SYNTHETIC STUDIES TOWARD NAGAHAMIDE A, SANGLIFEHRIN A, L-*ido*-CARBA-SUGARS AND HYDROXYGLIMEPIRIDE

BY

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A THESIS

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BY

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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.

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CERTIFICATE

The research work presented in thesis entitled "**Synthetic studies toward Nagahamide A, Sanglifehrin A, L-*ido*-Carba-sugars and Hydroxyglimepiride**" has been carried out under my supervision and is a bonafide work of **Mr. Siddhartha Ray Chaudhuri**. This work is original and has not been submitted for any other degree or diploma of this or any other University.

Pune-8

March 2005

(Dr. M. K. Gurjar)

Research Guide

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ABBREVIATIONS

Ac	-	Acetyl
Ac_2O	-	Acetic anhydride
AcOH	-	Acetic acid
AIBN	-	2,2'-Azobisisobutyronitrile
BF_3:OEt_2	-	Boron trifluoride diethyl ether complex
H_3B:SMe_2	-	Borane dimethyl sulfide complex
BH_3:THF	-	Borane tetrahydrofuran complex
Bn	-	Benzyl
BnBr	-	Benzyl bromide
Boc	-	*tert*-Butoxy carbonyl
$(Boc)_2O$	-	Di-*tert*-butyl dicarbonate
Bu_2BOTf	-	Dibutylboron triflate
*n*BuLi	-	*n*-Butyl lithium
nBu_3SnH	-	*n*-Tributyltin hydride
*m*CPBA	-	*m*-Chloroperbenzoic acid
CSA	-	Camphorsulphonic acid
Cy_2BCl	-	Chlorodicyclohexylborane
DBU	-	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCC	-	Dicyclohexylcarbodiimide
DDQ	-	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DEAD	-	Diethyl azodicarboxylate
DIBAL-H	-	Diisobutylaluminium hydride
DIPEA	-	Diisopropyl ethylamine
DMF	-	*N*,*N*-Dimethylformamide
DMP	-	2,2-Dimethoxypropane
DMSO	-	Dimethyl sulfoxide
EDCI	-	1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
Et	-	Ethyl
Et_3N	-	Triethylamine

Et_2O	-	Diethyl ether
EtOAc	-	Ethyl acetate
EtOH	-	Ethanol
Fmoc	-	9-Fluorenylmethoxycarbonyl
FmocCl	-	9-Fluorenylmethyl chloroformate
HOBt	-	1-Hydroxybenzotriazole hydrate
Im	-	Imidazole
LAH	-	Lithium aluminium hydride
LDA	-	Lithium diisopropylamine
LiHMDS	-	Lithium hexamethyl disiloxane
Me	-	Methyl
MeI	-	Methyl iodide
MeOH	-	Methanol
Ms	-	Methanesulfonyl
MsCl	-	Methanesulfonyl chloride
NaOAc	-	Sodium acetate
NMM	-	*N*-Methylmorpholine
NMO	-	*N*-Methylmorpholine *N*-oxide
PCC	-	Pyridinium chlorochromate
Pd/C	-	Palladium on Carbon
$Pd(OH)_2/C$	-	Palladium hydroxide on Carbon
Ph	-	Phenyl
Piv	-	Trimethylacetyl (pivaloyl)
PivCl	-	Trimethylacetyl chloride
PMB	-	*p*-Methoxybenzyl
PMB-Br	-	*p*-Methoxybenzyl bromide
PMB-Cl	-	*p*-Methoxybenzyl chloride
Py	-	Pyridine
TBAF	-	Tetra-*n*-butylammonium fluoride
TBAI	-	Tetra-*n*-butylammonium iodide
TBS	-	*tert*-Butyldimethylsilyl
TBSCl	-	*tert*-Butyldimethylsilyl chloride

TBSOTf	-	*tert*-Butyldimethylsilyl trifluoromethanesulphonate
Tf_2O	-	Trifluoromethanesulphonic anhydride
THF	-	Tetrahydrofuran
TIBAL	-	Triisobutylaluminium
TIPS	-	Triisopropylsilyl
TIPSCl	-	Triisopropylsilyl chloride
TMS	-	Trimethylsilyl
TMSOTf	-	Trimethylsilyl trifluoromethanesulphonate
TPAP	-	Tetra-*n*-propylammonium perruthenate (VII)
Trt	-	Triphenylmethyl (trityl)
TrtOH	-	Triphenylmethanol
*p*TSA	-	*p*-Toluenesulfonic acid
TsCl	-	*p*-Toluenesulfonyl chloride

GENERAL REMARKS

❋ ^{1}H NMR spectra were recorded on AC-200 MHz, MSL-300 MHz, and DRX-500 MHz spectrometers 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 spectrometers.

❋ EI Mass spectra were recorded on Finngan MAT-1020 spectrometer at 70 *eV* using a direct inlet system.

❋ 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 were 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

The thesis entitled "**Synthetic studies toward Nagahamide A, Sanglifehrin A, L-*ido*-Carba-sugars and Hydroxyglimepiride**" consists of four chapters and each chapter is further sub-divided into the following sections: Introduction, Present work, Experimental, Spectroscopic data and References. Chapter I describes the synthetic studies toward nagahamide A while the stereoselective synthesis of C13-C18 fragment of sanglifehrin A is outlined in the Chapter II. Chapter III involves a strategy for the synthesis of L-*ido*-configured 6-, 7-, and 8-membered carba-sugars. Chapter IV highlights the total synthesis of *cis*- and *trans*-hydroxyglimepiride.

Chapter I: **Synthetic studies toward nagahamide A**

Nagahamide A (**1**), an antibacterial depsipeptide was isolated from the marine sponge *Theonella swihoei*. The structure of nagahamide A is characterized by six amino acids peptide backbone (**2**), which is joined in a macrocyclic structure through a polyketide chain (**3**). The polyketide acid (**3**) of nagahamide A contains four contiguous chiral centers with a terminal *E*,*E*-dienoic group. As a part of our interest on the synthesis of nagahamide A (**1**), we first undertook a carbohydrate-based preparation of the polyketide ester (**4**) and synthesis of suitably protected three unusual amino acids: (*S*)-Boc-AHBA (TBS)-OH (**9a**), L-*erythro*-FmocNH-β-Me-Asn (Trt)-OBn (**10a**) and L-*erythro*-FmocNH-β-OH-Asn (Trt)-OBn (**11a**) and tripeptide (**5**).

Synthesis of polyketide ester (4)

Cyclopropanated carbohydrate provides an interesting mixture of strained and reactive cyclopropane combined with optical activity inherent in carbohydrates and started to introduce much interest in the synthesis of bioactive compounds and the development of new synthetic methods.

Our strategy was founded on the study of stereoselective cyclopropanation of the α,β-unsaturated ketone (**15**) as the key step. Therefore, developing a stereocontrolled strategy to simultaneously introduce a methyl and propyl group at C-5 *via* stereoselective

cyclopropanation followed by regioselective ring opening reaction of cyclopropyl group was envisaged.

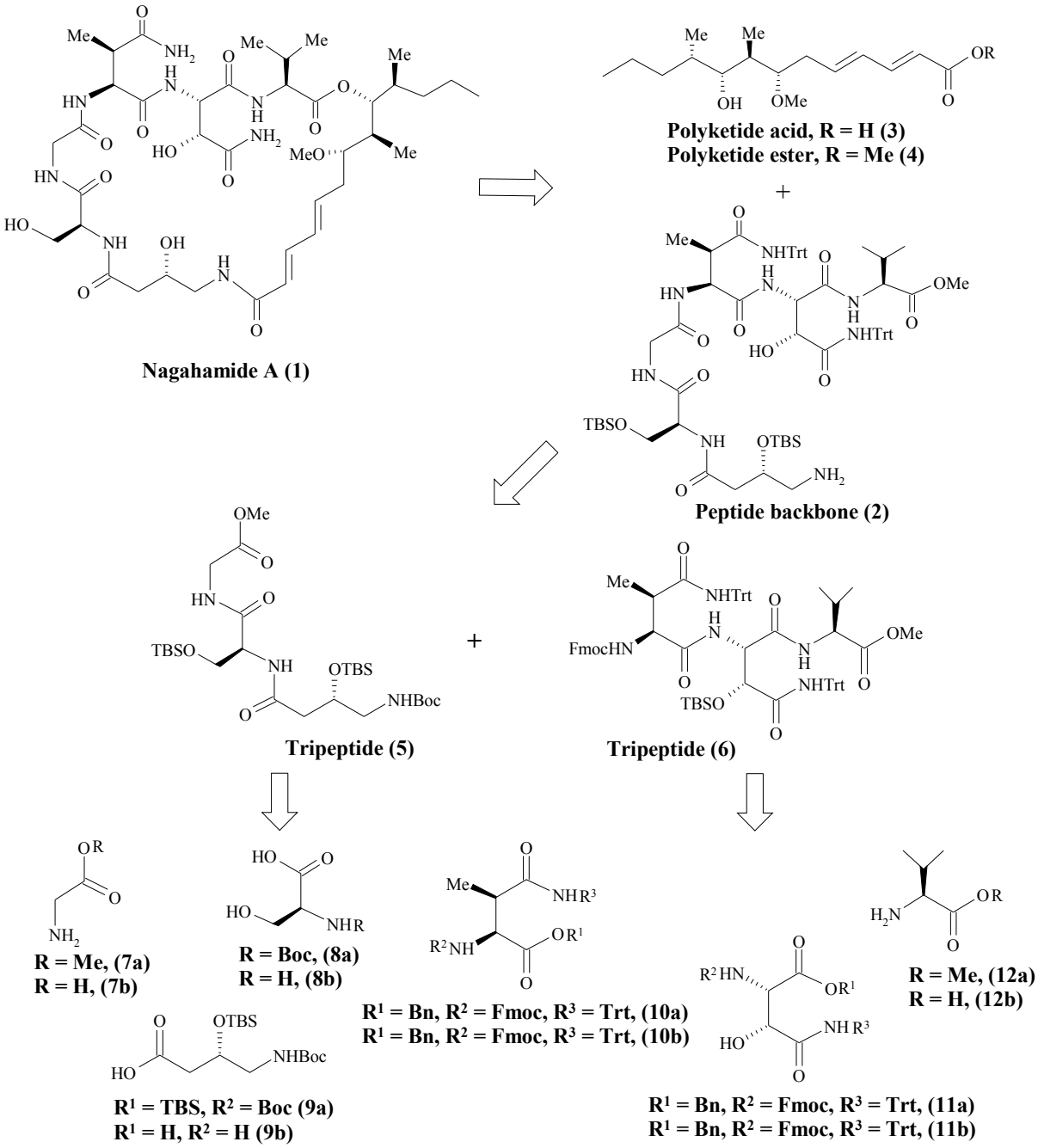
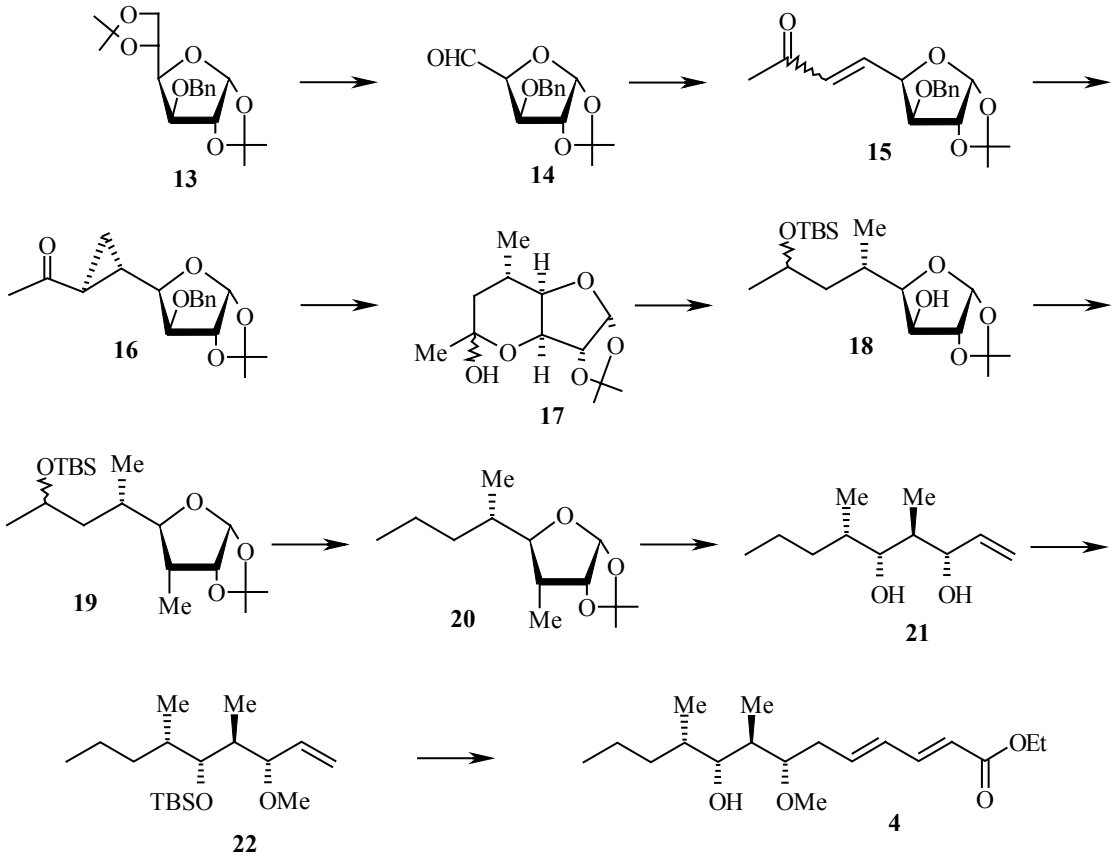


Figure 1

3-*O*-Benzyl-1,2;5,6-di-*O*-isopropylidene-α-D-glucofuranose (**13**) was converted into the aldehyde **14** by two known steps, which was subjected to Wittig olefination with acetonyltriphenylphosphorane to give *E*/*Z* mixture of unsaturated ketone **15** in 3:2 ratio

(Scheme 1). Compound **15** was then treated with $(CH_3)_3SOI$ in the presence of NaH to afford the cyclopropane derivative (**16**). The absolute stereochemistry of **16** was confirmed from the subsequent reactions. The regioselective reduction of the cyclopropane ring of **16** over 10% Pd/C at 200 psi in EtOAc gave **17**. The LAH reduction of **17** in THF produced the diol whose less hindered secondary hydroxyl group was protected as its mono TBS ether (**18**). Successive Swern oxidation, one carbon Wittig homologation and hydrogenation of **18** afforded **19**. Removal of TBS group followed by Barton-radical deoxygenation provided **20**. De-isopropylidination of **20** and subsequent treatment with an excess $Ph_3P{=}CH_2$ gave the diol **21**. The selective methylation of the allylic hydroxyl group and subsequent TBSOTf treatment afforded the silyl ether derivative (**22**). Finally, compound **22** was transformed into the *E*,*E*-dienoic polyketide ester (**4**) in four steps involving hydroboration-oxidation, Dess-Martin Periodinane oxidation, Wittig-Horner chain homologation with methyl 4-(diethyl phosphono) crotonate and 1% HCl-EtOH (Scheme 1). The ^{1}H NMR and ^{13}C NMR spectroscopy confirmed the structure of **4**.

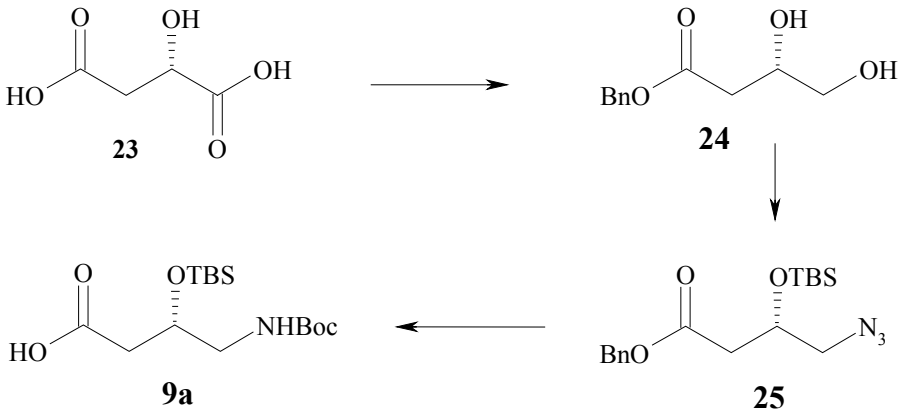
Scheme 1



Synthesis of (*S*)-Boc-AHBA (TBS)-OH (9a)

The synthesis of **9a** was initiated with a readily available L-malic acid (**23**), which was converted into the diol **24** by two known steps. The selective mesylation and nucleophilic azide substitution of **24** afforded the azide derivative (**25**). The reduction of azide group to amine, its protection and reductive removal of benzyl group were effected in one pot operation by hydrogenation of **25** over 10% Pd/C in the presence of $(Boc)_2O$ in EtOAc at 20 psi H_2 atmosphere to provide (*S*)-Boc-AHBA (TBS)-OH (**9a**) (Scheme 2). The structure of **9a** was confirmed by its ^1H NMR, ^{13}C NMR, IR and elemental analysis.

Scheme 2

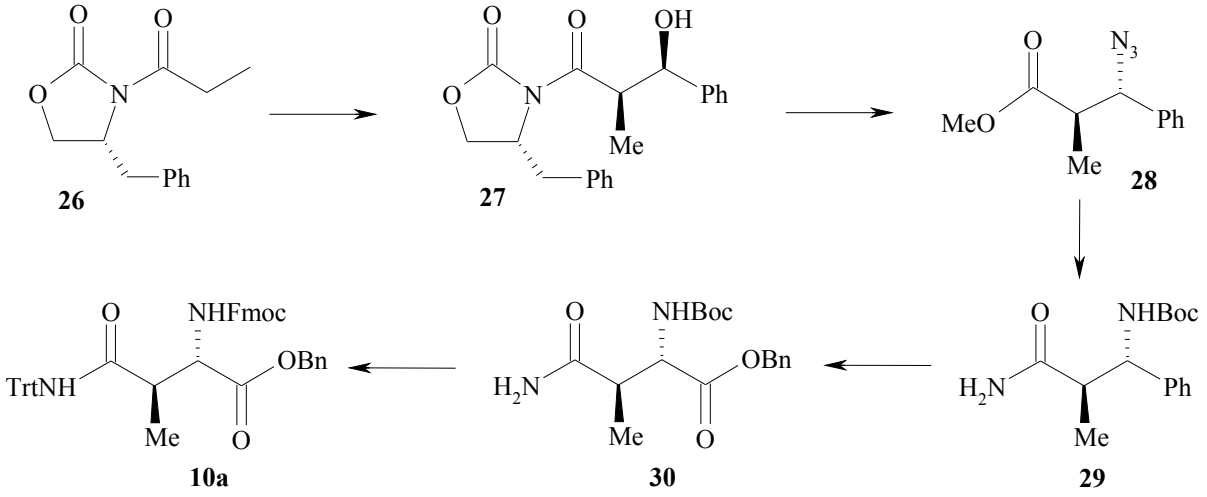


Synthesis of L-*erythro*-FmocNH-*β*-Me-Asn (Trt)-OBn (10a)

The synthetic strategy for an effective asymmetric synthesis of L-*erythro*-FmocNH-*β*-Me-Asn (Trt)-OBn (**10a**) was based on Evans asymmetric aldol reaction. Thus, Evans aldol condensation of the imide **26** and PhCHO using Bu_2BOTf and Et_3N provided the 1,2-*syn*-aldol product (**27**), which on removal of the chiral auxiliary followed by nucleophilic azide substitution gave **28** (Scheme 3). Sequential reduction of the azide group to amine, Boc protection and direct aminolysis of the methyl ester provided the amide derivative (**29**). The latent carboxylic acid was unmasked by treating **29** with ruthenium tetraoxide generated *in situ* and subsequently protected as a benzyl ester to furnish **30**. The Boc protecting group was removed and the resulting amine salt was reacted with FmocCl to provide the corresponding Fmoc derivative whose free amide group was protected with a trityl group under acidic conditions to afford L-*erythro*-FmocNH-*β*-Me-Asn (Trt)-OBn (**10a**) (Scheme 3). The

structure of **10a** was thoroughly investigated by its ^{1}H NMR, ^{13}C NMR, IR and elemental analysis.

Scheme 3

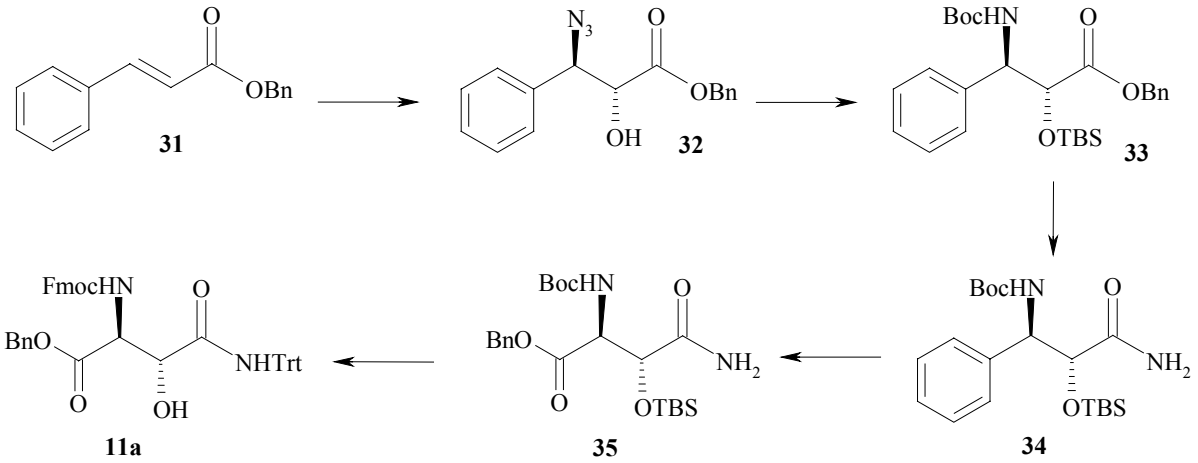


Synthesis of L-*erythro*-FmocNH-β-OH-Asn (Trt)-OBn (11a)

Our strategy for the asymmetric synthesis of L-*erythro*-FmocNH-β-OH-Asn (Trt)-OBn (**11a**) was based on enantiocontrolled Sharpless dihydroxylation reaction followed by β-hydroxyl-selective functionalization of *syn*-2,3-dihydroxy ester. Thus, Sharpless AD reaction of benzyl cinnamate (**31**) using AD-mix-α gave the corresponding diol which under Mitsunobu reaction conditions in the presence of HN_3 afforded exclusively *anti*-α-hydroxy-β-N_3 ester derivative (**32**) (Scheme 4). Sequential TBS protection of the free hydroxyl group and single step reduction of the azide group to amine and its protection afforded **33**. The conversion of **33** into **34** was accomplished by involving debenzylation followed by amidation reaction using HOBt, EDCI, *N*-methylmorpholine and NH_4OH. The oxidative cleavage of the aromatic ring of **34** by treating with ruthenium tetraoxide generated *in situ* and subsequent protection as a benzyl ester produced **35**. Finally, a single step Boc and TBS group removal was accomplished by treatment of **35** with 4 N HCl-EtOAc. This was followed by treatment of the amine with FmocCl and $NaHCO_3$ to furnish the corresponding Fmoc derivative whose free amide group was protected with a trityl group under acidic conditions in

the presence of Ac_2O to afford L-*erythro*-FmocNH-*β*-OH-Asn (Trt)-OBn (**11a**) (Scheme 4). The structure of **11a** was established by its ^1H NMR, ^{13}C NMR, IR and elemental analysis.

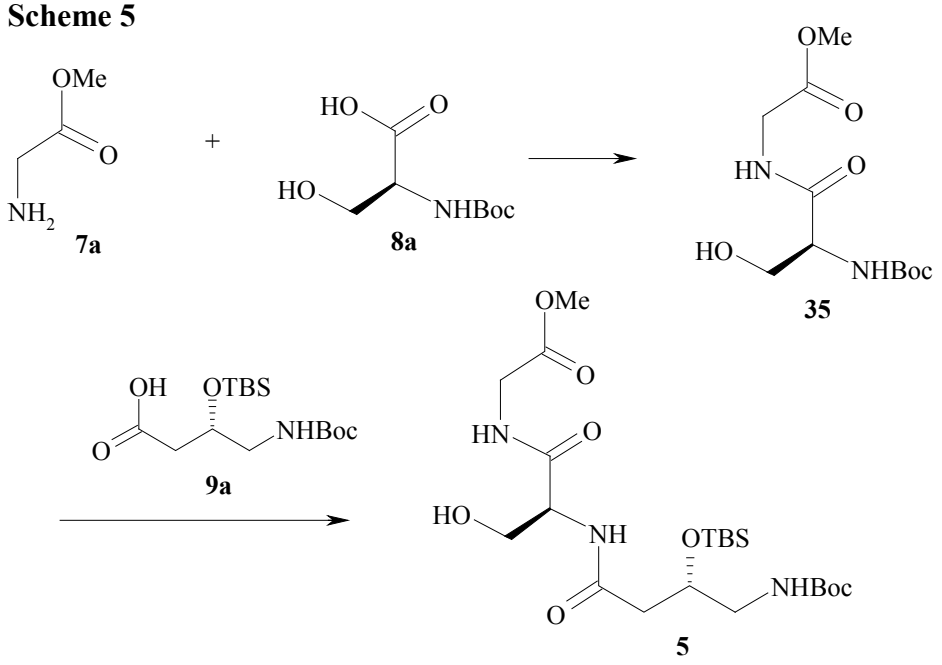
Scheme 4



Synthesis of tripeptide (5)

The synthesis of tripeptide (**5**) was initiated by coupling of gly-OMe (**7a**) with Boc-L-Ser-OH (**8a**) by using coupling reagents HOBt and DCC to afford the dipeptide (**35**) (Scheme 5). The free hydroxyl group of **35** was protected as its TBS ether which underwent coupling with **9a** after the removal of Boc group by the action of excess TMSOTf and 2,6-lutidine.

Scheme 5

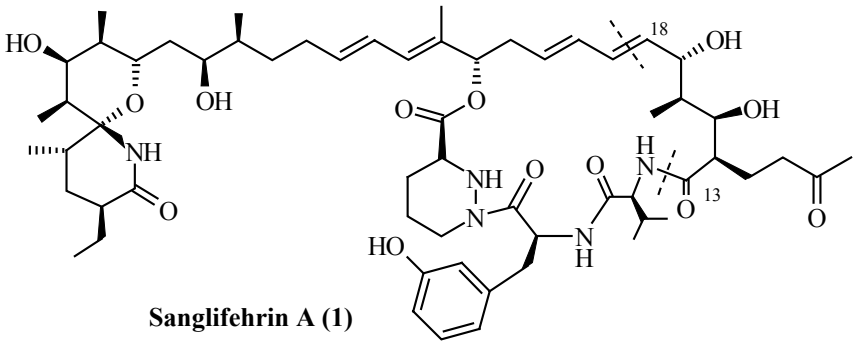


The coupling of the resulting amine with (*S*)-Boc-AHBA (TBS)-OH (**9a**) was brought about in the presence of EDCI, HOBt and Et_3N to provide the tripeptide (**5**) (Scheme 5).

In conclusion, we have developed the stereoselective synthesis of the polyketide chain (**4**) of nagahamide A. This work furnishes a route *via* regioselective ring opening reaction of cyclopropyl group to introduce methyl and propyl substituents simultaneously. We have successfully accomplished the synthesis of suitably protected three unusual amino acids, (*S*)-Boc-AHBA (TBS)-OH (**9a**), L-*erythro*-FmocNH-*β*-Me-Asn (Trt)-OBn (**10a**) and L-*erythro*-FmocNH-*β*-OH-Asn (Trt)-OBn (**11a**) and the tripeptide (**5**).

Chapter II: Stereoselecticve synthesis of the C13-C18 fragment of sanglifehrin A

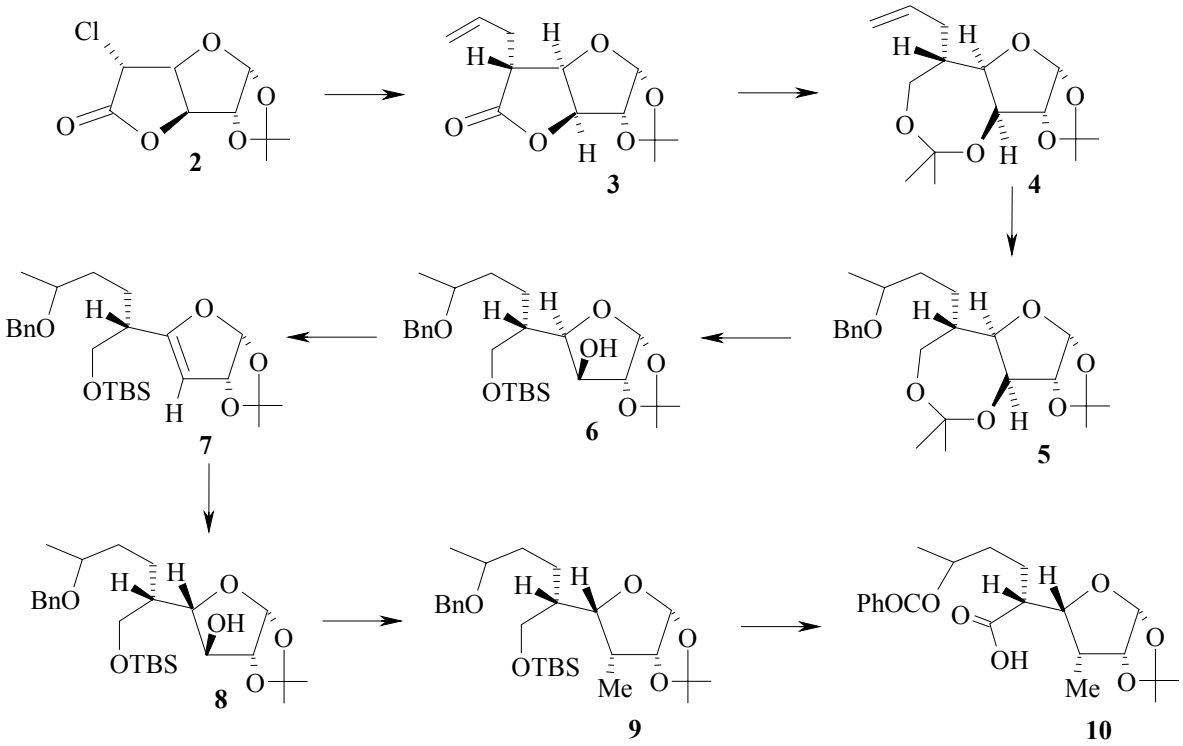
Sanglifehrin A (SFA) (**1**) was isolated from *streptomyces flaveolus* in 1995 by scientists at Novartis. Sanglifehrin A is a potent immunosuppressant and has a remarkably high ability for an intracellular binding protein called cyclophilin. It showed immunosuppressive activity against both T- and B-lymphocytes. Our initial strategy involved the synthesis of C13-C18 segment of sanglifehrin A starting from 1,2-*O*-isopropylidine-α-D-glucurono-6,3-lactone. The synthesis started with the stereoselective C-C bond formation through a radical mediated reaction of the 5-chloro-5-deoxy-glucurono-6,3-lactone derivative (**2**) with allyltri-*n*-butyltin.



Sanglifehrin A (1)

The reaction of **2** with allyltri-*n*-butyltin in the presence of AIBN in refluxing benzene gave exclusively **3**. The stereochemistry of **3** at C-5 was confirmed by its ^1H NMR spectrum. The treatment of **3** with LAH afforded a diol which was protected as its 7-membered acetonide derivative (**4**). Compound **4** was subjected to hydroboration-oxidation in the presence of $H_3B{:}SMe_2$ in THF to furnish the primary alcohol derivative whose successive oxidation, Grignard reaction with CH_3MgI and benzylation provided **5** (Scheme 1).

Scheme 1

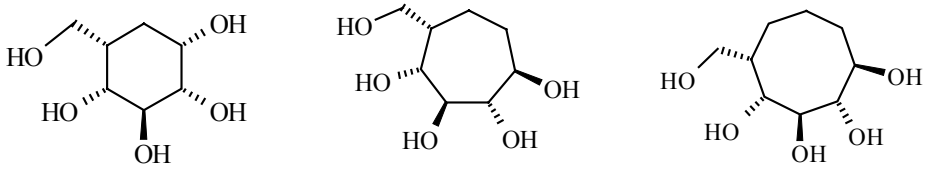


The 7-membered isopropylidine group of **5** was removed to obtain the diol whose primary hydroxyl was protected as its TBS ether (**6**). In order to effect the epimerization at C-4 *via* the intermediate **7**, compound **6** was subjected to an elimination reaction followed by hydroboration-oxidation to furnish **8** (Scheme 1). Subsequently compound **8** on oxidation under Swern reaction conditions, one carbon Wittig olefination with $CH_2=PPh_3$, hydroboration-oxidation and Barton-radical deoxygenation gave **9**. Removal of the silyl protective group and oxidation with $RuCl_3/NaIO_4$ in $CH_3CN/CCl_4/H_2O$ afforded **10** in which the benzyl group was also oxidized to the benzoate. The ^1H NMR, ^{13}C NMR, mass spectroscopy and elemental analysis of **10** were in support of the assigned structure.

In conclusion, we have developed an efficient stereoselective synthesis of C13-C18 segment of sanglifehrin A (**1**) *via* a highly stereocontrolled radical C-C bond formation on glucurono-6,3-latone.

Chapter III: **Synthesis of L-*ido*-configured 6-, 7-, and 8-membered carba-sugars**

It has been already well established that carba-sugars (or pseudo-sugars) are metabolically more stable and conformationally more flexible compared to their corresponding oxygen analogues. The conversion of carbohydrate derivatives into carba-sugars, sugars in which the endocyclic oxygen atom has been replaced by a methylene group is well documented for C5 and C6 series (Figure 1). However only a few approaches has been dedicated to analogues routes in the C7 and C8 series. The synthesis of medium-sized rings, notably C7 and C8 ring systems, has usually been hampered by entropic/enthalpic factors and transannular interactions between the methylene groups. Pseudo-sugars and some related carbocyclic compounds are components of some antibiotics (validamycins) and enzyme inhibitors (adipocins).

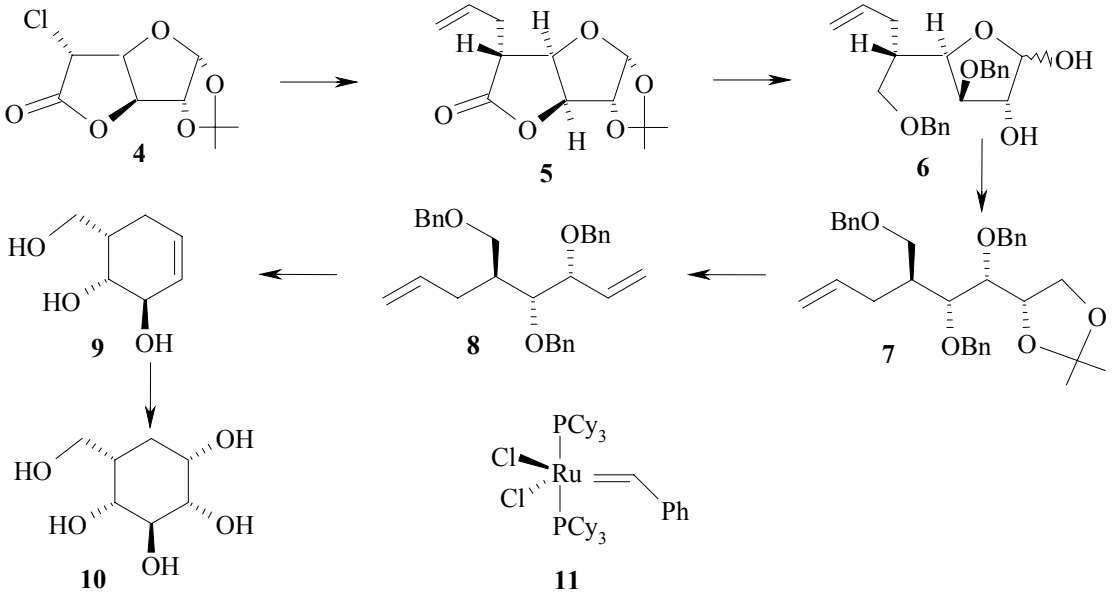


C6 (1) **C7 (2)** **C8 (3)**

Figure 1

Our strategy for the construction of L-*ido*-configured C6, C7, and C8 carba-sugars was founded on the stereoselective radical allylation and ring closing olefin metathesis as the key

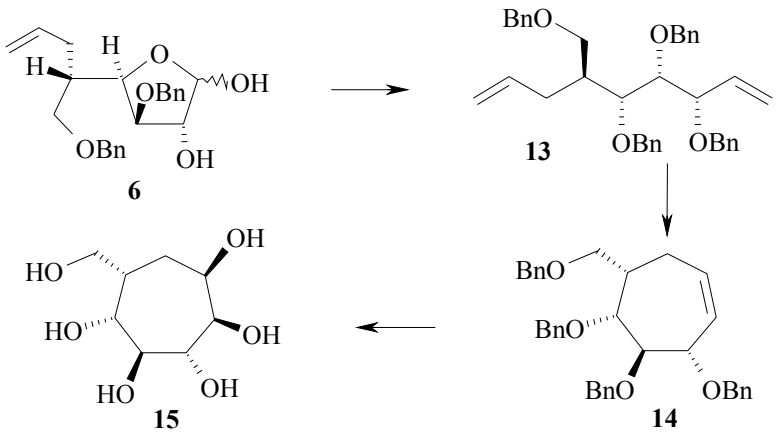
Scheme 1



steps. Radical allylation of 5-chloro-5-deoxy-L-iduronolactone (**4**) gave exclusively **5** with the retention of configuration, which corresponds the required stereochemistry at C-5 for L-*ido*-carba-sugars (Scheme 1). The reduction of **5** with LAH provided the diol whose dibenzyl protection followed by de-isopropylidination afforded the lactol derivative (**6**). The successive $NaBH_4$ reduction, isopropylidination and benzylation of **6** gave **7**. Diene **8** was obtained from **7** following a sequence of de-isopropylidination, dimesylation, and elimination reaction. Ring closing metathesis of **8** gave the pseudo glycal **9** using the Grubbs' catalyst [$(PCy_3)_2Cl_2Ru$=CHPh] (**11**). Dihydroxylation, followed by debenzylation of **9** resulted L-*ido*-C6 carba-sugar (**10**) (Scheme 1).

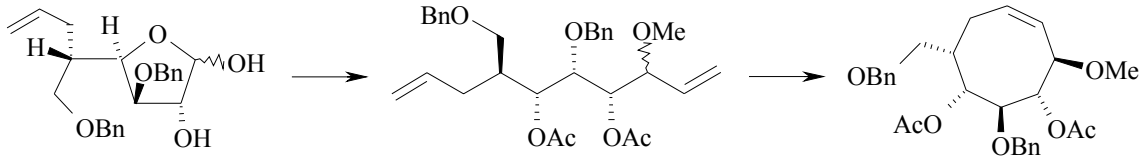
The treatment of **6** with excess of Ph_3P=CH_2 and subsequent benzylation gave **13** which on ring closing metathesis using the Grubbs' catalyst (**11**) provided **14** (Scheme 2). Dihydroxylation, followed by debenzylation of **14** resulted the polyhydroxylated 7-membered carba-sugar (**15**). The structure of **15** was confirmed by its ^{1}H NMR, ^{13}C NMR spectroscopy and elemental analysis.

Scheme 2



In a similar fashion, treatment of **6** with vinylmagnesium bromide resulted an inseparable diastereomeric mixture of triol, which on sequential methylation of allylic hydroxyl group and acetylation gave diacetates **16** (Scheme 3). Ring closing metathesis was accomplished by exposure of diene **16** to Grubbs' catalyst (**11**) in C_6H_6 at reflux temperature for 3 days to obtain cyclooctene **17** as a single isomer in a modest 25% yield along with recovered starting material (50%, Scheme 3). The structure of **17** was extensively characterized by its ^{1}H NMR, ^{13}C NMR, NOE and elemental analysis.

Scheme 3

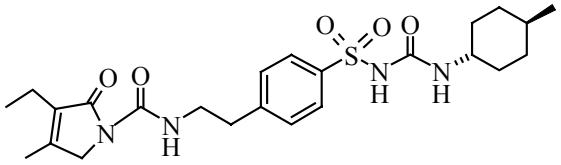


6 **16** **17**

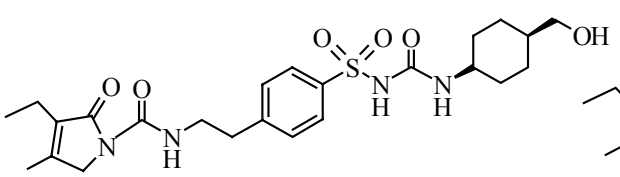
In summary, we have amplified the utility of the 5-chloro-5-deoxy-1,2-*O*-isopropylidine-β-L-idofuranurono-6,3-lactone (**2**) derived building block **5** by obtaining 6-, 7- and 8-membered carba-sugars through simple synthetic operations and ring closing olefin metathesis as the key step.

Chapter IV: Total synthesis of *cis*- and *trans*-hydroxyglimepiride

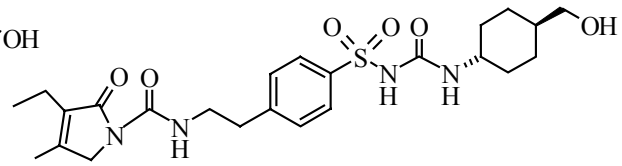
Antidiabetic glimepiride (**1**) is pharmacologically distinct from other sulfonylurea with a profile of potent and long lasting blood glucose lowering effect. Its biological activity coupled with binding to the 65 KD protein of the putative receptor. The metabolism of glimepiride has been observed in animals and humans *via* oxidative pathways giving rise to



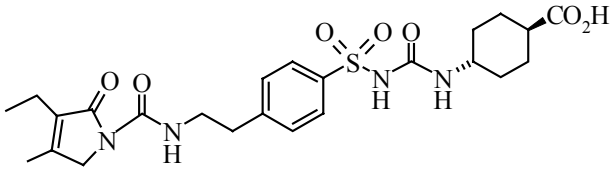
Glimepiride (1)



***cis*-Hydroxyglimepiride (2a)**



***trans*-Hydroxyglimepiride (2b)**



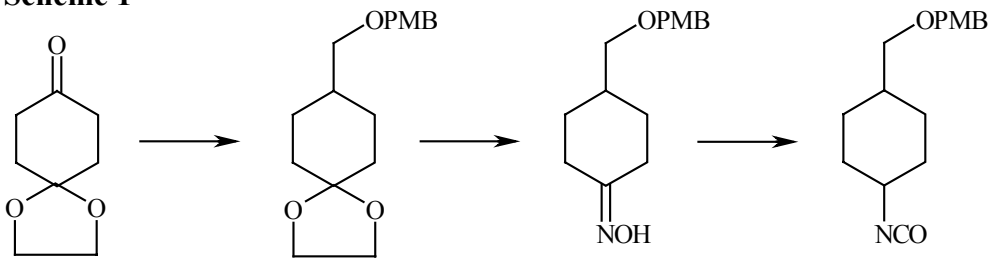
Carboxyglimepiride (3)

Figure 1

two active metabolites, *trans*-hydroxyglimepiride (**2b**) and carboxyglimepiride (**3**) (Figure 1). Animal studies have shown hydroxyglimepiride to exhibit some hypoglycaemic effects while carboxyglimepiride does not appear to have any pharmacological activity. Hydroxyglimepiride significantly decreased the minimum serum concentration (Cmin) of glucose by 12% and the average serum glucose concentration over the first four hours of treatment (Cavg 0-4) by 9%.

Our synthetic plan was initiated with the synthesis of isocynate derivative (**7**) from commercially available 1,4-cyclohexanedione *mono*-ethyleneketal (**4**). One carbon Wittig olefination of **4** with $Ph_3P{=}CH_2$ in THF gave the *exo*-methylene product which on hydroboration-oxidation followed by PMB protection afforded **5**. The ketone, which was

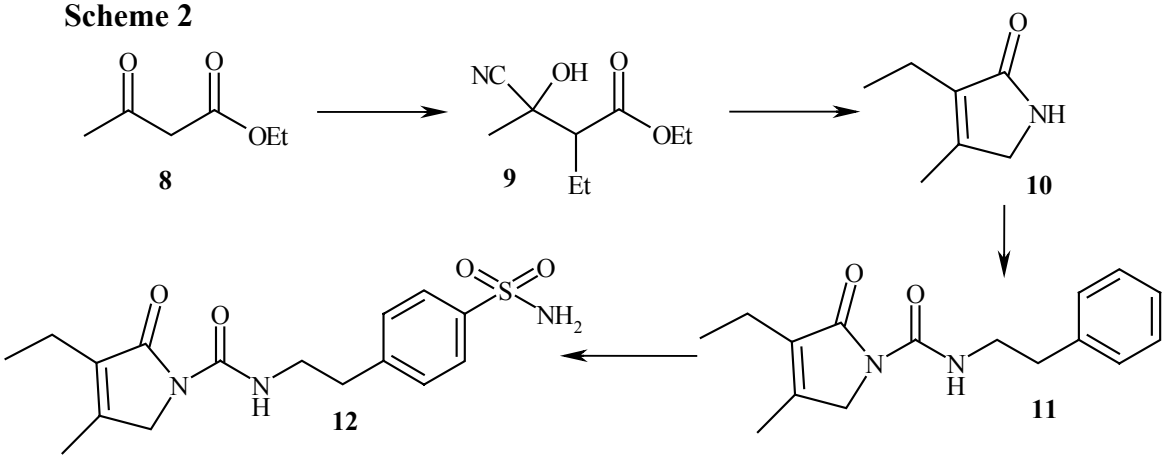
Scheme 1



4 **5** **6** **7**

obtained from **5** by the acidic cleavage of ethylene ketal group, converted into the oxime derivative (**6**) by treating with $NH_2OH.HCl$ in refluxing EtOH. The reduction of **6** with LAH provided an inseparable mixture of *cis*- and *trans*-cyclohexyl amine derivative which was transformed into the isocyanate **7** using phosgene in toluene (Scheme 1).

Scheme 2

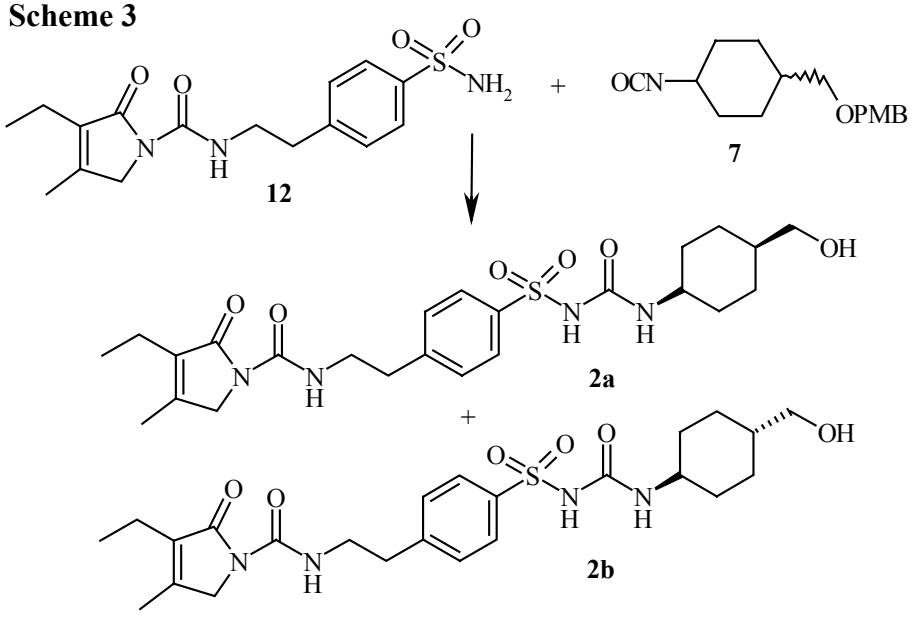


8 **9** **10** **11** **12**

The synthesis of sulfonamide intermediate (**12**) was accomplished by the following procedure shown in Scheme 2.

Finally, the condensation of isocyanate **7** with sulphonamide **12** in the presence of K_2CO_3 in CH_3COCH_3 gave a coupled product which on deprotection of the PMB group using a catalytic amount of BF_3:OEt_2 in CH_2Cl_2 afforded a mixture of *cis*- and *trans*-hydroxyglimepiride. Reverse phase preparative HPLC under specific conditions (mobile phase, 40:60 CH_3CN : pH=3 buffer) using ODS column gave optically pure *cis*-hydroxyglimepiride (**2a**) and *trans*-hydroxyglimepiride (**2b**) (Scheme 3). Based on the comparison of their ^1H and ^{13}C NMR spectroscopic data with that of authentic glimepiride (**1**), the structures for the *cis* (**2a**) and *trans* (**2b**) of hydroxyglimepiride were assigned.

Scheme 3



In summary, we have successfully synthesized the *cis* (**2a**) and *trans* (**2b**) of hydroxyglimepiride using a straightforward method.

Introduction

Natural products chemistry described from sponges reminds of terrestrial plant chemistry in its diversity and general distribution over the phylum. Secondary metabolites such as terpenoids, alkaloids and peptides, as well as bioactive fatty acids, lipids and steroids are common in most sponge groups. Biological activity of sponge compounds is very diverse (more than 20 activity categories for various sponge compounds have been found), but cytotoxic, antibiotic, antifungal, antitumour, antiviral, antifouling and enzyme-inhibitory activities are commonest.

Among marine organisms, sponges are the most productive sources of bioactive compounds.[1] Natural products continue to be described from sponges at an increasing rate, so the extent of sponge bioactivity is not yet apparent. So far elucidated structures have been described from about 475 species of sponges, but many species more have been shown to be bioactive in various bioassays. The exact source of the bioactive compounds extracted from sponges is a controversial issue. It has been demonstrated that microsymbionts living in sponges may indeed be the source of bioactive compounds, but that sponge cells themselves also appear to produce them.

Marine Sponge: Source of Biologically Active Peptides

Sponges appeared on the earth in the Cambrian Age (more than 6 million years ago) and are widely found from pole to pole and from intertidal zones to water thousands of meters deep. As biomass, they are enormous and naturally have been a target for extensive studies to isolate new substances since Bergmann's pioneering work on sterols and novel nucleosides in the 1940s.[2] These research activities have resulted in isolation of a variety of new compounds, among which are included structurally novel and highly biologically active metabolites.[3]

Sponges are actually simple cell aggregates, which are usually referred to as “the most undeveloped multicellular animals”. Therefore, sponges provide lodging for many organisms; brittle stars, bivalves, gastropods, crustaceans, and annelid worms are common guests. In addition to these macroorganisms, bacteria, blue-green algae, and dinoflagellates are observed in many species.[4] In an extreme case, bacteria occupy more than 40% of the tissue volume of a sponge.[4] It is therefore reasonable to believe that some sponge metabolites are produced by symbiotic microorganisms. In fact, certain classes of compounds are structurally identical

with or similar to those known from terrestrial microorganisms; representative examples are dysidin from *Dysidea herbacea,*[5] malyngolide A from the blue-green alga, *Lyngbya majuscula,*[6] swinholides and bistheonellides from *Theonella swinhoei*,[7] scytophycins from the blue-green algae *Scytonema* sp.,[8] aurantosides from *Theonella* swinhoei,[9] lipomycin from *Streptomyces aureofaciens,*[10] cylindramide from *Halichondria cylindrata,*[11] and ikarugamycin from *Streptomyces phaeochromogenes*. [12]

Bioactive Sponge Peptides

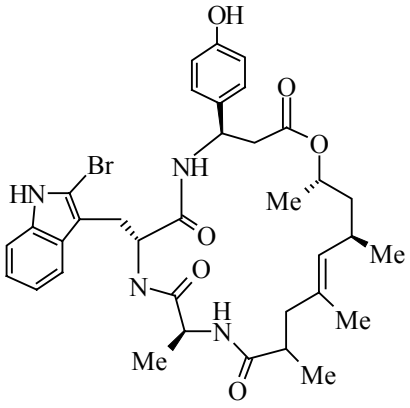
Most marine natural product chemists have attempted to isolate peptides from sponges by using a specific bioassay. The most significant feature of sponge peptides is the presence of unusual amino acids in the molecules, which may conceivably be connected to symbiotic microorganisms, particularly blue-green algae (cyanobacteria). In fact, some peptides from both sponges and blue-green algae share some common features in constituent amino acids. If blue-green algae participate in synthesis of peptides in sponges, what are their roles? Why are some peptides contained in unexpectedly large quantities, while some are present in trace amounts? Why are some peptides highly bioactive? Defensive roles of bioactive metabolites in sponges have been suggested. However, hard-bodied species or those which are overgrown by epiphytes often contain highly bioactive peptides. We may have to wait for the answer until culture of sponge cells, or culture of symbiotic microbes become possible.

Sponge peptides appear to be important potential drugs; cyclotheonamides serve as a model compound for antithrombin drugs; discodermins are potential antitumor promoting drugs; theonellamide F exhibits an antifungal drug; calyculins are useful biochemical reagents.

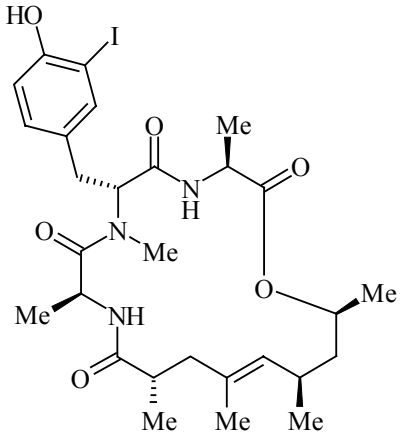
Several reasons can be listed for progress in the chemistry of sponge peptides: (1) Development of reversed-phase HPLC enabled the isolation of peptides from a mixture of related metabolites. (2) Advances in spectroscopy, especially 2D NMR and FAB mass spectroscopy were indispensable for the structural study of peptides from marine sponges, because sequence analysis of unusual peptides cannot be accomplished by Edman degradation due to the presence of blocked N-termini and β- or γ-amino acid residues. (3) Progress in chiral chromatography allowed the assignment of absolute configuration of amino acids with small amounts of material. (4) Marine natural product chemists encountered sponges of the order Lithistida, which includes sponges rich in bioactive peptides.

Peptides From Choristida Sponge

Jaspamide (**1**) was the first bioactive peptide from sponges of the order Choristida;[13] isolation of geodiamolides (**2**) followed shortly.[14] They are four-residue cyclic depsipeptides sharing similar structural features: presence of an 11-carbon hydroxy acid and a halogenated aromatic amino acid.



Jaspamide(1)



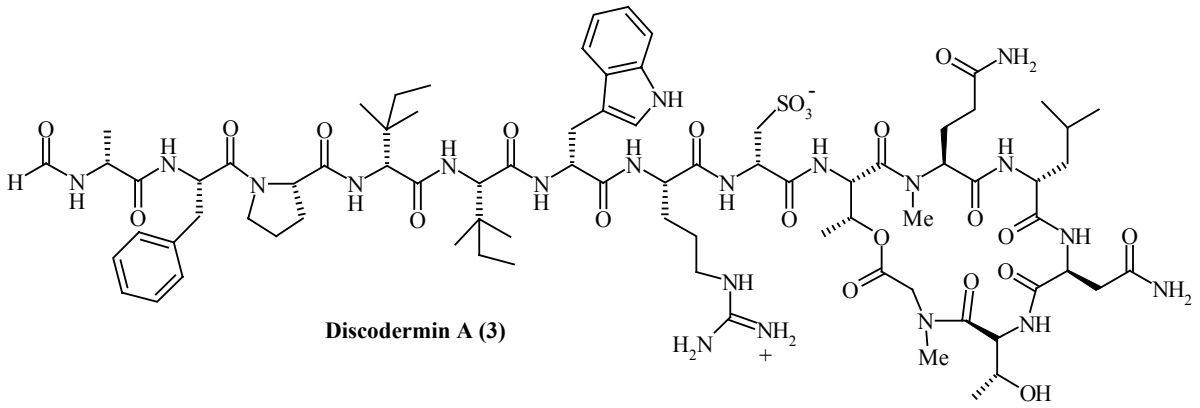
GeodiamolideA (2)

Peptides From Lithistida Sponges

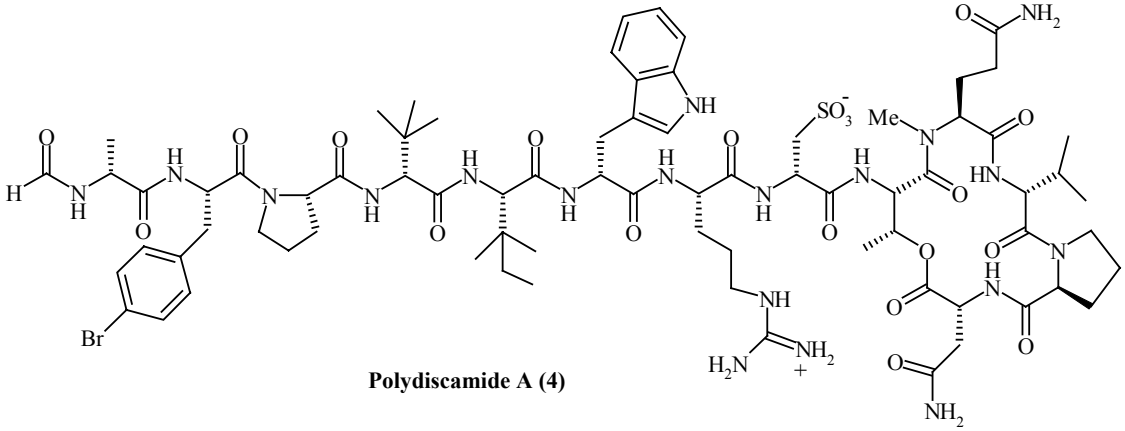
Sponges of two genera *Discodermia* and *Theonella* of lithistida have proved to be a rich source of bioactive metabolites. Most of the secondary metabolites reported from the sponges of this order are nitrogenous, *viz.* isocyano or amino sesquiterpenes, indole derivatives, tetramic acids, and peptides.[3] Similarity between metabolites of lithistid sponges and those isolated from the blue-green algae raised the question of the true producer of these metabolites.[15] It had been proposed that soft-bodied sponges have a higher probability of containing bioactive compounds than those with hard bodies, because they need chemical defense against predators. However, *Discodermia kiiensis* and calyculin-containing *D. calyx,* which not only have hard bodies, but also epiphytes, contain large amount of bioactive metabolites. This is the case for other sponges of the order Lithistida.

Discodermins were the first bioactive peptides isolated from marine sponges,[16] from *Discodermia kiiensis* as antimicrobial constituents. They are tetradecapeptides with the N-terminus blocked by a formyl group and the C-terminus lactonized with the ninth (Thr) residue from the N-terminus. Structural study was mainly performed on the major metabolite, discodermin A (**3**). The other bioactive peptide Polydiscamide A (**4**),[17] possessing common

structural features with Discodermins, was isolated from a Caribbean sponge *Discodermia* sp. Discokiolides (**5a-b**) are unrelated peptides from *Discodermia kiiensis*.[18] They are cyclic depsipeptides containing unusual β-hydroxy acids named discokiic acids as well as β-methoxyphenylalanine residues. Actually, discokiolides could not be isolated as their natural free carboxylic acid forms; they were separated by reversed-phase HPLC after conversion to the methyl esters. Stereochemistry of the component amino acids and hydroxy acid remain to be elucidated.

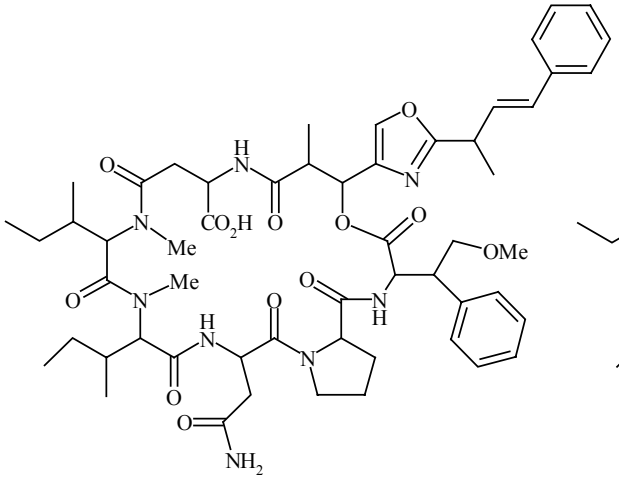


Discodermin A (3)

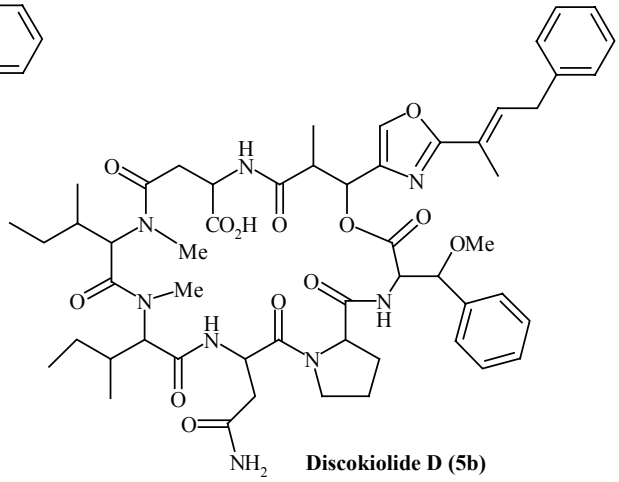


Polydiscamide A (4)

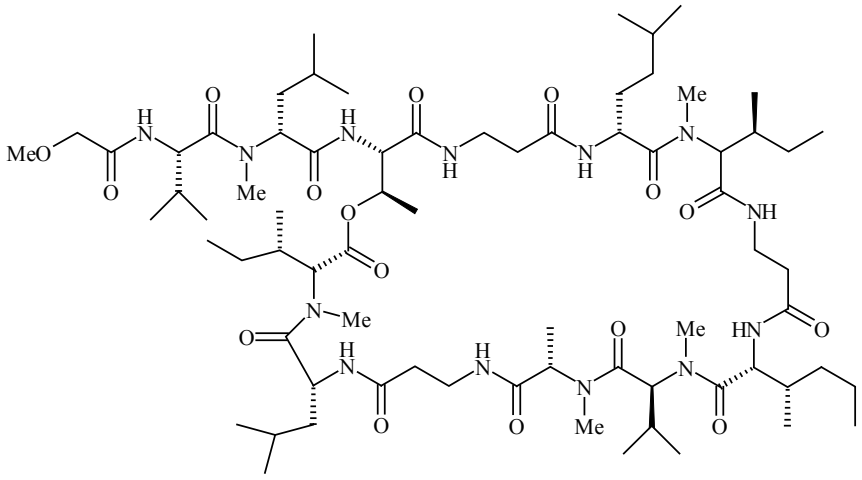
Chemistry of the sponges of the order Lithistida includes *Theonella* sponge collected off Hachijo-jima Island and bistheonellides A and B isolated from the less polar fraction of the EtOH extract.[19] The polar fraction was also active and bioassay-guided isolation afforded theonellamide F (**6**). Further separation of the antifungal fraction of the sponge extract afforded five related peptides, theonellamides (A-E). Although swinholides and bistheonellides are closely related to each other, theonellamides turned out to be quite different from theonellapeptolides (**7**).



Discokiolide A (5a)



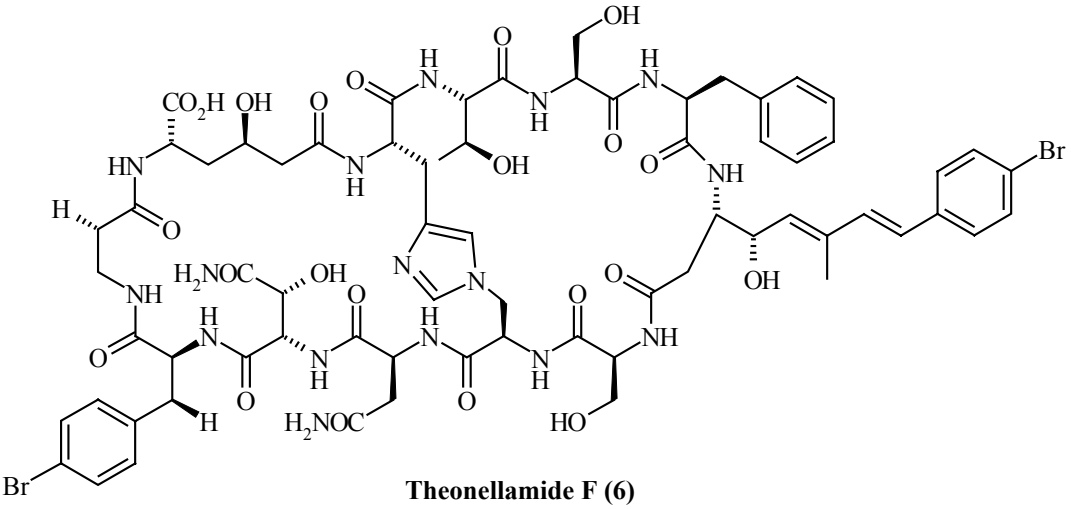
Discokiolide D (5b)



Theonellapeptolide Id (7)

Theonellamide F (**6**),[19] an antifungal and cytotoxic cyclic dodecapeptide, exhibits a characteristic structural feature, especially because of the presence of a histidinoalanine bridge. Another unusual amino acid, (3*S*,4*S*,5*E*,7*E*)-3-amino-4-hydroxy-6-methy1-8-(*p*-bromophenyl)-5,7-octadienoic acid (Aboa), was interesting in view of biogenetic considerations, since closely related amino acid, 3-amino-9-methoxy-2,6,8-trimethyl-l0-phenyl-decadienoic acid (Adda) is found in microcystins,[20] hepatotoxic cyclic peptides, and (2*S*,3*R*,5*S*)-3-amino-2,5,9-trihydroxy-10-phenyldecanoic acid (Ahad) is contained in scytonemin A,[21] a peptide with calcium antagonistic activity, both of which were reported from blue-green algae. Also a biogenetically related δ-hydroxy acid was found in cryptophycin, a cytotoxic peptide from a blue-green alga.[22] To date, *β*-amino acids of these classes have never been encountered in peptides from bacteria, fungi, or plants. Therefore, it

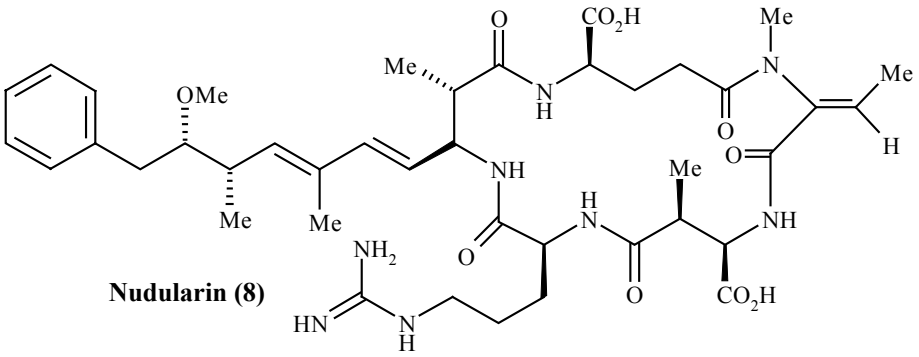
is likely that a symbiotic blue-green alga (algae) play(s) important parts in the production of theonellamide F. Bistheonellides A and B are also related to scytophycins, metabolites of blue-green algae of the genus *Scytonema*. Actually, numbers of blue-green alga(e) were observed in the tissue of a *Theonella* sponge which contains swinholides and theonellapeptolides.



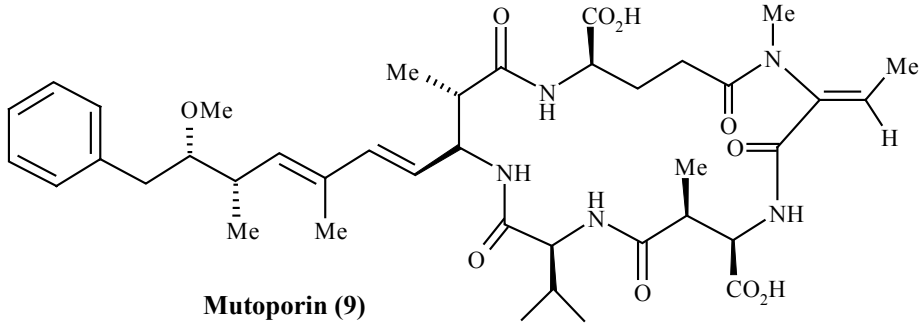
Theonellamide F (6)

Peptide From *Theonella swinhoei* (Lithistida Sponge)

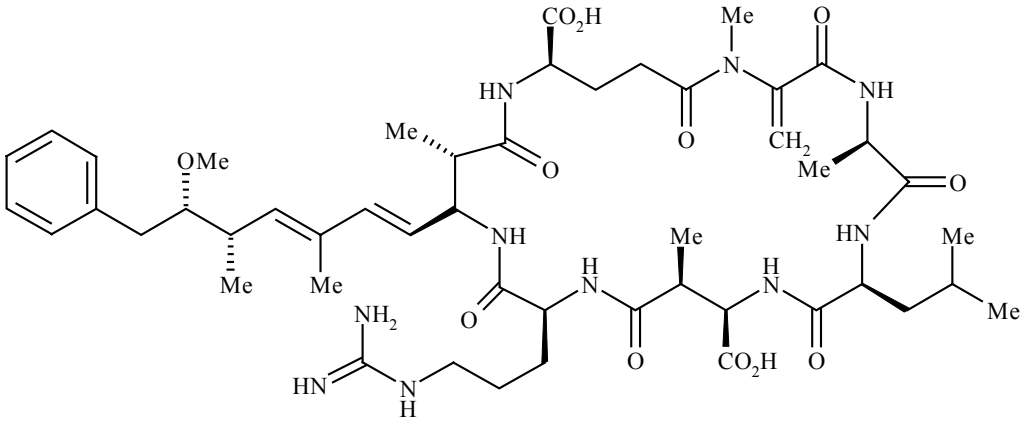
Several years ago marine chemists undertook a biogeographical comparison of the lithistid sponge *Theonella swinhoei* because this species is especially rich in cyclic peptides with uncommon amino acids. The diverse array of *Theonella swinhoei* derived cyclic polypeptides headed by cyclotheonamides,[23] keramamides,[24] motuporin,[25] perthamide B,[26] theonellamides,[27] theonegramide,[28] theonellapeptolides,[29] and theopalauamide[30] made it an ideal candidate for such a project. A further curious circumstance is that there are close similarities between metabolites reported from *Theonella* sponges and cultured cyanobacteria. The most striking is that nodularin (**8**), motuporin (**9**) and microcystins LR (**10**) are marine derived natural products that contain the unusual amino acid (2*S*,3*S*,8*S*,9*S*)-3-amino-9-methoxy-2,6,8-trimethyl-10-phenyl-4,6-decadienoic acid (Adda). Nodularin[31] and the microcystins[20,31] have been isolated from cyanobacteria while motuporin[25] was obtained from the marine sponge *Theonella swinhoei*. Nodularin and microcystins are hepatotoxins and tumor promoters whereas motuporin displays *in* V*itro* cytotoxicity against various cancer cell lines.[31,32]



Nudularin (8)



Mutoporin (9)



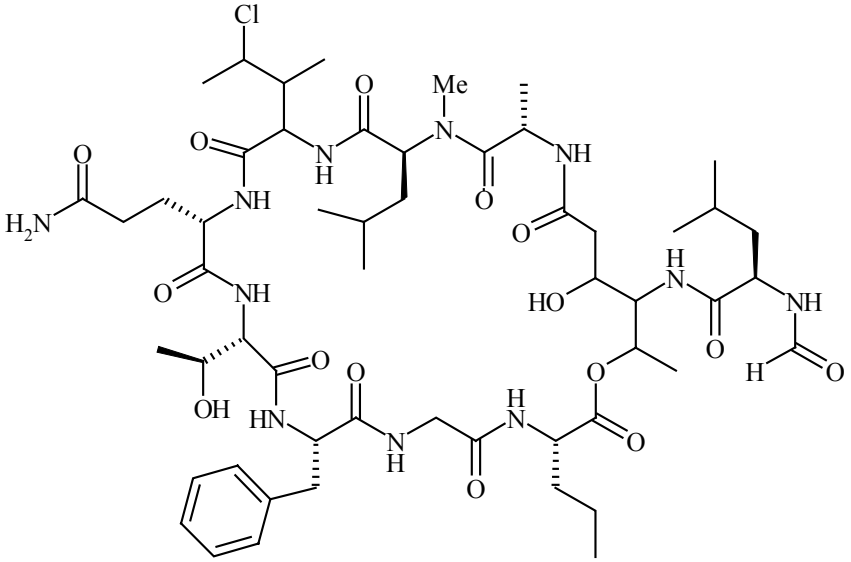
Microcystin LR (10)

Recently Isolated Peptides from *Theonella swinhoei*

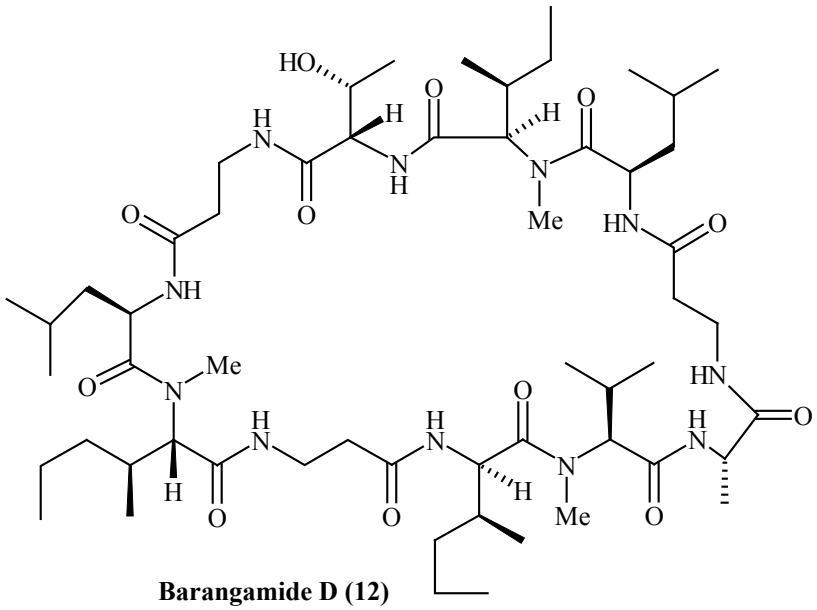
In 1998, Crews *el al.* isolated[33] a novel antifungal cyclic depsipeptide, cyclolithistide A (**11**), from a marine sponge, *Theonella swinhoei*. Higa *et al*. reported[34] the isolation of three new cyclic peptides, barangamides B, C, and D (**12**) and a new depsipeptide, theonellapeptolide IIe along with known theonellapeptolides Ia, Id, Ie, IId from the sponge Theonella swinhoei collected in Baranglompo Island, Indonesia.

