STUDIES TOWARD THE SYNTHESIS OF A NOVEL CARBOCYCLIC NUCLEOSIDE, FR 901483, TAN 1251 (A, B, C & D) AND CHEIMONOPHYLLON E

BY

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Studies toward the synthesis of a novel carbocyclic nucleoside, FR 901483, TAN 1251 (A, B, C & D) and cheimonophyllon E

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DEDICATED

TO MY BELOVED

PARENTS

DECLARATION

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

Organic Chemistry: Technology
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December 2006 **(K. Maheshwar)**

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CERTIFICATE

The research work presented in thesis entitled "**Studies toward the synthesis of a novel carbocyclic nucleoside, FR 901483, TAN 1251 (A, B, C & D) and cheimonophyllon E**" has been carried out under my supervision and is a bonafide work of **Mr. K. Maheshwar**. This work is original and has not been submitted for any other degree or diploma of this or any other University.

Pune-411008
December 2006

(Dr. M. K. Gurjar)
Research Guide

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ABBREVIATIONS

Ac	-	Acetyl
AcOH	-	Acetic acid
Ac_2O	-	Acetic anhydride
AIBN	-	2,2'-Azobisisobutyronitrile
Bn	-	Benzyl
BnBr	-	Benzyl bromide
$BH_3 \cdot Me_2S$	-	Boron dimethyl sulfide complex
Boc	-	*tert*-Butoxy carbonyl
$(Boc)_2O$	-	Di-*tert*-butyl dicarbonate
BuLi	-	Butyl Lithium
DCM	-	Dichloromethane
DDQ	-	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DIBAL	-	Diisobutylaluminiumhydride
DMP	-	Dess–Martin periodinane
DMP	-	2,2-Dimethoxypropane
DMF	-	*N, N′*-Dimethylformamide
DMAP	-	*N,N′*-Dimethylaminopyridine
DMSO	-	Dimethyl sulfoxide
EtOH	-	Ethanol
Et	-	Ethyl
Et_2O	-	Diethyl ether
EtOAc	-	Ethyl acetate
Et_3N	-	Triethylamine
IBS	-	Iodoxybenzoic Acid
Im	-	Imidazole
LDA	-	Lithium diisopropylamide
MeOH	-	Methanol
MsCl	-	Methanesulfonyl chloride
Ms	-	Methanesulfonyl

Me	-	Methyl
MeI	-	Methyl iodide
MPM	-	*p*-Methoxyphenylmethyl
$NaBH_4$	-	Sodiumborohydride
NaH	-	Sodium hydride
NOE	-	Neuclear Overhauser Effect
Ph	-	Phenyl
Py	-	Pyridine
PDC	-	Pyridiniumdichromate
p-TSA	-	*par*a-Toluenesulfonic acid
RCM	-	Ring closing metathesis
TEA	-	Triethylamine
TBAI	-	Tetra-*n*-butylammonium iodide
TBAF	-	Tetra-*n*-butylammonium fluoride
TBDMSCl	-	*tert*-Butyldimethyl chlorosilane
TBDMS	-	*tert*-Butyldimethyl silyl
THF	-	Tetrahydrofuran
TPP	-	Triphenylphosphine
*P*TSA	-	*p*-Toluenesulphonic acid
TsCl	-	*p*-Toluenesulphonyl chloride

GENERAL REMARKS

- ^{1}H NMR spectra were recorded on AC-200 MHz, MSL-300 MHz, and DRX-500 MHz spectrometer using tetramethylsilane (TMS) as an internal standard. Chemical shifts have been expressed in ppm units downfield from TMS.
- ^{13}C NMR spectra were recorded on AC-50 MHz, MSL-75 MHz, and DRX-125 MHz spectrometer
- EI Mass spectra were recorded on Finngan MAT-1020 spectrometer at 70 *eV* using a direct inlet system.
- The X-Ray Crystal data were collected on *Bruker SMART APEX* CCD diffractometer using Mo K_{α} radiation with fine focus tube with 50 kV and 30 mA.
- Infrared spectra were scanned on Shimadzu IR 470 and Perkin-Elmer 683 or 1310 spectrometers with sodium chloride optics and are measured in cm^{-1}.
- Optical rotations were measured with a JASCO DIP 370 digital polarimeter.
- Melting points were recorded on Buchi 535 melting point apparatus and are uncorrected.
- All reactions are monitored by Thin Layer chromatography (TLC) carried out on 0.25 mm E-Merck silica gel plates (60F-254) with UV light, I_2 and anisaldehyde in ethanol as development reagents.
- All solvents and reagents were purified and dried by according to procedures given in Vogel's Text Book of Practical Organic Chemistry. All reactions were carried out under nitrogen or argon atmosphere with dry, freshly distilled solvents under anhydrous conditions unless otherwise specified. Yields refer to chromatographically and spectroscopically homogeneous materials unless otherwise stated.
- All evaporations were carried out under reduced pressure on Buchi rotary evaporator below 40 °C.
- Silica gel (60–120) used for column chromatography was purchased from ACME Chemical Company, Mumbai, India.

CONTENTS

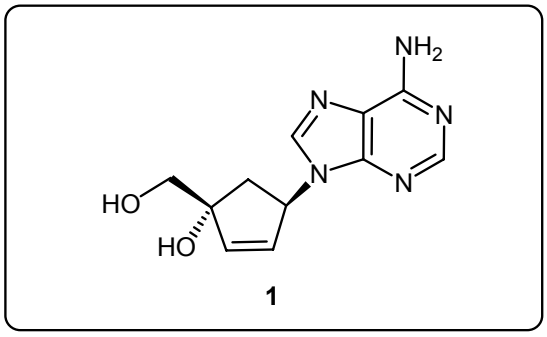
ABSTRACT

ABSTRACT

The thesis entitled **"Studies toward the synthesis of a novel carbocyclic nucleoside, FR901483, TAN 1251 (A, B, C and D) and cheimonophyllon E"** consists of three chapters. First chapter describes the synthesis of a novel carbocyclic nucleoside. The second chapter deals with the studies toward the synthesis of enantiopure FR901483 and TAN1251 family of compounds. The final chapter III discusses synthetic studies towards (+)-cheimonophyllon E, using chiral pool strategy.

CHAPTER 1:

Synthesis of a novel carbocyclic nucleoside (1):



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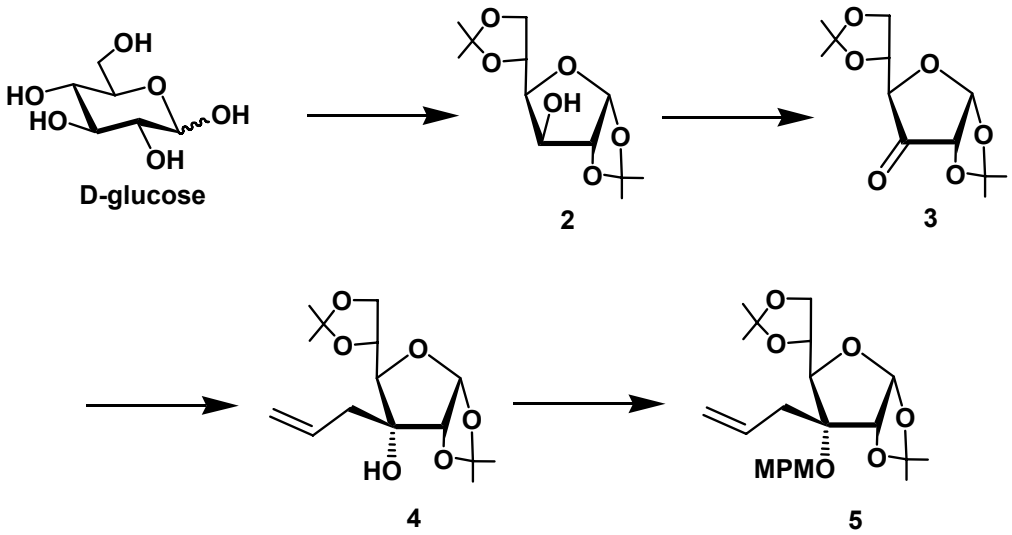
Nucleosides are fundamental building blocks of biological systems that show a wide range of important biological activities. Consequently, extensive modifications have been made to both the heterocyclic base and the sugar moiety in order to avoid the drawbacks shown by nucleosides or analogues in certain applications, mainly due to enzymatic degradations. Nucleoside analogues have been extensively investigated in the search for agents effective against the human immuno deficiency virus (HIV), the causative agent of the AIDS epidemic. One important discovery has been that replacement of the oxygen in the sugar portion of the nucleoside with a methylene unit results in

Carbocyclic nucleoside analogues which are highly resistant to phosphorylases. We have designed a novel Carbocyclic nucleoside (**1**) having both tertiary center and unsaturation in the carbocyle part, which were the two separate features that were present in potent nucleosides.

Carbohydrates can be manipulated to provide interesting class of compounds containing required stereochemistry, which can serve as potent intermediates to access complex bioactive molecules. Similarly, our synthetic strategy was involved to synthesize an intermediate cyclic carbonate derivative **12** from D-glucose, which was used for coupling with 6-amino purine base employing Trost's Pd-catalyzed allylic coupling methodology to achieve the designed target carbocyclic nucleoside **1**.

We initiated our synthesis by converting D-glucose into 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose **2**. The allyl group at C-3 was stereoselectively introduced by oxidizing 3-hydroxyl group of **2** to its corresponding keto compound **3** on treatment with PDC followed by Grignard reaction using allyl magnesium bromide in refluxing THF to provide allyl alcohol **4** exclusively. Tertiary alcohol of **4** was protected as its *p*-methoxy pheny methyl (MPM) ether by exposing to MPM-Br in the presence of NaH in THF to obtain **5** (Scheme 1).

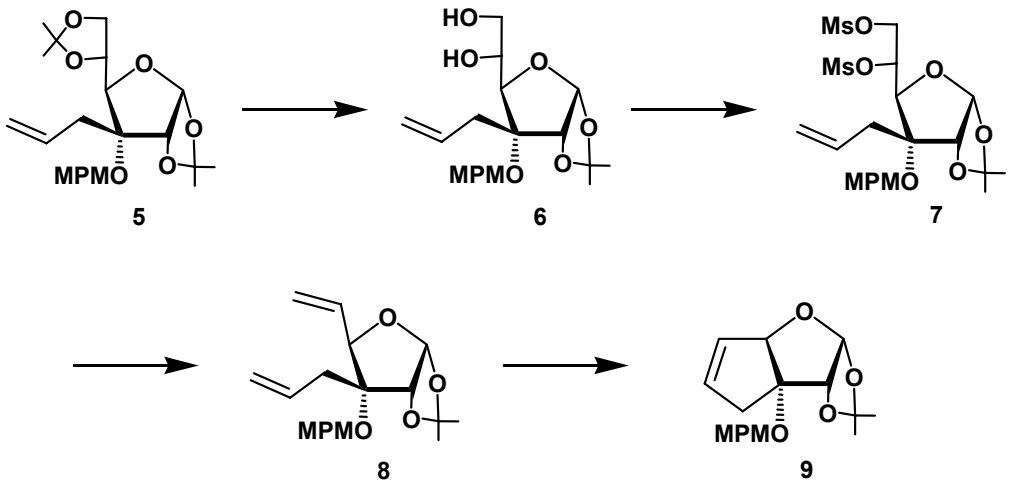
Scheme 1:



Selective 5,6-isopropylidene hydrolysis of **5** was accomplished using 0.8% aq. H_2SO_4 in MeOH to get diol **6**, which was then mesylated using methane sulphonyl chloride in dichloromethane to yield dimesylate **7**. In order to obtain the diene derivative,

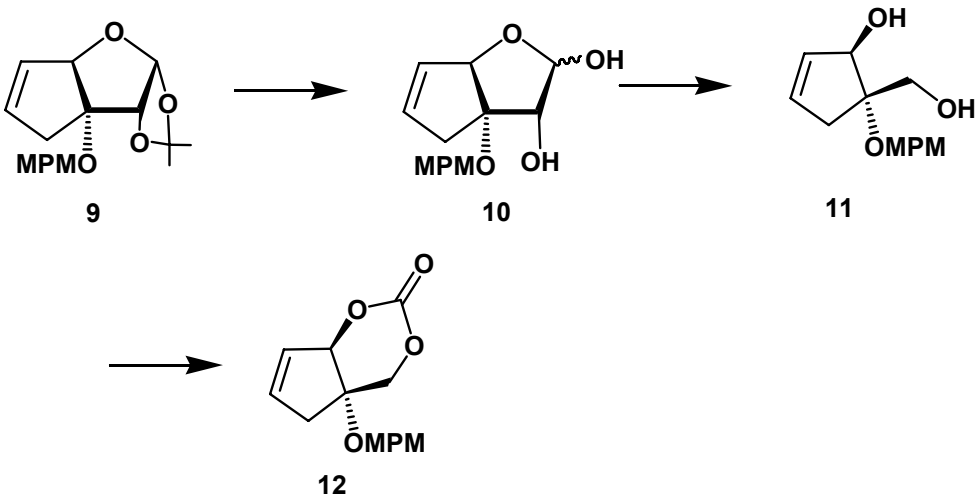
compound **7** was subjected to NaI promoted elimination by refluxing in 2-butanone provided the diene **8**. Ring-closing metathesis of **8** in the presence of 5 mol% of Grubbs' 1st generation catalyst [$(PCy_3)_2Cl_2Ru{=}CHPh$] in CH_2Cl_2 at room temperature afforded tricyclic compound **9** (Scheme 2).

Scheme 2:



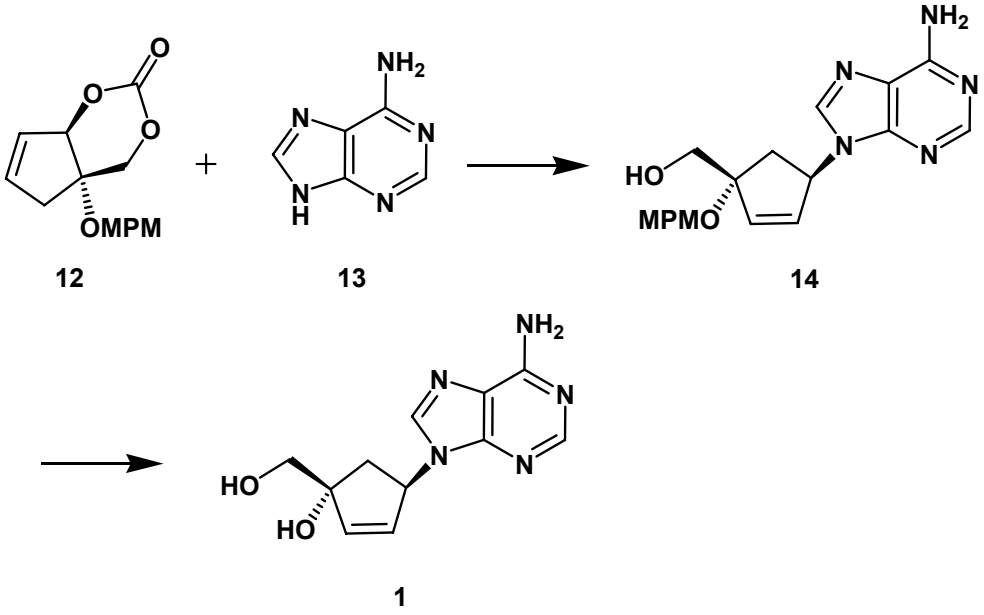
The acid hydrolysis of 1,2-acetonide group of **9** was effected by refluxing in aq. 0.4% H_2SO_4/dioxane to obtain bicyclic lactol **10**, which on $NaIO_4$ mediated oxidative cleavage followed by $NaBH_4$ reduction in MeOH provided diol **11**. The resulting diol compound was then treated with *N,N′*-carbonyldiimidazole in refluxing benzene to get cyclic allylic carbonate **12** (Scheme 3).

Scheme 3:



Trost's Pd-catalyzed allylic coupling between 6-amino purine **13** and cyclic carbonate **12** was accomplished by using tetrakis(triphenylphosphine)palladium(0) in DMSO:THF (1:1) at 45 ^{o}C for 2h to furnish MPM-protected carbocyclic nucleoside derivative **14** as a single diastereomer. Finally, oxidative cleavage of MPM ether using DDQ in dioxane:H_2O provided the target carbocyclic nucleoside **1** (Scheme 4).

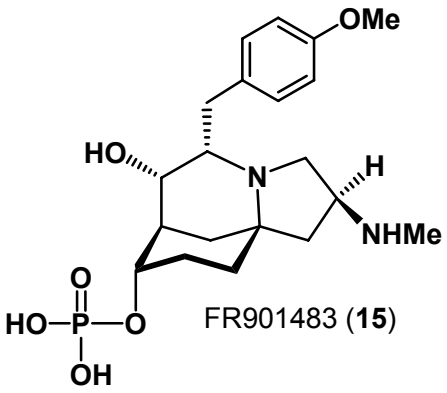
Scheme 4:



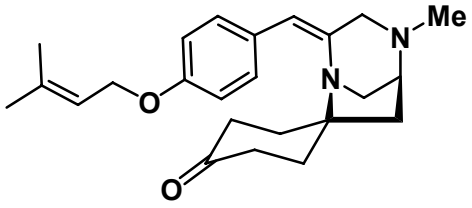
CHAPTER 2:

Studies toward the synthesis of FR901483 and TAN1251 (A, B, C and D):

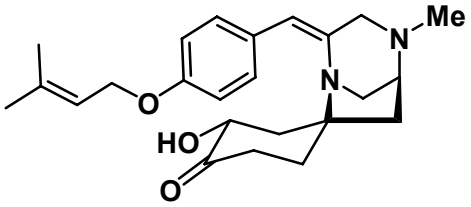
1-Azaspirane alkaloids are widely distributed in microbes, plants, animals and various marine organisms and a variety of these conformationally restricted nitrogen bearing alkaloids are found to display an extensive range of important biological activities. In our studies toward the synthesis of both immunosuppressant FR901483 (**15**) and antimuscarinic TAN1251 family (**16 – 19**), our initial target was the synthesis of 3-Amino-1-azaspiro[4.5]decan-8-one (**20**), from which the above mentioned natural compounds can be derived. In our strategy we have planned our synthesis starting with *trans*-4-Hydroxy-L-proline as the chiral source and envisioned to achieve the spiro-system by using Aldol



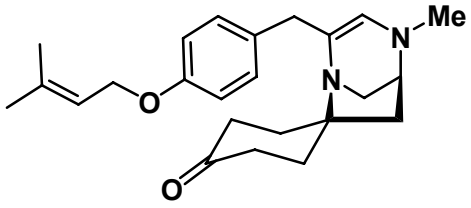
FR901483 (**15**)



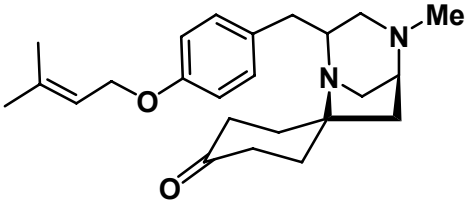
TAN1251A (**16**)



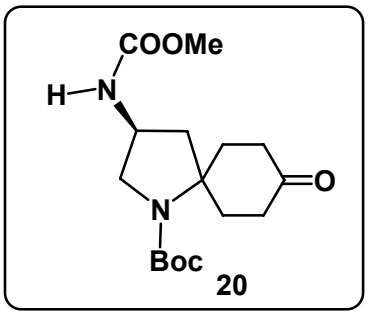
TAN 1251B (**17**)



TAN1251C (**18**)



TAN1251D (**19**)



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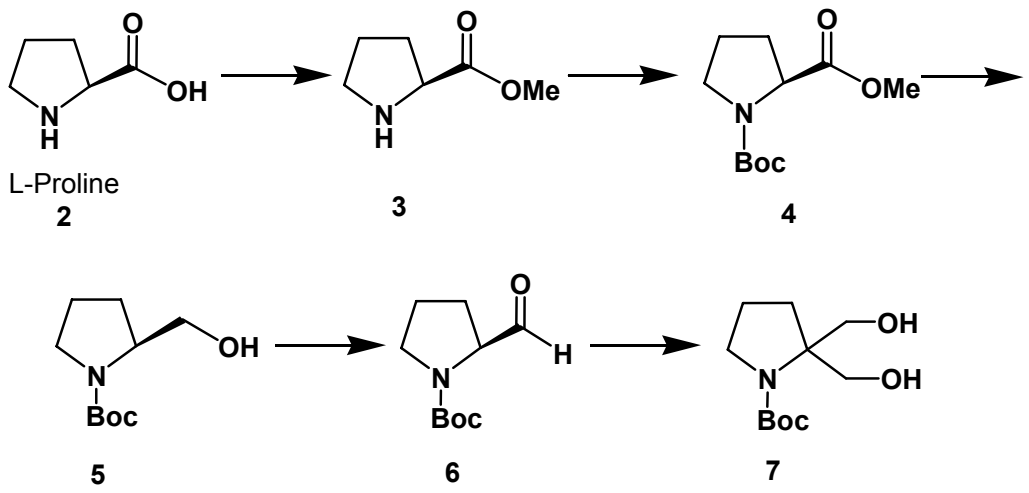
followed by reduction and Dieckmann cyclizaiton reactions as key steps. Construction of the spiro-system was ensured by the model studies on L-proline.

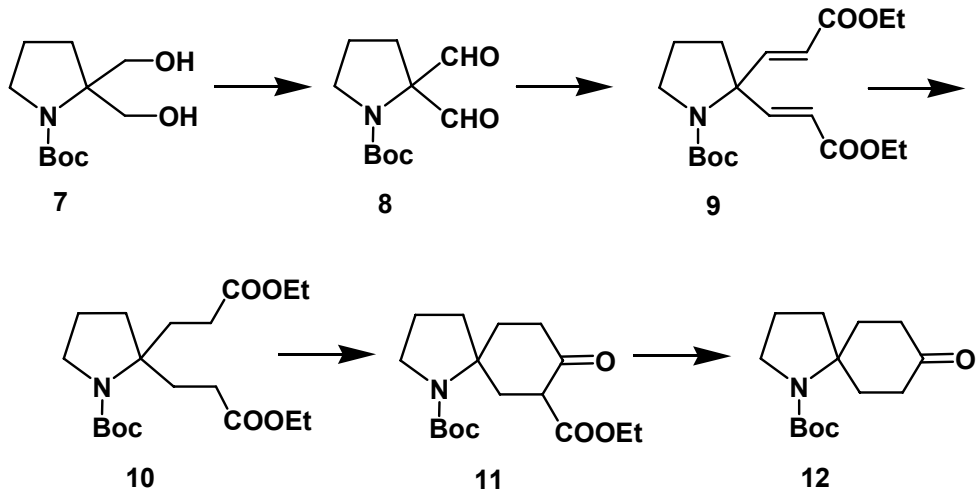
Thus, L-proline (**21**) was converted to prolinal by a sequence of reactions involving esterification of acid by refluxing in MeOH in the presence of thionyl chloride, Boc protection of the amino group using $(Boc)_2O$ in CH_2Cl_2 in the presence of Et_3N and reduction of the resulting ester **23** using $LiBH_4$ and oxidation of the primary alcohol in **24** by refluxing with IBX in EtOAc provided N-Boc-prolinal **25**. Aldol reaction on aldehyde **6** was effected by treating with aq. 37% formaldehyde solution in the presence of 1N NaOH and the resulting hydroxy aldehyde intermediate was immediately reduced with $NaBH_4$ to afford the diol **26** (Scheme 5).

Scheme 1:



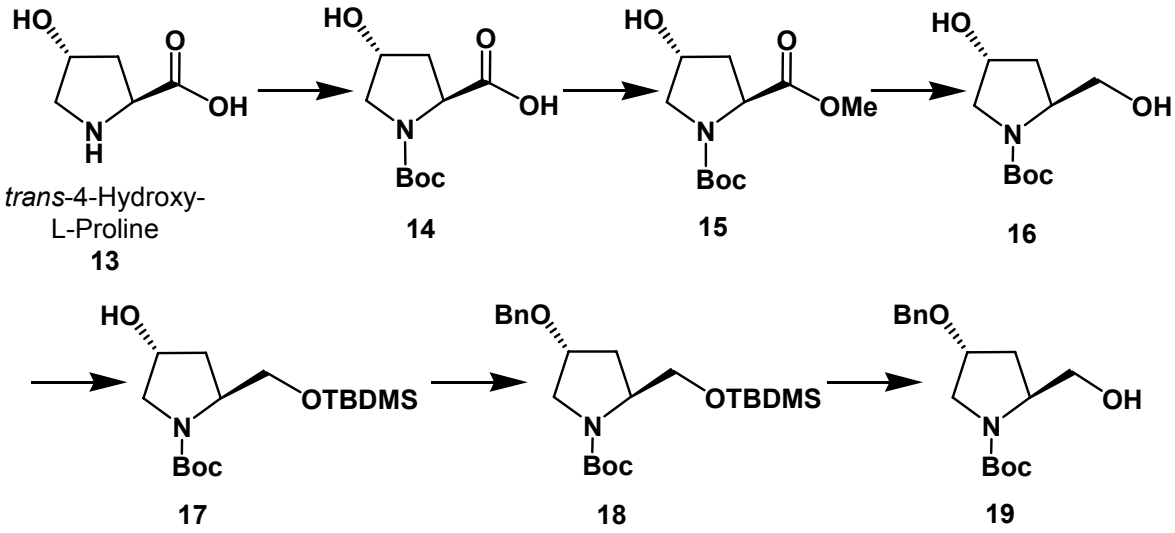
Precursor for the Dieckmann cyclization, the diester **29**, was achieved by Swern oxidation of the diol **26** followed by a two carbon Wittig homologation using $Ph_3P{=}CHCO_2Et$ in refluxing benzene resulted α,β-unsaturated ester **28**, which was then subjected to Pd/C catalyzed hydrogenation reaction to furnish the required diester **29**. Dieckmann cyclization of diester **29** was accomplished by treating with NaH in THF to afford β-keto ester **30**. Decarboxylation of the ester **30** was effected using Krapcho's conditions, by heating at 160-170 ^{o}C with NaCl in DMSO in the presence of catalytic amount of H_2O resulted the required azaspiro ketone **31** (Scheme 6).

Scheme 2:



After having established an efficient synthetic route for the construction of spiro-ring system, we then focused on to making the 3-amino-1-azaspiro[4.5]decane-8-one (**20**) starting from *trans*-4-Hydroxy-L-proline (**32**). Thus, amino group of hydroxy proline was first protected with Boc group using $(Boc)_2O$ in the presence of 10% NaOH to get **33**, which was then esterified by treating with Me_2SO_4 in refluxing acetone in the presence of

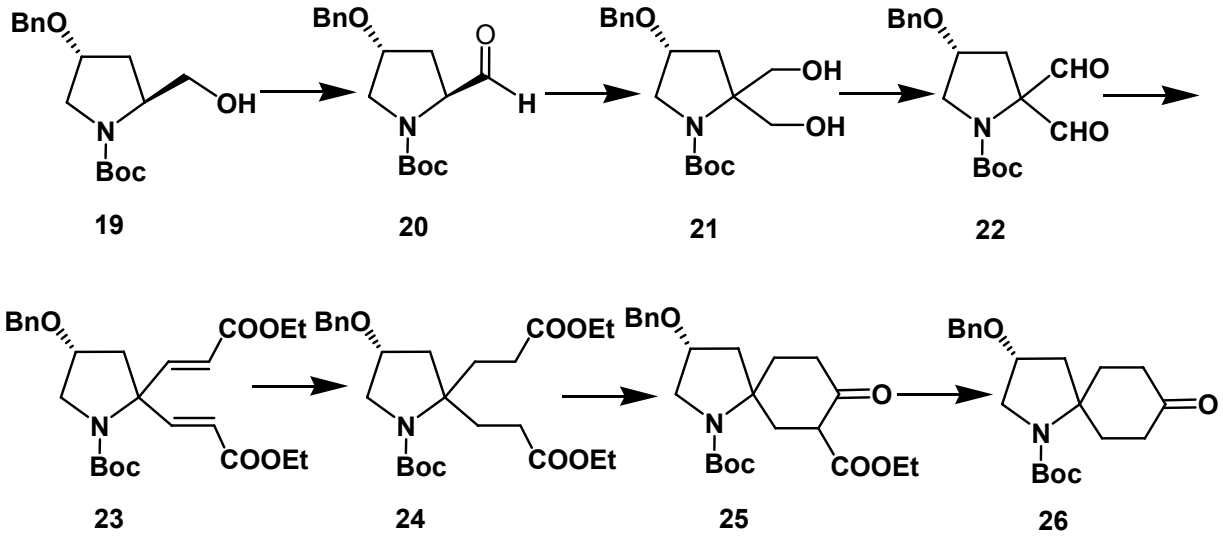
Scheme 3:



K_2CO_3 to obtain **34**. Reduction of the ester to alcohol was effected by using $LiBH_4$ to afford diol **35**, which on selective protection of primary hydroxyl as its silyl ether by treating with TBDMSCl, imidazole in CH_2Cl_2 provided **36**. Secondary hydroxyl group of **36** was protected as its benzyl ether using BnBr in the presence of NaH in THF to give **37**, which on desilylation by treating with TBAF in THF provided the required primary alcohol derivative **38** (Scheme 7).

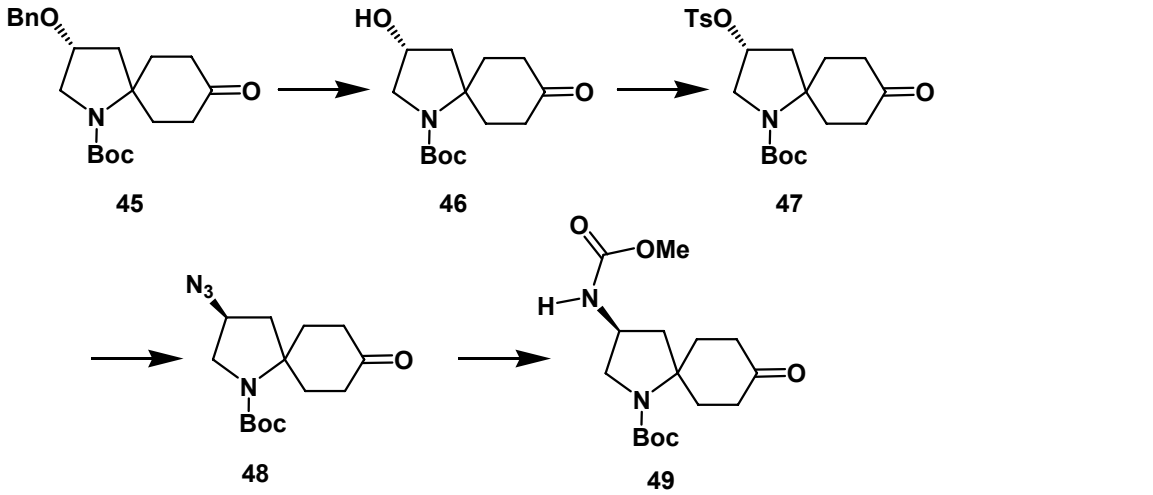
In order to construct the spiro-ring system we have followed the same sequence of reactions on **38** as in the case of proline. Thus, IBX mediated oxidation of **38** followed by aldol reaction using aq. 37% formaldehyde then reduction using $NaBH_4$ resulted the expected diol **40**. Swern oxidation of **40**, two carbon Wittig homologation and hydrogenation of the double bonds over Raney Ni in the presence of H_2 provided the diester **43**. Dieckmann cyclization followed by decarboxylation of **43** afforded spiro-keto derivative **45** (Scheme 8).

Scheme 4:



Reductive cleavage of the benzyl ether in **45** using 20% $Pd(OH)_2/C$ in the presence of H_2 furnished hydroxy compound **46**. The introduction of the azido group at C-3 was achieved by tosylation of the hydroxyl group of **46** by treating with TsCl in pyridine followed by heating the resulting tosyl compound **47** with NaN_3 at 75-85 ^oC in DMF

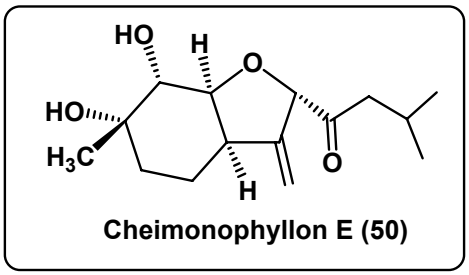
Scheme 9:



provided the azide **48**. Reduction of the azide **48** was performed by refluxing with PPh_3 in THF in the presence of catalytic amount of H_2O to afford corresponding amine, which on treatment with methyl chloroformate in the presence of K_2CO_3 furnished the required azaspiro compound **49** (Scheme 9).

CHAPTER 3:

Studies toward the synthesis of Cheimonophyllon E:

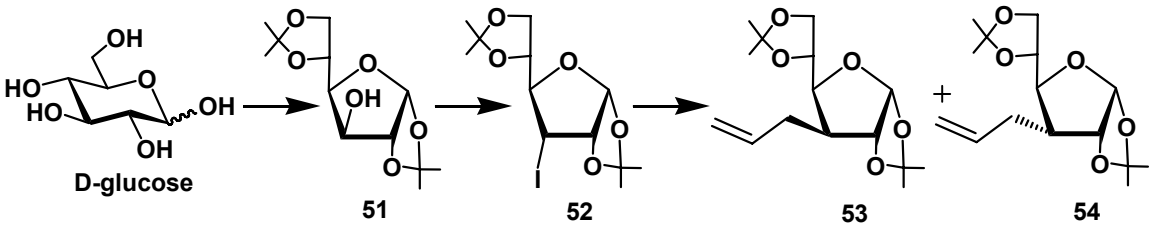


Cheimonophyllon E (50)

Cheimonophyllon E is one of the six bisabolane-type sesquiterpenoids isolated from the culture fluid of the basidiomycete *Cheimonophyllum candidissimum*. These natural products are found to exhibit nematicidal, antifungal, antibacterial and cytotoxic activities. Cheimonophyllon E (**50**) possesses five stereogenic carbons in a highly oxygenated 7-oxabicyclo[4.3.0]nonane core skeleton. Our interest in its intriguining structural and biological activities led us to study the synthesis of **50** by adopting chiral pool approach starting from D-glucose.

Thus, D-glucose was converted into 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose **51**, which on iodination using Ph_3P, imidazole and iodine refluxing in toluene yielded 3-iodo derivative **52**. Stereoselective introduction of allyl group at C-3 was accomplished successfully by radical allylation of compound **52** on treatment with allyltributylstannane in refluxing benzene in the presence of a radical initiator, AIBN, provided 3-allyl derivatives **53** & **54** as a diastereomeric mixture (3:1) and the required isomer **53** was formed predominantly (Scheme 10).

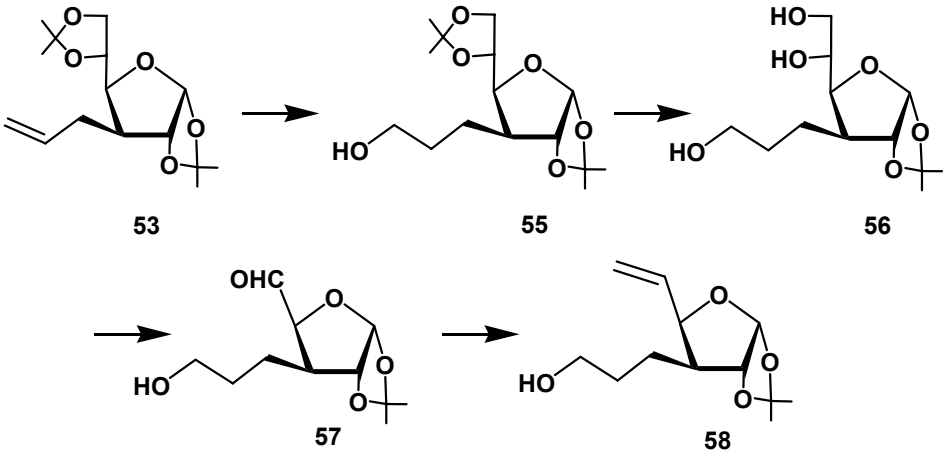
Scheme 10:



Hydroboration oxidation of the allyl compound was done by using Borane:DMS complex in THF to give alcohol **55**, which on selective 5,6-acetonide cleavage by treating with aq. 0.8% H_2SO_4 afforded triol **56**. Oxidative cleavage of the 5,6-diol of **56** was

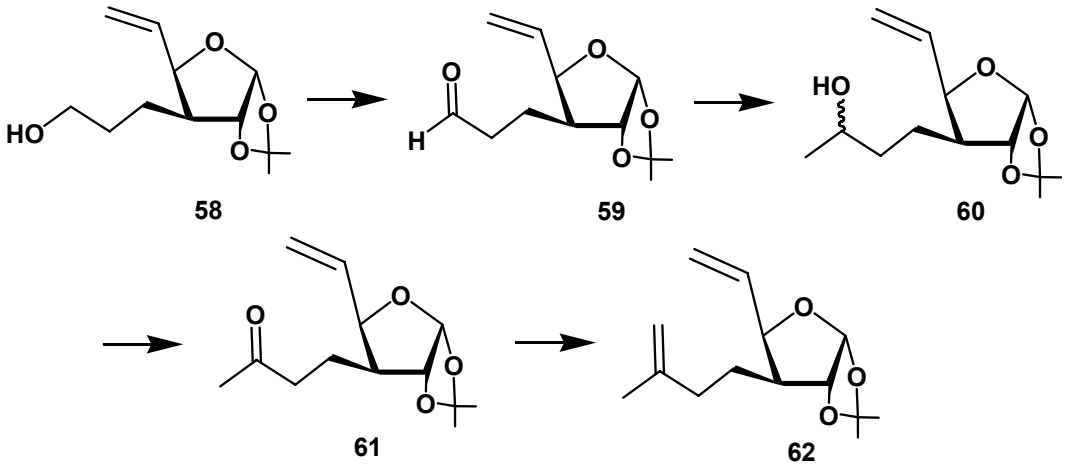
effected by exposing to $NaIO_4$ in CH_2Cl_2 resulted an aldehyde **57**, which on one carbon Wittig homologation using $Ph_3P{=}CH_2$ in THF:ether provided alcohol **58** (Scheme 11).

Scheme 11:



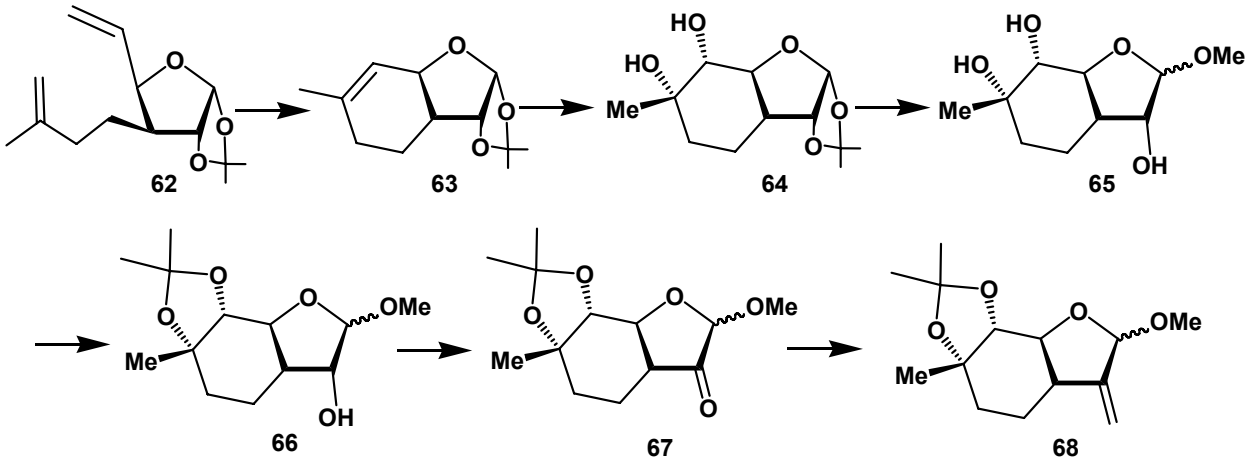
The precursor for the ring closing metathesis, diene **62**, was achieved by a sequence of reactions on **58** involving Swern oxidation to give corresponding aldehyde **59**, methyl grignard of which using methyl magnesium chloride in THF afforded diastereomeric mixture of **60**. Oxidaton of the secondary alcohol in **60** by refluxing with IBX in EtOAc yielded the ketone **61**, which on one carbon Wittig homologation using $Ph_3P{=}CH_2$ in THF:ether provided the diene **62** (Scheme 12).

Scheme 12:



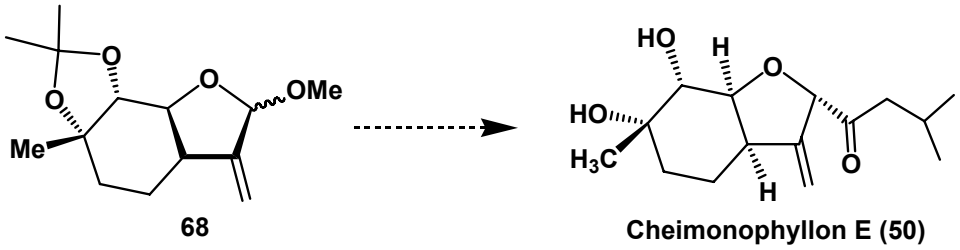
Ring-closing metathesis of the diene **62** was accomplished using 5 mol% of Grubbs' 1st generation catalyst in CH_2Cl_2 at room temperature furnished **63**, which on treatment with OsO_4 in the presence of NMO in acetone:H_2O underwent substrate induced stereoselective dihydroxylation to provide diol **64** exclusively as a single diastereomer. The stereochemistry of **64** was confirmed by single crystal X-ray diffraction studies. Acid hydrolysis of 1,2-acetonide group in **64** was effected by refluxing in MeOH in the presence of amberlyst-15 obtained methyl glycoside **65** as a mixture, which on exposing to dimethoxypropane in the presence of catalytic *p*-toluene sulphonic acid in CH_2Cl_2 furnished **66**. Dess-martin periodinane oxidation of alcohol **66** gave ketone **67** followed by a one carbon Wittig homologation using $Ph_3P{=}CH_2$ in THF provided **68** (Scheme 13).

Scheme 13:



Although several attempts have been made to introduce the said chain to complete the total synthesis of Cheimonophyllon E (**50**), we have not been successful so far. However, in continuation of this work, efforts are going on in our laboratory to accomplish the total synthesis of **50** (Scheme 14).

Scheme 14:

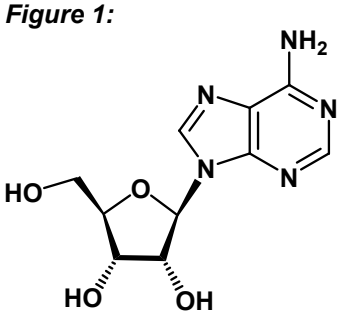


CHAPTER -I

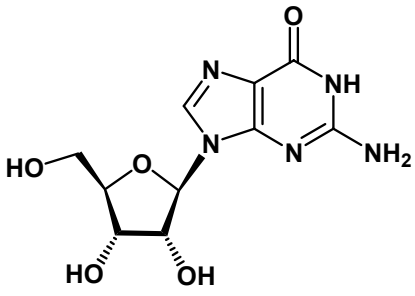
Synthesis of a novel carbocyclic nucleoside

Natural nucleosides adenosine (**1**), guanosine (**2**), cytidine (**3**), uridine (**4**), and their 2'-deoxy analogs and thymidine (**5**) are the building blocks of nucleic acids - deoxyribonucleic acid (DNA), ribonucleic acid (RNA) and play very important role in cellular metabolism (Figure **1**).[1] Nucleosides are important structural moieties in several coenzymes such as NAD^+, $NADP^+$, FAD and coenzyme A. They also serve as part of biological signal molecules and metabolic regulators and function as activated intermediates in numerous biosynthetic reactions. Due to this importance, analogs of these nucleosides have been used as templates in drug design leading to potent antiviral,

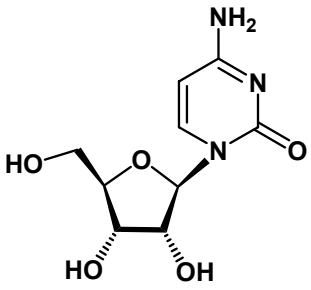
Figure 1:



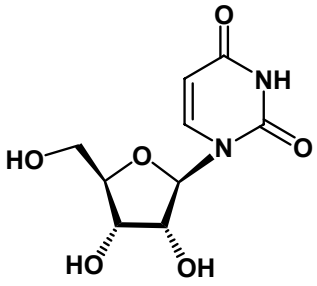
Adenosine (**1**)



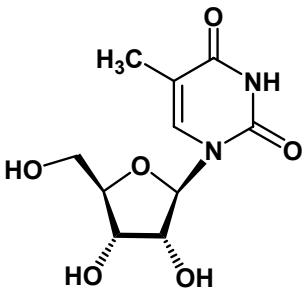
Guanosine (**2**)



Cytidine (**3**)



Uridine (**4**)

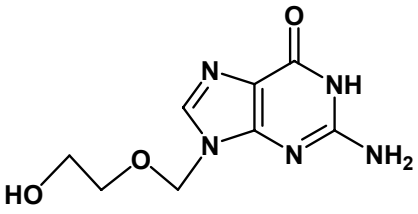


Thymidine (**5**)

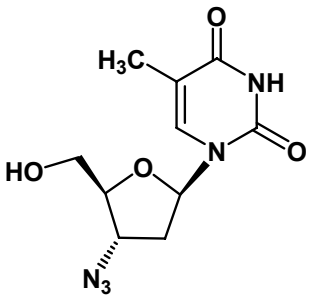
antitumor and antibacterial agents.[2] Modification of the natural nucleosides for drug design can be divided into three categories: (1) sugar modified, (2) base modified, and (3) in the nucleotide form, phosphate modified.[3] Many compounds have been studied over the years and the base and sugar type modifications have shown the most promise. Acyclovir [(9-hydroxyethoxy)methyl guanine] (**6**) (Figure **2**),[4] the first successful antiviral drug discovered in 1974 is a sugar-modified nucleoside that lacks the 2′ and 3′-carbons of the traditional nucleosides. Active metabolite of **6** is its triphosphate and it inhibits selectively

the DNA polymerase of herpes simplex virus type 1, HSV 1. The source of the selectivity of this nucleoside analog is two fold since it requires viral thymidine kinases for the conversion into its monophosphate resulting in accumulation only in infected cells. Host cell enzymes then convert the monophosphate to the diphosphate and ultimately to the triphosphate. This finding triggered the intense investigation on compounds where the

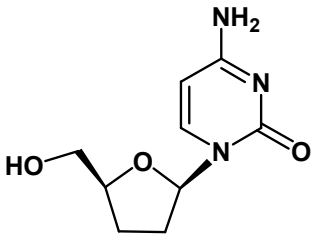
Figure 2:



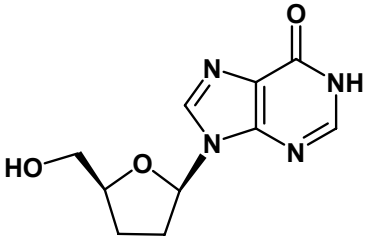
Acyclovir (**6**)
Zovirax



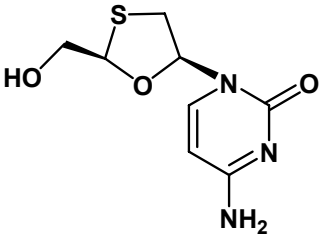
AZT (**7**)



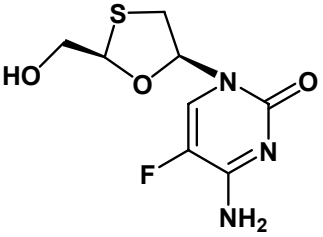
ddC (**8**)



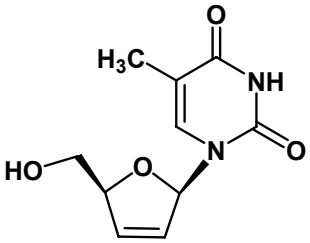
ddI (**9**)



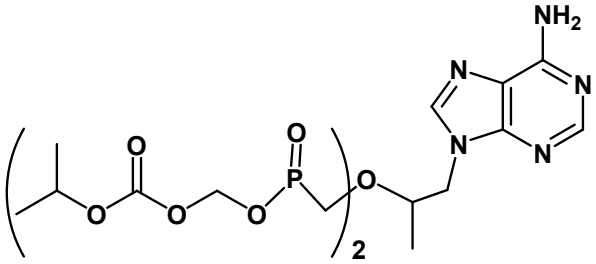
3TC (**10**)



FTC (**11**)



d4T (**12**)



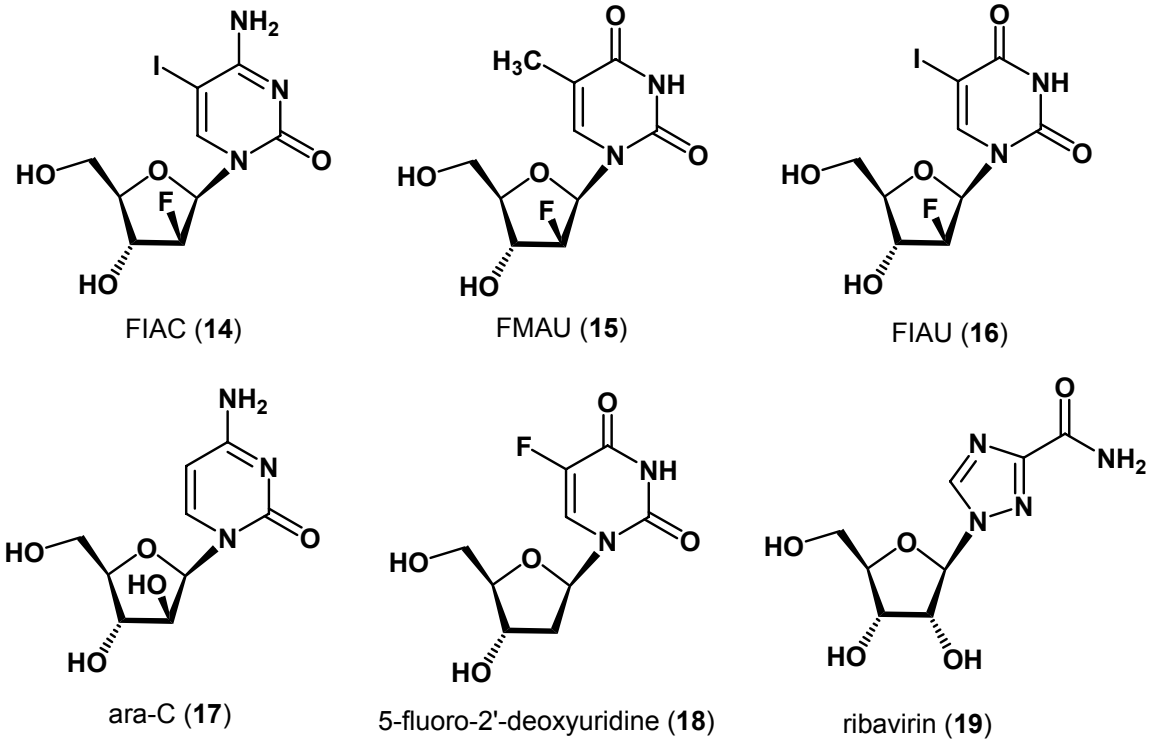
bis(POC)PMP A (**13**)

heterocycle and sugar components of the nucleoside have departed significantly from the natural form. For example 2′,3′-Dideoxynucleosides (ddNs) and 2′,3′-didehydro-2′,3′-dideoxynucleosides (d4Ns), namely the nucleoside reverse transcriptase inhibitors (NRTI), form the most important class of compounds active against the human immunodeficiency virus (HIV), which causes AIDS. The NRTI approved by the US Food and Drug Administration (US FDA) for the treatment of AIDS are 3′-azido-2′,3′-dideoxythymidine

(AZT, zidovudine)[5] (**7**), 2′,3′-dideoxycytidine (ddC, zalcitabine)[6] (**8**), 2′,3′-dideoxyinosine (ddI, didanosine)[7] (**9**), 2′,3′-dideoxy-3′-thia-β-L-cytidine (3TC, lamivudine)[8] (**10**), 5-fluoro-2′,3′-dideoxy-3′-thia-β-L-cytidine (FTC, emtricitabine)[9] (**11**), 2′,3′-didehydro-2′,3′-dideoxythymidine (d4T, stavudine)[10] (**12**) and (POP)PMPA (tenofovir disoproxil fumarate, viread)[11] (**13**) (Figure **2**). To exemplify the mode of action of these drugs, for instance, in case of AZT, cellular kinases convert AZT to its triphosphate, the active metabolite, and is incorporated into the elongating nucleic acid by HIV reverse transcriptase and this incorporation blocks further elongation by causing DNA chain termination.

2′-fluoro-5-iodo-1-β-D-arabinofuranosyl cytosine (FIAC) (**14**), 2′-fluoro-5-methyl-1-β-D-arabinofuranosyluracil (FMAU) (**15**) and 2′-fluoro-5-iodo-1-β-D-arabinofuranosyl(FIAU) (**16**) exhibited activity against herpes simplex virus (HSV).[12] The selectivity of these compounds depends on their preferential activation (phosphorylation) by the viral enzyme thymidine kinase. 1-β-D-arabinofuranosylcytosine (ara-C) (**17**)[13a] and 5-fluoro-2′-deoxyuridine (**18**) [13b-e] also displayed some anti-cancer activities. (Figure **3**).

Figure 3:

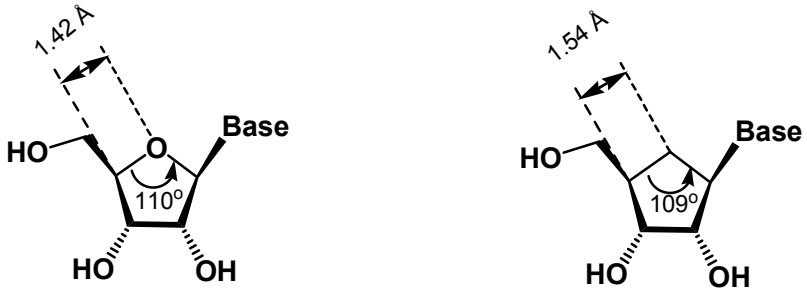


Another promising example, ribavirin (**19**), β-D-ribofuranosyl-1,2,4-triazole-3-carboxamide, has a broad spectrum activity against both RNA and DNA viruses and is

currently used in the treatment of hepatitis C, respiratory syncytial infection and lassa fever virus infection. The triphosphate of ribavirin inhibits viral RNA polymerase and the viral specific mRNA capping enzyme guanylyl transferase. It is also believed that the monophospate of ribavirin causes the depletion of intracellular GTP level. More recently it has been proposed that ribavirin works by creating such extreme mutation rates in viruses that it drives them into "genetic meltdown" (Figure **3**).[14]

However, these nucleosides are also substrates for phosphorylases, enzymes that cleave the N-glycosidic bond between the heterocyclic moiety and the sugar, as well as deaminases.[15] In order to avoid these enzymatic degradations and to improve the biological activities of nucleosides, the sugar portion of molecule was modified. The replacement of the oxygen of the furan ring by a methylene group results in carbocyclic nucleoside analogs which are highly resistant to phosphorylases and hydrolases.[16] The original concept of introducing the "carba" part was to consider the following: 1. Carba-nucleosides, compared to their natural nucleosides counterparts, have a stable C-N bond instead of a glycosidic bond. Thus, they are expected to possess greater metabolic stability under physiological conditions, in which the normal nucleosides will be cleaved more easily by the phosphorylase and deaminase enzymes. 2. They also become more stable in acidic pH conditions. 3. The comparatively higher lipophilicity of carba-nucleosides enhances cell membrane penetration and increases the bioavailability of these

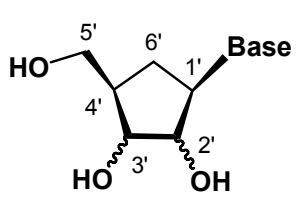
Figure 4:



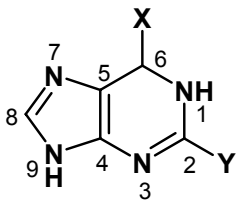
Ribonucleoside Carbocyclic nucleoside

carbocyclic compounds. 4. The replacement of furanose oxygen with methylene maintains the similarity of the structures to the nucleosides. For example, the bond lengths and bond angles between the tetrahydrofuran ring and the cyclopentane are rather similar (Figure **4** & **5**).

Figure 5:

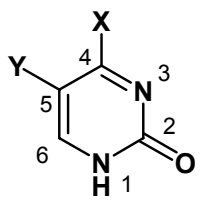


carbocyclic nucleoside



X = NH_2, Y = H - Adenine

X = OH, Y = NH_2 - Guanine



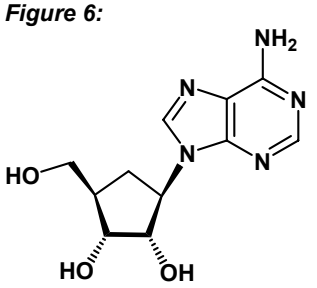
X = NH_2, Y = H - Cytosine

X = OH, **Y = H** - Uracil

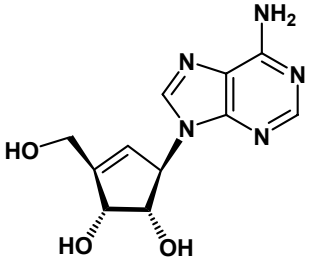
X = OH, **Y = CH_3** - Thymine

While the carbocyclic analog of adenosine was first described by Shealy and Clayton[17] in 1966 it was the discovery that the natural carbocyclic nucleosides aristeromycin **20**[18a] and neplanocin A **21**[18b] display antibiotic and antitumor activity which sparked the search for other carbocyclic nucleoside analogs with biological activity. Subsequently, other synthetic carbocyclic nucleosides with important therapeutic properties were discovered. Particularly carbovir **22**[19a], Abacavir **23**[19b], BCA **24**[19c] as well as Cyclobut A **25** have been shown to be inhibitors of the human immunodeficiency virus (HIV), the causative agent for the acquired immune deficiency syndrome (AIDS) (Figure **6**).

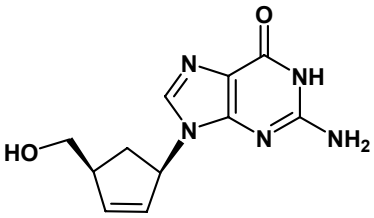
Figure 6:



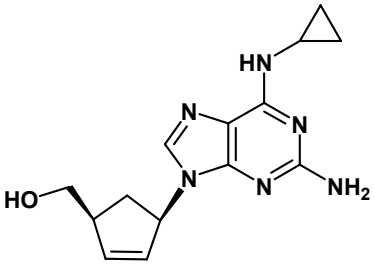
aristeromycin (**20**)



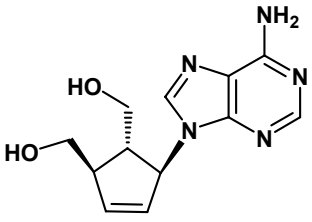
neplanocin A (**21**)



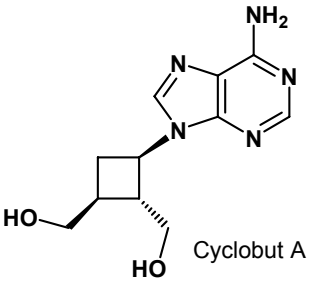
carbovir (**22**)



abacavir (**23**)



(-)-BCA (**24**)



Cyclobut A (**25**)

Based on the size of the carbocyclic ring, unnatural carbocyclic nucleosides, generally, can be divided into five different types: three-membered ring, four-membered ring, five-membered ring, six-membered ring and bicyclic nucleosides.

