A Sugar Alkynol Cycloisomerization Approach Towards the Total Synthesis of Aflastatin A, Zooxanthellamide D; and Synthesis of some C-Glycosyl Analogues of β-DPA as Novel Antitubercular Agents

Thesis
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By

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December - 2012

Dedicated

To

My Beloved Parents

&

Teachers

Declaration

The research work embodied in this thesis has been carried out at National Chemical Laboratory, Pune under the supervision of **Dr. C. V. Ramana**, Organic Chemistry Division, CSIR–National Chemical Laboratory, Pune – 411008. This work is original and has not been submitted in part or full, for any degree or diploma of this or any other university.

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December - 2012

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Certificate

The research work presented in thesis entitled ***"A Sugar alkynol cycloisomerization approach towards the total synthesis of Aflastatin A, Zooxanthellamide D; and synthesis of some C-glycosyl analogues of β-DPA as novel antitubercular agents"*** has been carried out by **Mr. Sachin B. Narute** under my supervision. This work is original and has not been submitted for any other degree or diploma of this or any other University.

Pune - 411008
December - 2012

Dr. C. V. Ramana
(Research Supervisor)

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As I complete my journey to the most cherished dream, it gives me immense pleasure and sense of satisfaction to record my heartfelt gratitude to all those persons who have made this possible for me.

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wife, for her love, affection and support extended to me during last 1.5 years. She has brought a great deal of happiness and positive change to my life. Also I am really grateful to have very big chiller party - Rahul, Nikita, Poonam, Rohit, Amol, Gauri, Nikhil, Arti, Vicky, Akash and Pooja as family members who brought everlasting cheerfulness in my life.

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Sachin B. Narute

Definition and Abbreviations

Ac	–	Acetyl
Ac_2O	–	Acetic anhydride
AcOH	–	Acetic acid
Bu	–	Butyl
Bn	–	Benzyl
Bz	–	Benzoyl
Cat.	–	Catalytic/catalyst
DCM	–	Dichloromethane
Conc.	–	Concentrated
COSY	–	Correlation spectroscopy
DIAD	–	Diisopropyl azodicarboxylate
DMP	–	2,2'-Dimethoxypropane
DMF	–	*N*,*N*-Dimethylformamide
DMAP	–	*N*,*N*'-Dimethylaminopyridine
DMSO	–	Dimethyl sulfoxide
EtOAc	–	Ethyl acetate
HRMS	–	High Resolution Mass Spectrometry
LDA	–	Lithium diisopropylamide
Liq.	–	Liquid
m-CPBA	–	3-Chloroperbenzoic acid
Ms/Mesyl	–	Methanesulfonyl
Me	–	Methyl
MIC	–	Minimum Inhibitory Concentration
NIS	–	*N*-iodosuccinamide
NMR	–	Nuclear Magnetic Resonance
NOESY	–	Nuclear Overhauser effect spectroscopy
Py	–	Pyridine
p-TSA	–	*para*-Toluenesulfonic acid
Ph	–	Phenyl
i-PrOH	–	*iso*-Propanol

rt	–	Room temperature
Sat.	–	Saturated
TBS	–	*tert*-Butyldimethylsilyl
TBAB	–	Tetra-*n*-butylammonium bromide
TBAF	–	Tetra-*n*-butylammonium fluoride
THF	–	Tetrahydrofuran
TMSOI	–	Trimethylsulfoxonium iodide
TMSOTf	–	Timethylsilyl trifluromethanesulfonate
TPP	–	Triphenylphosphine

Abbreviations used for NMR spectral informations:

br	Broad	q	Quartet
d	Doublet	s	Singlet
m	Multiplet	t	Triplet

General Remarks

- All reactions were carried out under nitrogen or argon atmosphere with dry and/or freshly distilled solvents under anhydrous conditions unless otherwise specified. Yields refer to chromatographically and spectroscopically homogeneous materials unless otherwise stated.

- All reactions are monitored by Thin Layer Chromatography (TLC) carried out on 0.25 mm E-Merck silica gel plates (60F–254) with UV light, I_2, and anisaldehyde in ethanol as developing agents.

- All evaporations were carried out under reduced pressure on Büchi rotary evaporator below 45 °C unless otherwise specified.

- Silica gel (60–120), (100–200), and (230–400) mesh were used for column chromatography.

- The melting points are uncorrected and the temperatures are in the degree centigrade scale.
- Optical rotations were measured with a JASCO DIP 370 digital polarimeter.

- 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}.

- ^{1}H NMR spectra were recorded on AV–200 MHz, AV–400 MHz, and DRX–500 MHz spectrometer using tetramethylsilane (TMS) as an internal standard. Chemical shifts have been expressed in ppm units downfield from TMS.

- ^{13}C NMR spectra were recorded on AV–50 MHz, AV–100 MHz, and DRX–125 MHz spectrometer.
- EI Mass spectra were recorded on Finngan MAT–1020 spectrometer at 70 *eV* using a direct inlet system.

- HRMS were recorded on PI QStar Pulsar (Hybrid Quadrupole-TOF LC/MS/MS) and 4800 plus MALDI TOF/TOF Applied Biosystem spectrometer.

- Elemental analysis data were obtained on a Thermo Finnigan Flash EA 1112 Series CHNS Analyzer.

Contents

ABSTRACT

Abstract

The thesis entitled "*A Sugar alkynol cycloisomerization approach towards the total synthesis of Aflastatin A, Zooxanthellamide D; and synthesis of some C-glycosyl analogues of β-DPA as novel antitubercular agents*" consist of three chapters. The first chapter deals with the studies toward the synthesis of aflastatin A. In the next chapter, the preliminary investigations aiming the synthesis of C(11)–C(21) fragment of zooxanthellamide D which have ultimately led to the development of a new approach for the synthesis of carba-disacchaides of nonreducing sugars has been described. A stereoselective synthesis of β-*C*-allyl/ and β-*C*-propargyl-D-arabinofuranosides along with the synthesis and bilogical activity of some traizaoles derived from the CuAAc reaction of β-*C*-propargyl-D-arabinofuranoside form the main content of the last chapter.

Chapter I: Studies toward the synthesis of C(27)–C(48) fragment of aflastatin A:

Aflastatin A (**1**) was isolated by Sakuda and co-workers from the mycelia of *Streptomyces* species MRI 142. It belongs to the class of polyol natural products and contains a tetramic acid derivative with a highly oxygenated long alkyl side chain, as well as a tetrahydropyran ring. Aflastatin A exhibits strong inhibitory activity against aflatoxin production. The groups of Evans and McDonald have reported the synthesis of the C(9)–C(27) fragment of aflastatin A. In this chapter, we have provided our detailed investigations aimed at the synthesis of the C(27)–C(48) fragment of aflastatin A.

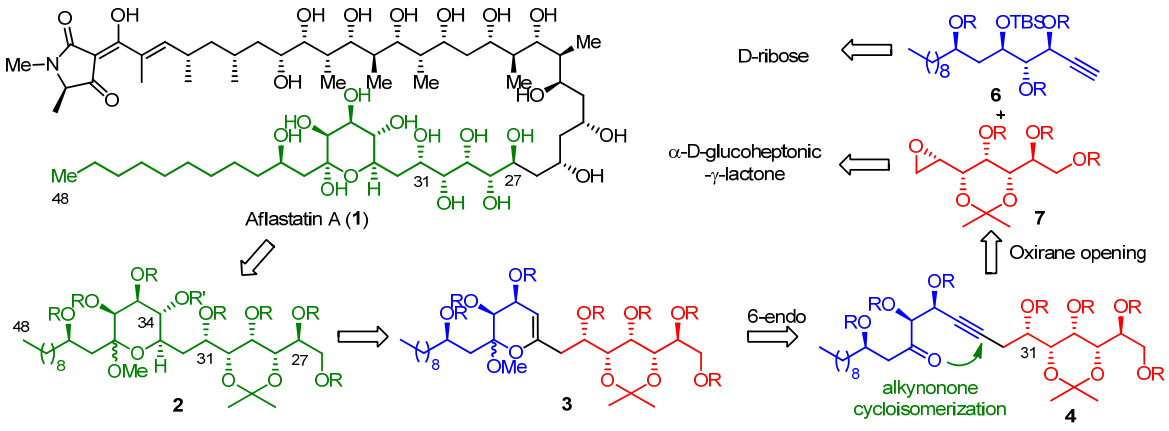


Figure 1. *Retrosynthetic disconnections for protected C(27)–C(48) fragment of aflastatin A*

Figure 1 shows our retrosynthetic approach toward the protected C(27)–C(48) fragment **2** of aflastatin A. Stereoselective hydroboration-oxidation of glycal **3** and metal mediated cycloisomerization on alkynone intermediate **4** were envisioned as the key transformations. We planned to synthesize alkynone **4** by employing the alkyne-epoxide cross coupling reaction.

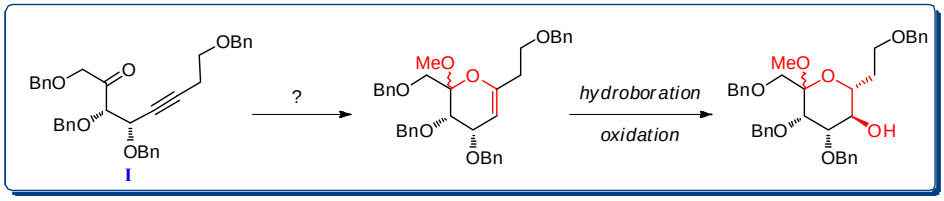
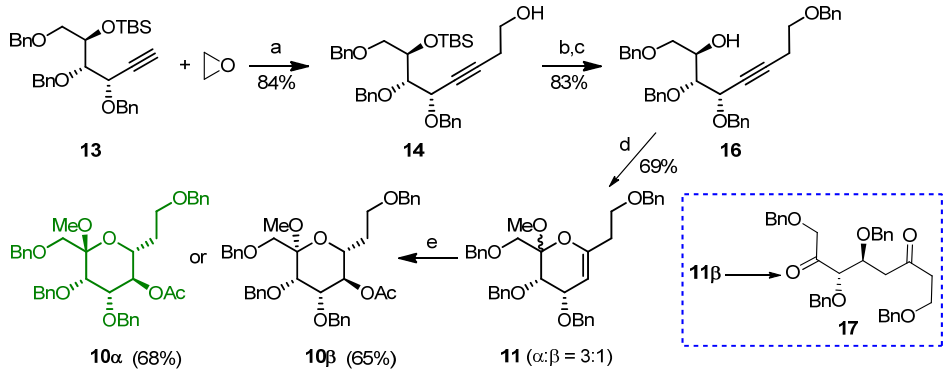


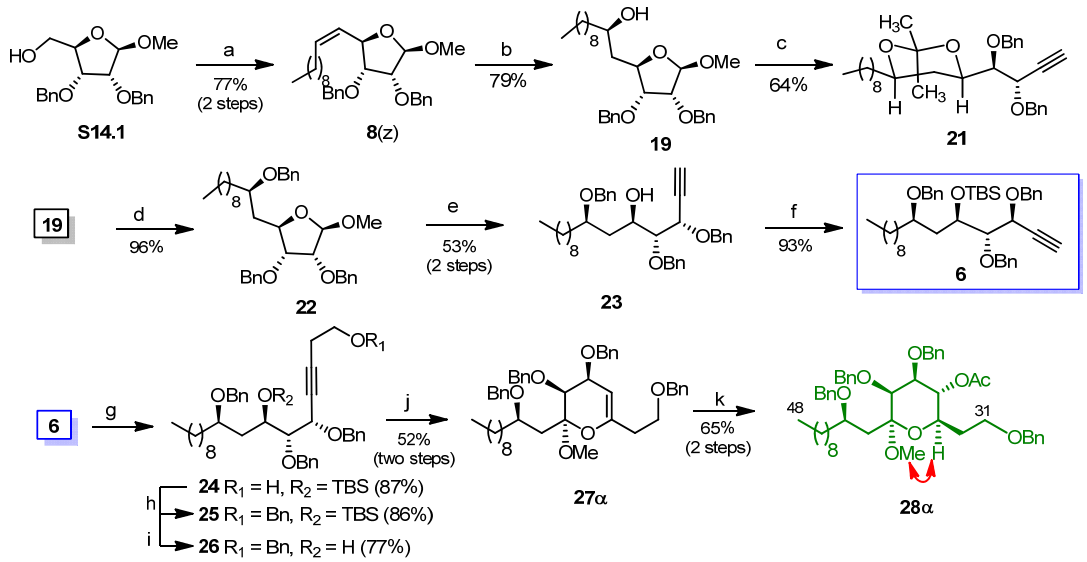
Figure 2. *Intended model alkynone for identifying the optimizing the cycloisomerization reaction*

Model Studies: Our initial efforts in this context started with examining the feasibility of alkynone cycloisomerization by employing a simple alkynone **I** as a model substrate (Figure 2). The synthesis of the model alkynone I started with the preparation of alkyne **13** from D-ribose followed by its coupling with ethylene oxide to produce the alcohol **14**. The free hydroxyl group was then protected as its benzyl ether **15**. Subsequent removal of the TBS group followed by oxidation of the resulting alkynol **16** with IBX gave the intermediate alkynone **I**. After screening various reported procedures, we found that the key cycloisomerization of crude **I** can be affected by employing $Pd(OAc)_2$ in methanol to obtain the glycals **11α** and **11β** in 3:1 proportion. During the NMR analysis, compound **11β** was found to be hydrolyzed to give dione **17**. Subsequent hydroboration of glycals **11α** and **11β** followed by acetylation gave the model compounds **10α** along with its epimer **10β**.



Scheme 1. *Reagents and conditions:* a) *n*-BuLi, $BF_3.Et_2O$, THF, –78 °C; b) NaH, BnBr DMF, rt, 2 h; c) TBAF, THF, rt, 4 h; d) i. IBX, EtOAc, reflux, 3 h; ii. $Pd(OAc)_2$, MeOH, rt, 2 h; e) i. BH_3.DMS,THF, 0 °C, H_2O_2, (30%) then 3N NaOH, rt, 8 h; ii. Ac_2O, Py, rt, 3 h.

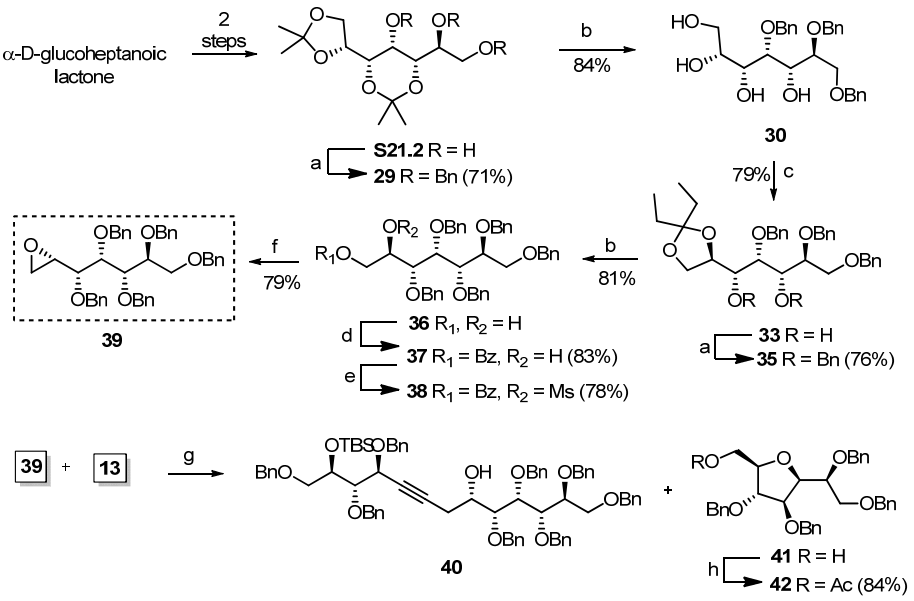
Synthesis of C(31)–C(48) fragment of aflastatin A: After having established the key cycloisomerization – hydroboration sequence for constructing the central pyran core, we next proceeded for the synthesis of the C(31)–C(48) fragment of aflastatin A. Our journey in this context started with the synthesis of the key alkyne intermediate **6**. The known ribose derived intermediate **S14.1** was subjected for Swern oxidation followed by Wittig olefination to obtain the alkene **8**. The regioselective Wacker oxidation of alkene **8** followed by the 1,3-syn reduction of the intermediate ketone delivered alcohol **19** (the stereochemistry was fixed by converting **19** into acetonide **21)**. Then, protection of the free hydroxyl group in **19** as its benzyl ether **22** followed by Ohira-Bestmann alkynylation and subsequent TBS protection delivered the alkyne **13**. The coupling of alkyne **13** with ethylene oxide gave the alcohol **24**, which after benzylation and TBS ether deprotection, delivered the key alkynol intermediate **26**. The alkynol thus obtained was subjected for oxidation followed by cycloisomerization to get the glycal **27α** which, after hydroboration oxidation and the acetylation of the resulting hydroxyl group delivered the protected C(31)–C(48) fragment **28α** of aflastatin A.



Scheme 2. *Reagents and conditions*: a) i) $(COCl)_2$, DMSO, Et_3N, DCM, –78 °C; ii) (*n*-decyl)$PPh_3^+Br^-$, *n*-BuLi, THF, 0 °C→rt; b) i) $PdCl_2$, DMA, H_2O, O_2, 90 °C, 12 h; ii) LiI, LAH, Et_2O, -100 °C, 45 min; c) i) HCl, *t*-BuOH:H_2O, reflux, 6 h; ii) Ohira-Bestmann reagent, K_2CO_3, MeOH, rt, 7 h; iii) *p*-TSA, DMP, 0 °C→rt, 2 h; d) NaH, BnBr, DMF, rt, 4 h; e) i) HCl, *t*-BuOH:H_2O, reflux, 7 h; ii) Ohira-Bestmann reagent, K_2CO_3, MeOH, rt, 9 h; f) TBSOTf, Et_3N, DCM, 0 °C, 2 h; g) *n*-BuLi, $BF_3.Et_2O$, ethylene oxide THF, –78 °C; h) NaH, BnBr, DMF, rt, 2 h; i) TBAF, THF, rt, 4h; j) i. IBX, EtOAc, reflux, 3 h; ii. $Pd(OAc)_2$, MeOH, rt, 2 h; k) i. BH_3.DMS,THF, 0 °C, 30% H_2O_2, 3N NaOH, rt, 8 h; ii. Ac_2O, Py, CH_2Cl_2, 3 h.

In order to address whether the observed α-anomeric selectivity was apparent due to the hydrolysis of the corresponding β-anomer during the isolation, oxidation, cyclization, hydroboration-oxidation and aacetylation was carried out on alkynol **26** to afford the separable mixture of acetates **28α** and **28β** in 6:1 proportion with 31% overall yield.

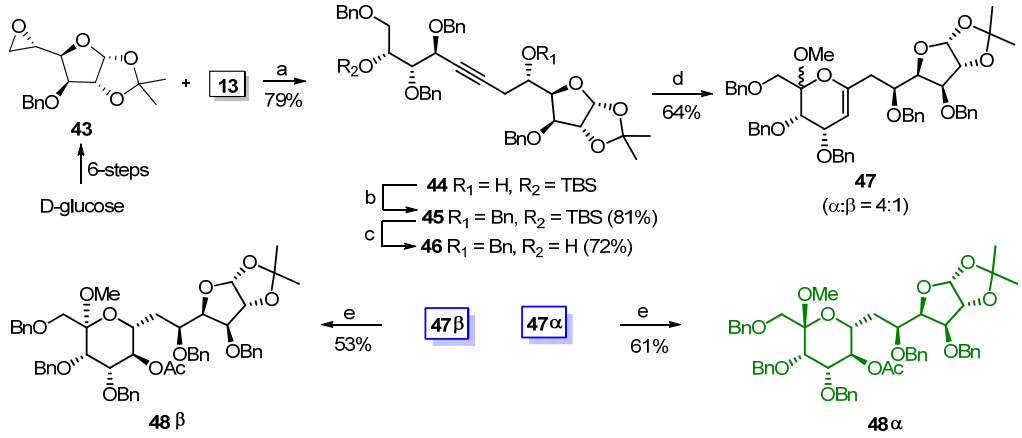
Synthesis of C(27)–(38) fragment of aflastatin A: Having synthesized the C(31)–C(48) fragment of aflastatin A, our next concern was the synthesis of the C(27)–C(48) fragment of aflastatin A by employing the epoxide **7** in place of the ethylene oxide.



Scheme 3. *Reaegnts and conditions:* a) NaH, BnBr, DMF, rt; b) 0.8% H_2SO_4, MeOH, rt; c) H_2SO_4, 3-pentanone, 0 °C; d) BzCl, TEA, DCM, 0 °C, 4 h; e) MsCl, TEA, DCM, 0 °C→rt; f) LiOH.H_2O, MeOH:THF; g) *n*-BuLi, $BF_3.Et_2O$, THF, –78 °C; h) Ac_2O, Py, rt.

The synthesis of the epoxide fragment was begun with the synthesis of benzyl ether **29** from a known triol **S21.1**. Complete acetonide hydrolysis to get tetraol **30**, followed by selective protection of terminal 1,2-doil and subsequent benzylation of hydroxyl groups delivered the compound **35** in good yield. The acid hydrolysis of **35** followed by selective protection of the primary hydroxyl group afforded compound **37**, which after mesylation of secondary hydroxyl group and subsequent treatment with LiOH delivered the epoxide **39** at an overall good yield. In order to optimize the reaction conditions, the epoxide **39** was treated with model alkyne **13** under basic conditions, which lead to the isolation of the undesired **41** as the major product (which was converted to the corresponding acetate **42** for the purpose of characterization) along with the

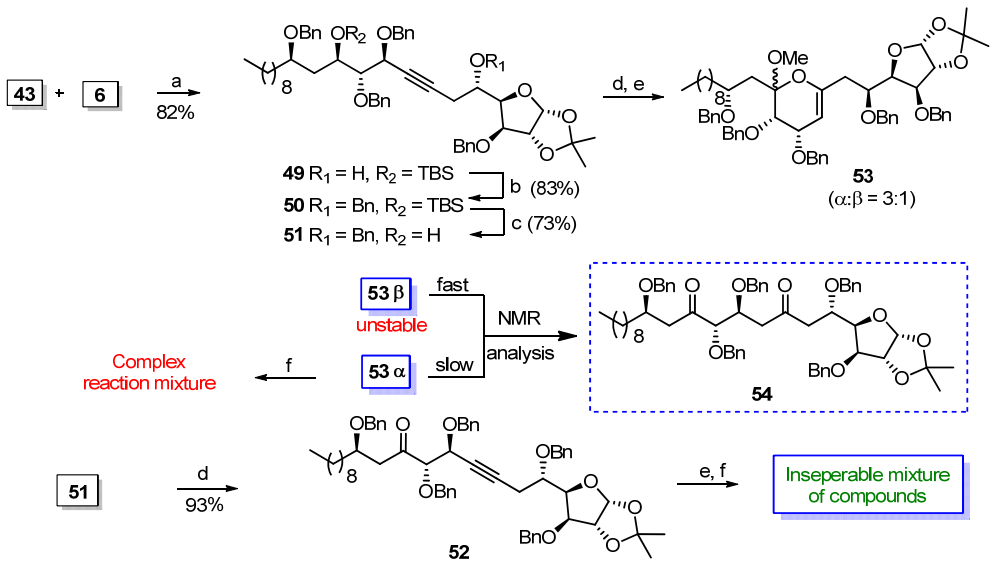
required product **40** in <5% yield. All unsuccessful attempts for epoxide opening led us to replace the epoxide **39** with **43** in order to avoid the side reaction.



Scheme 4. *Reagents and conditions*: a) *n*-BuLi, $BF_3.Et_2O$, THF, –78 °C; b) NaH, BnBr, DMF, rt; c) TBAF, THF, rt; d) i. IBX, EtOAc, reflux, 3 h; ii. $Pd(OAc)_2$, MeOH, rt; e) i. BH_3.DMS, THF, 3N NaOH, 30%H_2O_2, 0 °C→rt; ii. Ac_2O, Py, DCM, rt.

The coupling of the model alkyne **13** with epoxide **43** proceeded smoothly to provide **44**. The free hydroxyl group in compound **44** was protected as its benzyl ether **45** and then the TBS ether removed to get the alkynol **46**. The alkynol **46** was subjected for the sequential oxidation and cycloisomerization to afford the glycals **47α** and **47β** in 4:1 proportion. Both glycals were separately subjected for hydroboration-oxidation and acetylation to get the protected C(27)–C(38) fragments **48α** and **48β**.

Attempted synthesis of C(27)–C(48) fragment of aflastatin A: The coupling of the alkyne **6** and epoxide **43** proceeded smoothly to afford the alcohol **49** which, after benzylation and TBS ether deprotection delivered the key alkynol **51**. The oxidation of alkynol proceeded smoothly and yielded the key alkynone **52**. The cycloisomerization **52** afforded the separable mixture of glycals **53α** and **53β**. Both the compounds were found to be unstable and hydrolyzed during the recording of NMR, resulting mainly in the formation of a dione **54**. Hydroboration-oxidation of glycal **53** under various conditions led to the formation of a complex reaction mixture. Also, the sequential oxidation, cycloisomerization, hydroboration-oxidation and acetylation of alkynol **51** was found to be unsuccessful at delivering the required hydroboration products.



Scheme 5. *Reagents and conditions*: a) *n*-BuLi, $BF_3.Et_2O$, THF, –78 °C; b) NaH, BnBr, DMF, rt; c) TBAF, THF, rt; d) IBX, EtOAc, reflux, 3 h; e) $Pd(OAc)_2$, MeOH, rt; f) i. BH_3.DMS, THF, 3N NaOH, 30% H_2O_2, 0 °C→rt; ii. Ac_2O, Py, DCM, rt.

Further studies aiming to develop a convergent approach that involves the construction of the key tetrahydropyran unit with a minimum number of carbons and the subsequent chain elongation in order to extend the strategy in direction of total synthesis of aflastatin A are under progress in our group.

Chapter II. Studies toward the synthesis of zooxanthellamide D; one-pot alkynol cycloisomerization and reduction approach for the synthesis of *C*-disaccharides.

Zooxanthellamide D (**55**, Figure 3), a marine secondary metabolite was isolated by Ojika and co-workers from the *Symbiodinium* strain JCUCS-1 and found to exhibit moderate cytotoxicity against two human tumor cell lines- A431 vulval-derived epidermoid carcinoma and Nakata oral squamous cell carcinoma. Zooxanthellamide D was characterized by the presence of a polyhydroxy polyene amide consisting of a C_{22}-acid part and a C_{32}-amine part and furnishes three tetrahydropyran rings and five isolated butadiene units. In light of our ongoing research project on the development of new methods for the synthesis of *C*-disaccharides present in the natural products, we were particularly interested in the C(11)–C(21) fragment that contains a bis-disaccharide unit.

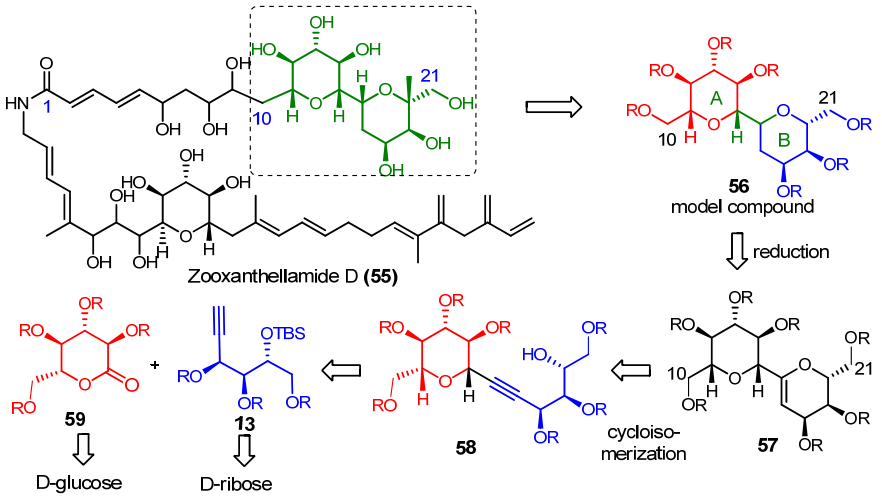
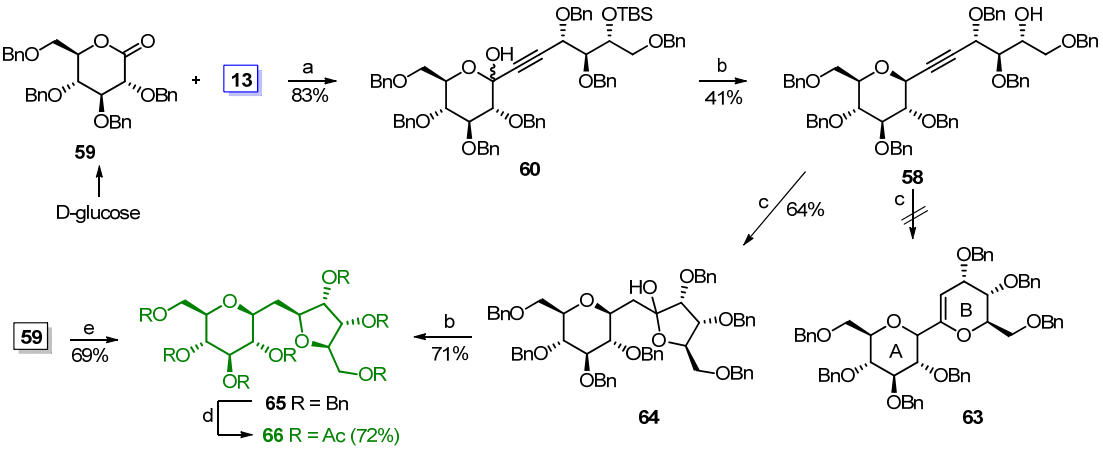


Figure 3. *Retrosynthetic disconnections*

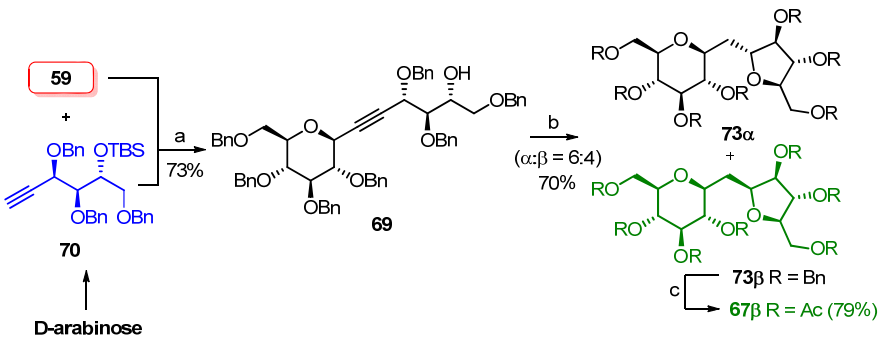
To construct the model perhydro-bipyran ring system **56** of zooxanthellamide D, alkynol cycloisomerization on **58** followed by reduction of resulting glycal **57** were thought to be suitable transformations and the alkyne **13** and lactone **59** have been identified as the suitable starting points in this regard.



Scheme 6. *Reagents and conditions*: a) *n*-BuLi, THF, –78 °C; b) Et_3SiH, $BF_3.Et_2O$; DCM:CH_3CN; –10 °C; c) $Pd(CH_3CN)_2Cl_2$, CH_3CN, rt, 2.5 h; d) i. Pd/C, H_2, MeOH, rt, 48 h; ii. Ac_2O, Py, rt, 14 h; e) $AuCl(PPh_3)/AgSbF_6$, DCM, rt, 2 h then Et_3SiH, $BF_3.Et_2O$, 0 °C.

The required alkyne **13** was prepared form D-ribose and lactone **59** from D-glucose according to literature procedures. The nucleophilic addition of lithiated alkyne to lactone delivered the hemiketal **60** which upon reduction with triethylsilane–$BF_3.Et_2O$ gave the key alkynol **58**. The Pd-mediated alkynol cycloisomerization of **58** gave the hemiketal **64** exclusively

resulting from the 5-exo-dig mode of cyclization followed by the hydrolysis of the intermediate exo-enol ether. Various other metal complexes have been screened in pursuit of synthesizing the requisite 6-endo product **63**. However, in all the cases the 5-*exo*-dig mode of cyclization was found to be the predominant pathway. The face selective triethylsilane reduction of **64** followed by debenzylation and acetylation delivered the *C*-disaccharide **66**. To this end, we found that a one-pot gold mediated cycloisomerization on alkynol **58** followed by triethylsilane reduction was effectively employed as the best strategy in order to increase step economy of this approach.



Scheme 7. *Reagents and conditions*: a) i. *n*-BuLi, THF, –78 °C; ii. Et_3SiH, $BF_3.Et_2O$; DCM:CH_3CN; –10 °C; b) $AuCl(PPh_3)/AgSbF_6$, DCM, rt, 2 h then Et_3SiH, $BF_3.Et_2O$, 0 °C; c) i. Pd/C, H_2, MeOH, rt, 48 h; ii. Ac_2O, Py, rt, 14 h.

In order to generalize the scope of this approach, different *C*-disaccharides were synthesized by changing the starting alkyne and lactone parts. The synthesis of *C*-disaccharide **73α** and **67β** was also completed according to the developed protocol as shown in Scheme 7.

Chapter III. Synthesis of *C*-glycosyl analogues of β-DPA as novel antitubercular agents

Tuberculosis (TB) is one of the most deadly infectious diseases, causing around two-three million deaths and additionally eight million new infections per year. β-D-arabinofuranosyl-l-monophosphoryldecaprenol (β-DPA) is an important substrate for the synthesis of arabinan polysaccharide portions of the cell wall of mycobacterium tuberculosis (main causative agent of TB). So the stable mimics of β-DPA have been considered as excellent candidates for the future drug development. In this context, we designed traizole analogues **II** as stable mimics of β-DPA (Figure 4).

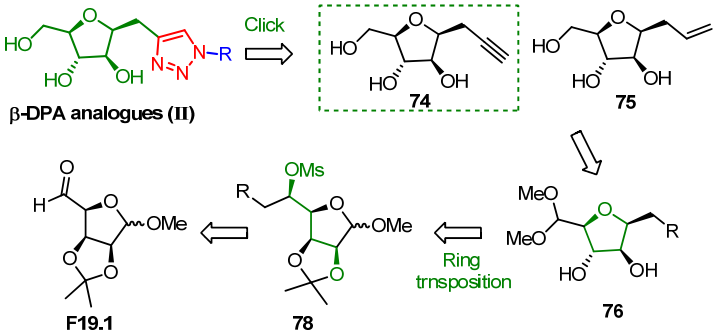
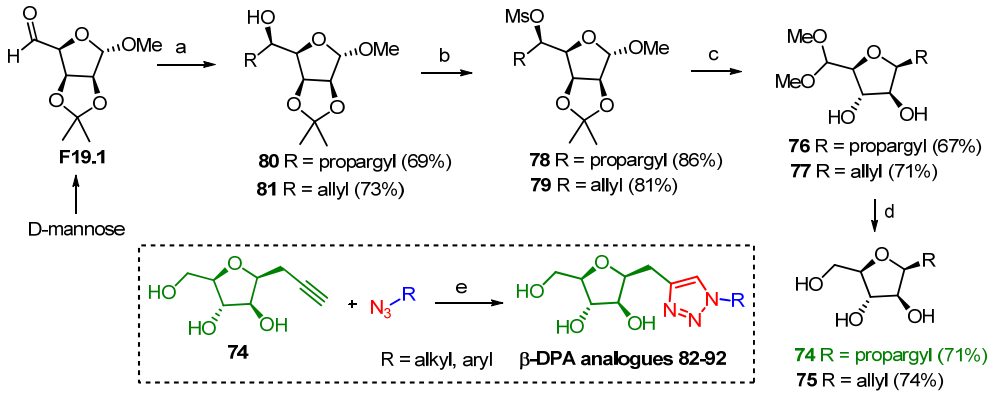


Figure 4. *β-DPA analogues and retrosynthetic strategy*

We planned to synthesize the designed β-DPA analogues by using the azide-alkyne cycloaddition reaction. The acid mediated ring transposition reaction was envisioned as the key transformation to address the major issue in the synthesis of the key alkyne intermediate **74**. The substrate **78** required for ring transposition can be synthesized from the aldehyde **F19.1**.



Scheme 8. *Reagents and conditions*: a) allyl/propargyl bromide, Zn, THF, rt, 2 h, then NH_4Cl, 0° C, 2 h; b) MsCl, Et_3N, DCM, 0 °C, 3 h; c) p-TSA, MeOH, reflux, 72 h; d) i. aq. TFA (60%), rt, 8 h; ii $NaBH_4$, MeOH, rt, 6 h; e) $CuSO_4$, Na-asorbate, *t*-BuOH:H_2O, rt, 7 to 9 h.

Our synthetic journey was started with the synthesis of aldehyde **F19.1** from D-mannose according to literature reports. The stereoselective Barbier reaction using propargyl/allyl bromide followed by mesylation of resulting alcohols delivered the mesylates **78**/**79**. The acid mediated furan ring transposition of these mesylates afforded the dimethyl acetals **76**/**77** which, after acid hydrolysis followed by sodium borohydride reduction, delivered the required β-*C*-propargyl and allyl-D-arabinofuranosides **74** and **75** respectively, at overall good yields.

Having successfully synthesized β-*C*-propargyl-D-arabinofuranoside **74**, the *C*-glycosyl analogues **82**–**92** having the long chain alkyl groups and also various aryl groups have been prepared by applying the azide-alkyne cycloaddition reaction under standard click reaction conditions.

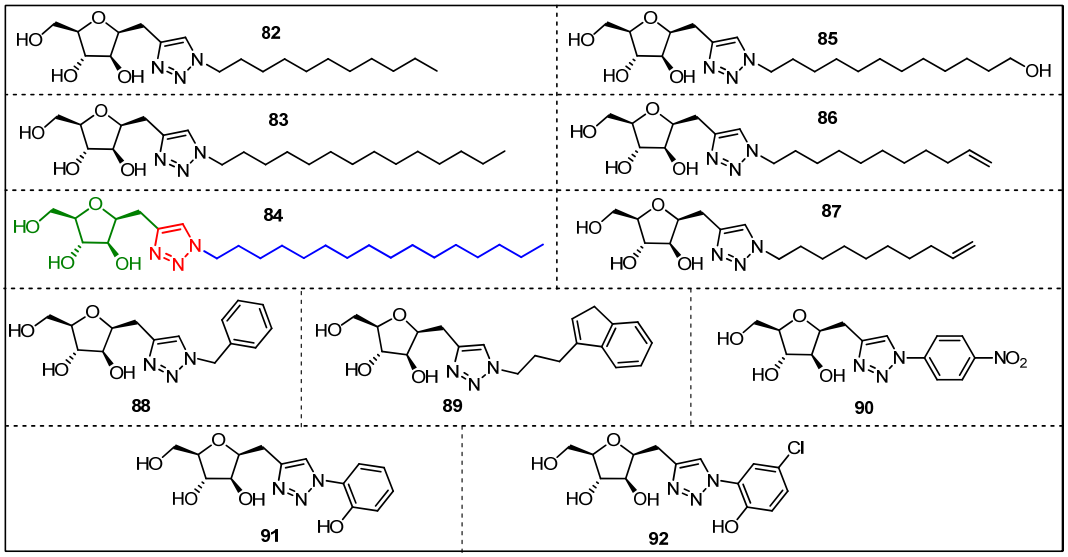


Figure 4. *C-glycosyl analogues of β-DPA* ***82–92*** *as novel antitubercular agents*

After the successful synthesis of the *C*-glycosyl analogues of β-DPA, all the compounds **82–92** were subjected for anti-mycobacterial evaluation. The *M. bovis* BCG strain has been used for this purpose and the inhibition studies have been carried out on the whole cell based HTS assay. The primary results obtained from this biological study revealed that the compound **87–92** having the aryl side chains are not at all active whereas the compounds **82–87** having alkyl side chain showed moderate to good activity. The compound **84** having a 16-carbon side chain was found to be the best in this series.

Summary:

- The synthesis of protected C(31)–C(38), C(31)–C(48) and C(27)–C(38) fragments of aflastatin A has been accomplished.
- A novel strategy for the synthesis of *C*-disaccharides of non-reducing sugars has been developed.
- The stereoselective synthesis of β-*C*-glycosyl analogues of β-DPA was accomplished and their evaluation as antitubercular agents was done.

CHAPTER-I

Studies toward the synthesis of C(27)–C(48) fragment of aflastatin A

Introduction

Mycotoxins (myco = fungus, toxin = poison) are the toxic secondary metabolites produced by the organisms of the fungus kingdom.[1] The term 'mycotoxin' is usually reserved for the toxic chemical compounds produced by fungi that readily colonize crops. One species may produce many different mycotoxins and the same mycotoxin may be produced by several species. According to FAO estimates, 25% of the world crops are affected by mycotoxins each year.[2] Aflatoxins, trichothecenes, zearalenone, fumonisin, ochratoxins, slaframine etc. are the diverse mycotoxins that affect the world crops, among which aflatoxins are probably the well known and most intensively researched mycotoxins because of their potent carcinogenic effect on laboratory rats and their acute poisonous effects on humans.[3]

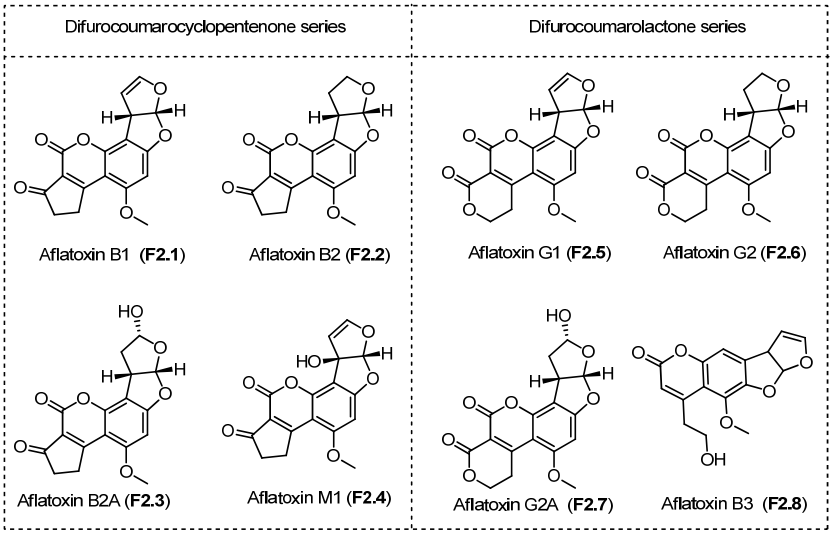


Figure 1. *Structures of aflatoxins B1, B2, B2A, M1, G1, G2, G2A and B3*

Humans are exposed to aflatoxins by consuming food material contaminated with products of fungal growth which is difficult to avoid because, fungal growth in food is not easy to prevent. Evidence of acute aflatoxicosis in humans has been reported from many countries of the world, namely the Taiwan, Uganda, India, etc.[4] The syndrome is characterized by vomiting, abdominal pain, pulmonary edema, convulsions, coma and death with cerebral edema and fatty involvement of the liver, kidneys and heart. In 1988, the IARC placed aflatoxin B1 on the list of human carcinogens. This is supported by a number of epidemiological studies done in Asia

and Africa that have demonstrated a positive association between dietary aflatoxins and Liver Cell Cancer (LCC). Additionally, the expression of aflatoxin related diseases in humans may be influenced by factors such as age, sex, nutritional status, and/or concurrent exposure to other causative agents such as viral hepatitis or parasite infestation.

Aflatoxin inhibitors:

Aspergillus flavus and *Aspergillus* parasiticus are the filamentous fungi that infect the oil seeds and tree nuts and contaminate these supplies with toxic secondary metabolites known as aflatoxins (AFs). AFs belong to the polyketide class of secondary metabolites and are synthesized by the enzymes encoded within a large gene cluster. Since the discovery of AFs in the 1960s, researchers have screened numerous natural products and synthetic compounds, as well as extracts from diverse organisms for identifying the inhibitors of AF biosynthesis.[5] Also, substantial effort has been dedicated to identify the organisms that inhibit AF biosynthesis during the co-culture with aflatoxigenic Aspergilli, with the goal of developing biocontrol organisms or finding new sources of inhibitory compounds. Although, there are diverse aflatoxin inhibitors, still there is a need for novel inhibitors at minimum concentration levels without significantly affecting the growth of the parasite. Aflastatin A (Figure 1) was found to fit into this category.

Aflastatin A (**1**) was isolated by Sakuda and co-workers from the mycelia of *Streptomyces* species MRI 142.[6] Aflastatin A belongs to the class of polyol natural products and contains a tetramic acid derivative with a highly oxygenated long alkyl side chain integrated with a tetrahydropyran ring (Figure 2). Aflastatin A shows strong inhibitory activity against aflatoxin production.[7]

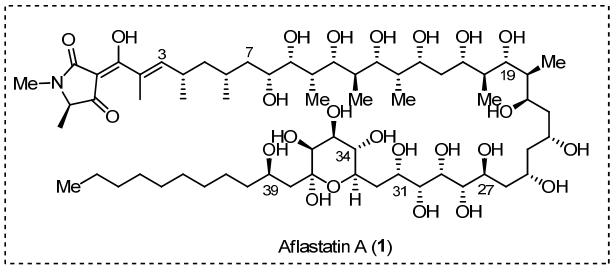


Figure 2. *Chemical structure of aflastatin A (**1**)*

- **Stereochemical assignment:**

Sakuda and co-workers proposed the relative and absolute structure of aflastatin A **F3.1** (Figure 3) in 2000. Since crystals of aflastatin A or its derivative suitable for X-ray analysis have been not obtained, the absolute configuration has been determined with the help of chemical degradation and extensive NMR studies.[8] Aflastatin A was chemically degraded in to fragment **F3.2**, **F3.3**, **F3.4**, **F3.5**, and **F3.6** (Figure 3), which were used to determine the absolute configuration of proposed struture. Absolute configurations at C(5′), C(4) and C(6), C(33), and C(39) of **F3.1** was clarified by determination of the absolute structures of **F3.3**–**F3.6**. Due to presence of 1,2- or 1,3-methine system in **F3.2** the relative configuration of **F3.2** was determined by the *J*-based configuration analysis, which afforded the relative configurations from C(10)–C(25) of **F3.1**. The remaining relative configurations from C(6)–C(10) and from C(25)–C(33) of **F3.1** was fixed by the determination of those of the counterparts in **F3.6**, which was also analyzed by the *J*-based method. Finally, connecting the absolute configurations at C(6) and C(33) of **F3.1** with the relative configurations from C(6)–C(33) and from C(33)–C(37), the complete absolute configuration of **F3.1** was determined as shown in Figure 3.

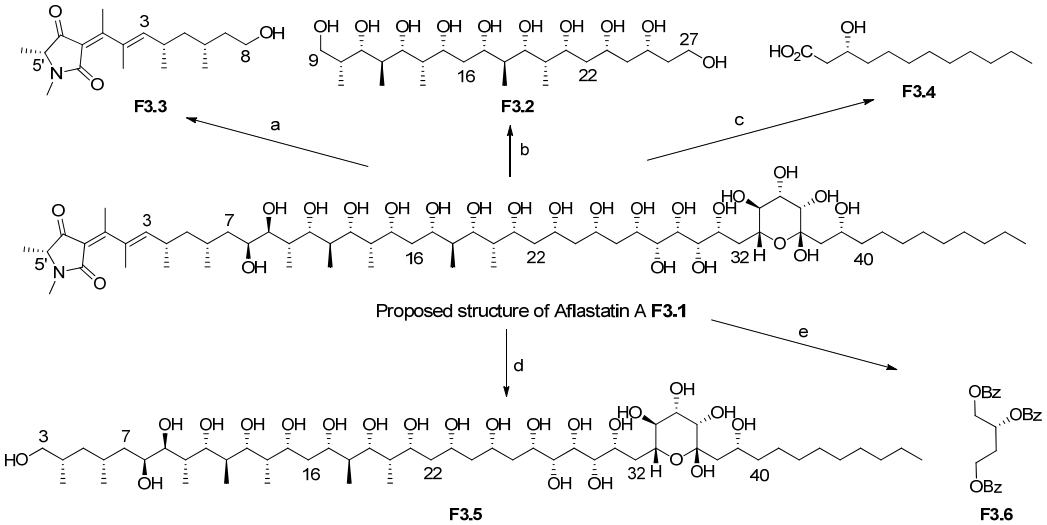
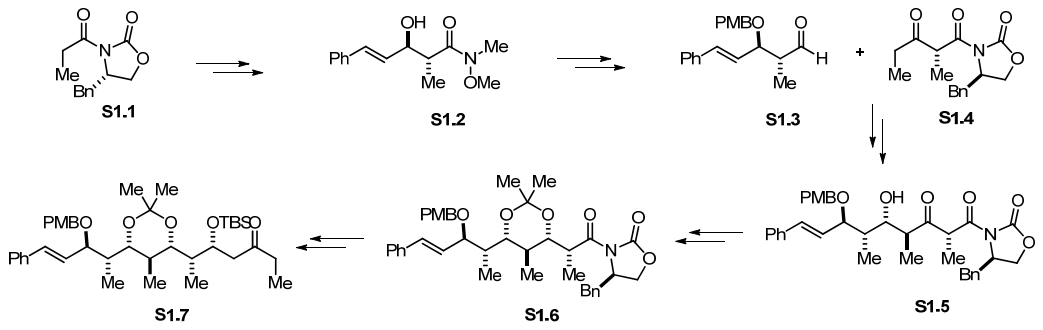


Figure 3. *Chemical degradation of proposed structure of aflastatin A*

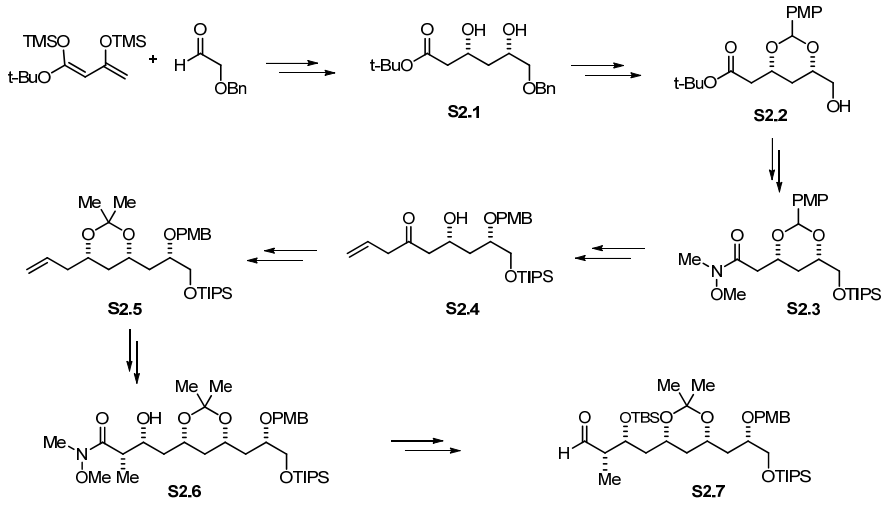
The assigned absolute stereochemistry of the degradation product C(9)–C(27) polyol has been cross-checked by chemical synthesis and correlation studies by Evans *et al.*[9] Also the initially proposed configurations at the diol C(8), C(9) and pentaol C(25)–C(29) moieties have been recently revised by partial chemical synthesis and NMR correlations in light of the remarks from Kishi's group[10] where they pointed out that erythro/threo/threo/threo is the correct relative stereochemistry at the pentaol moiety and revised structure of aflastatin A (**1**) was published as in Figure 2.[11] From the structural point of view aflastatin A is identified with the presence diverse sub-structural units such as tetramic acid, polyketide chain, 1,3-polyol chain and a carba disaccharide unit. The major challenge was its stereochemical complexity - 27 contiguous stereocenters. Thus, the synthesis of aflastatin A is one of the tough challenges that have been not yet addressed. There are only two reports in literature that deal with the synthesis of polyketide fragment of aflastatin A. In 2005, Evans *et al.* reported the synthesis of C(9)–C(27) fragment of aflastatin A.[9] Three years later, the same fragment has been synthesized by McDonald and co workers.[12] Our group has been working in the area synthesis of polyol natural products and also on *C*-glycosides synthesis.[13] The presence of both the sub-structural units in the same molecule has attracted our attention and thus a program directed towards the development of methods for the synthesis of polyol fragment including the carba-saccharide unit has been identified as a first step in our journey towards the total synthesis of aflastatin A (**1**). Following are the salient features of the two reports available on the synthesis of polypeptide fragment of aflastatin A.

- **Evans approach for C(9)–C(27) fragment of aflastatin A**:



Scheme 1. *Synthesis of C(8)–C(18) ketone fragment*

Evans *et al*. reported the synthesis of C(9)–C(27) fragment of aflastatin A, that relied on stereoselective aldol processes.[9] The synthesis comprises an *anti* aldol union of the (E) boron enolate of ketone **S1.7** [C(8)–C(18) fragment] with the an aldehyde **S2.7** [C(19)–C(28) fragment]. The synthesis of ketone **S1.7** was began with the $MgCl_2$-catalyzed direct aldol addition to provide the known *anti*-aldol adduct which was converted into the Weinreb amide **S1.2**. The protection of the free hydroxyl group of **S1.2** as its PMB ether followed by selective reduction afforded the aldehyde **S1.3**. The boron-mediated anti-aldol reaction of aldehyde **S1.3** with α-ketoimide **S1.4** delivered the aldol product **S1.5.** Subsequent 1,3-*syn*-selective reduction of **S1.5** followed by acetonide protection gave acetonide **S1.6**. The reductive removal of chiral auxiliary, oxidation followed by (–) DIP-Cl mediated reaction with butanone and TBS protection delivered the required ketone fragment **S1.7** (Scheme 1).



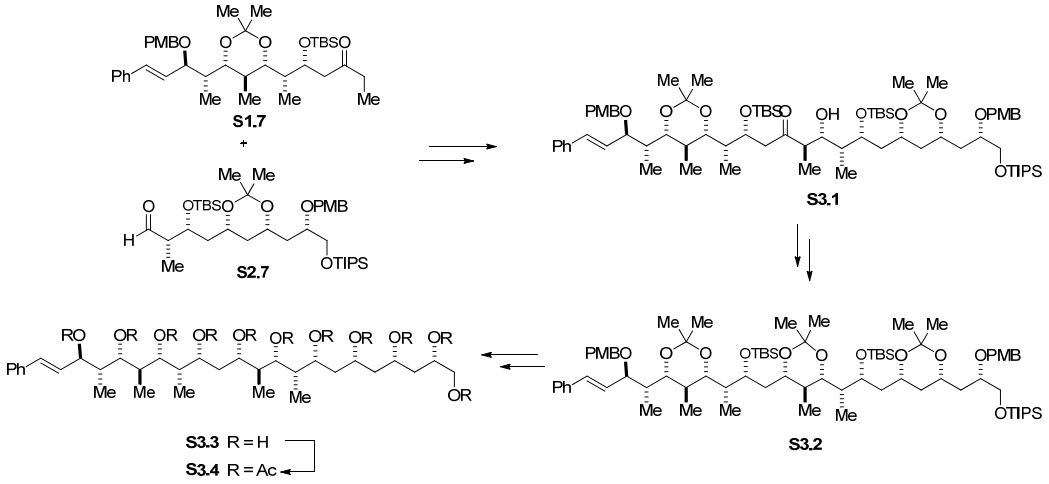
Scheme 2. *Synthesis of C(19)–C(28) aldehyde fragment*

The synthesis of C(19)–C(28) fragment commenced with an enantioselective [Cu(*S*,*S*)-PhPybox)]$(SbF_6)_2$-catalyzed aldol addition followed by 1,3-*syn*-reduction to give diol **S2.1.** Treatment of diol with anisaldehyde dimethylacetal afforded the PMP acetal, which after benzyl ether deprotection gave hydroxy ester **S2.2**. Silylation followed by trans-amidation provided the Weinreb amide **S2.3**. The compound **S2.3** was then subjected for a carbonyl-directed acetal cleavage using $MgBr_2$ and Bu_3SnH. Allylation, Et_2BOMe-mediated *syn*-reduction, and acid-catalyzed acetonide formation furnished the protected all-*syn* triol derivative **S2.5**. Ozonolysis, auxiliary controlled

syn-aldol reaction followed by cleavage of the auxiliary under standard conditions delivered the Weinreb amide **S2.6**. Then TBS protection followed by DIBAL reduction completed the synthesis of aldehyde fragment **S2.7** (Scheme 2).

Synthesis of C(9)–C(27) fragment of aflastatin A:

Boron enolate mediated anti aldol union of ketone fragment **S1.7** with the aldehyde fragment **S2.7** gave **S3.1** which after $Zn(BH_4)_2$ reduction afforded the 1,3-*syn*-diol. The 1,3-diol unit was protected as its acetonide **S3.2**. The ozonolysis of **S3.2** followed by reduction, protection, deprotection delivered the C(9)–C(27) fragment of aflastatin A **S3.3** (Scheme 3).

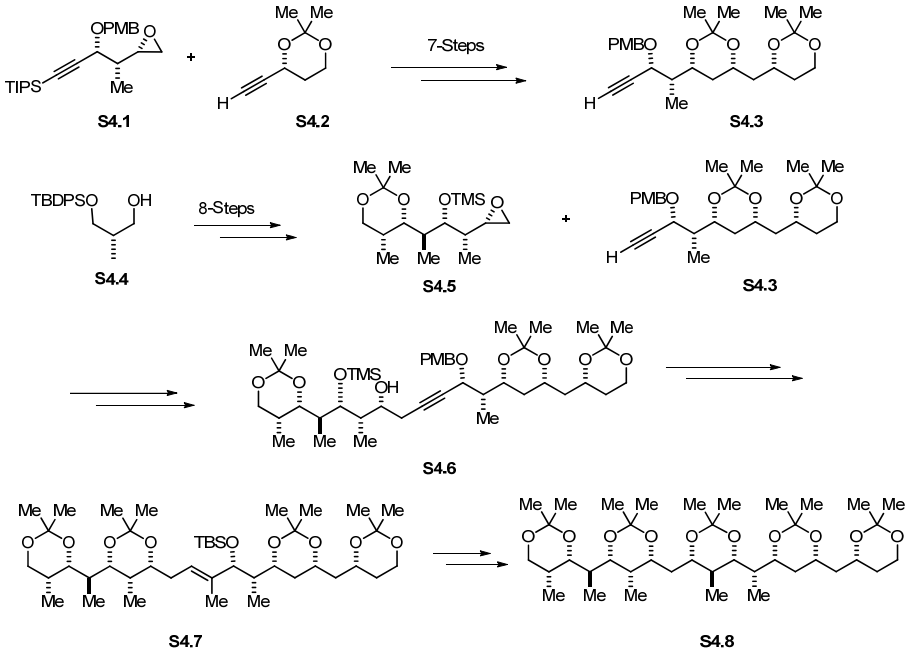


Scheme 3. *Anti-aldol coupling for synthesis of C(7)–C(27) fragment of aflastatin A*

- **McDonald approach for C(9)–C(27) fragment of aflastatin A**:

Three years after the Evans synthesis of C(9)–C(27) fragment of aflastatin A, in 2008, McDonald *et al.* documented the synthesis of the same fragment by using alkyne-epoxide cross coupling reaction as a key reaction (Scheme 4).[12] Initially, McDonald *et al.* prepared the alkyne fragment **S4.3** by cross coupling of epoxide **S4.1** and alkyne **S4.2** in seven steps (Scheme 4). Epoxide fragment **S4.5** was synthesized from the alcohol **S4.4** in eight steps (Scheme 4). Reliable cross-coupling of the alkynyl lithium from **S4.3** with epoxide **S4.5** provided alkynyl alcohol **S4.6.** After some protective group manipulations, the introduction of the C(18)-methyl substituent was accomplished by attachment of a bromomethylsilyl ether at O(19) of **S4.6**, which

underwent radical cyclization followed by protiodesilylation to afford the *E*-trisubstituted alkene **S4.7** stereoselectively. Hydroboration-oxidation of the allylic alcohol followed by acetonide protection delivered the pentaacetonide derivative **S4.8** corresponding to the C(9)–C(27) fragment of aflastatin A (Scheme 4).



Scheme 4. *Alkyn-epoxide cross coupling for the synthesis of C(9)–C(27) fragment*

From above discussions, it is very apparent that, since the isolation, only the synthesis of the C(9)–C(27) polyol fragment has been addressed by Evans and McDonald groups.[9,12] Due to our immense interest in the synthesis of *C*-glycosides and polyol natural products, aflastatin A has been chosen as a target. More particularly we are interested in the C(27)–C(48) fragment having a tetrahydropyran unit as central core.

Results and discussion

Aflastatin A (**1**) was isolated by Sakuda and co-workers from the mycelia of *Streptomyces* species MRI 142.[6] Aflatoxins are the naturally occurring mycotoxins produced by many species of aspergillus, a fungus, the most notable examples of which are *Aspergillus flavus* and *Aspergillus parasiticus*. Aflastatin A belongs to the class of polyol natural products and contains a tetramic acid derivative with a highly oxygenated long alkyl side chain, as well as a tetrahydropyran ring (Figure 4).

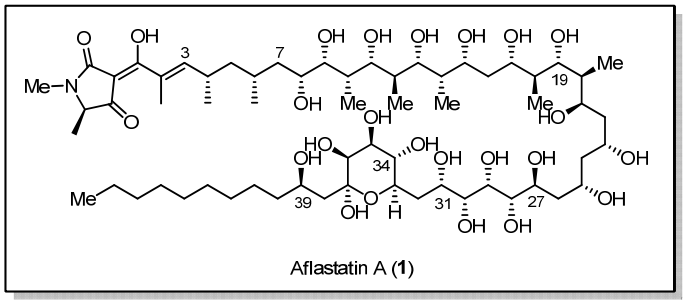


Figure 4. *Revised structure of aflastatin A (**1**)*

Aflastatin A shows strong inhibitory activity against aflatoxin production. As mentioned in the introduction, the group of Evans and McDonald have reported the synthesis of the C(9)−C(27) fragment.[9,12] In line of our recent program in the area of synthesis of polyol natural products and *C*-glycosides synthesis, and considering the presence of both the sub-structural units in the same molecule, aflastatin A has attracted our attention. A program directed towards the development of methods for the synthesis of polyol fragment including the carba-saccharide unit has been identified as a first step in our journey towards the total synthesis of aflastatin A (**1**). Specifically, we are interested in the assembly of C(27)–(48) fragments in a systematic manner.

As a first step towards the intended objective, the retrosynthetic strategy was designed for the construction of protected C(27)–C(48) fragment **2** as shown in Figure 5. The major challenge in the synthesis of fragment **2** was the construction of the fully functionalized tetrahydropyran unit with requisite stereochemistry. This made us explore the metal mediated ω-alkynone cycloisomerization[14] and subsequent regio- and stereoselective hydroboration-oxidation of the resulting *C*-glycal **3**.[15]

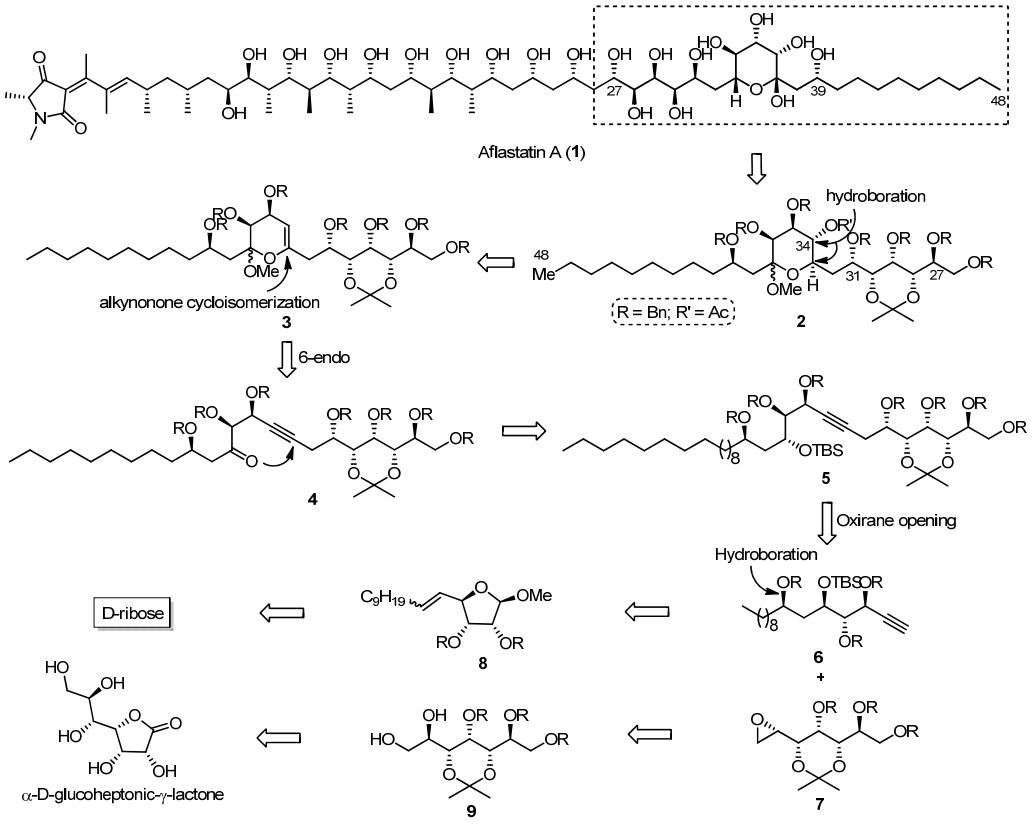


Figure 5. *Retrosynthetic disconnections for protected C(27)–C(48) fragment of aflastatin A*

Alkynone cycloisomerization is a straight forward way for the synthesis of cyclic enol ethers involving the intramolecular addition of the carbonyl oxygen of ketone/aldehyde to alkyne (carbon-carbon triple bond).[14] In this process, the metal-catalyst plays a dual role. Initially, it acts as a Lewis acid to enhance the reactivity of carbonyl carbon by forming a complex with electron lone pairs of oxygen and so facilitate the nucleophilic attack of nucleophile (Nu) such as methanol to the carbon bearing a partial positive charge (Figure 6). Next, it forms a π-complex with the alkyne and thus facilitates the intramolecular attack of oxygen leading to an alkenyl-palladium intermediate. The protodepalladation takes place in the presence of HX and delivers the required cyclic enolether and thus regenerate the Pd-catalyst. [14a]

Though there exists two possible competitive pathways for the cycloisomerization; considering our previous results, a preference for 6-*endo*-dig over the 5-*exo*-dig cyclization was foreseen.[13,14]

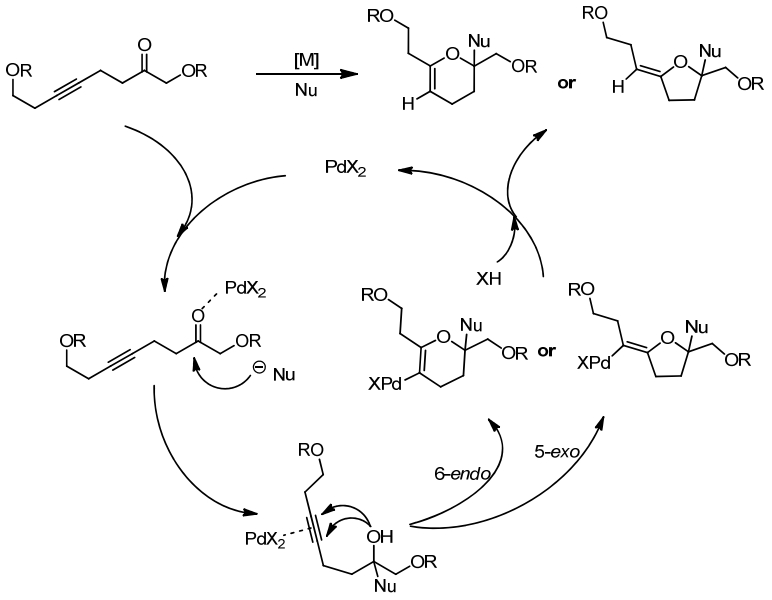


Figure 6. *Intended alkynone cycloisomerization and proposed mechanism*

The key alkynone intermediate **4** would be assembled from the TBS ether **5**, which, in turn, could be synthesized by addition of the alkyne **6** to epoxide **7** using alkyn-epoxide cross coupling as the principal coupling strategy.[16] For the construction of the key alkyne **6**, the D-ribose containing requisite stereochemistry at C(2) and C(3), matching with that of C(35) and C(36) respectively of aflastatin A (Figure 5), was selected as a chiral precursor. The C(1) of the ribose derivative can be further extended to the alkyne C(33)–C(34) unit and C(4) to the carbonyl present at C(37). The synthesis of olefine **8** has been planned by the chain extension of the C(5) hydroxyl through oxidation followed by 10-carbon Wittig-olefination on ribo-derivative, which, in turn, can be synthesized from naturally occurring D-ribose by a selective protection and deprotection technique. Inspection of the stereochemical details of the epoxide fragment **7** led us to identify the α-D-glucoheptanoic-γ-lactone as a suitable chiral precursor, where the configuration of the hydroxyl groups at C(2)–C(5) matches perfectly with the stereochemistry of the hydroxyl groups at C(27)–C(30) in aflastatin A. The sterochemistry at C(6) of α-D-glucoheptanoic-γ-lactone can be inverted during the formation of key epoxide **7**, the functional unit that was opted for, in oredr to address the C(32)–C(33) bond formation.

1. Synthesis of C(27)–(48) fragment of aflastatin A:

Considering the fact that the alkynone cycloisomerization has, in general, been applied on simple derivatives and looking at the complexity of the substrate that we would like to explore for this particular reaction, we initially planned to go for a step by step construction of the complex structural outlay. Hence, the synthetic journey in this project to reach the intended target commenced with planning the halts in terms of the small targets. According to the plan, the initial target was to check the feasibility of key transformations with simple substrates. The synthesis of model compound **10** [C(31)–(38) fragment] having the same stereochemistry at C(33), C(34), C(35), C(36), and C(37) of aflastatin A was selected as a first exploration and the alkynone **12** as the model substrate for the key cycloisomerization.

1.1 Model study for synthesis of central tetrahydropyran core:

The synthesis of alkynone **12** was planned by the opening of ethylene oxide with alkyne **13** which, in turn, can be equipped from D-ribose by employing selective protection, deprotection and functional group transformations.

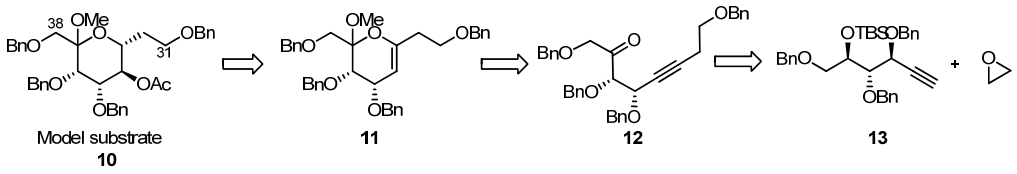
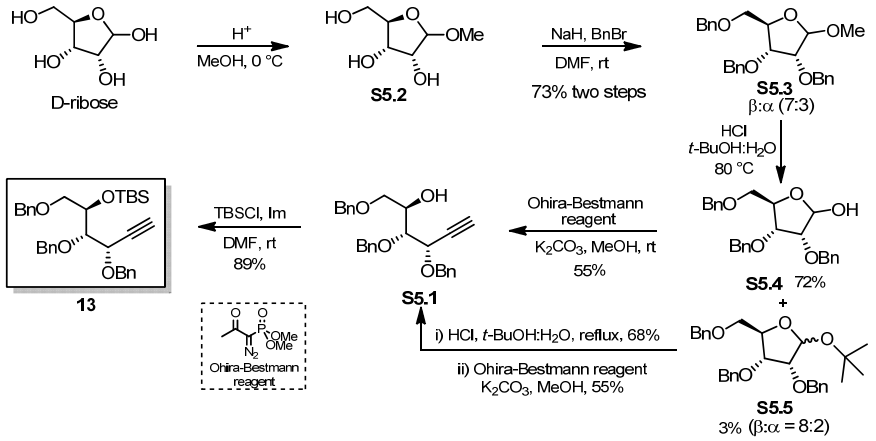


Figure 7. *Model study plan for the synthesis of C(31)–C(38) fragment **10** of aflastatin A*

- **Synthesis of alkyne 13:**

According to the synthetic plan, the synthesis of alkyne **13** was the very first objective. Scheme 5 saliently describes the synthesis of the key intermediate **S5.1** from D-ribose. 1-*O*-methyl-D-ribofuranoside **S5.2** was prepared from D-ribose by treatment with acid in anhydrous methanol. The free hydroxyl groups in **S5.2** have been protected as their benzyl ethers by using sodium hydride and benzyl bromide to get a (β:α=7:3) anomeric mixture of compounds **S5.3** in 73% yield over two steps. Both the anomers were separated by column chromatography. In the ^{1}H NMR spectrum, the characteristic anomeric proton in β-anomer was observed as a singlet at 4.91 ppm and that of α-anomer was resonated as a doublet at 4.88 ppm with J = 3.9 Hz. The major anomer was put forward for the acid hydrolysis under different

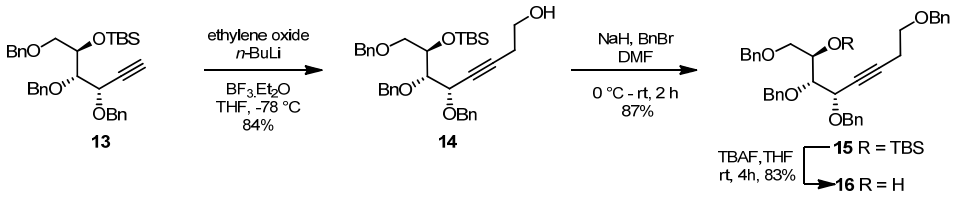
conditions. To this end, heating a solution of **S5.3** in *t*-BuOH and water at 80 °C in the presence of aq. HCl was found to be the optimum condition to get the lactol **S5.4** in very good yields along with trace amounts of *t*-butyl glycosides **S5.5**.



Scheme 5. *Synthesis of alkyne **13** from D-ribose*

The lactol **S5.4** thus obtained was treated with the Ohira-Bestmann reagent in methanol to procure the alkyne **S5.1** with 55% yield.[17] The characteristic doublet of acetylenic proton at 2.56 ppm with J = 2.2 Hz in the ^{1}H NMR spectrum of **S5.1** confirmed the presence of a alkyne unit. The *t*-butyl ribofuranosides **S5.5** obtained as side products during the hydrolysis of methyl ribofuranoside **S5.3** were also converted into the required alkyne **S5.1** (Scheme 5) under similar conditions used for conversion of methyl ribofuranoside **S5.3**. Finally, the free hydroxyl group of compound **S5.1** was protected as its silyl ether by using TBSCl, imidazole in DMF to furnish the alkyne **13** in 89% yield. The presence of TBS signals [δ −0.08 (s, 6H) and 0.71 (s, 9H)] in ^{1}HNMR spectrum confirmed the structure of the TBS protected compound **13**.

- **Synthesis of key alkynol intermediate 16:**

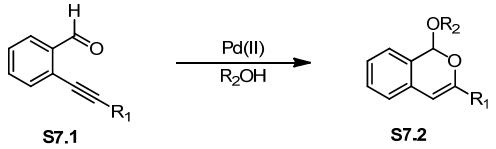


Scheme 6. *Synthesis of alkynol intermediate **16***

Having the alkyne **13** in hand, the next aim was the oxirane opening reaction. The optimized conditions involve the treatment of alkyne **13** with *n*-BuLi and $BF_3.Et_2O$ in THF at −78 °C followed by addition of ethyleneoxide and further stirring for 1.5 h at −78 °C to afford alcohol **14** (Scheme 6). The disappearance of the characteristic doublet of terminal acetylenic C–H at 2.51 ppm and the presence of a doublet of triplet at 2.46 ppm with a coupling constant of J = 1.6, 6.2 Hz integrating for two protons supported the formation of alcohol **14**. The free hydroxyl group of alcohol **14** was then protected as its benzyl ether by treating it with sodium hydride and benzyl bromide to get the compound **15**. The removal of the TBS group in **15** by using TBAF in THF gave the requisite alkynol **16** in good yields.

- **Some selected reports for the alkynone cycloisomerizations:**

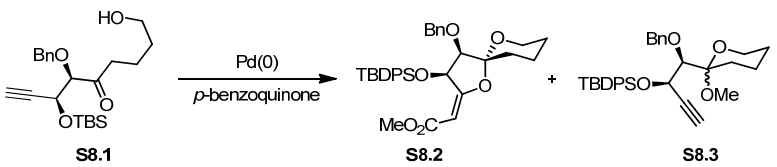
Yamamoto *et al*. were the first who report that a Pd(II) catalyst really exhibits dual roles (Lewis acid and π-activation).[14a] In this report, they explored $Pd(OAc)_2$ as a suitable catalyst for reaction of alkynylaldehydes **S7.1** with ROH to give the alkenyl cyclic ethers **S7.2** in good to high yields. Here, the attack of ROH to aldehyde is catalyzed by Lewis acidic $Pd(OAc)_2$, and the nucleophilic oxygen of the resulting hemiacetal reacts with alkyne complexed by Pd(II), giving the alkenyl ethers.



S7.1 S7.2

Scheme 7. *Pd(II) mediated cycloisomerization*

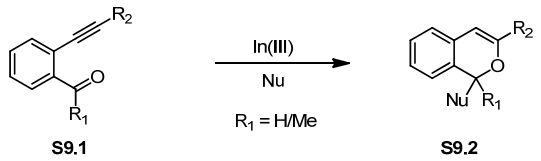
Later, in 2005, Mukai and co-workers documented the use of Pd(II) catalysts in presence of *p*-benzoquinone as an oxidant under an atmosphere of CO to furnish the spiroacetal enol ether derivative **S8.2** along with the tetrahydropyran derivative **S8.3**, both in low yields from the alkynone **S8.1**.[14b] After screening different catalysts, the use of Pd(0) in the presence of excess *p*-benzoquinone was reported as the suitable catalytic system for the said transformation.



S8.1 S8.2 S8.3

Scheme 8. *Pd-mediated alkynone cycloisomerisation*

Subsequently, in 2007, Takemoto *et al.* have efficiently utilized an In(III) catalyst for the synthesis of 1*H*-isochromenes.[18] $In(OTf)_3$ was also found to play a duel role during the tandem addition and cyclization of 2-(1-Alkynyl)arylaldehydes/ ketones **S9.1** to deliver 1*H*-isochromenes **S9.2** in good yields (Scheme 9).

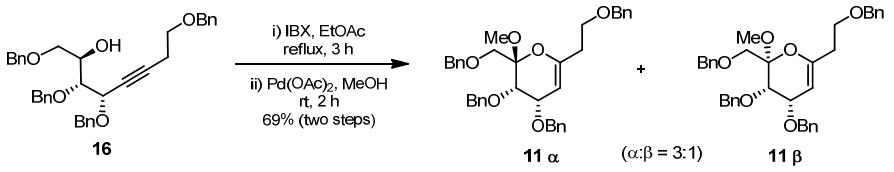


S9.1 **S9.2**

Scheme 9. *In(III) mediated tandem addition and cyclization*

- **Synthesis of model compound [C(31)–C(38) fragment] 10:**

With having look on the literature reports, the oxidation of the alkynol intermediate **16** using IBX in refluxing ethyl acetate was carried out to prepare the key alkynone intermediate **12**, which was immediately subjected for alkynone cycloisomerization employing various metal complexes like $Pd(PPh_3)_4$/*p*-benzoquinone, $PdCl_2(CH_3CN)_2$, $PdCl_2(PhCN)_2$, $PdCl_2$ and $[Pd(OAc)_2$ in MeOH without any purification. Amongst the all complexes we tried, $Pd(OAc)_2$ was found better for the desired transformation. The cycloisomerization of the intermediate alkynone **12** gave two separable products in 69% yield, the structures of which have been confirmed as dihydropyrans **11α** and **11β** (3:1).



16 **11 α** **11 β**

Scheme 10. *Synthesis of glycal **11** employing alkynone cycloisomerization*

The constitution of the dihydropyrans **11α** and **11β** was determined with the help of spectral and analytical data and the anomeric configuration was determined after the hydroboration-oxidation and acetylation. The presence of quaternary carbon at 147.8 ppm, olefinic C–H at 98.9 ppm and –OMe at 48.5 ppm in the ^{13}C NMR spectrum of **11α** indicated the presence of a dihydropyran unit. Similarly, the presence of the quaternary carbon at 150.3 ppm, a olefinic carbon at 97.3 ppm and an –OMe at 50.5 ppm confirmed the structure of dihydropyran **11β**.

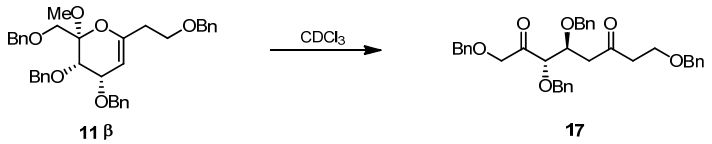
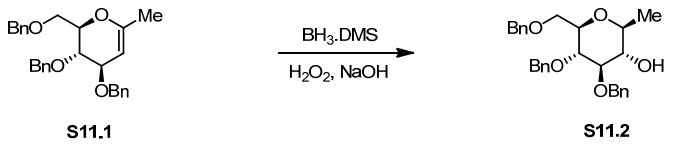


Figure 8. *Hydrolysis of glycal **11β** into diketone **17** during NMR analysis*

During the spectral analysis, the major isomer **11α** was found to be stable, however, the minor isomer **11β** was hydrolysed slowly in $CDCl_3$ giving a 1,5-diketone **17** (Figure 8). The structure of diketone **17** was confirmed by the presence of characteristic signals in ^1H and ^{13}C NMR spectra. In the ^1H NMR spectrum of compound **17**, the absence of a singlet at 3.33 ppm for three protons and the presence of a triplet at 2.67 ppm with J = 6.2 Hz for two protons, doublet of doublet at 2.74 ppm with J = 5.6, 17.5 Hz for one proton, doublet of doublet at 2.85 ppm with J = 7.1, 17.5 Hz for another proton and a triplet at 3.69 ppm with J = 6.2 Hz for two protons clearly indicated that the dihydropyran was completely converted to diketone. The structure of this dicarbonyl compound was further supported by the absence of the quartet corresponding to the methyl group the –OMe at 50.0 ppm and the presence of two triplets at 43.7 and 44.1 ppm corresponding to the two vicinal dimethyl groups, and two singlets at 206.8 and 207.5 ppm characteristic of the two carbonyl groups in the ^{13}C NMR spectrum.

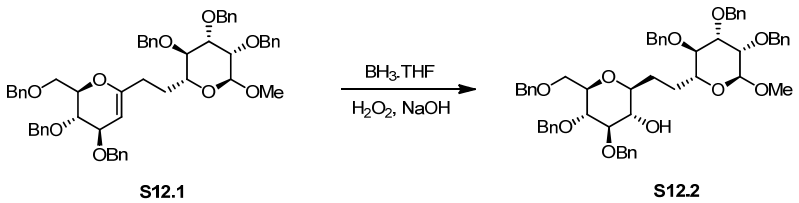
- **Regio and stereoselective hydroboration-oxidation on sugar templates:**

After successful synthesis and structural analysis of dihydropyrans or glycals (**11α** and **11β)** and diketone **17**, hydroboration-oxidation was the next step to be carried out in the synthetic sequence. Literature search revealed that, glycals can undergo regio- and stereoselective hydroboration-oxidation to form the corresponding sugar derivatives. Hanessian *et al.* in 1986 reported the regio- and stereoselective hydroboration-oxidation of glucal **S11.1** (Scheme 11) employing the BH_3.DMS complex in combination with H_2O_2 and aq. NaOH for the synthesis of *C*-glycoside **S11.2**.[15a]



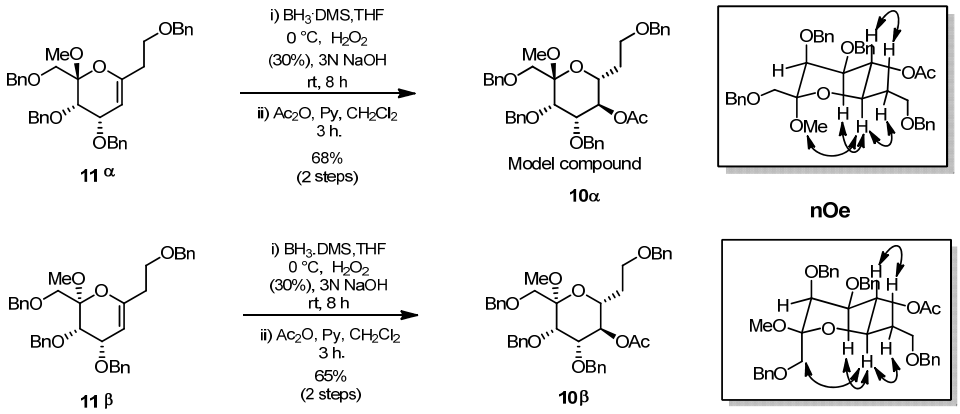
Scheme 11. *BH_3.DMS mediated hydroboration-oxidation for synthesis of a C-glycoside*

Apart from this, BH_3·THF has also been employed as an efficient reagent for the hydroboration of glycal derivatives. Very recently, in 2010, Werz and co-workers applied BH_3·THF complex in combination with H_2O_2 and aq. NaOH for the synthesis of *C*-disaccharides in quite efficient manner (Scheme 12).[19]



Scheme 12. *BH_3·THF mediated hydroboration-oxidation for synthesis of C-disaccharides*

Having look on the literature, hydroboration-oxidation of glycal **11α** and **11β** has been carried out separately (Scheme 13) using BH_3·DMS in THF at 0 °C followed by addition of aq. NaOH (3 N), 30% aq. H_2O_2 and the resulting alcohols were converted to the corresponding acetates **10α** and **10β** for structural characterization.



Scheme 13. *Stereo- and regioselective hydroboration-oxidation of glycal **11α** and **11β***

In the ^{1}H NMR of **10α**, the C–H attached to acetate appeared down field at 5.24 ppm with diaxial coupling constants ($J \approx 10$ Hz) indicating a *trans*-orientation with respect to the adjacent methine hydrogens. The anomeric configuration of **10α** was determined as alpha with the help of nOe studies. For example, in the NOESY spectrum of the compound **10α**, the C(37)–OMe showed a strong nOe with both the C(33)–H and C(35)–H. The anomeric configuration of minor product **10β** was also determined with the help of nOe studies, where C(38)–CH_2, instead of C(37)–OMe, shows strong nOe with C(33)–H and C(35)–H. In this way, the model study has been

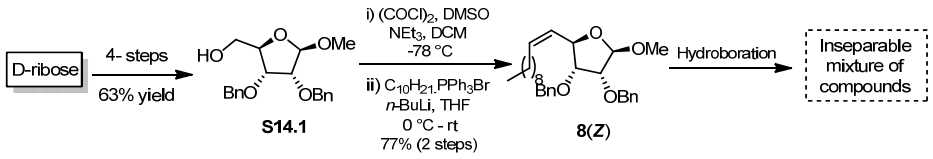
successfully completed with the synthesis of C(31)–(38) fragment **10α** along with its epimer **10β.**

1.2 Synthesis of the C(31)–(48) fragment of aflastatin A:

Having established the feasibility of the alkynone cycloisomerization and face selective hydroboration-oxidation for the construction of the central tetrahydropyran unit of aflastatin A, our next synthetic goal was to extend this strategy for the synthesis of the C(27)–(48) fragment of aflastatin A. However, since it possesses quite high number of oxygen functionalities, we decided to go for another model study that comprises the introduction of the left hand ten carbon side-chain with one stereocentre at C(39) position. This has resulted in the identification of the C(31)–(48) fragment of aflastatin A as the next target in our synthetic endeavor.

- **Synthesis of the alkyne fragment 6:**

To achieve this target, the synthesis of the required alkyne **6** was planned from D-ribose. The known D-ribose derivative **S14.1** was prepared by following the four step reaction sequence: i) treatment with acid in anhydrous methanol; ii) selective protection of primary hydroxyl group by using trityl chloride, triethylamine, DMAP in DMF:DCM (3:7); iii) protection secondary hydroxyl groups as benzyl ethers using sodium hydride and benzyl bromide in DMF and iv) finally trityl ether deprotection using silica supported $KHSO_4$ in DCM:MeOH (9:1).

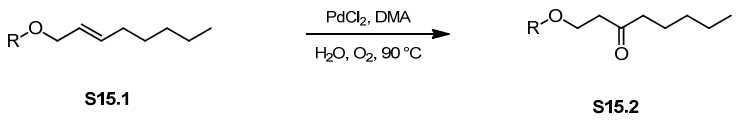


Scheme 14. *Attempts for stereo- and regioselective hydroboration-oxidation*

The oxidation of the primary hydroxyl group of **S14.1** under Swern oxidation conditions using oxalyl chloride, DMSO, triethylamine in DCM at −78 °C and the subsequent Wittig olefination with the ylide generated from decyltriphenylphosphonium bromide and base (*n*-BuLi) afforded the olefine **8**(***Z***) (Scheme 14). In the ^{1}H NMR spectrum of **8**(***Z***), the two olefinic protons resonated down field at 5.35 (J = 10.8 Hz) and 5.69 ppm (J = 10.8 Hz) while in ^{13}C NMR spectrum, the olefinic carbons appeared at 129.5 and 134.9 ppm respectively. After

having olefine in hand, the next job was to introduce the hydroxyl group at the C(39) position. Initially, the hydroboration oxidation reaction was carried out under standard conditions i.e. treatment with BH_3.DMS in THF at 0 °C, followed by addition of NaOH (3N) and 30% aq. H_2O_2, but unfortunately, an inseparable mixture of products was obtained. The use of different borane reagents and different stoichiometric ratios of these reagents also ended up with formation of inseparable mixture of products.

As all attempts for stereo- and regioselective hydroboration-oxidation failed to provide the desired product, the regioselective oxidation followed by 1,3-*syn* reduction of the resulting ketone was considered as an alternative way to rich the desired target. In literature, large number of reports are available for the oxidation of olefine using a catalytic system consisting of palladium with copper, is commonly known as the Wacker oxidation process. Since the discovery of this process, this Pd/Cu catalyst system has been extended to the oxidation of diverse terminal olefins using water under liquidphase conditions, which offered a powerful method for the synthesis of methyl ketones. However, this catalyst system has been inevitably limited to the oxidation of terminal olefins. This limitation arises because the internal olefins show extremely low reactivity and selectivity; that is, non-regioselective oxidations occur to yield various undesired oxygenated products through isomerization of the olefinic bonds. In 2010, Kaneda *et al.* reported a new catalytic system to overcome the low reactivity of the internal olefins.[20] They made use of Pd/DMA (*N,N*-dimethylacetamide) under O_2 atmosphere for the regioselective oxidation of the internal olefine compound **S15.1** to afford the carbonyl compound **S15.2** (Scheme 15).

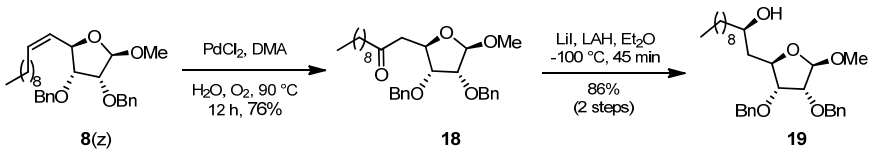


S15.1 **S15.2**

Scheme 15. *Regioselective Wacker type oxidation of internal olefine*

By considering the similarity in the structure of functional olefine in compound **8**(*Z*) with **S15.1**, it was subjected for the Wacker type oxidation as per literature procedure. After screening several Pd-complexes at different conditions, the regioselective oxidation of **8**(*Z*) could successfully be carried out by employing $PdCl_2$ in *N,N*-dimethylacetamide and water at 90 °C for 12 h under O_2 atmosphere (Scheme

16). The ketone **18** was obtained in 76% yield with 100% regioselectivity. The signals observed at δ 2.44 (t, J = 7.4 Hz, 2H), 2.62 (d, J = 6.7 Hz, 2H) in the ^{1}H NMR spectrum and a singlet at 208.7 in the ^{13}C NMR spectrum confirmed the structure of ketone **18**.



Scheme 16. *Regioselective Wacker type oxidation and 1,3-syn reduction*

Then the stereoselective reduction of ketone **18** employing lithium iodide and LAH delivered alcohol **19** and the diastereomeric ratio was found to be 9:1.[21] The major diastereomer was separated and the stereochemistry of the newly generated asymmetric centre was fixed by converting it into the acetonide derivative.

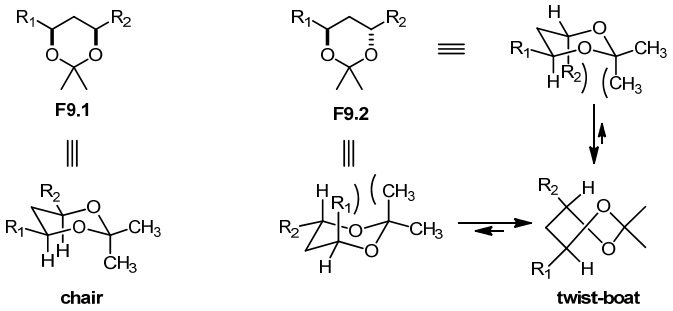
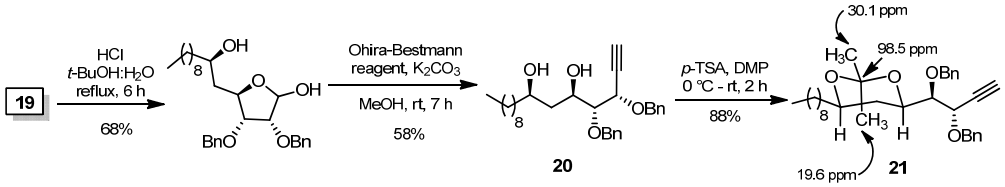


Figure 9. *Conformation based stereochemical identification of 1,3-diols*

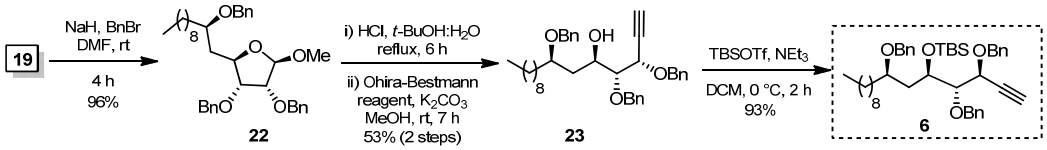
In 1993, Rychnovsky *et al*. have developed a method based on the ^{13}C chemical shifts of the acetal methyl groups and the acetal carbon in ^{13}C NMR spectrum.[22] This method for the stereochemical identification of l,3-diols relies on the conformational properties of the corresponding 1,3-diol acetonides. A syn-acetonide **F9.1** exists in a well defined chair conformation in which both methyl groups experience the different electronic environment. On the other hand, in order to avoid the l,3-diaxial interactions present in chair conformation, the anti-acetonide **F9.2** exists in a twist-boat conformation (Figure 9) in which both methyl groups experience the same electronic environment. Therefore, in general, the syn-diol acetonides, the methyl group of the acetal unit resonate at around 19 and 30 ppm and acetal carbon

resonate around at 98 ppm, whereas in the case of anti-diol acetonides, both methyl groups resonate at ≈25 ppm and acetal carbon at around 100 ppm.



Scheme 17. *Synthesis and confirmation of stereochemistry of acetonide **21***

Scheme 17 describes the details of the synthesis of acetonide **21** and some characteristic ^{13}C NMR signals. The synthesis of acetonide **21** started with the hydrolysis of the anomeric –OMe group under previously established conditions i.e. heating with HCl in a mixture of *t*-butanol and water (8:2). The intermediate lactol was immediately treated with Ohira-Bestmann reagent and K_2CO_3 in methanol at room temperature to procure the alkyne **20** (Scheme 17). The structure of alkyne **20** was confirmed by the presence of a doublet corresponding to the acetylenic proton with a coupling constant J = 2.1 Hz at 2.59 ppm which is characteristic of a terminal alkyne. The treatment of alkyne **20** with *p*-TSA and 2,2-dimethoxy propane (DMP) at room temperature delivered the acetonide derivative **21**. In the ^{1}H NMR spectrum of the acetonide **21**, the two methyl singlets appeared at 1.34 and 1.39 ppm which indicated the formation of acetonide. In the ^{13}C NMR spectrum, the acetal carbon was seen to resonate at 98.5 ppm whereas the two methyl carbons at 19.6 and 30.1 ppm, which is a characteristic of the acetonide of a 1,3-*syn* diol.



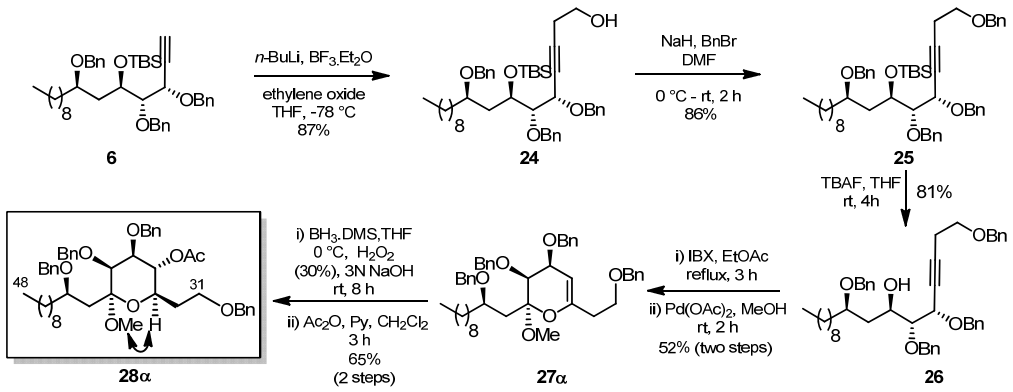
Scheme 18. *Synthesis of alkyne fragment **6***

After the confirmation of stereochemistry of the newly generated stereocentre, the next target was the synthesis of alkyne **6** (Scheme 18). To achieve this target, the free hydroxyl group of alcohol **19** was first protected as its benzyl ether **22** using sodium hydride and benzyl bromide at room temperature in DMF. Then acid mediated hydrolysis of the compound **22** afforded the intermediate lactol which was further treated with Ohira-Bestmann reagent and K_2CO_3 in methanol to procure the

alkyne **23** in 61% yield over two steps.[17] The presence of the characteristic doublet at 2.58 ppm with J = 2.2 Hz confirmed the formation of alkyne **23** which was further supported by the ^{13}C NMR spectrum. The attempt to protect the secondary hydroxyl group in alkyne **23** as TBS ether using TBSCl, imidazole in DMF ended up with the recovery of starting material. The use of TBSOTf and triethyl amine in DCM at 0 °C led to the formation of a faster moving spot on TLC, which was the first indication along with the presence of two singlets for three protons at 0.00, 0.03 ppm and a singlet for nine protons at 0.82 ppm in ^{1}H NMR was the second indication for the formation of expected TBS protected alkyne **6**. The peaks observed in the ^{13}C NMR and HRMS spectrum have given the further support for the formation of the alkyne **6**.