Recently,[35] another bioactive cyclic peptide, nagahamide A, was isolated from marine sponge, *theonella swinhoei*. Nagahamide A (**13**) was characterized by seven-residue

depsipeptide containing three unusual amino acids and a polyketide acid. The structural features of nagahmide A, especially the presence of the polyketide acid with a terminal *E,E*-dienoic moiety, were unprecedented among the peptides from natural sources.



Cyclolithistide A (11)



Barangamide D (12)

Isolation of Nagahamide A

In 2002, Fusetani *et al*. reported[35] isolation and structure of nagahamide A (**13**), a depsipeptide, as the major metabolite of a sponge, *Theonella swinhoei*, collected off southern Japan. The *n*BuOH-soluble portion of *n*BuOH/H_2O partition was fractionated by ODS flash chromatography with aqueous MeOH, yielding a crude antifungal, which was to ODS HPLC

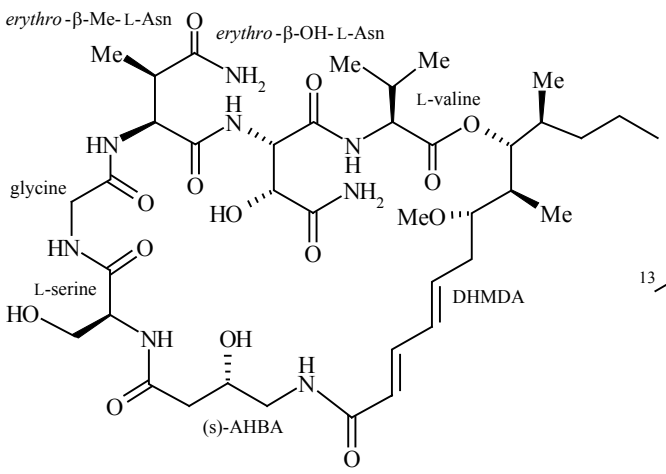
with *n*PrOH/H_2O (32:68) containing 100 nM $NaClO_4$ to afford theonellamides,[27] together with a peak exhibiting antibacterial activity. Further purification ODS HPLC with *n*PrOH/H_2O (24:76) containing 100 nM $NaClO_4$ afforded nagahamide A, as a white powder.

Structure Elucidation of Nagahamide A (13)

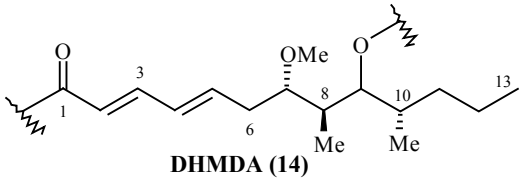
The peptide nature of nagahamide A was evident by the interpretation of ^{1}H NMR, ^{13}C NMR, COSY, HOHAHA, NOESY, HMBC and HMQC spectroscopies. The sequence of amino acid residues was determined by NOESY and HMBC spectra. The absolute configuration of amino acid residues was established by retention times of standard amino acids and Marfey's analysis. The ^{1}H NMR spectrum of **13** indicated the presence of ten amide and six α-protons whereas ^{13}C NMR revealed the presence of eight amide carbons and six α-carbons. The amino acid analysis of the acid hydrolysate resulted in 1 mol each of Glycine, Valine and Serine, together with three unusual amino acids. The analysis of COSY spectrum led to two *β*-substituted asparagine residues, one of which was assigned as *β* hydroxyasparagine (*β*-OH-Asn) on the basis of the presence of the *β*-methine proton (δ 4.06) attached to a carbon at δ 72.0. This proton showed NOESY cross-peaks with a pair of amide protons (δ 7.06 and 7.18). The other asparagine derivative was assigned as *β* methylasparagine (*β*-Me-Asn); the α-proton was coupled to the *β*-proton (δ 2.81), which was in turn correlated with a methyl signal (δ 1.01). The *β*-proton exhibited NOESY cross-peaks with a pair of amide protons (δ 6.93 and 7.46). The remaining unusual amino acid residue was a *γ*-amino acid; connectivities of NH-CH_2-CH(OH)-CH_2CO were readily derived by COSY and HOHAHA data, thereby establishing the 4-amino-3-hydroxybutanoic acid (AHBA) residue.

The remaining ^{1}H NMR signals consisted of four olefinic protons, four methines including two oxymethines, three methylenes, and four methyls including one oxymethyl. Interpretation of COSY data led to connectivities from H-2 to H-6; H-6 protons were coupled to the oxymethine (H-7), which showed no correlation with other protons. The other oxymethine proton (H-9) was coupled to a two-proton multiplet centering at 1.68 ppm (H-8 and H-10), which was further coupled to two methyl signals at δ 0.75 (Me-8) and 0.77 (Me-10). The HOHAHA spectrum led to connectivities from H-10 to H-13, while HMBC cross-

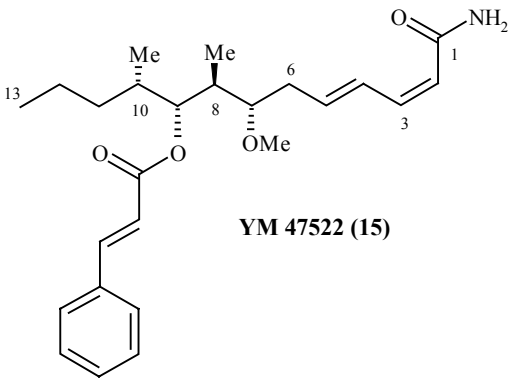
peaks not only connected C-7 and C-8 but also placed a methoxyl group on C-7, thus constructing 8,10-dimethyl-9-hydroxy-7-methoxytrideca-2,4-dienoic acid (DHMDA, **14**).



Nagahamide A (13)



DHMDA (14)



YM 47522 (15)

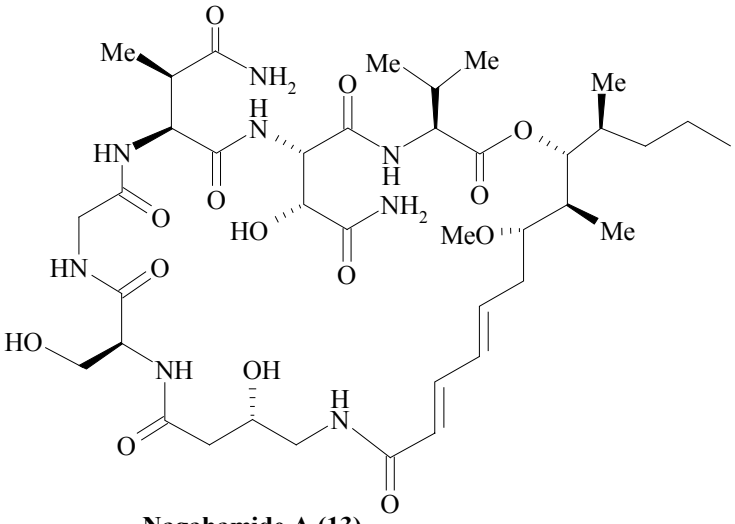
The sequence of the above residues was established by HMBC cross-peaks: Val-NH/OH-Asn-CO; OH-Asn-NH/Me-Asn-CO; Me-Asn-NH/Gly-CO; Gly-NH/Ser-CO; Ser-NH/AHBA-CO; AHBA-NH/DHMDA-CO; DHMDA-H9/Val-CO.

The absolute configuration of Val, Ser and AHBA was determined to be L by application of Marfey's method.[36] The absolute configuration of *β*-OH-Asn in the acid hydrolyzate of **13** was determined by Marfey's method using *erythro*-*β*-OH-L-Asn, which was prepared from the acid hydrolyzate of theonellamide F[27] as a standard and assigned the configuration as *erythro*-*β*-OH-L-Asn. Similarly the absolute configuration of *β*-Me-Asn in the acid hydrolyzate of **13** was established by Marfey's analysis using *erythro*-*β*-OH-D-Asn obtained from the acid hydrolyzate of microcystin LR[20] as a standard and assigned the configuration as *erythro*-*β*-Me-L-Asn.

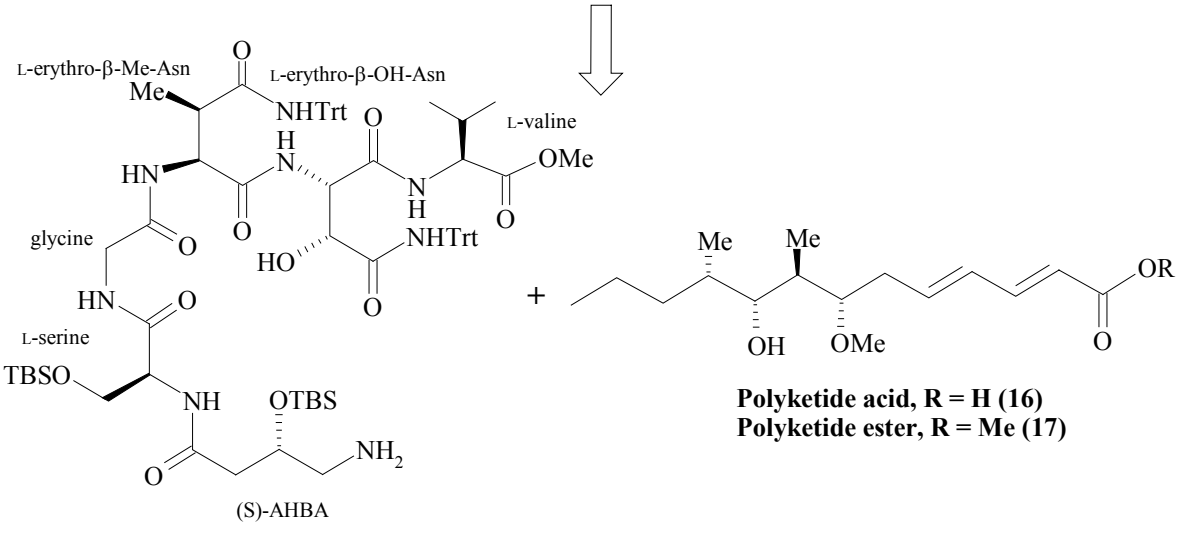
The important core of nagahamide A is the presence of DHMDA (**14**) residue, which is closely related to YM-47522 (**15**), an antifungal metabolite of *Bacillus* sp., except the geometry of one double bond. The stereochemistry of **15** was determined to be 7*S*,8*S*,9*R*,10*S* by synthesis.[37] The relative stereochemistry of the DHMDA was assigned by comparison of NMR data with those of **15**; but the absolute stereochemistry of the DHMDA residue in **14** remains to be elucidated.

Present Work

The interesting biological profile coupled with structural parameters of nagahamide A (**13)** prompted us to undertake its synthesis. The structure of nagahamide A[35] is characterized by six amino acids peptide backbone joined together in a macrocyclic structure and incorporated a novel polyketide chain (**16**) (Figure 1). The six amino acids peptide backbone consists of three unusual amino acids. The polyketide acid (**16**) of nagahamide A (**13)** contains four contigous chiral centers with a terminal *E,E*-dienoic moiety.[37c]



Nagahamide A (13)



Peptide backbone (18)

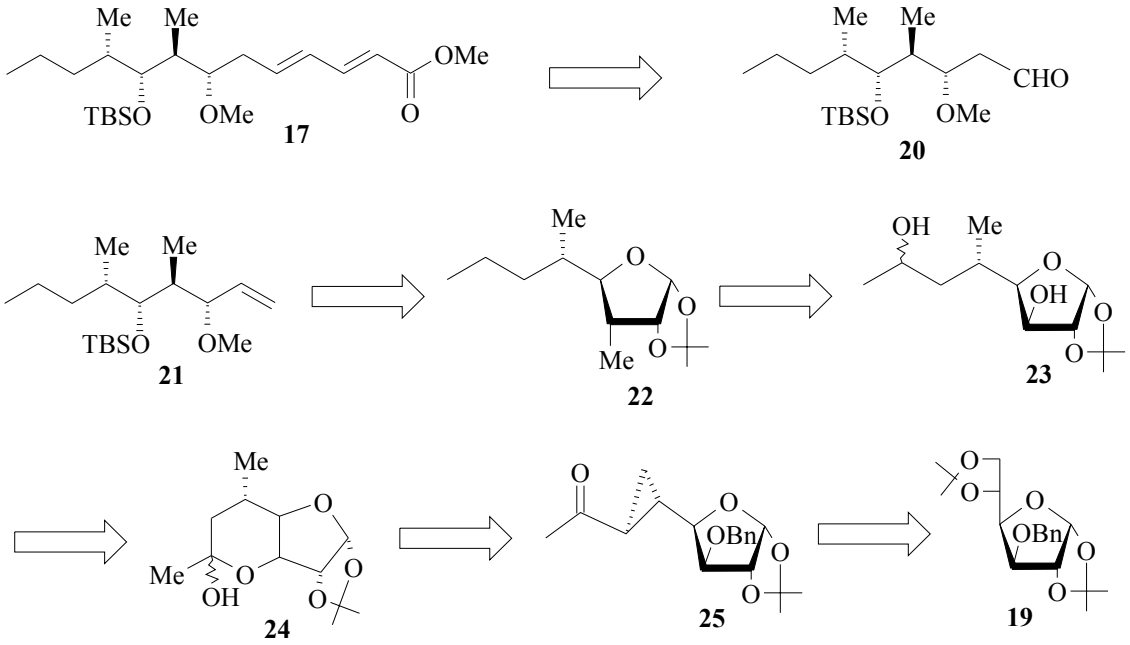
Polyketide acid, R = H (16)
Polyketide ester, R = Me (17)

Figure 1

Synthesis of polyketide ester (17)

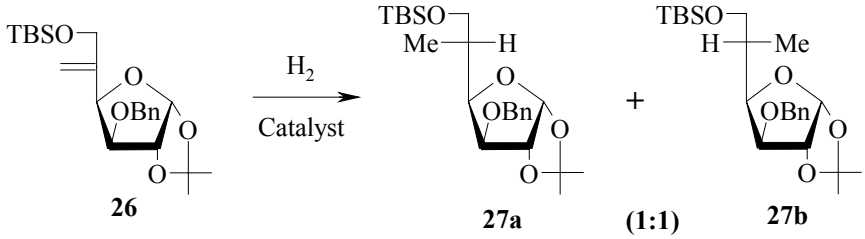
For the stereoselective synthesis of **17**, a carbohydrate based chiral pool approach was considered. Accordingly, a novel strategy was envisaged which involved stereoselective synthesis of the cyclopropyl sugar derivative (**25**) followed by reductive opening of cyclopropyl ring to install stereoselectively the methyl and propyl groups would provide **22** (Scheme 1). The Wittig-Horner chain homologation could eventually complete the synthesis of polyketide ester (**17**) of nagahamide A (**13**).

Scheme 1: ***Retrosynthetic analysis for 17***



Prior to discussion on the proposed strategy, it is pertinent to mention some issues observed during off-templete C_5-alkylation reaction.[38] For example, Fraser-Reid *et al*.[39] have studied the hydrogenation of 3-*O*-benzyl-6-*O*-(*tert*-butyldimethylsilyl)-5-deoxy-1,2-*O*-isopropylidine-5-*C*-methylene-α-D-*xylo*-hexofuranose (**26**) with Pd/C-H_2, which gave a 1:1

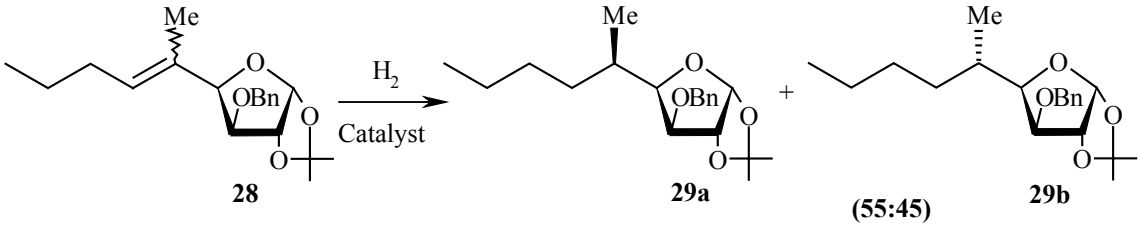
Scheme 2



mixture of the C-5 epimers **27a** and **27b** (Scheme 2), implying that compound **26** did not react with any favored conformation.

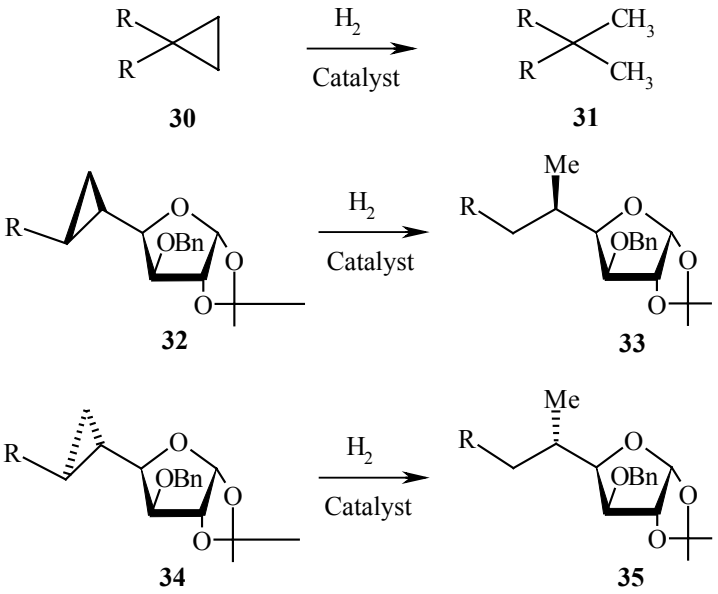
Gurjar *et al*.[38a] have reported the hydrogenation of more substituted olefin **28** also produced a mixture (55:45) of diastereomers **29a** and **29b** (Scheme 3), indicating that compound **28** with four rigid chiral centers did not show any Π-facial selectivity at C-5.

Scheme 3



But the cyclopropane ring however, can be cleaved at the least substituted bond by catalytic hydrogenation in a general synthesis of *gem*-dimethyl groups or to introduce stereoselectively a methyl and an alkyl substituents.[40] The introduction of a methyl and alkyl substituents can be realized by regioselective reductive fission of three-membered carbocycles (Scheme 4).

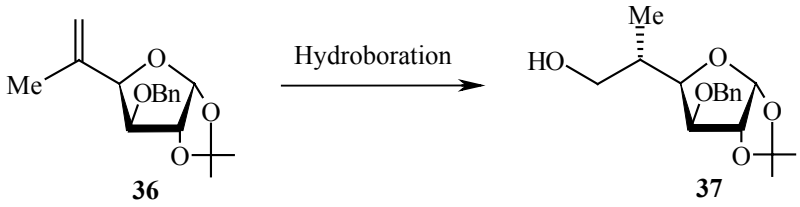
Scheme 4



Fraser-Reid and coworkers,[39] however, circumvented the diastereofacial selectivity of hydration with hydroboration-oxidation reaction. For instance, compound **36** underwent

hydroboration-oxidation reaction (Scheme 5) leading to **37** which could be explained by means of the Redlich and Neumann[41] postulations.

Scheme 5

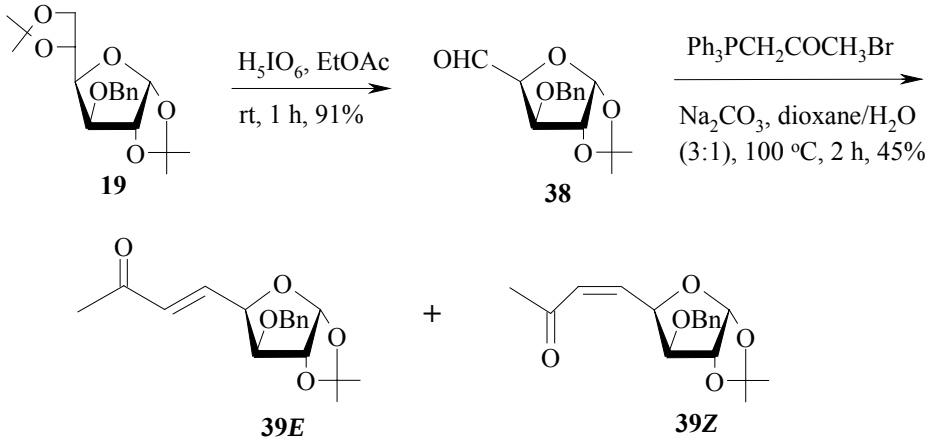


36 **37**

From these reports we envisaged an approach to selectively carry out C_5-alkylation by initiating the 5,6-cyclopropyl sugar derivative (**25**). The cyclopropanated carbohydrate derivatives have started to introduce much interest in the synthesis of bioactive compounds and the development of new synthetic methods. However, no report has got been published to describe the preparation of 5,6-cyclopropyl sugar derivatives.

In order to investigate stereocontrolled cyclopropanation reaction, the required cyclopropyl derivative (**25**) was prepared as follows. Compound **19** was treated with H_5IO_6 in EtOAc at rt to afford an aldehyde **38**.[42] The Wittig condensation of **38** with acetonyltriphenylphosphonium bromide[43] in 3:1 dioxane/H_2O at reflux temperature gave a 3:2 mixture of *E*/*Z* isomers of *α*,*β*-unsaturated ketone (**39*E***, **39*Z***) (Scheme 6). The *E*/*Z* isomers were conveniently separated by silica gel chromatography. In the ^{1}H NMR spectrum of **39*E***, the olefinic protons appeared as a set of two double-doublet at 6.37 ppm ($J_{6,4}$ = 1.5 Hz, $J_{6,5}$ =

Scheme 6



19 **38**

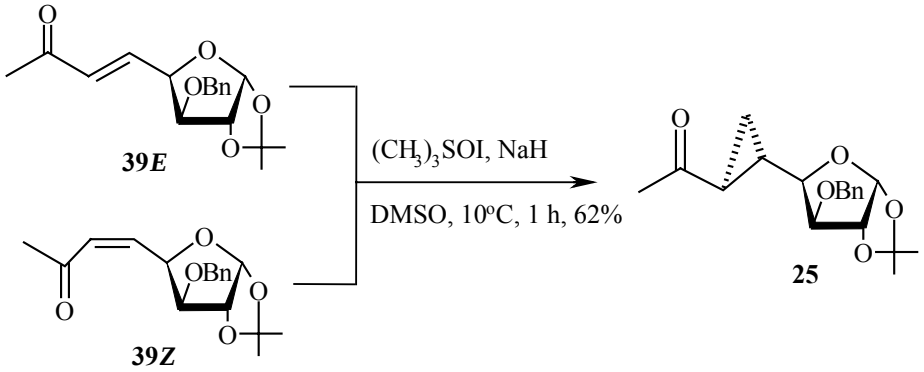
39E ***39Z***

16.2 Hz) and 6.76 ppm ($J_{5,4}$ = 5.4 Hz, $J_{5,6}$ = 16.2 Hz), thereby confirming the *trans*-stereochemistry. On the other hand, the ^{1}H NMR spectrum of **39*Z*** showed that the olefinic

protons resonated as multiplets between 6.17-6.33 ppm. All the other protons resonated at their expected chemical shift values.

Our next concern involved the stereoselective synthesis of cyclopropane intermediate (**25**). For this endeavor, the major isomer **39*E*** was treated with the sulfur ylide [$(CH_3)_2S(O)CH_2$] (prepared from trimethylsulfoxonium iodide[44] and NaH) in DMSO at 10 ^oC for 1 h to furnish **25** (Scheme 7).[45] The ^1H NMR and ^{13}C NMR spectra clearly indicated that only one product had been obtained. Although the absolute stereochemistry of **25** could not be determined at this stage, we believe[41] that the steric influence of C-3 substituent (OBn) has influenced the stereochemical outcome of the reaction. A probable mechanistic consideration has been presented in Figure 2. The ^1H NMR spectrum of **25** showed the four-cyclopropane ring protons at 1.19 ppm (ddd, 1 H, J = 4.1, 6.6, 9.3 Hz), 1.37 ppm (dt, 1 H, J = 4.4, 9.3 Hz), 1.90 ppm (dt, 1 H, J = 4.4, 6.6 Hz) and 1.94-1.98 ppm (m, 1 H). The other protons resonated at their respective chemical shift values. The ^{13}C NMR and elemental analysis further supported the assigned structure **25**.

Scheme 7



Gratifyingly, compound **39*Z*** also underwent cyclopropanation with the same stereoselectively to produce **25**, comparable with the sample obtained above (Scheme 7). These results could be rationalized by the mechanism of cyclopropanation reaction, which first involved the Micheal type 1,4-addition followed by cyclisation (Figure 2).

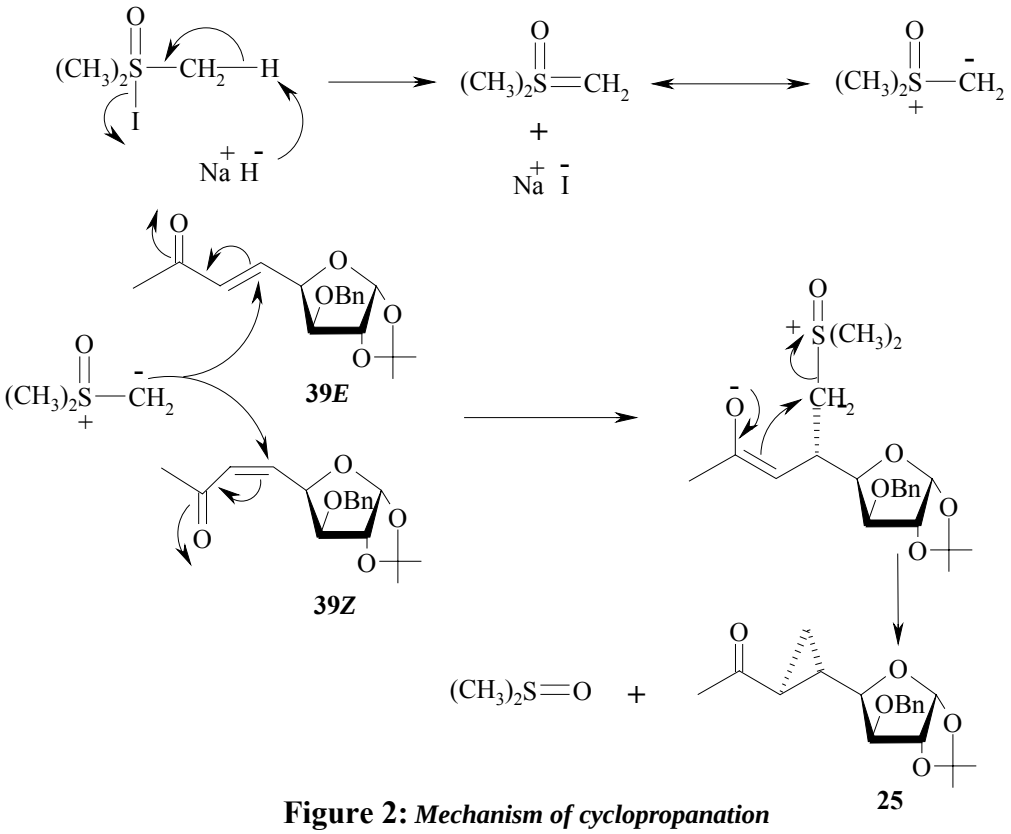
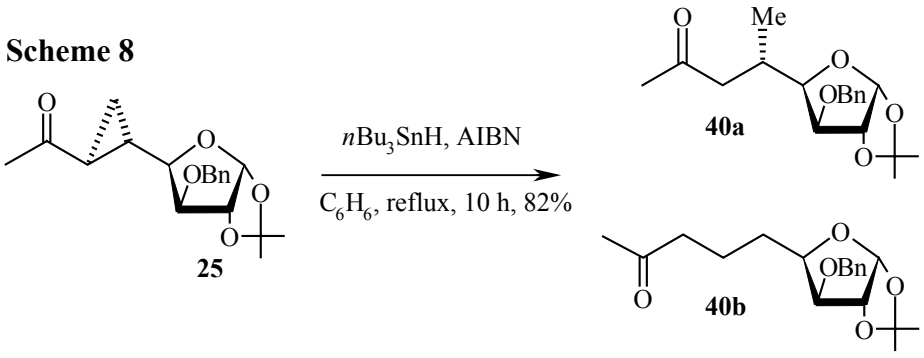


Figure 2: ***Mechanism of cyclopropanation***

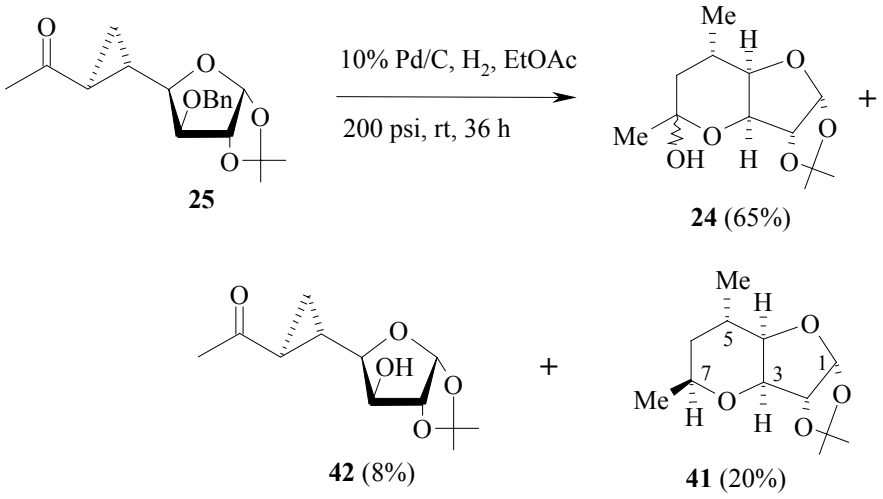
Our next step involved radical mediated[46] cyclopropyl ring opening reaction in which **25** was treated with nBu$_3$SnH in the presence of catalytic amount of AIBN in refluxing benzene for 10 h (Scheme 8). The ^{1}H NMR spectrum of the newly formed product did not correspond to the structure **40a**. However, based on the ^{1}H NMR and ^{13}C NMR spectroscopic data, structure **40b** was proposed. For instance, in the ^{1}H NMR spectrum, the absence of a doublet due to C$_5$-Me group clearly indicated the formation of linear structure **40b**. The DEPT spectrum revealed the presence of four methylene groups resonated at 20.4, 27.3, 43.4 and 71.6 ppm also supported the structure of **40b**.

Scheme 8

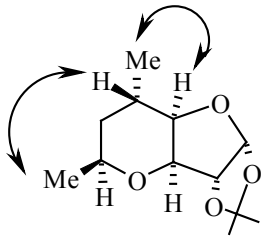


Next our attention directed for the regioselective reduction[47] of the cyclopropane ring of **25** to introduce the methyl and propyl substituents at C-5. Compound **25** was subjected to hydrogenation over 10% Pd/C in EtOAc at 200 psi at rt for 36 h to produce predominantly **24** along with **41** and **42** as minor products (Scheme 9). In order to increase the reaction rate, the temperature was raised to 60 ^{o}C, but this modification gave **41** as a major product. Compound **41** was originated from the over reduction of **24**. The ^{1}H NMR, ^{13}C NMR spectra, elemental

Scheme 9



analysis and NOESY experiments confirmed the assigned structure **41**. For instance, in the ^{1}H NMR spectrum, the C_5-Me resonated as a doublet at 1.09 ppm (J = 7.6 Hz) whereas the C_7-Me appeared at 1.12 ppm (J = 6.1 Hz) as a doublet. The appearance of two multiplet between 2.23-2.38 ppm and 3.58-3.64 ppm corresponding to C_5-methine and C_7-methine protons respectively. Other resonances were fully in agreement with the assigned structure **41**. The NOESY spectrum of **41** showed a strong NOE between C_5-Me and C_4-methine proton indicating their *cis*-relationship. The C_7-Me showed a NOE signal with C_5-methine proton and



41

Figure 3: ***NOE studies on 41***

confirmed the *trans*-relationship between the C_7-Me and C_5-Me groups (Figure 3). These observations evidently confirmed that parent product **25** had stereochemical assignments as indicated.

The assignment of absolute stereochemistry at C-5 center of cyclopropane derivative (**25**) was further determined based on single crystal X-ray crystallographic studies[48] of the debenzylated product **42**. The ORTEP diagram of **42** (Figure 4) revealed that the cyclopropanation occurred from the α-face. The details of crystal data and structure refinement (Table 1), bond lengths and bond angles (Table 2) and torsion angles (Table 3) are given at the end of this section (Page No. 53 to 55).

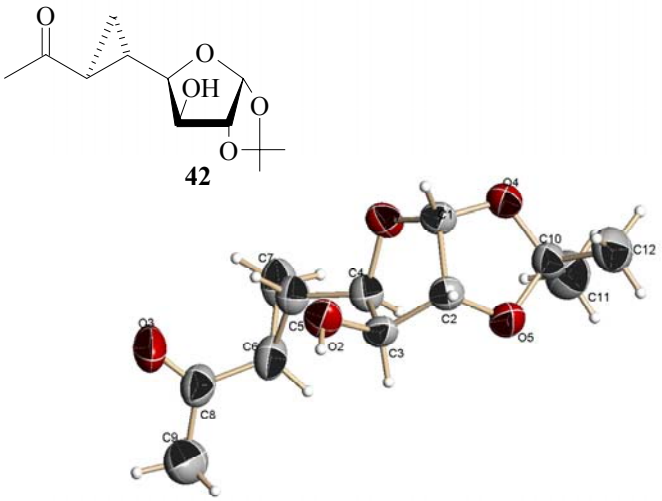
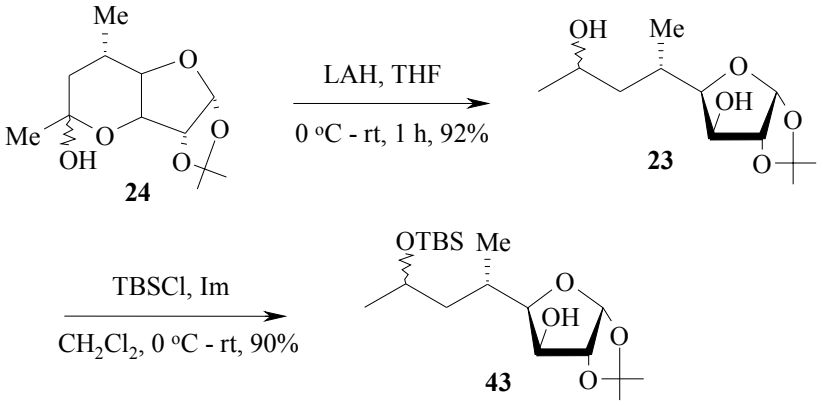


Figure 4: ***X-ray crystal structure of 42***

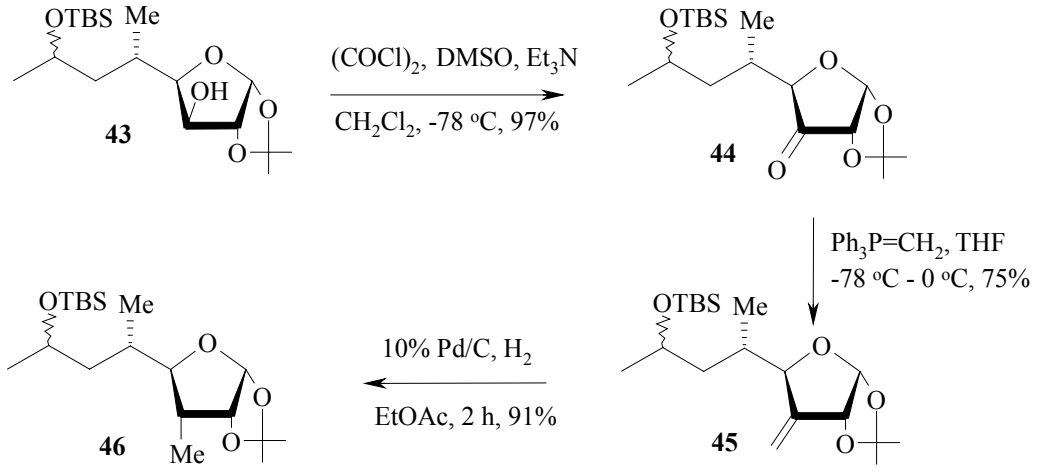
Our next concern involved the introduction of methyl group at C-3 center for which **24** was reduced with LAH in THF to provide (1:1) diastereomeric mixture (based on ^{1}H and ^{13}C NMR spectra) of diol **23** (Scheme 10). It is pertinent to mention that the newly formed C-7 stereocenter of **23** was of no consequence, as it would finally be destroyed. Therefore, we decided to continue our synthetic strategy with a mixture. The less hindered secondary hydroxyl group of **23** was protected as its TBS ether (**43**) by using TBSCl and imidazole in CH_2Cl_2 (Scheme 10). In the ^{1}H NMR spectrum of **43**, the characteristic signals due to TBS group were located in the upfield region. The ^{13}C NMR spectroscopy and elemental analysis were in full agreement with the assigned structure **43**.

Scheme 10



The transformation of **43** into **46** was accomplished in the following manner. Oxidation of **43** under Swern[49] condition using $(COCl)_2$, DMSO, and Et_3N at –78 °C afforded **44** (Scheme 11) which was subjected to one carbon Wittig homologation[50] with methylenetriphenylphosphorane. The *exo*-methylene derivative (**45**) showed in its ^1H NMR spectrum signals due to *exo*-methylene protons as multiplet between 4.80-4.86 ppm. Subsequent hydrogenation of double bond present in **45** over 10% Pd/C in EtOAc under H_2 atmosphere for 2 h gave **46** (Scheme 11). In the ^1H NMR spectrum of **46**, a characteristic triplet due to H-2 proton was observed at 4.50 ppm (J = 3.9 Hz) indicating that the H-2 was

Scheme 11

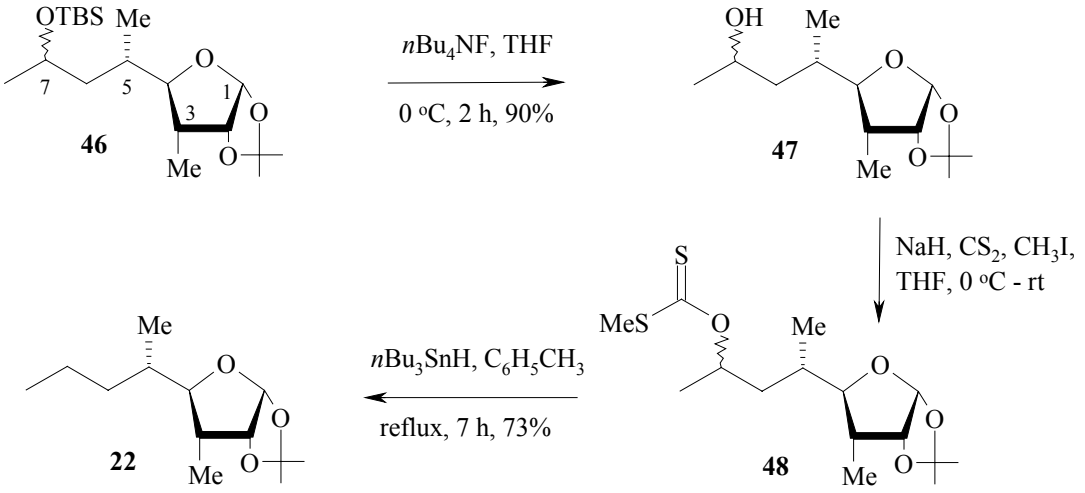


cis to both H-1 and H-3. Due to 1,2-isopropylidine group, the hydrogenation of C_3-*exo*-methylene group was expected to occur from β-face. The characteristic three doublets observed at 0.84 ppm (J = 7.3 Hz), 1.01 ppm (J = 6.6 Hz) and 1.13 ppm (J = 6.3 Hz) were attributed to methyl groups present at C_5-Me, C_3-Me and C_7-Me. Other resonances were in

accord with the assigned structure **46**. The structure of **46** was further confirmed by its ^{13}C NMR spectroscopy and elemental analysis.

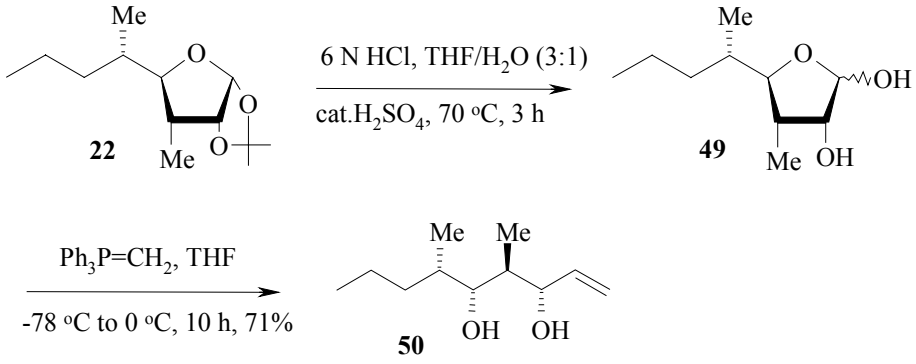
In order to deoxygenate the hydroxyl group at C-7, Barton radical deoxygenation protocol[51] was adopted. Thus, the TBS group of **46** was cleaved by using TBAF in THF at 0 ^{o}C and then transformed into the xanthate derivative (**48**) by treating with NaH, CS_2 and MeI in THF (Scheme 12). Treatment of **48** with nBu$_3$SnH in presence of AIBN in refluxing toluene for 7 h gave the 7-deoxy derivative (**22**). The structure of **22** was confirmed by its ^{1}H NMR, ^{13}C NMR spectroscopy and elemental analysis. For instance, the ^{1}H NMR spectrum of **22** showed a clean triplet at 0.90 ppm (J = 7.1 Hz) due to terminal methyl group.

Scheme 12



Compound **22** was converted into the lactol derivative (**49**) by de-isopropylidination with 6 N HCl in THF:H_2O (3:1) at 70 ^{o}C followed by one carbon Wittig olefination[48] with

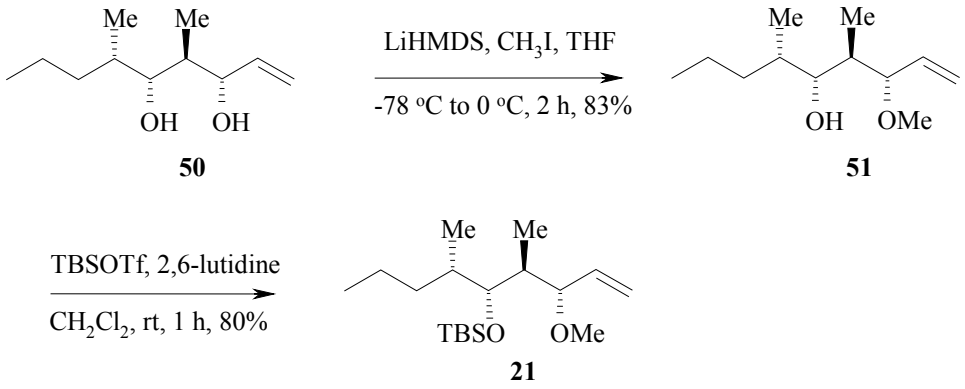
Scheme 13



methylenetriphenylphosphorane to afford **50**. The formation of **50** was confirmed by its ^{1}H NMR, ^{13}C NMR spectroscopy and elemental analysis. For example, in the ^{1}H NMR spectrum, a multiplet between 5.16-5.27 ppm integrating for two protons and another multiplet between 5.80-5.92 ppm integrating for one proton were due to terminal double bond protons.

The advantage of higher reactivity of allylic hydroxyl group was explored for selective methylation. Thus **50** was treated with MeI and LiHMDS at –78 ^{o}C to 0 ^{o}C for 2 h to yield **51** (Scheme 14). In the ^{1}H NMR spectra of both **50** and **51**, the resonances due to H-3 were clearly apparent as a triplet but whereas the chemical shift of all other protons were comparable, that due to H-3 showed an upfield shift of 0.56 ppm. The secondary hydroxyl group of **51** was protected as its TBS ether (**21**) by using TBSOTf and 2,6-lutidine in CH_2Cl_2 (Scheme 14). In the ^{1}H NMR spectrum of **21**, the two singlets in the upfield region at 0.06 and 0.89 ppm integrating for six and nine protons respectively were assigned to TBS group. All other protons resonated at their respective chemical shift values.

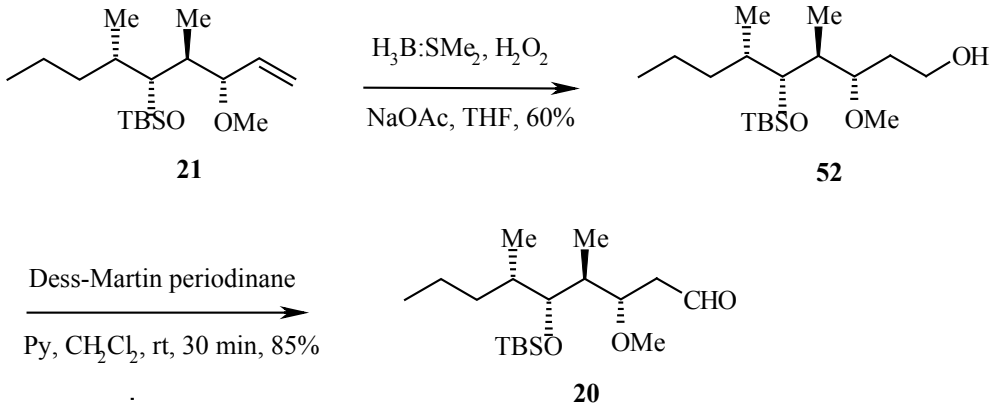
Scheme 14



50 **51** **21**

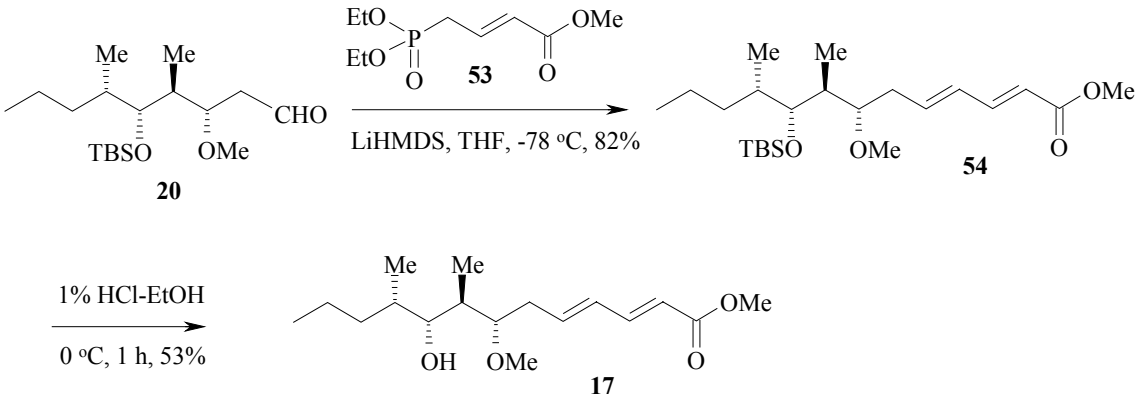
With a view to transform **21** into the corresponding aldehyde derivative (**20**), **21** was exposed to $H_3B{:}SMe_2$ in THF followed by oxidative workup with H_2O_2 and NaOAc to produce the desired primary alcohol **52** (Scheme 15). In the ^{1}H NMR spectrum, a characteristic triplet at 3.78 ppm (J = 5.6 Hz) clearly revealed the presence of CH_2OH group. In addition, the ^{13}C NMR spectrum showed a peak at 61.7 ppm corresponding to CH_2OH. The preparation of aldehyde **20** was accomplished by Dess-Martin periodinane[52] oxidation of **52** in CH_2Cl_2 at rt (Scheme 15).

Scheme 15



Having made the aldehyde **20** with correct stereocenters, our attention turned to introducing the *E*,*E*-dienoate moiety. For this endeavor, Wittig-Horner chain homologation of **20** by reaction with methyl 4-(diethylphosphono) crotonate (**53**)[53] in the presence of LiHMDS furnished exclusively *E*,*E*-dienoate **54** (Scheme 16). The structure of **54** was thoroughly investigated by its ^{1}H NMR, ^{13}C NMR spectroscopy and elemental analysis. The ^{1}H NMR of **54** showed H-2 at 5.69 ppm ($J_{2,3}$ = 15.2 Hz) as a doublet, H-3 at 7.25 ppm ($J_{3,2}$ = 15.2 Hz, $J_{3,4}$ = 9.9 Hz) as a double-doublet and H-4 as a doublet of doublet at 6.14 ppm ($J_{4,3}$ = 9.9 Hz, $J_{4,5}$ = 15.1 Hz). A characteristic doublet of triplet observed due to H-5 proton at 6.10 ppm ($J_{5,4}$ = 15.1 Hz, $J_{5,6}$ = 7.8 Hz). From the above observations, it was clearly revealed that the presence of *E*,*E*-dienoate moiety in **54**.

Scheme 16



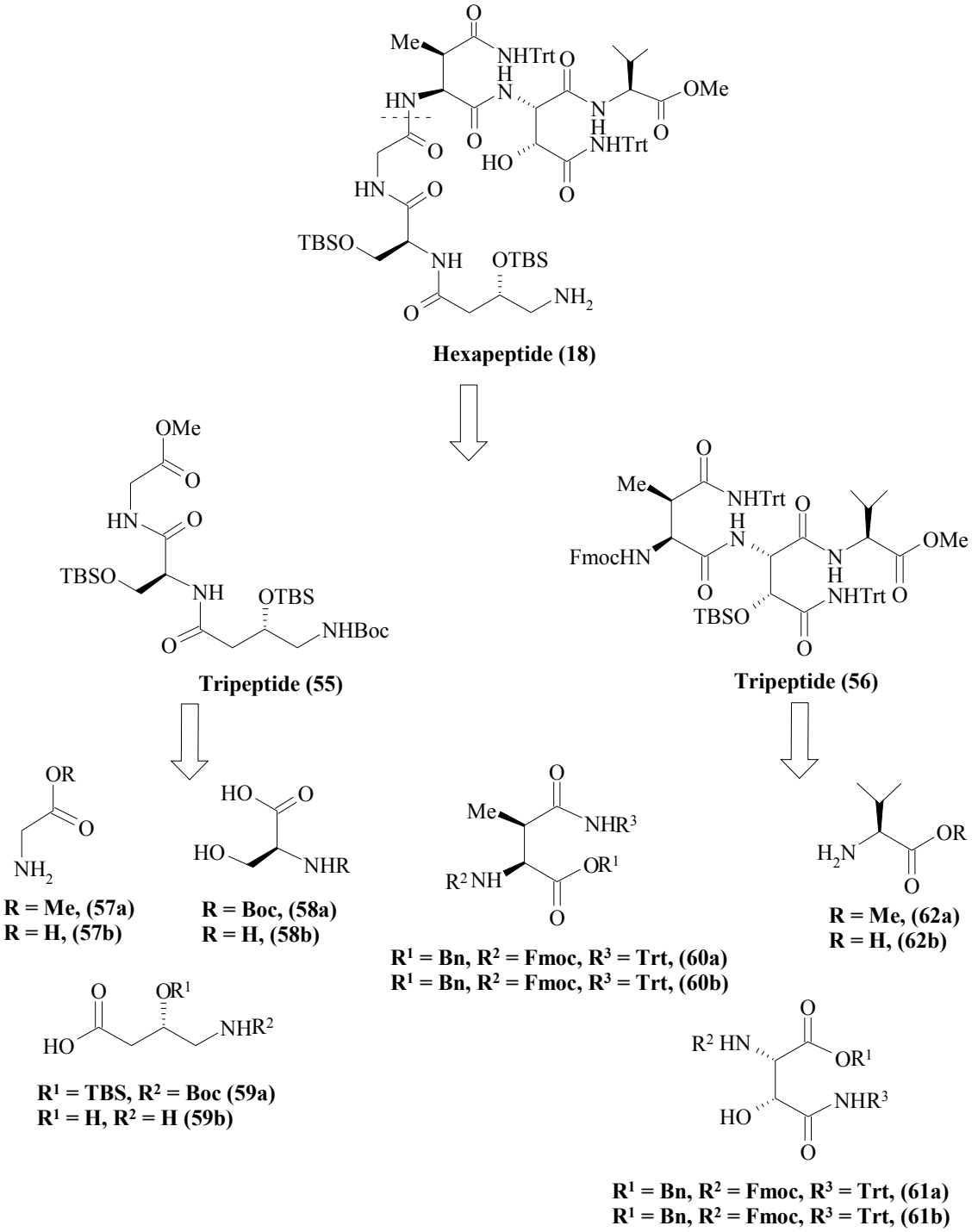
To complete the synthesis of polyketide ester **17**, the deprotection[54] of TBS was carefully carried out with 1% HCl-EtOH at 0 °C to afford **17** (Scheme 16). The structure of **17** was confirmed by its ^{1}H NMR and ^{13}C NMR spectroscopic data. For example, its ^{1}H NMR

spectrum revealed signals due to olefin protons at δ 5.69 (d, $J_{2,3}$ = 15.2 Hz), 7.25 (dd, $J_{3,2}$ = 15.2 Hz, $J_{3,4}$ = 9.9 Hz), 6.14 (dd, $J_{4,3}$ = 9.9 Hz, $J_{4,5}$ = 15.1 Hz) and 6.10 (dt, $J_{5,4}$ = 15.1 Hz, $J_{5.6}$ = 7.8 Hz). A characteristic triplet due to C_{13}-Me protons observed at 0.91 ppm (J = 7.5 Hz).

Studies Towards the Synthesis of Hexapeptide (18)

After the successful completion of the synthesis of polyketide chain (**17**) with all required stereocenters, our attention drawn towards the synthesis of the hexapeptide (**18**). The

Scheme 17: ***Retrosynthetic analysis for 18***

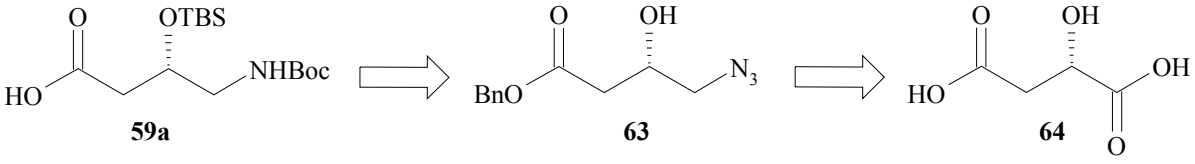


hexapeptide (**18**) was characterized by two key subunits composed of the tripeptides (**55**) and (**56**). The tripeptide (**55**) contains residues glycine (**57b**), L-serine (**58b**) and unusual *γ*-amino acid, (*S*)-4-amino-3-hydroxy-butanoic acid (**59b**) whereas tripeptide (**56**) possesses residues L-valine (**62b**) and two unusual amino acids, namely, L-*erythro*-*β*-Me-asparagine (**60b**) and L-*erythro*-*β*-OH-asparagine (**61b**) (Scheme 17). The indicated coupling site was carefully chosen to minimize the use of protecting groups and to prevent late stage opportunities for racemization.

Synthesis of (*S*)-Boc-AHBA (TBS)-OH (59a)

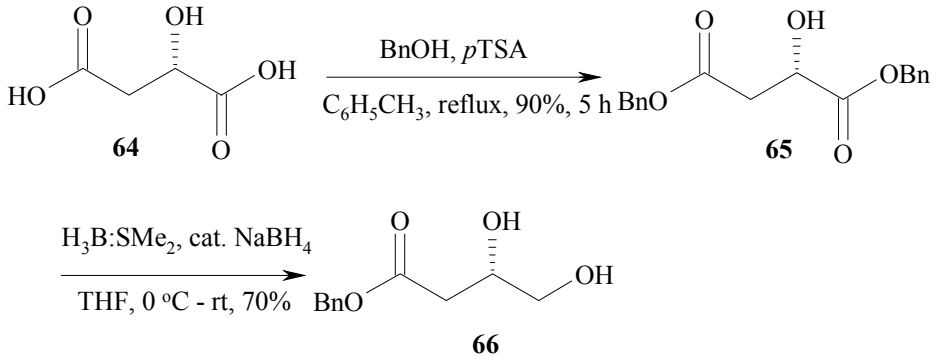
The general strategy for the synthesis of **59a** is described in the retrosynthetic analysis in Scheme 18.

Scheme 18: ***Retrosynthetic analysis for 59a***



The synthesis of **59a** was initiated with a readily available L-malic acid (**64**), which was converted into dibenzyl L-malate (**65**) by the known procedure[55a] using BnOH and *p*TSA in $C_6H_5CH_3$ (Scheme 19). In the ^{1}H NMR spectrum of **65**, the benzylic protons resonated at 5.15 ppm as ABq (J = 12.9 Hz). The conversion[56] of **65** into **66** was effected by regioselective reduction of benzyloxy carbonyl group adjacent to hydroxyl group with $H_3B{:}SMe_2$ and

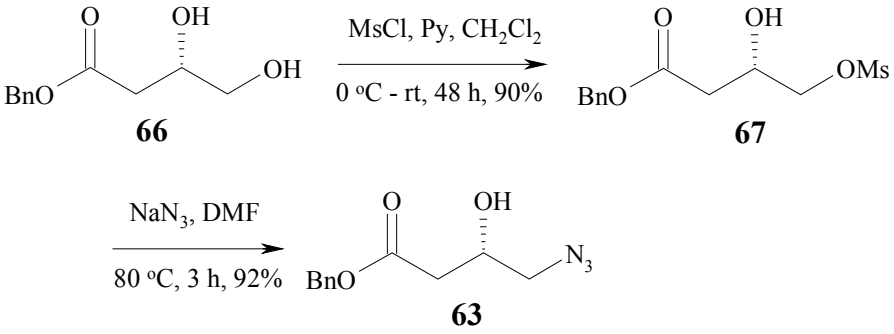
Scheme 19



$NaBH_4$ in THF (Scheme 19). The structure of **66** was confirmed by its ^1H NMR, ^{13}C NMR spectroscopy and elemental analysis.

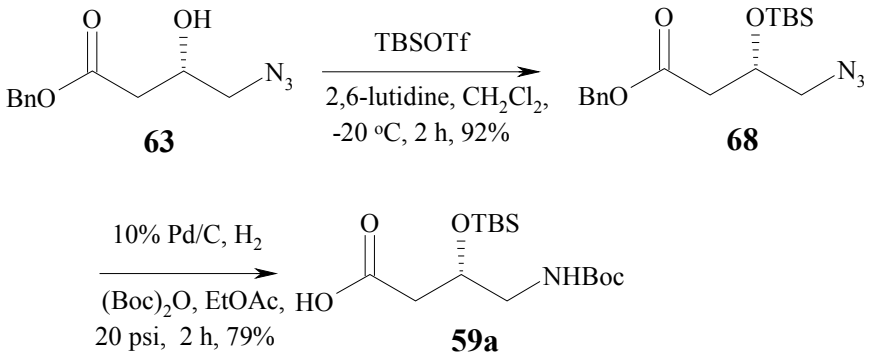
The treatment[55a] of **66** with MsCl in Py/CH_2Cl_2 effected selective mesylation of the primary hydroxyl group to obtain **67** (Scheme 20). Nucleophilic substitution of OMs with NaN_3 in DMF gave **63**[55c] in whose ^1H NMR spectrum, the benzylic protons signal were displayed at 4.68 ppm as a singlet. The ^{13}C NMR spectrum revealed two characteristic resonances at 38.4 and 55.3 ppm due to two methylene carbons adjacent to ester and azide groups. In addition, the IR spectrum exhibited an absorption at 2099 cm^{-1} for N_3.

Scheme 20



The free hydroxyl group of **63** was protected as its TBS ether (**68**) by using TBSOTf and 2,6-lutidine in CH_2Cl_2 (Scheme 21). The ^1H NMR spectrum of **68** was in agreement with the assigned structure. Reduction of the azide group to amine, its protection and reductive removal of benzyl group were effected in one pot operation by hydrogenation of **68** over 10% Pd/C in the presence of $(Boc)_2O$ in EtOAc at 20 psi which provided (*S*)-Boc-AHBA (TBS)-OH (**59a**) (Scheme 21). The ^1H NMR, ^{13}C NMR, IR and elemental analysis confirmed the

Scheme 21

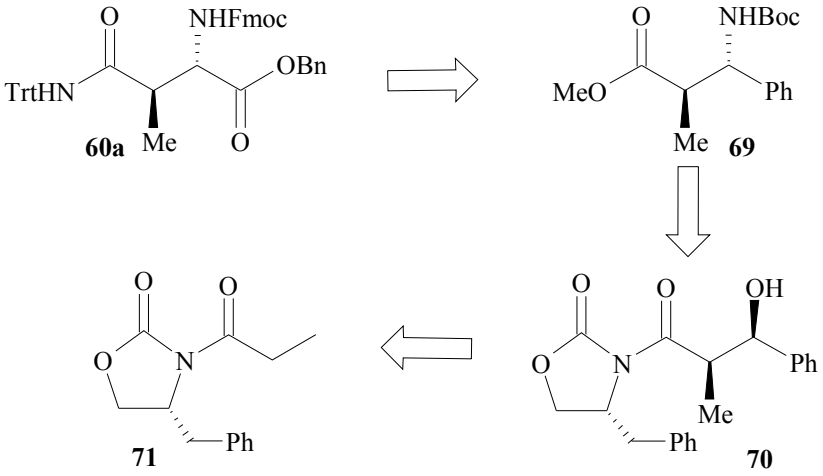


assigned structure **59a**. For instance, in the ^{1}H NMR spectrum, the methylene protons adjacent to CO_2H group appeared as a clean doublet at 2.48 ppm (J = 5.9 Hz) whereas the chemical shift due to another methylene protons adjacent to NHBoc appeared at 3.23 ppm as a triplet (J = 5.3 Hz). The ^{13}C NMR spectrum showed two characteristic peaks at 155.7 (rotamer at 157.2) and 175.4 ppm corresponding to carbonyl carbons of NHBoc and CO_2H groups respectively. In addition, the IR spectrum exhibited a typical absorption at 1712 cm^{-1} due to CO_2H group.

Synthesis of L-*erythro*-FmocNH-*β*-Me-Asn (Trt)-OBn (60a)

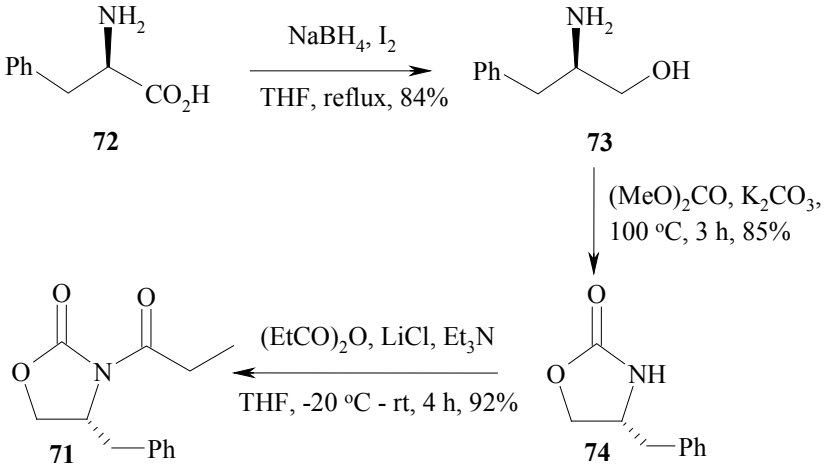
Our synthetic strategy to effectively synthesize the L-*erythro*-FmocNH-*β*-Me-Asn (Trt)-OBn (**60a**) was based on Evans asymmetric aldol reaction. The retrosynthetic analysis for **60a** is outlined in Scheme 22.

Scheme 22: ***Retrosynthetic analysis for 60a***



The synthesis began with the preparation of oxazolidinone derivative (**71**)[57] starting from D-phenyl alanine (**72**) by a standardized three steps synthetic sequence (Scheme 23).[58]

Scheme 23



A short account on Evans asymmetric aldol reaction:

The asymmetric aldol condensation is a reaction of fundamental importance in organic synthesis. Consequently considerable efforts has been employed to develop stereoregulated variants of this methodology by Evans and Heathcock.[59]It has been well appreciated that kinetic aldol stereoselection is in part, defined by enolate geometry where two stereocenters are generated. According to the postulate put forward by Evans et. al, the most boron-mediated aldol reactions are pericyclic in nature and proceed through a chair-like transition state proposed by Zimmerman and Traxler, where (Z)-boron enolates give syn-aldol products and (E)-boron enolates afford anti-aldol products.[60] The controlling influence in these reactions is the avoidance of severe 1,3-diaxial interactions in the cyclic transition states (Figure X). A combination of small ligands on boron (e.g., n-butyl), a good leaving group (e.g., triflate) and a bulky amine base (iPr_2NEt) usually leads to a (Z)-selective enolization. On the other hand, use of sterically demanding ligands on boron (e.g., cyclohexyl), a poor leaving group (e.g., chloride) and a small amine base (e.g., Et_3N) usually promotes (E)-enolate formation.[61] The relative stereochemistry of an aldol adduct depends on the enolate geometry whereas the absolute stereochemistry is dependent on the configuration of the substituent in the imide ring.[62]

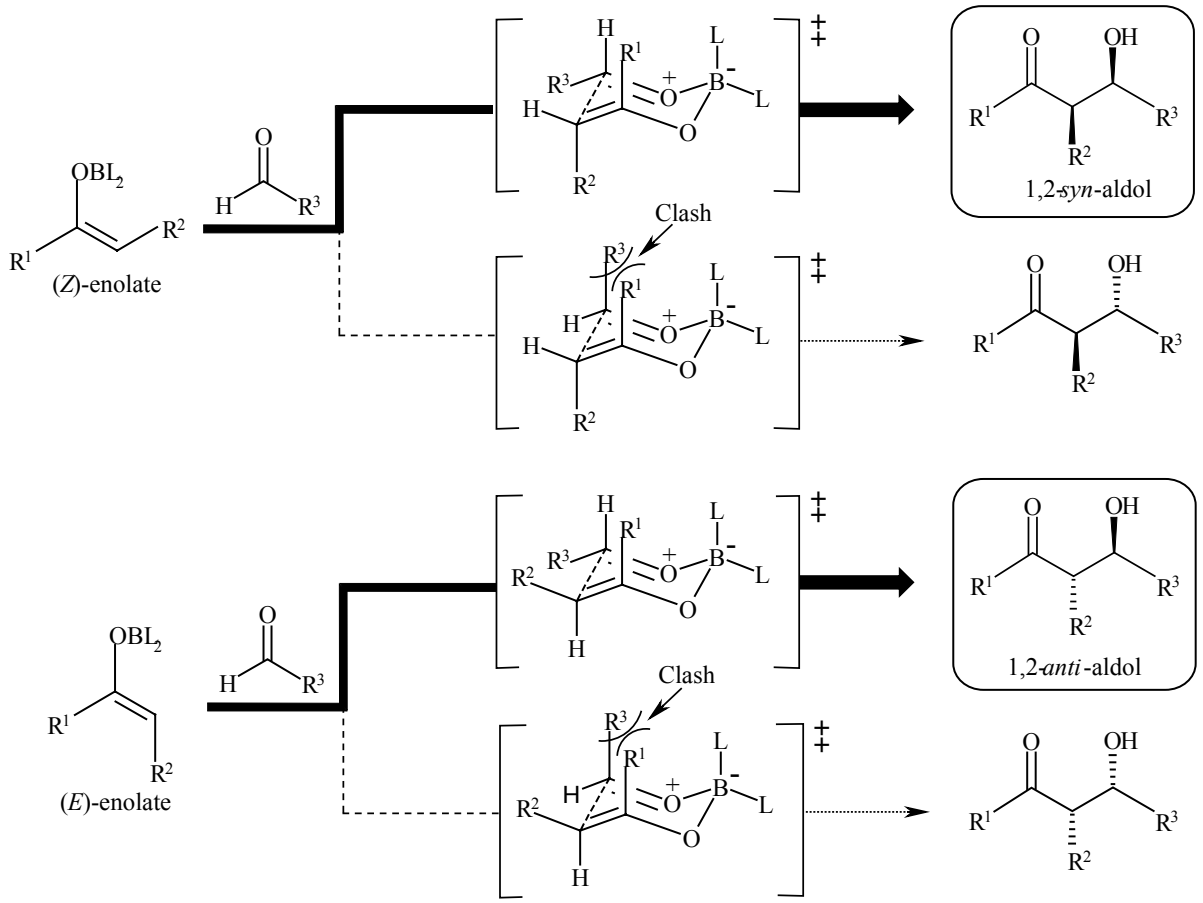
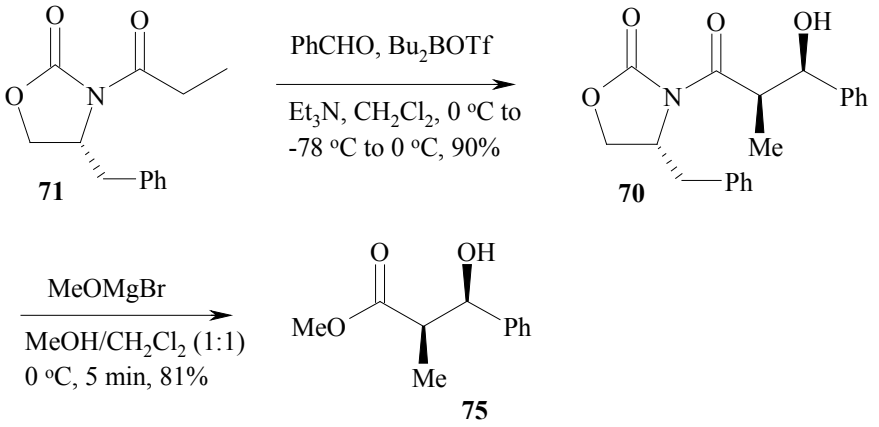


Figure 5: ***Transition states for (Z)- and (E)-enolates***

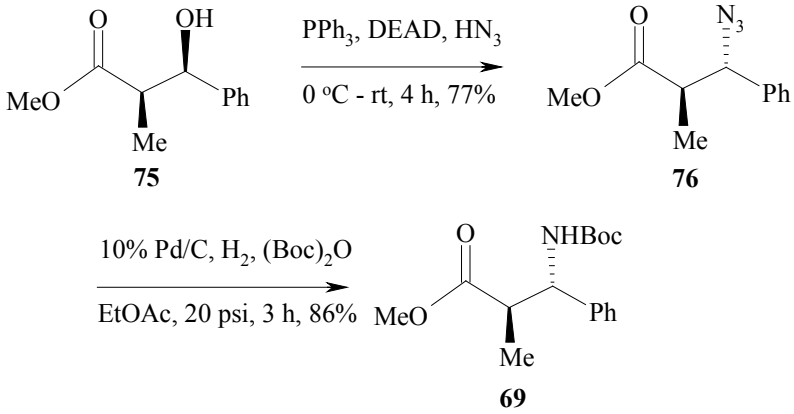
The Evans aldol condensation of the imide **71** and PhCHO using Bu_2BOTf and Et_3N in CH_2Cl_2 at 0 °C to –78 °C gave the diastereomerically pure product **70** (Scheme 24).[63] The ^1H NMR spectrum of **70** showed typical methyl resonances at 1.22 ppm as a doublet (J = 7.1 Hz). Another doublet in the downfield region at 5.06 ppm (J = 4.3 Hz) appeared due to methine proton adjacent to hydroxyl group. All other protons resonated at their respective chemical shift values. The ^{13}C NMR, IR and elemental analysis further supported the assigned structure **70**. Removal of the chiral auxiliary proceeded smoothly with magnesium methoxide in 1:1 $MeOH/CH_2Cl_2$ at 0 °C for 5 min to give corresponding ester **75**.[64] In the ^1H NMR spectrum of **75**, signals due to oxazolidinone ring protons were conspicuously absent. The structure of **75** was further supported by its ^{13}C NMR, IR and elemental analysis. The absolute stereochemistry of **75** was determined by comparing its optical rotation, $[\alpha]_D$ +21.1 (*c* 1.73, $CHCl_3$) with the reported[59a] sample $[\alpha]_D$ +21.5 (*c* 1.73, $CHCl_3$).

