DEVELOPMENT OF ASYMMETRIC ROUTES TO BIOLOGICALLY ACTIVE CYCLIC MOLECULES: SYNTHESIS OF CARBOCYCLES AND HETEROCYCLES

By

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DECLARATION

I, hereby declare that the investigation presented in the thesis has been carried out by me. The work is original and has not been submitted earlier as a whole or in part for a degree / diploma at this or any other Institution / University.

Sibanarayan Tripathy.

Sibanarayan Tripathy

Dedicated to my

Beloved

BOU and NANA

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.....Siba (Pintu)

Live as if you were to die tomorrow. Learn as if you were to live forever.

Mahatma Gandhi

CONTENTS

SYNOPSIS

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SYNOPSIS

Organic compounds form the basis of earthy life. One of the characteristic features of life is that many of its functions are controlled by highly enantioriched molecules. Thus, chiral homogeneity of biomolecules *i.e.* homochirality is one of the desired aspects of many life processes and is thought to be closely related to the origin of life. In this perspective, chemists and biologists have been jointly exploring the functions of different classes of chiral organic molecules in living systems for over a century. It began with the discovery of glucose, amino acids, vitamins, hormones, neurotransmitters, lipid mediators and many others. Especially, during the second half of the 20th century, there has been a continuous increase in the use of a variety of chiral organic molecules of relatively smaller sizes as probes (tool compounds) to study different life processes.[1] Consequently, synthetic chemists over the years continue to play a tremendous role by preparing a variety of molecules in their optically pure form possessing diverse structural features that have desired therapeutic or other biological activities. Furthermore, in many collaborative research programs efforts were also directed to utilize various chiral synthetic analogues to have an insight view of several biological processes.

In view of the aforementioned facts, during the last several decades considerable attention has been focussed on asymmetric synthesis of different classes of organic molecules of biological relevance in their homochiral form. In this pursuit, development of efficient asymmetric synthetic strategies for various complex molecules, many of which contain multiple stereogenic centres remained a great challenge to organic chemist till date. It is well known that a large variety of biomolecules possess cyclic structural skeleton *viz.* macrolides[2] of different sizes, cyclic peptides,[3] nucleosides,[4] different sugars, small sized lactones[4c] etc. Thus, over the years synthesis of cyclic biomolecules has become the topic of considerable attention of both organic and bio-organic chemists

in order to study their biological efficacy in varied areas. In the same vein, the present thesis describes a number strategies developed by us for asymmetric syntheses of several types of biologically relevant chiral molecules possessing cyclic structures. Throughout this entire work we focussed on the development of operationally simple and practically viable asymmetric strategies to prepare our target molecules. About asymmetric strategies adopted by us, we emphasized on utilizing easily accessible chiral templates (*R*)-2,3-*O*-cyclohexylideneglyceraldehydeof (**D**)-mannitol origin[5] and TBDMS-derivative of 2,3-*O*-cyclohexyledene-(**L**)-threose of (**L**)-(+)-tartaric acid origin[6] in versatile manners, performing several metal mediated stereo-differentiating allylations/alkylations[7] of prochiral carbonyls etc. The thesis has been divided into five chapters *viz.* **Chapter-1** (Title: **Introduction to asymmetric synthesis**), **Chapter-2** (Title: **Stereo divergent route to the 2′,3′-carbocyclic core of Olefinic carbocyclic nucleoside: Synthesis towards Carbovir**), **Chapter-3** (Title: **Stereodivergent route to 1,4-disubstituted-2′,3′-carbocyclic core of 5′-olefinic carbocyclic nucleoside : Formal synthesis of Homocarbovir**), **Chapter-4** (Title: **Versatile route to carba-furanose via intramolecular allylation**) and **Chapter-5** (Title: **Synthesis of oxygenated heterocyclic bioactive molecules**).

Chapter-1: Introduction to asymmetric synthesis

This chapter initially deals with the relationship between biology and chemistry and then elaborates the role of organic molecules for a sustainable life. Also, there will be a brief discussion on the perception of chirality and the physico-chemical properties of some chiral molecules commonly encountered in our day to day life.[8] Subsequently, there will be sequentially a brief discussion on stereo-differentiating reaction, introduction to different methods of asymmetric induction and the role of kinetics and thermodynamics that governs the selectivity of the formation of one diastereomer over the other in a

stereo-differentiating reaction.[9] As mentioned earlier, a good part of our asymmetric strategy in the present work relied on judicious exploitation of an easily accessible chiral template (*R*)-2,3-O-cyclohexyledenegleceraldehydeand several stereo-differentiating reactions[8,10] with it or other templates derived from it. Hence, it will be appropriate for us to explain the stereodifferentiation of some of these reactions in brief and different parameters related to acyclic stereocontrol[11] in this chapter using various theoretical models like Felkin-Anh,[12] Cram chelate[13], Zimmerman-Traxler[14] etc. Also, in this chapter there will be a discussion on some of the crucial reactions performed by us in this work *viz.* Grubbs RCM[15], Wittig olefination,[16] Luche's allylation,[17] allylation/crotylation employing bimetal redox strategy[7d,7f,7h] etc.

It needs to be mentioned at this point that a good part of work in this thesis described the strategies developed by us for the construction of different types of carbocyclic molecules which serve as the frame work of different carbocyclic molecules of biological relevance *viz.* analogues of natural nucleosides, carbasugars etc. Accordingly, we attempted to divide our work on carbocycles syntheses in a three chapters (2, 3 & 4) while chapter 5 described our work on the synthesis of oxygenated heterocycles (substituted tetrahydrofuran and macrolides).

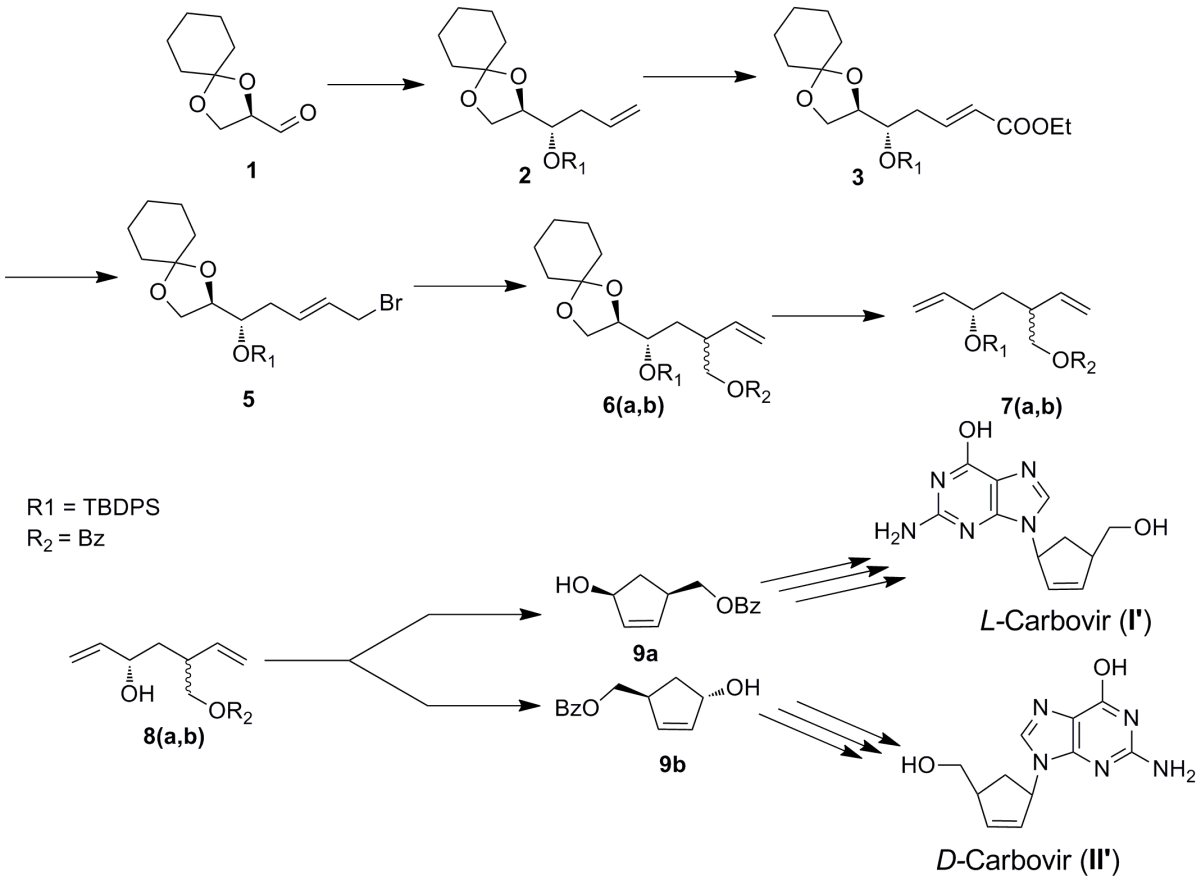
Chapter-2: Stereo divergent route to the 2′,3′-carbocyclic core of Olefinic carbocyclic nucleoside: Synthesis towards Carbovir.

Since the emergence of 3′-azido-3′-deoxythymidine (AZT) as an agent for the treatment of acquired immunodeficiency syndrome (AIDS), considerable attention has been focussed on the developments of different variety of sugar modified nucleosides[4b] in the search for superior compounds that are more efficacious with respect to their stability as well as selectivity in operation. This led to considerable thrust on the search of

carbocyclic nucleosides where the furanose oxygen of the natural ones is replaced by a methylene group. The absence of glycoside moiety makes these structural analogues of natural nucleosides to have greater metabolic stability. It has been observed that several carbanucleosides have prominent anti-viral and antitumor therapeutic properties.[18] Included among carbanucleosides are a number of olefinic nucleosides with **D**-configuration *viz.* **D**-(-)-carbovir,[19] a potent and selective inhibitor of HIV reverse transcriptase (as its triphosphate), its pro-drug abacavir,[20] carbocyclic 2′,3′-didehydro-2′,3′-dideoxyadenine,[21] entecavir[22] etc. Furthermore, it has been observed that (*L*)- (+) carbovir showed both anti HIV and anti HBV activities.[23] This chapter describes our successful effort to develop an easy and stereo divergent approach towards the syntheses of both (**D**)-(-) (**I′**) - and (**L**)-(+) (**II′**) carbovir. In this work we prepared the corresponding 2′, 3′-carbocyclic core of both these isomers of carbovir from **1** which is outlined below (**Scheme 1**).

2.1 Synthesis of (±) Carbovir

The schematic synthesis of both **D**- and **L**- diastereomer of carbovir is being explained in **Scheme 1**.We began our work with the silylated homoallyl alcohol (**2**) derived from **1**. This was converted into (2*E*)-unsaturated ester (**3**) *via* ozonolysis of **2** and Wittig Horner olefination of the resulting aldehyde. Later it was converted to the substituted allyl bromide **5** in two steps. In the next crucial step, a C-branching in the carbon chain of **5** was introduced



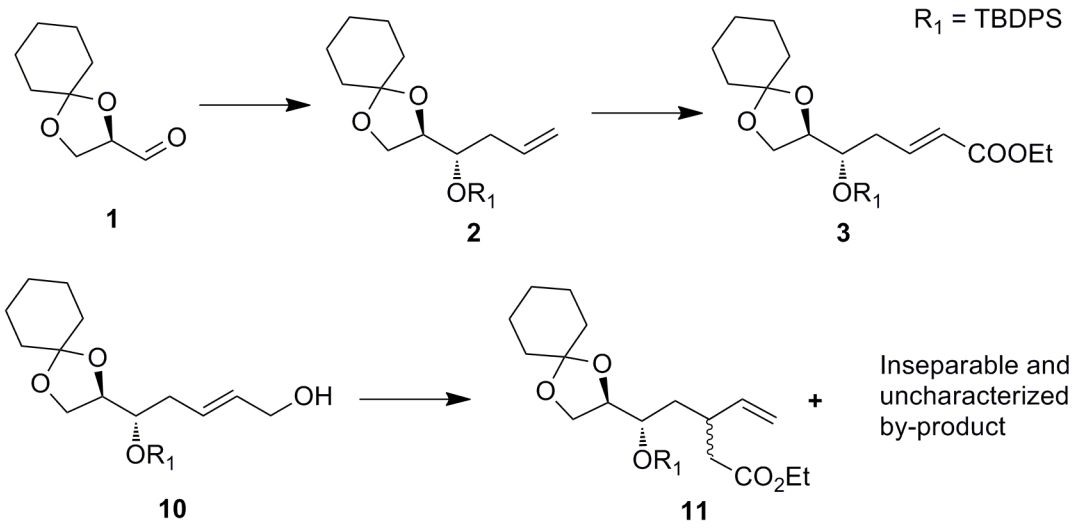
Scheme 1

by its reaction with gaseous formaldehyde following Luche's allylation procedure which took place with moderate stereoselectivity to yield **6** as a mixture of chromatographically inseparable diastereomers (**6a,b**). This was converted into diastereomeric mixture of di-olefin (**7a,b**) in three steps. Its desilylated product (**8a,b**) was subjected to Grubb's RCM reaction to afford a mixture of **9a,b** which was nicely separable from each other by column chromatography. Both **9a,b** could be treated as the precursors for formal syntheses of (**L**)- and (**D**)- carbovir respectively following usual reaction protocols.

Chapter-3 Stereodivergent route to 1,4-diisubstituted-2′,3′-carbocyclic core of 5′-olefinic carbocyclic nucleoside : Formal synthesis of Homocarbovir.

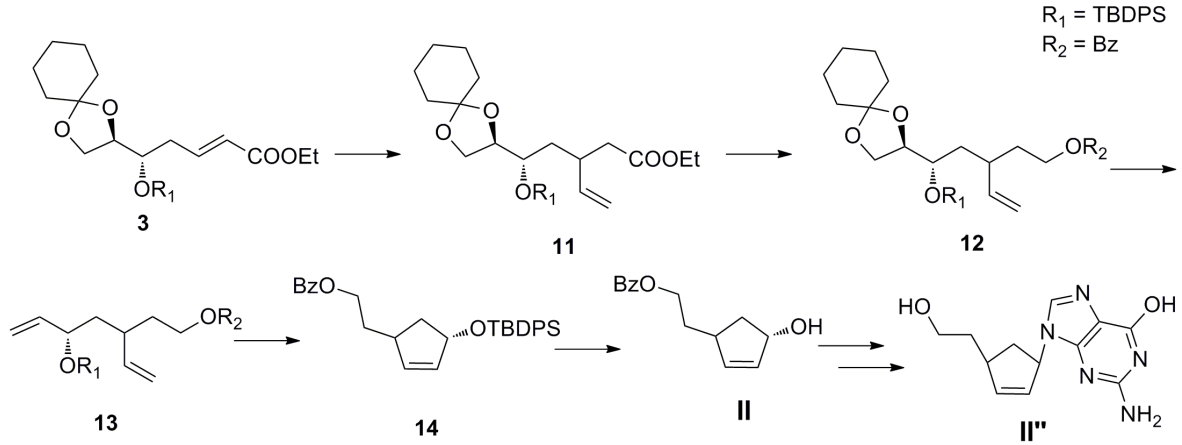
Carbovir and Abacavir are among the synthetic five membered carbocyclic ring bearing nucleosides, both are well known to show a great degree of antiviral and anticancer activities. In order to have a great library of antiviral drugs, other analog of carbocyclic nucleosides are to be synthesized and its biological activities are to be studied to have lesser side effects and with higher activity against the virus infection. Along with the success of carbovir, there has been continued interest in the syntheses of new analogues to search for better antiviral activity. Accordingly, a new class of 2′,3′-olefinic carbanucleosides has been developed which is termed 5′-homocarbovir (**II′′**). Structurally, **II′′** has one CH_2 unit more in the 4′-C carbon chain of their carbocycle core with respect to carbovir. Its synthesis has drawn considerable attention in recent years.[24] We have developed a stereoselective strategy for the 2′,3′-olefinic carbocyclic core of 5′-homocarbovir.

In this case our synthetic endeavour started with the silylation of the *anti*- homo allyl alcohol (**2**) which had been obtained as the major product by Luche's allylation of (*R*)-2,3-*O*-cyclohexylideneglyceraldehyde (**1**) (**Scheme 1**) from which the *α,β*-unsaturated conjugated ester (**3**) was obtained as explained in **scheme 1**. In the first attempt to introduce the side chain the allylic alcohol (**10**) obtained by the reduction of **3** was subjected to Claisen ortho ester rearrangement. The rearranged product (**11**) was associated with a substantial amount of unwanted by product which was difficult to separate even after reduction of the ester to alcohol (**Scheme 2**).



Scheme 2

Due to such non separability of the complex mixture of products (**Scheme 2**) it was difficult for us to proceed further. Hence, we decided to make an effort to have access to intermediate **5** following an alternate approach which has been outlined in **Scheme 3**. In this case the *α,β*-unsaturated conjugated ester (**3**) was subjected to a crucial 1,4-conjugated vinyl addition on treatment with vinyl cuprate at -78^{0}C. The reaction took place with absolute stereoselectivity producing the only diastereomer **11** in good yield**.** This was transformed into



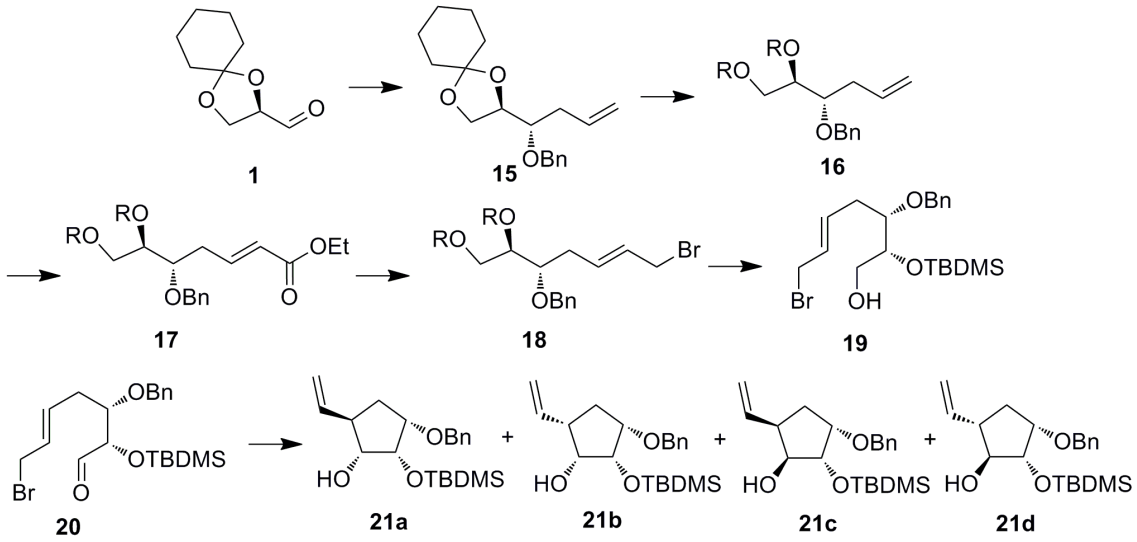
Scheme 3

the benzoylated alcohol **12** by reduction of the ester followed by protection of the resulting alcohol by benzoyl group. The resulting intermediate **12** was converted to diene

13 in three steps. Next, Grubbs RCM reaction of **13** afforded **14** which possess the basic carbon skeleton of Homocarbovir. This on desilylation afforded **II**, a precursor for formal synthesis of 5′-homocarbovir **II′′**.

Chapter-4: Versatile route to carba-furanose via intramolecular allylation

This chapter describes a versatile route to the construction of sterically diverse carbasugars where the endocyclic oxygen of furanose sugar is replaced with a methylene group. These sugar analogues are being used to construct the sugar modified carbocyclic nucleoside, glycosidic inhibitors,[25] many other bioactive compound like prostraglandins[26] and also used as mimicking agent to normal sugars in biological system. These pseudosugar can be linked to another carbasugar or carbohydrate to form pseudo disaccharides which mimics the natural disaccharides that are stable towards hydrolysis[27]



Scheme 4

There is a continued demand for the study of the chemistry and the biological application of such structures. For this, a library of carbasugars with diverse structures as well as stereochemistry needs to be synthesised. The present work, described our effort in this direction.

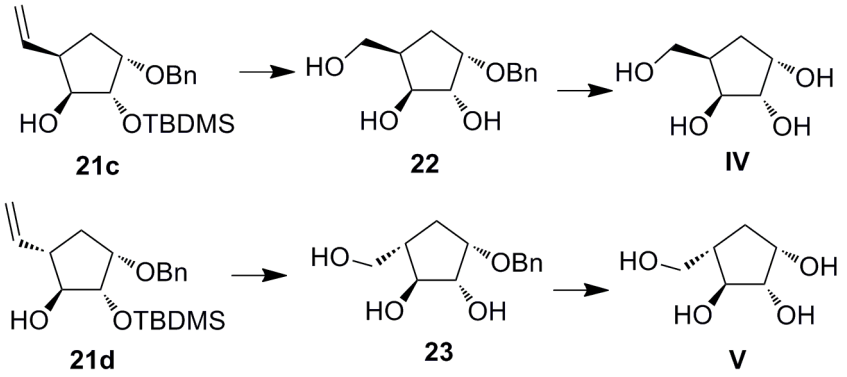
The synthetic endeavour started with benzylated homoallyl alcohol **15** obtained from **1** as described in **Scheme 4**. This on ketal hydrolysis, followed by disilylation gave **16** whose terminal olefin was manipulated in a similar fashion as done by us earlier (**Scheme 1**) to afford allylic bromide **18**. Conversion of **18** into aldehyde **20** was effected *via.* selective desilylation and oxidation. Next, in a crucial step carbafuranose moiety (**21**) was constructed by subjecting **20** to intramolecular metal mediated allylation reaction. With a view to attaining its practical viability this crucial allylation reaction was performed in wet conditions in presence of five different metal mediators *viz.* Luche's [17] zinc three low valent metals iron, copper and tin[7d,7f,7h] and metal indium.[28]Here, the successful reactions took place along with simultaneous generation of its two stereo-centres at its C-3 and C-4 producing **21** as a mixture of four diastereomers (**21a-d**). The efficacy as well as stereoselectivity of all the reactions have been outline in **Table 1** and will be discussed in detail in the thesis.

Table 1: Intramolecular allylation of aldehyde **20**

Entry	Metal/salt or Metal salt/ metal	Solvent	Time(hr)	Overall yield of **21** (%)	**21a & 21b:21c:21d**[a]
a	Zn/ NH_4Cl	THF	18	74.7	8.7: 20.8: 70.5
b	$FeCl_3$/Zn	THF	18	68.2	10.2: 23.2: 66.6
c	$SnCl_2.2H_2O$ / Zn	THF	18	87.5	11.4: 62.7: 25.9
d	$CuCl_2.2H_2O$ / Zn	THF	18	NR	-
e	In	H_2O / THF	48	NR	-

NR: No reaction; a) relative ratio of chromatographically separated product

The stereochemistry of **21c** could be established by transforming it into a known carba α-**D**-xylofuranose through a number of steps **(Scheme 5)** that involved its functional manipulation only without affecting any of its stereo-centres. Accordingly, **21c** was subjected to a series of reactions *viz*. a) ozonolysis, b) reduction of the crude aldehyde obtained by $LiAlH_4$ which took place with concomitant desilylation to afford **22**. This on



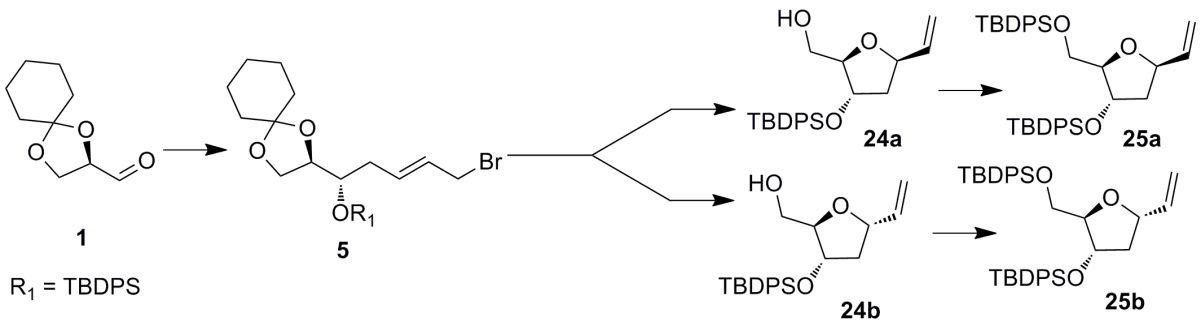
Scheme 5

catalytic hydrogenation afforded **IV** whose optical and spectral data were in well conformity with the reported ones.[29] Following the same reaction protocols, **21d** was transformed into carba-β-**L**-arabinofuranose **V** through intermediate **23**. The optical as well as spectral data of our synthesized **V** were in accordance with the reported ones.[30]

Chapter-5: Synthesis of oxygenated heterocyclic bioactive molecules

5.1- Stereo divergent synthesis of 2, 3, 5-trisubstituted tetrahyrdofurans.

This part of the chapter describes simple and stereo divergent strategy for the syntheses of both *cis* and *trans* 2,3,5-trisubstituted tetrahyrdofurans. Several naturally occurring compounds especially a wide variety of important polyethers,[31] antibiotics,[32] contains tetrahydrofuran rings with a diversity in substitution pattern and stereochemistry.

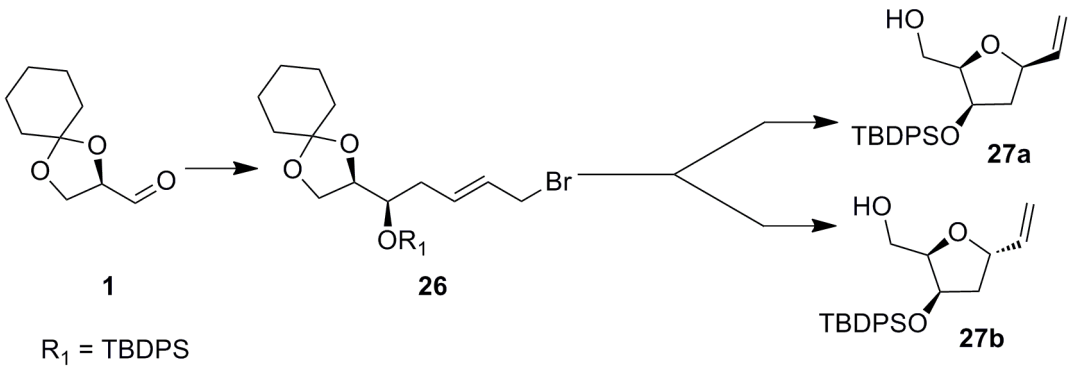


Scheme 6

Among the other applications these kind of the molecules are being used for the recognition of inverted base pairs within the DNA triple helix.[33]

We have developed a simple and efficient route to have access to two types of 2,3,5-trisubstituted THF (**24**) starting from **1**. Compound **5**, which had been prepared earlier (in **Chapter 2**), was treated with trifluoro acetic acid. The reaction directly yielded **24** as a mixture of two diastereoisomers (**24a,b**), via deketalisation, followed by intramolecular conjugate addition of 2° hydroxyl to allylic bromide. The reaction took place with moderate stereoselectivity producing around similar proportion of both the THF isomers (**Scheme 6**). The two diastereomeric furans were separable from each other by column chromatography and could be identified from their spectral and optical data that were in conformity with the reported ones.[33]

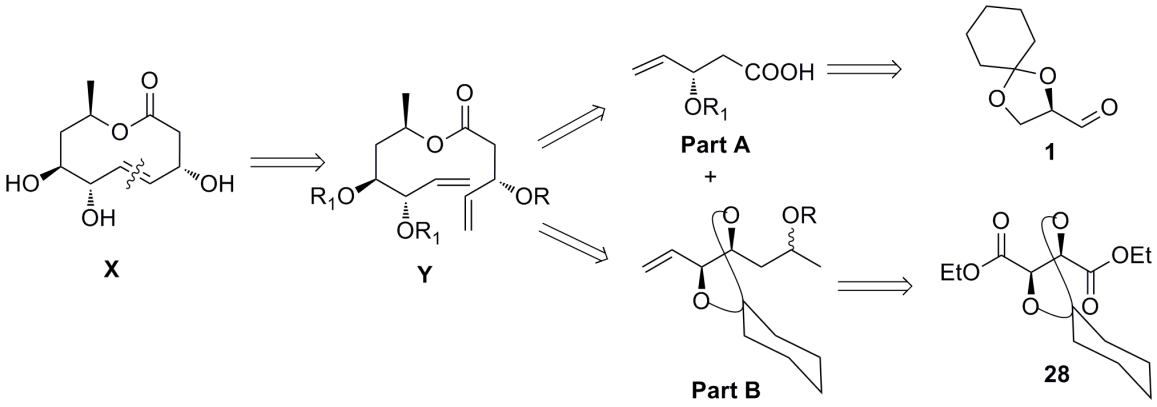
We next, turned our attention to employ the same strategy with the corresponding syn-isomer (**26**) of **5**. This was treated with trifluoro acetic acid to produce a diastereomeric mixture of two trisubstituted tetrahyrdofurans (**27a,b**) with moderate selectivity. Here both the stereoisomers were difficult to separate from each other by column chromatography (**Scheme 7**).



Scheme 7

5.2: Total synthesis of Decarestrictine O

This part of the chapter deals with the synthesis of Decarestrictine-O (**X**) a secondary metabolite which belongs to the family of decanolides.[34] These classes of compound are important due to their cholesterol inhibiting properties. These properties are important particularly for the treatment of coronary diseases; this has prevalent importance in Indian scenario due to higher fat food habits and also genetic factors.

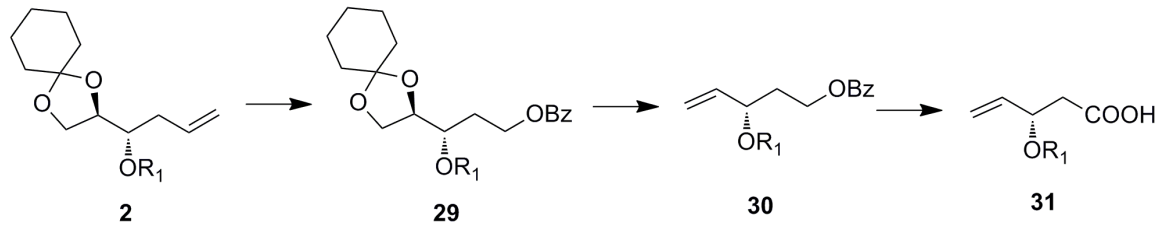


Scheme 8

Retrosynthetic analysis of **X** suggested that its synthesis could be achieved by combination of two olefinic fragments (**A & B**) through RCM strategy. Accordingly, we are developing efficient and stereoselective routes for the preparation of both theses fragments starting from **1** and (**L**)- (+)-tartaric acid respectively (**Scheme 8**).

Fragment A:

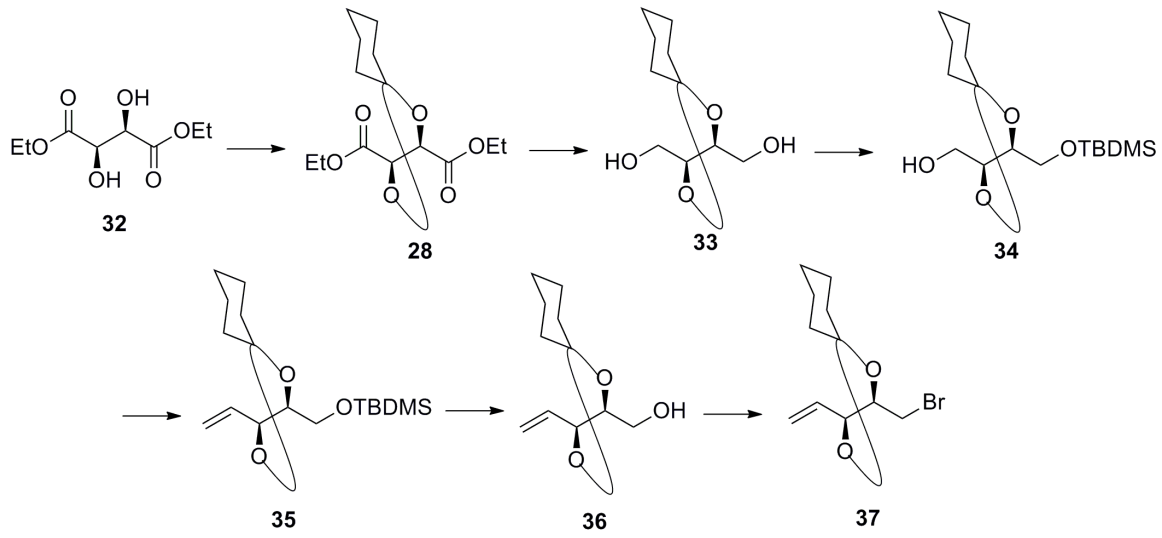
Cleavage of the terminal olefin of compound **2** by ozonolysis and subsequent reduction afforded the corresponding alcohol which was protected (benzoate) to obtain **29** (**Scheme 9**). Acid hydrolysis of ketal moiety of **29** afforded diol which was converted into a terminal olefin **30** through di-tosylation and subsequent reaction with Zn/NaI. Compound **30** was subject to de-benzoylation and PDC oxidation will afford fragments **A** (**31**).



Scheme 9

Fragment B:

Oxidation of monoprotected diol (**33**) obtained from commercially available (**L**)-(+)-diethyl tartarate (**32**) to the corresponding aldehyde followed by Wittig olefination of the corresponding aldehyde with methyltriphenylphosphonium iodide gave olefin (**35**). The olefin was subjected to desilylation to produce alcohol **36** which was subjected to modified Apple's reaction [35] to give the bromide **37**. The bromide will be subjected to lithiation reaction with Li metal followed by *in situ* reaction of the corresponding organo lithium with freshly distilled acetaldehyde will produce the desired alcohol. This will afford alcohol fragment **B**. Later, fragment **A** and **B** will be condensed and the bisolefin product will be subjected to RCM reaction to obtain the core structure of **X** as proposed in **Scheme 8**.



Scheme 10

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A. Published:

1. Chattopadhyay, A.; Tripathy, S. Stereodivergent route to the carbocyclic core of 2',3'-olefinic carbanucleosides: toward the synthesis of (L)-(+)- and (D)-(-)-carbovir. *J. Org. Chem.* **2011**, *76*, 5856–61.

B. Accepted:

1. Tripathy, S.; Chattopadhyay, A. (R) -2 , 3-O-Cyclohexylideneglyceraldehyde : a Useful Template for a Simple Entry into Carbafuranose Stereoisomers *Tetrahedron Asymmetry* **2012** (in press).

C. Manuscript under preparation.

1. Tripathy, S.; Chattopadhyay, A. A stereoselective route to carbocyclic core of 2',3'-olefinic carbanucleosides: towards the synthesis of homocarbovir.

D. Abstract presented in national conferences.

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2. Tripathy, S.; Chattopadhyay, A. A Simple and Stereodivergent routetowards the synthesis of of (L)-(+) - and (D)-(-) – Carbovir, Research Scholar's Meet 2012,

Indian Chemical Society Mumbai Branch, SIES college, Mumbai-India (oral presentation- 2012)

Signature of the student:

(Sibanarayan Tripathy)

Date:

Doctoral Committee:

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2.	Prof.(Dr.) Angshuman Chattopadhyay	Guide & Convener		
3.	Prof.(Dr.) Sunil K. Ghosh	Member		
4.	Prof.(Dr.) Sharmila Banerjee	Member		

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LIST OF ABBREVIATIONS

BINAP	2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl
HOMO	Highest occupied molecular orbital
LUMO	Lowest unoccupied molecular orbital
DMF	Dimethylformamide
THF	Tetrahydro furan
DCM	Dichloro methane
DMAP	4-Dimethyl amino pyridine
DMSO	Dimethyl sulfoxide
TFA	Trifluoro acetic acid
DEAD	Diethyl azodicarboxylate
TBAF	Tetra-n-butylammonium fluoride
DIBAL-H	Diisobutylaluminium hydride
LAH	Lithium aluminium hydride
DIAD	Diisopropyl azodicarboxylate
RCM	Ring closing metathesis
HMPA	Hexamethylphosphoramide
DIPEA	N,N-Diisopropylethylamine
NMO	N-Methylmorpholine N-oxide
PDC	Pyridinium dichromate
PCC	Pyridinium chlorochromate
DHP	Dihydropyran
PTSA	p-Toluenesulfonic acid
PPTS	Pyridine p-toluenesulfonate

CHAPTER 1

Introduction to Asymmetric Synthesis

1.I Chemistry & Biology……..

The two phonetically different words Chemistry and Biology although are two distinct branch of science but their cross section can be defined by the most cited statement **"Cells obeys the laws of chemistry"**. This is the succinct definition of the relationship between the two parts of science. In this context, it is worth mentioning some of the lines of the famous paper by Watson and Crick**: "*We wish to suggest a structure for the salt of deoxyribose nucleic acid (D.N.A.). This structure has novel features which are of considerable biological interest*"**.[1] Biology which was previously thought to only relate to the living organism has changed its definition from the science of living to the true molecular science after the structural elucidation of DNA and understating its role in fundamental process of life. While scientist thought that the science of living is a molecular science; Arthur Kornberg made an important caution about the relationship between two scientific culture; that these two are from two distinct culture and the gap between them is serious, unappreciated, and counterproductive.[2] But to our delight the continued development in science and working hand in hand both chemist and biologist are able to bridge that gap and particularly the field of genomic research was able to erode the boundary of differences in culture.

Chemists and biologists have been exploring the functions of different molecules in living systems for over a century, beginning with the discovery of glucose, amino acids, vitamins, hormones, neurotransmitters and many others. The basic structure of Chemistry-Biology correlation can better be understood with provisos as chemistry explains the biological phenomena with the language of chemical processes, principle and molecular structures. This relation is better explained with the Wöhler's experiment where he prepared urea a well-known biological substance by heating the abiotic compound ammonium cyanate.[3] In his letter to his mentor Jöns Jakob Berzelius, Wöhler

wrote: "***I cannot, so to say, hold my chemical water and must tell you that I can make urea without thereby needing to have kidneys, or anyhow, an animal, be it human or dog***". The results of Wöhler's experiment triggered two important conceptual changes; it falsifies the vital force theory which was considered essential for the generation of substances of biological (i.e., natural) origin and it represents the birth of organic chemistry as a discipline.

1.II Organic Chemistry……..

"**Organic synthesis**" is a compound-creating activity mostly focused on the syntheses of biologically active molecules.[4] During the second half of the twentieth century it is well understood, that with the structural information of different biomolecules, their role in biological systems can be interpreted in terms of molecular interaction.

Organic synthesis contributes to the discovery of biologically active small molecules in several ways. By yielding structurally diverse small molecules having features well suited for binding macromolecules, it delivers starting points for probes or drugs. Structure/activity relationships resulting from the strategic synthesis of analogs are central to the identification of optimized variants of the starting compounds. Efficient syntheses of the optimized variants are essential for practical applications of probes and drugs.

1.III Asymmetric Synthesis……

The profound development in stereochemistry was greatly influenced by the visionary statements by Louis Pasteur about 100 years ago, "***Life is dominated by dissymmetrical actions……***". Today in modern chemistry *chirality* is an important term to describe dissymmetry. Chirality whose grammatical congener is handedness can be explained with the help of a pair of hands like which the two enantiomers of a chiral

compound are the mirror images of each other which cannot be superimposed (**Figure 1.1**).

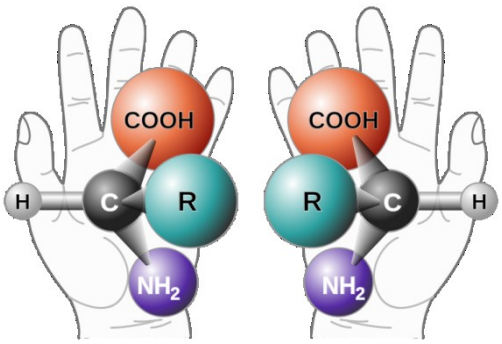


Figure 1.1 Non superimposability of mirror images

It is worth mentioning that although the two enantiomers have same physical and chemical properties but they have different chiral surroundings which results in their different behavior with respect to any given biological activity. As a result of this, synthesis of any bioactive molecule in enantiomerically pure form is of high importance which brings about the need of asymmetric synthesis. In technical term " *Asymmetric synthesis is a reaction or a sequences of reactions that selectively creates one configuration of one or more new stereogenic elements by the action of a chiral reagent or auxiliary, acting on heterotopic faces, atoms, or groups of a substrate. The stereoselectivity is primarily influenced by the chiral catalyst, reagent, or auxiliary, despite any stereogenic elements that may be present in the substrate*."

1.IV Significance of chirality and stereoisomeric discrimination……

Nonsuperimposable mirror image is the basic criteria for a molecule to be called as chiral. In such case there is a possibility of existing two forms of the same object which are related to each other by mirror are called as *enantiomers* and the relation between two object is called enantiomeric. Taking the simple example of the compound "cabcd" form

i.e. lactic acid which can be obtained in two forms of enantiomers **A** and **B** and they are related to each other by mirror image and are nonsuperimposable (**Figure 1.2**).

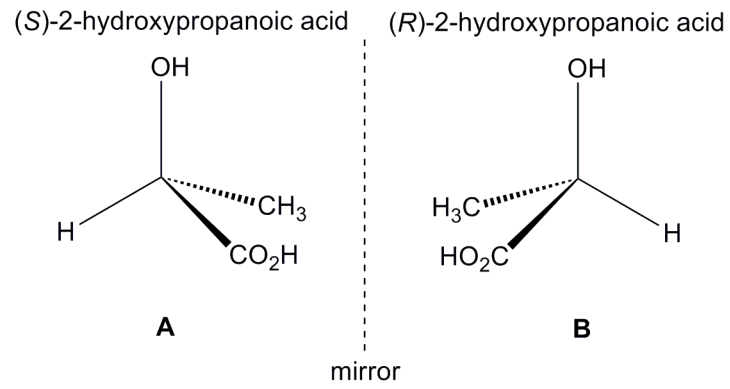


Figure 1.2 Mirror image of enantiomer

As discussed earlier the enantiomeric compounds have identical chemical and physical properties in an achiral environment i.e. in the absence of any external chiral influence. With the example of **A** and **B** it is to be understood that both of these molecules has same melting point, NMR spectroscopy, IR Spectroscopy, retention time in chromatography etc. however enantiomeric compounds differs from each other and achiral compounds only with one property i.e. how they rotate the direction of plane polarized light which is called as *optical activity* or *optical rotation*. Thus the compound **A** which rotes the plane polarized light in anti clock wise direction can be called as (-)-lactic acid while the compound **B** which rotates the plane polarized light with exactly same and opposite direction can be called as (+)-lactic acid. The mechanism for recording the direction of rotation of plane polarized light is understood from **Figure 1.3**.

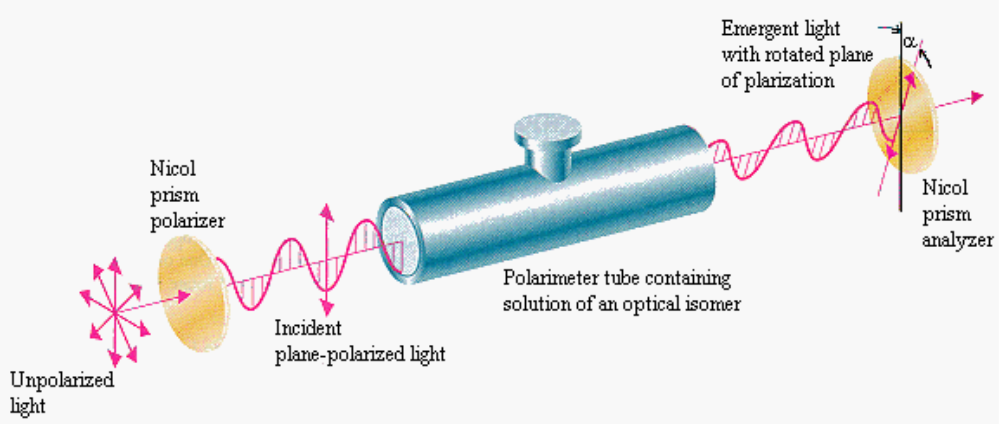


Figure 1.3 Principle of optical rotation

Although chiral compounds have same physical and chemical property in achiral environment but they behave differently in chiral environment. As most of the biological macromolecules exits in one enantiomeric form only the chiral biologically active molecules interacts with its receptor in a chiral manner. Hence the biological receptors can discriminate the enantiomers in a very different way. Thus the two enantiomer of the same drug may interact differently leading to different effects. Since the enzymes and receptors on cell surface are chiral the two enantiomers of a racemic drug may show different pharmacokinetic behavior starting from absorption, degradation and elimination from the body which is the basis of their different kind of activity.[5] Such differences can be exemplified from the activities of d- and l-DOPA where only l- enantiomer is being used as a drug for the treatment of Parkinson's diseases, but d- isomer is not effective. The active drug Dopamine is formed after *in-vivo* enzyme catalyzed decarboxylation by l-DOPA-decarboxylase enzyme. Since the active drug dopamine can't cross the blood brain barrier to reach the active site, it is administered in its prodrug form as l-DOPA (**Figure 1.4**). Out of the two stereoisomers of DOPA only l-DOPA is specifically decarboxylated by the enzyme for which it is essential to administer l-DOPA in its enantiomeric pure form.[6] The racemic mixture of d- and l-DOPA is not advisable as a drug because the d-

form cannot be metabolized by human body and further accumulation of unwanted d-form may cause some serious problem.

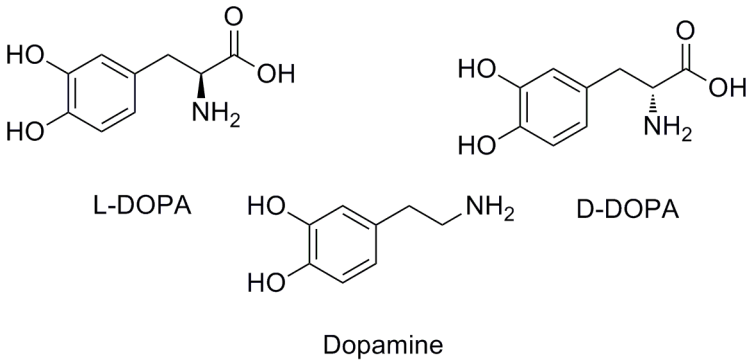


Figure 1.4 Active and inactive enantiomer

With the example of stereoisomers of DOPA it is quite evident that in biological system the stereoisomeric discrimination is a most prominent feature and for which the chirality of the active site of macro biomolecules like enzyme, receptors *etc.* plays the central role. The biological activity of the chiral compounds can broadly be divided in to four categories

1. Only one enantiomer has the desired bio activity
2. Both have equivalent or nearly equivalent activity
3. Both have quantitatively different activity
4. Both have completely different kind of activity

The following **Figure 1.5** contains a number of examples of enantiomers having difference in properties. Some of the examples listed have difference in taste, odor moreover difference in pharmacological behavior. Starting with the example of **D**- and **L**-limonene where **L**- enantiomer is responsible for the smell of lemon and the smell of orange comes from the **D**- enantiomer, similarly (*S*)-carvone has caraway odor whereas (*R*)-carvone has spearmint odor, the stereoisomer of asparagine differ in taste from each

other as the natural **L**-asparagine is bitter in taste at the same time the D-enantiomer is sweet to taste.

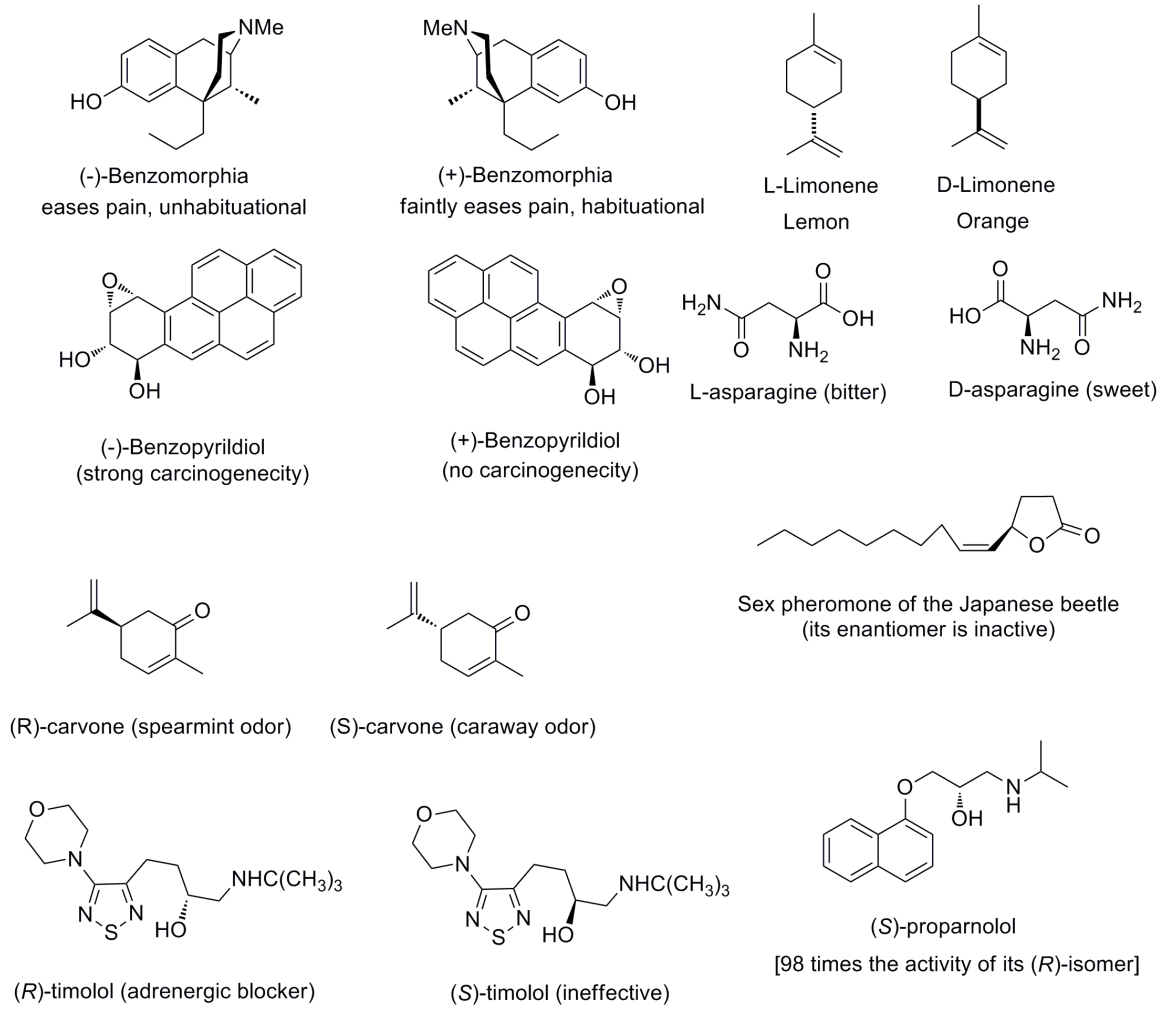


Figure 1.5 Enantiomers with different properties

In some cases both the enantiomers differ in their biological activity this is evident from the example of Disparlure, a sex pheromone of gypsy moth, which is used to trap the male gypsy moth. It has been reported that the (+) enantiomer is highly effective in very dilute concentration whereas (-)-Disparlure is inactive at very high concentration and also reduces the activity of (+)-Disparlure when present as a trace impurity.[7] Similar kind of activity has also been observed in the case of sex pheromone of Japanese beetle. In this case, the (*R*)-isomer has significant activity which could be reduced by three times when

contaminated with 2% of its (*S*)-enantiomer.[8] In some cases, the presence of one inactive enantiomer hardly interferes with the activity of the other. Considerable amount of bio-discrimination has been encountered in the field of chiral drug, herbicides, pesticides etc. For example, (*S*)-propranolol which is a *β*-blocker drug has as high as 98 times more activity than its (*R*)- counterpart.[9] Thalidomide which was used as a powerful sedative and anti-nausea agent especially during early pregnancy was administered as its racemic mixture. During 1950 it was found that the drug has serious teratogenic effect. Further study on the teratogenicity of thalidomide revealed that the (*S*)-enantiomer which has very little sedative effect is responsible for the teratogenic effect while (*R*)-isomer (active sedative) was not found to cause any deformities in animals even at very high dose.[10] Similarly the natural occurring (-)-nicotine has higher toxic effect over the unnatural (+)-nicotine.

The aforementioned examples clearly demonstrate the stereo-discrimination of enantiomers in biological system for which it is necessary to synthesize biologically relevant molecules in homochiral form. In view of this, development of enantiomeric synthesis of a molecule has assumed a great significance as this is a highly important requisite in pharmaceutical industries, since the enantiomers of any chiral drug is considered as two different entities in biological system. Enantiomeric synthesis of target compounds can be accomplished using different strategies which are discussed below in brief.

1.V General Strategies for Asymmetric synthesis

Asymmetric synthesis is a reaction or a sequence of reactions that creates selectively one configuration of one or more new stereogenic elements by the action of a chiral reagent or auxiliary, acting on hetero topic faces, atoms, or groups of substrates.

The stereoselectivity is primarily influenced by the chiral catalyst, reagent, or auxiliary, despite any stereogenic element present in the substrate

Today asymmetric organic synthesis has become an important tool for various studies like probing different reaction mechanism, determining absolute and relative stereochemistry, especially regarding the synthesis of optically pure compounds with biological importance. Industries particularly pharmaceutical industries have shown a many fold rise of interest in asymmetric organic reactions. In the present era a large fraction of the drugs, agrochemicals, food additives, perfumery compounds available in the market are of synthetic origin. Most of the times the desired target compounds were obtained by the resolution of corresponding racemates. As only one among the two compounds is useful hence most of the time half of the synthetic product was discarded. The process of resolution of racemates not only a wasteful practice it's a tedious repetitious and laborious process. Hence from the practical and economical point of view it's always better to discard the unwanted optical isomer at the earliest stage. In order to make an effective use of raw materials it's always better to choose an early step for the asymmetric operation in the asymmetric sequence and careful consideration of the convergent synthesis.

One of the important techniques that have been adopted to have enantiomerically pure compound is the resolution of racemates. Other methods involve chiral pool where readily available natural chiral compounds like amino acids, tartaric and lactic acids, terpene, alkaloids, carbohydrates etc are used to convert the target compound through appropriate functional and stereochemical manipulations. Another approach to obtain enantiomerically pure compound involves treatment of enzyme or the whole microorganism with a prochiral precursors. Along with enzymatic or the microorganism reactions during the last few decades the field of organic synthesis witnessed a

tremendous upsurge in the development of a variety of stereo-selective chemical reactions that complement the former.

1.V.I "Chiron" Approaches

Nature provides a wide array of chiral molecules with diverse structural features which can be used as starting materials. The natural repositories of such optically active and enantiomerically pure compounds are usually referred as the chiral pool materials.[11] Very commonly used natural compounds are the amino acids, terpenes, carbohydrates etc. Some of the well known chiral pool materials are shown in **Figure 1.6**.

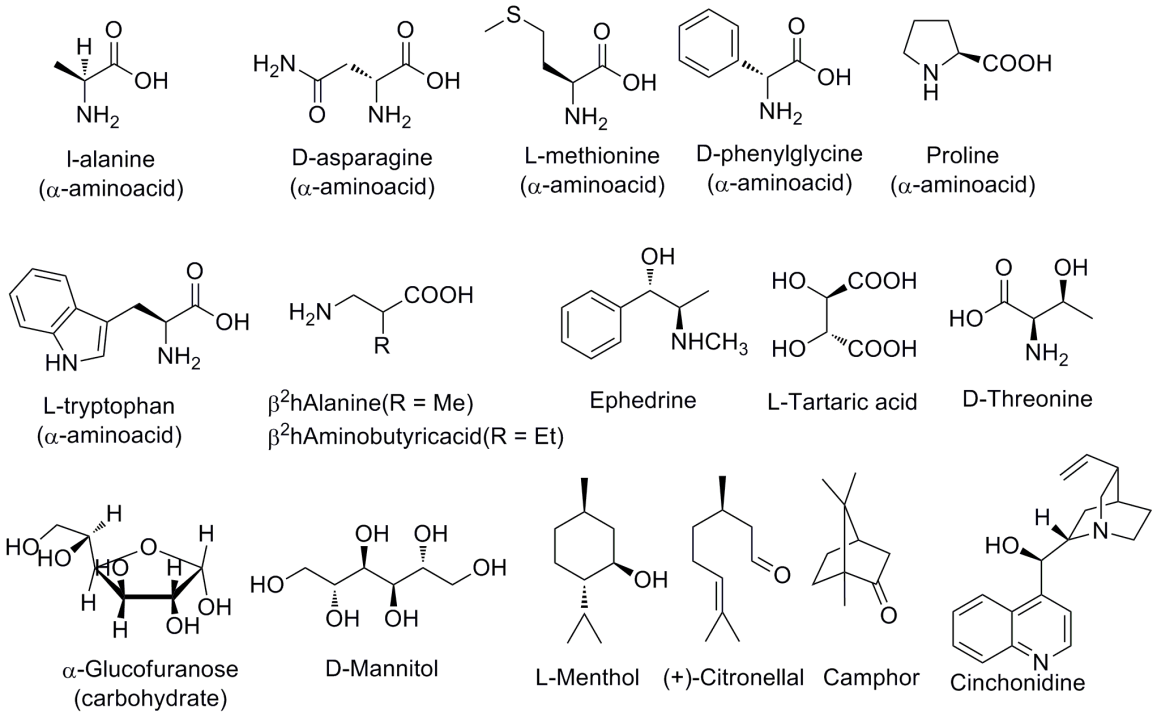
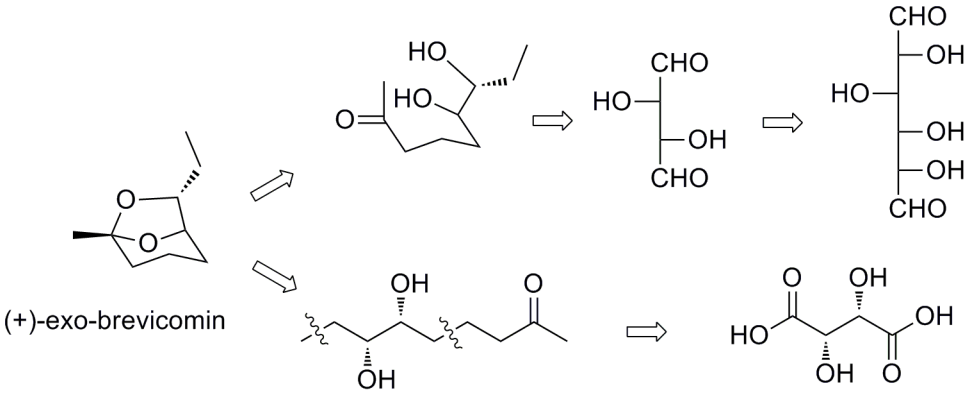


Figure 1.6 Possible chiral pool materials

Despite good availability of these chirons from natural sources in enantiomeric pure form, their utilization are restricted to the syntheses of the target molecules that have somewhat good resemblance with the starting chirons regarding the sequence of chirality as well as functionality. In addition, many times these molecules are available in nature in one of their enantiomeric form *viz.* naturally available carbohydrates and amino acids are

only available in the **D-** or **L-** configuration respectively. Hence it will be troublesome to synthesize target compounds that bear opposite stereochemistry with respect to the natural pool compounds at some of their stereo centers. Carbohydrates are the most preferred chiral starting material due to their possession of a series of contiguous hydroxyl stereo centers but it requires several protection and deprotection of these hydroxyls to exploit them elaborately. A well known example of this synthetic approach is the synthesis of (+)-exo-brevicomin, an aggregating pheromone of the western pine beetle synthesized both from tartaric acid[12] and glucose[13] the retro synthesis is shown in **scheme 1.1**.



Scheme 1.1

1.V.II Acyclic stereo-control approach

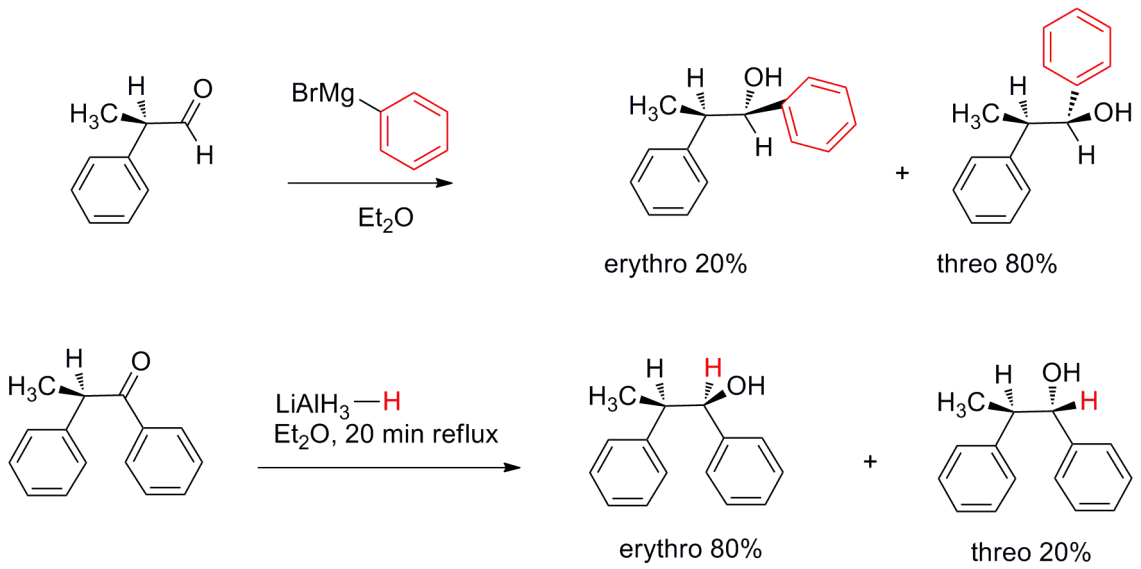
In view of the limitations of the Chiron approach mentioned above, synthetic chemists felt it highly necessary to prepare chiral molecules following alternate strategies. This led to the emergence of asymmetric synthesis of chiral molecules where the main motto was to perform a stereo-differentiating reaction at a carbon centre to impart chirality in it. Accordingly, during the last several decades' synthetic chemists' paid enormous attention on development of varieties of stereo-differentiating reactions to obtain various structural units with varied stereochemistry. In most of the cases, the

reactions progress through acyclic stereocontrol. The outcome of an asymmetric reaction depends on the diastereomeric transition state created by the combination of the substrate and reagent. There should be an element of chirality either on substrate or the reagent which influence the induction of asymmetry at the site of reaction. It's a usual practice to introduce the asymmetry by converting a trigonal carbon to tetrahedral at the site of functionality.

In principle asymmetric synthesis involves the formation of a new stereogenic unit in the substrate under the influence of a chiral moiety existing near the reaction site. This approach can be classified into four major categories depending on the mode of chiral induction taking place during the reaction: (1) substrate controlled methods; (2) auxiliary-controlled methods; (3) reagent-controlled methods, and (4) catalyst-controlled methods.

1.V.II.I Substrate controlled methods

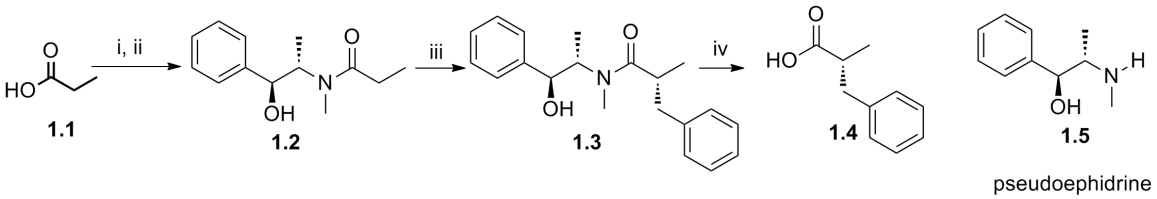
These kinds of reactions are more often referred as first generation of asymmetric synthesis in which the new stereogenic center is generated by the reaction of an achiral reagent at a diastereotopic site of the substrate. The stereochemistry of the new center largely depends on the preexisting chirality of the substrate near to the site of reaction. A good example is provided by the addition of Grignard reagent of Bromobenzene to (*R*)-2-phenylpropionaldehyde and lithium aluminium hydride (LAH) reduction of (R)-1,2-diphenyl-1-propanone to give a mixture of threo and erythro product with different ratio in two different cases (**Scheme 1.2**). During the Grignard reaction the major product was threo (80%) where as in case of reduction the threo product was minor (20%).[14] The addition reaction to the carbonyl group is influenced by the adjacent stereogenic centre in accordance to Cram's rule (discussed later).



Scheme 1.2

1.V.II.II Auxiliary controlled methods

The auxiliary controlled reactions are more often referred to as the second generation of asymmetric organic reaction. This approach is almost similar to substrate controlled approach in which the asymmetric control was achieved intra molecularly by the influence of a stereogenic unit that already present in the molecule. The difference between this two approach lies with the fact that in this case the stereo directing group "chiral auxiliary" is deliberately attached to a originally achiral substrate in order to carry out the enantioselective reaction. This chiral auxiliary is an enantiomerically pure compound whose chirality is used to provide bias in the stereoselectivity at the site of asymmetry. The auxiliary is removed in the subsequent reactions and is reused in other reactions. After removal of the auxiliary, the final product is obtained in very high enantiomeric excess. An example is the diastereoselective alkylation of propionic acid **1.1** via its amide formation with ([1S, 2S]-(+))-Pseudoephedrine to give **1.4** in >97% ee **(Scheme 1.3)**.[15]

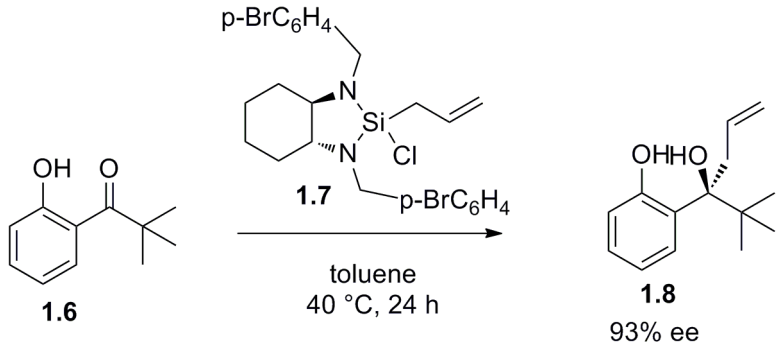


i) $SOCl_2$, pyridine; ii) pseudoephedrine, reflux; iii) $PhCH_2Br$, 2 equiv. LDA, 6 equiv. LiCl, THF, 0 °C; iv) H_2SO_4, dioxane.

Scheme 1.3

1.V.II.III Reagent controlled methods

The two extra steps involved in the second generation asymmetric synthesis namely the attachment and the removal of the auxiliary sometimes very cumbersome, brings a major drawback to this approach. The reagent controlled method which is otherwise called as the third generation of asymmetric synthesis takes the advantage of inducing chirality in an achiral substrate with the help of a chiral reagent. In this approach the stereocontrol is achieved intermolecularly in contrast to the previous two approaches. An example is provided by the asymmetric allylation of **1.6** in presence of a strained allylsilane **1.7** to prepare enantiomerically enriched **1.8** in enantiomeric excesses up to 93% ee (**Scheme 1.4**).[16]

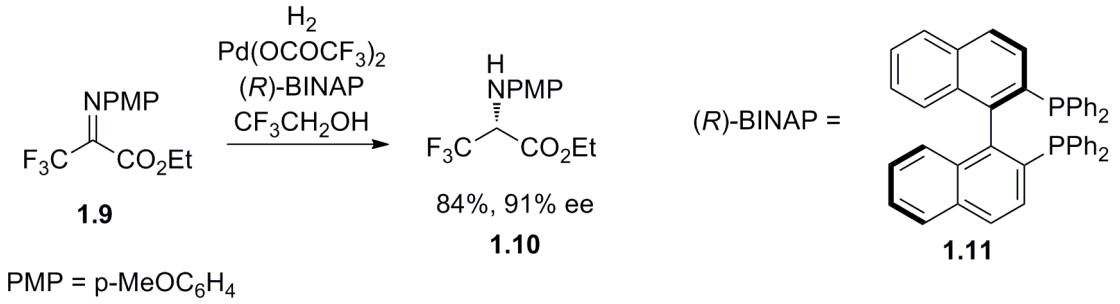


Scheme 1.4

1.V.II.IV Catalyst controlled methods

In this approach the chirality is introduced to an achiral substrate with the help of a chiral catalyst. This has been the focus of last few decades to use the chiral catalyst or

ligand accelerated catalysis in which a ligand accelerates the rate of an already existing catalytic transformation, both the approach complements each other. This can be explained with the example of catalytic hydrogenation of α-fluorinated iminoesters **1.9** in presence of catalytic amount of palladium(II)trifluoroacetate and 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (BINAP) **1.11** under hydrogen pressure to give *β*-fluorinated *α*-aminoesters **1.10** with ee up to 91%[17] (**Scheme 1.5**).



Scheme 1.5

The chemical catalyst has various advantages over the biocatalyst like chemical catalyst has greater stability while enzymes are most often very sensitive towards pH and temperature. The rate of reaction and selectivity largely depends on the nature of the ligand and its interaction with other part of the metal complex. The main advantage of this process is a very small amount of the catalyst is required for the generation of a large quantity of chiral compound and the catalyst after regeneration can be used multiple times.

1.V.III Double asymmetric induction

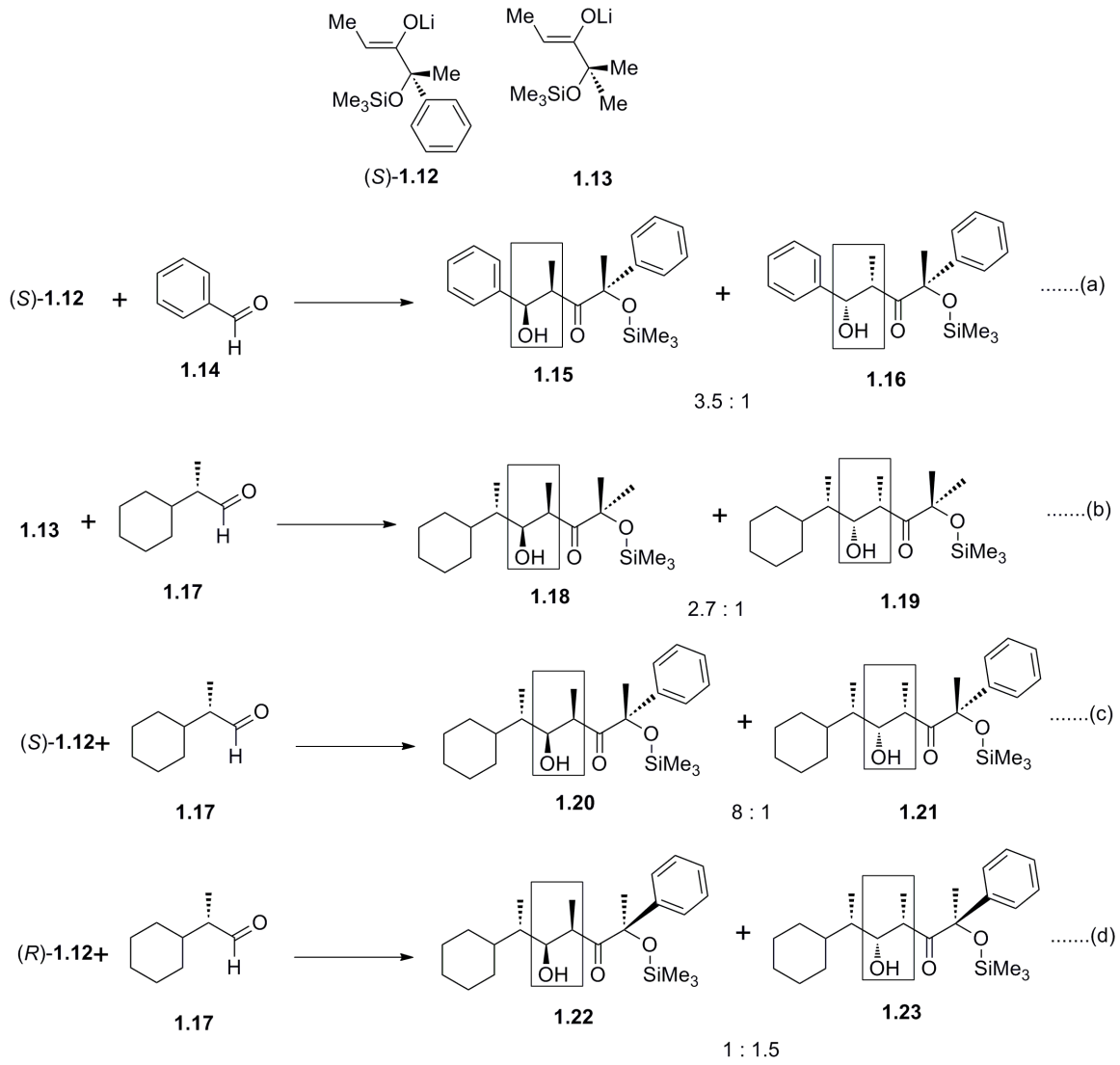
In all the previous cases we have discussed that the single chirality element present either on substrate or reagent or catalyst directs the selective formation of one stereoisomer over another by preferential reaction at one heterotopic faces (*Re/Si*) of a trigonal atom, which is called as single asymmetric induction **Figure 1.7**.

Nucleophilic addition to carbonyl Electrophilic addition to enolates

Two types of reactions that distinguishes heterotopic faces

Figure 1.7 Heterotopic faces

The asymmetric reaction between an enantiomerically pure substrate and an enantiomerically pure reagent *e.g.* when a chiral nucleophile is made to react with a chiral carbonyl compound is called the double asymmetric induction. The chirality present on both the substrate and the reagent try to influence the stereoselectivity either in concert or in opposition.[18] This is well exemplified with the following examples (**Scheme 1.6**). The first two examples (**a**) and (**b**) gives a clear picture of the stereoselectivity due to each of the chiral partner in closely related single asymmetric inductions. In each of the two cases of single asymmetric induction we have seen a very low selectivity. In scheme **1.6** (**a**) the reaction between (*S*)-Z-O-enolate **1.12** and an achiral Benzaldehyde **1.14** yields two diastereomers in the ratio **3.5 : 1** similarly when the chiral aldehyde **1.17** treated with the achiral enolate **1.13** two diastereomers formed with similar kind of lower selectivity **2.7 : 1**. The results are quite interesting when the chiral aldehyde **1.17** is treated with (*S*)-Z-O-enolate (**1.12**) a matched pair was found (*S*)-**1.17** and (*S*)-**1.12 (Scheme 1.6….(c))** the expected product was found with a higher selectivity **8 : 1**[18b,19]. In **scheme 1.6….(d)** where (*R*)-enolate reacts with (*S*)-aldehyde **1.17** is an example of mismatched double asymmetric reaction the products were formed in the ratio **1 : 1.5** [18b].



Scheme 1.6

1.VI Selectivity: kinetic and thermodynamic control

The predominant formation of one stereoisomer over the other depends on various factors; however the factors can be categorized in to two major group *i.e.* thermodynamic control and kinetic control. The stereoisomers are formed by the preferential addition of either electrophile or nucleophile to the heterotopic faces of a trigonal atom. From illustration point of view the faces of an unsymmetrical carbonyl group is heterotopic either enantiotopic or diastereotopic (**Figure 1.8**). The predominance of one stereoisomer over the other achieved only when the transition state resulting from attack on *Re* or *Si*

face is diastereomeric. This is achieved only when either of the substrate or reagent or both are chiral.

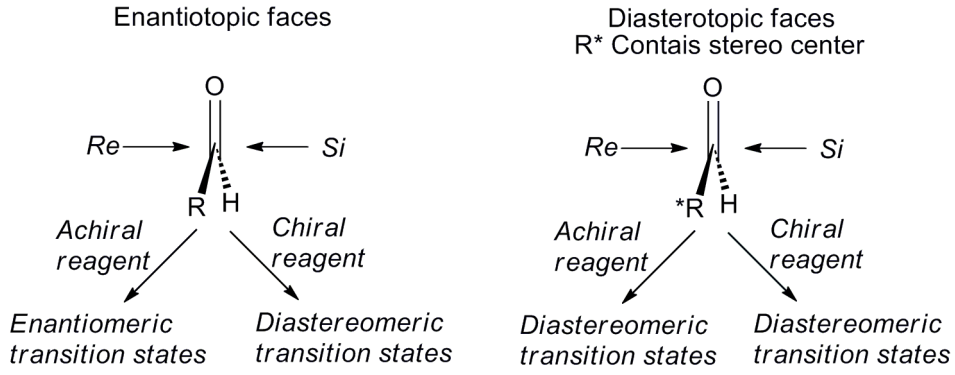


Figure 1.8 Enantiomeric and diastereomeric transition states

As discussed earlier the asymmetric induction due to any given process can be classified into two major categories either thermodynamic control or kinetic control. For the illustrative purpose consider a equilibrium reaction with starting material **A,** that gives two possible products, **B** and **C**. The process of equilibrium to afford an equilibrium mixture of **B** and **C** by one of two possible routes is being illustrated in **Figure 1.9.a**. The reactions **A** ⟶ **B** and **A** ⟶ **C** might be reversible, or **B** and **C** could equilibrate by a

$$C/B = \frac{[C]}{[B]} = K = e^{-\Delta G/RT} \quad \text{.....(1.1)}$$

route that does not involve **A**. either way, the product ratio (**C**/**B**) is given by where ΔG is the difference of free energy between **B** and **C** under this circumstance the reaction is thermodynamic control.

Figure 1.9.b represents the condition where the reaction is kinetic control; in such conditions the conversion of **A** either to **B** or **C** is irreversible. The selectivity achieved in these reactions will depend on the energy differences of activation, $\Delta\Delta G^{\ddagger}$. This implies that the most abundant product is that originating *via* the lowest activation energy. When

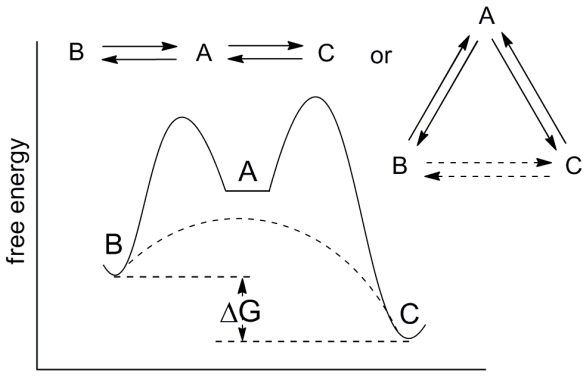


Figure 1.9.a

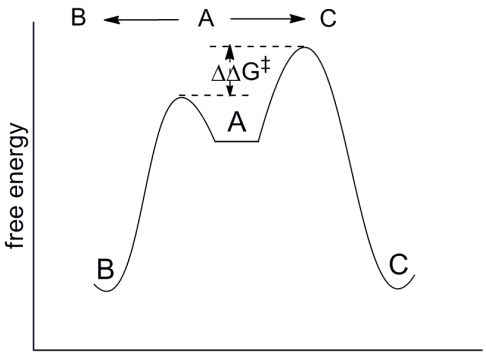


Figure 1.9.b

Figure 1.9 Energy profile diagram of thermodynamic and kinetic controlled reactions

the products in the asymmetric synthesis are diastereomeric; the selectivity can be dictated also by the difference in kinetic energies (kinetic control). The ratio of the product **C** and **B** is controlled by the rates of formation of **C** and **B** which can be represented as

$$C/B = \frac{k_1}{k_2} = e^{-\Delta\Delta G^{\ddagger}/RT} \quad \text{……..1.2}$$

$$\Delta\Delta G^{\ddagger} = \Delta\Delta G^{\ddagger}_{B} - \Delta\Delta G^{\ddagger}_{C} \quad \text{……..1.3}$$

Where k_1 and k_2 are the rate of formation of **B** and **C** respectively and $\mathbf{\Delta\Delta G^{\ddagger}}$ is the difference in the energy of activation or transition state energy for each process.

Hence diastereoselectivity and enantioselectivity are the two kind of process which can be used to establish the new stereogenic center in a given asymmetric reaction. Diastereoselective reactions can be expressed as either thermodynamic or kinetic controlled where as enantioselective reactions are always kinetic controlled since the products formed are isoenergetic.[20]

Many examples of kinetic/thermodynamic control of enantioselectivity are available in the literature. It becomes clear from various observations that the design of an asymmetric reaction must aim at maximization of $\Delta\Delta\mathbf{G}^{\ddagger}$ or $\Delta G°$, depending on whether product formation is kinetically or thermodynamically controlled. In spite of all these attributes, and even after handling hundreds of asymmetric reactions, very little is known regarding the nature of the transition states of a particular reaction. But, it has become clear that more rigid and organized transition states magnify the effect of the strike interactions, hydrogen bonds, selective solvation *etc*. Considering that the rigidity of the transition state is more pronounced at lower temperatures, asymmetric induction is usually best achieved by carrying out the reactions at lower temperatures however this not always true. Regarding the effect of temperature on selectivity, reliance on equations such as **1.1** and **1.2** can be misleading, since free energy itself is temperature dependent

$$G = H - T\Delta S \qquad \text{(1.4)}$$

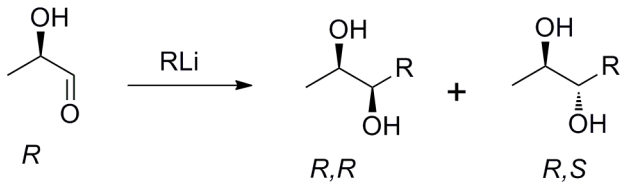
Combination of both the equation **1.3** and **1.4** gives

$$\frac{k_1}{k_2} = (e^{-\Delta\Delta H^{\ddagger}/RT})(e^{-\Delta\Delta S^{\ddagger}/R}) \qquad \text{(1.5)}$$

where $\Delta\Delta\mathbf{H}^{\ddagger}$ and $\Delta\Delta\mathbf{S}^{\ddagger}$ are the differences in enthalpy and entropy of activation for the formation of **B** and **C**, defined as was $\Delta\Delta\mathbf{G}^{\ddagger}$ in equation **1.3.c**. Equation **1.5.e** shows that only the enthalpy term is temperature dependent. The effect of enthalpy on selectivity is well explained by *Zioudrou et al.* with the example of addition of organolithium reagent to lactaldehyde [21] **Scheme 1.7**.

The addition of methyllithium has $\Delta\Delta\mathbf{H}^{\ddagger}$ = -260 cal/mole and $\Delta\Delta\mathbf{S}^{\ddagger}$ = 0. Since $\Delta\Delta\mathbf{H}^{\ddagger}$ is negative, the exponent of the first term is positive and lowering the temperature from 35^0C to -65^0C results in an increase in k_l/k_2. In contrast, the addition of

phenyllithium has $\Delta\Delta\mathbf{H}^{\ddagger}$= +340 cal/mole and $\Delta\Delta\mathbf{S}^{\ddagger}$ = +28 e.u. With a positive $\Delta\Delta\mathbf{H}^{\ddagger}$ and $\Delta\Delta\mathbf{S}^{\ddagger}$, **C** is favored by enthalpy and **B** is favored by entropy. In this case, the reaction is



R	*R,R/R,S*	(°C)
Me	60:40	35
Me	65:35	-65
Ph	73:27	35
Ph	68:32	-60

Scheme 1.7

entropy controlled: since the exponent of the first term is negative, lowering the temperature decreases the preference for **B**; nevertheless, the entropic preference prevails and **B** is still the major product, albeit in lower amount. Thus, although lowering the temperature often increases selectivity, it does not necessarily do so in all cases.

Eliel has summarized conditions for an efficient asymmetric process as follows:

i) The synthesis must be highly stereoselective.

ii) If the chiral auxiliary (adjuvant) is an integral part of the starting material, the chiral center (or other chirality element) generated in the asymmetric synthesis must be readily separable from the auxiliary without racemization [of the new stereocenter].

iii) The chiral auxiliary or reagent must be recoverable in good yield and without racemization

iv) The chiral auxiliary or catalyst should be readily and inexpensively available in enantiomerically pure form.

1.VII Theoretical prediction of selectivity

As per the earlier discussion under **section 1.V** we have seen that the stereochemistry of asymmetric induction by the reaction at a trigonal carbon has a strongest influence of the chiral center in close proximity. There is an overwhelming number of examples for 1,2-induction, and consequently, models to explain such diastereoselectivity. Almost 60 years ago D. J. Cram[14,22] gave the models which can explain the stereoselectivity obtained when nucleophiles are added to R-chiral carbonyl compounds, which later known as the Cram's rule.[23] This is found to be most fruitful in understanding, predicting, and controlling diastereoselectivity induced due to a remote stereocenter. There are several modification and extension to the fundamental models like Cram's model and Felkin Anh model are reported in literature.

1.VII.I Cram's Model

The analysis of stereoselectivity for 1,2 asymmetric induction in the addition of nucleophiles to carbonyl compounds bearing an adjacent stereocenter **1.24** to give alcohols **1.25** was reported by Cram[14] in 1952. In this case the stereocenter adjacent to the carbonyl group is denoted as **L** (large), **M** (medium), **S** (small) where **L** adopts a conformation *anti*- to the carbonyl group due to steric interaction. The incoming

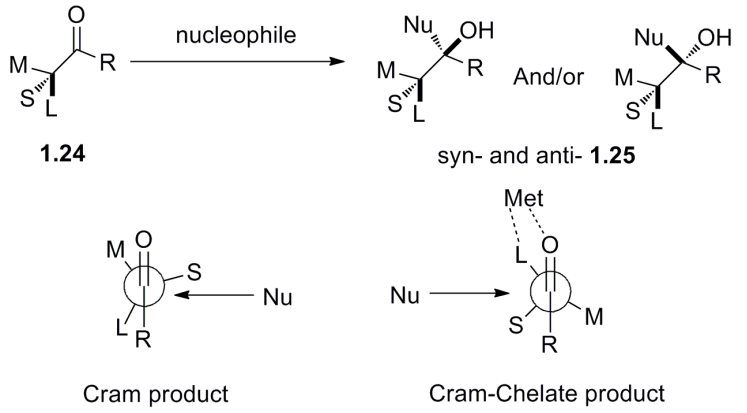


Figure 1.10 Cram's chelate model

nucleophile approaches the carbonyl group from the small (**S**) group side. The outcome of the reaction is modified when there is a group (usually metal) which can chelate the carbonyl oxygen and any of the substituent on the adjacent stereocenter. In this case the **L** group is eclipse to the carbonyl oxygen but still the nucleophile approaches from the side of the **S** substituent (**Figure 1.10**).

1.VII.II Cornforth model

Until and unless there is any polar substituent at the stereocenter adjacent to the carbonyl group the Cram's rule is reliable in its explanation for stereoselectivity. If the α-stereocenter contains a polar acceptor groups like chlorine or trimethyl siloxy, they took on the role of **L** even though sterically more demanding substituents could be present. *Cornforth* studying on the Grignard and alkyllithium addition reaction to α-chloro ketones explained the selectivity with the cram type model which represents a nearly eclipsing arrangement between the carbonyl dipole and the C-Cl bond.[24] The nucleophile approaches to the carbonyl center in the similar fashion as Cram's model from the side of **S** substituent (**Figure 1.11**).

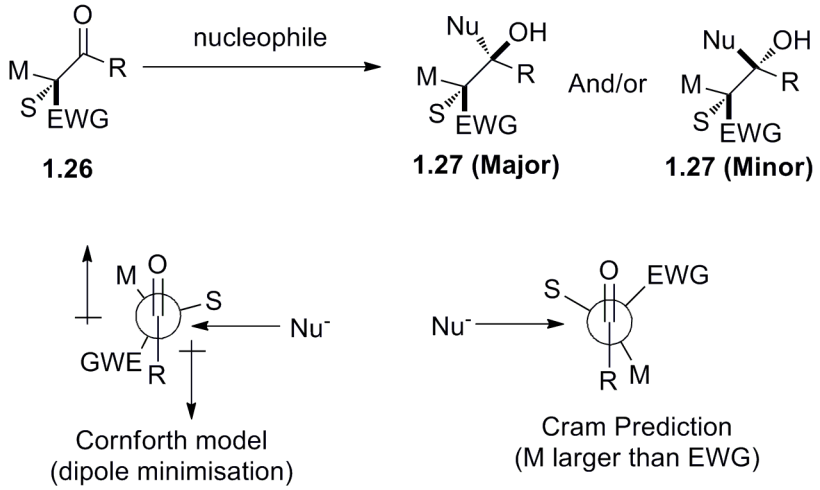


Figure 1.11 Cornforth Model

1.VII.III Felkin-Anh model

In another modification to Cram's model *Karabatsos* suggested a transition-state model **1.29** and highlighted the importance of the nucleophile attacking along the less hindered trajectory.[25] Felkin gave an alternative interpretation,[26] that if by increasing the size of the **L** group leads to a reduction in stereoselectivity, due to the steric strain between the **L** and **R** substituents then the path of the incoming nucleophile is assumed to be governed by either Karabatsos or Cram-type transition state. The experimental investigation of reduction of a ketone adjacent to a stereocenter in combination with an examination of polar effects by lithium aluminium hydride suggested the reaction can be best described by the staggered transition state **1.30** (**Figure 1.12**).

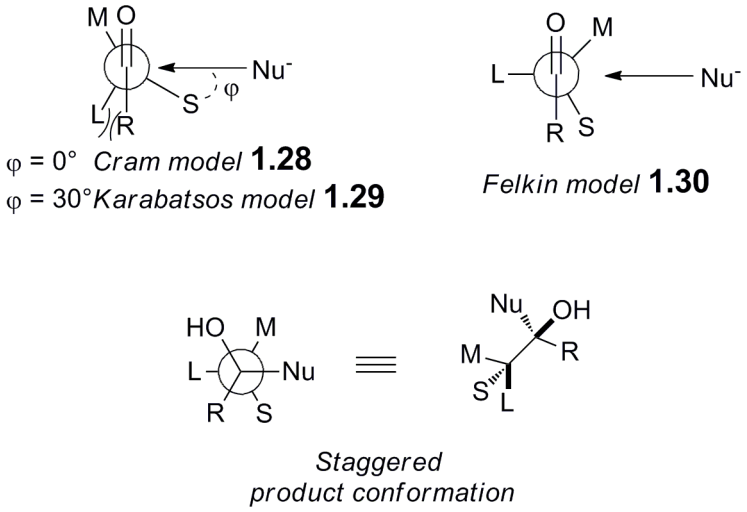


Figure 1.12 Felkin-Anh model

In this case, the largest, or most electronegative, group lies perpendicular to the plane of the carbonyl, antiparallel to the approach of the nucleophile. Additionally, the staggered Felkin transition state **1.30** is preferable to the analogous Cram transition state **1.28** in that it leads directly to the more stable staggered conformation of the product (**Figure 1.12**).

Anh and Eisenstein,[26b,27] bring some other refinements to the Cram's model by investigating the factors responsible for the antiperiplanar approach of the nucleophile to the largest or most donating group. They have suggested that there is an overlapping of the C_2-L σ* and C=O π* orbitals, due to the perpendicular arrangement of C_2-L and the carbonyl bond which results in the lowering of the energy of LUMO. Hence the antiperiplanar attack of the nucleophile gives a more favorable overlap with the combination of orbitals than syn-periplanar attack (**Figure 1.13**).

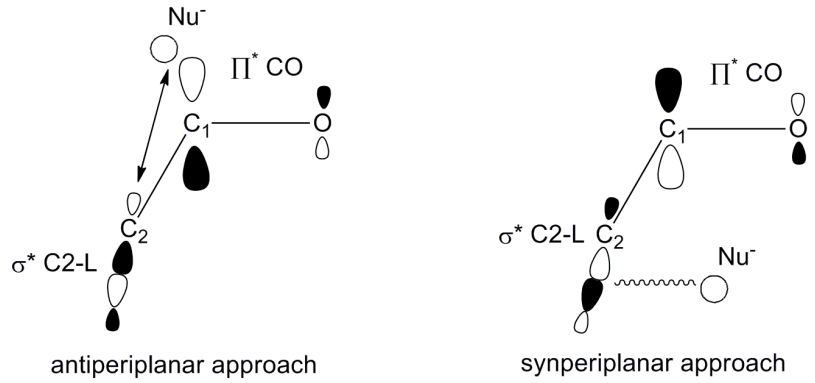


Figure 1.13 Anh and Eisenstein explanation of anti periplanar approach

In another improvement, taking Bürgi-Duintz[28] angle in to consideration *i.e.* the nucleophile approaches at an angle about 109° with respect to the plane of carbonyl group, which is in agreement with the least hindered approach of the nucleophile as suggested by *Karabatsos*; Felkin-Anh model was proposed. **Figure 1.14** presents the Felkin-Anh model for the addition of the nucleophile to a carbonyl group.

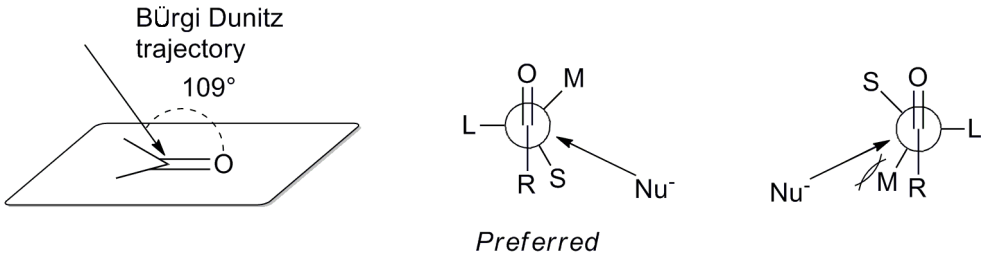
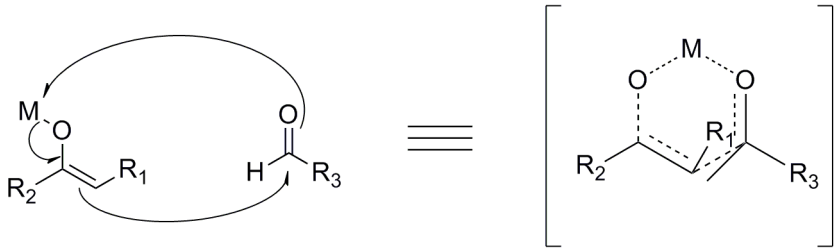


Figure 1.14 Bürgi-Duintz approach and Felkin-Anh Model

1.VII.IV Zimmerman-Traxler transition state model

Many addition reactions to carbonyl compounds proceeds via cyclic six-membered transition states. Stereoselectivity in the reactions particularly ene, allylation, and aldol type can be understood with help of cyclic transition state. In a aldol reaction both the aldehyde and the enolate have the heterotopic faces, so there are two ways how they can approach to each other in a relative sense where the stereochemical outcome depends on the cis-trans configuration of the enolate anion[29]. **Scheme 1.8** shows a simple aldol reaction where R_1 and R_2 are the two different substituents on



Scheme 1.8

the enolate anion and R_3, are the substituent of the aldehyde and metal respectively. It was observed that the stereoselectivity largely depends on the bulkiness of the **R_2** group. The experimental observations was rationalized in terms of the transition state model based on closed chair like structure involving coordination between the two oxygen atom and the metal center[30] **Figure 1.15**. If it is accepted that the dominant steric interaction is between **R_1** and **R_3**, it can be readily visualized that the transition state leading from the *cis* enolate to the anti aldol product is disfavored, as is the transition state for the *trans* enolate leading to the syn product.

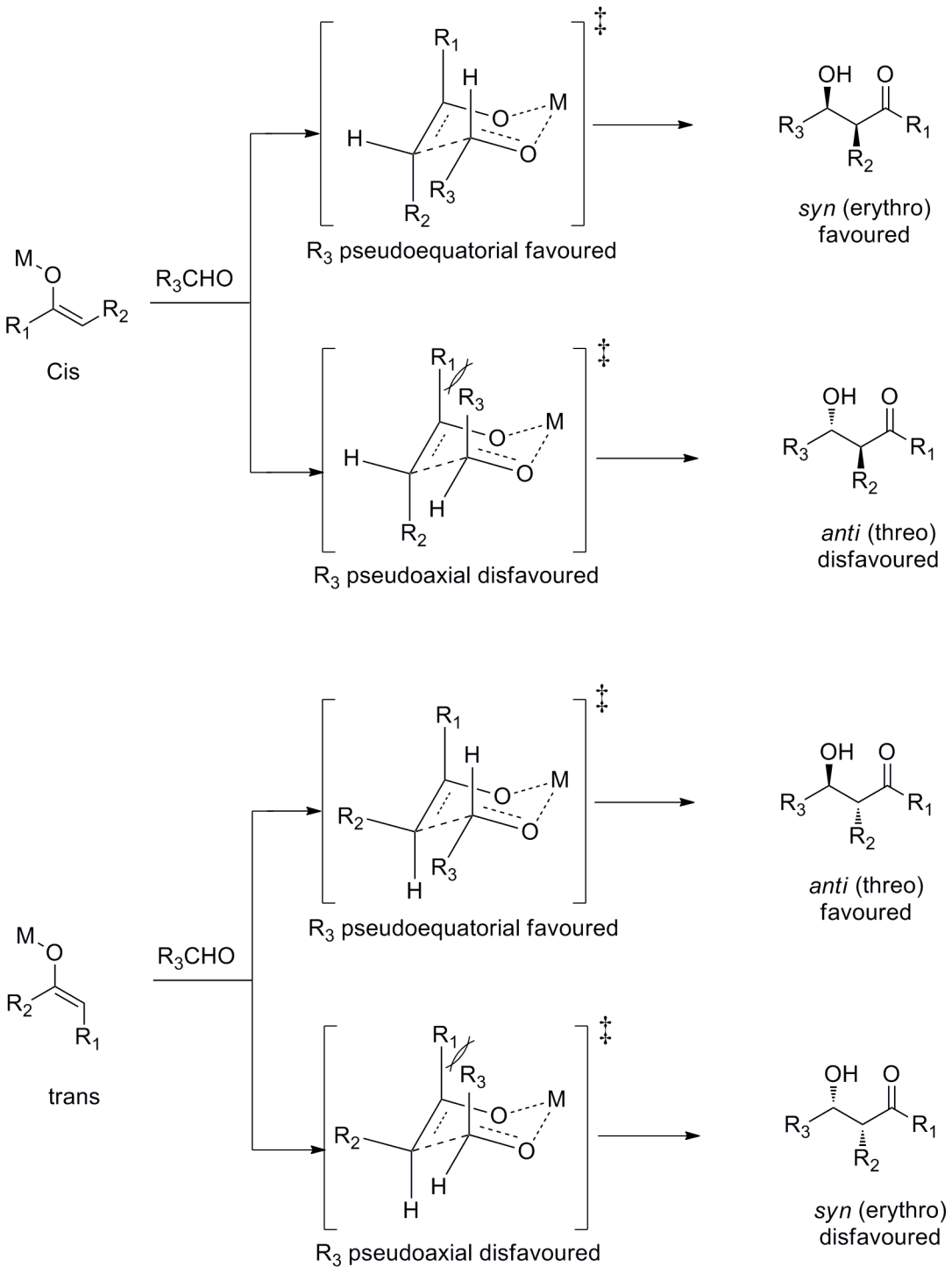
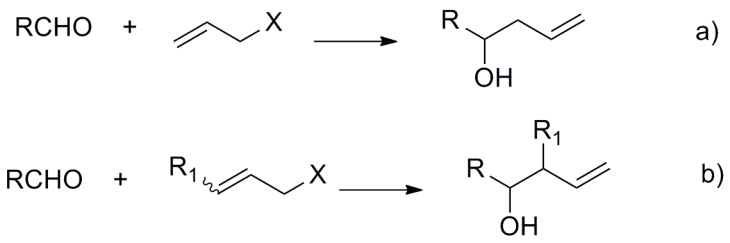


Figure 1.15 Zimmerman-Traxler transition state model

1.VIII Some Important C-C Bond Forming Reactions

The remaining part of this chapter will cover a brief outline of some of the important carbon-carbon bond forming reactions that has been dealt with during the work of this dissertation.

1.VIII.I Allylation/crotylation of aldehydes



Scheme 1.9

Carbon-carbon bond forming reactions is the essence of organic synthesis. Among many C-C bond forming reactions carbonyl allylations constitute an important class which can be treated as a valuable alternative to conventional aldol reactions.[31] Understandably, due to the presence of olefin in the product homoallylic alcohol could be amenable for versatile functional maneuver through chain extension, dihydroxylation, terminal hydroxylation, ozonolysis, coupling etc (as shown in **Figure 1.16**). Crotylation of aldehydes has higher implications in organic synthesis as it leads to the formation of an additional stereogenic centre in the corresponding product homoallylic alcohol. Indeed, the product homoallylic alcohols are very useful blocks for elaboration into polyacetate and propionate units that are commonly found in numerous biologically interesting marine macrolides, polyhydroxylated natural products, polyether antibiotics and other natural products. In view of their importance, considerable attention has been paid during the last decades to develop their various procedures of allylation/crotylation of carbonyls to meet up the need of synthetic chemists.

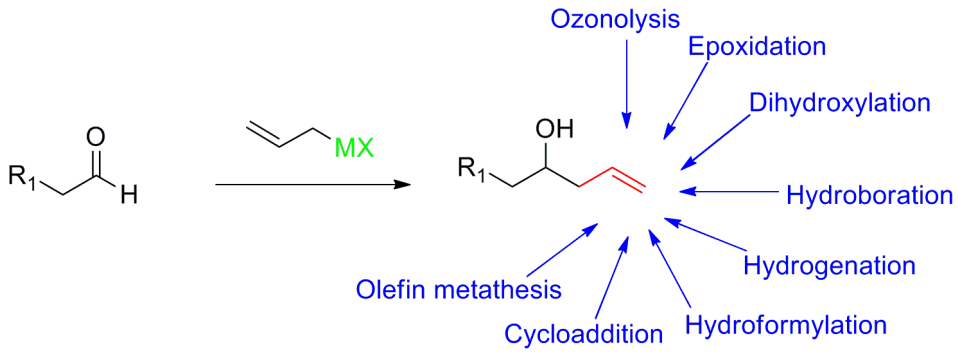


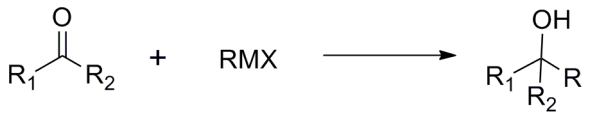
Figure 1.16 Versatile functionalisability of homo allylic product

A very basic approach for performing such reactions was through the addition of allylic-metals to carbonyls. Prior to the late 1970s allylic organometallic compounds were primarily studied by a limited number of organometallic chemists whose interests lay in the structural determination of the allylic metals e.g. 1,3-transposition of metals on the allylic systems, stereochemistry of the olefin of the allylic systems and regioselectivity of the addition. Beginning in the late 1970s, a new venture got prominence in this field. Significant synthetic interest began to emerge in the control of stereochemistry of C-C bond formation in the reactions of allyl metals with aldehydes and ketones. This important topic has been triggered by three papers[32]: Heathcock's[32a] discovery that the Himaya (*E*)-crotyl-chromium reagent undergoes highly anti selective addition to aldehydes, Hoffman's[32b] finding that (*Z*)-crotylboronates produce syn-homoallylic alcohols stereoselectively and Yamamoto's[32c] discovery that the Lewis acid mediated reaction of crotyl-tin with aldehydes produces syn homoallylic alcohols regardless of the geometry of the olefin in the allylic tins.

1.VIII.I.I Aqueous Barbier type allylation of carbonyls

Since the days of yore, the addition of organic halides to carbonyls to produce alcohols has become a topic of ever increasing attention of synthetic chemists. In this endeavor, they utilized different metals that could play a great role to facilitate this

transformation either with the help of organometallics or sung them as such. During the last few decades there has been an enormous attention from synthetic chemists to develop different C-C bond forming reactions in aqueous medium with a view to attaining their practical viability. Earlier such efforts were only restricted to the electrochemical processes. Unfortunately, for addition of organometallics (RM) to carbonyls, in many cases the former in general show a great degree of reactivity towards water. Thus, such reactions need to be performed in highly anhydrous conditions and the presence of water is considered to be undesirable for Barbier type reactions and a very limited application has been explored. In their most general form of Barbier type reactions a carbon nucleophile in the form of **RMX** (an organometallic reagent) which leads to the C-C bond formation. In the cases where the electrophile is a carbonyl compound the transformations are generally referred as Barbier-Grignard type reactions (**Scheme 1.11**).



Scheme 1.10

The basic difference between Barbier and Grignard type reaction lies at the formation of the organometallic reagent; if it is formed in situ it is referred as Barbier otherwise Grignard if it is formed in stepwise manner. But the basic necessity of both the type is the strict exclusion of moisture. These kinds of restrictions bring the limitation to the synthetic design which requires protection of various acidic hydrogens present in the substrate.

However the viability of some of the organometallic compounds like arylmercuric chlorides, large scale production of tribenzylstannyl halide etc indicated the sustainability of these kinds of reactions under special circumstances. Wolinsky *et al.* in 1977,[33] observed that the allylation of various carbonyl compounds can be carried out by

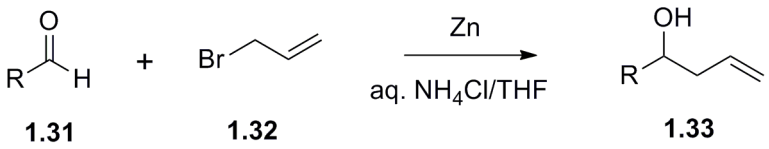
allylbromide mediated by activated zinc in 95% ethanol and t-butyl alcohol albeit with a moderate yield but during this time period a significant progress has been made showing that the reaction can be carried out in aqueous medium through the use of a variety of metal mediators like zinc, tin, indium, bismuth, lead, and cadmium. It can be generalized that the metals used in these kinds of reactions are relatively "soft" which remains unaffected by the "hard" solvent water.

The use of aqueous media has some advantages like[34]

1. Convenience of not handling inflammable and anhydrous organic solvents.
2. protection-deprotection processes for some acidic hydrogen can be avoided which ultimately contribute to the yield of the process
3. Water-soluble compounds, such as carbohydrates, can be used directly without the need of derivatization.
4. Such processes greatly reduce the burden of solvent disposal and its impact upon environment.

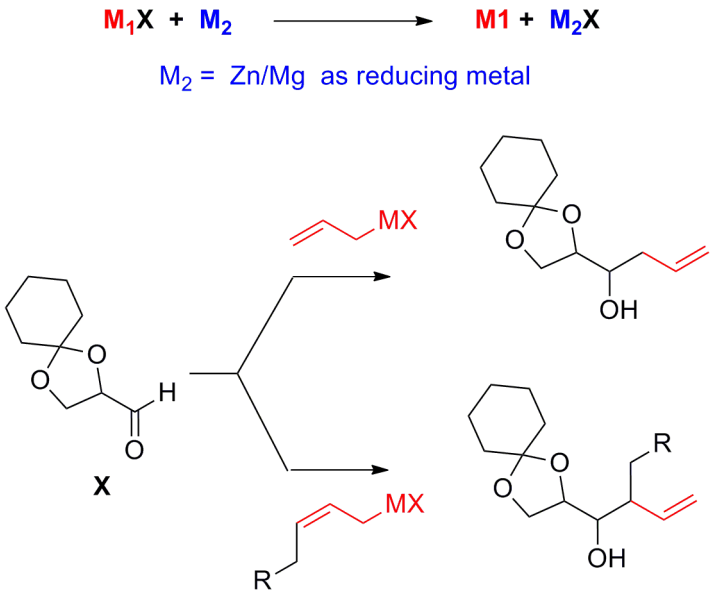
Allylation is the most successful Barbier type reaction in aqueous media. As told earlier the first ever this kind of reaction was reported in 1977 by Wolinsky[33] after which various modifications were brought to improve the yield of the reaction by changing the solvent and metal and also a metal in combination with another metal and sometimes activators.[23a,35]

During the year 1985 Luche *et al.* found that the use of Zinc metal with ultrasonic radiation increases the yield dramatically also use of saturated NH_4Cl/THF instead of water/THF increases the yield.[36]



Scheme 1.11

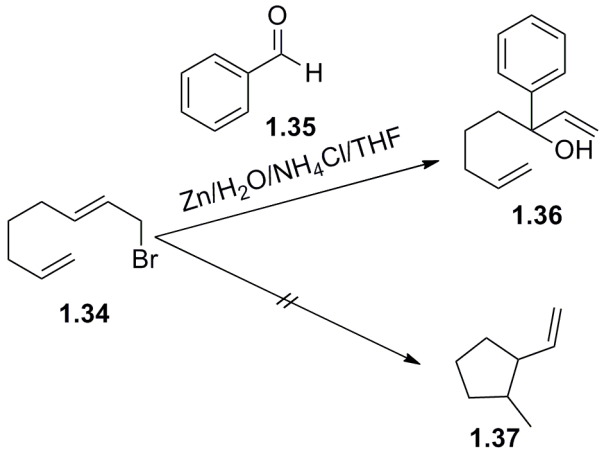
Recently Chattopadhyay *et al.*[36-37] reported the Barbier type allylation, crotylation and Reformatsky reaction of chiral aldehyde (*R*)-2,3-(*O*)-Cyclohexylideneglyceraldehyde (**X**) in aqueous media by the use of bimetallic redox strategy. Where we have used a metal salt in combination with a reducing metals like Zn or Mg to produce the nascent low valent metals like Cu, Fe, Co, Sn etc by reduction of the corresponding metal salt in situ (**Scheme 1.12**).



Scheme 1.12

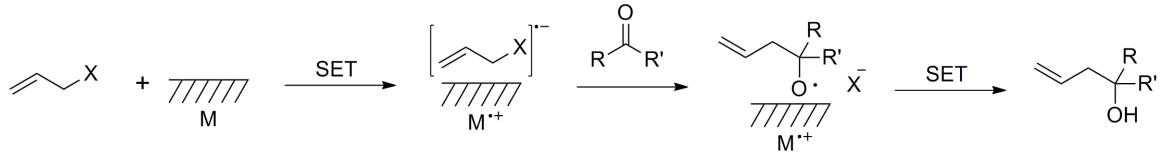
Apart from the various metal mediated allylation reaction there are several diastereoselective allylation reaction such as Brown *et al.*[35c,38] developed asymmetric allylboration of aldehydes using B-allyldiisopinocampheylborane, B-allylbis(4-isocarany1)borane, and B-allylbis(2-isocaranyl) borane at -78 ^{o}C in Et_2O.[36,38]

The mechanism of Barbier type reactions remains intriguing since most of the organometallic compounds react violently with water. There are various suggestions for the mechanism as Luche *et al.*[39] suggested the radical pair mechanism where a radical produced from the halide involved in the reaction at the carbonyl center. To which contradictory results were found by *Wilsons et al.*[40] where they have used radical probe to study the mechanism and found in case of *α,β*-unsaturated conjugated ester mostly the addition occurs at the carbonyl center whereas if it could have been radical pair process the 1,4-conjugated addition product should be obtained. Similarly in the case shown in **scheme 1.13** instead of the cyclic product **1.37** the normal regioselective addition product **1.36** formations strongly contradicts the radical pair mechanism.



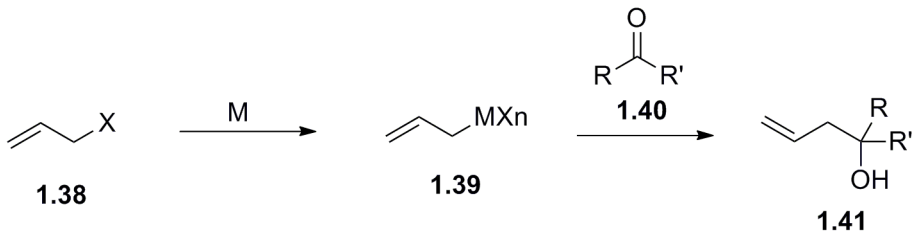
Scheme 1.13

Chan and coworkers had[34d] proposed a mechanism involving a radical anion that is coordinated on the metal surface. In this pathway, a single electron transfer (SET) process is involved (**Scheme 1.14**).



Scheme 1.14

In another case the work done by different groups such as by Whitesides *et al.*,[41] Grieco *et al.*,[42] and Marshall *et al.* [43] suggested it is possible to carry out the alkylation in aqueous media with preformed allyl metal reagent **1.39**. These results raise another possibility of involvement of discreet organometallic reagent in the transformation (**Scheme 1.15**).



Scheme 1.15

It has been understood that not a single mechanism of action in case of aqueous media alkylation works each proposed mechanism has its own element of validity. Depending on various factors like metal/substrate/conditions of reaction, one mechanism may reflect the more than the other. It has been generalized[34h] that a mechanism radical-anion-covalent (C-M) triangle (**Figure 1.17**) may play the role. In any given case the preferred pathway is within the triangle at an exact location determined by the substrates, the metal being used, and the reaction conditions. The three corners only represent extreme situations.

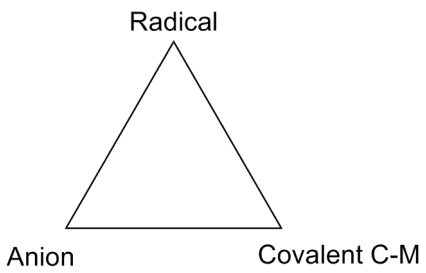
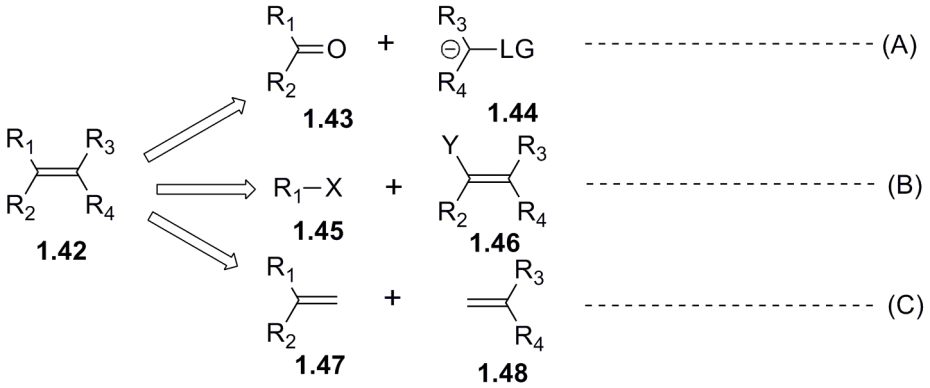


Fig 1.17 Radical-anion-covalent triangle

1.VIII.II Introduction to olefination

The synthesis of alkene is an indispensable strategy in organic chemistry for the construction of various structurally complex organic molecules. The first olefination of carbonyl compounds was reported years back in 1953 by Georg Wittig[44] for which he was awarded Nobel prize in 1979. The alkene can be prepared by various functional group transformations like the selective hydrogenation of alkyne[45] to form the alkene. The basic routes to prepare alkene can be generalized in to three basic categories depending on the structure and functional group tolerance

A. Reaction of a carbonyl group with a carbanion stabilized by a electron withdrawing group (EWG) at the same time the EWG acts as a leaving group (LG) (**Scheme 1.16 (A))**
B. transition metal catalyzed cross coupling reactions (**Scheme 1.16 (B))**
C. alkenes metathesis reactions (**Scheme 1.16 (C))**



Scheme 1.16

Each category of the **scheme 1.16** has many different variant depending up on the basic structure of the reactants. In category **A Scheme 1.16** a carbonyl functional group bearing compound **1.43** when **1.44** it reacts with a carbanion gives the alkene moiety. Depending on the LG of the transformations are known as Wittig reaction[44,46] (LG =

PR_3), Horner-Wordsworth-Emmons (HWE) [47]reaction (LG = $P(O)(OR)_2$), Julia olefination[48] (LG = SO_2R), Peterson olefination [49] (LG = SiR_3).

The strategy **B** Scheme **1.16** involves the transition metal catalyzed cross coupling reactions of alkenes **1.46** and alkyl group to form alkenes with different substitutions. Depending on the nature of **Y** of the alkene formation has different path way and mechanism of reaction like; direct coupling of alkenes (Heck reaction [50]: Y = H) or alkenyl metals (Stille reaction [51]: Y = SnR_3; Suzuki-Miyaura reaction [52]: Y = BR_2; Negishi reaction [53] Y = ZnR) with appropriately activated aryl, alkenyl or even alkyl substrates **1.45.**

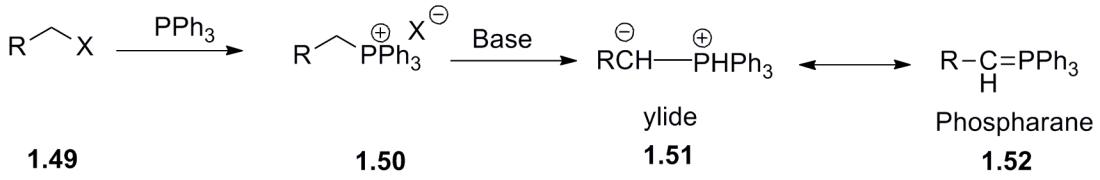
The other kind of reaction (**Scheme 1.16 (C)**) that involves the direct coupling of two alkene moiety which is being facilitated with development of different kind catalyst and this is known as olefin metathesis. With the discovery of robust and readily available metal based catalyst Molybdenum [54] (Shrock's) and especially Ruthenium [55] (Grubb's) has changed the synthetic scenario not only for the make of alkene molecules but also for different kind of structurally complex carbocycles and heterocycles.

The preceding part of this chapter contains a brief discussion of olefination of carbonyl compounds with phosphorous reagents and olefin metathesis.

1.VIII.II.I Introduction to Olefination via phosphorous reagents

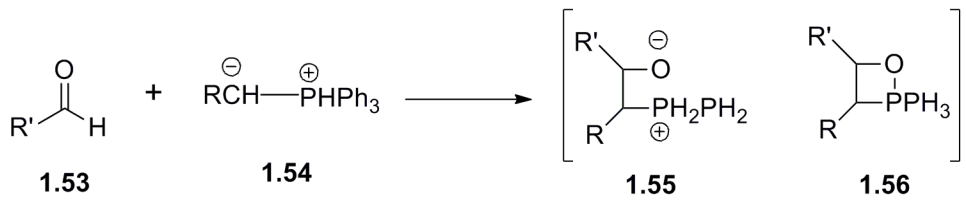
As told earlier these kind of reaction was discovered in 1953 and are named after the discoverer as Wittig reaction. The phosphorous atom that carries a positive charge especially when attached to EWG, it makes the proton adjacent to it more acidic. The phosphonium salt **1.50** is formed when alkyl halide **1.49** treated with triphenyl phosphine

which on treatment with a base forms the ylide **1.51** or phosphorane **1.52** (**Scheme 1.178**).



