ABSTRACT

This thesis entitled "**Synthesis of Some Cyclitols and Aminocyclitols by using Ring Closing Metathesis"** is divided into three chapters.

Chapter I: It deals with "A new stereoselective approach for *N*-Benzyl amino(hydroxylmethyl) cyclopentitols using RCM and study of their glycosidase inhibitory activity".

Chapter II: It describes "Formal synthesis of (-)-neplanocin F"

Chapter III: It is further sub-divided into two sections

Section A: "A common strategy for the synthesis of (+)-gabosine N, (+)-gabosine O and some methyl cyclohexitols using a Nozaki-Hiyama-Kishi reaction and RCM".

Section B: "Synthesis of (+)-pericosine C using Ring Closing Ene-Yne Metathesis".

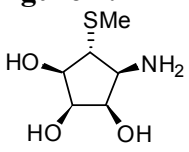
CHAPTER-I:

A new stereoselective approach for *N*-Benzyl amino(hydroxymethyl) cyclopentitols using RCM and study of their glycosidase inhibitory activity:

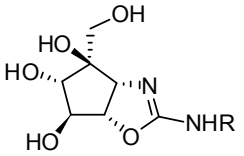
Glycosidases are involved in several metabolic pathways. The development of inhibitors for glycosidases is an important challenge towards the treatment of diseases such as diabetes, cancer and viral infections. Recently aminocyclopentitols have drawn considerable attention as potent glycosidase inhibitors. Aminocyclopentitol sub-structures (Figure 1) are found in a number of bioactive natural products such as mannostatin A **1**, trehazolin **2**, allosamidin **3** and the carbocyclic nucleosides namely aristeromycin **4**, neplanocin A **5**. It should be pointed out that, the aminocyclopentitol BCX 1812 **6** which is neuraminidase inhibitor, is in clinical development to treat influenza. In the context of glycosidase inhibition, aminocyclopentitols can be considered as structural analogs of monosaccharide containing basic nitrogen function at the anomeric centre. Particularly, the amino group mimics the protonated form of

the leaving group oxygen atom in α or β orientation in the transition state of glycosidase catalyzed reaction. Due to interesting biological activity and fascinating structural features, there has been a remarkable growth in design, synthesis, and evaluation of new glycosidase inhibitors, such as Merrell-Dow cyclopentylamine **7**, *α*-D-*gluco, β*-D-*gluco, α*-D-*galacto, β*-D-*galacto, α*-D-*manno, β*-D-*manno, α*-L-*fuco, and β*-L-*fuco* configured aminocyclopentitols *etc*. Recent studies by Reymond and co-workers revealed that the *N*-benzyl derivatives of aminocyclopentitols showed an enhanced inhibitory potency. Jager and co-workers reported that the presence of hydroxymethyl functionality in amino cyclopentane skeleton may serve as a general framework to generate a new family of glycosidase inhibitors. However, glycosidase inhibition by aminocyclopentitols as a function of their structural and stereo chemical features still remains to be fully understood. Hence the synthesis of new analogs can provide not only better understanding of glycosidase functioning but also lead to inhibitors with more therapeutic value.

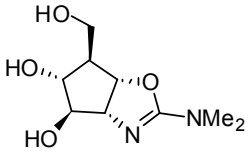
Figure 1:



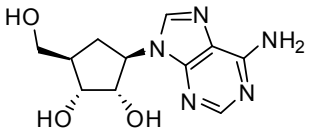
Mannostatin A **1**
(α-mannosidase inhibitor)



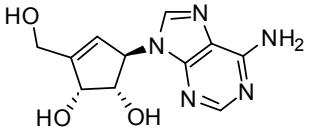
Trehazolin **2**
(α,α-trehalase inhibitor)



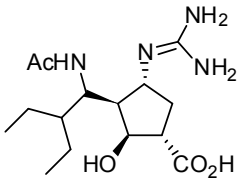
Allosamidin **3**
(chitinase inhibitor)



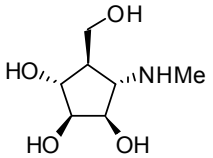
Artisteromycin **4**
(anti-viral ,
antitumor & AdoHcy hydrolase)



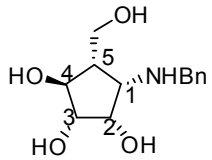
Neplanocin A **5**
(anti-viral & anticancer)



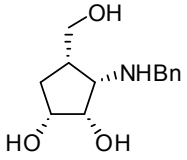
BCX-1812 **6**
(neuraminidase inhibitor)



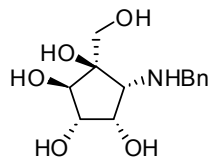
Merrell-Dow cyclopentylamine **7**
(α-mannosidase inhibitor)



N-benzyl-α-L-manno
aminocyclopentitol **8a**



4-deoxy-*N*-benzyl-α-L-manno
aminocyclopentitol **8b**

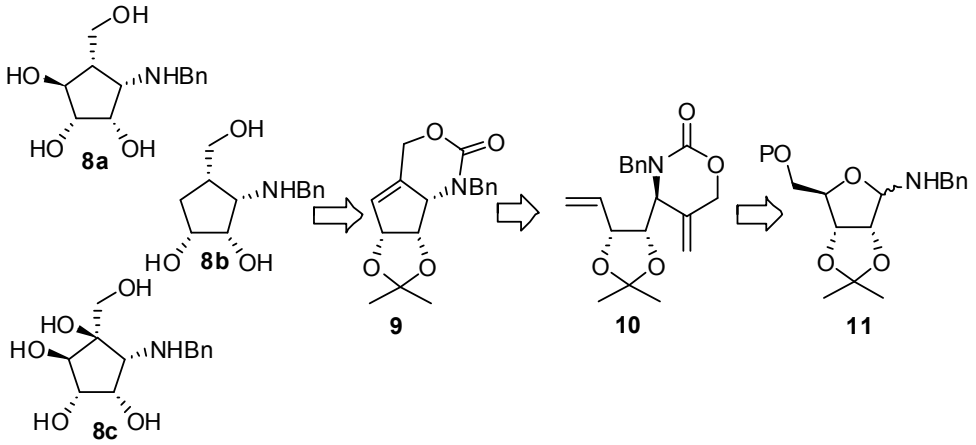


N-benzyl-6,7-di-epi
trehalamine **8c**

Due to the biological importance of glycosidase inhibitors, we have developed stereoselective synthesis of novel *N*-benzyl derivatives of amino(hydroxylmethyl)cyclopentitols, for instance *N*-benzyl *α*-L-*manno* aminocyclopentitol **8a**, 4-deoxy-*N*-benzyl-*α*-L-*manno* aminocyclopentitol **8b** and *N*-benzyl 6,7-di-*epi*-trehalamine **8c** using stereoselective allylation on lactamine and ring closing metathesis (RCM) as key steps. The retro synthetic analysis of aminocyclopentitol skeletons **(8a-8c)** is depicted in **Scheme 1** which shows the importance of key intermediate **9** from which a variety of aminocyclopentitols can be prepared. It was further envisaged that the presence of 1, 3-dioxalane ring in **9** could be helpful in getting better selectivity during further transformations.