- **Synthesis of C(31)–C(48) fragment 27:**

Having alkyne **6** in hand, the next objective was the synthesis of the C(31)–C(48) fragment of aflastatin A by following the same reaction sequence as per the model study. Ethylene oxide was opened with alkyne **6** by treatment with *n*-BuLi and $BF_3.Et_2O$ at −78 °C in THF to afford the alcohol **24** with 87% yield.[16] The absence of a doublet corresponding to an acetylenic proton of alkyne at 2.51 ppm and the presence of methylene signal at 2.49 ppm and a broad singlet for −OH at 1.90 ppm confirmed the formation of alcohol (Scheme 19).



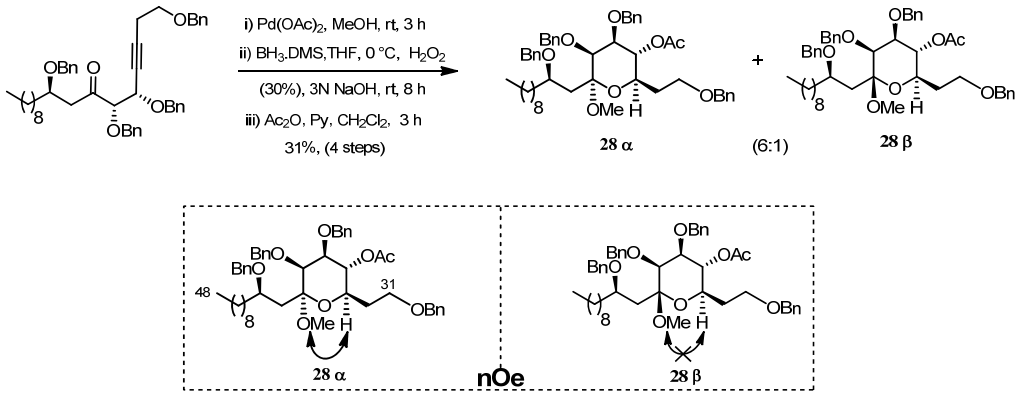
***Scheme 19**. Synthesis of C(31)–C(38) fragment **28** of aflastatin A*

The primary hydroxyl group of alcohol **24** was protected as its benzyl ether **25** by treatment with NaH and BnBr in DMF. Subsequently, the removal of the O–TBS group in compound **25** by using TBAF in THF at room temperature delivered the alkynol **26** (Scheme 19) in good yield. The disappearance of two singlets

corresponding to two methyl groups and of a singlet corresponding to *t*-butyl group confirmed the TBS deprotection. The secondary hydroxyl group in compound **26** has been oxidized to the corresponding ketone (alkynone) by treatment with IBX in ethyl acetate at reflux temperature. The crude alkynone thus obtained was utilized for Pd-mediated cyclization using $Pd(OAc)_2$ in anhydrous methanol followed by purification over a silica gel column to give the glycal **27α** in 52% yield over two steps. In the ^1H NMR spectrum of **27α**, the −OMe was found to resonate at 3.23 ppm and in the ^{13}C NMR spectrum, the presence of a quaternary olefinic carbon at 149.9 ppm and the olefinic =*C*H at 97.2 ppm confirmed the proposed structure of glycal **27α**. The assigned structure of **27α** was also supported by the HRMS spectrum. The stereochemistry of anomeric −OMe was confirmed at a later stage. Hydroboration-oxidation of glycal **27α** was carried out using BH_3·DMS, 3N NaOH and 30% H_2O_2 at 0 °C followed by acetylation of the resulting alcohol by treatment with acetic anhydride and pyridine in DCM afforded the acetate **28α** in 65 % yield (Scheme 19). The structure of acetate **28α** was confirmed by extensive NMR studies. In the ^1H NMR spectrum of the compound **28α**, the C–H attached to the acetate group appeared down field at 5.23 ppm with a characteristic large diaxial coupling constant ($J \approx 10$ Hz) indicating a *trans*-orientation with respect to the adjacent methine hydrogens. The anomeric configuration was determined as alpha with the help of nOe studies. In the NOESY spectrum of compound **28α**, the C(37)–OMe shows strong nOe with C(33)–H and C(35)–H, which indicated the presence of all these hydrogens in a same plane. Thus, the synthesis of the C(31)–(48) fragment of aflastatin A was accomplished using the protocol that we have developed in model studies.

Quite interestingly, as mentioned above, during the synthesis of the C(31)–(48) fragment, formation of only one anomer was observed as the outcome of the alkynone cycloisomerization. On the other hand, the formation of two anomers was observed in the model studies. Also, it was worth enough to note that, the glycal **11β** obtained during the cycloisomerization of the simple model substrate was found to be unstable and hydrolysed into the dicarbonyl compound **17** during the NMR studies. So, in order to address whether the observed α-anomeric selectivity was apparent due to the hydrolysis of the corresponding β-anomer during the isolation, hydroboration-oxidation was carried out on the crude product of the cycloisomerization reaction under the previously standardized conditions employing BH_3·DMS, 3N NaOH and

30% H_2O_2 at 0 °C in THF (Scheme 20). Acetylation of the resulting product using acetic anhydride and pyridine in DCM afforded a separable mixture of acetates **28α** and **28β** in 6:1 proportion with 31% yield over 4 steps. Structure of the acetate **28β** was confirmed by extensive spectral and analytical studies. For example, in the NOESY spectrum of **28β**, the presence of strong nOe between the C(37)–OMe with C(33)–H and C(35)–H indicated the assigned beta-anomeric configuration (Scheme 20).



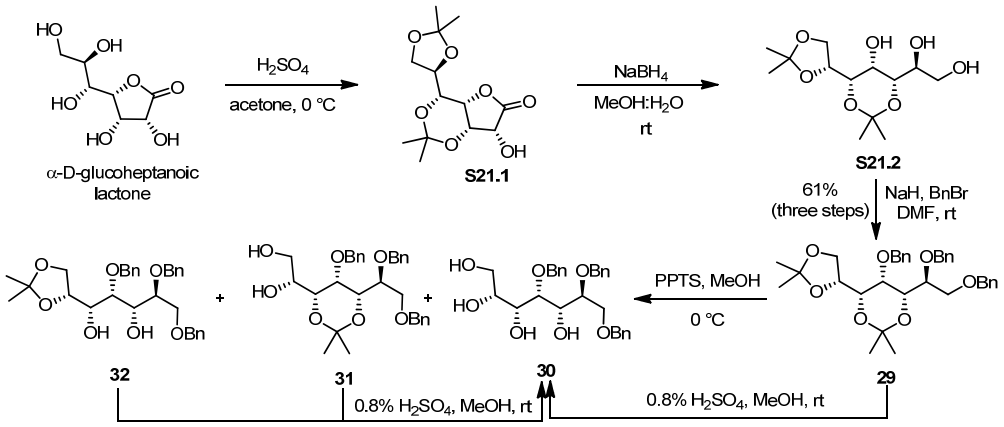
Scheme 20. *Attempt to address the anomeric selectivity of cyclization and structure confirmation by nOe study*

1.2 C(27)–(48) fragment of aflastatin A:

After the successful completion of the synthesis of C(31)–(48) fragment of aflastatin A, the synthesis of C(27)–(48) fragment has been undertaken as the next target. The objective of this exercise was to extend the right hand polyol side-chain by using epoxide **7** as shown in Figure 5.

- **Synthesis of epoxide fragment 7:**

As a first step, the synthesis of the epoxide fragment was began from the α–D–glucoheptanoic lactone (Scheme 21). The diacetonide protection of α–D–glucoheptanoic lactone was carried out by treatment of acid (H_2SO_4) in anhydrous acetone at 0 °C to get the diacetonide derivative **S21.1.** The complete reduction of **S21.1** using $NaBH_4$ in methanol-water at room temperature afforded triol **S21.2**.[23] The free hydroxyl groups in triol **S21.2** were treated with sodium hydride and benzyl bromide in DMF to get the tribenzyl ether **29** in 61% yield over three steps (Scheme 21).

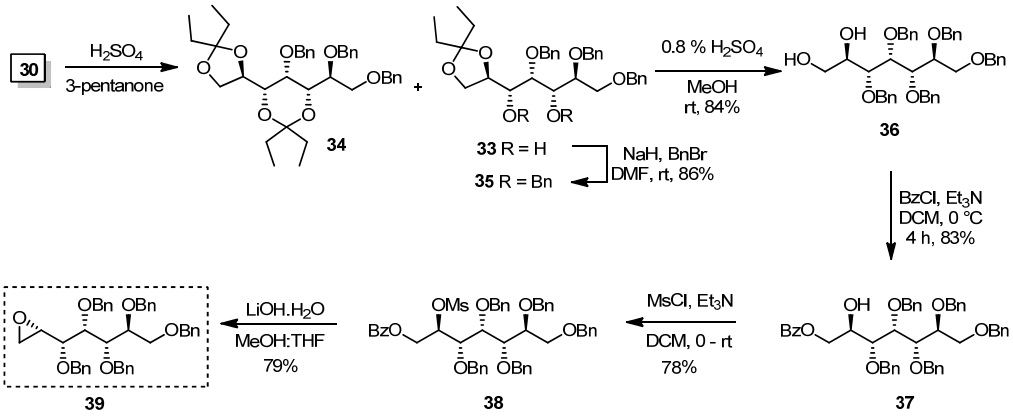


Scheme 21. *Attempts for selective acetonide hydrolysis and synthesis of tetraol **30***

The initial attempts to selectively hydrolyze the terminal acetonide of compound **29** under various conditions met with the isolation of the three possible hydrolysis products **30**–**32** in varying amounts. This led us to attempt the hydrolysis of both the acetonide groups followed by selective protection of the terminal diol unit. Thus, the treatment of **29** with 0.8% H_2SO_4 in methanol gave the tetraol **30** in quantitative yields. The structure of these compounds was confirmed by their ^1H and ^{13}C NMR spectra. The absence of the $–CH_3$ signal and the presence of four broad singlets corresponding to four –OH at 2.95, 3.10, 3.39 and 3.46 ppm confirmed the structure of tetraol **30**. The assigned structure for diol **31** [terminal] was supported by the presence of characteristic signals of two $–CH_3$ of six membered acetonide at 19.1 and 29.4 ppm and corresponding quaternary carbon at 98.8 ppm, whereas the presence of the two $–CH_3$ of five membered acetonide at 25.3 and 26.8 ppm and quaternary carbon at 109.5 ppm in ^{13}C NMR confirmed the allocated structure of diol **32**.

After synthesis of tetraol **30**, next the terminal 1,2-diol was distinguished from internal 1,3-diol by selective protection as its monopentylidene derivative **33** in 89% yield (Scheme 22) by treatment of **30** with catalytic H_2SO_4 in 3-pentanone at 0 °C. The formation of the dipentylidene ketal **34** as the side-product was found to be temperature and time dependent. If temperature increases above 5 °C, the formation of dipentylidene derivative **34** begins with respect to time. The assigned structure of the monopentylidene derivative **33** was confirmed by observing the triplet for six protons at 0.89 ppm with a vicinal coupling constant 7.5 Hz and a multiplet for four protons at 1.59–1.65 ppm in the ^1H NMR spectrum. The presence of a singlet for the

quaternary carbon at 113.2 ppm in ^{13}C NMR spectrum has given the further support for the formation of the five membered pentylidene ketal. In the same way, the structure of the dipentylidene derivative **34** was also confirmed with the help of spectral and analytical data. The presence of a singlet for quaternary carbon at 113.1 ppm of the five membered pentylidene and at 101.9 ppm of the six membered pentylidene in the ^{13}C NMR spectrum supported the structure of the compound **34**.



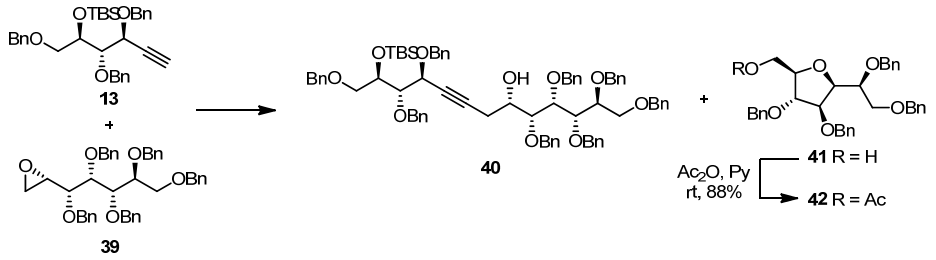
Scheme 22. *Synthesis of epoxide fragment **39** from teraol **30***

The free hydroxyl groups in **33** were protected as their benzyl ethers by using sodium hydride and benzyl bromide to procure the compound **35** in 86% yields. The deprotection of the pentylidene acetal in compound **35** was carried out using 0.8% H_2SO_4 in methanol at room temperature to afford the diol **36** in good yields. The structure of the diol was confirmed by the absence of $-CH_3$ and $-CH_2$ signals in $^1H/^{13}C$ NMR. Since the hydroxyl group at C(6) position had stereochemistry opposite to what was required, there is a need for the inversion of this centre during the epoxide formation. So, in order to achieve this, the primary hydroxyl group in compound **36** was selectively protected as its *O*-benzoate **37** in 83 % yield by reaction of the diol **36** with benzoyl chloride and triethylamine in anhydrous DCM at 0 °C. Then the secondary hydroxyl group was converted to corresponding *O*-methanesulphonate group by treatment with methane sulphonyl chloride (MsCl) and triethylamine in anhydrous DCM to get the mesylate **38** in 78% yield (Scheme 22). The appearance of singlet at 2.74 ppm for $-CH_3$ confirmed the structure of compound **38** which was further supported by the mass spectrum. This mesylate after treatment with lithium hydroxide in THF:MeOH delivered the required epoxide **39** in good yields by sequential benzoate deprotection followed by the S_N^2 displacement of the

mesylate by the resulting free hydroxyl group. The structure of epoxide was confirmed by absence of the $-CH_3$ signal and the presence of characteristic $-CH_2$ signals at δ 1.94 (dd, J = 2.4, 4.8 Hz, 1H) and 2.22 (dd, J = 4.0, 4.8 Hz, 1H) in ^{1}H NMR spectrum of compound **39**. The ^{13}C NMR and mass spectra are also in good agreement with the assigned structure.

- **Attempts for synthesis of C(27)–(38) fragment:**

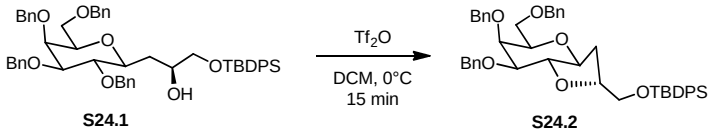
So far, the synthesis of C(31)–(38) and C(31)–(48) fragments have been successfully executed. In the process of extending this strategy towards the synthesis of the C(27)–(48) fragment, the synthesis of epoxide **39** has also been completed. Having the required epoxide **39** in hand, the next concern was its opening with the alkyne **6**. Earlier, dealing with the synthesis of the fragments **10** and **27**, the easily accesible alkyne **13** was used for the optimization studies. However, in that case, the epoxide used was the simple ethylene oxide. As the synthesis of key alkyne **6** involves a sequence of twelve linear steps, our initial intention was to use the alkyne **13** for optimizing the sequence and then proceed with the alkyne **6** in order to arrive at the desired objective.



Scheme 23. *Attempts for alkyne-epoxide cross coupling*

The attempted epoxide opening reaction with alkyne **13** using *n*-BuLi and $BF_3.Et_2O$ failed to give the required product **40** under various explored reaction conditions (Table 1). This reaction led to either formation of the epoxide-rearranged product **41** or the isolation of trace amounts of the required product **40**.

The rearranged product **41** was expected to be formed by $BF_3.Et_2O$ mediated debenzylative cycloetherification, a commonly entcountered problem when the reacting groups are in a 1,4-position. Kulkarni *et al.* recently reported the serendipitous debenzylative cycloetherification on a substrate **S24.1** having the reactive groups in 1,4-position to form a furan ring system **S24.2** (Scheme 24).[24]



Scheme 24. *Debenzylative cycloetherification for the synthesis of furans*

The structure of compound **41** was confirmed by ^{1}H and ^{13}C NMR spectra and further supported by mass spectroscopy. The ring CHs were found to resonate at 80.3, 81.7, 82.5, and 85.1 ppm and $–CH_2$ at 63.1 ppm, which is characteristic of a furanoside derivative. For further confirmation, compound **41** was converted to the corresponding acetate **42** by treatment with acetic anhydride and pyridine at room temperature. The structure of compound **42** was supported by shift of the C(5)–CH_2 signal from 63.1 to 64.6 ppm in the ^{13}C NMR spectrum.

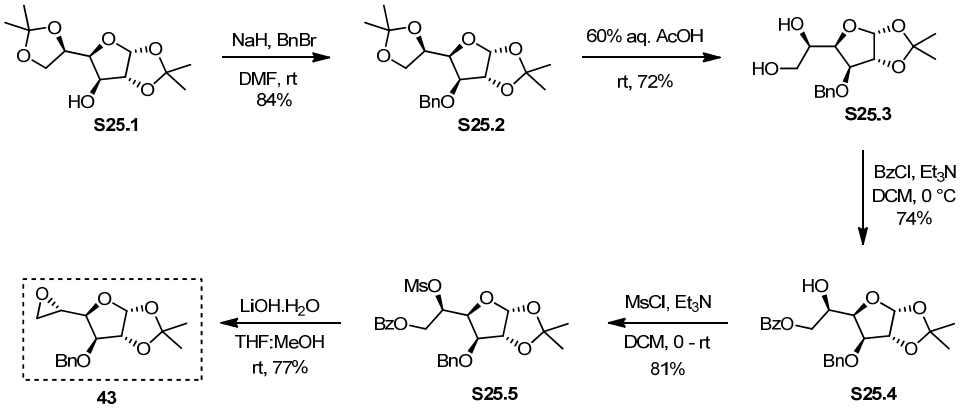
Table 1. *Reaction conditions and results for alkyne epoxide cross coupling reaction*

Sr.No.	Reagents used	Temperature	Results
1	*n*-BuLi (2 eq), $BF_3.Et_2O$ (3 eq)	–78 °C	72% (**41**)
2	*n*-BuLi (2 eq), $BF_3.Et_2O$ (2 eq)	–78 °C	68% (**41**)
3	*n*-BuLi (1 eq), $BF_3.Et_2O$ (1.1 eq)	–78 °C	64% (**41**) and 3% (**40**)
4	*n*-BuLi (1 eq)	–78 °C to rt	S.M. recovered
5	*n*-BuLi (1 eq), CuCN (2 eq)	–40 °C	S.M. recovered
6	*n*-BuMgBr (2 eq), CuCN (3 eq)	–40 °C to rt	S.M. recovered
7	*n*-BuMgBr (2 eq), CuI (3 eq)	–40 °C to rt	S.M. recovered
8	*n*- BuLi (2 eq), $MgBr_2$ (2 eq)	0 °C to rt	S.M. recovered
9	*n*- BuLi (2 eq), ZnI_2 (2 eq)	0 °C to rt	S.M. recovered
10	*n*- BuLi (2 eq), $ZnTf_2$ (1 eq)	0 °C to rt	S.M. recovered
11	*n*- BuLi (2 eq), $ScTf_3$ (1eq)	0 °C to rt	S.M. recovered

Since improving the yield of requisite product **40** turned to be a difficult proposition, we next intended to use an epoxide that had been appended on a furanoside unit, so that the chances of intramolecular epoxide opening could be reduced.

- **Synthesis of revised epoxide 43:**

According to the revised tactic, the epoxide **43** was selected as a suitable precursor for the next synthetic exercise. Epoxide **43** was assembled from D-glucose as shown in Scheme 25.

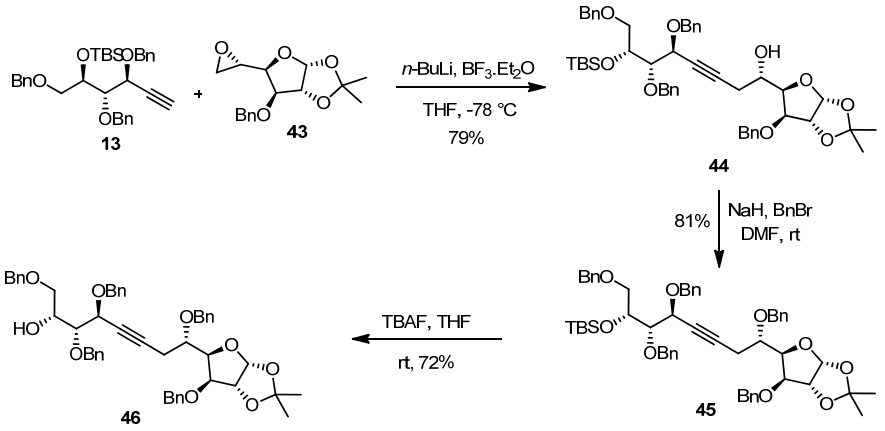


Scheme 25. *Synthesis of revised epoxide **43** from D-glucose*

The known glucose diacetonide derivative (GDA) **S25.1** was prepared from D-glucose by treatment with acid in acetone at room temperature. Then protection of the free hydroxyl group as its benzyl ether, followed by selective 5,6-acetonide deprotection in 60% aqueous acetic acid at room temperature led to formation of diol **S25.3**. The C(6)–OH group in diol **S25.3** was selectively protected as its *O*-benzoate by treating with benzoyl chloride and triethylamine in DCM at 0 °C. The secondary hydroxyl group was then converted to the corresponding mesylate **S25.5** by treatment with mesyl chloride and triethylamine in DCM, which, after treatment with lithium hydroxide in THF:MeOH (8:2), delivered the epoxide **43** in 77% yield. The structure of the epoxide **43** was confirmed by the presence of a characteristic CH_2 signal of epoxide ring [δ 2.54 (dd, J = 2.8, 4.8 Hz, 1H), 2.76 (dd, J = 4.4, 4.8 Hz, 1H)] in the ^{1}H NMR spectrum of compound **43**. This assignment was further supported by ^{13}C and HRMS spectral analyses.

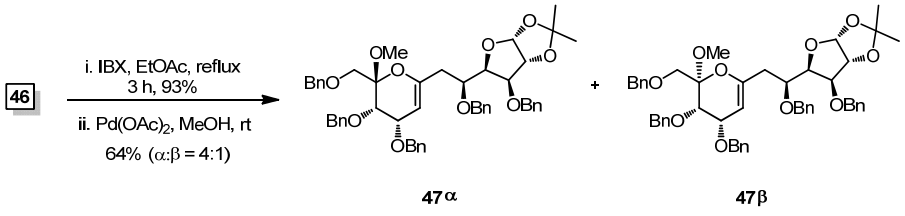
- **Synthesis of C(27)–(38) fragment aflastatin A 48*α*:**

After having the newly designed epoxide in hand, the next aim was the synthesis of alkynol **46** by following the protocols that we have developed during the model studies.



Scheme 26. *Synthesis of alkynol **46** using alkyne-epoxide cross coupling*

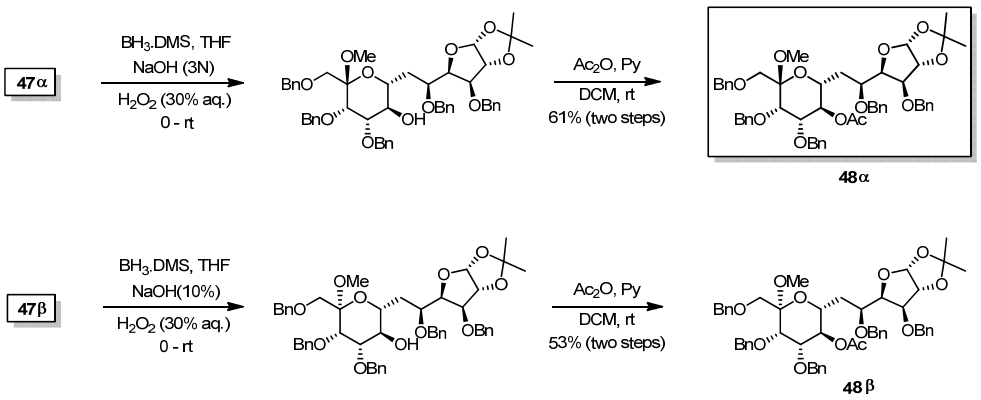
The epoxide **43** was opened with alkyne **13** using *n*-BuLi and $BF_3.Et_2O$ at −78 °C in THF to produce the desired product **44** in good yields (Scheme 26). The presence of signals at δ 1.32 (s, 3H), 1.42 (s, 3H) corresponds to acetonide $-CH_3$ and δ 2.50 (dd, J = 5.8, 16.8 Hz, 1H), 2.60 (dd, J = 7.1, 16.8 Hz, 1H) corresponds to $-CH_2$ in ^{1}H NMR spectrum confirmed the structure of compound **44**, which was also supported by ^{13}C and HRMS spectra. Then, the free hydroxyl group was protected as its benzyl ether in the usual way to get compound **45** in 81% yields. Finally, the deprotection of the TBS group in compound **45** using TBAF in THF at room temperature delivered the alkynol intermediate **46** in 72% yield. The absence of two methyl group signals and one *t*-butyl group signal at 0.01, 0.02 and 0.82 ppm respectively in proton NMR spectrum confirmed the structure of product **46**.



Scheme 27. *Pd-mediated alkynone cycloisomerization for synthesis of glycal **47***

The alkynol **46** thus obtained was then subjected for oxidation using IBX and ethyl acetate to obtain the intermediate alkynone which, after $Pd(OAc)_2$ catalyzed alkynone cycloisomerization in methanol, afforded dihydropyrans **47α** and **47β** in 64% yield (Scheme 27). The assigned structures of the products were confirmed with the help of spectral and analytical data. In the ^{1}H NMR spectrum of **47α**, −OMe was

found to resonate at 3.09 ppm, whereas in ^{13}C NMR spectrum, the presence of the quaternary olefinic carbon at 146.8 ppm, olefinic =*C*H at 100.4 ppm confirmed the structure of glycal **47α**. In the same way, the structure of **47β** was confirmed with the help of ^{1}H, ^{13}C NMR and HRMS spectra. The stereochemistry of the anomeric –OMe was confirmed after hydroboration-oxidation and acetylation.



Scheme 28. *Stereo- and regioselective hydroboration-oxidation*

Both the anomers were separately subjected for the hydroboration-oxidation using BH_3.DMS, 3N NaOH and 30% H_2O_2 at 0 °C followed by acetylation of the resulting alcohols using acetic anhydride and pyridine in DCM to afford the acetates **48α** and **48β** (Scheme 28).

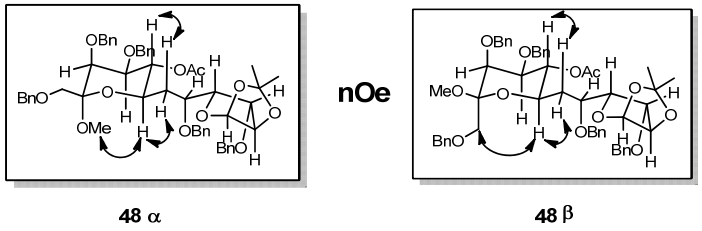


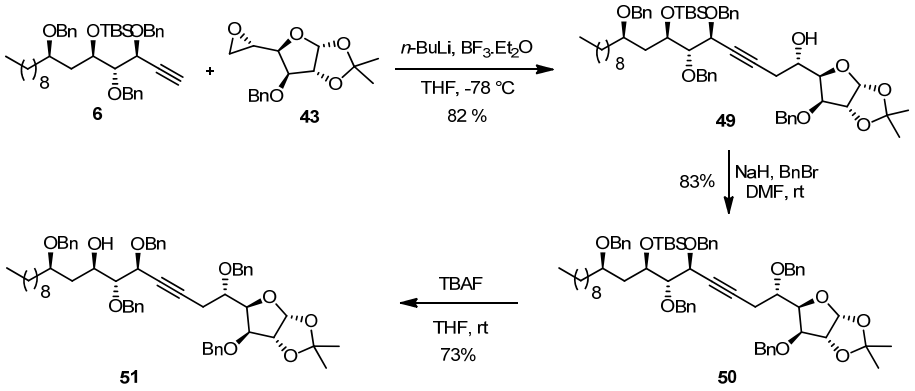
Figure 9. *Characteristic nOe correlations observed in the NOESY spectrums of compounds **48α** and **48β***

In the ^{1}H NMR spectrum of **47α**, the C–H attached to acetate appeared down field at 5.13 ppm with the characteristic large diaxial coupling constant (J = 10 Hz), which indicated a *trans*-orientation with respect to the adjacent methine hydrogens. The anomeric configuration of **48α** was determined as alpha with the help of nOe studies (Figure 9), where C(37)−OMe showed strong nOe with C(33)−H and C(35)−H. Also, in the ^{1}H NMR of **48β**, the C–H attached to acetate was found to

resonate at 5.22 ppm with diaxial coupling constants ($J \approx 9$ Hz) indicating a *trans*-orientation with respect to the adjacent methine protons. The anomeric configuration of the minor product **48β** was also determined with the help of nOe studies, where C(38)−CH_2 instead of C(37)−OMe showed strong nOe with C(33)−H and C(35)−H.

- **Synthesis of C(27)–(48) fragment:**

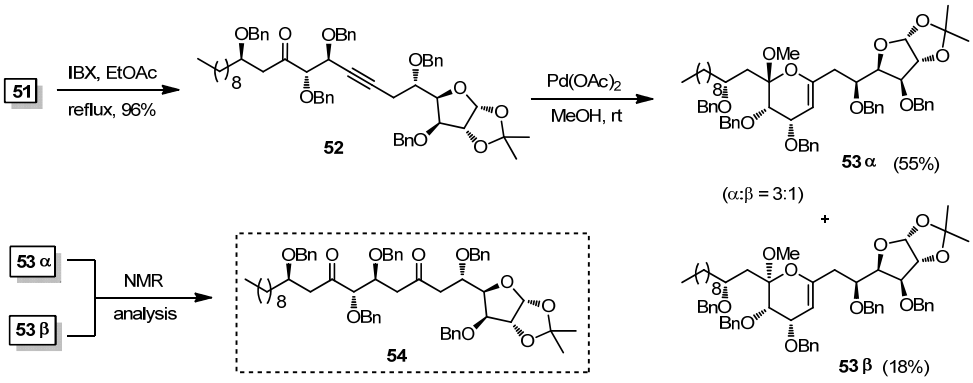
After having executed successfully executed the synthesis of the C(27)−(38) fragment **48α**, the next eventual synthetic goal was the assembly of the C(27)−C(48) fragment, utilizing the epoxide **43** and the key alkyne **6** as the starting points. The opening of the epoxide **43** with alkyne **6** proceeded smoothly and provided **49** in 82% yields. The benzylation of free –OH in **49** followed by TBS deprotection of the resulting compound **50** gave the alkynol fragment **51** in good yields. The structure of the alkynol **51** was confirmed with the help of spectral and analytical data.



Scheme 29. *Synthesis of alkynol **51** using alkyn-epoxide cross coupling reaction*

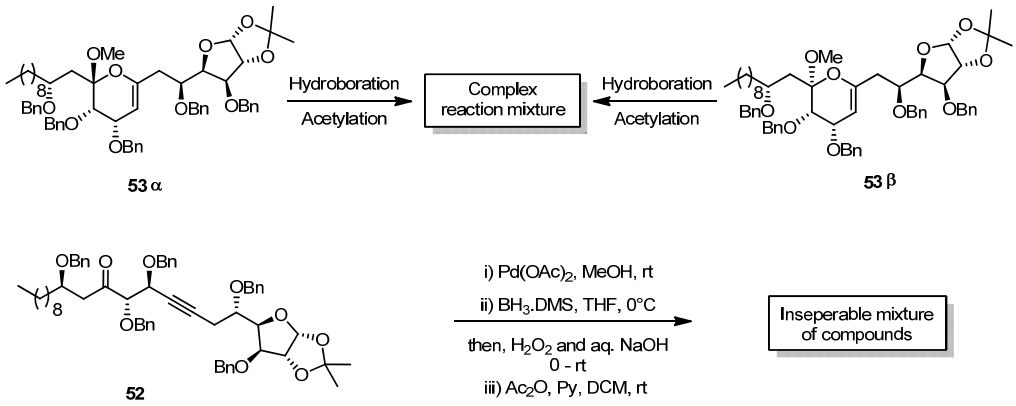
The alkynol **51** thus obtained was converted to an alkynone **52** by oxidation employing IBX in ethyl acetate under reflux conditions. The assigned structure of alkynone **52** was established with the help of spectral and analytical techniques. The presence of signals in ^{1}H and ^{13}C NMR spectra of alkynone are consistent with the allocated structure. The carbonyl carbon was found to resonate downfield (208.0 ppm) in the ^{13}C NMR spectrum which confirmed the formation of ketone/alkynone. Finally, HRMS spectral data also secured the structure of alkynone **52**. After having the alkynone intermediate in hand, the next job was to move forward for Pd-mediated alkynone cycloisomerization in anhydrous methanol to afford dihydropyarans **53α** and **53β** in (3:1) proportion. However, the characterization of these compounds

proved a demanding task. Both the compounds were found to be unstable during NMR analysis and were hydrolyzed easily to give the dicarbonyl compound **54** (Scheme 30) as was evident from the presence of characteristic signals in ^{1}H and ^{13}C NMR spectra. In ^{1}H NMR, the absence of singlet corresponding to –OMe at ≈3.33 ppm (in **53α** and **53β**) and the presence of signals at δ 2.44 (dd, J = 4.7, 17.5 Hz, 1H), 2.53 (dd, J = 5.6, 17.5 Hz, 1H), 2.58–2.70 (m, 1H), 2.72–2.89 (m, 1H), 3.05 (dd, J = 7.5, 17.6 Hz, 1H) and 3.85 (dd, J = 3.4, 6.1 Hz, 1H) clearly indicated that the dihydropyran was completely hydrolyzed into dione **54**. Also the presence of two carbonyl carbons at 205.8 and 210.3 ppm in the ^{13}C NMR spectrum further supported the assigned structure of **54**. After quick analysis of the freshly prepared samples of **53α** and **53β**, we were able to get the analytical data for **53α** whereas **53β** was found to be very unstable when compared to the **53α**, making the data difficult to record. ^{1}H and ^{13}C NMR spectra of **53β** always showed the peaks of dione **54** along with **53β**.



Scheme 30. *Synthesis of dihydropyran via Pd-catalyzed cycloisomerization*

Our attempts involving the direct hydroboration-oxidation and acetylation of freshly prepared **53α** and **53β** led to formation of a complex reaction mixture (Scheme 31), which indicates that the compounds may not be stable enough to do the hydroboration-oxidation. After these disappointing results, the alkynone was subjected for sequential cycloisomerization, hydroboration-oxidation and acetylation as done earlier in the previous report; but regrettably we ended up with the formation of an intractable mixture of compounds.



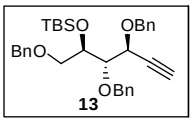
Scheme 31. *Attempts for hydroboration-oxidation to furnish the synthesis of C(27)–C(48) fragment of aflastatin A.*

2. Conclusion:

In conclusion, the syntheses of the C(31)−C(38), C(31)−C(48) and C(27)−C(38) fragments of aflastatin A has been successfully executed by employing the ω-alkynone cycloisomerization and stereoselective hydroboration-oxidation as focal transformations. The alkyne-epoxide cross coupling reaction has played a significant role in C−C bond formations. Also, we have attempted the synthesis of the C(27)−C(48) fragment by utilizing the same protocol. Though achieving the desired target proved to be difficult, our studies in that direction have opened a new door for the construction of a fully functionalized tetrahydropyran unit. Further studies aiming to develop a convergent approach that involves the construction of the key tetrahydropyran unit with minimum number of carbons and subsequent chain elongation are in progress.

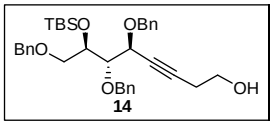
Experimental and data

1. Synthesis of alkyne 13:



To an ice-cooled solution of alcohol **S5.1** (200 mg, 0.48 mmol) and imidazole (186 mg, 2.9 mmol) in anhydrous DMF (2 mL) was added TBSCl (216 mg, 1.44 mmol) and stirred at room temperature for 4 h. Then reaction mixture was diluted with ethyl acetate (20 mL) and washed with water (3 × 5 mL), brine (5 mL), dried over sodium sulphate and evaporated under reduced pressure. The crude was purified by column chromatography (230-400 mesh silica gel, 5:95 ethyl acetate/petroleum ether) to afford compound **13** (227 mg, 89% yield) as a colorless oil. *Characterization data of compound **13***: $[\alpha]_D^{25}$ +21.1 (*c* 0.8, $CHCl_3$); IR ($CHCl_3$): 3297, 2917, 2838, 2137, 1642, 1453, 1071, 756, 652 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ −0.08 (s, 6H), 0.71 (s, 9H), 2.42 (d, *J* = 2.2 Hz, 1H), 3.43 (dd, *J* = 10.0, 4.4 Hz, 1H), 3.50 (dd, *J* = 10.0, 2.2 Hz, 1H), 3.74 (dd, *J* = 7.1, 3.7 Hz, 1H), 3.86–3.93 (m, 1H), 4.33 (s, 2H), 4.41 (dd, *J* = 3.7, 2.1 Hz, 1H), 4.45 (d, *J* = 12.1 Hz, 1H), 4.58 (d, *J* = 11.4 Hz, 1H), 4.80 (d, *J* = 12.1 Hz, 1H), 4.85 (d, *J* = 11.4 Hz, 1H), 7.14–7.28 (m, 15H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ −5.1 (q), −4.3 (q), 18.0 (s), 25.84 (q, 3C), 70.8 (d), 70.9 (t), 71.8 (t), 72.1 (d), 73.2 (t), 74.4 (t), 75.6 (d), 80.3 (s), 81.0 (d), 127.39 (d, 2C), 127.6 (d), 127.70 (d, 2C), 127.95 (d, 2C), 128.01 (d, 2C), 128.14 (d, 2C), 128.23 (d, 2C), 128.31 (d, 2C), 137.6 (s), 138.3 (s), 138.6 (s) ppm; ESI-MS (*m/z*): calcd for $C_{33}H_{42}O_4Si$ ($[M]^+$) 530.29, found 530.57; Anal. calcd for $C_{33}H_{42}O_4Si$: C, 74.68; H, 7.98; found: C, 74.63; H, 8.05.

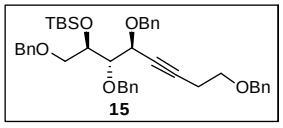
2. Synthesis of alcohol 14:



At −78 °C, a solution of alkyne **13** (1.3 g, 2.45 mmol) in anhydrous THF (10 mL) was treated with *n*-BuLi (1.84 mL, 1.6 M in hexane, 2.94 mmol) and stirred for 20 minutes. Then to this contents $BF_3.Et_2O$ (417 mg, 2.94 mmol) was introduced and stirred at –78 °C for 20 minutes. After that, a solution of ethylene oxide (6.2 M) in anhydrous THF (3 mL) was added slowly at –78 °C and the contents stirred for 1 h at the same temperature. Reaction mixture was quenched by adding saturated sodium bicarbonate (1 mL) and partitioned between ethyl acetate (80 mL) and water (20 mL). The organic layer was washed with brine (20 mL), dried over sodium sulphate and evaporated under reduced pressure. The crude was purified by column chromatography (230–400

mesh silica gel, 1:4 ethyl acetate/petroleum ether) to afford compound **14** (1.18 g, 84% yield) as a colorless oil. *Characterization data of compound **14***: $[\alpha]_D^{25}$ +62.6 (*c* 1.0, $CHCl_3$); IR ($CHCl_3$): 3436, 3017, 2929, 2858, 2112, 1455, 1099 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ −0.02 (s, 6H), 0.77 (s, 9H), 1.99 (br s, 1H), 2.46 (dt, *J* = 1.6, 6.2 Hz, 2H), 3.47 (dd, *J* = 4.9, 10.0 Hz, 1H), 3.53 (dd, *J* = 2.8, 10.0 Hz, 1H), 3.62 (t, *J* = 6.2, 1H), 3.79 (dd, *J* = 3.7, 7.0 Hz, 1H), 3.8–83.95 (m, 1H), 4.40 (br s, 2H), 4.44–4.50 (m, 2H), 4.64 (d, *J* = 11.4 Hz, 1H), 4.81 (d, *J* = 11.9 Hz, 1H), 4.89 (d, *J* = 11.4 Hz, 1H), 7.20–7.29 (m, 15H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ –5.1 (q), –4.3 (q), 18.0 (s), 23.2 (t), 25.81 (q, 3C), 60.9 (t), 70.8 (t), 71.2 (d), 71.8 (t), 72.1 (d), 73.2 (t), 74.4 (t), 78.8 (s), 81.3 (d), 84.7 (s), 127.4 (d), 127.5 (d), 127.6 (d), 127.73 (d, 2C), 127.91 (d, 2C), 128.08 (d, 2C), 128.19 (d, 4C), 128.31 (d, 2C), 137.8 (s), 138.3 (s), 138.5 (s); HRMS (MALDI-TOF) calcd for $C_{35}H_{46}O_5Si$ ($[M+K]^+$) 613.2752, found 613.2789; Anal. calcd for $C_{35}H_{46}O_5Si$: C, 73.13; H, 8.07; found: C, 73.35; H, 7.98.

3. Synthesis of benzyl ether 15:

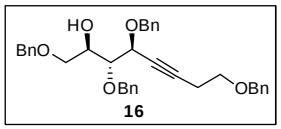


15

To a solution of alcohol **14** (540 mg, 0.94 mmol) in anhydrous DMF (5 mL), sodium hydride (60% oil suspension, 75 mg, 1.88 mmol) was added at 0 °C and allowed to stir for 10 minutes. To this cold reaction mixture benzyl bromide (192 mg, 1.13 mmol) was added slowly and stirred at room temperature for 2 h. After complete consumption of starting material reaction mixture was partitioned between ethyl acetate (50 mL) and water (10 mL). Organic layer was washed with water (3 × 10 mL), brine, dried (Na_2SO_4) and evaporated under reduced pressure. The crude was purified by column chromatography (230–400 mesh silica gel, 15:85 ethyl acetate/petroleum ether) to afford compound **15** (547 mg, 87% yield) as pale yellow oil. *Characterization data of compound **15***: $[\alpha]_D^{25}$ +30.1 (*c* 1.7, $CHCl_3$); IR ($CHCl_3$): 3017, 2928, 2858, 2136, 1455, 1101 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ −0.01 (s, 6H), 0.82 (s, 9H), 2.57−2.65 (m, 2H), 3.52 (dd, *J* = 10.0, 5.2 Hz, 1H), 3.57–3.67 (m, 3H), 3.76–3.79 (m, 1H), 4.00−4.02 (m, 1H), 4.43–4.47 (m, 2H), 4.48−4.52 (m, 2H), 4.53–4.58 (m, 2H), 4.67 (d, *J* = 11.5 Hz, 1H), 4.84 (d, *J* = 12.1 Hz, 1H), 4.91 (d, *J* = 11.5 Hz, 1H), 7.27–7.40 (m, 20H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ −5.1 (q), −4.3 (q), 18.0 (s), 20.3 (t), 25.8 (q, 3C), 68.6 (t), 70.7 (t), 71.0 (d), 71.9 (t), 72.2 (d), 72.9 (t), 73.2 (t), 74.3 (t), 77.5 (s), 81.5 (d), 84.6 (s), 127.4 (d, 2C), 127.5 (d), 127.6 (d, 2C), 127.7 (d, 2C), 127.9 (d, 2C), 128.9 (d, 3C), 128.5 (d, 2C), 128.3 (d, 2C), 128.8 (d,

2C), 128.8 (d), 129.0 (d), 138.0 (s), 138.1 (s), 138.4 (s), 138.8 (s); HRMS (MALDI-TOF) calcd for $C_{42}H_{52}O_5Si$ ($[M+K]^+$) 703.3221, found 703.3202; Anal. calcd for $C_{42}H_{52}O_5Si$: C, 75.86; H, 7.88; found: C, 75.63; H, 7.98.

4. Synthesis of alcohol 16:



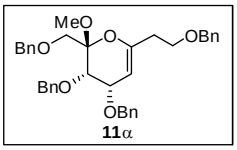
16

To an ice cooled solution of TBS ether **15** (560 mg, 0.84 mmol) in anhydrous THF (5 mL), was added a solution of TBAF (290 mg, 1.1 mmol) in anhydrous THF (1 mL) under argon atmosphere and allowed to stir at room temperature for 4 h. Then reaction mixture was concentrated and residue was purified by column chromatography (230–400 mesh silica gel, 1:4 ethyl acetate/petroleum ether) to afford compound **16** (387 mg, 83% yield) as a colorless oil. *Characterization data of compound **16***: $[\alpha]_D^{25}$ +65.5 (*c* 1.0, $CHCl_3$); IR ($CHCl_3$): 3445, 3030, 2864, 2111, 1496, 1099 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 2.57 (dt, *J* = 1.7, 7.0 Hz, 2H), 2.67 (br s, 1H), 3.53–3.63 (m, 4H), 3.74 (dd, *J* = 3.5, 7.0 Hz, 1H), 3.93 (br s, 1H), 4.42−4.46 (m, 2H), 4.48–4.50 (m, 4H), 4.59 (d, *J* = 11.4 Hz, 1H), 4.85 (d, *J* = 11.4 Hz, 1H), 4.87 (d, *J* = 11.4 Hz, 1H), 7.20–7.32 (m, 20H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 20.3 (t), 68.4 (t), 70.8 (t, 2C), 70.8 (d), 71.3 (d), 72.9 (t), 73.3 (t), 74.0 (t), 77.1 (s), 80.4 (d), 85.1 (s), 127.5 (d), 127.6 (d, 3C), 127.7 (d, 2C), 127.8 (d, 2C), 127.9 (d, 2C), 128.1 (d, 2C), 128.2 (d, 2C), 128.3 (d, 2C), 128.4 (d, 4C), 137.8 (s), 137.9 (s), 138.0 (s), 138.4 (s); HRMS (MALDI-TOF) calcd for $C_{36}H_{38}O_5$ ($[M+K]^+$) 589.2356, found 589.2347; Anal. calcd for $C_{36}H_{38}O_5$: C, 78.52; H, 6.96; found: C, 78.33; H, 6.91.

5. Pd(II)-mediated cycloisomerization and synthesis of glycals 11:

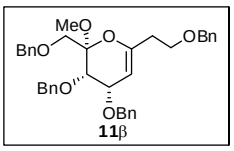
To a solution of alcohol **16** (100 mg, 0.18 mmol) in ethyl acetate (10 mL) was added IBX (76 mg, 0.26 mmol) at room temperature and stirred at reflux temperature for 3 h. After the complete consumption of the starting material, the reaction mixture was cooled in ice bath and filtered through celite bed, washed with ethyl acetate and the combined filtrate were evaporated under reduced pressure. The residual crude ketone (89 mg) was dissolved in anhydrous methanol (10 mL) and the solution was degassed by passing argon for 45 min. To this, $Pd(OAc)_2$ (4 mg, 16 μmol) was added and stirred for 2.5 h. After consumption of starting material, the reaction mixture was filtered through celite bed and the filtrate was concentrated under reduced pressure. The resulting crude was purified by column chromatography (230–400 mesh silica

gel, 1:4 ethyl acetate/petroleum ether) to procure compound **11α** (60 mg, 52% yield) and **11β** (19 mg, 17% yield) as colorless oils.



11α

Characterization data of compound 11α: $[\alpha]_D^{25}$ +19.4 (*c* 1.1, $CHCl_3$); IR ($CHCl_3$): 3015, 2928, 1454, 1099 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 2.38 (t, *J* = 6.9 Hz, 2H), 3.16 (s, 3H), 3.51 (d, *J* = 10.3 Hz, 1H), 3.55–3.60 (m, 2H), 3.70 (d, *J* = 10.3 Hz, 1H), 4.02 (dd, *J* = 1.8, 4.1 Hz, 1H), 4.34 (d, *J* = 12.1 Hz, 1H), 4.38–4.40 (m, 1H), 4.48 (br s, 2H), 4.51 (d, *J* = 6.6 Hz, 1H), 4.57 (br s, 2H), 4.62 (d, *J* = 11.7 Hz, 1H), 4.82 (br s, 1H), 4.93 (d, *J* = 11.7 Hz, 1H), 7.27–7.33 (m, 20H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 34.1 (t), 48.5 (q), 64.7 (t), 67.6 (t), 70.3 (d), 70.9 (t), 72.1 (d), 72.9 (t), 73.3 (t), 74.6 (t), 98.9 (d), 101.4 (s), 127.3 (d, 2C), 127.4 (d, 2C), 127.5 (d), 127.6 (d), 127.7 (d, 2C), 127.9 (d), 128.1 (d, 3C), 128.2 (d, 2C), 128.3 (d, 4C), 128.4 (d, 2C), 137.5 (s), 138.3 (s), 138.7 (s, 2C), 147.8 (s); MALDI-TOF: calculated for $C_{37}H_{40}O_6$ ($[M+K]^+$) 603.19, found 619.15; Anal. calcd for $C_{37}H_{40}O_6$: C, 76.53; H, 6.94; found: C, 76.75; H, 6.81.

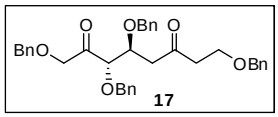


11β

Characterization data of compound 11β: $[\alpha]_D^{25}$ +29.1 (*c* 0.7, $CHCl_3$); IR ($CHCl_3$): 3019, 2928, 1455, 1096 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 2.41 (t, *J* = 6.8 Hz, 2H), 3.33 (s, 3H), 3.62 (t, *J* = 6.8 Hz, 2H), 3.69 (d, *J* = 8.9 Hz, 1H), 3.87–3.92 (m, 2H), 4.01 (d, *J* = 5.3 Hz, 1H), 4.48 (s, 2H), 4.52–4.55 (m, 2H), 4.56–4.61 (m, 3H), 4.70 (d, *J* = 11.9 Hz, 1H), 4.85 (d, *J* = 4.8 Hz, 1H), 7.24–7.36 (m, 20H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 34.3 (t), 50.0 (q), 66.2 (d), 67.4 (t), 68.6 (t), 71.0 (t), 72.6 (t), 72.9 (t), 73.5 (t), 74.1 (d), 97.3 (d), 100.2 (s), 127.4 (d), 127.5 (d, 2C), 127.6 (d, 3C), 127.8 (d, 2C), 128.1 (d, 2C), 128.2 (d, 4C), 128.3 (d, 4C), 128.4 (d, 2C), 138.0 (s), 138.1 (s), 138.2 (s), 139.0 (s), 150.3 (s); MALDI-TOF: calcd for $C_{37}H_{40}O_6$ ($[M+Na]^+$) 603.10, found 603.12; Anal. calcd for $C_{37}H_{40}O_6$: C, 76.53; H, 6.94; found: C, 76.40; H, 6.99.

Characterization data of diketone 17:

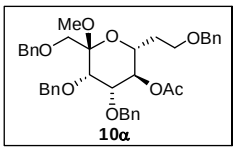
During the collection of the spectral data, compound **11β** (minor) in $CDCl_3$ was found to convert in to a diketone **17**. $[\alpha]_D^{25}$ –8.7 (*c* 0.8, $CHCl_3$); IR ($CHCl_3$): 3031, 2924, 1727, 1712, 1455, 1101 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 2.67 (t, *J* = 6.2 Hz, 2H), 2.74 (dd, *J* = 5.6, 17.5 Hz, 1H), 2.85 (dd, *J* = 7.1, 17.5 Hz, 1H), 3.69 (t, *J* = 6.2 Hz, 2H), 4.12 (d, *J* = 3.1 Hz, 1H), 4.31 (s, 2H), 4.39 (ddd, *J* = 3.1, 5.6, 7.1 Hz, 1H), 4.43–4.47



17

(m, 3H), 4.51–4.58 (m, 5H), 7.19–7.37 (m, 20H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 43.7 (t), 44.1 (t), 64.9 (t), 72.8 (t), 72.9 (t), 73.2 (t), 73.3 (t), 74.2 (t), 75.7 (d), 84.0 (d), 127.7 (d, 4C), 127.8 (d, 2C), 127.9 (d, 3C), 128.0 (d, 2C), 128.1 (d), 128.3 (d, 2C), 128.4 (d, 2C), 128.43 (d, 2C), 128.5 (d, 2C), 137.1 (s), 137.2 (s), 137.8 (s), 138.0 (s), 206.8 (s), 207.5 (s) ppm; HRMS (MALDI-TOF) calcd for $C_{36}H_{38}O_6$ ($[M+Na]^+$) 589.2566, found 589.2493; Anal. calcd for $C_{36}H_{38}O_6$: C, 76.30; H, 6.76; found: C, 76.38; H, 6.89.

6. Synthesis of acetates 10α:



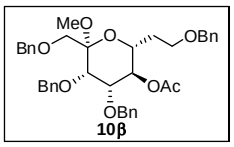
10α

To an ice cooled solution of compound **11α** (44 mg, 0.076 mmol) in anhydrous THF (4 mL), was added neat BH_3.DMS (16.4 μL, 0.152 mmol) and stirring was continued at room temperature for 3 h. The reaction mixture was cooled to 0 °C treated with 3N NaOH (0.5 mL) followed by 30% H_2O_2 (0.5 mL) and stirred at room temperature for 8 h. Then THF was evaporated under reduced pressure, residual material was extracted with diethyl ether (5 mL) and water (2 mL), organic layer dried over sodium sulphate and evaporated under reduced pressure. The crude product was dissolved in 1 mL anhydrous DCM. To this solution, acetic anhydride (0.5 mL) and pyridine (0.5 mL) were added. The contents were stirred for 3 h. After completion of reaction, reaction mixture was concentrated under reduced pressure; traces of solvent were removed by co-evaporation with toluene (10 mL) three times. Residue was purified by column chromatography (230–400 mesh silica gel, 15:85 ethyl acetate/petroleum ether) to procure compound **10α** (32 mg, 68% yield) as colourless oil. *Characterization data of compound **10α*:** $[\alpha]_D^{25}$ –2.4 (*c* 0.96, $CHCl_3$); IR ($CHCl_3$): 3019, 2929, 1739, 1371, 1115 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.66–1.72 (m, 1H), 1.80–1.87 (m, 1H), 1.97 (s, 3H), 3.12 (s, 3H), 3.42 (d, *J* = 10.1 Hz, 1H), 3.48–3.52 (m, 1H), 3.59 (dd, *J* = 4.9, 9.4 Hz, 1H), 3.63 (d, *J* = 10.1 Hz, 1H), 3.71 (dt, *J* = 2.4, 10.1, 1H), 3.98 (dd, *J* = 2.9, 9.8 Hz, 1H), 4.07 (d, *J* = 2.9 Hz, 1H), 4.40 (d, *J* = 12.1 Hz, 1H), 4.43 (s, 1H), 4.44 (s, 1H), 4.49 (d, *J* = 12.2 Hz, 1H), 4.53 (s, 1H), 4.56 (s, 1H), 4.65 (d, *J* = 12.1 Hz, 1H), 4.90 (d, *J* = 11.2 Hz, 1H), 5.24 (br t, *J* = 9.9 Hz, 1H), 7.23–7.37 (m, 20H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 21.1 (q), 31.6 (t), 47.8 (q), 65.2 (t), 66.0 (t), 67.7 (d), 71.7 (t), 71.8 (d), 72.9 (t), 73.4 (t), 74.8 (d), 74.9 (t), 78.4 (d), 100.8 (s), 127.3 (d, 2C), 127.4 (d), 127.42 (d), 127.5 (d), 127.6 (d, 2C), 127.9 (d), 127.97 (d, 2C), 128.1 (d, 2C), 128.2 (d, 2C), 128.27 (d, 2C), 128.3 (d, 2C), 128.4 (d, 2C), 137.6 (s), 138.1

(s), 138.5 (s), 138.6 (s), 170.1 (s); HRMS (MALDI-TOF) calcd for $C_{39}H_{44}O_8$ ($[M+Na]^+$) 663.2934, found 663.2907; Anal. Calcd for $C_{39}H_{44}O_8$: C, 73.10; H, 6.92; Found: C, 73.02; H, 6.98.

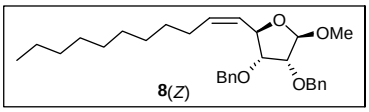
7. Synthesis of acetates 10β:

Following the above procedure the hydroboration of **11β** (19 mg, 33 μmol) followed by acetylation gave **10β** (14 mg, 65% yield) as colorless oil. *Characterization data of compound **10β***: $[\alpha]_D^{25}$ –15.4 (*c* 0.5, $CHCl_3$); IR ($CHCl_3$): 3019, 2927, 1738, 1452, 1095 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.84–1.94 (m, 2H), 1.97 (s, 3H), 3.28 (s, 3H), 3.46–3.52 (m, 3H), 3.56 (dd, *J* = 3.0, 9.1 Hz, 1H), 3.59 (dd, *J* = 4.9, 9.1 Hz, 1H), 3.62–3.66 (m, 1H), 4.10 (d, *J* = 3.0 Hz, 1H), 4.23 (d, *J* = 12.4 Hz, 1H), 4.37 (d, *J* = 4.1 Hz, 1H), 4.39 (d, *J* = 4.3 Hz, 1H), 4.46–4.52 (m, 3H), 4.69 (d, *J* = 12.1 Hz, 1H), 4.87 (d, *J* = 12.1 Hz, 1H), 5.21 (br t, *J* = 8.7 Hz, 1H), 7.16–7.40 (m, 20H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 21.1 (q), 32.8 (t), 49.4 (q), 65.8 (t), 66.8 (t), 70.7 (d), 71.1 (t), 71.9 (d), 72.9 (t), 73.4 (t), 74.2 (d), 74.9 (t), 76.6 (d), 100.3 (s), 127.3 (d), 127.5 (d, 2C), 127.6 (d, 2C), 127.7 (d, 2C), 127.75 (d, 2C), 127.9 (d), 128.0 (d, 2C), 128.2 (d, 4C), 128.3 (d, 2C), 128.5 (d, 2C), 137.6 (s), 138.1 (s), 138.4 (s), 138.8 (s), 170.0 (s); HRMS (MALDI-TOF) calcd for $C_{39}H_{44}O_8$ ($[M+K]^+$) 679.2673, found 679.2650; Anal. calcd for $C_{39}H_{44}O_8$: C, 73.10; H, 6.92; found: C, 73.37; H, 6.66.



8. Synthesis of olefin 8(*Z*):

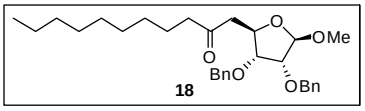
At –78 °C, a solution of DMSO (11.34 g, 145.2 mmol) in CH_2Cl_2 (55 mL) was treated with oxallyl chloride (11.06 g, 87.1 mmol) and stirred for 15 min. To this were added a solution of alcohol **S14.1** (10 g, 29 mmol) in CH_2Cl_2 (25 mL) and Et_3N (29.38 g, 290.4 mmol) after 15 min. The contents were stirred at –78 °C for another 15 minutes, and diluted with saturated NH_4Cl solution (50 mL). Two layers were separated and the aqueous layer was extracted with DCM (3 × 150 mL), dried over Na_2SO_4, volatiles were removed and the crude was directly used for next reaction without purification.



n-BuLi (72.6 mL, 116.1 mmol) was added to an ice cooled solution of decyl triphenylphophonium bromide (70.2 g, 145.1 mmol) in anhydrous THF (350 mL) and stirred at room temperature for 1 h. This ylide was transfered to a stirred solution of aldehyde (9.94 g, 29 mmol) in THF (100 mL) at 0 °C and stirred at room temperature for 2 h. The reaction mixture was quenched with sat NH_4Cl solution (20 mL); THF

was removed and the aqueous layer was extracted with ethyl acetate (3 × 70 mL), combined organic layers were dried over Na_2SO_4, volatiles were removed and the crude was purified by column chromatography (230–400 mesh silica gel, 5:95 ethyl acetate/petroleum ether) to provide the olefin **8***(Z)* (10.43 g, 77% yield) as a pale yellow oil. *Characterization data of compound* ***8(Z)*****:** $[\alpha]_D^{25}$ –10.9 (*c* 1.6, $CHCl_3$); IR ($CHCl_3$): 3064, 2954, 2854, 1715, 1606, 1465, 1455, 1145, 1046, 734, 697 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 0.88 (t, J = 6.6 Hz, 3H), 1.24 (br s, 14H), 2.00–2.21 (m, 2H), 3.32 (s, 3H), 3.82–3.91 (m, 2H), 4.51 (d, J = 12.2 Hz, 1H), 4.58 (d, J = 12.2 Hz, 1H), 4.66 (d, J = 12.3 Hz, 1H), 4.74 (d, J = 12.3 Hz, 1H), 4.87 (s, 1H), 4.94 (ddd, J = 0.8, 7.1, 9.1 Hz, 1H), 5.35 (dt, J = 10.8, 9.3 Hz, 1H), 5.69 (ddd, J = 6.4, 7. 3, 10.8 Hz, 1H), 7.30–7.40 (m, 10H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 14.1 (q), 22.6 (t), 27.7 (t), 29.3 (t, 2C), 29.5 (t, 2C), 29.8 (t), 31.9 (t), 54.9 (q), 72.3 (t), 72.4 (t), 76.9 (d), 80.0 (d), 82.7 (d), 106.1 (d), 127.5 (d, 2C), 127.6 (d), 127.8 (d), 128.0 (d, 2C), 128.3 (d, 2C), 128.4 (d, 2C), 129.5 (d), 135.0 (d), 137.8 (s), 137.9 (s); MALDI-TOF: 489.21 (68% $[M+Na]^+$), 505.18 (100% $[M+K]^+$); Anal. calcd for $C_{30}H_{42}O_4$: C, 77.21; H, 9.07; found: C, 77.49; H, 9.32.

9. Synthesis of ketone 18:

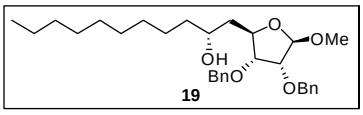


18

A solution of $PdCl_2$ (5 mg, 0.03 mmol) in *N,N*−dimethylacetamide (20 mL) and water (3 mL) was stirred at room temperature for 1 h under O_2 atmosphere (12 bar). Then to this, a solution of olefin **8(*Z*)** (1 g, 2.1 mmol) in *N,N*−dimethylacetamide (10 mL) was added and stirring was continued for 12 h at 90 °C under O_2 atmosphere (4 bar). Reaction mixture was cooled and partitioned between diethyl ether (2 × 50 mL) and water (30 mL). Combined organic phase was washed with brine (20 mL), dried and concentrated under reduced pressure. Crude compound was purified by column chromatography (230–400 mesh silica gel, 1:4 ethyl acetate/petroleum ether) to procure compound **18** [720 mg, 76% yield based on **8(*Z*)** recovered (78 mg)] as a colorless oil. *Characterization data of compound* ***18*****:** $[\alpha]_D^{25}$ +14.5 (*c* 0.7 in $CHCl_3$); IR (neat): 2926, 2855, 1714, 1455, 1046, 736, 698 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 0.87 (t, J = 6.5 Hz, 3H), 1.24 (br s, 12H), 1.51–1.58 (m, 2H), 2.44 (t, J = 7.4 Hz, 2H), 2.62 (d, J = 6.7 Hz, 2H), 3.30 (s, 3H), 3.79–3.88 (m, 2H), 4.46 (d, J = 11.8 Hz, 1H), 4.53–4.59 (m, 3H), 4.68 (d, J = 12.1 Hz, 1H), 4.88 (s, 1H), 7.30–7.36 (m, 10H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 14.1 (q), 22.6 (t), 23.5 (t), 29.1 (t), 29.2 (t), 29.4 (t,

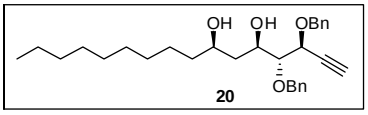
2C), 31.8 (t), 43.1 (t), 48.3 (t), 55.1 (q), 72.2 (t), 72.4 (t), 77.2 (d), 79.3 (d), 81.3 (d), 106.4 (d), 127.8 (d, 2C), 127.9 (d, 2C), 128.9 (d, 2C), 128.4 (d, 4C), 137.6 (s, 2C), 208.7 (s); HRMS (MALDI-TOF) calcd for $C_{30}H_{42}O_5$ ($[M+K]^+$) 521.2669, found 521.2703; Anal. calcd for $C_{30}H_{42}O_5$; C, 74.65, H, 8.77; found C, 74.59, H, 8.83.

10. Synthesis of alcohol 19:



LiI (2.77 g, 20.7 mmol) was added to a solution of ketone **18** (1g, 2.1 mmol) in diethyl ether (40 mL) at –40 °C and stirred for 10 min. Then reaction mixture was cooled to –100 °C and LAH (785 mg, 20.7 mmol) was introduced in three portions. Stirring was continued for next 45 minutes at the same temperature. Reaction mixture was quenched by 10% sodium potassium tartarate (5 mL) at –100 °C and allowed to warm to room temperature. Organic phase was separated and aqueous layer was extracted with diethyl ether (2 × 10 mL). Combined organic phase was washed with brine (25 mL), dried and concentrated under reduced pressure. The resulting crude compound (9:1 dr) was purified by column chromatography (100–200 mesh silica gel, 1:4 ethyl acetate/petroleum ether) to procure compound **19** (867 mg, 86% yield) as a colorless oil. *Characterization data of compound **19***: $[\alpha]_D^{25}$ +26.5 (*c* 1.2 in $CHCl_3$); IR (neat) 3479, 3016, 2928, 2856, 1455, 1216, 1045, 756, 698 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 0.82 (t, J = 6.5 Hz, 3H), 1.20 (br s, 14H), 1.33–1.36 (m, 2H), 1.45–1.53 (m, 1H), 1.67–1.77 (m, 1H), 3.26 (s, 3H), 3.71–3.73 (m, 1H), 3.76–3.78 (m, 1H), 3.79–3.82 (m, 1H), 4.20–4.26 (m, 1H), 4.37 (d, J = 11.7 Hz, 1H), 4.52 (d, J = 11.7 Hz, 1H), 4.54 (d, J = 12.1 Hz, 1H), 4.63 (d, J = 12.0 Hz, 1H), 4.84 (s, 1H), 7.19–7.32 (m, 10H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.1 (q), 22.6 (t), 25.5 (t), 29.3 (t), 29.51 (t), 29.58 (t), 29.63 (t), 31.9 (t), 37.3 (t), 41.9 (t), 55.2 (q), 71.2 (d), 72.3 (t), 72.6 (t), 78.7 (d), 80.9 (d), 82.2 (d), 106.3 (d), 127.9 (d, 4C), 128.0 (d, 2C), 128.4 (d, 4C), 137.4 (s), 137.5 (s); HRMS (MALDI-TOF) calcd for $C_{30}H_{44}O_5$ ($[M+Na]^+$) 507.3086, found 507.3083; Anal. calcd for $C_{30}H_{44}O_5$; C, 74.34, H, 9.15; found C, 74.45, H, 9.21.

11. Synthesis of diol 20:



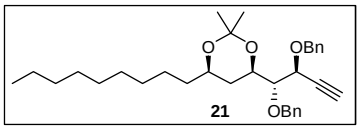
To a solution of alcohol **19** (100 mg, 0.21 mmol) in *t*-butanol (8 mL) and water (2 mL) was added conc. HCl (0.1 mL) at room temperature and stirring was continued at reflux for 6 h. After complete consumption of starting material as

indicated by TLC, the reaction mixture was cooled in ice bath and neutralized with triethylamine. Solvent was removed under vacuum and residual material was extracted with ethyl acetate (3 × 5 mL). The combined organic layer was washed with water (5 mL), brine (5 mL), dried over sodium sulphate and concentrated under reduced pressure. The crude product (92 mg, 0.19 mmol) was dissolved in anhydrous methanol (4 mL) and treated with K_2CO_3 (80 mg, 0.58 mmol) followed by a solution of dimethyl-1-diazo-2-oxopropyl phosphonate (110 mg, 0.58 mmol) in methanol (1 mL). After stirring for 7 h, the reaction mixture was filtered through celite bed and filtrate was concentrated. The residue was extracted with ethyl acetate (20 mL) and water (5 mL). Organic layer washed with brine (5 mL), dried over sodium sulphate and concentrated under reduced pressure. The residue was purified by column chromatography (230–400 mesh silica gel, 15:85 ethyl acetate/petroleum ether) to procure compound **20** (55 mg, 58% yield over two steps) as colorless oil. *Characterization data of compound **20***: $[\alpha]_D^{25}$ +48.2 (*c* 0.4 in $CHCl_3$); IR (neat): 3431, 3016, 2927, 2856, 2114, 1629, 1455, 1216, 1085, 624 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 0.87 (t, *J* = 6.5 Hz, 3H), 1.25 (br s, 14H), 1.34–1.43 (m, 3H), 1.80–1.83 (m, 1H), 2.59 (d, *J* = 2.1 Hz, 1H), 3.57 (dd, *J* = 4.7, 6.6 Hz, 1H), 3.78–3.82 (m, 1H), 3.98–4.02 (m, 1H), 4.43 (dd, *J* = 2.1, 4.7 Hz, 1H), 4.54 (d, *J* = 11.5 Hz, 1H), 4.65 (d, *J* = 11.2 Hz, 1H), 4.90 (d, *J* = 11.5 Hz, 1H), 4.92 (d, *J* = 11.2 Hz, 1H), 7.28–7.35 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.1 (q), 22.7 (t), 25.3 (t), 29.3 (t), 29.5 (t), 29.6 (t, 2C), 31.9 (t), 38.2 (t), 38.4 (t), 70.4 (d), 71.0 (t), 73.0 (d), 73.3 (d), 74.4 (t), 75.8 (d), 80.3 (s), 82.8 (d), 127.8 (d), 127.9 (d), 128.1 (d, 2C), 128.3 (d, 2C), 128.4 (d, 2C), 128.5 (d, 2C), 137.2 (s), 137.9 (s); HRMS (MALDI-TOF) calcd for $C_{30}H_{42}O_4$ ($[M+K]^+$) 505.2720, found 505.2705 ($[M+K]^+$); Anal. calcd for $C_{30}H_{42}O_4$; C, 77.21, H, 9.07; found C, 76.93, H, 9.18.

12. Synthesis of acetonide 21:

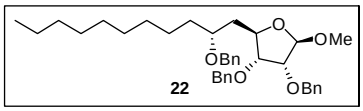
At 0 °C, to a solution of diol **20** (32 mg, 0.06 mmol) in 2,2 dimethoxy propane (1 mL) was added *p*-TSA (2 mg) and stirred at 0 °C for 20 min. The reaction mixture was warmed to room temperature and stirring was continued for next 2 h. After consumption of starting material the reaction mixture was neutralized with triethylamine and concentrated. Residual material was purified by column chromatography (230–400 mesh silica gel, 1:9 ethyl acetate/petroleum ether) to procure compound **21** (30 mg, 88% yield) as a colorless oil.

***Characterization data of compound 21*:** $[\alpha]_D^{25}$ +50.9 (*c* 0.5 in $CHCl_3$); IR ($CHCl_3$): 3306, 3018, 2928, 2857, 2131, 1216, 1110, 758, 621 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 0.88 (t, *J* = 6.9 Hz, 3H), 1.26 (br s, 12H), 1.28–1.32 (m, 4H), 1.34 (s, 3H), 1.39 (s, 3H), 1.44–1.47 (m, 1H), 1.65 (dt, *J* = 2.4, 12.9 Hz, 1H), 2.52 (d, *J* = 2.1 Hz, 1H), 3.63 (dd, *J* = 3.4, 7.3 Hz, 1H), 3.70–3.75 (m, 1H), 4.01 (ddd, *J* = 2.4, 7.4, 11.6 Hz, 1H). 4.47–4.49 (m, 1H), 4.52 (d, *J* = 11.7 Hz, 1H), 4.71 (d, *J* = 11.5 Hz, 1H), 4.90 (d, *J* = 11.7 Hz, 1H), 4.94 (d, *J* = 11.4 Hz, 1H), 7.26–7.37 (m, 10H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 14.1 (q), 19.6 (q), 22.7 (t), 24.8 (t), 29.3 (t), 29.5 (t, 3C), 30.1 (q), 31.9 (t), 33.0 (t), 36.4 (t), 68.8 (d), 68.9 (d), 70.8 (d), 71.1 (t), 74.5 (t), 75.3 (d), 79.9 (s), 82.1 (d), 98.5 (s), 127.5 (d), 127.6 (d), 127.8 (d, 2C), 128.2 (d, 2C), 128.3 (d, 2C), 128.5 (d, 2C), 137.8 (s), 138.4 (s); HRMS (MALDI-TOF) calcd for $C_{33}H_{46}O_4$ ($[M+Na]^+$) 529.3294, found 529.3257; Anal. calcd for $C_{33}H_{46}O_4$; C, 78.22, H, 9.15; found C, 78.31, H, 9.22.



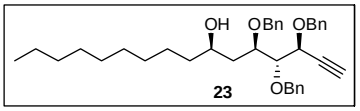
13. Synthesis of benzyl ether 22:

To an ice cooled solution of alcohol **19** (1.4 g, 2.89 mmol) in DMF (15 mL) was added NaH (0.084 g, 3.47 mmol) followed by benzyl bromide (0.3 mL, 3.18 mmol). The reaction mixture was warmed to room temperature and stirred for 3 h. The reaction mixture was partitioned between water (50 mL) and ethyl acetate (3 × 50 mL). Organic layer washed with water (3 × 30 mL), brine (25 mL), dried over Na_2SO_4, concentrated and the crude was purified by column chromatography (230–400 mesh silica gel, 1:9 ethyl acetate/petroleum ether) to afford compound **22** (1.58 g, 96% yield) as a colorless syrup. *Characterization data of compound 22*: $[\alpha]_D^{25}$ +21.3 (*c* 1.6, $CHCl_3$); IR ($CHCl_3$): 3019, 2927, 1653, 1454, 1215, 1045, 750, 669 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 0.88 (t, *J* = 6.82 Hz, 3H), 1.25 (br s, 16H), 1.59 (m, 2H), 3.33 (s, 3H), 3.47(m, 1H), 3.84 (dd, *J* = 0.73, 4.54 Hz 1H), 4.03 (dd, *J* = 7.6, 4.5 Hz, 1H), 4.21 (dd, *J* = 4.5, 7.6 Hz, 1H), 4.32 (d, *J* = 11.7 Hz, 1H), 4.50 (d, *J* = 11.7 Hz, 1H), 4.49–4.62 (m, 3H), 4.70 (d, *J* = 11.7 Hz, 1H), 4.93 (s, 1H), 7.26–7.38 (m, 15H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 14.1 (q), 22.7 (t), 25.5 (t), 29.3 (t), 29.6 (t, 3C), 29.8 (t), 30.6 (t), 31.9 (t), 54.9 (q), 72.2 (t), 72.3 (t), 72.3 (t), 77.9 (d), 79.3 (d), 79.7 (d), 82.7 (d), 105.5 (d), 127.3 (d), 127.6 (d, 2C), 127.8 (d), 127.8 (d), 128.1 (d, 2C), 128.1 (d, 2C), 128.2 (d, 2C), 128.3 (d, 2C), 128.4 (d, 2C), 137.6 (s), 137.7 (s), 139.0 (s); HRMS (MALDI-



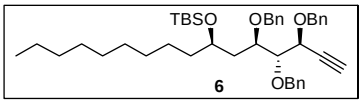
TOF) calcd for $C_{37}H_{50}O_5$ ([M+Na]$^+$) 597.3556, found 597.3557; Anal. calcd for $C_{37}H_{50}O_5$: C, 77.31; H, 8.77; found: C, 77.38; H, 8. 96.

14. Synthesis of alkyne 23:



A solution of benzyl ether **22** (2.0 g, 3.5 mmol) in 4:1 mixture of *t*-butanol/water (20 mL) was treated with conc. HCl (2 mL) and stirred at reflux for 6 h. Reaction mixture was neutralized with triethylamine, dioxane removed under reduced pressure and residue was extracted with ethyl acetate (3 × 40 mL). Combined organic layer dried over sodium sulphate, concentrated under reduced pressure. The crude was treated with K_2CO_3 (1.4 g, 10.2 mmol) and Ohira-Bestmann reagent (1.0 g, 5.1 mmol) at room temperature for 14 h. Reaction mixture was filtered through celite and concentrated under reduced pressure. The residue obtained was purified by column chromatography (230–400 mesh silica gel, 5:95 ethyl acetate/petroleum ether) to afford **23** (1.03 g, 53% yield) as colorless oil. *Characterization data of compound **23***: $[\alpha]_D^{25}$ +94.3 (*c* 1.6, $CHCl_3$); IR ($CHCl_3$): 3548, 3306, 3031, 2926, 2855, 2138, 1496, 1454, 1216, 1067, 757, 697, 614 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 0.88 (t, *J* = 6.7 Hz, 3H), 1.25 (br s, 16H), 1.59–1.70 (m, 2H), 2.58 (d, *J* = 2.2 Hz, 1H), 3.57 (dt, *J* = 1.1, 9.3 Hz, 1H), 3.69 (dt, *J* = 1.1, 6.7 Hz, 1H), 3.79 (dd, *J* = 2.2, 8.9 Hz, 1H), 4.20 (d, *J* = 11.4 Hz, 1H), 4.46–4.55 (m, 3H), 4.73 (t, *J* = 2.2 Hz, 1H), 4.94 (d, *J* = 11.7 Hz, 1H), 5.00 (d, *J* = 11.7 Hz, 1H), 7.20–7.40 (m, 15H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 14.1 (q), 22.7 (t), 25.5 (t), 29.3 (t), 29.5 (t), 29.6 (t, 2C), 29.8 (t), 30.8 (t), 31.9 (t), 71.2 (t), 71.9 (t), 72.1 (d), 72.2 (d), 73.5 (t), 76.2 (d), 76.7 (d), 79.6 (s), 80.2 (d), 127.6 (d), 127.6 (d, 2C), 127.7 (d, 2C), 127.8 (d, 2C), 128.2 (d, 2C), 128.3 (d, 6C), 137.8 (s), 138.4 (s), 138.4 (s); ESI–MS (*m/z*): 579.43 (100% [M+Na]$^+$); Anal. calcd for $C_{37}H_{48}O_4$: C, 79.82; H, 8.69; found: C, 79.60 H, 8.83.

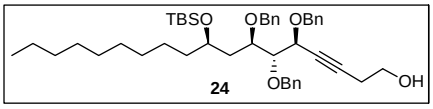
15. Synthesis of TBS ether 6:



To an ice cooled solution of alkynol **23** (117 mg, 0.2 mmol) and Et_3N (42 µL) in CH_2Cl_2 (5 mL) was added TBSOTf (60 µL, 0.2 mmol) and stirred at same temperature for 2 h. Usual workup followed by purification (230–400 mesh silica gel, 5:95 ethyl acetate/petroleum ether) gave the TBS ether **6** (0.132 g, 93% yield) as colorless thick oil. *Characterization data of compound **6***: $[\alpha]_D^{25}$ +52.6 (*c* 1.0 in $CHCl_3$); IR (neat): 3307, 2927, 2855, 2143, 1651, 1455, 1215, 1067, 757, 668, 618 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.00 (s,

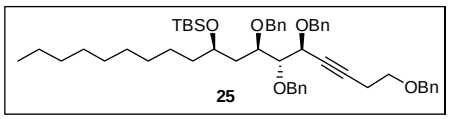
3H), 0.03 (s, 3H), 0.82 (s, 9H), 0.87 (t, J = 6.6 Hz, 3H), 1.20–1.23 (m, 16H), 1.41–1.51 (m, 2H), 2.51 (d, J = 2.2 Hz, 1H), 3.49–3.67 (m, 1H), 3.83 (dd, J = 4.4, 5.4 Hz, 1H), 3.94 (dd, J = 4.4, 5.4 Hz, 1H), 4.32–4.39 (m, 1H), 4.49 (d, J = 11.6 Hz, 1H), 4.51 (d, J = 12.2 Hz, 1H), 4.53–4.56 (m, 1H), 4.66 (d, J = 11.4 Hz, 1H), 4.88 (d, J = 11.6 Hz, 1H), 4.93 (d, J = 11.3 Hz, 1H), 7.23–7.39 (m, 15H); ^{13}C NMR (50 MHz, $CDCl_3$): δ –4.3 (q), –4.2 (q), 14.1 (q), 18.2 (s), 22.7 (t), 25.9 (t), 26.0 (q, 3C), 29.3 (t), 29.5 (t), 29.6 (t, 2C), 29.7 (t), 30.4 (t), 31.9 (t), 70.8 (t), 71.0 (d), 71.8 (t), 73.7 (d), 73.8 (t), 75.6 (d), 80.0 (d), 80.8 (s), 81.2 (d), 127.1 (d), 127.3 (d), 127.4 (d, 2C), 127.6 (d), 127.9 (d, 2C), 128.1 (d, 6C), 128.3 (d, 2C), 137.7 (s), 138.7 (s), 139.2 (s); HRMS (MALDI-TOF) calcd for $C_{43}H_{62}O_4Si$ ($[M+K]^+$) 709.4054, found 709.3989; Anal. calcd for $C_{43}H_{62}O_4Si$; C, 76.96, H, 9.31; found C, 77.03, H, 9.42.

16. Synthesis of alcohol 24:



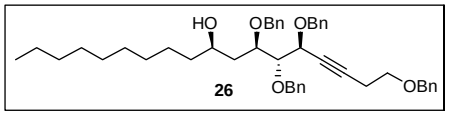
The alcohol **24** (462 mg, 87% yield) as a pale yellow oil was prepared from alkyne **6** (0.5 g, 0.74 mmol) and a solution of ethylene oxide (6.2 M) in anhydrous THF (2.5 mL) following the similar reaction conditions used for the synthesis of compound **24**. *Characterization data of compound **24***: $[\alpha]_D^{25}$ +31.8 (*c* 0.9, $CHCl_3$); IR ($CHCl_3$): 3434, 2927, 2856, 2126, 1454, 1216, 1095, 758, 668 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz): δ –0.01 (s, 3H), 0.02 (s, 3H), 0.82 (s, 9H), 0.86 (t, J = 6.3 Hz, 3H), 1.22 (br s, 16H), 1.44–1.52 (m, 2H), 1.90 (br s, 1H), 2.49 (dt, J = 1.7, 6.1 Hz, 2H), 3.42–3.55 (m, 2H), 3.63 (t, J = 6.1 Hz, 2H), 3.83 (dd, J = 4.0, 5.6 Hz, 1H), 3.91 (dd, J = 4.2, 5.6 Hz, 1H), 4.45 (d, J = 11.8 Hz, 1H), 4.48 (d, J = 11.7 Hz, 1H), 4.51–4.57 (m, 1H), 4.67 (d, J = 11.4 Hz, 1H), 4.84 (d, J = 12.1 Hz, 1H), 4.90 (d, J = 11.7 Hz, 1H), 7.24–7.37 (m, 15H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ –4.4 (q), –4.2 (q), 14.1 (q), 18.2 (s), 22.7 (t), 23.4 (t), 26.0 (q, 3C), 26.1 (t), 29.3 (t), 29.6 (t, 3C), 29.7 (t), 30.4 (t), 31.9 (t), 60.9 (t), 70.8 (t), 71.5 (d), 71.8 (t), 73.4 (d), 73.8 (t), 79.6 (s), 80.2 (d), 81.7 (d), 84.6 (s), 127.1 (d), 127.3 (d), 127.5 (d, 2C), 127.6 (d), 127.8 (d, 2C), 127.9 (d, 2C), 128.1 (d, 4C), 128.3 (d, 2C), 138.0 (s), 138.7 (s), 139.2 (s); HRMS (MALDI-TOF) calcd for $C_{45}H_{66}O_5Si$ ($[M+K]^+$) 753.4317, found 753.4371; Anal. calcd for $C_{45}H_{66}O_5Si$: C, 75.58; H, 9.30; found: C, 75.64; H, 9.48.

17. Synthesis of benzyl ether 25:



The benzylation of alcohol **24** (100 mg, 0.14 mmol) was carried out under the similar conditions used for the synthesis of compound **15** to afford benzyl ether **25** (96 mg, 86% yield) as colorless oil. *Characterization data of compound* ***25*****:** $[\alpha]_D^{25}$ +41.7 (*c* 1.2, $CHCl_3$); IR ($CHCl_3$): 3019, 2925, 2856, 2210, 1464, 1215, 1095, 757, 669 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 0.00 (s, 3H), 0.04 (s, 3H), 0.84 (s, 9H), 0.88 (t, *J* = 6.2 Hz, 3H), 1.20–1.24 (m, 16H), 1.42–1.53 (m, 2H), 2.59 (dt, *J* = 1.8, 7.3 Hz, 2H), 3.46–3.58 (m, 1H), 3.59 (t, *J* = 7.3 Hz, 2H), 3.78 (t, *J* = 4.9 Hz, 1H), 3.94 (t, *J* = 4.9 Hz, 1H), 4.45 (dd, *J* = 4.1, 11.8 Hz, 2H), 4.51–4.58 (m, 4H), 4.67 (d, *J* = 11.5 Hz, 1H), 4.86 (d, *J* = 12.0, 1H), 4.92 (d, *J* = 12.0, 1H), 7.23–7.39 (m, 20H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ –4.3 (q), –4.2 (q), 14.1 (q), 18.2 (s), 20.4 (t), 22.7 (t), 25.9 (t), 26.1 (q, 3C), 29.3 (t), 29.6 (t, 3C), 29.7 (t), 30.6 (t), 31.9 (t), 68.6 (t), 70.6 (t), 71.1 (d), 71.9 (t), 72.9 (t), 73.7 (t), 74.0 (d), 78.3 (s), 80.1 (d), 81.6 (d), 84.3 (s), 127.1 (d), 127.2 (d), 127.4 (d, 3C), 127.6 (d, 3C), 127.8 (d, 2C), 127.9 (d, 2C), 128.0 (d), 128.0 (d, 3C), 128.2 (d, 2C), 128.3 (d, 2C), 138. 1 (s, 2C), 139.0 (s), 139.3 (s); HRMS (MALDI-TOF) calcd for $C_{52}H_{72}O_5Si$ ($[M+K]^+$) 843.4786, found 843.4781; Anal. calcd for $C_{52}H_{72}O_5Si$: C, 77.56; H, 9.01; found: C, 77.65; H, 9.09.

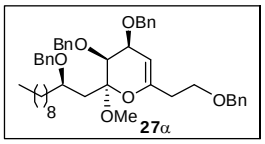
18. Synthesis of alcohol 26:



TBS ether deprotection of **25** (100 mg, 0.12 mmol) was done successfully following the similar reaction conditions used for preparation of compound **16** to afford alkynol **26** (70 mg, 81% yield) as a colorless oil. *Characterization data of compound* ***26*****:** $[\alpha]_D^{25}$ +39.6 (*c* 1.2, $CHCl_3$); IR ($CHCl_3$): 3475, 3018, 2925, 2132, 1454, 1215, 1095, 759, 667 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 0.88 (t, *J* = 6.7 Hz, 3H), 1.25 (br s, 16H), 1.57–1.70 (m, 2H), 2.43 (br s, 1H), 2.61 (dt, *J* = 1.8, 7.2 Hz, 2H), 3.54–3.59 (m, 1H), 3.62 (t, *J* = 7.1 Hz, 2H), 3.76 (d, *J* = 2.5, 8.7 Hz, 1H), 3.82–3.88 (m, 1H), 4.21 (d, *J* = 11.3 Hz, 1H), 4.46–4.54 (m, 5H), 4.67–4.70 (m, 1H), 4.93 (d, *J* = 11.5 Hz, 1H), 4.98 (d, *J* = 11.7 Hz, 1H), 7.21–7.34 (m, 20H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 14.1 (q), 20.4 (t), 22.7 (t, 2C), 24.5 (t), 29.3 (t), 29.6 (t, 2C), 29.8 (t), 31.9 (t, 2C), 68.5 (t), 70.4 (t), 70.8 (t), 71.1 (d), 71.9 (d), 73.0 (t), 74.3 (t), 76.8 (s), 80.2 (d), 83.2 (d), 84.7 (s), 127.5 (d), 127.5 (d, 2C), 127.6 (d),

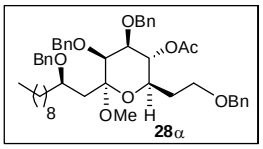
127.7 (d), 127.8 (d, 2C), 128.2 (d, 2C), 128.3 (d), 128.35 (d, 3C), 128.4 (d, 4C), 128.5 (d, 3C), 137.9 (s), 138.0 (s), 138.0 (s), 138.5 (s); HRMS (MALDI-TOF) calcd for $C_{46}H_{58}O_5$ ($[M+K]^+$) 729.3921, found 729.3822; Anal. calcd for $C_{46}H_{58}O_5$: C, 79.96; H, 8.46; found: C, 79.84; H, 8.48.

19. Pd(II)-Mediated cycloisomerization: synthesis of glycals 27:



The oxidation of alcohol **26** (40 mg, 58 μmol) and subsequent alkynone cycloisomerization was carried out using similar experimental procedure used for synthesis of glycal **11** to procure compound **27α** (22 mg, 52 % yield) as colourless oils. *Characterization data of compound **27α***: $[\alpha]_D^{25}$ +29.4 (*c* 0.3, $CHCl_3$); IR (neat): 3018, 2925, 1454, 1215, 1095, 759, 667 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 0.81 (t, *J* = 6.8 Hz, 3H), 1.19 (br s, 14H), 1.43–1.54 (m, 2H), 1.92 (dd, *J* = 4.7, 14.8 Hz, 1H), 2.29 (dd, *J* = 7.3, 14.8 Hz, 1H), 2.32 (t, *J* = 6.8 Hz, 2H), 3.23 (s, 3H), 3.47–3.50 (m, 1H), 3.55 (t, *J* = 6.8 Hz, 2H), 3.71 (d, *J* = 5.2 Hz, 1H), 3.81 (t, *J* = 5.2 Hz, 1H), 4.26 (d, *J* = = 11.3 Hz, 1H), 4.30–4.36 (m, 2H), 4.40–4.43 (m, 2 H), 4.46–4.54 (m, 3H), 4.81 (d, *J* = 5.1 Hz, 1H), 7.18–7.28 (m, 20H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 14.1 (q), 22.7 (t), 24.7 (t), 29.3 (t), 29.6 (t), 29.7 (t), 29.9 (t), 31.9 (t), 34.3 (t), 34.4 (t), 35.6 (t), 49.3 (q), 66.0 (d), 67.5 (t), 70.7 (t), 70.9 (t), 72.0 (t), 72.9 (t), 75.7 (d), 77.0 (d), 97.2 (d), 100.2 (s), 127.3 (d, 2C), 127.5 (d), 127.6 (d, 3C), 127.8 (d, 2C), 128.08 (d, 4C), 128.09 (d, 2C), 128.26 (d, 2C), 128.32 (d, 2C), 128.4 (d, 2C), 138.1 (s), 138.2 (s), 138.8 (s), 139.1 (s), 149.9 (s); MALDI-TOF: 743.62 (100%, $[M+Na]^+$), 759.60 (33% $[M+K]^+$); Anal. calcd for $C_{47}H_{60}O_6$: C, 78.30; H, 8.39; found: C, 78.25; H, 8.45.

20. Synthesis of acetate 28α:



Hydroboration-oxidation and acetylation of glycal **27α** (18 mg, 0.025 mmol) to get compound **28α** (12 mg, 65% yield) as colourless oil was carried out under similar reaction conditions used for synthesis of compound **10** α/β. *Characterization data of compound **28α***: $[\alpha]_D^{25}$ +37.9 (*c* 0.3, $CHCl_3$); IR ($CHCl_3$): 3018, 2925, 1736, 1459, 1216, 1095, 767, 669 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 0.88 (t, *J* = 6.8 Hz, 3H), 1.27–1.32 (m, 14H), 1.59–1.66 (m, 3H), 1.69–1.72 (m, 1H), 1.79–1.85 (m, 1H), 1.97 (s, 3H), 2.34 (dd, *J* = 10.1, 15.4 Hz, 1H), 3.11 (s, 3H), 3.50–3.54 (m, 1H), 3.56–3.59 (m, 3H), 3.60–3.63 (m, 1H), 3.64–3.68 (m, 1H), 3.92 (dd, *J* = 2.6, 9.8 Hz, 1H), 4.02 (d, *J* = 2.6 Hz, 1H), 4.31–4.41 (m, 3H), 4.44–4.47 (m, 2H), 4.50 (d, *J* = 12.4 Hz, 1H),

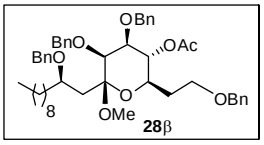
4.60 (d, J = 10.6 Hz, 1H), 4.62 (d, J = 10.6 Hz, 1H), 5.23 (br t, J = 9.8 Hz, 1H), 7.17–7.24 (m, 6H), 7.27–7.35 (m, 14H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 14.1 (q), 21.1 (q), 22.7 (t), 24.6 (t), 29.4 (t), 29.6 (t), 29.7 (t), 30.0 (t), 31.7 (t), 31.9 (t), 33.7 (t), 35.1 (t), 47.7 (q), 66.2 (t), 67.8 (d), 71.4 (t, 2C), 71.8 (d), 72.9 (t), 74.1 (t), 75.9 (d), 76.5 (d), 79.1 (d), 102.0 (s), 126.9 (d), 127.2 (d), 127.3 (d), 127.5 (d), 127.6 (d, 2C), 127.7 (d, 2C), 127.8 (d, 2C), 128.1 (d, 2C), 128.2 (d, 2C), 128.3 (d, 4C), 128.4 (d, 2C), 138.3 (s), 138.4 (s), 138.7 (s), 139.3 (s), 170.2 (s); HRMS (MALDI-TOF) calcd for $C_{49}H_{64}O_8$ ([M+Na]$^+$) 803.4499, found 803.4424; Anal. calcd for $C_{49}H_{64}O_8$: C, 75.35; H, 8.26; found: C, 75.39; H, 8.55.

21. Representative experiment for the sequence of oxidation-cyclization-hydroboration-acetylation to isolate the minor 28β:

To a solution of alcohol **26** (100 mg, 0.14 mmol) in ethyl acetate (10 mL) was added IBX (81 mg, 0.28 mmol) at room temperature and stirred at reflux temperature for 3 h. After the complete consumption of the starting material, the reaction mixture was cooled in ice bath and filtered through celite bed. Filtrate was evaporated under reduced pressure. The residual crude ketone (96 mg) was dissolved in anhydrous methanol (15 mL) and the solution was degassed by passing argon for 30 min. To this, $Pd(OAc)_2$ (9 mg, 42 μmol) was added and stirred for 2.5 h. After consumption of starting material, the reaction mixture was filtered through celite bed and the filtrate was concentrated under reduced pressure to procure crude compound (64 mg). The resulting crude glycal mixture was used immediately for hydroboration-oxidation and acetylation without any purification.

To an ice cooled solution of crude compound (64 mg, 89 μmol) in anhydrous THF (3 ml), was added neat BH_3.DMS (8.8 mL, 178 μmol) and stirring was continued at room temperature for 3 h. The reaction mixture was cooled to 0 °C treated with 3N NaOH (0.3 mL) followed by 30% H_2O_2 (0.4 mL) and stirred at room temperature for 6 h. Then THF was evaporated under reduced pressure, residual material was extracted with diethyl ether (5 mL) and water (2 mL), organic layer dried over sodium sulphate and evaporated under reduced pressure. The crude product was dissolved in 0.5 mL anhydrous DCM and treated with acetic anhydride (0.5 mL) and pyridine (0.5 mL). The contents were stirred for 3 h. After completion of reaction, reaction mixture was concentrated under reduced pressure; traces of solvent were removed by co-evaporation with toluene (3 × 5 mL). Residue was purified by column

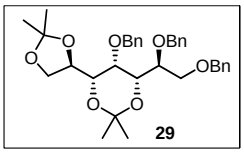
chromatography (230–400 mesh silica gel, 15:85 ethyl acetate/petroleum ether) to procure compound **28α** (30 mg, 26.5% yield, 4 steps) and **28β** (5 mg, 4.4% yield, 4 steps) as colourless oils.



28β

Characterization data of 28β: $[\alpha]_D^{25}$ +17.2 (*c* 0.2, $CHCl_3$); IR ($CHCl_3$): 3021, 2928, 1742, 1452, 1221, 1088, 769, 672 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 0.88 (t, *J* = 6.7 Hz, 3H), 1.27 (br s, 14H), 1.41–1.45 (m, 1H), 1.49–1.54 (m, 1H), 1.77 (dd, *J* = 4.5, 15.2 Hz, 1H), 1.81–1.94 (m, 3H), 2.00 (s, 3H), 3.35 (s, 3H), 3.38–3.43 (m, 1H), 3.51–3.55 (m, 1H), 3.56–3.64 (m, 3H), 3.76 (d, *J* = 3.1 Hz, 1H), 4.31 (d, *J* = 12.5 Hz, 1H), 4.38–4.43 (m, 3H), 4.45–4.49 (m, 2H), 4.72 (d, *J* = 12.0 Hz, 1H), 4.82 (d, *J* = 12.0 Hz, 1H), 5.26 (t, *J* = 9.2 Hz, 1H), 7.17–7.24 (m, 6H), 7.26–7.38 (m, 14H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 14.1 (q), 21.1 (q), 22.7 (t), 24.8 (t), 29.3 (t), 29.6 (t), 29.63 (t), 29.7 (t), 29.9 (t), 31.9 (t), 32.4 (t), 34.9 (t), 36.1 (t), 50.1 (q), 66.1 (t), 69.4 (d), 71.2 (t), 71.5 (t), 71.8 (d), 73.0 (t), 74.6 (t), 75.3 (d), 76.8 (d), 77.3 (d), 100.8 (s), 127.3 (d), 127.49 (d, 2C), 127.5 (d), 127.6 (d), 127.7 (d, 4C), 128.0 (d, 2C), 128.27 (d, 2C), 128.30 (d, 6C), 128.4 (d), 138.1 (s), 138.4 (s), 138.6 (s), 138.8 (s), 169.9 (s); HRMS (MALDI-TOF) calcd for $C_{49}H_{64}O_8$ ($[M+Na]^+$) 803.4499, found 803.4446; Anal. calcd for $C_{49}H_{64}O_8$: C, 75.35; H, 8.26; found: C, 75.41; H, 8.45.

22. Synthesis of tribenzyl compound 29:



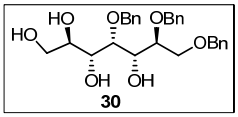
29

At 0 °C, a solution of triol **S21.2** (10 g, 34.2 mmol) and benzyl bromide (12.6 mL, 106 mmol) in anhydrous DMF (100 mL) was treated with sodium hydride (5.47 g, 60% oil emulsion, 137 mmol) and stirred at room temperature for 6 h. The reaction mixture was cooled and the excess NaH was quenched by adding cold water. The reaction mixture was partitioned between ethyl acetate (250 mL) and water (100 mL). The separated organic layer was washed with water (4 x 100 mL), brine (100 mL), dried (Na_2SO_4) and concentrated under reduced pressure. The resulting crude product was purified by column chromatography (230–400 mesh silica gel, 1.5:8.5 ethyl acetate/petroleum ether) to obtain compound **29** (15.6 g, 87%) as pale yellow syrup. *Characterization data of compound* ***29*****:** $[\alpha]_D^{25}$ +10.2 (*c* 2.9, $CHCl_3$); IR ($CHCl_3$): 3011, 2928, 1089 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.30 (s, 3H), 1.38 (s, 3H), 1.40 (s, 3H), 1.41 (s, 3H), 3.63–3.66 (m, 1H), 3.68–3.70 (m, 1H), 3.79–3.83 (m, 2H), 3.86 (dd, *J* = 2.3, 8.5 Hz, 1H), 3.88 (dt, *J* = 2.0, 8.4 Hz, 1H), 4.04–4.10 (m, 2H), 4.23–4.28 (m, 1H), 4.36

(dd, *J* = 2.0, 11.3 Hz, 1H), 4.52 (dd, *J* = 1.5, 12.3 Hz, 1H), 4.56 (d, *J* = 1.5 Hz, 1H), 4.62 (br d, *J* = 12.3 Hz, 1H), 4.71 (dd, *J* = 1.6, 11.3 Hz, 1H), 4.84 (dd, *J* = 2.1, 11.8 Hz, 1H), 7.21–7.37 (m, 15H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 19.2 (q), 25.1 (q), 26.9 (q), 29.4 (q), 67.4 (t), 67.43 (t), 69.7 (d), 70.6 (d), 71.2 (t), 73.3 (t), 73.4 (d), 74.0 (t), 74.4 (d), 76.5 (d), 98.6 (s), 109.1 (s), 127.1 (d, 3C), 127.4 (d, 2C), 127.6 (d, 2C), 127.7 (d, 2C), 128.1 (d, 2C), 128.2 (d, 2C), 128.24 (d, 2C), 138.3 (s), 138.34 (s), 139.1 (s); HRMS (MALDI-TOF) calcd for $C_{34}H_{42}O_7$ ($[M+Na]^+$) 585.2829, found 585.2813.

