ABSTRACT

ABSTRACT

This thesis entitled **"SYNTHETIC APPROACHES TO PENTENOMYCINS, SOME CARBASUGARS AND AMINOCARBASUGARS FROM CARBOHYDRATES"** is divided into four chapters.

Chapter I: It deals with the "Introduction to carbasugars and aminocarbasugars."

Chapter II: It is further sub divided into two sections.

Section A: It deals with the "Synthesis of (+)/(-) pentenomycins *via* Me_2AlCl induced cascade reaction".

Section B: It deals with the "Synthesis of 2,2,5-trimethyl-3a,6a-dihydro cyclopenta[1,3]dioxol-4-one using Mn/$CrCl_3$ mediated domino reactions and ring closing metathesis."

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

Section A: It deals with the "Synthesis of (+) methyl shikimate, (+) methyl-5-*epi*-shikimate, 5a-carba-α-D-mannopyranose, 5a-carba-β-D-mannopyranose, validamine analogue and valiolamine analogue utilizing Mn/$CrCl_3$ mediated domino reactions and ring closing metathesis".

Section B: It deals with the "Formal synthesis of Tamiflu, Synthesis of 5a-carba-α-D-glucopyaranose, 5a-carba-β-D-glucopyaranose, 5a-carba-β-L-altropyranose and 5a-carba-α-L-altropyranose."

Chapter IV: It is further sub divided into two sections.

Section A: It deals with the "Synthesis of 4a-carba-α-L-lyxofurnanose and 4a-carba-β-D-ribofuranose *via* one pot reductive elimination followed by intramolecular Nozaki-Hiyama-Kishi reaction."

Section B: It deals with the "Study of reductive ring opening followed by intramolecular Nozaki-Hiyama-Kishi reaction on six membered diiodo compounds."

CHAPTER I:

Introduction to carbasugars and aminocarbasugars:

Carbohydrates are a major class of biomolecules found in living organism along with lipids, peptides and nucleotides. They are found as monosaccharides, linked together in oligo- or polysaccharides, and covalently bound to non-carbohydrate moieties (aglycons). Carbohydrates are primarily recognized as energy storage molecules, *eg*., glucose can be stored in the form of glycogen in animals, where as in plants it is stored in the form of starch. Studies in glycobiology discipline have revealed many crucial roles of carbohydrates in cell-cell recognition, protein folding, cell growth, tumor cell metastasis, biological recognition events, and also immune response during inflammation.

Carbasugars:

Carbasugars are carbocyclic analogues of monosaccharides in which the ring oxygen is replaced by methylene group. The absence of anomeric functionality (Fig. 1(a)) makes them resistant to enzymatic degradation; therefore these compounds can be viewed as excellent inhibitors of glycoprocessing enzymes. The term pseudosugar was introduced by McCasland's in his very first paper to analogues of sugars they prepared. After some period of time the term "pseudosugar" was besmirched and employed for a large variety of sugar analogues, thus requiring a specification of the definition for different subclasses of mimetics. S. Ogawa proposed the use of the prefix "carba", preceded, where considered necessary, by the appropriate locant ("4a" for an aldofuranose, "5a" for an aldopyranose), followed by the name of the sugar (Fig. 1(b)).

Figure 1 (a):

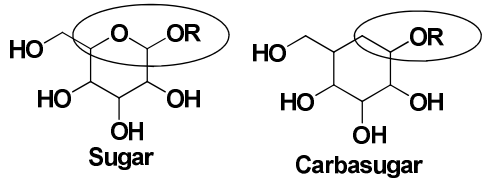
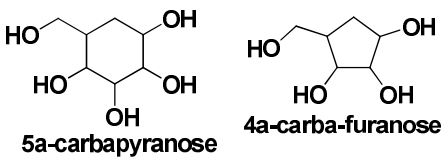


Figure 1 (b):



Carbasugar classification:

Carbasugars are further classified into two major categories they are (i) carbafuranoses and (ii) carbapyranoses

(i) **Carbafuranoses**:

The carbasugars which exists in five membered furanose form are termed as carbafuranoses. Carbafuranoses have not been found free but are subunits of products of natural sources. They are mostly found in carbanucleosides. There are only two carbocyclic carbohydrate analogues of furanoses found in nature they are caryose **1** and and calditol **2** Fig. 2.

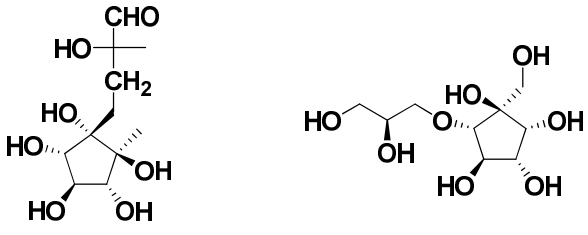


Fig: 2

(ii) **Carbapyranoses**:

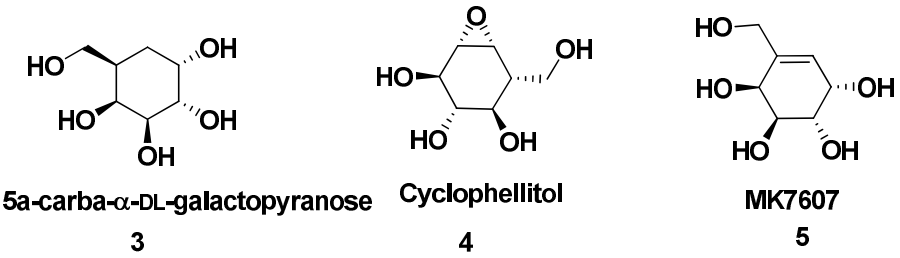


Fig: 3

Carbapyranoses have been rarely found in Nature; however, they are available in large amount as subunits of other natural products. Compounds such as carba-α-D-galactopyranose (**3**) isolated from *Streptomyces* sp. MA-4145, cyclophellitol (**4**) isolated from *Phellinus* sp., and MK7607 (**5**) which was isolated from *Curvularia*

eragestrides (Fig. 3). From a formal standpoint, carba-D-galactopyranose **3** is the only "*genuine*" carbasugar isolated from natural sources.

Aminocarbasugars:

As we discussed earlier carbasugars (or pseudosugars) are carbocyclic analogues of monosaccharides in which the ring-oxygen atom has been replaced by a methylene group. If the C1-OH in carbasugars is replaced by amino group then they are called as aminocarbasugars (Fig. 4). In the context of glycosidase inhibition, carba-glycosylamines (aminocyclitols) can be considered as structural analogs of monosaccharide containing basic nitrogen function at the anomeric center.

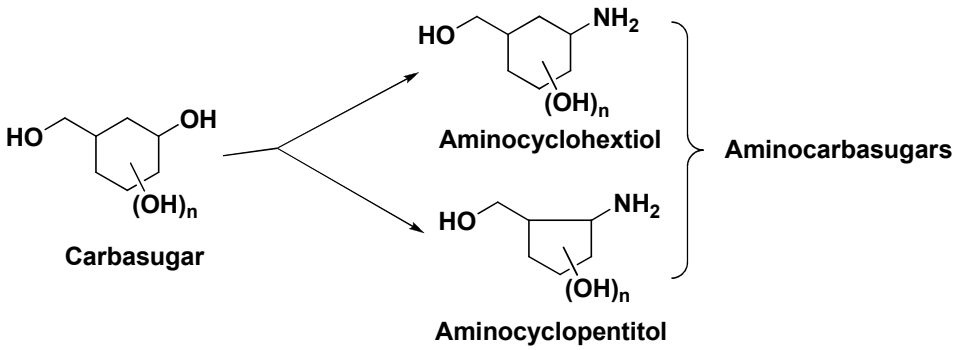


Fig: 4

Aminocyclohexitols:

The aminocyclohexitols are found in Nature as a part of complex molecules arising from the secondary metabolism of several microorganisms and plants. This is the case of valienamine **6**, validamine **7**, hydroxyvalidamine **8**, and valiolamine **9** which are essential components of the validamycins **10** a family of antibiotics found as secondary metabolites in the fermentation broth of *Streptomyces hygroscopicus*. Valienamine is also found as one of the subunits of adiposins **11** and salbostatin **12** (Fig. 5).

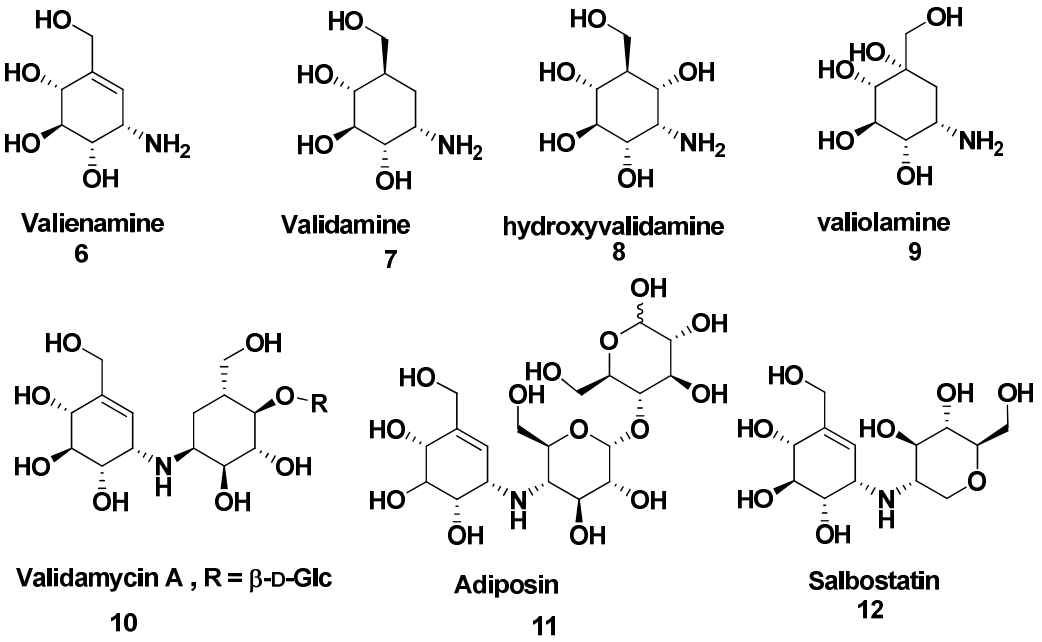


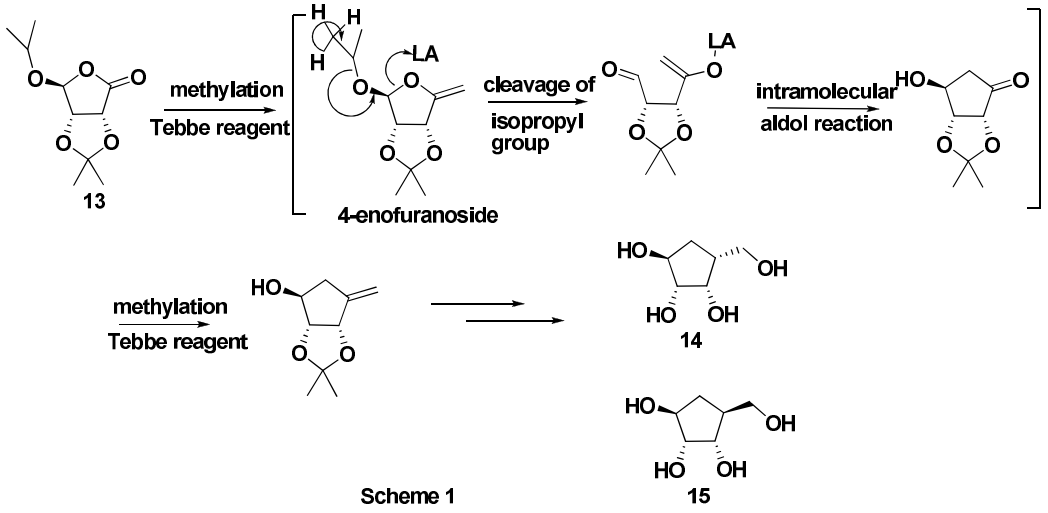
Fig: 5

CHAPTER II:

Section A:

Synthesis of (+)/(-) pentenomycins *via* Me_2AlCl induced cascade reaction.