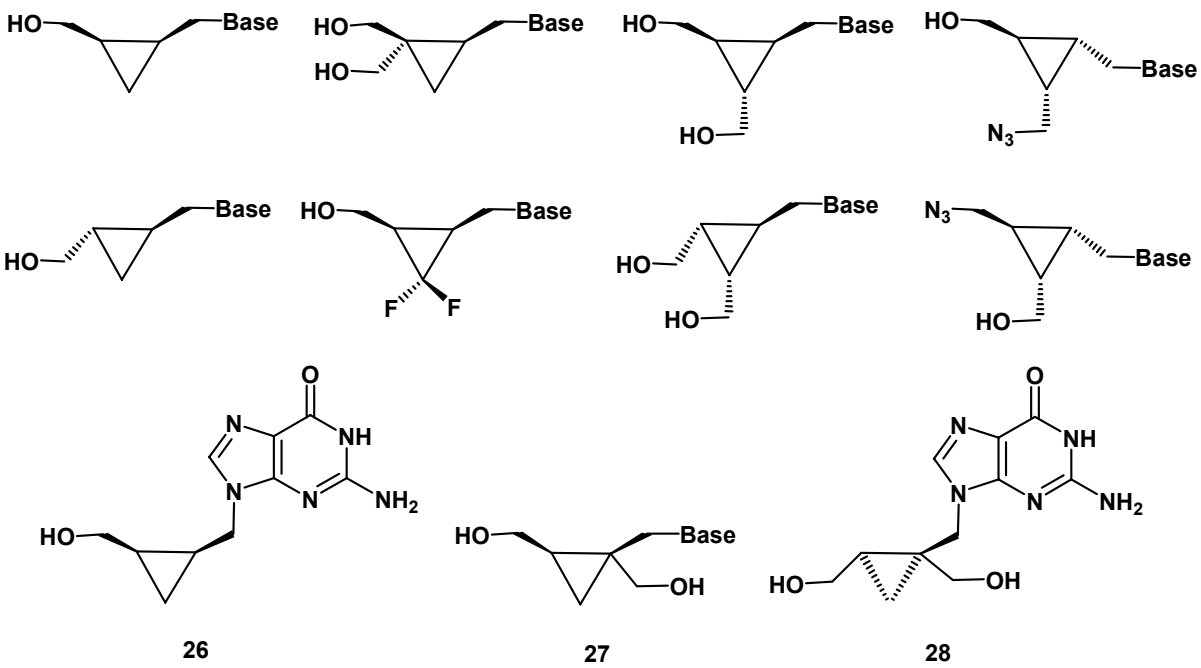
1. Three-membered carbocyclic nucleosides:

There are three major types of three-membered carbocyclic nucleosides: a) Base moiety connected to the carbocyclic ring through methylene linkage; b) Base moiety connected directly to the carbocyclic ring; c) Base moiety connected to the carbocyclic ring through a double bond.

a. Base moiety connected to the carbocyclic ring through methylene linkage:

These analogs were designed as conformationally constrained rotamers of the carba-analogues of acyclovir. These compounds possess a methylene spacer between the nucleic bases and the cyclopropane ring. Basically, the cycloprpyl moiety was introduced into the molecule as conformational restriction on acyclic nucleosides with one or two hydroxymethyl groups mimicking the 3'- and/or 5'hydroxyl groups of the 2'-deoxyribose. The adenine and guanine analogues are good substrates for HSV-1 thymidine kinase, while the thymidine analogues are poor substrates. Among these carbocyclic analogs compounds **26**, **27** and **28** are reported to exhibit strong antiviral activity (Figure **7**).[20]

Figure 7:

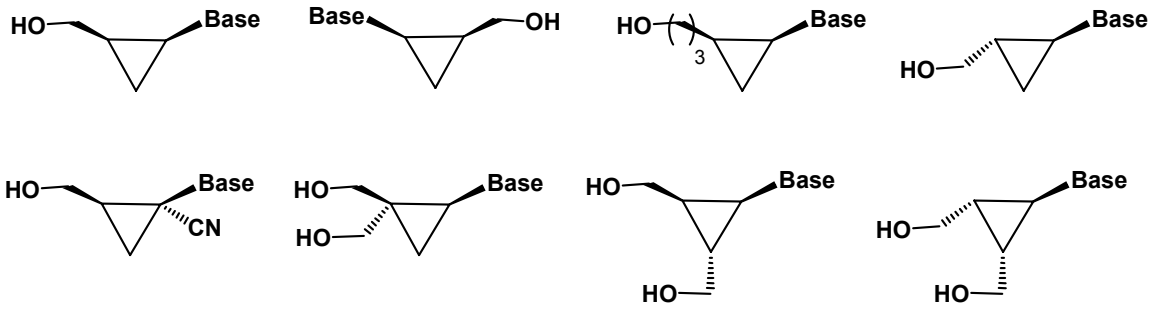


26 **27** **28**

b) Base moiety connected directly to the carbocyclic ring:

Although some derivatives of this type have been prepared, most of them do not exhibit significant biological activity. Previously, only racemic nucleosides were obtained as the result of achiral synthesis. The enantioselective synthesis of some cyclopropyl nucleosides was developed more recently by using natural sugar as the chiral source and both D- and L- cyclopropyl carbocyclic nucleosides were prepared in high optical purity (Figure **8**).[21]

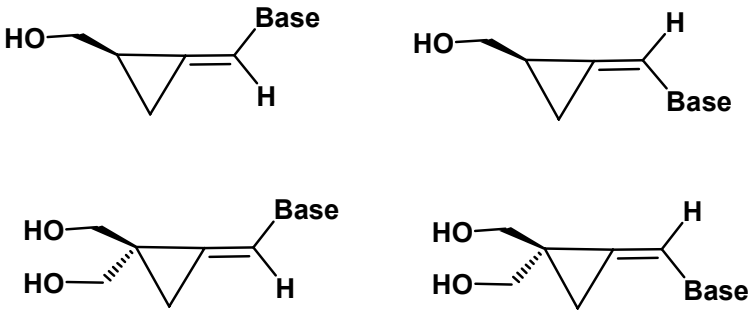
Figure 8:



c) Base moiety connected to the carbocyclic ring through a double bond:

The design of these compounds was based on a popular viewpoint that introducing a rigid structural element into the nucleoside or carbocyclic nucleoside can lead to effective antiviral analogues. A double bond was introduced as a linker between the heterocyclic base and the cycloproply ring. These molecules are structurally related to saturated cyclopropylmethyl nucleosides analogues shown in Figure **7**, but they are considerably more rigid. Because of the similarity of a single double bond and cyclopropane ring, they can also be regarded as analogues of adenallene and cytallene, which are good inhibitors of HIV replication (Figure **9**).[22]

Figure 9:

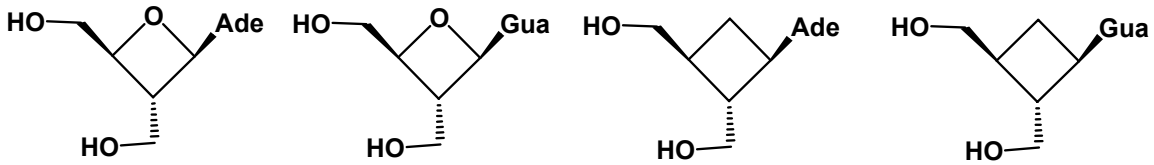


Among the first generation of this type of nucleosides, the (***Z***)-series nucleosides are named as synguanol, synadenol, syncytol and synthymol, etc. It is notable that most of the (***Z***)-carbocyclic nucleosides are more active than the (***E***)-isomers in antiviral evaluation. Synguanol was the most effective agent against HCMV, MCMV and EBV at submicromolar range but only limited potency against HSV-1 and HSV-2. Synadenol exhibited antiviral activity against HBV and VZV at micromolar concentrations. The second generation possessed the bis(hydroxymethyl)group at 4' position.[22d] Similar to the first generation series, the guanine (***Z***)-isomer showed potency against HCMV and MCMV at the submicromolar range and with no cytotoxicity.

2. Four-membered carbocyclic nucleosides:

Oxetanocin A (**29**) is the first and only known natural nucleoside with a four-membered ring. Both Oxetanocin A and its synthetic analogue Oxetanocin G (**30**), display good antiviral activity, especially against HIV.[23] The same rationale that suggested the synthesis of carbocyclic furanosyl nucleosides prompted the synthesis of cyclobutane carbocyclic nucleosides to overcome the instability of the oxetanosyl-N-glycosyl linkage. Biological evaluation of carba-oxetanocin A (**31**) and carba-oxetanocin G (**32**) show that they have excellent antiviral activity (Figure **10**).[24a]

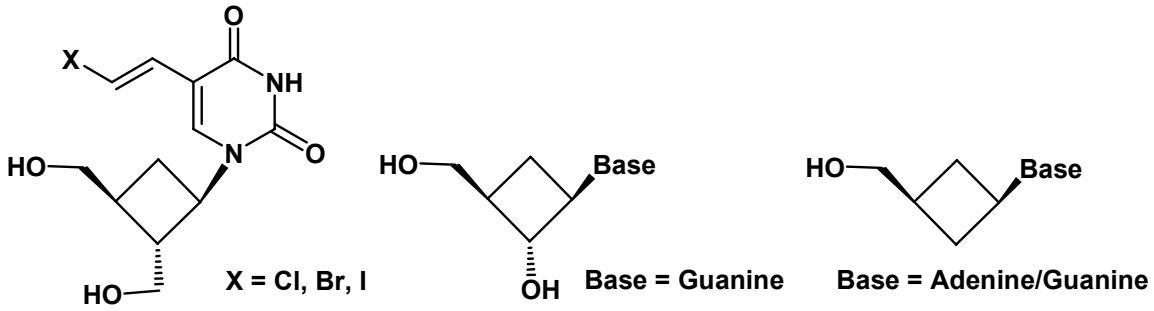
Figure 10:



Carba-oxetanocin A (**31**) is potent against VZV and HCMV. Carba-oxetanocin G (**32**) was found to possess broad-spectrum antiviral activity against several herpes viruses, including HSV-1, HSV-2, VZV, HCMV, EBV, as well as HIV.[24b] The anti-HIV activity of **32** was comparable to that of AZT.[24a] The halovinyl substitution on pyrimidine ring series, the (±)-carba-oxetanosyl-5-(halovinyl)uracil analogues **33** (X = Cl, Br, I), displayed excellent activities against VZV. The 2'-Nor-carba-oxetanocin G (**34**) is active against HSV-1, HSV-2, VZV and HCMV.[25a] Another example is the cis isomer of **35** of carba-

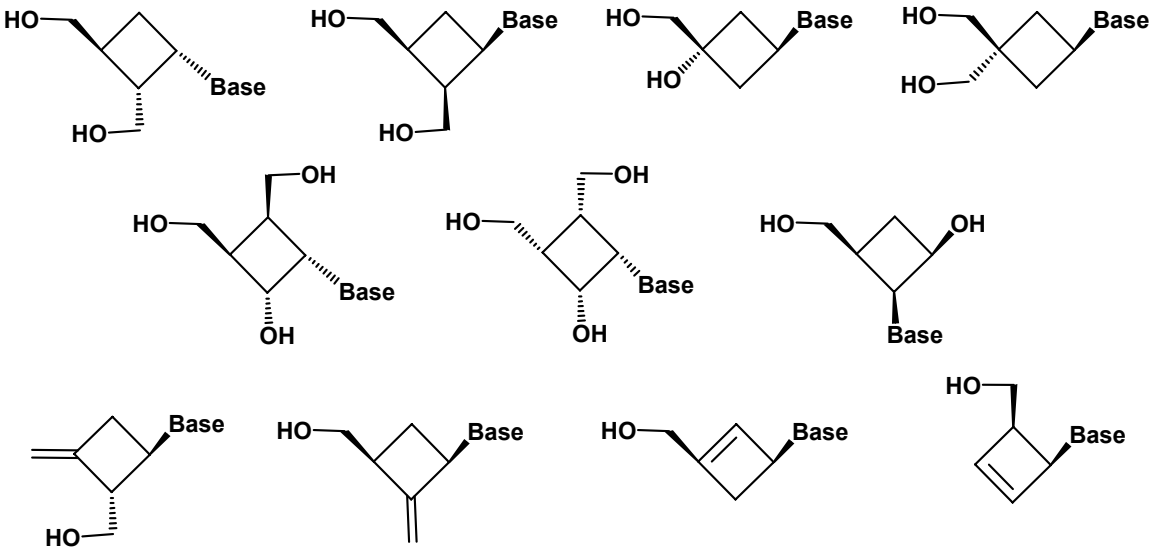
oxetanocin A/G analogues with 2'-hydroxymethyl missing is effective against HIV in MT2 and ATH8 cells (Figure **11**).[25b]

Figure 11:



Inspired by the activity of carba-oxetanocin A/G, efforts were endeavoured to synthesize related carba-oxetanosyl nucleosides with a modified cyclobutyl moiety. However, most of the modified compounds gave only poor or weak antiviral activity (Figure **12**).

Figure 12:



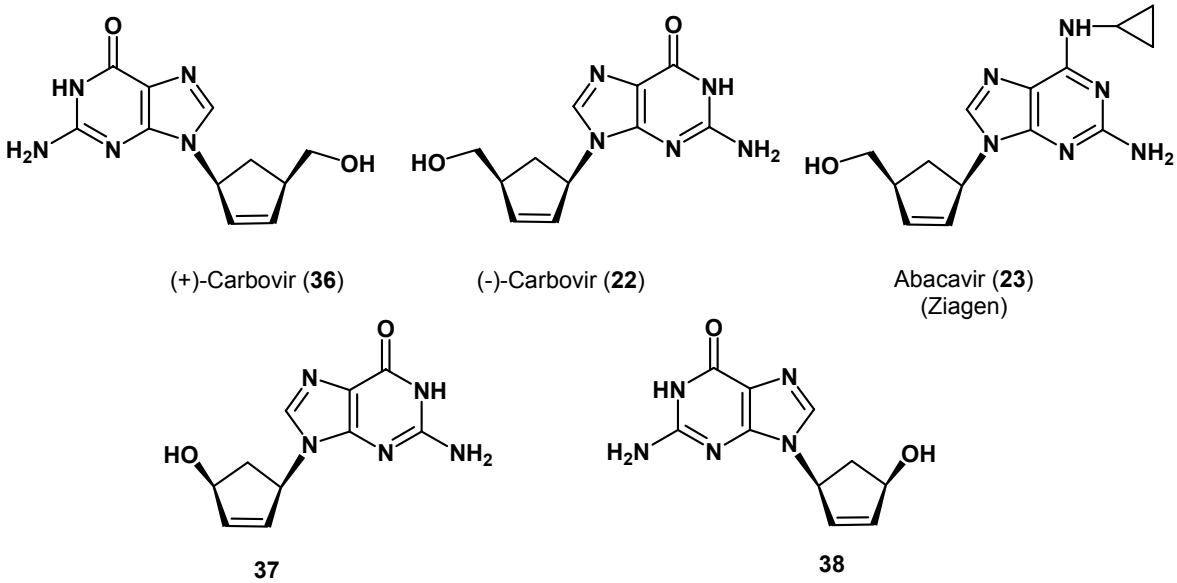
3. Five-membered carbocyclic nucleosides:

Carbovir and related carbocyclic nucleosides:

Carbovir is a HIV reverse transcriptase inhibitor and was reported for the first time by Vince et al in 1988.[26a] Carbovir belongs to the family of 2′,3′-dideoxy carbocyclic nucleosides. The two enantiomers of (±)-carbovir were resolved by the adenosine

deaminase (ADA) catalyzed deamination of racemic 2,6-diaminopurine analogue. The activity of inhibiting HIV replication in MT4 cells was highly enantioselective and (+)-carbovir (**36**) was found to be less active as an anti-HIV agent than (-)-carbovir (**22**) *in vitro*. The intracellular stepwise activation of carbovir converts the molecule to its triphosphate metabolite, which inhibits HIV reverse transcriptase.[26] Based on carbovir, abacavir (Ziagen) (**23**) was developed and was the first carbocyclic nucleside approved by the FDA for the treatment of HIV infection in adults and children. The fascinating antiviral potency of carbovir and abacavir triggered an explosive effort to prepare and investigate carbovir derivatives. Among the all other derivatives, (-)- and (+)-5′-Norcarbovir (**37**), (**38**) and their corresponding triphosphates have been reported to possess better potency against HIV-RT than triphosphate of (-)-carbovir (Figure **13**).

Figure 13:

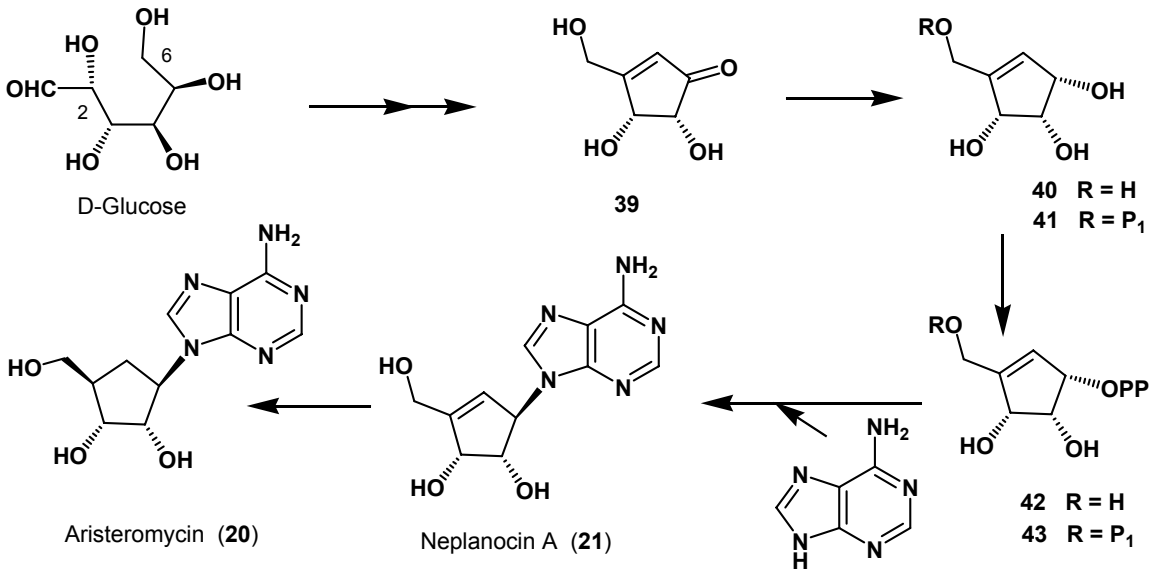


Aristeromycin, Neplanocin A and related carbocyclic nucleosides:

Aristeromycin (**20**) and neplanocin A (**21**) are naturally occurring carbocyclic nucleosides having broad-spectrum antiviral and antitumor activity. The proposed biosynthetic pathway suggests that neplanocin A is the direct precursor of aristeromycin and the carbocyclic ring is derived from D-glucose.[27] The central feature of this pathway is a linear route from the enone **39** to **20** without bifurcation. Reduction of the enone **39** to the tetrol **40** followed by activation at C1 would lead to the pyrophosphate **42** (these conversions may proceed via the phosphates **41** and **43**). Allylic displacement at C1 of **42**

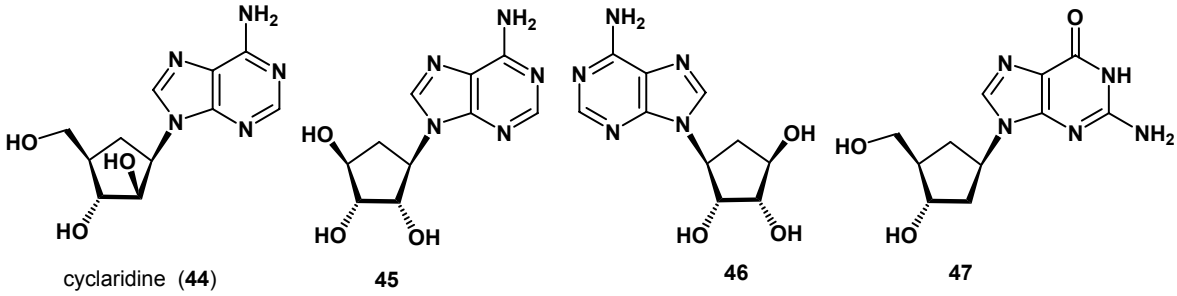
or **43** introduces the adenine base, yielding **21**, which undergoes reduction to **20** (Scheme **1**).

Scheme 1:



Quite a number of analogues of aristeromycin and neplanocin A were synthesized and some showed very promising antiviral activity. The carba-ara-adenosine (cyclaradine) (**44**),[28] carba-N6-methyl and 3-deaza and 8-aza adenosine are found to be good inhibitors of S-AdoHcy-ase and this activity correlated with their antiviral effect against vaccinia virus (VV). (-)-5'-Noraristeromycin (**45**) was found to have a broad-spectrum antiviral activity similar to other carbocyclic adenosine analogues that target S-AdoHcy-ase. (+)-5'-Noraristeromycin (**46**) showed favorable activity against HBV (Figure **14**).

Figure 14:



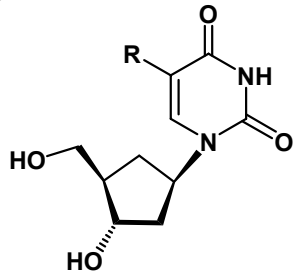
Neplanocin A analogues, such as cytidine analogue, 3-deaza-neplanocin A, (6'R)-6'-C-methyl neplanocin A (RMNRA),[29a] (6'R)-6'-C-ethylnyl neplanocin A (RENPA),[29b] 6'-homo neplanocin A and 2-fluoro neplanocin A[29c] displayed significant antiviral activity. Carba-2'-deoxyguanosine (**47**)[30] is very effective antiherpetic agent against HSV-1, HSV-

2, HCMV and also showed selective potency against HBV. A series of other carba-suger isosteres of guanine, 8-azaguanine or 7-deaza-guanine compounds, have also been investigated for their antiviral potentials. With the carba-ara configuration, only the 2,6-diaminopurine analogue displayed anti HSV-1 activity. With the carba-xylo configuration, both guanine and 8-azaguanine analogues exhibited relatively broad antiherpetic activity against HSV-1, HSV-2, HCMV and VZV. The carba-lyxo configuration guanine analogue showed significant potency against HSV-1 and HCMV. The 7-deaza-guanine carbocyclic nucleosides with carba-ribo, carba-ara, carba-lyxo sugar moiety have also been synthesized and are proved to be effective against HSV-2.[31]

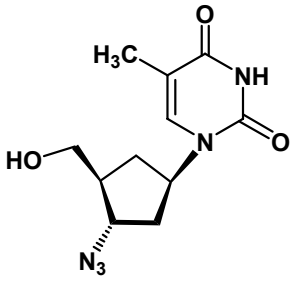
Five-membered carbocyclic pyrimidine nucleosides:

(±)-Carba BVDU (**48**) and carba-IVDU (**49**) are found to inhibit the replication of HSV-1 in primary rabbit kidney cells,[32a] but were less potent than parent nucleosides. Other carbocyclic uracil derivatives, such as carba-5-ethyl-2'-deoxyuridine (**50**) (carba-EDU), carba-5-fluoro-dUrd, carba-5-iodo-dUrd, etc were synthesized but showed only weak or moderate antiviral or antitumor activities. Carbocyclic thymidine (**51**) (C-Thy)[32b] displayed modest and reproducible activity against L1210 leukemia *in vivo*. 3'-Deoxy-3'-azido-1'-carba-thymidine (**52**) (carba-AZT)[32c] was found not to be active against HSV-1 or HSV-2 and contrary to AZT, this compound was totally devoid of anti-HIV activity (Figure **15**).

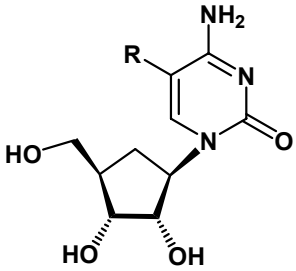
Figure 15:



R = CH=CH-Br, carba-BVDU **48**
R = CH=CH-I, carba-IVDU **49**
R = CH_2CH_3, carba-EDU **50**
R = CH_3, carba-thymidine **51**



52



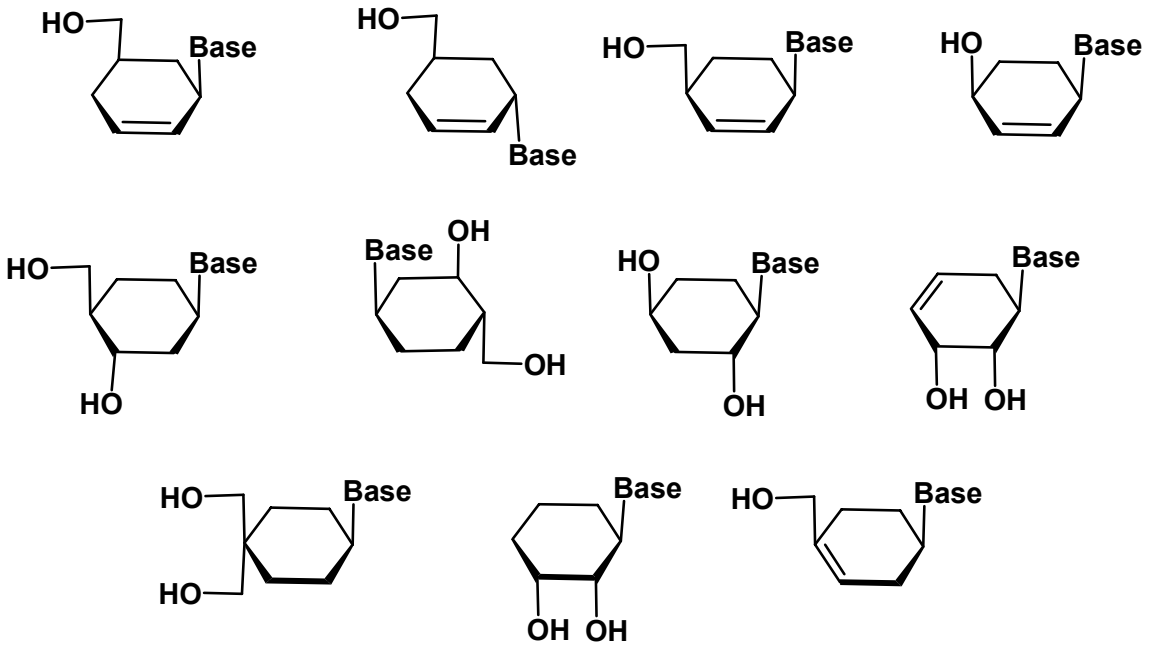
R = H, carbodine **53**
R = Br, I **54**

The carbocyclic cytidine analogues exhibited significant antiviral and antitumor activity when compared to their uridine counterparts. Carba-cytidine (**53**) (carbodine), 2'-deoxy-carbodine, carba-ara-cytidine, and their corresponding 5-halo (Br, I) derivatives **54**, demonstrated to be very effective against HSV-1 in vero cells.[32d]

4. Six-membered carbocyclic nucleosides:

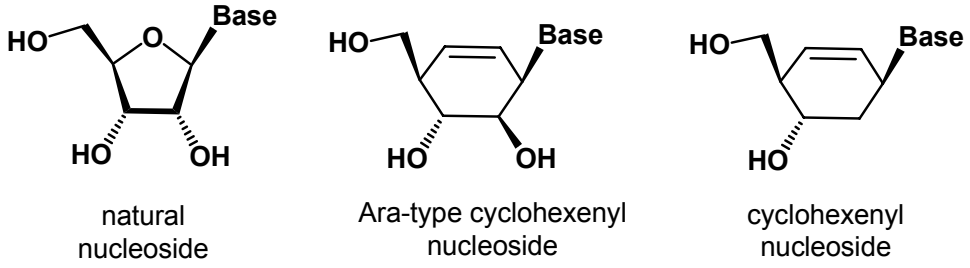
In the literature, several cyclohexane and cyclohexene carbocyclic nucleosides as well as some unsaturated hexitol nucleosides have been described.[33] However, none of the cyclohexane compounds showed antiviral activity (Figure **16**). For those cyclohexene and unsaturated congeners, only weak activity was observed.

Figure 16:



Recently, a new type of cyclohexenyl nucleosides, the oxygen atom in the furanose nucleoside is replaced with a C=C moiety, emerged as potential antiviral agents (Figure **17**).[34] Such compounds are considered to be the conformationally flexible analogues of the

Figure 17:



natural nucleoside | Ara-type cyclohexenyl nucleoside | cyclohexenyl nucleoside

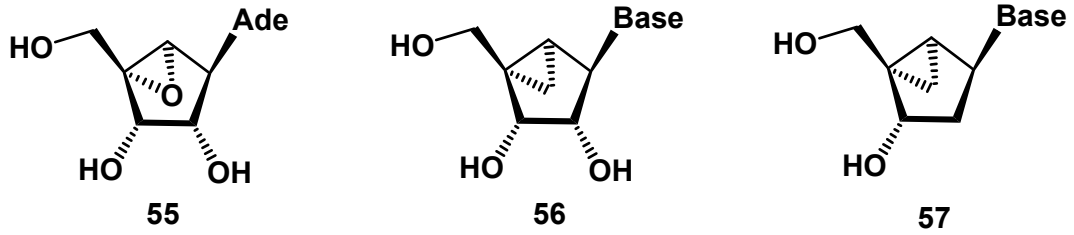
natural nucleosides and they are expected to establish the conformational preference of the nucleosides for different enzymes involved in their metabolic activation and biological

function. Both D- and L-cyclohexenyl-guanines exhibited potent and selective anti-herpes virus (HSV-1, HSV-2, VZV, CMV) activity.[34e]

5. Bicyclic carbocyclic nucleosides:

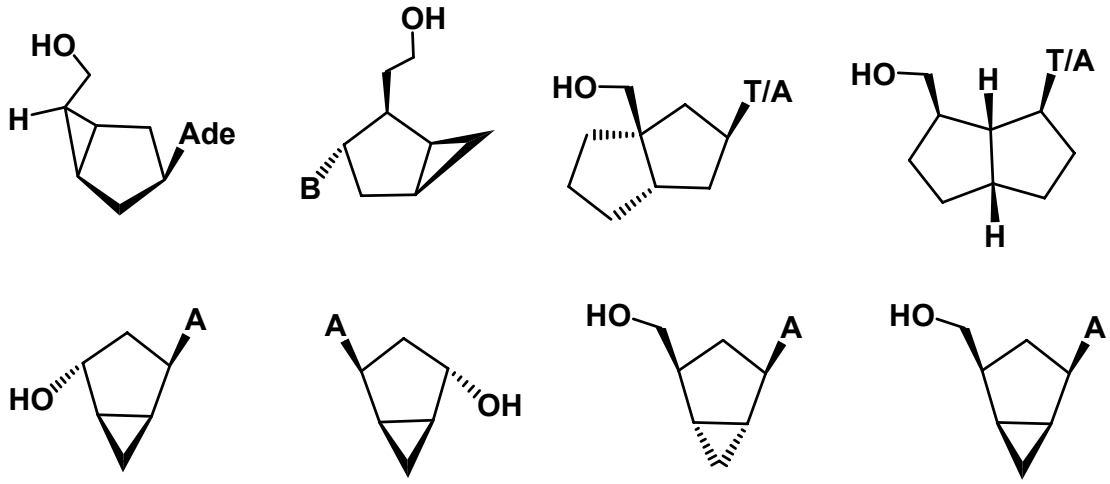
Inspired by the natural occurring bicyclic carbocyclic nucleoside, neplanocin C (**55**), a series of conformationally equivalent bicycle[3,1,0]hexane systems were synthesized and evaluated for their inhibitory effects on S-adenosylhomocysteine hydrolase(S-AdoHcy-ase) or for anti-HIV activity. Only the adenine analogue of **55** showed considerable activity (Figure **18**).[35a]

Figure 18:



Other carbocylic nucleosides built on varied bicyclic systems have also been reported. The series of 2',3'-endo- and exo-methanocarba purine analogues were synthesized and some compounds showed modest to good activity against HSV-1 compared to acyclovir (Figure **19**).[35b,c]

Figure 19:



Synthesis of carbocyclic nucleosides:

There are two fundamental approaches for the construction of carbocyclic nucleosides: 1) Convergent coupling of an intact heterocyclic base with an appropriately functionalized carbocyclic ring by substitution. 2) Linear construction of the heterocycle base with an amine substituent on the functionalized carbocycle.

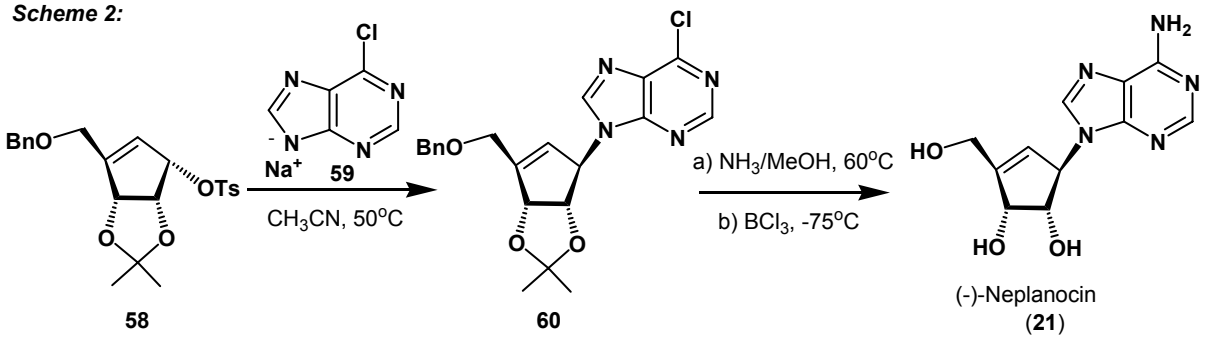
1. Coupling of the heterocyclic base with carbocyclic pseudo sugar:

Direct substitution can be accomplished by several methods: a) nucleophilic displacement of a halide ion or activated hydroxyl (mesylate, tosylate, or triflate); b) by a Mitsunobu reaction with a cycloalkanol; c) ring opening of an epoxide or cyclic sulfate; d) Michael addition to an activated olefin; e) palladium catalyzed displacement of an allylic ester or carbonate.

a. Nucleophilic displacement of a halide ion or activated hydroxyl group:

Carbocyclic halides, mesylates, tosylates and triflates have been utilized in direct S_N2 displacements by the heterocycle bases. Marquez et al[36] reported the first synthesis of a carbocyclic nucleoside by coupling of a heterocycle moiety to a tosylate of fuctionalized cyclopentane for the synthesis of (-)-neplanocin. Tosylate **58** has been prepared stereospecifically from D-ribonolactone and its coupling with the sodium salt of 6-chloropurine **59** in acetonitrile gave **60**. Ammonolysis of the chloro group and deprotection of the hydroxyl groups gave (-)-neplanocin (**21**)(Scheme 2).

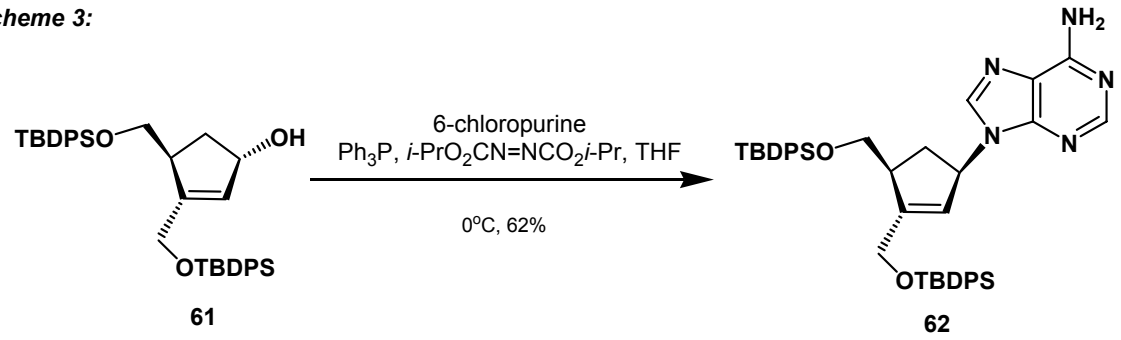
Scheme 2:



b. By Mitsunobu reaction:

One of the most useful and common methods for the coupling of the carbocylic sugar and the heterocyclic base is the Mitsunobu reaction.[37a] Activation of a hydroxyl by a complex formed from an azodicarboxylate and triphenylphosphine faciles the direct substitution of the alcohol and the reaction takes place with an inversion of the configuration (Scheme 3).[37b,c]

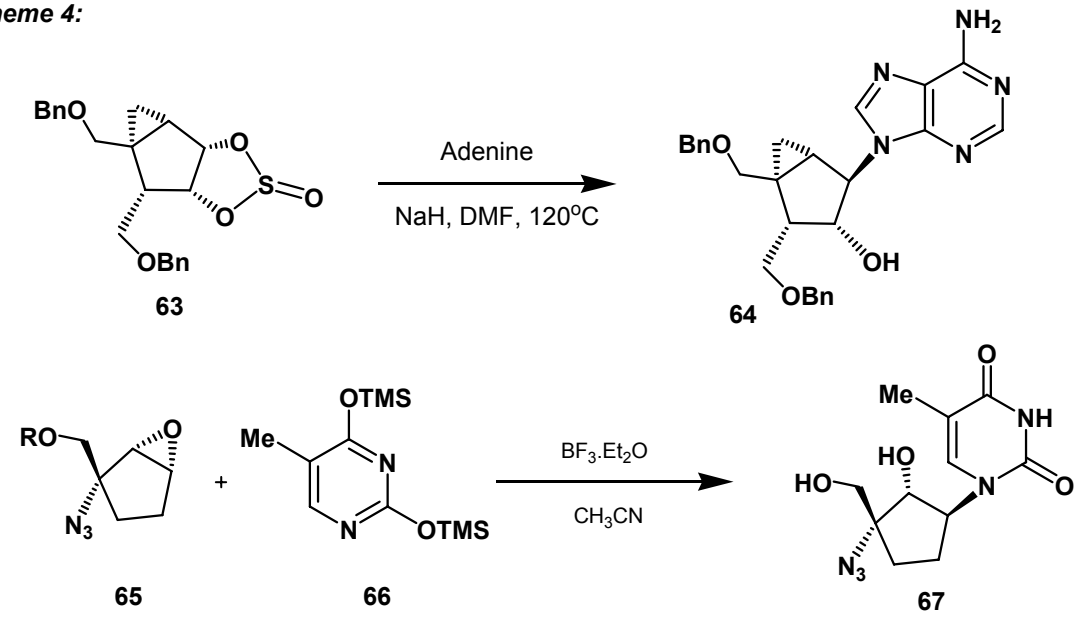
Scheme 3:



c. Ring opening of an epoxide or cyclic sulfate:

Epoxides, cyclic sulfates and sulfites are useful electrophiles for the coupling of the heterocylic base with carbocycle moiety for the synthesis of carbocyclic nucleosides as shown in Shceme 4.[38]

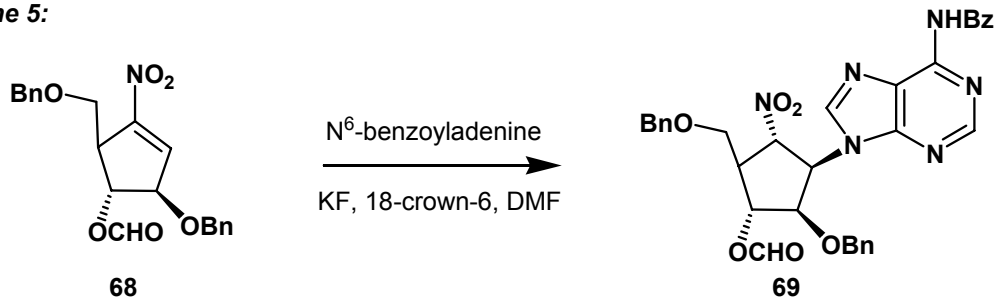
Scheme 4:



d. By Michael addition to an activated olefin:

Kitagawa et al.[39] have developed a new synthetic approach for carbocycles by utilizing the Michael addition of a purine to a nitrocyclopentene derivative **68** prepared from D-glucose as shown in Scheme 5.

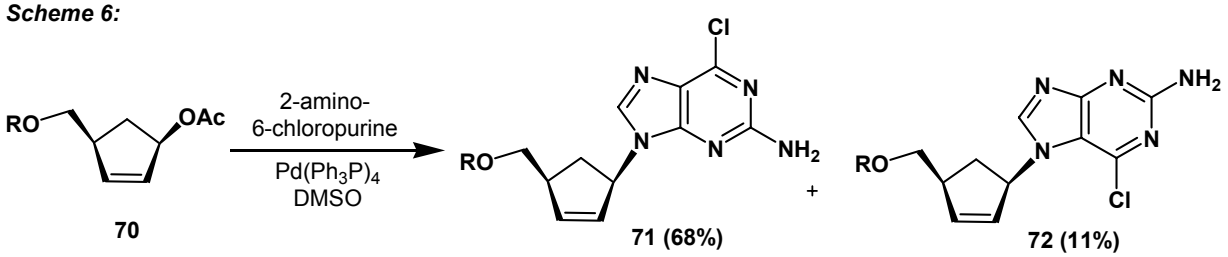
Scheme 5:



e. Palladium catalyzed displacement of an allylic ester or carbonate:

Palladium (0) catalyzed substitution of allylic esters and carbonates, developed by Trost,[40a] is highly useful strategy for the convergent coupling of heterocyclic base with the carbocycle moiety in which the heterocyclic anion attacks at the sterically more accessible end of the allyl metal complex with retention of configuration. This reaction has been widely employed in carbocyclic nucleoside synthesis and particularly for dideoxy analogs such as carbovir and abacavir (Scheme 6).[40b]

Scheme 6:



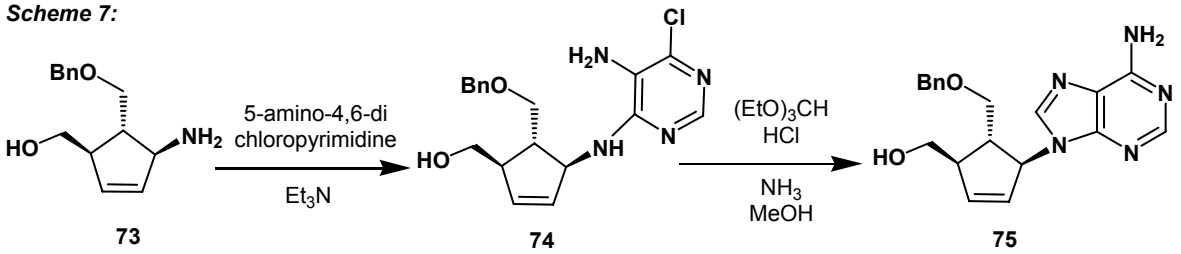
2. Linear construction of the heterocycle base from an aminocarbocycle:

The amino group on the carbocycle is used to construct a heterocycle purine or pyrimidines and amino group becomes the N9 of a purine moiety or the N1 of a pyrimidine.[41]

Synthesis of purines:

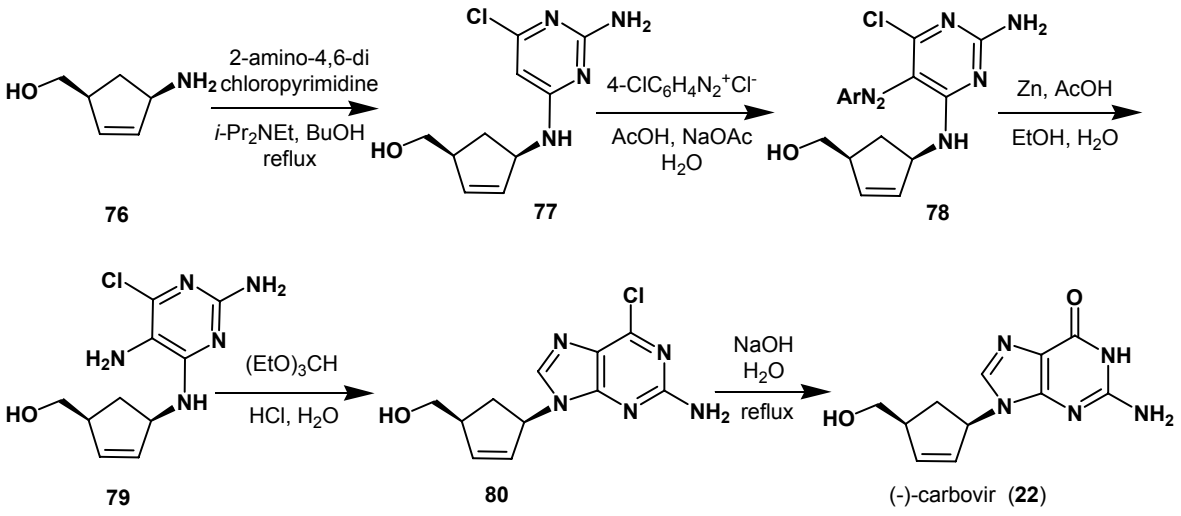
The synthesis of adenine derivatives is accomplished by reaction of a functionalized cycloalkylamine, for example **73**, with 5-amino-4,6-dichloropyrimidine to prepare the cycloalkylaminopyrimidine **74** which can be condensed with triethyl or trimethyl orthoformate to provide the 6-chloropurine. Displacement of the chlorine with ammonia provides the adenine derivative **75** (Scheme 7).[41b]

Scheme 7:



Guanines can also be synthesized in a similar sequence by the reaction of the cylcoalkylamine, for example **76** with 2-amino-4,6-dichloropyrimidine to give the cycloalkylaminopyrimidine **77** followed by the reaction with 4-chlorobenzene diazonium chloride to get **78**, which upon reduction with zinc provides the diaminopyrimidine **79**. The diaminopyrimidine **79** is then condensed with triethylorthoformate in the presence of acid to get 2-amino-6-chloropurine **80** and finally displacement of the chloride group with aqueous base completes the construction of the guanine derivative carbovir **22** (Shceme 8).[41c]

Scheme 8:

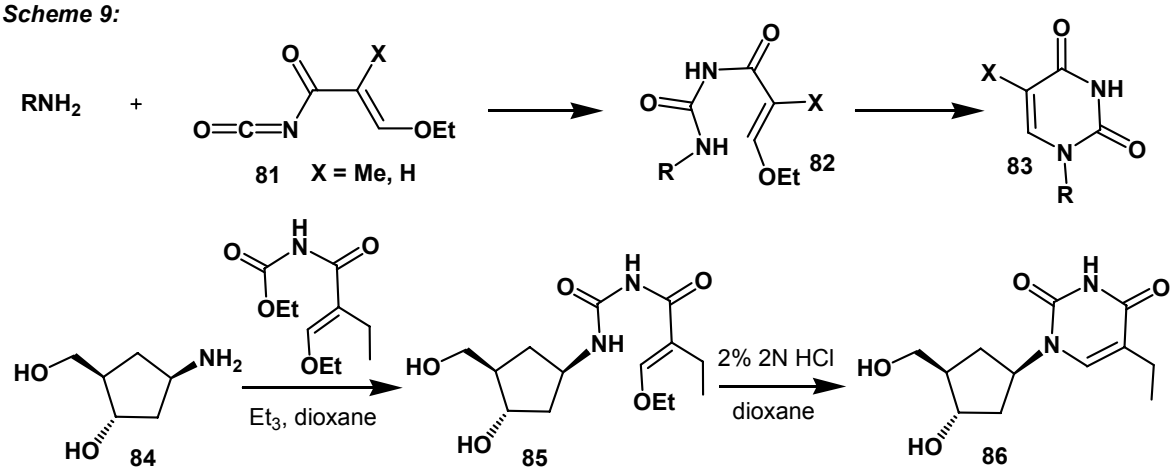


Synthesis of pyrimidines:

Shaw and Warrener[41e,f] developed an efficient method for the synthesis of pyrimidines from isocycanates. Isocyanate **81** reacts with a cyclopentylamine RNH_2 to give an acryloylurea intermediate **82**, which on treating with acidic or basic conditions provide cyclic compound **83**. When X = H in **83**, the heterocycle will be uracil, and when X = Me, it will be thymine. Pyrimidines can also be prepared by the reaction of a cycloalkylamine **84** with 3-ethoxy-N-carboethoxy-2-ethylacrylamide to give acryloylurea

intermediate **85** which can be readily converted to the pyrimidine **86** by an acid or base catalyzed addition-elimination. A variety of substituents can be incorporated at the 5-position of the pyrimidine by this approach (Scheme 9).[41d]

Scheme 9:



PRESENT WORK

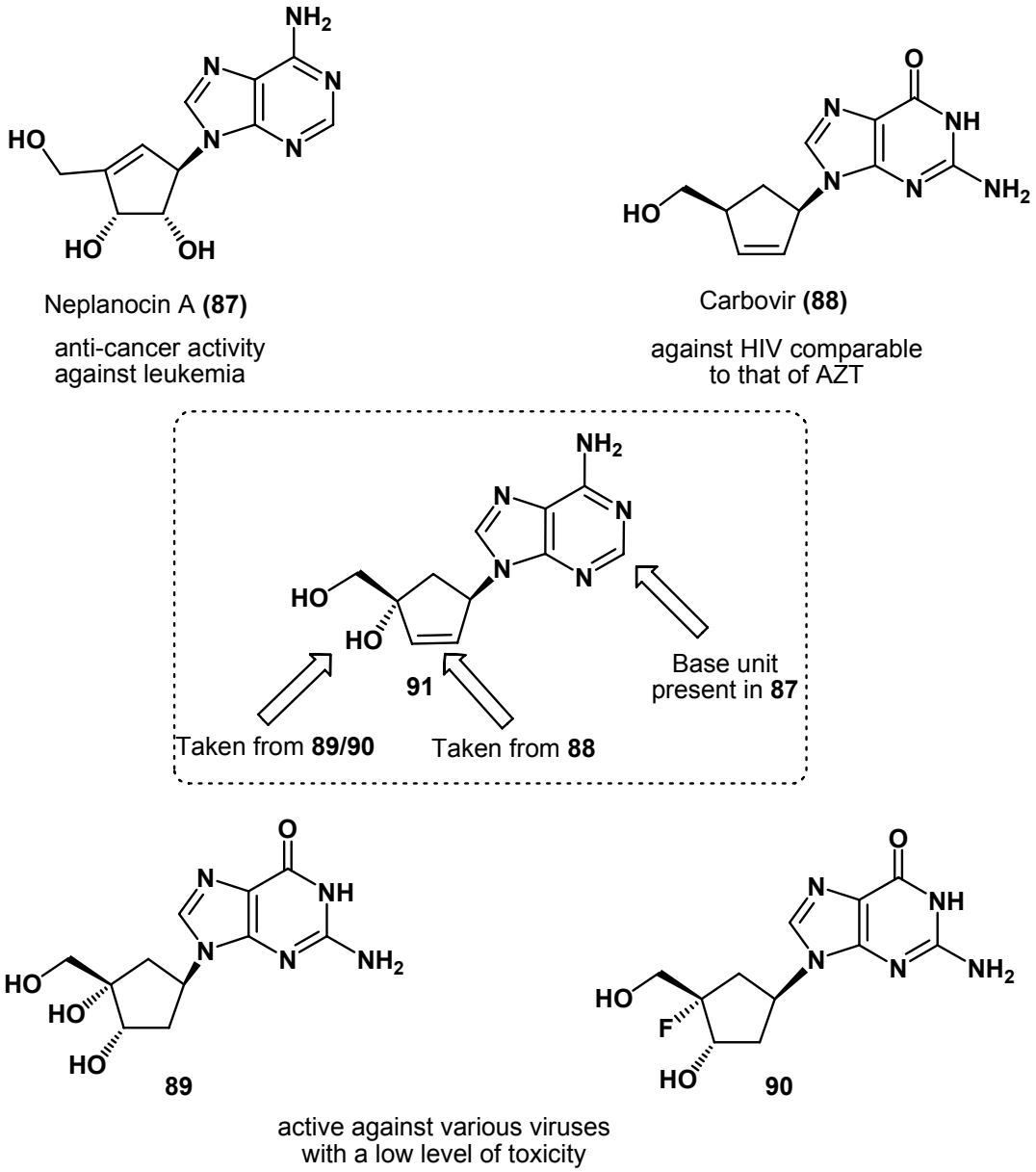
In the recent years nucleoside analogues have been investigated as potential anti-viral, fungicidal, and anti-cancer agents and especially in the search for agents effective against the Human Immunodeficiency virus (HIV), the causative agent of the AIDS epidemic. In this process several derivatives of natural nucleosides have been identified and used for the treatment of HIV. However, the major disadvantage with either natural nucleosides or their analogues is: they are also substrates for phosphorylases, enzymes that cleave the N-glycosidic bond between the heterocycle moiety and the sugar.[15,16] In order to avoid these enzymatic degradations and to improve the antiviral activities of nucleosides, a great number of modifications have been carried out on both the sugar and the heterocycle. The replacement of the oxygen of the furan ring by a methylene group, leads to the synthesis of carbocyclic analogs of nucleosides. While the carbocyclic analog of adenosine was first described by Shealy and Clayton in 1966,[17] however, it was the discovery that the natural carbocyclic nucleosides aristeromycin and neplanocin A display antibiotic and antitumor activity which sparked the search for other carbocyclic nucleoside analogs as potential anti-viral agents.[18]

Carbovir, Abacavir, BCA as well as Cyclobut belong to the family of carbocyclic nucleosides,[19] are discovered and introduced recently in the market for the treatment of HIV infected patients. The promising biological profile of carbocyclic nucleosides coupled with the need for effective treatment for other viral infections, in particular Herpes Simplex virus (HSV types 1 and 2), Varicella Zoster virus (VZV), Cytomegalovirus (CMV) and Epstein-Barr virus (EBV), which can prove lethal to AIDS patients, provided tremendous impetus in the major pharma companies all over the globe to search for new family members. This has resulted in an explosion of synthetic activity in the field of carbocyclic nucleosides and the filing of several derivatives with potential anti-viral activity.

In search of new carbocyclic nucleosides, a careful analysis of the structural features of some medicinally important carbocyclic nucleosides **87 – 90** has been carried out. The potent biological activities of these carbocyclic nucleoside analogs prompted us to design a novel carbocyclic nucleoside (**91**) resulting from integrating the important

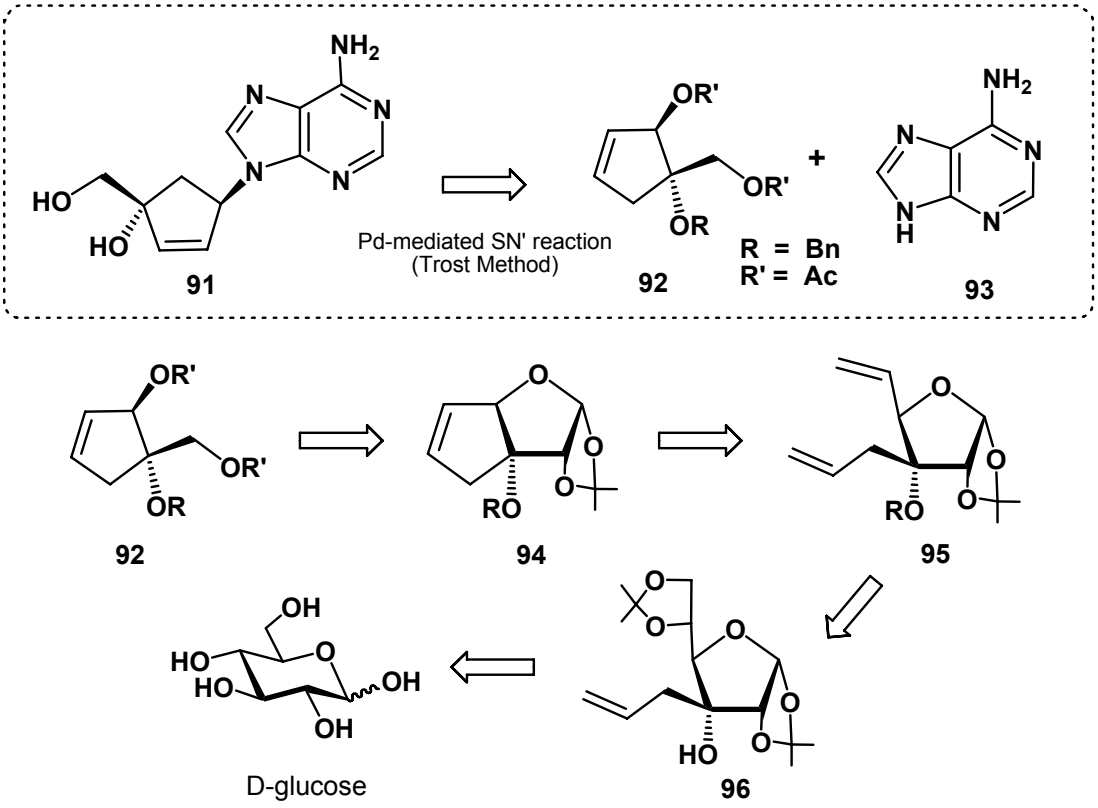
structural features of **87** – **90** in anticipation of exhibiting better chemical and biological activities like **87** and **88** (Figure 1) with A desired low toxicity levels as noticed with **89** and **90**. A cartoon picture representing the functional and structural similarities between **91** and **87** – **90** is provided in figure 1. As indicated the adenine was selected as a nucleobase considering **87**, an endocyclic olefin between C2 and C3 is taken from **88**, a 3°- hydroxyl group from **89** and **90**.

Figure 1:



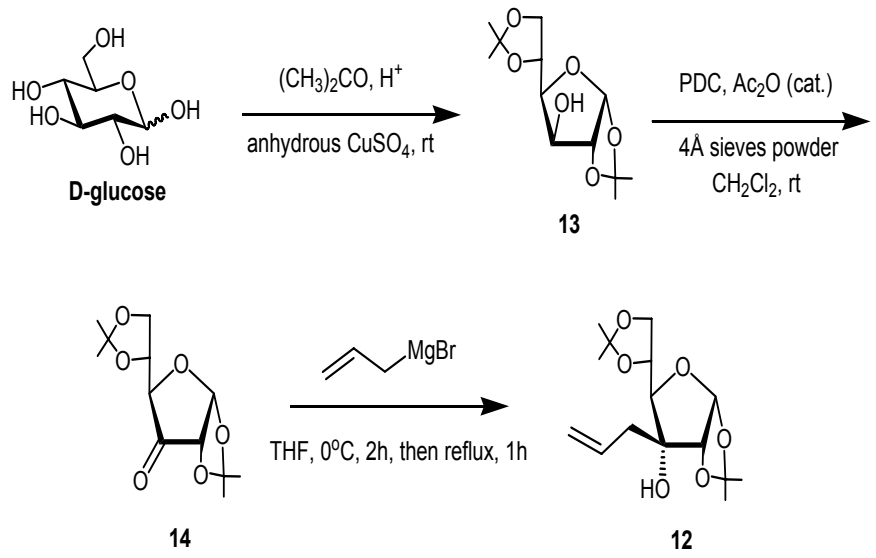
After designing a novel carbocyclic nucleoside derivative, now the objective was set to draw a flexible synthetic strategy that should address the synthesis of **91** along with related analogues if required. The key issues in the synthesis of the designed nucleoside **91** will be installation of the quaternary center and C1-N-Base bond in a stereo- and enantioselective manner. To address the issue of installing the key nucloside bond in a stereoselective fashion we have opted for a Pd-mediated SN' reaction (a successful methodology pioneered by Professor Trost) on a cyclopentene derivative **92** using adenine (**93**) as the nucleophile. Following retrosynthetic analysis warranted for a successful synthesis of tricyclic compound **94**, the key intermediate. A chiral pool approach using glucose diacetonide as the starting point and ring closing metathesis as the key reaction were selected to address the enantioselective construction of the advanced building block **94**. To achieve the same, 1,2:5,6-Di-*O*-isopropylidene-3-C-prop-1-enyl-α-D-allofuranose **96** was identified as potential precursor, which can be obtained from D-Glucose in 3 steps.[42] Scheme-1 saliently describes the intended retrosynthetic strategy for the designed carbocyclic nucleoside **91** based on the revelations as delineated above.

Scheme 1: Retrosynthetic analysis



Synthesis of the key cyclopentene unit **92** started with conversion of the D-Glucose into 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (**97**) by following the known procedure by treating glucose in acetone with anhydrous $CuSO_4$ in the presence of

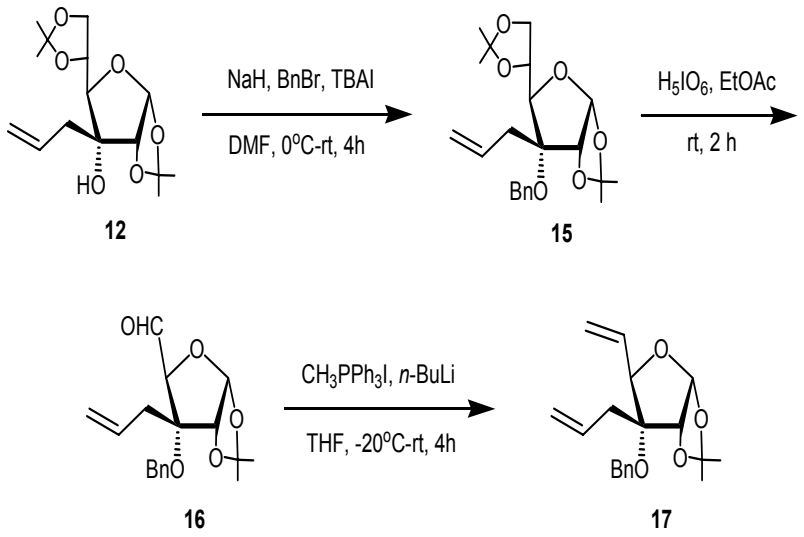
Scheme 2:



catalytic H_2SO_4. Subsequent oxidation of free OH group at C-3 was carried out using PDC in presence of 4Å molecular sieves powder and Ac_2O (cat.) in anhydrous CH_2Cl_2 to afford 1,2:5,6-di-*O*-isopropylidene-α-D-*ribo*-hexofuranos-3-ulose (**98**). Allylation of the ketone **98** was accomplished by Grignard reaction on treatment with allylmagnesium bromide in refluxing THF for 2h to furnish allyl alcohol **96** (Scheme 2). The ^1H and ^{13}C NMR spectral data and optical rotation value of **96** were in agreement with reported values.[42]

The free hydroxyl group present in the allyl alcohol derivative **96** was protected as its benzyl ether **99** using NaH, BnBr and TBAI in DMF. The ^1H NMR spectrum of **99** displayed resonances due to aromatic protons at δ 7.31 as a multiplet while benzylic protons resonated at δ 4.77 as an ABq (J = 12.6 Hz). In order to obtain the required diene derivative **95** for the ring closing metathesis, 5,6-acetonide group was subjected to selective oxidative cleavage using H_5IO_6 in EtOAc at room temperature to afford an aldehyde **100**,[43] followed by one carbon Wittig homologation[44] using methylenetriphenylphosphorane (CH_2=PPh_3) in THF (Scheme 3). The ^1H NMR spectrum

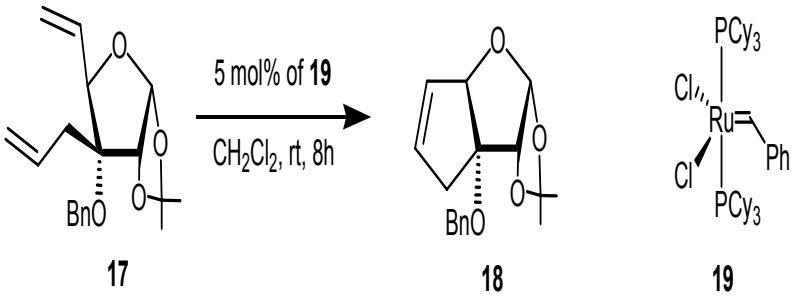
Scheme 3:



12 **15** **16** **17**

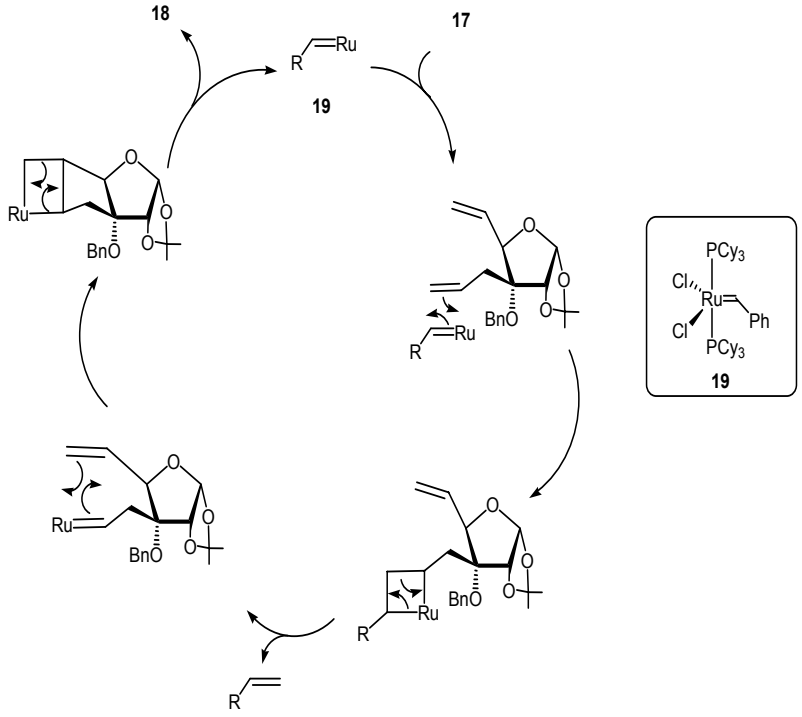
of **95** displayed signals due to olefinic protons as multiplets between δ 5.14-5.52 (4H) and at δ 5.95 (2H). And all the other protons appeared at their expected chemical shift values. The ring closing metathesis of the diene **95** was performed with 5 mol% of Grubbs' 1st generation catalyst [$(PCy3)_2Cl_2Ru$=CHPh] (**101**) in CH_2Cl_2 at room temperature to obtain tricyclic derivative **94** (Scheme 4).[45] In the ^{1}H NMR spectrum of **94** two olefinic protons along with H-4 resonated at δ 4.49-4.84 (3H) as a multiplet and H-1 resonated at δ 5.05 (anomeric H) as a singlet. All the other protons resonated at their expected chemical shift values. The proposed mechanism for the ring closing metathesis is outlined in Figure 2.

