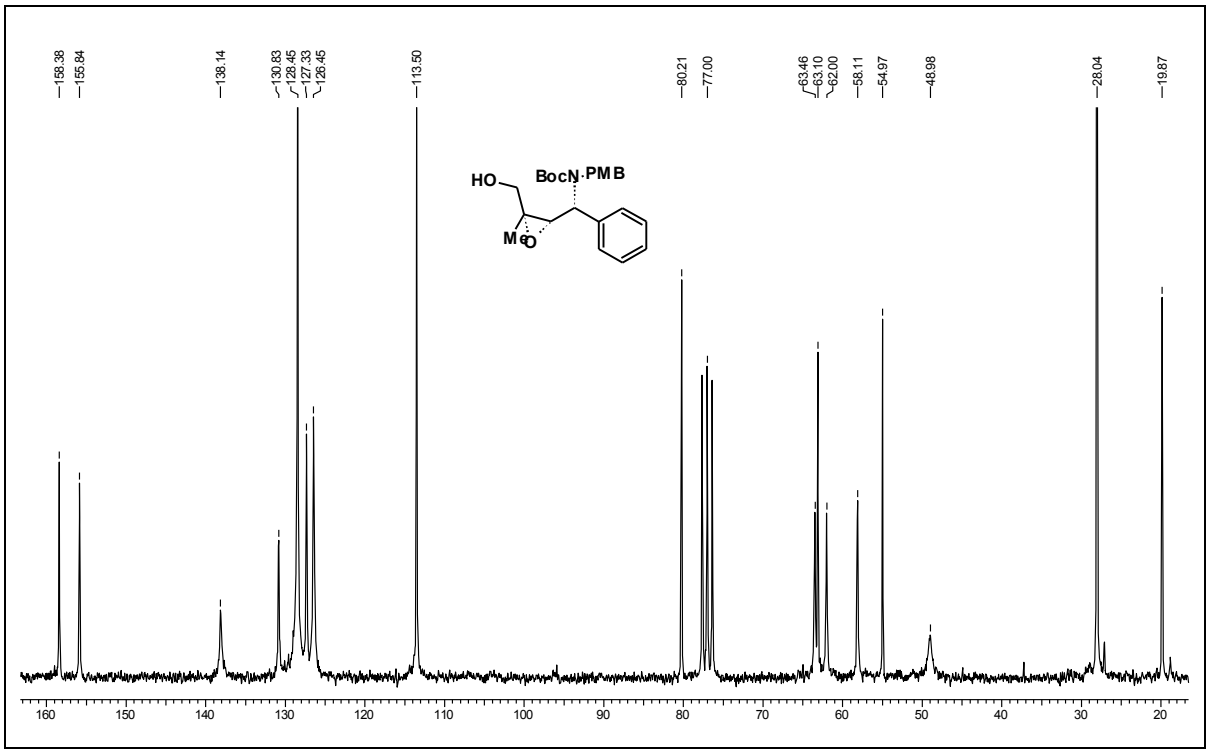
^{1}H NMR spectrum of compound 73 in DMSO-d_6



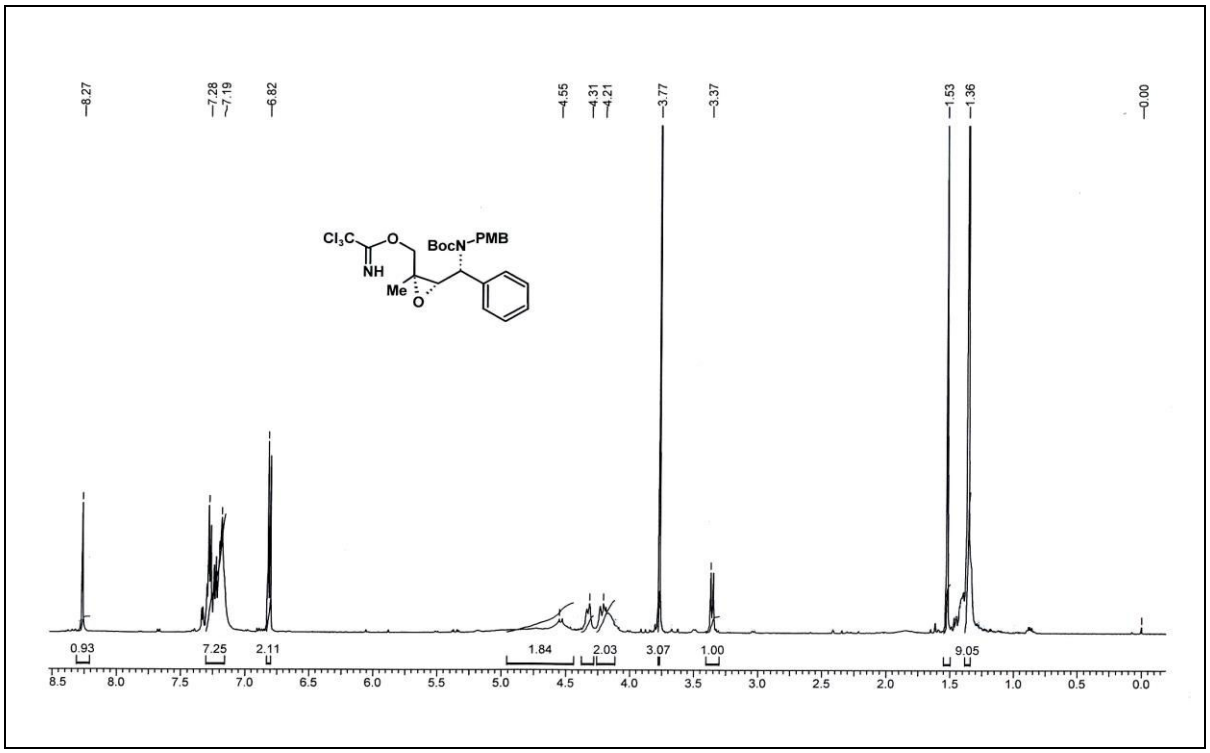
^{13}C NMR spectrum of compound 73 in $CDCl_3$



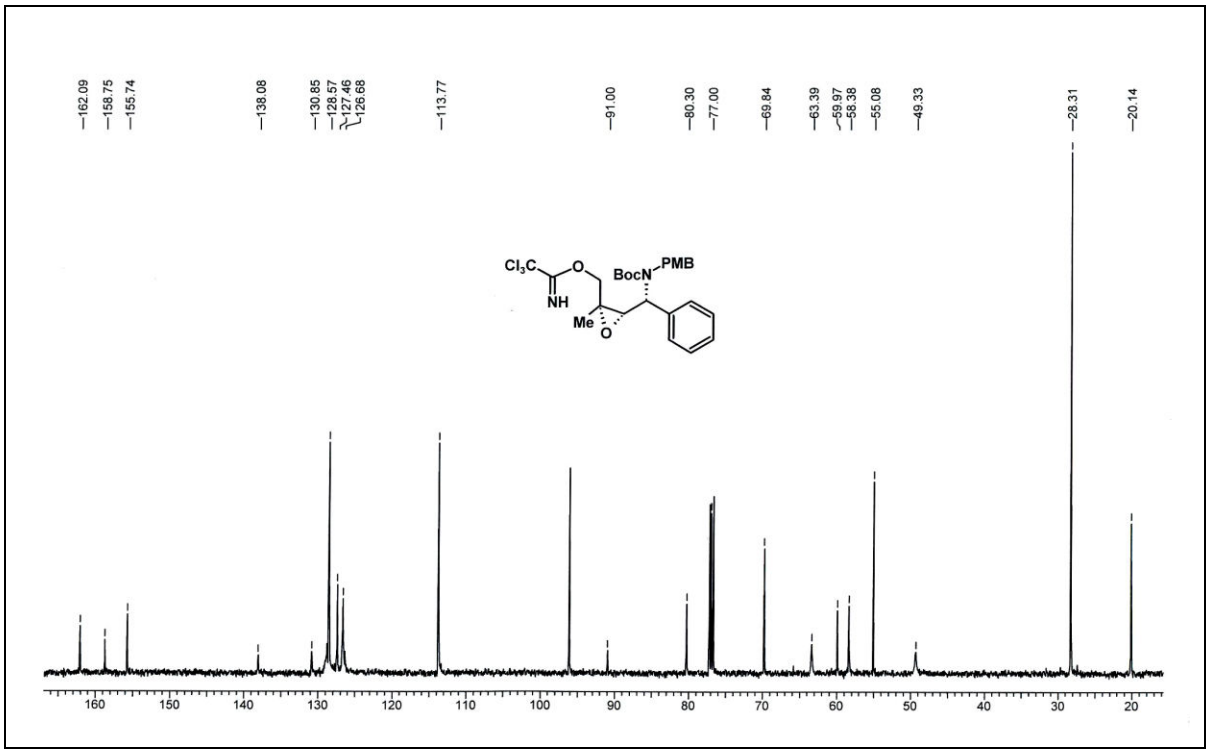
^{1}H NMR spectrum of compound 72 in DMSO-d_6



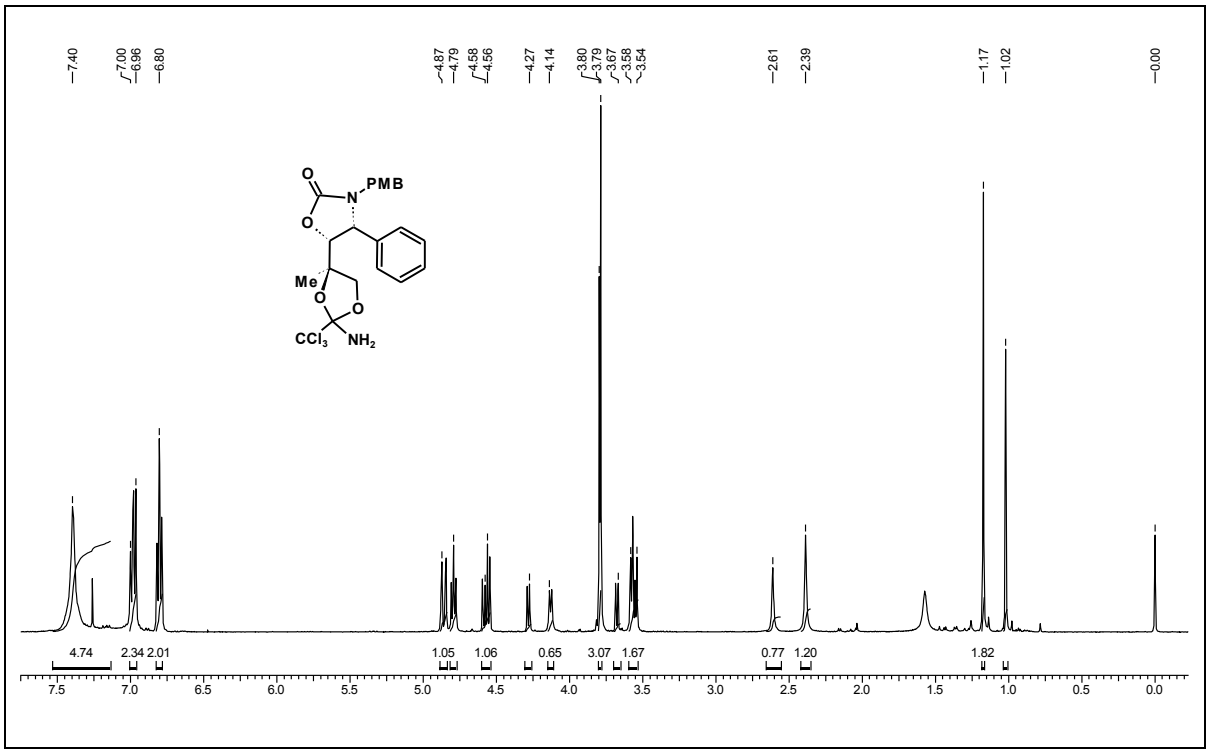
^{13}C NMR spectrum of compound 72 in $CDCl_3$



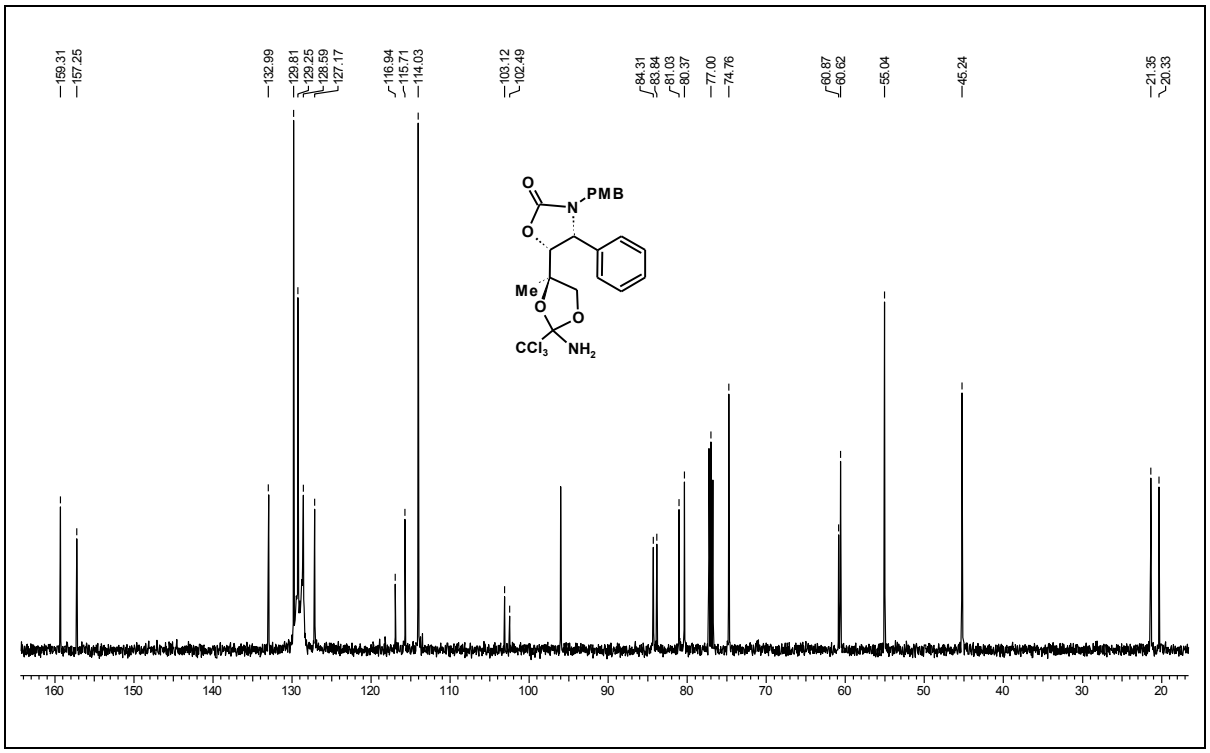
^{1}H NMR spectrum of compound 81 in $CDCl_3$



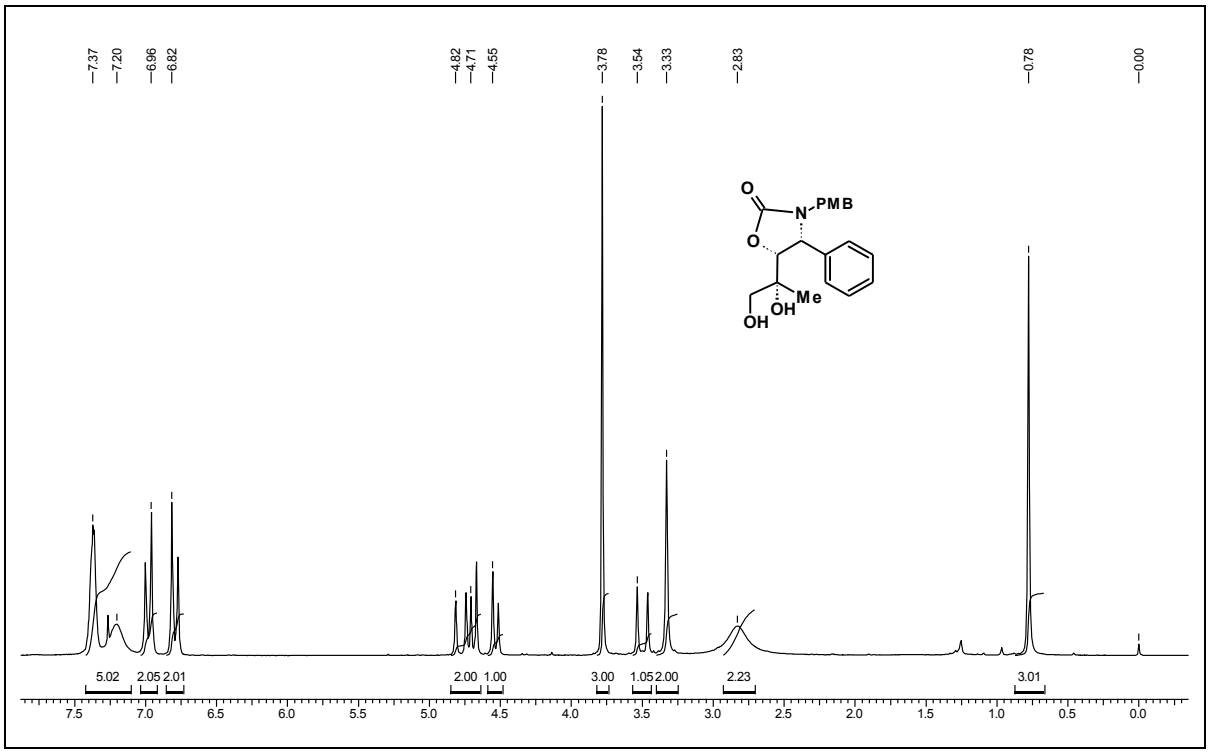
^{13}C NMR spectrum of compound 81 in $CDCl_3$



^{1}H NMR spectrum of compound 87 in $CDCl_3$



^{13}C NMR spectrum of compound 87 in $CDCl_3$



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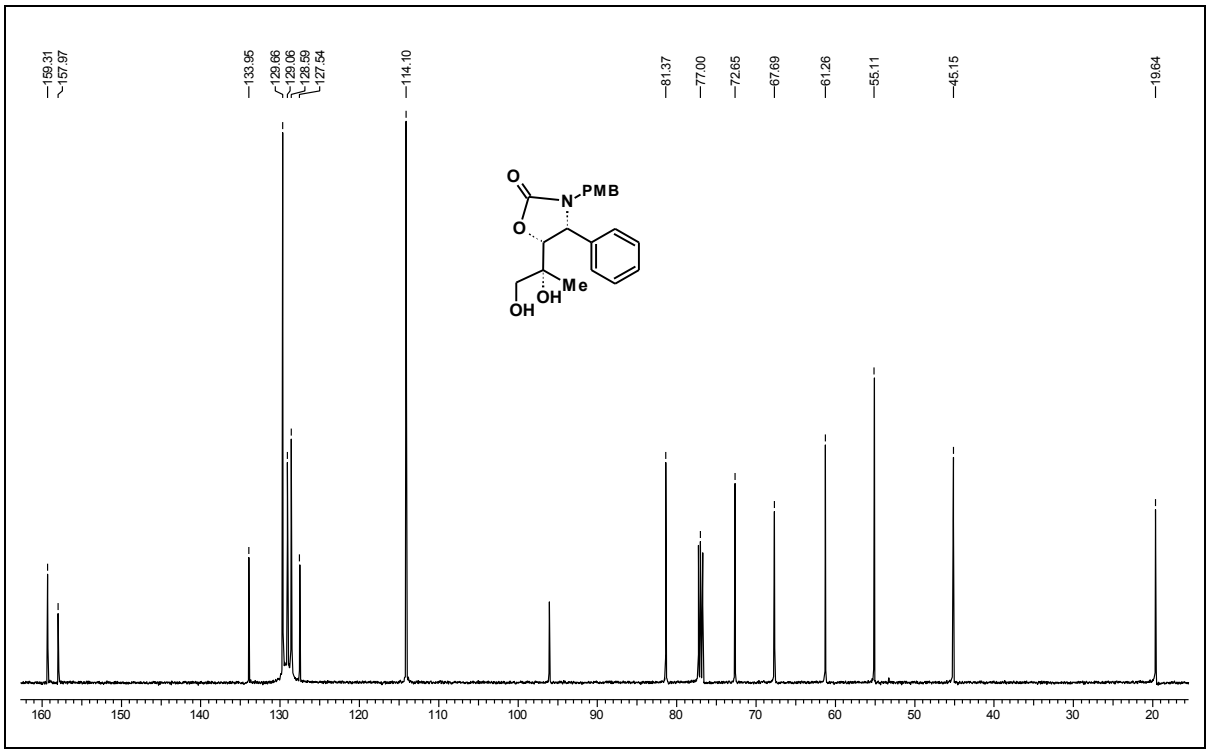
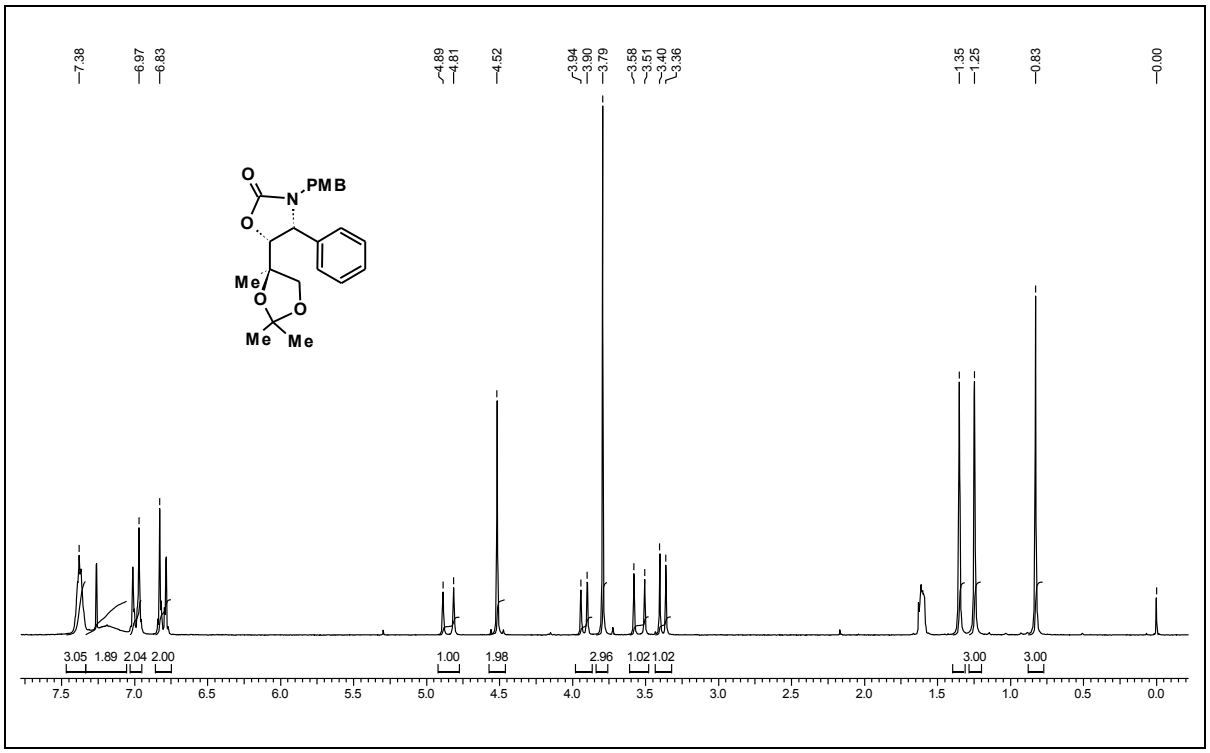


^{13}C NMR spectrum of compound 85 in $CDCl_3$



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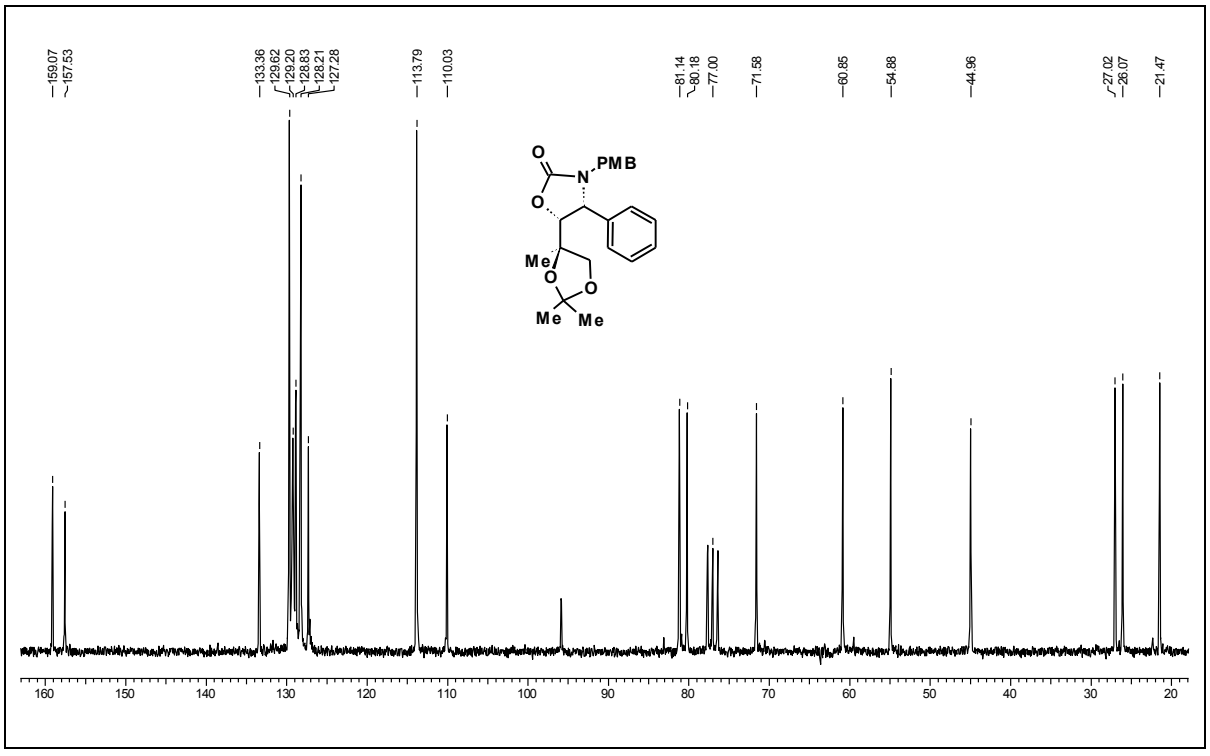

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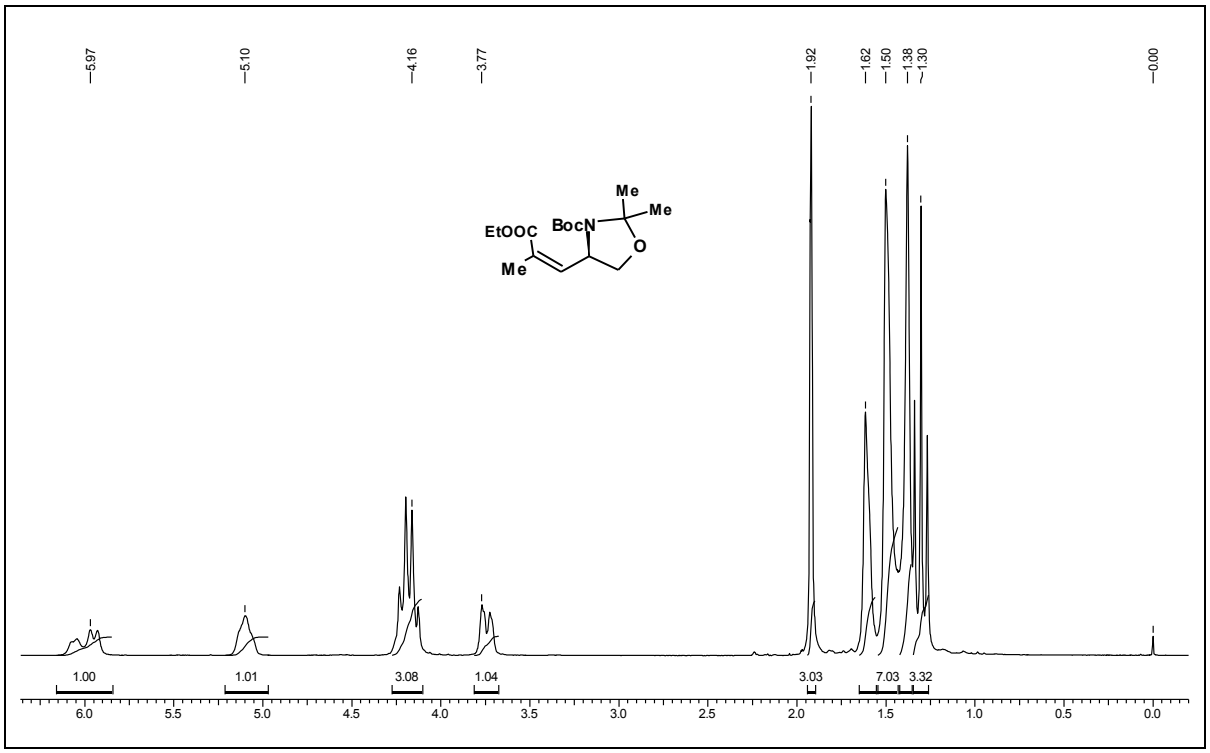
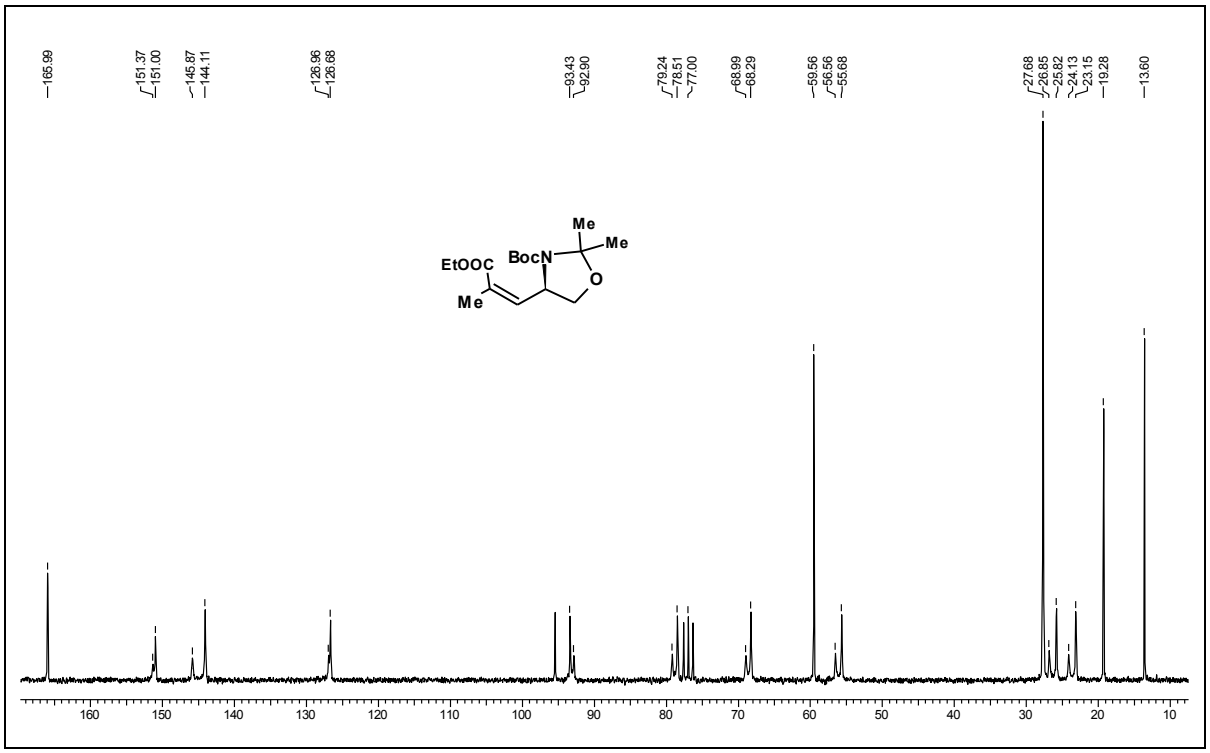
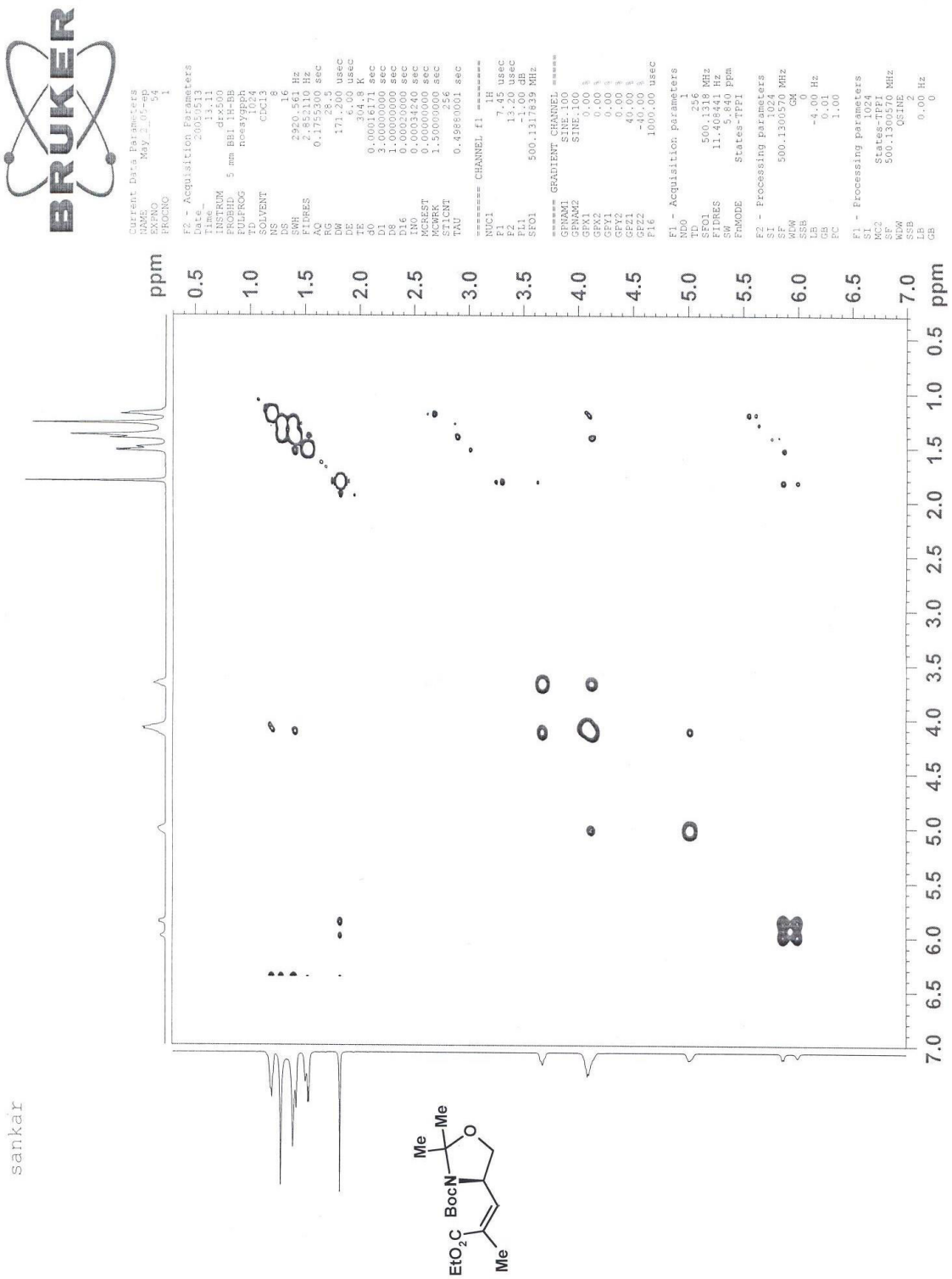


^{1}H NMR spectrum of compound 114 in $CDCl_3$



^{13}C NMR spectrum of compound 114 in $CDCl_3$



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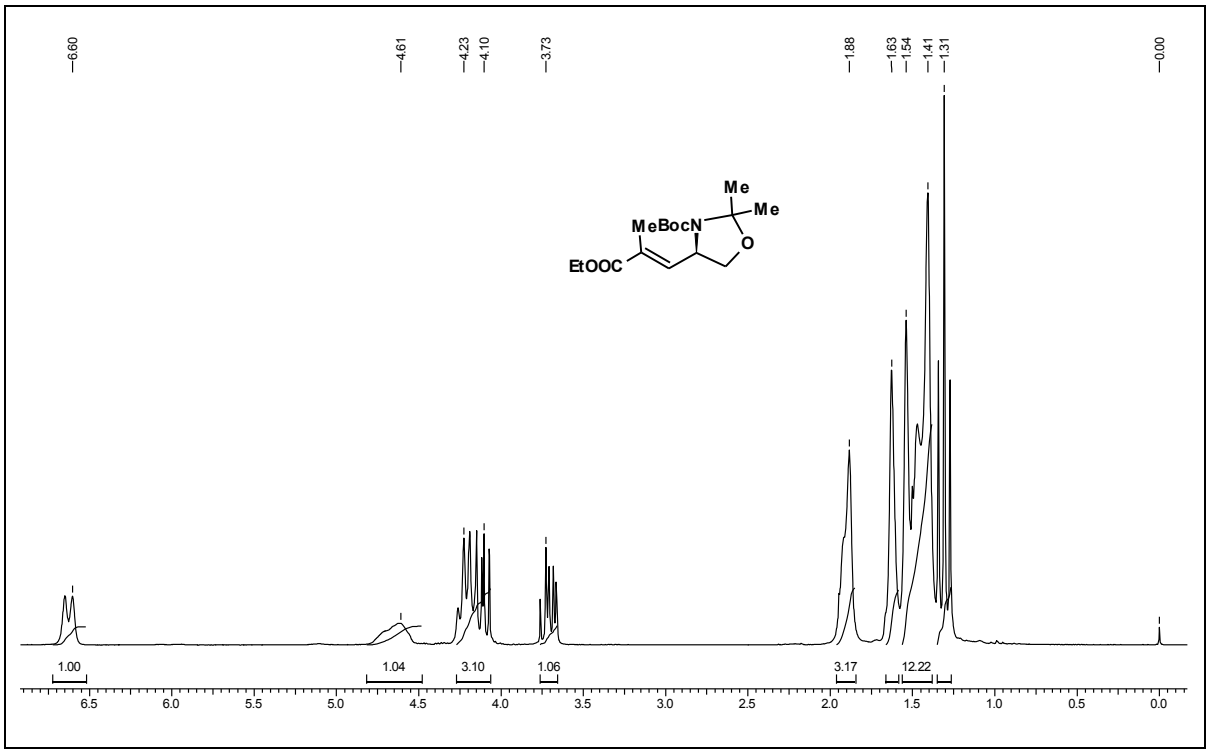