Scheme 24



The nucleophilic substitution of hydroxyl group of **75** with an azide was particularly difficult. The activation of the hydroxyl group in the form of a sulfonate or triflate under basic reaction conditions would be prone to β-elimination product. However, the nucleophilic substitution under non-basic reaction conditions would ensure requisite transformation. Accordingly, the Mitsunobu reaction on **75** with PPh_3 and DEAD in the presence of HN_3 was performed to afford exclusively **76** (Scheme 25).[65] In the ^1H NMR spectra of both **75** and **76**, the resonances due to H-3 were clearly apparent as a doublet but whereas the chemical shift of all other protons were comparable, that due to H-3 showed an upfield shift of 0.44 ppm. In addition, the IR spectrum exhibited a characteristic absorption at 2104 cm^{-1} due to N_3 indicating the formation of **76**. The ^{13}C NMR spectroscopy and elemental analysis were in accord with the assigned structure **76**. Reduction of azide group to amine and simultaneous protection were effected in one pot operation by hydrogenation of **76** over 10% Pd/C in the

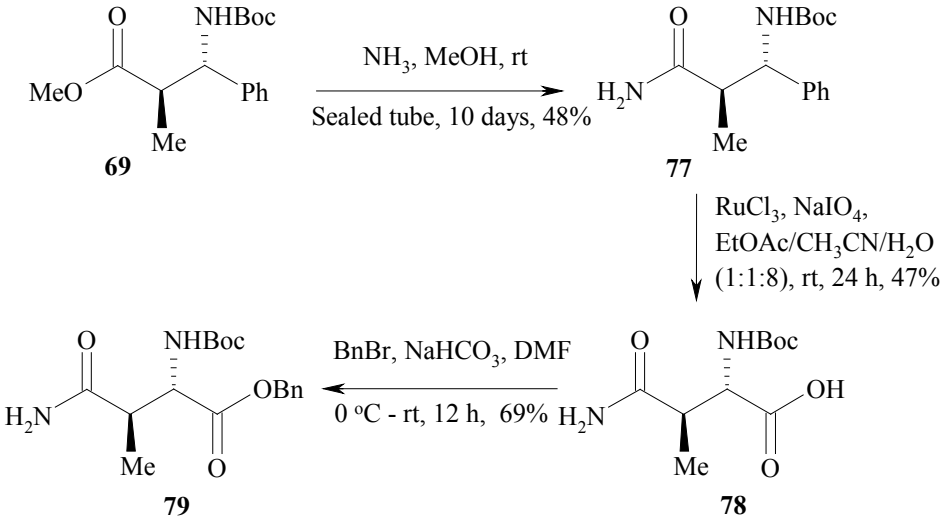
Scheme 25



presence of $(Boc)_2O$ in EtOAc at 20 psi hydrogen atmosphere to obtain **69** (Scheme 25). The NH proton resonated as a doublet at 5.80 ppm (J = 7.4 Hz) in the ^{1}H NMR spectrum of **69**. The resonances for the other protons were in agreement with the assigned structure **69**. The structure of **69** was further supported by its ^{13}C NMR, IR and elemental analysis.

Subsequent aminolysis[66] of **69** converted methyl ester into the primary amide derivative (**77**) (Scheme 26). The structure of **77** was established by its ^{1}H NMR, ^{13}C NMR, IR and elemental analysis. The IR spectrum displayed two characteristic absorption peaks at 1652 and 1682 cm^{-1} due to C=O stretching of amide functional groups. The phenyl group is a surrogate for carboxylic acid function. The oxidative cleavage[67] of the aromatic ring of **77** by treating with ruthenium tetraoxide generated *in situ* in a solvent system $EtOAc/CH_3CN/H_2O$ with vigorous stirring provided the carboxylic acid derivative (**78**) (Scheme 26). The ^{1}H NMR spectrum of **78** showed a double-doublet at 4.27 ppm (J = 3.8, 8.8 Hz) corresponding to the methine proton bearing the NHBoc whereas ^{13}C NMR spectrum exhibited three signals at 155.7, 172.6 and 177.2 ppm attributed to the carbonyl carbons of two amide and one acid functional groups. Compound **78** was protected as its benzyl ester using BnBr and $NaHCO_3$ in DMF to furnish **79** (Scheme 26). The appearance of the benzylic protons as a two set of doublets at 5.12 ppm (J = 12.2 Hz) and 5.24 ppm (J = 12.2 Hz) in the ^{1}H NMR spectrum indicated the formation of **79**.

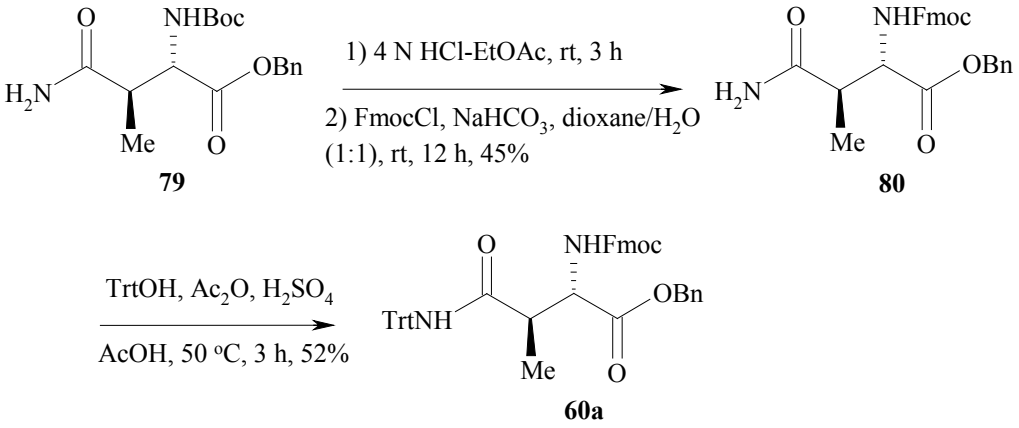
Scheme 26



Compound **79** was converted into the N-Fmoc-N-Trt derivative (**60a**) which has protecting group suitable for peptide bond formation. The N-Trt-N-Boc are prone to acid

hydrolysis, therefore, **79** was first reacted with 4 N HCl-EtOAc at rt for 2 h and the resulting amine salt was treated with FmocCl and $NaHCO_3$ in dioxane/H_2O (1:1) to afford the Fmoc-protected β-Me-Asn derivative (**80**) (Scheme 27). The structure of **80** was established by its ^1H NMR, ^{13}C NMR, IR and elemental analysis.

Scheme 27

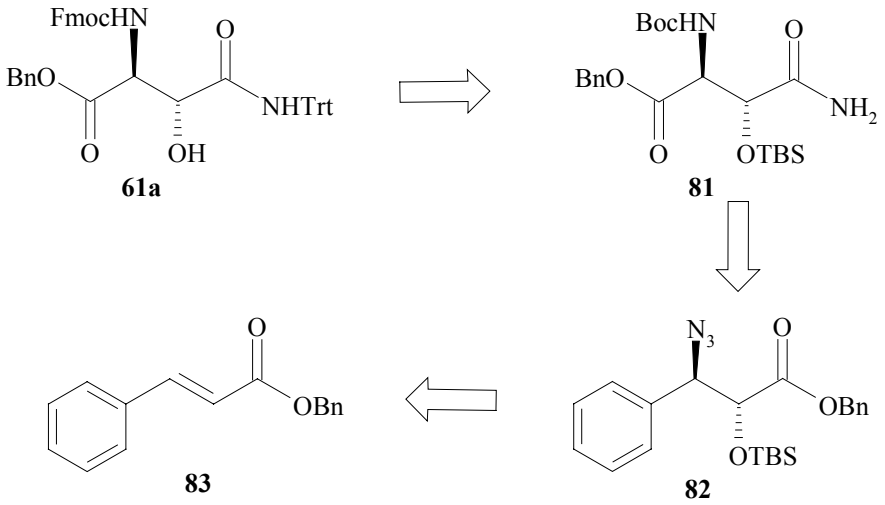


The protection of the carboxamide group of **80** with a trityl (Trt) group was necessary. The unprotected carboxamide of asparagine residue is known to undergo side reactions during peptide coupling. Thus, compound **80** was treated with TrtOH and Ac_2O which resulted the formation **60a** (Scheme 27). The structure of **60** was thoroughly investigated by its ^1H NMR, ^{13}C NMR, IR and elemental analysis. For instance, the ^1H NMR spectrum showed the characteristic signals due to trityl group in the aromatic region.

Synthesis of L-*erythro*-FmocNH-β-OH-Asn (Trt)-OBn (61a)

Our intended strategy for the asymmetric synthesis of suitably protected L-*erythro*-FmocNH-β-OH-Asn (Trt)-OBn (**61a**) was based on enantiocontrolled Sharpless dihydroxylation reaction followed oxidative cleavage of the phenyl ring to CO_2H group. The retrosynthetic analysis for **61a** is outlined in Scheme 28.

Scheme 28: ***Retrosynthetic analysis for 61a***



A short account on Sharpless asymmetric dihydroxylation (AD):

The stereospecific cis-dihydroxylation of olefins achieved by OsO_4 is one of the most valued transformations for introducing functionality into organic molecules. Initially the AD using derivatives of cinchona alkaloids was performed under stoichiometric conditions. Lateron, with the advent of: i) use of two phase conditions with $K_3Fe(CN)_6$ as reoxidant; ii) $MeSO_2NH_2$ for rate acceleration and iii) second generation ligands (phthalazine and diphenylpyrimidine, with two independent cinchona alkaloid units) by Sharpless et al., catalytic AD came into focus. The enantioselectivity in the AD reaction is due to the enzyme-like binding pocket present in the dimeric cinchona alkaloid ligands. The Cinchona alkaloid backbone is ideally suited for providing high ligand acceleration and enantioselectivity. The reaction rates are influenced by the nature of O-9 substituent of the Cinchona alkaloid. The rate enhancement is caused by a stabilization of the transition state due to aromatic stacking interactions. Although this kind of stabilization is operative even in monomeric first generation ligand, it is most effective in the dimeric second-generation ligands due to the presence of a binding pocket. Thus the almost perfect match between the phthalazine ligands and aromatic olefins with respect to rates and enantioselectivities can be readily explained by an especially good transition state stabilization resulting from offset-parallel interactions between the aromatic substituent of the olefin and the phthalazine floor of the ligand, as well as favorable edge-to-face interactions with the bystander methoxyquinoline ring.

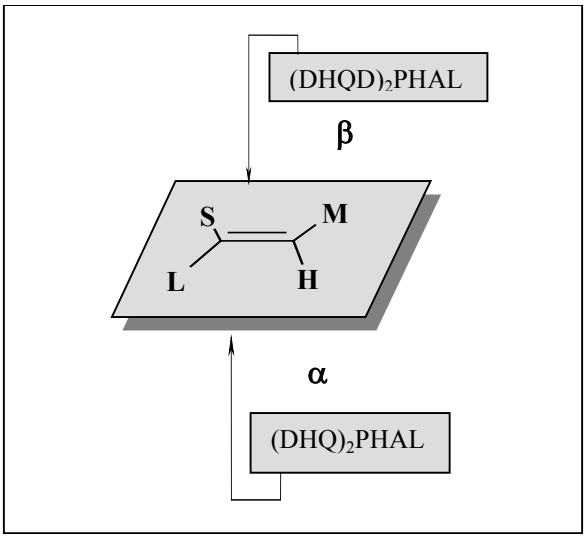


Figure 6: ***Mnemonic diagram*** *(S = small group, L = large group, M = medium group, H = proton).*

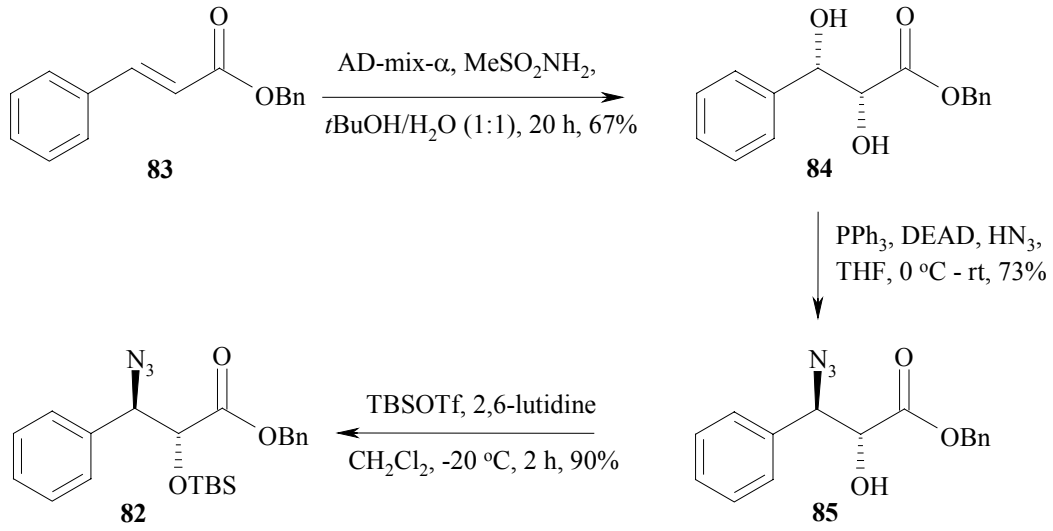
The above observations have led to a revised mnemonic device for predicting the enantiofacial selectivity in the reaction. An olefin positioned accordingly will be attacked either from the top face (β face) in the case of dihdroquinidine derivatives or from the bottom face (α face) in the case of dihydroquinine derived ligands.

The Sharpless AD reaction of benzyl cinnamate (**83**) using AD-mix-α[68] produced the diol **84** (Scheme 29). The ^{1}H NMR spectrum of **84** showed two clean doublets in the downfield region at 4.31 ppm (J = 3.3 Hz) and 4.91 ppm (J = 3.3 Hz) attributed to the two methine protons. All other resonances observed in their respective chemical shift values. In addition, the ^{13}C NMR spectroscopy and elemental analysis further supported the assigned structure **84**. The optical purity of **84** was based on empirical rules coupled with literature precedents.[68a,b]

Most of the previous works in the area of *syn*-2,3-dihydroxy esters resulted stereoselection at the α-hydroxyl group.[69-74] However, recently Ko *et al*.[65] postulated that Mitsunobu conditions, reaction took place at the β-hydroxyl group with complete regioselection. Accordingly, the Mitsunobu reaction[65] on **84** with PPh_3 and DEAD in the presence of HN_3 was performed to afford exclusively **85** (Scheme 29). In the ^{1}H NMR spectra of both **84** and **85**, the resonances due to H-3 were clearly apparent as a doublet but whereas

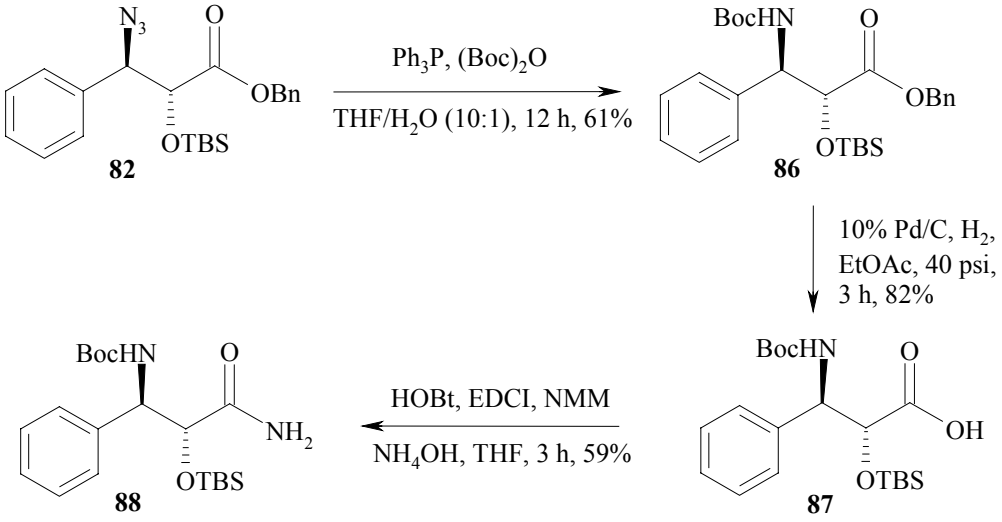
the chemical shift of all other protons were comparable, that due to H-3 showed a downfield shift of 0.26 ppm. In addition, the IR spectrum exhibited a characteristic absorption at 2108 cm^{-1} due to N_3. The ^{13}C NMR spectroscopy and elemental analysis further supported the assigned structure **85**. The free hydroxyl group of **85** was protected as its TBS ether (**82**) by using TBSOTf and 2,6-lutidine in CH_2Cl_2 (Scheme 29). The ^1H NMR spectrum of **82** showed the characteristic signals due to TBS group in the upfield region.

Scheme 29



The reduction of azide group present in **82** to amine under Staudinger conditions[75] and its protection were effected in one pot operation by using Ph_3P and $(Boc)_2O$ in THF/H_2O

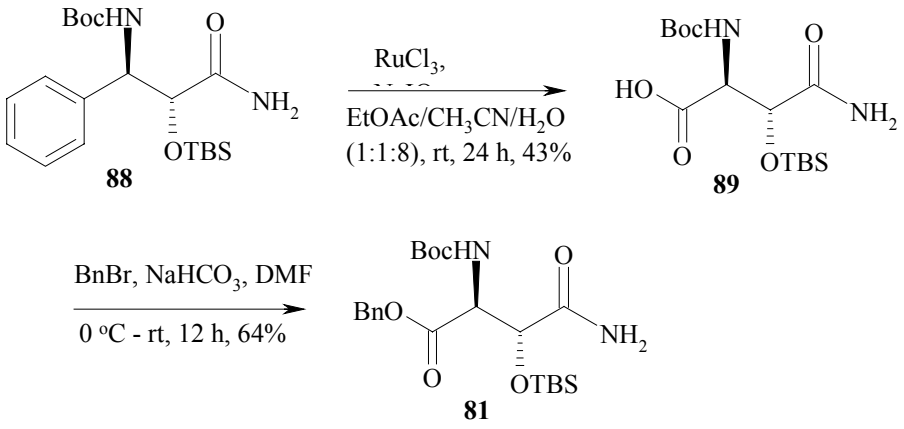
Scheme 30



(10:1) to furnish **86** (Scheme 30). In the ^{1}H NMR spectrum of **86**, a doublet of doublet due to H-3 appeared at 5.05 ppm (J = 3.6, 7.9 Hz). The NH proton showed a characteristic doublet in the downfield region at 5.32 ppm (J = 7.9 Hz). The IR spectrum exhibited a characteristic absorption at 3465 cm^{-1} due to N-H. The reductive removal of the benzyl group of **86** was accomplished by treating over 10% Pd/C in EtOAc at 40 psi hydrogen atmosphere to obtain **87** which was subjected to amidation reaction by using HOBt, EDCI, *N*-methylmorpholine and NH_4OH at 0 ^{o}C for 3 h to afford the amide derivative (**88**) (Scheme 30). The ^{1}H NMR, ^{13}C NMR, IR and elemental analysis confirmed the assigned structure **88**.

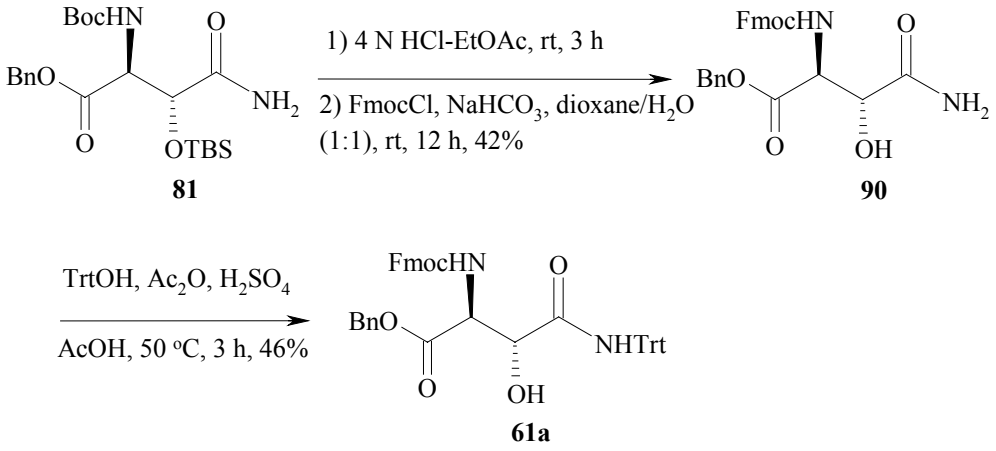
The oxidative cleavage[67] of the aromatic ring of **88** by treating with ruthenium tetraoxide generated *in situ* in a solvent system EtOAc/CH_3CN/H_2O with vigorous stirring provided the carboxylic acid derivative (**89**) (Scheme 31). The acid group of **89** was protected as its benzyl ester (**81**) by using BnBr and $NaHCO_3$ in DMF (Scheme 31). The structure of **81** was established by its ^{1}H NMR, ^{13}C NMR, IR and elemental analysis. For example, the IR spectrum exhibited a characteristic absorption at 1711 cm^{-1} due to ester group.

Scheme 31



Compound **81** was converted into the N-Fmoc-N-Trt derivative (**61a**) which has protecting group suitable for peptide bond formation. Accordingly, a single step Boc and TBS group removal was accomplished by treatment of 4 N HCl-EtOAc at rt for 2 h and the resulting amine salt was treated with FmocCl and $NaHCO_3$ in 50% dioxane/H_2O to provide the Fmoc-protected β-OH-Asn derivative (**90**) (Scheme 32). In the ^{1}H NMR spectrum of **90**, the methine proton bearing the FmocNH observed as a double-doublet at 4.74 ppm (J = 2.7, 9.0 Hz). The NH proton of FmocNH resonated as a doublet at 5.94 ppm (J = 5.2 Hz).

Scheme 32



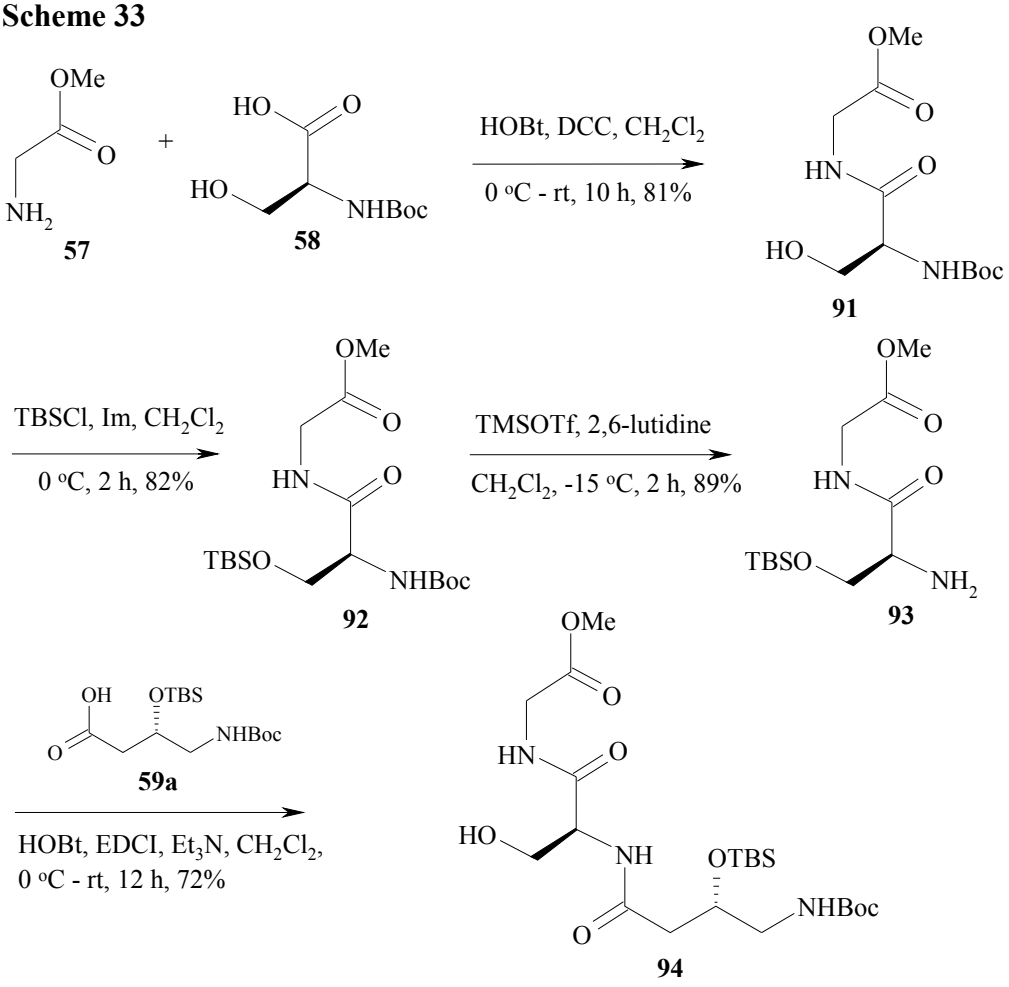
The protection of the carboxamide group of **90** with a trityl (Trt) under acidic conditions[76] was found to produce the acetate byproduct as the major product. However, the use of acetic anhydride as dehydrating agent minimized the formation of acetate byproduct. Accordingly, compound **90** was treated with TrtOH and Ac_2O under acidic conditions to provide Trt protected residue **61a** (Scheme 32). The structure of **61a** was thoroughly investigated by its ^{1}H NMR, ^{13}C NMR, IR and elemental analysis.

Synthesis of Tripeptide (55)

After the successful completion of the synthesis of three unusual amino acids **59a**, **60a** and **61a**, next our attention focused for the synthesis of tripeptide (**55**). The coupling of Gly-OMe (**57a**) with Boc-L-Ser-OH (**58a**) by using coupling reagents HOBt and DCC in CH_2Cl_2 gave the dipeptide (**91**) (Scheme 33). The ^{1}H NMR spectrum of **91** showed a singlet at 3.74 ppm due to OMe group. A clean doublet appeared at 5.66 ppm (J = 7.8 Hz) due to NH proton of NHBoc group. The structure of **91** was further supported by its ^{13}C NMR, IR and elemental analysis. The free hydroxyl group of **91** was protected as its TBS ether (**92**) by using TBSCl and imidazole in CH_2Cl_2 at 0 °C for 2 h (Scheme 33). The ^{1}H NMR spectrum of **92** showed two singlets in the upfield region at 0.07 and 0.88 ppm integrating for six and nine protons respectively were assigned to TBS group. The Boc group was removed from the TBS ether derivative (**92**) by the action of excess TMSOTf and 2,6-lutidine to afford **93**.[77] The anticipated union of **93** with **59a** was brought about in the presence of EDCI, HOBt and Et_3N, furnishing the tripeptide (**94**) where the primary TBS group also deprotected (Scheme 33).[78]

The ^{1}H NMR spectrum of **94** clearly indicated that the coupling had indeed taken place because the characteristic signals of both the coupling partners were distinctly visible. For instance, the methylene protons adjacent to NHBoc observed as a triplet at 3.18 ppm (J = 5.1 Hz) whereas another methylene protons of (*S*)-Boc-AHBA (TBS) moiety appeared at 2.52 ppm (J = 5.4 Hz). However, A singlet due to OMe group displayed at 3.76 ppm. The IR spectrum and elemental analysis further supported the assigned structure **94**.

Scheme 33



In conclusion, we have developed the stereoselective synthesis of polyketide chain (**17**) of nagahamide A. The 5,6-cyclopropyl sugar derivatives are useful intermediates for the synthesis of bioactive compounds. The above-mentioned synthesis elaborates an appropriate strategy to install stereoselectively an alkyl group at C-5. Additionally this work furnishes a route *via* regioselective ring opening reaction of cyclopropyl group to introduce methyl and propyl substituents simultaneously. We have successfully accomplished the synthesis of three unusual amino acids suitably protected for incorporation into a projected total synthesis of

nagahamide A, (*S*)-Boc-AHBA (TBS)-OH (**59a**), L-*erythro*-FmocNH-*β*-Me-Asn (Trt)-OBn (**60a**) and L-*erythro*-FmocNH-*β*-OH-Asn (Trt)-OBn (**61a**) and the tripeptide (**55**). The synthesis of tripeptide (**56**) and its coupling with **55** to provide hexapeptide (**18**) and finally union with polyketide chain (**17**) in order to complete the total synthesis of nagahamide A (**13**) are in progress in this laboratory.

Crystal data and structure refinement for Compound 42

Table 1

Empirical formula	$C_{12}H_{18}O_5$
Formula weight	242.271
Temperature	568(2) K
Wavelength	0.71073 Å
Crystal system, space group	Orthorhombic, P2(1)2(1)2(1)
Unit cell dimensions	a = 5.517(3) Å alpha = 90º
	b = 9.144(4) Å beta = 90º
	c = 26.180(13) Å gamma = 90º
Volume	1320.7(11) $Å^3$
Z, Calculated density	4, 1.218 mg/m^3
Absorption coefficient	0.094 mm^{-1}
F(000)	520
Crystal size	0.2 x 0.15 x 0.16 mm
Theta range for data collection	1.56 to 25.00 deg
Limiting indices	–6<=h<=6, –10<=k<=9, –31<=l<=21
Reflections collected / unique	6685 / 2337 [R(int) = 0.0297]
Completeness to theta = 25.00	100.0 %
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2337 / 0 / 158
Goodness-of-fit on F^2	1.044
Final R indices [I>2sigma(I)]	R1 = 0.0472, wR2 = 0.1038
R indices (all data)	R1 = 0.0724, wR2 = 0.1140
Absolute structure parameter	0.8(17)
Largest diff. peak and hole	0.165 and –0.106 e. $Å^{-3}$

Table 2. Bond lengths [Å] and angles [deg] for Compound 42

O(1)-C(1)	1.401(3)	C(1)-O(1)-C(4)	109.80(17)	C(7)-C(6)-H(6)	116.6
O(1)-C(4)	1.443(3)	C(3)-O(2)-H(2)	109.5	C(5)-C(6)-H(6)	116.6
O(2)-C(3)	1.412(3)	C(1)-O(4)-C(10)	110.34(19)	C(5)-C(7)-C(6)	61.19(19)
O(2)-H(2)	0.8200	C(10)-O(5)-C(2)	109.67(19)	C(5)-C(7)-H(7A)	117.6
O(3)-C(8)	1.195(3)	O(4)-C(1)-O(1)	112.61(19)	C(6)-C(7)-H(7A)	117.6
O(4)-C(1)	1.387(3)	O(4)-C(1)-C(2)	105.65(19)	C(5)-C(7)-H(7B)	117.6
O(4)-C(10)	1.423(3)	O(1)-C(1)-C(2)	106.90(19)	C(6)-C(7)-H(7B)	117.6
O(5)-C(10)	1.413(3)	O(1)-C(1)-H(1)	110.5	H(7A)-C(7)-H(7B)	114.8
O(5)-C(2)	1.416(3)	C(2)-C(1)-H(1)	110.5	O(3)-C(8)-C(6)	121.3(3)
C(1)-C(2)	1.520(3)	O(5)-C(2)-C(3)	110.0(2)	O(3)-C(8)-C(9)	121.0(3)
C(1)-H(1)	0.9800	O(5)-C(2)-C(1)	103.11(19)	C(6)-C(8)-C(9)	117.7(3)
C(2)-C(3)	1.508(3)	C(3)-C(2)-C(1)	103.99(19)	C(8)-C(9)-H(9A)	109.5
C(2)-H(2A)	0.9800	O(5)-C(2)-H(2A)	113.0	C(8)-C(9)-H(9B)	109.5
C(3)-C(4)	1.520(3)	C(3)-C(2)-H(2A)	113.0	H(9A)-C(9)-H(9B)	109.5
C(3)-H(3)	0.9800	C(1)-C(2)-H(2A)	113.0	C(8)-C(9)-H(9C)	109.5
C(4)-C(5)	1.479(4)	O(2)-C(3)-C(2)	110.33(19)	H(9A)-C(9)-H(9C)	109.5
C(4)-H(4)	0.9800	O(2)-C(3)-C(4)	108.50(19)	H(9B)-C(9)-H(9C)	109.5
C(5)-C(7)	1.461(4)	C(2)-C(3)-C(4)	101.47(18)	O(5)-C(10)-O(4)	106.20(18)
C(5)-C(6)	1.508(4)	O(2)-C(3)-H(3)	112.0	O(5)-C(10)-C(12)	111.1(2)
C(5)-H(5)	0.9800	C(2)-C(3)-H(3)	112.0	O(4)-C(10)-C(12)	108.2(2)
C(6)-C(8)	1.467(4)	C(4)-C(3)-H(3)	112.0	O(5)-C(10)-C(11)	107.9(2)
C(6)-C(7)	1.501(4)	O(1)-C(4)-C(5)	108.71(19)	O(4)-C(10)-C(11)	109.3(2)
C(6)-H(6)	0.9800	O(1)-C(4)-C(3)	103.31(19)	C(12)-C(10)-C(11)	113.9(3)
C(7)-H(7A)	0.9700	C(5)-C(4)-C(3)	117.3(2)	C(10)-C(11)-H(11A)	109.5
C(7)-H(7B)	0.9700	O(1)-C(4)-H(4)	109.1	C(10)-C(11)-H(11B)	109.5
C(8)-C(9)	1.481(5)	C(5)-C(4)-H(4)	109.1	H(11A)-C(11)-H(11B)	109.5
C(9)-H(9A)	0.9600	C(3)-C(4)-H(4)	109.1	C(10)-C(11)-H(11C)	109.5
C(9)-H(9B)	0.9600	C(7)-C(5)-C(4)	120.0(2)	H(11A)-C(11)-H(11C)	109.5

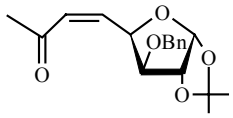
C(9)-H(9C) 0.9600	C(7)-C(5)-C(6) 60.73(19)	H(11B)-C(11)-H(11C) 109.5
C(10)-C(12) 1.499(4)	C(4)-C(5)-C(6) 118.6(2)	C(10)-C(12)-H(12A) 109.5
C(10)-C(11) 1.504(4)	C(7)-C(5)-H(5) 115.5	C(10)-C(12)-H(12B) 109.5
C(11)-H(11A) 0.9600	C(4)-C(5)-H(5) 115.5	H(12A)-C(12)-H(12B) 109.5
C(11)-H(11B) 0.9600	C(6)-C(5)-H(5) 115.5	C(10)-C(12)-H(12C) 109.5
C(11)-H(11C) 0.9600	C(8)-C(6)-C(7) 117.9(3)	H(12A)-C(12)-H(12C) 109.5
C(12)-H(12A) 0.9600	C(8)-C(6)-C(5) 118.5(2)	H(12B)-C(12)-H(12C) 109.5
C(12)-H(12B) 0.9600	C(7)-C(6)-C(5) 58.08(19)	
C(12)-H(12C) 0.9600	C(8)-C(6)-H(6) 116.6	

Table 3. Torsion angles [deg] for Compound 42

C(10)-O(4)-C(1)-O(1)	-104.9(2)	O(1)-C(4)-C(5)-C(7)	85.3(3)
C(10)-O(4)-C(1)-C(2)	11.5(3)	C(3)-C(4)-C(5)-C(7)	-158.1(2)
C(4)-O(1)-C(1)-O(4)	106.0(2)	O(1)-C(4)-C(5)-C(6)	156.1(2)
C(4)-O(1)-C(1)-C(2)	-9.5(2)	C(3)-C(4)-C(5)-C(6)	-87.2(3)
C(10)-O(5)-C(2)-C(3)	132.8(2)	C(7)-C(5)-C(6)-C(8)	-106.8(3)
C(10)-O(5)-C(2)-C(1)	22.4(3)	C(4)-C(5)-C(6)-C(8)	142.9(3)
O(4)-C(1)-C(2)-O(5)	-20.4(3)	C(4)-C(5)-C(6)-C(7)	-110.3(3)
O(1)-C(1)-C(2)-O(5)	99.7(2)	C(4)-C(5)-C(7)-C(6)	108.1(3)
O(4)-C(1)-C(2)-C(3)	-135.3(2)	C(8)-C(6)-C(7)-C(5)	107.8(3)
O(1)-C(1)-C(2)-C(3)	-15.1(2)	C(7)-C(6)-C(8)-O(3)	-38.8(5)
O(5)-C(2)-C(3)-O(2)	167.30(18)	C(5)-C(6)-C(8)-O(3)	28.0(5)
C(1)-C(2)-C(3)-O(2)	-82.9(2)	C(7)-C(6)-C(8)-C(9)	139.9(3)
O(5)-C(2)-C(3)-C(4)	-77.8(2)	C(5)-C(6)-C(8)-C(9)	-153.3(3)
C(1)-C(2)-C(3)-C(4)	32.0(2)	C(2)-O(5)-C(10)-O(4)	-16.2(3)
C(1)-O(1)-C(4)-C(5)	155.40(19)	C(2)-O(5)-C(10)-C(12)	101.3(3)
C(1)-O(1)-C(4)-C(3)	30.2(2)	C(2)-O(5)-C(10)-C(11)	-133.2(2)
O(2)-C(3)-C(4)-O(1)	78.4(2)	C(1)-O(4)-C(10)-O(5)	2.1(3)
C(2)-C(3)-C(4)-O(1)	37.8(2)	C(1)-O(4)-C(10)-C(12)	-117.3(3)
O(2)-C(3)-C(4)-C(5)	-41.1(3)	C(1)-O(4)-C(10)-C(11)	118.2(2)
C(2)-C(3)-C(4)-C(5)	-157.3(2)		

Experimental

3-*O*-Benzyl-5,6,8-trideoxy-1,2-*O*-isopropylidine-α-D-*xylo*-oct-5*Z*-enofuranos-7-ulose (39*Z*) and 3-*O*-Benzyl-5,6,8-trideoxy-1,2-*O*-isopropylidine-α-D-*xylo*-oct-5*E*-enofuranos-7-ulose (39*E*)



A solution of acetonyltriphenylphophonium bromide (62.0 g, 155.5 mmol) and Na_2CO_3 (16.5 g, 155.5 mmol) in dioxane/H_2O (3:1, 120 mL) was heated under reflux for 45 min and then **38** (24.0 g, 91.5 mmol) in MeOH (30 mL) was added drop wise. After 2 h, the reaction mixture was evaporated, the residue dissolved in EtOAc, washed with saturated Na_2CO_3 solution, dried (Na_2SO_4) and concentrated. The residue was stirred with hexane and EtOAc (20:1) for 1 h, filtered and the filtrate concentrated. The residue was purified on silica gel using EtOAc-light petroleum ether (1:9) to furnish **39*Z*** (7.0 g, 24%) as a colorless oil.

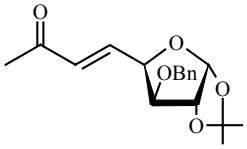
$[\alpha]_D$ −37.2 (*c* 0.8, $CHCl_3$);

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.32 (s, 3 H), 1.50 (s, 3 H), 2.20 (s, 3 H), 3.35 (d, 1 H, *J* = 3.4 Hz), 4.42 (d, 1 H, *J* = 11.7 Hz), 4.56 (d, 1 H, *J* = 12.2 Hz), 4.60 (d, 1 H, *J* = 3.9 Hz), 5.44 (dd, 1 H, *J* = 3.4, 5.4 Hz), 5.98 (d, 1 H, *J* = 3.9 Hz), 6.17-6.33 (m, 2 H), 7.23-7.34 (m, 5 H);

^{13}C NMR (125 MHz, $CDCl_3$): δ 26.1, 26.5, 30.6, 71.8, 78.4, 82.8, 84.0, 104.8, 111.2, 127.1, 127.2, 127.3, 127.9, 137.2, 143.1, 197.7;

Anal. Calcd for $C_{18}H_{22}O_5$ (Mol. Wt. 318.369): C, 67.90; H, 6.96. Found; C, 67.73; H, 6.76.

Further elusion gave **39*E*** (10.5 g, 36%) as a clear liquid.



$[\alpha]_D$ −63.7 (*c* 0.5, $CHCl_3$);

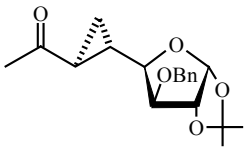
^{1}H NMR (200 MHz, $CDCl_3$): δ 1.33 (s, 3 H), 1.49 (s, 3 H), 2.27 (s, 3 H), 3.97 (d, 1 H, *J* = 3.4 Hz), 4.46 (d, 1 H, *J* = 12.2 Hz), 4.65 (d, 1 H, *J* = 12.2 Hz), 4.66 (d, 1 H, *J* = 3.9 Hz), 4.78

(ddd, 1 H, *J* = 1.6, 3.4, 5.4 Hz), 5.99 (d, 1 H, *J* = 3.9 Hz), 6.37 (dd, 1 H, *J* = 1.5, 16.2 Hz), 6.76 (dd, 1 H, *J* = 5.4, 16.2 Hz), 7.23-7.36 (m, 5 H);

^{13}C NMR (50 MHz, $CDCl_3$): δ 26.1, 26.7, 27.3, 72.0, 79.5, 82.6, 83.1, 104.9, 111.8, 127.6, 128.0, 128.4, 131.6, 136.9, 140.1, 197.2;

Anal. Calcd for $C_{18}H_{22}O_5$ (Mol. Wt. 318.369): C, 67.90; H, 6.96. Found; C, 67.85; H, 6.68.

3-*O*-Benzyl-5,6,8-trideoxy-1,2-*O*-isopropylidine-5,6-*C*-methylene-L-*glycero*-β-L-*ido*-octofuranos-7-ulose (25)



To a suspension of NaH (1.79 g, 60% dispersion in oil, 45.0 mmol), trimethylsulphoxonium iodide (9.9 g, 45.0 mmol) in DMSO (50 mL) under argon at 10 ^{o}C was added **39** (13.0 g, 40.9 mmol) in DMSO (50 mL) over a period of 30 min. The reaction was quenched with 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 (3:17) to afford **25** (8.41 g, 62%) as a semi-solid.

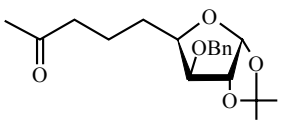
$[\alpha]_D$ +7.2 (*c* 1.0, $CHCl_3$);

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.19 (ddd, 1 H, *J* = 4.1, 6.6, 9.3 Hz), 1.33 (s, 3 H), 1.37 (dt, 1 H, *J* = 4.4, 9.3 Hz), 1.47 (s, 3 H), 1.90 (dt, 1 H, *J* = 4.4, 8.3 Hz), 1.94-1.98 (m, 1 H), 2.16 (s, 3 H), 3.72 (dd, 1 H, *J* = 3.4, 7.5 Hz), 3.85 (d, 1 H, *J* = 3.2 Hz), 4.54 (d, 1 H, *J* = 11.9 Hz), 4.63 (d, 1 H, *J* = 4.0 Hz), 4.71 (d, 1 H, *J* = 11.9 Hz), 5.92 (d, 1 H, *J* = 4.0 Hz), 7.29-7.37 (m, 5 H);

^{13}C NMR (50 MHz, $CDCl_3$): δ 15.4, 21.2, 25.0, 25.7, 26.3, 29.6, 71.4, 81.7 (2C), 82.1, 104.3, 110.8, 127.3, 127.5, 128.1, 137.1, 206.0;

Anal. Calcd for $C_{19}H_{24}O_5$ (Mol. Wt. 332.396): C, 68.65; H, 7.27. Found; C, 68.46; H, 7.10.

3-*O*-Benzyl-5,6,7,9-tetradeoxy-1,2-*O*-isopropylidine-α-D-*xylo*-nonofuranos-8-ulose (40b)



A solution of **25** (0.2 g, 0.6 mmol), *n*BuSnH (0.2 mL, 0.7 mmol), AIBN (15 mg) in benzene (10 mL) under 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 layers separated, dried (Na_2SO_4) and concentrated. The residue was purified on silica gel using EtOAc-light petroleum ether (3:17) to obtain **40b** (0.16 g, 82%) as a thick syrup.

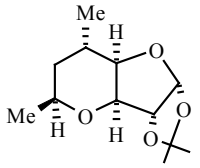
$[\alpha]_D$ −56.6 (*c* 1.0, $CHCl_3$);

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.31 (s, 3 H), 1.48 (s, 3 H), 1.58-1.70 (m, 4 H), 1.12 (s, 3 H), 2.42-2.48 (m, 2 H), 3.76 (d, 1 H, *J* = 2.9 Hz), 4.09 (dt, 1 H, *J* = 2.9, 6.8 Hz), 4.47 (d, 1 H, *J* = 12.2 Hz), 4.59 (d, 1 H, *J* = 3.9 Hz), 4.70 (d, 1 H, *J* = 12.2 Hz), 5.88 (d, 1 H, *J* = 3.9 Hz), 7.25-7.31 (m, 5 H);

^{13}C NMR (50 MHz, $CDCl_3$): δ 20.4, 26.1, 26.6, 27.3, 29.7, 43.4, 71.6, 80.0, 82.2 (2C), 104.6, 111.1, 127.6, 127.8, 128.3, 137.5, 207.9;

Anal. Calcd for $C_{19}H_{26}O_5$ (Mol. Wt. 334.412): C, 68.24; H, 7.83. Found; C, 67.98; H, 7.74.

3,7-Anhydro-5,6,8-trideoxy-1,2-*O*-isopropylidine-5-*C*-methyl-L-*glycero*-β-L-*ido*-octofuranose (41) and (7*R*/*S*)-5,6,8-trideoxy-1,2-*O*-isopropylidine-5-*C*-methyl-β-L-*ido*-octos-7-ulo-1,4-furano-3,7-pyranose (24)



A solution of **25** (3.0 g, 9.0 mmol) in EtOAc (25 mL) was hydrogenated in the presence of 10% Pd/C (0.3 g) at 200 psi. After 20 h, the reaction mixture was filtered through a pad of Celite, concentrated and the residue purified on silica gel by using EtOAc–light petroleum ether (1:9) to afford **41** (0.41 g, 20%) as a colorless liquid.

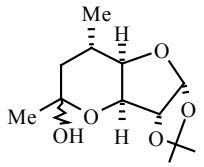
$[\alpha]_D$ +11.8 (*c* 1.0, $CHCl_3$);

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.08 (d, 3 H, *J* = 7.6 Hz), 1.12 (d, 3 H, *J* = 6.1 Hz), 1.20-1.23 (m, 1 H), 1.30 (s, 3 H), 1.49 (s, 3 H), 1.67-1.73 (m, 1 H), 2.23-2.28 (m, 1 H), 3.62 (ddq, 1 H, *J* = 1.9, 6.1, 12.1 Hz), 3.83 (s, 1 H), 3.98 (d, 1 H, *J* = 1.6 Hz), 4.45 (d, 1 H, *J* = 3.6 Hz), 5.88 (d, 1 H, *J* = 3.6 Hz);

^{13}C NMR (50 MHz, $CDCl_3$): δ 16.6, 21.3, 25.6, 26.2, 27.0, 33.5, 65.7, 76.0, 77.5, 83.7, 104.4, 110.4;

Anal. Calcd for $C_{12}H_{20}O_4$ (Mol. Wt. 228.288): C, 63.13; H, 8.83. Found; C, 63.41; H, 8.60.

Further elution afforded **24** (1.43 g, 65%) as a colorless oil.

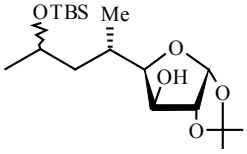


^{1}H NMR (200 MHz, Acetone-d_6): δ 1.08 and 1.26 (d, 3 H, *J* = 6.6 Hz), 1.33 and 1.35 (s, 3 H), 1.40 (s, 3 H), 1.48 and 1.49 (s 3 H), 2.10-2.19 (m, 2 H), 2.37-2.51 (m, 1 H), 3.06 and 3.09 (s, 1 H), 3.79-4.26 (m, 2 H), 4.54 and 4.56 (d, 1 H, *J* = 3.4 Hz), 5.90 (d, 1 H, *J* = 3.9 Hz);

^{13}C NMR (50 MHz, $CDCl_3$): δ 18.5 and 19.1, 26.1 and 26.3, 26.7 and 26.8, 28.4 and 29.9, 36.0, 48.2, 72.8 and 74.1, 80.5 and 84.5, 85.1 and 85.2, 96.6, 104.2 and 104.9, 111.0 and 111.2;

Anal. Calcd for $C_{12}H_{20}O_5$ (Mol. Wt. 244.287): C, 59.00; H, 8.25. Found; C, 58.87; H, 8.54.

5,6,8-Trideoxy-7-*O*-(*tert*-butyldimethylsilyl)-1,2-*O*-isopropylidine-5-*C*-methyl-D/L-*glycero*-β-L-*ido*-octofuranose (43)



A stirred suspension of LAH (0.57 g, 15.2 mmol), **24** (3.7 g, 15.2 mmol) in THF (20 mL) was stirred at rt for 1 h. The excess LAH was quenched with saturated solution of Na_2SO_4 and filtered and the residue thoroughly washed with EtOAc. The filtrate was concentrated and purified on silica gel using EtOAc-light petroleum ether (3:7) to obtain **23** (3.43 g, 92%) which was dissolved in dry CH_2Cl_2 (30 mL) and then imidazole (1.89 g, 27.9 mmol) and TBSCl (2.31 g, 15.3 mmol) were added. After 0.5 h, the reaction mixture was washed with saturated NH_4Cl solution, water, dried (Na_2SO_4), concentrated and purified on silica gel using EtOAc-light petroleum ether (1:9) to afford **43** (4.51 g, 90%).

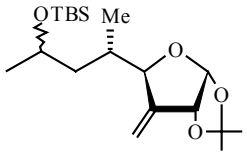
^{1}H NMR (200 MHz, $CDCl_3$): δ 0.09 and 0.10 (s, 6 H), 0.89 and 0.90 (s, 9 H), 1.10 and 1.12 (d, 3 H, *J* = 6.4 Hz), 1.16 and 1.19 (d, 3 H, *J* = 5.6 Hz), 1.30 (s, 3 H), 1.30-1.38 (m, 1 H), 1.48

and 1.49 (s, 3 H), 1.55-1.59 and 1.62-1.66 (m, 1 H), 1.90-2.03 (m, 1 H), 3.73 and 3.78 (t, 1 H, *J* = 2.8 Hz), 3.87-4.07 (m, 1 H), 4.11 and 4.17 (d, 1 H, *J* = 2.4 Hz), 4.51 (d, 1 H, *J* = 3.9 Hz), 5.88 (d, 1 H, *J* = 3.9 Hz);

^{13}C NMR (50 MHz, $CDCl_3$): δ –4.7, –4.5, 17.5 and 17.9, 18.0 and 18.7, 22.2 and 24.7, 25.8, 26.0, 26.6, 27.7 and 28.3, 41.9 and 43.0, 66.4 and 67.5, 73.9 and 74.2, 84.9 and 85.1, 85.6 and 85.7, 104.2 and 104.4, 110.6 and 110.7;

Anal. Calcd for $C_{18}H_{36}SiO_5$ (Mol. Wt. 360.567): C, 59.96; H, 10.06. Found; C, 60.25; H, 10.33.

7-*O*-(*tert*-Butyldimethylsilyl)-3,5,6,8-tetradeoxy-5-*C*-methyl-3-*C*-methylene-1,2-*O*-isopropylidine-D/L-*glycero*-β-L-*lyxo*-octofuranose (45)



Dry DMSO (2.6 mL, 36.7 mmol) and oxalyl chloride (1.6 mL, 18.3 mmol) in CH_2Cl_2 (20 mL) at –78 ^oC under N_2 were stirred for 30 min and then **43** (4.4 g, 12.2 mmol) in CH_2Cl_2 (10 mL) was added. After 1 h, the reaction was quenched by Et_3N (7.7 mL) at –78 ^oC, water (30 mL) was introduced. The organic layer was separated while the aqueous layer extracted with CH_2Cl_2. The combined organic extracts were dried (Na_2SO_4), filtered and concentrated to give crude **44** (4.24 g, 97%).

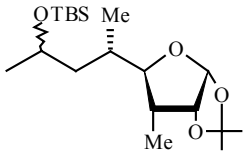
The above residue (4.24 g) was dissolved in anhydrous THF (20 mL) and cooled to –78 ^oC. Methylenetriphenylphosphorane [prepared from PPh_3CH_3I (9.5 g) and *n*BuLi (1.6 M, 1.5 mL)] was added. After 2 h stirring at rt, it was quenched by addition of saturated aqueous solution of NH_4Cl. The two layers 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 (1:19) to furnish **45** (3.16 g, 75%) as a colorless oil.

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.05, 0.06 (2 s, 6 H), 0.77 (d, 3 H, *J* = 6.7 Hz), 0.88 (s, 9 H), 1.14 (d, 3 H, *J* = 6.1 Hz), 1.37 (s, 3 H), 1.41-1.48 (m, 1 H), 1.50 (s, 3 H), 1.54-1.62 (m, 1 H), 1.87-1.99 (m, 1 H), 3.82-4.04 (m, 1 H), 4.68-4.86 (m, 2 H), 5.06-5.08 (m, 1 H), 5.42-5.45 (m, 1 H), 5.79 (d, 1 H, *J* = 4.0 Hz);

^{13}C NMR (50 MHz, $CDCl_3$): δ –5.0, –4.2, 12.2 and 13.7, 17.9, 24.0 and 24.5, 25.7, 27.0 and 27.1, 27.3 and 27.4, 32.2 and 32.3, 43.5 and 44.5, 66.0 and 66.1, 81.4 and 81.9, 84.0, 104.2 and 104.3, 111.0 and 11.1, 111.8, 148.2 and 148.3.

Anal. Calcd for $C_{19}H_{36}SiO_4$ (Mol. Wt. 356.579): C, 64.00; H, 10.17. Found; C, 64.13; H, 9.93.

7-*O*-(*tert*-Butyldimethylsilyl)-3,5,6,8-tetradeoxy-1,2-*O*-isopropylidine-3,5-*C*-dimethyl-D/L-*glycero*-β-L-*talo*-octofuranose (46)



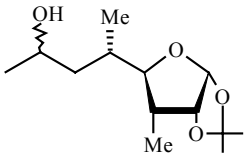
A solution of **45** (3.1 g, 8.7 mmol) in EtOAc (20 mL) was stirred in presence of 10% Pd/C (0.3 g) under hydrogen atmosphere. After 2 h, the reaction mixture was filtered through a pad of Celite and concentrated. The residue was purified on silica gel using EtOAc-light petroleum ether (1:19) to provide **46** (2.83 g, 91%).

^{1}H NMR (300 MHz, $CDCl_3$): δ 0.04, 0.05 (2 s, 6 H), 0.84 (d, 3 H, *J* = 7.3 Hz), 0.88 (s, 9 H), 1.01 (d, 3 H, *J* = 6.6 Hz), 1.13 (d, 3 H, *J* = 6.3), 1.31 (s, 3 H), 1.40-1.60 (m, 2 H), 1.49 (s, 3 H), 1.76-1.90 (m, 2 H), 3.76 (dd, 1 H, *J* = 2.2, 10.2 Hz), 3.89-3.96 (m, 1 H), 4.50 (t, 1 H, *J* = 3.9 Hz), 5.71 (d, 1 H, *J* = 3.9 Hz);

^{13}C NMR (75 MHz, $CDCl_3$): δ –4.5, –3.9, 9.5 and 9.6, 14.1 and 14.4, 18.1, 24.2 and 24.4, 26.0, 26.4, 26.7, 29.4, 39.6, 44.6 and 44.7, 66.5 and 66.7, 83.1, 83.8, 104.5, 110.9.

Anal. Calcd for $C_{19}H_{38}SiO_4$ (Mol. Wt. 358.595): C, 63.64; H, 10.68. Found; C, 63.48; H, 10.19.

3,5,6,8-tetradeoxy-3,5-*C*-dimethyl-1,2-*O*-isopropylidene-D/L-*glycero*-β-L-*talo*-octofuranose (47)



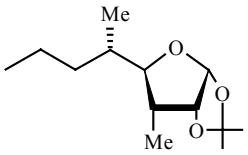
A solution of **46** (2.7 g, 7.5 mmol) and 1 M solution of nBu$_4$NF (8.3 mL, 8.3 mmol) were stirred for 30 min and concentrated. The crude was extracted with EtOAc, washed with water, dried (Na_2SO_4) and concentrated. The residue was chromatographed on silica gel using EtOAc-light petroleum ether (3:7) to obtain **47** (1.65 g, 90%).

^{1}H NMR (200 MHz, CDCl$_3$): δ 0.90 (d, 3 H, J = 7.3 Hz), 1.03 (d, 3 H, J = 6.8 Hz), 1.18 (d, 3 H, J = 6.4), 1.32 (s, 3 H), 1.49 (s, 3 H), 1.52-1.70 (m, 2 H), 1.81-1.96 (m, 2 H), 2.48 (br s, 1 H), 3.83 (dd, 1 H, J = 2.0, 10.2 Hz), 3.89-3.99 (m, 1 H), 4.52 (t, 1 H, J = 3.9 Hz), 5.72 (d, 1 H, J = 3.9 Hz);

^{13}C NMR (50 MHz, CDCl$_3$): δ 9.5 and 9.6, 13.4 and 13.5, 23.9, 26.4, 26.7, 29.8, 39.6, 44.4 and 44.6, 64.6, 83.0, 84.4, 104.4 and 104.5, 111.3.

Anal. Calcd for $C_{13}H_{24}O_4$ (Mol. Wt. 244.331): C, 63.84; H, 9.90. Found; C, 63.78; H, 10.20.

3,5,6,7,8-Pentadeoxy-1,2-*O*-isopropylidine-3,5-*C*-dimethyl-β-L-*talo*-octofuranose (22)



A solution of **47** (1.54 g, 6.3 mmol) in THF (10 mL) was added to a suspension of NaH (0.3 g, 7.6 mmol) in THF (5 mL). The resulting solution was stirred at rt for 30 min, CS_2 (0.6 mL) and MeI (0.6 mL) were added. After 1 h, reaction mixture was quenched by saturated aqueous NH_4Cl solution and organic layer separated, dried (Na_2SO_4), concentrated and the residue purified on silica gel using EtOAc-light petroleum ether (1:9) to provide **48** (1.77 g, 75%). The above product **48**, nBu$_3$SnH (1.5 mL, 5.6 mmol) and AIBN (15 mg) in toluene (15 mL) under argon were heated under reflux for 7 h, concentrated and chromatographed on silica gel using EtOAc-light petroleum ether (3:97) to afford **22** (0.78 g, 73%) as a clear liquid.

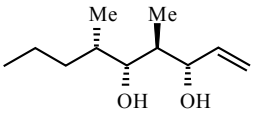
[α]$_D$ +46.7 (c 1.0, $CHCl_3$);

^{1}H NMR (300 MHz, CDCl$_3$): δ 0.84 (d, 3 H, J = 6.6 Hz), 0.90 (t, 3 H, J = 7.1 Hz), 1.01 (d, 3 H, J = 6.6 Hz), 1.31 (s, 3 H), 1.33-1.45 (m, 4 H), 1.49 (s, 3 H), 1.55-1.61 (m, 1 H), 1.79-1.84 (m, 1 H), 3.69 (dd, 1 H, J = 2.2, 10.2 Hz), 4.49 (t, 1 H, J = 4.4 Hz), 5.71 (d, 1 H, J = 4.4 Hz);

^{13}C NMR (75 MHz, CDCl$_3$): δ 9.5, 13.2,14.2, 20.5, 26.4, 26.7, 33.0, 36.8, 39.7, 83.1, 84.9, 104.5, 110.8;

Anal. Calcd for $C_{13}H_{24}O_3$ (Mol. Wt. 228.332): C, 68.38; H, 10.59. Found; C, 68.48; H, 10.64.

(3*S*,4*S*,5*R*,6*S*)-4,6-Dimethyl-non-1-en-3,5-diol (50)



Compound **22** (0.73 g, 3.2 mmol) and 6 N HCl (2 mL) in THF/H_2O (3:1, 16 mL) were heated at 70 ^oC for 3 h. The reaction mixture was neutralized by addition of solid $NaHCO_3$, filtered and concentrated. The residue was partitioned between EtOAc-water, the organic layer separated, washed with water, dried (Na_2SO_4) and concentrated. The residue was purified on silica gel using EtOAc-light petroleum ether (1:3) to obtain **49** (0.42 g) which was dissolved in THF (10 mL) and CH_2=PPh_3 [prepared from PPh_3CH_3I (2.7 g) and *n*BuLi (1.6 M, 0.4 mL)] at –78 ^oC was added. After 10 h stirring at rt, worked up as usual and the residue purified on silica gel using EtOAc-light petroleum ether (1:4) to furnish **50** (0.29 g, 71%) as a thick oil.

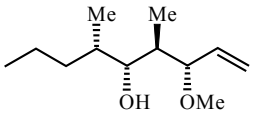
$[\alpha]_D$ +7.7 (*c* 0.7, $CHCl_3$);

^{1}H NMR (300 MHz, $CDCl_3$): δ 0.75 (d, 3 H, *J* = 6.6 Hz), 0.85 (d, 3 H, *J* = 7.3 Hz), 0.92 (t, 3 H, *J* = 6.6 Hz), 1.30-1.38 (m, 4 H), 1.65-1.75 (m, 2 H), 3.35 (br s, 2 H), 3.53 (dd, 1 H, *J* = 2.2, 8.2 Hz), 4.08 (t, 1 H, *J* = 8.0 Hz), 5.16-5.27 (m, 2 H), 5.80-5.92 (m, 1 H);

^{13}C NMR (75 MHz, $CDCl_3$): δ 12.0, 13.0, 14.3, 20.6, 34.7, 36.6, 41.0, 79.0 (2C), 116.5, 139.8;

Anal. Calcd for $C_{11}H_{22}O_2$ (Mol. Wt. 186.295): C, 70.92; H, 11.98. Found; C, 70.77; H, 12.16.

(3*S*,4*R*,5*R*,6*S*)-3-Methoxy-4,6-dimethyl-non-1-en-5-ol (51)



To a solution of **50** (0.2 g, 1.0 mmol) in dry THF (7 mL) at –78 ^oC, LiHMDS (1.06 M, 1.1 mL) was added. After15 min, MeI (0.1 mL, 1.7 mmol) in THF (0.5 mL) was introduced and the reaction mixture warmed to 0 ^oC. The reaction mixture was quenched with saturated aqueous NH_4Cl solution and extracted with EtOAc. The organic layer was dried (Na_2SO_4) and concentrated to provide a residue, which was purified on silica gel using EtOAc-light petroleum ether (1:19) to afford **51** (0.18 g, 83%) as a colorless liquid.

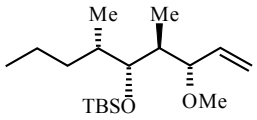
$[\alpha]_D$ −20.7 (*c* 1.0, $CHCl_3$);

^{1}H NMR (300 MHz, $CDCl_3$): δ 0.72 (d, 3 H, *J* = 7.3 Hz), 0.84 (d, 3 H, *J* = 6.6 Hz), 0.91 (t, 3 H, *J* = 6.8 Hz), 1.29-1.42 (m, 4 H), 1.53-1.63 (m, 1 H), 1.70-1.78 (m, 1 H), 3.29 (s, 3 H), 3.47 (dd, 1 H, *J* = 2.2, 8.8 Hz), 3.52 (t, 1 H, *J* = 8.4 Hz), 4.04 (br s, 1 H), 5.20 (dd, 1 H, *J* = 1.8, 17.1 Hz), 5.31 (dd, 1 H, *J* = 1.8, 10.2 Hz), 5.54-5.66 (m, 1 H);

^{13}C NMR (75 MHz, $CDCl_3$): δ 11.7, 14.6, 15.4, 21.1, 34.6, 38.6, 43.8, 56.2, 75.2, 79.5, 117.8, 137.5.

Anal. Calcd for $C_{12}H_{24}O_2$ (Mol. Wt. 200.322): C, 71.95; H, 12.07. Found; C, 71.82; H, 11.91.

(3*S*,4*S*,5*R*,6*S*)-5-[(*tert*-Butyldimethylsilyl)oxy]-3-methoxy-4,6-dimethyl-non-1-ene (21)



Compound **51** (0.13 g, 0.6 mmol), 2,6-lutidine (0.1 mL, 1.3 mmol) and TBSOTf (0.22 mL, 1.0 mmol) in CH_2Cl_2 (4 mL) were stirred at rt for 1 h, washed with water and concentrated. The residue was purified on silica gel using EtOAc-light petroleum (1:49) to furnish **21** (0.16 g, 80%) as a colorless liquid.

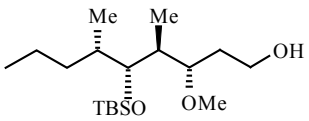
$[\alpha]_D$ +3.9 (*c* 1.0, $CHCl_3$);

^{1}H NMR (300 MHz, $CDCl_3$): δ 0.06 (s, 6 H), 0.80 (d, 3 H, *J* = 7.3 Hz), 0.86 (d, 3 H, *J* = 6.6 Hz), 0.89- 0.93 (m, 12 H), 1.27-1.36 (m, 4 H), 1.55-1.63 (m, 1 H), 1.83-1.90 (m, 1 H), 3.22 (s, 3 H), 3.46 (t, 1 H, *J* = 7.6 Hz), 3.80 (dd, 1 H, *J* = 2.2, 5.8 Hz), 5.16-5.27 (m, 2 H), 5.54-5.66 (m, 1 H);

^{13}C NMR (75 MHz, $CDCl_3$): δ –4.1, –3.8, 11.6, 14.4, 15.2, 18.6, 20.7, 26.2, 34.5, 38.4, 43.6, 56.0, 74.0, 84.8, 117.7, 137.3;

Anal. Calcd for $C_{18}H_{38}SiO_2$ (Mol. Wt. 314.586): C, 68.72; H, 12.17. Found; C, 68.70; H, 11.92.

(3*S*,4*S*,5*R*,6*S*)-5-[(*tert*-Butyldimethylsilyl)oxy]-4,6-dimethyl-3-methoxy-nonan-1-ol (52)



To a solution of **21** (0.11 g, 0.3 mmol) in anhydrous THF (3 mL) at 0 ^{o}C was added $H_3B{:}SMe_2$ (0.1 mL, 1.0 mmol). After stirring for 1 h, saturated NaOAc solution was introduced followed by the addition of 30% H_2O_2 (0.1 mL). The reaction mixture was further stirred at rt for 5 h, diluted with EtOAc, dried (Na_2SO_4) and concentrated. The crude was purified on silica gel using EtOAc-light petroleum ether (1:9) to provide **52** (70 mg, 60%).

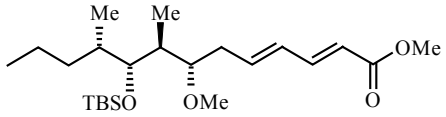
$[\alpha]_D$ –23.9 (*c* 0.8, $CHCl_3$);

^{1}H NMR (500 MHz, $CDCl_3$): δ 0.05, 0.06 (2 s, 6 H), 0.82 (d, 3 H, *J* = 7.2 Hz), 0.87 (d, 3 H, *J* = 6.8 Hz), 0.91-0.93 (m, 12 H), 1.17-1.20 (m, 1 H), 1.34-1.39 (m, 3 H), 1.60-1.65 (m, 1 H), 1.66-1.71 (m, 2 H), 2.06-2.10 (m, 1 H), 3.34 (s, 3 H), 3.48 (dd, 1 H, *J* = 2.4, 7.6 Hz), 3.64 (dt, 1 H, *J* = 4.4, 8.4 Hz), 3.78 (t, 2 H, *J* = 5.6 Hz);

^{13}C NMR (125 MHz, $CDCl_3$): δ –3.7, –3.4, 11.0, 14.3 (2C), 18.6, 20.9, 26.4, 31.2, 36.2, 37.1, 38.6, 55.2, 61.7, 76.9, 82.5;

Anal. Calcd for $C_{18}H_{40}SiO_3$ (Mol. Wt. 332.601): C, 65.00; H, 12.12. Found; C, 64.73; H, 12.20.