Scheme 4:



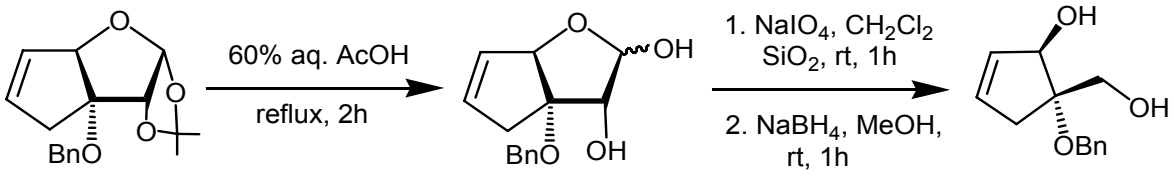
17 **18** **19**

***Figure 2*:** Mechanism of ring closing metathesis



Having the compound **94** in hand, our immediate concern was the transformation of **94** into its corresponding diol derivative **103**. Thus 1,2-acetonide of **94** was first subjected to acidic hydrolysis by refluxing in 60% aq. AcOH followed by the oxidative cleavage of resulted lactol derivative **102** using silica gel supported $NaIO_4$ in dichloromethane to afford an aldehyde which was immediately reduced by treating with $NaBH_4$ in MeOH at room temperatur to furnished diol derivative **103** (Scheme 5).[46,47] The ^{1}H NMR spectrum

Scheme 5:



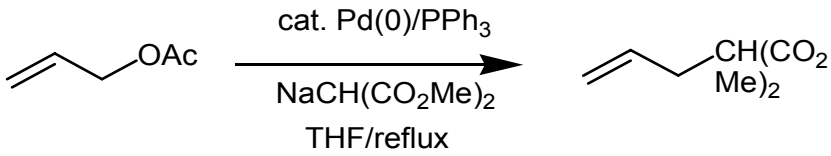
of **103** displayed signals due to olefinic protons as two multiplets at δ 5.76 (1H) and at δ 5.93 (1H). And the hydroxy methyl group appeared as a singlet at δ 3.86 (2H). After

successfully making the required carbocycle part with required functional groups, our next objective was to convert the diol derivative **103** to its diacetate derivative **92** for the evaluation of Tsuji-Trost palladium-catalyzed allylic substitution reaction[40a] with 6-amino purine (**93**).

A brief note on Pd(0) catalyzed allylic substitution reaction:

Palladium catalyzed reactions in particular have found widespread utility in a number of important chemical processes, including Stille couplings, Heck reactions, Wacker oxidation, and allylic substitution reactions which may involve C-C as well as C-X (X = H or heteroatom) bond formation. Palladium catalysed allylic substitution is a versatile process encompassing a wide range of allyl systems and their nucleophilic partners. Historically, η^3-allylpalladium complexes were first isolated and identified over 40 years ago, synthesized by the reaction of dienes with palladium(II) salts. In 1965, Tsuji demonstrated that a limited range of nucleophiles react with palladium allyl complexes, and in the early 1970's a catalytic variant was devised in which allylic alcohols reacted with amines to afford the allyl amine products. The basic process is illustrated by the reaction of allyl acetate with the sodium salt of dimethyl malonate in the presence of catalytic amounts of phosphine and palladium(O) (Scheme 6).

Scheme 6:

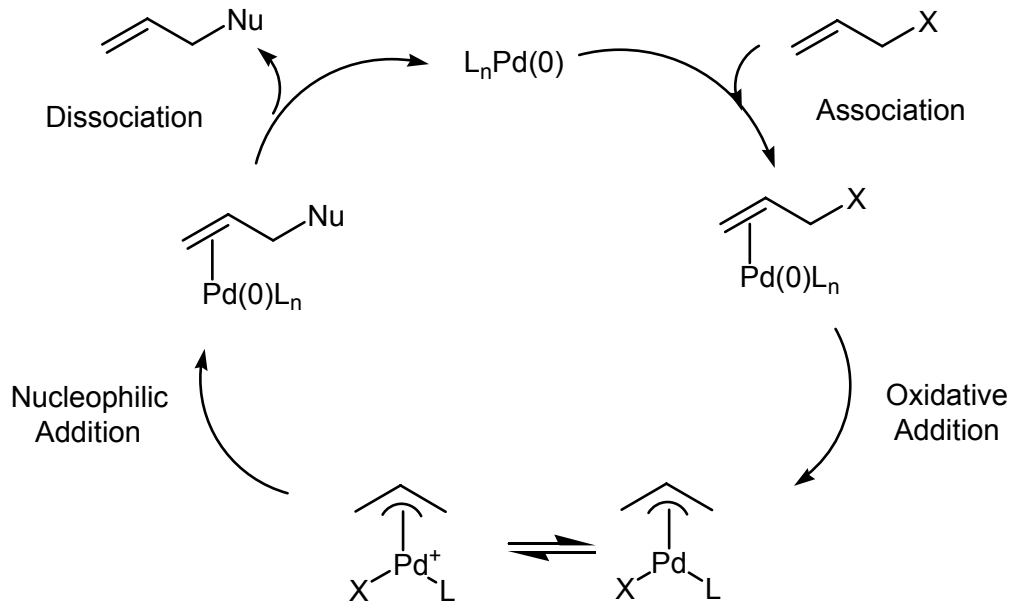


Mechanism:

The mechanism of palladium catalyzed substitution reaction involves the initial co-ordination of palladium(O) to the alkene, followed by an oxidative addition process to

afford an intermediate η^3-allyl complex. An equilibrium between a neutral and cationic complex results in the presence of phosphine and the cationic complex is favoured by the use of bidentate phosphine ligands. Nucleophilic addition to the cationic complex is favoured, and occurs at one of the allylic termini to afford the palladium(O) complex of product. Dissociation of the palladium(O) liberates the product, and regenerates the active palladium catalyst, as outlined in Figure 3.

Figure 3:



Geometry:

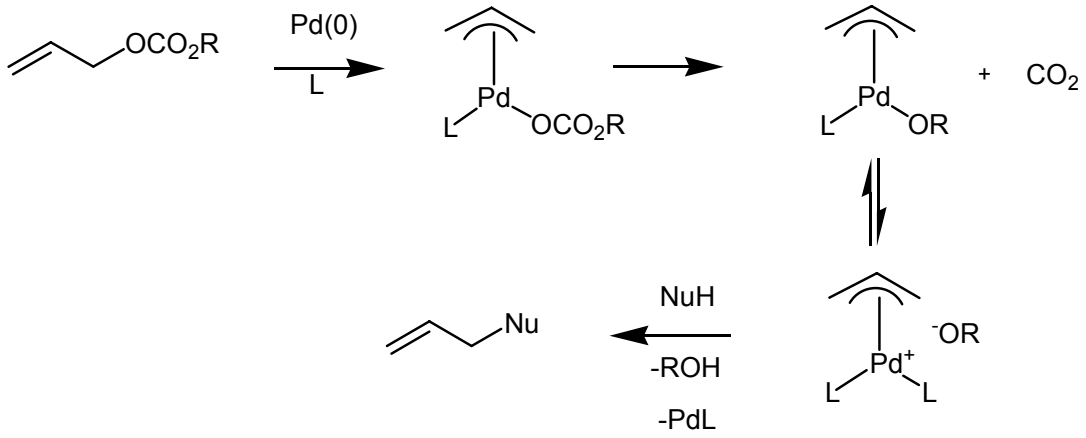
*For a mono-substituted allyl complex, between the two (**syn** and **anti**) geometric isomers, **syn** geometry is preferred. Similarly, di-substituted allyl complexes favour the **syn, syn** geometry and for more highly substituted allyl complexes, a similar geometrical preference is observed based on the steric requirements of the substituents involved. The isomeric forms are able to equilibrate by a π-σ-π mechanism (Figure 4).*

Figure 4

Substrates and Nucleophiles:

Whilst the most commonly employed substrates for palladium catalysed allylic substitution are the allylic acetates, a range of leaving groups such as halides, sulfones, carbonates, carbamates, epoxidesis and phosphates will also function effectively. The use of carbonates as leaving groups has gained in popularity since the development of these reagents by Tsuji. The initially displaced carbonate loses carbon dioxide generating an alkoxide. The alkoxide is sufficiently basic to deprotonate many of the nucleophiles employed in these reactions. The mechanism is outlined in Figure 5.

Figure 5



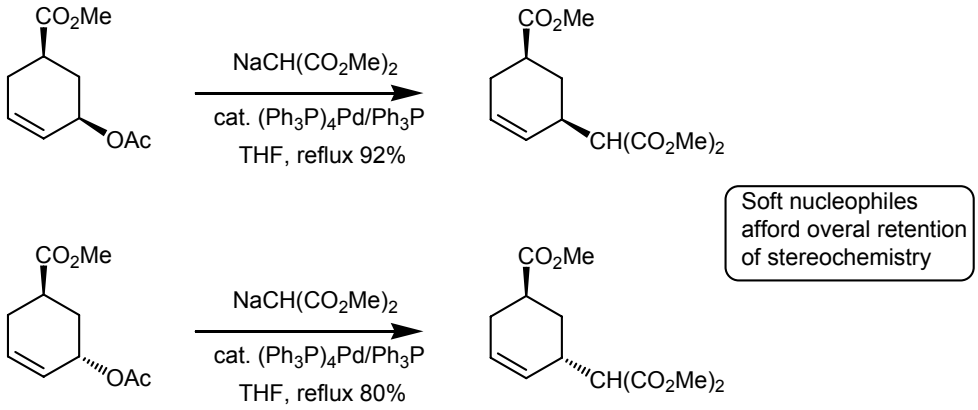
The most commonly employed nucleophiles are the 'soft' stabilized carbanions such as dimethyl malonate, but under suitable conditions, nitrogen based nucleophiles, sulfur nucleophiles, oxygen nucleophiles, phosphorus nucleophiles, silicon nucleophiles, vinyl boranes, hydrides (borohydrides / aluminohydrides and formates), tetraphenylborate,

organometallics (dialkylzincs, Grignards, organoaluminium reagents, organozirconium reagents and organotin reagents), have all been successfully employed. In the presence of carbon monoxide and suitable nucleophiles, carbonylation reactions have also been achieved.

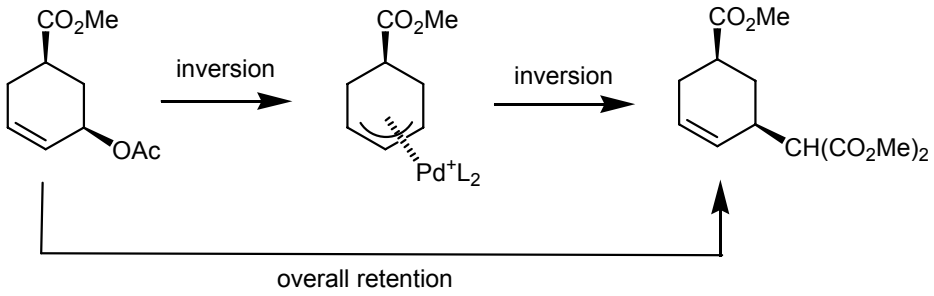
Stereoselectivity:

In the palladium catalyzed allylic substitution process, a number of elegant studies have illustrated that net retention of stereochemistry is observed for soft nucleophiles. Trost has employed the cyclohexenyl acetates as models in which the carbomethoxy group functions as a stereochemical marker. Reaction of the cis-substituted compound affords the cis-substituted product, whereas the trans-substituted compound affords the trans-substituted product (Scheme 7). Two sequential inversion steps rationalize this stereochemical outcome. The palladium displaces the leaving group with inversion, followed by the nucleophile that attacks from the exo face, again with inversion. Overall, this accounts for the observed net retention of stereochemistry (Scheme 8).

Scheme 7



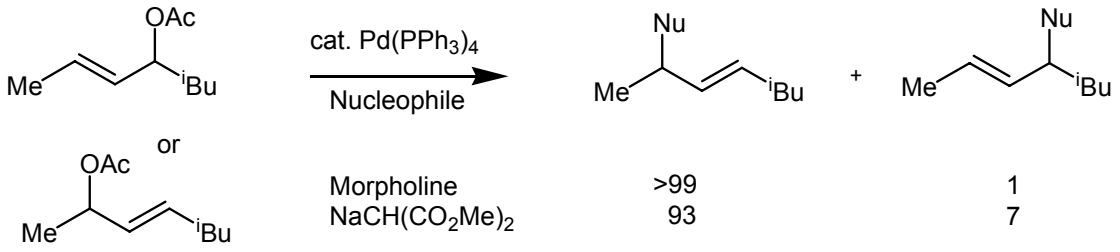
Scheme 8



Regioselectivity:

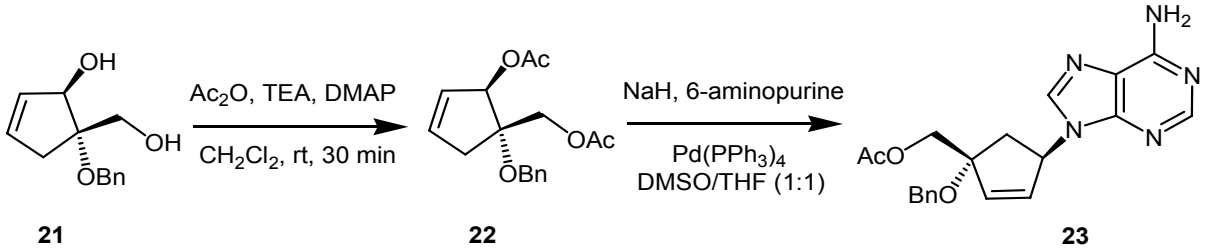
Typically, nucleophiles approach palladium complexes from the least substituted terminus, with a good level of selectivity. For example, morpholine reacts with the allyl acetates in the presence of a palladium(O) catalyst to afford a >99: 1 ratio of the products, and this regiochemical outcome is explained in terms of simple steric approach control arguments (Scheme 9).

Scheme 9



Thus, conventional acetylation of diol **103** with Ac_2O and DMAP (cat.) using Et_3N as a base afforded diacetate derivative **92**. The presence of a singlet integrating for six protons at δ 2.08 in the ^{1}H NMR spectrum of **92** indicated the presence of two acyl groups in support of the assigned structure. Convergent coupling of the carbocycle and purine base was successfully achieved by palladium catalyzed allylic ester substitution method. Thus, diacetate derivative **92** was made to react with 6-amino purine (**93**) in the presence of tetrakis(triphenylphosphine)palladium(0) and sodium hydride in DMSO:THF (1:1) to provide carbocyclic nucleoside derivative **104** as a single diastereomer (Scheme 10).[40]

Scheme 10:

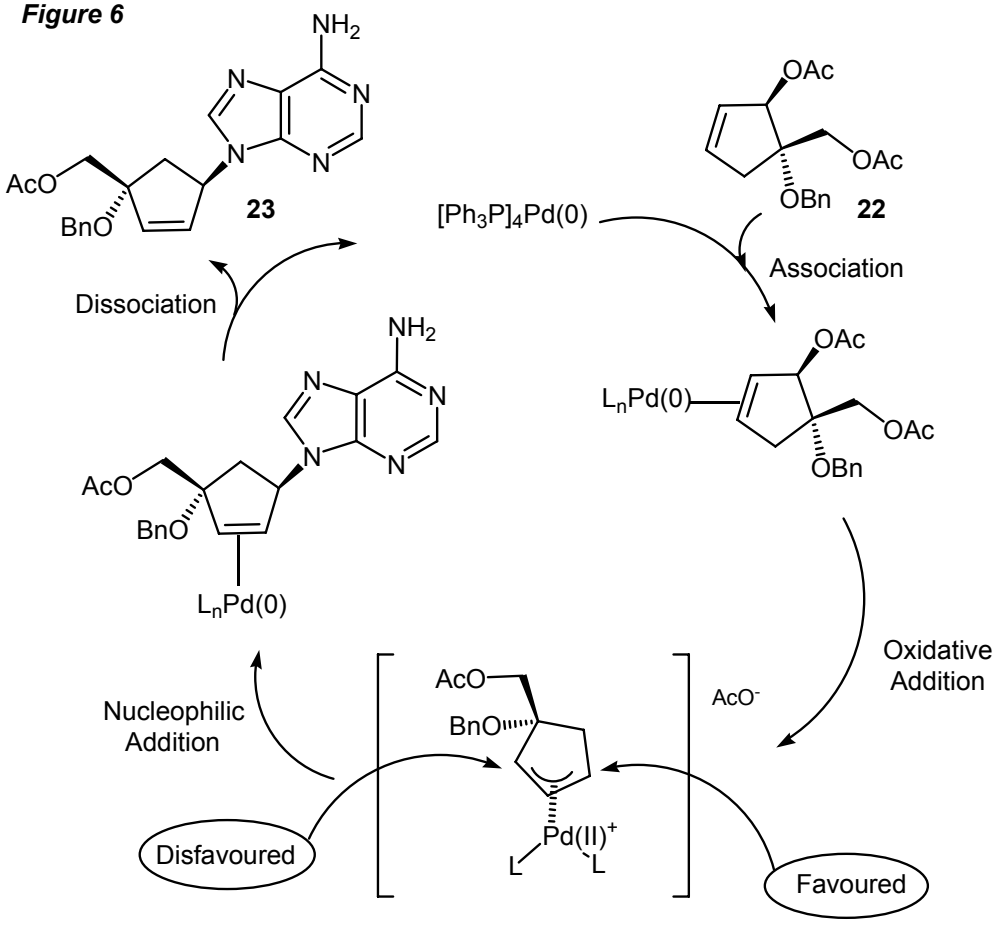


21 **22** **23**

The ^{1}H NMR spectrum of carbocyclic nucleoside derivative **104** displayed signals due to olefinic protons as a multiplet at δ 6.23 (2H), a singlet integrating for three protons

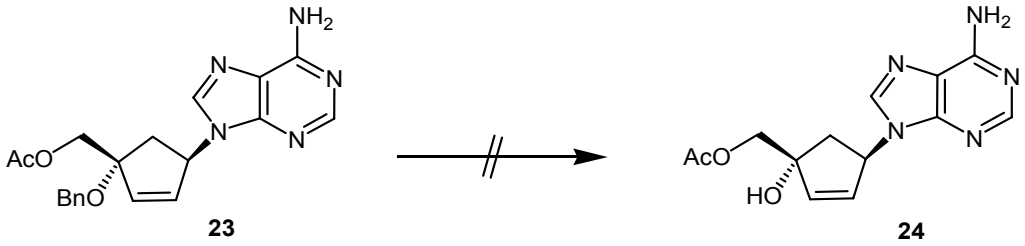
at δ 2.10 indicating the presence of only one acetate group, the other being substituted by purine base and characteristic H-2' and H-8' of the heterocycle moiety appeared as two singlets at δ 7.83 and 8.37 confirmed the coupling reaction. And all the other protons resonated at their expected chemical shift values. The ^{13}C NMR spectrum of **104** showed olefinic carbons at δ 127.67 and 134.91, carbonyl carbon of the acetate moiety resonated at δ 170.56 and MS (M^+, 379) spectroscopic data further supported the structure of **104**. The proposed mechanism for the coupling reaction is outlined in Figure 6.

Figure 6



After having compound **104** in hand, our immediate concern was to deprotect the benzyl ether in order to reach the target compound **91**. The presence of the C2, C3-double bond in **104** precluded the use of standard hydrogenolysis conditions for the benzyl ether deprotection. Unfortunately, all attempts at debenzylation of **104** using Birch-type reaction

Scheme 11:

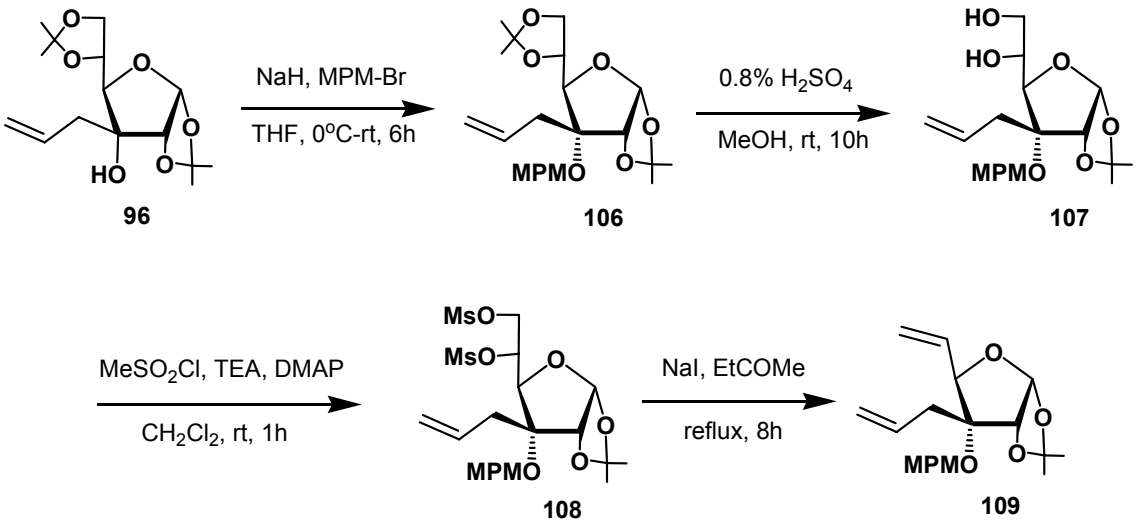


conditions (Li or Na/liquid NH_3, Li/$EtNH_2$/EtOH), use of BCl_3 and BBr_3 reagents resulted in complicated reaction mixtures (Scheme 11). At this stage of the synthesis, it became apparent that although a convergent, stereoselective synthesis of the **104** had been developed, the elaboration of this intermediate to complete the synthesis of carbocyclic nucleoside analogue **91** was likely to be difficult resulting from late-stage protecting-group manipulations. Benzyl ether removal placed us in a difficult position to complete the synthesis in seamless manner. Accordingly, we concluded that a more effective protecting-group strategy was necessary to achieve an efficient synthesis of **91**.

In the revised approach we have protected the tertiary hydroxyl group as its MPM-ether instead of benzyl ether and administered the same sequence of reactions. Thus, allylic alcohol derivative **96** was treated with MPM-bromide in the presence of NaH-THF to obtain MPM-ether derivative **106**. In the ^{1}H NMR spectrum of **106** characteristic signals due to aromatic protons of MPM-group were visualized as two doublets at δ 6.84 (2H, J = 8.0 Hz), 7.29 (2H, J = 8.0 Hz), benzylic protons appeared at δ 4.68 as a ABq (J = 12.9 Hz) and a singlet due to methoxy group appeared at δ 3.77 (3H). And all the other protons resonated at their expected chemical shift values. The ^{13}C and MS spectral data of **106** confirmed the formation of MPM-ether product. Transformation of **106** into the corresponding diene derivative **109** was achieved in three steps. Thus, 5,6-isopropylidene group in **106** was selectively hydrolyzed using 0.8 % H_2SO_4 in MeOH to yield 5,6-diol derivative **107**. In the ^{1}H NMR spectrum of **107** the disappearance of the signals due to 5,6-isopropylidene moiety supported the assigned structure. In addition, the mass spectroscopy showed a peak at 380 due to (M^+) ion and elemental analysis further confirmed the structure of **107**. Dimesylation of **107** was performed by using MsCl in the presence of Et_3N in anhydrous CH_2Cl_2 at 0 ^{o}C to afford dimesyl derivative **108**, which was subsequently subjected to iodine-mediated elimination by using excess NaI in refluxing 2-

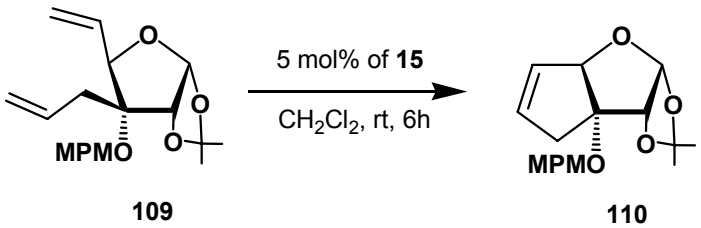
butanone to furnish diene derivative **109**.[48] In the ^{1}H NMR spectrum of **109** resonances due to olefinic protons appeared as two multiplets at δ 5.0-5.5 (4H) and at δ 5.9 (2H) in accordance with the diene system. And all the other protons resonated at their

Scheme 12:



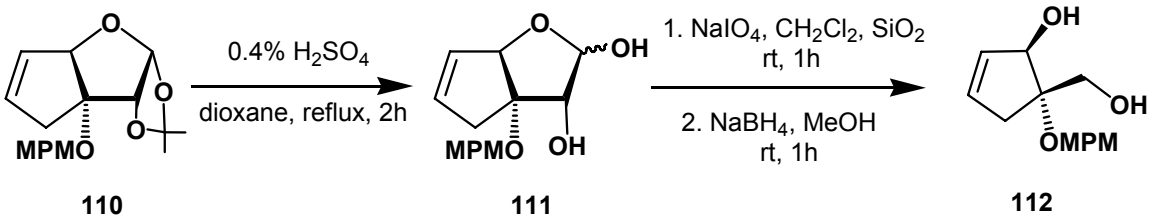
respective chemical shift values. The ^{13}C NMR, IR, MS (M^+, 346) spectroscopic data and elemental analysis further supported the structure of **109** (Scheme 12). Diene derivative **109** was subjected to ring closing metathesis by using 5 mol% of Grubbs' 1st generation catalyst [$(PCy_3)_2Cl_2Ru$=CHPh] (**101**) in CH_2Cl_2 at room temperature to afford tricyclic derivative **110**.[45] In the ^{1}H NMR spectrum of **110** resonances due to characteristic olefinic protons appeared as a multiplet at δ 5.90 (2H) and H-4 resonated at δ 5.81 as a doublet (J = 3.0 Hz). The ^{13}C NMR spectrum of **110** showed resonances due to olefinic carbons at δ 130.34 and 134.01. And all the other carbons resonated at their expected chemical shift values supporting the structure of **110**. The MS (M^+, 318) spectral data and elemental analysis are in agreement with the tricyclic derivative **110** (Scheme 13). Transformation of

Scheme 13:



tricyclic derivative **110** to its corresponding cyclopentenyl diol derivative **112** was witnessed in three steps. Acidic hydrolysis of 1,2-isopropylidene group of **110** by refluxing in 60% aq. AcOH, we observed the loss of MPM-group to some extent and to prevent the same, we followed an alternative method by refluxing with 0.4% H_2SO_4 in dioxane for 2h to obtain bicyclic lactol derivative **111** without any loss of MPM-group. Subsequent

Scheme 14:



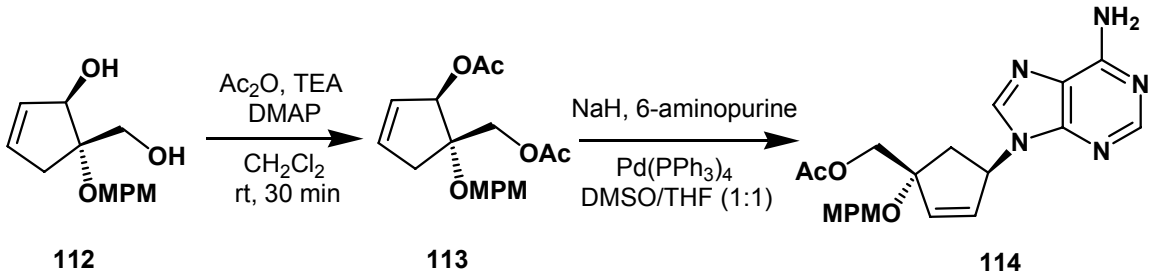
110 **111** **112**

oxidative cleavage of **111** by using silica gel supported $NaIO_4$ in dichloromethane resulted an aldehyde, which upon reduction with $NaBH_4$ in MeOH at room temperature afforded cyclopentenyl diol derivative **112** in good yield. In the ^{1}H NMR spectrum of **112** resonances due to olefinic protons appeared as a multiplet at δ 5.77-5.95 (2H). And all the other protons resonated at their expected chemical shift values. ^{13}C NMR showed signals due to olefinic carbons at δ 131.95 and δ 132.54 supported the structure of **112**. Further more MS (M^+, 250) spectral data and elemental analysis are in accordance with the structure (Scheme 14).

To facilitate the Pd(0) mediated coupling reaction between 6-amino purine (**93**) and the carbocyle moieties, diacetate derivative of the diol **112** was prepared in similar fashion mentioned for its benzyl analogue to get **113**. In the ^{1}H NMR spectrum of diacetate derivative **113**, resonances due to two acetate groups appeared as a singlet at δ 2.11 (6H). And all the other protons resonated at their expected chemical shift values in agreement with structure **113**. Convergent coupling of adenine (**93**) and diacetate derivative **113** was achieved by treating with tetrakis(triphenylphosphine)palladium(0) and sodium hydride in DMSO:THF (1:1) to provide carbocyclic nucleoside derivative **114** as a single diastereomer in 41% yield (Scheme 15).[40] In the ^{1}H NMR spectrum of **114** resonances due to characteristic H-2' and H-8' protons of heterocycle moiety were visualized at δ 7.82 (1H) and δ 8.36 (1H) as two singlets, olefinic protons resonated at δ 6.24 (2H) as a multiplet and

a singlet at δ 2.11 (3H) due to one acetate group convinced the assigned structure of **114**. And all the other protons resonated at their expected chemical shift values.

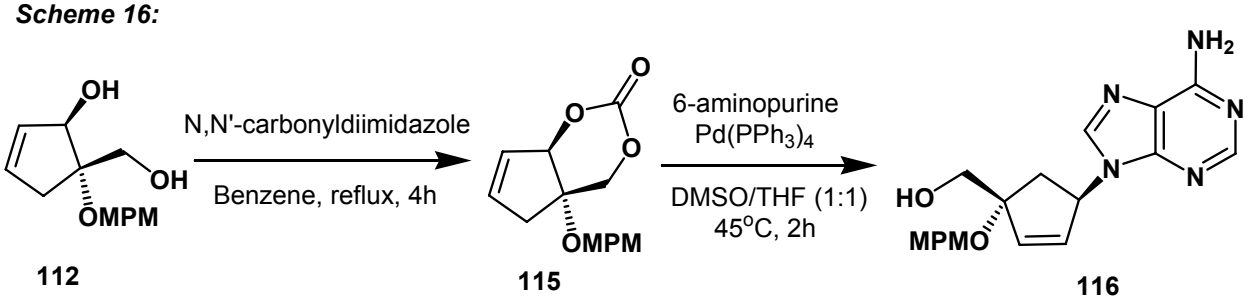
Scheme 15:



112 **113** **114**

Although the reaction was successful, relatively low yield of the reaction prompted us to investigate the possibility of improving the yield. While considering the other options, the allylic cyclic carbonate derivative **115** looked promising as it does not require much effort and can be easily made from diol derivative **112**, further it reduces one step in reaching the target molecule. Thus, the diol **112** was converted to its corresponding cyclic carbonate derivative **115** by treating with *N,N′*-carbonyldiimidazole in refluxing benzene for 4h.[40b] In the ^{1}H NMR spectrum of **115** resonances due to olefinic protons were visualized at δ 5.82 (1H) and δ 6.04 (1H) as two multiplets. And all the other protons appeared at their respective chemical shift values in agreement with the structure **115**. The ^{13}C NMR showed resonance due to carbonyl carbon at δ 150.5. IR (1762 cm^{-1}), MS (M^{+}, 276) spectroscopic data and elemental analysis further supported the structure of cyclic carbonate derivative **115**. The cyclic carbonate derivative **115** was allowed to react with 6-aminopurine (**93**) in the presence of tetrakis(triphenylphosphine)palladium(0) in DMSO:THF (1:1) at 45 ^{o}C for 2h to obtain carbocyclic nucleoside derivative **116** as a single diastereomer in relatively good yield (54%) (Scheme16).[40b] The ^{1}H NMR spectrum of **116** displayed signals due to characteristic H-2' and H-8' protons of heterocycle moiety at δ 8.10 (1H) and δ 8.20 (1H) as two singlets while olefinic protons at δ 6.23 (2H) as a multiplet. In the ^{13}C NMR spectrum resonances due to olefinic carbons visualized at δ 135.04 and δ 139.08. MS (M^{+}, 367) and elemental analysis also supported the structure of **116**.

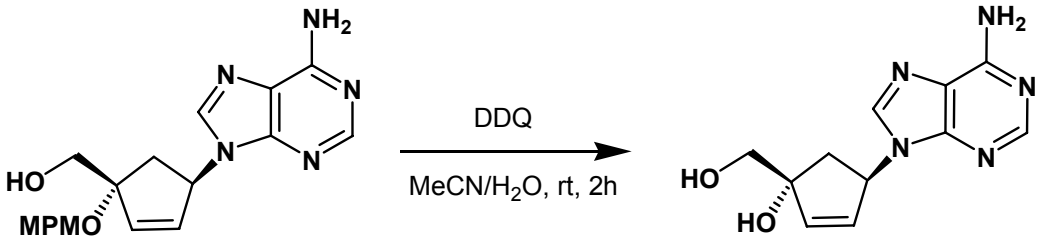
Scheme 16:



112 **115** **116**

Finally, the deprotection of MPM ether was accomplished by using DDQ[49] in dioxane:H_2O at room temperature for 2h to afford the carbocylic nucleoside analogue **91** (Scheme 17). In the ^{1}H NMR spectrum of **91**, the absence of a singlet at δ 3.76 (OMe) and A_2B_2 pattern in the aromatic region suggested that the reaction had occurred. In addition the two olefinic protons resonated at δ 6.16 as a multiplet, while the characteristic H-2' and H-8' protons of heterocycle moiety appeared at δ 8.03 (1H) and δ 8.20 (1H) as two singlets supported the structure of **91**. The ^{13}C NMR, MS (M^+, 247) spectral data and elemental analysis confirmed the structure of **91**.

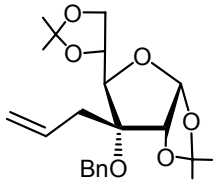
Scheme 17:



116 **91**

In conclusion we have designed and established an efficient methodology using ring closing metathesis and palladium(0) catalyzed allylic substitution reactions as key steps to prepare carbocylic nucleoside **91** having two important chromophores, unsaturation and well defined tertiary hydroxyl center in its structural framework. However the antiviral activity tested for our carbocyclic nucleoside analogue **91** was not encouraging enough.

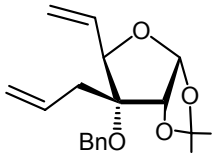
3-*C*-Allyl-1,2-*O*-isopropylidene-3-*O*-benzyl-α-D-allofuranose (99):



Compound **96** (6.0 g, 19.9 mmol) in DMF (20 mL) was added to a stirred suspension of NaH (960 mg, 60% dispersion in oil, 23.9 mmol) in DMF (20 mL) at 0 ^{o}C. The resulting solution was stirred at rt for 30 min., BnBr (2.6 mL, 21.9 mmol) and TBAI (50 mg) were added. After 4 h, the reaction was quenched by ice-cold water and extracted with EtOAc. The combined organic layer was washed with water, dried (Na_2SO_4) and concentrated. The residue was purified on silica gel using EtOAc-light petroleum ether (1:9) to obtain **99** as a thick liquid.

Yield	: 6.41 g (82%)
Mol. Formula	: $C_{22}H_{30}O_6$
Optical Rotation $[\alpha]_D^{25}$	: +55 (*c* 1.0, $CHCl_3$).
1H NMR ($CDCl_3$, 200 MHz)	: δ 1.32, 1.36, 1.60 (3s, 12 H), 2.41 (dd, 1 H, *J* = 6.6, 13.3 Hz), 2.69 (dd, 1 H, *J* = 6.6, 14.6 Hz), 3.91-4.27 (m, 4 H), 4.49 (d, 1 H, *J* = 3.6 Hz), 4.77 (ABq, 2 H, *J* = 12.6 Hz), 5.12 (m, 2 H), 5.61 (d, 1 H, *J* = 3.6 Hz), 6.01 (m, 1 H), 7.31 (m, 5 H) ppm.
EIMS: *m/z*	: 391 (M+1)
Elemental Analysis	Calcd.: C, 67.67; H, 7.74%. Found: C, 67.52; H, 7.62%.

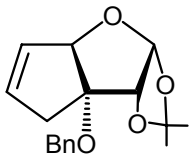
3-*C*-Allyl-5,6-dideoxy-1,2-*O*-isopropylidene-3-*O*-benzyl-α-D-*ribo*-hex-5-enofuranose (95):



H_5IO_6 (3.15 g, 13.8 mmol) was added to a solution of **99** (4.5 g, 11.5 mmol) in dried EtOAc (100 mL) at ambient temperature, and stirring was continued for 2 h. The mixture was filtered, the filter cake was washed (EtOAc), and the combined filtrate was evaporated. The residue was dissolved in anhydrous THF (20 mL), cooled to –20 ^oC, methylenetriphenylphosphorane [prepared from PPh_3CH_3I (9.34 g) and *n*-BuLi (1.6 M, 12.6 mL)] was added dropwise. After 4 h stirring at rt, it was quenched by addition of saturated aqueous solution of NH_4Cl. The two layers were separated, the organic layer dried (Na_2SO_4) and concentrated to form a residue which was purified on silica gel using EtOAc:light petroleum ether (1:20) to furnish **95** as colorless oil.

Yield	: 2.23 g (61%)
Mol. Formula	: $C_{19}H_{24}O_4$
Optical Rotation $[\alpha]_D^{25}$	: +48 (*c* 1.2, $CHCl_3$)
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 1.38, 1.65 (2s, 6 H), 2.37 (dd, 1 H, *J* = 5.9, 11.9 Hz), 2.57 (dd, 1 H, *J* = 5.9, 11.7 Hz), 4.50 (d, 1 H, *J* = 4.1 Hz), 4.69 (s, 3 H), 5.14-5.52 (m, 4 H), 5.75 (d, 1 H, *J* = 4.1 Hz), 5.95 (m, 2 H), 7.35 (m, 5 H) ppm.
EIMS: *e/z*	: 317 (M+1)
Elemental Analysis	**Calcd.:** C, 72.13; H, 7.65%. **Found:** C, 72.05; H, 7.54%.

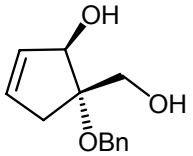
(2*R*, 3*R*, 4*S*, 5*R*)-2,3-*O*- isopropylidene-4-*O*-benzyl-1-oxabicyclo[3.3.0]oct-6-ene (94):



Compound **95** (1.6 g, 5.0 mmol) was dissolved in anhydrous CH_2Cl_2 (100 mL) and solution degassed with argon. 5 mol% of Grubbs' first generation catalyst **15** (0.2 g, 0.25 mmol) was added and mixture stirred at rt for 8 h. The solvent was removed and residue purified by column chromatography on silica gel using EtOAc:light petroleum ether (1:9) to obtain **94** as a colorless syrup.

Yield	: 1.15 g (79%)
Mol. Formula	: $C_{17}H_{20}O_4$
Optical Rotation $[\alpha]_D^{25}$	: +21 (*c* 1.3, $CHCl_3$).
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 1.46, 1.65 (2s, 6 H), 2.41 (m, 1 H), 2.89 (m, 1 H), 4.49-4.84 (m, 3 H), 5.05 (s, 1 H), 5.89 (m, 3 H), 7.32 (m, 5 H) ppm.
EIMS: *e/z*	: 288 (M^+)
Elemental Analysis	**Calcd.:** C, 70.81; H, 6.99%.
	Found: C, 70.69; H, 6.86%.

(1*S*, 2*R*)-1-Benzyloxy-1-hydroxymethyl-cyclopent-3-ene-2-ol (103):

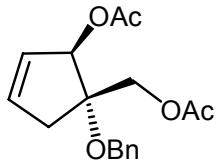


Compound **94** (1.1 g, 3.8 mmol) in 60% aq. AcOH (20 mL) was heated under reflux for 2 h. The reaction mixture was neutralized with solid Na_2CO_3 and evaporated. The residue was extracted with EtOAc, dried (Na_2SO_4), concentrated to give crude lactol derivative **102** (0.85 g). The above product (0.85 g, 3.4 mmol) was vigorously stirred with

CH_2Cl_2 (20 mL), 0.65 M $NaIO_4$ solution (7 mL), and chromatography grade SiO_2 (5 g) for 1 h. The solid was filtered and washed with CH_2Cl_2. The combined filtrate was evaporated and then dissolved in MeOH (20 mL). Solid $NaBH_4$ (0.15 g) was added, and after 1 h at room temperature, the reaction mixture concentrated. The residue was extracted with ethyl acetate, washed with brine, dried (Na_2SO_4), concentrated, and purified by silica gel by eluting with EtOAc:light petroleum ether (1:1) to give **103** as a thick liquid.

Yield	: 0.57 g (68%)
Mol. Formula	: $C_{13}H_{16}O_3$
Optical Rotation $[\alpha]_D^{25}$	: -58 (*c* 0.8, $CHCl_3$).
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 2.46 (m, 2 H), 2.97 (br s, 2 H), 3.86 (s, 2 H), 4.51 (ABq, 2 H, *J* = 8.3 Hz), 4.92 (s, 1 H), 5.76 (m, 1 H), 5.93 (m, 1 H), 7.33 (m, 5 H) ppm.
EIMS: *e/z*	: 220 (M^+)
Elemental Analysis	**Calcd.:** C, 70.89; H, 7.32%.
	Found: C, 70.76; H, 7.25%.

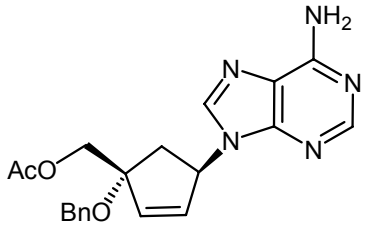
(1*S*, 2*R*)-1-Benzyloxy-1-acetyloxymethyl-2-acetyloxy-cyclopent-3-ene (92):



To a solution of **103** (0.5 g, 2.27 mmol) in anhydrous CH_2Cl_2 (10 mL) were added Ac_2O (0.53 mL, 5.61 mmol), Et_3N (0.95 mL, 6.81 mmol) and DMAP (20 mg), and stirred at room temperature for 30 min. The reaction mixture was diluted with water, extracted with CH_2Cl_2, washed with saturated aq. $NaHCO_3$, dried (Na_2SO_4), and the residue purified by silica gel column chromatography with EtOAc:light petroleum ether (2:8) as an eluent to afford **92** as a colorless syrup.

Yield	: 0.49 g (71%)
Mol. Formula	: $C_{17}H_{20}O_5$
Optical Rotation $[\alpha]_D^{25}$	: -35 (*c* 1.5, $CHCl_3$).
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 2.08 (s, 6 H), 2.63 (s, 2 H), 4.38 (ABq, 2 H, *J* = 12.3 Hz), 4.53 (s, 2 H), 5.75 (m, 1 H), 5.89 (s, 1 H), 6.02 (m, 1 H), 7.29 (m, 5 H) ppm.
EIMS: *e/z*	: 304 (M^+)
Elemental Analysis	**Calcd.:** C, 67.09; H, 6.62%. **Found:** C, 67.24; H, 6.55%.

(1′*R*, 4′*R*)-(4′-Benzyloxy-4′-acetyloxymethyl-cyclopent-2′-enyl)adenine (104):

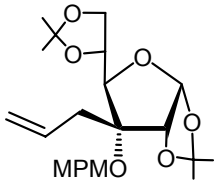


To a stirred suspension of NaH (63 mg, 60% dispersion in oil, 1.57 mmol) in 5 mL of DMSO under nitrogen was added 6-aminopurine (**93**) (195 mg, 1.44 mmol) and heated at 45 ^oC for 15 min. After allowing to cool to room temperature, tetrakis(triphenylphosphine)palladium(0) (152 mg, 0.13 mmol) was added followed by the addition of diacetate **92** (0.4 g, 1.31 mmol) in 5 ml of THF and heated at 45 ^oC overnight. The mixture was allowed to cool to room temperature and was quenched with water. The solution was extracted five times with ethyl acetate, combined organic layers were washed with water, concentrated and purified by column chromatography on silica gel using EtOAc:MeOH (20:1) to obtain **104** as a thick liquid.

Yield	: 0.21 g (42%)
Mol. Formula	: $C_{20}H_{21}N_5O_3$
Optical Rotation $[\alpha]_D^{25}$	: –67.6 (*c* 0.25, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 500 MHz)	: δ 2.10 (s, 3 H), 2.15 (dd, 1 H, *J* = 4.9, 15.3 Hz), 2.91 (dd, 1 H, *J* = 8.4, 15.3 Hz), 4.35 (ABq, 2 H, *J* = 11.5 Hz), 4.48 (s, 2 H), 5.95 (br s, 3 H), 6.23 (m, 2 H), 7.33 (m, 5 H), 7.83 (s, 1 H), 8.37 (s, 1 H) ppm.
^{13}C ($CDCl_3$, 125 MHz)	: δ 20.9, 39.8, 58.9, 65.7, 67.5, 89.2, 127.3, 127.7, 128.4, 134.9, 137.9, 152.9, 155.4, 170.6 ppm.
EIMS: *e/z*	: 379 (M^+)
Elemental Analysis	**Calcd.:** C, 63.31; H, 5.58; N, 18.46%.
	Found: C, 63.24; H, 5.42; N, 18.31%.

3-*C*-Allyl-1,2;5,6-di-*O*-isopropylidene-3-*O*-(4-methoxyphenylmethyl)-α-D-allofuranose (106):



Compound **96** (9.0 g, 30.0 mmol) in THF (30 mL) was added to a solution of NaH (50% dispersion in oil, 2.16 g, 45.0 mmol washed with 10 mL of hexane) in THF (50 mL). After 1 h at room temperature, MPM bromide (7.23 g, 36.0 mmol) in THF (20 mL) was added, and the mixture was stirred for 6 h and then concentrated. The residue was partitioned between ethyl acetate and water. The ethyl acetate layer was washed with brine, dried (Na_2SO_4), and concentrated. The residue was purified on silica gel by using hexanes-ethyl acetate (4:1) to give **106** as a colorless liquid.

Yield	: 10.83 g (86%)
Mol. Formula	: $C_{23}H_{32}O_7$
Optical Rotation $[\alpha]_D^{25}$	: +62.0 (*c* 2.8, $CHCl_3$).
IR ($CHCl_3$) $\tilde{\nu}$	: 1110, 1247, 1381, 1512, 1612, 2836, 2872, 2909, 2936, 2990 cm^{-1}.

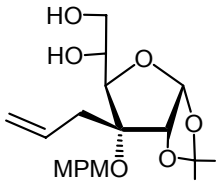
^{1}H NMR ($CDCl_3$, 200 MHz) : δ 1.32, 1.38, 1.43, 1.63 (4s, 12 H), 2.42 (dd, 1 H, *J* = 6.45, 12.9 Hz), 2.67 (dd, 1 H, *J* = 3.9, 12.9 Hz), 3.77 (s, 3 H), 3.93 (m, 1 H), 4.09 (m, 1 H), 4.16 (m, 2 H), 4.45 (d, 1 H, *J* = 3.2 Hz), 4.68 (ABq, 2 H, *J* = 12.9 Hz), 5.32 (m, 2 H), 5.61 (d, 1 H, *J* = 3.2 Hz), 6.00 (m, 1 H), 6.84 (d, 2 H, *J* = 8.0 Hz), 7.29 (d, 2 H, *J* = 8.0 Hz) ppm.

^{13}C ($CDCl_3$, 50 MHz) : 25.1, 26.3, 26.7, 35.6, 54.9, 66.4, 67.6, 72.8, 81.0, 82.7, 83.3, 103.2, 109.2, 112.3, 113.2, 118.2, 128.4, 131.1, 132.5 ppm.

EIMS: ***e/z*** : 420 (M^+)

Elemental Analysis **Calcd.:** C, 65.71; H, 7.62%.
Found: C, 65.33; H, 7.40%.

3-*C*-Allyl-1,2-*O*-isopropylidene-3-*O*-(4-methoxyphenylmethyl)-α-D-allofuranose (107):



Compound **106** (8.4 g, 20.0 mmol) and 0.8% sulfuric acid (3 mL) in methanol (50 mL) were stirred at room temperature for 10 h and neutralized with solid $NaHCO_3$. The solid was filtered, and the filtrate was concentrated. The residue was purified on silica gel with $CHCl_3$-MeOH (10:1) to afford the 5,6-diol **107** as a thick liquid.

Yield : 5.7 g, (75%)

Mol. Formula : $C_{20}H_{28}O_7$

IR ($CHCl_3$) $\tilde{\nu}$: 1034, 1088, 1167, 1218, 1248, 1379, 1513, 2932, 3011, 3488 cm^{-1}.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 1.37, 1.62 (2s, 6 H), 2.62 (m, 2 H), 3.62 (dd, 1 H, *J* =

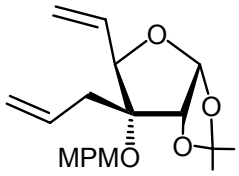
6.2, 12.5 Hz), 3.75 (dd, 1 H, *J* = 4.7, 12.5 Hz), 3.78 (s, 3 H), 3.90 (m, 1 H), 4.06 (d, 1 H, *J* = 10.0 Hz), 4.47 (d, 1 H, *J* = 3.1 Hz), 4.62 (s, 2 H), 5.25 (m, 2 H), 5.65 (d, 1 H, *J* = 3.1 Hz), 6.0 (m, 1 H), 6.90 (d, 2 H, *J* = 7.5 Hz), 7.34 (d, 2 H, *J* = 7.5 Hz) ppm.

EIMS: *e/z* : 380 (M^+)

Elemental Analysis **Calcd.:** C, 63.14; H, 7.42%.

Found: C, 63.25; H, 7.51%.

3-*C*-Allyl-5,6-dideoxy-1,2-*O*-isopropylidene-3-*O*-(4-methoxyphenylmethyl)-α-D-*ribo*-hex-5-enofuranose (109):



Compound **107** was taken in Et_3N (6.3 mL), DMAP (0.18 g), and CH_2Cl_2 (30 mL), and $MeSO_2Cl$ (3.6 mL, 36.0 mmol) was added. After 1 h, the reaction mixture was washed with saturated Na_2CO_3 and water, dried (Na_2SO_4), and concentrated. The crude dimesylate **108** (7.4 g, 13.8 mmol) and NaI (10.34 g, 69.0 mmol) in 2-butanone (50 mL) were heated under reflux for 8 h and concentrated. The residue was partitioned between ethyl acetate and saturated sodium thiosulfate. The organic layer was washed with brine, dried (Na_2SO_4), concentrated and purified by silica gel with hexanes-ethyl acetate (9:1) to give diene **109** as a colorless liquid.

Yield : 3.33 g, (64%)

Mol. Formula : $C_{20}H_{26}O_5$

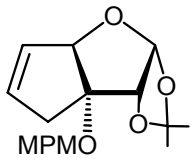
Optical Rotation $[\alpha]_D^{25}$: +53 (*c* 2.0, $CHCl_3$).

IR ($CHCl_3$) $\tilde{\nu}$: 1035, 1087, 1111, 1170, 1248, 1377, 1460, 1512, 1609, 1735, 2839, 2861, 2934, 2987 cm^{-1}.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 1.38, 1.60 (2s, 6 H), 2.31 (dd, 1 H, *J* = 6.1, 13.5 Hz),

	2.55 (dd, 1 H, *J* = 6.3, 13.5 Hz), 3.78 (s, 3 H), 4.44 (m, 2 H), 4.53 (s, 1 H), 4.60 (d, 1 H, *J* = 3.0 Hz), 5.0-5.5 (m, 4 H), 5.64 (d, 1 H, *J* = 3.0 Hz), 5.9 (m, 2 H), 6.8 (m, 2 H), 7.23 (m, 2 H) ppm.
^{13}C ($CDCl_3$, 50 MHz)	: δ 26.4, 26.7, 35.8, 55.0, 71.3, 81.5, 81.6, 84.0, 103.6, 112.3, 117.7, 117.9, 128.5-130.3, 132.3, 132.7 ppm.
EIMS: *e/z*	: 346 (M^+)
Elemental Analysis	**Calcd.:** C, 69.36; H, 7.51%.
	Found: C, 69.01; H, 7.42%.

(2*R*, 3*R*, 4*S*, 5*R*)-2,3-*O*- isopropylidene-4-*O*-(4-methoxyphenylmethyl)-1-oxabicyclo[3.3.0]oct-6-ene (110):

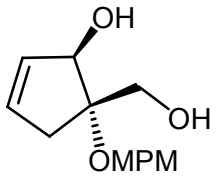


Compound **109** (1.73 g, 5.0 mmol) and Grubbs' catalyst (0.20 g) in CH_2Cl_2 (50 mL) were stirred for 6 h at room temperature and then evaporated. The residue was purified on silica gel with hexanesethyl acetate (4:1) to give **110** as a colorless solid.

Yield	: 1.27 g, (80%)
Mol. Formula	: $C_{18}H_{22}O_5$
M. P.	: 79-81 ^oC
Optical Rotation $[\alpha]_D^{25}$	: +24 (*c* 1.0, $CHCl_3$).
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 1.35, 1.60 (2s, 6 H), 2.33 (brd, 1 H, *J* = 17.5 Hz), 2.86 (dd, 1 H, *J* = 1.0, 17.5 Hz), 3.77 (s, 3 H), 4.43 (d, 1 H, *J* = 9.2 Hz), 4.52 (d, 1 H, *J* = 3.0 Hz), 4.64 (d, 1 H, *J* = 9.2 Hz), 4.98 (brs, 1 H), 5.81 (d, 1 H, *J* = 3.0 Hz), 5.90 (m, 2 H), 6.81 (d, 2 H, *J* = 7.7 Hz), 7.26 (d, 2 H, *J* = 7.7 Hz) ppm.

^{13}C ($CDCl_3$, 50 MHz)	: δ 27.2, 27.6, 39.6, 54.9, 67.3, 83.3, 90.5, 91.0, 106.5, 113.4, 128.9, 130.3, 134.0 ppm.
EIMS: ***e/z***	: 318 (M^+)
Elemental Analysis	**Calcd.:** C, 67.92; H, 6.91%.
	Found: C, 68.12; H, 6.85%.

(1*S*, 2*R*)-1-(4-Methoxyphenylmethoxy)-1-hydroxymethyl-cyclopent-3-ene-2-ol (112):

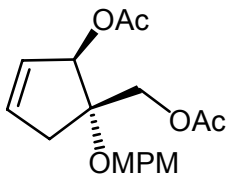


Compound **110** (3.81 g, 12.0 mmol), dioxane (30 mL), and 0.4% H_2SO_4 (40 mL) were heated under reflux for 2 h. The reaction mixture was neutralized with saturated Na_2CO_3 and evaporated. The residue was extracted with ethyl acetate, dried (Na_2SO_4), and concentrated to give crude lactol **111** (3.17 g). The above product (3.17 g, 11.4 mmol) was vigorously stirred with CH_2Cl_2 (30 mL), 0.65 M $NaIO_4$ solution (25 mL), and chromatography grade SiO_2 (20 g) for 1 h. The solid was filtered and washed with CH_2Cl_2. The combined filtrate was evaporated and then dissolved in MeOH (30 mL). Solid $NaBH_4$ (0.5 g) was added, and after 1 h at room temperature, the reaction mixture concentrated. The residue was extracted with ethyl acetate, washed with brine, dried (Na_2SO_4), concentrated, and purified by silica gel by eluting with hexanes-ethyl acetate (3:1) to give **112** as a thick liquid.

Yield	: 2.1 g (70%)
Mol. Formula	: $C_{14}H_{18}O_4$
Optical Rotation $[\alpha]_D^{25}$	: −78 (*c* 2.5, $CHCl_3$).
IR ($CHCl_3$) $\tilde{\nu}$	: 1035, 1092, 1111, 1216, 1246, 1512, 3013, 3414 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 2.45 (q, 2 H, *J* = 16.1 Hz), 3.89 (s, 3 H), 3.95 (s, 2 H), 4.43 (ABq, 2 H, *J* = 12.9 Hz), 4.91 (s, 1 H), 5.77-

	5.95 (m, 2 H), 6.84 (d, 2 H, *J* = 8.5 Hz), 7.25 (d, 2 H, *J* = 8.5 Hz) ppm.
^{13}C ($CDCl_3$, 50 MHz)	: δ 38.8, 55.2, 64.0, 65.2, 82.9, 87.6, 113.9, 128.7, 131.9, 132.5 ppm.
EIMS: ***e/z***	: 250 (M^+)
Elemental Analysis	**Calcd.:** C, 67.18; H, 7.25%.
	Found: C, 67.02; H, 7.11%.

(1*S*, 2*R*)-1-(4-Methoxyphenylmethoxy)-1-acetyloxymethyl-2-acetyloxy-cyclopent-3-ene (113):



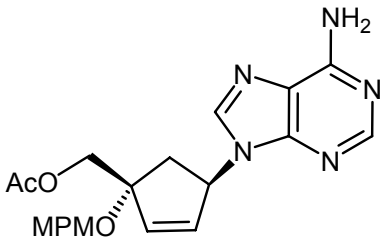
To a solution of **112** (0.5 g, 1.99 mmol) in anhydrous CH_2Cl_2 (10 mL) were added Ac_2O (0.83 mL, 4.98 mmol), Et_3N (0.83 mL, 5.95 mmol) and DMAP (20 mg), and stirred at room temperature for 30 min. The reaction mixture was diluted with water, extracted with CH_2Cl_2, washed with saturated aq. $NaHCO_3$, dried (Na_2SO_4), and the residue purified by silica gel column chromatography with EtOAc:light petroleum ether (1:9) as an eluent to afford **113** as colorless oil.

Yield	: 0.46 g, (69%)
Mol. Formula	: $C_{18}H_{22}O_6$
Optical Rotation $[\alpha]_D^{25}$	: -120.17 (*c* 3.0, $CHCl_3$)
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 2.11 (s, 6 H), 2.65 (s, 2 H), 3.82 (s, 3 H), 4.43 (ABq, 2 H, *J* = 11.9 Hz), 4.50 (s, 2 H), 5.79 (m, 1 H), 5.92 (s, 1 H), 6.05 (m, 1 H), 6.85 (d, 2 H, *J* = 8.9 Hz), 7.25 (d, 2 H, *J* = 8.9 Hz) ppm.
EIMS: ***e/z***	: 334 (M^+)

Elemental Analysis **Calcd.:** C, 64.66; H, 6.63%.

Found: C, 64.58; H, 6.56%.

(1′*R*, 4′*R*)-[4′-(4-Methoxyphenylmethoxy)-4′-acetyloxymethyl-cyclopent-2′-enyl]adenine (114):



To a stirred suspension of NaH (57 mg, 60% dispersion in oil, 1.42 mmol) in 5 mL of DMSO under nitrogen was added 6-aminopurine (**93**) (177 mg, 1.31 mmol) and heated at 45 ^{o}C for 15 min. After allowing to cool to room temperature, tetrakis(triphenylphosphine)palladium(0) (139 mg, 0.12 mmol) was added followed by the addition of diacetate **113** (0.4 g, 1.19 mmol) in 5 ml of THF and heated at 45 ^{o}C overnight. The mixture was allowed to cool to room temperature and was quenched with water. The solution was extracted five times with ethyl acetate, combined organic layers were washed with water, concentrated and purified by column chromatography on silica gel using EtOAc:MeOH (20:1) to obtain **114** as a thick liquid.

Yield : 202 mg, (41%)

Mol. Formula : $C_{21}H_{23}N_5O_4$

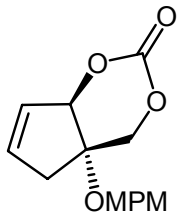
Optical Rotation $[\alpha]_D^{25}$: +2.2 (*c* 0.1, $CHCl_3$)

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 2.11 (s, 3 H), 2.17 (m, 1 H), 2.82 (dd, 1 H, *J* = 6.6, 14.6 Hz), 3.83 (s, 3 H), 4.31 (ABq, 2 H, *J* = 12.6 Hz), 4.42 (s, 2 H), 5.91 (m, 3 H), 6.24 (m, 2 H), 6.86 (d, 2 H, *J* = 7.3 Hz), 7.25 (d, 2 H, *J* = 7.3 Hz), 7.82 (s, 1 H), 8.36 (s, 1 H) ppm.

EIMS: *e/z* : 409(M^+)

Elemental Analysis	**Calcd.:** C, 61.60; H, 5.66%.
	Found: C, 61.48; H, 5.71%.

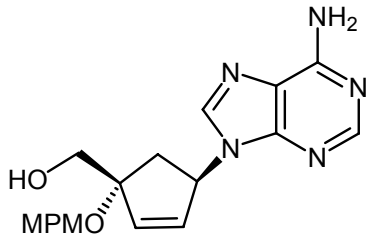
(1*S*, 2*R*)-5-(4-methoxyphenylmethoxy)-1,3-dioxabicyclo[4.3.0]non-7-ene-2-one (115):



A solution of compound **112** (0.275 g, 1.1 mmol) and *N*,*N*'-carbonyldiimidazole (0.27 g, 1.65 mmol) in benzene (5 mL) was heated under reflux for 4 h and concentrated. The residue was purified on silica gel with hexanes-ethyl acetate (9:1) as an eluent to give **115** as a colorless liquid.

Yield	: 0.21 g, (69%)
Mol. Formula	: $C_{15}H_{16}O_5$
Optical Rotation $[\alpha]_D^{25}$	: +40 (*c* 1, $CHCl_3$)
IR ($CHCl_3$) $\tilde{\nu}$	: 1030, 1070, 1115, 1175, 1247, 1356, 1384, 1461, 1512, 1611, 1762 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 2.53 (d, 1 H, *J* = 12.7 Hz), 2.82 (d, 1 H, *J* = 12.7 Hz), 3.78 (s, 3 H), 4.07 (d, 1 H, *J* = 7.0 Hz), 4.48 (m, 3 H), 5.41 (s, 1 H), 5.82 (m, 1 H), 6.04 (m, 1 H), 6.81 (d, 2 H, *J* = 6.8 Hz), 7.25 (d, 2 H, *J* = 6.8 Hz) ppm.
^{13}C ($CDCl_3$, 50 MHz)	: δ 39.0, 55.1, 66.1, 68.7, 81.2, 91.7, 113.8, 128.2, 128.8, 129.2, 134.9, 150.5 ppm.
EIMS: *e/z*	: 276 (M^+)
Elemental Analysis	**Calcd.:** C, 65.21; H, 5.79%.
	Found: C, 64.88; H, 5.62%.

