Total Synthesis of Naturally Occurring Sacidumlignans A, B, D and Stereoselective Synthesis of *C*-Disaccharides

Thesis Submitted to the AcSIR for the Award of
The Degree of
DOCTOR OF PHILOSOPHY
In Chemical Sciences

By

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UNDER THE GUIDANCE OF
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DECLARATION

The research work embodied in this thesis has been carried out at CSIR–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.

Organic Chemistry Division
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February–2015 **(Jeetendra Kumar Rout)**

CERTIFICATE

This is to certify that the work incorporated in this Ph.D. thesis entitled ***Total Synthesis of Naturally Occurring Sacidumlignans A, B, D and Stereoselective Synthesis of C-Disaccharides*** submitted by Mr. ***Jeetendra Kumar Rout*** to Academy of Scientific and Innovative Research (AcSIR) in fulfillment of the requirements for the award of the Degree of ***Doctor Of Philosophy***, embodies original research work under my supervision. We further certify that this work has not been submitted to any other University or Institution in part or full for the award of any degree or diploma. Research material obtained from other sources has been duly acknowledged in the thesis. Any text, illustration, table etc., used in the thesis from other sources, have been duly cited and acknowledged.

Jeetendra Kumar Rout
(Student)

Dr. C. V. Ramana
(Supervisor)

Dedicated

To

My Family

Acknowledgements

I would like to name a few people from the infinite personalities associated in the path of my research career and who have contributed enormously directly or indirectly for the success of the thesis.

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Jeetendra

ABREVIATIONS

Ac	Acetyl
Ac_2O	Acetic anhydride
AIBN	Azobisisobutyronitrile
aq.	Aqueous
anh.	Anhydrous
Bn	Benzyl
BnBr	Benzyl bromide
CH_2Cl_2	Dichloro methane
DCE	1,2-Dichloro ethane
DEAD	Diethyl azodicarboxylate
Cat.	Catalytic
TsCl	Tosyl chloride
Conc.	Concentrated
COSY	Correlation spectroscopy
DIBAL-H	Diisobutylaluminiumhydride
DIPEA	Diisopropylethyl amine
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DET	Diethyl tartrate
DMP	2,2'-Dimethoxypropane
DMF	*N,N*-Dimethylformamide
DMAP	*N,N'*-Dimethylaminopyridine
DMSO	Dimethyl sulfoxide
Et_3SiH	Triethylsilyl hydride
Et_2O	Diethyl ether
EtOAc	Ethyl acetate
Et_3N	Triethylamine
HMPA	Hexamethylphosphoramide
HRMS	High Resolution Mass Spectrometry
LAH	Lithium aluminium hydride
LiHMDS	Lithium1,1,1,3,3,3-hexamethyldisilazane
LDA	Lithium diisopropyamide
Ms/Mesyl	Methanesulfonyl

m-CPBA	*meta*-Chloroperbenzoic acid
Me	Methyl
NMR	Nuclear Magnetic Resonance
NBS	*N*-bromosuccinamide
NMO	*N*-Methylmorpholine N-oxide
NOESY	Nuclear Overhauser Effect Spectroscopy
Pd/C	Palladium on Carbon
p-TSA	*para*-Toluenesulfonic Acid
Ph	Phenyl
Py	Pyridine
PCC	Pryridinium chlorochromate
PMBCl	*p*-Methoxy benzyl chloride
TBSCl	*tert*-Butyldimethylsilyl chloride
TBAF	*tetra*-*n*-butylammonium fluoride
TBS	*tert*-Butyldimethyl chlorosilane
t-BuOOH	*tert*-Butyl hydroperoxide
PPh_3	Triphenylphosphine
rt	Room Temperature
sat.	Saturated
TBAI	*tetra*-Butylammonium iodide
Tf_2O	Triflic anhydride
t-BuOK	Potassium tertiary butoxide
TFA	Trifloroacetic acid
TMSOTf	Trimethylsilyl trifluoromethanesulfonate

Abbreviations used for NMR spectral informations:

br	broad	s	singlet	ddd	doublet of doublet of doublet
d	doublet	t	triplet	dddd	doublet of doublet of doublet of doublet
m	multiplet	dd	doublet of doublet	ddt	doublet of doublet of triplet
q	quartet	tq	triplet of quartet	ddq	doublet of doublet of quartet

GENERAL REMARKS

- All the moisture and air sensitive reactions have been carried out in anhydrous solvents under argon atmosphere in oven-dried glassware. The anhydrous solvents were distilled prior to use: CH_2Cl_2 and DMF from CaH_2; methanol from Mg cake; THF on Na/benzophenone; triethylamine and pyridine over KOH; acetic anhydride from sodium acetate. The commercially available reagents were used without further purification except boron trifluoride etherate and hexamethyldisilazane which were distilled prior to use.
- The reactions were monitored by thin layer chromatography (TLC) carried out on 0.25 mm E-Merck silica gel plates (60F–254) under UV light and anisaldehyde solution for charring purpose.
- All evaporations were carried out under reduced pressure on Buchi rotary evaporator at 45–50 °C unless otherwise specified.
- Purifications were carried out by Column Chromatography by using 100–200 mesh (0.075–0.150 mm) and 230–400 mesh (0.037–0.063 mm) silica gel and the Yields were referred to the quantity after purification.
- The NMR spectra of all the compounds were recorded on Bruker AC 200, Bruker DRX 400 and 500 MHz spectrometer in $CDCl_3$ or in Acetone-d_6 solutions using TMS as internal standard. The multiplicity of decoupled ^{13}C NMR signals was assigned with the help of DEPT spectra and the abbreviations used: s = singlet, d = doublet, t = triplet and q = quartet, represent C (quaternary), CH, CH_2 and CH_3 respectively. ^1H and ^{13}C NMR chemical shifts are reported in ppm downfield from Chloroform-d (δ = 7.25) or TMS and coupling constants (J) are reported in Hertz (Hz).
- Optical rotations were determined on a Jasco DIP-370 digital polarimeter. Specific optical rotations $[\alpha]_D^{25}$ are given in 10^{-1} x deg x cm^2 x g^{-1}.
- Mass spectroscopy was carried out on PI QStar Pulsar (Hybrid Quadrupole-TOF LC/MS/MS) and 4800 plus MALDI TOF/TOF Applied Biosystem spectrometer.
- 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}.

CONTENTS

ABSTRACT

The thesis entitled **"Total Synthesis of Naturally Occurring Sacidumlignans A, B, D and Stereoselective Synthesis of *C*-Disaccharides"** consists of two chapters. The first chapter deals with the total synthesis of Sacidumlignans A, B, and D and with the fixing of the absolute configuration of Sacidumlignans B and D. The second chapter presents a simple approach for the stereoselective synthesis of [1→1] and [1→6] linked *C*-disaccharides using a one-pot alkynol cycloisomerization-Kishi's deoxygenation reaction as the key step.

Chapter I: Total Synthesis of Naturally Occurring Sacidumlignans A, B, D

Among the known 10 species of the genus *Sarcostemma*, *Sarcostemma acidum* is one of the species prescribed as a medicine against chronic cough and postnatal hypogalactia in China. Yue and co-workers have isolated four new lignans including two degraded lignan derivatives from this species in 2005. The structures and their relative stereochemistry were elucidated comprehensively with the help of extensive 1D and 2D NMR spectral data analysis. From a structural perspective, Sacidumlignan D possesses an unprecedented dimethyl tetrahydrofuran moiety. Sacidumlignans A, B and C dispose naphthalene, dihydronaphthalene and tetrahydronaphthalene units respectively.

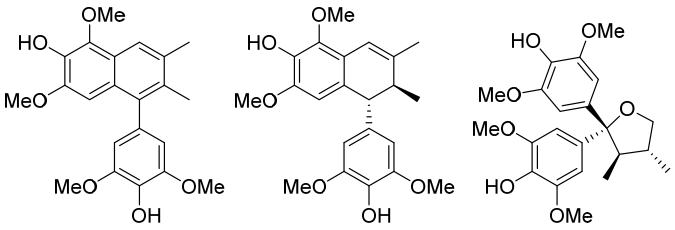


Figure 1. Structures of Sacidumlignans A, B and D

In 2011, we reported the first synthesis of (±)-Sacidumlignan D. In continuation, we have taken up the problem of fixing its absolute configuration and extending the developed synthetic route/key intermediates to access the other members of this family. For this, Evan's chiral auxiliary has been selected as a handle to introduce the chirality at one of the key centers in the core skeleton. The previously established diastereoselective *α*-methylation of the lactone in (±)-Sacidumlignan D was planned as the next key event for the other contiguous center and thus fabricating the complete skeleton **4**. The dehydrative cyclization of an aldehyde **6** (accessible from **4**, a carbon variant of Pomeranz−Fritsch isoquinoline synthesis) has been planned to construct the dihydronaphthalene core **5** of Sacidumlignan B.

Finally, aromatization of the dihydronaphthalene intermediate **5** should lead to the synthesis of the Sacidumlignan A (**3**). Coming to the key intermediate **4**, its synthesis was planned from a chiral ester **10** (Figure 3) by following some of the steps of racemic synthesis.

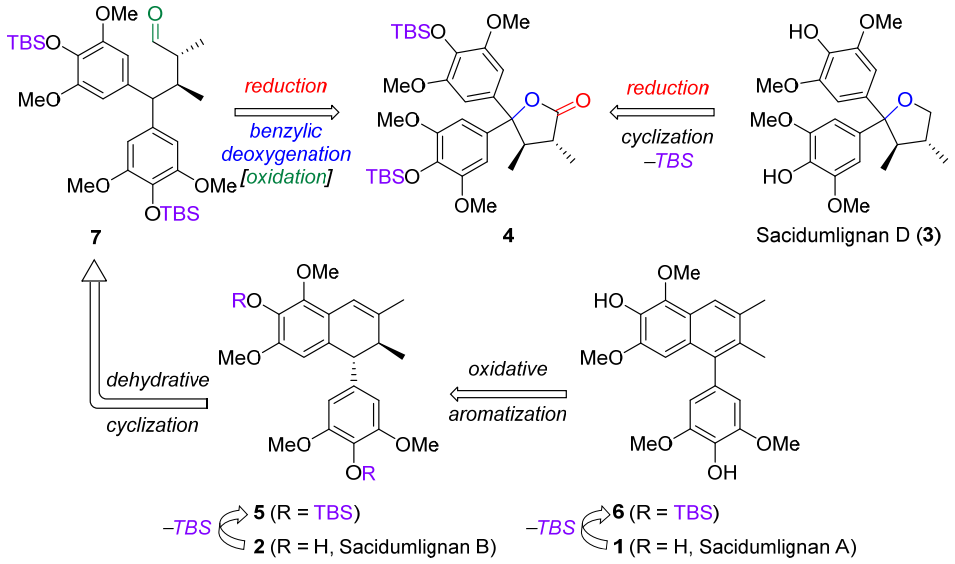


Figure 2. Planned approach for Sacidumlignans A, B and D

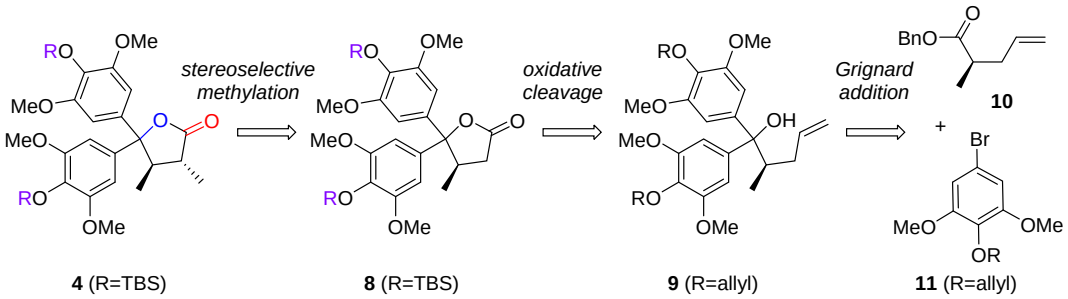
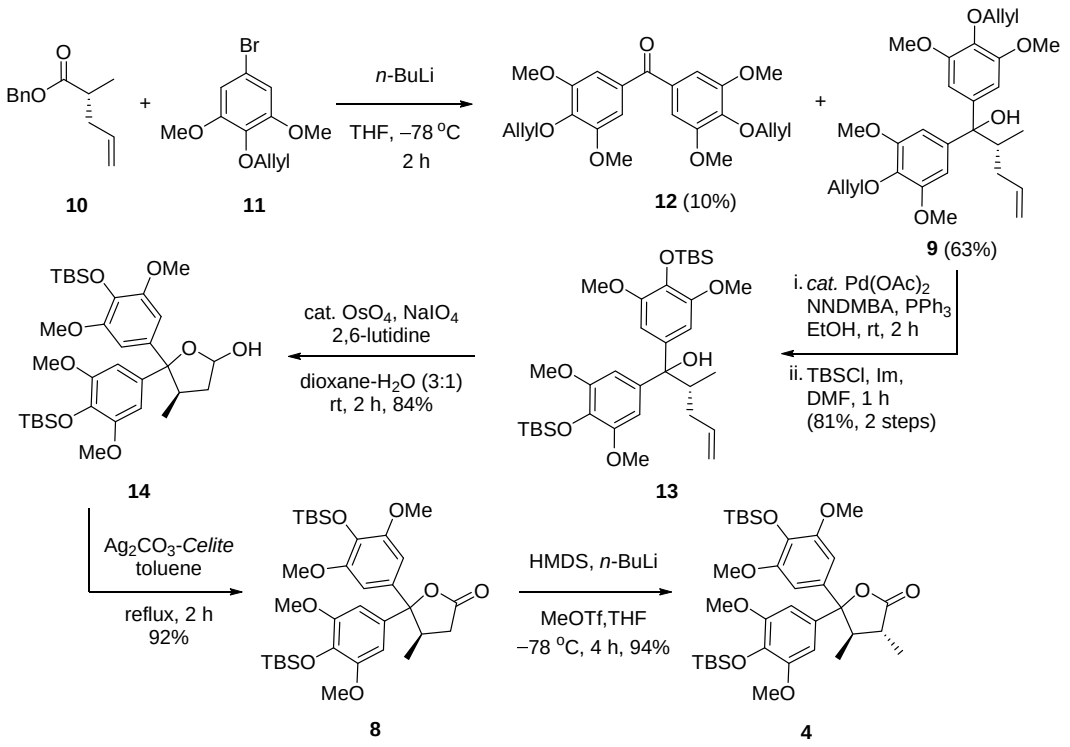


Figure 3. Retrosynthetic disconnections for key intermediate **4**

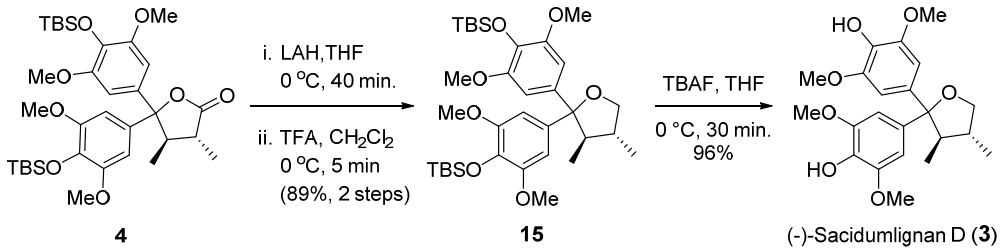
The synthesis of key intermediate **4** began with the lithiation of the bromo derivative **11** at –78 °C followed by its addition to the known chiral benzyl ester **10** to afford the required di-*O*-allyl addition product **9** in 63% yield. The decrease in the yield was accounted for by the isolation of a dehalogenated compound and the corresponding benzophenone **12** (10%) as the side products. The benzophenone **12** is assumed to form as a result of elimination of a carbanion from a tertiary oxide.



Scheme 1. The synthesis of key intermediate **4**

Then, the addition product **9** was subjected for deallylation with palladium acetate and N,N'-dimethylbarbituric acid (NNDMBA) as the allyl scavenger. Subsequently, the resulting intermediate triol was utilized for its phenolic *O*-TBS protection as it was found to be unstable. The compound **13** thus obtained, was subjected for a two-stage oxidation sequence involving a one-pot osmium tetroxide catalyzed dihydroxylation-sodium periodate mediated diol cleavage, leading to the formation a γ-butyrolactol **14**, which upon treatment with Celite supported silver carbonate in refluxing toluene afforded the γ-butyrolactone **8** in excellent yields. The diastereoselective α-methylation of lactone **8** was carried out under the established conditions (using HMDS, *n*-BuLi, MeOTf instead of readymade LiHMDS) to obtain the key intermediate **4** as the sole product in 94% yield. This advanced intermediate served as the midpoint for the synthesis of Sacidumlignans **1** – **3**.

The lactone **4** was later reduced with lithium aluminum hydride to a diol which was immediately subjected for the cyclization using TFA. To our delight, the formation of the *di*-*O*-TBS protected Sacidumlignan D **15** was accomplished within 5 minutes is upon TBS deprotection with TBAF, afforded the (–)-Sacidumlignan D (**3**).



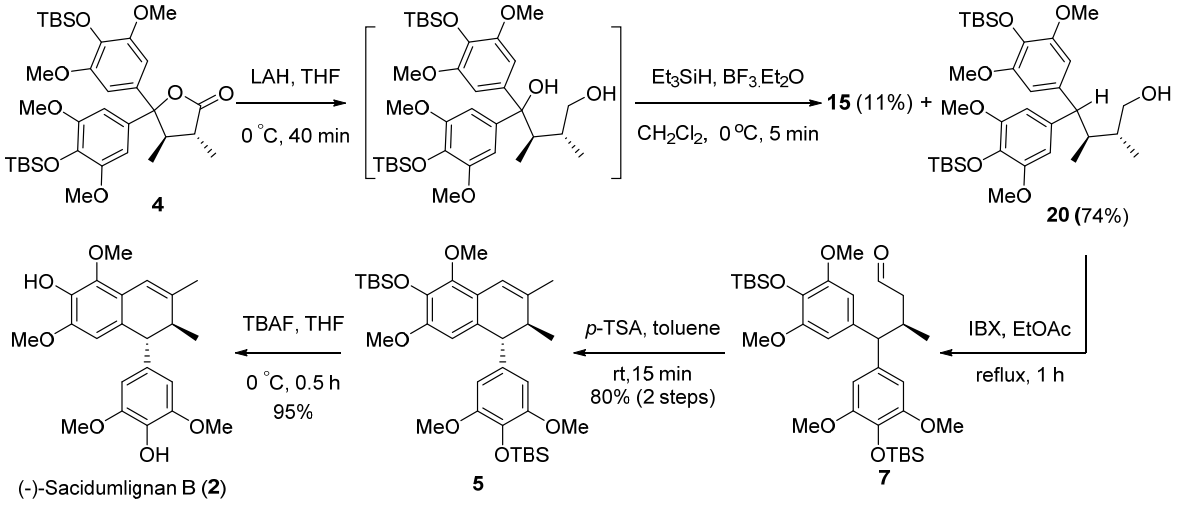
Scheme 2. Total synthesis of Sacidumlignan D (**3**)

The NMR spectra of the synthesized **3** was completely correlated with the reported spectra for the natural product, except for the extra phenolic OH peaks which were seen in its ^{1}H NMR spectrum which was confirmed by deuterium exchange. Chiral-HPLC analysis of racemic and optically active Sacidumlignan D samples revealed the enantiomeric excess (ee) as 96%. The physical data of synthetic (–)-Sacidumlignan D (**3**) was in full agreement with the data reported for the natural product there and was similarity in the sign and magnitude of the optical rotation {$[\alpha]^{25}_D$ = −138.2 (c 1.37, acetone); and for the natural product $[\alpha]^{25}_D$ = −115 (c 1.14, acetone)}, which revealed the synthesis of naturally occurring (–)-Sacidumlignan D.

Now, the main concern in the proposed strategy was the deoxygenation of the benzylic-OH group in the intermediate LAH reduction product without cyclization (Scheme 3). This was carefully optimized with the Lewis acid ($BF_3.Et_2O$) and reducing agent (triethylsilane) by altering the reaction conditions. TBS ether **15** was found to be the sole product when the deoxygenation was carried out at –78 °C. However, the mono alcohol **16** became the predominant product as the temperature was raised to 0 °C. Further increase in temperature led to low yield (in competition with the TBS deprotection) setting 0 °C as the optimum condition for the deoxygenation. Hence, the optimized conditions involve the addition of triethylsilane to a solution of diol in CH_2Cl_2 at 0 °C followed by the slow addition of freshly distilled $BF_3{\cdot}Et_2O$ and quenching of the reaction after 5 minutes of addition. Under these conditions, the requisite mono alcohol **16** was attained in 74% yield along with the cyclized ether **15** (11%).

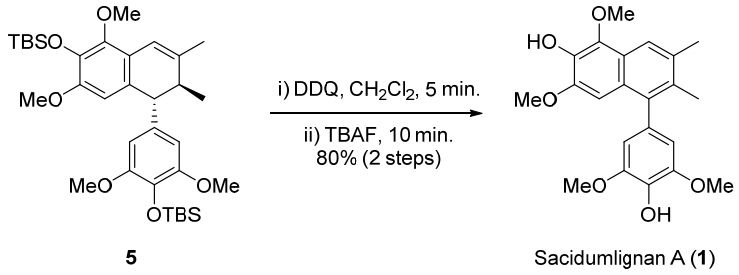
Oxidation of the mono alcohol **16** with 2-iodoxybenzoic acid (IBX) in ethyl acetate under reflux conditions gave the corresponding aldehyde in excellent yield. Without any characterization, it was employed for cyclization cum elimination (called dehydrative cyclization) catalyzed by *p*-TSA in toluene at room temperature, generating 80% yield in two steps and more than 99% diastereoselectivity. The cleavage of silyl ether concluded the synthesis of (–)-Sacidumlignan B (2). All the spectral and optical rotation properties of 2

($[\alpha]^{25}_D$ = −65.9 (c 0.8, acetone); lit.[1] $[\alpha]^{25}_D$ = −116 (c 1.44, acetone)) were well matched with the reported data and confirmed the natural Sacidumlignan B absolute configuration.