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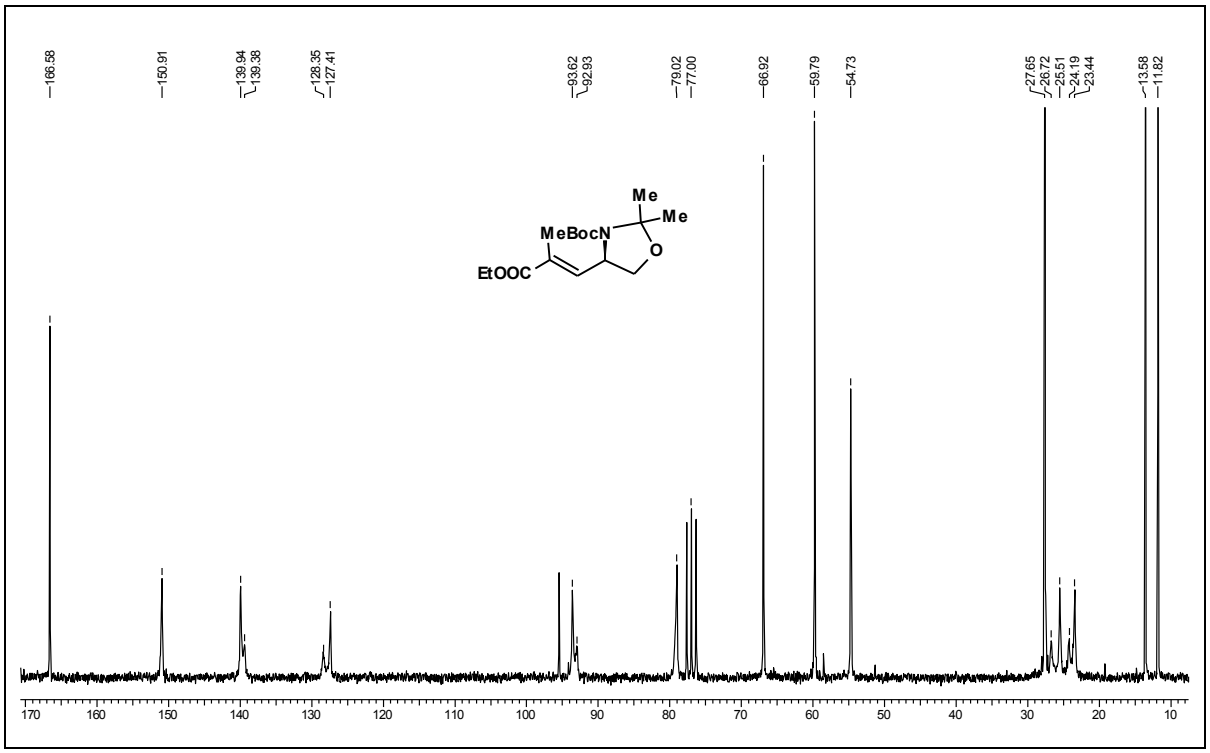
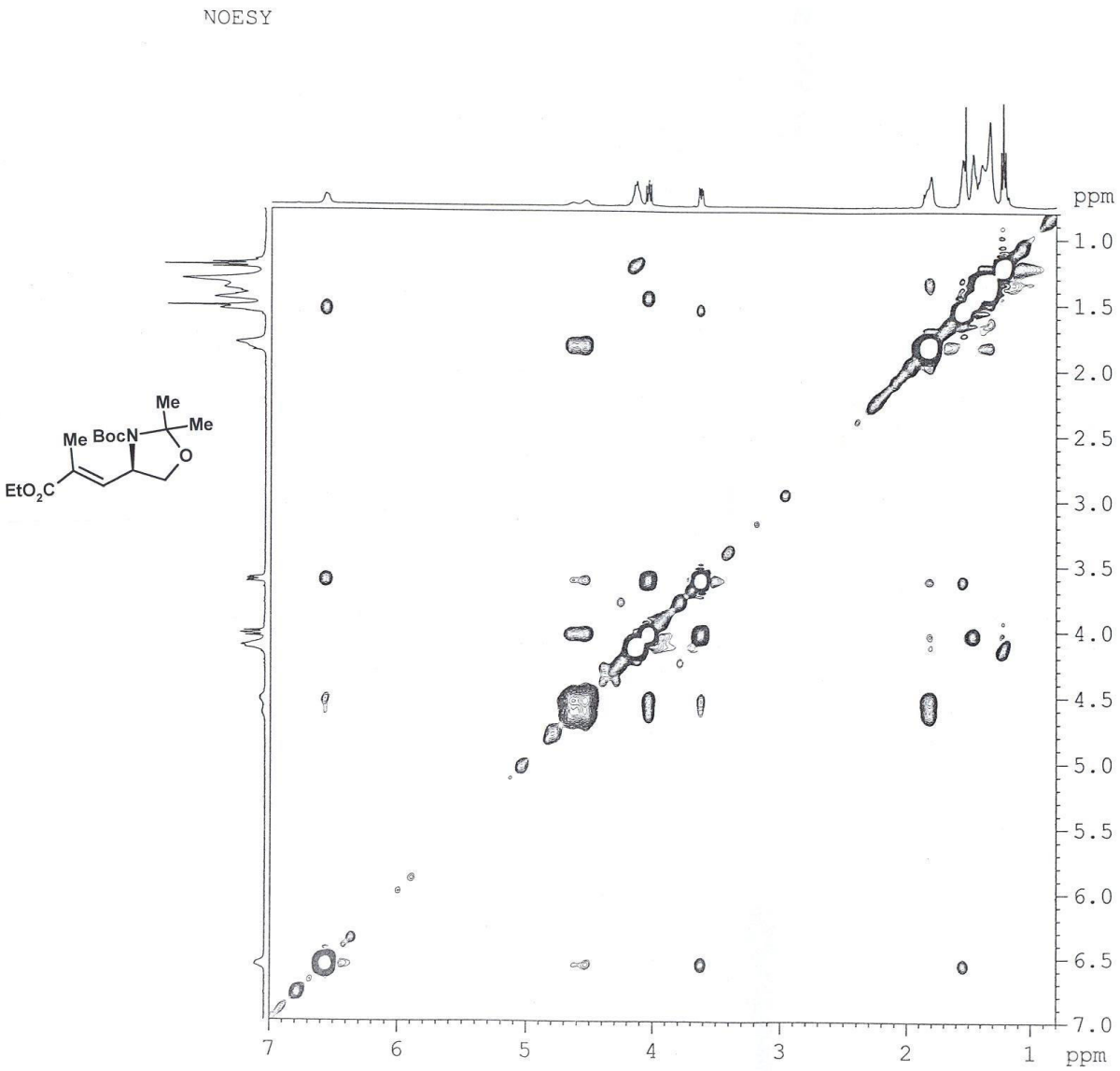


^{13}C NMR spectrum of compound 116 in $CDCl_3$

NOESY spectrum of compound 116



BRUKER

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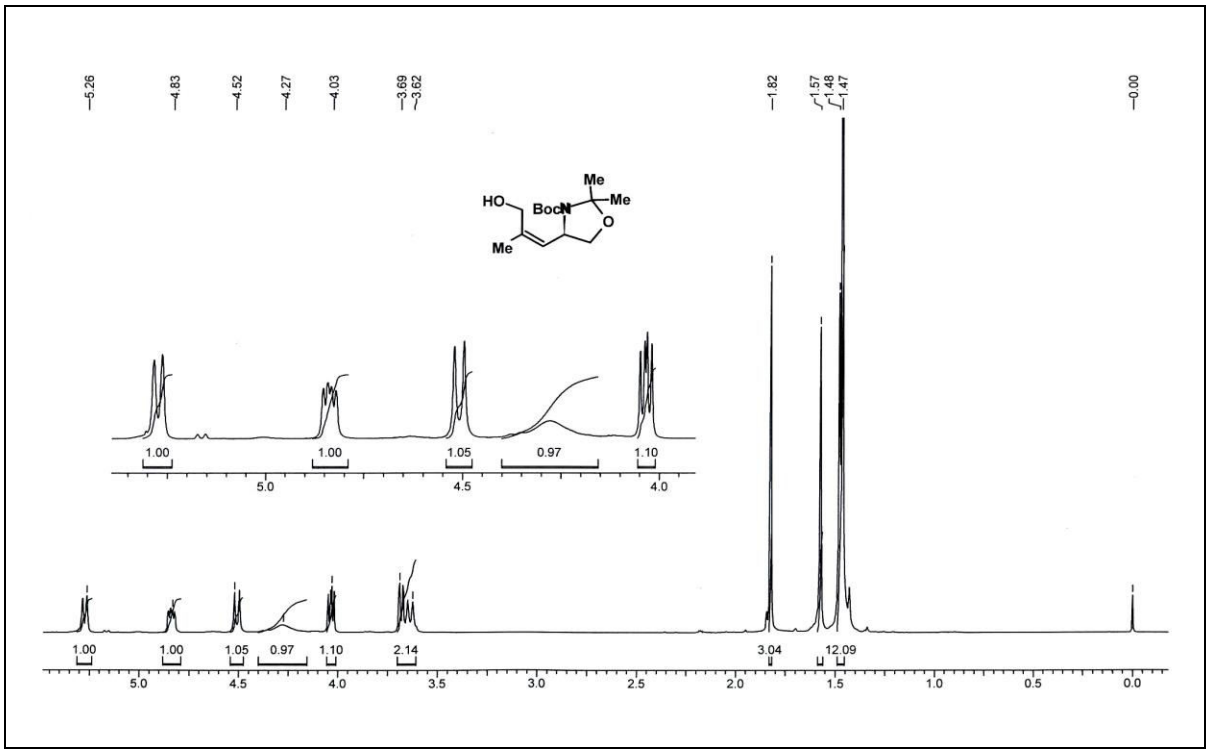

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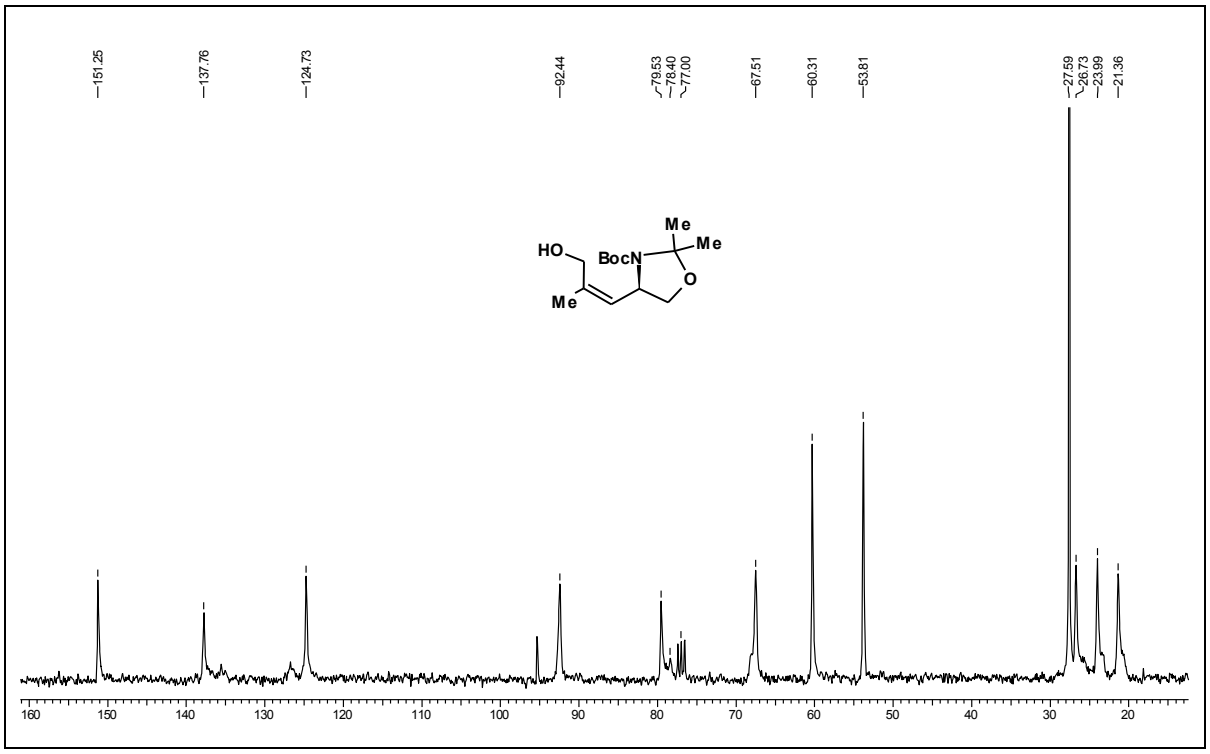

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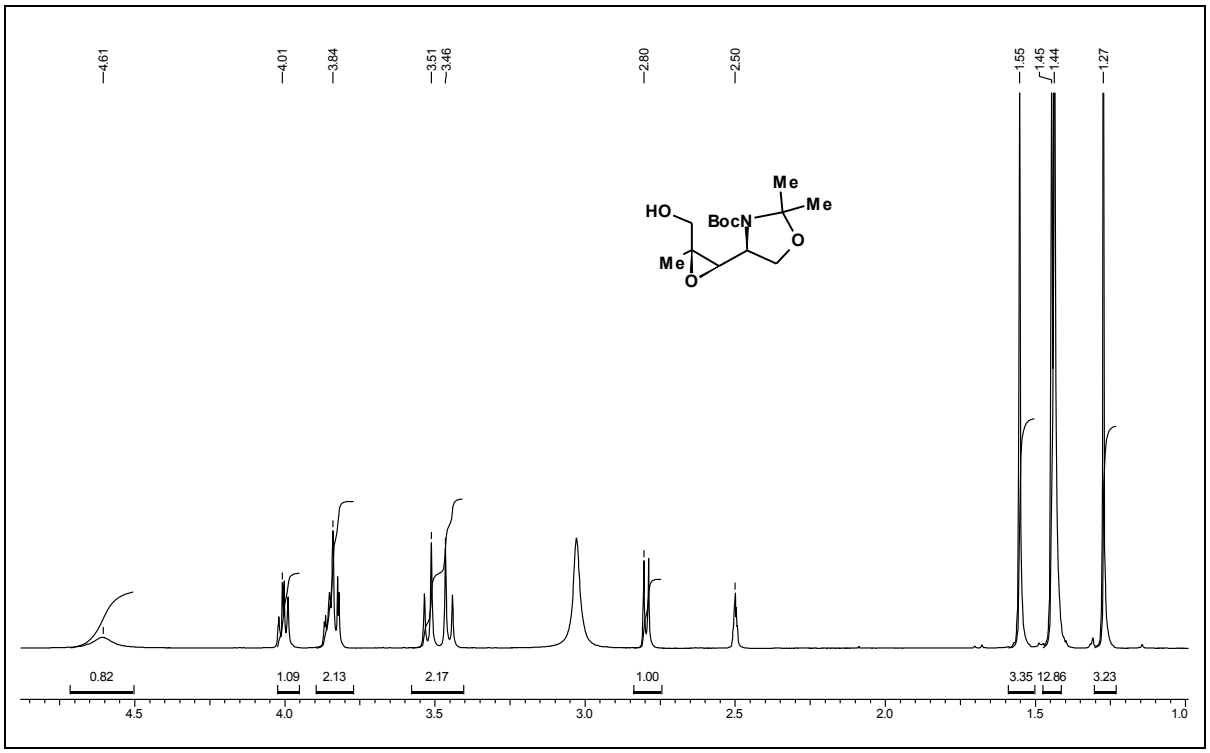

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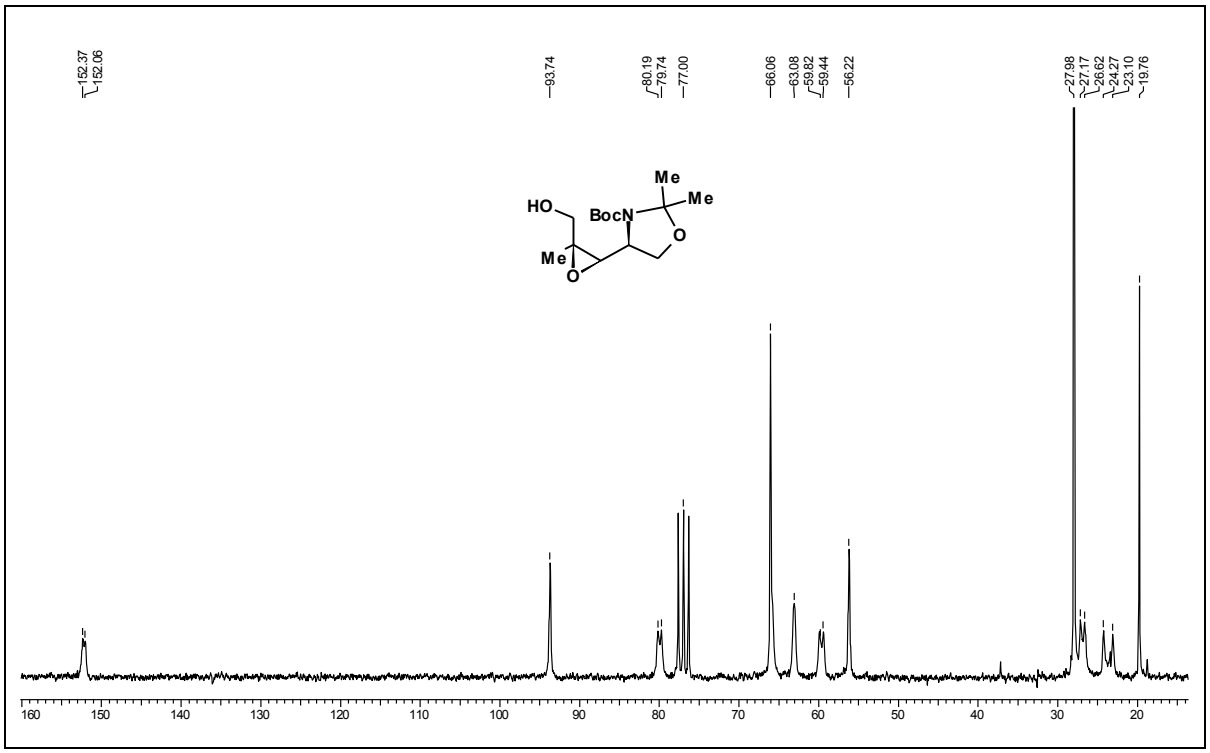
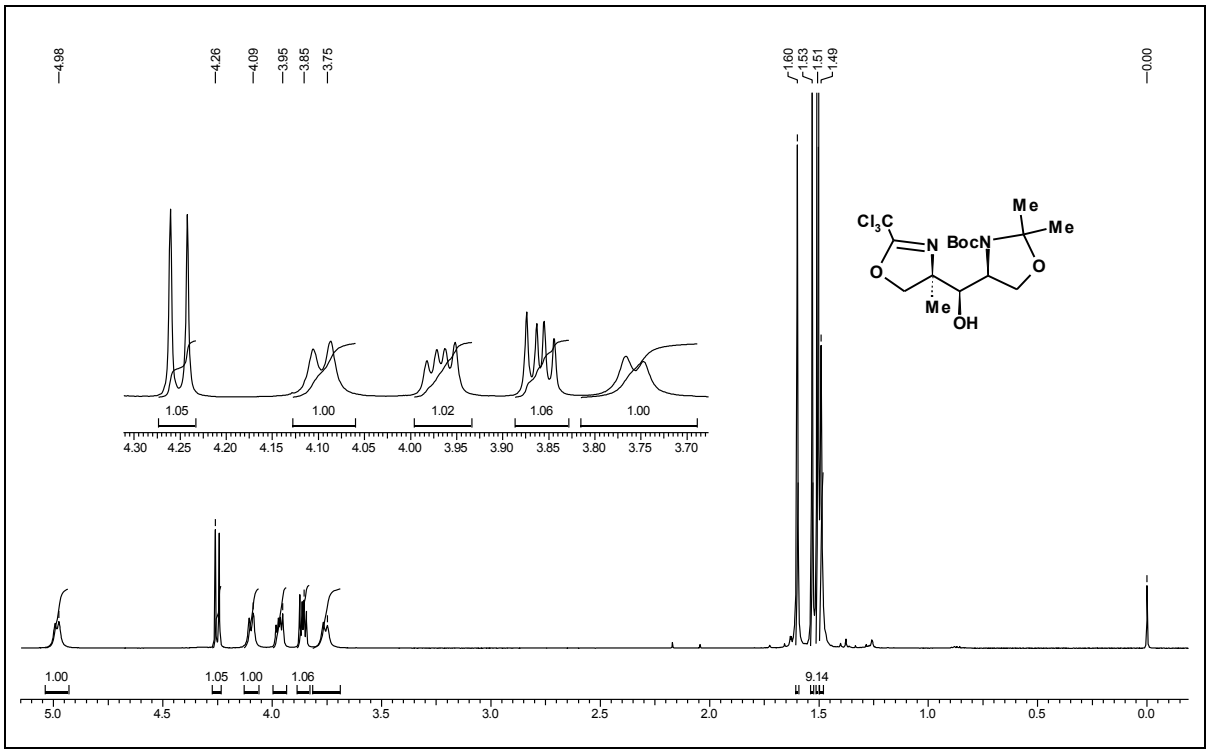
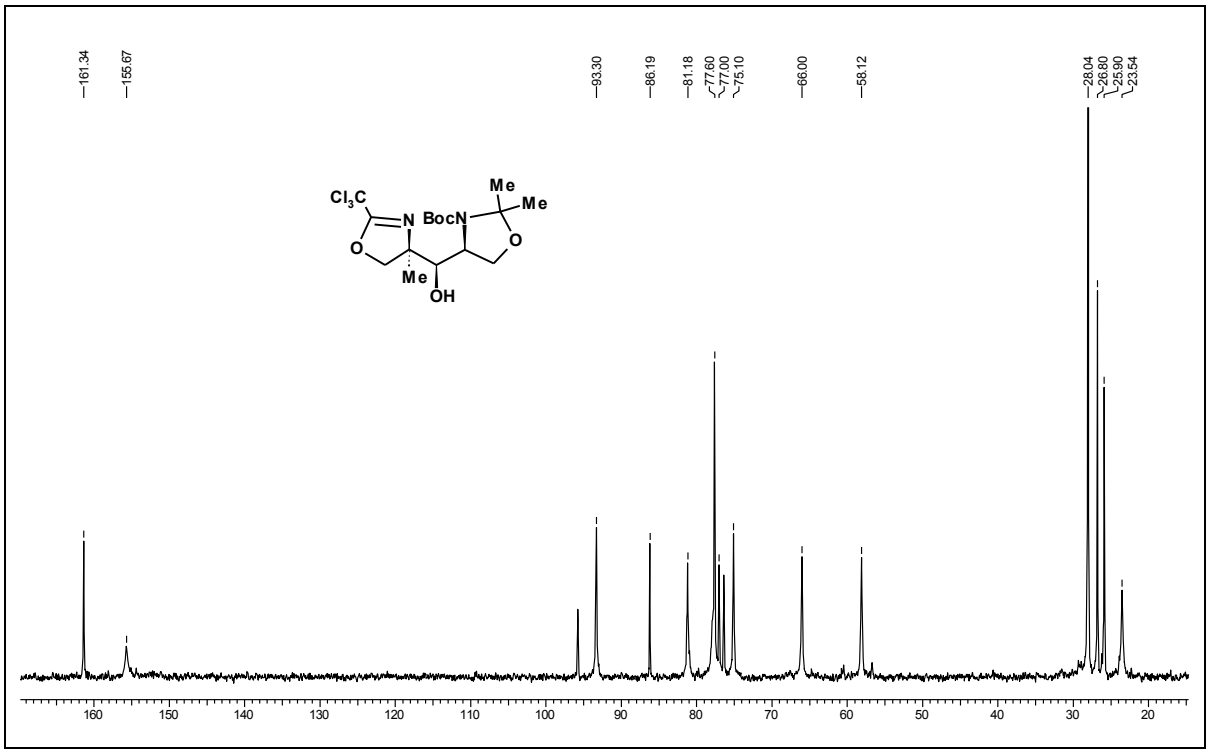


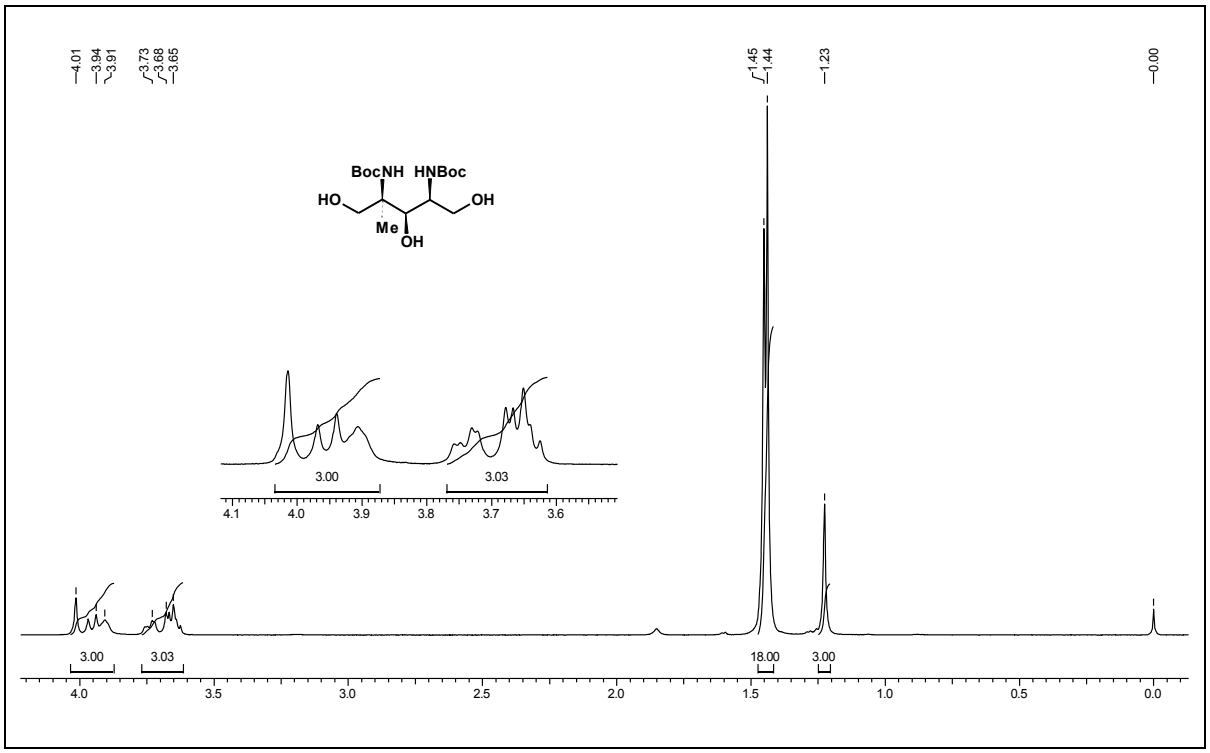
^{13}C NMR spectrum of compound 113 in $CDCl_3$



^{1}H NMR spectrum of compound 110 in $CDCl_3$ + D_2O



^{13}C NMR spectrum of compound 110 in $CDCl_3$



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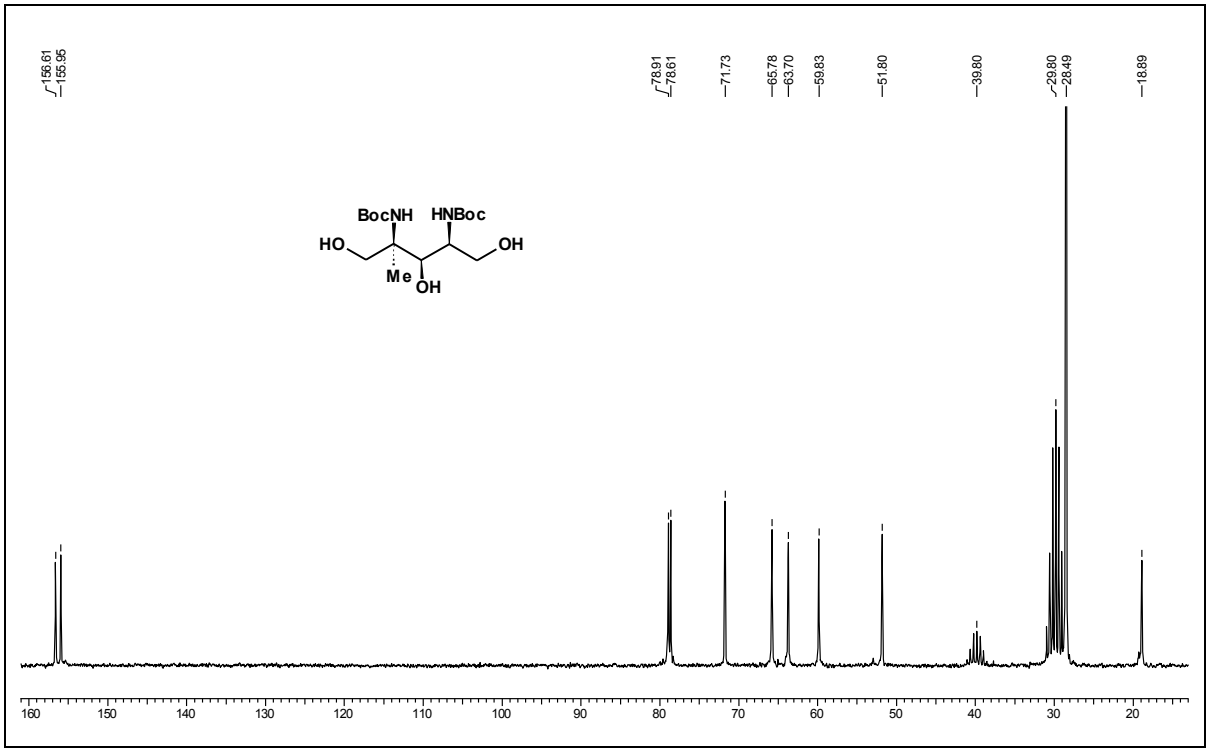
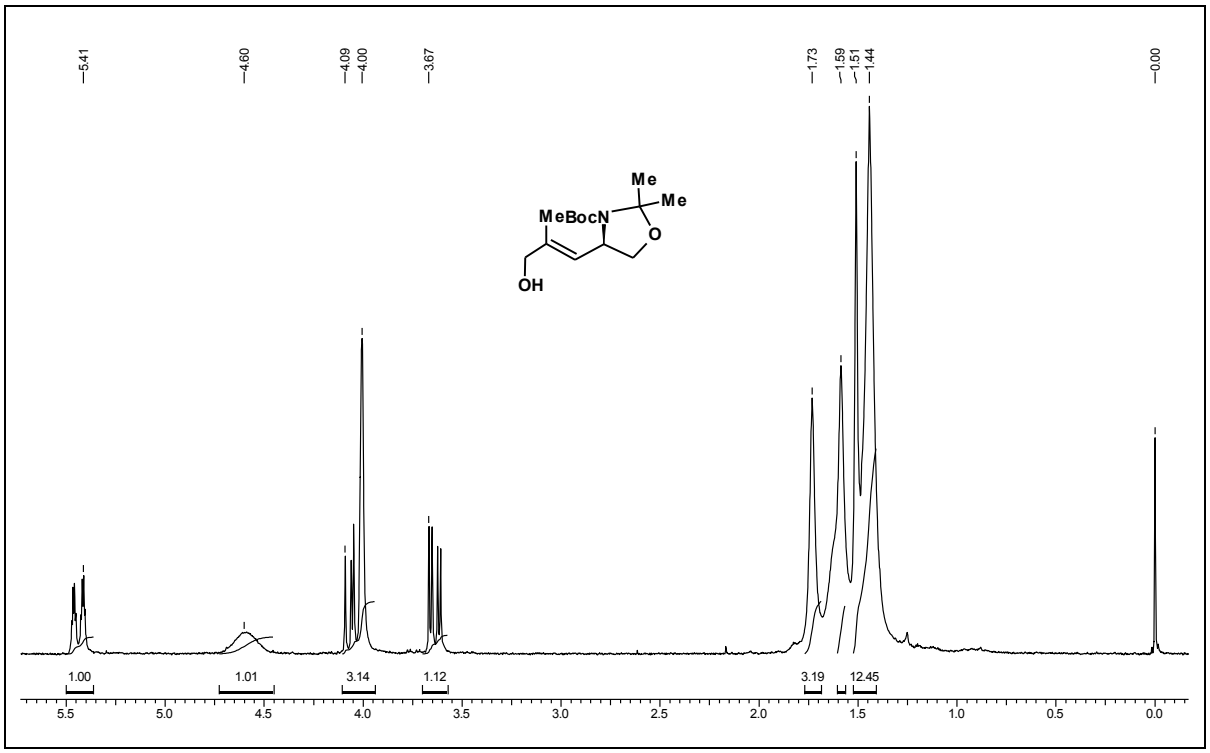
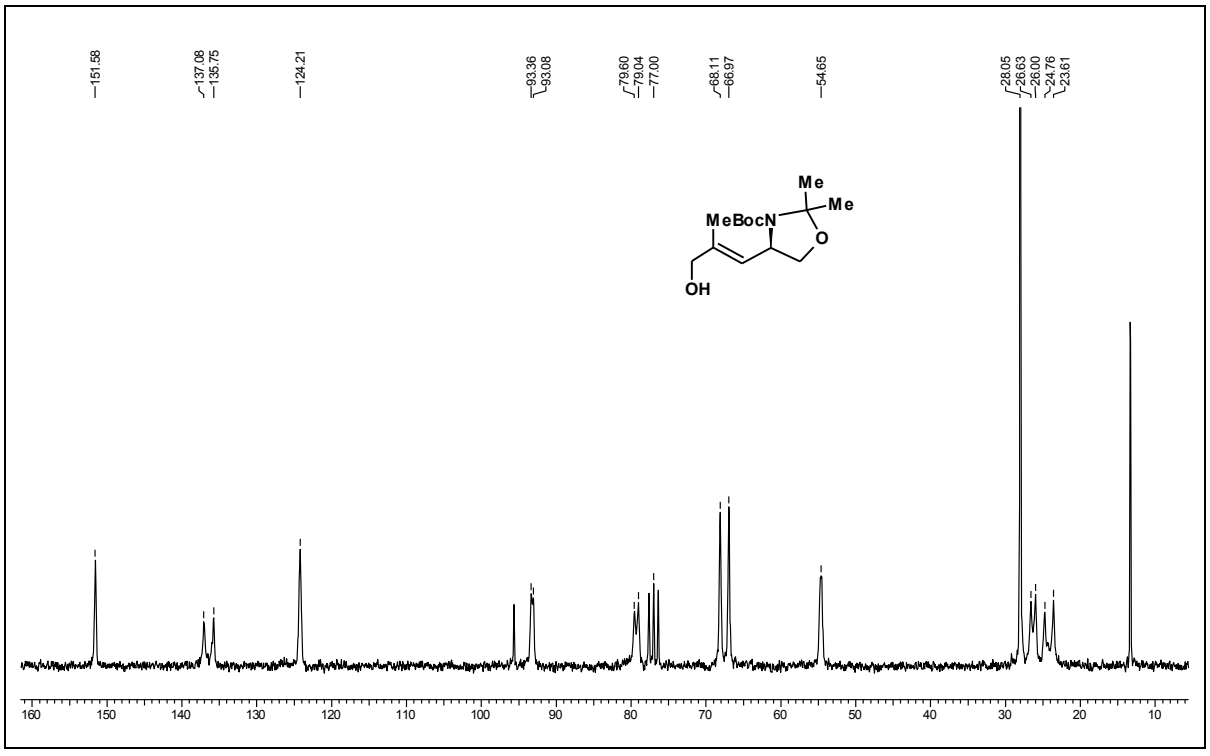


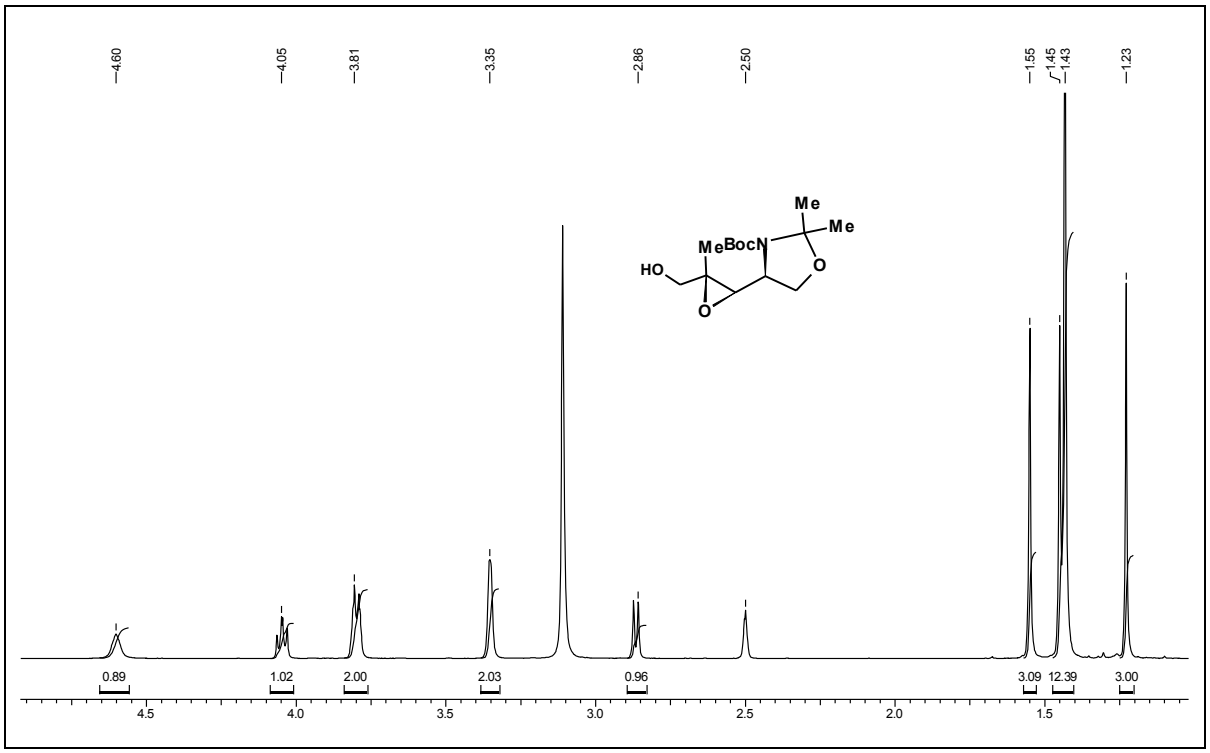
^{13}C NMR spectrum of compound 112 in DMSO-d_6 + Acetone-d_6