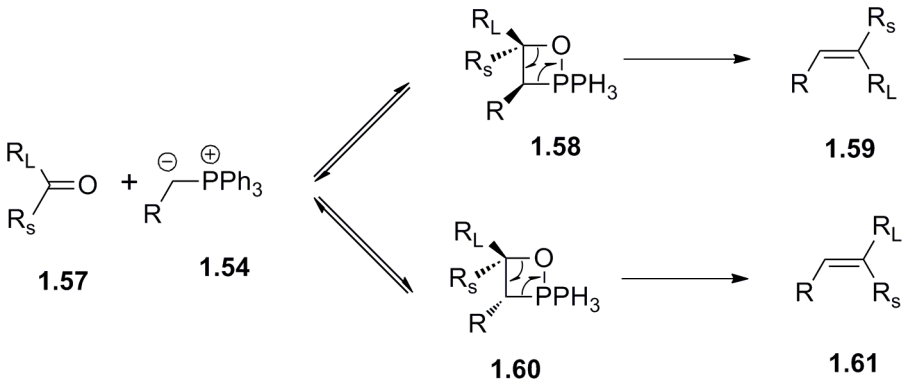
Scheme 1.17

The ylides formed in the above process can be isolated but usually used immediately after its formation. The mechanism and stereoselectivity of the reaction faced a heated debate in recent times, the controversy is centered around the structure of the intermediate formed after the addition of the ylide to the carbonyl compound whether the betaine[56] **1.55** which is observed under special circumstances[57] plays a major role in the reaction path way or the phosphaoxetane[58] **1.56** is formed directly via [2+2] cycloaddition reaction **Scheme 1.18**.



Scheme 1.18

Presently the accepted mechanism[59] is for the formation of alkene from the aldehyde **1.57** (R_L= large group, R_S= small group) is via phosphaoxetane **1.58** and **1.60**; which stereospecifically opens to the corresponding *Z*- or *E*- alkene **1.59** and **1.61** (**Scheme 1.19**).



Scheme 1.19

The selectivity of Z alkene over the E alkene in Wittig reactions shows that the sterically more crowed *cis*-phosphaoxetane **1.58** is kinetically more favorable than the *trans*-phophaoxetane **1.60**. It is observed that the nonstabilized ylides (R = H, alkyl, aryl and salt free condition M ≠ Li where M is the metal of the base used) followed the kinetically controlled pathway favoring the formation of phosphaoxetane **1.58** ultimately leading to *Z*- alkenes whereas in case of the stabilized ylides (R = EWG like CO_2R, COR, CN etc.) an equilibrium between the two diastereomeric pshosphaoxetane **1.58** and **1.60** exist via back reaction through **1.57** and **1.54**. The equilibrium ultimately favors the thermodynamically more stable *E*- alkenes.

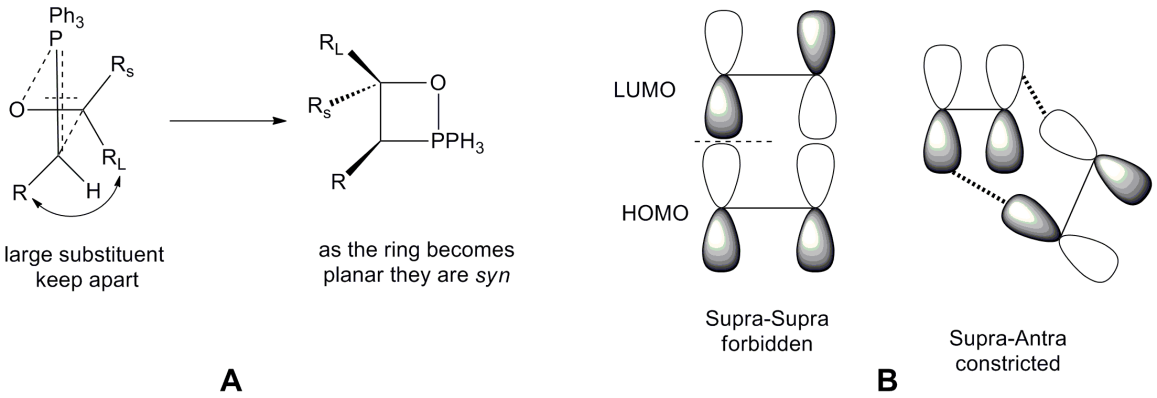
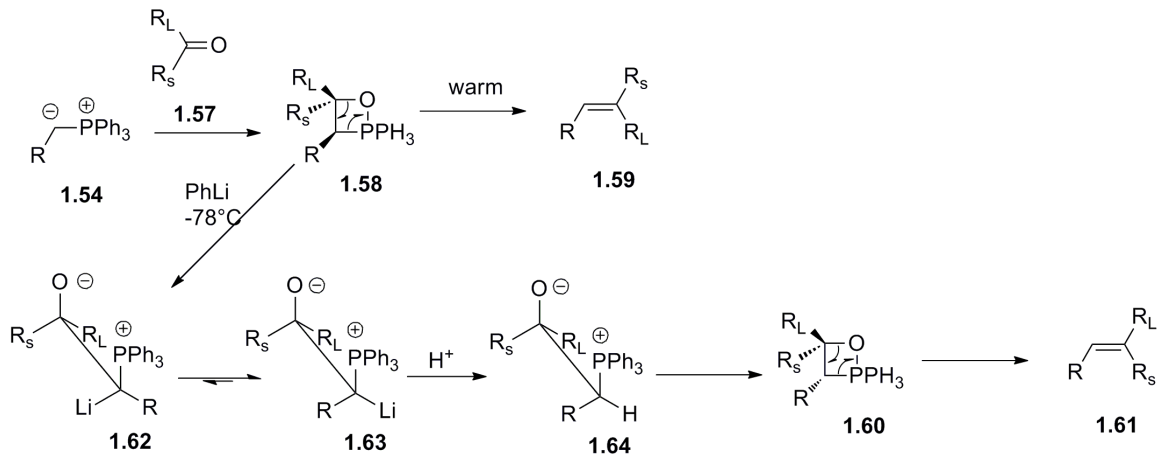


Figure 1.18 Criss-crossed transition state for phosphaoxetane

The possible explanation for the formation of sterically crowded Z alkenes can be understood by looking at the "criss-crossed" transition state[58a,60] structure for the

formation of the phosphaoxetane (**Figure 1.18 (A)**). It can be visualized that during the formation of the phosphaoxetane the two large groups arrange themselves at a larger distance from each other in order to avoid the non bonded interaction between them but after the formation of the planner structure they came to the same side which ultimately leads to the **Z-** alkene. The other possible explanation is by considering the molecular orbital structure[61] of the HOMO and LUMO of carbonyl and phosphorane considering the formation of phosphaoxetane via [2+2] cycloaddition reaction (**Figure 1.18 (B)**). In this case for thermal induced reactions the *supra-supra* reaction is symmetry forbidden whereas the *supra-antra* overlapping give rise to the Z alkene.

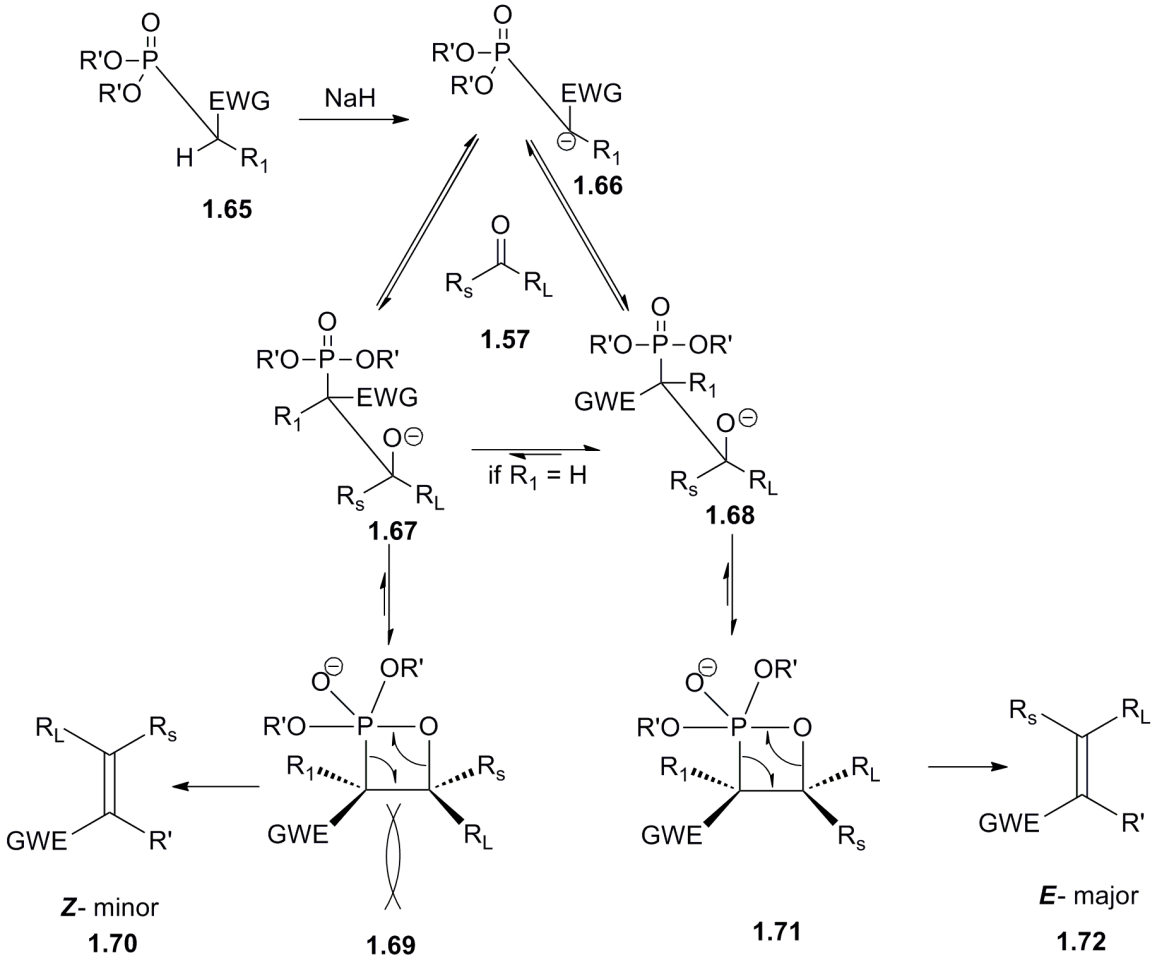
An important modification to the classical Wittig reaction was made by Schlosser & Christmann[62] where by the use of lithium salt to form the betaine followed by a deprotonation and reprotonation sequence at low temperature to obtain trans phosphaoxetane **1.60** ultimately leading to the formation of ***E***- alkene **1.61** in an stereoselective manner **(Scheme 1.20)**.



Scheme 1.20

In another modification to Wittig reaction where phosphonate are being used instead of phosphonium salt are called as Horner-Wadsworth-Emons (HWE)[47] reaction. The carbanion produced after the deprotonation of phosphonate are highly reactive than

the conventional ylides used in case of Wittig reactions; to stabilize the carbanion a EWG group is placed in conjugation to the carbanion produced. The stereoselectivity of the HWE reaction can be controlled by the steric and electronic properties of the alcohol group **R'** in the phosphonate; a high degree of ***E*** selectivity is obtained when the **R'** is a bulky alkyl group at the same time ***Z*** selective reaction occurs when the **R'** is $-CH_2CF_3$ (*Still-Genari* modification) [63] or –Ar (*Ando* modification) [64] (**Scheme 1.21**).



Scheme 1.21

The stereoselectivity of olefination of carbonyl compounds by these kind of methods precisely depends on various factors like base used to prepare the ylide, solvent, temperature , bulkiness of different group and the kind of substrate used[59,65].

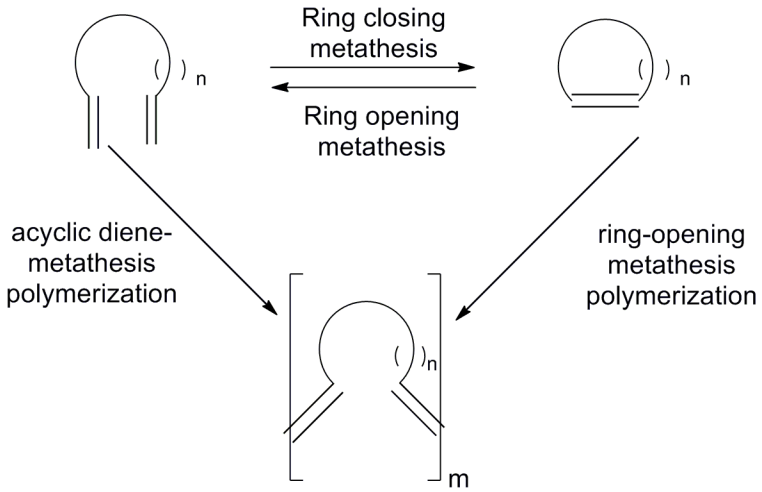
1.VIII.II.II Introduction to olefin metathesis

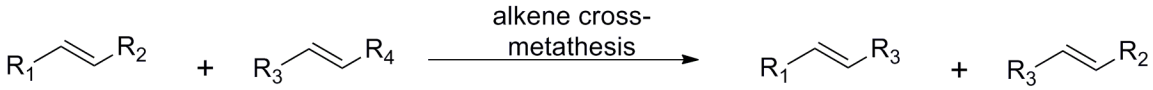
Olefin metathesis ('metathesis' from Greek meaning rearranging the syllabi in a word or change of position or transposition) is a metal-catalyzed transformation, which acts on carbon-carbon unsaturated bonds and rearranges them via cleavage and reassembly in presence of metal carbene complexes. The significance of the process can be defined as

I. Easy preparation of tri or tetra substituted olefins

II. Non- or minimum generation of byproducts, such as ethylene which can be removed by evaporation

III. No additional reagent beyond catalytic amount.





Scheme 1.22

Olefin metathesis can be utilized in three closely related categories of reactions[66]

Scheme 1.22

A. Ring opening metathesis polymerization (ROMP),

B. Ring closing metathesis (RCM)

C. Acyclic cross metathesis which when carried out on di-olefins results in polymers (ADMET).

The number of catalyst system that are available today to initiate the metathesis reaction is very large[55b,67]and list starts with the serendipitous discovery nearly 60 years ago. However most of the early works were associated with the disadvantage of using ill-defined multicomponent catalyst system. In recent years a very well defined single component metal carbene complex have been prepared and utilized for olefin metathesis. Although a number of titanium and tungsten catalyst system has been prepared and utilized in olefin metathesis and related reactions the well defined molybdenum complex **X** and ruthenium systems **Y** have seen the most application (**Figure 1.18**).

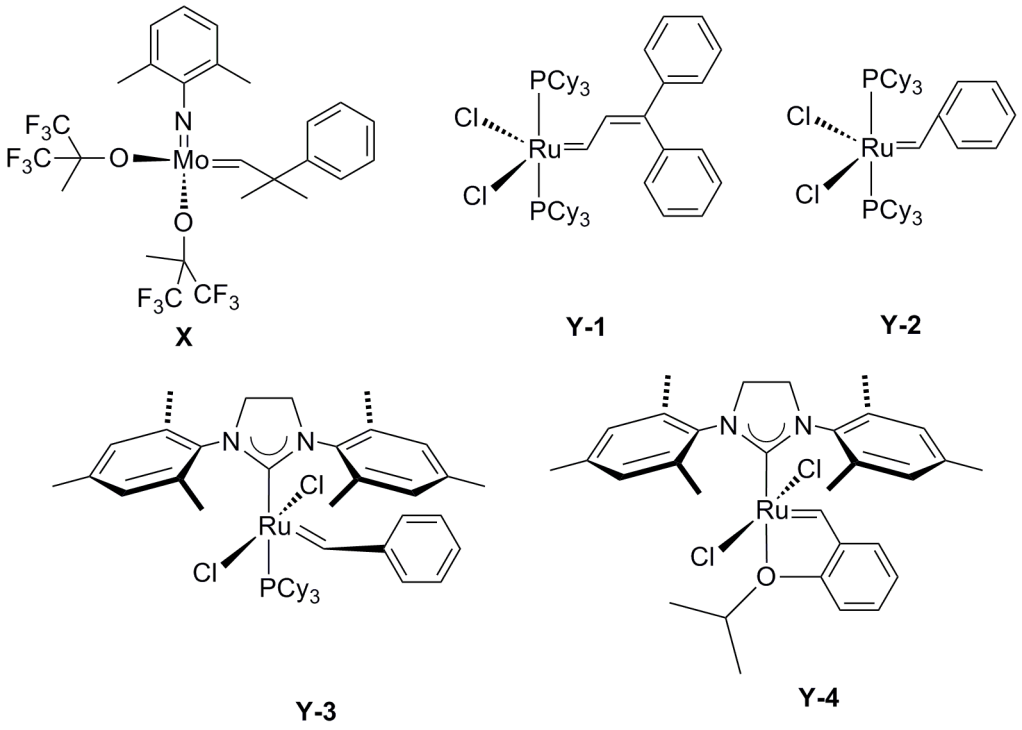
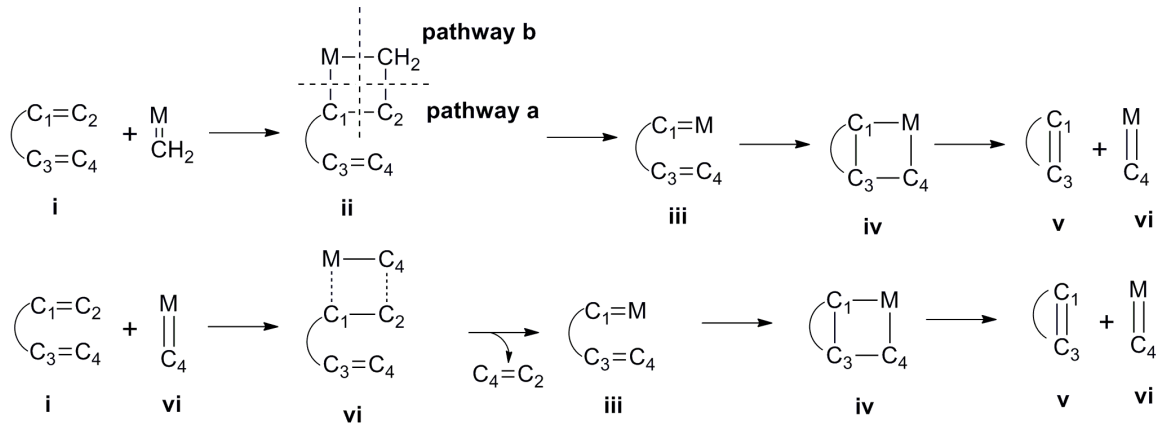


Figure 1.18 Catalyst of metathesis reaction

One of the important molybdenum catalyst reported by Schrock *et al.* [68] is alkoxy imino molybdenum complex **X** which has the major advantages over the other

molybdenum complexes is its high reactivity towards a wide range of substrates with many steric and electronic variants and the tunability of the alkoxide to adjust the reactivity. However these catalyst systems associated with a great no of disadvantages like functional group intolerance, high sensitivity towards air, moisture, and trace amount of impurity in solvent and thermal instability and at last expense of preparation. Grubbs and co-workers[55,66b] developed the ruthenium based catalyst system which has drawn a lot of attention during the last few decades due its high reactivity and remarkable functional group tolerance.

A general pathway illustrating how the catalytic transformation proceeds is shown in **Scheme 1.23**. All olefin metathesis reactions involve association of the metal with an olefin substrate. It is in this crucial interaction that one significant difference between Mo- and Ru- based catalysts present it, a high-oxidation state Mo center is a Lewis acid that chelates with a Lewis basic olefin. In contrast, in Ru catalyst, it is alkene substrate that serves primarily as a Lewis acid. Overall, that catalytic cycle consists of an initiation phase (generation of the active complex) and a propagation phase (the active complex promotes additional cycles) [69]. Catalysis commence by a CM between an active carbene or alkylidene and one of the two olefins of the substrate **i** to generate metallocyclobutane, **ii** the metallocyclobutane may revert to **I (pathway a)** or the other two bonds of the ring may rupture, furnishing **iii** where the metal **M** is within the substrate (**pathway B**). Formation of another metallocyclobutane **iv** and its disintegration furnishes the cyclic product **v** and the metal carbene **vi** which is the metal bearing agent serving as the catalyst. What typically drives the reaction is that the cyclic product **v** does not easily reacts with the active catalyst to cause ROM.



Scheme 1.23

The identity of the intermediates in the catalytic cycle is well understood. It is however often unclear whether it is catalyst-substrate association, formation of metallocyclobutane or its cleavage that is the irreversible, product or rate determining step. It is a daunting task to predict the most effective catalyst or to design in the true definition of the word one: what differentiate a selective process from one that is non-selective. These considerations indicate that seeking truly a general catalyst is likely to be futile different classes of substrate may require a different optimal catalyst. Chemist addresses such challenges through invention of a class of catalyst that are easily modifiable to tune the reactivity and selectivity. The more readily modifiable a catalyst class, the larger the no of available catalyst, and better the odds of obtaining more desirable result. However irrespective of this problem, there is a little doubt that olefin metathesis has elevated the art and science of chemical synthesis.

Among all type of metathesis reactions the RCM represents a key step in many synthetic transformations. The recent works describes the use of metathesis in among the other things construction of synthetically important building blocks such as heterocyclic rings containing Phosphorous [70], Sulfur[70] , Oxygen [71] or Nitrogen [71-72], including aromatic heterocycles[73], spirocycles[74], cyclophanes[74a] and polycyclic compounds[74]. These methods has shown its application in the synthesis of many different biologically and medicinally

relevant molecules such as peptidomimetics[75], carbohydrate derivatives[75a,76], alkaloids[75b,77], bioactive cyclic molecules[78], and polycyclic ethers[79], including aza-crown ethers[80] and topologically important molecules and molecular machines[81]. While the common rings of medium sizes (5-7) [82] historically been dominant, owing in part to their greater ease of access, important advances has been made in the synthesis of medium and macrocyclic[77d,80,83] targets.

CHAPTER 2

Stereo Divergent Route to the 2,3′-Carbocyclic Core of Olefinic Carbocyclic Nucleoside: Synthesis Towards Carbovir

2.I Introduction to Nucleosides and Analogs

The study of the biological activity of nucleosides has been a fundamental and fruitful field of research since the 1940s and 1950s. Nucleosides which serve as the fundamental building block of life are glycosylamines primarily consisting of two parts as nitrogenous base which is otherwise called as nucleobase and a pentose sugar unit. The nucleobase is linked to the pentose sugar via a glycosidic linkage. These nucleosides after sequential phosphorylation to the mono-, di- triphosphates processed in to nucleic acids by polymerase which forms the basic structural unit of life. Depending on the nature of sugar unit the nucleic acids are of two type viz. Deoxyribonucleic acid (DNA) in which the sugar is deoxyribose and the other one which contains ribose is called as Ribonucleic acid (RNA). The nucleobase are also of two different categories i.e. purine base and pyrimidine base which differ among each others in functional group and substitution. (**Figure 2.1)**

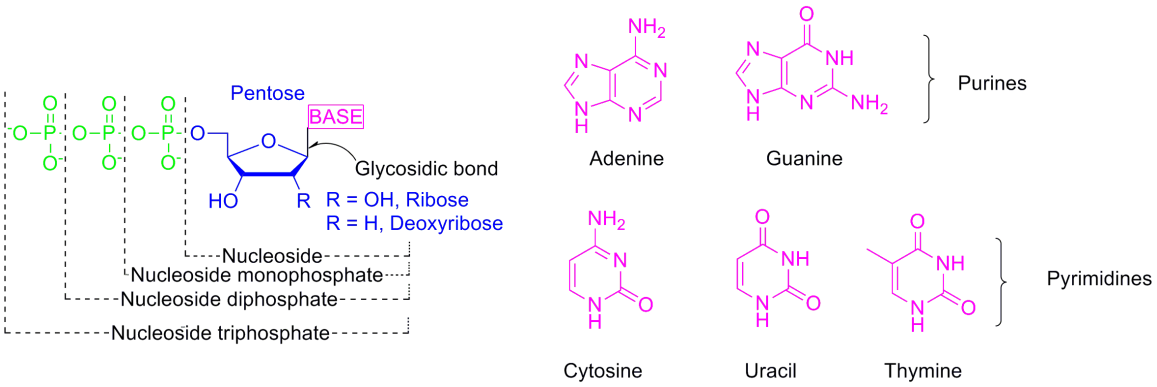


Figure 2.1 Nucleosides and Nucleotides

The nucleosides plays important role in biological system not only by forming the basic structural unit for the macromolecule like DNA and RNA, also by being important structural moieties for different coenzymes such as Nicotinamide adenine dinucleotide (**NAD**$^+$), Nicotinamide adenine dinucleotide phosphate (**NADP**$^+$), Flavin adenine dinucleotide (**FAD**), Coenzyme A (**CoA**). These nucleosides also serve as a part of biological signal molecules and metabolic regulators and function as activated

intermediates in numerous biosynthetic reactions. In addition to the above mentioned facts, the most important role played by these nucleosides and their 5′-O-phosphate, nucleotides are the fundamental way of conservation and transfer of genetic information. Hence nucleosides act as regulatory agents in many varieties of biological functions.

Due to the ubiquitous involvement of nucleosides in cellular processes it is expected that any structural modification to the natural nucleoside would result in many interesting biological properties which makes them excellent candidates for the synthesis of analogs. The investigation for close analogs of the different components of nucleosides emerges as a field of intense research during the last few decades as their metabolic processes became understood. Hence extensive alteration of natural nucleoside both at the sugar and heterocyclic base unit and also the linkage between the sugar and the base unit have been made in order to avoid the drawbacks shown by natural nucleosides in certain applications mainly due to enzymatic degradation, which has resulted in both desirable and deleterious biological properties. This strategy has been actively pursued to discover compounds which functions as antibiotic, anti cancer agents, immuno stimulants, antiviral, anti bacterial, and antitumor agents.[84]

The modified nucleosides and their derivatives became the cornerstones for many kind of antiviral therapy. The search for nucleoside analogs which functions as non-toxic, selective inhibitors of kinase and polymerase for the control of viral diseases has took a great pace during the latter part of 1980s. After Robert Gallo[85] and Luc Montagnier[86] independently declared that a novel retrovirus human immuno deficiency virus (HIV) may have been infecting AIDS patients, the search for a nucleoside analogs has gained a renewed urgency to investigate and find an effective agent against retrovirus. This has resulted in the discovery of a number of derivatives among which **AZT** (3′-azido-3′-deoxythyamidine), **ddI** (2′, 3′-dideoxyinosine), **ddC** (2′, 3′-dideoxycytidine), **d4T** (2′, 3′-

didehydro-3′dideoxythyamidine) are the four nucleoside approved by the FDA for the treatment of HIV infection as reverse transcriptase inhibitors (**Figure 2.2**). The clinical application of theses nucleosides is greatly limited due to their toxicity, side effects, drug resistance and instability due to enzymatic degradation.[87] Therefore it is necessary to search for more stable and less toxic antiviral agents which are not cross resistant with the existing drugs.

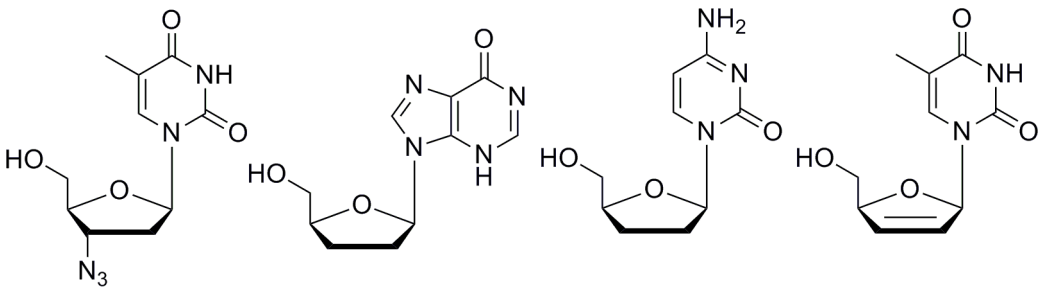


Figure 2.2 FDA approved nucleosidic drugs

In order to have increased resistance towards enzymatic degradation and/or to reduce the toxicity as antiviral agents those are not cross resistant with the existing drugs quite a few classes of nucleoside analogs were isolated or designed and synthesized. One class of analogs was incorporated with some unconventional nucleobases (**Figure 2.3**). For example, Ribavirin[88] has a triazolecarboxamide base which has the potential to mimic either adenine or guanine and it was reported to have a wide range of antiviral activities including influenza A and B. Another class of analogs was known as *C*-nucleosides[89], i.e. Pyrazofurin,[90] Tiazofurin,[91] Selenazofurin,[92] and Oxazofurin[93] characterized by the replacement of the acid labile C–N glycosidic bond by a stable C–C bond. Many of them possess antiviral and antineoplastic activities and are thus of interest in medicinal chemistry.[94]

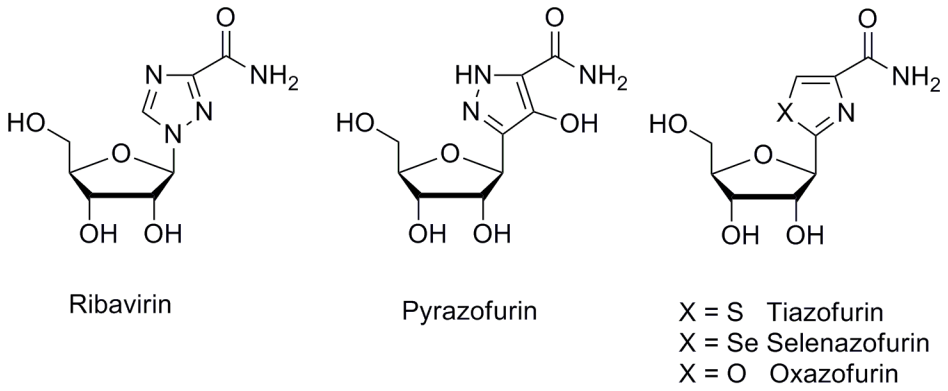


Figure 2.3 Modified nucleosides with unconventional nucleobases

In another kind of modifications where the ring oxygen (-O-) is replaced with other atoms (e.g. -S-, -NH-) in the furanose sugar ring of the nucleosides. With this kind of modification another series of analogs were prepared with varied biological properties. The incorporation of a nitrogen atom into the furanose ring provided a number of new, 3′-deoxynucleoside variations like varying the substitution R (H, CN, OH, NO)[95] on nitrogen of **2.1** (**Figure 2.4**) gives a series of structural analog of AZT. In similar kind of modification another series of azadideoxynucleoside[96] analogs were prepared by varying the nitrogenous base where the nucleobase is directly joined to the ring nitrogen instead of the C-N bond like conventional nucleoside[97] **2.2**. Introduction of a sulfur atom into the 3′-position of the furanose ring afforded structures such as **2.3** which on appropriate nucleobase incorporation give rise to a series of 3′-thiadideoxynucleoside analogs.[98]

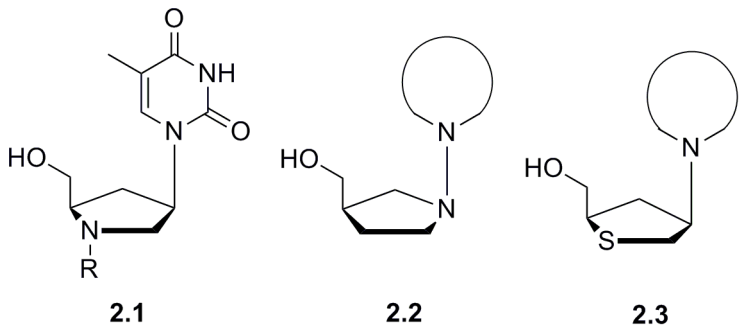


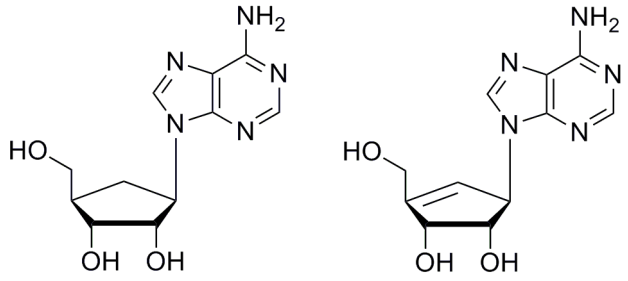
Figure 2.4 Modified nucleosides with varying substituted sugar

The displacement of the ring oxygen of the sugar with a methylene unit (-CH2-), results in carbocyclic nucleoside analogs. These analogs have potent metabolic stability because they are unaffected by phosphorylases and hydrolases that cleave the glycosidic bond of natural nucleosides.[99] On the other hand, they are still good substrates for cellular kinases. The pharmacological actions of conventional nucleosides have been extensively studied, especially as antiviral and antitumor agents. Interestingly, the same enzymes that recognize normal nucleosides displaying a wide range of biological properties also recognize their carba-analogs.

2.II Carbocyclic nucleosides

As discussed earlier the term carbocyclic nucleoside represents a group of compounds which are structurally equivalent to natural and synthetic nucleosides in which the furanose oxygen of the pentose sugar has been replaced by a methylene group. By this transformation the furanose ring is converted in to a cyclopentane unit. By replacing the furanose oxygen which helps[100] in the acid hydrolysis of natural nucleoside in the cell the labile glycosidic bond was now converted to a stronger C-N bond which shows greater metabolic stabilities to nucleoside phosphorylases, which cleaves natural nucleosides.[101] It is perhaps more correct to refer to these compounds as *carbocyclic nucleoside isosteres*[101a] because, strictly speaking, they are not nucleosides. Carbocyclic nucleosides, however, is a convenient term because these compounds undoubtedly exert their biological activity by mimicking the parent nucleosides. Consistent with the presence of the carbocyclic ring they are not subject to the action of nucleoside phosphorylases and hydrolases that cleave normal nucleosides. Conformationally, however, the expected similarity in bond lengths and bond angles between the tetrahydrofuran and cyclopentane rings allow these analogues to behave as substrates or inhibitors of the enzymes that activate and interconvert nucleosides and nucleotides in

living cells. As a result of this likeness, many of these compounds are endowed with an interesting range of biological activities, especially in the areas of antiviral and anticancer chemotherapy. The majority of carbocyclic nucleosides known to date are of synthetic origin but nature has provided two of the most active compounds, aristeromycin (**2.4**) and neplanocin-A (**2.5**) (**Figure 2.5**).



Aristeromycin **2.4**

Neplanocin-A **2.5**

Figure 2.5 Carbocyclic nucleosides in nature

The carbocyclic nucleosides are classified according to their ring sizes as:

2.II.I Three membered carbocyclic nucleosides

Acyclovir (**2.6**) and ganciclovir (**2.7**) are two guanosine analogs which are very effective antiviral drugs the acyclovir is very effective against Varicella zoster (**VZV**) (chickenpox) and Herpes zoster (shingles) infections where as the later one is used for the treatment of Cytomegalovirus (CMV) infection.[102] Compound **2.8** was designed (**Figure 2.6**) and prepared as the analog of acyclovir (**2.6**) and ganciclovir (**2.7**) where a cyclopropane group was employed to impart a certain degree of rigidity required to orientate the hydroxyl groups for molecular recognition. The relative position and special alignment of both the 3′- and 5′- hydroxyl groups of the 2′-deoxyribose ring were also considered.[103] Recently Sharma and co workers synthesized the fluoro derivative **2.9** and found effective against the HSV1-TK (Herpes Simplex Virus-1 Thymidine Kinase).[104] Of the synthesized carbocyclic nucleosides, **(±)-2.8** was very effective against HSV-1 and

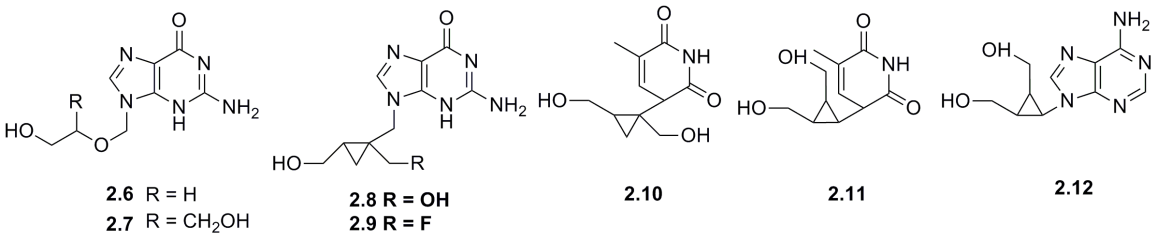


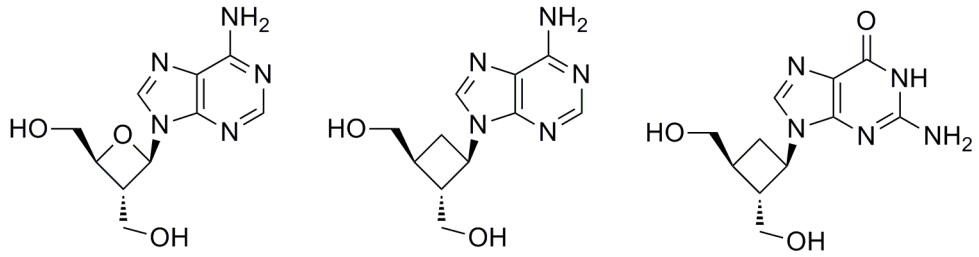
Figure 2.6 Three membered carbocyclic nucleosides

20 times more potent than acyclovir under the same assays conditions, while the pure enantiomer **(–)-2.8** was 2-fold more potent[105] than the racemic mixture. This unusual activity can be explained by the introduction of a conformational restriction modulated by the cyclopropane ring, which forced the hydroxyl groups to adapt a somewhat defined spatial orientation that is required for a better interaction with the involved enzymes. All of these cyclopropyl containing nucleosides are not completely rigid, and they do have preferential hydroxyl group orientation. In other words, their flexibility allows them to interact either with thymidine kinases or viral DNA polymerases in an efficient way leading to potent antiviral agents.

Considering that the proximity of the nucleobase to the carbocyclic ring would favor the interactions with the different involved enzymes, a new series of this family of compounds were designed with the base bonded to the cyclopropyl group instead of to the methylene group as in compound **2.8**. However, these compounds, including **2.10**,[106] **2.11** and **2.12**,[107] are devoid of antitumor activity.

2.II.II Four membered carbocyclic nucleosides

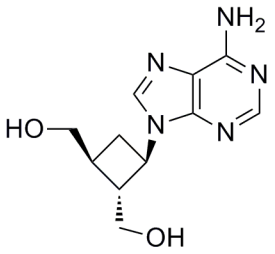
Nucleosides possessing the oxetanosyl N-glycoside feature are structurally an interesting class of compounds (**Figure 2.7**). Oxetanocin A (**2.13**), which was isolated from a culture filtrate of *Bacillus megaterium* by Shimada and co-workers in 1986,[108] is the first and, so far unique example of a natural four-membered ring nucleoside and later synthesized in various laboratory.[109] The ability of Oxetanocin A to display antiviral properties[110] led to the synthesis of many analogs including carbocyclic adenine and



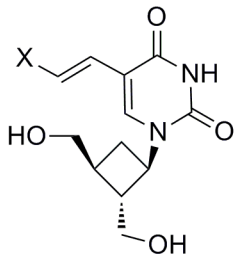
2.13 Oxetanocin A

2.14 Cyclobut-A

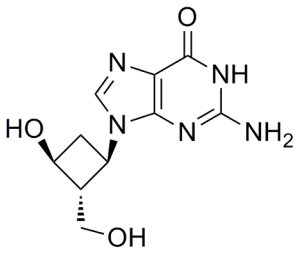
2.15 Lobucavir



2.16



2.17 X= Cl, Br, I



2.18

Figure 2.7 Four membered carbocyclic nucleosides

guanine derivatives. Among these compounds, **2.14**, **2.15,**[111] and **2.16**[112] exhibited a broad spectrum of meaningful antiviral activity toward the Herpes viruses, Hepatitis B virus, and HIV. Racemic carba-oxetanosyl-5-(halovinyl)-uracil **2.17** (X = Cl, Br, I)[113] had excellent activity against VZV (about tenfold more potent than acyclovir), and *2'-nor*-carba-oxetanocin **2.18**[114] showed antiviral activity comparable to that of acyclovir against HSV-1, HSV-2, and VZV, and was about tenfold more potent than acyclovir against human cytomegalovirus (HCMV).

2.II.III Six membered carbocyclic nucleosides

The discovery of potent anti HIV activity of anhydrohexitol **2.19**[115] led to synthesize a few six-membered both cyclohexanyl (**2.20-2.23**)[116] and cyclohexenyl (**2.24-2.28**)[117] carba-nucleosides and evaluation of their biological activity (**Figure 2.8**), but most have not shown significant activity in contrast to the anhydrohexitol nucleosides. The conformation of the carbocyclic sugar and the relative position of the base and the hydroxyl group is a decisive factor which is responsible for the inactivity of six-

membered carba-nucleosides against viruses.[116c] Nearly all the antiviral activity of anhydrohexitol nucleosides **2.20-2.28**[115b] disappeared when the oxygen atom was

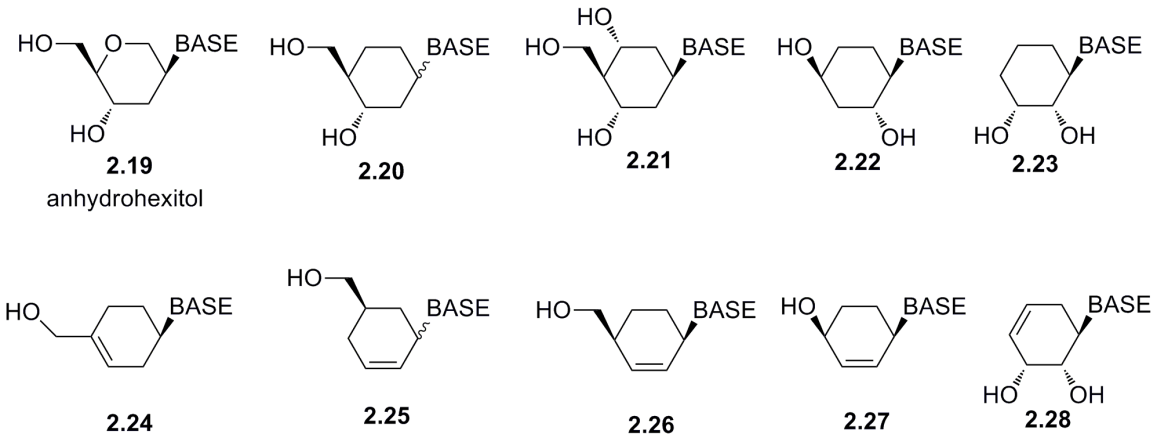


Figure 2.8 Six membered carbocyclic nucleosides

replaced by a methylene group. This lack of antiviral action of carbocyclic congeners may be attributable to the fact that in anhydro-nucleosides, the base adapts an axial position, while in the carbocyclic nucleosides the base is equatorially orientated. Moreover, NMR conformational studies indicate that carbocyclic nucleosides do not mimic well the characteristic 3′-endo conformation of conventional nucleosides (**Figure 2.9**), while the conformation found in anhydrohexitol nucleosides is almost similar to that found in normal nucleosides.[117a] Molecular modeling studies and careful analysis of the proton NMR spectra confirm that the pseudoaxial position of the base corresponds to the preferred conformer.

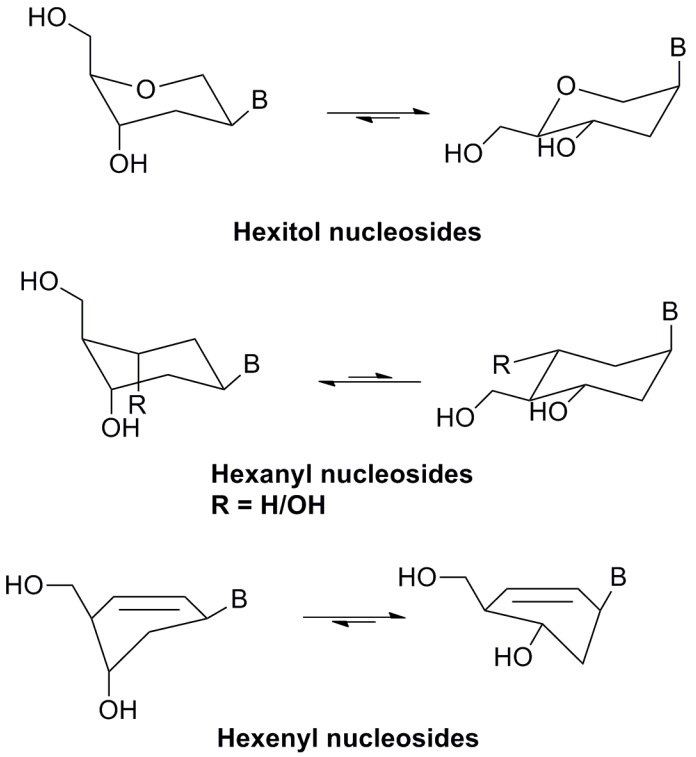


Figure 2.9 3′-endo conformations of conventional nucleosides

2.II.IV Five membered carbocyclic nucleosides

Among the carbocyclic nucleosides five-membered-ring carbocyclic nucleosides are found in numerous natural compounds that have displayed significant biological activities.[84j,118] The discovery and synthesis of modified nucleosides has been the object of great interest.[84k,119] Carbocyclic nucleosides (furanose nucleosides) are an important class of these modified nucleosides and have attracted much recent attention in the development of new antiviral and antitumor therapeutic agents.[120] In carbocyclic nucleosides, the furanose oxygen of the normal nucleoside has been replaced by a methylene group. Due to the absence of a glycosidic linkage, carbocyclic nucleosides are chemically more stable to cleavage by nucleoside phosphorylases and hydrolases.[100] The similar structure of carbocyclic nucleosides to normal nucleosides allows them to retain the potential for therapeutically useful interactions with other enzymes that are involved in nucleoside metabolism.[101a] Many carbocyclic nucleosides are found in natural compounds that display significant biological activities.

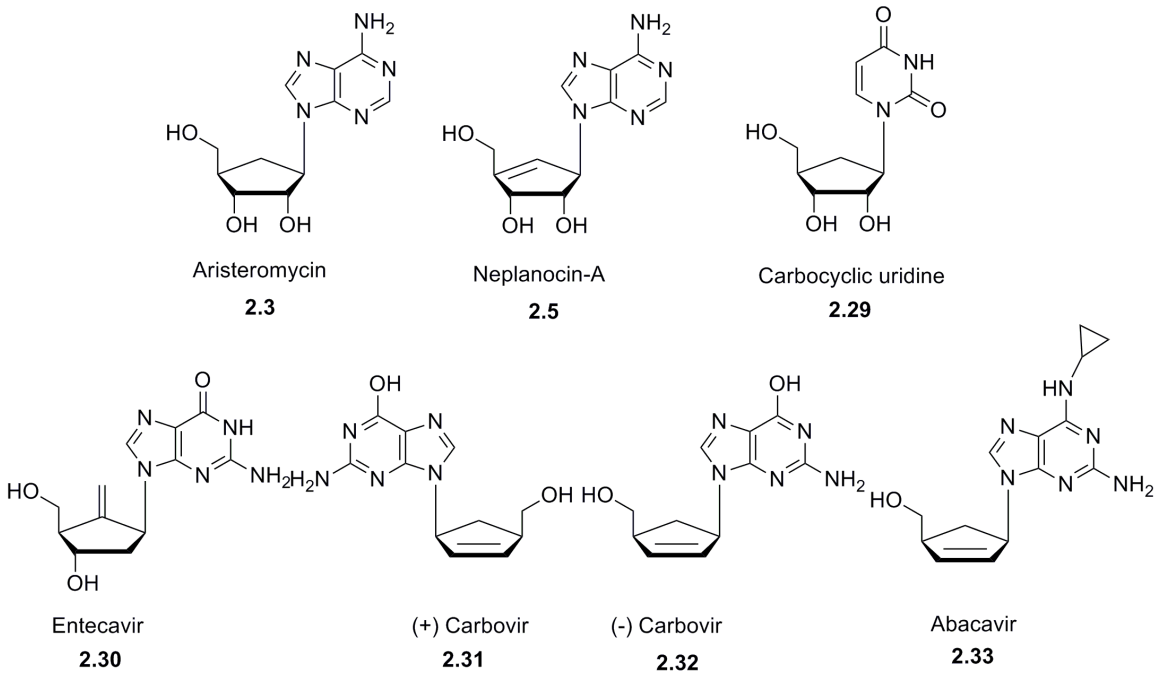


Figure 2.10 Five membered carbocyclic nucleosides

The structures shown in **Figure 2.10** are some of the significant carbocyclic nucleosides. Aristeromycin (**2.3**) and Neplanocin A (**2.5**) isolated from *Streptomyce citricolor*[119] and *Ampullariella regularis,*[121] respectively, showed strong antiviral activity due to their potent inhibition of the cellular enzyme S-adenosyl homocysteine hydrolase.[122] Neplanocin A also has been shown to possess anticancer activity especially against leukemia.[123] The therapeutic importance of natural Aristeromycin (**2.3**) and neplanocin A (**2.5**) attracted many group to synthesize the natural as well as the synthetic analog of the nucleosides. Among the others recently F.A. Khan *et al*. reported the synthesis of both the diastereomers of neplanocin A[124] and Jeong and co workers reported the synthesis of the fluoro homo neplanocin analog[125] similarly Stewart W. Schneller and co workers reported the synthesis 5′-methyl homolog of Aristeromycin.[126] The synthetic nucleoside Entecavir[127] was known to very effective for chronic hepatitis B infection.[128] Carbovir (**2.31-2.32**), a synthetic carbocyclic nucleoside was discovered and subsequently shown to possess significant *in vitro* activity as an inhibitor of HIV reverse transcriptase.[129] The cyclopropylamino derivative of carbovir, abacavir (Ziagen,

1592U89) (**2.33**), which has a higher oral bioavailability than carbovir is now an approved drug for HIV treatment. Although most of these carbocyclic nucleosides have not been developed into drugs, they have led to the development of analogs that are more effective and less toxic therapeutic agents. Accordingly, in search of different analogs, it became necessary to develop efficient synthetic routes that are not only short but also stereochemically and functionally divergent that will enable to incorporate various modifications somewhat easily.

The preceding part of the chapter explains the synthetic route for synthesis of both carbovir and homo-carbovir (analog of carbovir).

2.III Synthesis of 2′,3′-Olefinic Carbocyclic Core of (±) Carbovir

Among the nucleosides shown in figure **2.10** except (+) carbovir (**2.31**) all have **D**-configuration. Of all, (-)-carbovir (**2.32**) was the first analogue which exhibits potent anti-HIV activity in vitro. The first preparation of this isomer of carbovir was reported by Vince *et al*. in 1988.[130] The preparation of its enantiomer (**2.31**) (**Figure 2.11**) was initially attended through approaches like chemo-enzymatic[131] and [2+3] asymmetric cyclo addition reactions.[132] The anti-HIV and anti-HBV activities reside in its β-D enantiomer.[133] However, it is reported that the triphosphates of *β*-**D**- and *β*-**L**-carbovir were approximately equipotent as HIV-reverse transcriptase inhibitors, and the *β*-**L**-carbovir triphosphate exhibited more potent anti-HBV activity.[133-134] The above-mentioned findings prompted synthetic chemists to develop various methodologies until recently for the synthesis[118b,131b,135] of both **L**- and **D**-carbovir and their various analogues with a view to combating a wide range of viral diseases. Furthermore, as representative examples of 2′, 3′-olefinic carbanucleosides, any synthesis of either **D**- or **L**-carbovir assumes considerable significance in view of its application for the preparation of the similar isomers of other members of this class.

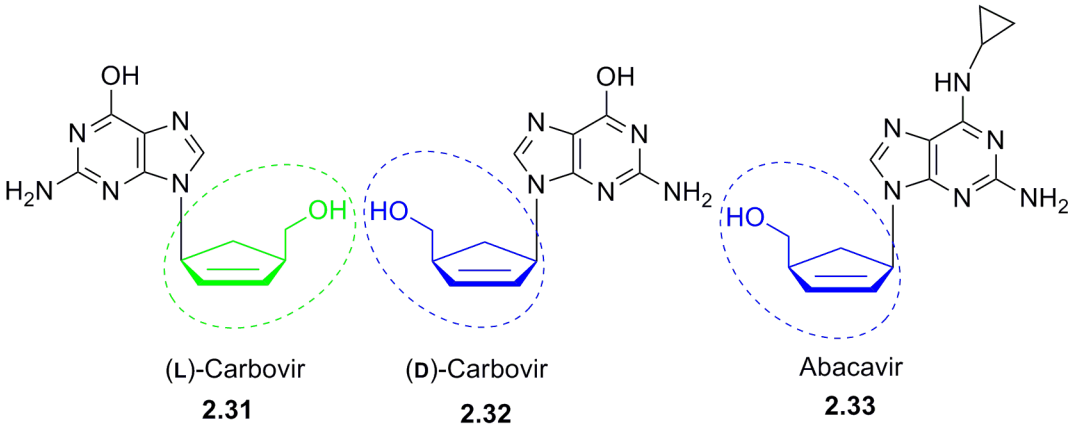


Figure 2.11 Carbovir and Abacavir

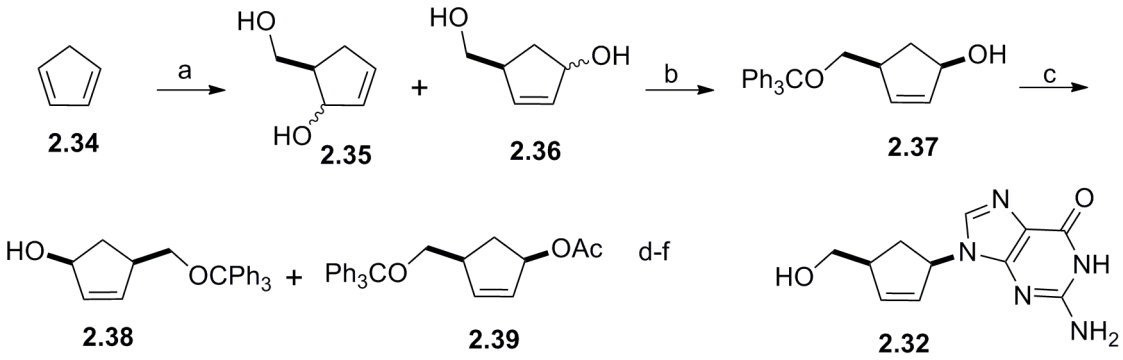
Carbovir (**2.32**) a novel carbocyclic nucleoside is the first synthetic carbanucleoside showing potent *in vitro* activity against human immunodeficiency virus, the causative agent of acquired immunodeficiency syndrome. Its prodrug Abacavir (Ziagen) (**2.33**) also found to possess a great degree of anti cancer and anti viral activity (especially anti HIV). Due to its toxicity carbovir was not developed beyond the preclinical phase but Abacavir was approved and lunched for the treatment of HIV infection. Close observation of the structure of both the **D**-Carbovir and Abacavir reveals that they both possess the same carbocyclic unit. Thus the synthesis of the carbocyclic unit of the nucleoside is of great importance as it opens the door to synthesize its other analogs by incorporating different other nucleobases and these analogs could be amenable for varied types of biological screening in elaborate manner.

After the first successful synthesis of the novel carbocyclic nucleoside carbovir by Vince *et al*. in 1988[130] and with the establishment of its striking biological activity against HIV virus many synthetic chemist has shown interest to synthesizes the carbanucleoside in its enantiomeric pure form. In this regard all these previous syntheses emphasized on the stereoselective synthesis of the desired carbocyclic unit and the combination of the nucleobase to the desired site through varied strategies *viz.* taking the help of enzymatic and chemical resolution of one of the intermediate Roberts *et al.*[131b], Gornowitz *et al.*,[136]

Mac Keith *et al.*,[137] used the cyclo-pentadiene and Prins[138] reaction to synthesize both carbovir and aristeromycin. Similarly Bennche and Gundersen *et al.*[139] synthesize the racemic mixture of Carbovir, at the same time Scheffold *et al.*[140] described a different approach of utilizing a cyclic carbonate and palladium catalyzed substitution reaction. Some other groups also synthesized the nucleoside analog utilizing the asymmetric synthetic path way among which few important syntheses like Hodgson *et al.*[135l,141]. synthesized (–)-Carbovir using the Sharpless direct epoxidation method, similarly using asymmetric cyclo addition reaction method Langlois *et al.*[132] accomplished the synthesis of (+)-Carbovir. Among the other synthesis the recent report employing asymmetric synthesis by Crimmins *et al.*,[135i,142] Florent *et al.*,[135j] Subrata Ghosh *et al.*,[135a] Riera *et al.*,[143] *and* Meier *et al.*,[135c] are to be discussed along with the Roberts[131b] synthesis in the subsequent part of this chapter.

2.III.I Earlier Work in Literature

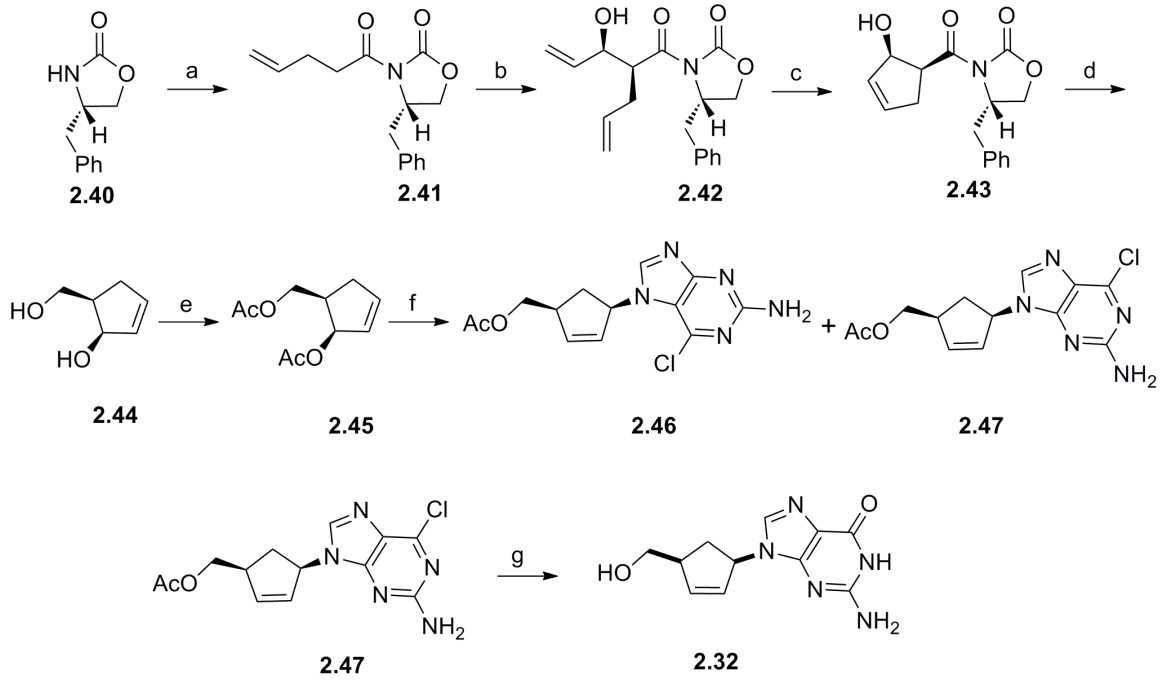
The chemical resolution by preparation of diastereomeric salt or chromatographically separable diastereomers as well as enzymatic resolution of *meso* intermediates and enzymatic resolution of chiral, racemic mixture have been utilized in the synthesis of carbocyclic nucleosides. Roberts and co workers[131b] began the synthesis of (-)-Carbovir by exploiting the known Prins[138] reaction of cyclopentadiene (**2.34**) with aqueous formaldehyde to produce a mixture of *cis* and *trans* 5-hydroxymethylcyclopent-2-en-1-ol (**2.35**) and 4-hydroxymethylcyclopent-2-en-1-ol (**2.36**) (**Scheme 2.1**). The racemic trityl ether **2.37** was obtained by selective protection of the primary alcohol and chromatographic separation of the mixture. The racemic mixture was resolved to access **2.39** in 95% e.e. Palladium catalyzed coupling of acetate **2.39** with 2-amino-6-chloropurine provided carbovir **2.32** after the removal of the trityl ether and displacement of the chloride.



a) CH_2O, HCO_2H, NaOH; b) Ph_3CCl, Separation; c) Vinyl acetate, *Pseudomonas, fluoroscence* lipase 95% e.e.; d) 2-amino-6-chloropurine, NaH, DMF, $Pd(PPh_3)_4$, THF; e) H_2O, HOAC; f) NaOH, H_2O.

Scheme 2.1

Crimmins and Bryan[142] used (*S*)-4-benzyl-2-oxalidinone (**2.40**) derived pentenoyloxalidinone (**2.41**) for Evans dialkylboron triflate protocol for diastereoselective syn aldol condensation with acrolein to produce the aldol product **2.42**, which on subjected to ring closing metathesis by Grubb′s 1st generation catalyst produces the cyclopentenol **2.43** (**Scheme 2.2**). The cyclopentenol (**2.43**) on reduction with $LiBH_4$ get

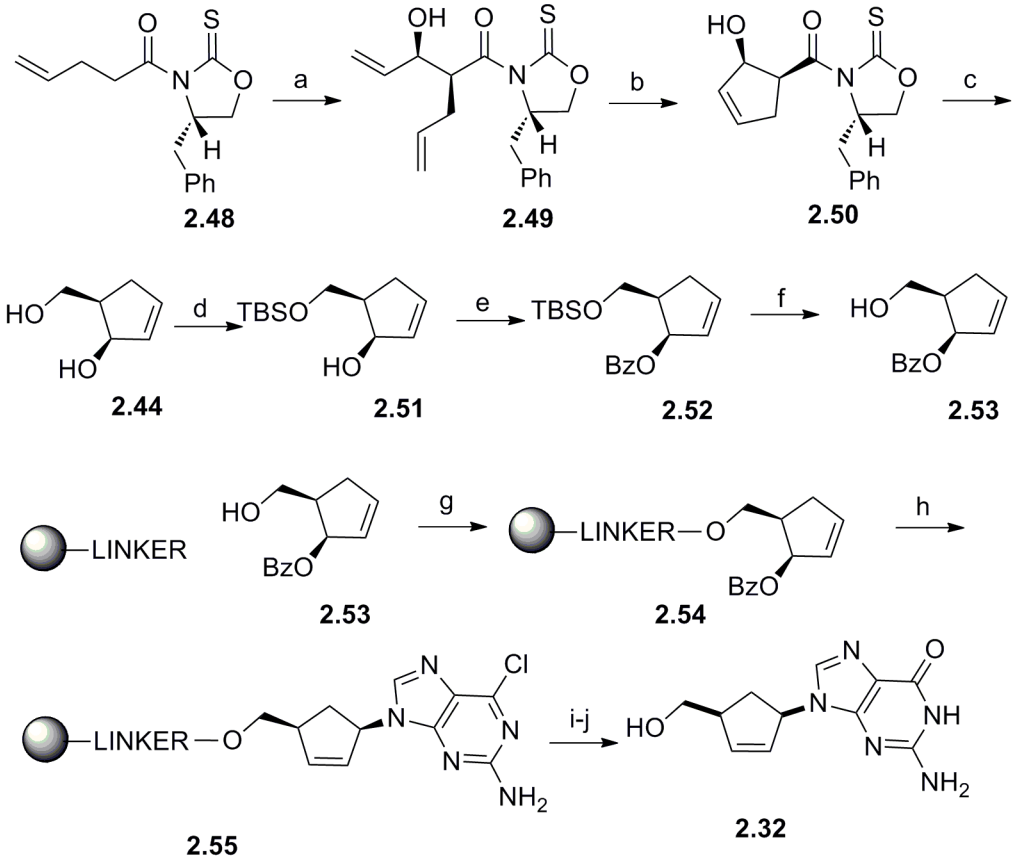


a) n-BuLi, pentenoic pivalic mixed anhydride, THF; b) Bu_2BOTf, Et_3N, CH_2=CHCHO; c) Grubb's 1st generation catalyst, DCM; d) $LiBH_4$, THF, MeOH; e) Ac_2O, Et_3N, DMAP, DCM; f) 2-amino-6-chloropurine, NaH, $Pd(PPh_3)_4$, 1:1 THF:DMSO; g) NaOH, H_2O.

Scheme 2.2

rid of the chiral auxiliary and gave the diol (**2.44**) which on treatment with acetic anhydride gave a diacetate (**2.45**). The diacetate produced was used for the palladium catalyzed coupling with 2-amino-6-chloropurine which produces a mixture of carbocyclic nucleoside **2.46** (N7 coupled) and **2.47** (N9 coupled). The N7 and N9 coupled product are separated through chromatography and the desired N9 (**2.47**) product on hydrolysis gave carbovir **2.32**.

In another modification Crimmins and William[135i] used a solid phase synthesis (**Scheme 2.3**) of the carbocyclic nucleoside to avoid the undesired N7 coupling product, as in the solution phase described in Scheme **2.2**. The key intermediate diol **2.44** was obtained in enantiomeric pure form 4-pentenoyloxazolidinethione **2.48** which was

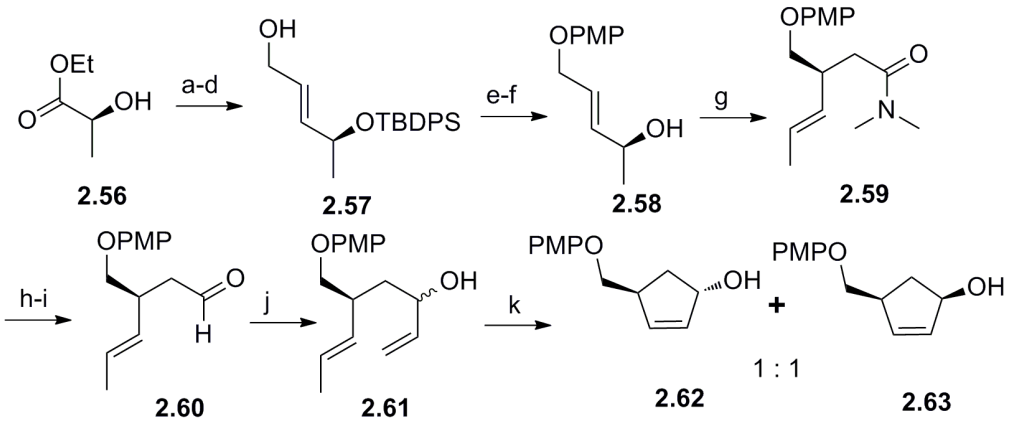


a) $TiCl_4$, EtN*i*-Pr_2, CH_2=CHCHO; b) Grubb's 1st generation catalyst, DCM; c) $LiBH_4$, THF, MeOH; d) TBSCl, Et_3N; e) Bz_2O, Et_3N, DMAP, DCM; f) 5% HF, CH_3CN; g) p-nitrophenyl Wang carbonate resin, EtN*i*-Pr_2, DMAP, DCM; h) 2-amino-6-chloropurine, $Pd_2(dba)_3/PPh_3$ 10 mol%, Pempidine, 1:1 THF:DMSO; i) 5% TFA, DCM; j) NaOH, H_2O

Scheme 2.3

subjected to asymmetric aldol reaction with acrolein followed by catalytic ring closing metathesis (**RCM**) and reductive elimination of the chiral auxiliary. Selective silylation of the primary alcohol in **2.44** with TBSCl and Et_3N was followed by acylation of the secondary alcohol in **2.51** with Bz_2O, Et_3N, and DMAP to provide **2.52**. Desilylation of **2.52** with 5% HF in CH_3CN afforded **2.53**. Allylic benzoate **2.53** was loaded onto *p*-nitrophenyl Wang carbonate resin in presence of EtN*i*-Pr_2 to give the resins bound product **2.54** which on subject to coupling with 2-amino-6-chloropurine in presence of $Pd_2(dba)_3/PPh_3$ 10 mol% and Pempidine gives the desired N9 coupled product **2.55**. The resin bound products **2.55** on treatment with 5% TFA get rid of the resin which after standard transformation gave the carbanucleoside **2.32**.

Florent and coworkers[135j] synthesized the carbocyclic core of (-)-carbovir employing ring closing metathesis as the key step. This has been used to construct the cyclopentenol moiety **2.62** and **2.63**. The work started with the silyl protection of readily available (*S*)-(-) ethyl lactate (**2.56**), followed by reduction of the ester moiety to aldehyde in two steps. The resulting aldehyde was subjected to salt free H-W-E olefination to give an *α,β*-unsaturated ester which on reduction gave the alcohol **2.57** (**Scheme 2.4**).

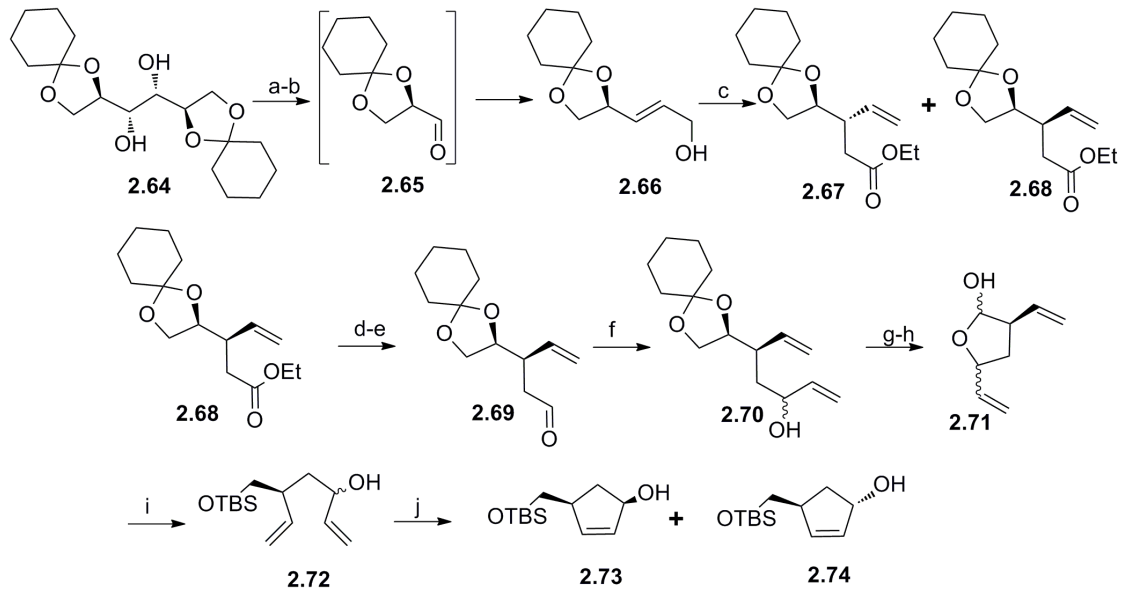


a) *tert*-$BuPh_2SiCl$, Imidazole, DCM; b) *iso*-Bu_2AlH, DCM; c) $Ph_3P{=}CHCO_2Et$, PhMe; d) *iso*-Bu_2AlH, DCM; e) DEAD, PPh_3, 4-MeOPhOH, THF; f) TBAF, THF; g) $Me_2N(MeO)_2CCH_3$, Decalin; h) $LiEt_3BH$, THF; i) $(COCl)_2$, DMSO, DCM, Et_3N; j) $BrHC{=}CH_2$, tert-BuLi, THF; k) Grubb's 1st generation catalyst, DCM.

Scheme 2.4

Protection (PMB) of the primary hydroxyl thus obtained and desilylation of the secondary hydroxyl gave **2.58**. This was subjected to a [3+3] sigmatropic rearrangement by treating with dimethylacetamide dimethylacetal to produce *S*-dimethylamide **2.59** exclusively. This was converted to the corresponding aldehyde **2.60** which on treatment with vinyllithium afforded 1, 6-dienes (**2.61**) as an inseparable mixture of diastereomers **2.61**. This was subjected to RCM to produce a mixture of cyclopentenol **2.62** and **2.63** which were separated by chromatography. Of them, **2.62** could be treated as a precursor of (-)-Carbovir.

Another approach using RCM as a key step to construct the cyclopentenol, the carbocyclic core of carbovir **2.32**, was adopted by S. Ghosh *et al*.[135a] Their synthesis started with Orthoester Claisen rearrangement of the allylic alcohol **2.66** which was obtained from (R)-2, 3-*O*-cyclohexylideneglyceraldehyde (**2.65**) which was prepared following a procedure developed in our laboratory.[144] The rearrangement gave a mixture of the unsaturated esters **2.67** and **2.68** in 1:1 ratio (**Scheme 2.5**). Compound **2.68** after



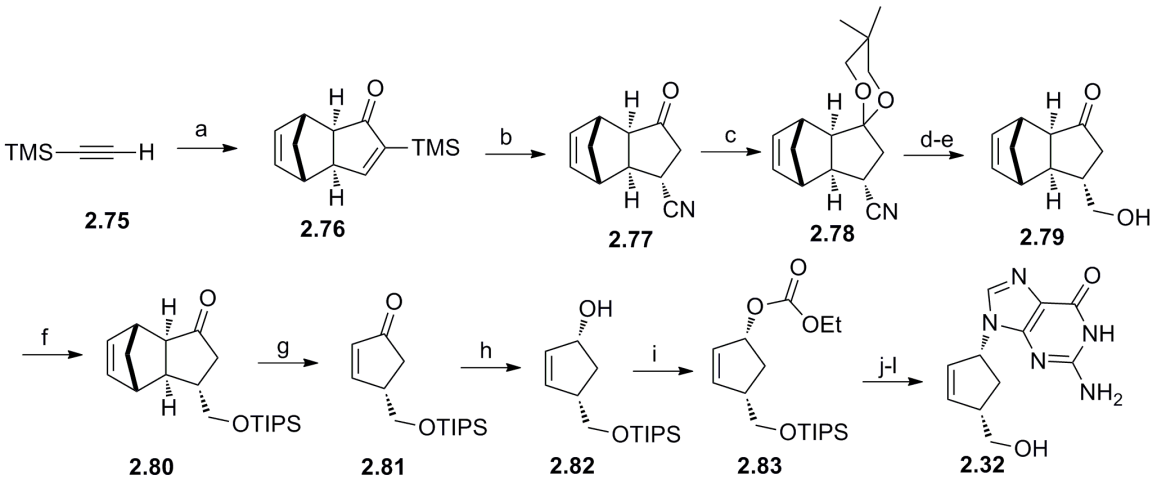
a) $NaIO_4$, CH_3CN/H_2O(3:2), $P(O)(OEt)_2CH_2CO_2Et$, K_2CO_3; b) $LiAlH_4$, Et_2O, -60°C; c) $CH_3CH(OEt)_3$, Propionic acid, 140°C; d) $LiAlH_4$, Et_2O; e) $(COCl)_2$, DMSO, DCM, Et_3N; f) $BrMgHC{=}CH_2$,THF; g) 6 M HCl, THF; h) $NaIO_4$, CH_3CN/H_2O (3:2); i) TBSCl, DMAP, Et_3N, Imidazole; j) Grubb's 1st generation catalyst, DCM; f) TBAF, THF,

Scheme 2.5

separation by chromatography reduced to the aldehyde **2.69** over two steps and the resulting aldehyde was subjected to vinyl-Grignard reaction to give the dienol **2.70** as a diastereomeric mixture in the ratio 1:1. Ketal hydrolysis of the dienol **2.70** followed by periodate cleavage of the vicinal diol produced gave the lactol **2.71** which upon reduction by LAH gave the dienol **2.72**. The dienol on subject to RCM with Grubb's 1st generation catalyst gave an intractable mixture from which the cyclopentenol separation was impossible where as the silyl protected dienol **2.72** gave a smooth reaction and the cyclized products **2.73** and **2.74** are separated by chromatography.

Riera and co workers[143] utilized the *Pauson Khand* adduct of trimethylsilylacetylene (**2.75**) and norbornadiene for an enantioselective synthesis of the carbocyclic nucleoside (**2.32**) (**Scheme 2.6**). The synthetic endeavor starts with the PKR adduct **2.76** obtained from Trimethylsilylacetylene and Norbornadiene, which was subjected to Michale addition of cyanide in presence of NH_4Cl to give the stereoselective addition product **2.77** with concomitant deprotection of methyl group. In order to convert the nitrile functionality to hydroxy methyl the carbonyl group of **2.77** was protected with neopentyl glycol to give **2.78** which was subjected to DIBAL-H reduction followed by reduction of the resultant aldehyde and deprotection of the ketal gave **2.79** over three steps. The free hydroxy of **2.79** was protected and the resulting **2.80** was subjected to retro Diels-Alder reaction using $AlMeCl_2$ as Lewis acid and maleic anhydride as cyclopentadiene scavenger gave cyclopentenone **2.81**. For the introduction of nucleobase the Ketone was reduced using DIBAL-H at low temperature to give allyl alcohol **2.82** with good diastereomeric ratio due to the presence of the large group TIPS on the other face which was separated by chromatography. The resulting allyl alcohol **2.82** was derivatized using ethyl chloroformate to give **2.83** which on treatment with 2-amino-6-chloropurine in presence of NaH and $Pd(PPh_3)_4$ gave the desired base coupled product

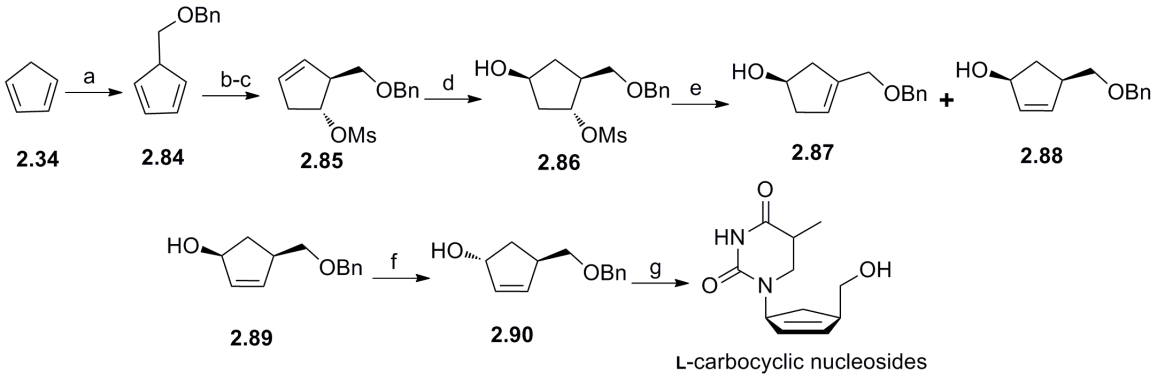
which on deprotection and conversion of the chloro to hydroxy by NaOH gave the desired carbocyclic nucleoside **2.32**.



a) (1) $Co_2(CO)_8$, Hexane, (2) tert-BuSON(CH_2Ph)(PPh_2), Toluene, (3) NMO, DCM; b) KCN. NH_4Cl, DMF, H_2O; c) Neopentyl glycol, p-TsOH, Toluene; d) (1) DIBAL-H, THF, 0°C, (2) $NaBH_4$, MeOH; e) HCl (1M), Acetone; f) TIPS-Cl, Imidazole, DMF; g) $AlMeCl_2$, $(CH_2)_2Cl_2$, 55°C; h) DIBAL-H, THF, -78°C; i) Ethyl chloroformate, Pyridine, DCM; j) 2-amino-6-chloropurine, NaH $Pd(PPh_3)_4$, DMF; k) TBAF, THF; l) NaOH, H_2O

Scheme 2.6

Recently Meier *et al*.[135c] reported the synthesis of **L**-carbocylicnucleosides starting with cyclopentadiene as the starting material. The asymmetric borohydration reaction (**Scheme 2.7**) of **2.84** obtained from **2.34** using (+)-$(ipc)_2BH$ gave the alcohol which was mesylated to give the corresponding mesylate **2.86**, a key intermediate for further transformation. The mesylated product was subjected to various conditions for the stereo selective hydration by 9-BBN with varying oxidizing agents but the result was optimized to best when oxone was used as an oxidizing agent to give the cyclopentenol **2.86**. Elimination of the mesyl from **2.86** in a stereoselective manner using KO-*t*-BU as the base gave a mixture of regioisomer (Saytzeff product) **2.87** and (Hofmann product) **2.88** in a ratio 1:99 respectively. The resulting allyl alcohol was subjected to a Mitsunobu to give the diastereomer **2.89** to which the desired base was coupled employing a modified Mitsunobu protocol to get the **L**-carbocyclic nucleoside.



a) NaH, THF, benzyl chloromethyl ether, DMF, –60 °C; b) (+)-$(ipc)_2BH$, THF, –60 °C NaOH, H_2O_2; c) Et_3N, MsCl, THF; d) 9-BBN, THF, Oxone; e) KO*t*Bu, DMF, reflux; f) PPh_3, DIAD, benzoic acid, Et_2O; g) PPh_3, DIAD, N_3-benzoylthymine, CH_3CN, –40 °C.

Scheme 2.7

2.III.II Our Work

Despite several synthetic procedures being reported for the synthesis of both **D**- (**2.32, 2.33**) and **L**- (**2.31**) carbovir, there is always a scope for the development of newer synthetic strategies that should have more stereo-chemical flexibility, especially regarding the construction of its 2′, 3′-olefinic carbocyclic core. As a result, it should have application towards the synthesis of both enantiomers of carbovir and also of other olefinic carbanucleosides through incorporation of different bases. It is worth mentioning that the majority of the reported procedures were associated with the formation of undesired byproduct during construction of the 2′, 3′-olefinic carbocyclic core. This

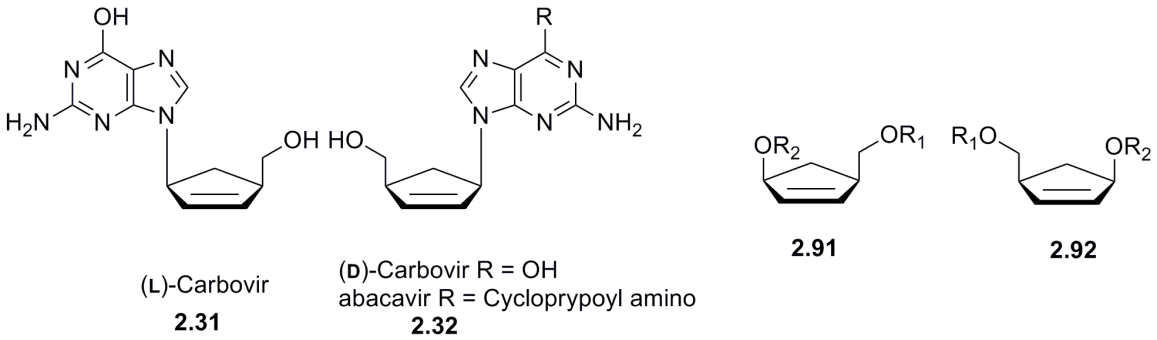
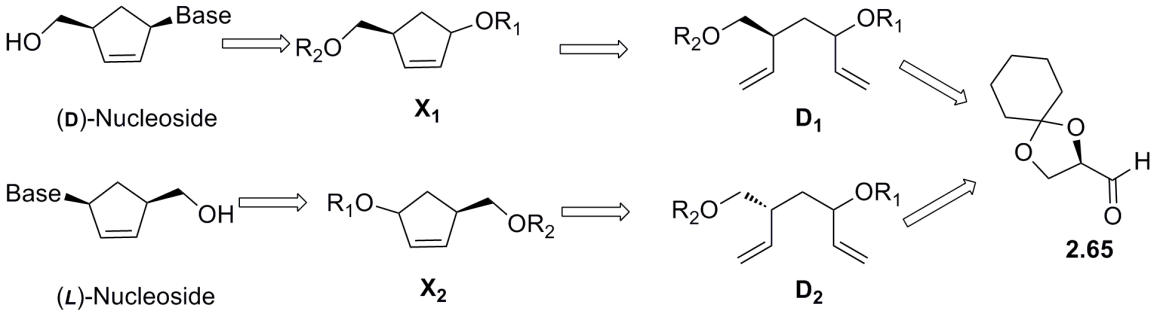


Figure 2.12 Carbocyclic core of 2′,3′-olefinic nucleoside

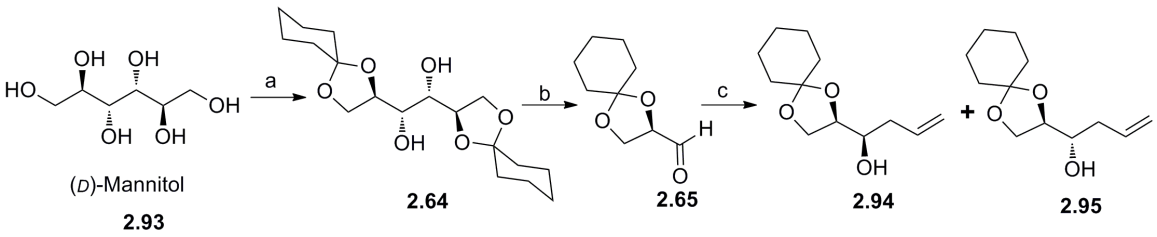
prompted us to look for a synthetic scheme which will produce the target molecule **2.91** and **2.92** with less or no unwanted stereoisomers (**Figure 2.12**).

Retrosynthetic analysis (**Scheme 2.8**) of **2.31** and **2.32** suggested that for convergent preparation of its (**L**)-(+)- and (**D**)-(-)-enantiomers it is desirable to construct the basic carbocyclic core, i.e., 1, 4- disubstituted 2, 3-cyclopentene precursors ($\mathbf{X_1}$ and $\mathbf{X_2}$) which should be amenable for stereo-differentiating nucleobase additions in the desired manner compatible with the enantiomer of **2.31** and **2.32** to be obtained. In this regard, there is a scope to develop efficient strategies to have access to branched 1,6-dienes $\mathbf{D_1}$ and $\mathbf{D_2}$ that would give rise to $\mathbf{X_1}$ and $\mathbf{X_2}$, respectively, through ring closing metathesis reaction.[55a,71,145] The intermediate $\mathbf{X_1}$ and $\mathbf{X_2}$ can be synthesized from easily accessible (*R*)-2,3-*O*-cyclohexylideneglyceraldehyde (**2.65**) which was synthesized from ***D***-mannitol following the standard protocol followed in our lab[144,146]. The synthesis of the intermediate $\mathbf{X_1}$ and $\mathbf{X_2}$ can lead to the formal synthesis of both the **D**- and **L**- carba nucleosides due its structural similarity.



Scheme 2.8

Our synthetic mission started with (*R*)-2, 3-*O*-cyclohexylideneglyceraldehyde (**2.65**) that was prepared by $NaIO_4$ cleavage of di-*O*-cyclohexylidine **D**-mannitol **2.64** of commercially available **D**-mannitol (**2.93**) origin. (**Scheme2.9**).[144a,146] Luche's[39] allylation of **2.65** gave the corresponding homoallylic alcohol in as a mixture of diastereomers (**2.94** and **2.95**) with predominant formation of *anti*-isomer [*syn* - **2.94:** *anti*-**2.95:: 5: 95**]. Both these isomers were separated easily by column chromatography to obtain each in homochiral form.

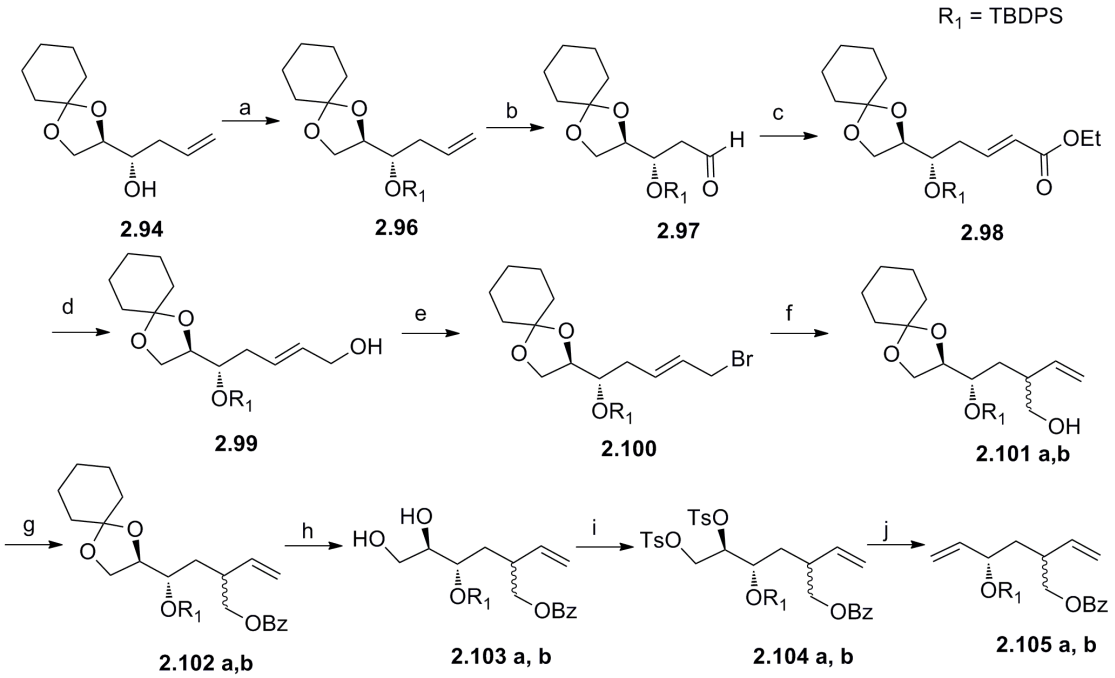


a) Cyclohexanone, BF_3 etherate, triethyl orthoformate, DMSO; b) $NaIO_4$, CH_3CN/H_2O(6:4); c) Allylbromide, Zn/NH_4Cl, THF.

Scheme 2.9

Silylation of the major *anti* alcohol **2.95** afforded **2.96** in quantitative yield. The formation of the product was evident from the absence of hydroxyl band in its IR and the appearance of the signals due to silyloxy and aromatic moiety in its PMR spectrum (**Figure 2.13-2.14**). Ozonolysis of its olefin and reduction of the resulting ozonide in situ with PPh_3 gave relatively unstable aldehyde **2.97** (**Figure 2.15-2.16**). This was quickly subjected to Wittig-Horner olefination[47] to obtain *α, β*-unsaturated ester **2.98** (NMR spectra in **Figure 2.17-2.18**). The presence of 2E-ester in **2.98** was ascertained from its ^{1}H-NMR spectrum (**Figure 2.17**) which showed the two olefinic protons at δ 5.66 as a doublet (J = 15.6 Hz) and at δ 6.90 as a td (J = 8, 15.6 Hz). Its ester carbonyl showed a signal at δ 166.2 in its ^{13} C-NMR spectrum (**Figure 2.18**). DIBAL-H reduction of **2.98** afforded allylic alcohol **2.99** (**Figure 2.19-2.20**) in good yield. The progress of the reaction was evident from the absence of all signal corresponding to ester functionality in IR as well as ^{13} C-NMR spectra of **2.95** and the presence of signals of olefinic protons [at δ 5.4-5.5 in ^{1}H-NMR spectrum (**Figure 2.19**) and at δ 127.4 and δ 127.6 in ^{13} C-NMR spectrum (**Figure 2.20**)] . This was converted into the allylic bromide **2.100** in two steps *viz.* mesylation and bromination of the corresponding mesylate with NaBr in good overall yield. The product **2.100** showed the absence of any D_2O exchangeable hydroxyl signal in its ^{1}H-NMR spectrum (**Figure 2.21**) and the presence of a signal at δ 45.0 due to CH_2Br in ^{13} C-NMR spectrum (**Figure 2.22**). In the next crucial step, formaldehyde (separately produced by heating paraformaldehyde) was subjected to allylation on

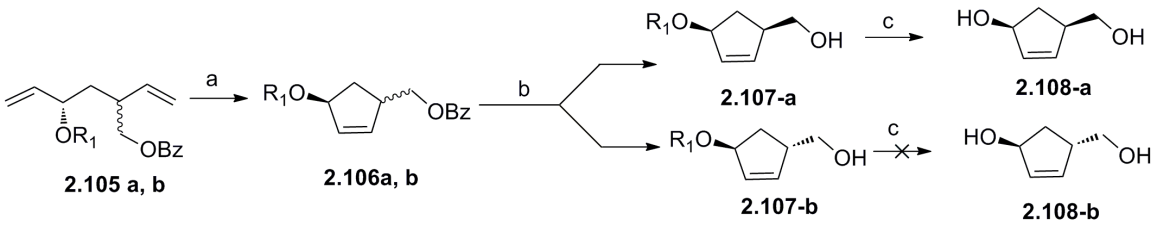
treatment with compound **2.100** following Luche's procedure[39]. The allylation reaction took place efficiently (**73.5**% yield) to obtain homoallylic alcohol **2.101** (**Figure 2.23-2.24**) as a mixture of diastereomers **2.101a** and **2.101b**. Unfortunately, the diastereomers (**2.101a**/ **2.101b)** could not be separated from each other by column chromatography. All our efforts to separate those using varied solvent combinations as eluent went in vain. The ^{1}H-NMR spectrum of compounds **2.101a**/**b** showed signals at δ 5.0 (2H) and δ 5.7-5.9 (1H) (**Figure 2.23**) corresponding to their terminal olefin that was produced by the above mentioned allylation reaction. Also in their ^{13}C-NMR spectrum, the same terminal olefin was evident from the signals at δ 116.8, 117.2 and 139.3 (**Figure 2.24**). The mixture of **2.101a** and **2.101b** was benzoylated to produce benzoate. The product was also found to be an inseparable mixture of diastereomers **2.102a, b** (NMR spectra in **Figure 2.25-2.26**). The benzoate moiety of the product showed a signal at δ 166.3 in its ^{13}C-NMR spectrum. This was subjected to deketalisation on treatment with aqueous trifluoroacetic acid to produce diol **2.103** as a chromatographically inseparable mixture of diastereoisomers **2.103a, b** (**Figure 2.27-2.28**). Its ^{1}H-NMR spectrum showed the disappearance of broad multiplets at δ 1.4-1.6 corresponding to cyclohexylidene protons (10H) (**Figure 2.27**). Conversion of the 1, 2-diol unit of **2.103** into a terminal olefin was accomplished in two steps, *viz.*, (a) di-tosylation and (b) treatment of the resulting ditosylate **2.104a, b** with Zinc/NaI in DMF. This resulted in the formation of the bis-olefin as a chromatographically inseparable diastereomeric mixture **2.105a, b** (**Figure 2.29-2.30**)



a) TBDPSCl, Imidazole, DMAP, DCM; b) O_3, PPh_3, DCM,-78 °C; c) NaH, $C_2H_5COOCH_2P(O)(OC_2H_5)_2$, THF, 25 °C; d) DIBAL-H, THF, -78 °C; e) (1) MsCl, Et_3N, DCM, 0 °C, (2) NaBr, $NaHCO_3$, Dry Acetone, 25 °C; f) Zn/NH_4Cl, CH_2O, THF, 25 °C; g) BzCN, Et_3N, DCM, 25 °C; h) Aq.TFA (80%), CH_2Cl_2, 0 °C; i) TsCl, Py, DMAP, 25 °C; (j) Zn, NaI, DMF, 80 °C;

Scheme 2.10

Having obtained the bis-olefin **2.105,** the stage was set for the construction of cyclopentene moiety through RCM. Accordingly, it was subjected to RCM using Grubbs 1st generation catalyst which produced 1, 4-disubstituted 2-cyclopentene **2.106** (**Figure 2.31-2.32**) as an inseparable mixture of two diastereomers **2.106a, b** (**Scheme 2.11**). Unfortunately, this time also the diastereomers couldn't be separated from each other by column chromatography. The mixture was subjected to alkaline hydrolysis to get rid of benzoate protection which enabled the separation of the two diastereomers in to **2.107a** (**Figure 2.33-2.34**) and **2.107b** (**Figure 2.35-2.36**). In the next step it was necessary to deprotect the 2° hydroxyl of **2.106 which** will enable coupling of the nucleobase to the pseudosugar to produce the corresponding carbanucleoside. In this endeavor, both the diastereomers **2.107a** and **2.107b** were individually subjected to desilylation. It was observed that desilylation reaction went smoothly in case of **2.107a** giving rise to **2.108a** (**Figure 2.37-2.38**) but in case of **2.107b** the reaction was unsuccessful even on stirring the reaction mixture overnight.

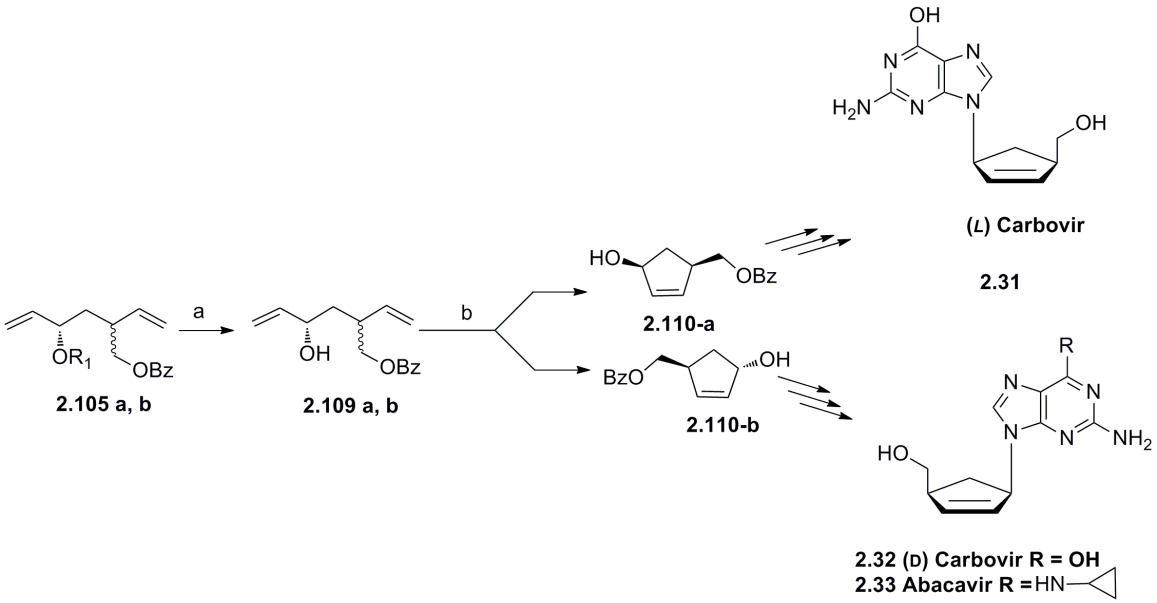


a) $(PCy_3)_2Cl_2RuCHPh$, Dry Benzene, 60 °C, 24 h; b) K_2CO_3, MeOH, 0 °C to 25 °C; c) TBAF, THF, 0 °C to 25 °C;

Scheme 2.11

This prompted us to modify our scheme by performing desilylation at an initial stage. Hence, **2.105** was desilylated by treating it with TBAF (**Scheme 2.12**) to afford an inseparable diastereomeric mixture of 1, 6-dienes **2.109a, b** (**Figure 2.39-2.40**). This was subjected to ring-closing metathesis reaction using first-generation Grubbs' catalyst $[Cl_2(PCy_3)_2RuCHPh]$[55b,66b,145]. The metathesis reaction produced 1,4-disubstituted-2-cyclopentene **2.110** in 90.5% yield, as a mixture of *cis*-**2.110a** and *trans*-**2.110b**. To our delight, compounds **2.110a** (**Figure 2.41-2.42**) and **2.110b** (**Figure 2.43-2.44**) were found to be easily separable from each other by column chromatography (silica gel, 0-10% EtOAc in hexane) to obtain both of them in homochiral form (*cis*-**2.110a** : *trans*-**2.110b** : 48.3:51.7). The presence of cyclopentene olefin of *cis*-**2.110a** and trans-**2.110b** was evident in their ^{1}H-NMR spectra at δ 5.92 and δ 5.9-6.0 respectively. The relative stereochemistry (*cis*-**2.110a** and *trans*-**2.110b**) between the substituents at **C-1** and **C-4** in the 2,3-cyclopentene **2.110** could be determined by analyzing the chemical shifts of their CH_2 protons at **C-5** in their respective ^{1}H-NMR spectra that were found to be comparable with the reported pattern [135c,135j]. The individual signals of both protons at C-5 [$H_{5\alpha}$: δ-1.52 (dt, J = 13.8, 4.5 Hz); $H_{5\beta}$: δ-2.4-2.6 (m, 1H)] in *cis*-**2.110a** were found to be widely separated from each other, whereas the corresponding signals of *trans*-**2.110b** were found to be almost overlapping [$H_{5\alpha}$ and $H_{5\beta}$: δ-1.9-2.1, m, 2H]. In hindsight, the stereoselectivity in Luche's allylation (step f, Scheme **2.10**) for the preparation of **2.101**could be tentatively ascertained from the relative ratio of the isolated amounts of

2.110a and **2.110b**, as the subsequent steps did not involve any stereo-differentiating reactions.



a) TBAF, THF, 0 °C to 25 °C; b) $(PCy_3)_2Cl_2RuCHPh$, Dry Benzene, 60 °C, 24 h;

Scheme 2.12

Both compounds **2.110a** and **2.110b**, possessing a free secondary hydroxyl at **C-1** and a benzoyloxymethyl at **C-4**, have good skeletal as well as stereochemical resemblance with the known precursors[131b,135k,135m] of (***L***)-(+)-carbovir and (***D***)-(-)-carbovir, respectively. For example, the 4-*O*-silyl ether analogue[135m] of *trans*-**2.110b** has been utilized for the synthesis of ***D***-(-)-carbovir through Mitsunobu coupling with 2-amino-6-chloropurine that was associated with inversion at **C-1**. On the other hand, the corresponding dicarbonate[135k] and 4-*O*-tritylhydroxymethyl-1-acetyl[131b] analogues of *cis*-**2.110a** have individually been utilized for the synthesis of ***L***-(+)-carbovir through tetrakis-Pd-mediated coupling with the same base employing Trost's procedure [135n,135q] that took place along with stereochemical retention at **C-1**.

Thus, a simple and stereo divergent approach has been developed for the formal synthesis of both enantiomers of carbovir. Among them, Luche's allylation of formaldehyde with **2.100** (step f, Scheme **2.10**) to obtain a C-branched homoallylic

alcohol **2.101** has been judiciously exploited to ultimately have a smooth access to the precursor (**2.105a,b**) of the metathesis reaction. It is worth noting that the moderate stereoselectivity of this crucial allylation reaction proved highly advantageous to achieve its stereo divergence in this route. This was finally realized by column chromatographic separation of the Grubb's metathesis product **2.110** to obtain good amount of both diastereomers **2.110a** and **2.110b** which eventually could be treated as the potential precursors of both enantiomers of carbovir. It can be presumed that the same intermediates **2.110a** and **2.110b**, either themselves or in their other hydroxyl protected forms, could be useful for the syntheses of other 2′,3′-olefinic carbocyclic nucleosides possessing (**L**)- and (**D**)- configurations, respectively.