Carbocyclitols are part structures of many interesting biologically active compounds. These molecules inhibit glycosidases and show interesting biological activity such as anti-diabetic, anti-HIV, anti-cancer, *etc*. Conversion of readily available carbohydrates into highly oxygenated carbocycles is an attractive route adopted by many synthetic chemists, since this approach gives the target compounds with high optical purity. Among the reported methods, Ferrier rearrangement is considered as useful transformation for the synthesis of cyclohexitols from 5-enopyranosides. Later, Sinay and co-workers also developed a methodology for the cyclohexitols from the 5-enohexopyranosides using TIBAL. However, these methods failed to give cyclopentitols from corresponding 4-enofuranosides, since they have to undergo unfavorable *5-(enol-endo)-exo-trig* cyclization.



Scheme 1

However, recently we developed a Tebbe-mediated cascade reaction for the synthesis of cyclopentitols **14** and **15** from fivemembered sugar lactone **13** *via* 5-*(enol-endo)-exo-trig* cyclisation (Scheme 1), which is considered as a disfavored reaction according to Baldwin rules. Herein we would like to present our observations while applying this cascade method for the synthesis (-) and (+) pentenomycins **16** and **17**(Fig. 6). (-) Pentenomycin **16** belongs to the pentenomycin group of antibiotics and was isolated by Umino et al. from *Streptomyces eurythermus*, which exhibits activity against both Gram positive and Gram negative bacteria.

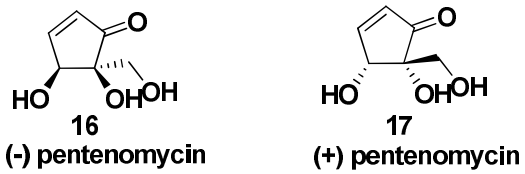
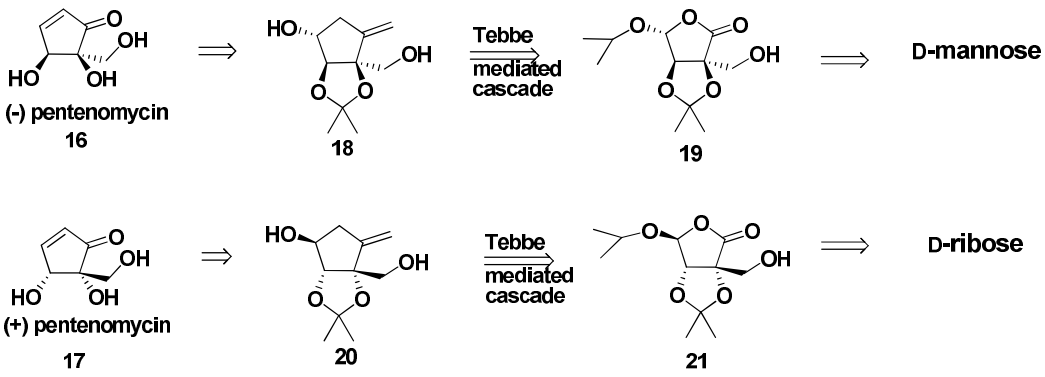


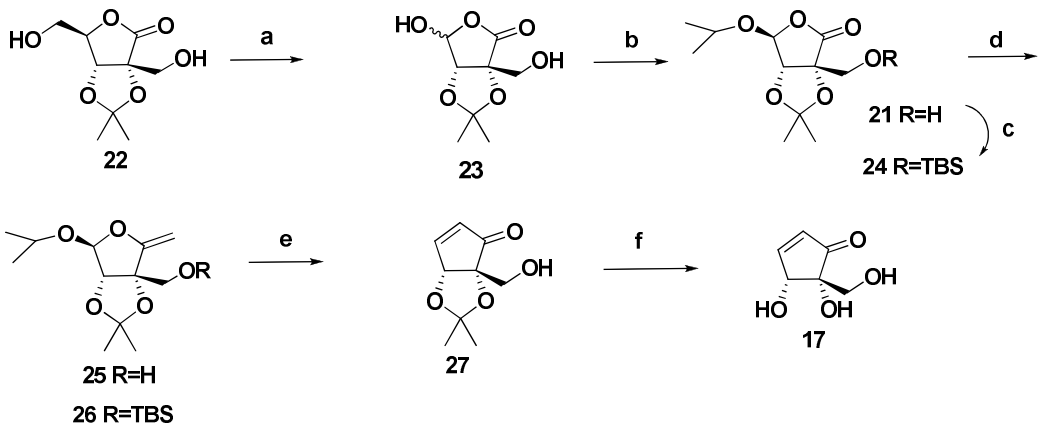
Fig: 6 structures of pentenomycins

The retrosynthesis for **16** and **17** (Scheme 2) was envisaged based on our Tebbe-mediated cascade method as shown in Scheme 1. Oxidative cleavage of the double bond followed by 1,2 elimination of water molecule in the proposed intermediates **18** and **20** should give pentenomycins **13** and **14**. The compounds **18** and **20** in turn can be obtained by treating the lactones **19** and **21**, respectively, with Tebbe reagent. The lactones **19** and **21** can be synthesized from the commercially available D-mannose and D-ribose, respectively.



Scheme 2

For the synthesis of (+) pentenomycin **17** (Scheme 3), D-ribose was converted to compound **22** in three steps using reported procedure. Treatment of **22** with NaOH followed by chopping the diol with $NaIO_4$ afforded the compound **23** in 80% yield. Refluxing compound **23** in presence of catalytic amount of PPTS in 2-propanol furnished the compound **21** required for the cascade reaction in 84% yield. When compound **21** was treated with Tebbe reagent (1.8 equiv.) the expected cascade reaction did not proceed, instead, olefination of lactone took place to give the enol ether **25** in 78% yield. Attempts to progress the cascade reaction by adding excess Tebbe reagent (4 equiv.) at 0 ^{o}C, at r.t. or at reflux are unsuccessful. In order to know whether free hydroxy group α to the lactone obstruct further reaction by complexing with the Tebbe reagent, the free hydroxy group was converted to TBS protected ether to give **24**. Treatment of compound **24** with Tebbe reagent also failed to give the desired transformation and culminated at olefin stage giving **26**. From the above experiment it was concluded that the quaternary centre adjacent to the enol ether in **25** and **26** may be preventing the molecule to undergo further transformation.



Scheme 3

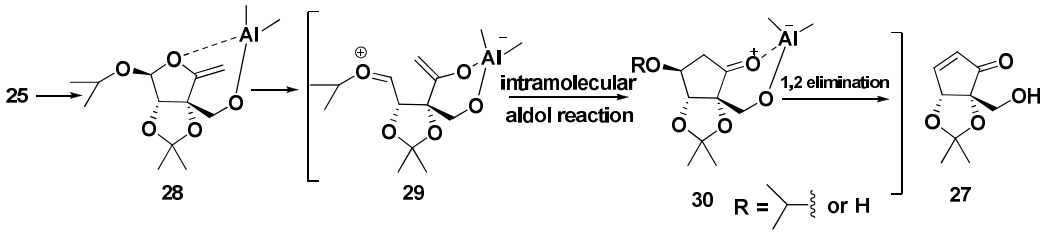
Synthesis of (+) pentenomycin **14:**. Reagents and conditions**:** (a) (i) NaOH, H_2O, 40 ^oC, 20 min. (ii) $NaIO_4$, O ^oC, $BaCl_2$, 30 min; 80%; (b) 2-propanol, PPTS (cat.), reflux, 80 ^oC, 1.5 h, 84%; (c) TBS-Cl, imidazole, DCM, DMAP(cat.) 1 h, 85%; (d) Tebbe reagent (1.8 equiv.), THF, 0 ^oC, 1 h, 78%; (e) Me_2AlCl (1.2 equiv.), -78 ^oC, 20 min, 70%; (f) Amberlyst®-15 in THF/H_2O (2:1), 70 ^oC, 5 h, 75%.

At this stage it was decided to screen various Lewis-Acids (Table 1) for the transformation of **25** to carbocycle. Different Lewis acids such as $BF_3.OEt_2$, $TiCl_4$, $SnCl_4$ in DCM and $ZnCl_2$ in THF/ H_2O were tried on **25** and none of them gave the required product and every time decomposition occurred and we failed to isolate any product in pure form. Then it was thought to use Me_2AlCl for this transformation, since it is known for its exceptional 1,3 chelating ability and also aluminum mediated transformation of vinyl acetal to tetrahydropyrans was well established in the literature which is popularly known as Petasis- Ferrier rearrangement.

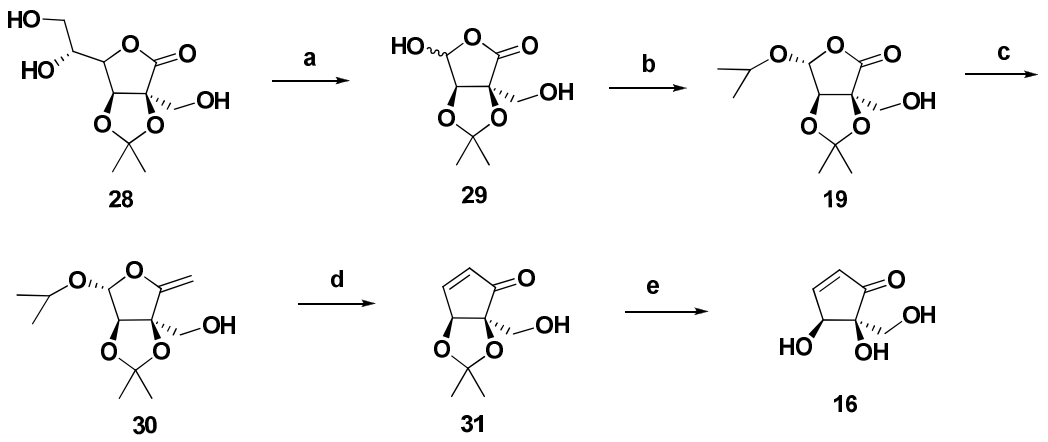
Table 1:

Entry	Reagent (Equiv.)	Conditions	Yield (27)
1	$BF_3.OEt_2$ (1.2)	DCM 0 ^oC, 30 min	Decomposition
2	$TiCl_4$ (1.2)	DCM 0 ^oC-rt, 1h	Decomposition
3	$SnCl_4$ (1.2)	DCM 0 ^oC-rt, 1h	Decomposition
4	$ZnCl_2$ (1.2)	THF/H_2O, 0 ^oC-rt, 7h	Decomposition
5	**Me_2AlCl (1.2)**	**DCM, -78 ^oC, 20min.**	**70% yield**

When enolether **25** was subjected to Me_2AlCl at -78 ^oC in DCM interestingly it resulted directly in compound **27** in 70% yield. Removal of isopropylidene group in **27** was achieved with Amberlyst®-15 in THF/H_2O (2:1) to give (+) pentenomycin **14** in 75% yield, whose analytical data were in good agreement with the reported values. Again attempts to continue the cascade reaction in presence of Me_2AlCl in THF or DCM/THF along with Tebbe reagent on **25** have met with failure.