In general the success of the RCM strategy depends on the efficient preparation of diene. In our strategy the RCM precursor **10** required for the construction of aminocyclopentene **9** could be prepared from lactamine **11** by allylation, oxidative cleavage of the double bond followed by condensation with Eschenmoser's salt and subsequent reduction.

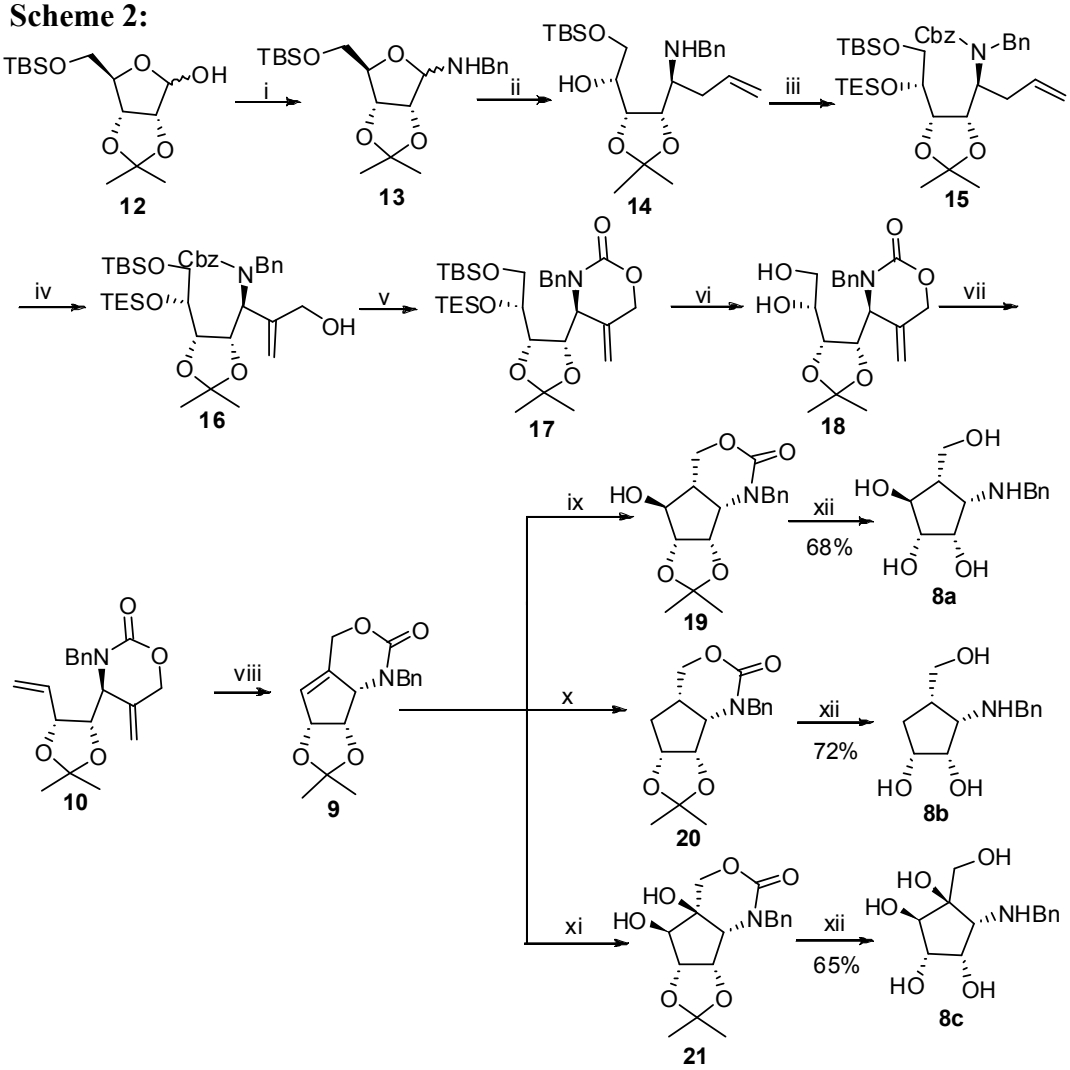
Scheme 1:



The starting material 5-*O*-*tert*-butyl dimethylsilyl-2,3-*O*-isopropylidene-D-ribofuranose **12,** required for our synthesis was prepared from D-ribose using reported procedure (Scheme 2)**.** Reaction on **12** with benzylamine gave ribosylamine **13.** Treatment of crude **13** with allylbromide and zinc furnished amino alcohol **14** exclusively as single isomer. The absolute configuration of the newly generated stereo center was not confirmed at this stage, but it was done at the later stages by

nOe correlations, which indicated the formation of *erythro* isomer. Previously there are some reports on the stereoselective nucleophilic addition on lactamine, Wilcox *et.al,* reported that the Grignard addition on *N,N*-dibenzyl ribosylamine having 2,3-*O*-isopropylidene unit gave *threo* amino ethers where the nucleophilic addition is taking place on non-chelated iminium ion. Later Nicotra *et.al*, reported that the nucleophilic addition on *N*-benzyl-tri-*O*-benzyl glucosamine also gave *threo* amino ethers. Here the selectivity was due to the chelation between imine and α-benzyloxy group, here in the case of compound **13**, allylation gave exclusively *erythro* isomer which presumably proceeded *via* seven membered transition state or Felkin-Anh model. In fact the formation of *erythro* isomer clearly shows that chelation between imine and isopropylidene group have not taken place due to steric strain.