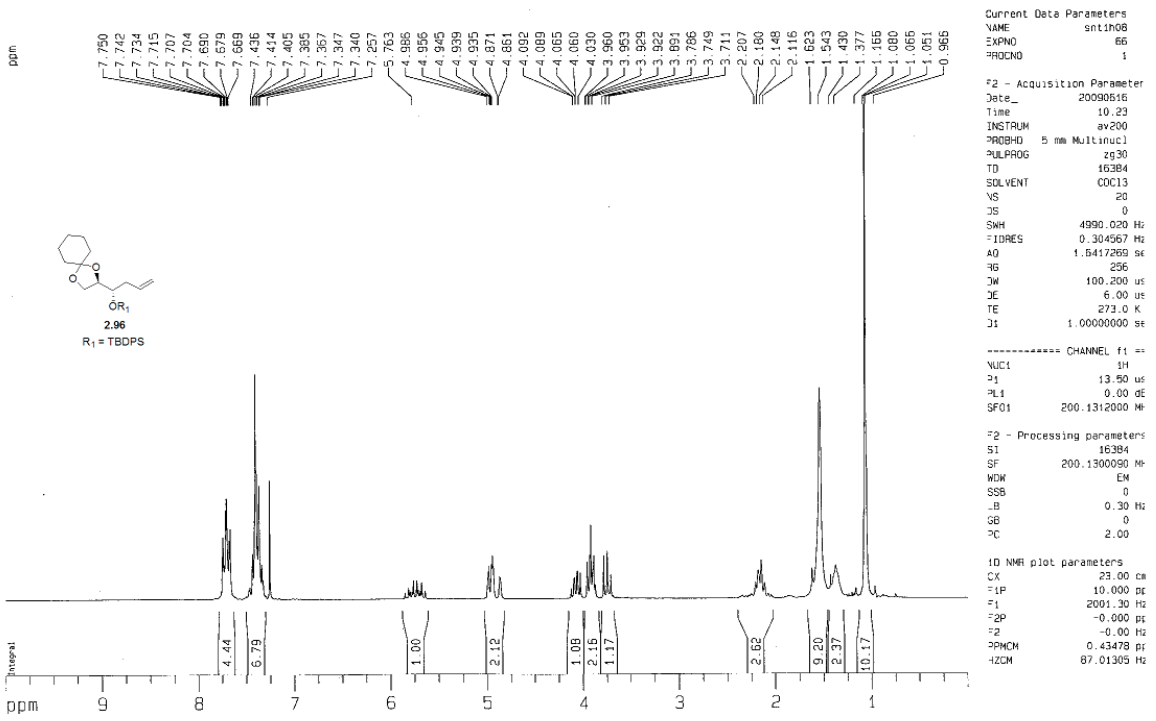


Figure 2.13 ^{1}H NMR spectrum of 2.96

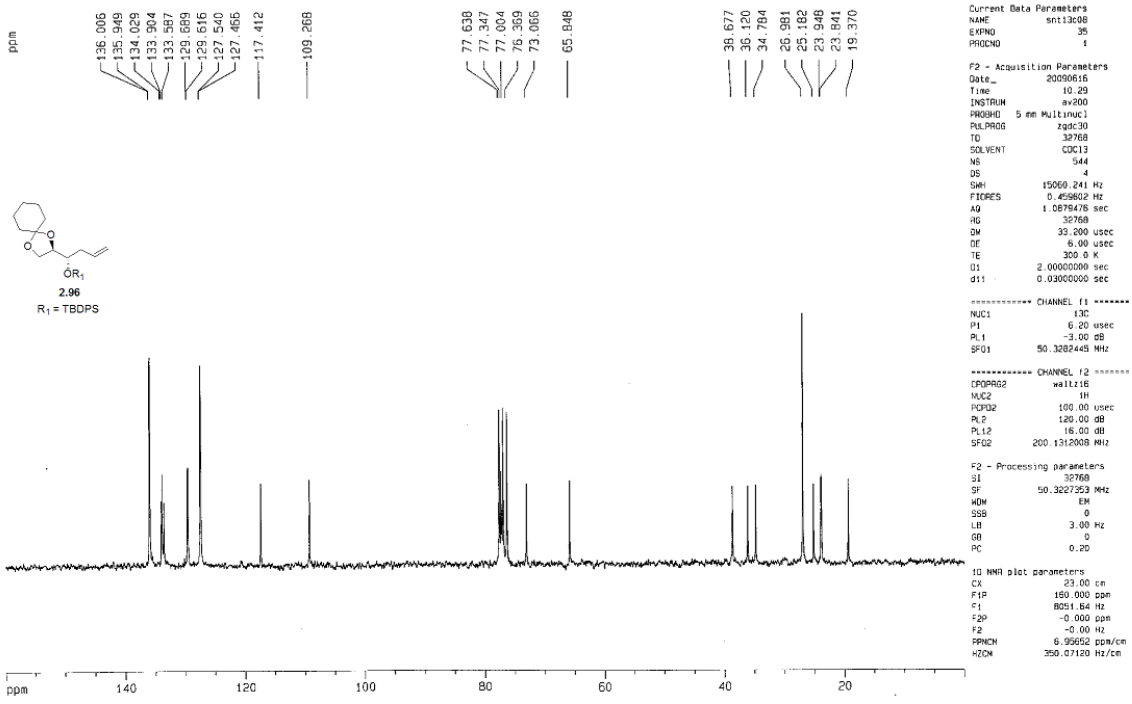


Figure 2.14 ^{13}C NMR spectrum of 2.96

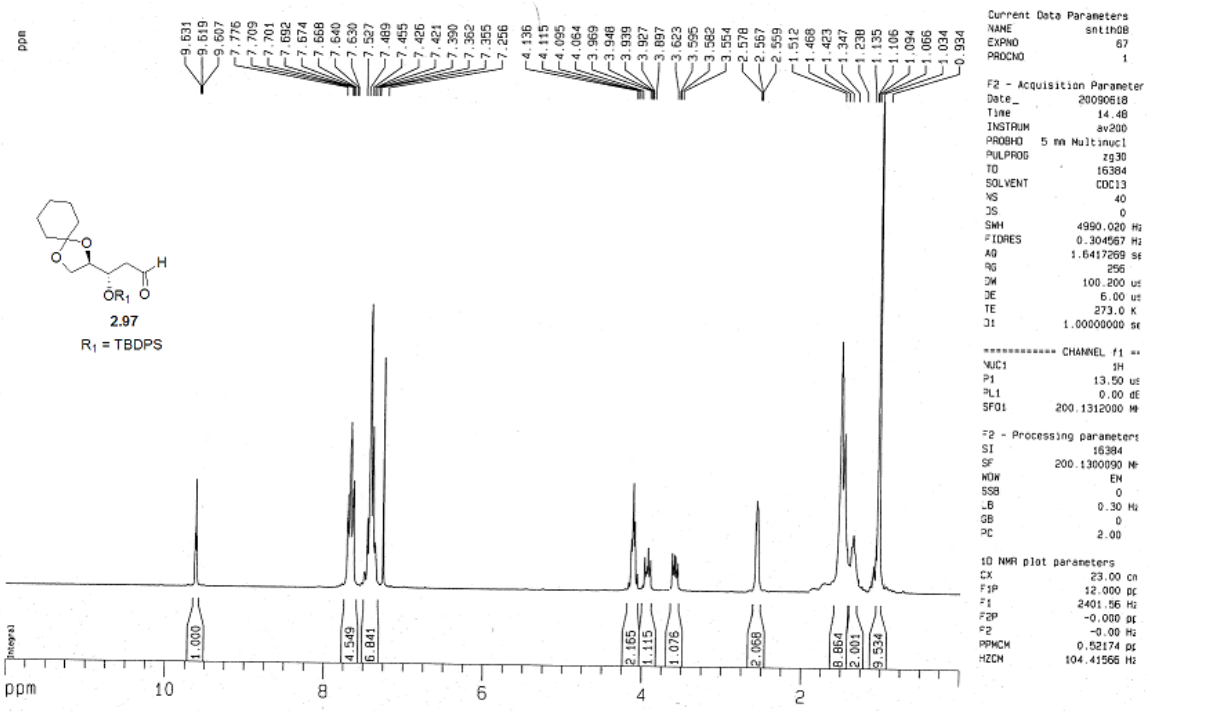


Figure 2.15 ^{1}H NMR spectrum of 2.97

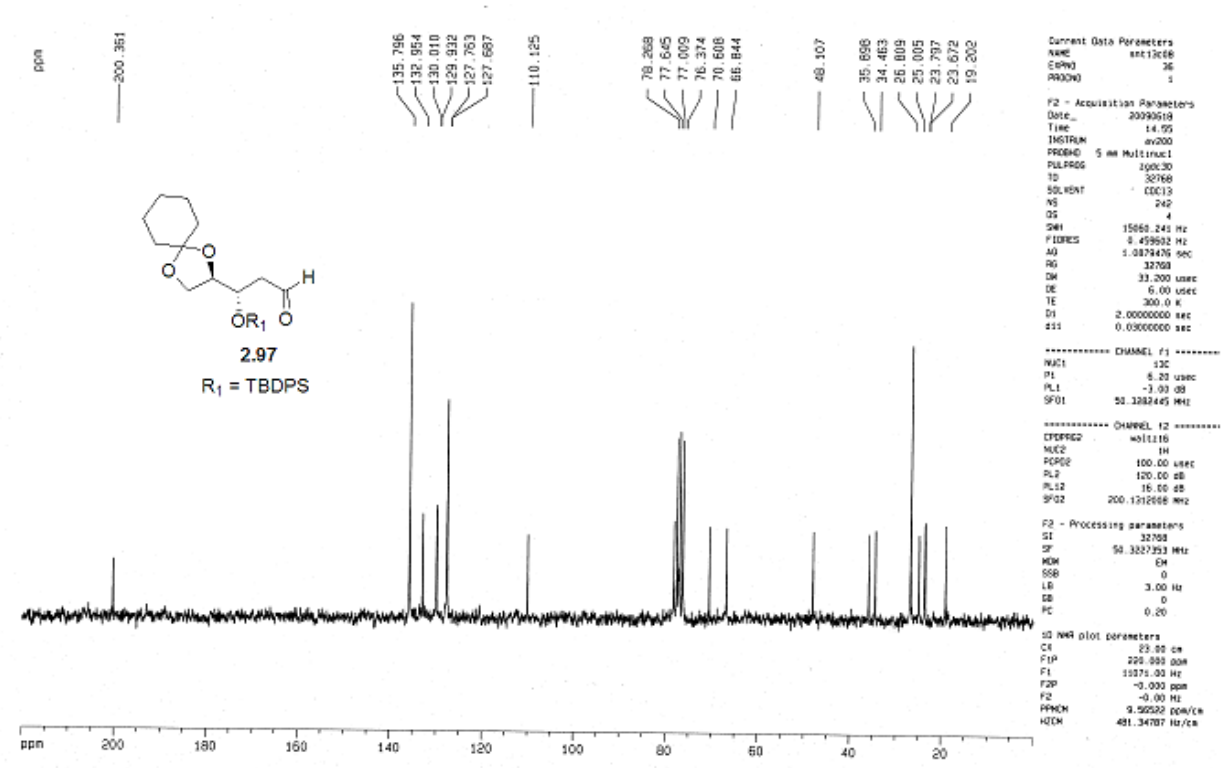


Figure 2.16 ^{13}C NMR spectrum of 2.97

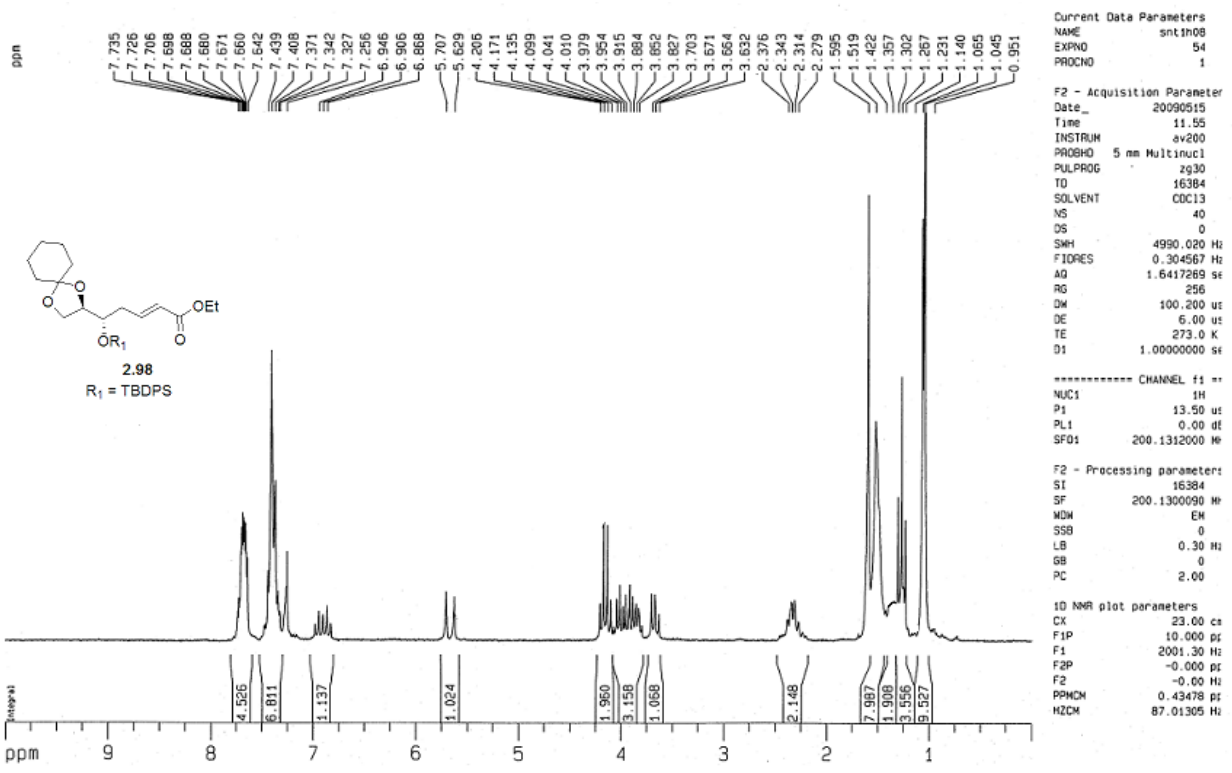


Figure 2.17 ^{1}H NMR spectrum of 2.98

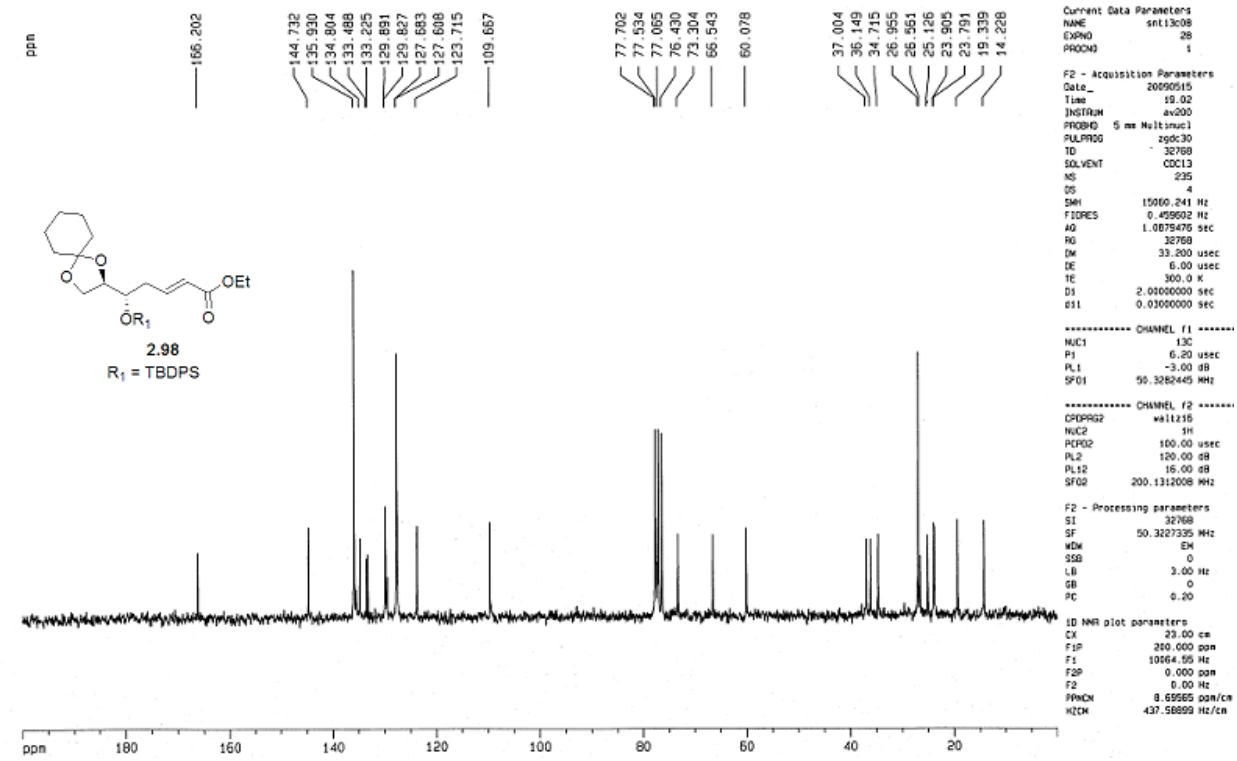


Figure 2.18^{13}C NMR spectrum of 2.98

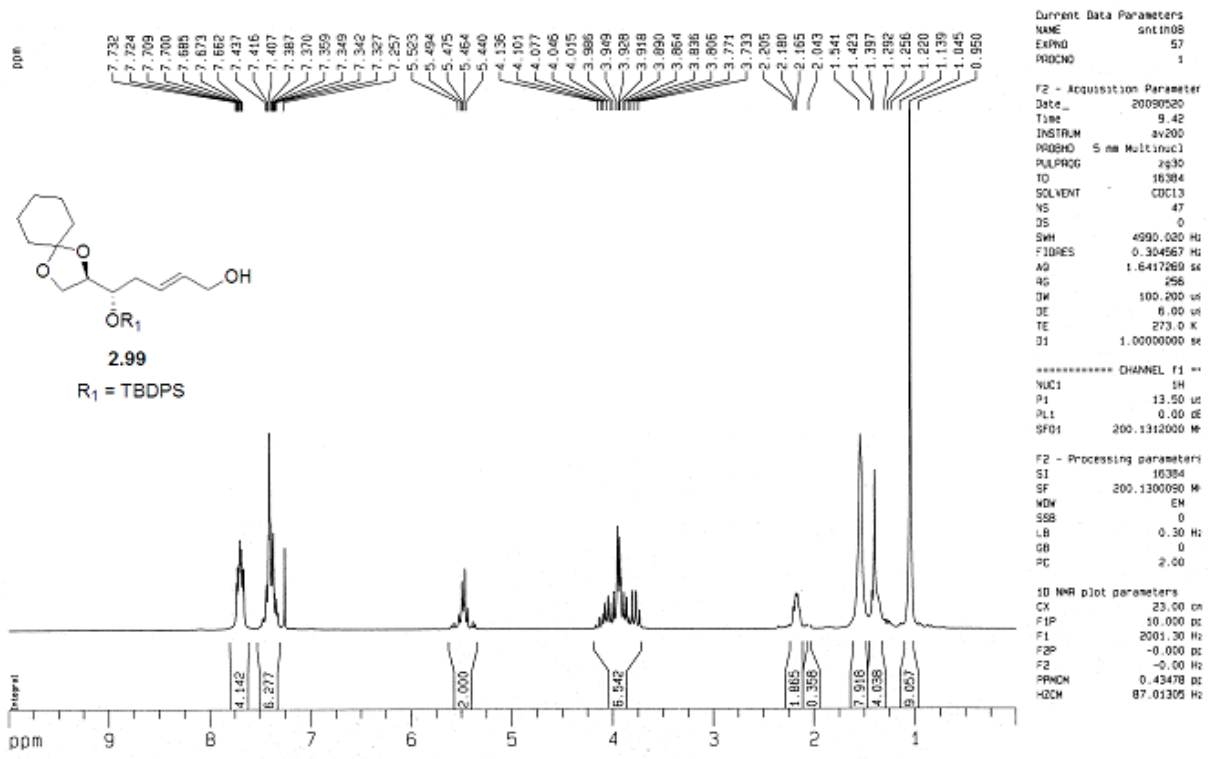


Figure 2.19 ^{1}H NMR spectrum of 2.99

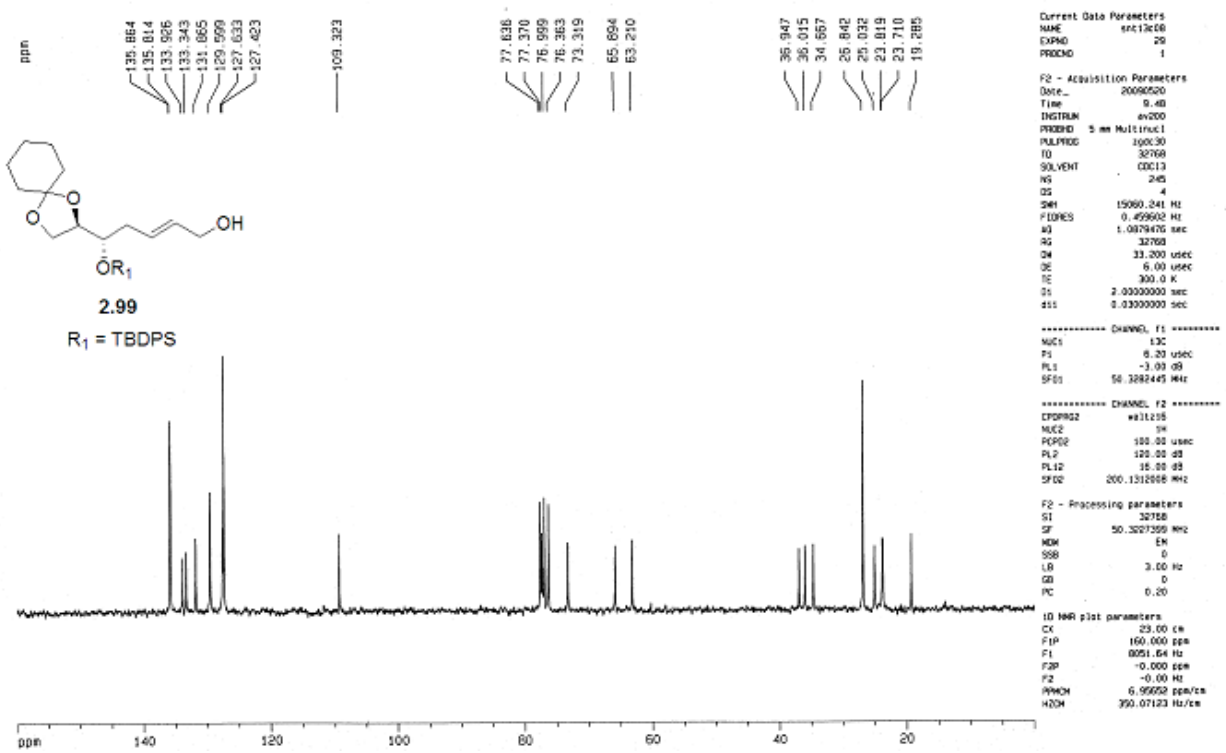


Figure 2.20 ^{13}C NMR spectrum of 2.99

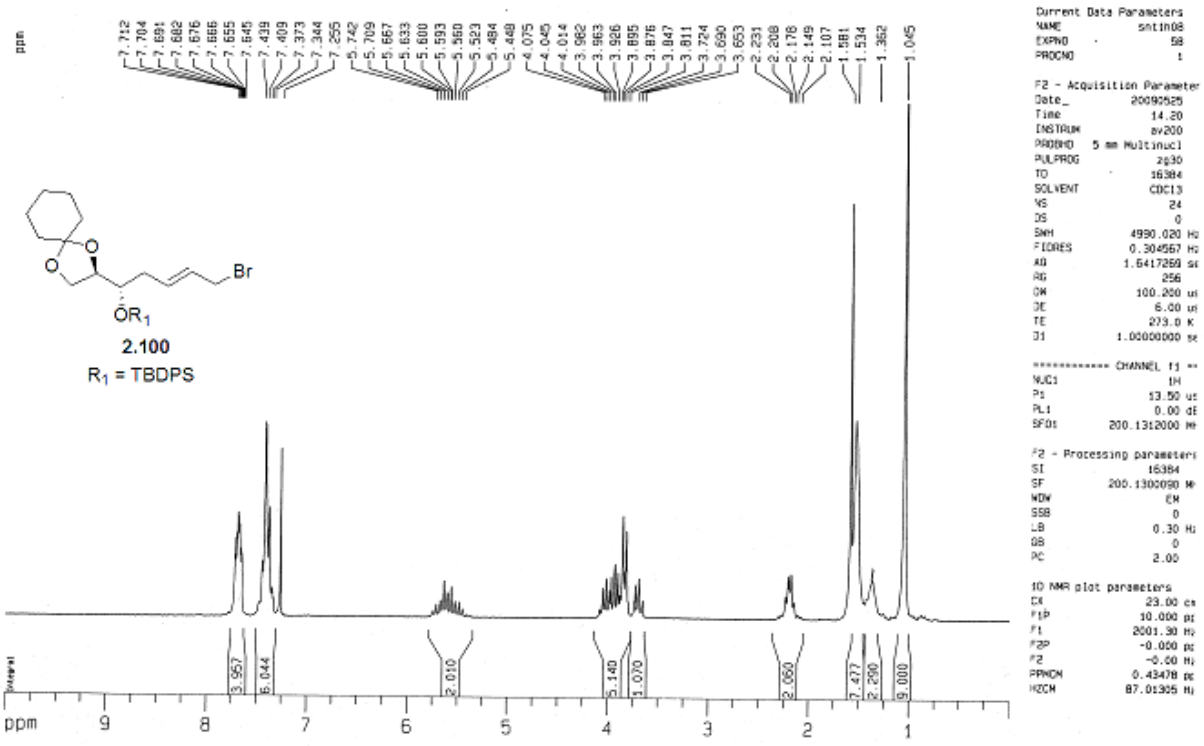


Figure 2.21 ^{1}H NMR spectrum of 2.100

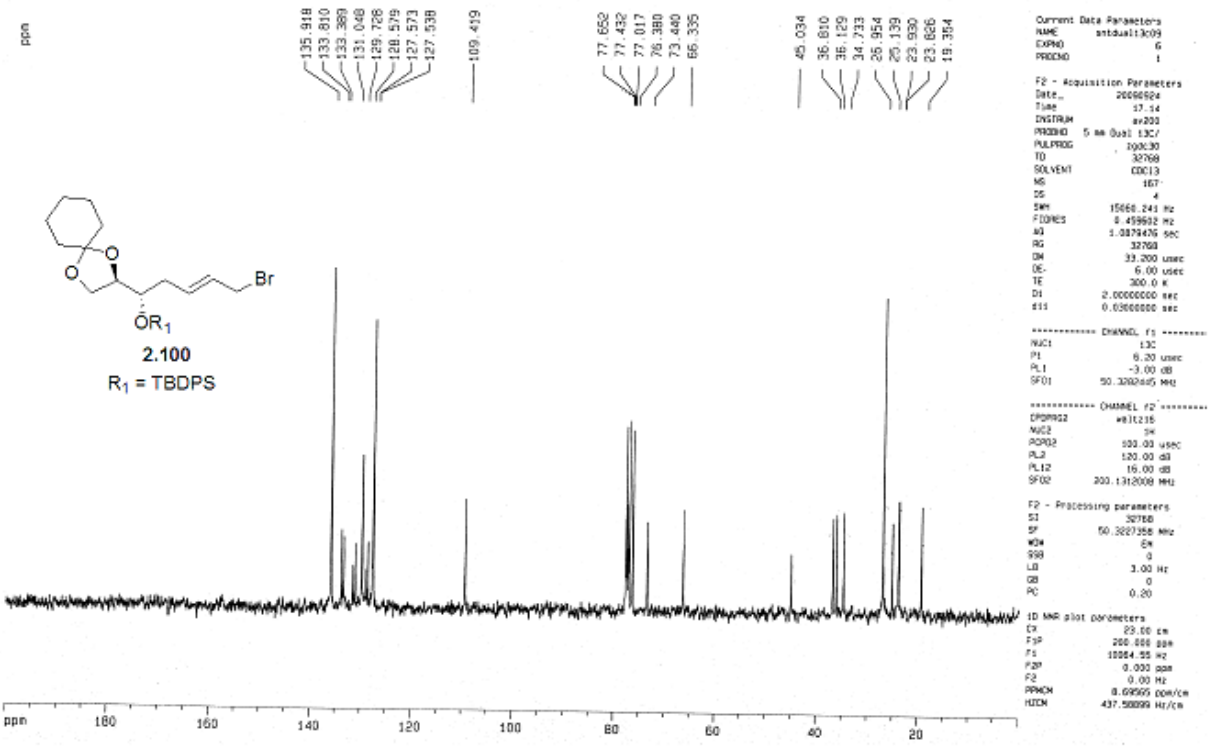


Figure 2.22 ^{13}C NMR spectrum of 2.100

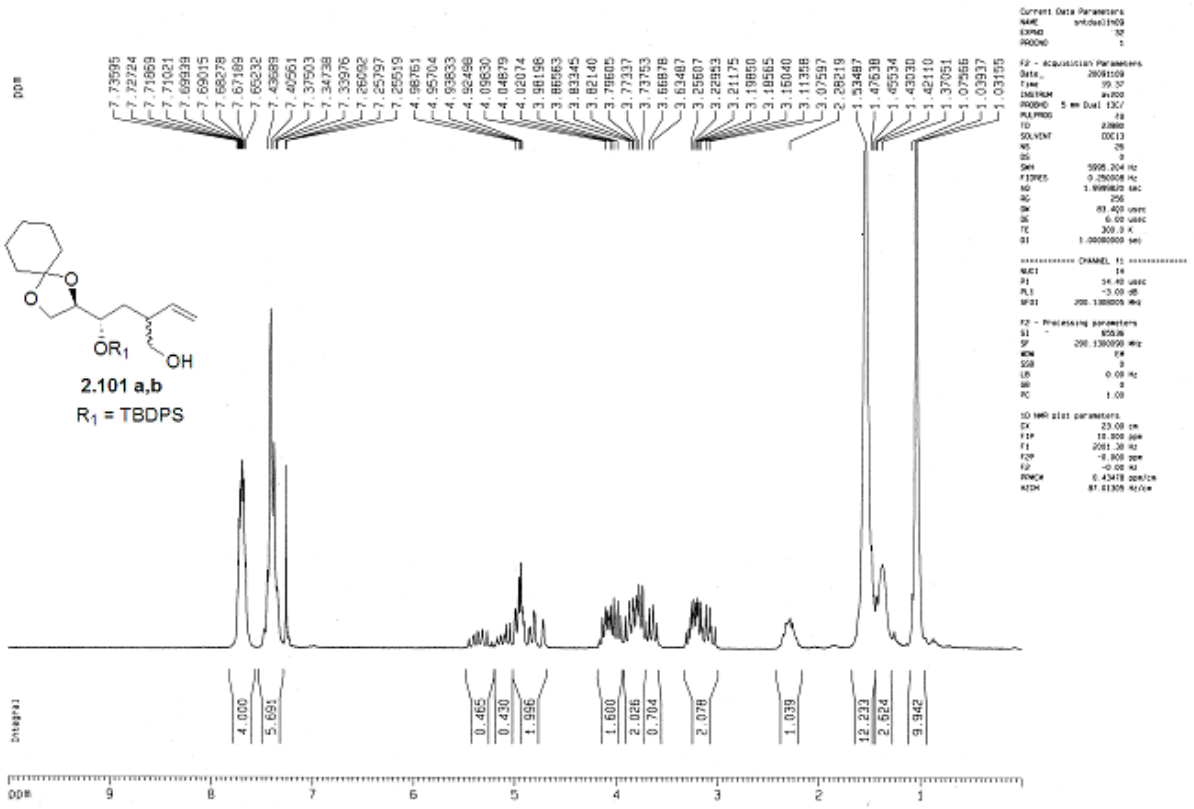


Figure 2.23 ^{1}H NMR spectrum of 2.101a, b

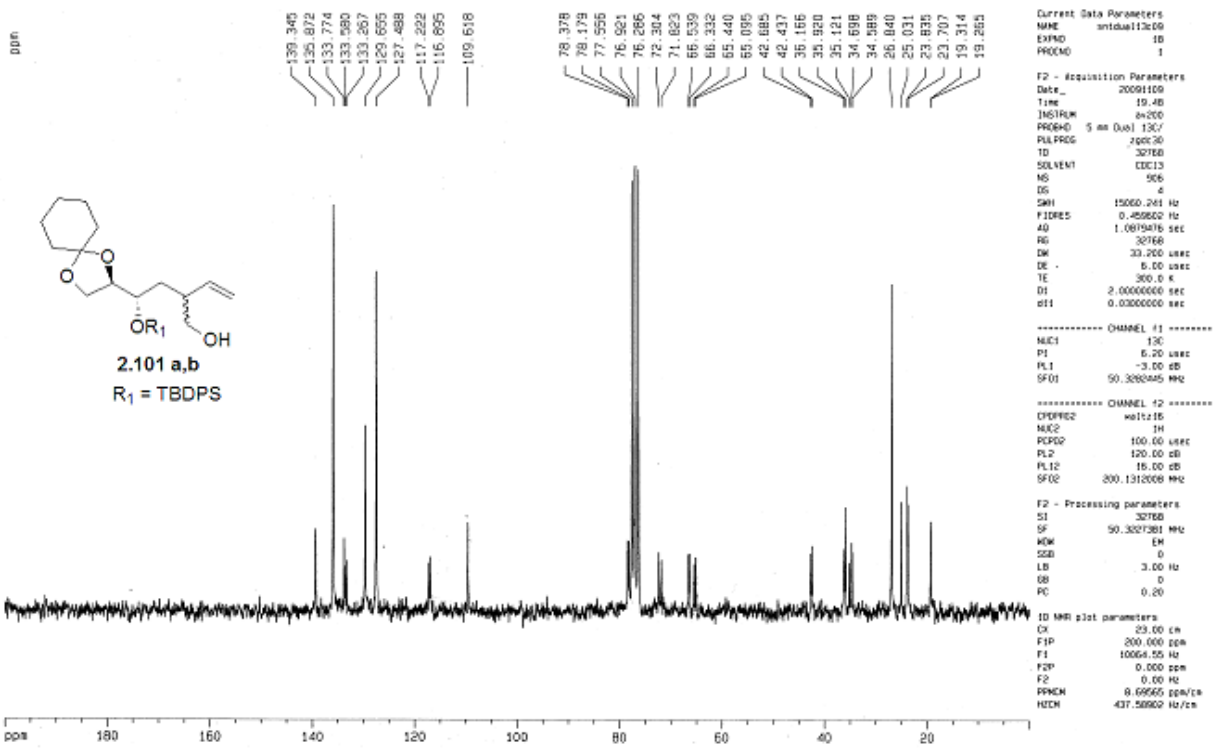


Figure 2.24 ^{13}C NMR spectrum of 2.101a, b

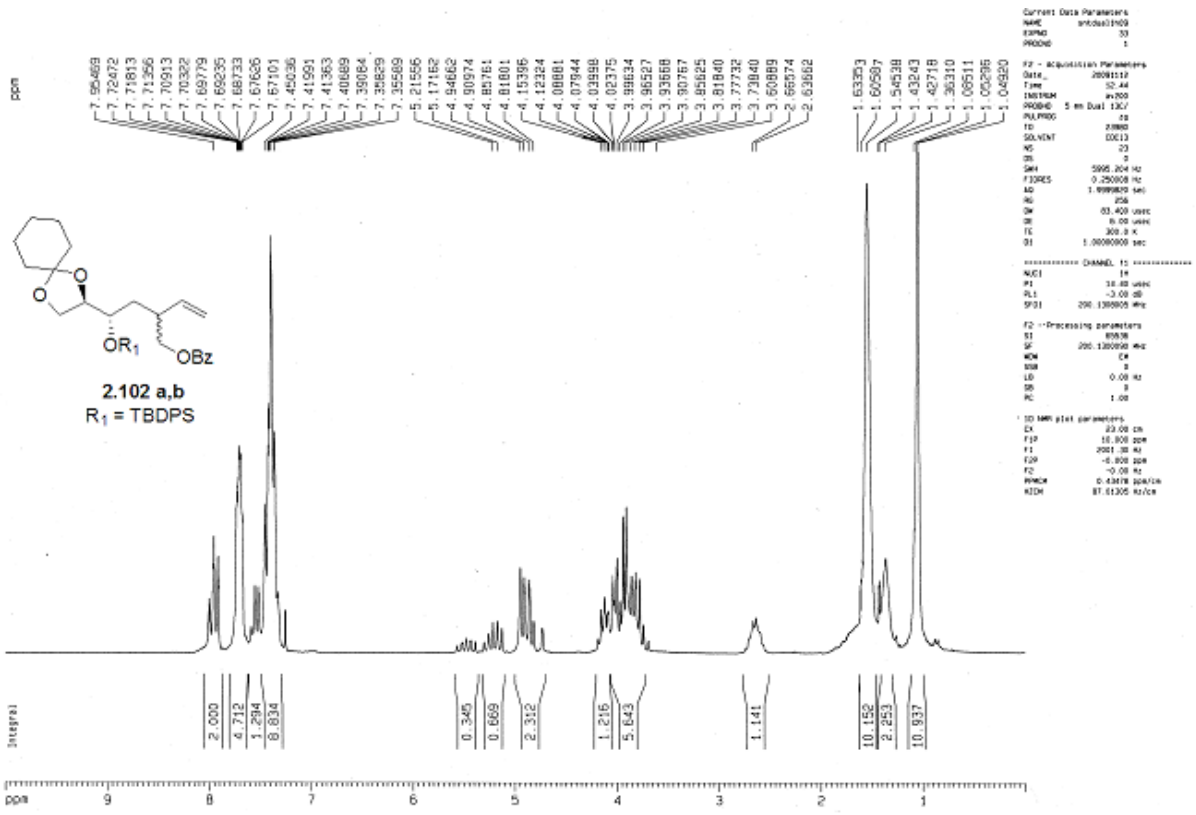


Figure 2.25 ^{1}H NMR spectrum of 2.102a, b

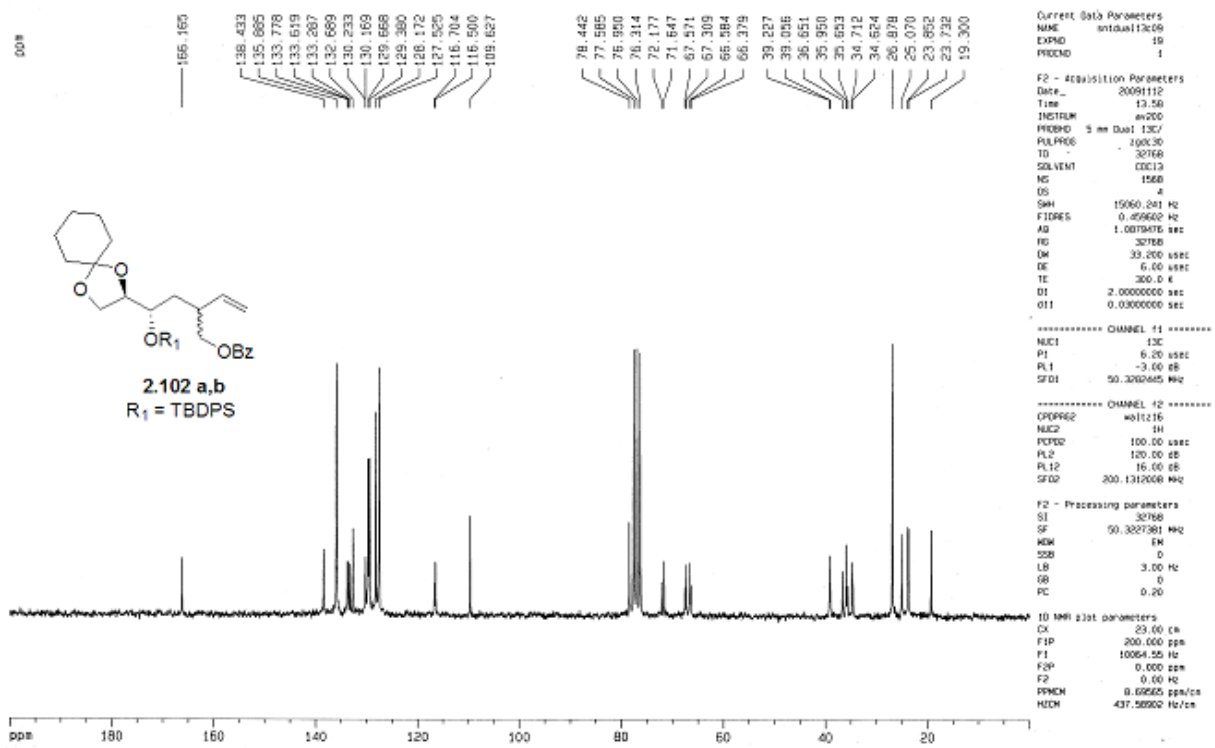


Figure 2.26 ^{13}C NMR spectrum of 2.102a, b

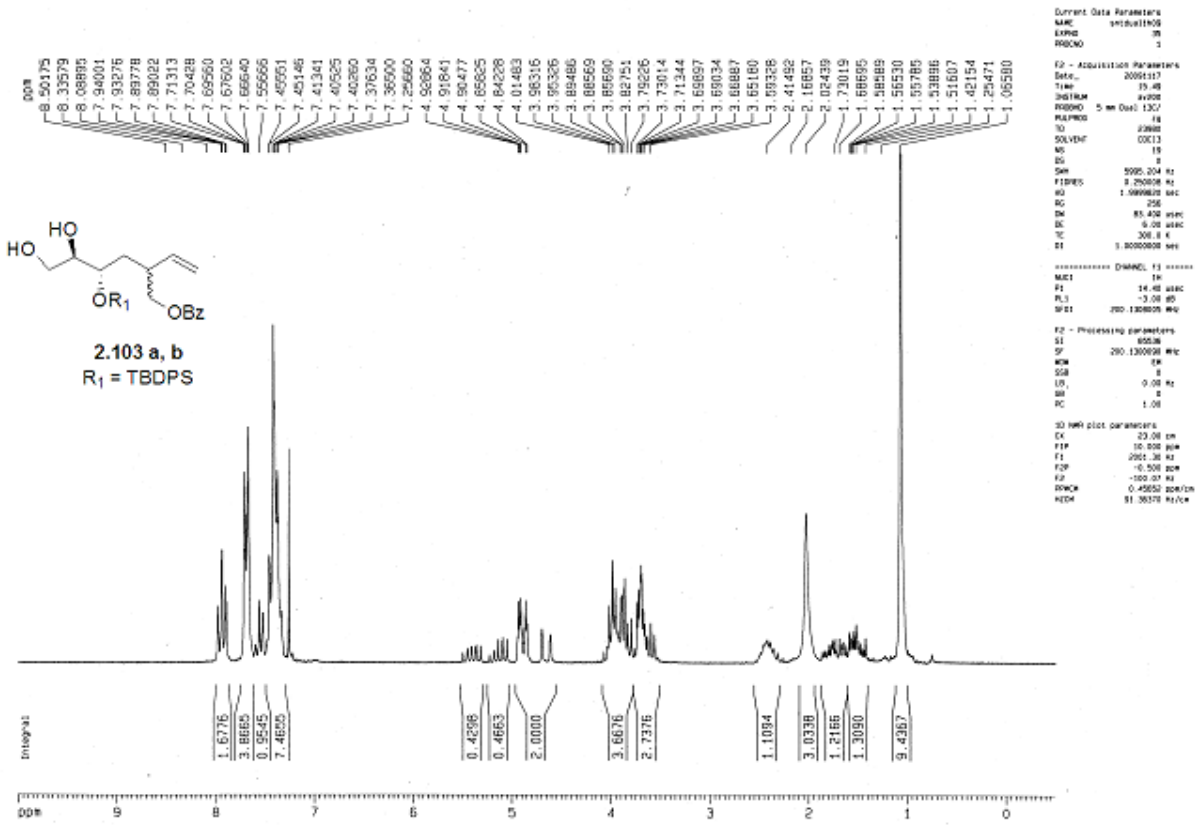


Figure 2.27 ^{1}H NMR spectrum of 2.103a, b

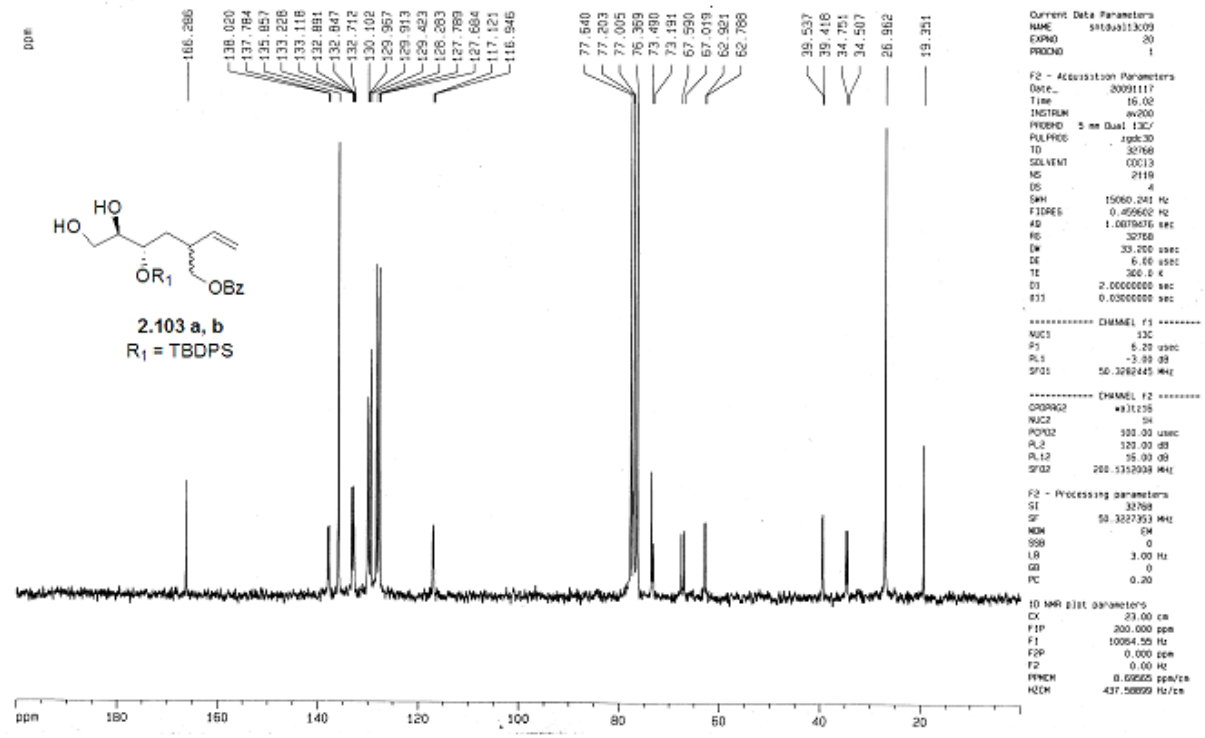


Figure 2.28 ^{13}C NMR spectrum of 2.103a, b

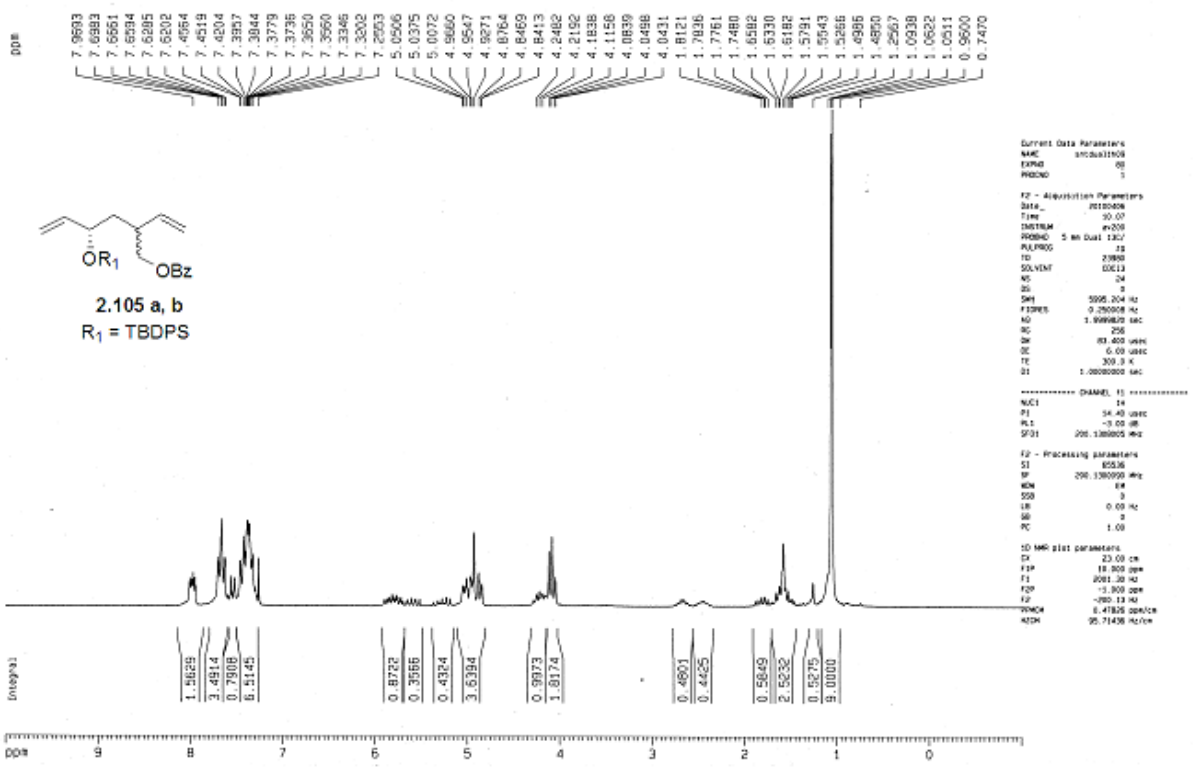


Figure 2.29 ^{1}H NMR spectrum of 2.105a, b

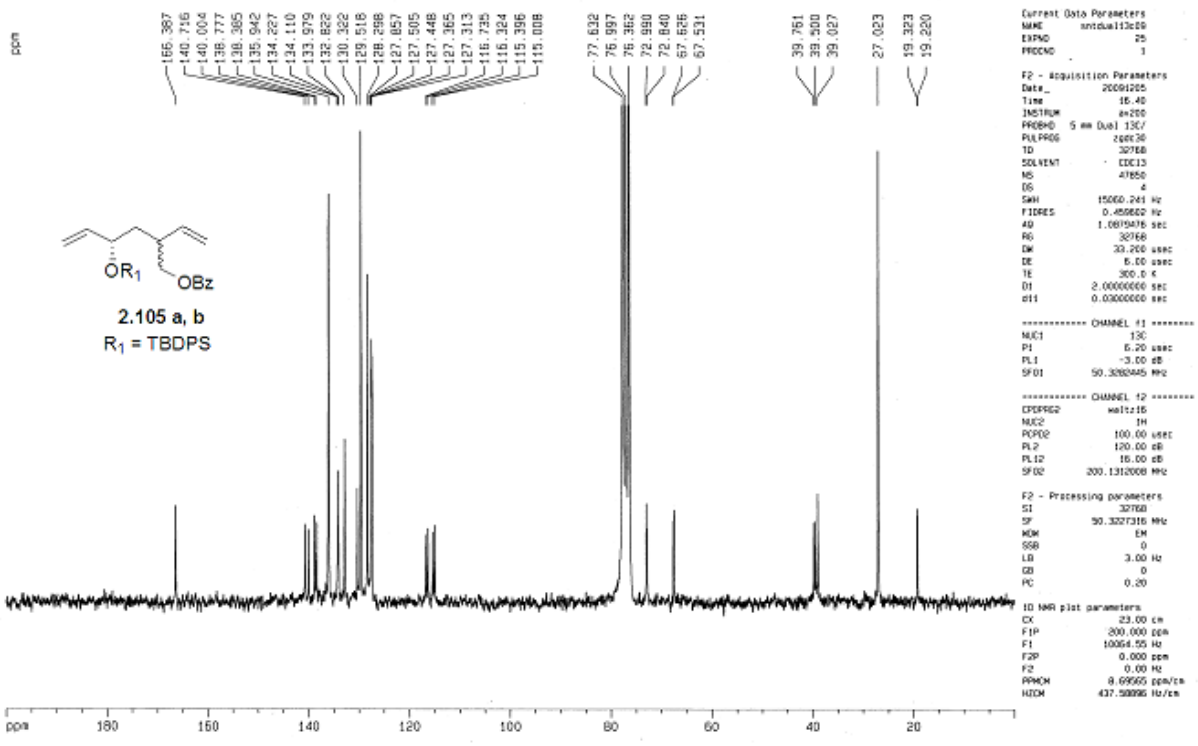


Figure 2.30 ^{13}C NMR spectrum of 2.105a, b

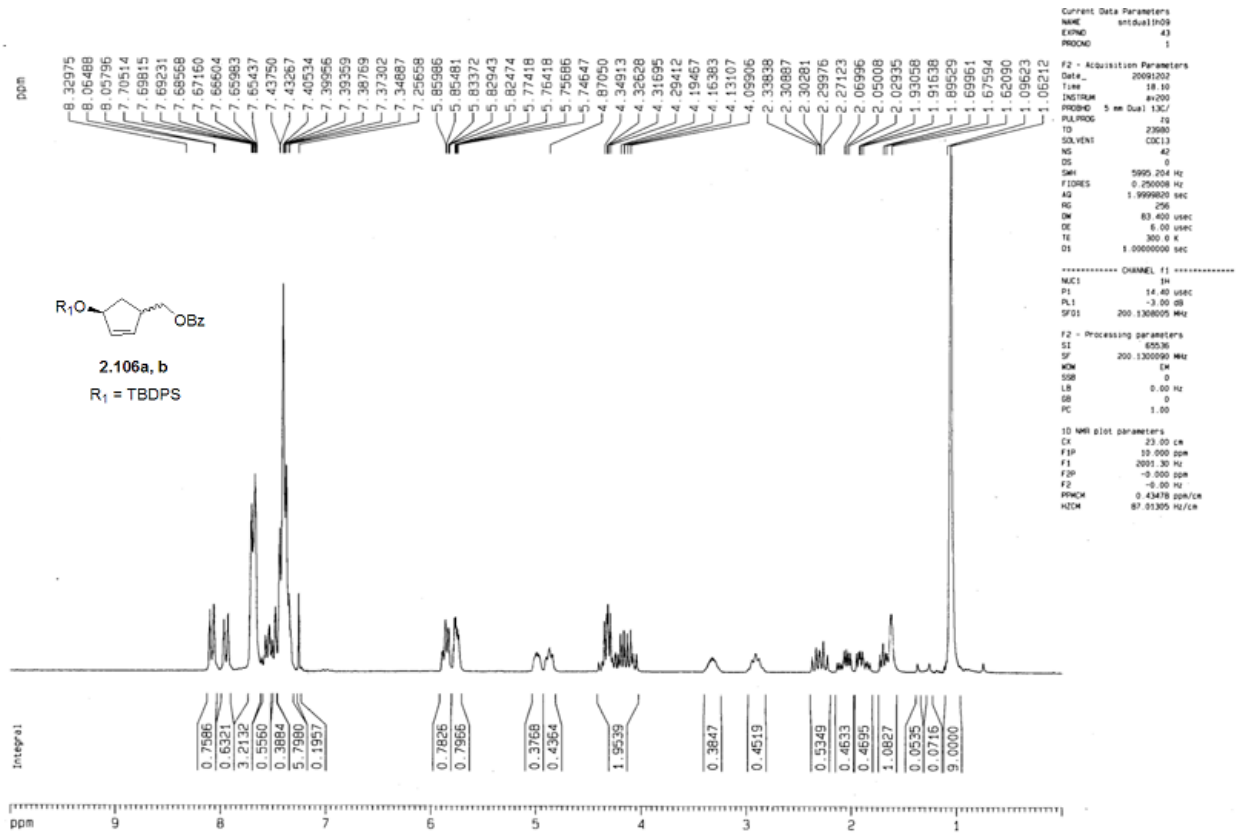


Figure 2.31 ^{1}H NMR spectrum of 2.106a, b

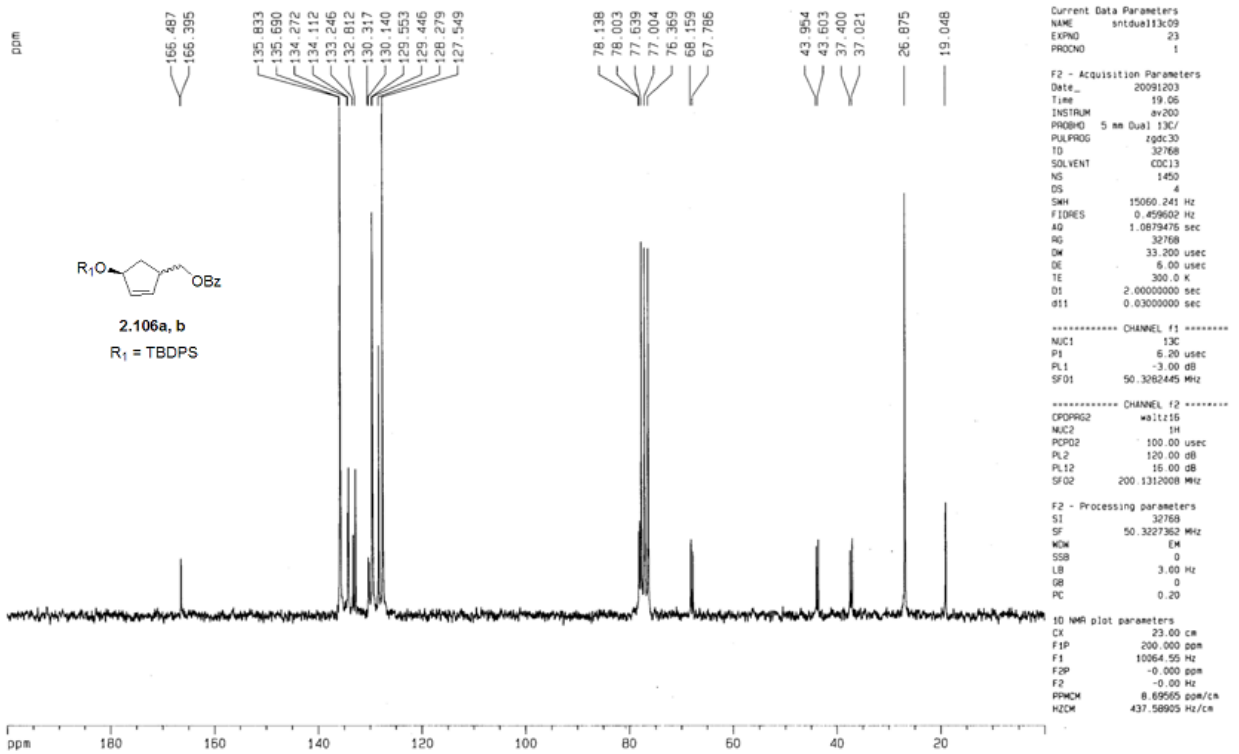


Figure 2.32 ^{13}C NMR spectrum of 2.106a, b

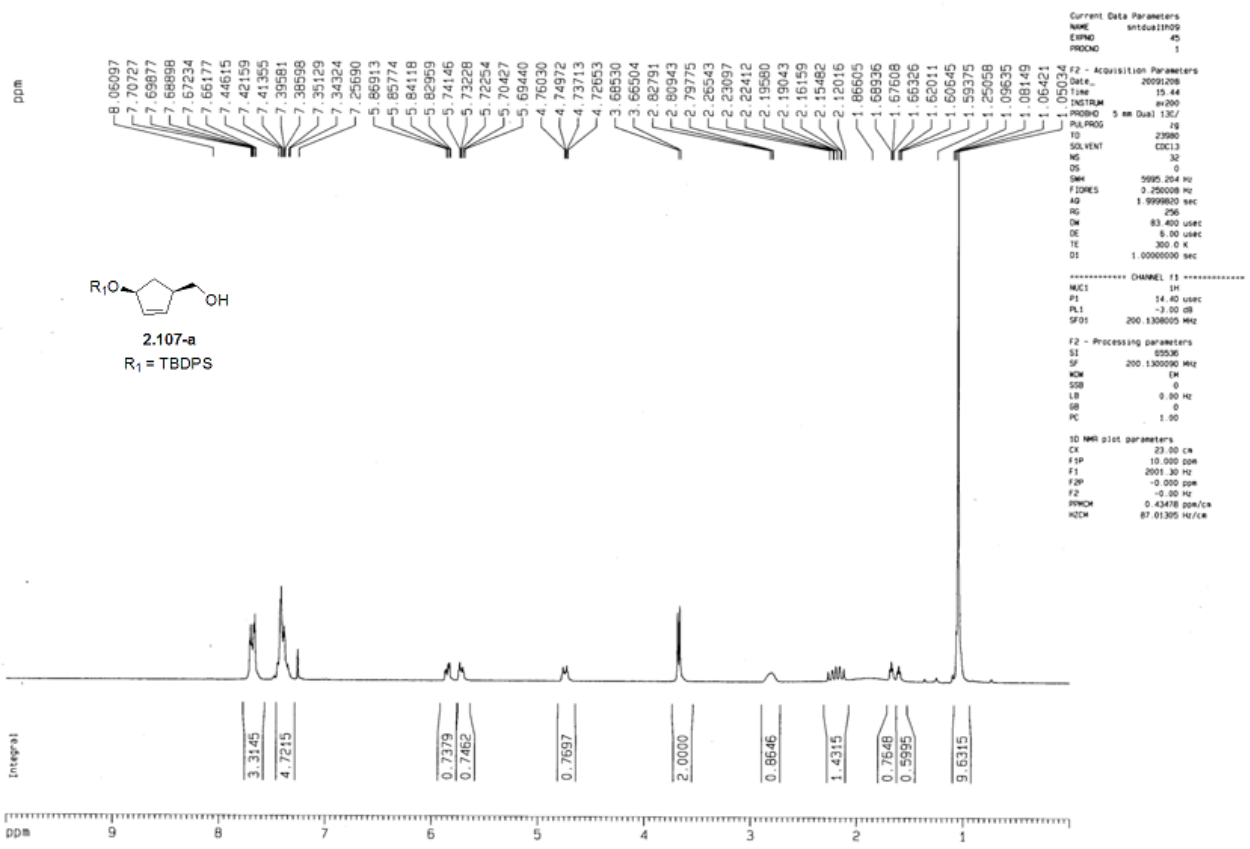


Figure 2.33 ^{1}H NMR spectrum of 2.107-a

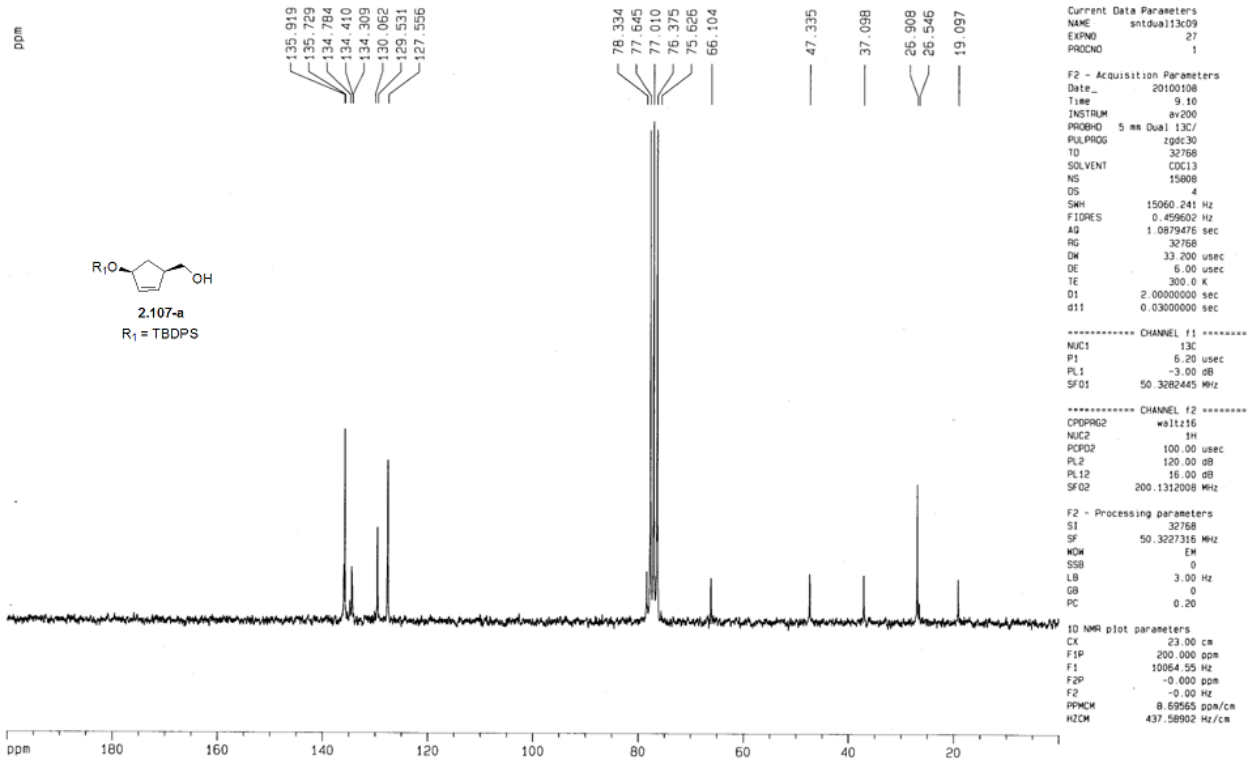


Figure 2.34 ^{13}C NMR spectrum of 2.107-a

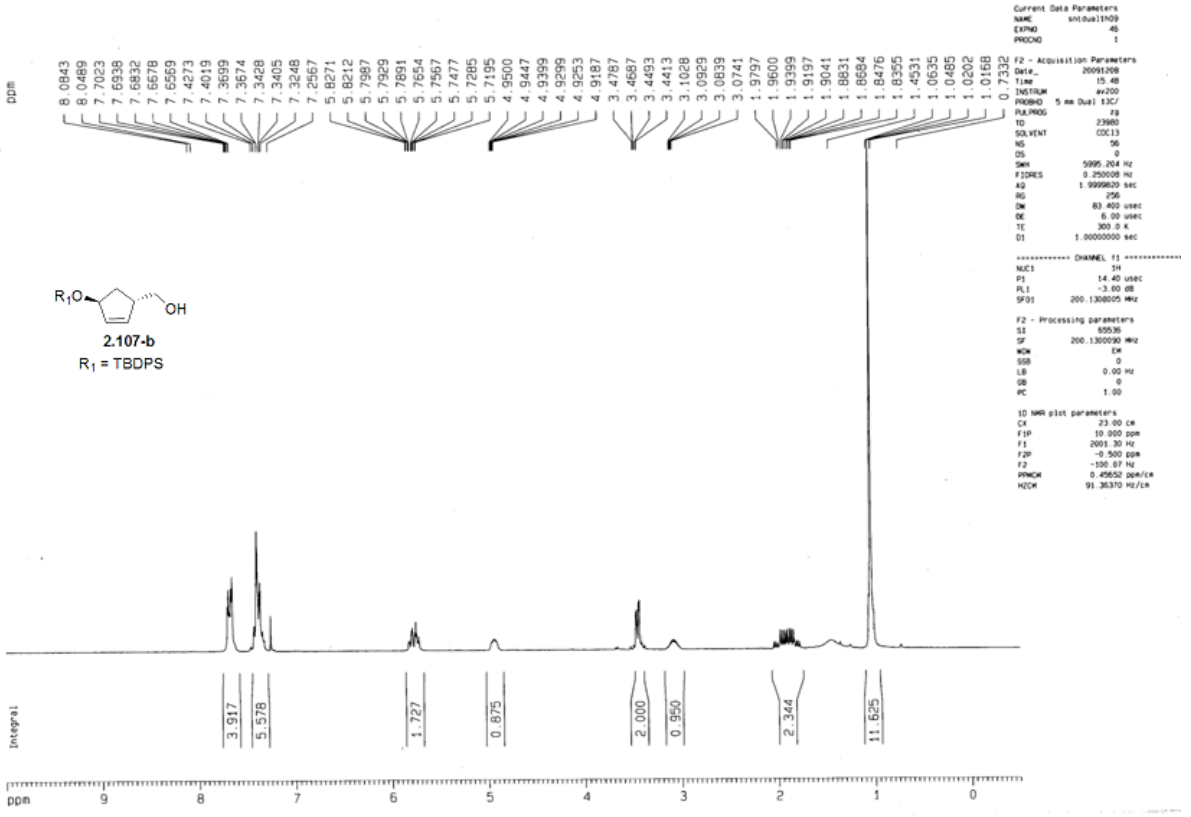


Figure 2.35 ^{1}H NMR spectrum of 2.107-b

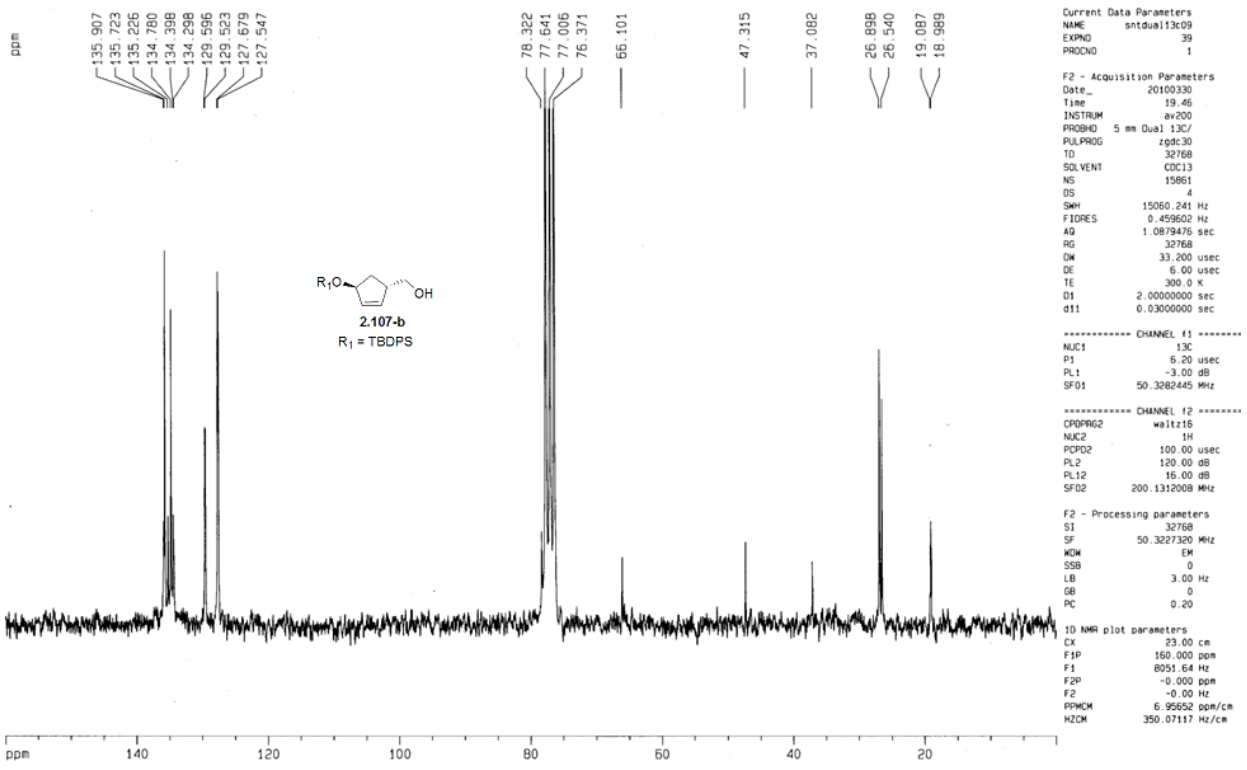


Figure 2.36 ^{13}C NMR spectrum of 2.107-b

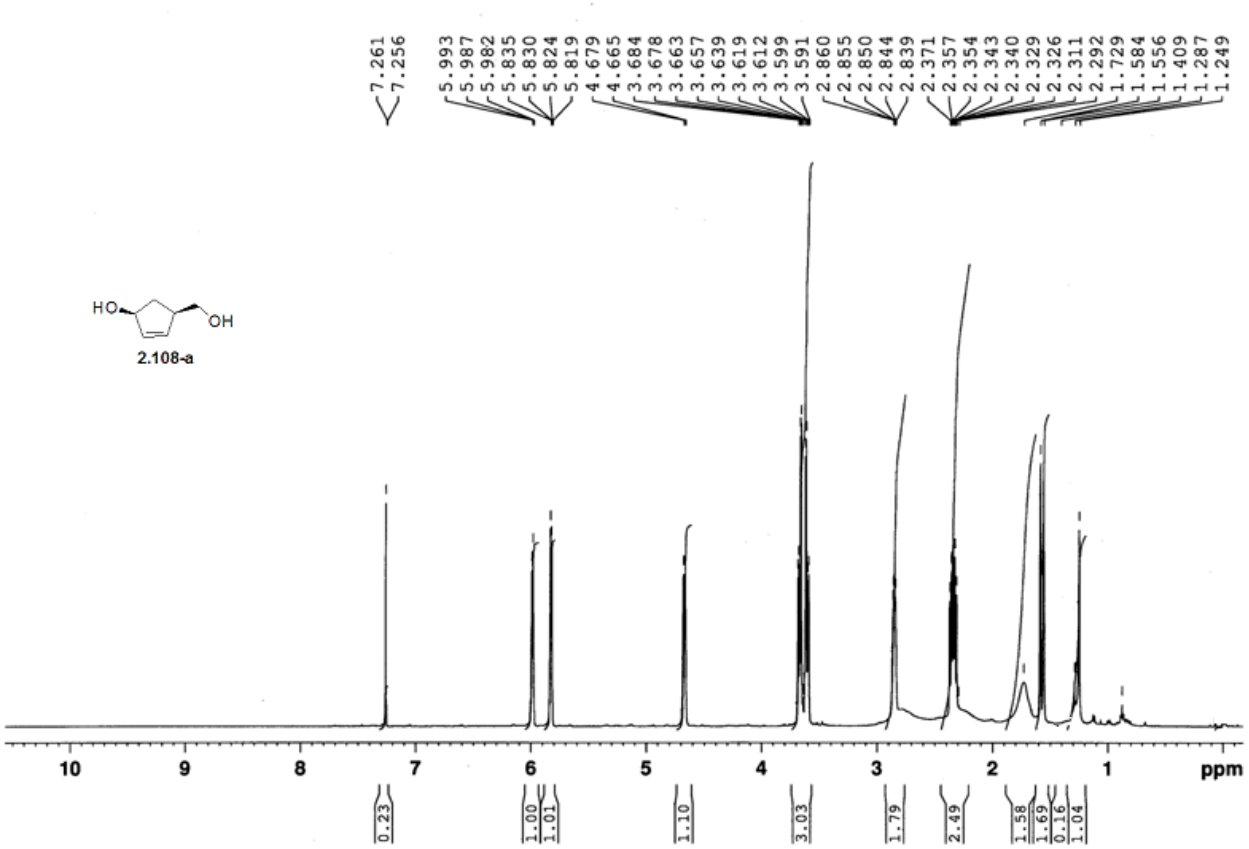


Figure 2.37 ^{1}H NMR spectrum of 2.108-a

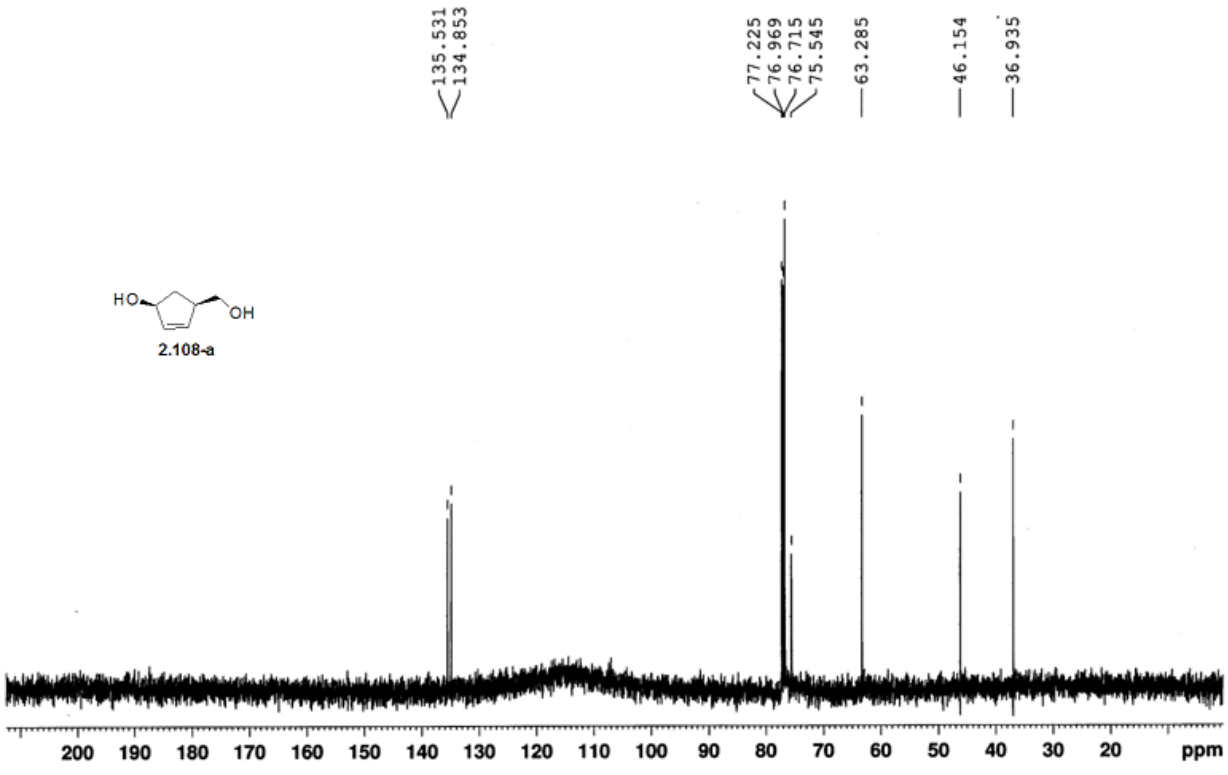


Figure 2.38 ^{13}C NMR spectrum of 2.108-a

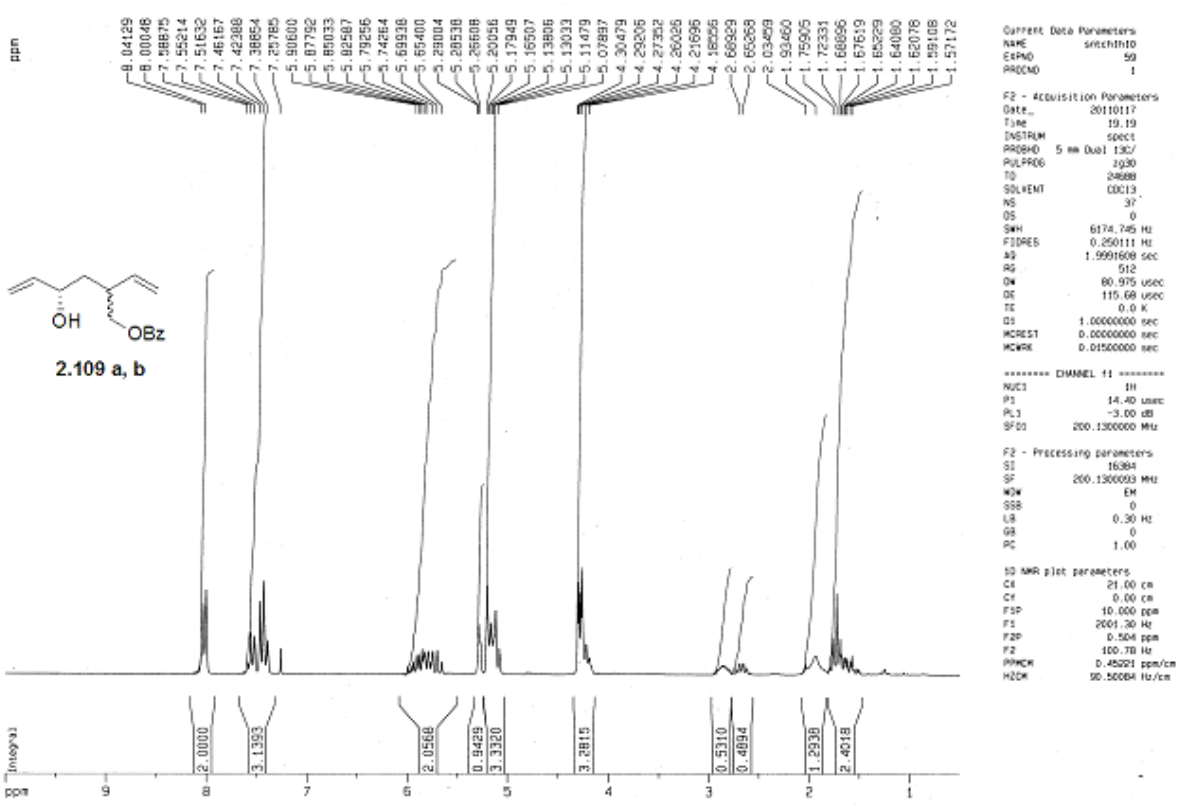


Figure 2.39 ^{1}H NMR spectrum of 2.109a, b

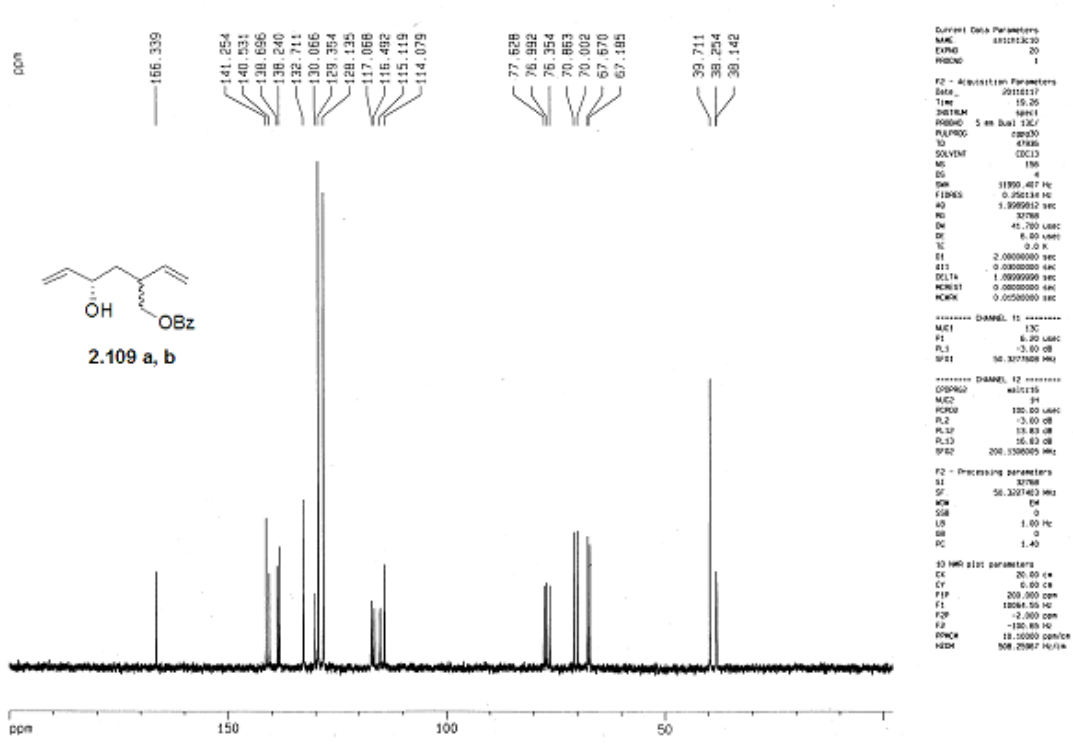


Figure 2.40 ^{13}C NMR spectrum of 2.109a, b

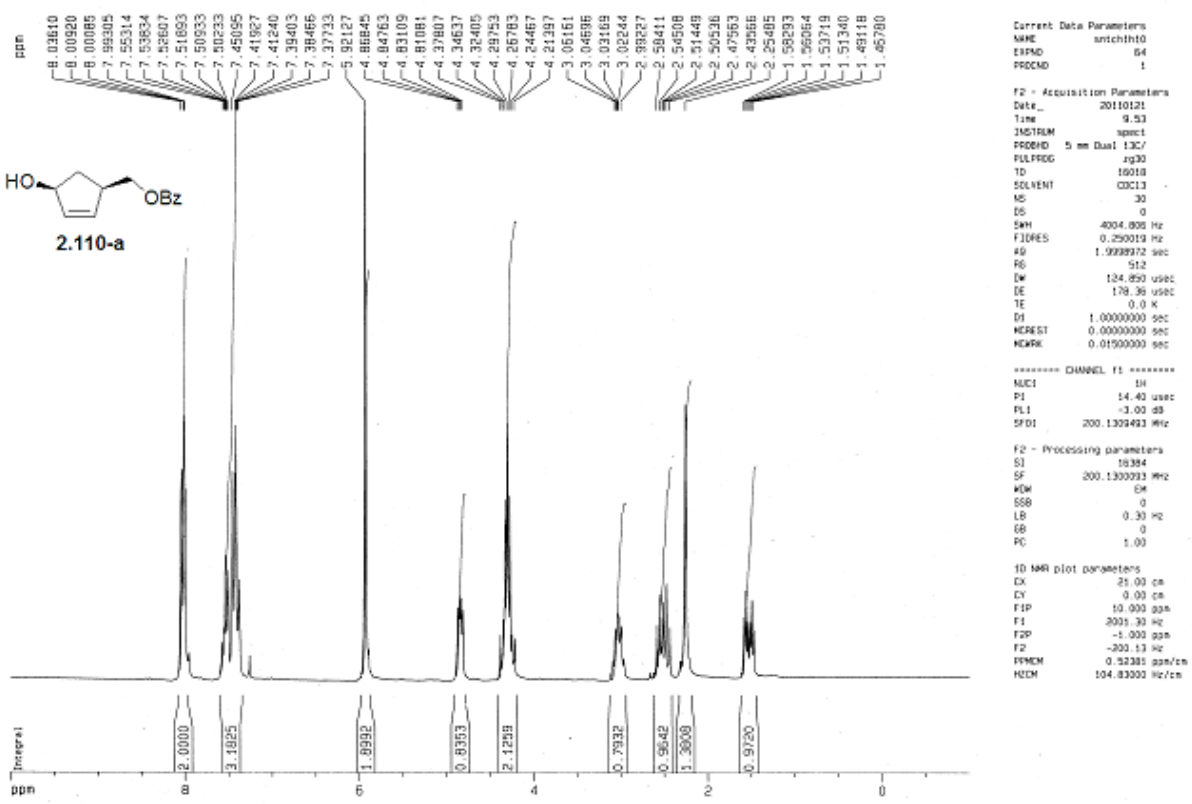


Figure 2.41 ^{1}H NMR spectrum of 2.110-a

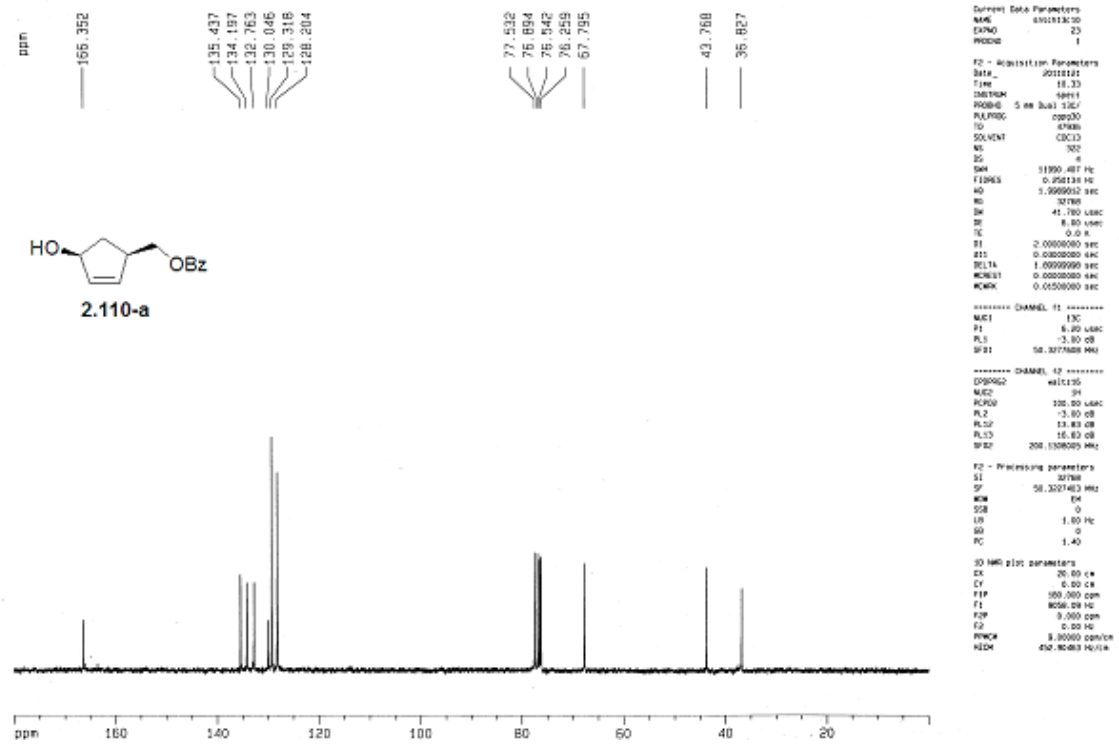


Figure 2.42 ^{13}C NMR spectrum of 2.110-a

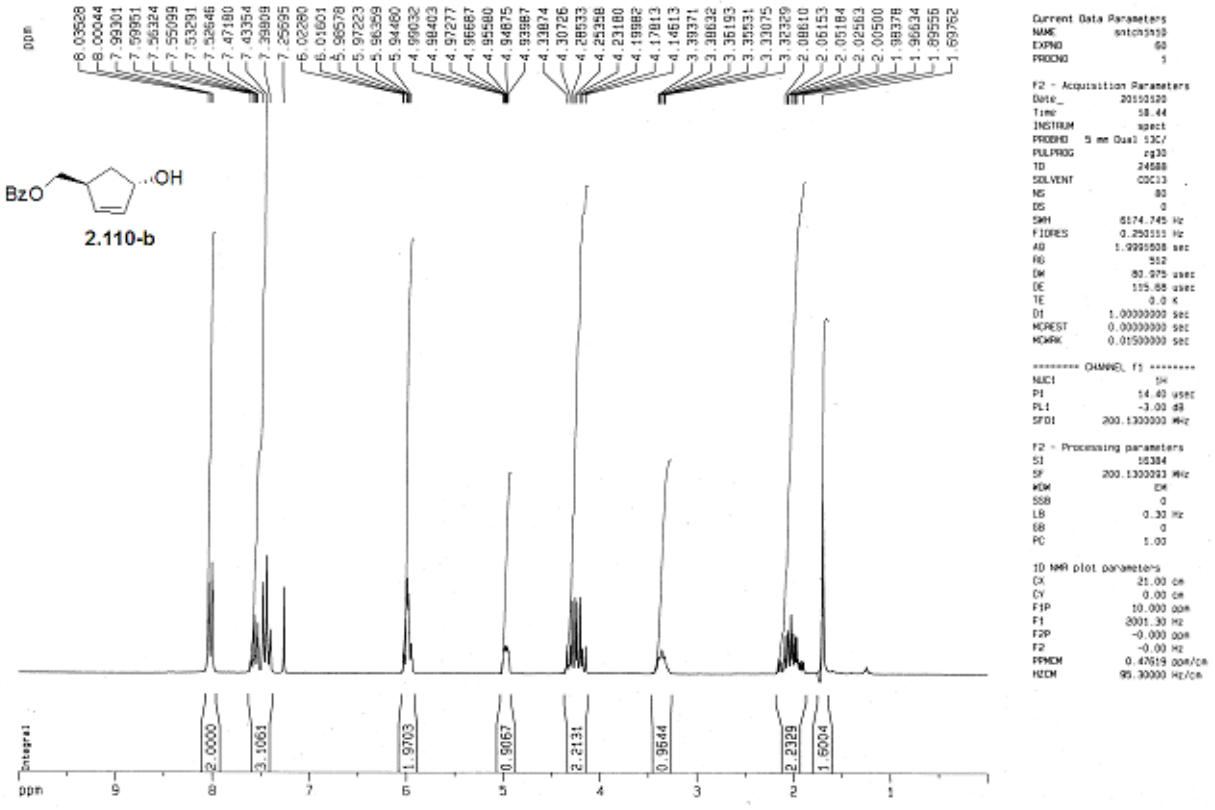


Figure 2.43 ^{1}H NMR spectrum of 2.110-b

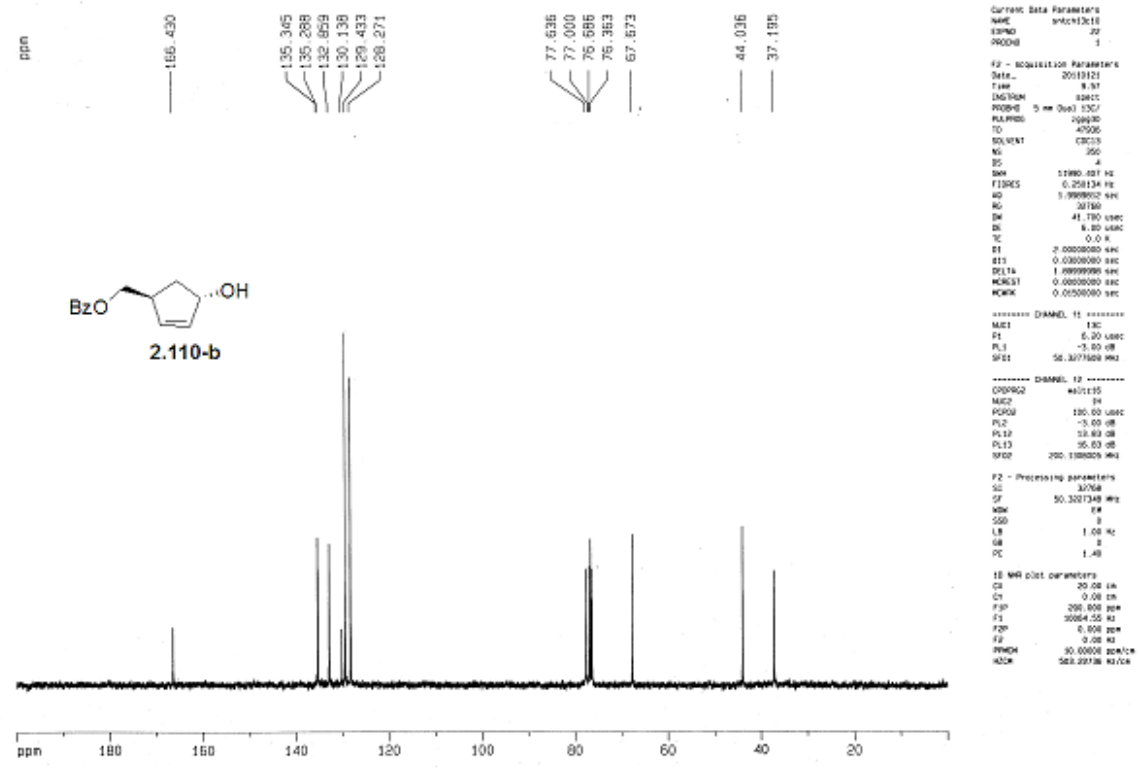


Figure 2.44 ^{13}C NMR spectrum of 2.110-b

2.IV Experimental

1,2 : 5,6-Di-*O*-cyclohexylidene-*D*-mannitol (2.64):

A mixture of 90 g of ***D***-mannitol, 150 ml of cyclohexanone, 50 ml of triethyl orthoformate and 5 ml of boron trifluoride etherate in 200 ml of DMSO was stirred overnight at room temperature. The mixture was then poured into ice-cooled sodium hydrogen carbonate solution and extracted with ether. The extract was washed with water and brine and dried over anhydrous sodium sulfate. Evaporation of the solvent afforded crude products containing excess cyclohexanone, which was roughly removed in *vacuo*. The residual syrup was crystallized from hexane and further recrystallized from hexane and the remaining cyclohexanone was removed by washing with hexane under *vacuo* to give 110 gm (65%) of fine crystals of **2.64**.

(*R*)-2,3-*O*-Cyclohexylideneglyceraldehyde (2.65):

To a stirred solution of **2.64** (68.4 g, 0.2 mol) in 300 ml of aqueous acetonitrile (60% Acetonitrile in H_2O) was added $NaIO_4$ (85.6 g, 0.4 mol) in small portions over a period of 40 minutes. The mixture was stirred for 2 hour more and filtered. The filtrate was mixed with water and extracted with chloroform. The combined organic layer was washed with water and brine and dried over Na_2SO_4. Solvent removal under reduced pressure afforded **2.65** in almost quantitative yield. This was sufficiently pure and hence used as such for the next step.

(4*R*,5*R*)-5, 6-*O*-cyclohexylidene-4,5, 6-trihydroxyhept-1-ene (2.94) and

(4*S*,5*R*)-5, 6-*O*-cyclohexylidene-4,5, 6-trihydroxyhept-1-ene (2.95):

To a cooled (10 °C) and well-stirred mixture of **2.65** (20.0 g, 0.13 mol), Zn dust (15.5 g, 0.25 mol) and allyl bromide (29.0 g, 0.24 mol) in THF (50 ml) was added a saturated aqueous solution of NH_4Cl (10 ml) dropwise over a period of 30 minute. The mixture was stirred for overnight at ambient temperature until the aldehyde was totally

consumed (by TLC). The mixture was filtered, and the precipitate was thoroughly washed with EtOAc. The aqueous layer was separated and treated with 5% HCl to dissolve the suspended turbid material. The clear solution was extracted with EtOAc. The combined organic layer was washed successively with 10% $NaHCO_3$, water, and brine. After solvent removal under reduced pressure, the residue was column chromatographed (silica gel 0-15% EtOAc in hexane) to give **2.94** (0.5 g, 3%) and **2.95** (19 g, 75%).

(4*S*,5*R*)-3-*O*-*tert*-butyl-diphenylsilyl-5,6-*O*-cyclohexylidene-4,5,6-trihydroxyhept-1-ene (2.96):

To the cooled (0 °C) solution of **2.95** (7.0 g, 33.01 mmol) and Imidazole (2.95 g, 43.38 mmol) in dry DCM (100 ml) was added a solution of TBDPSCl (11.8 g, 42.98 mmol) in dry DCM (100 ml) drop wise over a period of 15 minute. The mixture was stirred for 4 hour at room temperature on completion (by TLC) treated with water. The aqueous layer was extracted with chloroform. The combined organic layer was washed with water, brine and dried over Na_2SO_4. Solvent removal under reduced pressure afforded oily liquid containing the crude silylated product in almost quantitative yield which was chromatographed on silica gel (0-5% EtOAc in hexane) to afford pure **2.96** as a colorless liquid (13.93 g, 94.12%).

$[\alpha]_D^{27}$ = +28.71 (c, 1.01, $CHCl_3$), ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.05 (s, 9H), 1.36-1.59 (m, 10H), 2.1-2.2 (m, 2H), 3.7 (t, *J* = 7.4 Hz, 1H), 3.89-3.96 (m, 2H), 4.03-4.09 (m, 1H) 4.6-4.9 (m, 2H), 5.6-5.8 (m, 2H), 7.3-7.4 (m, 6H), 7.6-7.7 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 19.4, 23.8, 23.9, 25.2, 27.0, 34.8, 36.1, 38.6, 65.8, 73.0, 77.3, 109.2, 117.4, 127.4, 127.5, 129.5, 129.7, 133.6, 133.9, 134.0, 135.9, 136.0; Anal. Calcd for $C_{28}H_{38}O_3Si$: C, 74.62; H, 8.50. Found: C, 74.51; H, 8.44.

(3*S*,4*R*)-3-*O*-*tert*-butyl-diphenylsilyl-4,5-*O*-cyclohexylidene-3,4,5-trihydroxypentanal (2.97) :

To a cooled (-78 °C) solution of **2.96** (4.8 g, 10.65 mmol) in dichloromethane (40 ml) ozone gas was bubbled for 5 minutes till the reaction mixture became blue. The bluish solution was stirred for 10 min more and then treated with dry triphenylphosphine (4.2 g, 15.97 mmol). The mixture was gradually brought to room temperature and stirred for 3 hour more. The reaction mixture was concentrated in vacuo and the residue was passed through a short silica gel column eluting with 10% EtOAc in Hexane to afford **2.97** (4.14 g, 86%) as a colorless oil. This was found to be unstable on long standing and hence used immediately for the next step without further purification. A small portion of **2.97** was used for its spectroscopic characterization.

$[\alpha]_D^{25}$ = -13.52 (c, 1.12, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.09 (s, 9H), 1.2-1.5 (m, 10H), 2.56 (m, 2H), 3.55-3.62 (m, 1H), 3.8-3.9 (m. 1H), 4.0-4.1 (m, 2H), 7.5 (m, 6H), 7.6-7.8 (m, 4H), 9.61 (t, *J* = 2.5 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 19.2, 23.6, 23.7, 25.0, 26.8, 34.4, 35.8, 48.1, 66.8, 70.6, 78.2, 110.1, 127.6, 127.7, 129.9, 130.0, 132.9, 135.7, 200.3.

(5*S*,6*R*)-Ethyl-5-*O*-*tert*-butyl-diphenylsilyl-6,7-*O*-cyclohexylidene-5,6,7-trihydroxyhept-2*E*-enoate (2.98) :

To a cooled (0 °C) suspension of sodium hydride (0.47 g, 50% suspension in oil, 9.8 mmol, washed once with dry hexane) in THF (20 ml), triethyl phosphonoacetate (2.21 g, 9.86 mmol) in THF (10 ml) was added drop wise over a period of one hour under argon atmosphere. After the addition was over, the reaction mixture was gradually brought to room temperature and stirred till it became clear. Again the temperature was brought down to 0°C and a solution of **2.97** (4.06 g, 8.97 mmol) in dry THF (20 ml) was added drop wise over a period of 1 hour. The mixture was stirred at 0 °C for 1 hour and stirred at room temperature overnight (completion of reaction confirmed from TLC). The mixture was cooled to 0 °C, treated with water, neutralized by drop wise addition of

dilute HCl (2%) and extracted twice with EtOAc. The combined organic layer was washed successively with water, brine, dried over Na_2SO_4. Solvent removal under reduced pressure, column chromatography (silica gel, 0-5% EtOAc in Hexane) of the residue afforded pure **2.98** (3.75 g, 80%) as a colorless oil.

$[\alpha]_D^{29}$ = +19.54 (c, 0.87, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.04 (s, 9H), 1.26 (t, *J* = 7.2Hz, 3H), 1.35-1.59 (m, 10H), 2.27-2.37 (m, 2H), 3.6-3.7 (m, 1H), 3.8-4.0 (m, 3H), 4.15 (q, *J* = 7.2 Hz, 2H), 5.66 (d, *J* = 15.6 Hz, 1H), 6.90 (td, *J* = 8, 15.6 Hz, 1H), 7.5(m, 6H), 7.6-7.8 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.2, 19.3, 23.7, 23.9, 25.1, 26.5, 26.9, 34.7, 36.1, 37.0, 60.0, 66.5, 73.3, 77.5, 109.6, 123.7, 127.60, 127.68, 129.82, 129.89, 133.2, 133.4, 134.8, 135.9, 144.7, 166.2; Anal. Calcd for $C_{31}H_{42}O_5Si$: C, 71.23; H, 8.10. Found: C, 71.51; H, 8.24.

(5*S*,6*R*)-5-*O*-*tert*-butyl-diphenylsilyl-6,7-*O*-cyclohexylidene-1,5,6,7-tetrahydroxyhept-2*E*-ene (2.99):

To a cooled (-78 °C) solution of **2.98** (3.7g, 7.08 mmol) in dry THF (30 ml) DIBAL-H (14.2 ml, 1.0 M solution in hexane) was added drop wise over a period of one hour. The mixture was stirred for 1 hour at same temperature till the reaction was complete (confirmed by TLC). To the mixture, methanol (15 ml) was added. The mixture was stirred at room temperature for 2 hour and the resulting solid was filtered through a Celite pad. Concentration of the filtrate under reduced pressure, column chromatography (silica gel, 0 - 25% EtOAc in Hexane) of the residue afforded pure **2.99** (3.1 g, 91%) as a colorless oil.

$[\alpha]_D^{26}$ = +18.71 (c, 0.962, $CHCl_3$), ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.04 (s, 9H), 1.35-1.59 (m, 10H, overlapped with brs, 1H), 2.1-2.2 (m, 2H), 3.7-4.1 (m, 6H), 5.4-5.5 (m, 2H), 7.3-7.4 (m, 6H), 7.6-7.7 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 19.2, 23.7, 23.8, 25.0, 26.8, 34.6, 36.0, 36.9, 63.2, 65.8, 73.3, 77.3, 109.3, 127.4, 127.6, 129.5, 131.8,

133.3, 133.9, 135.81, 135.86; Anal. Calcd for $C_{29}H_{40}O_4Si$: C, 72.46; H, 8.39. Found: C, 72.21; H, 8.29.

(5*S*,6*R*)-1-Bromo-5-*O*-*tert*-butyl-diphenylsilyl--6,7-*O*-cyclohexylidene-5,6,7-trihydroxy-hept-2*E*-ene (2.100) :

To the cooled (0 °C) solution of **2.99** (3.0 g, 6.25 mmol) and triethylamine (1.07 g, 10.60 mmol) in dry DCM (15 ml) was added methane-sulfonylchloride (0.93 g, 8.11 mmol) drop wise over a period of 15 minute. The mixture was stirred for 3 hour at room temperature and treated with water. The aqueous layer was extracted with chloroform. The combined organic layer was washed with water, brine and dried over Na_2SO_4, Solvent removal under reduced pressure afforded yellow oily liquid containing the crude mesylated product in almost quantitative yield which was used in the next reaction without further purification. To a solution of crude mesylate in dry acetone (40 ml), dry NaBr (0.78 g, 7.5 mmol) and a catalytic amount of $NaHCO_3$ was added and stirred overnight (cf. TLC). The reaction mixture was concentrated under reduced pressure in order to get rid of the acetone, washed with dilute aqueous HCl (2%) for neutrality and extracted with $CHCl_3$. The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure to afford a colorless liquid which was chromatographed on silica gel (0-2% EtOAc in hexane) to afford pure **2.100** (3.06 g, 90%). The compound tended to become colored on long standing probably due to its being unstable and hence was immediately used for the next step.

$[\alpha]_D^{27}$ = +28.71 (c, 1.01, $CHCl_3$), ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.04 (s, 9H), 1.36-1.59 (m, 10H), 2.1-2.2 (m, 2H), 3.6-3.7 (m, 1H), 3.8-4.0 (m, 5H), 5.4-5.7 (m, 2H), 7.3-7.4 (m, 6H), 7.6-7.7 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 19.3, 23.8, 23.9, 25.1, 26.9, 34.7, 36.1, 36.8, 45.0, 66.3, 73.4, 77.4, 109.4, 127.53, 127.57, 128.5, 129.7, 131.0, 133.3, 133.8, 135.9.

(5*S*,6*R*)-3-Hydroxymethyl-5-*O*-*tert*-butyl-diphenylsilyl--6,7-*O*-cyclohexylidene-5,6,7-trihydroxy-hept-1-ene (2.101a,b):

To a solution of bromide **2.100** (2.0 g, 3.67 mmol) in distilled THF (10 ml) at room temperature Zn dust (0.5 g, 7.65 mmol) was added. The mixture was stirred for 10 minute. To this stirred mixture, gaseous formaldehyde (formed by heating paraformaldehyde in another container at 180 °C on a heating mantle under the flow of argon) was bubbled through an inlet tube. After stirring for 30 minute, saturated NH_4Cl (2 ml) was added drop wise into it with continued bubbling of formaldehyde gas. After 1 hour, heating of paraformaldehyde was stopped, while the reaction mixture was stirred overnight at room temperature. The bromide was found to be consumed totally (cf. TLC). The mixture was filtered and the filtrate was thoroughly and washed with EtOAc. The organic layer was washed with dilute aqueous HCl in order to dissolve the turbid suspensions. The aqueous layer was extracted with EtOAc. The combined organic layer was washed with, water, brine and dried over Na_2SO_4. Solvent removal under reduced pressure, column chromatography (silica gel, 0-20% EtOAc in hexane) of the residue afforded pure **2.101** (1.27 g, 70%) containing a chromatographically inseparable mixture of diastereomers **2.101a** & **2.101b** as a colorless oil.

^{1}H NMR (200 MHz $CDCl_3$): δ 1.04 (s, 9H), 1.3-1.6 (m, 12H, overlapped with a brs, 1H), 2.28 (m, 1H), 3.0-3.3 (m, 2H), 3.6-4.0 (m, 4H), 4.8-5.0 (m, 2H), 5.1-5.2 (m, 1H), 7.2-7.4 (m, 6H), 7.6-7.7 (m, 4H); ^{13}C NMR (50 MHz $CDCl_3$): δ 19.2, 19.3, 23.7, 23.8, 25.0, 26.8, 34.5,34.6, 35.1, 35.9, 36.1, 42.4, 42.6, 65.0, 65.4, 66.3, 66.5, 71.8, 72.3, 78.1, 78.3, 109.6, 116.8, 117.2, 127.4, 129.6, 133.2, 133.5, 133.7, 135.8, 139.3; Anal. Calcd. for $C_{30}H_{42}O_4Si$: C, 72.83; H, 8.56. Found: C, 73.01; H, 8.24.

(5*S*,6*R*)-3-Benzoyloxymethyl-5-*O*-*tert*-butyl-diphenylsilyl-6,7-*O*-cyclohexylidene-5,6,7-trihydroxy-hept-1-ene (2.102a,b):

To a cooled (0 °C) solution of the alcohol **2.101** (1.25 g, 2.52 mmol) and triethylamine (303 mg, 3 mmol) in dry CH_2Cl_2 (20 ml) a solution of benzoyl cyanide (0.36 g, 2.7 mmol) in CH_2Cl_2 (10 ml) was added in 5 minute. The mixture was stirred at 0 °C for 1 hour and then at room temperature for 4 hour. The solution was treated with water. The organic layer was separated and the aqueous layer was washed extracted with $CHCl_3$. The combined organic layer was washed with *dil.* aqueous HCl (2%) till neutral, water, brine and dried over Na_2SO_4. Solvent removal under reduced pressure, column chromatography (silica gel, (0-5% EtOAc in hexane) of the residue afforded pure **187** (1.12 g, 92%) as a mixture of diastereomers **2.102a** & **2.102b**.

^{1}H NMR (200 MHz $CDCl_3$): δ 1.04 (s, 9H), 1.35-1.7 (m, 12H), 2.6 (m, 1H), 3.7-4.1 (m, 6H), 4.8-4.9 (m, 2H), 5.1-5.5 (m, 1H), 7.3-7.4 (m, 9H), 7.6-7.7 (m, 4H), 7.8-8.0 (m, 2H); ^{13}C NMR (50 MHz $CDCl_3$): δ 19.3, 23.7, 23.8, 25.0, 26.8, 34.6, 34.7, 35.6, 35.9, 36.639.0, 39.2, 66.3, 66.5, 67.3, 67.5, 71.6, 72.1, 78.4, 109.6, 116.5, 116.7, 127.5, 128.1, 129.3, 129.6, 130.1, 130.2, 132.6, 133.2, 133.6, 133.7, 135.8, 138.4, 166.1; Anal. Calcd. for $C_{37}H_{46}O_5Si$: C, 74.21; H, 7.74. Found: C, 74.35; H, 7.46.

(5*S*,6*R*)-3-Benzoyloxymethyl-5-*O*-*tert*-butyl-diphenylsilyl-5,6,7-trihydroxy-hept-1-ene (2.104a,b):

To a cooled (0 °C) solution of **2.102a,b** (2.20 g, 2.12 mmol) in distilled CH_2Cl_2 (30 ml) was added 80% aqueous trifluoroacetic acid (10 ml). The mixture was stirred for three hour at 0 °C. The reaction mixture was diluted with $CHCl_3$ and water. The aqueous layer was extracted with $CHCl_3$. The combined organic layer was washed successively with 2% $NaHCO_3$ for neutrality, water and brine and dried over Na_2SO_4. Solvent removal under reduced pressure and column chromatography (silica gel, 0-5% MeOH in $CHCl_3$) of the residue afforded pure **2.103** (1.32 g, 70%) as mixture of diastereomers **2.103a** & **2.103b**.

^{1}H NMR (200 MHz $CDCl_3$): δ 1.06 (s, 9H), 1.2-1.6 (m, 2H), 2.02 (bs, 2H), 2.41 (m, 1H), 3.5-4.0 (m, 6H), 4.8-4.9 (m, 2H), 5.0-5.5 (m, 1H), 7.2-7.6 (m, 9H), 7.8-7.96 (m, 4H), 8.08-8.5 (m, 2H); ^{13}C NMR (50 MHz $CDCl_3$): δ 19.3, 26.9, 34.5, 34.7, 39.4, 39.5, 62.7, 62.9, 67.0, 67.5, 73.1, 73.4, 77.2, 116.9, 117.1, 127.6, 127.7, 128.2, 129.4, 129.91, 129.96, 130.1, 132.7, 132.84, 132.89, 133.1, 133.2, 135.8, 137.7, 138.0, 166.2; Anal. Calcd. for $C_{31}H_{38}O_5Si$: C, 71.78; H, 7.38. Found: C, 71.61; H, 7.44.

(5*S*)-3-Benzyloxymethyl-5-*O*-*tert*-butyl-diphenylsilyl-1,6-hexadiene (2.105a,b) :

To a cooled (0 °C) solution of **2.103** (1.30 g, 2.5 mmol) in dry pyridine (10 ml), p-toluenesulfonyl chloride (1.2 g, 6.26 mmol) and dimethylaminopyridine (100 mg) were added. The mixture was gradually brought to room temperature over a period of 6 hour and then stirred overnight. The reaction mixture was treated with 5% aqueous HCl and water for neutrality. The aqueous layer was extracted with $CHCl_3$. The combined organic layer was washed with water, brine and dried. It was concentrated under reduced pressure to afford the crude ditosylated product **2.104** (confirmed by TLC and IR of crude) which was taken in dry DMF (15 ml). To this solution were added Zn dust (0.50 g, 7.52 mmol) and dry NaI (1.12 g, 7.50 mmol). The mixture was stirred overnight at 90 °C. The mixture was filtered and the residue was thoroughly washed with EtOAc. The combined organic layer was washed with dilute aqueous HCl in order to dissolve the turbid material. The aqueous layer was separately extracted with EtOAc. The combined organic layer was washed with water, brine and dried over Na_2SO_4. Solvent removal under reduced pressure and column chromatography (silica gel, 0-10 % EtOAc in Hexane) of the residue afforded pure diene **2.105** (1.05 g, 86.6%) as a mixture of diastereomers **2.105a** & **2.105b**.

^{1}H NMR (200 MHz $CDCl_3$): δ 1.06 (s, 9H), 1.2-1.8 (m, 2H), 2.3-2.8 (m, 1H), 4.0-4.2 (m, 3H), 4.8-5.0 (m, 4H), 5.1-5.9 (m, 2H), 7.2-7.6 (m, 9H), 7.8-7.96 (m, 4H), 8.08-8.5 (m, 2H); ^{13}C NMR (50 MHz $CDCl_3$): δ 19.2, 19.3, 39.0, 39.5, 39.7, 67.5, 67.6, 72.8, 72.9,

115.0, 115.3, 116.3, 116.7, 127.31, 127.36, 127.4, 127.8, 128.2, 129.5, 130.3, 132.8, 133.9, 134.1, 134.2, 135.9, 138.3, 138.7, 140.0, 140.7, 166.3; Anal. Calcd for $C_{31}H_{36}O_3Si$: C, 76.82; H, 7.49. Found: C, 77.04; H, 7.34.

(1*S*)-1-*O-tert*-butyl-diphenylsilyl-4-Benzyloxymethyl-cyclopenten-2-enol (2.106a,b) :

A solution of diene **2.105** (300 mg, 0.6186 mmol) in dry benzene (50 ml) was degassed by bubbling argon. To it was added Grubb's 1st generation catalyst (15.27 mg, 0.0185 mmol) in one portion. The resulting pink solution was stirred under heating (60°C) for 24 hour. The solvent was removed under reduced pressure and the dark residue was purified by column chromatography (silica gel, 0-5% EtOAc in Hexane) to afford pure **191** (240.0 mg, 85%) as a diastereomeric mixture of **2.106a** and **2.106b**, the starting material **2.105** (40.0 mg) recovered in its pure form.

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.06 (s, 9H), 1.6 - 2.4 (m, 2H), 2.8-3.4 (m, 1H), 4.04-4.5 (m, 2H), 4.8-5.0 (m, 1H), 5.73-5.78 (m, 1H), 5.82-5.9 (m, 1H), 7.3-7.4 (m, 9H), 7.6-7.7 (m, 4H), 8.05-8.3 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 19.04, 26.87, 37.02, 37.4, 43.6, 43.9, 67.8, 68.1, 78.0, 78.2, 127.5, 128.3, 129.5, 129.55, 130.1, 130.3, 132.8, 133.2, 134.1, 134.2, 135.7, 135.8, 166.4, 166.5; Anal. Calcd for $C_{29}H_{32}O_3Si$: C, 76.28; H, 7.06. Found: C, 75.94; H, 7.34.

(1*S*,4*S*)-1-*O-tert*-butyl-diphenylsilyl-4-hydroxymethyl-cyclopenten-2-enol (**2.107a**) & **(1*S*,4*R*)-1-*O-tert*-butyl-diphenylsilyl-4-hydroxymethyl-cyclopenten-2-enol** (**2.107b**):

To a cooled (0 °C) solution of **2.106a,b** (200 mg, 0.438 mmol) in distilled MeOH (30 ml) was added Dry K_2CO_3 (65mg, 0.47 mmol). The mixture was stirred for three hour at 0 °C on completion (confirmed by TLC) the methanol was evaporated in vacuum. The reaction mixture was diluted with $CHCl_3$ and water. The aqueous layer was extracted with $CHCl_3$. The combined organic layer was washed successively with 2% HCl for neutrality,

water, brine and dried over Na_2SO_4. Solvent removal under reduced pressure and chromatography (silica gel, 0- 10% EtOAc in Hexane) of the residue afforded pure **2.107a** (70.2 mg) and **2.107b** (74.9 mg) in homo chiral form.

Compound 2.107a: R_f 0.5 (EtOAc : Hexane :: 1 : 10), $[\alpha]_D^{28}$ = +3.62 (c, 0.83, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.06 (s, 9H), 1.64 (td, *J* = 13.9, 2.61 Hz, 2H), 2.19 (dq, *J* = 7.03, 5.8 Hz, 1H), 2.7-2.8 (m, 1H), 3.6 (d, *J* = 4.0 Hz, 2H) 4.72-4.76 (m, 1H), 5.7-5.74 (td, *J* = 5.6, 1.95 Hz, 1H), 5.83-5.87(dd, *J* = 5.6, 2.2 Hz, 1H), 7.3-7.4 (m, 6H), 7.6-7.7 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 19.09, 26.5, 26.9, 37.1, 47.3, 66.1, 78.3, 127.5, 129.5, 130.1, 134.3, 134.4, 134.8, 135.7, 135.9; Anal. Calcd for $C_{22}H_{28}O_2Si$: C, 74.95; H, 8.01. Found: C, 75.03; H, 8.24

Compound 2.107b: R_f 0.4 (EtOAc : Hexane :: 1 : 10), $[\alpha]_D^{28}$ = -79.02 (c, 1.43, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.06 (s, 9H), 1.45 (bs, 1H), 1.9 (qq, *J* = 13.9, 4.1 Hz, 2H), 3.1 (m, 1H), 3.44-3.47 (m, 2H), 4.9 (m, 1H), 5.71-5.76 (td, *J* = 5.6, 1.7 Hz, 1H), 5.78-5.83 (ddd, *J* = 5.1, 2.0, 0.8 Hz, 1H), 7.3-7.4 (m, 6H), 7.6-7.7 (m, 4H); ^{13}C NMR: 18.9, 19.08, 26.5, 26.8, 37.1, 47.3, 66.1, 78.3, 127.5, 127.6, 129.52, 129.59, 134.29, 134.4, 134.8, 135.2, 135.7, 135.9; Anal. Calcd for $C_{22}H_{28}O_2Si$: C, 74.95; H, 8.01. Found: C, 74.63; H, 8.18

(1*S*,4*R*)-4-hydroxymethyl-cyclopenten-2-enol (**2.108a**);

Tetrabutylammonium fluoride in THF (0.3 ml, 1M solution) was added to a cooled (0 ^{O}C) solution of **2.107a** (70 mg, 0.2 mmol) in THF (10 ml). The resulting solution was stirred for 1 hour and after the completion of reaction confirmed by TLC the reaction was quenched by the addition of saturated aqueous solution of NH_4Cl (2 ml). The mixture was diluted with EtOAc while two phases were separated. The aqueous phase was extracted with EtOAc. The combined organic layer was washed successively

with water, brine and dried. Solvent removal under reduced pressure and column chromatography of the residue (silica gel, 0-5 % MeOH in $CHCl_3$) afforded pure **2.108a** (21 mg, 92.9%).

$[\alpha]_D^{24}$ = +34.36 (c, 0.78, $CHCl_3$) [Lit $[\alpha]_D^{20}$=+46.7, (c 1.55,CH_2Cl_2)][141] ; ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.45 (bs, 2H), 2.3 (m, 2H), 2.8 (m, 1H), 3.59 (dd, *J* = 10.5, 3.5 Hz, 1H), 3.66 (dd, *J* = 10.5, 3.5 Hz, 1H), 4.6 (d, *J* = 7Hz, 1H), 5.8 (dd, *J* = 5.5, 2.5 Hz, 1H), 5.9 (t, *J* = 2.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): 36.9, 46.1, 63.3, 75.5, 134.8, 135.5; Anal. Calcd for $C_6H_{10}O_2$: C, 63.14; H, 8.83. Found: C, 63.39; H, 9.06.

(5*S*)-3-Benzyloxymethyl-5-hydroxy-1,6-heptadiene (2.109a,b):

Tetrabutylammonium fluoride in THF (8 ml, 1M solution) was added to a cooled (0 ^{o}C) solution of **2.105** (968 mg, 2 mmol) obtained above in THF (30 ml). The resulting solution was stirred overnight at room temperature. The reaction was quenched by the addition of saturated aqueous solution of NH_4Cl (10 ml). The mixture was diluted with EtOAc while two phases were separated. The aqueous phase was extracted with EtOAc. The combined organic layer was washed successively with water, brine and dried. Solvent removal under reduced pressure and column chromatography of the residue (silica gel, 0-5 % MeOH in $CHCl_3$) afforded pure **2.109** (459 mg, 93.2%) as a mixture of diastereomers **2.109a** & **2.109b**.

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.5-1.7 (m, 2H), 1.9 (bs, 1H), 2.5-2.9 (m, 1H), 4.1-4.3 (m, 3H), 5.0-5.2 (m, 4H), 5.6-5.9 (m, 2H), 7.3-7.5 (m, 3H), 8.02 (d, *J* = 8.1 Hz, 2H); ^{13}C NMR: 38.1, 38.2, 39.7, 67.1, 67.6, 70.0, 70.8, 114.0, 115.1, 116.4, 117.0, 128.1, 129.3, 130.0, 132.7, 138.2, 138.6, 140.5, 141.2, 166.3; Anal. Calcd for $C_{15}H_{18}O_3$: C, 73.15; H, 7.37. Found: C, 73.44; H, 7.36.

(1*S*,4*S*)-4-(Benzyloxymethyl)-cyclopenten-2-enol (2.110a) & (1*S*,4*R*)-4-(Benzyloxymethyl)-cyclopenten-2-enol (2.110b):

A solution of diene **2.109** (150 mg, 0.6097 mmol) in dry benzene (50 ml) was degassed by bubbling argon. To it was added Grubb's 1st generation catalyst (30.57 mg, 0.0372 mmol) in one portion. The resulting pink solution was stirred under heating (60 °C) for 24 hour. The solvent was removed under reduced pressure and the dark residue was purified by column chromatography (silica gel, 0-10% EtOAC in Hexane) to afford **2.110a** (57.9 mg) and **2.110b** (62.0 mg) in homochiral form.

Compound 2.110a: R_f 0.5 (EtOAc : Hexane :: 1 : 9); $[\alpha]_D^{24}$ = +52.31 (c, 1.51, $CHCl_3$), ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.52 (dt, *J* = 13.8, 4.5 Hz, 1H), 2.25 (bs, 1H), 2.4-2.6 (m, 1H), 2.9-3.1 (m, 1H), 4.2-4.4 (m, 2H), 4.81-4.86 (m, 1H), 5.9 (m, 2H), 7.3-7.5 (m, 3H), 7.9-8.0 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 36.8, 43.7, 67.7, 76.5, 128.2, 129.3, 130.0, 132.7, 134.1, 135.4, 166.3; Anal. Calcd. for $C_{13}H_{14}O_3$: C, 71.54; H, 6.47. Found: C, 71.32; H, 6.53.

Compound 2.110b: R_f 0.4 (EtOAc:Hexane :: 1:9); $[\alpha]_D^{24}$ = -139.55 (c, 1.34, $CHCl_3$), ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.69 (s, 1H), 1.9-2.1 (m, 2H), 3.3-3.4 (m, 1H), 4.1-4.3 (m, 2H), 4.9 (m, 1H), 5.9-6.0 (m, 2H), 7.3-7.6 (m, 3H), 8.0 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 37.1, 44.0, 67.6, 76.6, 128.2, 129.4, 130.1, 132.8, 135.2, 135.3, 166.4; Anal. Calcd. for $C_{13}H_{14}O_3$: C, 71.54; H, 6.47. Found: C, 71.87; H, 6.42.

CHAPTER 3

Stereodivergent Route to 1,4-Disubstituted-2′,3′-Carbocyclic Core of 5′-Olefinic Carbocyclic Nucleoside : Formal Synthesis of Homocarbovir

3.I Synthesis of 2′, 3′-Olefinic Carbocyclic Core of Homocarbovir

Carbocyclic nucleosides represent a prominent class of compounds whose antiviral properties are similar to the inhibitors of *S*-adenosyl-**L**-homocysteine hydrolase which has shown a great degree of anti viral properties by disrupting the viral macromolecular methylation process.[147] In the recent times many carbocyclic nucleosides have been prepared and their biological properties have been studied among which the carbovir (**2.32**) and its prodrug abacavir (**2.33**) have shown a great degree of anti HIV activity. Carbovir and Abacavir are among the synthetic five membered carbocyclic ring bearing nucleosides among both having shown a great degree of antiviral and anticancer activities. Due to higher oral bioavailability of Abacavir (**2.33**) in comparison to the carbovir (**2.32**) and it's lesser toxicity made abacavir to an approved drug against retro viral infection. In order to have a great library of antiviral drugs, other analog of carbocyclic nucleosides are to be synthesized and its biological activities are to be studied to have lesser side effects and with higher activity against the virus infection. Due to the toxicity of carbovir it was not developed beyond preclinical phase although it was more effective against the retrovirus HIV.

Structural modification of different carbocyclic nucelosidic drug with the aim to have reduced toxicity yielded many meaning full drug candidates. Among the other modification one approach is the modification at the C-4 position of the carbocyclic sugar unit. Extension of the hydroxymethyl side chain at C-4 by a methylene group provides a C-5′ homologs of the carbocyclic nucleosides. Modification of the C-4 hydroxymethyl side chain by reduction or addition of methyl and addition of other functional group has not been explored much. The addition of a methylene group to the C-4 hydroxyl methyl side chain gave the 5′-Homo, C-5′ hydroxyl methyl side chain series similarly reduction of a methylene group gave the nor-carbocyclic nucleosides. Some of the representative

examples of the Homo and nor-carbocyclic nucleosides are 5′-Homoaristeromycin[147b,148] (**3.1**), 5′-Homocarbovir[149] (**3.2**), and 5′-Homoabacavir[149] (**3.3**), (±)-norcarbovir[150] (**3.4**) and (±)-norabacavir[150] (**3.5**). C-4 modified nucleosides involve not only the modification of the side chain it also involves the addition of other functionality like hydroxymethyl[151] (**3.6**), cyclopropyl[152] (**3.7**), cyano[153] (**3.8**), methyl[153] (**3.9**) etc (**Figure 3.1**).

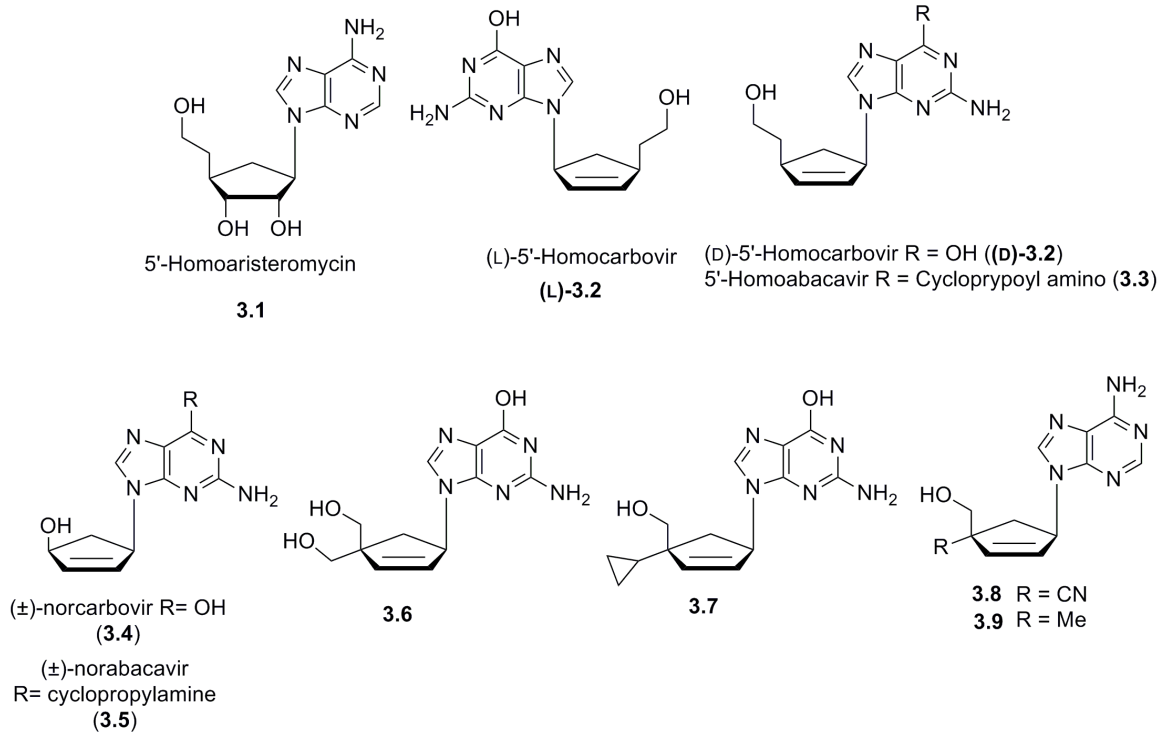


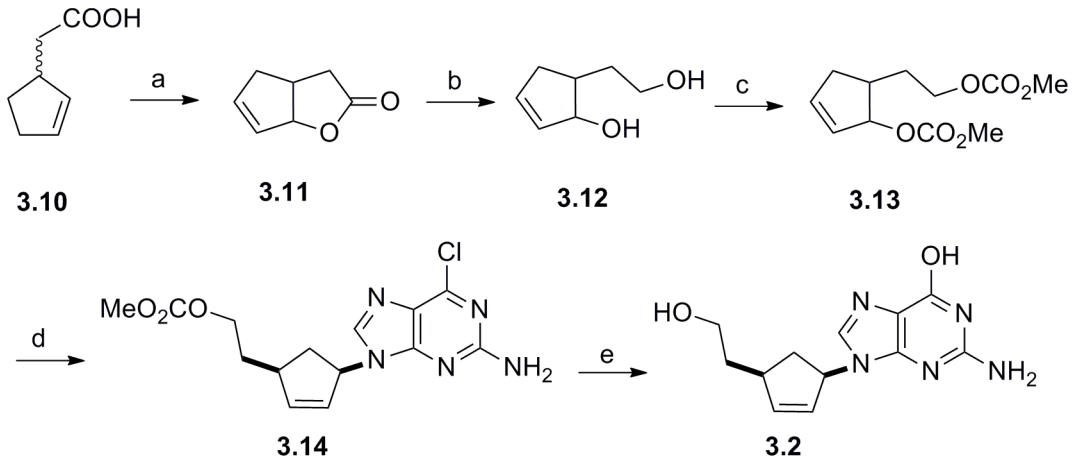
Figure 3.1 C-4 modified carbocyclic nucleosides

The first successful synthesis of the novel carbocyclic nucleoside (±)-5′-Homo-carbovir in its racemic form was reported by Vince *et al*. in 1996[154] after one year Olivo *et al*.[155] in 1997 reported the synthesis of 5′-Homocarbovir in an enantioselective manner. But the synthesis of this kind of modified nucleoside analogue unable to catch the attention of a large number of research groups due to its poor activity against the HIV retro viruses. After three years Rhee[156] and co workers synthesized (±)-5′-Homo-carbovir *via* π-allyl-palladium complex formation and recently Miller[149] and co workers synthesized both 5′-Homo-carbovir and *epi*-4′-homocarbovir *via* Palladium mediated

allylation reaction. Synthesis of 5′-hydroxymethyl modified carbocyclic nucleosides in its optically pure form is necessary in order to have an elaborate biological screening.

3.II Earlier Work in Literature

The first synthesis of (±)-5′-Homo-carbovir was reported in 1996 by Vince and co workers using Palladium catalyst and racemic 2-cyclopentene-1 acetic acid (**3.10**) as the starting material (**Scheme 3.1**).[154] Utilizing Palladium intramolecular acyloxy reaction **3.10** was successfully converted to the unsaturated lactone **3.11** which was reduced to the diol **3.12** using $LiALH_4$ reduction procedure. The diol **3.12** on treatment with dimethyl pyrocarbonate was converted to a mixture of mono and di carbonate which was separated and the dicarbonate **3.13** was used for the insertion of the nucleobase. The dicarbonate **3.133** upon treatment with 5 mol% $Pd(PPh_3)_4$ and 2-amino-6-chloro purine in presence of NaH gave the base coupled product **3.14** which on further transformation gave the racemic mixture of **3.2**.

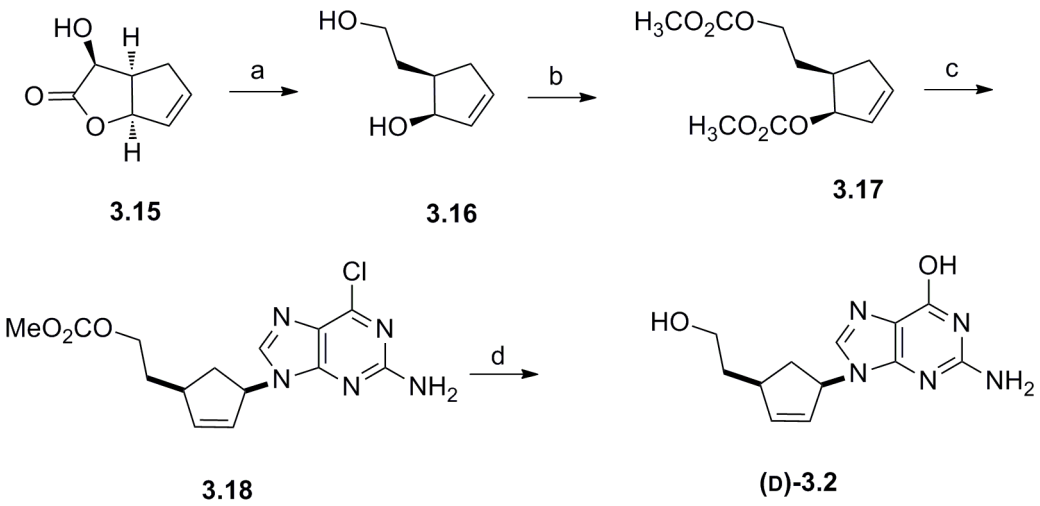


a) $Pd(OAc)_2$, NaOAc, O_2, DMF; b) $LiAlH_4$, Ether; c) DMAP, $O(CO_2CH_3)_2$; d) $Pd(PPh_3)_4$, NaH, 2-amino-6-chloro-purine, N_2 atm, THF; e) (1) CF_3CO_2H/H_2O (2:1), RT; (2) 0.5 N NaOH (aq), RT

Scheme 3.1

The first enantio selective synthesis of 5′-Homocarbovir was reported by Olivo and coworkers using *endo*-Hydroxylactone (**3.15**) as the starting material (**Scheme 3.2**)[157]. The *endo*-Hydroxylactone (**3.15**) was prepared in its enantiomerically pure form

by the water promoted hetero Diels-Alder reaction of cyclopentadiene and glyoxylic acid followed by enzymatic resolution of the resulting (±)-Hydroxylactone using *Pseudomonas fluoresecens*. The enantiomerically pure *endo*-Hydroxylactone (**3.15**) obtained after resolution was treated with $ZnBr_2$ in presence of triphenyl phosphine to give an intermediate which was treated with $LiAlH_4$, to obtain the diol **3.16** in its enantiomerically pure form. Treatment of the diol (**3.16**) with methyl chloroformate provided a mixture of dicarbonate (**3.17**) and monocarbonate. After the separation of the mono- and dicarbonate the allylic carbonate **3.17** was subjected to Trost's palladium catalyzed coupling of purine base 2-amino-6-chloro purine to give **3.18**. The resulting **3.18** after standard transformation was converted to the (**D**)**-3.2** in its enantiomeric pure form.