Methyl (7*S*,8*S*,9*R*,10*S*)-9-[(*tert*-butyldimethylsilyl)oxy]-8,10-dimethyl-7-methoxytrideca-2*E*,4*E*-dienoate (54)



A solution of **52** (45 mg, 0.14 mmol), pyridine (30 μL) and Dess-Martin periodinane (85 mg) in CH_2Cl_2 (2 mL) was stirred at rt for 30 min and then saturated solution of $NaHCO_3$ and $Na_2S_2O_3$ (1:1, 2 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 aldehyde **20** (38 mg).

To a solution of methyl 4-(diethylphosphono)crotonate (60 mg) in anhydrous THF (2 mL) at –78 ^{o}C, LiHMDS (0.25 mL, 1.0 M) was added. After 1 h, this solution was transferred *via* cannula into **20** (38 mg) in THF (2 mL) maintained at –78 ^{o}C. The reaction mixture was warmed to rt, stirred for 1 h, quenched with saturated aqueous NH_4Cl solution and extracted with EtOAc. The organic layer was dried (Na_2SO_4), concentrated and purified on silica gel using EtOAc-light petroleum ether (1:9) to afford **54** (39 mg, 82%) as a colorless liquid.

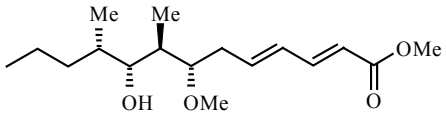
$[\alpha]_D$ −8.0 (*c* 0.7, $CHCl_3$);

^{1}H NMR (500 MHz, $CDCl_3$): δ 0.01, 0.03 (2 s, 6 H), 0.81 (d, 3 H, *J* = 7.0 Hz), 0.83 (d, 3 H, *J* = 6.5 Hz), 0.89- 0.91 (m, 12 H), 1.14-1.20 (m, 1 H), 1.28-1.40 (m, 3 H), 1.57-1.64 (m, 1 H), 1.96-2.02 (m, 1 H), 2.20-2.26 (m, 1 H), 2.41 (ddd, 1 H, *J* = 2.8, 5.4, 14.7 Hz), 3.29 (s, 3 H), 3.38 (ddd, 1 H, J = 2.8, 5.4, 8.5 Hz), 3.58 (dd, 1 H, *J* = 2.3, 6.5 Hz), 3.75 (s, 3 H), 5.80 (d, 1 H, *J* = 15.2 Hz), 6.18 (dt, 1 H, *J* = 7.4, 15.1 Hz), 6.22 (dd, 1 H, *J* = 9.9, 15.1 Hz), 7.28 (dd, 1 H, *J* = 9.9, 15.2 Hz);

^{13}C NMR (125 MHz, $CDCl_3$): δ −3.7, 11.2, 14.4, 14.7, 18.6, 20.9, 26.3, 33.6, 35.7, 37.6, 40.4, 51.3, 56.8, 76.2, 81.2, 119.2, 130.2, 141.1, 145.0, 167.4;

Anal. Calcd for $C_{23}H_{44}SiO_4$ (Mol. Wt. 412.687): C, 66.94; H, 10.74. Found; C, 67.15; H, 10.51.

Methyl (7*S*,8*S*,9*R*,10*S*)-8,10-dimethyl-9-hydroxy-7-methoxytrideca-2*E*,4*E*-dienoate (17)

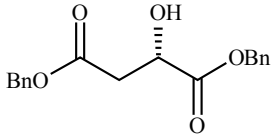


To compound **54** (32.5 mg, 0.075 mmol) was added 0.5 mL of 1% HCl-EtOH solution and stirred for 1 h at 0 ^oC, neutralized by adding solid $NaHCO_3$ and filtered. The filtrate was concentrated and purified with EtOAc-light petroleum ether (2:8) on silica gel to obtain **17** (12.5 mg, 53%) as a thick oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ 0.82 (d, 3 H, *J* = 7.0 Hz), 0.87 (d, 3 H, *J* = 6.5 Hz), 0.91 (t, 3 H, *J* = 7.5 Hz), 1.20-1.25 (m, 1 H), 1.30-1.40 (m, 3 H), 1.55-1.65 (m, 1 H), 1.86-1.95 (m, 1 H), 2.10-2.16 (m, 1 H), 2.32 (ddd, 1 H, *J* = 2.8, 5.5, 14.9 Hz), 3.20 (s, 3 H), 3.29 (ddd, 1 H, *J* = 2.8, 5.5, 8.3 Hz), 3.49 (dd, 1 H, *J* = 2.2, 6.6 Hz), 3.75 (s, 3 H), 5.69 (d, 1 H, *J* = 15.2 Hz), 6.10 (dt, 1 H, *J* = 7.8, 15.1 Hz), 6.14 (dd, 1 H, *J* = 9.9, 15.1 Hz), 7.25 (dd, 1 H, *J* = 9.9, 15.2 Hz);

^{13}C NMR (125 MHz, $CDCl_3$): δ 11.5, 14.9, 15.0, 21.0, 33.7, 35.9, 37.8, 40.6, 51.3, 56.9, 72.0, 78.8, 119.5, 130.3, 141.2, 145.0, 167.5.

Dibenzyl (*S*)-2-hydroxysuccinate (65)



A mixture of L-malic acid (**64**) (13.4 g, 100 mmol), BnOH (21.6 g, 200 mmol) and *p*TSA (0.19 g, 1.0 mmol) in dried $C_6H_5CH_3$ (150 mL) was heated under reflux in a Dean-Stark apparatus with azeotropic removal of H_2O. After 5 h, the reaction mixture was washed with saturated aqueous $NaHCO_3$ and brine, dried (Na_2SO_4) and concentrated to leave a residue, which was purified on silica gel using EtOAc-light petroleum (1:4) to provide **65** (28.3 g, 90%) as a thick oil.

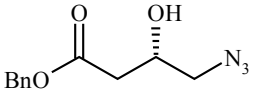
$[\alpha]_D$ −18.2 (*c* 1.9, $CHCl_3$); lit.,[55b] **$[\alpha]_D$** −19.3 (*c* 1.9, $CHCl_3$);

^{1}H NMR (200 MHz, $CDCl_3$): δ 2.86-2.90 (m, 2 H), 3.25 (d, 1 H, *J* = 5.5 Hz), 4.53 (q, 1 H, *J* = 5.1 Hz), 5.15 (ABq, 4 H, *J* = 12.9 Hz), 7.26-7.39 (m, 10 H);

^{13}C NMR (50 MHz, $CDCl_3$): δ 38.4, 66.4, 67.1, 67.2, 128.1, 128.2, 128.3, 134.8, 135.2, 170.0, 172.9;

Anal. Calcd for $C_{18}H_{18}O_5$ (Mol. Wt. 314.337): C, 68.78; H, 5.77. Found; C, 68.46; H, 5.53.

Benzyl (3*S*)-4-azido-3-hydroxybutanoate (63)



To a solution of **65** (15.0 g, 47.8 mmol) in anhydrous THF (150 mL) at 0 °C was added $H_3B{:}SMe_2$ (4.5 mL, 47.8 mmol) and stirred for 1 h. $NaBH_4$ (90 mg. 2.4 mmol) was added and stirring continued for 30 min at rt. The mixture was then quenched by addition of MeOH (20 mL), stirred for a further 30 min, concentrated and purified on silica gel using EtOAc-light petroleum (3:2) to afford the diol **66** (7.0 g, 70%) which was dissolved in dry CH_2Cl_2 (50 mL) and then Py (5.4 mL, 66.6 mmol) and MsCl (2.6 mL, 33.3 mmol) were added. The mixture was stirred for 48 h and washed with 2 N HCl solution, water, dried (Na_2SO_4) and concentrated to leave a crude residue **67** (8.6 g). This was stirred in DMF (40 mL) and treated with NaN_3 (13.6 g, 209.0 mmol) at 80 °C for 3 h, H_2O added, extracted with EtOAc, dried (Na_2SO_4), concentrated and purified on silica gel using EtOAc-light petroleum (1:9) to furnish **63** (6.5 g, 92%) as a colorless oil.

$[\alpha]_D$ +17.2 (*c* 2.0, H_2O); lit.,[55c] **$[\alpha]_D$** (enantiomer) –20.4 (*c* 2.0, H_2O);

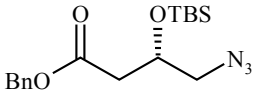
^{1}H NMR (200 MHz, $CDCl_3$): δ 2.57-2.60 (m, 2 H), 3.25 (br s, 1 H), 3.31-3.34 (m, 2 H), 4.14-4.29 (m, 1 H), 4.68 (s, 2 H), 7.29-7.40 (m, 5 H);

^{13}C NMR (50 MHz, $CDCl_3$): δ 38.4, 55.3, 66.3, 66.9, 127.9, 128.1, 128.3, 135.2, 171.3;

IR: 698, 755, 1168, 1282, 1731, 2091, 2930, 3017, 3455 cm^{-1};

Anal. Calcd for $C_{11}H_{13}N_3O_3$ (Mol. Wt. 235.243): C, 56.16; H, 5.57; N, 17.86. Found; C, 56.33; H, 5.74; N, 17.79.

Benzyl (3*S*)-4-azido-3-[(*tert*-butyldimethylsilyl)oxy]-butanoate (68)



Compound **63** (6.0 g, 0.6 mmol), 2,6-lutidine (5.9 mL, 76.5 mmol) and TBSOTf (6.2 mL, 28.0 mmol) in CH_2Cl_2 (40 mL) were stirred at –20 ^oC for 2 h, washed with water and concentrated. The residue was purified on silica gel by using EtOAc-light petroleum (1:19) to furnish **68** (8.2 g, 92%) as a colorless liquid.

$[\alpha]_D$ +9.9 (*c* 1.2, $CHCl_3$);

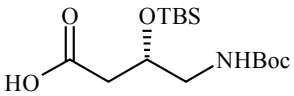
^{1}H NMR (200 MHz, $CDCl_3$): δ 0.08 (s, 3 H), 0.13 (s, 3 H), 0.88 (s, 9 H), 2.58-2.61 (m, 2 H), 3.29 (dq, 2 H, *J* = 4.5, 12.6 Hz), 4.21-4.32 (m, 1 H), 5.11 (s, 2 H), 7.29-7.39 (m, 5 H);

^{13}C NMR (50 MHz, $CDCl_3$): δ –5.3, –4.9, 17.7, 25.5, 39.7, 56.1, 66.1, 68.5, 128.1, 128.3, 135.5, 170.1;

IR: 697, 838, 1216, 1258, 1735, 2106, 2931, 3020 cm^{-1};

Anal. Calcd for $C_{17}H_{27}N_3O_3Si$ (Mol. Wt. 349.507): C, 58.42; H, 7.79; N, 12.02. Found; C, 58.32; H, 7.68; N, 11.81.

(3*S*)-4-[(*tert*-Butyloxycarbonyl)amino]-3-[(*tert*-butyldimethylsilyl)oxy]-butanoic acid (59a)



A solution of **68** (2.0 g, 5.7 mmol) and $(Boc)_2O$ (2.6 mL, 11.5 mmol) in EtOAc (15 mL) was stirred in presence of 10% Pd/C (0.2 g) under hydrogen atmosphere at 20 psi. After 2 h, the

reaction mixture was filtered through a pad of Celite and concentrated. The residue was purified on silica gel using EtOAc-light petroleum ether (3:7) to provide **59a** (1.5 g, 79%).

$[\alpha]_D$ −11.8 (*c* 1.0, $CHCl_3$);

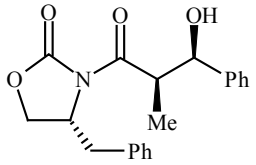
^{1}H NMR (200 MHz, $CDCl_3$): δ 0.07 (s, 3 H), 0.10 (s, 3 H), 0.88 (s, 9 H), 1.45 (s, 9 H), 2.48 (d, 2 H, *J* = 5.9 Hz), 3.23 (t, 2 H, *J* = 5.3 Hz), 4.19-4.26 (m, 1 H), 4.80 (t, 1 H, *J* = 5.3 Hz);

^{13}C NMR (50 MHz, $CDCl_3$): δ −5.3, −5.0, 17.6, 25.5, 28.1, 39.9, 45.8 (rotamer at 47.0), 68.1, 79.0 (rotamer at 80.5), 155.7 (rotamer at 157.2), 175.4;

IR: 778, 838, 1171, 1254, 1712, 2931 cm^{-1};

Anal. Calcd for $C_{15}H_{31}NO_5Si$ (Mol. Wt. 333.504): C, 54.02; H, 9.37; N, 4.20. Found; C, 54.09; H, 9.31; N, 4.38.

[3-(2*R*,3*R*)-4*R*]-3-(3-hydroxy-3-phenyl-2-methyl-1-oxopropyl)-4-(phenylmethyl) oxazolidin-2-one (70)



Bu_2BOTf (13.5 mL, 53.5 mmol), followed by Et_3N (8.4 mL, 60.0 mmol) were added dropwise to an ice-cooled solution of the imide **71** (10.6 g, 45.5 mmol) in CH_2Cl_2 (100 mL). The reaction mixture was then cooled to −78 ^oC and freshly distilled PhCHO (5.2 mL, 50.5 mmol) was added dropwise and stirred at the same temperature for 30 min and warmed to 0 ^oC for a further 1 h, pH 7 buffer (50 mL) and MeOH (150 mL) were added. A solution of MeOH/30% aqueous H_2O_2 (2:1, 150 mL) was added cautiously maintaining internal temperature below 10 ^oC and stirred at rt for 1 h, concentrated and extracted with EtOAc. The combined organic extracts were washed with 5% aqueous $NaHCO_3$, brine, dried (Na_2SO_4), concentrated and purified on silica gel using EtOAc-light petroleum ether (1:4) to provide **70** (13.9 g, 90%).

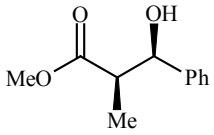
$[\alpha]_D$ −72.1 (*c* 1.0, CH_2Cl_2); lit.,[63] **$[\alpha]_D$** (enantiomer) +75.7 (*c* 1.0, CH_2Cl_2);

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.22 (d, 3 H, *J* = 7.1 Hz), 2.74 (dd, 1 H, *J* = 9.8, 13.3 Hz), 3.16 (br s, 1 H), 3.25 (dd, 1 H, *J* = 3.6, 13.3 Hz), 3.98-4.17 (m, 3 H), 4.50- 4.61 (m, 1 H), 5.06 (d, 1 H, *J* = 4.3 Hz), 7.16-7.41 (m, 10 H);

^{13}C NMR (50 MHz, $CDCl_3$): δ 10.9, 37.3, 44.4, 54.9, 65.7, 73.7, 125.8, 127.0, 127.1, 127.8, 128.6, 129.1, 134.9, 141.6, 152.6, 175.8;

Anal. Calcd for $C_{20}H_{21}NO_4$ (Mol. Wt. 339.391): C, 70.78; H, 6.24; N, 4.13. Found; C, 70.68; H, 6.31; N, 4.22.

Methyl (2*R*,3*R*)-3-hydroxy-3-phenyl-2-methylpropionate (75)



To a 0 °C solution of **70** (2 g, 5.9 mmol) in anhydrous MeOH/CH_2Cl_2 (1:1, 20 mL) was added a suspension formed by the addition of MeMgBr (2.0 mL, 6.5 mmol, 3.2 M in Et_2O) to anhydrous MeOH (8 mL). After 5 min, the reaction mixture was quenched by the addition of 1 N aqueous $NaHSO_4$ (20 mL), the organic layer isolated and the aqueous layer extracted with CH_2Cl_2. The combined organic phases were dried (Na_2SO_4), concentrated and purified on silica gel using EtOAc-light petroleum ether (1:9) to provide **75** (0.93 g, 81%).

$[\alpha]_D$ +21.1 (*c* 1.73, $CHCl_3$); lit.,[59a] **$[\alpha]_D$** +21.5 (*c* 1.73, $CHCl_3$);

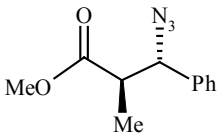
^{1}H NMR (200 MHz, $CDCl_3$): δ 1.11 (d, 3 H, *J* = 7.1 Hz), 2.69-2.82 (m, 1 H), 3.01 (br s, 1 H), 3.65 (s, 3 H), 5.07 (d, 1 H, *J* = 3.9 Hz), 7.20-7.41 (m, 5 H);

^{13}C NMR (50 MHz, $CDCl_3$): δ 10.8, 46.5, 51.2, 73.5, 125.6, 127.0, 127.7, 141.7, 175.2;

IR: 702, 769, 1198, 1455, 1725, 2951, 3492 cm^{-1};

Anal. Calcd for $C_{11}H_{14}O_3$ (Mol. Wt. 194.232): C, 68.02; H, 7.27. Found; C, 67.92; H, 7.10.

Methyl (2*R*,3*S*)-3-azido-3-phenyl-2-methylpropionate (76)



To a solution of **75** (5.0 g, 25.8 mmol) in anhydrous THF (30 mL) were added PPh_3 (10.2 g, 38.7 mmol) and HN_3 (55 mL of 0.93 M solution in C_6H_6, 51.6 mmol) at 0 °C. DEAD (6.5 mL, 41.3 mmol) in THF (15 mL) was added dropwise. After 4 h stirring at rt, the reaction mixture was partitioned between EtOAc and 10% aqueous $NaHCO_3$, the organic layer isolated, dried

(Na_2SO_4), concentrated and purified on silica gel using EtOAc-light petroleum ether (1:19) to furnish **76** (4.3 g, 77%).

$[\alpha]_D$ −162.5 (*c* 1.2, $CHCl_3$);

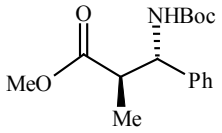
^{1}H NMR (200 MHz, $CDCl_3$): δ 0.93 (d, 3 H, *J* = 7.4 Hz), 2.70-2.86 (m, 1 H), 3.78 (s, 3 H), 4.63 (d, 1 H, *J* = 10.6 Hz), 7.26-7.42 (m, 5 H);

^{13}C NMR (50 MHz, $CDCl_3$): δ 14.3, 45.2, 51.5, 68.1, 127.4, 128.5, 128.6, 136.4, 174.1;

IR: 669, 771, 1216, 1735, 2104, 3020 cm^{-1};

Anal. Calcd for $C_{11}H_{13}N_3O_2$ (Mol. Wt. 219.244): C, 60.26; H, 5.97; N, 19.17. Found; C, 60.10; H, 6.07; N, 19.26.

Methyl (2*R*,3*S*)-3-[(*tert*-butyloxycarbonyl)amino]-3-phenyl-2-methylpropionate (69)



A solution of **76** (4.1 g, 18.7 mmol) and $(Boc)_2O$ (8.6 mL, 37.4 mmol) in EtOAc (30 mL) was stirred in presence of 10% Pd/C (0.4 g) under hydrogen atmosphere at 20 psi. After 3 h, the reaction mixture was filtered through a pad of Celite and concentrated. The residue was purified on silica gel using EtOAc-light petroleum ether (3:17) to provide **69** (4.7 g, 86%) as a colorless liquid.

$[\alpha]_D$ −27.5 (*c* 1.0, $CHCl_3$);

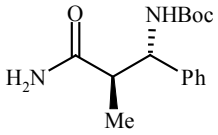
^{1}H NMR (200 MHz, $CDCl_3$): δ 1.23 (d, 3 H, *J* = 7.4 Hz), 1.41 (s, 9 H), 2.91 (quin, 1 H, *J* = 6.5 Hz), 3.57 (s, 3 H), 4.80 (t, 1 H, *J* = 7.1 Hz), 5.80 (d, 1 H, *J* = 7.4 Hz), 7.19-7.35 (m, 5 H);

^{13}C NMR (50 MHz, $CDCl_3$): δ 15.1, 28.0, 44.9, 51.3, 56.4, 78.9, 126.1, 127.0, 128.1, 140.8, 155.0, 174.1;

IR: 757, 1169, 1250, 1525, 1687, 1734, 2976, 3380 cm^{-1};

Anal. Calcd for $C_{16}H_{23}NO_4$ (Mol. Wt. 293.363): C, 65.51; H, 7.90; N, 4.78. Found; C, 65.40; H, 8.04; N, 4.77.

(1*S*,2*R*)-[2-Methyl-2-carbamoyl-1-phenylethyl]carbamic acid *tert*-butyl ester (77)



A sample of **69** (4.5 g, 15.4 mmol) was dissolved into CH_3OH (25 mL) and NH_3 was bubbled through the CH_3OH solution at 0 °C until saturation. The tube was sealed and stirred at rt for 10 days, concentrated and directly subjected to silica gel purification using EtOAc-light petroleum ether (3:2) which provided **77** (2.0 g, 48%) as a white solid.

$[\alpha]_D$ −45.0 (*c* 1.0, MeOH);

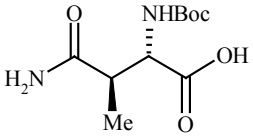
^{1}H NMR (500 MHz, DMSO-d_6 + $CDCl_3$): δ 1.01 (d, 3 H, *J* = 6.8 Hz), 1.37 (s, 9 H), 2.69 (quin, 1 H, *J* = 6.5 Hz), 4.55 (t, 1 H, *J* = 7.4 Hz), 6.69 (br s, 1 H), 7.11 (br s, 2 H), 7.19-7.30 (m, 5 H);

^{13}C NMR (125 MHz, DMSO-d_6 + $CDCl_3$): δ 14.5, 26.7, 42.5, 55.6, 76.4, 125.0, 125.1, 126.4, 140.8, 153.4, 175.1;

IR: 755, 1170, 1462, 1524, 1652, 1682, 2924, 3358, 3406 cm^{-1};

Anal. Calcd for $C_{15}H_{22}N_2O_3$ (Mol. Wt. 278.352): C, 64.72; H, 7.79; N, 10.06. Found; C, 64.63; H, 7.83; N, 9.96.

L-*erythro*-BocNH-*β*-Me-Asn-OH (78)



A solution of $NaIO_4$ (1.5 g, 7.2 mmol) in CH_3CN/H_2O (1:8, 18 mL) was treated with a solution of **77** (0.2 g, 0.72 mmol) in EtOAc (2 mL) followed by $RuCl_3$,$3H_2O$ (10 mg, 0.04 mmol) and $NaHCO_3$ (60 mg). The reaction mixture was stirred vigorously at rt for 24 h and extracted into saturated aqueous $NaHCO_3$ and washed with CH_2Cl_2. The aqueous layer was acidified with the addition of 10% aqueous HCl to pH 3-4 in an ice-bath and extracted with EtOAc several times. The combined organic layers were dried (Na_2SO_4) and concentrated to provide **78** (83 mg, 47%) as a white solid.

$[\alpha]_D$ +9.8 (*c* 1.0, MeOH);

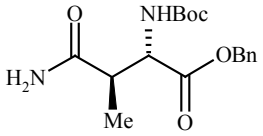
^{1}H NMR (200 MHz, DMSO-d_6 + $CDCl_3$): δ 1.24 (d, 3 H, *J* = 7.4 Hz), 1.44 (s, 9 H), 3.01-3.11 (m, 1 H), 4.27 (dd, 1 H, *J* = 3.8, 8.8 Hz), 6.05 (d, 1 H, *J* = 8.8 Hz), 6.58 (br s, 1 H), 7.30 (br s, 1 H);

^{13}C NMR (75 MHz, DMSO-d_6 + $CDCl_3$): δ 14.8, 28.1, 40.5, 55.5, 78.9,155.7, 172.6, 177.2;

IR: 759, 1216, 1506, 1682, 1707, 3020, 3408 cm^{-1};

Anal. Calcd for $C_{10}H_{18}N_2O_5$ (Mol. Wt. 246.263): C, 48.77; H, 7.37; N, 11.38. Found; C, 48.72; H, 7.11; N, 11.21.

L-*erythro*-BocNH-*β*-Me-Asn-OBn (79)



To a solution of **78** (0.5 g, 2.0 mmol) in DMF (4 mL) at 0 °C was added $NaHCO_3$ (0.34 g, 4.0 mmol) and BnBr (0.9 mL, 8.0 mmol). The reaction mixture was stirred at rt for 24 h, quenched by ice-cold water and extracted with EtOAc. The combined organic layers were washed with water, dried (Na_2SO_4) and concentrated. The residue was purified on silica gel using EtOAc-light petroleum ether (1:3) to obtain **79** (0.47 g, 69%) as a white solid.

$[\alpha]_D$ −11.4 (*c* 1.0, $CHCl_3$);

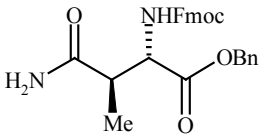
^{1}H NMR (200 MHz, $CDCl_3$): δ 1.28 (d, 3 H, *J* = 7.0 Hz), 1.44 (s, 9 H), 3.04-3.16 (m, 1 H), 4.43 (dd, 1 H, *J* = 4.0, 9.5 Hz), 5.12 (d, 1 H, *J* = 12.2 Hz), 5.24 (d, 1 H, *J* = 12.2 Hz), 5.47 (br s, 2 H), 5.81 (d, 1 H, *J* = 9.5 Hz), 7.31-7.38 (m, 5 H);

^{13}C NMR (75 MHz, $CDCl_3$): δ 14.8, 28.1, 40.8, 55.9, 66.8, 79.5, 127.8, 128.0, 128.3, 135.3, 156.1, 171.3, 176.6;

IR: 698, 838, 1167, 1252, 1495, 1717, 1756, 2930, 3456 cm^{-1};

Anal. Calcd for $C_{17}H_{24}N_2O_5$ (Mol. Wt. 336.388): C, 60.70; H, 7.19; N, 8.33. Found; C, 60.51; H, 6.92; N, 8.44.

L-*erythro*-FmocNH-*β*-Me-Asn-OBn (80)



A mixture of **79** (0.4 g, 1.2 mmol) and 4 N HCl-EtOAc (8 mL) was stirred at rt for 3 h. The removal of the excess HCl and EtOAc with N_2 provided a white solid which was dissolved in 50% dioxane/H_2O (10 mL) and then $NaHCO_3$ (0.2 g, 2.4 mmol) and FmocCl (0.46 g, 1.8 mmol) were added. After 12 h, the reaction mixture was partitioned between saturated aqueous $NaHCO_3$ and EtOAc. The aqueous layer was extracted with EtOAc for several times and the combined organic layers were dried (Na_2SO_4) and concentrated. The residue was purified on silica gel using EtOAc-light petroleum ether (1:1) to afford **80** (0.24 g, 45%) as a white solid.

$[\alpha]_D$ −17.6 (*c* 0.4, MeOH);

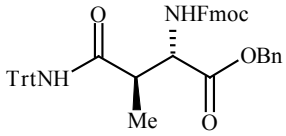
^{1}H NMR (200 MHz, d_6-DMSO): δ 1.25 (d, 3 H, *J* = 7.0 Hz), 3.04-3.14 (m, 1 H), 4.17-4.42 (m, 4 H), 5.15 (s, 2 H), 5.32 (br s, 1 H), 6.77 (d, 1 H, *J* = 9.4 Hz), 7.14 (br s, 1 H), 7.24-7.42 (m, 9 H), 7.61 (d, 2 H, *J* = 7.4 Hz), 7.75 (d, 2 H, *J* = 7.4 Hz);

^{13}C NMR (75 MHz, d_6-DMSO): δ 14.3, 39.6, 46.1, 55.8, 65.8, 65.9, 118.9, 124.2, 126.8, 126.9, 127.2, 127.5, 134.7, 140.1, 142.8, 143.0, 155.7, 170,2, 175.5;

IR: 665, 808, 1142, 1259, 1507, 1724, 1741, 2938, 3429 cm^{-1};

Anal. Calcd for $C_{27}H_{26}N_2O_5$ (Mol. Wt. 458.514): C, 70.73; H, 5.72; N, 6.11. Found; C, 70.57; H, 5.61; N, 5.90.

L-*erythro*-FmocNH-*β*-Me-Asn (Trt)-OBn (60a)



A solution of **80** (100 mg, 0.22 mmol) and TrtOH (570 mg, 2.2 mmol) in HOAc (0.8 mL) at 50 °C was treated successively with concentrated H_2SO_4 (7.5 μL, 0.13 mmol) and Ac_2O (51.6 μL, 0.55 mmol). After 3 h at 50 ^oC, the reaction mixture was partitioned between EtOAc and saturated aqueous $NaHCO_3$. The aqueous layer was extracted with EtOAc for several times and the combined organic layers were dried (Na_2SO_4) and concentrated. The residue was purified on silica gel using EtOAc-light petroleum ether (3:7) to afford **60a** (77 mg, 52%) as a white solid.

$[\alpha]_D$ −5.8 (*c* 1.2, $CHCl_3$);

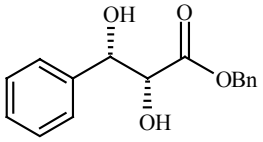
^{1}H NMR (300 MHz, $CDCl_3$): δ 1.32 (d, 3 H, *J* = 7.3 Hz), 3.24-3.32 (m, 1 H), 4.13-4.26 (m, 2 H), 4.40 (dd, 1 H, *J* = 7.0, 10.0 Hz), 4.54 (dd, 1 H, *J* = 3.8, 10.0 Hz), 5.11 (s, 2 H), 6.33 (d, 1 H, *J* = 9.8 Hz), 6.70 (br s, 1 H), 7.10-7.14 (m, 6 H), 7.22-7.31 (m, 18 H), 7.37 (t, 2 H, *J* = 7.4 Hz), 7.55 (dd, 1 H, *J* = 3.5, 7.4 Hz), 7.73 (d, 1 H, *J* = 7.4 Hz);

^{13}C NMR (75 MHz, $CDCl_3$): δ 15.3, 42.1, 47.2, 56.7, 67.4, 70.8, 77.2, 119.9, 125.2, 125.3, 127.1, 127.2, 127.6, 128.1, 128.2, 128.6, 135.3, 141.3, 143.8, 144.1, 144.4, 157.1, 171.1, 173.2;

IR: 668, 758, 909, 1216, 1449, 1491, 1682, 1720, 2928, 3020, 3428 cm^{-1};

Anal. Calcd for $C_{46}H_{40}N_2O_5$ (Mol. Wt. 700.835): C, 78.83; H, 5.76; N, 4.00. Found; C, 78.69; H, 5.63; N, 4.21.

Benzyl (2*R*,3*S*)-2,3-dihydroxy-3-phenylpropionate (84)



To a mixture of $K_3[Fe(CN)_6]$ (59.3 g, 180 mmol), K_2CO_3 (24.8 g, 180 mmol), $(DHQ)_2$ PHAL (0.467 g, 0.6 mmol), $MeSO_2NH_2$ (5.7 g, 60.0 mmol) and $K_2OsO_2(OH)_4$ (84 mg, 0.24 mmol) in *t*BuOH:H_2O (1:1, 600 mL) at 0 °C was added olefin **83** (14.3 g, 60.0 mmol) and stirred at rt. After 20 h, sodium sulphite (90.0 g) was added and solvent evaporated. The residue was extracted with EtOAc, washed with 2 N KOH solution, water, brine, dried (Na_2SO_4) and concentrated. The residue on purification by silica gel chromatography using EtOAc-light petroleum ether (1:3) afforded **84** (10.9 g, 67 %).

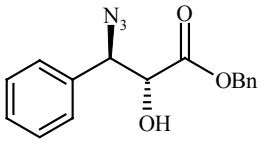
$[\alpha]_D$ +5.3 (*c* 2.3, $CHCl_3$); lit.,[68a] **$[\alpha]_D$** +4.94 (*c* 2.3, $CHCl_3$);

^{1}H NMR (200 MHz, $CDCl_3$): δ 3.33 (br s, 1 H), 3.59 (br s, 1 H), 4.31 (d, 1 H, *J* = 3.3 Hz), 4.91 (d, 1 H, *J* = 3.3 Hz), 5.11 (ABq, 2 H, *J* = 12.1 Hz), 7.19-7.32 (m, 10 H);

^{13}C NMR (75 MHz, $CDCl_3$): δ 67.3, 74.6, 75.1, 126.4, 127.9, 128.2, 128.3, 128.5, 135.0, 139.8, 172.5;

Anal. Calcd for $C_{16}H_{16}O_4$ (Mol. Wt. 272.304): C, 70.58; H, 5.92. Found; C, 70.49; H, 6.21.

Benzyl (2*R*,3*R*)-3-azido-2-hydroxy-3-phenylpropionate (85)



Mitsunobu reaction of **84** (5.5 g, 20.2 mmol) was performed as described earlier using PPh_3 (8.0 g, 30.3 mmol), HN_3 (43 mL of 0.93 M solution in C_6H_6, 40.4 mmol) and DEAD (5.0 mL, 32.3 mmol) in THF (40 mL) to obtain **85** (4.38 g, 73%) after silica gel column purification using EtOAc-light petroleum ether (1:9).

$[\alpha]_D$ −36.8 (*c* 2.0, $CHCl_3$);

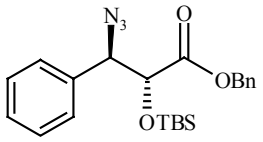
^{1}H NMR (200 MHz, $CDCl_3$): δ 2.77 (br s, 1 H), 4.57 (d, 1 H, *J* = 3.9 Hz), 4.86 (d, 1 H, *J* = 3.9 Hz), 5.14 (ABq, 2 H, *J* = 11.7 Hz), 7.23-7.39 (m, 10 H);

^{13}C NMR (75 MHz, $CDCl_3$): δ 67.1, 67.5, 73.7, 127.8, 128.4, 128.5, 134.4, 134.6, 171.1;

IR: 755, 1117, 1216, 1735, 2108, 3019, 3469 cm^{-1};

Anal. Calcd for $C_{16}H_{15}N_3O_3$ (Mol. Wt. 297.314): C, 64.64; H, 5.08; N, 14.13. Found; C, 64.45; H, 5.07; N, 13.95.

Benzyl (2*R*,3*R*)-3-azido-2-[(*tert*-butyldimethylsilyl)oxy]-3-phenylpropionate (82)



TBS protection of **85** (4.1 g, 13.8 mmol) was done as described earlier using 2,6-lutidine (3.2 mL, 41.4 mmol) and TBSOTf (3.4 mL, 15.2 mmol) in CH_2Cl_2 (30 mL) to give **82** (5.1 g, 90%) after silica gel column purification using EtOAc-light petroleum ether (1:19).

$[\alpha]_D$ −31.5 (*c* 1.3, $CHCl_3$);

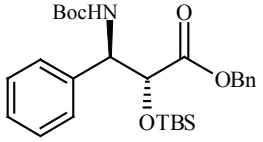
^{1}H NMR (200 MHz, $CDCl_3$): δ –0.20 (s, 3 H), –0.10 (s, 3 H), 0.78 (s, 9 H), 4.31 (d, 1 H, *J* = 6.8 Hz), 4.73 (d, 1 H, *J* = 6.8 Hz), 5.15 (ABq, 2 H, *J* = 11.9 Hz), 7.24-7.40 (m, 10 H);

^{13}C NMR (75 MHz, $CDCl_3$): δ –5.7, –5.4, 18.0, 25.5, 66.8, 67.4, 75.7, 128.3, 128.4, 128.6, 135.2, 135.5, 170.1;

IR: 759, 839, 1216, 1255, 1472, 1740, 1733, 2108, 2931 cm^{-1};

Anal. Calcd for $C_{22}H_{29}N_3O_3Si$ (Mol. Wt. 411.578): C, 64.20; H, 7.10; N, 10.21. Found; C, 63.94; H, 7.41; N, 10.38.

Benzyl (2*R*,3*R*)-3-[(*tert*-Butyloxycarbonyl)amino]-2-[(*tert*-butyldimethylsilyl)oxy]-3-phenylpropionate (86)



A solution of **82** (4.8 g, 11.7 mmol), Ph_3P (4.6 g, 17.6 mmol) and $(Boc)_2O$ (5.4 mL, 23.4 mmol) in THF/H_2O (10:1, 22 mL) was stirred at rt for 12 h, dried (Na_2SO_4) and concentrated. The residue was purified on silica gel using EtOAc-light petroleum (1:9) to furnish **86** (3.45 g, 61%) as a colorless liquid.

$[\alpha]_D$ +11.9 (*c* 1.7, $CHCl_3$);

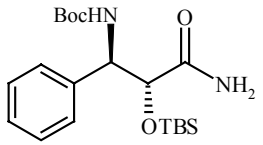
^{1}H NMR (500 MHz, $CDCl_3$): δ 0.03 (s, 6 H), 0.91 (s, 9 H), 1.42 (s, 9 H), 4.64 (d, 1 H, *J* = 3.6 Hz), 4.92-4.99 (m, 2 H), 5.05 (dd, 1 H, *J* = 3.6, 7.9 Hz), 5.32 (d, 1 H, *J* = 7.9 Hz), 7.17-7.30 (m, 10 H);

^{13}C NMR (75 MHz, $CDCl_3$): δ –5.6, –5.3, 18.0, 25.5, 28.2, 57.2, 66.4, 74.3, 79.4, 127.7, 128.1, 128.2, 128.3, 135.1, 137.9, 154.7, 170.5;

IR: 698, 780, 838, 1167, 1252, 1366, 1494, 1716, 1756, 2955, 3465 cm^{-1};

Anal. Calcd for $C_{27}H_{39}NO_5Si$ (Mol. Wt. 485.697): C, 66.77; H, 8.09; N, 2.88. Found; C, 66.53; H, 8.21; N, 3.02.

(1*R*,2*R*)-[2-{(*tert*-Butyldimethylsilyl)oxy}-2-carbamoyl-1-phenylethyl]carbamic acid *tert*-butyl ester (88)



A solution of **86** (1.0 g, 2.1 mmol) in EtOAc (10 mL) was treated 10% Pd/C (0.1 g) in the presence of H_2 atmosphere at 40 psi. After 3 h, the reaction mixture was filtered through a pad of Celite and concentrated to afford the acid **87** (0.67 g, 82%) which was dissolved in THF

(20 mL) and treated sequentially at 0 °C with *N*-methylmorpholine (0.4 mL, 3.4 mmol), HOBt (0.46 g, 3.4 mmol) and EDCI (0.65 g, 3.4 mmol). The reaction mixture was stirred at 0 °C for 1 h and then NH_4OH solution (1.0 mL) was added. The reaction mixture was further stirred at 0 °C for 2 h, quenched with H_2O. The aqueous layer was extracted with EtOAc and the combined organic layers washed with H_2O, brine, dried (Na_2SO_4) and concentrated. The residue was purified on silica gel using EtOAc-light petroleum ether (1:1) to afford **88** (0.39 g, 59%) as a white solid.

$[\alpha]_D$ +9.3 (*c* 1.3, $CHCl_3$);

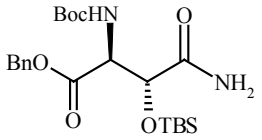
^{1}H NMR (500 MHz, $CDCl_3$): δ 0.04 (s, 6 H), 0.93 (s, 9 H), 1.41 (s, 9 H), 4.44 (d, 1 H, *J* = 4.5 Hz), 4.89-5.01 (m, 1 H), 5.20 (br s, 1 H), 5.27 (br s, 1 H), 5.93-5.99 (m, 1 H), 7.26-7.31 (m, 5 H);

^{13}C NMR (75 MHz, $CDCl_3$): δ −5.5, −5.4, 17.9, 25.7, 28.2, 58.0, 76.0, 79.6, 127.7, 127.9, 128.0, 138.0, 154.7, 174.1;

IR: 759, 1215, 1692, 1713, 3020, 3406, 3626 cm^{-1};

Anal. Calcd for $C_{20}H_{34}N_2O_4Si$ (Mol. Wt. 394.588): C, 60.88; H, 8.68; N, 7.10. Found; C, 60.62; H, 8.91; N, 6.96.

L-*erythro*-BocNH-*β*-OTBDMS-Asn-OBn (81)



The oxidative cleavage of the phenyl ring of **88** (0.2 g, 0.5 mmol) was carried out as described earlier using $NaIO_4$ (1.0 g, 5.0 mmol), $RuCl_3$,$3H_2O$ (10 mg, 0.04 mmol) and $NaHCO_3$ (60 mg) in EtOAc/CH_3CN/H_2O (1:1:8, 20 mL) to afford **89** (79 mg, 43%) which was dissolved in DMF (3 mL) at 0 °C and $NaHCO_3$ (38 mg, 0.44 mmol) and BnBr (0.1 mL, 0.88 mmol) were added. The reaction mixture was stirred at rt for 24 h, quenched by ice-cold water and extracted with EtOAc. The combined organic layers were washed with water, dried (Na_2SO_4) and concentrated. The residue was purified on silica gel using EtOAc-light petroleum ether (1:3) to obtain **81** (63 mg, 64%).

$[\alpha]_D$ +11.9 (*c* 2.6, $CHCl_3$);

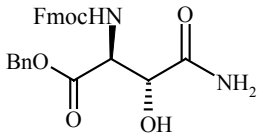
^{1}H NMR (500 MHz, $CDCl_3$): δ 0.01 (s, 3 H), 0.04 (s, 3 H), 0.79 (s, 9 H), 1.36 (s, 9 H), 4.52 (d, 1 H, *J* = 2.7 Hz), 4.77 (dd, 1 H, *J* = 2.7, 7.6 Hz), 5.14 (ABq, 2 H, *J* = 12.1 Hz), 5.15-5.23 (m, 1 H), 5.96 (br s, 1 H), 6.15 (br s, 1 H), 7.22-7.29 (m, 5 H);

^{13}C NMR (75 MHz, $CDCl_3$): δ –5.4, –5.0, 17.9, 25.6, 28.2, 57.5, 67.3, 74.3, 80.1, 128.4, 128.5, 135.2, 154.9, 168.8, 173.6;

IR: 668, 758, 1215, 1499, 1711, 3019, 3439 cm^{-1};

Anal. Calcd for $C_{22}H_{36}N_2O_6Si$ (Mol. Wt. 452.624): C, 58.38; H, 8.02; N, 6.19. Found; C, 58.12; H, 7.98; N, 5.97.

L-*erythro*-FmocNH-*β*-OH-Asn-OBn (90)



A mixture of **81** (0.3 g, 0.66 mmol) and 4 N HCl-EtOAc (7 mL) was stirred at rt for 3 h. The removal of the excess HCl and EtOAc with N_2 provided a white solid which was dissolved in dioxane/H_2O (1:1, 8 mL) and then $NaHCO_3$ (0.11 g, 1.3 mmol) and FmocCl (0.25 g, 1.0 mmol) were added. After 12 h, the reaction mixture was partitioned between saturated aqueous $NaHCO_3$ and EtOAc. The aqueous layer was extracted with EtOAc for several times and the combined organic layers were dried (Na_2SO_4) and concentrated. The residue was purified on silica gel using EtOAc-light petroleum ether (3:2) to afford **90** (0.13 g, 42%) as a white solid.

$[\alpha]_D$ +36.1 (*c* 0.45, $CHCl_3$);

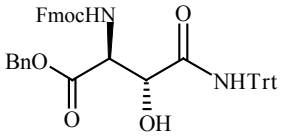
^{1}H NMR (200 MHz, DMSO-d_6 + $CDCl_3$): δ 4.15-4.36 (m, 5 H), 4.74 (dd, 1 H, *J* = 2.7, 9.0 Hz), 5.08 (d, 1 H, *J* = 12.9 Hz), 5.13 (d, 1 H, *J* = 12.9 Hz), 5.94 (d, 1 H, *J* = 5.2 Hz), 7.04 (br s, 1 H), 7.19-7.42 (m, 10 H), 7.66 (d, 2 H, *J* = 7.2 Hz), 7.77 (d, 2 H, *J* = 7.2 Hz);

^{13}C NMR (50 MHz, DMSO-d_6 + $CDCl_3$): δ 45.0, 55.8, 64.4, 64.5, 70.9, 118.2, 123.4, 125.3, 125.8, 125.9, 126.1, 126.5, 133.9, 139.1, 141.9, 142.0, 154.3, 167.4, 170.8;

IR: 657, 761, 1169, 1240, 1482, 1709, 1727, 2940, 3461 cm^{-1};

Anal. Calcd for $C_{26}H_{24}N_2O_6$ (Mol. Wt. 460.486): C, 67.82; H, 5.25; N, 6.08. Found; C, 67.65; H, 5.01; N, 6.34.

L-*erythro*-FmocNH-β-OH-Asn (Trt)-OBn (61a)



Trt protection of **90** (100mg, 0.22 mmol) was performed as described earlier using TrtOH (570 mg, 2.2 mmol), H_2SO_4 (7.5 μL, 0.13 mmol) and Ac_2O (51.6 μL, 0.55 mmol) in HOAc (0.8 mL) to obtain **61a** (70 mg, 46%) as a white solid after silica gel column purification using EtOAc-light petroleum ether (2:3).

$[\alpha]_D$ +25.2 (*c* 1.0, $CHCl_3$);

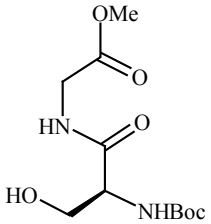
^{1}H NMR (300 MHz, $CDCl_3$): δ 4.19 (t, 1 H, *J* = 7.0 Hz), 4.36-4.47 (m, 2 H), 4.71 (t, 2 H, *J* = 7.0 Hz), 5.15 (s, 2 H), 5.20 (br s, 1 H), 5.87 (d, 1 H, *J* = 6.0 Hz), 7.14-7.38 (m, 24 H), 7.54 (d, 1 H, *J* = 7.2 Hz), 7.56 (d, 1 H, *J* = 7.2 Hz), 7.69 (d, 1 H, *J* = 7.2 Hz), 7.75 (d, 1 H, *J* = 7.2 Hz);

^{13}C NMR (75 MHz, $CDCl_3$): δ 29.7, 47.1, 58.0, 67.9, 70.4, 75.0, 120.0, 120.1, 125.0, 127.1, 127.8, 128.0, 128.3, 128.5, 128.6, 135.1, 141.3, 143.4, 143.5, 144.4, 158.4, 167.7, 169.2;

IR: 669, 759, 909, 1216, 1513, 1692, 1742, 2928, 3020, 3397 cm^{-1};

Anal. Calcd for $C_{45}H_{38}N_2O_6$ (Mol. Wt. 702.807): C, 76.90; H, 5.45; N, 3.99. Found; C, 77.01; H, 5.24; N, 3.89.

Boc-L-Ser-Gly-OMe (91)



A solution of **57a** (1.8 g, 20.2 mmol) and **58a** (4.1 g, 20.2 mmol) in CH_2Cl_2 (20 mL) was treated sequentially at 0 ^oC with HOBt (3.0 g, 22.2 mmol) and DCC (5.0 g, 24.2 mmol). After 10 h at rt, the reaction mixture was quenched with H_2O and extracted with EtOAc. The combined organic layers were washed with H_2O, dried (Na_2SO_4), concentrated and purified on silica gel using EtOAc-light petroleum ether (3:2) to afford **91** (4.52 g, 81%) as a white solid.

$[\alpha]_D$ −31.8 (*c* 1.0, $CHCl_3$);

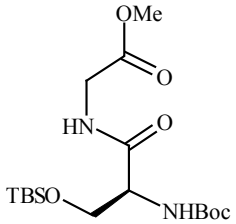
^{1}H NMR (200 MHz, $CDCl_3$): δ 1.44 (s, 9 H), 3.67 (dd, 1 H, *J* = 5.5, 11.4 Hz), 3.74 (s, 3 H), 4.03-4.09 (m, 3 H), 4.18-4.29 (m, 1 H), 5.66 (d, 1 H, *J* = 7.8 Hz), 7.22 (t, 1 H, *J* = 5.8 Hz);

^{13}C NMR (50 MHz, $CDCl_3$): δ 28.1, 41.1, 52.2, 55.5, 62.7, 80.2, 155.8, 170.4, 171.7;

IR: 758, 1166, 1216, 1369, 1502, 1674, 1745, 3019, 3425 cm^{-1};

Anal. Calcd for $C_{11}H_{20}N_2O_6$ (Mol. Wt. 276.292): C, 47.82; H, 7.30; N, 10.14. Found; C, 47.77; H, 7.44; N, 7.93.

Boc-L-Ser (TBS)-Gly-OMe (92)



To a solution of **91** (1.0 g, 3.6 mmol) in CH_2Cl_2 (10 mL) at 0 ^oC were added imidazole (0.7 g, 10.8 mmol) and TBSCl (0.8 g, 5.4 mmol). After 2 h at 0 ^oC, the reaction mixture was washed with saturated NH_4Cl solution, water, dried (Na_2SO_4), concentrated and purified on silica gel using EtOAc-light petroleum ether (3:17) to afford **92** (1.16 g, 82%).

$[\alpha]_D$ +22.6 (*c* 1.1, $CHCl_3$);

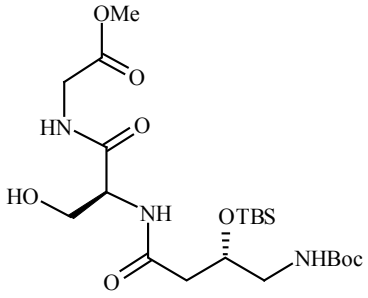
^{1}H NMR (200 MHz, $CDCl_3$): δ 0.07 (s, 6 H), 0.88 (s, 9 H), 1.45 (s, 9 H), 3.65 (dd, 1 H, *J* = 5.5, 10.1 Hz), 3.98-4.07 (m, 3 H), 4.09-4.20 (m, 1 H), 5.85 (d, 1 H, *J* = 6.3 Hz), 7.03 (t, 1 H, *J* = 5.0 Hz);

^{13}C NMR (50 MHz, $CDCl_3$): δ –5.6, 18.1, 25.7, 28.2, 41.1, 52.1, 55.4, 63.1, 79.8, 155.2, 169.6, 170.6;

IR: 758, 1164, 1216, 1369, 1489, 1680, 1712, 1750, 3020, 3428 cm^{-1};

Anal. Calcd for $C_{17}H_{34}N_2O_6Si$ (Mol. Wt. 390.553): C, 52.28; H, 8.78; N, 7.17. Found; C, 52.58; H, 8.58; N, 7.47.

(*S*)-Boc-AHBA (TBS)-L-Ser-Gly-OMe (94)



To a solution of **92** (0.2 g, 0.5 mmol) in CH_2Cl_2 (5 mL) at –15 ^oC was added TMSOTf (0.18 mL, 1.0 mmol) dropwise. After stirring at –15 ^oC for 1 h, 2,6-lutidine (0.17 mL, 1.5 mmol) was added dropwise and the mixture stirred at –15 ^oC for 1 h, quenched with saturated aqueous $NaHCO_3$ and extracted with EtOAc for several times. The combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated to obtain **93** (0.13 g, 89%). The residue **93** and **59a** (0.15 g, 0.45 mmol) were dissolved in CH_2Cl_2 (7 mL) at 0 ^oC and HOBt (91 mg, 0.68 mmol), EDCI (0.13 g, 0.68 mmol) and Et_3N (0.15 mL, 1.35 mmol) were added successively. After 12 h at rt, the solution was diluted with CH_2Cl_2, washed with saturated aqueous $NaHCO_3$ solution, brine, dried (Na_2SO_4) and concentrated. The residue was purified on silica gel using EtOAc-light petroleum ether (1:1) to afford **94** (0.16 g, 72%) as a white solid.

$[\alpha]_D$ –37.1 (*c* 0.7, $CHCl_3$);

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.05 (s, 3 H), 0.07 (s, 3 H), 0.85 (s, 9 H), 1.45 (s, 9 H), 2.52 (d, 2 H, *J* = 5.4 Hz), 3.18 (t, 2 H, *J* = 5.1 Hz), 3.76 (s, 3 H), 3.81-4.02 (m, 3 H), 4.08-4.18 (m, 1 H), 4.41 (d, 2 H, *J* = 3.4 Hz), 4.88 (t, 1 H, *J* = 5.1 Hz);

IR: 667, 760, 1219, 1341, 1495, 1682, 1720, 1741, 3022, 3421 cm^{-1};

Anal. Calcd for $C_{21}H_{41}N_3O_8Si$ (Mol. Wt. 491.662): C, 51.30; H, 8.41; N, 8.55. Found; C, 51.06; H, 8.33; N, 8.39.

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Introduction

The life of every organism is constantly threatened by other organisms, this is the nature of living world. In response, each species has evolved protective mechanisms varying from camoufiage colors, to poisons, to effective running muscles. From the continual battle with microorganisms, vertebrates have evolved an elaborate set of protective measures called collectively, the immune system. The study of the immune system constitutes the discipline of immunology. [1]

The immune system works by a learning process accompanied by a memorizing network. Our first encounter with a bacterial, fungal, protozoan viral pathogen leads to an infection, often accompanied by disease symptoms. The immune system aids in recovery from the infection and after recovery, we usually remain free of that disease forever. Our immune system has learned to recognize this specific pathogen as a foreign infecting agent and remembers. If it attacks us again, it will be rapidly killed.

A key process carried out by the immune system is recognition. The system must recognize the presence of a invader. It must also be able to discriminate between foreign invaders and natural constituents of the body. The recognition is only the first step; it must be followed by steps that will kill and eliminate the invader, which is known as destructive response. Precise recognition is the function of cells called lymphocytes while destruction is carried out both by lymphocytes and by the cells called macrophages and neutrophills.

Overview of Immunity

The immune system works in three fundamentally different ways[2]: by humoral immunity, by cellular immunity and by secretion of stimulatory proteins, called lymphokines. The humoral immunity relies on molecules in solution in the body. These molecules are proteins collectively called immunoglobin. A single immunoglobin molecule is called an antibody, but “antibody” is also used to mean many individually different molecules all directed against the same target molecule. Humoral immunity also involves complement, a set of proteins that are activated to bacteria both nonspecifically and in conjunction with antibody.

In cellular immunity, intact cells are responsible for recognition and elimination reactions. The body’s first line of defense is the recognition and killing of microorganisms by

phagocytes; cells specialized for the ingestion and digestion of unwanted materials. These cells include neutrophills and macrophages. A key role of antibodies is to help phagocytes recognize foreign material. There is also an important class of cells that carry antibody like recognition molecules on their surface and can directly kill cells infected by microorganisms called lymphocytes. These types of cells carrying recognition molecules respond by secretion of lymphokines. The substance that provokes antibody or lymphocyte formation or is recognized by an antibody or lymphocyte, is called an antigen.

Once the body is invaded by a potential pathogen, a number of lines of defense come into play instantaneously. Before antibody response develops, phagocytic cells are activated by encounter with bacterial cell wall; they engulf the bacterium and kill it. Complement is also activated by the cell walls of pathogen and it kills many pathogens. Cells that are infected with viruses make interferon, these protein interact with the receptors on neighboring cells, triggering a response that makes the cells poor hosts for further infection. These are all nonspecific reactions.

The nonspecific initial responses to infection are superseded by specific responses, mediated by activated lymphocytes. The lymphocytes are activated either directly by the surface of a pathogen or indirectly macrophages that digest a pathogen. The lymphocytes recognize the foreign nature of these materials and initiate antibody formation.

The immune system also has other abilities besides the recognition and killing of invading pathogens. The immune system also prevents tissue transplantations between individuals.

Immunosuppression

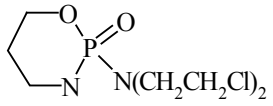
The immune system is a multicellular ensemble designed to eliminate foreign entities from the body. The sophisticated response brought into play when such an event occurs involves the growth and proliferation of cells that recognize and ultimately reject the substance.[3] This phenomenon is triggered as the result of signal transduction, that process wherein extracellular molecules influence intracellular events.[4] In the past decade or so, several important signaling drugs have been discovered that become intimately involved in the orchestration of the immune response. These powerful biochemical tools exhibit specific cellular effects that allow dissection of the mechanisms of signal transduction at the molecular

level, shed light on intracellular signaling pathways involved in T-cell activation, and make possible organ transplantation.

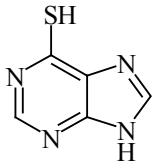
Development of Immunosuppressive Chemotherapy

With the advent of organ transplantation, immunosuppression became a pressing problem. The use of immunosuppressive agents has proven of therapeutic value for organ transplantation as well as many autoimmune diseases eg. ureitis, myasthenia gravis, juvenile diabetes, psoriasis, primary biliary cirrhosis, ulcerative colitis, systemic lupus erythematasus and rheumatoid arthritis.

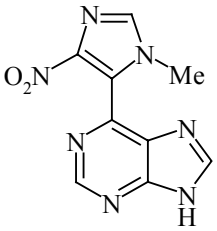
The first stage in the development of immunosuppression introduced in the late 1950s and early 1960s consisted of using cytostatic drugs and anti metabolites which are used to control the proliferation of neoplastic cells.[5] Those cytostatic or cytotoxic agents which proved of some value were alkylating agents like cyclophosphamide (**1**), purine analogs like 6-mercaptopurine (**2**) and azathioprine (**3**), folate analogs (anti metabolites) like amethopterin (**4**) and pyrimidine analogs like cytosine arabinoside (**5**).



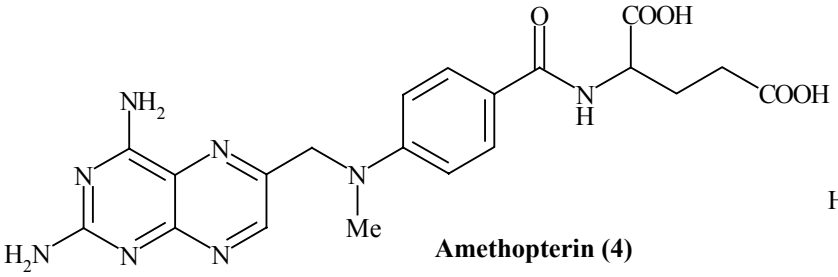
Cyclophosphamide (1)



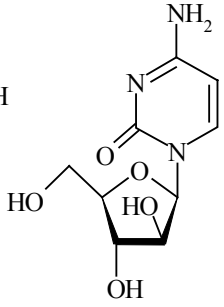
6-Mercaptopurine (2)



Azathioprine (3)



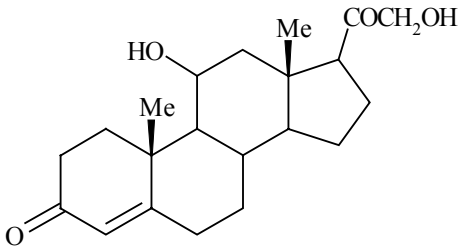
Amethopterin (4)



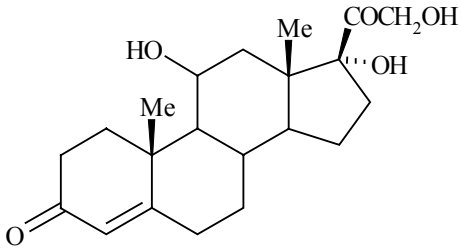
Cytosine arabinoside (5)

The major drawback in the use of these nonspecific cytotoxic drugs is the high risk of overwhelming infections by organisms, because the action of these drugs is not limited to the immunocompetent cells and acts indiscriminately blocking or damaging all cells that happen to be in mitosis. Although tissue transplantation can be done by the use of these drugs, the toxicity usually so severe the overall results are not considered satisfactory.

The next step was, therefore the development of lymphocytotoxic drugs which were mostly restricted to the elimination of immunocompetent cells, mainly the lymphocytes. Corticosteroids are naturally occurring hormones secreted by the adrenal cortex, of which cortisol (**6**) and hydrocortisone (**7**) are by far the most powerful component known to possess lymphocytolytic activity, particularly with respect to the T-lymphocytes, to inhibit lymphokine production. Corticosteroids are still used in autoimmune disorder, allergic reactions and organ transplantation. These are safer than cytotoxic agents because even at the higher dosage used in clinical therapy, bone marrow toxicity has not been observed. But these agents suffer from serious adrenal suppression which could lead to various physiological disorders.



Cortisol (6)

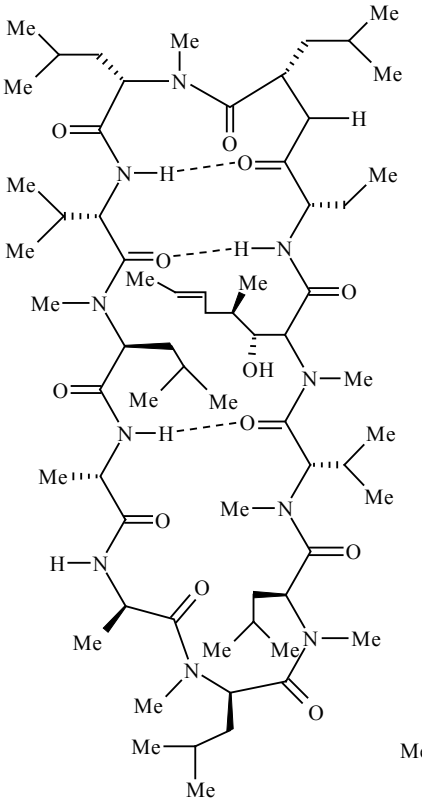


Hydrocortisone (7)

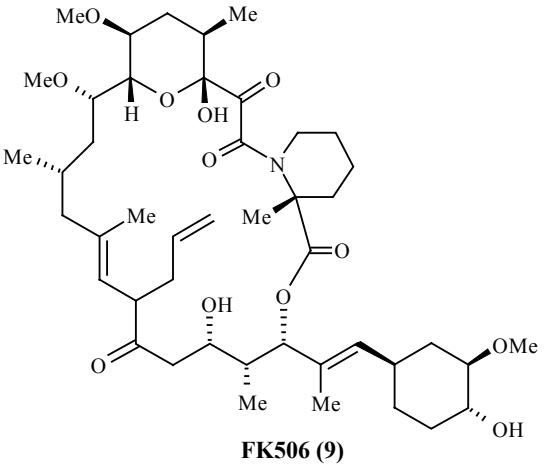
More than two decades ago, the discovery of cyclosporin A (CsA, **8**)[6] allowed a spectacular progress in the field of organ transplantation.[7] Since then, the number of transplanted organs has grown continuously, and the search for novel immunosuppressants has been intensified.[8] Besides its important therapeutic use, CsA has also proven to be a powerful tool for dissecting signal transduction pathways at the molecular level.[9] It has been shown that the biological activity of CsA is mediated by an intracellular binding protein called cyclophilin (CyP). However, although CyP binding is required, it is not sufficient for the immunosuppressive activity of this drug. Full biological activity is obtained only once the CyP-CsA complex binds to and inhibits the serine-threonine phosphatase activity of calcineurin, thereby blocking the production of cytokines including interleukin-2.[10]

To identify compounds which might potentially interfere with other signaling pathways not involving calcineurin and which thereby might exert novel biological effects, a screening for novel cyclophilin-binding entities was performed with methanolic extracts of actinomycete broths. This approach was stimulated by findings related to two other immunosuppressive drugs, namely FK506 (**9**)[11] and rapamycin (**10**).[12] Both drugs bind to the

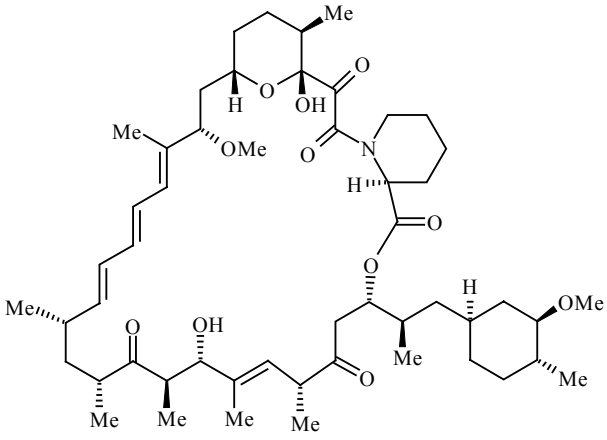
same intracellular binding protein FKBP.[13] However, the corresponding drug-FKBP complexes interact with two different effector molecules: the FK506-FKBP complex binds to calcineurin as does the CsA-CyP complex. Consequently, FK506 inhibits T-cell activation *via* the same signaling pathways as CsA does.[14] In contrast, the rapamycin-FKBP complex binds to a different protein, *i.e. m*TOR, which is involved in growth factor mediated intracellular signal-transduction pathways.[15] Accordingly, rapamycin has a different activity profile, inhibiting the clonal expansion of cells at a later stage. The effect of rapamycin is not restricted to T-cells; in general, rapamycin inhibits the proliferation of cells in response to growth factors.[16]



Cyclosporin A (CsA, 8)



FK506 (9)

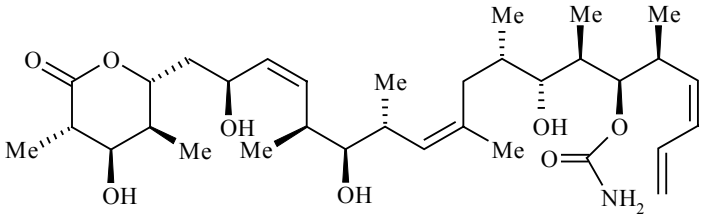


Rapamycin (10)

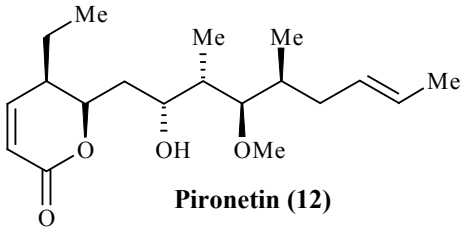
Recent Trends in Immunosuppressive Chemotherapy

Recently, two other important immunosuppressive compounds, namely discodermolide (**11**)[17] and pironetin (**12**)[18] have attracted much attention, because of their simple structure as compared to CsA, FK506 and rapamycin and also because of their unique

mode of action. Discodermolide was found to inhibit P388 leukemic cell proliferation and showed potent immunosuppressive activity. Pironetin was found to inhibit both T- and B-lymphocytes simultaneously but associated with cytotoxicity.



Discodermolide (11)



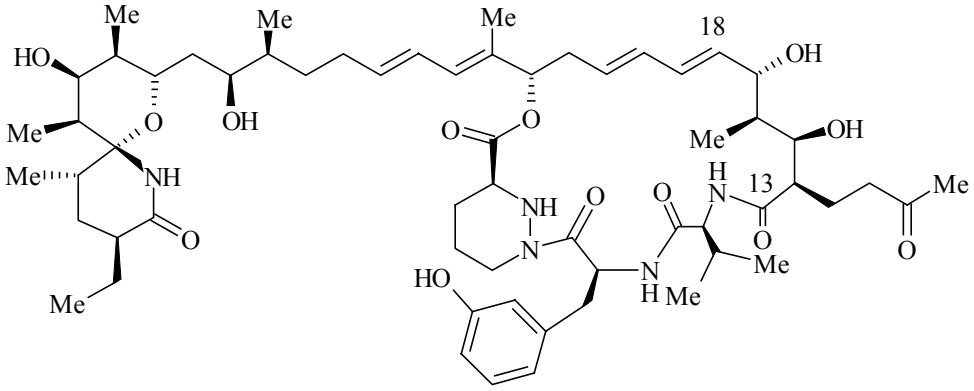
Pironetin (12)

We wondered whether other ligands for cyclophilin might exist which would interfere with signaling pathways not involving calcineurin. The screening of microbial broth extracts for CyP-binding substances led to the isolation from *Streptomyces flaveolus* of a new class of compounds named sanglifehrins.[19] Among the 20 different sanglifehrins isolated so far from this strain, sanglifehrin A (SFA, **13**) is the most abundant component. The affinity of SFA for cyclophilin is remarkably high (IC_{50} = 2-4 nM),[20] approximately 20-fold higher than that of CsA (K_i = 82 nM). Sanglifehrin A displays potent immunosuppressive activity in the mixed lymphocyte reaction (IC_{50} = 170 nM), an in vitro immune response assay.[17] However, SFA does not affect T-cell receptor-mediated cytokine production, indicating a mode of action different from that of CsA. Moreover, in contrast to the T-cell selective drug CsA, SFA inhibits mitogen-induced B-cell proliferation (IC_{50} = 90 nM). These data clearly indicate that the immunosuppressant SFA acts by a new mode of action. However, the details of the mechanism by which this compound exerts its immunosuppressive activity at the molecular level are unknown.

Studies Directed Toward the Stereoselective Synthesis of C13-C18 Fragment of Sanglifehrin A (13)

Recently, an exciting new immunosuppressive compound, sanglifehrin A (SFA, **13**), was discovered by scientists at Novartis[21] during their screening for compounds that would interfere with signaling molecules other than calcineurin. Produced by *Streptomyces* sp A92-309110 found in a soil sample in Dembo-Bridge in Malawi, SFA possesses impressive biological properties.[19] These include strong binding to cyclophilin, immunosuppressive

activity and inhibition of both T-cell and B-cell proliferation.[19,21] Studies concerning the mode of action of SFA and analogues thereof should advance our understanding of the immune response at the molecular level and thereby facilitate the design of immunosuppressants in the future.[22]



Sanglifehrin A (SFA, 13)

Past Work

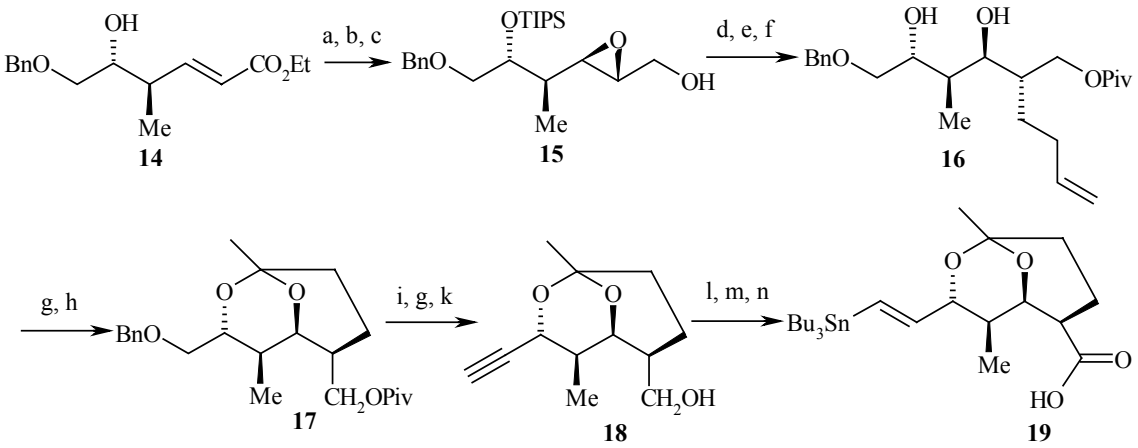
Nicolaou's approach[23]

The synthesis of the C13-C19 fragment **19** was initiated with the α,β-unsaturated ester **14**, which was converted to **15** by the sequence of reactions, TIPS protection, DIBAL-H reduction and *m*CPBA-mediated epoxidation. Regioselective epoxide opening of **15** by CH_2=$CHCH_2CH_2MgBr$ followed by selective protection as a pivaloate ester and desilylation gave **16** which was subjected to Wacker oxidation and internal ketalization to afford **17**. Sequential hydrogenolysis, TPAP-NMO oxidation and reaction with $(MeCO)C(=N_2)PO(OMe)_2$ led to terminal alkyne **18**. Regio- and stereoselective addition of Bu_3SnH in the presence of $PdCl_2(PhCN)_2$ followed by oxidation by sequential treatment with TPAP-NMO and $NaClO_2$ afforded carboxylic acid **19** (Scheme 1).