^{1}H NMR spectrum of compound 119 in $CDCl_3$



^{13}C NMR spectrum of compound 119 in $CDCl_3$



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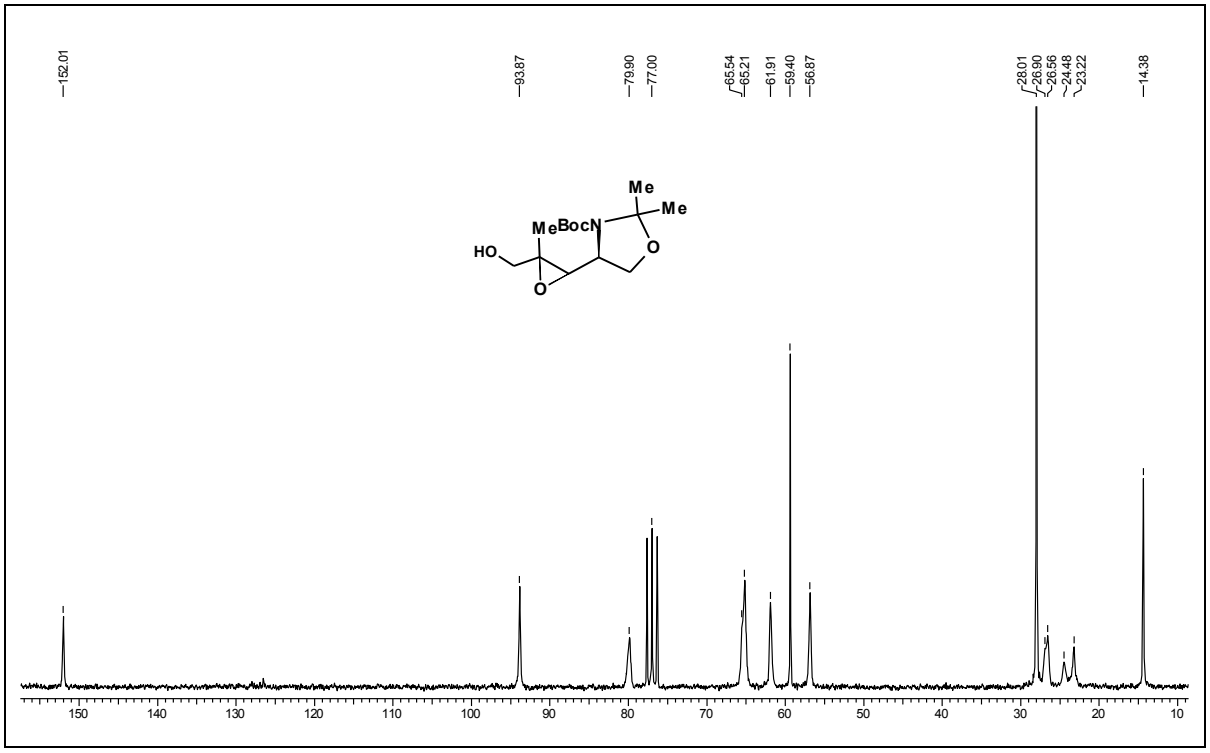
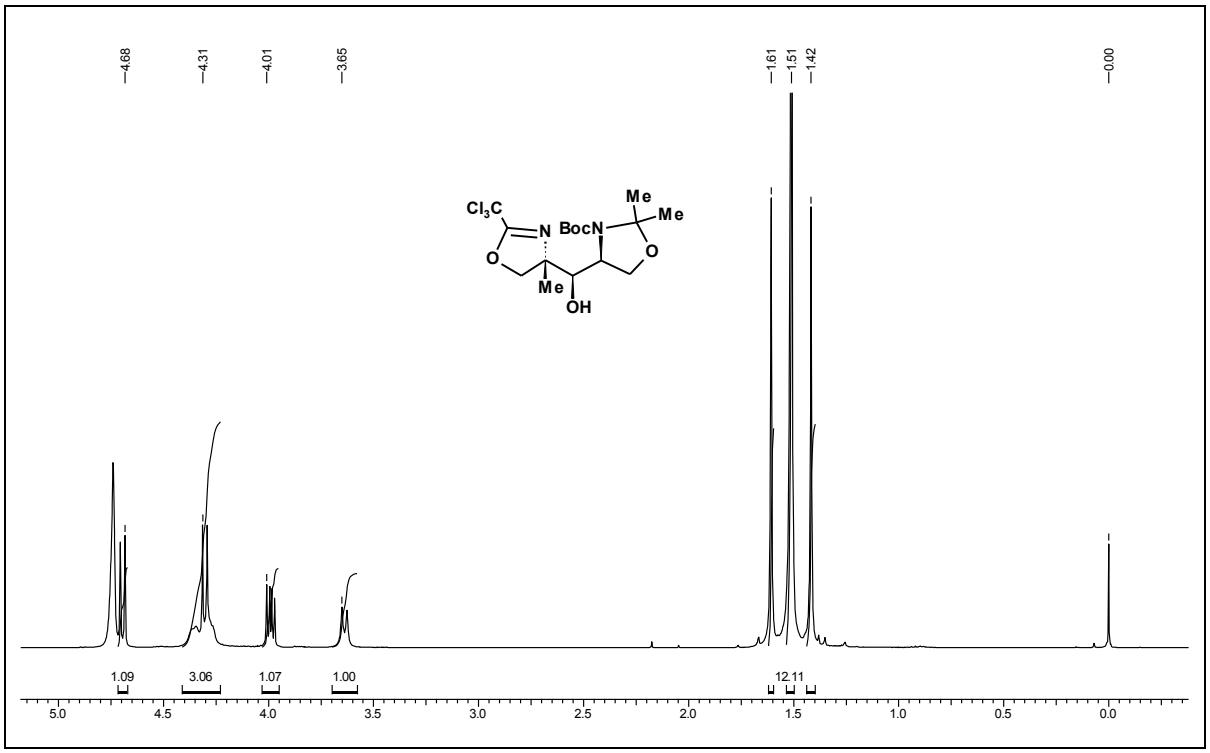
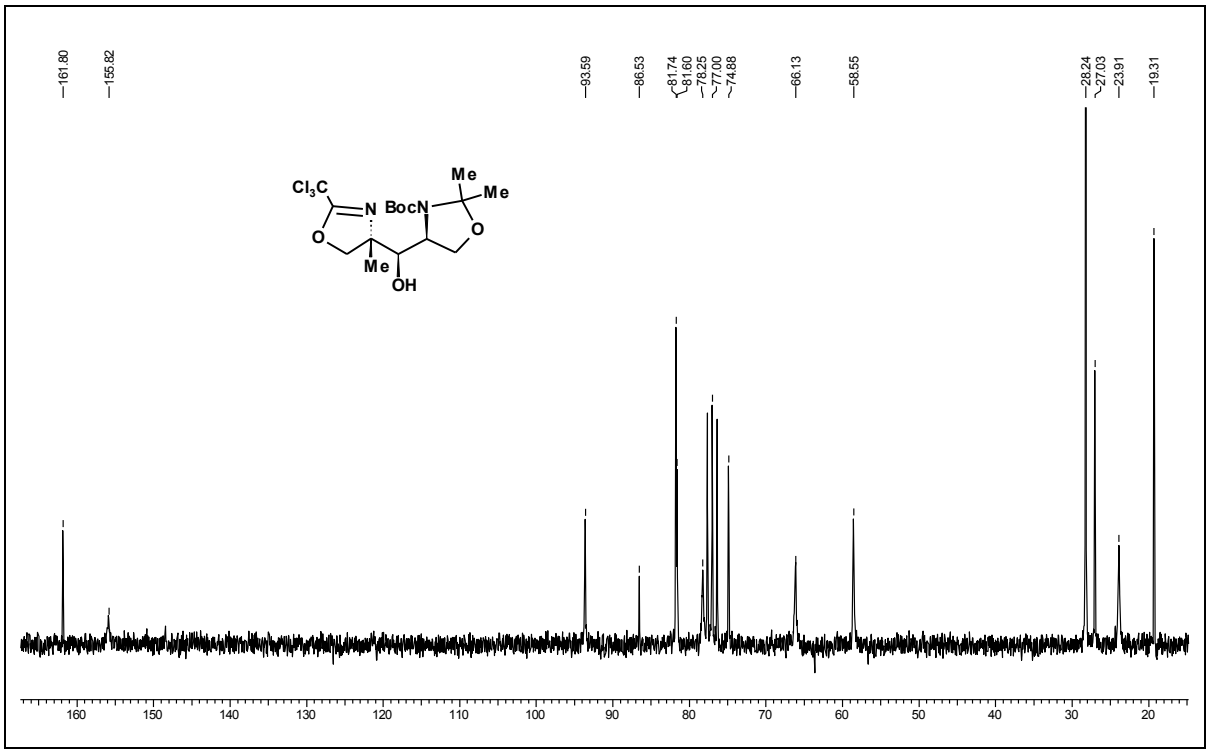


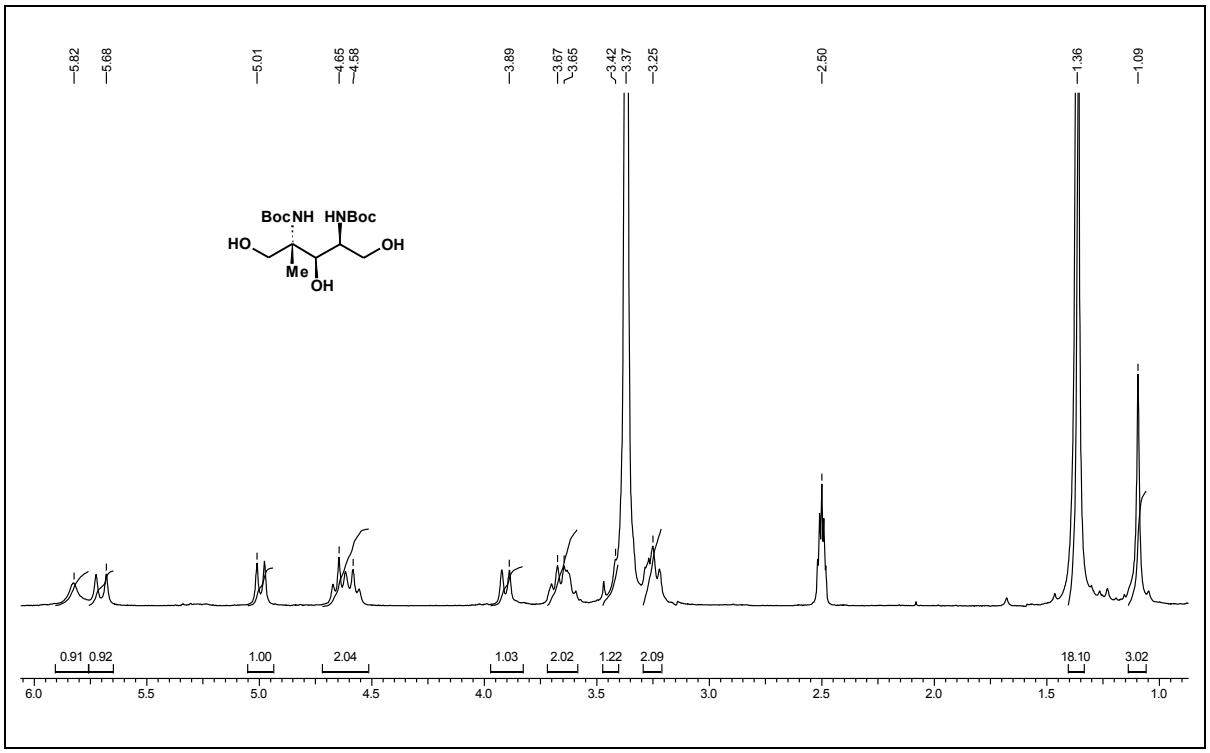
^{13}C NMR spectrum of compound 120 in $CDCl_3$



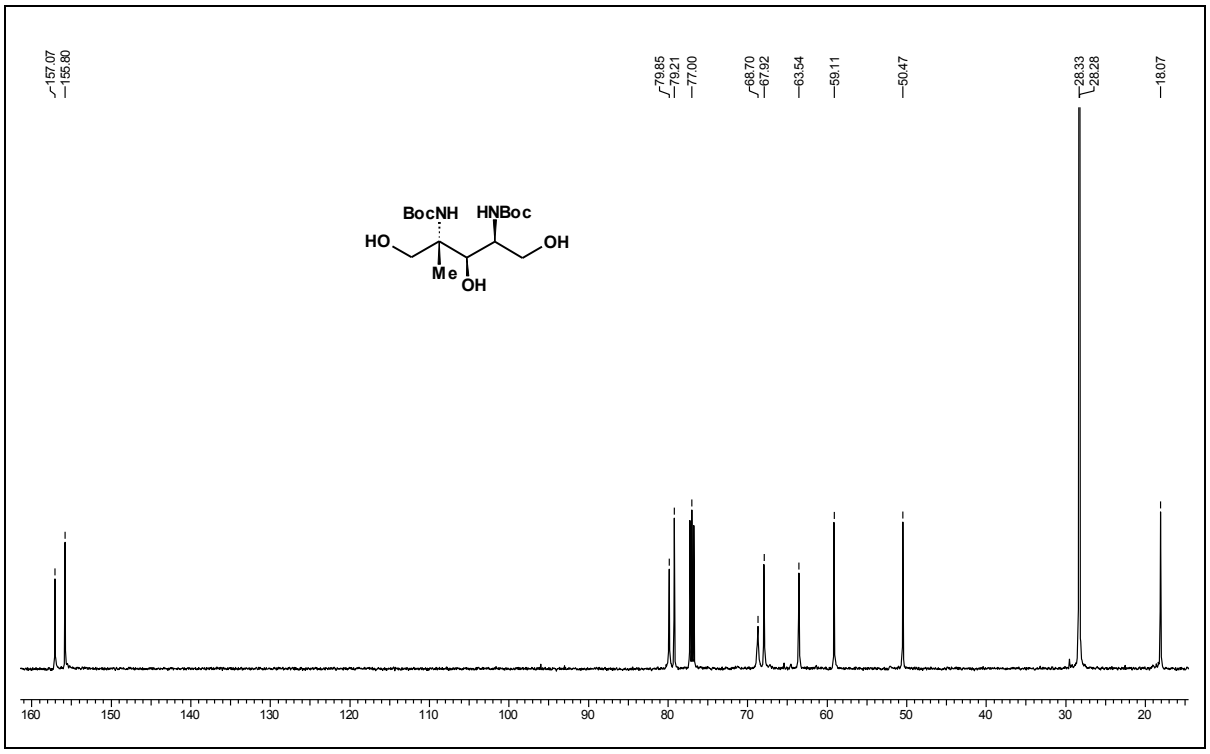
^{1}H NMR spectrum of compound 122 in $CDCl_3$ + D_2O



^{13}C NMR spectrum of compound 122 in $CDCl_3$



^{1}H NMR spectrum of compound 123 in DMSO-d_6

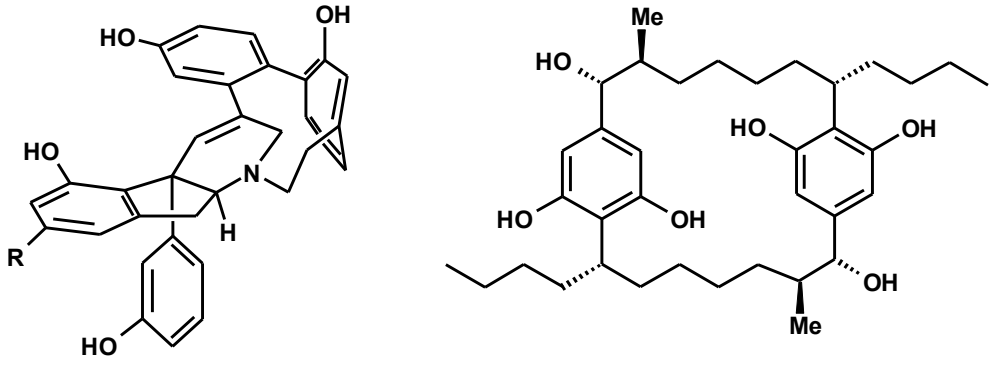


^{13}C NMR spectrum of compound 123 in $CDCl_3$

CHAPTER-3

Studies toward the synthesis of Pondaplin

A wide variety of bridged aromatic compounds, known as cyclophanes,[1,2] have become available as a result of extensive research over the past 50 years. The unique physical and chemical properties of cyclophanes, a direct result of their unusual architecture, vary considerably on the basis of size and constitution.[3] Notably, larger cyclophanes possess intramolecular cavities suitable for the formation of inclusion complexes, leading to applications in host-guest chemistry[3a,c,4] and mimicry of natural enzymes.[3a,c,5] Other applications include template-directed synthesis,[6] anion binding,[7] and catalysis.[8] Planar-chiral paracyclophanes are increasingly recognized as attractive chiral sources for various stereoselective reactions.[9] Though most of these studies are on designed cyclophanes, there are a number of natural products containing paracyclophane unit in their skeleton, which have been reported. Some of these natural products which represent an unusual class of compounds have been listed below.



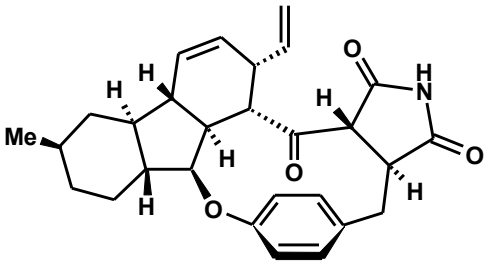
1 R= H, Haouamine A
2 R=OH, Haouamine B

3 Cylindrocyclophane A

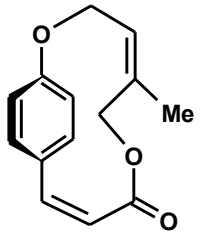
Figure 1

Haouamines A (**1**) and B (**2**), novel [7]-paracyclophane metabolites, were recently isolated from the ascidian *Aplidium haouarianum*, collected off Tarifa Island in the south of Spain.[10] Belonging to an unprecedented class of alkaloids, these compounds are characterized by two constrained ring systems, particularly the strained aza-paracyclophane moiety. The strain in the cyclophane portion is evident from the reported X-ray crystal structure and molecular models, which show the paradisubstituted benzene ring to be nonplanar. In 1990, Moore and co-workers reported the isolation of cylindrocyclophane A (**3**) and nostocyclophanes D.[11a] Five additional members of the

cylindrocyclophane family were then reported in 1992.[11b] Interestingly, these 22-membered [7,7]-paracyclophanes were found to be the major cytotoxic components in three different strains of the terrestrial blue-green algae *Cylindrospermum lichenforme*, displaying in vitro cytotoxicity against the KB and LoVo tumor cell lines.



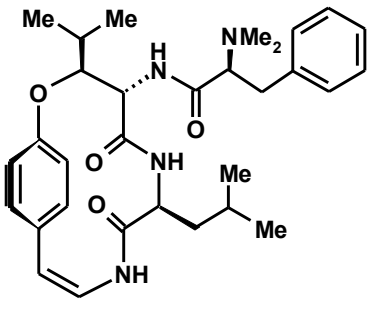
4 Hirsutellone A



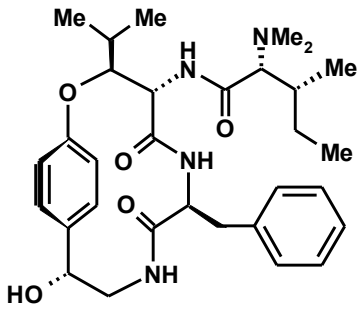
5 Pondaplin

Figure 2

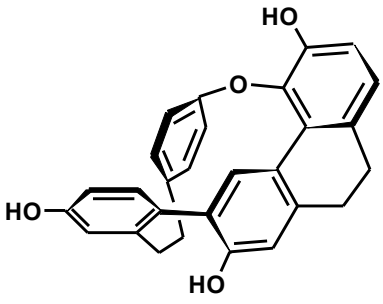
Hirsutellone A (**4**), a [8]-paracyclophane was isolated from *Hirsutella nivea* BCC 2594 by Isaka and co-workers recently.[12] A highly strained 12-membered ring containing a succinimide, a para-substituted phenyl ether, and a tricyclic polyketide are characteristic of these class of alkaloids. Pondaplin (**5**), isolated from the bioactive ethanolic extracts of the leaves of *Annona glabra* L. (Annonaceae) in 1999 by McLaughlin and co-workers was found to have moderate antitumor activity with selectivities for the breast (MCF-7) and prostate (PC-3) cancer cell lines.[13] It is a structurally unique molecule as it appears to be the only example of a [9]-paracyclophane natural product. This thirteen-membered macrolide contains a short tether that bears five sp^2 centers (two isolated double bonds and a lactone), imparting a high degree of strain energy and a potentially significant deformation of the aromatic ring from planarity.



6 Sanjoinine A



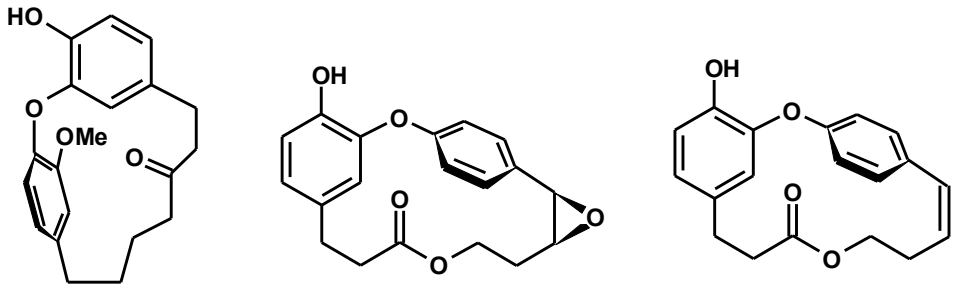
7 Pandamine



8 Cavicularin

Figure 3

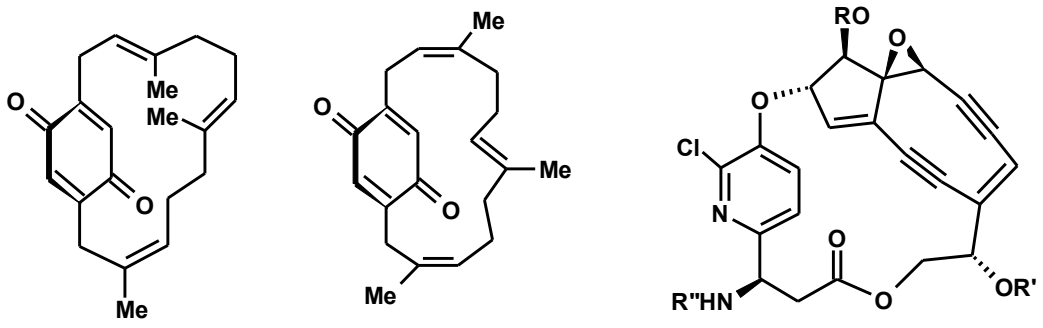
Cyclopeptide alkaloids are para or meta cyclophanes with a polypeptide tether. The wide-spread occurrence of these 13, 14, and 15-membered macrocyclic molecules in different plants such as rhamnaceae, pendaceae, and rubiaceae has made them an important class of natural products. Sanjoinine A (**6**) and pandamine (**7**) are examples of [10]-paracyclophane cyclopeptide alkaloids.[14a,b] Cavicularin (**8**) is also a [10]-paracyclophane, isolated from *Cavicularia densa* Steph. Its three-dimensional structure was characterized by X-ray crystallographic analysis. It was shown to be a cyclic bibenzyl-dihydrophenanthrene derivative, having a highly strained paradisubstituted phenyl ring. It possesses both planar and axial chirality.[15]



9 Galeon **10 Combretastatin D-1** **11 Combretastatin D-2**

Figure 4

Galeon (**9**), a [7,1]-metaparacyclophane isolated from the stems of *Myrica gale* L, has a seven membered carbon chain that connects both the aromatic rings. Although it does not contain any chiral center, restricted rotation around the para-substituted aromatic ring gives optical activity for this compound.[16] Combretastatins D-1 (**10**) and D-2 (**11**) are 15-membered [8,1]-metaparacyclophane macrolides isolated from the South African tree *Combretum caffrum* that have been found to inhibit PS cell line growth.[17]



12 Longithorone B **13 Longithorone C** **14 Kedarcidin core**

Figure 5

Longithorones B (**12**) and C (**13**) are benzoquinones bridged across the para-position by a farnesyl unit, isolated from a tunicate, *Aplidium longithorax*. These compounds show atropisomerism due to restricted rotation of the quinone ring.[18] Kedarcidin is a chromoprotein antitumor antibiotic family consisting of a carrier apoprotein and a cytotoxic nine-membered enediyne chromophore. Kendarcidin chromophore (**14**) possesses a [13]-paracyclophane macrolide.[19]

Pondaplin **5**, isolated from the bioactive ethanolic extract of the leaves of *Annona glabra* L. (Annonaceae), as colorless crystals, mp 194-195 °C is a structurally unique molecule as it appears to be the only example of a [9]-paracyclophane natural product. It was found to have moderate antitumor activity with selectivities for the breast (MCF-7) and prostate (PC-3) cancer cell lines when screened across six human tumer cell lines in a seven day MTT human solid tumor cytotoxicity test. This thirteen-membered macrolide contains a short tether that bears five sp^2 centers (two isolated double bonds and a lactone), imparting a high degree of strain energy and a potentially significant deformation of the aromatic ring from planarity. The geometry of both the olefins were found to be in *Z*-configurations and the whole structure was characterized by NMR, IR and mass spectral studies.[13] These interesting structural features and its significant biological properties made it an intriguing target for total synthesis.

Inspection of structure **5** led to the identification of the trisubstituted olefin as well as the ester functionality as the appropriate strategic sites for the retrosynthetic disconnection through RCM[20] and macrolactonization reactions respectively. We opted for the first one, RCM mainly for the construction of the macrolide and the trisubstituted olefin simultaneously and this disconnection simplified the target to a cinnamate derivative **15**, which in turn could be synthesized from 4-hydroxy benzaldehyde **17** by allylation and Wittig-Horner olefination to get the α,β-unsaturated ethyl ester **16** followed by transesterification with methallyl alcohol (Figure **6**).

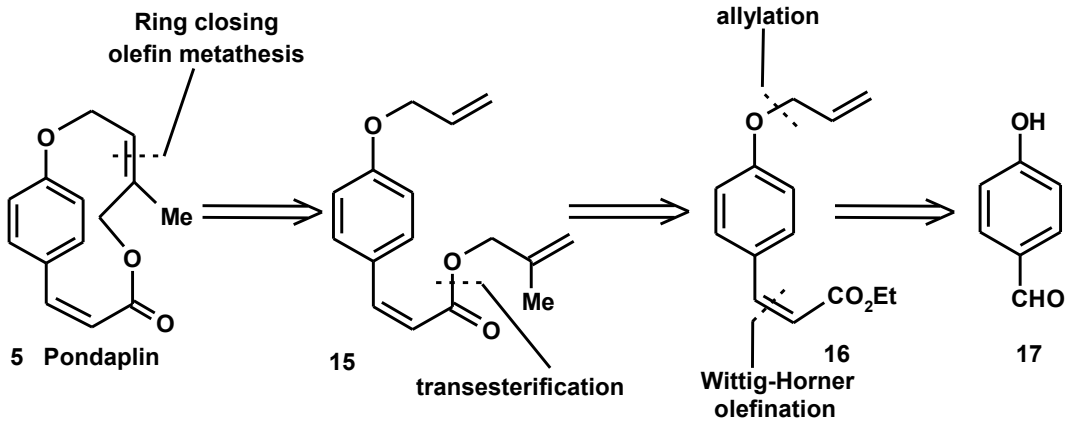
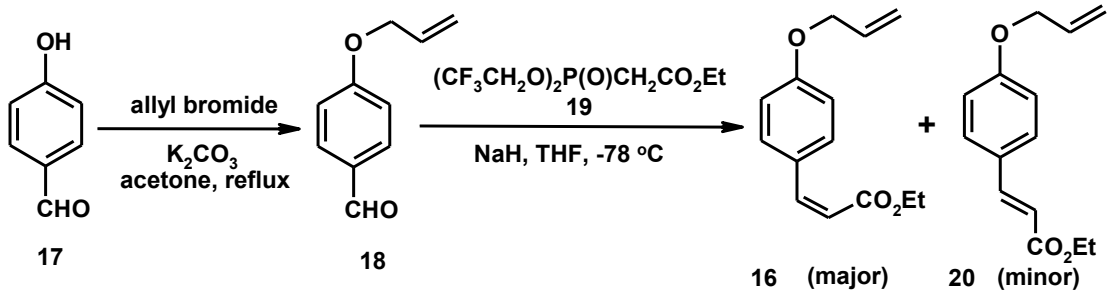


Figure 6 : synthetic strategy (RCM approach)

Our synthesis started with the readily available 4-hydroxybenzaldehyde (**17**), which was converted to 4-allyloxy benzaldehyde (**18**) using allyl bromide and K_2CO_3 in refluxing acetone for 3 h. For the stereoselective construction of the cis-cinnamate ester **16**, the modified phosphonate reagent developed by Still was used.[21] Accordingly, treatment of aldehyde with the anion generated from phosphonate **19** and NaH, in THF at –78 °C gave a mixture of α,β-unsaturated esters in a ratio of 8:1 (87% yield). These esters were separated by silica gel column chromatography and characterized thoroughly. In the ^{1}H NMR spectrum of the major isomer **16**, signals due to the conjugated olefinic protons appeared at 5.79 and 6.79 ppm as doublets with J = 12.8 Hz which indicated the cis-geometry of this olefin. In the minor isomer **20**, the signals for the olefinic protons were observed at 6.26 and 7.60 ppm as doublets with J = 16.1 Hz which was assigned for the trans olefin. Signals for the carbonyl carbons in ^{13}C NMR spectra were noticed at 165.7 and 166.2 ppm for cis and trans-isomers respectively. Mass spectrum [m/z 233 for $(M+H)^+$], IR spectrum (1719 cm^{-1} for cis and 1710 cm^{-1} for trans ester C=O groups) and elemental analysis were supportive of the assigned structures (Scheme **1**).

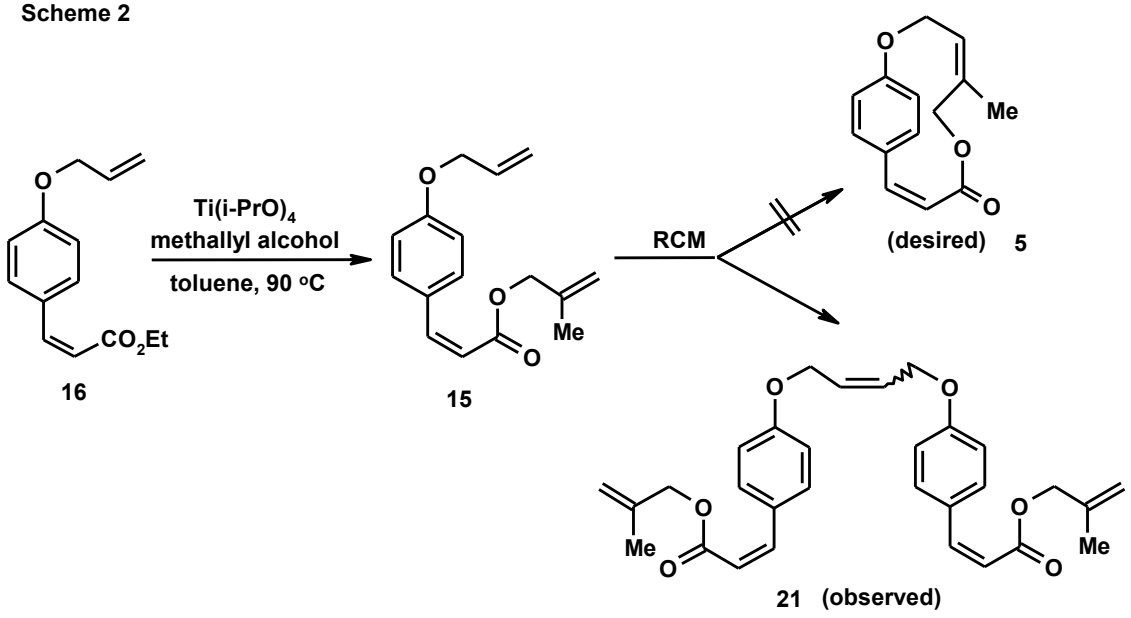
Scheme 1

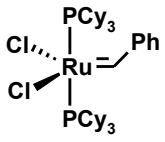


Our next concern was conversion of the ethyl ester **16** into the methallyl ester **15**, which was required to execute the RCM reaction to reach the target molecule. For this transformation, compound **16** was treated with excess of methallyl alcohol (20 eq.) in presence of catalytic (0.5 eq.) amount of $Ti(OiPr)_4$ in toluene at 90 °C for 26 h.[22] In the ^{1}H NMR spectrum of compound **15**, the signals due to the protons of methallyl group were observed at 1.75 ppm [$-OCH_2C(C\underline{H}_3)=CH_2$], 4.92 and 4.97 ppm [$-OCH_2C(CH_3)=C\underline{H}_2$]. In the ^{13}C NMR spectrum, resonances for the methallyl olefinic carbons were noticed at 112.3 (methylene) and 139.5 (quaternary) ppm whereas the resonance due to the methallyl $-\underline{C}H_3$ carbon was at 19.1 ppm. Mass spectrum [m/z 281 for $(M+Na)^+$] and elemental analysis were satisfactory.

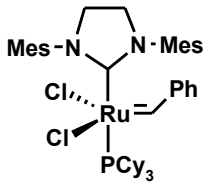
Having synthesized the required triene **15**, we subjected the compound for the final ring closure. Thus, treatment of compound **15** with Grubbs 1st generation catalyst (**22)** in refluxing CH_2Cl_2 (0.005 M solution) produced a more polar compound along with the unreacted starting material. The ^1H NMR spectrum showed disappearance of resonances due to the terminal olefinic protons of the allylic (-$OCH_2CH=C\underline{H}_2$) group whereas the methallyl group was intact. From this observation it was clear that the new compound formed was a dimer at the monosubstituted olefin (cross metathesis product) instead of the desired RCM product. In the ^{13}C NMR spectrum, a signal at 128.2 ppm was assigned for the newly formed internal olefin. This dimeric structure was confirmed from mass spectrum [m/z 489 for $(M+H)^+$]. Use of Grubbs 2nd generation catalyst (**23**) in refluxing benzene also gave the dimer but not the natural product. This failure of RCM could be attributed to the ring strain that would develop in the transition state required to achieve the ring closure (Scheme **2**).

Scheme 2





Grubbs 1st generation catalyst (22)



Grubbs 2nd generation catalyst (23)

Revised strategy (macrolactonization approach)

With the failure of RCM reaction for the synthesis of pondaplin, we have devised an alternative approach to synthesize the target molecule through a final stage macrolactonization. Our strategy for the synthesis of the macrolide has been outlined in figure **7**, which includes two stereoselective Wittig-Horner olefination reactions for the construction of both the *Z*-olefins present in the target molecule. We envisaged that the protected seco-acid **24** could be obtained from compound **25** by cleavage of dithiolane followed by olefination with the modified phosphonate reagent. Compound **25** in turn could be made from ester **27**, through the intermediate **26**, by reduction of the ester to the corresponding aldehyde, Wittig-Horner olefination followed by conversion into the allylic alcohol. Compound **27** could be prepared in a straightforward method from the readily available 4-hydroxy benzaldehyde (**17**) by alkylation using ethyl bromoacetate followed by protection of the aldehyde group as its dithiolane derivative (Figure **7**).

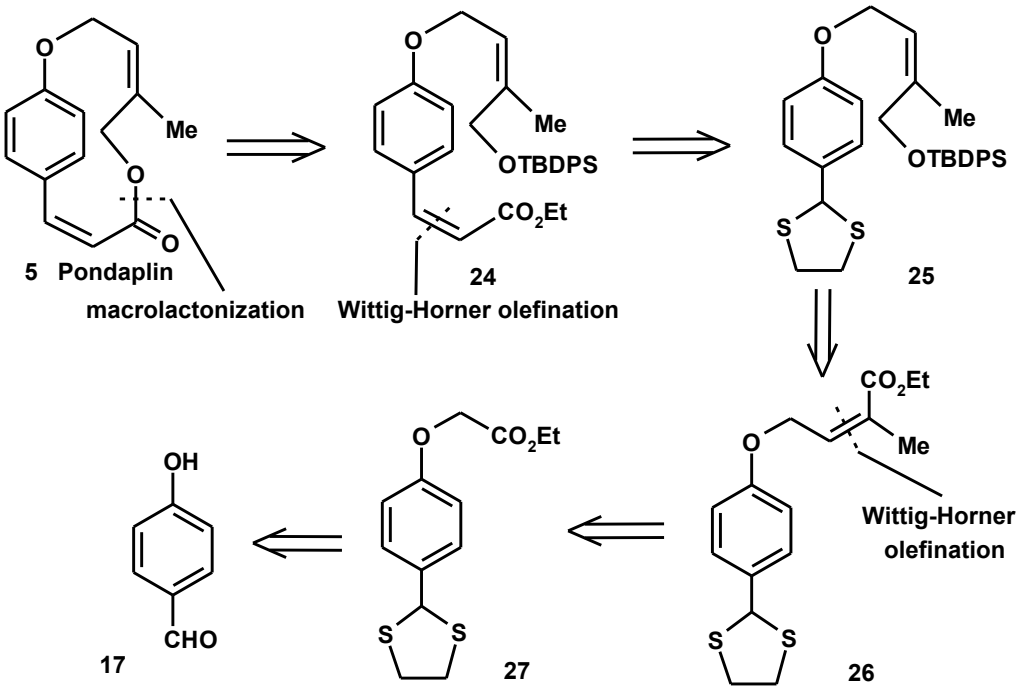
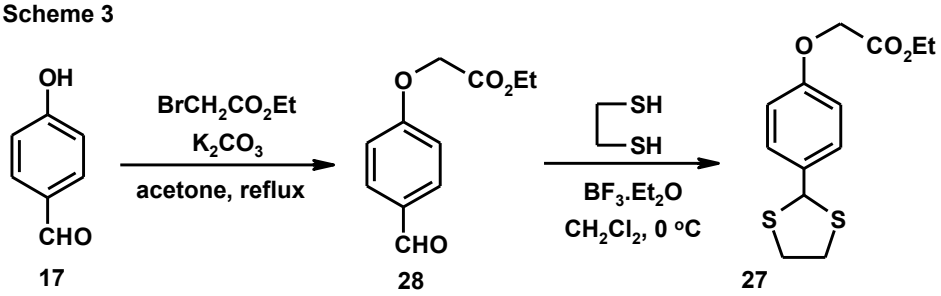


Figure 7: Revised strategy (macrolactonization approach)

According to our plan, 4-hydroxybenzaldehyde **17** on treatment with ethyl bromoacetate and K_2CO_3 in refluxing acetone for 3 h gave the aryl ether **28** in 96 % yield. Compound **28** showed signals at 9.88 and 4.70 ppm for –C<u>H</u>O and –OC<u>H</u>$_2$CO$_2$Et protons

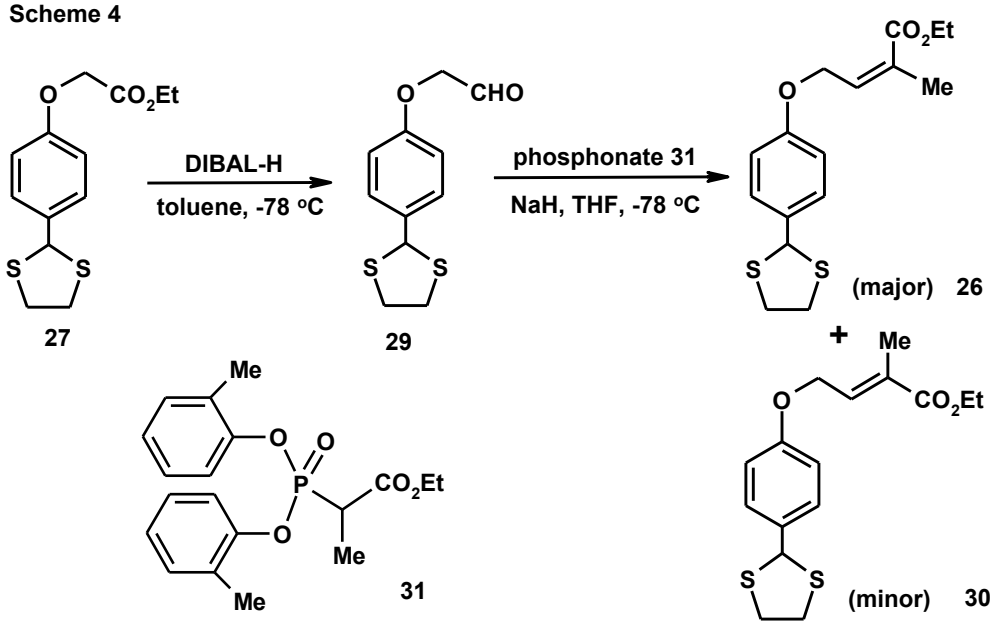
in the ^{1}H NMR spectrum. In the ^{13}C NMR spectrum, the aldehyde carbon resonance was observed at 189.9 ppm whereas the signal due to –$\underline{C}O_2Et$ was at 167.5 ppm. The IR spectrum displayed two characteristic absorption peaks at 1715 and 1695 cm^{-1} due to the ester and aldehyde C=O groups. Before going into the construction of trisubstituted *Z*-olefin, the aldehyde group in compound **28** was protected as its dithiolane derivative **27** using ethane-1,2-dithal[23] in CH_2Cl_2 in the presence of a catalytic amount of $BF_3.OEt_2$ at 0 °C (89 %). With the absence of signal for the aldehyde proton, we could observe resonances for methylene protons at 3.38 ppm (4H, m) and the benzylic methine proton at 5.58 ppm (1H, s) of the dithiolane group in the ^{1}H NMR spectrum of compound **27**. In the ^{13}C NMR spectrum, the methine carbon of dithiolane was noticed at 55.3 ppm. Mass spectrum [m/z 285 for $(M+H)^+$] and elemental analysis were supportive of the assigned structure **27** (Scheme **3**).