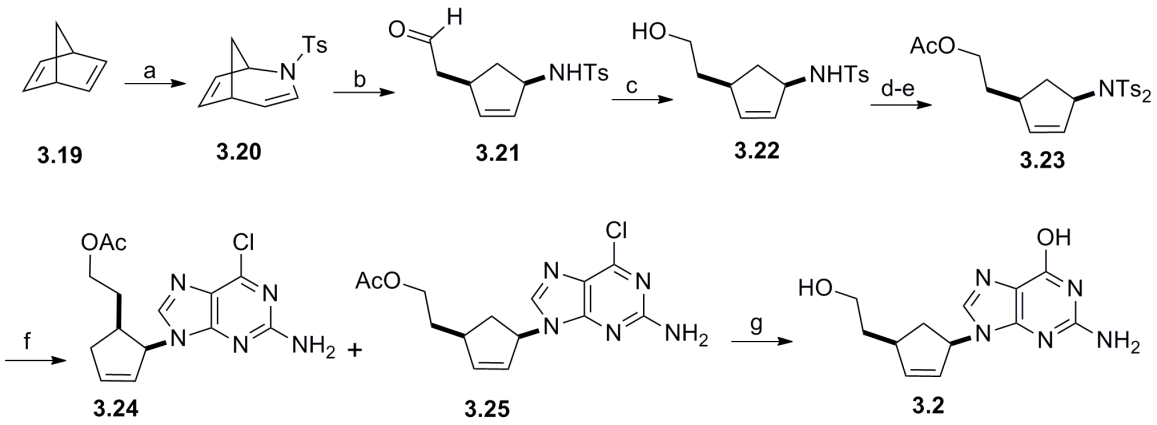


a) $LiAlH_4$, Ether; b) Methylchloroformate, Pyridine, DMAP; c) $Pd(PPh_3)_4$, NaH, 2-amino-6-chloro-purine, N_2 atm, DMSO; d) 0.33 N NaOH (aq), Reflux

Scheme 3.2

Rhee[156] and co workers synthesized (±)-Homocarbovir via π-allyl palladium complex formation. They used Meinwald type rearrangement to prepare N-tosyl bicyclic enamine (**3.20**) starting from norbornadiene (**3.19**) (**Scheme 3.3**). Hydrolysis of the tosyl enamine (**3.20**) produced the *N*-tosyl amido aldehyde **3.21** which was reduced with

$NaBH_4$ to the corresponding *N*-tosyl amido alcohol (**3.22**). Selective acetylation of **3.22**, followed by N-tosylation gave **3.23**. The key coupling of **3.23** was then effected on its treatment with the sodium salt of 2-chloro-6-amino purine in THF/DMSO (1:1) mixture in presence of $Pd[P(OPr^{i})_3]_4$ to produce the desired coupled product **3.25** along with a mixture of its isomer **3.24**. Thus, N, N-ditosyl amido cyclopentene served as the key intermediate in the formation of the π-allyl palladium complex. Finally, **3.25** was treated with base to obtain (±)-homocarbovir **3.2**.

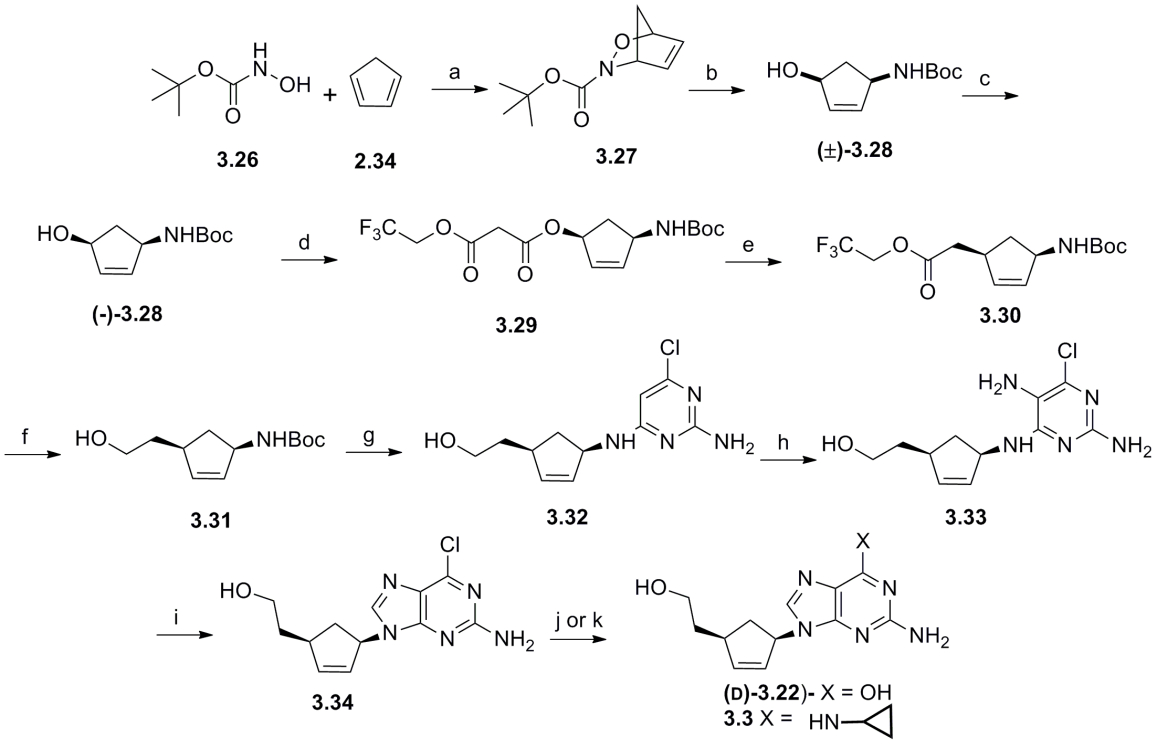


a) Ts_3N, Benzene; b) 2.0 M HCl, THF, Reflux; c)$NaBH_4$, THF d) Ac_2O, Pyridine; e) (1)NaH, THF, (2) TsCl, HMPA, THF; f) $Pd(OAc)_2$, (*i*-PrO)$_3$, THF, (2) *n*-BuLi, (3) 2-amino-6-chloro-purine, NaH, DMSO; g) 1.0 *N*NaOH, Reflux.

Scheme 3.3

Recently Miller[149] and coworkers reported the synthesis of 5′-homocarbovir (**3.2**) and 5′-homoabacavir (**3.3**) in its optically pure form using facially selective palladium mediated allylation reaction. The synthesis of the carbanucleoside started with the mission to synthesize optically pure **(-)-3.28** by enzymatic resolution of **(±)-3.28**. The racemic **(±)-3.28** was obtained by the CP_2TiCl catalyzed reduction of Boc cyclo adduct obtained from the Acylo-nitroso derived hetero Diels-Alder cycloadduct of **3.26** and **2.34** (**Scheme 3.4**). After resolution of optically pure **(-)-3.28** it was coupled with 3-oxo-3-(2, 2, 2-trifluoroethoxy) propanoic acid to give **3.29** which on subjected to a facile decarboxylative rearrangement in presence of $Pd(dba)_2$ and dppe provided homoallylic

ester **3.30**. DIBAL-H reduction of the corresponding homoallylic ester **3.30** gave the desired alcohol **3.31** which was coupled to 2-amino-4,6-dichloropyrimidine to afford alcohol **(+)-3.32**. Azo coupling of **3.32** with 4-chlorobenzenediazonium chloride followed by the reduction of the resulting azo group afforded triamino pyridine **3.33**. Cyclization of **3.33** with triethyl orthoformate in presence of catalytic acid provided chloro guanine **3.34** which on subject to standard transformation gave 5′-Homocarbovir when refluxed with 0.33*N* NaOH or gave 5′-Homoabacavir when subjected to heating with excess cyclopropyl amine.



a) $NaIO_4$, $MeOH/H_2O$; b) Cp_2TiCl_2, Mn, TMSCl, 2,4,6-trimethylpyridine, THF; c) (1)*Candida Antarctica B*, Vinyl avetate, (2) K_2CO_3, MeOH; d) 3-oxo-3-(2,2,2-trifluoroethoxy)propanoic acid, EDC.HCl, DMAP, DCM; e) $Pd(dba)_2$, dppe, THF, 75°C; f) DIBAL-H, THF; g) (1) 12M HCl, EtOH, (2) Et_3N, 2-amino-4,6-dichloropyrimidine ; h) (1) 4-chlorobenzenediazonium chloride,H_2O, ACOH, (2) Zn, ACOH, 2-Propanol; i) Triethyl orthoformate, 12M HCl; j) 0.33 N NaOH, Reflux; k) Cyclopropyl amine (excess), 2-Propanol, 70°C.

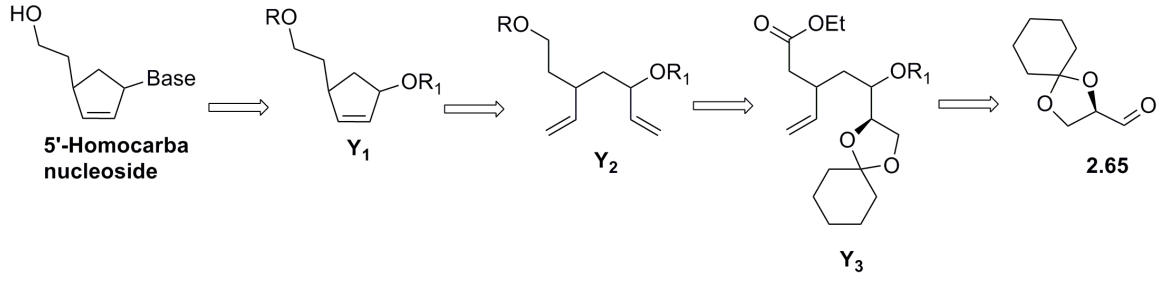
Scheme 3.4

3.III Our work

Although a number of syntheses have been reported for 5′-homocarbanucleosides both in its racemic and enantiomeric pure form but most of the synthetic strategies involved either relatively expensive reactions protocol or expensive starting materials.

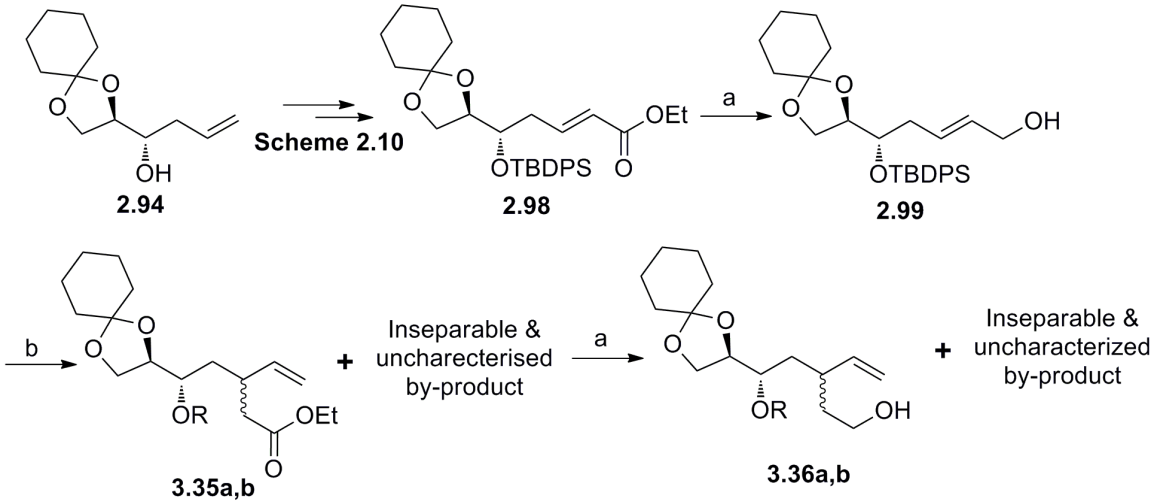
We felt that it would be prudent to develop an operationally simple and inexpensive strategy to construct different stereoisomers of the carbocyclic core of homocarbanucleosides. Later, this carbocyclic core would be subjected to coupling with appropriate bases to have access to varied stereoisomers of homo carbanucleosides in their enantiomeric pure form that would be amenable to their elaborate biological screening for anti viral studies, Earlier, we synthesized the 2′, 3′- olefinic carbocyclic core of the (-)-5′-carbovir and (-)-5′-homoabacavir utilizing RCM approach as the key step for the formation of the cyclopentene unit.[158] We thought of adopting a similar approach for the construction of the carbocyclic core of homo carbanucleosides also.

Retro synthetic analysis of the 5′-homocarbanucleosides (**Scheme 3.5**) suggested that for the convergent preparation of the nucleoside it's desirable to prepare the carbocyclic core of the 5′-homocarbanucleosides i.e., 1,4- disubstituted 2,3-cyclopentenol precursors $\mathbf{Y_1}$. The preparation of $\mathbf{Y_1}$ makes the synthetic strategy amenable for the synthesis of a variety of base divergent carba nucleosides. The precursor for the carbanucleoside $\mathbf{Y_1}$ can be obtained employing RCM protocol to the branched 1,6-dienes $\mathbf{Y_2}$. The intermediate $\mathbf{Y_2}$ can be obtained in a stereo divergent manner from the (R)-2, 3-*O*-cyclohexylideneglyceraldehyde[144] (**2.65**) derived $\mathbf{Y_3}$. Hence the synthesis of the intermediate $\mathbf{Y_3}$ in a stereoselective manner can lead to the formal synthesis of the 5′-homocarbanucleosides.



Scheme 3.5

With our aim of preparing intermediate $\mathbf{Y_3}$ in stereochemically pure form we started with silylation of the *anti* homo allyl alcohol (**2.95**) which had been obtained as the major product by Luche's allylation of (*R*)-2,3-*O*-cyclohexylideneglyceraldehyde (**2.65**) (**Scheme 2.9**). Following the same reactions protocol as shown in Scheme **2.10,** compound **2.95** was converted to **2.98** which was reduced with DIBAL-H to give substituted allyl alcohol **2.99** in good yield. This was subjected to Claisen orthoester rearrangement by treating it with triethyl orthoacetate in presence of propanoic acid as catalyst (**Scheme 2.18**). This gave the ester **3.35** as an inseparable mixture of isomers (**3.35a** & **3.35b**) (**Figure 3.2**) along with another inseparable by-product in substantial amount (confirmed by NMR). With a hope of eliminating the undesired product in the next step, the crude product of this Claisen orthoester rearrangement was subjected to DIBAL-H reduction, however it was found that the undesired by-product of the previous reaction also reacted resulting to a chromatographically inseparable mixture of several compounds along with the desired alcohol **3.36a,b** (**Figure 3.3**).



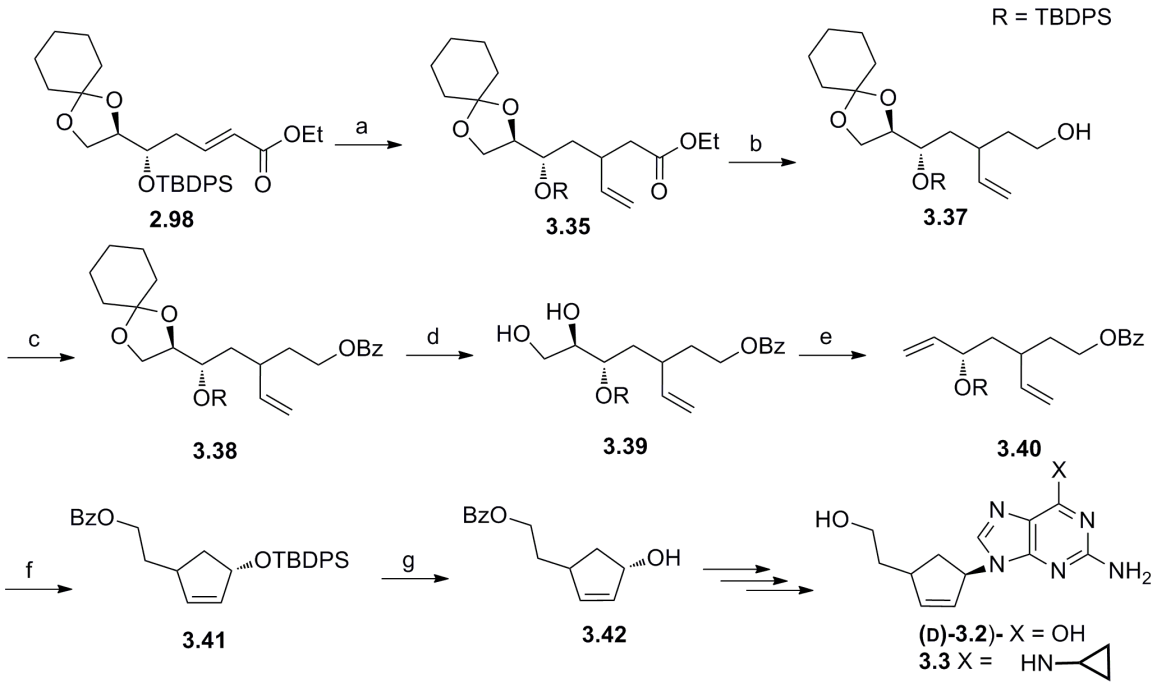
a) DIBAL-H, THF, -78°C; b) Triethyl ortho acetate, Propanoic acid, 150°C

Scheme 3.6

Understandably, due to such non-separability of the complex mixture of products (**Scheme 3.6**) it was difficult for us to proceed further. Hence, we decided to make an

effort to have access to intermediate **Y_3** following an alternate approach which has been outlined in **Scheme 3.7**. Here, in a crucial step compound **2.98** was subjected to 1, 4-conjugate addition by treating it with vinyl cuprate, formed *in situ* by the addition of vinyl magnesium bromide to CuI in THF (**Scheme 3.7**) . The reaction gave the unsaturated ester **3.35** in 65% yield. To our delight the vinyl cuprate addition took place with absolute stereo-selectivity giving a single diastereomer **3.35** (**Figure 3.4-3.5**) of the product. This could be understood from its ^{13}C-NMR spectrum (especially from a singlet at δ 109.7 due to cyclohexylidene ketal carbon). The presence of a terminal olefin in **3.35** could be understood from the two signals at δ 4.7-4.9 (m, 2H) and 5.4 -5.6(m, 1H) in its ^{1}H-NMR spectrum. However, at this stage it was difficult to determine the stereochemistry at newly generated stereocenter (C-3) of the addition product. The unsaturated ester **3.35** was then reduced with DIBAL-H at an elevated temperature (-30 ^{o}C) to give alcohol **3.37** (**Figure 3.6-3.7**). This on benzoylation (benzoyl cyanide/TEA) gave the protected alcohol **3.38** (**Figure 3.8-3.9**) which showed the appearance of a signal at 166.1 in its ^{13}C-NMR spectrum (**Figure 3.9**) due to benzoate carbonyl. Ketal hydrolysis of **3.38** gave the vicinal diol **3.39** (**Figure 3.10-3.11**) which was converted to the bisolefin **3.40** (**Figure 3.12-3.13**) over two steps *viz.*, (a) di-tosylation of the vicinal diol **3.39** and (b) reduction of the ditosylate by Zn with NaI. The presence of two terminal olefin in **3.40** could be indicated from signals at δ 4.7-4.9 (m, 4H, $=CH_2$), δ 5.2-5.4 (m, 1H, -CH=) and δ 5.5-5.7 (m, 1H, -CH=) in its ^{1}H-NMR spectrum (**Figure 3.12**). The 1,6-diene **3.40** was equivalent to the synthon **Y_3** as shown in scheme **3.5**, which was subjected to ring closing metathesis reaction using Grubbs first generation catalyst $[Cl_2(PCy_3)_2RuCHPh]$. This metathesis produced 1,4-disubstituted-2-cyclopentene **3.41** (**Figure 3.14-3.15**) in 85% yield. In fact, initially the reaction proceeded to some extent with the formation of metathesis product, while some amount of starting material remained unreacted which was recovered from

the reaction mixture by column chromatography (silica gel, 0-5% EtOAc in Petroleum ether). This then resubjected to RCM to get the same cyclopentene **3.41**. The compound has been characterized by the presence of two multiplets at δ 5.6 and δ 5.8 due to carbocycle olefin protons (**Figure 3.14**). In order to make its secondary hydroxyl free for the insertion of the nucleobase to the carbasugar, the cyclopentene **3.41** was treated with TBAF in THF which gave the de-silylated 1,4-disubstituted-2-cyclopentenol **3.42** (**Figure 3.16-3.17**). The stereochemistry at C-5 in the cyclopentene unit of **3.41** will be determined after converting it into a known intermediate of homocarbovir. At the present stage, this could be treated as an operationally simple and inexpensive approach for the construction of carbocyclic core of homo-carbanucleosides. Quite evidently, employing the same route there is a scope to impart more stereochemical variations in the carbocycle core of homo-carbanucleosides starting from *syn* homoallylic alcohol (**2.94**).



a) Vinyl magnesium bromide, CuI (Anhydrous), THF, -30°C to 25°C; b) DIBAL-H, THF, -30°C to 0°C; c) BzCN, Et_3N, DCM, 0°C to 25°C; d) CF_3COOH/H_2O (8:2), DCM, 0°C; e) (1) TsCl, Pyridine, DMAP, 0°C to 25°C, (2) Zn, NaI, DMF, 90°C, 12 h; f) $(PCy_3)_2Cl_2RuCHPh$, Dry Benzene, 60 °C, 24 h; c) TBAF, THF, 0 °C to 25 °C;

Scheme 3.7

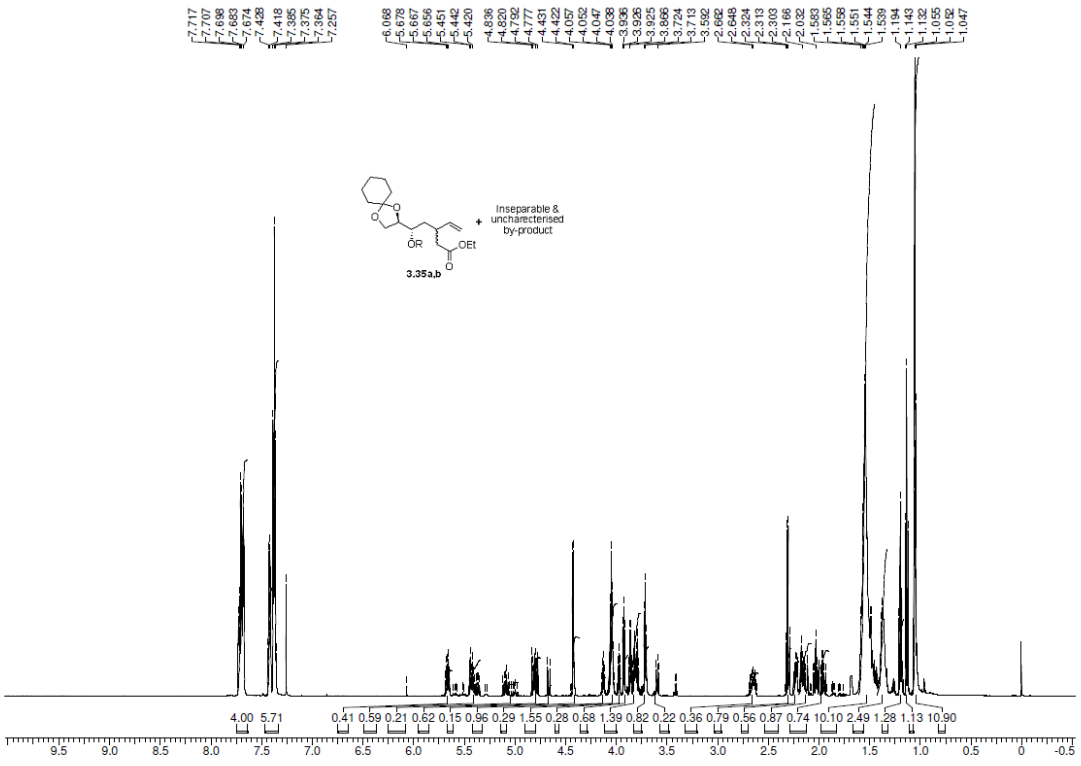


Figure 3.2 ^{1}H NMR spectrum of 3.35 a,b

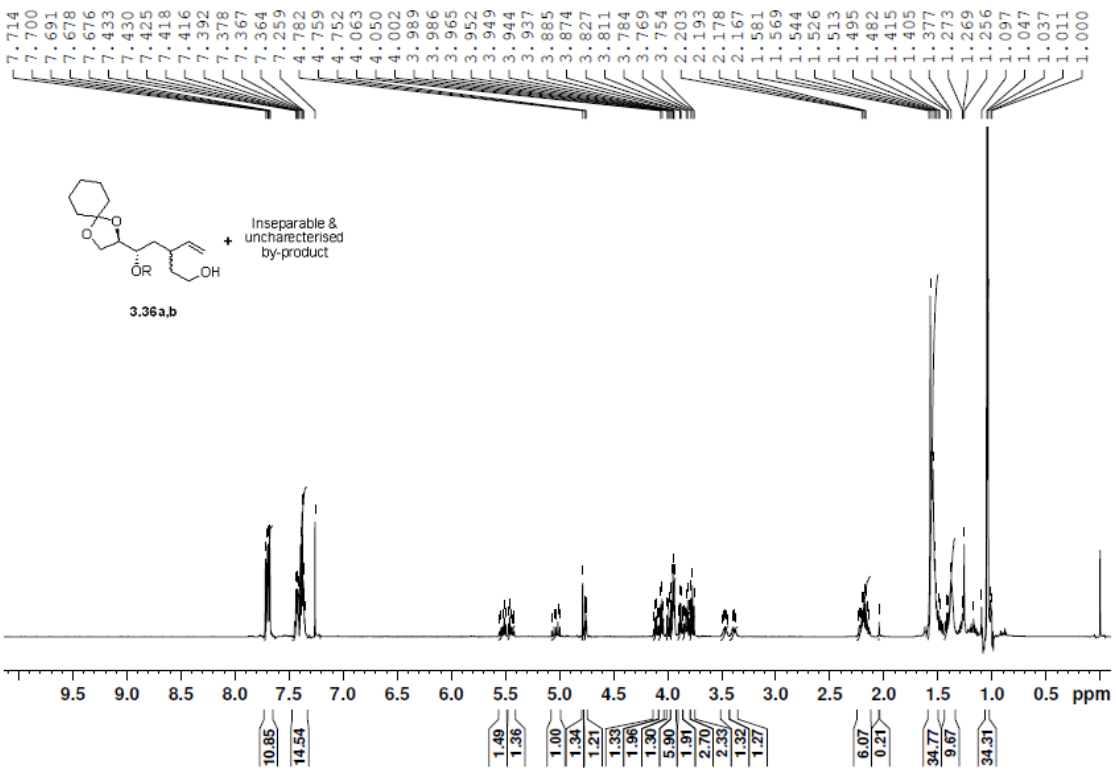


Figure 3.3 ^{1}H NMR spectrum of 3.36 a,b

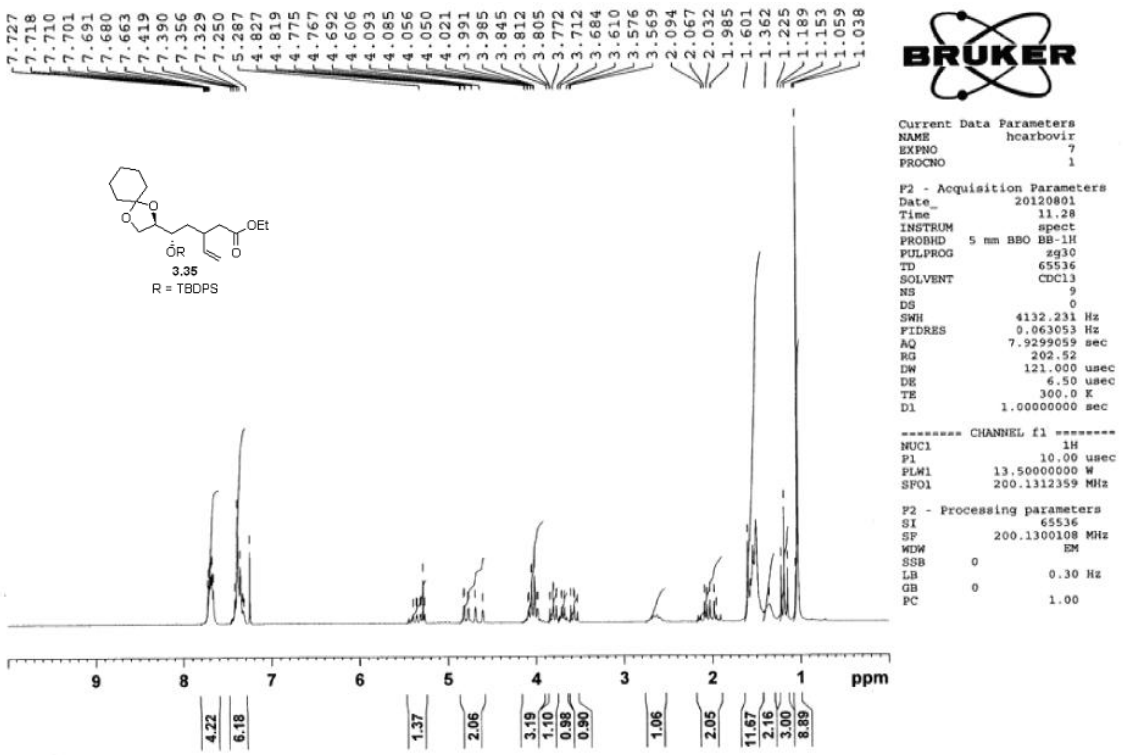


Figure 3.4 ^{1}H NMR spectrum of 3.35

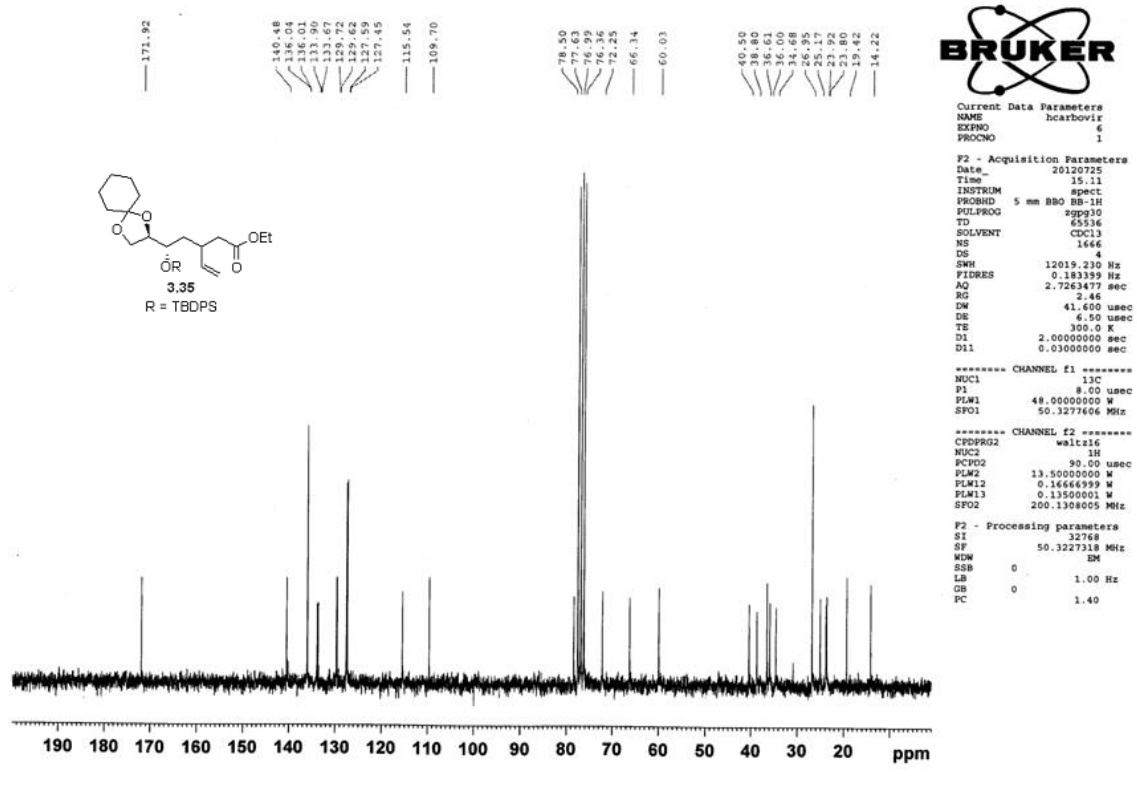


Figure 3.5 ^{13}C NMR spectrum of 3.35

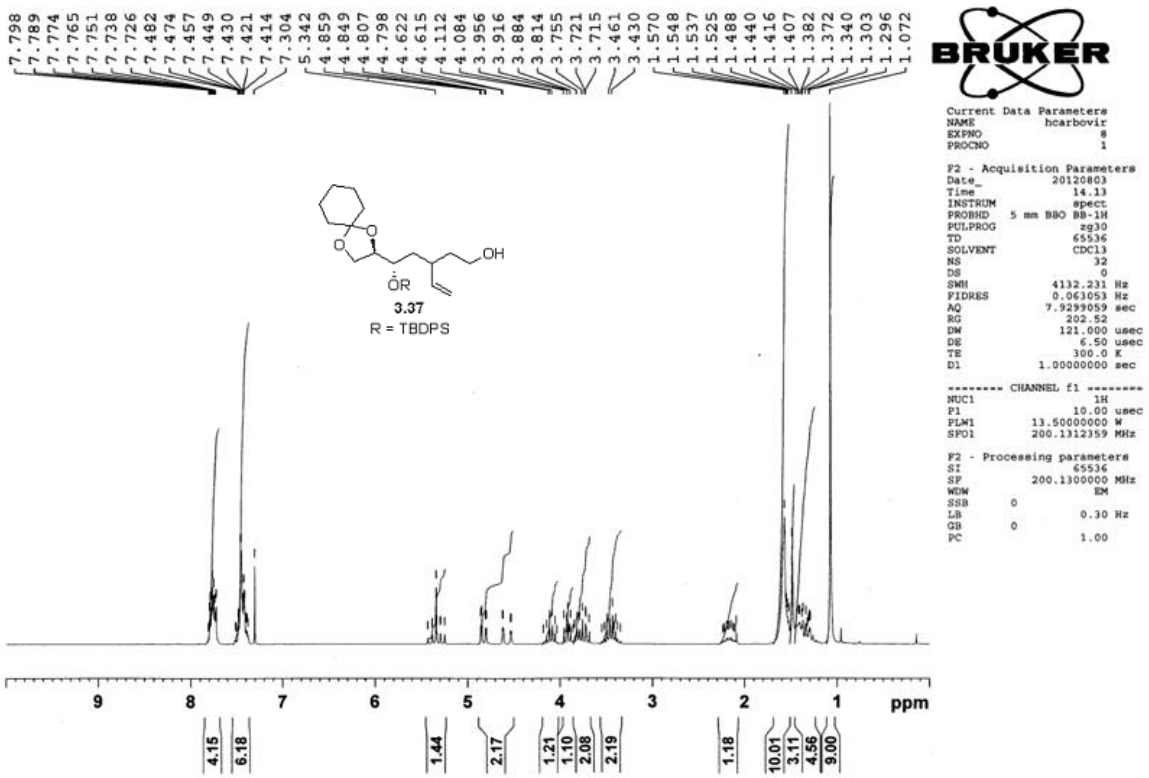


Figure 3.6 ^{1}H NMR spectrum of 3.37

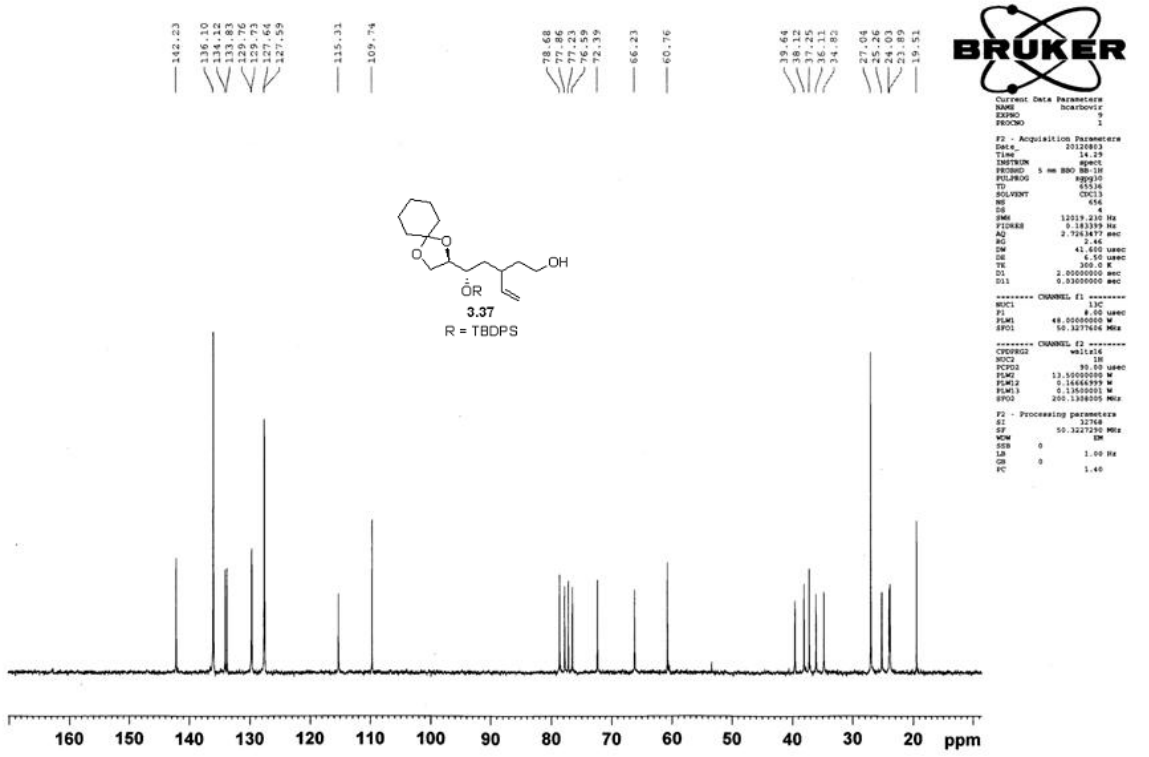


Figure 3.7 ^{13}C NMR spectrum of 3.37

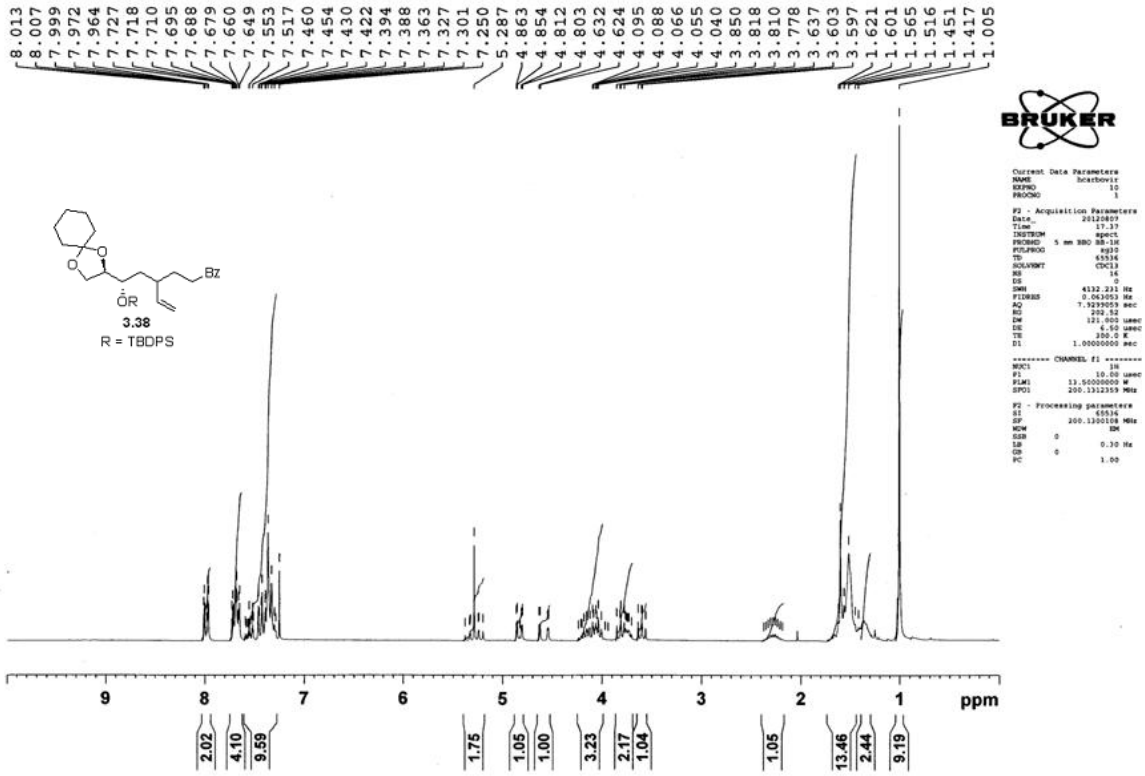


Figure 3.8 ^{1}H NMR spectrum of 3.38

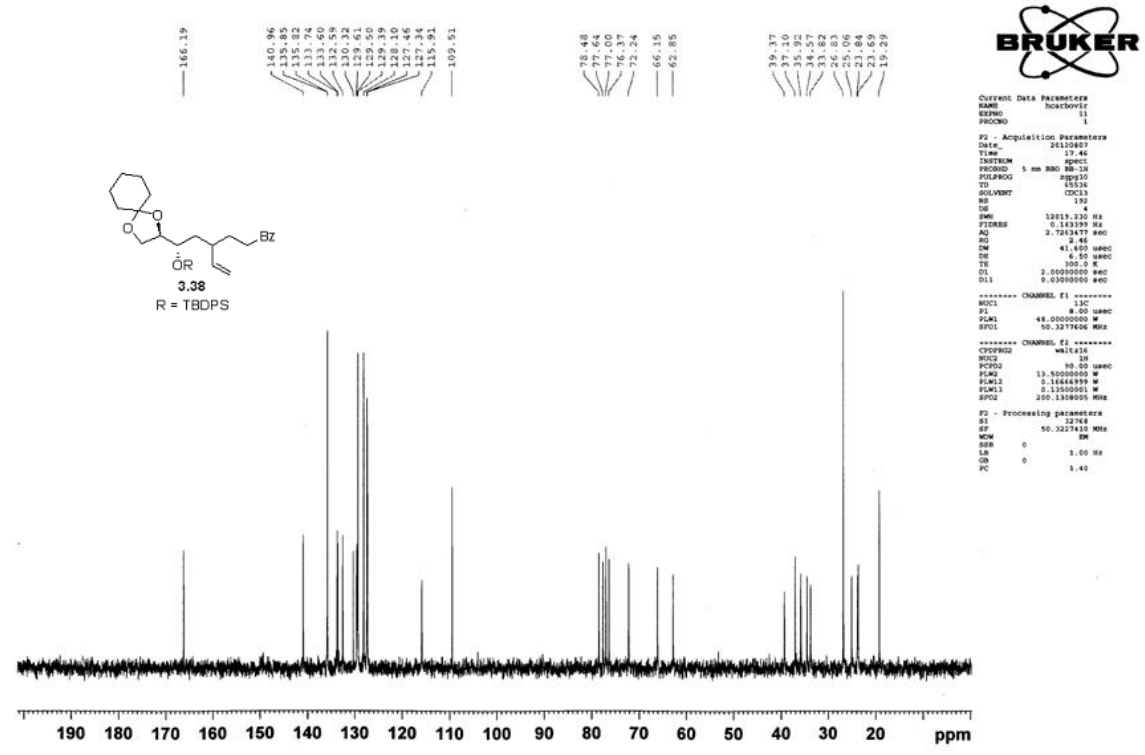


Figure 3.9 ^{13}C NMR spectrum of 3.38

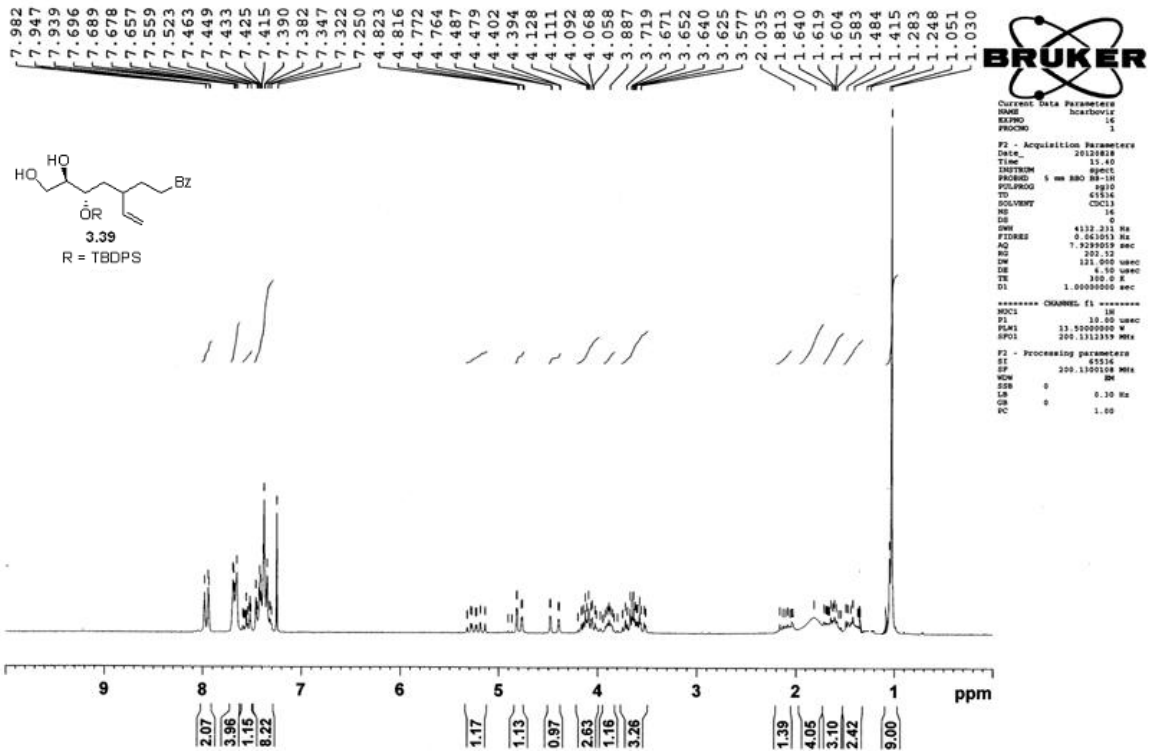


Figure 3.10 ^{1}H NMR spectrum of 3.39

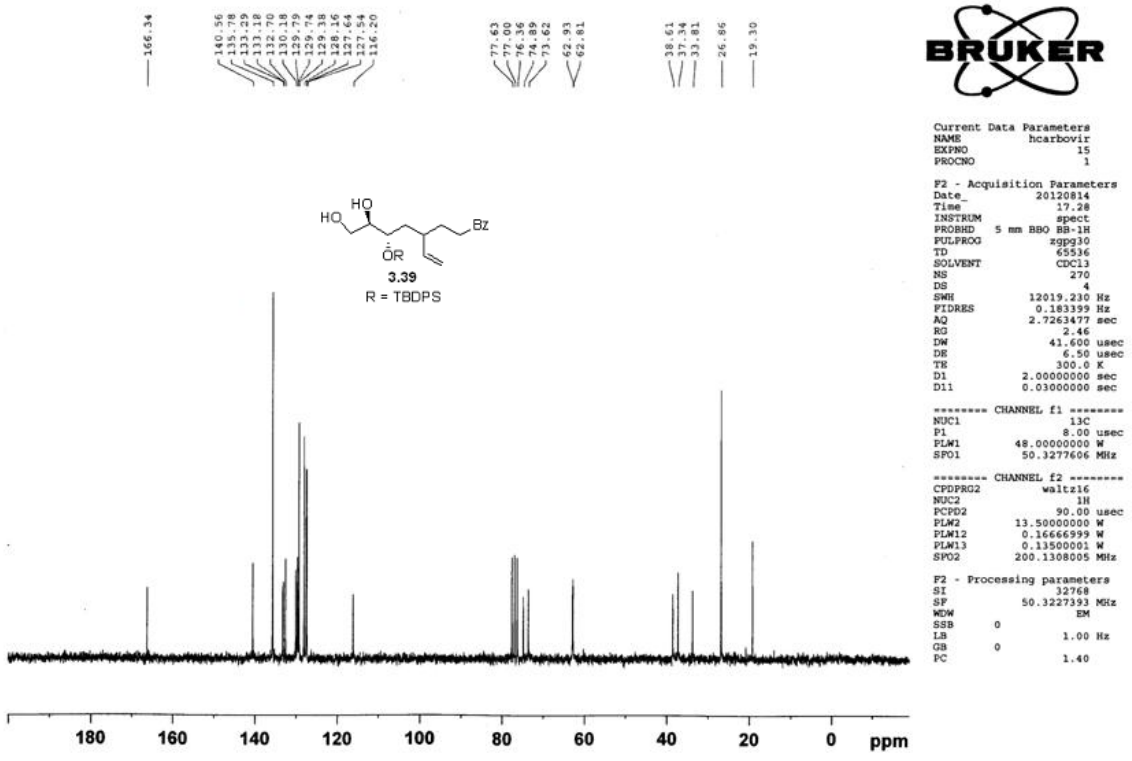


Figure 3.11 ^{13}C NMR spectrum of 3.39

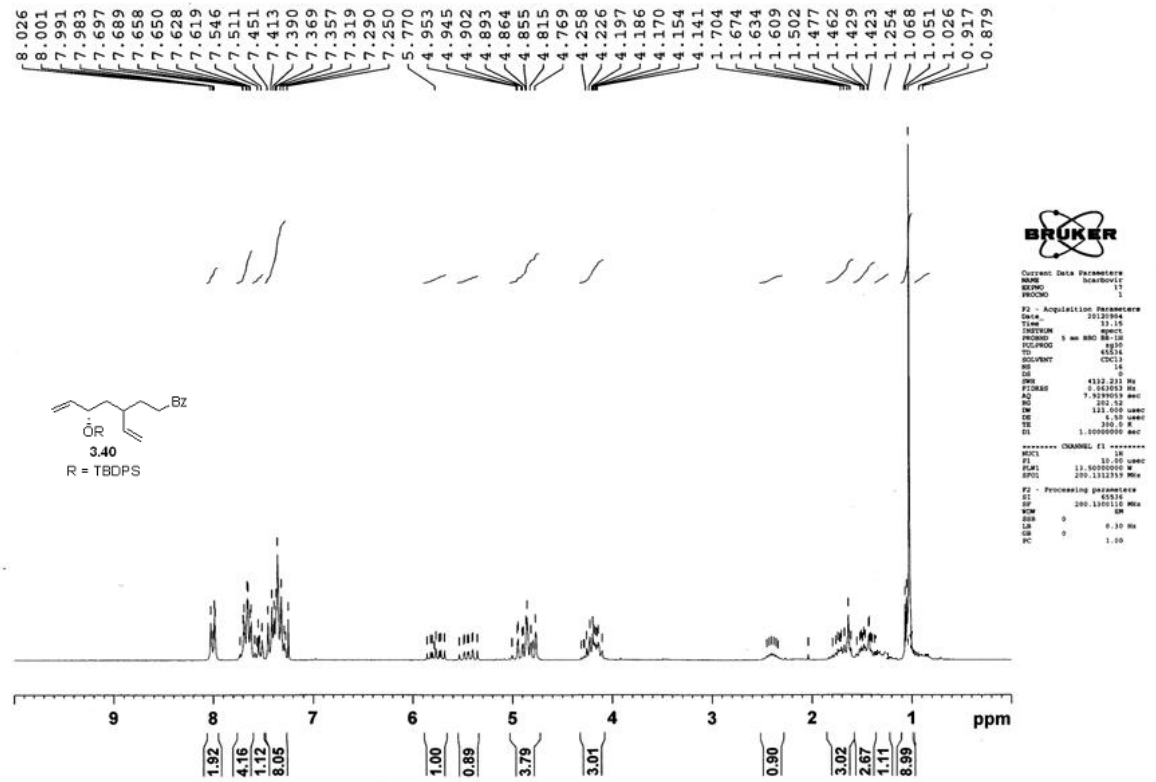


Figure 3.12 ^{1}H NMR spectrum of 3.40

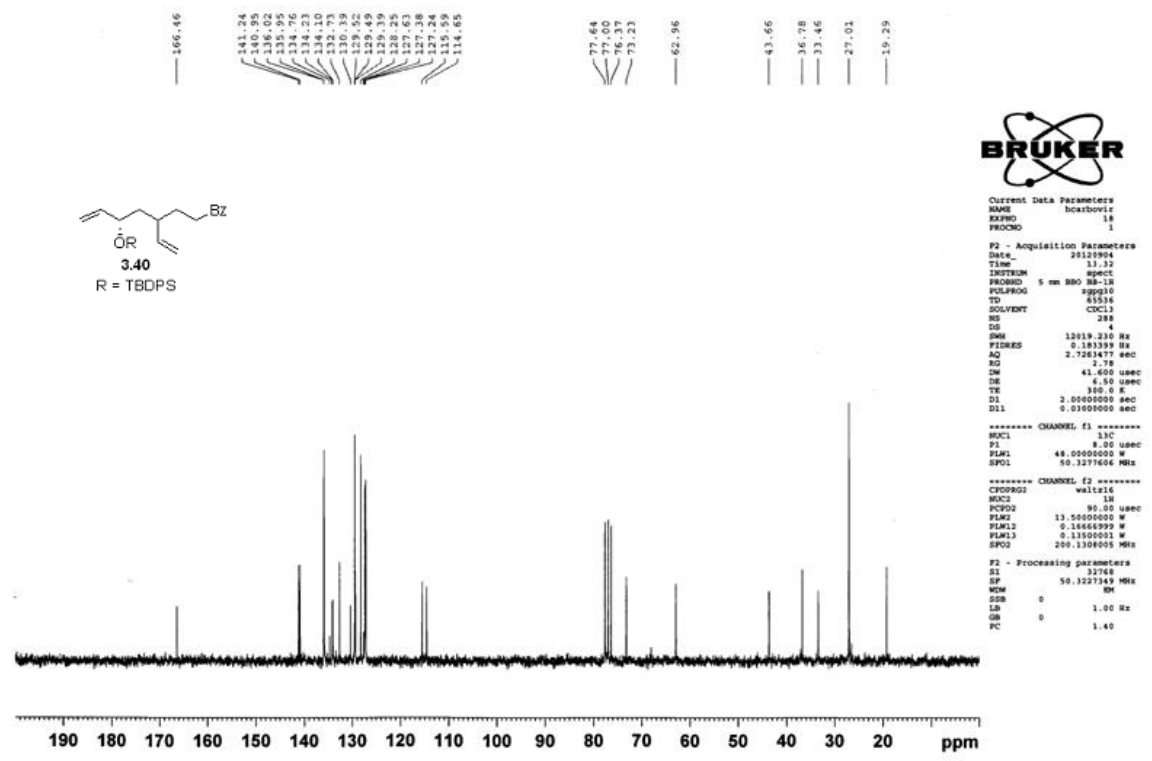


Figure 3.13 ^{13}C NMR spectrum of 3.40

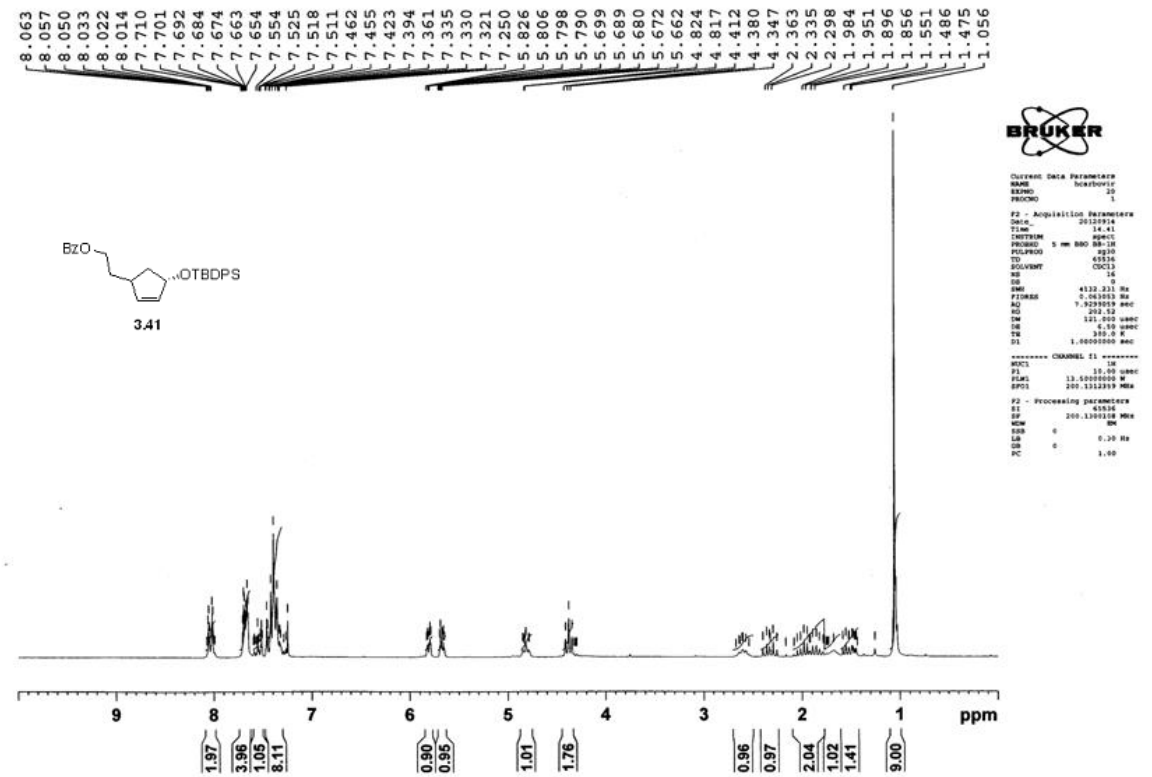


Figure 3.14 ^{1}H NMR spectrum of 3.41

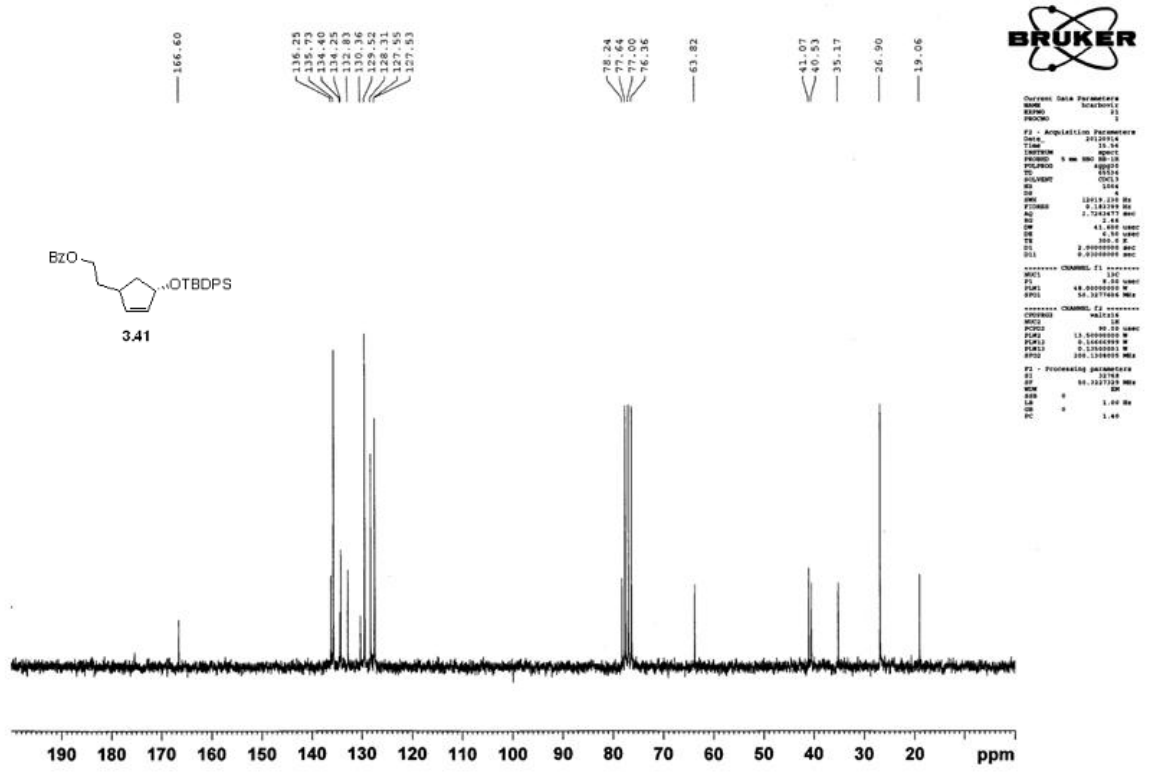


Figure 3.15 ^{13}C NMR spectrum of 3.42

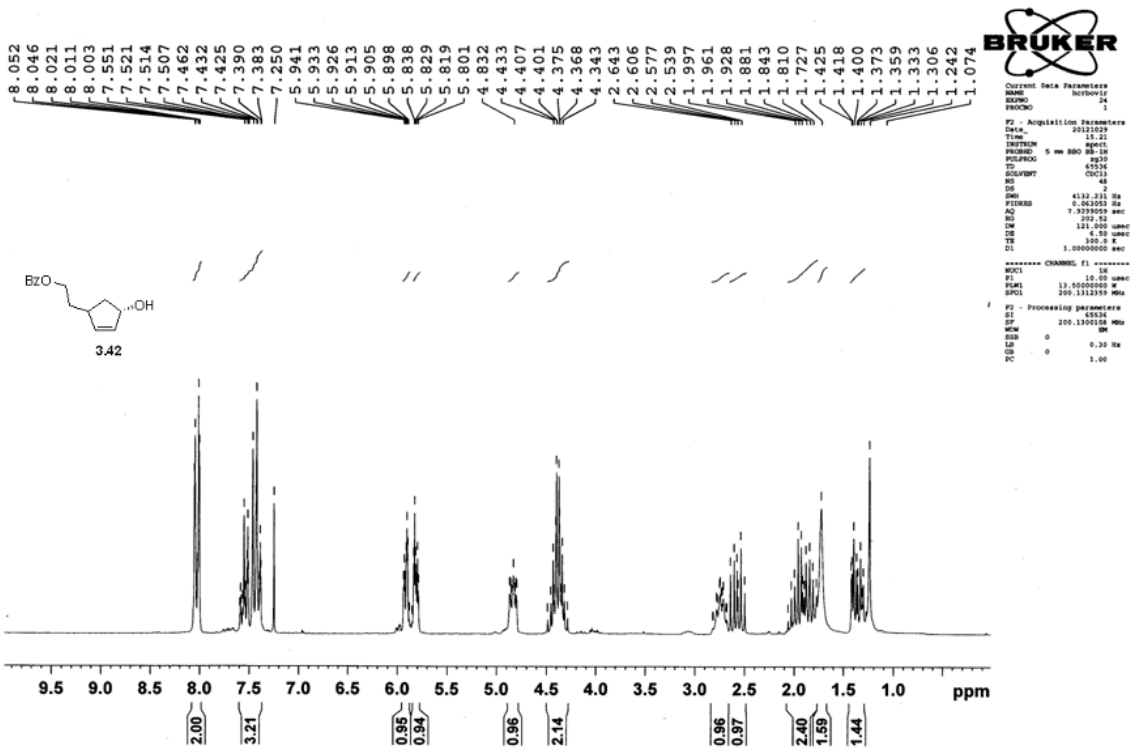


Figure 3.16 ^{1}H NMR spectrum of 3.42

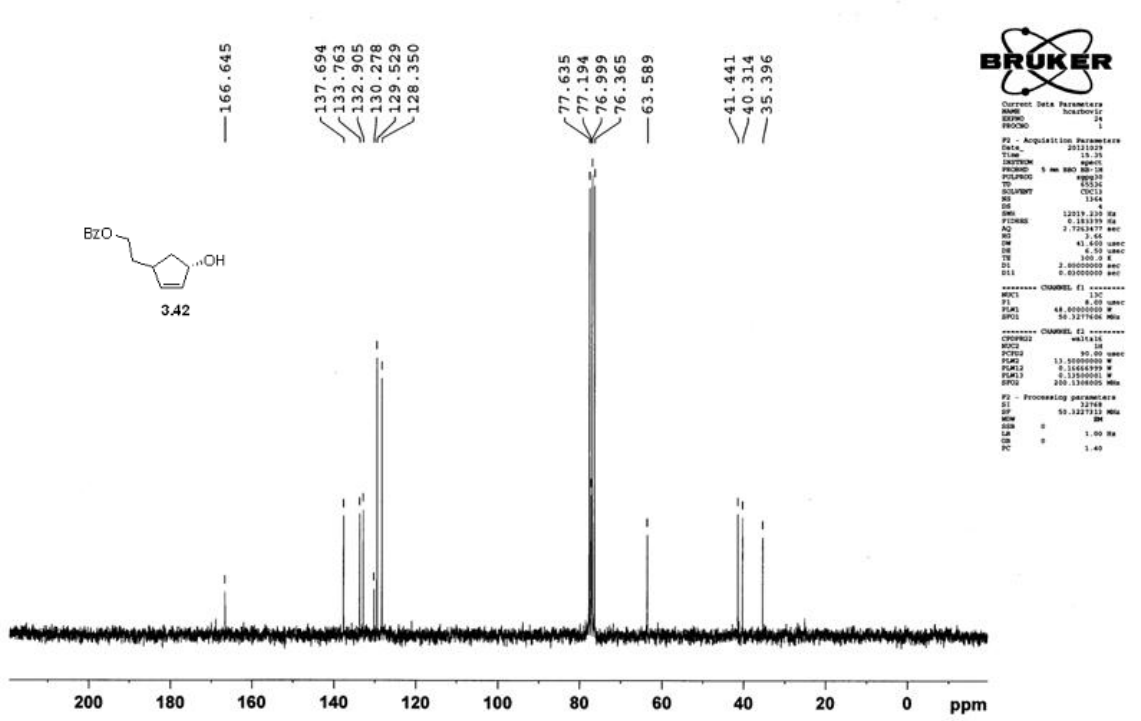


Figure 3.17 ^{13}C NMR spectrum of 3.42

3.III Experimental

General procedure for Orthoester Claisen rearrangement reaction:

A mixture of allylic alcohol **2.99** (1.0 g, 2.08 mmol), triethylorthoacetate (2.5 mL) and propionic acid (0.05 mL) was refluxed under argon atmosphere at 180 °C for 8 hour. The excess triethyl orthoacetate was removed under vaccum. Chromatography of the residual mass afforded the mixture of unsturated ester **3.35a, b** with an inseparable bi-product.

(5*S*,6*R*)-Ethyl-5-*O*-*tert*-butyl-diphenylsilyl-6,7-*O*-cyclohexylidene-3-vinyl-5,6,7-trihydroxyheptanoate (3.35) :

To a cooled (0 °C) solution of CuI (2.9 g, 15.23 mmol) in distilled THF (50 ml) was added vinyl magnesium bromide solution (15.3 ml, 1 molar solution in THF, 15.3 mmol) in THF and stirred for 10 minute at same temperature. The reaction mixture was again cooled to -78°C to which the solution of **2.98** (4 g, 7.6 mmol) was added drop wise over a period of one hour and stirred for three hour at same temperature. Then the reaction mixture was gradually brought to 0 °C and stirred for 2.5 hour on completion (confirmed by TLC) a saturated solution of NH_4Cl was added dropwise. The reaction mixture was diluted with EtOAc and water. The aqueous layer was extracted with EtOAc. The combined organic layer was washed successively with water, brine and dried over Na_2SO_4. Solvent removal under reduced pressure and chromatography (silica gel, 0-10% EtOAc in Hexane) of the residue afforded pure **3.35** (2.9 g, 69%) as a color less oil.

$[\alpha]_D^{24}$ = -10.31 (c,1.51, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.03 (s, 9H), 1.19 (t, *J* = 7.16 Hz, 3H), 1.30-1.43 (m, 2H), 1.43-1.59 (m, 10H), 1.89-2.19 (m, 2H), 2.54-2.75 (m, 1H), 3.57 (dd, *J* = 8.01, 6.81 Hz, 1H), 3.70 (q, *J* = 5.44 Hz, 1H), 3.76-3.87 (m, 1H), 3.91-4.12 (m, 3H), 4.57-4.86 (m, 2H), 5.25-5.47 (m, 1H), 7.29-7.48 (m, 6H), 7.63-7.75 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.2, 19.4, 23.8, 23.9, 25.2, 27.0, 34.7, 36.0,

36.5, 38.8, 40.5, 60.0, 66.3, 72.3, 78.5, 109.7, 115.5, 127.4, 127.6, 129.6, 129.7, 133.7, 133.9, 136.0, 136.0, 140.2, 140.5, 171.9; Anal. Calcd for $C_{33}H_{46}O_5Si$: C, 71.96; H, 8.42. Found: C, 71.61; H, 8.24.

(5*S*,6*R*)-3-(1-hydroxy-ethyl)-5-*O*-*tert*-butyl-diphenylsilyl-6,7-*O*-cyclohexylidene-5,6,7-trihydroxyhept-1-ene (3.37):

To a cooled (-30 °C) solution of **3.35** (2.5 g, 4.5 mmol) in dry THF (50 ml) DIBAL-H (5.9 ml, 1.0 M solution in hexane) was added drop wise over a period of one hour. The mixture was stirred for 2 hour at same temperature till the reaction was complete (confirmed by TLC). The mixture, at 0 °C was diluted with 15 ml EtOAc followed by the addition of 0.2 M HCl and gradually brought to room temperature and stirred for another one hour. The white gelatinous precipitate formed during the process was dissolved by addition of 0.2 M HCl with continuously monitoring the pH between 8-6 by litmus paper. The reaction mixture was diluted with EtOAc and water. The aqueous layer was extracted with EtOAc. The combined organic layer was washed successively with water, brine and dried over Na_2SO_4. Solvent removal under reduced pressure and chromatography (silica gel, 0-15% EtOAc in Hexane) of the residue afforded pure **3.37** (2.2 g, 95.6%) as a color less oil.

$[\alpha]_D^{24}$ = -8.57 (c, 1.05, CH_2Cl_2); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.07 (s, 9H), 1.25-1.46 (m, 4H), 1.49 (s, 1H), 1.51-1.66 (m, 10H), 2.07-2.28 (m, 1H), 3.33-3.56 (m, 2H), 3.67-3.85 (m, 2H), 3.87-3.98 (m, 1H), 4.02-4.20 (m, 1H), 4.58 (dd, *J* = 17.18, 1.36 Hz, 1H), 4.83 (dd, *J* = 10.25, 1.86 Hz, 1H), 5.23-5.45 (m, 1H), 7.36-7.55 (m, 6H), 7.68-7.83 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 19.5, 23.9, 24.0, 25.3, 27.0, 34.8, 36.1, 37.2, 38.1, 39.6, 60.8, 66.2, 72.4, 78.7, 109.7, 115.3, 127.6, 127.64, 129.7, 129.8, 133.8, 134.1, 136.1, 142.2; Anal. Calcd for $C_{31}H_{44}O_4Si$: C, 73.18; H, 8.72. Found: C, 73.33; H, 8.89.

(5*S*,6*R*)-3-(1-*O*-benzoyloxyethyl)-5-*O*-*tert*-butyl-diphenylsilyl-6,7-*O*-cyclohexylidene-5,6,7-trihydroxyhept-1-ene (3.38):

To a cooled (0 °C) solution of the alcohol **3.37** (2.1 g, 4.13 mmol) and triethylamine (630 mg, 6.2 mmol) in dry CH_2Cl_2 (20 ml) a solution of benzoyl cyanide (650 mg, 4.96 mmol) in CH_2Cl_2 (10 ml) was added in 5 minute. The mixture was stirred at 0 °C for 1 hour and then at room temperature for 6 hour. The solution was treated with water. The organic layer was separated and the aqueous layer was washed extracted with $CHCl_3$. The combined organic layer was washed with *dil.* aqueous HCl till neutral, water, brine and dried over Na_2SO_4. Solvent removal under reduced pressure, column chromatography (silica gel, 0-5% EtOAc in Hexane) of the residue afforded pure **3.38** (2.4 g, 94.8 %) as a colorless oil.

$[\alpha]_D^{23}$ = -13.37 (c, 1.72, CH_2Cl_2); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.08 (s, 9H), 1.28-1.43 (m, 3H), 1.43-1.74 (m, 11H), 2.28 (dt, *J* = 9.38, 4.61 Hz, 1H), 3.60 (dd, *J* = 8.04, 6.78 Hz, 1H), 3.68-3.88 (m, 2H), 3.99-4.25 (m, 3H), 4.59 (dd, *J* = 17.15, 1.58 Hz, 1H), 4.76-4.90 (m, 1H), 5.17-5.41 (m, 1H), 7.27-7.61 (m, 9H), 7.61-7.76 (m, 4H), 7.91-8.05 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 19.3, 23.7, 23.8, 25.1, 26.8, 33.8, 34.6, 35.9, 37.1, 39.4, 62.8, 66.1, 72.2, 78.5, 109.5, 115.9, 127.3, 127.5, 128.1, 129.4, 129.5, 129.6, 130.3, 132.6, 133.6, 133.7, 135.8, 135.85, 141.0, 166.2; Anal. Calcd for $C_{38}H_{48}O_5Si$; C, 74.47; H, 7.89. Found: C, 74.15; H, 7.93.

(5*S*,6*R*)-3-(1-*O*-benzoyloxyethyl)-5-*O*-*tert*-butyl-diphenylsilyl-5,6,7-trihydroxyhept-1-ene (3.39):

To a cooled (0 °C) solution of **3.38** (2.30 g, 3.7 mmol) in distilled CH_2Cl_2 (30 ml) was added 80% aqueous trifluoroacetic acid (10 ml). The mixture was stirred for three hour at 0 °C. The reaction mixture was diluted with $CHCl_3$ and water. The aqueous layer was extracted with $CHCl_3$. The combined organic layer was washed successively with 2%

$NaHCO_3$ for neutrality, water, brine, and dried over Na_2SO_4. Solvent removal under reduced pressure and column chromatography (silica gel, 0-5% MeOH in $CHCl_3$) of the residue afforded pure **3.39** (1.46 g, 73.5%) as a colorless oil.

$[\alpha]_D^{23}$ = 12.77 (c, 2.35, CH_2Cl_2); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.03 (s, 9H), 1.31-1.51 (m, 2H), 1.52 1.73 (m, 2H), 2.02 (bs, 2H), 2.05-2.21 (m, 1H), 3.50-3.68 (m, 3H), 3.83-3.93 (m, 1H), 3.94-4.22 (m, 2H), 4.43 (dd, *J* = 17.0, 1.58 Hz 1H), 4.79 (dd, *J* = 10.21, 1.51 Hz, 1H), 5.12-5.34 (m, 1H), 7.29-7.61 (m, 9H), 7.61-7.73 (m, 4H), 7.92-8.02 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 19.3, 26.9, 33.8, 37.3, 38.6, 62.8, 62.9, 73.6, 74.9, 116.2, 127.5, 127.6, 128.2, 129.4, 129.7, 129.8, 130.2, 132.7, 133.2, 133.3, 135.8, 140.6, 166.3; Anal. Calcd for $C_{32}H_{40}O_5Si$; C, 72.14; H, 7.57, Found: C, 71.86; H, 7.23.

(5*S*)-3-(1-*O*-benzoyloxy ethyl)-5-*O*-*tert*-butyl-diphenylsilyl-1,6-hexadiene (3.40):

To a cooled (0 °C) solution of **3.39** (1.4 g, 2.63 mmol) in dry pyridine (10 ml), p-toluenesulfonyl chloride (1.25 g, 6.56 mmol) and dimethylaminopyridine (100 mg) were added. The mixture was gradually brought to room temperature over a period of 6 hour and then stirred overnight. The reaction mixture was treated with 5% aqueous HCl and water for neutrality. The aqueous layer was extracted with $CHCl_3$. The combined organic layer was washed with water, brine and dried over Na_2SO_4. It was concentrated under reduced pressure to afford the crude ditosylated product (confirmed by TLC and IR of crude) which was taken in dry DMF (15 ml). To this solution were added Zn dust (0.52 g, 8.0 mmol) and dry NaI (1.20 g, 8.01 mmol). The mixture was stirred overnight at 90 °C. The mixture was filtered and the residue was thoroughly washed with EtOAc. The combined organic layer was washed with dilute aqueous HCl in order to dissolve the turbid material. The aqueous layer was separately extracted with EtOAc. The combined organic layer was washed with water, brine and dried over Na_2SO_4. Solvent removal

under reduced pressure and column chromatography (silica gel, 0-10 % EtOAc in Hexane) of the residue afforded pure diene **3.40** (1.15 g, 88.5 %) as a color less oil.

$[\alpha]_D^{24}$ = -6.65 (c, 1.25, CH_2Cl_2); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.03 (s, 9H), 1.3-1.57 (m, 2H), 1.59-1.86 (m, 2H), 2.40 (td, *J* = 8.91, 4.19 Hz, 1H), 4.08-4.32 (m, 3H), 4.72-5.02 (m, 4H), 5.44 (ddd, *J* = 17.07, 10.17, 8.89 Hz, 1H), 5.66-5.88 (m, 1H), 7.26-7.60 (m, 9H), 7.60-7.75 (m, 4H), 7.95-8.06 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 19.3, 27.0, 33.5, 36.8, 43.7, 63.0, 73.2, 114.7, 115.6, 127.2, 127.4, 127.6, 128.2, 129.4, 129.49, 129.52, 130.4, 132.7, 134.1, 134.2, 134.8, 135.95, 136.0, 141.0, 141.2, 166.5; Anal. Calcd for $C_{32}H_{38}O_3Si$; C, 77.06; H, 7.68. Found: C, 77.06; H, 7.98.

(1*S*)-1-*O*-*tert*-butyl-diphenylsilyl-4-Benzyloxyethyl-cyclopenten-2-en-1-ol (3.41) :

A solution of diene **3.40** (500 mg, 1.003 mmol) in dry benzene (50 ml) was degassed by bubbling argon. To it was added Grubb's 1st generation catalyst (24.75 mg, 0.03007 mmol) in one portion. The resulting pink solution was stirred under heating (60 °C) for 48 hour. The solvent was removed under reduced pressure and the dark residue was purified by chromatography (silica gel, 0-5% EtOAc in Hexane) to afford pure **3.41** (352.7 mg, 74.8%) as a slight pink colored oil, the starting material **3.40** (112.2 mg) recovered in its pure form.

$[\alpha]_D^{28}$ = + 4.43 (c, 2.26, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.08 (m, 9H), 1.42-1.59 (m, 1H), 1.77-2.10 (m, 2H), 2.33 (dt, *J* = 13.05, 7.44 Hz, 1H), 2.51-2.69 (m, 1H), 4.38 (t, *J* = 6.53 Hz, 2H), 4.76-4.89 (m, 1H), 5.68 (dt, *J* = 5.58, 1.97 Hz, 1H), 5.81 (dt, *J* = 5.61, 1.54 Hz, 1H), 7.26-7.48 (m, 9H), 7.48-7.61 (m, 1H), 7.63-7.73 (m, 4H), 7.99-8.09 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 19.1, 26.9, 35.2, 40.5, 41.1, 63.8, 78.2, 127.5, 127.6, 128.3, 129.5, 130.4, 132.8, 134.2, 134.4, 135.7, 136.2, 166.6; Anal. Calcd for $C_{30}H_{34}O_3Si$; C, 76.55; H, 7.28. Found: C, 76.81; H, 7.38.

(1*S*)-4-Benzoyloxyethyl-cyclopenten-2-en-1-ol (**3.42**);

Tetrabutylammonium fluoride in THF (0.3 ml, 1 M solution) was added to a cooled (0 ^{o}C) solution of **3.41** (70 mg, 0.2 mmol) in THF (10 ml). The resulting solution was stirred for 1hour and after the completion of reaction confirmed by TLC the reaction was quenched by the addition of saturated aqueous solution of NH_4Cl (2 ml). The mixture was diluted with EtOAc while two phases were separated. The aqueous phase was extracted with EtOAc. The combined organic layer was washed successively with water, brine and dried. Solvent removal under reduced pressure and column chromatography of the residue (silica gel, 0-5 % MeOH in $CHCl_3$) afforded pure **3.42** (21 mg, 92.9%) as a colorless oil.

$[\alpha]_D^{24}$ = -2.86 (c, 1.05, CH_3Cl); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.24 (s, 1H), 1.29-1.44 (m, 2H), 1.73 (br. s., 2H), 1.77-2.07 (m, 3H), 2.48-2.65 (m, 1H), 2.66-2.84 (m, 1H), 4.28-4.50 (m, 2H), 4.78-4.89 (m, 1H), 5.81 (dt, *J* = 5.60, 1.99 Hz, 1H), 5.92 (dt, *J* = 5.61, 1.48 Hz, 1H), 7.36-7.49 (m, 2H), 7.49-7.61 (m, 1H), 7.98-8.08 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 29.7, 35.4, 40.3, 41.4, 63.6, 76.4, 77.0, 77.2, 77.6, 128.3, 129.5, 130.3, 132.9, 133.8, 137.7, 166.6; Anal. Calcd for $C_{14}H_{16}O_3$; C, 72.39; H, 6.94, Found: C, 72.39; H, 6.94.

CHAPTER 4

Versatile Route to Carba-Furanose via Intramolecular Allylation

4.I Carbohydrate

Carbohydrates are the most abundant and intriguingly complex molecules that are responsible for most of the important biological activity in other words these molecules are pantheon of life on earth. They provide structural stability to the living organism as they are found in food, drug, paper, textile, and more importantly in the biomolecules like DNA, RNA, enzymes and coenzymes etc.[159] The presence of these molecules in biomolecule made them to as the mode of communication or cell signaling, and stored the energy in the form of starch or glycogen in cells and take part in countless interactions in nature.[160] Over the years it has been studied how the carbohydrates participate in intricate biological processes ranging from blood clotting to fertilization, all involve carbohydrates, and the biological implications of these compounds are strongly related with diseases such as cancer, diabetes, or inflammatory processes immune system, cell differentiation and tumor cell metastasis.[160d,161] Hence the synthesis of these poly functional compounds and study of the biological property is an important field.

Carbohydrates are the class of compounds which formally consists of carbon and water with the chemical formula $C_n(H_2O)_n$, however this basic formula doesn't satisfy the all class of carbohydrates today. Over the years the classification of what carbohydrates are widened which includes the derivatives of carbohydrates. In general polyhydroxylated aldehydes or ketones along with deoxysugars, aminosugars, alditols, uronoic acids, Inisitols etc. (**Figure 4.1**) are today considered as carbohydrates.[160a,b,162]

As discussed earlier the polyhydroxy aldehydes and ketones which are the basic class of carbohydrate compounds, the classifications of these monosaccharides are based on the position of the carbonyl group, the number of skeletal carbons and the chiral handedness of the structure. When the carbonyl group is situated at C-1, being an aldehyde, the carbohydrate is called an aldose, whereas when the carbonyl is a ketone, the

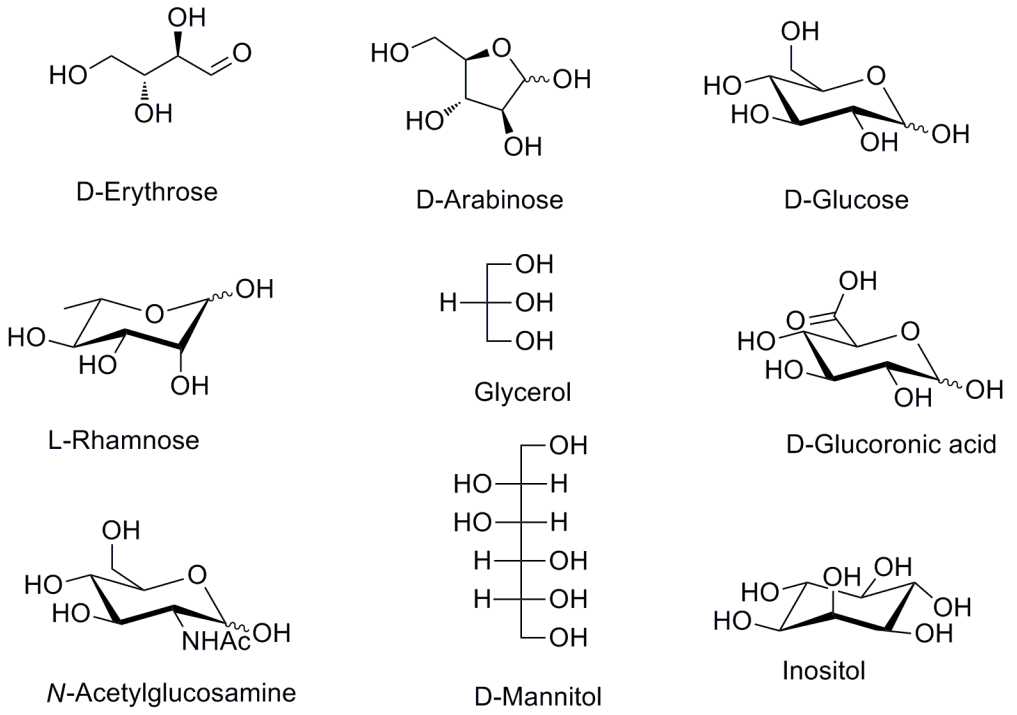


Figure 4.1 Non $C_n(H_2O)_n$ carbohydrates

carbohydrate is referred to as a ketose. An aldose with four carbons in the carbohydrate backbone is called a tetrose; Pentoses (five carbons), hexoses (six carbons) and heptoses (seven carbons) are classified in the same way. Carbohydrates can also undertake different isomeric forms such as furanose (5-membered ring) and pyranose (6-membered ring) configurations (**Figure 4.2**). These configurations may freely interchange as long as the C-1 hydroxyl remains a hydroxyl (hemiacetal) but become locked once C-1 is converted to an acetal.

The different isomeric form of **D**-Glucose is presented in Figure **4.2**. As mentioned earlier both the pyranose and furanose forms are presented where the C-4 (Fischer projection) hydroxyl (red) and the C-5 (Fischer projection) hydroxyl (blue) act as the endocyclic oxygen, giving rise to the furanose and pyranose isomers. The orientation of the anomeric hydroxyl (green) determines the **α/β** configuration. C-5 is the asymmetric center furthest from the aldehyde and determines whether the carbohydrate is the **D**- or **L**-

enantiomer as seen by the orientation in the Fischer projection (hydroxyl to the right = **D**, hydroxyl to the left = **L**).

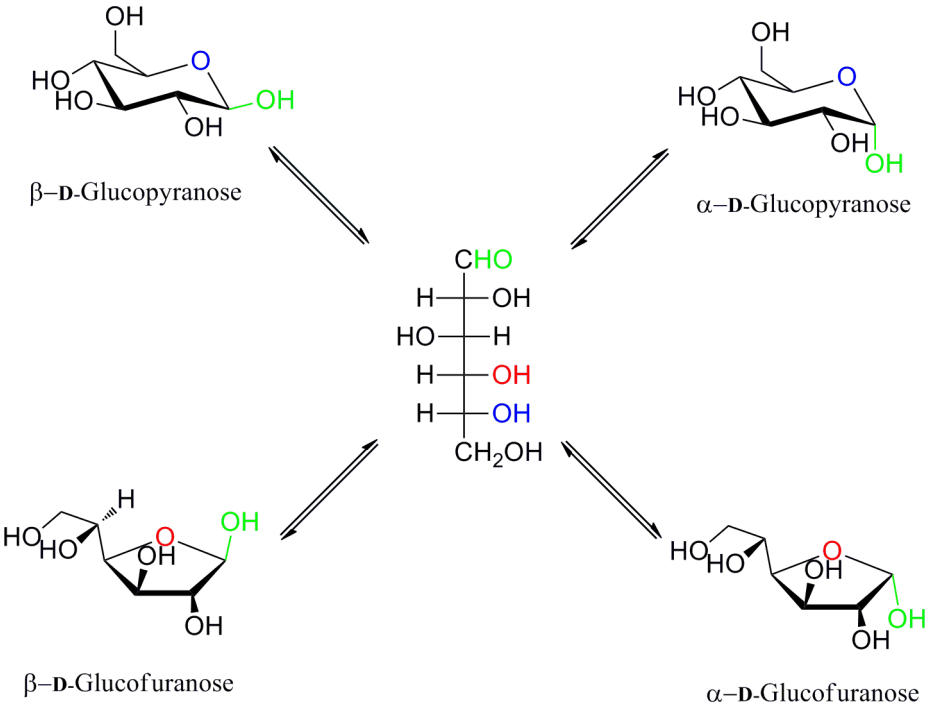


Figure 4.2 Anomeric forms of Glucose

Nature is the major source of carbohydrates where these are often found in the form of larger structures than monosaccharides, ranging from disaccharides to oligosaccharides to polysaccharides and also in the form of glycoconjugates where the carbohydrate is covalently bound to another chemical species like protein. Linking two monosaccharides together forms disaccharides and common examples are lactose (combination of Galactose and Glucose in *α,β*-1→4 glycosidic linkage commonly found in milk known as milk sugar), sucrose (combination of Glucose and fructose in *α,β*-1→2 glycosidic linkage commonly known as table sugar) and Maltose (combination of two units of Glucose joined with an *α*-(1→4) bond known as malt sugar) *etc*. Oligosaccharides are structures built up of two or more (mostly up to ten) monosaccharides and there is no strict borderline drawn between oligosaccharides and polysaccharides, although oligosaccharides often have a defined structure as opposed to

polysaccharides that are viewed as polymers. A polysaccharide can either be linear or branched. For example, rigid and linear polysaccharides like cellulose in plants and chitin in the exoskeleton of insects form strong supportive tissues (**Figure 4.3**).

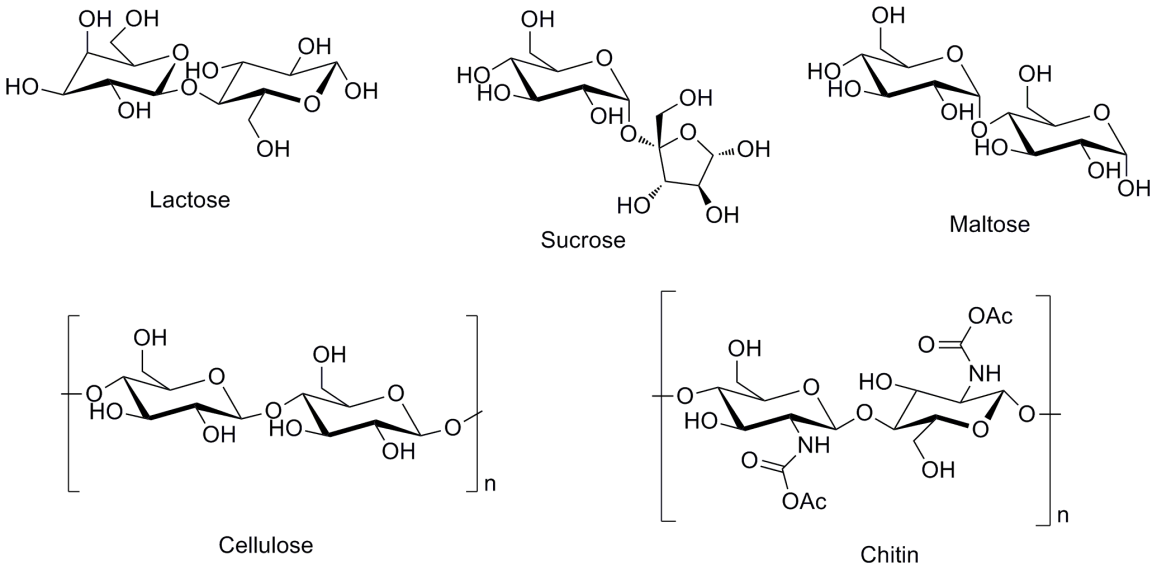


Figure 4.3 Natural forms of carbohydrates

4.II Carbohydrate analogues

The carbohydrate analogues were designed in order to have better stability towards hydrolysis. These modified carbohydrate analogs should have features of the natural substrate such as structural similarity and polarity. The continuous search for carbohydrate mimics and the evaluation of their biological properties is an important field of research.[163] There are different classes of monosaccharide analogues. For example, by replacing one atom in **D**-galactofuranose, a range of analogues can be obtained (**Figure 4.4**). The acetal functionality has now been replaced by a secondary amine[163f-h] to form an iminosugar, an ether[163c-e] to form a *C*-glycoside or a thioacetal[163a,b], the replacement of the endocyclic oxygen with a methylene group gave the carbasugar analogue of **D**-galactofuranose.[163i,j]

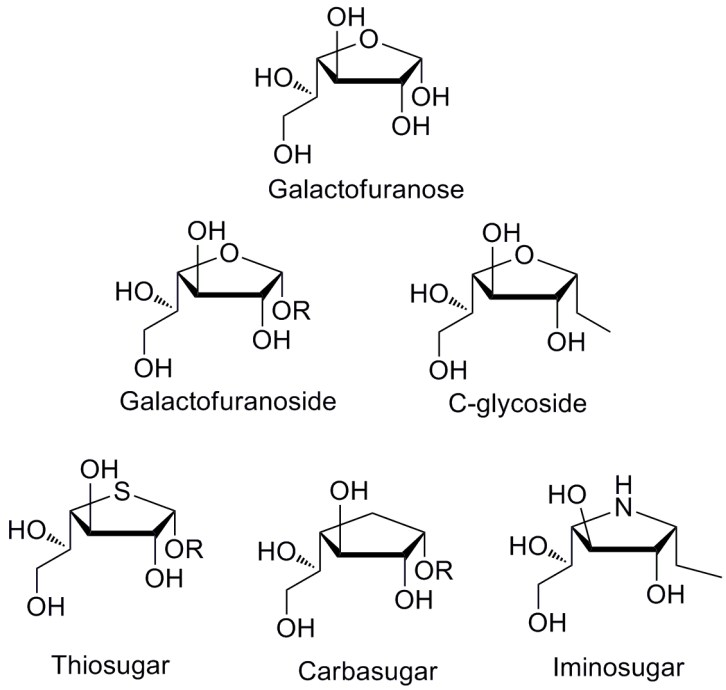


Fig 4.4 Analogs of **D**-galactofuranose

4.II.I Carbasugar

The pioneering synthesis of the carbasugars was made by McCasland *et al.* long back in 1966. They had synthesized the first series of carbasugars where the endocyclic oxygen of monosaccharides was replaced by a methylene group and they named this series of modified sugar as *pseudosugars*.[164] Since then, this subtle change brought about the possibility of new class of sugars having high similarity with the *true* sugars. It would lead to the compounds that are more stable toward endogenous degradative enzymes. They have first synthesized the series of carbocyclic counterpart of different carbohydrates like *α*-**D**-talopyranose i.e. 5a-carba-*α*-**DL**-talopyranose,[164a] *α*-**D**-galactopyranose i.e. 5a-carba-*α*-**DL**-galactopyranose[164c] and *β*-**DL**-gulopyranose i.e. 5a-carba-*β*-**DL**-gulopyranose[164b] (**Figure 4.5**) in their racemic form. The term *pseudosugars* coined by them today is of less use now-a-days. These structures are known as *carbasugars*.[165] McCasland envisioned that theses modified carbohydrates would be recognized by enzymes much like carbohydrates, although they would be stable to

hydrolysis due to their lack of acetal or hemiacetal functionality. To date, many of the carbasugar analogues of common pyranose and furanose monosaccharides have been synthesized. The common classes of carbasugars that are generally synthesized are the carbahexopyranose, carbahexofuranose and carbapentofuranose.

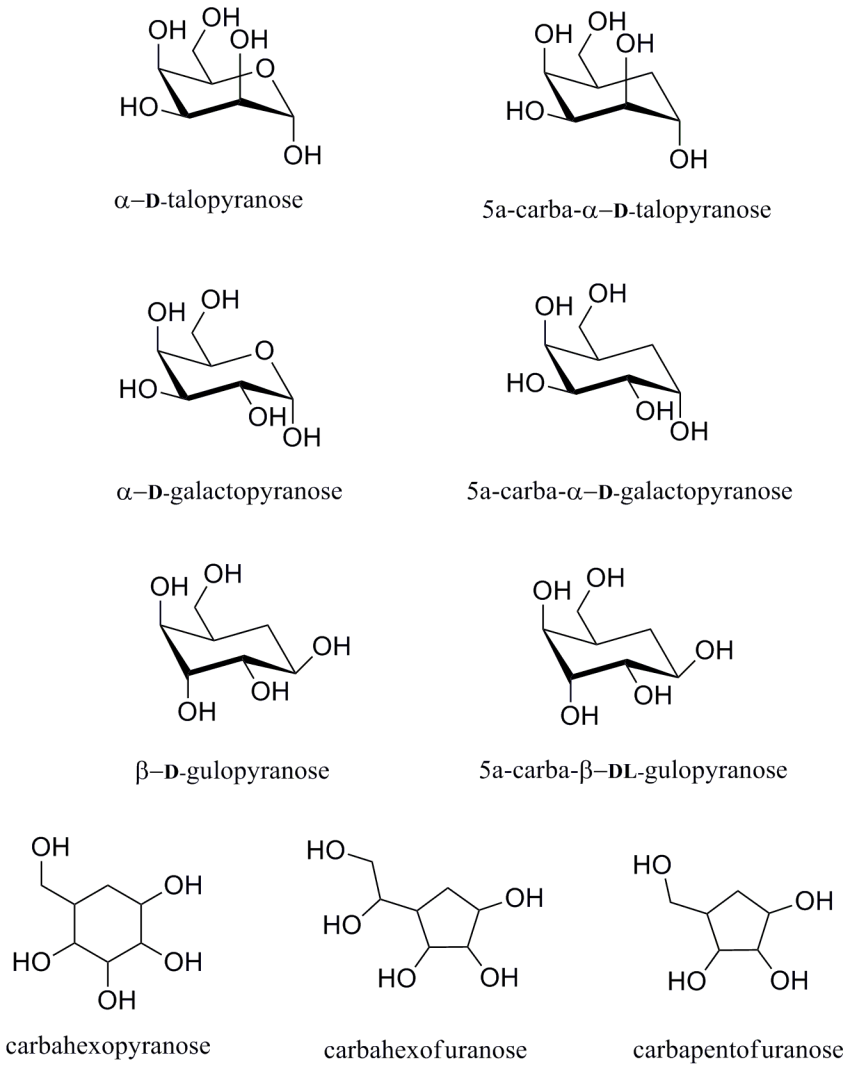


Figure 4.5 First synthesized the series of carbocyclic carbohydrates

4.II.II Carbasugar in Nature

4.II.II.I Carba pyranose in Nature

5a-carba-*α*-**D**-galactopyranose (**Figure 4.6**) was isolated from a fermentation of both *Streptomyces* sp. MA-4145 by Miller *et al.* in 1973[166] only after a few year of its chemical synthesis by McCasland and co workers in 1968.[164c] Unfortunately this was the

only natural *true* carbasugar[135t] known to date but it has a very low biological profile than its usual carbohydrate counterpart which may be attributed to the methylene incompatibility with the enzyme.

Carbapyranoses have rarely been found to have free existence in nature; however, these are found abundantly as subunits of many natural products. Compounds such as carba-*α*-**D**-galactopyranose[164c] (**Figure 4.5**), cyclophellitol (isolated from *Phellinus* sp.),[167] or MK7607 (isolated from *Cur*V*ularia eragestrides*)[168] were isolated directly from natural sources, whereas aminocarbasugars such as valienamine (**Figure 4.6**) have mainly been found as subunits of several, more complex, molecules. Aminocarbasugar derivatives, such as valienamine,[169] validamine,[170] hydroxyvalidamine,[170] and valiolamine[170] (**Figure 4.6**), are secondary metabolites exclusively produced by microorganisms. They have been detected only as minor components in the fermentation broth of *Streptomyces hygroscopicus* subsp. *limoneus*.[171] They are mainly found in validamycins[172], acarbose[173] (**Figure 4.7**), and related carbaoligosaccharides.

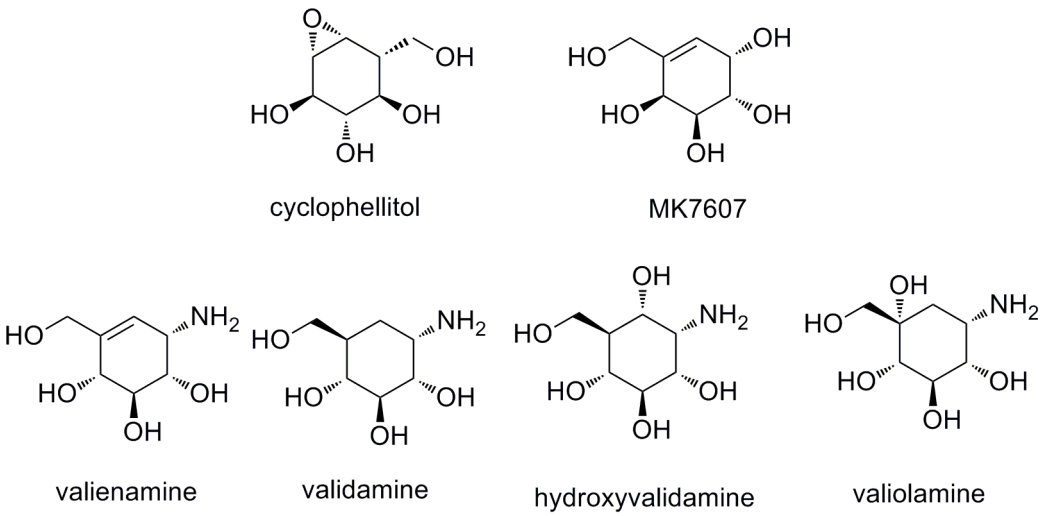


Figure 4.6 Naturally occurring carba pyranose

Acarbose[173] which is considered as one of the most clinically important *α*-amylase inhibitor was found in a screening of strains of various *Actinomycete* genera. Currently this compound is used for the treatment of type II insulin-independent diabetes

(**Figure 4.7**). Structurally, acarbose is a carbatrisaccharide consisting of valienamine, a deoxyhexose, and maltose. During the screening for new antibiotics, researchers at Takeda Chemical Company in 1970 discovered a family of antibiotics from the fermentation culture of *Streptomyces hygroscopicus* subsp. *Limoneus* and named the series as validamycins (A-H).[174] Validamycin A (Figure **4.7**), the main component of the complex, is a pseudo trisaccharide consisting of a core moiety, validoxylamine A, and D-glucopyranose.

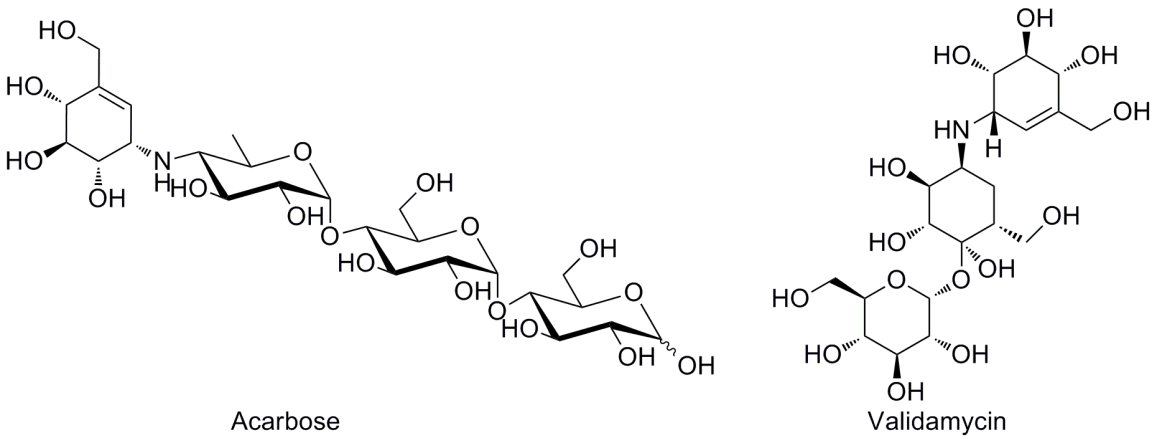


Fig 4.7 Carbapyranose as a part other large molecules

4.II.II.II Carba furanose in Nature

Unlike carbapyranose, carbafuranose have not been found to have any free natural existence till today. However, these are found to be subunits of several products isolated from natural sources, in particular carbanucleosides. These carbafuranose units are very

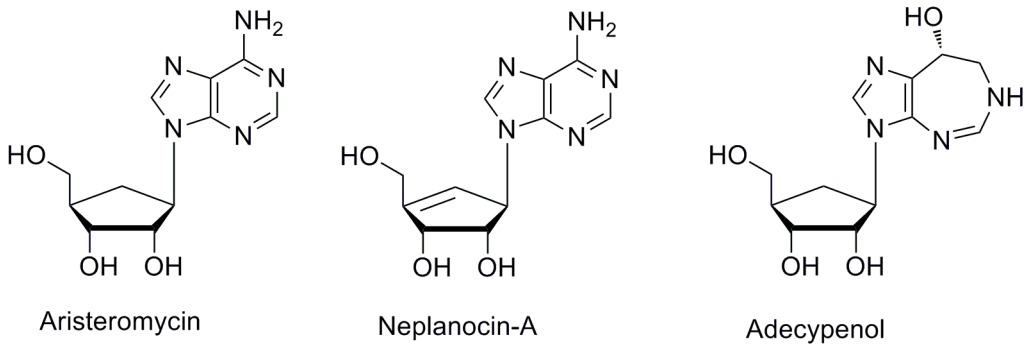


Figure 4.8 Carbafuranose as part of naturally occurring carbocyclic nucleosides

important synthetic targets due to being the structural part of carbocyclic nucleosides like Aristeromycin[119], Neplanocin-A,[84j,118a,120] Adecypenol[175] (**Figure 4.8**) which are known to possess high degree of antibiotic and anti tumor activities.

It should be mentioned here that five-membered cyclitols, such as caryose[176] or calditol[177] (**Figure 4.9**), have been isolated as natural products. There are no other examples of five-membered carbocyclic carbohydrate analogues that were reportedly isolated from natural sources.[135t]

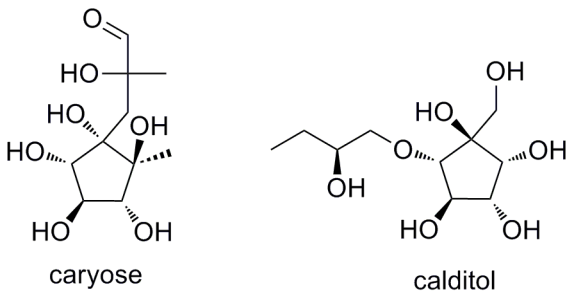


Figure 4.9 Carbafuranose as part of natural products

4.III Synthesis of carbafuranose

As discussed in the previous sections chiral polyoxygenated cyclopentanes are constituents of many bioactive compounds, such as glycosidase inhibitors,[178] carbocyclic nucleosides [84e,101a,118a,120,135d,135r,179] and prostaglandins[180]. They are also referred to as carbafuranoses and treated as analogues of monosaccharides in which the ring oxygen of a furanose has been replaced by a methylene (-CH2-) group. This modification transforms the (hemi-) acetal anomeric centre of a natural sugar unit into an ether (alcohol) group in the resulting carbasugar. The lack of an acetal moiety preserves the carbafuranoses from hydrolysis as compared to sugar derivatives. In addition, this modification has a positive effect on the conformational changes in their structures. Over the last few decades, the chemistry of carbafuranoses and other carbasugars has emerged as a topic of intense investigation in bioorganic research.[101a,135t,181] In view of this, since the first synthesis

reported by Wilcox et al.,[182] considerable attention has been focused on the synthesis[135c,183] of carbafuranoses and analogues in their different stereochemical forms in order to make them amenable for varied applications. In the pioneering work about carbafuranose Wilcox *et al.* synthesized the carbocyclic analogue of **D**-fructofuranose and carba-**D**-fructofuranose-6-phosphate which shows almost 5-20 times higher activity than its natural counterpart for phosphofructokinase and 6-phosphofructo-2-kinase in glycolytic path way. The carbocyclic analog inhibits fructose-2,6-bisphosphatase about 500 times higher than that of fructose-6-phosphate.[184] These interesting results attracted many research groups worldwide to synthesize various carbasugars in their enantiomeric pure form.

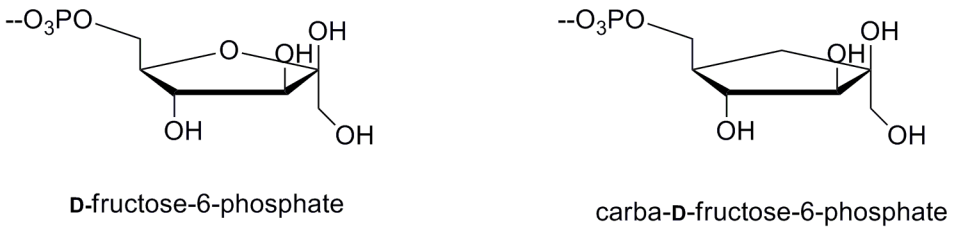
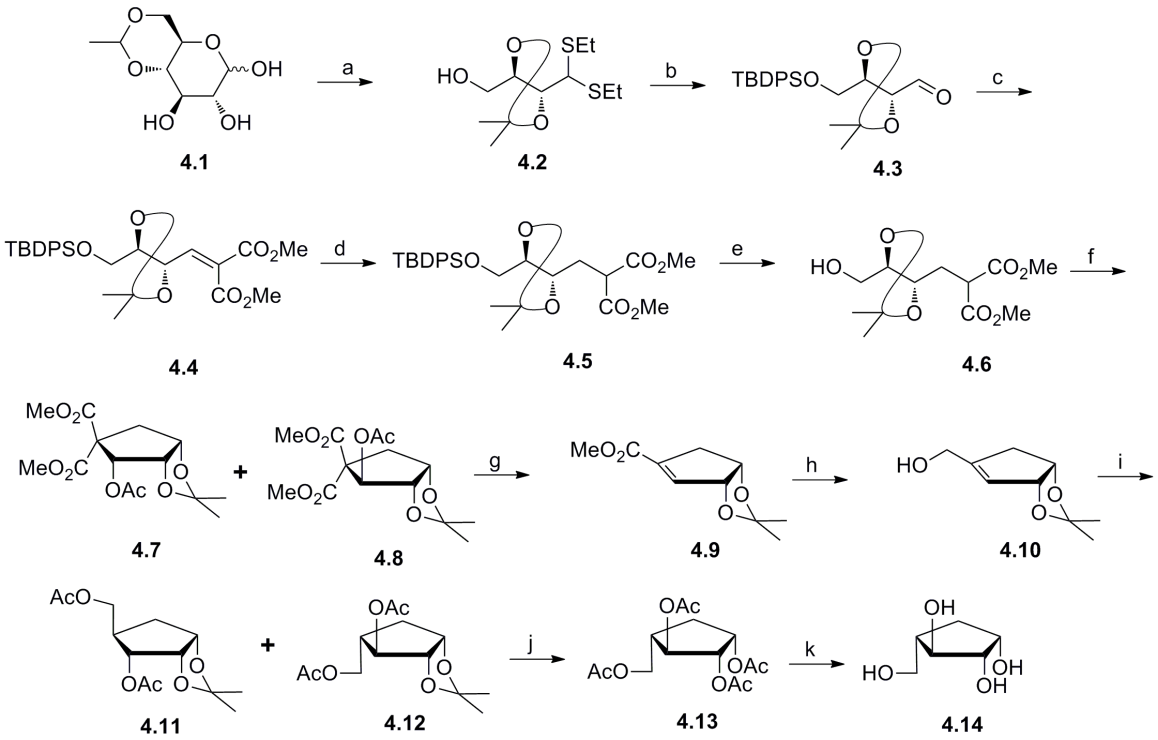


Figure 4.10 Natural and synthetic analog of **D**-fructose-6-phosphate

4.III.I Work from literature

Prior to Wilcox[184] in 1986, synthesis of many carbocyclic molecules have been reported especially carbocyclic nucleosides due to the important biological properties like anti HIV activity[185] associated with these molecules (discussed in **Chapter 2** & **3**). The synthesis of these modified sugars gained an equal urgency due to the important biological activity reported by Wilcox *et al*. In 1988 Tadano and coworkers reported the synthesis of carbocyclic analog of pentofuranose (**Scheme 4.1**).[183r] The synthesis started with the conversion of 4,6-*O*-ethylidene-**D**-glucose (**4.1**) to **D**-erythrose diethyl dithioacetal (**4.2**) following a reported procedure by MacDonald *et al*.[186] This dithioacetal (**4.2**) was converted to aldehyde **4.3** by silylation of the primary alcohol of **4.2** followed by dethioacetalization of the corresponding product. Knoevenagel condensation of diethyl

malonate with **4.3** followed by 1,4-conjugate reduction of the resulting 2E-unsaturated ester with $NaBH_4$ gave **4.5**. This was desilylated, the intermediate **4.6** was then subjected to oxidative cyclization to produce alcohol possessing a carbocycle core. Acetylation of the resulting alcohol gave a mixture of acetylated product **4.7** and **4.8**. This was converted to **4.10** over two steps. The olefinic unit of **4.10** was subjected to hydroboration to yield a mixture of diastereomers which was acetylated and separated and the major product **4.12** was converted to carba-*β*-**L**-arabinofuranose **4.14**.

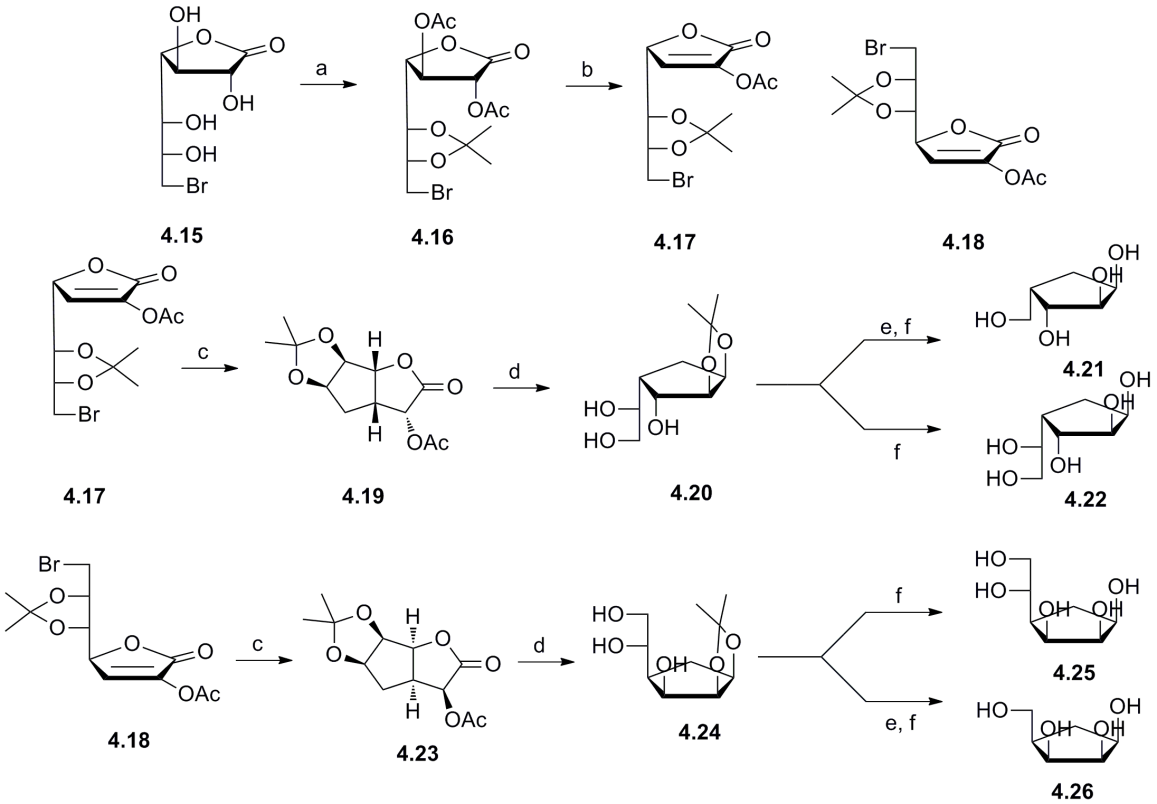


a) ref 186; b) (1) TBDPSCl, Imidazole, DMF, (2) 2,2-dimethoxy propane, D-CSA, Acetone, (3) $HgCl_2$, $CaCO_3$, CH_3CN: H_2O: 10:1; c) Dimethyl malonate, Ac_2O, Py, 41 h; d) $NaBH_4$, MeOH; e) TBAF, THF; f) (1) PCC, CH_2Cl_2, 4 A^o Molecular seives, (2) Ac_2O, Py; g) Me_2SO (aq) (4:1), NaCl, 160 °C, h) DIBAL-H, CH_2Cl_2, -78 °C; i) (1) Borane, THF, then H_2O, 3M NaOH, aq H_2O_2, Na_2SO_3 aq (unsaturated), EtOH, (2) Ac_2O, Py; j) (1) AcOH (80 %), (2) Ac_2O, Py; k) NaOMe, MeOH, Amberlite IR 120, 0 °C.