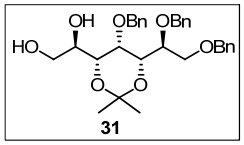
23. Acetonide deprotection:

<u>*Method (A):*</u> Pyridinium *p*-toluenesulfonate (50 mg) was added to a solution of compound **29** (1.0 g) in methanol (10 mL) at 0 °C and the reaction mixture was stirred at same temperature for 1 h. The TLC showed formation of new three slower moving spots along with starting material. Therefore reaction mixture was basified with triethylamine and solvent was evaporated under reduced pressure to get a mixture of **30**−**32** which were separated by column chromatography (100–200 mesh silica gel, 2:8 to 9:11 ethyl acetate/petroleum ether) to procure pure compounds **30** (211 mg, 37%), **31** (141 mg, 23%), **32** (107 mg, 17%) and starting material **29** (338 mg, all yields are based on starting material recovered).



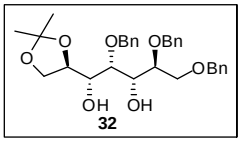
30

Characterization data of compound 30: $[\alpha]_D^{25}$ +9.1 (*c* 1.6, $CHCl_3$); IR ($CHCl_3$): 3460, 3010, 2918, 1452, 1089 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.95 (br s, 1H), 3.10 (br s, 1H), 3.39 (br s, 1H), 3.46 (br s, 1H), 3.62 (br s, 1H), 3.64–3.75 (m, 3H), 3.72 (dd, *J* = 4.5, 10.5 Hz, 1H), 3.73–3.75 (m, 1H), 3.83 (dd, *J* = 3.3, 10.5 Hz, 1H), 3.95 (t, *J* = 6.6 Hz, 1H), 4.02 (t, *J* = 2.8 Hz, 1H), 4.40 (d, *J* = 11.5 Hz, 1H), 4.52 (d, *J* = 11.7 Hz, 2H), 4.56 (d, *J* = 12.1 Hz, 1H), 4.66 (d, *J* = 11.5 Hz, 1H), 4.69 (d, *J* = 11.5 Hz, 1H), 7.24–7.34 (m, 15H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 63.7 (t), 69.2 (t), 71.6 (d), 71.7 (t), 72.3 (d), 73.5 (t), 73.6 (d), 74.6 (t), 76.4 (d), 78.0 (d), 127.7 (d), 127.7 (d), 127.8 (d, 2C), 127.9 (d, 3C), 128.0 (d, 2C), 128.4 (d, 4C), 128.5 (d, 2C), 137.9 (s), 137.95 (s), 137.97 (s); HRMS (MALDI-TOF) calcd for $C_{28}H_{34}O_7$ ($[M+Na]^+$) 505.2203, found 505.2184.



31

Characterization data of compound 31: $[\alpha]_D^{25}$ −2.1 (*c* 1.4, $CHCl_3$); IR ($CHCl_3$): 3440, 2998, 2910, 1110 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.38 (s, 3H), 1.39 (s, 3H), 3.58 (dd, *J* = 3.8, 10.7 Hz, 1H), 3.66–3.71 (m, 4H), 3.82 (s, 1H), 3.87 (dd, *J* = 1.8, 10.7 Hz, 1H), 3.91 (ddd, *J* = 1.8, 3.4, 9.1 Hz, 1H), 4.09 (dd, *J* = 1.0, 9.1 Hz, 1H), 4.40 (d, *J* = 11.4 Hz, 1H), 4.54 (d, *J* = 12.2 Hz, 1H), 4.60 (d, *J* = 12.2 Hz, 1H), 4.68 (d, *J* = 11.4 Hz, 1H), 4.73 (d, *J* = 12.0 Hz, 1H), 4.83 (d, *J* = 11.4 Hz, 1H), 7.24–7.34 (m, 15H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 19.1 (q), 29.4 (q), 63.9 (t), 67.6 (t), 68.7 (d), 69.4 (d), 71.0 (t), 71.1 (d), 73.37 (t), 73.38 (d), 73.6 (t), 76.5 (d), 98.8 (s), 127.5 (d), 127.6 (d), 127.66 (d, 3C), 127.67 (d, 2C), 127.8 (d, 2C), 128.3 (d, 2C), 128.34 (d, 2C), 128.4 (d, 2C), 138.3 (s), 138.4 (s), 138.7 (s); HRMS (MALDI-TOF) calcd for $C_{31}H_{38}O_7$ ($[M+Na]^+$) 545.2516, found 545.2519.



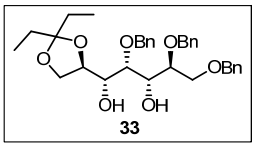
32

Characterization data of compound 32: $[\alpha]_D^{25}$ +9.4 (*c* 0.6, $CHCl_3$); IR ($CHCl_3$): 3410, 2995, 2928, 1065 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.34 (s, 3H), 1.40 (s, 3H), 2.92 (d, *J* = 6.1 Hz, 1H), 2.97 (br s, 1H), 3.64 (dt, *J* = 3.6, 7.8 Hz, 1H), 3.71–3.75 (m, 2H), 3.85 (dd, *J* = 3.2, 10.5 Hz, 1H), 3.93–3.98 (m, 2H), 4.03 (t, *J* = 2.5 Hz, 1H), 4.07–4.10 (m, 2H), 4.44 (d, *J* = 11.7 Hz, 1H), 3.54–3.56 (m, 3H), 4.72 (d, *J* = 11.3 Hz, 1H), 4.73 (d, *J* = 11.7 Hz, 1H), 7.28–7.35 (m, 15H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 25.3 (q), 26.8 (q), 67.3 (t), 69.4 (t), 71.8 (t), 73.1 (d), 73.5 (t), 74.7 (t), 75.3 (d), 75.4 (d), 76.2 (d), 78.0 (d), 109.5 (s), 127.7 (d, 4C), 127.8 (d, 3C), 127.9 (d, 2C), 128.37 (d, 2C), 128.4 (d, 2C), 128.42 (d, 2C), 138.0 (s), 138.1 (s), 138.12 (s); HRMS (MALDI-TOF) calcd for $C_{31}H_{38}O_7$ ($[M+Na]^+$) 545.2516, found 545.2532.

Compound **30** can also be prepared by alternate procedure:

<u>*Method (B):*</u> To a solution of compound **29** (15 g, 26.6 mmol) in methanol (150 mL) was added 0.8% solution of H_2SO_4 in methanol (15 mL) and the stirring was continued for 8 h at rt. After completion of the reaction, as indicated by TLC, the contents were cooled in an ice bath and neutralized with solid K_2CO_3. The reaction mixture was filtered through *Celite* pad and the filtrate was evaporated under reduced pressure. The crude was purified by column chromatography (100–200 mesh silica gel, 9:11 ethyl acetate/petroleum ether) to afford tetrol **30** (10.8 g, 84% yield) as colorless gum.

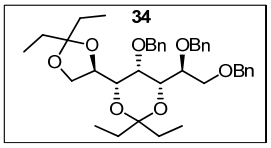
24. Synthesis of monopentylidene derivative 33:



33

To an ice cold solution of tetrol **30** (5 g, 10.4 mmol) in 3-pentanone (50 mL), was added five drops of concentrated H_2SO_4 and stirring was continued at same temperature for next 3 h [formation of dipentylidene derivative **34** was also observed if the temperature increases above 5 °C]. After complete consumption of starting material, the reaction mixture was basified by triethylamine (2 mL) and the solvent was evaporated under reduced pressure. The resulting crude was purified by column chromatography (230–400 mesh silica gel, 3:7 ethyl acetate/petroleum ether) to isolate pure product **33** (4.9 g, 89%) as pale yellow gum.

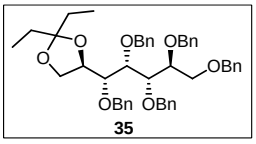
Characterization data of compound 33: $[\alpha]_D^{25}$ +9.4 (*c* 0.6, $CHCl_3$); IR ($CHCl_3$): 3396, 3009, 2891, 1121 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 0.89 (t, *J* = 7.5 Hz, 6H), 1.59–1.65 (m, 4H), 2.90 (d, *J* = 6.9 Hz, 1H), 2.96 (d, *J* = 4.8 Hz, 1H), 3.63 (ddd, *J* = 3.4, 4.6, 7.9 Hz, 1H), 3.70–3.72 (m, 1H), 3.73 (dd, *J* = 4.6, 10.5 Hz, 1H), 3.85 (dd, *J* = 3.3, 10.5 Hz, 1H), 3.89 (dd, *J* = 5.9, 7.9 Hz, 1H), 3.94 (dt, *J* = 2.3, 7.3 Hz, 1H), 4.06 (t, *J* = 2.5 Hz, 1H), 4.07–4.11 (m, 1H), 4.14 (dd, *J* = 6.3, 7.9 Hz, 1H), 4.41 (d, *J* = 11.6 Hz, 1H), 4.54 (d, *J* = 11.3 Hz, 1H), 4.56 (br s, 2H), 4.73 (d, *J* = 11.6 Hz, 1H), 7.27–7.34 (m, 15H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 8.1 (q), 8.3 (q), 29.1 (t), 29.6 (t), 68.1 (t), 69.4 (t), 71.8 (t), 73.3 (d), 73.6 (t), 74.8 (t), 75.5 (d), 75.9 (d), 76.4 (d), 78.1 (d), 113.2 (s), 127.7 (d, 4C), 127.8 (d, 2C), 127.86 (d), 127.9 (d, 2C), 128.4 (d, 2C), 128.42 (d, 2C), 128.5 (d, 2C), 138.1 (s), 138.17 (s), 138.19 (s); HRMS (MALDI-TOF) calcd for $C_{33}H_{42}O_7$ ($[M+Na]^+$) 573.2829, found 573.2790.



***Characterization data of compound 34*:** $[\alpha]_D^{25}$ +15.7 (*c* 1.0, $CHCl_3$); IR ($CHCl_3$): 3011, 2916, 1092 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 0.79–0.92 (m, 12H), 1.54–1.66 (m, 6H), 1.71–1.81 (m, 2H), 3.67 (dd, *J* = 3.4, 10.6 Hz, 1H), 3.72 (br d, *J* = 8.5 Hz, 1H), 3.77–3.84 (m, 3H), 3.89 (ddd, *J* = 2.1, 3.2. 9.1 Hz, 1H), 4.06 (dd, *J* = 1.0, 9.1 Hz, 1H), 4.09 (dd, *J* = 6.5, 8.3 Hz, 1H), 4.25 (dt, *J* = 6.2, 8.3 Hz, 1H), 4.35 (d, *J* = 11.4 Hz, 1H), 4.52 (d, *J* = 12.3 Hz, 1H), 4.58 (d, *J* = 13.0 Hz, 1H), 4.61 (d, *J* = 12.3 Hz, 1H), 4.73 (d, *J* = 11.5 Hz, 1H), 4.87 (d, *J* = 12.1 Hz, 1H), 7.23–7.35 (m, 15H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 7.1 (q), 8.1 (q), 8.15 (q), 8.3 (q), 21.1 (t), 29.0 (t), 29.7 (t), 30.7 (t), 67.6 (t), 68.3 (t), 69.7 (d), 70.0 (d), 71.2 (t), 73.4 (t), 73.8 (t), 73.9 (d), 74.0 (d),

76.6 (d), 101.9 (s), 113.1 (s), 126.7 (d, 2C), 127.0 (d), 127.5 (d), 127.52 (d), 127.6 (d, 2C), 127.8 (d, 2C), 128.1 (d, 2C), 128.3 (d, 4C), 138.3 (s), 138.5 (s), 139.4 (s); HRMS (MALDI-TOF) calcd for $C_{38}H_{50}O_7$ ($[M+Na]^+$) 641.3455, found 641.3453.

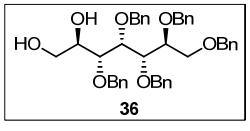
25. Synthesis of benzyl ether 35:



35

To a solution of diol **33** (4 g, 7.3 mmol) in anhydrous DMF (40 mL) was added benzyl bromide (1.8 mL, 15.3 mmol) at room temperature and the reaction mixture was cooled to 0 °C. To this, sodium hydride (871 mg, 21.8 mmol) was added portion wise. After complete addition, reaction mixture was allowed to stir at room temperature for 4 h. The reaction mixture was cooled and the excess NaH was quenched by adding cold water. The reaction mixture was partitioned between ethyl acetate (100 mL) and water (50 mL). The separated organic layer was washed with water (4 x 50 mL), brine (50 mL), dried (Na_2SO_4) and concentrated under reduced pressure. The crude was purified by column chromatography (230–400 mesh silica gel, 1:4 ethyl acetate/petroleum ether) to obtain **35** (4.6 g, 86%) as pale yellow syrup. *Characterization data of compound **35***: $[\alpha]_D^{25}$ +2.9 (*c* 1.7, $CHCl_3$); IR ($CHCl_3$): 3021, 2917, 1448, 1131 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 0.85 (t, *J* = 7.5 Hz, 3H), 0.86 (t, *J* = 7.5 Hz, 3H), 1.53–1.64 (m, 4H), 3.73 (dd, *J* = 5.1, 10.0 Hz, 1H), 3.77–3.82 (m, 2H), 3.83–3.88 (m, 2H), 3.92 (t, *J* = 4.7 Hz, 1H), 3.96 (dd, *J* = 6.3, 7.9 Hz, 1H), 4.04 (dd, *J* = 4.6, 6.3 Hz, 1H), 4.10 (dt, *J* = 5.6, 8.0 Hz, 1H), 4.45 (d, *J* = 11.9 Hz, 1H), 4.51 (d, *J* = 12.1 Hz, 1H), 4.55 (d, *J* = 12.1 Hz, 1H), 4.59 (d, *J* = 11.6 Hz, 1H), 4.62 (d, *J* = 11.4 Hz, 1H), 4.65–4.74 (m, 3H), 4.76 (d, *J* = 11.4 Hz, 1H), 7.24–7.33 (m, 25H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 8.3 (q, 2C), 28.5 (t), 29.5 (t), 66.7 (t), 69.7 (t), 71.9 (t), 73.3 (t), 74.0 (t), 74.4 (t), 75.2 (t), 76.8 (d), 79.4 (d), 79.5 (d), 79.7 (d), 80.5 (d), 112.2 (s), 127.4 (d, 3C), 127.5 (d, 4C), 127.6 (d, 2C), 127.7 (d, 2C), 127.9 (d, 2C), 128.0 (d, 2C), 128.2 (d, 4C), 128.23 (d, 4C), 128.3 (d, 2C), 138.3 (s), 138.5 (s), 138.54 (s), 138.6 (s), 138.8 (s); HRMS (MALDI-TOF) calcd for $C_{47}H_{54}O_7$ ($[M+Na]^+$) 753.3768, found 753.3756.

26. Synthesis of diol 36:

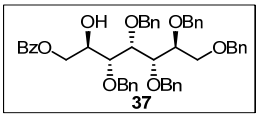


36

To a solution of compound **35** (4.5 g, 6.7 mmol) in methanol (50 mL) was added 0.8% solution of H_2SO_4 in methanol (5 mL) and stirred for 6 h before neutralizing with solid K_2CO_3. The contents were filtered through *Celite* bed and the filtrate was evaporated under

reduced pressure. The residue was purified by column chromatography (230–400 mesh silica gel, 3:7 ethyl acetate/petroleum ether) to afford **36** (3.4 g, 84%) as colorless gum. *Characterization data of compound **36*:** $[\alpha]_D^{25}$ +2.9 (*c* 1.1, $CHCl_3$); IR ($CHCl_3$): 3398, 3012, 2921, 1451, 1102 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 3.59 (dd, *J* = 4.3, 11.4 Hz, 1H), 3.66 (dd, *J* = 3.2, 11.4 Hz, 1H), 3.70–3.73 (m, 2H), 3.79 (dd, *J* = 4.1, 7.6 Hz, 1H), 3.84 (dd, *J* = 3.5, 10.3 Hz, 1H), 3.86–3.90 (m, 2H), 4.06 (t, *J* = 4.3 Hz, 1H), 4.47 (d, *J* = 12.0 Hz, 1H), 4.50–4. 57 (m, 6H), 4.68 (br d, *J* = 11.7 Hz, 2H), 4.77 (d, *J* = 11.2 Hz, 1H), 7.24–7.31 (m, 25H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 63.6 (t), 69.5 (t), 71.8 (d), 72.0 (t), 73.3 (t), 73.4 (t), 74.0 (t, 2C), 76.5 (d), 78.2 (d), 78.6 (d), 78.9 (d), 127.5 (d), 127.6 (d, 2C), 127.6 (d, 2C), 127.7 (d, 2C), 127.8 (d), 127.9 (d), 128.0 (d, 2C), 128.1 (d, 2C), 128.3 (d, 6C), 128.35 (d, 2C), 128.4 (d, 4C), 137.7 (s), 137.8 (s), 138.2 (s, 2C), 138.5 (s); HRMS (MALDI-TOF) calcd for $C_{42}H_{46}O_7$ ($[M+Na]^+$) 685.3142, found 685.3163.

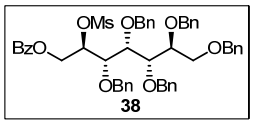
27. Synthesis of benzoate 37:



37

At 0 °C, a solution of diol **36** (3 g, 4.5 mmol) and Et_3N (0.76 mL, 5.4 mmol) in anhydrous CH_2Cl_2 (30 mL) was added benzoyl chloride (0.5 mL, 4.5 mmol) and the contents stirrred at same temperature for 2.5 h. Then reaction mixture was partitioned between CH_2Cl_2 (100 mL) and water (60 mL). The organic layer was separated, washed with brine (50 mL), dried (Na_2SO_4) and concentrated under reduced pressure. The residue obtained was purified by column chromatography (230–400 mesh silica gel, 1:4 ethyl acetate/petroleum ether) to procure **37** (2.9 g, 83%) as colorless syrup. *Characterization data of compound **37*:** $[\alpha]_D^{25}$ +6.4 (*c* 1.4, $CHCl_3$); IR ($CHCl_3$): 3421, 2998, 2912, 1732, 1083 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 3.72–3.77 (m, 2H), 3.87 (dd, *J* = 3.1, 10.2 Hz, 1H), 3.89–3.99 (m, 2H), 4.04–4.13 (m, 2H), 4.35 (dd, *J* = 5.7, 11.6 Hz, 1H), 4.44–4.54 (m, 6H), 4.62 (br s, 2H), 4.69 (d, *J* = 11.6 Hz, 1H), 4.71 (d, *J* = 11.4 Hz, 1H), 4.78 (d, *J* = 11.4 Hz, 1H), 7.22–7.32 (m, 25H), 7.39–7.42 (m, 2H), 7.53–7.55 (m, 1H), 7.99–8.07 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 66.3 (t), 69.5 (t), 70.4 (d), 72.0 (t), 73.2 (t), 73.4 (t), 74.1 (t), 74.2 (t), 76.6 (d), 78.3 (d), 78.5 (d), 78.9 (d), 127.5 (d), 127.6 (d, 2C), 127.7 (d, 3C), 127.8 (d, 2C), 128.1 (d, 2C), 128.14 (d, 2C), 128.3 (d, 6C), 128.4 (d, 7C), 129.7 (d, 2C), 130.1 (d), 132.9 (d, 2C), 137.6 (s), 137.8 (s, 2C), 138.1 (s), 138.2 (s), 138.5 (s), 166.6 (s); HRMS (MALDI-TOF) calcd for $C_{49}H_{50}O_8$ ($[M+Na]^+$) 789.3404, found 789.3425.

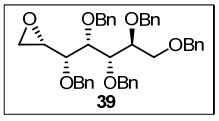
28. Synthesis of mesylate 38:



38

At 0 °C, a solution of compound **37** (2.5 g, 3.3 mmol) and Et_3N (0.6 mL, 4.2 mmol) in anhydrous CH_2Cl_2 (30 mL) was treated with methanesulfonyl chloride (0.3 mL, 3.6 mmol) and the contents were stirred at room temperature for 2.5 h. The crude product isolated after the usual aqueous workup was purified by column chromatography (230–400 mesh silica gel, 15:85 ethyl acetate/petroleum ether) to afford **38** (2.1 g, 78%) as colorless gum. *Characterization data of compound **38*:** $[\alpha]_D^{25}$ +17.5 (*c* 2.3, $CHCl_3$); IR ($CHCl_3$): 3011, 2913, 1461, 1121 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 2.74 (s, 3H), 3.71 (dd, *J* = 6.1, 11.4 Hz, 1H), 3.85–3.90 (m, 3H), 3.96 (t, *J* = 5.1 Hz, 1H), 4.16 (dd, *J* = 2.8, 5.9 Hz, 1H), 4.50 (br d, *J* = 11.2 Hz, 3H), 4.58 (dd, *J* = 8.3, 12.7 Hz, 1H), 4.65–4.69 (m, 6H), 4.72 (dd, *J* = 2.4, 12.7 Hz, 1H), 4.75 (d, *J* = 11.4 Hz, 1H), 5.20 (dt, *J* = 2.4, 8.3 Hz, 1H), 7.15–7.32 (m, 25H), 7.42 (t, *J* = 7.8 Hz, 2H), 7.54–7.57 (m, 1H), 8.02–8.03 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 38.4 (q), 63.7 (t), 69.4 (t), 72.1 (t), 73.3 (t), 73.8 (t), 74.9 (t), 75.0 (t), 78.3 (d), 78.7 (d), 79.5 (d), 80.3 (d), 81.3 (d), 127.5 (d), 127.6 (d), 127.63 (d), 127.7 (d, 3C), 127.8 (d, 3C), 128.1 (d, 2C), 128.2 (d), 128.22 (d, 4C), 128.3 (d, 2C), 128.32 (d, 5C), 128.4 (d, 2C), 129.0 (d), 129.7 (d), 129.72 (d, 2C), 133.1 (d), 137.7 (s), 137.8 (s), 138.1 (s), 138.2 (s), 138.3 (s), 138.4 (s), 166.1 (s); HRMS (MALDI-TOF) calcd for $C_{50}H_{52}O_{10}S$ ($[M+Na]^+$) 867.3179, found 867.3156.

29. Synthesis of epoxide 39:

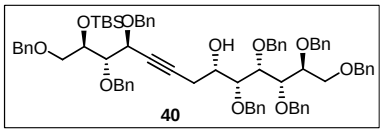


39

Solid lithium hydroxide (300 mg, 7.1 mmol) was added to a solution of compound **38** (2 g, 2.4 mmol) in THF:MeOH (7:3, 20 mL) at 0 °C. After 30 min stirring at 0 °C, the reaction mixture was stirred for next 7 h at rt. The reaction mixture was concentrated under reduced pressure and the residue obtained was purified by column chromatography (230–400 mesh silica gel, 15:85 ethyl acetate/petroleum ether) to obtain **39** (1.2 g, 79%) as a colorless gum. *Characterization data of compound **39*:** $[\alpha]_D^{25}$ −27.2 (*c* 1.5, $CHCl_3$); IR ($CHCl_3$): 3055, 2921, 1131 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.94 (dd, *J* = 2.4, 4.8 Hz, 1H), 2.22 (dd, *J* = 4.0, 4.8 Hz, 1H), 3.06–3.11 (m, 2H), 3.63 (dd, *J* = 5.2, 9.7 Hz, 1H), 3.70 (dt, *J* = 3.5, 5.2 Hz, 1H), 3.76 (dd, *J* = 3.1, 7.0 Hz, 1H), 3.85 (dd, *J* = 5.2, 9.7 Hz, 1H), 4.18 (dd, *J* = 3.5, 7.0 Hz, 1H), 4.40–4.46 (m, 3H), 4.53 (d, *J* = 12.0 Hz, 1H), 4.54 (d, *J* = 11.7 Hz, 1H), 4.59 (br d, *J* = 11.6 Hz, 1H), 4.75 (d, *J* = 11.3 Hz,

1H), 4.77 (d, J = 11.6 Hz, 1H), 4.85 (br d, J = 12.0 Hz, 2H), 7.22–7.36 (m, 25H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 42.4 (t), 53.3 (d), 67.5 (t), 71.8 (t), 72.0 (t), 73.4 (t), 74.5 (t), 74.8 (t), 78.9 (d), 79.7 (d), 80.1 (d), 80.6 (d), 127.3 (d, 2C), 127.4 (d, 2C), 127.6 (d), 127.7 (d, 2C), 127.8 (d, 2C), 127.9 (d, 2C), 128.1 (d, 2C), 128.2 (d, 2C), 128.25 (d, 4C), 128.3 (d, 2C), 128.4 (d, 2C), 128.6 (d, 2C), 138.1 (s), 138.13 (s), 138.3 (s), 138.6 (s), 138.9 (s); HRMS (MALDI-TOF) calcd for $C_{42}H_{44}O_6$ ([M+Na]$^+$) 667.3036, found 667.3065.

30. Synthesis of alcohol 40:

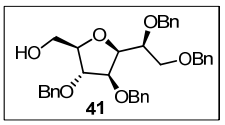


40

At –78 °C, a solution of alkyne **6** (493 mg, 0.9 mmol) in anhydrous THF (6 mL) was treated with *n*-BuLi (0.2 mL, 1.6 M in hexane, 0.3 mmol) and stirred for 20 min and then introduced a solution of $BF_3.Et_2O$ (48 mg, 0.3 mmol) and stirred at –78 °C for 20 min. To this, a solution of epoxide **39** (200 mg, 0.3 mmol) in anhydrous THF (2 mL) was added slowly at –78 °C and the contents were stirred for 2.5 h at the same temperature. Reaction mixture was quenched by adding saturated sodium bicarbonate (1 mL) and partitioned between ethyl acetate (80 mL) and water (20 mL). The organic layer was washed with brine (20 mL), dried over sodium sulphate and evaporated under reduced pressure. The crude compound was purified by column chromatography (230–400 mesh silica gel, 1:5 ethyl acetate/petroleum ether) to afford compound **40** (11 mg, 3% yield) as colorless syrup and compound **41** (112 mg, 64% yield) as pale yellow gum.

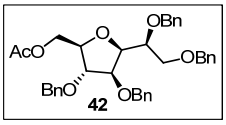
Characterization data of compound 40: $[\alpha]_D^{25}$ +27.1 (*c* 2.2, $CHCl_3$); IR ($CHCl_3$): 3398, 3013, 2912, 1441, 1086 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 0.05 (s, 6H), 0.85 (s, 9H), 2.24 (ddd, J = 1.9, 5.7, 16.5 Hz, 1H), 2.52 (ddd, J = 1.9, 7.7, 16.5 Hz, 1H), 2.63 (br s, 1H), 3.55 (dd, J = 5.2, 10.0 Hz, 1H), 3.60 (dd, J = 2.8, 10.0 Hz, 1H), 3.75 (dd, J = 4.5, 10.1 Hz, 1H), 3.77–3.82 (m, 3H), 3.91–3.95 (m, 3H), 4.01 (dd, J = 3.0, 7.4 Hz, 1H), 4.04 (ddd, J = 3.0, 5.2, 8.2 Hz, 1H), 4.42–4.6 (m, 4H), 4.47–4.59 (m, 5H), 4.66 (d, J = 11.6 Hz, 1H), 4.68 (d, J = 12.0 Hz, 1H), 4.69 (d, J = 11.6 Hz, 1H), 4.75 (d, J = 11.5 Hz, 1H), 4.76 (d, J = 11.4 Hz, 1H), 4.77 (d, J = 11.2 Hz, 1H), 4.80 (d, J = 12.0 Hz, 1H), 4.90 (d, J = 11.5 Hz, 1H), 7.21–7.34 (m, 40H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ –5.0 (q), –4.3 (q), 18.0 (s), 25.8 (q, 3C), 69.5 (d), 69.8 (t), 70.8 (t), 71.1 (d), 71.9 (t, 2C), 72.3 (d), 73.2 (t), 73.3 (t), 73.5 (t), 74.4 (t, 2C), 74.7 (t), 74.9

(t), 78.0 (d), 78.8 (s), 79.1 (d), 79.4 (d), 80.1 (d), 81.7 (d), 84.6 (s), 127.3 (d), 127.4 (d, 2C), 127.5 (d, 2C), 127.54 (d), 127.6 (d, 2C), 127.7 (d, 6C), 127.8 (d, 2C), 128.0 (d, 2C), 128.02 (d, 2C), 128.1 (d, 4C), 128.16 (d, 2C), 128.19 (d, 2C), 128.26 (d, 5C), 128.3 (d, 7C), 137.9 (s), 138.2 (s, 2C), 138.3 (s), 138.4 (s), 138.43 (s), 138.6 (s), 138.7 (s); HRMS (MALDI-TOF) calcd for $C_{75}H_{86}O_{10}Si$ ($[M+Na]^+$) 1197.5888, found 1197.5919.



Characterization data of compound 41: $[\alpha]_D^{25}$ +37.2 (*c* 6.4, $CHCl_3$); IR ($CHCl_3$): 3427, 3022, 2913, 1127 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 3.62 (dd, *J* = 4.2, 11.7 Hz, 1H), 3.67 (dd, *J* = 5.6, 10.7 Hz, 1H), 3.73 (dd, *J* = 3.1, 11.7 Hz, 1H), 3.87 (dd, *J* = 1.9, 10.7 Hz, 1H), 3.99–4.08 (m, 4H), 4.14 (dd, *J* = 3.1, 9.1 Hz, 1H), 4.39 (d, *J* = 11.4 Hz, 1H), 4.46 (d, *J* = 11.9 Hz, 1H), 4.49 (d, *J* = 11.4 Hz, 1H), 4.50–4.56 (m, 4H), 4.78 (d, *J* = 11.5 Hz, 1H), 7.20–7.33 (m, 20H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 63.1 (t), 70.9 (t), 71.6 (t), 71.7 (t), 72.5 (t), 73.4 (t), 75.8 (d), 80.3 (d), 81.7 (d), 82.5 (d), 85.1 (d), 127.4 (d, 2C), 127.5 (d, 4C), 127.6 (d, 2C), 127.9 (d, 4C), 128.2 (d, 4C), 128.5 (d, 4C), 137.2 (s), 137.5 (s), 138.4 (s), 138.7 (s); HRMS (MALDI-TOF) calcd for $C_{35}H_{38}O_6$ ($[M+Na]^+$) 577.2566, found 577.2577.

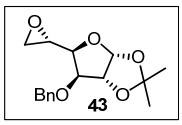
31. Synthesis of acetate 42:



To a solution of compound **41** (80 mg, 0.2 mmol) in pyridine (1 mL), acetic anhydride (1 mL) was added slowly at 0 °C. The contents were stirred for 3 h at room temperature. The reaction mixture was diluted with ethyl acetate (10 mL), washed with water (5 mL), brine (5 mL), dried over sodium sulphate and concentrated under reduced pressure. The residue was purified by column chromatography (230–400 mesh silica gel, 15:85 ethyl acetate/petroleum ether) to procure compound **42** (79 mg, 88%) as colourless gum. *Characterization data of compound* ***42*****:** $[\alpha]_D^{25}$ +33.1 (*c* 3.4, $CHCl_3$); IR ($CHCl_3$): 3022, 2931, 1731, 1461, 1112 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 2.00 (s, 3H), 3.70 (dd, *J* = 5.6, 10.6 Hz, 1H), 3.84–3.91 (m, 2H), 4.03–4.06 (m, 1H), 4.09–4.13 (m, 4H), 4.19 (dd, *J* = 3.3, 9.0 Hz, 1H), 4.42–4.53 (m, 5H), 4.59 (br s, 2H), 4.81 (d, *J* = 11.4 Hz, 1H), 7.24–7.34 (m, 20H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 20.8 (q), 64.6 (t), 71.0 (t), 71.4 (t), 71.7 (t), 72.5 (t), 73.3 (t), 76.0 (d), 80.5 (d), 81.9 (d), 82.0 (d), 83.0 (d), 127.4 (d, 2C), 127.6 (d, 8C), 127.7 (d), 127.9 (d), 128.2 (d, 4C), 128.4

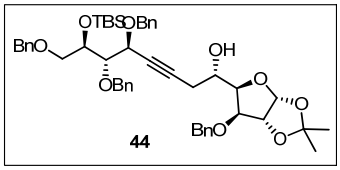
(d, 2C), 128.5 (d, 2C), 137.5 (s), 137.7 (s), 138.6 (s), 138.8 (s), 170.7 (s); HRMS (MALDI-TOF) calcd for $C_{37}H_{40}O_7$ ($[M+Na]^+$) 619.2672, found 619.2660.

32. Synthesis of epoxide 43:



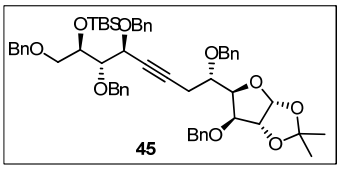
Epoxide **43** (1.4 g, 77%) as colorless thick oil was prepared from compound **S25.5** (3 g, 6.09 mmol) under similar reaction conditions used for the synthesis of epoxide **39**. *Characterization data of compound **43***: $[\alpha]_D^{25}$ +7.40 (*c* 0.69, $CHCl_3$); IR ($CHCl_3$): 3052, 2913, 1447, 1081 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.31 (s, 3H), 1.44 (s, 3H), 2.54 (dd, *J* = 2.8, 4.8 Hz, 1H), 2.76 (dd, *J* = 4.4, 4.8 Hz, 1H), 3.27 (ddd, *J* = 2.8, 4.4, 6.2 Hz, 1H), 3.80 (dd, *J* = 3.5, 6.2 Hz, 1H), 3.96 (d, *J* = 3.5 Hz, 1H), 4.53 (d, *J* = 12.2 Hz, 1H), 4.64 (d, *J* = 3.8 Hz, 1H), 4.77 (d, *J* = 12.2 Hz, 1H), 6.00 (d, *J* = 3.8 Hz, 1H), 7.29–7.35 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 26.2 (q), 26.8 (q), 43.1 (t), 50.1 (d), 71.8 (t), 82.0 (d), 82.3 (d), 82.6 (d), 105.4 (d), 111.9 (s), 127.6 (d, 2C), 128.0 (d), 128.5 (d, 2C), 137.2 (s); HRMS (MALDI-TOF) calcd for $C_{16}H_{20}O_5$ ($[M+Na]^+$) 315.1209, found 315.1196.

33. Synthesis of alcohol 44:



Following the similar experimental procedure used for synthesis of compound **14**, alcohol **44** (1.1 g, 79%) as pale yellow thick oil was prepared from **13** (2.72 g, 5.1 mmol) and epoxide **43** (500 mg, 1.7 mmol). *Characterization data of compound **44**:* $[\alpha]_D^{25}$ +19.1 (*c* 1.9, $CHCl_3$); IR ($CHCl_3$): 3468, 3021, 2931, 1099 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ –0.01 (s, 3H), 0.01 (s, 3H), 0.80 (s, 9H), 1.32 (s, 3H), 1.42 (s, 3H), 2.50 (dd, *J* = 5.8, 16.8 Hz, 1H), 2.60 (dd, *J* = 7.1, 16.8 Hz, 1H), 3.52 (dd, *J* = 5.0, 10.1 Hz, 1H), 3.58 (dd, *J* = 2.7, 10.1 Hz, 1H), 3.79 (dd, *J* = 4.2, 6.5 Hz, 1H), 3.97–3.99 (m, 2H), 4.08 (dd, *J* = 6.2, 10.9 Hz, 1H), 4.34 (t, *J* = 3.8 Hz, 1H), 4.42–4.53 (m, 5H), 4.63–4.73 (m, 3H), 4.81 (d, *J* = 11.9 Hz, 1H), 4.90 (d, *J* = 11.6 Hz, 1H), 6.00 (d, *J* = 3.8 Hz, 1H), 7.23–7.36 (m, 20H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ –5.0 (q), –4.3 (q), 18.0 (s), 23.9 (t), 25.8 (q, 3C), 26.4 (q), 26.9 (q), 68.9 (d), 70.8 (t), 71.0 (d), 71.8 (t, 2C), 72.2 (d), 73.2 (t), 74.3 (t), 78.8 (s), 80.5 (d), 81.4 (d), 82.3 (d), 83.1 (d), 83.9 (s), 104.9 (d), 111.9 (s), 127.3 (d, 2C), 127.5 (d), 127.7 (d, 2C), 127.8 (d, 2C), 127.9 (d, 2C), 128.1 (d, 2C), 128.13 (d, 2C), 128.2 (d, 2C), 128.3 (d, 3C), 128.7 (d, 2C), 136.6 (s), 137.9 (s), 138.4 (s), 138.7 (s); HRMS (MALDI-TOF) calcd for $C_{49}H_{62}O_9Si$ ($[M+Na]^+$) 845.4061, found 845.3998.

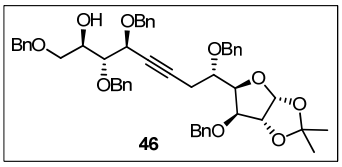
34. Synthesis of benzyl ether 45:



45

The benzyl protection of hydroxyl in compound **44** (1 g, 1.2 mmol) was carried out under similar conditions used for synthesis of compound **15** to afford benzyl ether **45** (903 mg, 81%) as pale yellow syrup. *Characterization data of compound **45*:** $[\alpha]_D^{25}$ +23.1 (*c* 1.6, $CHCl_3$); IR ($CHCl_3$): 3028, 2913, 1451, 1093 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 0.01 (s, 3H), 0.02 (s, 3H), 0.82 (s, 9H), 1.33 (s, 3H), 1.44 (s, 3H), 2.46 (ddd, *J* = 1.6, 6.3, 17.1 Hz, 1H), 2.57 (ddd, *J* = 1.7, 4.3, 17.1 Hz, 1H), 3.56 (dd, *J* = 4.8, 9.9 Hz, 1H), 3.61 (dd, *J* = 3.0, 9.9 Hz, 1H), 3.80 (dd, *J* = 4.3, 6.3 Hz, 1H), 3.92 (dt, *J* = 4.7, 6.6 Hz, 1H), 4.00–4.04 (m, 2H), 4.40–4.49 (m, 6H), 4.60–4.66 (m, 3H), 4.71 (d, *J* = 11.9 Hz, 1H), 4.78 (d, *J* = 11.5 Hz, 1H), 4.83 (d, *J* = 11.9 Hz, 1H), 4.92 (d, *J* = 11.9 Hz, 1H), 5.99 (d, *J* = 4.0 Hz, 1H), 7.22–7.36 (m, 25H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ –4.9 (q), –4.3 (q), 18.0 (s), 21.6 (t), 25.9 (q, 3C), 26.6 (q), 27.0 (q), 70.6 (t), 71.00 (d), 71.7 (t), 72.0 (t), 72.2 (d), 72.9 (t), 73.2 (t), 74.3 (t), 76.5 (d), 78.0 (s), 81.7 (d), 82.3 (d), 82.4 (d), 82.6 (d), 84.3 (s), 105.1 (d), 112.0 (s), 127.3 (d, 2C), 127.35 (d), 127.4 (d), 127.7 (d, 4C), 127.8 (d, 2C), 127.9 (d, 2C), 127.95 (d, 2C), 128.0 (d), 128.1 (d, 2C), 128.13 (d, 2C), 128.2 (d, 2C), 128.24 (d, 2C), 128.5 (d, 2C), 137.1 (s), 138.0 (s), 138.4 (s), 138.8 (s), 138.9 (s); HRMS (MALDI-TOF) calcd for $C_{56}H_{68}O_9Si$ ($[M+Na]^+$) 935.4531, found 935.4512.

35. Synthesis of alkynol 46:



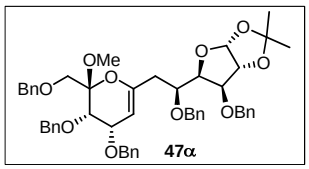
46

TBS ether deprotection of **45** (900 mg, 1.0 mmol) was successfully carried out using similar reaction conditions used for the synthesis of compound **16** to get alkynol **46** (596 mg, 72% yield) as a colorless gum. *Characterization data of compound **46*:** $[\alpha]_D^{25}$ +30.6 (*c* 1.0, $CHCl_3$); IR ($CHCl_3$): 3442, 3038, 2943, 1451, 1081 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 1.32 (s, 3H), 1.44 (s, 3H), 2.43 (dd, *J* = 6.1, 17.1 Hz, 1H), 2.53 (dd, *J* = 3.3, 17.1 Hz, 1H), 2.65 (br s, 1H), 3.59 (dd, *J* = 5.7, 9.6 Hz, 1H), 3.65 (dd, *J* = 2.8, 9.6 Hz, 1H), 3.76 (dd, *J* = 3.6, 7.5 Hz, 1H), 3.91 (dt, *J* = 3.6, 6.5 Hz, 1H), 3.95 (br s, 1H), 4.00 (d, *J* = 3.6 Hz, 1H), 4.40–4.42 (m, 2H), 4.47 (d, *J* = 11.8 Hz, 1H), 4.48 (d, *J* = 11.7 Hz, 1H), 4.51 (d, *J* = 11.8 Hz, 1H), 4.52–4.54 (m, 1H), 4.57–4.64 (m, 3H), 4.70 (d, *J* = 11.6 Hz, 1H), 4.79 (d, *J* = 11.6 Hz, 1H), 4.86 (d, *J* = 12.2 Hz, 1H), 4.88 (d, *J* = 11.6 Hz, 1H), 5.99 (d, *J* =

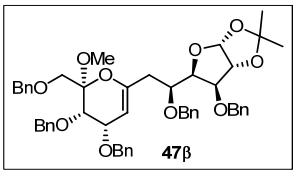
3.9 Hz, 1H), 7.20–7.37 (m, 25H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 21.6 (t), 26.5 (q), 26.9 (q), 70.8 (d), 70.82 (t), 70.9 (t), 71.4 (d), 71.7 (t), 73.0 (t), 73.3 (t), 73.9 (t), 76.4 (d), 77.6 (s), 80.5 (d), 82.1 (d), 82.3 (d), 82.7 (d), 84.7 (s), 105.1 (d), 112.0 (s), 127.3 (d), 127.5 (d), 127.6 (d), 127.7 (d, 3C), 127.8 (d, 2C), 127.83 (d, 4C), 128.0 (d, 3C), 128.16 (d, 2C), 128.2 (d, 2C), 128.3 (d, 2C), 128.4 (d, 2C), 128.5 (d, 2C), 137.0 (s), 137.8 (s), 138.0 (s), 138.5 (s), 138.8 (s); ESI-MS: m/z 821.43 ([M+Na]$^+$).

36. Pd-mediated cyclization - Synthesis of glycal 47:

The glycal **47α** (52 mg, 53% yield) and **47β** (15 mg, 14% yield) were successfully prepared from compound **46** (100 mg, 0.1 mmol) following the similar procedure used for synthesis of glycal **11**. Both the compounds were separated by column chromatography and analyzed with help of spectroscopic data.



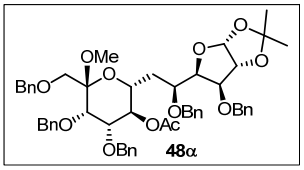
Characterization data of compound 47α : $[\alpha]_D^{25}$ +9.2 (*c* 0.7, $CHCl_3$); IR ($CHCl_3$): 3019, 2928, 1455, 1096 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.31 (s, 3H), 1.43 (s, 3H), 2.19–2.35 (m, 2H), 3.09 (s, 3H), 3.45 (d, *J* = 10.3 Hz, 1H), 3.71 (d, *J* = 10.3 Hz, 1H), 3.90 (d, *J* = 3.7 Hz, 1H), 3.95 (dt, *J* = 4.6, 7.7 Hz, 1H), 4.04 (dd, *J* = 1.8, 4.1 Hz, 1H), 4.24 (dd, *J* = 3.8, 7.4 Hz, 1H), 4.29 (d, *J* = 12.2 Hz, 1H), 4.44 (m, 2H), 4.50 (d, *J* = 11.7 Hz, 1H), 4.53–4.57 (m, 3H), 4.60–4.63 (m, 3H), 4.65 (d, *J* = 12.2 Hz, 1H), 4.87 (d, *J* = 11.4 Hz, 1H), 4.90 (br s, 1H), 5.95 (d, *J* = 4.0 Hz, 1H), 7.15–7.36 (m, 25H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 26.5 (q), 26.9 (q), 36.0 (t), 48.7 (q), 64.7 (t), 70.7 (d), 70.8 (t), 71.8 (t), 72.4 (d), 73.3 (t), 73.5 (t), 74.9 (t), 75.3 (d), 82.1 (d), 82.7 (d), 83.2 (d), 100.4 (d), 101.6 (s), 105.1 (d), 111.8 (s), 127.1 (d), 127.2 (d, 2C), 127.3 (d, 2C), 127.6 (d, 2C), 127.8 (d), 127.9 (d, 3C), 128.0 (d, 2C), 128.1 (d, 2C), 128.2 (d, 2C), 128.3 (d, 2C), 128.32 (d, 2C), 128.4 (d, 2C), 128.5 (d, 2C), 137.2 (s), 137.6 (s), 138.6 (s), 138.8 (s), 139.1 (s), 146.8 (s); HRMS (MALDI-TOF) calcd for $C_{51}H_{56}O_{10}$ ([M+Na]$^+$) 851.3771, found 851.3724.



Characterization data of compound 47β: $[\alpha]_D^{25}$ −8.5 (*c* 0.6, $CHCl_3$); IR ($CHCl_3$): 3014, 2923, 1451, 1109 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.33 (s, 3H), 1.46 (s, 3H), 2.18 (dd, *J* = 8.7, 14.3 Hz, 1H), 2.28 (dd, *J* = 2.9, 14.3 Hz, 1H), 3.34 (s, 3H), 3.67 (d, *J* = 10.0 Hz, 1H), 3.87–3.89 (m, 2H), 3.92 (d, *J* = 3.4 Hz, 1H), 4.01 (d, *J* = 4.1 Hz, 1H), 4.05 (dt, *J* = 3.4, 8.2 Hz, 1H), 4.24 (dd, *J* = 3.4, 7.7 Hz, 1H),

4.43 (d, *J* = 12.0 Hz, 1H), 4.46 (d, *J* = 11.8 Hz, 1H), 4.48 (d, *J* = 12.0 Hz, 1H), 4.52 (d, *J* = 12.3 Hz, 1H), 4.54 (d, *J* = 12.1 Hz, 1H), 4.61–4.64 (m, 3H), 4.67 (d, *J* = 11.1 Hz, 1H), 4.69 (d, *J* = 11.4 Hz, 1H), 4.82 (d, *J* = 11.1 Hz, 1H), 4.86 (d, *J* = 4.8 Hz, 1H), 6.01 (d, *J* = 4.1 Hz, 1H), 7.16–7.39 (m, 25H); ^{13}C NMR ($CDCl_3$, 125 MHz): *δ* 26.5 (q), 26.9 (q), 36.1 (t), 50.0 (q), 69.0 (t), 70.4 (t), 71.6 (t), 72.4 (t), 73.3 (t), 73.5 (t), 73.9 (d), 76.0 (d), 81.9 (d), 82.1 (d), 83.3 (d), 98.1 (d), 100.4 (s), 105.1 (d), 111.8 (s), 127.2 (d), 127.4 (d), 127.5 (d), 127.6 (d, 3C), 127.9 (d, 5C), 128.0 (d), 128.1 (d, 4C), 128.2 (d, 6C), 128.3 (d, 2C), 128.5 (d, 2C), 137.0 (s), 137.9 (s), 138.1 (s), 138.8 (s), 139.0 (s), 149.8 (s); HRMS (MALDI-TOF) calcd for $C_{51}H_{56}O_{10}$ ($[M+Na]^+$) 851.3771, found 851.3724.

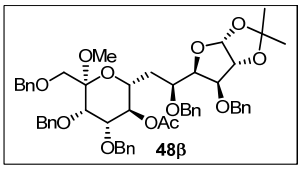
37. Synthesis of acetate 48α:



The hydroboration-oxidation followed acetylation of compound **47α** (45 mg, 54.3 μmol) under similar reaction conditions used for the synthesis of compound **10** afforded the acetate **48α** (31 mg, 61% yield) as colorless gum. *Characterization data of compound **48α*:** $[\alpha]_D^{25}$ −16.9 (*c* 0.7, $CHCl_3$); IR ($CHCl_3$): 3011, 2933, 1721, 1450, 1092 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): *δ* 1.28 (s, 6H), 1.47–1.49 (m, 1H), 1.78–1.81 (m, 1H), 1.93 (s, 3H), 3.16 (s, 3H), 3.33 (d, *J* = 6.5 Hz, 1H), 3.45 (d, *J* = 10.1 Hz, 1H), 3.63 (d, *J* = 10.1 Hz, 1H), 3.78–3.90 (m, 2H), 3.95 (dd, *J* = 2.8, 6.8 Hz, 1H), 4.07 (d, *J* = 2.8 Hz, 1H), 4.37–4.38 (m, 1H), 4.40 (d, *J* = 11.0 Hz, 1H), 4.43 (d, *J* = 11.7 Hz, 1H), 4.49 (d, *J* = 12.5 Hz, 1H), 4.52 (d, *J* = 3.7 Hz, 1H), 4.53–4.60 (m, 3H), 4.61–4.66 (m, 2H), 4.72 (d, *J* = 12.1 Hz, 1H), 4.91 (d, *J* = 11.4 Hz, 1H), 5.13 (t, *J* = 10.0 Hz, 1H), 5.94 (d, *J* = 3.9 Hz, 1H), 7.20–7.36 (m, 20H), 7.45–7.49 (m, 2H), 7.53–7.56 (m, 1H), 7.64–7.70 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): *δ* 21.1 (q), 26.2 (q), 26.7 (q), 33.5 (t), 50.1 (q), 67.1 (t), 70.0 (d), 71.0 (t), 71.6 (d), 71.7 (t), 72.5 (t), 73.4 (t), 74.7 (d), 75.0 (t), 75.4 (d), 77.1 (d), 81.7 (d), 82.3 (d), 83.3 (d), 100.5 (s), 105.2 (d), 111.4 (s), 127.2 (d, 2C), 127.5 (d, 4C), 127.7 (d, 4C), 127.9 (d, 2C), 128.0 (d, 2C), 128.2 (d, 4C), 128.24 (d, 3C), 128.5 (d, 4C), 137.2 (s), 137.6 (s), 138.1 (s), 139.0 (s), 139.2 (s), 169.9 (s); HRMS (MALDI-TOF) calcd for $C_{53}H_{60}O_{12}$ ($[M+Na]^+$) 911.3983, found 911.3994.

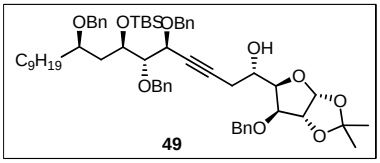
38. Synthesis of acetate 48β:

Following the above procedure the hydroboration of **47β** (21 mg, 25 μmol) followed by acetylation gave **48β** (14 mg, 53% yield) as pale yellow gum. *Characterization*



data of compound ***48β*****:** $[\alpha]_D^{25}$ −29.4 (*c* 0.6, $CHCl_3$); IR ($CHCl_3$): 3010, 2919, 1726, 1452, 1087 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.28 (s, 3H), 1.38 (s, 3H), 1.45–1.49 (m, 2H), 1.92 (s, 3H), 3.22–3.31 (m, 1H), 3.38 (s, 3H), 3.49 (d, *J* = 10.8 Hz, 1H), 3.56 (br d, *J* = 10.9 Hz, 1H), 3.87–3.90 (m, 2H), 4.04 (d, *J* = 3.1 Hz, 1H), 4.10 (d, *J* = 3.1 Hz, 1H), 4.22 (d, *J* = 12.4 Hz, 1H), 4.33 (dd, *J* = 3.1, 8.4 Hz, 1H), 4.40 (d, *J* = 12.4 Hz, 1H), 4.44–4.48 (m, 3H), 4.51–4.54 (m, 3H), 4.71 (d, *J* = 11.5 Hz, 1H), 4.74 (d, *J* = 11.5 Hz, 1H), 4.88 (d, *J* = 11.9 Hz, 1H), 5.22 (t, *J* = 9.1 Hz, 1H), 5.95 (d, *J* = 3.9 Hz, 1H), 7.16–7.24 (m, 10H), 7.27–7.31 (m, 13 H), 7.41–7.43 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 21.1 (q), 26.2 (q), 26.7 (q), 32.3 (t), 48.5 (q), 65.2 (t), 67.1 (d), 71.6 (t), 71.62 (t), 71.7 (d), 72.1 (t), 73.4 (t), 74.8 (d), 74.9 (t), 75.5 (d), 78.4 (d), 81.4 (d), 82.2 (d), 83.6 (d), 101.1 (s), 105.1 (d), 111.2 (s), 127.2 (d, 2C), 127.4 (d, 2C), 127.9 (d), 127.95 (d, 3C), 128.1 (d, 3C), 128.1 (d), 128.3 (d, 3C), 128.4 (d, 4C), 128.5 (d), 131.9 (d), 132.0 (d, 2C), 132.1 (d, 2C), 137.0 (s), 137.7 (s), 138.5 (s), 138.8 (s), 139.2 (s), 170.0 (s); HRMS (MALDI-TOF) calcd for $C_{53}H_{60}O_{12}$ ($[M+Na]^+$) 911.3983, found 911.3994.

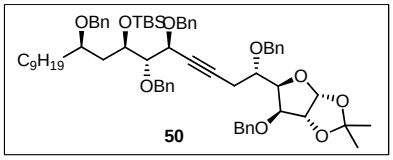
39. Synthesis of alcohol 49:



The alkyne **6** (3.44 g, 5.1 mmol) was treated with epoxide **43** (500 mg, 1.7 mmol) under similar reaction conditions used for synthesis of compound **14** to get compound **49** (1.35 g, 82%) as colorless gum. *Characterization data of compound* ***49*****:** $[\alpha]_D^{25}$ +7.5 (*c* 0.6, $CHCl_3$); IR ($CHCl_3$): 3471, 3009, 2918, 1439, 1101 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ –0.01 (s, 6H), 0.82 (s, 9H), 0.86 (t, *J* = 4.8 Hz, 3H), 1.24 (br s, 14H), 1.31 (s, 3H), 1.42 (s, 3H), 1.46–1.51 (m, 2H), 1.69–1.75 (m, 1H), 1.95–2.08 (m, 1H), 2.48 (ddd, *J* = 1.6, 6.0, 16.7 Hz, 1H), 2.60 (ddd, *J* = 1.7, 6.9, 16.7 Hz, 1H), 3.17 (br s, 1H), 3.65 (dd, *J* = 2.0, 7.6 Hz, 1H), 3.73 (t, *J* = 5.1 Hz, 1H), 3.96–4.17 (m, 3H), 4.26–4.35 (m, 2H), 4.39–4.54 (m, 4H), 4.62–4.71 (m, 3H), 3.74–4.84 (m, 2H), 6.00 (d, *J* = 3.8 Hz, 1H), 7.19–7.38 (m, 20H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ –4.5 (q), –4.3 (q), 14.1 (q), 17.9 (s), 22.7 (t, 2C), 23.9 (t), 25.3 (t), 25.9 (q), 25.91 (q), 26.0 (q), 26.4 (q), 26.9 (q), 29.3 (t), 29.6 (t, 2C), 29.7 (t), 29.9 (t), 31.9 (t), 68.9 (d), 70.7 (t), 71.9 (t), 74.2 (t), 74.5 (t), 75.8 (d), 76.3 (d), 77.2 (d), 77.4 (s), 80.4 (d), 82.3 (d), 83.3 (d), 84.1 (d), 85.1 (s), 105.0 (d), 112.0 (s), 127.3 (d, 2C), 127.6 (d), 127.8 (d, 4C), 127.9 (d, 3C), 128.2 (d,

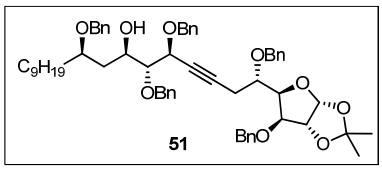
5C), 128.3 (d, 3C), 128.7 (d, 2C), 136.6 (s), 137.8 (s), 139.0 (s), 139.1 (s); HRMS (MALDI-TOF) calcd for $C_{59}H_{82}O_9Si$ ($[M+Na]^+$) 985.5626, found 985.5698.

40. Synthesis of benzyl ether 50:



The compound **50** (893 mg, 83%) was prepared from **49** (1 g, 1.0 mmol) by usual benzyl protection following the similar procedure used for synthesis of compound **15**. *Characterization data of compound **50**:* $[\alpha]_D^{25}$ +10.1 (*c* 3.2, $CHCl_3$); IR ($CHCl_3$): 3032, 2911, 1453, 1098 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ –0.03 (s, 3H), –0.01 (s, 3H), 0.80 (s, 9H), 0.84 (t, *J* = 4.6 Hz, 3H), 1.21 (br s, 14H), 1.29 (s, 3H), 1.42 (s, 3H), 1.51–1.72 (m, 3H), 1.98–2.05 (m, 1H), 2.38 (ddd, *J* = 1.7, 6.2, 17.2 Hz, 1H), 2.51 (ddd, *J* = 1.9, 4.2, 17.2 Hz, 1H), 3.53–3.63 (m, 1H), 3.70 (t, *J* = 5.1 Hz, 1H), 3.85–3.89 (m, 1H), 3.95–3.99 (m, 2H), 4.26–4.42 (m, 6H), 4.58 (d, *J* = 3.6 Hz, 1H), 4.60 (d, *J* = 4.2 Hz, 1H), 4.63 (d, *J* = 11.6 Hz, 1H), 4.65 (d, *J* = 11.5 Hz, 1H), 4.72 (d, *J* = 10.7 Hz, 1H), 4.75 (d, *J* = 11.5 Hz, 1H), 4.80 (d, *J* = 11.5 Hz, 1H), 5.96 (d, *J* = 4.0 Hz, 1H), 7.15–7.32 (m, 25H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ –4.5 (q), –4.2 (q), 14.1 (q), 21.5 (t), 22.7 (t), 25.3 (t), 25.9 (q, 2C), 26.0 (q), 26.6 (q), 27.0 (q), 29.3 (t), 29.6 (t), 29.7 (t), 29.9 (t), 31.9 (t), 34.5 (t), 37.2 (t), 70.1 (d), 70.6 (d), 70.7 (t), 71.7 (t), 72.9 (t), 74.2 (t), 75.5 (t), 76.3 (d), 76.4 (d), 78.7 (s), 82.3 (d), 82.4 (d), 82.5 (d), 84.0 (s), 84.2 (d), 105.1 (d), 112.0 (s), 127.2 (d), 127.3 (d, 2C), 127.5 (d), 127.7 (d, 2C), 127.8 (d, 5C), 127.9 (d, 2C), 128.0 (d, 2C), 128.1 (d, 4C), 128.2 (d, 2C), 128.3 (d, 2C), 128.5 (d, 2C), 137.1 (s), 137.9 (s), 138.8 (s), 139.1 (s), 139.14 (s); HRMS (MALDI-TOF) calcd for $C_{66}H_{88}O_9Si$ ($[M+Na]^+$) 1075.6096, found 1075.6082.

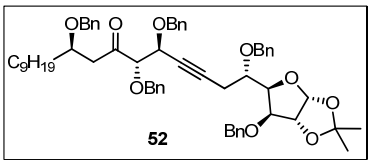
41. Synthesis of alkynol 51:



Deprotection of TBS ether in compound **50** (900 mg, 0.8 mmol) was successfully carried out following the standardized procedure used preparation of compound **16** to afford compound **51** (601 mg, 73% yield) as a colorless gum. *Characterization data of compound **51**:* $[\alpha]_D^{25}$ +8.5 (*c* 2.9, $CHCl_3$); IR ($CHCl_3$): 3458, 3014, 2923, 1451, 1129 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 0.88 (t, *J* = 4.4 Hz, 3H), 1.25 (br s, 14H), 1.32 (s, 3H), 1.43 (s, 3H), 1.50–1.57 (m, 3H), 1.76–1.91 (m, 1H), 2.41–2.47 (m, 1H), 2.53 (ddd, *J* = 2.1, 4.2, 17.1 Hz, 1H), 3.56 (dd, *J* = 3.7, 6.5 Hz, 1H), 3.58–3.61 (m, 1H), 3.91–3,95 (m,

2H), 4.00 (br d, J = 3.3 Hz, 1H), 4.36–4.49 (m, 5H), 4.57 (br d, J = 11.5 Hz, 1H), 4.61–4.72 (m, 4H), 4.79 (d, J = 11.1 Hz, 1H), 4.85 (d, J = 12.1 Hz, 1H), 4.91 (d, J = 11.7 Hz, 1H), 5.99 (d, J = 4.0 Hz, 1H), 7.19–7.37 (m, 25H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 14.1 (q), 21.7 (t), 22.7 (t), 24.6 (t), 26.5 (q), 26.9 (q), 29.3 (t), 29.5 (t), 29.6 (t), 29.9 (t), 31.9 (t), 33.4 (t), 36.6 (t), 70.4 (t), 70.7 (t), 71.1 (d), 71.7 (t), 71.8 (d), 73.1 (t), 74.2 (t), 76.6 (d), 77.9 (s), 80.2 (d), 82.2 (d), 82.4 (d), 82.6 (d), 83.4 (d), 84.5 (s), 105.1 (d), 112.0 (s), 127.3 (d), 127.5 (d, 2C), 127.7 (d, 3C), 127.8 (d, 2C), 127.84 (d, 4C), 128.0 (d, 2C), 128.2 (d, 5C), 128.3 (d, 2C), 128.4 (d, 2C), 128.5 (d, 2C), 137.0 (s), 138.0 (s), 138.1 (s), 138.6 (s), 138.8 (s); HRMS (MALDI-TOF) calcd for $C_{60}H_{74}O_9$ ([M+Na]$^+$) 961.5231, found 961.5281.

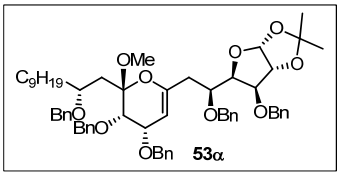
42. Synthesis of alkynone 52:



52

To a solution of alcohol **51** (100 mg, 106 μmol) in ethyl acetate (10 mL) was added IBX (45 mg, 160 μmol) at room temperature and stirred at reflux temperature for 3 h. After the complete consumption of starting material, the reaction mixture was cooled in ice bath, filtered through celite bed, washed with ethyl acetate and the combined filtrate evaporated under reduced pressure. The crude compound was purified by column chromatography (100–200 mesh silica gel, 15:85 ethyl acetate/petroleum ether) to procure pure product **52** (96 mg, 96%) as colorless syrup. *Characterization data of compound **52***: $[\alpha]_D^{25}$ +7.4 (*c* 0.7, $CHCl_3$); IR ($CHCl_3$): 3011, 2919, 1722, 1085 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.88 (t, J = 6.0 Hz, 3H), 1.23 (br s, 16H), 1.33 (s, 3H), 1.44 (s, 3H), 2.39–2.52 (m, 3H), 2.72–3.10 (m, 1H), 3.87–4.06 (m, 4H), 4.36–4.47 (m, 6H), 4.51–4.64 (m, 4H), 4.72 (d, J = 11.9 Hz, 1H), 4.75 (d, J = 11.7 Hz, 1H), 4.78 (d, J = 11.7 Hz, 1H), 6.00 (d, J = 4.1 Hz, 1H), 7.23–7.36 (m, 25H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 14.1 (q), 21.6 (t, 2C), 22.7 (t), 25.2 (t), 26.5 (q), 26.9 (q), 29.3 (t), 29.6 (t), 29.7 (t), 31.9 (t), 34.5 (t), 44.4 (t), 69.9 (d), 70.6 (t), 71.6 (t), 71.7 (t), 73.0 (t), 73.1 (t), 74.9 (d), 76.4 (d), 77.3 (s), 82.1 (d), 82.3 (d), 82.6 (d), 85.2 (s), 85.7 (d), 105.1 (d), 112.0 (s), 127.4 (d, 2C), 127.7 (d, 3C), 127.8 (d, 2C), 127.9 (d, 2C), 128.0 (d, 4C), 128.2 (d, 5C), 128.3 (s, 5C), 128.5 (d, 2C), 137.0 (s), 137.3 (s), 137.34 (s), 138.7 (s), 138.8 (s), 208.0 (s); HRMS (MALDI-TOF) calcd for $C_{60}H_{72}O_9$ ([M+Na]$^+$) 959.5074, found 959.5085.

43. Pd-mediated cycloisomerization:

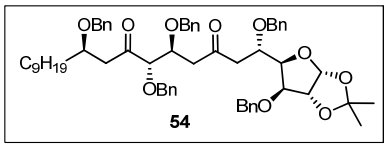


To a solution of alcohol **51** (100 mg, 0.1 mmol) in ethyl acetate (10 mL) was added IBX (45 mg, 0.2 mmol) at room temperature and stirred at reflux temperature for 3 h. After the complete consumption of starting material, the reaction mixture was cooled in ice bath, filtered through celite bed and the filtrate was evaporated under reduced pressure. The residual crude ketone **52** (96 mg, 102 μmol) was dissolved in anhydrous methanol (15 mL) and the solution was degassed by passing argon gas for 45 min. To this, $Pd(OAc)_2$ (7 mg, 31 μmol) was added and stirred for 2.5 h. After consumption of starting material, the reaction mixture was filtered through celite bed and the filtrate was concentrated under reduced pressure. The resulting crude compound was purified by column chromatography (230–400 mesh silica gel, 1:3 ethyl acetate/petroleum ether) to procure compound **53α** (55 mg, 55% yield) and **53β** (18 mg, 18% yield) as colourless gums.

Characterization data of compound 53α:

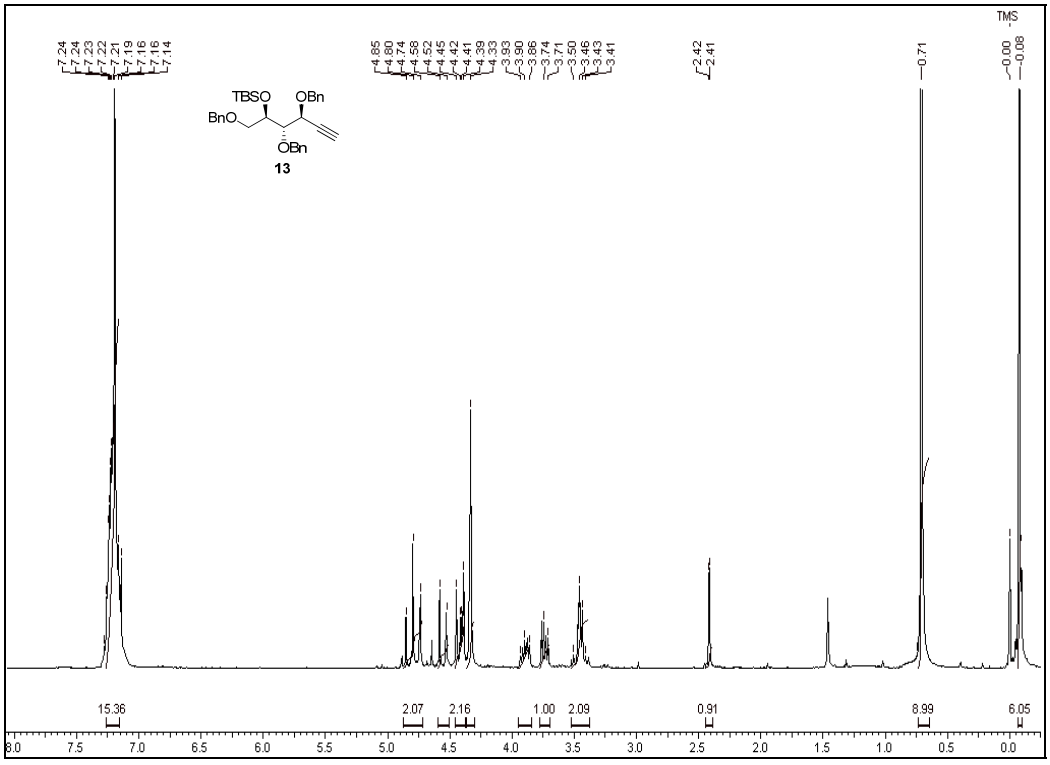
^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.87 (t, J = 6.2 Hz, 3H), 1.24 (br s, 14H), 1.26–1.28 (m, 2H), 1.32 (s, 3H), 1.37–1.40 (m, 2H), 1.47 (s, 3H), 2.23–2.34 (m, 2H), 3.29 (s, 3H), 3.75–3.84 (m, 2H), 3.95–4.03 (m, 2H), 4.21 (dd, J = 1.8, 5.9 Hz, 2H), 4.30–4.34 (m, 2H), 4.37–4.43 (m, 2H), 4.49 (br s, 2H), 4.53–4.59 (m, 2H), 4.61–4.64 (m, 2H), 4.78 (d, J = 11.3 Hz, 1H), 4.87 (d, J = 4.7 Hz, 1H), 5.99 (d, J = 4.0 Hz, 1H), 7.19–7.23 (m, 13H), 7.27–7.35 (m, 12H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 14.1 (q), 22.7 (t), 26.5 (q), 26.9 (q), 29.1 (t), 29.4 (t), 29.6 (t), 29.63 (t), 29.7 (t), 29.72 (t), 30.0 (t), 31.9 (t), 36.0 (t), 48.6 (q), 70.7 (t), 71.3 (t), 71.8 (t), 73.4 (t), 74.1 (t), 75.3 (d), 75.8 (d, 2C), 77.2 (d), 82.3 (d), 82.7 (d), 83.2 (d), 99.9 (d), 103.2 (s), 105.1 (d), 111.7 (s), 126.8 (d), 127.0 (d), 127.1 (d), 127.2 (d, 2C), 127.24 (d), 127.3 (d), 127.5 (d), 127.6 (d), 127.7 (d, 2C), 127.75 (d), 127.8 (d), 127.9 (d), 128.03 (d), 128.1 (d, 2C), 128.2 (d, 4C), 128.3 (d), 128.4 (d), 128.41 (d), 128.5 (d), 138.0 (s), 138.8 (s), 139.0 (s), 139.1 (s), 139.4 (s), 151.9 (s); HRMS (MALDI-TOF) calcd for $C_{61}H_{76}O_{10}$ ($[M+Na]^+$) 991.5336, found 991.5309.

Characterization data of Dicarbonyl compound 54:

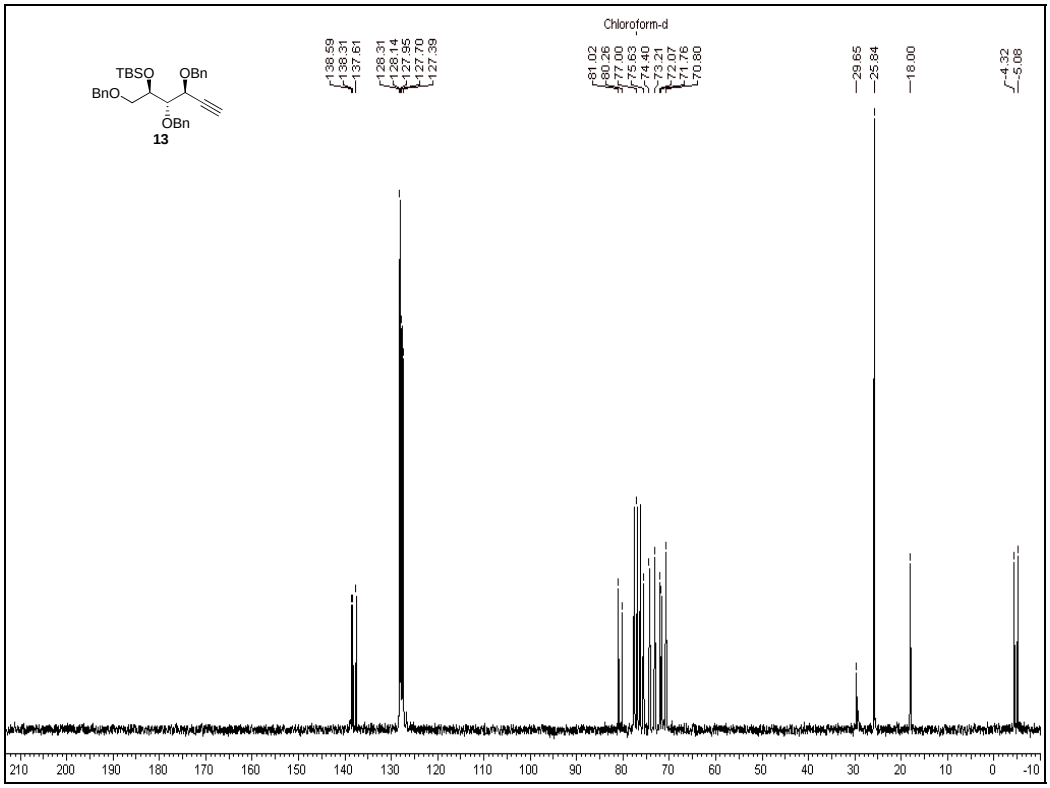


54

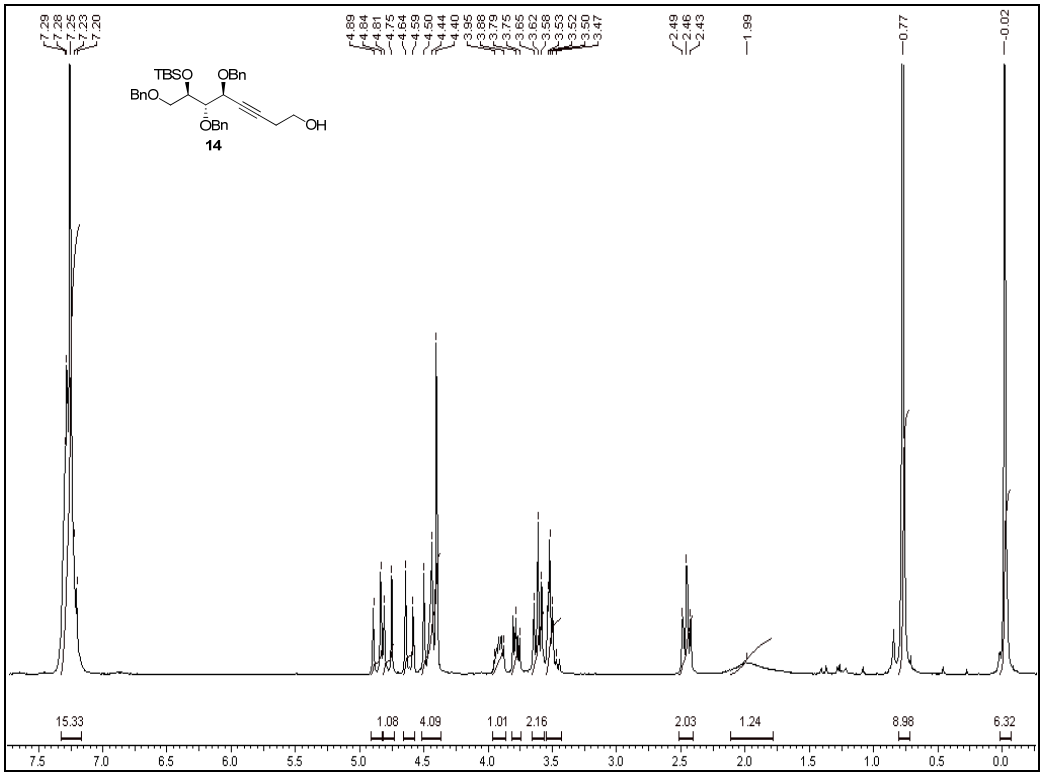
$[\alpha]_D^{25}$ –24.7 (*c* 1.3, $CHCl_3$); IR ($CHCl_3$): 3031, 2938, 1723, 1716, 1451, 1092 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 0.89 (t, *J* = 6.3 Hz, 3H), 1.25–1.31 (br m, 16H), 1.34 (s, 3H), 1.49 (s, 3H), 2.25–2.40 (m, 1H), 2.44 (dd, *J* = 4.7, 17.5 Hz, 1H), 2.53 (dd, *J* = 5.6, 17.5 Hz, 1H), 2.58–2.70 (m, 1H), 2.72–2.89 (m, 1H), 3.05 (dd, *J* = 7.5, 17.6 Hz, 1H), 3.85 (dd, *J* = 3.4, 6.1 Hz, 1H), 3.92–4.03 (m, 2H), 4.18–4.23 (m, 1H), 4.31–4.41 (m, 3H), 4.43–4.50 (m, 3H), 4.51–4.54 (m, 1H), 4.56–4.63 (m, 3H), 4.64–4.67 (m, 1H), 4.70–4.85 (m, 2H), 6.1 (d, *J* = 3.9 Hz, 1H), 7.20–7.39 (m, 25H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 14.1 (q), 22.7 (t, 2C), 25.2 (t), 26.4 (q), 26.8 (q), 29.3 (t), 29.6 (t), 29.7 (t), 31.9 (t), 34.3 (t), 44.6 (t), 45.1 (t), 45.2 (t), 71.4 (t), 71.6 (t), 72.6 (t), 73.0 (t), 73.9 (t), 74.5 (d), 75.1 (d), 75.8 (d), 77.2 (d), 81.8 (d), 83.1 (d), 86.0 (d), 105.2 (d), 111.8 (s), 127.0 (d), 127.3 (d), 127.4 (d), 127.7 (d), 127.8 (d, 4C), 127.9 (d, 3C), 128.0 (d), 128.1 (d), 128.2 (d), 128.24 (d, 4C), 128.4 (d, 2C), 128.6 (d, 3C), 129.0 (d), 129.7 (d), 136.8 (s), 137.4 (s), 138.0 (s), 138.7 (s), 138.8 (s), 205.8 (s), 210.3 (s); HRMS (MALDI-TOF) calcd for $C_{60}H_{74}O_{10}$ ($[M+Na]^+$) 977.5180, found 977.5149.