Metternich's approach[24]

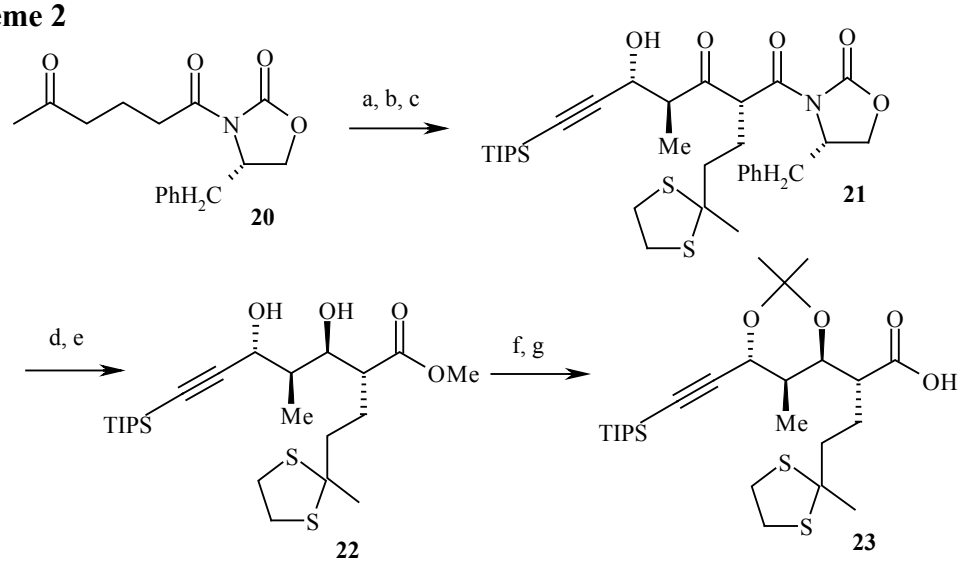
This methodology involved a diastereoselective boron aldol reaction developed by Evans between β-ketoimide and triisopropylsilyl propargyl aldehyde. Ditholane protection of the ketone present in **20** followed by acylation and boron complex-mediated Evans aldol reaction resulted **21**. Direct reduction of **21** with $Me_4NBH(OAc)_3$ served to complete elaboration of the four contiguous stereogenic centers. The sequential transesterification with MeOMgBr-MeOH, acetalization and hydrolysis produced **23** (Scheme 2).

Scheme 1



Reagents and conditions: (a) TIPSCl, imidazole, DMF, 60 °C, 24 h; (b) DIBAL-H, CH_2Cl_2, −78 °C, 2 h; (c) *m*CPBA, CH_2Cl_2, −25 °C; (d) $H_2C{=}CHCH_2CH_2MgBr$, CuI, Et_2O/THF (1:1), −20 °C, 18 h; (e) PivCl, pyridine, 25 °C, 24 h; (f) TBAF, THF, 25 °C, 1 h; (g) $PdCl_2$, benzoquinone, DMF/H_2O (7:1), 25 °C, 3 h; (h) *p*TSA, H_2O, benzene, reflux; (i) H_2, 10% Pd/C, EtOH, 25 °C, 1 h; (j) TPAP, NMO, 4 Å MS, CH_2Cl_2, 25 °C, 20 min; (k) $MeC(O)C(=N_2)PO(OMe)_2$, K_2CO_3, MeOH, 25 °C, 13 h; (l) *n*Bu_3SnH, $PdCl_2(PhCN)_2$, P(*o*-tol)$_3$, DIPEA, CH_2Cl_2, −20 °C, 1 h; (m) TPAP, NMO, 4 Å MS, CH_2Cl_2, 25 °C, 15 min; (n) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene(2 M in THF), *t*BuOH:H_2O (5:1), 25 °C, 15 min.

Scheme 2

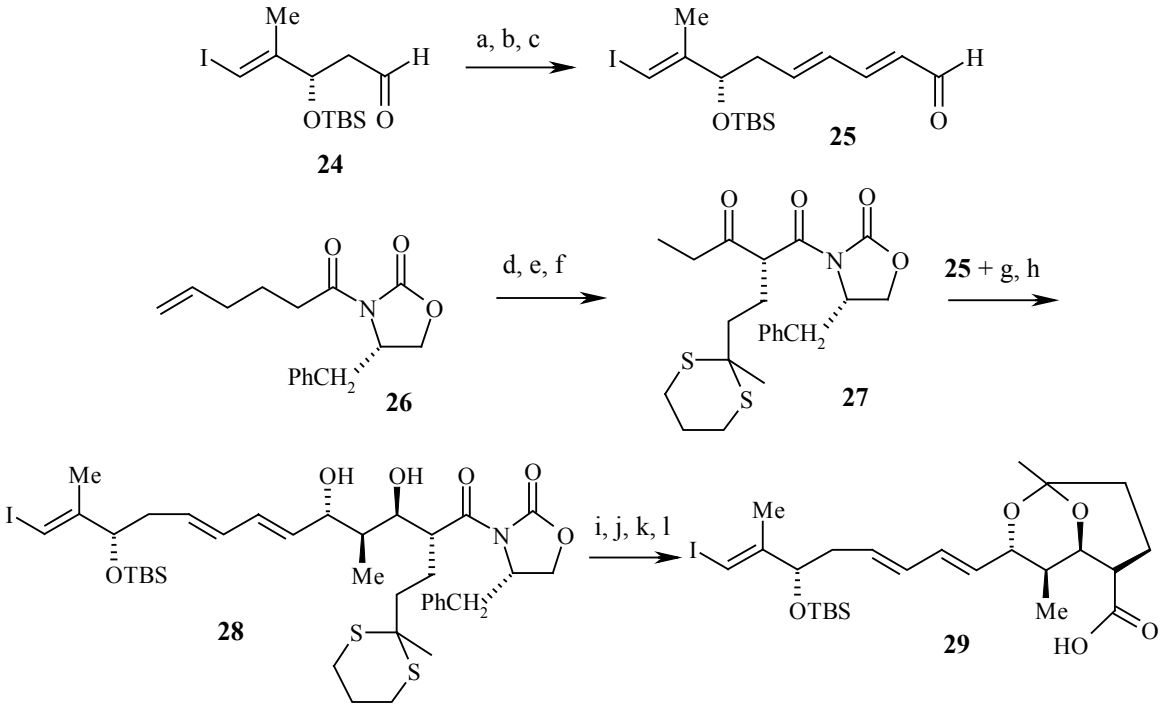


Reagents and conditions: (a) $(CH_2SH)_2$, $TiCl_4$, CH_2Cl_2, 0 °C; (b) LDA, CH_3CH_2COCl, THF, −78 °C; (c) Cy_2BCl, trisiopropylsilylpropargyl aldehyde, −78 °C; (d) $Me_4NBH(OAc)_3$, AcOH-MeOH; (e) MeMgBr, MeOH/CH_2Cl_2; (f) DMP, CH_3COCH_3, CSA, 12 h; (g) NaHTe, DMF, 80 °C, 12 h.

Paquette's approach[25]

This synthesis explored the methodology of Evans aldol reaction between β-ketoimide **27** and aldehyde **25** as the key step (similar to previous approach) (Scheme 3).

Scheme 3



Reagents and conditions: (a) LiHMDS, methyl 4-(diethylphosphono)crotonate, THF, –45 °C; (b) DIBAL-H, THF, –78 °C; (c) MnO_2, CH_2Cl_2; (d) CuCl, $PdCl_2$, O_2, DMF, H_2O; (e) $HS(CH_2)_3SH$, *p*TSA, AcOH; (f) LDA, CH_3CH_2COCl, THF, –78 °C, (g) **25**, Cy_2BCl, Et_2O, –78 °C; (h) $Me_4NBH(OAc)_3$, CH_3CN, AcOH, 0 °C; (i) $PhI(OCOCF_3)_2$, CH_2Cl_2; (j) $NaBH_4$, THF, H_2O; (k) Dess-Martin periodinane, CH_2Cl_2; (l) $NaClO_2$, $Me_2C{=}CHMe$, NaH_2PO_4, *t*BuOH, H_2O.

Present Work

Sanglifehrin A (**13**) is a recently disclosed cyclophilin binding immunosuppressant possessing activity against both B- and T-lymphocytes. The wide range of biological activities[19b] coupled with low yield of the natural product from natural resources, the total synthesis of sanglifehrin A (**13**) should make an ideal target for investigation. The first total synthesis has been described by Nicolaou's group.[23c]

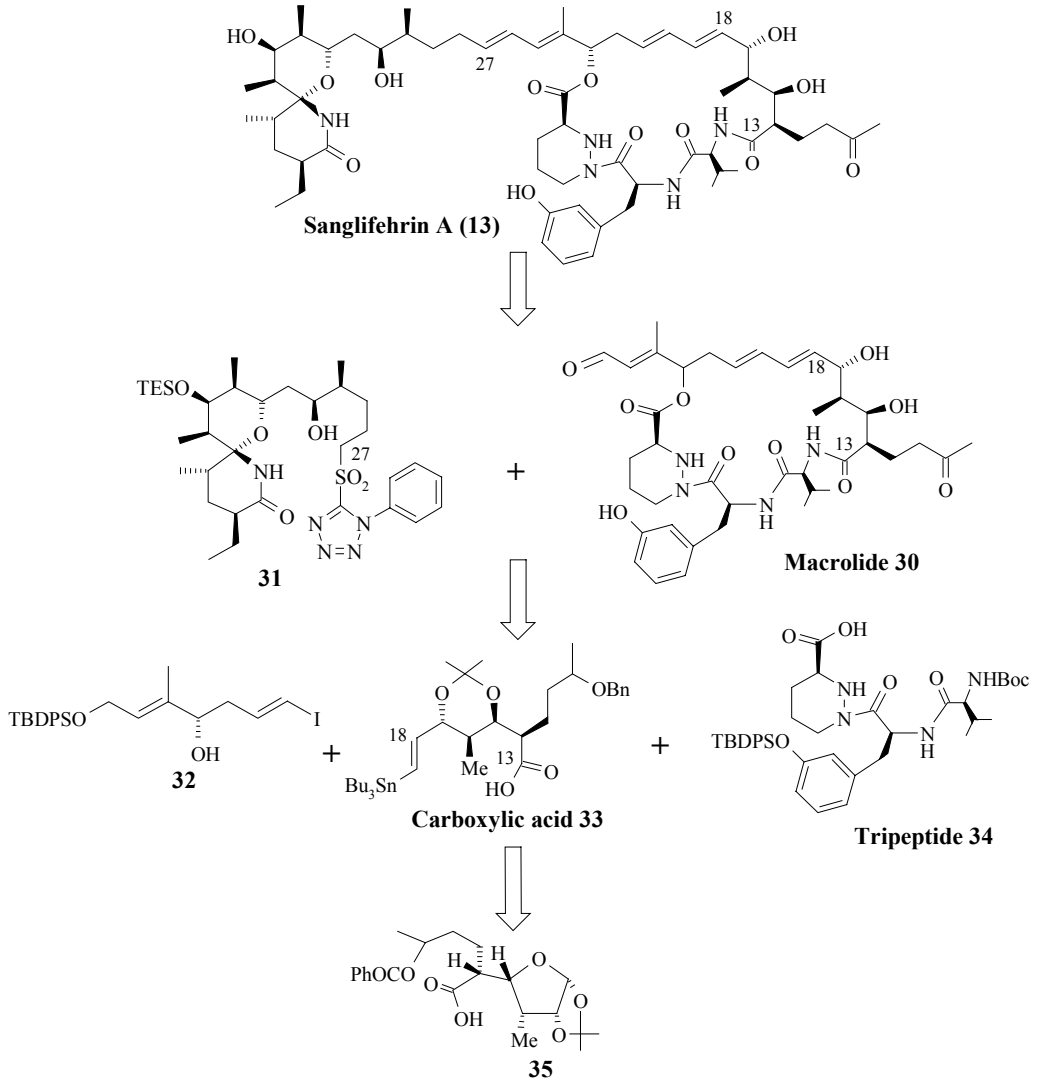


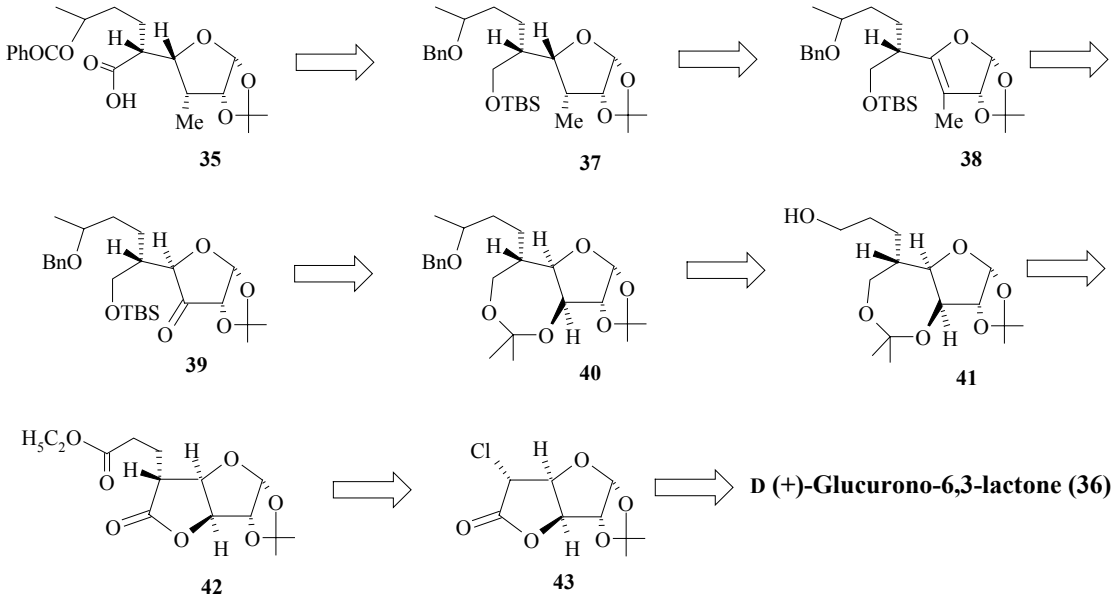
Figure 1

Sanglifehrin A (**13**) has complex structural parameters and therefore the most promising strategy would be a convergent route in which many small but critical intermediates could be proposed as shown in Figure 1. Each of these fragments **32**, **33** and **34**

should form the basic objective of the total plan. In these laboratories, the total synthesis of Sanglifehrin A has been identified as an overall objective. I am assigned the work to investigate the synthesis of C13-C18 fragment of Sanglifehrin A. Therefore this chapter deals with the synthesis of intermediate **35**.

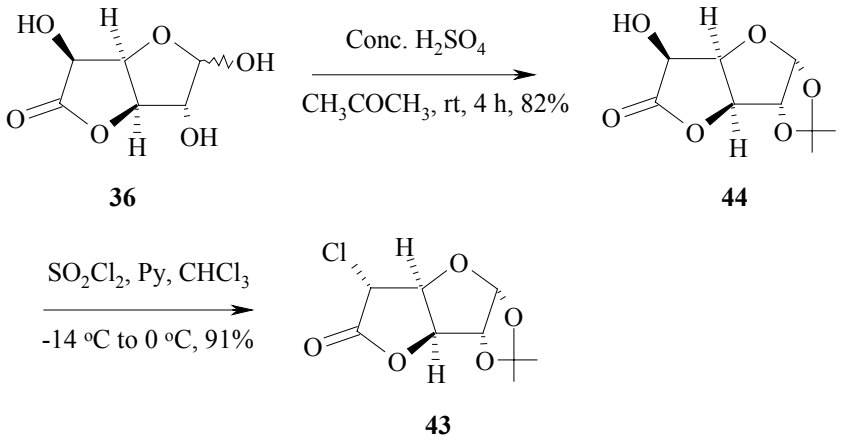
Having settle down with the crucial intermediate **35** as our immediate target, its retrosynthetic analysis was proposed (Scheme 4). Many chiral centers present in **35** could be correlated with D-glucose. The synthesis of **35** from D-glucurono-6,3-lactone (**36**) was finalized as a suitable strategy.

Scheme 4: ***Retrosynthetic analysis for 35***



The synthesis initiated with a readily available D-glucurono-6,3-lactone (**36**), which was converted into the 5-chloro-5-deoxy-1,2-*O*-isopropylidine-β-L-idofuranurono-6,3-lactone (**43**) by two known steps[26] (Scheme 5). The first step involved treatment[26] of compound **36** with conc. H_2SO_4 in acetone at rt to afford 1,2-*O*-isopropylidine-α-D-glucurono-6,3-lactone (**44**). The ^{1}H NMR spectrum showed two singlets at 1.35 ppm and 1.52 ppm corresponding to the acetonide group. The chlorination[27a] of **44** was carried out using sulfuryl chloride and pyridine in $CHCl_3$ at –14 ^oC - 0 ^oC to give **43**. In the ^{1}H NMR spectrum of **43**, the H-5 appeared as singlet at 4.26 ppm.

Scheme 5



36 **44**

43

Our intended study involved the stereoselective C-C bond formation through a radical mediated reaction of the **43** with different electrophiles.[28]

A brief account on free radical mediated C-C bond formation:

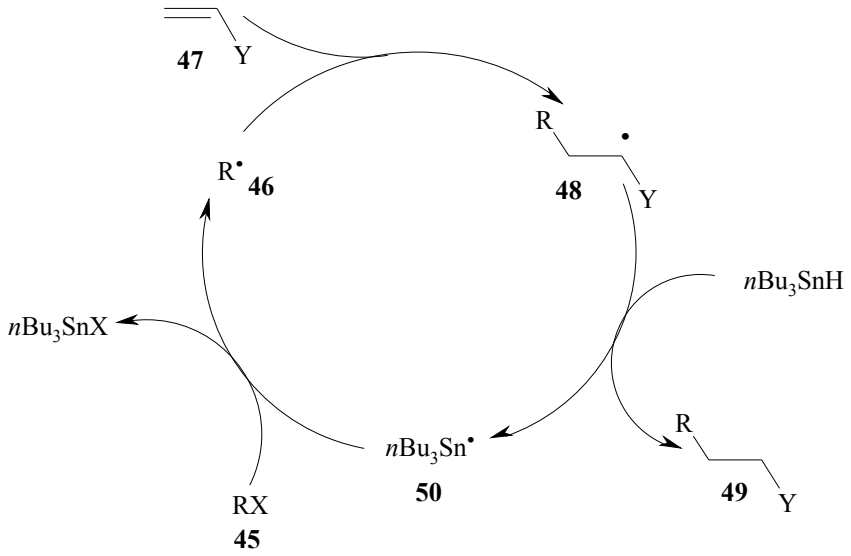
Free radical reactions provided an extraordinary much interest in the synthesis of biologically active molecules and the development of new synthetic methods. Free radical (or "one electron") methods for the synthesis of organic intermediates, particularly for the construction of C-C bond formation are very useful.[29] The radical C-C bond formation takes place either by the "two electron" union of nucleophiles and electrophiles, or by biradical dimerization processes. Free radical reactions, however, always have advantages of tolerance quite complex functionality in the substrate.

The majority of radical reactions of interest to synthetic chemists are chain processes in which radicals are generated by some initiation process, undergo a series of propagation steps generating fresh radicals, and finally disappear, usually by mutual coupling or disproportionation. In order to design a successful, high yielding, free radical chain process, one must control the following reaction processes:

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.*

Scheme 6: ***Radical mechanism for C-C bond formation***

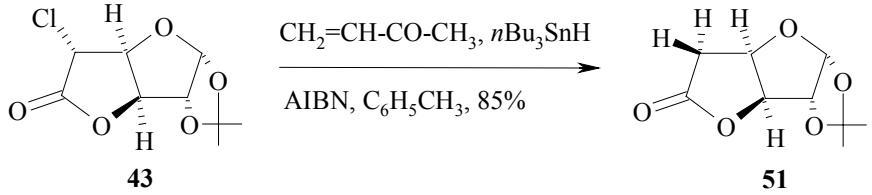


The most important methodology for the synthesis of aliphatic C-C bonds via radical reactions is the addition of alkyl radicals ***46*** *to alkenes* ***47****. This reaction leads to adduct radicals* ***48*** *that must be converted to non-radical products* ***49*** *before polymerization occurs (Scheme 6). Polymerization is avoided either by intermolecular trapping of adduct radicals* ***48*** *or by intramolecular, homolytic bond cleavage. Hydrogen atom donors, (e.g. nBu₃SnH) are used as trapping agents.*

In the alkene/radical trap competition system, educt radicals ***46*** *must react faster with alkenes* ***47****, and adduct radicals* ***48*** *must react faster with radical traps. If this is not the case, either educt radicals are trapped before they can form a C-C bond or adduct radicals react with alkenes to give polymers. This selectivity requirement can be fulfilled by choosing suitable substituted alkenes* ***47****. Alkyl radicals* ***46****, substituted with electron-releasing groups (alkyl, alkoxy, amino etc.), behave like nucleophiles and react very fast with alkenes* ***47*** *substituted with electron-withdrawing substituents (nitrile, ketone, ester etc.).*[30,31] *On the other hand, alkyl radicals* ***46*** *with electron-withdrawing substituents behave like electrophiles and react fast with electron-rich alkenes* ***47****.*[30,32] *These selectivity changes reduce the amount of polymerization because the more nucleophilic the radical is, the faster is the reaction with an electron-poor alkene and vice versa.*

Treatment of **43** with excess equivalent of methyl vinyl ketone in the presence of nBu$_3$SnH and AIBN at reflux temperature gave predominantly the hydrodechlorination product **51** which was attributed to the poor electrophilic character of methyl vinyl ketone (Scheme 7). The ^{1}H NMR spectrum of **51** showed a characteristic doublet integrating for two protons of C_5-methylene group at 2.70 ppm (J = 3.4 Hz).

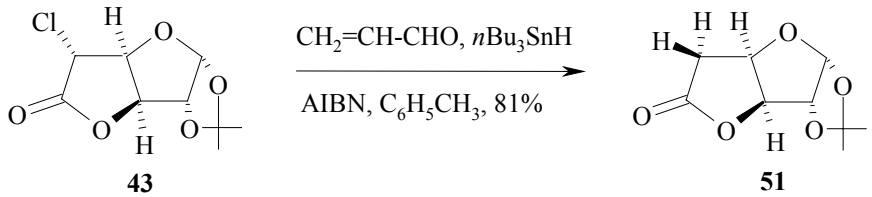
Scheme 7



43 **51**

Our attempt to react **43** with acrolein under similar reaction conditions also failed while the deoxy compound **51** was isolated (Scheme 8).

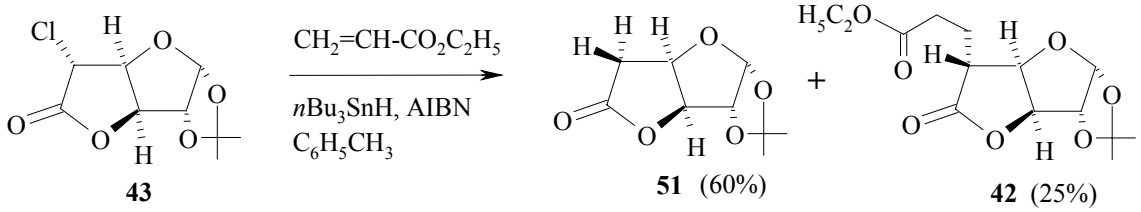
Scheme 8



43 **51**

However, the reaction of **43** with ethyl acrylate gave the desired product **42** but in 25% yield, the major product being **51** (Scheme 9). The ^{1}H and ^{13}C NMR spectra of **42** revealed the formation of single isomer. Our next concern was to ascertain the absolute stereochemistry of **42** at C-5. The ^{1}H NMR spectrum of **42** showed a characteristic doublet

Scheme 9

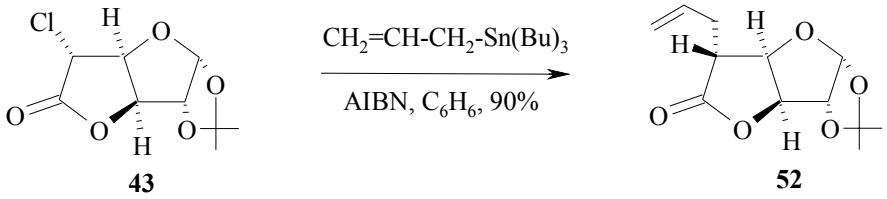


43 **51** (60%) **42** (25%)

due to H-4 resonated at 4.71 ppm ($J_{4,3}$ = 3.2 Hz). In addition, a triplet for H-5 appeared in the upfield region at 2.76 ppm ($J_{5,6}$ = 8.7 Hz). The lack of any coupling between H-4 and H-5 confirmed the *trans* relationship which suggests that the assigned structure **42** was correct.

The most promising results were obtained from the reaction of **43** with allyltri-*n*-butyltin in the presence of AIBN in refluxing benzene to furnish **52** in excellent yield (Scheme 10). The structure of **52** and its absolute stereochemistry at C-5 was confirmed from its ^{1}H NMR spectroscopy. The double-doublet due to H-5 was appeared at 2.81 ppm (J = 6.0, 8.0 Hz). The H-4 proton was observed as a clean doublet at 4.71 ppm ($J_{4,3}$= 3.4 Hz). Thus,

Scheme 10

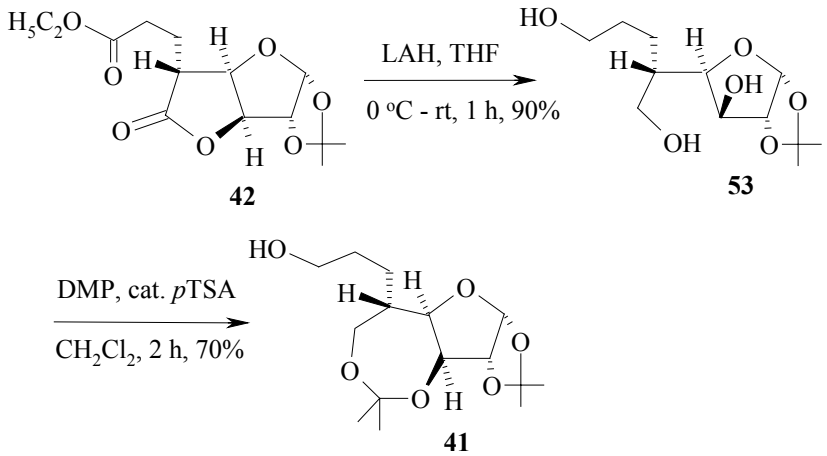


43 **52**

lack of any coupling between H-4 and H-5 clearly revealed the *trans* relationship, which was also observed with **42**. In addition, the multiplets at 5.15-5.23 ppm integrating for two protons and at 5.68-5.89 ppm integrating for one proton indicated the presence of terminal double bond. The first order splitting signals due to H-1 and H-2 appeared as doublets at 5.94 ppm (J = 4.0 Hz) and 4.81 ppm (J = 4.0 Hz) respectively. The structure of **52** was further confirmed by its ^{13}C NMR spectroscopy and elemental analysis.

The reduction of **42** with LAH in THF provided the triol **53** whose ^{1}H NMR spectrum gave signals due to H-1, H-2 and H-3 at 5.89 ppm (d, J = 3.9 Hz), 4.53 ppm (d, J = 3.9 Hz)

Scheme 11



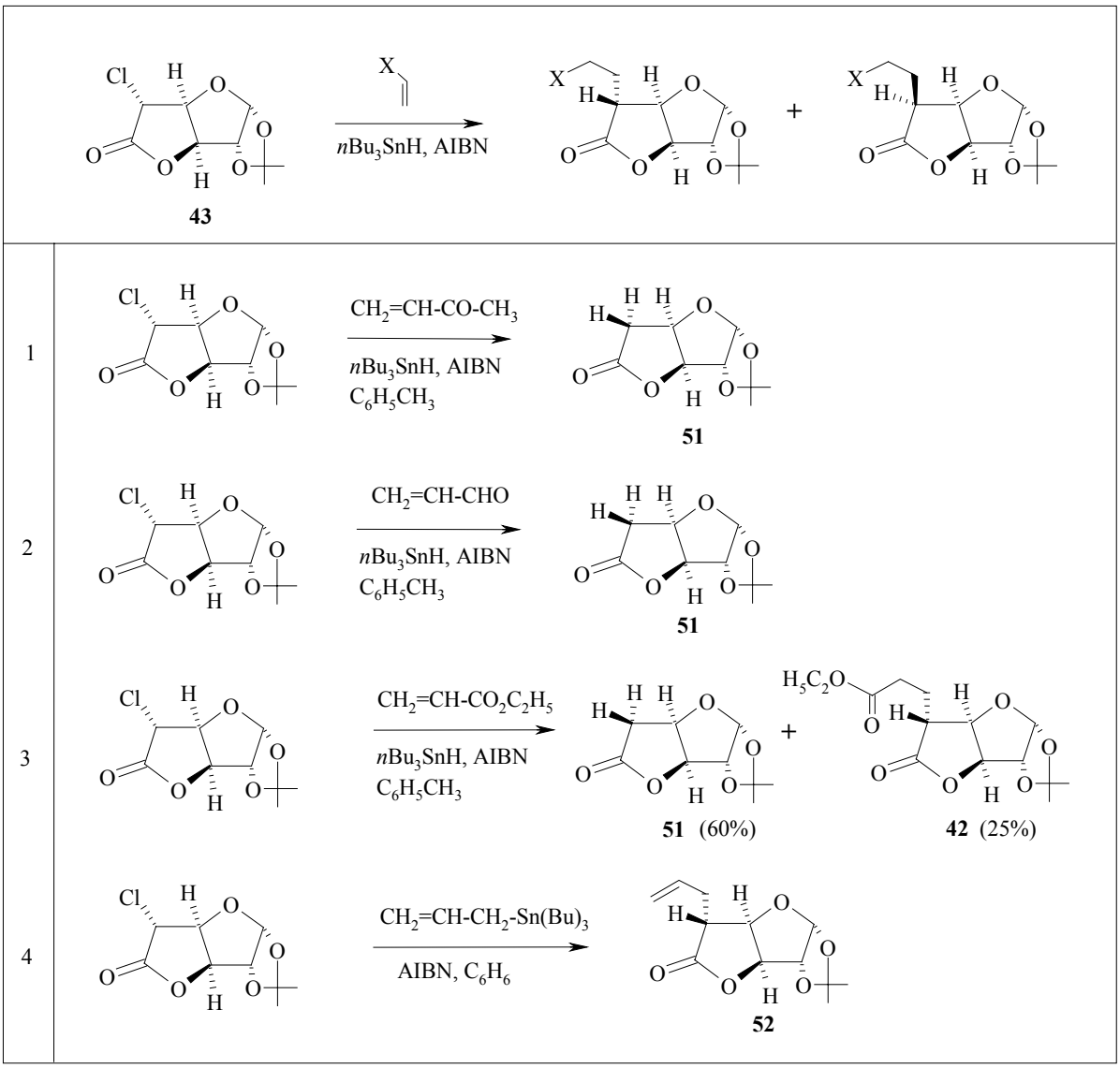
42 **53**

41

and 4.14 ppm (d, J = 2.4 Hz) respectively. A double-doublet corresponding to H-4 resonated at 3.94 ppm (J = 2.4, 9.2 Hz). The resonances due to H-6 and H-6′ appeared as double-doublet at 3.75 ppm (J = 2.4, 11.2 Hz) and 3.53 ppm (J = 3.4, 11.2 Hz). Compound **53** was protected

as its isopropylidene derivative (**41**) with 2,2-dimethoxypropane in CH_2Cl_2 and catalytic amount of *p*TSA (Scheme 11). In the ^{1}H NMR spectrum of **41**, the resonances due to two isopropylidene groups were noted.

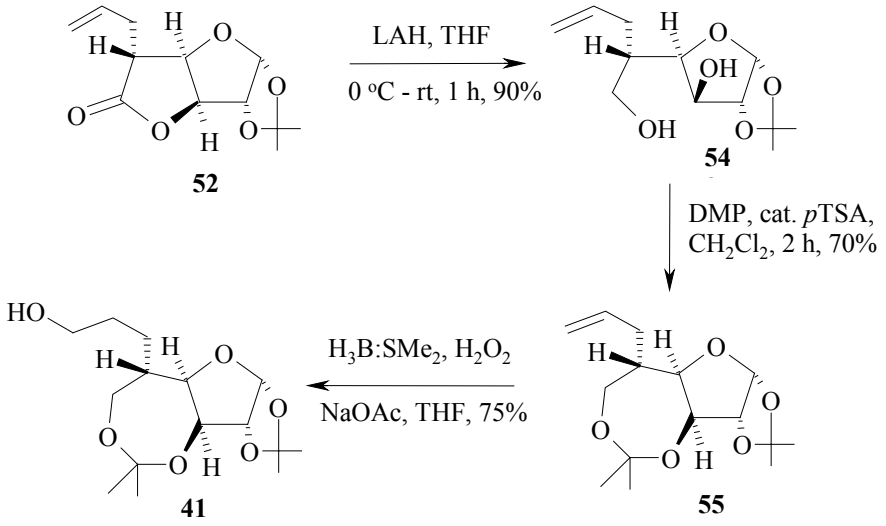
Table 1: ***Summary of the redical reactions***



Although the synthesis of **41** from **42** was satisfactory, the yield of the synthesis of **42** by radical C-C bond formation was poor. Therefore, the conversion of **52** to **41** was explored. For this endeavor, **52** was reduced with LAH in THF to furnish the diol **54** (Scheme 12). The structure of **54** was confirmed by its ^{1}H NMR, ^{13}C NMR, mass spectroscopy and elemental analysis. For example, the ^{1}H NMR spectrum clearly revealed the signals due to H-1, H-2 and H-3 as doublets at 5.87 ppm (J = 3.6 Hz), 4.52 ppm (J = 3.6 Hz) and 4.15 ppm (J = 2.0 Hz).

Compound **54** was protected as its acetonide derivative (**55**) using 2,2-dimethoxypropane and cat. *p*TSA in CH_2Cl_2. In the ^1H NMR spectrum, the two acetonide groups appeared at 1.26 ppm (s, 6 H), 1.31 ppm (s, 3 H) and 1.44 ppm (s, 3 H). In addition, the ^{13}C NMR spectrum revealed a characteristic peak at 101.3 ppm corresponding to 7-membered ketal carbon. The hydroboration-oxidation sequence using $H_3B{:}SMe_2$, H_2O_2, NaOAc in THF on **55** gave **41** (Scheme 12). The ^1H NMR spectrum of **41** was identical with product obtained above.

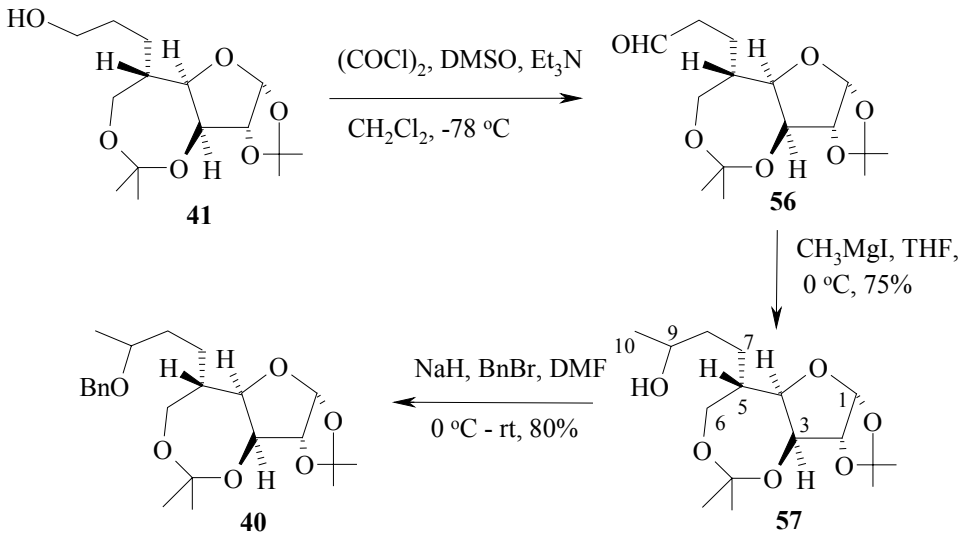
Scheme 12



In order to effect one carbon extension, compound **41** was first oxidized under Swern reaction condition[33] using $(COCl)_2$, DMSO and Et_3N at –78 °C to provide the aldehyde **56** which was immediately subjected to the Grignard reaction with CH_3MgI in THF at 0 °C to afford predominantly (>95%) of a single diastereomer **57** based on ^1H NMR and ^{13}C NMR spectroscopy (Scheme 13). The newly formed stereocenter of **57** was of no consequence, as it would finally be transformed into the ketone functionality. The structure of **57** was supported by its ^1H NMR, ^{13}C NMR, mass spectroscopy and elemental analysis. For instance, the ^1H NMR spectrum confirmed the presence of the newly introduced methyl group which appeared as a doublet at 1.20 ppm (J = 6.4 Hz). All other resonances were in accord with the assigned structure **57**. A characteristic resonance at 23.3 ppm was observed due to C-10 in the ^{13}C NMR spectrum. The free hydroxyl group present in **57** was then protected conveniently as the corresponding benzyl ether (**40**) using NaH and BnBr in DMF (Scheme 13). The ^1H NMR spectrum showed the resonances due to aromatic protons of the benzyl group between 7.29-

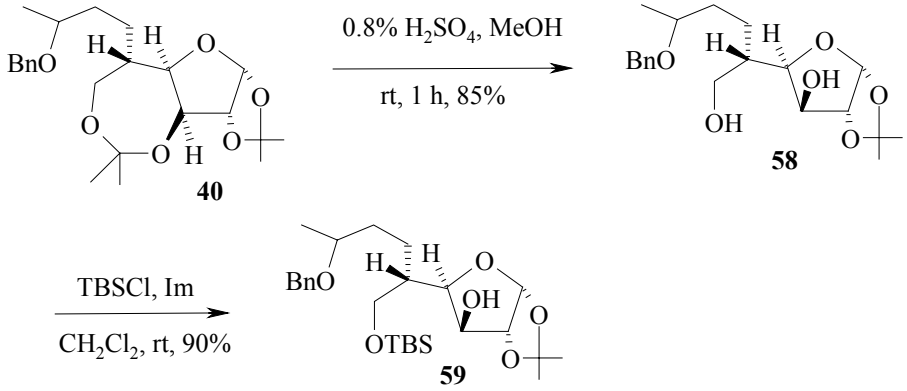
7.33 ppm as a multiplet. All other protons signals appeared at their respective chemical shift values. The mass spectroscopy showed a peak at 391 due to (M^+–15) ion.

Scheme 13



Selective cleavage of the 7-membered acetonide present in **40** under mild acidic conditions using 0.8% H_2SO_4 in MeOH resulted the formation of the diol **58** whose primary hydroxyl group was protected as its TBS ether (**59**) by using TBSCl and imidazole in CH_2Cl_2 (Scheme 14). The ^{1}H NMR spectrum of **59** displayed resonances characteristic of TBS group.

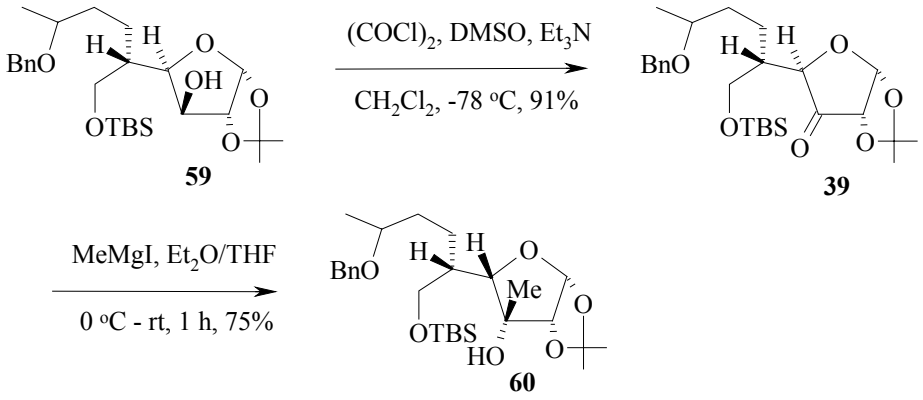
Scheme 14



Our next concern was to introduce the methyl group at C-3 with concomitant epimerization at C-4. For this purpose, **59** was oxidized under Swern reaction condition[33] (Scheme 15) and then the ketone **39** was analyzed for structural elucidation by the ^{1}H NMR and ^{13}C NMR spectroscopy. A significant downfield shifts for the H-2 and H-4 resonances were noted. Its ^{13}C NMR spectrum showed carbonyl carbon signal at 210.0 ppm. The

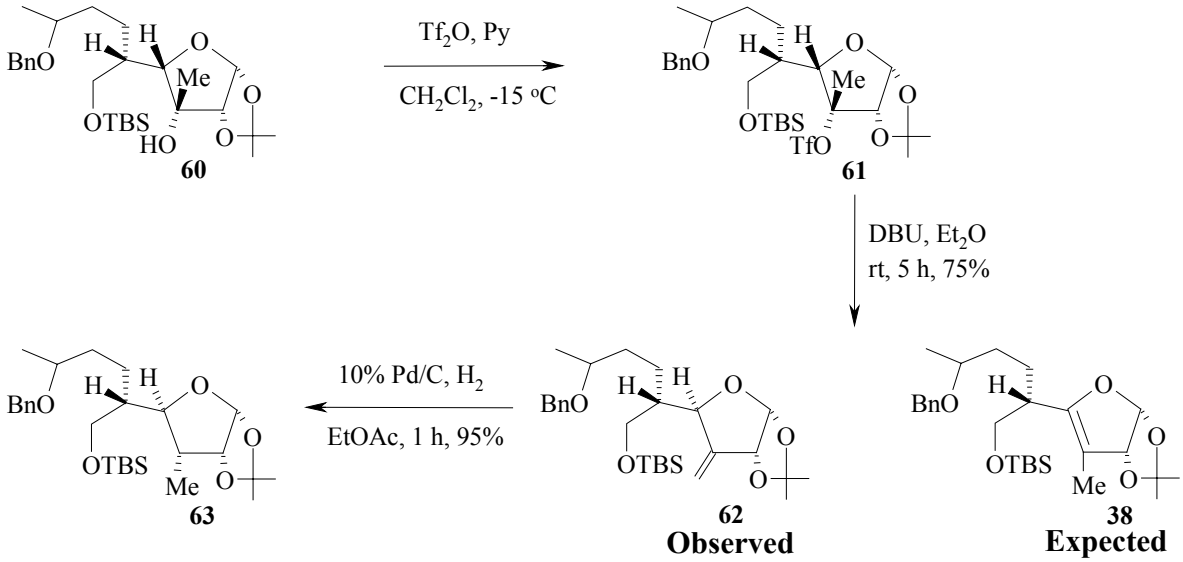
Grignard reaction of **39** with CH_3MgI in THF-Et_2O furnished the carbinol derivative (**60**). We believed based on the literature precedents[34] that the methyl group approaches the C=O group from the top face leading to **60** as the exclusive product.

Scheme 15



The next step was critical to establish the stereochemistry at C-3 and C-4 centers. The Tf_2O mediated elimination reaction of **60** first involved the synthesis of the triflate derivative (**61**) by using Tf_2O and Py in CH_2Cl_2 (Scheme 16). Subsequent treatment with DBU in Et_2O at rt for 5 h gave a new product. However, on the basis of the ^1H NMR and ^{13}C NMR spectroscopic analyses, the presence of *exo*-methylene group was noted and therefore the structure **62** was proposed. The *exo*-methylene protons appeared as a multiplet between 4.98-5.06 ppm. The ^{13}C NMR spectrum revealed the two characteristic resonances at 148.6 and

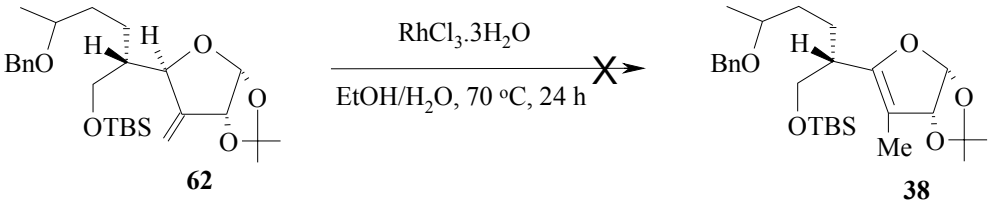
Scheme 16



110.6 ppm corresponding to olefinic carbons. The structure of **62** was further supported when it was hydrogenated over 10% Pd/C in EtOAc to obtain **63** (Scheme 16). Compound **63** was characterized by its ^{1}H NMR, ^{13}C NMR, mass spectroscopy and elemental analysis. A characteristic doublet due to C_3-Me appeared at 1.01 ppm (J = 6.6 Hz) in the ^{1}H NMR spectrum of **63**. The benzyl group remained untouched under this reaction condition.

The recent reports[35] that transition metal complexes can isomerise *exo*-double bonds to *endo*-double bonds. In order to explore the double bond migration reaction, **62** was treated with $RhCl_3.3H_2O$ in EtOH-H_2O at 70 ^oC for 24 h, but the reagent proved to be unsuccessful to produce **38** (Scheme 17).

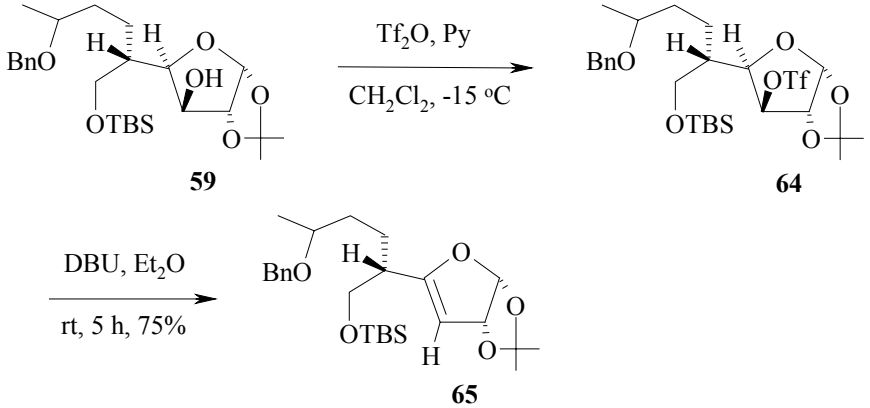
Scheme 17



62 **38**

Therefore, we revised our initial strategy, according to which first the epimerization at C-4 was done. We adopted the strategy reported by Heinatz *et al*.[36] and thus **59** was treated with Tf_2O in the presence of Py in CH_2Cl_2 at –15 ^oC to provide the triflate **64** which when reacted with DBU in Et_2O at rt for 5 h afforded **65** (Scheme 18). The structure of **65** was confirmed by its ^{1}H NMR, ^{13}C NMR, mass spectroscopy and elemental analysis. The chemical shift for H-2 appeared as a doublet in the downfield region at 5.26 ppm (J = 4.4 Hz). The peak due to H-3 appeared at 5.26 ppm. The ^{13}C NMR spectrum showed a peak at 163.0

Scheme 18

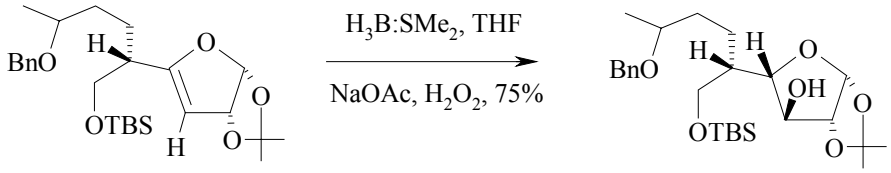


59 **64** **65**

ppm corresponding to C-4. In addition, the mass spectrum exhibited a peak at 462 corresponding to (M^+) ion.

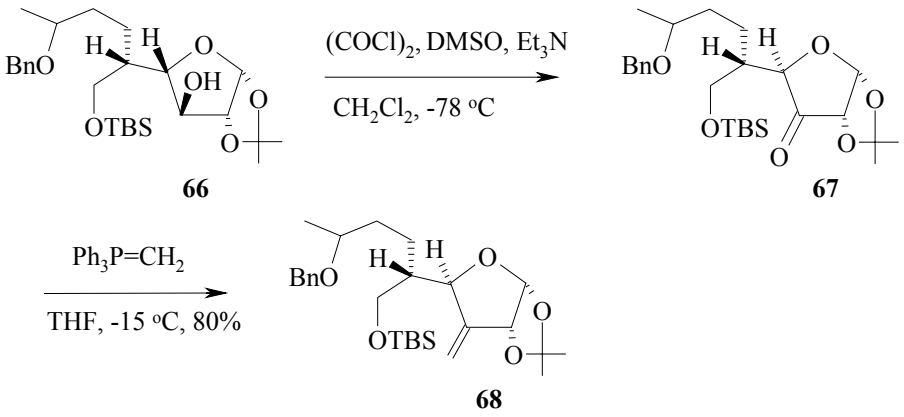
In order to invert C-4 and concomitantly add OH group at C-3, **65** was exposed to $H_3B{:}SMe_2$ in THF followed by oxidative workup with H_2O_2 and NaOAc to obtain the desired product **66** (Scheme 19). In the ^1H NMR spectrum of **66**, H-2 resonated as a doublet at 4.50 ppm (J = 3.9 Hz). All other proton signals were observed at their respective chemical shifts.

Scheme 19



The transformation of **66** into **68** was accomplished in the following two steps. Swern oxidation[33] of **66** using $(COCl)_2$, DMSO and Et_3N at –78 ^oC afforded **67** which with $Ph_3P{=}CH_2$ gave the *exo*-methylene derivative (**68**) (Scheme 20). The ^1H NMR spectrum showed multiplets at 5.14-5.18 ppm and 5.40-5.44 ppm due to *exo*-methylene protons. The structure of **68** was further supported by its mass spectroscopy indicating a peak at 461 corresponding to (M^+–15) ion.

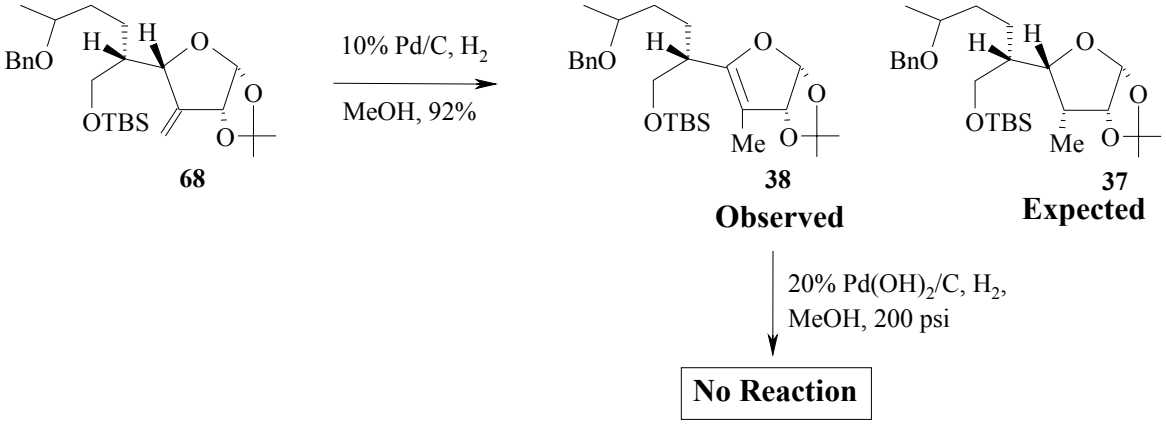
Scheme 20



The hydrogenation of **68** should introduce the methyl group by a stereocontrolled way at C-3. Thus, **68** was stirred with 10% Pd/C in MeOH under H_2 (Scheme 21), but to our surprise, the ^1H NMR, ^{13}C NMR and mass spectroscopy of the newly formed product did not correspond to the expected structure **37**. However, based on spectroscopic data, the *exo-endo*

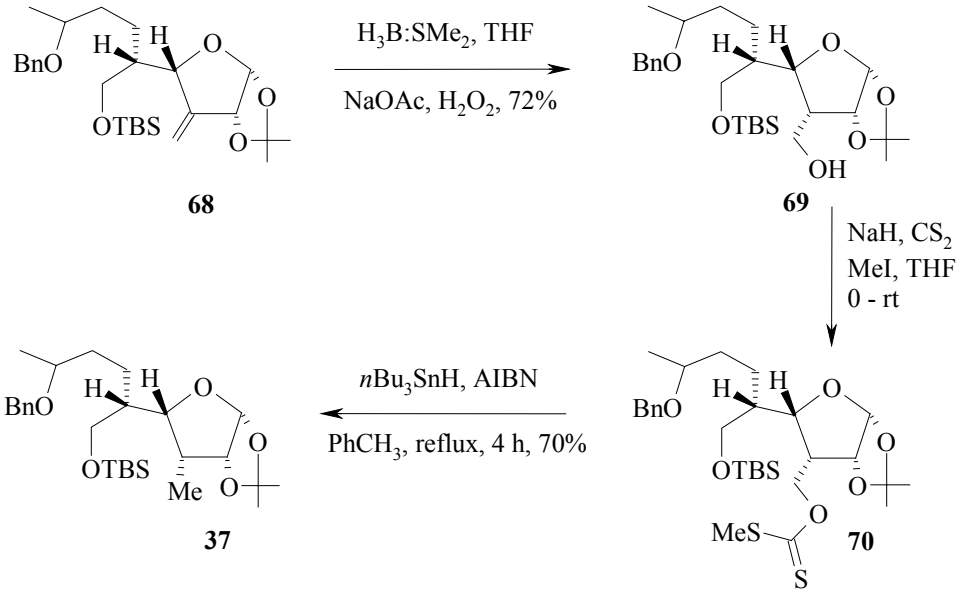
double bond isomerization was noted and structure **38** was proposed. In the ^{1}H NMR spectrum, the C_3-Me group resonated as a singlet at 1.67 ppm. The ^{13}C NMR spectrum showed resonances for C-3 and C-4 at 106.9 ppm and 153.4 ppm, which clearly revealed the presence of double bond. In addition, the mass spectroscopy exhibited a peak at 476 corresponding to (M^+) ion. However, further reduction of the endocyclic double bond of **38** even over 20% $Pd(OH)_2/C$ at 200 psi of H_2 was not successful.

Scheme 21



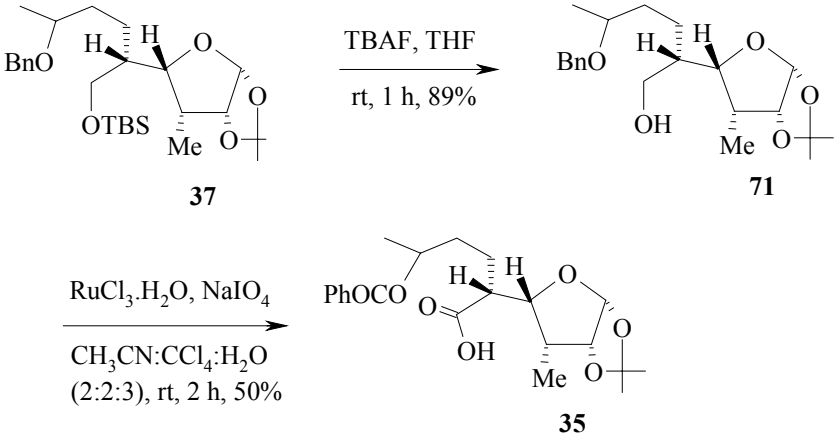
Alternative approach to overcome the problem was envisaged. Hydroboration-oxidation of **68** with $H_3B{:}SMe_2$ in THF followed by oxidative workup with H_2O_2 and NaOAc furnished the desired primary alcohol derivative (**69**) (Scheme 22). The ^{1}H NMR spectrum showed a double-doublet for H-2 at 4.82 ppm ($J_{2,1}$ = 4.4 Hz, $J_{2,3}$ = 6.3 Hz) indicating *cis*–relationship with H-1 and H-3. The ^{13}C NMR spectrum revealed characteristic peak at 59.0 ppm corresponding to CH_2OH. A peak at 479 due to (M^+–15) in the mass spectrum also supported the structure **69**. Compound **69** was then transformed into the deoxy product **37** by Barton reaction.[37] Thus, **68** was treated with NaH, CS_2 and MeI in THF to provide the xanthate derivative (**70**). Subsequent treatment of **70** with nBu$_3$SnH in the presence of AIBN in refluxing toluene for 4 h gave the deoxy product **37** (Scheme 22). The structure of **37** was confirmed by its ^{1}H NMR, ^{13}C NMR, mass spectroscopy and elemental analysis. In the ^{1}H NMR spectrum of **37**, a doublet due to C_3-Me group appeared at 1.12 ppm (J = 6.8 Hz) and the H-3 proton resonated as a multiplet between 2.28-2.38 ppm. The structure of **37** was further supported by its mass spectroscopy indicating a peak at 463 corresponding to (M^+–15) ion.

Scheme 22



Having made **37** with C-3, C-4 and C-5 required stereocenters, next our attention turned to prepare the carboxylic acid derivative (**35**). For this endeavor, the TBS group of **37** was cleaved with TBAF in THF at rt to provide the alcohol **71** (Scheme 23). Finally the free hydroxyl group of **71** was converted[38] into the acid functionality with $RuCl_3.H_2O/NaIO_4$ in $CH_3CN/CCl_4/H_2O$ to afford **35** in which the benzyl group was also oxidized to the benzoate.[39] The structure of **35** was supported by its ^1H NMR, ^{13}C NMR, mass spectroscopy and elemental analysis. The ^1H NMR spectrum of **35** showed a multiplet at 5.05-5.20 ppm for H-9

Scheme 23



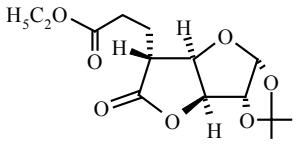
indicating the presence of a benzoate group at this carbon. In addition, in the ^1H NMR spectra of **37** and **35**, the resonances due to H-5 were clearly apparent as a multiplet but whereas

chemical shift due to H-5 of **35** showed a downfield shift of 0.67 ppm compared to **37**. The ^{13}C NMR spectrum of **35** revealed the two characteristic signals at 166.2 ppm and 177.0 ppm corresponding to benzoate and acid groups. The mass spectroscopy showed a peak at 377 due to (M^+−15) ion.

In conclusion, we have developed a highly stereocontrolled radical C-C bond formation on 5-chloro-5-deoxy-1,2-*O*-isopropylidine-β-L-idofuranurono-6,3-lactone (**43**) and elegant synthetic route to complete the C13-C18 segment of sanglifehrin A (**13)**. Further work on peptide segment and to couple with the carboxylic acid fragment **35** followed by synthetic elaboration at C-1 are in progress in this laboratory.

Experimental

5-Deoxy-5-*C*-(ethylpropiono)-1,2-*O*-isopropylidine-β-L-idofuranurono-6,3-lactone (42) and 5-Deoxy-1,2-*O*-isopropylidine-α-D-*xylo*-hexofuranurono-6,3-lactone (51)



To a solution of **43**[27a] (2.0 g, 8.5 mmol) in anhydrous toluene (300 mL) were added ethyl acrylate (13.8 mL, 127.8 mmol) and AIBN (20 mg) and the reaction mixture degassed with argon and heated under reflux. The nBu$_3$SnH (2.5 mL, 8.5 mmol) in toluene (25 mL) was introduced drop wise to the refluxing solution over a period of 3 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 on silica gel using EtOAc-light petroleum ether (1:9) to obtain **42** (0.64 g, 25%).

$[\alpha]_D$ +21.6 (*c* 1.0, $CHCl_3$);

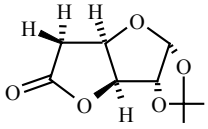
^{1}H NMR (500 MHz, $CDCl_3$): δ 1.27 (t, 3 H, *J* = 7.6 Hz), 1.35 (s, 3 H), 1.54 (s, 3 H), 1.94 (m, 2 H), 2.52 (m, 2 H), 2.76 (t, 1 H, *J* = 8.7 Hz), 4.18 (q, 2 H, *J* = 7.6 Hz), 4.71 (d, 1 H, *J* = 3.2 Hz), 4.83 (d, 1 H, *J* = 3.4 Hz), 4.84 (d, 1 H, *J* = 3.2 Hz), 6.0 (d, 1 H, *J* = 3.4 Hz);

^{13}C NMR (125 MHz, $CDCl_3$): δ 14.3, 23.2, 26.5, 27.0, 31.3, 46.5, 60.8, 82.3, 82.9, 84.2, 106.0, 112.7, 172.0, 175.9;

MS: 285 (M^+–15);

Anal. Calcd for $C_{14}H_{20}O_7$ (Mol. Wt. 300.305): C, 55.99; H, 6.72. Found; C, 55.82; H, 6.88.

Further elution gave **51** (1.0 g, 60%).

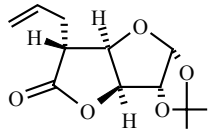


$[\alpha]_D$ +102.7 (*c* 0.89, $CHCl_3$); lit.,[27b] **$[\alpha]_D$** +104.0 (*c* 0.89, $CHCl_3$);

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.34 (s, 3 H), 1.50 (s, 3 H), 2.70 (d, 2 H, *J* = 3.4 Hz), 4.78 (d, 1 H, *J* = 3.4 Hz), 4.82 (d, 1 H, *J* = 3.9 Hz), 4.97 (dt, 1 H, *J* = 2.0, 3.4 Hz), 5.95 (d, 1 H, *J* = 3.9 Hz);

Anal. Calcd for $C_9H_{12}O_5$ (Mol. Wt. 200.189): C, 53.99; H, 6.04. Found; C, 53.70; H, 6.21.

5-*C*-Allyl-5-deoxy-1,2-*O*-isopropylidine-β-L-idofuranurono-6,3-lactone (52)



A solution of **43** (9.0 g, 38.4 mmol), allyltri-*n*-butyltin (12.9 mL, 42.2 mmol), AIBN (25 mg) in benzene (75 mL) under 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 on silica gel using EtOAc-light petroleum ether (1:9) to obtain **52** (8.47 g, 92%) as a colorless oil.

$[\alpha]_D$ +70.9 (*c* 1.0, $CHCl_3$);

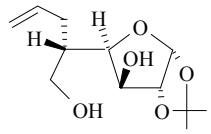
^{1}H NMR (200 MHz, $CDCl_3$): δ 1.34 (s, 3 H), 1.50 (s, 3 H), 2.32 (dt, 1 H, *J* = 8.0, 14.0 Hz), 2.49 (dt, 1 H, *J* = 6.0, 14.0 Hz), 2.81 (dd, 1 H, *J* = 6.0, 8.0 Hz), 4.71 (d, 1 H, *J* = 3.4 Hz), 4.75 (d, 1 H, *J* = 3.4 Hz), 4.81 (d, 1 H, *J* = 4.0 Hz), 5.18 (d, 1 H, *J* = 10.7 Hz), 5.22 (d, 1 H, *J* = 16.6 Hz), 5.69-5.90 (m, 1 H), 5.94 (d, 1 H, *J* = 4.0 Hz);

^{13}C NMR (50 MHz, $CDCl_3$): δ 25.9, 26.0, 31.6, 46.4, 81.7, 82.0, 83.7, 105.4, 111.8, 118.0, 132.8, 175.7;

MS: 225 (M^+–15);

Anal. Calcd for $C_{12}H_{16}O_5$ (Mol. Wt. 240.253): C, 59.99; H, 6.71. Found; C, 59.92; H, 6.75.

5-*C*-Allyl-5-deoxy-1,2-*O*-isopropylidine-β-L-idofuranose (54)



A suspension of LAH (1.26 g, 33.3 mmol), **52** (8.0 g, 33.3 mmol) in THF (50 mL) was stirred at rt for 1 h. The excess LAH was quenched with saturated solution of Na_2SO_4 and filtered and the residue thoroughly washed with EtOAc. The filtrate was concentrated and purified on silica gel using EtOAc-light petroleum ether (1:1) to afford **54** (7.32 g, 90%) as a thick oil.

$[\alpha]_D$ −17.7 (*c* 1.0, $CHCl_3$);

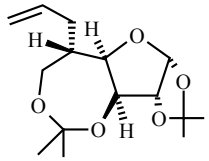
^{1}H NMR (200 MHz, $CDCl_3$): δ 1.31 (s, 3 H), 1.48 (s, 3 H), 1.95-2.18 (m, 2 H), 2.41-2.50 (m, 1 H), 3.20 (br s, 1 H), 3.49 (dd, 1 H, *J* = 2.0, 10.5 Hz), 3.78 (dd, 1 H, *J* = 2.0, 10.5 Hz), 3.91 (dd, 1 H, *J* = 2.0, 8.8 Hz), 4.14-4.24 (m, 1 H), 4.15 (d, 1 H, *J* = 2.0 Hz), 4.52 (d, 1 H, *J* = 3.6 Hz), 5.05 (d br, 1 H, *J* = 10.2), 5.07 (br d, 1 H, *J* = 17.2 Hz), 5.68-5.84 (m, 1 H), 5.88 (d, 1 H, *J* = 3.6 Hz);

^{13}C NMR (50 MHz, $CDCl_3$): δ 25.8, 26.4, 33.0, 39.4, 61.2, 74.5, 82.7, 84.7, 103.6, 110.8, 116.7, 135.3;

MS: 229 (M^+–15);

Anal. Calcd for $C_{12}H_{20}O_5$ (Mol. Wt. 244.285): C, 59.01; H, 8.25. Found; C, 58.81; H, 8.49.

5-*C*-Allyl-5-deoxy-1,2;3,6-di-*O*-isopropylidine-β-L-idofuranose (55)



A solution of **54** (7.1 g, 29.1 mmol), 2,2-dimethoxypropane (7.1 mL, 58.2 mmol), *p*TSA (50 mg) in CH_2Cl_2 (40 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 chromatographed on silica gel using EtOAc-light petroleum ether (1:19) to furnish **55** (5.78 g, 70%).

$[\alpha]_D$ +36.6 (*c* 1.0, $CHCl_3$);

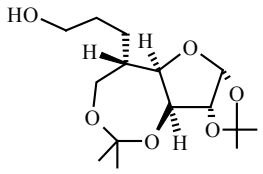
^{1}H NMR (200 MHz, $CDCl_3$): δ 1.26 (s, 6 H), 1.31 (s, 3 H), 1.44 (s, 3 H), 1.94-2.28 (m, 3 H), 3.32 (dd, 1 H, *J* = 3.4, 12.2 Hz), 3.91-3.98 (m, 2 H), 4.18 (br s, 1 H), 4.43 (d, 1 H, *J* = 3.9 Hz), 4.99-5.08 (m, 2 H), 5.68-5.85 (m, 1 H), 5.80 (d, 1 H, *J* = 3.9 Hz);

^{13}C NMR (50 MHz, $CDCl_3$): δ 24.0, 24.8, 26.0, 26.4, 34.5, 40.1, 59.6, 74.6, 79.9, 84.3, 101.0, 103.6, 110.9, 116.5, 135.9;

MS: 269 (M^+–15);

Anal. Calcd for $C_{15}H_{24}O_5$ (Mol. Wt. 284.349): C, 63.36; H, 8.50. Found; C, 63.10; H, 8.35.

5-Deoxy-5-*C*-(3-hydroxypropyl)-1,2;3,6-di-*O*-isopropylidine-β-L-idofuranose (41)



To a solution of **55** (7.1 g, 25.0 mmol) in anhydrous THF (50 mL) at 0 ^{o}C was added $H_3B{:}SMe_2$ (2.6 mL, 27.5 mmol). After stirring for 1 h, saturated NaOAc solution was introduced followed by the addition of 30% H_2O_2 (5.6 mL). The reaction mixture was further stirred at rt for 5 h, diluted with EtOAc, dried (Na_2SO_4) and concentrated. The crude was purified on silica gel using EtOAc-light petroleum (3:7) to provide **41** (5.7 g, 75%) as a colorless oil.

$[\alpha]_D$ +28.0 (*c* 1.0, $CHCl_3$);

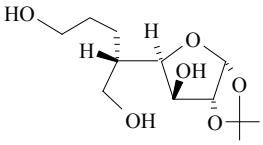
^{1}H NMR (200 MHz, $CDCl_3$): δ 1.30 (s, 6 H), 1.35 (s, 3 H), 1.40-1.73 (m, 4 H), 1.50 (s, 3 H), 1.92-2.01 (m, 1 H), 3.38 (dd, 1 H, *J* = 3.4, 12.2 Hz), 3.66 (t, 2 H, *J* = 6.3 Hz), 3.90 (br s, 1 H), 4.01 (dd, 1 H, *J* = 2.2, 12.2 Hz), 4.23 (br s, 1 H), 4.47 (d, 1 H, *J* = 3.9 Hz), 5.84 (d, 1 H, *J* = 3.9 Hz);

^{13}C NMR (50 MHz, $CDCl_3$): δ 24.4, 25.1, 26.2, 26.5, 26.7, 30.1, 40.5, 59.9, 62.6, 75.1, 81.3, 84.7, 101.3, 103.9, 110.9;

MS: 302 (M^+);

Anal. Calcd for $C_{15}H_{26}O_6$ (Mol. Wt. 302.367): C, 59.58; H, 8.67. Found; C, 59.49; H, 8.95.

5-Deoxy-5-*C*-(3-hydroxypropyl)-1,2-*O*-isopropylidine-β-L-idofuranose (53)



A suspension of LAH (0.1 g, 2.7 mmol), **42** (1.1 g, 3.7 mmol) in THF (8 mL) was stirred at rt for 1 h. The excess LAH was quenched with saturated solution of Na_2SO_4 and filtered and the residue thoroughly washed with EtOAc. The filtrate was concentrated and purified on silica gel using EtOAc-light petroleum ether (9:1) to obtain **53** (0.08 g, 90%) as a thick oil.

$[\alpha]_D$ +2.2 (*c* 1.0, $CHCl_3$);

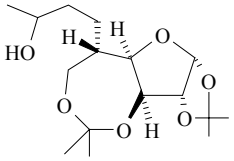
^{1}H NMR (200 MHz, $CDCl_3$): δ 1.31 (s, 3 H), 1.38-1.71 (m, 4 H), 1.48 (s, 3 H), 1.93-2.12 (m, 1 H), 3.53 (dd, 1 H, *J* = 3.4, 11.2 Hz), 3.61-3.67 (m, 2 H), 3.75 (dd, 1 H, *J* = 2.4, 11.2 Hz), 3.94 (dd, 1 H, *J* = 2.4, 9.2 Hz), 4.14 (d, 1 H, *J* = 2.4 Hz), 4.53 (d, 1 H, *J* = 3.9 Hz), 5.89 (d, 1 H, *J* = 3.9 Hz);

^{13}C NMR (50 MHz, $CDCl_3$): δ 24.8, 25.9, 26.5, 29.5, 39.6, 61.0, 62.2, 74.3, 83.2, 84.9, 103.9, 111.0;

MS: 247 (M^+–15);

Anal. Calcd for $C_{12}H_{22}O_6$ (Mol. Wt. 262.299): C, 54.94; H, 8.46. Found; C, 54.75; H, 8.50.

5-Deoxy-5-*C*-(3*R*/*S*-hydroxybutyl)-1,2;3,6-di-*O*-isopropylidine-β-L-idofuranose (57)



Dry DMSO (4.3 mL, 60.9 mmol) and $(COCl)_2$ (2.6 mL, 30.5 mmol) in CH_2Cl_2 (30 mL) at –78 ^{o}C under N_2 were stirred for 30 min and then **41** (4.6 g, 15.2 mmol) in CH_2Cl_2 (15 mL) was added. After 1 h, the reaction was quenched by Et_3N (12.7 mL, 91.4 mmol) at –78 ^{o}C and quenched 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), filtered and concentrated to give crude aldehyde **56** (4.3 g).

The above product (4.3 g) was dissolved in anhydrous THF (25 mL) and cooled to 0 ^{o}C. A 2 M solution of MeMgI in THF (10.7 mL, 21.4 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 (1:4) to furnish **57** (3.61 g, 75%, two steps).