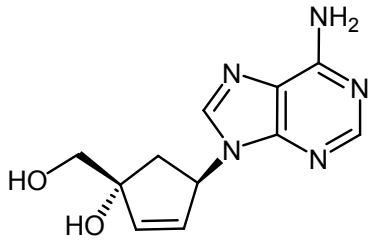
(1′*R*, 4′*R*)-[4′-(4-Methoxyphenylmethoxy)-4′-hydroxymethyl-cyclopent-2′-enyl]adenine (116):



To a solution of 6-aminopurine (**93**) (73 mg, 0.54 mmol) and $Pd(PPh_3)_4$ (62 mg) in DMSO (2 mL) under nitrogen was added **115** (150 mg, 0.54 mmol) in THF (2 mL). After being stirred for 2 h at 45 °C, the reaction mixture was diluted with water and repeatedly extracted with ethyl acetate. The combined organic layer was washed with water, dried (Na_2SO_4), and concentrated. The residue was purified by silica gel with ethyl acetate-MeOH (9:1) to give compound **116** as a colorless solid.

Yield	: 108 mg, (54%)
Mol. Formula	: $C_{19}H_{21}N_5O_3$
M. P.	: 167-169 ^oC
Optical Rotation $[\alpha]_D^{25}$	: +124 (*c* 1, MeOH)
^{1}H NMR (DMSO-d_6, 200 MHz)	: δ 2.10 (dd, 1 H *J* = 4.7, 13.3 Hz), 2.66 (dd, 1 H, *J* = 6.0, 13.3 Hz), 3.53 (ABq, 2 H, *J* = 12.6 Hz), 3.76 (s, 3 H), 4.36 (t, 2 H, *J* = 13.3 Hz), 5.83 (br s, 1 H), 6.23 (m, 2 H), 6.90 (d, 2 H, *J* = 6.8 Hz), 7.26 (d, 2 H, *J* = 6.8 Hz), 8.10 (s, 1 H), 8.20 (s, 1 H) ppm.
^{13}C (DMSO-d_6, 50 MHz)	: δ 39.0, 55.8, 59.7, 65.2, 66.2, 92.0, 114.4, 129.9, 131.8, 135.0, 139.0, 152.4 ppm.
EIMS: *e/z*	: 367 (M^+)
Elemental Analysis	**Calcd.:** C, 62.11; H, 5.76; N, 19.06%.
	Found: C, 61.97; H, 5.77; N, 18.91%.

(1′*R*, 4′*R*)-(4′-Hydroxy-4′-hydroxymethyl-cyclopent-2′-enyl)adenine (91):



Compound **116** (91 mg, 0.25 mmol) and DDQ (85 mg) in dioxane containing two drops of water (3 mL) were stirred at room temperature for 2 h. The reaction mixture was washed with saturated $NaHCO_3$ and brine and dried (Na_2SO_4). The solvent was evaporated, and the residue was chromatographed on silica gel with ethyl acetate-MeOH (5:1) to give compound **91** as a thick syrup.

Yield	: 44 mg, (72%)
Mol. Formula	: $C_{11}H_{13}N_5O_2$
Optical Rotation $[\alpha]_D^{25}$	: +82 (*c* 0.3, MeOH).
^{1}H NMR (CD_3COCD_3, 500 MHz)	: δ 2.33 (dd, 1 H, *J* = 3.3, 14.8 Hz), 2.60 (dd, 1 H, *J* = 6.6, 14.8 Hz), 3.70 (ABq, 2 H, *J* = 13.3 Hz), 5.90 (m, 1 H), 6.16 (m, 2 H), 6.26 (brs, 1 H), 8.03 (s, 1 H), 8.20 (s, 1H) ppm.
^{13}C (CD_3COCD_3, 125 MHz)	: δ 42.7, 59.2, 67.8, 85.1, 131.9, 139.1, 140.9, 152.6, 156.2 ppm.
EIMS: *e/z*	: 247 (M^+)
Elemental Analysis	**Calcd.:** C, 53.44; H, 5.26; N, 28.34%. **Found:** C, 53.39; H, 5.60; N, 28.11%.

REFERENCES

1. (a) *Progress in Medicinal Chemistry*; Ellis, G. P., Wells, G. B., Elsevier Science Publishers: New York, **1986**. (b) Mansuri, M. M.; Martin, J. C. *Ann. Rep. Med. Chem.* **1988**, *23*, 161. (c) Mansuri, M. M.; Martin, J. C. *Ann. Rep. Med. Chem.* **1989**, *24*, 129.
2. (a) De Clercq, E.; Holy, A. *J. Med. Chem*. **1979**, *22*, 510. (b) Montgomery, J. A. *Med. Res. Rev*. **1982**, *2*, 271. (c) Kensler, T. W.; Clooney, D. A.; *In Design of Enzyme Inhibitors as Drugs*; Sanler, M., Smith, H. J., Eds.; Oxford University Press; Oxford, **1989**, 379-401. (d) Perigaud, C.; Gosselin, G.; Imbach, J. L. *Nucleosides Nucleotides* **1992**, *11(2-4)*, 903. (e) Mentel, R.; Wegner, U. *Recent Developments Antiviral Research* **2001**, *1*, 1-20.
3. (a) Gotor, V.; Ferrero, M. *Chem. Rev*. **2000**, *100*, 4319. (b) Ichikawa, E.; Kato, K. *Curr. Med. Chem*. **2001**, *8*, 385.
4. (a) Schaeffer, J. H.; Beauchamp, L.; De Miranda, P.; Elion, G.; Bauer, D. J.; Collins, P. *Nature* **1978**, *272*, 583. (b) Elion, G. B.; Furman, P. A.; Fyfe, J. A.; De Miranda, P.; Bequchamp, L.; Schaeffer, H. *J. Proc. Natl. Acad. Sci. U. S. A*. **1977**, *74*, 5716. (c) Furman, P. A.; St. Clair, M. H.; Fyfe, J. A.; Rideout, J. L.; Keller, P. M.; Elio, G. B. *J. Virol*. **1979**, *32*, 72.
5. (a) Mitsuya, H.; Weinhold, K. J.; Furman, P. A.; St Clair, M. H.; Nusinoff-Lehrman, S.; Gallo, R. C.; Bolognesi, D.; Barry, D. W.; Broder, S. *Proc. Natl. Acad. Sci. U.S.A*. **1985**, *82*, 7096-7100. (b) Herdewijn, P.; Balzarini, J.; De Clercq, E.; Pauwels, R.; Baba, M.; Broder, S.; Vanderhaeghe, H. *J. Med. Chem.* **1987**, *30*, 1270-1278. (c) Daluge, S. M.; Purifoy, D. J.; Savina, P. M.; St Clair, M. H.; Parry, N. R.; Dev, I. K.; Novak, P.; Ayers, K. M.; Reardon, J. E.; Roberts, G. B.; Fyfe, J. A.; Blum, M. R.; Averett, D. R.; Domsife, R. E.; Domin, B. A.; Ferone, R.; Lewis, D. A.; Krenitsky, T. A. *Antimicrob. Agents Chemother.* **1994**, *38*, 1590-1603. (d) Larder, B. A.; Kemp, S. D.; Harrigan, P. R. *Science* **1995**, *269*, 696-699.
6. Mitsuya, H.; Broder, S. Proc. Natl. Acad. Sci. *U.S.A.* **1986**, *83*, 1911-1915. (b) Chu, C. K.; Schinazi, R. F.; Arnold, B. H.; Cannon, D. L.; Doboszewski, B.; Bhadti, V. B.; Gu, Z. *Biochem. Pharmacol.* **1988**, *37*, 3543-3548.

7. (a) De Clercq, E.; Van Aerschot, A.; Herdewijn, P.; Baba, M.; Pauwels, R.; Balzarini, J. *Nucleosides Nucleotides* **1989**, *8*, 659-671. (b) Schinazi, R. F.; Sommadossi, J. P.; Saalmann, V.; Cannon, D. L.; Xie, M. Y.; Hart, G. C.; Smith, G. A.; Hahn, E. F. *Antimicrob. Agents Chemother.* **1990**, *34*, 1061-1067.
8. (a) Coates, J. A. V.; Cammack, N.; Jenkinson, H. J.; Mutton, I. M.; Pearson, B. A.; Storer, R.; Cameron, J. M.; Penn, C. R. *Antimicrob. Agents Chemother.* **1992**, *36*, 202-205. (b) Schinazi, R. F.; Lloyd, R. M.; Nguyen, M. N.; Cannon, D. L.; Mcmillan, A.; Ilksoy, N; Chu, C. K.; Liotta, D. C.; Bazmi, H. Z.; Mellors, J. W. *Antimicrob. Agents Chemother.* **1993**, *37*, 875-881.
9. (a) Rousseau, F. S.; Kahn, J. O.; Thompson, M.; Mildvan, D.; Shepp, D.; Sommadossi, J. P.; Delehanty, J.; Simpson, J. N.; Wang, L. H.; Quinn, J. B.; Wakeford, C.; van der Horst, C, *J. Antimicrob. Chemother.* **2001**, *48*, 507-513. (b) Molina, J. M.; Ferchal, F.; Rancinan, C.; Raffi, F.; Rozenbaum, W.; Sereni, D.; Morlat, P.; Journot, V.; Decazes, J. M.; Chene, G. *J. Infect. Dis.* **2000**, *182*, 599-602.
10. (a) Lin, T. S.; Schinazi, R. F.; Prusoff, W. H. *Biochem. Pharmacol.* **1987**, *36*, 2713-2718. Balzarini, J.; Van Aerschot, A.; Herdewijn, P.; De Clercq, E. *Biochem. Pharmacol.* **1989**, *38*, 869-874.
11. (a) Arimilli, M. N.; Kim, C. U.; Dougherty, J.; Mulato, A.; Oliyai, R.; Shaw, J. P.; Cundy, K. C.; Bischofberger, N. *Antiviral Chem. Chemother.* **1997**, *8*, 557-564. (b) Robbins, B. L.; Srinivas, R. V.; Kim, C.; Bischofberger, N.; Fridland, A. *Antimicrob. Agents Chemother.* **1998**, *42*, 612-617.
12. (a)Brodfuehrer, P.; Brundidge, S; Howell, J.; Howell, H.; Sapino, C.; Tann, C. *J. Org. Chem.* **1985**, *50*, 3644. (b) Fox, J.; Reichman, U.; Watanabe, K. *Carbohyd. Res.* **1967**, *5*, 292. (c) Fox, J.; Schinazi, R.; Su, T. L.; Watanabe, K. *J. Med. Chem.* **1986**, *29*, 151. (d) Benigni, D.; Brodfuehrer, P.; Brundidge, S.; Howell, H.; Sapino, C. *J. Org. Chem*. **1988**, *53*, 85.
13. (a) Creasy, W. *Handb. Exp. Pharmacol*. **1975**, *38*, 232. (b) Heidelberger, C. Handb. Exp. Pharmacol **1975**, *38*, 193. (c) Heidelberger, C.; Ansfield F. *Cancer Res*. **1963**, *23*, 1226. (d) Carter, S. *Cancer Res*. **1972**, *30*, 1543. (e) Harbers, E.; Chanduri, N.; Heidelberger, C. *J. Biol. Chem*. **1959**, *234*, 1255.

14. (a) Eriksson, B.; Helgstand, E.; Hohansson, N. G.; Larsson, A.; Misiorny, A.; Noren, J. O.; Philpson, L.; Stenberg, K.; Sterning, G.; Stridh, S.; Oberg, B. *Antimicrob. Agents Chemother*. **1977**, *11*, 946. (b) Goswami, B. B.; Borek, E.; Sharma, O. K. *Biochem. Biophys. Res. Commun.* **1979**, *89*, 830. (c) Malinoski, F.; Stollar, V. *Virology* **1981**, *110*, 281. (d) Crotty, S. M.; Arnold, D.; Zhong, J. J.; Lau, W.; Hong, J. Y.; Andino, R.; Cameron, C. E. *Nat. Med*. **2000**, *6*, 1357.

15. (a) Desgranges, C.; Razaka, G.; Drouillet, F.; Bricaud, H.; Herdewijn, P.; De Clercq, E. *Nucleic Acids Res.* **1984**, *12*, 2081. (b) Slama, J. T.; Simmons, A. M. *Biochemistry* **1989**, *28*, 7688. (c) Bondoc, L. L. Jr.; Shannon, W. M.; Secrist, J. A., III.; Vince, R.; Fridland, A. *Biochemistry* **1990**, *29*, 9839. (d) Noble, S. A.; Bedall, N. E.; Beveridge, A. J.; Marr, C. L.; Myers, P. L.; Penn, C. R.; Storer, R.; Woods, J. M. *Nucleotides Nucleosides* **1991**, *10*, 478.

16. (a) Bricaud, H.; Herdewijn, P.; De Clercq, E. *Biochem. Pharmacol.* **1983**, 3583. (b) Desgranges, C.; Razaka, G.; Rabaud, M.; Bricaud, H.; Herdewijn, P.; De Clercq, E. *Biochem. Pharmacol*. **1983**, *32*, 3583. (c) Houston, D. M.; Matuszewska, B.; Borchardt, R. T. *J. Med, Chem*. **1985**, *28*, 478. (d) Herdewijn, P.; De Clercq, E.; Balzarini, J.; Vanderhaeghe *J. Med. Chem*. **1985**, *28*, 550.

17. (a) Shealy, Y. F.; Clayton, J. D. *J. Am. Chem. Soc.* **1966**, *88*, 3885-3887. (b) Shealy, Y. F.; Clayton, J. D. *J. Am. Chem. Soc*. **1969**, *91*, 3075-3083. (c) Shealy, Y. F.; Clayton, J. D. *J. Pharm. Sci.* **1973**, *62*, 1432.

18. (a) Kusaka, T.; Yamamoto, H.; Shibata, M.; Muroi, M.; Kishi, T.; Mizuno, K. *J. Antibiot.* **1968**, *21*, 255-271. (b) Yaginuma, S.; Muto, N.; Tsujino, M.; Sudate, Y.; Hayashi, M.; Otani, M. *J. Antibiot.* **1981**, *34*, 359-366.

19. (a) Vince, R.; Hua, M. *J. Med. Chem.* **1990**, *33*, 17-21. (b) "Therapeutic Nucleosides" Daluge, S. M. *U.S. Patent* **1991**, patent number 5,034,394. (c) Katagiri, N.; Nomura, M.; Sato, H.; Kaneko, C.; Yusa, K.; Tsuruo, T. *J. Med. Chem.* **1992**, *35*, 1882-1886.

20. (a) Ashton, W. T.; Meurer, L. C.; Cantone, C. L.; Field, A. K.; Hannah, J. *J. Med. Chem.* **1988**, *31*, 2304-2315. (b) Sekiyama, T.; Hatsuya, S.; Tanaka, Y.; Uchiyama, M.; Ono, N. *J. Med. Chem.* **1998**, *41*, 1284-1298.

21. (a) Zhao, Y.; Yang, T.-F.; Lee, M.; Chun, B, K.; Du, J. *Tetrahedron Lett.* **1994**, *35*, 5405-5408. (b) Lee, M.; Lee, D.; Zhao, Y.; Newton, M. G.; Chun, M. W. *Tetrahedron Lett.* **1995**, *36*, 3499-3502. (c) Zhao, Y.; Yang, T.; Lee, M.; Lee, D.; Newton, M. G. *J. Org. Chem*. **1995**, *60*, 5236-5242. (d) Yang, T.-F.; Kim, H.; Kotra, L. P.; Chu, C. K. *Tetrahedron Lett*. **1996**, *37*, 8849-8852. (e) Zhu, X.-F. *Nucleosides, Nucleotides & Nucleic Acids.* **2000**, *19*, 651-690.

22. (a) Winter, H.; Maeda, Y.; Mitsuya, H.; Zemlicka, J. *J. Med. Chem.* **1996**, *39*, 3300-3306. (b) Qiu, Y. L.; Ksebati, M. B.; Ptak, R. G.; Fan, B. Y.; Breitendbach, J. M. *J. Med. Chem.* **1998**, *41*, 10-23. (c) Qiu, Y. L.; Ptak, R. G.; Breitenbach, J. M.; Lin, J. S.; Cheng, Y. C. *Antiviral Chemistry & chemotherapy*. **1998**, *9*, 341-352. (d) Zhou, S.; Breitenbach, J. M.; Borysko, K. Z.; Drach, J. C.; Kern, E. R. *J. Med. Chem*. **2004**, *47*, 566-575.

23. (a) Shimada, N.; Hasegawa, S.; Harada, T.; Tomisawa, T.; Fujii, A. *J. Antibiotics.* **1986**, *39*, 1623-1625. (b) Nakamura, H.; Hasegawa, S.; Shimada, N.; Fujii, A.; Takita, T. *J. Antibiotics.* **1986**, *39*, 1626-1629. (c) Hoshino, H.; Shimizu, N.; Shimada, N.; Takita, T.; Takeuchi, T. *J. Antibiotics.* **1987**, *40*, 1077-1078.

24. (a) Nishiyama, Y.; Yamamoto, N.; Yamada, Y.; Daikoku, T.; Ichikawa, Y. *J. Antibiotics.* **1989**, *42*, 1854-1859. (b) Hayashi, S.; Norbeck, D. W.; Rosenbrook, W.; Fine, R.L.; Matsukura, M. *Antimicrob. Agents Chemother*. **1990**, *34*, 287-294.

25. (a) Jacobs, G. A.; Tino, J. A.; Zahler, R. *Tetrahedron Lett.* **1989**, *30*, 6955-6958. (b) Maruyama, T.; Sato, Y.; Horii, T.; Shiota, H.; Nitta, K. *Chem. Pharm. Bull*. **1990**, *38*, 2719-2725.

26. (a) Vince, R.; Hua, M.; Brownell, J.; Daluge, S.; Lee, F.; Shannon, W.; Lavelle, G.; Qualls, J.; Weislow, O. *Biochem. Biophys. Res. Comm.* **1988**, *156*, 1046-1053. (b) Vince, R.; Hua, M. *J. Med. Chem.* **1990**, *33*, 17-21. Vince, R.; Brownell, J. *Biochem. Biophys. Res. Comm.* **1990**, *168*, 912-916. Bondoc, L. L., Jr.; Shannon, W. M.; Secrist, J. A., III; Vince, R.; Fridland, A. *Biochemistry* **1990**, *29*, 9839-9843.

27. (a) Parry, R. J.; Jian, Y. Tetrahedron Lett. 19994, 35, 9665-9668. Hill J. M.; Jenkins, G. N.; Rush, C. P.; Turner, N. J.; Willetts, A. J. J. Am. Chem. Soc. 1995,

117, 5391-5392. (c) Jenkins, G. N.; Turner, N. J. *Chem. Soc. Rev.* **1995**, *24*, 169-176.

28. (a) Vince, R.; Daluge, S. J. Med. Chem. 1977, 20, 612-613. (b) Vince, R.; Daluge, S.; Lee, H.; Shannon, W. M.; Arnett, G.; Schafer, T.; Nagabhushan, T.; Reichert, P.; Tsai, H. *Science* **1983**, *221*, 1405-1406.
29. (a) Niizuma, S.; Shuto, S.; Matsuda, A. *Tetrahedron* **1997**, *53*, 13621-13632. (b) Shuto, S.; Obara, T.; Saito, Y.; Yamashita, K.; Tanaka, M. *Chem. Pharm. Bull.* **1997**, *45*, 1163-1168. (c) Shuto, S.; Obara, T.; Itoh, H.; Kosugi, Y.; Saito, Y. *Chem. Phram. Bull*. **1994**, *42*, 1163-1168.
30. (a) Shealy, Y. F.; O'Dell, C. A.; Shannon, W. M.; Arnett, G. *J. Med. Chem.* **1984**, *27*, 1416-1421. (b) Bennett, L. L., Jr.; Shealy, Y. F.; Allan, P. W.; Rose, L. M.; Shannon, W. M. *Biochem. Pharm.* **1990**, *40*, 1515-1522. (c) Biggadike, K.; Borthwick, A. D.; Exall, A. M.; Krik, B. E.; Robers, S. M. *J. Chem. Soc. Chem. Comm.* **1987**, 1083-1084.
31. (a) Lee, H.; Vince, R. *J. Pharm. Sci*. **1980**, *69*, 1019-1021. (b) Vince, R.; Turakhia, R. H.; Shannon, W. M.; Arnett, G. *J. Med. Chem.* **1987**, *30*, 2026-2030. (c) Peterson, M. L.; Vince, R. *J. Med. Chem*. **1990**, *33*, 1214-1219. (d) Legraverent, M.; Ngongo-Tekam, R. M. N.; Bisagni, E.; Zeiral, A. *J. Med. Chem.* **1985**, *28*, 1477-1480.
32. (a) De Clercq, E.; Balzarini, J.; Bernaerts, R.; Herdewijn, P.; Verbruggen, A. *Biochem. Biophys. Res. Comm.* **1985**, *126*, 397-403. (b) Shealy, Y. F.; O'Dell, C. A.; Shannon, W. M.; Arnett, G. *J. Med. Chem.* **1983**, *26*, 156-161. (c) Shealy, Y. F.; O'Dell, C. A.; Shannon, W. M.; Arnett, G. *J. Med. Chem.* **1986**, *29*, 483-488. (d) Shannon, W. M.; Arnett, G.; Westbrook, L.; Shealy, Y. F.; O'Dell, C. A. *Antimicrob. Agents Chemother*. **1981**, *20*, 769-776.
33. (a) Konkel, M. J.; Vince, R. *Nucleosides & Nucleotides*. **1995**, *14*, 2061-2077. (b) Konkel, M. J.; Vince, R. *Tetrahedron* **1996**, *52*, 8969-8978. (c) Konkel, M. J.; Vince, R. *Tetrahedron* **1996**, *52*, 799-808. (d) Mikhailov, S. N.; Blaton, N.; Rozenski, J.; Balzarini, J.; De Clercq, E., *Nucleosides & Nucleotides* **1996**, *15*, 867-878. (e) Perez-Perez, M.-J.; Rozenski, J.; Busson, R.; Herdewijn, P. *J. Org. Chem.* **1995**, *60*, 1531-1537.

34. (a) Wang, J.; Froeyen, M.; Herdewijn, P. *Adv. Antivir. Drug Design* **2004**, *4*,119-145. (b) Wang, J.; Herdewijn, P. *J. Org. Chem.* **1999**, *64*, 7820-7827. (c) Wang, J.; Herdewijn, P. *Nucleosides & Nucleotides* **1999**, *18*, 591-592. (d) Wang, J.; Morral, J.; Hendrix, C.; Herdewijn, P. *J. Org. Chem.* **2001**, *66*, 8478-8482. (d) Wang, J.; Vina, D.; Busson, R.,; Herdewijn, P. *J. Org. Chem.* **2003**, *68*, 4499-4505. (e) Wang, J.; Foeyen, M.; Hendrix, C.; Andrei, G.; Snoeck, R.; De Clercq, E.; Herdewijn, P. *J. Med. Chem.* **2000**, *43*, 736-745.

35. (a) Marquez, V. E. *Adv. Antivir. Drug Design* **1996**, *2*, 89-146. (b) Bhushan Rashmi, G.; Vince, R. *Bioorg. Med. Chem.* **2002**, *10*, 2325-2333. (c) Dorr, D. R. Q.; Vince, R. *Nucleosides, Nucleotides & Nucleic Acids.* **2002**, *21*, 665-680.

36. (a) Marquez, V.; Lim, M.; Tseng, C.; Markovac, A.; Priest, M.; Khan, M.; Kaskar, B. *J. Org. Chem.* **1988**, *53*, 5709. (b) Tseng, C.; Marquez, V. *Tetrahedron Lett.* **1985**, *26*, 3669.

37. (a) Mitsunobu, O.; *Synthesis* **1981**, *14*, 405-408. (b) Wachtmeister, J.; Classon, B.; Samuelsson, B.; Kvarnstrom, D.; *Tetrahedron* **1995**, *51*, 2029-2038. (c) Wachtmeister, J.; Classon, B.; Samuelsson, B.; Kvarnstrom, D.; *Nucleosides and Nucleotides* **1995**, *14*, 405-408.

38. (a) Maag, H.; Rydzewski, R. *J. Org. Chem.* **1992,** *57*, 5823. (b) Jeong, L. S.; Marquez, V. E. *Tetrahedron Lett*. **1996**, *37*, 2353-2356.

39. (a) Yoshikawa, M.; Nakae, T.; Cha, B.; Yokokawa, Y.; Kitagawa, I. *Chem. Pharm. Bull*. **1989**, *37*, 545. (b) Yoshikawa, M.; Okaichi, Y.; Cha, B.; Kitagawa, I. *Tetrahedron* **1990**, *46*, 7459.

40. (a) Trost, B. M.; Kuo, G.-H.; Benneche, T. *J. Am. Chem. Soc.* **1988**, *110*, 621-622. (b) Crimmins, M. T.; King, B. W. *J. Org. Chem.* **1996**, *61*, 4192-4193.

41. (a) Clausen, F. P.; Juhl-Christensen, J. *Organic Prep. and Proc. Int.* **1993**, *25*, 373-401. (b) Katagiri, N.; Nomura, M.; Sato, H.; Kaneko, C.; Yusa, K.; Tsuruo, T. *J. Med. Chem*. **1992**, *35*, 1882-1886. (c) Evans, C. T.; Roberts, S. M.; Shoberu, K. A.; Sutherland, A. G. *J. Chem. Soc. Perkin Trans. I*, **1992**, 589-592. (d) Wyatt, P. G.; Anslow, A. S.; Coombs, B. A.; Cousins, R. P. C.; Evans, D. N.; Gilbert, V. S.; Humber, D. C.; Paternoster, I. L.; Sollis, S. L.; Tapolczay, D. J.; Weingarten, G. G.

Nucleosides and Nucleosides **1995**, *14*, 2039-2049. (e) Shaw, G.; Warrener, R. *J. Chem. Soc*. **1958**, 153. (f) Shaw, G.; Warrener, R. *J. Chem. Soc.* **1958**, 157.

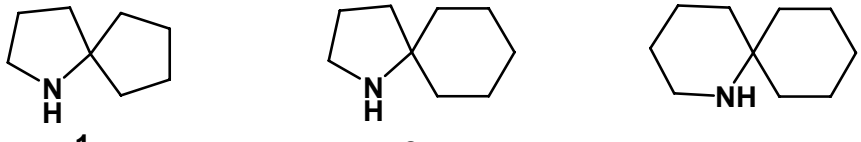
42. Patra, R.; Bar, N. C.; Roy, A.; Achari, B.; Mandal, S. B. *Tetrahedron* **1996**, *52*, 11265-11272.
43. Robins, M. J.; Wnuk, S. F.; Yang, X.; Yuan, C.-S.; Borchardt, R. T.; Balzarini, J.; De Clercq, E. *J. Med. Chem.* **1998**, *41*, 3857-3864.
44. (a) Wittig, G.; Geissler, G. *Justus Leibigs Ann. Chem*., **1953**, *580*, 44. (b) Wittig, G.; Schollkopf, U. *Ber*. **1954**, *87*, 1318.
45. (a) Grubbs, R. H.; Pine, S. H. In *Comprehensive Organic Synthesis,* Trost, B. M.; Fleming, I.; Paquette, L. A. Eds.; Pergamon: New York, 1991, Vol. 5, Chapter 9.3 (b) Schrock, R. R. In *The Strem Chemiker,* Vol. XIV, Strem Chemicals, Newburgport, 1992, No. 1, pp. 1-6. (c) Ivin, K. J.; Mol, J. C. *Olefin Metathesis and Metathesis Polymerization,* Academic Press, San Diego, 1997. (d) For a recent reviews, see: Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413. (e) Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res.* **2001**, *34*, 18. (f) Furstner, A. *Angew. Chem. Int. Ed.* **2000**, *39,* 3012. (g) Kotha, S.; Sreenivasachary, N. *Ind. J. Chem. B,* **2001**, *40*, 763.
46. (a) Reist, E. J.; Goodman, L. *Biochemistry,* **1964**, *3,* 15. (b) Kam, B. L.; Barascut, J.-L.; Imbach, J.-L. *Carbohydr. Res.* **1979**, *69*, 135.
47. Robins, M. J.; Wnuk, S. F.; Yang, X.; Yuan, C.-S.; Borchardt, R. T.; Balzarini, J.; Clercq, E. D. *J. Med. Chem.* **1998**, *41*, 3857-3864.
48. Gurjar, M. K.; Patil, V. J.; Pawar, S. M. *Carbohydr. Res.* **1987**, *165*, 313.
49. Oikawa, Y.; Yoshioka, T.; Yonemitsu, O. *Tetrahedron Lett.,* **1982**, *23*, 885-888.

CHAPTER II

Studies toward the synthesis of FR 901483 and TAN 1251 (A, B, C & D)

1-Azaspirane alkaloids are widely distributed in microbes, plants, animals and various marine organisms.[1] 1-Azspiro[4.4]nonane (**1**), 1-azaspiro[4.5]decane (**2**) and 1-azaspiro[5.5]undecane (**3**) systems form the skeletons of a diverse range of natural products which, almost without exception, are imbued with biological activities (Figure 1). For the last two decades, a variety of these conformationally restricted nitrogen bearing alkaloids were isolated and identified to display an extensive range of important biological activities and are of great interest to the pharmaceutical industry.[2] For

Figure 1:



example, **4**, a GABAa agonist, has the potential for treatment of anxiety and seizure disorders,[3] while compound **5** is an antipruritic α-receptor agonist,[4] bisphosphonic acid derivatives **6** (n = 1,2) are anti-osteoporosis agents,[5] and methoxyamide **7** is a powerful insecticide.[6] In addition, azaspiro[4.5]decanyl amide **8** and its analogs are potent and

Figure 2:

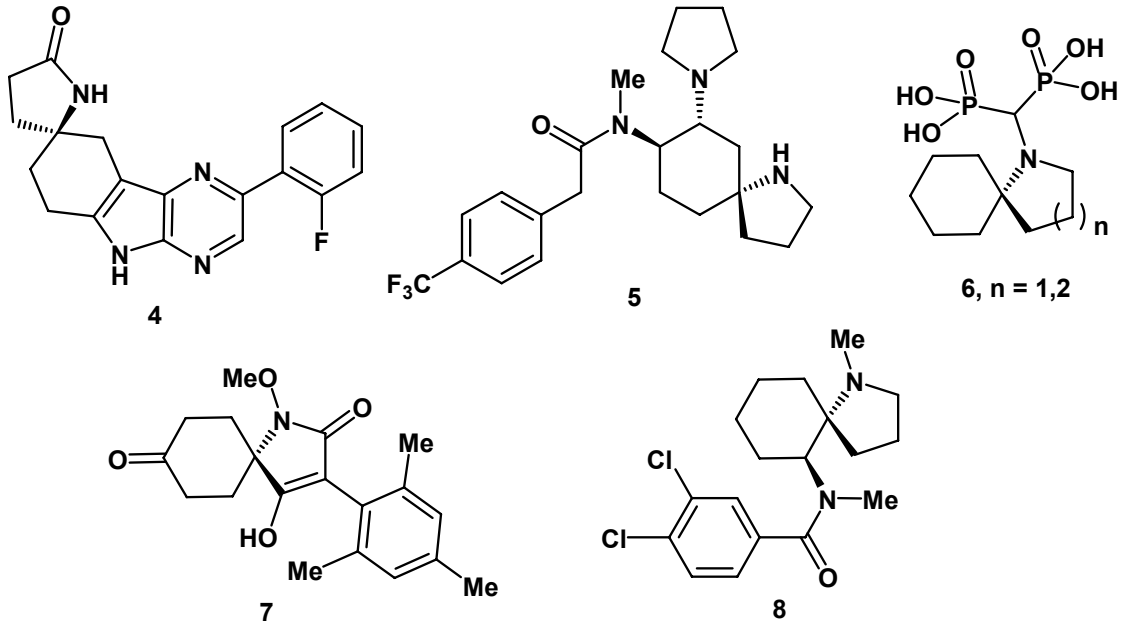
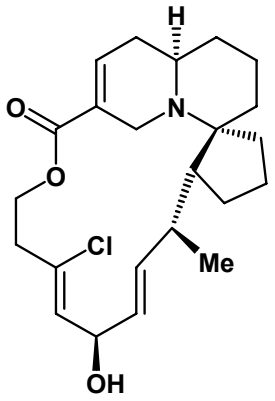
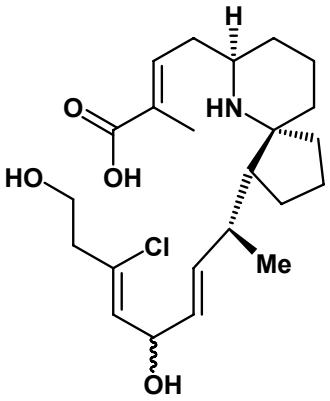


Figure 3:



(+)-Halichlorine (9)



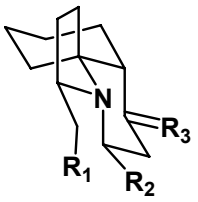
(+)-Pinnaic acid (10)

elective binders to the opioid μ-receptor and display analgesic activity (Figure 2).[7] (+)-Halichlorine (**9**), isolated from the marine sponge *Halichondria okadai* by Uemura, inhibits the expression of VCAM-1 (vascular cell adhesion molecule-1), an important target for the treatment of inflammation and coronary heart disease.[8] Interestingly, the structurally related (+)-pinnaic acid (**10**), isolated from the Okinawan bivalve *Pinna muricata*, is not active against VCAM-1 but is a specific inhibitor of cytosolic phospholipase A_2 (cPLA_2), with IC_{50} value of 0.2 mM (Figure 3).[9]

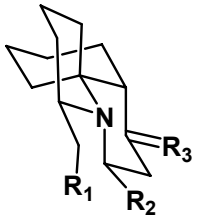
Marine ascidians have become a focus of attention in the last decade as a rich source of bioactive alkaloids. Sine the first members of the cylindricine family A (**11a**) and B (**11b**) were reported in 1993,[10] eight other members of this family have been identified from the Tasmanian ascidians *Clavelina cylindrical*.[11] Also related to this group are lepadiformine (**12**), from the Tunisian ascidian *Clavelina lepadiformis*,[12] fasicularin (**13**) from the Micronesian ascidian *Nephteis fasicularis*[13] and clavepictine A (**14**) isolated from the tunicate *Clavelina picta*.[14] In this general ensemble of compounds, cylindricines exhibited activity in the brine shrimp toxicity bioassay, lepadiformine possessed cytotoxicity toward various tumor cell line, fasicularin shown cytotoxicity toward vero cells, bioactivity agains a DNA-repair-deficient yeast strain and clavepictine A inhibited the growth of murine leukemia and human solid tumor cell lines. (-)-Histrionicotoxin (**15**), isolated in 1971 from the Colombian frog species, *Dendrobates histrionicus*,[15] is a potent noncompetitive blocker of neuromuscular nicotinic receptor-gated channels which,

together with its equally active perhydro derivative (-)-perhydrohistrionicotoxin (**16**), has been used extensively as a biochemical probe (Figure 4).[16]

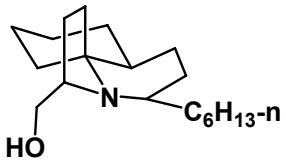
Figure 4:



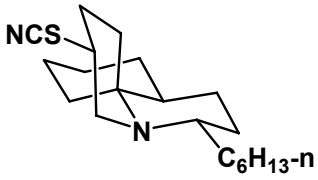
Cylindricines (11a)
R_1 = Cl; OH; OMe;SCN; NCS
R_2 = C_6H_{13}-n; C_4H_9-n
R_3 = O; β-H, α-OAc



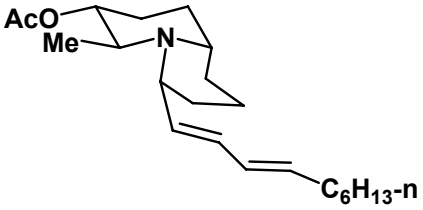
Cylindricines (11b)
R_1 = Cl; NCS
R_2 = C_6H_{13}-n; C_4H_9-n
R_3 = O; β-H, α-OAc



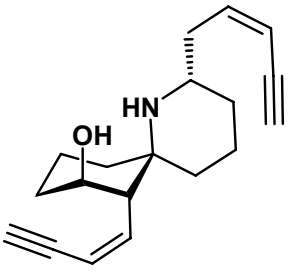
Lepadiformine (12)



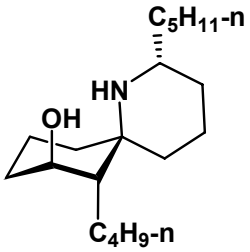
Fasicularin (13)



Clavepictine (14)



(-)-Histrionicotoxin (15)

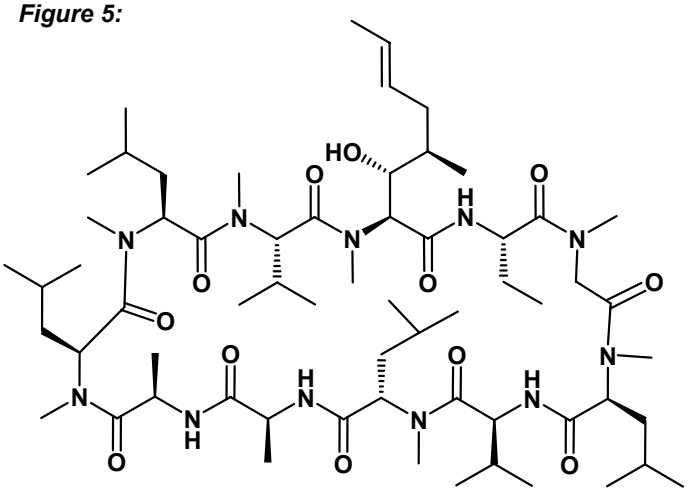


(-)-Perhydrohistrionicotoxin (16)

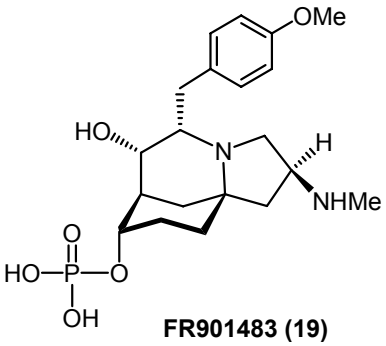
The survival of organ transplant recipients frequently depends on treatment with immunosuppressants. Hence, the introduction of cyclosporine A (CsA) (**17**) in the early 1980s revolutioned the field of organ transplantation by leading to a remarkable increase in the success rate.[17] About a decade later, tacrolimus (formerly designated as FK-506) (**18**), an immunosuppressant that is 10-100 times more potent than CsA, has been marketed clinically.[18] The two compounds exhibit a very similar mechanism of action by suppressing various T cells that play a central role in the induction of immune responses. Because CsA and tacrolimus were found to be toxic at higher doses, the Fujisawa company embarked a screening program to find immunosuppressants that operate by a different

mechanism of action. As a result, the potent immunosuppressant FR901483 (**19**) was isolated from the fermentation broth of *Cladobotrym* sp. No. 11213.[19] It is believed that **19** inhibits purine nucleotide biosynthesis and hence, it functions by a different mechanism that CsA and tacrolimus. FR901483 has been shown to prolong graft survival time in the rat skin allograft model significantly. (Figure 5)

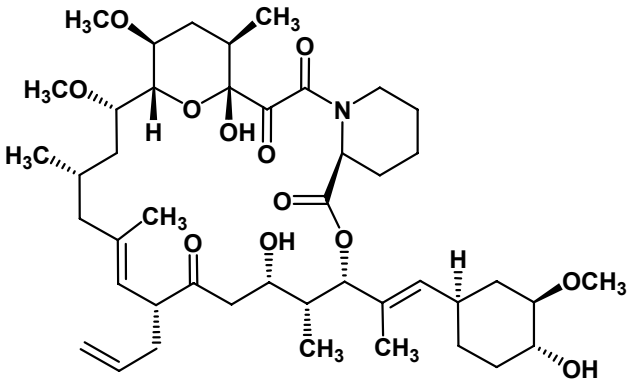
Figure 5:



Cyclosporin A (17)



FR901483 (19)

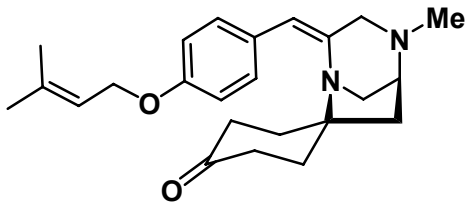


FK 506 (18)

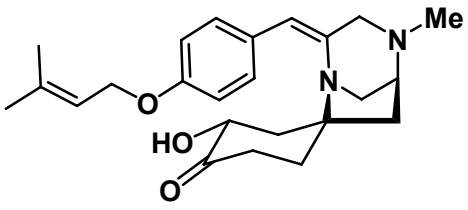
TAN1251A-D (**20-23**) form a family of novel tricyclic alkaloids that were isolated from a culture broth of *Penicillium thomii* RA-89 by Takeda Industries in 1992 (Figure 6).[20] Both TAN1251A (**20**) and TAN 1251B (**21**) are selective and highly potent M_1 muscarinic receptor antagonists, inhibiting the acetylcholine-induced contraction of Guinea-pig ileum with an ED_{50} of 8.0 and 10.0 nM, respectively. Muscarinic receptors, one of the two types of choligergic receptors of acetylcholine, are located primarily on the

post-synaptic cell membranes of smooth muscle, cardiac muscle and glandular tissue at the ends of parasympathetic nerve pathways. These receptors play an important role in the physiological effects of the parasympathetic nerve activities such as heart rate, contraction of a wide range of smooth muscles and vasodilatation. They are also present at the ends of peripheral parasympathetic neurons and control the auto-inhibition of the transmitter release. Lastly, they are widely spread in the central nervous system and play important roles in the limbic system and basal ganglia function.

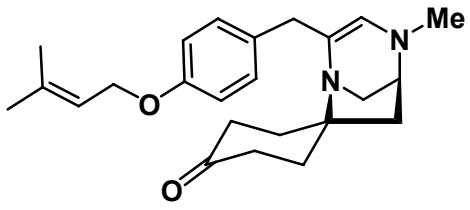
Figure 6:



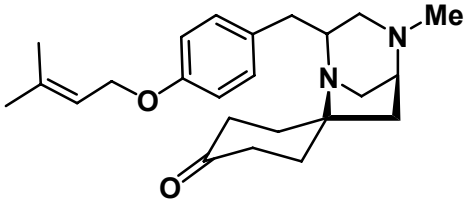
(-)-TAN1251A (20)



(+)-TAN 1251B (21)



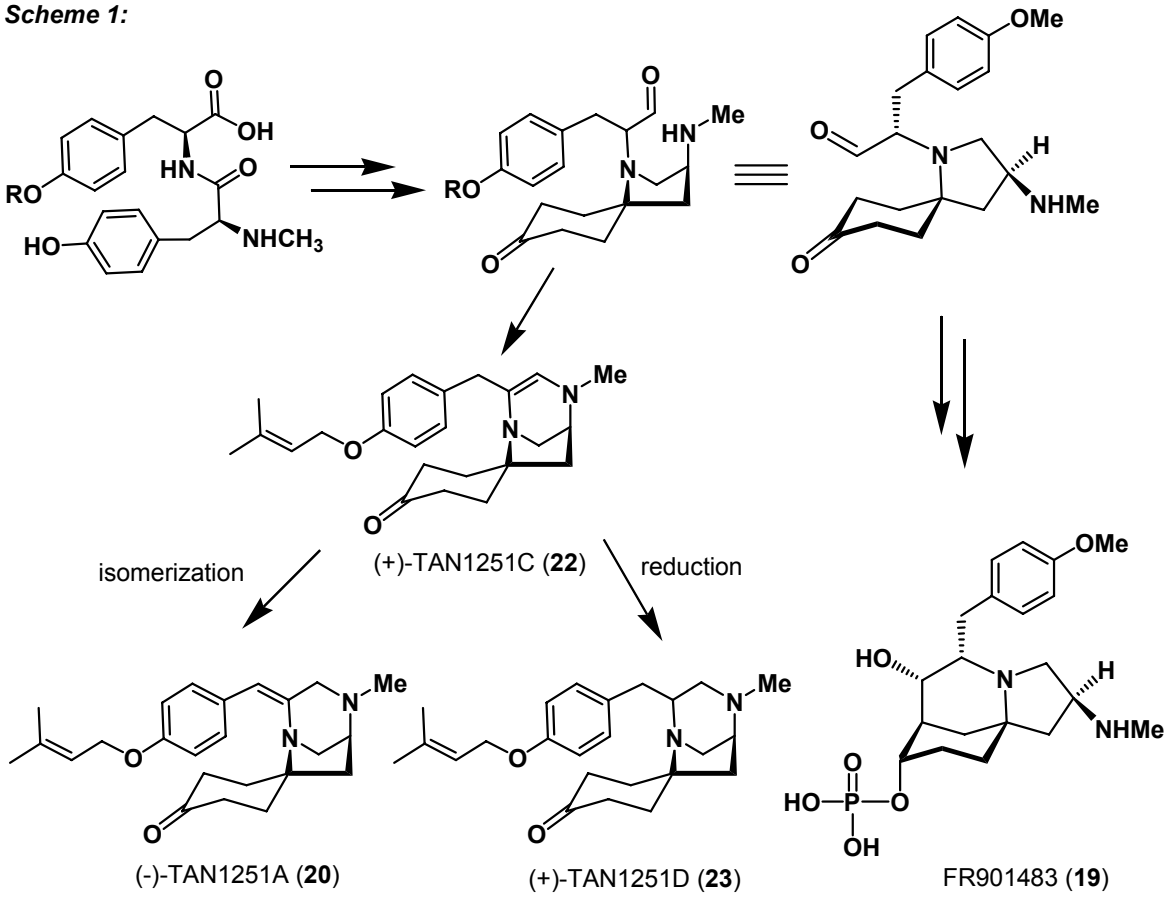
(+)-TAN1251C (22)



(+)-TAN1251D (23)

It is believed that FR901483 and TAN1251 compounds are biosynthetically related, which may be biosynthesized from a tyrosine dimer **24** by an oxidative coupling to close the pyrrolidine ring providing intermediate **25**. Intramolecular aldol condensation of **25** leads to the tricyclic skeleton of FR901483 (**19**). Enamine formation of **25** should be providing TAN1251C (**22**), which could be isomerized to TAN1251A (**20**) or reduced to TAN1251D (**23**) (Scheme 1).

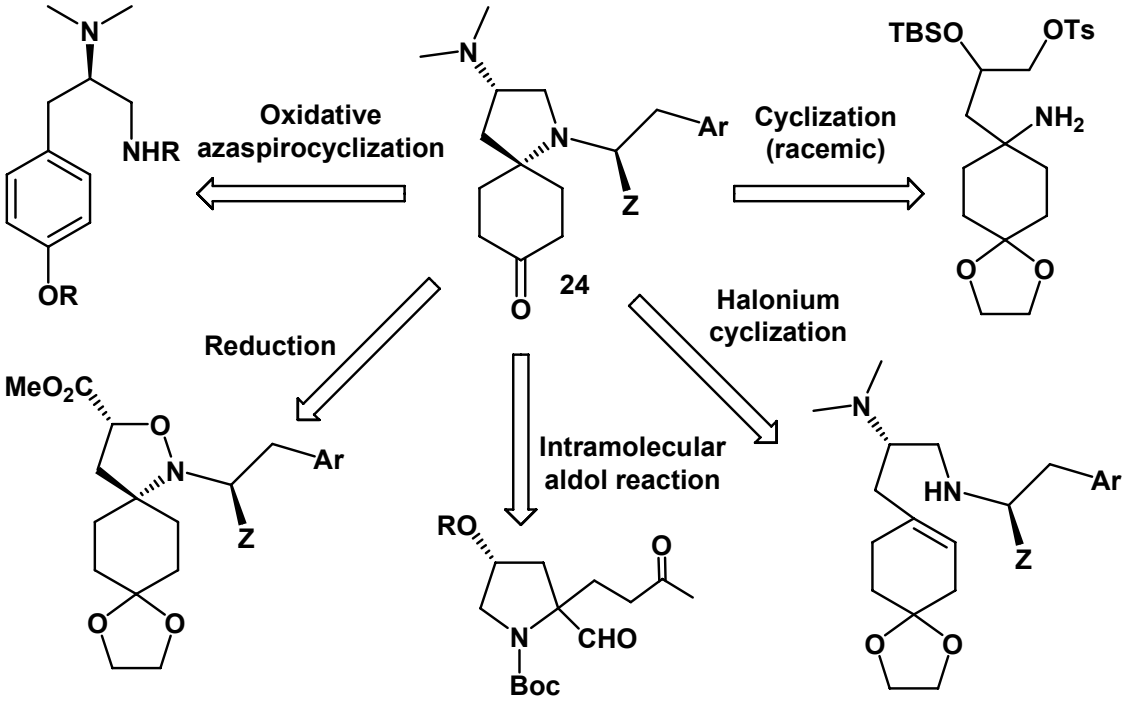
Scheme 1:



Past Work:

Several procedures have been described for the preparation of enantiopure spiro-bicyclic framework **24** enroute total synthesis of FR901483 and TAN1251 compounds. Snider's approach[21] consisted an intramolecular nitrone/alkene cycloaddition reaction as the key step followed by reduction of the labile N-O bond and lactamization. Approaches by Sorensen,[22] Ciufolini,[23] Wardrop,[24] and Honda[25] are based on the oxidative azaspirocyclization of tyrosine derivatives to give the corresponding 4,4-disubstituted cyclohexadienones, which after hydrogenation give compounds of type **24**, while Bonjoch's approach was based on the iodine promoted iodoaminocyclization[26] and halonium promoted cyclization of amino-tethered cyclohenenes.[27] Kawahara[28] reported the first synthesis of racemic 1-Azaspiro[4.5]decane skeleton in the synthesis of (±)-TAN1251A, however, the same group disclosed the synthesis of compound type **24** starting from 4-Hydroxy-L-proline as chiral source (Figure 7).[29]

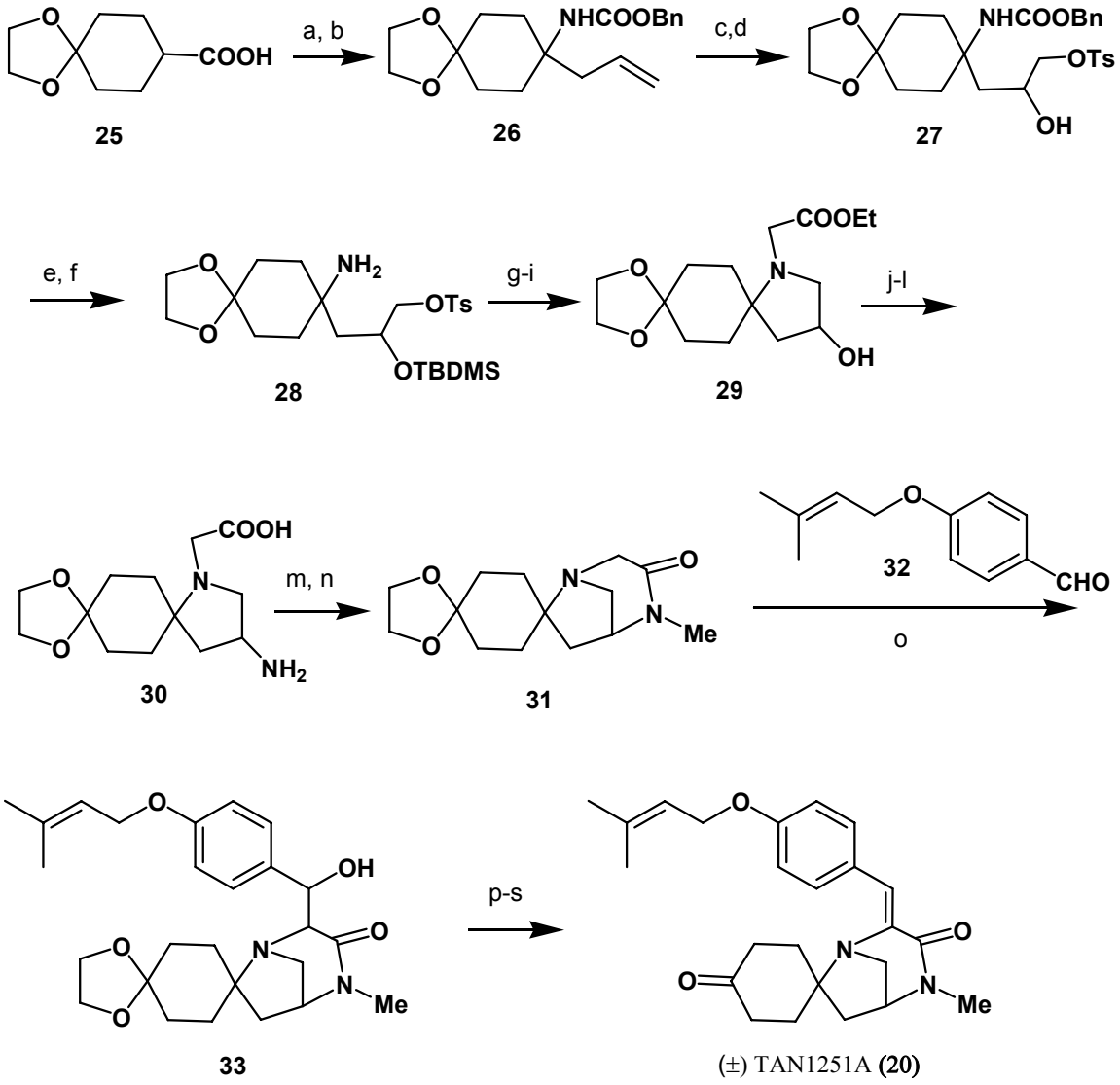
Figure 7:



Kawahara's approach:

In 1998, Kawahara and co-workers reported the first total synthesis of (±)-TAN1251A (**20**).[28] Synthesis was initiated by allylation of carboxylate **25** in the presence of LDA and the resulting allyl derivative was then subjected to curtius rearrangement using DPPA followed by benzylation to obtain **26**. Dihydroxylation followed by monotosylation provided **27**, subsequent protection of the secondary hydroxyl as its silyl ether and hydrogenation yielded **28**. Alkali mediated cyclization followed by treatment with ethylbromoacetate resulted in the azaspiro derivative **29**. Introducing azide group using Mitsunobu conditions followed by reduction and ester hydrolysis provided **30**, which was further subjected DPPA mediated cyclization and N-methylation to get tricyclic derivative **31**. Inter molecular Aldol reaction between **31** and **32** resulted in the aldol adduct **33**. Finally, mesylation, elimination followed by treatment with acid provided the target (±)-TAN1251A (**20**) (Scheme 2).

Scheme 2:

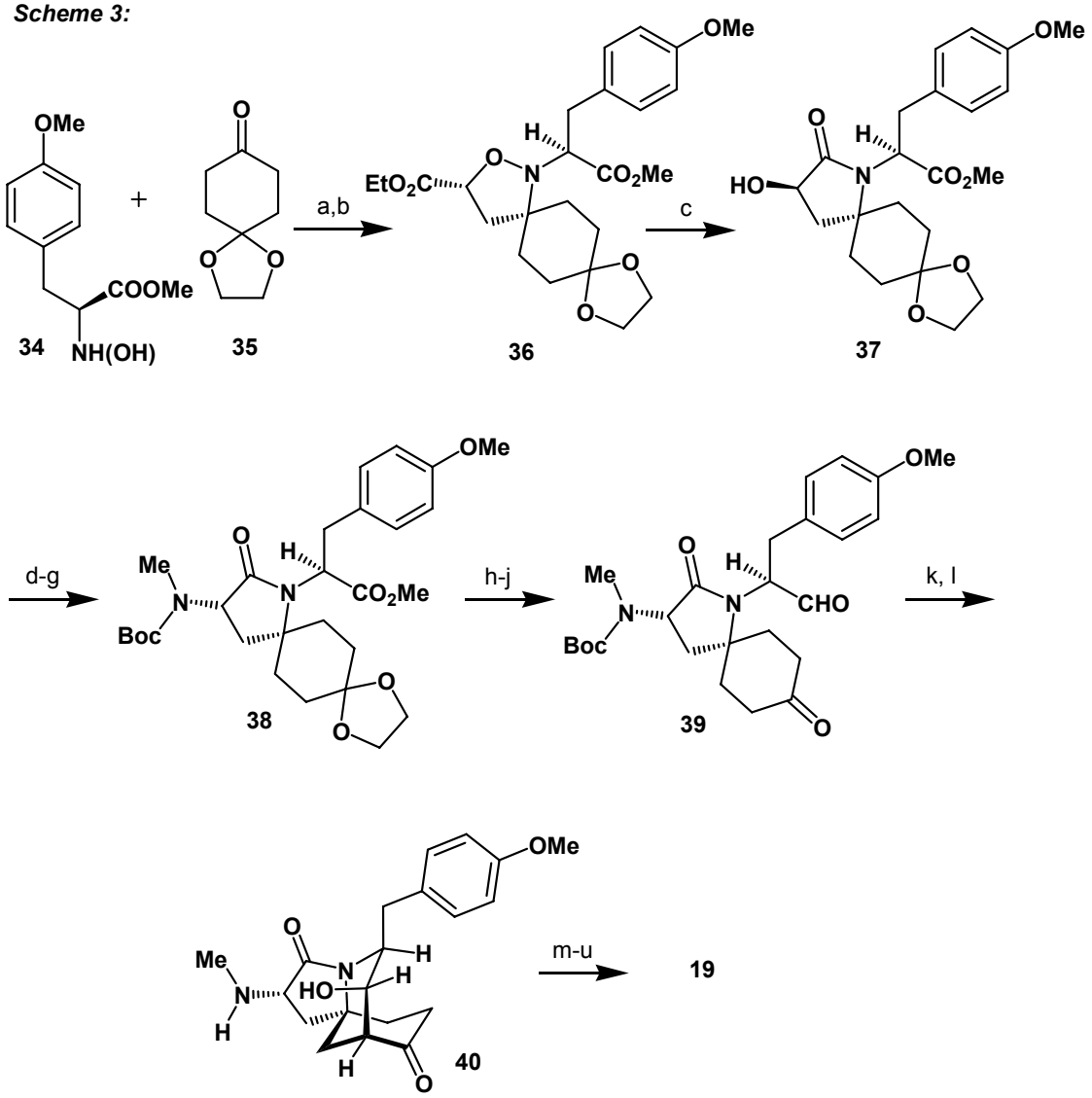


Reagents and conditions: a) LDA, allylbromide, THF; b) DPPA, benzene, reflux then BnOH; c) cat. OsO_4, NMO, Acetone/H_2O; d) TsCl, DMAP, pyridine; e) TBDMSCl, Imidazole, CH_2Cl_2; f) 5% Pd/C, MeOH; g) DBU, benzene, reflux; h) Ethylbromoacetate, K_2CO_3; i) TBAF, THF; j) DPPA, DEAD, THF, toluene; k) 5% Pd/C, MeOH; l) LiOH, H_2O; m) DPPA, Et_3N, DMF; n) MeI, NaH, THF; o) LDA, THF, -78^o C; p) MsCl, Et_3N, CH_2Cl_2 q) ^{t}BuOK, THF; r) $LiAlH_4$, $AlCl_3$, ether; s) 1N HCl, acetone

Snider's approach:

In 1998, Barry Snider reported the synthesis of (±)-desmethylamino FR901483 and in 1999, disclosed the first total synthesis of (-)-FR901483 (**19**) and established the absolute stereochemistry.[21] His strategy invoked the use of a 1,3-dipolar cycloaddition and

Scheme 3:



Reagents and conditions: a) EtOH, 25^{o} C; b) Ethylacrylate, toluene, reflux; c) 45 psi, H_2, Pd/C,AcOH; d)TsCl, DMAP, Et_3N, DMF; e) NaN_3, DMF; f) H_2, Pd/C, Boc_2O; g) NaH, MeI, DMF; h) $LiBH_4$, THF then HCl, AcOH/H_2O; i) Boc_2O, Et_3N; j) Dess-Martin; k) KO*t*-Bu, *t*-BuOH; l) TFA/CH_2Cl_2; m) LAH, THF, -78^{o} C to 65^{o} C; n) Et_3N, CbzCl; o) *p*-NO_2PhSO_2Cl, DMAP, Et_3N; p) TESOTf, Et_3N; q) CsOAc, 18-crown-6, benzene, reflux; r) K_2CO_3, MeOH; s) Tetrazole, $(BnO)_2PN(i\text{-}Pr)_2$ then *t*-BuOOH;t) TBAF/THF; u) HCl, then H_2/Pd, MeOH

an intramolecular aldol reaction as the key steps arriving at the tricyclic core of compound **40**. Snider started with known hydroxylamine **34**, which is available in three steps from N-Boc-L-tyrosine *via* methylation of the carboxylic acid moiety, hydrolysis of the Boc group and oxidation of the resulting secondary amine. Condensation of **34** with ketone **35** provided an optically active nitrone, which was heated with ethyl acrylate to yield the 1,3-dipolar cycloadduct **36**. Palladium catalyzed hydrogenation of **36** provided lactam **37**.

Tosylation and reaction with sodium azide provided an azide, which upon hydrogenolysis in the presence of Boc-anhydride and methylation furnished N-methylcarbamate **38**. A one-pot reduction of the methyl ester to the corresponding alcohol and hydrolysis of the acetal took place with concurrent cleavage of the Boc protecting group. Reintroduction of the Boc-group and Dess-Martin oxidation provided the crude aldol precursor **39**. Intramolecular aldol condensation of **39** gave the desired product **40** as the major compound after Boc-protecting group removal. Reduction of **40** with LAH and acylation with CbzCl resulted in a carbamate. The equatorial alcohol at C-9 was converted to the nosylate, followed by protection of the C-7 axial alcohol as a triethylsilyl ether, subsequent displacement of the nosylate with cesium acetate, followed by hydrolysis of the resulting axial acetate and phosphorylation introducted the phosphate ester moiety at C-9. Cleavage of the triethylsilyl protecting group at C-7, formation of the monochloride salt and hydrogenolysis yielded the desired monohydrochloride salt of (-)-FR901483. The first asymmetric synthesis of compound **19** was accomplished in 22 steps and 2% overall yield (Scheme 3).