Scheme 3. Total synthesis of Sacidumlignan B (**2**)

Finally, the dihydronaphthalene intermediate **5** was subjected for a one-pot aromatization with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in CH_2Cl_2, followed by TBS deprotection by inserting TBAF produced the Sacidumlignan A (**1**) in 80% yield over two steps.



Scheme 4. Total synthesis of Sacidumlignan A (**1**)

Conclusion: The total synthesis of naturally occurring Sacidumlignans A, B, and D were achieved and their relative as well as absolute configurations have been determined. Two newly developed methodologies such as dehydrative cyclization and temperature dependent deoxygenation have successfully been implemented for the synthesis of the Sacidumlignans B and A. On the other hand, Sacidumlignan D followed the same path as in racemic synthesis except for the induction of chirality.

Chapter II: Stereoselective Synthesis of *C*-disaccharides

C-glycosides are the carbon counterpart of natural *O*-glycosides with proven *in-vivo* and *in-vitro* stability for the glycosidases/mineral acids. A disaccharide containing a carbon linkage unit (methylene group) instead of oxygen, called *C*-disaccharides, is inert towards chemo-enzymatic hydrolysis. There are some analogues with proven therapeutic utilities in the treatment of AIDS, cancer, diabetes etc. Eribulin is an anticancer drug marketed by Eisai Co, a macrocyclic ketone analogue of the natural product Halicondrin B that contains a *C*-disaccharide unit. On the other hand, several pharmacologically active natural products hold the *C*-glycosidic linkage. The selected examples include Halichondrin B, Tunicamycin, Showdomycin, and Vienomycin. Apart from this, the *C*-glycosides are also observed with an aromatic aglycon in several flavonoids, for e.g. Isoschaftoside, Spinosin, and Luteolin-6-*C*-apioside-8-*C*-glucoside. Starting with the first report by Sinay and Rouzaud on the *C*-disaccharide synthesis, in the past, there have been several approaches reported for the synthesis of *C*-glycosides with various linkages ([1→3], [1→4], and [1→6]) employing diverse building blocks. However, mild, modular and general approaches are still rare for the synthesis of [1→1] lined *C*-disaccharides. In the context of the synthesis of the heavily hydroxylated C(10)–C(21) bis-pyran fragment of the recently isolated natural product Zooxanthellamide D (ZAD-D) moiety, we intended to explore the possibility of alkynol cycloisomerization of an internal alkyne and the subsequent Kishi's deoxygenative cyclization of the resulting ketal. Considering the stereochemical features of the bis-pyran unit, the C-alkynyl glycoside **21** having the D-*ribo* configuration for the alkyne unit and a D-*gluco* configuration for the pre-installed pyran unit has been selected as the model substrate.

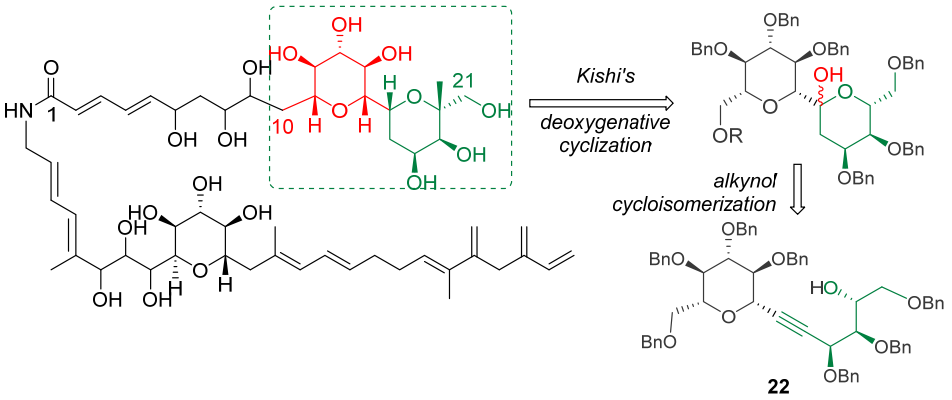
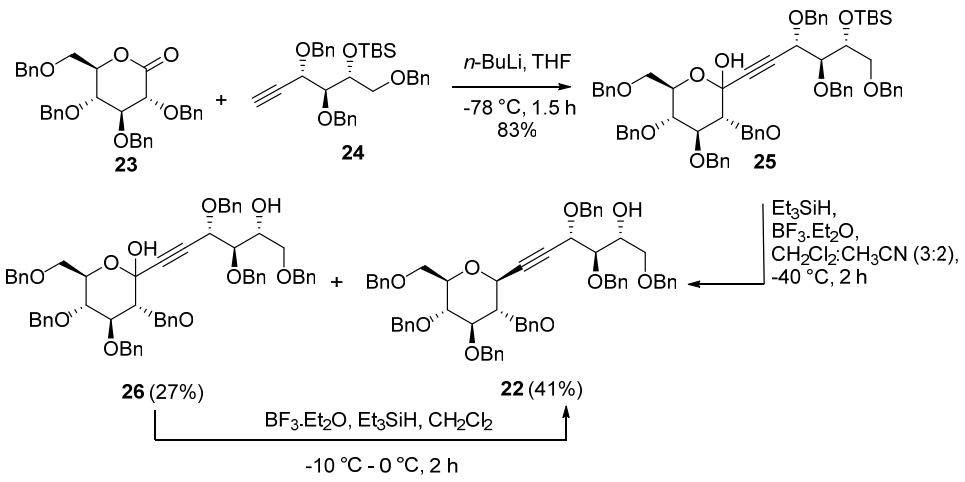


Figure 4. The structure of Zooxanthellamide D and the intended approach for the key bis-pyran unit

Synthesis of the key alkynol 22

The journey of synthesis of alkynol **22** was started with the lithiation of the ribose derived alkyne **24** in THF at –78 ^{o}C followed by addition of glucose derived lactone **23** to generate an inseparable mixture of hemiketals **25** in 83% yield. The resulting hemiketals **25** was then subjected for the Kishi's reductive-deoxygenation by using 5 eq. of triethylsilane and 2 eq. of $BF_3 \cdot Et_2O$ at –40 °C in CH_2Cl_2 and CH_3CN (3:2 ratio).



Scheme 5. Synthesis of key alkynol **22**

During this reductive deoxygenation, the TBS ether was also found to cleave to furnish the required *β*-configured alkynol **22** (41%) along with an inseparable mixture of diol **26** in substantial amounts (27%). Later, this diol **26** was again subjected for the deoxygenation from –10 to 0 °C using excess of triethylsilane (15 eq.) and $BF_3 \cdot Et_2O$ (10 eq.) to obtain the alkynol **22** exclusively. In order to find a suitable catalyst for the planned alkynol cycloisomerization of the key alkynol **22**, various palladium and gold complexes were screened. Among them, the cationic gold complex generated *in situ* from $AuCl(PPh_3)$ and $AgSbF_6$ in CH_2Cl_2 gave the best result. The obtained enol ether readily hydrolyzed under these conditions (due to hygroscopic catalyst and atmospheric moisture) and afforded the hemiacetals **32**. As expected, the face selective $Et_3SiH/BF_3 \cdot Et_2O$ mediated reduction of hemiketals **32** delivered the benzyl protected *C*-disaccharide **27** in 71% yield as a single diastereomer (a pyran/furan combination *C*-disaccharide). The constitution of the **27** has been established with the help of the corresponding peracetate **28** prepared by the hydrogenolysis of **27** and subsequent peracetylation (Scheme 7). The results in terms of the cycloisomerization were similar with the other metal complexes although the overall yield was varied.

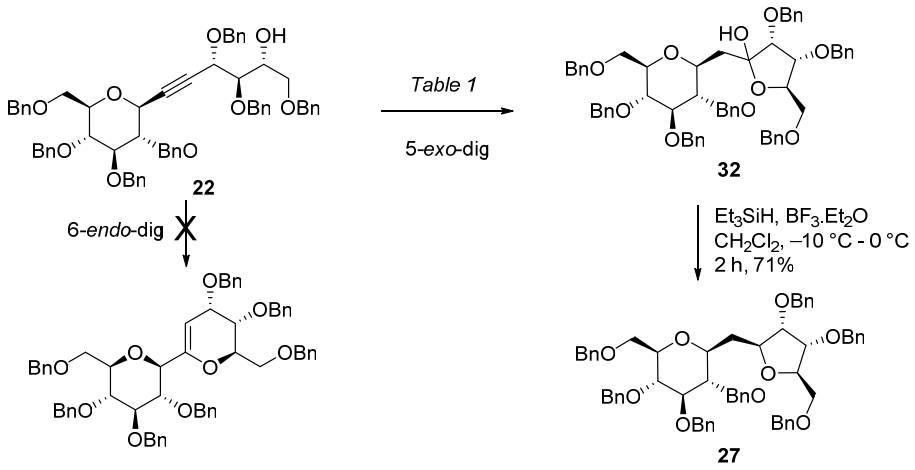
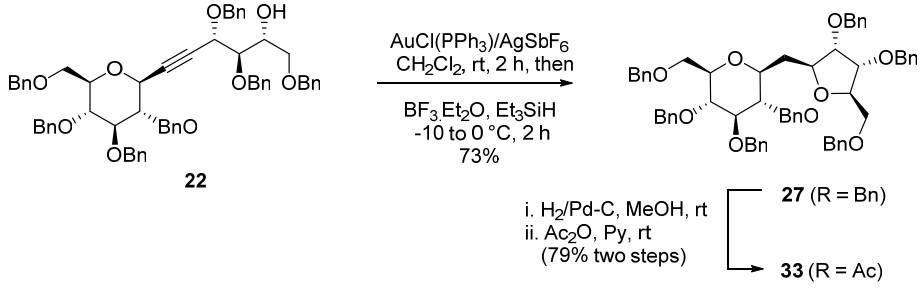


Table 1. Catalyst screening for the cycloisomerization of alkynol **22**

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

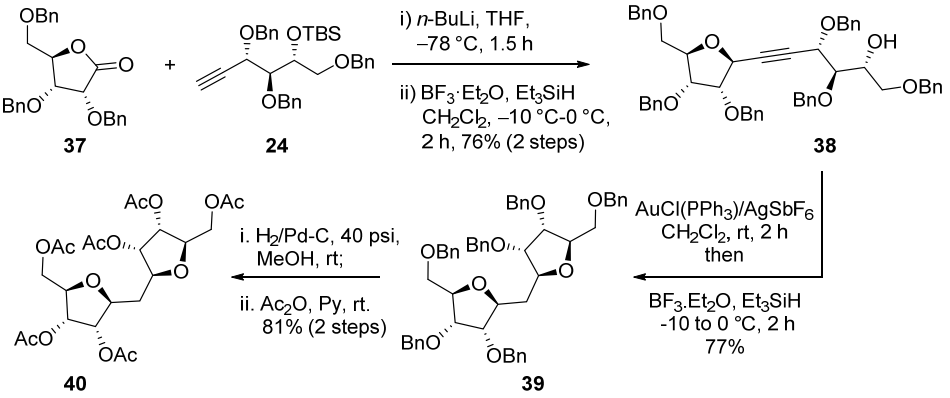
Scheme 6. The cycloisomerization of alkynol **22** followed by Kishi's deoxygenative cyclization

At this point of time, we realized that although the regioselectivity of the alkynol cycloisomerization is undesired in the context of the synthesis of the projected bis-pyran core of the Zooxanthellamide D, it provided a simple solution for the synthesis of [1→1]-linked *C*-disaccharides. So, in light of making this protocol more attractive, we looked at the possibility of combining both the events – cycloisomerization and Kishi's deoxygenative cyclization in one-pot. As shown in Scheme 7, the treatment of the alkynol **22** with the *in-situ* generated cationic gold(I)-complex for 2 h at rt, followed by the addition of the excess $Et_3SiH/BF_3{\cdot}Et_2O$ at –10 °C allowing the reaction to stir at 0 °C for 2 h and usual workup and purification provided the *C*-disaccharide **27** in very good yield. Having established a one-pot protocol, we next proceeded for the synthesis of various [1→1]-linked *C*-disaccharides having the three possible combinations of furan and pyran units.



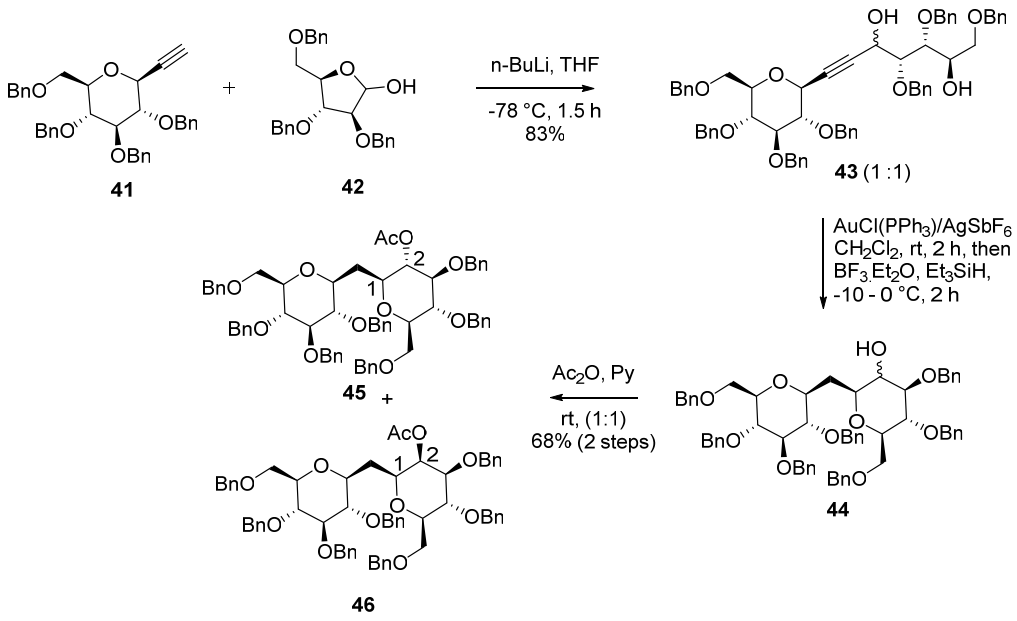
Scheme 7. One-Pot cycloisomerization and Kishi's deoxygenative cyclization

Synthesis of [1→1]-linked Furan-Furan *C*-disaccharides: Our journey in the context of the generalization of this approach began with the synthesis of [1→1]-linked *C*-disaccharides having a furan-furan combination. As shown in Scheme 8, the C_2-symmetric [1→1]-linked *C*-disaccharide **40** has been synthesized from the known D-ribonolactone **37** and the D-ribose derived alkyne **24** as the coupling partners (Scheme 2). The synthesis of **40** started with the addition of the lithiated alkyne **24** to the lactone **37** followed by Kishi's deoxygenation to give the alkynol **38** in 76% yield. The cycloisomerization-deoxygenation of **38** then delivered the C_2-symmetric [1→1]-linked *C*-disaccharide **39** in good yield and was further hydrogenated and acetylated to obtain **40** for the purpose of characterization.



Scheme 8. Synthesis of C_2-Symmetric *C*-disaccharide **40**

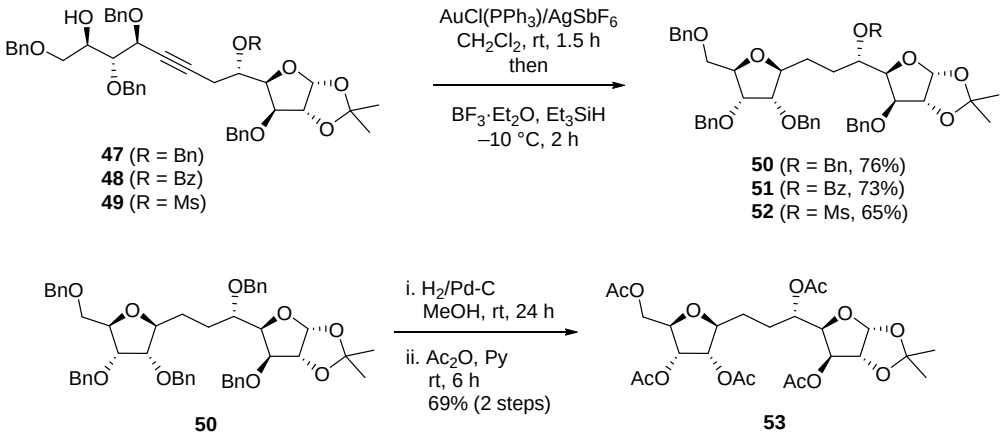
Synthesis of [1→1]-linked Pyran-Pyran *C*-disaccharides: The methodology was further extended for the [1→1]-linked *C*-disaccharides having a pyran-pyran combination. For that, we tailored a C1-ethynyl *β*-C-glucoside **41** with an arabino furanose derivative **42** at –78 °C in THF using *n*-BuLi to achieve a 1:1 inseparable mixture of alkynols **43** in 83% yield. The mixture was then set up for the one-pot cycloisomerization-deoxygenation under standardized conditions: for instance, another inseparable diastereomeric mixture of C-disaccharides **44** was identified. For easy separation, the hydroxyl groups in **44** were capped with acetate that, in turn, provided easily separable disaccharides **45** and **46** having a good splitting pattern of the characteristic protons in ^{1}H NMR and distinguished both the C2 epimers. Although the diastereoselectivity is poor (1:1), this accessed the synthesis of two epimers having [1→1]-linked *C*-disaccharides, one of which is a trehalose *C*-disaccharide **45**.



Scheme 9. Synthesis of [1→1]-linked pyran-pyran *C*-disaccharides and of trehalose analogue **45**

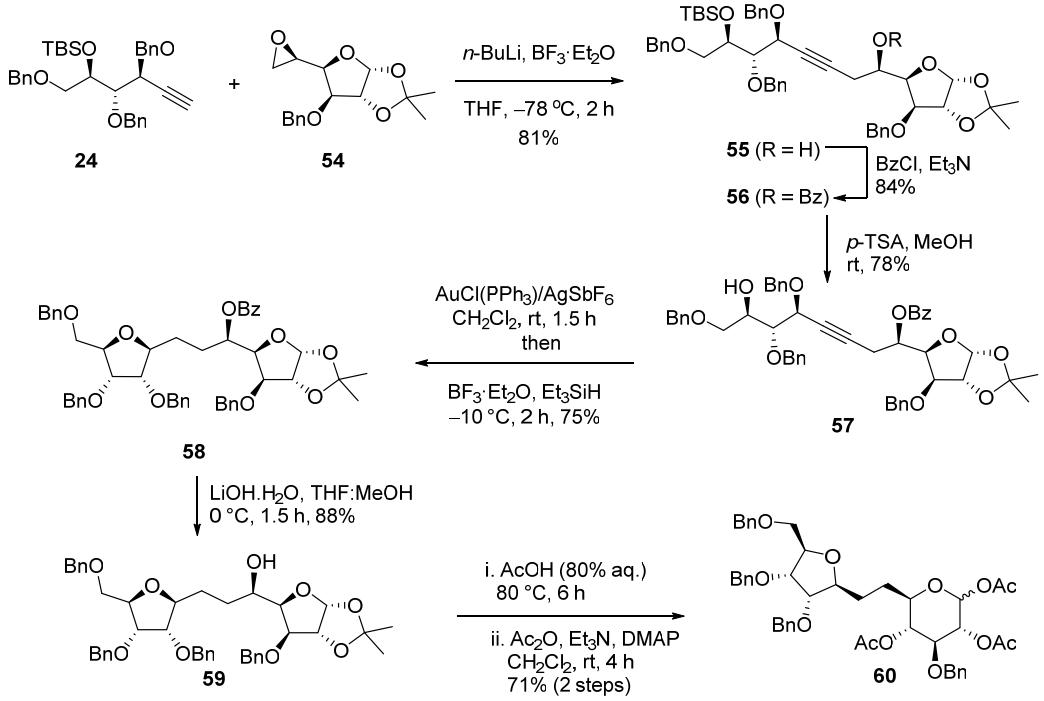
Synthesis of [1→1]-linked Pyran-Furan, Pyran-Pyran *C*-disaccharides

After successful synthesis of [1→1]-linked *C*-disaccharides with all three possible combinations, we then focused on the synthesis of [1→6]-linked *C*-disaccharides (Scheme 10). The planned synthesis for [1→6]-linked *C*-disaccharides attributed the key alkynol through an epoxide as 5,6-anhydrohexofuranose-alkyne coupling that has been reported earlier in our group. The protecting group of the resulting C5–OH (after the epoxide-alkyne coupling) was differentiated (OBn, OBz, OMs) from the rest of the *O*-protecting groups for further use. This also proved the survival of different protecting groups under the existing *C*-glycosylation conditions. The one-pot cycloisomerization-deoxygenation proceeded smoothly for the entire protecting group employed at C5–OH. Hydrogenation-acetylation of the intermediate **50** having the perbenzyl protection was carried out to prepare **53** for the purpose of characterization (Scheme 10).