$[\alpha]_D$ +23.0 (*c* 1.0, $CHCl_3$);

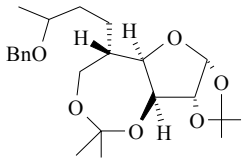
^{1}H NMR (200 MHz, $CDCl_3$): δ 1.20 (d, 3 H, *J* = 6.4 Hz), 1.30 (s, 6 H), 1.35 (s, 3 H), 1.43-1.59 (m, 4 H), 1.50 (s, 3 H), 1.89-1.98 (m, 1 H), 3.34 (dd, 1 H, *J* = 3.6, 12.0 Hz), 3.72-3.83 (m, 1 H), 3.87-3.92 (m, 1 H), 3.96-4.02 (m, 1 H), 4.19-4.24 (m, 1 H), 4.47 (d, 1 H, *J* = 3.9 Hz), 5.84 (d, 1 H, *J* = 3.9 Hz);

^{13}C NMR (50 MHz, $CDCl_3$): δ 23.3, 24.2, 24.9, 26.0, 26.1, 26.5, 36.4, 40.4, 59.5, 67.3, 74.8, 81.1, 84.4, 101.0, 103.6, 110.9;

MS: 301 (M^+–15);

Anal. Calcd for $C_{16}H_{28}O_6$ (Mol. Wt. 316.394): C, 60.73; H, 8.93. Found; C, 60.65; H, 9.04.

5-*C*-(3*R*/*S*-Benzyloxybutyl)- 5-deoxy-1,2;3,6-di-*O*-isopropylidine-β-L-idofuranose (40)



Compound **57** (3.2 g, 10.1 mmol) in DMF (10 mL) was added to a stirred suspension of NaH (0.44 g, 60% dispersion in oil, 11.1 mmol) in DMF (10 mL) at 0 ^oC. The resulting solution was stirred at rt for 30 min, BnBr (1.2 mL, 10.1 mmol) was added. After 1 h, the reaction was quenched by ice-cold water and extracted with EtOAc. The combined organic layers were 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 **40** (3.28 g, 80%).

$[\alpha]_D$ +16.3 (*c* 1.0, $CHCl_3$);

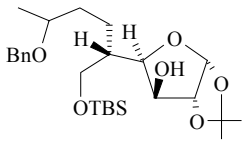
^{1}H NMR (200 MHz, $CDCl_3$): δ 1.20 (d, 3 H, *J* = 6.4 Hz), 1.31 (s, 6 H), 1.35 (s, 3 H), 1.44-1.90 (m, 5 H), 1.51 (s, 3 H), 3.26-3.52 (m, 2 H), 3.90-4.10 (m, 2 H), 4.24-4.54 (m, 4 H), 5.85 (d, 1 H, *J* = 3.9 Hz), 7.29-7.33 (m, 5 H);

^{13}C NMR (50 MHz, $CDCl_3$): δ 19.4, 24.3, 25.1, 25.8, 25.9, 26.1, 33.8, 40.5, 59.5, 70.1, 74.5, 74.9, 81.0, 84.5, 101.1, 103.8, 111.1, 127.2, 127.6, 128.1, 128.5, 138.9;

MS: 391 (M^+–15);

Anal. Calcd for $C_{23}H_{34}O_6$ (Mol. Wt. 406.519): C, 67.95; H, 8.44. Found; C, 68.20; H, 8.31.

5-*C*-(3*R*/*S*-Benzyloxybutyl)-6-*O*-(*tert*-butyldimethylsilyl)-5-deoxy-1,2-*O*-isopropylidine-β-L-idofuranose (59)



A solution of **40** (2.8 g, 6.9 mmol), 0.8% H_2SO_4 (2 mL) in MeOH (10 mL) was stirred at rt for 1 h, neutralized with solid $NaHCO_3$, filtered and concentrated. The residue was partitioned between EtOAc-water, the organic layer dried (Na_2SO_4), concentrated and chromatographed on silica gel using EtOAc-light petroleum ether (6:4) to furnish **58** (2.1 g, 85%) which was dissolved in dry CH_2Cl_2 (15 mL) and then imidazole (0.7 g, 11.1 mmol) and TBSCl (0.9 g, 6.1 mmol) were added. After 1 h, the reaction mixture was washed with saturated NH_4Cl solution, water, dried (Na_2SO_4) and concentrated and the residue on silica gel column purification using EtOAc-light petroleum ether (3:17) afforded **59** (2.4 g, 90%).

$[\alpha]_D$ +22.1 (*c* 1.0, $CHCl_3$);

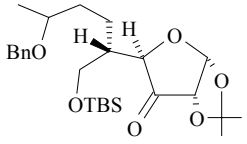
^{1}H NMR (200 MHz, $CDCl_3$): δ 0.11 (s, 6 H), 0.92 (s, 9 H), 1.19 (d, 3 H, *J* = 6.2 Hz), 1.32 (s, 3 H), 1.39-1.81 (m, 4 H), 1.49 (s, 3 H), 1.93-2.03 (m, 1 H), 3.40-3.56 (m, 2 H), 3.73 (dd, 1 H, *J* = 2.0, 10.2 Hz), 3.85-3.92 (m, 2 H), 4.08 (br s, 1 H), 4.40-4.60 (m, 3 H), 5.88 (d, 1 H, *J* = 3.6 Hz), 7.21-7.34 (m, 5 H);

^{13}C NMR (50 MHz, $CDCl_3$): δ –6.1, 17.7, 19.0, 24.3, 25.4, 25.8, 26.4, 33.3, 39.8, 62.7, 69.8, 74.3, 74.5, 83.2, 84.6, 103.8, 110.3, 126.8, 127.1, 127.8, 138.6;

MS: 465 (M^+–15);

Anal. Calcd for $C_{26}H_{44}SiO_6$ (Mol. Wt. 480.718): C, 64.96; H, 9.23. Found; C, 65.26; H, 9.24.

5-*C*-(3*R*/*S*-Benzyloxybutyl)-6-*O*-(*tert*-butyldimethylsilyl)-5-deoxy-1,2-*O*-isopropylidine-β-L-*lyxo*-hexofuranos-3-ulose (39)



Swern oxidation of **59** (0.45 g, 0.9 mmol) was done as described earlier using $(COCl)_2$ (0.16 mL, 1.9 mmol), DMSO (0.26 mL, 3.8 mmol) and Et_3N (0.78 mL, 5.6 mmol) to give **39** (0.4 g, 91%) after silica gel column purification using EtOAc-light petroleum ether (1:19).

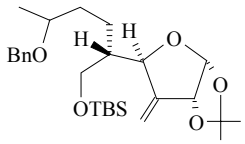
$[\alpha]_D$ +31.6 (*c* 1.7, $CHCl_3$);

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.05 (s, 6 H), 0.89 (s, 9 H), 1.19 (d, 3 H, *J* = 6.3 Hz), 1.35-1.55 (m, 4 H), 1.42 (s, 3 H), 1.46 (s, 3 H), 1.95-2.03 (m, 1 H), 3.43-3.55 (m, 2 H), 3.76-3.85 (m, 1 H), 4.35-4.60 (m, 4 H), 5.97 (d, 1 H, *J* = 2.6 Hz), 7.23-7.33 (m, 5 H);

^{13}C NMR (50 MHz, $CDCl_3$): δ –6.3, 17.6, 18.7, 21.4, 25.1, 26.6 (2C), 34.0, 43.6, 61.0, 69.5, 73.7, 75.7, 76.2, 102.0, 112.7, 126.6, 126.8, 126.9, 127.5, 138.2, 210.0;

Anal. Calcd for $C_{26}H_{42}SiO_6$ (Mol. Wt. 478.702): C, 65.23; H, 8.84. Found; C, 64.99; H, 8.55.

5-*C*-(3*R*/*S*-Benzyloxybutyl)-6-*O*-(*tert*-butyldimethylsilyl)-3,5-dideoxy-1,2-*O*-isopropylidine-3-*C*-methylene-β-L-*lyxo*-hexofuranose (62)



The Grignard reaction of **39** (0.3 g, 0.6 mmol) was carried out as described earlier using 1 M solution of MeMgI in THF (0.8 mL, 0.8 mmol) to obtain **60** (0.22 g, 75%) after silica gel column purification with EtOAc-light petroleum ether (3:17).

The above product (0.22 g) was dissolved in anhydrous CH_2Cl_2 (15 mL) and cooled to –15 ^oC. Pyridine (0.13 mL, 1.6 mmol) and Tf_2O (0.11 mL, 0.7 mmol) were added. After 2 h, it was quenched by ice-water and $NaHCO_3$. The organic layer was separated while the aqueous layer extracted with CH_2Cl_2 (3 x 30 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated to furnish **61** (0.18 g) which was dissolved in Et_2O (5 mL) and DBU (0.1 mL) added. After stirring at rt for 5 h, the solvent was removed and purified on silica gel using EtOAc-light petroleum ether (1:9) to obtain **62** (0.16 g, 75%) as a clear oil.

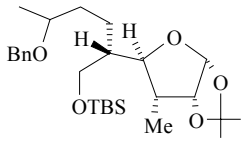
$[\alpha]_D$ +96.4 (*c* 2.2, $CHCl_3$);

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.06 (s, 6 H), 0.89 (s, 9 H), 1.15 (d, 3 H, *J* = 6.0 Hz), 1.36 (s, 3 H), 1.39-1.59 (m, 4 H), 1.47 (s, 3 H), 1.64-1.77 (m, 1 H), 3.36-3.47 (m, 1 H), 3.55-3.71 (m, 2 H), 4.48 (ABq, 2 H, *J* = 11.7 Hz), 4.80-4.84 (m, 1 H), 5.02-5.08 (m, 2 H), 5.40 (dd, 1 H, *J* = 1.0, 2.4 Hz), 5.72-5.76 (m, 1 H), 7.22-7.31 (m, 5 H);

^{13}C NMR (50 MHz, $CDCl_3$): δ –5.4, 18.2, 19.4, 21.3, 25.9, 27.3 (2C), 35.1, 44.2, 63.4, 70.1, 74.7, 78.8, 82.0, 104.2, 110.6, 111.8, 127.2, 127.4, 128.1, 138.9, 146.6;

Anal. Calcd for $C_{27}H_{44}SiO_5$ (Mol. Wt. 476.725): C, 68.03; H, 9.30. Found; C, 67.88; H, 9.52.

5-*C*-(3*R*/*S*-Benzyloxybutyl)-6-*O*-(*tert*-butyldimethylsilyl)-3,5-dideoxy-1,2-*O*-isopropylidine-3-*C*-methyl-β-L-talofuranose (63)



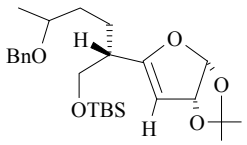
A solution of **62** (0.2 g, 0.4 mmol) in EtOAc (5 mL) was hydrogenated in the presence of 10% Pd/C (20 mg) at rt. After 1 h, the reaction mixture was filtered through a pad of Celite, concentrated and the residue purified on silica gel using EtOAc-light petroleum ether (1:49) to afford **63** (0.19 g, 95%) as a colorless syrup.

$[\alpha]_D$ +12.9 (*c* 0.8, $CHCl_3$);

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.04 (s, 6 H), 0.88 (s, 9 H), 1.01 (d, 3 H, *J* = 6.6 Hz), 1.19 (d, 3 H, *J* = 6.1 Hz), 1.31 (s, 3 H), 1.40-1.70 (m, 5 H), 1.48 (s, 3 H), 1.83-1.95 (m, 1 H), 3.40-3.70 (m, 3 H), 3.92 (d, 1 H, *J* = 2.2 Hz), 4.40-4.60 (m, 3 H), 5.70 (d, 1 H, *J* = 3.6 Hz), 7.23-7.32 (m, 5 H);

Anal. Calcd for $C_{27}H_{46}SiO_5$ (Mol. Wt. 478.741): C, 67.74; H, 9.68. Found; C, 67.57; H, 9.71.

5-*C*-(3*R*/*S*-Benzyloxybutyl)-6-*O*-(*tert*-butyldimethylsilyl)-3,5-dideoxy-1,2-*O*-isopropylidine-β-L-*threo*-hex-3-enofuranose (65)



The triflate reaction of **59** (1.5 g, 3.1 mmol) was carried out as described earlier using Tf_2O (0.8 mL, 5.0 mmol) and pyridine (0.1 mL, 11.9 mmol) in CH_2Cl_2 (10 mL) to give **64** (1.55 g) which was dissolved in Et_2O (10 mL) and the elimination reaction was performed as described earlier using DBU (0.6 mL) to afford **65** (1.1 g, 75%, two steps) after silica gel purification using EtOAc-light petroleum ether (1:9).

$[\alpha]_D$ +8.8 (*c* 1.0, $CHCl_3$);

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.03 (s, 6 H), 0.90 (s, 9 H), 1.19 (d, 3 H, *J* = 6.4 Hz), 1.43 (s, 3 H), 1.48 (s, 3 H), 1.49-1.70 (m, 4 H), 2.25-2.40 (m, 1 H), 3.40-3.70 (m, 3 H), 4.44-4.60 (m,

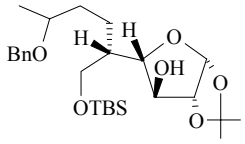
2 H), 4.96 (d, 1 H, *J* = 1.5 Hz), 5.26 (d, 1 H, *J* = 4.4 Hz), 5.99 (d, 1 H, *J* = 4.4 Hz), 7.29-7.34 (m, 5 H);

^{13}C NMR (50 MHz, $CDCl_3$): δ –5.4, 18.3, 19.5, 24.3, 25.9, 28.0, 28.3, 34.1, 42.1, 63.7, 70.3, 74.6, 83.8, 98.6, 105.6, 111.8, 127.3, 127.5, 128.3, 139.1, 163.0;

MS: 462 (M^+);

Anal. Calcd for $C_{26}H_{42}SiO_5$ (Mol. Wt. 462.703): C, 67.48; H, 9.15. Found; C, 67.26; H, 8.94.

5-*C*-(3*R*/*S*-Benzyloxybutyl)-6-*O*-(*tert*-butyldimethylsilyl)-5-deoxy-1,2-*O*-isopropylidine-β-L-altrofuranose (66)



Hydroboration-oxidation of olefin **65** (0.9 g, 1.9 mmol) was done as described earlier using $H_3B{:}SMe_2$ (0.22 mL, 2.3 mmol), saturated aqueous NaOAc solution (1 mL) and 30% H_2O_2 (0.3 mL, 2.9 mmol) in THF (5 mL) to afford **66** (0.7 g, 75%) after silica gel column purification using EtOAc-light petroleum ether (1:4) as a clear oil.

$[\alpha]_D$ +9.2 (*c* 1.0, $CHCl_3$);

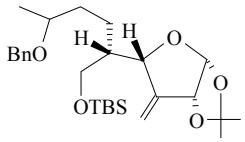
^{1}H NMR (200 MHz, $CDCl_3$): δ 0.06 (s, 6 H), 0.90 (s, 9 H), 1.21 (d, 3 H, *J* = 6.5 Hz), 1.33 (s, 3 H), 1.49 (s, 3 H), 1.51-1.65 (m, 4 H), 1.80-1.90 (m, 1 H), 3.46-3.55 (m, 1 H), 3.71-3.76 (m, 3 H), 4.08-4.10 (m, 1 H), 4.43 (d, 1 H, *J* = 11.7 Hz), 4.50 (d, 1 H, *J* = 3.9 Hz), 4.57 (d, 1 H, *J* = 12.2 Hz), 5.75 (d, 1 H, *J* = 3.9 Hz), 7.25-7.34 (m, 5 H);

^{13}C NMR (50 MHz, $CDCl_3$): δ –5.5, 18.3, 19.4, 21.5, 25.9, 26.8, 27.6, 34.0, 42.2, 62.1, 70.3, 74.9, 76.0, 86.9, 87.8, 104.2, 113.1, 127.4, 127.6, 128.3, 138.9;

MS: 465 (M^+–15);

Anal. Calcd for $C_{26}H_{44}SiO_6$ (Mol. Wt. 480.718): C, 64.96; H, 9.23. Found; C, 64.87; H, 9.44.

5-*C*-(3*R*/*S*-Benzyloxybutyl)-6-*O*-(*tert*-butyldimethylsilyl)-3,5-dideoxy-1,2-*O*-isopropylidine-3-*C*-methylene-β-L-*arabino*-hexofuranose (68)



Swern oxidation of **66** (0.54 g, 1.2 mmol) was done as described earlier using $(COCl)_2$ (0.2 mL, 2.2 mmol), DMSO (0.3 mL, 4.5 mmol) and Et_3N (0.9 mL, 6.8 mmol) to obtain **67** (0.5 g) which was dissolved in anhydrous THF (10 mL) and cooled to –15 ^oC. Methylenetriphenylphosphorane [prepared from PPh_3CH_3I (0.8 g, 2.0 mmol) and $NaNH_2$ (75 mg, 1.9 mmol) was added. After 0.5 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 (1:19) to furnish **68** (0.43 g, 80%) as a colorless oil.

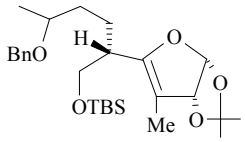
$[\alpha]_D$ –4.8 (*c* 1.0, $CHCl_3$);

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.06 (s, 6 H), 0.89 (s, 9 H), 1.21 (d, 3 H, *J* = 6.5 Hz), 1.33 (s, 3 H), 1.48-1.68 (m, 7 H), 1.76-1.91 (m, 1 H), 3.40-3.58 (m, 1 H), 3.72-3.87 (m, 2 H), 4.35-4.60 (m, 3 H), 4.85 (d, 1 H, *J* = 4.0 Hz), 5.16 (m, 1 H), 5.42 (m, 1 H), 5.77 (d, 1 H, *J* = 4.0 Hz), 7.25-7.31 (m, 5 H);

^{13}C NMR (50 MHz, $CDCl_3$): δ –5.6, 18.1, 19.3, 22.6, 25.8, 25.9, 26.8, 33.5, 44.7, 60.6, 69.9, 74.8, 81.6, 82.6, 104.7, 112.3, 113.3, 127.0, 127.3, 128.0, 139.0, 146.4;

Anal. Calcd for $C_{27}H_{44}SiO_5$ (Mol. Wt. 476.725): C, 68.03; H, 9.30. Found; C, 67.86; H, 9.43.

5-*C*-(3*R*/*S*-Benzyloxybutyl)-6-*O*-(*tert*-butyldimethylsilyl)-3,5-dideoxy-1,2-*O*-isopropylidine-3-*C*-methyl-β-L-*threo*-hex-3-enofuranose (38)



Hydrogenation of **68** (50 mg, 0.1 mmol) with 10% Pd/C (10 mg) in MeOH (3 mL) was performed as described earlier to obtain **38** (45 mg, 92%) after silica gel column purification using EtOAc-light petroleum ether (3:97).

$[\alpha]_D$ +1.9 (*c* 1.0, $CHCl_3$);

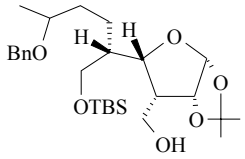
^{1}H NMR (200 MHz, $CDCl_3$): δ 0.01, 0.04 (2 s, 6 H), 0.87 (s, 9 H), 1.18 (d, 3 H, *J* = 6.3 Hz), 1.35-1.60 (m, 4 H), 1.44 (s, 6 H), 1.67 (s, 3 H), 2.40-2.53 (m, 1 H), 3.40-3.74 (m, 3 H), 4.43 (d, 1 H, *J* = 11.7 Hz), 4.55 (d, 1 H, *J* = 11.7 Hz), 5.06 (dd, 1 H, *J* = 2.7, 5.3 Hz), 5.86 (d, 1 H, *J* = 5.3 Hz), 7.28-7.34 (m, 5 H);

^{13}C NMR (50 MHz, $CDCl_3$): δ −5.6, 9.0, 18.0, 19.4, 24.1, 25.8, 28.0 (2C), 34.2, 40.2, 64.1, 70.1, 74.3, 87.2, 103.5, 106.9, 111.2, 127.1, 127.3, 128.0, 139.1, 153.4;

MS: 476 (M^+);

Anal. Calcd for $C_{27}H_{44}SiO_5$ (Mol. Wt. 476.725): C, 68.03; H, 9.30. Found; C, 67.92; H, 9.74.

5-*C*-(3*R*/*S*-Benzyloxybutyl)-6-*O*-(*tert*-butyldimethylsilyl)-3,5-dideoxy-3-*C*-hydroxymethyl-1,2-*O*-isopropylidine-β-L-mannofuranose (69)



Hydroboration-oxidation **68** (0.3 g, 0.63 mmol) was performed as described earlier using $H_3B{:}SMe_2$ (0.07 mL, 0.7 mmol), saturated aqueous NaOAc solution (1 mL) and 30% H_2O_2 (0.1 mL, 0.9 mmol) in THF (5 mL) to provide **69** (0.22 g, 72%) after silica gel column purification using EtOAc-light petroleum ether (1:3) as a thick liquid.

$[\alpha]_D$ +11.5 (*c* 1.0, $CHCl_3$);

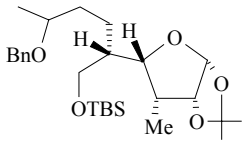
^{1}H NMR (200 MHz, $CDCl_3$): δ 0.04 (s, 6 H), 0.88 (s, 9 H), 1.20 (d, 3 H, *J* = 6.3 Hz), 1.35 (s, 3 H), 1.54-1.90 (m, 8 H), 2.44-2.58 (m, 1 H), 3.44-3.60 (m, 1 H), 3.67-3.99 (m, 6 H), 4.50 (ABq, 2 H, *J* = 11.7 Hz), 4.82 (dd, 1 H, *J* = 4.4, 6.3 Hz), 5.68 (d, 1 H, *J* = 4.4 Hz), 7.29-7.36 (m, 5 H);

^{13}C NMR (50 MHz, $CDCl_3$): δ −5.6, 18.1, 19.5, 22.3, 25.8, 26.2, 26.6, 33.5, 40.4, 45.9, 59.0, 61.0, 70.2, 74.8, 80.2, 82.3, 104.6, 113.5, 127.3, 127.5, 128.2, 139.0;

MS: 479 (M^+−15);

Anal. Calcd for $C_{27}H_{46}SiO_6$ (Mol. Wt. 494.740): C, 65.54; H, 9.37. Found; C, 65.66; H, 9.23.

5-*C*-(3*R*/*S*-Benzyloxybutyl)-6-*O*-(*tert*-butyldimethylsilyl)-3,5-dideoxy-1,2-*O*-isopropylidine-3-*C*-methyl-β-L-mannofuranose (37)



A solution of **69** (0.15 g, 0.3 mmol) in THF (3 mL) was added to a suspension of NaH (15 mg, 0.4 mmol) in THF (5 mL) at 0 ^{o}C. The resulting solution was stirred at rt for 30 min, CS_2 (0.03 mL) and MeI (0.03 mL) were added. After 1 h, reaction mixture was quenched by saturated aqueous NH_4Cl solution and organic layer separated, dried (Na_2SO_4), concentrated and the residue purified on silica gel using EtOAc-light petroleum ether (1:9) to provide **70** (0.13 g).

The above product **70**, *n*Bu_3SnH (0.07 mL, 0.25 mmol) and AIBN (15 mg) in toluene (10 mL) under argon were heated under reflux for 4 h, concentrated and chromatographed on silica gel using EtOAc-light petroleum ether (1:19) to afford **37** (0.1 g, 70%, two steps).

$[\alpha]_D$ −9.3 (*c* 0.6, $CHCl_3$);

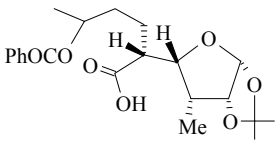
^{1}H NMR (200 MHz, $CDCl_3$): δ 0.05 (s, 6 H), 0.89 (s, 9 H), 1.12 (d, 3 H, *J* = 6.8 Hz), 1.20 (d, 3 H, *J* = 6.3 Hz), 1.32 (s, 3 H), 1.47-1.75 (m, 7 H), 1.82-1.97 (m, 1 H), 2.28-2.38 (m, 1 H), 3.42-3.55 (m, 1 H), 3.69-3.92 (m, 3 H), 4.42-4.61 (m, 3 H), 5.66 (d, 1 H, *J* = 4.4 Hz), 7.24-7.34 (m, 5 H);

^{13}C NMR (50 MHz, $CDCl_3$): δ −5.4, 9.7, 18.4, 19.7, 23.0, 26.0, 26.3, 26.6, 33.6, 38.9, 40.5, 61.5, 70.2, 75.0, 82.1, 83.2, 104.9, 112.5, 127.3, 127.5, 128.2, 139.0;

MS: 463 (M^+−15);

Anal. Calcd for $C_{27}H_{46}SiO_5$ (Mol. Wt. 478.746): C, 67.73; H, 9.69. Found; C, 67.59; H, 9.51.

5-*C*-(3*R*/*S*-Benzoyloxybutyl)-3,5-dideoxy-1,2-*O*-isopropylidine-3-*C*-methyl-β-L-mannofuranoic acid (35)



A solution of **37** (50 mg, 0.1 mmol) and 1M solution of nBu$_4$NF (0.12 mL, 0.12 mmol) in THF were stirred for1 h and concentrated. The crude was extracted with EtOAc, washed with water, dried (Na_2SO_4), concentrated. The residue was chromatographed on silica gel using EtOAc-light petroleum ether (3:7) to give **71** (33 mg, 89%) as colorless thick syrup.

The above product **71** (33 mg, 0.09 mmol) was dissolved in 0.2 mL of CCl_4, 0.2 mL of CH_3CN and 0.3 mL of H_2O ($CCl_4/CH_3CN/H_2O$ = 2:2:3, v/v). $NaIO_4$ (80 mg, 0.37 mmol) and $RuCl_3.H_2O$ (3 mg) were added. The entire mixture was stirred vigorously for 2 h at rt, diluted with CH_2Cl_2 (5 mL), organic layer separated while aqueous layer extracted with CH_2Cl_2. The combined organic layer dried (Na_2SO_4), concentrated and chromatographed on silica gel using EtOAc-light petroleum ether (3:7) to afford **35** (18 mg, 50%) as a colorless liquid.

$[\alpha]_D$ –29.2 (*c* 0.7, $CHCl_3$);

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.10-1.19 (m, 3 H), 1.31 (s, 3 H), 1.34 (d, 3 H, *J* = 6.3 Hz), 1.55-1.85 (m, 4 H), 1.65 (s, 3 H), 2.30-2.50 (m, 1 H), 2.92-3.15 (m, 1 H), 4.13 (dd, 1 H, *J* = 8.0, 10.0 Hz), 4.57 (dd, 1 H, *J* = 2.0, 4.8 Hz), 5.05-5.20 (m, 1 H), 5.76 (d, 1 H, *J* = 2.0 Hz), 7.39-7.59 (m, 3 H), 8.02 (d, 2 H, *J* = 7.0 Hz);

^{13}C NMR (50 MHz, $CDCl_3$): δ 9.6, 20.1, 25.6, 26.2, 29.2, 33.6, 39.5, 48.4, 70.9, 71.4, 83.2, 105.1, 112.6, 128.3, 129.5, 130.7, 132.8, 166.2, 177.0;

MS: 377 (M^+–15);

Anal. Calcd for $C_{21}H_{28}O_7$ (Mol. Wt. 392.445): C, 64.26; H, 7.20. Found; C, 64.54; H, 7.44.

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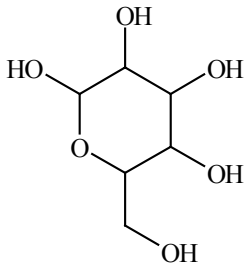
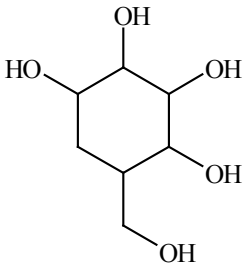
Introduction

The term "pseudo-sugar or carba-sugar **2**" is the name that has been used for a class of compounds wherein the ring-oxygen atom of aldopyranose **1** is replaced by a methylene group. The term, which is vague, was first proposed by the American Professor G. E. McCasland and coworkers[1] when they synthesized the first such compounds, which they called "pseudo-α-DL-talopyranose." The most reactive functional group in a true sugar, that is, an aldehyde or a ketone group, does not exists in the carba-sugars; and, accordingly, carba-sugars do not exhibit any characteristic reaction of a reducing sugar, such as reduction of heavy-metal salts in alkaline solution, mutarotation, and formation of osazones or hydrazones.

Historically, the name pseudo-oligosaccharides had been used to designate oligosaccharides containing nontypical "sugars" such as cyclitols or aminocyclitols, and also those containing carba-sugars or amino carba-sugars.



Aldopyranose (1)



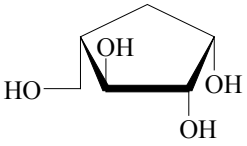
Carba-sugar (2)

Carba-monosaccharides

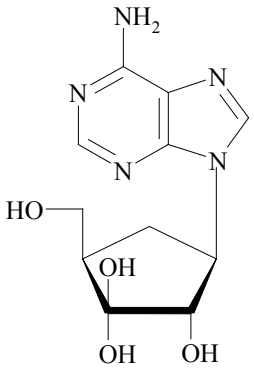
There are two forms of carba-sugars: carba-pyranoses and -furanoses. The former, especially the carba-hexopyranoses, have been extensively studied during the past two decades, ever since their derivatives were found in nature as components of important antibiotics. However, very little is known about carba-furanoses, except for carba-β-L-arabinofuranose (**3**) and carba-β-D-ribofuranosylamine (**4**)[2,3] moiety of the antibiotic aristeromycin (**5**).[4-6]

The first recognized carba-sugar, carba-α-DL-talopyranose (**6**), was synthesized by McCasland and coworkers,[1] and they prepared two more carba-sugars, carba-β-DL-gulopyranose (**7**)[7] and carba-α-DL-galactopyranose (**8**).[8] They suggested[7] that carba-sugars may possess biological effects, owing to their structurally close resemblance to sugars and

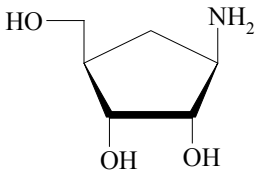
hope was expressed that, in some cases, a carba-sugar might be accepted by enzymes or biological systems in place of a true sugars and thus might serve to inhibit growth of malignant or pathogenic cells. In fact, carba-α-D-galactopyranose (**9**) was discovered[9] in a fermentation broth of *streptomyces* sp. MA-4147 in 1973, seven years after this suggestion, which exhibits inhibitory activity against *Klebsiella pneumonia* MB-1264.



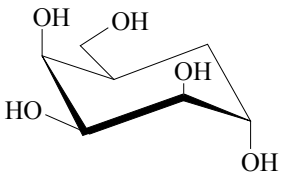
Carba-β-L-arabinofuranose (3)



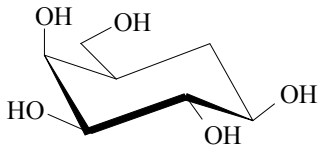
Carba-aristeromycin (5)



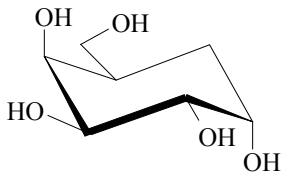
Carba-β-D-ribofuranosylamine (4)



Carba-α-DL-talopyranose (6)



Carba-β-DL-gulopyranose (7)



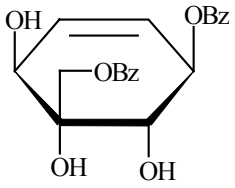
Carba-α-DL-galactopyranose (8)
Carba-α-D-galactopyranose (9)

Other examples of naturally occurring carbasugars include streptol,[10] zeylenol (**10**),[11] ferrudiol (**11**),[12] valienamine (**12**)[13] and validamine (**13**).[14] MK7067 (**14**) is a recent example of carba-sugar which was isolated from the fermentation broth of *Curvularia eragrostidis* D2452 and was found to have an effective herbicidal activity.[15]

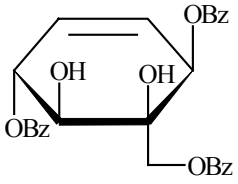
Carba-oligosaccharides

Complex oligosaccharides are currently emerging as promising therapeutic agents.[16] A possible drawback of such drugs is their vulnerability towards in vivo degradation by glycosidases and this has prompted the search for non-hydrolysable oligosaccharide mimetics. Carba-sugars are hydrolytically stable analogues of their parent sugars and are of interest as tools for the elucidation of the (spatial) role of sugar hydroxyl groups in biological systems.[17] Furthermore, it is possible to substitute the pyranoid-ring oxygen of one sugar in an

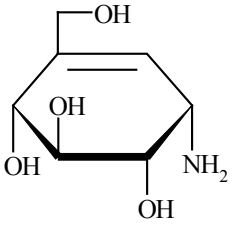
oligosaccharide with a methylene group, whilst retaining significant biological activity.[18] Carba-oligosaccharides as mimetics of biologically important systems are, therefore, attractive synthetic targets.



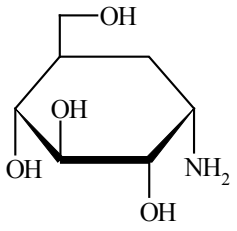
Zeylenol (10)



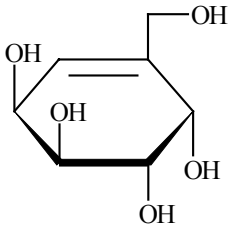
Ferrudiol (11)



Valienamine (12)



Validamine (13)



MK7067 (14)

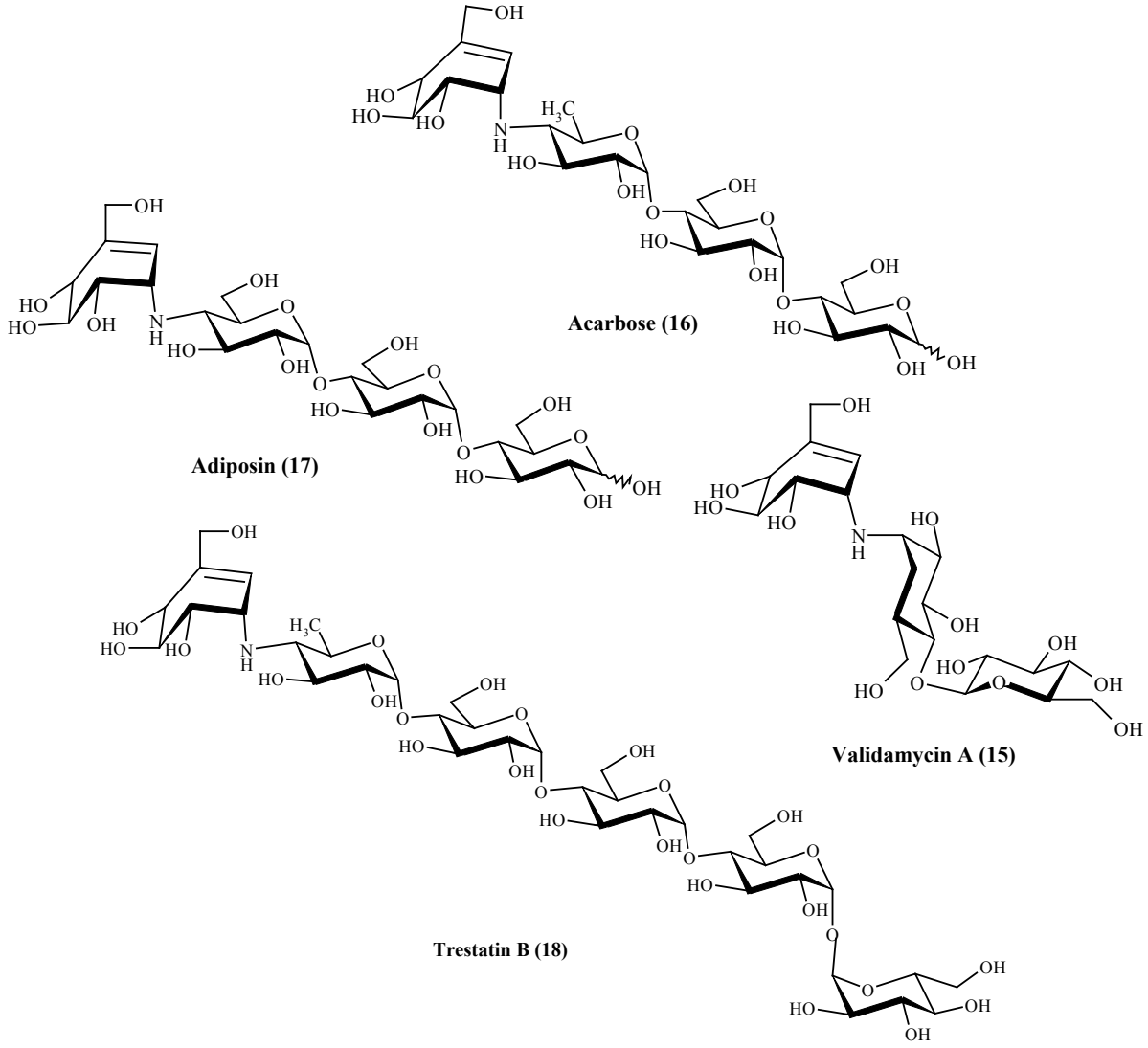
Prior to the discovery of carba-α-D-galactopyranose (**9**), carba-trisaccharidic antibiotics, validamycins, had been discovered[19] in 1970. Validamycins are obtained from a fermentation beer of *streptomyces hygroscopicus* var. *limoneus*, and validamycin A (**15**) is the most active component, which exhibits strong inhibitory activity against the sheath blight of rice plants and "damping off" of cucumber seedlings caused by an infection of *Pellicularia sasakii* and *Rhizoctania solani*.[19] Validamycins have been widely used in Japan as farming antibiotics.

The carba-oligosaccharidic antibiotics acarbose (**16**),[20] adiposin (**17**),[21] trestatins (**18**)[22] and oligostatins[23] have been discovered in fermentation broths as inhibitors.

Medium Size Carba-sugar

In the last couple of years, higher analogues of carba-sugars based on polyhydroxylated 7- and 8-membered rings have attracted a lot of attention as new types of potential glycomimics. An advantageous feature of the cycloheptane and cyclooctane polyols is that they offer opportunities for new distributions of hydroxyl functionalities for biological interactions in a conformationally flexible environment compared to the classical conformations present in **1** and **2**. The synthesis of medium-sized rings, notably 7- and 8-

membered ring systems, has usually been hampered by entropic/enthalpic factors and transannular interactions between the methylene groups.[24] These are serious limitations, which have usually resulted in low chemical yields of the desired products. In particular, Sinaÿ and coworkers[25] in the year 2000 have reported the first synthesis of 8-membered carba-sugar from glucose.



Biological Effects of Carba-sugars

Besides the sweetness of pseudo-sugars, a pseudo-sugar may have a biological activity, owing to its structural close resemblance to a true sugar. They are stable to enzymatic hydrolysis in biological systems, and often display a range of biological activities, particularly as glycosidase inhibitors.[26]

Pseudo-α-D-galactopyranose (**9**) has been found in a fermentation broth *streptomyces* sp. MA-4145 as an antibiotic.[9] The potency of the antibiotic was rather low. A concentration of about 125 ug/ml is required to produce a standard inhibition zone of 25 mm (diameter) against *Klebsiella pneumonia* MB-1264, using 13 mm assay discs in a discplate assay. A sample of the synthetic pseudo-α-DL-galactopyranose (**8**)[3] showed to be about half as potent as natural product (**9**) in the same assay system, thus indicating that the L-enantiomer is probably inactive.

An inhibition of glucose-stimulated insulin release has been studied by using pseudo-α-DL-glucopyranose as a glucokinase inhibitor. That is, pseudo-α-DL-glucopyranose and pseudo-β-DL-glucopyranose were used as synthetic analogs of D-glucose anomers to study the mechanism of glucose-stimulated insulin release by pancreatic islets. And it was found that pseudo-sugar was neither phosphorylated by liver glucokinase, nor stimulated an insulin release from islets. Incubation of the islets with pseudo-α-DL-glucopyranose resulted in an accumulation of the pseudo-sugar, probably the D-enantiomer in the islets. Pseudo-α-DL-glucopyranose inhibited both glucose-stimulated insulin release (44% inhibition at 20 mM) and islet glucokinase activity (36% inhibition at 20 mM), but pseudo-β-DL-glucopyranose did not show any activity.

These results strongly suggested that the inhibition of glucose-stimulated insulin release by pseudo-α-DL-glucopyranose due to the inhibition of islet glucokinase by the pseudo-sugar, providing an additional evidence for the essential role of islet glucokinase in glucose-stimulating insulin.[27]

It is well recognised that idose residues (as L-iduronic acid) play a crucial role in determining the biological activity of glycosaminoglycans.[28] The critical importance of L-iduronic acid in the antithrombin III binding sequence of heparin[29] and FGF-2 binding of heparan sulfate[30] has been specifically demonstrated.

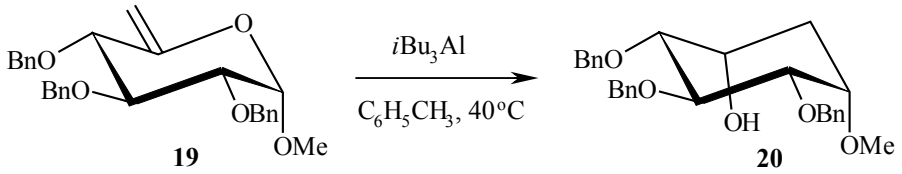
Past Work

6-Membered Carba-sugars

1) By Triisobutylaluminium (TIBAL)-induced Rearrangement

Recently Sinaÿ and coworkers[31] have reported that *C*-glycosides of 6-deoxyhex-5-enopyranoses undergo smooth TIBAL-mediated carbocyclization. When **19** was treated with TIBAL, the desired carba-sugar **20** was obtained as the major product (Scheme 1).

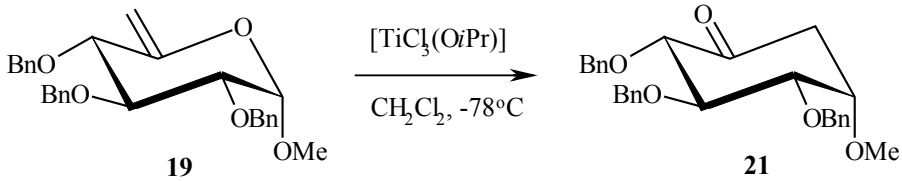
Scheme 1



2) By Ti(IV)-promoted Non-reductive Rearrangement

Sinaÿ and coworkers[31] have developed a strategy for the conversion of sugar pyranosides into highly functionalized cabocyclic derivatives using Ti(IV) derivatives as Lewis acids. Ti(IV)-promoted non-reductive rearrangement of readily available 6-deoxyhex-5-enopyranoside **19** provided **21** (Scheme 2).

Scheme 2



3) By Oxy-mercuration

Barton and coworkers[32] reported the methodology for the preparation of D- and L-pseudo-sugars from D-glucose. The synthetic strategy was initiated with the known ketone **22**, obtained from D-glucose. Treatment of **22** with MeOCH=PPh$_3$ followed by oxy-mercuration using Hg(II) acetate provided three products **24**, **25** and **26** *via* the intermediate **23**. Finally debenzylation of **25** and **26** gave carba-β-L-idopyranose (**28**) and carba-α-D-glucopyranose (**27**) respectively (Scheme 3).

4) By Free Radical Cyclization

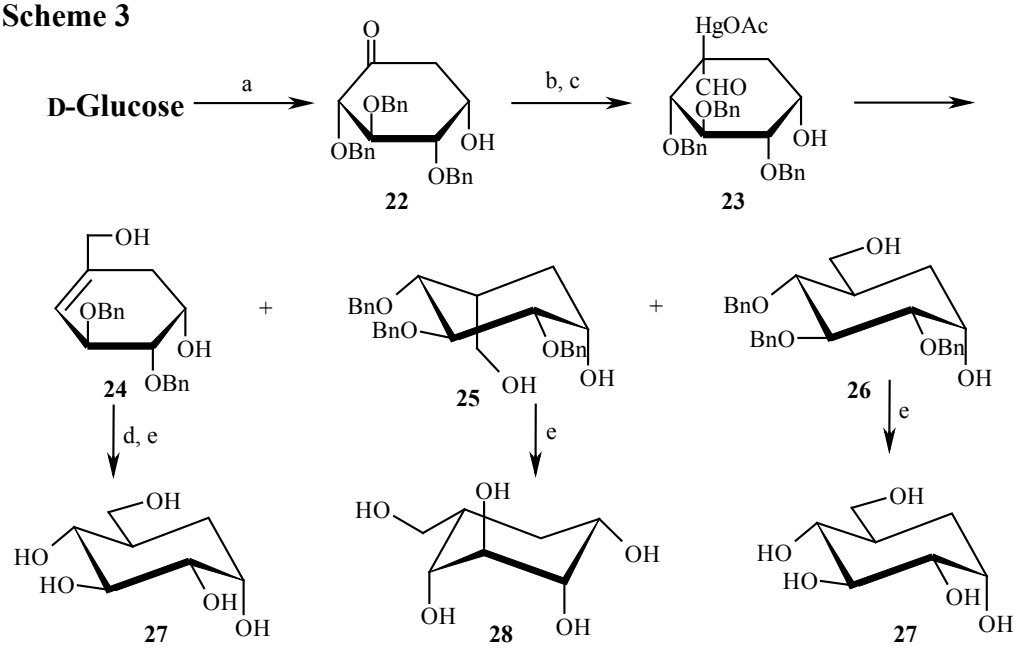
Marco-Contelles and coworkers[34] described a strategy for the synthesis of 6-membered carba-sugars based on Fraser-Reid's[35] 6-exo free radical cyclization of acyclic carbohydrate intermediates. The radical precursor **30** was prepared from 6-bromo-6-deoxy-1,2-*O*-isopropylidine-α-D-glucofuranose (**29**). The nBu$_3$SnH-mediated free radical cyclization of **30** afforded aminocyclitol **31a** and **31b** (Scheme 4).

5) By Claisen Rearrangement

Nagarajan *et al*.[36a] have reported the synthesis of pseudo-sugars from sugars utilizing the claisen rearrangement as the key step. The precursor of claisen rearrangement **33** was

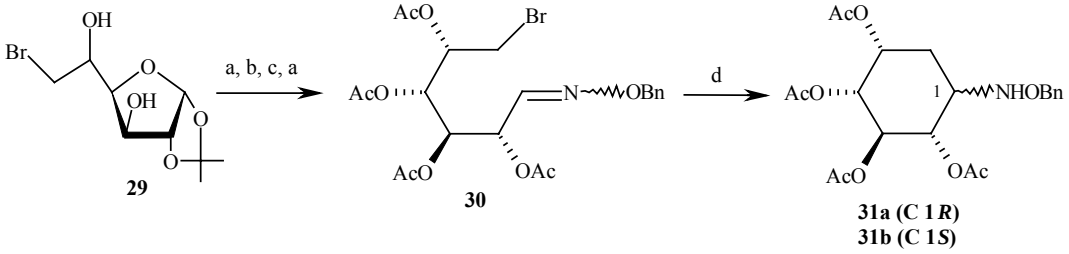
prepared from **32**. Claisen rearrangement on **33** gave **34** which was transformed to **35** by the following set of reactions, $NaBH_4$ reduction, OsO_4 dihydroxylation and hydrogenolysis (Scheme 5).

Scheme 3



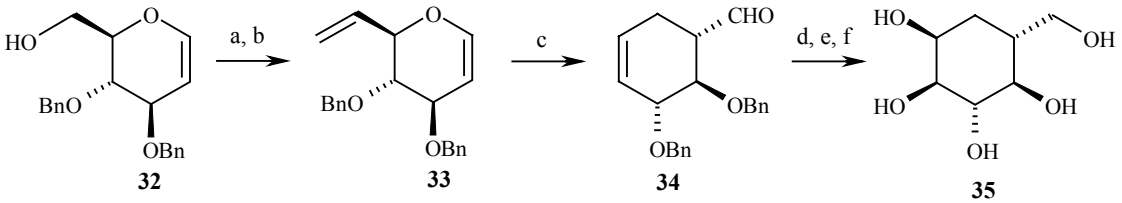
Reagents and conditions: (a) Ref. 33; (b) $MeOCH{=}PPh_3$, DME, 0 ^oC; (c) $Hg(OAc)_2$, CH_3CN/H_2O; (d) BH_3:THF, H_2O_2, NaOH; (e) H_2, 10% Pd/C.

Scheme 4



Reagents and conditions: (a) Ac_2O, Py; (b) TFA, H_2O; (c) $BnONH_3Cl$, Py, CH_2Cl_2/H_2O; (d) *n*Bu_3SnH, AIBN, toluene.

Scheme 5



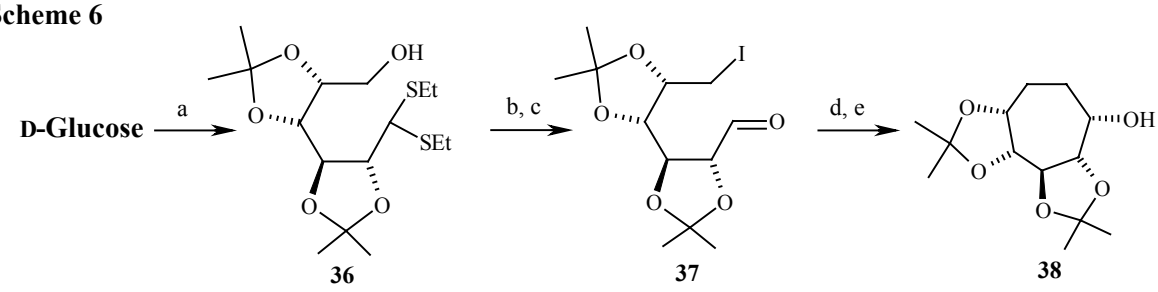
Reagents and conditions: (a) PDC, MS. 4 Å, CH_2Cl_2; (b) CH_3PPh_3I, $NaNH_2$, Et_2O; (c) *o*-dichlorobenzene, 240 ^oC; (d) $NaBH_4$, THF; (e) OsO_4, $K_3Fe(CN)_6$, K_2CO_3, *t*BuOH, H_2O; (f) H_2, 20% $Pd(OH)_2/C$.

7-Membered Carba-sugars

1) By Free Radical-mediated Cyclization

Marco-Contelles and coworkers[37a] have developed a methodology for the synthesis of highly functionalized 7-membered carba-sugar involving free radical cyclization as the key step. They described the examples of the 7-exo free radical cyclization of acyclic radical precursors derived from sugar. Iodination of **36** followed by oxidative desulfurization gave aldehyde **37**. Addition of vinylmagnesium bromide to this aldehyde and radical cyclization afforded **38** (Scheme 6).

Scheme 6



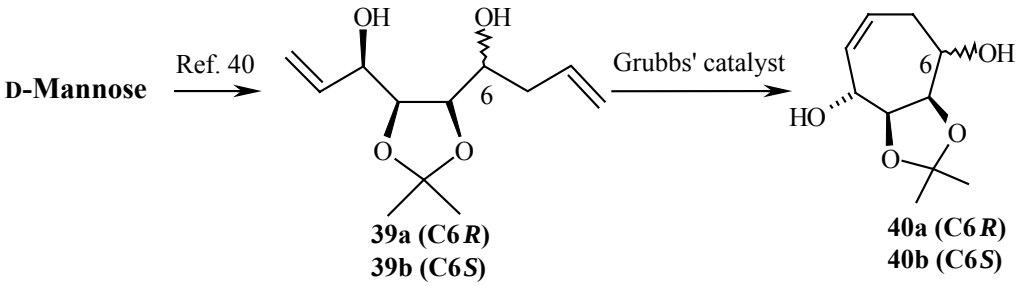
Reagents and conditions: (a) Ref. 38; (b) I_2, Ph_3P, Im, $C_6H_5CH_3$; (c) HgO, $HgCl_2$, CH_3COCH_3; (d) vinylmagnesium bromide, THF, 0 ^oC; (e) AIBN, nBu_3SnH, $C_6H_5CH_3$.

2) By RCM

a) From D-Mannose

Marco-Contelles and coworkers[39] have used D-mannose as the starting material for the conversion of sugars into 7-membered carbocycles involving RCM as the key step (Scheme 7).

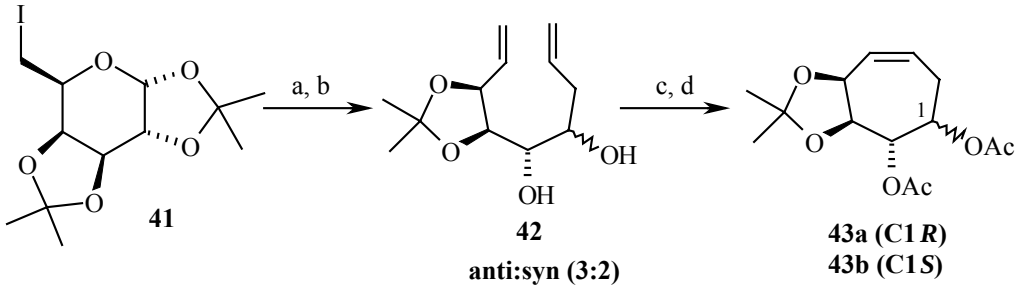
Scheme 7



b) From D-Galactose

Hanna *et al*.[41] prepared the RCM precursor from 6-deoxy-6-iodo-1,2:3,4-di-*O*-isopropylidene-D-galactopyranoside (**41**).[42] Reductive ring opening of **41** with Zn dust under sonication followed by treatment with allylmagnesium bromide afforded a mixture of diastereomers **42** (anti:syn, 3:2). The free hydroxyl groups were esterified as their acetates and subjected to RCM to obtain carbocycles **43a** and **43b** (Scheme 8).

Scheme 8



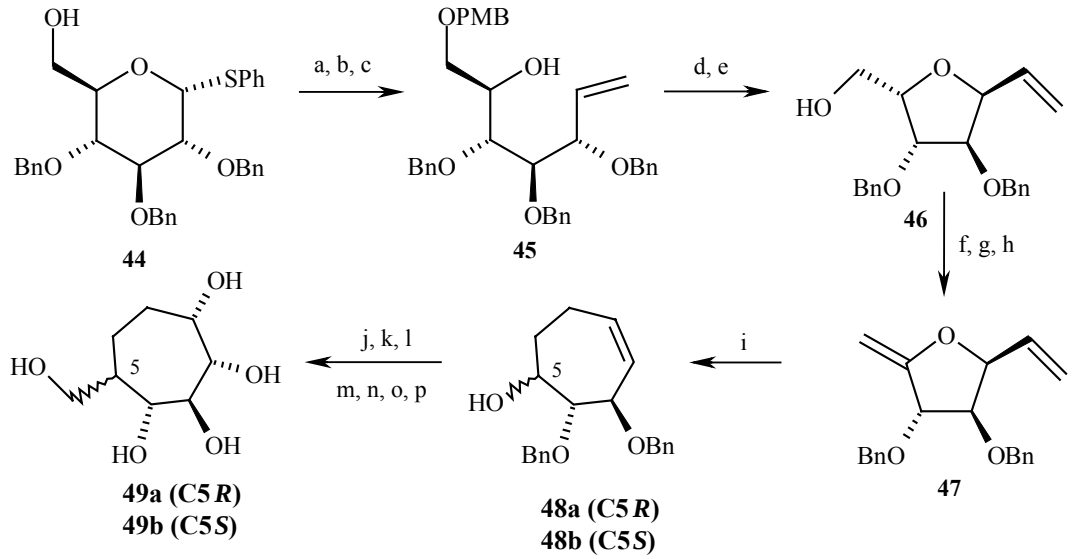
41 **42** **anti:syn (3:2)** **43a (C1 *R*)** **43b (C1 *S*)**

Reagents and conditions: (a) Zn, sonication, THF/H_2O; (b) allylmagnesium bromide, Et_2O; (c) Ac_2O, Py; (d) $[(PCy_3)_2Cl_2Ru{=}CHPh]$, CH_2Cl_2.

3) By TIBAL-promoted Claisen Rearrangement

Sinaÿ *et al*.[43] have reported the TIBAL-promoted reductive claisen rearrangement for the construction of a cycloheptane ring from the key diene **47**, which was synthesized from known alcohol **44** (Scheme 9).

Scheme 9



44 **45** **46** **47** **49a (C5 *R*)** **49b (C5 *S*)** **48a (C5 *R*)** **48b (C5 *S*)**

Reagents and conditions: (a) PMB-Cl, NaH, DMF; (b) $AgNO_3$, MeCOMe/H_2O, rt; (c) Ph_3PMeBr, BuLi, DME, 80 ^oC; (d) Tf_2O, Py, CH_2Cl_2, –40 ^oC - rt; (e) DDQ, CH_2Cl_2, H_2O, rt; (f) TsCl, Py, CH_2Cl_2; (g) NaI, *n*Bu_4NI, DMSO, MS 4 Å, 80 ^oC; (h) DBU, DMSO, MS 4 Å, 80 ^oC; (i) *i*Bu_3Al, $C_6H_5CH_3$, 60 ^oC; (j) OsO_4, NMO, MeCOMe/H_2O, rt; (k) DMP, CSA, CH_2Cl_2; (l) PCC, MS 4 Å, CH_2Cl_2; (m) Tebbe reagent, THF/Py, –40 ^oC - rt; (n) BH_3:THF, H_2O_2, NaOH; (o) TFA, dioxane/H_2O; (p) H_2, Pd/C, MeOH.

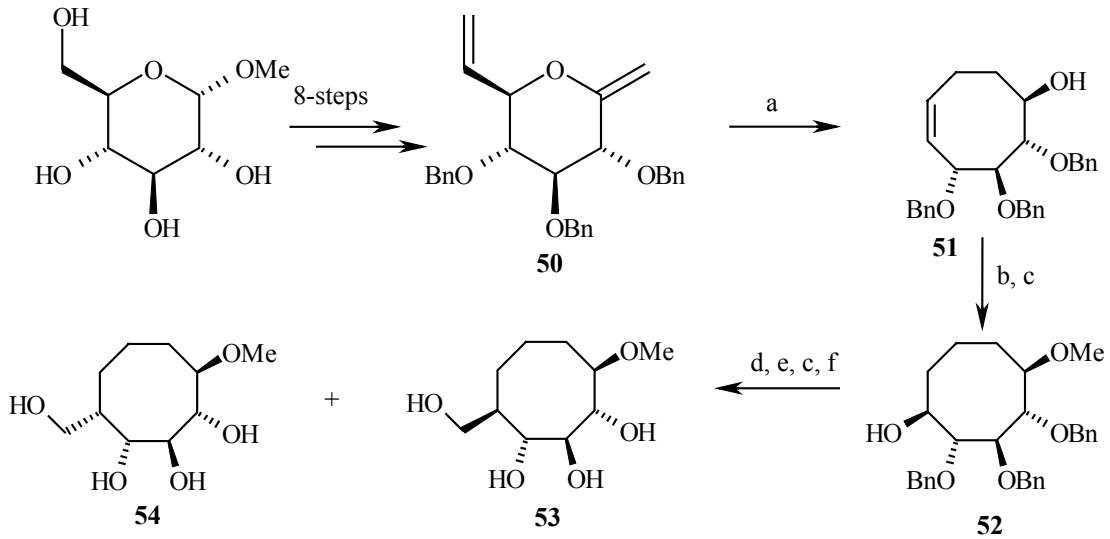
Other methods have been used for the conversion of sugars into 7-membered carba-sugars are: 1,3-dipolar cycloadditions,[44] intramolecular nucleophilic attack,[45] and enlargement of cyclohexanones.[46a-b]

8-Membered Carba-sugar

1) By TIBAL-promoted Claisen Rearrangement

Sinaÿ and coworkers[47] developed a methodology for the synthesis of cyclooctanic carba-glucose from glucose describing the TIBAL-catalyzed sigmatropic rearrangement of the gluco derivative **50** as the key step. Compound **51** was transformed into **52** by sequential reactions, methylation, regio- and stereoselective hydroboration. Oxidation of **52** followed by successive treatment with the Tebbe reagent, regioselective hydroboration and debenzylation gave the cyclooctanic mimetic **53** as a major product along with minor isomer **54** (Scheme 10).

Scheme 10

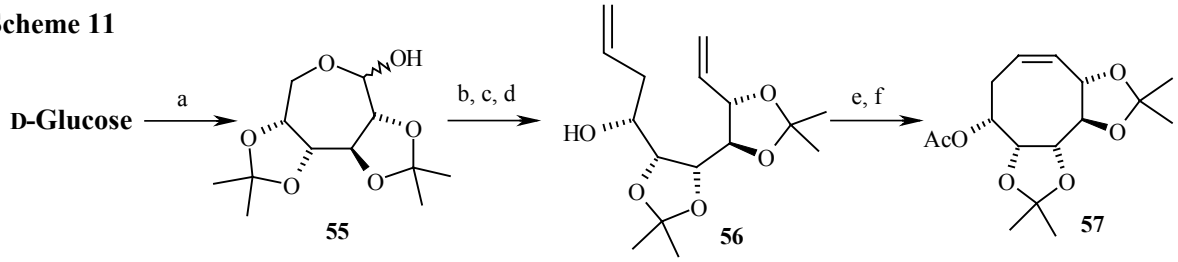


Reagents and conditions: (a) *i*Bu_3Al, $C_6H_5CH_3$, 50 ^oC; (b) NaH, MeI, DMF; (c) BH_3:THF, H_2O_2, NaOH; (d) PCC, CH_2Cl_2, 0 ^oC; (e) Tebbe reagent, Py/THF; (f) H_2, Pd/C, MeOH.

2) By RCM

Marco-Contelles *et al*.[48a] have synthesized 8-membered carba-sugar starting from the lactol **55**, which converted into **56** using three straight-forward reactions, one carbon Wittig homologation, oxidation and Grignard reaction with allylmagnesium bromide. The free hydroxyl group was protected as its acetate ester and subjected to RCM reaction to produce **57** (Scheme 11).

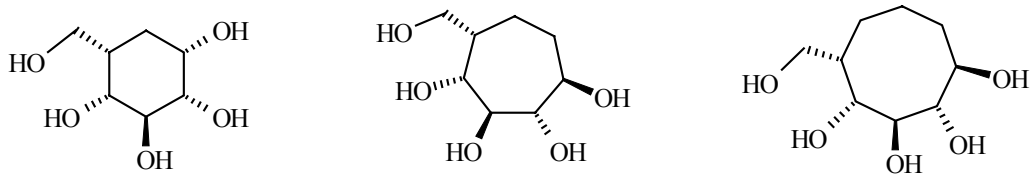
Scheme 11



Reagents and conditions: (a) Ref. 49; (b) $Ph_3P{=}CH_2$, THF, –20 ^oC; (c) DMSO, DCC, TFA, $C_6H_5CH_3$, rt; (d) allylmagnesium bromide, THF, 0 ^oC; (e) Ac_2O, Py; (f) $[(PCy_3)_2Cl_2Ru{=}CHPh]$, CH_2Cl_2, rt.

Present Work

Carbocyclic polyols are important constituents of many biologically active molecules.[20-23] The replacement of the endocyclic oxygen atom of sugar, for instance, α-DL-talopyranose by a methylene group would result a six membered carba-sugar.[1] L-iduronic acid was found to be the major component of glycosaminoglycans. L-iduronic acid plays an important role in the antithrombin III binding sequence of heparin and FGF-2 binding of heparan sulfate.[29,30] These interesting biological profiles of L-iduronic acid prompted us to explore the synthesis of carba-L-*ido* sugar derivatives. Various approaches[36] have been dedicated for the synthesis of 6-membered L-*ido*-carba-sugars. However, very few synthetic efforts have been reported towards the selective construction of medium-sized L-*ido*-carba-sugars, notably seven[37a,43] and eight membered ring.[47,48a] We have designed a method for the synthesis of 6-, 7-, and 8-membered L-*ido*-carba-sugars.



C6 (28) **C7 (58)** **C8 (59)**

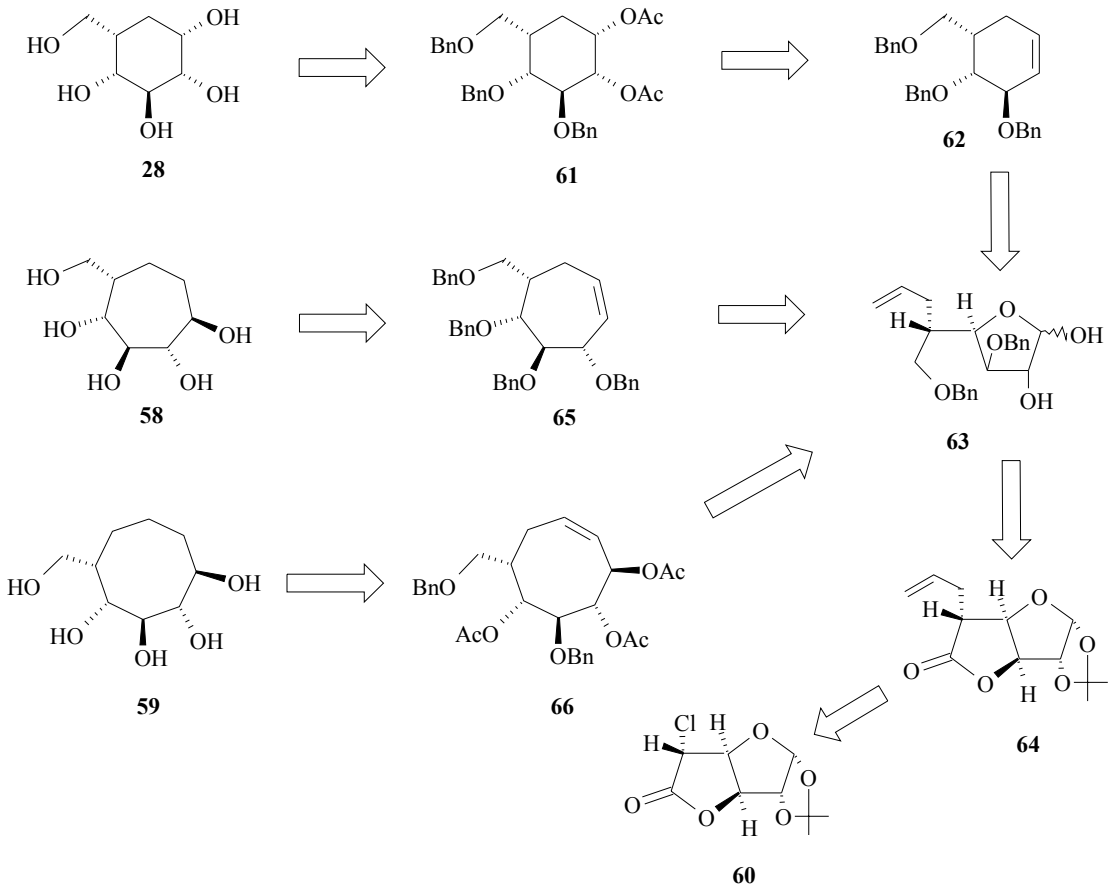
Figure 1

The strategy for the syntheses of **28**, **58** and **59** are described in the retrosynthetic analysis in Scheme 12. Our synthetic strategy for the construction of L-*ido*-configured 6-, 7-, and 8-membered carba-sugars was based upon our observation[50] that radical allylation of 5-chloro-5-deoxy-1,2-*O*-isopropylidine-β-L-idofuranurono-6,3-lactone (**60**)[51] gave exclusively **64** with retention of configuration.

Synthesis of 6-membered carba-sugar

The LAH reduction of **64** in THF gave the diol **67** which was protected as its dibenzyl ether derivative (**68**) using NaH, BnBr and TBAI in DMF (Scheme 13). The structure of **68** was supported by its ^{1}H NMR, ^{13}C NMR spectra and elemental analysis. For example, the ^{1}H NMR spectrum of **68** displayed resonances due to benzylic protons as four doublets at 4.28 ppm (J = 11.7 Hz), 4.32 ppm (J = 12.2 Hz), 4.42 ppm (J = 11.7 Hz) and 4.58 ppm (J = 11.7

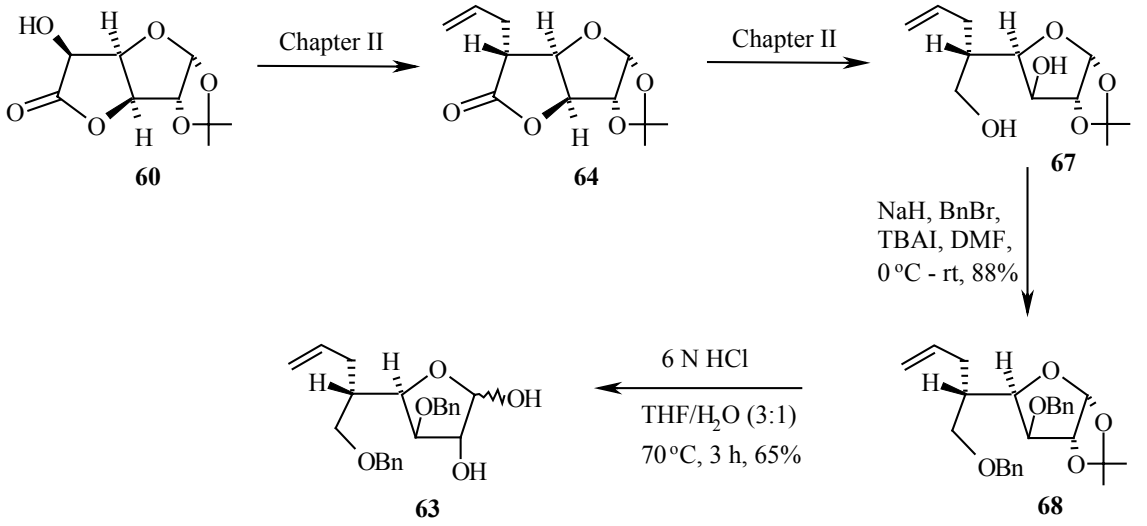
Scheme 12: ***Rtrosynthetic analysis for 28, 58 and 59***



Hz) and the aromatic protons resonated as a multiplet between 7.22-7.37 ppm. A characteristic double-doublet due to H-4 appeared at 4.11 ppm (J = 2.9, 9.3 Hz). The signals due to H-1, H-2 and H-3 were revealed at 5.90 ppm (J = 3.9 Hz), 4.57 ppm (J = 3.9 Hz) and 3.80 ppm (J = 2.9 Hz) respectively. The acetonide functionality of **68** was cleaved by treating with 6 N HCl in THF/H_2O (3:1) at 70 ^oC for 3 h to afford **63** (Scheme 13).