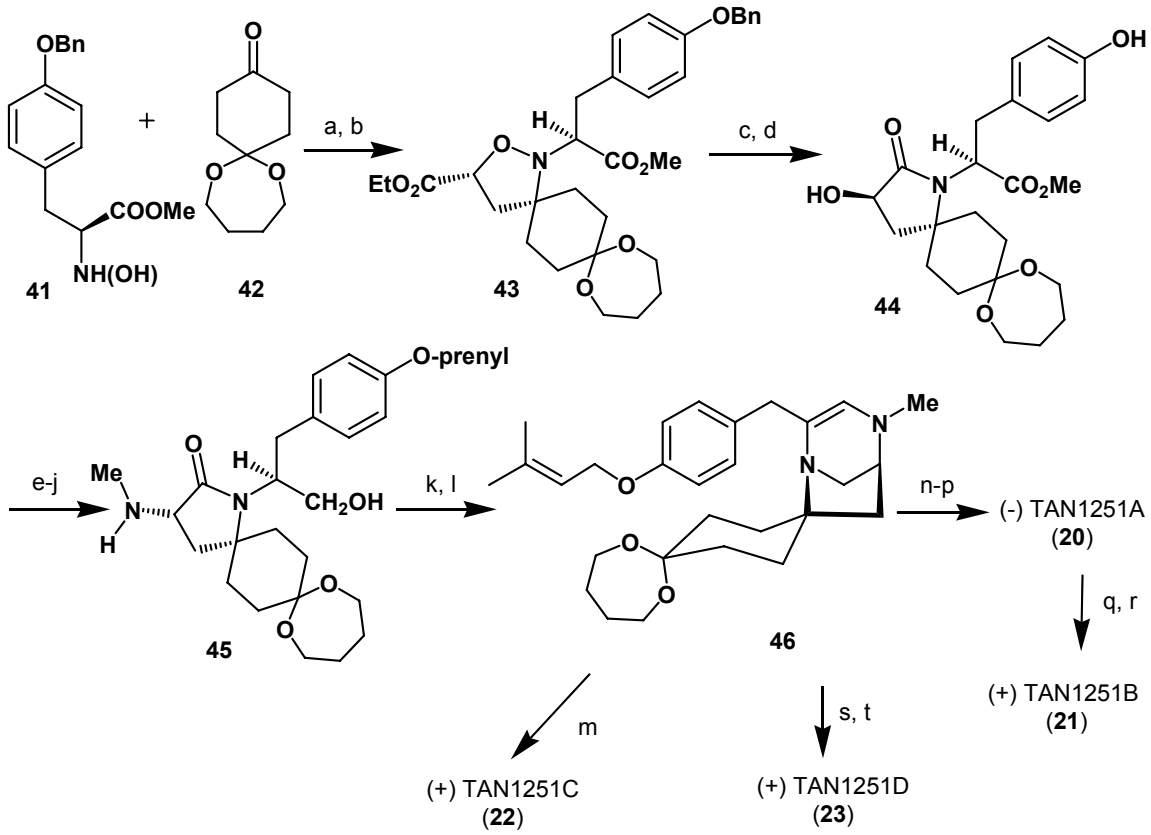
Implying the same synthetic strategy, Snider reported the first total synthesis of (+)-TAN1251B, (+)-TAN1251C, (+)-TAN1251D and enantiomeric synthesis of (-)-TAN1251A. 1,3-Dipolar cycloaddition of chiral nitrone obtained from the condenation of **41** and **42** with ethyl acrylate produced spirocycle **43**. Transformation of **43** to 1-azaspiro[4.5]decane **44** was achieved by hydrogenolysis of the N-O bond and cyclization to form the spirolactam. Alkylation of the phenol moiety in **44**, tosylation of the secondary alcohol and substitution with sodium azide and subsequent reduction and protection of the amine group resulted **45**. Oxidation of the primary alcholol **45** followed by cyclization yielded **46**, which on acidic hydrolysis of the acetal group provided the natural product (+) TAN1251C (**22**). (-)-TAN1251A (**20**) and (+)-TAN1251D (**23**) were also made from **46** while (+)-TAN1251B (**21**) was derived from **20** (Scheme4).

Sorensen's approach:

In 2000, Erik Sorensen published the second total synthesis of (-)-FR901483.[22] His strategy invoked the use of an oxidative spiroannulation for azaspirane system and an intramolecular aldol addition reaction to form the tricyclic core of the natural product.

Sorensen started with aldehyde **47** and amine **48**, both obtained in 2 and 5 steps respectively from commercially available N-Boc-L-tyrosine. Reductive coupling of **47** and **48** yielded phenol **49**. Exposure of **49** to iodobenzene diacetate resulted in the desired spiroannulation product **50**. Exchange of the nosyl for the more sturdy Boc protecting group was followed by reduction of the dienone moiety to yield an inconsequential mixture

Scheme 4:

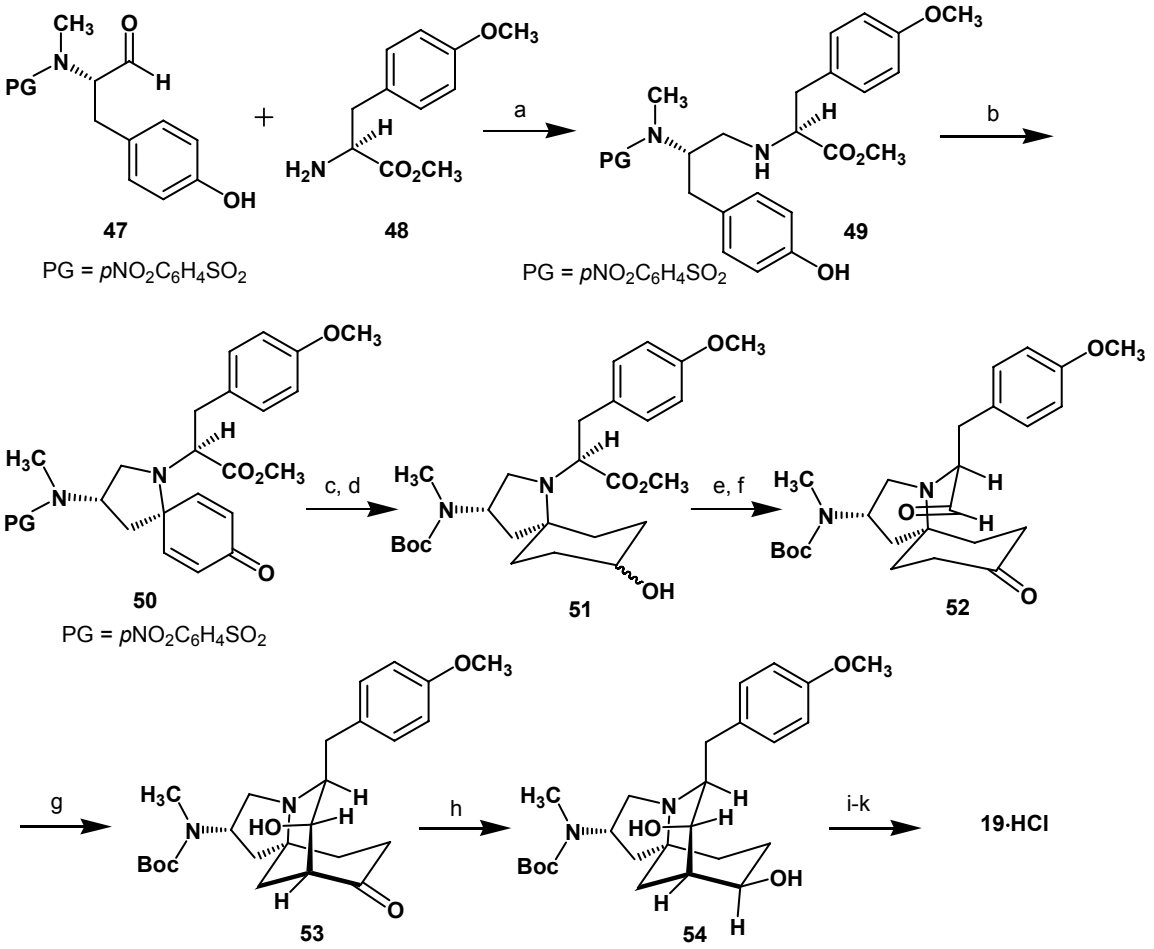


Reagents and conditions: a) EtOH, 25° C; b) Ethylacrylate, toluene, 100° C c) 45 psi, H_2, Pd/C,AcOH; d) 5% AcOH/CH_2Cl_2; e) prenyl bromide, Cs_2CO_3, 50° C, acetone; f) TsCl, Et_3N, DMAP; g) NaN_3, DMF; h) LAH, THF, reflux; i) HCO_2Ac; j) LAH, THF; k) TFAA, Et_3N, DMSO; l) K_2CO_3, MeOH/H_2O; m) 0.1 M HCl, aq. acetone; n) DDQ, CH_2Cl_2; o) $NaCNBH_3$, MeOH/AcOH; p) 0.1 M HCl, aq. acetone; q) LDA, THF, -78° C then TMSCl; r) OsO_4, NMO, *t*-BuOH; s) $NaCNBH_3$, $(CF_3)_2CHOH$; t) 0.1 M HCl, aq. acetone

of alcohol products at C-9 in azaspirane compound **51**. Reduction of the methyl ester and Swern oxidation gave ketoaldehyde **52** as a single stereoisomer. Aldol cyclization afforded the desired compound **53** in a modest yield. Hydrogenation of **53** with Raney Nickel resulted in compound **54** as a single diastereomer. Mitsunobu-type inversion of the C-9 stereochemistry installed the desired monophosphate ester with a modest yield, but in an

unprecedented reaction fashion in complex natural product synthesis. Hydrogenolysis of the dibenzylphosphate moiety and removal of the Boc-protecting group furnished the hydrochloride salt of the target **19** (Scheme 5).

Scheme 5:



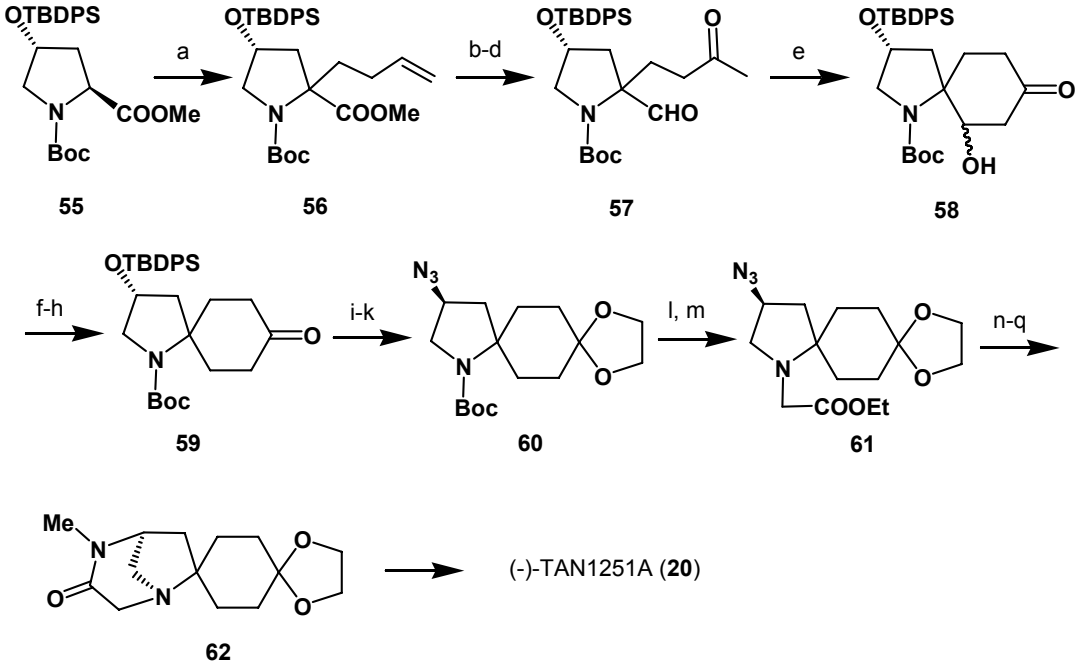
Reagents and conditions: a) $NaBH(OAc)_3$, 4ÅMS, 0^o C, 1h, then RT, 24 h; b) $PhI(OAc)_2$, $(CF_3)_2CHOH$; c) NaSPh, DMSO; then $(Boc)_2$, pyr.; d) H_2, Raney Ni, EtOAc/EtOH; e) $LiAlH_4$, THF, -78^o C; f) $(COCl)_2$, DMSO. CH_2Cl_2, -78^o C, then iPr_2NEt, -78^o C; g) NaOMe, MeOH, 0^o C; h) H_2, Raney Ni, EtOAc/EtOH; i) dibenzyl hydrogen phosphate, tris(4-chlorophenyl)phosphine, DIAD, Et_3N, toluene; j) H_2, Pd/C, MeOH; k) 4N HCl, dioxane, 0^o C

Nagumo and Kawahara's approach:

In 2002, Nagumo and Kawahara reported the synthesis of (-)-TAN1251A (**20**) using *trans*-4-Hydroxy-L-proline as a chiral source.[29] They have initiated the synthesis by alkylation of **55** with 4-iodo-1-butene using LDA to afford diastereomeric mixture of **56**. They have carried out the synthesis using both the isomers separately to get **59**, a same

intermediate for the synthesis of **20**. DIBAH reduction of **56**, oxidation of the resulting alcohol using TPAP followed by Wacker oxidation resulted in ketoaldehyde **57**. Aldol cyclization of **57** under alkaline conditions produced azaspiro derivative **58**, which on mesylation followed by silicagel-assisted elimination and hydrogenation provided azaspiro-keto compound **59**. Acetalization of **59** with ethyleneglycol, desilylation and Mitsunobu-type reaction to introduce azide group using DPPA yielded azide **60**. Removal of the Boc group and alkylation with ethylbromoacetate afforded **61**, which was then converted into tricyclic amide **62** by the sequence of catalytic hydrogenation, hydrolysis of the ester group, lactam ring formation and methylation. As Kawahara already described the synthesis of (±)-TAN1251A from racemic **62**, same can be followed to obtain the target (-)-TAN1251A (**20**) (Scheme 6)

Scheme 6:

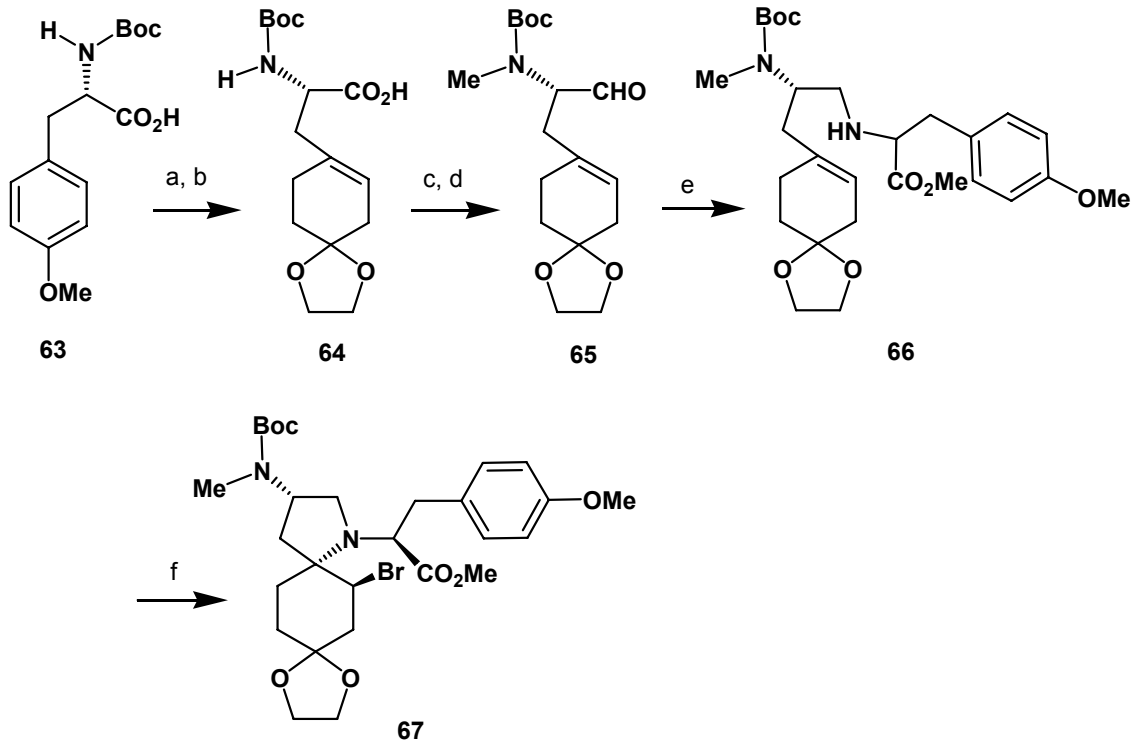


Reagents and conditions: a) LDA, HMPA, 4-iodo-1-butene, THF, -78^{o} C; b) DIBAH, toluene, -39^{o} C; c) TPAP, NMO, CH_2Cl_2; d) $PdCl_2$, $CuCl_2$, O_2, H_2O, DMF; e) KOH, EtOH, 0^{o} C; f) MsCl, Et_3N, CH_2Cl_2; g) silicagel column chromatography; h) 20% $Pd(OH)_2/C$, H_2, benzene; i) $(CH_2OH)_2$, TsOH, benzene, reflux; j) TBAF, THF; k) DPPA, Ph_3P, DEAD, THF; l) TFA; m) $BrCH_2COOEt$, K_2CO_3,CH_3CN; n) 5% Pd/C, H_2, MeOH; o) LiOH, H_2O; p) DPPA, Et_3N, DFM; q) CH_3I, NaH, THF.

Bonjoch's approach:

In 2003, Bonjoch reported the synthesis of enantiopure 3-amino-1-azaspiro[4.5]decan-8-ones by halonium promoted cyclization of amino-tethered cyclohexnes.[27] They have started their synthesis with a Birch reduction on tyrosine derivative **63** to give the corresponding dihydroanisole, enol ether of which was converted into the ethylene acetal to afford carboxylic acid **64**. N-methylation and esterification of **64**, followed by DIBAL-H reduction of ester provided aldehyde **65**. Reductive amination of **65** with (di-OMe)-L-tyrosine furnished **66**. Haloaminocyclization of **66** was carried out using 2,4,4,6-tetrabromo-2,5-cyclohexadienone as a source of bromonium ions to provide **67** as a mixture of diastereoisomers. Both the isomers are useful intermediates for the synthesis of FR901483 (**19**) and TAN1251 series of compounds (Scheme 7).

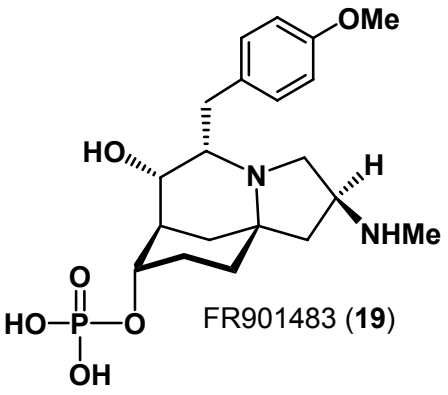
Scheme 7:



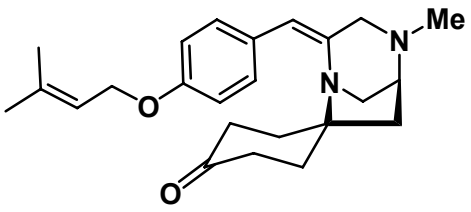
Reagents and conditions: a) Li, NH_3, EtOH, -78^o C; b) $(CH_2OH)_2$, $BF_3.Et_2O$, THF; c) MeI, NaH, DMF; d) DIBAL-H, toluene, -78^o C; e) (diOMe)-L-tyrosine, $MgSO_4$, CH_2Cl_2; then $NaBH_4$, MeOH; f) 2,44,6-tetra bromo-2,5-cyclohexanedienone, CH_2Cl_2.

Immunosupressant FR901483 (**19**)[19] and antimuscarinic TAN1251 family (**20**, **21**, **22** & **23**)[20] are architecturally interesting natural products that display a novel tricyclic azaspirane core. Due to their attractive biological properties and structural novelty, FR901483 and TAN1251 series of compounds have been the subject of extensive synthetic research. There has been a growing interest over the last few years in the development of novel synthetic methodologies to achieve the enantiopure synthesis of aforementioned natural products, mainly because of their structural challenges from synthetic point of view (Figure 1).

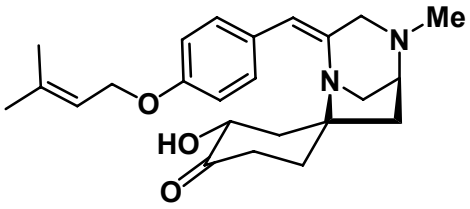
Figure 1:



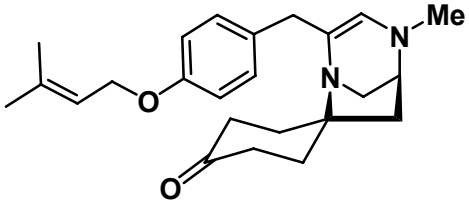
FR901483 (**19**)



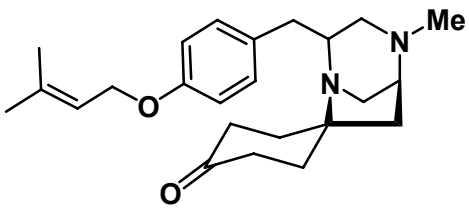
TAN1251A (**20**)



TAN 1251B (**21**)



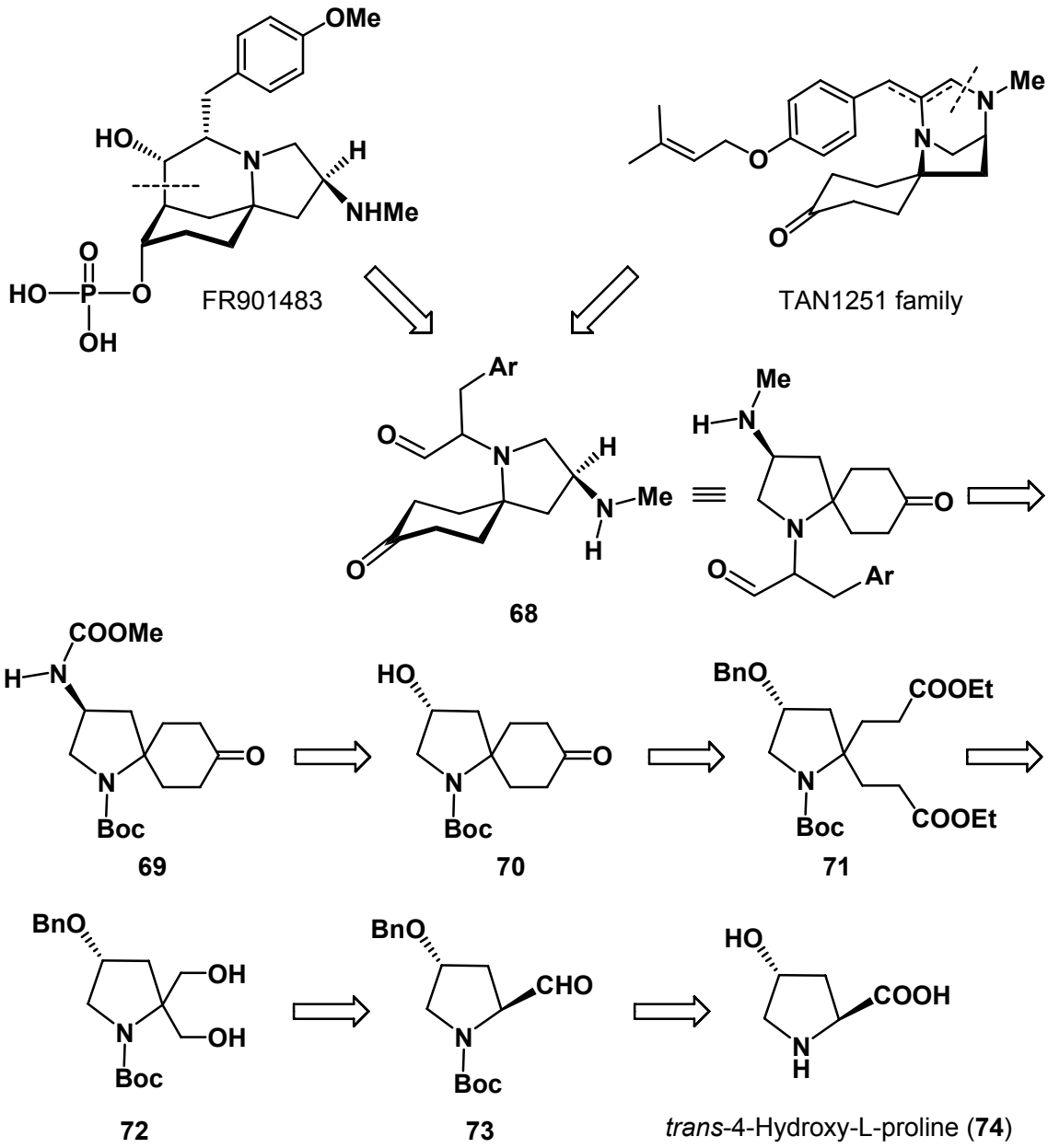
TAN1251C (**22**)



TAN1251D (**23**)

The retrosynthetic analysis of FR901483 (**19**) and TAN1251 family of compounds envisioned 3-amino-1-azaspiro-[4.5]decan-8-one (**69**) as an advanced potential common intermediate from which the total synthesis of all the above mentioned natural products could be achieved. Further, **69** can be obtained by installation of an azide group and N-alkylation of compound **70**, which in turn would be accessed by the

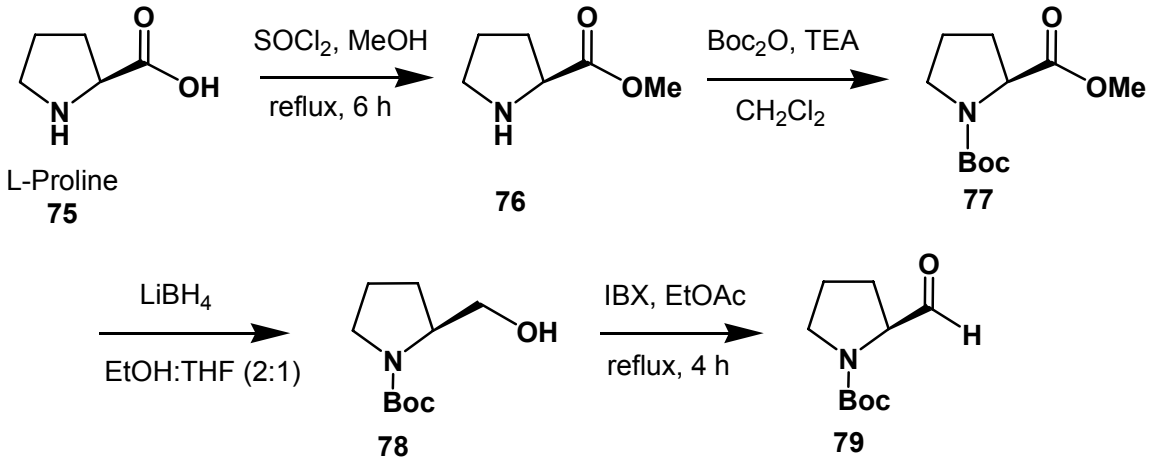
Scheme 1:



Dieckmann cyclization followed by Krapcho's decarboxylation of diester **71**. The diester **71** could be obtained by a two carbon Wittig homologation and reduction of the resulting unsaturated ester of compound **72**. In order to establish the spiro-ring system, it is

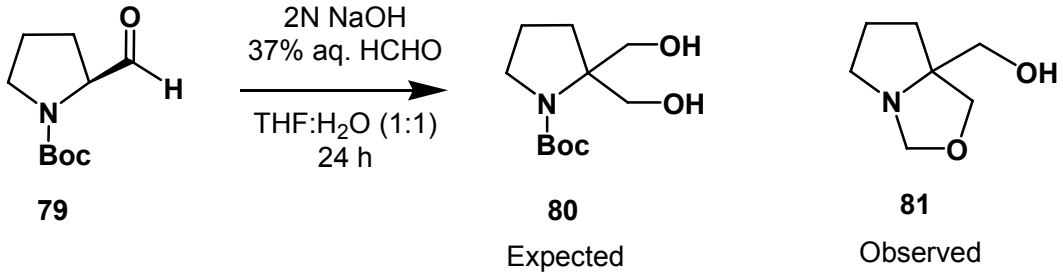
envisioned to introduce the hydroxymethyl group at C-5 by Tollens's reaction on aldehyde derivative **73,** which can be derived from naturally occurring *trans*-4-hydroxy-L-proline (**74**) (Scheme 1). To study the success of constructing the spiro-ring system by this strategy we chose naturally occurring L-proline (**75**) as initial starting material. Thus, L-proline was converted to its corresponding methyl ester derivative **76** by refluxing in MeOH in the presence of thionyl chloride for 6 h. It was then treated with Boc_2O in CH_2Cl_2 in the

Scheme 2:



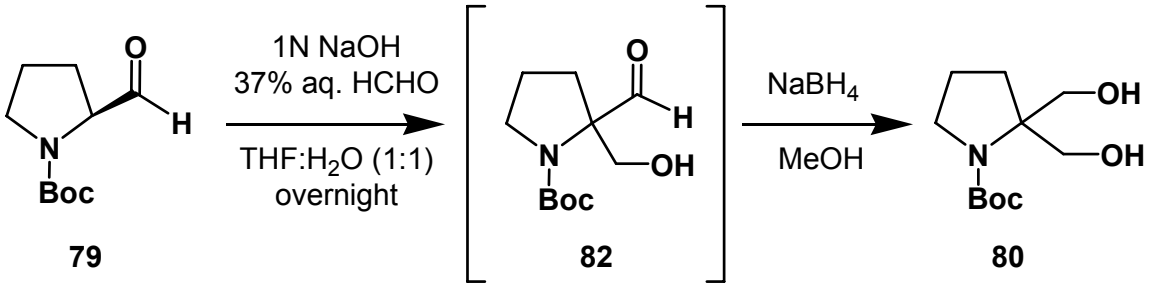
presence of TEA to yield N-Boc-proline ester **77**. $LiBH_4$ reduction of **77** in EtOH:THF (2:1) at room temperature provided the N-Boc-prolinol (**78**), which was subjected to IBX mediated oxidation reaction[30] in refluxing EtOAc to furnish the aldehyde derivative **79** (Scheme 2). Following the lines of retrosynthetic analysis aldehyde derivative **79** was exposed to Tollen's reaction conditions[31] to install hydroxymethyl group at C-2. Exposing to the usual Tollen's conditions did not give the expected diol derivative **80**, but upon using excessive reagents witnessed the formation of a very unusual and unexpected bicyclic oxazole derivative **81** in good yield (Scheme 3). Compound **81** was thoroughly

Scheme 3:



characterized by ^{1}H, ^{13}C NMR, IR, mass spectra and elemental analysis, which suggested the structure of **81**. For instance, in the ^{1}H NMR spectrum signals due to methylene protons linked to O and N appeared at δ 4.25 and δ 4.47 as two sets of doublet (J = 6.5 Hz) whereas the second methylene group of the oxazole ring appeared at δ 3.58 as a ABq (J = 8.5 Hz). The hydroxymethyl protons appeared at δ 3.44 as a ABq (J = 11.1 Hz). In the ^{13}C NMR spectrum, resonances due to carbon linked to O and N was visualized at δ 87.4 while quaternary carbon resonated at δ 74.1. Presence of six methylenic carbons and one quaternary carbon as indicated by its DEPT spectra. The characteristic signals due to Boc group were missing. In the IR spectroscopy C=O adsorption was missing. The mass spectral analysis and Elemental analysis further supported the assigned structure for **81**. After monitoring the reaction closely it is observed that the initial aldol reaction on aldehyde derivative is occurring but failing to undergo successive cross-Cannizaro reduction of the resulting hydroxy aldehyde **82** under the conditions employed. To prevent the formation of undesired oxazole derivative **81** and to obtain the desired diol derivative **80** we have modified the reaction conditions. Under the modified reaction conditions the initial aldol reaction was administered by careful addition of 1 N NaOH (3 equiv.) followed by 37% aqueous HCHO (2 equiv.) and successive reduction of the resulting hydroxyl aldehyde **82** was accomplished by using $NaBH_4$ to obtain required diol derivative **80** successfully (Scheme 4). In the ^{1}H NMR spectrum of **80**, four hydroxylmethyl protons appeared at δ 3.56 (2H, multiplet) and 3.86 (2H, doublet, J = 11.8 Hz) whereas all the other protons appeared in accordance with the assigned structure

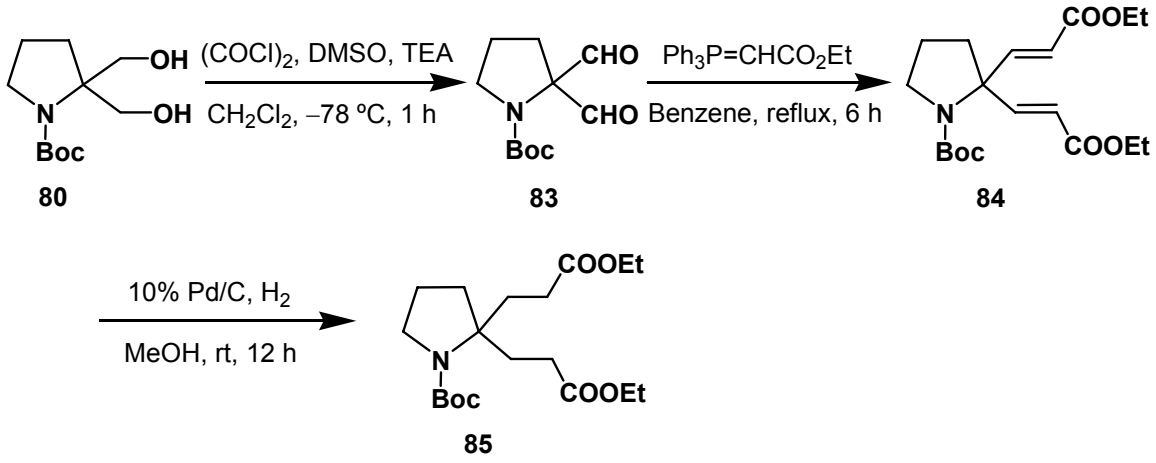
Scheme 4:



of **80**. In the ^{13}C NMR spectrum quaternary carbon resonated at δ 80.5 and all the other carbons resonated at their expected chemical shift values. The IR, mass spectra and elemental analysis were in agreement with the structure of **80**. After having the prerequisite

diol derivative in hand, our immediate concern was to extend the carbon chain in order to construct the six membered spiro-ring system under Dieckmann cyclization conditions. Thus the diol derivative **80** was oxidized under Swern oxidation conditions[32] to give its corresponding dialdehyde derivative **83** which was immediately subjected to a two carbon Wittig olefination[33] in refluxing benzene with $Ph_3P{=}CHCO_2Et$

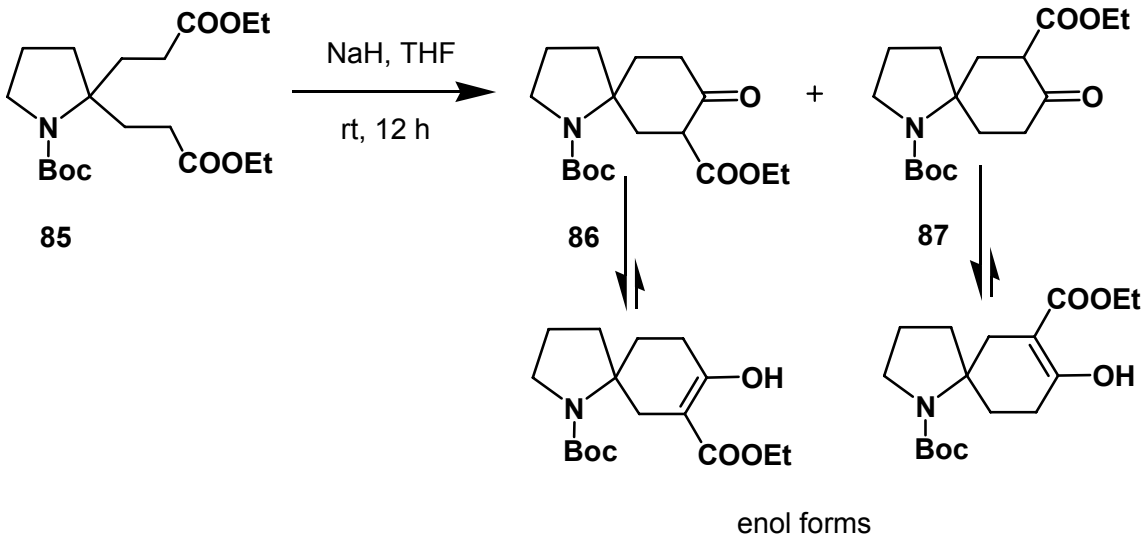
Scheme 5:



to furnish *bis*-α,β-unsaturated ester derivative **84**. In the ^{1}H NMR spectrum of **84**, the characteristic signals of olefinic protons appeared at δ 5.80 (2H) and 7.04 (2H) as two doublets (J = 15.9 Hz). Two methyl groups of the carbethoxy esters appeared as a triplet at δ 1.31 (6 H, J = 7.1 Hz), whereas methylene groups resonated as a quartet at δ 4.21 (4 H, J = 7.1 Hz). In the ^{13}C NMR spectrum of **84**, the olefinic carbons resonated at δ 120.4 and 148.8, while all other carbons appeared at their expected chemical shift values. IR, mass spectral data and elemental analysis are in accordance with the assigned structure of **84**. Hydrogenation of the double bonds of **84** was carried out in the presence of catalytic 10% Pd/C in MeOH at normal temperature and pressure to afford **85** (Scheme 5). The ^{1}H NMR, ^{13}C NMR spectra of **85** were in complete agreement with the assigned structure.

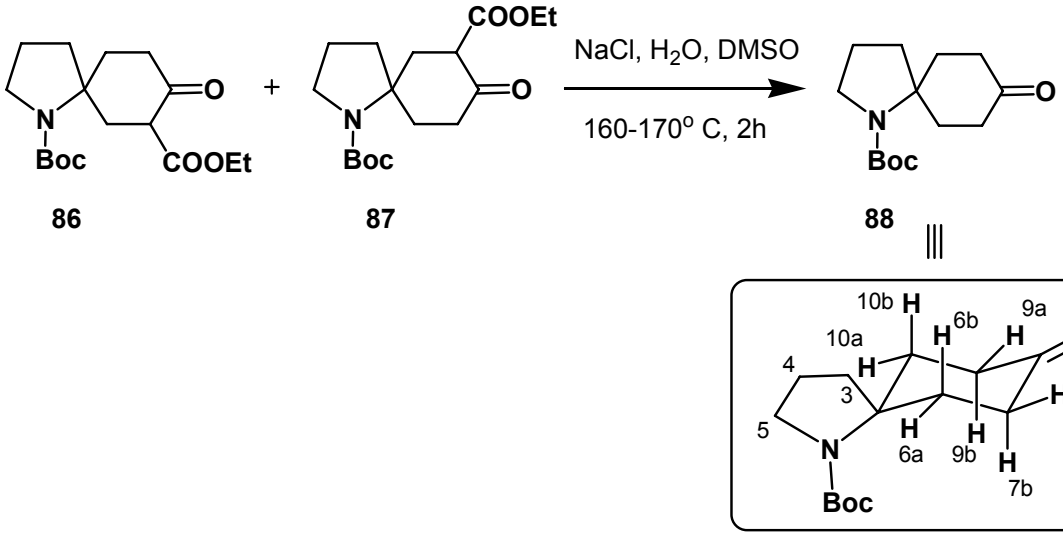
The Dieckmann cyclization reaction[34] of **85** was effected by the treatment with NaH in THF at room temperature to afford inseparable mixture of β-ketoester derivatives **86** and **87** (Scheme 6). In the ^{1}H NMR spectrum of **86** and **87**, the resonances due to methyl appeared at δ 1.31 (3H, triplet, J = 7.1 Hz) while methylene appeared at δ 4.21 (2H, quartet, J = 7.1 Hz) accounting for only one carbethoxy group, where as the sharp singlet appeared at δ 12.22 accounting for 0.82 protons clearly indicated that they exist in keto-

Scheme 6:



enol equilibrium and preferably stay in more stable enol form. The ^{13}C NMR, IR, mass spectral data and elemental analysis were all in full agreement with the assigned structures of **86**/**87**. The mixture of **86/87** was heated at 160-170 ^{o}C in DMSO in the presence of NaCl and catalytic amount of water to furnish the spiro-keto compound **88** (Scheme 7). The ^{1}H NMR spectrum of **88** shown signals due to the characteristic Boc group at δ 1.45 (s, 9 H); C-3 methylene protons between δ 1.61-1.74 (m, 2 H); C-4

Scheme 7:

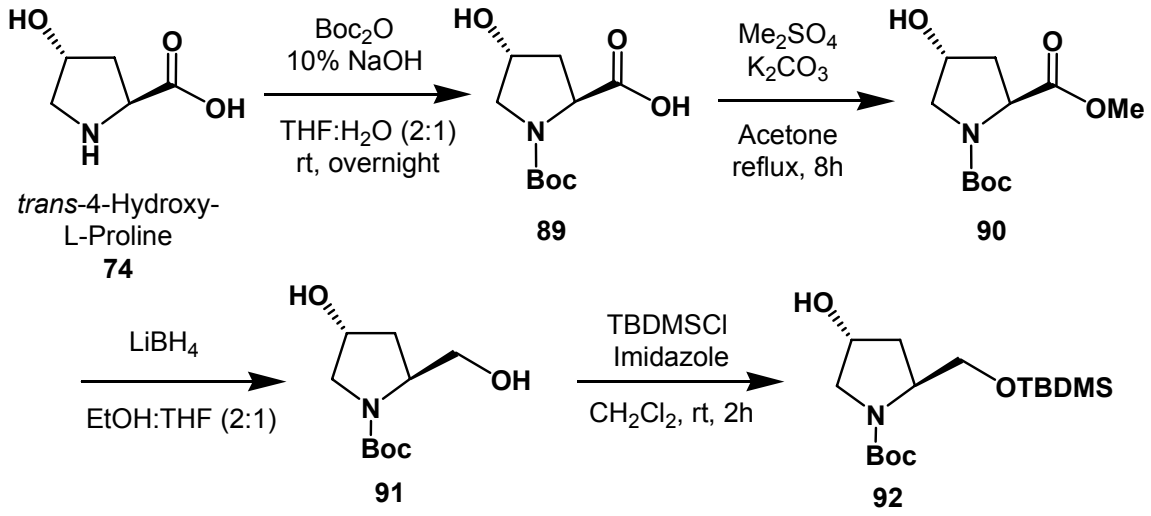


methylene protons at δ 1.84 (quin, 2 H, J = 6.9 Hz); C-5 methylene protons between δ 3.39-3.56 (m, 2 H); H-7a, H-9a (equatorial protons) between δ 2.62-2.77 (br s, 1 H) and 2.87-3.02 (m, 1 H); H-6a, H-7b, H-9b and H-10a between δ 2.27-2.51 (m, 4 H); H-6b and

H-10b (axial protons) between δ 2.0-2.20 (m, 2 H) supporting the structure of **88**. The downfield shifts of the equatorial protons were attributed to the anisotropic deshielding by the σ-electrons in their corresponding β–γ bonds. In the ^{13}C NMR spectrum, carbonyl carbon resonated at δ 210.5. In the IR spectroscopy absorption due to C=O group was observed at 1716 cm^{-1}. The mass spectral data and elemental analysis were in full agreement with the assigned structure of **88**.

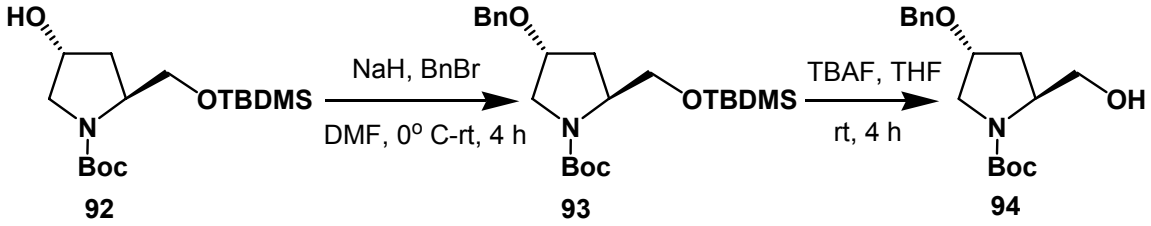
After successfully establishing an efficient synthetic route for the construction of spiro-ring system our next objective was to utilize this strategy for the synthesis of enantiopure 3-Amino-1-azaspiro-[4.5]decan-8-one (**69**) starting from the naturally occurring *trans*-4-Hydroxy-L-proline (**74**). *trans*-4-Hydroxy-L-proline (**74**) was converted into silyl ether derivative **92** in four steps by employing the literature procedures.[36] Thus, **74** was first treated with Boc_2O in the presence of 10% NaOH in THF:H_2O (2:1) at room temperature overnight to obtain the N-Boc derivative **89**. It was then refluxed in acetone with Me_2SO_4 in the presence of K_2CO_3 for 8 h to furnish the corresponding methyl ester derivative **90**. Compound **90** was subjected to reduction with $LiBH_4$ in EtOH:THF (2:1) at room temperature to afford the diol derivative **91**. As we have planned to introduce amino group after the construction of spiro-ring system it was necessary to protect the secondary hydroxyl group as its benzyl ether and to achieve the same we have followed a sequence of protection-deprotection reactions to obtain hydroxylmethyl derivative **94**. Thus, selective primary hydroxyl protection of the diol **91**

Scheme 8:



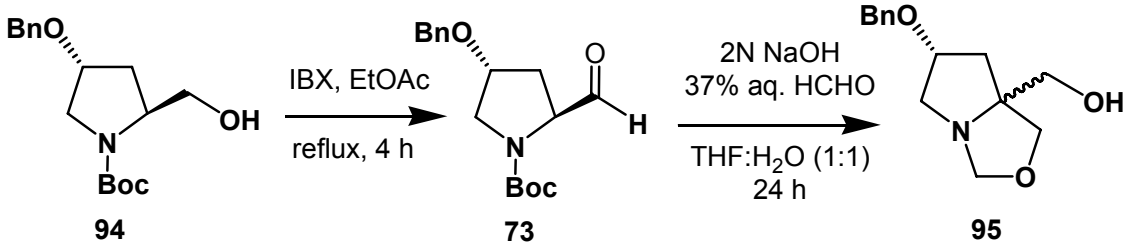
was accomplished by treating with TBDMSCl in the presence of imidazole in anhydrous CH_2Cl_2 to afford the silyl ether derivative **92** (Scheme 8). The ^1H NMR, ^{13}C NMR, IR, mass spectral data and elemental analysis of **92** were in full agreement with the literature values.[36b] The secondary hydroxyl of **92** was protected as its benzyl ether by exposing to BnBr in the presence NaH in anhydrous DMF to furnish **93**.[37] The ^1H NMR spectrum of **93** displayed resonances due to aromatic protons at δ 7.31 (5 H) as a multiplet while benzylic protons resonated at δ 4.50 (2 H). The ^{13}C NMR spectrum of **93** showed resonances due to benzylic carbon at δ 70.7 while all other carbons appeared at their expected chemical shift values suggesting **93** was indeed formed. The IR, mass

Scheme 9:



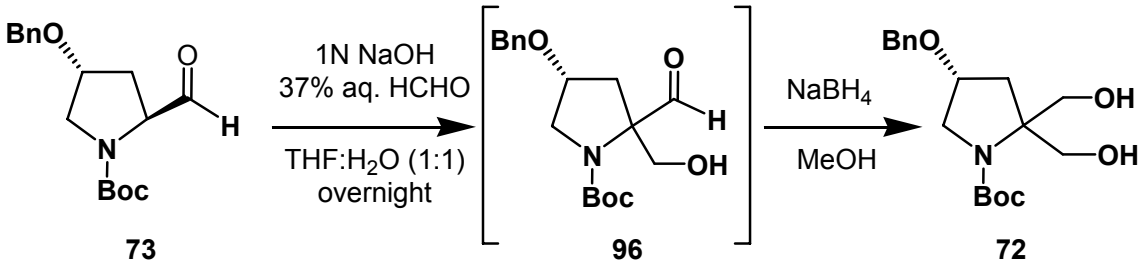
spectroscopy and elemental analysis further supported the structure of **93**. Deprotection of the silyl ether group of **93** was carried out by using TBAF in THF at room temperature to afford primary alcohol derivative **94** (Scheme 9). In the ^1H NMR spectra, resonances due to TBS group were abscent while t-butyl group of Boc group resonated at δ 1.39 (9 H) as a singlet. The benzylic protons appeared at δ 4.42 (2 H) as a singlet. The IR, mass spectral data and elemental analysis further confirmed the structure of **94**. The alcohol **94** was treated with IBX in refluxing EtOAc to obtain the corresponding aldehyde **73**,[30] which was immediately exposed to Tollen's reaction conditions.[31] As expected, the

Scheme 10:



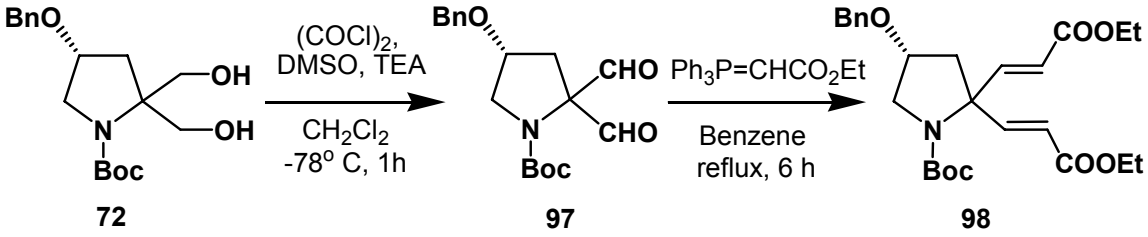
Tollen's reaction did not yield the required diol **72**, but gave the bicyclic oxazole derivatives **95** as inseparable diastereomeric mixture (Scheme 10). The structure of **95** was thoroughly studied by the ^{1}H NMR, ^{13}C NMR, IR, mass spectral data and elemental analysis. The aldehyde **73** was initially made to react with 37% aqueous HCHO (2 equiv.) in the presence of 1N NaOH (3 equiv.) and the resulting hydroxy aldehyde derivative **96** was then reduced by using $NaBH_4$ in MeOH to afford requisite diol derivative **72** (Scheme 11). In the ^{1}H NMR spectrum of **72**, resonances due to the protons one of two hydroxy methyl groups were visualized between δ 3.93-4.17 (2 H) as a multiplet while the other

Scheme 11:



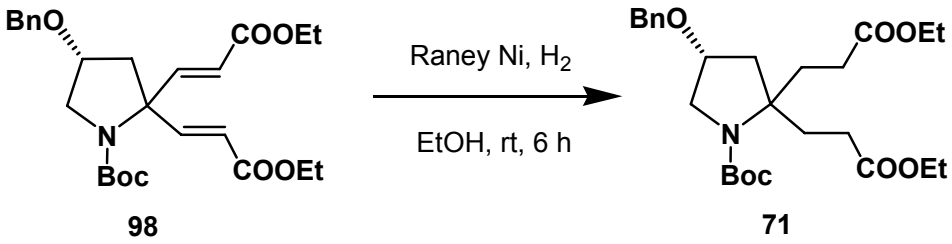
hydroxy methyl protons along with H-4 appeared between δ 3.60-3.90 (3 H) as a multiplet. The t-butyl of the Boc group resonated at δ 1.45 (9 H) as a singlet, benzylic protons appeared at δ 4.50 (2 H) as a quartet (J = 11.8 Hz) and aromatic protons appeared at δ 7.32 (5 H) as a multiplet. The ^{13}C NMR spectrum showed signals due to quaternary carbon at δ 68.0 and two hydroxy methyl carbons at δ 64.1 and 65.2. The presence of five methylenic carbons and two quaternary carbons in its DEPT spectra supported the assigned structure. The IR, mass spectroscopy and elemental analysis were all in full agreement with the structure of **72**. Oxidation of the diol **72** to its corresponding dialdehyde derivative **97** was achieved under Swern oxidation conditions[32]

Scheme 12:



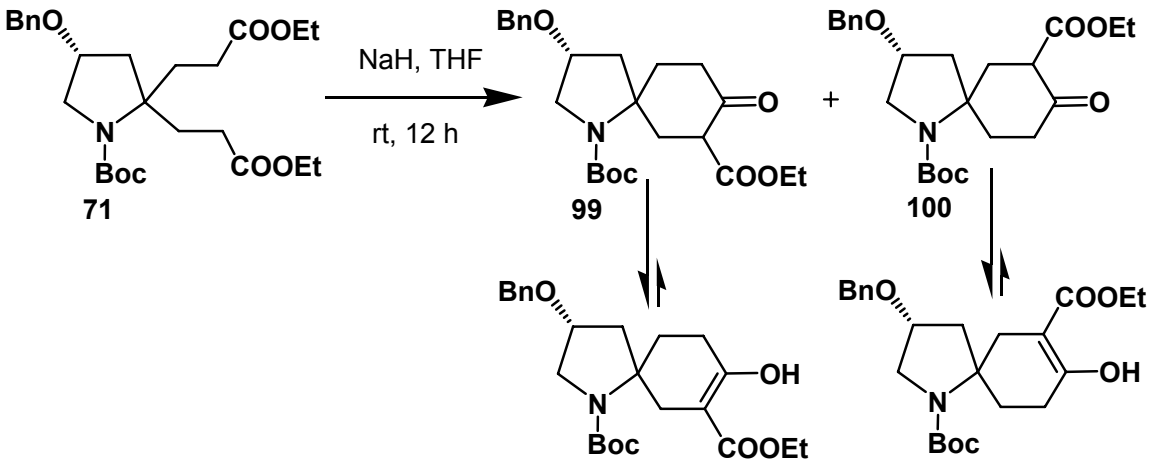
followed by a two carbon Wittig homologation using $Ph_3P{=}CHCO_2Et$ in refluxing benzene resulted in the formation of *bis*-α,β-unsaturated ester derivative **98** (Scheme 12). In the ^1H NMR spectrum of **98** resonances due to characteristic olefinic protons were visualized at δ 5.81 (2 H) and 6.95-7.19 (2 H) while two methyl groups resonated at δ 1.29 (6 H) as a

Scheme 13:



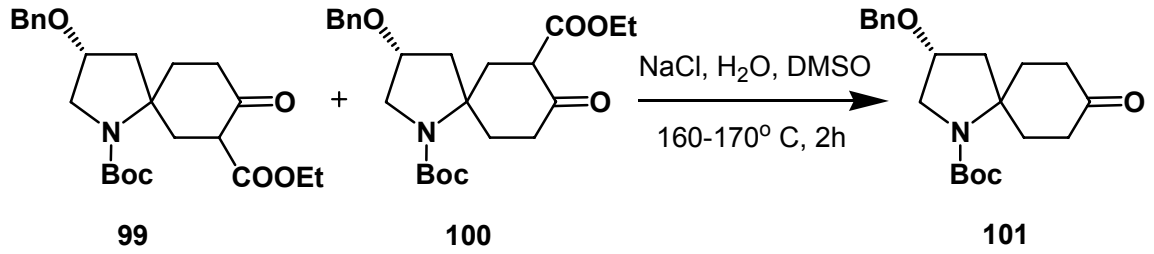
multiplet and two methylene groups of two carbethoxy group along with H-4 resonated at δ 4.01-4.31 (5 H) as a multiplet. In the ^{13}C NMR spectrum, the olefinic carbons appeared at δ 120.4, 120.5, 148.6 and 149.1 supporting the assigned structure of **98**. The IR, mass spectroscopy and elemental analysis are in accordance with the structure **98**. Hydrogenation of the double bonds of **98** in the presence of benzyl group was accomplished by exposing to Raney Ni under hydrogen atmosphere in EtOH at normal temperature and pressure to furnish the saturated diester derivative **71** (Scheme 13). In the ^1H NMR spectra of **71**, resonances due to olefinic protons were disappeared while benzylic protons still resonated at δ 4.48 as a ABq (J = 11.5 Hz), the aromatic protons appeared at δ 7.31 as a multiplet while other protons resonated at their expected chemical shifts suggesting the formation of **71**. The ^{13}C NMR, IR, mass spectral data and elemental analysis further confirmed that the selective reduction of double bonds in the presence of benzyl group had occurred. The Dieckmann cyclization of **71** in the presence of NaH in THF resulted in the formation of cyclic β-keto esters **99**/**100** as inseparable mixture (Scheme 14).[34] The NMR spectra, IR, mass spectroscopy and elemental analysis were in full agreement with structures of **99**/**100**. The decarboxylation of the β-keto esters **99/100**

Scheme 14:



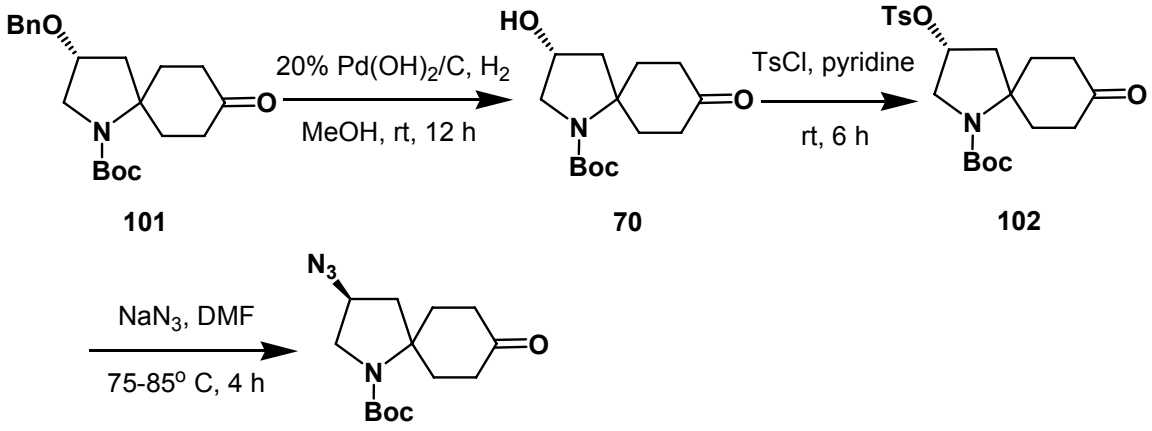
was successfully achieved by exposing to Krapcho's reaction conditions[35] as described earlier to furnish spiro-keto derivative **101** (Scheme 15). In the ^{13}C NMR spectrum, the carbonyl resonated at δ 209.8. In the IR spectroscopy absorption due to keto group was observed at 1716 cm^{-1}. The mass spectral data and elemental analysis further confirmed the structure of **101**. After having spiro-keto derivative **101** at hand,

Scheme 15:



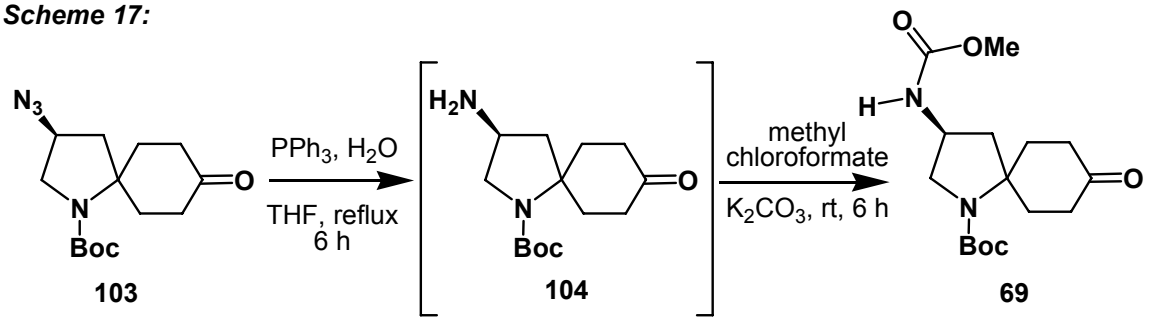
our next concern was to introduce amino group at C-4. Thus, compound **101** was subjected to hydrogenation reaction in the presence of 20% $Pd(OH)_2/C$. The reductive cleavage of benzyl ether was ensured to provide the hydroxy keto derivative **70**. The ^1H NMR, ^{13}C NMR, IR spectral data was in agreement with structure of **70**. Treatment of **70**

Scheme 16:



with TsCl in pyridine at room temperature for 6 h gave corresponding 4-*O*-tosylate derivative **102**. The SN^2 displacement reaction of **102** with NaN_3 was accomplished by heating with NaN_3 in DMF at 85 ^oC for 4 h to provide the azide derivative **103** (Scheme 16).[38] The ^1H, ^{13}C NMR, IR, mass spectroscopy and elemental analysis confirmed the structure of **103**. For instance, in the ^1H NMR spectrum H-4 proton resonated at δ 4.15 as a quintet (J = 5.1 Hz) while all the other protons appeared at their expected chemical shift values. In addition, the IR spectrum exhibited absorption due to azide group at 2104 cm^{-1}.

Scheme 17:

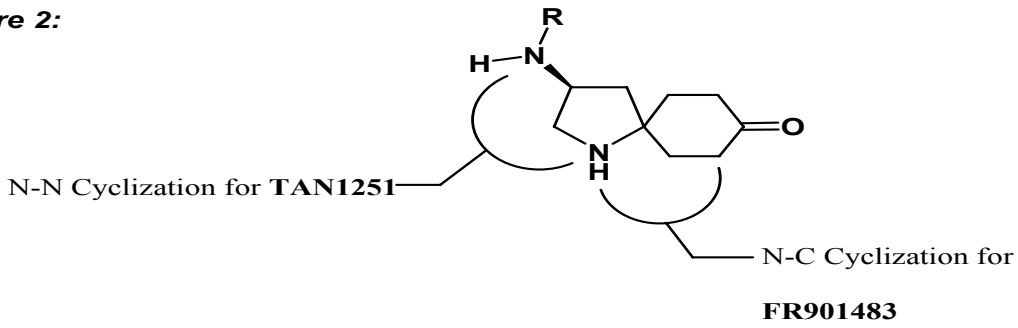


Finally, the reduction of azide group to amine and subsequent protection was effected in one pot by first refluxing **103** with PPh_3 in the presence of H_2O in THF [38] for 6 h followed by treatment with methyl chloroformate in the presence of K_2CO_3 at room temperature for another 6 h to furnish N-protected 3-amino-1-azaspiro-[4.5]decan-8-one (**69**) (Scheme 17). In the ^1H NMR spectrum of **69** resonances due to H-4 proton appeared at δ 4.24 as a broad singlet, methyl protons of methyloxycarbonyl group appeared as a singlet at δ 3.69 (3 h) while t-butyl protons of Boc group appeared at δ 1.45 (9 H) as a

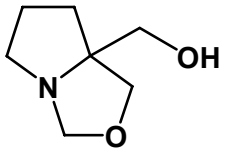
singlet. In the ^{13}C NMR spectrum, carbonyl carbons of keto, methyloxy carbonyl group and Boc group resonated at δ 209.9, 156.5 and 153.1 respectively supporting the structure of **69**. The IR, mass spectra and elemental analysis are in full agreement with the assigned structure of **69**.