Scheme 2:



Reagents & Conditions: (i) $BnNH_2$, MeOH, reflux, 12 h (ii) allylbromide, Zn, THF, 0 ^oC-RT, 4 h, 70% (over 2 steps) (iii) a) TES-Cl, Imidazole, DCM, 0 ^oC, 10 min, 93% b) NaH, CbzCl, THF, 0 ^oC, 1 h, 85% (iv) a) $OsO_4/NaIO_4$, acetone, water 4:1, 0 ^oC-RT, 3h b) Et_3N, Eschenmoser's salt, DCM, 0 ^oC-RT, 4 h c) $NaBH_4$, $CeCl_3.7H_2O$, MeOH, -78^oC, 30 min, 70% (over 3 steps) (v) NaH, THF, 0 ^oC-RT, 2 h, 85% (vi) TBAF, THF, RT, 5 h, 92% (vii) TPP, I_2, imidazole, toluene, reflux, 3 h, 83% (viii) Grubbs 2nd generation catalyst, toluene, reflux, 18 h, 75% (ix) BH_3.DMS, H_2O_2, NaOH, THF, -15 ^oC-RT, 3 h, 50% (x) Pd/C, H_2, MeOH, 30 min, 90% (xi) OsO_4, NMO, acetone-water, 4:1, RT, 3 h, 85% (xii) aq. 6N HCl, reflux, 12 h.

Having the amino compound **14** in hand we proceeded to the next stage. Secondary hydroxyl group of compound **14** was protected as its triethylsilyl ether and then amino functionality was converted to carbamate with CbzCl to give **15**. The next step is the introduction of 1,1-disubstituted olefin required for RCM. Oxidative cleavage of terminal double bond in **15** with $OsO_4/NaIO_4$ produced aldehyde which on treatment with Eschenmoser's salt yielded α-methylene aldehyde. The crude aldehyde was further reduced to alcohol **16** under Luche condition at -78^oC, yielding the required olefin without any α-elimination. In order to protect the primary hydroxyl group, compound **16** was treated with sodium hydride to give the cyclic carbamate **17**. Global deprotection of *bis*-silylether in **17** with TBAF gave diol **18**. Diol functionality of **18** was converted to olefin using I_2/TPP to give diene **10**. The diene **10** was subjected to ring closing metathesis using Grubbs second generation catalyst in toluene under reflux conditions produced the key intermediate aminocyclopentene **9** in 75% yield.

The compound **9** was transformed to various aminocyclopentitol derivatives with high stereoselectivity as follows. Hydroboration of aminocyclopentene **9** with BH_3-DMS complex gave hydroxy product **19**. Chemoselective hydrogenation of aminocyclopentene **9** using Pd/C afforded **20** and dihydroxylation of **9** with OsO_4 gave dihydroxy compound **21**. The stereochemistry of compounds **19, 20,** and **21** was established from ^{1}H-NMR couplings and nOe experiments. Global deprotection of carbamate and 2,3-*O*-isopropylidene group in **19, 20,** and **21** were achieved with aq. 6N HCl under reflux to give new *N*-benzyl aminocyclopentitols **8a, 8b** and **8c** respectively.

Glycosidase inhibitory study:

The glycosidase inhibitory activity against α-glucosidase (yeast), β-glucosidase (almonds), α-galactosidase (green coffee beans), β-galactosidase (Kluyveromyces lactis) for compounds **8a-c** were studied and the IC_{50} values are summarized in Table 1. The residual hydrolytic activities of the glycosidases were measured spectrometrically of the corresponding chromogenic nitrophenyl glycosides as substrates in aqueous phosphate buffer at pH 6.8. All the enzymes and substrates were purchased from Sigma-Aldrich Co., U.S.A.

The assays performed with fixed concentration of the substrate (1.6 mM) in phosphate buffer and enzyme concentration is 100 µl (1 mg/ml) in 20mL of substrate solution. Substrate and compounds were preincubated for 1min and the reaction was started by the addition of the enzyme. The reaction for enzyme activity was followed for 5 min at 405nm.

The compounds **8a** and **8b** have shown better inhibition against β-galactosidase and the deoxy compound **8b** also exhibited good inhibition against α-glucosidase.

Table 1: Glycosidase inhibitory activity, IC_{50} values in mM

Compounds	α-glucosidase	β-glucosidase	α–galactosidase	β-galactosidase
8a	0.5	0.41	NI	0.065
8b	0.09	0.21	0.79	0.098
8c	1.0	0.20	NI	NI

NI: no inhibition at 2mM concentration

In conclusion we have successfully demonstrated a general strategy for the synthesis of some novel *N*-benyl aminocyclopentitols. Also we studied their activity against glycosidases. The salient features of our approach are nucleophilic addition on lactamine for the introduction of chiral amino group and efficient preparation of

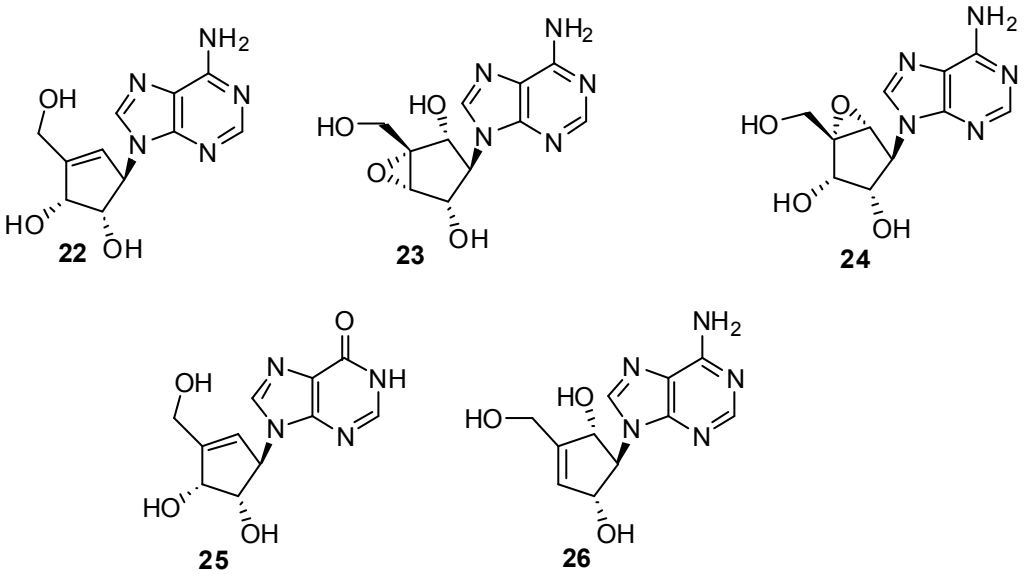
1,1-disubstituted olefin for the RCM using Eschenmoser's salt. This strategy is also helpful in designing related skeletons for better activity. Application of this strategy for higher membered amino carbasugars and azasugars are under progress in our laboratory.