Scheme 3



Our next task was to synthesize the trisubstituted *Z*-allylic alcohol. For this transformation, first the ester **27** was reduced to the corresponding aldehyde **29** using 1.2 M solution of DIBAL-H in toluene at –78 °C. The crude aldehyde obtained was used for the next reaction without further purification. Thus, compound **29** on treatment with the anion generated from the phosphonate[24] **31** and NaH, in THF at –78 °C for 6 h afforded a mixture of *Z*- and *E*-isomers of the α, β-unsaturated ester in the ratio of 6:1. In the ^{1}H NMR spectrum of the major isomer **26**, the olefinic proton appeared at 6.21 ppm as a multiplet due to the coupling with vicinal methylene and allylic methyl protons. But in compound **30**, it appeared at 6.90 ppm as a triplet (J =5.7 Hz). Generally, the *E*-olefinic proton has higher chemical shift value due to deshielding of the olefinic proton by the ester carbonyl than the *Z*-isomer for system like, -C$\underline{H}$=C(CH_3)CO_2R. From the chemical shift values and the splitting pattern, it was clear that the major isomer had the *Z*-configuration. This was further confirmed by NOESY studies on compound **26**, in which NOE was observed

Scheme 4



between the olefinic proton and the allylic methyl protons (Figure **8**). In the ^{13}C NMR spectra, signals due to the methine carbon of the olefins were observed at 139.8 and 135.8 ppm for *Z* and *E*-isomers respectively. Mass [m/z 325 for $(M+H)^+$ in both isomers], IR (1710 and 1712 cm^{-1} for the C=O stretching in *Z*- and *E*-isomers respectively) and elemental analysis were supportive of the assigned structures (Scheme **4**).

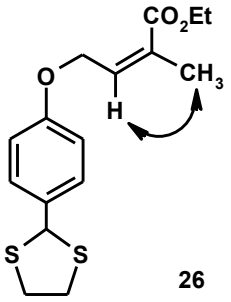
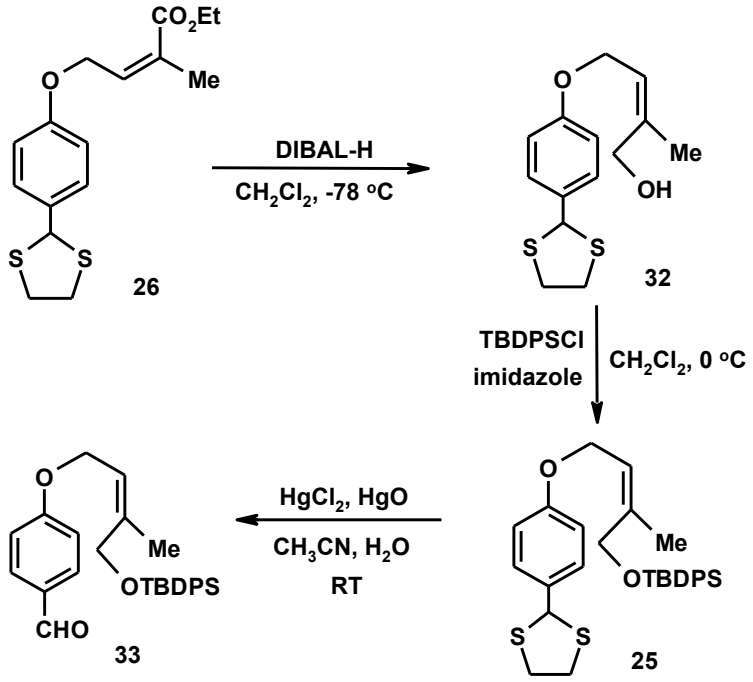


Figure 8 : NOE studies

The *Z*-unsaturated ester **26** was reduced to the corresponding allylic alcohol **32** using DIBAL-H in CH_2Cl_2 at –78 °C. Resonance due to the $–CH_2OH$ in the ^1H NMR spectrum was observed at 4.18 ppm (2H, s) with the concomitant disappearance of resonances due to ethyl protons. Absence of signal due to the ester carbonyl was noticed in the ^{13}C NMR and IR spectra. Mass spectrum [m/z 283 for $(M+H)^+$] confirmed this transformation. The allylic hydroxyl group was then protected as its TBDPS-ether (**25**) using TBDPSCl and imidazole in CH_2Cl_2 at 0 °C in 96 % yield. The resonances due to the *tert*-butyl and phenyl

groups were observed at 1.05 (9H, s), 7.38 (8H, m) and 7.66 (2H, m) ppm in the ^{1}H NMR spectrum. A signal at m/z 543 for $(M+Na)^+$ was noticed in the mass spectrum of compound **25**. In order to construct the conjugated carboxylic acid present in the target molecule, we needed to liberate the aldehyde group from the dithiolane. For this endeavor, compound **25** was treated with $HgCl_2$ and HgO[25] in a 3:1 mixture of acetonitrile and water to get the aromatic aldehyde **33** in 88 % yield after silica gel column chromatography. In the ^{1}H NMR spectrum the -CHO proton signal was observed at 9.87 ppm as a singlet whereas in the ^{13}C NMR spectrum aldehyde carbon was noticed at 190.7 ppm. In the IR spectrum, a signal at 1686 cm^{-1} was assigned for the aldehyde C=O group. Mass spectrum [m/z 445 for $(M+H)^+$] and elemental analysis also confirmed the structure **33** (Scheme **5**).

Scheme 5



Simultaneously, we have designed another method for the synthesis of compound **33**, in which we planned to make the trisubstituted olefin first and couple with the aromatic part by Mitsunobu etherification so that we could avoid the protection/deprotection steps for the aromatic aldehyde. Wittig-Horner olefination on protected hydroxy acetone **35** followed by reduction of the ester was our plan to synthesise the trisubstituted allylic alcohol **34** (Figure **9**).

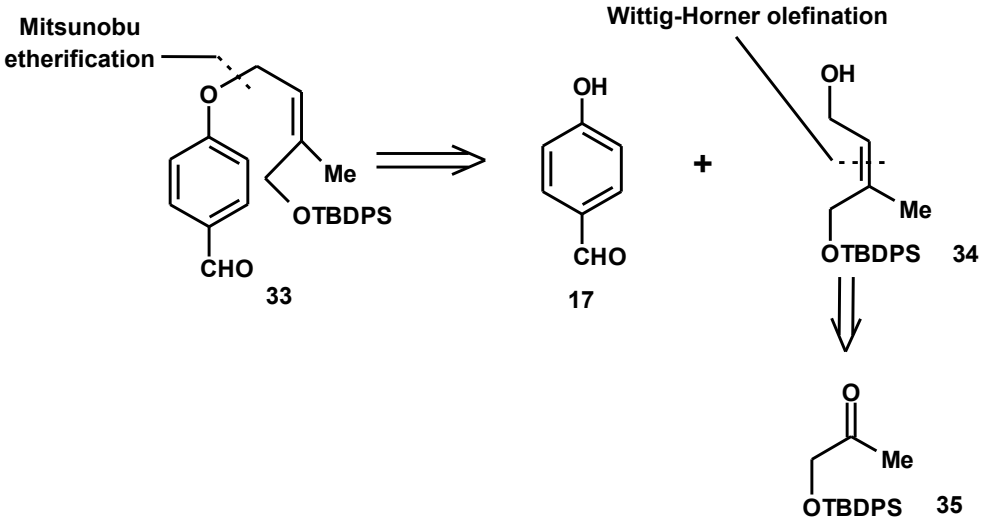
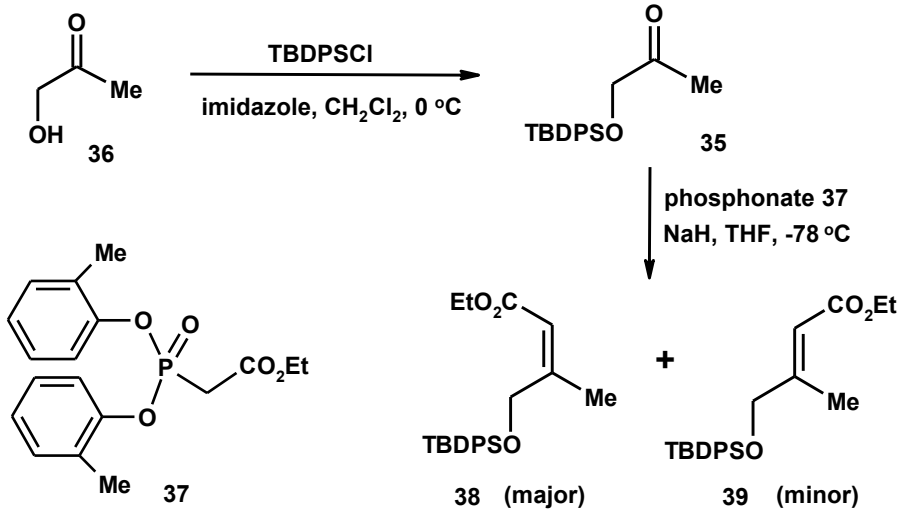


Figure 9 : synthetic strategy

Accordingly, hydroxy acetone was protected as its TBDPS-ether **35** using TBDPSCl and imidazole in good yield and was characterized thoroughly by spectroscopic and analytical methods. Since the yield of pure compound was less due to decomposition in silica gel column chromatography, crude material was used for the next reaction without purification. Analytical sample was obtained by a short column chromatography. This ketone on treatment with the phosphonate[24] **37** and NaH in THF at –78 °C gave a separable mixture of *Z*- and *E*-conjugated esters (**38** and **39**) in favor of the desired *Z*-isomer. (4:1). Signals due to the olefinic protons in the ^{1}H NMR spectra were observed at 5.62 ppm for compound **38** and at 6.18 ppm for compound **39** (Scheme **6**).

Scheme 6



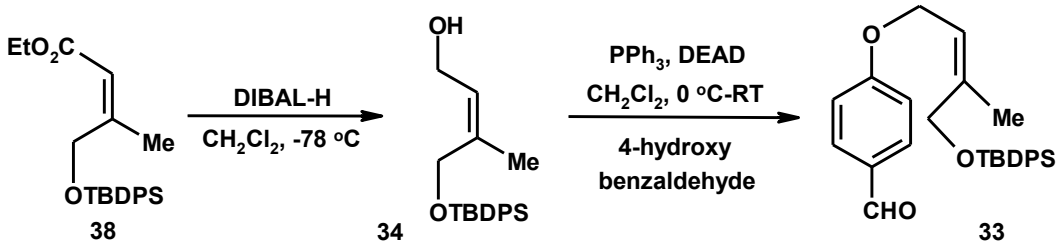
Configurations of the olefins were confirmed from the NOE studies. In the major isomer **38**, NOE was observed between the olefinic proton and the –C<u>H</u>$_3$ protons, which clearly indicated the *Z*-geometry of the olefin. Similarly, in the minor isomer **39**, NOE was observed between the olefinic proton and the –C<u>H</u>$_2$OSi protons which confirmed the *E*-geometry (Figure **10**).

38 major isomer (Z) **39 minor isomer (E)**

Figure 10 : NOE studies

The ester group in compound **38** was reduced to the corresponding allylic alcohol **34** using DIBAL-H in CH_2Cl_2 at –78 °C. In the ^{1}H NMR spectrum, resonance due to the –C<u>H</u>$_2$OH protons was observed at 3.89 ppm as a doublet with J = 7.0 Hz. In the ^{13}C NMR spectrum, the olefinic carbon signals were noticed at 125.8 (-<u>C</u>H=C<) and 137.9 (-CH=<u>C</u><) ppm. Mass spectrum [m/z 341 for $(M+H)^+$] and elemental analysis confirmed the assigned structure. Treatment of this allylic alcohol with 4-hydroxy benzaldehyde, PPh_3 and DEAD (Mitsunobu condition)[26] afforded the aryl allyl ether **33** in 81 % yield (Scheme **7**). Compound **33** obtained in this method was identical in all respects with the one prepared by deprotection of the dithiolane **25** earlier.

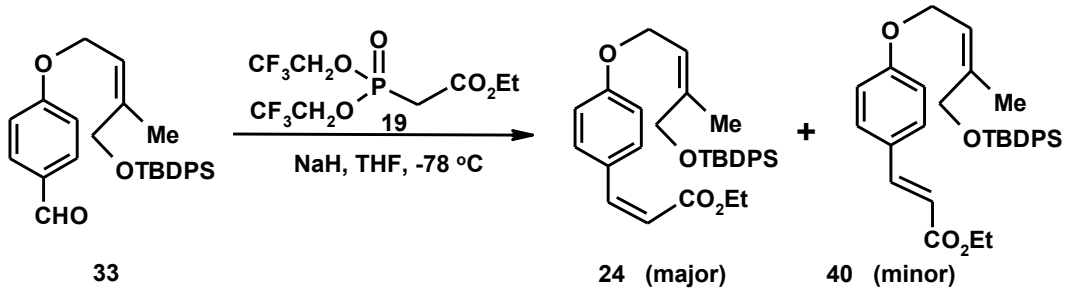
Scheme 7



With the required aldehyde in hand by a relatively short method, our next concern was the construction of the cis-unsaturated carboxylic acid **42**. For this endeavor, the compound **33** was first treated with the anion generated from the phosphonate[21] **19** with NaH in THF at –78 °C for 4 h. The required cis-cinnamate derivative **24** was isolated along with the minor trans isomer **40** in 79 % yield (cis: trans-7:1) combined yield. In the ^{1}H

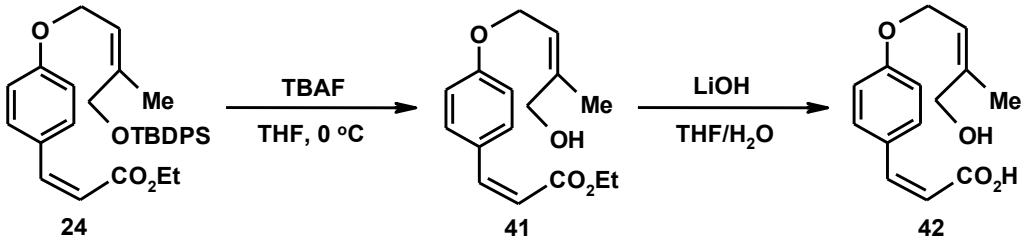
NMR spectrum of the major isomer, coupling constant for the newly formed olefinic protons was 12.8 Hz that is typical for a cis-olefin whereas in minor isomer that was 15.9 Hz (trans isomer). In the IR spectra the stretching frequencies for ester C=O were observed at 1717 and 1703 cm^{-1} for the cis and trans isomers respectively. Mass spectrum [m/z 515 for $(M+H)^+$ in both the isomers] and elemental analysis were supportive of the olefination products (Scheme **8**).

Scheme 8



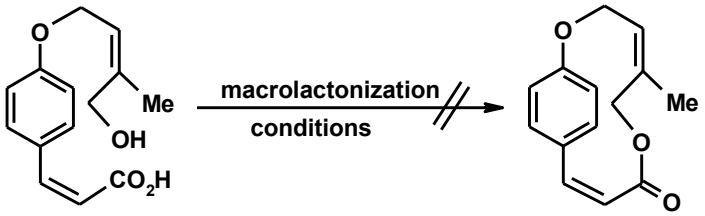
With this olefination, the complete skeleton for the target molecule was in place. To get the seco acid **42**, compound **24** was first subjected to the silyl deprotection using a 1.0 M solution of TBAF in THF at 0 °C to free the hydroxyl functionality. This transformation was confirmed from the absence of signals due to the TBDPS group in both the ^1H and ^{13}C NMR spectra. Mass spectrum [m/z 277 for $(M+H)^+$] and elemental analysis were supportive of the assigned structure **41**. This hydroxyl ester was hydrolyzed to the free acid by treatment of the compound **41** in a mixture of THF and water (2:1) with $LiOH.H_2O$ at rt for 15 h. This seco acid **42** was characterized thoroughly by spectral and elemental analysis. In the mass spectrum, m/z 249 for $(M+H)^+$ was observed (Scheme **9**).

Scheme 9



Having synthesized the seco-acid **42**, we have attempted for the final macrolactonization under different reaction conditions. But in our hands all the methods that we tried failed to produce the required macrolide natural product **5** due to the formation of a complex mixture and the difficulty in isolation of them (Scheme **10**).

Scheme 10



42 Pondaplin 5

Reaction conditions

1. 2,4,6-Trichlorobenzoyl chloride, Et_3N, DMAP[27]
2. 2,2'-dithiopyridine, PPh_3[28]
3. PPh_3, DEAD[29]
4. DCC, DMAP[30]
5. DCC, DMAP.HCl, DMAP[30]

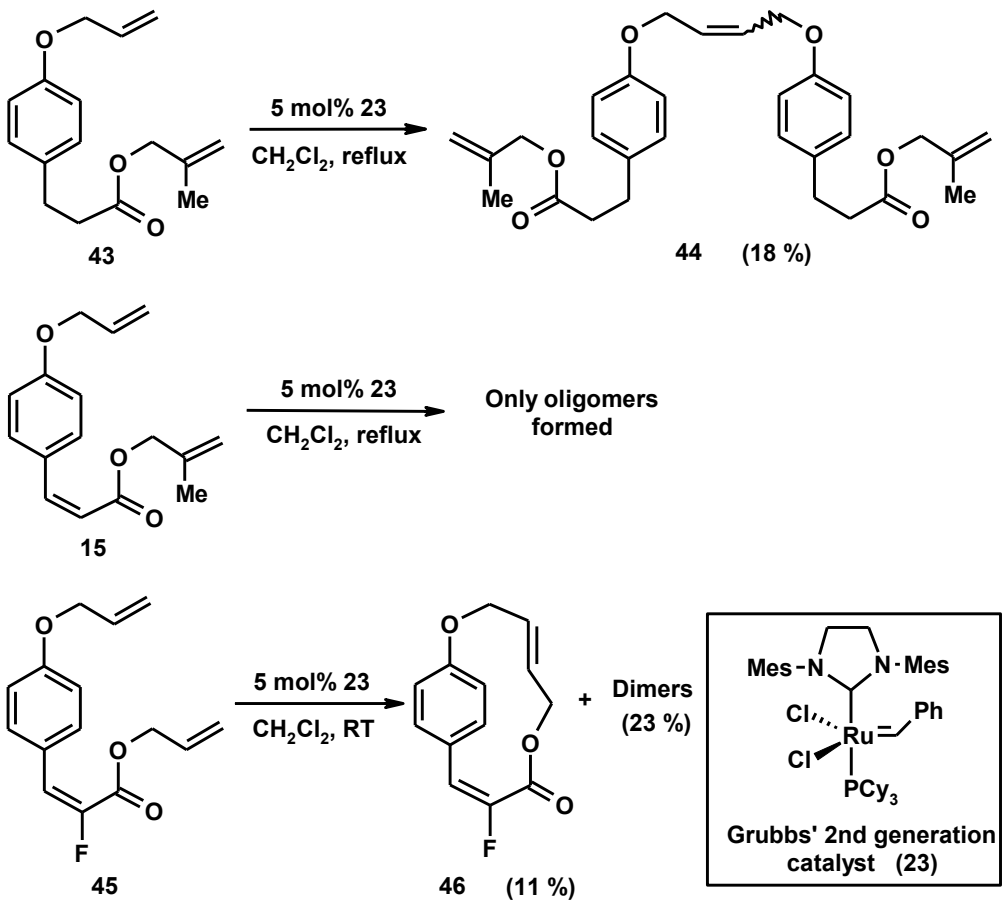
In conclusion, our attempt for the synthesis of pondaplin **5** through RCM yielded an open chain dimer instead of highly strained macrolide. Also we have synthesized the seco acid of the macrolide using Wittig-Horner olefination for the construction of both the *Z*-olefins present in the molecule. But all our attempts to synthesize the macrolide under various conditions failed.

Synthetic studies on pondaplin by other groups (Post work)

Bressy's RCM approach (2003)

Bressy *et al*. have studied the ring closing olefin metathesis reaction for the synthesis of pondaplin and its analogues. Although they could not make the natural product, due to the formation of dimers and oligomers, a fluorine substituted analogue **46** has been synthesized (Scheme **11**).[31]

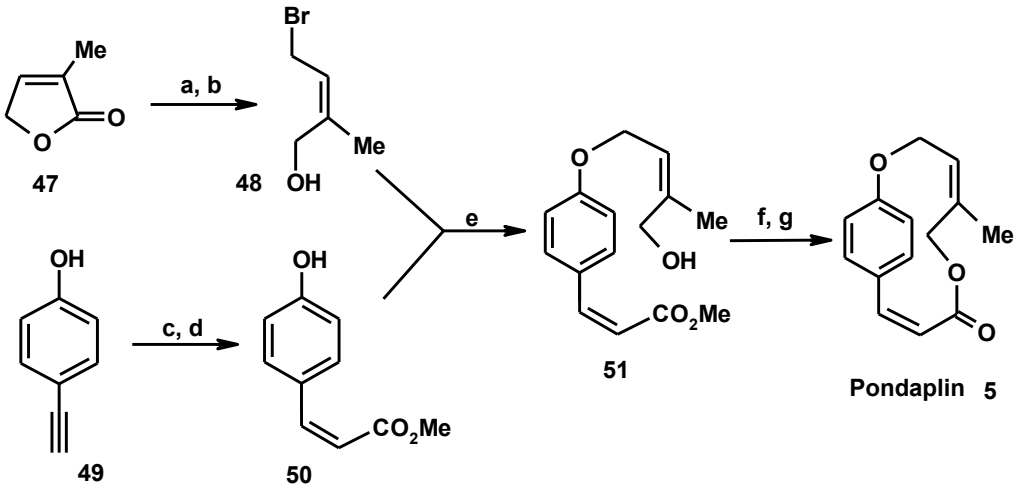
Scheme 11



Macrolactonization approach by Cheng *et al.* (2003)

Cheng *et al*. reported the first total synthesis of pondaplin **5** by macrolactonization using DCC/DMAP as the key step through a convergent approach. The trisubstituted olefin **48** was made from methylbutenolide and the cinnamate part **50** was prepared by stereoselective phenyltellurenylation of arylacetylene **49** (Scheme **12**).[32]

Scheme 12

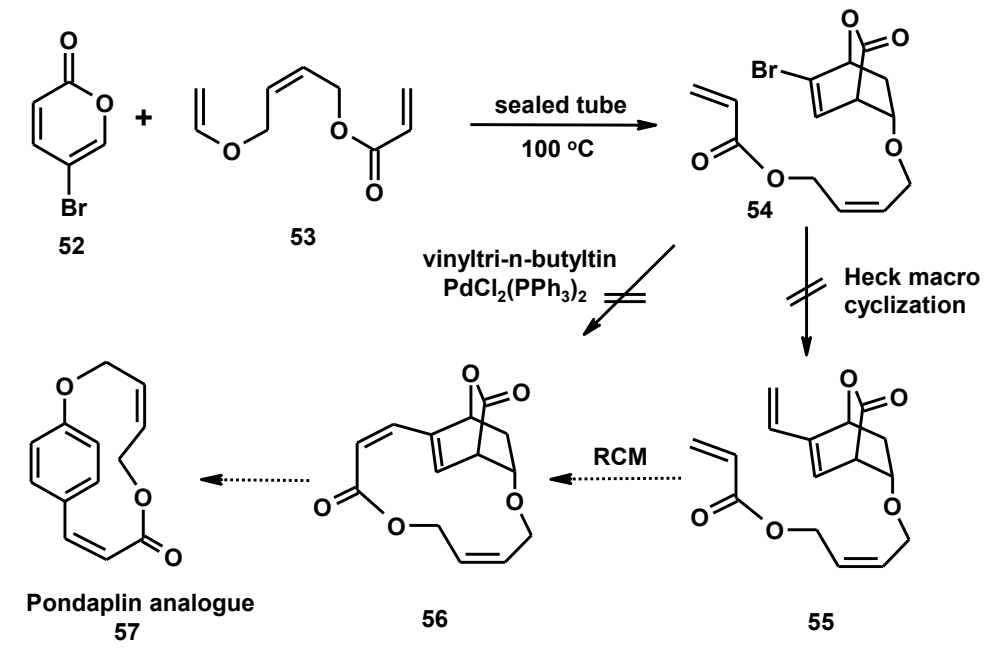


Reagents: a) 48% HBr, $MgBr_2$; b) $LiAlH_4$; c) $(PhTe)_2$, $NaBH_4$; d) CO, $PdCl_2/CuCl_2$, Et_3N, MeOH; e) NaH; f) NaOH then HCl; g) DCC, DMAP.

Leonard's approach (2004)

Leonard and co-workers have devised a novel strategy that would construct a macrocycle **56** containing a core that would serve as a masked aromatic ring and would not impose strain on the molecule during the cyclization events. Accordingly they had prepared the Diels-Alder adduct **54** and subjected to the direct macrocyclization by Heck

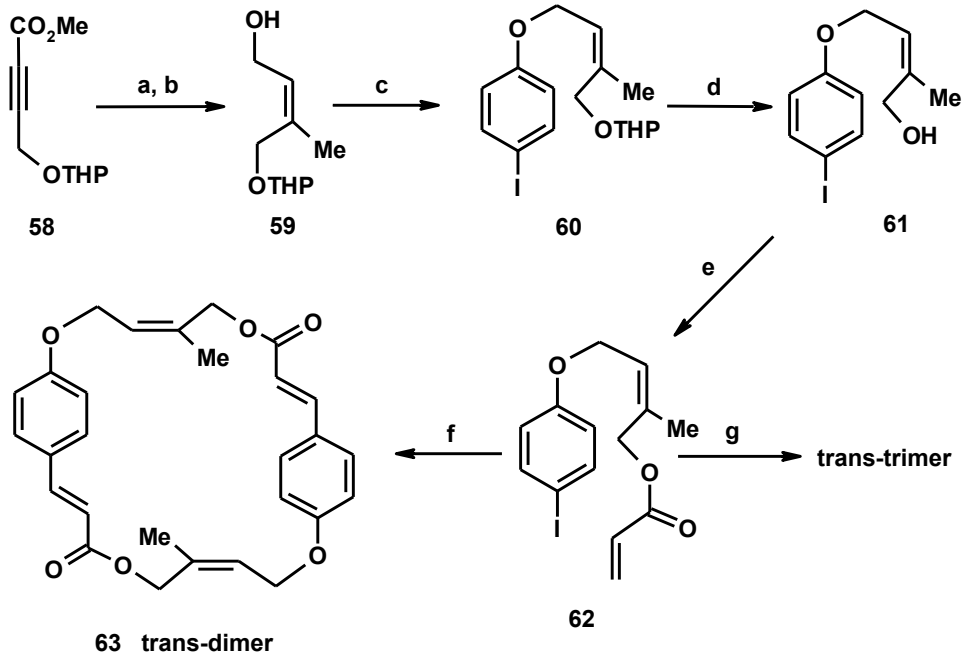
Scheme 13



reaction and also by coupling with vinyltin reagent to get the triene **55** which could be used for the synthesis of pondaplin analogue **57** by RCM reaction. But both the reactions failed to deliver the desired products (Scheme **13**).[33]

Having failed in these methods, they have synthesized the iodo compound **62** and subjected to the Heck macrocyclization. Even under high dilution conditions they could isolate only the trans-dimer **63** and trimer but not the natural product **5** (Scheme **14**).

Scheme 14

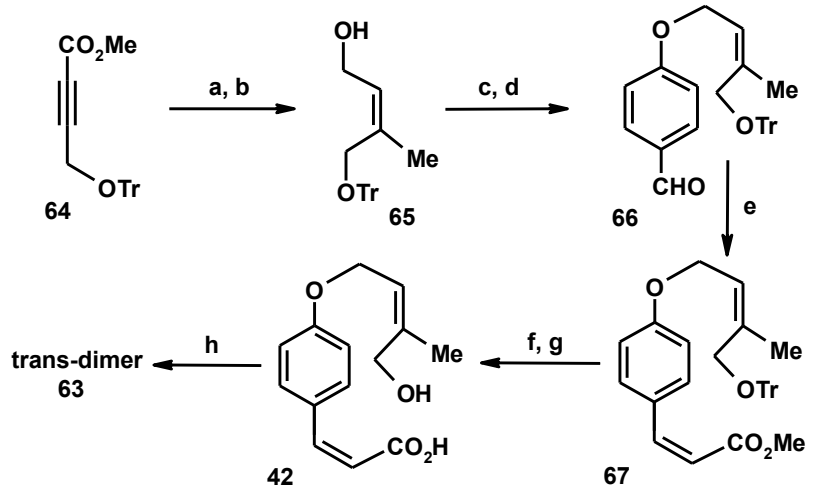


Reagents: a) Me_2CuLi; b) DIBAL-H; c) p-iodophenol, DEAD, PPh_3; d) 50% aq. AcOH; e) acryloyl chloride, Et_3N; f) $Pd(OAc)_2$, PPh_3, CF_3CO_2Ag, DMF (1 mM); g) $Pd(OAc)_2$, P(2-furyl)$_3$, CF_3CO_2Ag, DMF (10 mM).

Macrolactonization approach by Yadav *et al.* (2005)

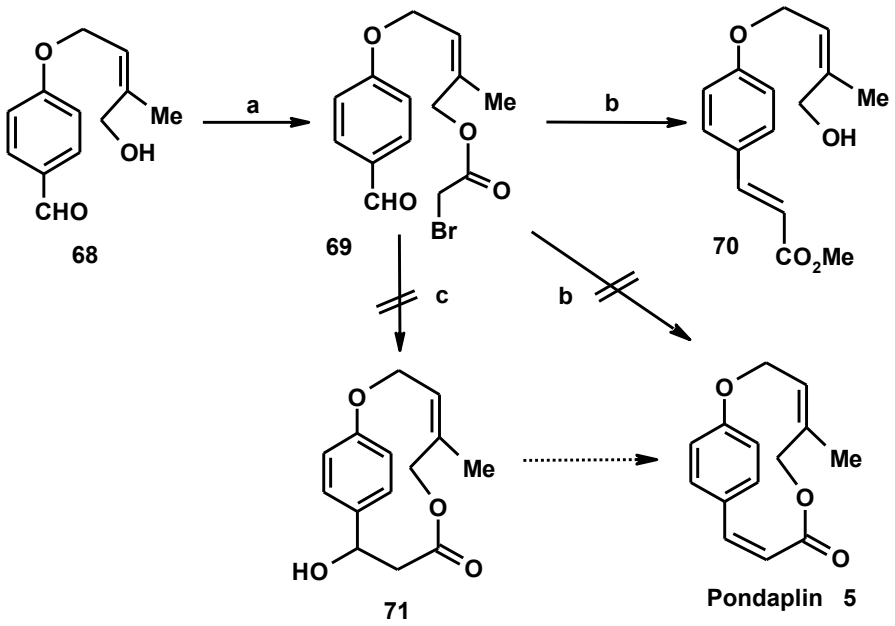
Yadav and co-workers also attempted for the total synthesis of pondaplin through macrolactonization. But the lactonization under the same conditions reported by the Chinese group failed. They could isolate only the trans-dimer **63** in this reaction (Scheme **15**).[34] Having failed with the lactonization method, intramolecular Wittig and Reformatzky reactions were studied for the final ring closure. But none of them gave the desired macrolide (Scheme **16**).

Scheme 15



Reagents: a) Me_2CuLi; b) $LiAlH_4$, $AlCl_3$; c) MsCl, LiBr, Et_3N; d) NaH, 4-hydroxybenzaldehyde; e) NaH, $(CF_3CH_2O)_2P(O)CH_2CO_2Me$; f) PPTS; g) aq. LiOH, MeOH; h) DCC, DMAP.

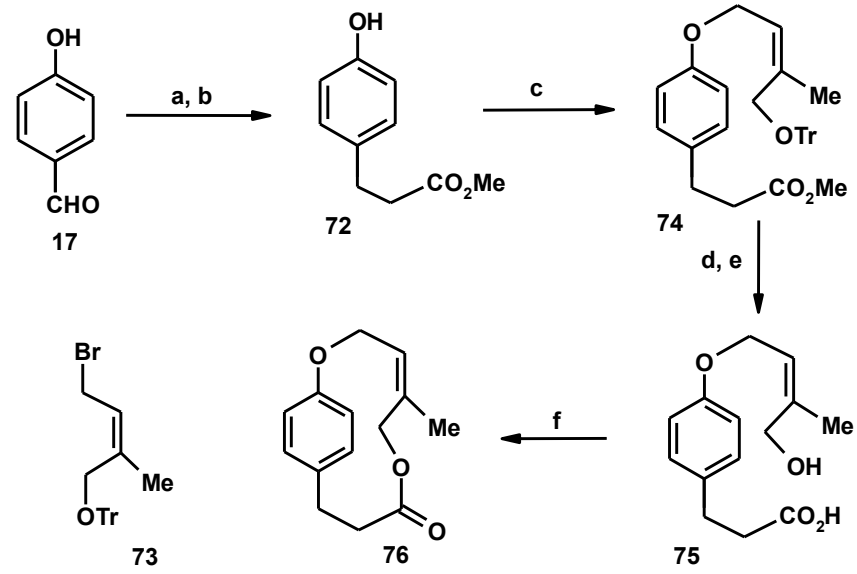
Scheme 16



Reagents: a) $BrCOCH_2Br$, 2,6-lutidine; b) NaH, $P(OEt)_3$; c) SmI_2.

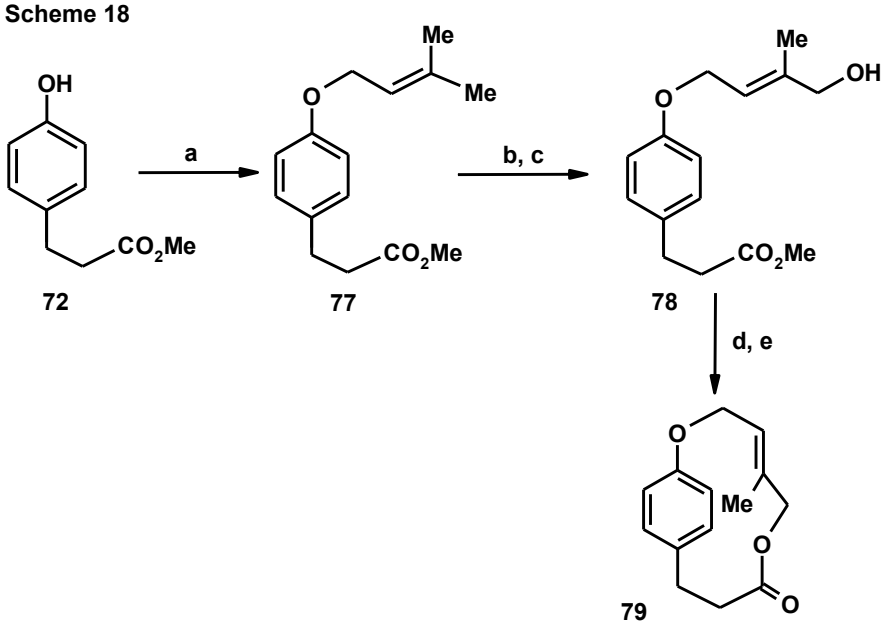
Next the dihydro-analogues, in which the strain in the aromatic ring was expected to be relatively less than the natural product, were targeted through lactonization for the synthesis of both the *Z* and *E*-isomers of the macrolide **76** and **79** (Schemes **17** and **18**).

Scheme 17



Reagents: a) $Ph_3P{=}CHCO_2Me$; b) Mg/MeOH; c) NaH, **73**; d) PPTS, MeOH; e) aq. LiOH, MeOH; f) DCC, DMAP.

Scheme 18

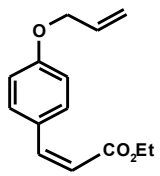


Reagents: a) Prenyl bromide, K_2CO_3; b) SeO_2; c) $NaBH_4$; d) aq. LiOH, MeOH; e) DCC, DMAP.

(*Z*)-Ethyl-4-allyloxy cinnamate (16) and (*E*)-Ethyl-4-allyloxy cinnamate (20)

A solution of phosphonate **19** (5.0 g, 15.2 mmol) in THF (20 mL) was added slowly to a suspension of NaH (564 mg, 14.1 mmol) in THF (5 mL) at 0 °C and stirred for 15 min at room temperature. The reaction mixture was cooled to –78 °C and a solution of the aldehyde **18** (1.9 g, 11.7 mmol) in THF (10 mL) was added dropwise. After stirring for 4 h at –78 °C, reaction was quenched by the addition of aq NH_4Cl. THF was removed under reduced pressure and the residue was partitioned between ethyl acetate and water. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated. The crude material was purified by silica gel column chromatography using light petroleum and ethyl acetate (19:1) as eluent to afford the less polar *cis*-α,β-unsaturated ester **16** followed by the trans isomer **20** (2.36 g, 87%) as colourless liquids in the ratio 8:1.

Compound 16



^{1}H NMR (300 MHz, $CDCl_3$): δ 1.27 (t, 3H, *J* = 7.2 Hz), 4.17 (q, 2H, *J* = 7.2 Hz), 4.53 (d, 2H, *J* = 5.1 Hz), 5.26 (d, 1H, *J* = 10.3 Hz), 5.39 (d, 1H, *J* = 17.6 Hz), 5.79 (d, 1H, *J* = 12.8 Hz), 6.02 (m, 1H), 6.79 (d, 1H, *J* = 12.8 Hz), 6.86 (d, 2H, *J* = 8.8 Hz) 7.67 (d, 2H, *J* = 8.8 Hz).

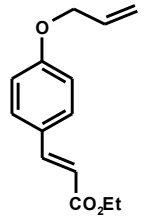
^{13}C NMR (50 MHz, $CDCl_3$): δ 13.8, 59.5, 68.1, 113.6, 116.6, 117.1, 127.1, 132.0, 132.6, 142.8, 159.1, 165.7

IR ($CHCl_3$, cm^{-1}): 3084, 2982, 2937, 2872, 1719, 1625, 1602, 1509, 1254 and 1171.

MS (ESI) m/z: 233 $(M+H)^+$

Anal. Calcd. for $C_{14}H_{16}O_3$ (MW. 232): C, 72.39; H,6.94; Found C, 72.00; H, 6.89.