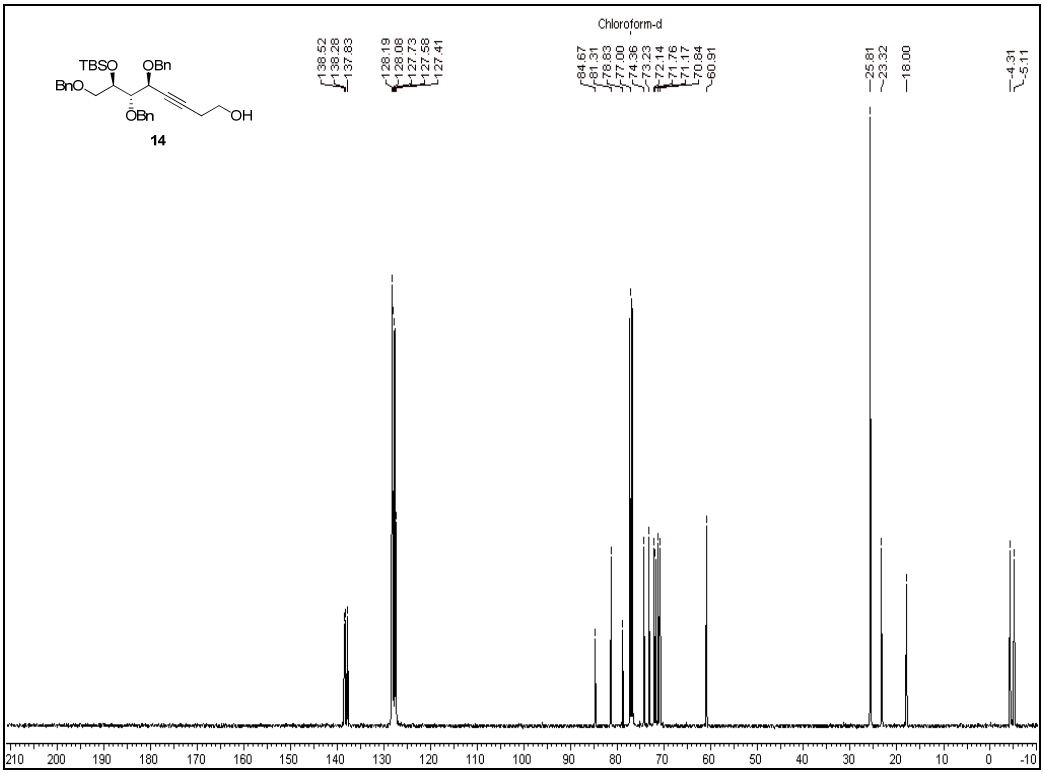
^{1}H NMR of compound 13



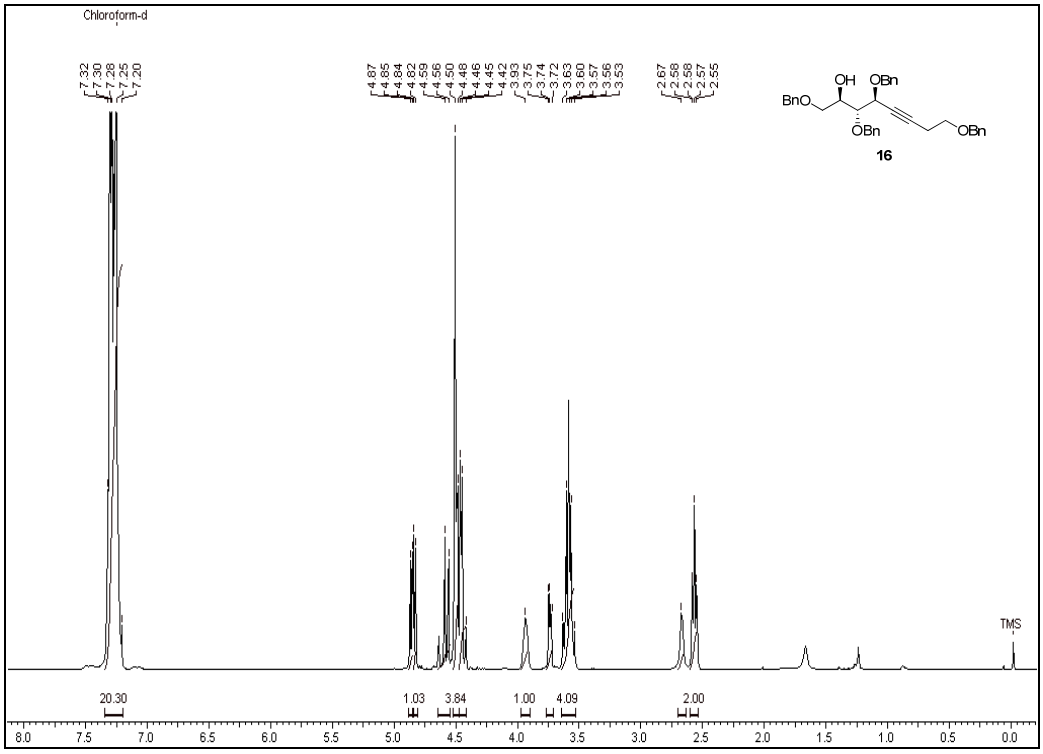
^{13}C NMR of compound 13



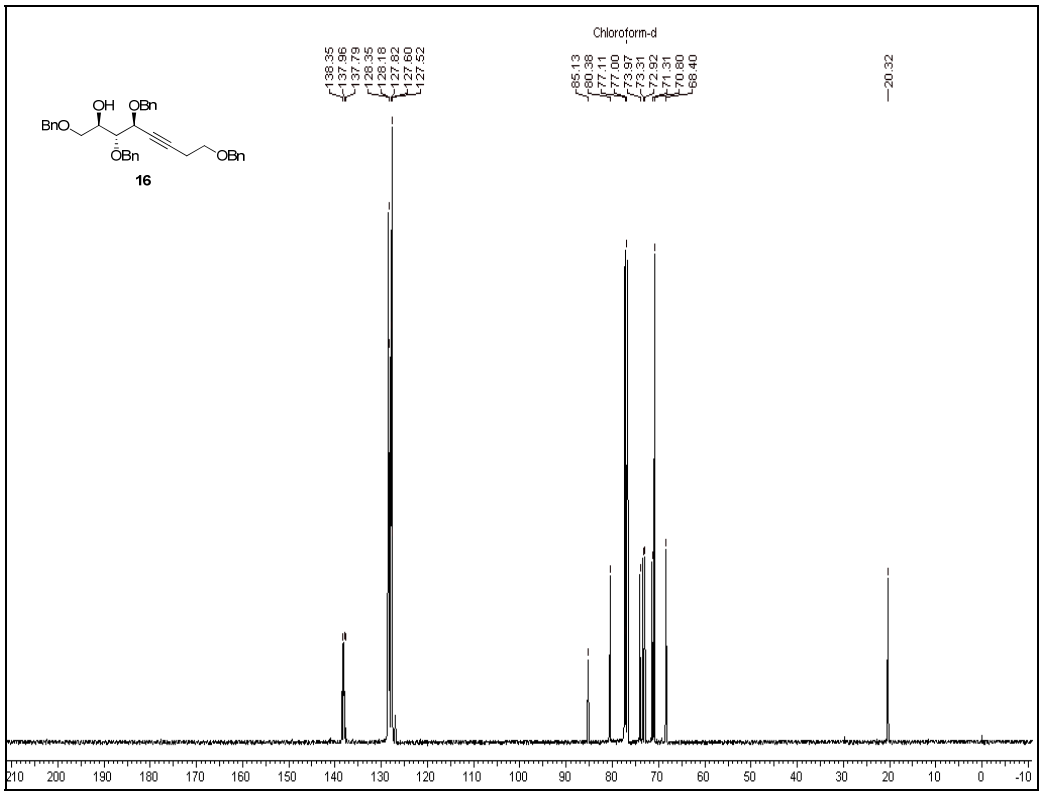
^{1}H NMR of compound 14



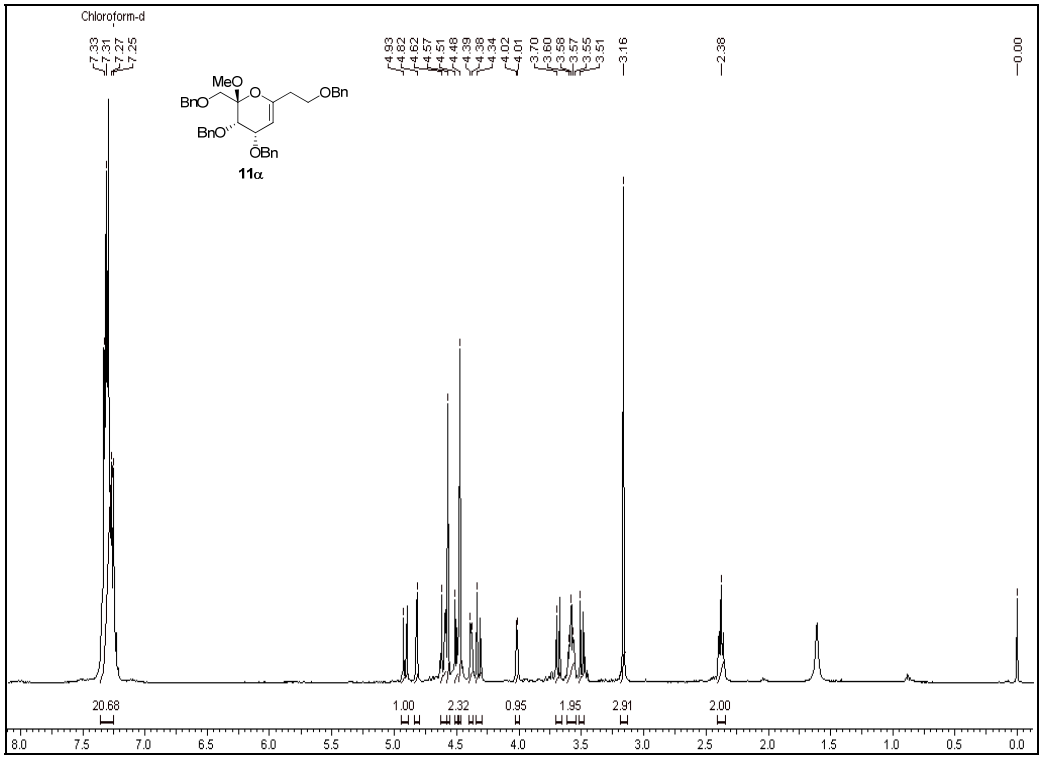
^{13}C NMR of compound 14



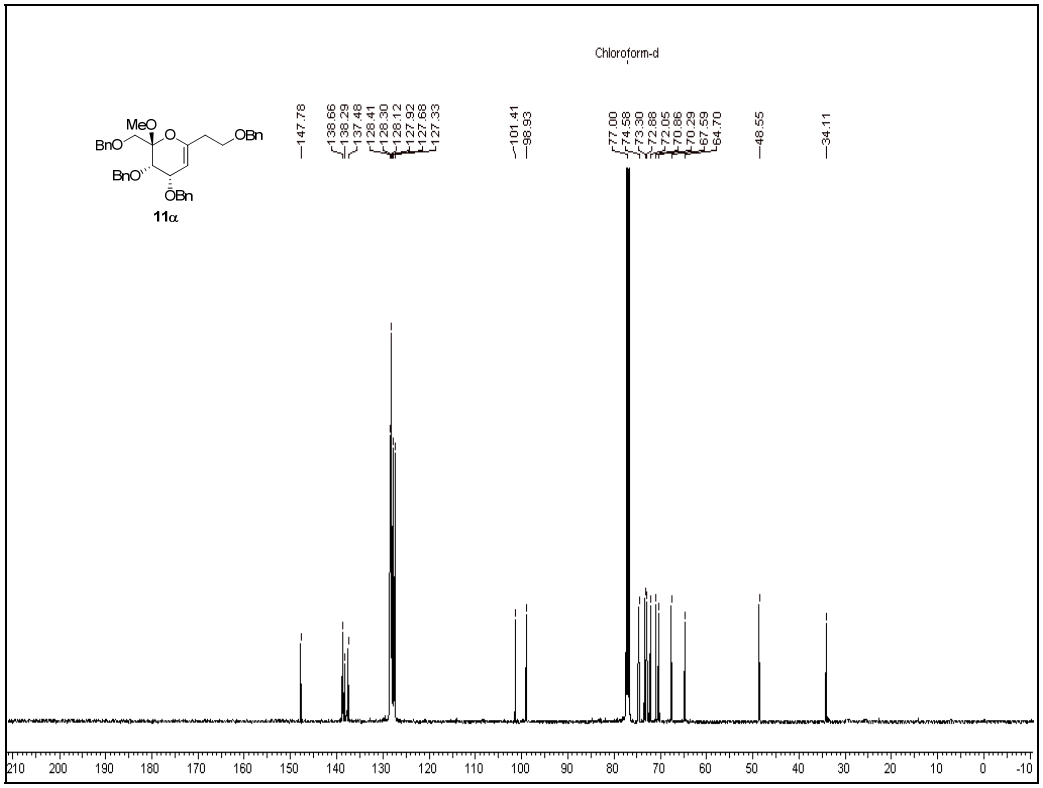
^{1}H NMR of compound 16



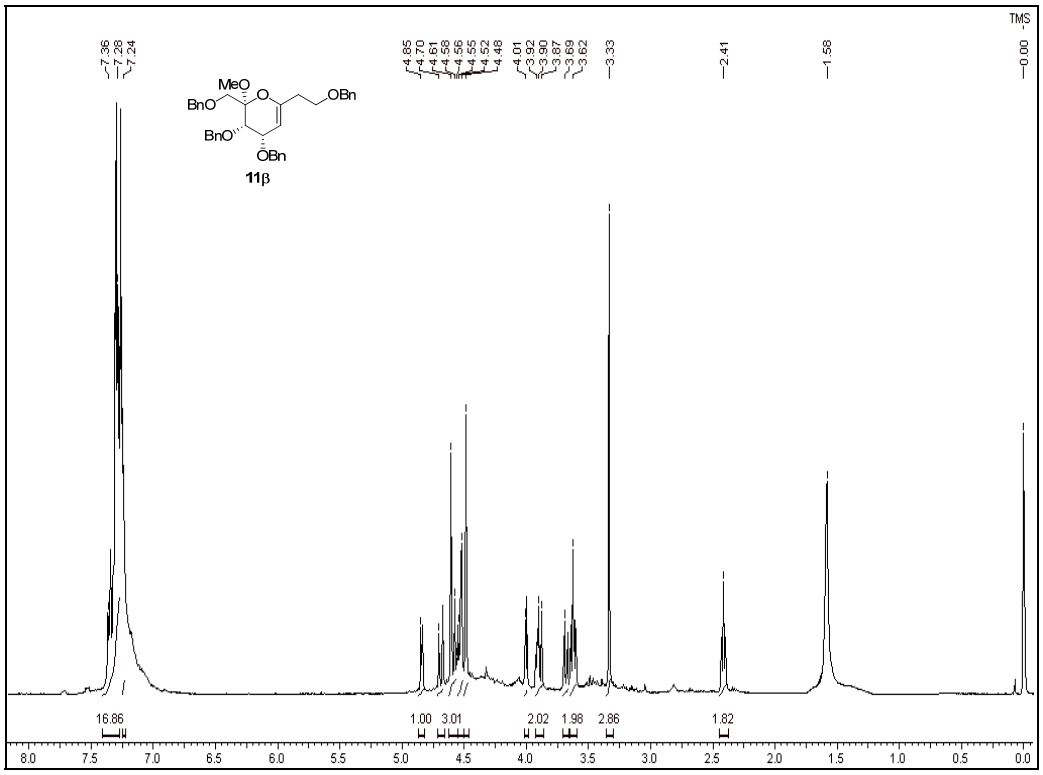
^{13}C NMR of compound 16



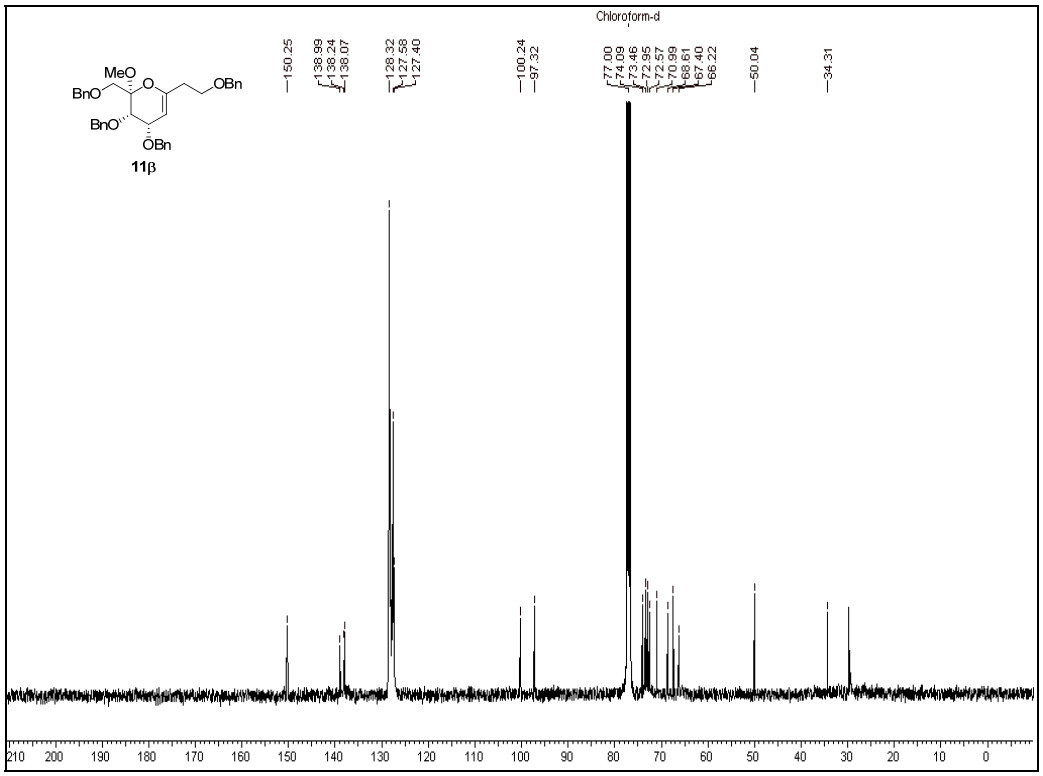
^{1}H NMR of compound 11α



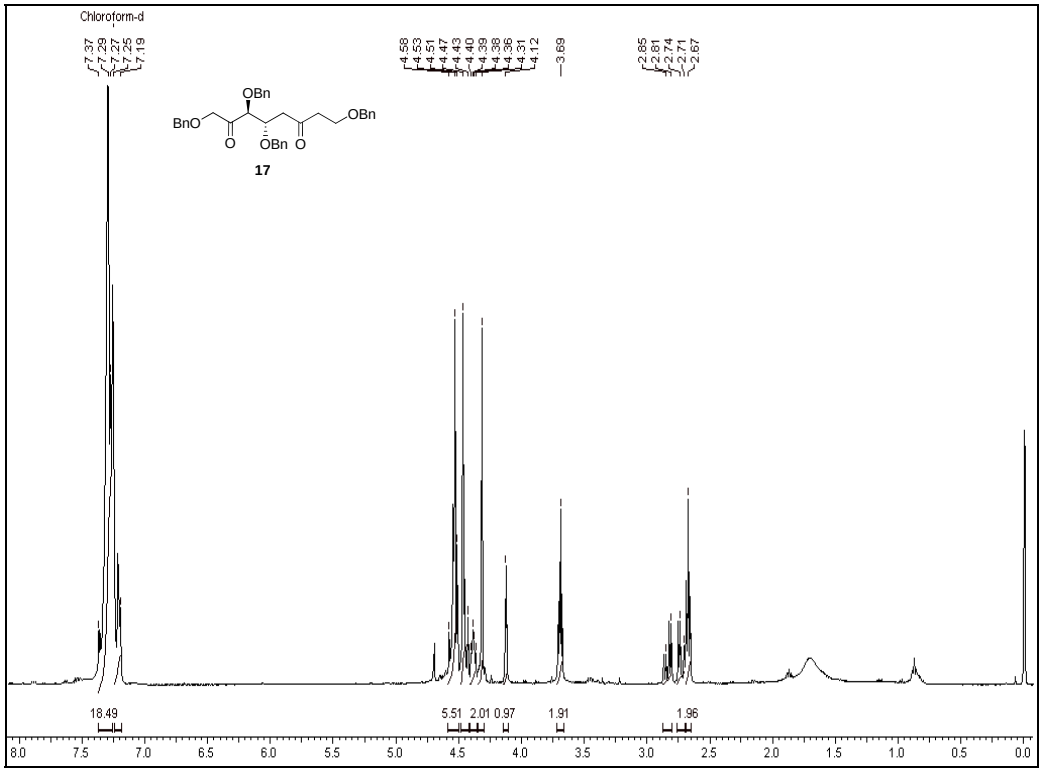
^{13}C NMR of compound 11α



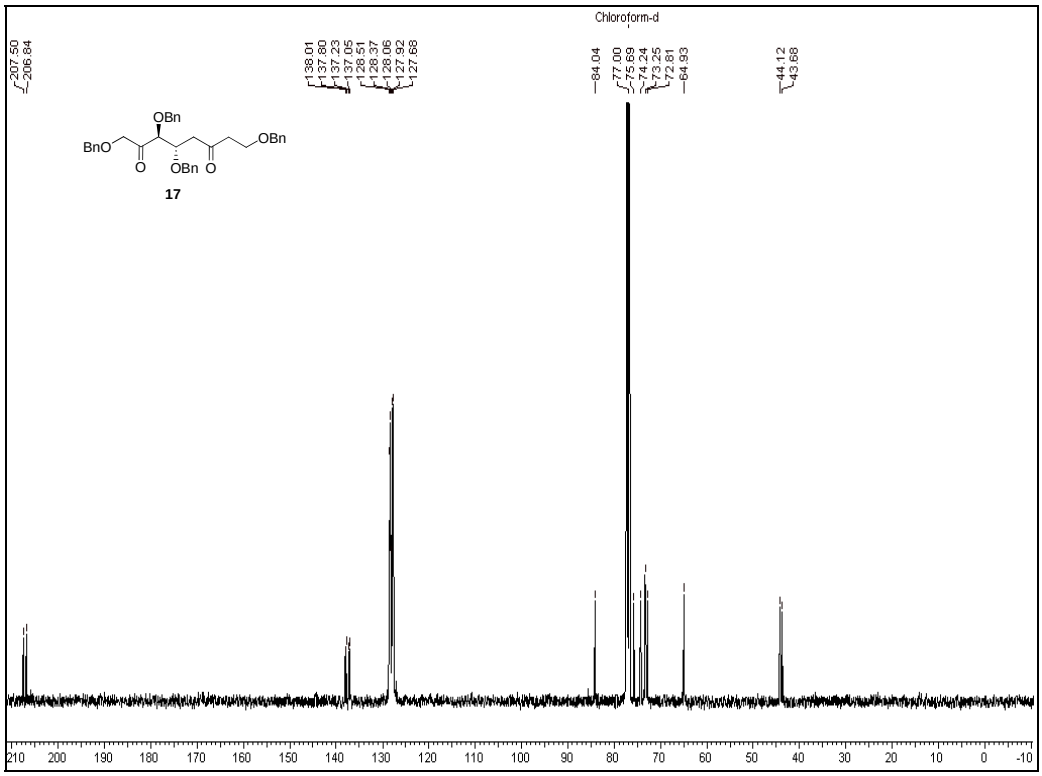
^{1}H NMR of compound 11β



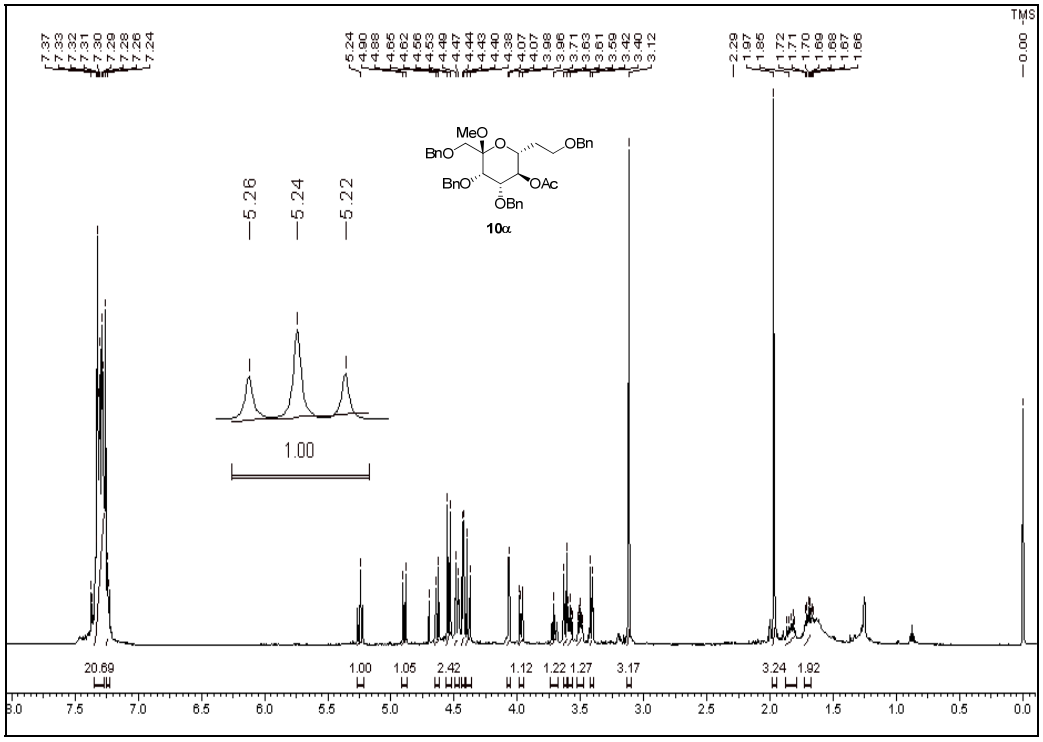
^{13}C NMR of compound 11β



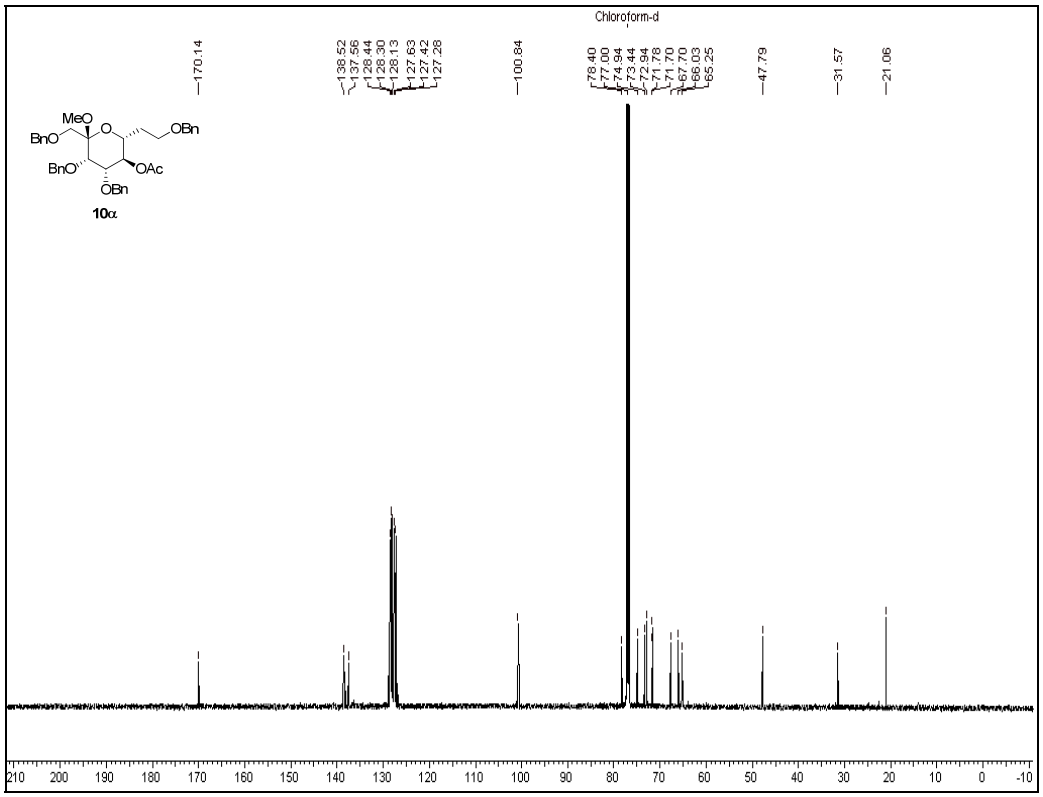
^{1}H NMR of compound 17



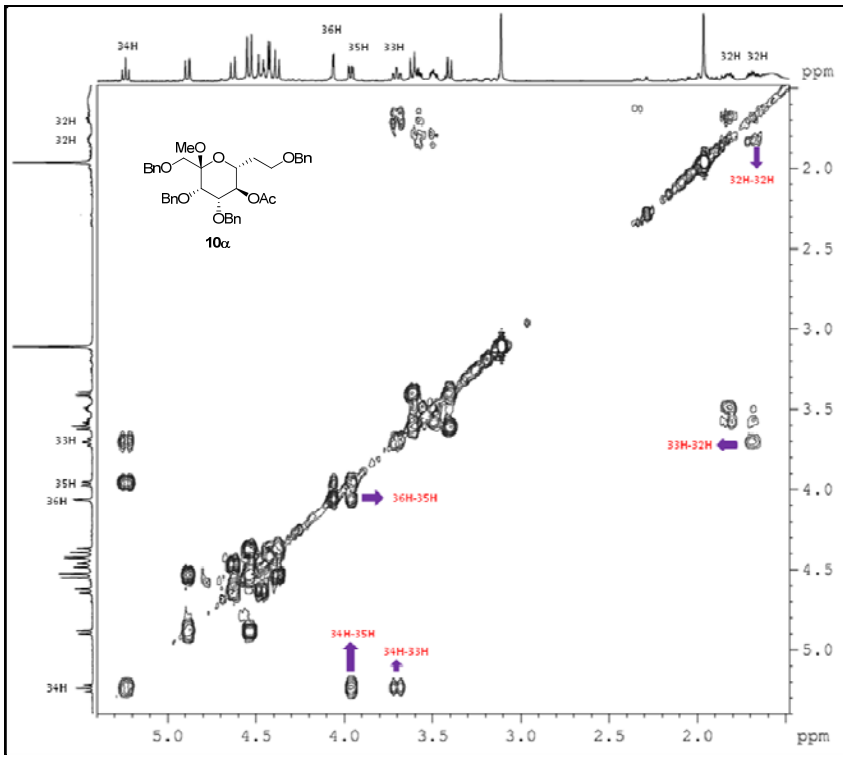
^{13}C NMR of compound 17



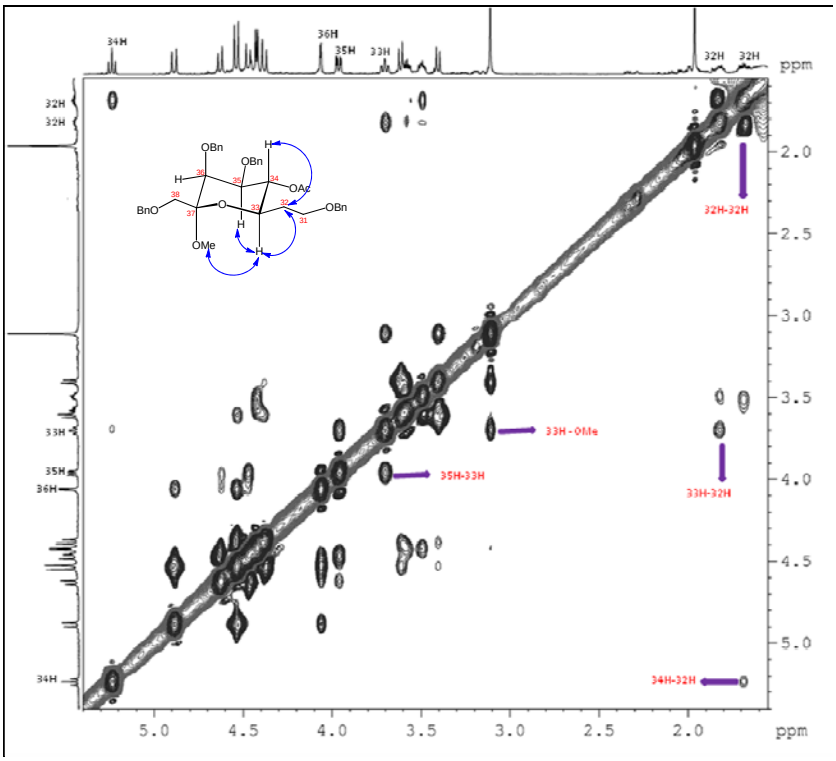
^{1}H NMR of compound 10α



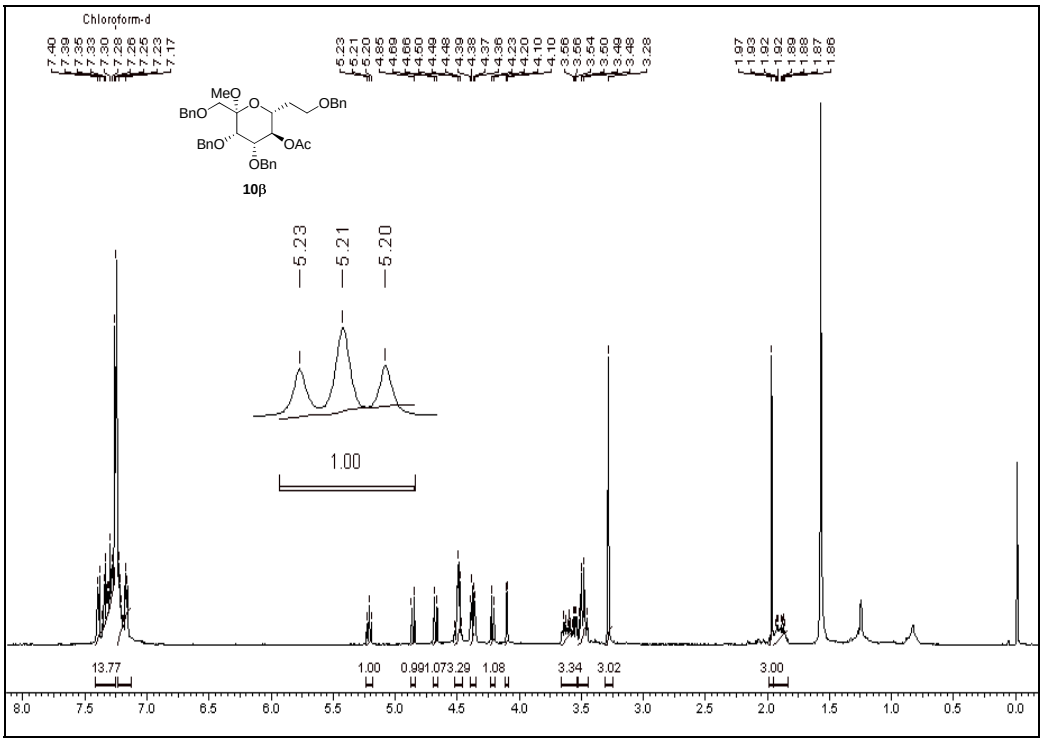
^{13}C NMR of compound 10α



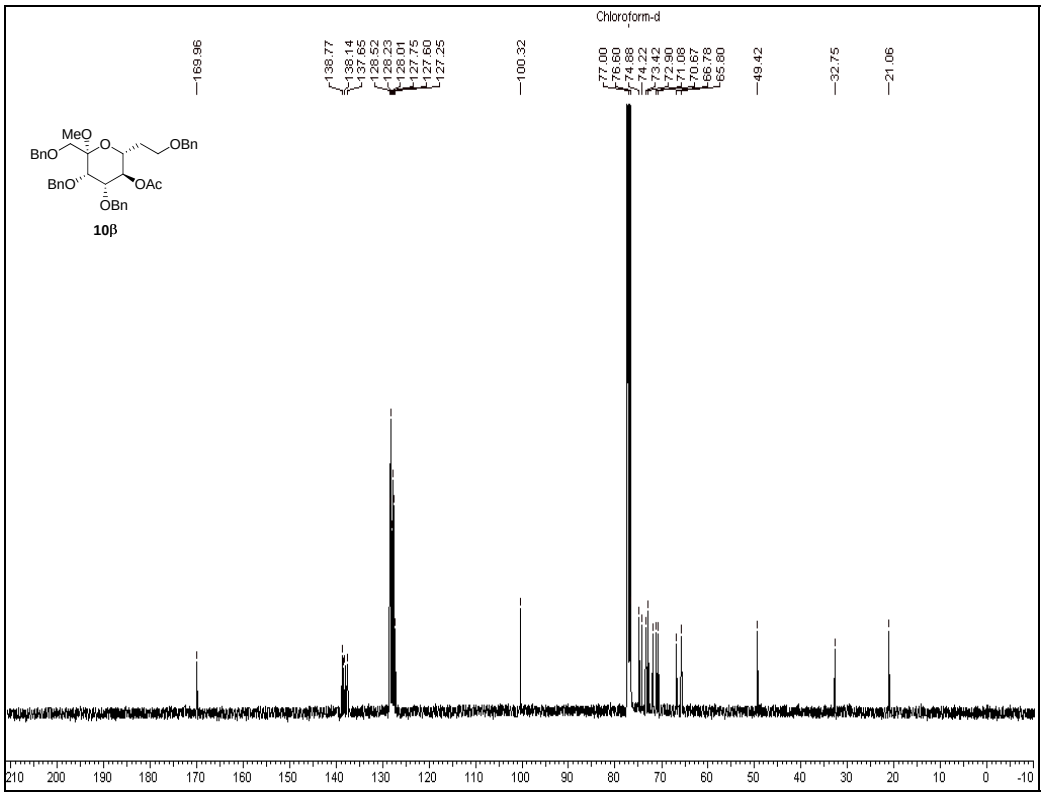
COSY of compound 10α



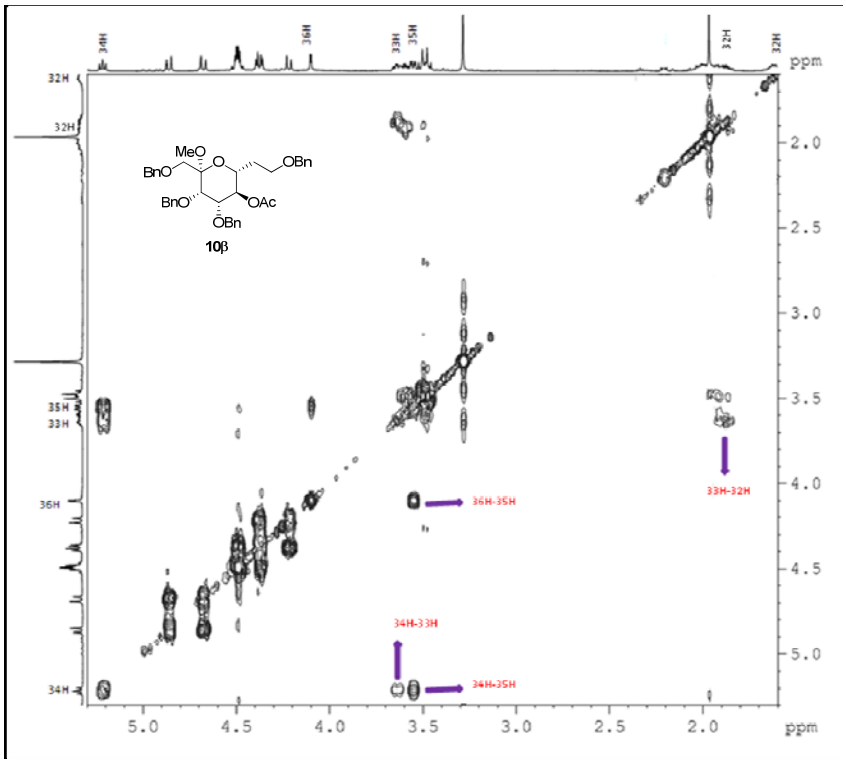
NOESY of compound 10α



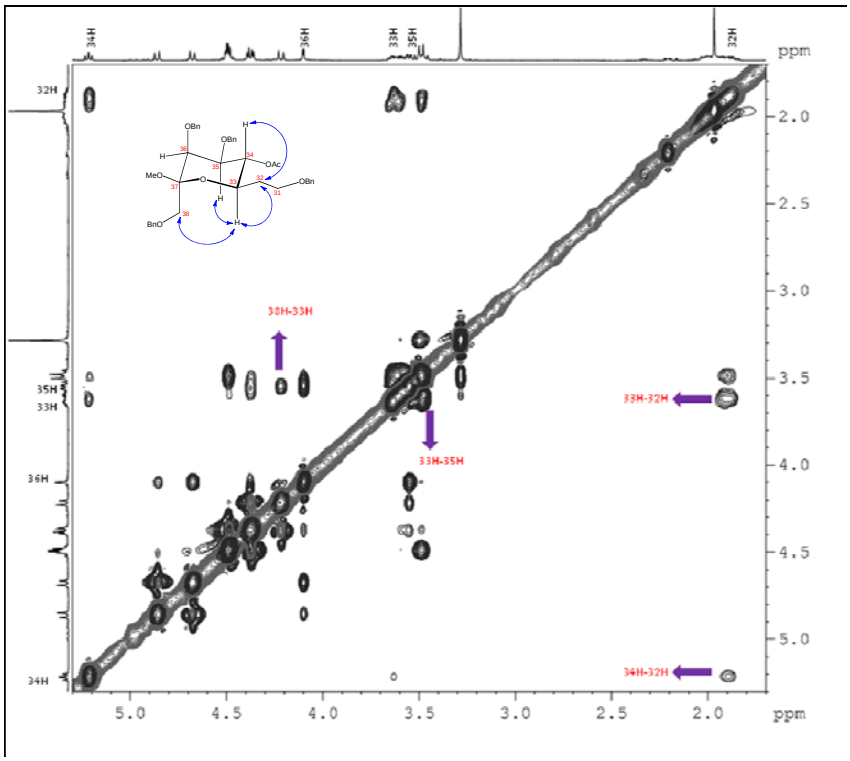
^{1}H NMR of compound 10β



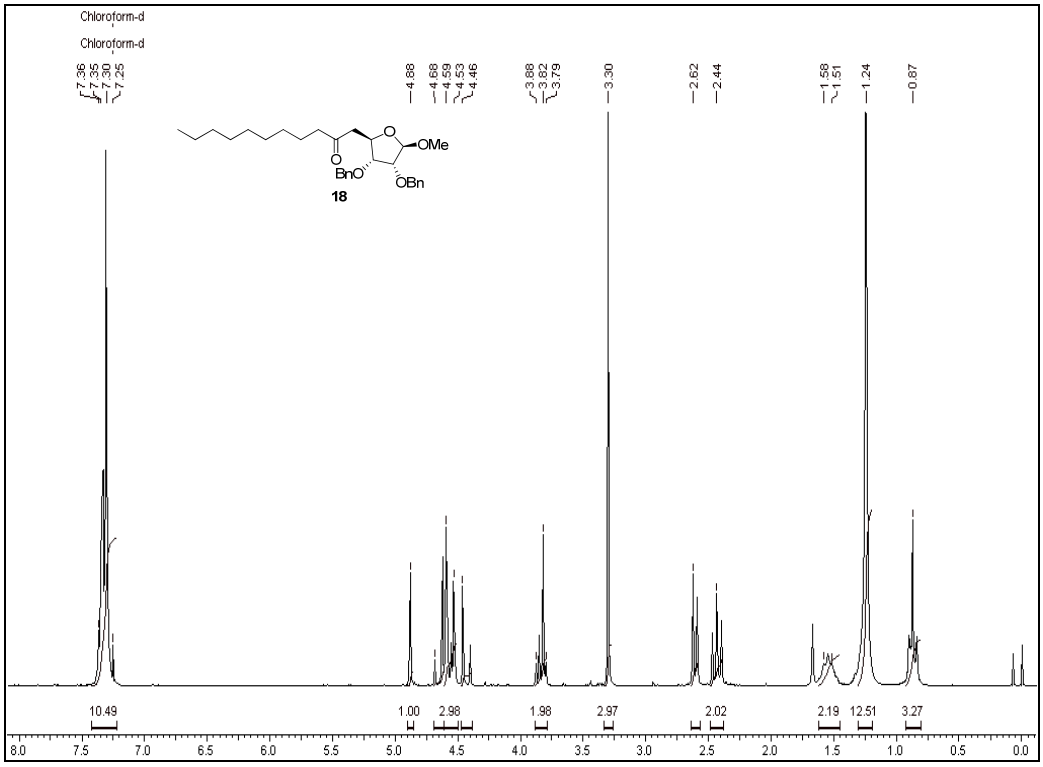
^{13}C NMR of compound 10β



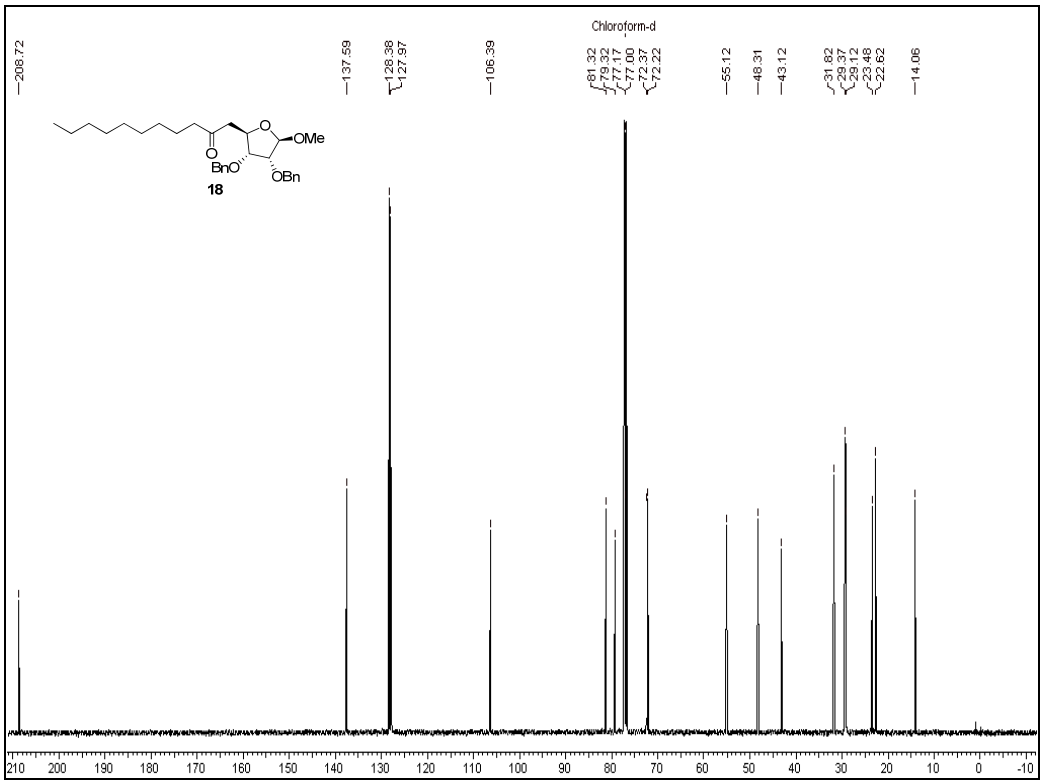
COSY of compound 10β



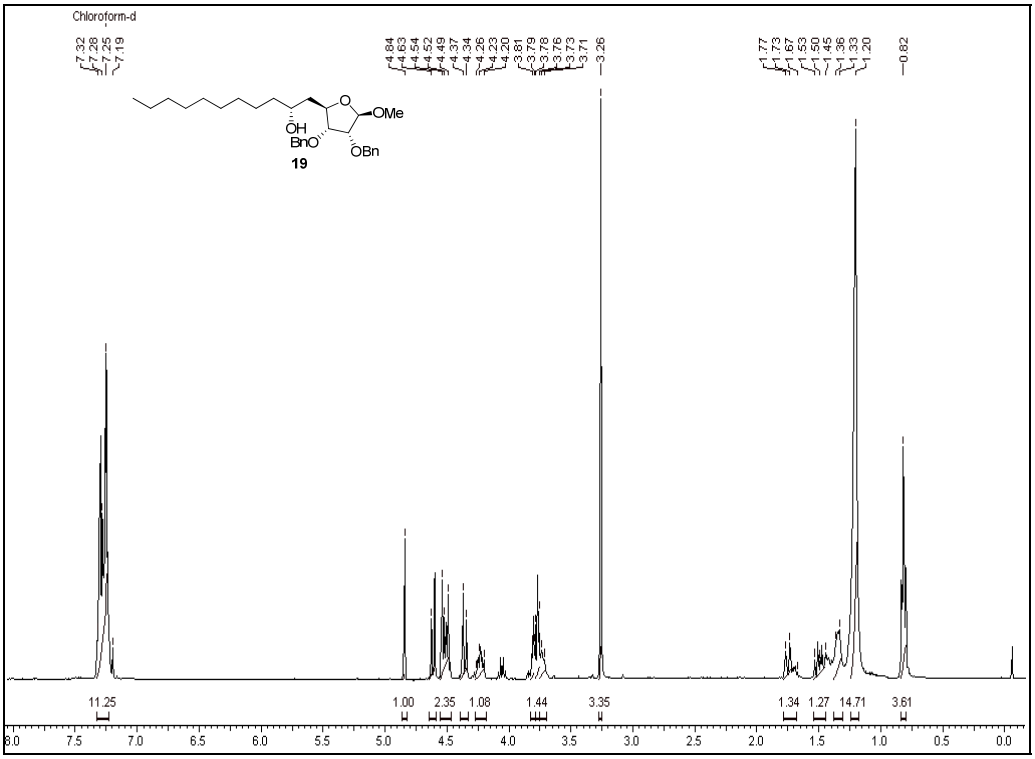
NOESY of compound 10β



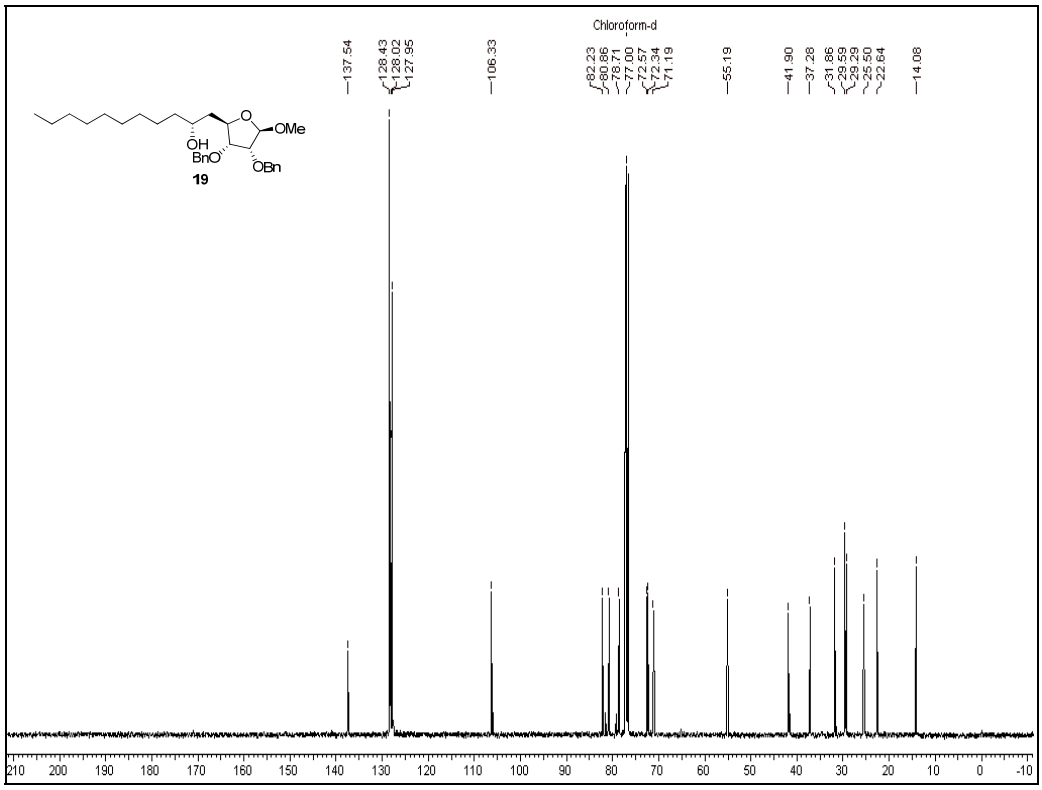
^{1}H NMR of compound 18



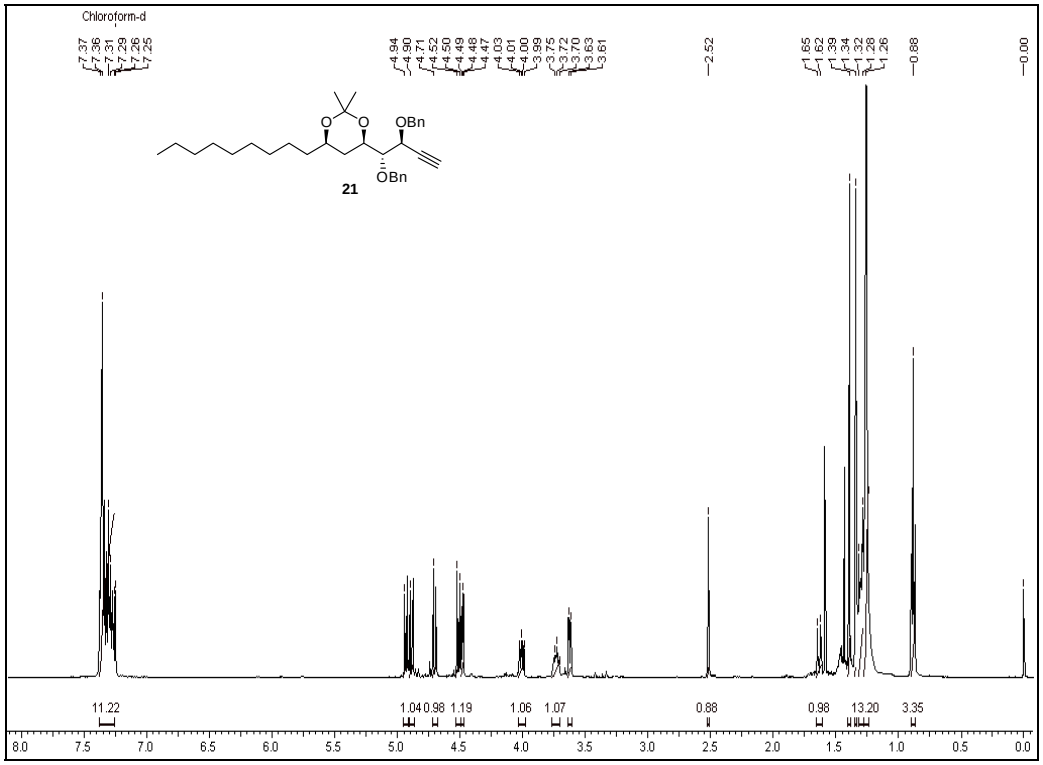
^{13}C NMR of compound 18



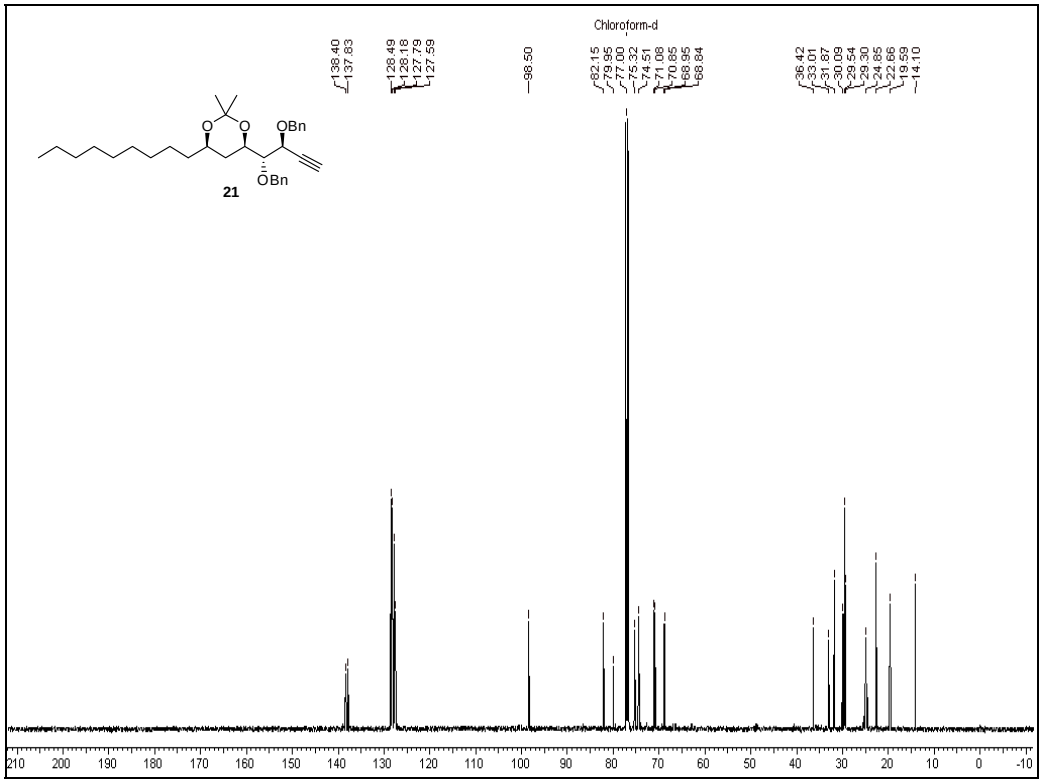
^{1}H NMR of compound 19



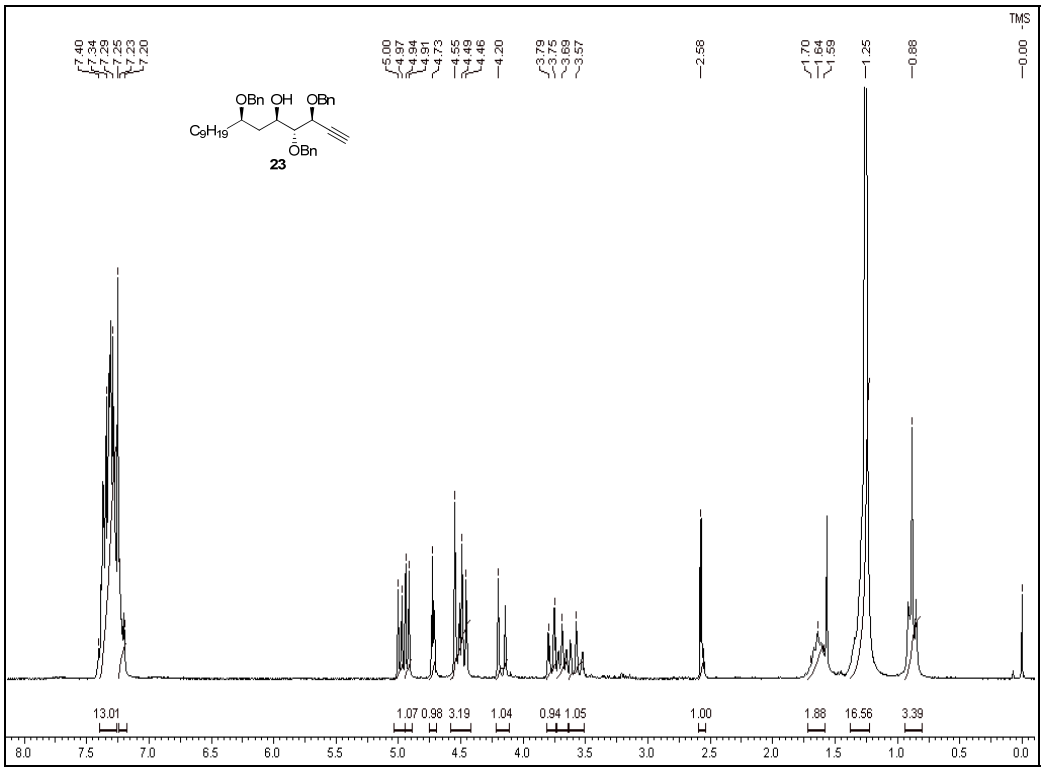
^{13}C NMR of compound 19



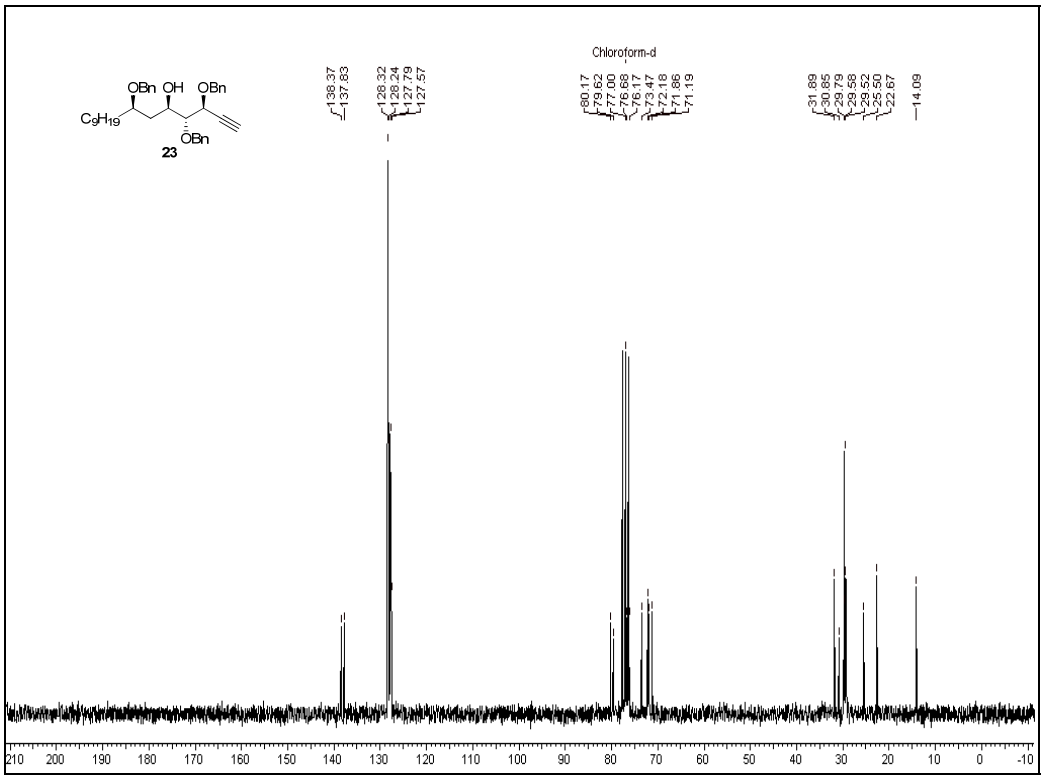
^{1}H NMR of compound 21



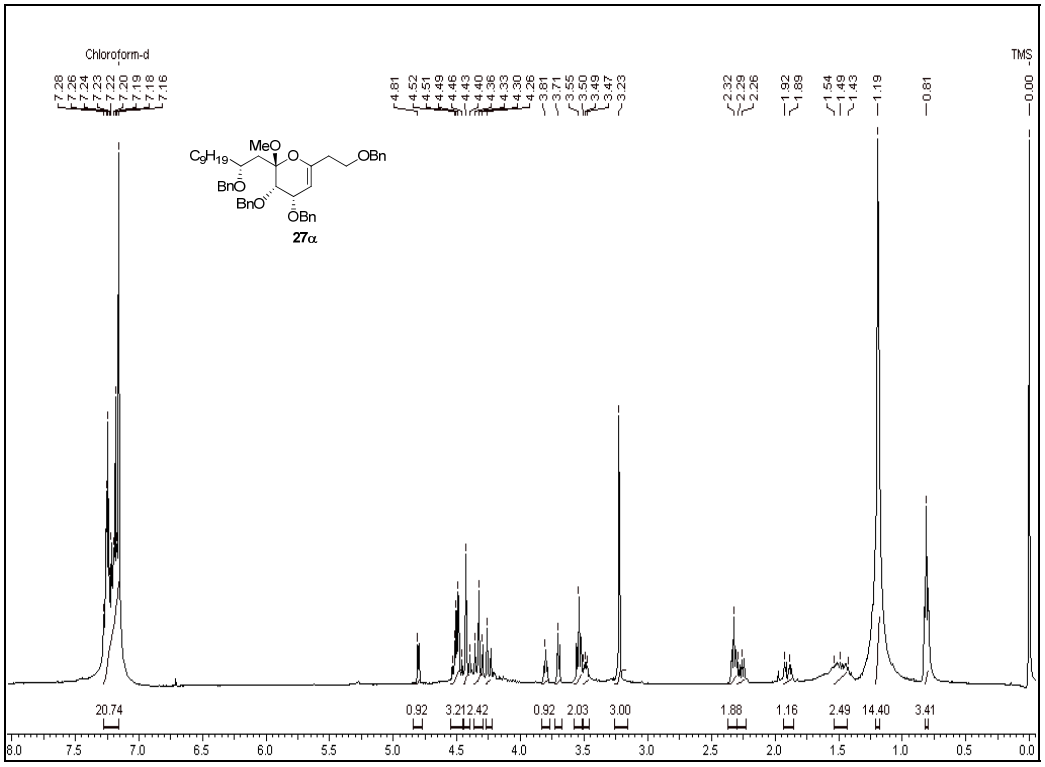
^{13}C NMR of compound 21



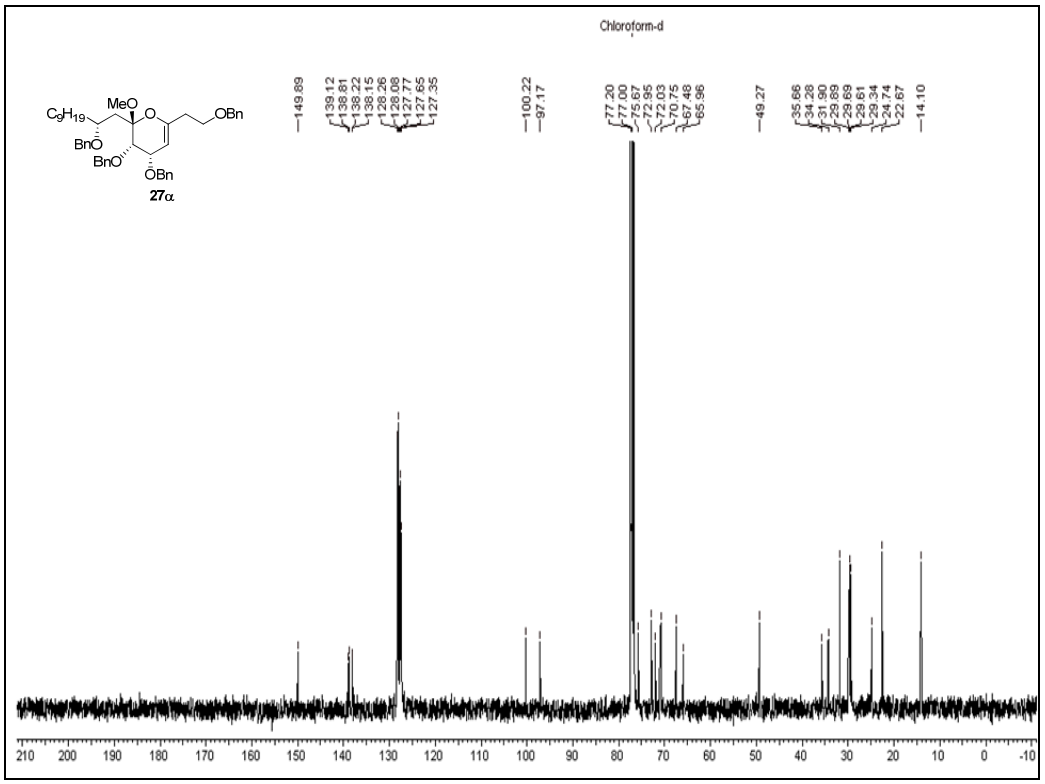
^{1}H NMR of compound 23



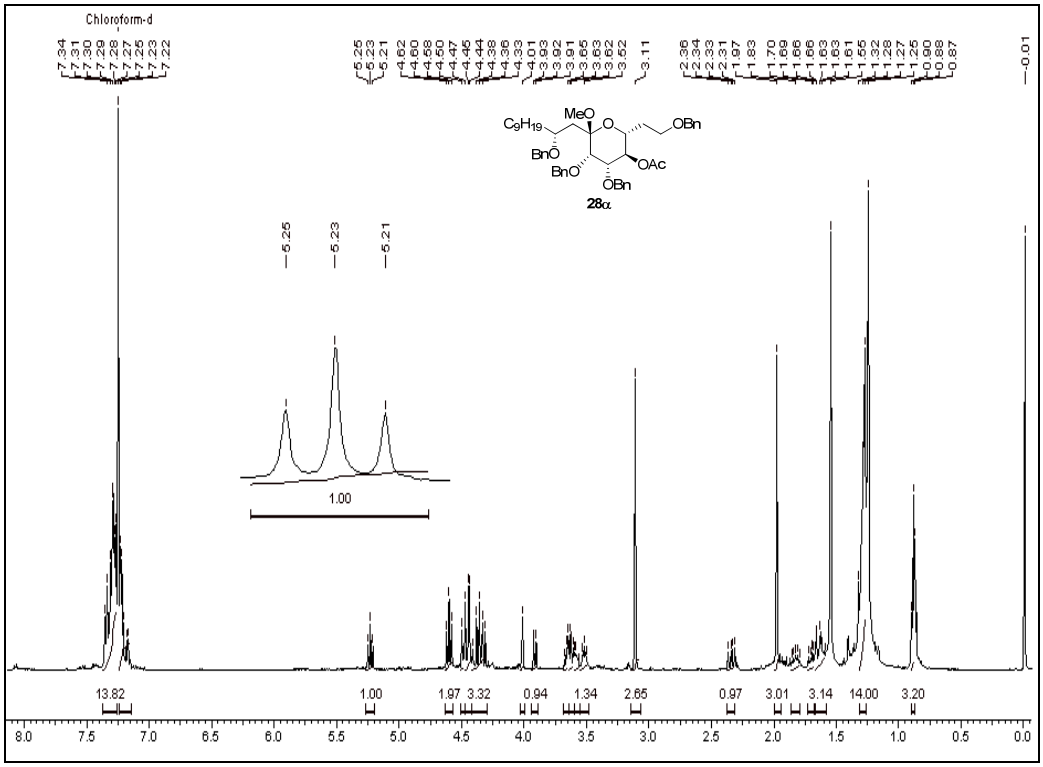
^{13}C NMR of compound 23



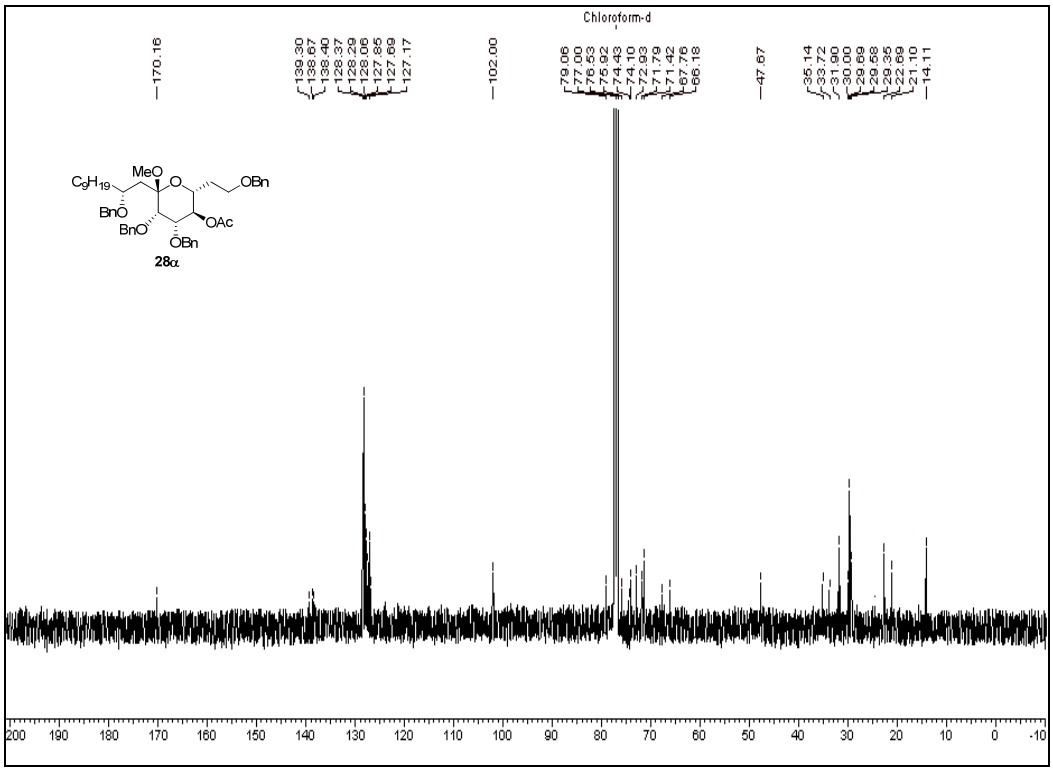
^{1}H NMR of compound 27α



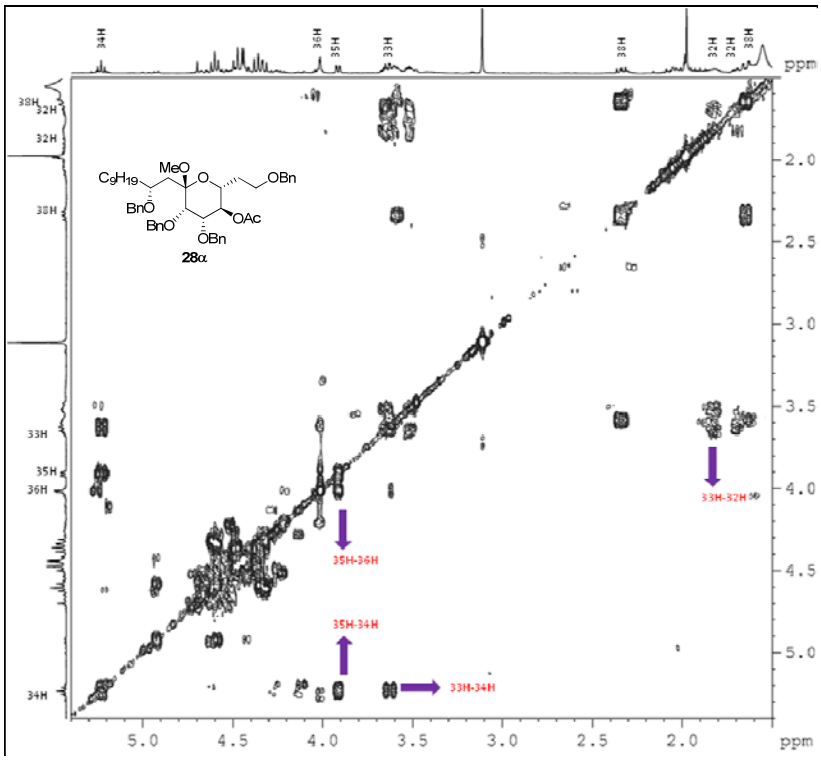
^{13}C NMR of compound 27α



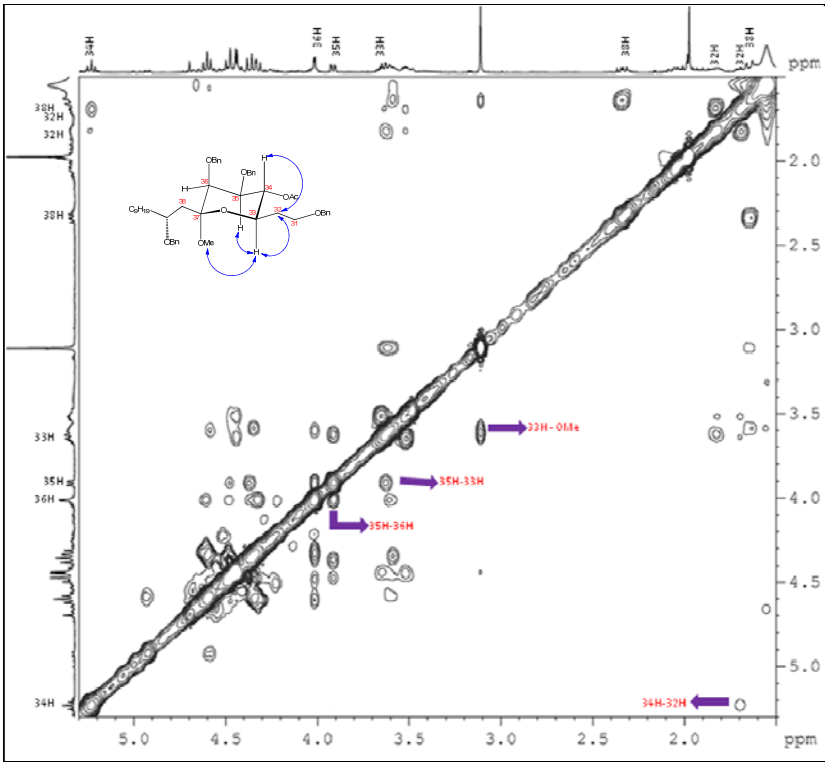
^{1}H NMR of compound 28α



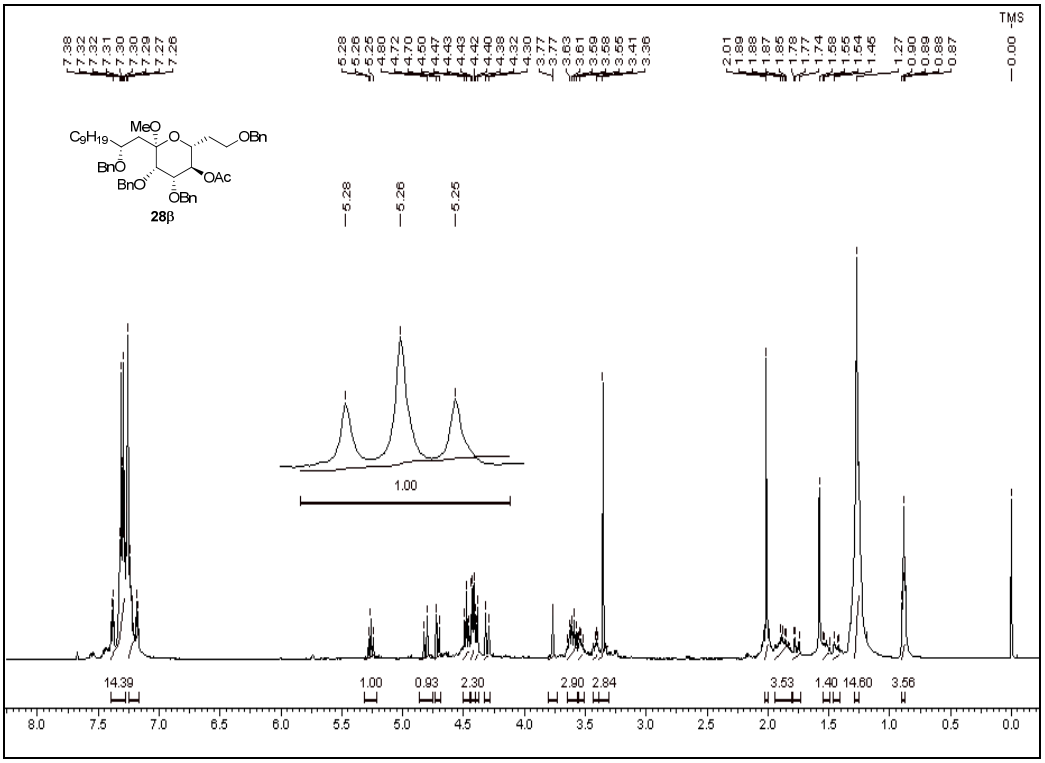
^{13}C NMR of compound 28α



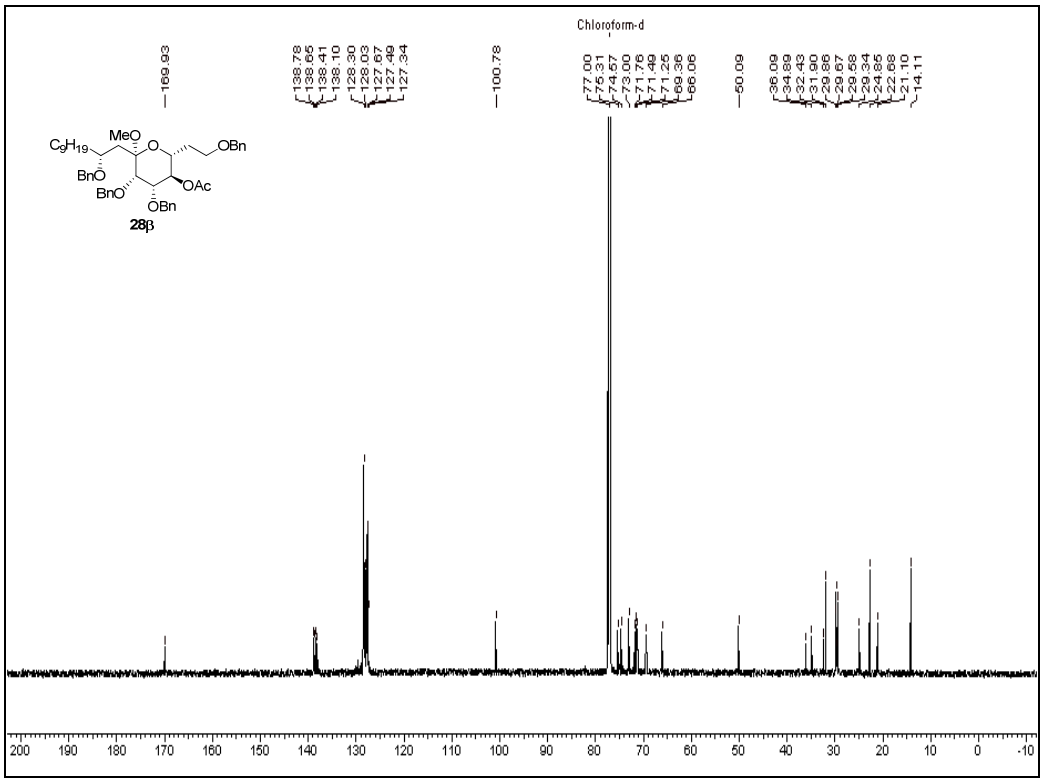
COSY of compound 28α



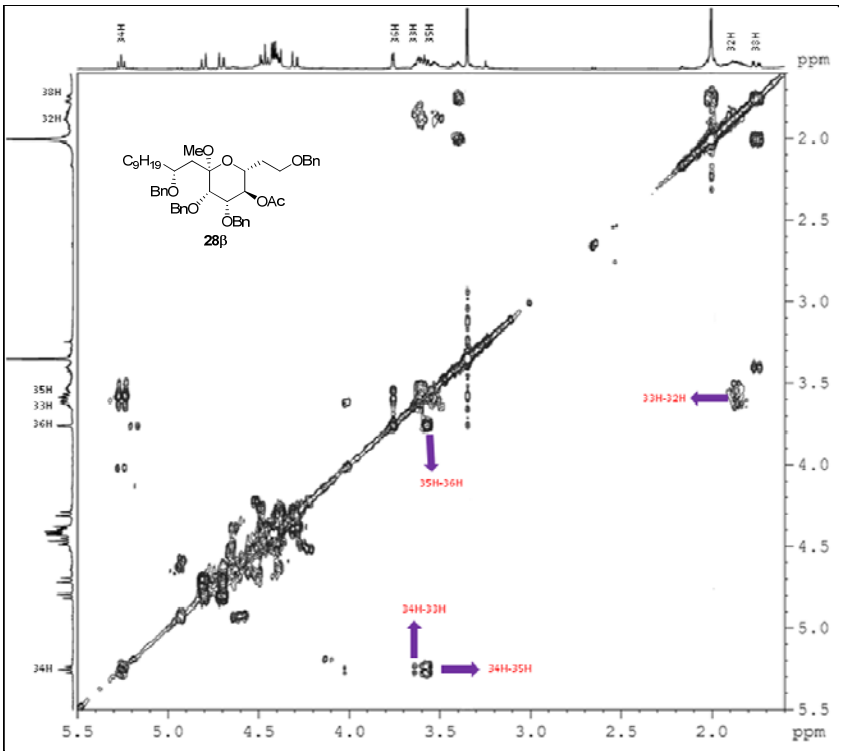
NOESY of compound 28α



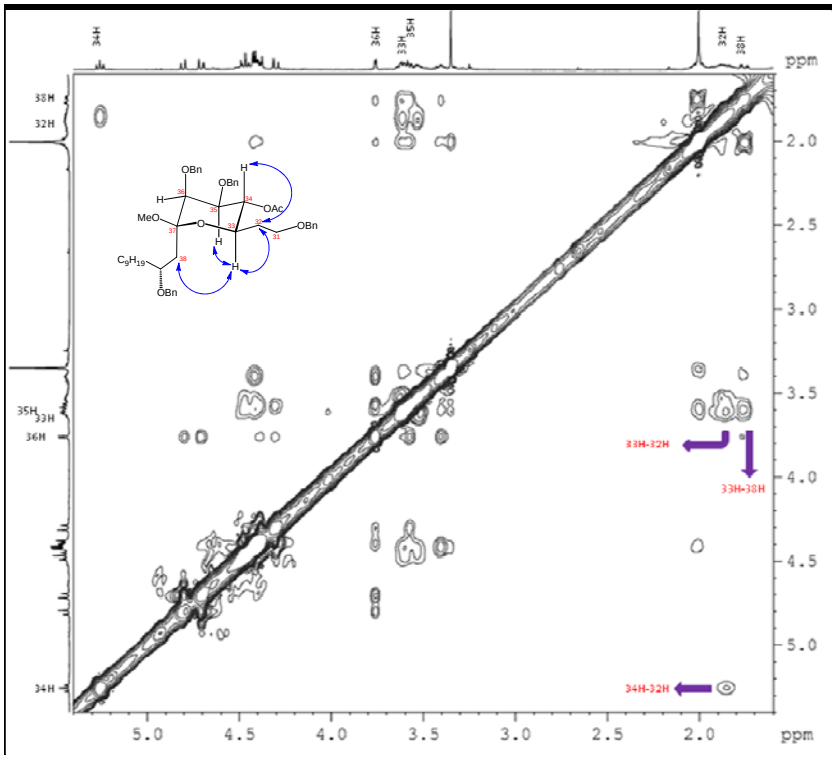
^{1}H NMR of compound 28β



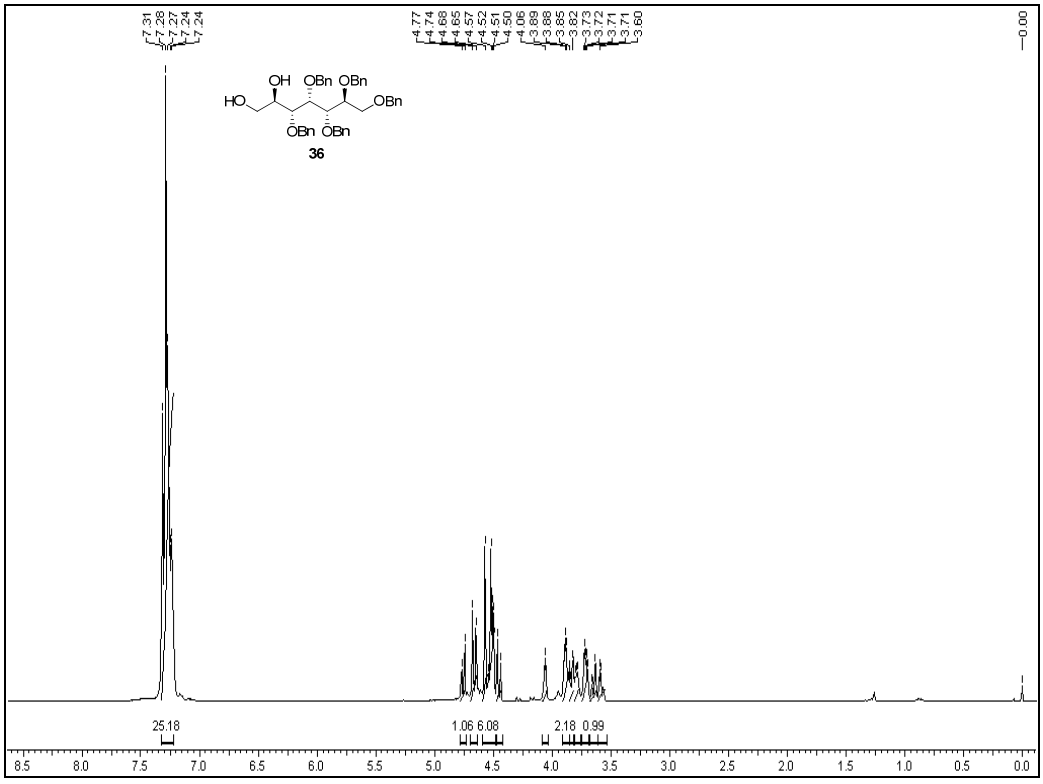
^{13}C NMR of compound 28β



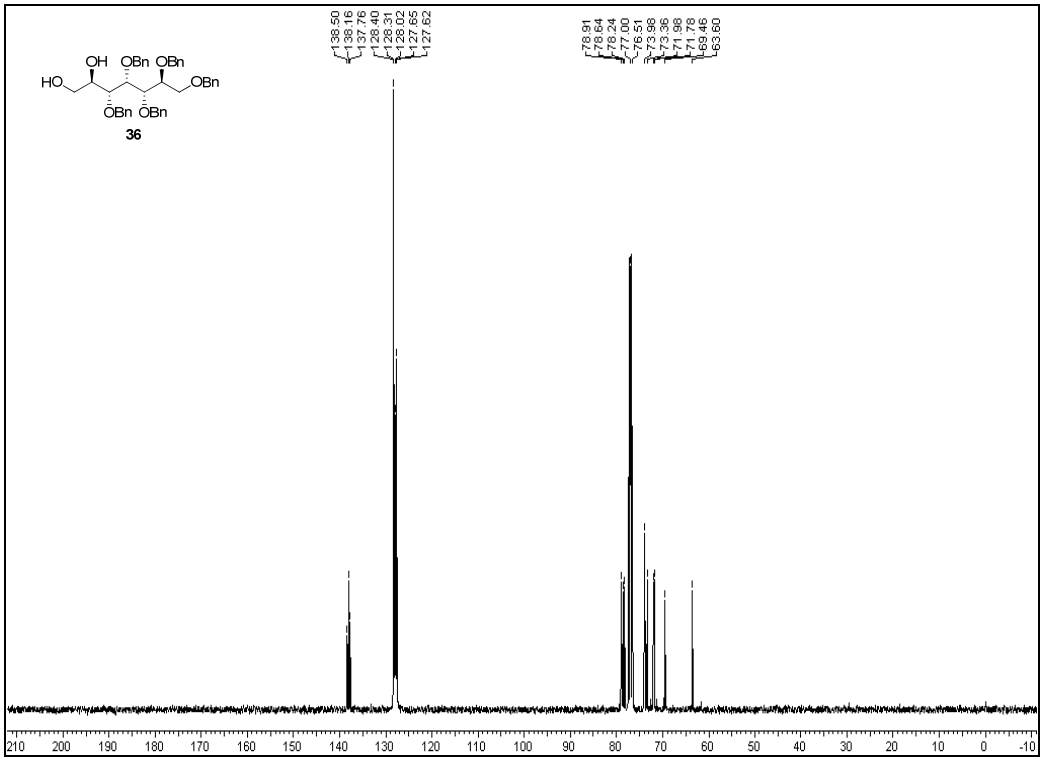
COSY of compound 28β



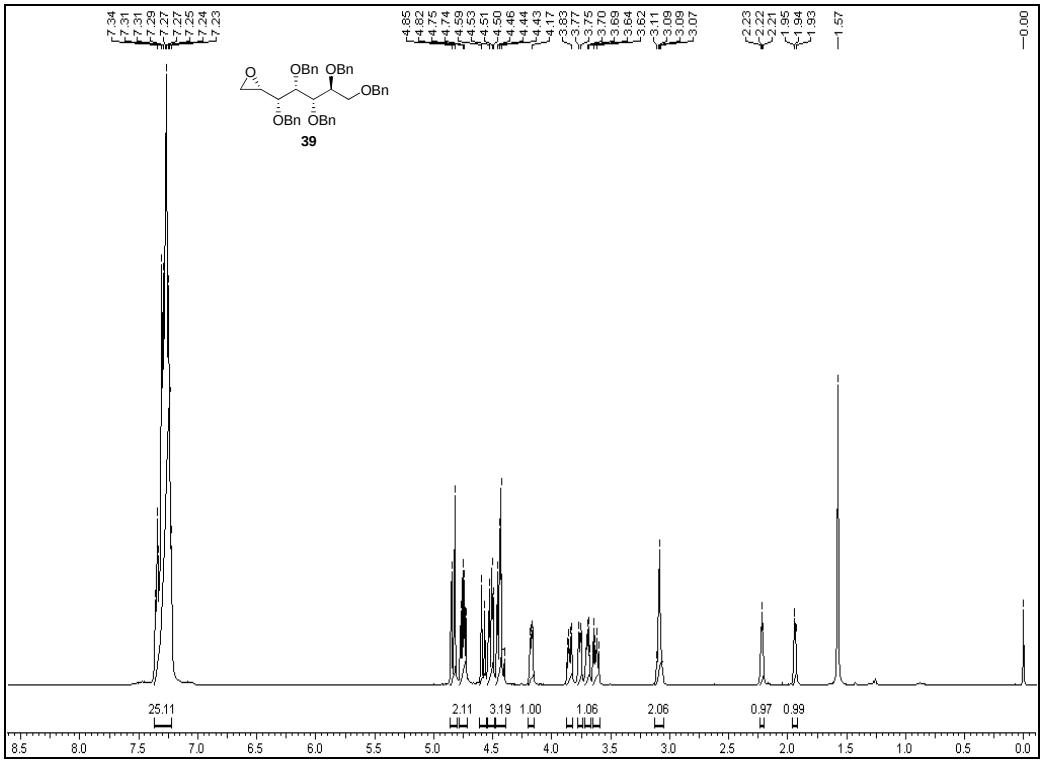
NOESY of compound 28β



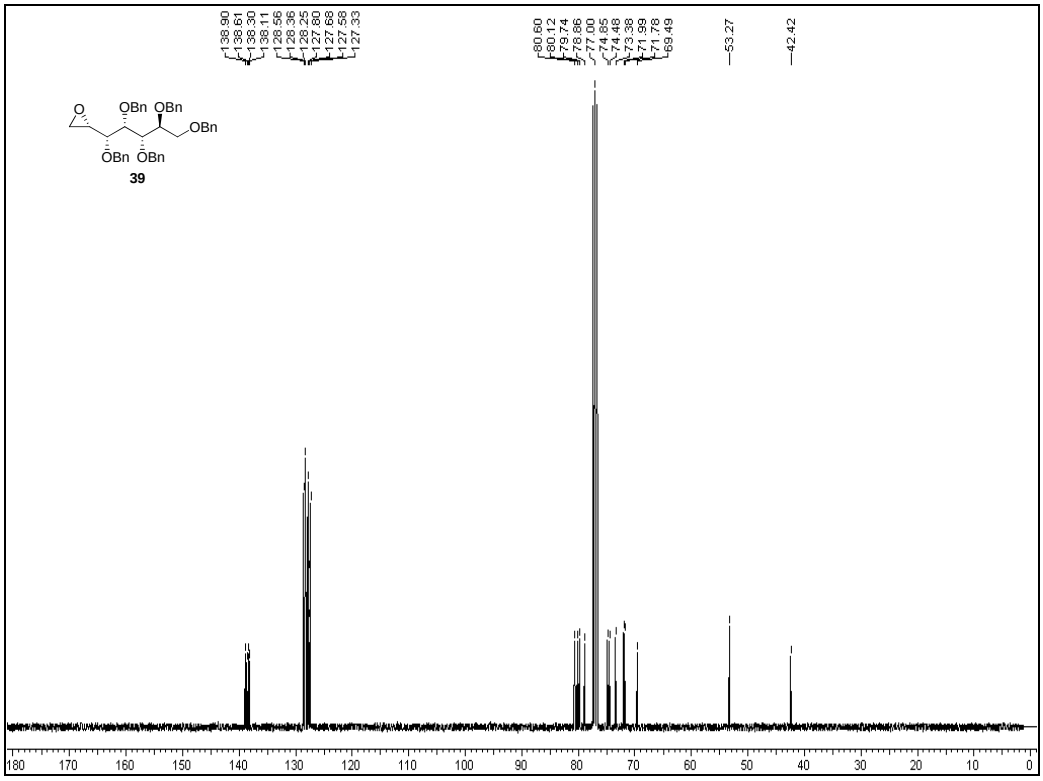
^{1}H NMR of compound 36



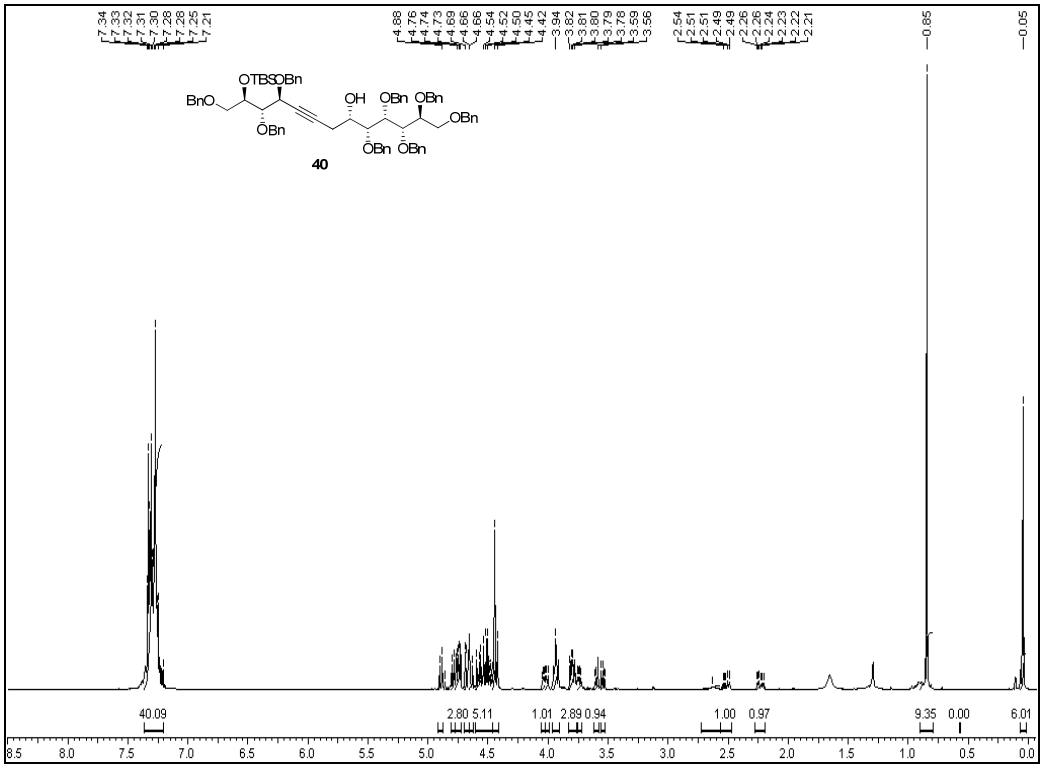
^{13}C NMR of compound 36



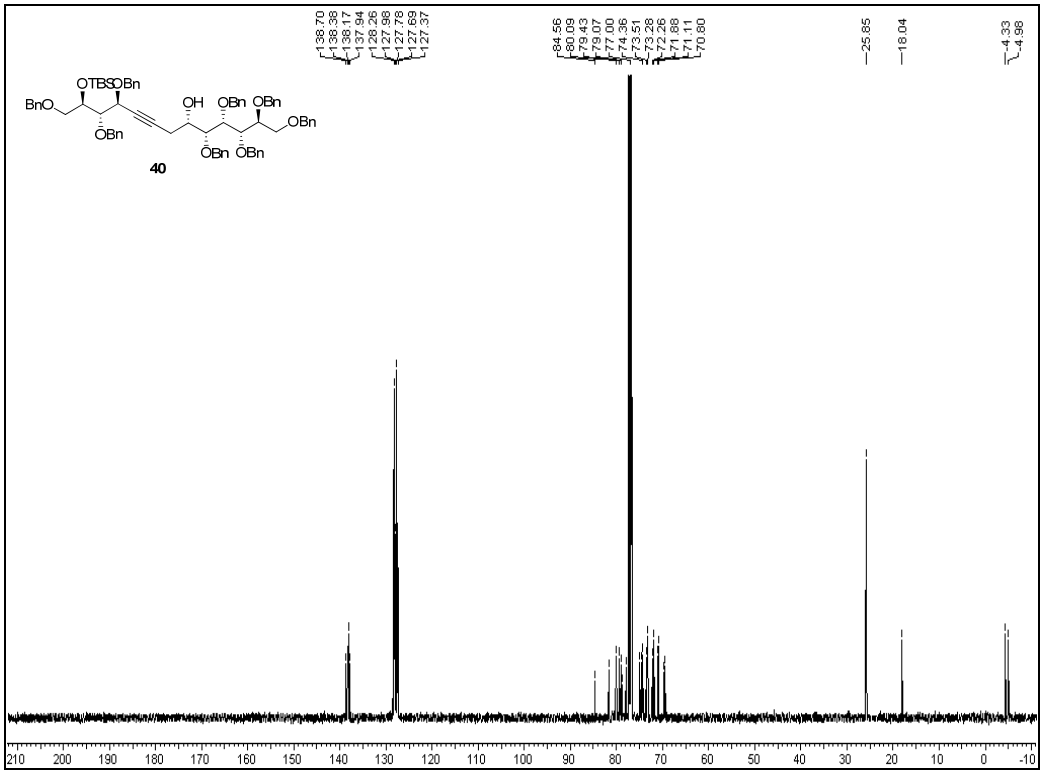
^{1}H NMR of compound 39



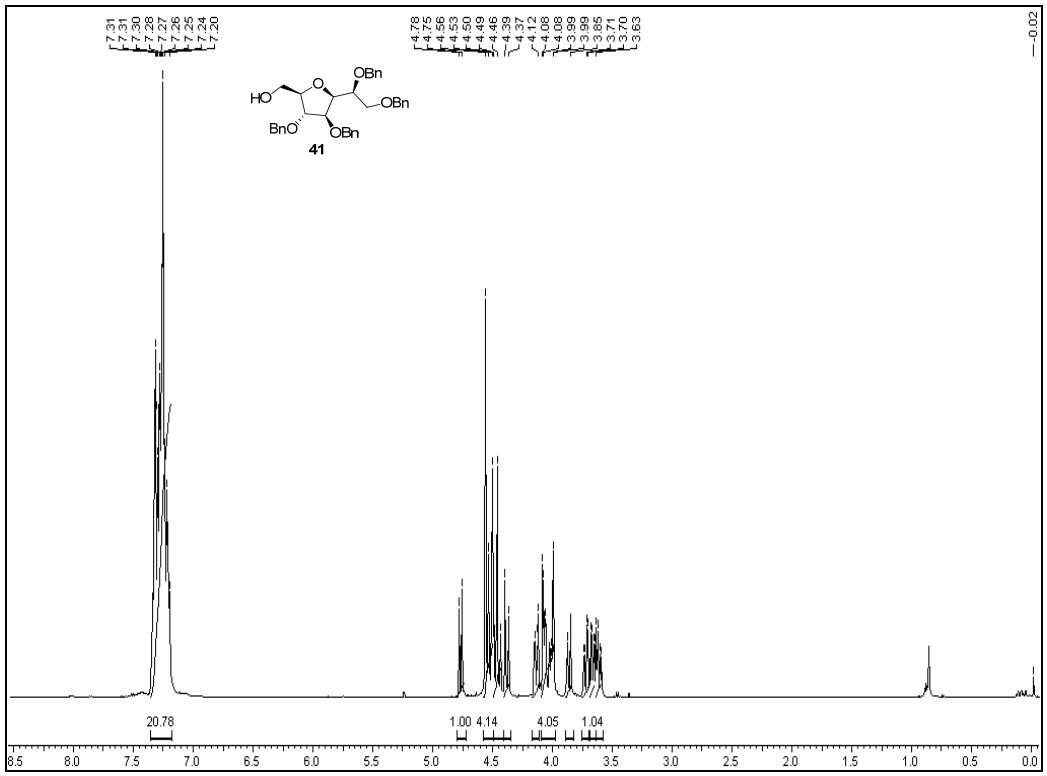
^{13}C NMR of compound 39



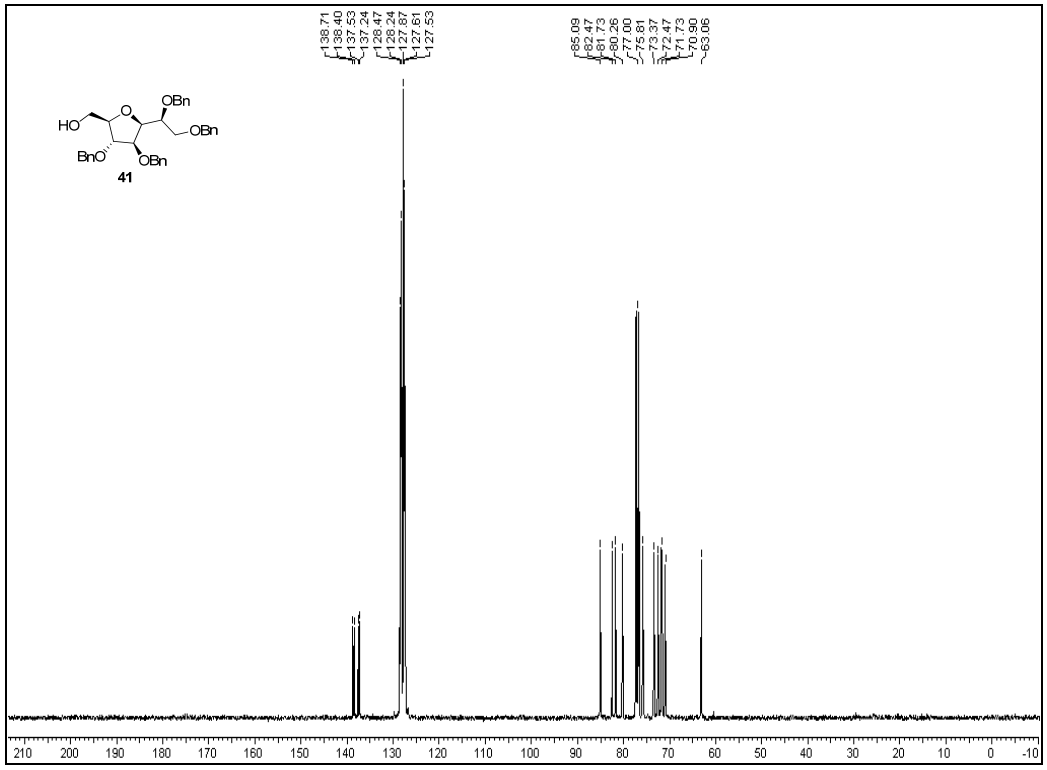
^{1}H NMR of compound 40



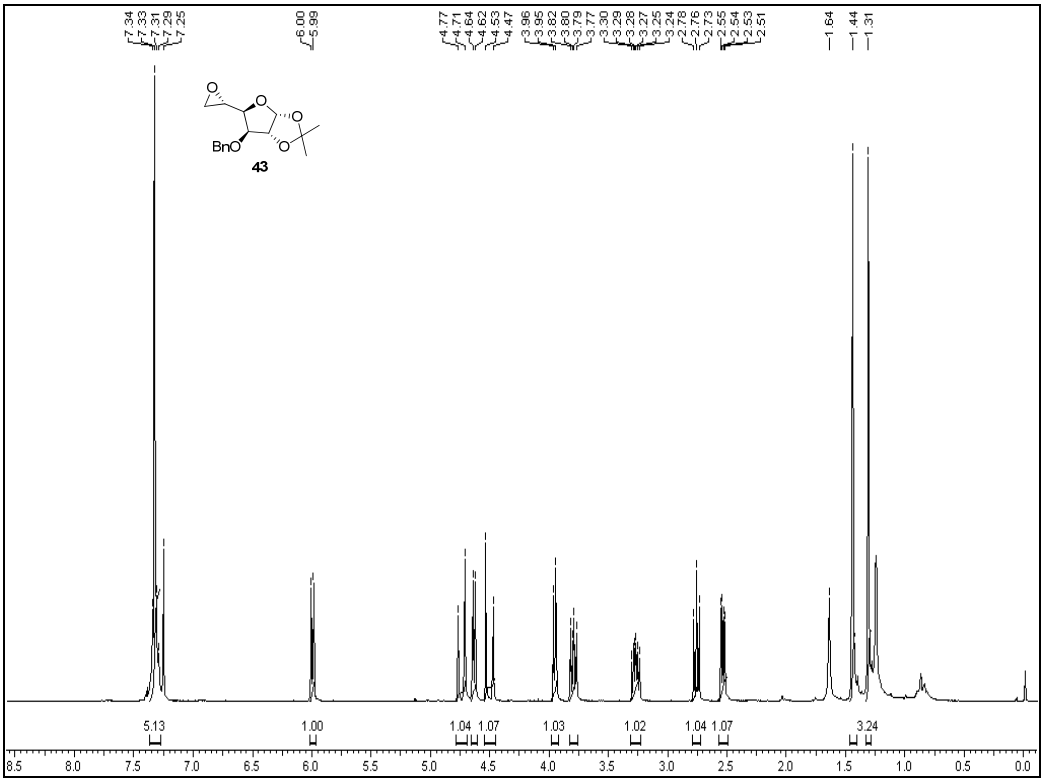
^{13}C NMR of compound 40



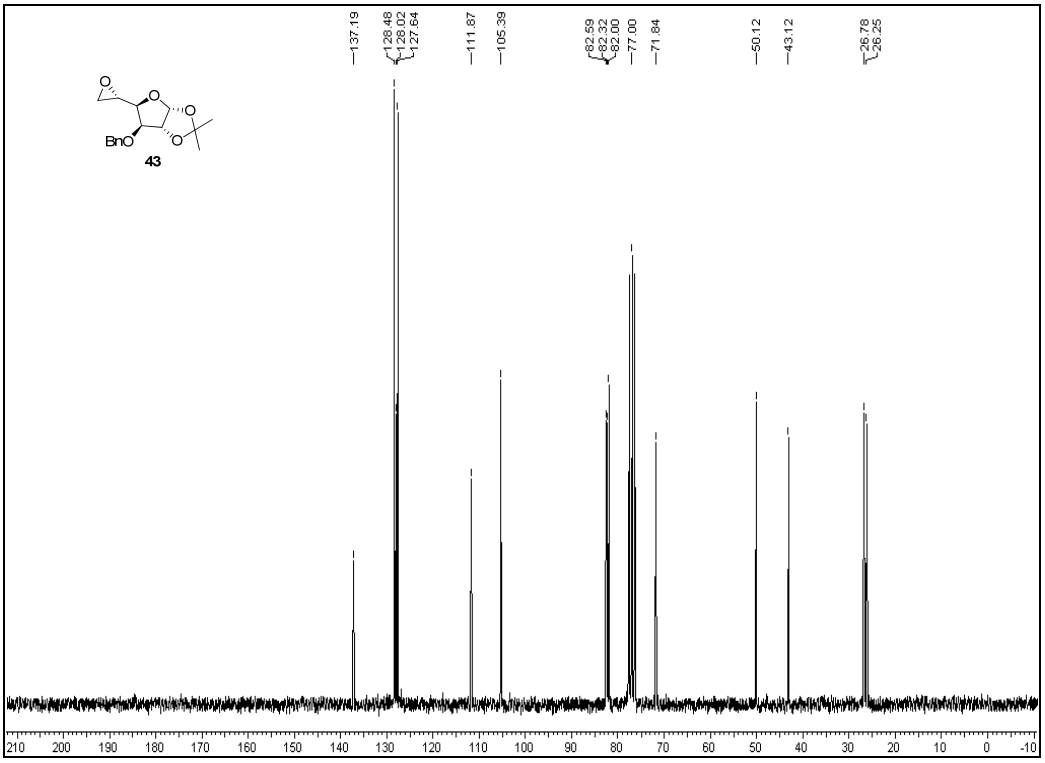
^{1}H NMR of compound 41



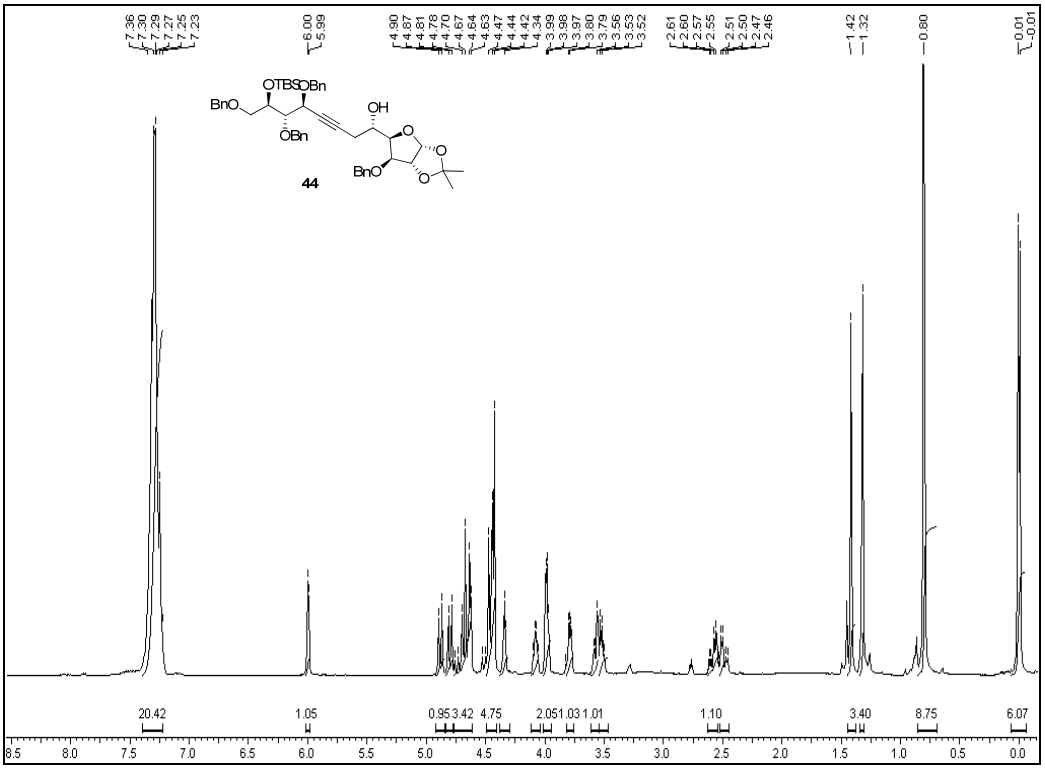
^{13}C NMR of compound 41



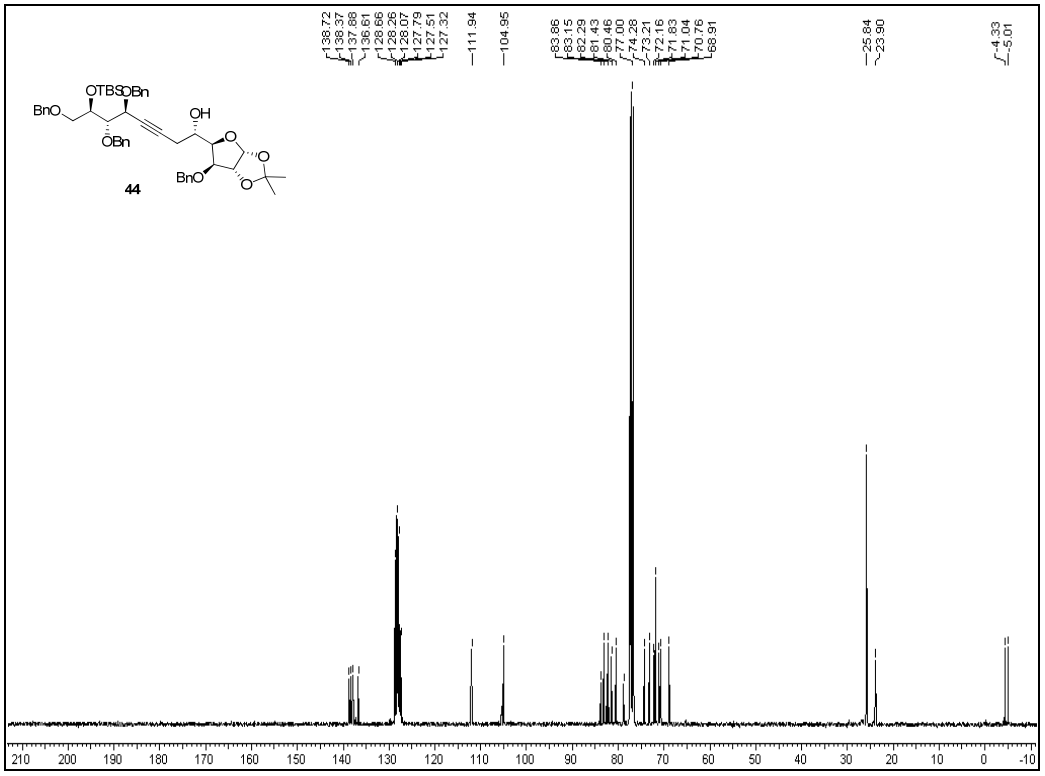
^{1}H NMR of compound 43



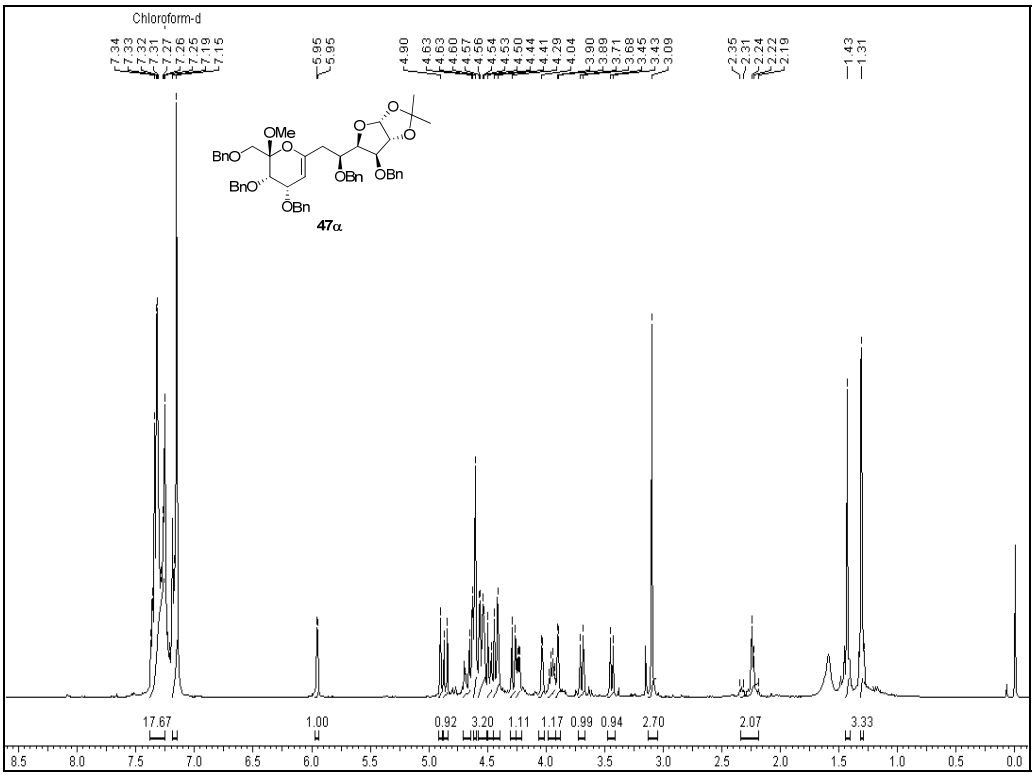
^{13}C NMR of compound 43



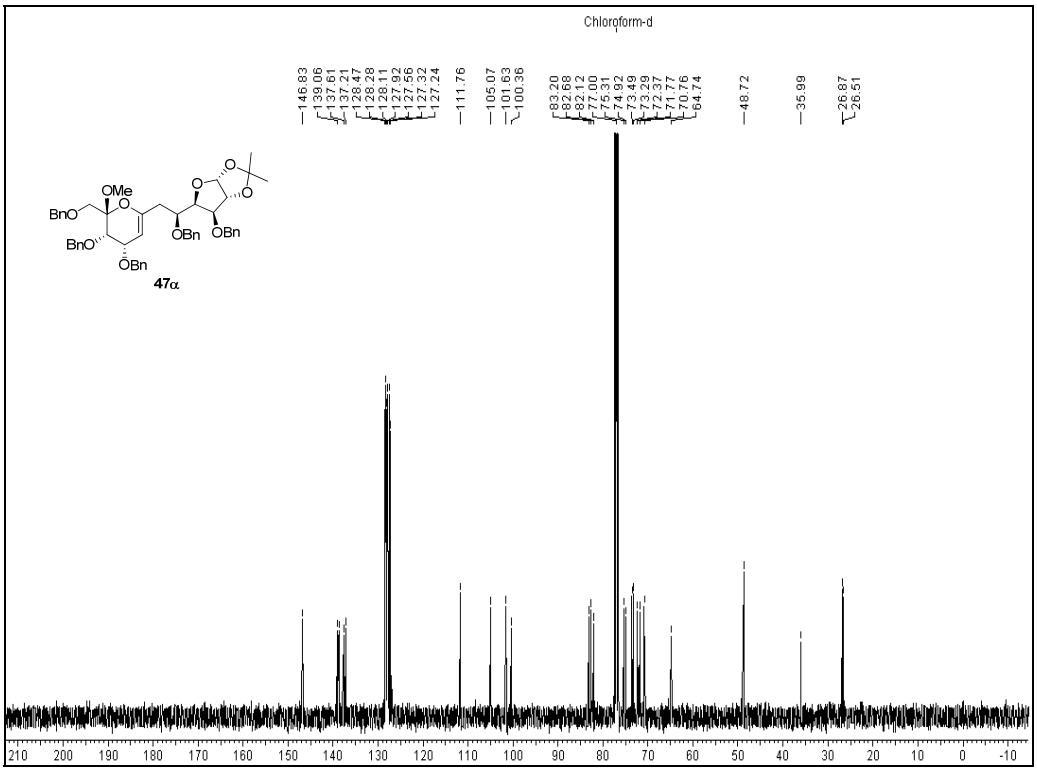
^{1}H NMR of compound 44



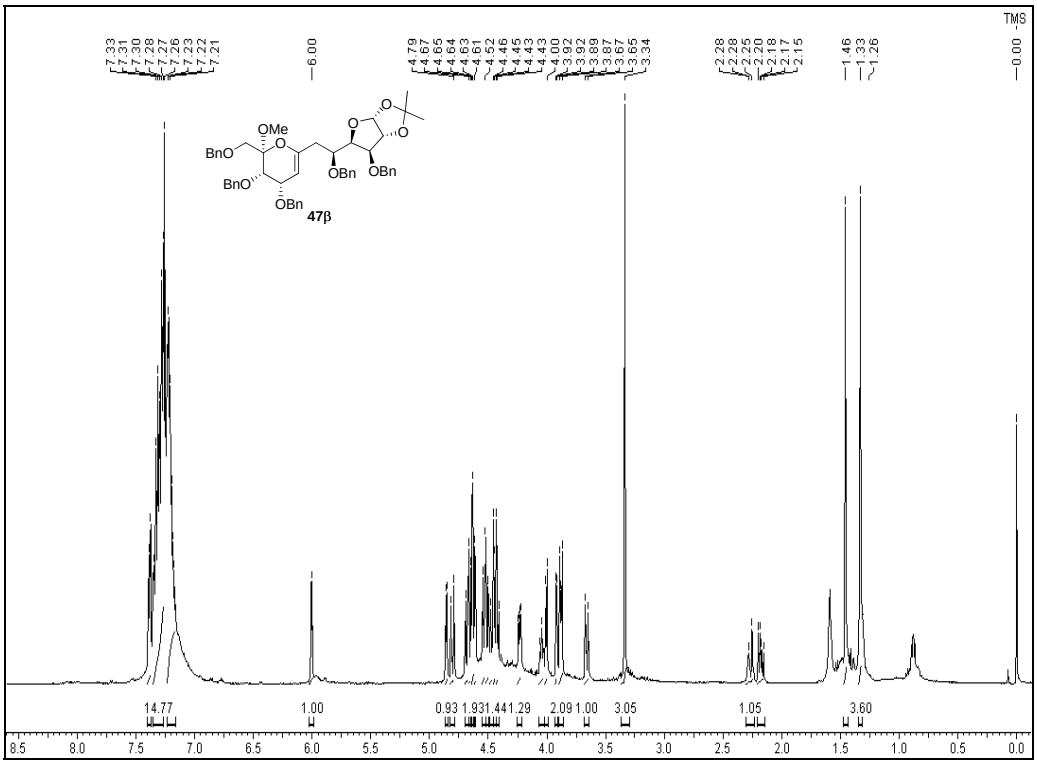
^{13}C NMR of compound 44



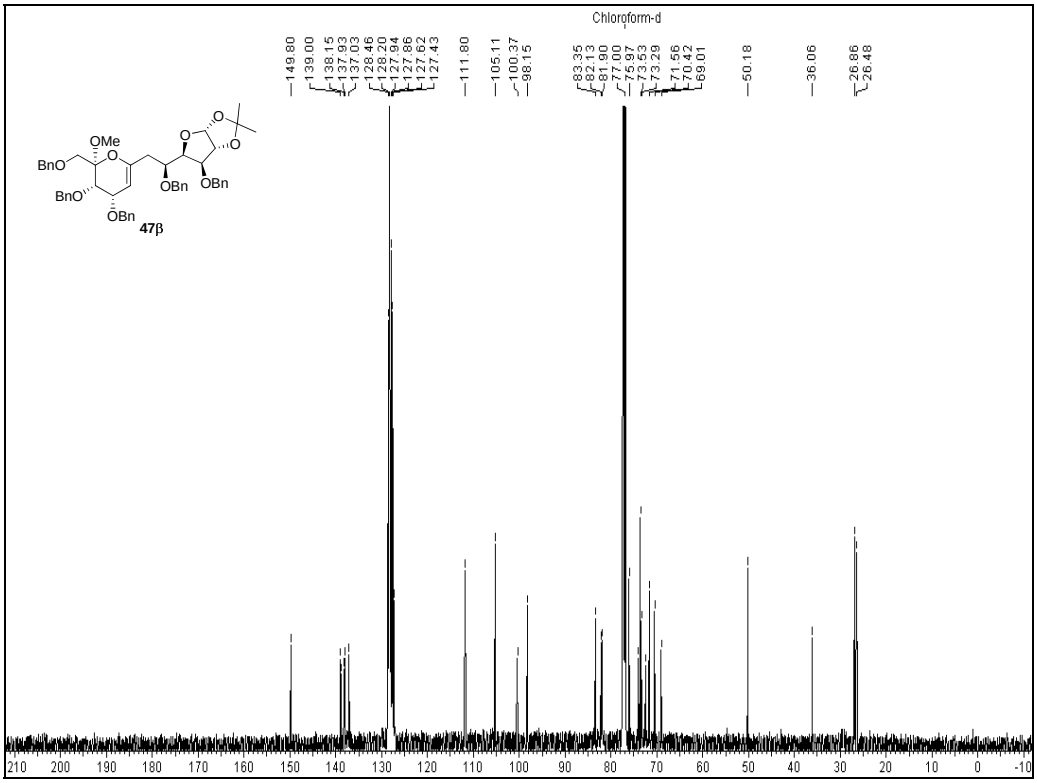
^{1}H NMR of compound 47α



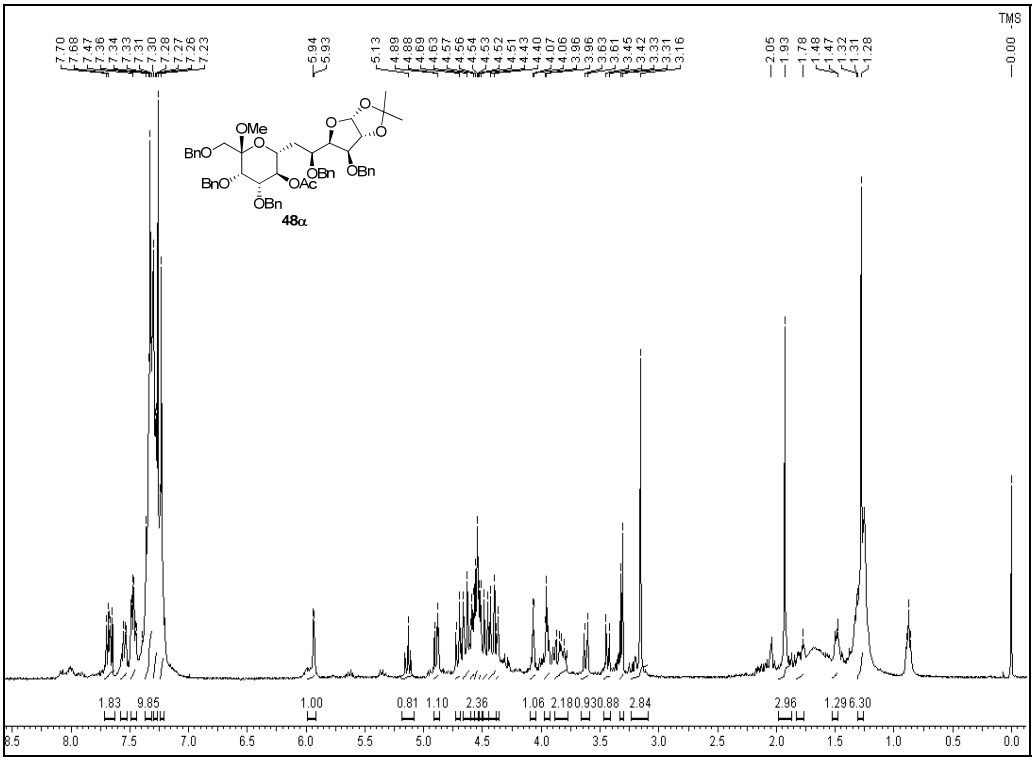
^{13}C NMR of compound 47α



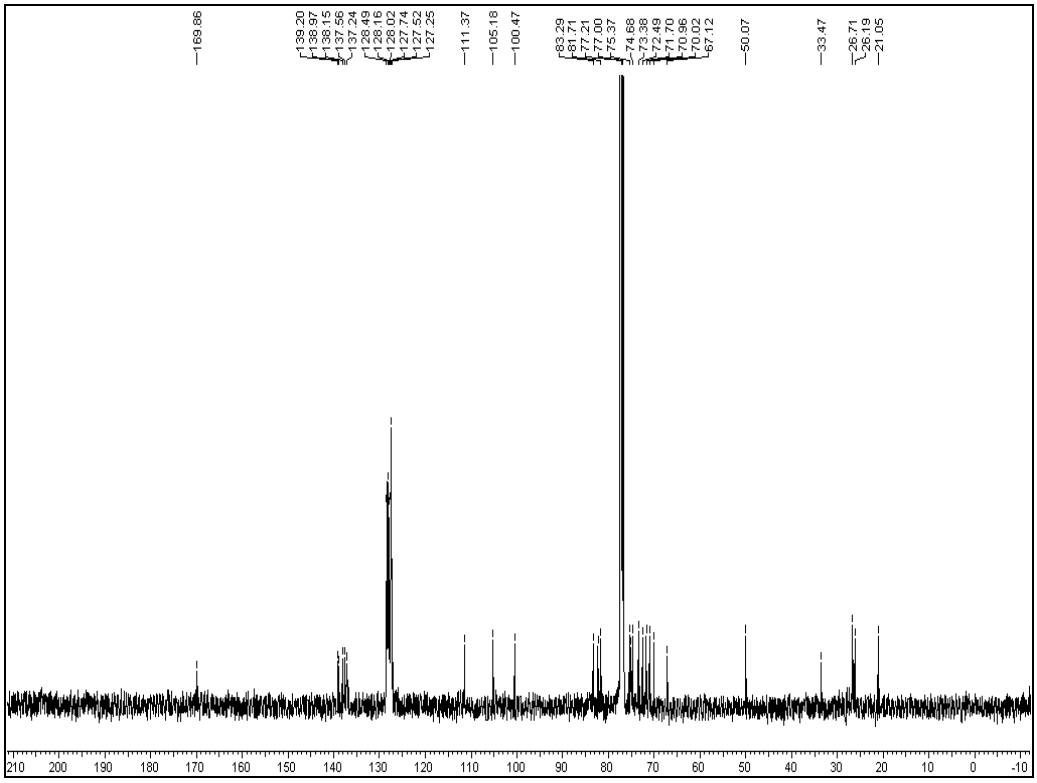
^{1}H NMR of compound 47β



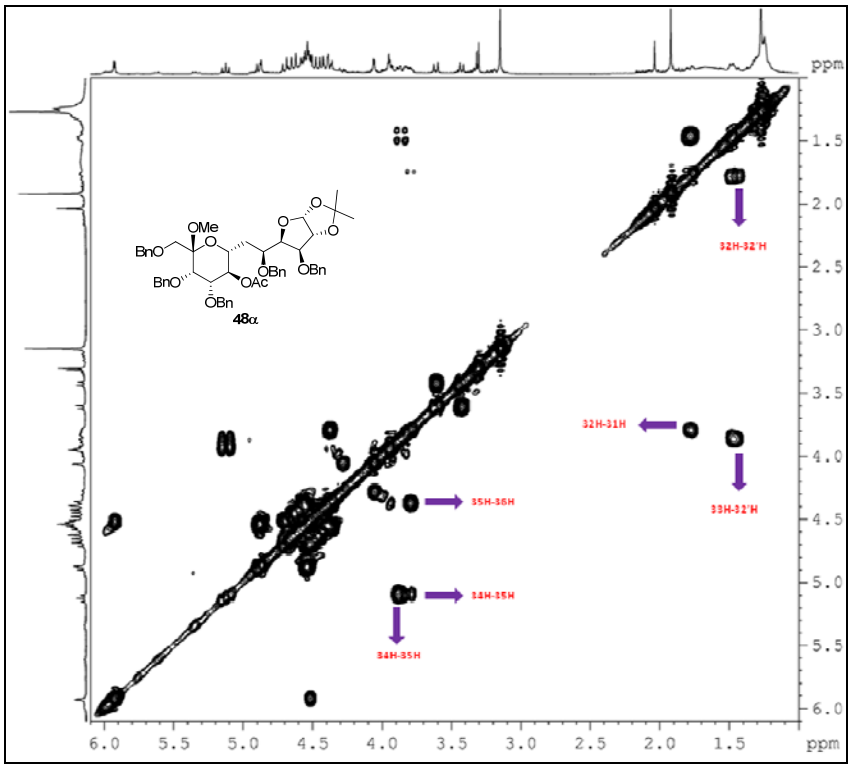
^{13}C NMR of compound 47β



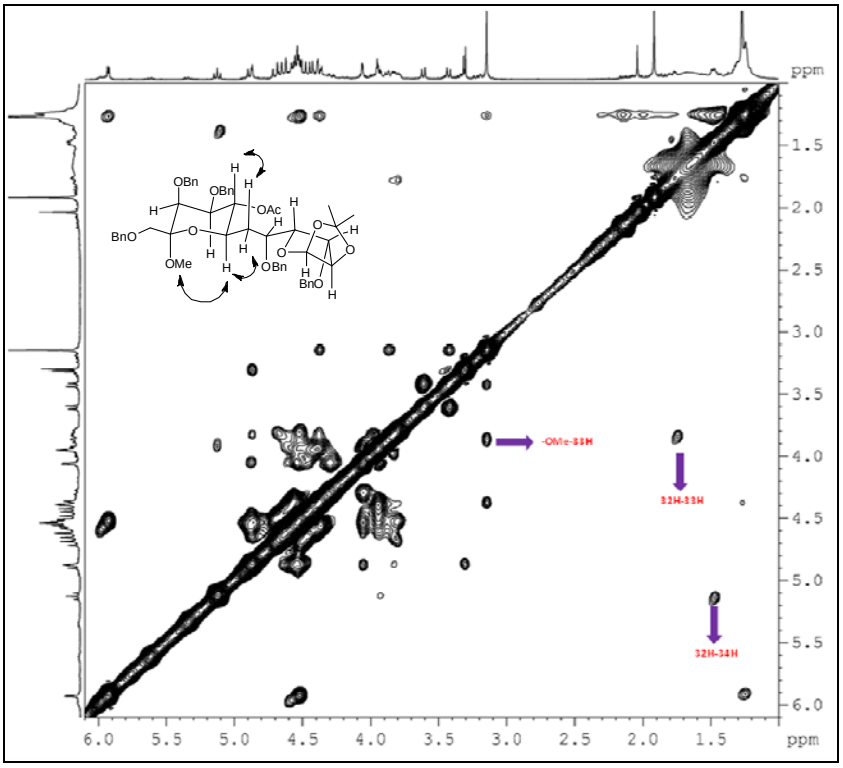
^{1}H NMR of compound 48α



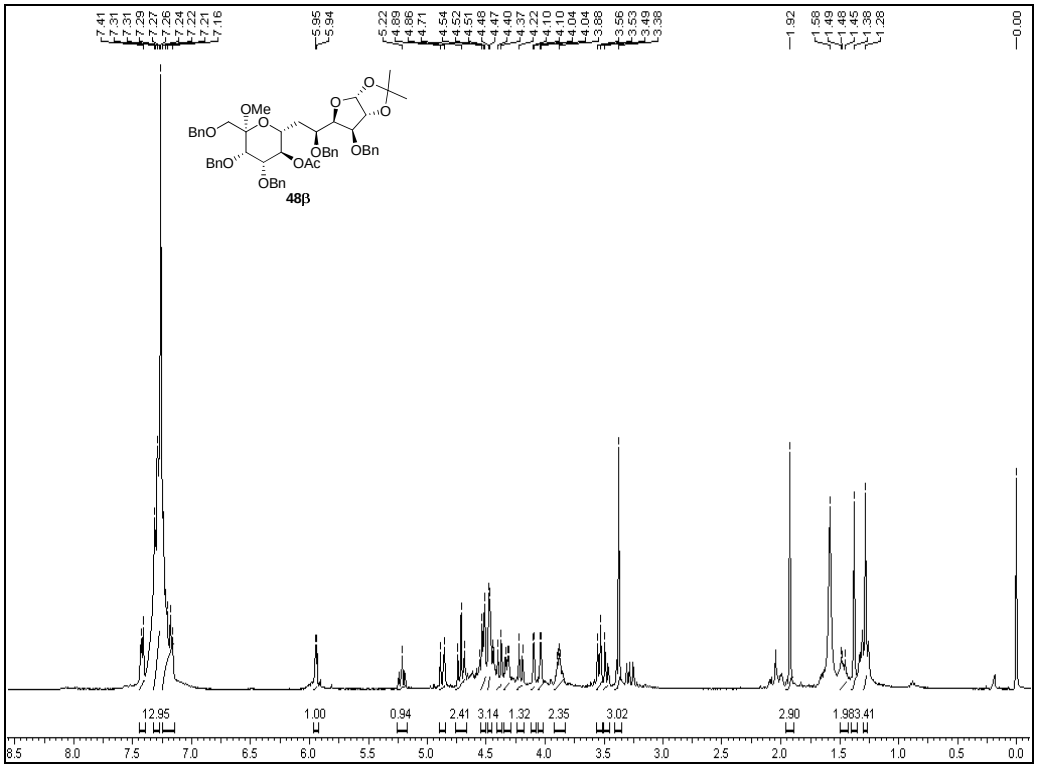
^{13}C NMR of compound 48α



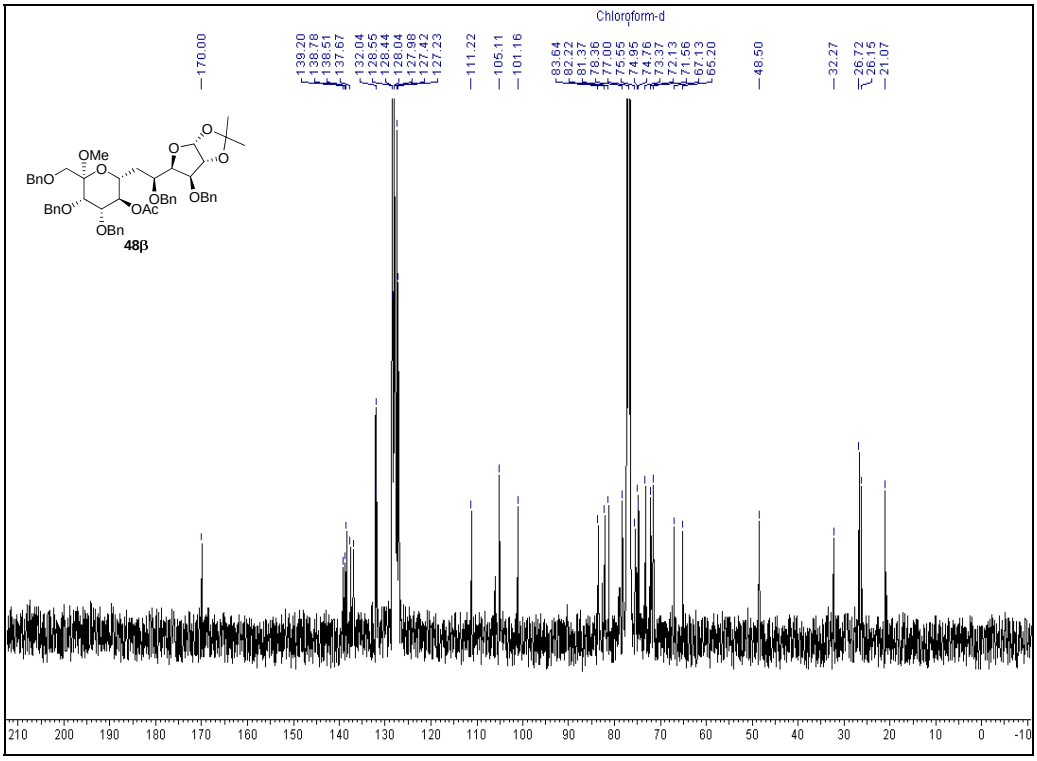
COSY of compound 48α



NOESY of compound 48α



^{1}H NMR of compound 48β



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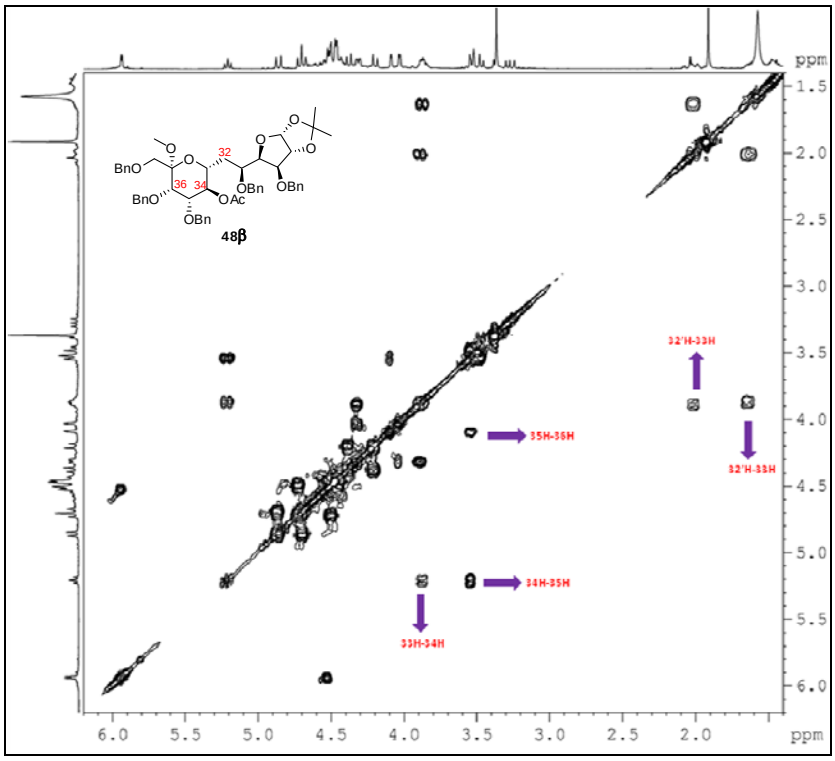

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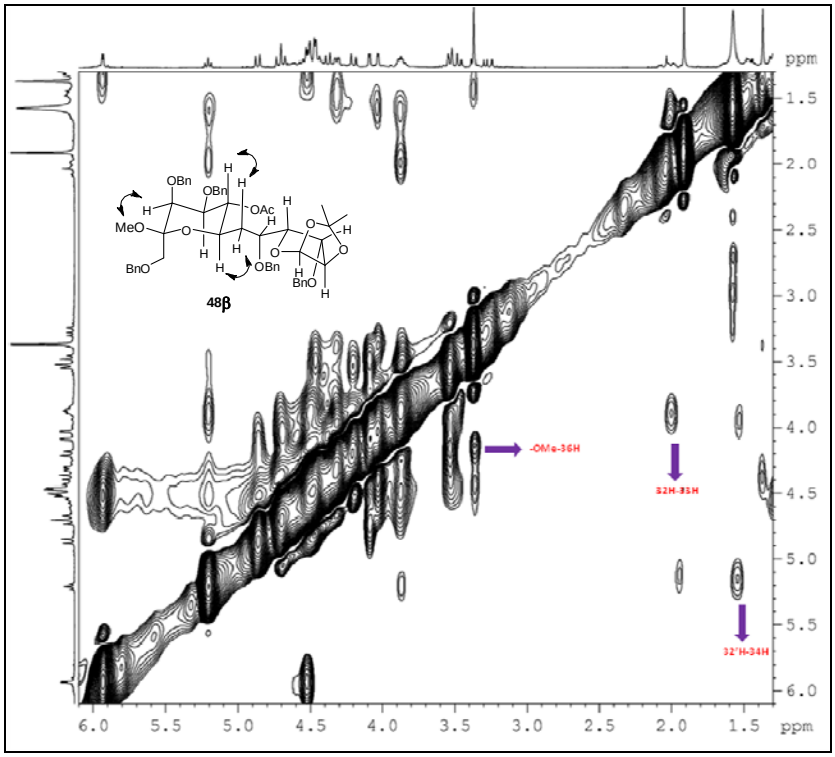

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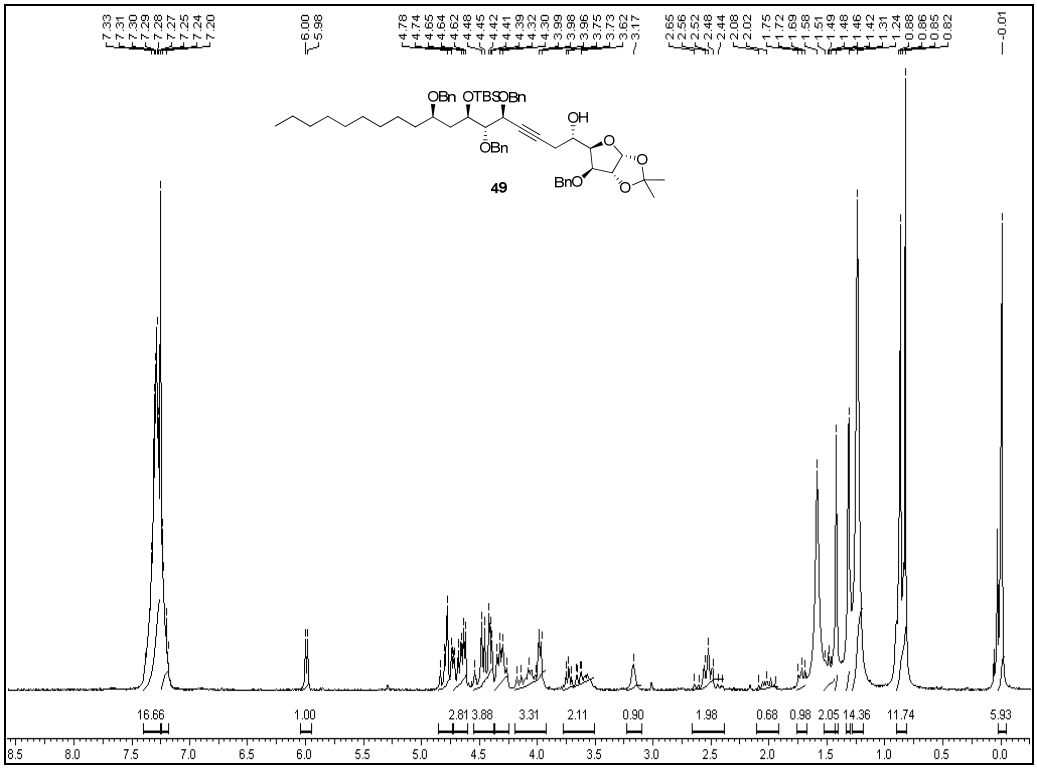

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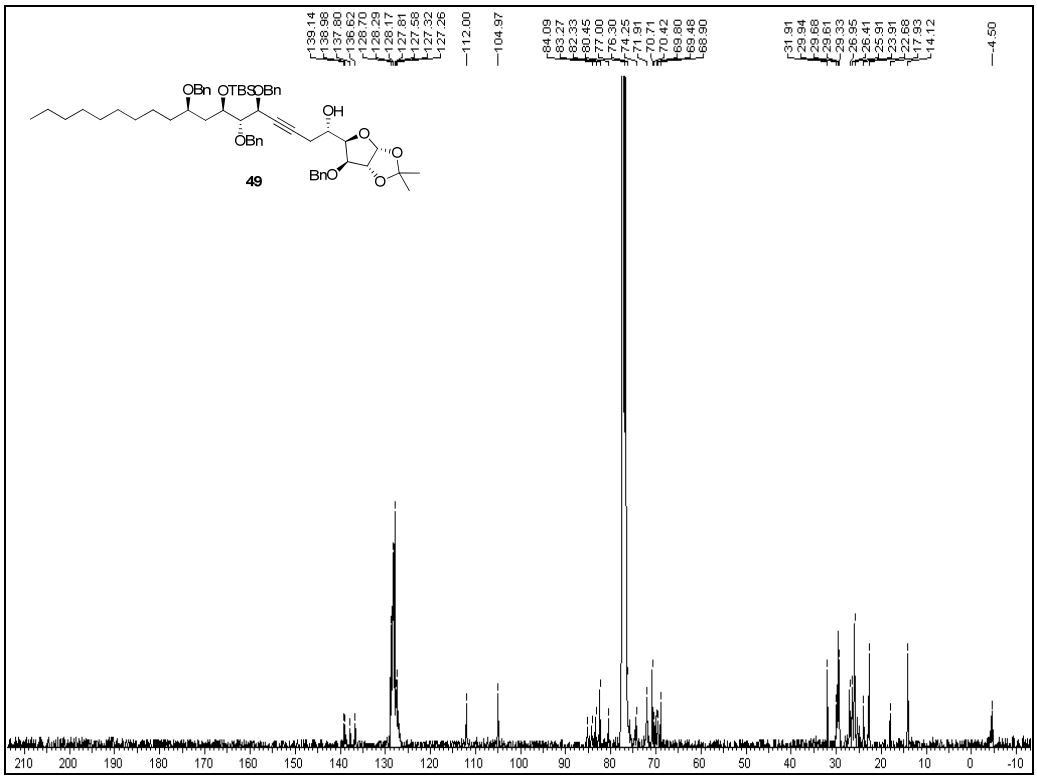

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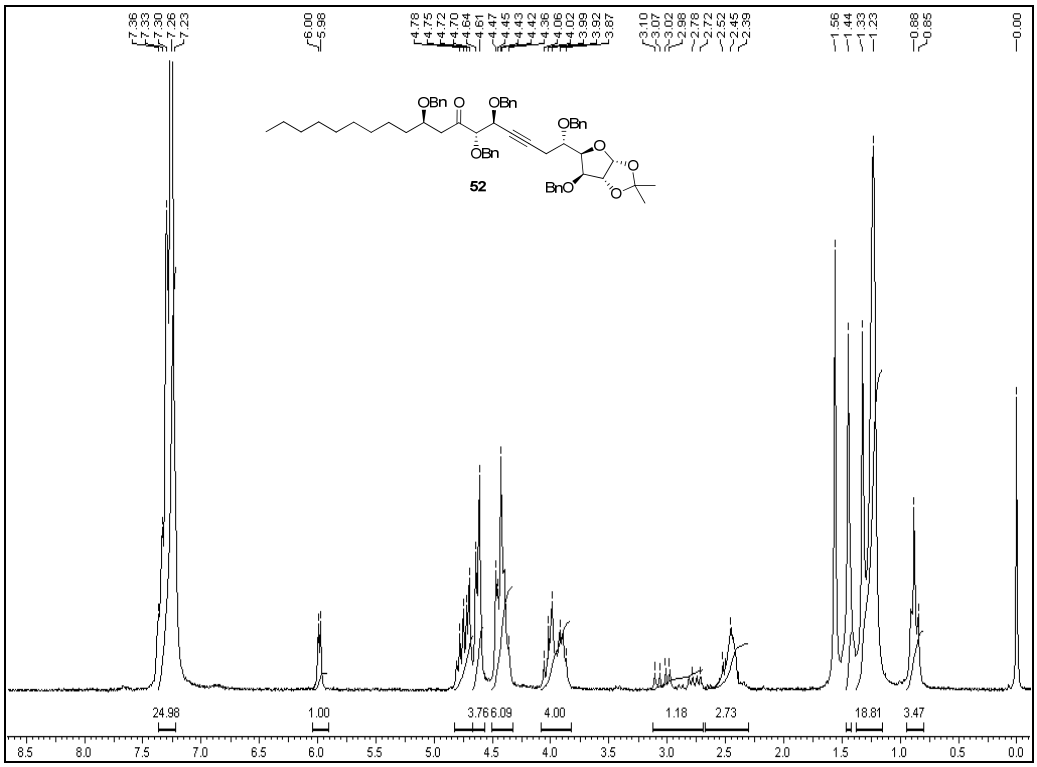

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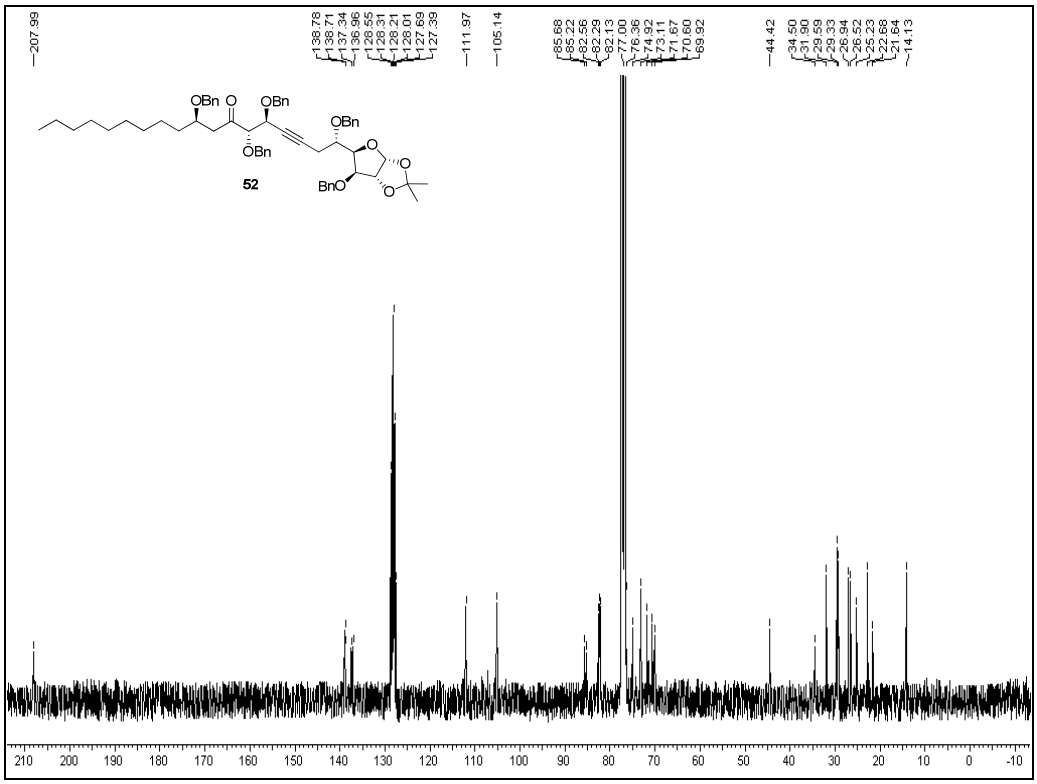

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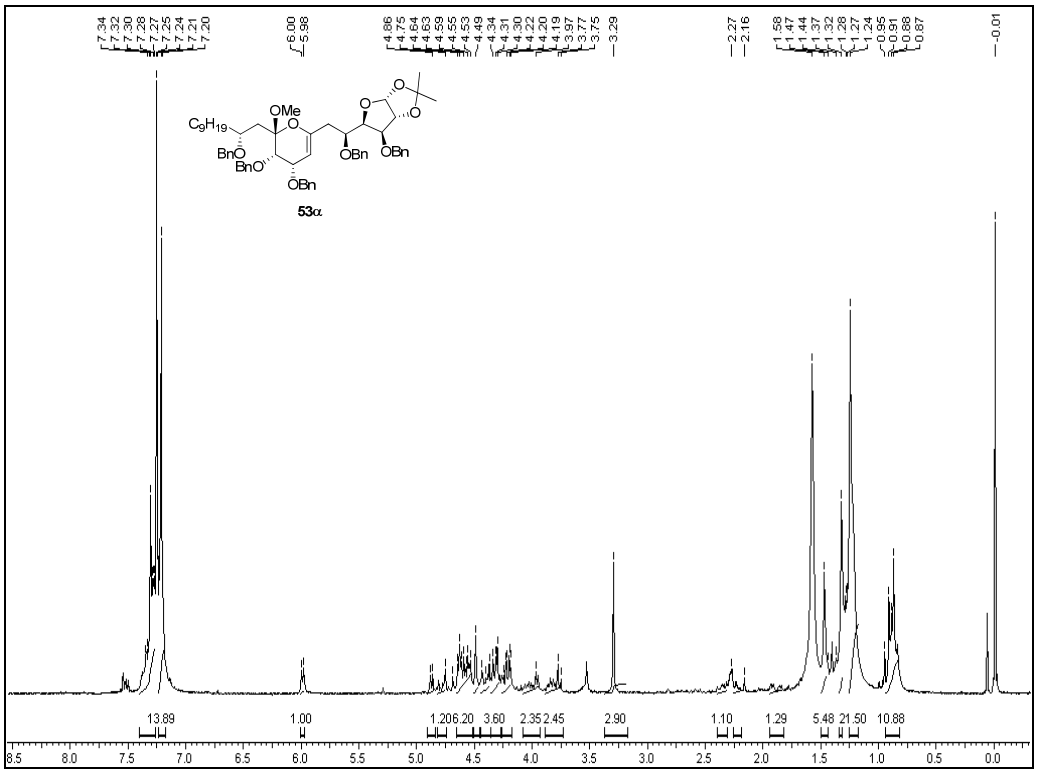

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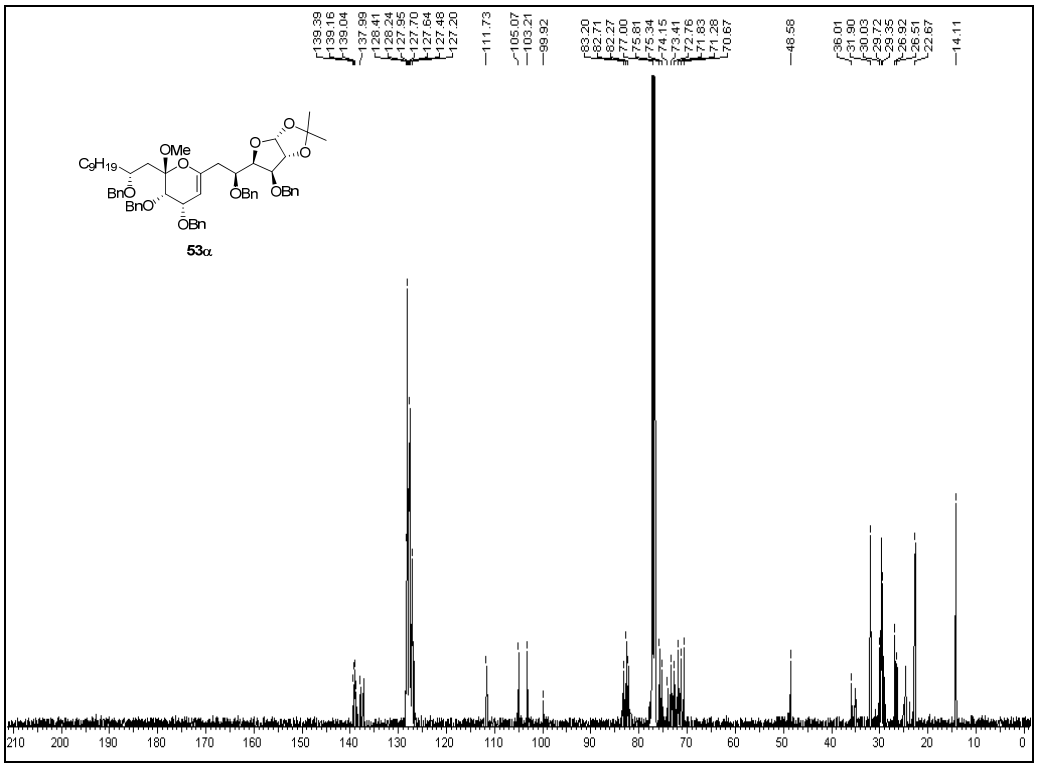

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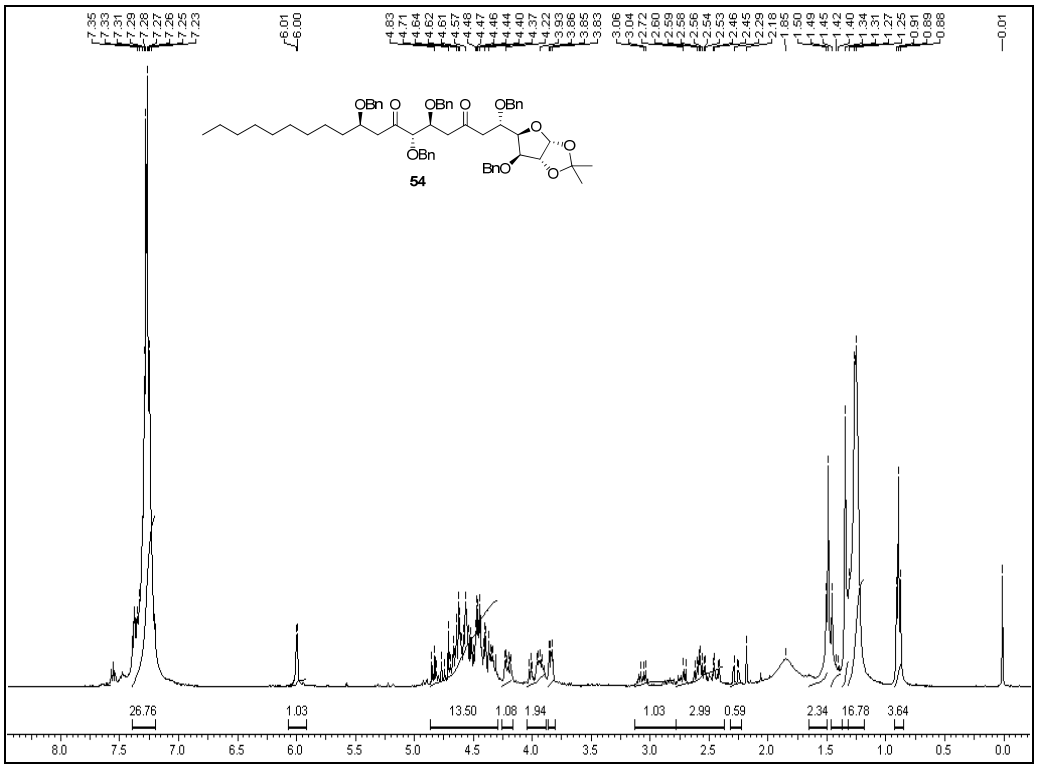

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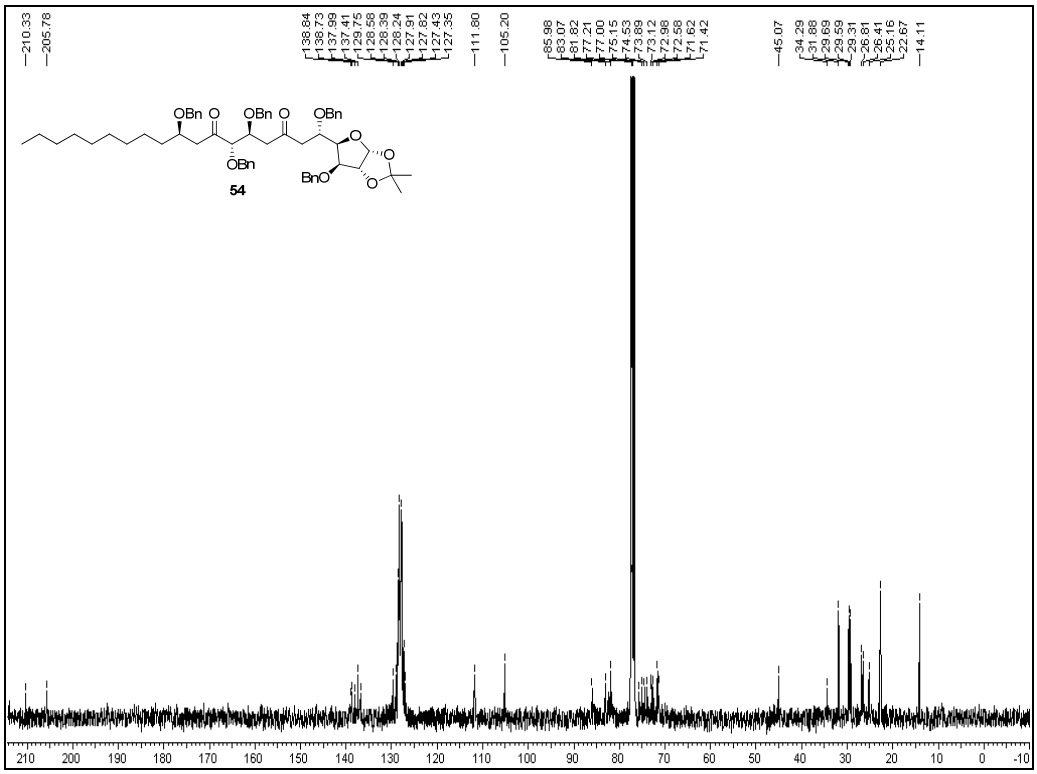


^{13}C NMR of compound 54

References

1. (a) Richard, J. L. *Int. J. Food Microbiol.* **2007**, *119*, 3–10; (b) Bennett, J. W.; Klich, M. *Clin. Microbiol. Rev.* **2003**, *16*, 497– 516.

2. (a) Atanda S. A.; Agoda S.; Isong I. U.; Adekalu O. A.; Echendu M. A. *Afr. J. Microbiol. Res.* **2011**, *5*, 4373–4382; (b) Mary, T.; Sara, H.; Garnett, W. In *International Handbook of Foodborne Pathogens*; CRC Press, **2003**.

3. (a) Massey, T. E.; Daniels, J. M.; Liu, L. *Proc. Exp. Biol. Med.* **1995**, *208*, 213–227; (b) Hudler, G. *Princeton University Press* **1998**.

4. (a) Mwanda O C; Omonge E. *East Afr Med J.* **2005**, *82*, 320–324; (b) Pereyra, M. L. G.; Carvalho, E. C. Q.; Tissera, J. L.; Keller, K. M.; Magnoli, C. E.; Rosa, C. A. R.; Dalcero, A. M.; Cavaglieri, L. R. *J. Vet. Diagn. Inv.* **2008**, *20*, 853–856; (c) Azziz, B. *Environmental Health Perspectives* **2006**, *114*, A90.

5. Gnonlonfin, G. J. B.; Adjovi, Y.; Gbaguidi, F.; Gbenou, J.; Katerere, D.; Brimer, L.; Sanni, A. *J. Food Safety* **2011**, *31*, 553–558.

6. Sakuda, S.; Ono, M.; Furihata, K.; Nakayama, J.; Suzuki, A.; Isogai, A. *J. Am. Chem. Soc.* **1996,** *118*, 7855–7856.

7. (a) Ono, M.; Sakuda, S.; Suzuki, A.; Isogai, A. *J. Antibiot.* **1997**, *50*, 111–118; (b) Sakuda, S.; Ono, M.; Ikeda, H.; Nakamura, T.; Inagaki, Y.; Kawachi, R.; Nakayama, J.; Suzuki, A.; Isogai, A.; Nagasawa, H. *J. Antibiot.* **2000**, *53*, 1265–1271; (c) Ono, M.; Sakuda, S.; Ikeda, H.; Furihata, K.; Nakayama, J.; Suzuki, A.; Isogai, A. *J. Antibiot.* **1998**, *51*, 1019–1028.

8. Ikeda, H.; Matsumori, N.; Ono, M.; Suzuki, A.; Isogai, A.; Nagasawa, H.; Sakuda, S. *J. Org. Chem.* **2000**, *65*, 438–444.

9. Evans, D. A.; Trenkle, W. C.; Zhang, J.; Burch, J. D. *Org. Lett.* **2005**, *7*, 3335–3338.

10. Higashibayashi, S.; Czechtizky, W.; Kobayashi, Y.; Kishi, Y. *J. Am. Chem. Soc.* **2003**, *125*, 14379–14393.

11. Sakuda, S.; Matsumori, N.; Furihata, K.; Nagasawa, H. *Tetrahedron Lett.* **2007**, *48*, 2527–2531.

12. Robles, O.; McDonald, F. E. *Org. Lett.* **2008**, *10*, 1811–1814.

13. (a) Ramana, C. V.; Patel, P.; Gonnade, R. G. *Tetrahedron Lett.* **2007**, *48*, 4771–4774; (b) Ramana, C. V.; Mallik, R.; Gonnade, R. G. *Tetrahedron* **2008**, *64*, 219–233; (c) Ramana, C. V.; Induvadana, B. *Tetrahedron Lett.* **2009**, *50*, 271–273; (d) Ramana, C. V.; Induvadana, B.; Srinivas, B.; Yadagiri, K.; Deshmukh, M. N.; Gonnade, R. G. *Tetrahedron* **2009**, *65*, 9819–9832; (e) Ramana, C. V.; Mallik, R.; Sahoo, G. *Tetrahedron Lett.* **2009**, *50*, 4844–4847; (f) Ramana, C. V.; Suryawanshi, S. B.; Gonnade, R. G. *J. Org. Chem.* **2009**, *74*, 2842–2845.

14. (a) Asao, N.; Nogami, T.; Takahashi, K.; Yamamoto, Y. *J. Am. Chem. Soc.* **2002**, *124*, 764–765; (b) Miyakoshi, N.; Aburano, D.; Mukai, C. *J. Org. Chem.* **2005**, *70*, 6045–6052; (c) Abbiati, G.; Canevari, V.; Caimi, S.; Rossi, E. *Tetrahedron Lett.* **2005**, *46*, 7117–7120.

15. (a) Hanessian, S.; Martin, M.; Desai, R. C. *J. Chem. Soc.-Chem. Comm.* **1986**, 926–927; (b) Friesen, R. W.; Daljeet, A. K. *Tetrahedron Lett.* **1990**, *31*, 6133–6136; (c) Steunenberg, P.; Jeanneret, V.; Zhu, Y. H.; Vogel, P. *Tetrahedron-Asymm.* **2005**, *16*, 337–346; (d) Schmidt, R. R.; Preuss, R.; Betz, R. *Tetrahedron Lett.* **1987**, *28*, 6591–6594; (e) Koester, D. C.; Leibeling, M.; Neufeld, R.; Werz, D. B. *Org. Lett.* **2010**, *12*, 3934–3937.

16. Yamaguchi, M.; Hirao, I. *Tetrahedron Lett.* **1983**, *24*, 391–394.

17. Xu, M.; Miao, Z. W.; Bernet, B.; Vasella, A. *Helv. Chim. Acta* **2005**, *88*, 2918–2937.

18. Obika, S.; Kono, H.; Yasui, Y.; Yanada, R.; Takemoto, Y. *J. Org. Chem.* **2007**, *72*, 4462–4468.

19. Koester, D. C.; Leibeling, M.; Neufeld, R.; Werz, D. B. *Org. Lett.* **2010**, *12*, 3934–3937.

20. Mitsudome, T.; Mizumoto, K.; Mizugaki, T.; Jitsukawa, K.; Kaneda, K. *Angew. Chem. Int. Ed.* **2010**, *49*, 1238–1240.

21. Ghosh, A. K.; Lei, H. *J. Org. Chem.* **2002**, *67*, 8783–8788.

22. Rychnovsky, S. D.; Rogers, B.; Yang, G. *J. Org. Chem.* **1993**, *58*, 3511–3515.

23. Shing, T. K. M.; Tsui, H. C.; Zhou, Z. H.; Mak, T. C. W. *J. Chem. Soc. Perkin Trans. 1* **1992**, 887–893.

24. (a) Gray, G. R.; Hartman, F. C.; Barker, R. *J. Org. Chem.* **1965**, *30*, 2020–2027; (b) Martin, O. R.; Yang, F.; Xie, F. *Tetrahedron Lett.* **1995**, *36*, 47–50; (c) Reddy, L. V. R.; Roy, A. D.; Roy, R.; Shaw, A. K. *Chem. Comm.* **2006**, 3444–3446; (d) Yang, B. H.; Jiang, J. Q.; Ma, K.; Wu, H. M. *Tetrahedron Lett.* **1995**, *36*, 2831–2834; (e) Cribiu, R.; Cumpstey, I. *Chem. Comm.* **2008**, 1246–1248; (f) Thota, V. N.; Gervay-Hague, J.; Kulkarni, S. S. *Org. Biomol. Chem.* **2012**, *10*, 8132–8139.

CHAPTER-II

Studies toward the synthesis of C(11)–C(21) fragment of zooxanthellamide D; Synthesis of C-disaccharides

Introduction

- **Natural products having tetrahydropyran structural outlay:**

The tetrahydropyran unit is one of the common structural unit present in a wide variety of natural products. Over the last few decades, the number of biologically active natural products isolated, which contain substituted tetrahydropyran units has increased dramatically. However, the study of their biological activity is oftentimes hampered by the lack of availability of the natural products in sufficient quantities. This is often due to the fact that the natural products are isolated from their marine or terrestrial sources in minute amounts, which means that chemical synthesis is the only way to deliver the molecule in considerable amount for their biological and other studies.

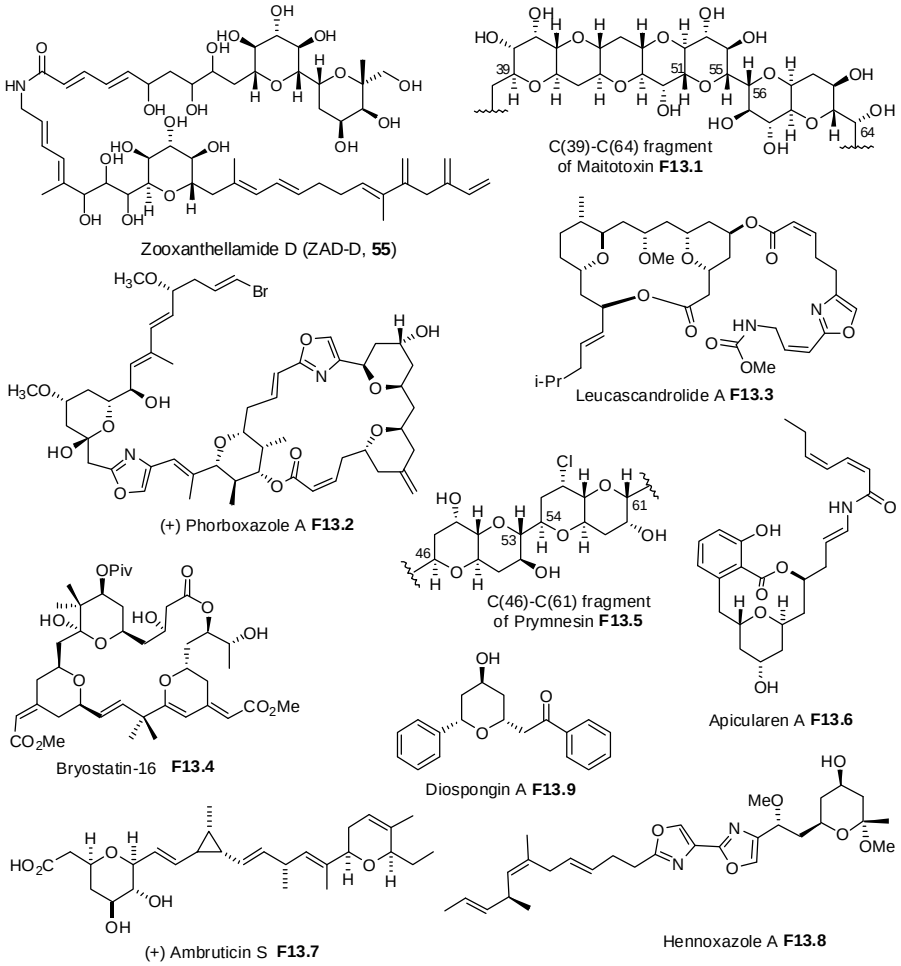


Figure 10. *Natural products having the tetrahydropyran structural subunit*

The synthesis of the tetrahydropyran-containing natural products is not a trivial exercise as the substitution patterns around the tetrahydropyran ring varies immensely, as does the position and number of tetrahydropyran rings in these natural products. This challenge has spurred the synthetic community to innovate and develop new and more selective and efficient chemical reactions to construct the tetrahydropyran rings of all types.

As a result of the discovery of these natural products (some representative natural products or their core structures **55**, **F10.1**–**F10.9** are shown in Figure 10), various new strategies for the synthesis of tetrahydropyran units have been reported in literature. For example, many conventional approaches like Maitland–Japp reaction,[1] Petasis–Ferrier rearrangement,[2] Prins reaction,[3] [4+2] cycloaddition[4] and oxy-Michael reaction[5] have been devoted towards the synthesis of this complex structural outlay. Forsyth *et al.* utilized the hetero Diels-Alder reaction for the construction of tetrahydropyran unit of phorboxazole A (**F13.2)**.[6] The titanium tetrabromide mediated Mukaiyama aldol-Prins reaction was used by Rychnovsky and co-workers to provide a stereoselective method for assembling the tetrahydropyran core of leucascandrolide A (**F13.3**).[7] A strategy comprising the ring closing metathesis followed by asymmetric dihydroxylation has been employed by Crimmins *et al*. for making the densely substituted tetrahydropyran unit of the amphidinol 3.[8] In 2004, Panek *et al.* established a [4+2] annulation as a simple tool for the tetrahydropyran part of apicularen A (**F13.6**).[4] An intramolecular addition of alcohol to aldehyde placed at suitable position[9] or addition of alcohol to epoxide are the commonly used tools for the synthesis of tetrahydropyran units.

In recent years, the use of transition metals, such as gold, palladium, tungsten, iron and platinum have obviated many of the problems associated with more conventional approaches for the synthesis of tetrahydrofuran/pyran rings. Recently, Cossy *et al.* reported eco-friendly and highly diastereoselective synthesis of substituted *cis*-2,6-tetrahydropyrans using Fe(III) catalyst.[10] Gold-mediated alkynol cycloisomerization employed by B. M. Trost during the total synthesis of bryostatin 16 (**F13.4**)[11] is one of the best example for the construction of the pyran sub-unit of complex natural products. The Au/Pd-catalyzed cyclization reactions of monoallylic

diols/triols based on 1,3 chirality transfer represents the beauty of the transition metal catalyzed synthesis of substituted tetrahydropyarns.[12] Even though, quite high number of protocols have been documented for the construction of tetrahydropyran unit, the synthesis of fully functionalized tetrahydropyran with requisite stereochemistry is still a challenge for the synthetic chemists.

The zooxanthellamide D (**55**), shown in Figure 10, is one of the complex natural products having densely functionalized bis-tetrahydropyran (*C*-glycoside) moiety as sub-structuralunit.[13] Due to our interest in the natural product inspired synthesis of *C*-glycosides using metal mediated cycloisomerization on sugar building blocks, zooxanthellamide D was identified as a suitable target for the synthetic exercise.

- **Zooxanthellamide D:**

The marine dinoflagellates of the genus *Symbiodinium* are among the most interesting microalgae that can produce novel metabolites. Since 1995, different marine metabolites such as zooxanthellatoxins (ZTs),[14] zooxanthellamides (ZADs),[15] and zooxanthellamide C's (ZAD-C's)[15c] have been isolated from the different strains of symbiotic marine dinoflagellate *Symbiodinium* sp. The zooxanthellatoxins (ZTs) are the compounds that contain a 62-membered lactone and exhibit potent vasoconstrictive activity were isolated from Y-6 strain of a symbiotic marine dinoflagellate by Nakamura and co-workers. After that, from the HA3-5 strain of *Symbiodinium*, another class of large polyols, zooxanthellamides (ZAD-A, ZAD-B and ZAD-C's) have been isolated.[15] These ZADs are distinguishable from the Zooxanthellatoxins (ZTs) by three substructures connected via amide functionalities.

In 2007, Ojika *et al.* reported the isolation of zooxanthellamide D (Figure 10) from the *Symbiodinium* strain JCUCS-1.[13] Zooxanthellamide D consists of two substructures connected via an amide group. JCUCS-1 is a *Symbiodinium* strain originally isolated by Dr. Robert Trench from the jellyfish *Cassiopeia xamachana.*[16] The cells obtained from a 140 L culture broth were extracted with 70% EtOH and this extract was defatted and extracted with BuOH. Finally, the ZAD-D in pure form was procured by polystyrene column chromatography of this BuOH extract.

After having pure and well characterized sample of zooxanthellamide D in hand, it was tested for cytotoxicity against two human carcinoma cell lines, i) A431 vulval-derived epidermoid carcinoma and ii) Nakata oral squamous cell carcinoma. The results obtained from this cytotoxicity study (IC_{50} values 4.5 and 6.6 μM, respectively) indicate that, zooxanthellamide D exhibits moderate cytotoxicity against these two human carcinoma cell lines.[17] The antifungal activity was also evaluated against the plant pathogen *Phytophthora capsici* using a paper disk assay. However, the results obtained against a phytopathogenic fungus, *Phytophthora capsici* are not encouraging.[18]

- **Stereochemical assignment:**

ZAD-D is a long-chain polyhydroxy polyene amide consisting of a C_{22}-acid part and a C_{32}-amine part and comprising of three tetrahydropyran rings as well as six isolated butadiene chromophores. The complete relative stereochemistry of ZAD-D has been not yet established and only the relative stereochemistry of the tetrahydropyran ring systems was elucidated with the help of extensive NMR studies.[13] Partial structural assignment was done with help of mass, IR, UV and extensive ^{1}H and ^{13}C NMR studies. The molecular formula ($C_{54}H_{83}NO_{19}$) was obtained by a high-resolution ESI-TOFMS measurement using the bivalent ion peak. Presence of α,β,γ,δ-unsaturated carbonyl group was determined by the UV absorption at 243 nm.

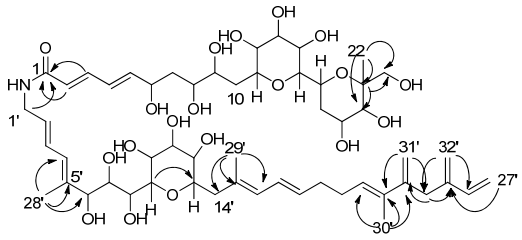


Figure 11. *HMBC correlations of zooxanthellamide D*

The conventional NMR techniques were used for the structure elucidation of the major part of ZADD. All the proton connectivities [CH(2) to CH(19), CH_2(1') to CH(4'), CH(6') to CH_2(14'), CH(16') to CH(21'), and CH(26')═CH_2(27')] were fixed with help of $^{1}H-^{1}H$ COSY spectrum. HMBC experiments (Figure 11) have been used to connect these partial structures through the quaternary carbons and

isolated methyl and methylene groups, providing two large substructures, C-2 to C-22 and C-1' to C-32'. The HMBC correlations of H-1'/C-1, H-2/C-1, and H-3/C-1 indicated that the two large substructures were connected via an amide linkage, which was further supported by the IR data. The IR bands at 1656, 1633, 1608, and 1597 cm^{-1} were consistent with the presence of an unsaturated secondary amide group. The *E* geometry of four 1,2-disubstituted olefins [C(2)−C(3), C(4)−C(5), C(2')−C(3') and C(17')−C(18')] and three trisubstituted olefins [C(4')−C(5'), C(15')−C(16') and C(21')−C(22')] were all determined on the basis of the large coupling constants (15.0−15.6 Hz) and NOE correlations.

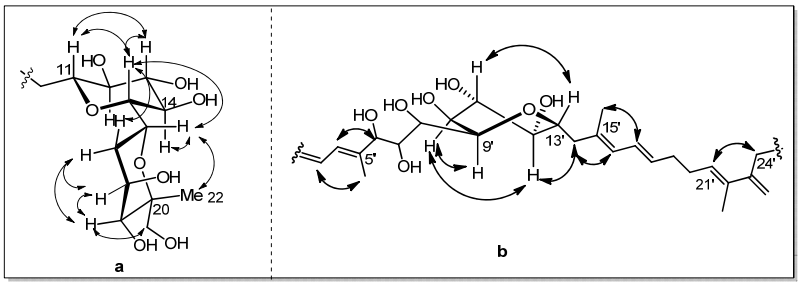


Figure 12. *nOe correlations (ROESY) of zooxanthellamide D*

The relative stereochemistry of the tetrahydropyran ring systems C(11)−C(20) was determined with help of the NOE correlations combined with the coupling constants. The NOE correlations shown in figure 3a clarified the proton orientation on these rings and, accordingly, the relative stereochemistry of C(11)−C(20). On the other hand, the protons on the third ring C(9')−C(13') showed intermediate vicinal *J* values (4.6−7.0 Hz), suggesting a twist-boat conformation for this ring. The NOE correlations around this ring system finally led to a plausible conformation with the *trans* carbon substituent (Figure 13b), revealing the relative stereochemistry of C(9')−C(13').

To the best of our knowledge, there have been no preliminary efforts directed towards the synthesis of any zooxanthellamide D have been documented. This fact taken together with our continuous interest over the alkynol cycloisomerization on sugar building blocks for synthesis of complex natural products containing oxygenated heterocycles, the zooxanthellamide D has been chosen as a target for synthetic studies.

Results and discussion