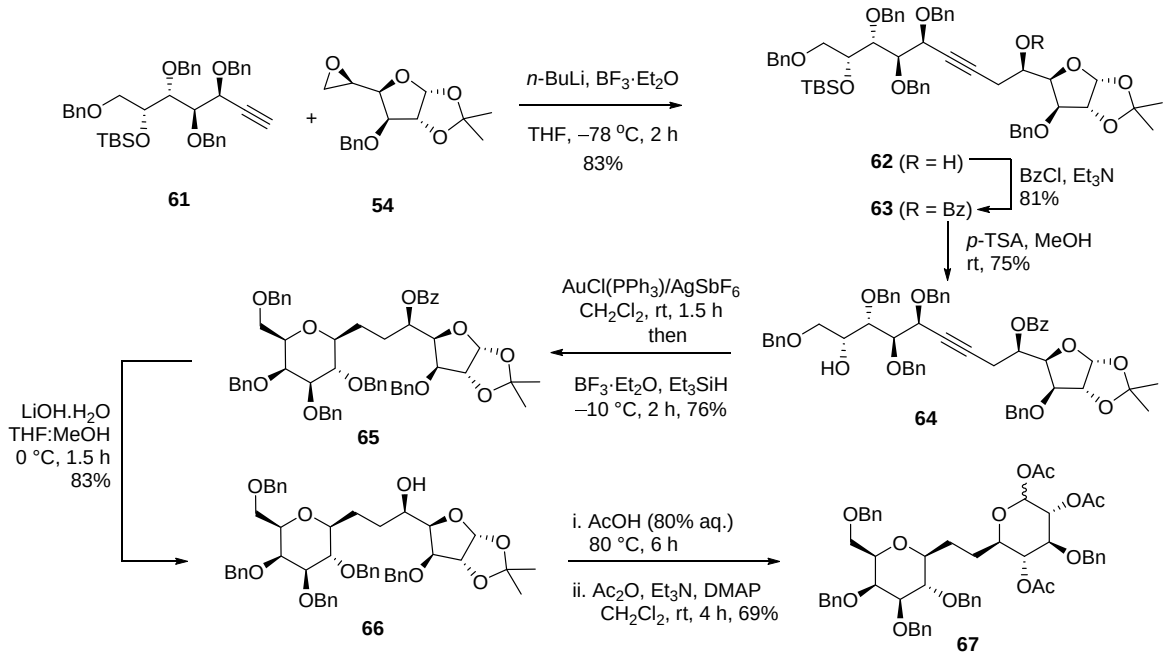
Scheme 10. Synthesis of [1→6]-linked *C*-disaccharides & Scope of protecting groups

The established [1→6]-linked *C*-disaccharide strategy was repeated with *gluco*-configured 5,6-epoxide **54** and the D-ribose alkyne **24**, so as to have a combination of furan-pyran system (Scheme 11). The epoxide **54** in THF was added to the lithiated D-ribose derived alkyne **24** in the presence of $BF_3{\cdot}Et_2O$ at –78 °C to provide the homopropargylic alcohol **55**. The alcohol was protected with benzoylate and silyl ether was cleaved with *p*-TSA in methanol to set up the alkynol cycloisomerization-deoxygenation. The key reaction accelerated smoothly and the resulting *C*-glycoside **58** was later saponified by lithium hydroxide to give **59**. Acetonide of **59** was finally cleaved with 80% aqueous acetic acid at 80 °C and subsequent peracetylation gave the *C*-disaccharide **52** as a *α*/*β*-anomeric mixture.



Scheme 11. Synthesis of [1→6]-linked *C*-disaccharide with pyran-furan combination

To test the impact of a lengthier alkynol on the outcome of cycloisomerization, a one carbon homologation of the present alkyne **61** but having a D-*galacto*-configuration was chosen. The same reaction sequence was repeated. Like previous results, no new observation was realized. One-pot cycloisomerization-deoxygenation was seen to occur in the same manner to render the 6-exo-dig cyclization as a singular event. All the compounds were easily characterized by means of experience gained as discussed above. This result elucidated a pyran-pyran combination of [1→6]-linked *C*-disaccharide **67**.



Scheme 12. Synthesis of [1→6]-linked C-disaccharide with pyran-pyran combination

In conclusion, a simple protocol comprising a one-pot "gold-catalyzed alkynol cycloisomerization followed by Kishi's deoxygenative cyclization" has been introduced as a simple tool for the synthesis of [1→1]- and [1→6]-linked *C*-disaccharides with possible furan and pyran combinations. The adopted approach for the synthesis of key alkynol fragments is highly modular and employs simple building blocks. Three different approaches developed in this context employ the sugar derived alkynes as the nucleophiles and sugar derived lactones, lactols or epoxides have been found to be suitable as the electrophiles.

CHAPTER I:

Total Synthesis of Naturally Occurring Sacidumlignans A, B, D

INTRODUCTION

Plants involve and exist in all forms of lives directly or indirectly in terms of shelter, attire and ultimately diet. They are the storekeepers of highly precious objects in different parts of their structures. In ancient times, human ailments got cured by the use of folk medicines which are generally derived from plants. Even today, the Ayurvedic medicines (Hindu traditional medicine) are being used as alternative medicine in the Indian subcontinent.[1] For better treatment, today's science exploits the plant kingdom to explore new therapeutic formulas and believes the cure of highly deadly diseases lies somewhere in the plants. For instance, several metabolites such as Vinblastine, Taxol and Morphine have originated from plant sources. They and their analogues are now engaged as therapeutic agents in various illnesses. For better activity, low toxicity, and better solubility they have been modified on several occasions. Despite the advance in drug discovery, the medicinal potential of a very small fraction of plants on earth has been examined. In the middle of the 20th century, the organic chemists were busy in establishing the stereochemistry and their structural interpretation of unknown molecules, but now they paid their attention towards the exploration of molecular utilities and diverse biological behaviors. Hundreds of secondary metabolites are being isolated weekly from different sources of plants (as well as animals) worldwide. Collection of plants (and animals) is not limited only to soil but they have also assembled from underneath the sea (termed as "marine natural products"). The number of natural products discovered and characterized till now is considered as a trace of existence. For simplification in study, the scientific community is somehow able to categorize most of them. The major portion of natural products is notably covered by the big groups such as alkaloids, terpenoids, lignans etc. On phytochemical and taxonomical basis, the lignan has proved itself as one of the important class.

The term "lignan" was first coined by Haworth in 1948 to address a fraction of naturally occurring compounds that possess *n*-propylbenzene derivatives.[2] These are the secondary metabolites[3] widely encountered in plants in the form of fruits, roots, foliage, heartwood, or resinous exudates. They are also found in vegetables such as asparagus, broccoli and carrots, grains such as barley, wheat, and oats, legumes such as lentils, beans, and soybeans etc. The external look of most of the lignans is dimeric in which the aromatic units get ornamented with different oxygenated functionalities such as hydroxy, methoxy and methylenedioxy. On the other hand, lignin is a complex biopolymer which constitutes the inner cell wall of the plants. They structured by different hydroxycinnamyl alcohols connected with a variety of linkages.

Nomenclature and Classification of Lignans: Lignans are considered as the dimers of propylbenzene characterized by two C_6C_3 units. The number in propylbenzene starts from the quaternary phenyl carbon and encircles the ring from 1 to 6 followed by aliphatic chain 7 to 9. In dimeric lignan structure, the second fragment numbers as primes and follows the same sequence. The meeting positions of the two C_6C_3 units are 8, 8' and the bond is termed as the *β–β*' linkage. In general, the lignans were usually oxidized at their C9 and C9′ positions which led to oxygen incorporation into the skeleton. In a broader sense, these lignans are classified into two groups such as classical lignans and neolignans (oxyneolignans are included). The neolignans are characterized by the absence of the direct involvement of the C–C bond at the *β*, *β*' position in the two C_6C_3 units. When they are linked by two oxygen units (which are the 1,4-dioxane derivatives) instead of carbon, they were referred to as "oxyneolignans". Higher homologues such as sesquineolignans, dineolignans contain three and four C_6C_3 units respectively.[4]

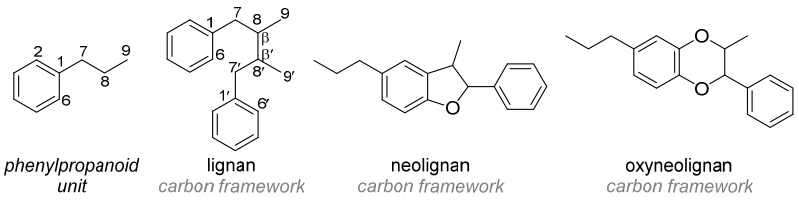


Figure S1.1. Numbering of the lignan skeleton – the dimer of the phenylpropanoid

The classical lignans are again classified in eight subgroups such as furan, furofuran, dibenzylbutane, dibenzylbutyrolactol, dibenzylbutyrolactone, aryltetralin, arylnaphthalene and dibenzocyclooctadiene having *β–β*' linkages.

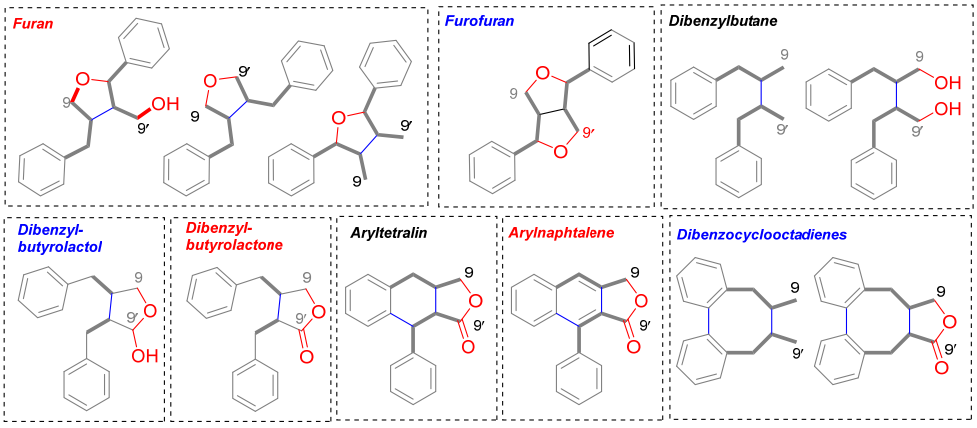


Figure S1.2. Classical lignans & their classification based on the core

The different types of neolignans (lack of *β–β'* linkages) are shown below. Besides this, other lignans such as oligomeric lignans, hybrid lignans, lignan glycosides, flavonolignans, and norlignans are also known. The lignan glycoside is a hybrid of lignan and glycoside moieties through the oxygen or the carbon bridge.

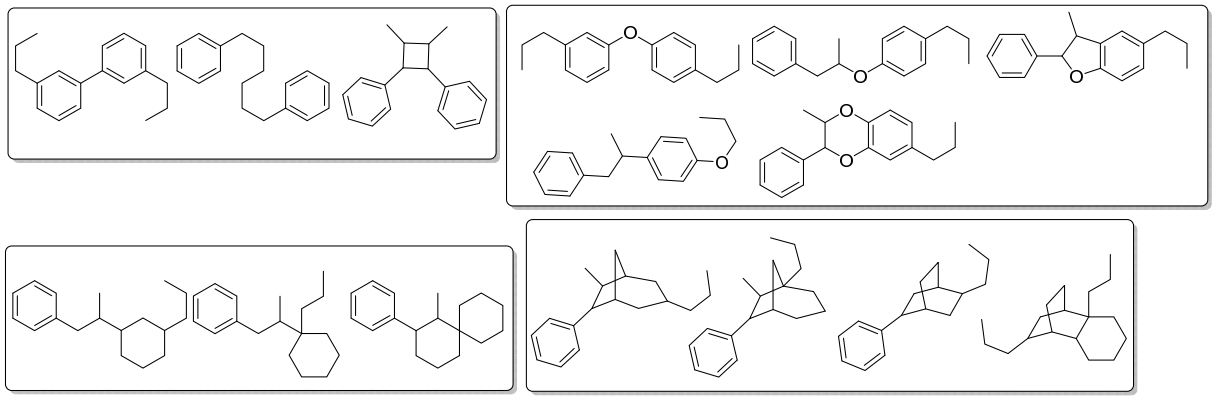


Figure S1.3. Neolignans and Oxyneolignans and their structural diversity

Biosynthesis:[5] Secondary metabolites are often found in plants and not in animals. That is because the most important pathway the "*Shikimic Acid Pathway*"[6] required for life in biological systems is only restricted to the plants. The essential amino acids needed in animals for the growth, reproduction and locomotion usually are synthesized by this vital pathway. L-Phenyl alanine and L-Tyrosine are the needy resources for signaling, transduction in animals and are the preliminary stuff for various lignan productions during the Shikimic acid pathway. The *p*-Coumaryl alcohol, Coniferyl alcohol and Sinalpyl alcohol serve as the other essential components in lignan biosynthesis. Most of the lignan found in nature exists in dimeric form of these alcohols and are formed *via* radical pathway in the presence of peroxidases in taxonomical system. Oxygenation and methylation get carried out efficiently by a range of well-designed biocatalysts in a very selective manner. The oxygenation occurs through atmospheric molecular oxygen in presence of **N**icotinamide **A**denine **D**inucleotide **P**hosphate **H**ydride (NADPH) whereas methylation uses S-adenosyl methionine as the methyl transferring agent. The reduction of acids often facilitated by other co-enzymes such as coenzyme A (HSCoA) to their corresponding alcohols. These allylic alcohols are the leading precursors to dimerization, combination, rearrangement, fragmentation etc by different enzymes and contribute to the infinite population of lignans and lignin in nature.

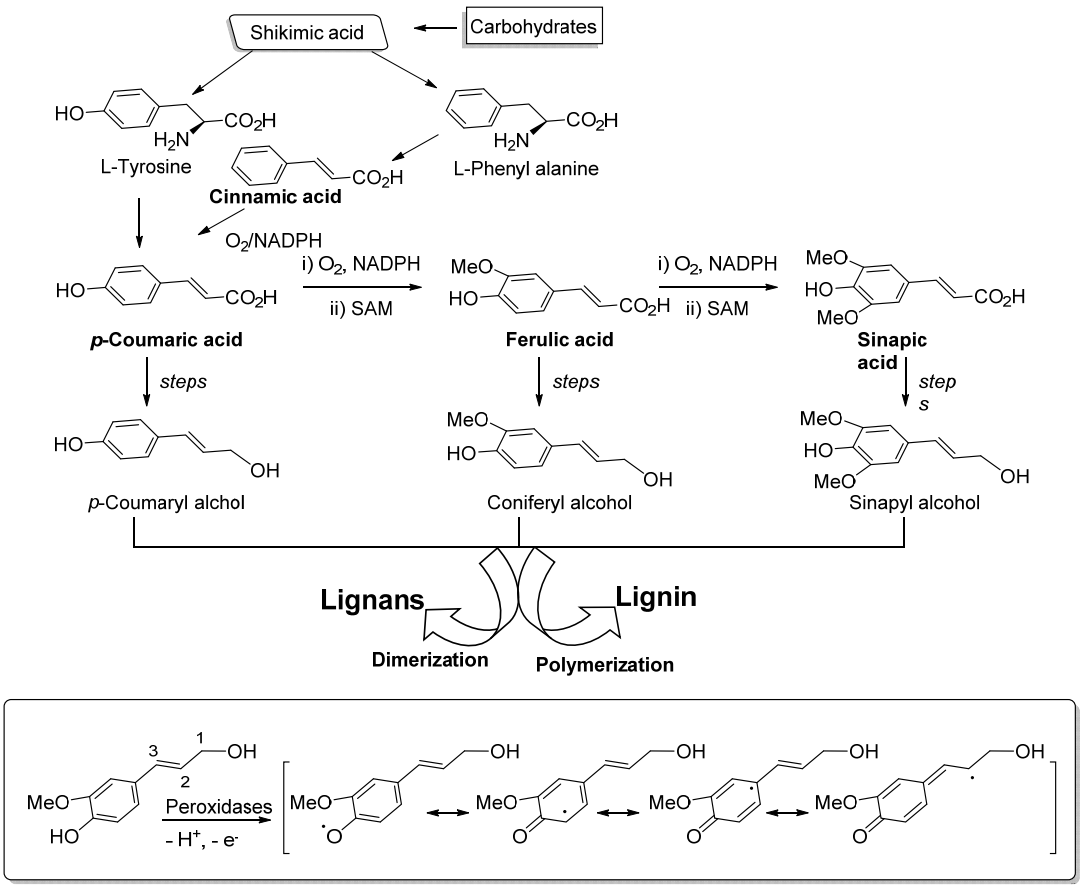


Figure S1.4. The biosynthetic pathway for the production of lignan/lignin

The biosynthesis of lignans always requires to a stereo-controlled oxidative coupling to induce chirality whereas there is no order in their repeating units of lignin. The sequence of different units in lignin is still not much understood. Participation of peroxidases with allylic alcohol after the Shikimic acid pathway induces a one-electron (1e) oxidation of the phenolic group. Delocalization of the free radical leads to the creation of many probable combinations which are expressed in their resonance forms (Figure 4). Dimerization at any instant allows access to the infinite neolignan's core. The radical pairing engineers various reactive species which are prone to nucleophilic attack by the pendant hydroxyl groups. Appropriate understanding of these biogenetic mechanisms is certainly very much important to chemists as they provide fundamental insights. The biogenesis of lignans, however, has been explored significantly more compared to lignin.

Biological Significance: Lignans are widespread in many plants and constitute as one of the major classes of natural entities. It has created a long history by serving many civilizations by its tremendous biological activities. The old civilizations exploited these plant based lignans impressively in the daily life of the citizens. The Sushruta Samhita and Charaka Samhita, two important classical Sanskrit texts written in 6th century BC in India describe the biological utilities of different plants.[7] At that time people were not aware about the particular cause (or molecule) which isresponsible for the behavior of the plant.However, at the advent of the 20th century, people tried to explore the exact reason associated behind the plant's behavior. They classified wholeplant-based natural products into various groups and sub-groups. Like alkaloid (contain mostly basic nitrogen atoms), terpenoid (derived from five-carbon isoprene units), another large and diverse class of naturally occurring organic chemicals were termed as "lignan" to describe the phenylpropanoid derivatives as discussed earlier. The lignans, however, certainly impressed the scientific community through their extraordinary behavior. They showed a broad spectrum of pharmacological activities like antitumor, antimitotic, antiviral, antimicrobial, antifeedant and insecticidal along with unique stereochemical properties.[8] To achieve better therapeutic agents, their structural interpretation and biological evaluation were being investigated from the last five decades. Furthermore, the understanding the mechanistic pathway for their biosynthesis has advanced significantly in during the last decade. In this time, by seeing the exponential growth of publication in recent years, one could imagine the seriousness and curiosity of people towards these irreplaceable moieties.

For example, Podophyllotoxin[9] has attracted considerable interest for the last two decades because of its high toxicity and antiviral activity. It was isolated from the roots of *Podophyllum* species and also from other genus such as *Linum*. This aryltetralin lignan was employed as an anticancer drug in 1990. It normally destroys the cytoskeletal framework in the cytoplasm causing inhibition to the cell division in the metaphase. The major drawback in Podophyllotoxin's use as drug is its attack to normal cells along with cancerous cells causing many side effects. In order to have an ideal anticancer drug candidate, the Podophyllotoxin was modified in different instances. Several semi-synthetic podophyllotoxin derivatives such as Etoposide, Teniposide, and Etoposide phosphate proved good as topoisomerase II inhibitors. In You's view (2005), podophyllotoxin is still a hot sample in the 21st century for the development of novel anticancer agents.

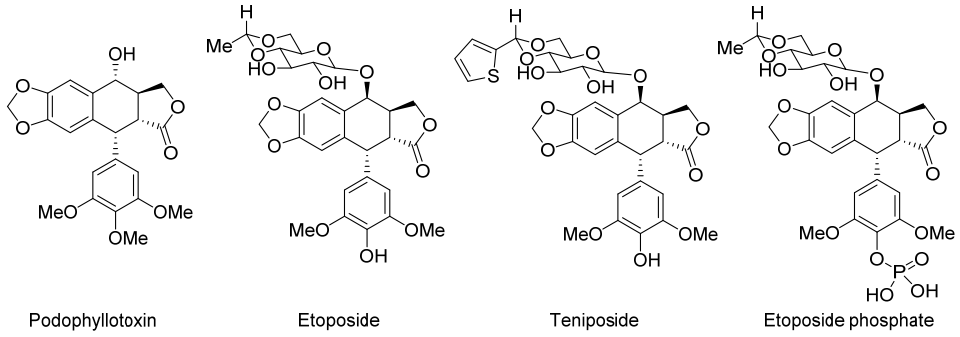


Figure S1.5. Podophyllotoxin and its modified analogues

About 100 lignans containing the dibenzocyclooctadiene core were isolated from the plants of the Schizandraceae family. In addition to insecticidal and antifeedant activity, they inhibit cyclic-AMP phosphodiesterases, which are essential for the regulation of cellular processes. Some of them reduce the binding of the platelet activating factor to receptors on platelets and some act as immunosuppressive agents. The (–)-Wuweizisu C is known for its antihepatotoxic activity. Gomisin-G showed the most potent anti-HIV activity with an EC_{50} value of 0.006 µg/mL. Similarly, the Xchizantherin-D, Kadsuranin, and (–)-Wuweizisu C exhibited good activity with EC_{50} values 0.5, 0.8, and 1.2 µg/mL.[10]

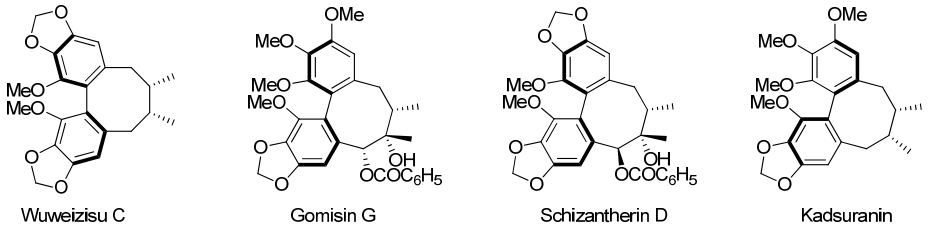


Figure S1.6. Representative lignans with dibenzocyclooctadiene core

Brevitaxin,[11] a terpenolignan, was isolated from the twigs of the Himalayan yew T. brevifolia. It showed cytotoxicity in the NCI 60-cell line assay. Similarly, the (–)-Sesquipinsapol B pentaacetate and (+)-Sesquimarocanol B hexaacetate[12] exhibited the cytotoxicity against the cancer lines P-388, A-549, HT-29 and MEL-28 (human melanoma).