Scheme 4.1

In 1998 Lundt *et al*. reported the synthesis of both carbahexofuranose and carbapentofuranose *via* radical cyclization of unsaturated bromide **4.17** and **4.18** (**Scheme 4.2**)[183e] derived from bromo lactone (**4.15**) of **D**-glyceraldehyde origin. Protection of 6,7-dihydroxyl of **4.15** as isopropylidene derivative, followed by di-

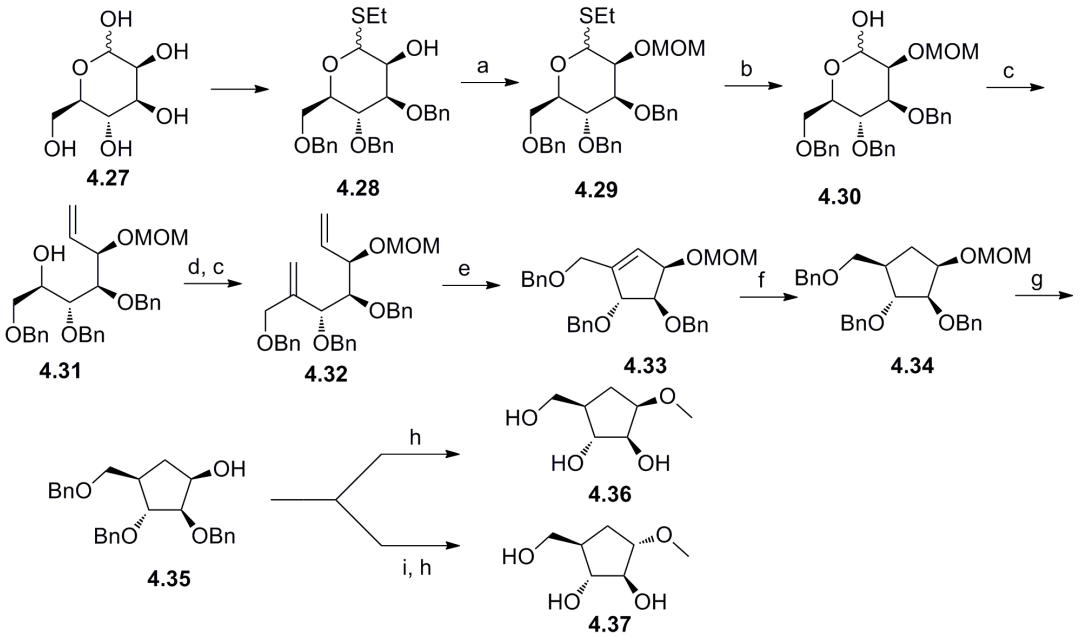
acetylation of the 4,5-dihydroxyl gave **4.16**. This on *β*-elimination gave a mixture of C-4 isomeric unsaturated bromo lactone **4.17** and **4.18** which were separately subjected to radical cyclization with tributyltin hydride to produce bicyclic lactones **4.19** and **4.23** respectively in stereoselective manner. The lactone **4.19** was used for the preparation of carba-*α*-**L**-xylofuranose (**4.21**) and carba-*α*-**L**-glucofuranose (**4.22**). Reduction of the lactone by $NaBH_4$ followed by the degradation of the vicinal diol to aldehyde which follows the reduction and acidic hydrolysis of the isopropylidene gave carba-*α*-**L**-xylofuranose (**4.21**). In a similar fashion lactone **4.23** was converted to carba-*β*-**D**-lyxofuranose (**4.26**). The lactone **4.19** and **4.23** when treated separately for the reduction of lactone followed by hydrolysis of the isopropylidene gave the carba-*α*-**L**-glucofuranose (**4.22**) and carba-*β*-**D**-mannofuranose (**4.25**) respectively.



a) (1) Acetone, H^+, (2) Ac_2O, Py; b) Et_3N, CH_2Cl_2; c) Bu_3SnH, AIBN, EtOAC; d) $NaBH_4$, NaOMe, MeOH; e) (1) $NaIO_4$, H_2O, (2) $NaBH_4$, H_2O; f) aq HCl

Scheme 4.2

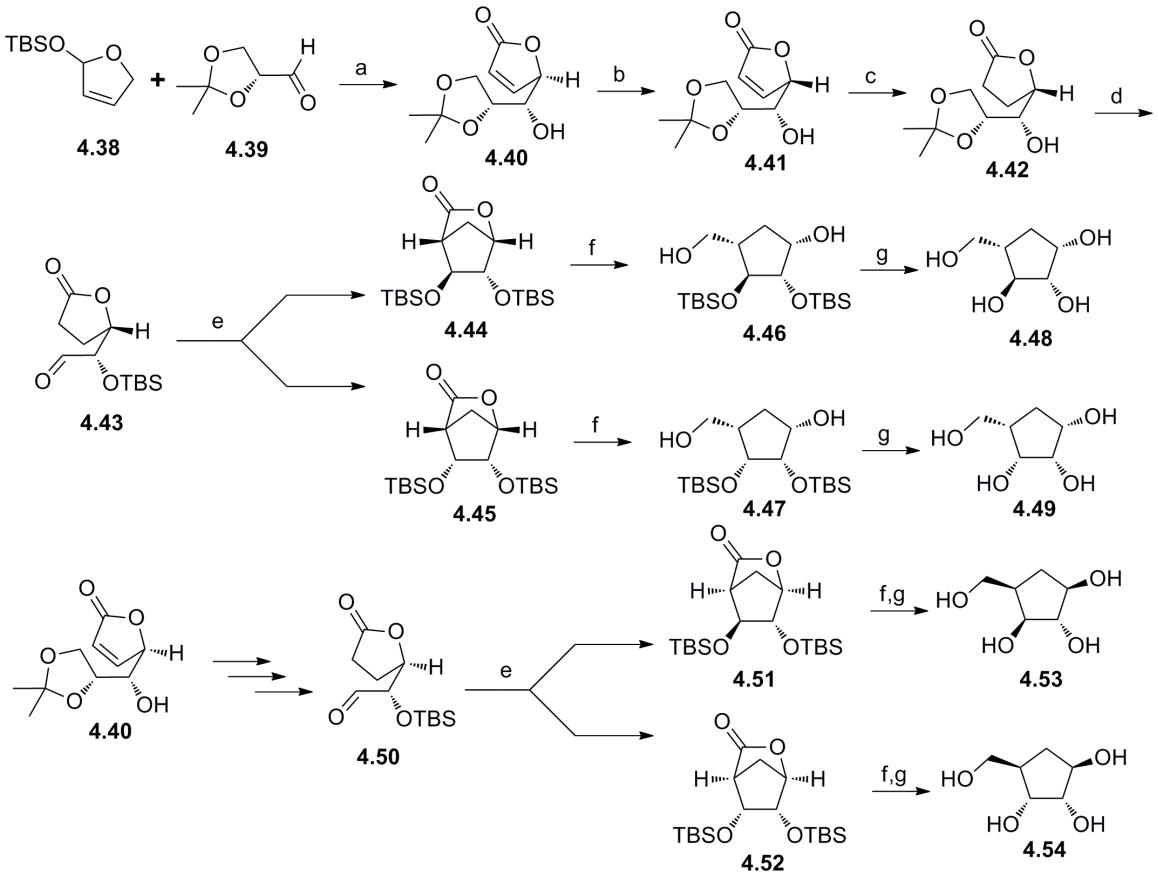
Using **D**-mannose (**4.27**) as the starting material Lowry and coworkers synthesized methyl 4a-carba-α-**D**-arabinofuranoside (**4.37**) and 4a-carba-β-**D**-arabinofuranoside (**4.36**) (**Scheme 4.3**).[183n] They employed ring closing metathesis as a key step to construct the cyclopentane ring. The Mannose **4.27** was converted to the thioacetal **4.28** over five steps and after protection of the free hydroxyl to MOM ether **4.29** was subjected to thiol hydrolysis followed by Wittig olefination to give **4.31**. The alcohol **4.31** was subsequently oxidized to a ketone which was then subjected to Wittig olefination to yield the diene **4.32**. The diene was subjected to ring closing metathesis using Schrock's catalyst in drybox yielded the substituted cyclopenten **4.33**. This upon stereoselective reduction using Wilkinson's catalyst gave the major product **4.34** with desired stereochemistry. Deprotection of its MOM ether gave **4.35** which on methylation, followed by debenzylation gave 4a-carba-β-**D**-arabinofuranoside (**4.36**). Similarly hydroxyl of **4.35** was subjected stereochemical inversion under Mitsunobu condition, followed by methylation and debenzylation gave 4a-carba-α-**D**-arabinofuranoside (**4.37**).



a) MOMCl, NaH, THF, rt; b) NIS, AgOTf, CH_2Cl_2, H_2O (5 equiv), rt; c) Ph_3PCH_3Br, *n*-BuLi, THF, -78 °C to rt; d) PCC, NaOAc, 4 Å molecular seives, CH_2Cl_2; e) Schrock's Catalyst, Toluene, 60 °C, drybox; f) $(PPh_3)_3RhCl$, H_2, Toluene, rt; g) trace conc. HCl, CH_3OH, rt; h) CH_3I, NaH, THF, rt, then Pd/C, H_2, CH_3OH, AcOH, rt; i) DEAD, PPh_3, *p*-$O_2NC_6H_4CO_2H$, Toluene, rt then $NaOCH_3$, CH_3OH, rt;

Scheme 4.3

Rassu *et al*. in 2001 reported the synthesis of *β*-**D**-Xylo (**4.53**), *β*-**D**-Ribo (**4.54**), *β*-**L**-Arabino (**4.48**), *β*-**L**-Lyxo (**4.49**) 4a- carbafuranose using a common intermediate **4.40** (**Scheme 4.4**)[183f] obtained by vinylogous aldolization between furan based dienoxy silane (**4.38**) and 2,3-*O*-isopropylidene-**D**-glyceraldehyde (**4.39**). The threo configured butenolide **4.40** was subjected to Et_3N promoted C-4 epimerization to give the erythro derivative **4.41** which was later reduced with $NiBH_4$ to give **4.42**. The lactone **4.42** was converted to aldehyde **4.43** over three steps consisting of (i) silylation of the free secondary alcohol (ii) deacetonidation and (iii) oxidative cleavage of terminal vicinal diol. This aldehyde **4.43** was subjected to enolization/aldolization with TBSOTf/DIPEA couple to give a mixture of **4.44** and **4.45**. Both of them were then individually converted into *β*-**L**-arabino-4a-carbafurnose (**4.48**) and *β*-**L**-lyxo-4a-carbafurnose respectively over

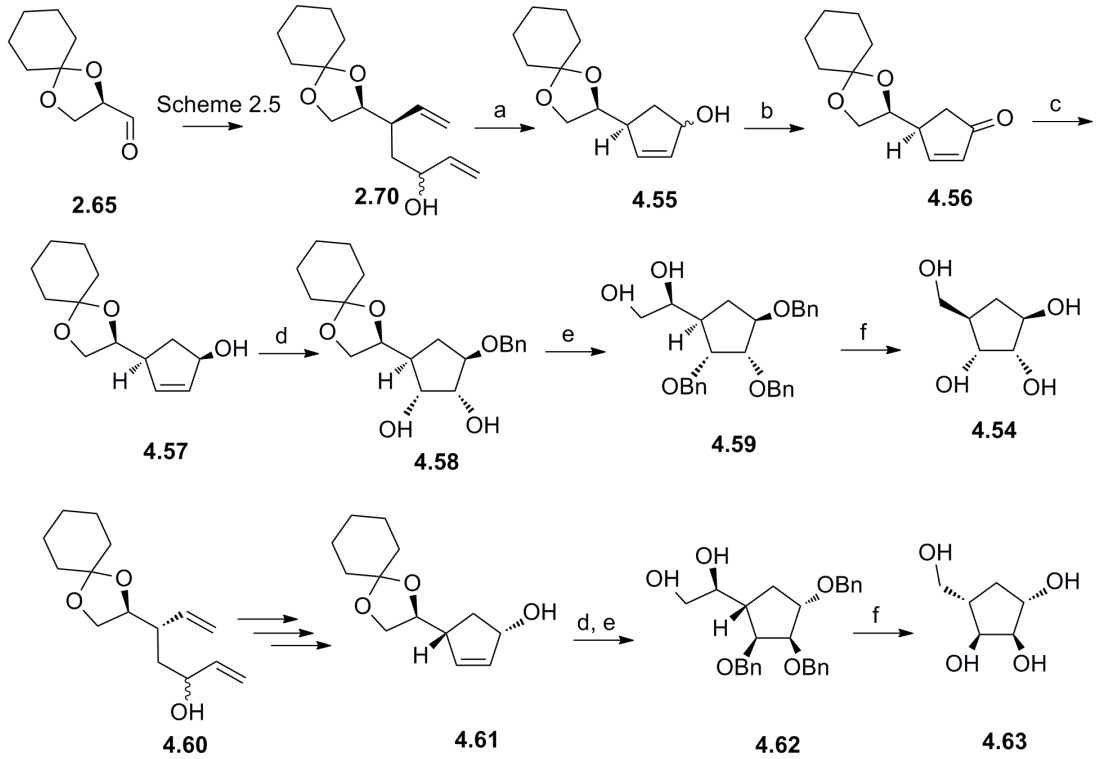


a) $BF_3.Et_2O$, CH_2Cl_2, -80 °C; b) Et_3N (3 cycles); c) $NiCl_2.6H_2O$, $NaBH_4$, MeOH; d) (1) TBSOTf, 2,6-Lutidine, CH_2Cl_2 (2) AcOH (aq) (80 %) 50 °C, (3) 0.65 M $NaIO_4$ (aq), SiO_2 (Chromatography grade), CH_2Cl_2; e) DIPEA, TBSOTf, CH_2Cl_2, -90 °C; f) $LiBH_4$, THF, 0 °C to rt; g) HCL-THF-MeOH (1:2:2).

Scheme 4.4

two steps, *viz* $LiBH_4$ reduction of lactone followed by de-silylation. Similarly the intermediate **4.40** was directly used (without C-4 epimerization) to prepare *β*-**D**-xylo-4a-carbafurnose (**4.53**) and *β*-**D**-ribo-4a-carbafurnose (**4.54**) following similar reactions sequences.

Ghosh *et al*. used **D**-Mannitol derived (*R*)-2,3-(*O*)-cyclohexylidene glyceraldehyde (**2.65**) as the starting material for the construction of *β*-**D**-Ribo (**4.54**), *β*-**L**-Ribo (**4.63**) (**Scheme 4.5**),[183d] *α*-**D**-Ribo (**4.67**), *α*-**D**-Arabino (**4.71**), *β*-**D**-Arabino (**4.72**) (**Scheme 4.6**)[183d] 4a-carbafurnose. For the construction of *β*-**D**-Ribo (**4.54**) and *β*-**L**-Ribo (**4.63**) **2.70** of scheme **2.5** (**Chapter 2**) was subjected to RCM using Grubbs 1st generation catalyst to give cyclopentene **4.55** which was subjected to Jone's oxidation followed by low temperature facial selective reduction to give **4.57** as the major product. The free hydroxyl of **4.57** was protected and upon subjected to OsO_4 dihydroxylation gave **4.58** as

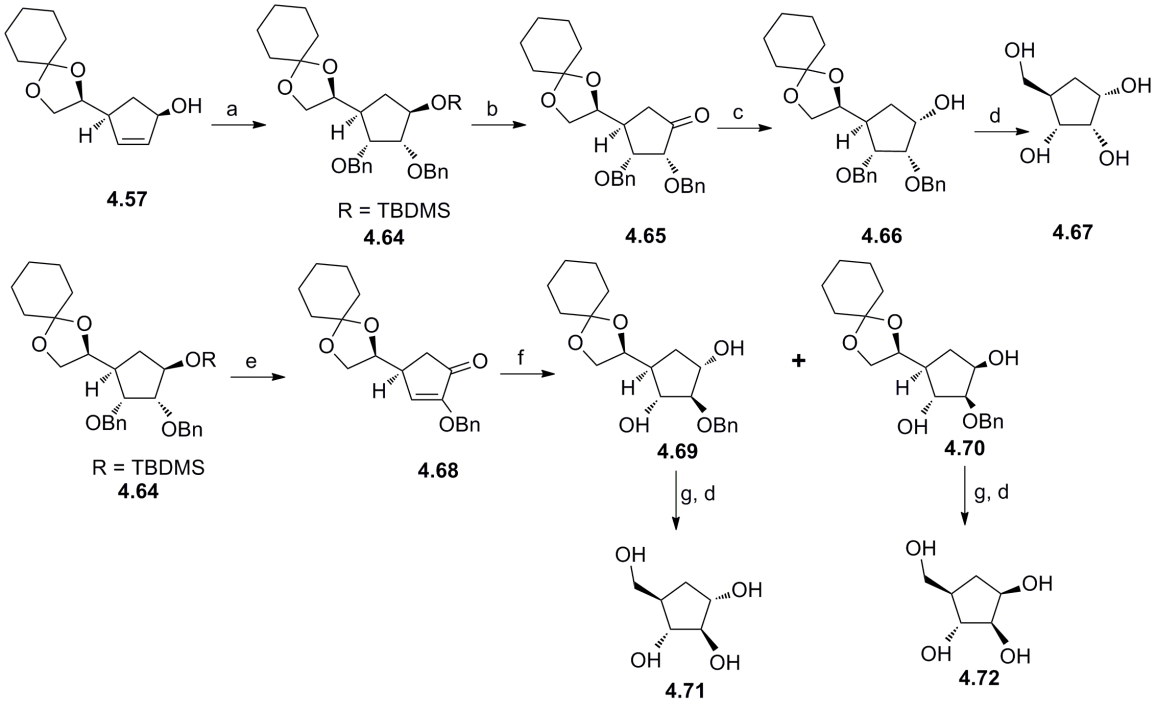


a) Grubb's 1st generation catalyst, DCM; b) Jone's reagent, Acetone; c) $LiAlH_4$, Et_2O, -60 °C; d) (1) NaH, BnBr, THF, (2) OsO_4, NMO.H_2O, Acetone/H_2O (4:1); e) (1) NaH, BnBr, THF, (2) AcOH:H_2O (4:1); f) (1) $NaIO_4$, MeOH: H_2O (3:1), 0 °C; (2) $NaBH_4$, MeOH, 0 °C, (3) 10 % Pd-C, H_2, MeOH.

Scheme 4.5

the major diastereomer which was later converted to 4a-carba-*β*-**D**-ribofuranose (**4.54**) over five steps (I benzylation of hydroxyl, (ii) hydrolysis of the ketal moiety, (iii) cleavage of the vicinal diol into aldehyde, (iv) reduction of the aldehyde to alcohol and (v) deprotection of all the benzyl group. Following same reaction sequences **4.60** (derived from **2.67** Scheme **2.5 Chapter 2**) was converted to 4a-carba-*β*-**L**-ribofuranose (**4.63**).

Similarly starting with the intermediate **4.57** but with a little different strategy Ghosh *et al*. prepared *α*-**D**-Ribo (**4.67**), *α*-**D**-Arabino (**4.71**), *β*- **D**-Arabino (**4.72**) (**Scheme 4.6**).[183d] For the preparation of *α*-**D**-Ribo (**4.67**) the intermediate **4.57** was protected as OTBDMS instead of benzyl (as in **Scheme 4.5**) which was later subjected to dihydroxylation and dibenzylation of the free hydroxyl to obtain **4.64**. This on desilylation, followed by Jones oxidation afforded ketone **4.65** which on low temperature reduction afforded **4.66**. This was subjected to usual reactions sequence as explained in scheme **4.5** to obtain 4a-carba-*α*-**D**-ribofuranose (**4.67**) as the major product.

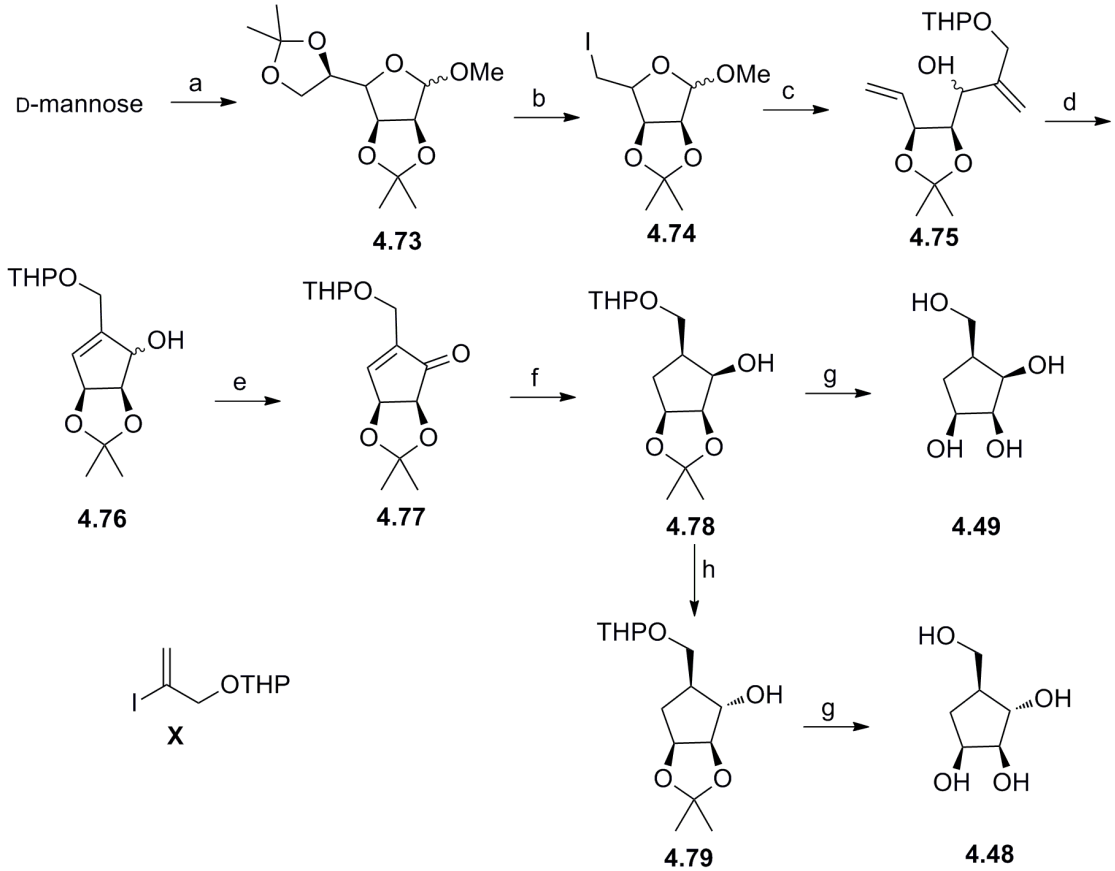


a) (1) TBDMSCl, DMAP, Et_3N, Imidazole, CH_2Cl_2, (2) OsO_4, NMO.H_2O, Acetone/H_2O (4:1), (3) NaH, BnBr, THF; b) (1) TBAF, THF, (2) Jone's reagent, Acetone; c) $LiAlH_4$, Et_2O, -60 °C; d) (1) AcOH:H_2O (4:1) (2) $NaIO_4$, MeOH: H_2O (3:1), 0 °C; (3) $NaBH_4$, MeOH, 0 °C, (4) 10 % Pd-C, H_2, MeOH; e) TBAF, THF, (2) Swern's Oxidation; f) BH_3, THF, 3N NaOH, 30 % H_2O_2; g) NaH, BnBr, THF.

Scheme 4.6

While preparing Arabino carbasugars *i.e.* **4.71** and **4.72** when the dibenzyl ether **4.64** after desilylation was subjected to Swern's oxidation it gave cyclopentenone **4.69** by Et_3N assisted *β*- elimination process. Hydroboration of the resulting enone landed up with a mixture of two diastereomers **4.69** and **4.70** which were later converted separately to 4a-carba-*α*-**D**-arabinofuranose (**4.71**) and carba-*β*-**D**-arabinofuranose (**4.72**) respectively via standard transformation as explained in **Scheme 4.5**, after converting the resulting hydroxyl to benzyl ether.

Recently Rao and co-workers reported the synthesis of *β*-**L**-lyxo (**4.49**) and *β*-**L**-arabino (**4.48**) 4a-carbafuranose utilizing **D**-mannose as the starting material (**Scheme 4.7**).[183j] The diacetonide *O*-methoxy **D**-mannose (**4.73**) obtained from **D**-mannose was



a) MeOH, Acetone, H_2SO_4, 0 °C to rt; b) (1) H_5IO_6, THF, 0 °C to rt, (2) $NaBH_4$, MeOH, 0 °C to rt, (3) PPh_3, I_2, Imidazole, toluene, 0 °C to rt; c) Mn/$CrCl_3$ (20:1), THF:DMF (1:1), then $NiCl_2$, TMSCl, **X**, TMSCl, 50 °C, then TBAF; d) Grubbs 2nd generation catalyst, CH_2Cl_2, reflux; e) PDC, CH_2Cl_2; f) $CeCl_{3.7}H_2O$, $NaBH_4$, CH_2Cl_2, -78 °C; g) (1) Pd/C, H_2, MeOH, (2) 2M HCl in MeOH; h) DIAD, PPh_3, *p*-$O_2NC_6H_4CO_2H$, Toluene, rt then $LiOH.H_2O$, rt.

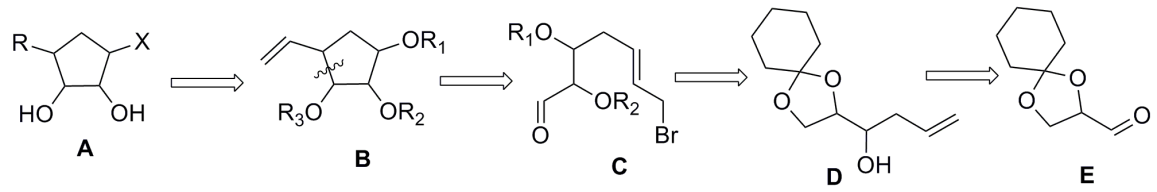
Scheme 4.7

converted into iodo intermediate **4.74** which was subjected to Nozaki-Hiyama-Kishi reaction with **X** to yield a diastereomeric mixture of dienol **4.75**. This was subjected to RCM using Grubbs 2nd generation catalyst to give the cyclopentenol **4.76** which was later oxidized to ketone followed by stereoselective Luche's reduction to yield **4.78** as the major diastereomer. Global deprotection of **4.78** gave 4a-carba-*β*-**L**-lyxofuranose (**4.49**). On the other hand, reversal of hydroxyl stereochemistry of **4.78** under Mitsunobu condition, and global deprotection of the resulting compound **4.79** afforded 4a-carba-*β*-**L**-arabinofuranose (**4.48**).

4.III.II Our Work

As discussed earlier the carbocyclic furanose (penta and hexa) are the basic structure of many modified carbocyclic nucleoside along with their presence in a number of biologically active macromolecules made them a very important synthetic target. In the present work we have developed a tunable, simple and efficient route for the preparation of carbafuranose sugars in their different stereo and regioisomeric forms (carba-hexafuranose and carba-pentafuranose and carbocyclic nucleosides). This is shown here by the synthesis of **4.108c** and **4.108d.**

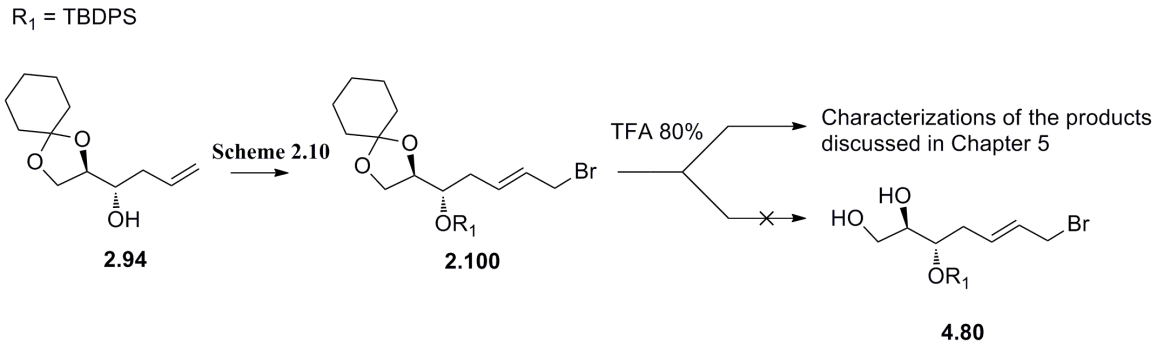
Retrosynthetic analysis (**Scheme 4.8**) of carbafuranose sugar skeleton, **A** suggested that it could be obtained from its olefinic precursor **B**. Consequently, the C-3 and C-4 stereocenters of **B** could simultaneously be constructed *via* intramolecular allylation of intermediate **C**, which are accessible starting from either of the two homoallylic alcohols **2.94**, **2.95** (**Scheme 2.9**) derived from (*R*)-2,3-*O*-cyclohexylideneglyceraldehyde **2.65** (**E**).



X = Nucleobase, R = -CH_2OH (**carbocyclic nucleosides**)
R = -CH_2OH, X = OH (**carba pentafuranose**)
R = -CH(OH)CH_2OH, X = OH (**carba hexafuranose**)

Scheme 4.8

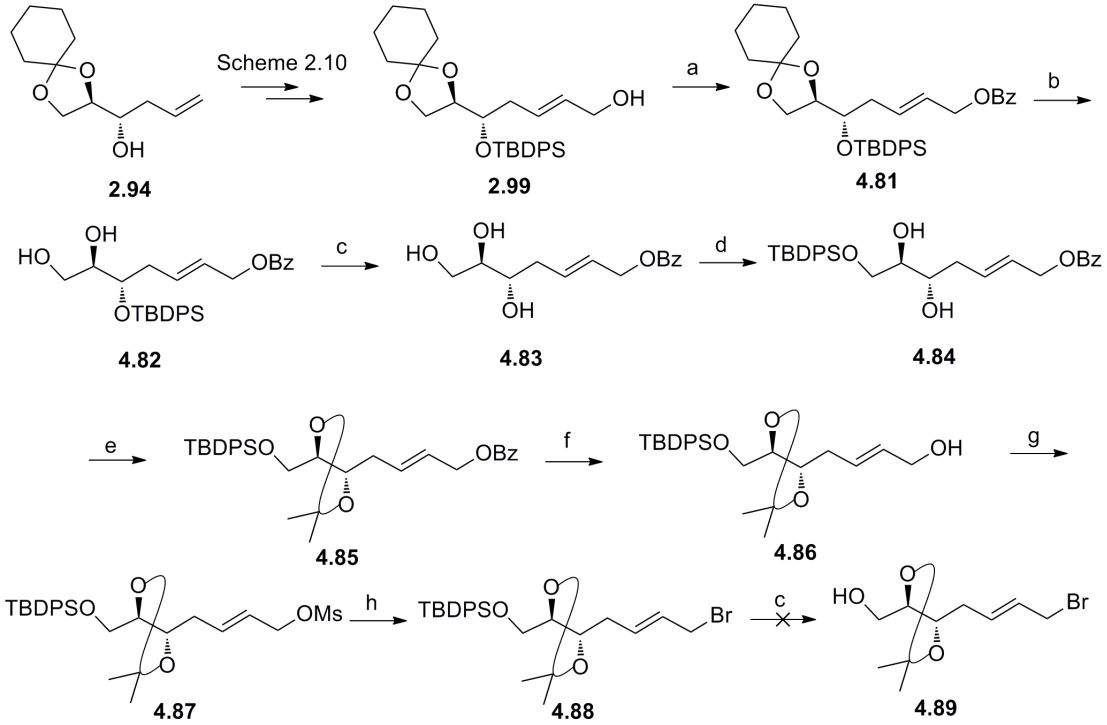
In order to prepare the intermediate **C** we choose to start with **2.94** which had been obtained as the major diastereomer during allylation of **2.65**. As described earlier (Scheme **2.10** in **Chapter 2**) homoallylic alcohol **2.94** was converted into allylbromide **2.100**. This was treated with 80 % TFA in DCM at 0 °C for hydrolysis of its ketal moiety. However, the reaction gave a different product in good yield (76 %) instead of the desired diol **4.80**. The characterization of this byproduct will be discussed later in **Chapter 5**.



Scheme 4.9

The failure to prepare diol **4.80**, an early intermediate for the synthon **C** (**Scheme 4.8**), described above prompted us to synthesize **C** in a different manner using homoallyl alcohol **2.94** as the starting material once again. In this case **2.94** was converted to the allylic alcohol **2.99** following the same procedure as explained in Scheme **2.10** (**Chapter 2**). The resulting alcohol was protected as benzoate ester **4.81** (**Scheme 4.10**). The formation of the ester **4.81** was characterized by a doublet at δ 4.66 in its ^{1}H NMR due to CH_2-OBz and the appearance of a signal at δ 166.6 in its ^{13}C NMR (**Figure 4.11-4.12**). The benzoate ester **4.81** was subjected to ketal hydrolysis using 80 % TFA to afford the

diol **4.82** which was characterized by the disappearance of a broad multiplet (10H) at δ 1.42 in ^{1}H NMR (**Figure 4.13-4.14**) spectrum. Desilylation of compound **4.82** by treating it with TBAF afforded triol **4.83**. The progress of the reaction was confirmed by the disappearance of the signal at δ 1.06 (9H) due to OTPS moiety in ^{1}H NMR (**Figure 4.15-4.16**). This triol **4.83** was subjected to regioselective mono-silylation at low temperature (0 ^{o}C) with TBDPSCl and Imidazole to give the monosilylated diol **4.84** with an overall yield of 74.8 % and the recovered starting material was again subjected to monosilylation. The signal at δ 1.06 (9H) in ^{1}H NMR and the appearance of δ 26.7 and



a) BzCN, Et_3N, DCM, 25 °C; b) Aq.TFA (80%), CH_2Cl_2, 0 °C; c) TBAF, THF, 0 °C; d) TBDPSCl, Imidazole, DMAP, CH_2Cl_2, 0 °C, over 5h; e) 2,2-Dimethoxy propane, PPTS, CH_2Cl_2, 0 °C to rt; f) K_2CO_3, MeOH, 0 °C; g) MsCl, Et_3N, CH_2Cl_2, 0 °C; h) NaBr, $NaHCO_3$ (cat), Acetone;

Scheme 4.10

19.0 signal along with the down field shift of δ 62.88 peak in ^{13}C NMR of triol **4.83** to δ 64.6 ^{13}C NMR (**Figure 4.17-4.18**) confirmed the formation of the monosilylated diol **4.84**. The diol **4.84** was treated with 2,2-dimethoxy propane in presence of PPTS as catalyst to give acetonide **4.85** which was later subjected to base hydrolysis of the benzoate ester to form the free primary hydroxyl to gave the allyl alcohol **4.86**. The

formation of acetonide was confirmed from the appearance of δ 1.38, 1.33 two singlet, each of 3H (**Figure 4.19-4.20**). Similarly, disappearance of signal in the range δ 7.62-7.68 in ^{1}H NMR and 166.6 in ^{13}C NMR due to -OBz (**Figure 4.21-4.22**) confirmed the formation of **4.86**. The primary hydroxyl of **4.86** was transformed to bromide to give the allyl bromide **4.88** over two steps with very good overall yield of 87.5 % [(i) mesylation of the hydroxyl to give mesylate **4.87** (ii) treatment of mesylate with NaBr in dry Acetone]. The formation of the bromide **4.88** was confirmed by the up field shift of the signal at δ 63.2 to δ 44.7 in its ^{13}C NMR (**Figure 4.23-4.24**). Next, desilylation of **4.88** was attempted by treating it with TBAF to obtain **4.89** with regard to preparing intermediate **C** through oxidation of the latter (**Scheme 4.8**). Unfortunately, the desilylation reaction was found to be incompatible leading to decomposition of allyl bromide **4.88** to produce an undesired by product that is yet to be characterized.

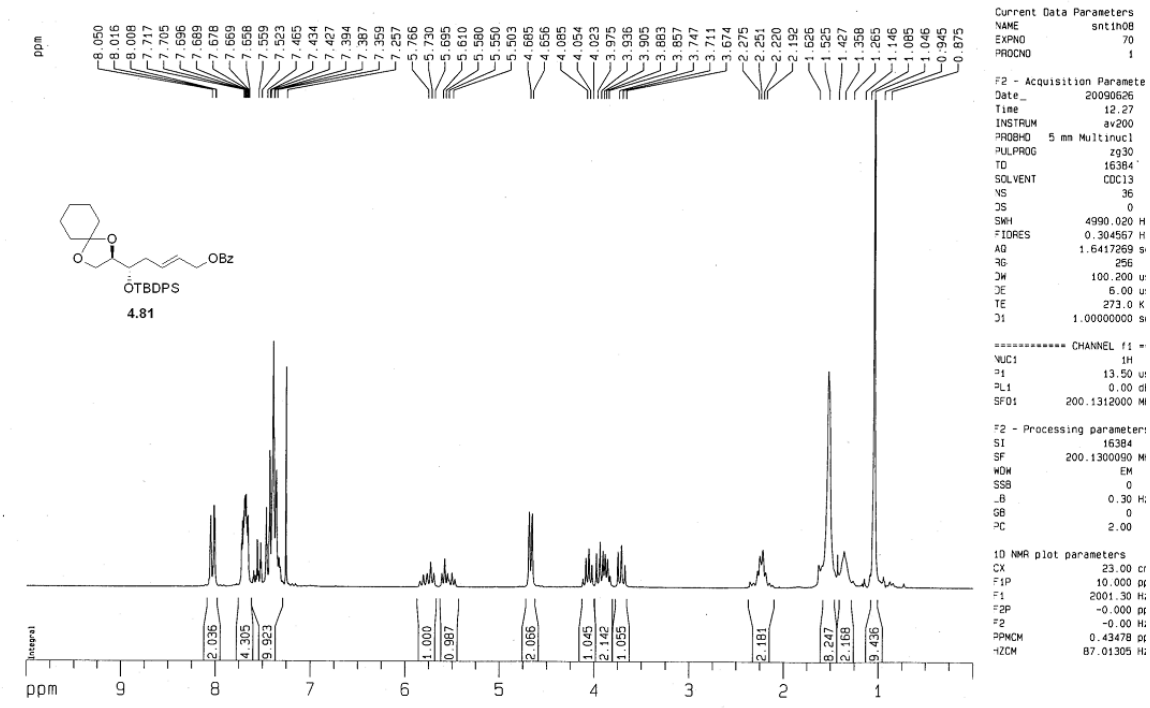


Figure 4.11 ^{1}H NMR spectrum of 4.81

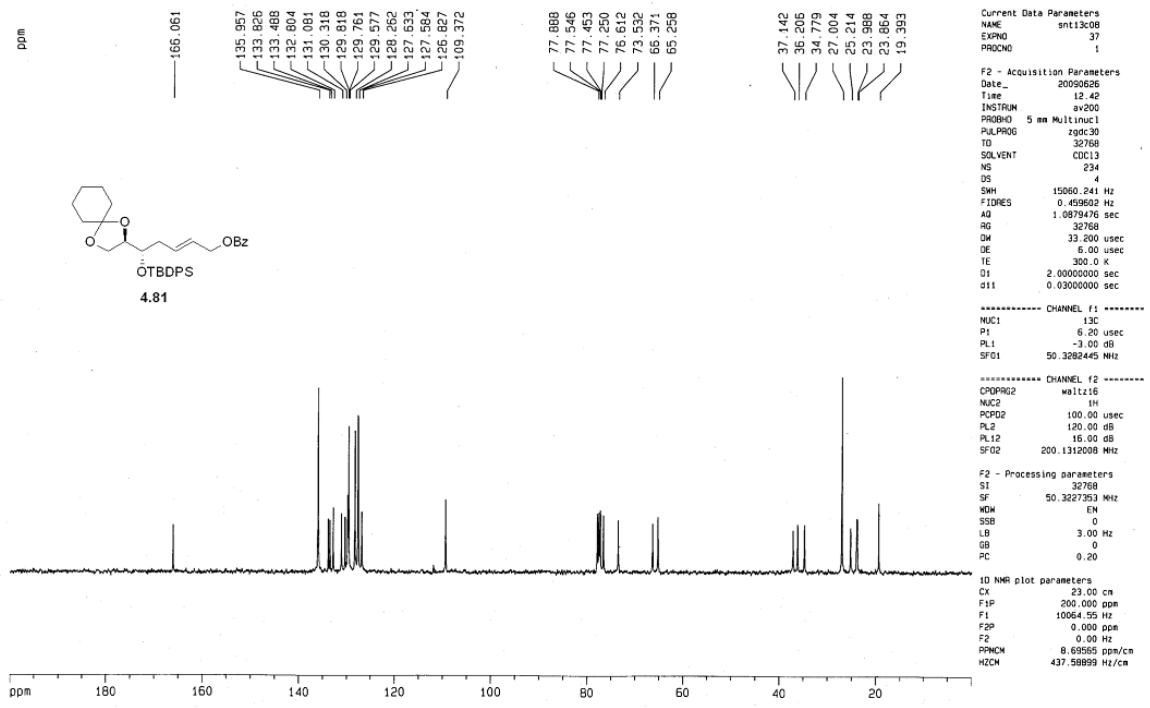


Figure 4.12 ^{13}C NMR spectrum of 4.81

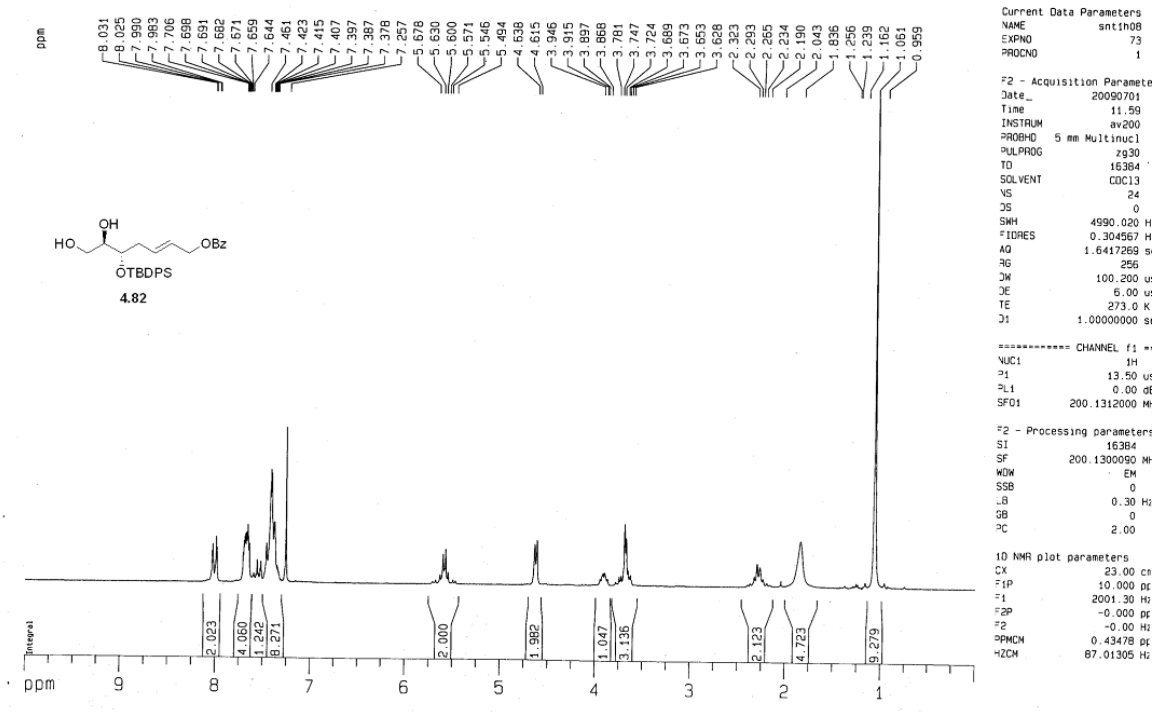


Figure 4.13 ^{1}H NMR spectrum of 4.82

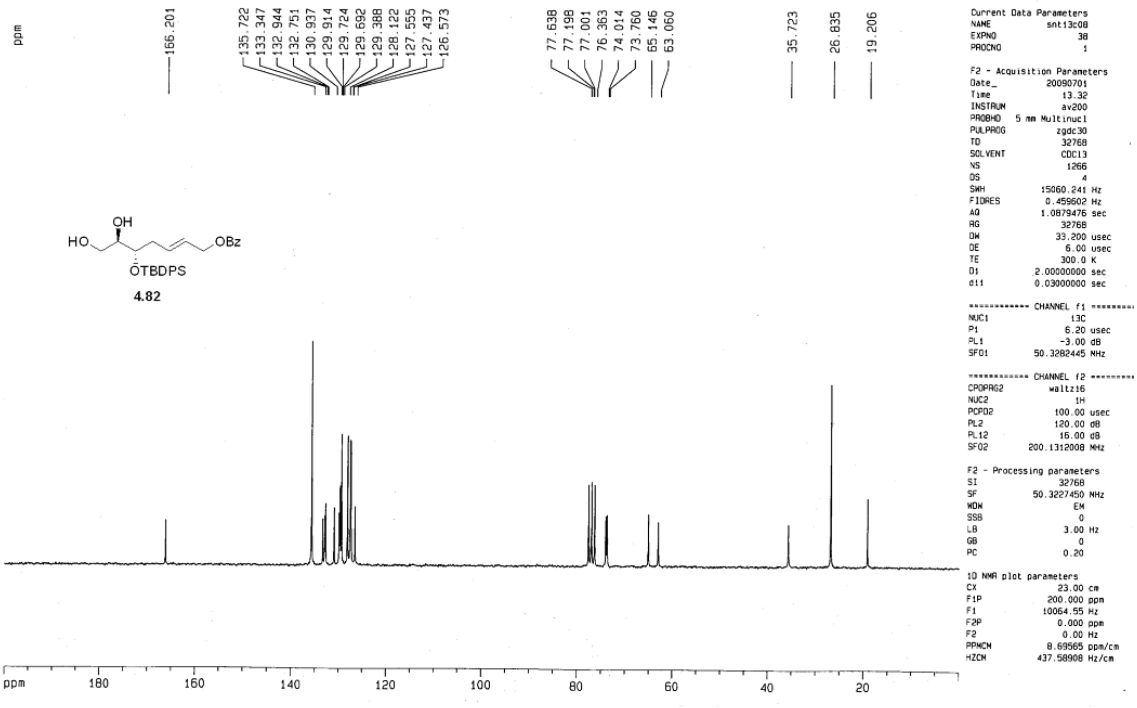


Figure 4.14 ^{13}C NMR spectrum of 4.82

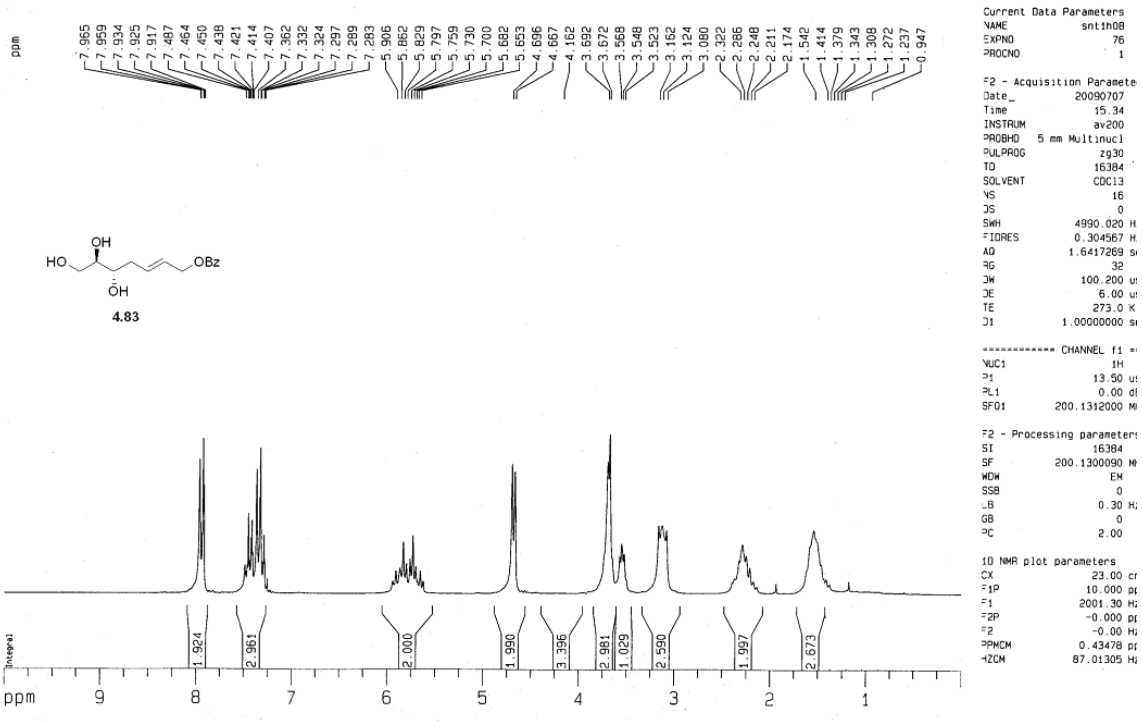


Figure 4.15 ^{1}H NMR spectrum of 4.83

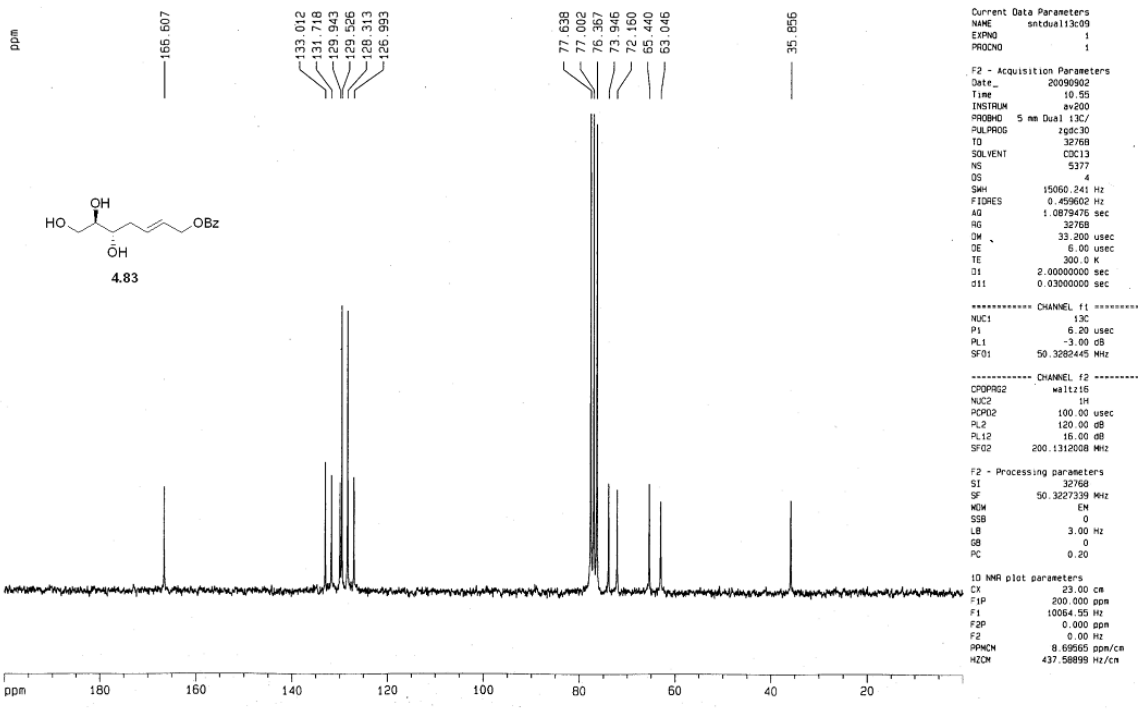


Figure 4.16 ^{13}C NMR spectrum of 4.83

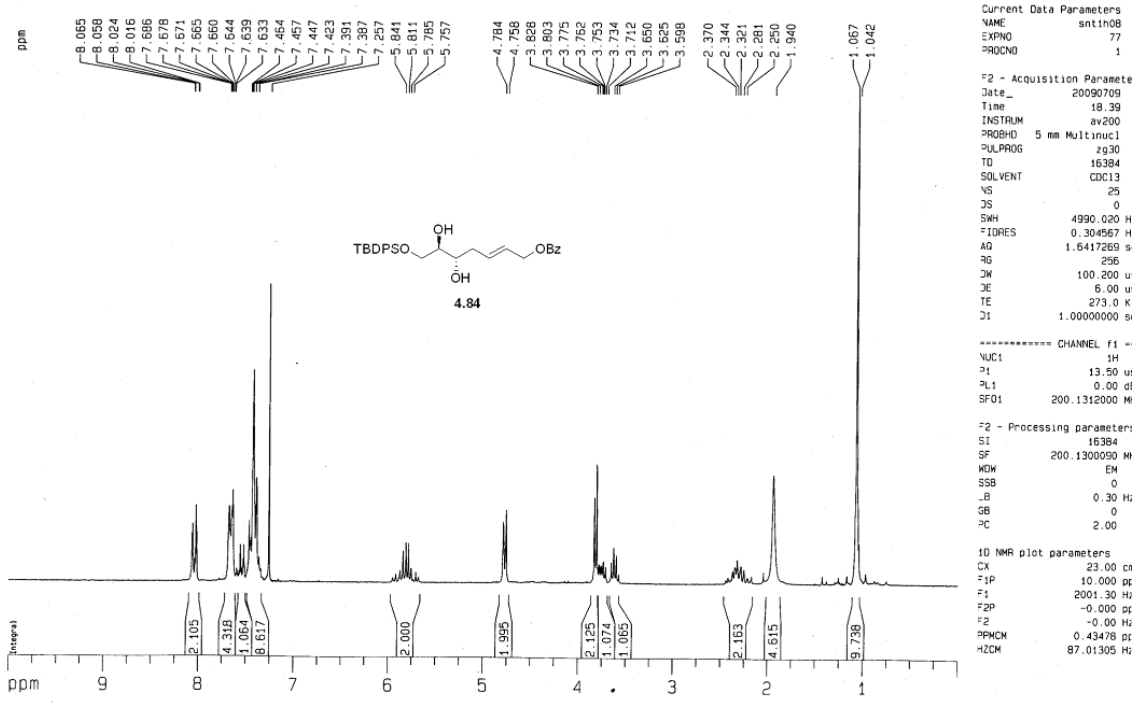


Figure 4.17 ^{1}H NMR spectrum of 4.84

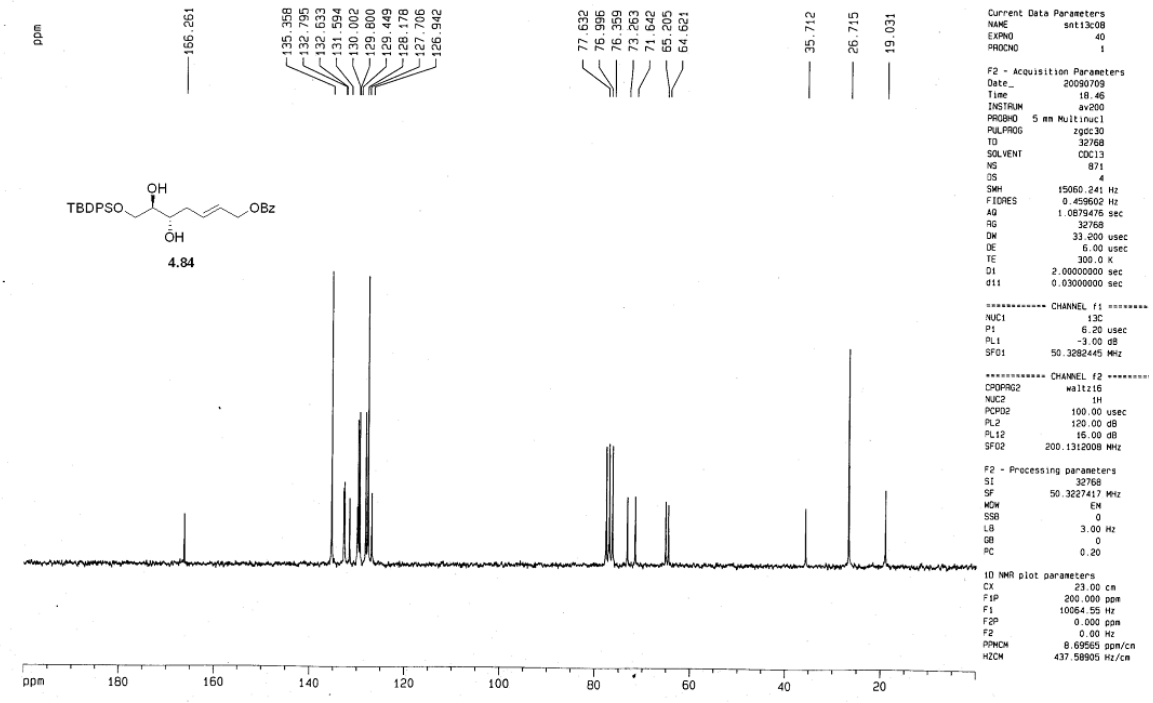


Figure 4.18 ^{13}C NMR spectrum of 4.84

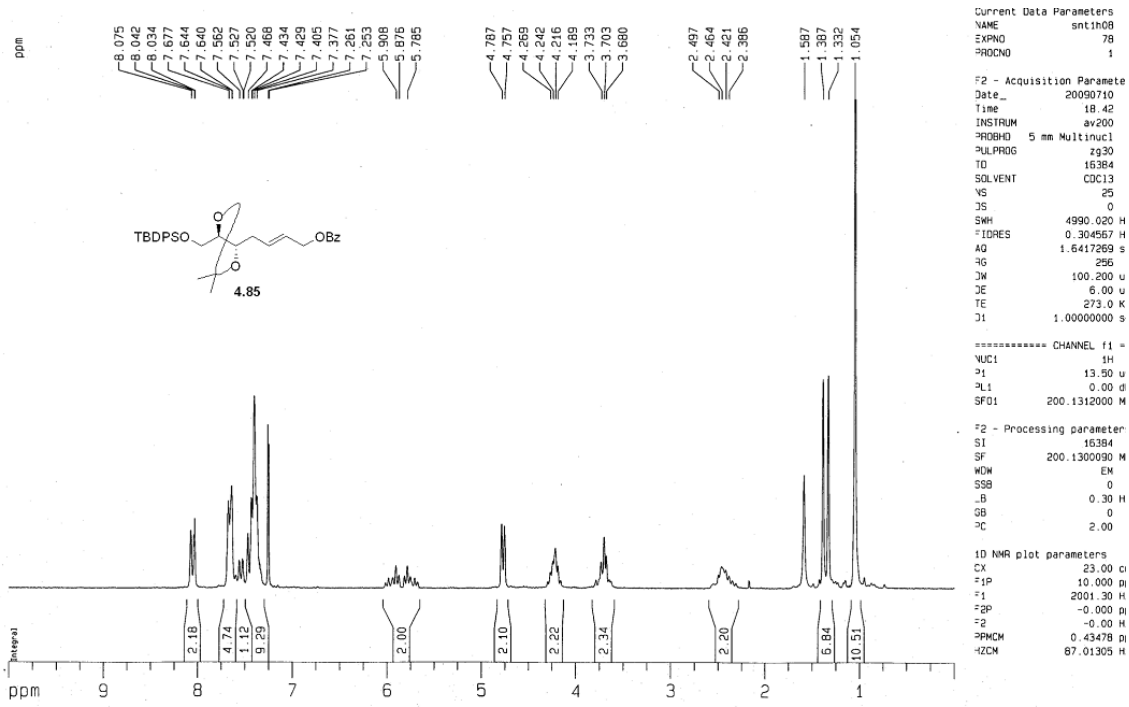


Figure 4.19 ^{1}H NMR spectrum of 4.85

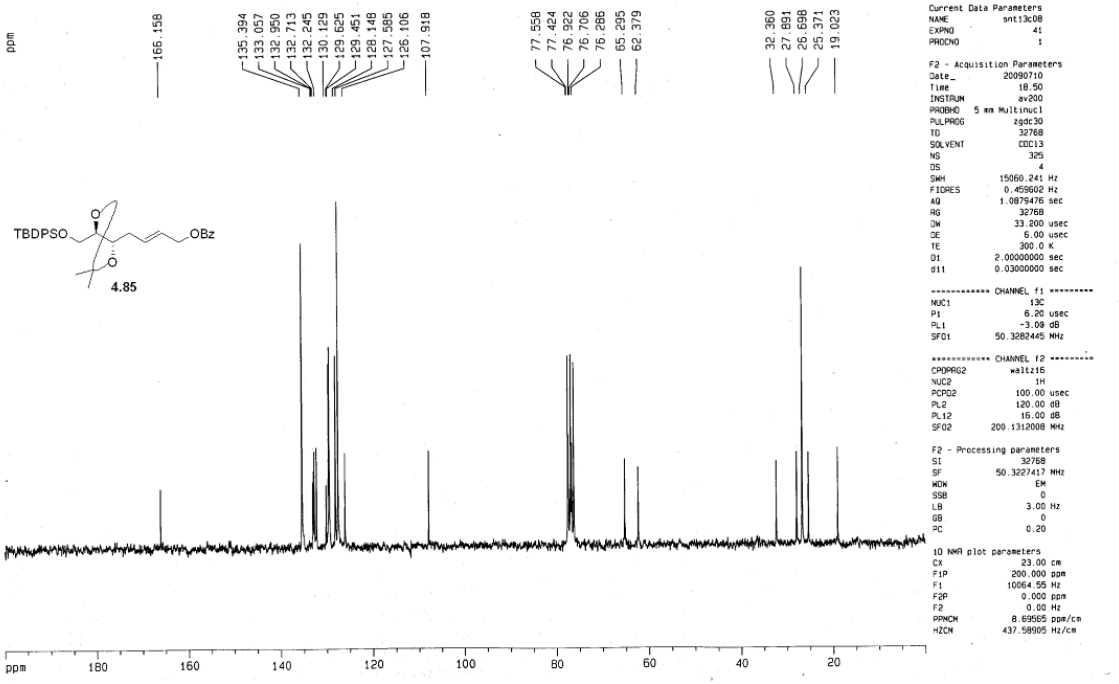


Figure 4.20 ^{13}C NMR spectrum of 4.85

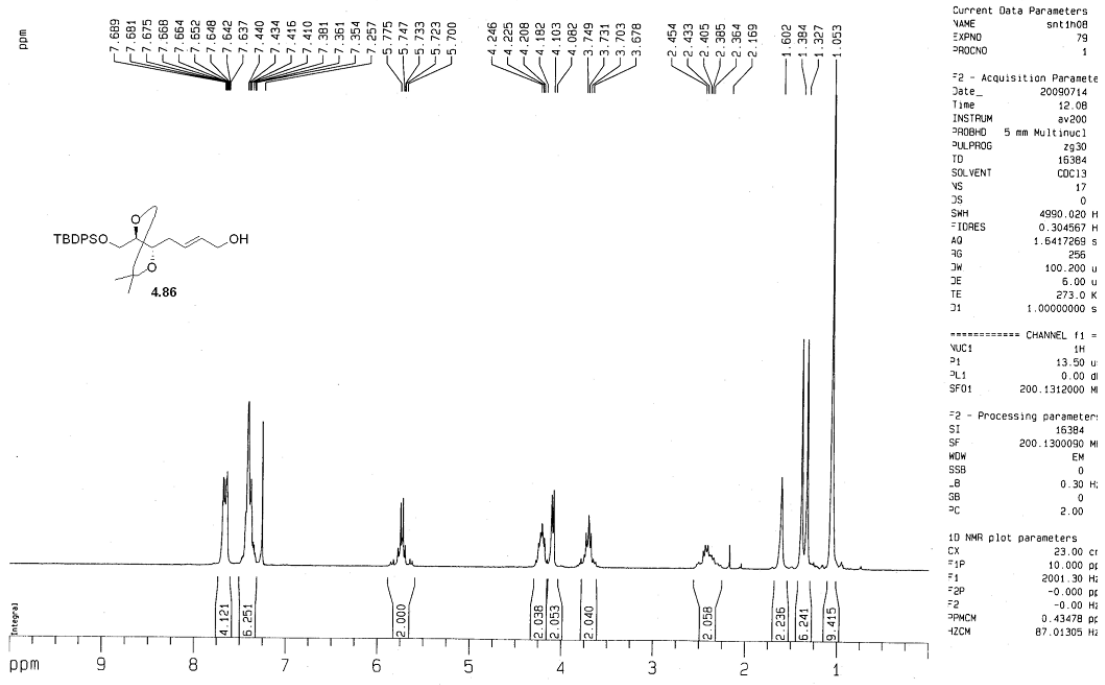


Figure 4.21 ^{1}H NMR spectrum of 4.86

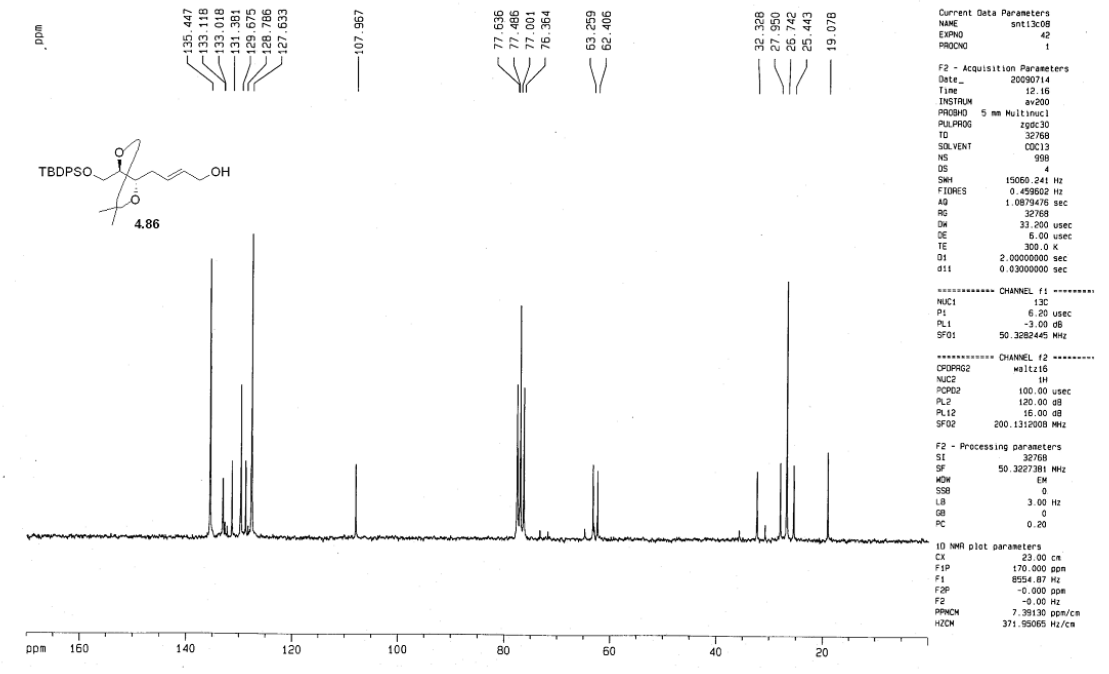


Figure 4.22 ^{13}C NMR spectrum of 4.86

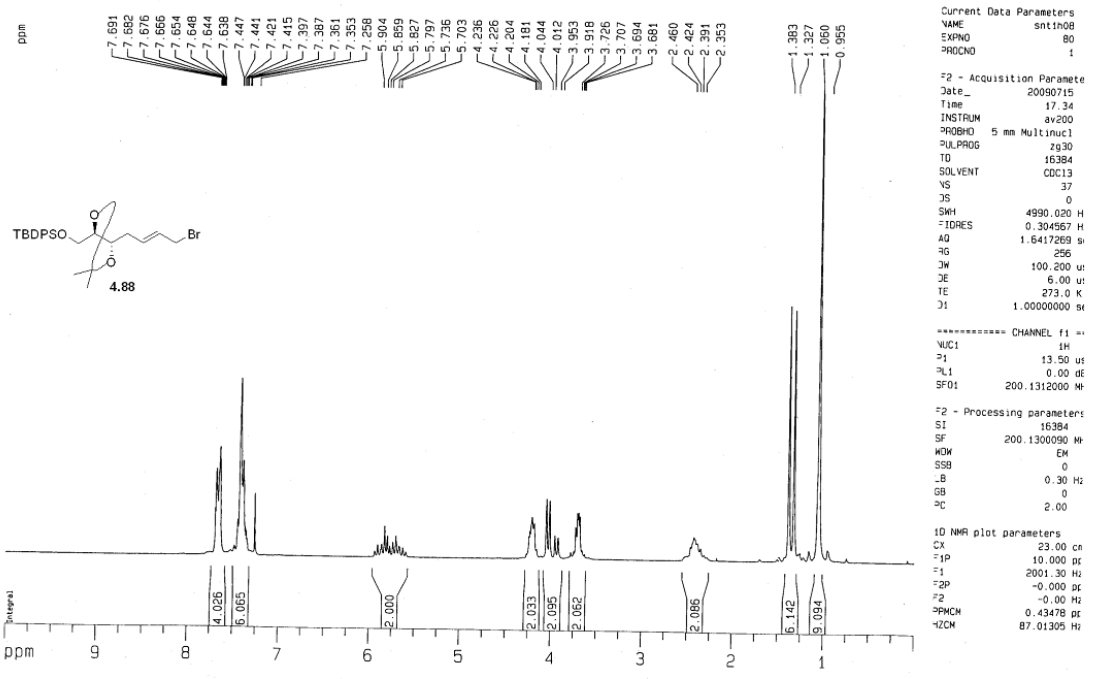


Figure 4.23 ^{1}H NMR spectrum of 4.88

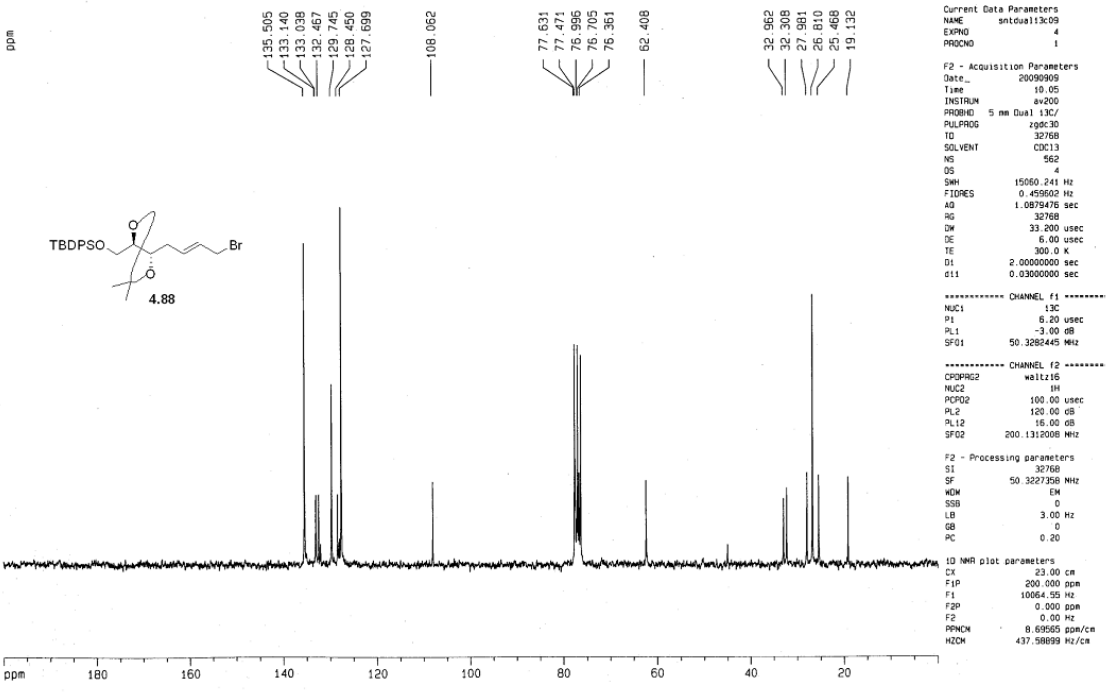
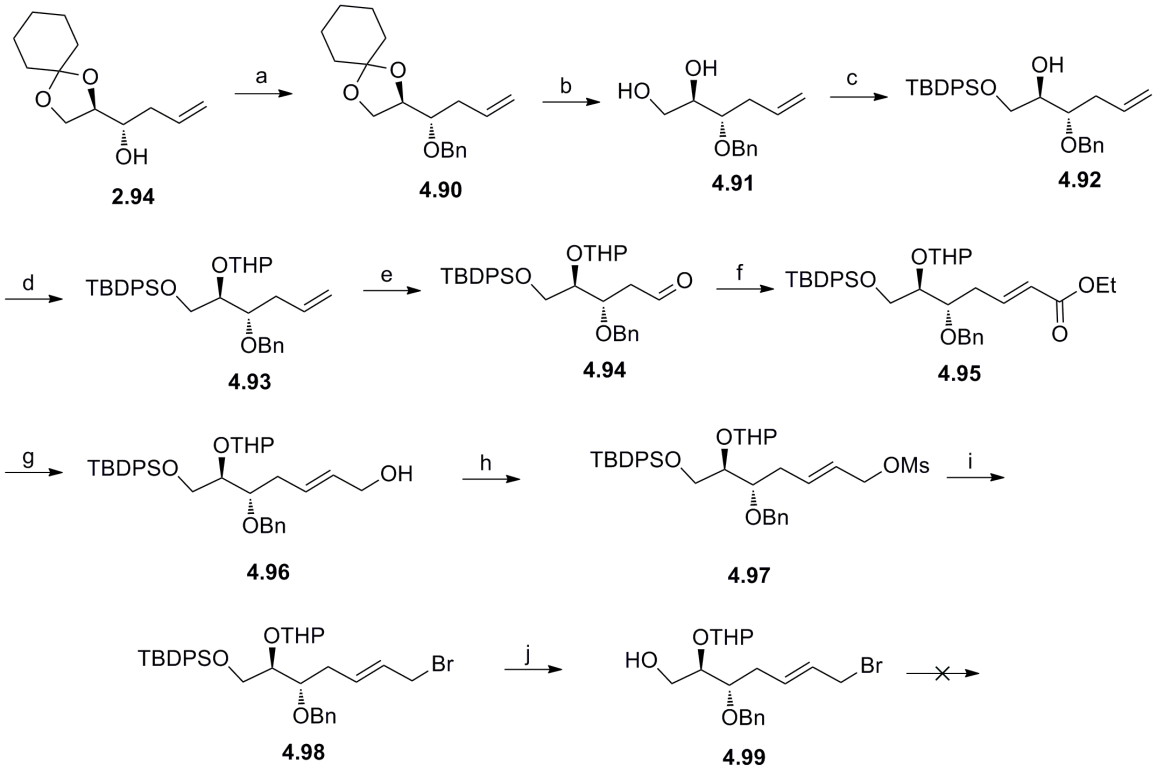


Figure 4.24 ^{13}C NMR spectrum of 4.88

The decomposition of intermediate **4.88** led us to make some alteration in our earlier approach using different protections of hydroxyls (**Scheme 4.11**). In this case we have started with the protection of same anti homoallylic alcohol **2.94** with benzyl to give the benzyl ether **4.90** which was subjected to ketal hydrolysis to obtain the diol **4.91**. The benzyl ether **4.90** was characterized by the characteristic peak of benzyl -CH_2- as a "AB q" at δ 4.6 in ^{1}H NMR (**Figure 4.25-4.26**) similarly the absence of 10 H multiplet at δ 1.3-1.6 in ^{1}HNMR (**Figure 4.27-4.28**) confirmed the formation of the diol **4.91**. This was subjected to regioselective mono-silylation at low temperature (0 ^{o}C) with TBDPSCl and imidazole to give the monosilylated alcohol **4.92** with an overall yield of 85 % and the chromatographically recovered unreacted starting material was again subjected for monosilylation. The signal at δ 1.06 (9H) in the ^{1}H NMR of **4.92** and the appearance of signals at δ 26.8 and 19.2 in its ^{13}C NMR (**Figure 4.29-4.30**) confirmed the formation of the monosilylated alcohol in it. The other hydroxyl of **4.92** was protected as THP ether to give **4.93** in quantitative yield. This was subjected to ozonolysis of its olefin, followed by *in situ* PPh_3 reduction of the ozonide to produce aldehyde **4.94**. The presence of the -OTHP group makes the entire molecule **4.94** a diastereomeric mixture which was indicted from both the ^{1}H NMR and ^{13}C NMR of **4.93** (**Figure 4.31-4.32**). The presence of aldehyde functionality in it was confirmed from the two triplets due to diastereomeric mixture at δ 9.71 and 9.78 in its ^{1}H NMR and two signals at δ 201.3 and 201.4 in its ^{13}C NMR (**Figure 4.33-4.34**). The aldehyde was then subjected to W-H-E reaction using NaH as base gave the *α, β*-unsaturated conjugated ester **4.95** (**Figure 4.35-4.36**) with 100% *E* selective alkene formation. This was reduced at low temperature (-78 ^{o}C) using DIBAL-H to give the allylic alcohol **4.96** (**Figure 4.37-4.38**) with 90 % yield. The allylic alcohol **4.96** was then converted into the allyl bromide **4.98** over two steps with a very good overall yield of 87 %, *viz.* (i) mesylation of the hydroxyl to give mesylate **4.97** (ii)

conversion of the mesylate to bromide using NaBr. The presence of -CH_2Br in **4.98** was confirmed from the signal at δ 44.9 in its ^{13}C NMR (**Figure 4.39-4.40**). The allylic bromide **4.98** was desilylated on treatment with TBAF to yield primary alcohol **4.99** (**Figure 4.41**) in quantitative yield. Next, **4.99** was subjected to oxidation using Dess Martin periodinane. Unfortunately the compound decomposed to highly polar uncharacterized material rather yielding the required aldehyde equivalent to synthon **C**.



a) BnBr, NaH, TBAI, THF 25 °C; b) Aq.TFA (80%), CH_2Cl_2, 0 °C; c) TBDPSCl, Imidazole, DMAP, CH_2Cl_2, 0 °C, over 5h; d) DHP, PTSA (cat), CH_2Cl_2, 0 °C to rt; e) O_3, PPh_3, CH_2Cl_2, -78 °C to rt; f) NaH, $C_2H_5COOCH_2P(O)(OC_2H_5)_2$, THF, 25 °C; g) DIBAL-H, THF, -78 °C; h) MsCl, Et_3N, CH_2Cl_2, 0 °C; i) NaBr, $NaHCO_3$ (cat), Acetone; j) TBAF, THF, 0 °C.

Scheme 4.11

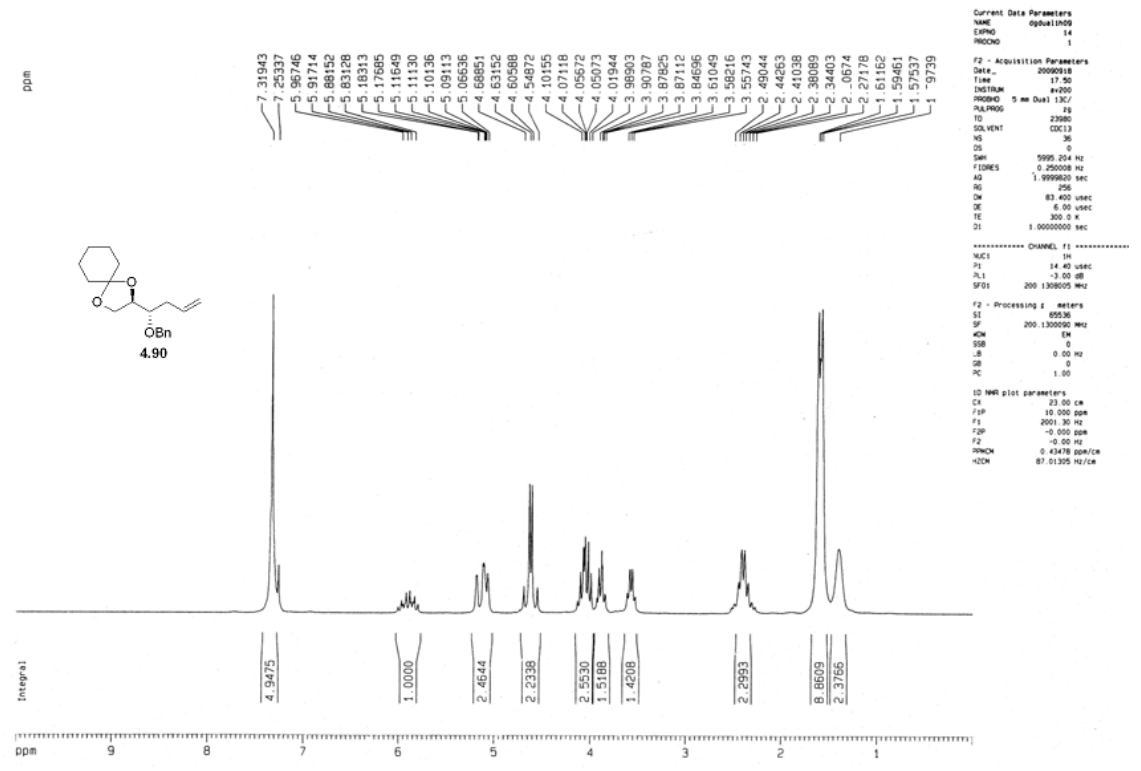


Figure 4.25 ^{1}H NMR spectrum of 4.90

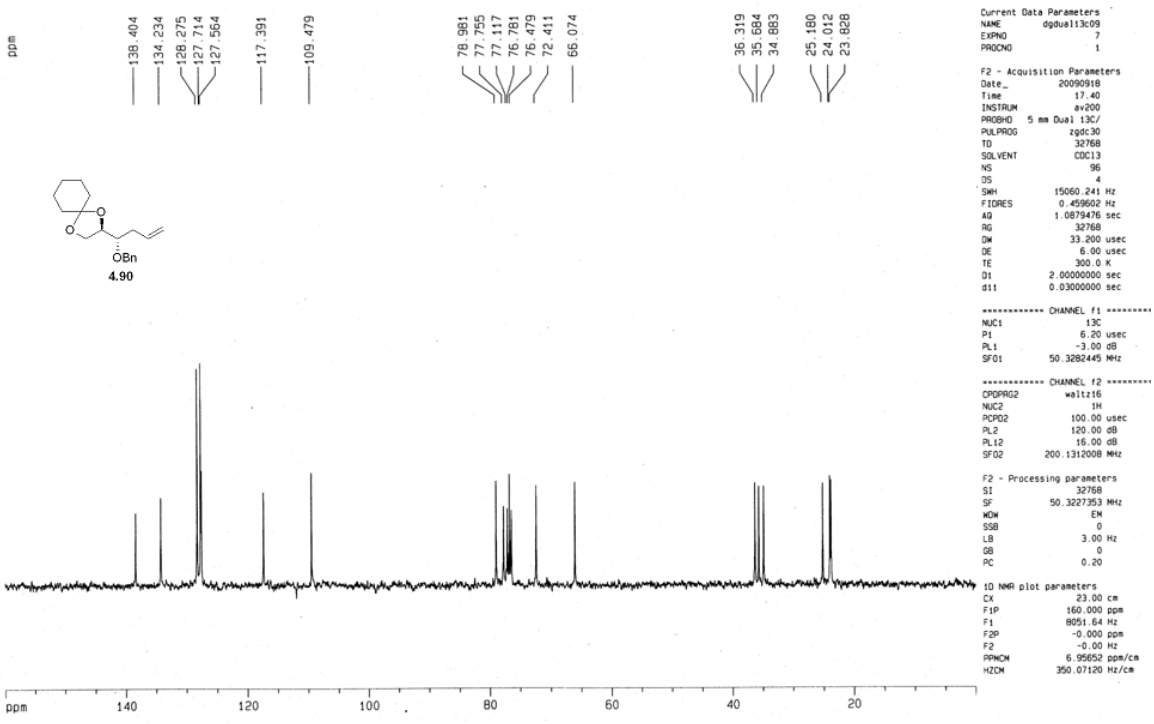


Figure 4.26 ^{13}C NMR spectrum of 4.90

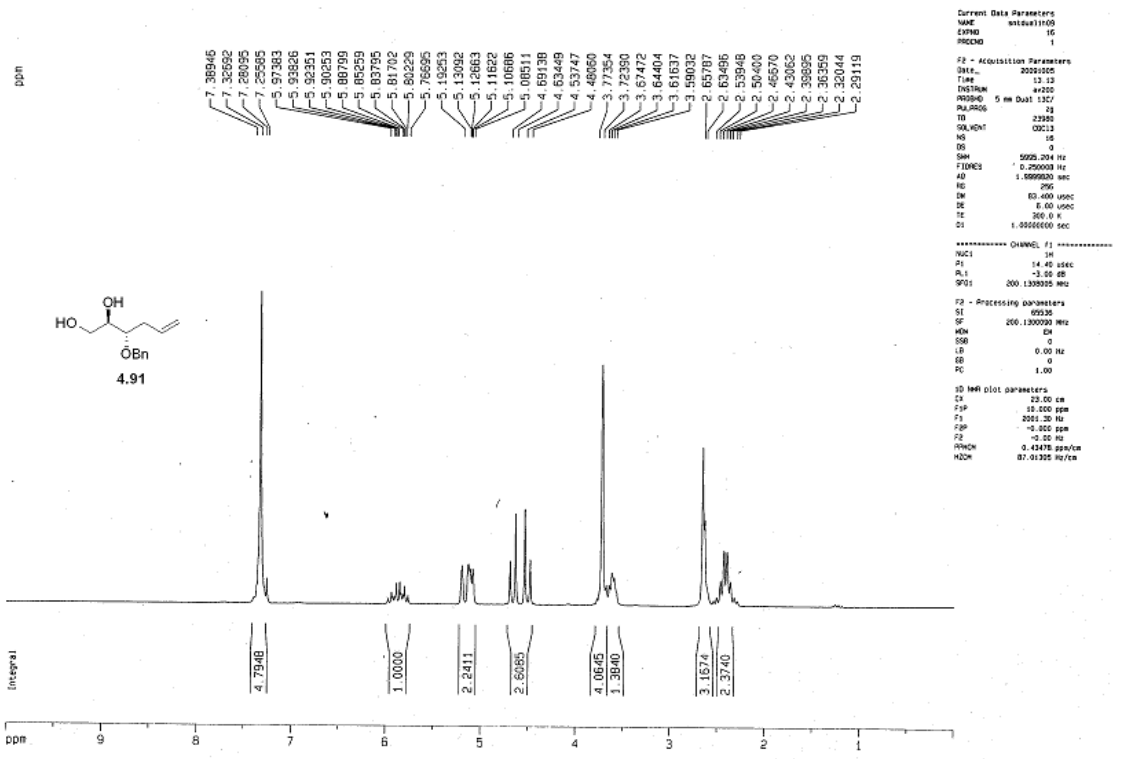


Figure 4.27 ^{1}H NMR spectrum of 4.91

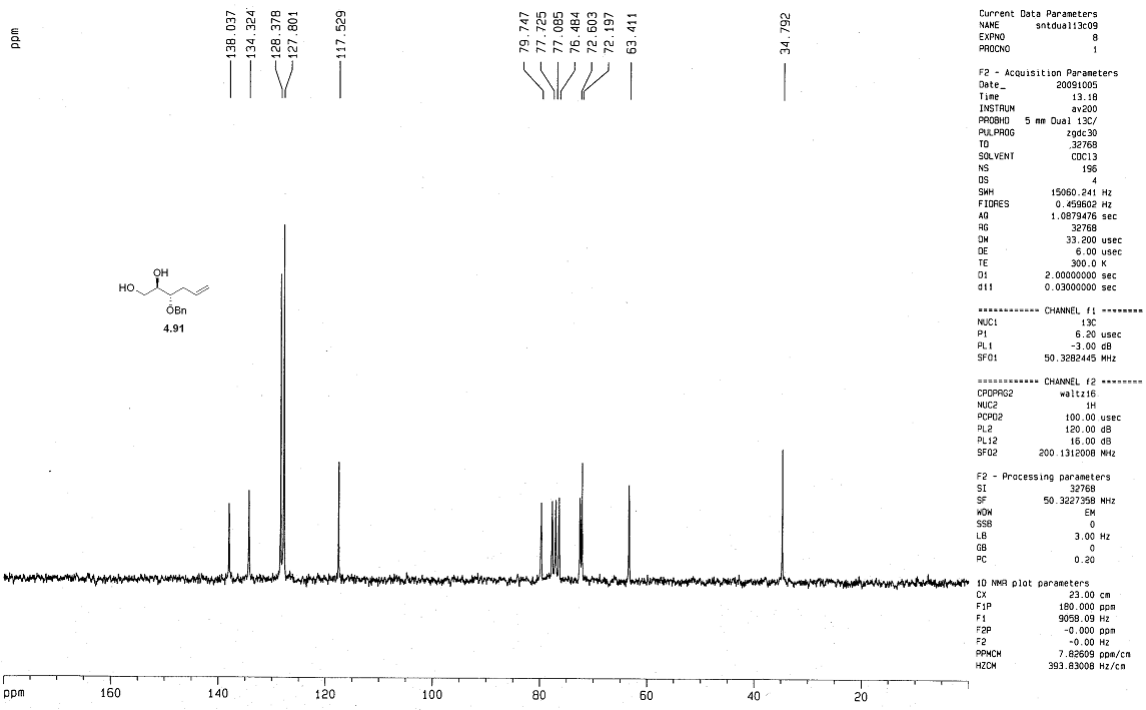


Figure 4.28 ^{13}C NMR spectrum of 4.91

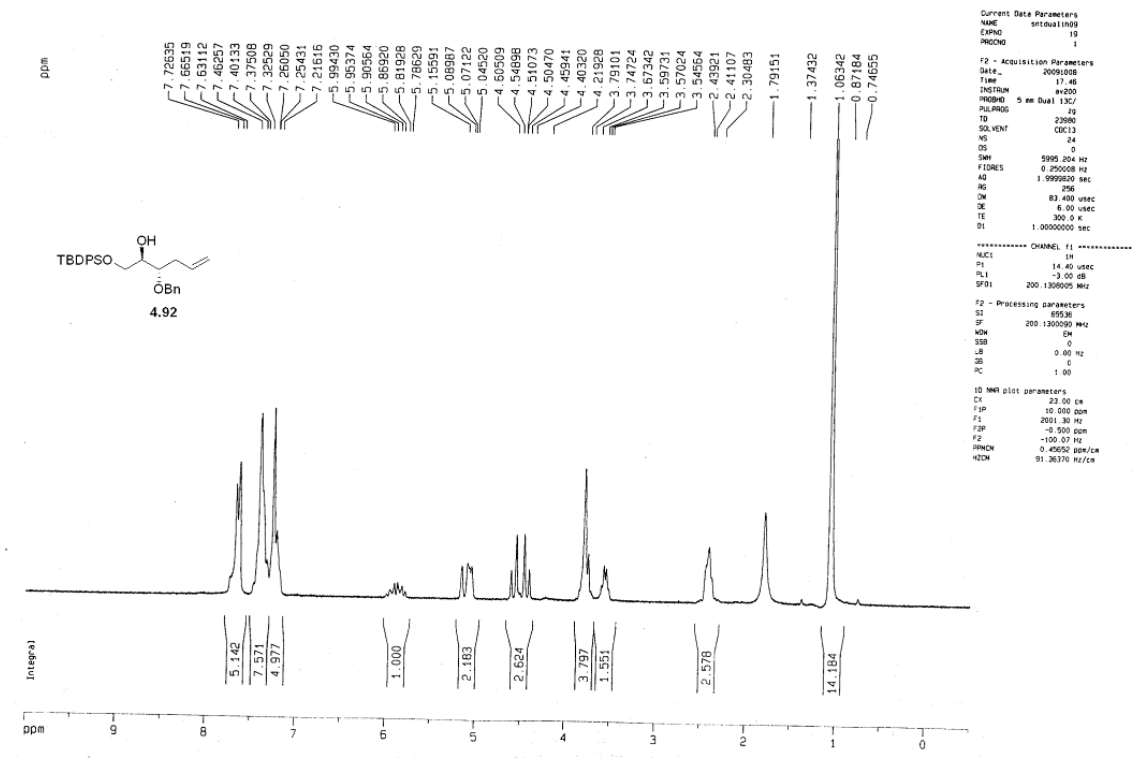


Figure 4.29 ^{1}H NMR spectrum of 4.92

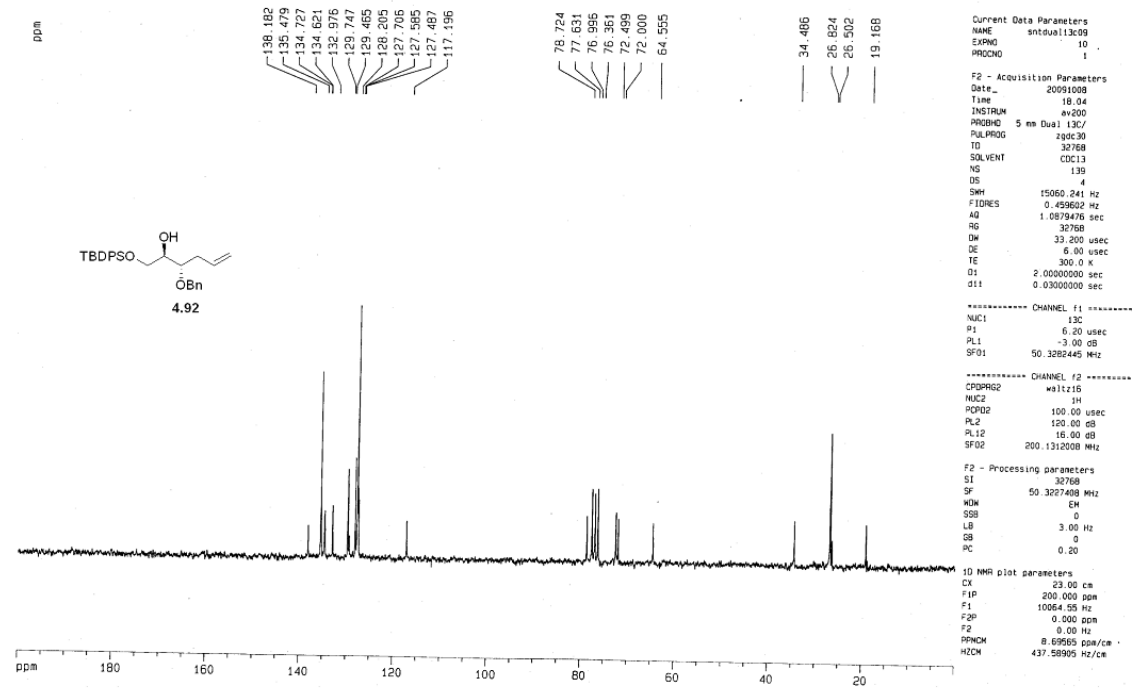


Figure 4.30 ^{13}C NMR spectrum of 4.92

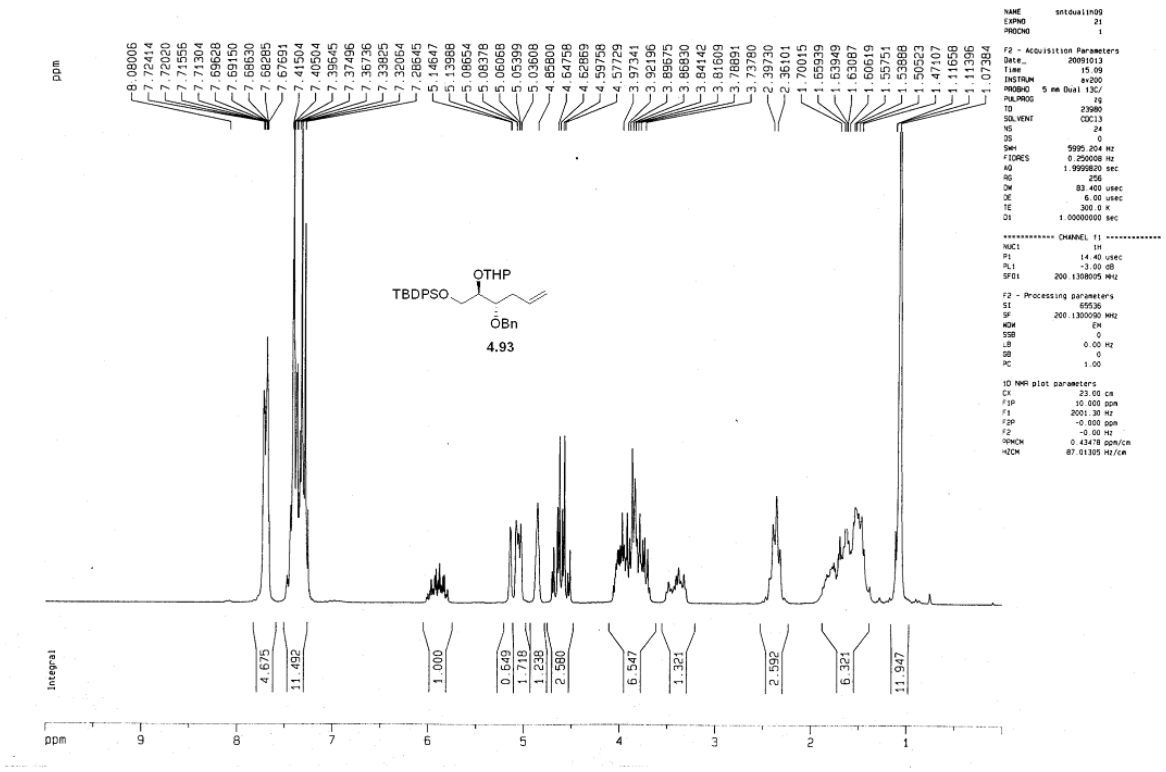


Figure 4.31 ^{1}H NMR spectrum of 4.93

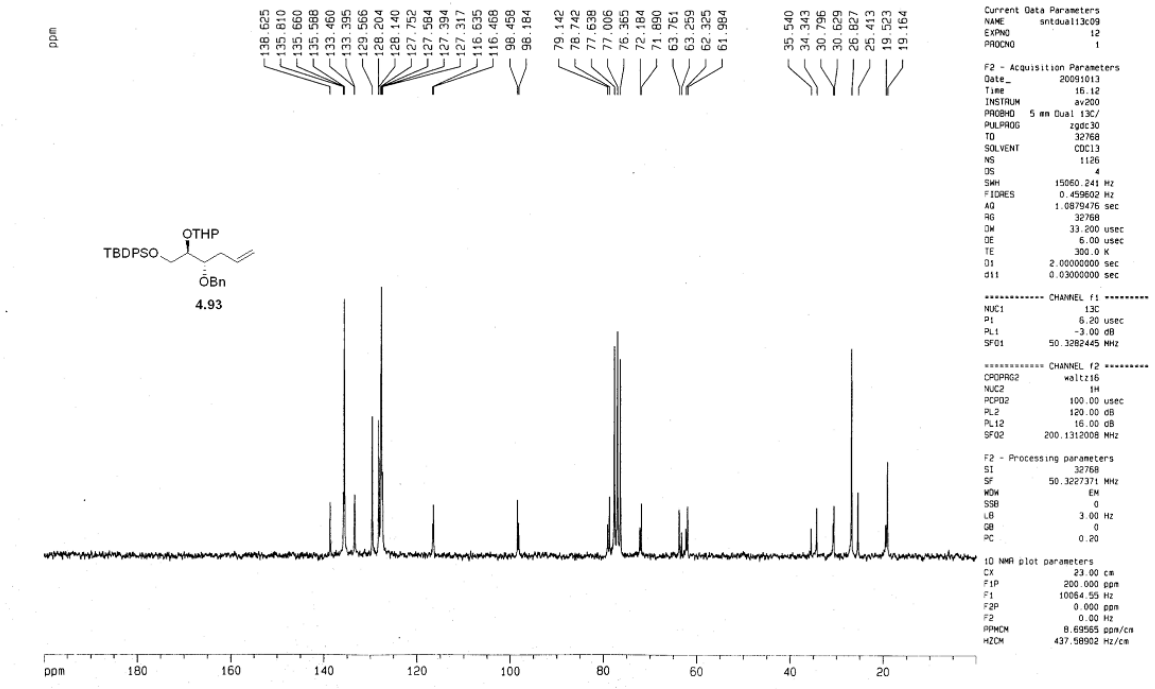


Figure 4.32 ^{13}C NMR spectrum of 4.93

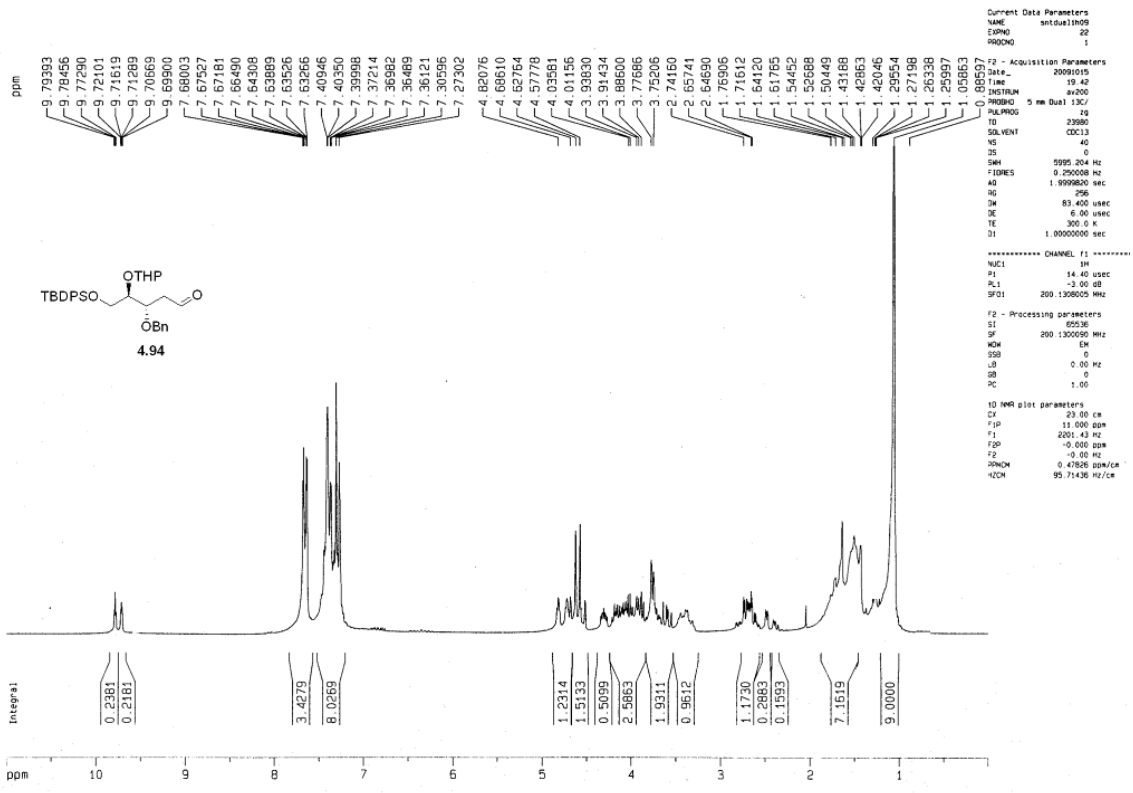


Figure 4.33 ^{1}H NMR spectrum of 4.94

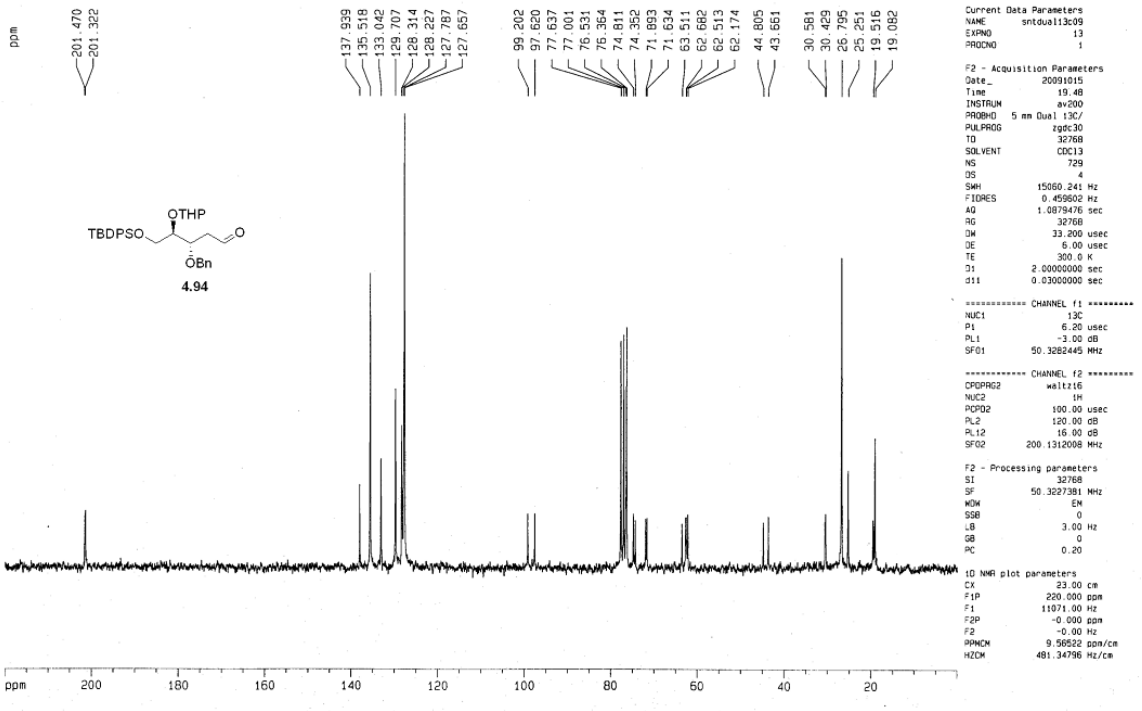


Figure 4.34 ^{13}C NMR spectrum of 4.94

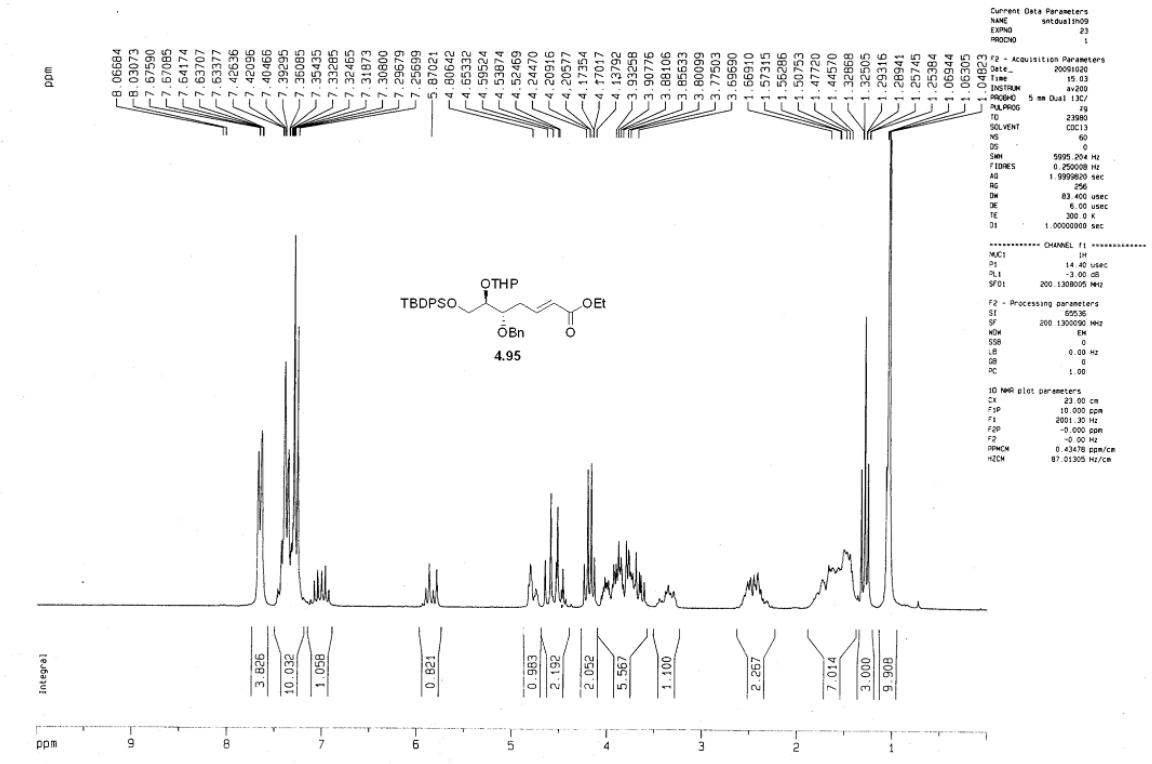


Figure 4.35 ^{1}H NMR spectrum of 4.95

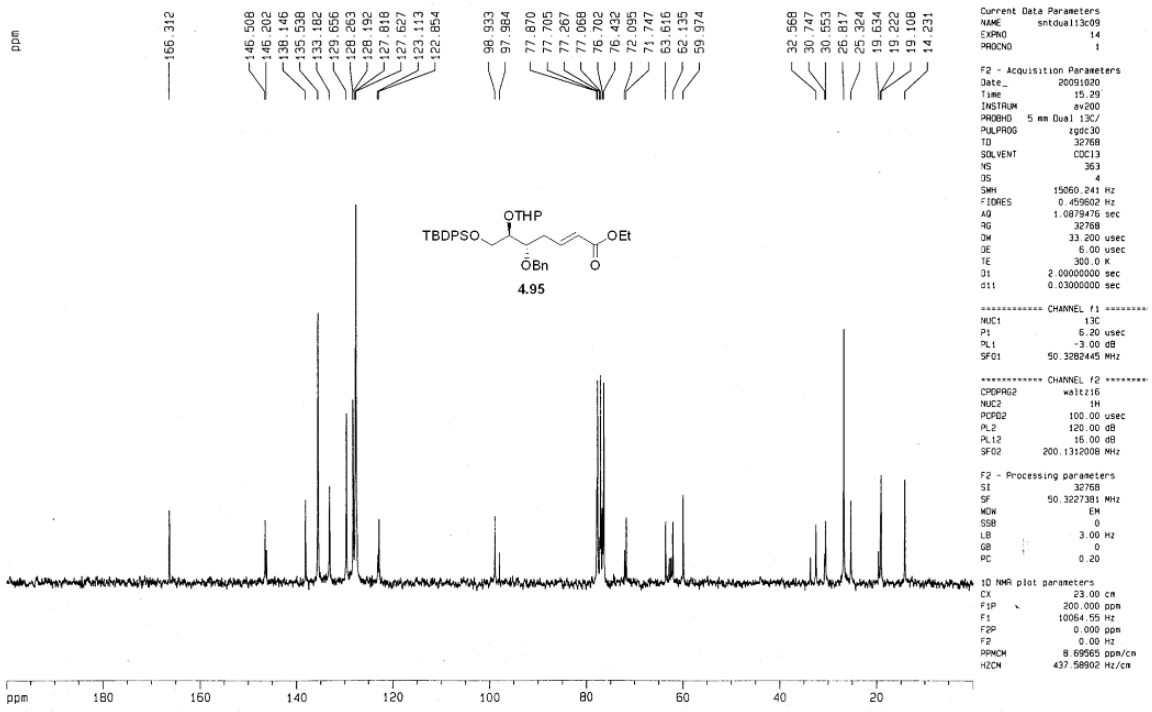


Figure 4.36 ^{13}C NMR spectrum of 4.95

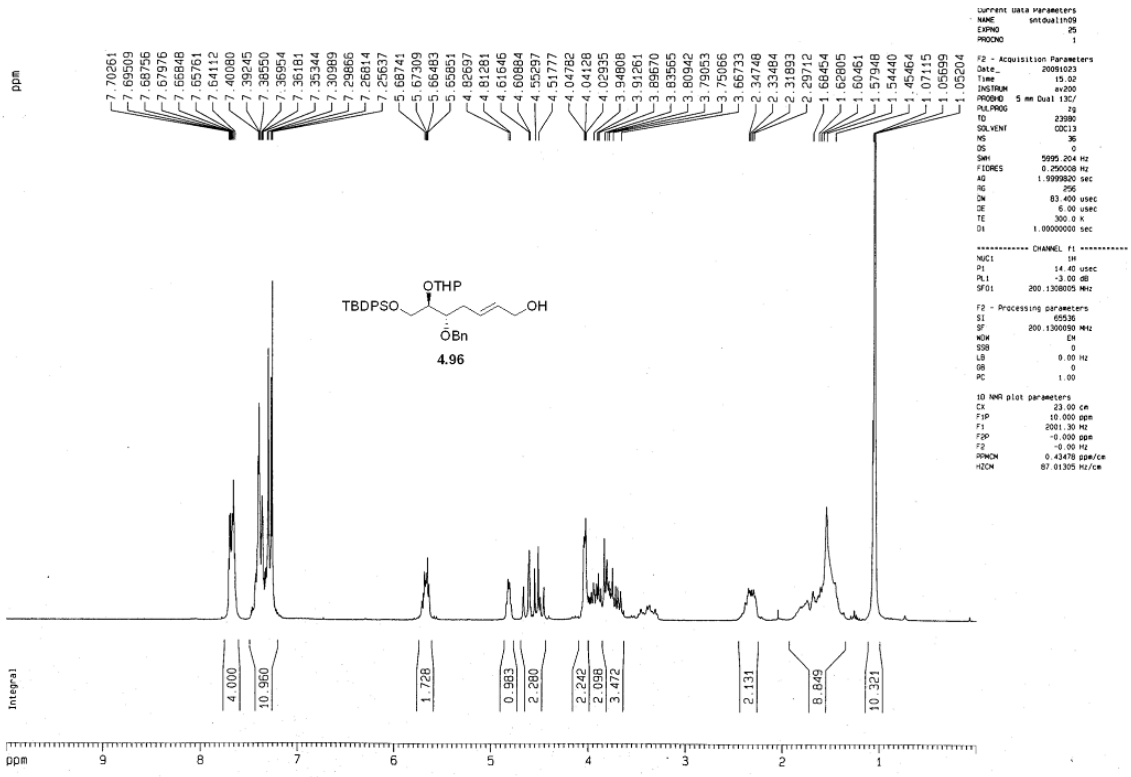


Figure 4.37 ^{1}H NMR spectrum of 4.96

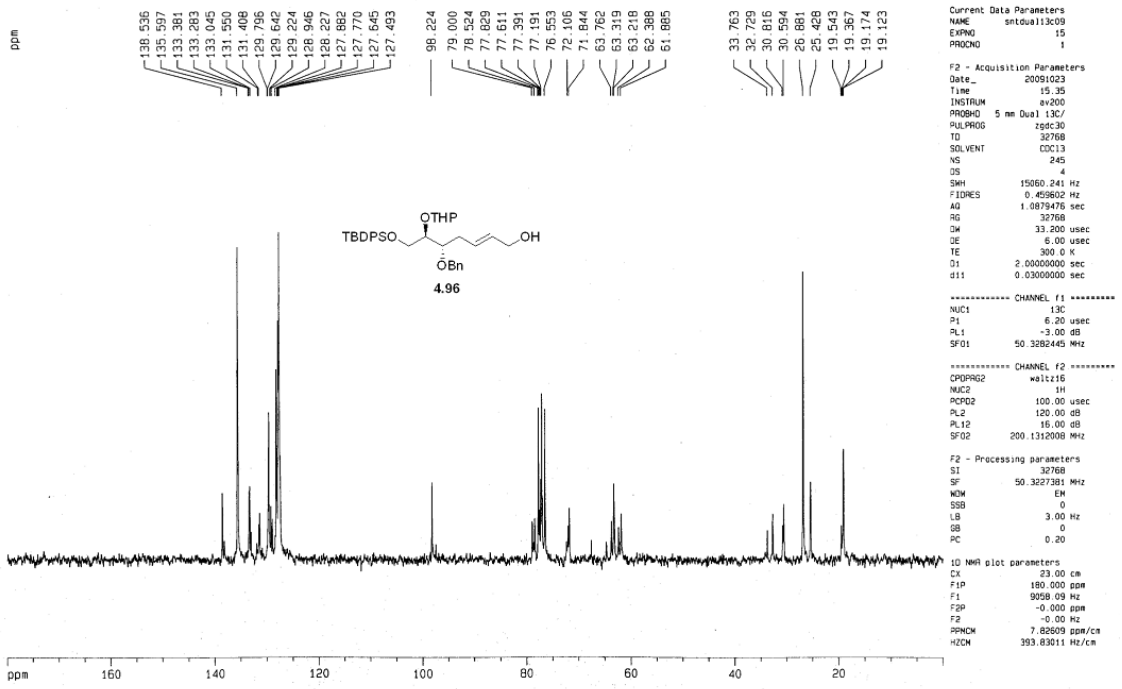


Figure 4.38 ^{13}C NMR spectrum of 4.96

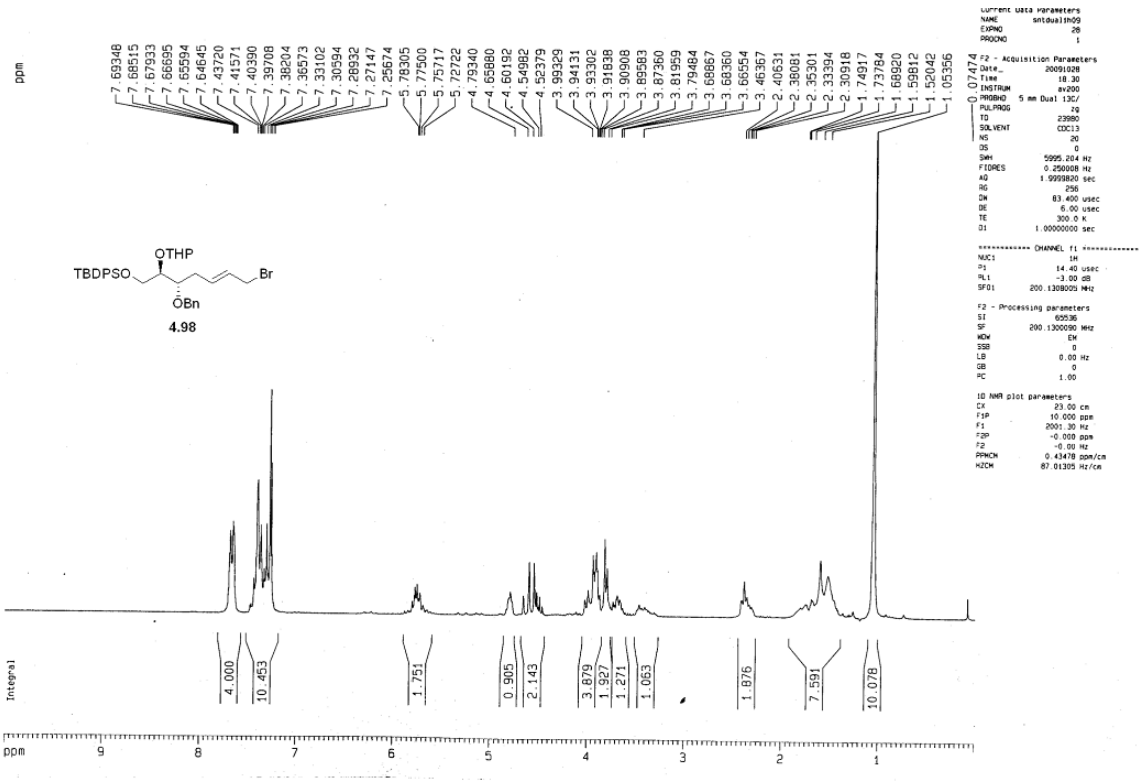


Figure 4.39 ^{1}H NMR spectrum of 4.98

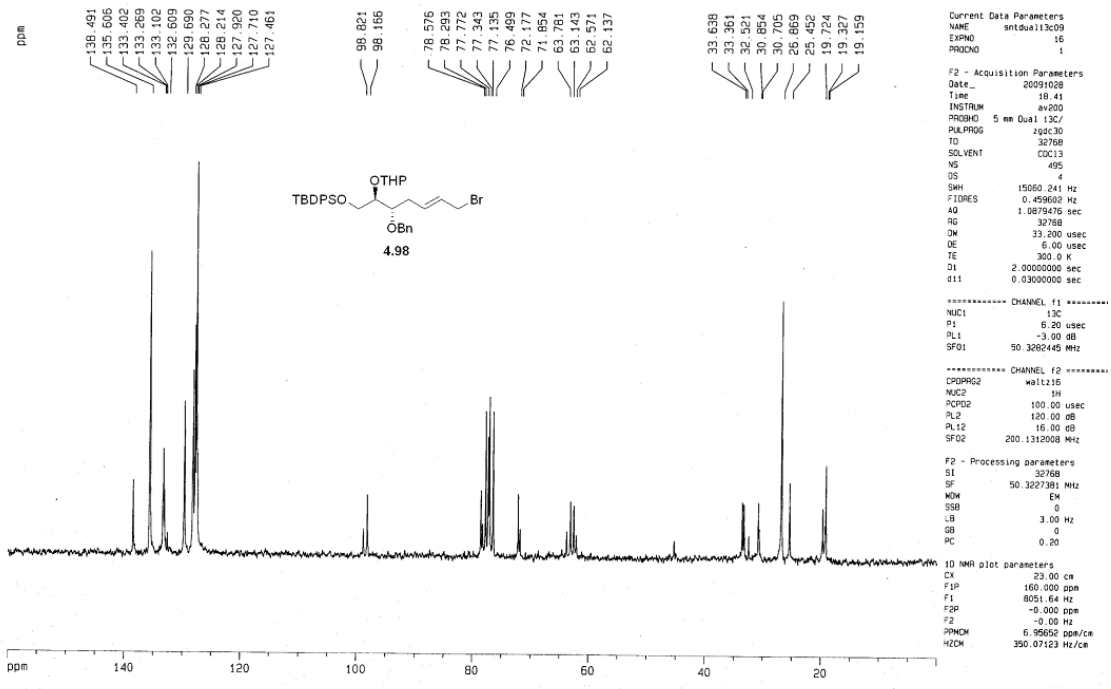


Figure 4.40 ^{13}C NMR spectrum of 4.98

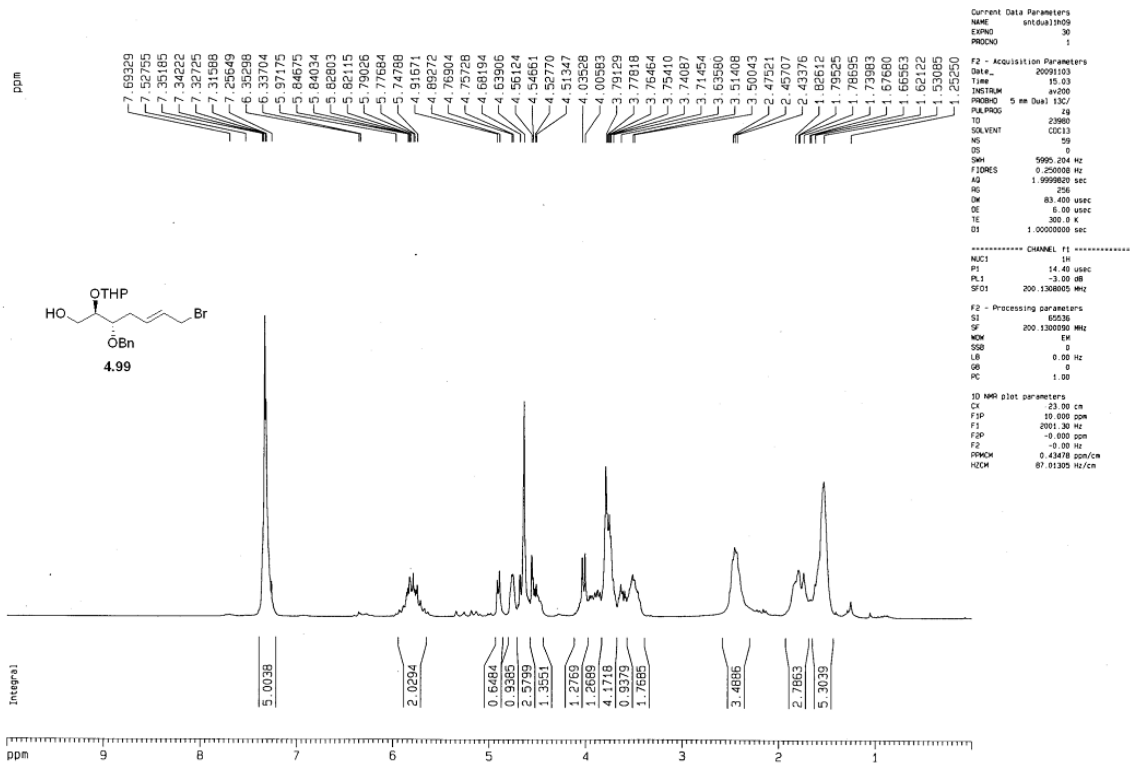
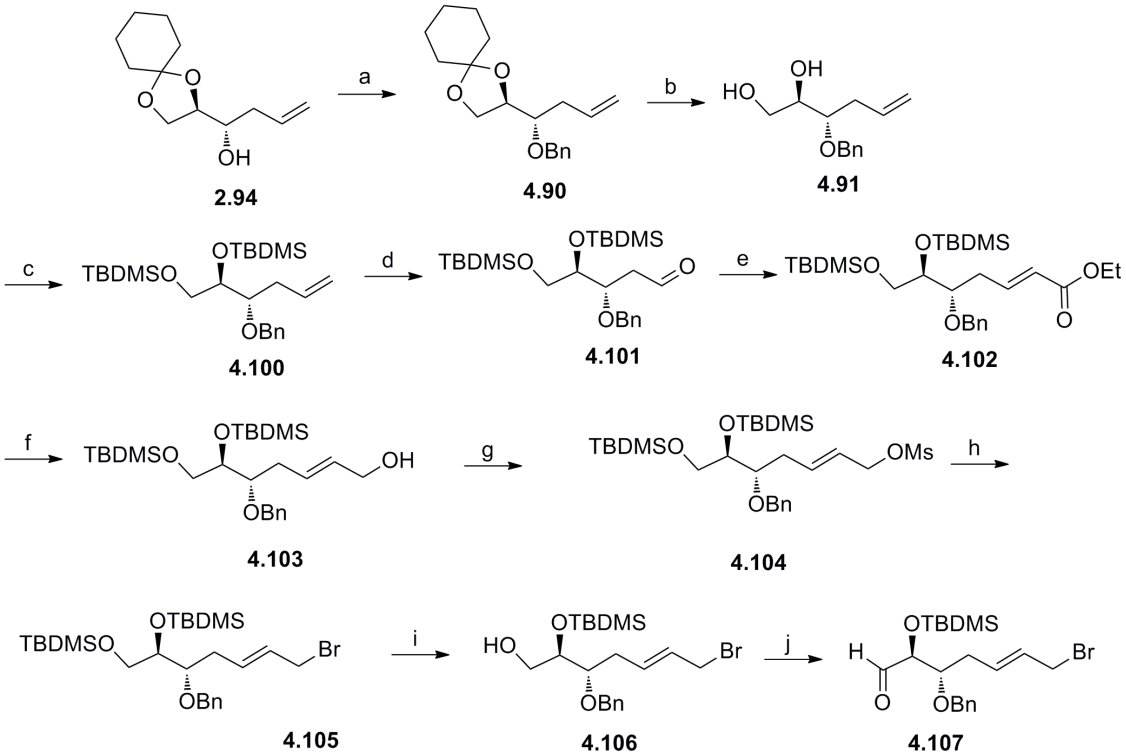


Figure 4.41 ^{1}H NMR spectrum of 4.99

After another unsuccessful attempt to prepare an intermediate aldehyde equivalent to **C** (**Scheme 4.8**), we had to adopt alteration of our approach once again to prepare the same starting from *anti*- homo allylic alcohol **2.94** (**Scheme 4.12**). This time, we began with diol **4.91**, an intermediate of the previous **Scheme 4.11**. Silylation of both hydroxyl of groups of **4.91** using two equivalents of TBDMS chloride and imidazole produced **4.100** in good overall yield. The product was characterized by the signal at δ 0.05 (2 singlet 6H each) due to its two –OTBDMS group in its ^{1}H NMR (**Figure 4.45-4.46**). Ozonolysis of the olefin of **4.100** and in situ PPh_3 reduction of the resulting ozonide afforded aldehyde **4.101** in good yield (86%). The formation of aldehyde was characterized by the signal at δ 9.77 triplets 1H in its ^{1}H NMR and a signal at δ 201.5 in its ^{13}C NMR (**Figure 4.47-4.48**). This was found to be unstable on standing, and so without further purification was quickly subjected to Wittig Horner olefination to obtain

the *α, β*-unsaturated conjugated ester **4.102** in good yield 80.8%. The *E* stereochemistry of the resulting olefin was confirmed by a doublet at δ 5.86 (*J* = 15.6 Hz, 1H) and a doublet of a triplet at δ 7.0 (*J* = 15.6, 7.2 Hz, 1H) (**Figure 4.49-4.50**). The DIBAL-H reduction of **4.102** afforded allylic alcohol **4.103** (**Figure 4.51-4.52**) which was transformed into bromide **4.105** in two steps, *viz.* (a) mesylation; (b) treatment of mesylate **4.104** with NaBr in acetone, in good overall yield (90.3%). The signal at δ 45.3 in its ^{13}C NMR (**Figure 4.53-4.54**) confirmed the formation of bromide **4.105**. Next, the regioselective desilylation of **4.105** was accomplished by stirring it in acidified $CHCl_3$ solution to afford **4.106** (**Figure 4.55-4.56**) in good yield (91.2%). The free hydroxyl of **4.106** was subjected to oxidation with Dess-Martin periodinane. To our great delight, this time we were successful in obtaining aldehyde **4.107**, which was the equivalent to **C** in Scheme **4.8**. The presence of CHO in **4.107** was confirmed from a triplet at δ 9.6 in its ^{1}H



a) BnBr, NaH, TBAI, THF 25 °C; b) Aq.TFA (80%), CH_2Cl_2, 0 °C; c) TBDMSCl, Imidazole, DMAP, DMF, 0 °C to rt; d) O_3, PPh_3, CH_2Cl_2, -78 °C to rt; e) NaH, $C_2H_5COOCH_2P(O)(OC_2H_5)_2$, THF, 25 °C; f) DIBAL-H, THF, -78 °C; g) MsCl, Et_3N, CH_2Cl_2, 0 °C; h) NaBr, $NaHCO_3$ (cat), Acetone; i) CH_3Cl saturated with Conc HCL; j) Dess Martin Periodinane, CH_2Cl_2, 0 °C to rt.