Zooxanthellamide D (**55**), a marine secondary metabolite was isolated by Ojika and co-workers from the *Symbiodinium* strain JCUCS-1.[13] It exhibits moderate cytotoxicity against two human tumor cell lines- A431 vulval-derived epidermoid carcinoma and Nakata oral squamous cell carcinoma.[17] The constitution of zooxanthellamide D was characterized by the presence of polyhydroxy polyene amide consisting of a C_{22}-acid part and a C_{32}-amine part and furnishes three tetrahydropyran rings and five isolated butadiene units. The relative stereochemistry of **55** has been partially assigned. The relative stereochemistry of all the three pyran rings has been assigned with the help of extensive NMR studies. Two of the pyran rings are directly connected head to head at the α-carbon to the oxygen of pyran ring - trivially called perhydro 2,2'-bipyran. Due to our continuing interest in alkynol cycloisomerization on sugar building blocks and the synthesis of natural products or their core structural outlay containing oxygenated heterocycles[19] and considering the fact that there is no report on the synthesis of zooxanthellamide D, this natural product has attracted our attention. In light of our ongoing research project on the development of new methods for the synthesis of *C*-glycosides[20] and *C*-disaccharides, we were particularly interested on the disaccharide part, the C(11)–C(21) fragment of the molecule and its construction using the alkynol cycloisomerization as the key transformation.

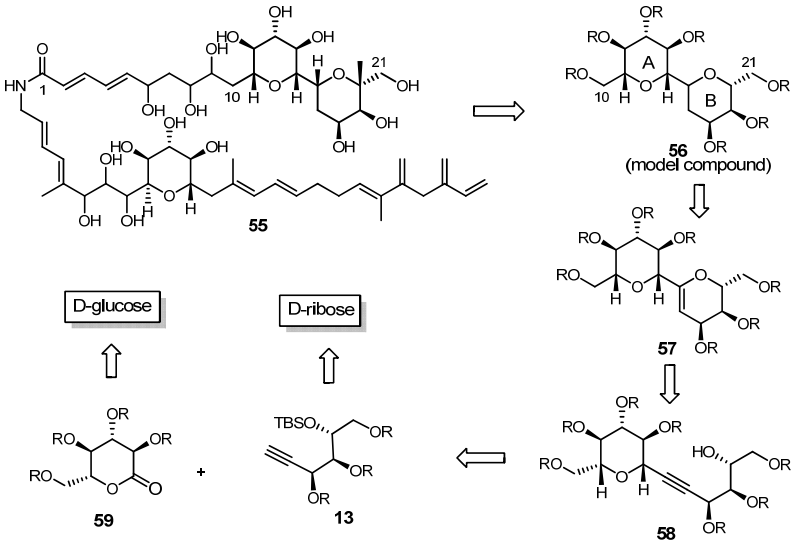


Figure 13. *Retrosynthetic disconnections for the model compound* ***56***

Due to the presence of the complex structural outlay in the chosen fragment of molecule **55**, a model study has been planned in order to check the viability of key transformations, which we would like to utilize for the construction of a tetrahydropyran ring with readily available substrates. Thus, our journey in this direction has been started from the synthesis of the C(11)−C(21) fragment of zooxanthellamide D. Figure 13 reveals the retrosynthetic disconnections for the designed model compound. The major issue in the synthesis of the model compound **56** was the construction of the bipyran ring system with the requisite stereochemistry. Both the pyran rings present a 2,6-*trans* configuration which is an interesting and important aspect. In order to address this concern, we thought of using Kishi's[21] cyclic ketal deoxygenation at two-stages that address the key *C*-glycoside synthesis inter alia the bipyran ring synthesis. The addition of a suitable alkyne to a D-gluconolactone and subsequent ketal deoxygenation was the first key event.[21] The intramolecular metal-mediated alkynol cycloisomerization[22] and the subsequent reduction of the resulting *C*-glycals or their hydrolyzed products were opted for as the next event in order to address the next key C–O bond forming reaction.

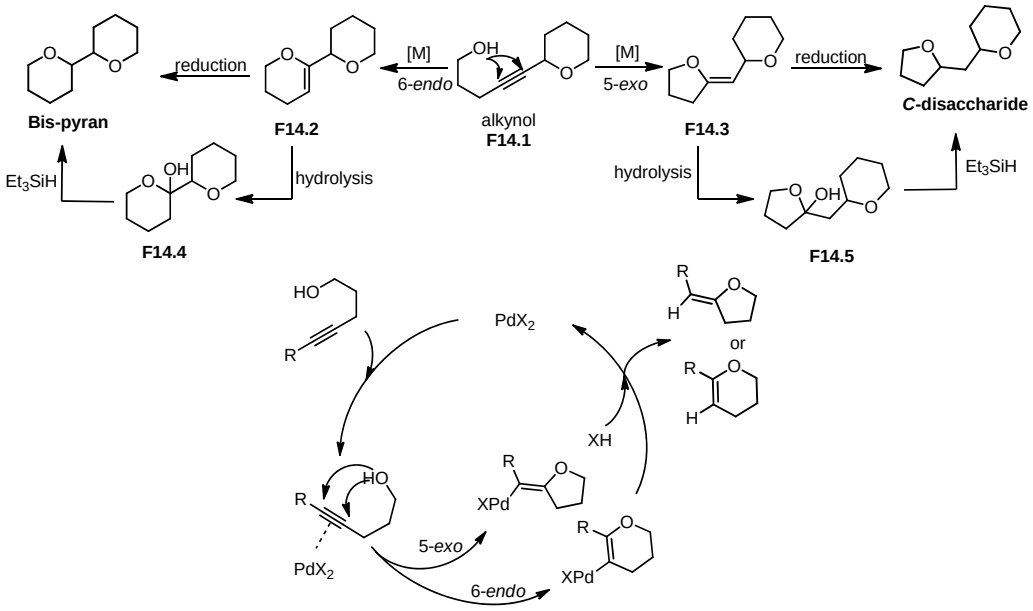


Figure 14. *Proposed mechanistic modes of cyclization for alkynol cycloisomerization*

However, one of key concerns in this strategy is the mode of cycloisomerization. There exist two possibilities according to Baldwin's rules: the 5-

exo-dig and the 6-*endo*-dig mode of cyclization.[23] Our earlier investigations have revealed that when the substituent on the other side of the alkyne (with respect to the incoming nucleophile) is a furan ring, in general, the 5-*exo*-dig mode of cyclization would be favored over the 6-*endo*-dig mode of cyclization.[19b, 19f] However, at the same time, if the incoming nucleophile is part of a densely oxygenated unit, the 6-*endo*-dig mode of cyclization is favored.[19a,19c,19e] Thus, the present system has a subtle electronic bias that determines the regioselectivity. As shown in Figure 14, if the cyclization occurs via a 6-*endo*-dig mode of addition, then the desired endocyclic enolether **F14.2** would be the expected product. On the other hand, if 5-*exo*-dig cyclization is favored, then it would lead to the formation of the exocyclic enolether **F14.3**, then hydrolysis followed by triethylsilane reduction, which would provide the carba-disaccharide skeleton of non-reducing sugars. It is quite important to highlight here that in either case, the present approach provides an important strategy for the synthesis of *C*-disaccharides which are rarely made.

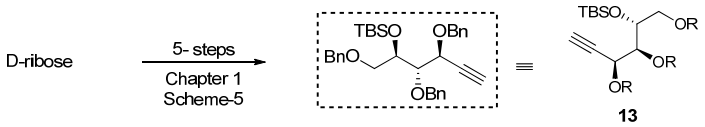
Therefore, it was finally decided that the alkynol cycloisomerization would be proceeded with by employing the simple substrate **58**. After careful examination of alkynol part **58**, the stereochemistry at C(2), C(3), C(4) and C(5) of D-glucose matches with that of C(11), C(12), C(13) and C(14) of the ring A and the stereocentre at the anomeric position [C(15)] can be generated during C−C bond formation using triethylsilane reduction of hemiketal resulting from the addition of alkyne to lactone (Figure 13). As far as ring B is concerned, the stereochemistry of C(18), C(19) and C(20) matches with that of C(2), C(3) and C(4) of D-ribose. So, the addition of the alkyne derived from D-ribose to the lactone derived from D-glucose followed by triethylsilane/$BF_3.Et_2O$ mediated reduction could be a proper choice for the synthesis of the key alkynol intermediate **58**.

1. Model study for synthesis of C(11)–C(21) fragment of zooxanthellamide D:

- **Synthesis of alkyne 13:**

As a first step towards the synthesis of the C(11)–(21) fragment of zooxanthellamide D, the journey was began with the designing of the synthetic strategy for the model study. We have already set the protocol for the synthesis of the

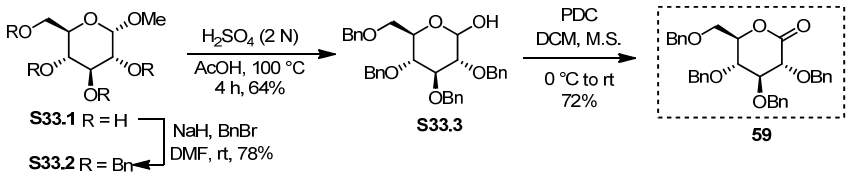
required alkyne fragment **13** from D-ribose in five steps (Scheme 5, Chapter I) during the model study of aflastatin A.



Scheme 32. *Synthesis of the alkyne fragment **13***

- **Synthesis of lactone 59:**

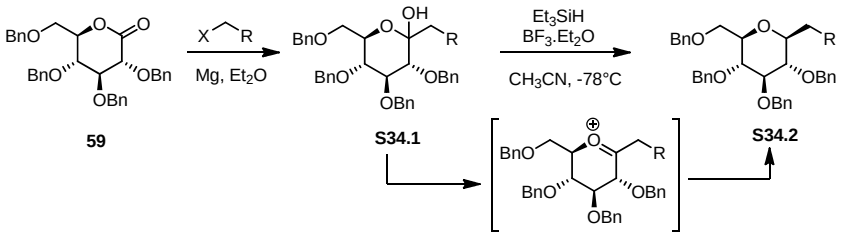
The synthesis of the known lactone **59** was commenced with the benzyl protection of the commercially available α-methyl-D-glucopyranoside using sodium hydride and benzyl bromide in DMF at room temperature to afford the compound **S33.1** in 78% yield. This benzyl ether **S33.1** was then subjected for the anomeric –OMe hydrolysis using previously standardized conditions (HCl, *t*-BuOH:H_2O/8:2, reflux, 6h) discussed in chapter 1 (Scheme 5). Under these conditions, the conversion was very poor - resulting in the isolation of 8% of the expected product along with the recovery of 72% of the starting material. The increase in reaction time also failed to improve the yield of the product. As anomeric hydrolysis of the methyl glucopyranoside **S33.2** under these conditions seems to be difficult, various conditions were tried in order to achieve the desired conversion. Among all the conditions that we tried, heating the methyl glucopyranosideside **S33.2** using 2N H_2SO_4 (aq.) in acetic acid for 4 h was found to be suitable. The yield of this reaction was also higher (64%) as compared to other conditions that suffer from either lower yield or the decomposition of the starting material. The lactol **S33.3** obtained in this way was subjected for the pyridinium dichromate (PDC) oxidation in DCM at room temperature in order to procure the lactone **59** with 72% yield (Scheme 33).



Scheme 33. *Synthesis of the lactone fragment **59***

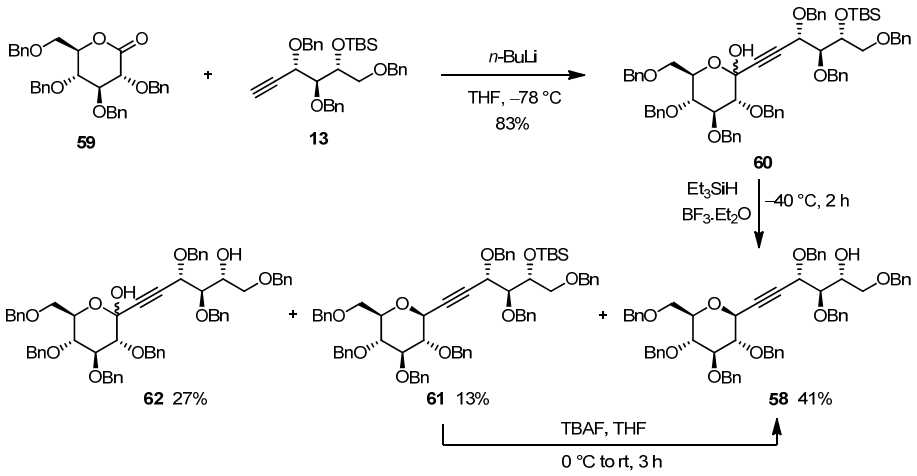
- **Synthesis of alkynol 58:**

Having both the fragments (alkyne **13** and lactone **59**) in hand, the next eventual target was to proceed further for the synthesis of the alkynol substrate **58**. In 1982, in the context of total synthesis of palytoxin, Kishi *et al.*[21] developed a simple strategy for the synthesis of β-*C*-glycosides. This approach involves the addition of a C-nucleophile to a glycolactone followed by the reduction of the intermediate hemiketal with triethylsilane in the presence of a Lewis acid such as borontrifluoride etherate. For example, the 2,3,4,6-tetrabenzyl glucopyranolactone **59** was treated with an alkynyl lithium to get the corresponding hemiketal, which was then reduced with triethylsilane and $BF_3.Et_2O$ in acetonitrile at –10 °C to furnish the ethynyl β-*C*-glycoside **S34.2** with overall good yields. The reaction goes via hemiketal **S34.1** followed formation of oxonium ion which should preferentially accept the nucleophile (hydride) from the α (axial) side due to the anomeric effect from the ring oxygen (Scheme 34).



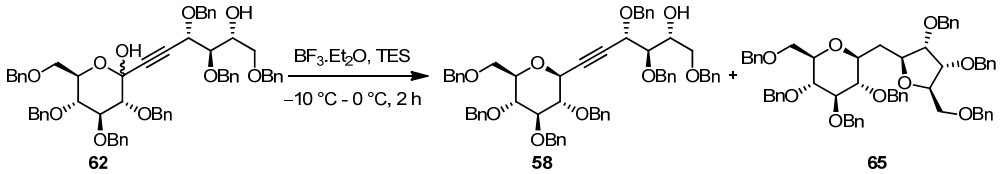
Scheme 34. *Synthesis of β-C-glycosides via nucleophilic addition followed by TES reduction*

With this information in mind, the addition of the lithiated alkyne to lactone using *n*-BuLi as base in THF at −78 °C was carried out to deliver the hemiketal **60** in 83% yield (Scheme 35). The structure of hemiketal was confirmed with the help of mass spectroscopy. ^{1}H NMR did not provide much information except the absence of a characteristic doublet of terminal acetylenic proton of alkyne **13** at 2.42 ppm. As it was a mixture of α and β anomers, the pattern of ^{1}H and ^{13}C NMR spectrum was very complex, which showed signals more than expected. The hemiketal **60** was subjected for the deoxygenation using triethylsilane and $BF_3.Et_2O$ in CH_3CN:DCM at −40 °C to deliver the expected alkynol **58** (41% yield) along with the deoxy compound **61** (13% yield) and only TBS deprotected compound **62** (27% yield).



Scheme 35. *Synthesis of key alkynol intermediate **58***

The structure of alkynol **58** was confirmed with help of ^{1}H, ^{13}C NMR and HRMS analysis. The TBS ether in compound **61** was deprotected by treatment of TBAF in THF at room temperature. The spectral data of the resulting TBS deprotected compound was found to be match well with that of alkynol **58**.



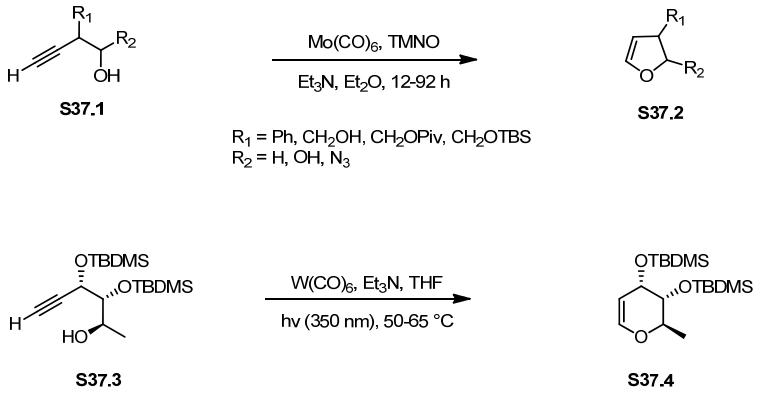
Scheme 36. *TES and $BF_3.Et_2O$ mediated reduction cum cyclization of diol **62***

Quite surprisingly, when the diol **61** was subjected for reduction (Scheme 36), it gave the required alkynol **58** (46% yield) along with another product **65** (18% yield). For this reaction, we have employed excess amount of triethylsilane (15 eq) and $BF_3{\cdot}Et_2O$ (10 eq) at a slightly elevated temperature (−10 °C to 0 °C), which might be a result of Lewis acid ($BF_3{\cdot}Et_2O$) mediated alkynol cycloisomerization followed by in situ triethylsilane reduction. The data obtained for this alkynol was compared with the previously prepared alkynol **58** in order to confirm the structure. The analytical data of the cyclized product was compared with the compound **65** prepared by using Pd-mediated alkynol cycloisomerization and triethylsilane reduction at the later stage (Scheme 39).

- **Some selected reports for alkynol cycloisomerization:**

After having the alkynol intermediate **58** in hand, the next goal was the construction of ring B which was intended for utilizing the metal mediated cycloisomerization. In literature, several reports are available for such cycloisomerization reactions. Despite the different studies carried out on the nucleophilic addition of alcohols to alkynes in super-basic catalytic systems, namely, alkali-metal hydroxides, transition-metal compounds are still the catalysts of choice to carry out the cycloisomerization of alkynols due to their effectiveness and wide scope of application.

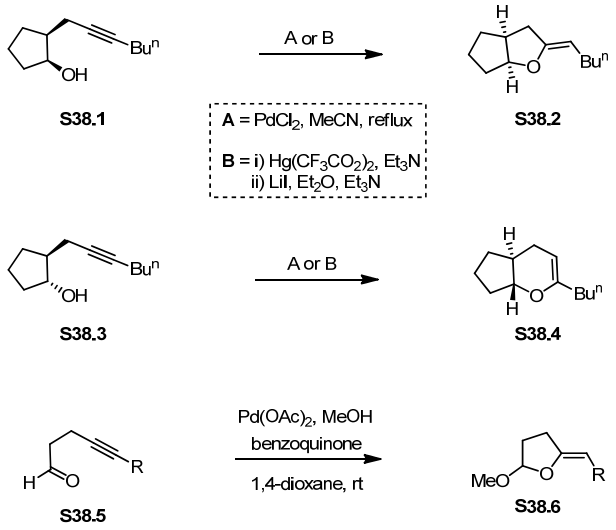
Metal vinylidene intermediates derived from terminal alkynes and metals such as chromium, molybdenum, tungsten, platinum, gold and ruthenium have also found application in these reactions. The cycloisomerization of alkynyl alcohols to endocyclic enol ethers through metal vinylidenes was first introduced by McDonald. In one of the first accounts, McDonald et al. reported a new synthesis of 2,3-dihydrofurans **S37.2** based on the cycloisomerization of 3-alkyn-1-ols **S37.1** with molybdenum hexacarbonyl and trimethylamine *N*-oxide (TMNO) (Scheme 37).[24a]



Scheme 37. *Molybdenum (Mo) and Tungesten (W) catalyzed alkynol cycloisomerization*

To extend the alkynol cycloisomerization methodology for the synthesis of the homologous 3,4-dihydro-2*H*-pyrans, tungsten hexacarbonyl was used as an efficient catalyst. McDonald *et al.* reported the alkynol cycloisomerization of 1-alkyn-5-ols **S37.3** with catalytic amounts of $W(CO)_6$ under 350 nm photolysis at or near THF

reflux in the presence of triethylamine to achieve the synthesis of dihydropyran **S37.4** (Scheme 37).[12b]



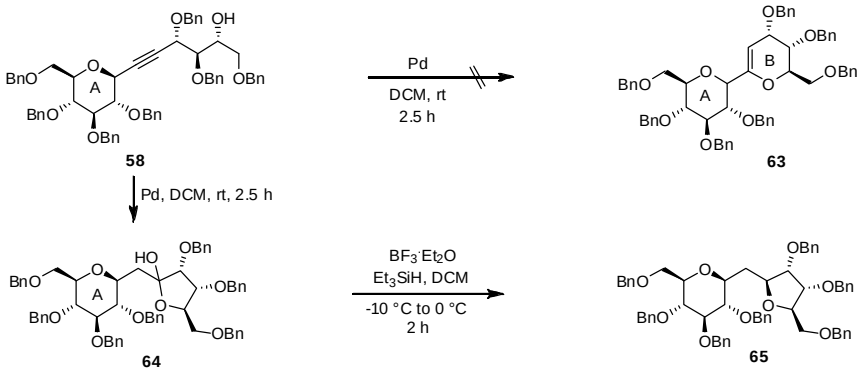
Scheme 38. *Palladium (Pd) catalyzed alkynol cycloisomerization*

Palladium catalysts are the most used catalysts for the activation of alkyne in alkynol cycloisomerization. Extensive work done by Utimoto *et al.* on the palladium-catalyzed synthesis of heterocycles also covers the application of $PdCl_2$ on diverse substrates, to furnish the corresponding oxygen-containing heterocycles.[25] Bicyclic 2,3-dihydrofuran **S38.2** and 3,4-dihydro-2*H*-pyran **S38.4** were prepared from the corresponding alkynols **S38.1** and **S38.3** (Scheme 38). The size of the ring in the product depends on the relative stereochemistry in the starting alkynol. Riediker and Schwartz also reported the conversion of alkynol **S38.1** and **S38.3** into fused bicyclic 2,3-dihydrofuran **S38.2** and 3,4-dihydro-2*H*-pyran **S38.4** respectively by using catalytic Hg(II) salts (mercury triflate).[26] Different cyclic alkenyl ethers were recently synthesized by Yamamoto *et al.* by reacting alkynyl aldehydes **S38.5** with methanol under Pd(II) catalysis.[27]

- **Attempts for construction of ring B and formation of compound 63:**

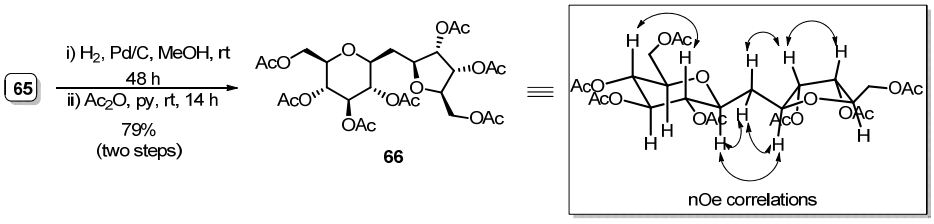
The alkynol **58** was then subjected for $Pd(CH_3CN)_2Cl_2$ mediated cycloisomerization in dichloromethane. The spectral and analytical analysis revealed that the actual product formed was the hemiketal **64** and not **63**. These observations

are in agreement with our previous studies (Chapter 1) which was expected as the result of alkynol cycloisomerization followed by hydrolysis of the resulting cyclic enol-ether.



Scheme 39. *Attempt for synthesis of **63** and structural confirmation of **65***

The formation of hemiketal **64** was confirmed by mass spectroscopy. As usual ^{1}H NMR spectrum was not much more informative. In ^{13}C NMR spectrum, two signals for quaternary carbons were observed at 103.1 ppm and 106.9 ppm, which indicate the mixture of anomers. Then, the hemiketal **64** was reduced using triethylsilane and $BF_3.Et_2O$ at −10 °C to 0 °C. The careful inspection of ^{13}C NMR spectrum, where four doublets were observed at 80.8, 81.2, 82.4 and 87.2 indicated the formation of five membered ring instead of six membered. For further confirmation, it was converted to the corresponding acetate **66** by complete benzyl ether deprotection under hydrogenation conditions and subsequent treatment with acetic anhydride and pyridine. The structure of acetate **66** was confirmed with the help of extensive NMR studies (1-D and 2-D NMR) and mass spectroscopy (Scheme 40).



Scheme 40. *Synthesis and characterization of carba-disaccharide **66***

As cycloisomerization of alkynol **58** resulted in the formation of the undesired product **64**, the different Pd and Au complexes (Table 2) were screened in order to achieve the required transformation. But unfortunately, in all the cases, the formation **64** was observed as the sole product. Amongst all the complexes tried for cycloisomerization, $AuCl(PPh_3)$ along with $AgSbF_6$ in DCM was found to be the best for this transformation.

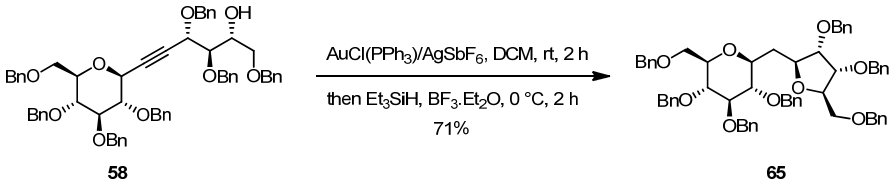
Table 2. *Different catalysts screened for alkynol cycloisomerization*

Sr. No.	Catalyst	Solvent	Time	% Yield
1	$PdCl_2(CH_3CN)_2$	CH_2Cl_2	2 h	68%
2	$PdCl_2(PhCN)_2$	CH_2Cl_2	2.5 h	61%
3	$Pd(OAc)_2$	CH_2Cl_2	3 h	46%
4	$AuBr_3$	CH_2Cl_2	0.5 h	Complex reaction mixture
5	$AuCl_3$	CH_2Cl_2	0.5 h	Complex reaction mixture
6	$AuCl(PPh_3)/AgSbF_6$	CH_2Cl_2	2 h	77%

During this model study, even though the desired model compound **56** had not been synthesized, however, at the same time it was noteworthy to mention that a new synthetic strategy for synthesis of 1-carbon linked *C*-disaccharide has been discovered.

- **One-pot alkynol cycloisomerization and reduction for synthesis of carba-disaccharide 65:**

In order to increase the efficiency of this protocol in terms of step economy, we wanted to check the one pot conversion of alkynol to compound **65**. To do so, alkynol cycloisomerization was carried out by using $AuCl(PPh_3)/AgSbF_6$ in DCM at room temperature. Then after consumption of the starting material on TLC, the reaction mixture was cooled to 0 °C and treated with triethylsilane/$BF_3.Et_2O$ (Scheme 41). The product obtained was purified in the usual way and characterized with the help of spectral and analytical data. The spectral data was in good agreement with the previously prepared compound **65**.



58 **65**

Scheme 41. *One-pot cycloisomerization followed by TES reduction*

Keeping in mind the importance of *C*-disaccharides and the challenges associated with the synthesis, we felt that the generalization of this protocol for the synthesis of various *C*-disaccharides would receive great appreciation in the field of carbohydrate chemistry. So, we focused our study towards the synthesis of one carbon linked *C*-disaccharides.

2. Carba-disaccharides:

Carba-disaccharides or *C*-disaccharides are the stable and non natural analogues of disaccharides where the exocyclic acetal oxygen atom is replaced with carbon/methylene and expected to have conformational and steric properties quite similar to corresponding *O*-disaccharides. The replacement of oxygen by carbon or methylene offers a great deal of stability against acid and enzymatic hydrolysis. The *C*-disaccharides, also known as pseudodisaccharides, have attracted a great deal of attention from a synthetic[28] as well as a biological[29] point of view, because of their hydrolytic stability and potent inhibitory properties against enzymes glycosyl hydrolases such as the disaccharidases of the digestive track.[30] Some analogues have proved to be of use in the therapeutic strategies for the treatment of cancer, AIDS and diabetes,[31] which clearly indicate the need for the *C*-disaccharides.

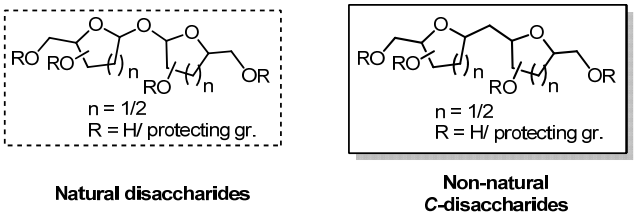


Figure 14. *General chemical structures of natural and non-natural C-disaccharides*

Since the first report on the synthesis of carba-disaccharide by Sinay and Rouzaud in 1983,[32] a number of synthetic approaches have been reported for the synthesis of this class of compounds having (1−6), (1–3) and (1–4) linkages,[33] but much less attention has been paid on the compound having a (1−1) linkage. To the best of our knowledge, all the known one carbon (1−1) linked *C*-disaccharides are of the bis-(D-glycopyranosyl) type[34] and not either of the pyranosyl-furanose or the furanosyl-furanose type. Since the first discovery of carba-disaccharide, its synthesis, in particular (1−1) linked *C*-disaccharides, has always remained a massive challenge for synthetic chemists over the last three decades.

➢ Design and synthesis of carba-disaccharides:

As a part of the research going in our group,[20] we have envisioned the extension of this approach for the efficient and selective synthesis of (1−1) linked *C*-

linked disaccharides comprised of pyranose-furanose and furanose-furanose combinations. In this context, some *C*-disaccharide molecules were designed as shown in Figure 15. The *C*-glucopyranosyl-arabinofuranoside **67** and ribofuranosyl-ribofuranoside **68** were chosen as representative targets in this regard. Our intension in this context was to apply the one-pot alkynol cycloisomerization followed by reduction of the resulting hemiketal in order to construct the furanoside as well as pyranoside part of the disaccharide in much efficient manner.

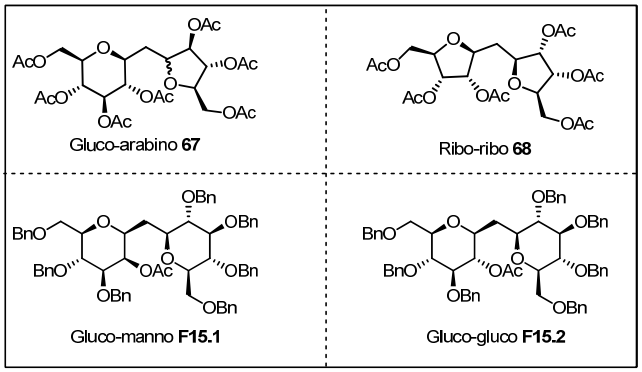


Figure 15. *C-disaccharides (targets) designed for synthetic exercise*

The journey towards the intended targets was started with the designing of the retrosynthetic strategy (Figure 16) for the synthesis of the targeted disaccharide **67**. Having sufficient experience in hand, the synthesis of disaccharide **67** was planned from the alkynol **69** by employing the newly developed one-pot [Au]-mediated alkynol cycloisomerization followed by triethylsilane reduction. The required alkynol can be synthesized from D-glucose derived lactone **59** and an alkyne **70** with suitable stereochemistry which can be easily accessible from D-arabinose.