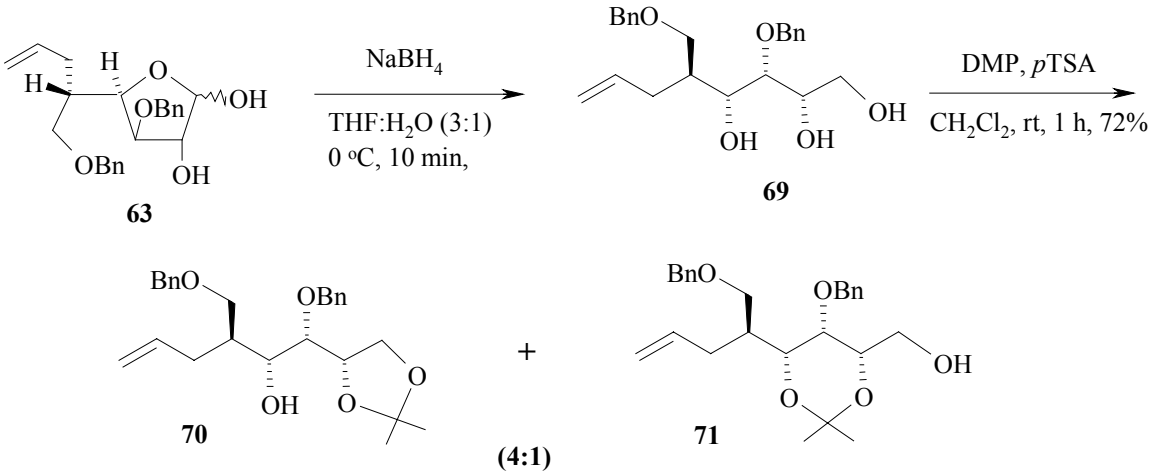
Our attention was drawn toward installation of second olefin group at C1-C2 for which **63** was subjected to $NaBH_4$ reduction in THF/H_2O (3:1) at 0 ^oC to afford the triol **69**. Upon treatment with DMP and catalytic amount of *p*TSA in CH_2Cl_2 at rt **69** gave the 1,3-dioxolane derivative (**70**) and 1,3-dioxane derivative (**71**) in 4:1 ratio (Scheme 14). The structures of **70** and **71** were confirmed by their ^1H NMR, ^{13}C NMR[52], mass spectroscopy and elemental analysis. For instance, in the ^1H NMR spectrum of **70**, the chemical shifts for *gem*-dimethyl groups appeared in the upfield region at 1.37 and 1.44 ppm. The C_1-methylene protons resonated as a clean triplet at 3.63 ppm (J = 8.0 Hz) and double-doublet at 4.03 ppm (J = 6.6, 8.0 Hz). A multiplet between 4.97-5.02 ppm integrating for two protons and another

Scheme 13



multiplet between 5.67-5.80 ppm integrating for one proton indicated the presence of terminal double bond. The ^{13}C NMR revealed a peak at 109.3 ppm attributed to the ketal carbon, which evidently confirmed the formation of 5-membered acetonide. The mass spectrum exhibited a signal at 426 due to (M^+) ion also supported the assigned structure **70**. In the ^{1}H NMR spectrum of **71**, the chemical shifts for *gem*-dimethyl groups observed in the upfield region at 1.42 and 1.44 ppm while the ketal carbon resonated at 98.7 ppm in the ^{13}C NMR spectrum which was indicative of a *cis*-6-membered acetonide moiety, thereby confirmed the assigned structure **71**.

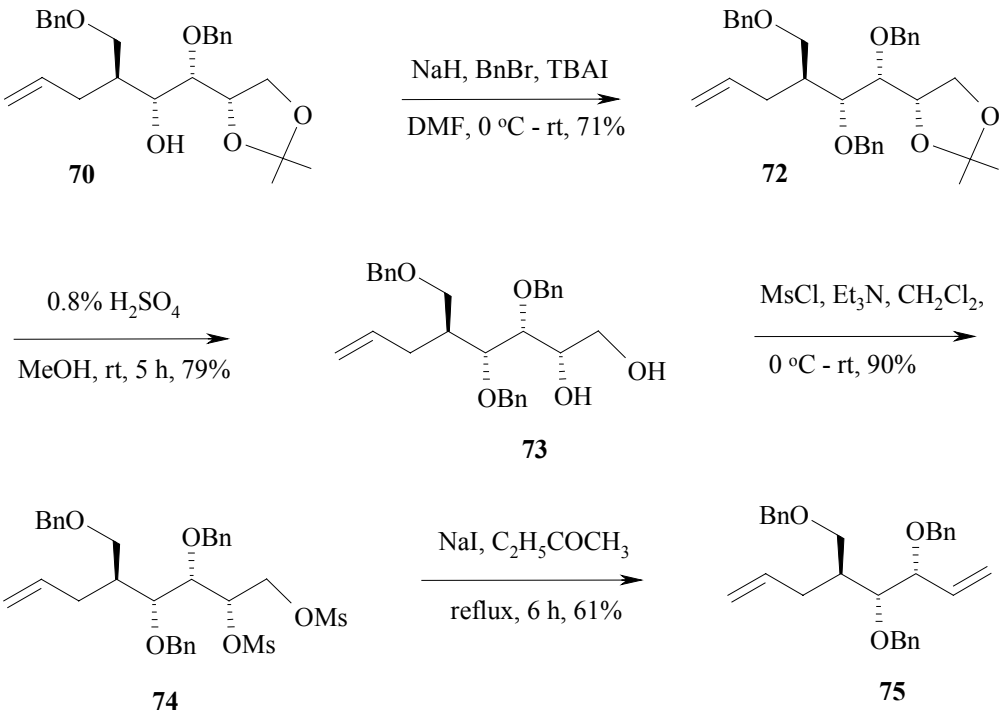
Scheme 14



The free hydroxyl group of **70** was protected as its benzyl ether **72** using NaH, BnBr and TBAI in DMF. The ^{1}H NMR spectrum revealed a triplet at 3.54 ppm (J = 5.3 Hz) due to

H-3 whereas the H-4 proton appeared as a triplet at 3.73 ppm (J = 4.6 Hz). The mass spectrum displayed a signal at 517 attributed to the (M^++1) ion and confirmed the assigned structure **72**. Transformation of **72** into the diene derivative (**75**) was achieved in three steps. Thus **72** was hydrolyzed with 0.8% H_2SO_4 in MeOH and dimesylated with MsCl and Et_3N in CH_2Cl_2 to afford **74** (Scheme 15). For elimination reaction, **74** was heated with NaI in 2-butanone to give **75**.[53] The assigned structure **75** was supported by its ^{1}H NMR, ^{13}C NMR spectra and elemental analysis.

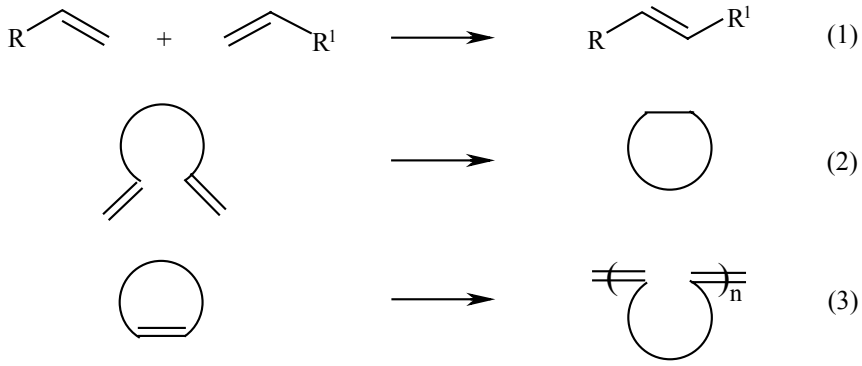
Scheme 15



A brief account on Ring Closing Metathesis (RCM)

The olefin metathesis reaction can be thought of as a reaction in which all the carbon-carbon double bonds in an olefin (alkene) are cut and then rearranged in a statistical fashion in the presence of metal carbene complexes.[54] The use of olefin metathesis in organic synthesis has grown considerably in recent years.[55] Olefin metathesis can be categorized into three different sections: (a) cross-metathesis (CM), in which two different alkenes undergo an intermolecular transformation to form a new olefinic product (eqn. 1); (b) ring-closing metathesis (RCM), a procedure which is useful for the formation of cyclic compounds (eqn.

2); and (c) ring-opening metathesis polymerization (ROMP), which involves the metathetic opening of strained cyclic olefins to give polymeric compounds (eqn. 3).



Olefin metathesis does not require the use of any additional reagents except for a catalytic amount of metal carbene, and the only by-product that forms is volatile ethylene gas. The importance of this carbon–carbon bond construction method is evident from the huge number of publications that have appeared within a short span of time.[56-58] *The reasons being:*

1) *Well designed, stable and highly active catalysts.*
2) *Mild reaction conditions, which is compatible with various functional groups.*
3) *A simple experimental protocol that usually affords high chemical yields.*
4) *Very high turnover number was observed in the catalytic process.*
5) *Its efficacy in medium to macro-ring cyclization.*
6) *Its superiority over other cyclization methods like macrocyclization, Diels-Alder etc., because of favorable thermodynamic profile.*
7) *Adaptable for both solution and solid phase reactions.*
8) *Water solubility enabling the metathesis in water and methanol.*
9) *Design of recyclable and polymer bound catalysts.*
10) *Applicability to broad scope of substrates like ene-yne and yne-yne metathesis, in addition to tri- and tetra-substituted systems.*
11) *Combinatorial RCM libraries.*
12) *Eco-friendly profile, including viability in solvents like super critical* CO_2.

The early examples of olefin metathesis employed classical catalysts which usually included a tungsten chloride or oxychloride and an alkyl metal species. These catalysts were less reactive to olefins due to their increased stability and yields were generally found to be

*low.[59] The other established catalyst is dichlorobis(2,6-dibromophenoxy)oxotungsten, $Cl_2(ArO)_2W=O$.[60] Although this system shows good functional group tolerance and has been used for many syntheses, it is considered to be unsuitable for industrial applications owing to its complexity and cost. Olefin metathesis began to receive more attention in 1993, when Basset and coworkers developed and applied the tungsten catalysts **76** and **77** for cross-metathesis reactions.[61,62] One of the most useful catalysts for olefin metathesis reactions is the molybdenum catalyst (**78**) developed by Schrock et al.[63] Although the major advantage of **78** is its high reactivity towards a broad range of substrates with a variety of functional groups, this catalyst also has some limitations. Its major drawbacks are that it is air sensitive and has moderate to poor functional group tolerance. Much work on the development of catalytic systems has been done by Grubbs' and coworkers using three very important ruthenium-*

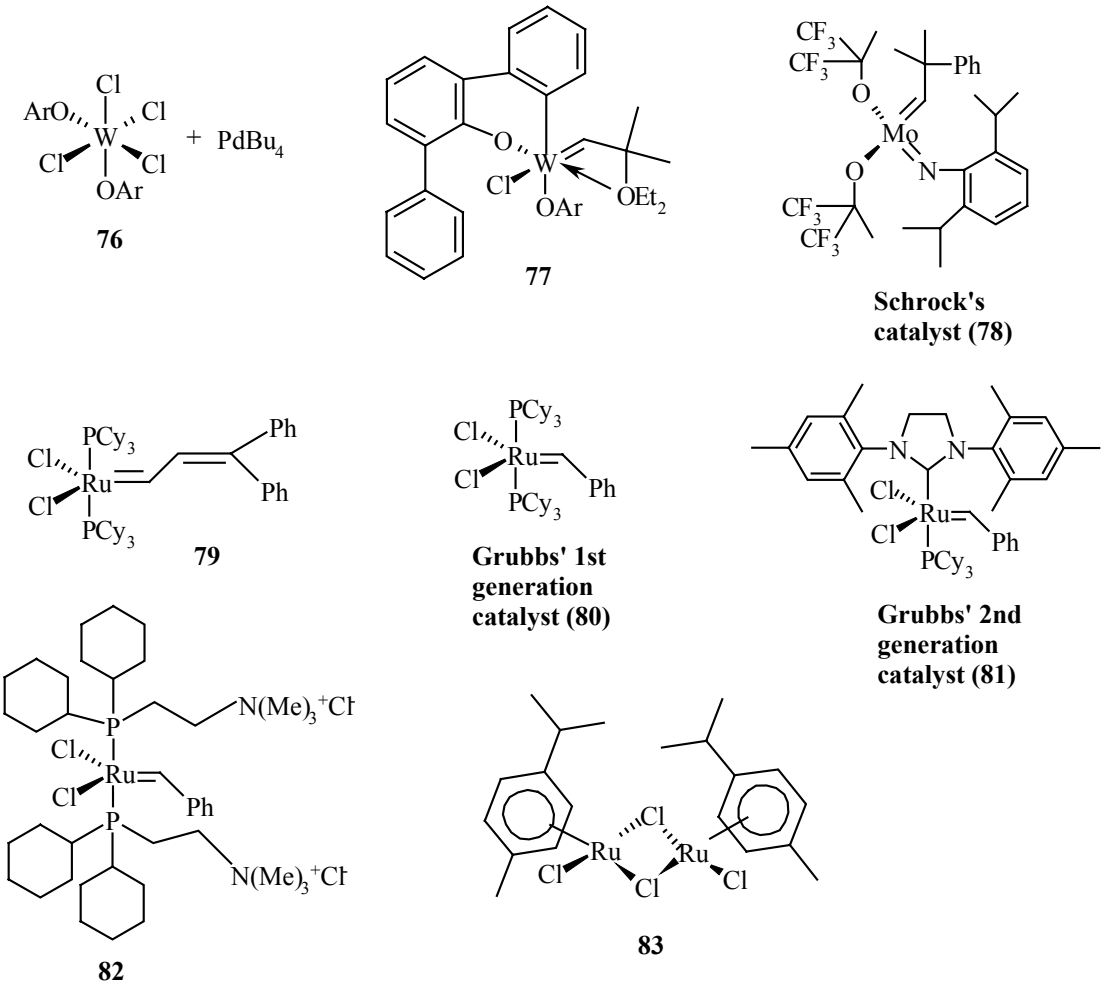


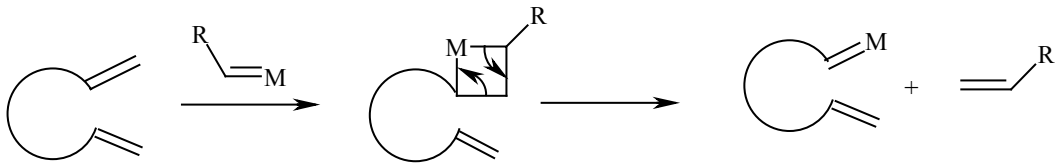
Figure 2: ***Tungsten, Molybdenum and ruthenium based Olefin Metathesis Catalysts***

based catalysts, ***79****,*[64] ***80****,*[65] *and* ***81****.*[66] *Although all the three catalysts benefit from the same impressive tolerance to air, moisture and various functional groups, catalyst* ***80*** *provides improved initiation rates and can be prepared easily. In addition to the catalytic systems discussed above, a few other transition metal catalysts have been prepared for olefin metathesis reactions. Among them, the water soluble ruthenium catalyst* ***82****,*[67] *also developed by Grubbs and coworkers, and a photoinducible dichloro(p-cymene)ruthenium(II) dimer (****83****), developed by Fürstner and Ackermann,*[68] *are noteworthy.*

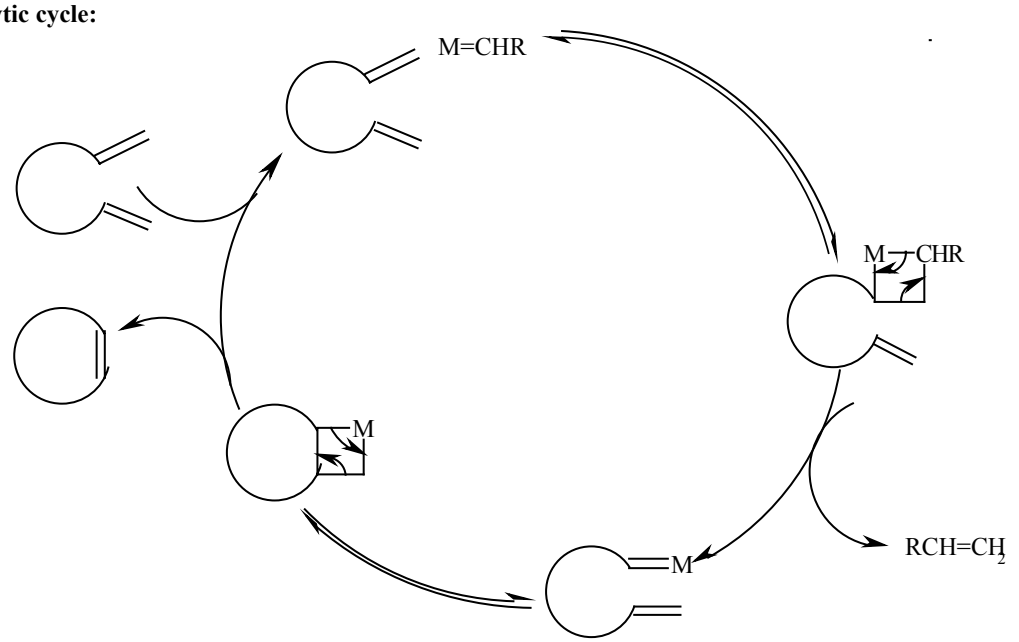
The postulated mechanism involves an iterative process of [2+2] cycloaddition and cycloreversion between the olefins, metal alkylidene and metallocyclobutane species.[69] *The initial retro-type intermolecular [2+2] cycloaddition between the catalyst and one of the olefins of diene leads to the incorporation of the metal alkylidene in the substrate. The second cycloaddition takes place in a facile intramolecular fashion and ring opening of resulting*

Scheme 16: ***Ring Closing Metathesis mechanism***

Initiation:



Catalytic cycle:



metallocyclobutane leads to the cycloalkene and regeneration of the metal carbene, which takes up another diene molecule and acts in same fashion. The key intermediate is a metallacyclobutane, which can undergo cycloreversion either towards products or back to starting materials. The volatile nature of the alkene by-product (the gaseous ethene in most cases) tends the reaction to proceed forward thermodynamically (Scheme 16).

RCM reaction of **75** using Grubbs' catalyst **80** (5 mol %) in CH_2Cl_2 at rt resulted in the formation of **62** which was characterized by its ^{1}H NMR, ^{13}C NMR spectra and elemental analysis (Scheme 17).[58a] The two olefinic protons resonated as a doublet of triplet at 6.02 ppm (J = 3.4, 9.7 Hz) and as a multiplet between 5.79-5.87 ppm. The signals due to H-3 and H-4 appeared as triplets at 4.06 ppm (J = 2.7 Hz) and 3.96 ppm (J = 2.7 Hz) respectively which confirmed the diequatorial relationship between H-3 and H-4. All other resonances were in support with the assigned structure **62**. The assigned L-*xylo* configuration to **62** was confirmed by its NOESY spectrum, where a weak NOE was observed between H-3 and H-6 and no NOE found between H-3 and H-5 (Figure 3).

Scheme 17

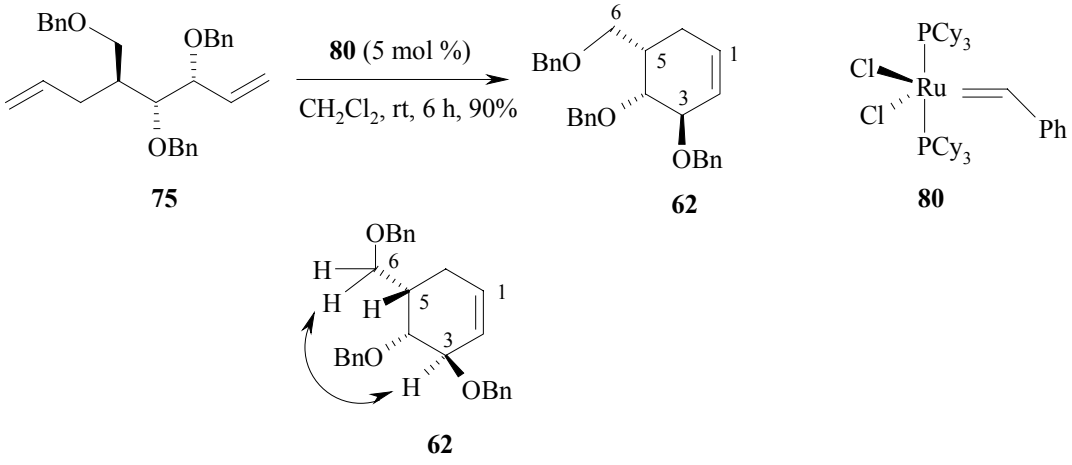
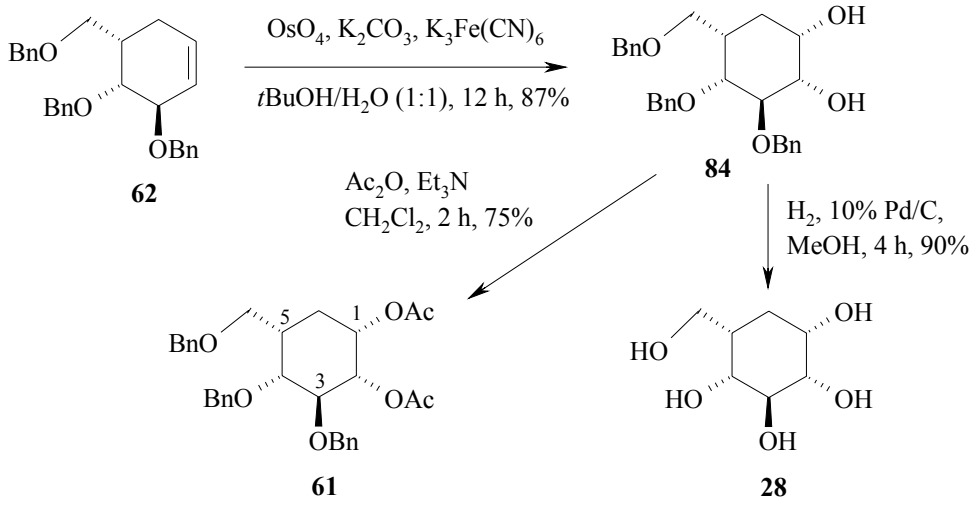


Figure 3: ***NOE studies on 62***

Compound **62** was treated with OsO_4, K_2CO_3 and $K_3Fe(CN)_6$ in *t*BuOH/H_2O (1:1) for 12 h to afford the diol **84** as a single product (Scheme 18).[36a] The high stereoselectivity obtained for **84** can be rationalized by the preferential approach of OsO_4 from the less hindered α-face (opposite to 3-OBn). Literature survey[36a] indicated that the *cis*-dihydroxylation of olefin flanked with a chiral center is influenced by the bulk of the adjacent

center and provide *anti*-dihydroxylation (*anti-syn* relationship). The diol **84** was esterified as the diacetate **61**. A small coupling constant (J = 3.9 Hz) between H-2/H-3, H-3/H-4 clearly indicated the *trans*-diequatorial relationship between H-2 and H-3 and provided the support for the formation of carba-β-L-idopyranose derivative (**61**). Finally debenzylation of **84** over 10% Pd/C in MeOH gave carba-β-L-idopyranose (**28**) (Scheme 18). The structure of **28** was supported by its ^{1}H NMR, ^{13}C NMR spectra and elemental analysis. A complex multiplet appeared between 3.61-3.83 ppm integrating for four protons corresponding to H-1, H-3, H-6 and H-6'. The H-2 and H-4 proton signals displayed as a triplet at 3.98 ppm (J = 4.9 Hz).

Scheme 18

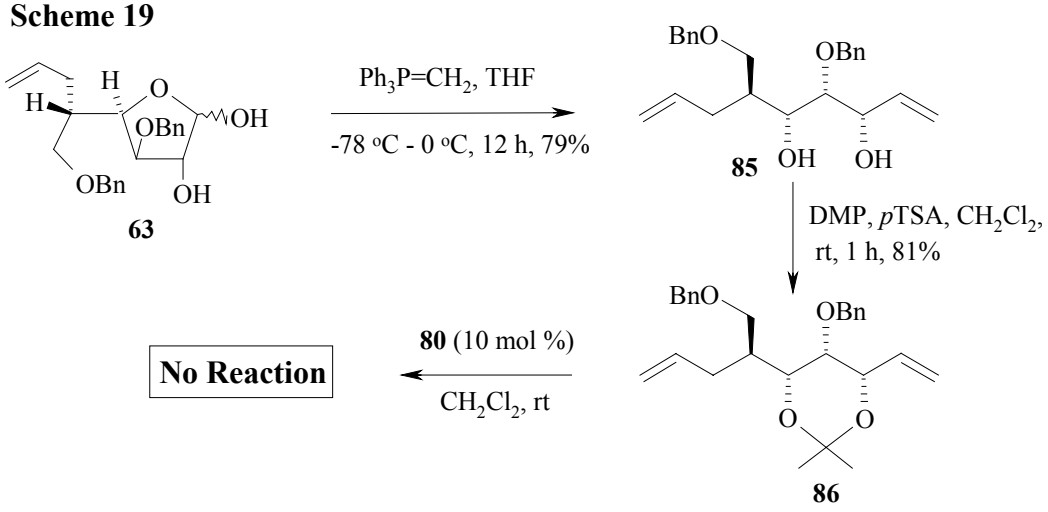


Synthesis of 7-membered carba-sugar

The same intermediate **63** was explored to prepare the 7-membered carbocycle. Compound **63** was treated with excess of $Ph_3P{=}CH_2$ to obtain the diol **85** (Scheme 19). The structure of **85** was established by its ^{1}H NMR, ^{13}C NMR, mass spectroscopy and elemental analysis. The ^{13}C NMR spectrum showed two characteristic resonances at 116.0 and 116.3 ppm attributed to the C-1 and C-9 which clearly revealed the presence of two terminal double bonds. In addition, the mass spectroscopy showed a peak at 382 due to (M^{+}) ion. Compound **85** was protected as its isopropylidine derivative (**86**) whose ^{1}H NMR spectrum revealed the acetonide methyls at 1.47 and 1.51 ppm. The ^{13}C NMR spectrum displayed a peak 98.9 ppm corresponding to the ketal carbon which supported the formation of *cis*-6-membered acetonide.[52] But attempts to perform RCM on **86** using Grubbs' catalyst **80** was not

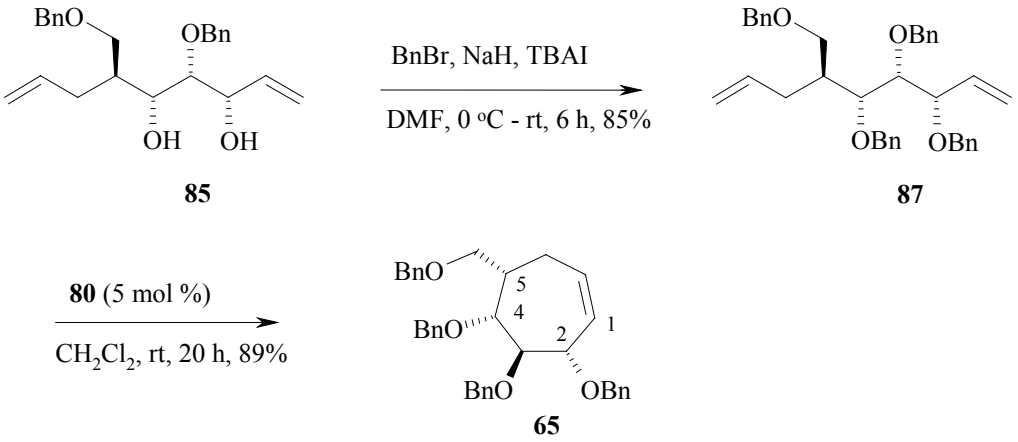
successful. We concluded that the inertness of **86** is due to the presence of an isopropylidine substituent which has a negative influence on RCM reaction.

Scheme 19

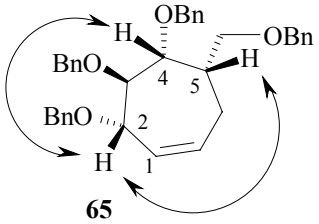


Thus, we revised our strategy by changing protection functionalities. Accordingly, diol **85** was protected as its benzyl ether (**87**) by using NaH and BnBr in DMF (Scheme 20). The ^{1}H NMR, ^{13}C NMR, mass spectroscopy and elemental analysis supported the assigned structure **87**. For example, the mass spectrum displayed a peak at 562 corresponding to (M^{+}) ion. When **87** was subjected to RCM using **80** (5 mol %) in CH_2Cl_2 at rt, the carbocycle **65** was obtained (Scheme 20).[58a] Compound **65** was characterized by its ^{1}H NMR, ^{13}C NMR, mass spectroscopy and elemental analysis. The chemical shift due to two olefinic protons appeared as a multiplet between 5.71-5.78 ppm. All other chemical shifts were in support with the assigned structure **65**. The two characteristic doublets due to olefinic carbons at 129.5 and

Scheme 20



130.8 ppm in the ^{13}C NMR indicated the formation of **65**. The assigned L-*ido* configuration to **65** was substantiated by NOE experiments, where a strong NOE was found between H-2 and H-4/H-5 (Figure 4).

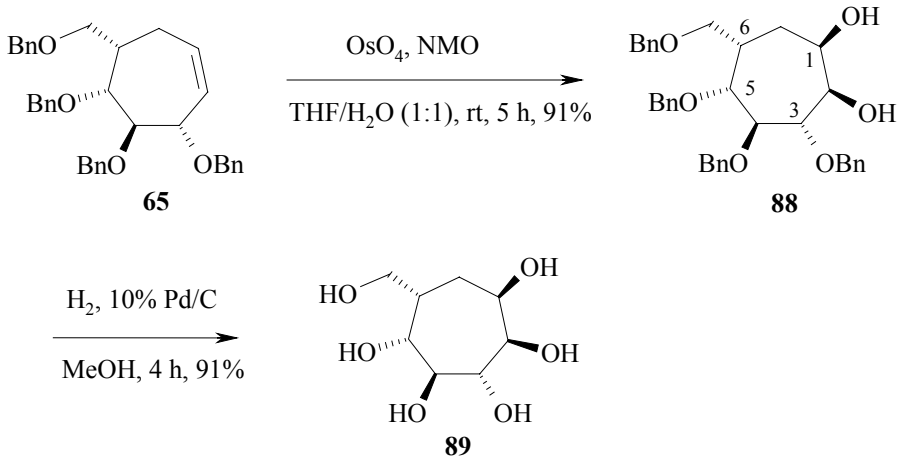


65

Figure 4: ***NOE studies on 65***

The *syn*-Dihydroxylation reaction of **65** in the presence of OsO_4 and NMO in THF-H_2O (1:1) at rt for 5 h resulted in the formation of the diol **88** (Scheme 21).[46g] Compound **88** was characterized by its ^1H NMR, ^{13}C NMR spectra and elemental analysis. For instance, the observed coupling constant $J_{3,4}$ of 9.6 Hz and $J_{4,5}$ of 5.5 Hz indicated a diaxial relation between H-3/H-4 and an axial-pseudoaxial relation between H-4/H-5. The observed $J_{2,3}$ of 6.7 Hz further indicated an axial-pseudoaxial relation between H-2/H-3. Finally, hydrogenation of **88** over 10% Pd/C in MeOH gave the polyhydroxylated 7-membered carba-sugar (**89**). The ^1H NMR, ^{13}C NMR spectra and elemental analysis supported the assigned structure **89**.

Scheme 21

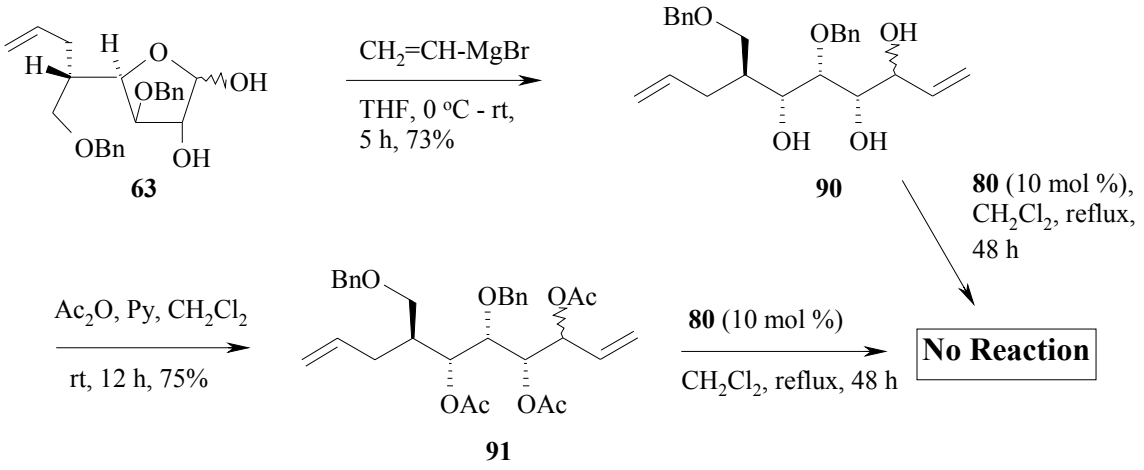


Synthesis of 8-membered carba-sugar

After having made 6- and 7-membered carba-sugars, we next turned our attention towards the synthesis of 8-membered carba-sugar. Compound **63** was treated with vinylmagnesium bromide in THF to obtain an inseparable mixture of diastereomers **90** (Scheme 22). Recently Paquette *et al.*[70] utilized Grubbs' catalyst in larger amount and

extended the period of reaction to get the annulated product albeit in moderate yields. Accordingly, **90** was subjected to RCM reaction with 10 mol % of the Grubbs' catalyst **80** but the reaction was not successful.[71] Even the triacetate derivative (**91**) failed to under RCM reaction.

Scheme 22



However, we were surprised to note that the derived **93** in the presence of Grubbs' catalyst **80** (10 mol %) in C_6H_6 under reflux for 3 days gave the cyclooctene derivative (**94**),

Scheme 23

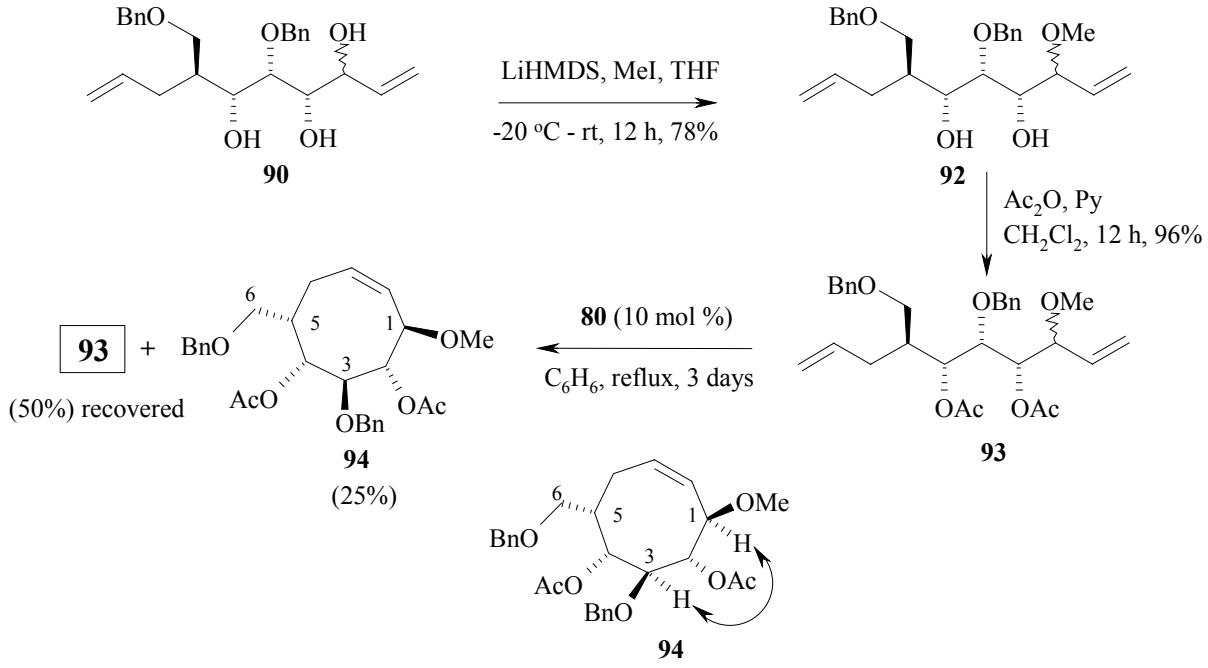


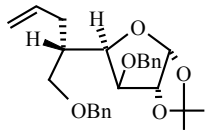
Figure 5: ***NOE studies on 94***

starting material (50%) was recovered (Scheme 23).[72] The structure of **94** was extensively characterized by its ^{1}H NMR, ^{13}C NMR spectra , elemental analysis and NOE experiments. The α-configuration at C-1 was supported by NOESY spectrum, where a strong NOE was found between H-1 and H-3 indicating a *syn*-relationship between them (Figure 5).

In conclusion, we have amplified the utility of the 5-chloro-5-deoxy-1,2-*O*-isopropylidine-β-L-idofuranurono-6,3-lactone (**60**) derived building block **64** by obtaining 6-, 7- and 8-membered carba-sugars through simple synthetic operations and ring closing olefin metathesis as the key step.

Experimental

5-*C*-Allyl-3,5-dibenzyl-5-deoxy-1,2-*O*-isopropylidine-β-L-idofuranose (68)



Compound **67** (8.0 g, 32.8 mmol) in DMF (20 mL) was added to a stirred suspension of NaH (3.27 g, 60% dispersion in oil, 82.0 mmol) in DMF (30 mL) at 0 ^{o}C. The resulting solution was stirred at rt for 30 min, BnBr (8.7 mL, 72.1 mmol) and TBAI (0.1 g) 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 **68** (12.23 g, 88%).

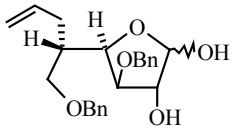
$[\alpha]_D$ –43.5 (*c* 1.0, $CHCl_3$);

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.34 (s, 3 H), 1.52 (s, 3 H), 2.15-2.37 (m, 2 H), 2.44-2.56 (m, 1 H), 3.27 (dd, 1 H, *J* = 4.2, 9.3 Hz), 3.36 (dd, 1 H, *J* = 4.4, 9.3 Hz), 3.80 (d, 1 H, *J* = 2.9 Hz), 4.11 (dd, 1 H, *J* = 2.9, 9.3 Hz), 4.28 (d, 1 H, *J* = 11.7 Hz), 4.32 (d, 1 H, *J* = 12.2 Hz), 4.42 (d, 1 H, *J* =11.7 Hz), 4.57 (d, 1 H, *J* = 3.9 Hz), 4.58 (d, 1 H, *J* = 11.7 Hz), 5.01 (dd, 1 H, *J* = 2.4, 9.8), 5.05 (dd, 1 H, *J* = 1.5, 17.1 Hz), 5.71-5.85 (m, 1 H), 5.90 (d, 1 H, *J* = 3.9 Hz), 7.22-7.37 (m, 10 H);

^{13}C NMR (50 MHz, $CDCl_3$): δ 26.1, 26.6, 32.7, 37.1, 68.7, 71.2, 72.8, 80.5, 81.6, 81.8, 104.1, 110.8, 116.3, 127.2, 128.0, 136.2, 137.4, 138.3;

Anal. Calcd for $C_{26}H_{32}O_5$ (Mol. Wt. 424.537): C, 73.56; H, 7.60. Found; C, 73.33; H, 7.85.

5-*C*-Allyl-3,5-dibenzyl-5-deoxy-α/β-L-idofuranose (63)



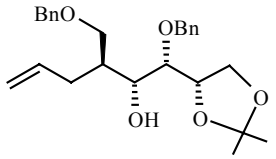
Compound **68** (3.0 g, 7.0 mmol) and 6 N HCl (10 mL) in THF-H_2O (30 mL) were heated at 70 ^{o}C for 3 h. The reaction mixture was neutralized by addition of solid $NaHCO_3$, filtered and concentrated. The residue was partitioned between EtOAc-water, the organic layer separated,

washed with water, dried (Na_2SO_4) and concentrated. The residue was purified on silica gel using EtOAc-light petroleum ether (1:3) to obtain **63** (2.0 g, 74%) as a thick oil.

^{1}H NMR (200 MHz, $CDCl_3$): δ 2.11-2.32 (m, 2 H), 2.41-2.51 (m, 1 H), 3.29-3.41 (m, 2 H), 3.48-3.56 (m, 2 H), 3.77-3.84 (m, 1 H), 4.12-4.61 (m, 6 H), 4.97-5.47 (m, 3 H), 5.70-5.92 (m, 1 H), 7.19-7.30 (m, 10 H);

^{13}C NMR (50 MHz, $CDCl_3$): δ 32.6 and 32.8, 37.6 and 38.4, 68.8 and 69.0, 71.3 and 71.8, 72.9 and 74.5, 76.4 and 77.3, 79.1 and 82.1, 82.2 and 83.6, 95.6 and 102.7, 116.3 and 116.4, 127.4, 127.5, 127.6, 128.0, 128.1, 128.3, 136.3 and 136.5, 136.9 and 137.6, 138.2;

(2*S*,3*S*,4*R*,5*S*)-3-Benzyloxy-5-benzyloxymethyl-1,2-*O*-isopropylidine-oct-7-en-4-ol (70) and (2*S*,3*S*,4*R*,5*S*)-3-Benzyloxy-5-benzyloxymethyl-2,4-*O*-isopropylidine-oct-7-en-1-ol (71)



To a solution of **63** (2.0 g, 5.2 mmol) in THF/H_2O (3:1, v/v, 20 mL) at 0 ^oC was added $NaBH_4$ (0.2 g, 5.2 mmol) in portions. After 10 min, solvent was removed and 1 N HCl (2 mL) added, extracted with EtOAc, dried (Na_2SO_4) and concentrated. The residue was purified on silica gel using EtOAc-light petroleum ether (9:1) to afford **69** (1.82 g) which was stirred with CH_2Cl_2 (10 mL), DMP (1.7 mL) and *p*TSA (30 mg) were added. After 1 h, the reaction mixture was neutralized with Et_3N and concentrated. The residue was partitioned between EtOAc-water, the organic layer dried (Na_2SO_4), concentrated and chromatographed on silica gel using EtOAc-light petroleum ether (1:4) to furnish **70** (1.44 g, 72%) as a colorless oil.

$[\alpha]_D$ −21.3 (*c* 1.0, $CHCl_3$);

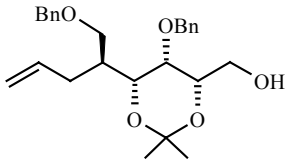
^{1}H NMR (300 MHz, $CDCl_3$): δ 1.37 (s, 3 H), 1.44 (s, 3 H), 1.79-1.88 (m, 1 H), 2.08-2.18 (m, 1 H), 2.36-2.45 (m, 1 H), 3.24 (dd, 1 H, *J* = 3.9, 9.6 Hz), 3.33 (dd, 1 H, *J* = 5.1, 9.6 Hz), 3.39-3.45 (m, 1 H), 3.52 (dd, 1 H, *J* = 1.4, 7.3 Hz), 3.63 (t, 1 H, *J* = 8.0 Hz), 4.03 (dd, 1 H, *J* = 6.6, 8.0 Hz), 4.31-4.46 (m, 3 H), 4.58 (d, 1 H, *J* =11.7 Hz), 4.88 (d, 1 H, *J* = 11.2 Hz), 4.97-5.02 (m, 2 H), 5.67-5.80 (m, 1 H), 7.24-7.34 (m, 10 H);

^{13}C NMR (50 MHz, $CDCl_3$): δ 25.6, 26.7, 32.2, 42.0, 66.2, 69.9, 72.5, 73.3, 73.6, 78.2, 79.5, 109.3, 116.3, 127.6-128.3, 137.1, 138.3, 138.6;

MS: 426 (M^+);

Anal. Calcd for $C_{26}H_{34}O_5$ (Mol. Wt. 426.545): C, 73.21; H, 8.03. Found; C, 72.95; H, 8.18.

Further elution gave **71** (0.32 g, 16%).



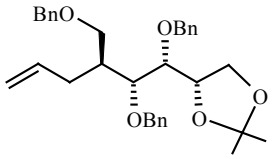
$[\alpha]_D$ −20.7 (*c* 1.0, $CHCl_3$);

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.42 (s, 3 H), 1.44 (s, 3 H), 2.04-2.09 (m, 1 H), 2.13-2.19 (m, 1 H), 2.43-2.50 (m, 1 H), 3.28-3.29 (m, 1 H), 3.30 (dd, 1 H, *J* = 4.0, 9.5 Hz), 3.34 (dd, 1 H, *J* = 4.0, 9.5 Hz), 3.55 (dd, 1 H, *J* = 4.9, 11.1 Hz), 3.73 (dd, 1 H, *J* = 7.2, 11.1 Hz), 3.80 (dd, 1 H, *J* = 1.2, 9.1 Hz), 3.89 (ddd, 1 H, *J* = 1.2, 4.9, 7.2 Hz), 4.35 (d, 1 H, *J* = 12.1 Hz), 4.45 (d, 1 H, *J* =12.1 Hz), 4.50 (d, 1 H, *J* = 11.9 Hz), 4.57 (d, 1 H, *J* = 11.9 Hz), 4.95-5.02 (m, 2 H), 5.69-5.78 (m, 1 H), 7.22-7.35 (m, 10 H);

^{13}C NMR (125 MHz, $CDCl_3$): δ 18.8, 29.4, 31.3, 38.6, 62.1, 67.7, 70.5, 72.3, 72.8, 73.1, 73.8, 98.7, 116.1, 127.2, 127.5, 127.6, 127.9, 128.0, 136.6, 138.0, 138.2.

Anal. Calcd for $C_{26}H_{34}O_5$ (Mol. Wt. 426.545): C, 73.21; H, 8.03. Found; C, 73.15; H, 8.10.

(2*S*,3*S*,4*R*,5*S*)-3,4-Bis-benzyloxy-5-benzyloxymethyl-1,2-*O*-isopropylidine-7-octene (72)



Benzylation of **70** (1.3 g, 3.0 mmol) was performed as described earlier using NaH (0.14 g, 3.7 mmol), TBAI (0.1 g) and benzyl bromide (0.4 mL, 3.4 mmol) in DMF (10 mL) to give **72** (1.11 g, 71%) after silica gel column purification using EtOAc-light petroleum ether (1:19) as a thick syrup.

$[\alpha]_D$ −7.3 (*c* 1.0, $CHCl_3$);

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.37 (s, 3 H), 1.45 (s, 3 H), 2.25 (m, 3 H), 3.37 (dd, 1 H, *J* = 4.6, 9.6 Hz), 3.49 (dd, 1 H, *J* = 5.3, 9.6 Hz), 3.54 (t, 1 H, *J* = 5.3 Hz), 3.66 (t, 1 H, *J* = 8.0 Hz),

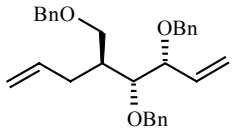
3.73 (t, 1 H, *J* = 4.6 Hz), 3.85 (dd, 1 H, *J* = 6.5, 8.0 Hz), 4.26-4.36 (m, 2 H), 4.43 (d, 1 H, *J* =11.7 Hz), 4.55 (s, 2 H), 4.66 (d, 1 H, *J* = 11.7 Hz), 4.78 (d, 1 H, *J* = 11.7 Hz), 4.99 (br d, 1 H, *J* = 10.2 Hz), 5.04 (br d, 1 H, *J* = 17.1 Hz), 5.67-5.87 (m, 1 H), 7.22-7.40 (m, 15 H);

^{13}C NMR (50 MHz, $CDCl_3$): δ 25.6, 26.5, 31.7, 39.7, 66.0, 69.8, 72.8, 73.0, 73.8, 76.8, 78.6, 79.7, 108.9, 116.0, 127.3, 128.1, 137.2, 138.6;

MS: 517 (M^++1);

Anal. Calcd for $C_{33}H_{40}O_5$ (Mol. Wt. 516.668): C, 76.71; H, 7.80. Found; C, 76.94; H, 7.80.

(3*R*,4*R*,5*S*)-3,4-Bis-benzyloxy-5-benzyloxymethyl-oct-1,7-diene (75)



A solution of **72** (1.0 g, 1.9 mmol), 0.8% H_2SO_4 (2 mL) in MeOH (10 mL) was stirred at rt for 5 h, neutralized with solid $NaHCO_3$, filtered and concentrated. The residue was partitioned between EtOAc and water, organic layer dried (Na_2SO_4), concentrated and chromatographed on silica gel using EtOAc-light petroleum ether (2:3) to furnish **73** (0.72 g, 79%) which was dissolved in CH_2Cl_2 (5 mL) and then Et_3N (0.6 mL, 4.5 mmol) and MsCl (0.3 mL, 3.7 mmol) were added. After 30 min, the reaction mixture was partitioned between EtOAc and water, organic layer dried (Na_2SO_4), concentrated and the residue on silica gel column purification using EtOAc-light petroleum ether (1:4) afforded **74** (0.86 g, 90%).

The above product **74** (0.86 g) and NaI (1.2 g, 8.1 mmol) in 2-butanone (10 mL) was heated under reflux for 6 h. The solvent was removed, residue partitioned between EtOAc and water, organic layer dried (Na_2SO_4), concentrated and chromatographed on silica gel using EtOAc-light petroleum ether (1:19) to afford **75** (0.36 g, 61%) as a clear oil.

$[\alpha]_D$ +12.1 (*c* 1.0, $CHCl_3$);

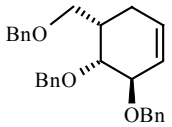
^{1}H NMR (200 MHz, $CDCl_3$): δ 2.01-2.18 (m, 2 H), 2.25-2.38 (m, 1 H), 3.38-3.52 (m, 2 H), 3.87 (dd, 1 H, *J* = 2.4, 6.8 Hz), 4.08 (t, 1 H, *J* = 7.3 Hz), 4.37 (d, 1 H, *J* = 12.2 Hz), 4.42 (d, 1 H, *J* = 11.2 Hz), 4.47 (d, 1 H, *J* = 12.2 Hz), 4.58 (d, 1 H, *J* = 11.2 Hz), 4.67 (d, 1 H, *J* = 11.7 Hz), 4.93-5.07 (m, 3 H), 5.35 (dd, 1 H, *J* = 2.3, 7.7 Hz), 5.38 (dd, 1 H, *J* = 2.3, 10.7 Hz), 5.68-5.97 (m, 2 H), 7.34-7.40 (m, 15 H);

^{13}C NMR (50 MHz, $CDCl_3$): δ 30.6, 40.0, 70.0, 70.5, 72.9, 74.9, 80.8, 83.4, 115.5, 118.8, 127.2, 127.6, 128.2, 135.7, 137.4, 138.5, 139.3;

MS: 351 (M^+–Bn);

Anal. Calcd for $C_{30}H_{34}O_3$ (Mol. Wt. 442.589): C, 81.41; H, 7.74. Found; C, 81.65; H, 7.78.

(3*R*,4*R*,5*S*)-3,4-Bis-benzyloxy-5-benzyloxymethyl-cyclohexene (62)



Compound **75** (0.2 g, 0.4 mmol) was dissolved in anhydrous CH_2Cl_2 (20 mL) and solution degassed with argon. Grubbs' catalyst **80** (18 mg, 5 mol%) was added and mixture stirred at rt for 6 h. The solvent was removed and residue purified by column chromatography on silica gel using EtOAc-light petroleum ether (3:97) to obtain **62** (0.17 g, 91%) as a colorless syrup.

$[\alpha]_D$ −77.3 (*c* 1.0, $CHCl_3$);

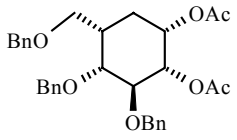
^{1}H NMR (200 MHz, $CDCl_3$): δ 2.08-2.16 (m, 2 H), 2.44 (dquin, 1 H, *J* = 2.3, 6.8 Hz), 3.51 (dd, 1 H, *J* = 6.8, 9.1 Hz), 3.66 (dd, 1 H, *J* = 7.6, 9.1 Hz), 3.89-3.96 (m, 2 H), 4.54 (s, 2 H), 4.56 (d, 1 H, *J* = 12.2 Hz), 4.59 (d, 1 H, *J* = 11.9 Hz), 4.64 (d, 1 H, *J* = 11.9 Hz), 4.67 (d, 1 H, *J* = 12.2 Hz), 5.79-5.87 (m, 1 H), 6.02 (dt, 1 H, *J* = 3.4, 9.7 Hz) 7.32-7.40 (m, 15 H);

^{13}C NMR (125 MHz, $CDCl_3$): δ 25.1, 34.4, 70.6, 71.1, 71.9, 72.4, 72.8, 75.5, 124.4, 127.3, 127.4, 127.5, 127.6, 128.1, 130.6, 138.6, 138.7.

MS: 323 (M^+–Bn);

Anal. Calcd for $C_{28}H_{30}O_3$ (Mol. Wt. 414.536): C, 81.13; H, 7.29. Found; C, 81.34; H, 7.50.

(1*S*,2*R*,3*S*,4*R*,5*S*)-1,2-Bis-acetoxy-3,4-bis-benzyloxy-5-benzyloxymethyl-cyclohexane (61)



A solution of K_2CO_3 (99 mg, 0.72 mmol) $K_3Fe(CN)_6$ (0.23 g, 0.72 mmol) and OsO_4 (0.04 M in toluene, 0.24 mL, 9.6 μmol) in *t*-BuOH-H_2O (1:1, v/v, 8 mL) was added to **62** (0.1 g, 0.24 mmol). After 12 h, the reaction mixture was quenched with Na_2SO_3 and extracted with EtOAc, dried (Na_2SO_4) and concentrated. Purification of the crude product by column

chromatography using EtOAc-light petroleum ether (3:7) afforded **84** (94 mg, 87%) which was treated with Ac_2O (0.06 mL, 0.63 mmol) and Et_3N (0.11 mL, 0.83 mmol) in CH_2Cl_2 (5 mL). The reaction mixture was partitioned between CH_2Cl_2 and water. The organic layer was separated, dried (Na_2SO_4) and concentrated. The residue was purified by column chromatography on silica gel using EtOAc-light petroleum ether (3:17) to give **61** (83 mg, 75%) as a colorless oil.

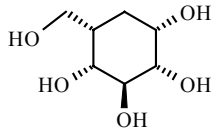
$[\alpha]_D$ −5.9 (*c* 1.1, $CHCl_3$);

^{1}H NMR (200 MHz, Acetone-d_6): δ 1.68 (dt, 1 H, *J* = 3.9, 12.2 Hz), 1.97 (s, 3 H), 2.02 (s, 3 H), 2.09-2.14 (m, 1 H), 2.40-2.55 (m, 1 H), 3.50 (dd, 1 H, *J* = 6.8, 8.8 Hz), 3.68 (dd, 1 H, *J* = 7.9, 8.8 Hz), 3.80 (t, 1 H, *J* = 3.4 Hz), 4.06 (t, 1 H, *J* = 3.9 Hz), 4.44 (d, 1 H, *J* = 11.7 Hz), 4.51 (s, 2 H), 4.57 (d, 1 H, *J* = 11.2 Hz), 4.64 (d, 1 H, *J* = 15.1 Hz), 4.73 (d, 1 H, *J* = 11.7 Hz), 5.17 (dt, 1 H, *J* = 3.9, 11.2 Hz), 5.29 (t, 1 H, *J* = 3.4 Hz), 7.23-7.39 (m, 15 H);

^{13}C NMR (50 MHz, $CDCl_3$): δ 20.8, 21.0, 24.2, 36.3, 69.3, 69.9, 70.5, 72.0, 72.8, 73.0, 73.6, 75.3, 127.5, 127.8, 128.2, 128.3, 137.8, 138.4, 170.1, 170.6;

Anal. Calcd for $C_{32}H_{36}O_7$ (Mol. Wt. 532.246) C, 72.16; H, 6.81. Found; C, 71.94; H, 6.86.

(1*S*,2*S*,3*S*,4*R*,5*S*)-5-Hydroxymethyl-cyclohaxane-1,2,3,4-tetrol (28)



A solution of **84** (50 mg, 0.11 mmol) in MeOH (5 mL) was hydrogenated in the presence of 10% Pd/C (10 mg) at rt. After 4 h, the reaction mixture was filtered through a pad of Celite, and concentrated to afford **28** (18 mg, 90%).

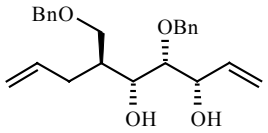
$[\alpha]_D$ +5.8 (*c* 1.5, MeOH); lit.,[32] **$[\alpha]_D$** +7.0 (*c* 1.5, MeOH);

^{1}H NMR (500 MHz, D_2O): δ 1.68 (dt, 1 H, *J* = 4.4, 13.5 Hz), 1.75 (dt, 1 H, *J* = 9.2, 13.5 Hz), 2.08-2.18 (m, 1 H), 3.68 (dd, 1 H, *J* = 6.4, 10.7 Hz), 3.76 (dd, 1 H, *J* = 6.6, 10.7 Hz), 3.77 (t, 1 H, *J* = 4.2 Hz), 3.83 (t, 1 H, *J* = 4.2 Hz), 3.99 (t, 2 H, *J* = 4.4 Hz);

^{13}C NMR (50 MHz, D_2O + Acetone-d_6): δ 26.4, 38.5, 62.8, 68.2, 71.0, 71.5, 73.4;

Anal. Calcd for $C_7H_{14}O_5$ (Mol. Wt. 178.084): C, 47.18; H, 7.92. Found; C, 47.44; H, 7.66

(3*S*,4*R*,5*R*,6*S*)-4-Benzyloxy-6-benzyloxymethyl-non-1,8-diene-3,5-diol (85)



To a solution of **63** (1.0 g, 2.6 mmol) in anhydrous THF (10 mL) at –78 ^{o}C, methylenetriphenylphosphorane [prepared from PPh_3CH_3I (2.1 g) and *n*-BuLi (1.6 M, 0.33 mL)] was added dropwise. After 12 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 (1:4) to furnish **85** (0.76 g, 77%) as a colorless oil.

$[\alpha]_D$ –16.1 (*c* 1.0, $CHCl_3$);

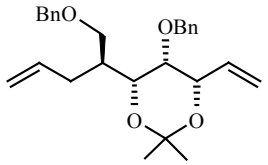
^{1}H NMR (200 MHz, $CDCl_3$): δ 1.83-1.99 (m, 1 H), 2.17 (dt, 1 H, *J* = 8.2, 14.2 Hz), 2.34-2.47 (m, 1 H), 2.68 (s br, 2 H), 3.45 (d, 2 H, *J* = 4.9 Hz), 3.59 (t, 1 H, *J* = 4.1 Hz), 3.81 (t br, 1 H, *J* = 4.7 Hz), 4.31 (t br, 1 H, *J* = 4.6 Hz), 4.45 (s br, 2 H), 4.65 (d, 1 H, *J* = 11.3 Hz), 4.76 (d, 1 H, *J* = 11.3 Hz) 5.03 (d br, 1 H, *J* = 10.0), 5.07 (d br, 1 H, *J* = 17.3 Hz), 5.25 (dt br, 1 H, *J* = 1.4, 10.4 Hz), 5.40 (dt br, 1 H, *J* = 1.4, 17.3 Hz), 5.69-6.02 (m, 2 H), 7.25-7.40 (m, 10 H);

^{13}C NMR (50 MHz, $CDCl_3$): δ 31.5, 41.7, 70.6, 73.0, 73.2, 73.7, 81.9, 116.0, 116.3, 127.6, 128.0, 128.4, 137.1, 138.2, 138.4;

MS: 382 (M^+), 291 (M^+–Bn);

Anal. Calcd for $C_{24}H_{30}O_4$ (Mol. Wt. 382.493): C, 75.36; H, 7.91. Found; C, 75.11; H, 8.18.

(3*S*,4*R*,5*R*,6*S*)-4-Benzyloxy-6-benzyloxymethyl-3,5-*O*-isopropylidine-non-1,8-diene (86)



The acetonide protection of **85** (0.11 g, 0.3 mmol) was performed as described earlier using DMP (0.1 mL), *p*TSA (10 mg) in CH_2Cl_2 (5 mL) to obtain **86** (0.98 g, 81%) after silica gel column purification using EtOAc-light petroleum ether (1:19) as a thick syrup.

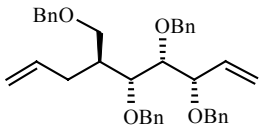
^{1}H NMR (200 MHz, $CDCl_3$): δ 1.47 (s, 3 H), 1.51 (s, 3 H), 1.99-2.11 (m, 1 H), 2.15-2.27 (m, 1 H), 2.44-2.56 (m, 1 H), 3.24 (dd, 1 H, *J* = 3.4, 9.3 Hz), 3.22-3.25 (m, 1 H), 3.33 (dd, 1 H, *J*

= 3.4, 9.7 Hz), 3.85 (dd, 1 H, *J* = 1.5, 8.7 Hz), 4.31-4.49 (m, 4 H), 4.73 (d, 1 H, *J* = 11.7 Hz), 4.97-5.02 (m, 2 H), 5.23 (dt, 1 H, *J* = 1.5, 10.5 Hz), 5.42 (dt, 1 H, *J* = 1.5, 17.1 Hz), 5.66-5.87 (m, 1 H), 5.93-6.10 (m, 1 H), 7.24-7.36 (m, 10 H);

^{13}C NMR (50 MHz, $CDCl_3$): δ 19.2, 29.9, 31.9, 39.4, 68.4, 72.8, 73.2, 73.4, 73.5, 74.8, 98.9, 116.0, 116.1, 127.3, 127.6, 127.9, 128.1, 128.3, 136.5, 137.2, 138.6, 139.0;

Anal. Calcd for $C_{27}H_{34}O_4$ (Mol. Wt. 422.556): C, 76.74; H, 8.11. Found; C, 76.45; H, 8.35.

(3*S*,4*R*,5*R*,6*S*)-3,4,5-Tris-benzyloxy-6-benzyloxymethyl-non-1,8-diene (87)



The benzyl protection of **85** (0.51 g, 1.3 mmol) was done as described earlier with NaH (0.13 g, 3.3 mmol), TBAI (0.1 g) and benzyl bromide (0.3 mL, 2.9 mmol) in DMF (10 mL) to give **87** (0.54 g, 73%) after silica gel column purification using EtOAc-light petroleum ether (1:19).

$[\alpha]_D$ +27.8 (*c* 1.0, $CHCl_3$);

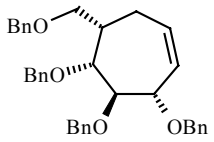
^{1}H NMR (200 MHz, $CDCl_3$): δ 2.07-2.34 (m, 3 H), 3.39 (dd, 1 H, *J* = 4.6, 9.0 Hz), 3.49 (dd, 1 H, *J* = 7.6, 9.0 Hz), 3.72 (dd, 1 H, *J* = 4.1, 7.0 Hz), 4.01 (dd, 1 H, *J* = 4.1, 7.5 Hz), 4.10 (dd, 1 H, *J* = 2.9, 7.0 Hz), 4.38 (d br, 2 H, *J* = 12.2 Hz), 4.47 (d, 1 H, *J* = 11.7 Hz), 4.58 (d, 1 H, *J* = 11.7 Hz), 4.66 (d, 1 H, *J* = 11.7 Hz), 4.74 (s, 2 H), 4.79 (d, 1 H, 11.2), 4.97 (d br, 1 H, *J* = 10.2 Hz), 5.02 (d br, 1 H, *J* = 17.6 Hz), 5.32 (d br, 1 H, *J* =16.6 Hz), 5.33 (d br, 1 H, *J* = 10.3 Hz), 5.60-5.80 (m, 1 H), 5.89-6.07 (m, 1 H), 7.29-7.33 (m, 20 H);

^{13}C NMR (50 MHz, $CDCl_3$): δ 31.3, 39.6, 70.4, 70.6, 72.9, 74.2, 74.8, 78.9, 80.7, 83.0, 115.8, 118.5, 127.5, 128.2, 135.8, 137.6, 138.2, 138.7, 139.4;

MS: 562 (M^+);

Anal. Calcd for $C_{38}H_{42}O_4$ (Mol. Wt. 562.738): C, 81.10; H, 7.52. Found; C, 81.40; H, 7.35.

(3*S*,4*R*,5*R*,6*S*)-3,4,5-Tris-benzyloxy-6-benzyloxymethyl-cycloheptene (65)



Compound **87** (0.4 g, 0.7 mmol) was dissolved in anhydrous CH_2Cl_2 (30 mL) and solution degassed with argon. Grubbs' catalyst **80** (29 mg, 5 mol%) was added and mixture stirred at rt for 20 h. The solvent was removed and the residue purified by column chromatography on silica gel using EtOAc-light petroleum ether (1:49) to furnish **65** (0.33 g, 87%) as a colorless oil.

$[\alpha]_D$ +11.2 (*c* 1.0, $CHCl_3$);

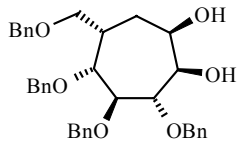
^{1}H NMR (500 MHz, $CDCl_3$): δ 2.06-2.10 (m, 1 H), 2.30-2.37 (m, 1 H), 2.39-2.45 (m, 1 H), 3.41 (dd, 1 H, *J* = 6.7, 8.8 Hz), 3.55 (dd, 1 H, *J* = 7.7, 8.8 Hz), 3.84 (dd, 1 H, *J* = 4.8, 9.5 Hz), 4.0 (dd, 1 H, *J* = 2.3, 4.8 Hz), 4.41 (dt, 1 H, *J* = 1.7, 9.5 Hz) 4.47 (d, 1 H, *J* = 11.9 Hz), 4.50 (d, 1 H, *J* = 11.9 Hz), 4.55 (d, 1 H, *J* = 11.6 Hz), 4.73 (d, 1 H, *J* = 11.0 Hz), 4.76 (s, 2 H), 4.80 (d, 1 H, *J* = 11.6), 4.98 (d, 1 H, *J* = 11.1 Hz), 5.71-5.78 (m, 2 H), 7.29-7.39 (m, 20 H);

^{13}C NMR (125 MHz, $CDCl_3$): δ 27.2, 38.4, 71.7, 72.9, 73.1, 74.3, 78.8, 81.5, 86.0, 127.3, 128.3, 129.5, 130.8, 138.4, 138.7, 138.9, 139.0;

MS: 443 (M^+–Bn);

Anal. Calcd for $C_{36}H_{38}O_4$ (Mol. Wt. 534.685): C, 80.87; H, 7.16. Found; C, 80.99; H, 7.27.

(1*R*,2*R*,3*S*,4*S*,5*R*,6*S*)-3,4,5-Tris-benzyloxy-6-benzyloxymethyl-cycloheptane-1,2-diol (88)



To a solution of **65** (30 mg, 56.17 μmol) in THF-H_2O (1:1, v/v, 2 mL) were added *N*-methylmorpholine *N*-oxide (50 wt % solution in water, 0.04 mL, 0.17 mmol) and OsO_4 (0.04 M solution in toluene, 0.06 mL, 2.24 μmol). After 5 h at rt, the mixture was diluted with EtOAc, washed with H_2O, saturated Na_2SO_3, dried (Na_2SO_4) and concentrated to give crude product which was purified by column chromatography on silica gel using EtOAc-light petroleum ether (1:4) to obtain **88** (29 mg, 91%) as a clear liquid.

$[\alpha]_D$ –47.9 (*c* 2.7, $CHCl_3$);

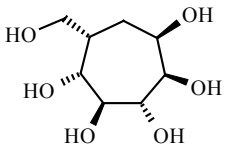
^{1}H NMR (500 MHz, $CDCl_3$): δ 1.42-1.47 (m, 1 H), 1.80-1.87 (m, 1 H), 2.29-2.35 (m, 1 H), 2.44 (br s, 1 H), 3.09 (s, 1 H), 3.20-3.27 (m, 2 H), 3.74 (dd, 1 H, *J* = 2.2, 6.7 Hz), 3.78 (dd, 1 H, *J* = 1.4, 9.6 Hz), 3.88-3.90 (m, 1 H), 3.92 (dd, 1 H, *J* = 6.7, 9.6 Hz), 4.03 (dd, 1 H, *J* = 1.4, 5.5 Hz), 4.24 (d, 1 H, *J* = 11.5 Hz), 4.26 (d, 1 H, *J* = 11.9 Hz), 4.40 (d, 1 H, *J* = 11.9 Hz), 4.51

(d, 1 H, *J* = 11.5), 4.52 (d, 1 H, *J* = 11.5 Hz), 4.54 (d, 1 H, *J* = 11.9 Hz), 4.57 (d, 1 H, *J* = 11.9 Hz), 4.82 (d, 1 H, *J* = 11.5 Hz), 7.14-7.26 (m, 20 H);

^{13}C NMR (50 MHz, $CDCl_3$): δ 28.0, 32.4, 69.6, 71.4, 72.1, 72.2, 72.4, 72.5, 75.3, 75.7, 80.3, 83.3, 127.4-128.6, 137.9, 138.0, 138.3, 138.5;

Anal. Calcd for $C_{36}H_{40}O_6$ (Mol. Wt. 568.699): C, 76.03; H, 7.09. Found; C, 76.17; H, 7.22.

(1*R*,2*R*,3*S*,4*S*,5*R*,6*S*)-6-hydroxymethyl-cycloheptane-1,2,3,4,5-pentol (89)



Hydrogenation of **88** (20 mg, 35.21 μmol) was done as described earlier with 10% Pd/C in MeOH (2 mL) to give **89** (6.7 mg, 92%).

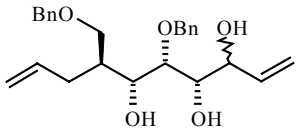
$[\alpha]_D$ −96.3 (*c* 0.7, MeOH);

^{1}H NMR (200 MHz, D_2O): δ 1.60-194 (m, 2 H), 2.07-2.27 (m, 1 H), 3.51-3.90 (m, 5 H), 4.01-4.09 (m, 1 H), 4.16-4.25 (m, 1 H);

^{13}C NMR (50 MHz, D_2O + Acetone-d_6): δ 27.6, 34.5, 64.4, 69.7, 71.8, 73.4, 74.5, 78.4;

Anal. Calcd for $C_8H_{16}O_6$ (Mol. Wt. 208.209): C, 46.15; H, 7.75. Found; C, 45.87; H, 7.58.

(3*R*/*S*,4*S*,5*S*,6*R*,7*S*)-5-Bezyloxy-7-benzyloxymethyl-dec-1,9-diene-3,4,6-triol (90)



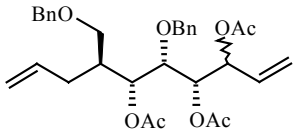
To a solution of **63** (1.0 g, 2.6 mmol) in anhydrous THF (5 mL) at 0 ^oC, CH_2=CHMgBr of 1.0 M in THF (10.0 mL, 10.4 mmol) was added. After 5 h stirring at rt, reaction mixture was quenched by addition of saturated aqueous solution of NH_4Cl (25 mL). The two layers were separated, aqueous layer extracted with EtOAc. The combined organic layers were dried (Na_2SO_4) and concentrated to form a residue which was purified on silica gel using EtOAc-light petroleum ether (9:1) to furnish **90** (0.78 g, 73%) as a thick oil.

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.80-2.03 (m, 1 H), 2.12-2.41 (m, 2 H), 3.05 (s, 3 H, -OH), 3.52 (d, 2 H, *J* = 5.8 Hz), 3.60-3.78 (m, 1 H), 3.95- 4.37 (m, 3 H), 4.45 (s, 2 H), 4.63 (d, 1 H,

J = 11.7 Hz), 4.72 (d, 1 H, *J* = 11.7 Hz), 5.02-5.13 (m, 3 H), 5.20-5.37 (m, 1 H), 5.67-5.91 (m, 2 H), 7.21-7.34 (m, 10 H);

Anal. Calcd for $C_{25}H_{32}O_5$ (Mol. Wt. 412.519): C, 72.79; H, 7.82. Found; C, 72.66; H, 7.67.

(3*R*/*S*,4*R*,5*S*,6*R*,7*S*)-3,4,6-Tris-acetoxy-5-bezyloxy-7-benzyloxymethyl-dec-1,9-diene (91)

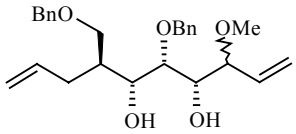


A solution of **90** (0.2 g, 0.48 mmol), Ac_2O (0.18 mL, 1.92 mmol) and Py (5 mL) was stirred at rt for 12 h. The reaction mixture was partitioned between EtOAc and 1 N HCl, organic layer dried (Na_2SO_4), concentrated and the residue purified by column chromatography on silica gel using EtOAc-light petroleum ether (3:17) to obtain **91** (0.19 g, 75%) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.93-2.25 (m, 11 H), 2.32-2.51 (m, 1 H), 3.26-3.41 (m, 2 H), 3.72-3.88 (m, 1 H), 4.37-4.44 (m, 2 H), 4.63-4.69 (m, 2 H), 4.97-5.04 (m, 2 H), 5.18-5.29 (m, 3 H), 5.34 (q, 1 H, *J* = 5.7 Hz), 5.53 and 5.61 (t, 1 H, *J* = 5.6 Hz), 5.65-5.81 (m, 2 H), 7.26-7.41 (m, 10 H);

Anal. Calcd for $C_{31}H_{38}O_8$ (Mol. Wt. 538.629): C, 69.13; H, 7.11. Found; C, 68.96; H, 7.37.