Compound 20

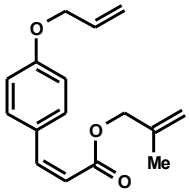


^{1}H NMR (300 MHz, $CDCl_3$): δ 1.32 (t, 3H, *J* = 7.1 Hz), 4.22 (q, 2H, *J* = 7.1 Hz), 4.51 (d, 2H, *J* = 5.1 Hz), 5.27 (d, 1H, *J* = 10.3 Hz), 5.39 (d, 1H, *J* = 17.6 Hz), 6.01(m, 1H), 6.26 (d, 1H, *J* = 16.1 Hz), 6.87 (d, 2H, *J* = 8.8 Hz), 7.42 (d, 2H, *J* = 8.8 Hz), 7.60 (d, 1H, *J* = 16.1 Hz).

^{13}C NMR (50 MHz, $CDCl_3$): δ 13.8, 59.5, 68.0, 114.4, 115.2, 117.0, 126.6, 129.1, 132.4, 143.5, 159.7, 166.2.

IR ($CHCl_3$, cm^{-1}): 3072, 2982, 2936, 2871, 1710, 1634, 1603, 1575, 1511, 1252 and 1172.
MS (ESI) m/z: 233 $(M+H)^+$
Anal. Calcd. for $C_{14}H_{16}O_3$ (MW. 232): C, 72.39; H,6.94; Found C, 72.33; H, 6.74.

(*Z*)-Methallyl-4-allyloxy cinnamate (15)



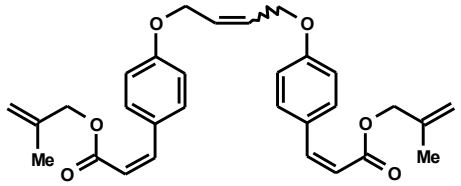
To a solution of the ethyl ester **16** (180 mg, 0.78 mmol) and methallyl alcohol (1.3 mL, 15.4 mmol) in toluene (6 mL), was added titanium tetraisopropoxide (0.12 mL, 0.39 mmol) and heated at 90 °C for 26 h. After removing the solvent under reduced pressure, the residue was dissolved in diethyl ether and washed successively with dil HCl, aq $NaHCO_3$, brine and concentrated. Purification on silica gel column using light petroleum and ethyl acetate (19:1) gave the methallyl ester **15** in 86% (172 mg) yield as a colourless liquid.

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.75 (s, 3H), 4.56 (m, 4H), 4.92 (s, 1H), 4.97 (s, 1H), 5.29 (d, 1H, *J* = 10.4 Hz), 5.41 (d, 1H, *J* = 17.3 Hz), 5.87 (d, 1H, *J* = 12.8 Hz), 6.04 (m, 1H), 6.86 (d, 1H, *J* = 12.8 Hz), 6.88 (d, 2H, *J* = 8.8 Hz), 7.71 (d, 2H, *J* = 8.8 Hz).

^{13}C NMR (50 MHz, $CDCl_3$): δ 19.1, 66.7, 68.0, 112.3, 113.6, 116.0, 117.0, 126.9, 132.1, 132.6, 139.5, 143.4, 159.1, 165.1.

IR ($CHCl_3$, cm^{-1}): 3083, 3032, 2975, 2924, 2871, 1720, 1623, 1602, 1510, 1255 and 1160.
MS (ESI) m/z: 281 $(M+Na)^+$
Anal. Calcd. for $C_{16}H_{18}O_3$ (MW. 258): C, 74.40; H,7.02; Found C, 74.33; H, 7.24.

Dimer (21)



To a 0.005 M solution of the triene **15** (120 mg, 0.47 mmol) in CH_2Cl_2 (100 mL) was added Grubbs 1st generation catalyst **22** (20 mg, 5 mol%) and refluxed for 22 h. After removal of the solvent, the residue was purified by silica gel column chromatography (light petroleum and ethyl acetate-19:1) to give the unreacted starting material (45 mg) followed by the more polar dimeric compound **21** (52 mg) as a colourless crystalline solid (Mp 76-77 °C) in 73% yield based on recovered starting material.

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.75 (s, 6H), 4.54 (s, 4H), 4.59 (m, 4H), 4.91 (s, 2H), 4.97 (s, 2H), 5.86 (d, 2H, *J* = 12.8 Hz), 6.06 (m, 2H), 6.85 (d, 2H, *J* = 12.8 Hz), 6.86 (d, 4H, *J* = 8.7 Hz), 7.70 (d, 4H, *J* = 8.7 Hz).

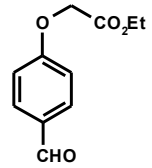
^{13}C NMR (75 MHz, $CDCl_3$): δ 19.5, 67.4, 67.5, 113.0, 114.2, 116.9, 127.7, 128.2, 132.3, 139.9, 143.6, 159.4, 165.7

IR ($CHCl_3$, cm^{-1}): 3082, 2978, 2926, 1717, 1625, 1602, 1509, 1254 and 1163.

MS (ESI) m/z: 489 $(M+H)^+$

Anal. Calcd. for $C_{30}H_{32}O_6$ (MW. 488): C, 73.75; H,6.60; Found C, 73.52; H, 6.61.

Ethyl-(4-formyl-phenoxy)-acetate (28)



A mixture of 4-hydroxybenzaldehyde (10.0 g, 82.0 mmol), ethyl bromoacetate (10.0 mL, 90.2 mmol) and K_2CO_3 (13.6 g, 98.4 mmol) in acetone (80 mL) was refluxed for 3 h. After removing the solvent in rotavapor, the residue was taken in ethyl acetate (100 mL) and washed with water, brine, dried over Na_2SO_4 and concentrated. The residue was purified by silica gel column chromatography using light petroleum and ethyl acetate (4:1) as eluent to afford compound **28** (16.3 g, 96%) as a colourless liquid.

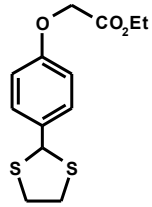
^{1}H NMR (200 MHz, $CDCl_3$): δ 1.30 (t, 3H, *J* = 7.0 Hz), 4.27 (q, 2H, *J* = 7.0 Hz), 4.70 (s, 2H), 7.00 (d, 2H, *J* = 8.7 Hz), 7.83 (d, 2H, *J* = 8.7 Hz), 9.88 (s, 1H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 13.6, 60.9, 64.7, 114.5, 130.4, 131.4, 162.3, 167.5, 189.9

IR ($CHCl_3$, cm^{-1}): 3086, 2985, 2938, 2831, 2742, 1757, 1695, 1601, 1509, 1278 and 1163.

Anal. Calcd. for $C_{11}H_{12}O_4$ (MW. 208): C, 63.45; H, 5.81; Found C, 63.26; H, 6.08.

Ethyl-(4-[1,3]dithiolan-2-yl-phenoxy)-acetate (27)



To a mixture of aldehyde **28** (8.5 g, 40.9 mmol) and ethane-1,2-dithiol (3.8 mL, 45.0 mmol) in CH_2Cl_2 (40 mL) at 0 °C, $BF_3.OEt_2$ (2.0 mL, 16.3 mmol) was added. After 30 min the reaction was quenched by addition of aq $NaHCO_3$ and the layers were separated. The aq layer was extracted with CH_2Cl_2 (2x 20 mL) and the combined organic layer was washed with brine, dried and concentrated. The residue was purified by silica gel column

chromatography using light petroleum and ethyl acetate (9:1) as eluent to afford the compound **27** (10.3 g, 89%) as a colourless thick liquid.

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.28 (t, 3H, *J* = 7.0 Hz), 3.38 (m, 4H), 4.25 (q, 2H, *J* = 7.0 Hz), 4.57 (s, 2H), 5.58 (s, 1H), 6.82 (d, 2H, *J* = 8.6 Hz), 7.43 (d, 2H, *J* = 8.6 Hz).

^{13}C NMR (75 MHz, $CDCl_3$): δ 13.6, 39.5, 55.3, 60.4, 64.8, 113.9, 128.6, 132.5, 157.0, 167.8

IR ($CHCl_3$, cm^{-1}): 3090, 2983, 2926, 1757, 1608, 1508, 1275 and 1174.

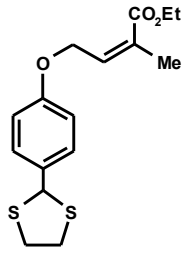
MS (ESI) m/z: 285 $(M+H)^+$

Anal. Calcd. for $C_{13}H_{16}S_2O_3$ (MW. 284): C, 54.90; H, 5.67; S, 22.55; Found C, 54.90; H, 5.40; S, 22.32.

Ethyl-4-(4-[1,3]Dithiolan-2-yl-phenoxy)-2-methyl-but-2(*Z*)-enoate (26) and Ethyl-4-(4-[1,3]Dithiolan-2-yl-phenoxy)-2-methyl-but-2(*E*)-enoate (30)

To a solution of the ester **27** (3.4 g, 12.0 mmol) in toluene (30 mL), a 1.2 M solution of DIBAL-H (12.0 mL, 1.44 mmol) was added at –78 °C and stirred for 1 h. The reaction was quenched by the addition of 2 mL of methanol followed by an excess of aq sodium potassium tartrate. The organic layer was separated and the aq layer was extracted with CH_2Cl_2 (2x20 mL). The combined organic layer was dried and concentrated under reduced pressure at room temperature to give the aldehyde **29** as a syrup (2.80 g), which was used in the next step without further purification. Conjugated esters **26** and **30** were made from the aldehyde **29** (2.80 g) using phosphonate **31** (5.4 g, 15.6 mmol) and NaH (576 mg, 14.4 mmol) in 67% (2.6 g, for two steps) yield as colourless thick liquids in the ratio of 6:1 by following the procedure described earlier. The reaction mixture was stirred for 6 h at –78 °C and light petroleum-ethyl acetate (24:1) was used for column chromatography.

Compound 26



^{1}H NMR (500 MHz, $CDCl_3$): δ 1.33 (t, 3H, *J* = 7.1 Hz), 1.95 (d, 3H, *J* = 1.8 Hz), 3.34 (m, 2H), 3.49 (m, 2H), 4.23 (q, 2H, *J* = 7.1 Hz), 4.99 (m, 2H), 5.63 (s, 1H), 6.21 (m, 1H), 6.83 (d, 2H, *J* = 8.7 Hz), 7.44 (d, 2H, *J* = 8.7 Hz).

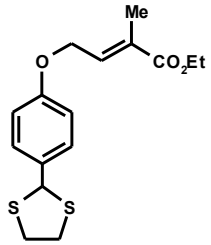
^{13}C NMR (75 MHz, $CDCl_3$): δ 13.9, 19.2, 39.7, 55.6, 60.1, 66.2, 114.1, 127.7, 128.7, 131.7, 139.8, 157.7, 166.3.

IR ($CHCl_3$, cm^{-1}): 2978, 2926, 1710, 1607, 1508, 1252 and 1172.

MS (ESI) m/z: 325 $(M+H)^+$

Anal. Calcd. for $C_{16}H_{20}S_2O_3$ (MW. 324): C, 59.23; H, 6.21; S, 19.76; Found C, 58.93; H, 6.05; S, 19.89.

Compound 30



^{1}H NMR (200 MHz, $CDCl_3$): δ 1.31 (t, 3H, *J* = 7.1 Hz), 1.92 (s, 3H), 3.41 (m, 4H), 4.21 (q, 2H, *J* = 7.1 Hz), 4.69 (d, 2H, *J* = 5.7 Hz), 5.60 (s, 1H), 6.81 (d, 2H, *J* = 8.6 Hz), 6.90 (t, 1H, *J* = 5.7 Hz), 7.42 (d, 2H, *J* = 8.6 Hz).

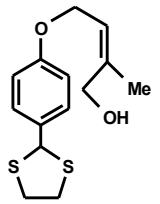
^{13}C NMR (75 MHz, $CDCl_3$): δ 12.6, 13.9, 39.8, 55.6, 60.4, 64.6, 114.1, 128.9, 129.7, 132.2, 135.8, 157.7, 166.6

IR ($CHCl_3$, cm^{-1}): 2980, 2926, 1712, 1607, 1508, 1250 and 1173.

MS (ESI) m/z: 325 $(M+H)^+$

Anal. Calcd. for $C_{16}H_{20}S_2O_3$ (MW. 324): C, 59.23; H, 6.21; S, 19.76; Found C, 58.91; H, 5.93; S, 19.91.

4-(4-[1,3]-Dithiolan-2-yl-phenoxy)-2-methyl-but-2(*Z*)-en-1-ol (32)



To a solution of the ester **26** (1.38 g, 4.26 mmol) in CH_2Cl_2 (10 mL) under argon at -78 °C, was added a 1.2 M solution of DIBAL-H (8.5 mL, 10.2 mmol) dropwise and stirred for 30 min. The reaction was quenched by the addition of methanol (2 mL) followed by an excess of aq sodium potassium tartrate, stirred for 1 h at rt and the layers were separated. The aq layer was extracted with CH_2Cl_2 (2x 10 mL) and the combined organic layer was dried over Na_2SO_4, concentrated and the residue was purified by silica gel column chromatography using light petroleum and ethyl acetate (3:2) as eluent to give the allylic alcohol **32** in 94% (1.13 g) yield as a colourless syrup.

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.80 (br s, 1H), 1.87 (s, 3H), 3.33 (m, 2H), 3.48 (m, 2H), 4.18 (s, 2H), 4.55 (d, 2H, *J* = 6.6 Hz), 5.62 (m, 2H), 6.84 (d, 2H, *J* = 8.6 Hz), 7.43 (d, 2H, *J* = 8.6 Hz).

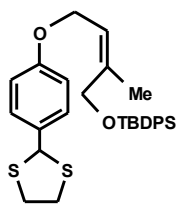
^{13}C NMR (50 MHz, $CDCl_3$): δ 20.9, 39.7, 55.5, 60.9, 63.5, 114.1, 121.8, 128.7, 131.6, 140.0, 157.7.

IR ($CHCl_3$, cm^{-1}): 3393, 2986, 2921, 1607, 1507, 1244 and 1172.

MS (ESI) m/z: 283 $(M+H)^+$

Anal. Calcd. for $C_{14}H_{18}S_2O_2$ (MW. 282): C, 59.54; H, 6.42; S, 22.71; Found C, 59.24; H, 6.35; S, 22.97.

1-*tert*-Butyldiphenylsilanyloxy-4-(4[1,3]dithiolan-2-yl-phenoxy)-2-methyl-but-2(*Z*)-ene (25)



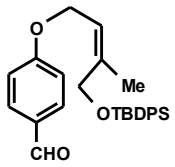
To a mixture of the allylic alcohol **32** (1.12 g, 4.0 mmol) and imidazole (350 mg, 5.2 mmol) in CH_2Cl_2 (8 mL) at 0 °C was added 1.23 mL of TBDPSCl (4.8 mmol) and stirred for 30 min. The solid formed was filtered and washed with CH_2Cl_2. The filtrate was concentrated and purified by silica gel column chromatography using light petroleum and ethyl acetate (9:1) to give the silyl ether **25** in 96% (1.98 g) yield as a colourless syrup.

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.05 (s, 9H), 1.88 (s, 3H), 3.40 (m, 4H), 4.20 (s, 2H), 4.28 (d, 2H, *J* = 6.3 Hz), 5.48 (m, 1H), 5.59 (s, 1H), 6.67 (d, 2H, *J* = 8.7 Hz), 7.38 (m, 8H), 7.66 (m, 4H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 19.1, 21.1, 26.7, 40.0, 56.0, 62.7, 63.8, 114.3, 121.6, 127.6, 128.9, 129.6, 131.4, 133.2, 135.4, 139.2, 158.3.

IR ($CHCl_3$, cm^{-1}): 2931, 2859, 1608, 1508, 1254 and 1172.
MS (ESI) m/z: 543 $(M+Na)^+$
Anal. Calcd. for $C_{30}H_{36}Si\ S_2O_2$ (MW. 520): C, 69.18; H, 6.97; S, 12.31; Found C, 69.37; H, 7.18; S, 12.56.

1-*tert*-Butyldiphenylsilanyloxy-4-(4-formyl-phenoxy)-2-methyl-but-2(*Z*)-ene (33)



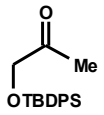
To a solution of the dithiolane **25** (2.0 g, 3.83 mmol) in acetonitrile (15 mL) and water (5 mL), 2.07 g of HgO (9.58 mmol) and 2.6 g of $HgCl_2$ (9.58 mmol) were added at room temperature. After stirring for 20 min, the reaction mixture was filtered through Celite. Solvent was removed at reduced pressure and the crude material was partitioned between chloroform and water. The organic layer was dried, concentrated and purified by silicagel column chromatography using light petroleum and ethyl acetate (9:1) to afford the aldehyde **33** (1.49 g, 88%) as a colourless syrup.

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.06 (s, 9H), 1.89 (s, 3H), 4.23 (s, 2H), 4.40 (d, 2H, *J* = 6.3 Hz), 5.51 (m, 1H), 6.86 (d, 2H, *J* = 8.7 Hz), 7.40 (m, 6H), 7.69 (m, 4H), 7.78 (d, 2H, *J* = 8.7 Hz), 9.87 (s, 1H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 19.2, 21.2, 26.7, 63.0, 64.4, 114.8, 120.6, 127.7, 129.7, 131.8, 133.2, 135.5, 140.3, 163.6, 190.7.

IR ($CHCl_3$, cm^{-1}): 2932, 2963, 2859, 1686, 1600, 1509, 1253 and 1160.
MS (ESI) m/z: 445 $(M+H)^+$
Anal. Calcd. for $C_{28}H_{32}SiO_3$ (MW. 444): C, 75.64; H, 7.25; Found C, 75.59; H, 7.47.

1-(*tert*-Butyldiphenylsilanyloxy)-propan-2-one (35)



TBDPSCl (7.6 mL, 29.7 mmol) was added to a mixture of hydroxyacetone (2.0 g, 27.0 mmol) and imidazole (2.2 g, 32.4 mmol) in CH_2Cl_2 (20 mL) at 0 °C. After 1 h the solid formed was filtered and washed with CH_2Cl_2. This filtrate was concentrated to afford the silylether **35** (1.49 g, 88%) as a colourless syrup that was used in the next step without further purification. Analytical sample was obtained by purification on silica gel column chromatography using light petroleum and ethyl acetate (19:1).

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.10 (s, 9H), 2.18 (s, 3H), 4.14 (s, 2H), 7.40 (m, 6H), 7.64 (m, 4H).

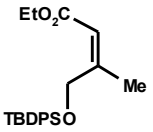
^{13}C NMR (100 MHz, $CDCl_3$): δ 19.1, 26.0, 26.7, 69.8, 127.8, 129.9, 132.5, 135.4, 207.2

IR ($CHCl_3$, cm^{-1}): 3051, 3072, 2960, 2932, 2859, 1718, 1589, 1487 and 1113.
MS (ESI) m/z: 335 $(M+Na)^+$
Anal. Calcd. for $C_{19}H_{24}SiO_2$ (MW. 312): C, 73.03; H, 7.74; Found C, 72.79; H, 7.80.

Ethyl-4-(*tert*-Butyldiphenylsilanyloxy)-3-methyl-but-(2*Z*)-enoate (38) and Ethyl-4-(*tert*-Butyldiphenylsilanyloxy)-3-methyl-but-(2*E*)-enoate (39)

Conjugated esters **38** and **39** were made from the ketone **35** (4.5 g, 14.4 mmol) using phosphonate **37** (6.54 g, 18.8 mmol) and NaH (692 mg, 17.3 mmol) in 82% (4.52 g) yield as colourless thick liquids in the ratio of 4:1 by following the procedure described earlier. The reaction mixture was stirred for 8 h at –78 °C and light petroleum-ethyl acetate (19:1) was used for column chromatography.

Compound 38



^{1}H NMR (200 MHz, $CDCl_3$): δ 1.08 (s, 9H), 1.16 (t, 3H, *J* = 7.1 Hz), 2.07 (s, 3H), 4.01 (q, 2H, *J* = 7.1 Hz), 4.86 (s, 2H), 5.62 (s, 1H), 7.38 (m, 6H), 7.65 (m, 4H).

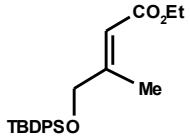
^{13}C NMR (50 MHz, $CDCl_3$): δ 14.2, 19.3, 21.6, 26.9, 59.5, 63.7, 115.4, 127.7, 129.6, 133.4, 135.5, 159.5, 165.6

IR ($CHCl_3$, cm^{-1}): 3072, 2959, 2932, 2858, 1708, 1644, 1589, 1150 and 1112.

MS (ESI) m/z: 383 $(M+H)^+$

Anal. Calcd. for $C_{23}H_{30}SiO_3$ (MW. 382): C, 72.21; H, 7.90; Found C, 72.43; H, 7.80.

Compound 39



^{1}H NMR (200 MHz, $CDCl_3$): δ 1.08 (s, 9H), 1.31 (t, 3H, *J* = 7.1 Hz), 2.00 (s, 3H), 4.10 (s, 2H), 4.19 (q, 2H, *J* = 7.1 Hz), 6.18 (s, 1H), 7.41 (m, 6H), 7.65 (m, 4H).

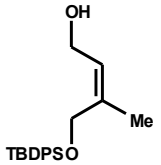
^{13}C NMR (50 MHz, $CDCl_3$): δ 14.3, 15.4, 19.2, 26.8, 59.4, 67.5, 113.5, 127.8, 129.8, 132.9, 135.4, 156.4, 166.8

IR ($CHCl_3$, cm^{-1}): 3071, 3050, 2958, 2932, 2858, 1716, 1661, 1589, 1151 and 1112.

MS (ESI) m/z: 383 $(M+H)^+$

Anal. Calcd. for $C_{23}H_{30}SiO_3$ (MW. 382): C, 72.21; H, 7.90; Found C, 72.24; H, 7.93.

4-(*tert*-Butyldiphenylsilanyloxy)-3-methyl-but-(2*Z*)-en-1-ol (34)



A 2.0 M solution of DIBAL-H (8.8 mL, 17.6 mmol) was added dropwise to a solution of the ester **38** (2.8 g, 7.3 mmol) in CH_2Cl_2 (15 mL) at –78 °C. After 40 min the reaction was quenched with MeOH (2 mL) and saturated aq sodium potassium tartrate. Stirring was continued for 1 h and the layers were separated. The aq layer was extracted with CH_2Cl_2 (2x 10 mL) and the combined organic layer was dried over Na_2SO_4, concentrated and the residue was purified by silica gel column chromatography using light petroleum and ethyl acetate (4:1) as eluent to give the allylic alcohol **34** in 89% (2.21 g) yield as a colourless syrup.

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.05 (s, 9H), 1.82 (s, 3H), 3.89 (d, 2H, *J* = 7.0 Hz), 4.17 (s, 2H), 5.43 (t, 1H, *J* = 7.0 Hz), 7.40 (m, 6H), 7.64 (m, 4H).

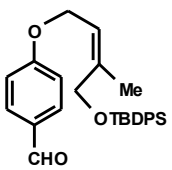
^{13}C NMR (50 MHz, $CDCl_3$): δ 19.2, 21.2, 26.8, 58.3, 62.6, 125.8, 127.7, 129.7, 133.3, 135.5, 137.9

IR ($CHCl_3$, cm^{-1}): 3351, 3071, 3049, 2958, 2931, 2890, 2857, 1670, 1589 and 1112.

MS (ESI) m/z: 341 $(M+H)^+$

Anal. Calcd. for $C_{21}H_{28}SiO_2$ (MW. 340): C, 74.07; H, 8.29; Found C, 73.82; H, 8.39.

1-*tert*-Butyldiphenylsilanyloxy-4-(4-formyl-phenoxy)-2-methyl-but-2(*Z*)-ene (33) by mitsunobu etherification

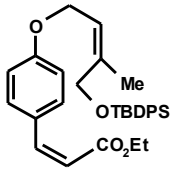


DEAD (0.93 mL, 5.9 mmol) was added slowly to a solution of allylic alcohol **34** (1.67 g, 4.92 mmol), 4-hydroxybenzaldehyde (600 mg, 4.92 mmol) and PPh_3 (1.55 g, 5.9 mmol) in dry THF (10 mL) at 0 °C under nitrogen atmosphere. After stirring for 2 h, the solvent was removed under reduced pressure and the resulting oil was purified by silica gel column chromatography using light petroleum and ethyl acetate (9:1) as eluent to afford the ether **33** (1.77 g, 81%) as a colourless oil.

Ethyl-4-[4-(*tert*-Butyldiphenylsilanyloxy)-3-methyl-but-(2*Z*)-enyloxy]-(*Z*)-cinnamate (24) and Ethyl-4-[4-(*tert*-Butyldiphenylsilanyloxy)-3-methyl-but-(2*Z*)-enyloxy]-(*E*)-cinnamate (40)

Conjugated esters **24** and **40** were made from the aldehyde **33** (1.6 g, 3.6 mmol) using phosphonate **19** (1.56 g, 4.7 mmol) and NaH (172 mg, 4.3 mmol) in 79% (1.46 g) yield as colourless thick liquids in the ratio of 7:1 by following the procedure described earlier. The reaction mixture was stirred for 6 h at –78 °C and light petroleum-ethyl acetate (19:1) was used for column chromatography.

Compound 24



^{1}H NMR (200 MHz, $CDCl_3$): δ 1.06 (s, 9H), 1.27 (t, 3H, *J* = 7.1 Hz), 1.88 (s, 3H), 4.18 (q, 2H, *J* = 7.1 Hz), 4.22 (s, 2H), 4.33 (d, 2H, *J* = 6.6 Hz), 5.49 (m, 1H), 5.79 (d, 1H, *J* = 12.8 Hz), 6.72 (d, 2H, *J* = 8.7 Hz), 6.80 (d, 1H, *J* = 12.8 Hz), 7.38 (m, 6H), 7.66 (m, 6H).

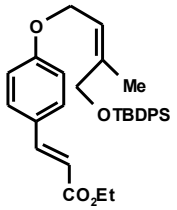
^{13}C NMR (50 MHz, $CDCl_3$): δ 14.1, 19.1, 21.1, 26.7, 59.8, 62.8, 63.8, 113.8, 116.8, 121.4, 127.1, 127.6, 129.6, 132.1, 133.1, 135.4, 139.3, 143.1, 159.3, 166.0

IR ($CHCl_3$, cm^{-1}): 3071, 2931, 2857, 1717, 1602, 1509, 1250 and 1162.

MS (ESI) m/z: 515 $(M+H)^+$

Anal. Calcd. for $C_{32}H_{38}SiO_4$ (MW. 514): C, 74.67; H, 7.44; Found C, 74.63; H, 7.54.

Compound 40

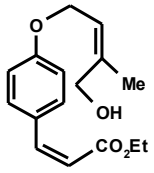


^{1}H NMR (200 MHz, $CDCl_3$): δ 1.06 (s, 9H), 1.32 (t, 3H, *J* = 7.1 Hz), 1.88 (s, 3H), 4.22 (s, 2H), 4.24 (q, 2H, *J* = 7.1 Hz), 4.33 (d, 2H, *J* = 6.3 Hz), 5.49 (m, 1H), 6.27 (d, 1H, *J* = 15.9 Hz), 6.73 (d, 2H, *J* = 8.7 Hz), 7.37 (m, 8H), 7.61 (d, 1H, *J* = 15.9 Hz), 7.67 (m, 4H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 14.4, 19.2, 21.2, 26.8, 60.1, 62.9, 64.1, 114.9, 115.6, 121.2, 127.0, 127.7, 129.5, 129.7, 133.3, 135.5, 139.8, 144.2, 160.4, 167.1

IR ($CHCl_3$, cm^{-1}): 2932, 2858, 1703, 1603, 1510, 1247 and 1171.
MS (ESI) m/z: 515 $(M+H)^+$
Anal. Calcd. for $C_{32}H_{38}SiO_4$ (MW. 514): C, 74.67; H, 7.44; Found C, 74.42; H, 7.33.

Ethyl-4-[4-hydroxyl-3-methyl-but-(2*Z*)-enyloxy]-(*Z*)-cinnamate (41)



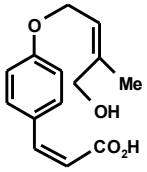
A 1.0 M solution of TBAF in THF (2.5 mL, 2.5 mmol) was added to a solution of the silylether **24** (1.09 g, 2.1 mmol) in THF (5 mL) at 0 °C under argon. After 30 min, the solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography using light petroleum and ethyl acetate (2:1) to afford the allylic alcohol **41** (530 mg, 91%) as a thick paste.

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.28 (t, 3H, *J* = 7.1 Hz), 1.78 (s, 1H), 1.88 (s, 3H), 4.17 (q, 2H, *J* = 7.1 Hz), 4.18 (s, 2H), 4.59 (d, 2H, *J* = 6.2 Hz), 5.62 (m, 1H), 5.80 (d, 1H, *J* = 12.8 Hz), 6.81 (d, 1H, *J* = 12.8 Hz), 6.85 (d, 2H, *J* = 8.8 Hz), 7.66 (d, 2H, *J* = 8.8 Hz).

^{13}C NMR (50 MHz, $CDCl_3$): δ 14.1, 21.2, 60.0, 61.3, 63.7, 113.9, 117.0, 122.0, 127.3, 132.0, 140.5, 143.1, 159.2, 166.3

IR ($CHCl_3$, cm^{-1}): 3440, 2983, 2926, 1712, 1603, 1509, 1252 and 1172.
MS (ESI) m/z: 277 $(M+H)^+$
Anal. Calcd. for $C_{16}H_{20}O_4$ (MW. 276): C, 69.55; H, 7.30; Found C, 69.30; H, 7.19.

4-[4-hydroxyl-3-methyl-but-(2*Z*)-enyloxy]-(*Z*)-cinnamic acid (42)



A mixture of compound **41** (470 mg, 1.7 mmol) and $LiOH.H_2O$ (357 mg, 8.51 mmol) in a solvent mixture of THF (7.5 mL) and water (5.0 mL) was stirred for 15 h at room temperature. After acidifying the reaction mixture with 1 N HCl, the solvent was removed under reduced pressure. The crude material was passed through a short bed of silica gel using light petroleum and ethyl acetate (3:7) as eluent to give the seco acid **42** as a colourless solid in 88% (375 mg) yield.

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.89 (s, 3H), 4.21 (s, 2H), 4.61 (d, 2H, *J* = 6.7 Hz), 5.65 (t, 1H, *J* = 6.7 Hz), 5.85 (d, 1H, *J* = 12.7 Hz), 6.88 (d, 2H, *J* = 8.7 Hz), 6.96 (d, 1H, *J* = 12.7 Hz), 7.68 (d, 2H, *J* = 8.7 Hz).

^{13}C NMR (125 MHz, $CDCl_3$): δ 21.4, 61.8, 63.9, 114.2, 116.2, 122.3, 127.2, 132.5, 140.9, 145.6, 159.5, 170.9

MS (ESI) m/z: 249 $(M+H)^+$

Anal. Calcd. for $C_{14}H_{16}O_4$ (MW. 248): C, 67.73; H, 6.50; Found C, 67.49; H, 6.53.

Lactonization of secoacid 42 under Yamaguchi condition

To an ice-cooled solution of compound **42** (100 mg, 0.4 mmol) in THF (5 mL) was added Et_3N (0.11 mL, 0.8 mmol) followed by 2,4,6-trichlorobenzoyl chloride (0.1 mL, 0.6 mmol). After stirring for 1 h at room temperature, the reaction mixture was diluted with toluene (50 mL) and added slowly to a refluxing solution of DMAP (98 mg, 0.8 mmol) in toluene (150 mL) over a period of 4 h. After refluxing for 8 h, the reaction mixture was concentrated under reduced pressure. The residue was dissolved in ethyl acetate and washed with saturated aqueous $NaHCO_3$ solution and dried over Na_2SO_4. Evaporation of the solvent and purification by column chromatography afforded an inseparable mixture of compounds.

Lactonization of secoacid 42 under Corey-Nicolaou condition

A solution of secoacid **42** (100 mg, 0.4 mmol), $(PyS)_2$ (440 mg, 2.0 mmol), and Ph_3P (524 mg, 2.0 mmol) in deoxygenated anhydrous THF (10 mL) was stirred for 5 h at room temperature under argon. The mixture was diluted with deoxygenated anhydrous toluene (50 mL) and then was added dropwise to the refluxing dry deoxygenated toluene (150 mL) over 3 h. The solution was refluxed under argon for 30 h. After removal of toluene, the residue was chromatographed on a silica gel column to afford a complex mixture of compounds.

Lactonization of secoacid 42 under Mitsunobu condition

To a solution of triphenylphosphine (157 mg, 0.6 mmol) in THF (175 mL) at reflux was added, over a period of 3 h, a solution of compound **42** (100 mg, 0.4 mmol) and diethyl azodicarboxylate (0.1 mL, 0.6 mmol) in THF (25 mL). The reflux was maintained for an additional 12 h and then the solvent removed under reduced pressure. The crude residue on silica gel column chromatography gave a complex mixture of compounds.

Lactonization of secoacid 42 under Keck condition (DCC/DMAP)

To a solution of dicyclohexylcarbodiimide (412 mg, 2.0 mmol) and 4-(dimethylamino)pyridine (244 mg, 2.0 mmol) in CH_2Cl_2 (150 mL) was added a solution of

compound **42** (100 mg, 0.4 mmol) in 50 mL of CH_2Cl_2 over a period of 4 h. After stirring for 8 h, the reaction mixture was cooled to room temperature and quenched with methanol (3 mL) and 10 drops of AcOH. The solution was concentrated, diluted with ether, and filtered through a pad of Celite. The solvent was removed and the crude material was passed through a silica gel column to give a complex mixture of compounds.

Lactonization of secoacid 42 under Keck condition (DCC/DMAP/DMAP.HCl)

To a solution of dicyclohexylcarbodiimide (412 mg, 2.0 mmol), 4-(dimethylamino)pyridine (244 mg, 2.0 mmol), and 4-(dimethylamino)pyridine hydrochloride (316 mg, 2.0 mmol) in chloroform (150 mL) at reflux was added a solution of compound **42** (100 mg, 0.4 mmol) in 50 mL of THF over a period of 3 h. After stirring for 12 h, the reaction mixture was cooled to room temperature and quenched with methanol (3 mL) and 10 drops of AcOH. The solution was concentrated, diluted with ether, and filtered through a pad of Celite. The solvent was removed and the crude material was passed through a silica gel column to give a complex mixture of compounds

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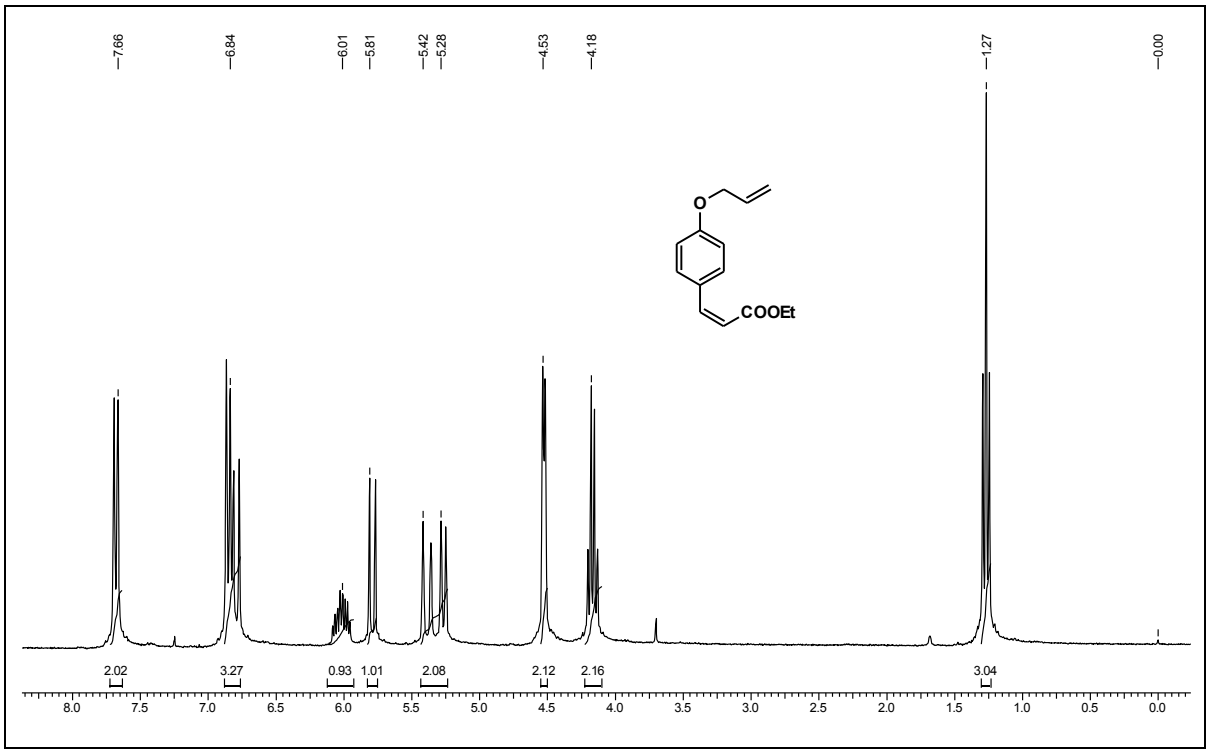
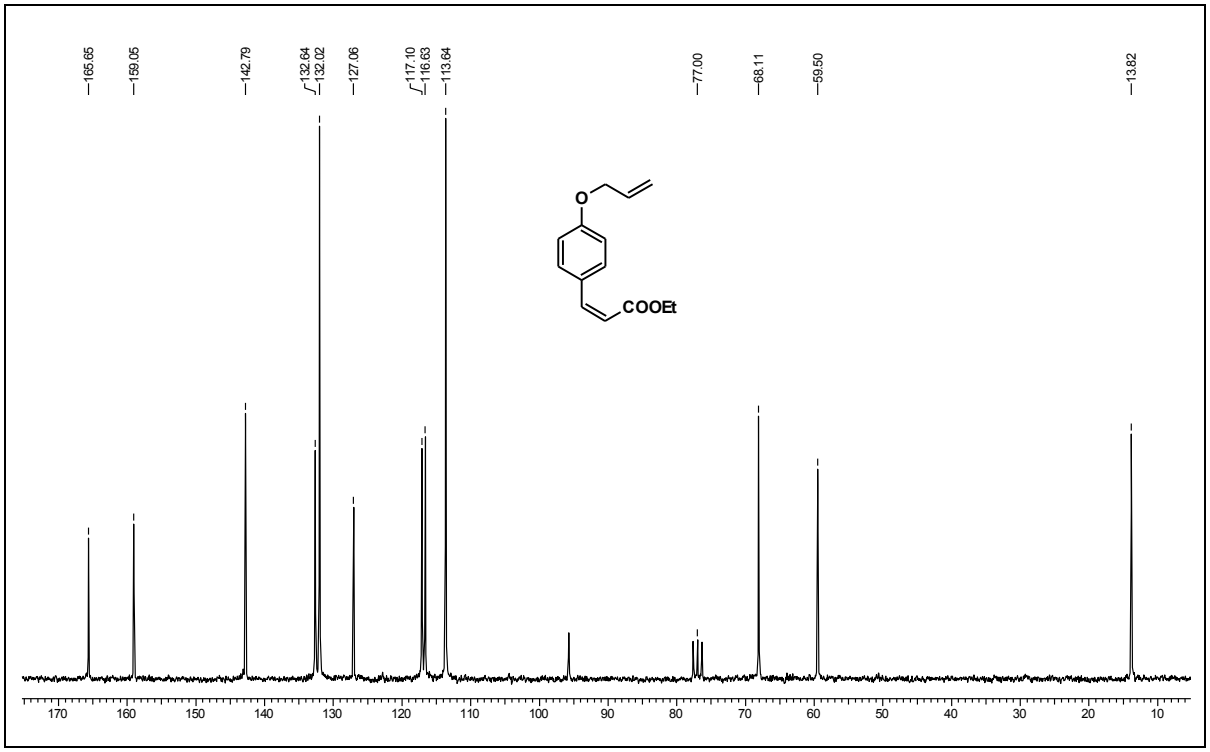
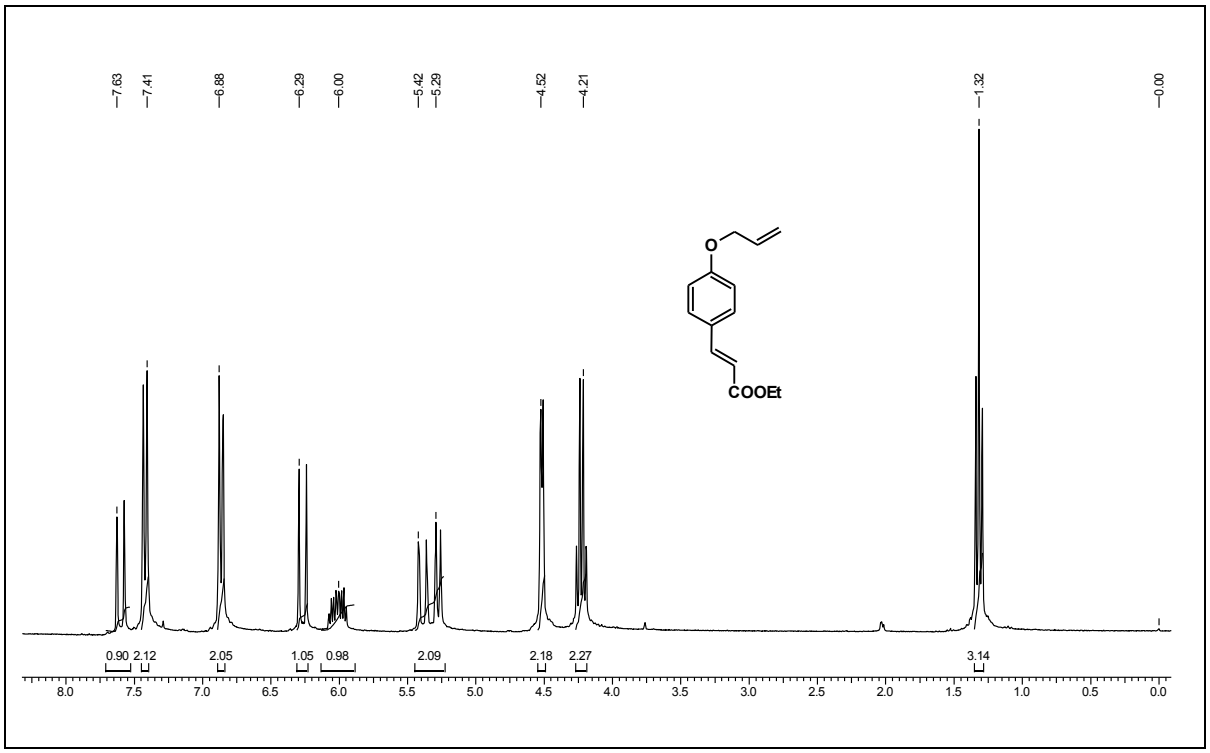