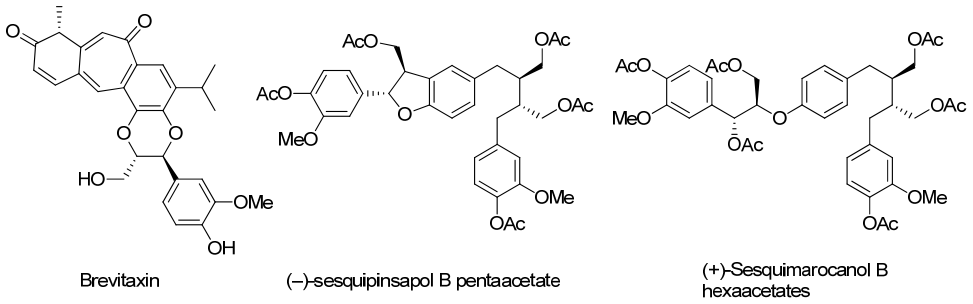


Figure S1.7. Structures of selected oxyneolignans

Most of the lignans are antioxidant in nature. To understand the effect of antioxidant properties of enhanced oxygenated functionality in natural products, a few experiments have been documented in the literature. Studies of the effect of oxidation at the benzylic position of phenolic lignans bearing a 4-hydroxy-3-methoxybenzyl group was revealed a substantial reductionin their antioxidant activities with a high degree of oxidation.[13] Here, the bis(4-hydroxy-3-methoxybenzyl)tetrahydrofuran lignin (**b**, Figure 8) showed the best antioxidant properties compared to the diketolignan derivative (**e**, Figure 8).This indicates nature's efficient selection and capability to design suitable structural skeletons for antioxidant properties. However, there is an exception of enhanced biological properties of synthesized compounds than their natural counterpart in different instances like in the case of the Podophyllotoxin derivative.

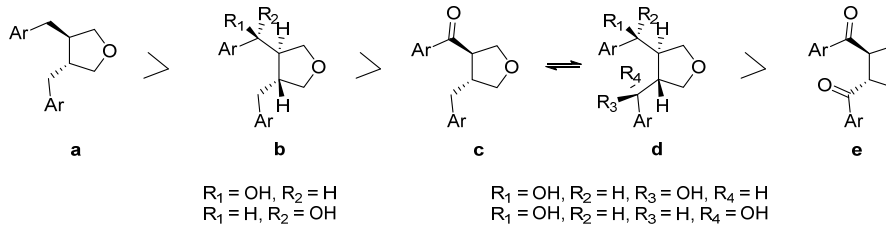


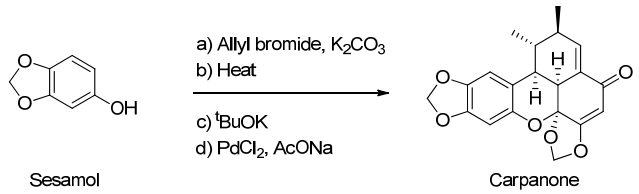
Figure S1.8. Structure associated anti-oxidant activity in lignans

Unprecedented Lignans

During the biosynthesis of lignans, nature usually prefers simple transformations like oxidation, reduction (using NADPH), and methylation (using SAM) but carries them in very efficient and systematic manner. It uses atmospheric oxygen to oxygenate the lignans at various positions leading to a large skeletal diversity. The dimerization in lignan production through one electron (1e) oxidation by peroxidases is another important aspect of the furnishing of simple to

complex molecular architectures. Podophyllotoxin is one of the popular examplesin this regard.All these reactions are very common and take place in most of the lignan's biosynthesis. Besides these it has been seen, sometimes, that the lignan biosynthesis follows extraordinary deviation in their original pathway than their usual route which leads to tremendous change in their skeletal constitution.Although their population is very small, yet they are regarded as pharmaceutically important due to their exceptional biological activities. The abnormal fragmentation and migration of varied substituents during biosynthesis are the additional crucial parameters in the generation ofnumerous unprecedented lignans.

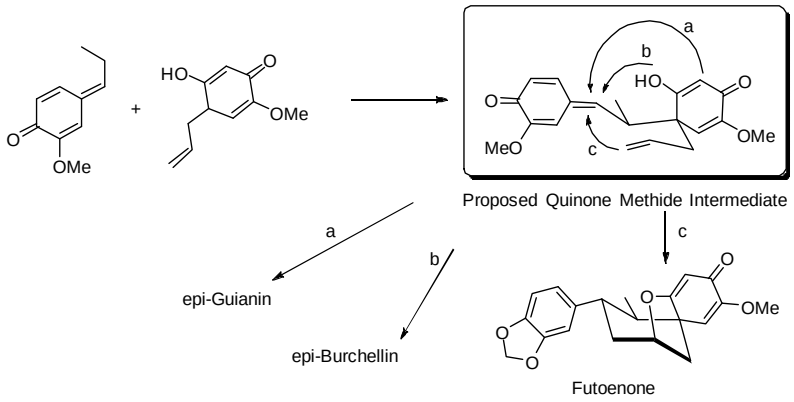
Carpanone is one of the popular unprecedented lignans. In 1969, it was isolated by Brophy and coworkers from the light petroleum extracts of the bark of the Carpano tree of the family *Lauraceae*.[14a] Even though the compound possesses five contiguous asymmetric centers, still it has no optical activity. Brophy was also involved in the isolation of the simpler Carpacin (an ortho-methoxy styrene derivative), a phenylpropanoid with a 9-carbon framework. A hypothesis regarding dimerization of Carpacin has been proposed to the complex Carpanone structure. By inspiring the proposed Brophy's hypothesis, Orville L. Chapman,[14b] in 1971, synthesized Carpanone and successfully mimicked the nature's pathway in a very efficient manner. He beautifully utilized an intramolecular Diels-Alder reaction of two *o*-quinonemethide units using $PdCl_2$ from a C_2-symmetric virtual precursor. The oxidative dimerization of phenols in general occurs by 1e oxidation but Chapman trailed a 2e Pd(II) species and treated the Desmethylcarpacin with $PdCl_2$ in the presence of sodium acetate to achieve the natural product. This popular example demonstrated the power of mimicking the biosynthetic pathway that has resulted in the synthesis of a complex molecular architecture in only 4 steps with a 50% overall yield.



Scheme S1.1. Biomimietic synthesis of Carpanone by Chapmann

Another unprecedented neolignan called "Futoenone"[15] was isolated in 1970. The Futoenone is a PAF receptor antagonist and 5-lipoxygenase inhibitor. It is used as a therapeutic

agent for asthma and also for various cardiovascular and inflammatory disorders. Its biosynthesis was proposed by Gottlieb. Büchi-Mak utilized the biosynthetic hypothesis in their racemic synthesis which followed a quinone-ketal cycloaddition reaction.



Scheme S1.2. Biomimietic synthesis of Fotoenone by Büchi

Pinobatol[16a] and Woorenol[16b] are two novel sesquineolignans with a unique spirodienone system, isolated in 1997 from the rhizomes *of Coptis japonica var. dissecta* and the Pine (*Pinussylvestris L.*). These show anti-inflammatory activity in the initial study though their biological and synthetic profile is not much explored. As a matter of fact, there is no single report regarding its synthesis despite its having such an unusual and attractive unit. Chimarrhinin[17] is another unnatural lignan that was recently isolated from *Chimarrhis turbinate* that exhibited antioxidant activity of IC_{50} value 7.50 (0.5 μmol L^{-1}. Besides this, infinite unprecedented lignans are hidden in the shade of nature whose synthetic and biological profiles are still not disclosed and many more are to be discovered.

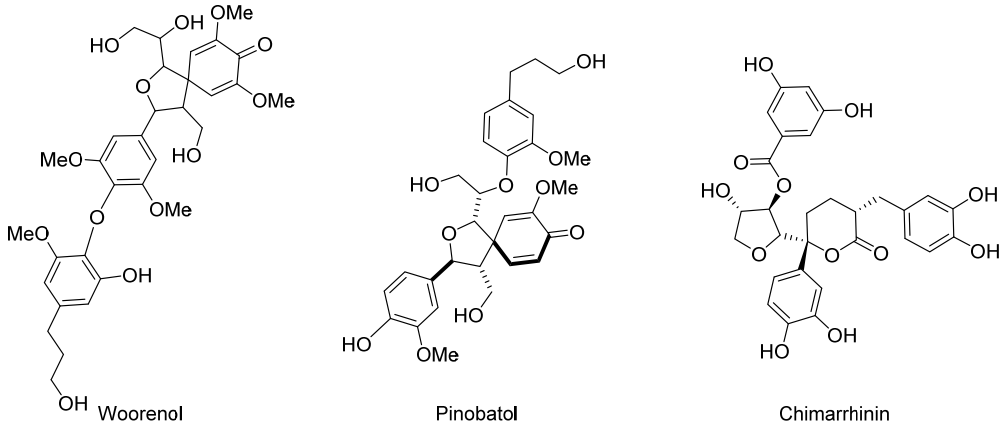


Figure S1.9. Structures of some representative unnatural lignans isolated recently

Unprecedented Lignans with *γ*-butyrolactone moiety (Eupomatilone)

Eupomatilones[18] are another important class of unusual lignans having a *γ*-butyrolactone moiety. Many groups have put forward various synthetic efforts over the last two decades. These are discussed below. Sacidumlignan D is another unprecedented lignan possessing a similar *γ*-butyrolactone core like Eupomatilone and other members of this family rearranged to naphthalene derivatives. As the next part of the thesis will be dealing with the synthesis of various Sacidumlignans, in the following section are presented some of the important Eupomatilone syntheses reported previously as, in general, they have provided the platform for the recently reported synthesis of Sacidumlignan D and its related members.

The Eupomatilone family constitutes a member of seven degraded lignans. Cleavage of one of the *Cα*-phenyl linkage in phenylpropanoid units categorized them as unusual among the lignan family. These structurally rearranged unprecedented lignans were first isolated by Carroll in 1991 from Australian shrub *EupomatiaBennettii F. Muell*. This shrub is also a rich source of other lignans such as eupomatenoids, eupobennettin, eupodienones, bennettinone etc. During the isolation, the absolute configuration of the lignans was not verified. However, the relative stereochemistry and structural interpretations were elucidated on the basis of extensive 1D and 2D NMR analysis. The n*O*e interactions mainly provided the authentication of relative positions of the methyl substituents in the *γ*-butyrolactone moiety. This family is addressed by a substituted biaryl system connected to the *γ*-position of the *γ*-lactone. Most of the lignans hold a *cis*-stereochemistry at C4-C5 in the butyrolactone ring and change is observed in their ring substituents and methyl substituents at the C2-C3 positions and more importantly, these methyl substituents on the ring generate enormous difference towards their identity.Another fundamental character of the Eupomatilone family is atropisomerism, although the isomers are in equilibrium due to the partial restricted rotation around the biaryl ring.

Laboratory synthesis is one of the most important techniques to provide evidence for the correct configuration of the wrongly interpreted molecules. The elucidation of relative stereochemistry and core structure of some of the natural products proved wrong in some instances and later they were able to revise by this method. For instance, take the example of the structure of Eupomatilone 6. Carroll had wrongly assigned the relative position of the methyl groups at the C2 and C3 positions of the 5-membered *γ*-butyrolactone ring system. While

working on the synthesis of the proposed configured system, our group has observed first this persistent discrepancy in 2004. In the next year, the relative and absolute configurations were defined by synthesizing both the racemic and chiral eupomatilone 6. Amongst the Eupomatilone family, Eupomatilone 6 has been studied relatively more, probably because of its putative structure.

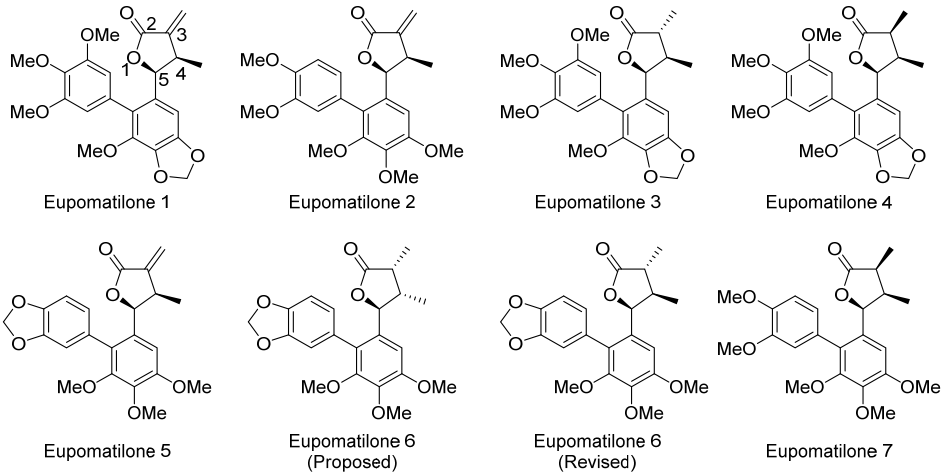


Figure S1.10. Proposed structures of Eupomatilones and some revision made

Various approaches have been put forward for the synthesis of Eupomatilone 6.[19] McIntosh was the first one to put in an effort to synthesize the Eupomatilone 6 in 2002 but ended with the synthesis of bis(3,5)-*epi*-Eupomatilone 6. After 2 years, our group proved that the assigned structure was wrongly interpreted and came with the synthesis of both racemic and chiral compounds. Coleman in 2004 synthesized the racemic natural product along with its 3-epimer. Next, Hall explained the synthesis of 3-epimer, 4-epimer, 3,4-epimer along with the natural product by using the allyl boronates in the presence and absence of Bronsted acids. Most of the synthesis has focused on fixing the methyl substituents in the ring at the final or penultimate stage of the synthesis. For that, they intended on-the-face selective hydrogenation of the internal alkene or exo-cyclic methylene group. But the McIntosh and Coleman approaches initially fixed the position of methyl groups through Claisen-Ireland and Lipshutz oxidative biarylcuprate couplings respectively, whereas our approach was based on a diastereoselective α-methylation at the final phase of the synthesis.

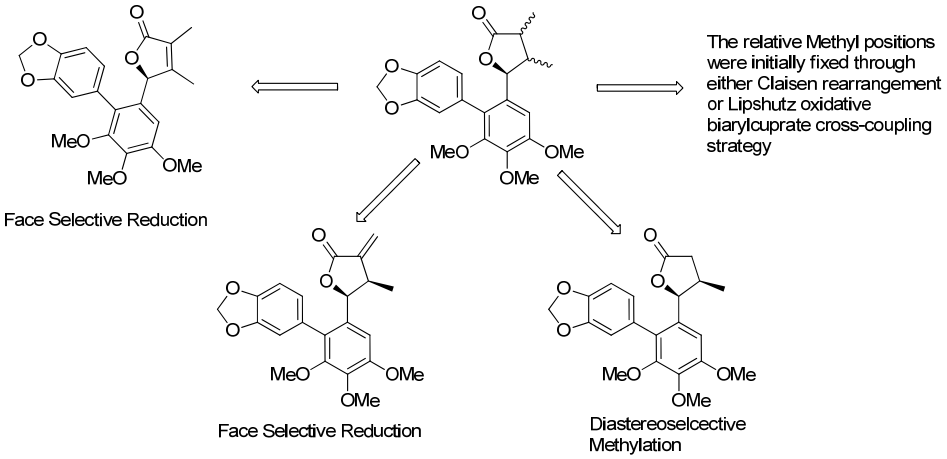
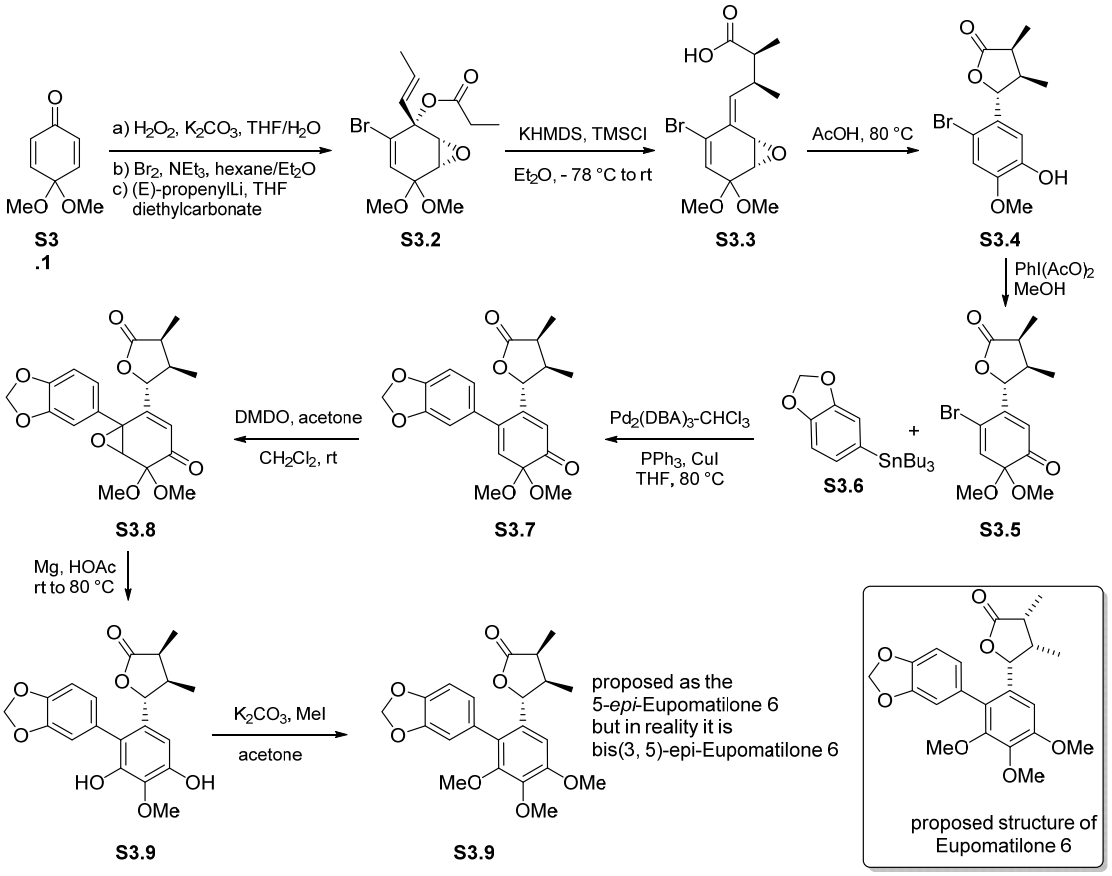


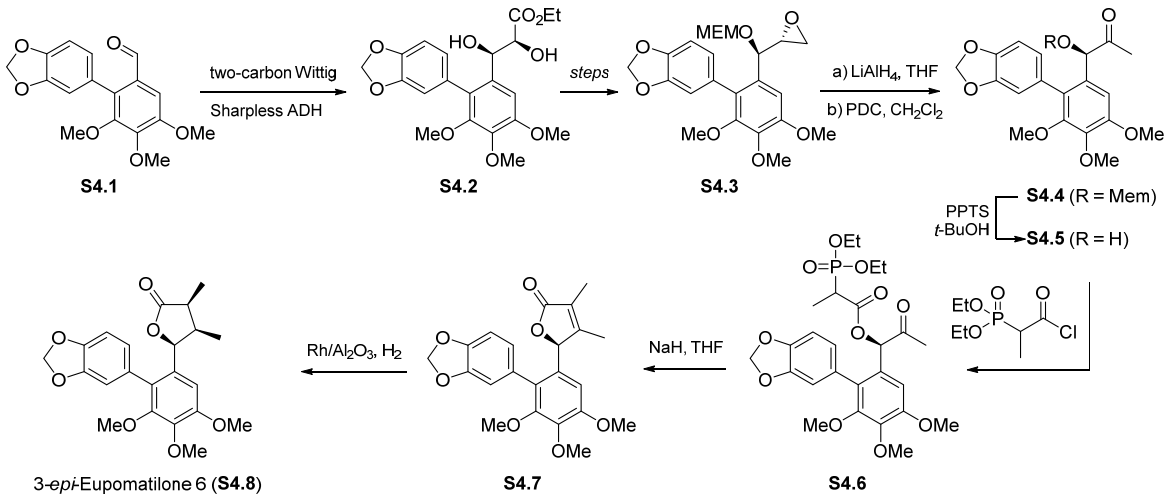
Figure S1.11. The key approaches employed for the installation of vicinal dimethyl groups in the synthesis of Eupomatilones

McIntosh's Approach (2002): McIntosh implemented an intramolecular Ireland-Claisen rearrangement of a densely functionalized bis-allylic ester in his 5-*epi*-eupomatilone 6 synthesis.[20] This method, however, could not lead to the synthesis of the required intermediate, but the approach to make the *γ*-butyrolactone along with the aromatic unit was completely novel. The fundamental way of ring formation and fixing of the methyl substituents in the *γ*-butyrolactone ring and, furthermore, construction of the hydroxyl moieties in the aromatic ring were absolutely impressive. The synthesis started with the commercially available *p*-quinone monoketal, which underwent a series of functional group transformations *via* epoxidation, bromination, nucleophilic addition, and propeonylation to get the Ireland-Claisen rearrangement precursor **S3.2**. The rearrangement was carried out with non-nucleophilic bases such as potassium hexamethyldisilazane (KHMDS) and TMSCl at –78 °C to room temperature to furnish the intended methyl groups in a stereospecific fashion. The heating of epoxide **S3.3** at 80 °C in acetic acid produces the *γ*-butyrolactone core. The lactone was further oxidized with $PhI(OAc)_2$, underwent Stille coupling, epoxidation, reductive ring opening of the epoxide with magnesium in acetic acid, and methylation of the phenol generated unwanted 5-*epi*-Eupomatilone 6. The resulted 5-*epi*-Epomatilone 6 in reality is also an epimer at the C3 position which was later proved in Gurjar's approach.