Scheme 4.12

NMR and a signal at δ 203.3 in its ^{13}C NMR (**Figure 4.57-4.58**), since compound **4.107** was relatively unstable on long standing, it was quickly subjected to intramolecular allylation resulting for construction of the carbafuranose unit of **4.108** (equivalent to intermediate **B** in **Scheme 4.8**) with simultaneous generation of its two stereocenters at C-3 and C-4. With a view to imparting practical viability in this approach , allylation was performed under wet conditions in the presence of five different metal mediators *viz* Luche's Zinc[39,187] and three low valent metals Iron, Copper and Tin [188] that were prepared *in situ* employing bimetallic redox strategy and Indium.[189] In order to ensure smooth progress, all of the heterogeneous low valent metal mediated allylation reactions were performed using an excess of metal/metal salts.

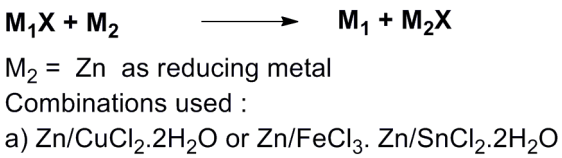
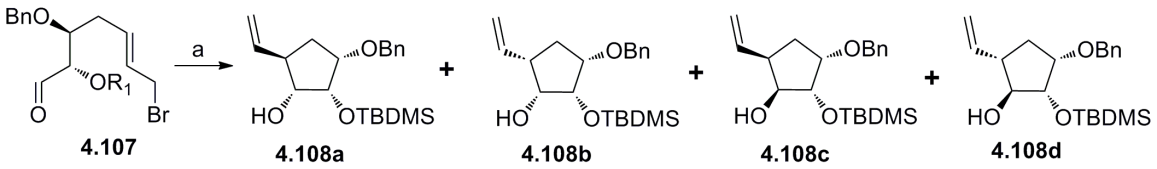


Figure 4.42 Principle of bi-metallic redox strategy

The bimetal redox strategy is used to produce a metal in active form which finally acts as a mediator in Barbier addition of an organic halide to a carbonyl substrate. In this process a metal salt (M_1X) is reduced on treatment with another metal (M_2) to produce M_1 in low valent state. The latter (M_1), in its nascent state becomes highly active and immediately reacts with bromide to produce the corresponding organometallic which in turn reacts with carbonyl substrate to produce the addition product.(**Figure 4.56**) All the reactions according to this strategy are favorable in moist condition due to good or partial solubility of metal salts in it. Different metal halides viz. $CuCl_2.2H_2O$, $FeCl_3$ and $SnCl_2.2H_2O$ were used along with Zn as the reducing metal.[37,190] To explore the viability of this approach for intramolecular allylation of **4.107**, Zn was chosen as the reducing metal in separate combinations with four commercially available salts *viz*. $Zn/CuCl_2.2H_2O$, $Zn/FeCl_3$ and $Zn/SnCl_2.2H_2O$. These were chosen in consideration of the

redox potentials of the following couples: $E^0_{Zn= Zn^{2+} + 2e}$ (+0.761 V), $E^0_{Cu= Cu^{2+} + 2e}$ (-0.337 V), $E^0_{Fe= Fe^{2+} + 2e}$ (+ 0.441 V), $E^0_{Fe^{2+} = Fe^{3+} + e}$ (- 0.771 V) and $E^0_{Sn= Sn^{2+} + 2e}$ (+0.140 V). Thus, the reduction of Cu(II), Fe(III) and Sn(II) salts can be effected on treatment with metallic Zn to produce Cu, Fe and Sn respectively in their zero valent states. Due to higher surface area, use of Zn in powdered form is advantageous for the reduction. The efficacies of all these allylation reactions (**Scheme 4.13**) are summarized in **Table 1**



a) (1) Zn/NH_4Cl, moist THF, (2) Zn/$FeCl_3$, moist THF, (3) Zn/$SnCl_2.2H_2O$, moist THF, (4) Zn/$CuCl_2.2H_2O$, moist THF, no reaction, (5) In/H_2O, moist THF, no reaction.

Scheme 4.13

Table 4.1 Intramolecular allylation of aldehyde **4.107**

Entry	Metal/salt or Metal salt/ metal	Solvent	Time(hr)	Overall yield of **32** (%)	**32a & 32b:32c:32d**[a]
a	Zn/ NH_4Cl	THF	18	74.7	8.7: 20.8: 70.5
b	$FeCl_3$/Zn	THF	18	68.2	10.2: 23.2: 66.6
c	$SnCl_2.2H_2O$ / Zn	THF	18	87.5	11.4: 62.7: 25.9
d	$CuCl_2.2H_2O$ / Zn	THF	18	NR	-
e	In	H_2O / THF	48	NR	-

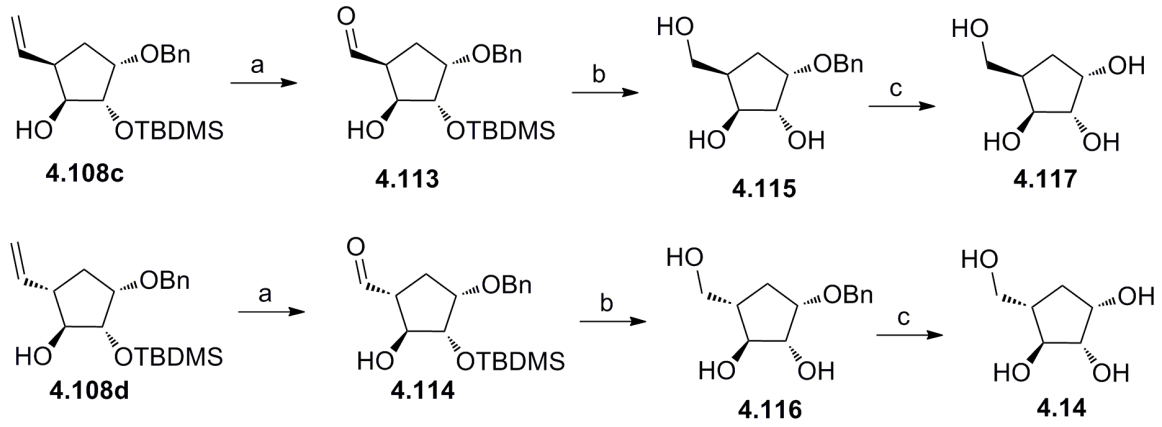
NR: No reaction; a) relative ratio of chromatographically separated product

Luche's allylation of **4.107** produced **4.108** in good yield. (74.7 %, **Table 1**, entry a). The product contained a mixture of its all four possible diastereomers (**4.108a-d**). Column chromatography of the product first eluted an inseparable mixture of **4.108a** and **4.108b** (**Figure 4.59-4.60**), (Our attempt to separate **4.108a** from **4.108b** by column chromatography of the fraction containing their mixture using several solvent mixtures as

eluents became unsuccessful.) followed by isolation of **4.108c** (**Figure 4.61-4.62**) and **4.108d** (**Figure 4.63-4.64**) successively to obtain each of them in their homochiral form. This reaction yielded **4.108d** as the major product, while **4.108c** was produced in higher amount than **4.108a/4.108b** together (**Table 1**, entry a). Low valent iron[37d] mediated reaction produced **4.108**, albeit in less yield (68.2 %, **Table 1**, entry b) compared to Luche's allylation. In this case also the reaction afforded **4.108d** as the major product. Low valent tin mediated reaction[37d] was found to be more efficacious compared to both the previous reactions that was evident from improved yield of **4.108** in this case (87.5 %, **Table 1**, entry c). However, this reaction yielded **4.108c** as the major product. Unfortunately, our next attempt to perform the same intramolecular allylation of **4.107** , separately in presence of low valent copper[37d] and Indium[189] mediators were found to be absolutely unsuccessful, as no reaction took place in either case even after stirring the reaction mixture for longer period (**Table 1**, entries d & e). The stereo-selectivity of all these successful allylation reactions (entries a-c, **Table 1**) could be determined after isolating the separable components of **4.108** by column chromatography as described earlier.

The stereochemistry of **4.108c** could be established by transforming it into a known carba α-**D**-xylofuranose **4.113**[183q] through a number of steps (**Scheme 4.14**) that involved its functional manipulation only without affecting any of its stereo-centers. Accordingly, **4.108c** was subjected to a series of reactions *viz*. a) ozonolysis and *in situ* PPh_3 reduction of the resulting crude ozonide to aldehyde **4.109**, c) $LiAlH_4$ reduction of the crude aldehyde obtained which took place with concomitant desilylation to afford **4.111** (NMR spectra in **Figure 4.65-4.66**). This on catalytic hydrogenation afforded **4.113** whose optical and spectral data (**Figure 4.69-4.70**) were in well conformity with the reported ones of α-**D**-xylofuranose $[\alpha]_D^{26}$ = 12.7 (c, 1.0, MeOH) [lit.,[183q] $[\alpha]_D^{20}$ = 12.1 (c,

0.7, MeOH)]. Following the same reactions protocol, **4.108d** was transformed into carba-*β*-**L**-arabinofuranose **4.14** through intermediate **4.112** (**Figure 4.67-4.68**). The optical as well as spectral data of our synthesized **4.14** (**Figure 4.71-4.72**) were in accordance with the reported ones of carba-*β*-**L**-arabinofuranose $[\alpha]_D^{24}$ = -8.6 (c, 1.4, MeOH) [lit.,[183f] $[\alpha]_D^{20}$ = -7.9 (c, 1.2, MeOH)].



a) O_3, PPh_3, CH_2Cl_2, -78 °C; b) $LiAlH_4$, Et_2O; c) 10% Pd/C, H_2, EtOH.

Scheme 4.14

The preferential formation of **4.108c,d** in the three successful intramolecular metal mediated allylations (**Table 1**, entries a-c) suggested that all these reactions predominantly took place through Felkin-Anh model[26a,27c] (**Figure-4.43**).

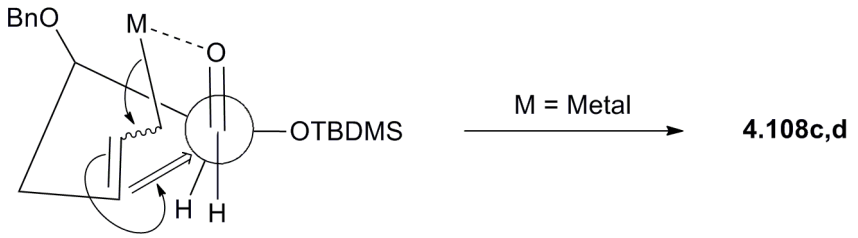


Figure 4.43 Felkin-Anh model for the major products

On the other hand, the opposite stereochemistry at C-4 in the two major products (4*R* in **4.108c** and 4*S* in **4.108d**) suggested that there was a possibility of isomerization between the initially formed *E*-crotyl metal (**E-M**) (from **4.107**) and *Z*-crotyl metal (**Z-M**). This was followed by intramolecular allylation of the aldehyde functionality through the corresponding Zimmerman-Traxler transition states (**Figure-4.44**).[30a,37d,61,191] Thus,

the relative ratio between two Felkin- Anh products **4.108c** and **4.108d** obtained in each of the successful reactions (**Table 1**, entries a-c) largely depended on the degree of isomerization between the corresponding ***E***-crotyl metal and ***Z***-crotyl metal during the reaction.

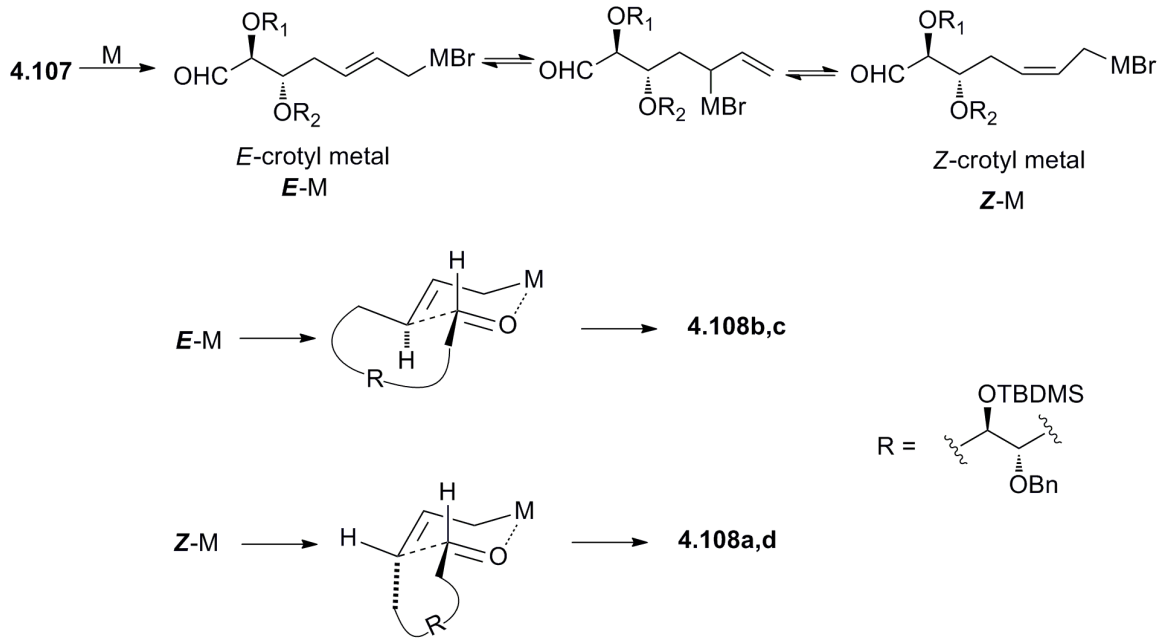


Figure 4.44 Zimmerman-Traxler transition states

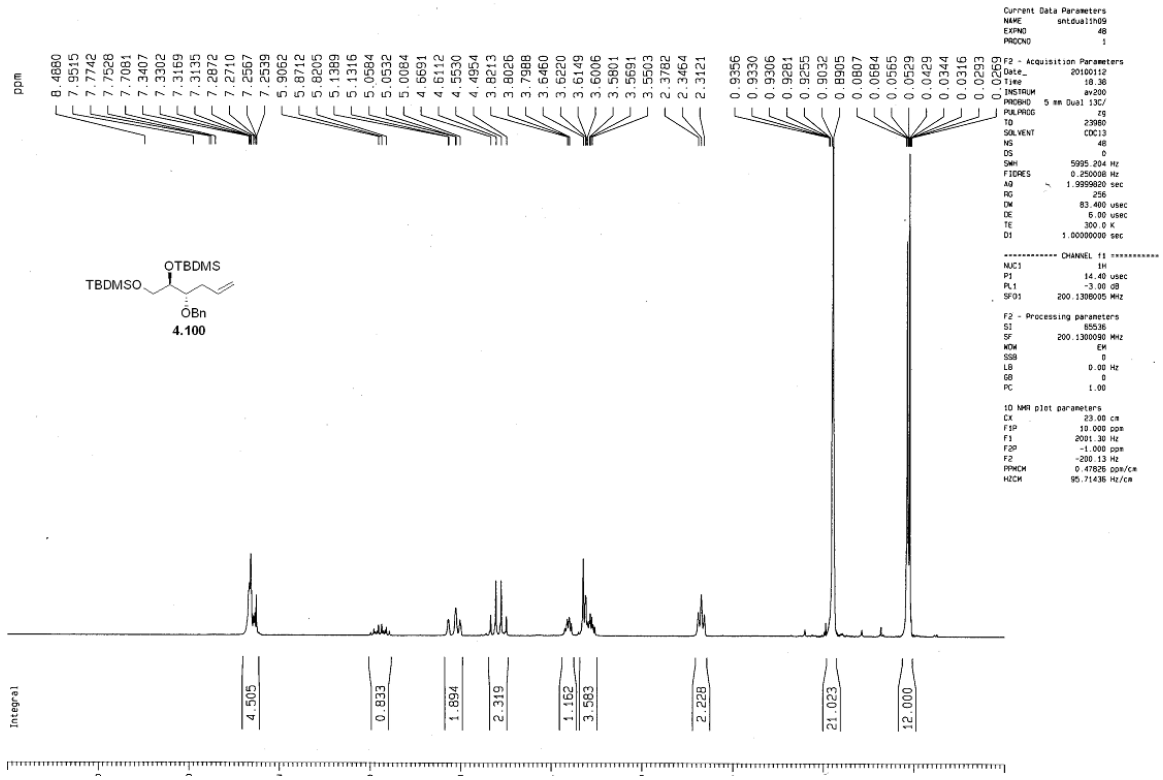


Figure 4.45 ^{1}H NMR spectrum of 4.100

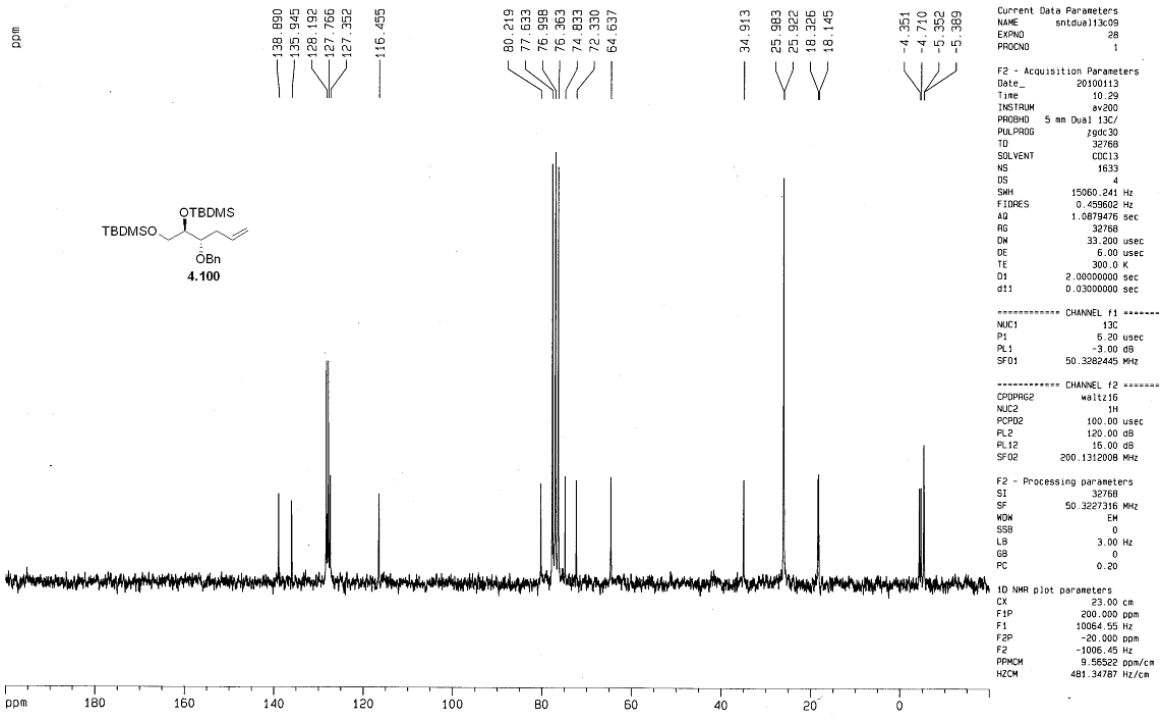


Figure 4.46 ^{13}C NMR spectrum of 4.100

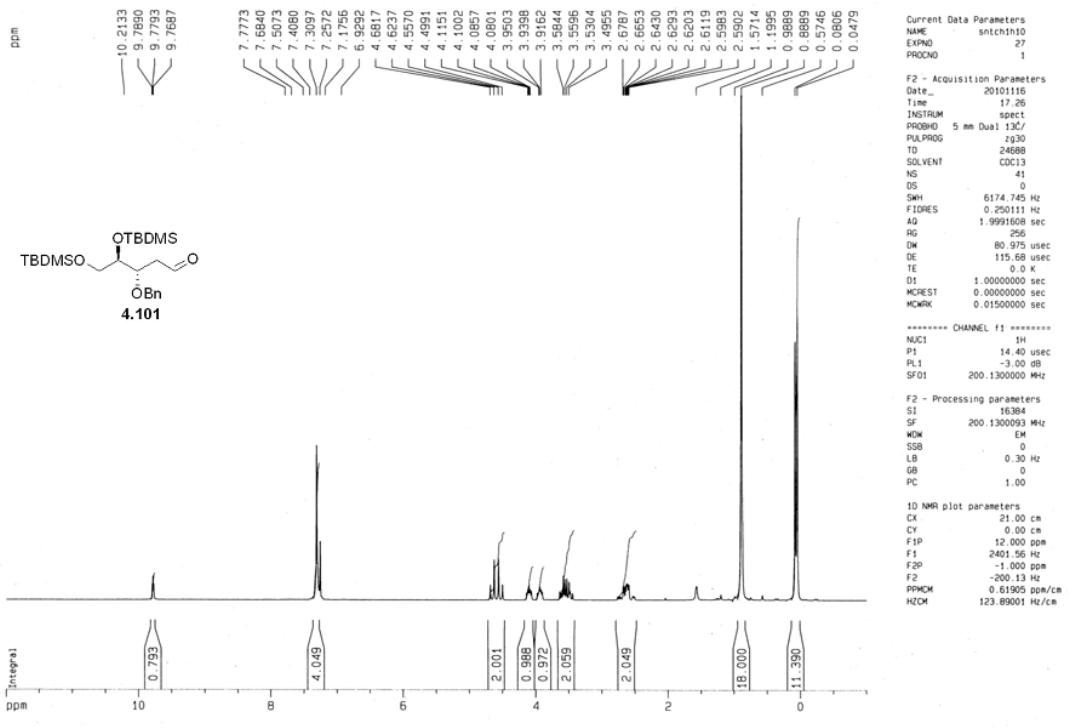


Figure 4.47 ^{1}H NMR spectrum of 4.101

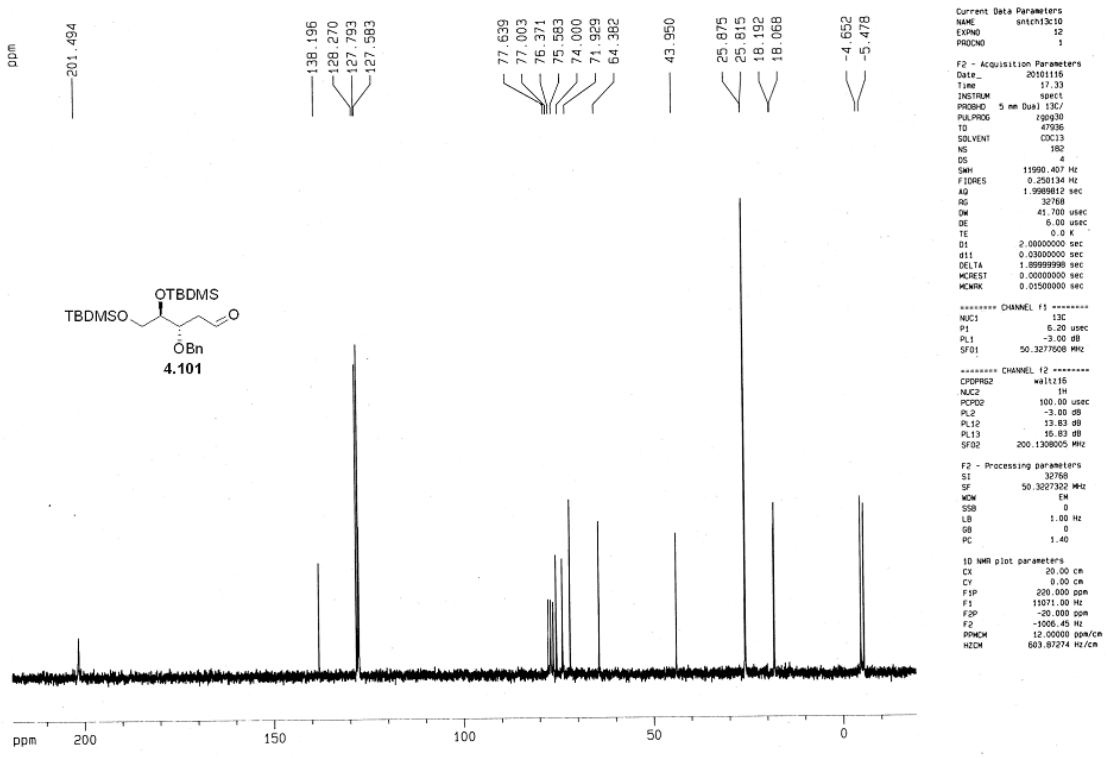


Figure 4.48 ^{13}C NMR spectrum of 4.101

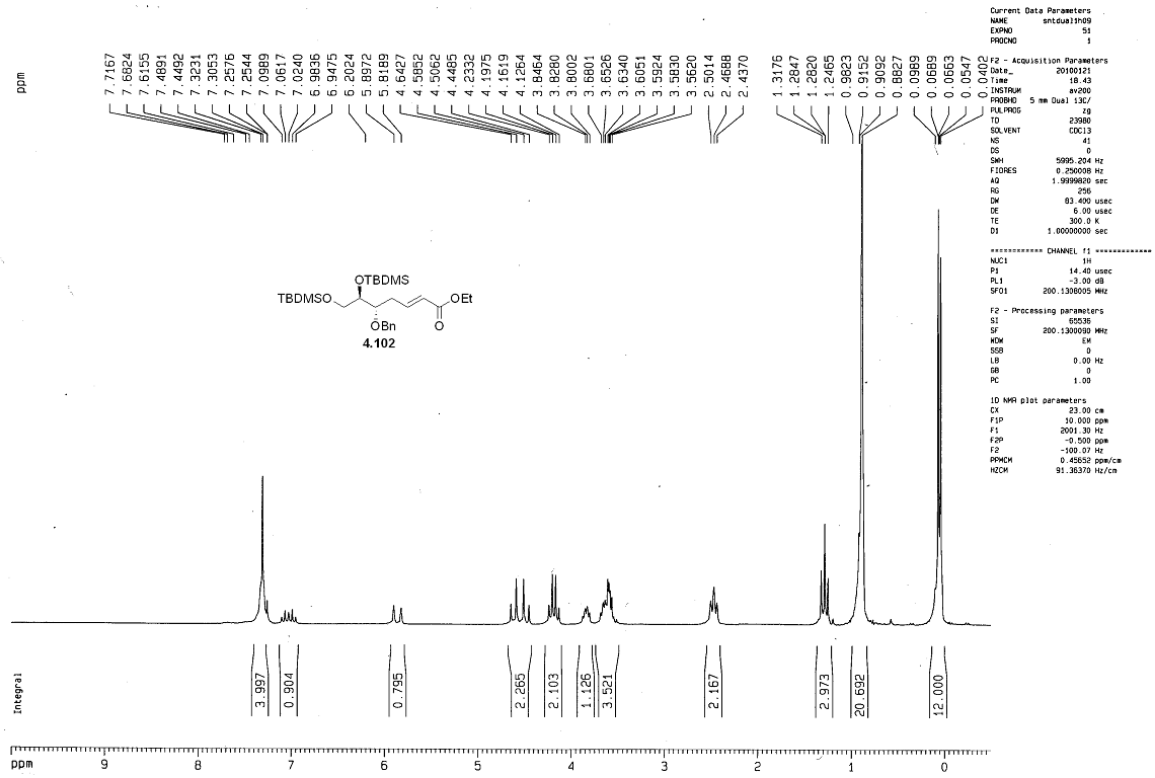


Figure 4.49 ^{1}H NMR spectrum of 4.102

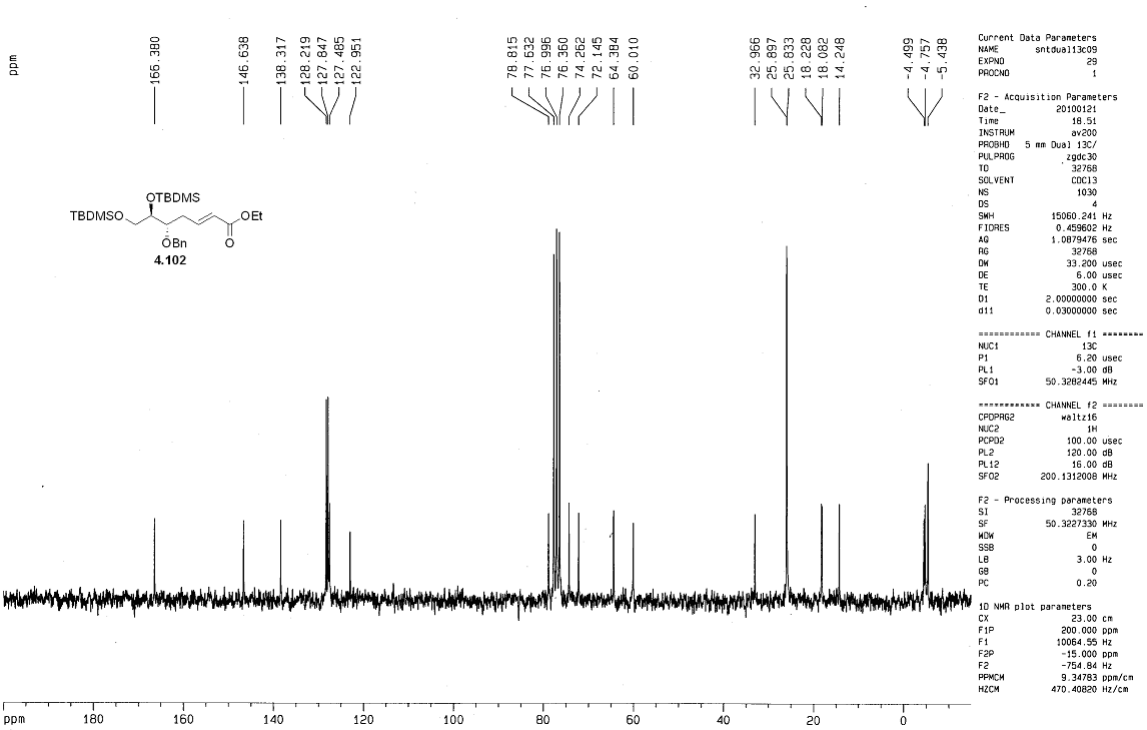


Figure 4.50 ^{13}C NMR spectrum of 4.102

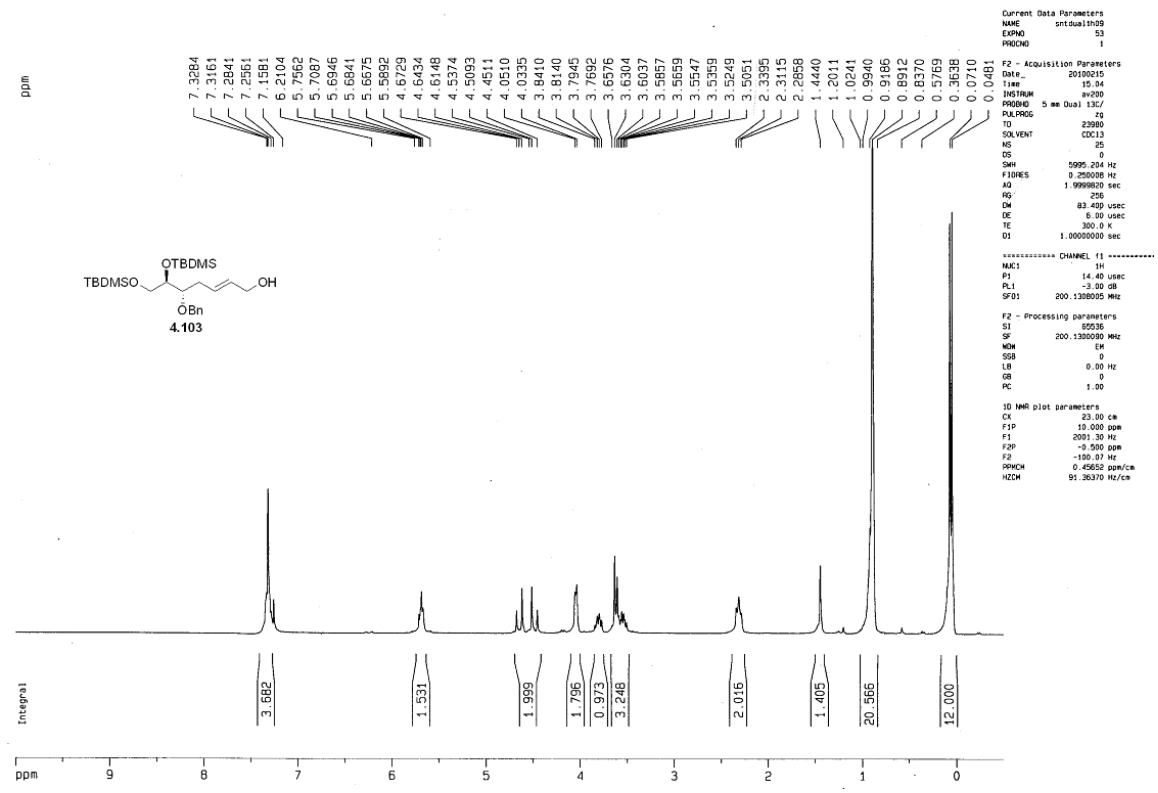


Figure 4.51 ^{1}H NMR spectrum of 4.103

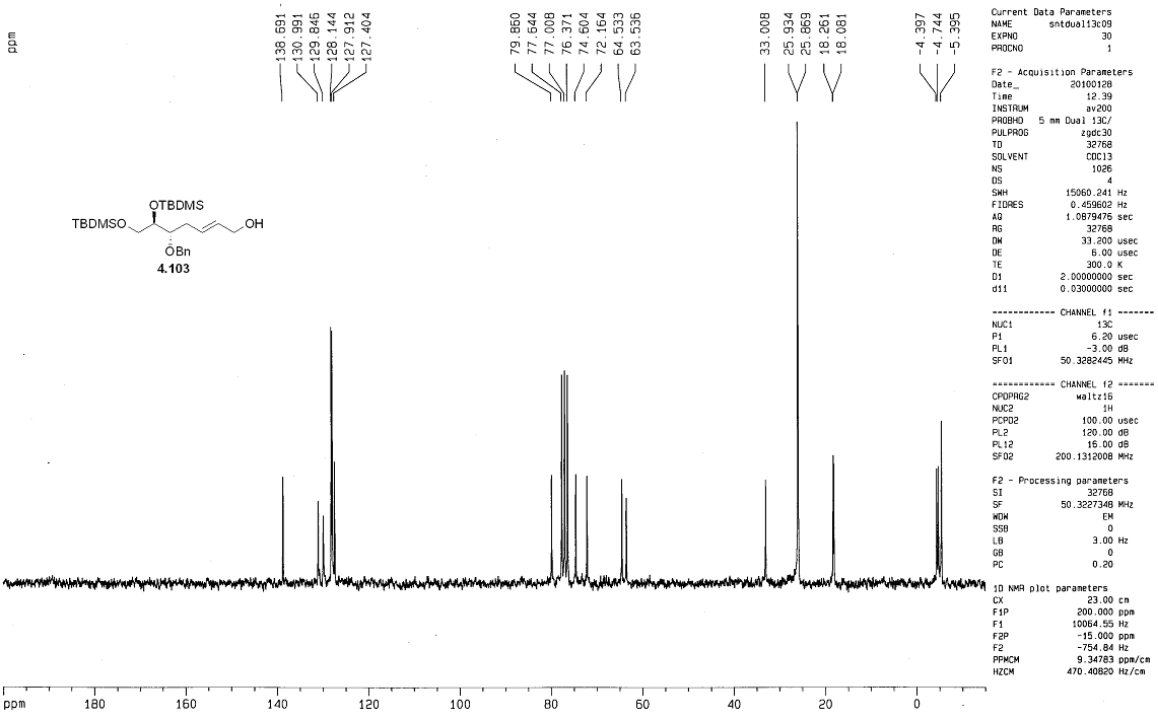


Figure 4.52 ^{13}C NMR spectrum of 4.103

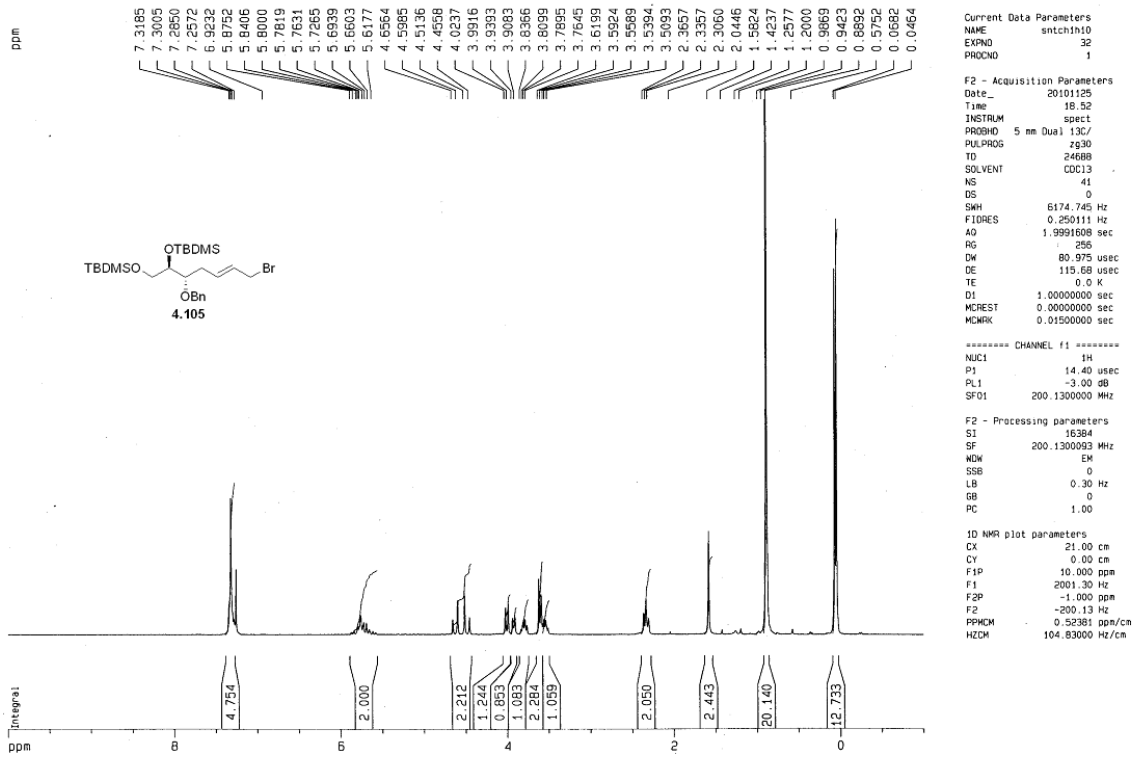


Figure 4.53 ^{1}H NMR spectrum of 4.105

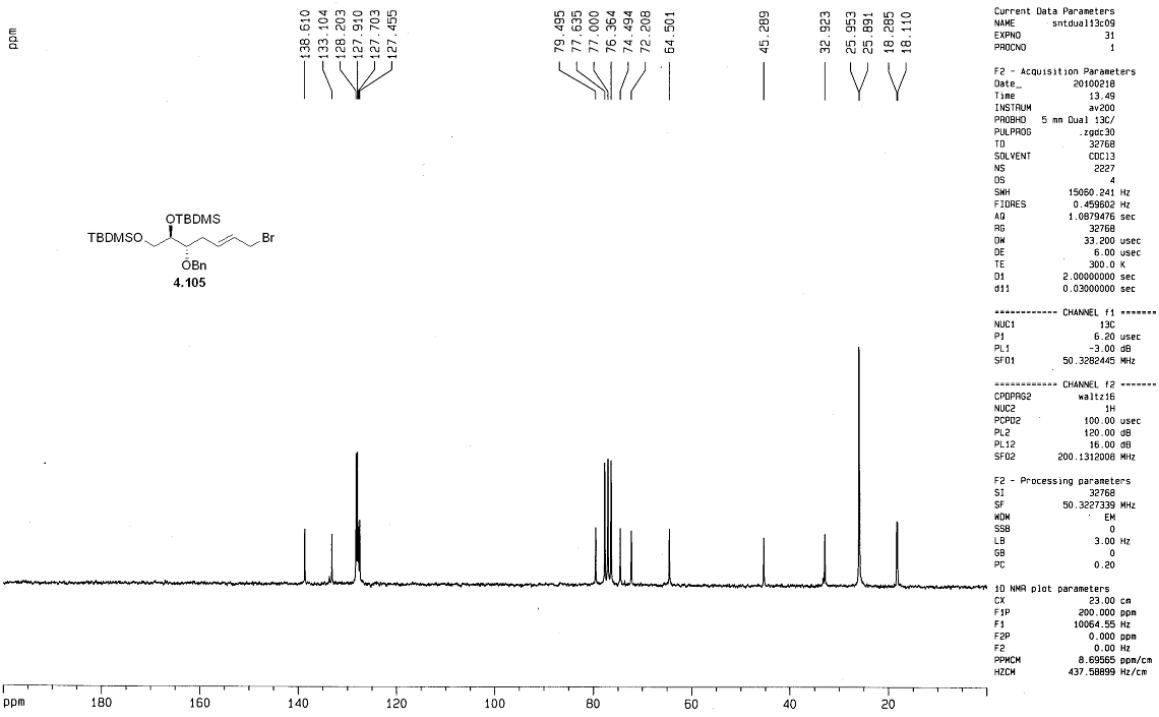


Figure 4.54 ^{13}C NMR spectrum of 4.105

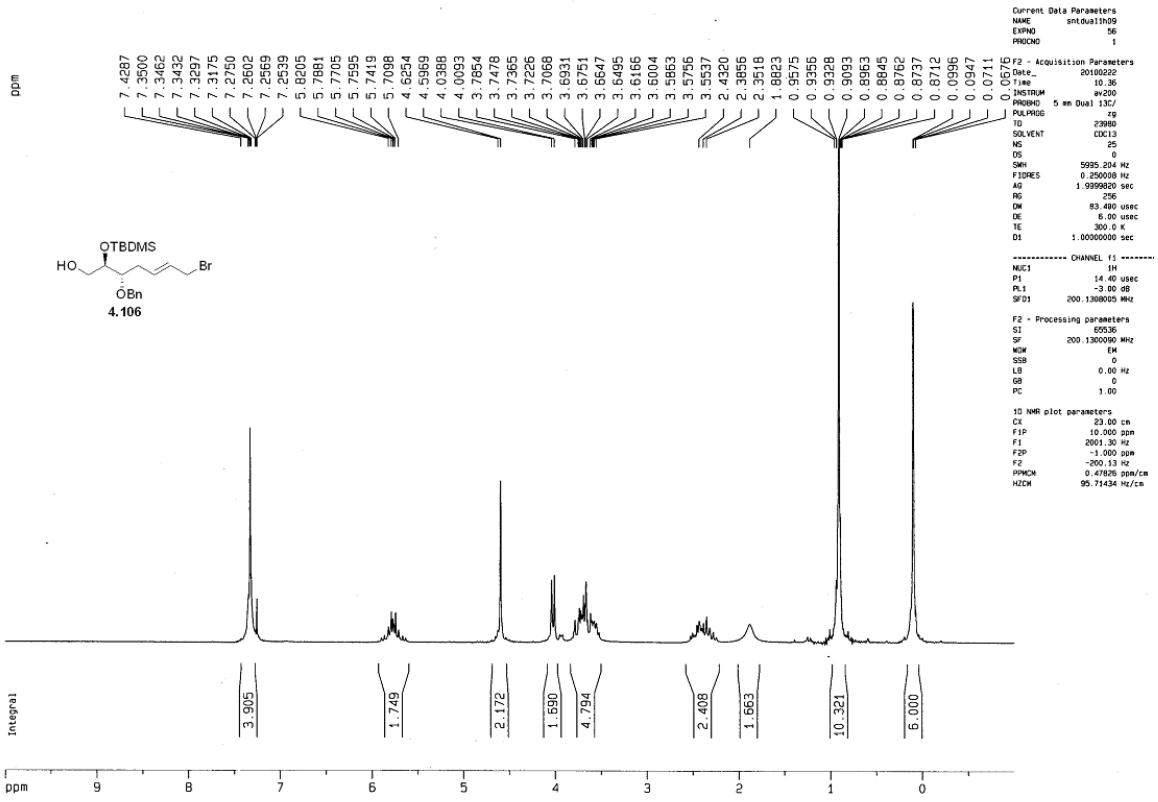


Figure 4.55 ^{1}H NMR spectrum of 4.106

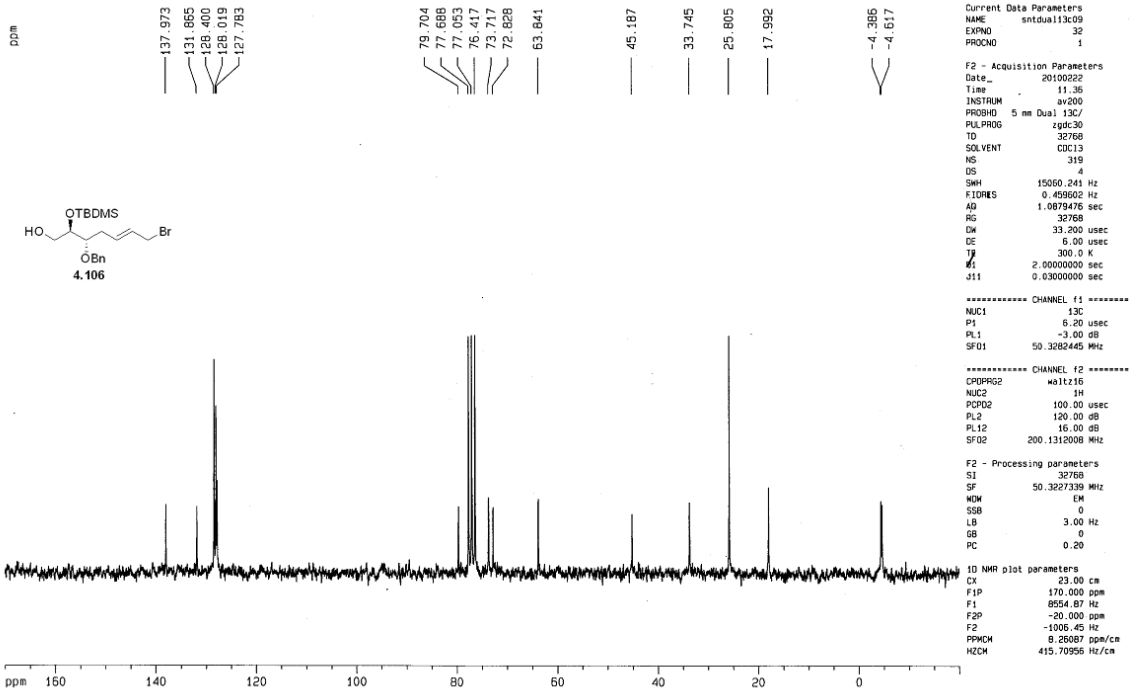


Figure 4.56 ^{13}C NMR spectrum of 4.106

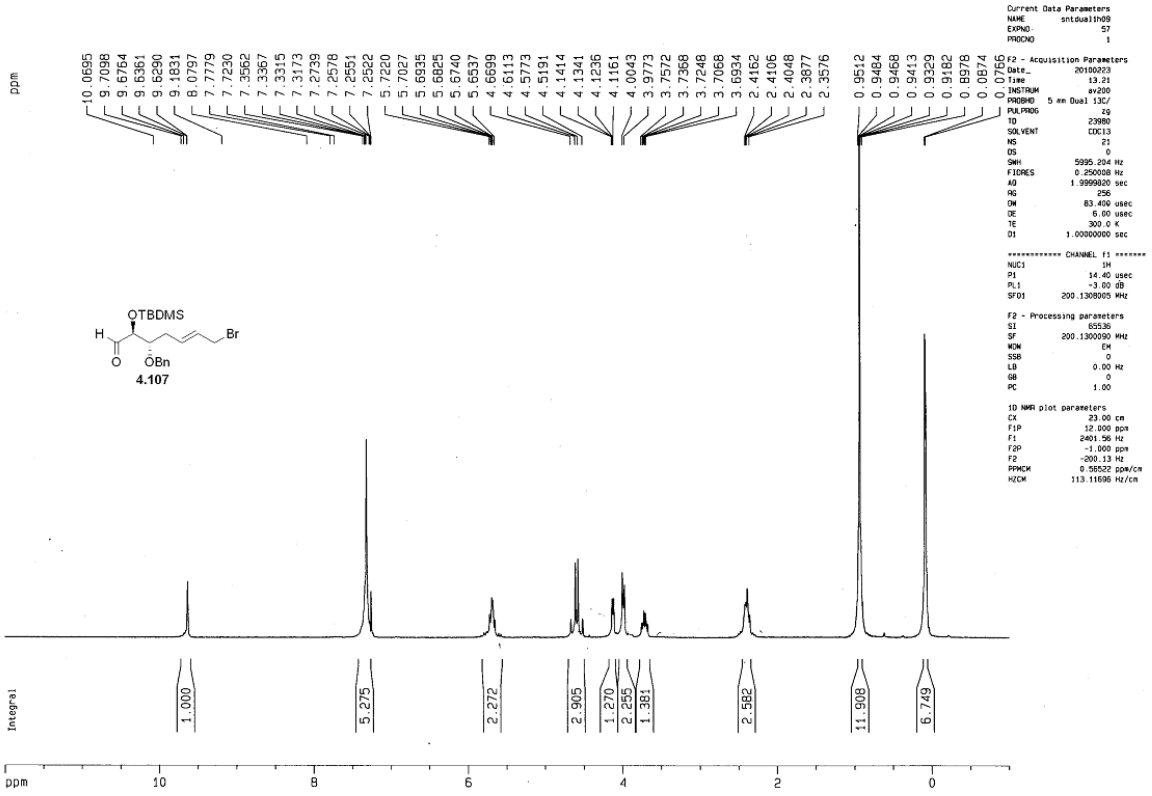


Figure 4.57 ^{1}H NMR spectrum of 4.107

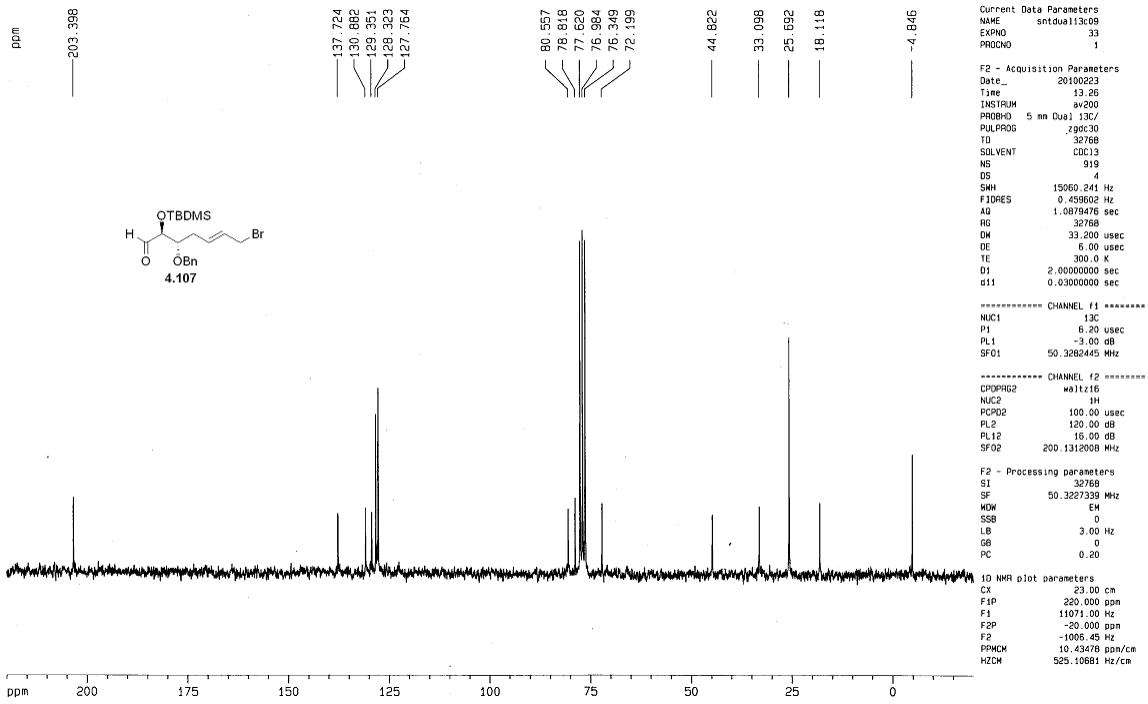


Figure 4.58 ^{13}C NMR spectrum of 4.107

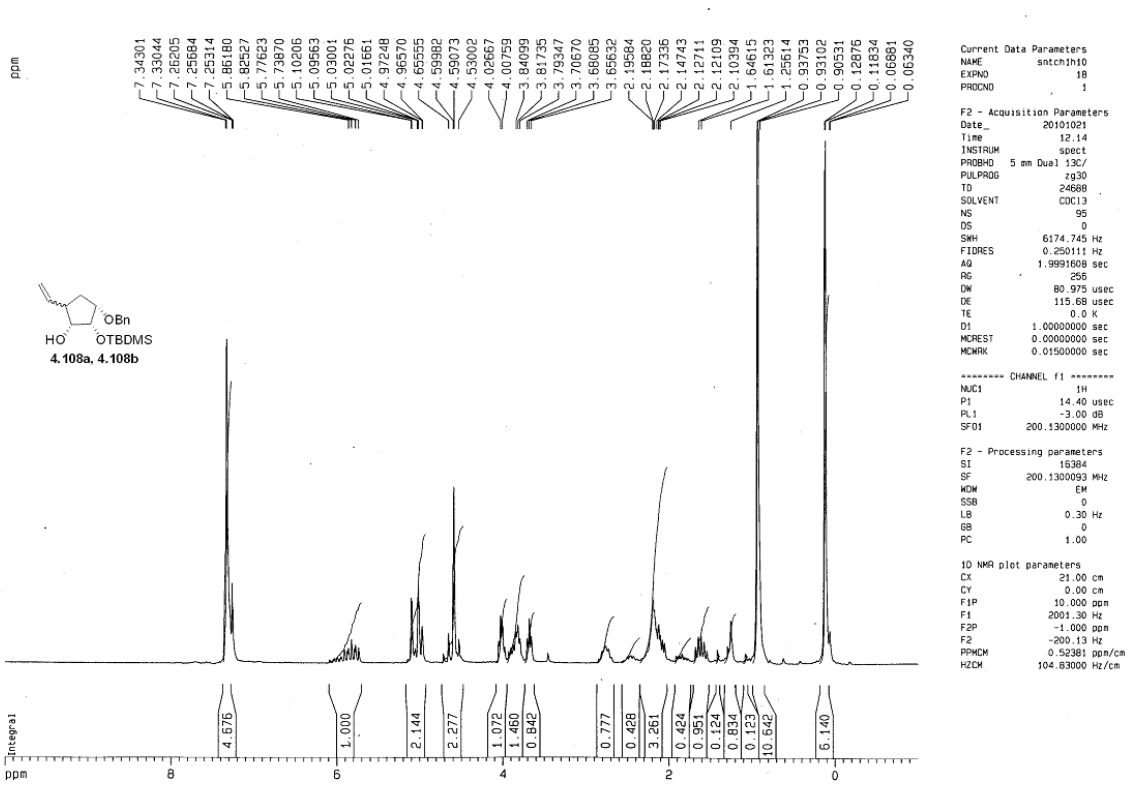


Figure 4.59 ^{1}H NMR spectrum of 4.108a, 4.108b

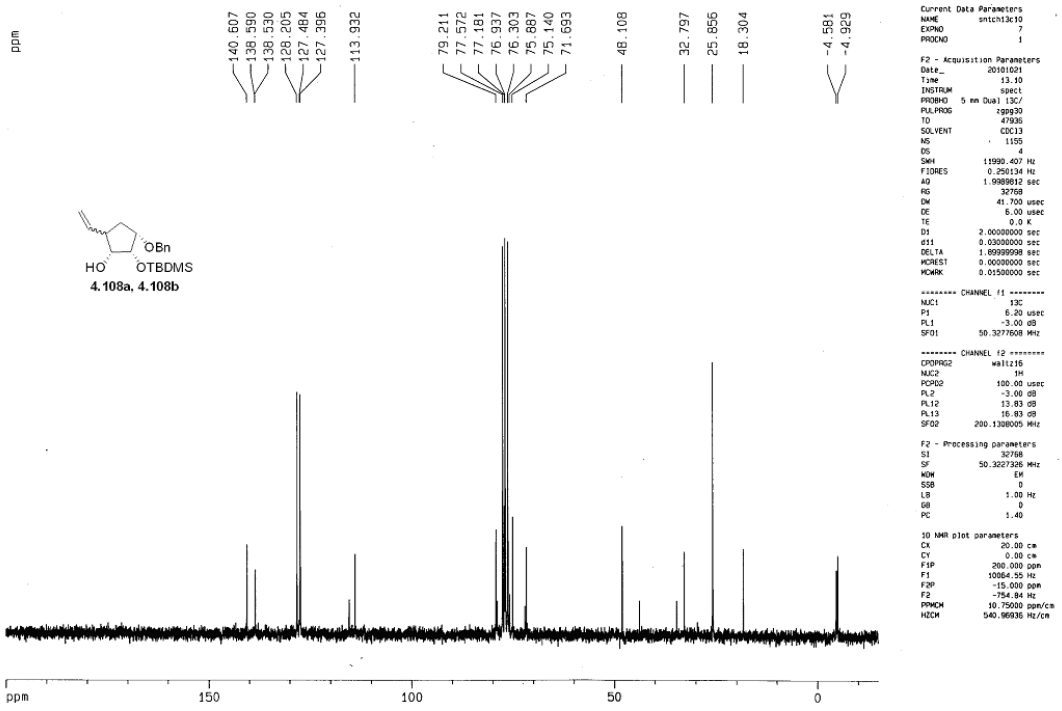


Figure 4.60 ^{13}C NMR spectrum of 4.108a, 4.108b

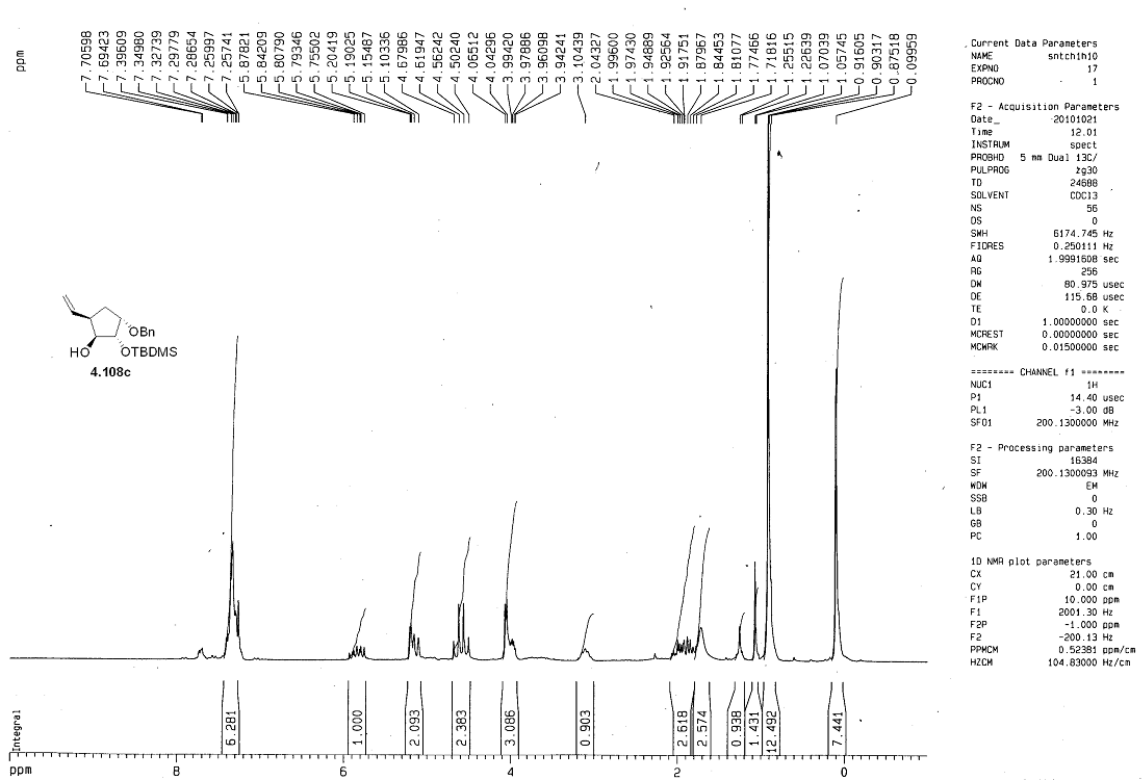


Figure 4.61 ^{1}H NMR spectrum of 4.108c

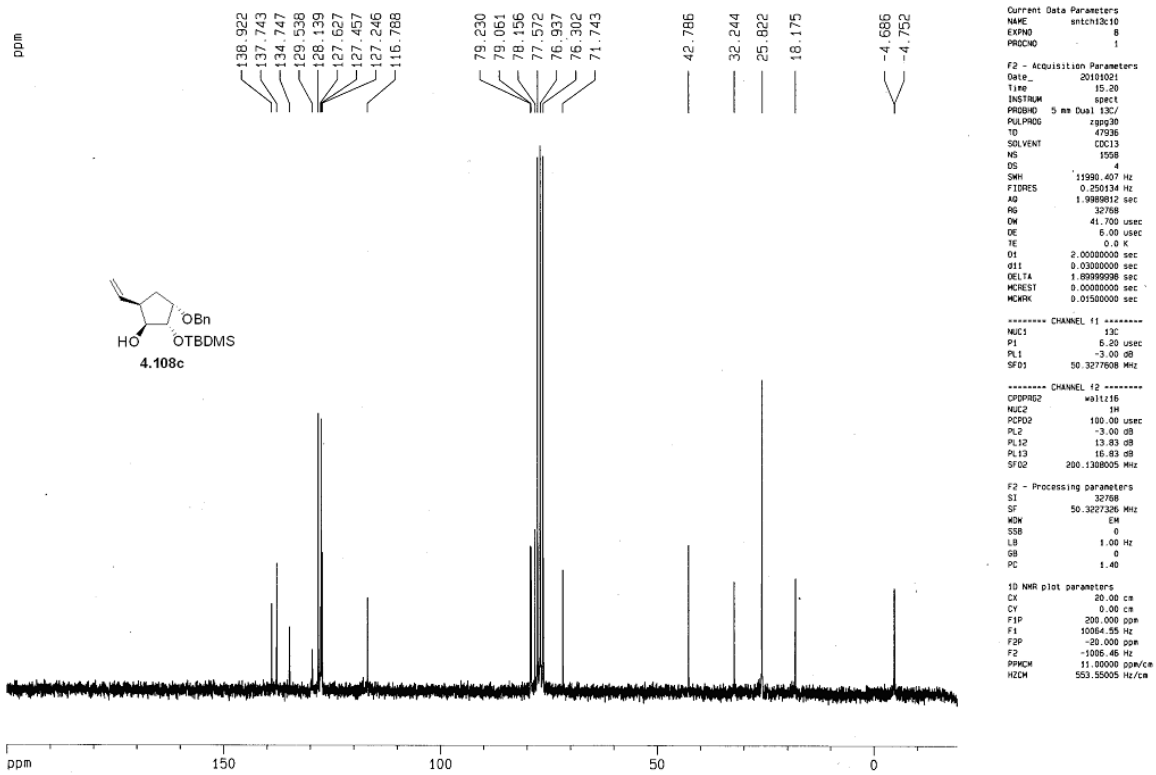


Figure 4.62 ^{13}C NMR spectrum of 4.108c

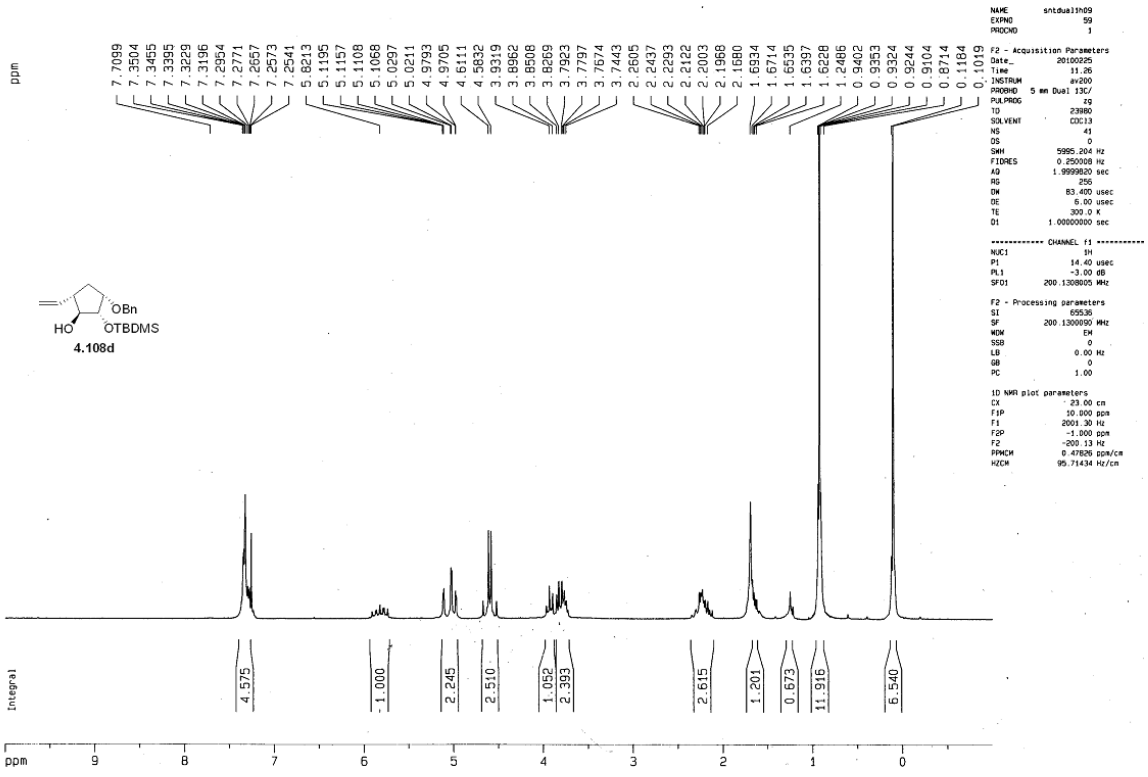


Figure 4.63 ^{1}H NMR spectrum of 4.108d

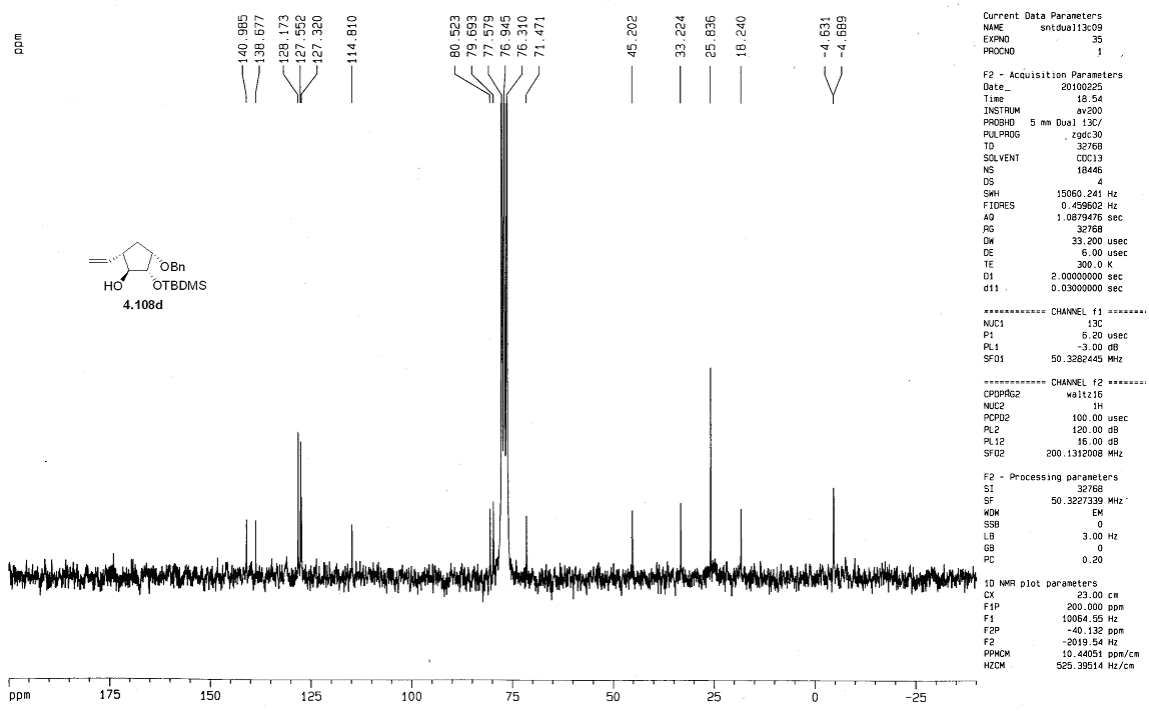


Figure 4.64 ^{13}C NMR spectrum of 4.108d

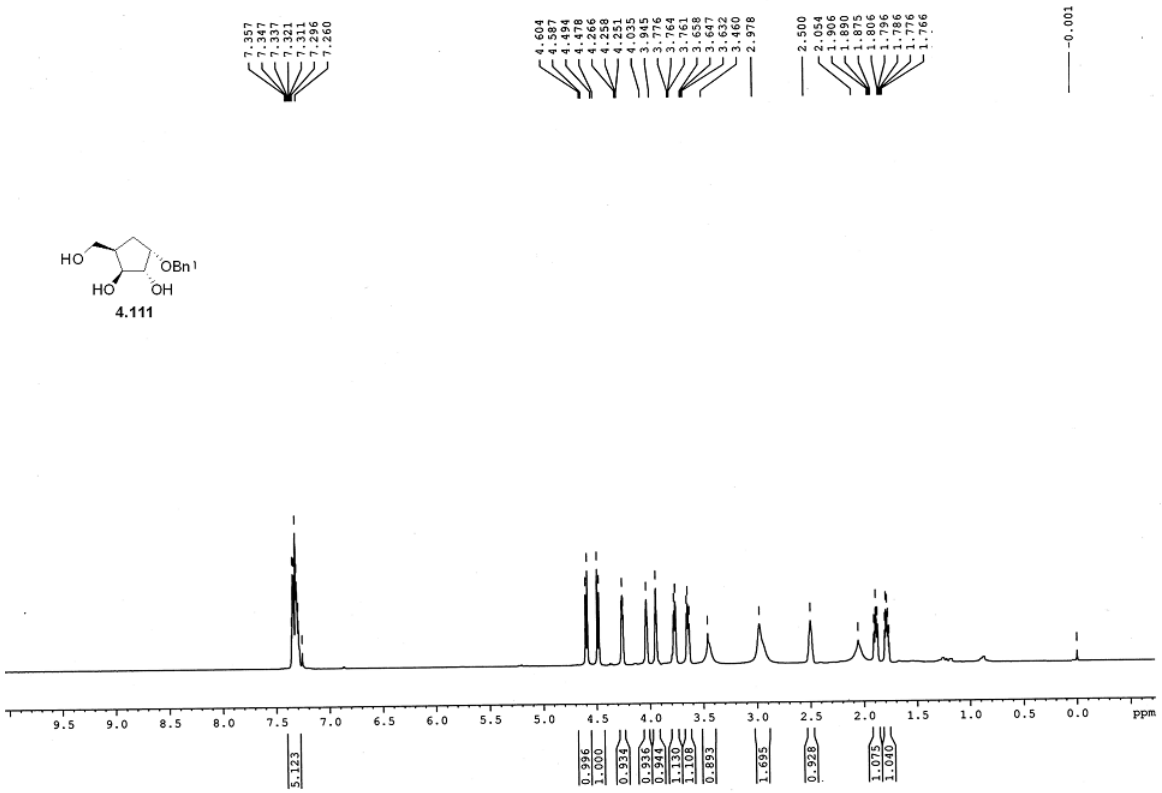


Figure 4.65 ^{1}H NMR spectrum of 4.111

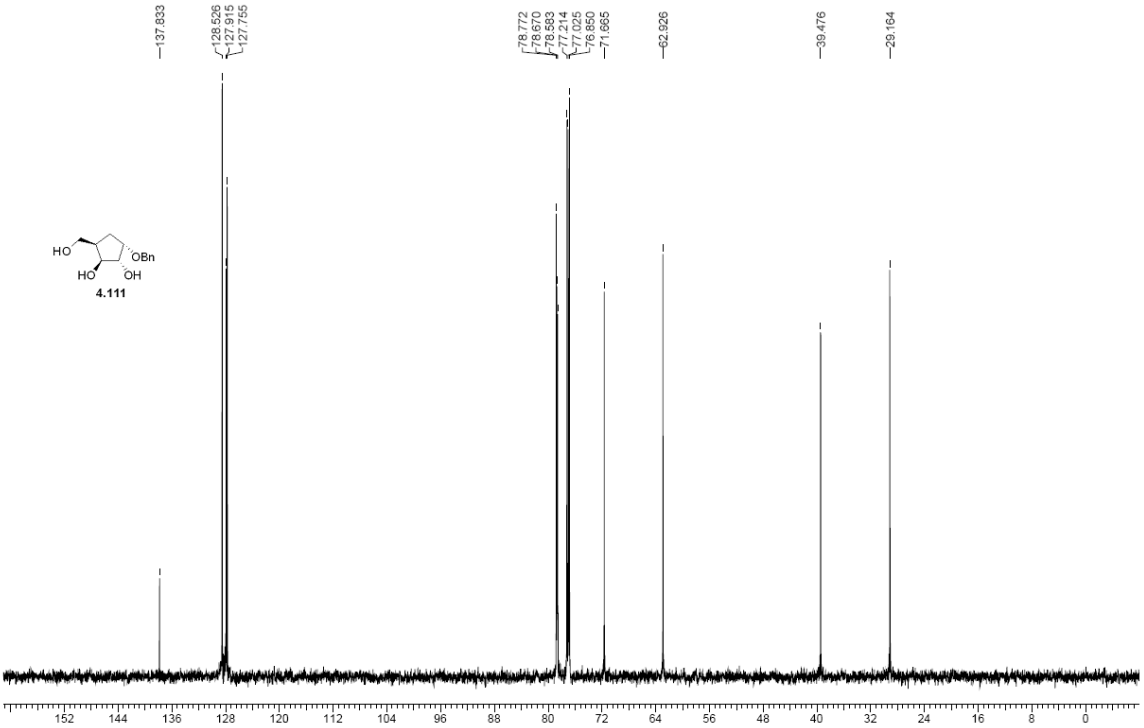


Figure 4.66 ^{13}C NMR spectrum of 4.111

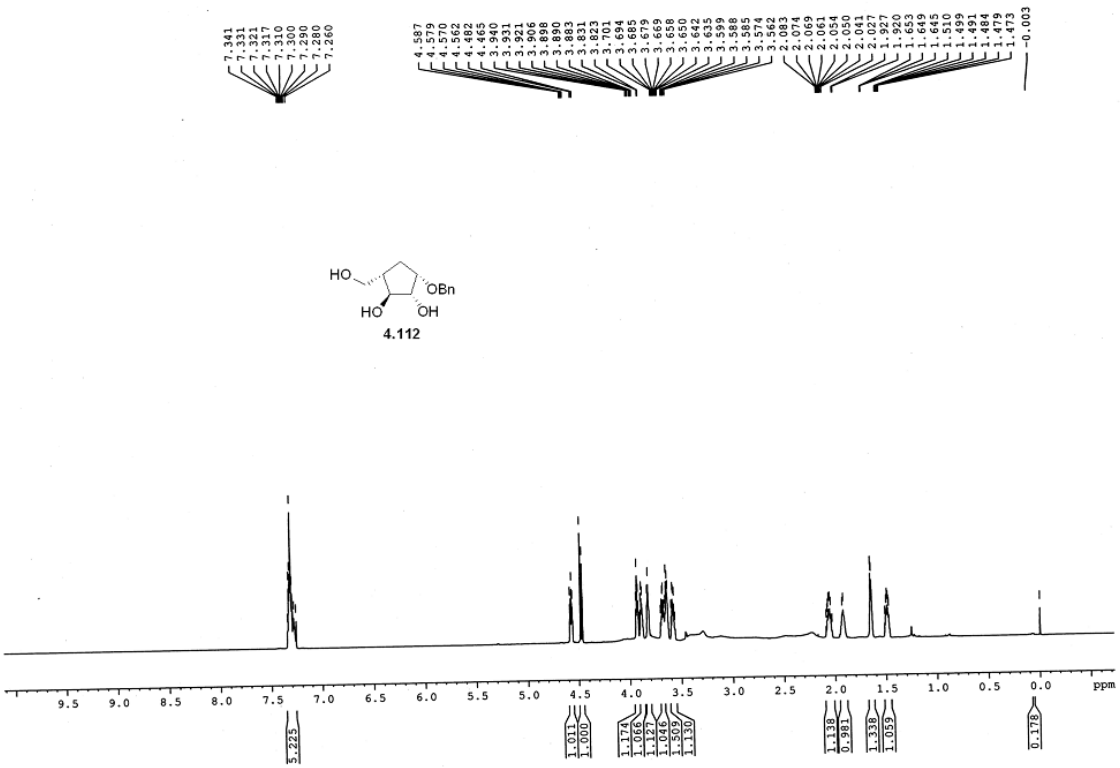


Figure 4.67 ^{1}H NMR spectrum of 4.112

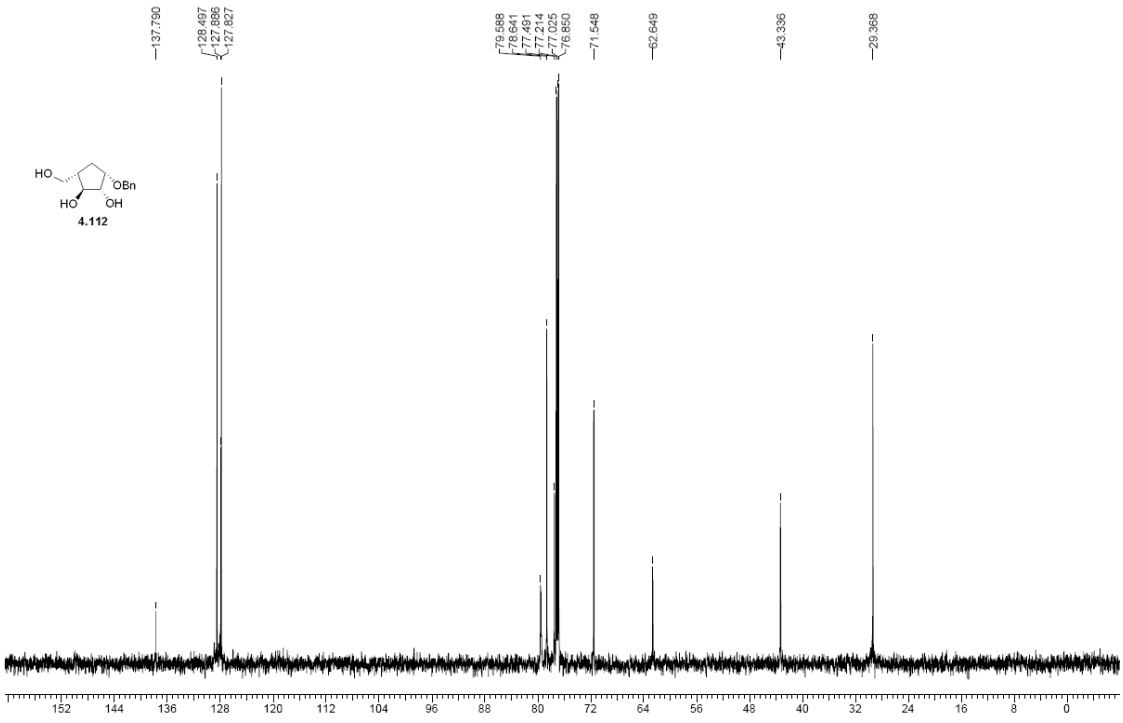


Figure 4.68 ^{13}C NMR spectrum of 4.112

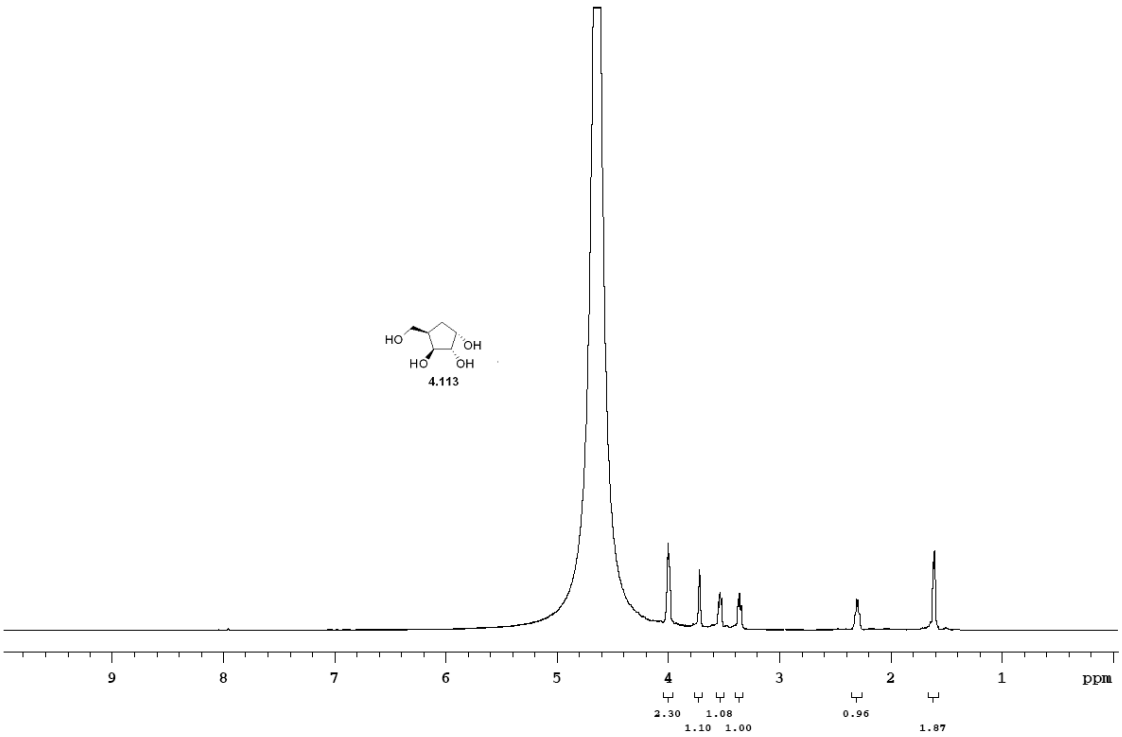


Figure 4.69 ^{1}H NMR spectrum of 4.113

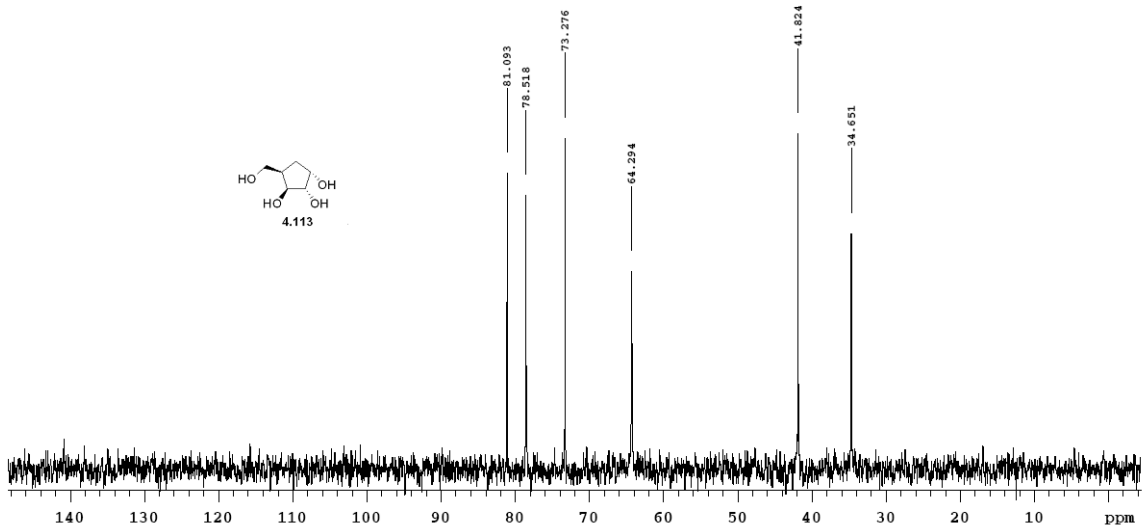


Figure 4.70 ^{13}C NMR spectrum of 4.113

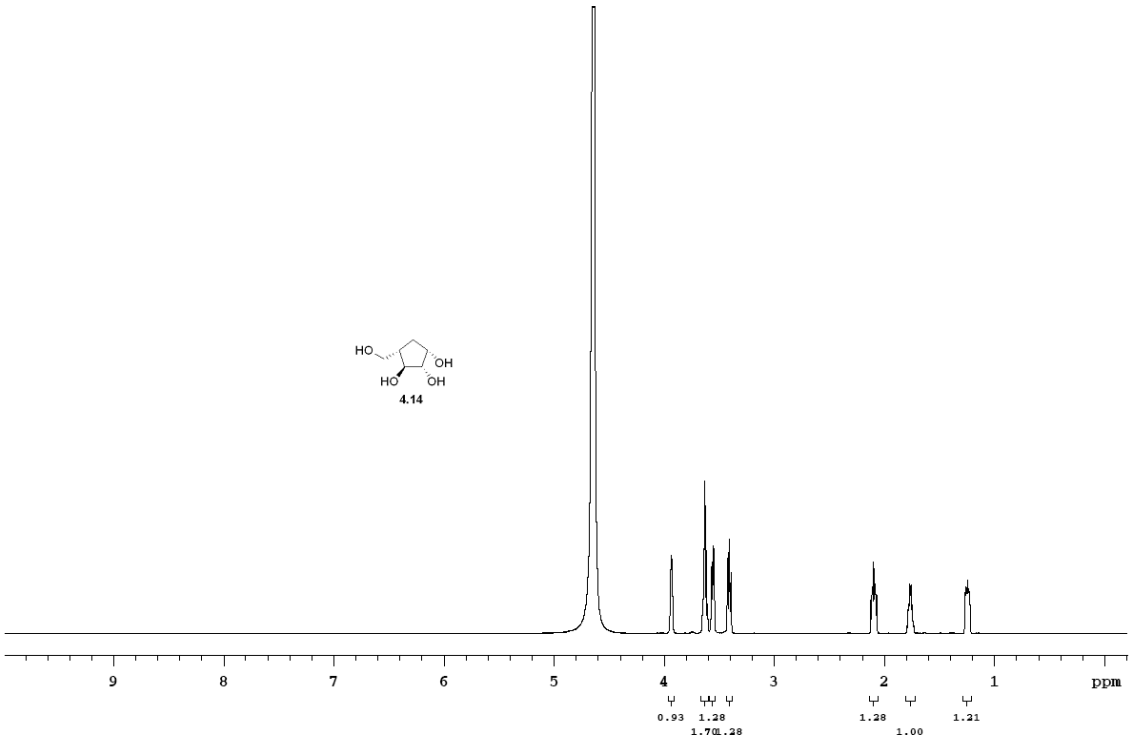


Figure 4.71 ^{1}H NMR spectrum of 4.14

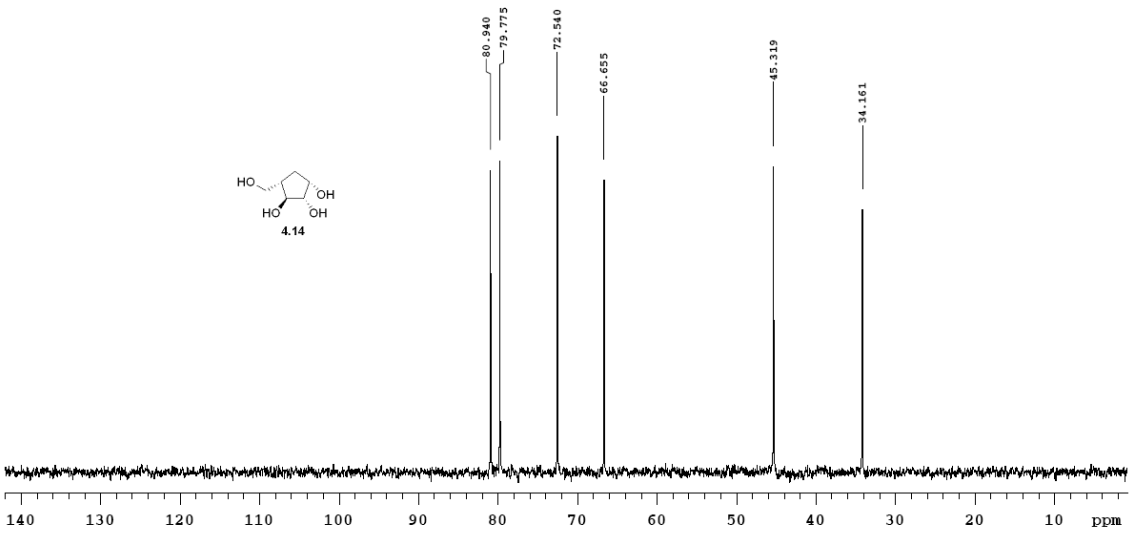


Figure 4.72 ^{13}C NMR spectrum of 4.14

4.IV Experimental

(5*S*,6*R*)-1-*O*-benzoyl-5-*O*-*tert*-butyl-diphenylsilyl-6,7-*O*-cyclohexylidene-1,5,6,7-tetrahydroxyhept-2*E*-ene (4.81):

To a cooled (0 °C) solution of the alcohol **2.99** (4.2 g, 10.27 mmol) and triethylamine (1.35 g, 13.83 mmol) in dry CH_2Cl_2 (50 ml) a solution of benzoyl cyanide (1.62 g, 12.35 mmol) in dry CH_2Cl_2 (20 ml) was added in 5 minute. The mixture was stirred at 0 °C for 1 hour and then at room temperature for 4 hour. The solution was treated with water. The organic layer was separated and the aqueous layer was washed with water and extracted with $CHCl_3$. The combined organic layer was washed with *dil.* aqueous HCl (2%) till neutral, water to remove get rid of HCl, brine and dried over Na_2SO_4. Solvent removal under reduced pressure, column chromatography (silica gel, 0-5% EtOAc in Hexane) of the residue afforded pure **4.81** (4.86 g, 95%).

$[\alpha]_D^{27}$ = +20.22 (c, 1.09, $CHCl_3$); ^{1}H NMR (200 MHz $CDCl_3$): δ 1.04 (s, 9H), 1.35-1.6 (m, 10H), 2.2 (m, 2H), 3.71 (t, *J* = 7.2 Hz, 1H), 3.8 (m, 2H), 4.02 (q, *J* = 6.2 Hz, 1H), 4.67 (d, *J* = 5.8 Hz, 2H), 5.5-5.6 (m, 1H), 5.69-5.7 (m, 1H), 7.3-7.4 (m, 9H), 7.6-7.7 (m, 4H), 7.8-8.0 (m, 2H); ^{13}C NMR (50 MHz $CDCl_3$): δ 19.4, 23.8, 23.9, 25.2, 27.0, 34.7, 36.2, 37.1, 65.2, 66.3, 67.3, 73.5, 76.6, 109.3, 126.8, 127.5, 127.6, 128.2, 129.5, 129.7, 129.8, 130.3, 131.0, 132.8, 133.5, 133.8, 135.9, 166.1; Anal. Calcd. for $C_{36}H_{44}O_5Si$: C, 73.94; H, 7.58. Found: C, 74.15; H, 7.66.

(5*S*,6*R*)-1-*O*-benzoyl-5-*O*-*tert*-butyl-diphenylsilyl-1,5,6,7-tetrahydroxyhept-2*E*-ene (4.82):

To a cooled (0 °C) solution of **4.81** (4.6 g, 7.87 mmol) in distilled CH_2Cl_2 (30 ml) was added 80% aqueous trifluoroacetic acid (10 ml). The mixture was stirred for three hour at 0 °C. The reaction mixture was diluted with $CHCl_3$ and water. The aqueous layer

was extracted with $CHCl_3$. The combined organic layer was washed successively with 2% $NaHCO_3$ for neutrality, water and brine and dried over Na_2SO_4. Solvent removal under reduced pressure and column chromatography (silica gel, 0-5% MeOH in $CHCl_3$) of the residue afforded pure **4.82** (2.85 g, 72%).

$[\alpha]_D^{27}$ = +23.4 (c, 1.12, $CHCl_3$); ^{1}H NMR (200 MHz $CDCl_3$): δ 1.06 (s, 9H), 1.83 (bs, 2H), 2.1-2.3 (m, 2H), 3.62-3.78 (m, 3H), 3.86-3.94 (m, 1H), 3.9 (q, *J* = 6.2 Hz, 1H), 4.62 (d, *J* = 4.6 Hz, 2H), 5.4-5.6 (m, 2H), 7.3-7.4 (m, 9H), 7.6-7.7 (m, 4H), 7.8-8.0 (m, 2H); ^{13}C NMR (50 MHz $CDCl_3$): δ 19.2, 26.8, 35.7, 63.0, 65.1, 73.7, 74.0, 126.5, 127.4, 127.5, 128.1, 129.4, 129.69, 129.72, 129.9, 130.9, 132.7, 132.9, 133.3, 135.7, 166.2; Anal. Calcd for $C_{30}H_{36}O_5Si$: C, 71.39; H, 7.19. Found: C, 70.98; H, 7.38.

(5*S*,6*R*)-1-*O*-benzoyl-1,5,6,7-tetrahydroxyhept-2*E*-ene (4.83):

Tetrabutylammonium fluoride in THF (8.0 ml, 1M solution) was added to a cooled (0 ^{O}C) solution of **4.82** (2.7 g, 5.35 mmol) in THF (20 ml). The resulting solution was stirred for 1 hour and after the completion of reaction confirmed by TLC the reaction was quenched by the addition of saturated aqueous solution of NH_4Cl (5 ml). The mixture was diluted with EtOAc while two phases were separated. The aqueous phase was extracted with EtOAc. The combined organic layer was washed successively with water, brine and dried over Na_2SO_4. Solvent removal under reduced pressure and column chromatography of the residue (silica gel, 0-7 % MeOH in $CHCl_3$) afforded pure **4.83** (1.3 g, 92.8%).

$[\alpha]_D^{27}$ = +10.5 (c, 0.89, $CHCl_3$); ^{1}H NMR (200 MHz $CDCl_3$): δ 1.54 (bs, 3H), 2.1-2.3 (m, 2H), 3.08-3.16 (3, 2H), 3.54 (t, *J* = 5 Hz, 1H), 3.6 (m, 1H), 4.67 (d, *J* = 5.8 Hz, 2H), 5.6-5.9 (m, 2H), 7.3-7.5 (m, 3H), 7.91-7.96 (m, 2H); ^{13}C NMR (50 MHz $CDCl_3$): δ

35.8, 63.0, 65.4, 72.1, 73.9, 126.9, 128.3, 129.5, 129.9, 131.7, 133.0, 166.6; Anal. Calcd for $C_{14}H_{18}O_5Si$: C, 63.15; H, 6.81. Found: C, 63.11; H, 6.69.

(5*S*,6*R*)-1-*O*-benzoyl-7-*O*-*tert*-butyl-diphenylsilyl-1,5,6,7-tetrahydroxyhept-2*E*-ene (4.84):

To a cooled (0 °C) solution of **4.83** (1.2 g, 4.5 mmol) in dry CH_2Cl_2 (50 ml) Imidazole (336.6 mg, 4.95 mmol) was added followed by the addition of catalytic amount of DMAP. To the mixture 0 °C a solution of TBDPSCl (1.35 g, 4.92 mmol) in dry CH_2Cl_2 (60 ml) was added dropwise over a period of 4 hour. The reaction mixture was diluted with $CHCl_3$ and water. The aqueous layer was extracted with $CHCl_3$ and the combined organic layer was washed successively with 2% HCl for neutrality, water and brine and dried over Na_2SO_4. Solvent removal under reduced pressure and column chromatography (silica gel, 0-5% MeOH in $CHCl_3$) of the residue afforded pure **4.84** (1.73 g, 74.8%).

$[\alpha]_D^{27}$ = -2.23 (c, 0.804, $CHCl_3$); ^{1}H NMR (200 MHz $CDCl_3$): δ 1.06 (bs, 9H), 1.94 (bs, 2H), 2.2-2.3 (m, 2H), 3.62 (t, *J* = 5.4 Hz, 1H), 3.59-3.82 (m, 3H), 4.67 (d, *J* = 5.2 Hz, 2H), 5.7-5.9 (m, 2H), 7.3-7.6 (m, 9H), 7.63-7.68 (m, 4H), 8.01-8.06 (m, 2H); ^{13}C NMR (50 MHz $CDCl_3$): δ 19.03, 26.71, 35.7, 64.6, 65.2, 71.6, 73.2, 126.9,127.7, 128.2, 129.4, 129.8, 130.0, 131.6, 132.6, 132.8, 135.3, 166.2; Anal. Calcd for $C_{30}H_{36}O_5Si$: C, 71.39; H, 7.19. Found: C, 71.23; H, 6.95.

(5*S*,6*R*)-1-*O*-benzoyl-5,6-*O*-isopropylidene-7-*O*-*tert*-butyl-diphenylsilyl-1,5,6,7-tetrahydroxyhept-2*E*-ene (4.85):

To a cooled (0 °C) solution of **4.84** (1.6 g, 3.17 mmol) in dry CH_2Cl_2 (30 ml) PPTS (0.4 g, 1.59 mmol) was added followed by the addition of 2,3-dimethoxy propane

(0.7 g, 6.7 mmol). The mixture was gradually brought to room temperature and stirred overnight at same temperature. On completion of the reaction (cf. TLC) the reaction mixture was diluted with $CHCl_3$ and water. The aqueous layer was extracted with $CHCl_3$. The combined organic layer was washed successively with water and brine and dried over Na_2SO_4. Solvent removal under reduced pressure and column chromatography (silica gel, 0-5% EtOAc in Hexane) of the residue afforded pure **4.85** (1.63 g, 95.8%).

$[\alpha]_D^{27}$ = -5.41 (c, 1.25, $CHCl_3$); ^{1}H NMR (200 MHz $CDCl_3$): δ 1.05 (bs, 9H), 1.32 (s, 3H), 1.38 (s, 3H), 2.46 (m, 2H), 3.7 (m, 2H), 4.1-4.2 (m, 2H), 4.76 (d, *J* = 6 Hz, 2H), 5.7-5.9 (m, 2H), 7.3-7.5 (m, 9H), 7.6-7.68 (m, 4H), 8.01-8.07 (m, 2H); ^{13}C NMR (50 MHz $CDCl_3$): δ 19.02, 25.3, 26.7, 27.9, 32.3, 62.3, 65.2, 76.7, 77.4, 107.9, 126.1, 127.5, 128.1, 129.4, 129.6, 130.1, 132.2, 132.7, 132.9, 133.0, 135.3, 166.1; Anal. Calcd for $C_{33}H_{40}O_5Si$: C, 72.76; H, 7.40. Found: C, 72.59; H, 7.55.

(5*S*,6*R*)-5,6-*O*-isopropylidene-7-*O*-*tert*-butyl-diphenylsilyl-1,5,6,7-tetrahydroxyhept-2*E*-ene (4.86):

To a cooled (0 °C) solution of **4.85** (1.5 g, 2.75 mmol) in distilled MeOH (30 ml) was added Dry K_2CO_3 (65mg, 0.47 mmol). The mixture was stirred for three hour at 0 °C on completion (cf. TLC) the methanol was evaporated in vacuum. The reaction mixture was diluted with $CHCl_3$ and water. The aqueous layer was extracted with $CHCl_3$. The combined organic layer was washed successively water, brine and dried over Na_2SO_4. Solvent removal under reduced pressure and chromatography (silica gel, 0- 10% EtOAc in Hexane) of the residue afforded pure **4.86** (1.1 g, 91.6%) in homo chiral form.

$[\alpha]_D^{27}$ = -8.99 (c, 0.912, $CHCl_3$); ^{1}H NMR (200 MHz $CDCl_3$): δ 1.05 (bs, 9H), 1.32 (s, 3H), 1.38 (s, 3H), 1.6 (bs, 1H), 2.36-2.45 (m, 2H), 3.7 (m, 2H), 4.1 (d, *J* = 4.2 Hz, 2H), 4.1-4.2 (m, 2H), 5.70-5.77 (m, 2H), 7.3-7.4 (m, 6H), 7.6-7.68 (m, 4H); ^{13}C NMR

(50 MHz $CDCl_3$): δ 19.02, 25.3, 26.7, 27.9, 32.3, 62.3, 65.2, 76.7, 77.4, 107.9, 126.1, 127.5, 128.1, 129.4, 129.6, 130.1, 132.2, 132.7, 132.9, 133.0, 135.3; Anal. Calcd for $C_{26}H_{36}O_4Si$: C, 70.87; H, 8.23. Found: C, 71.11; H, 7.96.

(5*S*,6*R*)-1-Bromo-1-*O*-*tert*-butyl-diphenylsilyl-6,7-*O*-isopropylidene-5,6,7-trihydroxy-hept-2*E*-ene (4.88) :

To the cooled (0 °C) solution of **4.86** (1.05 g, 2.38 mmol) and triethylamine (313 mg, 3.09 mmol) in dry DCM (30 ml) was added methane-sulfonylchloride (355 mg, 3.11 mmol) drop wise over a period of 10 minute. The mixture was stirred for 4 hour at room temperature and treated with water. The aqueous layer was extracted with chloroform. The combined organic layer was washed with water, brine and dried over Na_2SO_4, Solvent removal under reduced pressure afforded yellow oily liquid containing the crude mesylated product in almost quantitative yield which was used in the next reaction without further purification. To a solution of crude mesylate **4.87** in dry acetone (50 ml), dry NaBr (320 mg, 3.1 mmol) and a catalytic amount of $NaHCO_3$ was added and stirred overnight (cf. TLC). The reaction mixture was concentrated under reduced pressure in order to get rid of the acetone, washed with water and extracted with $CHCl_3$. The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure to afford a colorless liquid which was chromatographed on silica gel (0-5% EtOAc in hexane) to afford pure **4.88** (1.05 g, 87.5%).

$[\alpha]_D^{27}$ = -7.68 (c, 1.07, $CHCl_3$); ^{1}H NMR (200 MHz $CDCl_3$): δ 1.06 (bs, 9H), 1.32 (s, 3H), 1.38 (s, 3H), 2.35-2.46 (m, 2H), 3.68-3.72 (m, 2H), 4.02 (d, *J* = 6.4 Hz, 2H), 4.1-4.23 (m, 2H), 5.7-5.9 (m, 2H), 7.3-7.4 (m, 6H), 7.6-7.69 (m, 4H); ^{13}C NMR (50 MHz $CDCl_3$): δ 19.1, 25.4, 26.8, 27.9, 32.3, 32.9, 45.3, 62.4, 65.2, 76.7, 77.4, 108.0, 127.7, 128.4, 129.7, 132.4, 133.0, 135.5.

(4*S*,5*R*)-4-*O*-Benzyl-5,6-*O*-cyclohexylidene-4,5,6-trihydroxy-hex-1-ene (4.90):

To a cooled (0 °C) suspension of sodium hydride (1.1 g, 50%suspension in oil, 22.9 mmol washed twice with dry hexane) in THF the anti homoallyl alcohol **2.94** (4.0 g, 18.86 mmol) was added dropwise over a period of 1 hour and stirred for one more hour. The solution of Benzyl bromide (3.87 g, 22.6 mmol) in dry in THF (50 ml) was added dropwise over a period of 1 hour followed by the addition of catalytic amount of TBAI and stirred for overnight (completion of reaction confirmed by TLC). After cooling the reaction mixture to 0 °C it was treated with water and with 2% aqueous dilute HCl to make it neutral. The mixture was extracted twice with EtOAc. The combined organic layer was washed with water, brine and dried over Na_2SO_4. Solvent removal under reduced pressure, column chromatography (silica gel, 0-5 % EtOAc in Hexane) of the residue afforded pure **4.90** (5.4 g, 95%) as a colorless oil.

$[\alpha]_D^{24}$= +31.81 (c, 0.83, $CHCl_3$); ^{1}H NMR(200 MHz $CDCl_3$): δ 1.35-1.59 (m, 10H), 2.34-2.44 (m, 2H), 3.56-3.58 (m, 1H), 3.87-3.91 (m, 1H), 3.99-4.10 (m, 2H), 4.57 (d, *J* = 11.3 Hz, 1H), 4.66 (AB q, *J* = 11.3 Hz, 2H), 5.07-5.18 (m, 2H), 5.83-5.91 (m, 1H), 7.25-7.32 (m, 5H); ^{13}C NMR(50 MHz $CDCl_3$): δ 24.0,24.18, 25.35, 35.06, 35.89, 36.49,66.26, 72.60, 77.87, 79.23, 109.67, 117.50, 127.72, 127.88, 128.44, 134.43, 138.60; Anal. Calcd for $C_{19}H_{26}O_3$: C, 75.46; H, 8.67 Found: C, 75.49; H, 8.38.

(4*S*,5*R*)-4-*O*-Benzyl-4,5,6-trihydroxy-hex-1-ene (4.91):

To a cooled (0 °C) solution of **4.90** (5.3 g, 17.5 mmol) in distilled CH_2Cl_2 (30 ml) was added 80% aqueous trifluoroacetic acid (10 ml). The mixture was stirred for three hour at 0 °C. The reaction mixture was diluted with $CHCl_3$ and water. The aqueous layer was extracted with $CHCl_3$. The combined organic layer was washed successively with 2% $NaHCO_3$ for neutrality, water and brine and dried over Na_2SO_4. Solvent removal under

reduced pressure and column chromatography (silica gel, 0-5% MeOH in $CHCl_3$) of the residue afforded pure **4.91** (2.84 g, 73%).

$[\alpha]_D^{26}$= +37.77 (c, 1.006, $CHCl_3$); ^{1}H NMR(200 MHz $CDCl_3$): δ 2.29-2.53 (m, 2H), 2.65 (bs, 3H), 3.59-3.77 (m, 4H), 4.58 (AB q, *J* = 11.3 Hz, 2H), 5.08-5.19 (m, 2H), 5.76-5.97 (m, 1H), 7.25-7.38 (m, 5H). ^{13}C NMR(50 MHz $CDCl_3$): δ 34.79, 63.44, 72.19, 72.60, 79.74, 117.52, 127.80, 128.37, 134.32, 138.03. Anal. Calcd for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16 Found: C, 70.17; H, 8.21.

(4*S*,5*R*)-4-*O*-Benzyl-6-*O*-*tert*-butyl-diphenylsilyl-4,5,6-trihydroxy-hex-1-ene (4.92):

To a cooled (0 °C) solution of **4.91** (2.8 g, 12.6 mmol) in dry CH_2Cl_2 (60 ml) Imidazole (1.03 g, 15.1 mmol) was added followed by the addition of catalytic amount of DMAP. To the mixture at 0 °C a solution of TBDPSCl (4.14 g, 15.1 mmol) in dry CH_2Cl_2 (60 ml) was added dropwise over a period of 4 hour. The reaction mixture was diluted with $CHCl_3$ and water. The aqueous layer was extracted with $CHCl_3$ and the combined organic layer was washed successively with 2% HCl for neutrality, water and brine and dried over Na_2SO_4. Solvent removal under reduced pressure and column chromatography (silica gel, 0-20% EtOAc in Hexane) of the residue afforded pure **4.92** (4.52 g, 78%).

$[\alpha]_D^{25}$ = +7.81 (c, 0.87, $CHCl_3$); ^{1}H NMR (200 MHz $CDCl_3$): δ 1.06 (bs, 9H), 1.79 (bs, 1H), 2.3-2.4 (m, 2H), 3.5-3.6 (m, 1H), 3.59-3.8 (m, 3H), 4.51 (AB q, *J* = 11.2 Hz, 2H), 5.0-5.2 (m, 2H), 5.7-5.9 (m, 1H), 7.3-7.4 (m, 11H), 7.6-7.7 (m, 4H); ^{13}C NMR (50 MHz $CDCl_3$): δ 19.2, 26.5, 26.8, 34.5, 64.5, 72.0, 72.5, 78.7, 117.2, 127.5, 127.6, 127.7, 128.2, 129.4, 129.7, 132.9, 134.6, 134.7, 135.4, 138.2; Anal. Calcd for $C_{29}H_{36}O_3Si$: C, 75.61; H, 7.88. Found: C, 75.33; H, 8.01.

(4*S*,5*R*)-4-*O*-Benzyl-5-*O*-tetrahydro-*2H*-pyranyl-6-*O-tert*-butyl-diphenylsilyl-4,5,6-trihydroxy-hex-1-ene (4.93):

To a cooled (0 °C) solution of **4.92** (4.4 g, 9.56 mmol) in dry CH_2Cl_2 (50 ml) DHP (2.02 ml, 23.9 mmol) was added followed by the addition of catalytic amount of PTSA. The reaction mixture was allowed to stir overnight on completion (cf TLC) the reaction mixture was diluted with $CHCl_3$ and water. The aqueous layer was extracted with $CHCl_3$ and the combined organic layer was washed successively with 2% $NaHCO_3$ for neutrality, water and brine and dried over Na_2SO_4. Solvent removal under reduced pressure and column chromatography (silica gel, 0-5% EtOAc in Hexane) of the residue afforded pure **4.93** (4.94 g, 95%) as a mixture of two diastereomers.