(3*R*/*S*,4*S*,5*S*,6*R*,7*S*)-5-Bezyloxy-7-benzyloxymethyl-3-methoxy-dec-1,9-diene-4,6-diol (92)



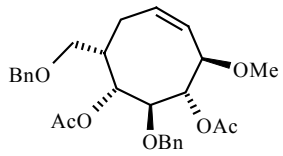
To a solution of **90** (0.3 g, 0.73 mmol) in dry THF (5 mL) at –20 ^{o}C, LiHMDS (1.06 M, 0.8 mL) was added. After15 min, MeI (0.1 mL, 1.6 mmol) in THF (0.5 mL) was introduced and the reaction mixture warmed to 0 ^{o}C. After 12 h, the reaction mixture was quenched with saturated aqueous NH_4Cl solution and extracted with EtOAc. The organic layer was dried (Na_2SO_4) and concentrated to provide a residue, which was purified on silica gel using EtOAc-light petroleum ether (3:7) to afford **92** (0.24 g, 78%) as a colorless liquid.

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.90-2.55 (m, 3 H), 3.01 (br s, 2 H), 3.30-3.45 (m, 3 H), 3.36 and 3.53 (d, 2 H, *J* = 5.6 Hz), 3.67-3.83 (m, 2 H), 4.01-4.13 (m, 1 H), 4.36 and 4.75 (ABq, 2

H, *J* = 12.4 Hz), 4.37 and 4.43 (s, 2 H), 4.42-4.51 (m, 1 H), 5.01-5.45 (m, 4 H), 5.62-5.95 (m, 2 H), 7.21-7.38 (m, 10 H);

Anal. Calcd for $C_{26}H_{34}O_5$ (Mol. Wt. 426.545): C, 73.21; H, 8.03. Found; C, 73.40; H, 7.92.

(3*R*,4*S*,5*S*,6*R*,7*S*)-4,6-Bis-acetoxy-5-bezyloxy-7-benzyloxymethyl-3-methoxy-cyclooctene (94)



Compound **93** (0.2 g, 0.39 mmol) was dissolved in anhydrous C_6H_6 (15 mL) and solution degassed with argon. Grubbs' catalyst **80** (35 mg, 10 mol%) was added and mixture was heated under reflux for 3 days. The solvent was removed and the residue purified by column chromatography on silica gel using EtOAc-light petroleum ether (1:9) to obtain **94** (47 mg, 25%) as a colorless syrup.

$[\alpha]_D$ −31.6 (*c* 1.1, $CHCl_3$);

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.93-1.97 (m, 1 H), 2.06 (s, 3 H), 2.10 (s, 3 H), 2.43-2.51 (m, 2 H), 3.31 (d, 2 H, *J* = 6.6 Hz), 3.34 (s, 3 H), 4.07 (dd, 1 H, *J* = 2.2, 8.4 Hz), 4.43 (d, 1 H, *J* = 12.1 Hz), 4.50 (t, 1 H, *J* = 8.9 Hz), 4.52 (d, 1 H, *J* = 12.1 Hz), 4.54 (d, 1 H, *J* = 12.1 Hz), 4.80 (d, 1 H, *J* = 12.1 Hz), 5.20 (dd, 1 H, *J* = 2.2, 9.9 Hz), 5.36 (d, 1 H, *J* = 8.5 Hz), 5.50 (dd, 1 H, *J* = 8.0, 10.5 Hz), 5.93-5.98 (m, 1 H), 7.27-7.38 (m, 10 H);

^{13}C NMR (125 MHz, $CDCl_3$): δ 21.0, 24.5, 38.7, 56.8, 71.6, 71.9, 72.1, 72.9, 75.3, 76.5, 76.8, 127.2, 127.4, 127.7, 128.2, 128.4, 129.6, 132.3, 138.1, 169.9, 170.3;

MS: 482 (M^+);

Anal. Calcd for $C_{28}H_{34}O_7$ (Mol. Wt. 482.565): C, 69.69; H, 7.10. Found; C, 69.96; H, 7.48.

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Introduction

Over the years, high blood glucose, also called hyperglycemia,[1] damages nerves and blood vessels, which can lead to complications such as heart disease and stroke, kidney disease, blindness, nerve problems, gum infections, and amputation.

What is Diabetes?

Diabetes[2] is a disease which is caused by the inadequate production of insulin by the body or by the body not being able to properly use the insulin that is produced thereby resulting in hyperglycemia or high blood glucose levels. There are two main types of diabetes, type I, which is insulin dependent,[3] usually seen in young people and type II, which is non-insulin dependent. It tends to affect adults over 40 and overweight people. They have insulin resistance, which means that their bodies don't use insulin properly. There are also other types of diabetes, Pregnancy diabetes, which is known as gestational diabetes associated with pregnancy and symptoms usually disappear after the birth and Secondary diabetes, which is caused as the result of another condition, e.g., inflammation of the pancreas, or by the use of certain medication such as diuretics or steroids.[4]

What Causes Diabetes?

There are two different diseases with the word diabetes that has different diabetes symptoms. Malfunctioning of two completely different organs causes those two diseases, 1) this type of diabetes is the more commonly known- Diabetes Mellitus, and 2) this is relatively unknown to the common people- Diabetes Insipidus.

Diabetes Mellitus[5]- This type of Diabetes is caused by malfunctioning of the organ- pancreas. This is an endocrine organ that is responsible, among other things, to maintain sugar balance in our body. It is situated close to stomach in our abdominal cavity. It produces two types of hormone- Insulin and Glucagon. The perfect harmony between these two hormones is needed to stay healthy and away from Diabetes Mellitus. Insulin's main function is to decrease blood sugar and so when we eat diet rich in sugar, pancrease increases the secretion of insulin which uses up the glucose and keep the blood glucose within its normal limits in people who don't have Diabetes Mellitus. When the blood sugar starts falling, pancrease secrets Glucagon which attempts to preserve glucose and thus tries to raise the blood sugar. The blood sugar level will rise if: a) the pancreas produces little or no insulin (Type 1 diabetes) and b) the

pancreas produces insulin, but it's inadequate for the body's needs and its effectiveness is reduced (Type 2 diabetes). It's thought Type 2 diabetes is related to factors associated with a Western lifestyle, since it's most common in people who are overweight and who don't get enough exercise.

Diabetes Insipidus- This type of Diabetes is caused by abnormally functioning pituitary gland. Pituitary gland is a small gland situated in the brain which is the main endocrine gland of the body. It controls all the other endocrine glands of the body. Pituitary gland is divided into front and back parts- Anterior Pituitary or Adenohypophysis and Posterior pituitary or Neurohypophysis. The hormone responsible for causing Diabetes Insipidus-anti diuretic hormone- is secreted by the back part-posterior pituitary gland also called neurohypophysis.

Common Symptoms of Diabetes

Diabetes Mellitus has some common symptoms occur more often with type 1 diabetes and type 2 diabetes. These are Frequent urination, Excessive thirst, Extreme hunger, Extreme tiredness, Unusual weight loss, Increased fatigue, Irritability, Blurry vision.

Type 2 diabetes develops slowly and the symptoms are usually less severe. Some people may not notice any symptoms at all and their diabetes is only picked up in a routine medical check up. Some people may put the symptoms down to 'getting older' or 'overwork'.

Type 1 diabetes develops much more quickly, usually over a few weeks, and symptoms are normally very obvious.

In both types of diabetes, the symptoms are quickly relieved once the diabetes is treated. Early treatment will also reduce the chances of developing serious health problems.[6]

Diabetes symptoms due to lack of Anti-Diuretic Hormone are: polyuria- excessive urination, polydipsia- excessive thirst. There is no excessive eating or weight loss involved in this condition.

Diagnosis of Diabetes

The oral glucose tolerance[7] test previously recommended by the National Diabetes Data Group has been replaced with the recommendation that the diagnosis[8] of diabetes mellitus be based on two fasting plasma glucose levels of 126 mg per dL (7.0 mmol per L) or higher. Other options for diagnosis include two 2-hour postprandial plasma glucose (PPG) readings of 200 mg per dL (11.1 mmol per L) or higher after a glucose load of 75 g (essentially, the criterion recommended[9] by WHO) or two casual glucose readings of 200 mg

per dL (11.1 mmol per L) or higher. Measurement of the fasting plasma glucose level[10] is the preferred diagnostic test, but any combination of two abnormal test results can be used. Fasting plasma glucose was selected as the primary diagnostic test because it predicts adverse outcomes (e.g., retinopathy) as well as the 2-hour PPG test but is much more reproducible than the oral glucose tolerance test or the 2-hour PPG test and easier to perform in a clinical setting.[11]

The choice of the new cutoff point for fasting plasma glucose levels is based on strong evidence from a number of populations linking the risk of various complications to the glycemic status of the patient. The risk of diabetic retinopathy based on the glycemic status of 40- to 74-year-old participants in the National Health and Nutritional Epidemiologic Survey (NHANES III).[12] The risk of retinopathy greatly increases when the patient's fasting plasma glucose level is higher than 109 to 116 mg per dL (6.05 to 6.45 mmol per L) or when the result of a 2-hour PPG test is higher than 150 to 180 mg per dL (8.3 to 10.0 mmol per L). However, the committee decided to maintain the cutoff point for the 2-hour PPG test at 200 mg per dL (11.1 mmol per L) because so much literature has already been published using this criterion. They selected a cutoff point for fasting plasma glucose of 126 mg per dL (7.0 mmol per L) or higher. This point corresponded best with the 2-hour PPG level of 200 mg per dL (11.1 mmol per L). The risk of other complications also increases dramatically at the same cutoff points.

Treatment of Diabetes

A class of drugs used in treating Type 2 diabetes. The first line of treatment for Type 2 diabetes consists of dietary changes and exercise, which help people with diabetes lose weight, improve the way their bodies make and use insulin, and lower blood glucose levels. Unfortunately, despite their best efforts, many people either cannot lose weight or cannot maintain their weight loss, or their blood glucose levels are poorly controlled in spite of weight loss. In these people, the only alternative is drug treatment.

At present, four therapeutic classes of drugs are in clinical use for the regulation of blood glucose: insulins, sulfonylureas, biguanidines and α-glucosidase inhibitors. Six new therapeutic approaches are being clinically studied, including euglycemic agents, α_2-adrenoceptor antagonists, thermogenic β_2-adrenoceptor antagonists,[13] adenosine A_2-agonists, insulin-releasing hormones and insulin-like growth factor.

Sulfonylurea pills work primarily by stimulating the pancreas to release more insulin.[14] The first-generation sulfonylureas, which have been around for many years, are acetohexamide (**1**), Gliquidone (**2**), Gliclazide (**3**), tolbutamide (Orinase, **4**), and tolazamide (Tolinase, **5**). Newer, more powerful second-line sulfonylureas, which have fewer side effects, include glipizide (Glucotrol, **6**), glyburide (**7**), and the newest drug, glimepiride (Amaryl, **8**) (Figure 1). A single-dose, extended-release form of glipizide called Glucotrol XL is also available.

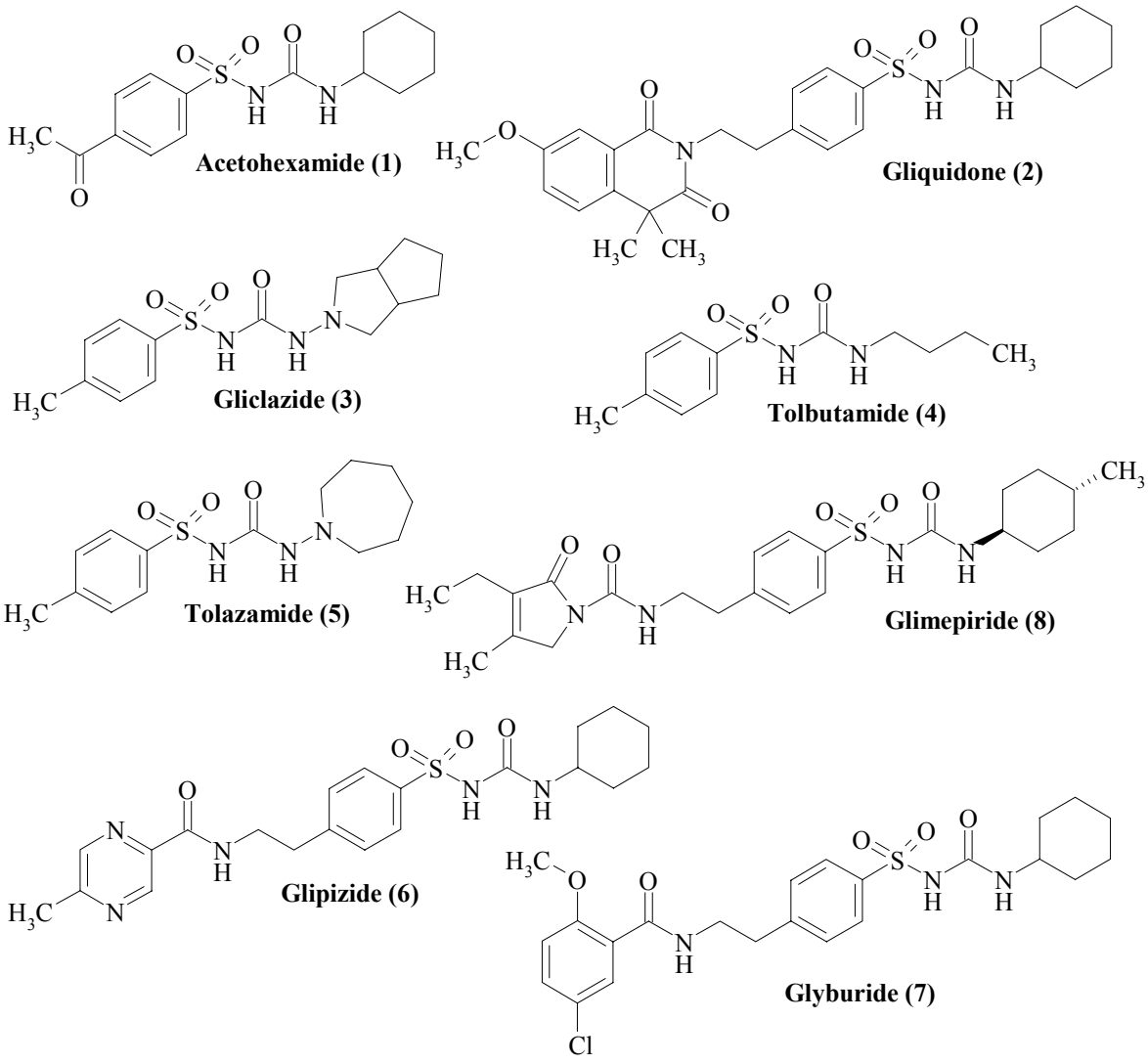


Figure 1: ***Chemical structures of sulfonylurea***

Unfortunately, sulfonylureas do not always succeed in controlling diabetes. With sulfonylurea therapy, some 10% to 20% of people will immediately fail to control their blood

glucose levels adequately on the highest recommended dose (a situation called "primary failure"). Sulfonylureas themselves tend to overwork the pancreas until it eventually "burns out" and is unable to secrete an adequate amount of insulin, so roughly 5% to 10% of people who initially respond to sulfonylurea therapy will subsequently fail each year (a situation called "secondary failure"). However, among the sulfonamide urea drugs,[15] glimepiride is the most superior to lower the sugar level in the blood by stimulating insulin to be secreted from the pancreas into the blood.[16]

Clinical Pharmacology of Glimepiride

Mechanism of Action

The primary mechanism of action of glimepiride in lowering blood glucose appears to be dependent on stimulating the release of insulin from functioning pancreatic beta cells. In addition, extrapancreatic effects may also play a role in the activity of sulfonylureas such as glimepiride. This is supported by both preclinical and clinical studies[17] demonstrating that glimepiride administration can lead to increased sensitivity of peripheral tissues to insulin. These findings are consistent with the results of a long-term, randomized, placebo-controlled trial in which AMARYL therapy improved postprandial insulin/C-peptide responses and overall glycemic control without producing clinically meaningful increases in fasting insulin/C-peptide levels. However, as with other sulfonylureas, the mechanism by which glimepiride lowers blood glucose during long-term administration has not been clearly established.

AMARYL is effective as initial drug therapy. In patients where monotherapy with AMARYL or metformin has not produced adequate glycemic control, the combination of AMARYL and metformin may have a synergistic effect,[18] since both agents act to improve glucose tolerance by different primary mechanisms of action. This complementary effect has been observed with metformin and other sulfonylureas, in multiple studies.

Pharmacodynamics

A mild glucose lowering effect first appeared following single oral doses as low as 0.5-0.6 mg in healthy subjects. The time required to reach the maximum effect (i.e., minimum blood glucose level [T_{min}]) was about 2 to 3 hours. In noninsulin-dependent (Type 2) diabetes mellitus (NIDDM) patients, both fasting and 2-hour postprandial glucose levels were significantly lower with glimepiride (1, 2, 4, and 8 mg once daily) than with placebo after 14

days of oral dosing. The glucose lowering effect in all active treatment groups was maintained over 24 hours.

In larger dose-ranging studies, blood glucose and HbA_{1c} were found to respond in a dose-dependent manner over the range of 1 to 4 mg/day of AMARYL. Some patients, particularly those with higher fasting plasma glucose (FPG) levels, may benefit from doses of AMARYL up to 8 mg once daily.[19] No difference in response was found when AMARYL was administered once or twice daily.

In two 14-week, placebo-controlled studies in 720 subjects, the average net reduction in HbA_{1c} for AMARYL (glimepiride tablets) patients treated with 8 mg once daily was 2.0% in absolute units compared with placebo-treated patients. In a long-term, randomized, placebo-controlled study of NIDDM patients unresponsive to dietary management, AMARYL therapy improved postprandial insulin/C-peptide responses, and 75% of patients achieved and maintained control of blood glucose and HbA_{1c}. Efficacy results were not affected by age, gender, weight, or race.

In long-term extension trials with previously treated patients, no meaningful deterioration in mean fasting blood glucose (FBG) or HbA_{1c} levels was seen after 2 1/2 years of AMARYL therapy.

Combination therapy with AMARYL and insulin (70% NPH/30% regular) was compared to placebo/insulin in secondary failure patients whose body weight was >130% of their ideal body weight. Initially, 5-10 units of insulin were administered with the main evening meal and titrated upward weekly to achieve predefined FPG values. Both groups in this double-blind study achieved similar reductions in FPG levels but the AMARYL/insulin therapy group used approximately 38% less insulin.

Pharmacokinetics

Absorption. After oral administration, glimepiride is completely (100%) absorbed from the GI tract. Studies with single oral doses in normal subjects and with multiple oral doses in patients with NIDDM have shown[20] significant absorption of glimepiride within 1 hour after administration and peak drug levels (C_{max}) at 2 to 3 hours. When glimepiride was given with meals, the mean T_{max} (time to reach C_{max}) was slightly increased (12%) and the mean C_{max} and AUC (area under the curve) were slightly decreased (8% and 9%, respectively).

Distribution. After intravenous (IV) dosing in normal subjects, the volume of distribution (Vd) was 8.8 L (113 mL/kg), and the total body clearance (CL) was 47.8 mL/min. Protein binding was greater than 99.5%.

Metabolism. Glimepiride is completely metabolized by oxidative biotransformation after either an intravenous or oral dose. The major metabolites are the cyclohexyl hydroxy methyl derivative (M1) and the carboxyl derivative (M2).[21] Cytochrome P450 2C9 has been shown to be involved in the biotransformation of glimepiride to cyclohexyl hydroxy methyl derivative (M1). Cyclohexyl hydroxy methyl derivative is further metabolized to M2 by one or several cytosolic enzymes. M1, but not M2, possesses about 1/3 of the pharmacological activity as compared to its parent in an animal model, however, whether the glucose lowering effect of M1 is clinically meaningful is not clear.

Excretion. When ^{14}C-glimepiride was given orally, approximately 60% of the total radioactivity was recovered in the urine in 7 days and M1 (predominant) and M2 accounted for 80-90% of that recovered in the urine. Approximately 40% of the total radioactivity was recovered in feces and M1 and M2 (predominant) accounted for about 70% of that recovered in feces. No parent drug was recovered from urine or feces. After intravenous dosing in patients, no significant biliary excretion of glimepiride or its M1 metabolite has been observed.[22]

Pharmacokinetic Parameters. The pharmacokinetic parameters of glimepiride obtained from a single-dose, crossover, dose-proportionality (1, 2, 4, and 8 mg) study in normal subjects and from a single- and multiple-dose, parallel, dose-proportionality (4 and 8 mg) study in patients with NIDDM and found that glimepiride did not accumulate in serum, and the pharmacokinetics of glimepiride were not different in healthy volunteers and in NIDDM patients.[23] Oral clearance of glimepiride did not change over the 1-8-mg dose range, indicating linear pharmacokinetics.

Variability. In normal healthy volunteers, the intra-individual variabilities of C_{max}, AUC, and CL/f for glimepiride were 23%, 17%, and 15%, respectively, and the inter-individual variabilities were 25%, 29%, and 24%, respectively.

Special Populations

Geriatric. Comparison of glimepiride pharmacokinetics in NIDDM patients ≤65 years and those >65 years was performed in a study using a dosing regimen of 6 mg daily. There

were no significant differences in glimepiride pharmacokinetics between the two age groups. The mean AUC at steady state for the older patients was about 13% lower than that for the younger patients; the mean weight-adjusted clearance for the older patients was about 11% higher than that for the younger patients.

Gender. There were no differences between males and females in the pharmacokinetics of glimepiride when adjustment was made for differences in body weight.

Renal Insufficiency. A single-dose, open-label study was conducted in 15 patients with renal impairment. AMARYL (3 mg) was administered to 3 groups of patients with different levels of mean creatinine clearance (CLcr); (Group I, CLcr = 77.7 mL/min, n = 5), (Group II, CLcr = 27.7 mL/min, n = 3), and (Group III, CLcr = 9.4 mL/min, n = 7). AMARYL was found to be well tolerated in all 3 groups. The results showed that glimepiride serum levels decreased as renal function decreased. However, M1 and M2 serum levels (mean AUC values) increased 2.3 and 8.6 times from Group I to Group III. The apparent terminal half-life ($T_{1/2}$) for glimepiride did not change, while the half-lives for M1 and M2 increased as renal function decreased. Mean urinary excretion of M1 plus M2 as percent of dose, however, decreased (44.4%, 21.9%, and 9.3% for Groups I to III).[24]

A multiple-dose titration study was also conducted in 16 NIDDM patients with renal impairment using doses ranging from 1-8 mg daily for 3 months. The results were consistent with those observed after single doses. All patients with a CLcr less than 22 mL/min had adequate control of their glucose levels with a dosage regimen of only 1 mg daily. The results from this study suggested that a starting dose of 1 mg AMARYL may be given to NIDDM patients with kidney disease, and the dose may be titrated based on fasting blood glucose levels.

Other Populations. There were no important differences in glimepiride metabolism in subjects identified as phenotypically different drug-metabolizers by their metabolism of sparteine.

The pharmacokinetics of glimepiride in morbidly obese patients were similar to those in the normal weight group, except for a lower C_{max} and AUC. However, since neither C_{max} nor AUC values were normalized for body surface area, the lower values of C_{max} and AUC for the obese patients were likely the result of their excess weight and not due to a difference in the kinetics of glimepiride.

Drug Interactions. The hypoglycemic action of sulfonylureas may be potentiated[25] by certain drugs, including nonsteroidal anti-inflammatory drugs and other drugs that are highly protein bound, such as salicylates, sulfonamides, chloramphenicol, coumarins, probenecid, monoamine oxidase inhibitors, and beta adrenergic blocking agents.[26] When these drugs are administered to a patient receiving AMARYL, the patient should be observed closely for hypoglycemia. When these drugs are withdrawn from a patient receiving AMARYL, the patient should be observed closely for loss of glycemic control.

Certain drugs tend to produce hyperglycemia and may lead to loss of control. These drugs include the thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, and isoniazid. When these drugs are administered to a patient receiving AMARYL, the patient should be closely observed for loss of control. When these drugs are withdrawn from a patient receiving AMARYL, the patient should be observed closely for hypoglycemia.

Coadministration of aspirin (1 g tid) and AMARYL led to a 34% decrease in the mean glimepiride AUC and, therefore, a 34% increase in the mean CL/f. The mean C_{max} had a decrease of 4%. Blood glucose and serum C-peptide concentrations were unaffected and no hypoglycemic symptoms were reported. Pooled data from clinical trials showed no evidence of clinically significant adverse interactions with uncontrolled concurrent administration of aspirin and other salicylates.

Coadministration of either cimetidine (800 mg once daily) or ranitidine (150 mg bid) with a single 4-mg oral dose of AMARYL did not significantly alter the absorption and disposition of glimepiride, and no differences were seen in hypoglycemic symptomatology. Pooled data from clinical trials showed no evidence of clinically significant adverse interactions with uncontrolled concurrent administration of H2-receptor antagonists.

Concomitant administration of propranolol (40 mg tid) and AMARYL significantly increased C_{max}, AUC, and $T_{1/2}$ of glimepiride by 23%, 22%, and 15%, respectively, and it decreased CL/f by 18%. The recovery of M1 and M2 from urine, however, did not change. The pharmacodynamic responses to glimepiride were nearly identical in normal subjects receiving propranolol and placebo. Pooled data from clinical trials in patients with NIDDM showed no evidence of clinically significant adverse interactions with uncontrolled concurrent

administration of beta-blockers. However, if beta-blockers are used, caution should be exercised and patients should be warned about the potential for hypoglycemia.

Concomitant administration of AMARYL (glimepiride tablets) (4 mg once daily) did not alter the pharmacokinetic characteristics of R- and S-warfarin enantiomers following administration of a single dose (25 mg) of racemic warfarin to healthy subjects. No changes were observed in warfarin plasma protein binding. AMARYL treatment did result in a slight, but statistically significant, decrease in the pharmacodynamic response to warfarin. The reductions in mean area under the prothrombin time (PT) curve and maximum PT values during AMARYL treatment were very small (3.3% and 9.9%, respectively) and are unlikely to be clinically important.

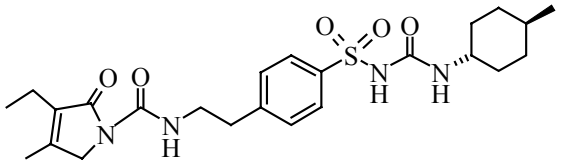
The responses of serum glucose, insulin, C-peptide, and plasma glucagon to 2 mg AMARYL were unaffected by coadministration of ramipril (an ACE inhibitor) 5 mg once daily in normal subjects.[27] No hypoglycemic symptoms were reported. Pooled data from clinical trials in patients with NIDDM showed no evidence of clinically significant adverse interactions with uncontrolled concurrent administration of ACE inhibitors.

A potential interaction between oral miconazole and oral hypoglycemic agents leading to severe hypoglycemia has been reported. Whether this interaction also occurs with the intravenous, topical, or vaginal preparations of miconazole is not known. There is a potential interaction of glimepiride with inhibitors (e.g. fluconazole) and inducers (e.g. rifampicin) of cytochrome P450 2C9.

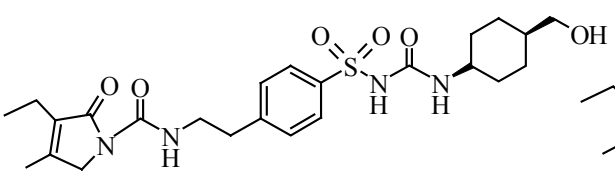
Although no specific interaction studies were performed, pooled data from clinical trials showed no evidence of clinically significant adverse interactions with uncontrolled concurrent administration of calcium-channel blockers, estrogens, fibrates, NSAIDS, HMG CoA reductase inhibitors, sulfonamides, or thyroid hormone.

Present Work

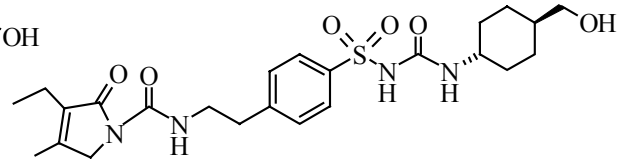
Among the sulfonylurea[28] class of anti-diabetic drugs, glimepiride (**8**)[29] has many distinctive advantages and is by far the most superior blood glucose lowering agent.[30] Glimepiride shows a three-fold faster rate of association and a nine-fold faster rate of dissociation than glibenclamide.[28,31] Studies on the metabolism of therapeutically active compounds are increasingly being realized because metabolites provide superior safety and efficacy profiles, but more importantly offer opportunities to study the metabolic pathways. The metabolism of glimepiride has been observed in animals and humans *via* oxidative pathways giving rise to two active metabolites represented by *trans*-hydroxyglimepiride (**9b**) and carboxyglimepiride (**10**)[32] (Figure 2). Animal studies have shown hydroxyglimepiride to exhibit some hypoglycaemic effects while carboxyglimepiride does not appear to have any pharmacological activity. In spite of their significance in metabolic studies, their syntheses are yet to be accomplished. However, we were confronted with the need to produce synthetically both *cis*-hydroxyglimepiride (**9a**) and *trans*-hydroxyglimepiride (**9b**), particularly for bio-equivalence studies.



Glimepiride (8)



***cis*-Hydroxyglimepiride (9a)**



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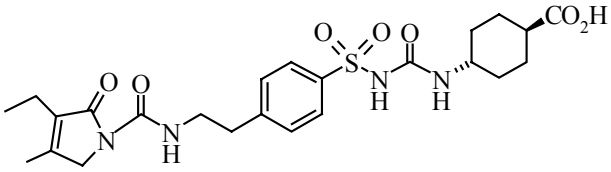


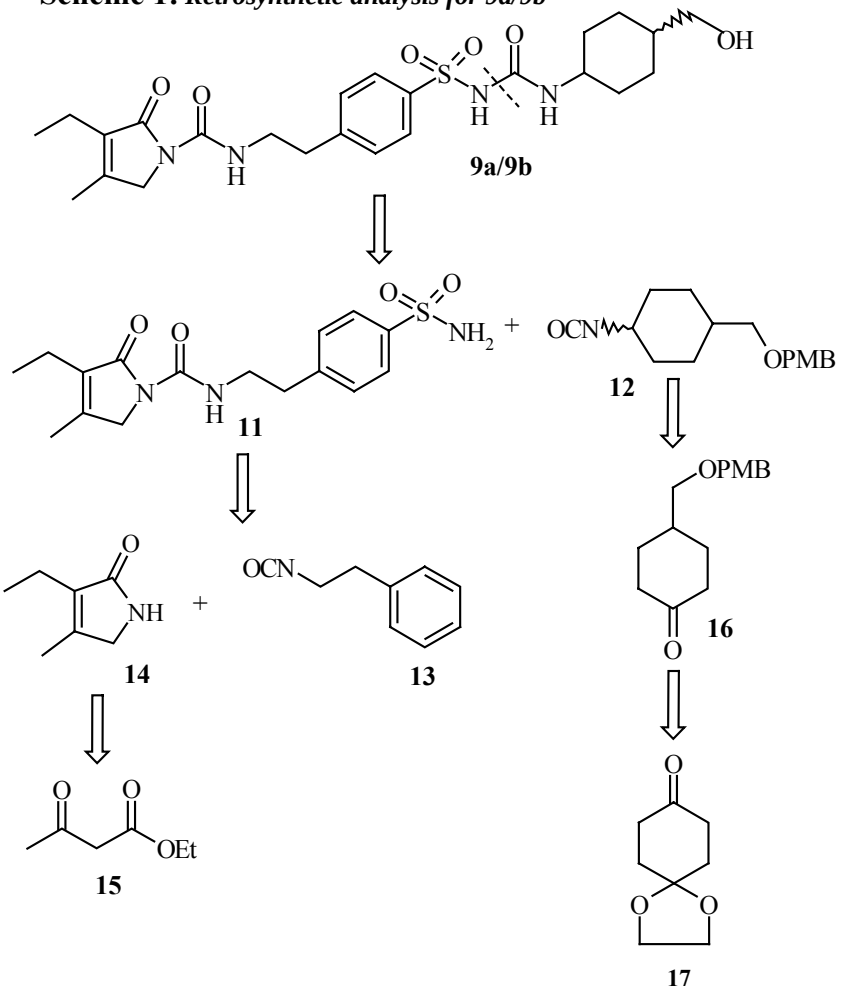
Carboxyglimepiride (10)

Figure 2

Hydroxyglimepiride significantly decreased the minimum serum concentration (Cmin) of glucose by 12% and the average serum glucose concentration over the first four hours of treatment (Cavg 0-4) by 9%. In addition, maximum serum C-peptide concentration (Cmax) and Cavg 0-4 were both increased by 7% after hydroxyglimepiride.[21]

The strategy for the construction of *cis*- and *trans*-hydroxyglimepiride (**9a**/**9b**) is described in the retrosynthetic plan (Scheme 1). Retrosynthetic scission of the indicated C-N bond in **9a**/**9b** would provide the intermediates **11** and **12**. It was anticipated that **17** could be an ideal precursor for the synthesis of **12**.

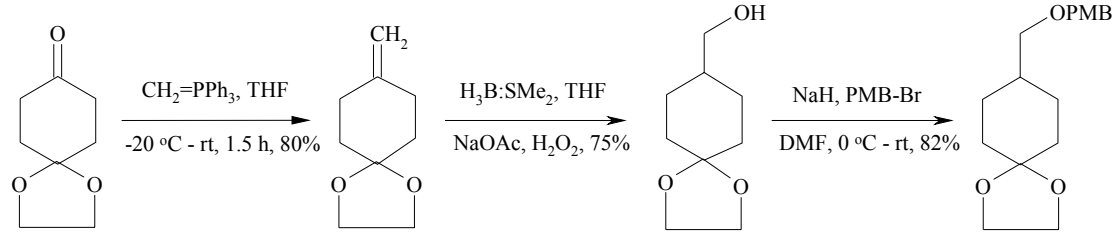
Scheme 1: ***Retrosynthetic analysis for 9a/9b***



The syntheses of *cis*- and *trans*-hydroxyglimepiride (**9a** and **9b**) were initiated from commercially available 1,4-cyclohexanedione *mono*-ethylene ketal (**17**). When **17** was subjected to one carbon Wittig homologation[33] with $Ph_3P{=}CH_2$ in THF gave the *exo*-methylene product **18**. In the ^1H NMR spectrum of **18**, the olefinic protons were located as a

singlet at 4.66 ppm. Compound **18** was subjected to hydroboration-oxidation reaction in the presence of 2 M $H_3B{:}SMe_2$ solution in THF followed by sequential treatment with H_2O_2 and NaOAc to provide **19** (Scheme 2). The ^1H NMR, ^{13}C NMR spectroscopy and elemental analysis confirmed the structure of **19**. For example, a doublet (J = 6.0 Hz) at 3.47 ppm in its ^1H NMR spectrum attributed to the CH_2OH group. The rest of the spectrum was in accord with the assigned structure. In addition, the ^{13}C NMR revealed a resonance at 67.1 ppm due to CH_2OH. The free hydroxyl group of **19** was protected as its PMB ether (**20**) which showed doublets in the downfield region at 6.89 ppm (J = 8.4 Hz) and 7.27 ppm (J = 8.4 Hz) due to aromatic protons in the ^1H NMR spectrum.

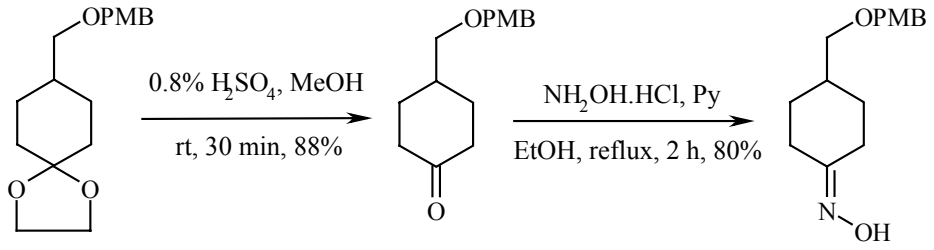
Scheme 2



17 **18** **19** **20**

Our next concern was to synthesize the oxime derivative (**21**). For this endeavor, the ketal protection of **20** was cleaved by using 0.8% H_2SO_4 in MeOH to obtain the ketone **16** which was analyzed for structural elucidation by the ^1H NMR, ^{13}C NMR spectroscopy and elemental analysis (Scheme 3). For instance, the ^{13}C NMR spectrum showed a peak at 211.5 ppm due to C=O group. Compound **16** was treated with $NH_2OH.HCl$ in refluxing EtOH for 2 h to afford the oxime **21** (Scheme 3). In the ^1H NMR spectrum, a doublet (J = 6.5 Hz) resonated at 3.29 ppm due to methylene protons adjacent to OPMB.

Scheme 3

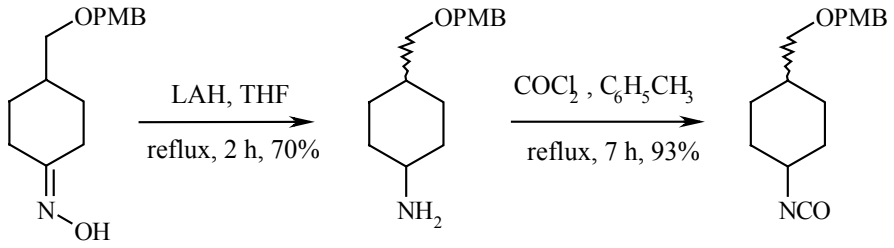


20 **16** **21**

The transformation of **21** into **12** was accomplished in the following manner. The reduction of **21** with LAH in refluxing THF provided the *cis*- and *trans*-mixture of

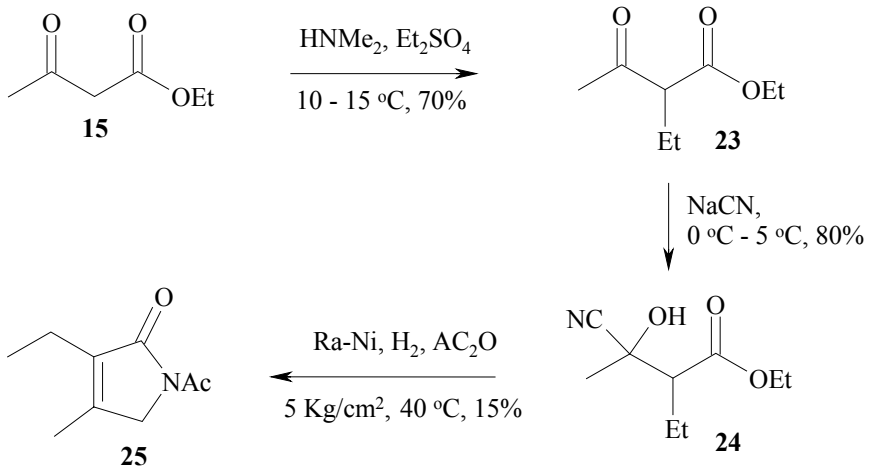
cyclohexylamine derivatives (**22**) (Scheme 4). At this stage, an attempt to separate the *cis*- and *trans*-mixture was not successful. Therefore, we decided to continue our synthetic strategy with the mixture and envisaged separation at a later stage of the synthetic sequence. The structure of **22** was confirmed by its ^{1}H NMR, mass spectroscopy and elemental analysis. For instance, the mass spectroscopy exhibited two peaks at 249 and 234 due to (M^+) and (M^+–15) ions respectively. The treatment of **22** with $COCl_2$ in refluxing toluene gave the isocyanate derivative (**12**)[34] whose IR spectrum displayed an absorption at 2262 cm^{-1} for NCO group.

Scheme 4



Having **12** in hand, next our concern involved to synthesize the sulfonamide intermediate (**11**) starting from *N*-Ac-pyrrolinone derivative (**25**), the later can be prepared from ethyl acetoacetate (**15**) by adopting the known procedure[35a] shown in Scheme 5.

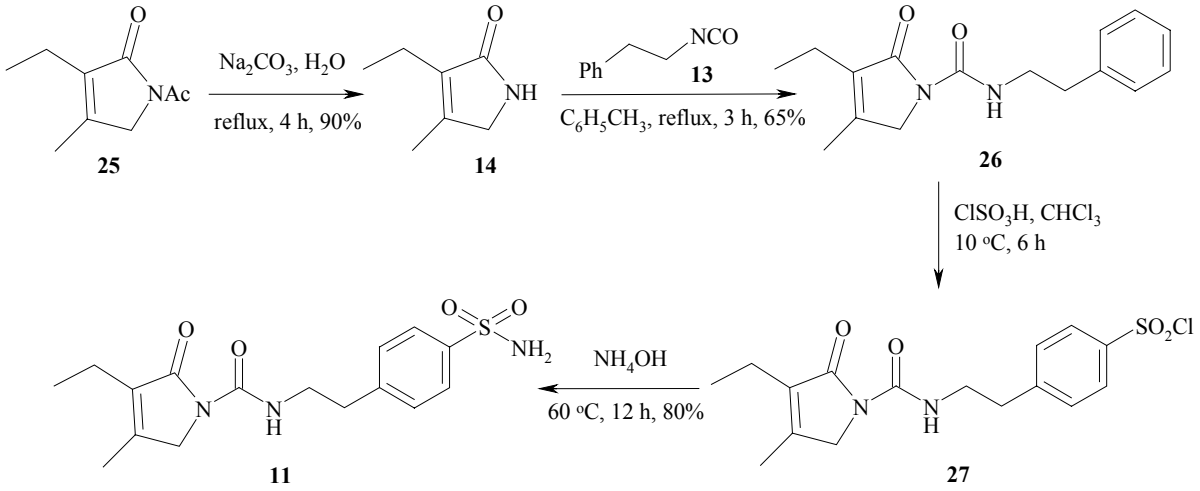
Scheme 5



The acetyl group of **25** was removed by the treatment with Na_2CO_3 in H_2O at reflux temperature to provide the pyrrolinone derivative (**14**) (Scheme 6). In the ^{1}H NMR spectrum of **14**, a triplet at 1.06 ppm (J = 7.6 Hz) and a quartet at 2.26 ppm (J = 7.6 Hz) revealed the

presence of the ethyl group. A singlet due to methylene protons of pyrrolinone ring appeared at 3.79 ppm. All other resonances displayed in their respective chemical shift values. The structure of **14** was further supported by its ^{13}C NMR spectroscopy and elemental analysis. The condensation reaction between **14** and **13**, the later was prepared from 2-phenylethyl amine and $COCl_2$, afforded the urea derivative (**26**) whose ^{1}H NMR and ^{13}C NMR spectroscopy clearly indicated that the characteristic signals for both the coupling partners. For instance, the ^{1}H NMR spectrum showed two methylene groups of the isocyanate moiety observed as a triplet at 2.88 ppm (J = 6.5 Hz) and a quartet at 3.57 ppm (J = 6.4 Hz) while the

Scheme 6

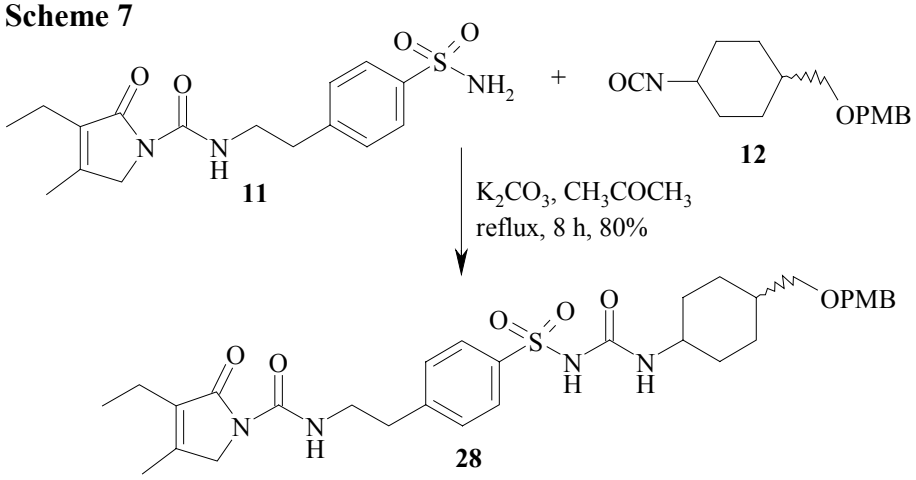


methylene protons of pyrrolinone ring appeared at 4.18 ppm as a singlet. The NH proton resonated as a triplet in the downfield region at 8.43 ppm (J = 6.2 Hz). Compound **26** was sulfonated with $ClSO_3H$ at 10 ^{o}C to yield the corresponding benzenesulfonyl chloride derivative (**27**) which was converted to benzenesulfonamide derivative (**11**) using concentrated NH_4OH at 60 ^{o}C (Scheme 6). In the ^{1}H NMR spectrum of **11**, the SO_2NH_2 protons resonated as a singlet at 6.54 ppm. The aromatic protons appeared as a two set of doublets at 7.46 ppm (J = 8.2 Hz) and 7.83 ppm (J = 8.2 Hz). The structure of **11** was further confirmed by its ^{13}C NMR spectroscopy and elemental analysis.

Having both the coupling partners **11** and **12** in hand, finally the condensation reaction between them was performed in the presence of K_2CO_3 in CH_3COCH_3 at reflux temperature for 8 h to afford the coupled product **28** in 80% yield (Scheme 7). The ^{1}H NMR spectrum of **28** clearly indicated that the coupling had indeed taken place because the characteristic signals

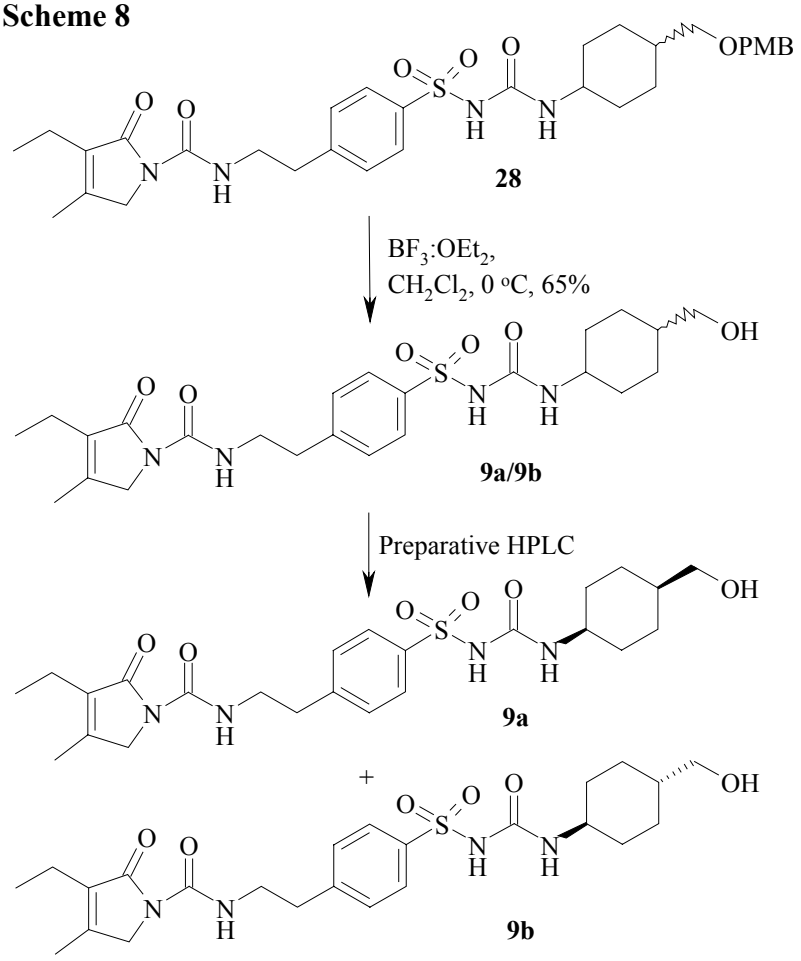
of both the coupling partners were distinctly visible. In the ^{1}H NMR spectrum, the two doublets located at 6.39 ppm (J = 7.4 Hz) and 6.71 ppm (J = 8.2 Hz) integrating for one proton observed due to NH proton adjacent to cyclohexyl ring. A singlet at 2.05 ppm integrating for three protons attributed to the methyl group of pyrrolinone moiety.

Scheme 7



Towards the end, our attention turned to deprotection of the PMB group and to separate the *cis*- and *trans*-mixture in order to complete the total synthesis of **9a** and **9b**. For this endeavor, **28** was treated with DDQ[36] in aqueous CH_3CN but produced a number of compounds which were difficult to separate. At this stage, the deprotection of the PMB group turned to be difficult. However, the best result for the deprotection was obtained when **28** was exposed to BF_3:OEt_2 in CH_2Cl_2 at 0 ^{o}C giving a mixture of *cis* (**9a**) and *trans* (**9b**) hydroxyglimepiride (Scheme 8). Finally, the separation of *cis*- and *trans*-mixture was accomplished by preparative HPLC under specific conditions (mobile phase, 40:60 CH_3CN : pH=3 buffer) using ODS column.[37] Based on the comparison of their ^{1}H and ^{13}C NMR spectroscopic data with that of authentic glimepiride (**8**), the structures for the *cis* (**9a**) and *trans* (**9b**) of hydroxyglimepiride were assigned. For instance, compound **9b** showed in its ^{1}H NMR spectrum a doublet (J = 7.6 Hz) at 6.43 ppm which was compatible with glimepiride (**8**) and confirmed the *trans*-stereochemistry. Compound **9a** showed a doublet (J = 8.5 Hz) at 6.71 ppm and confirmed the *cis*-stereochemistry. The FAB mass spectrum displayed peaks at *m*/*z* 529 and 507 attributed to the (M^{+}+Na) and (M^{+}+1) ions respectively.

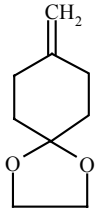
Scheme 8



In conclusion, we have successfully synthesized the *cis* (**9a**) and *trans* (**9b**) of hydroxyglimepiride using a very straightforward method. It is pertinent to mention that to the best of our knowledge deprotection of a PMB group with BF_3:OEt_2 is being reported for the first time.

Experimental

8-Methylene-1,4-dioxa-spiro [4.5] decane (18)



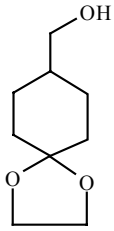
To a solution of **17** (5 g, 32.0 mmol) in anhydrous THF (25 mL) at –78 ^{o}C, methylenetriphenylphosphorane [prepared from PPh_3CH_3I (25.9 g) and *n*BuLi (1.6 M, 4.0 mL)] was added dropwise. After 1.5 h stirring at rt, it was quenched by addition of saturated aqueous solution of NH_4Cl. The two layers 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 **18** (3.95 g, 80%) as a colorless oil.

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.69 (t, 4 H, *J* = 5.3 Hz), 2.28 (t, 4 H, *J* = 5.3 Hz), 3.96 (s, 4 H), 4.66 (s, 2 H);

Anal. Calcd for $C_9H_{14}O_2$ (Mol. Wt. 154.209): C, 70.10; H, 9.15. Found; C, 69.93; H, 9.41.

.

(1,4-Dioxa-spiro [4.5] dec-8-yl)-methanol (19)



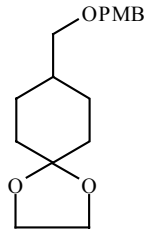
To a solution of **18** (3.8 g, 24.7 mmol) in anhydrous THF (10 mL) at 0 ^{o}C was added $H_3B{:}SMe_2$ (2 M, 18.5 mL, 37.0 mmol). After stirring for 1 h, saturated NaOAc solution was introduced followed by the addition of 30% H_2O_2 (5.6 mL). The reaction mixture was further stirred at rt for 5 h, diluted with EtOAc, the organic layer separated, dried (Na_2SO_4) and concentrated. The crude was purified on silica gel using EtOAc-light petroleum ether (1:4) to provide **19** (3.18 g, 75%) as a thick liquid.

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.20-1.36 (m, 2 H), 1.44-1.62 (m, 3 H), 1.73-1.82 (m, 4 H), 3.47 (d, 2 H, *J* = 6.0 Hz), 3.93 (s, 4 H);

^{13}C NMR (50 MHz, $CDCl_3$): δ 26.5 (2C), 33.9 (2C), 38.8, 63.9 (2C), 67.1, 108.9;

Anal. Calcd for $C_9H_{16}O_3$ (Mol. Wt. 172.224): C, 62.77; H, 9.36. Found; C, 62.52; H, 9.31.

8-(4-Methoxy-benzyloxymethyl)-1,4-dioxa-spiro [4.5] decane (20)



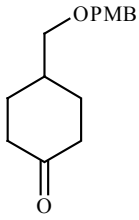
Compound **19** (3.0 g, 17.4 mmol) in DMF (10 mL) was added to a stirred suspension of NaH (1.4 g, 60% dispersion in oil, 34.8 mmol) in DMF (5 mL) at 0 ^{o}C. The resulting solution was stirred at rt for 30 min, PMB-Br (4.2 g, 20.9 mmol) in DMF (5 mL) was added. After 1 h, the reaction was quenched by ice-cold water and extracted with EtOAc. The combined organic layers were washed with water, dried (Na_2SO_4) and concentrated. The residue was purified on silica gel using EtOAc-light petroleum ether (1:19) to obtain **20** (4.18 g, 82%) as a thick liquid.

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.20-1.95 (m, 9 H), 3.29 (d, 2 H, *J* = 6.2 Hz), 3.83 (s, 3 H), 3.95 (s, 4 H), 4.44 (s, 2 H), 6.89 (d, 2 H, *J* = 8.4 Hz), 7.27 (d, 2 H, *J* = 8.4 Hz);

^{13}C NMR (50 MHz, $CDCl_3$): δ 26.7 (2C), 33.7 (2C), 36.4, 58.6, 63.7 (2C), 72.2, 74.5, 108.5, 113.3, 128.6, 130.4, 158.7;

Anal. Calcd for $C_{17}H_{24}O_4$ (Mol. Wt. 292.375): C, 69.84; H, 8.27. Found; C, 69.66; H, 8.51.

4-(4-Methoxy-benzyloxymethyl)-cyclohexanone (16)



A solution of **20** (4.0 g, 13.7 mmol), 0.8% H_2SO_4 (3 mL) in MeOH (15 mL) was stirred at rt for 30 min, neutralized with solid $NaHCO_3$, filtered and concentrated. The residue was partitioned between EtOAc-water, the organic layer dried (Na_2SO_4), concentrated and

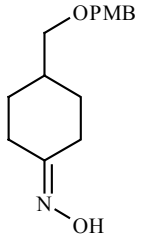
chromatographed on silica gel using EtOAc-light petroleum ether (3:17) to furnish **16** (2.99 g, 88%) as a colorless syrup.

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.35-1.57 (m, 2 H), 1.97-2.41 (m, 7 H), 3.35 (d, 2 H, *J* = 5.9 Hz), 3.81 (s, 3 H), 4.45 (s, 2 H), 6.87 (d, 2 H, *J* = 7.5 Hz), 7.24 (d, 2 H, *J* = 7.5 Hz);

^{13}C NMR (50 MHz, $CDCl_3$): δ 29.4 (2C), 36.4, 40.2 (2C), 57.8, 72.7, 73.8, 113.7, 129.0, 130.3, 159.1, 211.5;

Anal. Calcd for $C_{15}H_{20}O_3$ (Mol. Wt. 248.322): C, 72.55; H, 8.12. Found; C, 72.41; H, 8.37.

4-(4-Methoxy-benzyloxymethyl)-cyclohexanone oxime (21)

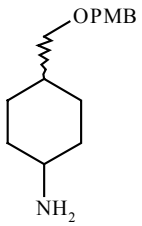


A solution of **16** (2.8 g, 11.3 mmol), Py (1.3 mL, 17.0 mmol), $NH_2OH.HCl$ (1.2 g, 17.0 mmol) in EtOH (20 mL) was heated under reflux for 2 h and concentrated. The residue partitioned between EtOAc and water, the organic layer separated, dried (Na_2SO_4) and concentrated. The residue was purified on silica gel using EtOAc-light petroleum ether (1:3) to provide **21** (2.38 g, 80%).

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.12-1.29 (m, 3 H), 1.74-2.20 (m, 5 H), 2.40-2.55 (m, 1 H), 3.29 (d, 2 H, *J* = 6.5 Hz), 3.82 (s, 3 H), 4.44 (s, 2 H), 6.87 (d, 2 H, *J* = 7.4 Hz), 7.25 (d, 2 H, *J* = 7.4 Hz);

Anal. Calcd for $C_{15}H_{21}NO_3$ (Mol. Wt. 263.337): C, 68.36; H, 8.04; N, 5.32. Found; C, 68.16; H, 7.84; N, 5.11.

4-(4-Methoxy-benzyloxymethyl)-cyclohexylamine (22)



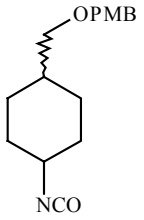
Compound **21** (2.2 g, 8.4 mmol) in THF (5 mL) was added to a stirred solution of LAH (0.32 g, 8.4 mmol) in THF (15 mL) and heated under reflux for 2 h. The excess LAH was quenched with saturated solution of Na_2SO_4 and filtered and the residue thoroughly washed with EtOAc. The filtrate was concentrated and purified on neutral silica gel using MeOH-Et_3N EtOAc (1:1:8) to obtain **22** (1.46 g, 70%).

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.01-1.30 (m, 2 H), 1.48-1.72 (m, 3 H), 1.80-2.05 (m, 5 H), 3.29 and 3.38 (d, 2 H, *J* = 6.1 Hz), 3.87 (s, 3 H), 4.43 and 4.47 (s, 2 H), 6.91 (d, 2 H, *J* = 8.0 Hz), 7.25 (d, 2 H, *J* = 8.0 Hz);

MS: 249 (M^+), 234 (M^+–15);

Anal. Calcd for $C_{15}H_{23}NO_2$ (Mol. Wt. 249.354): C, 72.25; H, 9.30; N, 5.62. Found; C, 72.05; H, 9.11; N, 5.39.

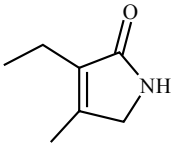
1-(4-Isocyanato-cyclohexylmethoxymethyl)-4-methoxy-benzene (12)



$COCl_2$ gas was bubbled through the $C_6H_5CH_3$ (15 mL) at 0 ^oC until saturation (10 g) and a solution of **22** (1.3 g, 5.2 mmol) in $C_6H_5CH_3$ (5 mL) added dropwise. The reaction mixture was heated to reflux for 7 h and concentrated to provide the crude **12** (1.34 g, 93%), which was used for the next reaction without further purification.

IR: 2262, 1604, 1494, 1247, 1080, 729 cm^{-1}.

3-Ethyl-4-methyl-1,5-dihydro-pyrrol-2-one (14)



A solution of **25** (1.0 g, 6.0 mmol) and Na_2CO_3 (0.8 g, 7.2 mmol) in H_2O (10 mL) was heated under reflux for 4 h, extracted with EtOAc, dried (Na_2SO_4) and concentrated. The residue was

purified on silica gel using EtOAc-light petroleum ether (3:7) to furnish **14** (0.68 g, 90%) as a white solid.

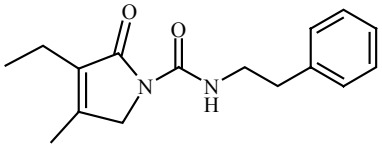
M.P. 98 ^{o}C; lit.,[35b] M.P. 102 ^{o}C;

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.06 (t, 3 H, *J* = 7.6 Hz), 1.97 (s, 3 H), 2.26 (q, 2 H, *J* = 7.6 Hz), 3.79 (s, 2 H), 7.33 (br s, 1 H);

^{13}C NMR (125 MHz, $CDCl_3$): δ 12.6, 12.8, 16.2, 49.9, 133.7, 148.5, 176.2;

Anal. Calcd for $C_7H_{11}NO$ (Mol. Wt. 125.171): C, 67.17; H, 8.85; N, 11.19. Found; C, 67.01; H, 8.91; N, 10.92.

3-Ethyl-4-methyl-2-oxo-2,5-dihydro-pyrrole-1-carboxylic acid phenethyl-amide (26)



A solution of **14** (0.5 g, 4.0 mmol) and **13** (0.59 g, 4.0 mmol) in $C_6H_5CH_3$ (10 mL) was heated under reflux for 3 h, the solvent evaporated and the residue recrystallized from EtOAc and hexane to obtain **26** (0.7 g, 65%) as a white crystalline solid.

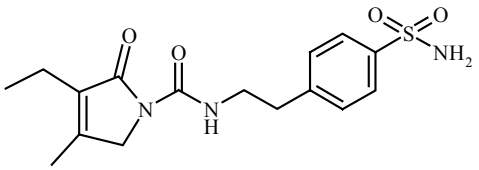
M.P. 101 ^{o}C; lit.,[35a] M.P. 104 ^{o}C;

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.06 (t, 3 H, *J* = 7.5 Hz), 2.04 (s, 3 H), 2.27 (q, 2 H, *J* = 7.5 Hz), 2.88 (t, 2 H, *J* = 6.5 Hz), 3.57 (q, 2 H, *J* = 6.4 Hz), 4.18 (s, 2 H), 7.21-7.32 (m, 5 H), 8.43 (t, 1 H, *J* = 6.2 Hz);

^{13}C NMR (125 MHz, $CDCl_3$): δ 12.7, 13.0, 16.5, 36.0, 41.1, 52.0, 126.2, 128.4, 128.6, 133.7, 138.8, 150.0, 152.4, 172.3;

Anal. Calcd for $C_{16}H_{20}N_2O_2$ (Mol. Wt. 272.348): C, 70.56; H, 7.40; N, 10.28. Found; C, 70.58; H, 7.54; N, 10.38.

3-Ethyl-4-methyl-2-oxo-2,5-dihydro-pyrrole-1-carboxylic acid[2-(4-sulfamoyl-phenyl)-ethyl]-amide (11)



To a solution of **26** (0.5 g, 1.84 mmol) in $CHCl_3$ (5 mL) at 10 ^oC was added $ClSO_3H$ (0.15 mL, 2.2 mmol). After stirring for 6 h, water was added, the organic layer separated and the aqueous layer extracted with EtOAc. The combined organic layers were dried (Na_2SO_4) and concentrated to provide crude **27** (0.62 g) which was dissolved in concentrated NH_4OH solution and heated at 60 ^oC for 12 h. The reaction mixture was extracted with EtOAc, dried (Na_2SO_4), concentrated and recrystallized from EtOAc and hexane to obtain **11** (0.51 g, 80%) as a white solid.

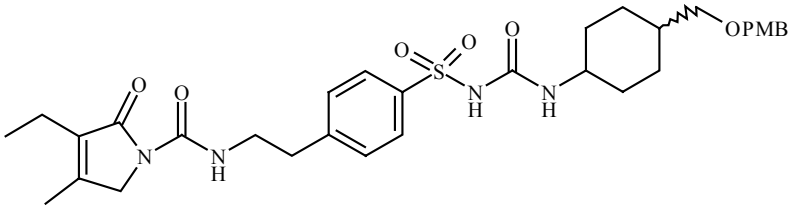
M.P. 175 ^oC; lit.,[35a] M.P. 176 ^oC;

^{1}H NMR (200 MHz, Acetone-d_6): δ 1.02 (t, 3 H, *J* = 7.6 Hz), 2.08 (s, 3 H), 2.24 (q, 2 H, *J* = 7.6 Hz), 2.97 (t, 2 H, *J* = 6.7 Hz), 3.58 (q, 2 H, *J* = 6.6 Hz), 4.17 (s, 2 H), 6.54 (br s, 2 H), 7.46 (d, 2 H, *J* = 8.2 Hz), 7.83 (d, 2 H, *J* = 8.2 Hz), 8.44 (t, 1 H, *J* = 6.3 Hz);

^{13}C NMR (50 MHz, DMSO-d_6): δ 12.8, 13.0, 16.2, 35.4, 40.9, 52.1, 126.0, 129.3, 132.3, 142.4, 143.6, 152.0, 152.2, 154.8, 172.1;

Anal. Calcd for $C_{16}H_{21}N_3O_4S$ (Mol. Wt. 351.423): C, 54.68; H, 6.02; N, 11.96; S, 9.12. Found; C, 54.84; H, 6.06; N, 12.09; S, 9.22.

PMB protected hydroxyglimepiride (28)



A solution of **11** (1.26 g, 3.6 mmol) and K_2CO_3 (0.6 g, 4.3 mmol) in CH_3COCH_3 (15 mL) was heated under reflux for 1.5 h and then **12** (1.0 g, 3.6 mmol) in CH_3COCH_3 (5 mL) was added dropwise. After 8 h, the reaction mixture was evaporated, partitioned between EtOAc and water, the organic layer dried (Na_2SO_4), concentrated and chromatographed on silica gel using MeOH-$CHCl_3$ (1:19) to furnish **28** (1.82 g, 80%).

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.10 (t, 3 H, *J* = 6.4 Hz), 1.20-1.91 (m, 9 H), 2.05 (s, 3 H), 2.20-2.35 (m, 2 H), 2.88-3.05 (m, 2 H), 3.17-3.31 (m, 2 H), 3.50-3.67 (m, 2 H), 3.84 (s, 3 H), 4.21 (s, 2 H), 4.45 (d, 2 H, *J* = 10 Hz), 6.39 (d, *J* = 7.4 Hz) and 6.71 (d, *J* = 8.2 Hz) for 1 H,

6.80-6.91 (m, 2 H), 7.15-7.29 (m, 2 H), 7.39 (d, 2 H, *J* = 8.2 Hz), 7.81 (d, 2 H, *J* = 8.2 Hz), 7.90-8.08 (m, 1 H), 8.40-8.56 (m, 1 H);

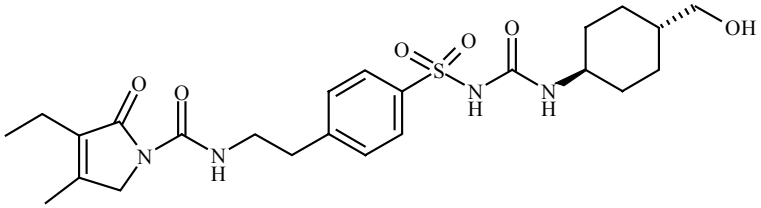
^{13}C NMR (50 MHz, $CDCl_3$): δ 8.5, 12.8, 13.1, 16.6, 24.7, 28.7, 29.4, 29.9, 36.0, 36.4, 45.4, 49.5, 52.2, 55.3, 72.7, 74.5, 75.3, 113.7, 127.0, 127.2, 129.1, 130.7, 133.8, 140.0, 143.9, 150.4, 152.6, 154.0, 159.1, 172.5;

Anal. Calcd for $C_{32}H_{42}N_4O_7S$ (Mol. Wt. 626.771): C, 61.32; H, 6.75; N, 8.94; S, 5.12. Found; C, 61.09; H, 6.94; N, 8.92; S, 4.88.

***cis*- and *trans*-Hydroxyglimepiride (9a and 9b)**

To a solution of **28** (0.5 g, 0.8 mmol) in anhydrous CH_2Cl_2 (8 mL) at 0 ^oC was added BF_3:OEt_2 (0.1 mL). After 1.5 h, the reaction mixture was neutralized with Et_3N and concentrated. The residue was partitioned between EtOAc-water, the organic layer dried (Na_2SO_4), concentrated and chromatographed on silica gel with EtOAc-light petroleum ether (4:1) to provide *cis*- and *trans*-hydroxyglimepiride (**9a + 9b**) (0.26 g, 65%). The mixture of *cis*- and *trans*-isomers was separated by preparative HPLC under specific conditions (mobile phase, 40:60 CH_3CN : pH=3 buffer) using ODS column.

***trans*-Hydroxyglimepiride (9b)**



^{1}H NMR (200 MHz, $CDCl_3$): δ 1.04 (t, 3 H, *J* = 6.5 Hz), 1.15-1.31 (m, 4 H), 1.50-2.01 (m, 5 H), 2.04 (s, 3 H), 2.28 (q, 2 H, *J* = 6.5 Hz), 2.94 (t, 2 H, *J* = 6.7 Hz), 3.42 (d, 2 H, *J* = 6.7 Hz), 3.53-3.63 (m, 3 H), 4.18 (s, 2 H), 6.43 (d, 1 H, *J* = 7.6 Hz), 7.39 (d, 2 H, *J* = 8.3 Hz), 7.83 (d, 2 H, *J* = 8.3 Hz), 8.52 (t, 1 H, J = 6.4 Hz);

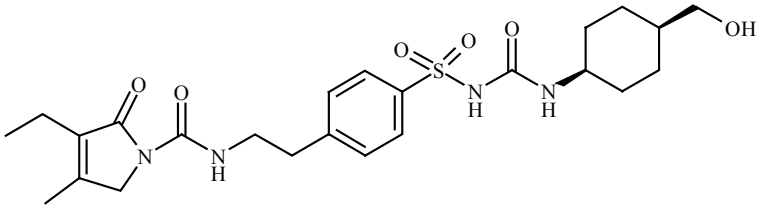
^{13}C NMR (125 MHz, $CDCl_3$): δ 12.8 (2C), 13.1, 16.7 (2C), 28.1, 32.5, 36.2, 39.5, 41.0, 49.7, 52.3, 67.8, 127.4, 129.6, 133.9, 138.1, 145.5, 150.8, 152.7, 172.5;

IR: 2924, 1700, 1684, 1540, 1280, 1161, 898 cm^{-1};

FAB MS: 529 (M^++Na), 507 (M^++1);

Anal. Calcd for $C_{24}H_{34}N_4O_6S$ (Mol. Wt. 506.624): C, 56.90; H, 6.76; N, 11.06; S, 6.33. Found; C, 56.73; H, 6.51; N, 10.82; S, 6.06.

***cis*-Hydroxyglimepiride (9a)**



^{1}H NMR (500 MHz, $CDCl_3$): δ 1.06 (t, 3 H, *J* = 6.4 Hz), 1.50-1.65 (m, 7 H), 1.68-1.77 (m, 2 H), 2.05 (s, 3 H), 2.27 (q, 2 H, *J* = 6.4 Hz), 2.97 (t, 2 H, *J* = 6.3 Hz), 3.51 (d, 2 H, *J* = 6.3 Hz), 3.62 (dd, 2 H, *J* = 7.8, 14.1 Hz), 3.87-3.93 (m, 1 H), 4.19 (s, 2 H), 6.71 (d, 1 H, *J* = 8.5 Hz), 7.41 (d, 2 H, *J* = 8.3 Hz), 7.87 (d, 2 H, *J* = 8.3 Hz), 8.52 (t, 1 H, J = 6.9 Hz);

^{13}C NMR (125 MHz, $CDCl_3$): δ 12.7, 13.1, 16.6, 24.0 (2C), 29.3 (2C), 36.1, 38.8, 40.5, 46.2, 52.2, 67.2, 127.3, 129.7, 133.9, 138.0, 145.6, 150.5, 152.6, 172.6;

Anal. Calcd for $C_{24}H_{34}N_4O_6S$ (Mol. Wt. 506.624): C, 56.90; H, 6.76; N, 11.06; S, 6.33. Found; C, 56.77; H, 6.94; N, 11.21; S, 6.09.

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LIST OF PUBLICATIONS

1. A stereoselective synthesis of the C13-C19 fragment of sanglifehrin A. Gurjar, M. K.; **Ray Chaudhuri, S.** *Tetrahedron Lett.* **2002**, *43,* 2435.

2. Total synthesis of *cis* and *trans*-hydroxyglimepiride: an active metabolite of glimepiride. Gurjar, M. K.; Joshi, R. A.; **Ray Chaudhuri, S.**; Joshi, S. V.; Barde, A. R.; Gediya, L. K.; Ranade, P. V.; Kadam, S. M.; Naik, S. J. *Tetrahedron Lett.* **2003**, *44*, 4853.