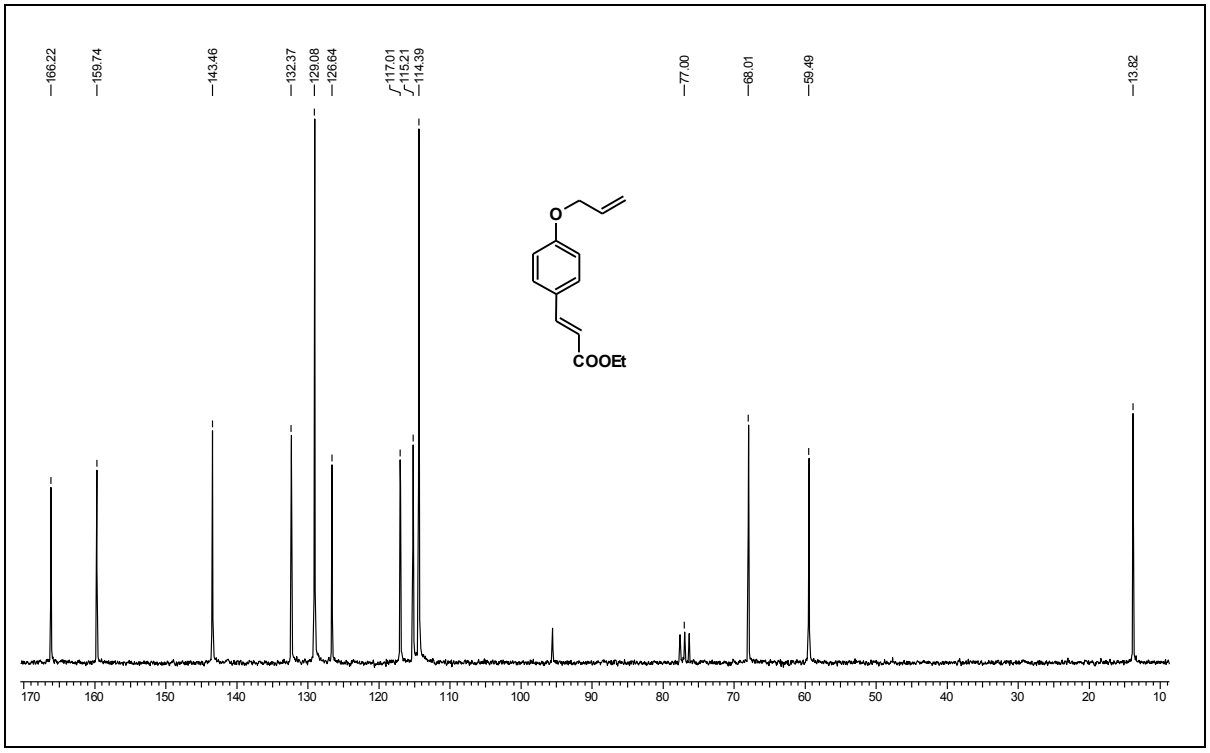
^{1}H NMR spectrum of compound 16 in $CDCl_3$



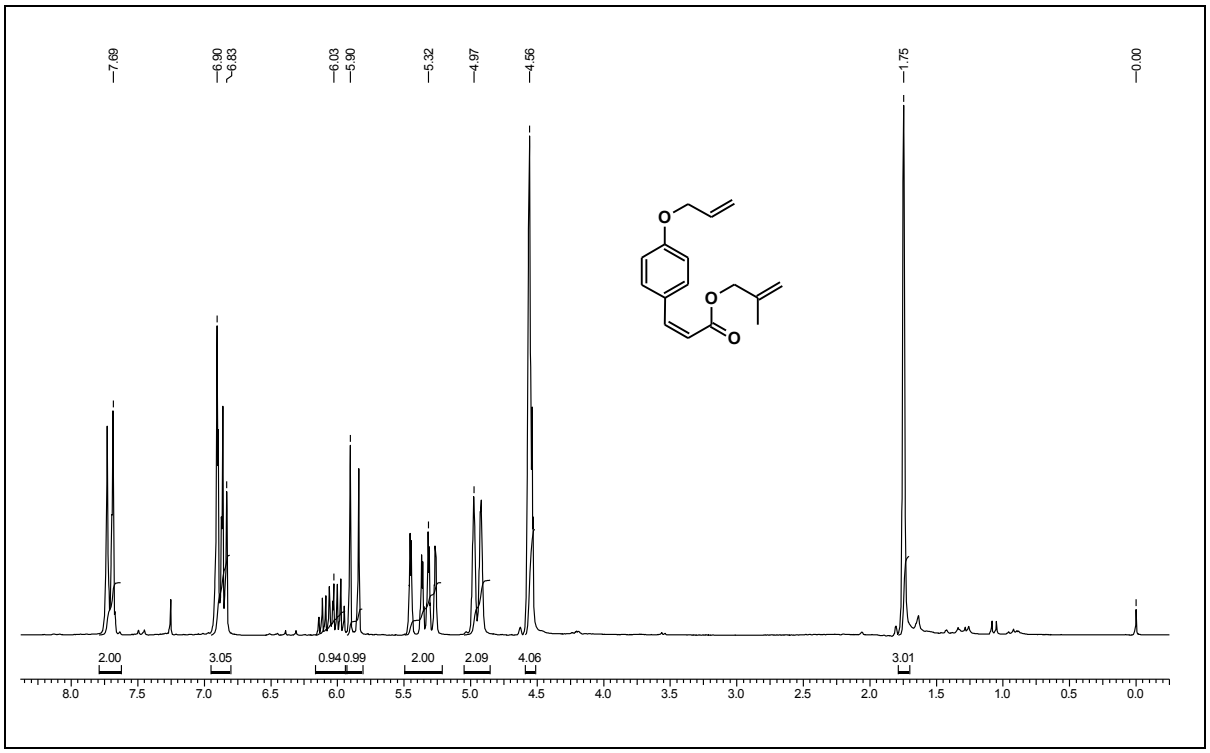
^{13}C NMR spectrum of compound 16 in $CDCl_3$



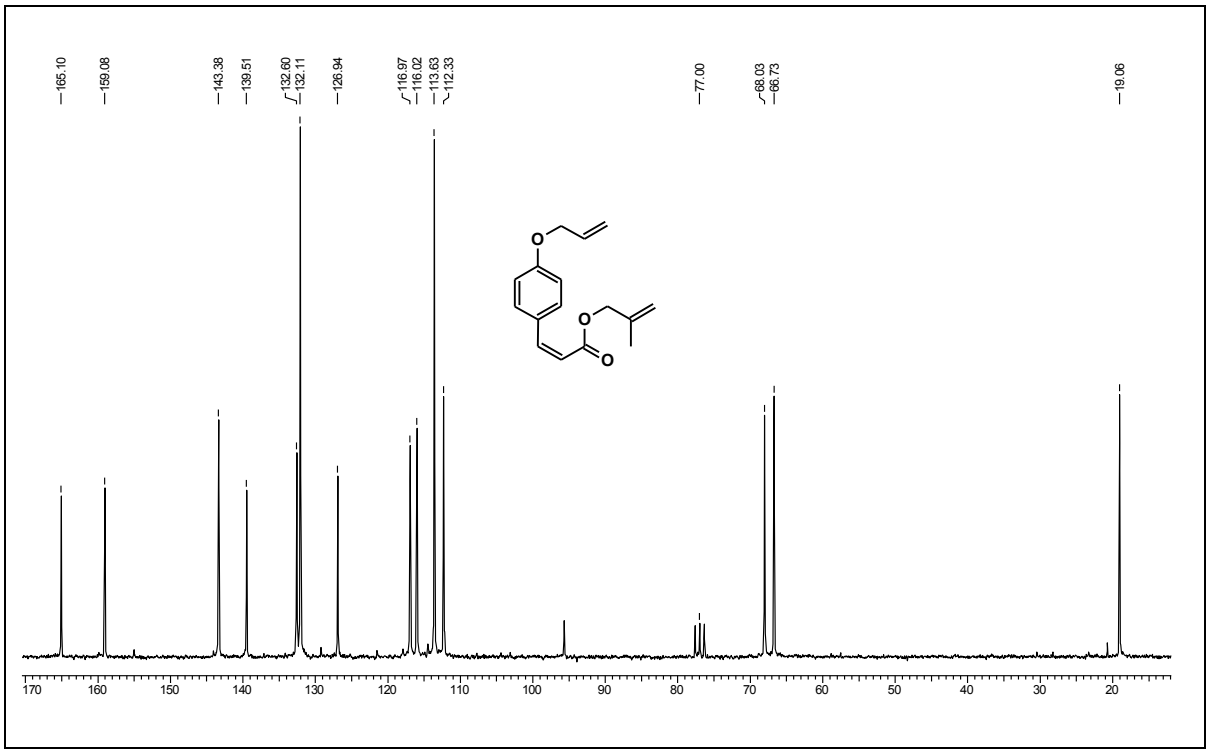
^{1}H NMR spectrum of compound 20 in $CDCl_3$



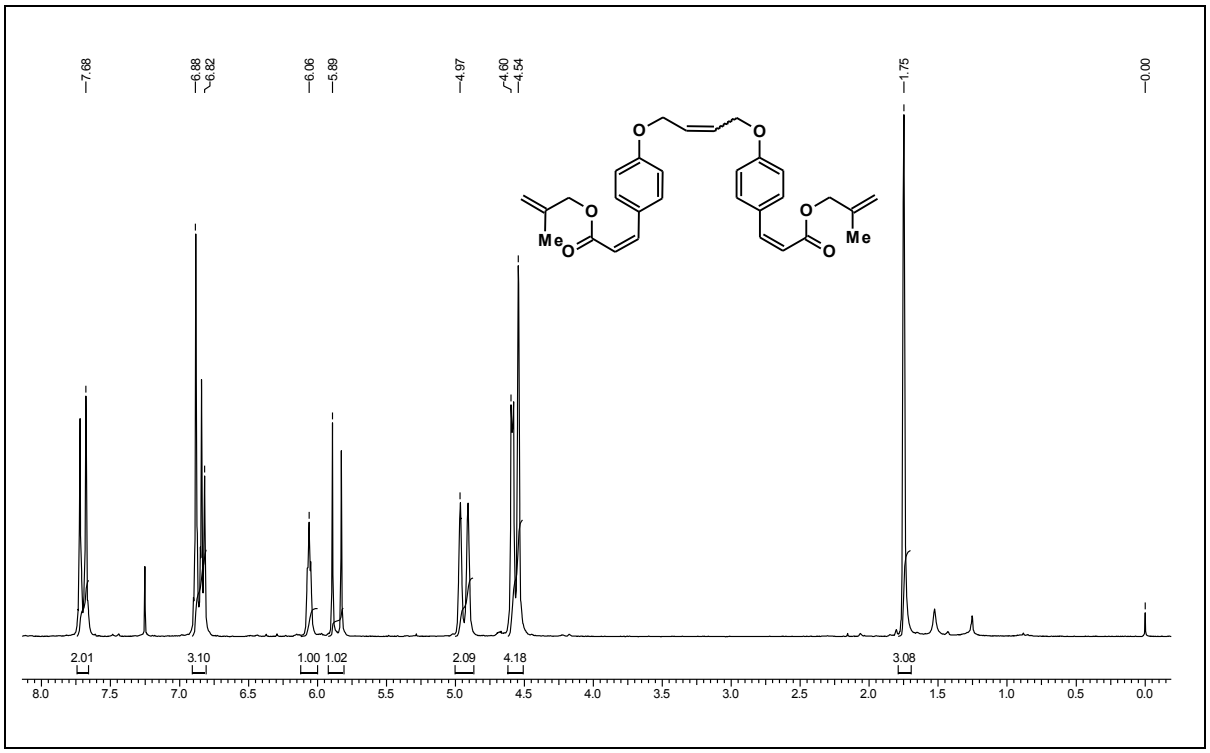
^{13}C NMR spectrum of compound 20 in $CDCl_3$



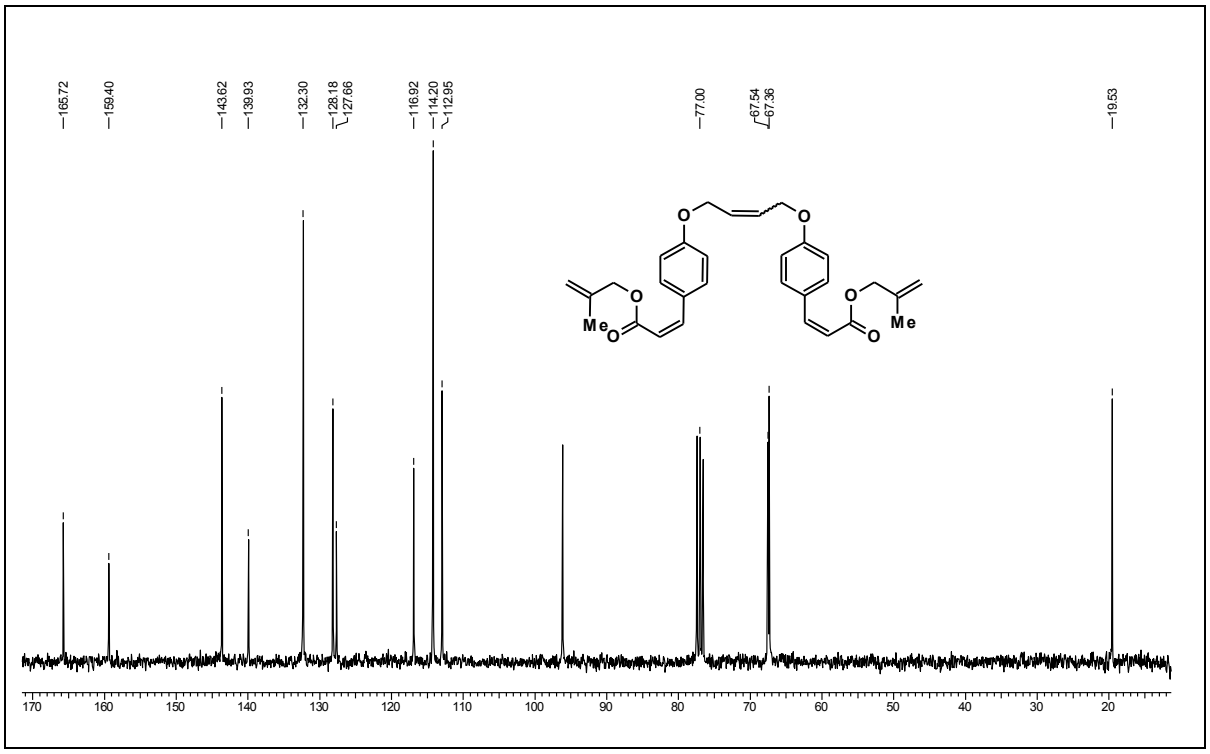
^{1}H NMR spectrum of compound 15 in $CDCl_3$



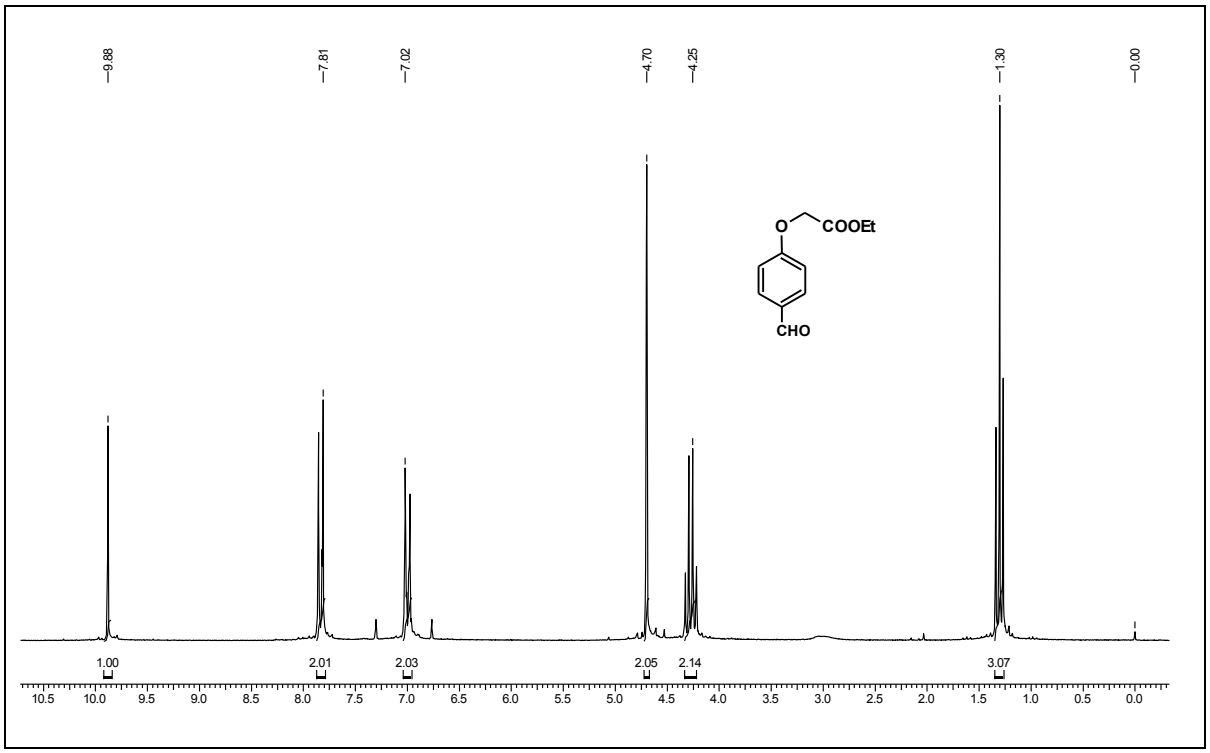
^{13}C NMR spectrum of compound 15 in $CDCl_3$



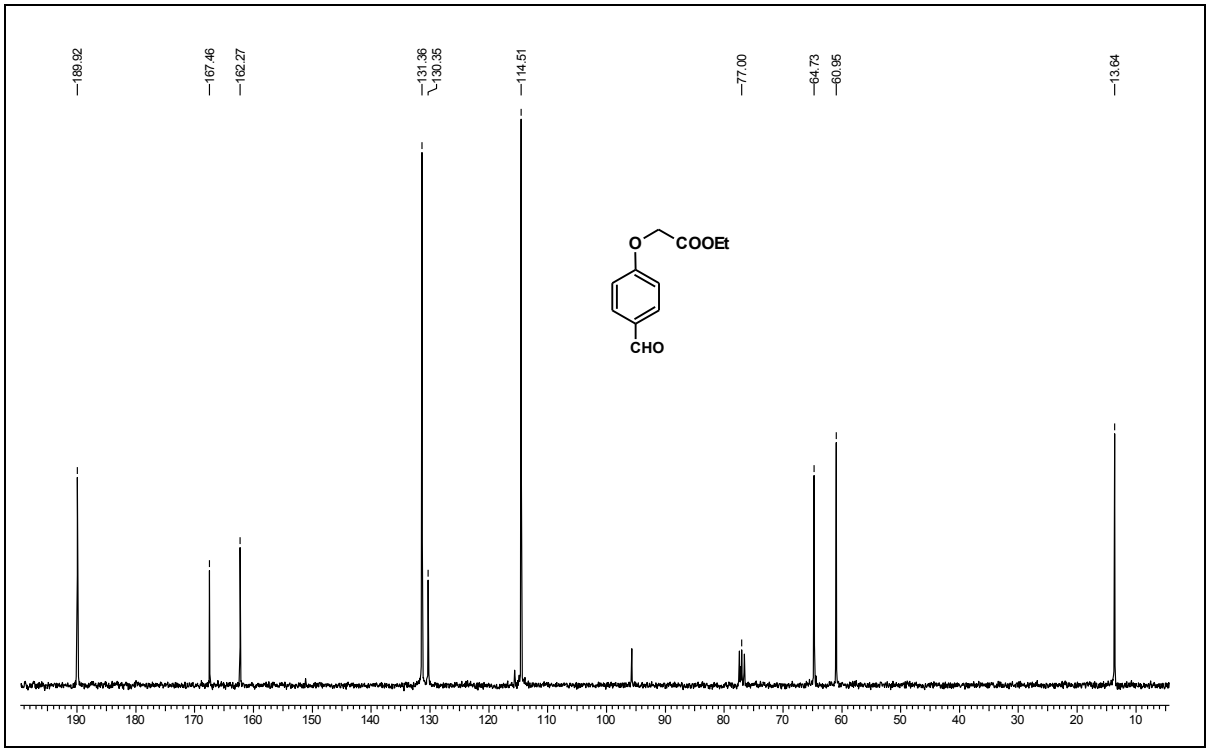
^{1}H NMR spectrum of compound 21 in $CDCl_3$



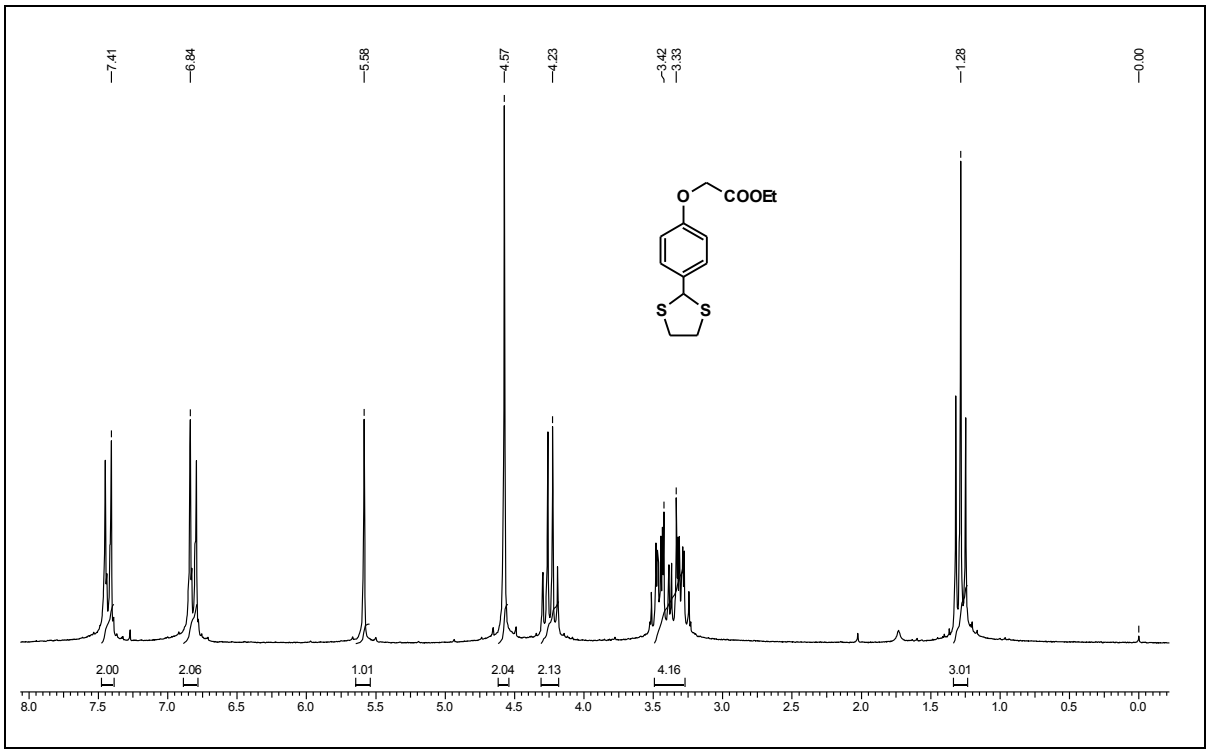
^{13}C NMR spectrum of compound 21 in $CDCl_3$



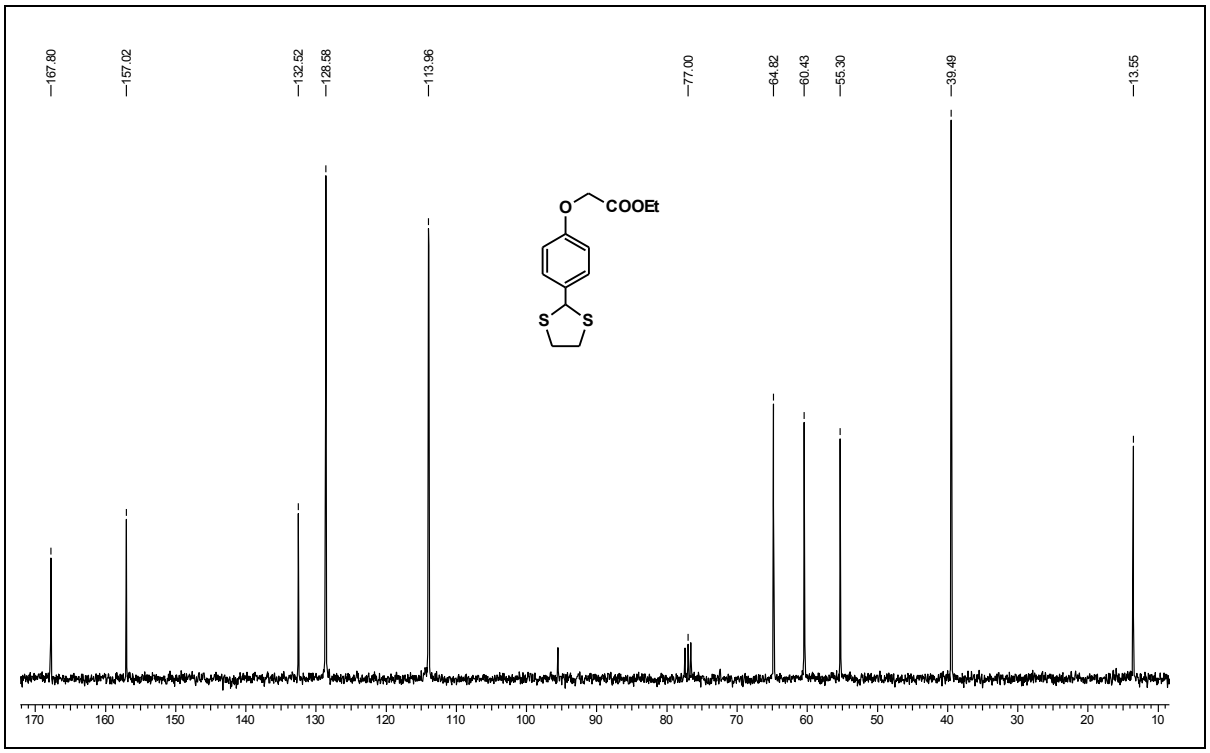
^{1}H NMR spectrum of compound 28 in $CDCl_3$



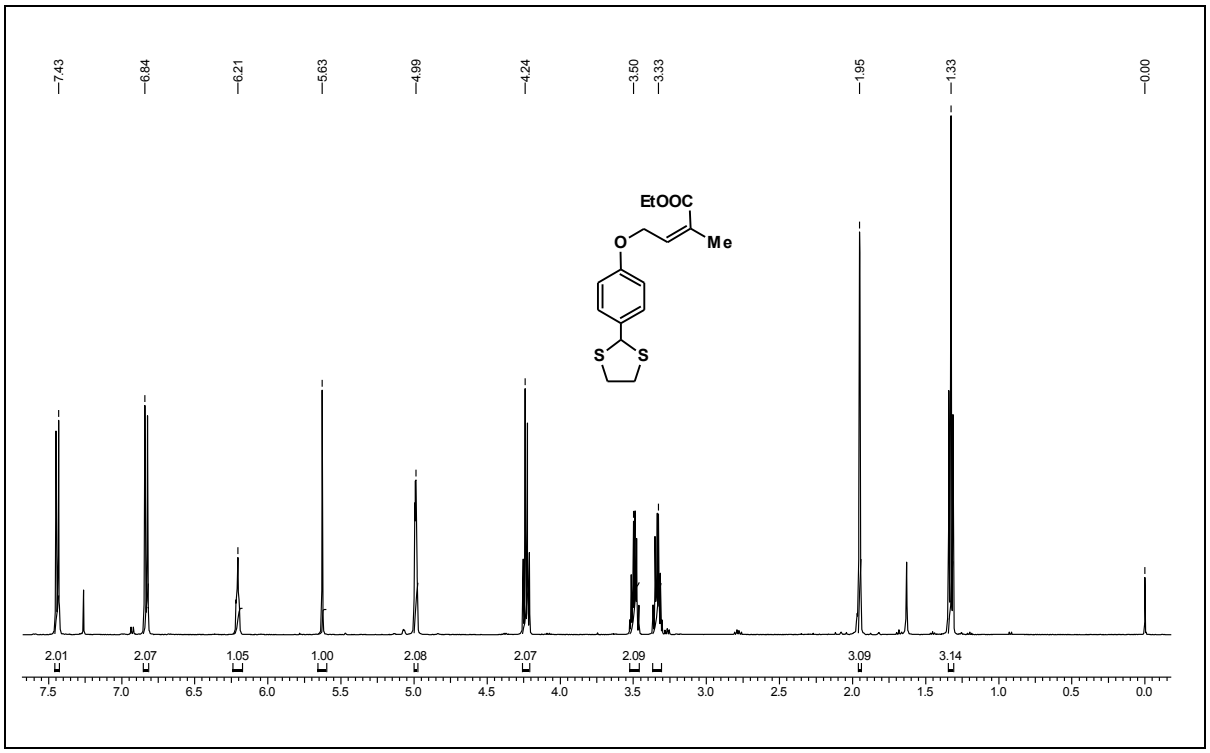
^{13}C NMR spectrum of compound 28 in $CDCl_3$



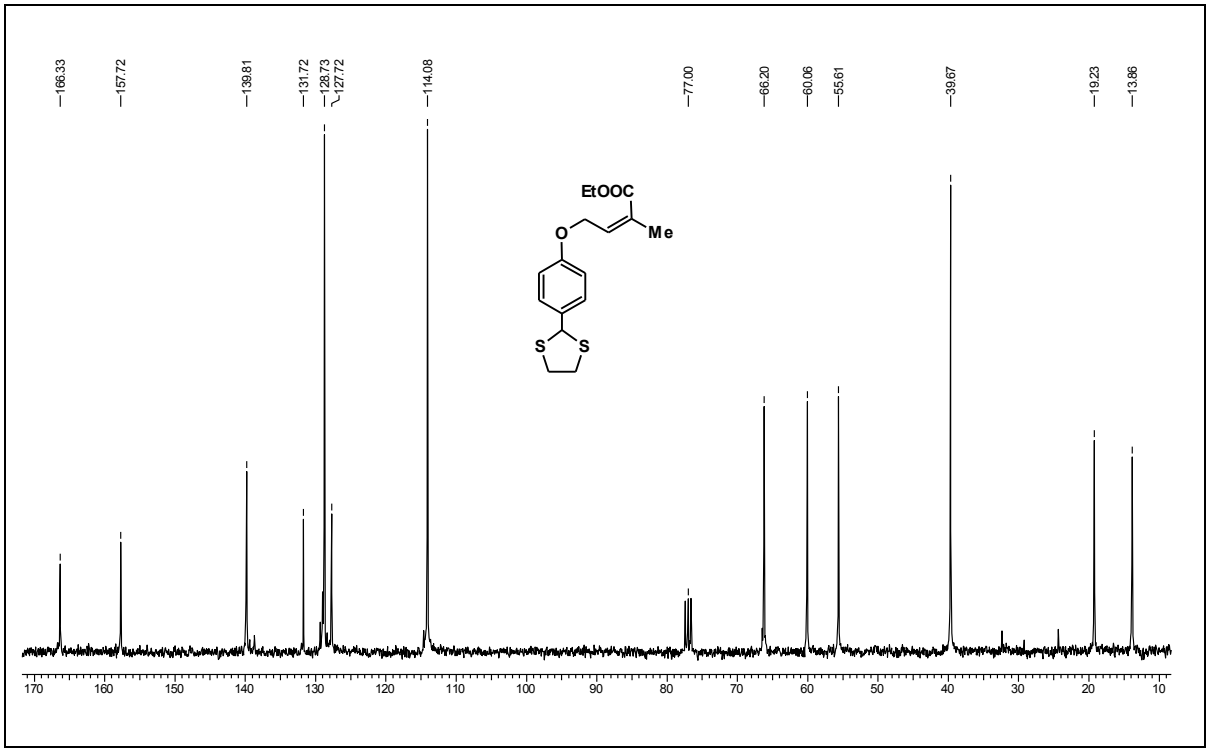
^{1}H NMR spectrum of compound 27 in $CDCl_3$



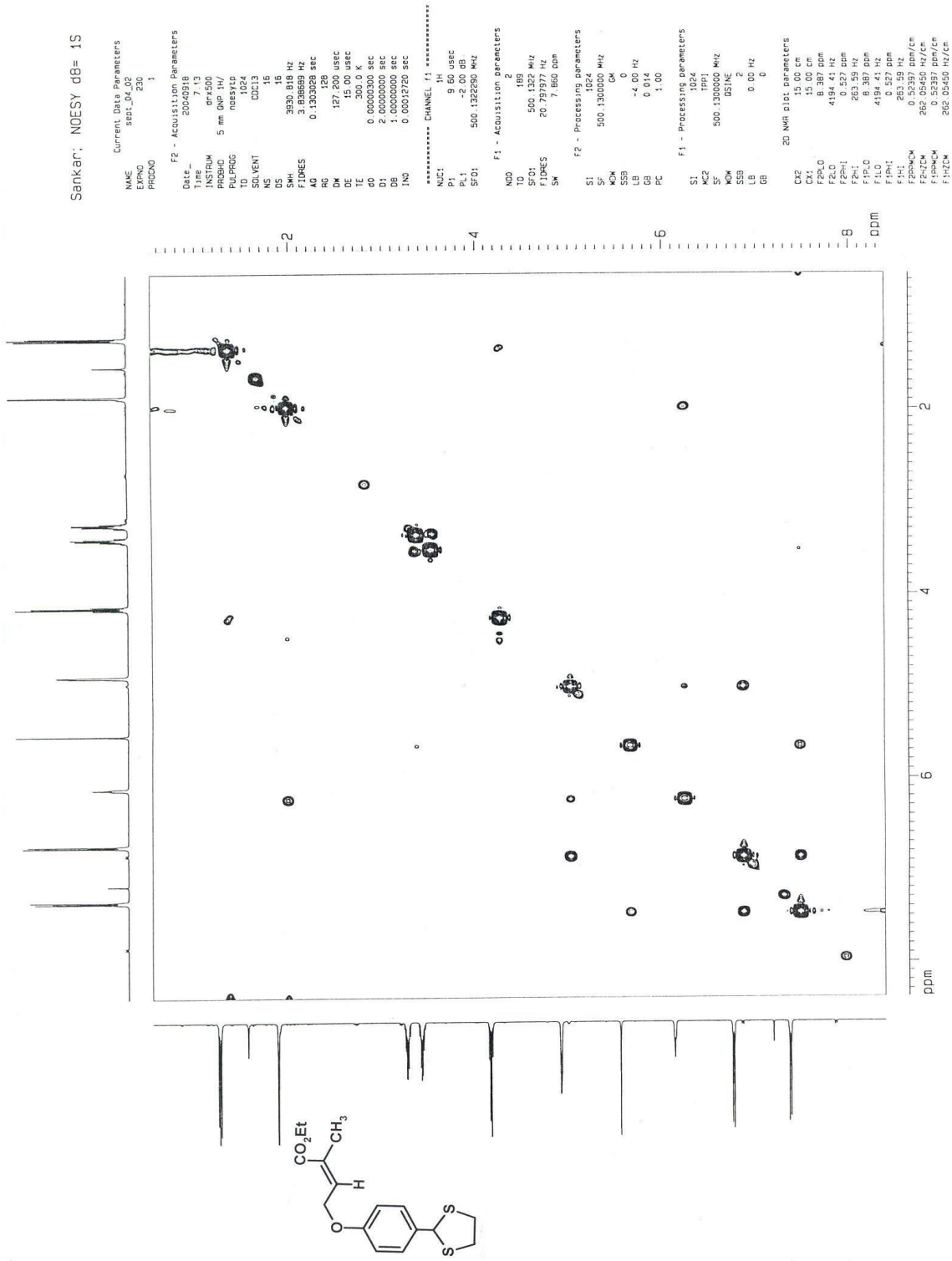
^{13}C NMR spectrum of compound 27 in $CDCl_3$