^{1}H NMR (200 MHz $CDCl_3$): δ 1.07 (bs, 9H), 1.4-1.7 (m, 6H), 2.36-2.4 (m, 2H), 3.4-3.5 (m, 1H), 3.7-3.9 (m, 6H), 4.5-4.6 (m, 2H), 5.0-5.2 (m, 2H), 5.7-5.9 (m, 1H), 7.3-7.4 (m, 11H), 7.6-7.7 (m, 4H); ^{13}C NMR (50 MHz $CDCl_3$): δ 19.1, 19.5, 25.4, 26.8, 30.6, 30.7, 34.3, 35.5, 61.9, 62.3, 63.2, 63.7, 71.9, 72.1, 78.7, 79.1, 98.1, 98.4, 116.4, 116.6, 127.3, 127.4, 127.5, 127.7, 128.1, 128.2, 129.5, 133.4, 133.46, 135.58, 135.66, 135.8, 138.6; Anal. Calcd for $C_{34}H_{44}O_4Si$: C, 74.96; H, 8.14. Found: C, 75.27; H, 8.22.

(3*S*,4*R*)-3-*O*-Benzyl-4-*O*-tetrahydro-*2H*-pyranyl-5-*O-tert*-butyl-diphenylsilyl-4,5,6-trihydroxy-pent-1-al (4.94):

Ozone was bubbled through a cooled (-78 °C) solution of **4.93** (4.8 g, 8.82 mmol) in CH_2Cl_2 (50 ml) till the solution turned blue. After stirring the reaction mixture for 10 min more, PPh_3 (3.4 g, 12.97 mmol) was added in portions and the mixture was gradually brought to room temperature and stirred for 1 hour. It was concentrated under reduced pressure to afford oily residue which was quickly purified by passing through a short pad of silica gel, eluting with 10 % hexane in EtOAc to obtain aldehyde **4.94** (4.25 g, 88.3%)

as colorless oil. The aldehyde was found to be unstable on long standing and hence a major portion of it was immediately used for the next step. A small portion was used for its spectroscopic characterization.

^{1}H NMR (200 MHz $CDCl_3$): δ 1.05 (bs, 9H), 1.4-1.7 (m, 6H), 2.36-2.6 (m, 2H), 3.4-3.5 (m, 1H), 3.7-4.4 (m, 6H), 4.5-4.8 (m, 2H), 7.3-7.4 (m, 11H), 7.6-7.7 (m, 4H), 9.69-9.79 (m, 1H); ^{13}C NMR (50 MHz $CDCl_3$): δ 19.08, 19.5, 25.2, 26.8, 30.4, 30.6, 43.6, 44.8, 62.1, 62.5, 62.7, 63.5, 71.6, 71.9, 74.3, 74.8, 97.6, 99.2, 127.6, 127.8, 128.2, 128.3, 129.7, 133.0, 133.5, 137.9, 201.3, 201.4; Anal. Calcd for $C_{33}H_{42}O_5Si$: C, 72.49; H, 7.74. Found: C, 72.56; H, 8.02.

(5*S*,6*R*)-Ethyl-5-*O*-benzyl-6-*O*-tetrahydro-*2H*-pyranyl-7-*O*-*tert*-butyl-diphenylsilyl-5,6,7-trihydroxy-hept-2*E*-enoate (4.95):

To a cooled (0 °C) suspension of sodium hydride (0.44 g, 50% suspension in oil, 9.16 mmol, washed twice with dry hexane) and dry THF (30 ml), triethyl phosphonoacetate (2.1 g, 9.37 mmol) in dry THF (30 ml) was added drop wise over a period of 30 minute under argon atmosphere. After the addition the reaction mixture was gradually brought to room temperature and stirred till the reaction mixture became clear. The mixture was again cooled to 0 °C. To it a solution of **4.94** (4.2 g, 7.69 mmol) in dry THF (50 ml) was added drop wise over a period of 45 minute. The mixture was gradually brought to room temperature and stirred for 4 hour more till the completion of reaction (confirmed from TLC). After cooling the reaction mixture to 0 °C it was treated with water and with 2% aqueous dilute HCl to make it neutral. The mixture was extracted twice with EtOAc. The combined organic layer was washed with water, brine and dried over Na_2SO_4. Solvent removal under reduced pressure, column chromatography (silica

gel, 0-15 % EtOAc in hexane) of the residue afforded pure **4.95** (4.2 g, 89.8%) as a colorless oil.

^{1}H NMR (200 MHz $CDCl_3$): δ 1.05 (bs, 9H), 1.25-1.32 (m, 2H), 1.36-1.66 (m, 6H), 2.36-2.5 (m, 2H), 3.4-3.5 (m, 1H), 3.7-4.1 (m, 6H), 4.13-4.2 (m, 2H), 4.52-4.80 (m, 2H), 4.81-4.9 (m, 1H), 5.8-5.9 (m, 1H), 6.9-7.1 (m, 1H), 7.3-7.4 (m, 11H), 7.6-7.7 (m, 4H); ^{13}C NMR (50 MHz $CDCl_3$): δ 14.2, 19.1, 19.2, 19.6, 25.3, 26.8, 30.5, 30.7, 32.5, 59.9, 62.1, 63.6, 71.7, 72.09, 76.7, 77.2, 77.8, 97.9, 98.9, 122.8, 123.1, 127.6, 127.8, 128.2, 128.3, 129.6, 133.2, 133.5, 138.1, 146.2, 146.5, 166.3; Anal. Calcd for $C_{37}H_{48}O_6Si$: C, 72.04; H, 7.84. Found: C, 71.89; H, 8.12.

(5*S*,6*R*)-5-*O*-Benzyl-6-*O*-tetrahydro-*2H*-pyranyl-7-*O*-*tert*-butyl-diphenylsilyl-1,5,6,7-tetrahydroxy-hept-2E-ene (4.96):

To a cooled (-78 °C) solution of **4.95** (4.2 g, 6.81 mmol) in THF , DIBAL-H (17.0 ml, 1.0 M solution in hexane) was added drop wise over a period of 30 minute. The mixture was stirred for one hour more at same temperature till the completion of the reaction (confirmed from TLC). To the mixture, methanol (15 ml) was added. The mixture was stirred at room temperature for 2 hour and the resulting solid was filtered through a Celite pad. Solvent removal under reduced pressure, column chromatography (silica gel, 0-20% EtOAc in hexane) of the residue afforded pure **4.96** (3.6 g, 92.1%) as a colorless oil.

^{1}H NMR (200 MHz $CDCl_3$): δ 1.05 (bs, 9H), 1.36-1.66 (m, 7H), 2.2-2.3 (m, 2H), 3.5-3.7 (m, 1H), 3.7-3.9 (m, 7H), 4.5-4.6 (m, 2H), 4.81-4.83 (m, 1H), 5.6-5.7 (m, 2H), 7.3-7.4 (m, 11H), 7.6-7.7 (m, 4H); ^{13}C NMR (50 MHz $CDCl_3$): δ 19.1, 19.2, 19.4, 19.5, 25.4, 26.9, 30.6, 30.8, 32.7, 33.7, 61.9, 62.3, 63.2, 63.3, 63.7, 71.8, 72.1, 77.4, 77.6, 78.5, 79.0, 98.2, 127.5, 127.6, 127.7, 127.8, 128.2, 128.9, 129.2, 129.6, 129.7, 131.4, 131.5,

133.0, 133.3, 133.4, 135.6, 138.5; Anal. Calcd for $C_{35}H_{46}O_5Si$: C, 73.13; H, 8.07. Found: C, 73.25; H, 7.92.

(5*S*,6*R*)-5-*O*-Benzyl-6-*O*-tetrahydro-*2H*-pyranyl-7-*O*-*tert*-butyl-diphenylsilyl-1-bromo-5,6,7-trihydroxy-hept-2*E*-ene (4.98):

To the cooled (0 °C) solution of **4.96** (3.5 g, 5.49 mmol) in dry CH_2Cl_2 (40 ml) Et_3N (0.72 g, 7.12 mmol) was added drop wise over a period of 15 minute followed by the addition of Methylsulfonyl chloride (0.81 g, 7.1 mmol) drop wise at the same temperature. The mixture was slowly brought to room temperature and stirred for 3 hours till the completion of the reaction (confirmed from TLC). The mixture was washed with water for neutrality and extracted with chloroform. The combined organic layer was washed with brine and dried over Na_2SO_4. Solvent removal under reduced pressure afforded a yellow oily liquid containing the crude mesylate (**4.97**) product which was used in the next reaction without further purification. To the solution of above crude product in dry acetone (50 ml), dry NaBr (0.84 g, 8.15 mmol) and a catalytic amount of $NaHCO_3$ was added and stirred overnight. The reaction mixture was concentrated under reduced pressure in order to get rid of the acetone, washed water and extracted with chloroform the combined organic layer was washed with brine, dried over Na_2SO_4. Solvent removal under reduced pressure, column chromatography (silica gel, 0-10% EtOAc in Hexane) of the residue afforded pure **4.98** (3.31 g, 85.3 %) as a colorless oil.

^{1}H NMR (200 MHz $CDCl_3$): δ 1.05 (bs, 9H), 1.36-1.66 (m, 6H), 2.3-2.4 (m, 2H), 3.3-3.5 (m, 1H), 3.4-3.9 (m, 7H), 4.5-4.6 (m, 2H), 4.81-4.83 (m, 1H), 5.72-5.8 (m, 2H), 7.3-7.4 (m, 11H), 7.6-7.7 (m, 4H); ^{13}C NMR (50 MHz $CDCl_3$): δ 19.1, 19.3, 19.7, 25.4, 26.9, 30.7, 30.8, 32.5, 33.3, 33.6, 46.1, 62.1, 62.5, 63.1, 63.8, 71.8, 72.1, 77.3, 78.3, 78.5,

98.2, 98.8, 127.5, 127.7, 127.9, 128.2, 128.3, 129.7, 132.6, 133.1, 133.3, 133.4, 135.6, 138.5; Anal. Calcd for $C_{35}H_{45}BrO_4Si$: C, 65.92; H, 7.11. Found: C, 66.18; H, 7.28.

(5*S*,6*R*)-5-*O*-Benzyl-6-*O*-tetrahydro-*2H*-pyranyl-1-bromo-5,6,7-trihydroxy-hept-2E-ene (4.99):

Tetrabutylammonium fluoride in THF (3.5 ml, 1M solution) was added to a cooled (0 ^{O}C) solution of **4.98** (1.5 g, 2.35 mmol) in THF (40 ml). The resulting solution was stirred for 1 hour and after the completion of reaction confirmed by TLC the reaction was quenched by the addition of saturated aqueous solution of NH_4Cl (10 ml). The mixture was diluted with EtOAc while two phases were separated. The aqueous phase was extracted with EtOAc. The combined organic layer was washed successively with water, brine and dried. Solvent removal under reduced pressure and column chromatography of the residue (silica gel, 0-20 %EtOAc in Hexane) afforded pure **4.99** (0.87 g, 92.6%).

^{1}H NMR (200 MHz $CDCl_3$): δ 1.36-1.82 (m, 7H), 2.3-2.4 (m, 2H), 3.3-3.5 (m, 1H), 3.4-3.9 (m, 7H), 4.5-4.9 (m, 2H), 5.7-5.9 (m, 2H), 7.3-7.4 (m, 5H);

(4*S*, 5*R*)-4-*O*-Benzyl-5,6-*O*-*tert*-butyldimethylsilyl-4,5,6-trihydroxy-hex-1-ene (4.100):

To a cooled (0 °C) solution of **4.91** (1.77 g, 8 mmol) in dry DMF (30 ml) containing DMAP (100 mg) was added imidazole (1.4 g, 20.5 mol), followed by the addition of *tert*-butyldimethylsilyl chloride (2.5 g, 16.6 mmol). The solution was stirred at room temperature overnight until completion of the reaction (confirmed by TLC). The mixture was treated with water and extracted with EtOAc. The combined organic extract was washed with water, brine and dried over Na_2SO_4. Solvent removal under reduced

pressure, and column chromatography (silica gel, 0-10% EtOAc in hexane) of the residue afforded pure **4.100** (3.38 g, 93.8%) as a colorless oil.

$[\alpha]_D^{26}$ = -17.9 (*c* 1.06, $CHCl_3$); ^1H NMR (200 MHz $CDCl_3$): δ 0.05 (2s, 6H each), 0.90 (bs, 18H), 2.34 (t, *J* = 6.8 Hz, 2H), 3.55-3.64 (m, 3H), 3.79-3.82 (m, 1H), 4.52, 4.64 (AB q, *J* = 11.6 Hz, 2H), 5.05 (m, 2H), 5.7-5.9 (m, 1H), 7.2-7.4 (m, 5H); ^{13}C NMR (50 MHz $CDCl_3$): δ -5.38, -5.35, -4.7, -4.4, 18.1, 18.3, 25.92, 25.98, 34.9, 64.6, 72.3, 74.8, 80.2, 116.5, 127.4, 127.8, 128.2, 135.9, 138.9; Anal. Calcd for $C_{25}H_{46}O_3Si_2$: C, 66.61; H, 10.29. Found: C, 66.48; H, 10.52.

(3*S*,4*R*)-3-*O*-Benzyl-4,5-*O*-di *tert*-butyldimethylsilyl-3,4,5-trihydroxypent-1-al (4.101):

Ozone was bubbled through a cooled (-78 °C) solution of **4.100** (4.8 g, 10.65 mmol) in CH_2Cl_2 (40 ml) till the solution turned blue. After stirring the reaction mixture for 10 min more, PPh_3 (4.2 g, 15.97 mmol) was added in portions and the mixture was gradually brought to room temperature and stirred for 1 hour. It was concentrated under reduced pressure to afford oily residue which was quickly purified by passing through a short pad of silica gel, eluting with 10 % hexane in EtOAc to obtain aldehyde **4.101** (4.14 g, 85.9%) as colorless oil. The aldehyde was found to be unstable on long standing and hence a major portion of it was immediately used for the next step. A small portion was used for its spectroscopic characterization.

^1H NMR(200 MHz $CDCl_3$): δ 0.04, 0.08 (2s, 6H each), 0.88 (s, 18H), 2.59-2.67 (m, 2H), 3.49-3.58 (m, 2H), 3.91-3.95 (m, 1H), 4.08-4.11 (m, 1H), 4.53, 4.66 (ABq, *J* = 11.5Hz, 2H), 7.17-7.40 (m, 5H), 9.77 (t, *J* = 1.9 Hz, 1H); ^{13}C NMR (50 MHz $CDCl_3$): δ -5.5, -4.7, 18.1, 18.2, 25.8, 25.9, 43.9, 64.4, 71.9, 74.0, 75.6, 127.6, 127.3 128.8, 138.2, 201.5.

(5*S*,6*R*)-Ethyl-5-*O*- benzyl-6,7-*O*-di *tert*-butyl-dimethylsilyl-5,6,7-trihydroxy-hept-2*E*-enoate (4.102) :

To a cooled (0 °C) suspension of sodium hydride (0.47 g, 50% suspension in oil, 9.8 mmol, washed twice with dry hexane) and dry THF (20 ml), triethyl phosphonoacetate (2.2 1 g, 9.86 mmol) in dry THF (10 ml) was added drop wise over a period of 30 minute under argon atmosphere. After the addition the reaction mixture was gradually brought to room temperature and stirred till the reaction mixture became clear. The mixture was again cooled to 0 °C. To it a solution of **4.101** (4.06 g, 8.97 mmol) in dry THF (20 ml) was added drop wise over a period of 45 minute. The mixture was gradually brought to room temperature and stirred for 4 hour more till the completion of reaction (confirmed from TLC). After cooling the reaction mixture to 0 °C it was treated with water and with 2% aqueous dilute HCl to make it neutral. The mixture was extracted twice with EtOAc. The combined organic layer was washed with water, brine and dried over Na_2SO_4. Solvent removal under reduced pressure, column chromatography (silica gel, 0-15 % EtOAc in hexane) of the residue afforded pure **4.102** (3.79 g, 80.8%) as a colorless oil.

$[\alpha]_D^{27}$= -25.00 (c, 1.24, $CHCl_3$); ^{1}H NMR (200 MHz $CDCl_3$): δ 0.04, 0.09 (2 s, 6H each), 0.88 (bs, 18H), 1.28 (t, *J* = 7.1 Hz, 3H), 2.46 (t, *J* = 6.5 Hz, 2H), 3.56-3.68 (m, 3H), 3.80-3.84 (m, 1H), 4.17 (q, *J* = 7.1 Hz, 2H), 4.47 , 4.62 (ABq, *J* = 11.5Hz, 2H), 5.86 (d, *J* = 15.6Hz, 1H), 7.02(dt, *J* = 15.6 Hz, 7.2 Hz, 1H) 7.25-7.32 (m, 5H); ^{13}C NMR (50 MHz $CDCl_3$): δ -5.4, -4.8, -4.5, 14.2, 18.1, 18.2, 25.8, 25.9, 32.9, 60.0, 64.4, 72.1, 74.3, 78.8, 122.9, 127.5, 127.8, 128.2, 138.3, 146.7, 166.4; Anal. Calcd for $C_{28}H_{50}O_5Si_2$: C, 64.32; H, 9.64. Found: C, 64.48; H, 9.55.

(5*S*,6*R*)-5-*O*-Benzyl-6,7-*O*-di-*tert*-butyl-dimethylsilyl-1,5,6,7-tetrahydroxy-hept-2E-ene (4.103):

To a cooled (-78 °C) solution of **4.102** (3.7 g, 7.07 mmol) in THF , DIBAL-H (14.3 ml, 1.0 M solution in hexane, 14.3 mmol) was added drop wise over a period of 30 minute. The mixture was stirred for one hour more at same temperature till the completion of the reaction (confirmed from TLC). To the mixture, methanol (15 ml) was added. The mixture was stirred at room temperature for 2 hour and the resulting solid was filtered through a Celite pad. Solvent removal under reduced pressure, column chromatography (silica gel, 0-20% EtOAc in hexane) of the residue afforded pure **4.103** (3.1 g, 91.1%) as a colorless oil.

$[\alpha]_D^{24}$= -21.73 (c, 0.92, $CHCl_3$); ^{1}H NMR (200 MHz $CDCl_3$): δ 0.04, 0.07 (2s, 12H), 0.89 (bs, 18H), 1.44 (bs, 1H), 2.31 (t, *J* = 5.6 Hz, 2H), 3.50-3.65 (m, 3H), 3.80 (dd, *J* = 9.1, 5.1 Hz, 1H), 4.04 (d, *J* = 3.5 Hz, 2H), 4.52, 4.64 (AB q, *J* = 5.6 Hz, 2H), 5.66-5.75 (m, 2H), 7.25-7.32 (m, 5H); ^{13}C NMR (50 MHz $CDCl_3$): δ -5.4, -4.7, -4.4, 18.118.3, 26.0, 25.9, 33.0, 63.5, 64.5, 72.2, 74.6, 79.9, 127.4, 127.9, 128.1, 129.8, 131.0, 138.7; Annal. Calcd for $C_{26}H_{48}O_4Si_2$; C, 64.95; H, 10.06; Found: C, 65.08; H, 10.19.

(5*S*,6*R*)-5-*O*-Benzyl-6,7-*O*-di-*tert*-butyl-dimethylsilyl-1-bromo-5,6,7-trihydroxy-hept-2E-ene (4.105):

To the cooled (0 °C) solution of **4.103** (3.0 g, 6.24 mmol) in dry CH_2Cl_2 (25 ml) Et_3N (1.07 g, 10.60 mmol) was added drop wise over a period of 15 minute followed by the addition of Methylsulfonyl chloride (0.93 g, 8.11 mmol) drop wise at the same temperature. The mixture was slowly brought to room temperature and stirred for 3 hours till the completion of the reaction (confirmed from TLC). The mixture was washed with water for neutrality and extracted with chloroform. The combined organic layer was washed with brine and dried over Na_2SO_4. Solvent removal under reduced pressure afforded a yellow oily liquid containing the crude mesylate (**4.104**) product which was used in the next reaction without further purification. To the solution of above crude

product in dry acetone (20 ml), dry NaBr (0.78 g, 7.5 mmol) and a catalytic amount of $NaHCO_3$ was added and stirred overnight. The reaction mixture was concentrated under reduced pressure in order to get rid of the acetone, washed with dilute HCL (2%) and extracted with chloroform the combined organic layer was washed with brine, dried over Na_2SO_4. Solvent removal under reduced pressure, column chromatography (silica gel, 0-10% EtOAc in Hexane) of the residue afforded pure **4.105** (3.06 g, 90.26 %) as a colorless oil.

$[\alpha]_D^{24}$ = -11.88 (c, 0.95, $CHCl_3$); ^{1}H NMR (200 MHz $CDCl_3$): δ 0.04, 0.06 (2s, 6H each), 0.94 (bs, 18H), 2.33 (t, *J* = 5.9 Hz, 2H), 3.50-3.62 (m, 3H), 3.80 (dd, *J* = 9.4Hz, 5.1Hz 1H), 3.91(d, *J* = 6.2 Hz, 1H), 4.01 (d, *J* = 6.2 Hz, 1H), 4.48, 4.62 (AB q, *J* = 11.58 Hz, 2H), 5.61-5.87 (m, 2H), 7.25-7.31 (m, 5H); ^{13}C NMR (175 MHz $CDCl_3$): δ -5.4, -5.3, -4.7, -4.4, 18.2, 18.3, 25.9, 26.0, 33.0, 45.3, 64.6, 72.3, 74.7, 79.7, 127.5, 127.7, 127.9, 128.2, 133.2, 138.7; Annal. Calcd for $C_{26}H_{47}BrO_3Si_2$; C, 57.43, H, 8.71; Found: C, 57.66; H, 8.61.

(5*S*,6*R*)-5-*O*-Benzyl-6-*O*-*tert*-butyl-dimethylsilyl-1-bromo-5,6,7-trihydroxy-hept-2E-ene (4.106):

Compound **4.105** (2.5 g, 4.59 mmol) was dissolved in chloroform (15 ml) which was saturated with aqueous concentrate HCl. The solution was stirred at room temperature for 36 hour till the completion of the reaction (confirmed by TLC). The organic layer was washed successively with water to remove HCl, brine and then dried over Na_2SO_4. Solvent removal under reduced pressure, column chromatography (silica gel, 0-20% EtOAc in Hexane) of the residue afforded pure **4.106** (1.8 g, 6.44mmol, 91.2%) as a pale yellow oil.

$[\alpha]_D^{24}$= -0.70 (c, 1.00, $CHCl_3$); ^{1}H NMR (200 MHz $CDCl_3$): δ 0.06 (s, 6H), 0.90 (bs, 9H), 1.88 (bs, 1H), 2.35-2.43 (m, 2H), 3.55-3.78 (m, 4H), 4.03 (d, *J* = 5.9 Hz, 2H),

4.62 (bm, 2H), 5.70-5.82 (m, 2H), 7.25-7.32 (m, 5H); ^{13}C NMR (50 MHz $CDCl_3$): δ -4.6, -4.4, 18.0, 25.8, 33.7, 45.2, 63.8, 72.8, 73.7, 79.7, 127.8, 128.0, 128.4, 131.9, 137.9; Annal. Calcd for $C_{20}H_{33}BrO_3Si$; C, 55.93; H, 7.75; Found: C, 56.21; H, 7.82.

(2*R*,3*S*)-2-*O*-*tert*-butyl-dimethylsilyl-3-*O*-Benzyl-7-bromo-2,3-dihydroxy-hept-5E-enal (4.107):

To the cooled (0 °C) solution of **4.106** (1.5 g, 3.50 mmol) in dry CH_2Cl_2 (35 ml) Dess martin periodinane (2.23 g, 5.25 mmol) was added in portions. The reaction mixture was stirred for 30 minutes at 0 °C, gradually brought to room temperature and stirred till the completion of the reaction (confirmed from TLC). It was diluted with chloroform (30 ml). The solution was poured into saturated aqueous $NaHCO_3$ (20 ml) containing a sevenfold excess of $Na_2S_2O_3$. The mixture was stirred to dissolve the solid. The organic layer separated. The aqueous layer was extracted with chloroform. The combined organic layer was washed with water, brine and dried over Na_2SO_4. Solvent removal under reduced pressure and the oily residue was passed through a short pad of silica gel eluting with 10% EtOAc in Hexane to obtain pure **4.107** (1.36 g, 91.4 %) as colorless oil. This was found to be unstable on long standing and hence a major part of it was immediately used as such for the next step. A small part was used for its tentative characterization.

$[\alpha]_D^{25}$ = -25.00 (c, 0.92, $CHCl_3$); ^{1}H NMR (200 MHz $CDCl_3$): δ 0.07 (s, 6H), 0.94 (bs, 9H), 2.35-2.41 (m, 2H), 3.69-3.75 (m, 1H), 4.00 (d, *J* = 5.4 Hz, 2H), 4.12 (dd, *J* = 3.6, 1.5 Hz, 1H), 4.54, 4.64 (AB q, *J* = 11.72 Hz, 2H), 5.65-5.72 (m, 2H), 7.25-7.35 (m, 5H), 9.6 (d, *J* = 1.5 Hz, 1H); ^{13}C NMR (50 MHz $CDCl_3$): δ -4.8, 18.1, 25.7, 33.1, 44.8, 72.2, 78.8, 80.6, 127.8, 128.3, 129.4, 130.9, 137.7, 203.4.

Luche's intramolecular allylation of 4.107.

To a well stirred mixture of aldehyde (**4.107**) (1 g, 2.5 mmol) and Zn dust (520 mg, 8 mmol) in THF (30 ml), was added saturated aqueous NH_4Cl solution (1.5 ml) drop

wise over a period of 20 minute. The reaction mixture was stirred overnight. The starting material disappeared totally (TLC). The mixture was filtered and thoroughly washed with EtOAc. The combined organic layer was washed with 5% HCl to dissolve the suspended turbid material and then with water, brine and dried. Solvent removal under reduced pressure and column chromatography (silica gel, 0-20 % EtOAc in Hexane) of the residue afforded **4.108a**/**4.108b** (53 mg) as an inseparable mixture of compounds which eluted first **,** followed by **4.108c** (127 mg) and **4.108d** (430 mg) which eluted successively to obtain each in homochiral form.

General procedure for intramolecular allylation of 4.107 employing bimetal redox strategy.

To a cooled (15 ^{0}C) solution of aldehyde **(4.107)** (1 g, 2.5 mmol) in THF (30 ml) was added metal salt [$FeCl_3$ (1.29 g, 8.0 mmol) or $SnCl_2.2H_2O$ (1.8 g, 8.0 mmol) or $CuCl_2.2H_2O$ (1.36 g, 8.0 mmol)]. The mixture was stirred well for 5 minute. To this stirred suspension Zn dust (650 mg, 10 mmol) was added in portions over a period of 20 minute. The reaction mixture was gradually brought to ambient temperature and stirred for the period as mentioned in **Table 1**. Low valent iron and tin mediated reactions showed total disappearance of starting material **9** and the formation of the product **4.108** (while monitored by TLC). However, no reaction was found to take place in the case of low valent copper mediated reaction. Finally, in both the successful reactions (iron and tin mediated reactions) the reaction mixture was treated successively with diethyl ether (50 ml), and water (25 ml). It was then stirred for 10 minute more and filtered. The filtrate was treated with 2% aqueous HCl to dissolve a little amount of suspended particles. The organic layer was separated and the aqueous layer was extracted with EtOAc. The combined organic extract was washed with water, brine and then dried. Solvent removal under reduced pressure and column chromatography (silica gel, 0-20% EtOAc in Hexane)

of the residue gave **4.1080a**/**4.108b** as an inseparable mixture of compounds, **4.108c** and **4.108d** in homochiral form. Thus, chromatography of low valent iron mediated reaction gave 57 mg **4.108a**/**4.108b,** 129 mg **4.108c** and 370 mg **4.108d**. Similarly, low valent tin mediated reaction gave 81 mg **4.108a**/**4.108b**, 447 mg **4.108c** and 185 mg **4.108d**.

Indium mediated intramolecular allylation of 4.107 in H_2O/THF.

To a magnetically stirred solution of **4.107** (1 g, 2.5 mmol) in a 1:1 solvent mixture of water and THF (8 ml) was added indium (99.99% pure ingot, Alfa Aesar make, 632 mg, 5.5 mmol). The reaction mixture was stirred for 48 hour. No reaction took place (TLC).

(1*S*,2*S*,3*R*,4*R*)-1-*O*-Benzyl-2-*O*-*tert*-butyldimethylsilyl-4-vinyl-cyclopentane-1,2,3-triol (4.108a) & (1*S*,2*S*,3*R*,4*S*)-1-*O*-Benzyl-2-*O*-*tert*-butyldimethylsilyl-4-vinyl-cyclopentane-1,2,3-triol (4.108b):

^{1}H NMR (200 MHz $CDCl_3$): δ 0.06 (bs, 6H), 0.93 (bs, 9H), 1.61-1.64 (m, 1H), 2.1-2.5 (m, 2H, overlapped with a bs, 1H), 3.65-3.70 (m, 1H), 3.81-3.84 (m, 1H), 4.0 (m, 1H), 4.53-4.65 (m, 2H), 4.9-5.1 (m, 2H), 5.73-5.86 (m, 1H), 7.25-7.34 (m, 5H); ^{13}C NMR (50 MHz $CDCl_3$): δ -4.9, -4.6, 18.3, 25.9, 32.8, 48.1, 71.7, 72.1, 75.1, 75.9, 77.2, 77.6, 78.9, 79.2, 113.9, 127.4, 127.5, 128.2 138.5, 138.6, 140.6.

(1*S*,2*S*,3*S*,4*R*)-1-*O*-Benzyl-2-*O*-*tert*-butyldimethylsilyl-4-vinyl-cyclopentane-1,2,3-triol (4.108c):

$[\alpha]_D^{24}$ = +3.84 (c, 0.51, $CHCl_3$); ^{1}H NMR (200 MHz $CDCl_3$): δ 0.09 (bs, 6H), 0.91 (bs, 9H), 1.6-2.1 (m, 2H, overlapped with a bs, 1H), 3.10 (m, 1H), 3.94-4.06 (m, 3H), 4.53, 4.64 (AB q, *J* = 12.0 Hz, 2H), 5.1-5.2 (m, 2H), 5.7-5.9 (m, 1H), 7.2-7.4 (m, 5H); ^{13}C NMR (50 MHz $CDCl_3$): δ -4.8, -4.7, 18.2, 25.8, 32.2, 42.8, 71.7, 78.2, 79.1, 79.2, 116.8, 127.2, 127.5, 127.6 128.1, 129.6, 134.7, 137.7, 138.9 Annal. Calcd for $C_{20}H_{32}O_3Si$; C, 68.92; H, 9.25; Found: C, 68.71; H, 9.15.

(1*S*,2*S*,3*S*,4*S*)-1-*O*-Benzyl-2-*O*-*tert*-butyldimethylsilyl-4-vinyl-cyclopentane-1,2,3-triol (4.108d):

$[\alpha]_D^{25}$ = +12.95 (c, 1.39, $CHCl_3$); ^1H NMR (200 MHz $CDCl_3$): δ 0.10 (bs, 6H), 0.94 (bs, 9H), 1.62-1.69 (m, 1H, overlapped with a bs, 1H), 2.16-2.26 (m, 2H), 3.74-3.93 (m, 3H), 4.59(d, *J* = 5.5 Hz, 2H), 4.97-5.11 (m, 2H), 5.72-5.91 (m, 1H), 7.25-7.35 (m, 5H); ^{13}C NMR (50 MHz $CDCl_3$): δ -4.68, -4.63, 18.2, 25.8, 33.2, 45.2, 71.4, 77.2, 79.6, 80.5, 114.8, 127.3, 127.6, 128.2, 138.7, 140.9; Anal. Calcd for C20H32O3Si; C, 68.92; H, 9.25; Found: C, 68.65; H, 9.08.

(1*S*,2*S*,3*S*,4*R*)-1-*O*-Benzyl-4-hydroxymethyl-cyclopentane-1,2,3-triol (4.111):

To a cooled (-78 ^0C) solution of **4.108c** (348 mg, 1.0 mmol) in CH_2Cl_2 (25 ml) was bubbled ozone gas until blue color persisted. To it was added PPh_3 (300 mg, 1.15 mmol). The blue color disappeared immediately. The solution was brought to room temperature and stirred for 40 minute more. Solvent was removed from the reaction mixture under reduced pressure. The residue was passed through a short (2") silica gel column being quickly eluted with 0-25% EtOAc in Hexane to obtain an unstable aldehyde which was taken in THF (25 ml). This solution was slowly added to a stirred suspension of $LiAlH_4$ (77 mg, 2.0 mmol) in THF (20 ml) at 10 ^0C. The mixture was stirred for 1 hour at 10 ^0C and then at room temperature overnight. It was then cooled with ice water. The excess hydride was decomposed by drop wise addition of saturated aqueous solution of Na_2SO_4. The white precipitated formed was filtered and washed with dry diethyl ether. Solvent was removed from the combined washing under reduced pressure and the residue was passed through a short (2") silica gel column being quickly eluted with 0-10% MeOH in $CHCl_3$ to obtain **4.111** (174 mg, 73.1%) as a colorless oil which was used as such for the next reaction. A portion of the residue was subjected to spectral analysis for its characterization.

$[\alpha]_D^{27}$ = +22.01 (c,1.09, CH_2Cl_2); ^{1}H NMR (700 MHz $CDCl_3$): δ 1.77 (dt, *J* = 12.0, 6.0 Hz, 1H), 1.89 (m, 1H), 2.50 (m, 1H), 2.97 (bs, 2H), 3.46 (bs, 1H), 3.63-3.65 (m, 1H), 3.76-3.77 (m, 1H), 3.94 (m, 1H), 4.03 (m, 1H), 4.25 (t, *J* = 5.6 Hz, 1H), 4.48, 4.59 (AB q, *J* = 11.9 Hz, 2H), 7.26-7.35 (m, 5H); ^{13}C NMR (175 MHz $CDCl_3$): δ 29.2, 39.5, 62.9, 71.7, 78.6, 78.7, 78.8, 127.8, 127.9, 128.5, 137.8; Anal. Calcd for $C_{13}H_{18}O_4$; C, 65.53; H, 7.61; Found: C, 65.70; H, 7.45.

(1*S*,2*S*,3*S*,4*R*)- 4-hydroxymethyl-cyclopentane-1,2,3-triol [Carba-*α*-D-xylofuranose] (4.113):

A solution of **4.111** (125 mg) in EtOH (20 ml) was treated with 10% Pd-C (20 mg). The mixture was stirred under H_2 atmosphere for 10 hour till the reaction was complete (monitored by TLC). The mixture was filtered through a Celite pad and solvent was removed under reduced pressure. The residue was column chromatographed to afford pure **4.113** (73 mg) as a colorless oil.

$[\alpha]_D^{26}$ = 12.7 (c, 1.0, MeOH) [lit.[183q], $[\alpha]_D^{20}$ = 12.1 (c, 0.7, MeOH)]; ^{1}H NMR (600 MHz, D_2O): δ 1.61 (m, 2H), 2.28-2.31 (m, 1H), 3.36 (dd, *J* = 7.2, 10.2 Hz, 1H), 3.53 (dd, *J* = 7.2, 10.2 Hz, 1H), 3.72 (m, 1H), 3.99 (m, 2H); ^{13}C NMR (150 MHz, D_2O): δ 34.7, 41.8, 64.3, 73.3, 78.5, 81.1.

(1*S*,2*S*,3*S*,4*S*)-1-*O*-Benzyl-4-hydroxymethyl-cyclopentane-1,2,3-triol (4.112):

Following the same reactions protocol as done above for the preparation of **4.111**, compound **4.108d** (348 mg, 1.0 mmol) has been transformed into **4.112** (179 mg, 75.3%) as a colorless oil.

$[\alpha]_D^{27}$ = +29.16 (c, 2.16, CH_2Cl_2); ^{1}H NMR (700 MHz $CDCl_3$): δ 1.48 (m, 1H), 1.64 (bs, 1H), 1.92 (m, 1H), 2.06 (m, 1H), 3.57 (m, 1H), 3.63-3.70 (m, 1H, overlapped with a bs, 2H), 3.82(m, 1H), 3.88-3.90 (m, 1H), 3.93 (t, *J* = 7 Hz, 1H), 4.47 (d, *J* = 11.9 Hz, 1H), 4.574 (dd, *J* = 11.9, 5.6 Hz, 1H), 7.26-7.34 (m, 5H); ^{13}C NMR (175 MHz

$CDCl_3$): δ 29.4, 43.3, 62.6, 71.6,77.49, 78.6, 79.6, 127.8, 127.9, 128.5, 137.8; Anal. Calcd for for $C_{13}H_{18}O_4$; C, 65.53; H, 7.61; Found: C, 65.41; H, 7.79.

(1*S*,2*S*,3*S*,4*S*)-4-Hydroxymethyl-cyclopentane-1,2,3-triol [Carba-*β*-L-arabinofuranose] (4.14) :

Following a same procedure as done above for the preparation of **I, 12** (125 mg) was hydrogenated to afford pure **I** (70 mg) as a thick oil.

$[\alpha]_D^{24}$ = -8.6 (c, 1.4, MeOH) [lit.[183f], $[\alpha]_D^{20}$ = -7.9 (c, 1.2, MeOH)]; ^{1}H NMR (600 MHz, D_2O): δ 1.22-1.26 (m, 1H), 1.73-1.79 (m, 1H), 2.07-2.12 (m, 1H), 3.39-3.42 (m, 1H), 3.54-3.57 (m, 1H), 3.60-3.65 (m, 2H), 3.92-3.95 (m, 1H); ^{13}C NMR (150 MHz, D_2O): δ 34.2, 45.3, 66.7, 72.5, 79.8, 80.9.

CHAPTER 5

Synthesis of Oxygenated Heterocyclic Bioactive Molecules

5.I.I Stereo divergent synthesis of 2,3,5-trisubstituted tetrahyrdofurans

Saturated oxygen heterocycles are observed as an important structural moiety in varieties of biologically active natural products.[192] Synthesis of these natural products largely depends on the efficient stereoselective construction of these essential cyclic components. Among these oxygenated heterocycles, in recent years functionalized tetrahydrofuran derivatives[193] are receiving enormous attention due to their frequent occurrence as subunits in various types of bioactive natural products (**Figure 5.1**) *viz.* cytotoxic polyether,[194] polyether antibiotics,[195] annoceous acetogenins,[196] and several groups of macrolides.[197] The development of methodologies to prepare substituted tetrahydofurans stereoselectively has become an area of great interest due to the increasing report of their biological activity in the areas like antibiotic, antimicrobial, cytotoxic, pesticidal, antimalarial, antiviral *etc*.

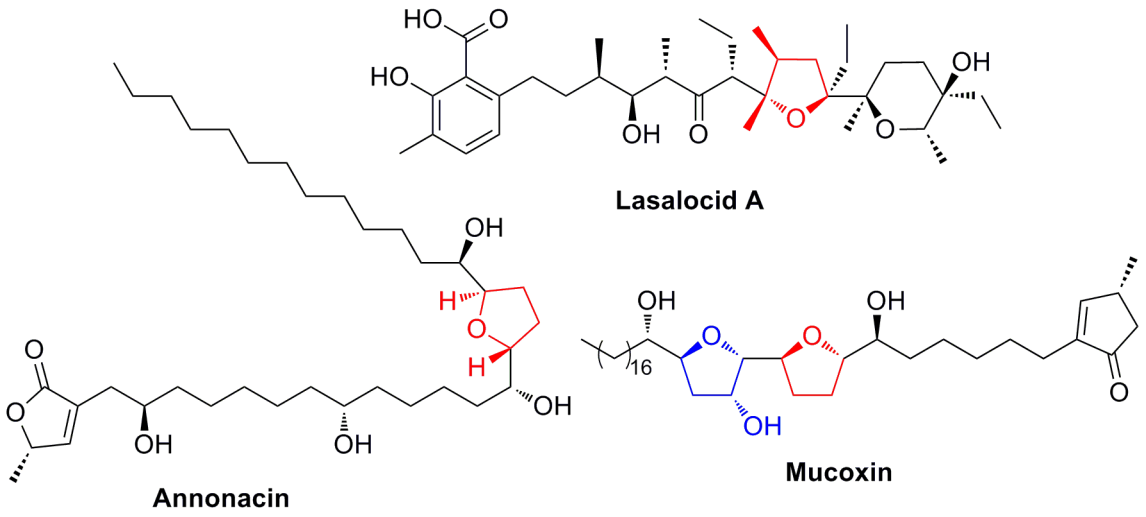


Figure 5.1 Substituted THF as subunit of natural products

The annoceous acetogenins are a class of more than 400 natural products isolated exclusively from the tropical plants family *Annonaceae* (custard-apple family).[198] They exhibit high antitumor, antimalarial, pesticidal, and immunosuppressive activity.[199] Since the substituted tetrahydrofurans forms the basic structure of these kinds of natural

products, in view of these, development of efficient and stereochemical flexible strategy to generate tetrahydrofuran subunits possessing other functionalities in different homochiral forms assumes enormous significance in organic synthesis.[200] In particular, the 3-hydroxy-2,5-disubstituted tetrahydrofuran skeletons are found in a number of natural products isolated from various marine sources (**Figure 5.2**).[201]

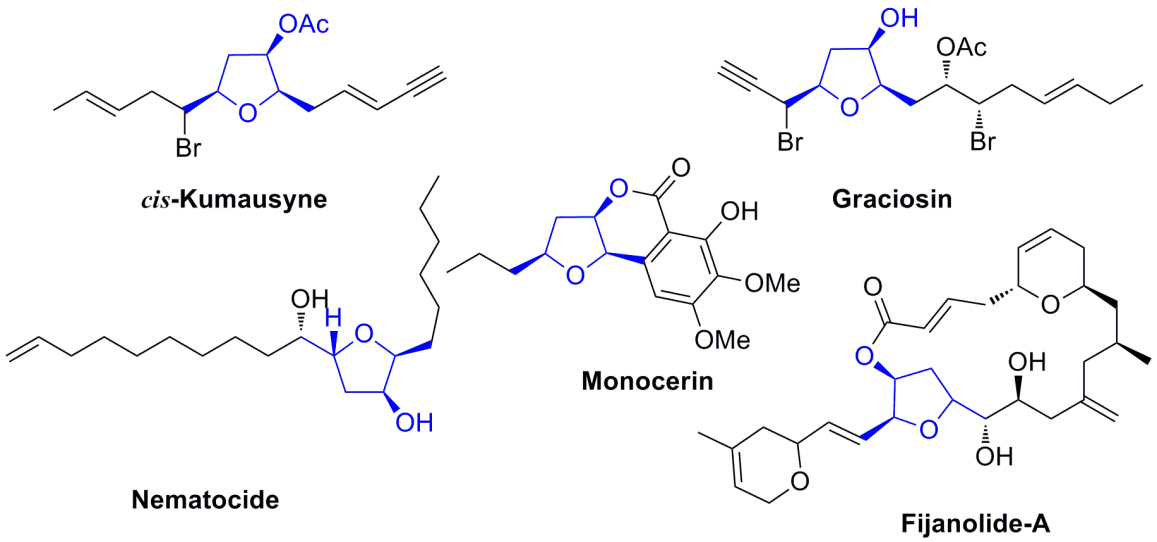


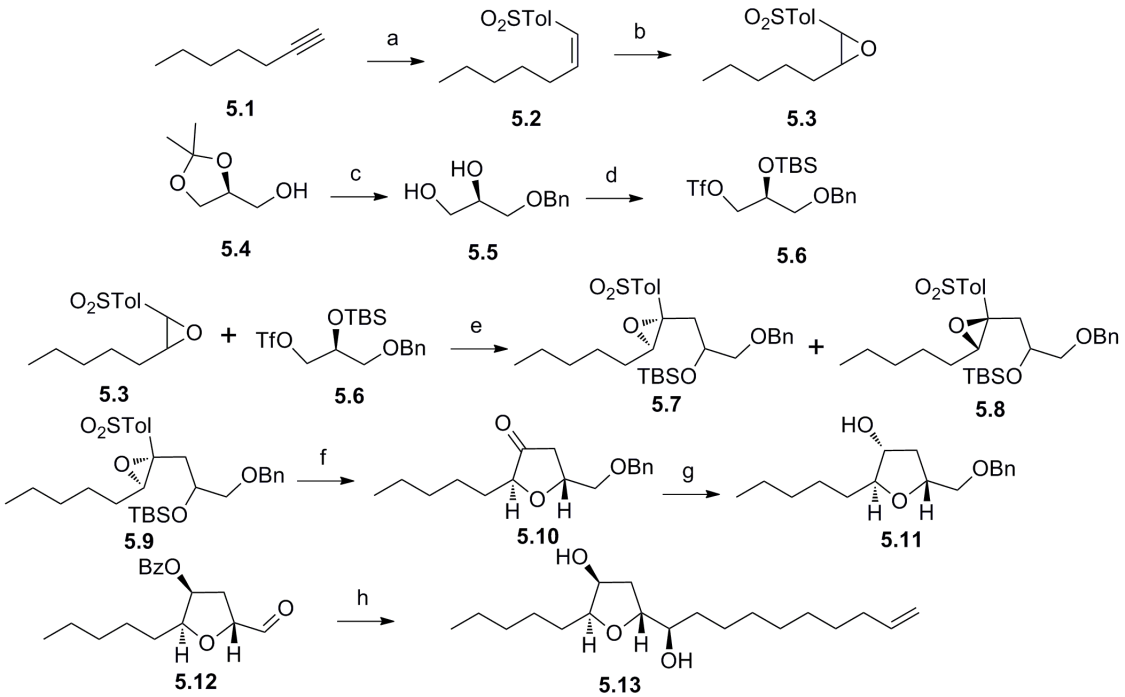
Figure 5.2 3-hydroxy-2,5-disubstituted THF as subunit of marine natural products

Owing to the important biological activities of these natural products synthesis of the 3-hydroxy-2,5-disubstituted tetrahydrofuran skeletons assumed considerable importance in organic synthesis.

5.I.II Earlier Work in Literature

So far several strategies have been adopted using different substrate and different approaches to furnish stereoselective construction of all the diastereomers of 3-hydroxy-2,5-disubstituted tetrahydrofurans. In this endeavor Mori *et al.* in the year 1999 reported the synthesis of the tetrahydrofuran (**5.11**) a key intermediate for the stereo selective construction of the marine epoxy lipid (**5.13**) (**Scheme 5.1**)[201m] using an oxiranyl anion strategy. The synthesis started with the conversion of 1-heptyene (**5.1**) to the racemic

epoxy sulfone (**5.3**) which was later made to react with triflate (**5.6**) obtained from (*S*)-(+)-2,2-dimethyl-1,3-dioxalone-4-methanol (**5.4**). This alkylation of **5.3** and **5.6** gave a 1:1 mixture of epoxy sulfone **5.7** and **5.8** which are separated by HPLC. The epoxy sulfone **5.7** when subjected to desilylation under goes stereospecific 5-endo cyclization to afford the tetrahydrofuranyl ketone **5.10** which was reduced to give the 3-hydroxy-2,5-substituted tetrahydrofuran **5.11**. The tetrahydrofuran **5.11** was later subjected to Mitsunobu condition to have the desired stereochemistry at 3-hydroxy and after standard transformation converted to the marine epoxy lipid (**5.13**).

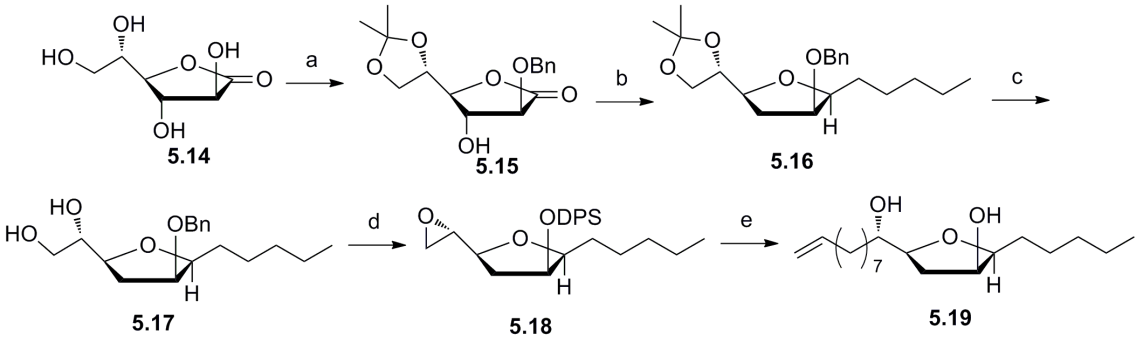


a) (1) p-TolSO_2Na, I_2, EtOAc, (2) H_2, 5% Pd-C, quinoline, MeOH; b) t-BuO_2H, n-BuLi, THF, -20 °C; c) (1) NaH, BnCl, (2) HCl, MeOH; d) Tf_2O, 2,6-lutidine, CH_2Cl_2, -78 °C, then TBSOTf, -78 °C to 0 °C; e) n-BuLi, DMPU, THF, -100 °C; f) BF_3-OEt_2 CH_2Cl_2, 0 °C; g) $NaBH_4$, MeOH, -78 °C; h) (1) DEAD, PPh_3, BzOH, C_6H_6, (2) H_2, $Pd(OH)_2$, EtOAc, (3) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78 °C to 20 °C; h) $BrMg(CH_2)_7CH{=}CH_2$, Et_2O, -78 °C to 0 °C.

Scheme 5.1

Yoda *et al.*[2011] reported the synthesis of another marine epoxy lipid **5.19** (**Scheme 5.2**) containing 3-hydroxy-2,5-disubstituted tetrahydrofuran as a basic structural unit. The synthesis started with the acetonide formation of the lactone **5.14** followed by regioselective benzylation to give **5.15**. This was subjected to reductive deoxygenation of

its free hydroxyl at C-3, which was followed by the Grignard addition at its carbonyl and subsequent BF_3OEt_2 promoted hydrogenation to give the required trisubstituted tetrahydrofuran framework **5.16**. Its acetonide moiety was hydrolyzed to give the diol **5.17** which was subjected to a series of reactions viz. conversion of diol moiety into epoxide, removal of benzyl and silylation of the free hydroxyl to give **5.18**. This was subjected to coupling reaction with 7-octenyl Grignard in presence of CuI, followed by desilylation of hydroxyl to give the required marine lipid **5.19**.

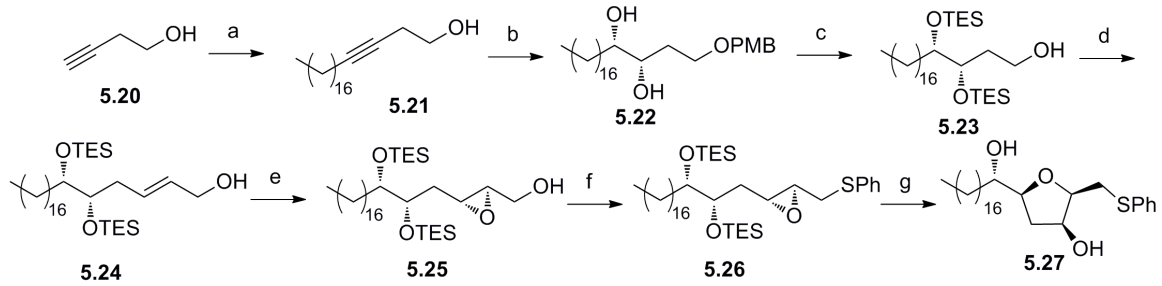


a) (1) $(CH_3)_2C(OCH_3)_2$, CH_3COCH, *p*-TsOH, (2) BnBr, Ag_2O, CH_3COOEt; b) (1) $ClC(S)OC_6H_5$, Py, DMAP, CH_3CN; (2) Bu_3SnH, AIBN (*cat*), Toluene, 90 °C, (3) $BrMgC_5H_{11}$, $CeCl_3$, -78 °C, THF, (4) Et_3SiH, BF_3OEt_2 , CH_2Cl_2, -78 °C; d) (1) *p*-TsOH, MeOH, (2) TsCl, Bu_2SnO, Et_3N, CH_2Cl_2, (3) K_2CO_3, MeOH, (4) Pd (black), 4.4% HCOOH-MeOH. (5) DPSCl, CH_2Cl_2; e) (1) $CH_2CH(CH_2)_6MgBr$, CuI (*Cat*), THF, -50 °C, (2) TBAF, THF

Scheme 5.2

For the synthesis of Mucoxin (**Figure 5.1**) Borhan *et al*.[201h] developed a regio and stereoselective strategy for tetrahydrofuran ring synthesis. The 3-hydroxy-2,5-disubstituted tetrahydrofuran thiophenyl ether **5.27** (**Scheme 5.3**) was synthesized as a part of the total synthesis of Mucoxin. The synthesis of the fragment **5.27** was started with the alkylation of TBS acetylide derived from 3-butynol (**5.20**) followed by desilylation to give **5.21**. The homopropargylic alcohol **5.21** was converted to *E*-homoallylic alcohol in a stereoselective manner using LAH as the reducing agent followed by the protection of the primary alcohol by PMB and Sharpless asymmetric dihydroxylation of the corresponding PMB protected homoallylic alcohol using Ad-mix-α

gave the syn diol **5.22**. The homo allylic alcohol **5.24** was obtained from **5.22** following 1) protection of the diol **5.22**, 2) removal of the PMB to give **5.23** and oxidation of the corresponding alcohol to aldehyde, 3) Wittig olefination and reduction of the corresponding *α,β*-unsaturated ester using DIBAL-H. Sharpless asymmetric epoxidation of the homo allylic alcohol gave the epoxide **5.25** which was converted to the thiophenyl ether **5.26**. Lewis acid mediated epoxide ring opening of the thiophenyl ether gave a regioselective product **5.27**.

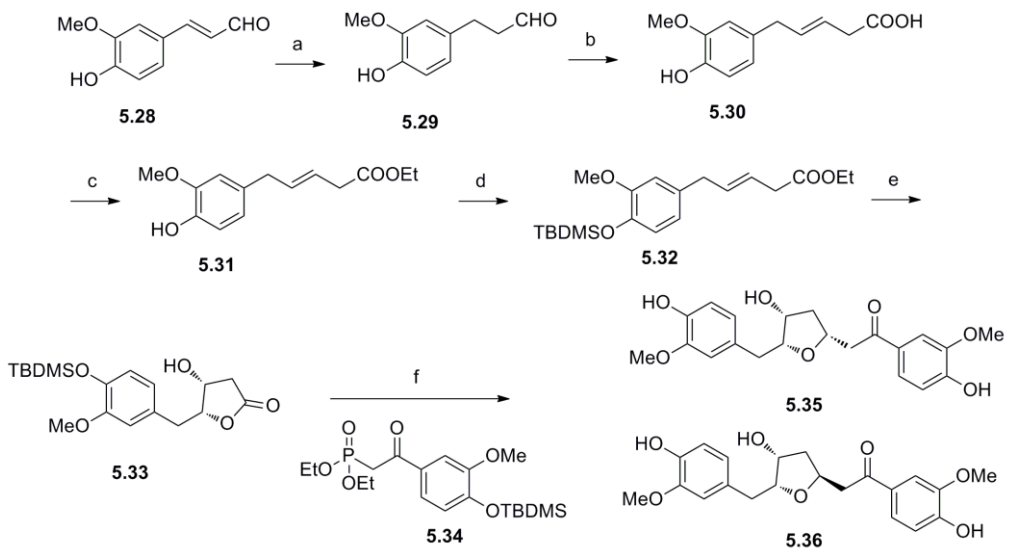


a) (1) TBSCl, Imidazole, DMF, (2) *n*-BuLi, $CH_3(CH_2)_{16}I$, THF/HMPA(3:1), 0 °C, (3) TBAF, THF; b) (1) LAH, Diglyme, 125 °C, (2) NaH, PMBCl, TBAI, THF, 60 °C, (3) AD-mix-α, $MeSO_2NH_2$, $K_2OsO_4.2H_2O$, *t*-BuOH/H_2O (1:1); c) (1) TESCl, Et_3N, DMAP, THF, (2) DDQ, CH_2Cl_2,/pH 7 Phosphate Buffer,(10:1), 0 °C; d) (1) $(PhI(OAc)_2$, TEMPO, CH_2Cl_2, (2) $Ph_3P{=}CHCO_2Et$, THF, reflux, (3) DIBAL-H, Et_2O, 0 °C, (4) (D)-DIPT/$Ti(O^iPr)_4$ (1.2:1.0), *t*-BuOH, MS 4 Å, CH_2Cl_2, -20 °C; f) $(PhS)_2$, Bu_3P, TEA, 0 °C; g) BF_3OEt_2, (6 equiv), Et_2O (0.04M), 0 °C to RT.

Scheme 5.3

G. Sabitha *et al*. reported the synthesis of 3-hydroxy-2,5-trisubstituted tetrahydrofuran as part of the synthesis of Renealtin A and B (**5.35, 5.36)** (**Scheme 5.4**). The synthesis was started with regioselective reduction of the *α,β*-unsaturated substituted cinnamaldehyde (**5.28**) to the corresponding saturated aldehyde **5.29**, this was subjected to microwave irradiation with malonic acid to give the *β,γ*-unsaturated acid **5.30**. The acid **5.30** was converted to the ester **5.31** with BF_3OEt_2 followed by TBDMS protection to give *β,γ*-unsaturated ester **5.32**. Asymmetric dihydroxylation of the ester **5.32** was associated with the concomitant lactonization to give the lactone **5.33** which when subjected to a Wittig-Horner reaction followed by oxy-Michael reaction in one pot gave

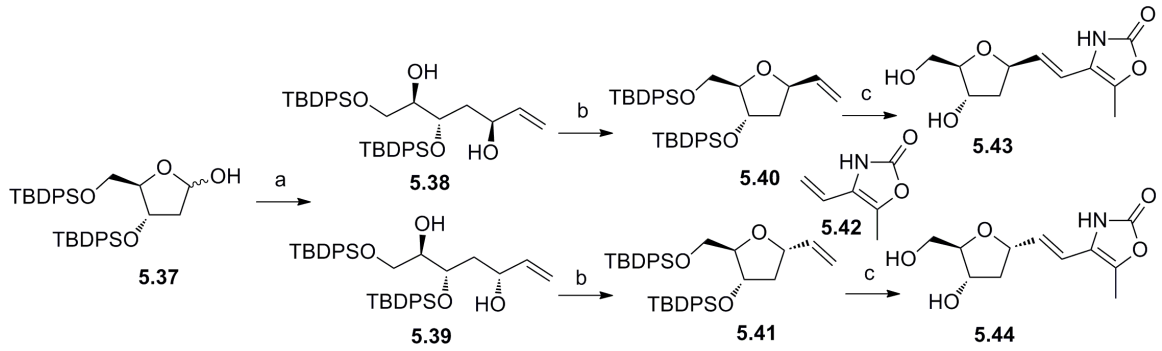
the diastereomers which are separated and the global deprotection gave the Renealtin A (**5.35**) and B (**5.36**) separately.



a) $NaBH_4$, $NiCl_2.6H_2O$, MeOH, H_2O; b) SiO_2, Malonic acid, MW (600 W); c)EtOH, $BF_3.OEt_2$, 0°C; d) TBDMSCl, Imidazole, CH_2Cl_2; e) AD-Mix-β, $CH_3SO_2NH_2$; f) (1) DIBAL-H, CH_2Cl_2, -78 °C, (2) 4.34, *n*-BuLi, THF, -78 °C, (3) TBAF, CH_2Cl_2.

Scheme 5.4

Recently Rothman *et al*. synthesized both the diastereomers of 3-hydroxy-2,5-disubstituted tetrahydrofuran (**5.40**, **5.41**) (**Scheme 5.5**)[201f] which they have used for the synthesis of ethenyl heterocyclic C-nucleosides **5.43** and **5.44** and used this for the recognition of inverted base pairs in DNA triple helix. The synthesis started with addition of vinyl carbanion to 3,5-di-*O*-silyl-protected 2-deoxyribonolactone which gave rise to diol **5.38** and **5.39**. The diol **5.38** and **5.39** are separately treated with MsCl/Pyridine which gave the tetrahydrofuran **5.40** and **5.41** respectively. The ethylene C-nucleosides are obtained by the cross metathesis of the vinylic THF **5.40** and **5.41** with the synthesized precursor **5.42** to give **5.43** and **5.44** respectively.



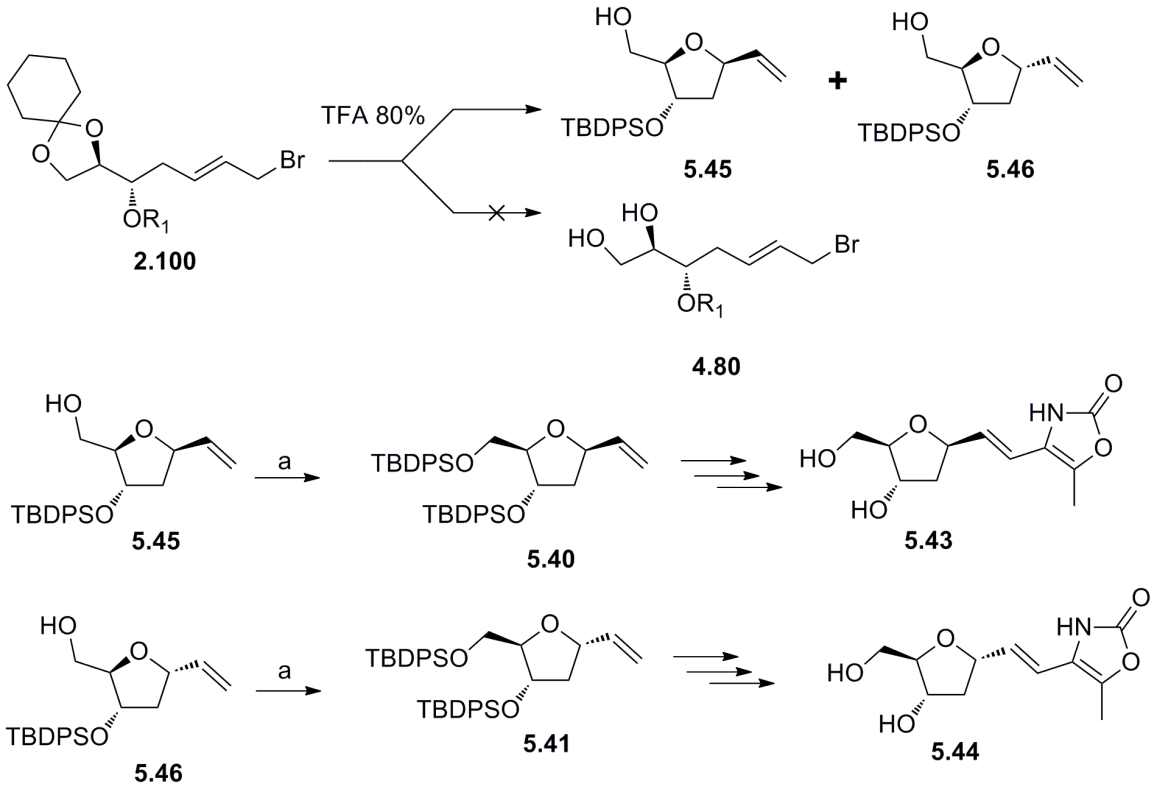
a) CH_2=CHMgBr, THF; b) MsCl, CH_2Cl_2, Py, -20 °C; c) (1) Hoveyda-Grubbs-I catalyst, CH_2Cl_2, 40 °C, (2) TBAF, THF.

Scheme 5.5

5.I.III Our Work

Our synthetic approach for the construction of 2,3,5-trisubstituted tetrahydrofuran started with homoallylic alcohol that had been obtained by allylation of **2.65**. In order to establish our strategy, we began with *anti*-homoallylic alcohol (**2.94**) which could be easily obtained as the major product via practically viable allylation of **2.65** in wet media mediated with Zn employing Luche's procedure or mediated with low valent Sn or Fe or Cu in wet medium employing a procedure developed recently by our group. Homoallylic alcohol was then transformed into allylic bromide **2.100** following a series of reactions as demonstrated in **Chapter 4 (Scheme 4.9)**. Bromide was subjected to deketalization of its acetal moiety by treating it with aqueous trifluoroacetic acid. The reaction straightway yielded a 3-hydroxy-2,5-disubstituted tetrahydrofuran moiety as a mixture of two diastereomers **5.45** and **5.46** which could be isolated in homochiral form after being easily separated from each other by column chromatography . The presence of terminal double bond was confirmed from the signal at δ 5.1-5.3 (m, 2H) and δ 5.7-5.9 (m, 1H) (**Figure 5.3**) of PMR of **5.45**. Similarly the signal at δ 5.1-5.24 (m, 2H) and δ 5.9-6.1 (m, 1H) (**Figure 5.4**) confirmed the presence of a vinyl side chain in **5.46**. For further confirmation of the structures and stereochemistry of the product tetrahydrofurans **5.45** and **5.46**, both of them were separately subjected to silylation reactions by treating

each with TBDPSCl and imidazole to obtain the products whose spectral and optical data were in well conformity with the known[10f] tetrahydrofurans **5.40** and **5.41** respectively. The NMR of **5.40** and **5.41** prepared by us are shown in **Figures 5.7-5.8** and **Figures 5.9-5.10** respectively. The ^{1}H-NMR (**Figures 5.7**) of **5.40** showed two signals at δ 0.92 and 1.07 each due to 9 protons which indicated the presence of di-*O*-silyl moiety in it. Likewise, signals at δ 0.92 and 1.04 due to 9 protons each in the PMR of **5.41** (**Figure 5.9)** confirmed the presence of two –OTBS in it. Thus, the present work demonstrated a judicious application of easily accessible (*R*)-2,3-*O*-cyclohexylideneglyceraldehyde to develop a simple and stereo divergent strategy for the preparation of two stereoisomers of 2,3,5-trisubstituted tetrahydrofurans, *viz.* (2*R*,3*S*,5*R*)-2-(methoxy-*O*-*tert*-butyl-diphenylsilyl)-3-*O*-*tert*-butyl-diphenylsilyl-5-vinyltetrahydrofuran (**5.40**) and (2*R*,3*S*,5*S*)-2-(methoxy-*O*-*tert*-butyl-diphenylsilyl)-3-*O*-*tert*-butyl-diphenylsilyl-5-vinyltetrahydrofuran (**5.41**). It is worth noting that both these tetrahydrofurans possess different substituents, each of which is amenable to versatile chemical maneuvers independent of other. It was expected that by employing a similar reactions protocol as done here with the corresponding *syn*-homoallylic alcohol of **2.65** origins, there is a possibility of obtaining another series of THF with similar structural feature as that of **5.40** and **5.41**, but having different stereo-chemical combinations.



a) TBDPSCl, Imidazole, DMAP. CH_2Cl_2, 0 °C to RT.

Scheme 5.6

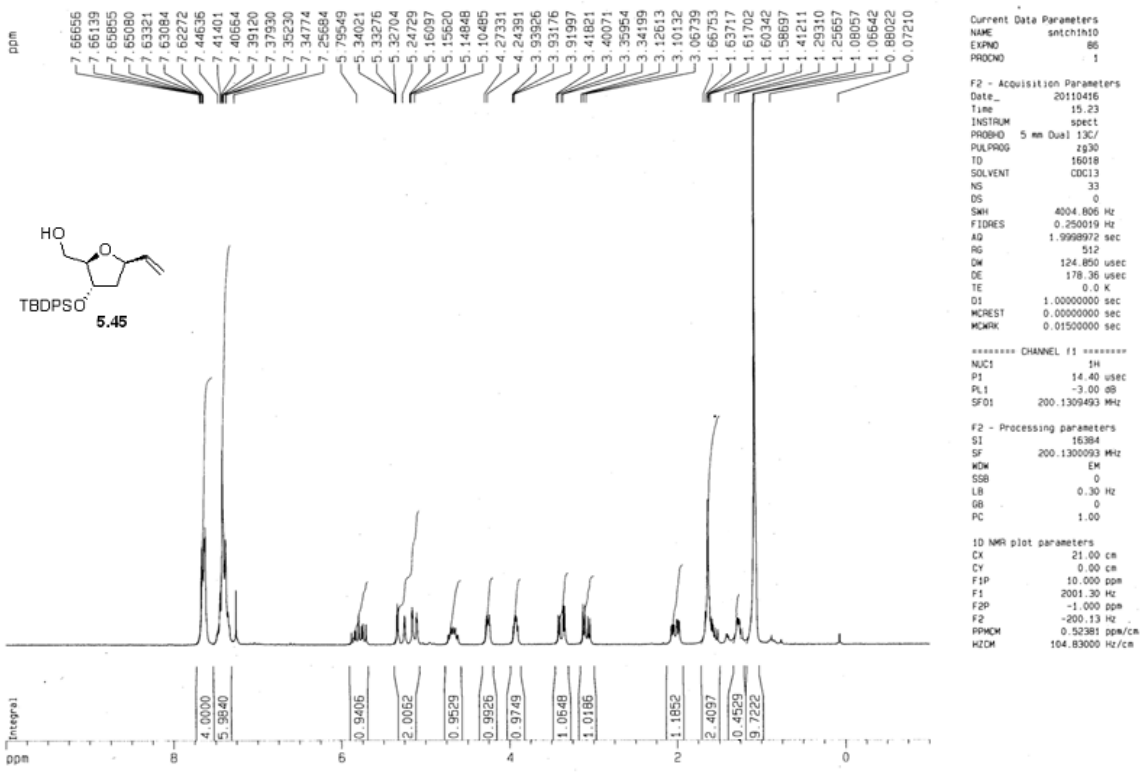


Figure 5.3 ^{1}H NMR spectrum of 5.45

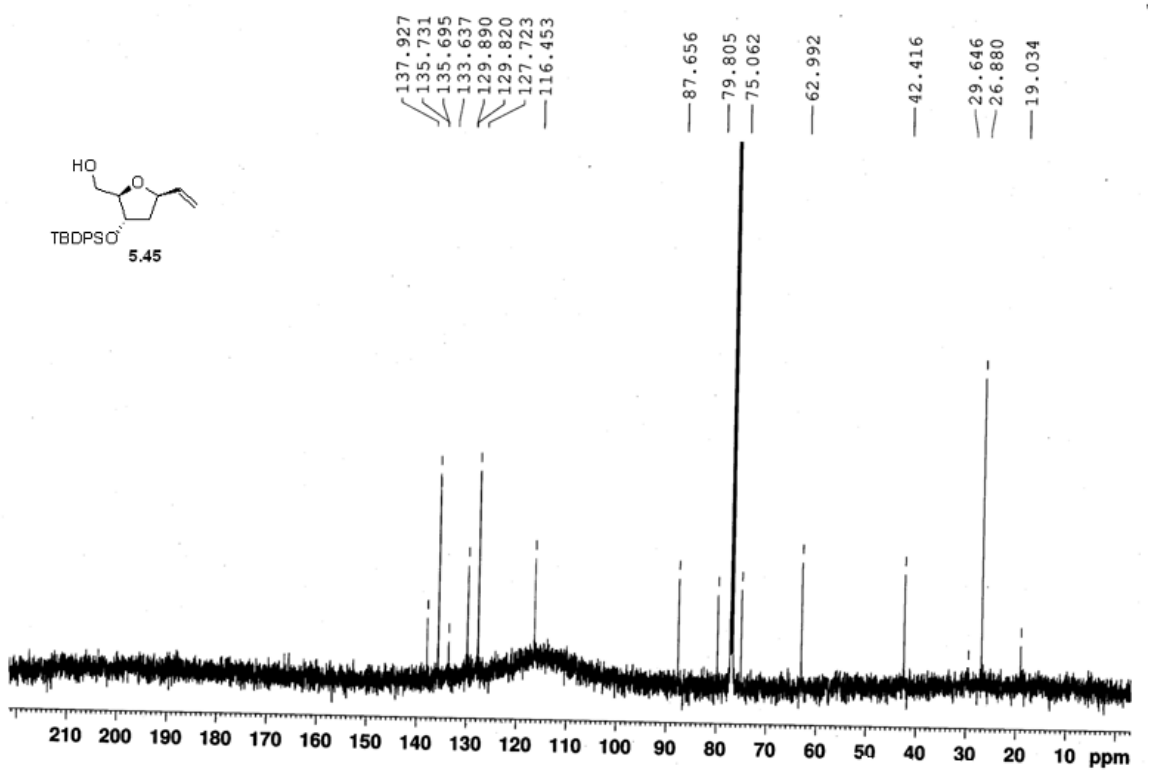


Figure 5.4 ^{13}C NMR spectrum of 5.45

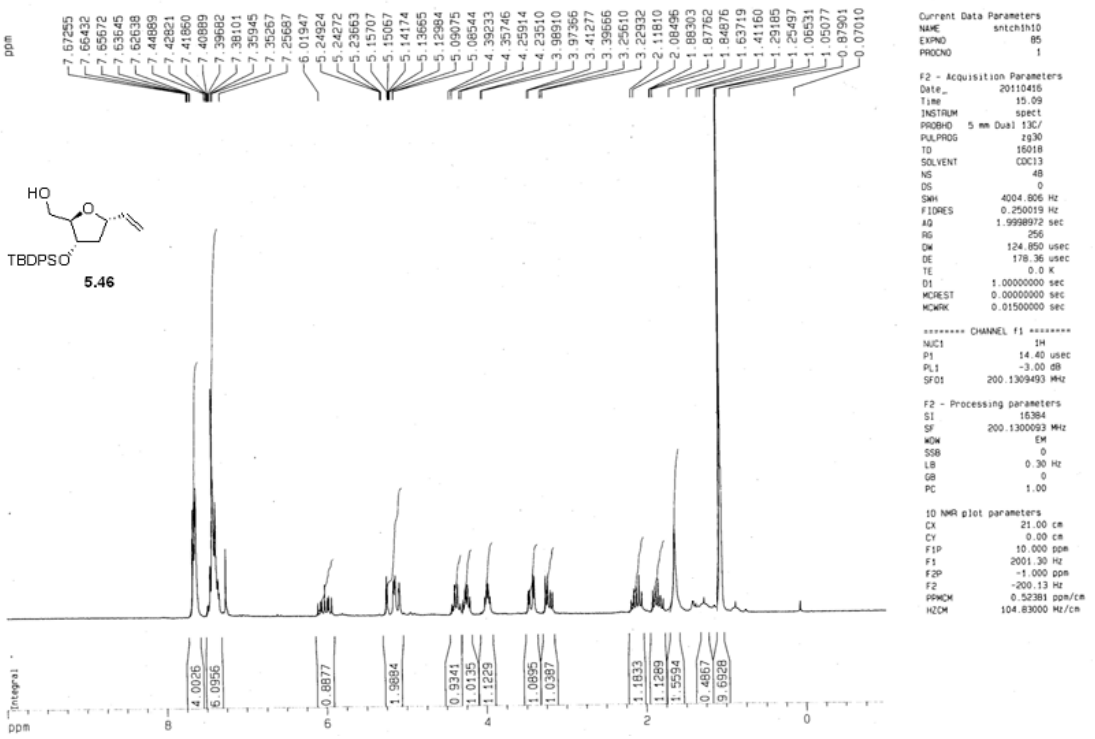


Figure 5.5 ^{1}H NMR spectrum of 5.46

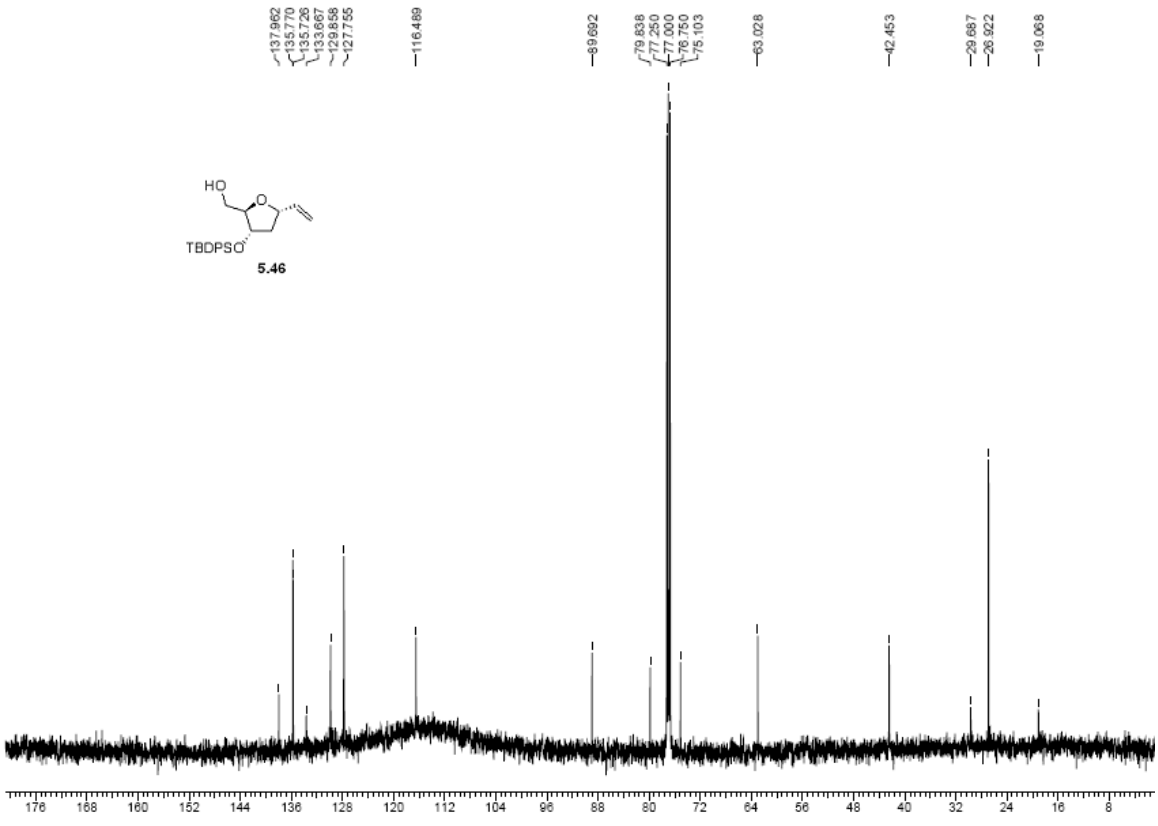


Figure 5.6 ^{1}H NMR spectrum of 5.46

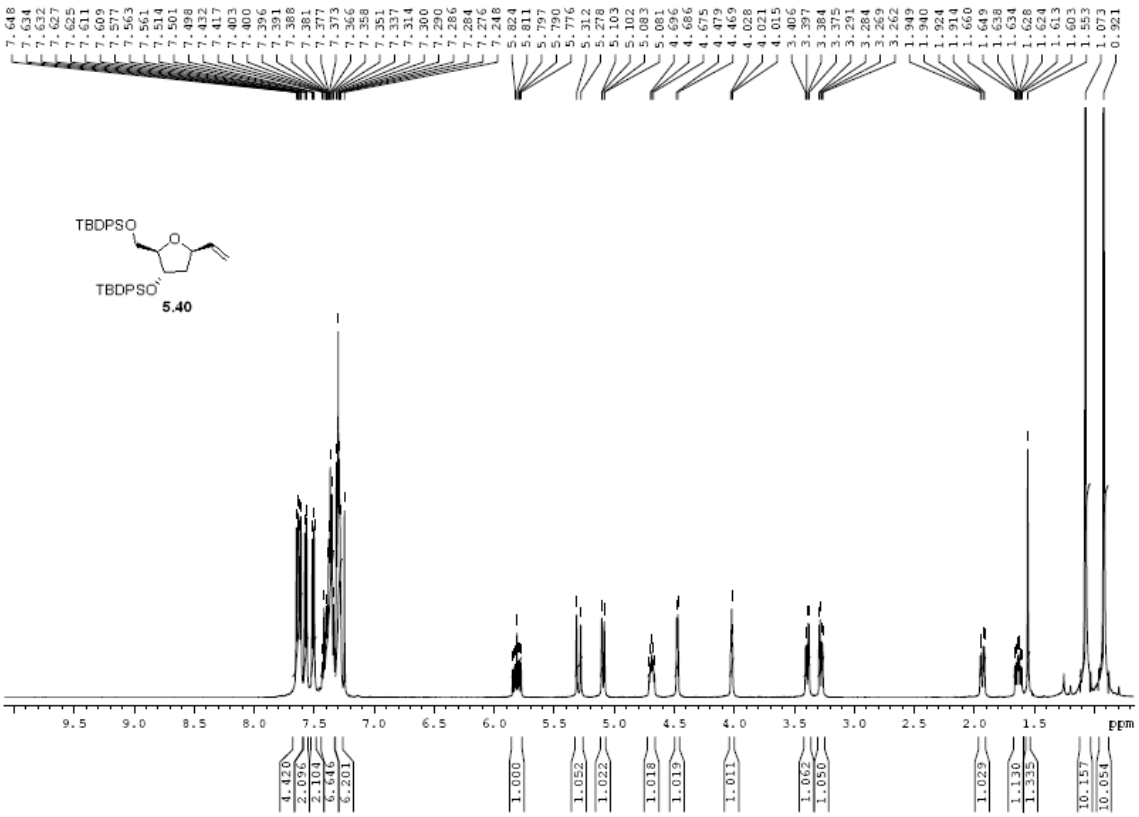


Figure 5.7 ^{1}H NMR spectrum of 5.40

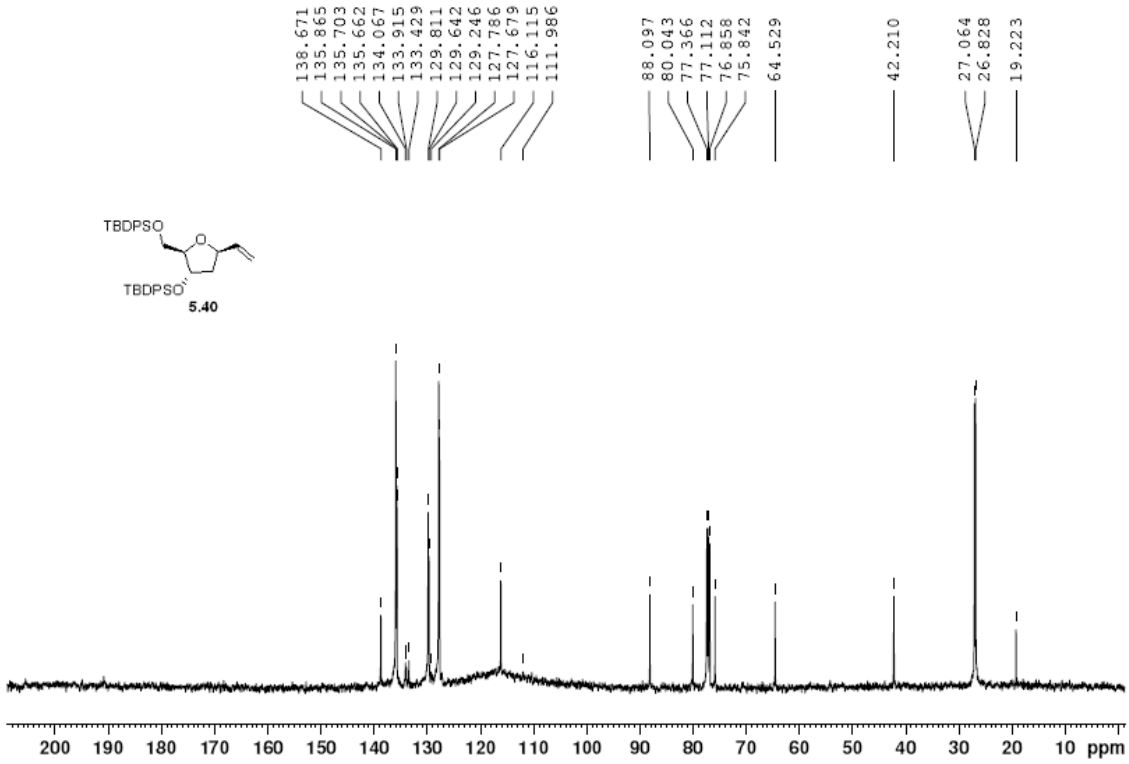


Figure 5.8 ^{13}C NMR spectrum of 5.40

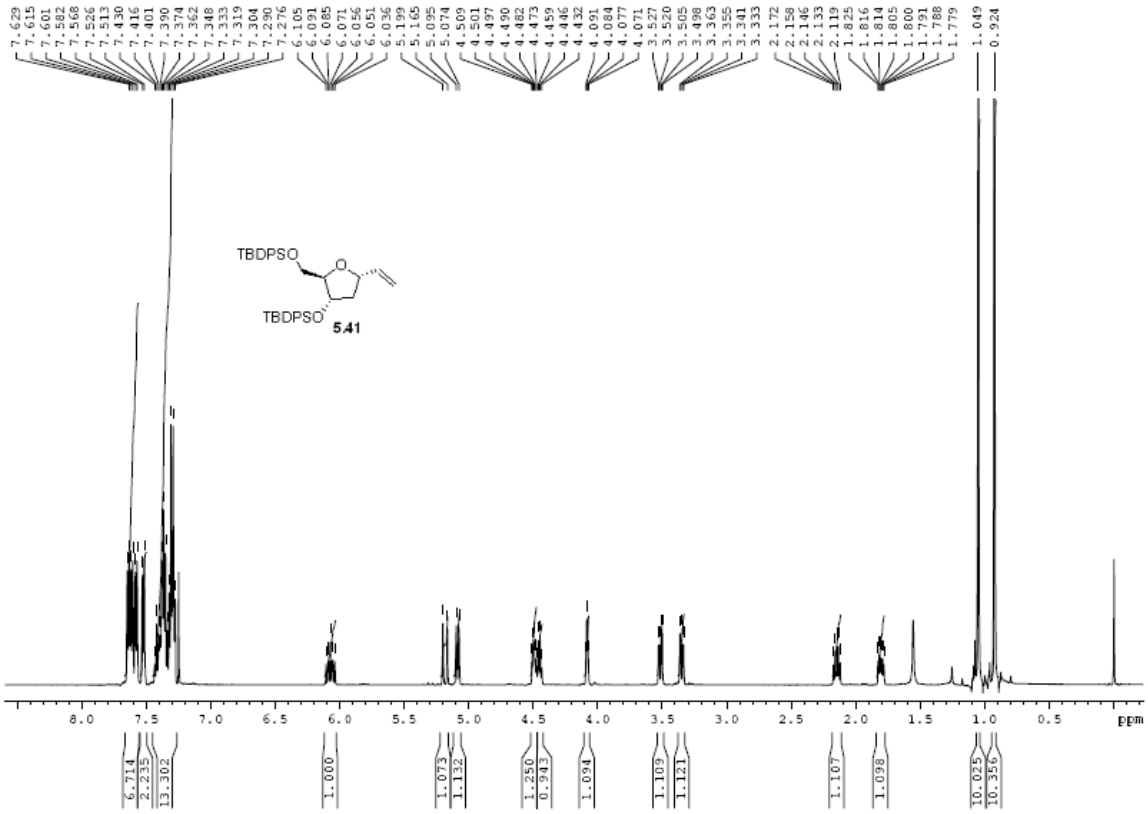


Figure 5.9 ^{1}H NMR spectrum of 5.41

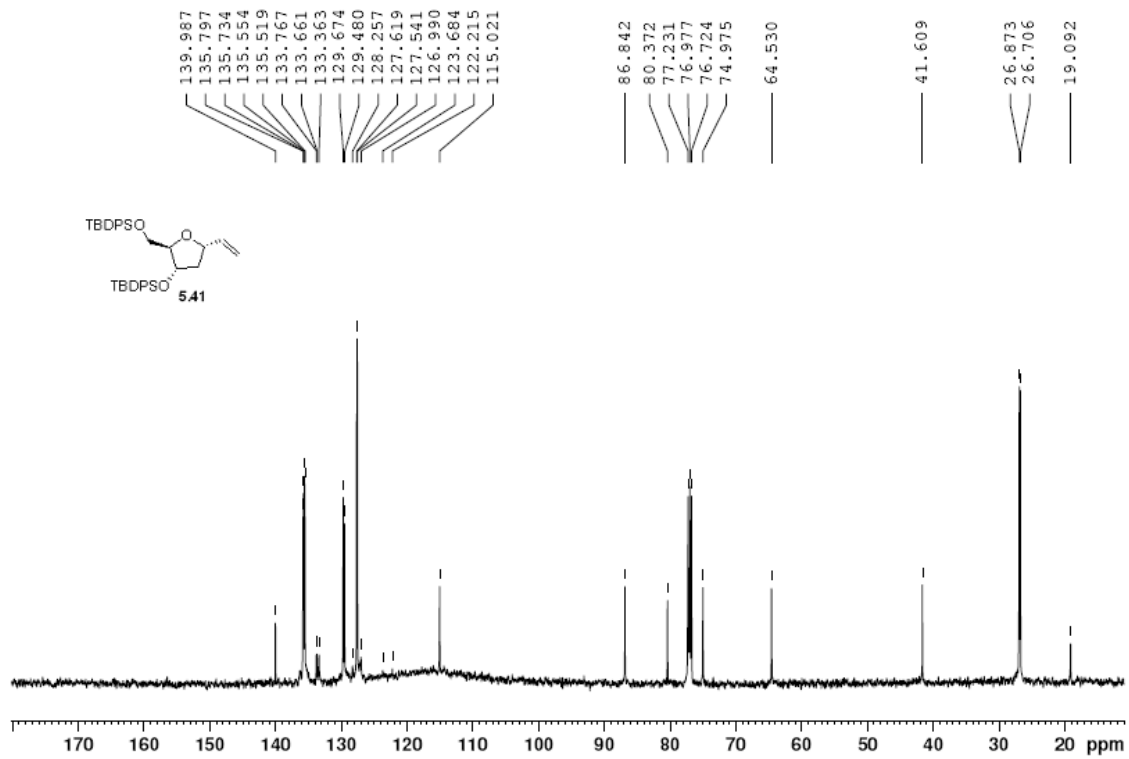
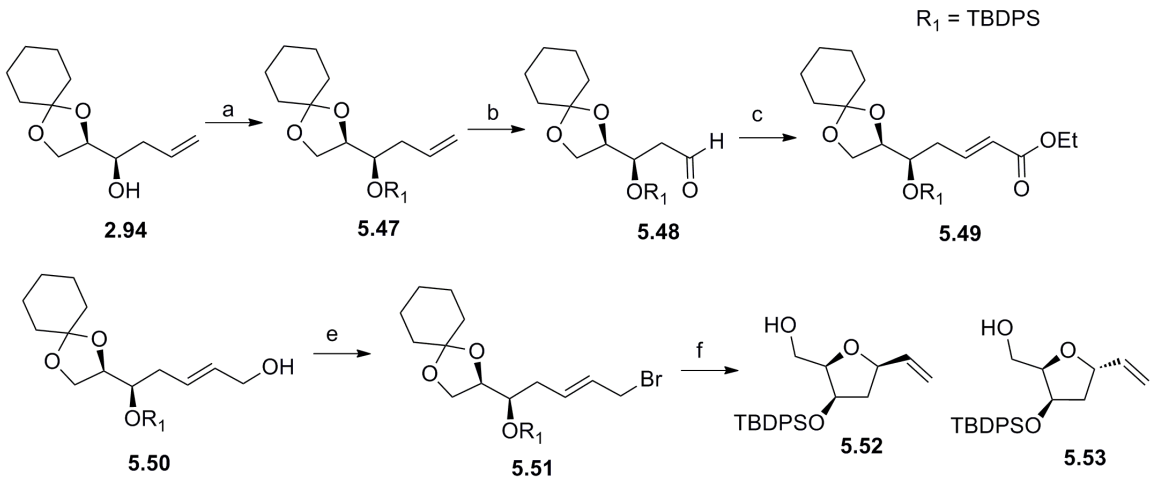


Figure 5.10 ^{13}C NMR spectrum of 5.41

Accordingly we started with *syn*–homoallylic alcohol (**2.94**) which was obtained stereoselectively from **2.65**[202] (**Scheme 2.9**). Silylation of **2.94** afforded **5.47** in quantitative yield. The formation of the product was evident from the absence of hydroxyl band in its IR and the appearance of the signals due to silyloxy and aromatic moiety in its PMR spectrum (**Figure 5.11-5.12**). Ozonolysis of its olefin and reduction of the resulting ozonide in situ with PPh_3 gave relatively unstable aldehyde **5.48** (**Figure 5.13-5.14**). This was quickly subjected to Wittig-Horner olefination[47] to obtain *α,β*-unsaturated ester **5.49** (**Figure 5.15-5.16**). The presence of 2E-ester in **5.49** was ascertained from its ^{1}H-NMR spectrum (**Figure 5.15**) which showed the two olefinic protons at δ 5.69 as a doublet (J = 15.4 Hz) and at δ 6.87 as a dt (J = 15.4, 7.0 Hz). Its ester carbonyl showed a signal at δ 166.1 in its ^{13} C-NMR spectrum (**Figure 5.16**). DIBAL-H reduction of **5.49** afforded allylic alcohol **5.50** (**Figure 5.17-5.18**) in good yield. The progress of the reaction was evident from the absence of all signal corresponding to ester functionality in IR as well as ^{13} C-NMR spectra of **5.50** and the presence of signals of olefinic protons at δ 5.4 in ^{1}H-NMR spectrum (**Figure 5.17**) and at δ 127.4 and δ 127.6 in ^{13}C-NMR spectrum (**Figure 5.18**) . This was converted into the allylic bromide **5.51** in two steps *viz.* mesylation and bromination of the corresponding mesylate with NaBr in good overall yield. The product **5.51** showed the absence of any D_2O exchangeable hydroxyl signal in its ^{1}H-NMR spectrum (**Figure 5.19**) and the presence of a signal at δ 45.0 due to CH_2Br in ^{13} C-NMR spectrum (**Figure 5.20**). The allylic bromide **5.51** was subjected to ketal hydrolysis with TFA (aq) 80% which yielded vinylic tetrahydrofuran as a mixture of diastereoisomers **5.52** and **5.53**. This time, unfortunately these two diastereoisomers couldn't be separated from each other by column chromatography using different solvent combinations as eluent. The ^{1}H NMR analysis of this mixture suggested that both the diastereomers (**5.52** & **5.53)** were

produced almost in a ratio 1:1 (**Figure 5.21**). This could be determined from the integration of the separate signals corresponding to the similar olefinic protons of the two diastereomers.



a) TBDPSCl, Imidazole, DMAP, DCM; b) O_3, PPh_3, DCM,-78 °C; c) NaH, $C_2H_5COOCH_2P(O)(OC_2H_5)_2$, THF, 25 °C; d) DIBAL-H, THF, -78 °C; e) (1) MsCl, Et_3N, DCM, 0 °C, (2) NaBr, $NaHCO_3$, Dry Acetone, 25 °C; f) Aq.TFA (80%), CH_2Cl_2, 0 °C;

Scheme 5.7

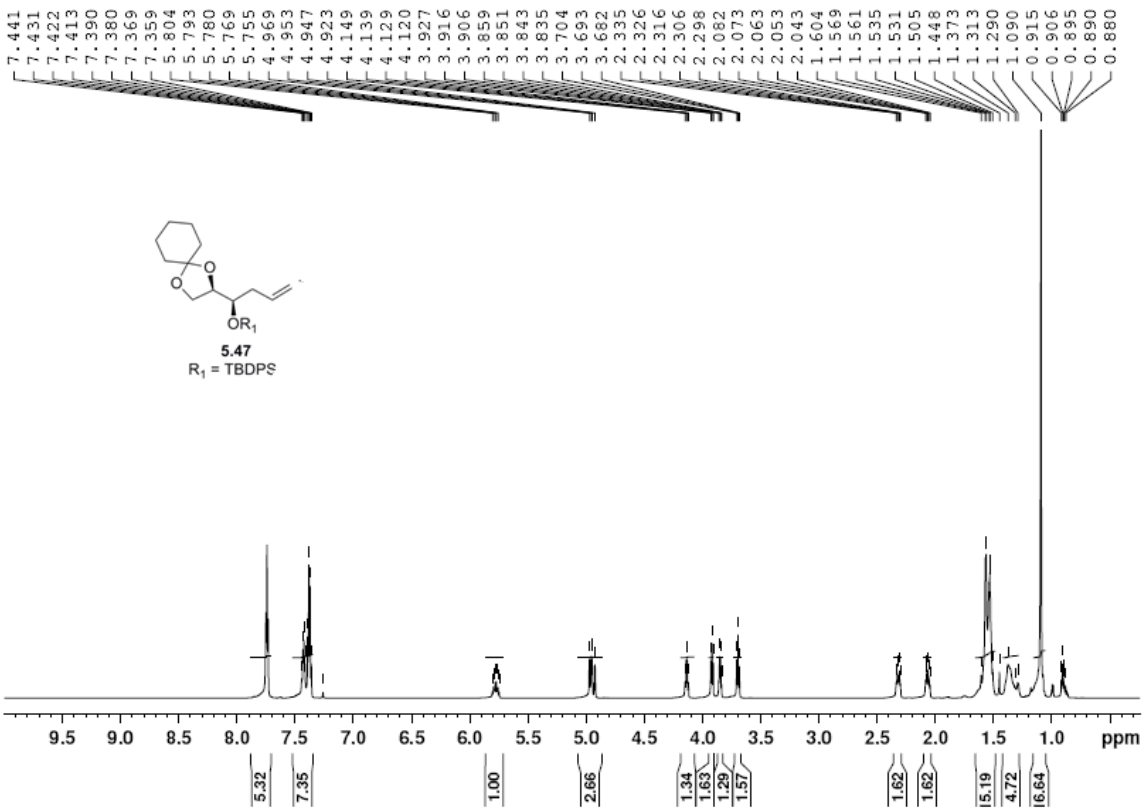


Figure 5.11 ^{1}H NMR spectrum of 5.47

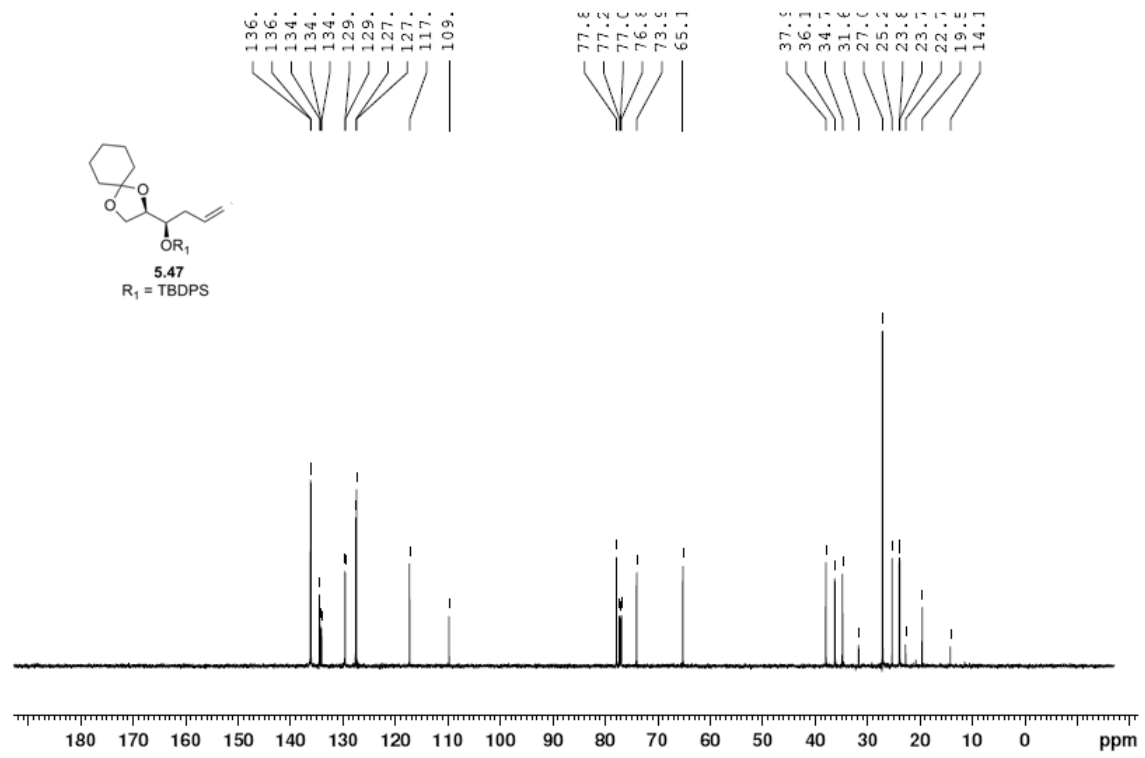


Figure 5.12 ^{13}C NMR spectrum of 5.47

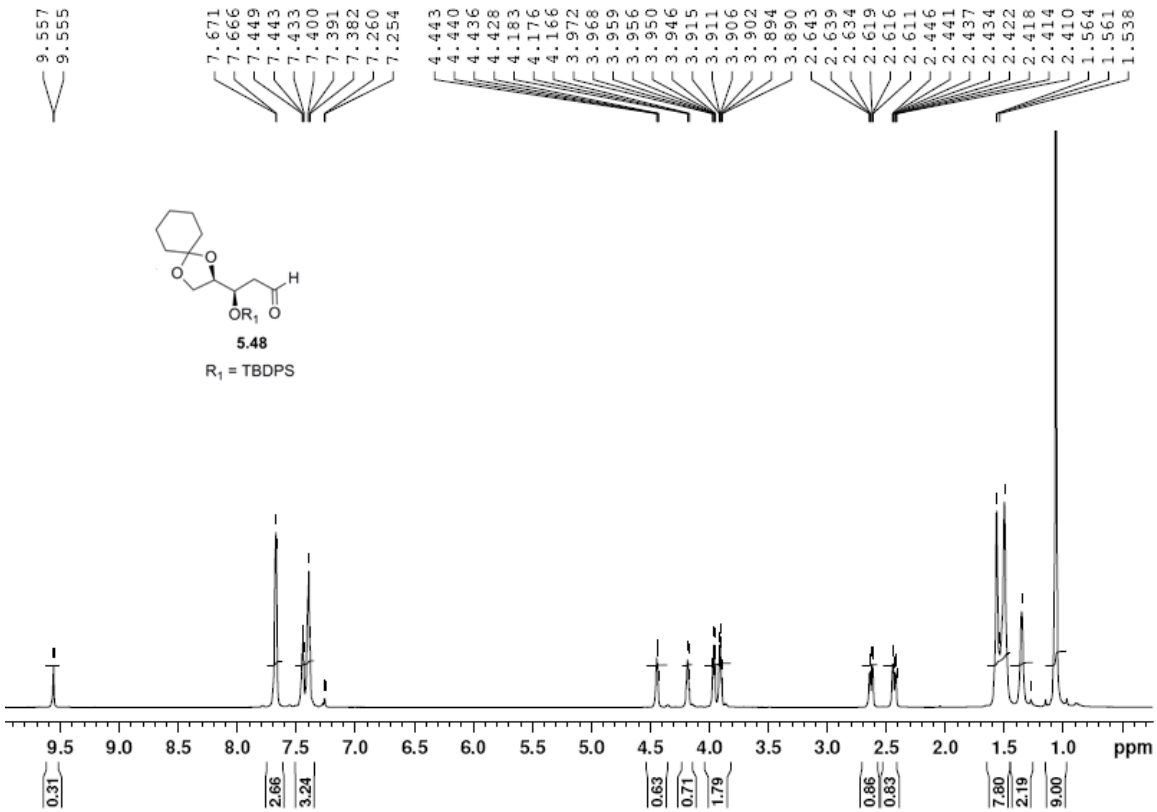


Figure 5.13 ^{1}H NMR spectrum of 5.48

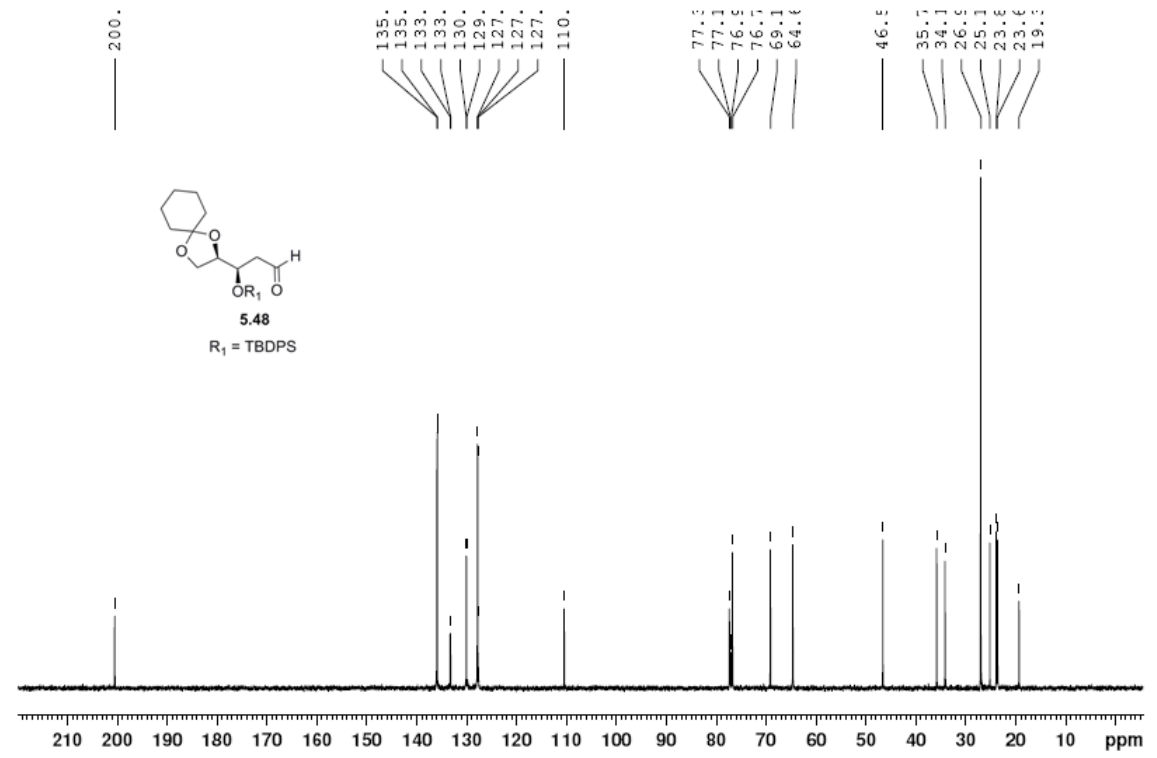


Figure 5.14 ^{13}C NMR spectrum of 5.48

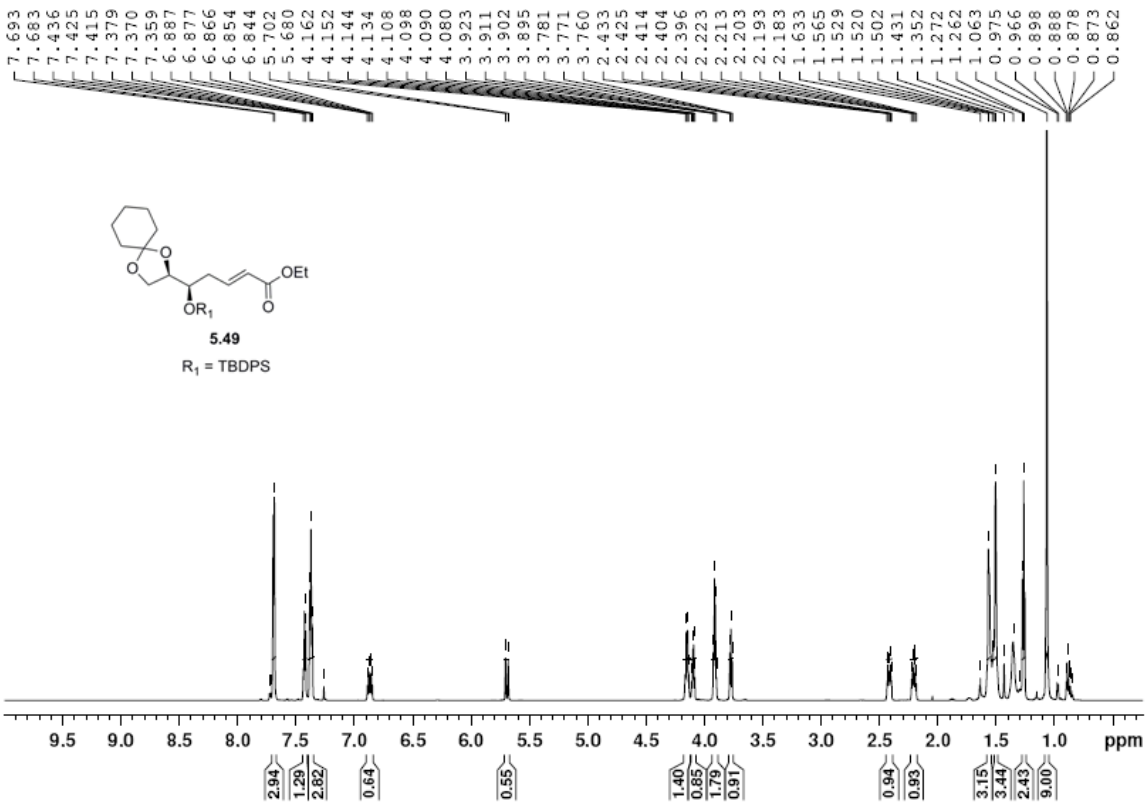


Figure 5.15 ^{1}H NMR spectrum of 5.49

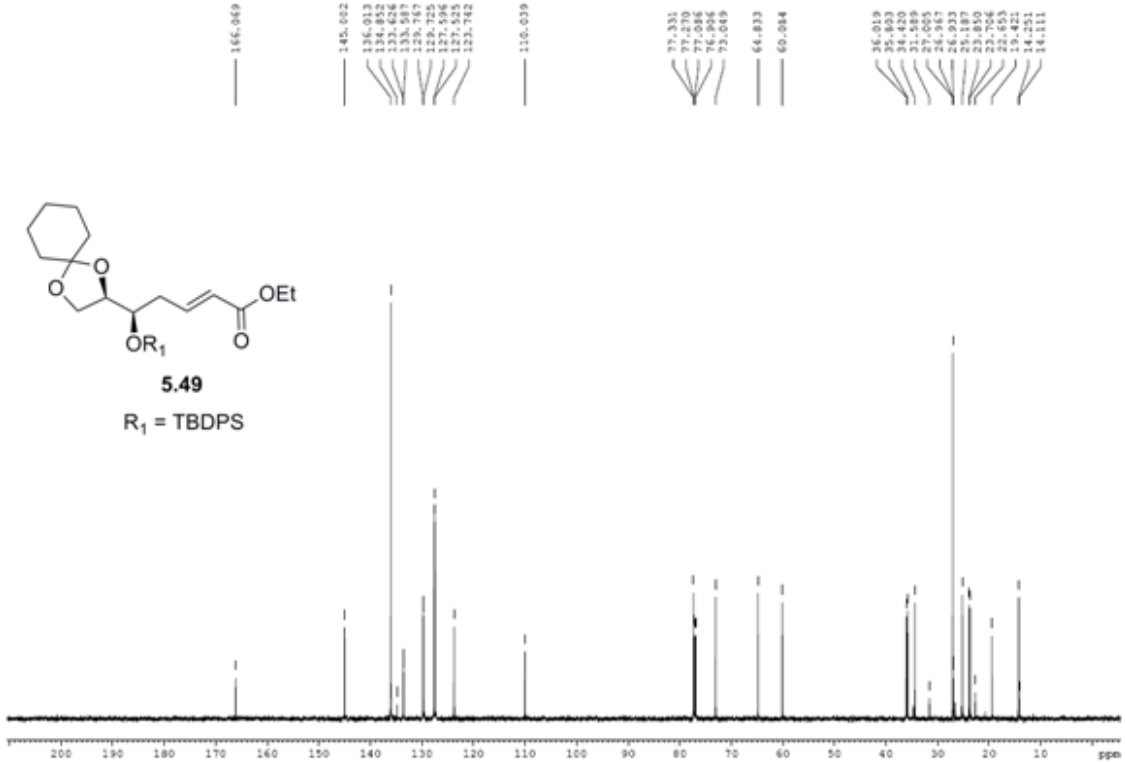


Figure 5.16 ^{13}C NMR spectrum of 5.49

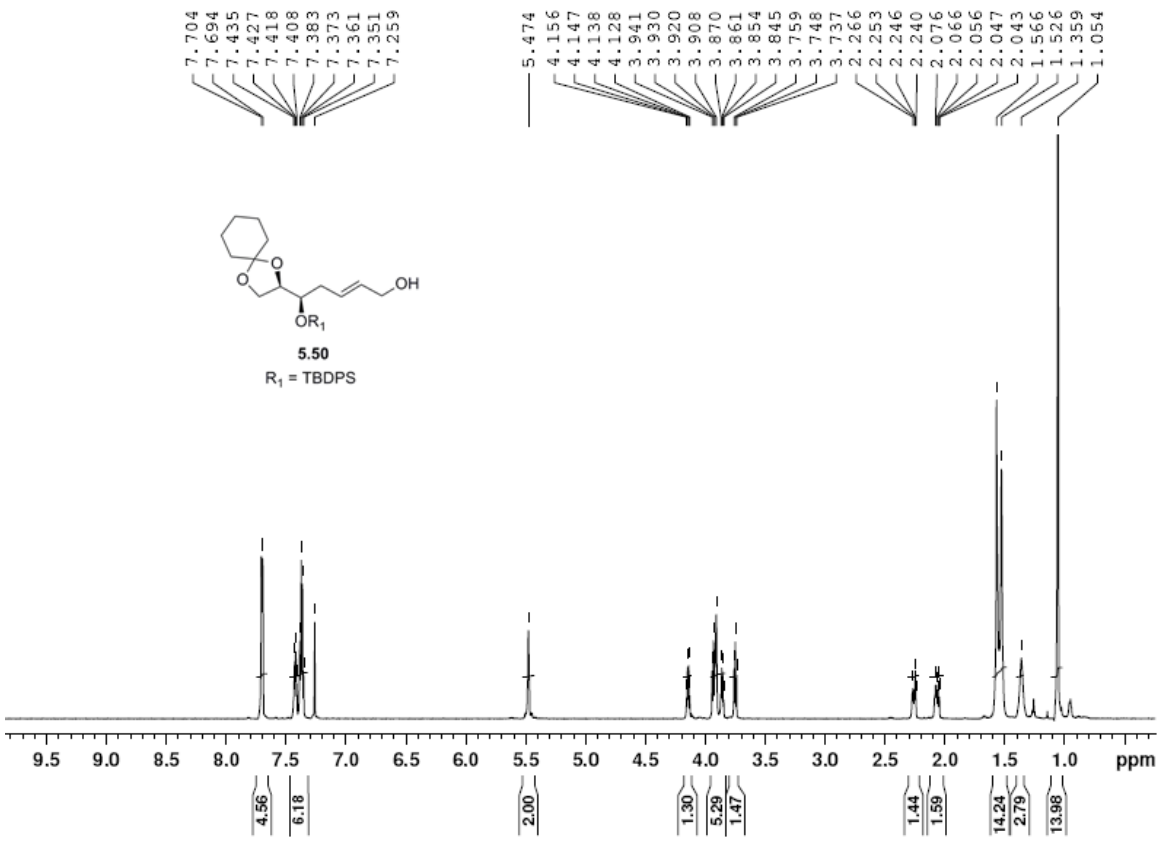


Figure 5.17 ^{1}H NMR spectrum of 5.50

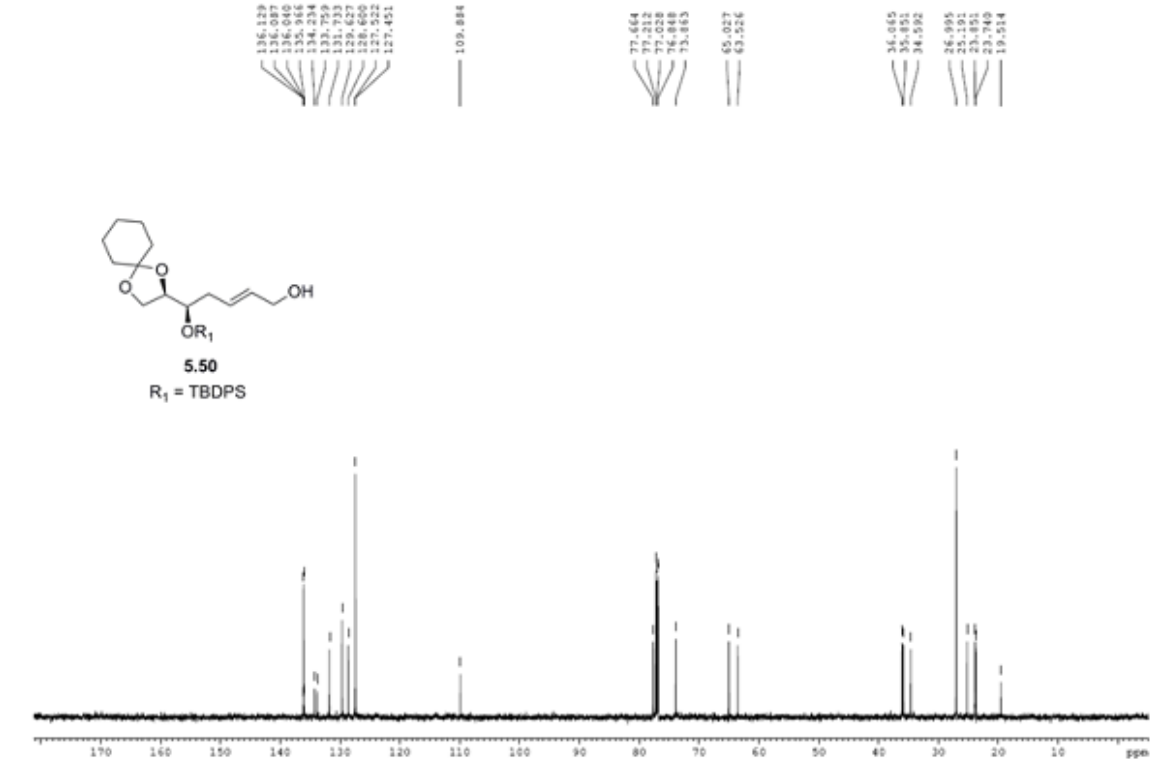


Figure 5.18 ^{13}C NMR spectrum of 5.50

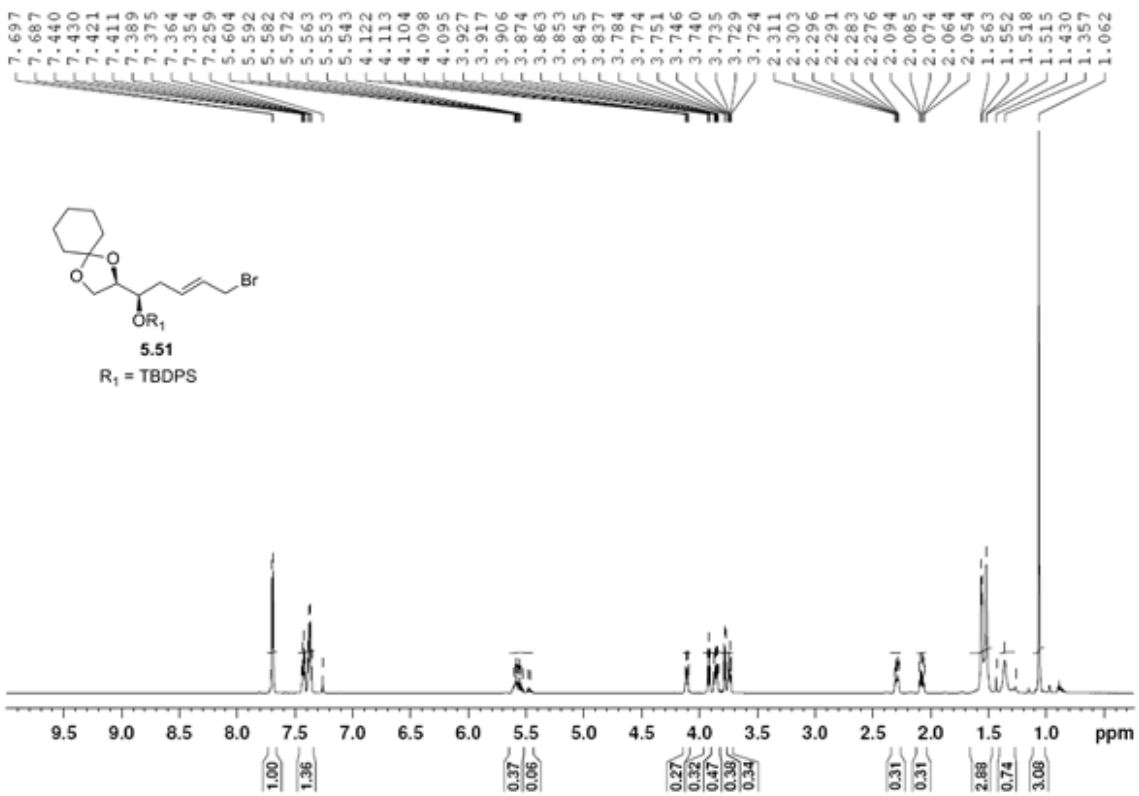


Figure 5.19 ^{1}H NMR spectrum of 5.51

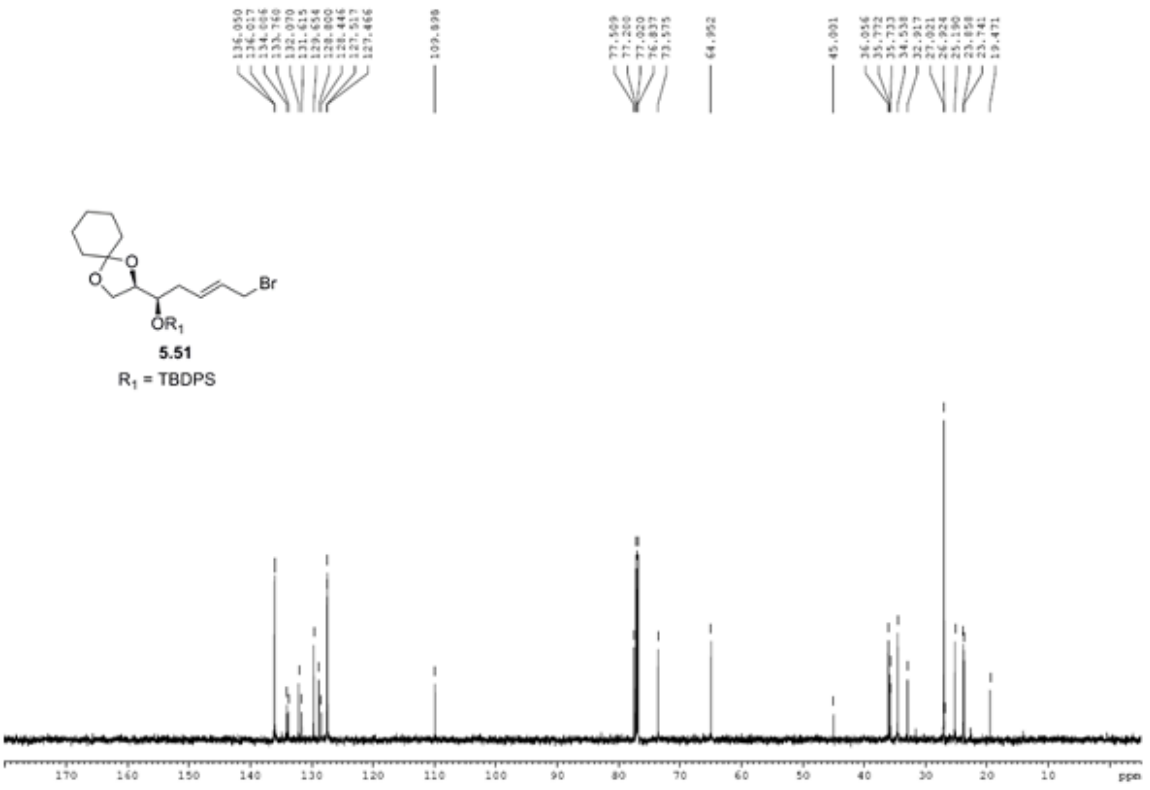


Figure 5.20 ^{13}C NMR spectrum of 5.51

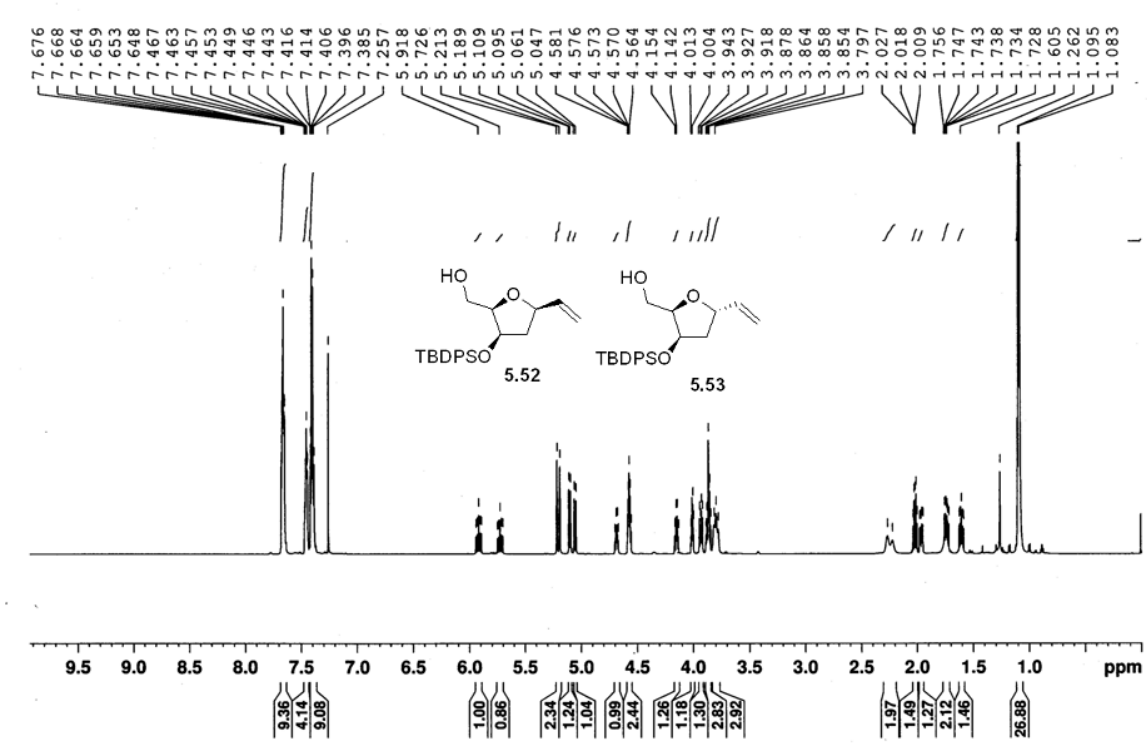


Figure 5.21 ^{1}H NMR spectrum of 5.52 and 5.53

5.II.I Towards Stereo divergent formal synthesis of Decarestrictine-O.