In conclusion we have successfully established an efficient strategy for the synthesis of 3-Amino-1-azaspiro-[4.5]decan-8-one (**69**), further efforts in order to achieve N-N cyclization which gives access to TAN1251 compounds and C-N cyclization which provides FR901483 are in progress in our laboratory (Figure 2).

Figure 2:



(Hexahydropyrrolo[1.2-*c*]oxazol-7a-yl)methanol (81):



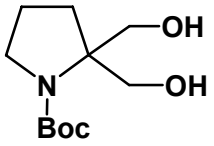
The alcohol **78** (5.0 g, 24.8 mmol) was dissolved in ethyl acetate and IBX (20.87 g, 74.5 mmol) was added. The resulting suspension was heated under reflux for 4 h, cooled to room temperature and filtered through a bed of Celite. The filtrate was concentrated, purified on silica gel using EtOAc:light petroleum ether (2:8) as an eluent to afford **79** (4.65 g, 94%) as a thick syrup.

The above aldehyde **79**, 2N aqueous sodium hydroxide (116 mL) were stirred at 0 ^{o}C and then the aldehyde (4.65 g, 23.3 mmol) in water (50 mL), THF (50 mL) followed by 37% aqueous formaldehyde (19 mL) were added. The resulting mixture was then stirred for 24 h at room temperature, neutralized with formic acid and evaporated to dryness. The resulting residue was extracted with ethyl acetate, washed with water, dried on Na_2SO_4, concentrated and purified on silica gel using EtOAc:MeOH (9:1) an eluent to afford **81** as a thick syrup.

Yield	: 2.27 g (68% for two steps)
Mol. Formula	: $C_7H_{13}NO_2$
IR ($CHCl_3$) $\tilde{\nu}$	: 926, 1061, 1162, 1392, 1457, 1626, 2856, 2927, 3015, 3370 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 1.65-1.92 (m, 3 H), 2.02 (m, 1 H), 2.8 (m, 1 H), 3.22 (m, 1 H), 3.44 (ABq, 2 H, *J* = 11.1 Hz), 3.58 (ABq, 2 H, *J* = 8.5 Hz), 4.25 (d, 1 H, *J* = 6.5 Hz), 4.47 (d, 1 H, *J* = 6.5 Hz) ppm.
^{13}C ($CDCl_3$, 50 MHz)	: δ 25.6, 34.3, 55.5, 65.5, 73.5, 74.1, 87.4 ppm.
ESI MS (m/z)	: 144 (M+1)

Elemental Analysis	**Calcd.:** C, 58.72; H, 9.15; N, 9.78%.
	Found: C, 58.42; H, 9.05; N, 10.12%.

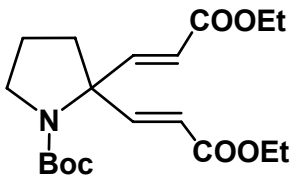
***tert*-Butyl-2,2-di-hydroxymethyl-pyrrolildine-1-carboxylate (80):**



To 1N aqueous sodium hydroxide (60 mL) and **79** (4.0 g, 20.0 mmol), in water (40 mL) and THF (30 mL), 37% aqueous formaldehyde (3.2 mL) was added and stirred at room temperature overnight. It was neutralized with formic acid and evaporated to dryness. The residue was dissolved in MeOH (30 mL) and $NaBH_4$ (0.76 g, 20.1 mmol) was added at 0 ^oC. After 0.5 h, excess of $NaBH_4$ was decomposed with acetic acid, solvent removed and extracted with $CHCl_3$. The organic layer was washed with water, dried (Na_2SO_4) and evaporated. The crude product was purified on silica gel with EtOAc:light petroleum ether (6:4) as an eluent to give **80** as a colorless solid.

Yield	: 1.78 g (78%, two steps)
Mol. Formula	: $C_{11}H_{21}NO_4$
M. P.	: 118-119 ^oC
IR ($CHCl_3$) $\tilde{\nu}$	: 979, 1043, 1120, 1158, 1307, 1369, 1392, 1688, 1718, 2400, 2929, 2980, 3380 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 1.45 (s, 9 H), 1.77 (s, 4 H), 3.37 (t, 2 H, *J* = 6.9 Hz), 3.56 (m, 2 H), 3.86 (d, 2 H, *J* = 11.8 Hz), 4.86 (br s, 2 H) ppm.
^{13}C ($CDCl_3$, 50 MHz)	: δ 21.4, 28.4, 32.4, 48.6, 64.4, 67.9, 80.5, 156.3 ppm.
ESI MS (m/z)	: 231 (M^+)
Elemental Analysis	**Calcd.:** C, 57.12; H, 9.15; N, 6.06%.
	Found: C, 57.08; H, 9.22; N, 5.94%.

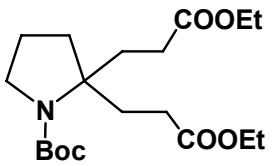
***tert*-Butyl-2,2-*bis*[(E)-3-ethoxy-3-oxoprop-1-enyl]pyrrolidine-1-carboxylate (84):**



Dry DMSO (6.13 mL, 86.5 mmol) and $(COCl)_2$ (3.75 mL, 43.2 mmol) in CH_2Cl_2 (20 mL) at –78 ^oC under N_2 were stirred for 30 min and then the diol **80** (2.5 g, 10.8 mmol) in CH_2Cl_2 (10 mL) was added. After 1h, the reaction was quenched with Et_3N (18.1 mL, 129.7 mmol) at –78 ^oC and diluted with water (40 mL). The organic layer was separated while the aqueous layer extracted with CH_2Cl_2. The combined organic extract was dried (Na_2SO_4) and concentrated to give crude aldehyde **83** (2.3 g) which was reacted with $Ph_3P{=}CHCO_2Et$ (14.1 g, 40.5 mmol) in benzene (50 mL) under reflux for 6 h. Solvent was removed and the residue passed through a short column of silica gel eluting with EtOAc:light petroleum ether (3:7) to give the α,β-unsaturated ester **84** as a thick syrup.

Yield	: 2.97 g (75% for two steps)
Mol. Formula	: $C_{19}H_{29}NO_6$
IR ($CHCl_3$) $\tilde{\nu}$	: 1041, 1179, 1368, 1392, 1651, 1687, 1714, 2982, 3447 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 1.31 (t, 6 H, *J* = 7.1 Hz), 1.36 (s, 6 H), 1.46 (s, 3 H), 1.84 (quin, 2 H, *J* = 6.8 Hz), 2.04 (t, 2 H, *J* = 6.8 Hz), 3.56 (t, 2 H, *J* = 6.8 Hz), 4.21 (q, 4 H, *J* = 7.1 Hz), 5.80 (d, 2 H, *J* = 15.9 Hz), 7.04 (d, 2 H, *J* = 15.9 Hz) ppm.
^{13}C ($CDCl_3$, 50 MHz)	: δ 14.2, 21.6, 28.1, 39.9, 47.6, 60.4, 65.9, 80.4, 120.4, 148.8, 153.3, 165.9 ppm.
ESI MS (m/z)	: 367 (M^+)
Elemental Analysis	**Calcd.:** C, 62.11; H, 7.96; N, 3.81%.
	Found: C, 61.95; H, 7.95; N, 3.78%.

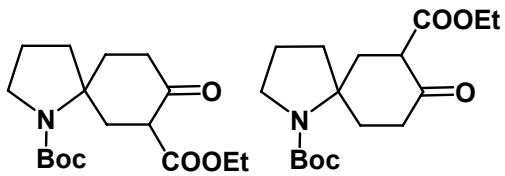
***tert*-Butyl-2,2-*bis*(3-ethoxy-3-oxopropyl)pyrrolidine-1-carboxylate (85)**



A solution of **84** (1.6 g, 4.35 mmol), MeOH (20 mL) and 10% Pd/C (50 mg) was stirred under H_2 for 12 h, filtered through a pad of Celite and the filtrate concentrated to give **85** as a viscous liquid.

Yield	: 1.55 g (96%)
Mol. Formula	: $C_{19}H_{33}NO_6$
IR ($CHCl_3$) $\tilde{\nu}$	: 1033, 1167, 1369, 1393, 1727, 2400, 2935, 2981, 3451 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 1.19 (t, 6 H, *J* = 7.1 Hz), 1.37, 1.42 (2s, 9 H), 1.47-2.05 (m, 7 H), 2.19 (m, 5 H), 3.02, 3.30 (2t, 1 H, *J* = 6.7 Hz), 3.39 (t, 1 H, *J* = 6.7 Hz), 4.05, 4.06 (2q, 4 H, *J* = 7.1 Hz) ppm.
^{13}C ($CDCl_3$, 50 MHz)	: δ 14.1, 21.5, 21.8, 26.8, 28.0, 28.2, 28.3, 29.6, 29.8, 31.4, 32.2, 33.7, 34.5, 35.7, 36.1, 48.7, 48.8, 60.1, 60.3, 63.7, 64.3, 78.8, 79.9, 153.2, 153.8, 155.9, 173.3, 173.6 ppm.
ESI MS (m/z)	: 371 (M^+)
Elemental Analysis	**Calcd.:** C, 61.43; H, 8.95; N, 3.77%.
	Found: C, 61.23; H, 9.10; N, 3.92%.

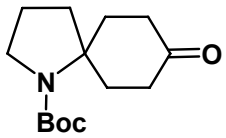
***tert*-Butyl-7-ethoxycarbonyl-8-oxo-1-azaspiro[4.5]decane-1-carboxylate (86/87):**



To an ice cooled solution of **85** (1.3 g, 3.5 mmol) in THF (20 mL), NaH (280 mg, 60% dispersion in oil, 6.99 mmol) was added and stirred for 12 h at room temperature. The reaction mixture was then quenched with ice water, THF removed, the residue was partitioned between water and ethyl acetate. The organic layer was dried (Na_2SO_4), concentrated and the residue purified on silica gel with EtOAc:light petroleum ether (2:8) as an eluent to give **86**/**87** as colorless oil.

Yield	: 1.48 g (80%)
Mol. Formula	: $C_{17}H_{27}NO_5$
IR ($CHCl_3$) $\tilde{\nu}$	: 1068, 1173, 1286, 1391, 1620, 1656, 1680, 2400, 2930, 2978 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 1.31 (t, 3 H, *J* = 7.1 Hz), 1.46 (s, 9 H), 1.6 (s, 2 H), 1.68 – 2.0 (m, 3 H), 2.02 – 2.21 (m, 1 H), 2.24 – 2.51 (m, 2 H), 2.54 – 3.18 (m, 2 H), 3.34 (m, 1 H), 3.59 (m, 1H), 4.21 (q, 2 H, *J* = 7.1 Hz), 12.22 (s, 1 H) ppm.
^{13}C ($CDCl_3$, 50 MHz)	: δ 14.1, 14.3, 21.3, 21.9, 22.7, 27.9, 28.1, 28.6, 29.3, 29.7, 29.9, 30.7, 31.1, 31.9, 36.8, 37.5, 48.1, 60.3, 61.3, 61.7, 78.9, 79.7, 96.7, 153.5, 154.2, 170.8, 172.6 ppm.
ESI MS (m/z)	: 325 (M^+)
Elemental Analysis	**Calcd.:** C, 62.75; H, 8.36; N, 4.30%.
	Found: C, 62.91; H, 8.40; N, 4.12%.

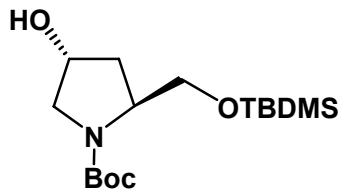
***tert*-Butyl-8-oxo-1-azaspiro[4.5]decane-1-carboxylate (88):**



A mixture of **86**/**87** (0.7 g, 2.15 mmol), NaCl (188 mg, 3.2 mmol) and H_2O (58 μL) in DMSO (10 mL) was heated at 160-170 ^oC for 2 h and partitioned between ether and H_2O. The ether layer was dried (Na_2SO_4), concentrated and the residue was purified by silica gel column chromatography using EtOAc-light petroleum ether (1:9) to get **88** as a colorless solid.

Yield	: 390 mg (72%)
Mol. Formula	: $C_{14}H_{23}NO_3$
M. P.	: 79-81 ^oC
IR ($CHCl_3$) $\tilde{\nu}$	: 991, 1048, 1109, 1169, 1242, 1390, 1681, 1716, 2881, 2975, 3426 cm^{-1}.
^{1}H NMR ($CDCl_3$, 500 MHz)	: δ 1.45 (s, 9 H), 1.61 – 1.74 (m, 2 H), 1.84 (quin, 2 H, *J* = 6.9 Hz), 2.0 – 2.20 (m, 2 H), 2.27 – 2.51 (m, 4 H), 2.62 – 2.77 (br s, 1 H), 2.87 – 3.02 (m, 1 H), 3.39 – 3.56 (m, 2 H) ppm.
^{13}C ($CDCl_3$, 125 MHz)	: δ 21.6, 22.1, 28.6, 29.7, 31.9, 33.4, 36.5, 37.2, 38.5, 38.7, 48.0, 61.8, 62.1, 79.0, 80.0, 153.3, 153.9, 210.5 ppm.
ESI MS (m/z)	: 253 (M^+)
Elemental Analysis	**Calcd.:** C, 66.37; H, 9.15; N, 5.53%. **Found:** C, 66.51; H, 9.22; N, 5.25%.

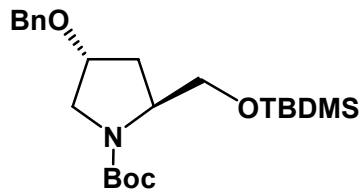
(2*S*, 4*R*)-*tert*-Butyl-2-(*tert*-butyldimethylsilyloxymethyl)-3-hydroxy-pyrrolidine-1-carboxylate (92):



TBDMSCl (9.71 g, 64.4 mmol) was added to a mixture of **91** (10.0 g, 46.0 mmol) and imidazole (3.44 g, 50.6 mmol) in anhydrous CH_2Cl_2 (100 mL) and stirred at room temperature for 2 h. The reaction mixture was quenched with saturated aq. $NaHCO_3$ solution (20 mL) and extracted with CH_2Cl_2. The organic layer was washed with brine, dried (Na_2SO_4), concentrated and the residue purified by silica gel column chromatography using EtOAc-light petroleum ether (4:6) as an eluent to afford **92** as a viscous liquid.

Yield	: 13.1 g, (86%)
Mol. Formula	: $C_{16}H_{33}NO_4Si$
Optical Rotation $[\alpha]_D^{25}$	: −59.0 (*c* 1.0, $CHCl_3$), lit.[36b] −53.9 (*c* 0.83, CH_2Cl_2).
IR ($CHCl_3$) $\tilde{\nu}$	: 1053, 1119, 1167, 1255, 1410, 1472, 1682, 2400, 2858, 2930, 2956, 3427 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 0.03 (s, 6 H), 0.87 (s, 9 H), 1.46 (s, 9 H), 1.97 (m, 1 H), 2.21 (m, 1 H), 3.33-3.81 (m, 3.5 H), 3.98 (m, 1.5 H), 4.48 (m, 1 H) ppm.
^{13}C ($CDCl_3$, 50 MHz)	: δ -5.7, 17.8, 25.6, 28.2, 36.1, 36.8, 54.8, 55.1, 57.2, 62.2, 63.7, 68.6, 69.3, 78.9,79.2, 154.4, 154.5 ppm.
ESI MS (m/z)	: 354 (M+23)
Elemental Analysis	**Calcd.:** C, 57.97; H, 10.03; N, 4.22%.
	Found: C, 57.80; H, 10.24; N, 4.54%.

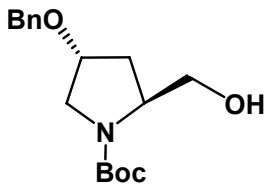
(2*S*, 4*R*)-*tert*-Butyl-2-(*tert*-butyldimethylsilyloxymethyl)-3-benzyloxy-pyrrolidine-1-carboxylate (93):



Compound **92** (11.5 g, 34.7 mmol) in DMF (40 mL) was added to a stirred suspension of NaH (2.08 g, 60% dispersion in oil, 52.0 mmol) in DMF (60 mL) at 0 ^{o}C. The resulting solution was stirred at rt for 30 min, BnBr (5 mL, 41.6 mmol) and TBAI (0.1 g) were added. After 4 h, the reaction was quenched by ice-cold water, brine, dried (Na_2SO_4) and concentrated. The residue was purified on silica gel using EtOAc-leight petroleum ether (2:8) to obtain **93** as a colorless oil.

Yield	: 12.0 g (82%)
Mol. Formula	: $C_{23}H_{39}NO_4Si$
Optical Rotation $[\alpha]_D^{25}$	: -30.66 (*c* 1.2, $CHCl_3$)
IR ($CHCl_3$) $\tilde{\nu}$	: 916, 1028, 1070, 1118, 1168, 1255, 1366, 1407, 1472, 1685, 2858, 2930, 2955, 3011, 3437 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 0.01 (s, 6 H), 0.85 (s, 9 H), 1.45 (s, 9 H), 1.92-2.27 (m, 2 H), 3.29-3.75 (m, 3.5 H), 3.80-4.08 (m, 1.5 H), 4.20 (m, 1 H), 4.50 (m, 2 H), 7.31 (m, 5 H) ppm.
^{13}C ($CDCl_3$, 50 MHz)	: -5.7, 17.9, 25.6, 28.2, 33.6, 34.8, 51.4, 52.1, 57.3, 63.1, 64.0, 70.7, 75.8, 76.4, 78.6, 78.8, 127.2, 128.0, 137.9, 154.0 ppm.
ESI MS (m/z)	: 443 (M+23)
Elemental Analysis	**Calcd.:** C, 65.52; H, 9.32; N, 3.32%. **Found:** C, 65.39; H, 9.28; N, 3.25%.

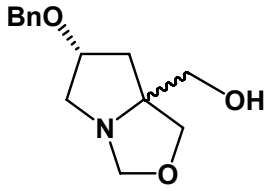
(2*S*, 4*R*)-*tert*-Butyl-2-hydroxymethyl-3-benzyloxy-pyrrolidine-1-carboxylate (94):



To a solution of **93** (10.5 g, 24.9 mmol) in anhydrous THF (40 mL) was added 1M solution of TBAF in THF (29.9 mL, 29.9 mmol) and stirred at room temperature for 4 h. After completion of the reaction, solvent was removed and the resulted residue purified on silica gel using EtOAc-light petroleum (3:7) as an eluent to obtain **94** as a viscous liquid.

Yield	: 6.65 g (87%)
Mol. Formula	: $C_{17}H_{25}NO_4$
Optical Rotation $[\alpha]_D^{25}$	: -32.43 (*c* 1.0, $CHCl_3$).
IR ($CHCl_3$) $\tilde{\nu}$	: 1028, 1084, 1114, 1165, 1367, 1412, 1674, 2933, 2980, 3011, 3395 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 1.39 (s, 9 H), 1.59 (m, 0.5 H), 2.08 (m, 1.5 H), 3.18–3.74 (m, 4 H), 4.01 (m, 2 H), 4.42 (s, 2 H), 7.23 (m, 5 H) ppm.
^{13}C ($CDCl_3$, 125 MHz)	: δ 27.8, 33.6, 34.2, 51.2, 52.1, 57.2, 58.0, 62.9, 64.8, 68.2, 70.1, 75.7, 79.1, 79.5, 126.9, 127.8, 128.4, 129.1, 137.5, 154.4, 155.7 ppm.
ESI MS (m/z)	: 307 (M^+)
Elemental Analysis	**Calcd.:** C, 66.43; H, 8.20; N, 4.56%.
	Found: C, 66.39; H, 8.30; N, 4.86%.

(6*R*)-(6-(Benzyloxy)-hexahydropyrrolo[1.2-*c*]oxazol-7a-yl)methanol (95):

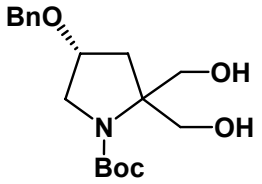


Oxidation of **94** (1.2 g, 3.9 mmol) was performed as described earlier using IBX (3.2 g, 11.7 mmol) in ethyl acetate to provide **73** (1.09 g, 92%) as a colorless oil.

Aqueous sodium hydroxide (18 mL of 2N) was added to a stirred solution of aldehyde **73** (1.09 g, 3.6 mmol) in water (20 mL), THF (30 mL) at 0 ^{o}C. This was followed by adding 37% aqueous formaldehyde (2.9 mL). The resulting mixture was then stirred for 24 h at room temperature and worked as described earlier. The residue was purified on silica gel using EtOAc:MeOH (9:1) as an eluent to afford **95** as a thick syrup.

Yield	: 0.56 g (63%)
Mol. Formula	: $C_{14}H_{19}NO_3$
IR ($CHCl_3$) $\tilde{\nu}$	: 914, 1027, 1064, 1110, 1398, 1454, 2869, 2937, 3013, 3439 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 1.93 (m, 1 H), 2.31 (m, 1 H), 2.92 (m, 1 H), 3.32-3.86 (m, 4 H), 4.20 (m, 3 H), 4.47 (m, 3 H), 7.31 (m, 5 H) ppm.
^{13}C ($CDCl_3$, 50 MHz)	: δ 38.4, 39.9, 58.3, 59.3, 65.1, 65.3, 70.6, 71.4, 73.4, 73.7, 73.8, 74.0, 78.5, 78.8, 86.8, 86.9, 127.3, 127.4, 127.5, 128.2, 137.6, 137.8 ppm.
ESI MS (m/z)	: 249 (M^+)
Elemental Analysis	**Calcd.:** C, 67.45; H, 7.68; N, 5.62%.
	Found: C, 67.23; H, 7.54; N, 5.54%.

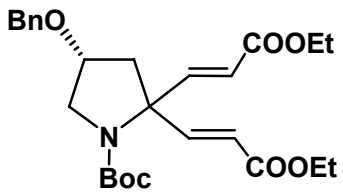
(4*R*)-*tert*-Butyl-2,2-di-hydroxymethyl-4-benzyloxy-pyrrolidine-1-carboxylate (72):



The Aldol condensation followed by reduction of **73** (5.85 g, 19.1 mmol) was performed as described earlier using aq. sodium hydroxide (57.4 mL, 1 N), 37% aq. formaldehyde (3.1 mL, 38.3 mmol) in THF and water followed by treating with $NaBH_4$ (725 mg, 19.1 mmol) in MeOH to afford **72** (4.4 g, 68 %) after silica gel column purification using EtOAc-light petroleum ether (4:6) as a thick liquid.

Yield	: 4.4 g (68%)
Mol. Formula	: $C_{18}H_{27}NO_5$
Optical Rotation $[\alpha]_D^{25}$	: -20.73 (*c* 0.3, $CHCl_3$).
IR ($CHCl_3$) $\tilde{\nu}$	: 927, 1112, 1166, 1368, 1400, 1670, 1717, 2401, 2930, 2980, 3396 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 1.45 (s, 9 H), 1.89 (dd, 1 H, *J* = 5.6, 13.9 Hz), 2.14 (dd, 1 H, *J* = 3.3, 13.9 Hz), 3.55 (d, 2 H, *J* = 4.4 Hz), 3.60-3.90 (m, 3 H), 3.93-4.17 (m, 2 H), 4.50 (q, 2 H, *J* = 11.8 Hz), 7.32 (m, 5 H) ppm.
^{13}C ($CDCl_3$, 50 MHz)	: δ 28.3, 37.9, 54.5, 64.1, 65.2, 68.0, 70.9, 74.8, 80.7, 127.6, 127.8, 128.4, 137.5, 156.1 ppm.
ESI MS (m/z)	: 360 (M+23)
Elemental Analysis	**Calcd.:** C, 64.07; H, 8.07; N, 4.15%.
	Found: C, 64.12; H, 8.16; N, 4.02%.

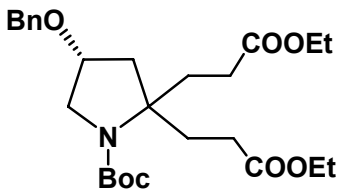
(4*R*)-*tert*-Butyl-2,2-*bis*[(*E*)-3-ethyoxy-3-oxoprop-1-enyl]-4-benzyloxy-pyrrolidine-1-carboxylate (98):



Swern oxidation followed by two carbon wittig olefination of **72** (3.62 g, 10.7 mmol) was done as described earlier using $(COCl)_2$ (3.75 mL, 42.9 mmol), DMSO (6.1 mL, 85.8 mmol) and Et_3N (17.95 mL, 128.7 mmol) to obtain **97** (3.22 g) which was dissolved in benzene, $Ph_3P{=}CHCO_2Et$ (13.46 g, 38.63 mmol) was added and heated under reflux for 6 h. After usual work up the product was purified on silica gel using EtOAc:light petroleum ether (2:8) as an eluent to afford **98** as a viscous liquid.

Yield	: 3.8 g (75% for two steps)
Mol. Formula	: $C_{26}H_{35}NO_7$
Optical Rotation $[\alpha]_D^{25}$	: –8.95 (*c* 0.3, $CHCl_3$)
IR ($CHCl_3$) $\tilde{\nu}$	: 979, 1040, 1110, 1181, 1274, 1392, 1654, 1718, 2400, 2931, 2981 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 1.29 (m, 6 H), 1.37, 1.45 (2s, 9 H), 2.27 (m, 2 H), 3.67 (m, 2 H), 4.01-4.31 (m, 5 H), 4.47 (m, 2 H), 5.81 (m, 2 H), 6.95-7.19 (m, 2 H), 7.29 (m, 5 H) ppm.
^{13}C ($CDCl_3$, 50 MHz)	: δ 14.2, 28.1, 45.0, 52.6, 60.3, 60.5, 65.1, 71.1, 74.4, 80.8, 120.4, 120.5, 127.4, 127.7, 128.3, 137.4, 148.6, 149.1, 153.2, 165.8, 165.9 ppm.
ESI MS (m/z)	: 493 (M+23)
Elemental Analysis	**Calcd.:** C, 65.94; H, 7.45; N, 2.96%.
	Found: C, 65.76; H, 7.34; N, 2.88%.

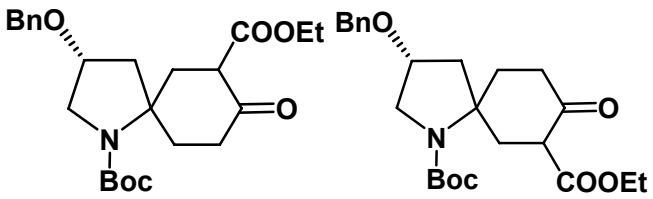
(4*R*)-*tert*-Butyl-2,2-*bis*(3-ethoxy-3-oxopropyl)-4-benzyloxy-pyrrolidine-1-carboxylate (71):



A mixture of **98** (2.86 g, 6.0 mmol) and Raney Ni (1 g) in ethanol (20 mL) was stirred under hydrogen atmosphere at normal temperature and pressure. After 6 h, the catalyst was filtered through a bed of Celite and washed with ethanol. The filtrate was concentrated and crude product was purified on silica gel using EtOAc:light petroleum ether (2:8) as an eluent to afford **71** as colorless liquid.

Yield	: 2.65 g (92%)
Mol. Formula	: $C_{26}H_{39}NO_7$
Optical Rotation $[\alpha]_D^{25}$	: +4.03 (*c* 0.4, $CHCl_3$).
IR ($CHCl_3$) $\tilde{\nu}$	: 926, 1028, 1096, 1168, 1307, 1368, 1393, 1685, 1728, 2935, 2981, 3360 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 1.24 (2t, 6 H, *J* = 7.1 Hz), 1.44, 1.49 (2s, 9 H), 1.75-2.55 (m, 10 H), 3.30-3.72 (m, 2 H), 4.00 (m, 1 H), 4.11 (2q, 4 H, *J* = 7.1 Hz), 4.48 (ABq, 2 H, *J* = 11.5 Hz), 7.31 (m, 5 H) ppm.
^{13}C ($CDCl_3$, 50 MHz)	: δ 14.1, 28.3, 29.5, 32.6, 32.7, 34.1, 34.2, 40.2, 41.5, 53.8, 54.0, 60.3, 60.4, 63.9, 64.5, 71.2, 73.7, 74.5, 79.3, 80.3, 127.5, 127.6, 128.4, 137.7, 153.1, 153.8, 173.1, 173.2, 173.5 ppm.
ESI MS (m/z)	: 477 (M^+)
Elemental Analysis	**Calcd.:** C, 65.39; H, 8.23; N, 2.93%.
	Found: C, 65.42; H, 8.45; N, 2.88%.

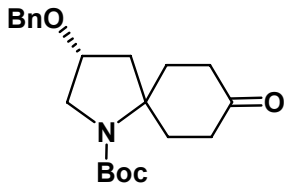
(3*R*)-*tert*-Butyl-3-benzyloxy-7-ethoxycarbonyl-8-oxo-1-azaspiro[4.5]decane-1-carboxylate (99/100):



The Dieckmann condensation of **71** (2.21 g, 4.6 mmol) was performed as described earlier using NaH (370 mg, 60% dispersion in oil, 9.2 mmol) in THF. After usual work up the crude product was purified on silica gel using EtOAc:light petroleum ether (1:9) as an eluent to afford **99**/**100** as a viscous liquid.

Yield	: 1.53 g (77%)
Mol. Formula	: $C_{24}H_{33}NO_6$
IR ($CHCl_3$) $\tilde{\nu}$	: 948, 1028, 1066, 1163, 1285, 1392, 1454, 1618, 1654, 1684, 2935, 2980, 3384 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 1.24, 1.30 (2t, 3 H, *J* = 7.1 Hz), 1.45 (s, 9 H), 1.7 (m, 1 H), 1.84-2.19 (m, 2 H), 2.20–2.49 (m, 2.5 H), 2.50-3.30 (m, 2.5 H), 3.33-3.90 (m, 2 H), 3.96-4.30 (m, 3 H), 4.49 (m, 2 H), 7.31 (m, 5 H), 12.19, 12.22 (2 s, 0.9 H) ppm.
^{13}C ($CDCl_3$, 100 MHz)	: δ 14.1, 26.8, 27.7, 27.8, 28.0, 28.4, 29.4, 29.5, 30.5, 31.0, 31.7, 32.1, 40.9, 41.9, 42.7, 52.6, 53.8, 54.4, 60.1, 61.2, 61.3, 61.6, 70.5, 71.3, 73.6, 74.5, 74.7, 75.6, 77.2, 79.0, 79.6, 96.6, 96.7, 127.3, 127.4, 127.6, 128.1, 128.3, 137.9, 138.0, 153.1, 153.8, 170.3, 170.7, 172.2, 172.4 ppm.
ESI MS (m/z)	: 432 (M+1)
Elemental Analysis	**Calcd.:** C, 66.80; H, 7.71; N, 3.25%. **Found:** C, 66.58; H, 7.53; N, 3.32%.

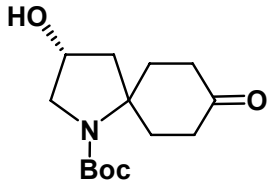
(3*R*)-*tert*-Butyl-3-benzyloxy-8-oxo-1-azaspiro[4.5]decane-1-carboxylate (101):



Decarboxylation of **99**/**100** (1.3 g, 3.0 mmol) was performed as described earlier using NaCl (260 mg, 4.5 mmol), H_2O (8 μL, 4.5 mmol) in DMSO (20 mL). After the usual work up the crude product was purified by silica gel column chromatography using EtOAc:light petroleum ether (3:7) to afford **101** as white solid.

Yield	: 0.76 g (70%)
Mol. Formula	: $C_{21}H_{29}NO_4$, white solid.
M. P.	: 90-92^{o}C
Optical Rotation $[\alpha]_D^{25}$	: -11.17 (*c* 0.88, $CHCl_3$)
IR ($CHCl_3$) $\tilde{\nu}$	: 913, 1114, 1216, 1240, 1391, 1366, 1454, 1685, 1716, 2976, 3011, 3422 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 1.45 (s, 9 H), 1.61 (br s, 1 H), 2.13 (m, 2 H), 2.40 (m, 5 H), 2.61-3.16 (m, 2 H), 3.61 (m, 2 H), 4.09 (quin, 1 H, *J* = 3.9), 4.54 (m, 2 H), 7.33 (m, 5 H) ppm.
^{13}C ($CDCl_3$, 100 MHz)	: 28.3, 31.6, 33.0, 33.4, 35.0, 38.3, 41.2, 42.0, 53.0, 62.0, 71.0, 74.2, 75.1, 79.1, 79.9, 127.3, 127.5, 128.2, 137.8, 153.0, 153.6, 209.8 ppm.
ESI MS (m/z)	: 360 (M+1)
Elemental Analysis	**Calcd.:** C, 70.17; H, 8.13; N, 3.90%.
	Found: C, 70.32; H, 8.22; N, 4.16%.

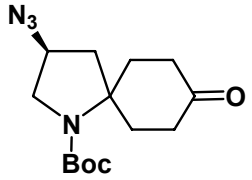
(3*R*)-*tert*-Butyl-3-hydroxy-8-oxo-1-azaspiro[4.5]decane-1-carboxylate (70):



To a solution of **101** (0.7 g, 1.9 mmol) in MeOH (10 mL) was added 20% $Pd(OH)_2/C$ (0.04 g), and the mixture degassed with argon and flushed with H_2 for 5 min. After stirring under an atmosphere of H_2 for 12 h, the mixture was filtered through a pad of Celite and concentrated. The residue was purified on silica gel using EtOAc:light petroleum ether (1:1) to afford **70** as a thick syrup.

Yield	: 0.46 g (88%)
Mol. Formula	: $C_{14}H_{23}NO_4$
Optical Rotation $[\alpha]_D^{25}$	: -14.07 (*c* 0.88, $CHCl_3$).
IR ($CHCl_3$) $\tilde{\nu}$	: 927, 993, 1072, 1160, 1392, 1681, 1713, 2978, 3444 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 1.45 (s, 9 H), 1.63 (m. 1 H), 2.13 (m, 3 H), 2.41 (m, 5 H), 2.75 (br s, 1 H), 2.96 (br s, 1 H), 3.60 (m, 2 H), 4.44 (quin, 1 H, *J* = 4.1 Hz) ppm.
^{13}C ($CDCl_3$, 100 MHz)	: δ 28.4, 32.0, 33.4, 34.9, 38.4, 44.1, 55.8, 62.1, 67.2, 67.8, 79.2, 80.3, 153.2, 153.9, 210.6, 211.0 ppm.
ESI MS (m/z)	: 269 (M^+)
Elemental Analysis	**Calcd.:** C, 62.43; H, 8.61; N, 5.20%.
	Found: C, 62.47; H, 8.63; N, 5.26%.

(3*S*)-*tert*-Butyl-3-azido-8-oxo-1-azaspiro[4.5]decane-1-carboxylate (103):

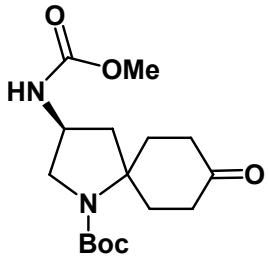


A solution of **70** (1.4 g, 5.2 mmol) in pyridine (10 mL) and TsCl (1.48 g, 7.8 mmol) was stirred at rt for 6 h. Pyridine was removed under vacuum and the residue was extracted with EtOAc, washed with 1 N HCl, water, brine, dried (Na_2SO_4) and evaporated. The residue was purified by silica gel column chromatography eluting with EtOAc:light petroleum ether (3:7) to afford tosylate **102** (2 g, 91%) as a colorless liquid.

A mixture of **102** (2 g, 4.72 mmol) and NaN_3 (1.22 g, 18.88 mmol) in anhydrous DMF (20 mL) were heated at 75-85 ^oC for 4 h. Then the reaction mixture was diluted with water, extracted with ether, washed with brine, dried (Na_2SO_4) and concentrated. The residue was purified by silica gel column chromatography using EtOAc:light petroleum ether (2:8) as eluent to afford **103** as a colorless liquid.

Yield	: 1.14 g (82%)
Mol. Formula	: $C_{14}H_{22}N_4O_3$
Optical Rotation $[\alpha]_D^{25}$	: +5.45 (*c* 1.6, $CHCl_3$).
IR ($CHCl_3$) $\tilde{\nu}$	: 994, 1112, 1158, 1385, 1687, 1716, 2104, 2978, 3438 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 1.46 (s, 9 H), 1.64 (m, 1 H), 1.97 (m, 1 H), 2.37 (m, 6 H), 2.60-3.13 (m, 1 H), 3.53 (m, 1 H), 3.72 (m, 1 H), 4.15 (quin, 1 H, *J* = 5.1 Hz) ppm.
^{13}C ($CDCl_3$, 100 MHz)	: δ 28.1, 31.9, 32.7, 33.1, 34.3, 38.1, 40.9, 52.1, 57.1, 61.8, 79.4, 80.1, 152.5, 153.0, 208.9 ppm.
ESI MS (m/z)	: 297 (M+3)
Elemental Analysis	**Calcd.:** C, 57.13; H, 7.53; N, 19.03%.
	Found: C, 57.27; H, 7.65; N, 18.91%.

(3*S*)-*tert*-Butyl-3-methoxycarbonylamino-8-oxo-1-azaspiro[4.5]decane-1-carboxylate (69):



A solution of **103** (0.35 g, 1.2 mmol), THF (10 mL), triphenylphosphine (625 mg), and water (43 μL, 2.4 mmol) were heated under reflux for 6 h and then allowed to come to room temperature. Methyl chloroformate (0.18 mL, 2.3 mmol), K_2CO_3 (330 mg) and stirred for 6 h. The reaction mixture was diluted with water, filtered, extracted with ethyl acetate. The organic layer was washed with brine, dried (Na_2SO_4), concentrated and purified on silica gel using EtOAc:light petroleum ether (6:4) as an eluent to afford **69** as a thick syrup.

Yield	: 0.25 g (64% for two steps)
Mol. Formula	: $C_{16}H_{26}N_2O_5$
Optical Rotation $[\alpha]_D^{25}$	: +3.26 (*c* 1.0, $CHCl_3$)
IR ($CHCl_3$) $\tilde{\nu}$	: 926, 993, 1039, 1106, 1157, 1391, 1515, 1685, 1716, 2401, 2978, 3441 cm^{-1}.
^{1}H NMR ($CDCl_3$, 400 MHz)	: δ 1.45 (s, 9 H), 1.74 (br s, 2 H), 1.92 (m, 1 H), 2.29–2.52 (m, 4 H), 2.60 (br s, 1 H), 2.86 (br s, 1 H), 2.96–3.35 (m, 2 H), 3.69 (s, 3 H), 3.88 (dd, 1 H, *J* = 7.3, 10.8 Hz), 4.24 (br s, 1 H), 5.02 (br s, 1H) ppm.
^{13}C ($CDCl_3$, 125 MHz)	: δ 28.4, 31.5, 33.6, 34.8, 38.5, 42.4, 47.5, 52.6, 61.7, 79.8, 153.1, 156.5, 209.9 ppm.
ESI MS (m/z)	: 326 (M^+)
Elemental Analysis	**Calcd.:** C, 58.88; H, 8.03; N, 8.58%.
	Found: C, 58.94; H, 8.02; N, 8.65%.

REFERENCES

1. (a) Kelly, J. E. Ed, *Amino Acids, Peptides, Porphyrins and Alkaloids,* In *Comprehensive Natural Products Chemistry,* Barton, D.; Nakanishi, K.; Meth-Chon, O. Eds.; Elsevier: New York, **1999**, vol 4; (b) Glasby, J. S. *Encyclopedia of the Alkaloids,* Plenum Press: New York, **1975-**; 4 vols.
2. Armour, D. R.; Watson, S. P.; Pegg, N. A.: Heron, N. M.; Middlemiss, D,; Chan, C.; Cholerton, T. J.; Hubbard, T.; Vinader, M. V.; Davies, H. G.; Cocker, J. D.; Bays, D. E.; Ward, P. *Bioorg. Med. Chem. Lett.* **1995**, 5, 2671-2676.
3. Blum, C.; Hutchison, A. U.S. Patent 5,668,283, 1997.
4. Farrar, J. J.; Chang, A.; Kumar, V.; Zhang, W. Y.; Cowan, A. U.S. Patent 5,760,023, 1998.
5. Mimura, M.; Hayashida, M.; Nomiyama, K.; Ikegami, S.; Iida, Y.; Tamura, M.; Hiyama, Y.; Ohishi, Y. *Chem. Pham. Bull.* **1993**, *41*, 1971-1986.
6. Mio, S.; Ito, M.; Ichinose, R.; Okui, H.; Iwasaki, T.; Kodama, S.; Iwabuchi, J. *PCT Int. Appl.* **2000**, WO 00 68, 196.
7. Fujimoto, R. A.; Boxer, J.; Jackson, R. H.; Simke, J. P.; Neale, R. F.; Sonwhill, E. W.; Barbaz, B. J.; Williams, M.; Sills, M. A. *J. Med. Chem.* **1989**, 32, 1259-1265.
8. (a) Kuramoto, M.; Tong, C.; Yamada, K.; Chiba, T.; Hayashi, Y.; Uemura, D. *Tetrahedron Lett.* **1996**, *37*, 3867-3870; (b) Arimoto, H.; Hayakawa, I.; Kuramoto, M.; Uemura, D. *Tetrahedron Lett.* **1998**, *39*, 861-864.
9. Chou, T.; Kuramoto, M.; Otani, Y.; Shikano, M.; Yazawa, K.; Uemura, D. *Tetrahderon Lett.* **1996**, *37*, 3871-3874.
10. Blackman, A. J.; Li, C.; Hockless, D. C. R.; Skelton, B. W.; White, A. H. *Tetrahedron* **1993**, *49*, 8645-8656.
11. (a) Li, C.; Blackman, A. J. *Aust. J. Chem.* **1994**, *47*, 1355-1361; (b) Li, C.; Blackman, A. J. *Aust. J. Chem.* **1995**, *48*, 955-965.
12. (a) Biard, J. F.; Guyot, S.; Roussakis, C.; Verbist, J. F.; Vercauteren, J.; Weber, J. F.; Bouker, K. *Tetrahedron Lett.* **1994**, *35*, 2691-2694. (b) Weinreb, S. M. *Acc. Chem. Res.* **2003**, *36*, 59-65.

13. Patil, A. D.; Freyer, A. J.; Reichwein, R; Carte, B.; Killmer, L. B.; Faucette, L.; Johnson, R. K.; Faulkner, D. J. *Tetrahedron Lett*, **1997**, *38*, 363-364.
14. Raub, M. F.; Cardelina, J. H., II; Choudhary, M. I.; Ni, C.-Z.; Clardy, J.; Alley, M. C. *J. Am. Chem. Soc.* **1991**, *113*, 3178-3180.
15. Daly, J. W.; Karle, I.; Myers, C. W.; Tokuyama, T.; Waters, J. A.; Witkop, B. *Proc. Natl. Acad. Sci. U. S. A.* ***1971****, 68*, 1870-1875.
16. (a) Daly, J. W. *J. Nat. Prod.* **1998**, *61*, 162-172; (b) Daly, J. W.; Garraffo, H. M.; Spande, T. F. In *The Alkaloids*; Cordell, G. A., Ed.; Academic Press: San Diego, CA, **1993**, *43*, 185-288. (c) Sobel, A.; Heidmann, T.; Hofler, J.; Changeux, J. P. *Proc. Natl. Acad. Sci. U. S. A* **1978**, *75*, 510-514; (d) Rapier, C.; Wonnacott, S.; Lunt, G. G.; Albuquerque, E. X. *FEBS Lett.* **1987**, *212*, 292-296; (e) Oliveira, L.; Madsen, B. W.; Kapai, N.; Sherby, S. M.; Swanson, K. L; Eldefrawi, M. E.; Albuquerque, E. X. *Eur. J. Pharmacol.* **1987**, *140*, 331-342.
17. Borel, J. F. In *Cyclosporin A*; White, D. J. G., Ed.; Elsevier Biomedical Press: Amsterdam, 1982, p 5-17.
18. (a) Kino, T.; Hatanaka, H.; Hashimoto, M.; Nishiyama, M.; Goto, T.; Okuhara, M.; Kosaka, M.; Aoki, H.; Imanaka, H. *J. Antibiot.* **1987**, *40*, 1249-1255. (b) Kino, T.; Hatanaka, H.; Miyata, S.; Inamura, N.; Nishiyama, M.; Yajima, T.; Goto, T.; Okuhara, M.; Kosaka, M.; et al. *J. Antibiot.* **1987**, *40*, 1256-1265. (c) Tanka, H.; Kuroda, A.; Marusawa, H.; Hatanaka, H.; Kino, T.; Goto, T.; Hashimoto, M.; Taga, T. *J. Am. Chem. Soc.* **1987**, *109*, 5031-5033.
19. Sakamoto, K.; Tsujii, E.; Abe, F.; Nakanishi, T.; Yamashita, M.; Shigematsu, N.; Izumi, S.; Okuhara, M. *J. Antibiot.* **1996**, *49*, 37-44.
20. Shirafuji, H.; Tsubotani, S.; Ishimaru, T.; Harada, S. PCT Int. Appl. **1991**, WO 91 13,887; *Chem Abstr.* **1992**, *116*, 39780t.
21. (a) Snider, B. B.; Lin, H. *J. Am. Chem. Soc.* **1999**, *121*, 7778-7786. (b) Snider, B. B.; Lin, H. *Org. Lett.* **2000**, *2*, 643-646.
22. Scheffler, G.; Seike, H.; Sorensen, E. *J. Angew. Chem. Int. Ed.* **2000**, *39*, 4593-4596.

23. (a) Ousmer, M.; Braun, N. A.; Ciufolini, M. A. *Org. Lett.* **2001**, *3*, 765-767. (b) Ousmer, M.; Braun, N. A.; Bavoux, C.; Perrin, M.; Ciufolini, M. A. *J. Am. Chem. Soc.* **2001**, *123*, 7534-7538.
24. Wardrop, D. J.; Basak, A. *Org. Lett.* **2001**, *3*, 1053-2056.
25. Mizutani, H.; Takayama, J.; Soeda, Y.; Honda, T. *Tetrahedron Lett.* **2002**, *43*, 2411-2414.
26. Bonjoch, J.; Diaba, F.; Puigbo, G.; Sole, D.; Segarra, V.; Santamaria, L.; Beleta, J.; Ryder, H.; Palacios, J.-M. *Bioorg. Med. Chem.* **1999**, *7*, 2891-2897.
27. Puigbo, G; Diaba, F.; Bonjoch, J. *Tetrahedron* **2003**, *59*, 2657-2665.
28. Nagumo, S.; Nishida, A.; Yamazaki, C.; Murashige, K.; Kawahara, N. *Tetrahedron Lett.* **1998**, *39*, 4493-4496.
29. Nagumo, S.; Nishida, A.; Yamazaki, C.; Matoba, A.; Murashige, K.; Kawahara, N. *Tetrahedron* **2002**, *58*, 4917-4924.
30. More, J. D.; Finney, N. S. *Org. Lett.* **2002**, *4*, 3001-3003.
31. (a) Youssefyeh, R. D.; Verhuyden, J. P. H.; Moffatt, J. G. *J. Org. Chem.* **1979**, *44*, 1301-1309. (b) Shimida, K.; Kaburagi, Y.; Fukuyama, T. *J. Am. Chem. Soc.* **2003**, *125*, 4048-4049. (c) Jones, G. H.; Taniguchi, M.; Tegg, D.; Moffat, J. G. *J. Org. Chem.* **1979**, *44*, 1309-1317.
32. (a) Huang, S. L.; Omura, K.; Swern, D. *J. Org. Chem.* **1976**, *41*, 3329-3331. (b) Mancuso, A J.; Huang, S. L.; Swern, D. *ibid*. **1978**, *43*, 2480-2482. (c) Huang, S. L.; Omura, K.; Swern, D. *ibid*. **1978**, *43*, 4537-4538.
33. (a) Wittig, G.; Geissler, G. *Justus Leibigs Ann. Chem*., **1953**, *580*, 44. (b) Wittig, G.; Schollkopf, U. *Ber*. **1954**, *87*, 1318.
34. (a) Schaefer, J. P.; Bloomfield, J. J. *Org. React.* **1967**, *15*, 1. (b) d'Angelo, J.; Revial, G.; Chassagnard, C.; Ambroise, L. *Tetrahedron: Asymeetry* **1991**, *2*, 407-410.
35. For a comprehensive review on "Synthetic Applications of Dealkoxycarbonylations of Malonate Esters, β-Keto Esters, α-Cyano and Related Compounds in Dipolar Aprotic Media", see: Krapcho, A. P. *Synthesis* **1982**, 805-822 (Part I) and 893-914 (Part II).

36. (a) Rajeev, K. G.; Sanjayan, G. J.; Ganesh, K. N. *J. Org. Chem.* **1997**, *62*, 5169-5173. (b) Del Valle, J. R.; Goodman, M. *J. Org. Chem*. **2003**, *68*, 3923-3931.
37. (a) Nicolaou, K. C.; Liu, J. J.; Hwang, C.-K.; Dai, W.-M.; Guy, R. K. J. *J. Chem. Soc., Chem. Commun.* **1992**, 1118-1120. (b) Evans, D. A.; Bender, S. L.; Morris, J. *J. Chem. Soc.* **1988**, *110*, 2506-2526.
38. Tamaki, M.; Han, G.; Hruby, V. J. *J. Org. Chem.* **2001**, *66*, 1038-1042.

CHAPTER –III

Studies toward the synthesis of Cheimonophyllon E

INTRODUCTION

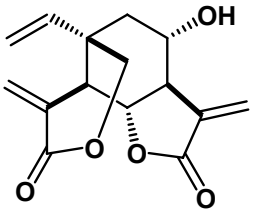
Nature is unrivaled in its ability to synthesize highly diverse organic molecules, some of which possess exquisitely selective biological activities. In the early 1800's, an emerging fascination with such molecules, later known as 'natural products' or secondary metabolites, gave rise to the field of organic chemistry, so named for its emphasis on the chemistry of living things. Natural products have since provided a focal point for wide-ranging efforts aimed at isolating the chemical ingredients of nature, elucidation their structures and establishing their biosynthetic pathways, and synthesizing these compounds, as well as evaluating the relationships between their structure and activity. Natural products once served humankind as the source of all drugs, and higher plants provided most of these therapeutic agents. Today, natural products (and their derivatives and analogs) still represent over 50% of all drugs in clinical use.

The terpenoids form a large class of chemically related, naturally occurring compounds. Terpenoid natural compounds have been isolated from many plant and fungi species around the globe, and they display an impressive array of bioactivities that are of medicinal value. Among the terpenoids, sesquiterpenoids are one of the largest groups,[1] with over 200 skeletal types and several thousand compounds of the class have been isolated and identified. In general, the term "sesquiterpenoids" is used as for the entire class, including hydrocarbons and oxygenated compounds, whereas "sesquiterpene" should refer only to the hydrocarbons.

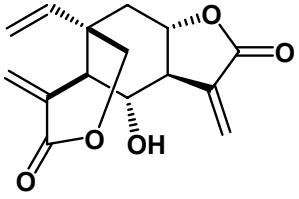
Sesquiterpenoids are very widespread constituents of essential oils and are widely distributed in plants, liverworts, fungi, algae, insects, and in a very few bacteria.[1a,b] Some of them are having considerable industrial value in the flavour and perfumery industries. And some sesquiterpenoids are found to have essential biological functions, acting as plant growth regulators or insect juvenile hormones in their host organism.[2] The majority of them are thought to serve as feeding deterrents,[3a,b] pollination attractants,[3b,c] insect phermones[4] or phytoalexins[5] to mediate important ecological interactions between the host organism and environment. Some of the first sesquiterpenoids with potential antitumor activity were vernolepin (**1**) and vernomenin (**2**), which were isolated as tumor inhibitors

from *Vernonia hymenolepis* by Kupchan and colleagues in 1968. They showed cytotoxicity (ED_{50}) against KB cell culture at 2 and 20 μg/mL, respectively, and vernolepin also showed significant inhibitory activity against the Walker intramuscular carcinosarcoma 256 in the rat at 12 mg/kg.[6]

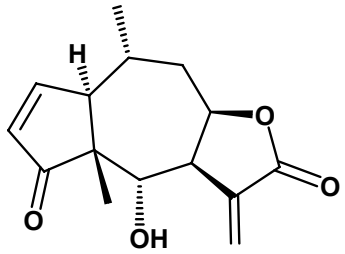
Scheme 1:



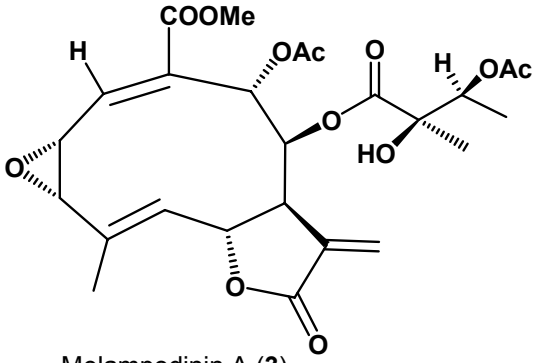
Vernolepin (**1**)



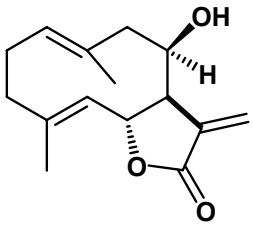
Vernomenin (**2**)



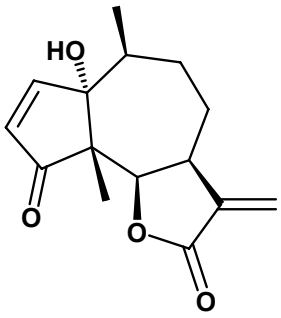
Helenalin (**4**)



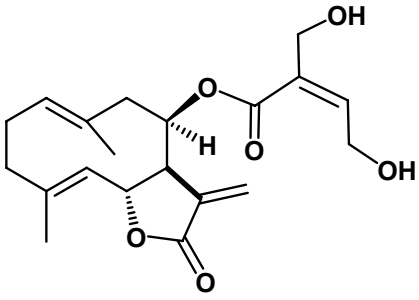
Melampodinin A (**3**)



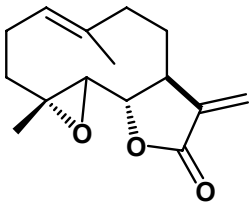
Eupatolide (**5**)



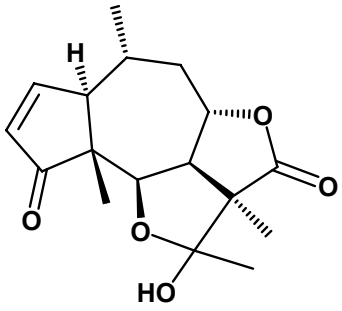
Parthenin (**7**)



Eupatoriopicrin (**6**)



Parthenolide (**8**)



Tenulin (**9**)

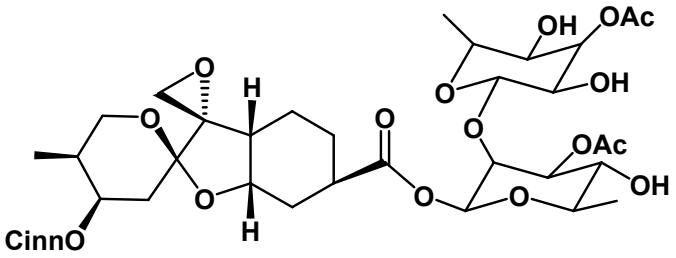
The discovery of vernolepin and of its antitumor properties was the impetus for a decade of intensive searching for cytotoxic and anti-cancer active sesquiterpenoid lactones during the 1970s. A large number of active agents were isolated from plants, primarily from plants in the family Compositae (Asteraceae). A majority of the hundreds of

compounds evaluated were cytotoxic, and a small number have shown activity in vivo against P-388 leukemia and other tumor systems. Melampodinin A (**3**), isolated in 1976 by N. H. Fischer and colleagues,[7] is the major constituent in a number of populations of the yellow-rayed species *Melampodium americanum* frm Mexico. It showed inhibitory activity *in vivi* against lymphocytic leukemia P-388, exhibiting an optimum % T/C 140 at 12 mg/kg.[8] Melampodinin A was determined to be a sequiterpenoid lactone, and other antitumor-active sesquiterpenoid lactones include the following compounds with different skeletal types: helenalin (**4**),[9] eupatolide (**5**),[10] eupatoriopicrin (**6**),[10] parthenin (**7**),[11] parthenolide (**8**),[12] and tenulin (**9**).[13] In gerenal, an α-methylene-γ-butyrolactones or cyclopentenone group is a necessary and usually sufficient condition for activity. Activities are generally enhanced by the presence of further alkylating groups (epoxides, α,β-unsaturated ketones and esters), which represent reactive receptor sites for biological nucleophiles, in particular thiol and amino groups. In spite of the large number of anti-tumor active sesquiterpenoid lactones, none of them have been considered for clinical testing, which is partly due to their high toxicity (Scheme 1).[14]

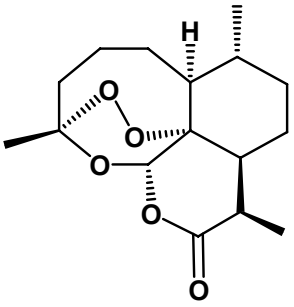
The glycoside phyllanthoside (**10**), obtained from *Phyllanthus acuminatus*, has a marked antineoplastic activity against the NCI murine B-16 melanoma.[15] Besides cytotoxic and antitumor activity, sesquiterpenoids exhibit a rich variety of other biological properties. The endoperoxide artemisinin (qinghaosu) (**11**),[16] isolated from the Chinese herb *Artemisia annua*, has been employed for the treatment of malaria. The main sesquiterpenoid mycotoxins are the trichothecenes (**12**),[17] which are associated with a wide variety of human and animal toxic effects. They are also phytotoxic compounds and potent anticancer agents, and some have antibacterial activity, such as verrucarin (**13**). The drimane sesquiterpenoids warbruganal (**14**) and polygodial (**15**), isolated from *Warburgia stuhlmannii*, are examples of insect antifeedant substances (Scheme 2).[18]

During a screening of the higher fungal metabolites for nematicidal activities, six new bisabolane-type sesquiterpenoids, cheimonophyllons A-E and cheimonophyllal (**16 – 21**), were isolated from the submerged cultures of basidiomycete *Cheimonophyllum candidissimum*.[19] These compounds were found to exhibit not only nematicidal but also antifunal, antibacterial, and cytotoxic activities. Their relative structures have been determined by extensive ^{1}H and ^{13}C NMR spectroscopic analysis.[20] Among these

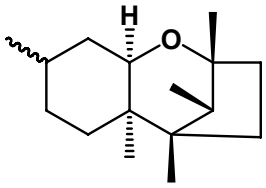
Scheme 2:



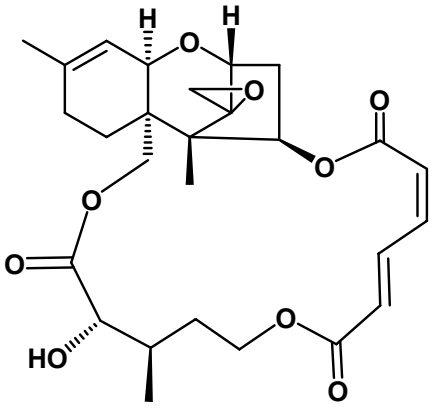
Phyllanthoside (**10**)



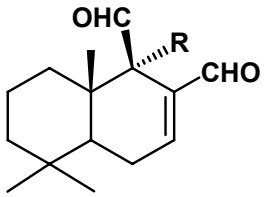
Qinghaosu (**11**)



Trichothecanes (**12**)



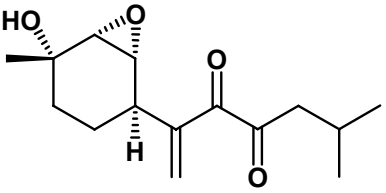
Verrucarin (**13**)



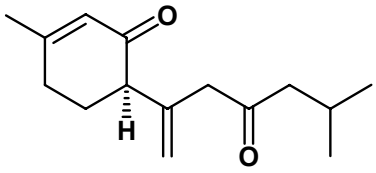
Warburganal R = OH (**14**)
Polygodial R = H (**15**)

cheimonophyllons, **20** and **21** possess five or four stereogenic carbons, respectively, in a highly oxygenated 7-oxabicyclo[4.3.0]nonane core skeleton (Scheme 3).