Scheme S1.3. Total synthesis of putative 5-*epi*-Eupomatilone 6 by McIntosh

Gurjar's 1st Approach (2004): Following the failure of McIntosh to synthesize the requisite moiety, our group specified the second synthetic endeavor to the mysterious core. It successfully solved the puzzle associated and described the synthesis of the putative structure of Eupomatilone-6. The main variance in fitting the methyl substituents were produced during face selective hydrogenation. The diastereoselectivity that resulted was pretty good; nevertheless the fingerprints of the NMR pattern disagree with the isolated NMR and McIntosh's synthesized eupomatilone NMR. Unanimously, the revision of the proposed structure was reasonably warranted.[21]

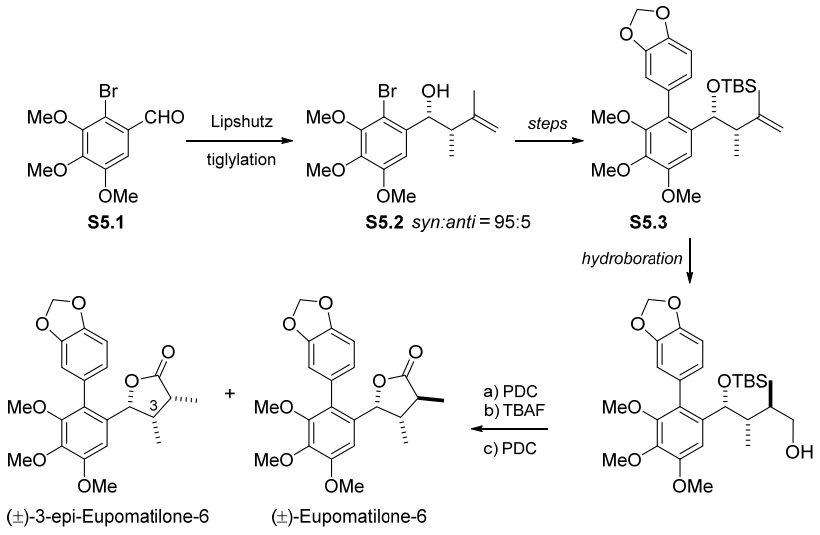


Scheme S1.4. Total synthesis of 3-*epi*-Eupomatilone 6 by Gurjar

The synthesis includes a Suzuki coupling of the easily-made bromo-intermediate to form a biaryl system. Wittig reaction followed by asymmetric hydroxylation induced chirality in the system. The epoxide **S4.3** formation was achieved through a series of simple organic transformations of the vicinal diol **S4.2**. Regioselective reduction of the epoxide with lithium aluminum hydride, oxidation of the resulting alcohol, deprotection of the α-hydroxy ketone, and coupling with a phosphonate acid chloride furnished an intramolecular alkene precursor **S4.6**. The intramolecular Horner-Wadsworth-Emmons reaction was carried out in the presence of sodium hydride to produce the unsaturated-γ-lactone **S4.7**. A planned face-selective heterogeneous hydrogenation in presence of Rh/Al_2O_3 supplied the γ-butyrolactone **S4.8**. The dissimilarity in physical and spectroscopy character of the synthesized moiety with the natural counterpart finally justified a structural modification. However, the compound synthesized was later known to be a C3-epimer of the Eupomatilone 6 (in Gurjar's 2nd approach).

In the same year after the declaration of structural revision of the Eupomatilone 6, Coleman synthesized the racemic Eupomatilone 6 and its 3-epimer by using a novel Lipshutz oxidative biaryl cuprate cross-coupling strategy. Diastereoselectivity was induced with a syn:anti ratio 95:5 during the coupling of an allyl indium complex with the known bromo aldehyde intermediate. The resulted alcohol was protected as silyl ether to produce a chromatographically separable mixture. A copper mediated cross coupling was intended in the presence of tertiary butyl lithium to explore the necessary biaryl system **S5.3**. Hydroboration/oxidation was the other key phenomena occurred in stereo- and regio-selective fashion to provide the requisite

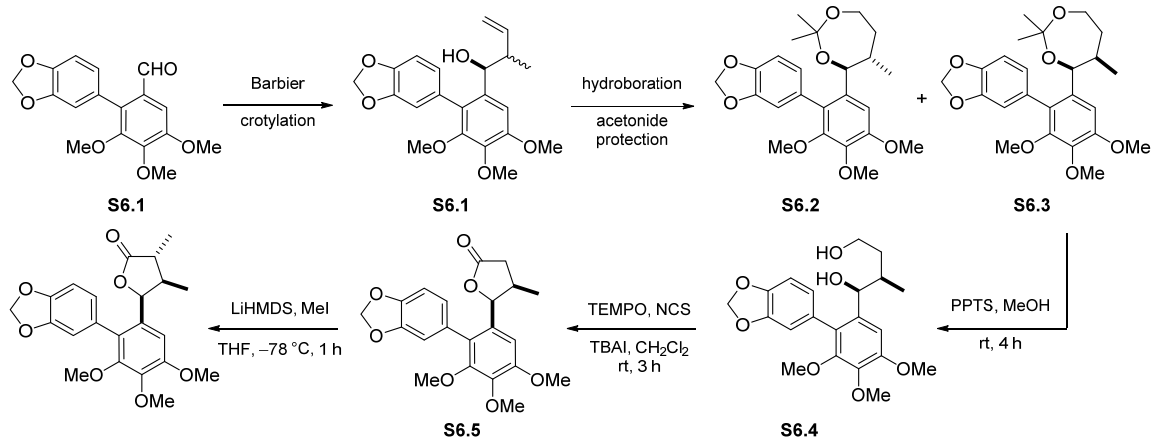
stereochemistry of methyl group at the C3 position. The use of tetra-*n*-butyl ammonium fluoride (TBAF) for TBS ether deprotection was believed to epimerize at the C3 centre (under basic condition) to produce the 3-*epi*-Eupomatilone 6 along with racemic Eupomatilone 6 in 1:3 diastereomeric ratio respectively.



Scheme S1.5. Total synthesis of racemic Eupomatilone 6 and 3-*epi*-Eupomatilone 6 by Coleman

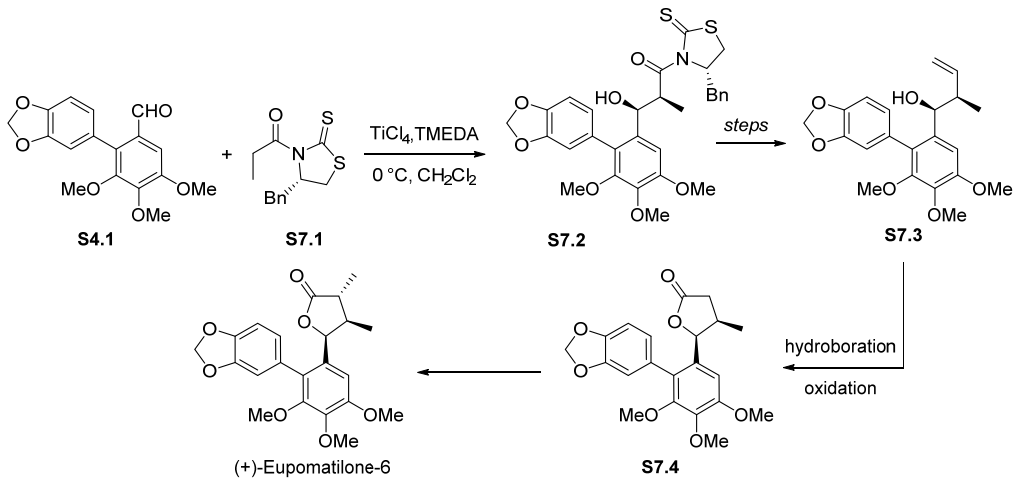
Gurjar's 2nd Approach (2005): It is to be noted that our group was the leading team at that time in the investigation linked behind the ambiguity in the structural interpretation of Eupomatilone 6. The evidence from Coleman's racemic synthesis of Eupomatilone 6 additionally energized us to explore the synthesis of the real natural product. We manufactured both the racemic as well as asymmetric compounds. For that we relied on the employment of a diastereoselective methylation of the γ-butyrolactone instead of face selective hydrogenation at the final step of the synthetic endeavor. This time too the same Suzuki coupled biaryl intermediate **S4.1** was taken as the starting material with simple variation in the synthetic strategy for racemic synthesis. The Zn-mediated Barbier crotylation followed by hydroboration produced an inseparable diastereomeric mixture which was separated after their conversion to a 7-membered cyclic intermediate using dimethoxy propane in the presence of PPTS. The diastereomers **S6.2** and **S6.3** were easily analyzed with the help of n*O*e. With the required diastereomer **S6.3**, the further vital transformations proceeded with no haziness. The deprotection of acetonide was carried out with the PPTS in methanol. A successful regioselective oxidation of **S6.4** in the presence of TEMPO

and NCS led to the formation of the advanced intermediate **S6.5**. The final destination was accomplished by the *α*-methylation of **S6.5** with methyl iodide in presence of LiHMDS. The dual possibility of diastereoselectivity occurred completely in face selective manner and ensured a single racemic product.[22]



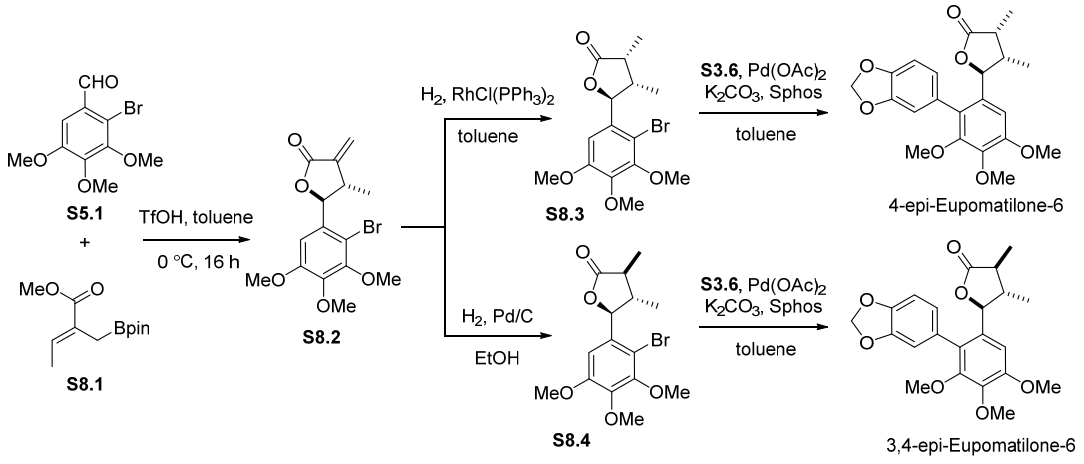
Scheme S1.6. The synthesis of racemic Eupomatilone 6

In order to introduce the chirality inside the molecule, a chiral *N*-propionyl derivative of thiazolidinone adjunct **S7.1** was selected. The well-known Ti-mediated aldolization was followed between the biaryl aldehyde **S4.1** and the chiral precursor under acidic condition. This face-selective aldol formation established the C4 methyl and C5 aryl position of the natural product with suitable configuration. The obtained secondary alcohol was protected as its silyl ether in the presence of TBSOTf before removing the chiral appendage. An efficient succession of chemical transformation such as reduction with sodium borohydride, oxidation by Dess-Martin periodinane, Wittig olefination, and *t*-butyl silyl ether deprotection led to meet a homoallylic alcohol **S7.3**. Hydroboration/oxidation of the terminal alkene **S7.3** resulted in the chiral version of the primary alcohol **S6.4** (see racemic synthesis). Finally, the previously established protocols were repeated to pursue the long awaited natural product. This thus simultaneously established the absolute configuration as well.



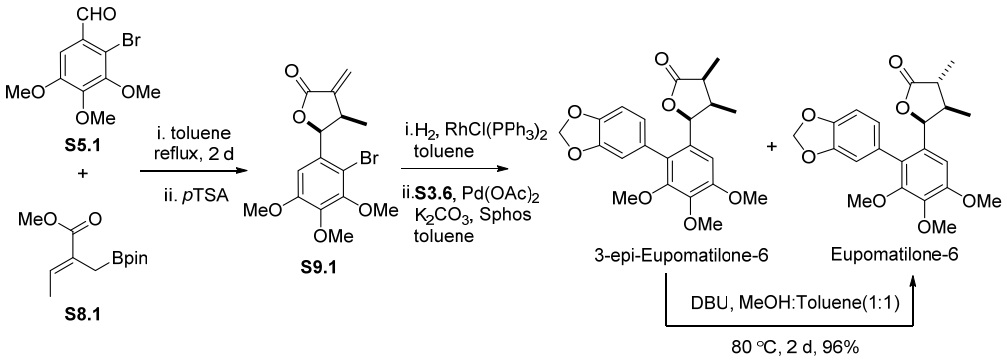
Scheme S1.7. The total synthesis of (–)-Eupomatilone 6

Hall's Approach (2005): In 2005, Hall and co-workers synthesized all four possible combinations of C3 and C4 methyl diastereomers of Eupomatilone 6 effortlessly by using Bronsted acid allylboration. An allylboronate **S8.1** was treated with the known aromatic aldehyde **S5.1** in the presence of triflic acid at 0 °C to procure an exocyclic methylene *γ*-butyro lactone **S8.2**. For the hydrogenation of **S8.2**, different outcomes were realized under different conditions. The Rh-catalyzed heterogeneous hydrogenation of **S8.2** produces 3,4-*epi*-Eupomatilone 6 and the homogeneous reduction in presence of Wilkinson's catalyst ended with 4-*epi*-Eupomatilone 6.[23]



Scheme S1.8. Hall's synthesis of Eupomatilone 6 diastereomers

On the other hand, the allylboronate ester was heated in toluene at 110 °C in the absence of acid catalyst to produce an acyclic ester having the methyl and hydroxyl group syn to each other. Diastereoselectivity of the reaction is believed to originate through a chair-like transition state. The lactonization in presence of *p*-TSA in toluene led to the formation of the exocyclic methylene *γ*-butyrolactone. Homogeneous reduction in presence of Wilkinson catalyst and coupling in presence of $Pd(OAC)_2$ produced 3-*epi*-Eupomatilone 6 in 79%. During Suzuki coupling, 3-epimer was produced along with 5–20% of the natural diastereomer (i.e. Eupomatilone 6). This result suggests that 5–20% of the natural diastereomer (all-cis) has epimerized to the more stable 3,4-trans isomer under basic condition. The final isomerization was carried out with the hindered base, DBU in methanol and toluene heated at 80 °C for 2 days to give an equilibrium ratio of 1:1 of the two separable epimers.



Scheme S1.9. Hall's synthesis of Eupomatilone 6 and its *C*3-epimer

Sacidumlignan D– Unprecedented Lignan

In 2005, Yue and co-workers isolated four lignans, Sacidumlignans A–D along with two degraded lignan derivatives, Sacidumols A and B from the ethanolic extraction of the plant *Sarcostemma acidum*.[24] About 10 species of the genus *Sarcostemma* are dispersed extensively over the tropical and subtropical areas of Asia, Africa, and America. Some, among them are toxic to the nervous system. The plant *Sarcostemma acidum* (*Roxb.*) collected from Hainan Island of China was anciently used as folklore medicine to remedy chronic cough and postnatal hypogalactia. These plants are also accessible widely in India. The structures and relative configuration of the Sacidumlignans were elucidated by 1D and 2D NMR techniques. Sacidumlignan D was believed to form as a rearranged tetrahydrofuran lignan and its skeleton

was realized as unprecedented. The Sacidumlignans A–C is believed to originate by a novel mechanism from Sacidumlignan D. Unlike Sacidumlignan B, an anonymous molecule specifically "Orthosilignin",[25] with similar structural appearance was formulated in 2002. However, the molecular architecture profile such as relative/absolute stereochemistry and biological profile were not completely addressed at the time of isolation. Conversely, the absolute configuration of Sacidumlignans like Eupomatilones was also not elucidated except for their pharmacological properties. Sacidumlignan A exhibited moderate antimicrobial activities against two Gram-positive bacteria viz. *S. aureus* and *S. epidermidis in-vitro*.

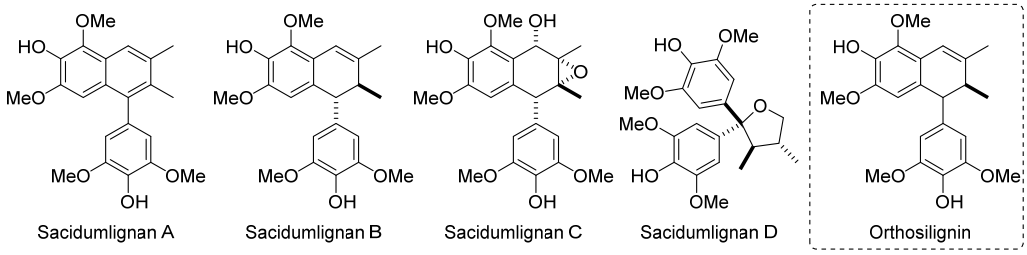


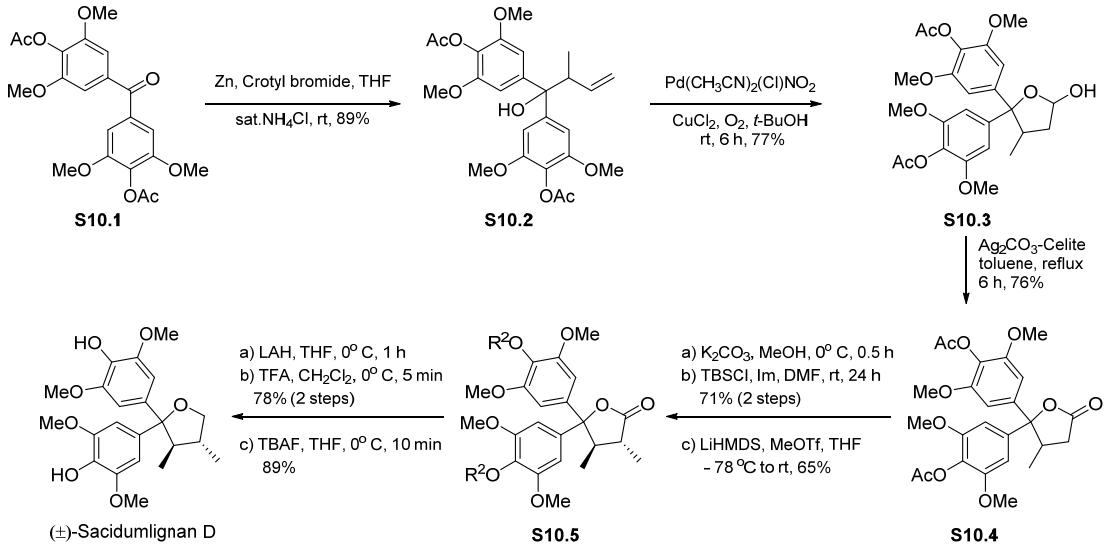
Figure S1.12. The structures of Sacidumlignans A-D and of previously reported Orthosilignin

The similarity in stereochemistry of the methyl substituents in Eupomatilone 6 with Sacidumlignan D prompted us to consider whether we could devise a route to its synthesis by applying the previously developed diastereoselective methylation protocol. Of course, producing plenty of material for further biological studies was an imperative motto for approving these targets.

Synthesis of Sacidumlignans: Till date, there are only two approaches reported for the synthesis of Sacidumlignans. Our group was the first to synthesize the racemic Sacidumlignan in 2011 by using the previously developed diastereoselective α-methylation protocol as the key phenomenon. The second racemic approach was implemented by Peng in 2013 after our chiral approach was proposed. As a key transformation, Peng used the Ueno–Stork radical cyclization for the synthesis of γ-butyrolactonecore but later he repeated Ramana's synthetic protocol to acquire the molecule.