CHAPTER-II:

Formal synthesis of (-)-neplanocin F from Garner's aldehyde:

Carbanucleoside are compounds in which ring oxygen of sugar nucleoside is replaced by methylene group. The neplanocin family is an important class of naturally occurring carbanucleosides isolated from *Ampullariella regularis.* These are named as neplanocin A **22**, neplanocin B **23**, neplanocin C **24**, neplanocin D **25**, and neplanocin F **26** (Figure 2). Generally these nucleosides exhibits broad spectrum of antiviral and anticancer activity. Neplanocin A has received much attention due to its interesting biological properties. On the other hand, neplanocin F is a minor member of this family; several of its analogues were prepared and tested against HIV. Due to its biological importance, we have developed an efficient strategy for the formal synthesis of (-)-neplanocin F.

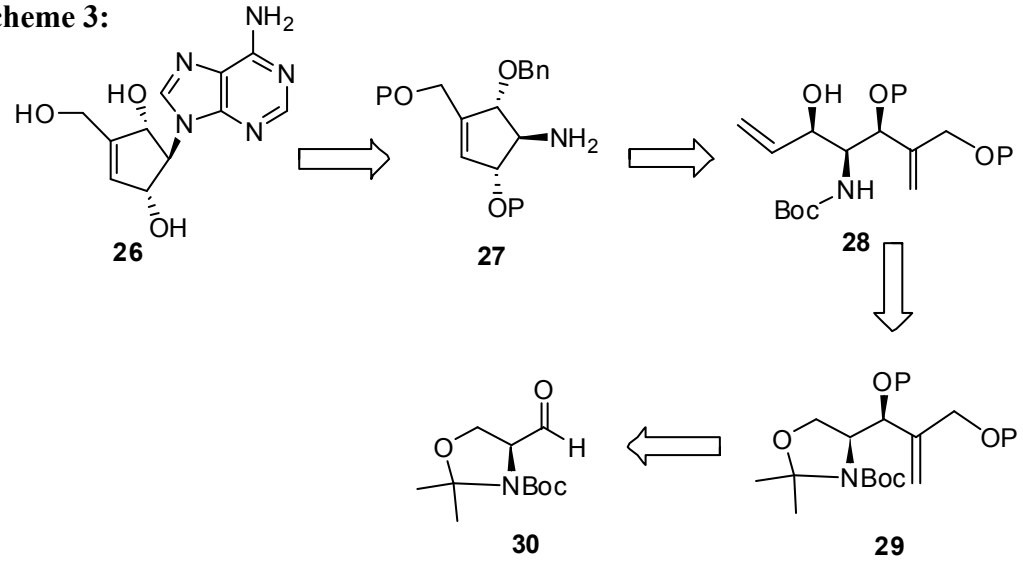
Figure 2:



Many of these carbanucleosides has been synthesized from carbohydrate building block as starting materials. We have undertaken the synthesis of (-)-neplanocin F **26** from (S)-Garner's aldehyde which involves stereoselective introduction of hydroxyl groups and RCM (ring closing metathesis) as key steps. This synthetic approach can be extended for the preparation of other aminocylopentitols. In general creation of new chiral elements by means of internal asymmetric induction utilizing substrate based diastereo chemical relay often represented a more direct and efficient approach. The ideal scenario entails formation of three asymmetric centers of the target compound starting from a single stereo genic point without any additional external chiral source being used in the synthesis.

The retrosynthetic analysis of neplanocin F is depicted in **Scheme 3**. The synthesis of neplanocin F **26** was envisaged from protected carbocyclic precursor **27**. This carbocyclic precursor was prepared by using RCM from diene **28**. The diene compound **28** inturn can be obtained from Garner's aldehyde **30** *via* comound **29**.

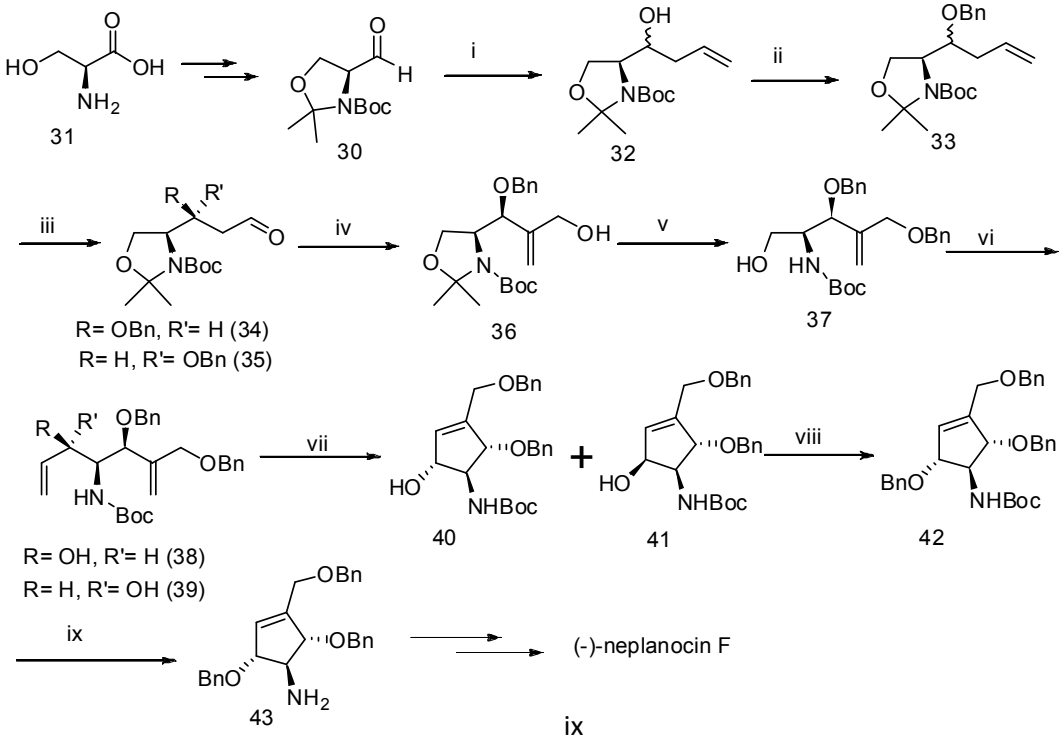
Scheme 3:



Our synthesis commenced from *S*-Garner aldehyde **30**, which was prepared from L-serine **31** according to the reported procedure (Scheme 4). Garner's aldehyde **30** was treated with allylmagnesium chloride at -78 °C gave homo allylic alcohol **32** as mixture with the ratio of 2:1 (syn/anti), these two isomers were separated at later stages. The alcohol in **32** protected as its benzyl ether using NaH, BnBr to give compound **33**. Ozonolysis of terminal olefin in compound **33** gave mixture of

aldehydes **34**/**35** in 2:1 ratio, here both the isomers were separated using coloumn chromatography. The major compound **34** was treated with Eschenmoser's salt to give α-methylene aldehyde, reduction of this α, β-unsaturated aldehyde gave alcohol **36** by using Luche's condition. The alcohol functionality in **36** was protected as its benzyl ether by using NaH and benzyl bromide followed by *N*, *O*-isopropylidene deprotection with 80% aq.aceticacid to give amino alcohol **37**. The second olefin part was introduced on compound **37** by oxidation of primary alcohol with Dess-Martin periodinane (DMP) which gave α-amino aldehyde, this aldehyde was treated with vinylmagnesiumbromide at -78^{o}C to furnish *syn* allylic alcohol **38** along with *anti* alcohol **39** in the ratio of 3:1. These two isomers were not separated at this stage, we proceeded for next reaction. Mixture of isomers **38** and **39** were subjected to ring closing metathesis using 5 mol% Grubbs 2nd generation catalyst in DCM to give cyclopentene derivative **40** as major isomer along with minor isomer **41**. Alcohol in compound **40** was protected as its benzyl derivative using Ag_2O and benzyl bromide to give compound **42**. Finally, removal of Boc protecting group in **42** was achieved with aq. 3N HCl and neutralization with triethylamine gave carbocyclic precursor of (-)-neplanocin F **43**. The spectral characteristics are correlating with reported values.

Scheme 4:



Reagents & conditions: (i) allyl magnesium chloride, THF, -78 °C, 80% (ii) NaH, benzyl bromide, DMF, 4 h, 85% (iii) O_3, DMS, DCM, -78^oC, 1 h, 83% (iv) a) Eschenmoser's salt, Et_3N, DCM, 3 h, 83% b) $NaBH_4$, $CeCl_3.7H_2O$, MeOH, 30 min, 87% (v) a) NaH, benzyl Bromide, THF, 3 h, 84% b) 80% Acetic acid, 12 h, 90% (vi) a) DMP, DCM, 1 h b) vinylmagnesiumbromide, THF, -78 ^oC, 3 h (70% over 2steps) (vii) 5 mol% Grubbs 2nd generation catalyst, DCM, 4 h, 85% (viii) Ag_2O, benzyl bromide, DCM, 24 h, 77% (ix) a) aq.3N HCl, MeOH, 3 h b) Et_3N, 3 h 60%.

In conclusion we have successfully demonstrated the formal synthesis of (-)-neplanocin F by using stereoselective introduction of hydroxyl groups and ring closing metathesis. Our strategy is helpful to prepare other carbanucleosides, aminocyclopentitols and 2-aminocarbafuranoses.

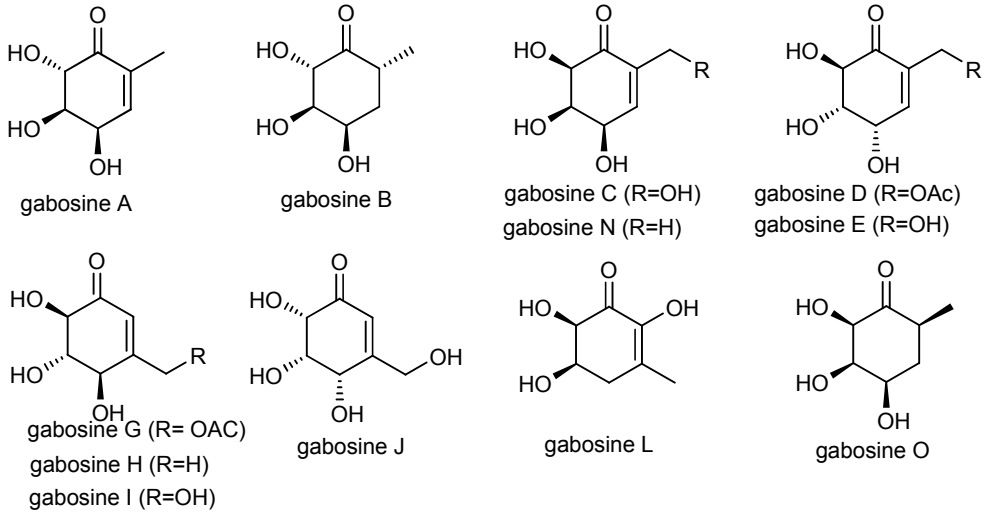
CHAPTER-III:

Section A:

A common strategy for the synthesis of (+)-gabosine N, (+)-gabosine O and some methyl cyclohexitols using a Nozaki-Hiyama-Kishi reaction and RCM:

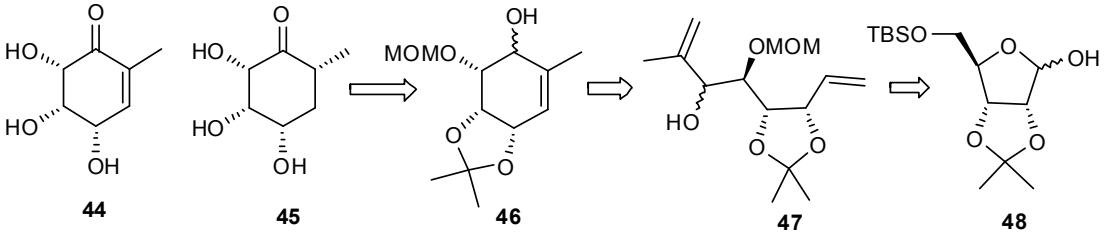
Carbasugars are analogues of monosaccharide in which ring oxygen is replaced with methylene group and have attracted considerable interest as inhibitors of glycosidases. Glycosidase enzymes are involved in numerous biological processes and their inhibition has enormous potential for the treatment of many diseases. Gabosines isolated from *Streptomyces* strains, belong to the sub class of carbasugars called as ketocarbasugars. Gabosines exhibit a variety of biological activities such as antiprotozoal activity, DNA binding properties and enzyme inhibition. Up till now fifteen different gabosines have been isolated and they posses trihydoxy methyl (hydroxymethyl) cyclohexenone or cyclohexanone skeleton in common (Figure 3). Because of their interesting biological activity and fascinating structural features, they attracted the attention of many synthetic chemists and biologists. Furthermore gabosines can be considered as chemical precursor of 6-deoxy-carba pyranose derivatives which are known for the inhibition of oligosaccharide processing enzymes.

Figure 3: Gabosine family



Prompted by their biological importance of gabosines and carbapyranoses, herein we are presenting a short, efficient and common strategy for the synthesis of (+)-gabosine N **44**, (+)-gabosine O **45**, carba-α-L-rhamnose **60**, and carba-6-deoxy-α-L-talose **61**. Earlier few synthesis for gabosine N and gabosine O have been reported. The synthesis for carba-β-D-rhamnose has been reported by Singh and co-workers whereas perbenzoyl derivative of carba-6-deoxy-α-L-talose has been reported by Redlich and co-workers. Retrosynthetic analysis of gabosine N and gabosine O (Scheme 5) reveals that the chiral hydroxyl groups at C_4, C_5, and C_6 can be obtained from D-ribose. For instance, one carbon homologation at C-1 and propenyl group introduction at C-5 on compound **48** will give the RCM precursor **47** which can be elongated to the cyclohexene core **46**. The key aspect of the synthesis is to find the stereoselectivity at the newly generated centre in **47** during the nucleophilic addition of propenyl unit.

Scheme 5:

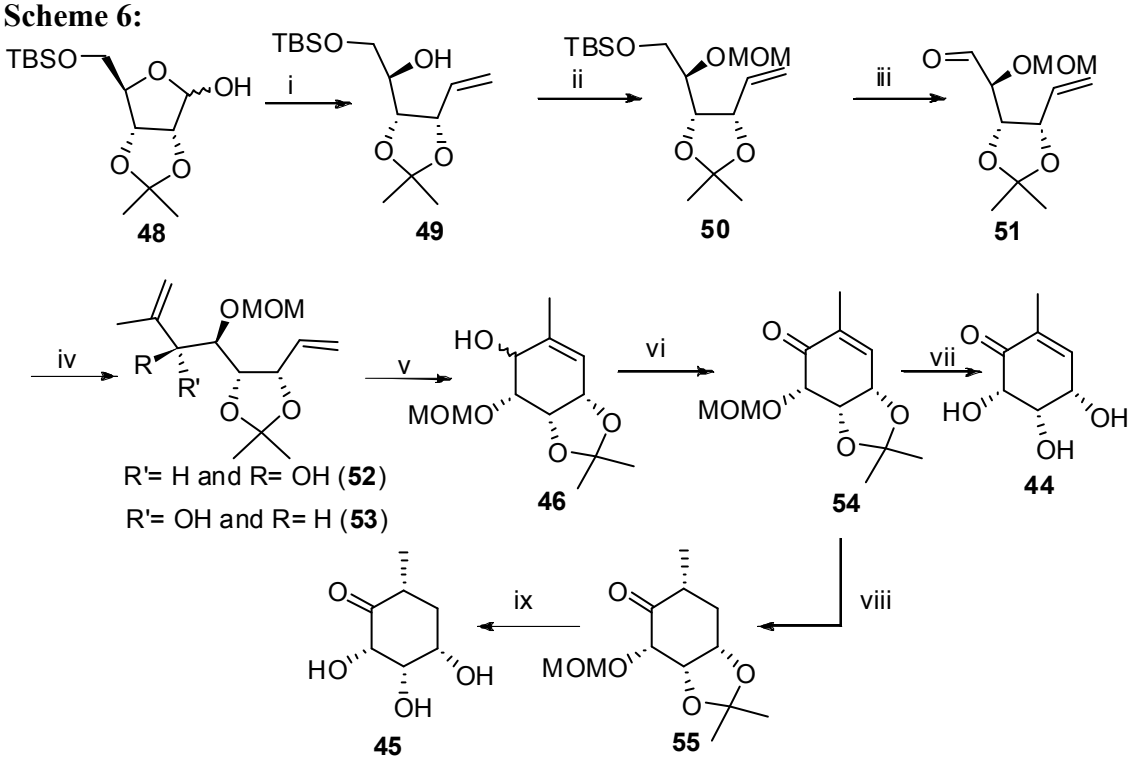


We synthesized (+)-gabosine N and (+)-gabosine O starting from 5-*O*-tert-butyldimethylsilyl-2, 3-*O*-isopropylidene-D-ribofuranose **48** as shown in Scheme 6**.** One carbon homologation of the lactol **48** afforded the olefin compound **49** using Wittig reaction**.** Secondary hydroxy group of **49** was protected as MOM ether using methoxy methyl chloride to give **50**. Deprotection of the silyl group in compound **50**, followed by oxidation of resultant alcohol under Swern conditions gave α-alkoxy aldehyde **51**.

Nucleophilic addition on α-alkoxy aldehyde with 2-bromo propene under Nozaki-Hiyama-Kishi (NHK) conditions in DMF gave *anti* alcohol **53** as major product along with **52** in the ratio of 3.8:1. When addition was carried out under Gringard condition in THF at -78 ^{o}C interestingly *syn* alcohol **52** was obtained as major compound along with **53** in the ratio of 4:1, both the isomers were separated by coloum chromatography. The reversal of stereoselectivities in the above case can be explained as follows. Generally during the NHK reaction, the nucleophile undergoes addition *via* non-chelated Felkin-Anh model, whereas in the case of Grignard addition, chelation of magnesium ion with α-alkoxy group, allowed nucleophilic addition to give *syn* isomer **52** as major.