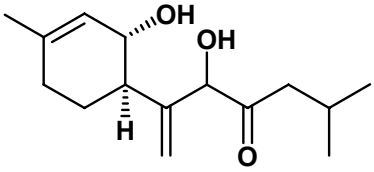
Scheme 3:



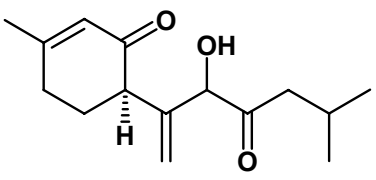
Cheimonophyllon A (**16**)



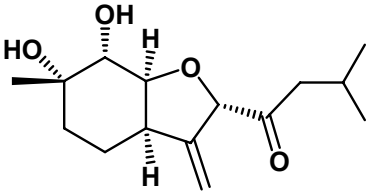
Cheimonophyllon B (**17**)



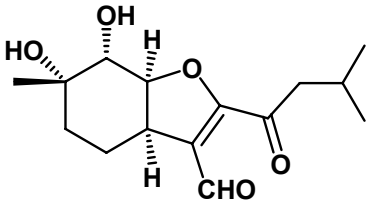
Cheimonophyllon C (**18**)



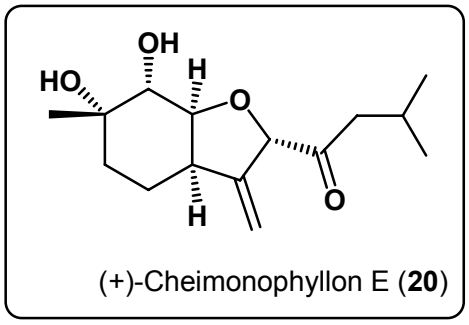
Cheimonophyllon D (**19**)



Cheimonophyllon E (**20**)



Cheimonophyllal (**21**)



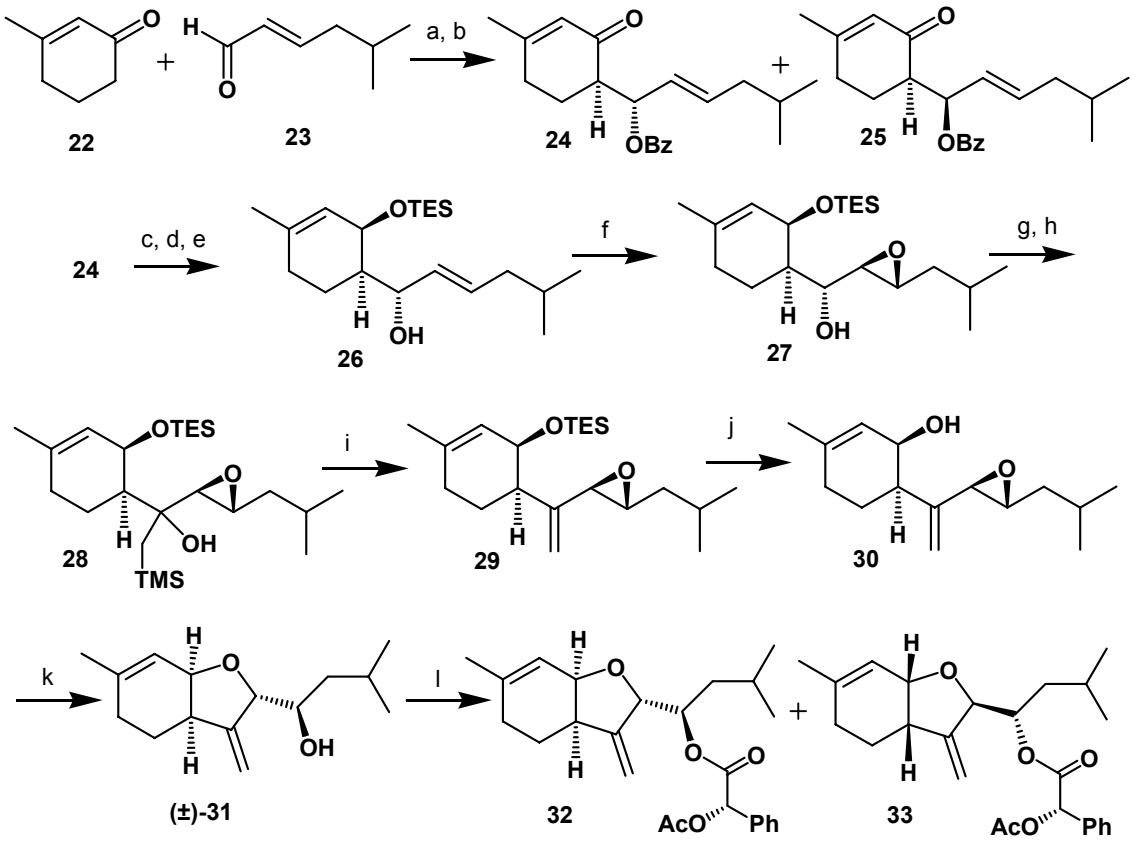
(+)-Cheimonophyllon E (**20**)

Previous Work:

Tadano's Approach:

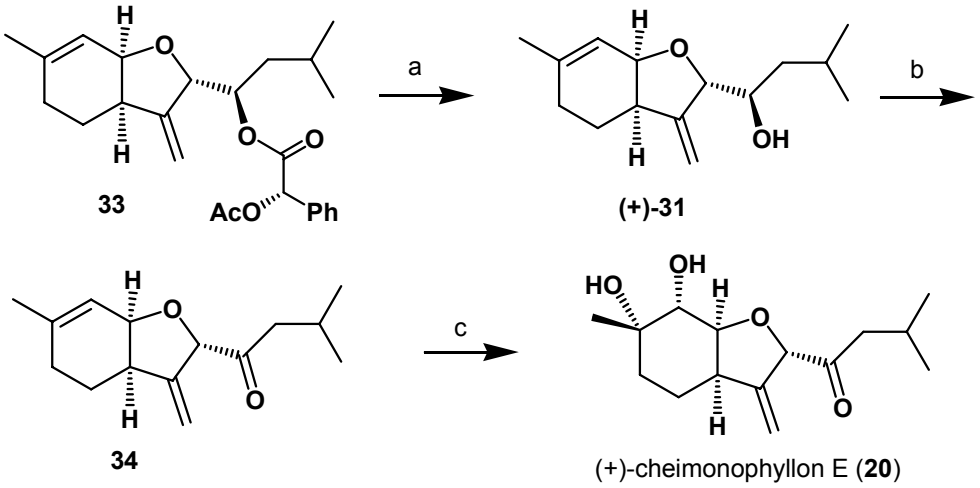
In 2001 Tadano *et al* reported the first total synthesis of (+)-cheimonophyllon E (**20**) using an optical resolution strategy and established the previously unknown absolute stereochemistry.[21] They have initiated the synthesis by aldol reaction of enone **22** and aldehyde **23** using LDA followed by benzoylation of the aldol mixture provided **24** (*syn*) and **25** (*anti*). The 1,2-reduction of the enone in **24** was conducted using the Luche's conditions to afford the desired allylic alcohol, which on a protection-deprotection sequence resulted **26**. A vanadium-catalyzed oxidation of the allylic alcohol **26** predominantly provided *anti*-α,β-eopxy alcohol **27**. Introduction of the *exo*-methylene group in the tetrahydrofuran ring in **20** was achieved by a Peterson olefination strategy on **27** to obtain exo-methylene-epoxide **29**. Desilylation of the TES group in **29** using *n*-Bu_4NF obtained **30**, which on stereoselective epoxy ring opening by treating with CSA underwent intramolecular cyclization to provide racemic (±)-**31** exclusively. When racemic (±)-**31** was acylated with (*S*)-*O*-acetylmandelic acie, resulted in readily separable diastereomeric esters which on Dibal-H reduction produced optically pure (+)- and (-)-**31**. Oxidation of (+)-**31** using Dess-Martin periodinane furnished ketone **34**. Compound **34** on subjecting to OsO_4-NMO oxidation, stereoselective dihydroxylation occurred preferentially at the endocyclid double bond to provide (+)-cheimonophyllon E (**20**) (Schemes 4 & 5).

Scheme 4:



Reagents and conditions: (a) LDA, THF, -18^{o} C, 66% (1.2:1 mixture); (b) BzCl, pyridine, 50% (c) $NaBH_4$, $CeCl_3.7H_2O$, MeOH, 0^{o} C, quant.;(d) imidazole, TESCl, DMF, 0^{o} C, 91%; (e) Dibal-H, CH_2Cl_2, -78^{o} C, 90%; (f) $VO(acac)_2$, *t*-BuOOH, CH_2Cl_2, 0^{o} C, 78%; (g) Dess-Martin periodinane, CH_2Cl_2; (h) $TMSCH_2MgCl$, THF, 0^{o} C, 87%; (i) KHMDS, THF, 0^{o} C, 93%; (j) *n*-Bu_4NF, THF, 0^{o} C, 98%; (k) CSA, CH_2Cl_2, -18^{o} C, 98%; (l) (*S*)-*O*-acetylmandalic acid, WSC.HCl, Et_3N, 4-DMAP, CH_2Cl_2, 46%

Scheme 5:

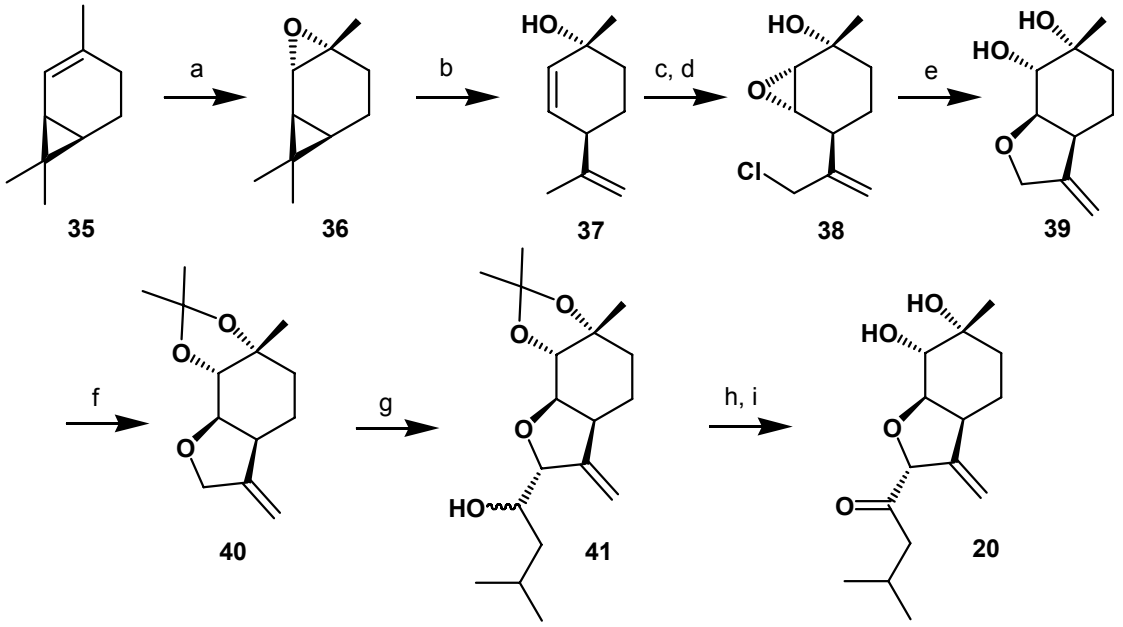


Reagents and conditions: (a) Dibal-H, CH_2Cl_2, -78^{o} C, quant.; (b) Dess-Martin periodinane, CH_2Cl_2, 0^{o}C, 98%, (c) OsO_4, NMO, acetone-*t*-BuOH-H_2O, O^{o} C, 48%

Brocksom's Approach:

In 2005, Brocksom and co-workers reported the total synthesis of cheimonophyllon E starting from (+)-2-carene (**35**).[22] MCPBA oxidation of **35** obtained 2-carene epoxide (**36**), which on ZrO_2 – TiO_2 catalyzed isomerisation reaction provided 2,8- *para*-menthadienol-1 (**37**). Stereoselective *syn*-epoxidation of **37** gave an epoxide, which was subjected to allylic chlorination with $Ca(OCl)_2$ leading to compound **38**. The simultaneous hydrolysis and cyclization of **38** using water/HMPA furnished tetrahydrofuran **39**. Protection of the diol function in **39** with 2,2-dimethoxypropane provided **40**, which on metallation at –65 ^oC with 1 equiv of *sec*-butyllithium, exchange to the organozinc species, and reaction with isovaleraldehyde led to **41**. Finally, PDC oxidation of **41** followed by deprotection of the acetonide group provided cheimonophyllon E (**20**) (Scheme 6).

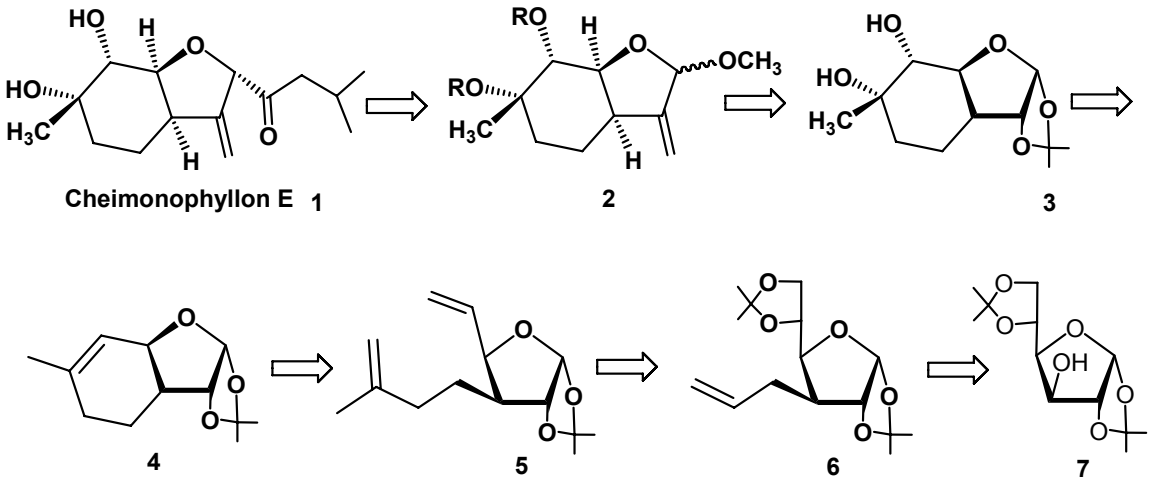
Scheme 6:



Reagents and conditions: (a) MCPBA, $NaHCO_3$, CH_2Cl_2, rt, 4h; (b) ZrO_2 - TiO_2, dry toluene,80^{o}oC, 10 min (50% for two steps); (c) *t*-BuOOH (90%), $VO(acac)_2$, benzene, rt, 20 h, 60%; d) $Ca(OCl)_2$ 70%, H_2O, dry ice, CH_2Cl_2, 1 h, 57%; e) HMPA/H_2O, 60^o C, 22 h, 75%; f) $Me_2C(OMe)_2$, PTSA (cat), acetone, rt, 3 h, 85%; g) -65^o C (1 equiv) *sec*-BuLi (0.52 M), (1 equiv) $ZnCl_2$, 10 min, $(CH_3)_2CHCH_2CHO$, 10 min, 72%; h) PDC, CH_2Cl_2, rt, 24 h, 70%; i) PPTS, MeOH, 50^o C, 48 h, 78%

Cheimonophyllon E (**20**)[19] possesses five stereogenic carbons in a highly oxygenated 7-oxabicyclo[4.3.0]nonane core skeleton. Our interest in its intriguining structural features coupled with biological activity led us to study the synthesis of the cheimonophyllon E. Keeping the unique structural parameters in mind, we planned straightforward disconnection approach for cheimonophyllon E as shown in Scheme 1. The obvious disconnection of side chain in cheimonophyllon E led to the methyl glycoside **42**. A sequence of acidic hydrolysis, oxidation of the resulting secondary alcohol to ketone and one carbon Wittig homologation on diol **43** expected to provide the methyl glycoside **42**. As a part of our interest in the observations on asymmetric induction of furanose monosaccharide unit to its emerging side chain, we planned a substrate induced stereoselective dihydroxylation on rigid tricyclic olefin **44**. Synthesis of methyl substituted tricyclic olefin **44** was designed using ring closing metathesis reaction on the corresponding diene **45** which can be obtained from allyl derivative **46**. In turn compound **46** can be derived from readily available 1,2;5,6-di-*O*-isopropylidene-α-D-glucofuranose **47**.

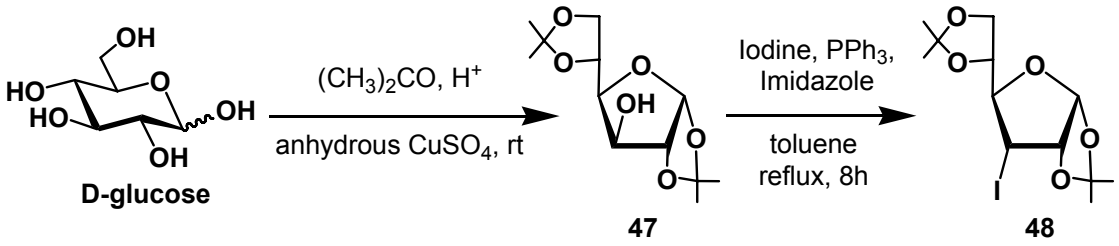
Scheme 1:



Following the lines of retrosynthetic analysis, synthesis was initiated using readily available D-glucose, which was converted into the 3-deoxy-3-iodo-1,2:5,6-di-*O*-

isopropylidene-α-D-allofuranose (**48**) in two steps by employing literature procedures. Thus, D-glucose was converted into 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose **47** on combined action of acetone and anhydrous $CuSO_4$ in the presence of H_2SO_4, subsequent conversion of 3-hydroxyl group to 3-iodo was accomplished by refluxing **47** with triphenylphosphine, imidazole and iodine in toluene for overnight to provide iodo compound **48** (Scheme 2). The ^1H NMR, ^{13}C NMR, IR, mass spectral data, elemental analysis and optical rotation of **48** were all in full agreement with the reported literature values.[23]

Scheme 2:



In our synthetic strategy, stereoselective introduction of the allyl group at C-3 can be attributed as one of the key steps and for which we opted for free radical C-C bond formation by allyltri-*n*-butylstannane.[24]

A brief note on free radical C-C bond formation by allylstannanes:

The explosive growth of free radicals in organic synthesis is largely due to the recognition that radical reactions, even with highly functionalized molecules, can be conducted in a highly efficient yet selective manner, and they often have advantages over alternative ionic processes.[25] Free radical or "one-electron" methodology for carbon-carbon bond forming reactions using allylstannanes have the advantages of tolerating quite complex functionality in the substrate and of being nearly stoichiometric in reagents, and not requiring extensive experimentation for application to new substrates.[24b] Most of the free radical reactions including reactions of allylstannanes are chain processes. To design a successful, high yielding, free radical chain process, controlling of the following reaction processes are crucially important.

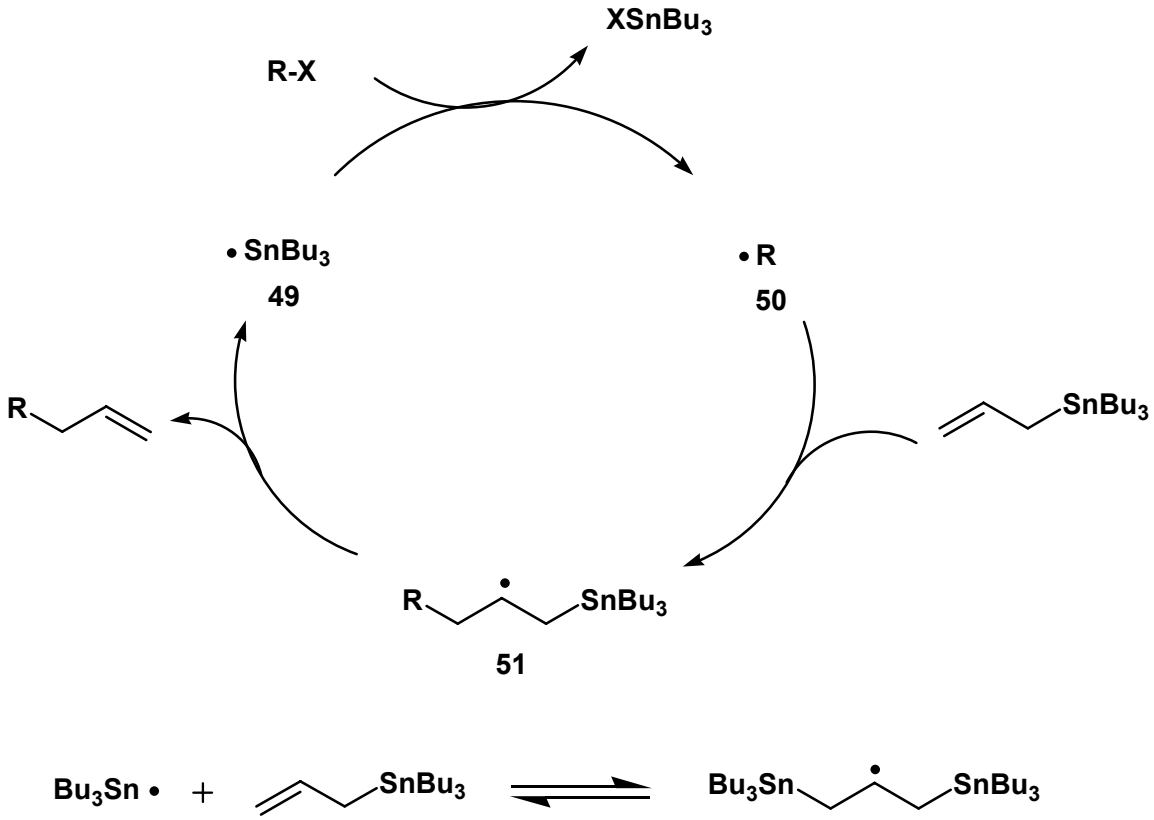
1. Specific generation of initiator radicals.

2. Selective, low energy pathways for the production of substrate radicals

3. Chain carrying steps with reagents which preclude the formation of highly reactive, indiscriminate radicals.

4. Reasonable termination steps to produce innocuous by-products which do not disturb the chain.

Figure 1: Reaction mechanism of allylation:



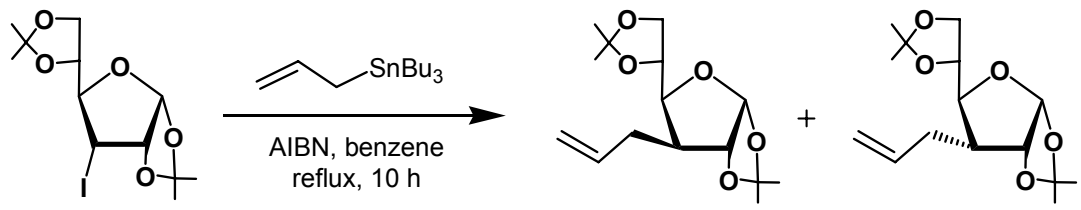
*The reaction mechanism for allylation by allyltri-n-butylstannane is shown in Figure 1. Three radicals, **49**, **50**, and **51** must be generated and each must react selectively in the same reagent pool. The desired reaction of the tributyltin radical **49** is atom transfer and the competing reaction is addition to allylstannane. Addition of tributyltin radical to an unactivated alkene is much slower than addition to an activated alkene. Therefore, rapid elimination regenerates the starting tin radical and allylstannane, therefore even less reactive radical precursors such as activated chlorides and phenylsulfides can be used. Radical **51** is a β-stannyl radical and undergoes rapid fragmentation to propagate the chain.*

For allylation and methallylation reactions using allyltri-n-butylstannane and methallyltri-n-butylstannane, on photochemical initiation or initiation by azo-bis-isobutyronitrile (AIBN), substrates that provide carbon centered radicals, alkyl halides, selenides, thioacyl derivatives must be obtained in pure form in order to succeed the reaction with better yields.

In many instances, good stereochemical control can be achieved in the introduction of such substituents. The observed products may in general be predicted by assuming preferential addition of allyltri-n-butylstannane to the less hindered face of an intermediate radical, and good stereoselectivity in such reactions appears to require a significant steric bias in the substrate. Good stereoselectivity was observed in the reaction of the substrates with conformationally locked ring systems.

Treatment of iodo compound **48** with allyltri-*n*-butyltin in the presence of AIBN in refluxing benzene gave both α- and β-allylated compounds **46** & **52** in 3:1 ratio respectively (Scheme 3). Predominant formation of the desired β-allyl derivative **46** can be attributed to the steric factors, which control this radical reaction. In the ^{1}H NMR spectrum of **46** the characteristic signals due to olefin of the allyl group were distinctly visible at δ 5.06 (1 H), 5.14 (1H) and 5.85 (1 H) as multiplets. In addition, a doublet at δ 4.51 with characteristic coupling constant (J = 3.7 Hz) assigned to H-2 clearly indicated that the allyl group was present in *gluco* configuration. The ^{13}C NMR spectrum showed resonances due to olefinic carbons at δ 116.5 and 135.5, in support of the structure **46**. Further, structure of **46** was confirmed by IR, mass spectroscopy and elemental analysis.

Scheme 3:

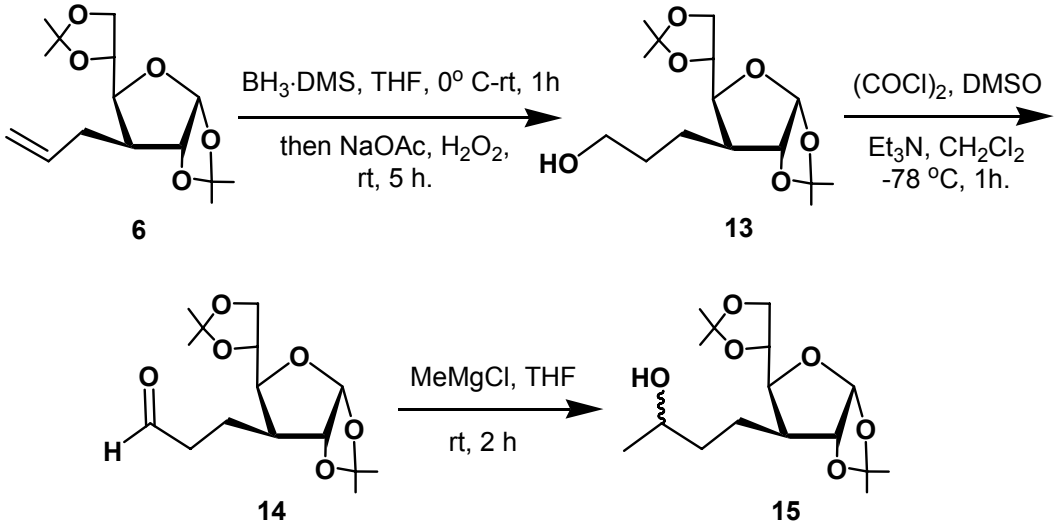


8 **6** **(75:25)** **12**

Compound **46** was subjected to hydroboration-oxidation reaction in the presence of 97% H_3B:SMe_2 solution in THF followed by sequential treatment with H_2O_2 and NaOAc to provide alcohol **53**.[26] The ^{1}H NMR, ^{13}C NMR, IR, mass spectroscopy and elemental

analysis confirmed the structure of **53**. For instance, resonances due to olefinic protons disappeared in its ^{1}H NMR spectrum while a multiplet at δ 3.67 (2 H) was visualized due to hydroxymethyl group and all the other protons appeared at their expected chemical shift values. The primary alcohol of **53** was oxidized under Swern conditions[27] to furnish corresponding aldehyde **54**, which was immediately subjected to Grignard reaction using MeMgCl in THF to afford **55** as a diastereomeric mixture (Scheme 4). In the ^{1}H NMR spectrum resonances due to newly introduced methyl group appeared at δ 1.21 (3 H) as a multiplet while in ^{13}C NMR corresponding carbon resonated at δ 23.2 and 23.5 supporting the assigned structure of **55**. Further evidence in support of the structure **55** was obtained from its IR, mass spectroscopy and elemental analysis. Oxidation of the secondary

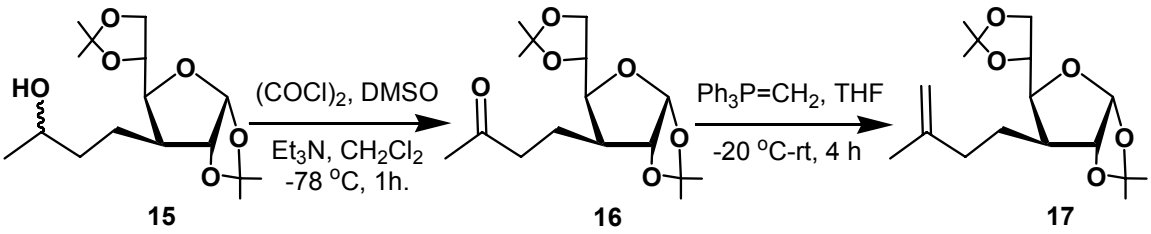
Scheme 4:



alcohol **55** was effected again under Swern conditions[27] to provide ketone **56**. In the ^{1}H NMR spectrum, signals due to protons of methyl group adjacent to the keto group appeared at δ 2.16 (3 H) as a singlet while the methylene group was visualized at δ 2.59 as a triplet (J = 7.6 Hz). In the ^{13}C NMR spectrum resonances due to the carbonyl group were observed at δ 207.1, confirming the structure of **56**. One carbon Wittig homologation[28] of the ketone **56** was accomplished by exposing to methylenetriphenylphosphorane in THF to furnish **57** (Scheme 5). The ^{1}H NMR spectrum showed the signals due to *exo*-methylenic protons at δ 4.73 (1 H) and 4.75 (1 H) as two singlets while the ^{13}C NMR shown signals due to olefinic carbons at δ 110.6 and 144.5 respectively supported the assigned structure

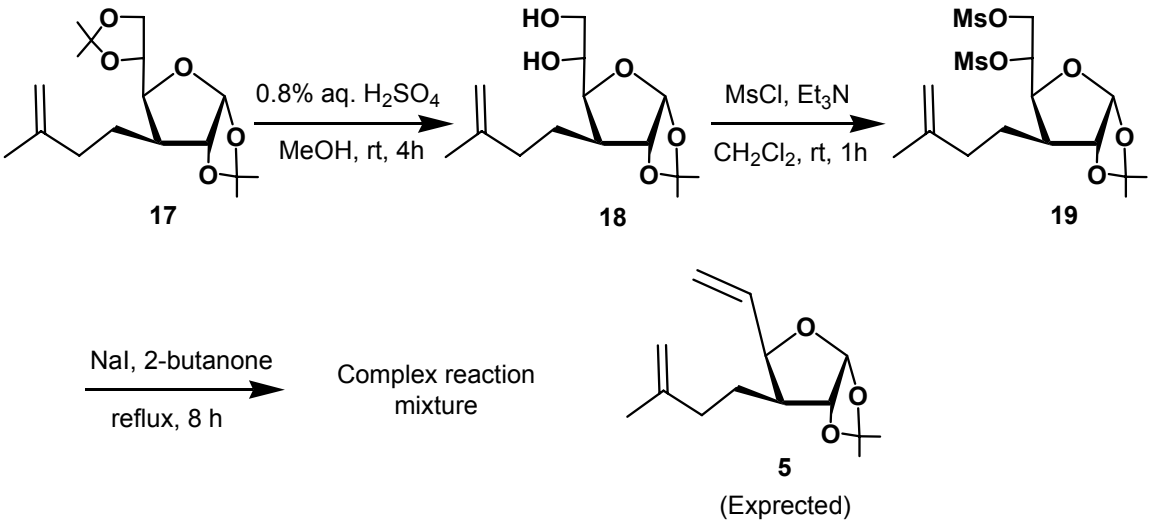
of **57**. In the IR spectrum, absorption due to olefin moiety was observed at 1650 cm^{-1}. Mass spectroscopy and elemental analysis further confirmed the structure of **57**.

Scheme 5:



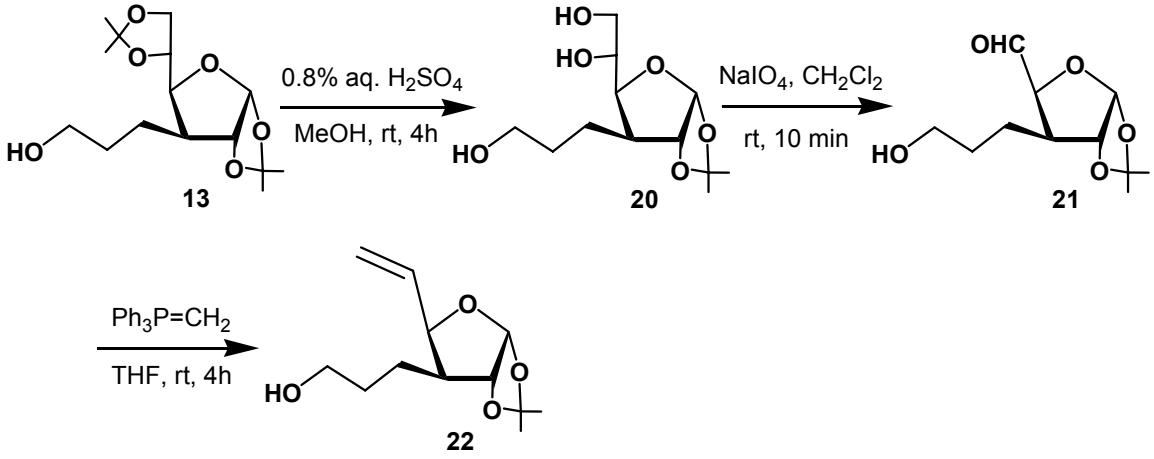
In order to obtain the precursor for the ring closing metathesis, 5,6-isopropylidene group of **57** was selectively hydrolyzed using 0.8% H_2SO_4 in MeOH to obtain diol **58**.[29] The structure of **58** was confirmed by its ^1H NMR, ^{13}C NMR, IR, mass spectroscopy and elemental analysis. For instance, in the ^1H NMR spectrum, appearance of two singlets at δ 1.30 and 1.50 accounting for six protons indicated the presence of only one isopropylidene group, while all the other protons appeared at their respective chemical shift values. Conversion of the diol **58** to its corresponding dimesylate **59** was achieved by treating with MsCl in the presence of triethylamine in CH_2Cl_2. Exposing the dimesylate **59** to NaI in refluxing 2-butanone did not give the expected diene **45** instead, resulted in a complex mixture of compounds (Scheme 6). However, compound **58** on treatment with silica gel supported $NaIO_4$ underwent oxidative cleavage[30] of 5,6-diol to give its corresponding aldehyde which on subjecting to one carbon Wittig homologation

Scheme 6:



afforded required diene **45**, but in very low yields. We have attributed these discouraging results to the sensitivity posed by *exo*-olefinic double bond which can isomerise to give a mixture of compounds. Based on these observations we have altered our strategy, where in we have planned to introduce the *exo*-olefinic group after the installation of 5,6-double bond. Accordingly, 5,6-isopropylidene group of alcohol **53** was selectively cleaved by exposing to 0.8% aq. H_2SO_4 in MeOH to furnish the triol **60**. In the ^{1}H NMR spectra of **60**, resonances at δ 1.30 and 1.50 (6 H) accounted for only one isopropylidene group clearly indicated the formation of triol **60**. Further, the ^{13}C NMR, IR, mass spectroscopy and elemental analysis are in accordance with the assigned structure **60**. Oxidative cleavage of 5,6-diol of triol **60** using silica gel supported $NaIO_4$[30] in dichloromethane afforded the corresponding hydroxy aldehyde derivative **61**, which was immediately subjected to one carbon Wittig homologation[28] by treating with methylenetriphenylphosporane in THF to give alcohol **62** (Scheme 7). The structure of **62** was confirmed by its ^{1}H NMR, ^{13}C NMR, IR, mass spectroscopy and elemental analysis. For instance, in the ^{1}H NMR spectrum, characteristic olefinic protons appeared at δ 5.19-5.42 (m, 2 H) and at δ 5.72-5.93 (m, 1 H), while anomeric proton (H-1) was visualized at δ 5.81 as a doublet (J = 3.8 Hz) where as ^{13}C NMR showed resonances due to olefinic carbons at δ 117.3 and 133.8.

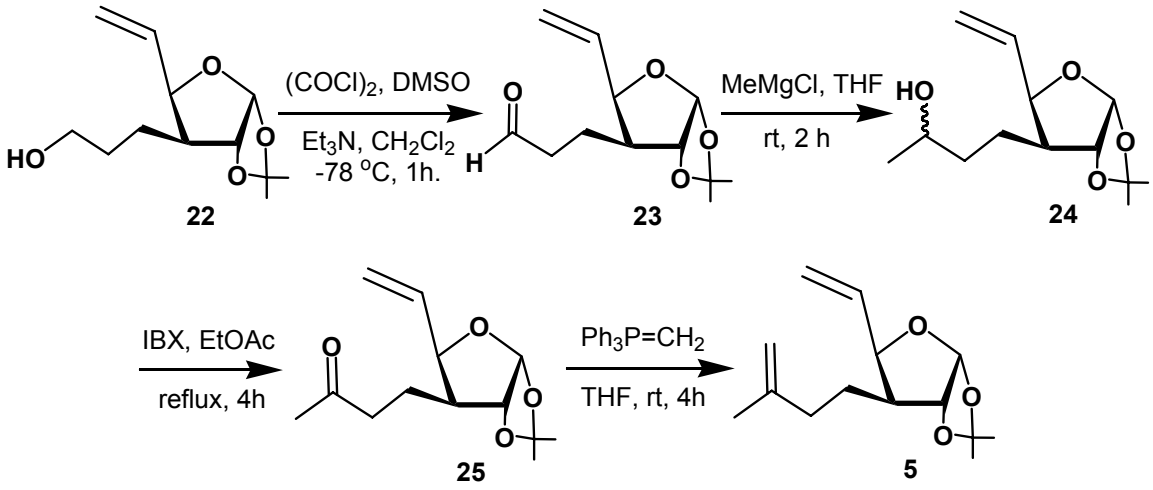
Scheme 7:



Oxidation of the primary alcohol of **62** under Swern conditions[27] furnished corresponding aldehyde **63**, which on Grignard reaction with MeMgCl in THF furnished **64** as a diastereomeric mixture. The ^{1}H NMR spectrum of **64** showed signals due to newly introduced methyl protons at δ 1.17 and 1.20 (3 H) as two doublets (J = 1.5 Hz) clearly

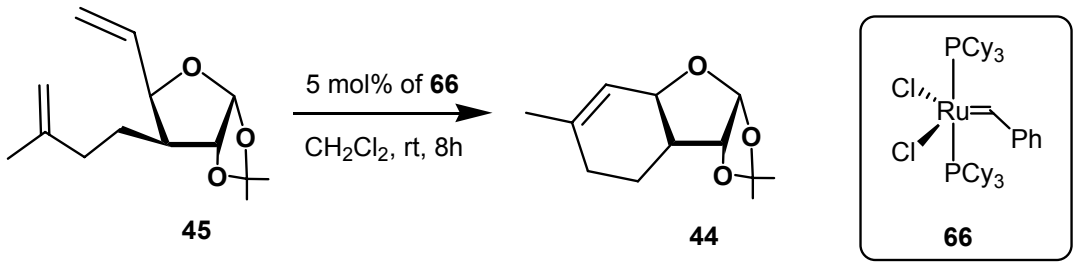
indicated the formation of **64**. The ^{13}C NMR, IR, mass spectroscopy and elemental analysis further supported the assigned structure of **64**. Secondary alcohol of **64** was oxidized by refluxing with IBX in ethyl acetate to obtain the corresponding ketone **65**.[31] The ^{1}H NMR, ^{13}C NMR, IR, mass spectroscopy and elemental analysis were all in accordance with the structure **65**. In the ^{13}C NMR, ketonic carbon resonated at δ 207.5 while in IR spectroscopy, absorption due to keto group was observed at 1715 cm^{-1} confirming the assigned structure of **65**. One carbon Wittig homologation of the ketone **65** by exposing to methylenetriphenylphosphorane in THF provided the desired diene derivative **45** (Scheme 8). In the ^{1}H NMR spectrum of **45**, signals due to 5,6-olefinic protons appeared at δ 5.20-5.43 (2 H) and at δ 5.74-5.93 (1 H) as two multiplets, while anomeric proton (H-1) visualized at δ 5.83 as a doublet (J = 3.8 Hz), where as the two *exo*-olefinic protons along with H-4 resonated at δ 4.64-4.81 (3 H) as a multiplet supporting the assigned structure of **45**. The ^{13}C NMR, IR, mass spectroscopy and elemental analysis further confirmed the structure of diene **45**.

Scheme 8:



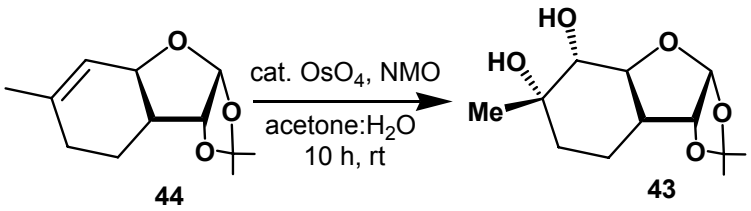
After having diene **45** at our hand, our immediate concern was the ring closing metathesis of diene to the corresponding cyclic olefin. Thus, the ring closing metathesis of **45** was successfully accomplished by treating with 5 mol% of Grubbs' 1st generation catalyst (**66**) in CH_2Cl_2 at room temperature to obtain **44** (Scheme 9).[32] The structure of **44** was confirmed by ^{1}H NMR, ^{13}C NMR, IR, mass spectroscopy and elemental analysis. For instance, in the ^{1}H NMR spectrum, resonances due to the olefinic proton appeared at δ 5.64

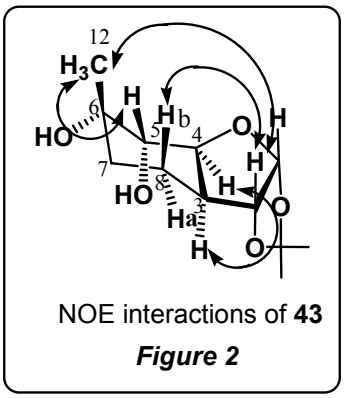
Scheme 9:



as a broad singlet while in ^{13}C NMR two olefinic carbons resonated at δ 118.3 and 141.7. Having precursor **44** in hand, our next aim was dihydroxylation. Accordingly, cyclic olefin **44** was subjected to dihydroxylation reaction by using catalytic OsO_4 along with co-oxidant NMO in acetone:water (9:1)[33] to provide the diol **43** (Scheme 10), whose NMR spectral data indicated the formation of a single diastereomer. The ^1H NMR spectrum of **43** showed disappearance of the olefinic proton while the new hydroxymethine proton appeared at δ 3.72 as a singlet and all the other protons appeared at their respective chemical shift values. The ^{13}C NMR spectrum of **43** displayed two new hydroxymethine carbons at δ 71.1 and 79.8. The stereochemistries of newly formed centers were assigned by the COSY and the NOESY studies (Figure 2). In the NOESY spectrum of **43**, a strong NOE between H-8_b, H-2 methine protons, H-2, H-12 methyl protons, H-5, H-12 methyl protons, and between H-3 and H-4 methine protons were observed indicating their *cis* relationship.

Scheme 10:





NOE interactions of **43**

Figure 2

Furthermore, the structure of **43** was unambiguously deduced by its X-ray diffraction studies. The ORTEP diagram of **43** clearly established the a*nti* periplaner selectivity in the dihydroxyaltion reaction and confirmed the formation of required diastereomer (Figure 3). The details of crystal data and structure refinement (Table **1**),

bond lengths and bond angels (Table **2**) and torsion angles (Table **3**) are given at the end of this section.

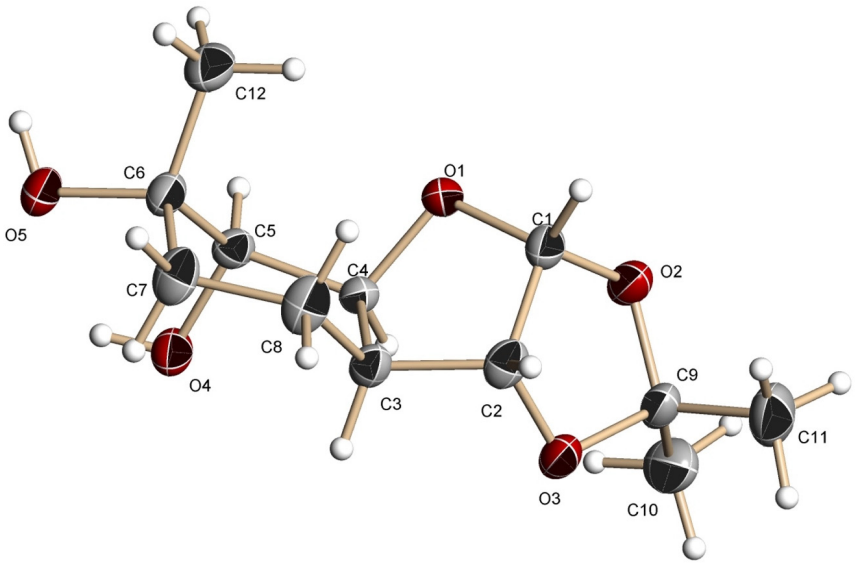
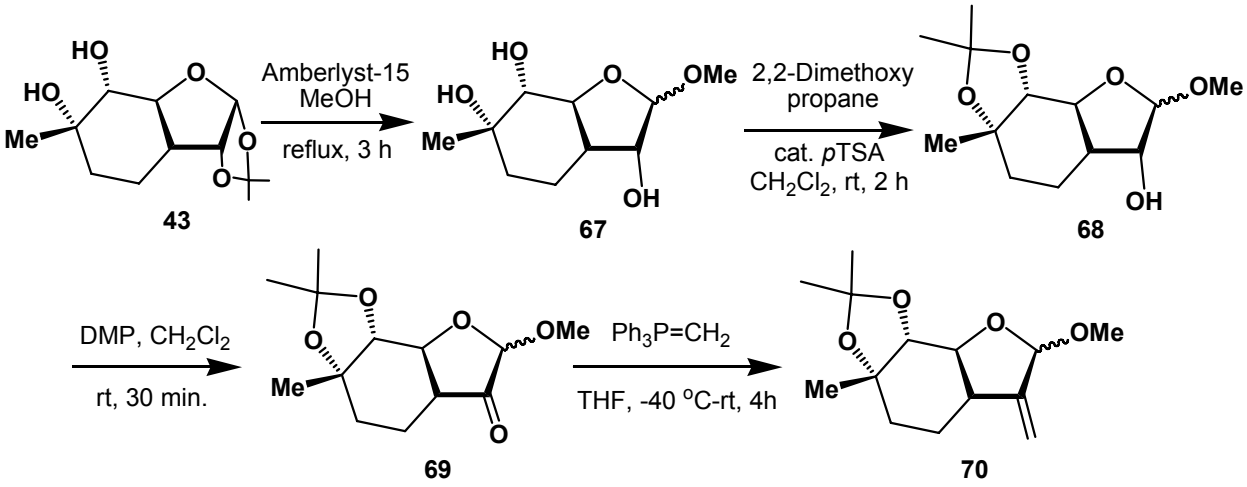


Figure 3

Treatment of **43** with the acidic resin, Amberlyst-15 in refluxing MeOH afforded inseparable α,β-mixture of methyl glycosides **67**. The structure of **67** was confirmed by its ^{1}H NMR, ^{13}C NMR, IR, mass spectroscopy and elemental analysis. For instance, in the ^{1}H NMR spectrum, signals due to the protons of OMe moiety were appeared at δ 3.44 and 3.47 as two singlets accounting for three protons and all other protons appeared at their expected chemical shift values. The ^{13}C NMR showed resonances due to OMe carbon at δ78.2 and 78.7, due to the presence of both the diastereomers. Transformation of **67** to its isopropylidene derivative was accomplished by exposing to 2,2-dimethoxypropane in the presence of catalytic amount of *p*TSA in CH_2Cl_2 at room temperature to provide **68**, again as an inseparable α,β-mixture of methyl glycosides. The ^{1}H NMR spectrum of **68** displayed resonances due to three methyl groups, visually, 6-methyl and two methyl groups of isopropylidene moiety, at δ 1.35, 1.38 and 1.46 respectively. The ^{13}C NMR, IR, mass spectroscopy and elemental analysis are all in accordance with the assigned structure of **68**. Installation of the *exo*-methylene at C-2 was achieved by oxidation followed by one carbon Wittig homologation. Thus, the oxidation of the 2-hydroxyl group to its corresponding ketone was effected by using Dess-martin periodinane (DMP)[34] in anhydrous CH_2Cl_2 at room temperature to obtain **69**. The resulting ketone was immediately

subjected to one carbon Wittig homologation by treating with methylenetriphenylphosphorane in THF to furnish **70** as a diastereomeric α,β-mixture of methyl glycosides (Scheme 11). The structure of **70** was confirmed by ^{1}H NMR, ^{13}C NMR, IR, mass spectroscopy and elemental analysis. For instance, in the ^{1}H NMR

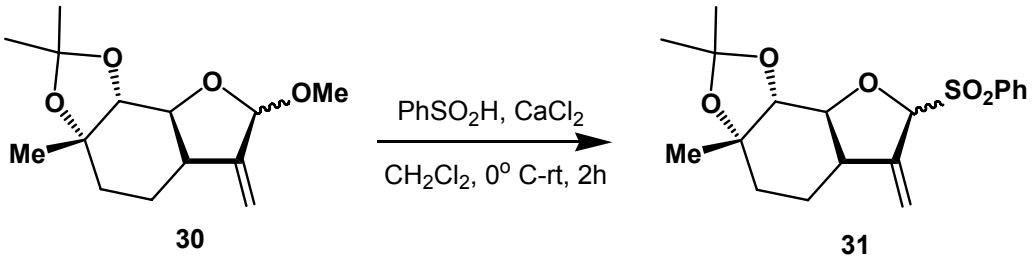
Scheme 11:



spectrum, resonances due to *exo*-olefinic protons along with anomeric (H-1) proton were observed at δ 5.15-5.32 as a multiplet accounting for three protons. While the ^{13}C NMR displayed signals due to *exo*-olefinic carbons at δ 110.1, 110.5, 152.7 and 153.2, indicating the presence of both the diastereomers.

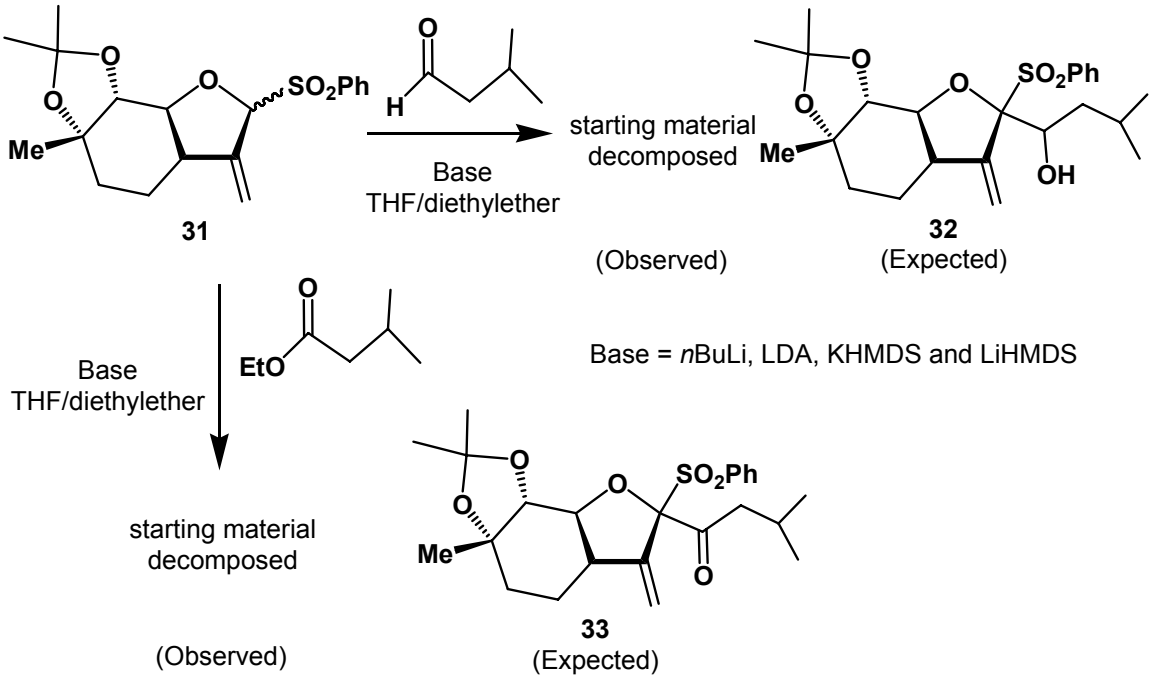
After successful construction of the bicyclic core of the target molecule with the right substituents and stereochemistry, our next aim was to introduce the side chain, which requires C-C bond formation. For that purpose, we have considered Ley's protocol,[35] which involves the electrophilic addition on anion generated from 2-benzenesulphonly tetrahydrofuran. Thus, compound **70** was treated with freshly prepared benzenesulphinic acid in the presence of anhydrous $CaCl_2$ in CH_2Cl_2 to obtain sulphone derivative **71** (Scheme 12). The sulphone **71** was found to be not so stable and was

Scheme 12:



characterized by ^{1}H NMR spectra, which shown peaks due to aromatic protons of benzenesulphinic moiety at δ 7.58 (2 H), 7.68 (1 H), and 7.93 (2 H) as multiplets and all the other protons resonated at their expected chemical shift values, confirming the formation of **71**. However, the sulphone **71** on deprotonation using various bases (*n*BuLi, Lithiumdiisopropylamide, KHMDS and LiHMDS) and exposing the resulting anion to electrophiles (isovaleraldehyde and ethylisovalerate) did not yield the expected C-C coupled products (**72** and **73**),[35b] instead, decomposition of the starting material in the above mentioned reactions was observed (Scheme 13).

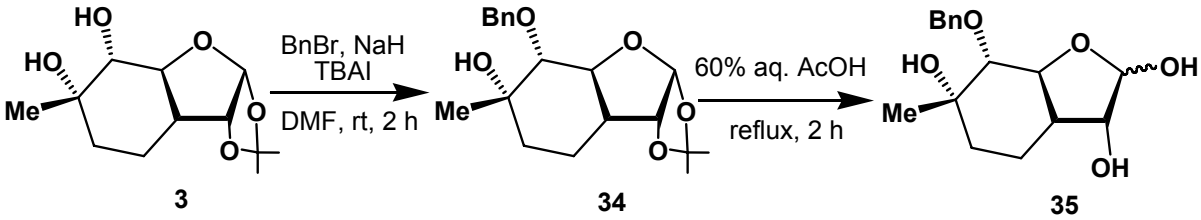
Scheme 13:



After facing repeated failures to construct the side chain on compound **71**, we have then considered to extend the side chain at anomeric carbon before introducing the *exo*-double bond. Accordingly, in order to protect the hydroxyl groups as their benzyl ethers, diol **43** was treated with NaH and BnBr in the presence of TBAI in DMF to furnish monobenzylated derivative **74**. Expected dibenzylation of the **43** did not occur and secondary hydroxyl group only got protected as its benzyl ether. In the ^{1}H NMR spectrum of **74**, benzylic protons appeared as a multiplet at δ 4.55-4.78 (2 H) while the aromatic protons were observed at δ 7.34 (5 H) as a multiplet indicating the presence of only one

benzyl group. The ^{13}C NMR, IR, mass spectroscopy and elemental analysis further confirmed the structure of **74**. Acidic hydrolysis of the 1,2-isopropylidene of **74** was performed by refluxing with 60% aq. AcOH to provide lactol derivative **75** (Scheme 14).[36] The ^{1}H NMR, ^{13}C NMR, IR, mass spectroscopy and elemental analysis confirmed the

Scheme 14:

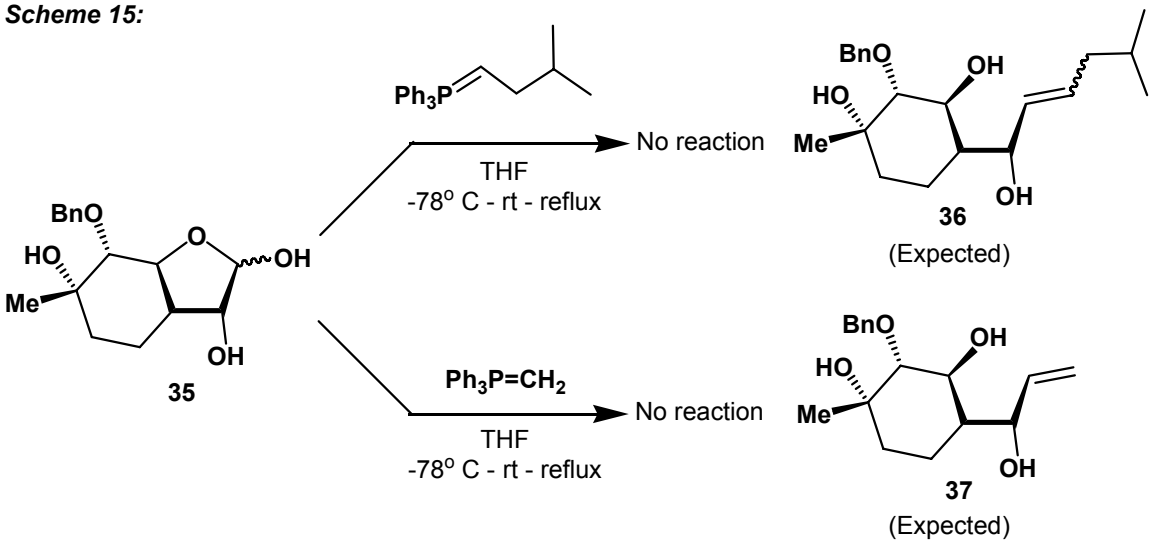


formation of **75**. For instance, in the ^{1}H NMR spectrum, resonances due to 1,2-isopropylidene moiety were disappeared while all the other protons appeared at their expected chemical shift values. So as to extend the carbon chain on anomeric carbon by C-C bond formation, following reactions have been performed.

Wittig reaction:[28]

Lactol **75** on exposing to isovalerenetriphenylphosphorane (prepared by the action of *n*BuLi on isovalaryltriphenlyphosphonium bromide in THF) in anhydrous THF, even though by employing excessive reagent due to the presence of free hydroxyl groups, did not yield the desired compound **76**. Whatsoever, there was no reaction and starting material was recovered. Same results were observed even in the case of one carbon Wittig homologation conditions, which did not give the expected compound **77** (Scheme 15).

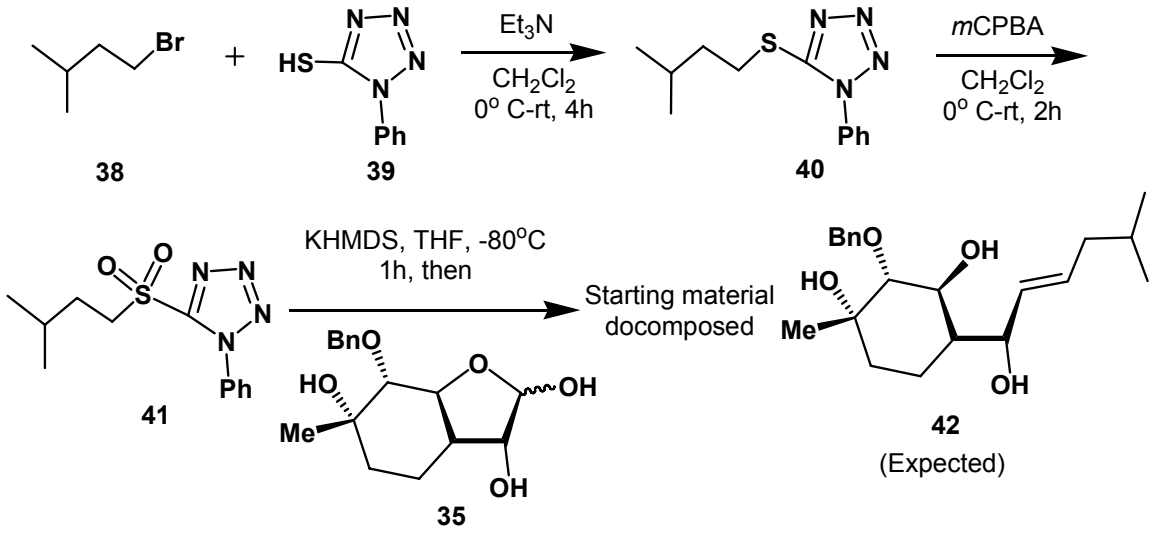
Scheme 15:



Julia-Kocienski reaction:[37]

To perform Julia-Kocienksi olefination reaction on lactol **75**, the required sulphone **81** was prepared from isovalerylbromide **78**. Thus, **78** on treatment with 1-Phenyl-1H-tetrazole-5-thiol (**79**) in the presence of Et_3N in CH_2Cl_2 afforded sulphide derivative **80**, which on subjecting to *m*CPBA oxidation in CH_2Cl_2 provided the sulphone **81**. The structures of both the sulphide **80** and sulphone **81** were studied and characterized by ^1H NMR and ^{13}C NMR spectroscopy. Lactol **35** was made to react with excess sulphone **81** in the presence of a base (KHMDS or LiHMDS) in THF at –80 ^oC. Instead of getting the expected compound **82**, decomposition of the starting material was observed (Scheme 16).

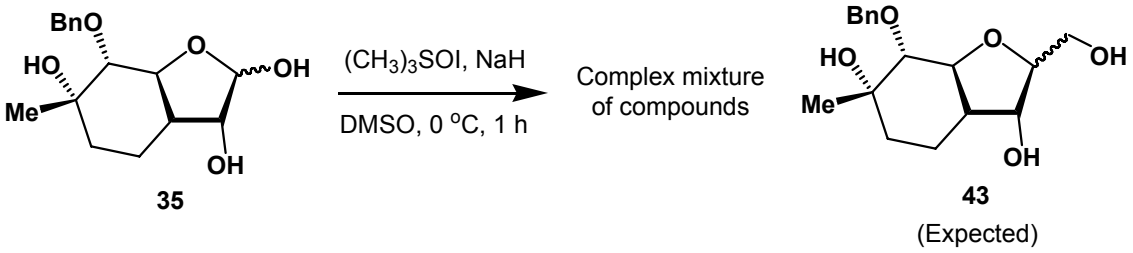
Scheme 16:



Corey-Chaykovsky reaction:[38]

It is anticipated that lactol **75** on subjecting to the Corey-Chaykovsky reaction conditions should give an epoxide at C-1, which will immediately be opened by C-4 hydroxyl group to give the hydroxy methyl derivative **83**. But in contrast, treatment of **75** with sulfur methylide (prepared from trimethylsulfoxonium iodide and NaH) in DMSO at 0 °C for 1 h resulted in a complex mixture of products (Scheme 17).

Scheme 17:



In conclusion, we have established an efficient synthetic route for the construction of enantiopure C1-C10 bicyclic core of cheimonophyllon E. Our approach included stereoselective introduction of allyl group using radical reaction and generation of two new stereo centers based on substrate induced stereoselectivity. Further efforts in order to accomplish the total synthesis of cheimonophyllon E are in progress in our laboratory.