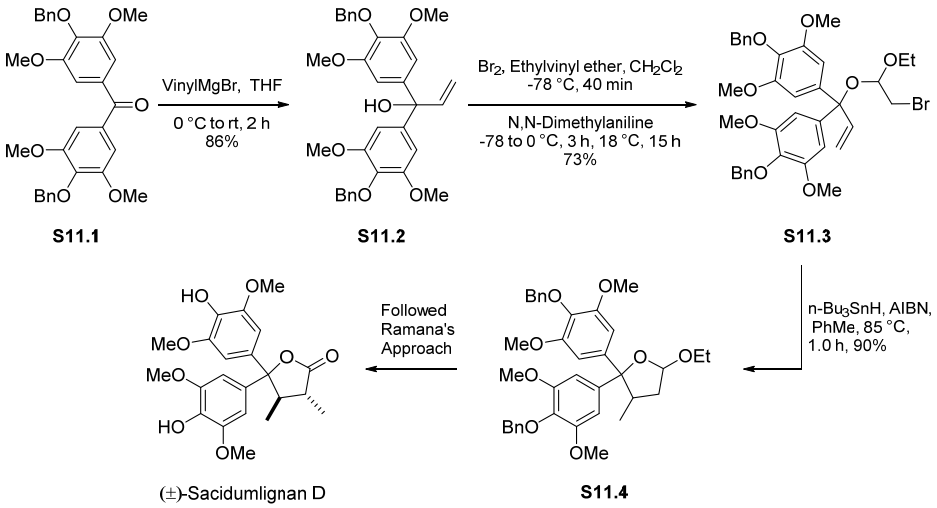
Ramana's Approach for Sacidumlignan D (2011): It featured a Zn-mediated Barbier crotylation and reverse Wacker oxidation to constitute the key precursor γ-butyrolactol core. The lactol was further oxidized to its lactone with celite supported silver carbonate. The

diastereoselective α-methylation in the presence of a non-nucleophilic base and a highly reactive methyl triflate provided the requisite product. Reduction, cyclization, and silyl ether cleavage of the lactone **S10.5** in sequence produced the racemic Sacidumlignan D.[26]



Scheme S1.10. Ramana's synthesis of racemic Sacidumlignan D

Peng's Approach for Sacidumlignan D and A (2013): In 2013, Peng efficiently introduced the making of the C3–C4 bond through Ueno–Stork radical cyclization and subsequently utilized pretty well Ramana's strategy in his Sacidumlignan A and D synthesis. Their synthesis started with the addition of vinyl Grignard (instead of Zn mediated Barbier crotylation like Ramana's approach) to the benzophenone. The resulted alcohol was then converted to the Ueno–Stork radical precursor by reaction with ethyl vinyl ether in the presence of Br_2. The intramolecular radical transformation in the presence of tributyltin hydride and radical initiator AIBN led to the formation of the ethyl acetal of the γ-butyrolactol that has been transformed to Sacidumlignan D following the sequence that has been earlier established by Ramana's group.[27]



Scheme S1.11. Peng's approach for the synthesis of Sacidumlignan D

Thus, so far there are only two reports including one from our group on the total synthesis of Sacidumlignan D alone in its racemic form. In continuation, we have taken up the problem of fixing its absolute configuration and extending the developed synthetic route/key intermediates to synthesize the other members of this family. In the following section, we describe the total synthesis of Sacidumlignans A, B, and D and the development of acid catalyzed dehydrative cyclization as a tool for the synthesis of the dihydronaphthalene core of the Sacidumlignans B and A.

RESULT AND DISCUSSION

The lignans constitute as one of the large class of natural products widely distributed in plants. These polyphenolic compounds are intuitively born from L-phenylalanine through the dimerization of various cinnamic alcohols in the Shikimic acid pathway and possess a *β,β'*-linkage. In addition, they also produce assembles of molecules, proving them as unusual lignans in the absence of such linkage, manifesting their importance in industry and academia. Although the number is less in comparison to the genuine lignans, they are highly precious. For instance, Sacidumlignan D bearing an unprecedented lignan architecture isolated from *Sarcostemma acidum* plant is rare in nature and believed to formulate the other individual, Sacidumlignans A–C through rearrangement. Once upon a time, the plants that produced these natural products used to be prescribed as medicines in India and China. The structures of Sacidumlignans are intimately associated thus indicating they all originated from a common precursor. From a structural perspective, Sacidumlignan D possesses a rearranged dimethyl tetrahydrofuran moiety, while Sacidumlignans B and C contain a di- and tetrahydronaphthalene ring respectively. On the other hand, the Sacidumlignan A is attributed with a naphthalene skeleton (Figure 1).

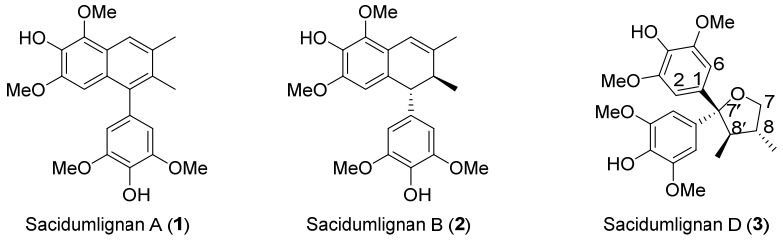


Figure 1. Structure of Sacidumlignan A, B, and D

The reason behind targeting Sacidumlignan D (**3**) was its unusual structural motif. The possession of a tertiary carbon center at C(7') with gem-diaryl unit and, of course, two contiguous stereogenic carbons at C(8), C(8') made it an attractive target. The other principal objective for the intended goal was to provide a complete address to the Sacidumlignan family in terms of the absolute stereochemistry. To fix the absolute configuration, we were interested in extending the previously manifested racemic Sacidumlignan D synthetic strategy towards its asymmetric version, thus also providing a unified platform to access to other Sacidumlignans A (**1**) and B (**2**). With this idea in mind, the retrosynthetic analysis was begun by assuming the asymmetric configuration of **2** and **3** as given in Figure 1.

Retrosynthetic analysis

The Sacidumlignans were split retrosynthetically in such a way that all the three natural products**1** – **3** could be accessed from one single precursor **4**, the racemic version of which has been used earlier in the synthesis of (±)-Sacidumlignan D.[26] Coming to the Sacidumlignans A and B, the *di-O-TBS* protected Sacidumlignan B (**5**) has been identified as the penultimate intermediate in their synthesis. A simple deprotection of **5** should provide **2** whereas **1** can be accessed by the oxidative aromatization of **5** followed by desilylation. The dehydrative cyclization[28] of a *γ,γ'*-diaryl aldehyde **7** has been postulated as a novel tool in the synthesis of this key intermediate **5** that has been rarely documented. The synthesis of **7** is a direct proposition from **4** *via* sequential reduction of lactone and the deoxygenation of benzylic oxygen.

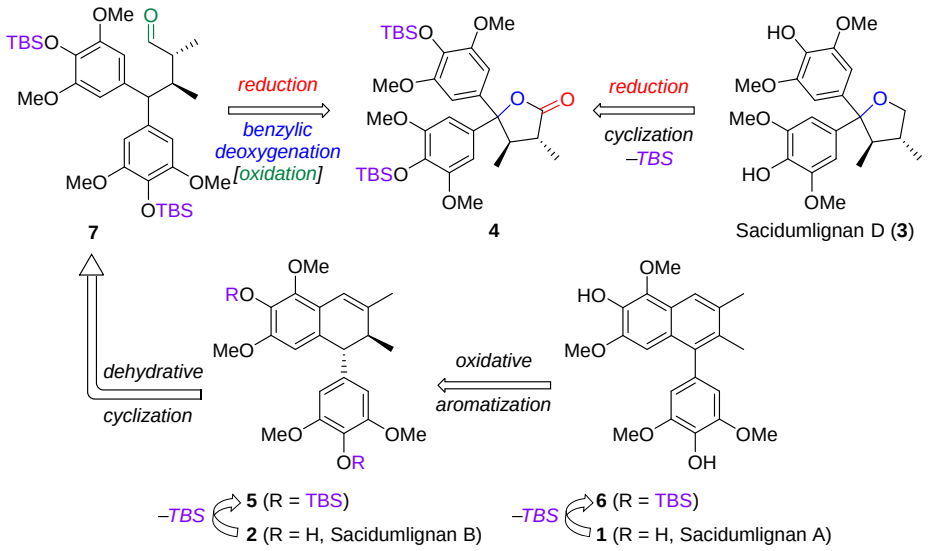


Figure 2. Planned approach for Sacidumlignans A, B and D

The intended synthesis of the key precursor **4** was partly founded upon the previously established synthetic route – such as diastereoselective *α*-methylation of **8**. In the racemic synthesis of (±)-Sacidumlignan D, the synthesis of (±)-**8** involved a Zn-mediated Barbier crotylation of a benzophenone derivative and the reverse Wacker oxidation of a homoallylic alcohol. To have **8** with the proposed absolute configuration, we selected an oxidative olefin cleavage of a chiral pent-4-en-1-ol derivative **9**. Keeping the proposed absolute stereochemistry at C8' of Sacidumlignans B and D in mind, we designed a tactical approach that employs the chiral benzyl ester **10** and its Grignard reaction employing the aryl bromide **11**. As discussed

earlier, the lignan and lignin originate from common precursors in the Shikimic acid pathway by a series of conversion procedures and L-phenyl alanine is one amongst them. Here, by accident, we selected an alternate trail to the nature's biosynthetic model by providing chirality through artificial means in terms of Evan's oxazolidinone, though it was being used as an appendage in the synthesis of **10**.

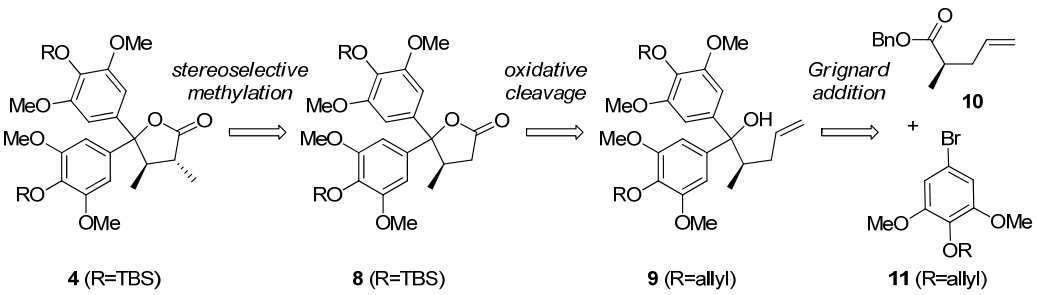
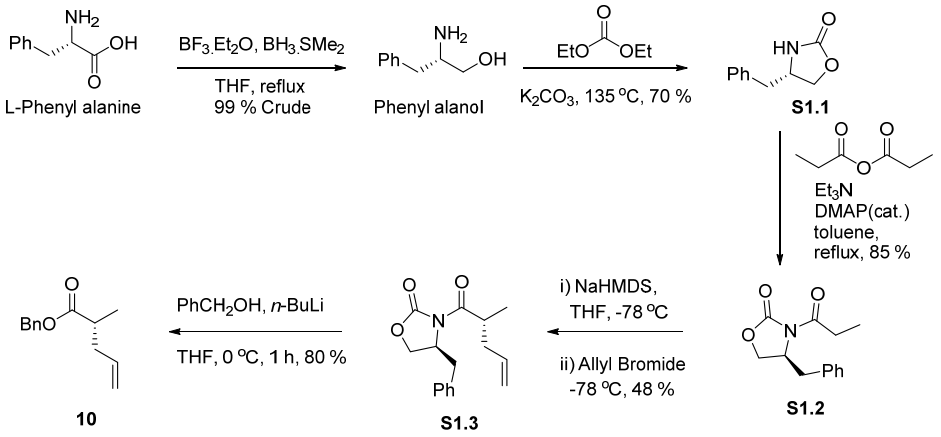


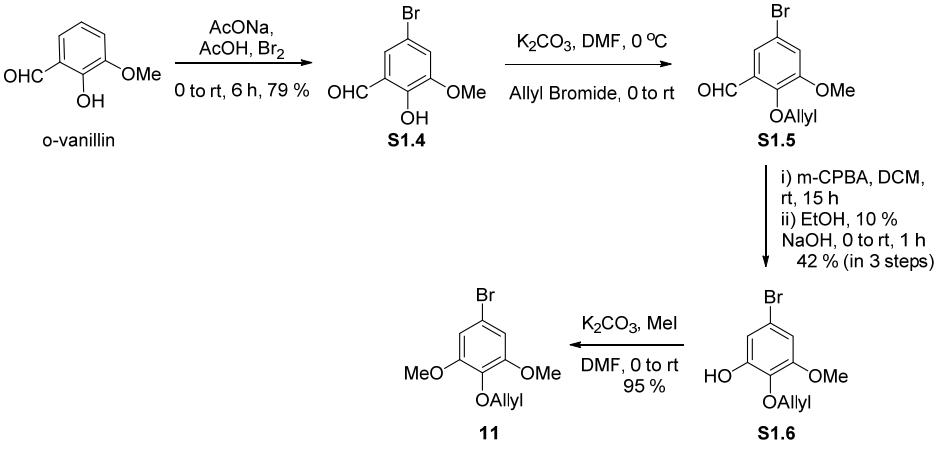
Figure 3. Retrosynthetic disconnections for key intermediate **4**

Synthesis of the Chiral Ester:[29] The journey of our total synthesis started with the preparation of ester **10** by following the literature reported protocols. The commercially available L-phenyl alanine was reduced to L-phenyl alaninol under reflux conditions with $BH_3.SMe_2$ in the presence of boron trifluoride etherate complex. It was later carbonylated with diethyl carbonate at higher temperature. This heating reaction was carried out in a 3-necked round bottom flask in which one neck was fixed with a distillation condenser to collect the *in situ* liberated ethanol. The obtained oxazolidinone was *N*-acylated with propionic anhydride in the presence of N,N-dimethylaminopyridine (DMAP). After *N*-propionylation, the diastereoselective *C*-allylation was carried out employing allyl bromide and sodium hexmethyldisilazide (NaHMDS) at –78 °C to furnish the required α-allyl product. The lithiation of benzyl alcohol followed by addition to the oxazolidinone provided the requisite chiral benzyl ester.



Scheme 1. Synthesis of the chiral ester

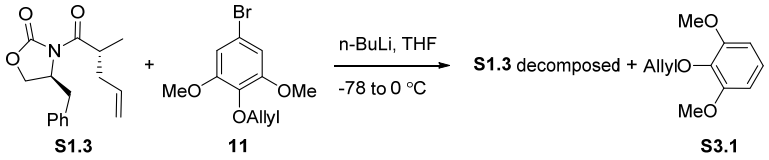
Synthesis of the Bromo Intermediate:[26] The aryl bromide intermediate **11** has been prepared by the earlier established strategy by our group. The synthesis commenced with the bromination of commercially available *o*-vanillin in the presence of bromine and sodium acetate in acetic acid. The resulting bromo-o-vanillin was subjected for O-allylation with allyl bromide and potassium carbonate followed by the Baeyer-Villiger oxidation with *m*-chloro perbenzoic acid and subsequent alkaline hydrolysis to obtain the phenol S2.3, which upon *O*-methylation with potassium carbonate and methyl iodide gave the key aryl bromide intermediate **11**.



Scheme 2. Synthesis of the bromo-intermediate

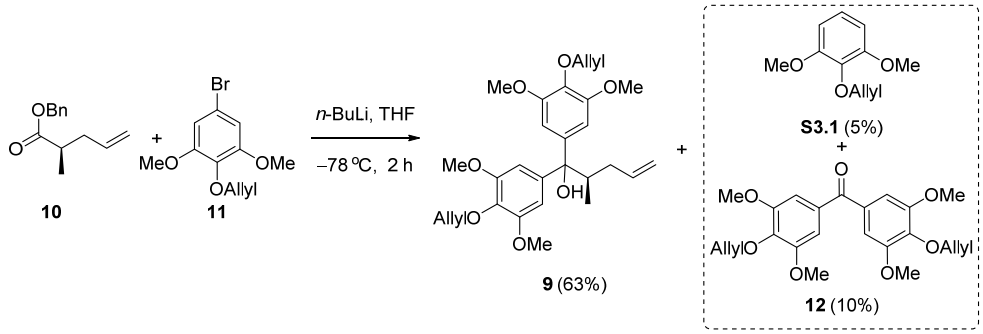
The initial experiment started with a coupling of the allyl protected bromo intermediate **11** with the *C*-allylated benzyl oxazolidinone **S1.3**. At –78 °C, the halide/metal exchange of 2-(allyloxy)-5-bromo-1,3-dimethoxybenzene was done with *n*-butyl lithium followed by slow addition of the oxazolidinone. But unfortunately, the oxazolidinone couldn't survive in the

reaction conditions even after many alterations were made, whereas the bromo intermediate always ended with dehalogenation.



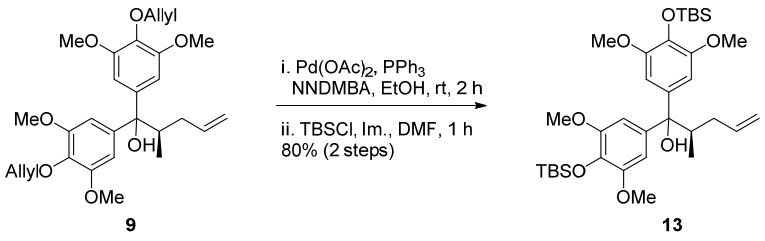
Scheme 3. Attempted arylation of oxazolidinone intermediate to synthesize

The synthesis of pent-4-en-1-ol derivative **7** (Scheme 4) was initiated with the lithiation of the bromo intermediate **11** followed by its addition to the chiral benzyl ester **10** to get the necessary diaryl-addition product **9** in 63% yield. The structure of **9** was established with the help of spectral and analytical data. For example, in the ^{1}HNMR spectrum of compound **9**, the two doublets of four aryl protons were seen to resonate at δ 6.73 (s, 2H), 6.69 (s, 2H), one singlet for tertiary OH at δ 2.14 and methylene protons of *C*-allyl separated from the methylene protons of *O*-allyl at δ 2.23 (brdd, J = 13.8, 5.6 Hz, 1H), 1.84 (br dt, J = 13.8, 8.9 Hz, 1H) ppm. In the ^{13}CNMR spectrum of compound **9**, the characteristic tertiary carbon containing the hydroxyl group appeared at δ 81.0 (s) along with the methyl at δ14.0 (q), methylene at δ 36.2 (t), and methine of the pent-1-ene at δ 40.8 (d). Additionally, the mass peak at 507.2317 satisfied the expected constitution. Decrease in the yield was reasoned for by the recognition of a dehalogenated compound **S3.1** (5%) and the corresponding benzophenone **12** (10%) as the side products. The benzophenone side product **10** is presumably replicated as a result of an elimination of a carbanion (probably a pentyl carbanion).[30]



Scheme 4. Synthesis of the allyl pent-4-en-1-ol derivative **9**

The next task was making the product **9** ready for the oxidative olefin claveage to prepare the lactone **8**. This requires the replacing of allyl protecting groups to TBS. The allyl pent-4-en-1-ol **9** was therefore subjected to the palladium (II) acetate, triphenyl phosphine and N,N′-dimethylbarbituric acid (NNDMBA) in ethanol for 2 h at room temperature for deallylation.[31] Here, NNDMBA is used as an allyl scavenger which is catalyzed by Pd(0). The reactive species Pd(0) is generated *in situ* from the Pd(II) acetate in the presence of the ligand, triphenyl phosphine (PPh_3). The Pd(0) then forms an η^3 complex with the allyl group, making it a good leaving group which is then transferred to the NNDMBA. As the resultant naked phenol containing a tertiary benzyl alcohol was found to be too unstable to characterize, it was subjected for the *O*-silylation employing *t*-butyldimethylsilyl chloride (TBSCl) and imidazole in *N*,*N*-dimethylformamide (DMF) to obtain the TBS pent-4-en-1-ol derivative **13**. In the ^{1}HNMR spectrum of compound **13**, the appearance of *t*-butyldimethylsilyl protons at δ 1.00 (s, 18H), 0.11 (br s, 12H) and singlet for the tertiary alcohol at δ 2.03 (s, 1H) ppm established the proposed structure. The question here could be asked: why did we not use the TBS protected aryl halide in the beginning directly for nucleophilic addition reaction? This is because the phenolic TBS compounds are highly susceptible for deprotection under slightly acidic, basic and/or even nucleophilic reaction conditions. Another question might be asked: why did we not proceed with the same allyl protected group? The answer probably is, the allyl group is itself able to react during oxidative cleavage (the next step) and may create discrepancies.



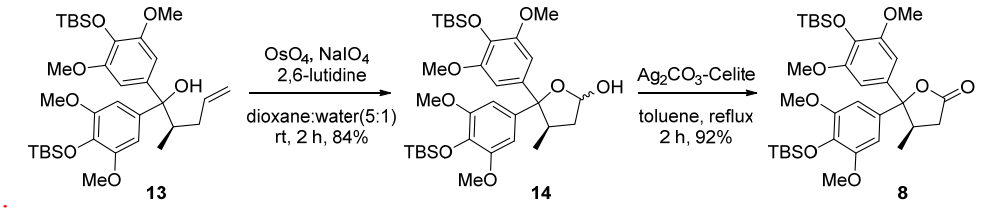
Scheme 5. Synthesis of the TBS pent-4-en-1-ol derivative **13**

Our next step was the synthesis of the lactone **8**. As per our plan, a two phase reaction sequence utilizing a one-pot osmium tetroxide catalyzed dihydroxylation followed by sodium periodate mediated diol cleavage[32] facilitated the requisite γ-butyrolactol **14** in 84% yield as an 1:2.3 inseparable anomeric mixture. In the ^{1}HNMR spectrum of compound **14**, the disappearance of the allylic protons at δ 5.85 (dddd, J = 16.2, 10.8, 7.9, 6.4 Hz, 1H), 5.01–4.93 (m, 2H) present

in **13**, and the appearance of a mixture of epimers for the C2 center at δ 5.79 (br t, J = 4.9 Hz, 0.7H) and 5.61 (dd, J = 9.9, 4.7 Hz, 0.3H) ppm preliminarily suggested the formation of the requisite intermediate lactone. Later this was confirmed by both ^{13}CNMR and HRMS.

The highly toxic osmium (VI) tetroxide here is used as a catalyst for the dihydroxylation of the terminal alkene. The isolation of the dihydroxylated product was never attempted. The cleavage of the C–C bond in the presence of sodium periodate in the same pot ended with a γ-lactol as a mixture of two epimers at C(7). The lactol and aldehyde-alcohol were believed to exist in equilibrium. However, at room temperature, there is no aldehyde found (revealed from the NMR). For instance, the oxidative cleavage of the naked phenol of pent-4-en-1-ol (resulting from the deallylation) had been initially explored, and resulted in a poor yield. This was the other reason why we selected TBS ether as the protecting group after the allyl deprotection.