Scheme 4: Plausible mechanism for the formation fo 27



Scheme 5

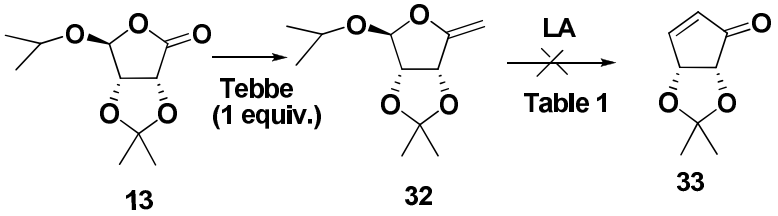
Synthesis of (-) pentenomycin 1. Reagents and conditions: (a) (i) NaOH, H_2O, 40 ^oC, 20 min. (ii) $NaIO_4$, O ^oC, $BaCl_2$, 30 min, 80%; (b) 2-propanol, PPTS (cat.), reflux, 80 ^oC, 1.5h, 84%; (c) Tebbe reagent (1.8 eq.), THF, 0 ^oC, 1 h, 78%; (d) Me_2AlCl (1.2 equiv.), -78 ^oC, 20 min ,70%; (e) Amberlyst®-15 in THF/H_2O (2:1), 70 ^oC, 5 h, 75%.

The mechanism is depicted in Scheme **4** for the formation of product **27**. 1,3 Chelation of the alkoxyaluminum with ring oxygen in **28** might have exerted effective activation for the opening of the ring to give active species **29**, which resulted in **30**

through intramolecular aldol reaction *via* 5-*(enol-endo)-exo-trig*-cyclization. Further, 1,2 elimination has taken place in the same pot to give required enone **27**.

After successfully achieving the (+) pentenomycin **14**, we turned our attention to synthesize the natural (-) pentenomycin **13** (Scheme 5). For this the required lactone **28** was prepared from D-mannose in 4 steps. Ring opening of **28** with NaOH followed by chopping the diol gave the compound **29** in 80 % yield. Lactone **19** was obtained by treatment of **29** with acid in 2-propanol in 84 % yield. Tebbe olefination of **19** gave the enol ether **30** in 78 % yield. Compound **30** when subjected to Me_2AlCl gave the required compound **31**, whose analytical data were in good agreement with the reported values.. Removal of isopropylidene group in **31** was achieved with Amberlyst®-15 in THF/H_2O (2:1) to give (-) pentenomycin **13** in 75% yield, whose analytical data were in good agreement with the reported values.

To further understand the mechanism, we then applied this reaction on unsubstituted enol ether **32** (Scheme 6) where there is no possibility of above said 1,3 chelation. For this, compound **13** obtained from D-ribose was converted to **32**. When **32** was subjected to various Lewis- acids including Me_2AlCl as listed in Table 1, the required product transformation was not observed, every time decomposition occurred. This further supports the specific reactivity of Me_2AlCl with **25** and **30** by 1,3 chelation which helped the required transformation to occur.



Scheme 6

In conclusion we developed a Tebbe mediated cascade method for the synthesis of (+) and (-) pentenomycins. During this approach we observed that the Tebbe reaction on tertiary substituted lactones **19** and **21** gave only enol ethers **25** and **30** instead of the cyclopentitols which we observed earlier. For the transformation of **25** and **30** to cyclopentenones **27** and **31** different Lewis- acids have been studied. It was found that Me_2AlCl is a suitable reagent for this transformation which is taking

place *via* 5-*(enol-endo)-exo-trig* cyclization a disfavored transformation as per Baldwin rules. The failure of Me_2AlCl condition for the conversion of simple enol ether **32** to **33** can be attributed to the lack of internal 1,3 chelation.

Section B:

Synthesis of 2,2,5-trimethyl-3a,6a-dihydro cyclopenta[1,3]dioxol-4-one using Mn/$CrCl_3$ mediated domino reactions and ring closing metathesis

Highly oxygenated cyclopentenoid 2,2,5-trimethyl-3a, 6a-dihydro-cyclopenta [1, 3] di oxol-4-one **34** (Fig. 7) is a key intermediate in the synthesis of biologically active calabar bean alkaloids (-) physostigmine **25**, (-) physovenine **36**, norbenzomorphan natural alkaloid (-) aphanorphine **37** and estrogenic hormone (+) estrone **38**.

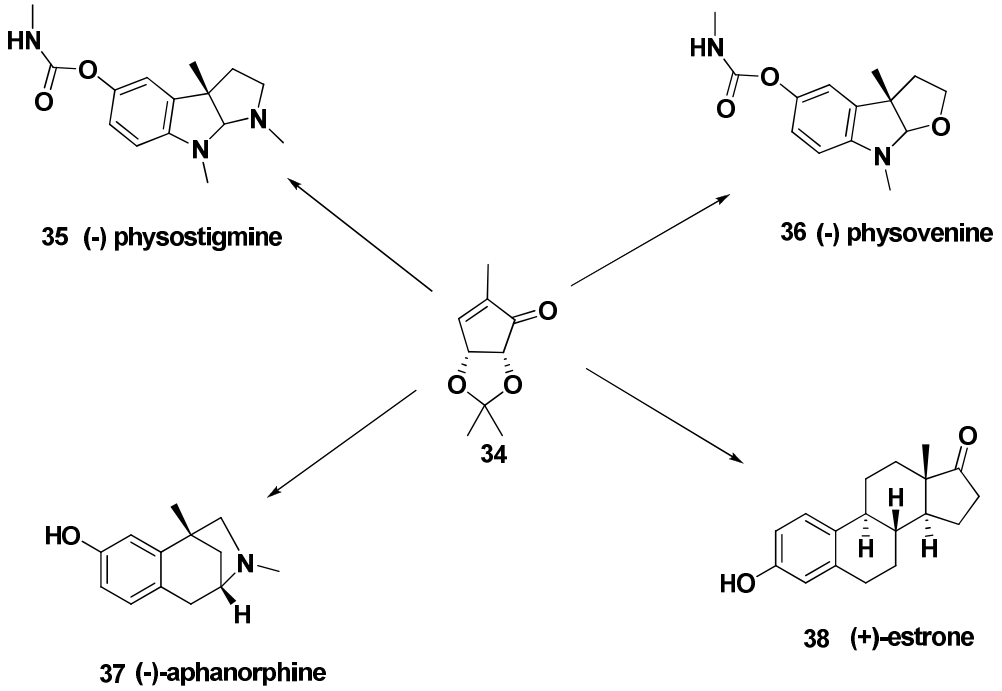
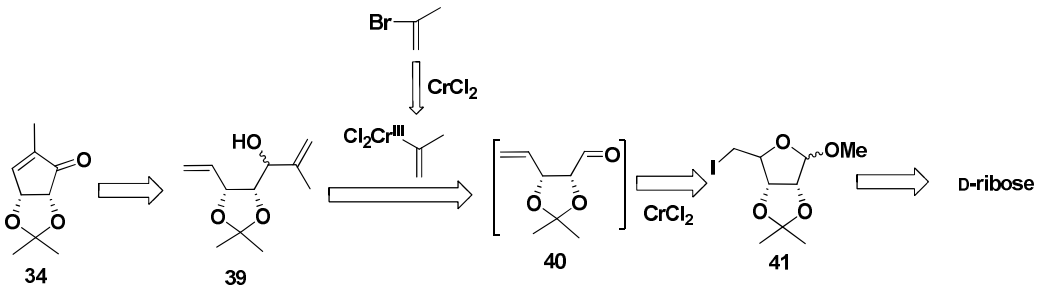


Fig 7: Biologically active compounds commenced from chiral oxygenated cyclopentenone 2, 2, 5-trimethyl-3a, 6a-dihydro-cyclopenta [1, 3] di oxol-4-one

In our synthetic strategy methyl 2,3–*O*-isopropylidiene-D-ribofuranoside was taken as a starting material for the synthesis of 2,2,5-trimethyl-3a, 6a-dihydro-cyclopenta [1,3]dioxol-4-one **34** because the two hydroxyl centres of D-ribose were correlating very well with that of the target molecule. The retrosynthetic analysis

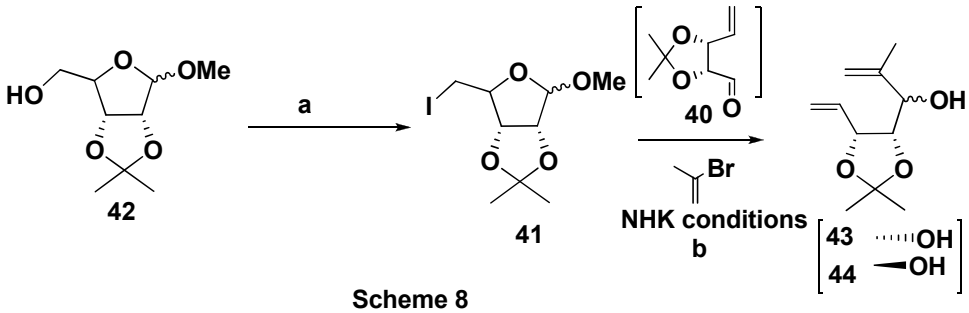
(Scheme 7**)** of compound **34**, revealed that it can be synthesized from the diene precursor **39** using RCM.



Scheme 7

The diene **39** was envisaged to obtain from nucleophilic addition of 2-bromopropene to the aldehyde **40** under NHK/ Grignard conditions. The required aldehyde **40** can be obtained from the reductive-elimination of compound **41** under Bernet-Vasella condition, which in turn can be obtained from D-ribose.

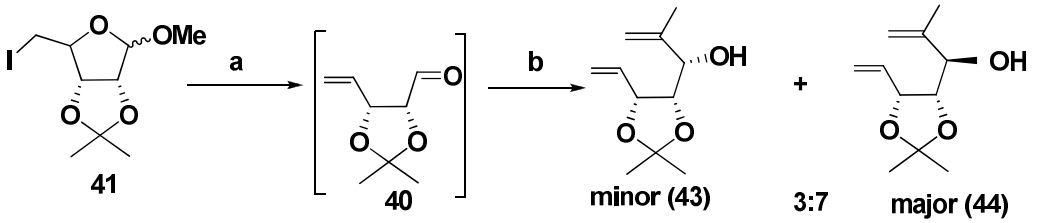
Methyl 2,3 isopropylidene D-ribofuranose **42** obtained from D-ribose on reaction with imidazole, TPP, iodine in DCM at 0 °C afforded iodo compound **41**. After getting iodo compound **41** we were ready to carry out the *in situ* reaction using Mn and $CrCl_3$ redox couple **(**scheme 8**)**. To Mn/$CrCl_3$ (20:1) in THF/DMF (5:1), 1 eq. of iodo compound **41** was added under inert atmosphere. Generation of anhydrous $CrCl_2$ was confirmed by change of color from violet to pale blue. After the formation of aldehyde (monitored by TLC) a catalytic amount of anhydrous $NiCl_2$ was added to the reaction mixture to facilitate the NHK reaction. Then 2.5 eq. 2-bromopropene followed by 1.5 eq. TMSCl at 50 ^oC for 4h afforded two diastereomers **43** (42%) and **44** (18%) in 7:3 ratio in 60 % yield.



Scheme 8

Reagents and conditions (a) I_2, TPP, imidazole, DCM, 0 ^{o}C-rt, 3h.; (b) $Mn/CrCl_3$ (20:1), THF/ DMF (1:1), 8h then $NiCl_2$ (cat), 2-bromopropene, TMSCl, r.t., 4h, TBAF, 2h, 60 % [**43:44** = 7:3].