The Decarestrictines are secondary metabolites form a family of inhibitors of cholesterol biosynthesis, produced by different strains of *Penicillium*. So far only 6 members of the decanolides family have been discovered (**Figure 5.22**). This 10-membered lactone varies in their oxygenation pattern from C-3 to C-7 and the location, or absence, of a double bond. These decarestrictine has been demonstrated to inhibit cholesterol biosynthesis in HEP-G2 liver cells and *in vivo* studies. Hence these molecules have pharmaceutical properties for the treatment of coronary diseases which are widely prevalent all over the world. Due to its high importance, preparation of decarestrictine drew considerable attention of synthetic chemists over the ages.

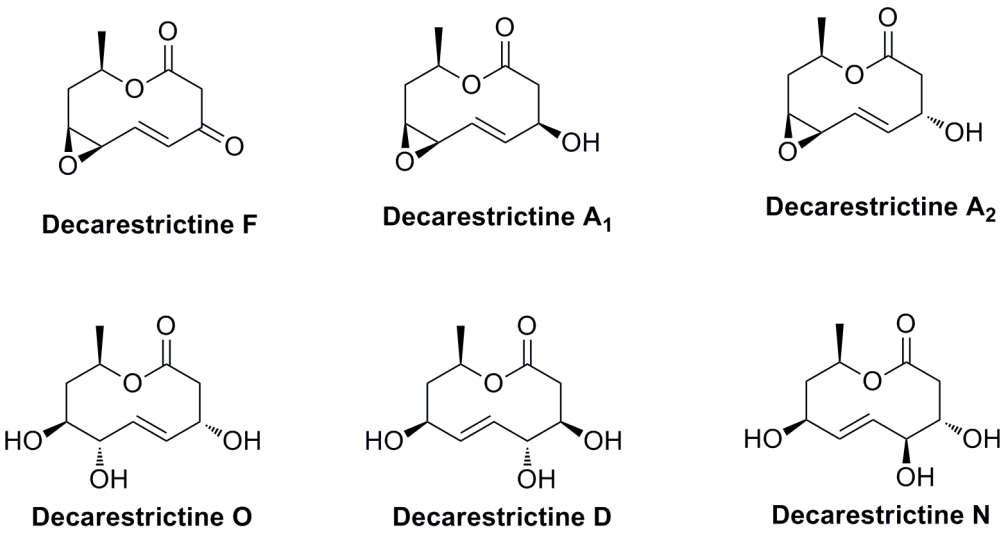
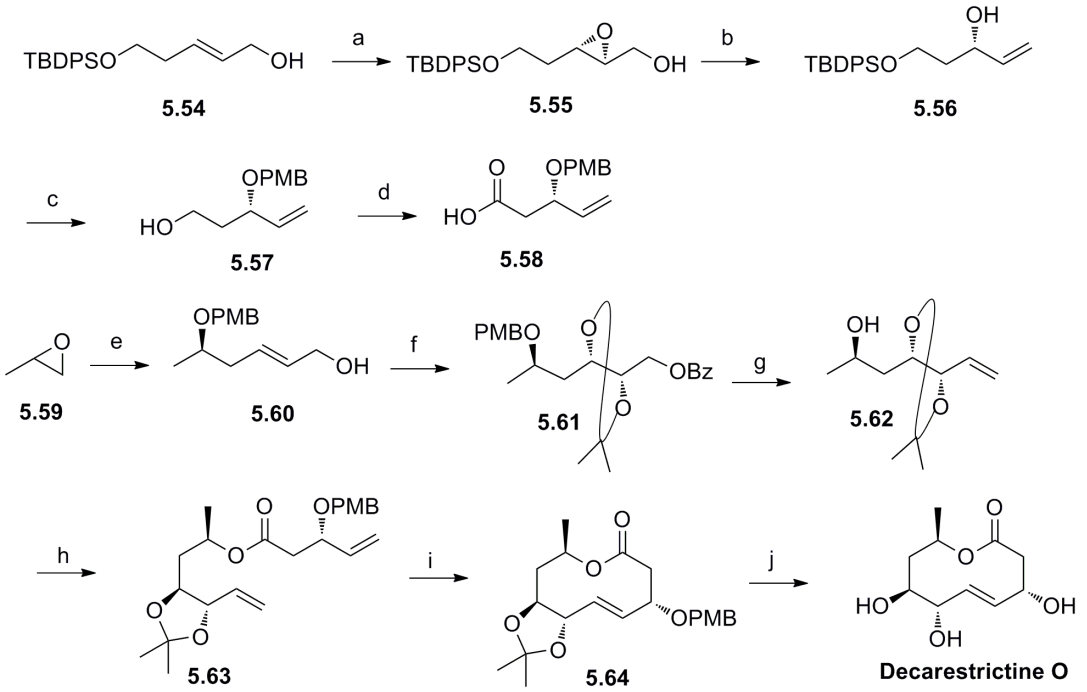


Figure 5.22 Family of Decarestrictine

5.II.II Earlier Work in Literature

The first stereoselective synthesis of Decarestrictine-O was reported by P. R. Krishna *et al*.[203] the synthetic process involves Jacobsen's kinetic resolution, Sharpless asymmetric epoxidation, Yamaguchi esterification and ring closing metathesis as the key steps (**Scheme 5.8**). The complete synthesis was done in two parts where the synthesis of part one (**5.58**) starts with the allylic alcohol **5.54** obtained from propane diol which was subjected to Sharpless asymmetric epoxidation to afford the epoxy alcohol **5.55**. The epoxy alcohol **5.55** was converted to the allylic alcohol **5.56** by first converting it to a chloro epoxy alcohol which follows the elimination reaction to give **5.56**. The alcohol was protected with PMB followed by desilylation and oxidation of the primary alcohol obtained to acid completes the synthesis of part one (**5.58**). The second part of the molecule (**5.62**) was synthesized from a chiral propylene oxide **5.59** which was converted to the allylic alcohol **5.60** following a reported procedure.[204] The allylic alcohol **5.60** after benzoylation was subjected to Sharpless asymmetric di-hydroxylation (AD-mix-α) gave the *syn* diol and protection of the diol with acetonide gave **5.61**. Compound **5.61** on debenzoylation, Swern's oxidation followed by Wittig olefination and PMB group

removal gave **5.62**. Previously synthesized compound **5.58** was subjected to Yamaguchi esterification with **5.62** to afford the diene **5.63**; this was subjected to RCM to yield **5.64** which follows global deprotection to give the desired compound Decarestrictine-O.

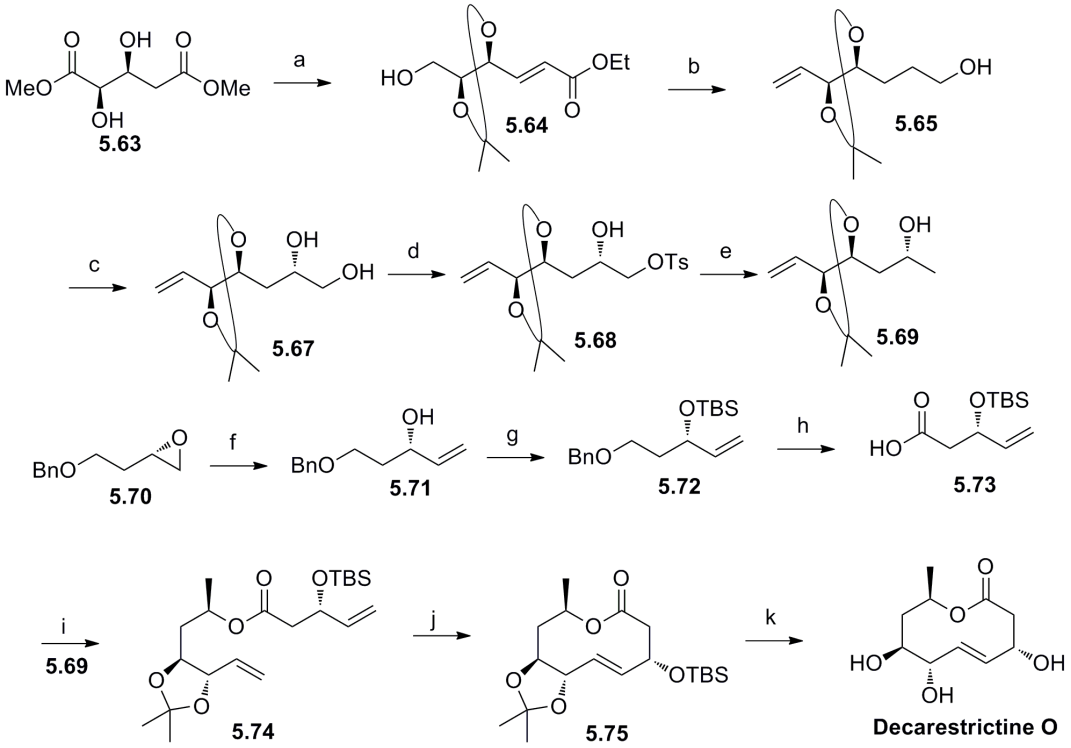


a) (+)-DIPT, $Ti(O^iPr)_4$, Cumenehydroperoxide, CH_2Cl_2, -20 °C; b) (1) CCl_4, PPh_3, $NaHCO_3$, reflux, (2) Na/ether, ether, 0 °C to RT; c) (1) NaH, PMBBr, THF, (2) TBAF, THF; d) (1) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78 °C, (2) $NaClO_2$, $NaH_2PO_4.2H_2O$, *t*-BuOH/2-methyl-2- butene(3:1), 0 °C to RT; e) ref 204; f) (1) BzCl, Et_3N, (2) AD-mix-β, (3) 2,2–DMP, CH_2Cl_2, PTSA,; g) (1) K_2CO_3, MeOH, (2) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78 °C, (3) Ph_3PCH_3I, KO^t-Bu, THF, (4) DDQ, CH_2Cl_2/H_2O(19:1); h) 2,4,6-trichlorobenzylchloride, Et_3N, THF, then DMAP, **5.62**, toluene, 0 °C; i) Grubb's II generation catalyst, CH_2Cl_2, reflux; j) TFA, CH_2Cl_2

Scheme 5.8

J. S. Yadav *et al.*[205] recently reported the stereoselective synthesis of Decarestrictine-O employing RCM as one of the key steps to construct the macrolide (**Scheme 5.9**). The total synthesis comprises of the synthesis of two parts **5.69** and **5.73**. Synthesis of the compound **5.69** started with the synthesis of ε-hydroxy-*α,β*-unsaturated ester (**5.64**) from trans dimethyl L-tartarate(**5.63**). The ε-hydroxy-*α,β*-unsaturated ester (**5.64**) was subjected to hydrogenation reaction to yield the saturated ε-hydroxy ester which was subjected to oxidation of the alcohol followed by C1 Wittig olefination

followed by the reduction of the ester to give the corresponding alcohol **5.65**. The alcohol **5.65** upon oxidation gave the corresponding aldehyde which was subjected to MacMillan α-hydroxylation followed by reduction with $NaBH_4$ and cleavage of O-N bond with $CuSO_4$ gave the diol **5.67**. The primary hydroxyl of the diol **5.67** was selectively



a) (1) 2,2–DMP, benzene, PTSA, reflux, (2) DIBAL-H, $[(EtO)_2POCHCO_2Et]^-Na^+$, -78 °C to RT; b) (1) H_2 Pd/C, EtOH, (2) IBX, DMSO, CH_2Cl_2, 0 °C to RT, (3) Ph_3PCH_3, KO^tBu, THF, -10 °C to RT; c) PhNO, D-proline, DMSO, $NaBH_4$, MeOH, $CuSO_4.5H_2O$ -20 °C to RT; d) TsCl, Et_3N, Dibutyl tin oxide, , CH_2Cl_2, 0 °C to RT; e) $LiAlH_4$, THF, reflux; f) $Me_3S^+I^-$, n-BuLi, THF, -20 °C to RT; g) TBSCl, Imidazole, DMAP, CH_2Cl_2, 0 °C to RT; h) (1) Li/Napthalene, THF, -20 °C, (2) IBX, DMSO, CH_2Cl_2, 0 °C to RT, (3) $NaClO_2$, NaH_2PO_4, 2-metlyl-2-butene, t-BuOH, H_2O; i) DCC, DMAP, CH_2Cl_2, 0 °C to RT; j) Grubb's II generation catalyst, CH_2Cl_2, Reflux; k) PTSA, MeOH, 0 °C to RT.

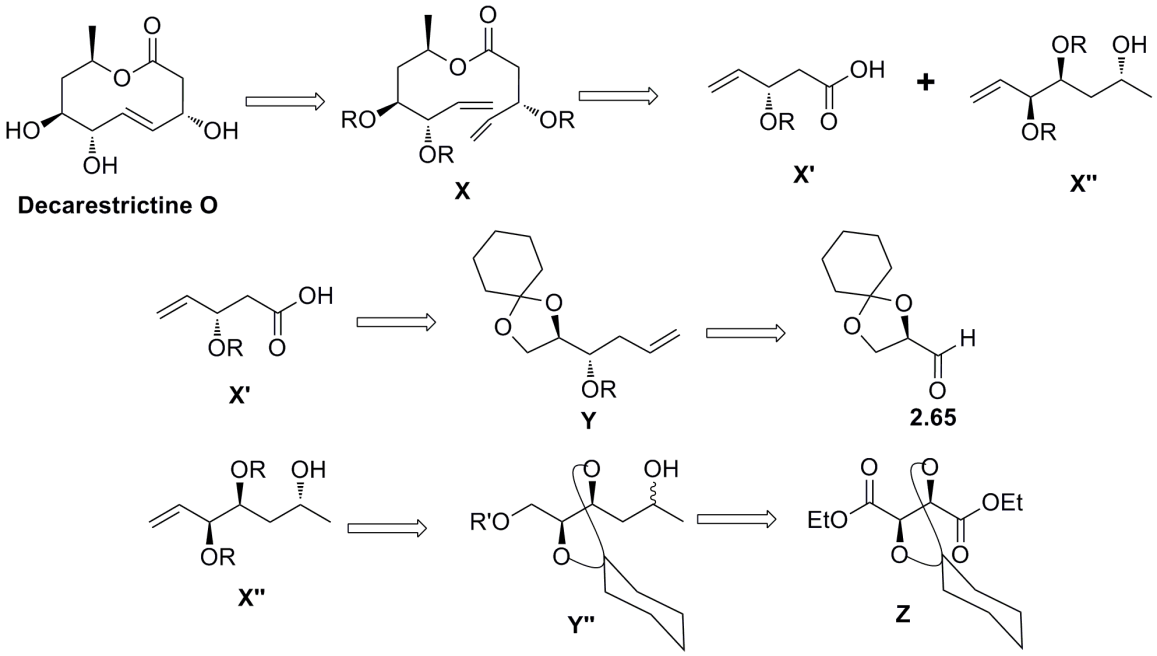
Scheme 5.9

protected with tosyl to give the tosylate **5.68** which on treatment with LAH at elevated temperature get reduced to give the alcohol **5.69**. The acid fragment was synthesized by Jacobsen's hydrolytic kinetic resolution of the racemic epoxide to give the *S*-epoxide **5.70** which was subjected to ring opening with trimethylsulfonium iodide to give the alcohol **5.71**. The hydroxyl of compound **5.71** was protected with TBS and debenzylation followed by oxidation of the corresponding alcohol gave the acid **5.73**. The acid **5.73** was

coupled with the alcohol of **5.69** via esterification reaction to give **5.74** which was subjected to RCM with Grubbs II generation catalyst to yield the cyclized product **5.75**; this on global deprotection gave Decarestrictine-O.

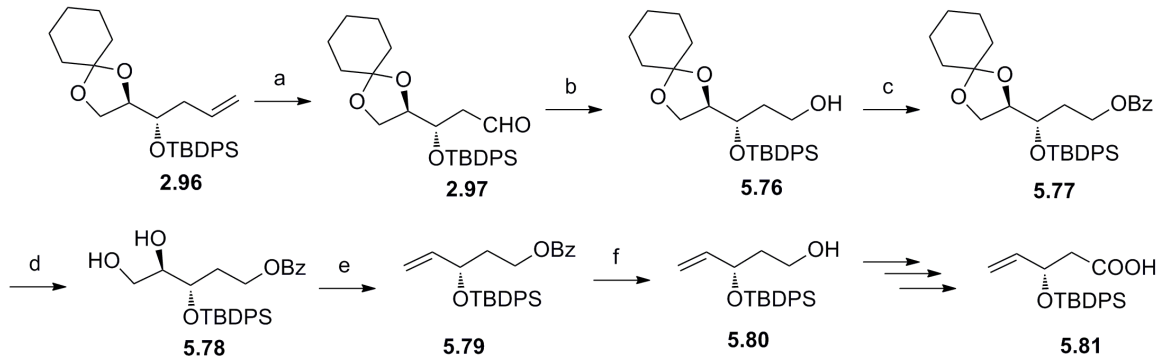
5.II.III Our Work

Considering the biological importance we wish to develop a simple and stereodivergent synthetic strategy for Decarestrictine-O. The retro synthetic analysis shows that the total synthesis can be achieved by the RCM of the diene **X** which can be synthesized by condensation of two different fragments **X'** and **X''** *via* esterification process (**Scheme 5.10**). Fragment **X'** could be synthesized from homoallylic alcohol obtained from the allylation of the (*R*)-2,3-*O*-cyclohexylideneglyceraldehyde (**2.65**). On the other hand, fragment (**X''**) was planned to be synthesized from the 2,3-*O*-cyclohexylidene-**L**-(+)-diethyltartarate (**Z**) which had been prepared in our laboratory from commercially available **L**-(+)-diethyltartarate.[206]



Scheme 5.10

The synthesis of the acid fragment was started with the ozonolysis of olefin of the silylated *anti*-homoallylic alcohol obtained in scheme **2.10** (**Chapter 2**), followed by concomitant reduction of the resulting ozonide with PPh_3 to obtain aldehyde (**2.97**). This was reduced with $NaBH_4$ to obtain alcohol **5.76** in good yield. The progress of the reaction was confirmed due to the absence of the signals due to aldehyde functionality both in the ^{1}HNMR (**Figure 5.23**) and ^{13}CNMR (**Figure 5.24**) of **5.76**. The alcohol **5.76** was then benzoylated using benzoyl cyanide to give a quantitative yield of **5.77**. This was confirmed from the presence of an ester signal at δ 166.3 in the ^{13}CNMR (**Figure 5.25-5.26**) of **5.77**. The benzoate **5.77** was subjected to ketal hydrolysis to give the diol **5.78** which was characterized due the absence of the signals at the aliphatic region between δ 1.5-1.7 in ^{1}H NMR (**Figure 5.27-5.28**). The resulting diol **5.78** was converted to the olefin **5.79** (**Figure 5.29-5.30**) over two steps (i) ditosylation of the diol using TsCl and pyridine, (ii) reduction of the corresponding ditosylate by NaI/Zn. Compound **5.79** could be transformed into the acid fragment of Decarestrictine-O **5.81** through hydrolysis of its benzoate on base treatment, followed by oxidation of the resulting alcohol **5.80**.



a) O_3, PPh_3,CH_2Cl_2, -78 °C; b) $NaBH_4$, MeOH; c) BzCN, Et_3N, CH_2Cl_2, 25°C; d) TFA:DCM (2:8); e) TsCl, Py, Zn, NaI, DMF,80°C; f) K_2CO_3 MeOH.

Scheme 5.11

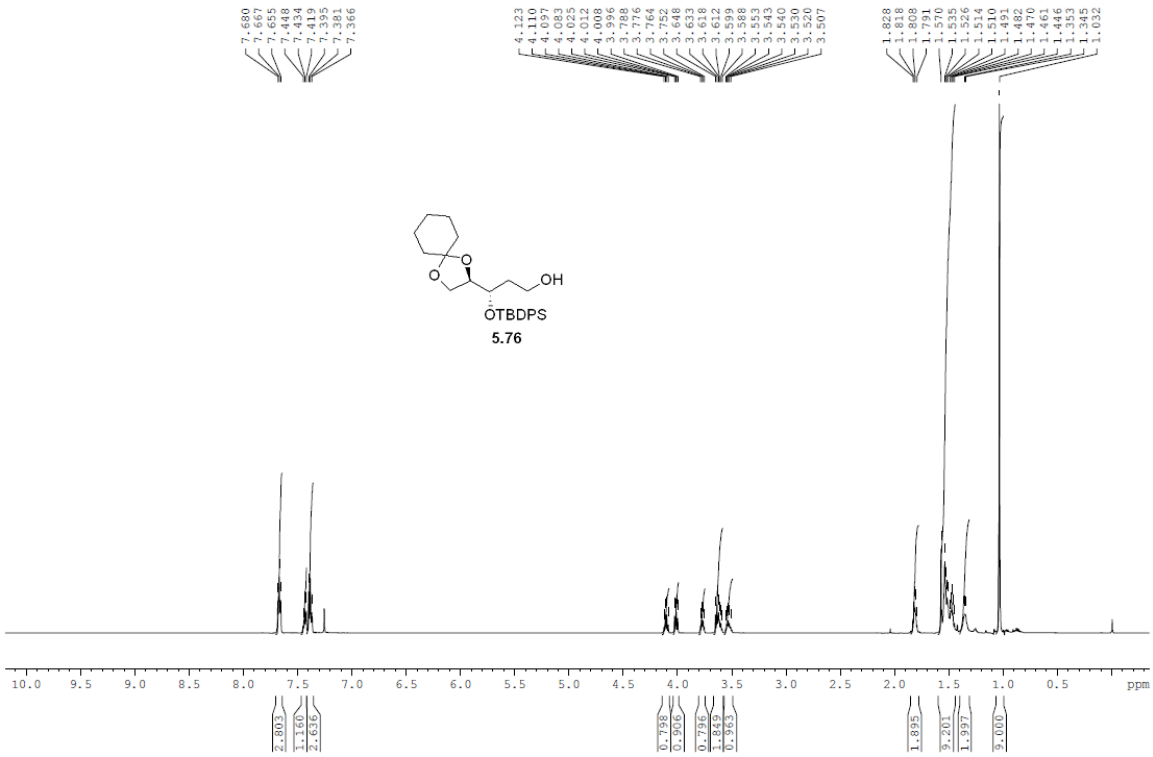


Figure 5.23 ^{1}H NMR spectrum of 5.76

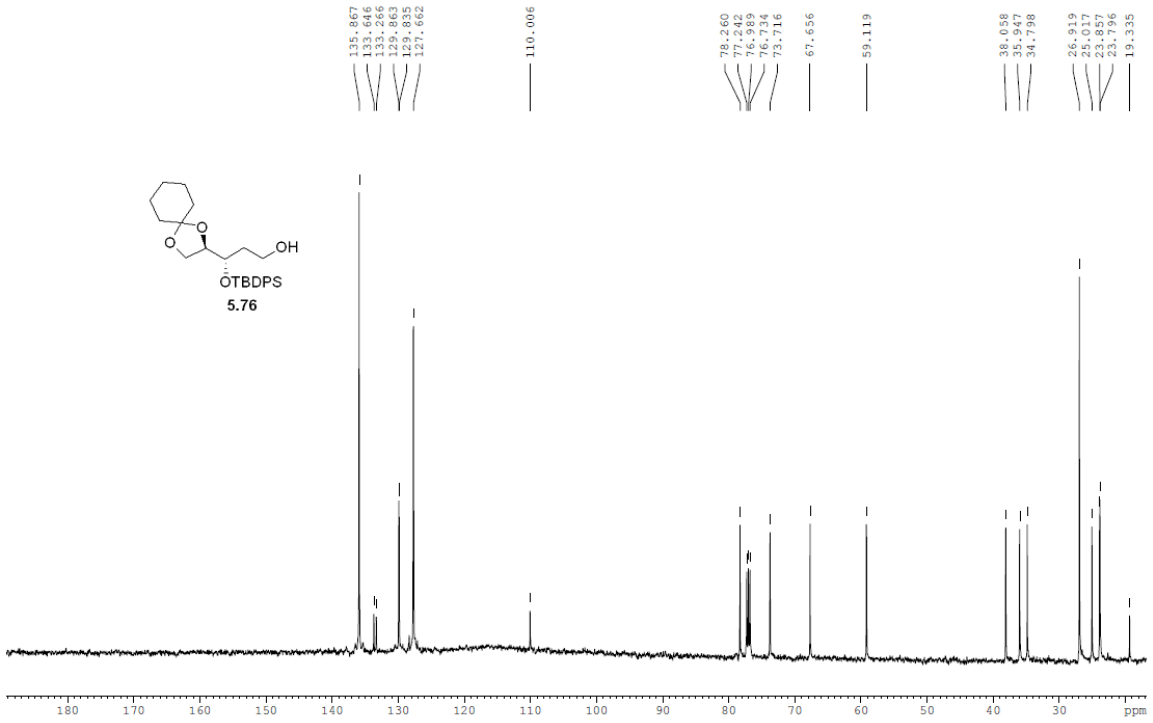


Figure 5.24 ^{13}C NMR spectrum of 5.76

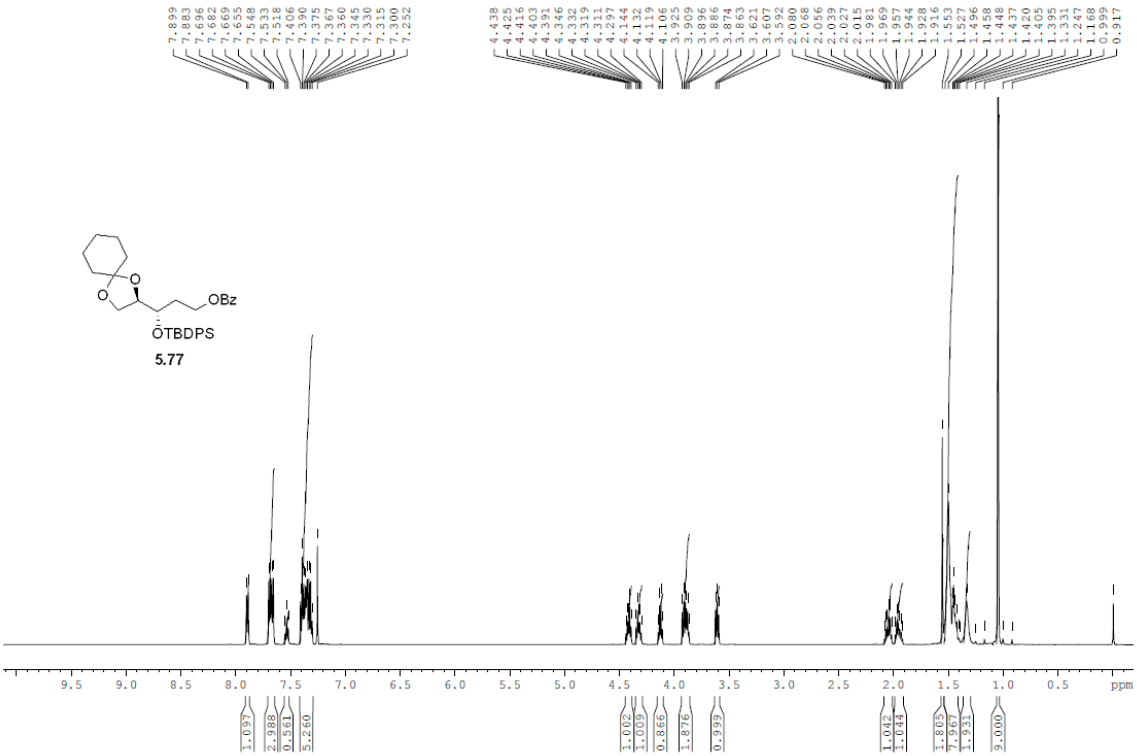


Figure 5.25 ^{1}H NMR spectrum of 5.77

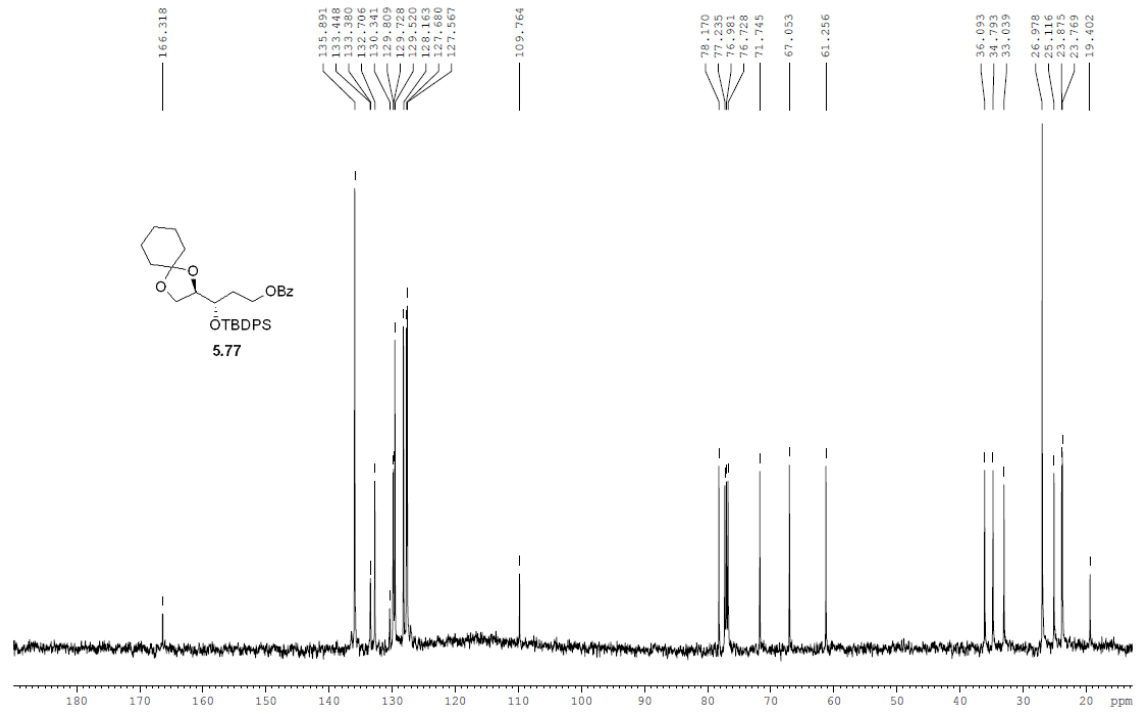


Figure 5.26 ^{13}C NMR spectrum of 5.77

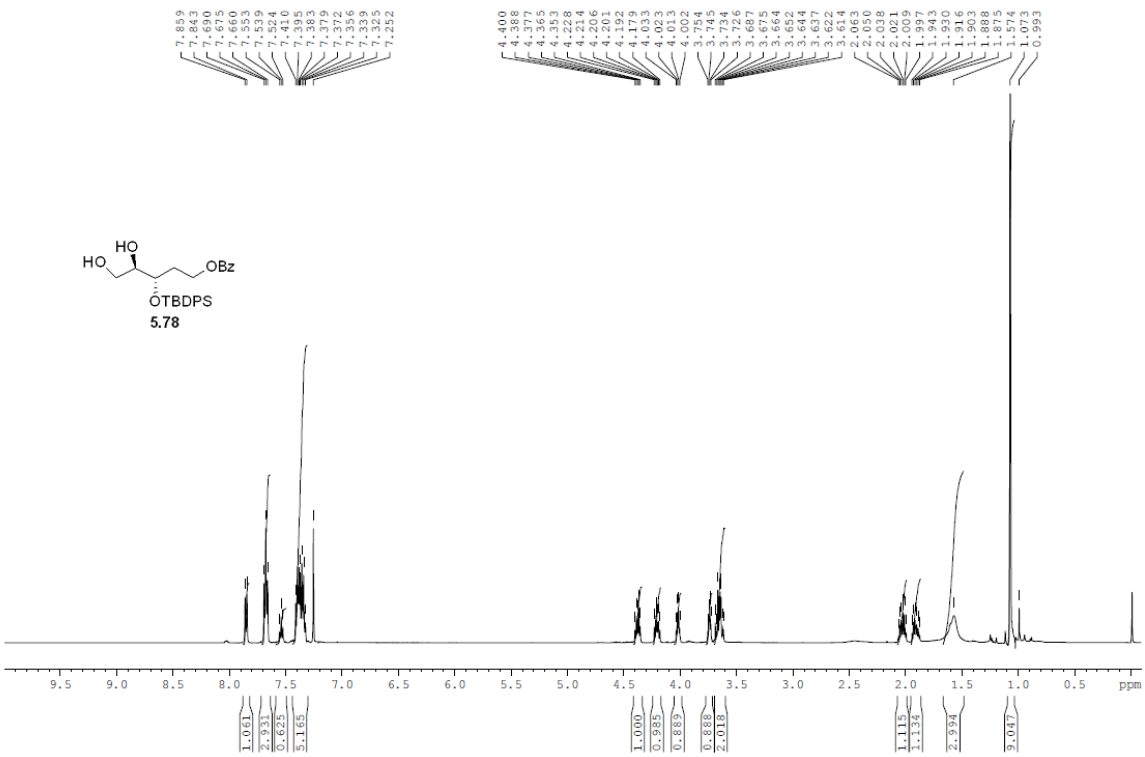


Figure 5.27 ^{1}H NMR spectrum of 5.78

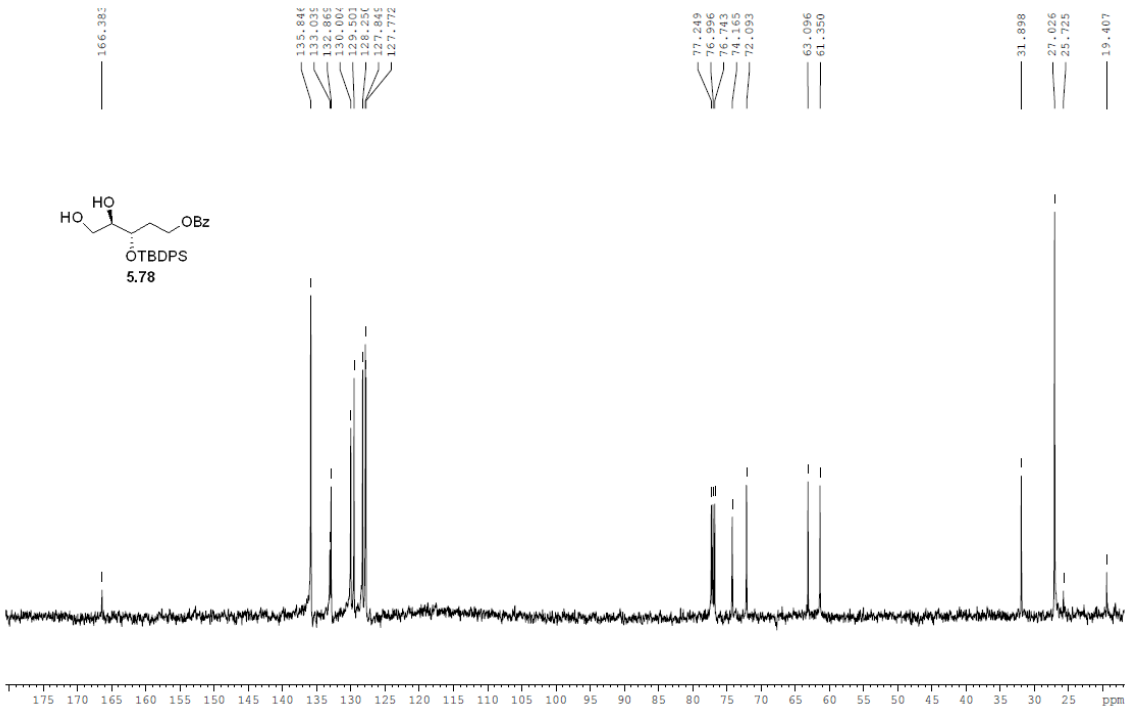


Figure 5.28 ^{13}C NMR spectrum of 5.78

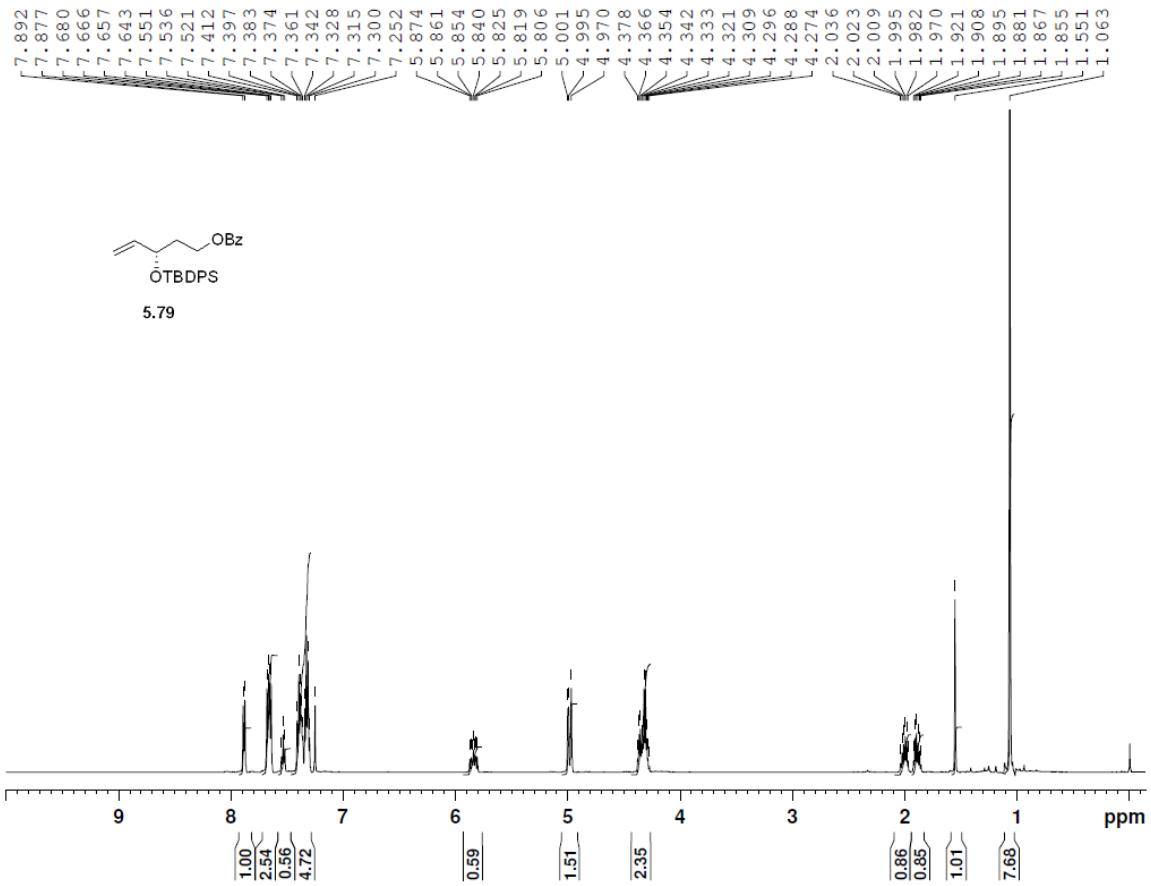


Figure 5.29 ^{1}H NMR spectrum of 5.79

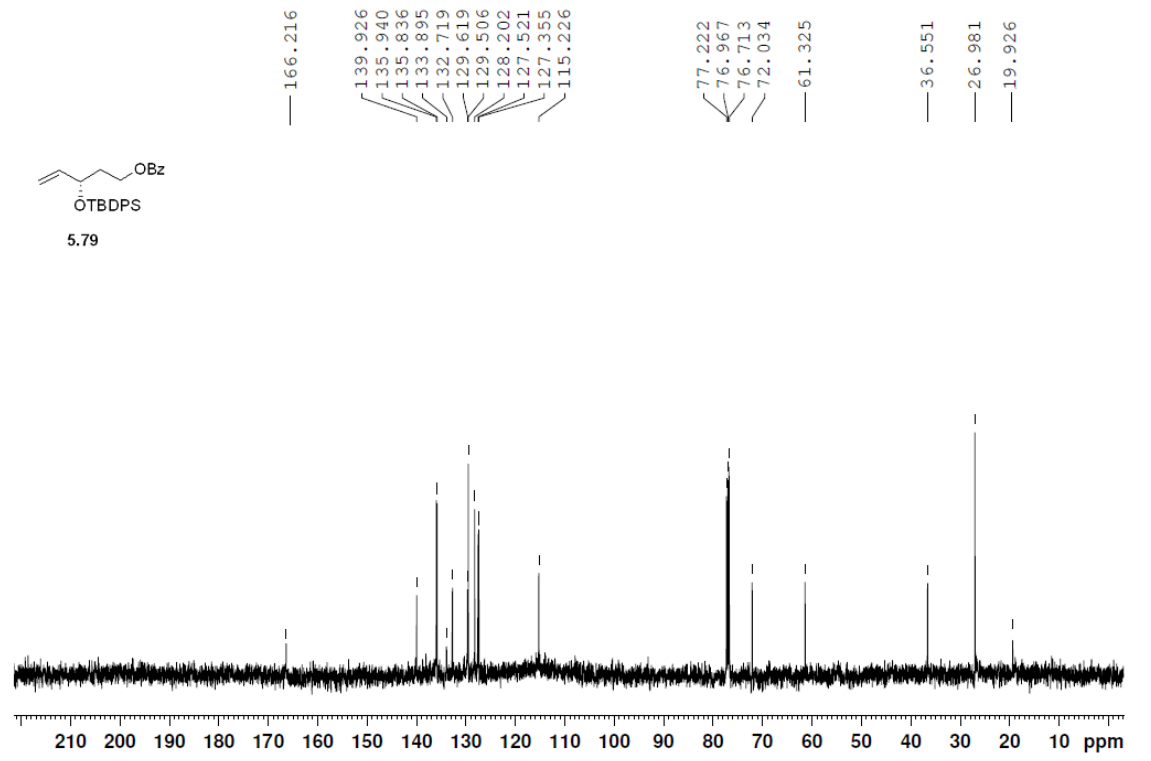
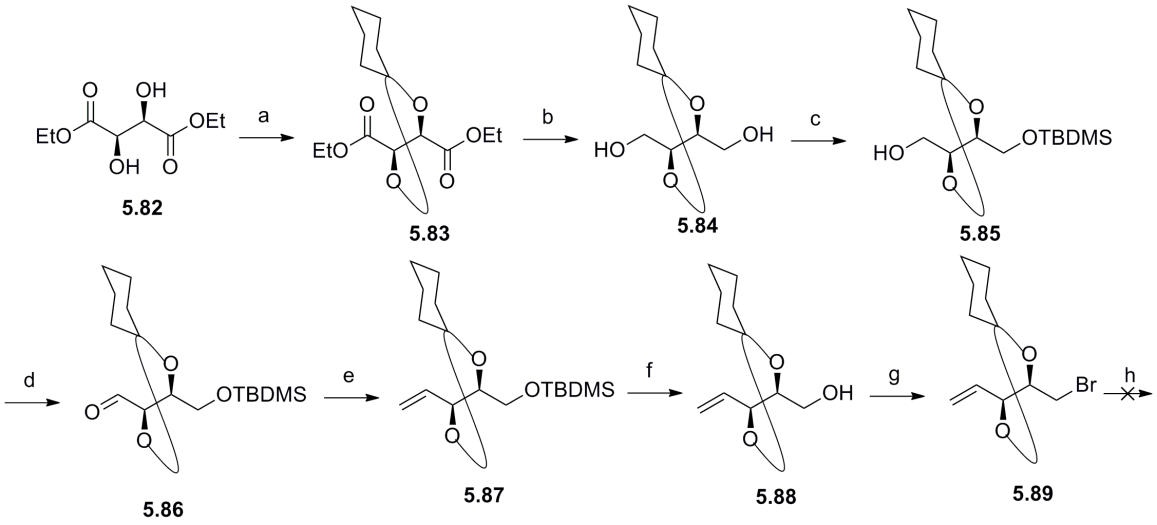


Figure 5.30 ^{1}H NMR spectrum of 5.79

As per the retro synthetic analysis, we proposed to synthesize the alcohol fragment **X''** using **L**-(+)-diethyltartarate (**5.82**) as the starting material (**Scheme 5.12**). The synthesis started with the protection of the **5.82** with cyclohexanone to yield **5.83** by heating **5.82** and cyclohexanone in benzene in presence of PTSA as catalyst. The reaction proceeded with continuous removal of water formed in the reaction using a Dean Stark apparatus to produce **5.83** with a good overall yield. The cyclohexylidene diethyltartarate (**5.83**) formed, without being subject to further purification was reduced in its crude form to its corresponding diol (**5.84**) by LAH with an overall yield of 76% over two steps. The diol **5.84** was confirmed due to the absence of any ester functionality in its ^{1}H NMR and ^{13}C NMR (**Figure 5.31-5.32**) which was regioselectively mono protected with TBDMSCl as the silylating agent to give the mono silylated alcohol **5.85**. The reaction proceeds with a yield of 75 % and the recovered diol was resubjected to mono silylation. The monosilylated compound **5.85** was characterized by the appearance of two signals at δ 0.06 and 0.9 in the PMR corresponding to 6H and 9H respectively (**Figure 5.33-5.34**). The alcohol **5.85** was subjected to oxidation to yield the aldehyde **5.86** using Dess Martin periodinane as the oxidizing agent. The resulting aldehyde **5.86** was found to be unstable so without any further purification and characterization it was subjected to Wittig olefination to yield the olefin **5.87** with an overall yield of 55% over two steps. The progress of the reaction was confirmed due the signal at δ 5.2 and 5.3 corresponding to 1H each as two doublets and 1H ddd at δ 5.84 in the ^{1}H NMR (**Figure 5.35-5.36**) of the product **5.87**. This was subjected to desilylation to give the alcohol **5.88** which was characterized due to the absence of any signals at δ 0.06 and 0.9 in the PMR corresponding to 6H and 9H respectively (**Figure 5.37-5.38**) this was subjected to Appel reaction to convert the primary alcohol to the corresponding bromide **5.89** using CBr_4 as the brominating agent.[207] The bromide **5.89** was characterized due to the absence any

deuterium exchangeable band in the PMR (**Figure 5.39-5.40**). The bromide **5.89** was subjected to lithiation reaction by treating it with Li metal in THF at -30^0 C and the resulting organolithium was subjected to two carbon homologation by treating with freshly distilled acetaldehyde in order to obtain the desired alcohol. Unfortunately, this reaction didn't take place in our hand. Hence, there is a scope to develop a procedure to carry out this two carbon homologation employing a different procedure that will be duly attempted.



a) Cyclohexanone, PTSA, Benzene, reflux in Dean-Stark apparatus; b) $LiAlH_4$, THF; c) TBDMSCl, Imidazole, DMAP, CH_2Cl_2, 0 °C; d) Dess Martin periodinane, CH_2Cl_2 0 °C to RT; e) $Ph_3PCH_3^+I^-$, *n*-BuLi, THF, -30 °C to RT; f) TBAF, THF, 0 °C; g) PPh_3, CBr_4, DCM, RT; h) Li (metal), THF, CH_3CHO.

Scheme 5.12

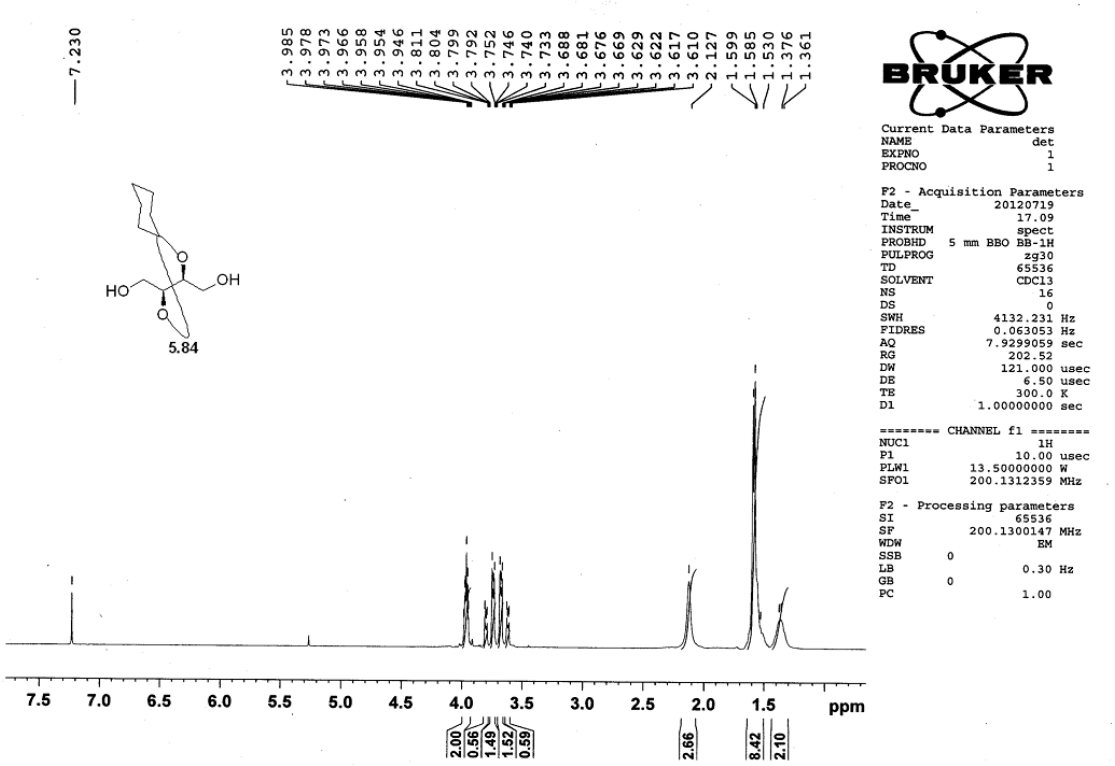


Figure 5.31 ^{1}H NMR spectrum of 5.84

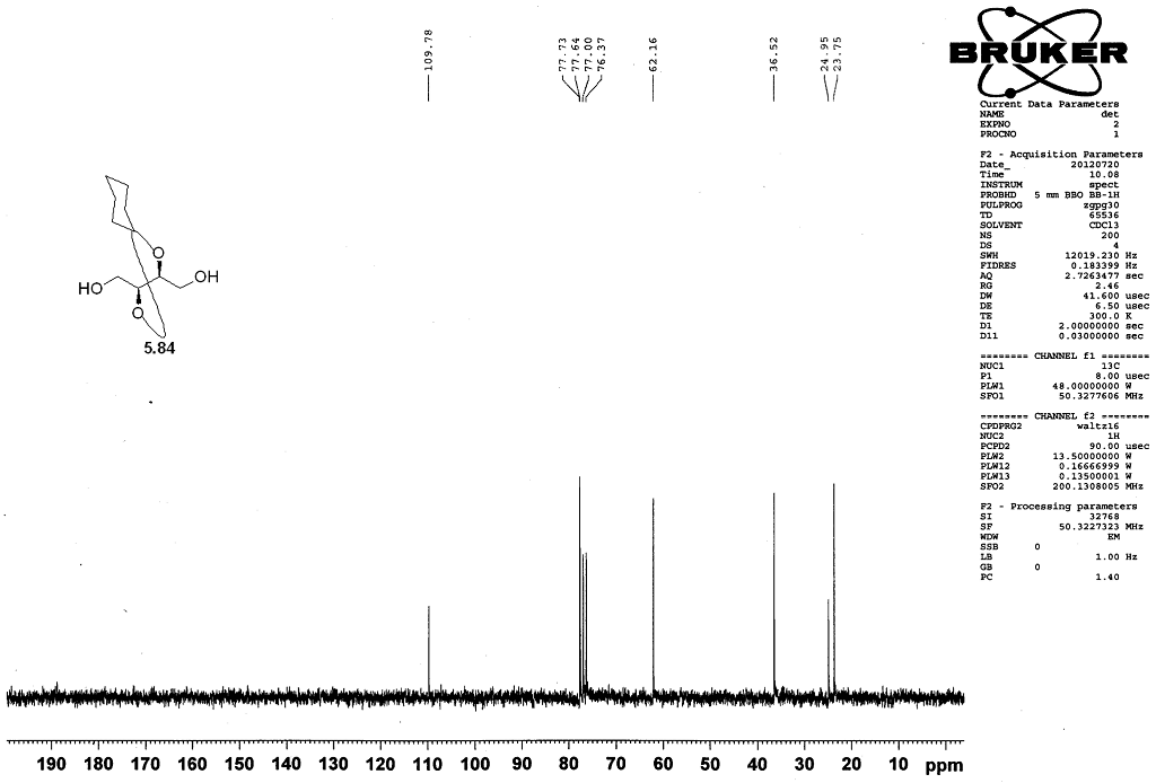


Figure 5.32 ^{13}C NMR spectrum of 5.84

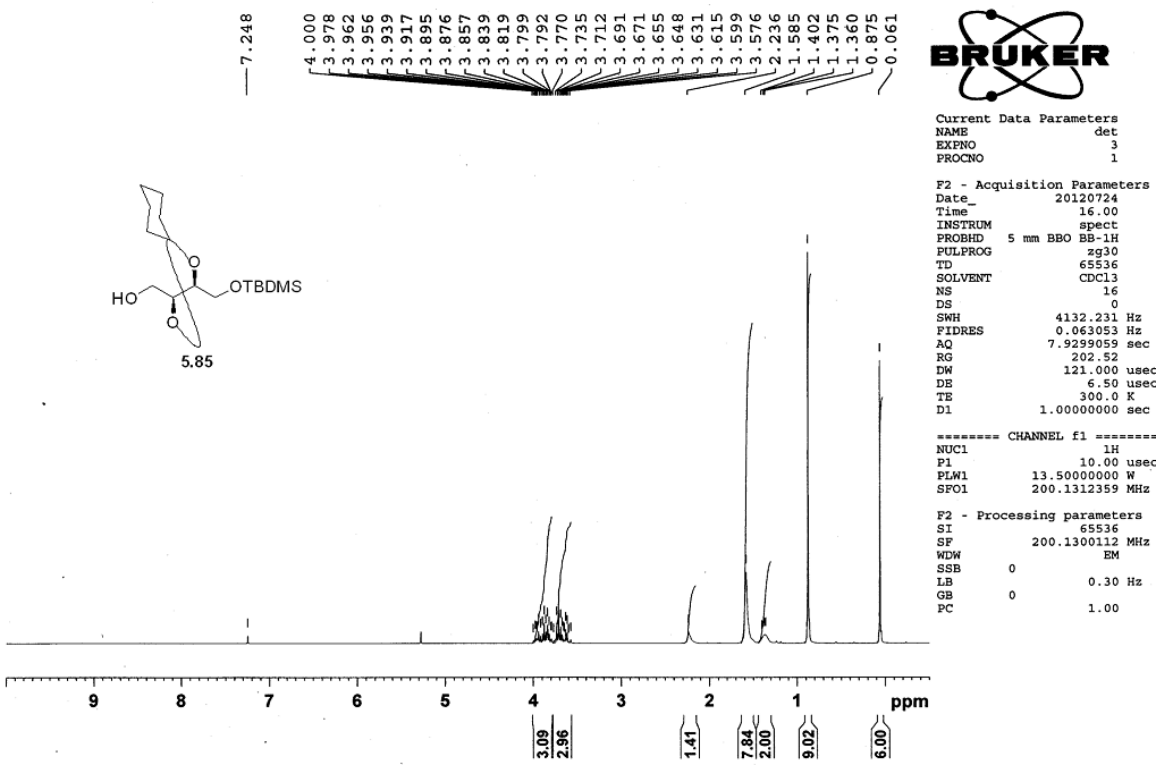


Figure 5.33 ^{1}H NMR spectrum of 5.85

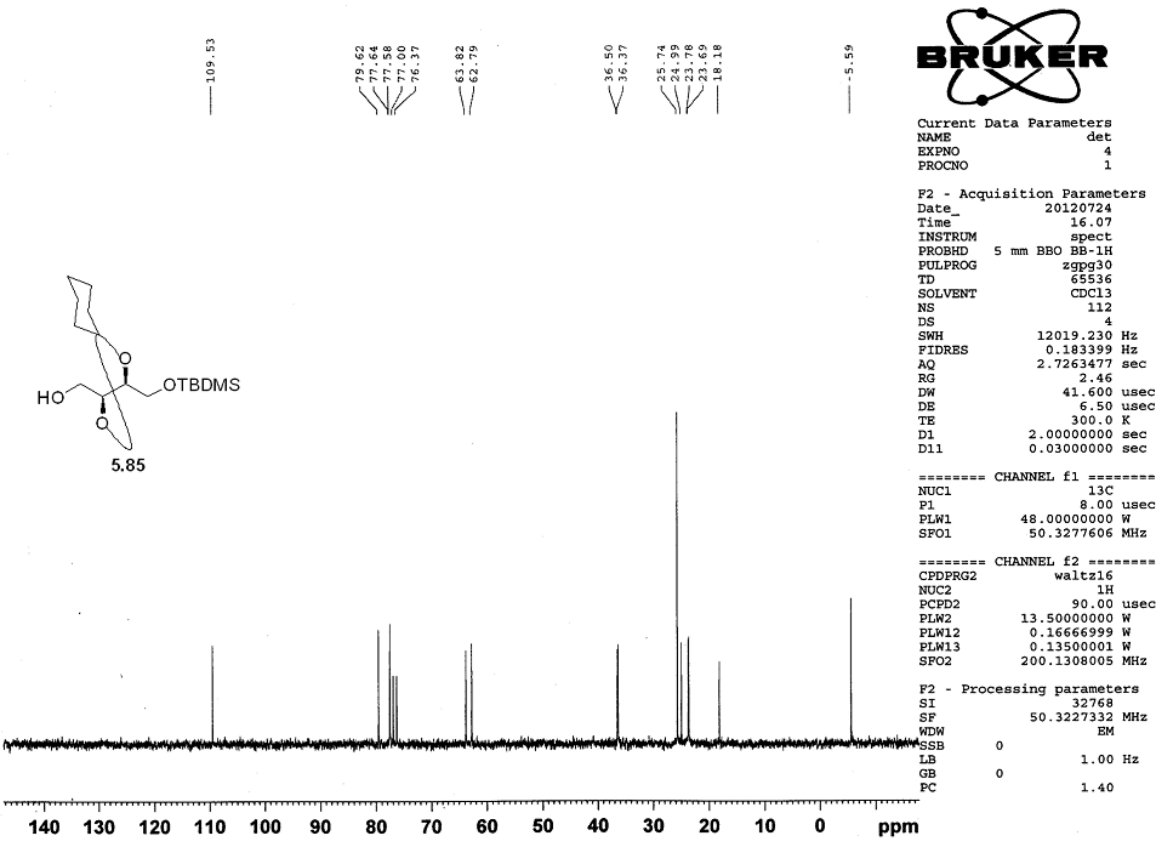


Figure 5.34 ^{13}C NMR spectrum of 5.85

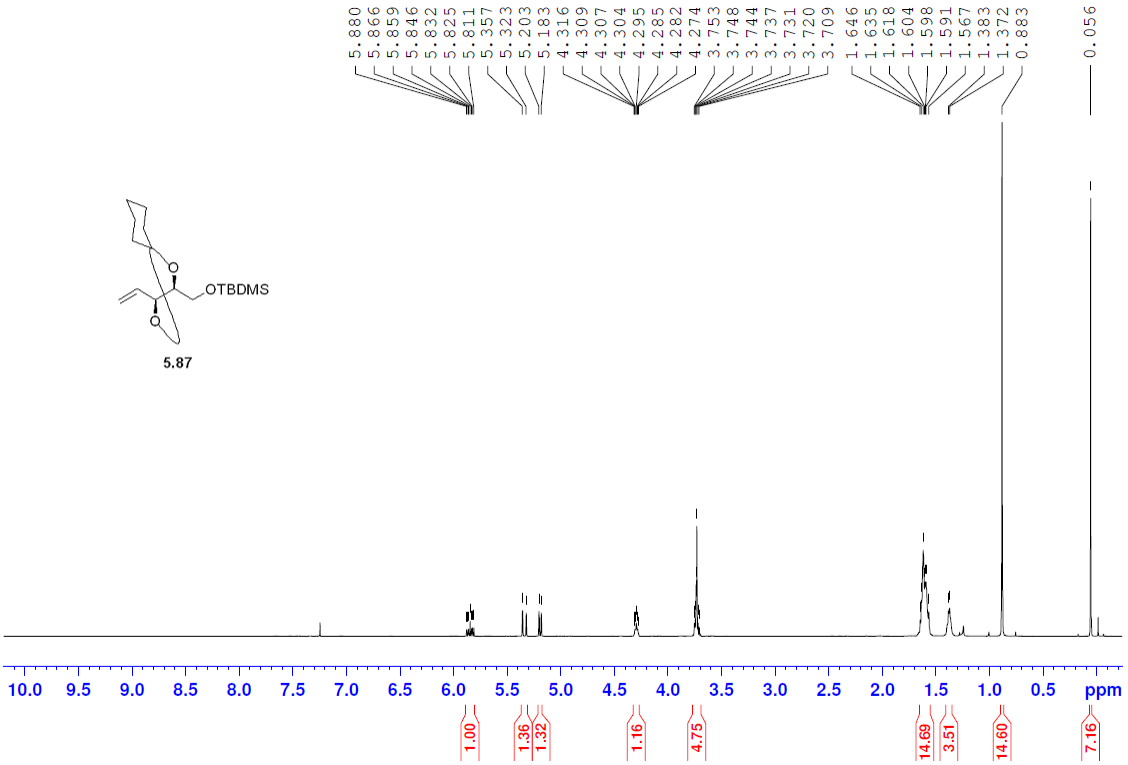


Figure 5.35 ^{1}H NMR spectrum of 5.87

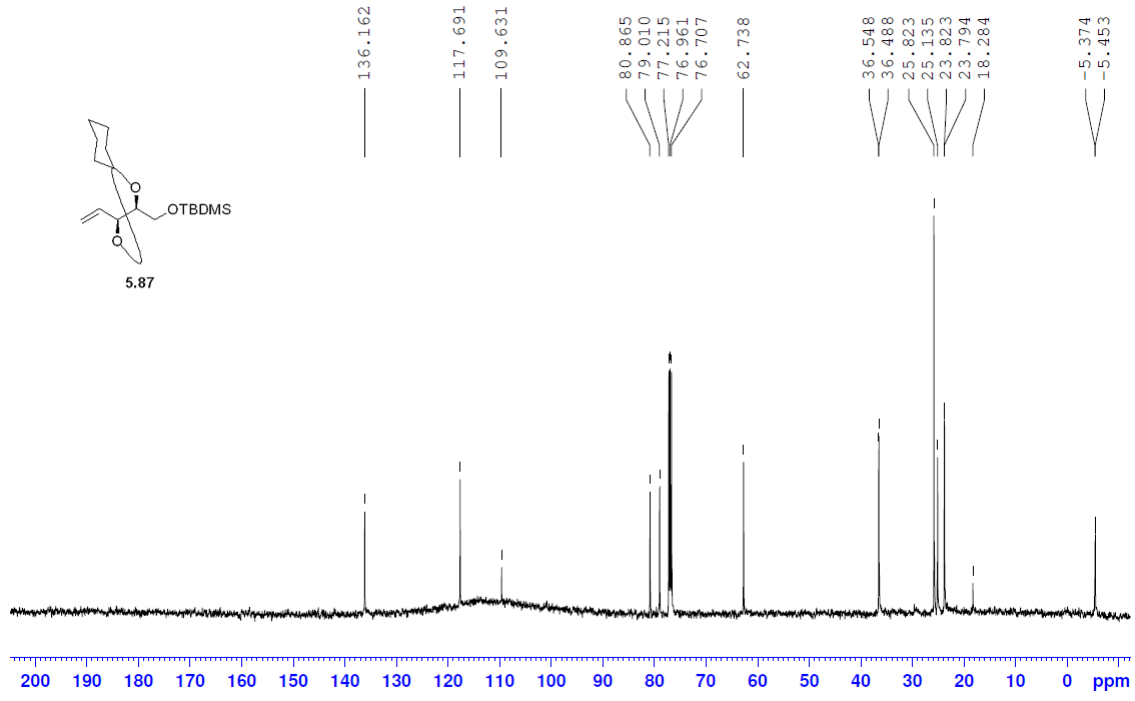


Figure 5.36 ^{13}C NMR spectrum of 5.87

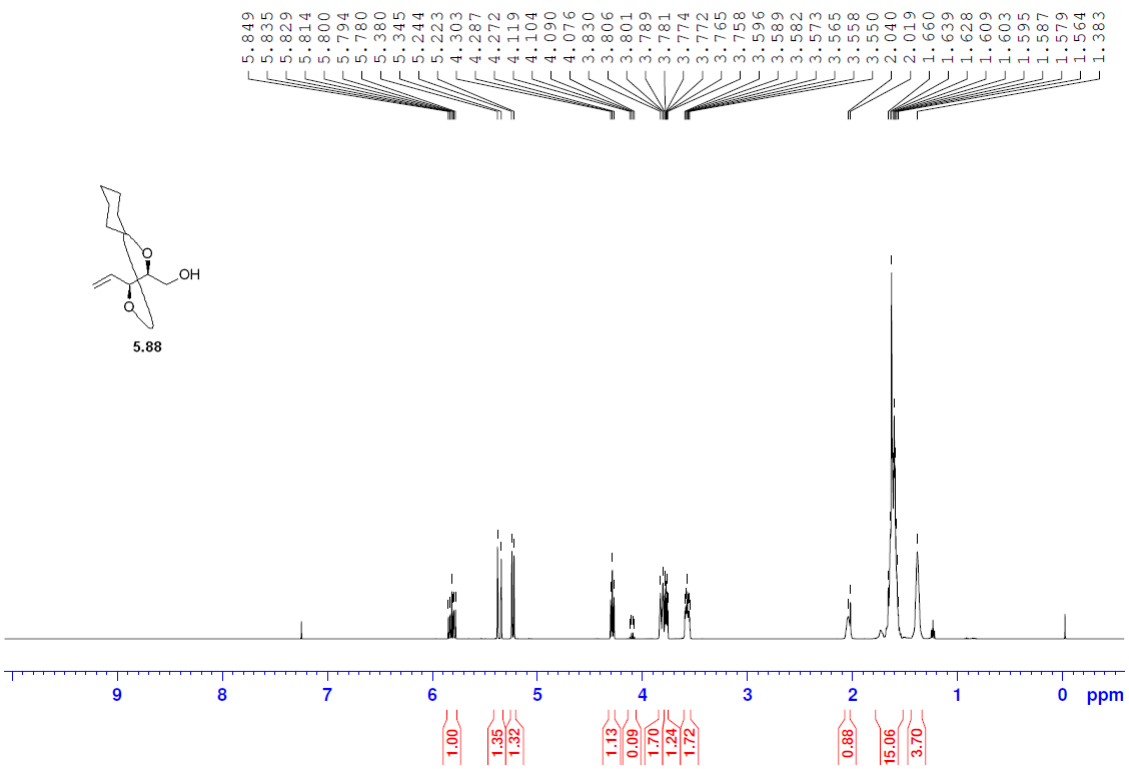


Figure 5.37 ^{1}H NMR spectrum of 5.88

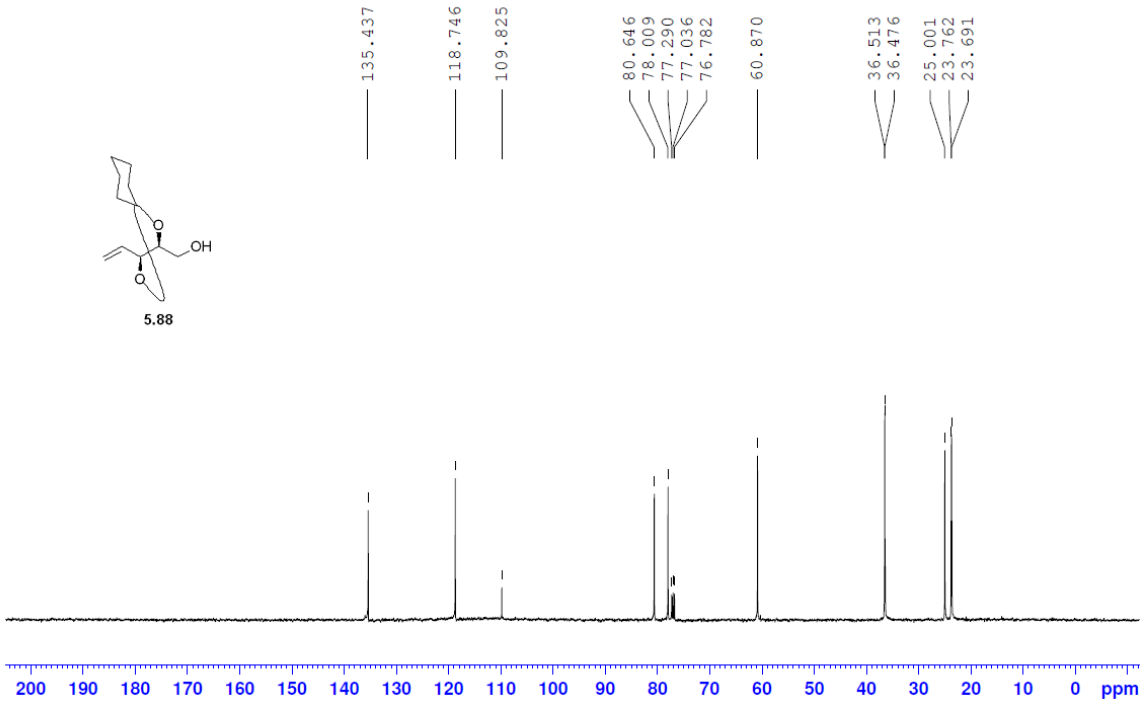


Figure 5.38 ^{13}C NMR spectrum of 5.88

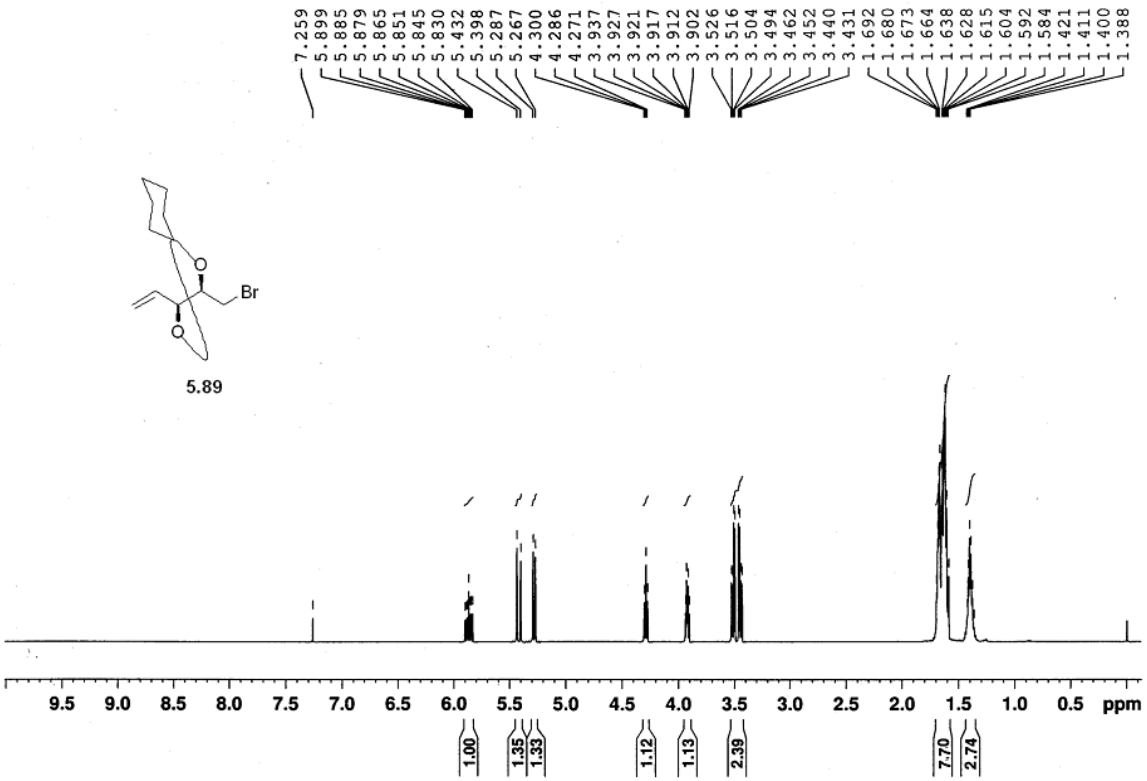


Figure 5.39 ^{1}H NMR spectrum of 5.89

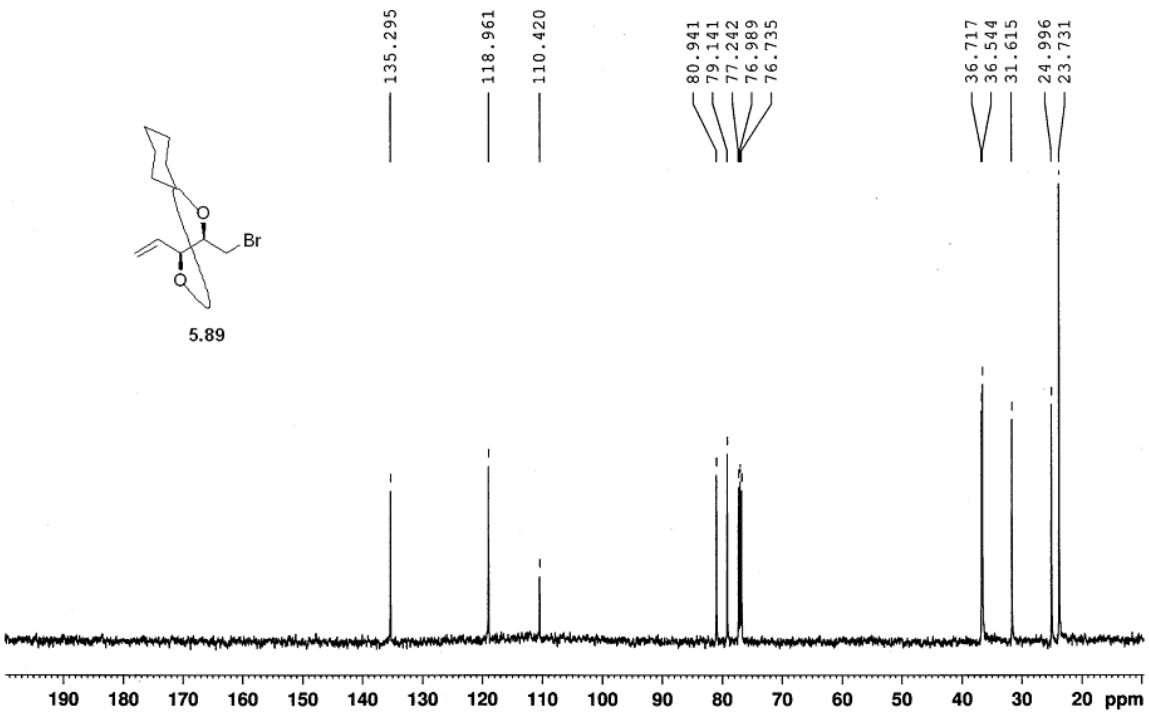


Figure 5.40 ^{13}C NMR spectrum of 5.89

5.III Experimental

(2*R*,3*S*,5*R*)-2-methoxy-3-*O-tert*-butyl-diphenylsilyl-5-vinyltetrahydrofuran (5.45),

(2*R*,3*S*,5*S*)-2-methoxy-3-*O-tert*-butyl-diphenylsilyl-5-vinyltetrahydrofuran (5.46):

To a cooled (0 °C) solution of **2.100** (1.5 g, 2.75 mmol) in distilled CH_2Cl_2 (20 ml) was added 80% aqueous trifluoroacetic acid (8 ml). The mixture was stirred for three hour at 0 °C. The reaction mixture was diluted with $CHCl_3$ and water. The aqueous layer was extracted with $CHCl_3$. The combined organic layer was washed successively with 2% $NaHCO_3$ for neutrality, water and brine and dried over Na_2SO_4. Solvent removal under reduced pressure and column chromatography (silica gel, 0-20% EtOAc in Hexane) of the residue afforded pure **5.45** (0.37 g) and **5.46** (0.34 g) with an overall yield of 67.6 % and in a ratio **5.45**:**5.46** /1:1.

Compound 5.45 : R_f 0.5 (EtOAc : Hexane :: 1:4) $[\alpha]_D^{25}$= +31.56 (c, 0.95, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.08 (s, 9H), 1.5-1.75 (bm, 2H), 2.02 (ddd, *J* = 12.9, 5.22, 1.6 Hz, 1H), 3.08 (dd, *J* = 11.74, 4.96 Hz, 1H), 3.37 (dd, *J* = 11.74, 3.5 Hz, 1H), 3.93 (m, 1H), 4.25 (dt, *J* = 5.8, 1.77 Hz, 1H), 4.67 (m, 1H), 5.09-5.34 (m, 2H), 5.79 (ddd, *J* = 17.04,11.5,7.9 Hz, 1H), 7.34-7.44 (m, 6H), 7.62-7.66 (m, 4H); ^{13}C NMR (175 MHz, $CDCl_3$) δ ppm 19.03, 26.9, 42.4, 62.9, 75.0, 79.8, 87.6, 116.4, 127.7, 129.8, 129.9, 133.6, 135.69, 135.73, 137.9; Anal. Calcd. for $C_{23}H_{30}O_3Si$: C, 72.21; H, 7.90. Found: C, 72.56; H, 8.18.

Compound 5.46 : R_f 0.45 (EtOAc : Hexane :: 1:4) $[\alpha]_D^{26}$= +15.45 (c, 0.86, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.08 (s, 9H), 1.5-1.75 (bm, 1H), 1.84 (ddd, *J* = 12.7, 6.95, 5.86 Hz, 1H), 2.05-2.18 (m, 1H), 3.2 (dd, *J* = 11.8, 5.4 Hz, 1H), 3.43 (dd, *J* = 11.8, 3.2 Hz, 1H), 3.96 (td, *J* = 4.98, 3.3 Hz, 1H), 4.20-4.26 (m, 1H), 4.67 (q, *J* = 6.7 Hz,

1H), 5.07-5.34 (m, 2H), 5.96 (ddd, *J* = 17.2, 10.2, 7.05 Hz, 1H), 7.34-7.44 (m, 6H), 7.62-7.66 (m, 4H); ^{13}C NMR (175 MHz, $CDCl_3$) δ ppm 19.06, 26.9, 29.6, 42.4, 63.0, 75.1, 79.8, 89.7, 116.5, 127.7, 129.8, 133.6, 135.7, 135.77, 137.9; Anal.Calcd for $C_{23}H_{30}O_3Si$: C, 72.21; H, 7.90. Found: C, 72.56; H, 8.18.

(2*R*,3*S*,5*R*)-2-(methoxy-*O*-*tert*-butyl-diphenylsilyl)-3-*O*-*tert*-butyl-diphenylsilyl-5-vinyltetrahydrofuran (5.40):

To a cooled (0 °C) solution of **5.45** (0.3 g, 0.78 mmol) in dry DCM (10 ml) containing DMAP (5 mg) was added imidazole (80 mg, 1.17 mol), followed by the addition of *tert*-butyldiphenylsilyl chloride (0.26 g, 0.94 mmol). The solution was stirred at room temperature overnight until completion of the reaction (confirmed by TLC). The mixture was treated with water and extracted with EtOAc. The combined organic extract was washed with water, brine and dried over Na_2SO_4. Solvent removal under reduced pressure, and column chromatography (silica gel, 0-10% EtOAc in hexane) of the residue afforded pure **5.40** (0.44 g, 91.6 %) as a colorless oil.

$[\alpha]_D^{26}$= +44.5 (c, 1.02, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.92 (s, 9H), 1.07 (s, 9H), 1.63 (ddd, *J* = 12.50, 10.90, 5.24 Hz, 1H), 1.93 (dd, *J* = 12.61, 4.70 Hz, 1H), 3.28 (dd, *J* = 11.01, 3.74 Hz, 1H), 3.39 (dd, *J* = 11.01, 4.38 Hz, 1H), 4.02 (t, *J* = 3.31 Hz, 1H), 4.47 (d, *J* = 4.92 Hz, 1H), 4.65 - 4.72 (m, 1H), 5.06 - 5.11 (m, 1H), 5.26 - 5.33 (m, 1H), 5.81 (ddd, *J* = 17.15, 10.31, 6.95 Hz, 1H), 7.26 - 7.44 (m, 12H), 7.49 - 7.54 (m, 2H), 7.54 - 7.59 (m, 2H), 7.59 - 7.67 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 19.2, 26.8, 27.0, 42.2, 64.5, 75.8, 80.0, 88.0, 116.1, 127.6, 127.8, 129.2, 129.6, 1298, 133.4, 133.9, 134.0, 135.6, 135.7, 135.8, 138.6; Anal.Calcd for $C_{39}H_{48}O_3Si$: C, 75.43; H, 7.79. Found: C, 75.68; H, 8.01.

(2*R*,3*S*,5*S*)-2-(methoxy-*O*-*tert*-butyl-diphenylsilyl)-3-*O*-*tert*-butyl-diphenylsilyl-5-vinyltetrahydrofuran (5.41):

To a cooled (0 °C) solution of **5.46** (0.3 g, 0.78 mmol) in dry DCM (10 ml) containing DMAP (5 mg) was added imidazole (80 mg, 1.17 mol), followed by the addition of *tert*-butyldiphenylsilyl chloride (0.26 g, 0.94 mmol). The solution was stirred at room temperature overnight until completion of the reaction (confirmed by TLC). The mixture was treated with water and extracted with EtOAc. The combined organic extract was washed with water, brine and dried over Na_2SO_4. Solvent removal under reduced pressure, and column chromatography (silica gel, 0-10% EtOAc in hexane) of the residue afforded pure **5.41** (0.41 g, 85.4 %) as a colorless oil.

$[\alpha]_D^{26}$= +35.87 (c, 1.16, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.92 (s, 9H), 1.05 (s, 9H), 1.80 (ddd, *J* = 12.56, 5.93, 4.38 Hz, 1H), 2.15 (dt, *J* = 12.88, 6.71 Hz, 1H), 3.35 (dd, *J* = 11.01, 3.74 Hz, 1H), 3.51 (dd, *J* = 11.11, 3.42 Hz, 1H), 4.08 (q, *J* = 3.42 Hz, 1H), 4.42 - 4.48 (m, 1H), 4.48 - 4.52 (m, 1H), 5.08 (d, *J* = 10.26 Hz, 1H), 5.18 (d, *J* = 17.10 Hz, 1H), 6.07 (ddd, *J* = 17.26, 10.10, 7.27 Hz, 1H), 7.26 - 7.45 (m, 12H), 7.52 (d, *J* = 7.05 Hz, 2H), 7.55-7.66 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 19.1, 26.7, 26.8, 41.6, 64.5, 74.9, 80.3, 86.8, 115.0, 126.9, 127.5, 127.6, 128.2, 129.4, 129.6, 133.4, 133.6, 133.7, 135.5, 135.6, 135.7, 135.8, 139.9; Anal.Calcd for $C_{39}H_{48}O_3Si$: C, 75.43; H, 7.79. Found: C, 75.12; H, 7.58.

(4*R*,5*R*)-3-*O*-*tert*-butyl-diphenylsilyl-5,6-*O*-cyclohexylidene-4,5,6-trihydroxyhept-1-ene (5.47):

To the cooled (0 °C) solution of **2.94** (7.0 g, 33.01 mmol) and Imidazole (2.95 g, 43.38 mmol) in dry DCM (100 ml) was added a solution of TBDPSCl (11.8 g, 42.98 mmol) in dry DCM (100 ml) drop wise over a period of 15 minute. The mixture was

stirred for 4 hour at room temperature on completion (by TLC) treated with water. The aqueous layer was extracted with chloroform. The combined organic layer was washed with water, brine and dried over Na_2SO_4. Solvent removal under reduced pressure afforded oily liquid containing the crude silylated product in almost quantitative yield which was chromatographed on silica gel (0-5% EtOAc in hexane) to afford pure **5.47** as a colorless liquid (13.93 g, 94.12%)

$[\alpha]_D^{25}$= +12.26 (c, 1.006, $CHCl_3$); ^{1}H NMR (700 MHz, $CDCl_3$) δ 1.09 (s, 9H), 1.29-1.39 (m, 2H), 1.50-1.60 (m, 8), 2.04-2.08 (m, 1H), 2.29-2.33 (m, 1H), 3.69 (t, *J* = 7.7 Hz, 1H), 3.85 (q, *J* = 5.6 Hz, 1H), 3.92 (t, *J* = 7.7 Hz, 1H), 4.13 (q, *J* = 7.0 Hz, 1H), 4.92-4.96 (m, 2H), 5.74-5.80 (m, 1H), 7.34-7.50 (m, 6H), 7.74 (m, 4H); ^{13}C NMR (175 MHz, $CDCl_3$) ẟ ppm 14.2, 19.5, 23.8, 23.9, 25.3, 27.1, 34.7, 36.2, 37.9, 65.2, 74.0, 76.9, 77.1, 77.3, 77.8, 109.8, 117.3, 127.4, 127.5, 129.5, 129.6, 134.0, 134.3, 134.4, 136.1, 136.1. Anal.Calcd for$C_{28}H_{38}O_3Si$: C, 74.62; H, 8.50. Found: C, 74.62; H, 8.50

(3*R*,4*R*)-3-*O*-*tert*-butyl-diphenylsilyl-4,5-*O*-cyclohexylidene-3,4,5-trihydroxypentanal (5.48) :

To a cooled (-78 °C) solution of **5.47** (4.8 g, 10.65 mmol) in dichloromethane (40 ml) ozone gas was bubbled for 5 minutes till the reaction mixture became blue. The bluish solution was stirred for 10 min more and then treated with dry triphenylphosphine (4.2 g, 15.97 mmol). The mixture was gradually brought to room temperature and stirred for 3 hour more. The reaction mixture was concentrated in vacuo and the residue was passed through a short silica gel column eluting with 10% EtOAc in Hexane to afford **5.48** (4.14 g, 86%) as a colorless oil. This was found to be unstable on long standing and hence used immediately for the next step without further purification. A small portion of **5.48** was used for its spectroscopic characterization.

^{1}H NMR (700 MHz, $CDCl_3$) δ ppm 1.06 (s, 9H), 1.35, 1.50 (2s., 4H each), 2.41-2.44 (m, 1H), 2.61-2.64 (m, 1H), 3.89 - 3.93 (m, 1H), 3.94-3.97 (m, 1H), 4.16-4.18 (m, 1H), 4.42-4.44 (m, 1H), 7.26 - 7.44 (m, 6H), 7.64-7.72 (m, 4H), 9.55(t, *J*=1.4 Hz, 1H); ^{13}C NMR (175 MHz, $CDCl_3$) δ ppm 19.3, 23.6, 23.9, 25.15, 26.9, 34.1, 35.79, 46.6, 64.6, 69.1, 76.7, 110.4, 127.77, 127.8, 129.9, 130.0, 133.19, 133.24, 135.86, 135.92, 200.47. Anal.Calcd for$C_{27}H_{36}O_4Si$:C, 71.64; H, 8.02. Found: C, 71.64; H, 8.02.

(5*R*,6*R*)-Ethyl-5-*O*-*tert*-butyl-diphenylsilyl-6,7-*O*-cyclohexylidene-5,6,7-trihydroxyhept-2*E*-enoate (5.49) :

To a cooled (0 °C) suspension of sodium hydride (0.47 g, 50% suspension in oil, 9.8 mmol, washed once with dry hexane) in THF (20 ml), triethyl phosphonoacetate (2.21 g, 9.86 mmol) in THF (10 ml) was added drop wise over a period of one hour under argon atmosphere. After the addition was over, the reaction mixture was gradually brought to room temperature and stirred till it became clear. Again the temperature was brought down to 0°C and a solution of **5.48** (4.06 g, 8.97 mmol) in dry THF (20 ml) was added drop wise over a period of 1 hour. The mixture was stirred at 0 °C for 1 hour and stirred at room temperature overnight (completion of reaction confirmed from TLC). The mixture was cooled to 0 °C, treated with water, neutralized by drop wise addition of dilute HCl (2%) and extracted twice with EtOAc. The combined organic layer was washed successively with water, brine, dried over Na_2SO_4. Solvent removal under reduced pressure, column chromatography (silica gel, 0-5% EtOAc in Hexane) of the residue afforded pure **5.49** (3.75 g, 80%) as a colorless oil.

$[\alpha]_D^{26}$= +6.56 (c, 1.55, $CHCl_3$); ^{1}H NMR (700 MHz, $CDCl_3$) δ ppm 1.06 (s, 9H), 1.27 (t, *J* = 7.0 Hz, 3H), 1.35 (br. s, 2H), 1.46-1.60 (m, 8H), 2.20 (dt, *J* = 14.36, 7.18 Hz, 1H), 2.39-2.43 (m, 1H), 3.77 (t, *J* = 7.7 Hz, 1H), 3.88-3.92 (m, 2H), 4.09 (q, *J* = 7.0 Hz,

1H), 4.12-4.18 (m, 2H), 5.69 (d, *J* = 15.4 Hz, 1H), 6.87 (dt, *J* = 15.4, 7.0 Hz, 1H), 7.35-7.40 (m, 4H), 7.40-7.45 (m, 2H), 7.69 (d, *J* = 7.18 Hz, 5H); ^{13}C NMR (175 MHz, $CDCl_3$) δ ppm 14.2, 19.4, 23.7, 23.8, 25.18, 27.0, 34.4, 35.8, 36.0, 60.08, 64.8, 73.04, 77.33, 110.03, 123.7, 127.5, 127.59, 129.7, 129.76, 133.58, 133.62, 136.0, 145.0, 166.1. Anal.Calcd for$C_{31}H_{42}O_5Si$: C, 71.23; H, 8.10. Found: C, 71.23; H, 8.10.

(5*R*,6*R*)-5-*O*-*tert*-butyl-diphenylsilyl-6,7-*O*-cyclohexylidene-1,5,6,7-tetrahydroxyhept-2*E*-ene (5.50):

To a cooled (-78 °C) solution of **5.49** (3.7g, 7.08 mmol) in dry THF (30 ml) DIBAL-H (14.2 ml, 1.0 M solution in hexane) was added drop wise over a period of one hour. The mixture was stirred for 1 hour at same temperature till the reaction was complete (confirmed by TLC). To the mixture, methanol (15 ml) was added. The mixture was stirred at room temperature for 2 hour and the resulting solid was filtered through a Celite pad. Concentration of the filtrate under reduced pressure, column chromatography (silica gel, 0 - 25% EtOAc in Hexane) of the residue afforded pure **5.50** (3.1 g, 91%) as a colorless oil.

$[\alpha]_D^{26}$= +7.68 (c, 1.13, $CHCl_3$); ^{1}H NMR (700 MHz, $CDCl_3$) δ ppm 1.05 (s, 9H), 1.36 (br. s., 2H), 1.49-1.59 (m, 8H), 2.04-2.07 (m, 2H), 2.24-2.26 (m, 1H), 3.75 (t, *J* = 7.7 Hz, 1H), 3.84-3.87 (m, 1H), 3.90 - 3.94 (m, 4H), 4.14 (q, *J* = 6.3 Hz, 1H), 5.47 (br. s., 2H), 7.37 (q, *J* = 7.0 Hz, 4H), 7.40-7.45 (m, 2H), 7.70 (d, *J* = 6.88 Hz, 4H); ^{13}C NMR (175 MHz, $CDCl_3$) δ ppm, 19.5, 23.7, 23.8, 25.19, 26.99, 34.59, 35.8, 36.06, 63.5, 65.0, 73.86, 77.66, 109.88, 127.4, 128.6, 129.6, 131.7, 133.7, 134.2, 136.04, 136.08.Anal.Calcd for$C_{29}H_{40}O_4Si$: C, 72.46; H, 8.39; Found: C, 72.46; H, 8.39

(5*R*,6*R*)-1-Bromo-5-*O*-*tert*-butyl-diphenylsilyl--6,7-*O*-cyclohexylidene-5,6,7-trihydroxy-hept-2*E*-ene (5.51) :

To the cooled (0 °C) solution of **5.50** (3.0 g, 6.25 mmol) and triethylamine (1.07 g, 10.60 mmol) in dry DCM (15 ml) was added methane-sulfonylchloride (0.93 g, 8.11 mmol) drop wise over a period of 15 minute. The mixture was stirred for 3 hour at room temperature and treated with water. The aqueous layer was extracted with chloroform. The combined organic layer was washed with water, brine and dried over Na_2SO_4, Solvent removal under reduced pressure afforded yellow oily liquid containing the crude mesylated product in almost quantitative yield which was used in the next reaction without further purification. To a solution of crude mesylate in dry acetone (40 ml), dry NaBr (0.78 g, 7.5 mmol) and a catalytic amount of $NaHCO_3$ was added and stirred overnight (cf. TLC). The reaction mixture was concentrated under reduced pressure in order to get rid of the acetone, washed with dilute aqueous HCl (2%) for neutrality and extracted with $CHCl_3$. The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure to afford a colorless liquid which was chromatographed on silica gel (0-2% EtOAc in hexane) to afford pure **5.51** (3.06 g, 90%). The compound tended to become colored on long standing probably due to its being unstable and hence was immediately used for the next step.

$[\alpha]_D^{26}$= +16.54 (c, 1.04, $CHCl_3$); ^{1}H NMR (700 MHz, $CDCl_3$) δ ppm, 1.06 (s, 9H), 1.36 (br. s., 2H), 1.52-1.56 (m, 8H), 2.05-2.09 (m, 1H), 2.27 -2.31 (m, 1H), 3.72-3.75 (m, 1H), 3.78 (d, *J* = 7.0 Hz, 1H), 3.83-3.87 (m, 2H), 3.91 (t, *J* = 7.33 Hz, 1H), 4.09-4.12 (m, 1H), 5.46-5.60(m, 2H), 7.35-7.44 (m, 6H), 7.69 (d, *J* = 7.1 Hz, 4H); ^{13}C NMR (175 MHz, $CDCl_3$) δ ppm, 19.47, 23.7, 23.8, 25.19, 27.0, 32.9, 34.5, 35.73, 35.77, 36.05, 45.0, 65.95, 73.5, 77.5, 109.89, 127.4, 127.5, 128.4, 128.8, 129.6, 131.6, 132.07, 133.7, 134.0, 136.0, 136.0; Anal. Calcd for$C_{29}H_{39}BrO_3Si$: C, 64.07; H, 7.23; Found: C, 64.07; H, 7.23.

(2*R*,3*S*)-1,2-*O*-cyclohexylidene-3-*O*-*tert*-butyl-diphenylsilyl-1,2,3,5-tetrahydroxypentanol (5.76) :

To a cooled (0 °C) solution of **2.97** (3.5 g, 7.07 mmol) in MeOH (50 ml) $NaBH_4$ (145.7 mg, 3.85 mmol) was added over a period of 10 min. After the completion of the reaction (Cf. by TLC) the methanol was completely evaporated under vaccum and the remaining reaction mixture was washed with water and extracted with $CHCl_3$. The combined organic layer was washed with water, brine and dried over Na_2SO_4. Solvent removal under reduced pressure afforded a oily liquid containing the crude alcohol in almost quantitative yield which was chromatographed on silica gel (0-10% EtOAc in hexane) to afford pure **5.76** (3.2 g, 91.16%) as a colorless liquid.

$[\alpha]_D^{25}$ = -2.49 (c, 0.82, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.03 (s, 9H), 1.3-1.4 (m, 2H), 1.45-1.6 (m, 9H), 1.79-1.82 (m, 2H), 3.50-3.5 (m, 1H), 3.6-3.65 (m. 2H), 3.77 (q, *J* = 6.0 Hz, 1H), 4.00 (dd, *J* = 8.05, 6.0 Hz, 1H), 4.00 (q, *J* =, 6.5 Hz, 1H), 7.3-7.5 (m, 6H), 7.6-7.7 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 19.3, 23.8, 23.85, 25.0, 26.9, 34.8, 35.9, 38.0, 59.1, 67.6, 73.7, 78.2, 110.0, 127.6, 129.8, 129.86, 133.2, 133.6, 135.8; Anal. Calcd for $C_{27}H_{38}O_4Si$: C, 71.32; H, 8.42; Found: C, 71.19; H, 8.57.

(2*R*,3*S*)-1,2-*O*-cyclohexylidene-3-*O*-*tert*-butyl-diphenylsilyl-5-*O*-benzoyl-1,2,3,5-tetrahydroxypentanol (5.77):

To a cooled (0 °C) solution of the alcohol **5.76** (3.0 g, 6.6 mmol) and triethylamine (870 mg, 8.59 mmol) in dry CH_2Cl_2 (50 ml) a solution of benzoyl cyanide (1.04 g, 7.9 mmol) in CH_2Cl_2 (20 ml) was added in 5 minute. The mixture was stirred at 0 °C for 1 hour and then at room temperature for 4 hour. The solution was treated with water. The organic layer was separated and the aqueous layer was washed extracted with $CHCl_3$. The combined organic layer was washed with *dil.* aqueous HCl (2%) till neutral, water, brine and dried over Na_2SO_4. Solvent removal under reduced pressure, column

chromatography (silica gel, (0-5% EtOAc in hexane) of the residue afforded pure **5.77** (3.5 g, 95.1%) as a colorless oil.

$[\alpha]_D^{25}$ = +4.59 (c, 1.26, $CHCl_3$); ^{1}H NMR (500 MHz $CDCl_3$): δ 0.9 (s, 9H), 1.28-1.4 (m, 2H), 1.45-1.58 (m, 8H), 1.9-1.98 (m, 1H), 2.01-2.08 (m, 1H), 3.6 (t, *J* = 7.5 Hz, 1H), 3.86-3.93 (m. 2H), 4.12 (q, *J* = 6.5 Hz, 1H), 4.28-4.35 (m, 1H), 4.38-4.43 (m, 1H), 7.3-7.5 (m, 9H), 7.6-7.7 (m, 4H) 7.88-7.89 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 19.4, 23.8, 23.87, 25.1, 26.9, 34.0, 34.8, 36.0, 61.2, 67.0, 71.7, 78.1, 109.7, 127.5, 127.7, 128.1, 129.5, 129.7, 129.8, 130.3, 132.7, 133.3, 133.4, 135.9, 166.3; Anal. Calcd for $C_{34}H_{42}O_5Si$: C, 73.08; H, 7.58; Found: C, 73.26; H, 7.46.

(2*R*,3*S*)-3-*O*-*tert*-butyl-diphenylsilyl-5-*O*-benzoyl-1,2,3,5-tetrahydroxypentanol (5.78):

To a cooled (0 °C) solution of **5.77** (3.2 g, 5.73 mmol) in distilled CH_2Cl_2 (50 ml) was added 80% aqueous trifluoroacetic acid (10 ml). The mixture was stirred for three hour at 0 °C. The reaction mixture was diluted with $CHCl_3$ and water. The aqueous layer was extracted with $CHCl_3$. The combined organic layer was washed successively with 2% $NaHCO_3$ for neutrality, water and brine and dried over Na_2SO_4. Solvent removal under reduced pressure and column chromatography (silica gel, 0-5% MeOH in $CHCl_3$) of the residue afforded pure **5.78** (1.89 g, 68.97%) as colorless oil.

$[\alpha]_D^{25}$ = -3.78 (c, 1.09, $CHCl_3$); ^{1}H NMR (500 MHz $CDCl_3$): δ 0.9 (s, 9H), 1.45-1.7 (bs, 2H), 1.85-1.95 (m, 1H), 1.99-2.06 (m, 1H), 3.6-3.68 (m, 2H), 3.7-3.75 (m. 1H), 4.01(q, *J* = 5 Hz, 1H), 4.2 (dt, *J* = 11.0, 6.5 Hz, 1H), 4.37 (dt, *J* = 11.5, 5.5 Hz, 1H), 7.3-7.5 (m, 9H), 7.6-7.7 (m, 4H) 7.88-7.89 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 19.4, 25.7, 27.02, 31.8, 61.3, 63.0, 72.09, 74.1, 127.7, 127.8, 128.2, 129.5, 130.0, 132.8, 133.0, 135.8, 166.3; Anal. Calcd for $C_{28}H_{34}O_5Si$: C, 70.26; H, 7.16; Found: C, 70.39; H, 7.31.

(3*S*)-5-*O*-Benzylo-3-*O*-*tert*-butyl-diphenylsilylpentene (5.79):

To a cooled (0 °C) solution of **5.78** (1.7 g, 3.55 mmol) in dry pyridine (10 ml), p-toluenesulfonyl chloride (1.7 g, 8.91 mmol) and dimethylaminopyridine (100 mg) were added. The mixture was gradually brought to room temperature over a period of 6 hour and then stirred overnight. The reaction mixture was treated with 5% aqueous HCl and water for neutrality. The aqueous layer was extracted with $CHCl_3$. The combined organic layer was washed with water, brine and dried. It was concentrated under reduced pressure to afford the crude ditosylated product (confirmed by TLC and IR of crude) which was taken in dry DMF (15 ml). To this solution were added Zn dust (0.50 g, 7.52 mmol) and dry NaI (640 mg, 4.27 mmol). The mixture was stirred overnight at 90 °C. The mixture was filtered and the residue was thoroughly washed with EtOAc. The combined organic layer was washed with dilute aqueous HCl in order to dissolve the turbid material. The aqueous layer was separately extracted with EtOAc. The combined organic layer was washed with water, brine and dried over Na_2SO_4. Solvent removal under reduced pressure and column chromatography (silica gel, 0-10 % EtOAc in Hexane) of the residue afforded pure diene **5.79** (1.4 g, 89.17%) colorless oil.

$[\alpha]_D^{25}$ = +2.36 (c, 0.98, $CHCl_3$); ^{1}H NMR (500 MHz $CDCl_3$): δ 1.06 (s, 9H), 1.85-1.92 (m, 1H), 1.97-2.03 (m, 1H), 4.32-4.37 (m, 3H), 4.6-5.2 (m, 2H), 5.84 (ddd, *J* = 17.0, 10.5, 6.5 Hz, 1H), 7.3-7.5 (m, 9H), 7.6-7.7 (m, 4H) 7.88-7.89 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 19.4, 26.9, 36.5, 61.3, 72.03,115.2, 127.3, 127.5, 128.2, 129.5, 129.6, 132.7, 132.8, 133.8, 135.8, 135.9, 139.9 166.3; Anal. Calcd for $C_{28}H_{32}O_3Si$: C, 75.63; H, 7.25; Found: C, 75.26; H, 7.19.

(2*R*,3*R*)-2,3-*O*-cyclohexylidene-1,2,3,4-tetrahydroxybutanol (5.84):

A solution of diethyl (**L**)-tartarate **5.82** (30.9 g, 0.15 mol), cyclohexanone (16 g, 0.16 mol) and PTS (100 mg) in benzene (200 ml) was refluxed in a Dean–Stark apparatus for 6 h with continuous removal of water. The reaction was monitored with TLC and

stopped when the starting material had been consumed. The solution was washed with 10% aqueous Na_2CO_3 and water and dried. Solvent removal under reduced pressure afforded the residue containing diester **5.83** in almost quantitative yield. It was taken in dry THF (100 mL) and was added dropwise to a cooled (0 °C) suspension of $LiAlH_4$ (8.0 g, 0.21 mol) in dry THF (300 ml) over a period of 2 hour. The reaction mixture was gradually brought to room temperature and stirred at the same temperature for another 4 hours. After completion of the reaction (Cf. TLC) the reaction mixture was cooled with ice water and the excess hydride was decomposed by drop wise addition of saturated aqueous solution of Na_2SO_4. The white precipitated formed was filtered and washed with diethyl ether. Solvent removal under reduced pressure and column chromatography (silica gel, 0-5 % MeOH in Chloroform) of the residue afforded pure diol **5.84** (24.2 g, 79.08 %) as a colorless oil.

$[\alpha]_D^{25}$ = -6.39 (c, 1.42, $CHCl_3$); ^{1}H NMR (200 MHz $CDCl_3$): δ 1.3-1.4 (m, 2H), 1.5-1.6 (m, 8H), 2.12 (bs, 2H), 3.6-3.8 (m, 4H), 3.95-4.0 (m. 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 23.7, 24.95, 36.3, 62.2, 77.7, 109.8; Anal. Calcd for $C_{10}H_{18}O_4$: C, 59.39; H, 8.97; Found: C, 59.18; H, 9.13.

(2*R*,3*R*)-1-*O*-*tert*-butyldimethylsilyl-2,3-*O*-cyclohexylidene-1,2,3,4-tetrahydroxybutanol (5.85):

To a cooled (0 °C) solution of **5.84** (4.5 g, 22.2 mmol) in dry DCM (200 ml) containing DMAP (100 mg) was added imidazole (1.6 g, 23.5 mol), followed by the addition of a solution of *tert*-butyldimethylsilyl chloride (3.6 g, 23.88 mmol) in DCM (150 ml) over a period of 6 hours. The mixture was treated with water and extracted with $CHCl_3$. The combined organic extract was washed with water, brine and dried over Na_2SO_4. Solvent removal under reduced pressure, and column chromatography (silica gel, 0-10% EtOAc in hexane) of the residue afforded pure **5.85** (4.2 g, 59.7%)as a

colorless oil. The aqueous layer was evaporated under vacuum and the dry slat was washed with $CHCl_3$ to recover the starting **5.84** (2.1 g).

$[\alpha]_D^{25}$ = +4.26 (c, 1.25, $CHCl_3$); ^{1}H NMR (200 MHz $CDCl_3$): δ 0.06 (s, 6H), 0.08 (s, 9H), 1.3-1.4 (m, 2H), 1.5-1.6 (m, 8H), 2.2 (bs, 1H), 3.5-3.7 (m, 3H), 3.77-4.0 (m. 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ -5.5, 18.1, 23.7, 23.8, 24.9, 25.7, 36.3, 36.5, 62.8, 63.8, 77.6, 79.6, 109.5; Anal. Calcd for $C_{16}H_{32}O_4Si$: C, 60.72; H, 10.19; Found: C, 60.39; H, 10.45.

(3*R*,4*R*)-3,4-*O*-cyclohexylidene-5-*O*-*tert*-butyldimethylsilyl-3,4,5-trihydroxypentene (5.87):

To the cooled (0 °C) solution of **5.85** (4.0 g, 12.6 mmol) in dry CH_2Cl_2 (50 ml) Dess martin periodinane (8.05 g, 18.98 mmol) was added in portions. The reaction mixture was stirred for 30 minutes at 0 °C, gradually brought to room temperature and stirred till the completion of the reaction (confirmed from TLC). It was diluted with chloroform (30 ml). The solution was poured into saturated aqueous $NaHCO_3$ (20 ml) containing a sevenfold excess of $Na_2S_2O_3$. The mixture was stirred to dissolve the solid. The organic layer separated. The aqueous layer was extracted with chloroform. The combined organic layer was washed with brine and dried over Na_2SO_4. Solvent removal under reduced pressure and the oily residue was passed through a short pad of silica gel eluting with 10% EtOAc in Hexane to obtain pure **5.86** (3.7 g, 92.0 %) as colorless oil. This was found to be unstable hence was immediately used as such for the next step.

To a cooled (-10 °C) suspension of PH_3PCH_3I (11.9 g, 29.3 mmol) in dry THF (100 ml), n-BuLi solution(14.7 ml, 1.6 molar in Hexane) was added drop wise over a period of 20 minutes. The reaction mixture was gradually brought 0 °C and stirred at the same temperature for another 30 minutes. The reaction mixture cooled to -50 °C using a

dry ice acetone bath and a solution of aldehyde **5.86** in Dry THF (50 ml) was added dropwise over a period of 15 minute. The reaction mixture was gradually brought to room temperature and stirred for overnight. After completion of the reaction (Cf. TLC) the reaction mixture was cooled with ice water and the excess salt was decomposed by drop wise addition of saturated aqueous solution of NH_4Cl. The mixture was treated with water and extracted with EtOAc. The combined organic extract was washed with water, brine and dried over Na_2SO_4. Solvent removal under reduced pressure, and column chromatography (silica gel, 0-5% EtOAc in hexane) of the residue afforded pure **5.87** (2.4 g, 65.4 %) as a colorless oil.

$[\alpha]_D^{25}$ = +7.13 (c, 1.32, $CHCl_3$); ^{1}H NMR (500 MHz $CDCl_3$): δ 0.05 (s, 6H), 0.08 (s, 9H), 1.3-1.4 (m, 2H), 1.5-1.6 (m, 8H), 3.7-3.75 (m, 3H), 4.25-4.32 (m. 1H), 5.19 (d, *J* = 10 Hz, 1H), 5.33 (d, *J* = 17 Hz, 1H), 5.81-5.86 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ -5.4, -5.3, 18.3, 23.8, 23.82, 25.1, 25.8, 36.5, 36.54, 62.7, 79.0, 80.9, 109.6, 117.7, 136.2; Anal. Calcd for $C_{17}H_{32}O_3Si$: C, 65.33; H, 10.32; Found: C, 64.98; H, 10.24.

(3*R*,4*R*)-3,4-*O*-cyclohexylidene-3,4,5-trihydroxypentene (5.88):

Tetrabutylammonium fluoride in THF (8.0 ml, 1M solution in THF) was added to a cooled (0 ^{O}C) solution of **5.87** (2.3 g, 7.36 mmol) in THF (40 ml). The resulting solution was stirred for 1 hour and after the completion of reaction confirmed by TLC the reaction was quenched by the addition of saturated aqueous solution of NH_4Cl (10 ml). The mixture was diluted with EtOAc while two phases were separated. The aqueous phase was extracted with EtOAc. The combined organic layer was washed successively with water, brine and dried. Solvent removal under reduced pressure and column chromatography of the residue (silica gel, 0-20 %EtOAc in Hexane) afforded pure **5.88** (1.22 g, 84.1 %).

$[\alpha]_D^{25}$ = +2.42 (c, 1.44, $CHCl_3$); ^{1}H NMR (500 MHz $CDCl_3$): δ 1.3-1.4 (m, 2H), 1.5-1.6 (m, 8H), 2.02(bs, 1H), 3.5-3.6 (m, 2H), 3.75-3.8 (3, 1H), 4.25-4.3 (t, *J* = 8 Hz, 1H), 5.23 (d, *J* = 10.5 Hz, 1H), 5.36 (d, *J* = 17.5 Hz, 1H), 5.81-5.86 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 23.7, 23.8, 25.0, 36.4, 36.5, 60.9, 78.0, 80.6, 109.8, 118.7, 135.4; Anal. Calcd for $C_{11}H_{18}O_3$: C, 66.64; H, 9.15; Found: C, 66.49; H, 9.21.

(3*R*,4*R*)-3,4-*O*-cyclohexylidene-3,4-dihydroxy-5-bromo-pentene (5.89):

Triphenyl phosphine (3.2 g, 12.2 mmol) was added to a cooled (0 ^{O}C) solution of **5.88** (1.2 g, 6.06 mmol) and carbon tetrabromide (4.1 g, 12.38 mmol) in dry diethyl ether (20 ml). The resulting solution was transformed from colorless to a yellow color solution which was stirred for overnight and after the completion of reaction confirmed by TLC the reaction mixture was concentrated under vaccuo to get rid of the solvent. Column chromatography of the residue (silica gel, 0-5 % EtOAc in Hexane) afforded pure **5.89** (1.05 g, 80.1 %).

$[\alpha]_D^{25}$ = +6.29 (c, 1.32, $CHCl_3$); ^{1}H NMR (500 MHz $CDCl_3$): δ 1.3-1.4 (m, 2H), 1.5-1.6 (m, 8H), 3.44 (dd, *J* = 11.0, 5.0 Hz, 1H), 3.50 (dd, *J* = 11.0, 5.0 Hz, 1H), 3.91 (dt, *J* = 10.0, 5.0 Hz, 1H), 4.28 (t, *J* = 7.5 Hz, 1H), 5.27 (d, *J* = 10.5 Hz, 1H), 5.36 (d, *J* = 17.0 Hz, 1H), 5.83-5.89 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 23.7, 24.9, 31.6, 36.5, 36.7, 79.1, 80.9, 110.4, 118.9, 135.3; Anal. Calcd for $C_{11}H_{17}BrO_3$: C, 50.59; H, 6.56; Found: C, 5.87; H, 6.22.

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1. **Tripathy, S**.; Dubey. A. K.; Chattopadhyay, A.; A stereoselective route to carbocyclic core of 2',3'-olefinic carbanucleosides: towards the synthesis of Homocarbovir (manuscript under preparation)
2. **Tripathy, S**.; Dubey. A. K.; Chattopadhyay, A.; Stereodivergent route to the carbocyclic core of 2′,3′-olefinic carbanucleosides: Toward the synthesis of carbocyclic BCA. (manuscript under preparation)
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1. **Tripathy, S**.; Chattopadhyay, A.; Synthesis of (L)-(+) - and (D)-(-) - Carbovir utilizing (R)-2, 3-cyclohexylideneglyceraldehyde via RCM. Department of

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Now this is not the end. It is not even the beginning of the end. But it is, perhaps, the end of the beginning.

Winston Churchill