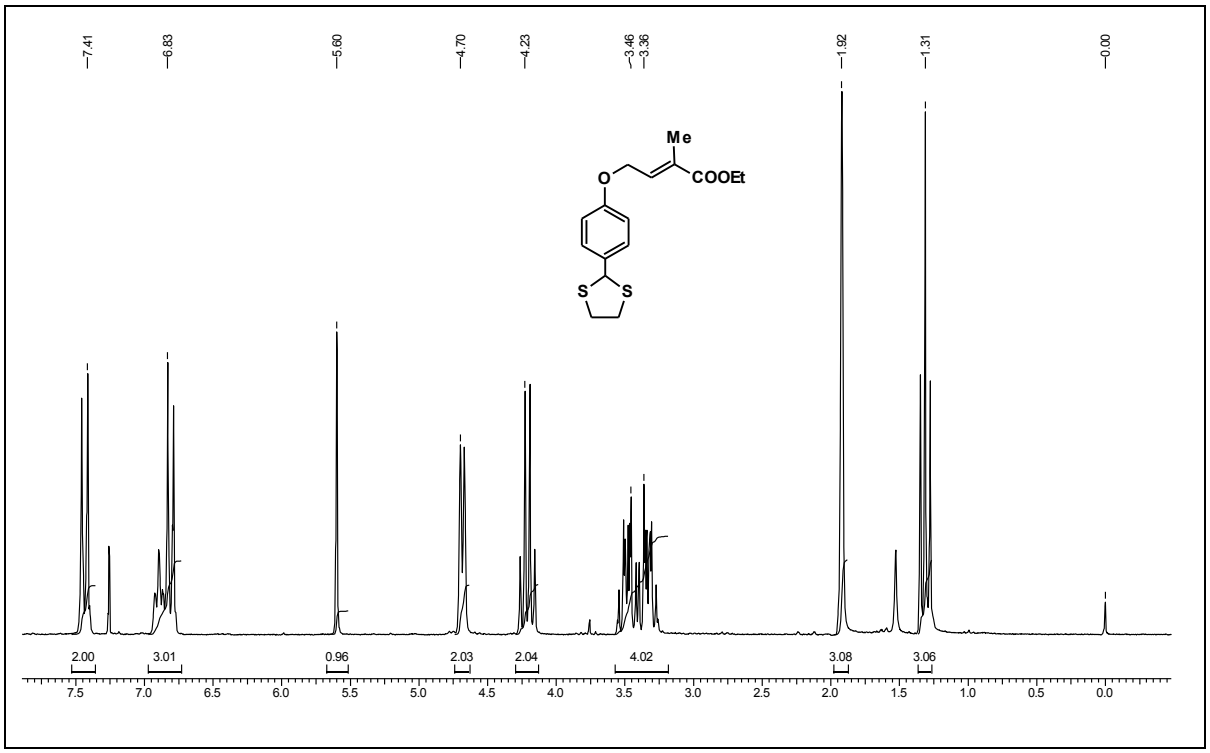
^{1}H NMR spectrum of compound 26 in $CDCl_3$



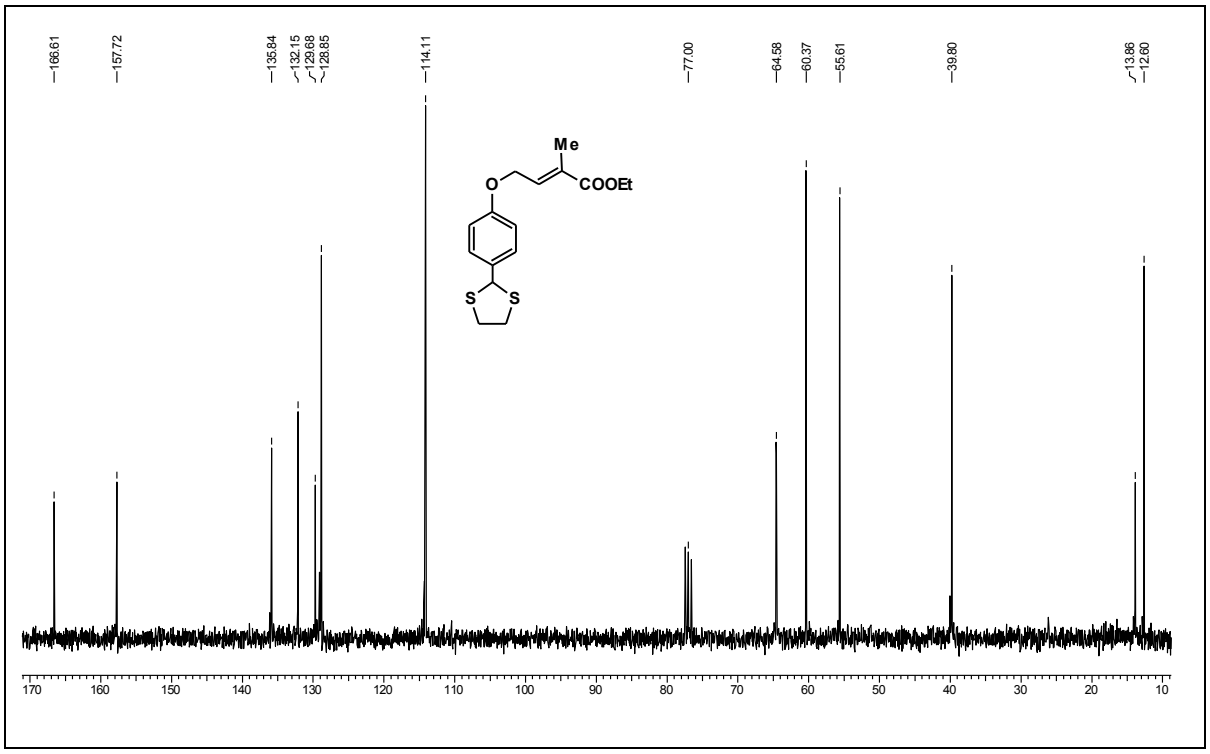
^{13}C NMR spectrum of compound 26 in $CDCl_3$



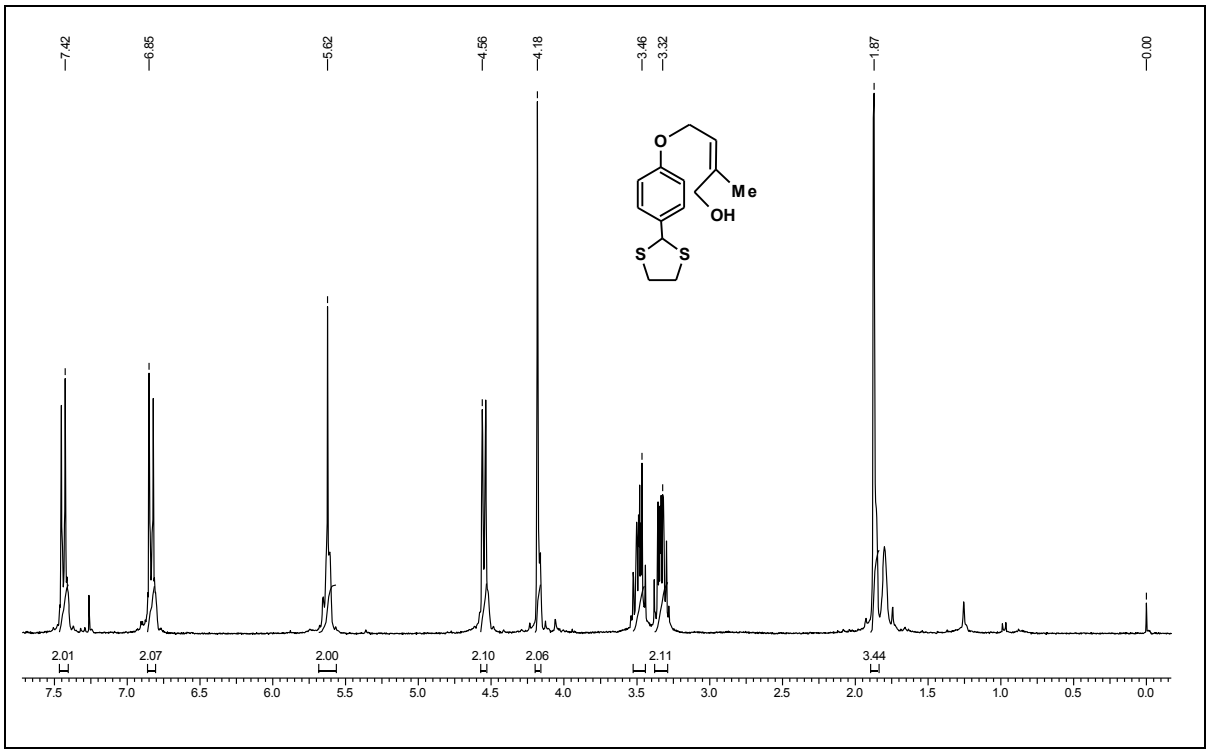
NOESY spectrum of compound 26



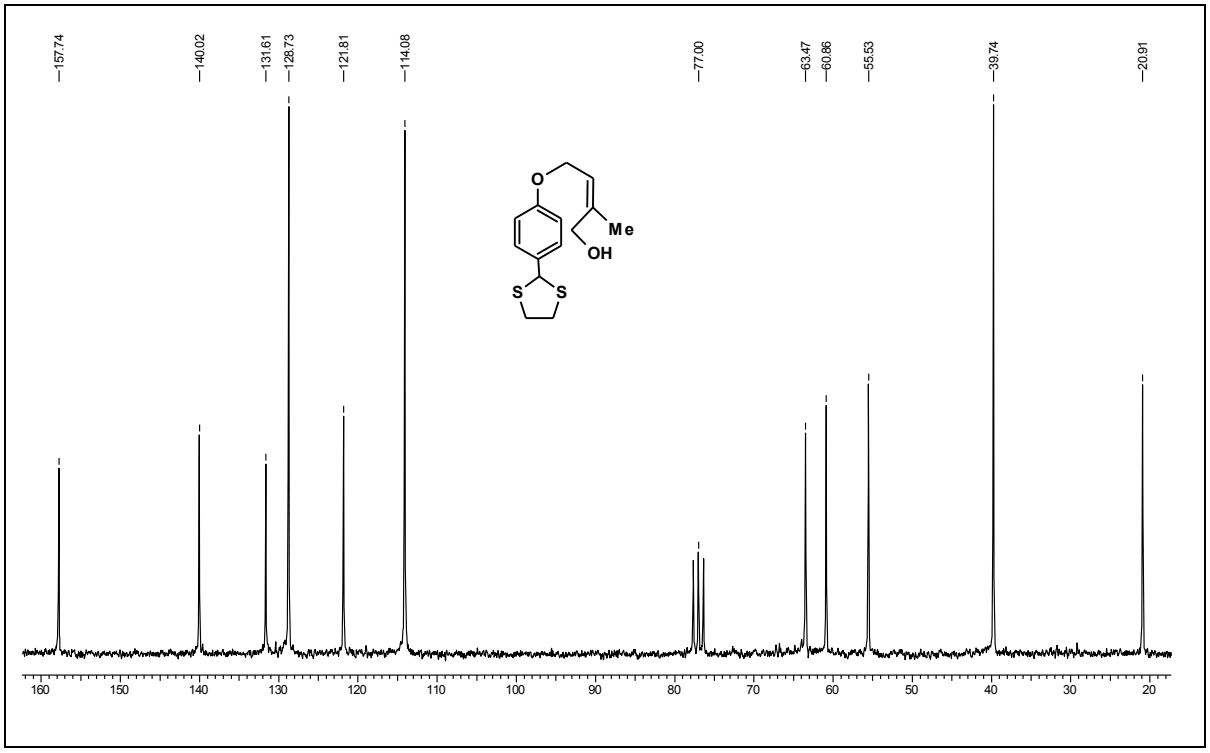
^{1}H NMR spectrum of compound 30 in $CDCl_3$



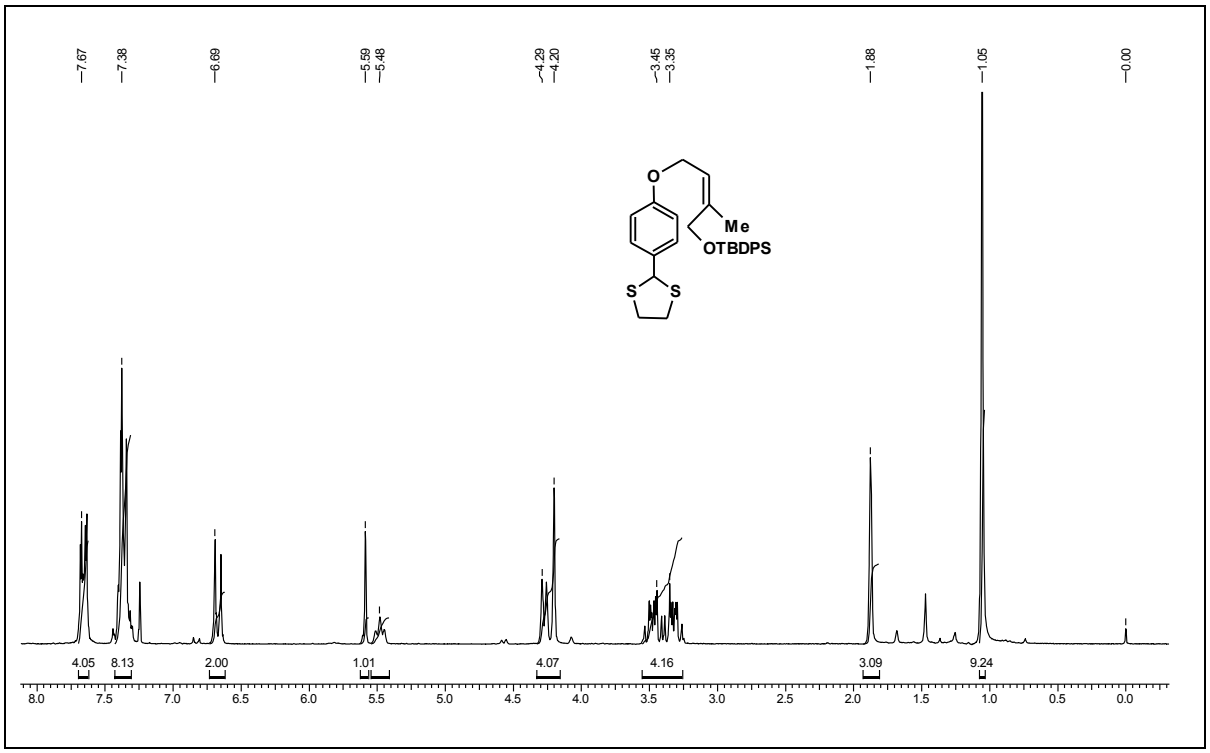
^{13}C NMR spectrum of compound 30 in $CDCl_3$



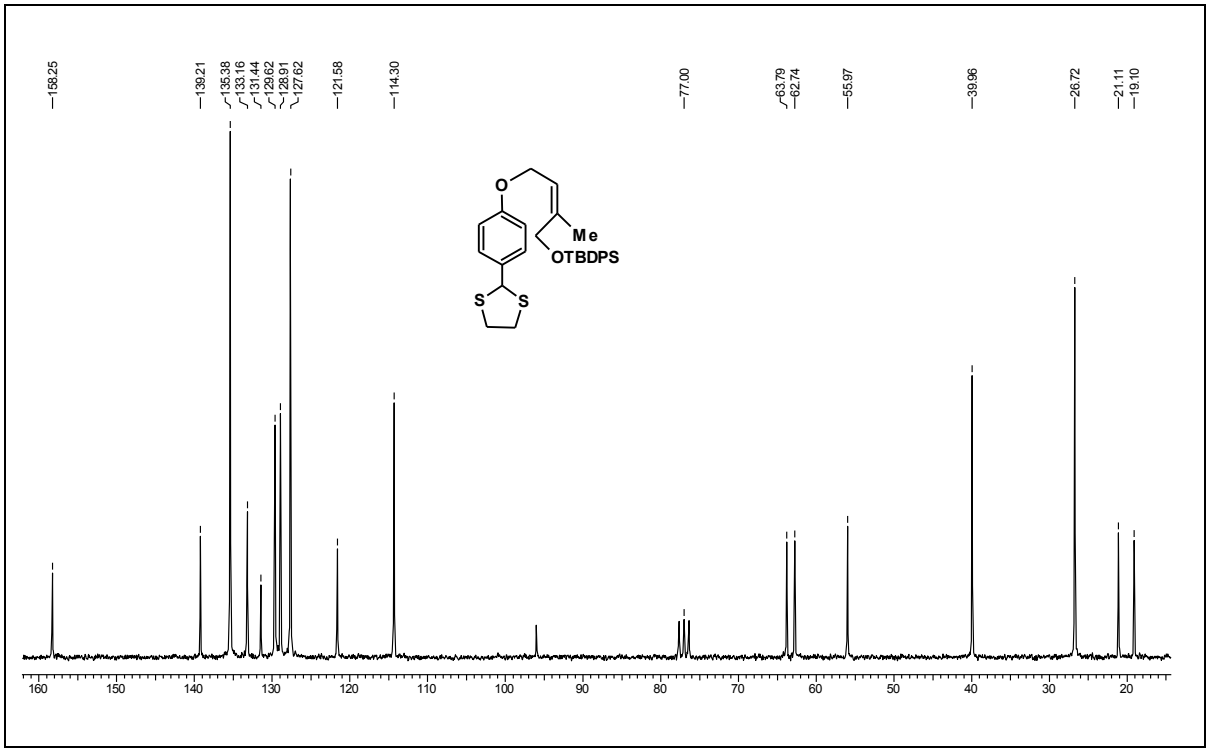
^{1}H NMR spectrum of compound 32 in $CDCl_3$



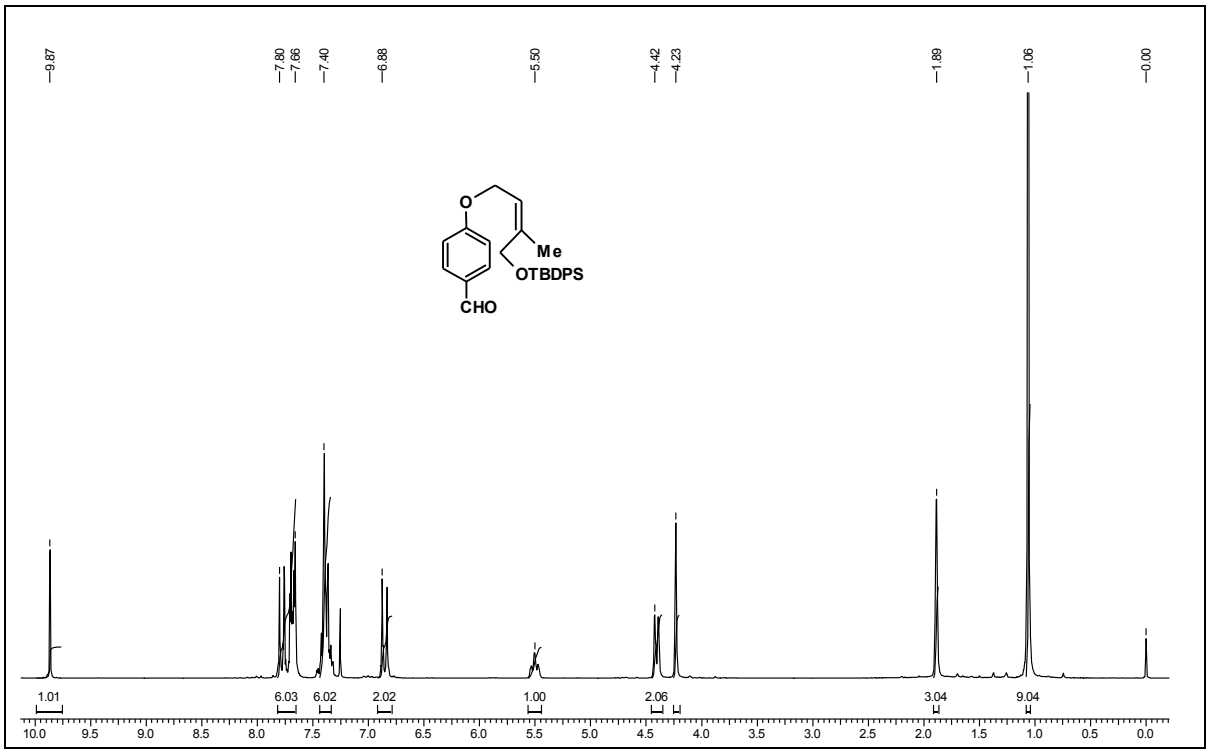
^{13}C NMR spectrum of compound 32 in $CDCl_3$



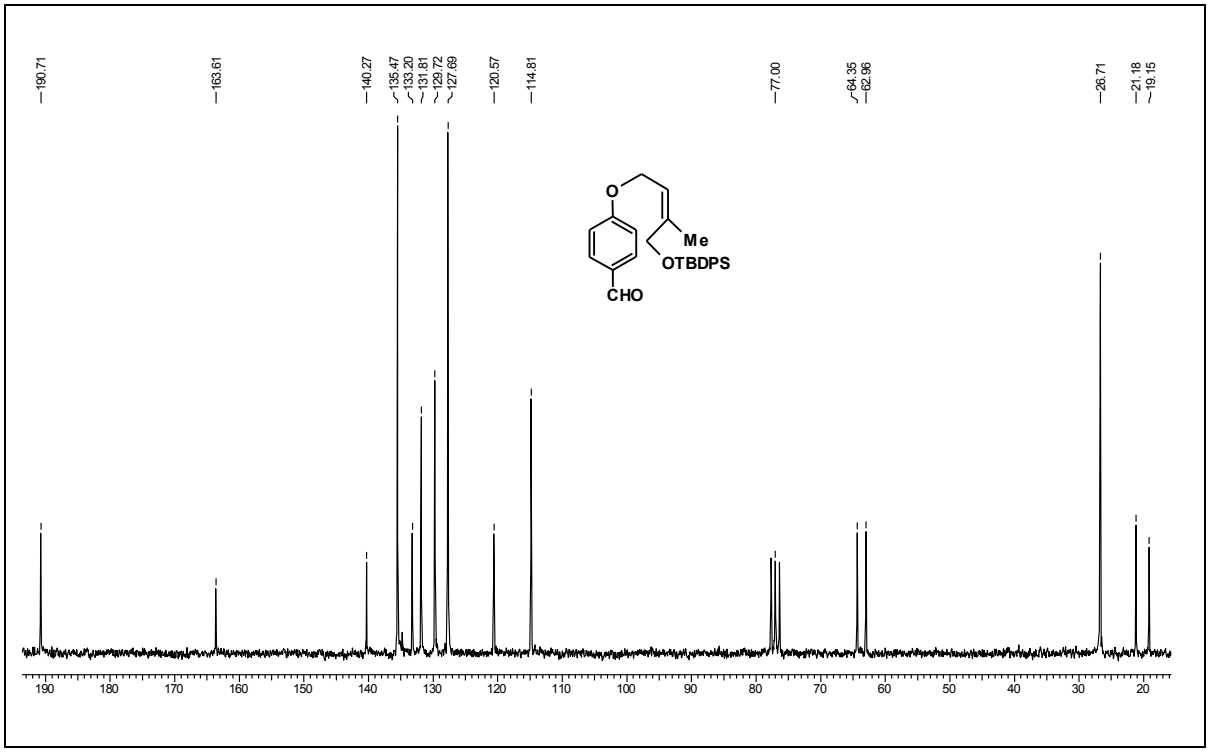
^{1}H NMR spectrum of compound 25 in $CDCl_3$



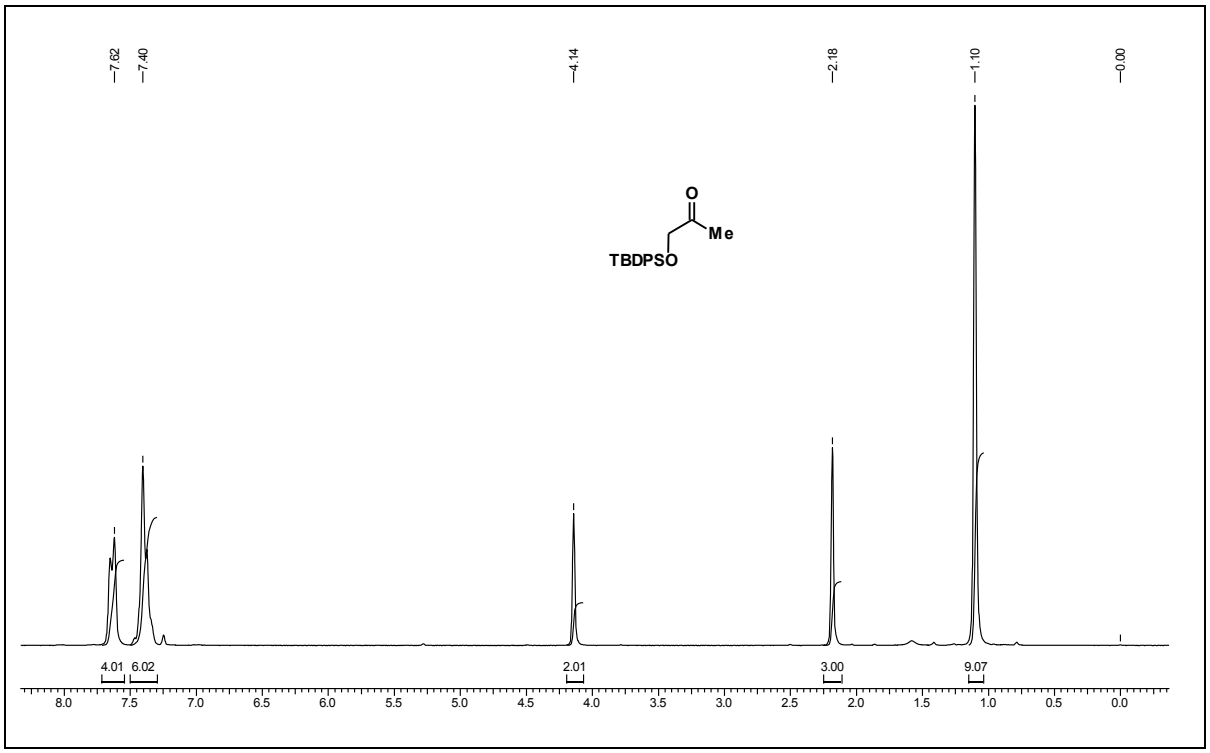
^{13}C NMR spectrum of compound 25 in $CDCl_3$



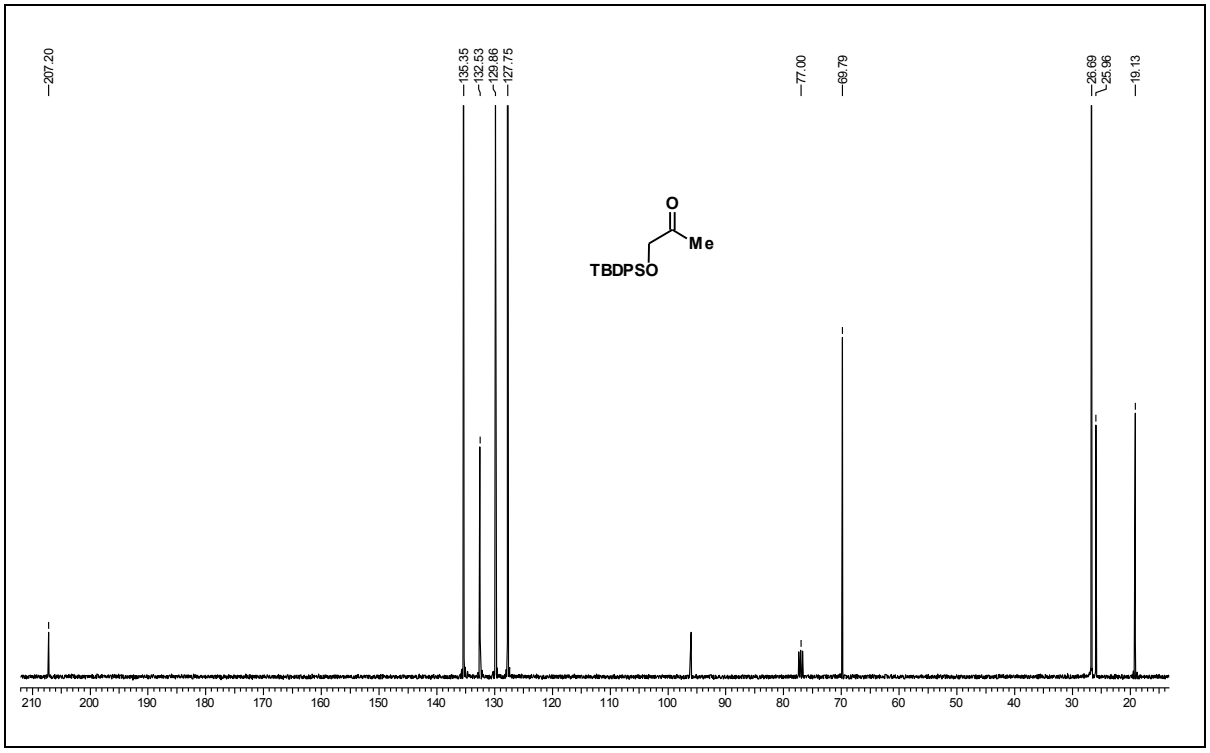
^{1}H NMR spectrum of compound 33 in $CDCl_3$



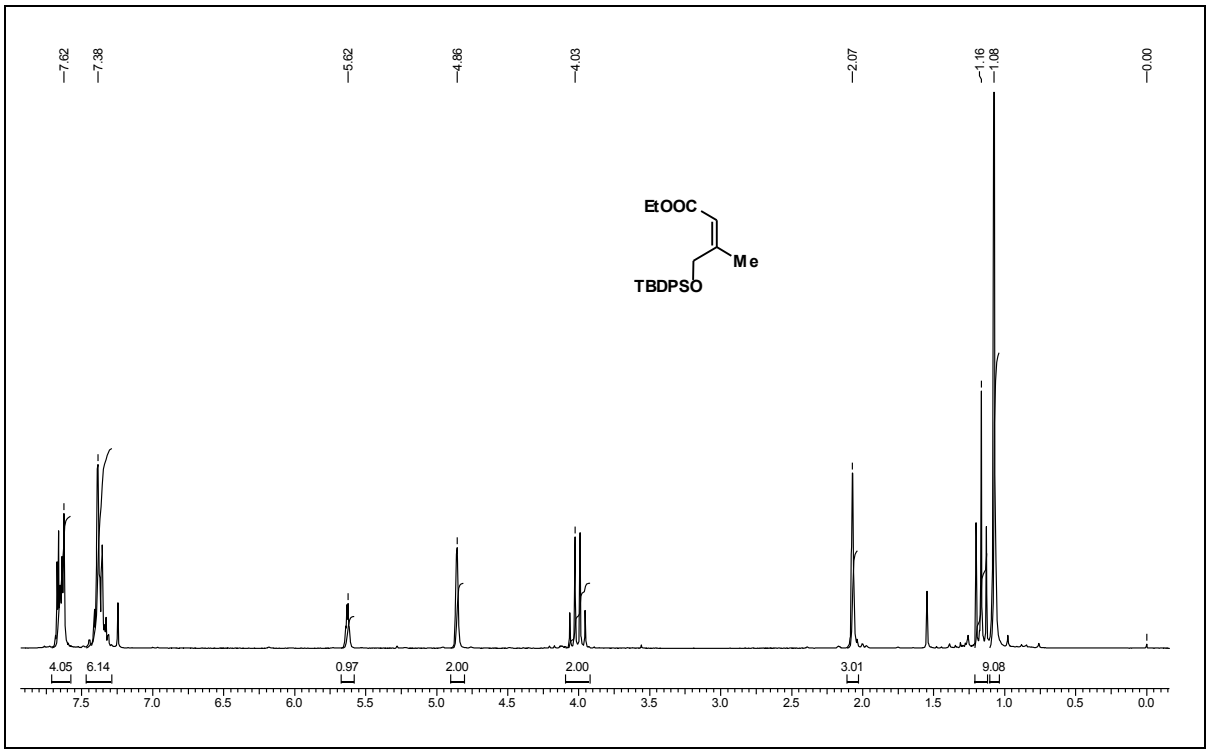
^{13}C NMR spectrum of compound 33 in $CDCl_3$



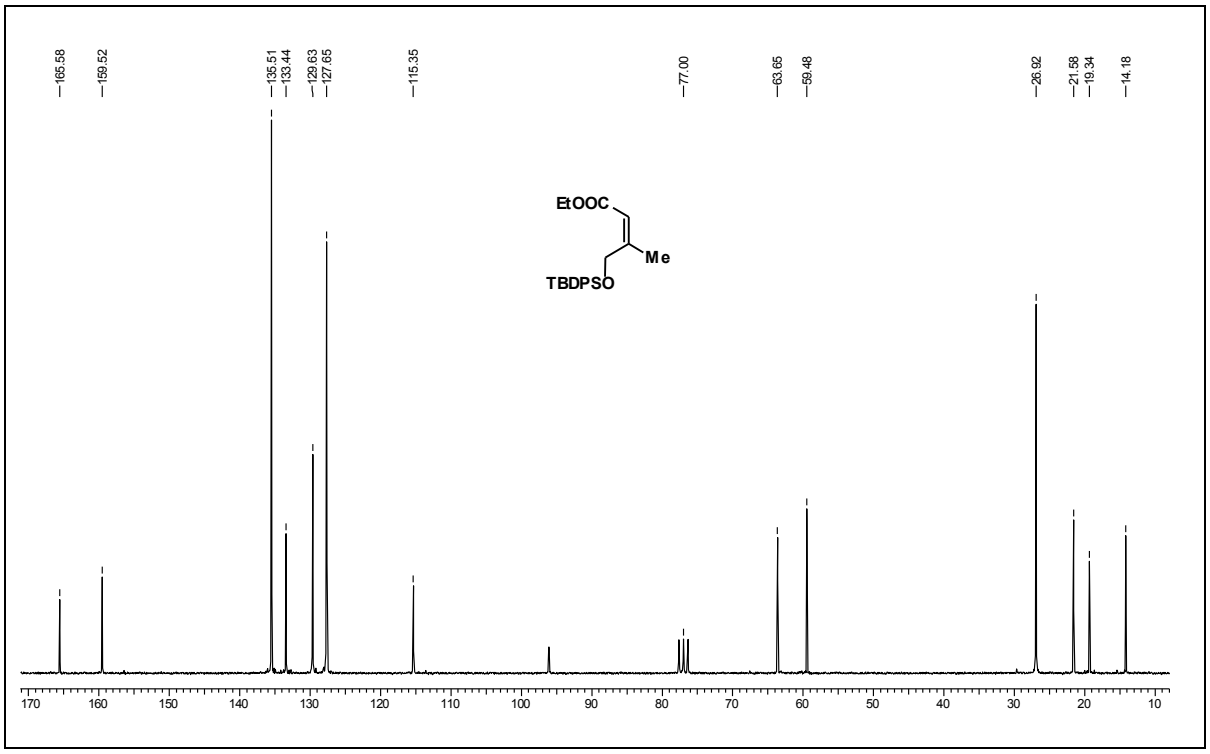
^{1}H NMR spectrum of compound 35 in $CDCl_3$



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



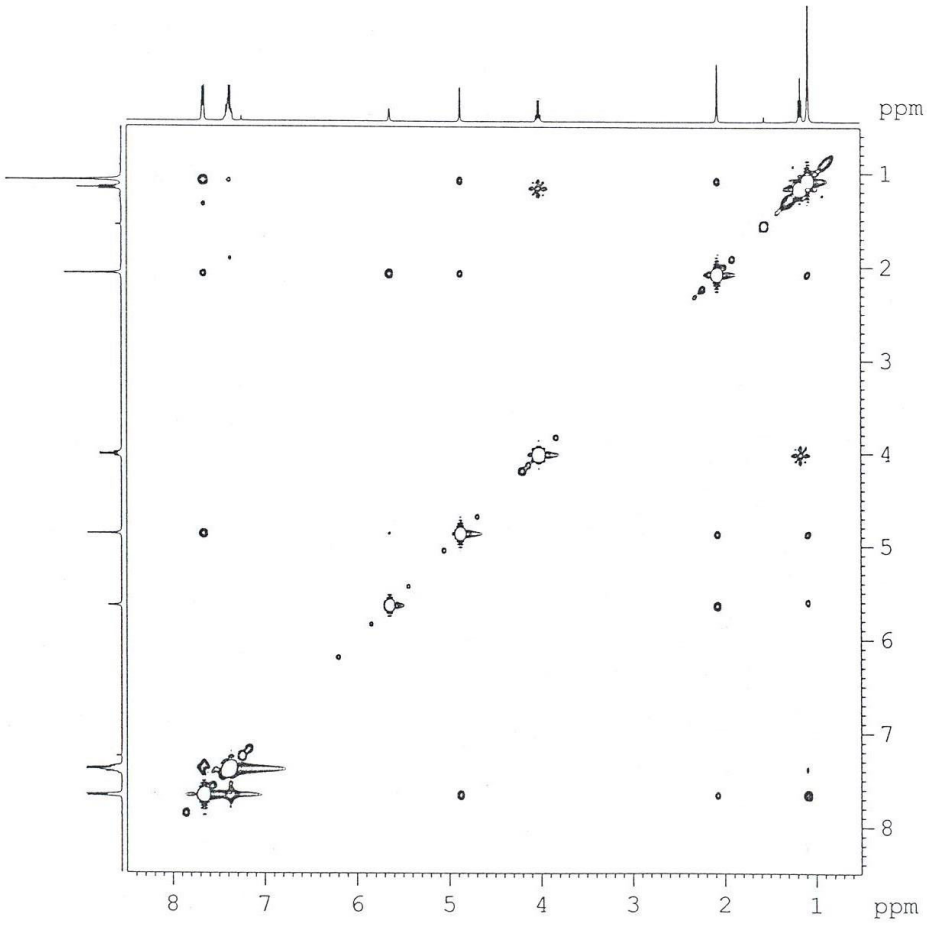
^{1}H NMR spectrum of compound 38 in $CDCl_3$

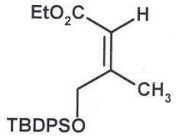


^{13}C NMR spectrum of compound 38 in $CDCl_3$

NOESY spectrum of compound 38

Shankar;NOESY





BRUKER

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PROCNO                  1

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PULPROG          noesygpph
TD                   1024
SOLVENT              CDCl3
NS                      8
DS                     16
SWH               3201.024 Hz
FIDRES            3.126000 Hz
AQ                0.1599988 sec
RG                     128
DW                 156.200 usec
DE                  20.00 usec
TE                  299.8 K
d0              0.00013920 sec
D1              3.00000000 sec
D8              1.00000000 sec
D16             0.00010000 sec
IN0             0.00031240 sec
ST1CNT                 128
TAU             0.49840000 sec

======== CHANNEL f1 ========
NUC1                    1H
P1                  13.35 usec
P2                  28.40 usec
PL1                  1.00 dB
SFO1          400.1317000 MHz

====== GRADIENT CHANNEL =====
GPNAM1           SINE.100
GPNAM2           SINE.100
GPZ1                40.00 %
GPZ2               -40.00 %
P16               1500.00 usec

F1 - Acquisition parameters
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TD                    241
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FIDRES          13.282259 Hz
SW                  8.000 ppm
FnMODE       States-TPPI

F2 - Processing parameters
SI                   1024
SF            400.1300135 MHz
WDW                    GM
SSB                     0
LB                  -2.00 Hz
GB                  0.015
PC                   1.00