When the aldehyde **40** was treated with Grignard reaction using 2-bromopropene and Mg in THF at – 78 °C, gave the **43** and **44** in 3:7 ratio (Scheme **9**).

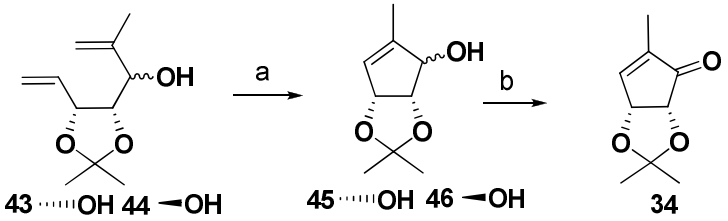


Scheme 9

Reagents and conditions (a) $Mn/CrCl_3$(20:1), THF:DMF (1:1), 8 h, 65%, (b) 2-bromopropene, Mg, THF, -78 °C-r.t., 2h, 75 %.

The reversal of selectivity in this case can be explained as follows. Generally during NHK reaction the nucleophile undergoes addition *via* non-chelated Felkin-Anh Model, since Cr(II) doesn't chelate well, whereas in case of the Grignard addition chelation of the magnesium ion gave *syn* isomer **44** as the major product (Fig 8)

Fig: 8



Scheme 10

Reagents and conditions (a) Grubbs 2nd gen. cat. DCM, reflux, 5h, 85%; (b) PDC, DCM, 4Å MS, r.t., 3h, 95%.

In conclusion, we have developed a strategy for the synthesis of 2,2,5-trimethyl-3a,6a-dihydro-cyclopenta[1,3]dioxol-4-one **34** by using domino reductive elimination, nucleophilic addition using modified NHK conditions and ring-closing metathesis as the key steps. This strategy is helpful in making different analogues of highly oxygenated cyclopentenones.

CHAPTER III:

Section A:

Synthesis of (+) methyl shikimate, (+) methyl-5-*epi*-shikimate, 5a-carba-α-D-mannopyranose, 5a-carba-β-D-mannopyranose, validamine analogue and valiolamine analogue utilizing Mn/$CrCl_3$ mediated domino reactions and ring closing metathesis

Carbasugars or pseudosugars are carbocyclic analogues of monosaccharides in which the ring oxygen is replaced by methylene. If C-1 OH in carbasugars is replaced by amino group then they are called as aminocarbasugars. These compounds are excellent glycosidase inhibitors and shows interesting biological activity such as *anti*-cancer, *anti*- diabetic, *anti*- HIV, *etc*. Shikimic acid is a key intermediate in the synthesis of aromatic amino acids by plants, fungi and microorganisms. Shikimic acid and their derivatives such as (+) methyl shikimate **47** and (+) methyl-5-*epi*-shikimate **48** are biologically important compounds. Moreover several carbasugars and aminocarbasugars have been synthesised starting from shikimic acid and their intermediates.

We have developed NHK-RCM approach and applied for the synthesis of cyclopentenone derivative which was discussed in chapter II section B. Herein, we demonstrated the application of NHK-RCM approach for the synthesis of some carbahexopyranoses (Fig. 9) they are namely (+) methyl shikimate **47**, (+) methyl-5-*epi* shikimate **48**, pseudo-α-D-mannopyranose **49**, pseudo-β-D-mannopyranose **50**, validamine analogue **51** and valiolamine analogue **52**.

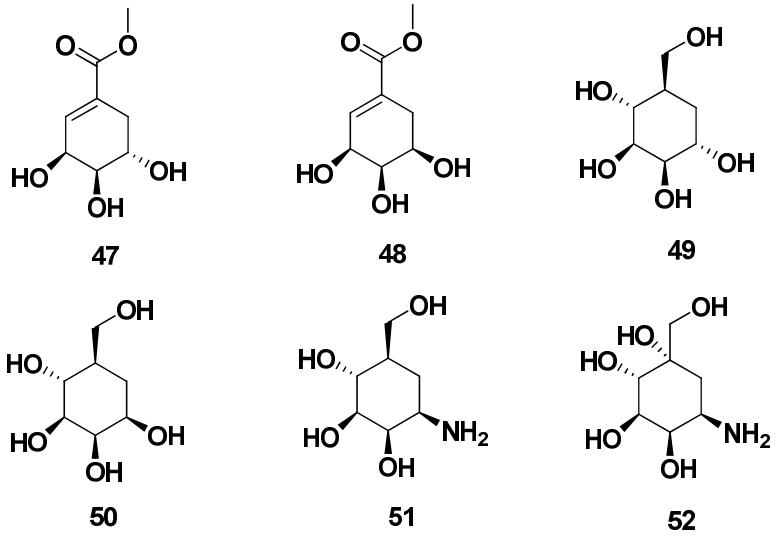
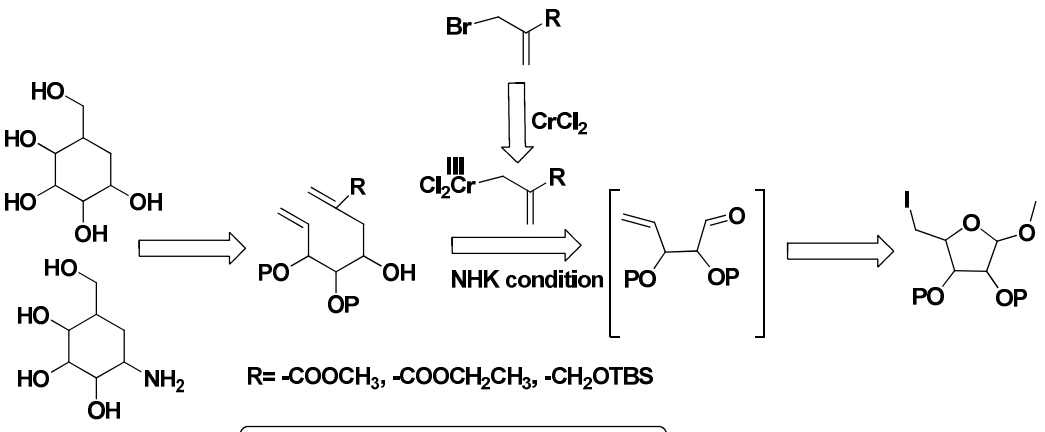


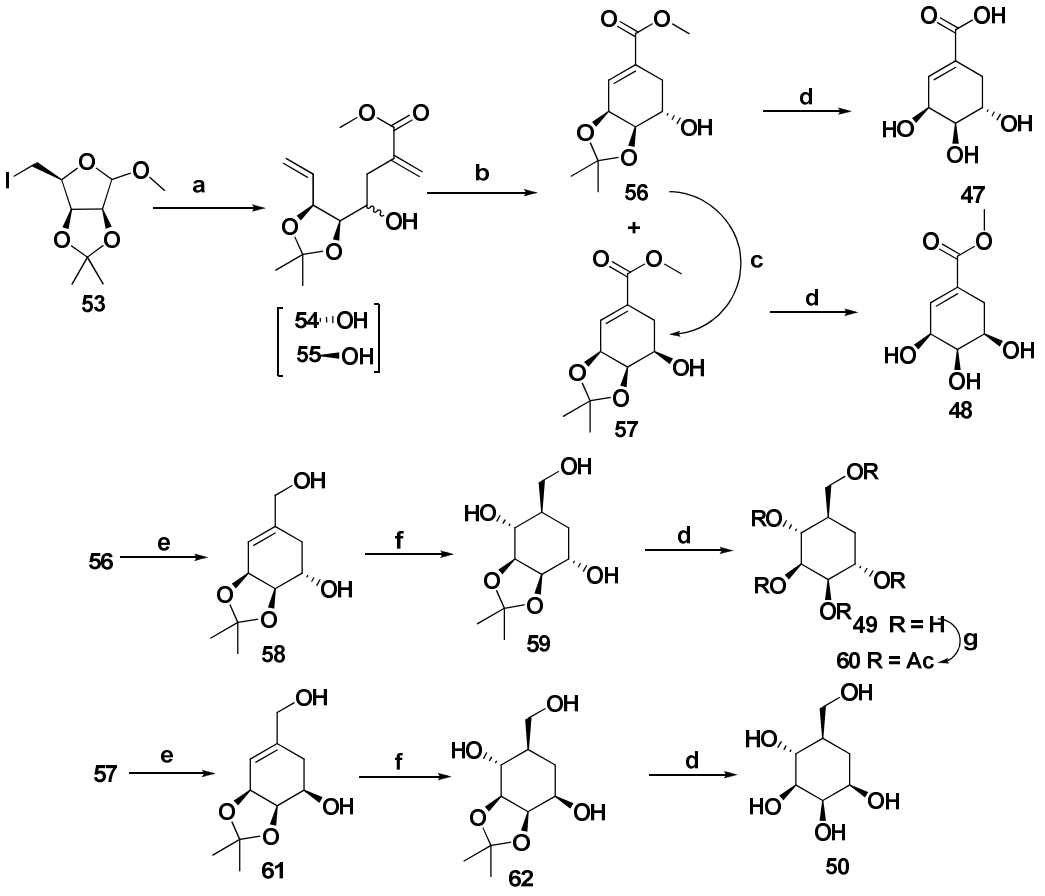
Fig:9 some carbahexopyranoses

Reductive elimination of 5-deoxy-5-halofuranosides under Bernet-Vasella protocol giving chiral 4-pentenals, has many synthetic applications. The reductive elimination can be carried out with different metallic reagents such as Zn, In, $CrCl_2$, SmI_2, Mn/ $PbCl_2$, BuLi and acetyliron. Reductive ring opening of 5-deoxy-5-halofuranosides followed by intermolecular C-C bond coupling in one pot have been performed by using Zn and In under ultrasonication. Our group has earlier developed $CrCl_3$/Zn condition for the generation of olefin-aldehyde in which Zn is used for the conversion of $CrCl_3$ to $CrCl_2$ and the aldehyde was trapped by vinyl chromium (NHK reaction) to form diene precursor for the RCM, which was carried further for the synthesis of carbafuranoses. Later for this purpose, we utilized Furstner's modified NHK condition for the generation of $CrCl_2$ from $CrCl_3$ using Mn as reductant which remains inert throughout the reaction. Herein we wish to describe the synthetic utility of our domino NHK and RCM strategy for the synthesis of various carbapyranoses from 5-deoxy-5-halo manno/ribo/xylo furanosides. The retrosynthetic analysis was depicted in scheme **11**.

From the retrosynthetic analysis, carbasugars and aminocarbasugars was obtained from RCM of diene compound which in turn could be obtained from domino Bernet-Vasella type reductive ring opening of 5-deoxy-5-iodo-furanoside followed by C-C bond formation with nucleophile under NHK condition.