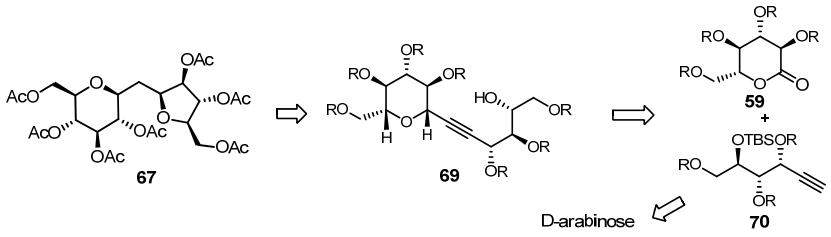
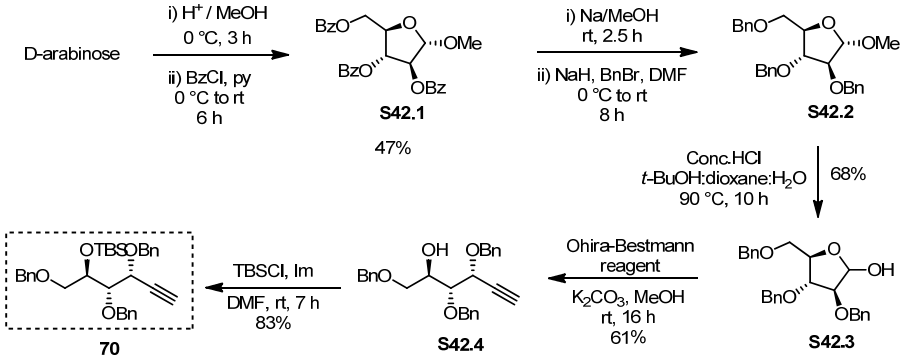


Figure 16. *Retrosynthetic disconnections for C-disaccharide **66***

➢ **Synthesis of alkyne fragment 70:**

The synthesis of the alkyne fragment was begun from the known 1-α-*O*-methyl 2,3,5-*O*-tribenzoyl-D-arabinofuranoside **S42.1**. The removal of benzoyl protecting group was carried out successfully by using sodium methoxide in methanol followed by protection of the resulting free hydroxyl groups as their benzyl ethers using sodium hydride and benzyl bromide to obtain the tri-*O*-benzyl derivative **S42.2** in 74% yield over two steps. The compound **S42.2** was subjected for the acid hydrolysis under acidic conditions (heating at 90 °C using HCl in mixture of *t*-BuOH, dioxane and water/4:4:1) to deliver lactol **S42.3** in 68% yield.



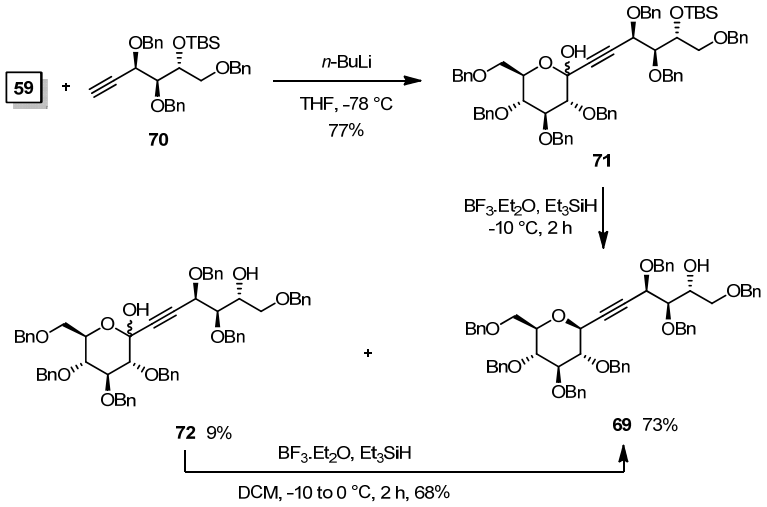
Scheme 42. *Synthesis of alkyne **70** with requisite stereochemistry*

The lactol **S42.3** thus obtained was treated with the Ohira-Bestmann reagent in methanol to procure the alkyne **S42.4** in 61% yield. The characteristic doublet of acetylenic proton at 2.56 ppm with J = 2.2 Hz in ^{1}H NMR spectrum confirmed the structure of alkyne **S42.4**. Finally, the free hydroxyl group was protected as the silyl ether using TBSCl, imidazole in DMF to get the alkyne **70** with 83% yield. The presence of the TBS signals [δ −0.08 (s, 6H) and 0.71 (s, 9H)] in the ^{1}HNMR spectrum confirmed the structure of TBS protected alkyne **70**.

➢ **Synthesis of alkynol intermediate 68:**

Having the alkyne **70** in hand, the next reaction sequence (Scheme 43) was carried out as done earlier. The addition of lithiated alkyne **70** to lactone **59** using *n*-BuLi as base in THF at −78 °C delivered the hemiketal **71** in 77% yield. The structure of hemiketal was confirmed with the help of HRMS. As usual, the ^{1}H NMR did not

provide much information, except, the absence of characteristic doublet of terminal acetylenic proton of alkyne at 2.58 ppm.

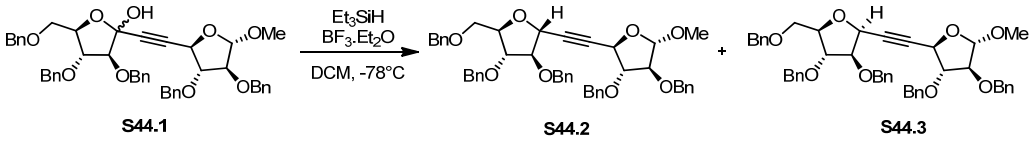


Scheme 43. *Synthesis of alkynol intermediate **69***

The hemiketal **71** was then subjected for the deoxygenation using triethylsilane and $BF_3{\cdot}Et_2O$ in DCM at −10 °C to deliver the expected alkynol **69** (73% yield) along with the only TBS deprotected compound **72** (9% yield). The compound **72** was again subjected for triethylsilane reduction using excess amount of reagent [triethylsilane (20 eq) and $BF_3{\cdot}Et_2O$ (10 eq)] at –10 °C to 0 °C to procure alkynol **69**. The structure of alkynol **69** was confirmed with the help of ^1H, ^{13}C NMR which was further supported by the HRMS spectrum.

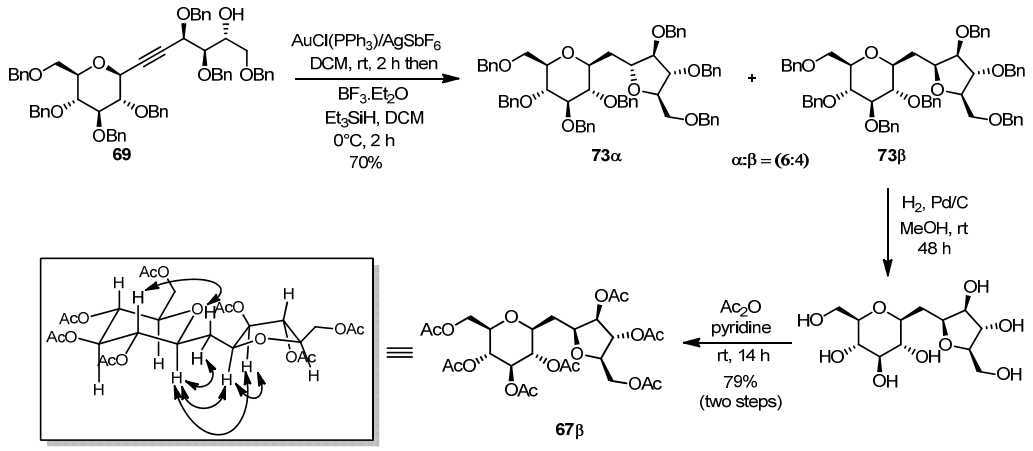
- **Synthesis of *C*-disaccharide 67:**

Coming to the reduction of the hemiacetals of the D-arabinofuranosyl unit, in dealing with the synthesis of *C*-disaccharide analogues of the α-D-arabinofuranosyl-(1–5)-α-D-arabinofuranosyl motif of mycobacterial cell AG complex, Wightman *et al.* have reported that the addition of hydride to the oxonium ion is non-diastereoselective and results in the formation of both α-arabinofuranoside **S44.2** as well as β-arabinofuranoside **S44.3** (Scheme 44).[35] This earlier report warranted the possibility of formation of a mixture of two disaccharides during the second phase ketal reduction.



Scheme 44. *Triethylsilane (TES) reduction of arabino hemiketal **S44.1***

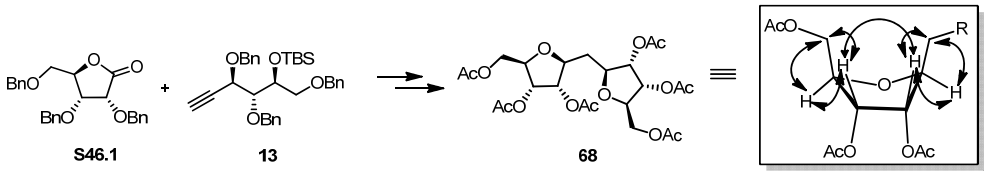
The alkynol **69** was subjected for the cycloisomerization using $AuCl(PPh_3)/AgSbF_6$ in DCM followed by treatment of triethylsilane and $BF_3{\cdot}Et_2O$ in the same pot after consumption of the starting alkynol to afford the separable mixture of compound **73** (β:α = 4:6) in 69% yield. The minor annomer **73β** was subjected for the complete benzyl deprotection under hydrogenation conditions and the resulting free hydroxyl groups were protected as *O*-acetates to get acetyl protected disaccharide **67β** in 79% yield over two steps. The structure of the product was confirmed by NMR studies and further supported by HRMS. The stereochemistry of the disaccharide was confirmed with the help of 2-D NMR spectroscopy. In this way, the synthesis of the *C*-linked disaccharide **67β** has been completed with overall good yields (Scheme 45).



Scheme 45. *One-pot cycloisomerization and TES reduction for the synthesis of C-disaccharide **67β***

At the same time, one of our group members has completed the synthesis of another designed *C*-disaccharide **68** (Scheme 46) using the same protocol; where the lactone **S46.1** as well as alkyne **13** derived from D-ribose were used as primary building blocks. The structure of the final disaccharide **68** was confirmed by

observing C_2 symmetric ^1H and ^{13}C NMR spectrum. Also the COSY, NOESY correlations have given further support for the assigned structure.



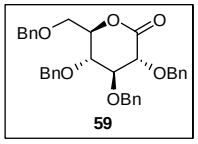
Scheme 46. *Synthesis and structure determination of C-disaccharide **68***

3. Conclusion:

In conclusion, though our efforts have not led to the synthesis of the required model compound **56**, at the same time, a new methodology has been discovered for the synthesis of one carbon linked *C*-disaccharides. Further studies toward the modification of strategy; optimization of reaction conditions for synthesis of model compound and thereafter, synthesis of the C(11)–(21) fragment of zooxanthellamide D are in progress. Also, we have generalized the newly discovered protocol for the synthesis of one carbon (1-1) linked *C*−disaccharides (**66**, **67β**, **73β** and **68**) with overall good yields and selectivity. The above mentioned results reveal the viability of one-pot alkynol cycloisomerization and triethylsilane reduction approach for the synthesis of one carbon (1-1) linked *C*−disaccharides with different pyran-furan and furan-furan combinations in overall good yield and selectivity.

Experimental and data

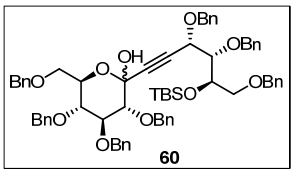
1. Synthesis of lactone 59:



59

Activated molecular sieves were added to the solution of lactol **S33.3** (4.0 g, 7.4 mmol) in anhydrous dichloromethane (50 mL) and stirred for 10 min. Then to this, PDC (4.17 g, 11.1 mmol) was added at room temperature. Then reaction container was covered with aluminum foil and stirred at same temperature for overnight. After complete consumption of starting material, reaction mixture was filtered through celite. Filtrate was concentrated under reduced pressure and crude was purified by column chromatography (60–120 mesh silica gel, 15:85 ethyl acetate/petroleum ether) to afford pure product **59** (2.93 g, 72%) as colorless gum. *Characterization data of compound **59***: $[\alpha]_D^{25}$ +73.7 (*c* 2.5, $CHCl_3$); IR ($CHCl_3$): 2930, 1755, 1421, 1028 cm^{-1}; ^1H NMR ($CDCl_3$ 200 MHz): δ 3.67 (dd, *J* = 3.2, 11.0 Hz, 1H), 3.75 (dd, *J* = 2.5, 11.0 Hz, 1H), 3.87–3.99 (m, 2H), 4.13 (dd, *J* = 1.6, 5.6 Hz, 1H), 4.41–4.56 (m, 4H), 4.59–4.76 (m, 4H), 5.02 (d, *J* = 11.4 Hz, 1H), 7.14–7.19 (m, 2H), 7.27–7.39 (m, 18H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 68.2 (t), 73.5 (t), 73.7 (t, 2C), 73.9 (t), 76.0 (d), 77.3 (d), 78.1 (d), 80.9 (d), 127.8 (d, 3C), 127.9 (d), 128.0 (d, 5C), 128.1 (d), 128.3 (d, 3C), 128.4 (d, 5C), 128.5 (d, 2C), 136.9 (s), 137.4 (s), 137.5 (s), 137.52 (s), 169.3 (s); LCMS (*m/z*): 561.21 (100% $[M+Na]^+$).

2. Synthesis of hemiketal 60:

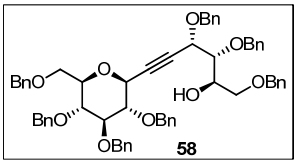


60

To the solution of alkyne **13** (0.30 g, 0.6 mmol) in anhydrous THF (20 mL) was slowly added 15 % *n*-BuLi solution in hexane (0.24 mL, 0.6 mmol) at –78 °C. Stirring was continued for 45 min at same temperature. Then to this, a solution of lactone **59** (200 mg, 0.4 mmol) in THF (5 mL) was added slowly and stirred at same temperature for 3 h. After complete consumption of starting material, reaction mixture was quenched with saturated solution of ammonium chloride (10 mL) at –78 °C. The crude product was isolated by extraction with ethyl acetate (100 mL) and water (30 mL). Organic layer was separated, dried (Na_2SO_4) and evaporated under reduced pressure. The crude compound was purified by column chromatography (100–200 mesh silica gel, 1:3 ethyl acetate/petroleum ether) to procure pure product **60** (0.33 g, 83%) as thin oil. *Characterization data of compound*

***60*:** IR ($CHCl_3$): 3436, 2930, 1498, 1047 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 0.04 (s, 3H), 0.01 (s, 3H), 0.76 (s, 5H), 0.80 (s, 4H), 1.82 (br s, 1H), 3.51–3.54 (m, 3H), 3.59–3.61 (m, 1H), 3.64–3.72 (m, 2H), 3.79–3.87 (m, 2H), 3.96–4.00 (m, 2H), 4.40–4.45 (m, 3H), 4.48–4.52 (m, 2H), 4.55–4.59 (m, 3H), 4.70–4.78 (m, 1H), 4.79–4.81 (m, 2H), 4.82–4.84 (m, 2H), 4.86–4.92 (m, 1H), 5.02–5.05 (m, 1H), 7.12–7.24 (m, 15H), 7.26–7.37 (m, 20H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ –5.0 (q), –4.9 (q), –4.4 (q), –4.3 (q), 17.9 (s) 18.0 (s), 25.8 (q), 25.9 (q), 68.4 (t), 68.7 (t), 70.6 (d), 70.8 (d), 70.9 (t), 71.2 (t), 71.6 (t), 71.7 (t), 71.9 (d), 72.0 (d), 73.22 (t), 73.24 (t), 73.3 (t), 73.4 (t), 74.2 (d), 74.4 (t), 74.5 (t), 74.6 (t), 74.7 (t), 75.67 (t), 75.70 (t), 75.8 (t), 77.3 (d), 77.6 (d), 80.5 (s), 81.3 (d), 82.4 (d), 83.3 (s), 83.8 (d), 84.2 (d), 84.3 (d), 84.9 (s), 86.6 (s), 91.5 (s), 95.5 (s), 125.3 (d), 127.3 (d), 127.4 (d), 127.5 (d), 127.52 (d), 127.6 (d), 127.67 (d), 127.70 (d), 127.74 (d), 127.8 (d), 127.84 (d), 127.9 (d), 128.0 (d), 128.1 (d), 128.12 (d), 128.2 (d), 128.3 (d), 128.33 (d), 129.0 (d), 137.4 (s), 137.5 (s), 137.8 (s), 137.83 (s), 138.0 (s), 138.1 (s), 138.2 (s), 138.4 (s), 138.5 (s), 138.6 (s), 138.7 (s); LCMS (*m/z*): 1091.06 (100% $[M+Na]^+$), 1107.22 (60% $[M+K]^+$).

3. Synthesis of compound 58:

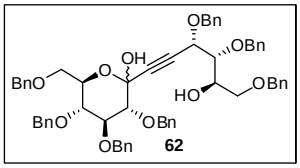


58

Triethylsilane (0.17 g, 1.49 mmol) was added to the solution of alcohol **60** (0.32 g, 0.3 mmol) in DCM:CH_3CN (3:2, 10 mL) at 0 °C under argon atmosphere and stirred for 5 min. Then reaction mixture was cooled to –40 °C and to this $BF_3.Et_2O$ (0.21 g, 1.5 mmol) was added slowly and allowed to stir at same temperature for 1.5 h. After complete consumption of starting material, reaction mixture was quenched with saturated $NaHCO_3$ (5 mL) at –40 °C. Crude product was isolated by extraction with ethyl acetate (50 mL) and water (20 mL). Organic layer washed with saturated $NaHCO_3$ (20 mL), water (20 mL), brine (15 mL), dried over sodium sulphate and evaporated under reduced pressure. The residual material was purified by column chromatography (230–400 mesh silica gel, 1:4 ethyl acetate/petroleum ether) to afford pure compound **58** (0.11 g, 41%), compound **61** (41 mg, 13%) and compound **62** (77 mg, 27%).

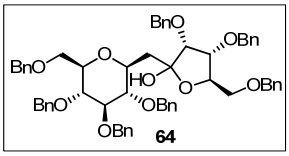
Characterization data of compound 58: $[\alpha]_D^{25}$ +38.97 (*c* 1.8, $CHCl_3$); IR ($CHCl_3$): 3401, 2930, 1496, 1028 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 3.47–3.49 (m, 1H), 3.59

(dd, *J* = 5.7, 9.7 Hz, 1H), 3.65 (dd, *J* = 3.2, 9.7 Hz, 1H), 3.66–3.70 (m, 3H), 3.74 (dd, *J* = 4.1, 11.0 Hz, 1H), 3.78 (dd, *J* = 1.9, 11.0 Hz, 1H), 3.85 (dd, *J* = 3.4, 7.9 Hz, 1H), 4.00–4.03 (m, 1H), 4.20−4.22 (m, 1H), 4.46 (d, *J* = 11.8 Hz, 1H), 4.50 (d, *J* = 11.8 Hz, 1H), 4.51−4.53 (m, 1H), 4.55–4.58 (m, 2H), 4.61 (d, *J* = 8.7 Hz, 1H), 4.63 (br s, 1H), 4.66 (br s, 1H), 4.71 (dd, *J* = 1.4, 3.4 Hz, 1H), 4.78 (d, *J* = 10.9 Hz, 1H), 4.84–4.89 (m, 3H), 4.93–4.95 (m, 2H), 5.10 (d, *J* = 10.5 Hz, 1H), 7.17–7.23 (m, 5H), 7.29–7.39 (m, 30H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 68.6 (t), 69.9 (d), 70.4 (d), 70.8 (t), 71.2 (t), 71.6 (d), 73.2 (t), 73.4 (t), 74.1 (t), 75.0 (t), 75.2 (t), 75.5 (t), 77.5 (d), 79.0 (d), 80.4 (d), 82.0 (s), 82.2 (d), 84.9 (s), 85.9 (d), 126.9 (d), 127.4 (d), 127.5 (d), 127.6 (d, 2C), 127.65 (d, 4C), 127.7 (d, 2C), 127.9 (d, 4C), 128.0 (d, 2C), 128.1 (d, 3C), 128.3 (d, 14C), 128.4 (d), 137.6 (s), 137.8 (s), 137.9 (s, 3C), 138.2 (s), 138.5 (s); HRMS: calcd for $C_{61}H_{62}O_9$ ($[M+Na]^+$) 961.4292, found 961.4279.



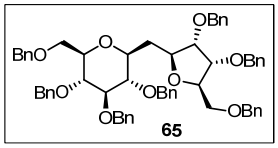
Characterization data of compound 62: $[\alpha]_D^{25}$ +63.3 (*c* 1.8, $CHCl_3$); IR ($CHCl_3$): 3402, 2932, 1480, 1070 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.58 (br s, 1H), 2.61 (br s, 1H), 3.51–3.57 (m, 2H), 3.61–3.63 (m, 1H), 3.67 (d, *J* = 12.7 Hz, 1H), 3.71 (d, *J* = 9.3 Hz, 1H), 3.80–3.82 (m, 1H), 3.87 (dd, *J* = 9.3, 18.4 Hz, 1H), 3.92–3.96 (m, 1H), 3.99–4.03 (m, 1H), 4.40–4.45 (m, 1H), 4.47–4.48 (m, 1H), 4.50–4.51 (m, 1H), 4.53 (d, *J* = 3.5 Hz, 1H), 4.55–4.57 (m, 2H), 4.60 (d, *J* = 14.1 Hz, 1H), 4.62–4.64 (m, 2H), 4.75–4.79 (m, 1H), 4.80–4.83 (m, 2H), 4.87 (d, *J* = 11.6 Hz, 1H), 4.89 (d, *J* = 11.6 Hz, 1H), 5.04 (two d, *J* = 11.4, 10.8 Hz, 1H), 7.11–7.23 (m, 10H), 7.26–7.37 (m, 25H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 68.4 (t), 68.5 (t), 70.4 (d), 70.43 (d), 70.6 (t), 70.65 (t), 71.1 (d), 71.2 (t), 71.4 (t), 71.43 (d), 71.9 (d), 73.3 (t), 73.4 (t), 74.1 (t), 74.2 (t), 74.3 (d), 74.7 (t), 74.9 (t), 75.0 (t), 75.67 (t), 75.70 (t), 75.73 (t), 77.3 (d), 77.6 (d), 80.0 (d), 80.41 (d), 80.44 (d), 82.4 (d), 83.4 (s), 83.8 (d), 84.0 (d), 84.4 (d), 84.8 (s), 86.9 (s), 91.6 (s), 95.6 (s), 99.9 (s), 127.4 (d), 127.5 (d), 127.58 (d), 127.60 (d), 127.61 (d), 127.7 (d), 127.75 (d), 127.8 (d), 127.83 (d), 127.9 (d), 127.92 (d), 128.0 (d), 128.1 (d), 128.20 (d), 127.22 (d), 128.28 (d), 128.31 (d), 128.35 (d), 128.37 (d), 128.4 (d), 137.4 (s), 137.5 (s), 137.7 (s), 137.82 (s), 137.84 (s), 137.9 (s), 138.0 (s), 138.10 (s), 138.13 (s), 138.2 (s), 138.6 (s); HRMS: calcd for $C_{61}H_{62}O_{10}$ ($[M+Na]^+$) 977.4241, found 977.4223.

4. Alkynol cycloisomerization:



To the solution of alkynol **58** (20 mg, 0.02 mmol) in anhydrous CH_3CN (2 mL) was bubbled argon gas for 45 min. Then to this reaction mixture $Pd(CH_3CN)_2Cl_2$ (1 mg, 2.1 μmol) was added and stirring was continued till starting material consumed completely. After that, solvent was evaporated under reduced pressure. Crude material thus obtained was purified by column chromatography (230–400 mesh silica gel, 1:3 ethyl acetate/petroleum ether) to isolate pure product **64** (13 mg, 64%). *Characterization data of compound **64*:** IR ($CHCl_3$): 3370, 2927, 2855, 1466, 1071 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 1.84 (dd, J = 9.4, 14.6 Hz, 1H), 2.14–2.24 (m, 1H), 3.34–3.42 (m, 1H), 3.47 (br d, J = 4.0 Hz, 1H), 3.51–3.54 (m, 2H), 3.57–3.61 (m, 2H), 3.64–3.74 (m, 3H), 3.97–4.01 (m, 1H), 4.26–4.40 (m, 2H), 4.44–4.47 (m, 2H), 4.49–4.53 (m, 4H), 4.55–4.59 (m, 2H), 4.74–4.79 (m, 1H), 4.81–4.82 (m, 1H), 4.85–4.86 (m, 2H), 4.89–4.90 (m, 1H), 7.14–7.24 (m, 10H), 7.27–7.31 (m, 25H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 34.7 (t), 39.4 (t), 69.1 (t), 69.8 (t), 71.7 (t), 72.2 (t), 72.9 (t), 73.2 (t), 73.3 (t), 73.5 (t), 75.0 (t), 75.5 (t), 76.2 (d), 77.2 (d), 78.2 (d), 78.4 (d), 79.6 (d), 79.7 (d), 80.4 (d), 81.1 (d), 81.3 (d), 81.4 (d), 87.0 (d), 103.1 (s), 106.9 (s), 127.5 (d), 127.7 (d), 127.74 (d), 127.8 (d), 127.9 (d), 128.0 (d), 128.1 (d), 128.3 (d), 128.4 (d), 137.8 (s), 137.84 (s), 137.9 (s), 137.94 (s), 138.0 (s), 138.04 (s), 138.1 (s), 138.2 (s), 138.4 (s), 138.5 (s), 138.51 (s); LCMS (*m/z*): 414.95 (100%), 979.20 (50% $[M+Na]^+$).

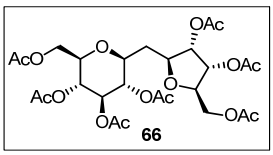
5. Synthesis of compound 65:



To the solution of alcohol **64** (10 mg, 11 μmmol) in DCM:CH_3CN (3:2, 1 mL) at 0 °C under argon atmosphere was added triethylsilane (6 mg, 55 μmol) followed by addition of $BF_3.Et_2O$ (7.5 mg, 55 μmol) at 0 °C and stirring was continued at same temperature for 2.5 h. After complete consumption of starting material reaction mixture was quenched with saturated $NaHCO_3$ at 0 °C. Solvent was evaporated under reduced pressure. Crude material thus obtained was purified through column chromatography (230–400 mesh silica gel, 1:4 ethyl acetate/petroleum ether) to procure pure product **65** (7 mg, 71%). *Characterization data of compound **65**:* $[\alpha]_D^{25}$

4.1 (*c* 1.3, $CHCl_3$); IR ($CHCl_3$): 2930, 1419, 1080 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 1.49–1.54 (m, 1H), 1.76 (dd, *J* = 9.9, 13.3 Hz, 1H), 3.13–3.17 (m, 1H), 3.30 (br d, *J* = 5.7 Hz, 1H), 3.38–3.41(m, 2H), 3.56–3.64 (m, 5H), 3.82 (t, *J* = 5.1 Hz, 1H), 4.20–4.24 (m, 1H), 4.40–4.55 (m, 12H), 4.73–4.81 (m, 4H), 7.08–7.26 (m, 35H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 36.5 (t), 68.7 (t), 70.5 (t), 71.8 (t, 2C), 73.3 (t), 73.5 (t), 74.93 (t), 75.0 (t), 75.5 (t), 75.9 (d), 77.5 (d), 77.6 (d), 78.3 (d), 78.7 (d), 80.8 (d), 81.2 (d), 82.4 (d), 87.2 (d), 127.5 (d, 2C), 127.6 (d, 4C), 127.6 (d, 2C), 127.7 (d, 3C), 127.8 (d, 2C), 127.8 (d, 2C), 127.9 (d, 2C), 127.9 (d, 3C), 128.1 (d, 2C), 128.3 (d, 9C), 128.4 (d, 2C), 128.4 (d, 2C), 138.0 (s), 138.1 (s, 2C), 138.2 (s, 2C), 138.3 (s), 138.6 (s); HRMS: calcd for $C_{61}H_{64}O_9$ ($[M+Na]^+$) 963.4448, found 963.4436.

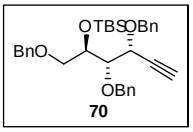
6. Synthesis of compound 66:



66

$Pd(OH)_2/C$ (10%, 4 mg) was added to the solution of benzyl ether **65** (13 mg) in methanol (2 mL) and allowed to stir at room temperature under H_2 atmosphere at balloon pressure for 48 h. After disappearance of starting material on TLC, reaction mixture was filtered through celite bed and washed ten times with methanol. Filtrate was evaporated under reduced pressure to afford crude material which was treated with pyridine (0.5 mL) and acetic anhydride (0.5 mL) for overnight. The crude product was isolated by co-evaporation with toluene and purified by column chromatography (230–400 mesh silica gel, 4:6 ethyl acetate/petroleum ether) to afford pure product **66** (6 mg, 72%). *Characterization data of compound* ***66*****:** $[\alpha]_D^{25}$ +2.83 (*c* 1.3, $CHCl_3$); IR ($CHCl_3$): 2929, 2858, 1728, 1471, 1073 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 1.60–1.62 (m, 1H), 1.74–1.79 (m, 1H), 1.99 (s, 3H), 2.01 (s, 3H), 2.04 (s, 3H), 2.07 (s, 9H), 2.08 (s, 3H), 3.62−3.66 (m, 2H), 4.07−4.12 (m, 4H), 4.27−4.30 (m, 2H), 4.86 (t, *J* = 9.6 Hz, 1H), 4.94 (t, *J* = 5.8 Hz, 1H), 5.08 (t, *J* = 9.7 Hz, 1H), 5.13−5.18 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 20.6 (q, 4C), 20.7 (q), 20.8 (q), 20.8 (q), 35.4 (t), 62.1 (t), 63.5 (t), 68.4 (d), 71.5 (d), 71.9 (d), 74.2 (d, 2C), 74.3 (d), 75.5 (d), 76.8 (d), 79.1 (d), 169.5 (s), 169.7 (s), 169.8 (s, 2C), 170.3 (s), 170.5 (s), 170.7 (s); HRMS: calcd for $C_{26}H_{36}O_{16}$ ($[M+Na]^+$) 627.1901, found 627.1885.

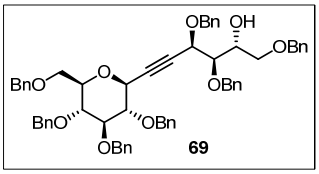
7. Synthesis of TBS alkyne 70:



70

To the solution of alcohol **S42.4** (200 mg, 0.5 mmol) in anhydrous DMF (2 mL), imidazole (186 mg, 2.9 mmol) was added and cooled to 0 °C. To this, TBSCl (216 mg, 1.4 mmol) was added and stirring was continued at room temperature for 6 h. The extraction with ethyl acetate (50 mL) and water (20 mL) followed by washing with water (4 x 15 mL), brine (15 mL) and evaporation under reduced pressure afforded sticky mass which was purified by column chromatography (230–400 silica gel, 5:95 ethyl acetate/petroleum ether) to get pure product **70** (210 mg, 83% yield) as a colourless oil. *Characterization data of compound **70***: $[\alpha]_D^{25}$ −15.93 (*c* 2.06, $CHCl_3$); IR ($CHCl_3$): 3292, 2921, 2835, 1639, 1448, 1076, 751 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 0.02 (s, 3H), 0.03 (s, 3H), 0.85 (s, 9H), 2.52 (d, *J* = 2.1 Hz, 1H), 3.55 (dd, *J* = 5.3, 10.0 Hz, 1H), 3.72 (dd, *J* = 4.4, 10.0 Hz, 1H), 3.80 (dd, *J* = 4.2, 6.2 Hz, 1H), 4.27 (dd, *J* = 4.6, 9.5 Hz, 1H), 4.41 (dd, *J* = 2.1, 6.2 Hz, 1H), 4.46 (d, *J* = 12.0 Hz, 1H), 4.50 (d, *J* = 12.0 Hz, 1H), 4.53 (d, *J* = 11.6 Hz, 1H), 4.75 (d, *J* = 11.4 Hz, 1H), 4.84 (d, *J* = 11.7 Hz, 1H), 4.87 (d, *J* = 11.2 Hz, 1H), 7.23–7.33 (m, 15H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ –4.8 (q), –4.4 (q), 18.1 (s), 25.9 (q, 3C), 69.5 (d), 71.0 (t), 71.4 (t), 71.8 (d), 73.2 (t), 75.2 (t), 75.8 (d), 81.1 (s), 84.0 (d), 127.4 (d, 2C), 127.5 (d), 127.6 (d, 2C), 127.8 (d, 2C), 127.9 (d, 2C), 128.1 (d, 2C), 128.2 (d, 4C), 137.9 (s), 138.4 (s), 138.9 (s); HRMS: calcd for $C_{33}H_{42}O_4Si$ ($[M+Na]^+$) 553.2750, found 553.2740.

8. Synthesis of alkynol 69:



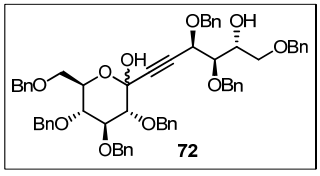
69

To the solution of alkyne **70** (739 mg, 1.4 mmol) in anhydrous THF (25 mL) was slowly added 15 % *n*-BuLi solution in hexane (0.9 mL, 1.4 mmol) at –78 °C. Stirring was continued for 30 min at same temperature. Then to this, a solution of lactone **59** (500 mg, 0.93 mmol) in THF (10 mL) was added slowly and stirring was continued at same temperature for 2.5 h. After complete consumption of starting material on TLC, reaction mixture was quenched with saturated solution of ammonium chloride (10 mL) at –78 °C. The crude compound was isolated by extraction with ethyl acetate (100 mL) and water (30 mL). The separated organic layer was dried (Na_2SO_4) and concentrated under reduced pressure to afford crude

product **71** (920 mg) which was dissolved in DCM:CH_3CN (3:2, 10 mL). To this solution, triethylsilane (0.728 g, 4.3 mmol) was added slowly at 0 °C followed by addition of $BF_3.Et_2O$ (0.61 g, 4.3 mmol) at –10 °C and stirring was continued at same temperature for 1.5 h. After complete consumption of starting material, reaction mixture was quenched with saturated $NaHCO_3$ (10 mL) at –10 °C and extracted with ethyl acetate (80 ml) and water (30 mL). Organic layer washed sequentially with saturated $NaHCO_3$ (20 mL), water (30 mL), brine (25 mL), dried (Na_2SO_4) and solvent was evaporated under reduced pressure to afford crude product, which was purified by column chromatography (230–400 mesh silica gel, 1:4 ethyl acetate/petroleum ether) to procure pure compound **69** (0.590 g, 73%) and compound **72** (74 mg, 9%).

Characterization data of compound 69: $[\alpha]_D^{25}$ −4.32 (*c* 1.59, $CHCl_3$); IR ($CHCl_3$): 3398, 2934, 1488, 1032 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 2.59 (br s, 1H), 3.43–3.46 (m, 1H), 3.58–3.62 (m, 2H), 3.63–3.66 (m, 2H), 3.70–3.72 (m, 1H), 3.75 (dd, *J* = 3.9, 7.3 Hz, 1H), 4.11–4.15 (m, 2H), 4.42–4.47 (m, 3H), 4.49–4.51 (m, 2H), 4.53–4.54 (m, 1H), 4.57 (d, *J* = 11.1 Hz, 1H), 4.59 (d, *J* = 7.3 Hz, 1H), 4.61 (d, *J* = 6.8 Hz, 1H), 4.65–4.73 (m, 2H), 4.80 (d, *J* = 10.6 Hz, 1H), 4.82 (d, *J* = 8.8 Hz, 1H), 4.84 (d, *J* = 6.8 Hz, 1H), 4.89 (dd, *J* = 7.1, 11.1 Hz, 1H), 4.98–5.00 (m, 1H), 7.12–7.24 (m, 12H), 7.27–7.37 (m, 23H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 68.7 (t), 69.1 (d), 69.9 (d), 70.1 (d), 70.6 (t), 71.1 (t), 73.3 (t), 73.5 (t), 74.4 (t), 75.1 (t), 75.3 (t), 75.7 (t), 77.6 (d), 79.1 (d), 80.2 (d), 80.5 (s), 82.2 (d), 82.8 (s), 86.1 (d), 127.0 (d), 127.6 (d, 4C), 127.7 (d, 4C), 127.8 (d, 2C), 127.9 (d), 127.93 (d, 4C), 128.0 (d, 2C), 128.2 (d, 2H), 128.3 (d, 4H), 128.4 (d, 10C), 128.5 (d), 137.2 (s), 137.6 (s), 137.9 (s), 137.98 (s), 138.00 (s), 138.5 (s), 140.8 (s); HRMS: calcd for $C_{61}H_{62}O_9$ ($[M+Na]^+$) 961.4292, found 961.4283.

Characterization data of compound 72:



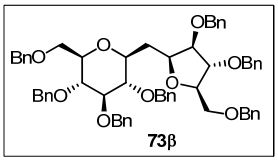
72

IR ($CHCl_3$) 3391, 2932, 2865, 1459, 1068 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 3.51–3.57 (m, 2H), 3.58–3.62 (m, 1H), 3.65 (d, *J* = 11.6 Hz, 1H), 3.67 (d, *J* = 7.5 Hz, 1H), 3.71 (d, *J* = 9.4 Hz, 1H), 3.73–3.77 (m, 2H), 3.82 (dd, *J* = 3.4, 8.8 Hz, 1H), 3.86–3.94 (m, 1H), 4.00–4.03 (m, 1H), 4.09 (dt, *J* =

4.0, 7.8 Hz, 1H), 4.40–4.44 (m, 2H), 4.46–4.49 (m, 2H), 4.50–4.54 (m, 2H), 4.55–4.59 (m, 2H), 4.64–4.69 (m, 1H), 4.76–4.86 (m, 5H), 5.01 (d, J = 11.6 Hz, 1H), 7.16–7.34 (m, 35H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 68.4 (t), 68.5 (t), 68.6 (d), 68.9 (d), 69.9 (d), 70.0 (d), 70.5 (t), 71.2 (t), 71.4 (t), 71.9 (d), 73.3 (t), 73.4 (t), 74.4 (d), 74.43 (t), 74.8 (t), 75.0 (t), 75.7 (t), 77.3 (d), 77.6 (d), 80.2 (d), 80.3 (d), 80.7 (s), 82.5 (d), 83.4 (s), 83.7 (d), 83.9 (d), 84.3 (d), 85.2 (s), 86.7 (s), 91.6 (s), 95.5 (s), 127.5 (d), 127.6 (d), 127.62 (d), 127.7 (d), 127.8 (d), 127.83 (d), 127.9 (d), 128.0 (d), 128.1 (d), 128.2 (d), 128.23 (d), 128.3 (d), 128.4 (d), 137.1 (s), 137.11 (s), 137.7 (s), 137.9 (s), 137.93 (s), 138.1 (s), 138.12 (s), 138.4 (s), 138.5 (s); LCMS (*m/z*): 977.52 (100% $[M+Na])^+$, 993.51 (15% $[M+K]^+$); HRMS: 977.4241 ($[M+Na]^+$) calculated, 977.4224 ($[M+Na]^+$) observed.

9. Synthesis of compound 73:

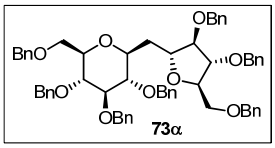
To the solution of alkynol **69** (70 mg, 74.5 µmol) in anhydrous DCM (2 mL) $AuCl(PPh_3)$ (737 µg, 1.49 µmol) and $AgSbF_6$ (512 µg, 1.49 µmol) was added sequentially at room temperature. Reaction container was covered with silver foil and stirred for 2 h. After consumption of starting material, triethylsilane (52 mg, 447 µmol) was added to it and cooled to 0 °C. Then to this cold solution, $BF_3.Et_2O$ (53 mg, 372 µmmol) was added slowly and stirred at same temperature for 2 h. Reaction mixture was quenched by adding $NaHCO_3$ solution (2 mL) and extracted with DCM (25 mL) and water (5 mL). Organic layer dried over sodium sulphate, and evaporated under reduced pressure. Crude was purified by column chromatography (230–400 mesh silica gel, 1:4 ethyl acetate/petroleum ether) to afford pure **73α** (28 mg, 42%) and **73β** (18 mg, 28%) as colorless oil.



73β

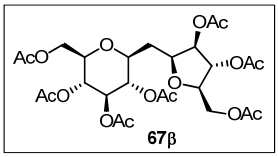
Characterization data of compound 73β: $[\alpha]_D^{25}$ −3.23 (*c* 1.92, $CHCl_3$); IR ($CHCl_3$): 2933, 1421, 1077 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.93–2.04 (m, 1H), 2.19 (ddd, J = 2.9, 7.8, 11.4 Hz, 1H), 3.55–3.42 (m, 2H), 3.51–3.76 (m, 7H), 3.88–4.00 (m, 2H), 4.18–4.25 (m,1H), 4.38–4.47 (m, 4H), 4.49–4.55 (m, 5H), 4.58–4.70 (m, 2H), 4.77–4.80 (m, 2H), 4.86–4.92 (m, 2H), 7.12–7.31 (m, 35H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 35.0 (t), 69.0 (t), 70.4 (t), 71.4 (t), 71.6 (t), 73.3 (t), 73.4 (t), 75.0 (t), 75.1 (t), 75.5 (t), 76.2 (d), 78.5 (d), 78.9 (d), 79.3 (d), 81.5 (d), 81.9 (d), 85.4 (d), 87.2 (d), 87.3 (d),

127.5 (d, 5C), 127.6 (d, 4C), 127.7 (d, 3C), 127.73 (d, 4C), 127.9 (d), 127.95 (d, 2C), 128.0 (d, 2C), 128.3 (d, 4C), 128.4 (d, 10C), 137.9 (s), 138.0 (s), 138.1 (s, 2C), 138.2 (s, 2C), 138.6 (s); LCMS (*m/z*): 963.50 (100% $[M+Na])^+$, 979.46 (15% $[M+K]^+$); HRMS: 963.4448 ($[M+Na]^+$) calculated, 963.4431 ($[M+Na]^+$) observed.



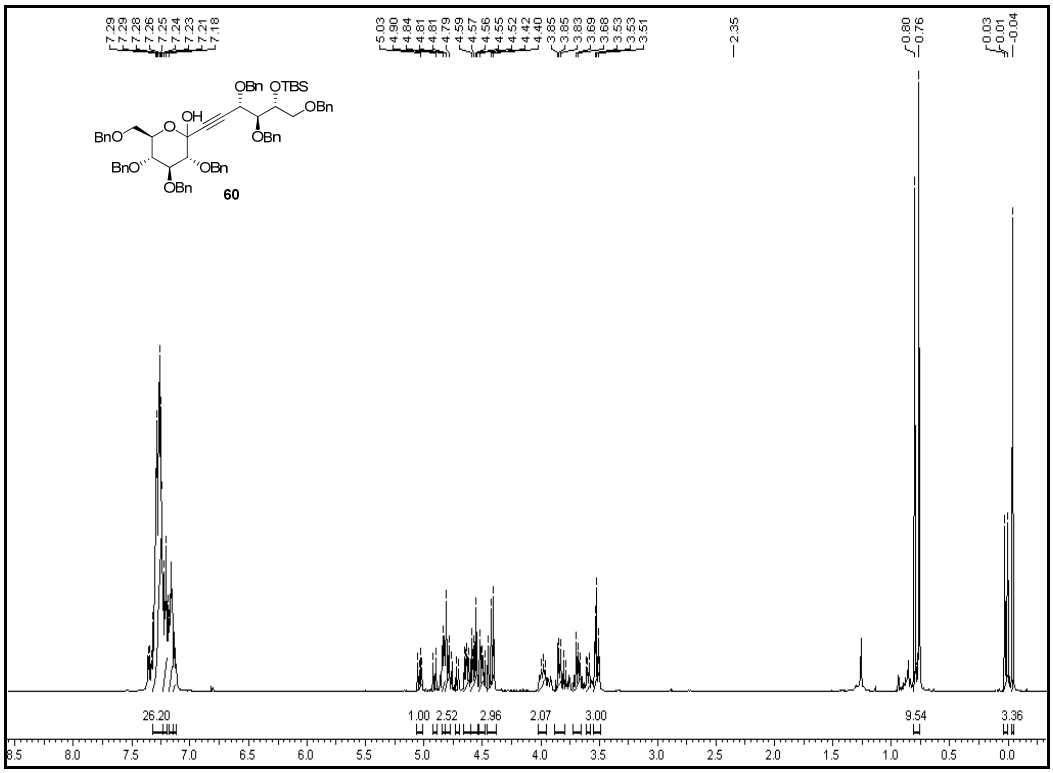
Characterization data of compound 73α: $[\alpha]_D^{25}$ +6.30 (*c* 1.53, $CHCl_3$); IR ($CHCl_3$): 2926, 1429, 1081 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.59 (ddd, *J* = 3.8, 10.2, 14.0 Hz, 1H), 1.83 (ddd, *J* = 1.5, 9.6, 14.0 Hz, 1H), 3.22 (dt, *J* = 2.4, 9.1 Hz, 1H), 4.36–4.38 (m, 1H), 3.46–3.50 (m, 2H), 3.63–3.71 (m, 5H), 3.89 (t, *J* = 5.1 Hz, 1H), 4.18 (dd, *J* = 4.3, 9.1 Hz, 1H), 4.29 (ddd, *J* = 4.0, 5.3, 9.3 Hz, 1H), 4.42–4.61 (m, 11H), 4.82 (d, *J* = 10.8 Hz, 1H), 4.85 (d, *J* = 11.1 Hz, 1H), 4.87–4.90 (m, 2H), 7.12–7.22 (m, 8H), 7.24–7.32 (m, 27H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 36.6 (t), 86.8 (t), 70.5 (t), 71.8 (t, 2C), 73.4 (t), 73.5 (t), 74.9 (t), 74.94 (t), 75.5 (t), 76.0 (d), 77.6 (d), 77.7 (d), 78.4 (d), 78.7 (d), 80.8 (d), 81.3 (d), 82.4 (d), 87.2 (d), 127.6 (d, 6C), 127.65 (d), 127.7 (d), 127.74 (d, 2C), 127.8 (d, 2C), 127.85 (d, 2C), 127.9 (d, 4C), 128.0 (d, 2C), 128.3 (d, 15C), 138.0 (s), 138.2 (s, 2C), 138.28 (s), 138.29 (s), 138.3 (s), 138.7 (s); LCMS (*m/z*): 963.50 (100% $[M+Na])^+$, 979.48 (10% $[M+K]^+$); HRMS: 963.4448 ($[M+Na]^+$) calculated, 963.4434 ($[M+Na]^+$) observed.

10. Synthesis of acetate 67β:

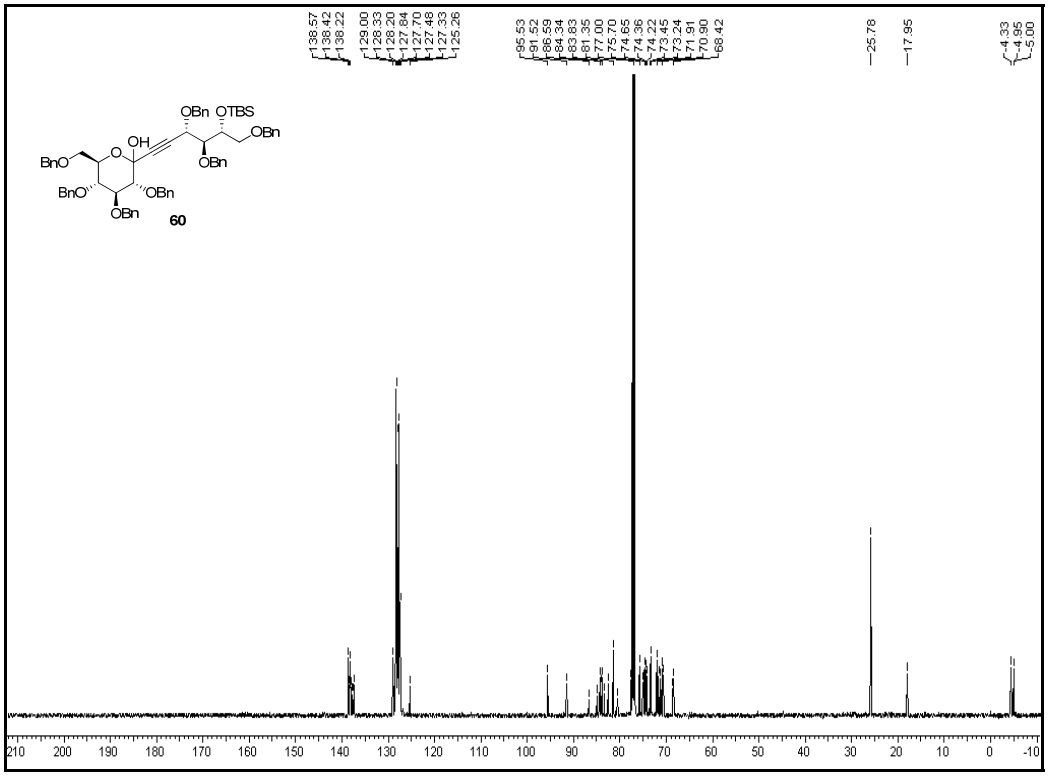


$Pd(OH)_2/C$ (10%) (10 mg) was added to solution of benzyl ether **73β** (28 mg) in methanol (4 mL) and allowed to stir at room temperature under H_2 atmosphere at balloon pressure for 48 h. After disappearance of starting material on TLC, reaction mixture was filtered through celite pad and washed ten times with methanol. Filtrate was evaporated under reduced pressure to afford crude material which was dissolved in pyridine (0.5 mL) and treated with acetic anhydride (0.5 mL) at 0 °C. Then reaction mixture was allowed to stir at room temperature for overnight. After complete consumption of starting material reaction mixture was diluted with ethyl acetate (10 mL) and washed with water (3 x 5 mL). Organic layer dried over sodium sulphate and concentrated under reduced pressure. The crude compound obtained was purified by flash column chromatography (230–400 mesh silica gel, 45:55 ethyl

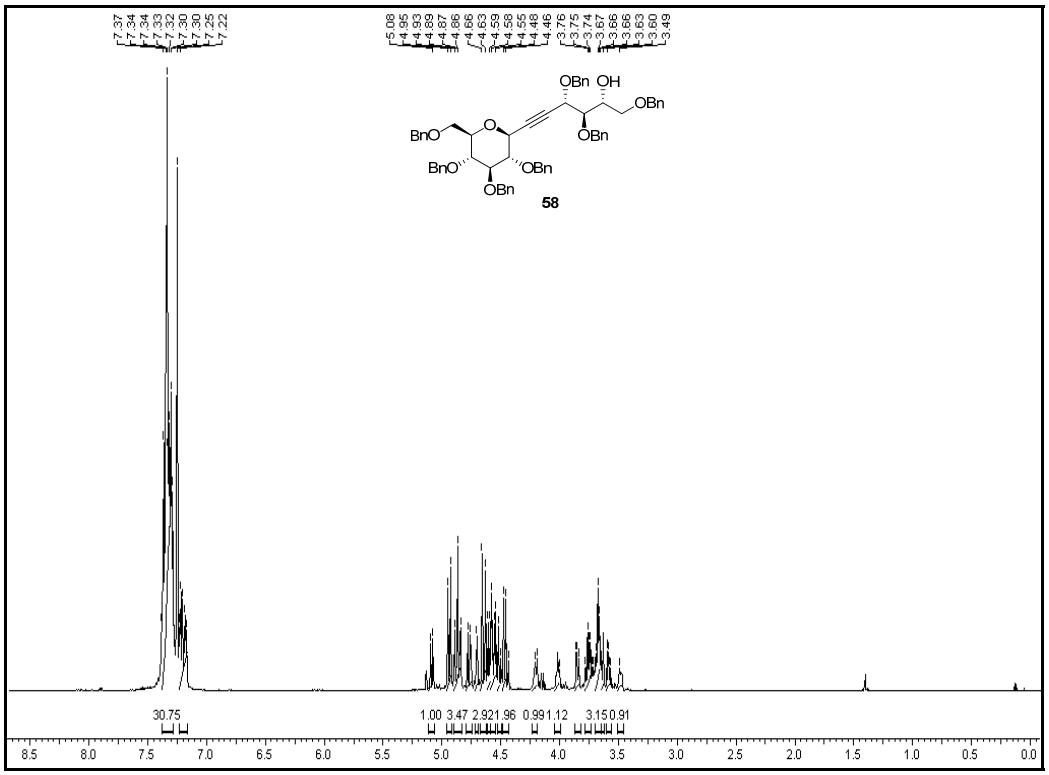
acetate/petroleum ether) to afford pure product **67β** (14 mg, 79%) as colorless thick oil. *Characterization data of compound **67β*:** $[\alpha]_D^{25}$ +6.05 (*c* 1.87, $CHCl_3$); IR ($CHCl_3$) 2925, 2863, 1726, 1468, 1078 cm^{-1}; ^1H NMR (C_6D_6, 500 MHz) δ 1.65 (s, 3H), 1.66 (s, 3H), 1.75 (s, 6H), 1.81 (s, 3H), 1.84 (s, 3H), 1.85 (s, 3H), 1.94–2.06 (m, 2H), 3.47 (ddd, *J* = 2.3, 4.5, 9.6 Hz, 1H), 3.70 (ddd, *J* = 3.7, 7.0, 10.3 Hz, 1H), 4.23 (dd, *J* = 2.3, 12.4 Hz, 1H), 4.29–4.32 (m, 1H), 4.33–4.35 (m, 1H), 4.36–4.38 (m, 1H), 4.43 (dd, *J* = 6.3, 11.2 Hz, 1H), 4.49–4.53 (m, 1H), 5.25 (dd, *J* = 9.2, 9.3 Hz, 1H), 5.34–5.37 (m, 2H), 5.38–5.42 (m, 1H), 5.43–5.47 (m, 1H); ^{13}C NMR (C_6D_6, 125 MHz) δ 20.1 (s), 20.2 (s, 2C), 20.24 (s), 20.3 (s, 2C), 20.33 (s), 34.1 (t), 62.1 (t), 63.1 (t), 68.7 (d), 72.2 (d), 74.8 (d), 75.0 (d), 76.2 (d), 79.2 (d), 80.1 (d), 80.6 (d), 81.2 (d), 169.0 (s), 169.1 (s), 169.4 (s), 169.6 (s), 170.0 (s), 170.05 (s), 170.1 (s); HRMS: 627.1901 ($[M+Na]^+$) calculated, 627.1882 ($[M+Na]^+$) observed.



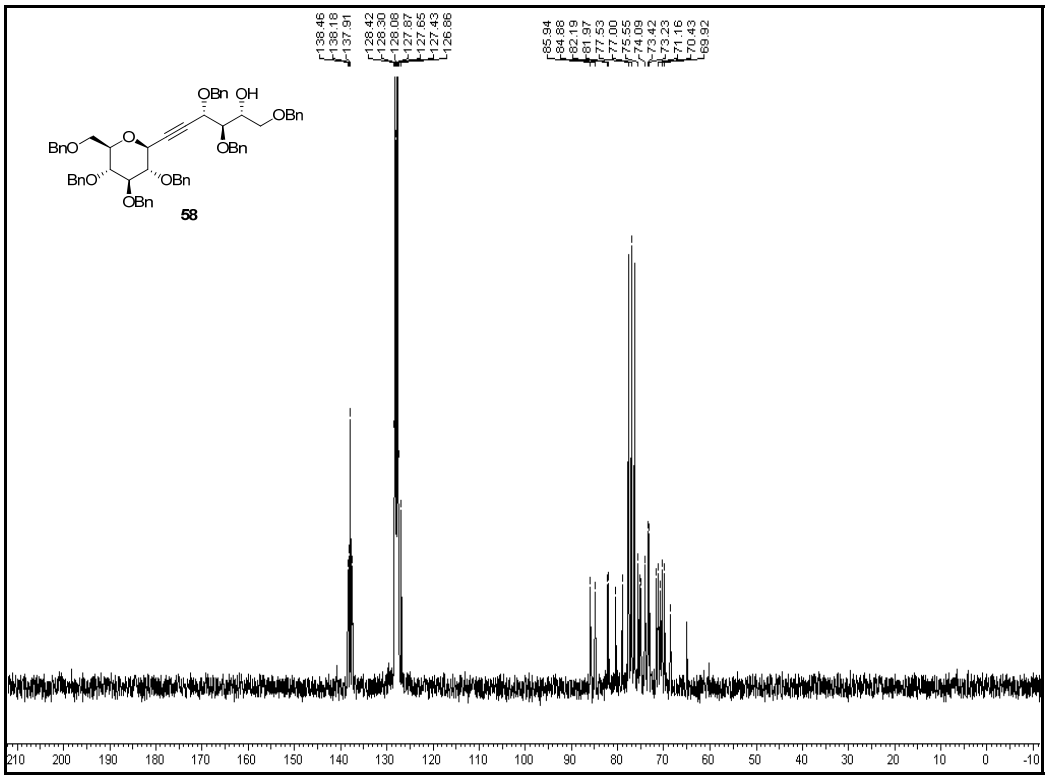
^{1}H NMR of compound 60



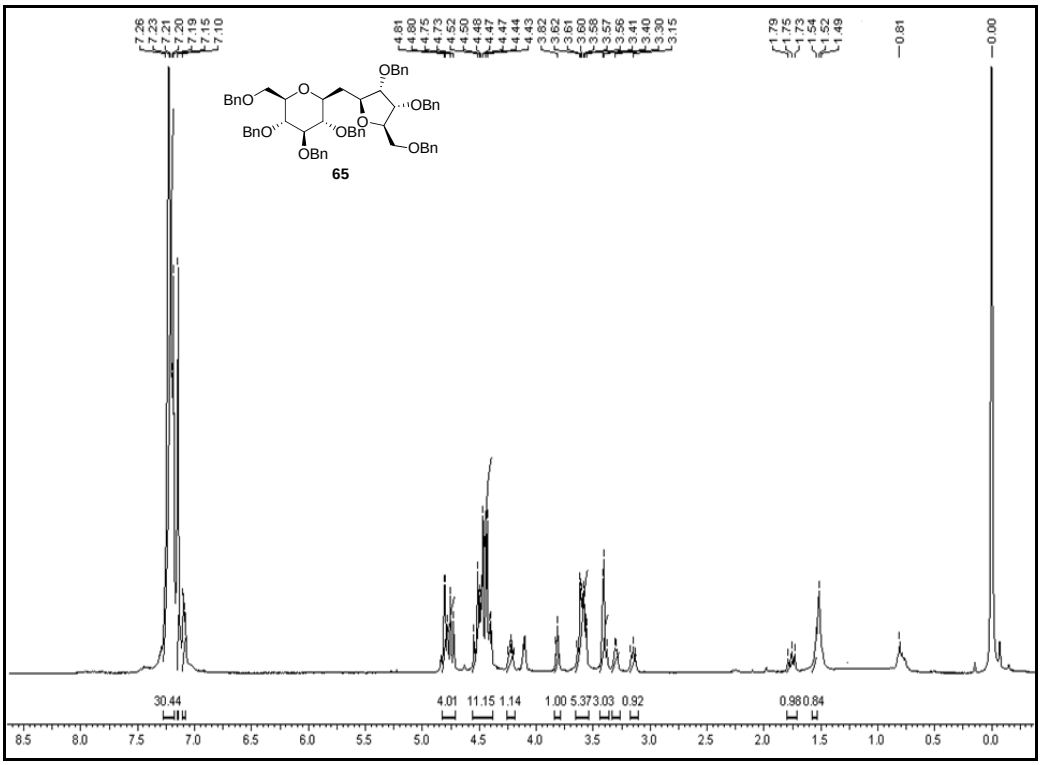
^{13}C NMR of compound 60



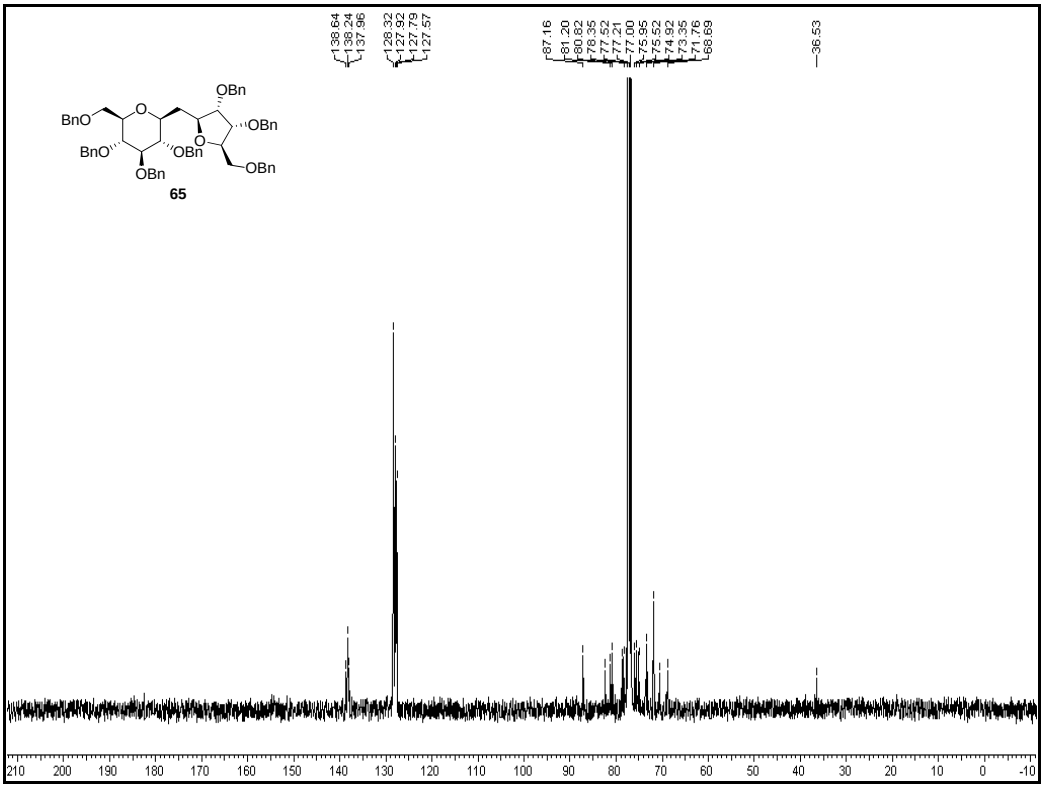
^{1}H NMR of compound 58



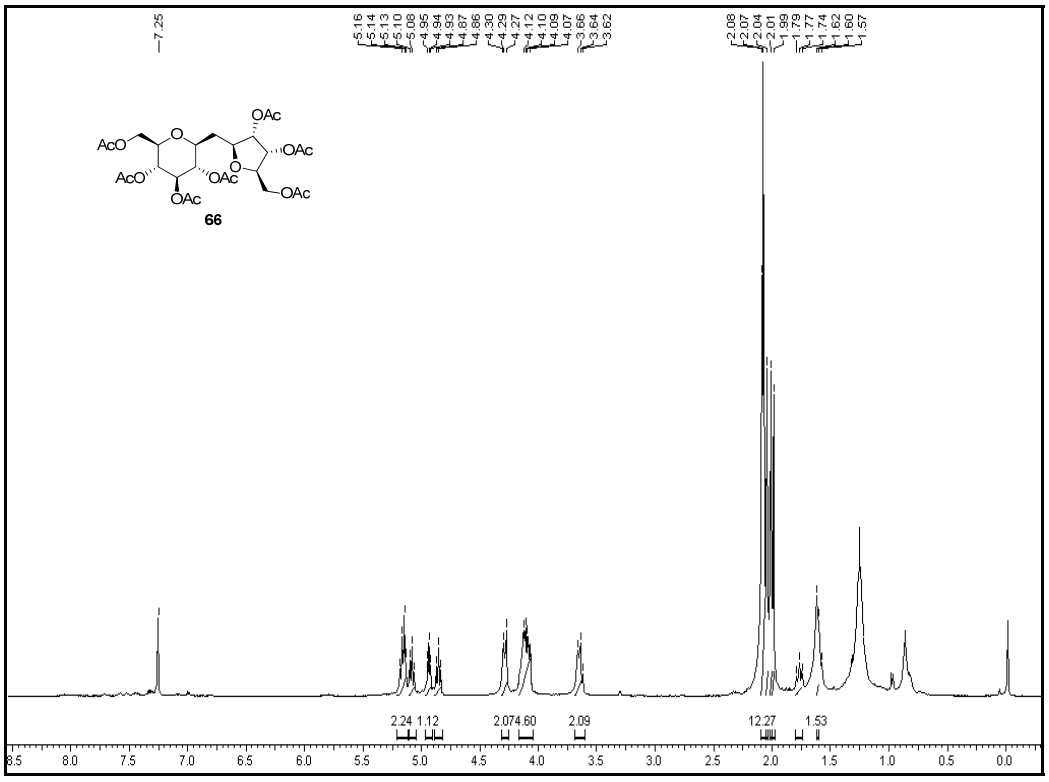
^{13}C NMR of compound 58



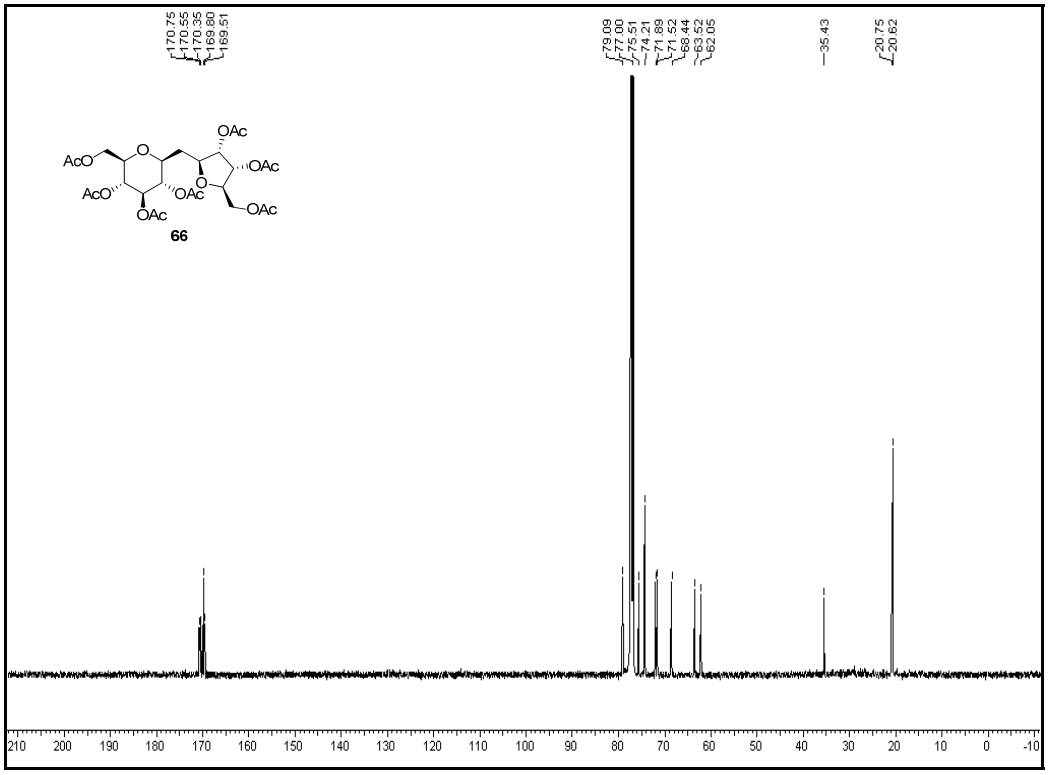
^{1}H NMR of compound 65



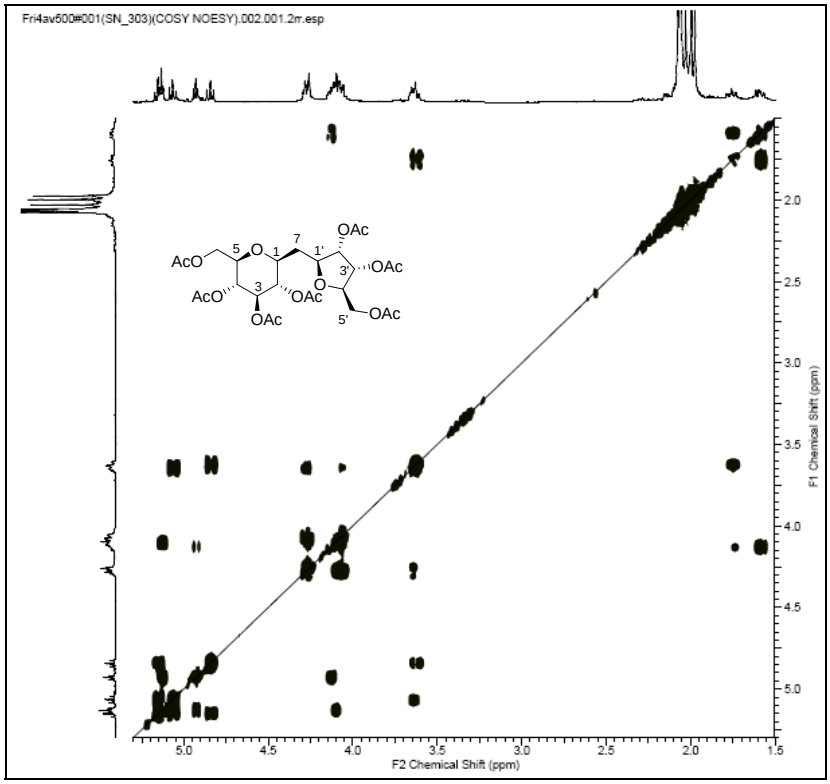
^{13}C NMR of compound 65



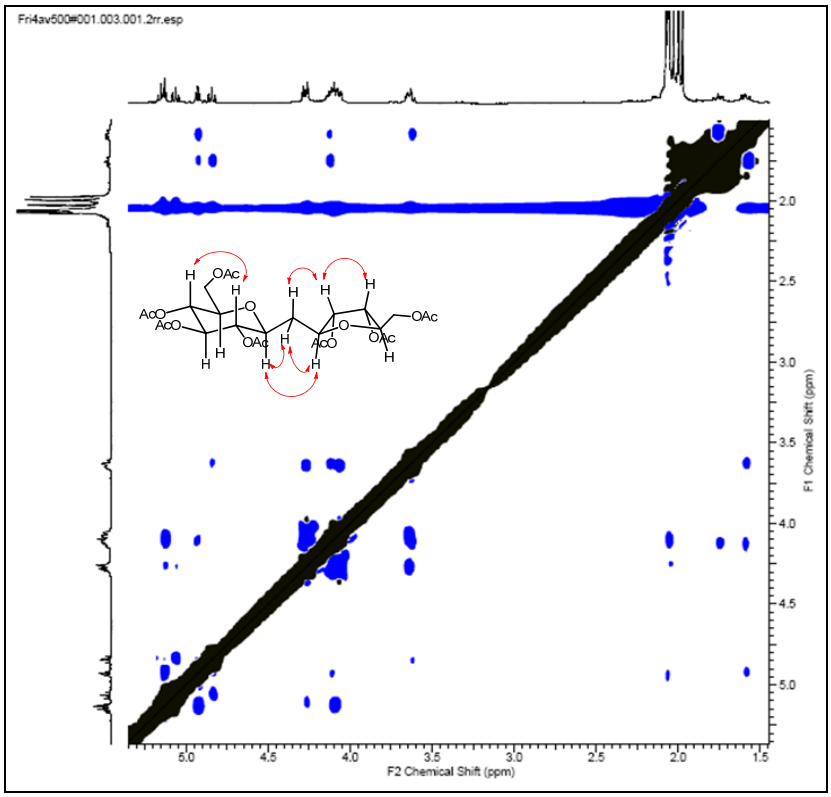
^{1}H NMR of compound 66



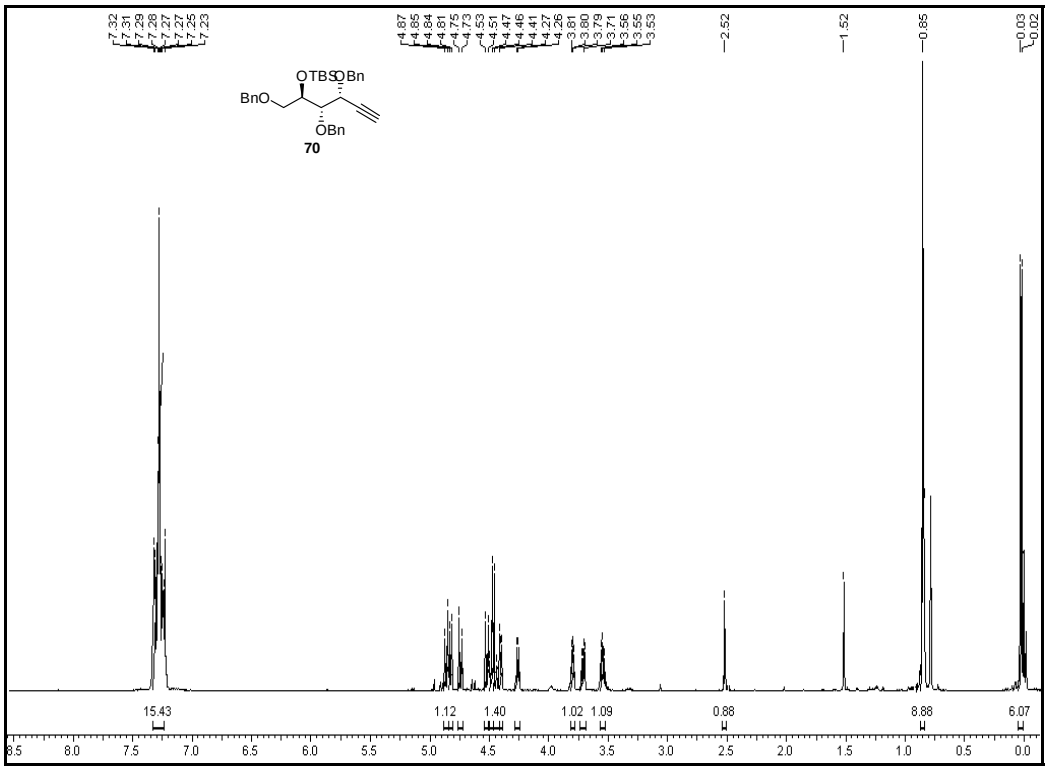
^{13}C NMR of compound 66



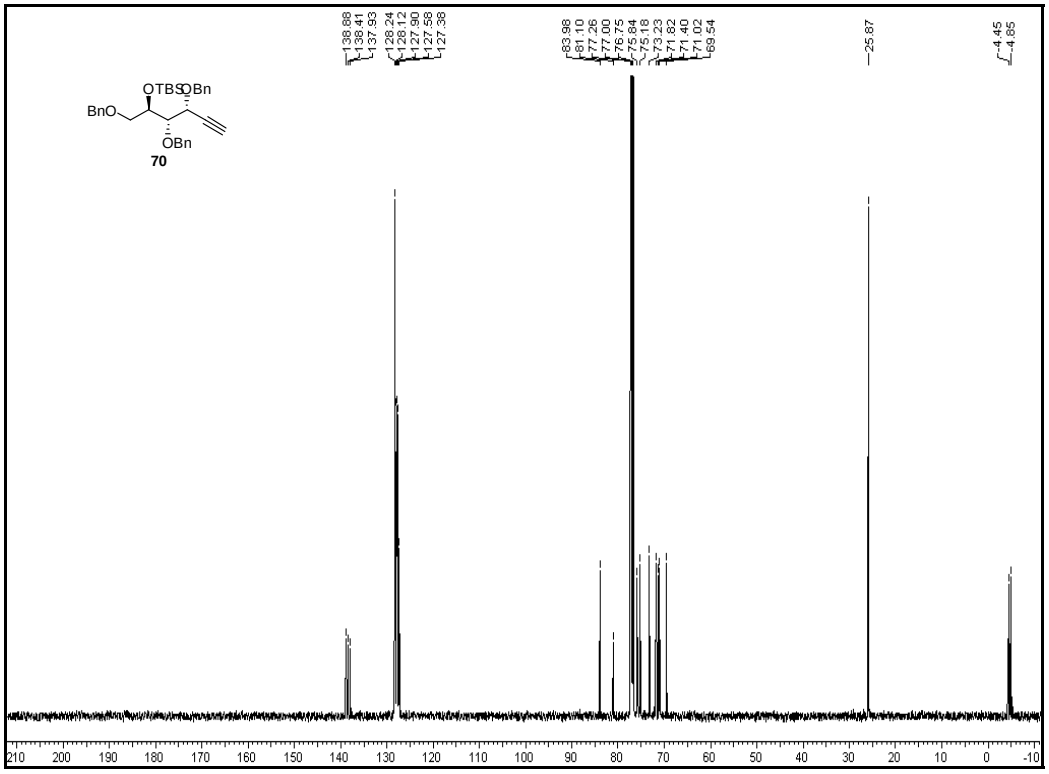
COSY of compound 66



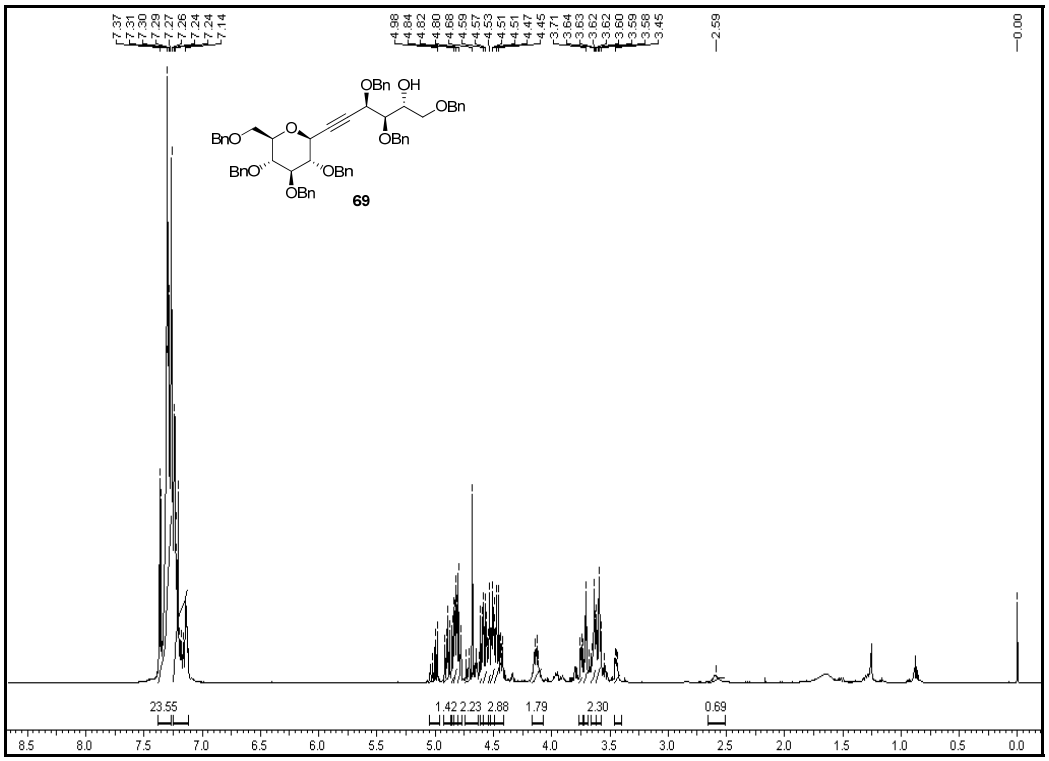
NOESY of compound 66



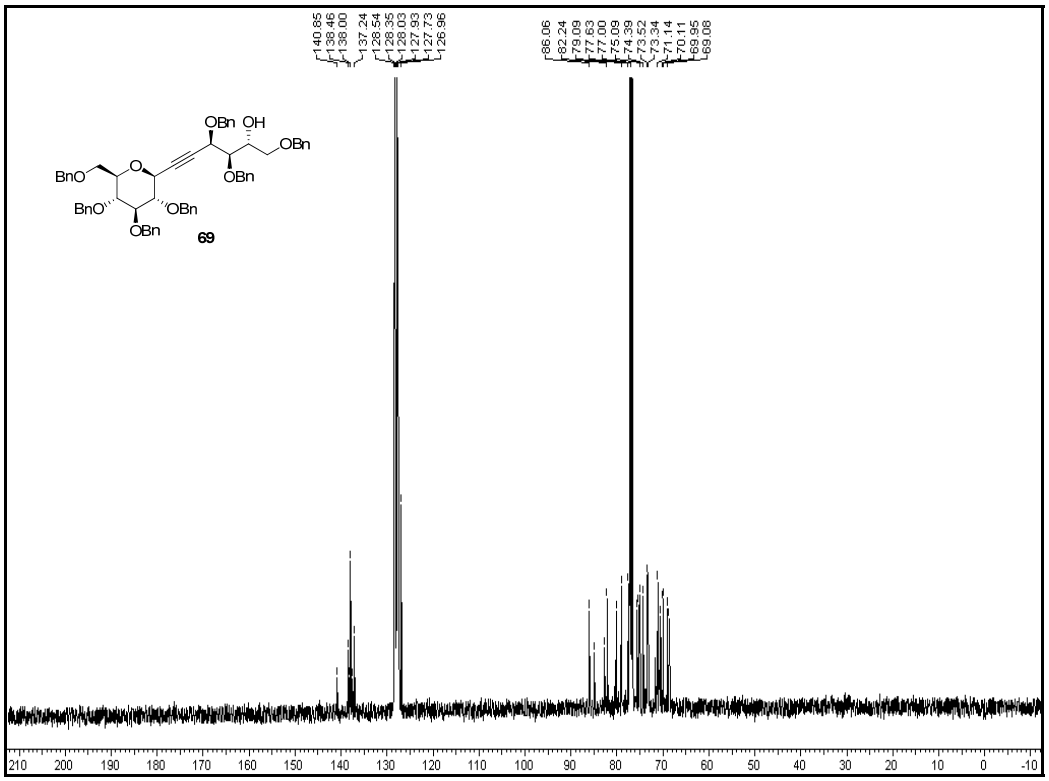
^{1}H NMR of compound 70



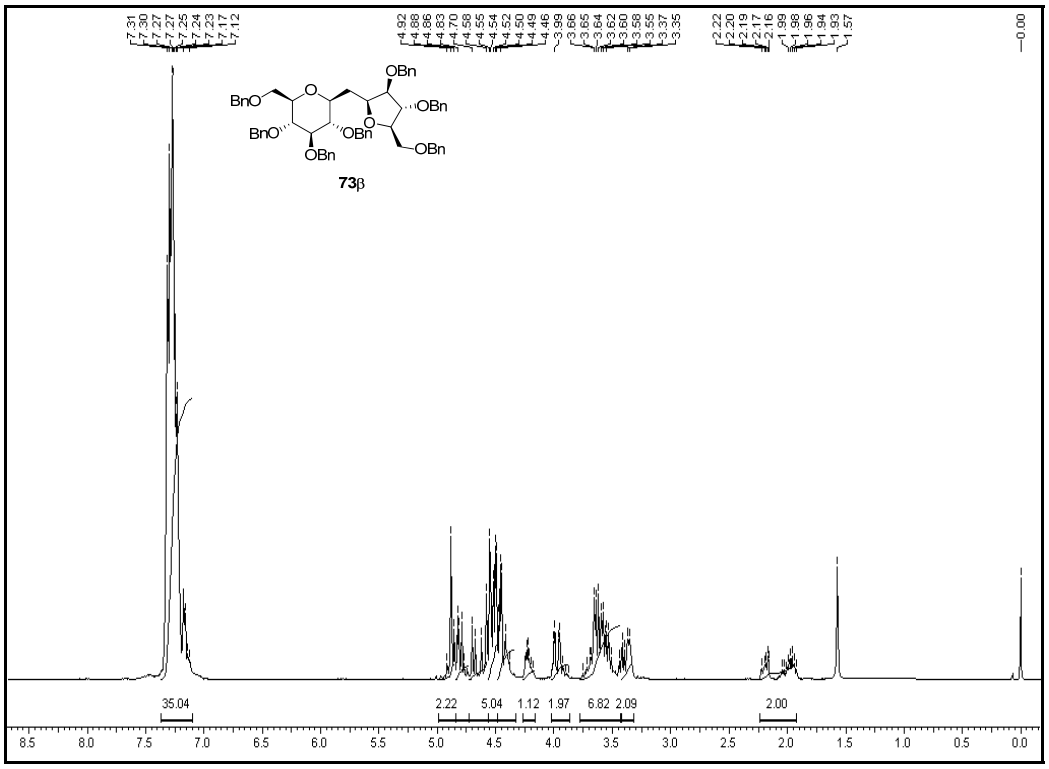
^{13}C NMR of compound 70



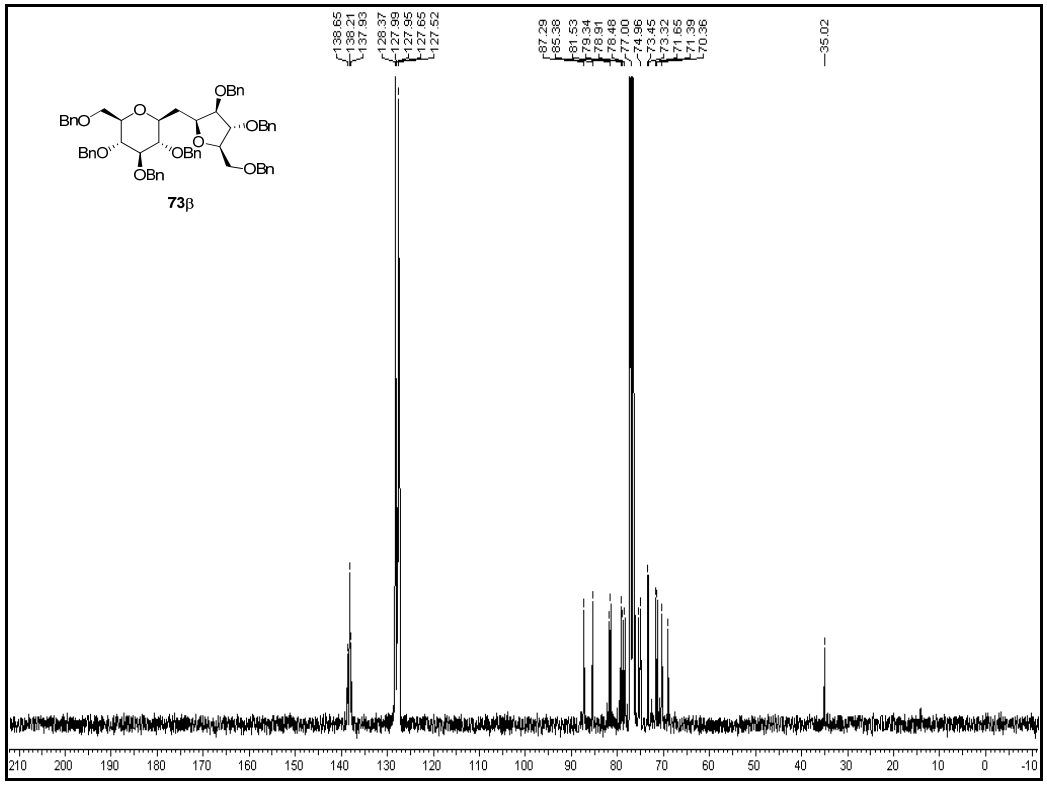
^{1}H NMR of compound 69



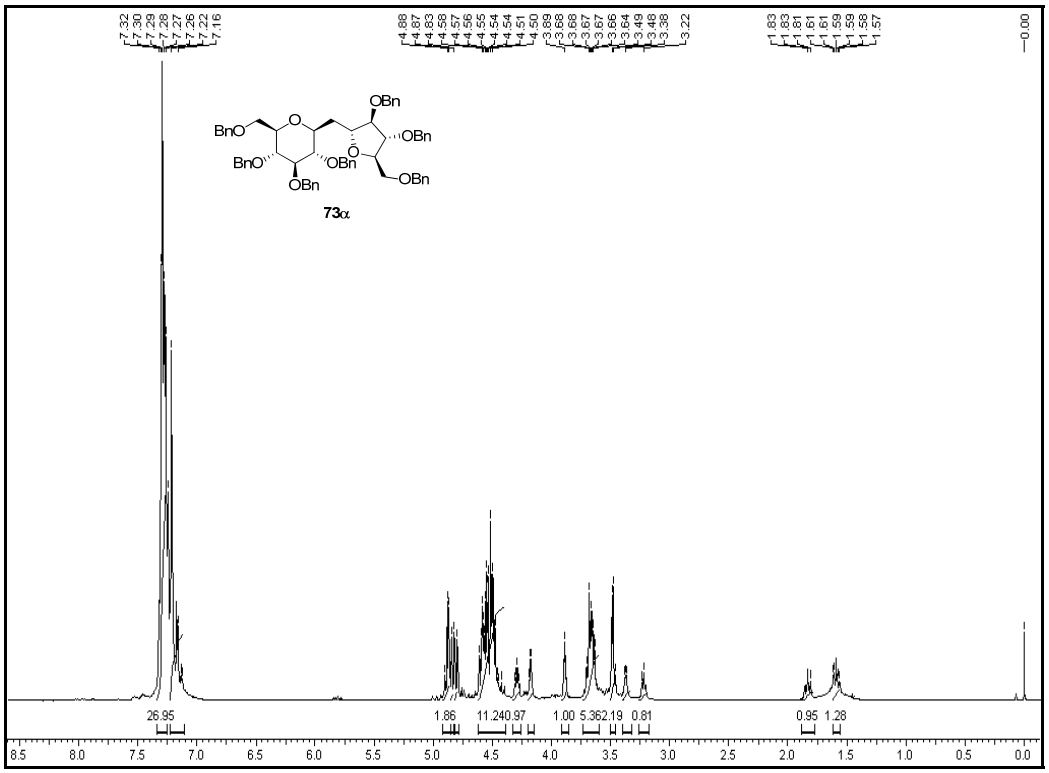
^{13}C NMR of compound 69



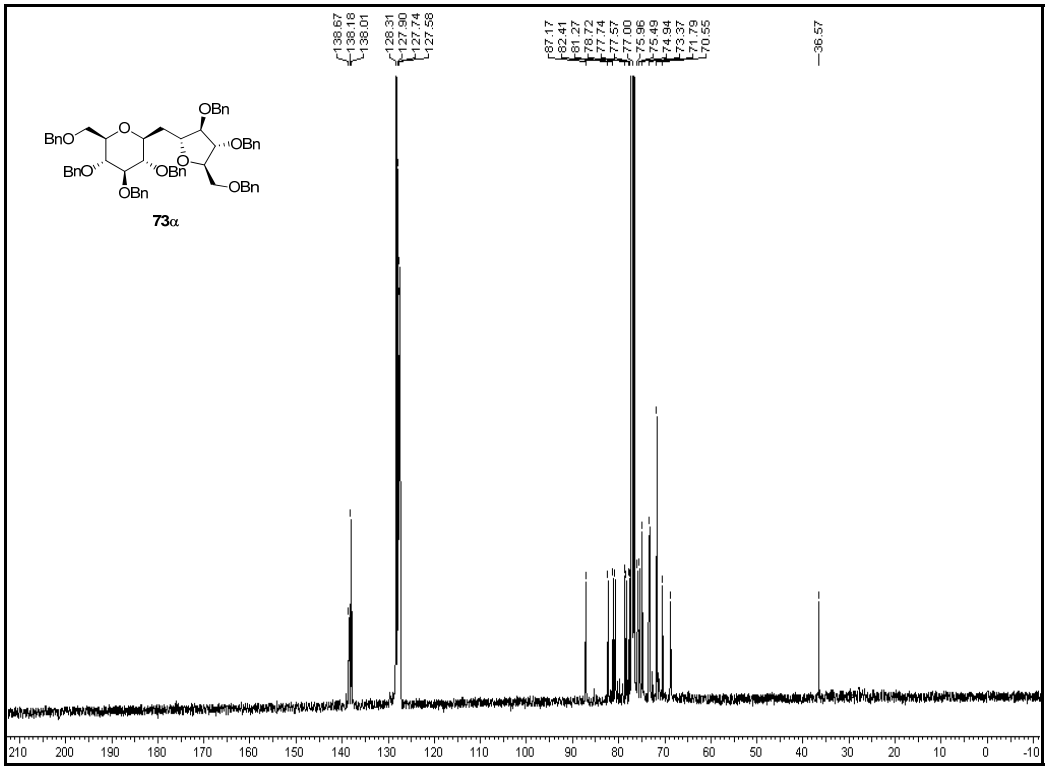
^{1}H NMR of compound 73β



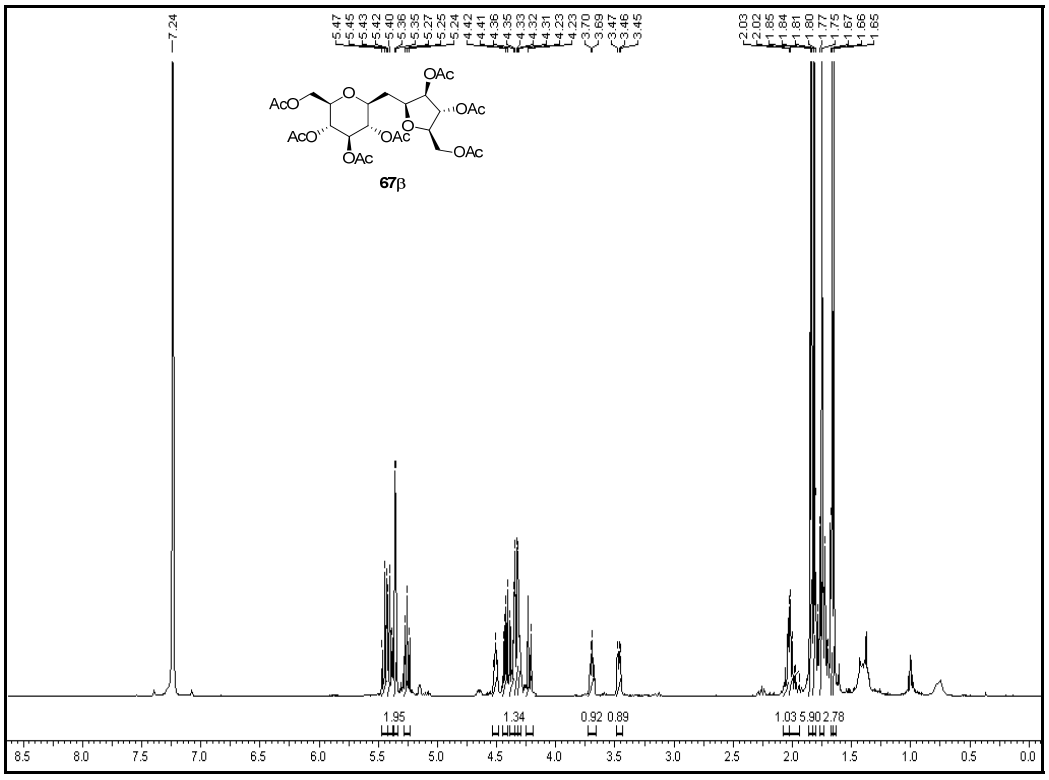
^{13}C NMR of compound 73β



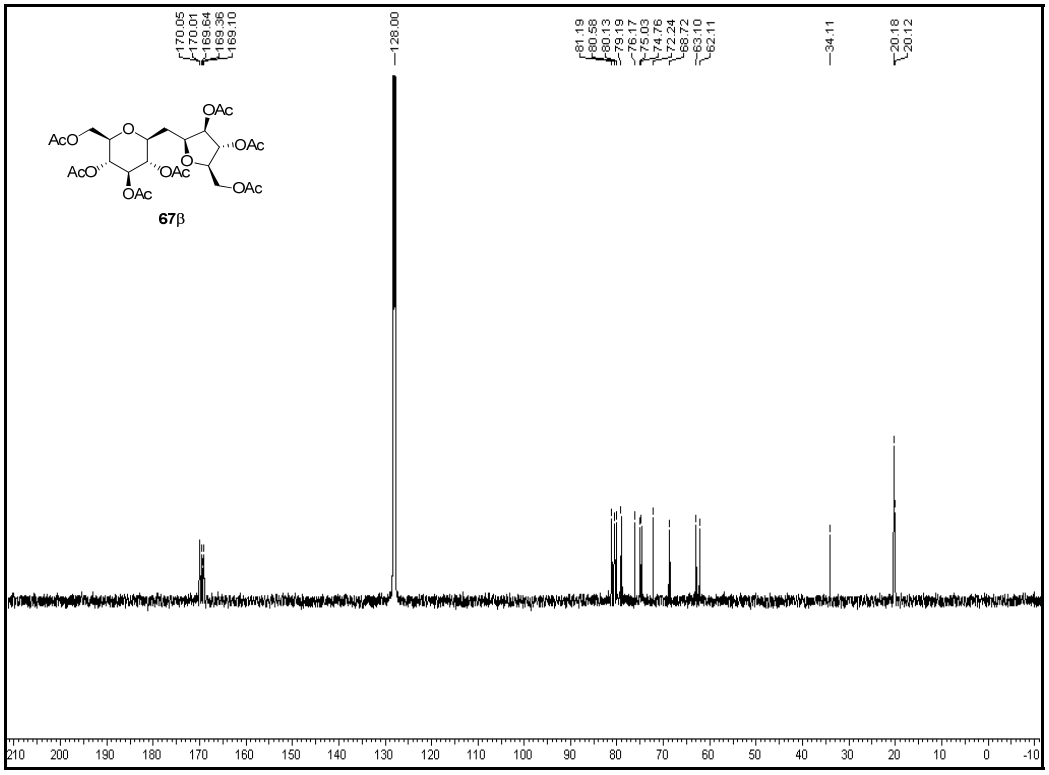
^{1}H NMR of compound 73α



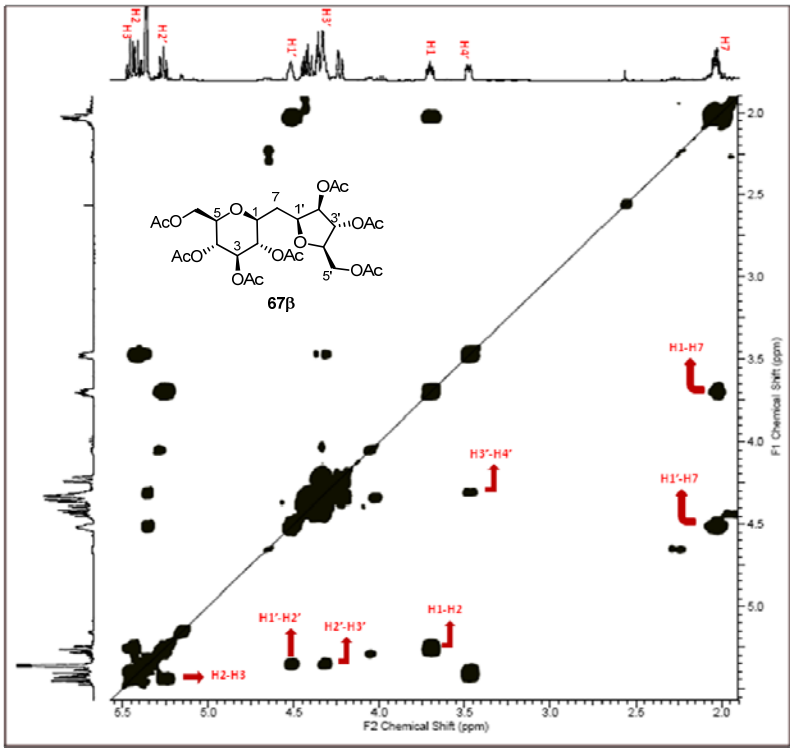
^{13}C NMR of compound 73α



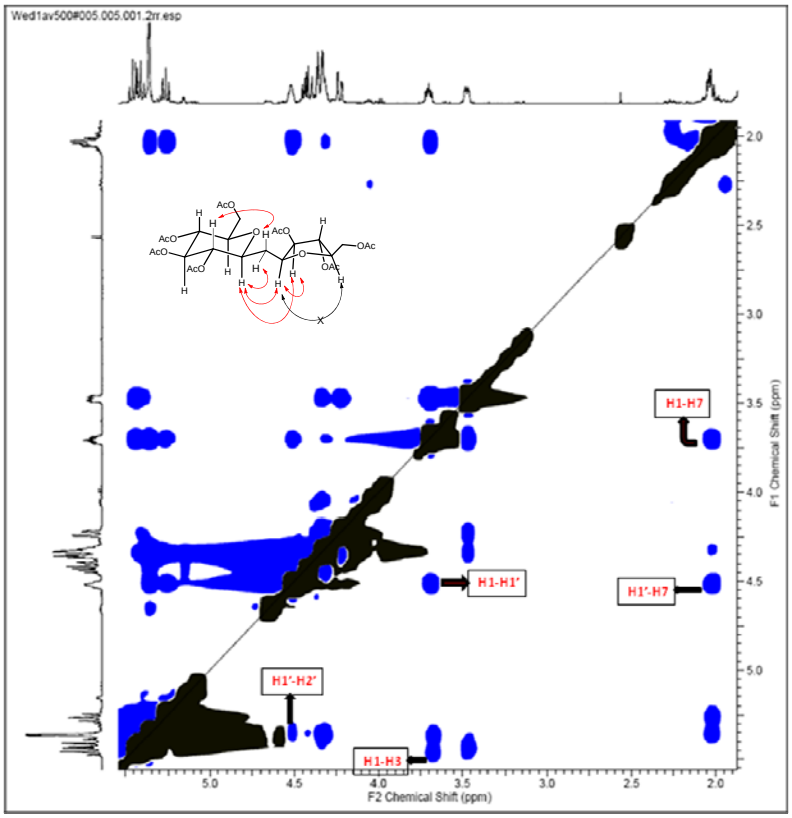
^{1}H NMR of compound 67β



^{13}C NMR of compound 67β



COSY of compound 67β



NOESY of compound 67β

References

1. a) Japp, F. R.; Maitland, W. *J. Chem. Soc. Trans.* **1904**, *85*, 1473–1489; b) Clarke, P. A.; Martin, W. H. C. *Tetrahedron* **2005**, *61*, 5433–5438.