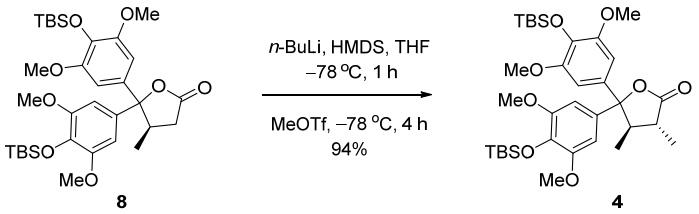
Having had the lactols **14** in hand, we next proceeded for its oxidation with Celite supported silver carbonate[33] in refluxing toluene for 2 h (Fétizon's reaction conditions)[34] to obtain the key lactone **8**. The formation of lactone **8** was easily established just by looking at the clear distinct pattern of both the NMRs. The ^{13}CNMR spectrum of compound **8** clearly indicated the presence of a γ-lactone by showing the quaternary carbon peak at δ 176.1 (s) ppm and was ultimately proved by the mass at 655.3107. This oxidizing condition was found to be good among the other reaction conditions tried. A single epimer (γ-butyrolactone) was accomplished with excellent yield.



Scheme 6. Synthesis of the γ-butyrolactone **8**

Our next concern was about face selective α-methylation of lactone **9** that was carried out initially under the established reaction conditions (LiHMDS, MeOTf) to yield the key intermediate **4** in 65% as a single diastereomer. As this intermediate **4** is the crucial divergence point in the proposed synthesis of **1** – **3**, this prompted us to further optimize this alkylation reaction in view of improving the yield. After a careful experimentation, the yield was

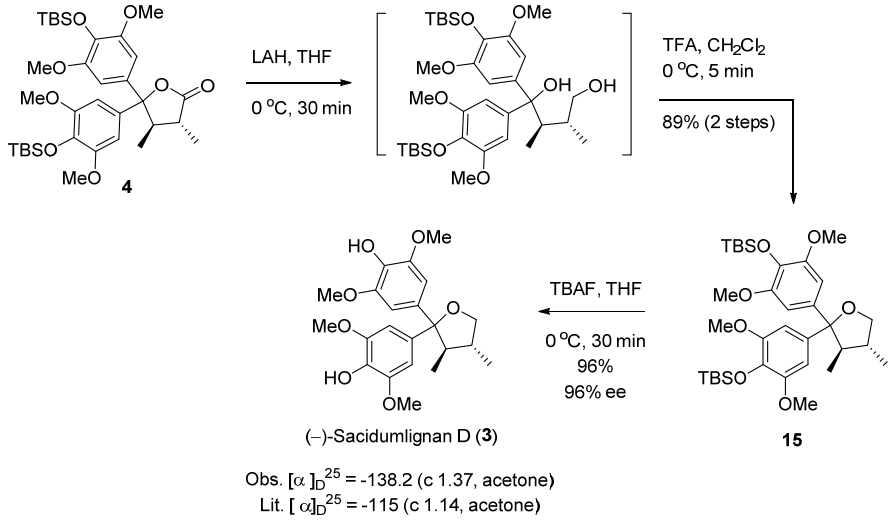
significantly amplified to 94% when the reaction was performed in hexamethyldisilazane (HMDS), *n*-butyl lithium, and methyl triflate. The *in situ* generated LiHMDS in the present circumstances proved to be a better non-nucleophilic base rather than the readily available material. The strong leaving ability of triflate group (OTf^-) in MeOTf on the other side made it easier as a good methylating agent. Hence, the optimum conditions employed involve the *in situ* generation and addition of LiHMDS at –78 °C to the lactone **9** and stirring for 1 h for the complete conversion to its enolate form followed by the insertion of methyl triflate and additional 4 h stirring at the same temperature. The reason for the single α-diastereomer with an *anti*-geometry of the methyl groups is accounted for by the steric hindrance created by the C(8') methyl group. In the ^{1}HNMR spectrum of compound **4**, the newly introduced methyl peak was seen to appear at δ 1.29 (d, J = 7.0 Hz, 3H), and the two methine protons appeared as two separate doublet of quartets at δ 2.86 (dq, J = 11.8, 6.7 Hz, 1H) and 2.43 (dq, J = 11.8, 7.0 Hz, 1H) ppm. Obviously ^{13}CNMR and HRMS provided the additional support for the proposed structure. The n*O*e interaction provided extra evidence to support the α-configuration, as in the racemic case.



Scheme 7. Synthesis of the advanced intermediate

Total Synthesis of (–)-Sacidumlignan D: With the compound **4** having the whole skeleton, we enthusiastically proceeded towards the synthesis of Sacidumlignan D with the intended absolute configuration. The next easy target was the reduction of the ester bond. To have the tetrahydrofuran unit, an intermediate possessing a primary and a tertiary benzyl alcohol was aimed for so that an intramolecular ring closure could be attempted. Reduction of compound **4** with LAH proceeded smoothly within half an hour at 0 °C to the intermediate diol, which was used for the next step without any characterization. The tertiary benzyl alcohols are highly prone towards acid to generate a benzyl carbocation and furthermore this is stabilized by the mesomeric effect of the electron donating alkoxy groups. As per plan, the primary alcohol was made available to capture the benzyl carbocation. Consequently, the treatment of crude diol with

trifluoro acetic acid in CH_2Cl_2 fulfilled our ambition by providing a cyclic ether called *di-O*-TBS protected Sacidumlignan D (**15**) within five minutes after acid addition. The spectra of **15** were found to be identical with the earlier reported spectra for its racemic version. Finally, the deprotection of TBS groups in **15** employing tetra-*n*-butylammonium fluoride (TBAF) thus afforded the (–)-Sacidumlignan D. The chiral-HPLC analysis revealed the ee as 96%. The enantiomeric ratio was calculated by comparing both the racemic and chiral compound. The NMR spectra of the synthesized compound were completely correlated with the reported spectra. A comparative study of both ^{1}H & ^{13}C coupling constants (*J*) and/or chemical shifts for natural and synthetic Sacidumlignan D was done in Table 1. The resemblance in the sign and comparable magnitude of the optical rotation revealed that the naturally occurring (–)-sacidumlignan D has been ultimately synthesized.



Scheme 8. Synthesis of (–)-Sacidumlignan D

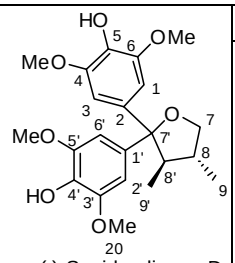
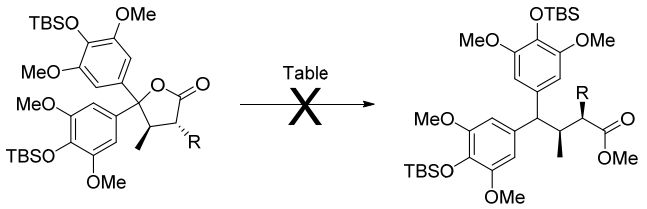
 (-)-Sacidumlignan D **4**	***Natural***		***Synthetic***	
	δ_H, *J* (Hz)	**δ_C**	**δ_H, *J* (Hz)**	**δ_C**
1,3	6.50 (2H, s)	106.6	6.53 (2H, s)	106.4
2		137.1		137.1
4, 6		148.1		148.0
5		135.8		135.7
7	**7α**: 3.20 (1H, dd, 10.0, 8.0) **7β:** 4.25 (1H, dd, 8.0, 7.7)	74.3	**7α:** 3.33 (1H, dd, 10.1, 8.2) **7β:** 4.26 (1H, t, 7.7)	74.2
8	2.00 (1H, m)	42.3	1.99 (1H, m)	42.3
9	0.96 (3H,d, 6.5)	15.4	0.98 (3H,d, 6.5)	15.4
1’		139.4		139.4
2’, 6’	6.76 (2H, s)	106.3	6.78 (2H, s)	106.0
3’, 5’		148.5		148.4
4’		136.2		136.2
7’		91.7		91.5
8’	2.40 (1H, dq, 9.6, 6.9)	51.2	2.42 (1H, dq, 9.6, 6.9)	51.2
9’	0.85 (3H, d, 6.9)	17.0	0.86 (3H, d, 6.9)	17.0
4,6-OMe	3.72 (6H, s)	57.0	3.73 (6H, s)	56.9
3’, 5’-OMe	3.78 (6H, s)	57.2	3.80 (6H, s)	57.1
4’, 5-OH	*Not observed*		7.06 (1H, s), 7.17 (1H, s)	

Table 1. Comparative ^{1}H &^{13}C Coupling Constants (*J*) and/or Chemical Shifts for Natural and Synthetic Sacidumlignan D

Synthesis of Sacidumlignans A and B

We next focused our attention towards the synthesis of Sacidumlignans A and B. The main concern in the proposed retrosynthetic strategy was the cleavage of the benzylic C–O bond in compound **4**. A literature survey revealed that the benzylic C–O bonds are prone to cleave under heterogeneous hydrogenolysis. For that, various reduction conditions were attempted to seek the break up in both the lactones **4** and **8**. But unfortunately in our case, the starting materials were intact even after being kept for longer period of time. An alteration in solvent, catalyst, and neutral to basic reaction conditions, had no influence on the C–O bond. This includes Pd-C/H_2, MeOH; $Pd(OH)_2$-C/H_2, MeOH; Pd-C/H_2, EtOAc, K_2CO_3 etc. Reduction under

acidic condition was never tried due to the presence of acid labile TBS groups. To this end, the steric hindrance exhibited by the two geminal bulky aryl groups along with a methyl group at C4 position around the C–O bond has been concluded as a cause for failure.



8 (R = H)
4 (R = Me)

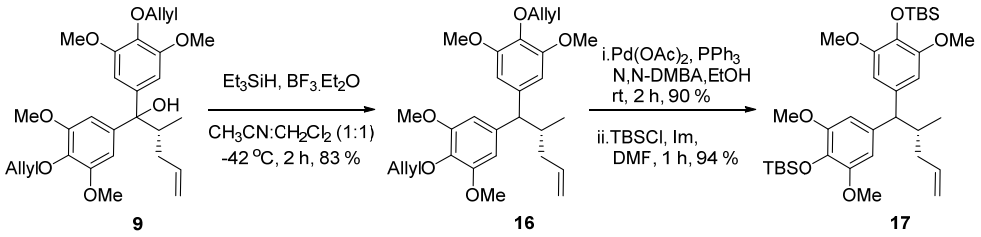
Sl No.	Reaction Conditions	Results
1	Pd-C, H_2, MeOH, rt	No Reaction
2	$Pd(OH)_2$-C, H_2, MeOH, rt	No Reaction
3	Pd-C, H_2, EtOAc, K_2CO_3, rt	No Reaction

Table 2. Catalyst screening to break the benzylic C–O Bond

Apart from the proposed benzylic deoxygenation, the projected dehydrative cyclization of a γ,γ'-diaryl aldehyde leading to a dihydronaphthalene was another important issue that needs to be addressed. As working on these two important tasks especially using the advanced lactone intermediate **4** was a costly affair, we have intended to experiment on these aspects by employing one of the intermediates of the early stages of the synthesis. A careful examination of the available intermediates had led to the identification of the *di-O*-allyl pent-4-en-1-ol derivative **9** as the suitable precursor and its reductive benzylic deoxygenation as the first task. The resulting deoxygenation product can be transformed to the key γ,γ'-diaryl aldehyde directly by OsO_4-$NaIO_4$ mediated oxidative cleavage, which in turn can be explored for the projected dehydrative cyclization.

With this plan, the deoxygenation of **9** was carried out at –42 °C in the presence of triethylsilane and boron trifluoride etherate complex to obtain **16** in 83% as single product.[35] The HRMS data and the emergence of the benzylic proton at δ 3.34 (d, J = 10.8 Hz, 1H) and the

corresponding carbon at δ 59.0 (d) ppm in ^{1}HNMR and ^{13}CNMR respectively confirmed the specified structure. The previously established allyl deprotection technique was followed here as well to give the free hydroxyl deoxygenated product in excellent yield. This was further protected as its silyl ether **17** by using TBSCl. The *O-di*-TBS compound was proved with no hesitation from its ^{1}HNMR spectrum. The disappearance of allyl groups and the appearance of two singlet at δ 0.09 (s, 12H), and 0.98 (s, 18H) ppm for two silyl ether groups were the proof for the proposed structure.

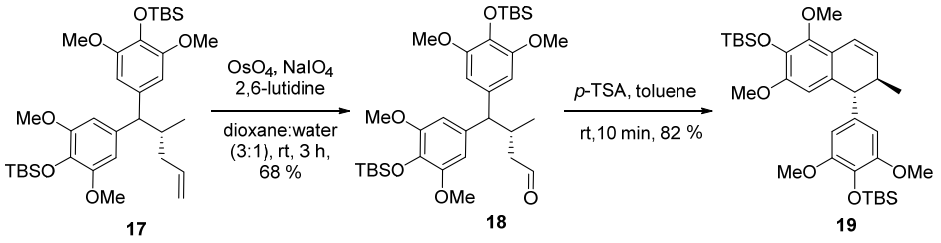


Scheme 9. Synthesis of TBS pent-4-ene derivative

Next, the *di-O*-TBS **17** was subjected for oxidative cleavage by using the previously established reaction conditions to obtain the aldehyde **18**. This was characterized by its characteristic proton as a triplet at δ 9.63 (br t, J = 1.1 Hz, 1H) in its ^{1}HNMR spectrum and a carbonyl signal at δ 202.3 (d) ppm in its ^{13}CNMR. Having the key aldehyde **18** in our hand our next concern was its dehydrative cyclization leading to a dihydronaphthalene derivative **19**. Coming to the origin of this proposal, while inspecting the literature in the context of the retrosynthesis of Sacidumlignan B, one old article came to our notice. That was a procedure for the synthesis of isoquinoline, called the Pomeranz–Fritsch reaction.[36] Those intermolecular elimination reactions were reported at high temperature under acidic condition. The intramolecular version of isoquinoline derivative synthesis was also found to be known.

Therefore, we thought to apply this reaction in the present circumstances as a carbon variant. On the other hand, this would be a typical Friedel-Crafts reaction. The Friedel-Crafts acylations usually occur with an acyl halide in presence of a Lewis acid. This thus describes the uniqueness of the protocol as it uses a less reactive species, aldehyde in presence of a Bronsted acid. At the moment, the key aldehyde encompasses two symmetrical aryl groups having enormous electron donating substituents to activate the ring for the Friedel-Crafts reactions. The reaction was carried out in toluene in the presence of 5 mol% of *p*-toluene sulfonic acid (*p*-TSA)

at room temperature. It normally takes 10–15 minutes to complete. The reaction was also observed to be very fast with the increase in the amount of catalyst. At higher temperatures, the reaction mixtures were found to be decomposed. A good yield was realized under these optimum conditions.

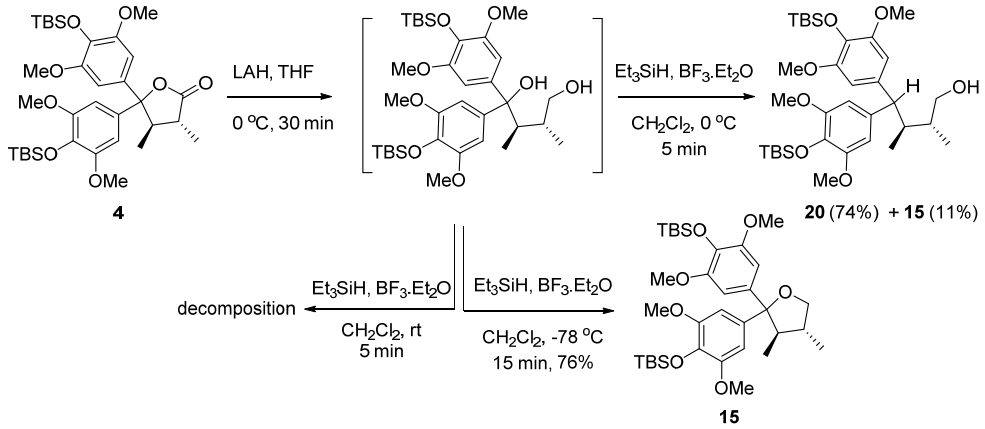


Scheme 10. Dehydrative cyclization

The formation of a secondary benzyl alcohol during cyclization was attempted for the purpose of recovery. For that the reactions were performed at lower temperature. At –78 °C, no reaction was detected, but at 0 °C after 1.5 h a little of conversion was realized, which indicated the formation of the dehydrate product **19** (not the intermediate alcohol). The actual intention was the oxidation of alcohol to ketone followed by α-methylation to arrive at the Sacidumlignan B directly. However, this idea did not work. Therefore, an alternate pathway was investigated. The Wacker oxidation of the dihydronaphthalene **19** has been examined using $PdCl_2$ in DMA and water and oxygen as oxidant to procure a β-ketone. But the amounts of the ketone obtained were not sufficient to proceed further. In this way, again this strategy proved itself as not a reliable one for the Sacidumlignan B, albeit the projected dehydrative cyclization in our retrosynthetic plan could be successfully realized under very mild conditions with excellent yield.

Without finding any hope of success, we revisited the synthesis of the originally planned advanced intermediate **4** and tried to adopt the newly discovered synthetic tool. Now, the worry in the original strategy was to deoxygenate the benzylic-OH group present in the intermediated diol resulting from the LAH reduction of the key lactone **4** (Scheme 11) with no cyclization employing triethylsilane in the presence of $BF_3 \cdot Et_2O$.[35] As we mentioned earlier that this kind of benzylic alcohol is highly sensitive towards cyclization, so the deoxygenation has to be carried out very carefully. The optimized conditions employed include addition of triethylsilane to the

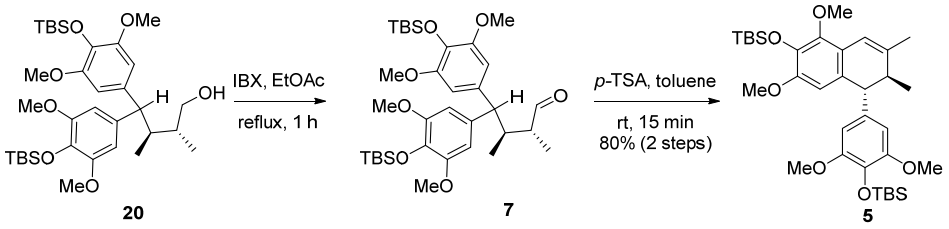
crude diol in CH_2Cl_2 at 0 ºC followed by the slow addition of $BF_3 \cdot Et_2O$. The reaction was quenched after five minutes of addition. Under this condition the crucial alcohol **20** was obtained in 74% yield along with 11% cyclized product **15**. The primary alcohol in compound **20** was characterized by a broad alcohol peak at δ 1.64 ppm whereas two methylene protons and a benzylic proton resonated at δ 3.4–3.48 ppm. Furthermore, the carbon peaks referred to the methylene carbon and benzylic carbon resonated at δ 67.0 (t), 56.7 (d) ppm to satisfy the probable structure. TBS ether-**15** was found to be the sole product when the deoxygenation reaction was carried out at –78 °C. However, a mixture of products emerged as the temperature was raised to 0 °C. Further increase in temperature led to low yield in competition with the TBS deprotection and other side products.



Scheme 11. Optimization of the Et_3SiH, $BF_3 \cdot Et_2O$-mediated deoxygenation

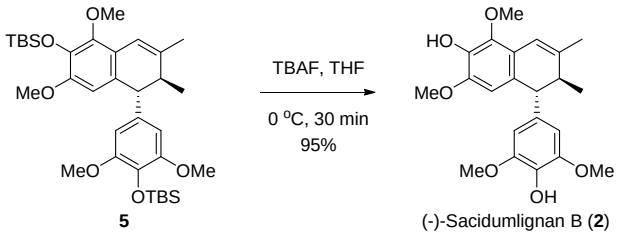
Oxidation of the alcohol **20** with 2-iodoxybenzoic acid (IBX) in ethyl acetate under reflux conditions[37] gave the required aldehyde **7** in excellent yield. Without any characterization, it was subjected for dehydrative cyclization. The *p*-TSA mediated dehydrative cyclization of aldehyde **7** proceeded smoothly at room temperature to give the *di-O*-TBS-Sacidumlignan **5** in excellent yields.[28,36] A significant variation in ^{1}H NMR was felt at the advent of the new core. The newly formed alkene proton was seen to resonate at δ 6.42 (d, J = 1.2 Hz, 1H), and a methyl at δ 1.78 (d, J = 1.2 Hz, 3H) ppm was observed. In ^{13}CNMR of compound **5**, peaks at δ 104.9 (d, 2C), 108.6 (d), 115.3 (d) ppm were observed as characteristic peaks corresponding to the two symmetric aryl CH carbons of one ring, one CH of other ring, and alkene carbon CH respectively. The ultimate proof was provided by the HRMS. Interestingly, under this condition, the silyl protecting groups were found to be unharmed and the reaction exhibited more than 99%

diastereoselectivity. This novel cyclization occurred in a manner such that the required *anti* geometry of methyl and aromatic groups has been fixed automatically and created a single diastereomer, which is the beauty of the method. In this fashion, the central dihydronaphthalene core of the Sacidumlignan B was made.[38]



Scheme 12. Oxidation and dehydrative cyclization

The TBS ether cleavage in compound **5** with TBAF completed the (–)-Sacidumlignan B synthesis. Like Sacidumlignan D, the spectral and optical rotation data {$[\alpha]_D^{25}$ = –65.9 (*c* 0.8, acetone); Lit.[1] $[\alpha]_D^{25}$ = –116 (c 1.44, acetone)} of the isolated and synthesized molecule were matched except for a little discrepancy in the magnitude of the optical rotation data. The extra phenolic OH peaks were confirmed by the deuterium exchange study (Figure 4). A comparative study of both ^{1}H &^{13}C coupling constants (*J*) and/or chemical shifts for natural and synthetic Sacidumlignan B was done in Figure 4 and Table 3. Finally, the similarity in spectral and physical parameters established the absolute configuration of (–)-Sacidumlignan B.