Scheme 11: Retrosynthetic analysis



Scheme 12: Synthesis of (+) methyl shikimate (47), (+) methyl-5-*epi*-shikimate (48), 5a-carba-α-D-mannopyranose (49) and 5a-carba-β-D-mannopyranose (50)

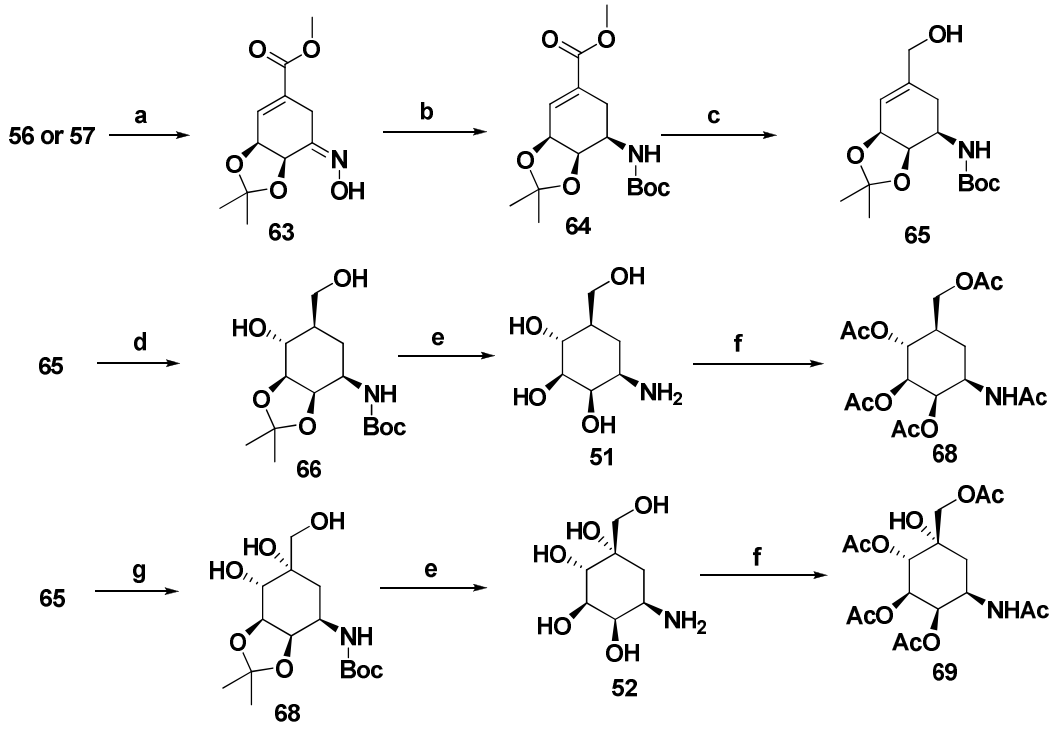
Reagents and conditions: (a) $Mn/CrCl_3$ (20:1), THF:DMF (5:1), 8h then $NiCl_2$ (cat), methyl-2(bromomethyl)acrylate, TMSCl, 50 ^oC, 5h, TBAF, r.t., 5h, 75%; (b) Hoveyda-Grubbs 2nd generation catalyst, 1,2 dichloroethane, reflux, 3h, 96%; (c) (i) Dess-Martin periodinane, DCM, r.t., 1h (ii) $NaBH_4$,

MeOH, 0 °C, 1h; (d) 50% aqueous CF_3COOH, r.t., 4h, 95% for (**47**) and (**48**), 98% for (**49**) and (**50**) (e) DIBAL-H, DCM, 0°C, 2h, 78%; (f) BH_3.DMS, THF 0 °C to r.t., 2h, then NaOH, H_2O_2, 0 °C, 2h, 65%; (g) pyridine, Ac_2O, DMAP, 24h, 70%.

For the synthesis of (+) methyl shikimate **47**, (+) methyl-5-*epi*-shikimate **48**, pseudo-α-D-mannopyranose **49** and pseudo-β-D-mannopyranose **50** (Scheme 12), the iodo furanoside compound **53** obtained from D-mannose was treated with Mn/$CrCl_3$ (20:1) for 8h in THF/DMF. The change in colour from violet to pale blue confirmed the formation of $CrCl_2$. After the consumption of starting iodo compound (confirmed by TLC), catalytic amount of $NiCl_2$, methyl 2-(bromomethyl)acrylate followed by TMSCl at 50 °C were added to carry out the NHK reaction. The reaction completed in 5h and gave an inseparable mixture of diastereomers **54** and **55** in 1:1 ratio in 75% yield (over 2 steps). Mixture of **54** and **55** were reacted with Hoveyda-Grubbs 2nd generation catalyst to afford compounds **56** and **57** in 96% yield which were separated using column chromatography. The compound **56** on oxidation with Dess-Martin periodinane followed by stereo selective reduction with $NaBH_4$ produced compound **57** exclusively. Though NHK reaction gave two diastereomeric alcohols in 1:1 ratio, the oxidation and reduction strategy provided a way for obtaining the single diastereomeric compound **57**. Deprotection of **56** and **57** independently using aqueous TFA afforded (+) methyl shikimate **47** and (+) methyl-5-*epi*-shikimate **48** respectively. The physical and spectral data of compound **47** and **48** are in accordance with the reported values. For the synthesis of pseudo-α-D-mannopyranose **49** and pseudo-β-D-mannopyranose **50**, first the ester functionalities in compounds **56** and **57** were reduced using DIBALH to furnish alcohols **58** and **61** respectively. Next the compounds **58** and **61** on stereoselective hydroboration/oxidation afforded triol compounds **59** and **62** respectively. Deprotection of acetonide functionality in compounds **59** and **62** using 50% aqueous TFA afforded pseudo-α-D-mannopyranose **49** and pseudo-β-D-mannopyranose **50** respectively. Compound **49** was converted to its acetate derivative **60** for further confirmation. The physical and spectral data of compounds **49**, **60** and **50** are in good agreement with the reported values.

For the synthesis of validamine analogue **51** and valiolamine analogue **52** (Scheme **13**), compounds **56** and **57** were treated with Dess-Martin periodinate to furnish unstable keto compound, which on reaction with hydroxylamine

hydrochloride salt in ethanol and pyridine (1:1) afforded oxime **63**. Stereoselective reduction of oxime **63** with $NaBH_4$ in presence of MoO_3 afforded amine. The crude amine was treated with di-*tert*-butyl dicarbonate to furnish Boc protected amine compound **64**, which on reduction with DIBALH afforded **65**. Regio- and stereoselective reduction of **65** in presence of BH_3.DMS followed by $NaOH/H_2O_2$ afforded alcohol **66** exclusively. Deprotection of **66** using 50% aqueous TFA gave validamine analogue **51**. For the sake of proper characterization, the crude product **51** was peracetylated with acetic anhydride to give **67** in 90% yield over 2 steps, whose spectral data was in accordance with the reported values. The compound **65** on reaction with OsO_4 afforded trihydroxy compound **68**, which on deprotection with 50% aqueous TFA gave valiolamine analogue **52**. The crude compound on acetylation afforded peractylated compound **69** in 90% yield over 2 steps, whose physical and spectral data are in accordance with reported values.



Scheme 13 : Synthesis of validamine analouge 51 and valiolamine analouge 52

Reagents and conditions: (a) (i) Dess-Martin periodinane, DCM, r.t., 1h (ii) $NH_2OH.HCl$, EtOH, Py, r.t., 2h, 70% (over 2 steps); (b) (i) MoO_3, $NaBH_4$, MeOH, 0 °C, 1h, di-*tert*-butyl diocarbonate, 2h, 70% (over 2 steps); (c) DIBAL-H in toluene, DCM, 0°C, 2h, 78%; (d) BH_3.DMS, THF 0 °C to r.t., 2h, then

NaOH, H_2O_2, 0 °C, 2h, 65% (e) 50% aqueous CF_3COOH, r.t., (f) Ac_2O, Py, r.t., 2h, 90%; (g) OsO_4, NMO, acetone: water (4:1), 0°C, 2h, 90%;

In conclusion, we have successfully demonstrated the utility of NHK-RCM approach and developed a common strategy for the synthesis of (+) methyl shikimate **47**, (+) methyl-5-*epi*-shikimate **48**, pseudo-α-D-mannopyranose **49**, pseudo-β-D-mannopyranose **50**, validamine analogue **51** and valiolamine analogue **52**.

Section B:

Formal synthesis of Tamiflu, Synthesis of 5a-carba-α-D-glucopyaranose, 5a-carba-β-D-glucopyaranose, 5a-carba-β-L-altropyranose and 5a-carba-α-L-altropyranose.

This section deals with the formal synthesis of Tamiflu **70**, which related to aminocarbasugar structure and is widely used for the treatment of H5N1 influenza as well as H1N1 influenza. Some more carbasugars depicted in figure **10**, they were 5a-carba-α-D-glucopyaranose **71**, 5a-carba-β-D-glucopyaranose **72**, 5a-carba-β-L-altropyranose **73** and 5a-carba-α-L-altropyranose **74** (Fig. 10).

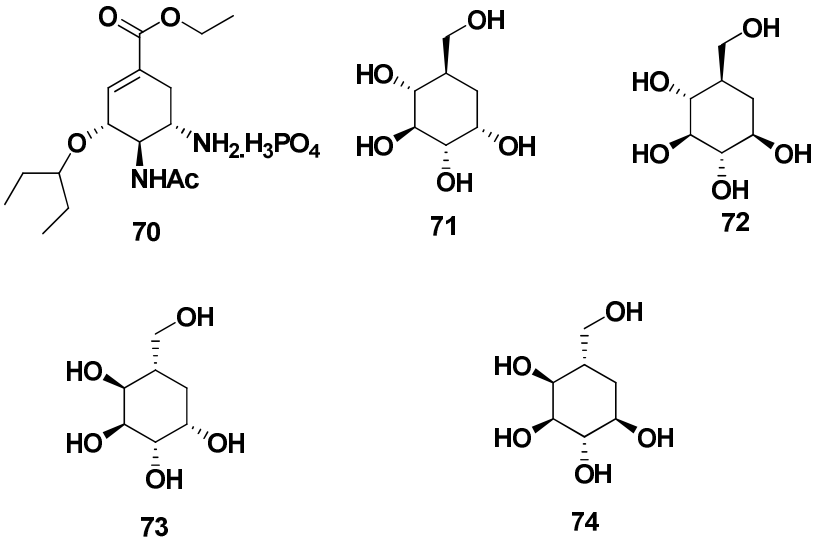
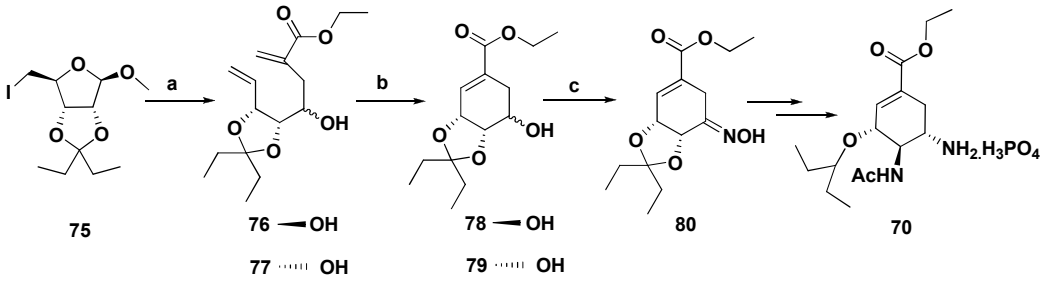


Fig 10: Tamiflu and some carbasugars

Racemic pseudo-α-D-glucopyranose **71** shows inhibition of glucose stimulated-insulin release and islet glucokinase activity. (±) Carbasugar **72** is a

substrate of the cellobioside phosphorylase of *cellvibro gilvuse*, and also the taste (sweet) of (±) carba-β-DL-glucopyranose **72** is same as that of D-glucose.

After successfully applying our NHK-RCM strategy on mannose for the synthesis of carbahexopyranoses chapter III (section A), we designed an approach for the formal synthesis of Tamiflu from D-ribose. Earlier synthesis for the Tamiflu **70** reported with the use of Zn and In metal mediated reductive ring opening of 5-deoxy-5-halo-ribofuranoside **75** followed by C-C bond formation using ethyl 2-(bromomethyl) acrylate to give **77** under ultrasonication. The above reaction also gave bi products posing problem in isolation of the product in pure form, and also ultrasonication condition is not practical for higher scale synthesis. To study the product formation in our condition, we carried the reductive elimination of **75** and allylation using ethyl 2-(bromomethyl) acrylate.