The diene mixture **52** and **53** were subjected to ring closing metathesis using Grubbs 2nd generation catalyst in toluene under reflux to give cyclohexene derivative **46**. Allylic alcohol in compound **46** was oxidized with PDC to yield the enone derivative **54.** Global deprotection of MOM and isopropylidene in compound **56** was achived with Amberlyst® 15 in THF: H_2O (2:1) to give (+)-gabosine N **44** as white solid whose physical and spectral data were identical with the reported values. Hydrogenation of **54** gave **55**. Global deprotection of MOM and isopropylidene group in **55** was achieved with Amberlyst® 15 to give (+)-gabosine O **45** as white solid whose physical and spectral data were identical with the reported values.

Scheme 6:

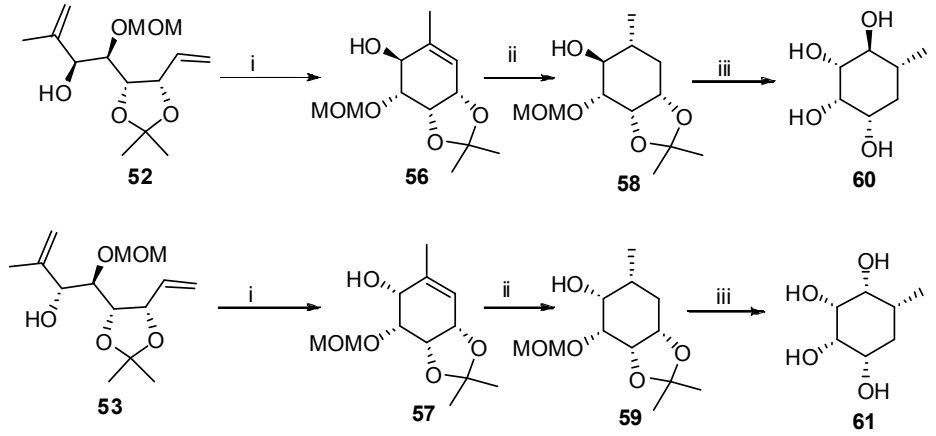


Reagents & conditions: (i) $Ph_3P=CH_2$, THF, -78 ^oC to rt, 4 h, 76% (ii) MOM-Cl, DIPEA, cat. DMAP, CH_2Cl_2, -15 ^oC to rt, 12 h, 93% (iii) (a) TBAF, THF, 4 h, 95% (b) $(COCl)_2$, DMSO, CH_2Cl_2, Et_3N, -78^oC, 2 h (iv) 2-bromo propene, $CrCl_2$, cat. $NiCl_2$, DMF, 12 h, 72% or 2-bromo propene, Mg, THF, -78 ^oC, 4 h, 85% (v) 10 mol% Grubbs catalyst 2nd generation, toluene, reflux, 12 h, 85% (vi) PDC, CH_2Cl_2, 4A^o MS, 12 h, 82% (vii) Amberlyst® 15, THF:H_2O (2:1), 70 ^oC, 5 h, 75% (viii) H_2, Pd/C, MeOH, 1 h, 95% (ix) Amberlyst® 15, THF:H_2O (2:1), 70 ^oC, 5 h, 85%.

We extended this strategy for the synthesis of 6-deoxy carbasugars such as carba-α-L-rhamnose **60** and carba-6-deoxy-α-L-talose **61** (Scheme 7), also these compounds resemble the structures of ampelomins. Diene **52** and **53** were independently subjected to ring closing metathesis using Grubbs 2nd generation catalyst in toluene under reflux condition to give cyclohexene derivatives **56** and **57**. Stereoselective reduction of double bond in **56** and **57** was achieved with hydrogenation using PtO_2 as catalyst to give **58** and **59**. Global deprotection of **58** and **59** with aq. 6N HCl in methanol gave carbapyranoses **60** and **61**. The spectral and physical data of **60** was identical with the reported values, thus confirming the configuration of the newly generated chiral centre in **52**. Furthermore, it also

confirms the configuration of the hydroxyl group generated by propenyl addition in **53**.

Scheme 7:



***Reagents & Conditions**:* (i) 10 mol% Grubbs catalyst 2nd generation, toluene, reflux, 12 h, 85% (ii) (a) H_2, PtO_2, MeOH, 4 h, 90% (b) aq. 6N HCl, MeOH, RT, 80%.

In conclusion, we have developed a diversity oriented general strategy for the synthesis of (+)-gabosine N, (+)-gabosine O and carbapyranoses by using nucleophilic addition on α-alkoxy aldehyde under NHK and Grignard conditions followed by ring closing metathesis.

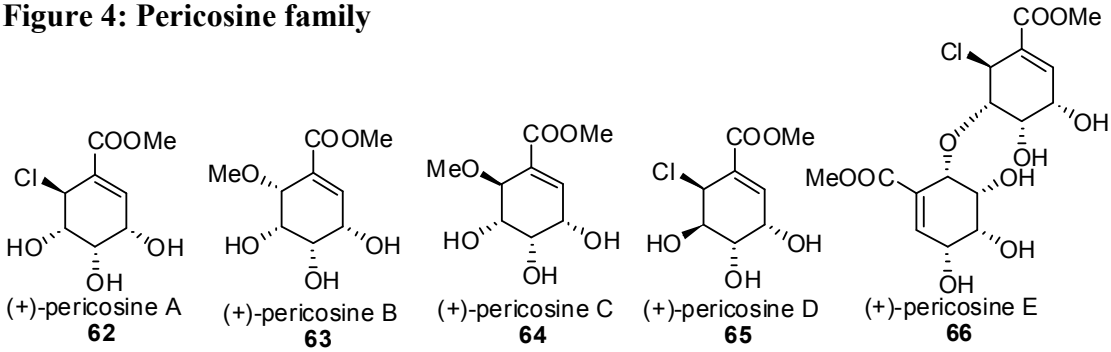
Section B:

Stereoselective synthesis of (+)-pericosine C using Ring Closing Ene-Yne Metathesis (RCEYM) :