F1 - Processing parameters
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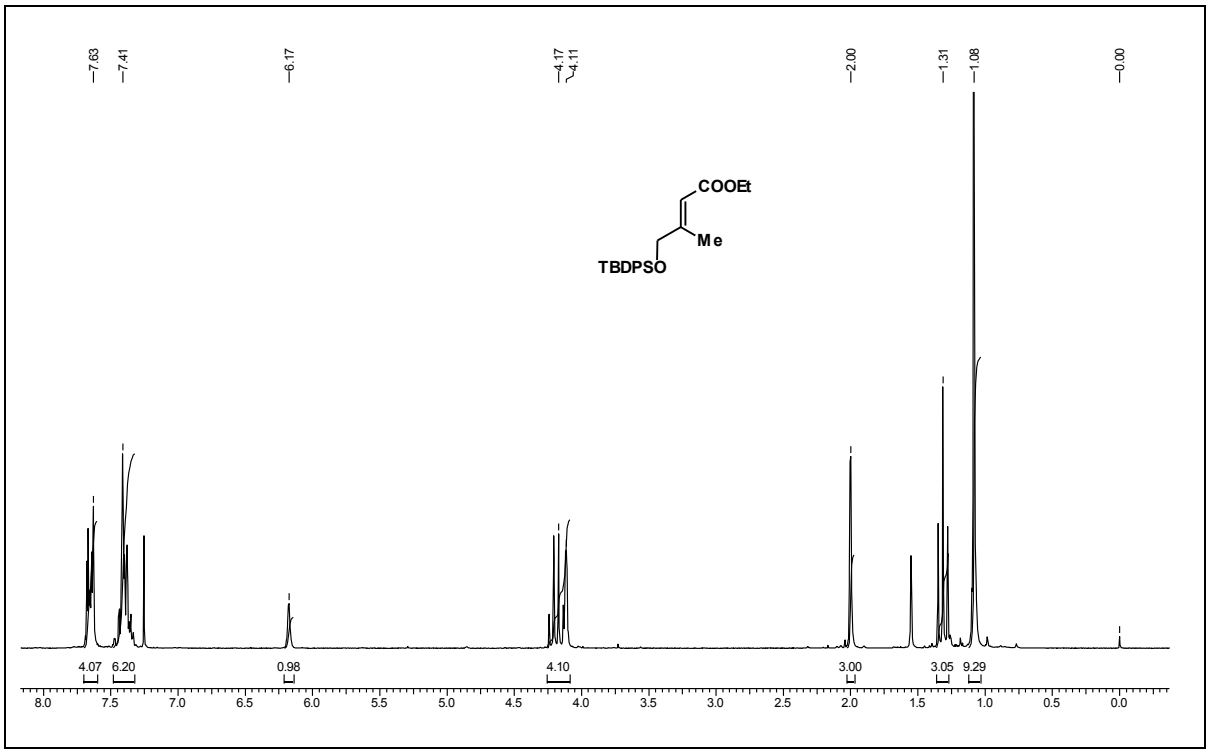
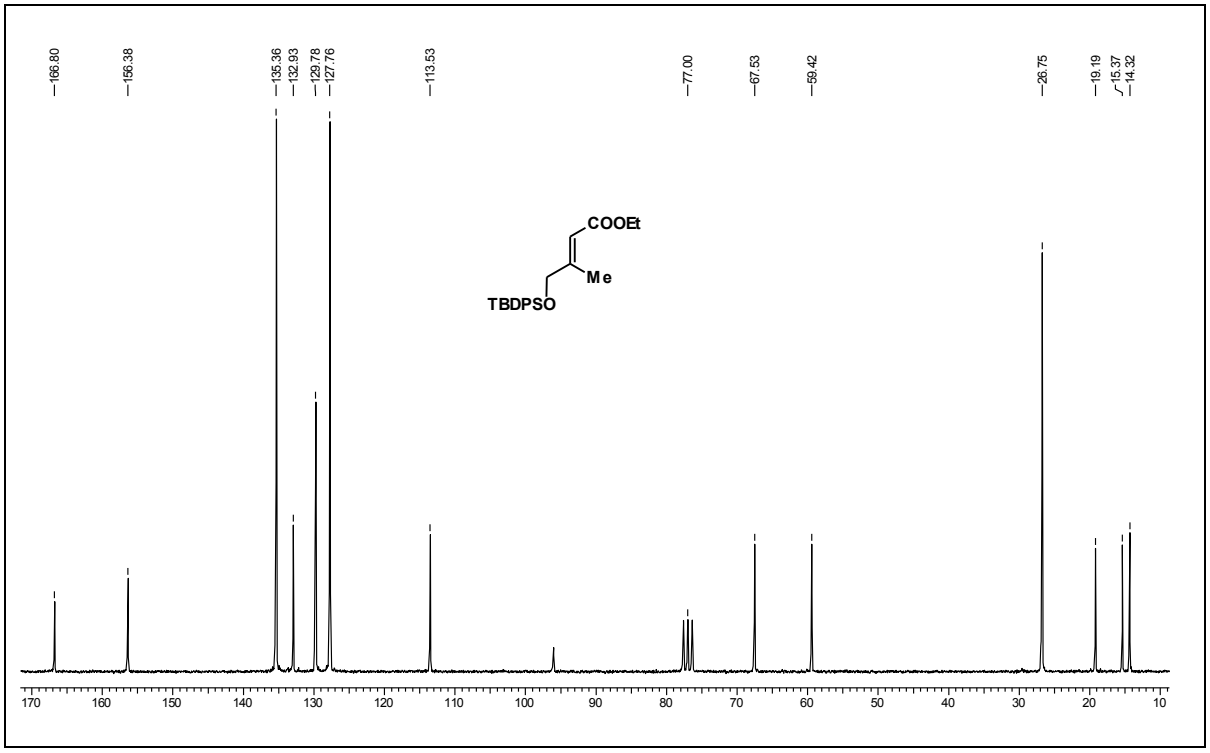
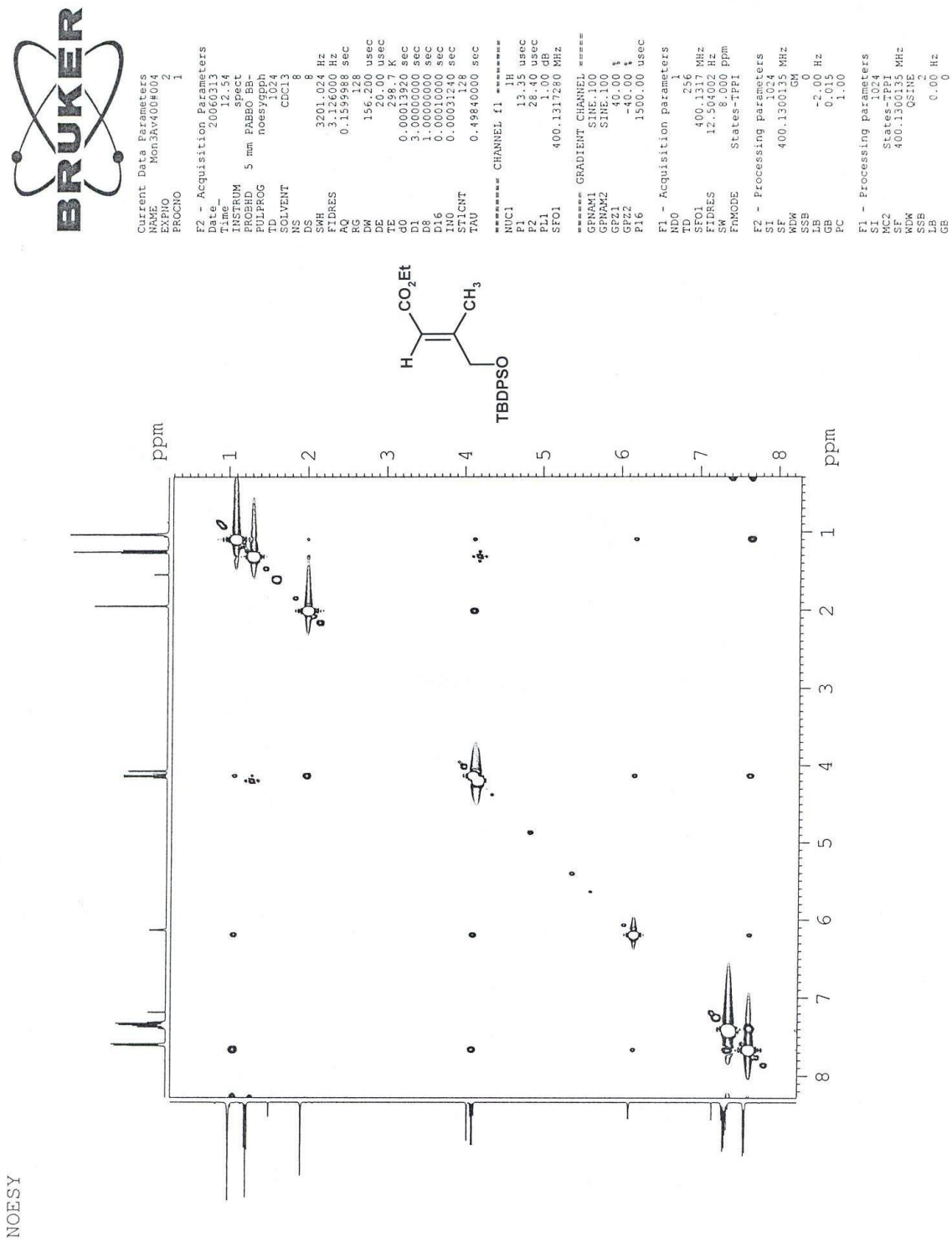


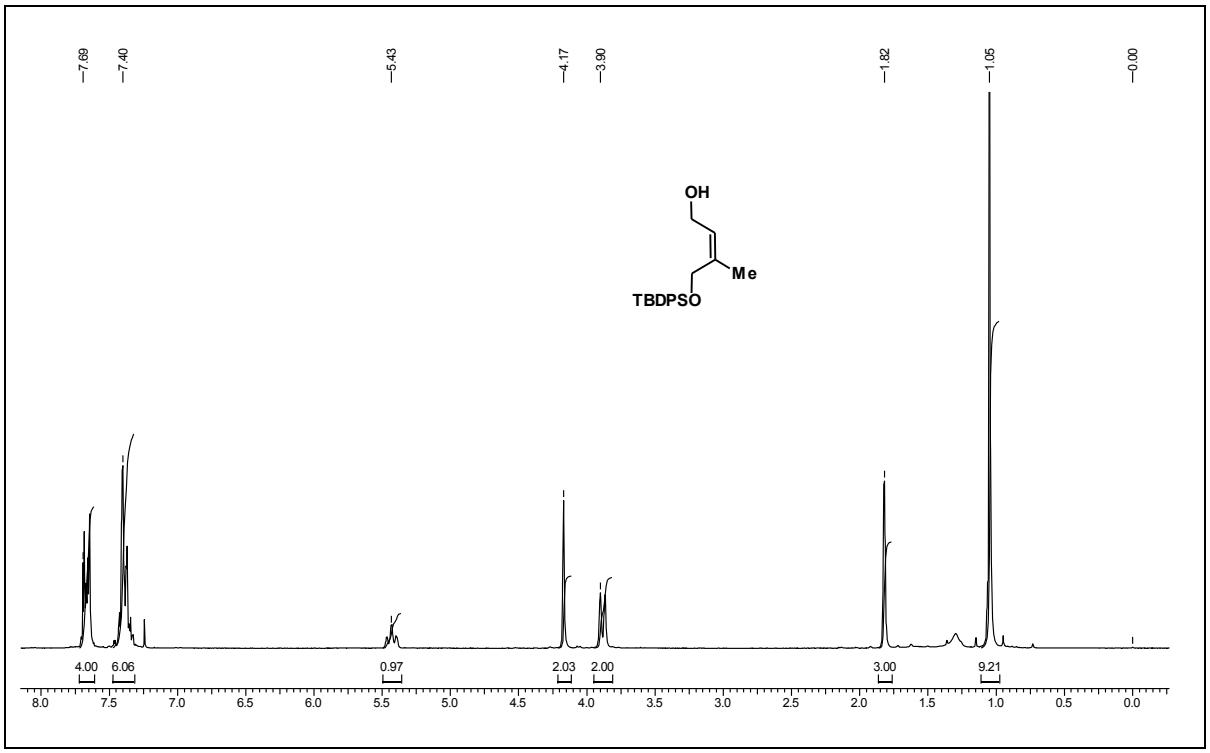
^{1}H NMR spectrum of compound 39 in $CDCl_3$



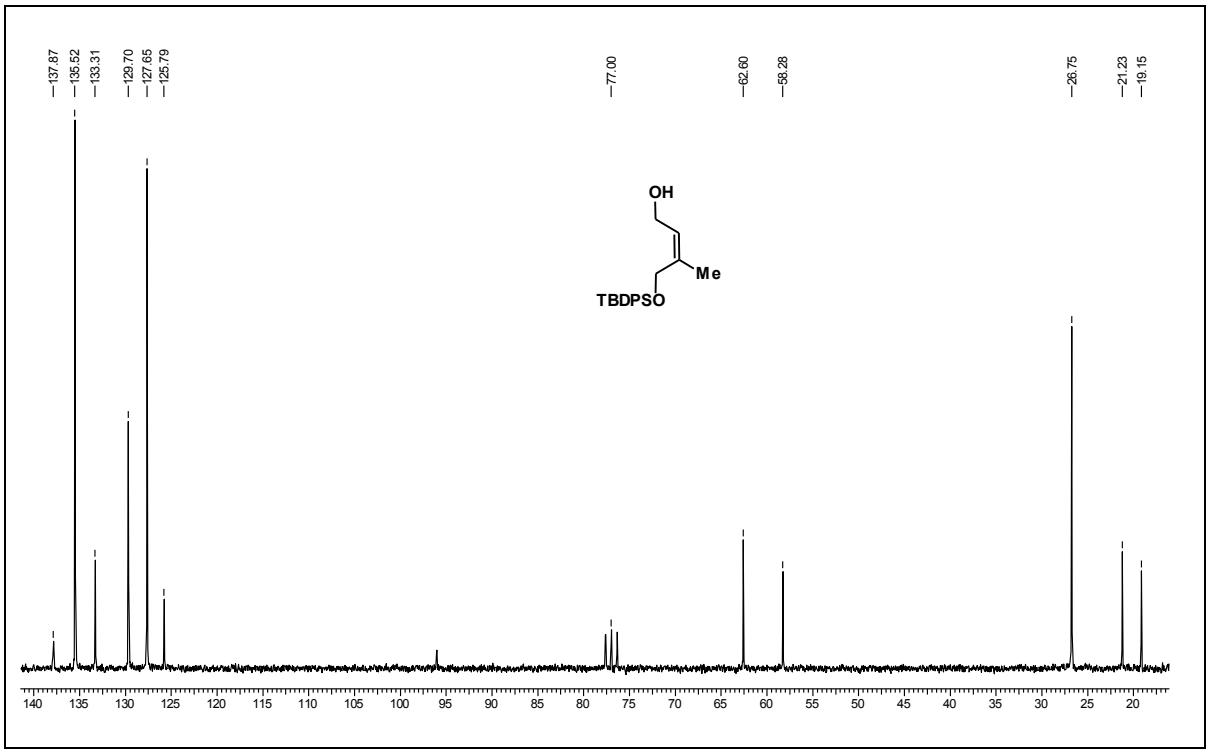
^{13}C NMR spectrum of compound 39 in $CDCl_3$



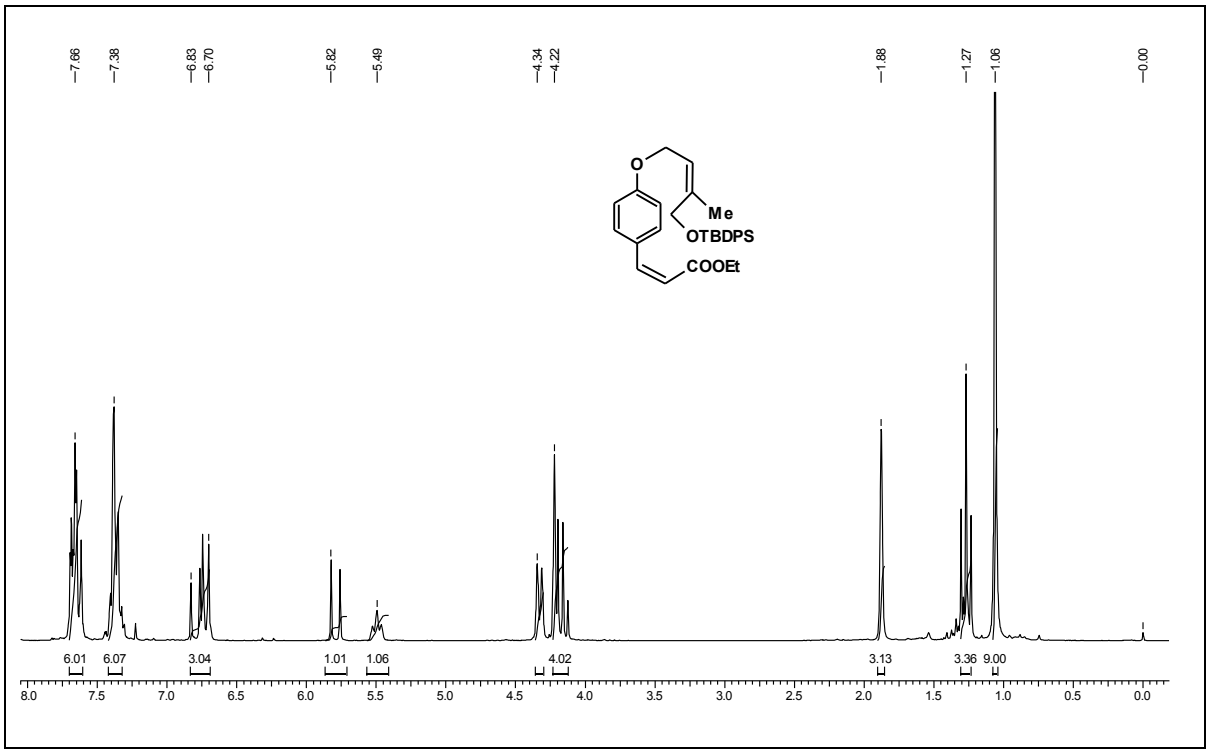
NOESY spectrum of compound 39



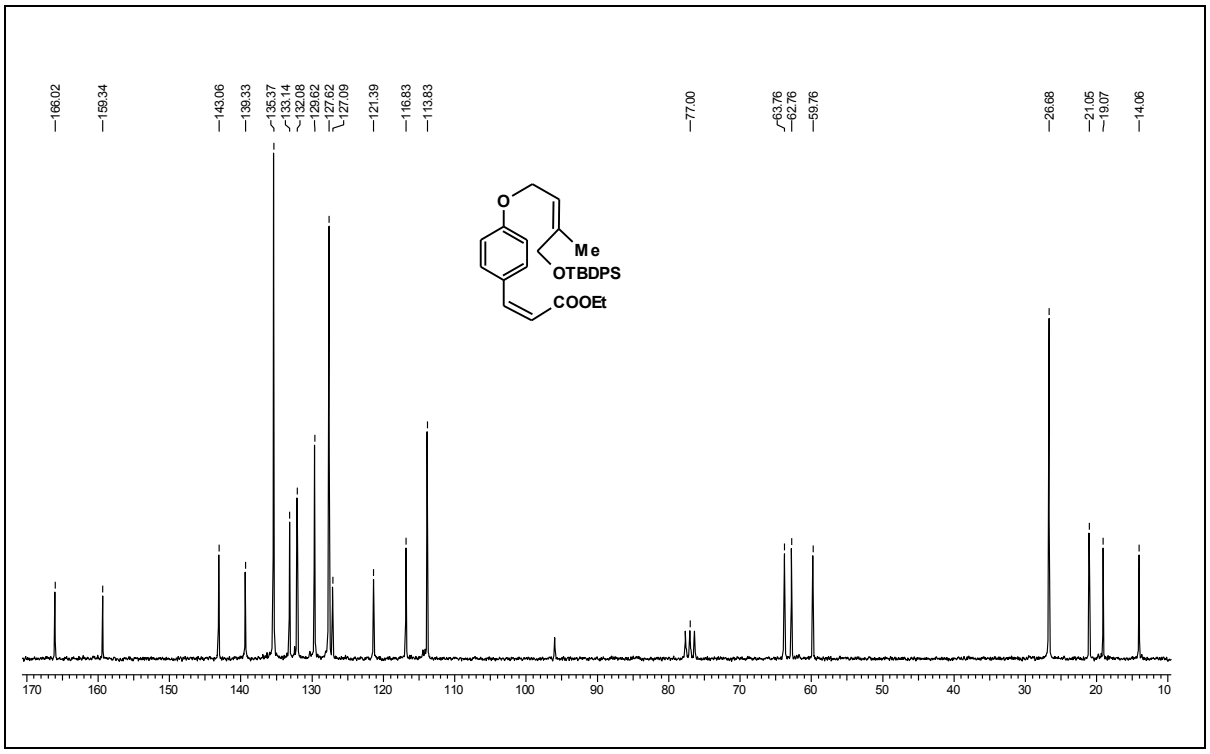
^{1}H NMR spectrum of compound 34 in $CDCl_3$



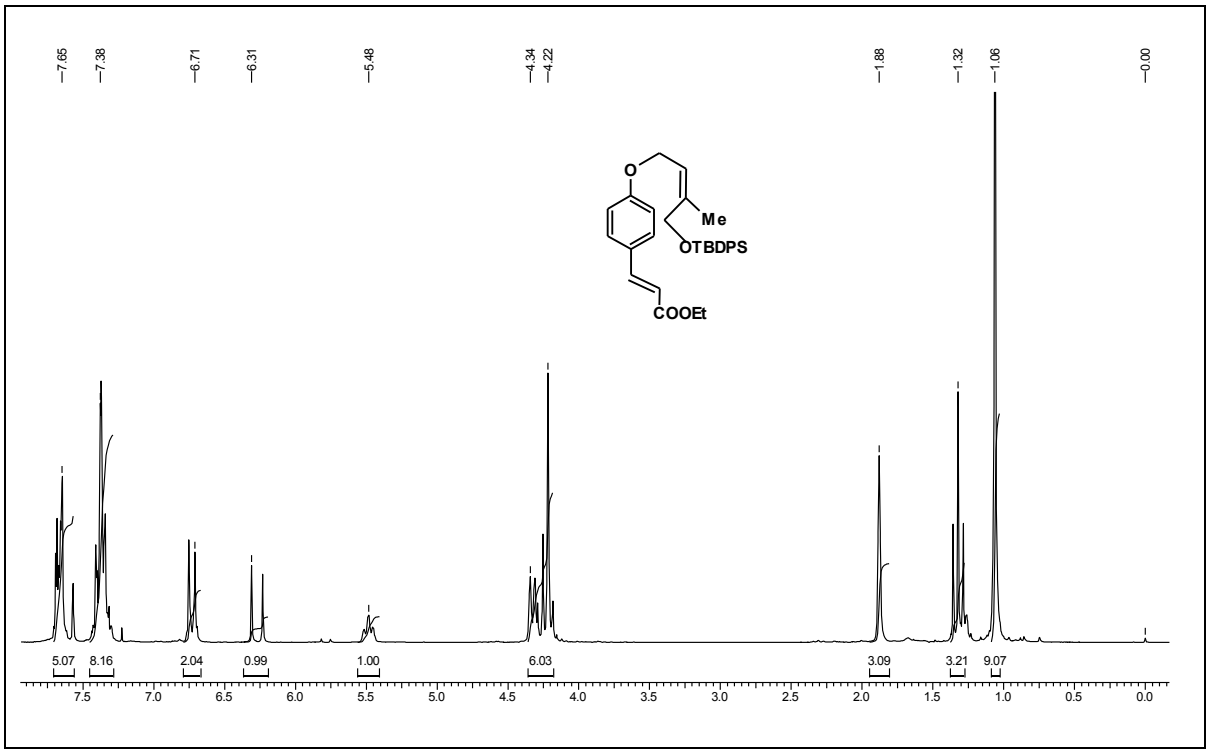
^{13}C NMR spectrum of compound 34 in $CDCl_3$



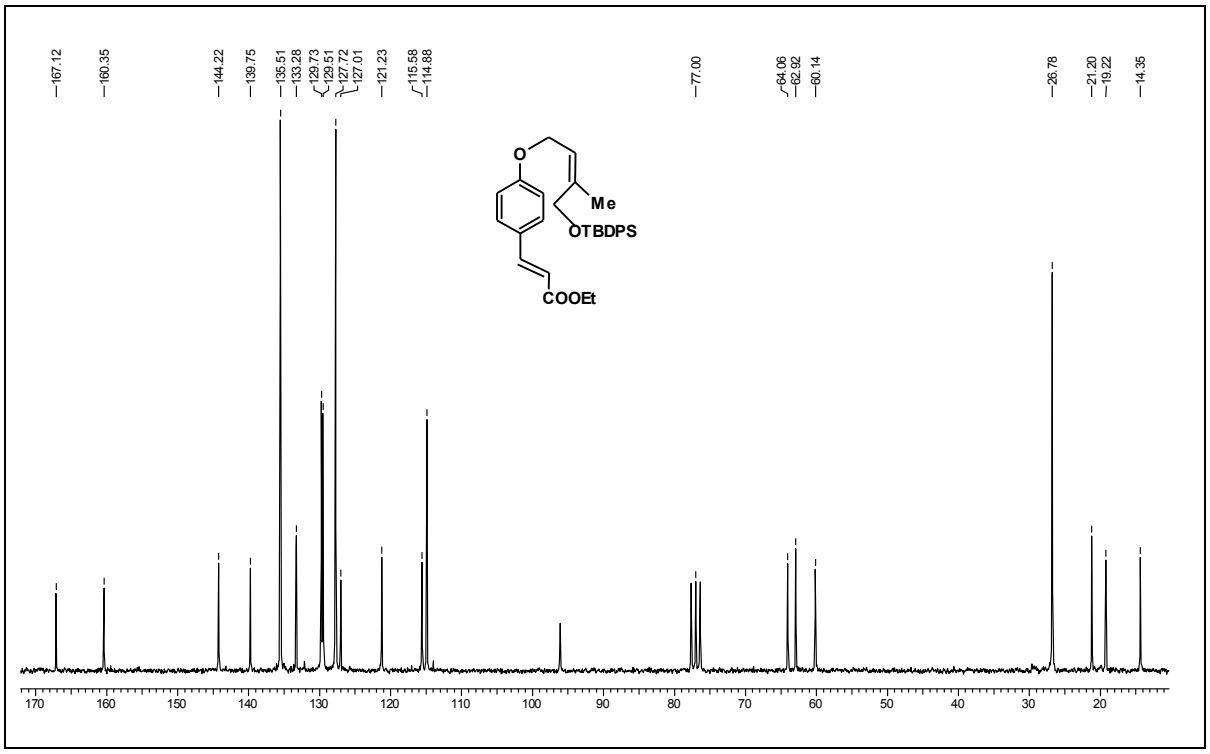
^{1}H NMR spectrum of compound 24 in $CDCl_3$



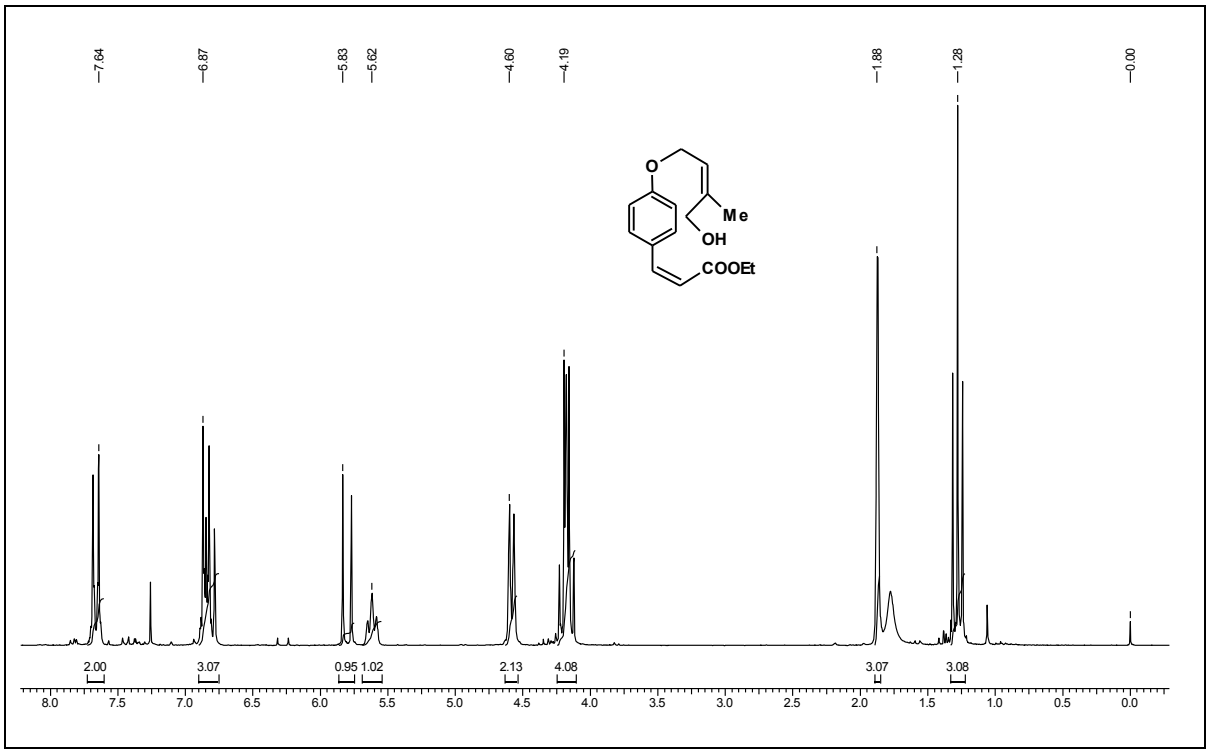
^{13}C NMR spectrum of compound 24 in $CDCl_3$



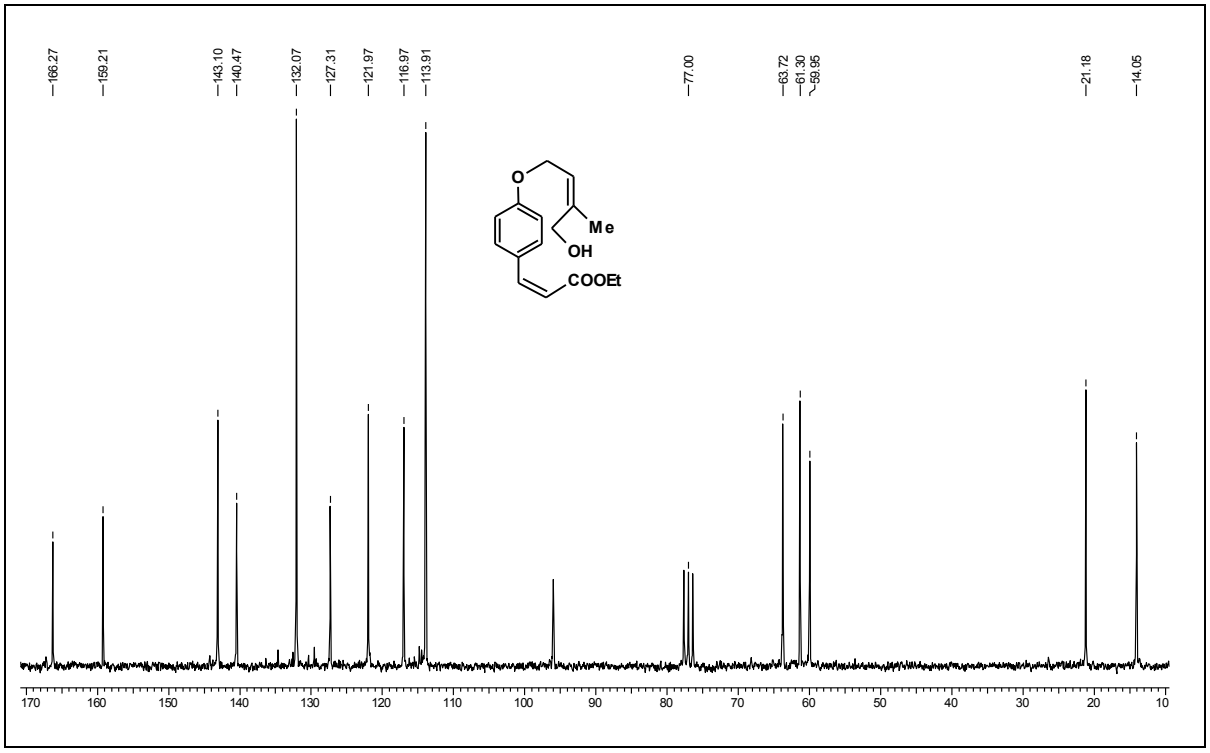
^{1}H NMR spectrum of compound 40 in $CDCl_3$



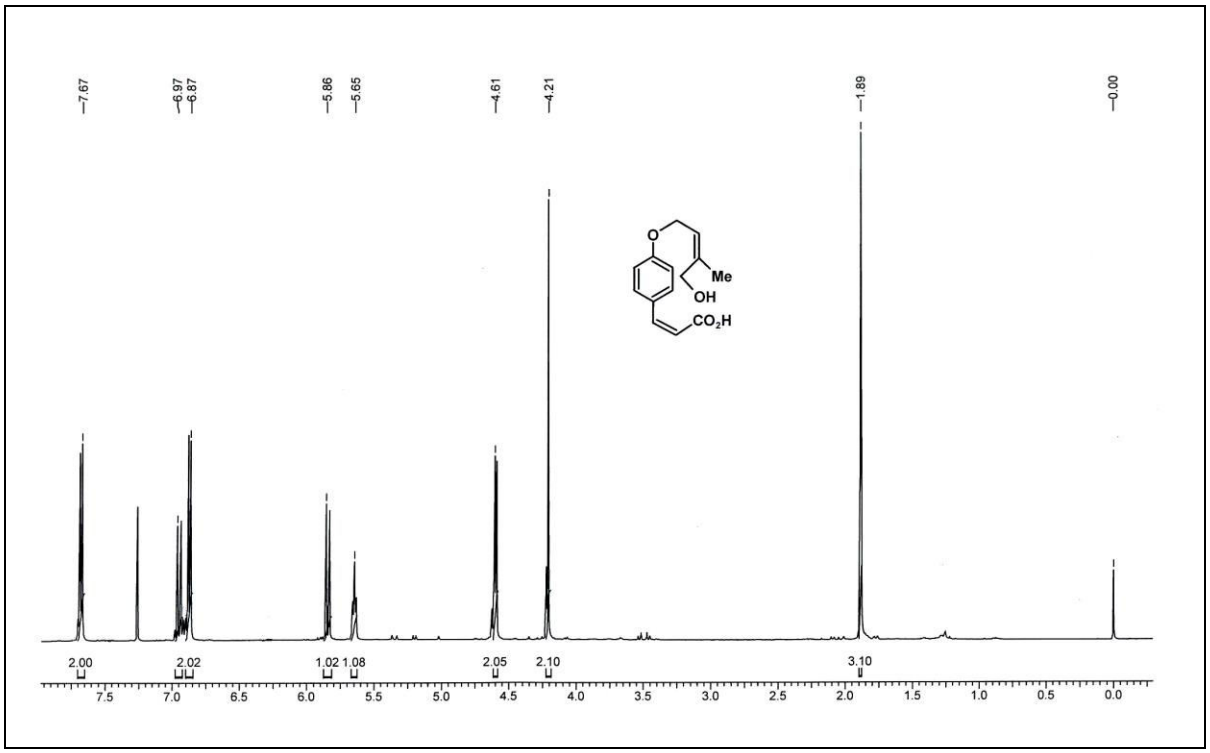
^{13}C NMR spectrum of compound 40 in $CDCl_3$



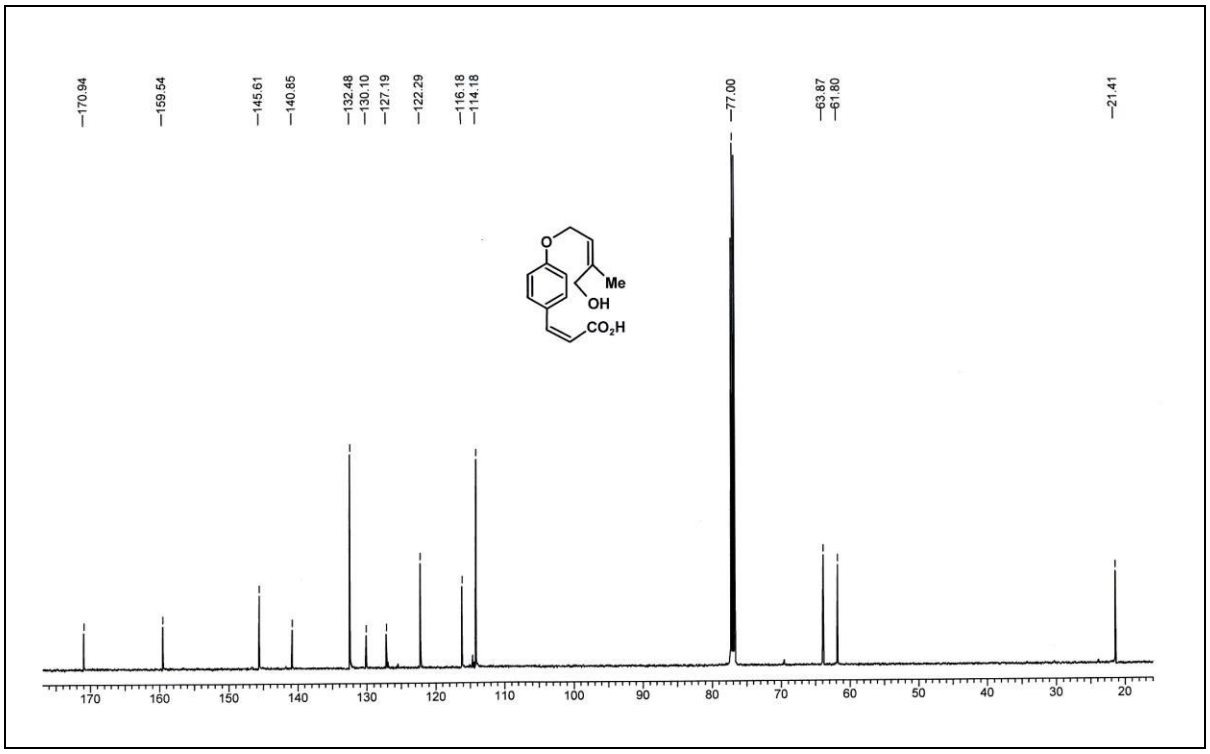
^{1}H NMR spectrum of compound 41 in $CDCl_3$



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



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



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

List of publications

1. Synthesis of spirocycles *via* ring closing metathesis of heterocycles carrying *gem*-diallyl substituents obtained *via* ring opening of (halomethyl)cyclopropanes with allyltributyltin. Mukund K. Gurjar, Somu V. Ravindranadh, Kuppusamy Sankar, Sukhen Karmakar, Joseph Cherian, Mukund S. Chorghade, *Org. Biomol. Chem.* **2003**, 1366.
2. Synthesis of aminocarbocycle with a quaternary carbon center: Application of carbohydrate based cyclopropylmethyl radical. Kuppusamy Sankar (manuscript communicated).

Erratum