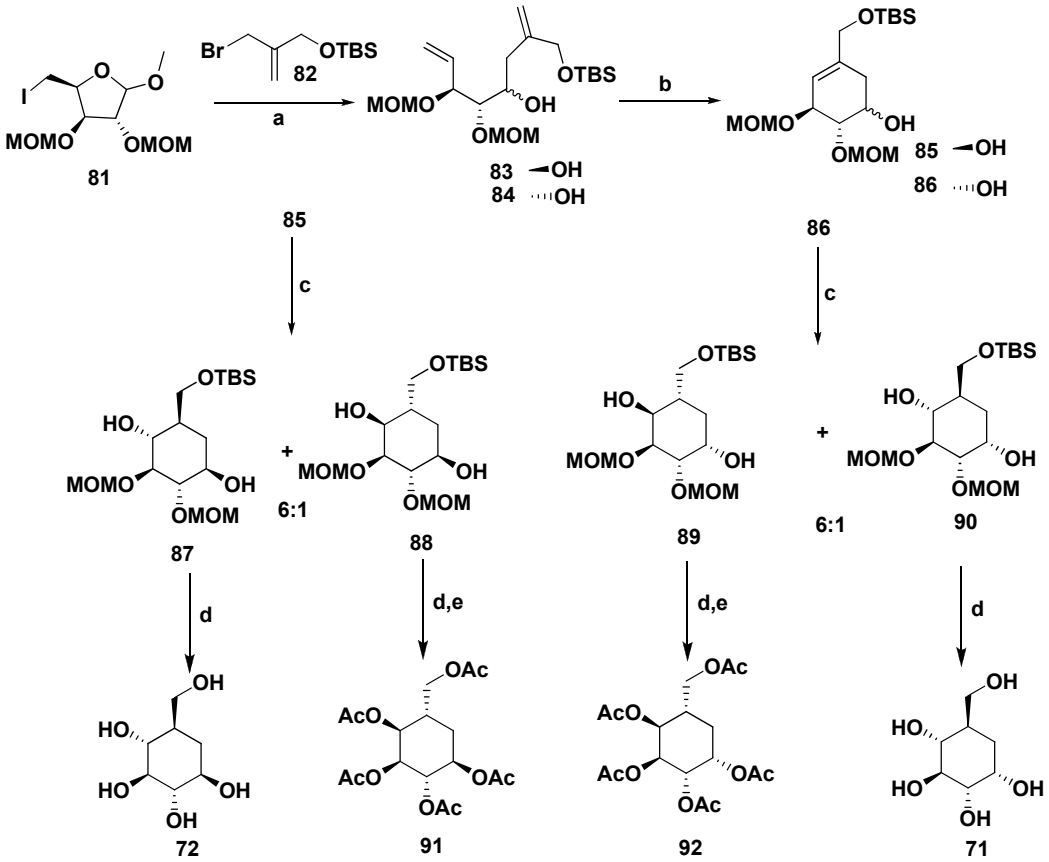
Scheme 14: Formal synthesis of Tamiflu

Reagents and conditions: (a) $Mn/CrCl_3$ (20:1), THF:DMF (5:1), 8h then $NiCl_2$ (cat), ethyl 2-(bromomethyl) acrylate, TMSCl, 50 ^oC, 5h, TBAF, r.t., 2h, 75%; (b) Hoveyda-Grubbs 2nd generation catalyst, 1,2 dichloroethane, reflux, 3h, 92%; (c) Dess-Martin periodinane, DCM, r.t., 1h, $NH_2OH.HCl$, Py, r.t., 2h, 70%.

5-deoxy-5-iodo-ribosyl compound **75** obtained from D-ribose was treated with ethyl 2-(bromomethyl)acrylate under standard $Mn/CrCl_3$ mediated domino NHK condition. The reaction completed in 5h and yielded diastereomeric mixture of compounds **76** and **77** in 1:1 ratio without any visible impurities on the TLC, the products were well purified by simple column chromatographic technique. This method is useful for the scaling up of intermediate compounds **76** and **77** for the synthesis of Tamiflu **70**, which doesn't require any ultrasound assistance. Ring closing metathesis of diolefinic compounds **76** and **77** using Hoveyda-Grubbs catalyst 2nd generation gave

products **78** and **79** respectively. Oxidation of secondary alcohol in **78** and **79** using Dess-Martin periodinane gave unstable ketone which on reaction with hydroxylamine hydrochloride salt in pyridine solvent afforded oxime **80** required for the synthesis of Tamiflu **70**.

Most of the carbasugars have pendant hydroxymethyl group in their structure. Generally in the carbasugar synthesis the hydroxymethyl group was introduced by reduction of corresponding ester. To avoid the reduction step and to get directly hydroxymethyl on carbasugar core structure, we prepared NHK precursor **82** as a nucleophile, and utilized this for the synthesis of 5a-carba-α-D-glucopyranose **71**, 5a-carba-β-D-glucopyranose **72**, 5a-carba-β-L-altropyranose **73** and 5a-carba-α-L-altropyranose **74** starting from D-xylose. The general retrosynthetic analysis is depicted in scheme 11.



Scheme 15: Synthesis of 5a-carba-α-D-glucopyaranose 71, 5a-carba-β-D-glucopyaranose 72, 5a-carba-β-L-altropyranose 73 and 5a-carba-α-L-altropyranose 74

Reagents and conditions: (a) Mn/$CrCl_3$ (20:1), THF:DMF (5:1), 8h then $NiCl_2$ (cat), **82**, TMSCl, 50 ^oC, 5h, 1N HCl, rt, 2h, 75%; (b) Grubbs 2nd generation catalyst, toluene, reflux, 3h, 90%; (c) BH_3.DMS, THF 0 °C to r.t., 2h, then NaOH, H_2O_2, 0 °C, 2h, 70% ; (d) 6N MeOH (HCl), reflux, 1h, 95% quantitative; (e) pyridine, Ac_2O, DMAP, 12h, 95%.

The 5-deoxy-5-iodo xylofuranose compound **81** was prepared from D-xylose in 3 steps. The compound **81** on reaction with allyl nucleophile **82** under standard domino reductive ring opening, followed by allylation under Mn/$CrCl_3$ (NHK reaction) conditions afforded compounds **83** and **84** in 1:1 ratio. In the Fursntner's modified NHK condition[27] one has to use TBAF to deprotect the OTMS to get OH. Here in this case, TBAF will deprotect both the OTMS and OTBS groups. Therefore here we used 1N HCl for work up which could deprotect the OTMS group selectively giving rise to compounds **83** and **84**. The stereochemistry of the newly generated chiral center in **83** and **84** were assigned after cyclisation in presence of Grubbs 2nd generation catalyst which afforded compounds **85** and **86**. The stereochemistry of the newly created centre C-1 of **85** was ascertained by analyzing coupling constants for 6a-H (2.05, 1H, m, major couplings J = 9.4 Hz, 17.0 Hz), 6e-H (2.40, dd, 1H, J = 5.9 Hz, 17.0 Hz) and 1a-H (3.76, m, 1H, one of coupling J = 9.4 Hz) suggesting the orientation of hydroxyl group in equitorial in six membered skeleton. Similarly the stereochemistry at C-1 of **86** was ascertained by analyzing the coupling constants for 6a-H (2.11, dd, 1H, J = 7.1, 17.3), 6e-H (2.28, dd, 1H, J = 4.8 Hz, 17.3 Hz) and 1e-H (3.77, dd, 1H, J = 2.2 Hz, 4.8 Hz) suggesting the orientation of hydroxyl group is axial. Hydroboration-oxidation of olefin compound **85** using BH_3.DMS followed by NaOH/H_2O_2 afforded **87** and **88** in 6:1 ratio. Deprotection of **87** afforded pseudo-β-D-glucopyranose **72** whose data was in good accordance with the reported values. Deprotection of **88** afforded pseudo-α-L-altropyranose **74**, which was confirmed by converting to peracetyl derivative **91**, whose data was in good agreement with the literature values. Hydroboration-oxidation of olefin compound **86** using BH_3.DMS followed by NaOH/H_2O_2 treatment gave **89** and **90** in 6:1 ratio. Deprotection of **89** afforded pseudo-β-L-altropyranose **73** which was converted to peracetyl derivative **92**, whose data was also in good agreement with the reported values. Deprotection of **90** afforded pseudo-α-D-glucopyranose **71**, the physical and spectral data of **71** are in good accordance with the reported values. Here, noteworthy to mention is the facial

selectivity of BH_3.DMS reduction of olefin, which was decided by the chirality at C-1 position. Major product being formed is *anti* to the existing C-1 hydroxy chiral center.

In conclusion, we have successfully demonstrated the utility of NHK-RCM approach for the formal synthesis of Tamiflu **70** from D-ribose and synthesis of 5a-carba-α-D glucopyranose **71**, 5a-carba-β-D-glucopyranose **72**, 5a-carba-β-L-altropyranose **73** and also 5a-carba-α-L-altropyranose **74** from D-xylose.

CHAPTER IV:

Section A:

Synthesis of 4a-carba-α-L-lyxofurnanose and 4a-carba-β-D-ribofuranose *via* one pot reductive elimination followed by intramolecular Nozaki-Hiyama-Kishi reaction on five membered diiodo compound

Carbocyclitols are part structures of many interesting biologically active compounds and many enzyme inhibitors. Some examples are the glycoside inhibitors such as mannostatin A, allosamizoline, trehalostatin, carbafuranoses and carbonucleosides such as neplanocin A, aristeromycin *etc*.

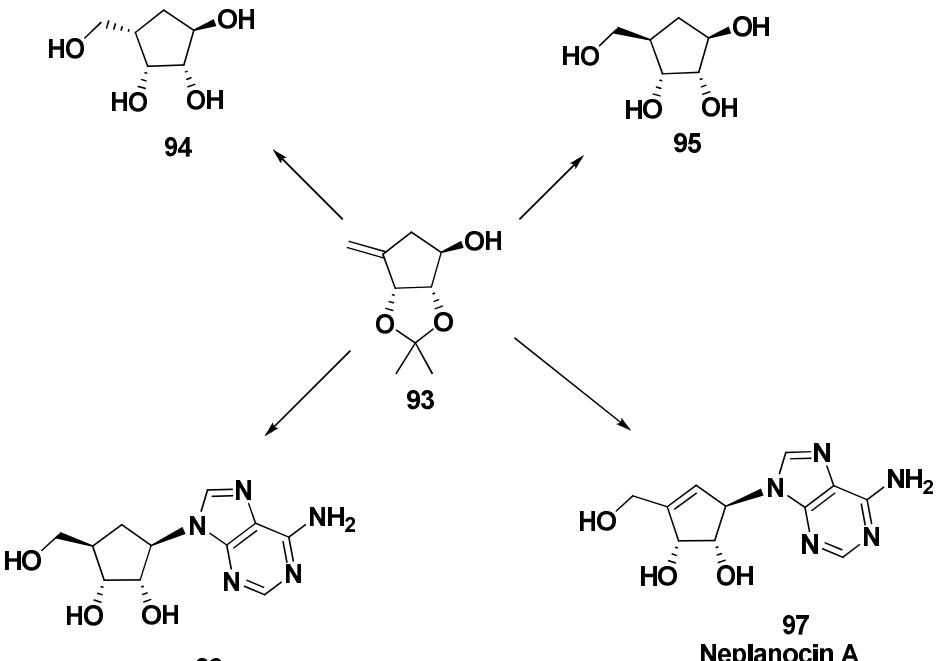
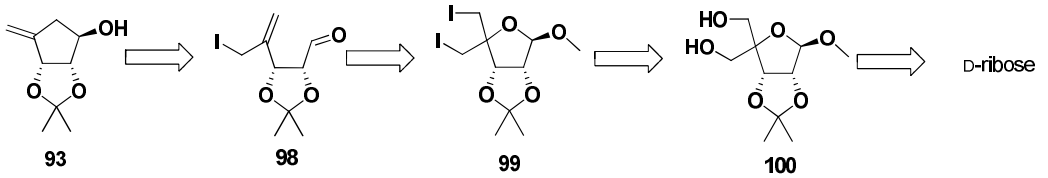


Fig: 11

Our group has been constantly working for the development of new methods for the synthesis of carbocyclitols from carbohydrates, they are domino reductive elimination and NHK-RCM as discussed in chapter II, section A and chapter III and also Tebbe mediated cascade approach for the synthesis of cyclopentitols, and its application for the synthesis of pentenomycins as discussed in chapter II, section A. Herein we devised a new approach for the synthesis of an advance intermediate for the synthesis of carbocyclitols i.e. 4-hydroxy cyclopentene **93** which on functional group interconversion produced the 4a-carba-α-L-lyxofurnanose **94**, 4a-carba-β-D-ribofuranose **95** and also formal synthesis of aristeromycin **96** and neplanocin A **97** (Fig. 11).