2. a) Petasis, N. A.; Lu, S. P. *Tetrahedron Lett.* **1996**, *37*, 141–144; b) Wang, Z. In *Comprehensive Organic Name Reactions and Reagents*; John Wiley & Sons, Inc., 2010.

3. Liu, F.; Loh, T. P. *Org. Lett.* **2007**, *9*, 2063–2066.

4. Su, Q.; Panek, J. S. *J. Am. Chem. Soc.* **2004**, *126*, 2425–2430.

5. Yakushiji, F.; Maddaluno, J.; Yoshida, M.; Shishido, K. *Tetrahedron Lett.* **2009**, *50*, 1504–1506.

6. Wang, B.; Hansen, T. M.; Wang, T.; Wu, D.; Weyer, L.; Ying, L.; Engler, M. M.; Sanville, M.; Leitheiser, C.; Christmann, M.; Lu, Y.; Chen, J.; Zunker, N.; Cink, R. D.; Ahmed, F.; Lee, C.-S.; Forsyth, C. J. *J. Am. Chem. Soc.* **2011**, *133*, 1484–1505.

7. Van Orden, L. J.; Patterson, B. D.; Rychnovsky, S. D. *J. Org. Chem.* **2007**, *72*, 5784–5793.

8. a) Crimmins, M. T.; Martin, T. J.; Martinot, T. A. *Org. Lett.* **2010**, *12*, 3890–3893; b) Scott, R. W.; Mazzetti, C.; Simpson, T. J.; Willis, C. L. *Chem. Commun.* **2012**, *48*, 2639–2641.

9. Kuntiyong, P.; Lee, T. H.; Kranemann, C. L.; White, J. D. *Org. Biomol. Chem.* **2012**, *10*, 7884–7899.

10. Guerinot, A.; Serra-Muns, A.; Gnamm, C.; Bensoussan, C.; Reymond, S.; Cossy, J. *Org. Lett.* **2010**, *12*, 1808–1811.

11. Trost, B. M.; Dong, G. *Nature* **2008**, *456*, 485–488.

12. a) Uenishi, J. i.; Vikhe, Y. S.; Kawai, N. *Chem. Asian J.* **2008**, *3*, 473–484; b) Aponick, A.; Biannic, B. *Org. Lett.* **2011**, *13*, 1330–1333.

13. Fukatsu, T.; Onodera, K.; Ohta, Y.; Oba, Y.; Nakamura, H.; Shintani, T.; Yoshioka, Y.; Okamoto, T.; ten Lohuis, M.; Miller, D. J.; Kawachi, M.; Ojika, M. *J. Nat. Prod.* **2007**, *70*, 407–411.

14. a) Nakamura, H.; Asari, T.; Ohizumi, Y.; Kobayashi, J.; Yamasu, T.; Murai, A. *Toxicon* **1993**, *31*, 371–376; b) Nakamura, H.; Asari, T.; Murai, A.; Kan, Y.; Kondo, T.; Yoshida, K.; Ohizumi, Y. *J. Am. Chem. Soc.* **1995**, *117*, 550–551; c) Nakamura, H.; Asari, T.; Fujimaki, K.; Maruyama, K.; Murai, A.; Ohizumi, Y.; Kan, Y. *Tetrahedron Lett.* **1995**, *36*, 7255–7258; d) Moriya, T.; Ishida, Y.; Nakamura, H.; Asari, T.; Murai, A.; Ohizumi, Y. *Eur. J. Pharmacol.* **1998**, *350*, 59–65.

15. a) Onodera, K.; Nakamura, H.; Oba, Y.; Ojika, M. *Tetrahedron* **2003**, *59*, 1067–1071; b) Onodera, K. I.; Nakamura, H.; Oba, Y.; Ojika, M. *Biosci. Biotechnol., Biochem.* **2004**, *68*, 955–958; c) Onodera, K.; Nakamura, H.; Oba, Y.; Ohizumi, Y.; Ojika, M. *J. Am. Chem. Soc.* **2005**, *127*, 10406–10411.

16. a) Carlos, A. A.; Baillie, B. K.; Kawachi, M.; Maruyama, T. *J. Phycol.* **1999**, *35*, 1054–1062; b) Baillie, B. K.; Belda-Baillie, C. A.; Maruyama, T. *J. Phycol.* **2000**, *36*, 1153–1161.

17. Nakamura, M.; Kakuda, T.; Qi, J. H.; Hirata, M.; Shintani, T.; Yoshioka, Y.; Okamoto, T.; Oba, Y.; Nakamura, H.; Ojika, M. *Biosci. Biotechnol., Biochem.* **2005**, *69*, 1749–1752.

18. Ojika, M.; Suzuki, Y.; Tsukamoto, A.; Sakagami, Y.; Fudou, R.; Yoshimura, T.; Yamanaka, S. *J. Antibiot.* **1998**, *51*, 275–281.

19. a) Ramana, C. V.; Patel, P.; Gonnade, R. G. *Tetrahedron Lett.* **2007**, *48*, 4771–4774; b) Ramana, C. V.; Mallik, R.; Gonnade, R. G. *Tetrahedron* **2008**, *64*, 219–233; c) Ramana, C. V.; Induvadana, B. *Tetrahedron Lett.* **2009**, *50*, 271–273; d) Ramana, C. V.; Induvadana, B.; Srinivas, B.; Yadagiri, K.; Deshmukh, M. N.; Gonnade, R. G. *Tetrahedron* **2009**, *65*, 9819–9832; e) Ramana, C. V.; Mallik, R.; Sahoo, G. *Tetrahedron Lett.* **2009**, *50*, 4844–4847; f) Ramana, C. V.; Suryawanshi, S. B.; Gonnade, R. G. *J. Org. Chem.* **2009**, *74*, 2842–2845.

20. Narute, S. B.; Kiran, N. C.; Ramana, C. V. *Org. Biomol. Chem.* **2011**, *9*, 5469–5475.

21. Lewis, M. D.; Cha, J. K.; Kishi, Y. *J. Am. Chem. Soc.* **1982**, *104*, 4976–4978.

22. Asao, N.; Nogami, T.; Takahashi, K.; Yamamoto, Y. *J. Am. Chem. Soc.* **2002**, *124*, 764–765.

23. a) Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734–736; b) Baldwin, J. E.; Thomas, R. C.; Kruse, L. I.; Silberman, L. *J. Org. Chem.* **1977**, *42*, 3846–3852.

24. a) McDonald, F. E.; Connolly, C. B.; Gleason, M. M.; Towne, T. B.; Treiber, K. D. *J. Org. Chem.* **1993**, *58*, 6952–6953; b) McDonald, F. E.; Bowman, J. L. *Tetrahedron Lett.* **1996**, *37*, 4675–4678.

25. Utimoto, K. *Pure Appl. Chem.* **1983**, *55*, 1845–1852.

26. Riediker, M.; Schwartz, J. *J. Am. Chem. Soc.* **1982**, *104*, 5842–5844.

27. Asao, N.; Nogami, T.; Takahashi, K.; Yamamoto, Y. *J. Am. Chem. Soc.* **2002**, *124*, 764–765.

28. a) Postema, M. H. D.; Calimonte, D. *In Glycochemistry Principles, Synthesis and Applications;* Bertozzi, C., Wang, P. G., Eds.; Marcel Dekker: *New York* **2000**, 77–131; b) Du, Y.; Linhardt, R. J.; Vlahov, I. R. *Tetrahedron* **1998**, *54*, 9913–9959; c) Beau, J. M.; Gallagher, T. In *Glycoscience Synthesis of Substrate Analogs and Mimetics* **1997**, pp. 1–54.

29. Bertozzi, C.; Bednarski, M. in *Modern Methods in Carbohydrate Synthesis; Khan, S. H., O'Neil, R. A. O., Eds.; Harwood Academic Publishers: Amsterdam* **1996**, 316–351.

30. Truscheit, E.; Frommer, W.; Junge, B.; Müller, L.; Schmidt, D. D.; Wingender, W. *Angew. Chem. Int. Ed.* **1981**, *20*, 744–761.

31. a) Truscheit, E.; Hillebrand, I.; Junge, B.; Muller, L.; Puls, W.; Schmidt, D. *Prog. Clin. Biochem. Med.* **1988**, 17–99; b) Groopman, J. E. *Rev. Infect. Dis.* **1990**, *12*, 908–911; c) Zitzmann, N.; Mehta, A. S.; Carroue, S.; Butters, T. D.; Platt, F. M.;

McCauley, J.; Blumberg, B. S.; Dwek, R. A.; Block, T. M. *Proc. Nat. Acad. Sci.* **1999**, *96*, 11878–11882.

32. Rouzaud, D.; Sinay, P. *J. Chem. Soc. Chem. Comm.* **1983**, 1353–1354.

33. a) Yuan, W.; Babirad, S. A.; Kishi, Y. *J. Org. Chem.* **1992**, *57*, 468–481; b) Postema, M. H. D.; Calimente, D.; Liu, L.; Behrmann, T. L. *J. Org. Chem.* **2000**, *65*, 6061–6068; c) Wan, Q.; Lubineau, A.; Guillot, R.; Scherrmann, M. C. *Carbohydr. Res.* **2008**, *343*, 1754–1765.

34. a) Griffin, F. K.; Paterson, D. E.; Taylor, R. J. K. *Angew. Chem. Int. Ed.* **1999**, *38*, 2939–2942; b) Martin, O. R.; Lai, W. *J. Org. Chem.* **1993**, *58*, 176–185.

35. Aslam, T.; Fuchs, M. G. G.; Le Formal, A.; Wightman, R. H. *Tetrahedron Lett.* **2005**, *46*, 3249–3252.

CHAPTER-III

Synthesis of C-glycosyl analogues of β-DPA as novel antitubercular agents

Introduction

- **Tuberculosis (TB):**

Tuberculosis is a chronic infection caused by various strains of mycobacteria usually *Mycobacterium tuberculosis* (and occasionally other variants of *Mycobacterium*).[1] It typically attacks the lungs, but other organs of the body can also be attacked.[2] Today, tuberculosis (TB) tends to be concentrated among inner city dwellers, ethnic minorities and recent immigrants from areas of the world where the disease is still common. Alcoholics, who are often malnourished, are at high risk of developing this disease, as are people infected with HIV.[3] It can occur anywhere and no one is exempted from the threat of infection. TB is caused by a germ that is transmitted from person to person by airborne droplets. Usually this infection is passed on as a result of very close contact, so family members of an infected person are endangered if the person continues to live in the same household and has not undergone proper treatment. An individual with active TB coughs or sneezes without covering the mouth and nose, droplets containing the tuberculosis germs are sprayed into the air and if it is inhaled by anyone near the person can also get infected. The vast majority of people who have TB germs in their bodies do not have an active case of the disease. Even if the disease is active, the disease is quite advanced. TB in children often occurs with childhood diseases. A simple skin test is available to detect individuals who have been or are infected with the TB germ. Those who have been infected will have a reaction where the skin becomes swollen. Once infected, most persons will generally test positive for the rest of their lives. A positive reaction to the tuberculin test does not mean the person is ill or contagious to others. It means that the germs causing tuberculosis have been or are present in the body and unless other symptoms are evident, the germs are probably not active. About 5–10% of those without HIV, infected with tuberculosis, develop active disease during their lifetimes.[3] In contrast, 30% of those co-infected with HIV develop active disease.[3]

Based on the part or organ of body infected by *Mycobacterium tuberculosis,* TB is divided into two types.

1) **Pulmonary TB:** If *Mycobacterium tuberculosis* infection occurs in lungs then it is known as Pulmonary TB. The major symptoms of Pulmonary TB include chest pain and a prolonged cough producing sputum. About 25% of people may not have any symptoms (i.e. they remain "asymptomatic").[4] Occasionally, people may cough up blood in small amounts and in very rare cases the infection may erode into the pulmonary artery, resulting in massive bleeding.[3] Tuberculosis may become a chronic illness and cause extensive scarring in the upper lobes of the lungs.

2) **Extrapulmonary TB:** In 15–20% of active cases, the infection spreads outside the respiratory organs, causing other kinds of TB known as extrapulmonary tuberculosis.[5] Extrapulmonary TB occurs more commonly in immunosuppressed persons and young children. In those with HIV, this occurs in more than 50% of cases. Notable extrapulmonary infection sites include the pleura, the central nervous system, the lymphatic system, the genitourinary system and the bones and joints.[6] When infection spreads to the bones, it is also known as "osseous tuberculosis" a form of osteomyelitis. Extrapulmonary TB may co-exist with pulmonary TB as well.

General signs and symptoms of TB (along with prolonged cough producing sputum) include fever, chills, night sweats, loss of appetite, weight loss, fatigue and significant finger clubbing may also occurs.

The World Health Organization (WHO) declared that each year approximately 2 million people die due to tuberculosis. It is estimated that during the years 2002-2020, approximately 1000 million people will be newly infected, over 150 million people will develop disease, and 36 million will die of tuberculosis, if control is not improved.[7] Tuberculosis generally affects the lungs (pulmonary TB) as well as it can also affect other organs (extra pulmonary TB). Robert Koch first time discovered the cause of contagious bacterial infection tuberculosis is *Mycobacterium tuberculosis* on 24 March 1882,[8] who subsequently received the Nobel Prize in medicine for this discovery in 1905; and the bacterium is also known as “Koch bacillus” after this discovery.

- **Treatment of Tuberculosis:**

With proper treatment, the chances of full recovery are good. Although several treatment protocols for active TB are in wide use by specialists[9] and protocols sometimes change due to advances in our understanding of optimal therapy, they generally share three principles:

1. The regimen must include several drugs to which the organisms are susceptible.
2. The patient must take the medication on a regular basis.
3. Therapy must continue for a sufficient time (six to twenty four months).

Also, treatment recommendations are subject to change depending upon both the characteristics of the particular organism being treated and newer advances in therapeutic agents. Thus, consultation on treatment strategies with local public health and infectious disease experts is always advisable.

Isoniazid (INH) is one of the most common drugs used for TB. It is inexpensive, effective and easy to take. It can prevent most cases of TB and when used in conjunction with other drugs, cure most TB. Isoniazid preventive treatment is recommended for individuals who have: 1) close contact with a person with infectious TB; 2) positive tuberculin skin test reaction and an abnormal chest x-ray that suggests inactive TB; 3) a tuberculin skin test that converted from negative to positive within the past two years; 4) a positive skin test reaction and a special medical condition (e.g. AIDS or HIV infection or diabetes) or who are on corticosteroid therapy; 5) a positive skin test reaction, even with none of the above risk factors.

Isoniazid and rifampicin are the keystones of treatment, but because of increasing resistance to them, pyrazinamide and either streptomycin sulfate or ethambutol.HCl is added to regimens. If the patient is unable to take pyrazinamide, a nine-month regimen of isoniazid and rifampin is recommended. Even if susceptibility testing reveals that the patient is infected with an isoniazid-resistant strain, the isoniazid component is continued because some organisms may yet be sensitive. In addition, two drugs to which the organisms are likely to be sensitive also are

incorporated into the regimen. The beginning phase of treatment is crucial for preventing the emergence of drug resistance and ensuring a good outcome. Six months is the minimum acceptable duration of treatment for all adults and children with culture-positive TB.

Now days multiple drug resistant (MDR) and extensively-drug-resistant (XDR) have became a major problem in TB treatment.[10] It has been estimated that one in seven cases of tuberculosis is resistant to drugs that previously cured the disease. Resistance arises when patients fail to complete their drug therapy, lasting six months or longer. The hardiest TB bacteria are allowed to survive as a result and as they multiply, they spread their genes to a new generation of bacteria and to new victims. Drug resistance may be either primary or acquired. Primary resistance occurs in patients who have had no previous antimycobacterial treatment. Acquired resistance occurs in patients who have been treated in the past and it is usually a result of non-adherence to the recommended regimen or incorrect prescribing. The Center for Disease Control and Prevention have initiated the program to prevent further spread of drug-resistant TB, which include increasing use of directly observed therapy (DOT).[10b] At the same time development of new molecules for TB treatment is also on high demand.

- **Development of β-DPA analogues:**

As tuberculosis (TB) remains the most prevalent infectious disease worldwide (especially China and India), resulting in 2.9 million deaths annually,[11] the development of new potent drugs as well as new potent inhibitor for the mycobacterium tuberculosis remains a huge challenge for the scientific community. Among the unusual characteristics of mycobacteria that contribute to their resistance to mainstream antibacterials is an extraordinarily thick and complicated cell wall structure that provides the organism with a great deal of protection from its environment.[12] So it is very important to study the cell-wall structure and the enzymes involved in its biosynthesis.

The cell wall of *M*. tuberculosis differentiates it from prokaryotes and is unique in its own. Intensive efforts from chemical biologists resulted in an almost complete description of cell wall components at the molecular level.[13]

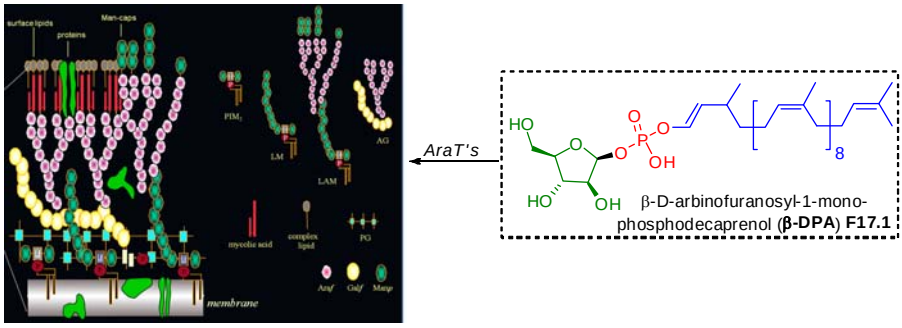


Figure 17. *Chemical structure of β-DPA and cell wall structure of M. tuberculosis*

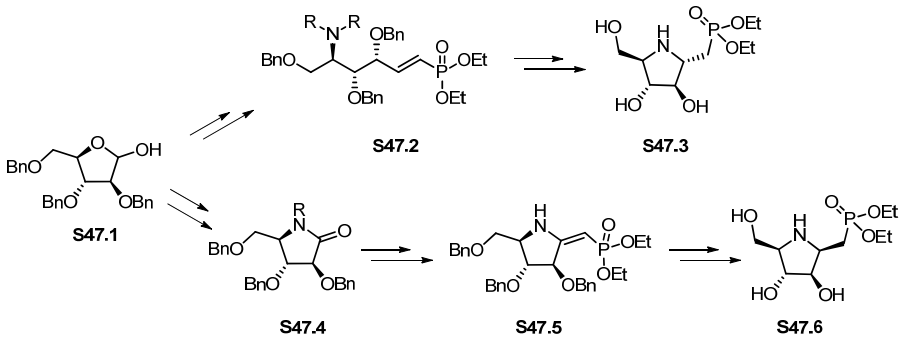
The cell wall is made up of plasma membrane, peptidoglycan, arabinogalactan (AG), lipoarabinomannan (LAM) and mycolic acid esters as major components.[14] Arabinogalactan and lipoarabinomannan are unusual in that all of the arabinose and galactose residues exist in the furanose ring form. Glycoconjugates that contain galactofuranose and arabinofuranose are xenobiotic to mammals and hence, the enzymes that are involved in the biosynthesis of these glycans are ideal targets for drug action.[15] Arabinofuranosyl transferases are the key enzymes involved in the biosynthesis of cell wall arabinan polysaccharides. The β-D-arabinofuranosyl-l-monophosphoryldecaprenol (β-DPA, Figure 17) is an immediate substrate used by these arabinofuranosyl transferases for the synthesis of arabinan polysaccharides.[16] Thus the synthesis of the stable analogues of β–DPA would provide the best strategy for development of potent inhibitors of arabinofuranosyl transferases which lead to inhibit the biosynthesis of either LAM or AG and represents a potentially selective opportunity for therapeutic intervention.

Literature reports:

As synthesis of potent inhibitors of arabinofuranosyl transferases represent the best opportunity for therapeutic inventions, synthetic efforts of scientific community have been extended towards the development of potential analogues of β–DPA.

- **Synthesis of Azasugar-derived phosphonate:**

In 1998 Eustache *et al.*[17] first time reported a short and stereoselective synthesis of new azasugar-derived phosphonates as versatile intermediates for the synthesis of glycosyltransferase inhibitors.

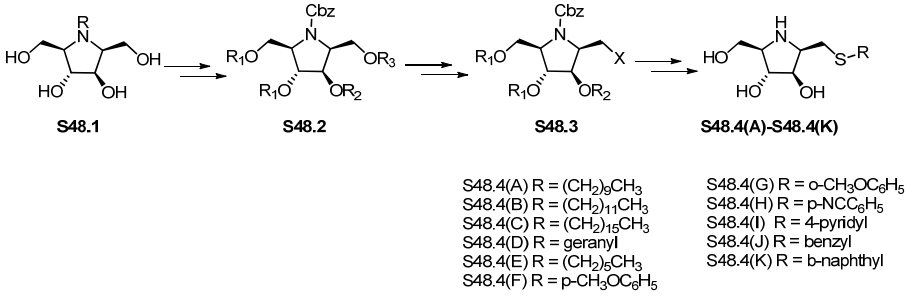


Scheme 47. *Synthesis of azasugar C-phosphate analogues of DPA*

Synthesis of azasugars (**S47.3** and **S47.6**) started from D-arabinose derivative **S47.1**. One carbon Wittig homologation followed by two successive Mitsunobu reactions with *p*-nitro benzoic acid and phthalimide delivered phosphonate **S47.2** which after iodo cyclization and subsequent replacement of iodo with diethyl phosphate and protecting group removal afforded alpha azasugar analogue of α-DPA **S47.3.** The conjugated phophonate **S47.5** was synthesized by addition of diethoxy phosphonomethyl lithium to lactam **S47.4** followed by reduction of resulting hemiketal. Then subsequent reduction of **S47.5** delivered the azasugar analogue of β-DPA **S47.6**.

- **Synthesis of homologated aza-analogues of β–DPA:**

In 1998 Reynold *et al.*[18] have prepared a series of hydrolytically-stable aza analogs of arabinofuranose and evaluated against *Mycobacterium tuberculosis and M. avium*. But most of the compounds displayed little activity in cell culture.



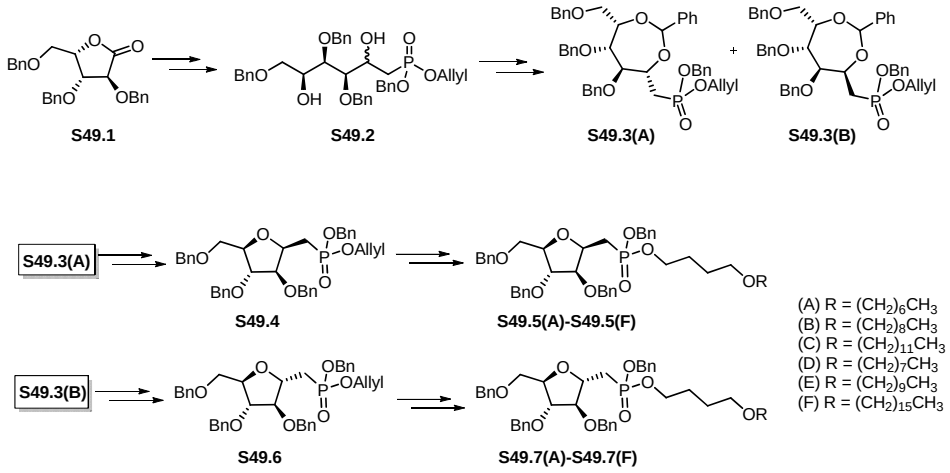
Scheme 48. *Synthesis of homologated aza analogues of DPA*

The protecting group manipulation of pyrrolidine **S48.1** to give **S48.2** followed by selective conversion of primary hydroxyl in iodo to get **S48.3** and

displacement of the iodine with the appropriate sodium salt of an alkyl thiol or a thiophenol followed by the deprotection the N-Cbz and TBS groups furnished azasugar thioethers **S48.4**.

- **Synthesis and evaluation of *C*-phosphonate analogues of DPA:**

Lowary *et al.*[16c] have reported the synthesis of a series of *C*-phosphonate analogues of DPA and evaluated for the antitubercular activity. One of the compounds synthesized by Lowary's group was found to be active with MIC value of 3.13 μg/mL.

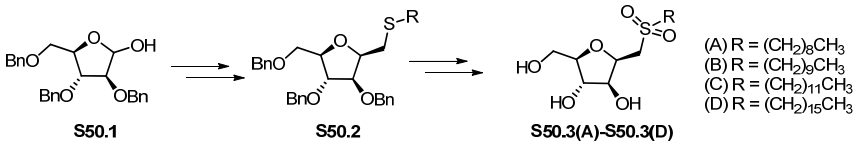


Scheme 49. *Synthesis of C-phosphate analogues of DPA*

The nucleophilic addition of lithiated phosphonate to L-xylofurano lactone **S49.1** followed by reduction of resulting hemiketal afforded diastereomeric diols. These diols were separated as their benzylidene acetals [**S49.3(A)** and **S49.3(B)]** and separately subjected for the acetal deprotection followed by cyclization to afford corresponding *C*-furanoside **S49.4** and **S49.6.** Further, the phosphonate allyl ester were coupled with various alkenes by cross metathesis and then olefin reduction followed by hydrogenolysis delivered desired DPA analogues **S49.5(A)**–**S49.5(F)** and **S49.7(A)**–**S49.7(F)**.

- **Synthesis of sulfone analogues of β-DPA:**

In 2004, Lowary *et al.*[19] reported the synthesis *C*-sulfone analogues of β-DPA and tested against in vitro against *Mycobacterium tuberculosis* strain H37Rv.

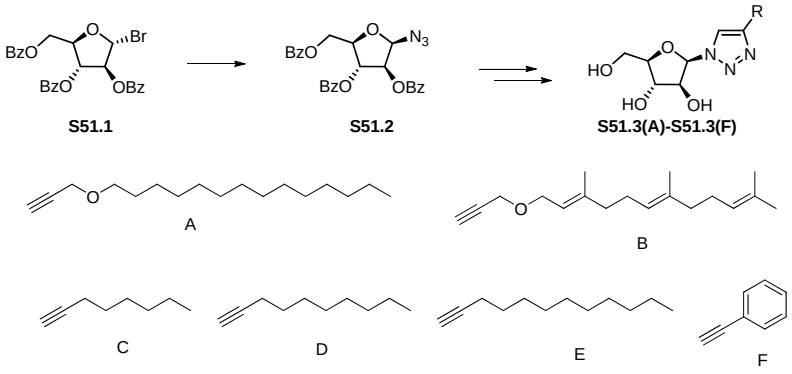


Scheme 50. *Synthesis of C-sulfone analogues of β-DPA*

The D-arabinose derivative **S50.1** was transformed to iododerivative which after nucleophilic displacement with potassium thioaetate, then reduction followed by alkylation of resulting thiol delivered **S50.2**. Oxidation of thiol followed by benzyl group deprotection delivered the sulfone analogues of β-DPA **S50.3(A)**–**S50.3(D)**. The screening of these analogues for antitubercular activity revealed the low to modest activity of these compounds.

- **Synthesis of arabino triazolyl analogues of β-DPA:**

Fairbanks *et al*. in 2008[20] reported the synthesis and biological evaluation of the some arabino triazolyl analogues of β-DPA. Biological testing of these analogues against *Mycobacterium bovis* BCG revealed low to moderate anti-mycobacterial activity



Scheme 51. *Synthesis of triazolyl analogues of β-DPA*

The arabinofuranosyl azide **S51.2** was synthesized from the corresponding bromo derivative **S51.1** using sodium azide. The treatment of this azide **S5.2** with various alkynes under click conditions followed by complete benzyl group deprotection delivered the arabino triazolyl analogues of β-DPA **S51.3(A)** to **S51.3(F)** showing low to moderate antitubercular activity.

In literature, till date, very few efforts have been taken for the synthesis and biological evaluation of various α and β–DPA analogues. Except one or two analogues, all were found to be either inactive or very less active. Some triazolyl analogues showed moderate activity but not good. The moderate activity of these triazole containing analogues was may be because of the enzymatic hydrolysis of the glycosidic C–N bond. If this was the case, then insertion of methylene group in between carbon and nitrogen would expect to increase the stability against enzymatic hydrolysis which may results in the improvement of activity of such triazolyl analogues. With this idea in mind and our interest toward the synthesis of *C*-glycosides, a project for synthesis and evaluation of *C*-glycosyl analogues of β–DPA has been planned.

Results and discussion

The cell wall components of *Mycobacterium tuberculosis* and other mycobacterial species are characterized by the presence of arabinogalactan (AG) and lipoarabinomannan (LAM) polysaccharides consisting of D-arabinose and D-galactose in their furanose form.[14] Since its absence in mammalian cells, combined with the fact that the well known antitubercular drug ethambutanol inhibits arabinofuranosyl transferases (AraT's),[21] the biosynthesis and activation of D-arabinose represents excellent potential sites for drug intervention. Arabinofuranosyl transferases are the key enzymes involved in the biosynthesis of cell wall arabinan polysaccharides[22] using β-D-arabinofuranosyl-l-monophosphoryldecaprenol (β-DPA) as an immediate substrate for arabinan polysaccharide synthesis and is an active starting point for the design and synthesis of substrates that are potential substrates for the AraT's. Thus, the structure of the β-DPA has attracted various groups towards developing new methods for the synthesis of long chain alkyl tethered arabinofuranosides and their evaluation as inhibitors of AraT's.

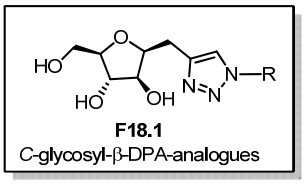


Figure 18. *Basic design for β-DPA analogues*

In literature, the synthesis and biological evaluation of some arabino glycosyl triazoles as β-DPA analogues has been reported,[20] where the antitubercular activity of these analogues were found to be in the range of low to moderate. The enzymatic hydrolysis of the anomeric C−N bond may be one of the most logical reasons for lower activity of these candidates. As shown in Figure 18, dealing with a program to develop new inhibitors for the arabinofuranosyl transferases, the compounds having the structure **F18.1** have been chosen as stable analogues for β-DPA analogues. The basic idea here is to replace the C−N bond with the C−C bond at the anomeric position, which would be expected to offer the higher stability against the enzymatic hydrolysis and may improve the activity of these newly designed analogues.

Figure 19 reveals the retrosynthetic strategy for the designed β−DPA analogues, where we relied on the [3+2] – alkyne-azide cycloaddition (click) reaction.[23] The β-*C*-propargyl D-arabinofuranosides **74** was identified as a key precursor for the azide-alkyne cycloaddition reaction. We have also realized that the known β-*C*-allyl-D-arabinofuranoside **75** having the terminal olefin can also act as an important intermediate for the synthesis of other types of *C*-arabinosides.

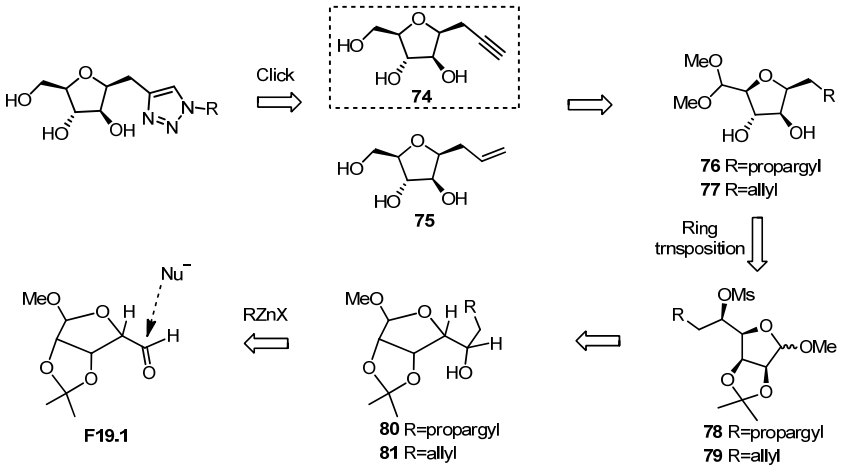
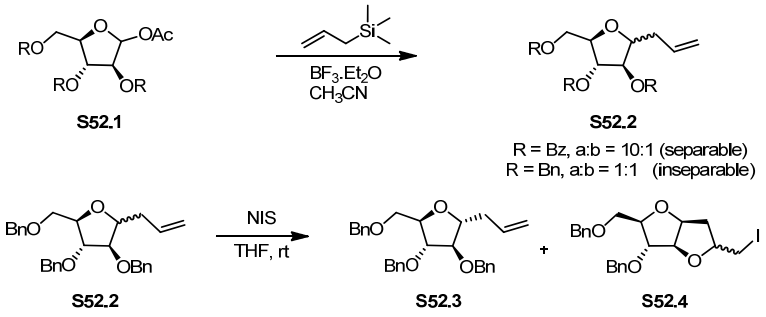


Figure 19. *Retrosynthetic disconnections for β-C-propargyl and β-C-allyl arabinofuranoside*

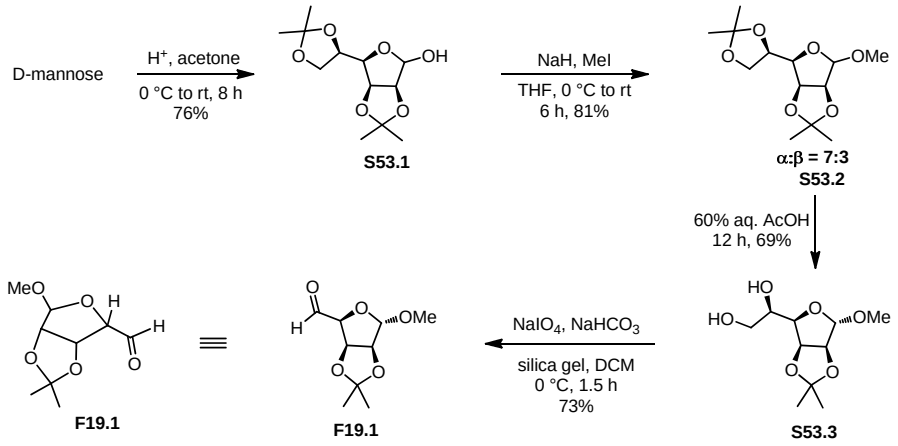
The synthesis of differently protected α- and β-*C*-allylarabinofuranosides has been already well established. In general, *C*-allylarabinofuranosides have been prepared by treatment of a protected arabinofuranoside with allyltrimethylsilane in the presence of a Lewis acid, which resulted either in an inseparable anomeric mixture or exclusively in the α-anomer depending upon the protecting groups employed.[24, 25]



Scheme 52. *Synthesis and separation of C-allyl-D-arabinofuranoside*

The synthesis of either anomer of the *C*-propargyl arabinofuranosides has been not yet documented. Since these derivatives are the key intermediates, their stereoselective preparation is an important synthetic task in our program. This has led us to seek a general route.

Figure 19 reveals our intended approach for the stereoselective synthesis of *C*-β-arabinofuranosides. The synthesis of *C*-arabinofuranosides was based on the stereoselective alkylation of methyl dialdo-D-lyxofuranoside **F19.1**[26] and subsequent acid-mediated ring transposition,[27] with –OMs acting as the handle. Therefore, just by changing the stereochemistry of –OMs group in compounds **78/79**, one can get access to either the α or the β anomer of the *C*-alkyl arabinofuranoside. The stereoselective alkylation[28] of aldehyde **F19.1** was opted for as a suitable transformation for the synthesis of alcohol **80/81** which, after mesylation, could provide the required mesylate **78/79**. The aldehyde **F19.1** could be easily accessed from D-mannose by the usual protection and deprotection techniques.

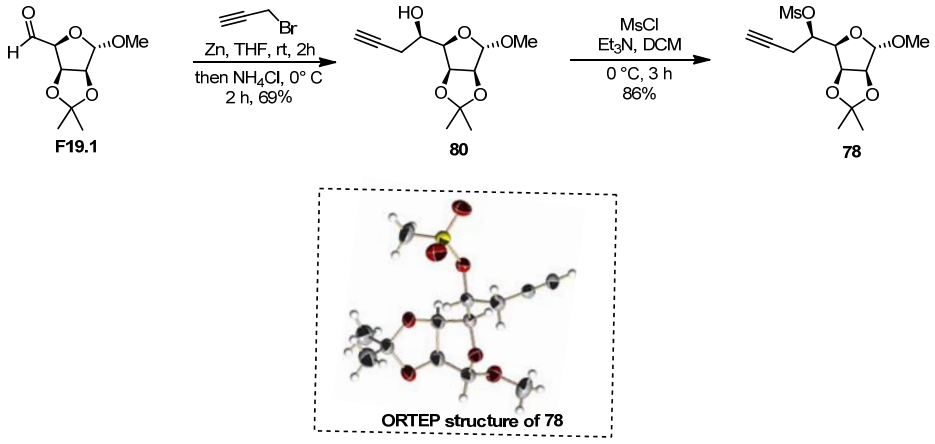


Scheme 53. *Synthesis of methyl dialdo-D-xylofuranoside **F19.1** from D-mannose*

The synthesis of the methyl dialdo-D-lyxofuranoside **F19.1** was began from the D-mannose as shown in Scheme 53. D-mannose, after treatment with acid in anhydrous acetone, delivered the mannose diacetonide **S53.1** in 76% yield. The methylation of the anomeric hydroxyl group was carried out in basic conditions using sodium hydride and methyl iodide in anhydrous DMF to get a separable mixture of compound **S53.2α** and **S53.2β** in 7:3 proportions (81% combined yield). The

anomeric stereochemistry was confirmed on the basis of coupling constants. In the ^{1}H NMR spectrum of **S53.2α** the anomeric proton shows a singlet at 5.07 ppm whereas, the anomeric proton of **S53.2β** shows a doublet at 4.97 ppm with the coupling constant J = 3.6 Hz. The major anomer **S53.2α** was subjected for the selective 5,6-acetonide deprotection using 60% aqueous acetic acid at room temperature. The disappearance of two methyl signals out of four in the ^{1}H NMR spectrum confirmed the acetonide deprotection, which was further supported by ^{13}C and mass spectra. The oxidative cleavage of the resulting diol **S53.3** using sodium periodate ($NaIO_4$) in DCM delivered the required aldehyde **F19.1** (Scheme 53). The crude aldehyde (without further purification) was subjected for the next reaction.

1. Synthesis of β-*C*-propargyl-D-arabinofuranoside 74:



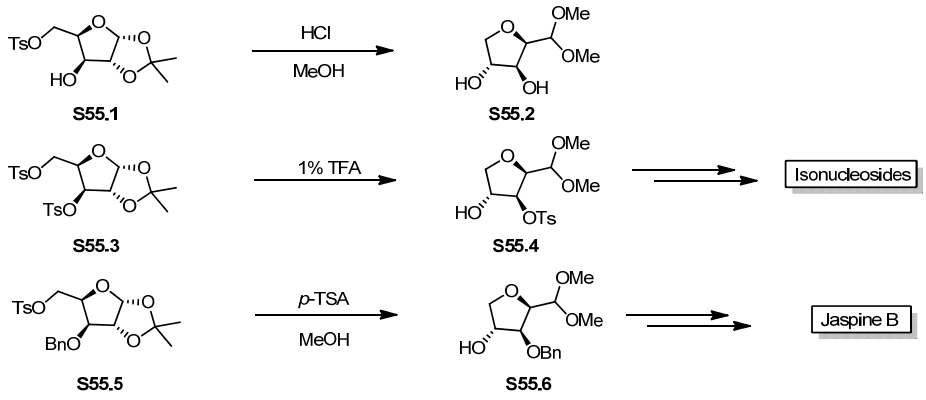
Scheme 54. *Synthesis and single crystal X-ray ORTEP digram of mesylate* ***76***

After successful synthesis of methyl dialdo-D-xylofuranoside **F19.1**, the next target was alkylation of aldehyde under Barbier conditions.[28] The propargylation of aldehyde **F19.1** employing zinc and propargyl bromide in THF delivered the alcohol **80** in 69% yield.[ref] The structure of the alcohol was confirmed with the help of mass spectra and NMR spectral studies. The characteristic signal corresponding to the terminal C–H of alkyne was found to resonated as a triplet with a coupling constant J = 2.7 Hz at 2.06 ppm in the ^{1}H NMR spectrum. The stereochemistry of the newly generated stereocentre was determined after the next step. The mesylation of alcohol **80** using methanesulfonyl chloride and triethylamine in DCM afforded the crystalline

mesylate **78** in good yield (Scheme 54). The structure of **78** was confirmed with the help of ^{1}H NMR (presence of singlet at 3.10 ppm for three protons in addition to singlet at 3.33 for three protons). In order to confirm the stereochemistry of the newly generated center during the Barbier reaction, the single crystal X-ray analysis of compound **78** has been carried out, which indicated the molecular structure of **78** as shown in Figure X, having the R configuration at C(5) center.[29]

- **Literature report for furan ring transposition reaction:**

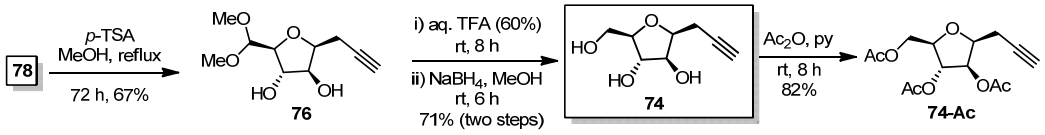
Horton *et al.* (1971) were the first who reported the acid mediated furan ring transposition reaction.[27a] In 1998, Zhang *et al.* used similar kind of transformation for the synthesis of one of the intermediate **S55.4** during the synthesis of isonucleosides.[30] Recently, in 2007, similar methodology has been utilized in our group for preparation of an advanced intermediate **S55.6** for the synthesis of jaspine B.[27c]



Scheme 55. *Acid mediated furan ring transposition reaction*

Having successfully accomplished the synthesis and structural assignment of mesylate **78**, it was subjected for the furan ring transposition to prepare β-*C*-glycoside **76**. After a careful evaluation of various reaction conditions (by varying the acid, temperature and time), the best results for the intended acid-mediated furan ring transposition of **78** were found when 4-toluenesulfonic acid (*p*-TSA) was employed in refluxing methanol for about 72 h. Under these optimized conditions, the ring transposition of **78** afforded the dimethylacetal **76** in 67% yield. The presence of signals corresponding to two methoxy groups (–OMe) at 3.50 and 3.56 ppm and a broad singlet for the –OH groups at 1.70 ppm in ^{1}H NMR spectrum confirmed the

structure of dimethyl acetal **76**. This was further supported by a m/z peak at 239.2 (sodium adduct) in the mass spectrum. The hydrolysis of the acetal group in compound **76** was carried out using 60% aqueous trifluoroacetic acid (TFA) at room temperature to obtain the intermediate aldehyde, which was immediately subjected for the $NaBH_4$ reduction in methanol to afford the required β-*C*-propargyl-D-arabinofuranoside **74**. The structure of the compound **74** was confirmed with the help of NMR and mass spectra. The peak corresponds to the sodium adduct at 195.1 in the mass spectrum and the absence of –OMe signals in the ^{1}H NMR spectrum indicated the formation of the required product. For further characterization, free hydroxyl groups were protected as acetates using acetic anhydride and pyridine to afford the triacetate acetate **74-Ac**. The structure of **74-Ac** was characterized with the help of spectral and analytical data. In the ^{1}H NMR spectrum of compound **74-Ac**, three signals corresponding to acetates were found to resonate at 2.08, 2.09 and 2.12 ppm. The assigned structure was further supported by ^{13}C NMR and mass spectra.

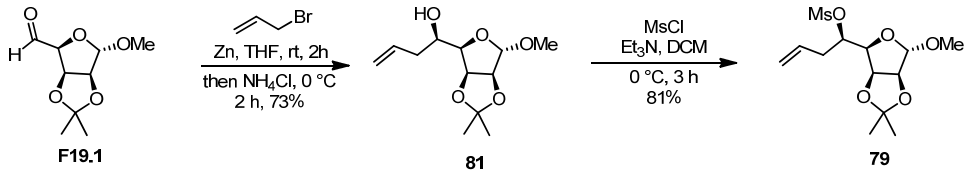


Scheme 56. *Synthesis of β-C-propargyl-D-arabinofuranoside* ***74***

2. Synthesis of β-*C*-allyl-D-arabinofuranoside 75:

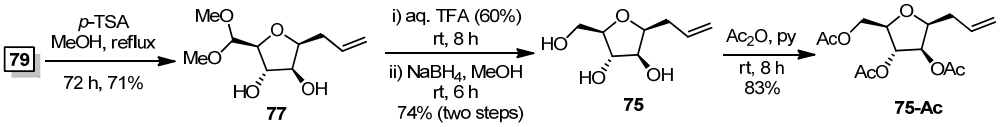
After having established a stereoselective synthesis of β-*C*-propargyl-D-arabinofuranoside, the next eventual target was to extend it for the synthesis of β-*C*-allyl-D-arabinofuranoside **75**. The synthesis of compound **75** was began with the allylation of methyl dialdo-D-lyxofuranoside **F19.1**[31] using allyl bromide and zinc powder in THF to obtain the the alcohol **81** in 73% yield. The presence of a characteristic signal corresponding to internal olefinic C–H as a dddd with coupling constants J = 6.8, 7.7, 10.2, 17.2 Hz at 5.92 ppm in the ^{1}H NMR spectrum and the presence of a triplet at 117.8 and a doublet at 134.3 ppm in the ^{13}C NMR spectrum confirmed the assigned structure of alcohol **81**. The assigned constitution was further supported by a peak of the sodium adduct at 267.3 in the mass spectrum. As was executed earlier with the corresponding propargyl derivative, the free hydroxyl group

in compound **81** was converted to the corresponding –OMs by treatment with methanesulfonyl chloride and triethylamine in DCM at 0 °C to afford the mesylate **79** in 81% yield. The methyl protons of the mesyl group were found to resonate at 3.08 as a singlet in the ^{1}H NMR spectrum of compound **79**. The sodium adduct peak at 345.2 in the mass spectrum was also in support of the assigned structure.



Scheme 57. *Synthesis of mesylate **79** using Barbier reaction*

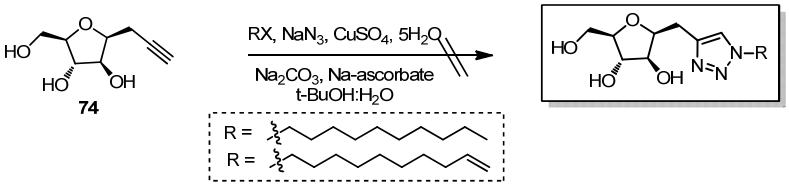
The mesylate **79** was treated with acid under previously standardized conditions i.e. reflux in methanol using 4-toluenesulfonic acid (*p*-TSA) to afford the dimethylacetal **77** in good yield (71%). The structure of the compound **77** was confirmed with the help of NMR and mass studies. In the ^{1}H NMR spectrum, the presence of two methyl groups of acetal as two singlets at 3.48, 3.55 ppm and the absence of two methyl groups of the acetonide unit indicated the formation of dimethylacetal **77**. This assignment was further supported by the peaks in the ^{13}C NMR spectrum, where the –OMe signals were observed at 56.3 and 57.7 ppm. The sodium adduct peak at 241.4 in the mass spectrum has also given support to the assigned structure. The hydrolysis of dimethylacetal **77** using 60% aqueous trifluoroacetic acid (TFA) at room temperature delivered an aldehyde which was reduced immediately by employing sodium borohydride ($NaBH_4$) in methanol at room temperature to afford the β-*C*-allyl-D-arabinifuranoside **75** at 74% yield over two steps. The absence of two methyl singlets in ^{1}H and two quartets in the ^{13}C NMR spectrum confirmed the formation of product **75**. The presence of the sodium adduct peak at 197.4 in the mass spectrum was also in support of the assigned structure. The data was in good agreement with the data reported earlier for this compound.[31] For the purpose of further characterization, the compound **75** was converted to the corresponding acetate **75-Ac**. The structure of the acetate was confirmed with the help of ^{1}H, ^{13}C NMR and mass spectra.



Scheme 58. *Synthesis of β-C-allyl-D-arabinofuranoside*

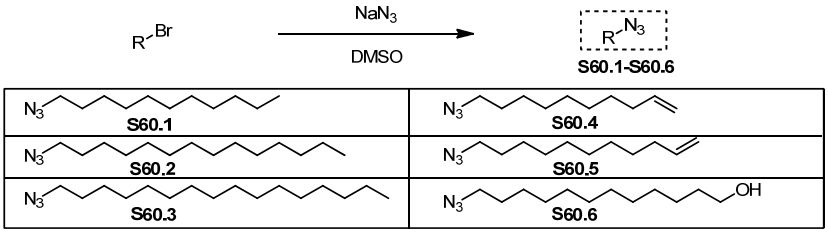
3. Synthesis of *C*-glycosyl analogues of β-DPA 82–92:

After successful synthesis of the β-*C*-propargyl and β-*C*-allyl-D-arabinofuranosides **74** and **75**, the next target was the synthesis of the *C*-glycosyl analogues of β-DPA employing alkyne-azide cycloaddition. Having alkyne fragment ready in hand, the next requirement was the preparation of various alkyl azides necessary for the preparation of different *C*-glycosyl triazoles.



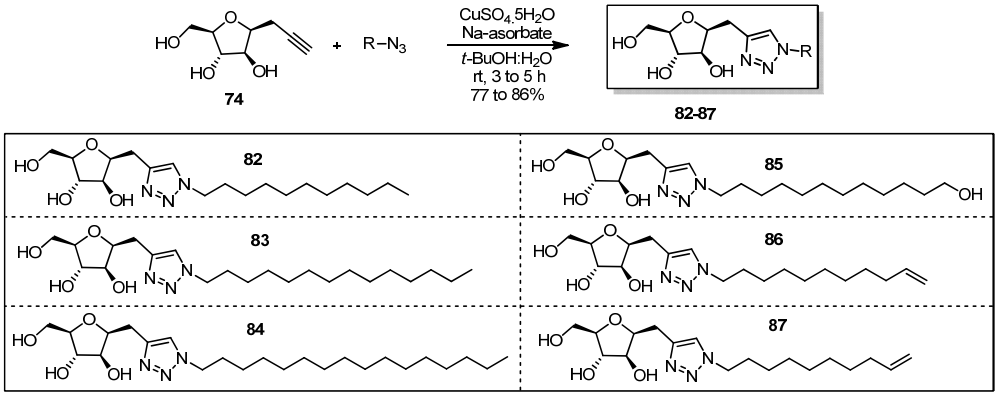
Scheme 59. *One-pot protocol for synthesis of β-DPA analogues*

Initial attempts were focused on optimization of a one pot protocol of azide formation (from corresponding alkyl halide and sodium azide) followed by azide-alkyne cycloaddition (Scheme 59) for the synthesis of different analogues of β-DPA.[32] So, accordingly, the alkyne (β-*C*-propargyl-D-arabinofuranoside) **74** was treated with the alkyl halide (1-bromo-decene) and sodium azide in presence of $CuSO_4.5H_2O$, sodium carbonate, L-proline and sodium ascorbate in a mixture of *t*-BuOH:water (3:1) at room temperature (Scheme 59). However, the reaction did not show the formation of the desired product. Only the starting materials were recovered. The results were found to be consistent at various conditions as well as with different alkyl halides.



Scheme 60. *Synthesis of various alkyl azides*

As this one-pot protocol met with failure at delivering the required transformation, the strategy was revised. Accordingly, the two step process i.e. synthesis of alkyl azides and then azide-alkyne cycloaddition under click conditions was proceeded for. So, according to the new tactics, different alkyl azides were prepared from the corresponding alkyl bromides (Scheme 60) by treatment with sodium azide in anhydrous dimethyl sulfoxide (DMSO) at room temperature. The formation of alkyl azides was confirmed by careful observation of TLC and by observing the characteristic $-N_3$ stretching frequencies in IR spectrums.



Scheme 61. *Synthesis of C-glycosyl analogues of β-DPA via alkyne-azide cycloaddition*

Now, in order to synthesize the *C*-glycosyl analogues of β-DPA, the alkyne as well as alkyl azides were subjected for the azide-alkyne cycloaddition reaction under standard click reaction conditions. Thus treatment of alkyne with alkyl azides in presence of $CuSO_4.5H_2O$ and sodium ascorbate delivered the different triazoles (β-DPA analogues) in good to excellent yield. All the compounds were characterized with the help of ^1H, ^{13}C NMR and mass spectroscopy. All triazoles **82**–**87** showed the 100% sodium adduct peaks in the LCMS spectrum. The presence of characteristic singlet of triazole ring C–*H* was observed in the ^1H NMR spectrum.

4. Biological evaluation of *C*-glycosyl analogues of β-DPA 82–87:

After successful synthesis of the *C*-glycosyl analogues of β-DPA, the next target of the project was the screening of these compounds for antitubercular activity. All the compounds [**82–87**] were subjected for anti-mycobacterial evaluation. The *M. bovis* BCG strain has been used for this purpose and the inhibition studies have been

carried out on the whole cell based HTS assay. The dose dependent inhibitions of M. bovis BCG by all the compounds are carried. The resulting decrease in growth of the organism by compounds was represented as percentage of inhibition of growth in the culture. Figure 3a shows the dose response curve for growth active and **3b** shows dose response curve for NR active of the most active compound **84**.

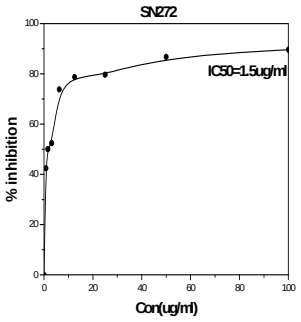


Figure 20a. *Dose response curve for growth active*

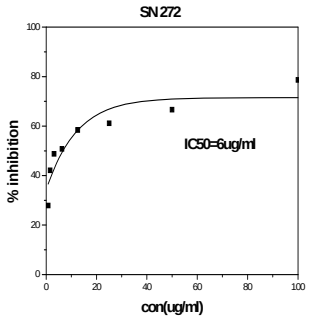
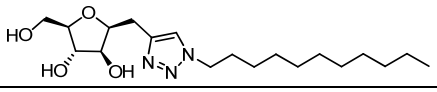
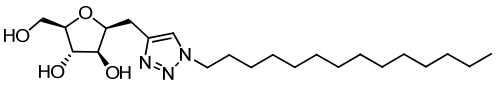
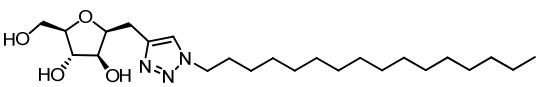
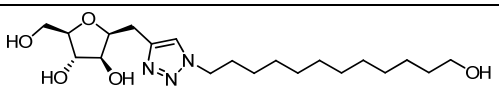
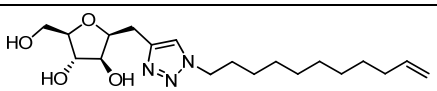
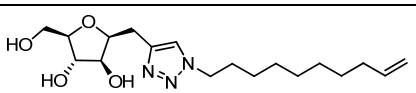


Figure 20b. *Dose response curve for NR active*

In same way, dose response curves are plotted for all compound that have been screened for antitubercular activity and the IC_{50} values obtained from the dose response curves have been presented in Table 3.

Table 3. *IC50 values of compound* ***82–87***

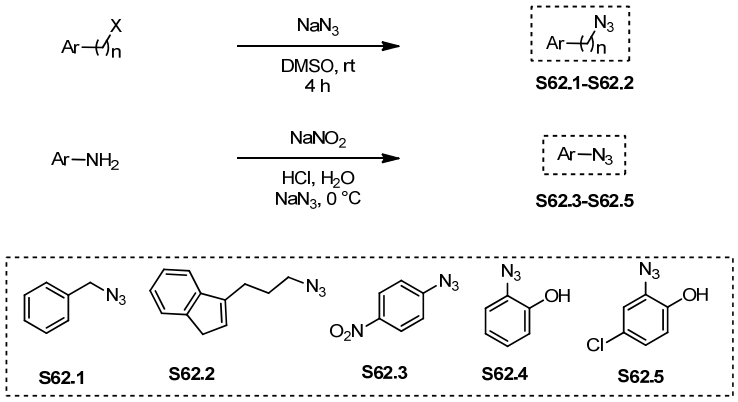
Sr. No.	Comp. No.	Structure	IC50 values μg/ml	
			Growth active	NR active
1	82		72	10
2	83		41	3.5
3	84		6	1.5
4	85		52	3.5
5	86		71	10
6	87		>100	–

The results obtained from these primary studies, it was found that the *C*-glycosyl triazoles (β-DPA analogues) having sixteen carbon hydrophobic side chain is the most active with IC50 = 6 μg/ml (growth active) and 1.5 μg/ml (NR active). These results indicate that, side chain attached to nitrogen atom plays an important role in the antitubercular activity of these compounds.

- **Synthesis of *C*-glycosyl analogues of β-DPA having aromatic side chains:**

After synthesis and evaluation of the *C*-glycosyl analogues **82**–**87** on *M. bovis* BCG strain of *M.* tuberculosis and observation of the primary results obtained from these studies, we were quite excited to see the effect of changing side chains from aliphatic to aromatic groups. In order to check this probability, different aryl azides were prepared from corresponding aryl halides or aryl amines (Scheme 62).

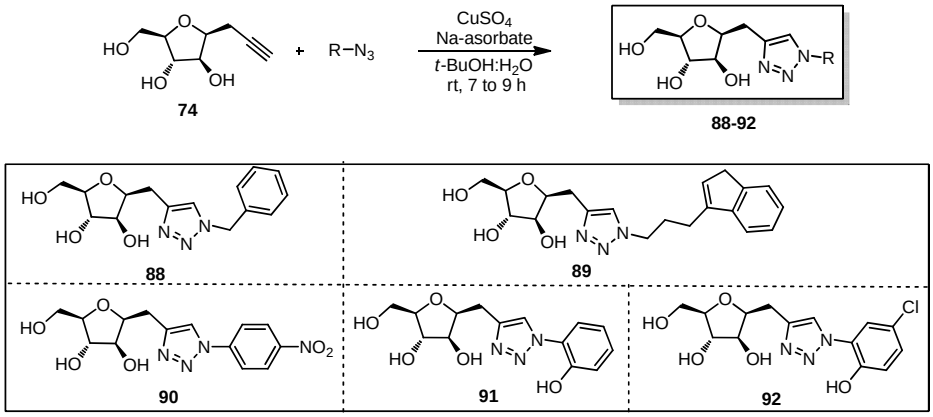
The aryl halides were treated with sodium azide in anhydrous DMSO to afford azide **S62.1** and **S62.2**. The structure of the aryl azide was confirmed by observing the characteristic $-N_3$ stretching frequencies in the IR spectrum. The aryl amines were treated with $NaNO_2$ and HCl in the aqueous medium followed by treatment with sodium azide to get the aryl azides **S62.3**–**S62.5**.



Scheme 62. *Synthesis of aryl azides **S62.1**–**S62.5***

Having different aryl azides in hand, the next eventual goal was to prepare the *C*-glycosyl analogues of β-DPA having the aryl side chains. The alkyne β-*C*-propargyl-D-arabinofuranoside **74** was treated with different aryl azides **S62.1–S62.5**

under previously standardized conditions for azide-alkyne cycloaddition, to afford the *C*-glycosyl analogues **88**–**92**, as shown in Scheme 63.



Scheme 63. *Synthesis of C-glycosyl analogues of β-DPA via alkyne-azide cycloaddition*

- **Biological evaluation of *C*-glycosyl analogues of β-DPA 88–92:**

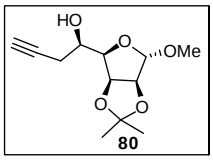
The newly synthesized analogues having aryl side chains **88**–**92** and subjected the same for anti-mycobacterial evaluation. The *M. bovis* BCG strain has been used for this purpose. All these compound **88**–**92** were found to show very poor activity.

5. Conclusion

To conclude, a general and stereoselective approach for the synthesis of β-configured *C*-propargyl and *C*-allyl D-arabinofuranosides was developed from easily available D-mannose through simple synthetic operations and with acid-catalyzed furan ring transposition as the key step. Also we have synthesized a small library of the *C*-glycosyl analogues of β-DPA **82**–**92** as novel antitubercular agents. Primary results of the biological screening of these compounds revealed that the compounds having hydrophobic alkyl side chain shows moderate to good activity whereas compounds having aromatic side chains shows very poor activity which indicates that aliphatic long carbon chain is also one of the structural requirement for the better antitubercular activity.

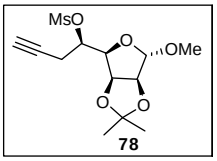
Experimental and data

1. Synthesis of alcohol 80:



To a suspension of activated Zn dust (0.58 g, 8.8 mmol) in THF (20 mL) was added a solution of propargyl bromide (1.05 g, 8.8 mmol) in THF (5 mL). The mixture was allowed to stir at room temperature for 1 h. Then to this a solution of aldehyde **F19.1** (1.7 g, 8.8 mmol) in THF (10 mL) was added dropwise. After complete addition the reaction mixture was allowed to stir at room temperature for 12 h, quenched with sat. NH_4Cl (24 mL) at 0 °C to 5 °C and again stirred at room temperature for 1 h. The mixture was partitioned between EtOAc and H_2O. The organic layer was washed with water, brine, dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was purified by column chromatography (230–400 mesh silica gel, 1:4 ethyl acetate/petroleum ether) to afford **80** (1.40 g, 69%) as colorless gum. *Characterization data of compound **80***: $[\alpha]_D^{25}$ +71.6 (*c* 1, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): δ 1.31 (s, 3H), 1.46 (s, 3H), 2.06 (t, *J* = 2.7 Hz, 1H), 2.55 (ddd, *J* = 2.7, 6.2, 16.9 Hz, 1H), 2.65 (br d, *J* = 5.7 Hz, 1H), 2.85 (ddd, *J* = 2.7, 4.7, 16.9 Hz, 1H), 3.31 (s, 3H), 3.95 (dd, *J* = 3.6, 7.9 Hz, 1H), 4.02–4.17 (m, 1H), 4.56 (d, *J* = 5.9 Hz, 1H), 4.85 (dd, *J* = 3.6, 5.9 Hz, 1H), 4.89 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 25.0 (t), 25.2 (q), 26.5 (q), 55.0 (q), 68.5 (d), 71.3 (d), 80.4 (d), 80.9 (s), 81.0 (d), 85.5 (d), 107.5 (d), 113.3 (s); MS (ESI): calcd for $C_{12}H_{18}O_5$ $([M+Na])^+$ 265.2, found 265.1; Anal. calcd for $C_{12}H_{18}O_5$: C, 59.49; H, 7.49; found C, 59.76; H, 7.37.

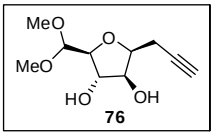
2. Synthesis of mesylate 78:



At 0 °C, a solution of **80** (1.2 g, 4.9 mmol) and triethylamine (1.58 mL, 11.3 mmol) in anhydrous DCM (15 mL) was treated with methane sulfonyl chloride (0.52 g, 6.7 mmol) and then stirred at room temperature for 1 h. After consumption of starting material on TLC, reaction mixture was partitioned between DCM and H_2O. The organic layer was washed with aq. $NaHCO_3$ solution, brine, dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was purified by column chromatography (230-400 silica gel, 1:4 ethyl acetate/petroleum ether) to afford **78** (1.37 g, 86%) as a colorless solid. Crystals suitable for single crystal X-ray structural analysis was grown

by slow evaporation of a solution of **78** in ethyl acetate–petroleum ether. *Characterization data of compound* ***78*****:** mp 93–94 °C; $[\alpha]_D^{25}$ +42.0 (*c* 1, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): δ 1.30 (s, 3H), 1.45 (s, 3H), 2.05 (t, *J* = 2.7 Hz, 1H), 2.77 (ddd, *J* = 2.7, 4.2, 17.8 Hz, 1H), 2.99 (ddd, *J* = 2.7, 3.8, 17.8 Hz, 1H), 3.10 (s, 3H), 3.33 (s, 3H), 4.25 (dd, *J* = 3.5, 8.4 Hz, 1H), 4.59 (d, *J* = 5.8 Hz, 1H), 4.75 (dd, *J* = 3.5, 5.8 Hz, 1H), 4.88 (br s, 1H), 4.89 (br dt, *J* = 4.0, 8.4 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 22.8 (t), 24.8 (q), 26.0 (q), 38.5 (q), 54.5 (q), 71.3 (s), 76.3 (d), 77.7 (d), 78.2 (s), 78.8 (d), 84.9 (d), 106.8 (d), 112.9 (s); MS (ESI): calcd for $C_{13}H_{20}O_7S$ ($[M+Na]^+$) 343.4, found 343.1; Anal. calcd for $C_{13}H_{20}O_7S$: C, 48.74; H, 6.29; S, 10.01; found C, 48.97; H, 6.25; S, 10.19.

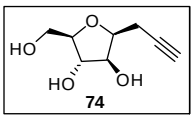
3. Synthesis of dimethyl acetal 76:



76

To the solution of **78** (500 mg, 1.56 mmol) in anhydrous MeOH (20 mL) at room temperature was added *p*-TSA (50 mg) and the mixture was refluxed for 72 h. The mixture was neutralized by addition of solid $NaHCO_3$ and filtered through celite. The celite pad was washed with MeOH and the combined filtrate was concentrated under reduced pressure. The crude product was purified by column chromatography (100-200 mesh silica gel, 3:7 ethyl acetate/petroleum ether) to afford **76** (227 mg, 67%) as pale yellow oil. *Characterization data of compound* ***76*****:** $[\alpha]_D^{25}$ +25.8 (*c* 1, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): δ 1.70 br s, 2H), 2.04 (t, *J* = 2.7 Hz, 1H), 2.58 (dd, *J* = 2.7, 7.0 Hz, 2H), 3.50 (s, 3H), 3.56 (s, 3H), 3.85–3.93 (m, 1H), 3.92 (dd, *J* = 1.8, 3.0 Hz, 1H), 4.20 (dt, *J* = 3.0, 7.0 Hz, 1H), 4.31 (s, 1H), 4.42 (d, *J* = 3.0 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 18.6 (t), 56.4 (q), 57.7 (q), 69.6 (d), 76.8 (d), 77.3 (d), 80.2 (d), 80.9 (s), 86.0 (d), 104.9 (d); MS (ESI): calcd for ($[M+Na]^+$) 239.2, found 239.2; Anal. calcd for $C_{10}H_{15}O_6$: C, 55.55; H, 7.46; found C, 55.48; H, 7.21.

4. Synthesis of β-*C*-propargyl-D-arabinofuranoside 74:

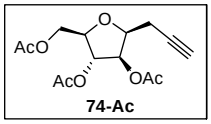


74

A solution of **76** (200 mg, 0.9 mmol) in 50% aq. trifluoroacetic acid (1 mL) was stirred at room temperature for 4 h. After consumption of starting material the mixture was concentrated under reduced pressure. To the resulting crude product in THF (5 mL) was added slowly a solution of $NaBH_4$ (500 mg, 13.2 mmol) in anhydrous MeOH (25 mL) at 0

°C and stirring was continued at same temperature for 1 h. The mixture was concentrated under reduced pressure and the crude product was purified by column chromatography (100-200 mesh silica gel, 1:9 methanol/dichoromethane) to afford **74** (113 mg, 71%) as semisolid. *Characterization data of compound* ***74*****:** $[\alpha]_D^{25}$ +48.2 (*c* 1, MeOH); ^{1}H NMR (400 MHz, acetone-*d*6): δ 2.34 (t, *J* = 2.7 Hz, 1H), 2.44 (ddd, *J* = 2.7, 6.5, 16.5 Hz, 1H), 2.55 (ddd *J* = 2.7, 7.5, 16.5 Hz, 1H), 2.97 (br s, 2H), 3.66 (dd, *J* = 3.3, 11.5 Hz, 1H), 3.70 (dd, *J* = 3.5, 11.5 Hz, 1H), 3.85 (dt, *J* = 1.9, 3.3 Hz, 1H), 3.87 (br d, *J* = 2.1 Hz, 1H), 4.11 (ddd, *J* = 3.0, 6.5, 7.5 Hz, 1H), 4.09–4.14 (m, 1H), 4.48 (br s, 1H); ^{13}C NMR (100 MHz, acetone-*d*6): δ 19.0 (t), 63.1 (t), 70.4 (d), 77.7 (d), 79.9 (d), 81.1 (d), 82.3 (s), 87.8 (d); MS (ESI): calcd for $C_8H_{12}O_4$ ($[M+Na]^+$) 195.1, found 195.1; Anal. calcd for $C_8H_{12}O_4$: C, 55.81; H, 7.02; found C, 56.10; H, 7.17.

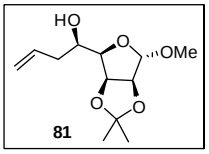
5. Synthesis of compound 74-Ac:



74-Ac

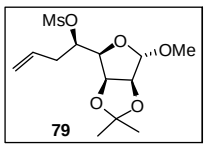
To a cooled (0 °C) solution of triol **74** (40 mg) in pyridine (0.5 mL) was added Ac_2O (0.5 mL and then allowed to stir at room temperature for 3 h. Afetr complete consumption of starting material, the mixture was partitioned between ethyl acetate-water. The organic phase washed with sat. $NaHCO_3$, H_2O, brine, dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was purified by column chromatography (230-400 mesh silica gel, 1:1 ethyl acetate/petroleum ether) to afford **74-Ac** (57 mg, 82%) as colorless oil. *Characterization data of compound* ***74-Ac*****:** $[\alpha]_D^{25}$ +23.4 *(c* 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.98 (t, *J* = 2.7 Hz, 1H), 2.08 (s, 3H), 2.09 (s, 3H), 2.12 (s, 3H), 2.51 (ddd, *J* = 2.7, 7.8, 16.6 Hz, 1H), 2.58 (ddd *J* = 2.7, 6.3, 16.6 Hz, 1H), 4.02 (ddd, *J* = 3.3, 4.8, 6.4 Hz, 1H), 4.15 (dd, *J* = 4.8, 11.6 Hz, 1H), 4.27 (ddd, *J* = 3.8, 6.5, 7.8 Hz, 1H), 4.35 (dd, *J* = 4.8, 11.6 Hz, 1H), 4.95 (dd, *J* = 1.1, 3.3 Hz, 1H), 5.31 (dd, *J* = 1.1, 3.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.9 (t), 20.6 (q), 20.7 (q), 20.8 (q), 63.6 (t), 70.2 (d), 76.4 (d), 78.4 (d), 78.7 (d), 79.1 (s), 81.8 (d), 169.5 (s), 169.6 (s), 170.7 (s); MS (ESI): calcd for $C_{14}H_{18}O_7$ $[M+Na]^+$) 321.1, found 321.1; Anal. calcd for $C_{14}H_{18}O_7$: C, 56.37; H, 6.08; found C, 56.45; H, 6.65.

6. Synthesis of alcohol 81:



To a suspension of activated Zn dust (710 mg, 11 mmol) in THF (30 mL) was added a solution of allyl bromide (1.330 g, 11 mmol) in THF (12 mL). The mixture was allowed to stir at room temperature for 1 h. Then to this, a solution of aldehyde **F19.1** (1.7 g, 8.4 mmol) in THF (20 mL) was added dropwise and stirring was continued at room temperature for 14 h, quenched with sat. NH_4Cl (15 mL) and allowed to stir at room temperature for 1 h. The mixture was partitioned between ethyl acetate and water. The organic layer was washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure. The crude product was purified by column chromatography (230-400 mesh silica gel, 1:4 ethyl acetate/petroleum ether) to afford **81** (1.49 g, 73%) as colorless oil. *Characterization data of compound* ***81*****:** $[\alpha]_D^{25}$ +65.9 (*c* 1, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.32 (s, 3H), 1.47 (s, 3H), 2.32 (ddt, *J* = 1.1, 7.6, 14.3 Hz, 1H), 2.38 (dddt, *J* = 1.3, 4.2, 6.7, 14.3 Hz, 1H), 3.30 (s, 3H), 3.78 (dd, *J* = 3.7, 7.7 Hz, 1H), 3.98 (dt, *J* = 4.1, 7.8 Hz, 1H), 4.56 (d, *J* = 5.9 Hz, 1H), 4.82 (dd, *J* = 3.7, 5.9 Hz, 1H), 4.91 (s, 1H), 5.12–5.33 (m, 2H), 5.92 (dddd, *J* = 6.8, 7.7, 10.2, 17.2 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 24.6 (q), 25.9 (q), 38.9 (t), 54.5 (d), 69.3 (d), 80.0 (d), 81.2 (d), 84.8 (d), 107.0 (d), 112.6 (s), 117.8 (t), 134.3 (d); MS (ESI): calcd for $C_{12}H_{20}O_5$ ($[M+Na]^+$) 267.3, found 267.3; Anal. calcd for $C_{12}H_{20}O_5$: C, 59.00; H, 8.25; found C, 58.96; H, 8.19.

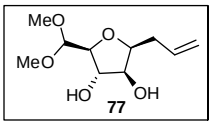
7. Synthesis of mesylate 79:



To the solution of **81** (640 mg, 2.6 mmol) in anhydrous DCM (10 mL) was added Et_3N (0.9 mL, 6.5 mmol) and the mixture was cooled to 0 °C. To this, MsCl (0.28 mL, 3.6 mmol) was added dropwise and the mixture was stirred at room temperature for 1 h. Then the mixture was partitioned between DCM and water. The organic layer was washed with aq. $NaHCO_3$ solution and brine, dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was purified by column chromatography (230-400 mesh silica gel, 1:4 ethyl acetate/petroleum ethar) to afford **79** (682 mg, 81%) as colorless oil. *Characterization data of compound* ***79*****:** $[\alpha]_D^{25}$ +11.0 (*c* 1, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.31 (s, 3H), 1.48 (s, 3H), 2.58 (br ddd, *J* = 4.8, 8.3, 15.0 Hz, 1H), 2.85 (br dddt, *J* = 1.2, 4.0, 5.8, 15.0 Hz, 1H), 3.08 (s, 3H), 3.31 (s, 3H), 4.02 (dd, *J* =

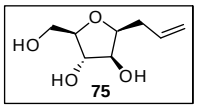
3.5, 8.8 Hz, 1H), 4.59 (d, *J* = 5.8 Hz, 1H), 4.70 (dd, *J* = 3.5, 5.8 Hz, 1H), 4.89 (br s, 1H), 4.96 (dt, *J* = 4.5, 8.8 Hz, 1H), 5.18–5.30 (m, 2H), 5.93 (dddd, *J* = 5.9, 8.3, 10.2, 16.6 Hz, 1H); ^{13}C NMR (50 MHz, CDCl3): δ 24.9 (q), 26.0 (q), 36.53 (t), 38.4 (q), 54.6 (q), 78.0 (d), 78.8 (d), 79.0 (d), 84.9 (d), 107.1 (d), 112.8 (s), 119.4 (t), 131.6 (d); MS (ESI): calcd for $C_{13}H_{22}O_7S$ ([M+Na]$^+$) 345.2, found 345.4; Anal. calcd for $C_{13}H_{22}O_7S$: C, 48.43; H, 6.88; S, 9.95; found C, 48.60; H, 7.01; S, 9.87.

8. Synthesis of dimethyl acetal 77:



To the solution of **79** (600 mg, 1.9 mmol) in anhydrous MeOH (20 mL) at room temperature was added *p*-TSA (60 mg) and the mixture was stirred at reflux temperature for 72 h. After that mixture was neutralized by addition of solid $NaHCO_3$, filtered through celite bed and concentrated under reduced pressure. The crude product was purified by column chromatography (100-200 mesh silica gel, 3:7 ethyl acetate/petroleum ether) to afford **77** (290 mg, 71%) as colorless oil. *Characterization data of compound* ***77*****:** $[\alpha]_D^{25}$ +3.2 (*c* 1, MeOH); ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.08 (br s, 1H), 2.28 (br s, 1H), 2.43 (br t, *J* = 6.8 Hz, 2H), 3.48 (s, 3H), 3.55 (s, 3H), 3.72–3.81 (m, 1H), 3.85 (dd, *J* = 1.7, 3.0 Hz, 1H), 4.01 (dt, *J* = 2.5, 6.9 Hz, 1H), 4.27 (br s, 1H), 4.38 (d, *J* = 2.8 Hz, 1H), 5.05–5.20 (m, 2H), 5.86 (dt, 6.9, 10.3, 17.0 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 32.8 (t), 56.3 (q), 57.7 (q), 77.0 (d), 77.6 (d) 81.3 (d), 85.7 (d), 105.1 (d), 117.0 (t), 134.5 (d); MS (ESI): calcd for $C_{10}H_{18}O_5$ ([M+Na]$^+$) 241.4, found 241.1; Anal. calcd for $C_{10}H_{18}O_5$: C, 55.03; H, 8.31; found C, 54.82; H, 8.59.

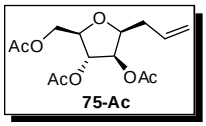
9. Synthesis of β-*C*-allyl-D-arabinofuranoside 75:



The dimethyl acetal **77** (300 mg, 1.38 mmol) was dissolved in ice cold 50% aq. TFA (2 mL) and stirred at room temperature for 4 h. After that TFA was removed under reduced pressure, the crude product was taken up in THF (5 mL) and cooled to 0 °C. Then to this cooled solution was slowly added a solution of $NaBH_4$ (700 mg, 18.5 mmol) in anhydrous MeOH (15 mL). After complete addition, the reaction mixture was stirred at 0 °C for 1 h. The mixture was concentrated under reduced pressure and the crude product was purified by column chromatography (100-200 mesh silica gel, 1:9 methanol/dichloromethane) to afford **75** (176 mg, 74%) as colorless gum. *Characterization data of compound* ***75*****:** $[\alpha]_D^{25}$

+27.2 (*c* 1, MeOH); ^{1}H NMR (200 MHz, acetone-*d*6): δ 2.35–2.42 (m, 2H), 3.00 (br s, 1H), 3.68 (br s, 2H), 3.76–3.80 (m, 2H), 3.95 (dt, *J* = 2.9, 7.0 Hz, 1H), 4.10 (br s, 1H), 4.32–4.45 (m, 2H), 4.97–5.16 (m, 2H), 5.93 (ddt, *J* = 7.0, 10.3, 17.2 Hz, 1H); ^{13}C NMR (125 MHz, acetone-*d*6): δ 34.0 (t), 63.2 (t), 78.2 (d), 80.2 (d), 82.0 (d), 87.3 (d) 116.5 (t), 136.6 (d); MS (ESI): calcd for ([M+Na]$^+$) 197.4, found 197.2; Anal. calcd for $C_8H_{14}O_4$: C, 55.16; H, 8.10; found C, 55.42; H, 8.14.

10. Synthesis of acetate 75-Ac:



75-Ac

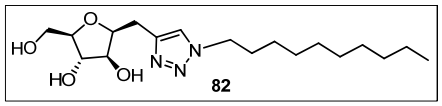
To the cooled (ice bath) solution of **75** (200 mg 1.15 mmol) in pyridine (1 mL) was added Ac_2O (1 mL). Then reaction mixture was allowed to stir at room temperature for 2 h. The mixture was partitioned between ethyl acetate and water. The organic layer was washed with sat. $NaHCO_3$ solution, water, brine, dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was purified by column chromatography (230-400 mesh silica gel, 1:1 ethyl acetate/petroleum ether) to afford **75-Ac** (289 mg, 83%) as colorless oil. *Characterization data of compound* ***75-Ac*****:** $[\alpha]_D^{25}$ +21.4 (*c* 1, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.03 (s, 6H), 2.05 (s, 3H), 2.28 (dt, *J* = 6.8, 14.0 Hz, 1H), 2.37 (dt, *J* = 7.0, 14.0 Hz, 1H), 3.92 (ddd, *J* = 3.4, 5.0, 6.5 Hz, 1H), 4.03 (dt, *J* = 3.6, 7.0 Hz, 1H), 4.10 (dd, *J* = 6.5, 11.5 Hz, 1H), 4.30 (dd, *J* = 5.0, 11.5 Hz, 1H), 4.88 (br d, *J* = 3.4 Hz, 1H), 5.00–5.07 (m, 2H), 5.15 (br d, *J* = 3.6 Hz, 1H), 5.7 (ddt, *J* = 7.0, 10.3, 17.2 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 20.7 (q), 20.73 (q), 20.8 (q), 33.0 (t), 63.8 (t), 76.8 (d), 78.9 (d), 80.1 (d), 81.2 (d), 117.6 (t), 133.4 (d), 169.6 (s, 2C), 170.7 (s); MS (ESI): calcd for $C_{14}H_{20}O_7$ ([M+Na]$^+$) 323.6, found 323.3; Anal. calcd for $C_{14}H_{20}O_7$: C, 55.99; H, 6.71; found C, 56.12; H, 6.74.

11. Representative procedure for synthesis of compounds 82–92:

To a solution of alkyne **74** (50 mg, 290 μmol) in *t*-BuOH and water (3:1, 4 mL) was added $CuSO_4.5H_2O$ (10 mg, 58 μmol) and sodium ascorbate (54 mg, 275 μmol) at room temperature and stirring was continued for 10 min. Then to this, a solution of azide (290 μmol) in *t*-BuOH (1 mL) was added and stirring was continued for 3 to 5 h. After the complete consumption of statrting material on TLC, reaction mixture was evaporated under reduced pressure, residue was purified by column chromatography

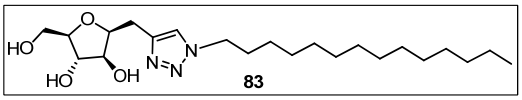
(100-200 mesh silica gel, 1:9 methanol/dichloromethane) to afford the compounds **82–92**.

Characterization data of compound 82:



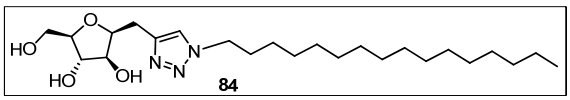
$[\alpha]_D^{25}$ +3.7 (*c* 0.5, $CHCl_3$); IR (neat): 3440, 3309, 2927, 2855, 1466, 1071 cm^{-1}; ^1H NMR (DMSO-*d6*, 200 MHz): δ 0.85 (t, *J* = 6.1 Hz, 3H), 1.23 (br s, 16H), 1.77 (quentet, *J* = 6.6 Hz, 2H), 2.79 (dd, *J* = 7.1, 14.8 Hz, 1H), 2.90 (dd, *J* = 6.6, 14.8 Hz, 1H), 3.46 (br s, 1H), 3.55–3.61 (m, 1H), 3.69 (br s, 1H), 3.81 (br s, 1H), 4.03−4.15 (m, 1H), 4.27 (br t, *J* = 7.0 Hz, 2H), 4.90−4.96 (m, 1H), 5.10 (d, *J* = 3.9 Hz, 1H), 7.83 (s, 1H); ^{13}C NMR (DMSO-*d6*, 50 MHz): δ 14.1 (q), 22.3 (t), 26.1 (t), 28.6 (t), 28.9 (t), 29.1 (t), 29.2 (t, 2C), 30.0 (t), 31.5 (t), 49.3 (t), 62.3 (t), 77.1 (d), 78.8 (d), 80.4 (d), 86.4 (d), 119.2 (d), 137.6 (s); LCMS (*m/z*): 440.45 (100%, $[M+1]^+$); Anal. calcd for $C_{18}H_{33}N_3O_4$: C, 60.82; H, 9.36; N, 11.82; O, 18.00; found C, 60.64; H, 9.40; N, 11.68.

Characterization data of compound 83:



$[\alpha]_D^{25}$ +5.7 (*c* 0.8, $CHCl_3$); IR (neat): 3421, 3370, 2931, 2841, 1456, 1076 cm^{-1}; ^1H NMR (DMSO-*d6*, 200 MHz): δ 0.85 (t, *J* = 6.4 Hz, 3H), 1.23 (br s, 22H), 1.77 (quentet, *J* = 6.6 Hz, 2H), 2.79 (dd, *J* = 7.5, 14.8 Hz, 1H) 2.90 (dd, *J* = 6.5, 14.8 Hz, 1H), 3.46 (br s, 2H), 3.59 (br s, 1H), 3.69 (br s, 1H), 3.82 (br s, 1H), 4.08 (dt, *J* = 3.2, 6.7 Hz, 1H), 4.27 (br t, *J* = 7.0 Hz, 2H), 4.91−4.97 (m, 2H), 5.12 (d, *J* = 3.2 Hz, 1H), 7.83 (s, 1H); ^{13}C NMR (MeOH-*d4*, 50 MHz): δ 14.4 (q), 23.7 (t), 27.5 (t), 30.1 (t), 30.5 (t), 30.55 (t), 30.6 (t), 30.7 (t, 2C), 30.8 (t, 3C), 31.3 (t), 33.1 (t), 51.4 (t), 63.6 (t), 78.8 (d), 80.4 (d), 82.0 (d), 87.6 (d), 120.2 (d), 140.1 (s); LCMS (*m/z*): 411.64 (100%, $[M+1]^+$); Anal. calcd for $C_{22}H_{41}N_3O_4$: C, 64.20; H, 10.04; N, 10.21; found C, 63.98; H, 10.22; N, 10.09.

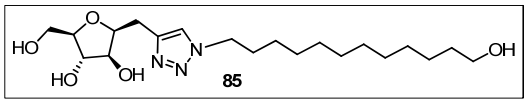
Characterization data of compound 84:



$[\alpha]_D^{25}$ +3.6 (*c* 0.5, $CHCl_3$); IR (neat): 3436, 3362, 2931, 2841, 1456, 1076 cm^{-1}; ^1H NMR (DMSO-*d6*, 200 MHz): δ 0.85 (t, *J* = 6.1 Hz, 3H), 1.23 (br s, 26H), 1.73−1.80 (m, 2H), 2.79 (dd, *J* = 7.1, 14.8 Hz, 1H) 2.90 (dd, *J* = 6.6, 14.8 Hz, 1H), 3.46 (br s, 2H), 3.58 (br s, 1H), 3.69 (br s, 1H), 3.81 (br s, 1H), 4.03−4.15 (m, 1H),

4.27 (br t, *J* = 7.0 Hz, 2H), 4.90−5.00 (m, 2H), 5.11 (d, *J* = 3.9 Hz, 1H), 7.83 (s, 1H); ^{13}C NMR (DMSO-*d6*, 50 MHz): *δ* 14.1 (q), 22.3 (t), 25.6 (t), 26.1 (t), 28.6 (t), 28.9 (t), 29.1 (t), 29.2 (t, 7C), 30.0 (t), 31.5 (t), 49.3 (t), 62.3 (t), 77.1 (d), 78.8 (d), 80.4 (d), 86.4 (d), 119.1 (d), 137.8 (s); LCMS (*m/z*): 440.45 (100%, $[M+1]^+$); Anal. calcd for $C_{24}H_{45}N_3O_4$: C, 65.57; H, 10.32; N, 9.56; found C, 65.43; H, 10.83; N, 9.24.

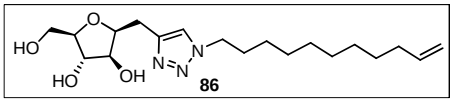
Characterization data of compound 85:



85

$[\alpha]_D^{25}$ +8.76 (*c* 0.7, MeOH); IR ($CHCl_3$): 3432, 3350, 2921, 2863, 1451, 1072 cm^{-1}; ^{1}H NMR (DMSO-*d6*, 200 MHz): *δ* 1.23 (bs, 16H), 1.33–1.39 (m, 2H), 1.77 (quentet, *J* = 6.6 Hz, 2H), 2.79 (dd, *J* = 14.6, 7.4 Hz, 1H) 2.90 (dd, *J* = 14.6, 6.5 Hz, 1H), 3.42−3.48 (m, 2H), 3.55−3.59 (m, 1H), 3.69 (br t, *J* = 4.1 Hz, 1H), 3.81 (br s, 1H), 4.08 (dt, *J* = 3.4, 6.8 Hz, 1H), 4.24–4.37 (m, 3H), 4.91 (d, *J* = 5.1 Hz, 1H), 4.97 (d, *J* = 6.1 Hz, 1H), 5.11 (d, *J* = 3.9 Hz, 1H), 7.83 (s, 1H); ^{13}C NMR (MeOH-*d4*, 50 MHz): *δ* 26.5 (t), 26.9 (t), 27.5 (t), 30.1 (t), 30.5 (t), 30.59 (t), 30.60 (t), 30.65 (t), 30.7 (t), 31.3 (t), 33.7 (t), 51.3 (t), 63.0 (t), 63.6 (t), 78.8 (d), 80.3 (d), 82.1 (d), 86.6 (d), 121.0 (d), 139.3 (s); LCMS (*m/z*): 399.49 (100%, $[M]^+$); Anal. calcd for $C_{20}H_{37}N_3O_5$ C, 60.12; H, 9.33; N, 10.52; found C, 60.23; H, 9.52; N, 10.41.

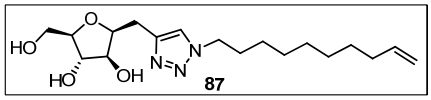
Characterization data of compound 86:



86

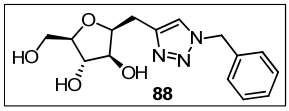
$[\alpha]_D^{25}$ +7.03 (*c* 0.7, $CHCl_3$); IR (neat): 3460, 2938, 2871, 1446, 1064 cm^{-1}; ^{1}H NMR (DMSO-*d6*, 200 MHz): *δ* 1.23 (br s, 12H), 1.77 (quentet, *J* = 6.7 Hz, 2H), 1.91–2.05 (m, 2H), 2.79 (dd, *J* = 7.4, 14.7 Hz, 1H) 2.90 (dd, *J* = 6.6, 14.7 Hz, 1H), 3.45 (br s, 2H), 3.55−3.62 (m, 1H), 3.68 (br t, *J* = 4.4 Hz, 1H), 3.81 (br s, 1H), 4.03−4.15 (m, 1H), 4.28 (br t, *J* = 7.1 Hz, 2H), 4.90−5.03 (m, 3H), 5.12 (d, *J* = 4.0 Hz, 1H), 5.79 (ddt, *J* = 6.7, 13.3, 17.0 Hz, 1H), 7.83 (s, 1H); ^{13}C NMR (DMSO-*d6*, 50 MHz): *δ* 25.7 (t), 26.1 (t), 28.5 (t), 28.6 (t), 28.7 (t), 28.9 (t), 29.0 (t), 29.9 (t), 33.4 (t), 49.3 (t), 62.3 (t), 77.1 (d), 78.8 (d), 80.4 (d), 86.4 (d), 114.9 (t), 121.7 (d), 139.0 (d), 141.7 (s); ESI-MS (*m/z*): 367.89 (100%, $[M+1]^+$); Anal. calcd for $C_{19}H_{33}N_3O_4$: C, 62.10; H, 9.05; N, 11.43; found C, 62.22; H, 9.17; N, 11.18.

Characterization data of compound 87:



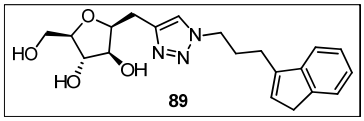
$[\alpha]_D^{25}$ +5.72 (*c* 0.8, $CHCl_3$); IR (neat): 3454, 2922, 2862, 1451, 1079 cm^{-1}; ^1H NMR (DMSO-*d6*, 200 MHz): δ 1.24 (br s, 10H), 1.77 (quentet, *J* = 6.7 Hz, 2H), 1.95–2.04 (m, 2H), 2.79 (dd, *J* = 7.5, 14.7 Hz, 1H) 2.90 (dd, *J* = 6.7, 14.7 Hz, 1H), 3.46 (br s, 2H), 3.59 (br s, 1H), 3.68 (br s, 1H), 3.81 (br s, 1H), 4.07 (dt, *J* = 3.4, 6.8 Hz, 1H), 4.28 (br t, *J* = 7.1 Hz, 2H), 4.90−5.03 (m, 3H), 5.11 (d, *J* = 4.0 Hz, 1H), 5.79 (ddt, *J* = 6.7, 10.1, 16.8 Hz, 1H), 7.83 (s, 1H); ^{13}C NMR (DMSO-*d6*, 50 MHz): δ 25.6 (t), 26.1 (t), 28.4 (t), 28.5 (t), 28.6 (t), 28.9 (t), 29.9 (t), 33.4 (t), 49.3 (t), 62.3 (t), 77.1 (d), 78.8 (d), 80.4 (d), 86.4 (d), 114.9 (t), 122.6 (d), 139.0 (d), 142.7 (s); LCMS (*m/z*): 353.66 (100%, $[M+1]^+$); Anal. calcd for $C_{18}H_{31}N_3O_4$: C, 61.17; H, 8.84; N, 11.89; found C, 60.98; H, 8.74; N, 11.68.

Characterization data for compound 88:



$[\alpha]_D^{25}$ +3.1 (*c* 0.76, MeOH); IR (neat): 3460, 3299, 2921, 2855, 1476, 1081 cm^{-1}; ^1H NMR (DMSO-*d6*, 500 MHz): δ 2.82 (dd, *J* = 7.5, 14.8 Hz, 1H), 2.90 (dd, *J* = 6.3, 14.8 Hz, 1H), 3.46 (s, 1H), 3.49 (s, 1H), 3.58 (dt, *J* = 2.5, 5.0 Hz, 1H), 3.69 (br t, *J* = 4.5 Hz, 1H), 3.81 (s, 1H), 4.08 (dt, *J* = 3.3, 6.8 Hz, 1H), 4.92 (br t, *J* = 5.3 Hz, 1H), 4.98 (d, *J* = 6.1 Hz, 1H), 5.12 (d, *J* = 3.9 Hz, 1H), 5.54 (s, 2H), 7.29–7.33 (m, 3H), 7.35–7.38 (m, 2H), 7.89 (s, 1H); ^{13}C NMR (DMSO-*d6*, 125 MHz): δ 25.6 (t), 52.9 (t), 62.3 (t), 77.1 (d), 78.8 (d), 80.3 (d), 86.4 (d), 128.1 (d, 2C), 128.3 (d), 129.0 (d, 2C), 136.5 (s), 144.9 (s); HRMS: calcd for $C_{15}H_{19}N_3O_4$ ($[M+Na]^+$) 328.1273, found 328.1257.

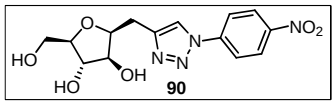
Characterization data for compound 89:



$[\alpha]_D^{25}$ +0.27 (*c* 0.59, MeOH); IR (neat): 3436, 3312, 2929, 2861, 1458, 1077 cm^{-1}; ^1H NMR (DMSO-*d6*, 400 MHz): δ 2.17 (quientet, *J* = 7.2 Hz, 2H), 2.83 (dd, *J* = 7.3, 14.8 Hz, 1H), 2.91 (dd, *J* = 6.6, 14.8 Hz, 1H), 3.32 (br s, 2H), 3.45–3.48 (m, 3H), 3.59 (dt, *J* = 2.6, 5.1 Hz, 1H), 3.71 (br s, 1H), 3.82 (br s, 1H), 4.10 (dt, *J* = 3.3, 6.9 Hz, 1H), 4.40 (t, *J* = 6.9 Hz, 1H), 4.91–4.97 (br m, 2H), 5.12 (br s, 1H), 5.74 (s, 1H), 6.31 (s, 1H), 7.18 (t, *J* = 7.3 Hz, 1H), 7.27 (t, *J* = 7.2 Hz, 1H), 7.33 (d, *J* = 7.2 Hz, 1H), 7.46 (d, *J* = 7.3 Hz, 1H), 7.89 (s, 1H); ^{13}C NMR (DMSO-*d6*, 100 MHz): δ

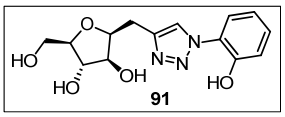
24.2 (t), 25.6 (t), 28.5 (t), 37.6 (t), 49.2 (t), 62.4 (t), 77.1 (d), 78.8 (d), 80.4 (d), 86.4 (d), 119.0 (d), 122.8 (d), 124.0 (d), 124.8 (d), 126.3 (d), 128.9 (d), 142.7 (s), 144.3 (s), 144.5 (s), 144.9 (s); HRMS: calcd for $C_{20}H_{25}N_3O_4$ ($[M+Na]^+$) 394.1743, found 394.1724.

Characterization data for compound 90:



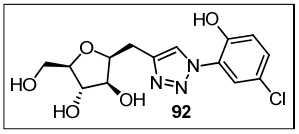
$[\alpha]_D^{25}$ −4.1 (*c* 0.45, MeOH); IR (neat): 3455, 3294, 2918, 2841, 1463, 1058 cm^{-1}; ^1H NMR (DMSO-*d6*, 400 MHz): δ 2.94 (dd, *J* = 7.9, 15.0 Hz, 1H), 3.02 (dd, *J* = 6.1, 15.0 Hz, 1H), 3.47 (dd, *J* = 5.7, 11.1 Hz, 1H), 3.52 (dd, *J* = 5.3, 11.1 Hz, 1H), 3.61 (dt, *J* = 2.7, 5.1 Hz, 1H), 3.79 (br t, *J* = 4.6 Hz, 1H), 3.85 (br s, 1H), 4.22 (ddd, *J* = 3.5, 6.1, 9.4 Hz, 1H), 4.90 (t, *J* = 5.3 Hz, 1H), 5.05 (d, *J* = 6.0 Hz, 1H), 5.18 (d, *J* = 4.1 Hz, 1H), 8.20 (d, *J* = 9.1 Hz, 2H), 8.44 (d, *J* = 9.1 Hz, 2H), 8.76 (s, 1H); ^{13}C NMR (DMSO-*d6*, 100 MHz): δ 25.7 (t), 62.3 (t), 77.1 (d), 78.8 (d), 80.0 (d), 86.4 (d), 120.5 (d, 2C), 121.5 (d), 125.8 (d, 2C), 141.2 (s), 146.7 (s, 2C); HRMS: calcd for $C_{14}H_{16}N_4O_6$ ($[M+Na]^+$) 359.0968, found 359.0951.