Table 1: Crystal data and structure refinement for Compound 03

Empirical formula	$C_{12}H_{20}O_5$
Formula weight	244.28
Temperature	293(2) K
Wavelength	0.71073 Å
Crystal system, space group	ORTHORHOMBIC, $P2_12_12_1$
Unit cell dimensions	a = 6.468(2) Å, α= 90º
	b = 10.189(3) Å, β = 90º
	c = 19.553(6) Å, γ = 90º
Volume	1288.4(7) $Å^3$
Z, Calculated density	4, 1.259 Mg/m^3
Absorption coefficient	0.097 mm^{-1}
F(000)	528

Crystal size	0.96 x 0.32 x 0.14 mm
Theta range for data collection	2.08º to 24.99º.
Limiting indices	-7<=h<=6, -10<=k<=12, -23<=l<=23
Reflections collected / unique	6471 / 2266 [R(int) = 0.0250]
Completeness to theta = 28.17	100.0 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9860 and 0.9122
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2266 / 0 / 160
Goodness-of-fit on F^2	1.113
Final R indices [I>2sigma(I)]	R1 = 0.0428, wR2 = 0.0984
R indices (all data)	R1 = 0.0476, wR2 = 0.1008
Absolute structure parameter	-0.1(13)
Largest diff. peak and hole	0.146 and -0.161 e.A^-3

Table 2. Bond lengths [Å] and angles [deg] for compound 03

O(1)-C(1)	1.407(2)	C(8)-H(8B)	0.9700
O(1)-C(4)	1.441(2)	C(7)-H(7A)	0.9700
O(4)-C(5)	1.426(2)	C(7)-H(7B)	0.9700
O(4)-H(4)	0.8200	C(10)-H(10A)	0.9600
O(3)-C(9)	1.423(3)	C(10)-H(10B)	0.9600
O(3)-C(2)	1.425(3)	C(10)-H(10C)	0.9600
C(5)-C(4)	1.523(3)	C(12)-H(12A)	0.9600
C(5)-C(6)	1.533(3)	C(12)-H(12B)	0.9600
C(5)-H(5)	0.9800	C(12)-H(12C)	0.9600
O(5)-C(6)	1.433(2)	C(11)-H(11A)	0.9600
O(5)-H(5A)	0.8200	C(11)-H(11B)	0.9600

C(4)-C(3)	1.518(3)	C(11)-H(11C)	0.9600
C(4)-H(4A)	0.9800	C(1)-O(1)-C(4)	106.28(15)
C(3)-C(2)	1.519(3)	C(5)-O(4)-H(4)	109.5
C(3)-C(8)	1.520(3)	C(9)-O(3)-C(2)	107.94(16)
C(3)-H(3)	0.9800	O(4)-C(5)-C(4)	103.68(15)
C(1)-O(2)	1.408(3)	O(4)-C(5)-C(6)	110.76(16)
C(1)-C(2)	1.531(3)	C(4)-C(5)-C(6)	115.00(18)
C(1)-H(1)	0.9800	O(4)-C(5)-H(5)	109.1
O(2)-C(9)	1.418(3)	C(4)-C(5)-H(5)	109.1
C(6)-C(12)	1.513(3)	C(6)-C(5)-H(5)	109.1
C(6)-C(7)	1.514(3)	C(6)-O(5)-H(5A)	109.5
C(9)-C(11)	1.506(4)	O(1)-C(4)-C(3)	103.26(16)
C(9)-C(10)	1.506(4)	O(1)-C(4)-C(5)	111.09(15)
C(2)-H(2)	0.9800	C(3)-C(4)-C(5)	115.32(17)
C(8)-C(7)	1.522(3)	O(1)-C(4)-H(4A)	109.0
C(8)-H(8A)	0.9700	C(3)-C(4)-H(4A)	109.0
C(5)-C(4)-H(4A)	109.0	C(1)-C(2)-H(2)	112.6
C(4)-C(3)-C(2)	100.35(17)	C(3)-C(8)-C(7)	111.1(2)
C(4)-C(3)-C(8)	112.36(17)	C(3)-C(8)-H(8A)	109.4
C(2)-C(3)-C(8)	111.83(19)	C(7)-C(8)-H(8A)	109.4
C(4)-C(3)-H(3)	110.6	C(3)-C(8)-H(8B)	109.4
C(2)-C(3)-H(3)	110.6	C(7)-C(8)-H(8B)	109.4
C(8)-C(3)-H(3)	110.6	H(8A)-C(8)-H(8B)	108.0
O(1)-C(1)-O(2)	110.89(19)	C(6)-C(7)-C(8)	112.80(19)
O(1)-C(1)-C(2)	107.35(16)	C(6)-C(7)-H(7A)	109.0
O(2)-C(1)-C(2)	104.90(16)	C(8)-C(7)-H(7A)	109.0
O(1)-C(1)-H(1)	111.2	C(6)-C(7)-H(7B)	109.0
O(2)-C(1)-H(1)	111.2	C(8)-C(7)-H(7B)	109.0
C(2)-C(1)-H(1)	111.2	H(7A)-C(7)-H(7B)	107.8
C(1)-O(2)-C(9)	109.98(17)	C(9)-C(10)-H(10A)	109.5
O(5)-C(6)-C(12)	110.00(18)	C(9)-C(10)-H(10B)	109.5

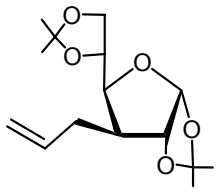
O(5)-C(6)-C(7)	106.32(17)	H(10A)-C(10)-H(10B)	109.5
C(12)-C(6)-C(7)	112.7(2)	C(9)-C(10)-H(10C)	109.5
O(5)-C(6)-C(5)	106.42(17)	H(10A)-C(10)-H(10C)	109.5
C(12)-C(6)-C(5)	110.98(19)	H(10B)-C(10)-H(10C)	109.5
C(7)-C(6)-C(5)	110.17(17)	C(6)-C(12)-H(12A)	109.5
O(2)-C(9)-O(3)	104.94(15)	C(6)-C(12)-H(12B)	109.5
O(2)-C(9)-C(11)	109.6(2)	H(12A)-C(12)-H(12B)	109.5
O(3)-C(9)-C(11)	110.3(2)	C(6)-C(12)-H(12C)	109.5
O(2)-C(9)-C(10)	108.7(2)	H(12A)-C(12)-H(12C)	109.5
O(3)-C(9)-C(10)	108.57(19)	H(12B)-C(12)-H(12C)	109.5
C(11)-C(9)-C(10)	114.3(2)	C(9)-C(11)-H(11A)	109.5
O(3)-C(2)-C(3)	110.12(18)	C(9)-C(11)-H(11B)	109.5
O(3)-C(2)-C(1)	104.31(18)	H(11A)-C(11)-H(11B)	109.5
C(3)-C(2)-C(1)	103.82(16)	C(9)-C(11)-H(11C)	109.5
O(3)-C(2)-H(2)	112.6	H(11A)-C(11)-H(11C)	109.5
C(3)-C(2)-H(2)	112.6	H(11B)-C(11)-H(11C)	109.5

Table 3: Torsion angles [deg] for compound 03

C(1)-O(1)-C(4)-C(3)	40.9(2)	C(1)-O(2)-C(9)-C(11)	-94.5(2)
C(1)-O(1)-C(4)-C(5)	165.13(17)	C(1)-O(2)-C(9)-C(10)	139.96(19)
O(4)-C(5)-C(4)-O(1)	164.83(17)	C(2)-O(3)-C(9)-O(2)	-29.2(2)
C(6)-C(5)-C(4)-O(1)	-74.1(2)	C(2)-O(3)-C(9)-C(11)	88.8(2)
O(4)-C(5)-C(4)-C(3)	-78.1(2)	C(2)-O(3)-C(9)-C(10)	-145.21(19)
C(6)-C(5)-C(4)-C(3)	42.9(2)	C(9)-O(3)-C(2)-C(3)	133.73(19)
O(1)-C(4)-C(3)-C(2)	-42.42(18)	C(9)-O(3)-C(2)-C(1)	22.9(2)
C(5)-C(4)-C(3)-C(2)	-163.78(17)	C(4)-C(3)-C(2)-O(3)	-82.66(19)
O(1)-C(4)-C(3)-C(8)	76.5(2)	C(8)-C(3)-C(2)-O(3)	158.01(18)
C(5)-C(4)-C(3)-C(8)	-44.8(2)	C(4)-C(3)-C(2)-C(1)	28.5(2)
C(4)-O(1)-C(1)-O(2)	92.06(19)	C(8)-C(3)-C(2)-C(1)	-90.8(2)
C(4)-O(1)-C(1)-C(2)	-22.0(2)	O(1)-C(1)-C(2)-O(3)	110.00(18)

O(1)-C(1)-O(2)-C(9)	-125.37(18)	O(2)-C(1)-C(2)-O(3)	-8.0(2)
C(2)-C(1)-O(2)-C(9)	-9.8(2)	O(1)-C(1)-C(2)-C(3)	-5.4(2)
O(4)-C(5)-C(6)-O(5)	-44.7(2)	O(2)-C(1)-C(2)-C(3)	-123.37(19)
C(4)-C(5)-C(6)-O(5)	-161.78(16)	C(4)-C(3)-C(8)-C(7)	52.1(3)
O(4)-C(5)-C(6)-C(12)	-164.33(19)	C(2)-C(3)-C(8)-C(7)	164.04(19)
C(4)-C(5)-C(6)-C(12)	78.6(2)	O(5)-C(6)-C(7)-C(8)	170.3(2)
O(4)-C(5)-C(6)-C(7)	70.2(2)	C(12)-C(6)-C(7)-C(8)	-69.1(3)
C(4)-C(5)-C(6)-C(7)	-46.9(2)	C(5)-C(6)-C(7)-C(8)	55.4(3)
C(1)-O(2)-C(9)-O(3)	24.0(2)	C(3)-C(8)-C(7)-C(6)	-59.1(3)

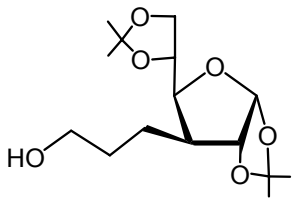
3-Deoxy-1,2;5,6-di-*O*-isopropylidene-3-C-allyl-α-D-glucofuranose (46):



A solution of **48** (20.0 g, 54.0 mmol), allyltri-*n*-butyltin (20.1 mL, 64.8 mmol), AIBN (100 mg) in benzene (100 mL), after thoroughly degassing with argon, was heated under reflux for 10 h and concentrated. A saturated solution of KF and ether were introduced, stirred vigorously for 4 h and the ether layer separated, dried (Na_2SO_4) and concentrated. The residue was purified by flash column chromatography on silica gel using EtOAc:light petroleum ether (1:20) to obtain **46** as a colorless oil.

Yield	: 10.4 g (68%)
Mol. Formula	: $C_{15}H_{24}O_5$
Optical Rotation $[\alpha]_D^{25}$	: -10.96 (*c* 0.4, $CHCl_3$).
IR ($CHCl_3$) $\tilde{\nu}$	: 846, 1016, 1067, 1372, 1455, 1641, 2891, 2936, 2987, 3078, 3335 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 1.30, 1.35, 1.42, 1.52 (4s, 12 H), 1.86 (m, 1 H), 2.43 (m, 2 H), 3.93 (m, 1 H), 4.10 (m, 3 H), 4.51 (d, 1 H, *J* = 3.7 Hz), 5.06 (m, 1 H), 5.14 (m, 1 H), 5.74 (d, 1 H, *J* = 3.7 Hz), 5.85 (m, 1 H) ppm.
^{13}C ($CDCl_3$, 125 MHz)	: δ 24.9, 25.7, 26.3, 26.4, 29.3, 44.8, 68.1, 72.8, 80.2, 83.1, 104.3, 108.7, 110.4, 116.5, 135.5 ppm.
ESI MS (m/z)	: 307 (M+Na)
Elemental Analysis	**Calcd.:** C, 63.36; H, 8.51%. **Found:** C, 63.40; H, 8.66%.

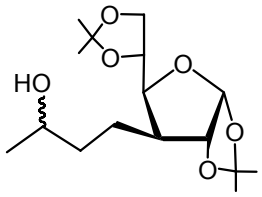
3-Deoxy-1,2;5,6-di-*O*-isopropylidene-3-C-(3-hydroxy-propyl)-α-D-glucofuranose (53):



To a solution of **46** (12.0 g, 42.2 mmol) in anhydrous THF (50 mL) at 0 ^{o}C was added $H_3B{:}SMe_2$ (97% solution in THF, 3.95 mL, 50.6 mmol). After stirring for 1 h, saturated NaOAc solution was introduced followed by the addition of 30% H_2O_2 (7.18 mL). The reaction mixture was further stirred at rt for 5 h, diluted with EtOAc, the organic layer separated, dried (Na_2SO_4) and concentrated. The crude was purified on silica gel using EtOAc:light petroleum ether (3:7) to provide **53** as a thick liquid.

Yield	: 9.57 g (75%)
Mol. Formula	: $C_{15}H_{26}O_6$
Optical Rotation $[\alpha]_D^{25}$	: -18.66 (*c* 1.0, CHCl3).
IR ($CHCl_3$) $\tilde{\nu}$	: 846, 1062, 1147, 1311, 1373, 1382, 1456, 2885, 2936, 2990, 3401 cm^{-1}.
^{1}H NMR ($CDCl_3$, 300 MHz)	: δ 1.30, 1.34, 1.41, 1.51 (4s, 12 H), 1.57-1.78 (m, 4 H), 2.27 (m, 1 H), 2.36 (brs, 1 H), 3.67 (m, 2 H), 3.92 (m, 1 H), 4.02-4.15 (m, 3 H), 4.50 (d, 1 H, *J* = 3.7 Hz), 5.74 (d, 1 H, *J* = 3.7 Hz) ppm.
^{13}C ($CDCl_3$, 125 MHz)	: δ 21.0, 25.1, 25.8, 26.4, 26.5, 30.0, 45.6, 61.7, 68.1, 73.0, 80.7, 83.8, 104.4, 108.9, 110.7 ppm.
ESI MS (m/z)	: 325 (M+Na)
Elemental Analysis	Calcd.: C, 59.58; H, 8.67%. Found: C, 59.45; H, 8.56%.

3-Deoxy-1,2;5,6-di-*O*-isopropylidene-3-C-(3-hydroxy-butyl)-α-D-glucofuranose (55):



Dry DMSO (6.1 mL, 86.0 mmol) and $(COCl)_2$ (3.75 mL, 43.0 mmol) in CH_2Cl_2 (30 mL) at –78 ^oC under N_2 were stirred for 30 min and then alcohol **53** (6.5 g, 21.5 mmol) in CH_2Cl_2 (30 mL) was added. After 1h, the reaction was quenched by Et_3N (18.0 mL, 129.0 mmol) at –78 ^oC and diluted with water (50 mL). The organic layer was separated while the aqueous layer extracted with CH_2Cl_2 (2 x 100 mL). The combined organic extract was dried (Na_2SO_4) and concentrated to give crude aldehyde **54** (6.1 g).

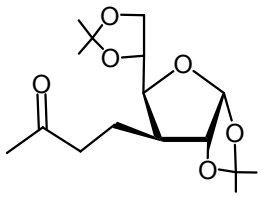
The above product (6.1 g) was dissolved in anhydrous THF (50 mL) and cooled to 0 ^oC. A 2 M solution of MeMgCl in THF (15.2 mL, 30.4 mmol) was added. After 2 h stirring at rt, it was quenched by addition of saturated aqueous solution of NH_4Cl (30 mL). The two layers were separated, the organic layer dried (Na_2SO_4) and concentrated to form a residue which was purified on silica gel using EtOAc:light petroleum ether (2:8) to furnish **55** as a viscous liquid.

Yield	: 5.13 g (75% for two steps)
Mol. Formula	: $C_{16}H_{28}O_6$
IR ($CHCl_3$) $\tilde{\nu}$	: 866, 1021, 1062, 1165, 1375, 1385, 1455, 2896, 2936, 2990, 3453 cm^{-1}.
^{1}H NMR ($CDCl_3$, 500 MHz)	: δ 1.21 (m, 3 H), 1.30, 1.34, 1.41, 1.50 (4s, 12 H), 1.52-1.79 (m, 4 H), 2.07 (br s, 1 H), 2.26 (m, 1 H), 3.82 (m, 1 H), 3.92 (m, 1 H), 4.06 (m, 2 H), 4.11 (m, 1 H), 4.48 (m, 1 H), 5.74 (m, 1 H) ppm.
^{13}C ($CDCl_3$, 125 MHz)	: δ 20.9, 21.0, 23.2, 23.5, 25.2, 25.9, 26.6, 26.7, 36.6, 45.7, 45.9, 67.1, 67.4, 68.3, 73.1, 73.2, 80.8, 83.9, 84.0, 104.5, 104.6, 109.0, 110.8 ppm.

ESI MS (m/z) : 339 (M+Na)

Elemental Analysis **Calcd.:** C, 60.74; H, 8.92%.
Found: C, 60.60; H, 8.77%.

3-Deoxy-1,2;5,6-di-*O*-isopropylidene-3-C-(3-oxobutyl)-α-D-glucofuranose (56):



Dry DMSO (4.3 mL, 60.6 mmol) and $(COCl)_2$ (2.65 mL, 30.3 mmol) in CH_2Cl_2 (20 mL) at –78 °C under N_2 were stirred for 30 min and then alcohol **55** (4.8 g, 15.1 mmol) in CH_2Cl_2 (20 mL) was added. After 1h, the reaction was quenched by Et_3N (12.7 mL, 91.1 mmol) at –78 °C and diluted with water (30 mL). The organic layer was separated while the aqueous layer extracted with CH_2Cl_2 (2 x 50 mL). The combined organic extract was dried (Na_2SO_4), concentrated and purified on silica gel using EtOAc:light petroleum ether (1:9) to afford **56** as a colorless oil.

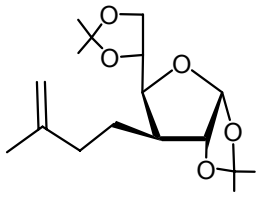
Yield : 4.4 g (92%)

Mol. Formula : $C_{16}H_{26}O_6$

^{1}H NMR ($CDCl_3$, 500 MHz) : δ 1.29, 1.33, 1.40, 1.50 (4s, 12 H), 1.35-1.43 (m, 2 H), 1.84 (m, 1 H), 2.16 (s, 3 H), 2.59 (t, 2 H, *J* = 7.6 Hz), 3.91 (m, 1 H), 4.04 (m, 2 H), 4.11 (m, 1 H), 4.38 (d, 1 H, *J* = 3.6 Hz), 5.73 (d, 1 H, *J* = 3.6 Hz) ppm.

^{13}C ($CDCl_3$, 125 MHz) : δ 18.7, 25.2, 25.9, 26.6, 26.7, 29.7, 41.4, 45.6, 68.3, 73.0, 80.6, 83.9, 104.5, 109.1, 110.9, 207.1 ppm.

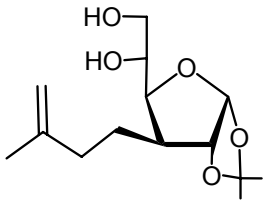
3-Deoxy-1,2;5,6-di-*O*-isopropylidene-3-C-(3-methyl-3-butenyl)-α-D-glucofuranose (57):



To a solution of **56** (4.2 g, 13.3 mmol) in anhydrous THF (20 mL) at –20 ^{o}C, methylenetriphenylphosphorane [prepared from PPh_3CH_3I (13.57 g) and *n*-BuLi (1.6 M, 18.4 mL)] was added dropwise. After 4 h stirring at rt, it was quenched by addition of saturated aqueous solution of NH_4Cl. The two layers were separated, the organic layer dried (Na_2SO_4) and concentrated to form a residue which was purified on silica gel using EtOAc:light petroleum ether (1:9) to furnish **57** as a colorless oil.

Yield	: 3.18 g (76%)
Mol. Formula	: $C_{17}H_{28}O_5$
Optical Rotation $[\alpha]_D^{25}$	: -30.55 (*c* 1.0, CHCl3).
IR ($CHCl_3$) $\tilde{\nu}$	: 890, 1020, 1062, 1158, 1373, 1382, 1455, 1650, 2936, 2989, 3362 cm^{-1}.
^{1}H NMR ($CDCl_3$, 500 MHz)	: δ 1.18 (m, 1 H), 1.31, 1.34, 1.40, 1.51 (4s, 12 H), 1.74 (s, 3 H), 1.79 (m, 1 H), 2.08 (m, 1 H), 2.17 (m, 1 H), 2.27 (dt, 1 H, *J* = 3.9, 10.8 Hz), 3.91 (dd, 1 H, *J* = 4.6, 8.2 Hz), 4.06 (m, 2 H), 4.12 (dd, 1 H, *J* = 5.5, 8.2 Hz), 4.49 (d, 1 H, *J* = 3.7 Hz), 4.73 (s, 1 H), 4.75 (s, 1 H), 5.74 (d, 1 H, *J* = 3.7 Hz) ppm.
^{13}C ($CDCl_3$, 125 MHz)	: δ 22.4, 22.6, 25.3, 26.0, 26.7, 26.8, 35.1, 45.5, 68.5, 73.3, 80.9, 83.9, 104.6, 109.1, 110.6, 110.9, 144.5 ppm.
ESI MS (m/z)	: 335 (M+Na)
Elemental Analysis	**Calcd.:** C, 65.36; H, 9.03%.
	Found: C, 65.25; H, 8.89%.

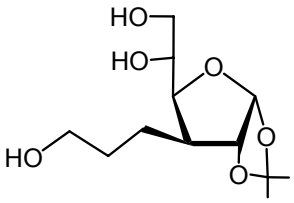
3-Deoxy-1,2-*O*-isopropylidene-3-C-(3-methyl-3-butenyl)-α-D-glucofuranose (58):



A mixture of **57** (3.0 g, 9.6 mmol), MeOH (10 mL) and 0.8% H_2SO_4 (15 mL) was stirred at room temperature. After 4 h the reaction mixture was neutralized with solid $NaHCO_3$. Solvent was removed on the rotavapour and the residue extracted with ethyl acetate. The organic layer was dried (Na_2SO_4), concentrated and the crude product purified on silica gel using ethyl acetate:light petroleum (7:3) as an eluent to afford compound **58** as a thick liquid.

Yield	: 2.13 g (81%)
Mol. Formula	: $C_{14}H_{24}O_5$
Optical Rotation $[\alpha]_D^{25}$	: -13.44 (*c* 1.5, $CHCl_3$).
IR ($CHCl_3$) $\tilde{\nu}$	: 894, 929, 1018, 1061, 1085, 1375, 1384, 1424, 1520, 1650, 2935, 3432 cm^{-1}.
^{1}H NMR ($CDCl_3$, 500 MHz)	: δ 1.15 (m, 1 H), 1.30 (s, 3 H), 1.50 (s, 3 H), 1.74 (s, 3 H), 1.80 (m, 1 H), 2.06 (m, 1 H), 2.17 (m, 1 H), 2.29 (dt, 1 H, *J* = 3.9, 11.2 Hz), 3.19 (br s, 2 H), 3.69 (m, 2 H), 3.83 (m, 1 H), 4.10 (dd, 1 H, *J* = 4.4, 8.7 Hz), 4.50 (d, 1 H, *J* = 3.6 Hz), 4.73 (d, 2 H, *J* = 8.2 Hz), 5.75 (d, 1 H, *J* = 3.6 Hz) ppm.
^{13}C ($CDCl_3$, 125 MHz)	: δ 22.4, 22.5, 26.0, 26.5, 35.2, 45.4, 64.8, 69.5, 79.2, 83.6, 104.6, 110.5, 111.0, 144.8 ppm.
ESI MS (m/z)	: 295 (M+Na)
Elemental Analysis	**Calcd.:** C, 61.74; H, 8.88%. **Found:** C, 61.59; H, 8.63%.

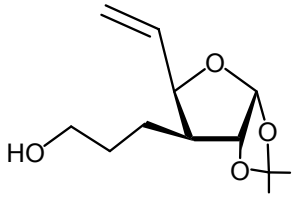
3-Deoxy-1,2-*O*-isopropylidene-3-C-(3-hydroxypropyl)-α-D-glucofuranose (60):



A mixture of **53** (6.0 g, 19.8 mmol), MeOH (20 mL) and 0.8% H_2SO_4 (20 mL) was stirred at room temperature. After 4 h the reaction mixture was neutralized with solid $NaHCO_3$. Solvent was removed on the rotavapour and the residue extracted with ethyl acetate. The organic layer was dried (Na_2SO_4), concentrated and the crude product purified on silica gel using ethyl acetate as an eluent to afford compound **60** as a thick liquid.

Yield	: 4.18 g (80%)
Mol. Formula	: $C_{12}H_{22}O_6$
Optical Rotation $[\alpha]_D^{25}$	: –21.95 (*c* 1.5, $CHCl_3$).
IR ($CHCl_3$) $\tilde{\nu}$	: 867, 1023, 1061, 1162, 1375, 1383, 1456, 2934, 3401 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 1.07 (m, 1 H), 1.30, 1.50 (2s, 6 H), 1.55-1.85 (m, 3 H), 2.28 (m, 1 H), 3.47-3.90 (m, 5 H), 3.92-4.38 (m, 4 H), 4.48 (d, 1 H, *J* = 3.1 Hz), 5.76 (d, 1 H, *J* = 3.1 Hz) ppm.
^{13}C ($CDCl_3$, 50 MHz)	: δ 20.7, 25.9, 26.5, 29.7, 45.2, 61.6, 65.0, 69.6, 79.3, 83.5, 104.6, 111.0 ppm.
ESI MS (m/z)	: 285 (M+Na)
Elemental Analysis	**Calcd.:** C, 54.95; H, 8.45%.
	Found: C, 54.76; H, 8.61%.

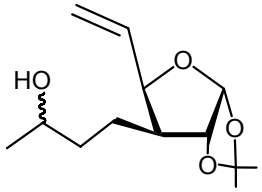
3-Deoxy-5,6-dideoxy-1,2-*O*-isopropylidene-3-C-(3-hydroxypropyl)-α-D-glucofuranose (62):



To a solution of triol **60** (4.0 g, 15.24 mmol) in CH_2Cl_2 (150 mL) was added silica supported $NaIO_4$ (30 g) at room temperature. After stirring for 10 min, the reaction mixture was filtered and concentrated. The residue was dissolved in anhydrous THF (20 mL), cooled to –20 ^oC, then methylenetriphenylphosphorane [prepared from PPh_3CH_3I (24.76 g) and *n*-BuLi (1.6 M, 36.2 mL)] was added dropwise. After 4 h stirring at rt, it was quenched by addition of saturated aqueous solution of NH_4Cl. The two layers were separated, the organic layer dried (Na_2SO_4) and concentrated to form a residue which was purified on silica gel using EtOAc:light petroleum ether (3:7) to furnish **62** as a syrup.

Yield	: 2.48 g (71% for two steps)
Mol. Formula	: $C_{12}H_{20}O_4$
Optical Rotation $[\alpha]_D^{25}$	: -57.98 (*c* 0.4, $CHCl_3$).
IR ($CHCl_3$) $\tilde{\nu}$	: 866, 930, 1019, 1060, 1162, 1375, 1383, 1456, 1646, 2870, 2938, 2992, 3476 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 1.12 (m, 1 H), 1.32 (s, 3 H), 1.52 (s, 3 H), 1.47-1.76 (m, 3 H), 2.16 (m, 1 H), 3.64 (t, 2 H, *J* = 6.3 Hz), 4.51 (d, 1 H, *J* = 3.8 Hz), 4.74 (dd, 1 H, *J* = 4.6, 5.9 Hz), 5.19-5.42 (m, 2 H), 5.81 (d, 1 H, *J* = 3.8 Hz), 5.72-5.93 (m, 1 H) ppm.
^{13}C ($CDCl_3$, 50 MHz)	: 21.8, 26.1, 26.7, 30.5, 48.3, 62.4, 80.5, 84.2, 104.3, 110.8, 117.3, 133.8 ppm.
ESI MS (m/z)	: 229 (M+1)
Elemental Analysis	**Calcd.:** C, 63.14; H, 8.83%. **Found:** C, 63.19; H, 8.59%.

3-Deoxy-5,6-dideoxy-1,2-*O*-isopropylidene-3-C-(3-hydroxybutyl)-α-D-glucofuranose (64):



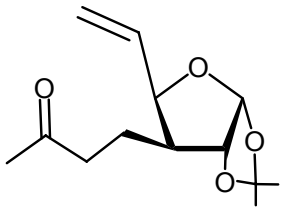
Dry DMSO (2.73 mL, 38.5 mmol) and $(COCl)_2$ (1.68 mL, 19.2 mmol) in CH_2Cl_2 (20 mL) at –78 ^oC under N_2 were stirred for 30 min and then alcohol **62** (2.2 g, 9.6 mmol) in CH_2Cl_2 (10 mL) was added. After 1h, the reaction was quenched by Et_3N (8.05 mL, 57.7 mmol) at –78 ^oC and diluted with water (20 mL). The organic layer was separated while the aqueous layer extracted with CH_2Cl_2 (2 x 50 mL). The combined organic extract was dried (Na_2SO_4) and concentrated to give crude aldehyde **63** (2.04 g).

The above product (2.04 g) was dissolved in anhydrous THF (50 mL) and cooled to 0 ^oC. A 2 M solution of MeMgCl in THF (6.75 mL, 13.5 mmol) was added. After 2 h stirring at rt, it was quenched by addition of saturated aqueous solution of NH_4Cl (20 mL). The two layers were separated, the organic layer dried (Na_2SO_4) and concentrated to form a residue which was purified on silica gel using EtOAc:light petroleum ether (2:8) to furnish **64** as a viscous liquid.

Yield	: 1.68 g, (72% for two steps)
Mol. Formula	: $C_{13}H_{22}O_4$
IR ($CHCl_3$) $\tilde{\nu}$	: 866, 930, 1020, 1062, 1163, 1375, 1456, 1646, 2868, 2930, 2998, 3456 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 1.02 (m, 1 H), 1.17, 1.20 (2d, 3 H, *J* = 1.5 Hz), 1.31 (s, 3 H), 1.43 (m, 1 H), 1.52 (s, 3 H), 1.62 (m, 2 H), 2.12 (m, 1 H), 3.76 (m, 1 H), 4.50 (d, 1 H, *J* = 3.6), 4.73 (t, 1 H, *J* = 5.3 Hz), 5.19-5.43 (m, 2 H), 5.79 (d, 1 H, *J* = 3.6 Hz), 5.72-5.92 (m, 1 H) ppm.
^{13}C ($CDCl_3$, 125 MHz)	: δ 21.5, 21.6, 23.4, 23.6, 26.0, 26.6, 36.9, 48.4, 67.4, 67.6, 80.4, 84.1, 84.2, 104.2, 110.7, 117.1, 117.2, 133.7, 133.8 ppm.

ESI MS (m/z)	: 265 (M+Na)
Elemental Analysis	**Calcd.:** C, 64.44; H, 9.15%.
	Found: C, 64.33; H, 9.06%.

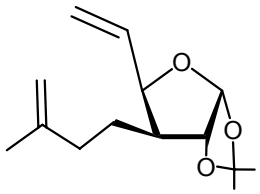
3-Deoxy-5,6-dideoxy-1,2-*O*-isopropylidene-3-C-(3-oxobutyl)-α-D-glucofuranose (65):



Alcohol **64** (1.5 g, 6.1 mmol) was dissolved in Ethyl acetate and IBX (5.2 g, 18.5 mmol) was added, the resulting suspension was heated under reflux for 4 h, then cooled to room temperature and filtered through Celite plug. The filter cake was washed with 3 x 20 mL of ethyl acetate and the combined filtrates were concentrated, purified on silica gel using EtOAc:light petroleum ether (2:8) as eluents to afford **65** as a colorless oil.

Yield	: 1.39 g, (93%)
Mol. Formula	: $C_{13}H_{20}O_4$
Optical Rotation $[\alpha]_D^{25}$	: -41.37 (*c* 1.2, $CHCl_3$).
IR ($CHCl_3$) $\tilde{\nu}$	: 865, 930, 1020, 1063, 1162, 1375, 1383, 1414, 1519, 1715, 2937, 2992, 3419 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 1.23 (m, 1 H), 1.32 (s, 3 H), 1.52 (s, 3 H), 1.72 (m, 1 H), 2.12 (m, 1 H), 2.15 (s, 3 H), 2.51 (m, 2 H), 4.45 (d, 1 H, *J* = 3.7 Hz), 4.74 (t, 1 H, *J* = 5.2 Hz), 5.21-5.46 (m, 2 H), 5.82 (d, 1 H, *J* = 3.7 Hz), 5.75-5.94 (m, 1 H) ppm.
^{13}C ($CDCl_3$, 50 MHz)	: δ 19.0, 25.8, 26.3, 29.7, 41.1, 47.6, 80.1, 83.9, 104.0, 110.6, 117.2, 133.3, 207.5 ppm.
ESI MS (m/z)	: 263 (M+Na)
Elemental Analysis	**Calcd.:** C, 64.98; H, 8.39%.
	Found: C, 65.14; H, 8.51%.

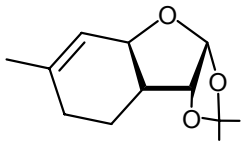
3-Deoxy-5,6-dideoxy-1,2-*O*-isopropylidene-3-C-(3-methyl-3-butenyl)-α-D-glucofuranose (45):



To a solution of **65** (1.2 g, 4.9 mmol) in anhydrous THF (10 mL) at –20 ^{o}C, methylenetriphenylphosphorane [prepared from PPh_3CH_3I (5.07 g) and *n*-BuLi (1.6 M, 6.85 mL)] was added dropwise. After 4 h stirring at rt, it was quenched by addition of saturated aqueous solution of NH_4Cl. The two layers were separated, the organic layer dried (Na_2SO_4) and concentrated to form a residue which was purified on silica gel using EtOAc:light petroleum ether (1:9) to furnish **45** as a colorless oil.

Yield	: 0.92 g, (77%)
Mol. Formula	: $C_{14}H_{22}O_3$
Optical Rotation $[\alpha]_D^{25}$	: -42.85 (*c* 0.8, $CHCl_3$).
IR ($CHCl_3$) $\tilde{\nu}$	: 866, 890, 929, 1018, 1062, 1160, 1375, 1383, 1454, 1524, 1648, 2938, 2991, 3076 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 1.15 (m, 1 H), 1.33 (s, 3 H), 1.53 (s, 3 H), 1.61 (m, 1 H), 1.70 (s, 3 H), 1.92-2.21 (m, 3 H), 4.52 (d, 1 H, *J* = 3.8 Hz), 4.64-4.81 (m, 3 H), 5.20-5.43 (m, 2 H), 5.83 (d, 1 H, *J* = 3.8 Hz), 5.74-5.93 (m, 1 H) ppm.
^{13}C ($CDCl_3$, 75 MHz)	: δ 22.0, 23.1, 25.8, 26.4, 35.2, 47.7, 80.0, 84.1, 104.0, 110.3, 111.9, 116.4, 133.8, 144.2 ppm.
ESI MS (m/z)	: 261 (M+Na)
Elemental Analysis	**Calcd.:** C, 70.56; H, 9.30%.
	Found: C, 70.65; H, 9.38%.

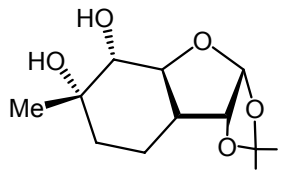
(1*R*,6*S*,7*R*,8*R*)- 3-Methyl-7,8-*O*-isopropylidene-9-oxabicyclo[4.3.0]non-2-ene (44):



Compound **45** (0.5 g, 2.0 mmol) was dissolved in anhydrous CH_2Cl_2 (60 mL) and solution degassed with argon. 5 mol% of Grubbs' first generation catalyst **20** (86 mg, 0.1 mmol) was added and mixture stirred at rt for 8 h. The solvent was removed and residue purified by column chromatography on silica gel using EtOAc:light petroleum ether (1:9) to obtain **44** as a colorless syrup.

Yield	: 0.38 g, (86%)
Mol. Formula	: $C_{12}H_{18}O_3$
Optical Rotation $[\alpha]_D^{25}$	: –20.14 (*c* 1.1, $CHCl_3$).
IR ($CHCl_3$) $\tilde{\nu}$	: 868, 907, 1025, 1066, 1165, 1383, 1449, 1520, 1671, 2835, 2936, 2992, 3499 cm^{-1}.
^{1}H NMR ($CDCl_3$, 500 MHz)	: δ 1.25 (m, 1 H), 1.30, 1.51 (2s, 6 H), 1.62 (m, 1 H), 1.74 (s, 3 H), 1.98 (m, 2 H), 2.09 (dt, 1 H, *J* = 4.4, 14.2 Hz), 4.40 (d, 1 H, *J* = 3.9 Hz), 4.48 (t, 1 H, *J* = 4.4 Hz), 5.64 (br s, 1 H), 5.83 (d, 1 H, *J* = 3.9 Hz) ppm.
^{13}C ($CDCl_3$, 125 MHz)	: δ 21.2, 23.7, 26.1, 26.7, 29.8, 42.8, 73.3, 85.3, 104.5, 110.6, 118.3, 141.7 ppm.
ESI MS (m/z)	: 233 (M+Na)
Elemental Analysis	**Calcd.:** C, 68.54; H, 8.63%.
	Found: C, 68.46; H, 8.58%.

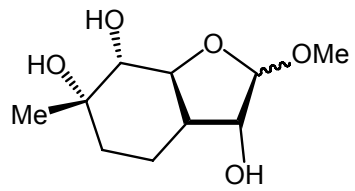
(1*S*,2*R*,3*S*,6*S*,7*R*,8*R*)-2,3-Dihydroxy-3-methyl-7,8-*O*-isopropylidene-9-oxabicyclo[4.3.0]nonane (43):



The compound **44** (1.6 g, 7.6 mmol) and 50% aq. NMO (3.55 mL, 15.1 mmol) in a mixture of acetone:H_2O (9 mL:1 mL) were stirred in the presence of catalytic amount of OsO_4 (0.05 M in toluene) at room temperature for 10 h. Excess OsO_4 was quenched with saturated aq.$NaHSO_3$, concentrated and the residue partitioned between water and ethyl acetate. Combined organic layers washed with brine, dried (Na_2SO_4), concentrated and the crude product was purified on silica gel column chromatography with EtOAc–light petroleum ether (6:4) as eluents to give the diol **43** as a colorless crystalline solid.

Yield	: 1.47 g (79%)
Mol. Formula	: $C_{12}H_{20}O_5$
M. P.	: 108-110 ^oC
Optical Rotation $[\alpha]_D^{25}$	: –22.08 (*c* 1.0, $CHCl_3$).
IR ($CHCl_3$) $\tilde{\nu}$	: 907, 965, 1013, 1164, 1252, 1375, 1383, 1453, 2870, 2938, 2992, 3452 cm^{-1}.
^{1}H NMR ($CDCl_3$, 500 MHz)	: δ 1.03 (dq, 1 H, *J* = 3.6, 13.7 Hz), 1.30 (s, 6 H), 1.42 (dt, 1 H, *J* = 3.5, 12.7 Hz), 1.51 (s, 3 H), 1.63 (m, 1 H), 1.78 (dt, 1 H, *J* = 4.1, 13.3 Hz), 2.24 (br s, 1 H), 2.32 (ddd, 1 H, *J* = 4.1, 6.1, 10.3 Hz), 2.98 (br s, 1 H), 3.72 (s, 1 H), 4.36 (d, 1 H, *J* = 3.6 Hz), 4.40 (t, 1 H, *J* = 3.4), 5.79 (d, 1 H, *J* = 3.6 Hz) ppm.
^{13}C ($CDCl_3$, 125 MHz)	: δ 22.1, 24.7, 26.0, 26.5, 32.2, 40.0, 71.1, 71.8, 79.8, 84.3, 104.2, 111.2 ppm.
ESI MS (m/z)	: 245 (M+1)
Elemental Analysis	**Calcd.:** C, 59.00; H, 8.25%.
	Found: C, 58.94; H, 8.29%.

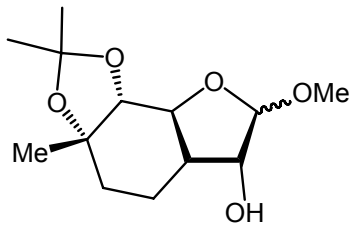
(1*S*,2*R*,3*S*,6*S*,7*R*)-2,3,7-Trihydroxy-3-methyl-8-methyloxy-9-oxabicyclo[4.3.0]nonane (67):



To a solution of **43** (1.2 g, 4.9 mmol) in anhydrous MeOH (20 mL) was added Amberlyst-15 (5 g) and refluxed for 3 h. The resin was filtered off through a plug of cotton and the filtrate concentrated. The residue was purified on silica gel with EtOAc to give **67** as a viscous syrup.

Yield	: 763 mg, (71%)
Mol. Formula	: $C_{10}H_{18}O_5$
IR ($CHCl_3$) $\tilde{\nu}$	: 926, 951, 1009, 1077, 1104, 1373, 1452, 2934, 3426 cm^{-1}.
^{1}H NMR ($CDCl_3$, 500 MHz)	: δ 1.26, 1.28 (2s, 3 H), 1.50 (m, 1 H), 1.69 (m, 2 H), 1.93 (m, 1 H), 2.31–2.46 (m, 1 H), 3.44, 3.47 (2s, 3 H), 3.17, 3.49 (2d, 1 H, *J* = 7.8 and 8.1 Hz), 3.92, 4.04 (2dd, 1 H, *J* = 4.8, 10.6 and 3.2, 8.7 Hz), 4.12, 4.16 (2t, 1 H, *J* = 7.4 and 7.8 Hz), 4.84, 4.88 (2d, 1 H, *J* = 4.8 and 3.2 Hz) ppm.
^{13}C ($CDCl_3$, 125 MHz)	: δ 18.0, 18.6, 26.6, 32.2, 32.4, 42.0, 45.0, 55.5, 56.2, 72.0, 73.0, 76.8, 78.2, 78.7, 80.9, 83.3, 101.6, 111.7 ppm.
ESI MS (m/z)	: 241 (M+Na)
Elemental Analysis	**Calcd.:** C, 55.03; H, 8.31%.
	Found: C, 54.95; H, 8.17%.

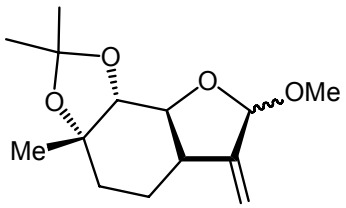
(1*S*,2*R*,3*S*,6*S*,7*R*)-2,3-*O*-Isopropylidene-3-methyl-7-hydroxy-8-methyloxy-9-oxabicyclo[4.3.0]nonane (68):



A solution of **67** (0.7 g, 3.2 mmol), 2,2-dimethoxypropane (0.78 mL, 6.4 mmol), *p*TSA (5 mg) in CH_2Cl_2 (10 mL) was stirred at rt for 2 h., neutralized with Et_3N and concentrated. The residue was partitioned between EtOAc-water, the organic layer dried (Na_2SO_4), concentrated and purified on silica gel using EtOAc:light petroleum ether (3:7) to furnish **68** as a viscous liquid.

Yield	: 0.6 g, (74%)
Mol. Formula	: $C_{13}H_{22}O_5$
IR ($CHCl_3$) $\tilde{\nu}$	: 989, 1035, 1060, 1100, 1244, 1374, 1450, 2936, 2990, 3448 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 1.35, 1.38 (2s, 6 H), 1.46 (s, 3 H), 1.64 (m, 3 H), 1.86 (m, 1 H), 2.16 (m, 1 H), 3.39, 3.48 (2s, 3 H), 3.90-4.07 (m, 2 H), 4.51, 4.63 (2dd, 1 H, *J* = 2.5, 7.1 and 1.9, 5.6 Hz), 4.78 (s, 0.6 H), 4.89 (d, 1 H, *J* = 4.6 Hz) ppm.
^{13}C ($CDCl_3$, 125 MHz)	: 21.0, 21.3, 24.6, 26.0, 26.6, 27.4, 27.5, 28.0, 29.6, 32.0, 33.1, 41.3, 42.1, 55.2, 55.7, 74.4, 78.0, 78.1, 78.2, 78.5, 81.8, 101.6, 107.0, 110.5 ppm.
ESI MS (m/z)	: 259 (M+1)
Elemental Analysis	**Calcd.:** C, 60.45; H, 8.58%.
	Found: C, 60.26; H, 8.69%.

(1*S*,2*R*,3*S*,6*R*)-2,3-*O*-Isopropylidene-3-methyl-7-methylene-8-methyloxy-9-oxabicyclo[4.3.0]nonane (70):



A solution of **68** (0.5 g, 1.9 mmol), pyridine (0.25 mL) and Dess-Martin periodinane (1.23 g, 2.8 mmol) in CH_2Cl_2 (15 mL) was stirred at rt for 30 min and then saturated solution of $NaHCO_3$ and $Na_2S_2O_3$ (1:1, 10 mL) was added. The organic layer was separated while aqueous layer extracted with CH_2Cl_2. The combined organic extract was dried (Na_2SO_4), filtered and concentrated to give crude ketone **69** (0.42 g).

To a solution of above product ketone **69** (0.42 g, 1.7 mmol) in anhydrous THF (10 mL) at –20 ^oC, methylenetriphenylphosphorane [prepared from PPh_3CH_3I (1.77 g, 4.3 mmol) and *n*-BuLi (1.6 M, 2.4 mL)] was added dropwise. After 4 h stirring at rt, it was quenched by addition of saturated aqueous solution of NH_4Cl. The two layers were separated, the organic layer dried (Na_2SO_4) and concentrated to form a residue which was purified on silica gel using EtOAc:light petroleum ether (1:9) to furnish **70** as a colorless oil.

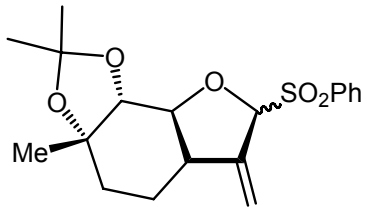
Yield	: 0.35 g, (71% for two steps)
Mol. Formula	: $C_{14}H_{22}O_4$
IR ($CHCl_3$) $\tilde{\nu}$	: 913, 1003, 1033, 1063, 1090, 1373, 1449, 1596, 2934, 2996, 3368 cm^{-1}.
^{1}H NMR ($CDCl_3$, 400 MHz)	: δ 1.37, 1.40 (2s, 6 H), 1.46 (2s, 3 H), 1.50-1.70 (m, 3 H), 1.93 (m, 1 H), 2.78-2.92 (m, 1 H), 3.40, 3.45 (2s, 3 H), 4.08, 4.13 (2d, 1 H, *J* = 2.5 Hz), 4.36, 4.58 (2dd, 1 H, *J* = 2.5, 6.9 and 2.6, 6.8 Hz), 5.15-5.32 (m, 3 H) ppm.
^{13}C ($CDCl_3$, 100 MHz)	: δ 24.5, 25.1, 25.8, 26.2, 27.1, 27.3, 27.6, 28.0, 31.8, 32.0, 37.4, 38.3, 54.5, 55.7, 76.2, 78.2, 78.6, 78.8, 79.0, 104.2, 104.7, 106.9, 107.1, 110.1, 110.5, 152.7, 153.2 ppm.

ESI MS (m/z) : 277 (M+Na)

Elemental Analysis **Calcd.:** C, 66.12; H, 8.72%.

Found: C, 66.08; H, 8.64%.

(1*S*,2*R*,3*S*,6*R*)-2,3-*O*-Isopropylidene-3-methyl-7-methylene-8-benzenesulphonyl-9-oxabicyclo[4.3.0]nonane (71):



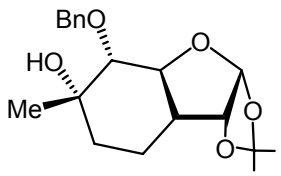
To a solution of **70** (0.2 g, 0.78 mmol) in dry CH_2Cl_2 (10 mL) containing powdered $CaCl_2$ (175 mg, 1.5 mmol) at 0 °C, freshly prepared benzenesulfinic acid (220 mg, 1.5 mmol) was added. The reaction mixture, after being stirred for 2 h at ambient temperature, was cooled to 0 °C, and neutralized with aqueous sodium bicarbonate solution. The suspension was filtered over celite pad and the filtrate washed with water and brine, dried (Na_2SO_4), concentrated and prurified on silica gel using EtOAc:light petroleum ether (2:8) to furnish **71** as a colorless oil.

Yield : 0.25 g, (87%)

Mol. Formula : $C_{19}H_{24}O_5S$

^{1}H NMR ($CDCl_3$, 500 MHz) : δ 1.26 (s, 3 H), 1.36 (s, 3 H), 1.37 (m, 2 H), 1.42 (s, 3 H), 2.01 (m, 2 H), 3.04 (m, 1 H), 4.03 (d, 1 H, J = 2.8 Hz), 4.83 (dd, 1 H, J = 2.8, 7.6 Hz), 5.17 (s, 1 H), 5.51 (s, 1 H), 5.74 (s, 1 H), 7.58 (m, 2 H), 7.68 (m, 1 H), 7.93 (m, 2 H) ppm.

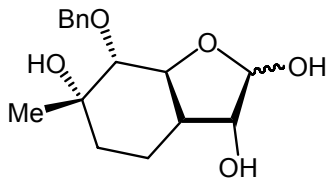
(1*S*,2*R*,3*S*,6*S*,7*R*,8*R*)-2-Benzyloxy-3-hydroxy-3-methyl-7,8-*O*-isopropylidene-9-oxabicyclo[4.3.0]nonane (74):



Compound **43** (1.0 g, 4.0 mmol) in DMF (10 mL) was added to a stirred suspension of NaH (410 mg, 60% dispersion in oil, 10.2 mmol) in DMF (10 mL) at 0 ^{o}C. The resulting solution was stirred at rt for 30 min, BnBr (1.0 mL, 8.9 mmol) and TBAI (25 mg) were added. After 2 h, the reaction was quenched by ice-cold water and extracted with EtOAc. The combined organic layer was washed with water, dried (Na_2SO_4) and concentrated. The residue was purified on silica gel using EtOAc:light petroleum ether (1:9) to obtain **74** as a viscous liquid.

Yield	: 1.21 g, (88%)
Mol. Formula	: $C_{19}H_{26}O_5$
Optical Rotation $[\alpha]_D^{25}$	: -30.30 (*c* 1.6, $CHCl_3$).
IR ($CHCl_3$) $\tilde{\nu}$	: 908, 1019, 1064, 1097, 1374, 1384, 1453, 1496, 2888, 2931, 2966, 2988, 3549 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 0.94 (m, 3 H), 1.25, 1.26 (2s, 6 H), 1.45-1.80 (m, 4 H), 2.31 (m, 1 H), 3.50 (s, 1 H), 4.35 (dd, 1 H, *J* = 3.6, 6.6 Hz), 4.47 (m, 1 H), 4.55-4.78 (m, 2 H), 5.82 (d, 1 H, *J* = 3.6 Hz), 7.34 (m, 5 H) ppm.
^{13}C ($CDCl_3$, 50 MHz)	: δ 21.8, 23.4, 25.7, 26.4, 33.7, 40.4, 70.0, 73.3, 77.3, 80.0, 84.1, 104.1, 110.8, 127.5, 127.7, 128.2, 137.6 ppm.
ESI MS (m/z)	: 335 (M+1)
Elemental Analysis	**Calcd.:** C, 68.24; H, 7.84%.
	Found: C, 68.12; H, 7.75%.

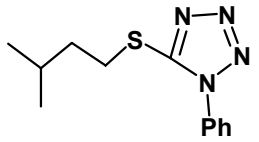
(1*S*,2*R*,3*S*,6*S*,7*R*)-2-Benzyloxy-3-methyl-3,7,8-trihydroxy-9-oxabicyclo[4.3.0]nonane (75):



Compound **74** (0.5 g, 1.4 mmol) in 60% aq. AcOH (10 mL) was heated under reflux for 2 h. The reaction mixture was neutralized with solid Na_2CO_3 and evaporated. The residue was extracted with EtOAc, dried (Na_2SO_4), concentrated, and purified by silica gel column chromatography using EtOAc:light petroleum (1:1) to give triol **75** as a colorless syrup.

Yield	: 0.37 g, (84%)
Mol. Formula	: $C_{16}H_{22}O_5$
IR ($CHCl_3$) $\tilde{\nu}$	: 947, 1018, 1073, 1370, 1453, 1496, 1619, 2930, 3011, 3399 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 1.23 (s, 3H), 1.41-1.74 (m, 3 H), 1.92 (m, 1 H), 2.40 (m, 1 H), 3.05, 3.40 (2d, 1 H, *J* = 6.5 and 7.7 Hz), 3.90, 4.01 (2dd, 1 H, *J* = 4.7, 8.7 and 3.3, 9.1 Hz), 4.34, 4.44 (2t, 1 H, *J* = 7.7 and 6.9 Hz), 4.58-4.96 (m, 2 H), 5.33 (d, 1 H, *J* = 4.7 Hz), 7.34 (m, 5 H) ppm.
^{13}C ($CDCl_3$, 50 MHz)	: δ 21.6, 24.7, 33.4, 41.3, 70.6, 73.4, 76.4, 79.8, 80.9, 97.6, 127.8, 128.3, 137.7 ppm.
ESI MS (m/z)	: 294 (M^+)
Elemental Analysis	**Calcd.:** C, 65.29; H, 7.53%.
	Found: C, 65.25; H, 7.48%.

5-(Isopentylthio)-1-phenyl-1*H*-tetrazole (80):

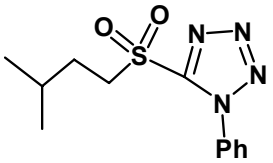


Mol. Formula : $C_{12}H_{16}N_2S$, viscous liquid.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 0.95, 0.98 (2s, 6 H), 1.71 (m, 3 H), 3.41 (m, 2 H), 7.57 (m, 5 H) ppm.

^{13}C ($CDCl_3$, 125 MHz) : δ 21.7, 27.0, 31.0, 37.4, 123.3, 129.3, 129.6, 133.3, 153.8 ppm.

5-(Isopentylsulphonyl)-1-phenyl-1*H*-tetrazole (81):



Mol. Formula : $C_{12}H_{16}N_4O_2S$, viscous liquid.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 0.98, 1.01 (2s, 6 H), 1.84 (m, 3 H), 3.74 (m, 2 H), 7.62 (m, 5 H) ppm.

^{13}C ($CDCl_3$, 125 MHz) : δ 21.5, 26.7, 29.6, 53.9, 124.9, 129.2, 130.9, 132.7, 153.1 ppm.

REFERENCES

1. (a) Hanson, J. R., in *Chemistry of Terpenes and Terpenoids*, Newman, A. A. Ed., Academic Press, New York, **1972**, pp. 1-5. (b) Giasby, J. S., *Encyclopaedia of Terpenoids*, Wiley, Chichester, **1982**, II. (c) Devon, T. K. and Scott, A. I., *Handbook of Naturally Occuring Compounds*, Academic Press, New York, **1972**.
2. Charlwood, B. B. and Banthorpe, D. V., in *Methods in Plant Biochemistry*, Edy, P. M. and Harborne, J. B. Eds., Academic Press, San Diego, CA, **1991**, *7*, pp. 213-220.
3. (a) Kubo, I.; Lee, Y. W.; Pettel, M. J.; Piliewicz, F. and Nakanishii, K., *J. Chem. Soc., Chem. Commun.,* **1976**, 1013-1014. (b) Langentheim, J. H., *J. Chem. Ecol*., **1994**, *26*, 1223-1280. (c) Doboson, H. E. M., in *Insect-plant Interactions*, Bemays, E. Ed., CRC Press, Boca Raton, FL, **1993**, *5*, pp. 47-81.
4. Gibson, R. W. and Pickett, J. A., *Nature*, **1983**, *302*, 608-609.
5. Harborne, J. B., in *Natural Resistance of Plant to Pests*, Am. Chem. Soc. Symposium Siries, 296, Green, M. B. and Hedin, P. A. Eds., *Am. Chem. Soc*., Washington, DC, **1986**, pp. 22-35.
6. Kupechan, S. M.; Hemingway, R. J.; Werner, D., Karim, A. *J. Am. Chem. Soc.* **1968**, *90*, 3596-3597.
7. Fischer, N. H.; Wiley, R. A.; Perry, D. L; Haegele, K. D. *J. Org. Chem*., **1976**, *41*, 3956-3959.
8. Malcolm, A., Difeo, D.; Fischer, N. H. *Phytochemistry*, **1982**, *21*, 151-155.
9. Herz, W.; Vivar, A. R. D.; Romo, J.; Viswanathan, N. *J. Am. Chem. Soc.* **1963**, *85*, 19-26.
10. Doskotch, R. W.; El-Ferlay, F. S. *J. Org. Chem*., **1970**, *35*, 1928-1936.
11. Herz, W.; Watanabe, H.; Miyazaki, M.; Kishida, Y. *J. Am. Chem. Soc.* **1962**, *84*, 2601-2610.
12. Govindachari, T. R.; Joshi, B. S.; Kamat, V. K. *Tetrahedron* **1965**, *21*, 1509-1519.
13. Herz, W.; Rohde, W. A.; Rabindran, K.; Jayaraman, P.; Viswanathan, N. *J. Am. Chem. Soc.* **1962**, *84*, 3857-3870.

14. Fischer, N. H. in *Terpenoids*; Charlwood, B. V.; Banthorpe, D. V., Eds., *Methods in Plant Biochemistry* Vol. 7, Academic Press, **1991**, pp. 187-211.
15. Kupchan, S. M.; LaVoie, E. J.; Branfman, A. R.; Fei, B. Y.; Bright, W. M.; Bryan, R. F. *J. Am. Chem. Soc.* **1977**, *99*, 3199-3201.
16. Klayman, D. L. *Science* **1985**, *228*, 1049-1055.
17. Jarvis, B. B.; Pavanasasivam, G.; Bean, G. A. in *Trichothecenes and Other Mycotoxins* Lacey, J., Ed., John Wiley & Sons Ltd., **1985**, pp. 221-231.
18. Fraga, B. M. in *Terpenoids*; Charlwood, B. V.; Banthorpe, D. V., Eds., *Methods in Plant Biochemistry* Vol. 7, Academic Press, **1991**, pp. 145-185.
19. (a) Stadler, M.; Anke, H.; Sterner, O. *J. Antibiot.* **1994**, *47*, 1284-1289. (b) Stadler, M.; Fouron, J.-Y.; Sterner, O.; Anke, H. Z. *Naturforcsch.* **1995**, *50c*, 473-475.
20. Stadler, M.; Anke, H.; Sterner, O. *Tetrahedron* **1994**, *50*, 12649-12654.
21. Takao, K.; Hara, M.; Tsujita, T.; Yoshida, K.; Tadano, K. *Tetrahedron Lett*. **2001**, *42*, 4665-4668.
22. Brocksom, T. J.; Zanotto, P. R.; Brocksom, U. *Tetrahedron Lett*. **2005**, *46*, 2397-2398.
23. Garegg, J.; Samuelsson, B. *J. Chem. Soc., Perkin Trans. 1,* **1980**, 2866-2870.
24. (a)Hanessian, S.; Leger, R.; Alpengiani. *Carbohydr. Res.* **1992**, *228*, 145-155. (b) Keck, G. E.; Enholm, E. J.; Yates, J. B.; Wiley, M. R. *Tetrahedron*, **1985**, *41*, 4079-4094.
25. (a) Hart, D. J. *Science* (Washington, D. C.), **1984**, *223*, 883. (b) Giese, B. *Radicals in Organic Synthesis: Formation of Carbon-Carbon Bond; Pergamon:* Oxford, 1986.
26. Rosental, A.; Sprinzl, M. *Can. J. Chem.* **1969**, *47*, 4477.
27. (a) Huang, S. L.; Omura, K.; Swern, D. *J. Org. Chem.* **1976**, *41*, 3329-3331. (b) Mancuso, A J.; Huang, S. L.; Swern, D. *ibid*. **1978**, *43*, 2480-2482. (c) Huang, S. L.; Omura, K.; Swern, D. *ibid*. **1978**, *43*, 4537-4538.
28. (a) Wittig, G.; Geissler, G. *Justus Leibigs Ann. Chem*., **1953**, *580*, 44. (b) Wittig, G.; Schollkopf, U. *Ber*. **1954**, *87*, 1318.
29. Gurjar, M. K.; Patil, V. J.; Pawar, S. M. *Carbohydr. Res.* **1987**, *165,* 313.

30. Robins, M. J.; Wnuk, S. F.; Yang, X.; Yuan, C.-S.; Borchardt, R. T.; Balzarini, J.; Clercq, E. D. *J. Med. Chem.* **1998**, *41*, 3857-3864.
31. More, J. D.; Finney, N. S. *Org. Lett.* **2002**, *4*, 3001-3003.
32. (a) Grubbs, R. H.; Pine, S. H. In *Comprehensive Organic Synthesis,* Trost, B. M.; Fleming, I.; Paquette, L. A. Eds.; Pergamon: New York, 1991, Vol. 5, Chapter 9.3 (b) Schrock, R. R. In *The Strem Chemiker,* Vol. XIV, Strem Chemicals, Newburgport, 1992, No. 1, pp. 1-6. (c) Ivin, K. J.; Mol, J. C. *Olefin Metathesis and Metathesis Polymerization,* Academic Press, San Diego, 1997. (d) For a recent reviews, see: Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413. (e) Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res.* **2001**, *34*, 18. (f) Furstner, A. *Angew. Chem. Int. Ed.* **2000**, *39,* 3012. (g) Kotha, S.; Sreenivasachary, N. *Ind. J. Chem. B,* **2001**, *40*, 763.
33. (a) Sweeney, J. B., in *Comprehensive Organic Functional Group Transformations, Ed.,* Katritzky, A. R.; Meth-Cohn, O.; Rees, C. W., Pergamon Press, **1995**, *2,* 44. (b) Cha, J. K., Kim, N.-S.; *Chem. Rev.,* **1995**, *95*, 1761-1795.
34. (a) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155-4156. (b) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277-7287. (c) Ireland, R. E.; Liu, L. *J. Org. Chem.* **1993**, *58*, 2899-2899.
35. (a) Brown, D. S.; Bruno, M.; Davenport, R. J.; Ley, S. V. *Tetrahedron* **1989**, *45*, 4293-4308. (b) Beau, J.-M.; Sinay, P. *Tetrahedron Lett.* **1985**, *26,* 6185-6188.
36. (a) Reist, E. J.; Goodman, L. *Biochemistry,* **1964**, *3,* 15. (b) Kam, B. L.; Barascut, J.-L.; Imbach, J.-L. *Carbohydr. Res.* **1979**, *69*, 135.
37. Blakemore, P. R.; Cole, W. J.; Kocienski, P. J.; Morley, A. *Synlett* **1998**, 26-28.
38. (a) Corey, E. J.; Chaykovsky, M. *J. Am. Chem. Soc.* **1962**, *84,* 867-868. (b) Childers, W. E.; Furth, P. S.; Shih, M.-J.; Robinson, C. H. *J. Org. Chem.* **1988**, *53,* 5947-5951.

List of publications

1. Stereoselective synthesis of a Novel Carbocyclic Nucleoside., Mukund K. Gurjar and Kundarapu Maheshwar. *J. Org. Chem.* **2001**, *66*, 7552-7554.
2. Synthesis of enantiopure 3-Amino1-azaspiro[4.5]decane-8-one using *trans*-4-hydroxy-L-proline as chiral source., Mukund K. Gurjar and Kundarapu Maheshwar. (manuscript communicated).