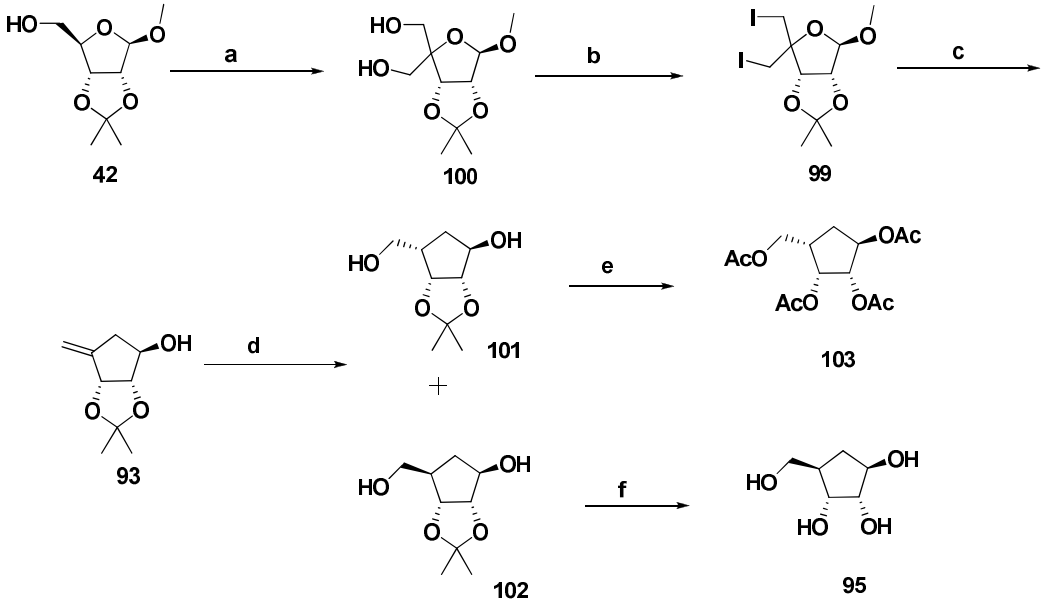
Earlier methods for the conversion of carbohydrates to carbocycles *via* cyclisation particularly for furanoses, involves a harsh conditions and sometimes low yields have been reported and some methods failed to give product for carbafuranoses due to stereochemical problem during cyclisation for eg. Ferrier rearrangement involves hydroxymercuration and aldol like intamolecular cyclisation of 5-enohexopyranosides and also Sinay and coworkers developed an approach whcih involves the TIBAL mediated cyclisation of 5-enohexopyranosides. Therefore a general practically applicable to different sizes for carbasugars in a short possible sequence and in good yields is indeed essential. Earlier, we developed NHK-RCM approach for the synthesis of carbasugars which involves the domino reductive elimination of 5-deoxy-5-iodo-furanosides to give olefin aldehyde which was trapped by vinyl/allyl nucleophile in the same pot under NHK condition to give diene precursor which on RCM afforded carbocyclitols. Herein, we want to develop a new strategy which would give directly carbasugar, involves a domino reductive elimination followed by intramolecular C-C bond formation under NHK condition to give compound **93**.

The retro synthetic analysis for the 4-hydroxy cyclopentene **93** was depicted in scheme **16**. Thus, compound **93** can be obtained by the reductive elimination of diiodo compound **99** to give aldehyde **98**. The aldehyde on intramolecular allylation under NHK condition in the same pot would provide the desired product **93**. The diiodo compound **99** could be obtained from iodination of diol **100** which in turn could be prepared from D-ribose



Scheme 16

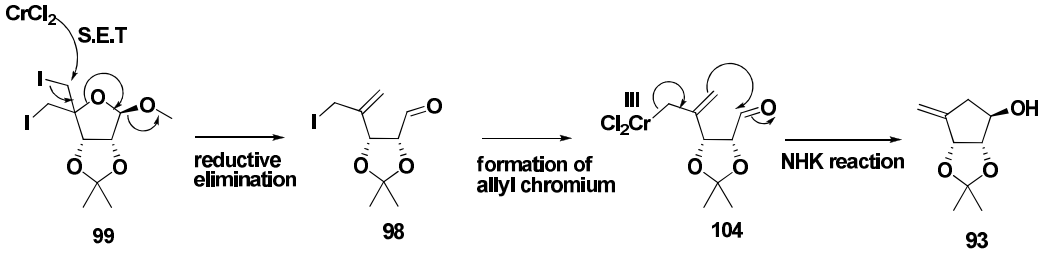
Methyl 2,3–*O*-isopropylidiene-D-ribofuranoside **42** obtained from D-ribose on Swern oxidation afforded aldehyde. This aldehyde on crossed aldol reaction with formalin, where hydride transfer similar to cannizaro reaction took place to give diol compound **100** in 85% yield. Compound **100** on reaction with imidazole, TPP, iodine in toluene:THF (4:1) solvent at 80 °C for 2h resulted in diiodo compound **99** in 68% yield. Diiodo compound **99** on reaction with Mn/$CrCl_3$ in THF:DMF (4:1) solvent in presence of TMSCl and catalytic amount of $NiCl_2$ at 50 °C for 2h followed by the addition of TBAF afforded **93** stereoselectively in 70% yield.



Scheme 17

Reagents and conditions: (a) (i) $(COCl)_2$, DMSO, Et_3N, -78 °C, DCM, 2h; (ii) (37%) HCHO, 2M NaOH, 0 °C-r.t., 20h, 85%; (b) imidazole, TPP, I_2, toluene:THF (5:1), 2h, 80 °C, 68%; (c) Mn/$CrCl_3$ (20:1), THF:DMF (5:1), 2h then $NiCl_2$ (cat), TMSCl, 50 °C, 2h, TBAF, r.t., 2h, 70%;(d) BH_3.DMS,

THF, 0 °C to r.t., 20h, then NaOH, H_2O_2, 0 °C, 2h, 68% (53% of **101** and 15% of **102**); (e) (i) MeOH/HCl, 0 °C, 5 min.(ii) Ac_2O, Py, DMAP, 6h, 92%; (f) MeOH/HCl, 0 °C, 5 min. 90%.



Scheme 18

The formation of the product was explained based on the mechanism depicted on scheme **18**. First, single electron transfer from $CrCl_2$ to compound **99** takes place to give **98** *via* reductive elimination. Next, allyl iodo reacts with $CrCl_2$ to give allyl chromium nucleophile **104** which further reacts with aldehyde under NHK condition to give *exo*-olefin compound **93** *via 5-exo-trig* cyclisation. Hydroboration-oxidation of exo-olefin **93** using BH_3.DMS followed by reaction with $NaOH/H_2O_2$ gave diols **101** and **102** in 53% and 15% yields respectively. Deprotection of acetonide functionality with in **101** using 2N methanolic HCl gave 4a-carba-α-L-lyxofuranose **94**, which on acetylation with acetic anhydride in pyridine afforded peracetylated compound **103**. Whose spectral and physical data were in excellent agreement with the reported values. Deprotection acetonide functionality in compound **102** was achieved by treating it with 2N mehanolic HCl to afford 4a-carba-β-D-ribofuranose **95**. The physical and spectral data of compound **95** were accordance with the literature values.

In conclusion we have developed a new strategy for the conversion of carbohydrate to carbocycle which was utilized for the synthesis of 4a-carba-α-L-lyxofuranose **94** and 4a-carba-β-D-ribofuranose **95**. The key step involves the reductive elimination followed by NHK reaction in one pot to give stereoselective alcohol **93** *via 5-exo-trig* cyclisation.

Section B:

Study of reductive ring opening followed by intramolecular Nozaki-Hiyama-Kishi reaction on six membered diiodo compound.

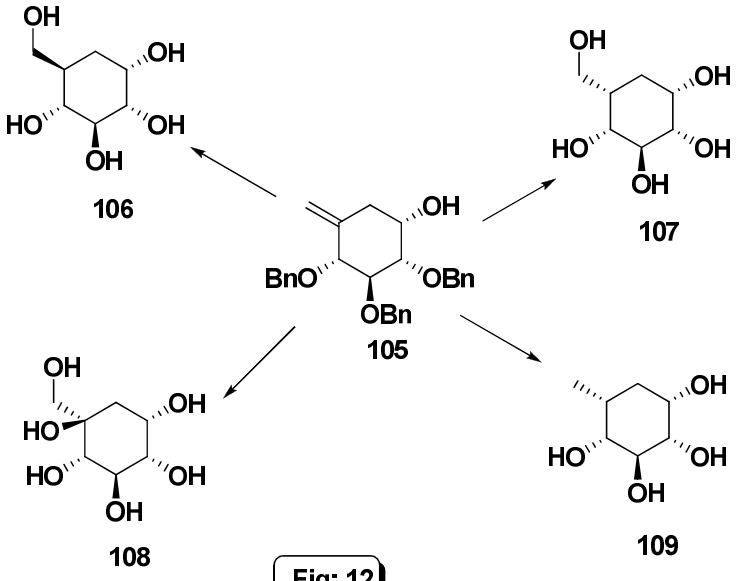
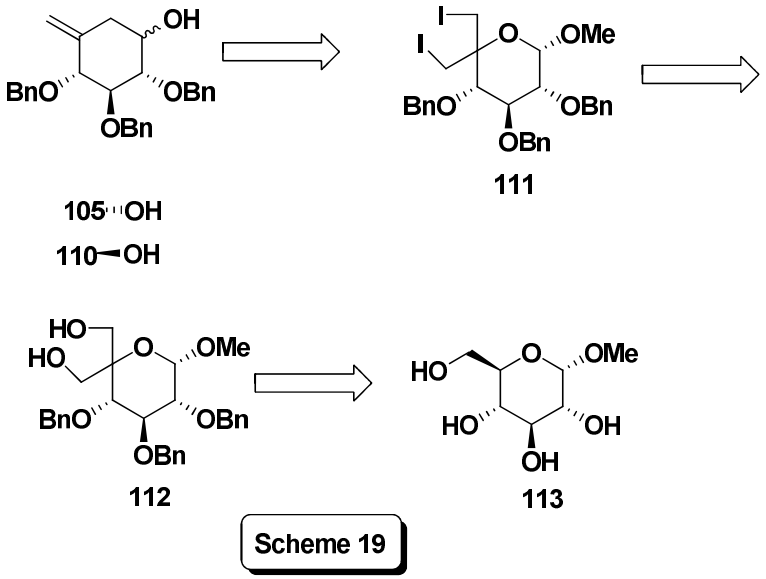