The isolation of pericosines A-E, **62-66** (Figure 4), respectively, as cytotoxic metabolites of *Periconia byssoides* OUPS-N133 originally separated from the sea hare, *Aplysia kurodai*, was reported in 1997 and 2007. There has been considerable interest in the synthesis of pericosines, due to their cytotoxicity against P388 lymphocytic leukemia cells, antitumor activity against murine P388 cells, and selective growth inhibition against human cancer cell lines HBC-5 and SNB-75. Because this series of compounds have a multifunctionalized cyclohexene core that is typical of carbasugars, we have been interested in their syntheses and the synthesis of

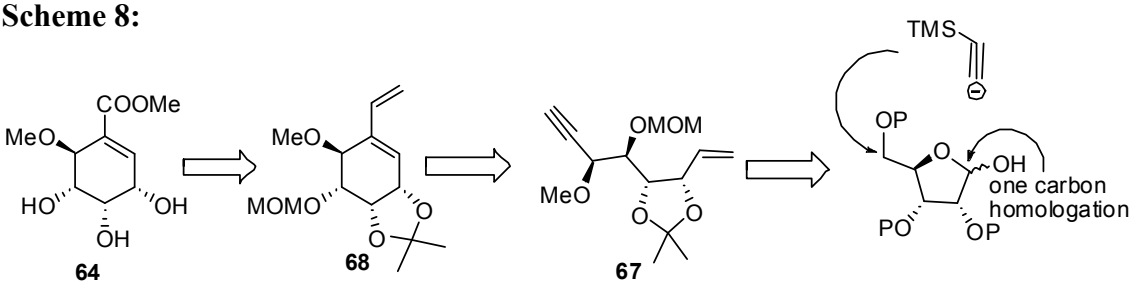
their related compounds. Herein we have developed ring closing metathesis based approach for the synthesis (+)-pericosine C **64**.

Figure 4: Pericosine family



Retrosynthetic analysis of (+)-pericosine C (Scheme 8) reveals that the chiral hydroxyl groups at C_3, C_4, and C_5 can be obtained from D-ribose. For instance, one carbon homologation at C-1 and ethynyl group introduction at C-6 will give the RCEYM precursor **67** which can be elongated to the cyclohexene core **68** of (+)-pericosine C.

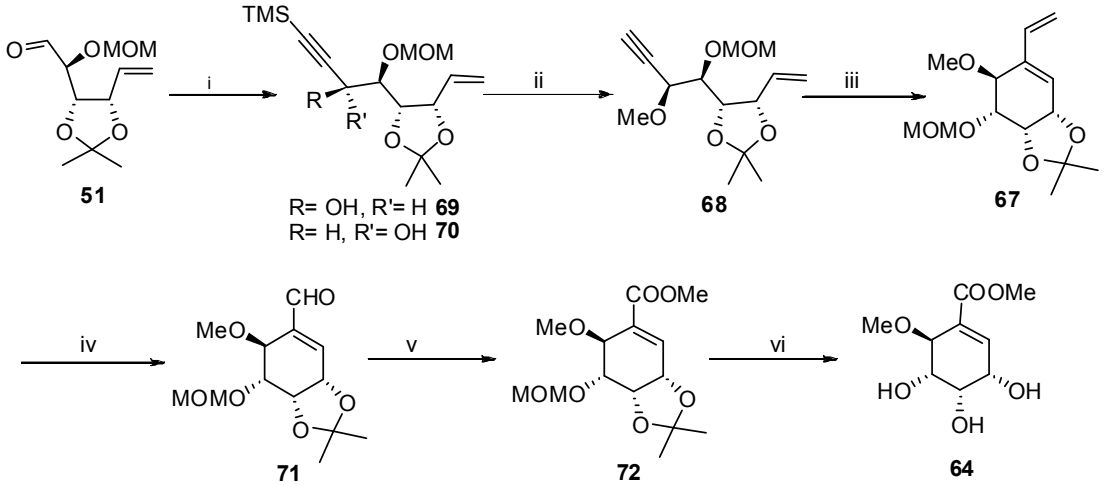
Scheme 8:



Accordingly the synthetic sequence began with aldehyde **51** which was discussed in earlier section (Scheme 6). Aldehyde **51** was treated with lithium-TMS acetylide in THF gave *syn* propargylic alcohol **69** as a major along with *anti* proparylic alcohol **70** in the ratio of 4:1, both the isomers were separated by column chromatography. *C*-Silyl group in major compound **69** was desilylated with K_2CO_3 in methanol, which on *O*-methylation with NaH and MeI afforded the required RCEYM precursor **67**. The ene-yne **67** was treated with 10 mol% Grubbs second generation catalyst in toluene at 80 °C under ethylene atmosphere to give cyclohexene **68** in 60% yield. Oxidative cleavage of terminal double in compound **68** was achieved with $OsO_4/NaIO_4$ to give α,β-unsaturated aldehyde **71**. Aldehyde was oxidized to acid

using Pinnick's protocol followed by esterification with K_2CO_3/MeI in acetone yielded the protected from of (+)-pericosine C **72**. Global deprotection of isopropylidine and methoxy methyl group in compound **72** was achieved with TFA in methanol to give (+)-pericosine C **64** (Scheme 9). The spectral and physical data of (+)-pericosine C **64** were identical with the reported values.

Scheme 9:



Reagents & conditions: (i) TMS-acetylene, n-BuLi, THF, -78 ^oC to rt, 3 h, 85% (ii) (a) K_2CO_3, MeOH, rt, 2 h, 85% (b) NaH, MeI, THF, 0 ^oC to rt, 3 h, 70% (iii) 10 mol% Grubbs catalyst 2nd generation, ethylene atmosphere, toluene, 80 ^oC, 12 h, 65% (iv) OsO_4/$NaIO_4$, acetone, water 4:1, 0 ^oC-RT, 4 h, 50% (v) (a) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, tBuOH, 2 h (b) K_2CO_3, MeI, acetone, rt, 2 h, 65% (over 2 steps) (vi) TFA, MeOH, rt, 2 h, 65%.

In conclusion, we have successfully developed RCM based approach for the synthesis (+)-pericosine C using stereoselective ethynylation and RCEYM and our strategy is helpful to make pericosine analogues and carbasugars.