Characterization data for compound 91:



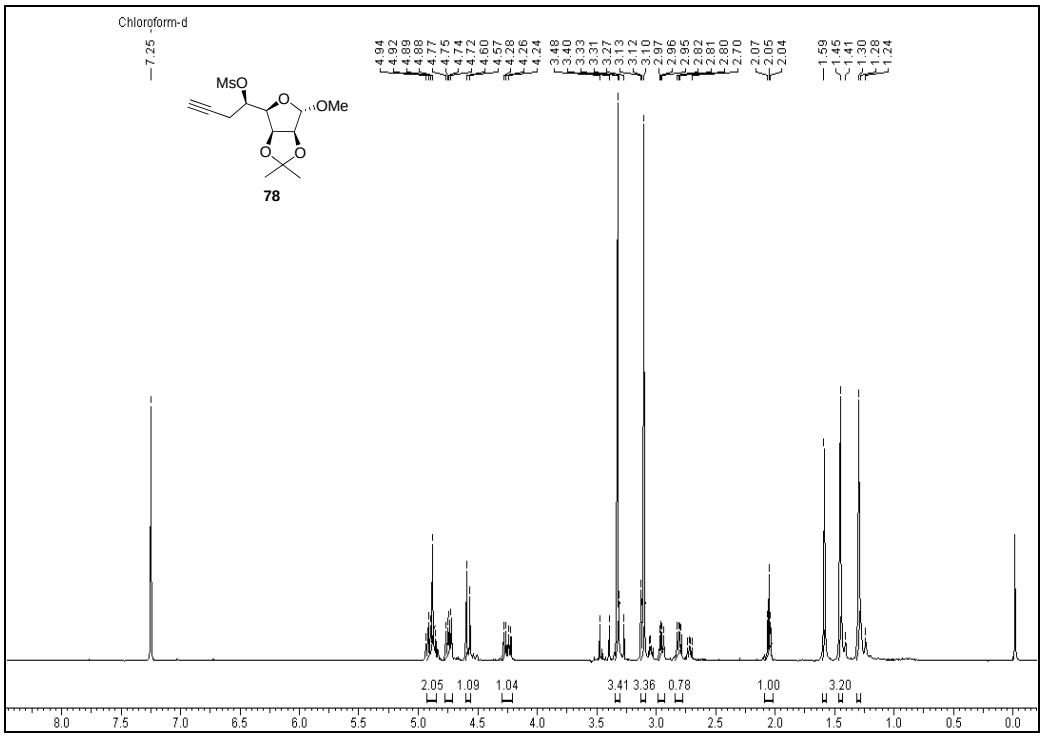
$[\alpha]_D^{25}$ +1.1 (*c* 0.83, MeOH); IR (neat): 3480, 3311, 2931, 2841, 1446, 1082 cm^{-1}; ^1H NMR (DMSO-*d6*, 400 MHz): δ 2.91 (dd, *J* = 7.7, 14.9 Hz, 1H), 2.99 (dd, *J* = 6.4, 14.9 Hz, 1H), 3.47 (s, 1H), 3.49 (s, 1H), 3.61 (dt, *J* = 2.6, 5.0 Hz, 1H), 3.75 (br s, 1H), 3.83 (s, 1H), 4.17 (dt, *J* = 3.3, 6.8 Hz, 1H), 4.93 (br t, *J* = 7.8 Hz, 1H), 5.04 (d, *J* = 5.5 Hz, 1H), 5.16 (br s, 1H), 6.97 (br t, *J* = 7.7 Hz, 1H), 7.10 (d, *J* = 8.1 Hz, 1H), 7.32 (dt, *J* = 1.6, 7.7 Hz, 1H), 7.58 (dd, *J* = 1.6, 8.0 Hz, 1H), 8.21 (s, 1H), 10.52 (s, 1H); ^{13}C NMR (DMSO-*d6*, 100 MHz): δ 25.6 (t), 62.4 (t), 77.2 (d), 78.9 (d), 80.4 (d), 86.5 (d), 117.3 (d), 119.8 (d), 124.4 (d), 125.0 (s), 125.3 (d), 130.2 (d), 144.7 (s), 149.7 (s); HRMS: calcd for $C_{14}H_{17}N_3O_5$ ($[M+Na]^+$) 330.1066, found 330.1052.

Characterization data for compound 92:

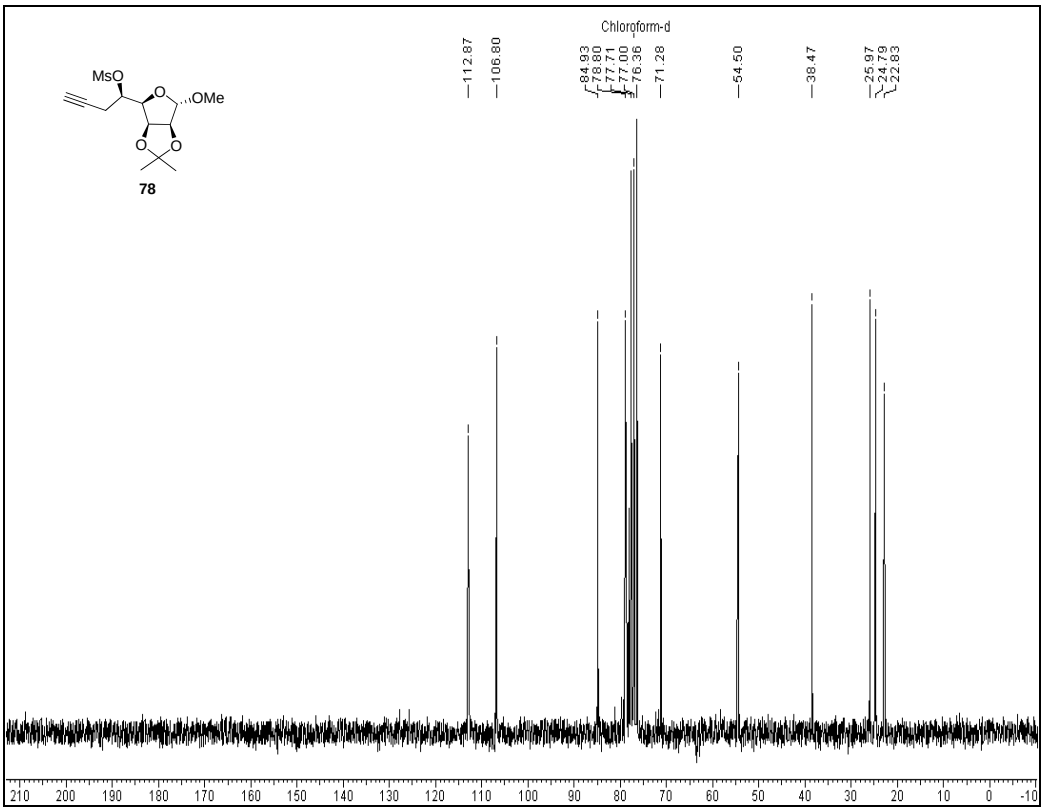


$[\alpha]_D^{25}$ +1.5 (*c* 0.62, MeOH); IR (neat): 3520, 3331, 2942, 2848, 1458, 1091 cm^{-1}; ^1H NMR (DMSO-*d6*, 400 MHz): δ 2.92 (dd, *J* = 7.7, 14.8 Hz, 1H), 2.99 (dd, *J* = 6.1, 14.8 Hz, 1H), 3.61 (dt, *J* = 2.6, 5.0 Hz, 1H), 3.75 (br s, 1H), 3.83 (s, 1H), 4.17 (dt, *J* = 3.2, 6.5

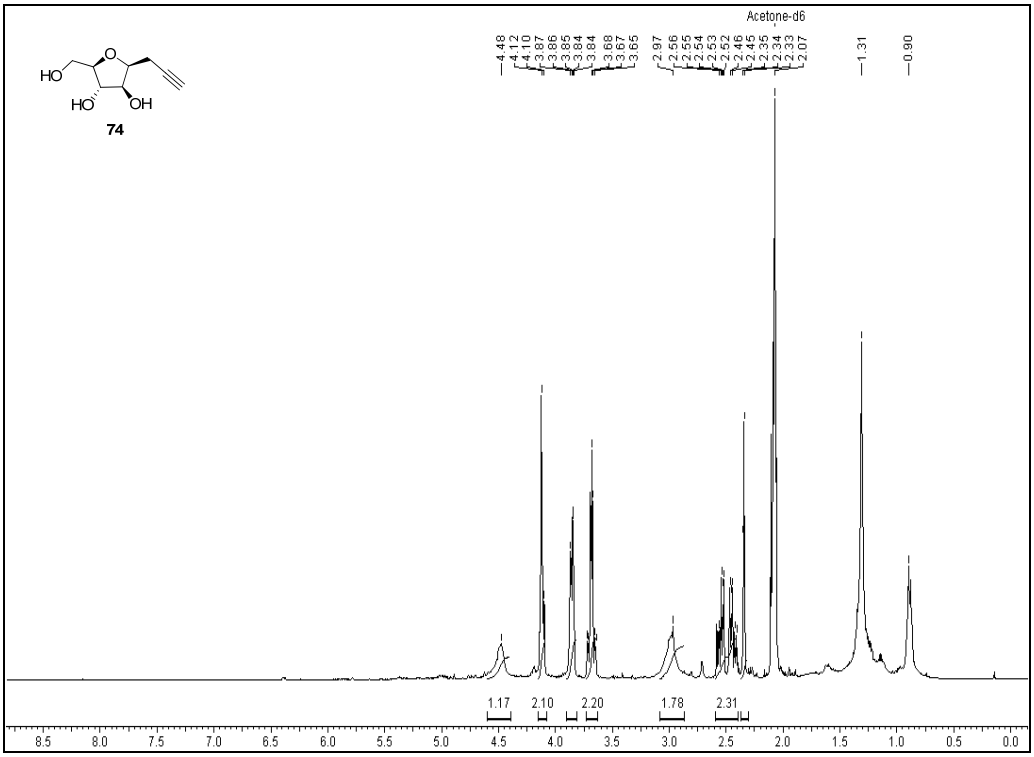
Hz, 1H), 4.94 (br s, 1H), 5.05 (d, J = 6.5 Hz, 1H), 5.17 (d, J = 2.6 Hz, 1H), 7.12 (d, J = 8.7 Hz, 1H), 7.38 (dd, J = 2.6, 8.7 Hz, 1H), 7.67 (d, J = 2.6 Hz, 1H), 8.27 (s, 1H), 10.9 (s, 1H); ^{13}C NMR (DMSO-*d6*, 100 MHz): δ 25.6 (t), 62.4 (t), 77.2 (d), 78.8 (d), 80.3 (d), 86.5 (d), 118.9 (d), 123.0 (s), 124.5 (d), 124.6 (d), 125.7 (s), 129.8 (d), 144.7 (s), 148.7 (s); LCMS (*m/z*): 364.02 (100%, $[M]^+$).



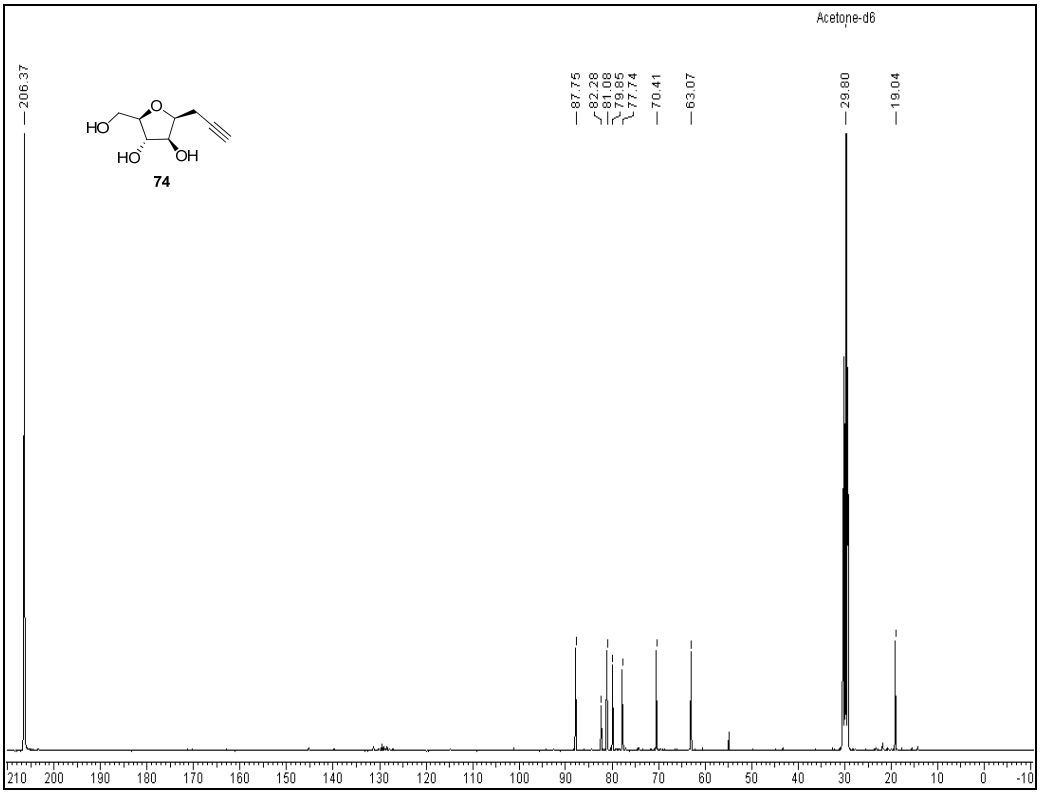
^{1}H NMR of compound 78



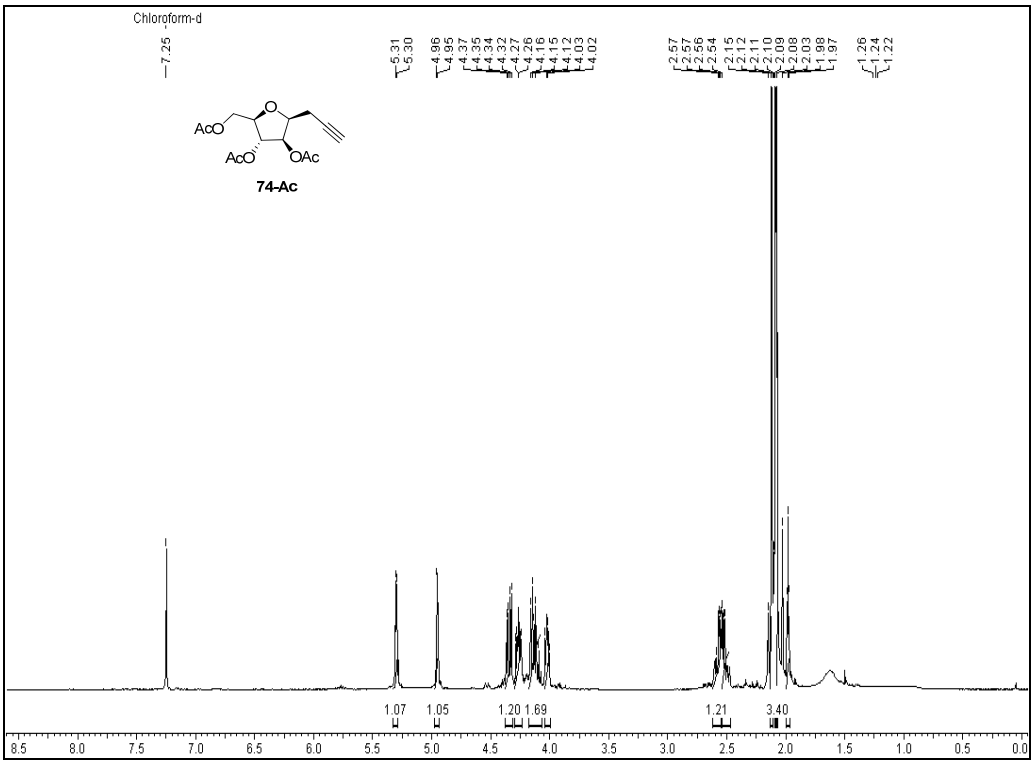
^{13}C NMR of compound 78



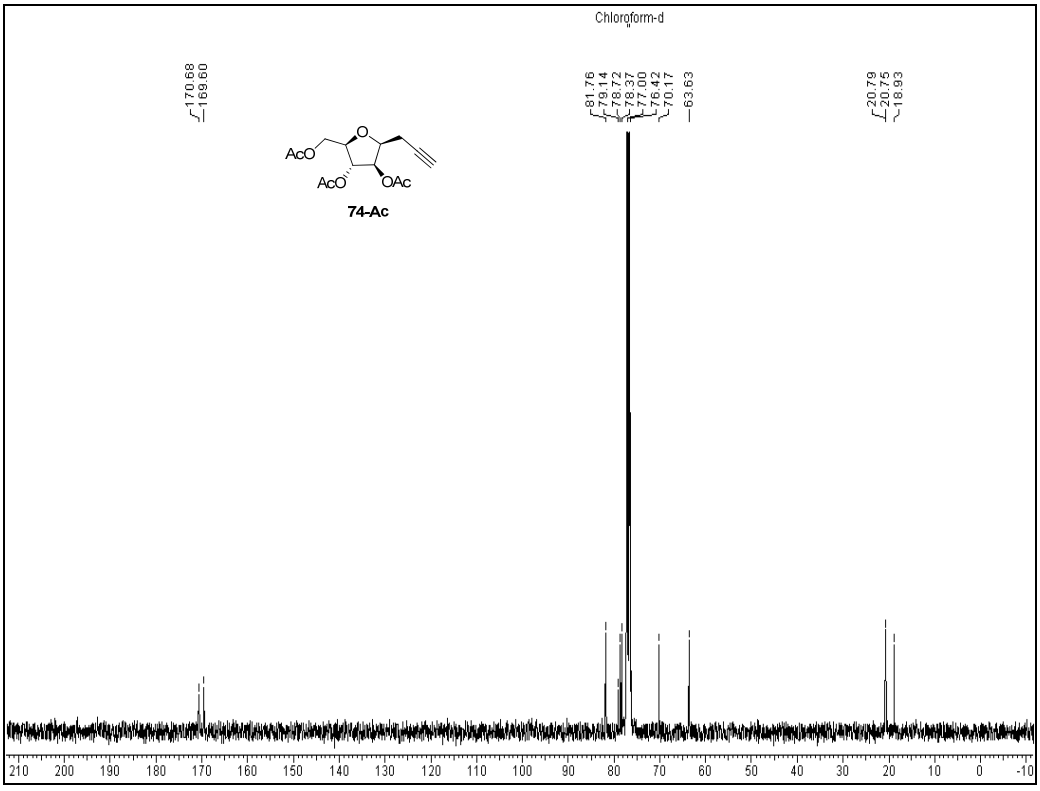
^{1}H NMR of compound 74



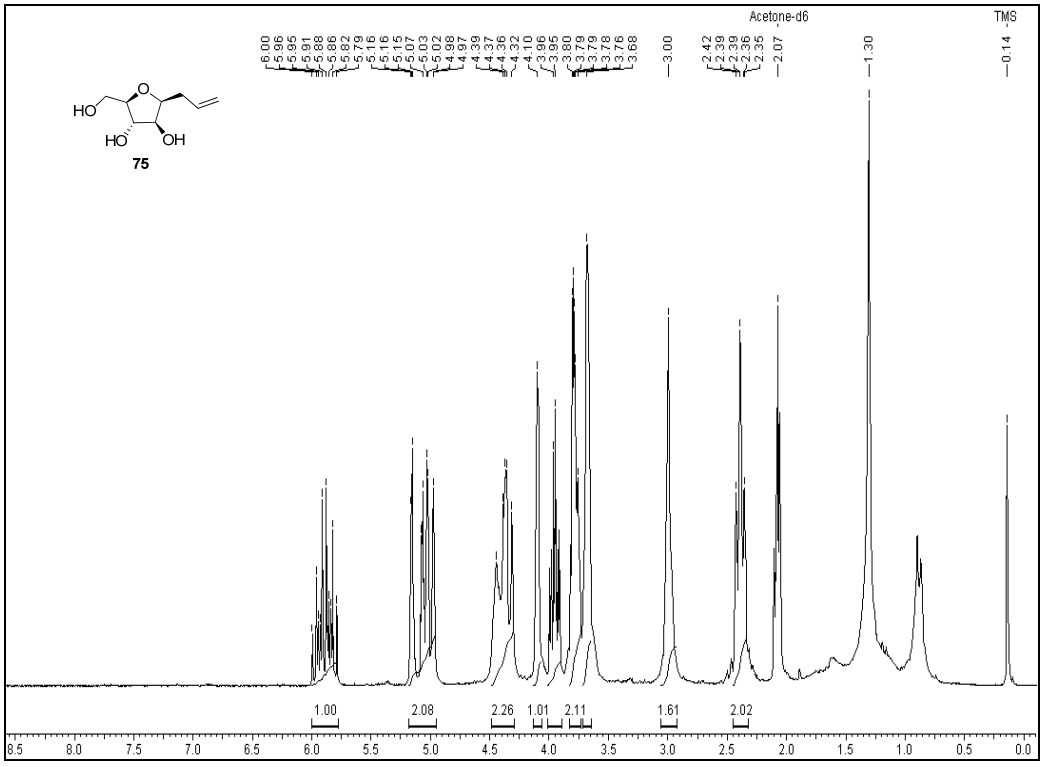
^{13}C NMR of compound 74



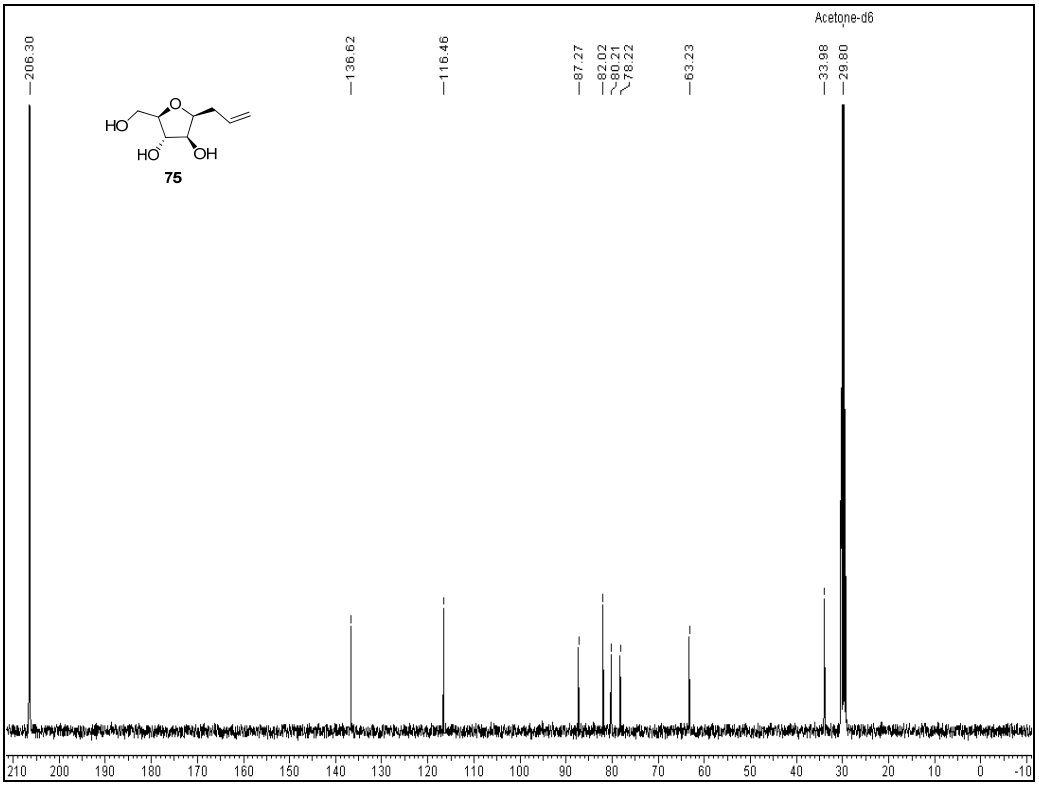
^{1}H NMR of compound 74-Ac



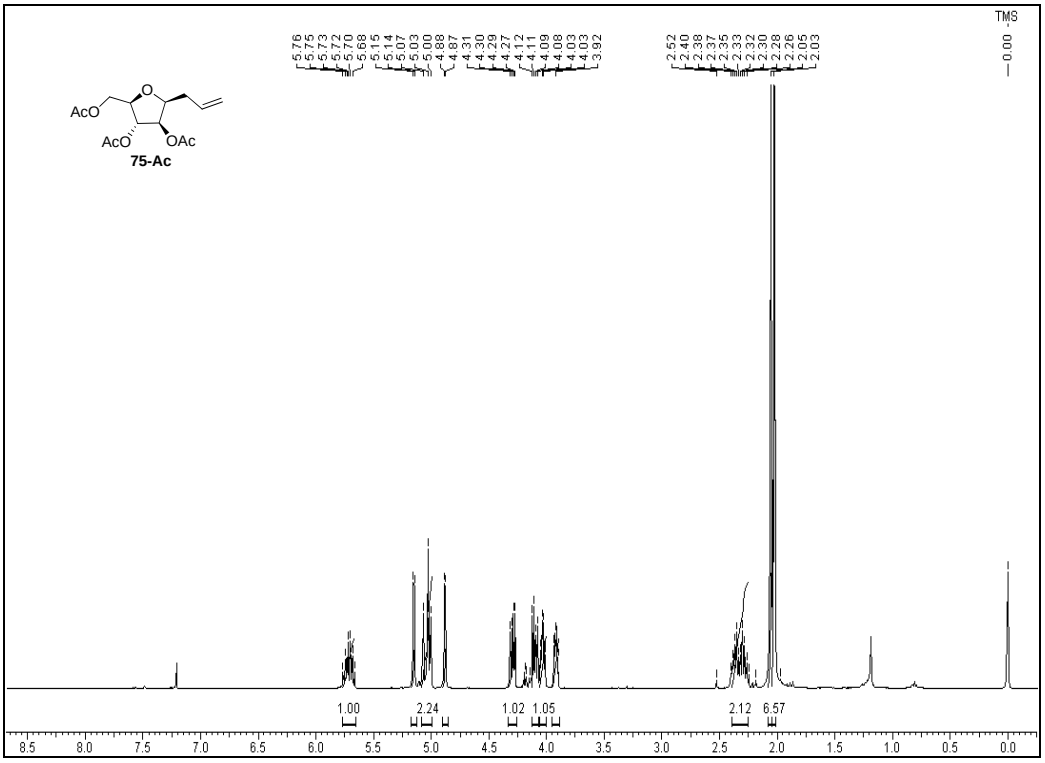
^{13}C NMR of compound 74-Ac



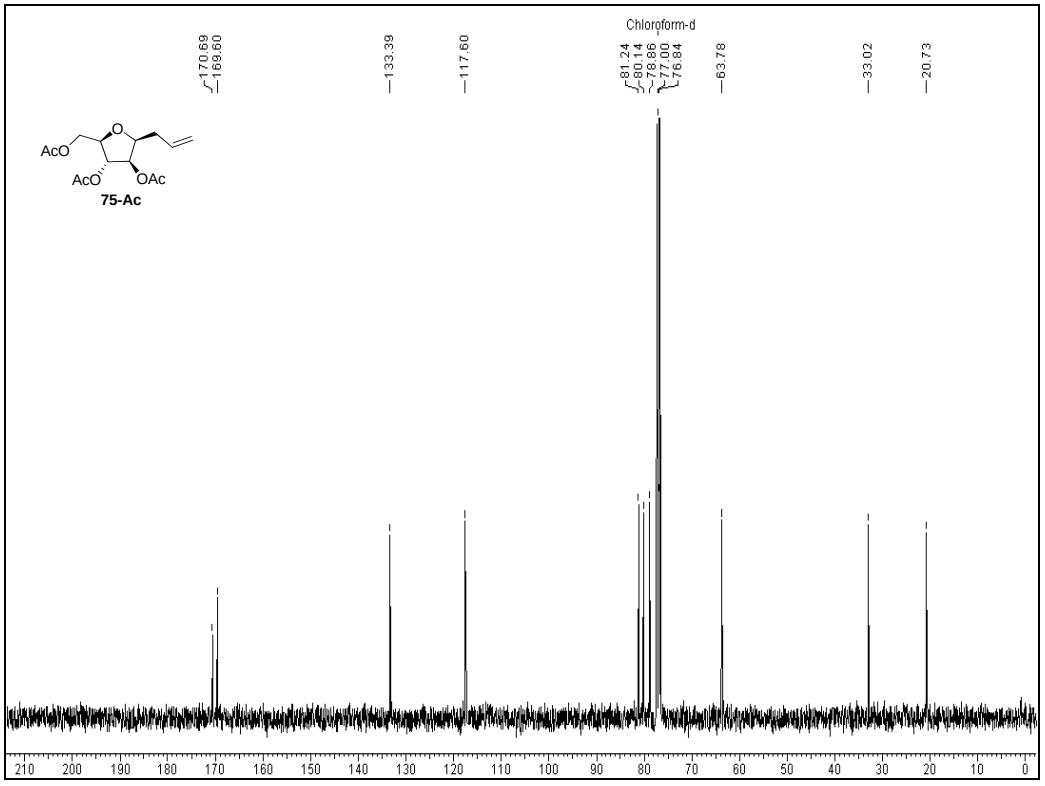
^{1}H NMR of compound 75



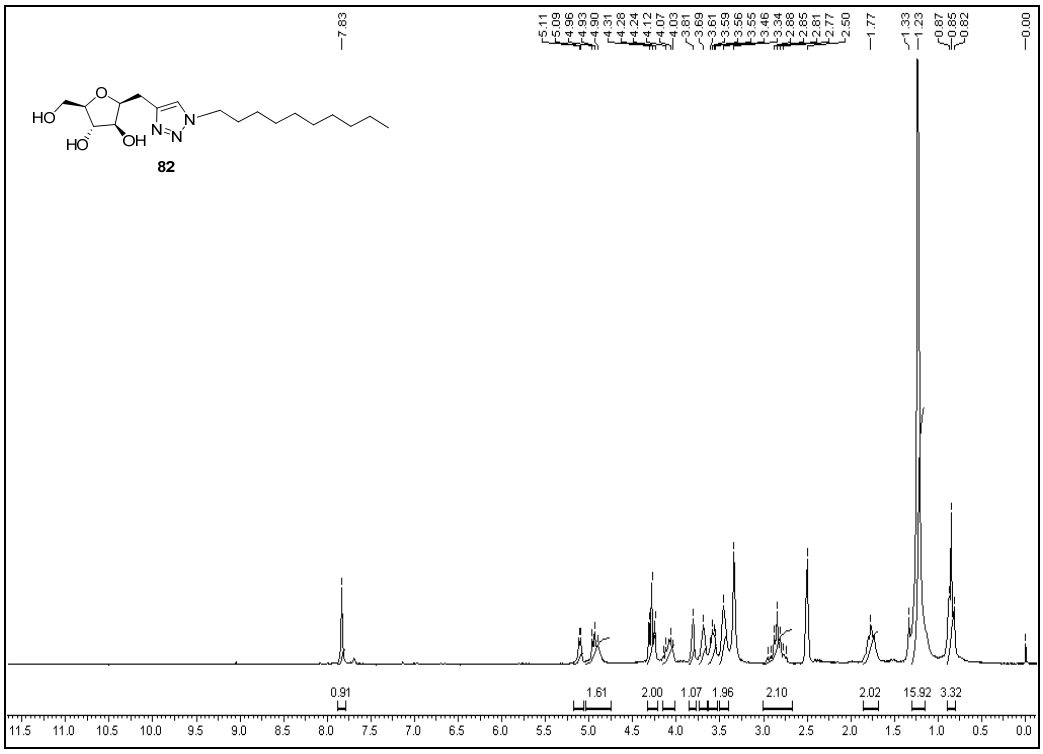
^{13}C NMR of compound 75



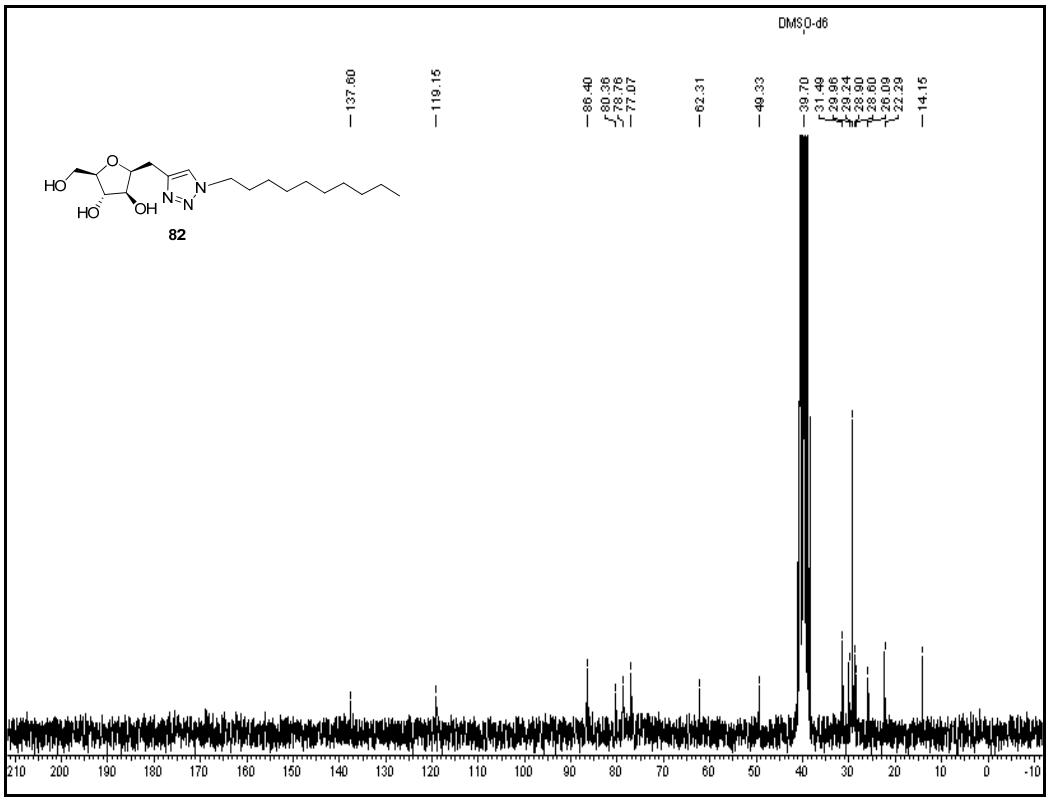
^{1}H NMR of compound 75-Ac



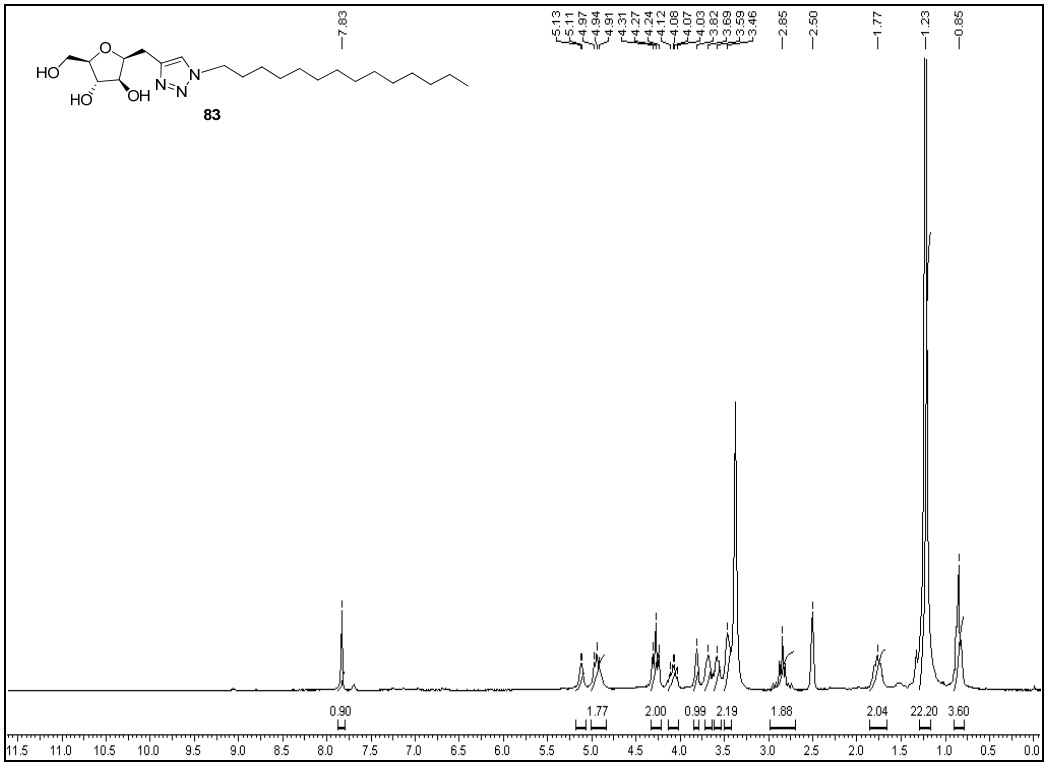
^{13}C NMR of compound 75-Ac



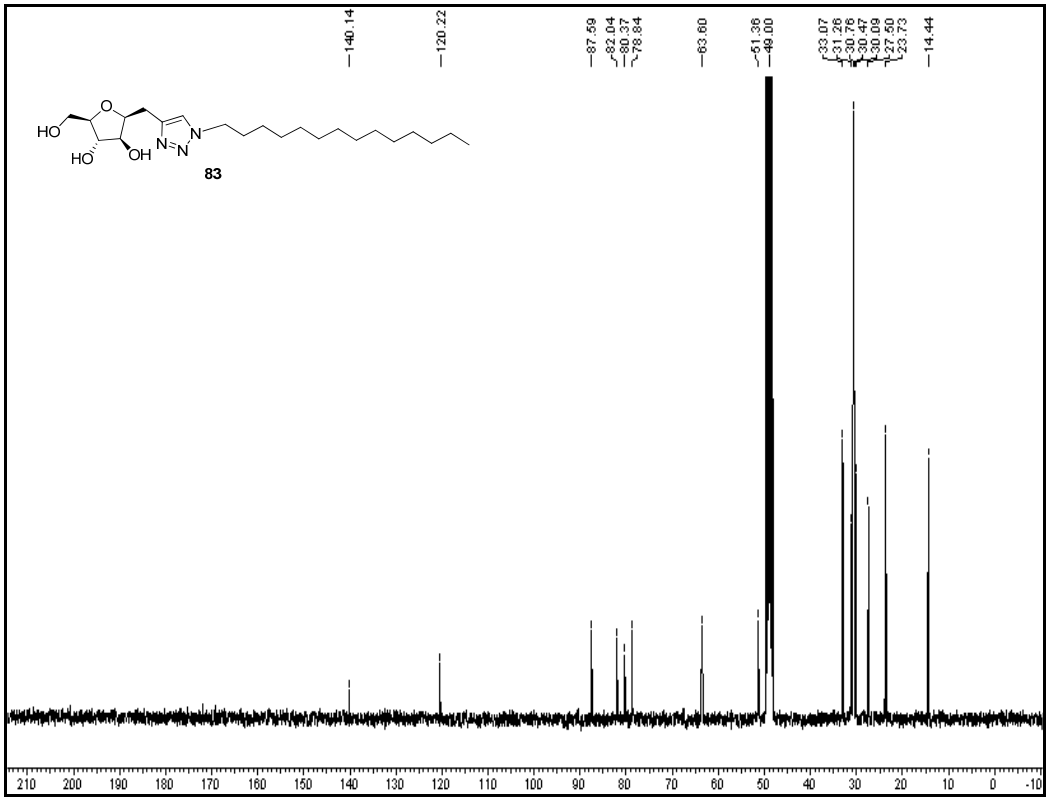
^{1}H NMR of compound 82



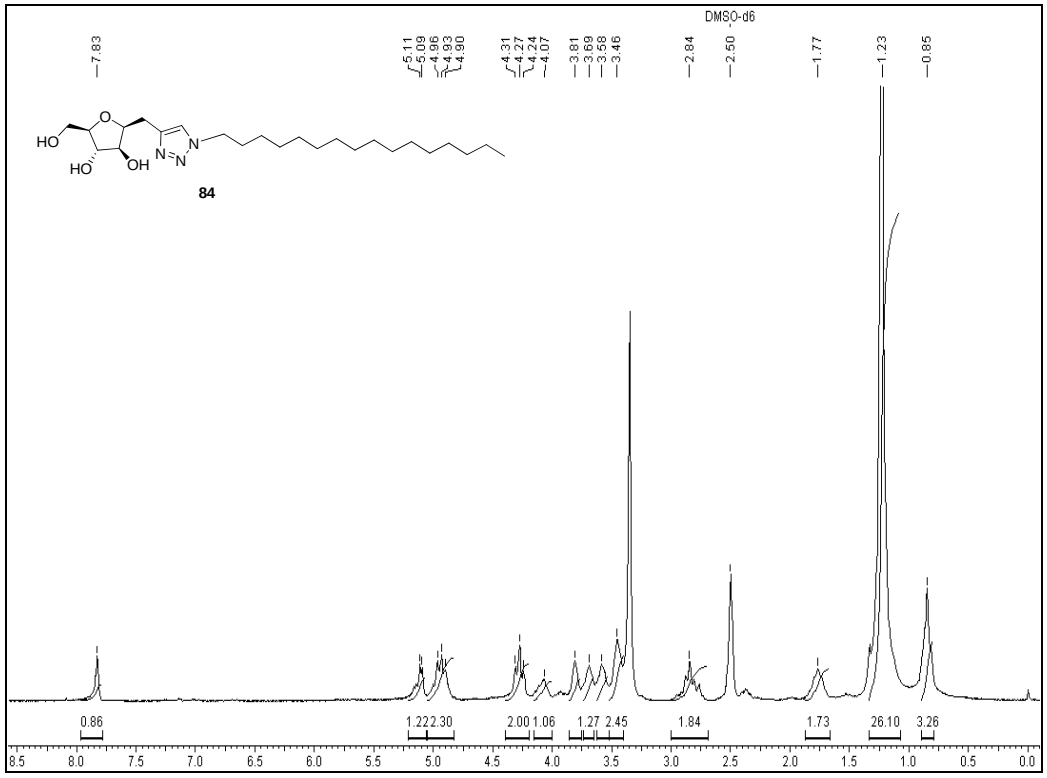
^{13}C NMR of compound 82



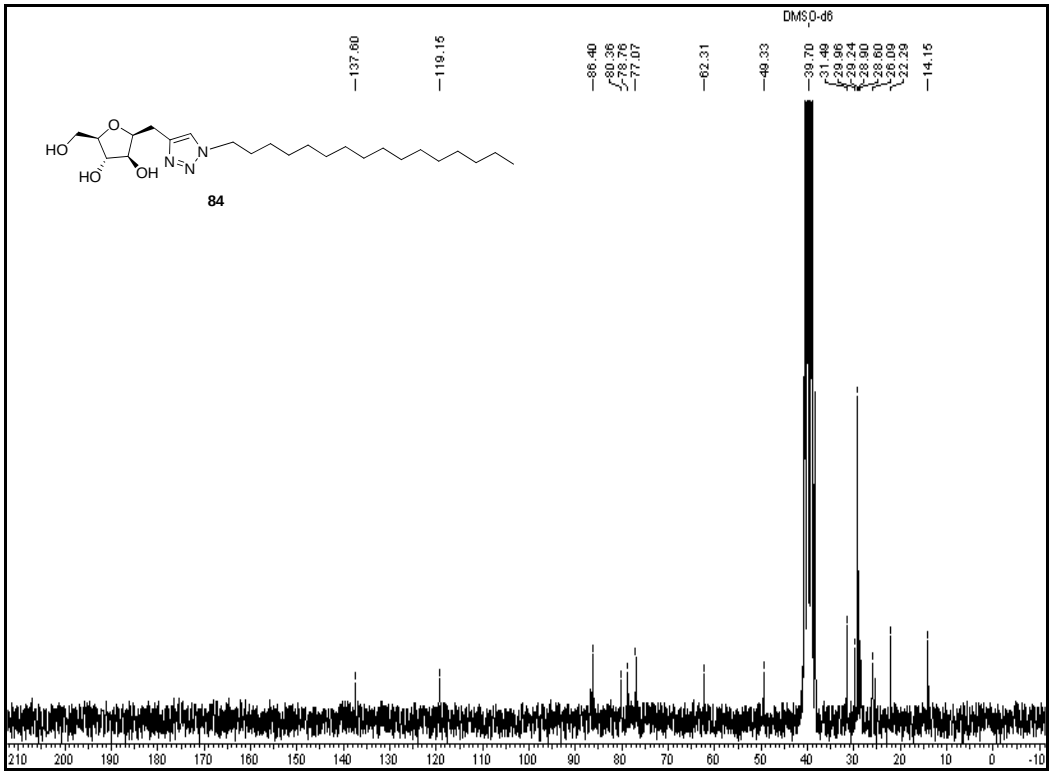
^{1}H NMR of compound 83



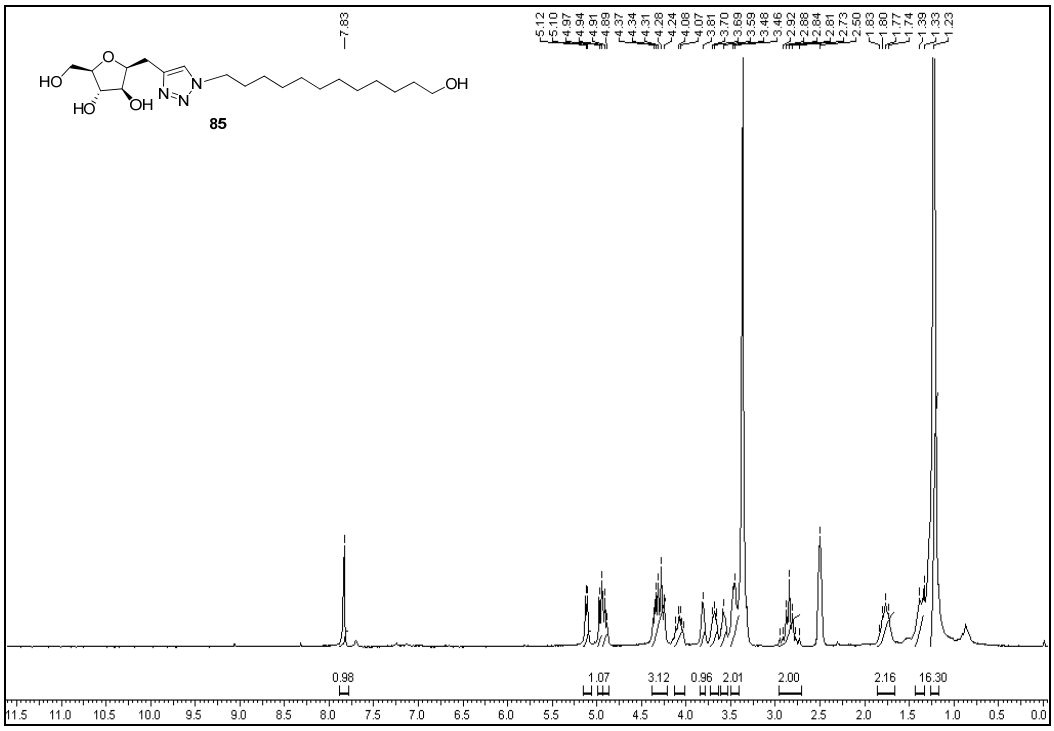
^{13}C NMR of compound 83



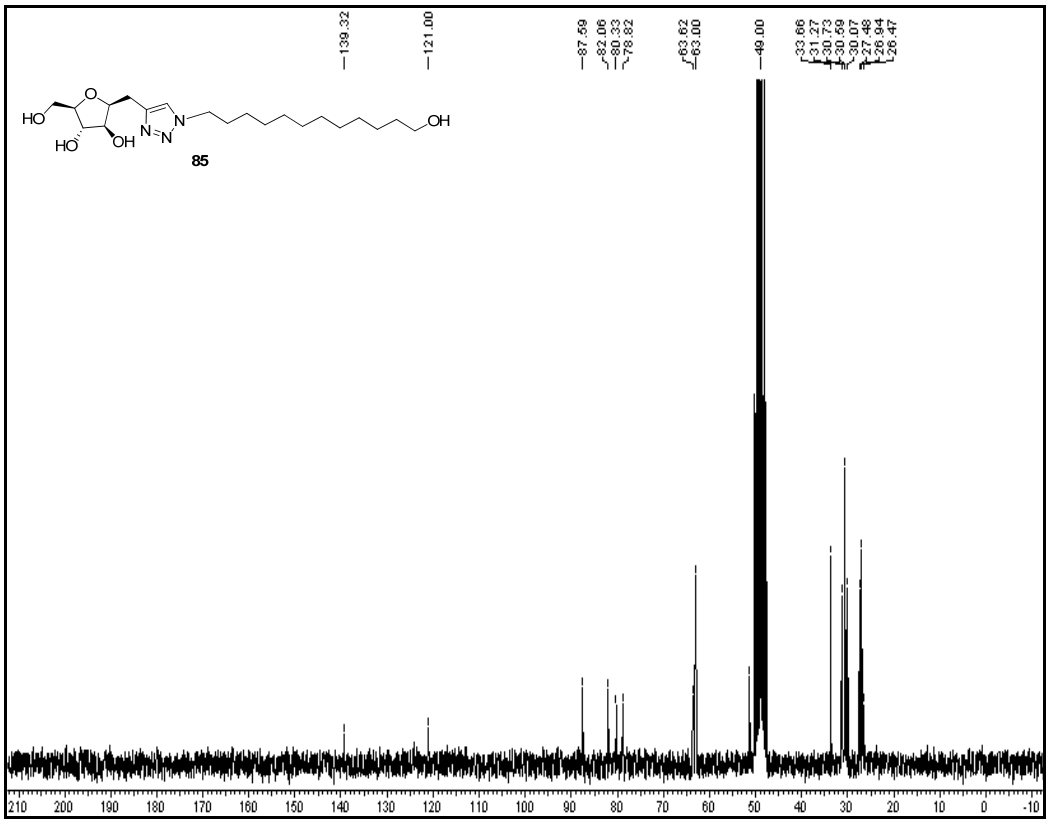
^{1}H NMR of compound 84



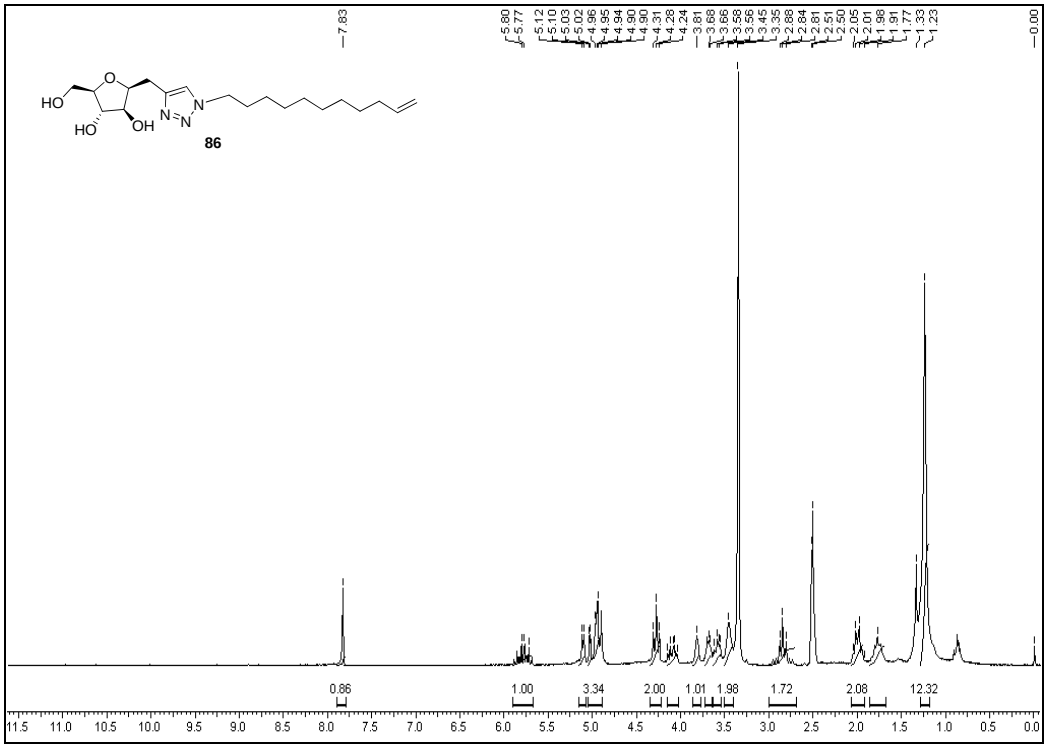
^{13}C NMR of compound 84



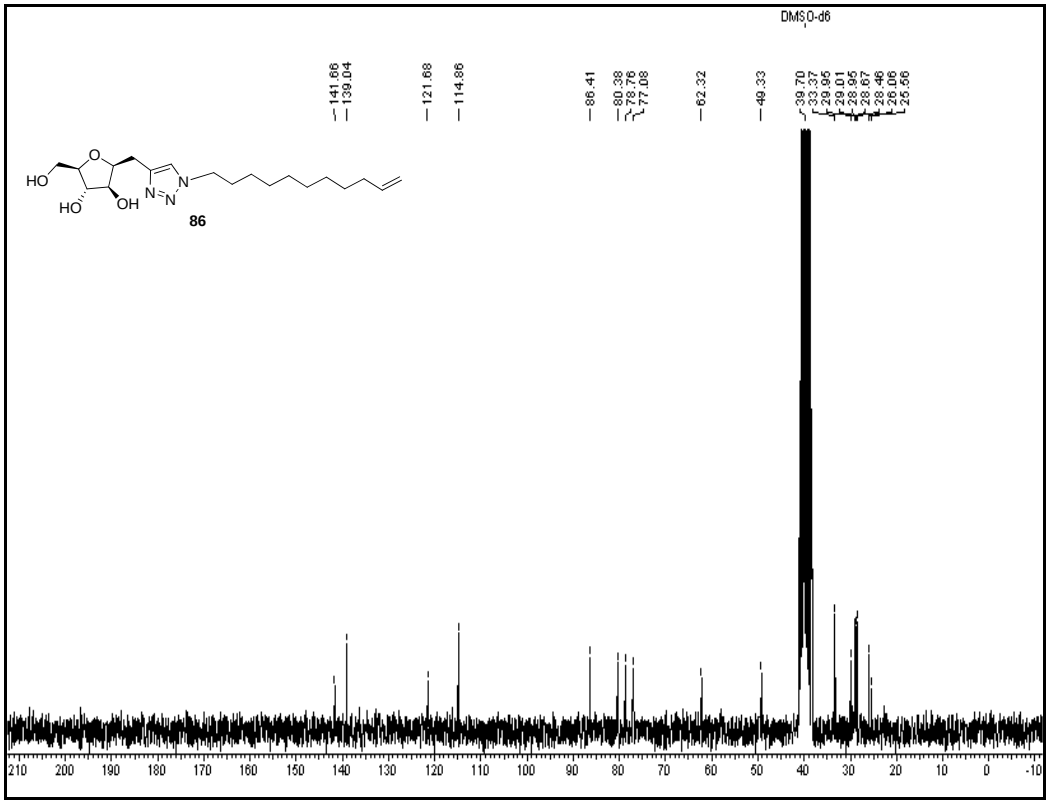
^{1}H NMR of compound 85



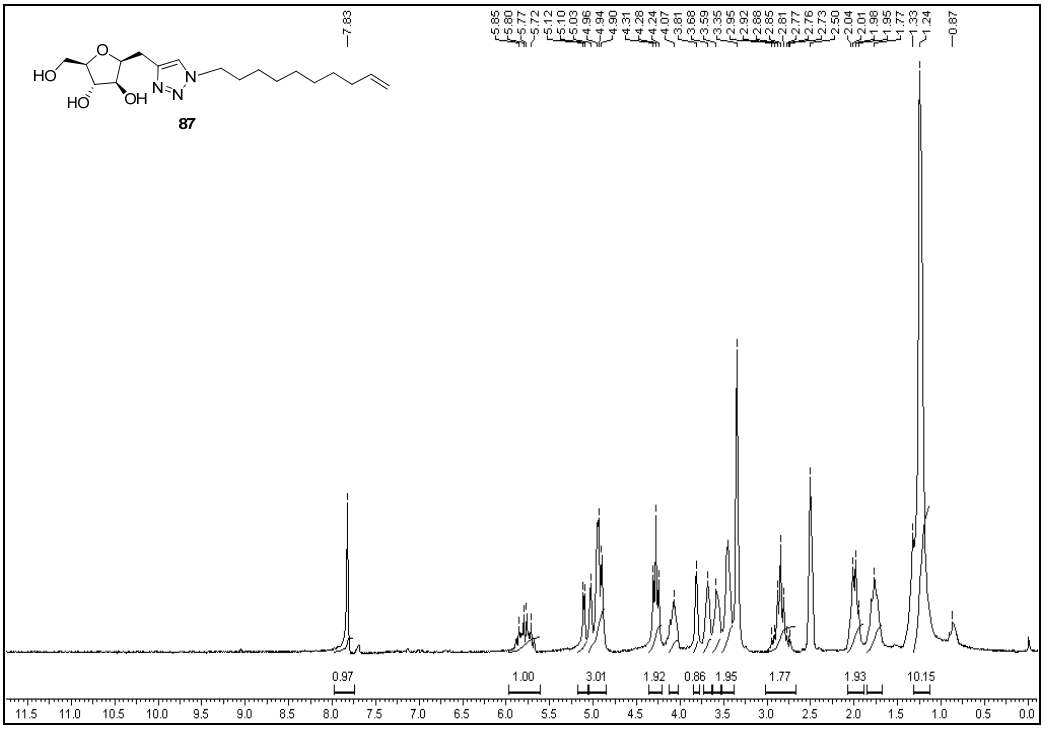
^{13}C NMR of compound 85



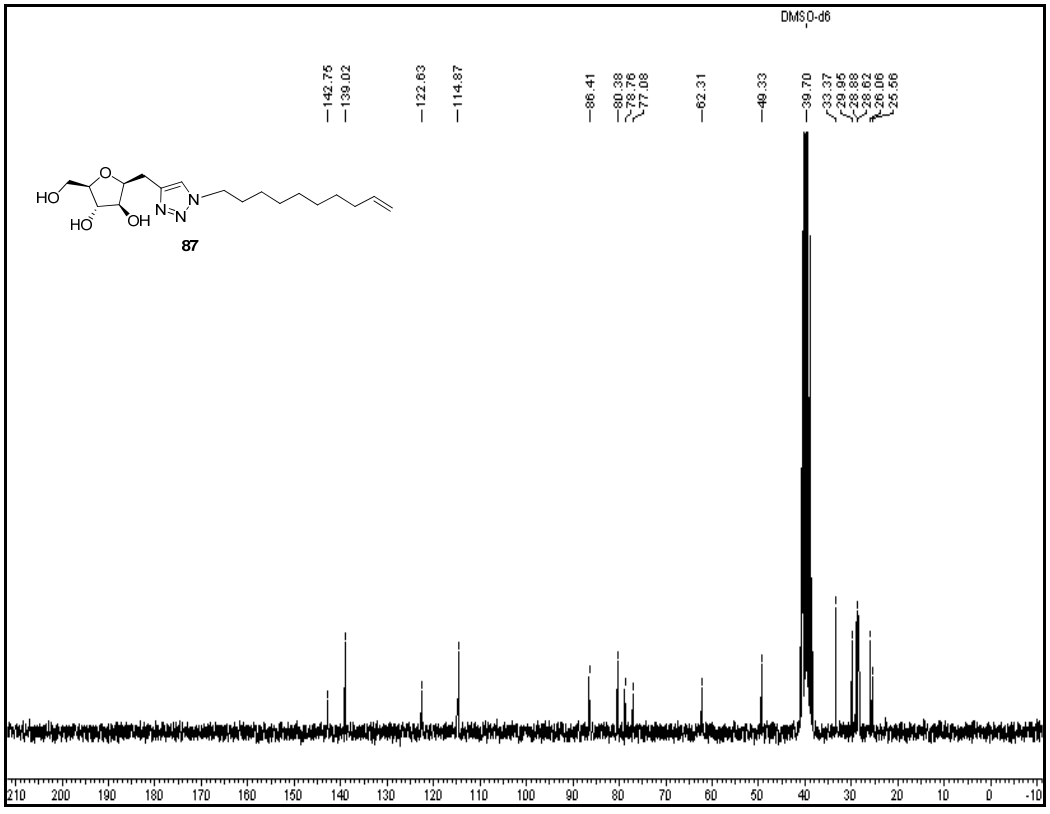
^{1}H NMR of compound 86



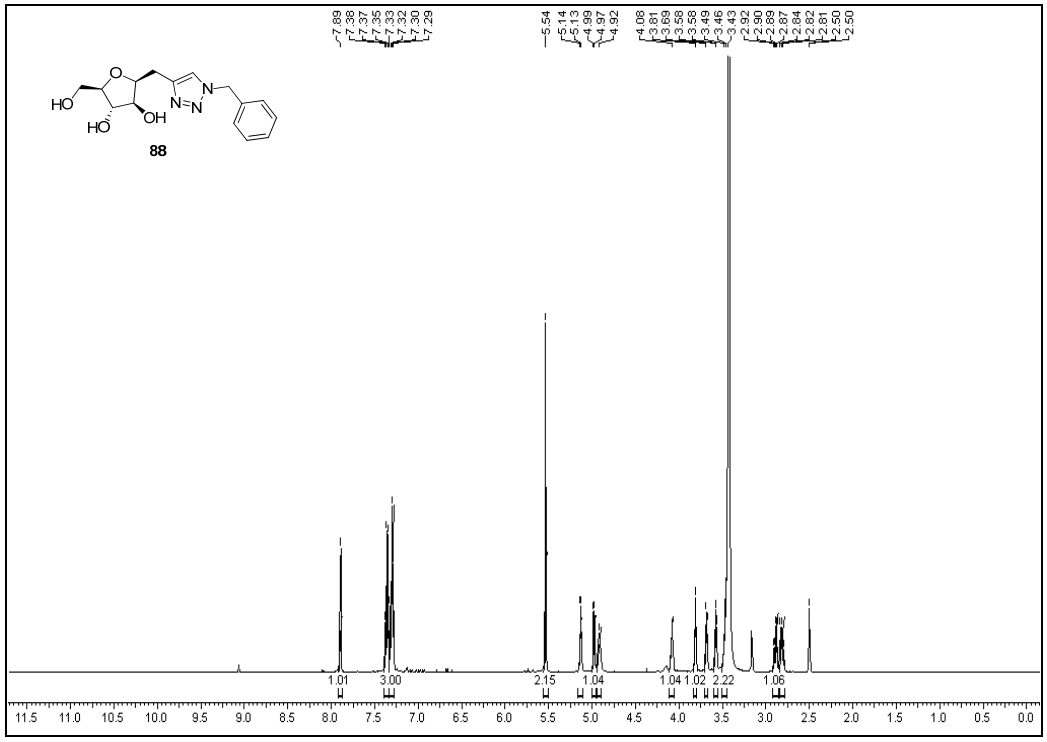
^{13}C NMR of compound 86



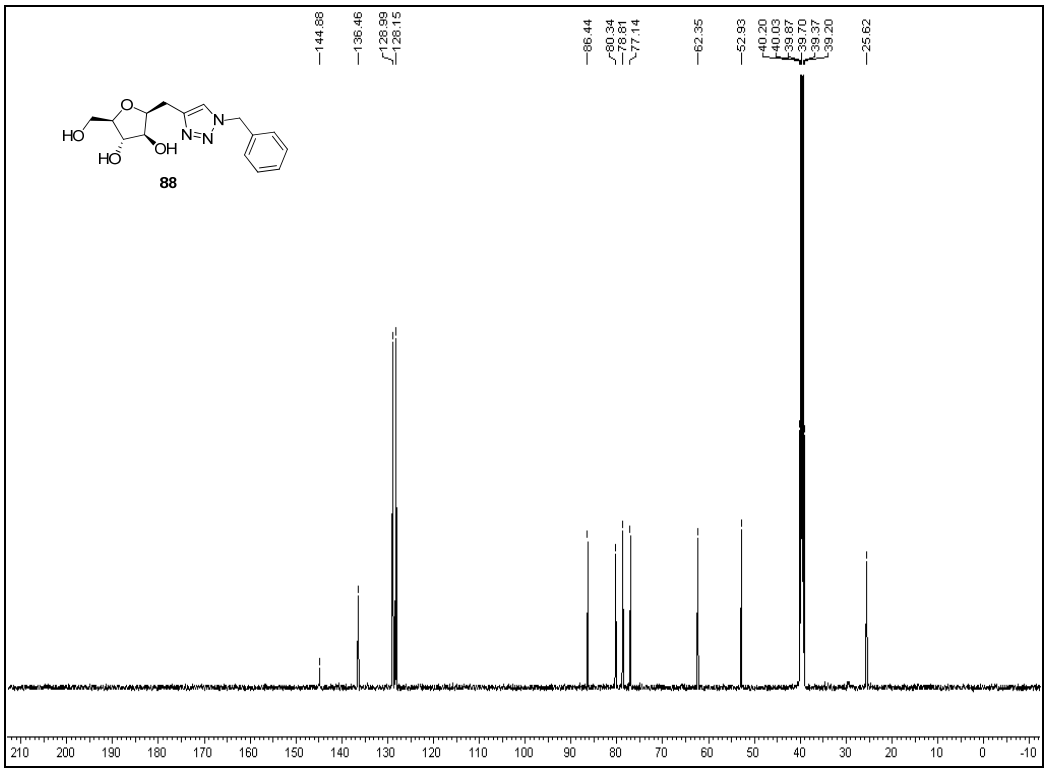
^{1}H NMR of compound 87



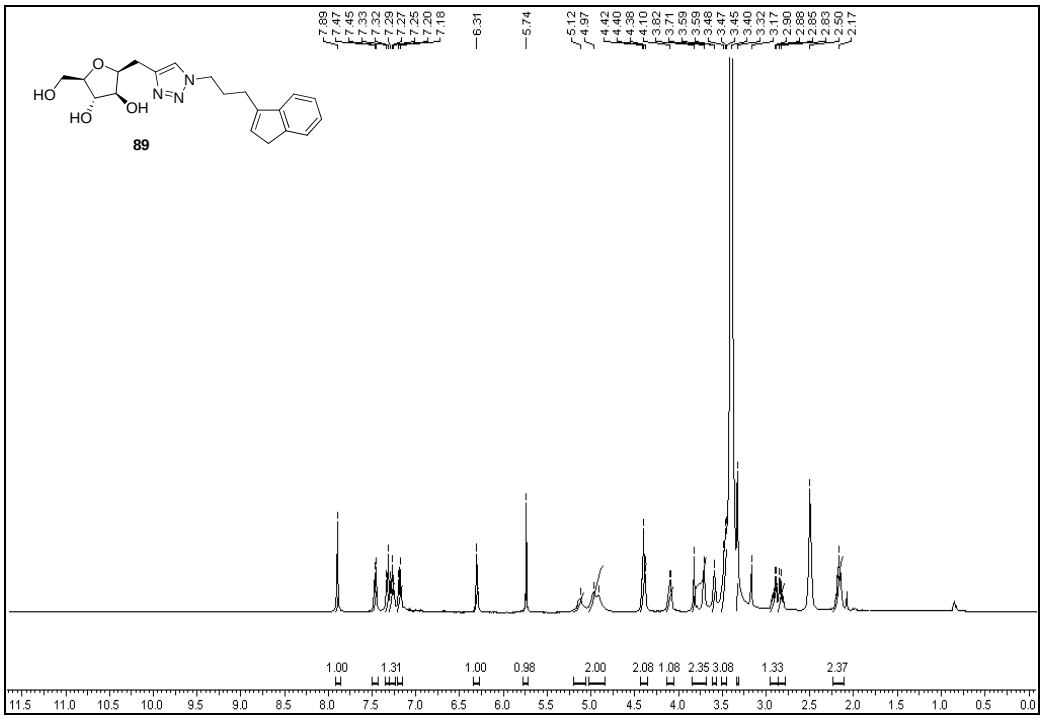
^{13}C NMR of compound 87



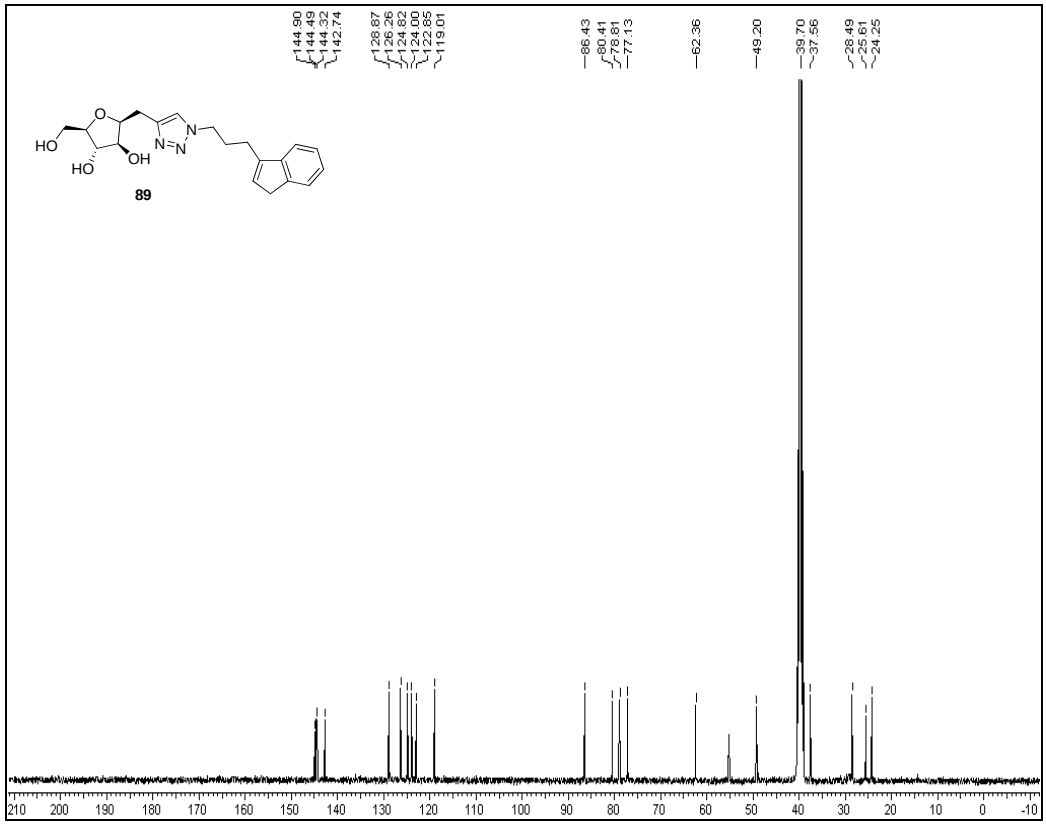
^{1}H NMR of compound 88



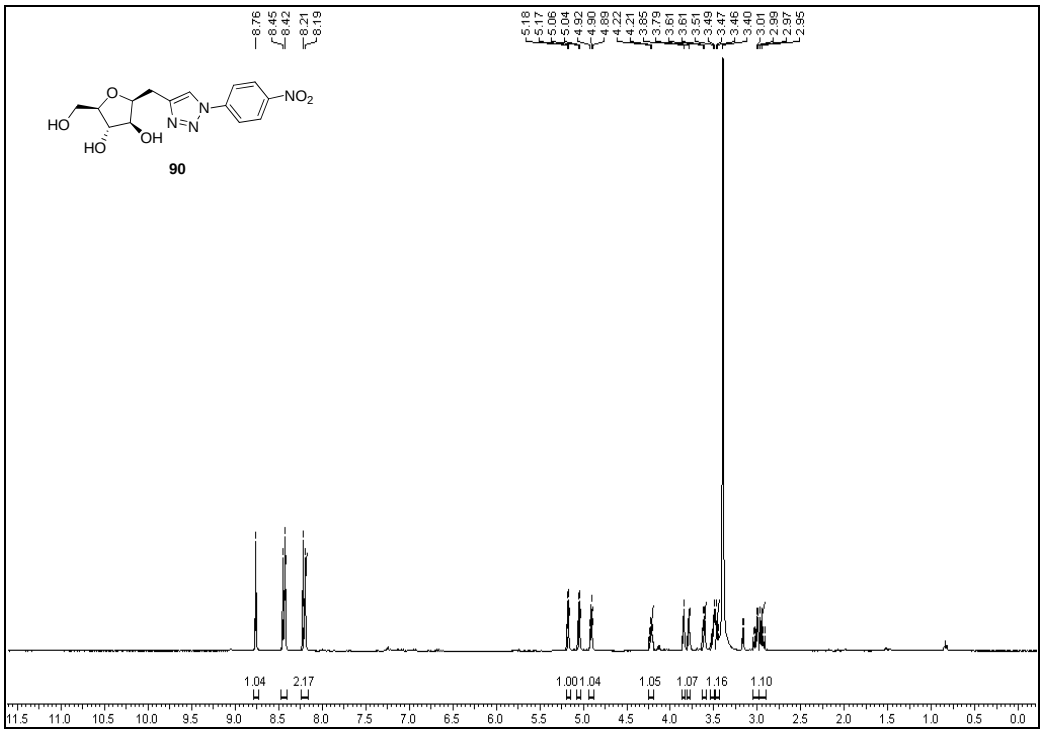
^{13}C NMR of compound 88



^{1}H NMR of compound 89



^{13}C NMR of compound 89



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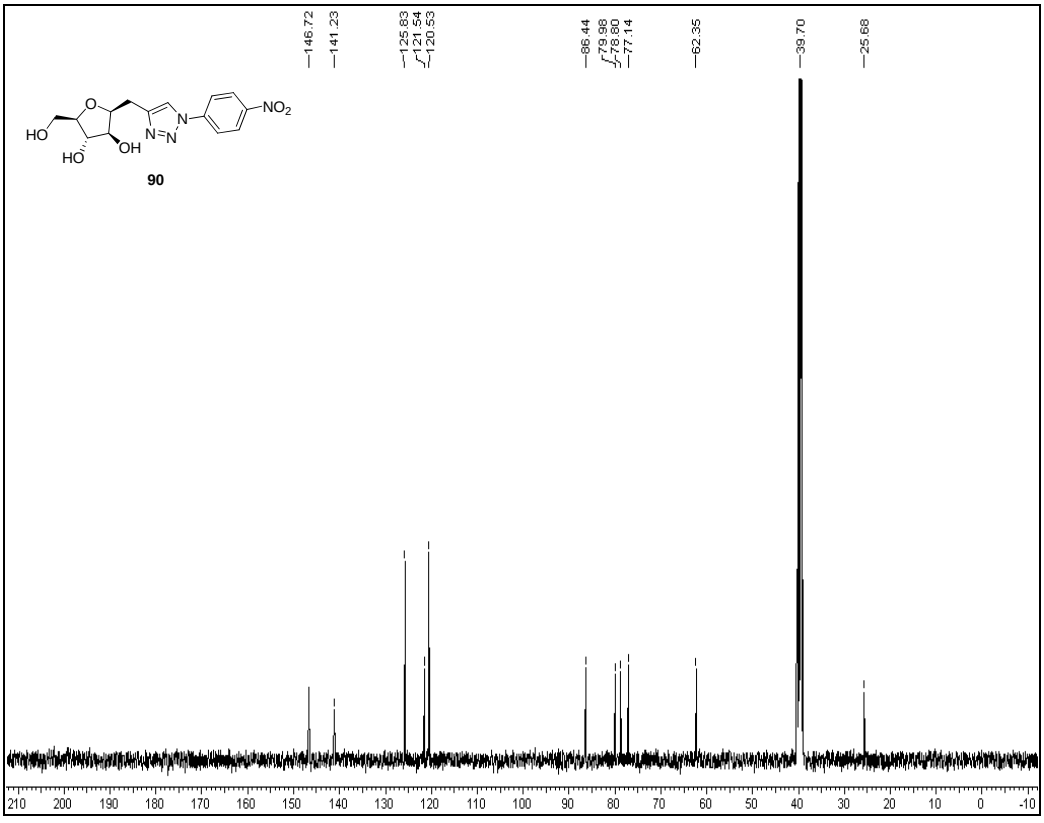

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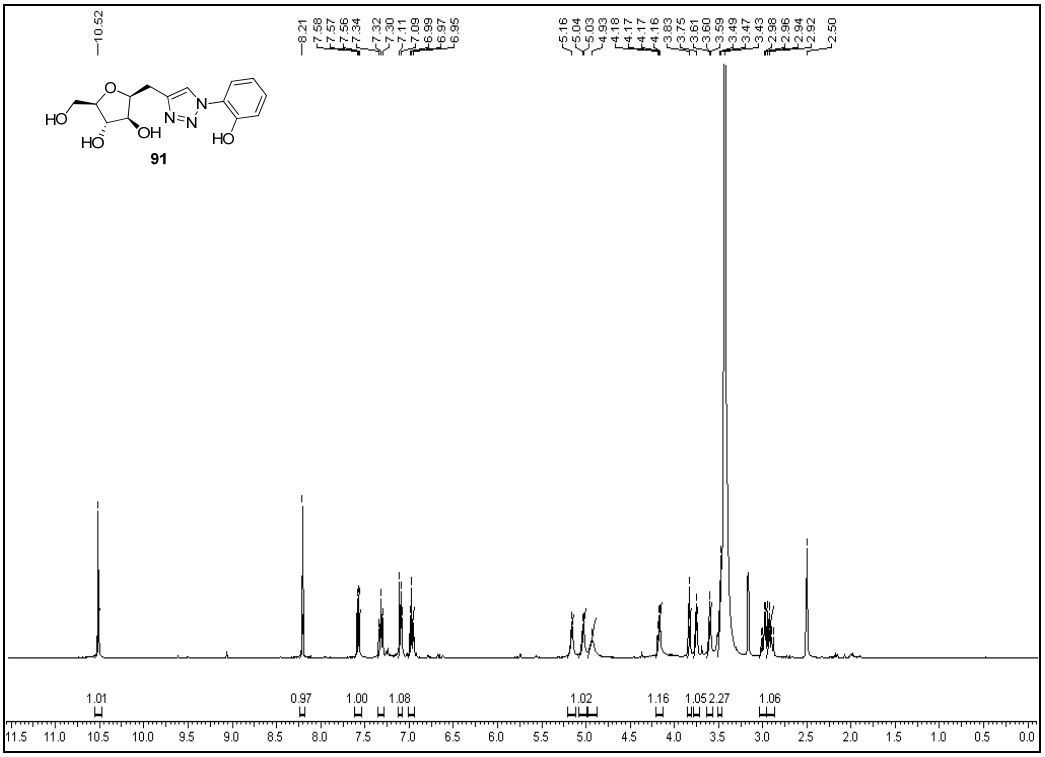
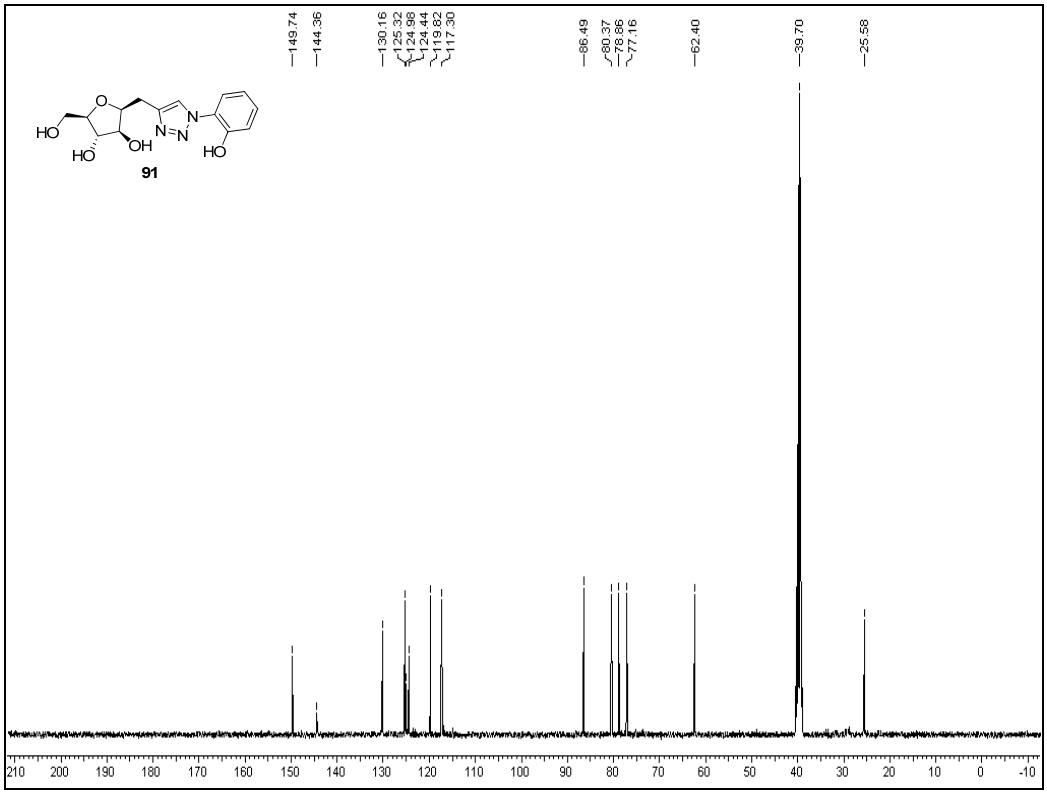
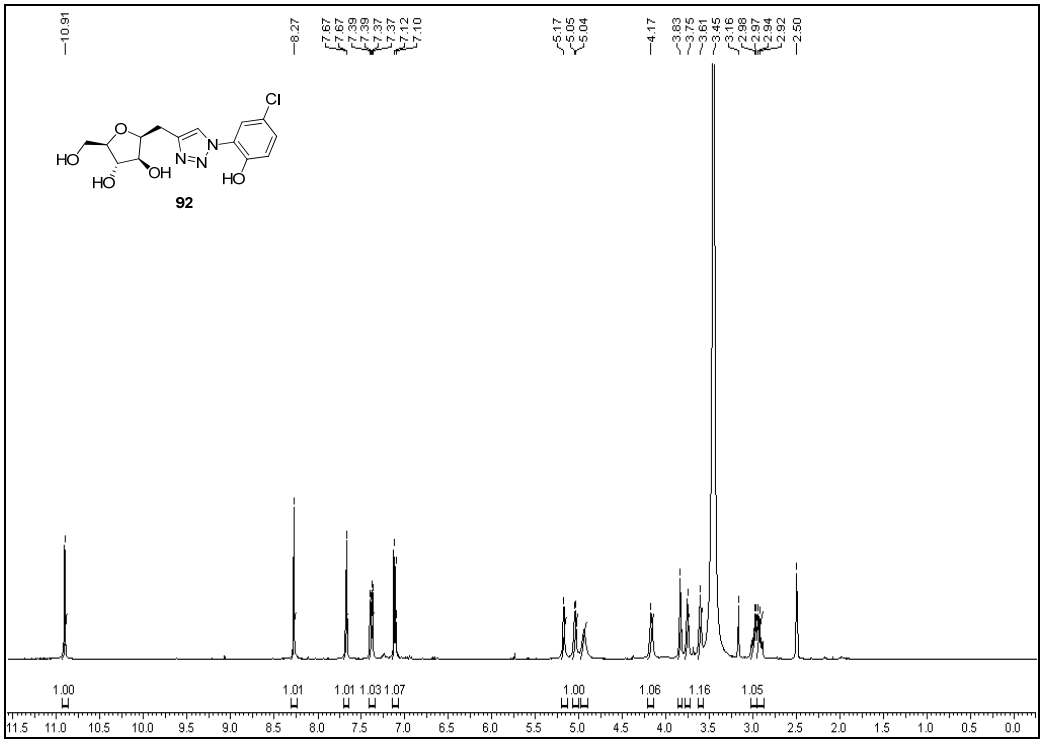


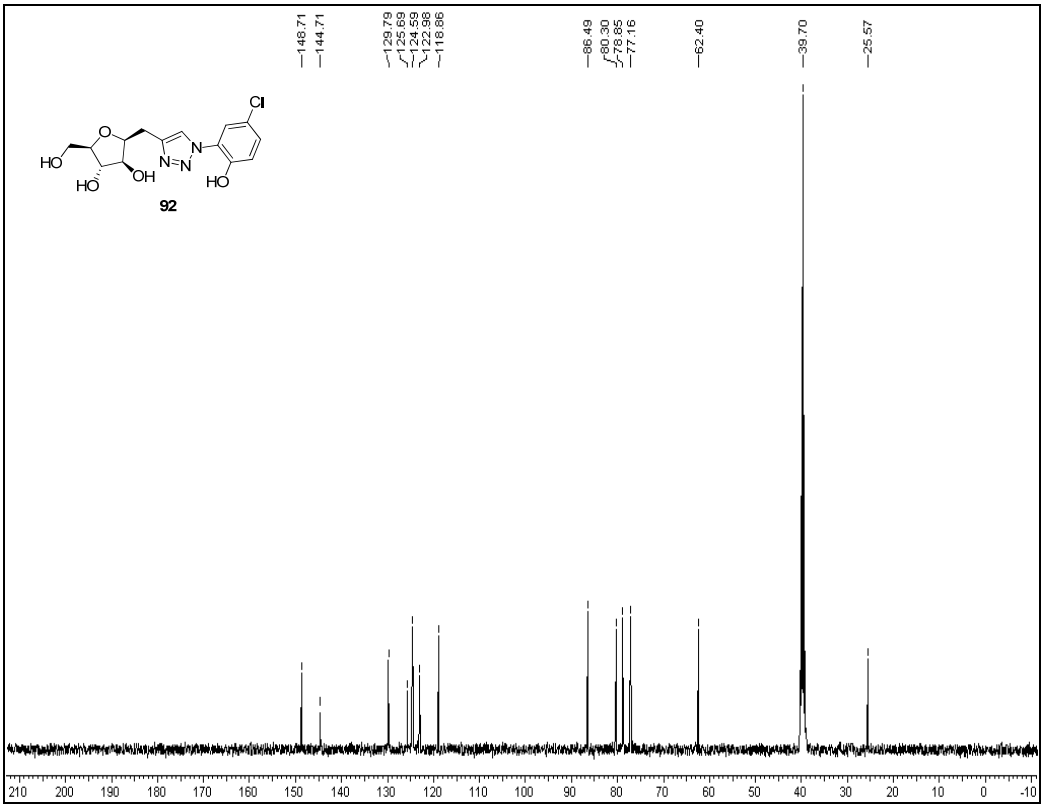
^{1}H NMR of compound 91



^{13}C NMR of compound 91



^{1}H NMR of compound 92



^{13}C NMR of compound 92

References

1. (a) Richard McGraw Hill.; Ismael Kassim; *Sherris Medical Microbiology (4th edition)* **2004**, ISBN 0-8385-8529-9; (b) Kumar V; Abbas AK; Fausto N; Mitchell RN. *Robbins Basic Pathology (8th ed.). Saunders Elsevier*. **2007**, pp. 516–522.

2. Gerald L. Mandell; John E. Bennett. *Raphael Mandell, Douglas, and Bennett's principles and practice of infectious diseases (7th ed.)* **2010**, *Chapter 250*, ISBN 978-0-443-06839-3.

3. (a) Peter G. Gibson; Michael Abramson. *Evidence-based respiratory medicine (1. publ. ed.). Oxford: Blackwell. ISBN 978-0-7279-1605-1* **2005**, 321; (b) Sharma SK; Mohan A; T., K. *Indian J. Med. Res.* **2005**, *121*, 550–67.

4. Lawn, S. D.; Zumla, A. I. *The Lancet* **2011**, *378*, 57–72.

5. (a) S.K. Sharma; Mohan, A. *Indian J. Med. Res.* **2004**, *120*, 316–356; (b) Golden MP; Vikram HR; . *Extrapulmonary tuberculosis: an overview. American Family Physician* **2005**, *72*, 1761–1768; PMID 16300038; (c) Jindal; editor-in-chief SK. *Textbook of pulmonary and critical care medicine. New Delhi: Jaypee Brothers Medical Publishers*, pp. 549. ISBN 978-93-5025-073-0.

6. (a) Kabra; [edited by] Vimlesh Seth. *Essentials of tuberculosis in children (3rd ed. ed.). New Delhi: Jaypee Bros. Medical Publishers.* **2006**, pp. 249. ISBN 978-81-8061-709-6.

7. *Global Tuberculosis Control 2011. World Health Organization.* 15 April **2012**.

8. (a) *Central European journal of public health* **2010**, *18*, 237; (b) Dye, C.; Williams, B. G. *Science* **2010**, *328*, 856–861.

9. (a) Chan E D; Iseman M D. *Br. Med. J.* **2002**, *325*, 1282–1286; (b) Drobniewski F A; Balabanova Y M. *Int. J. Infect. Dis* **2002**, *6*, S21–S31.

10. (a) *Centers for Disease Control and Prevention 2006 Emergence of Mycobacterium tuberculosis with extensive resistance to second-line drugs-worldwide; MMWR* 55 301–305; (b) Espinal M A; Dye C; Raviglione M. *Int. Tuberc. Lung Dis.* **1999**, *3*, 561–563; (c) Goble M; Iseman M D; Madsen L A. *N. Engl. J. Med.* **1993**, *328*, 527–532; (d) Shaw, K. J.; Barbachyn, M. R. *Ann. N.Y.*

Acad. Sci. **2011**, 1241–1248; (e) Dalton, T.; Cegielski, P.; Akksilp, S.; Asencios, L.; Caoili, J. C.; Cho, S.-N.; Erokhin, V. V.; Ershova, J.; Gler, M. T.; Kazennyy, B. Y.; Kim, H. J.; Kliiman, K.; Kurbatova, E.; Kvasnovsky, C.; Leimane, V.; van der Walt, M.; Via, L. E.; Volchenkov, G. V.; Yagui, M. A.; Kang, H. *The Lancet* **2012**, *380*, 1406–1417.

11. Arachi, A. *Tubercle* 191, *72*, 1.

12. Lee, R. E.; Brennan, P. J.; Besra, G. S. *Curr. Top. Microbiol. lmmunol.* **1996**, *215*, 1.

13. (a) Karakousis, P. C.; Bishai, W. R.; Dorman, S. E. *Cellular Microbiology* **2004**, *6*, 105–116; (b) Dover, L. G.; Alderwick, L. J.; Brown, A. K.; Futterer, K.; Besra, G. S. *Current Molecular Medicine* **2007**, *7*, 247–276; (c) Gautam, A.; Vyas, R.; Tewari, R. *Critical Reviews in Biotechnology* **2011**, *31*, 295–336; (d) Matsuba, T.; Nakajima, C.; Suzuki, Y. *Jpn. J. bacterial.* **2010**, *65*, 355.

14. (a) Crick, D. C.; Mahapatra, S.; Brennan, P. J. *Glycobiology* **2001**, *11*, 107R–118R; (b) Brennan, P. J. *Tuberculosis* **2003**, *83*, 91–97.

15. (a) Belanger, A. E.; Besra, G. S.; Ford, M. E.; Mikusova, K.; Belisle, J. T.; Brennan, P. J.; Inamine, J. M. *Proceedings of the National Academy of Sciences of the United States of America* **1996**, *93*, 11919–11924; (b) Besra, G. S.; Brennan, P. J. *Journal of Pharmacy and Pharmacology* **1997**, *49*, 25–30; (c) Lowary, T. L.; Tatsuta, K.; Thiem, J. *In Glycoscience: Chemistry and Chemical Biology; Springer: Berlin* **2001**, 2005–2080; (d) Kremer, L.; Besra, G. S. *Expert Opinion on Investigational Drugs* **2002**, *11*, 153–157; (e) Janin, Y. L. *Bioorg. Med. Chem.* **2007**, *15*, 2479–2513.

16. (a) Ayers, J. D.; Lowary, T. L.; Morehouse, C. B.; Besra, G. S. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 437–442; (b) Subramaniam, V.; Lowary, T. L. *Tetrahedron* **1999**, *55*, 5965–5976; (c) Cociorva, O. M.; Gurcha, S. S.; Besra, G. S.; Lowary, T. L. *Bioorg. Med. Chem.* **2005**, *13*, 1369–1379; (d) Centrone, C. A.; Lowary, T. L. *Bioorg. Med. Chem.* **2004**, *12*, 5495–5503; (e) Joe, M.; Lowary, T. L. *Carbohydr. Res.* **2006**, *341*, 2723–2730; (f) Bosco, M.; Bisseret, P.; Constant, P.; Eustache, J. *Tetrahedron Lett.* **2007**, *48*, 153–157.

17. Bouix, C.; Bisseret, P.; Eustache, J. *Tetrahedron Lett.* **2000**, *41*, 3269–3269.

18. Maddry, J. A.; Bansal, N.; Bermudez, L. E.; Comber, R. N.; Orme, I. M.; Suling, W. J.; Wilson, L. N.; Reynolds, R. C. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 237–242.

19. Centrone, C. A.; Lowary, T. L. *J. Org. Chem.* **2002**, *67*, 8862–8870.

20. Wilkinson, B. L.; Long, H.; Sim, E.; Fairbanks, A. J. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 6265–6267.

21. Wolucka, B. A.; McNeil, M. R.; Dehoffmann, E.; Chojnacki, T.; Brennan, P. J. *J. Bio. Chem.* **1994**, *269*, 23328–23335.

22. (a) Lee, R. E.; Mikusova, K.; Brennan, P. J.; Besra, G. S. *J. Am. Chem. Soc.* **1995**, *117*, 11829–11832; (b) Lee, R. E.; Brennan, P. J.; Besra, G. S. *Glycobiology* **1997**, *7*, 1121–1128; (c) McGurk, P.; Chang, G. X.; Lowary, T. L.; McNeil, M.; Field, R. A. *Tetrahedron Lett.* **2001**, *42*, 2231–2234; (d) Liav, A.; Brennan, P. J. *Tetrahedron Lett.* **2005**, *46*, 2937–2939; (e) Liav, A.; Huang, H. R.; Ciepichal, E.; Brennan, P. J.; McNeil, M. R. *Tetrahedron Lett.* **2006**, *47*, 545–547.

23. (a) *Proc. Chem. Soc.* **1961**, 357–396; (b) Kolb, H. C.; Finn, M. G.; Sharpless, K. B. *Angew. Chem. Int. Ed.* **2001**, *40*, 2004–2006; (c) Binder, W. H.; Kluger, C. *Curr. Org. Chem.* **2006**, *10*, 1791–1815.

24. (a) Chang, G. X.; Lowary, T. L. *Tetrahedron Lett.* **2006**, *47*, 4561–4564; (b) Peri, F.; Bassetti, R.; Caneva, E.; de Gioia, L.; La Ferla, B.; Presta, M.; Tanghetti, E.; Nicotra, F. *J. Chem. Soc.-Perkin Trans. 1* **2002**, 638–644.

25. Peri, F.; Bassetti, R.; Caneva, E.; Gioia, L. d.; Ferla, B. L.; Presta, M.; Tanghetti, E.; Nicotra, F. *J. Chem. Soc.-Perkin Trans. 1* **2002**, 638–644.

26. (a) Tronchet, J. M.; Baehler, B.; Eder, H.; Lehong, N.; Perret, F.; Poncet, J.; Zumwald, J. B. *Helv. Chim. Acta* **1973**, *56*, 1310–1317; (b) Krajewski, J. W.; Gluzinski, P.; Pakulski, Z.; Zamojski, A.; Mishnev, A.; Kemme, A. *Carbohydr. Res.* **1994**, *252*, 97–105.

27. (a) Defaye, J.; Horton, D.; Muesser, M. *Carbohydr. Res.* **1971**, *20*, 305; (b) Blumberg, K.; Fuccello, A.; Vanes, T. *Carbohydr. Res.* **1979**, *70*, 217–232; (c)

Ramana, C. V.; Giri, A. G.; Suryawanshi, S. B.; Gonnade, R. G. *Tetrahedron Lett.* **2007**, *48*, 265–268.

28. Pakulski, Z.; Zamojski, A. *Tetrahedron* **1997**, *53*, 2653–2666.

29. (a) X-ray intensity data of compound **76** was collected on a Bruker SMART APEX CCD diffractometer with omega and phi scan mode, l(MoKa) = 0.71073 Å at *T* = 297 (2) K. All the data were corrected for Lorentzian, polarization, and absorption effects using Bruker's SAINT and SADABS programs. The crystal structure was solved by direct methods using SHELXS-97 and the refinement was performed by full matrix least squares of *F*2 using SHELXL- 97 Hydrogen atoms were included in the refinement as per the riding model; (b) Sheldrick, G. M.; SHELX-97 program for crystal structure solution and refinement, University of Göttingen, Germany, 1997.

30. Yu, H. W.; Zhang, H. Y.; Yang, Z. J.; Min, J. M.; Ma, L. T.; Zhang, L. H. *Pure Appl. Chem.* **1998**, *70*, 435–438.

31. (a) Danishefsky, S. J.; Deninno, M. P.; Phillips, G. B.; Zelle, R. E.; Lartey, P. A. *Tetrahedron* **1986**, *42*, 2809–2819; (b) Wang, R. B.; Lim, C. M.; Tan, C. H.; Lim, B. K.; Sim, K. Y.; Loh, T. P. *Tetrahedron Asymm.* **1995**, *6*, 1825–1828; (c) Chattopadhyay, A. *J. Org. Chem.* **1996**, *61*, 6104–6107.

32. Petr Jansa; Petr Spacek; Ivan Votruba; Petra Břehova; Martin Dračínsky; Blanka Klepetarova ; Janeba, Z. *Collect. Czech. Chem. Commun.* **2011**, *76*, 1121–1131.

List of publication

1. "A [Pd]-mediated ω-alkynone cycloisomerization approach for the central tetrahydropyran unit and the synthesis of C(31)–C(48) fragment of Aflastatin A" **Sachin B. Narute**, Neella Chandra Kiran and Chepuri V. Ramana; *Org. Biomol. Chem*., **2011**, *9*, 5469–5475.

2. "Stereoselective synthesis of β-*C*-allyl and β-*C*-propargyl-D-arabinofuranosides C. V. Ramana, **Sachin B. Narute**, Rajesh G. Gonnade, Rahul S. Patil; *Synthesis* **2008**, *11*, 1783–1787.

3. "*C*-glycosides of dodecanoic acid: new capping/reducing agents for glyconanoparticle synthesis" C. V. Ramana, Kulbhushan A. Durugkar, Vedavati G. Puranik, **Sachin B. Narute**, B. L. V. Prasad; *Tetrahedron Lett.* **2008**, *49*, 6227–6230.

4. "Studies toward the synthesis of C(27)−C(48) fragment of Aflastatin A" **Sachin B. Narute** and C. V. Ramana *(Communicated)*.

5. "An efficient approach for synthesis of *C*-disaccharides of non-reducing sugars" Sachin B. Narute, J. K. Rout and C. V. Ramana *(To be communicated).*

6. "Synthesis of *C*-arabinofuranosyl analogues of β-DPA as novel antitubercular agents" **Sachin B. Narute**, S. Sarkar, D. Sarkar and C. V. Ramana *(To be communicated).*

Erratum