Fig: 12

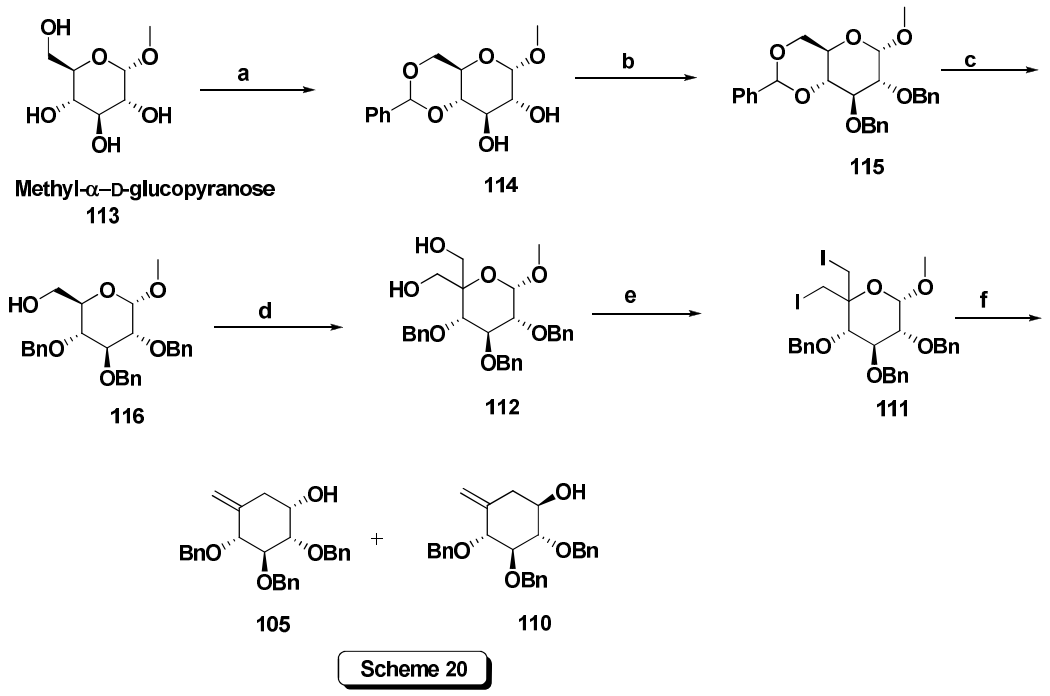
After successfully applying the reductive elimination followed by intramolecular NHK reaction on 5-membered diiodo compound obtained from D-ribose, we turned our attention to apply this strategy on 6-membered diiodo compound which commenced from D-glucose. We envisaged preparing compound **105** which is a common intermediate for the synthesis of carbasugars viz. 5a-carba-α-D-glcuopyranose **106**, 5a-carba-β-L-iodopyranose **107**, 5-hydroxy pseudo-α-D-glucopyranose **108** and 6-deoxy-β-L-iodopyranose **109** by the manipulation of exo olefin (Fig. 12).

The retro synthetic analysis for the 5-hydroxy cyclohexene **105/110** was depicted in scheme **19**. Reductive elimination of diiodo compound **111** followed by intramolecular allylation under NHK condition would provide the desired product **105/110**. The diiodo compound **111** could be obtained from iodination of diol **112** which in turn could be obtained from D-glucose.



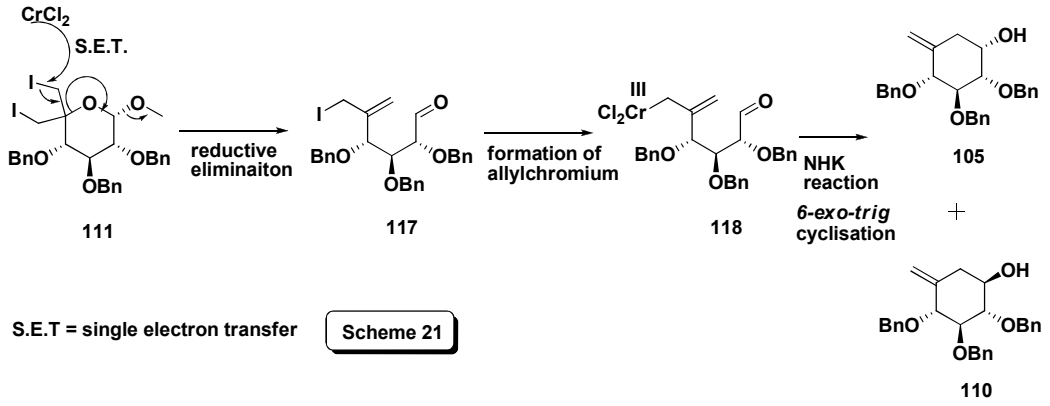
Scheme 19

To implement the strategy we have chosen methyl-α-D-glucopyranose **113** as a starting material. Methyl-α-D-glucopyranose on reaction with benzaldehyde dimethyl acetal in DMF at 80 °C afforded benzaldehyde acetal protected compound **114**. Protection of secondary alcohol functionality in compound **114** as benzylether using NaH in a mixture of THF:DMF afforded compound **115** in 80%. Selective ring opening of benzaldehyde acetal using DIBALH afforded primary alcohol **116** in 75% yield. Oxidation of primary alcohol functionality in compound **116** Dess-Martic periodinane followed by reaction with formalin solution in presence of 1M NaOH afforded diol compound **112**. The diiodo compound **111** required for the strategy is obtained by reacting the diol **112** with imidazole, TPP, iodine for 2h at 80 °C. Diiodo compound **111** on reaction with $Mn/CrCl_3$ in THF:DMF (4:1) solvent in presence of TMSCl and catalytic amount of $NiCl_2$ at 60 °C for 2h followed by the addition of TBAF afforded compound **105** and **110** in 1:1 ratio.



Scheme 20

Reagents and conditions: (a) $PhC(OMe)_2$, DMF, 80 °C, 4h, 80%; (b) NaH, BnBr, THF:DMF, 0 °C- r.t., 5h, 80%; (c) DIBALH, DCM, 0 °C-r.t., 6h, 75%; (d) (37%) HCHO, 1M NaOH, 0 °C-r.t., 20h, 45%;(e) imidazole, TPP, iodine, toluene, 80 °C, 2h, 70%; (e) (c) $Mn/CrCl_3$ (20:1), THF:DMF (5:1), 2h then $NiCl_2$ (cat), TMSCl, 50 ^oC, 4h, TBAF, r.t., 2h, 60% (**105** and **110** in 1:1 ratio)

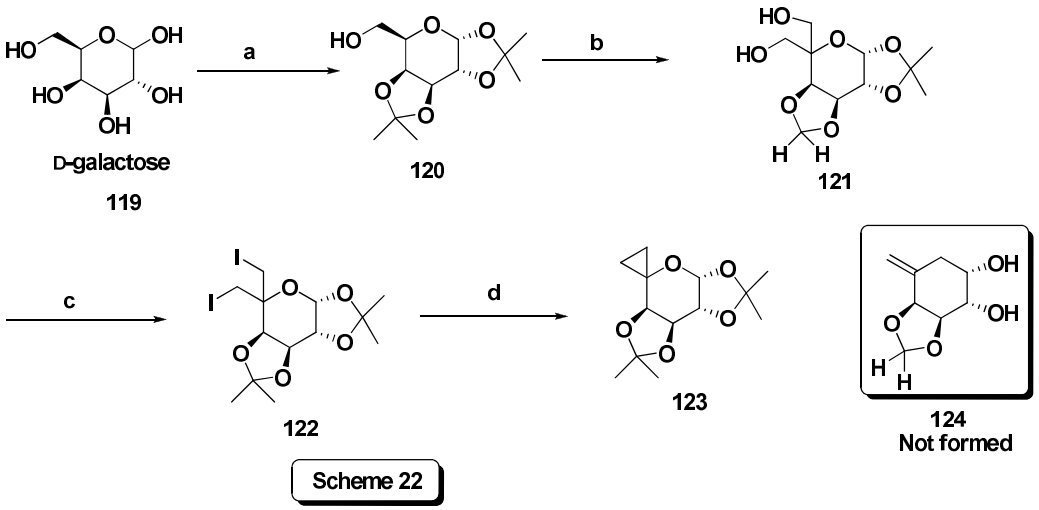


S.E.T = single electron transfer

Scheme 21

Plausible mechanism for the formation of products **105** and **110** was depicted in scheme **21**. First, single electron transfer from $CrCl_2$ to compound **111** initiated reductive ring elimination to give allyliodo compound **117**. Next, allyliodo compound on reaction with $CrCl_2$ gave allylchromium nucleophile **118** which in turn reacted with the aldehyde under NHK condition to afford alcohol products **105** and **110** in 1:1 ratio *via* *6-exo-trig* cyclisation.

Study of reductive elimination and C-C bond formation on galactose derived diiodo compound:



Scheme 22

Reagents and conditions: (a) acetone, HCl, 12h, 80%; (b) $(COCl)_2$, DMSO, Et_3N, -78 °C, DCM, 2h; (ii) (37%) HCHO, 1M NaOH, 0 °C-r.t., 20h, 53%; (c) imidazole, TPP, iodine, toluene, 80 °C, 2h, 70%; (d) $Mn/CrCl_3$ (20:1), THF:DMF (5:1), 2h then $NiCl_2$ (cat), TMSCl, 50 °C, 4h, TBAF, r.t., 1h , 80% **or** Zn, THF/H2O, reflux, 4h, 90% **or** Zn, MeOH, reflux, 1h, 97%.

To further study the reductive elimination followed by intramolecular reaction using $Mn/CrCl_3$ here we have chosen diiodo compound obtained from D-galactose. Here the anomeric methyl is replaced by acetonide group. D-Galactose **119** on reaction with acetone in presence of catalytic amount of HCl resulted in 1,2:3,4 diacetonide galactose **120**. Oxidation of primary alcohol functionality in **120** using Swern oxidation condition afforded aldehyde which on reaction with formalin solution in presence of 1M NaOH resulted in diol along with the replacement of 3,4 acetonide group by formaldehyde acetal to give **121**. Reaction of compound **121** with imidazole, TPP, iodine afforded diiodinated galactose compound **122**. The diiodo compound **122** on reaction with $Mn/CrCl_3$ mediated domino reductive elimination condition resulted in cyclopropane **123** instead of the expected cyclisation product **124**.

The reason for the inefficiency of the reductive ring opening might be attributed to structural parameters of the diiodo compound, more precisely the presence of acetonide group at anomeric position. And, furthermore cyclopropane

formation taken place even under Zn condition, which is known for the conversion of 1,3 dihalo propanes to cyclopropanes which proceeds *via 3-exo-tet* cyclisation.

Single electron transfer from $CrCl_2$ to iodo transfer is taking place which readily cyclised with another radical on another iodo which resulted in cyclopropane formation *via 3-exo-tet* manner.

In conclusion we have developed a new strategy for the conversion of carbohydrate to carbocycle which was applied for 6,6 diiodo methyl glucopyranoside derivative to give exo-olefinic compounds **105** and **110** in 1:1 ratio *via 6-exo-trig* cyclisation. And also we here studied the reductive elimination Vs radical cyclisation on 6,6 diiodo compound obtained from D-galactose derivative **123**, the result indicated that cyclopropane predominates when the reductive elimination fails to initiate.