Scheme 13. Total synthesis of (–)-Sacidumlignan B

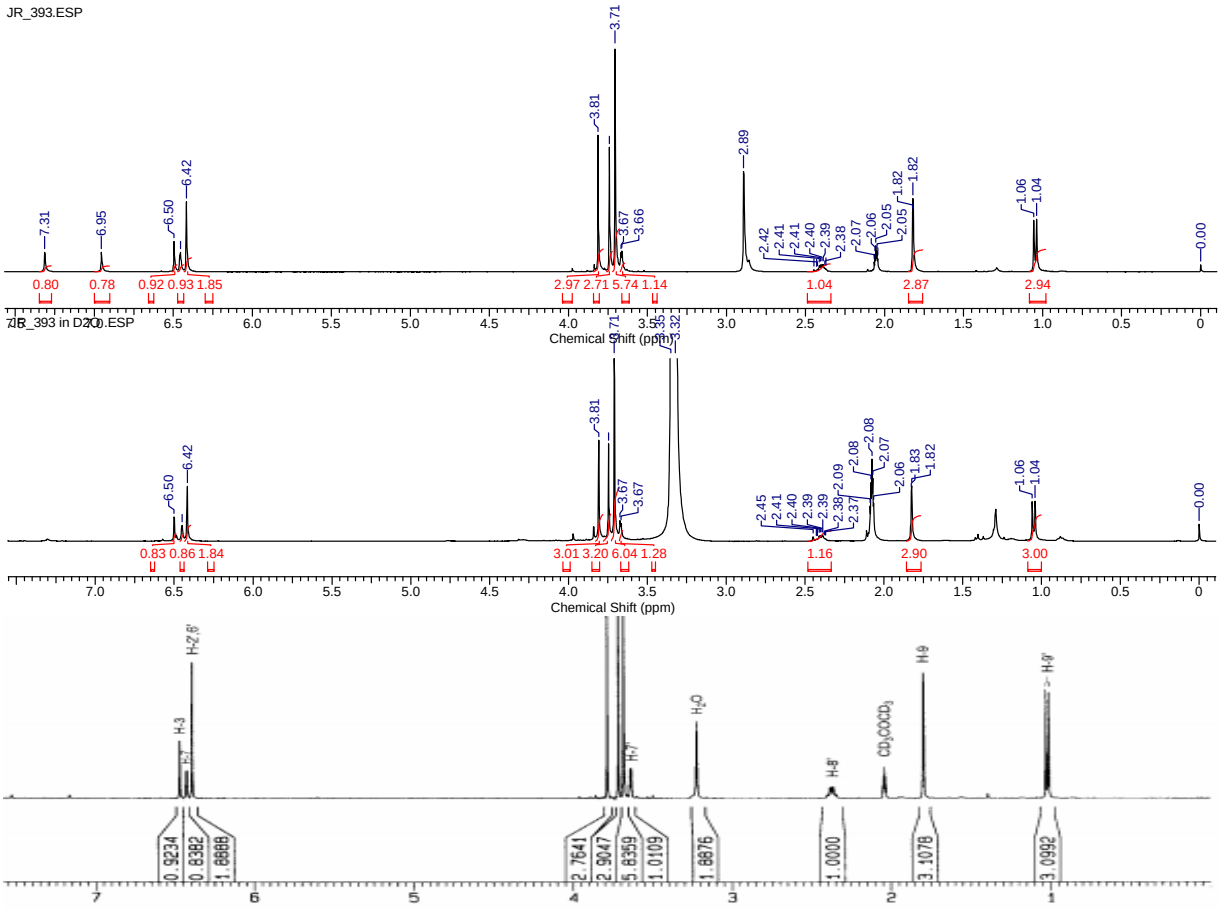


Figure 4. Comparison of (–)-Sacidumlignan B NMR spectra (Top & Middle) with natural isolated spectrum (Bottom): Top NMR in $CHCl_3$, Middle NMR in $CHCl_3$ + Two dorps of D_2O, Bottom NMR in $CHCl_3$

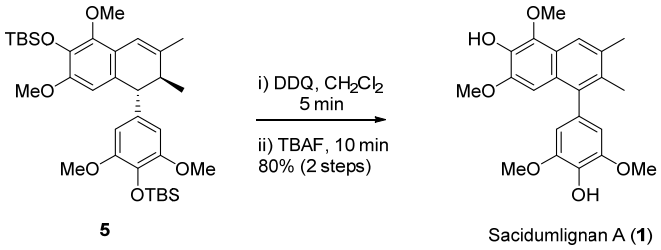
(-)-Sacidumlignan B **2**	***Natural***		***Synthetic***	
	δ_H, *J* (Hz)	**δ_C**	**δ_H, *J* (Hz)**	**δ_C**
1		121.3		121.4
2		127.1		127.2
3	6.47 (1H, s)	109.5	6.51 (1H, s)	109.4
4		147.8		147.8
5		138.7		138.8
6		143.9		143.9

7	6.43	116.0	6.47 (1H, d, 1.2)	116.1
8		139.1		139.1
9	1.80 (3H, d, 1.2)	22.6	1.83 (3H, d, 1.2)	22.7
1′		137.1		137.1
2′, 6′	6.39 (2H, s)	106.0	6.43 (2H, s)	105.9
3′, 5′		148.3		148.3
4′		135.0		135.1
7′	3.64 (1H, d, 3.0)	51.9	3.68 (1H, d, 3.0)	52.0
8′	2.04 (1H, dq, 7.0, 3.0)	42.4	2.42 (1H, dq, 7.0, 3.0)	42.5
9′	1.02 (3H, d, 7.0)	18.8	1.06 (3H, d, 7.0)	18.9
6-OMe	3.79 (3H, s)	60.9	3.83 (3H, s)	60.9
3′, 5′-OMe	3.68 (6H, s)	56.5	3.72 (6H, s)	56.5
4-OMe	3.72 (3H, s)	51.9	3.76 (3H, s)	52.0
4′, 5-OH	*Not observed*		6.97 (1H, s), 7.33(1H, s)	

TABLE 3. Comparative ^{1}H &^{13}C Coupling Constants (*J*) and/or Chemical Shifts for Natural and Synthetic Sacidumlignan B

Synthesis of Sacidumlignan A

At last, the Sacidumlignan A (**1**) was obtained by the one pot aromatization of the dihydronaphthalene **5** with DDQ[39] followed by TBS deprotection. The spectral properties of both natural and synthetic products were synchronized, except for the appearance of extra phenolic OH peaks in ^{1}HNMR (confirmed by deuterium exchange studies). A comparative study of both ^{1}H & ^{13}C coupling constants (*J*) and/or chemical shifts for natural and synthetic Sacidumlignan A is given in Table 4.



Scheme 14. Total synthesis of Sacidumlignan A

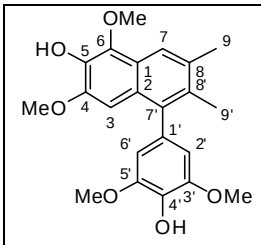
 Sacidumlignan A **1**	***Natural***		***Synthetic***	
	δ_H, *J* (Hz)	**δ_C**	**δ_H, *J* (Hz)**	**δ_C**
1		123.9		123.9
2		127.4		127.4
3	6.56 (1H, s)	101.8	6.56 (1H, s)	101.8
4		149.1		149.1
5		138.0		138.1
6		140.6		140.7
7	7.74 (1H, s)	120.4	7.75 (1H, s)	120.5
8		133.7		133.7
9	2.43	21.3	2.43 (3H, s)	21.4
1’		131.7		131.7
2’, 6’	6.47 (2H, s)	108.2	6.48 (2H, s)	108.2
3’, 5’		148.8		148.9
4’		135.6		135.7
7’		138.6		138.7
8’		131.7		131.8
9’	2.09	17.5	2.09 (3H, s)	17.6
6-OMe	3.95	60.7	3.96 (3H, s)	60.7
3’, 5’-OMe	3.82 (6H, s)	56.7	3.82 (6H, s)	56.7
4-OMe	3.66	55.9	3.66 (3H, s)	55.9
4’, 5-OH	*Not observed*		7.29 (1H, s), 7.71 (1H, s)	

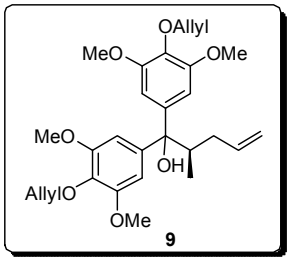
Table 4. **Comparative ^{1}H &^{13}C Coupling Constants (*J*) and/or Chemical Shifts for Natural and Synthetic Sacidumlignan A**

Conclusion

The total synthesis of naturally occurring Sacidumlignans A, B, and D was accomplished. More importantly, the absolute configuration of Sacidumlignans B and D was established. A diastereoselective α-methylation of a lactone was used as the key step for the entire

Sacidumlignan core. Furthermore, a temperature dependent deoxygenation provided the key precursor to the dihydronaphthalene core. Dehydrative cyclization was another important tool to achieve the dihydronaphthalene unit of Sacidumlignan B and the aromatization of it led to the synthesis of the Sacidumlignan A. To conclude, it must be emphasized that the synthesis of all the Sacidumlignans is executed very easily from a common advanced intermediate.

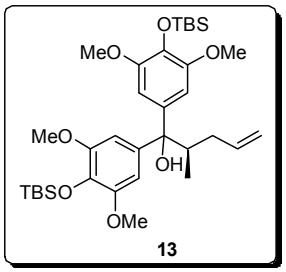
EXPERIMENTAL



9

(*R*)-1,1-Bis(4-(allyloxy)-3,5-dimethoxyphenyl)-2-methylpent-4-en-1-ol (9): At –78 °C, a solution of **11** (2.94 g, 10.8 mmol) in THF (15 mL) was treated with 1.6 M *n*-BuLi in hexane (6.43 mL, 10.3 mmol). After 1 h of vigorous stirring at –78 °C, a solution of the ester **10** (1.0 g, 4.9 mmol) in THF (15 mL) was added drop by drop and stirring was continued at the same temperature for 2 h. The reaction mixture was quenched with sat. NH_4Cl solution and warmed to rt. The reaction mixture was partitioned between water : CH_2Cl_2 and the aqueous layer was extracted with CH_2Cl_2. The combined organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was purified by column chromatography (100–200 silica gel, 20% EtOAc in pet ether) to procure **9** (1.49 g, 63%) as a low melting solid and the ketone **12** (200 mg, 10%) as byproduct. **9**: R_f = 0.3 (25% EtOAc in pet ether).

Characterization data of compound **9**: M.P. 73–75 °C; $[\alpha]^{25}_D$ = –13.6 (*c* 0.2, $CHCl_3$); IR ($CHCl_3$) ν 3501, 2935, 2854, 1589, 1504, 1463, 1415, 1320, 1237, 1124, 988, 923, 724 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.73 (s, 2H), 6.69 (s, 2H), 6.09 (2 x dddd, *J* = 17.2, 10.3, 8.1, 6.1 Hz, 2H), 5.86 (dddd, *J* = 16.9, 10.2, 8.0, 6.3 Hz, 1H), 5.29 (ddt, *J* = 17.2, 3.5, 1.6 Hz, 2H), 5.17 (br d, *J* = 10.3 Hz, 2H), 5.03–4.97 (m, 2H), 4.50–4.48 (m, 4H), 3.82 (br s, 12H), 2.58 (tq, *J* = 6.8, 2.5 Hz, 1H), 2.23 (br.dd, *J* = 13.8, 5.6 Hz, 1H), 2.14 (s, 1H), 1.84 (br dt, *J* = 13.8, 8.9 Hz, 1H), 0.90 (d, *J* = 6.6 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0 (q), 36.2 (t), 40.8 (d), 56.1 (q, 4C), 74.0 (t, 2C), 81.0 (s), 103.1 (d, 2C), 103.2 (d, 2C), 116.1 (t), 117.4 (t), 117.5 (t), 134.5 (d, 2C), 135.2 (s), 135.3 (s), 137.4 (d), 141.8 (s, 2C), 152.9 (s, 2C), 153.0 (s, 2C) ppm; HRMS (m/z) calcd for $C_{28}H_{36}O_7Na$ 507.2359; found 507.2317.



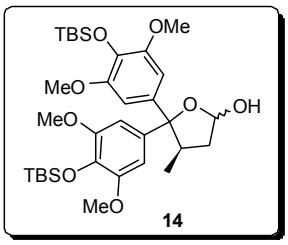
13

(*R*)-1,1-Bis(4-((*tert*-butyldimethylsilyl)oxy)-3,5-dimethoxyphenyl)-2-methylpent-4-en-1-ol (13): To a solution of PPh_3 (13 mg, 0.05 mmol) in EtOH (5 mL) was added $Pd(OAc)_2$ (6 mg, 0.025 mmol) followed by 1,3-dimethylbarbituric acid (213 mg, 1.36 mmol) and the contents were stirred at rt. After 10 minutes of stirring, the color of the solution was changed to orange. At that time, **9** (300 mg, 0.62 mmol) in ethanol (10 mL) was introduced and stirring was continued for additional 2 h. As the reaction proceeds, the color of the solution was changed to red and to blood red. The ethanol was evaporated and the crude was purified by column chromatography (100–200 silica gel, 40% EtOAc in pet ether) to

procure compound intermediate triol (210 mg, 84%) as a pale yellow syrup (R_f = 0.3, 50% EtOAc in pet ether) which was used for the next reaction without any characterization.

To an ice cooled solution of above triol (500 mg, 1.24 mmol) in anhydrous DMF (5 mL) was added imidazole (340 mg, 4.9 mmol) and TBSCl (470 mg, 3.1 mmol) and stirred for 1 h at rt. After the completion of reaction as indicated by TLC, the reaction mixture was partitioned between water–EtOAc and the aqueous layer was extracted with EtOAc. The combined organic layer was washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. The crude was purified by column chromatography (100–200 silica gel, 10% EtOAc in per ether) to obtain **13** (750 mg, 96%) as yellow liquid. R_f = 0.8 (30% EtOAc in pet ether).

Characterization data of compound **13**: $[\alpha]^{25}_D$ = –5.8 (*c* 2.8, acetone); IR ($CHCl_3$) ν 3525, 2933, 2857, 1587, 1511, 1463, 1415, 1328, 1249, 1186, 1131, 914, 838, 782, 753 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 6.66 (s, 2H), 6.63 (s, 2H), 5.85 (dddd, *J* = 16.2, 10.8, 7.9, 6.4 Hz, 1H), 5.01–4.93 (m, 2H), 3.75–3.74 (br s, 12H), 2.52 (tq, *J* = 6.7, 2.6 Hz, 1H), 2.26 (dd, *J* = 13.5, 5.8 Hz, 1H), 2.03 (s, 1H), 1.79 (ddd, *J* = 13.5, 7.9, 4.0 Hz, 1H), 1.00 (s, 18H), 0.89 (d, *J* = 6.7 Hz, 3H), 0.11 (br s, 12H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ –4.7 (q, 4C), 14.2 (q), 18.7 (s, 2C), 25.8 (q, 6C), 36.5 (t), 41.0 (d), 55.8 (q, 4C), 81.1 (s), 103.7 (d, 2C), 103.8 (d, 2C), 115.9 (t), 132.9 (s), 133.0 (s), 137.8 (d), 138.9 (s, 2C), 151.0 (s, 2C), 151.1 (s, 2C) ppm; HRMS (m/z) calcd for $C_{34}H_{56}O_7Si_2Na$ 655.3462; found 655.3469.



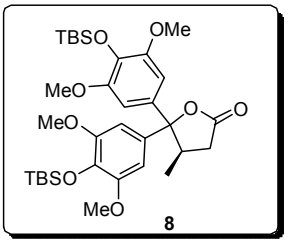
14

(4*R*)-5,5-Bis(4-((*tert*-butyldimethylsilyl)oxy)-3,5-dimethoxyphenyl)-4-methyltetrahydro-furan-2-ol (14): To a suspension of compound **10** (250 mg, 0.39 mmol), 2,6-lutidine (0.1 mL, 0.79 mmol) and $NaIO_4$ (127 mg, 0.59 mmol) in dioxane (5 mL)–water (1 mL) was added a solution of OsO_4 (2 mg) in toluene (10 µL) and stirred at rt for 2 h. After completion, the reaction mixture was partitioned between water and CH_2Cl_2. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic layer was washed with brine, dried (Na_2SO_4) and concentrated. Purification of the crude product by silica gel column chromatography (100–200, 20% EtOAc in pet ether) gave **14** (210 mg, 84%) as a colorless syrup. R_f = 0.2 (20% EtOAc in pet ether).

Characterization data of compound **14**: $[\alpha]^{25}_D$ = –82.5 (*c* 2.1, acetone); IR ($CHCl_3$) ν 3418, 2932, 2857, 1587, 1514, 1463, 1455, 1415, 1337, 1249, 1130, 910, 838, 782, 756 cm^{-1}.

Major Isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.67 (s, 1.4H), 6.29 (s, 1.4H), 5.79 (br t, J = 4.9 Hz, 0.7H), 3.76 (s, 4.5H), 3.68 (s, 4.1H), 3.27 (tq, J = 12.8, 6.9 Hz, 0.8H), 2.46 (d, J = 4.9 Hz, 0.7H), 2.08 (ddd, J = 12.8, 6.5, 1.4 Hz, 0.7H), 1.94 (ddd, J = 12.8, 9.8, 5.0 Hz, 0.7H), 1.00 (s, 10.3H), 0.99 (s, 8.1H), 0.83 (d, J = 6.9 Hz, 2.3H), 0.12 (s, 6.2H), 0.10 (s, 5.6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ–4.7 (q, 2C), –4.6 (q, 2C), 17.0 (q), 18.7 (s, 2C), 25.8 (q, 6C), 39.0 (d), 42.0 (t), 55.7 (q, 2C), 55.9 (q, 2C), 91.6 (s), 98.0 (d), 104.4 (d, 2C), 104.5 (d, 2C), 132.9 (s), 133.5 (s), 136.1 (s), 139.5 (s), 150.6 (s, 2C), 151.0 (s, 2C) ppm.

Minor Isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.63 (s, 0.6H), 6.60 (s, 0.5H), 5.61 (dd, J = 9.9, 4.7 Hz, 0.3H), 3.75 (s, 1.5H), 3.70 (s, 1.9H), 3.22 (d, J = 4.7 Hz, 0.2H), 2.99 (br st, 0.3H), 2.29 (ddd, J = 13.0, 6.9, 5.6 Hz, 0.3H), 1.77 (ddd, J = 13.0, 7.6, 4.9 Hz, 0.3H), 1.00 (s, 10.3H), 0.99 (s, 8.1H), 0.89 (dd, J = 6.9 Hz, 1H), 0.12 (s, 6.2H), 0.1 (s, 5.6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ–4.7 (q, 2C), –4.6 (q, 2C), 17.6 (q), 18.7 (s, 2C), 25.8 (q, 6C), 40.1 (d), 41.0 (t), 55.7 (q, 2C), 55.9 (q, 2C), 91.9 (s), 97.9 (d), 104.2 (d, 2C), 104.9 (d, 2C), 132.9 (s), 133.5 (s), 136.3 (s), 139.5 (s), 150.5 (s, 2C), 151.0 (s, 2C) ppm. HRMS (m/z) calcd for $C_{33}H_{54}O_8Si_2K$ 673.2994; found 673.2996.

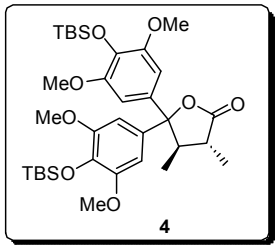


8

(*R*)-5,5-Bis(4-((*tert*-butyldimethylsilyl)oxy)-3,5-dimethoxyphenyl)-4-methyldihydrofuran-2(3H)-one (8): To a solution of lactols **14** (70 mg, 0.11mmol) in toluene (5 mL) was added silver carbonate on celite (152 mg, 0.55 mmol contains 1mmol of Ag_2CO_3 per 0.57 g of prepared reagent). The reaction mixture was refluxed at 130 ^{o}C for 2 h in dark. The reaction mixture was cooled, filtered and the filtrate was concentrated under reduced pressure. The crude product was purified by column chromatography (100–200 silica gel, 15% EtOAc in pet ether) to afford **8** (64 mg, 92%) as a colorless solid. R_f = 0.5 (30% EtOAc in pet ether).

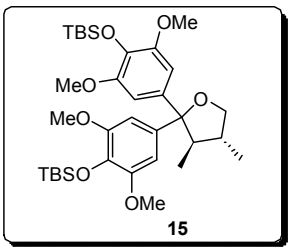
Characterization data of compound **8**: M.P. 145–146 ^{o}C; $[\alpha]^{25}_D$ = –97.2 (*c* 3.1, acetone); IR ($CHCl_3$) ν 2997, 2933, 2895, 2857, 1767, 1587, 1514, 1463, 1417, 1336, 1249, 1129, 972, 920, 839, 783, 760, 666 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.66 (s, 2H), 6.38 (s, 2H), 3.78 (s, 6H), 3.71 (s, 6H), 3.34–3.26 (m, 1H), 2.75 (dd, J = 17.2, 7.5 Hz, 1H), 2.34 (dd, J = 17.2, 5.0 Hz, 1H), 1.0 (s, 9H), 0.99 (s, 9H), 0.89 (d, J = 7.0 Hz, 3H), 0.12 (s, 6H), 0.11 (s, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ–4.7 (q, 4C), 17.2 (q), 18.6 (s, 2C), 25.7 (q, 6C), 37.7 (t), 38.3 (d), 55.7 (q, 2C),

56.0 (q, 2C), 92.7 (s), 103.1 (d, 2C), 104.1 (d, 2C), 133.1 (s), 133.5 (s), 134.4 (s), 135.1 (s), 151.1 (s, 2C), 151.3 (s, 2C), 176.1 (s) ppm; HRMS (m/z) calcd for $C_{33}H_{52}O_8Si_2Na$ 655.3099; found 655.3107.



4,4'-diphenyl-*O-TBS*-butyrolactone (4): At –78 °C, a solution of freshly distilled hexamethyldisilazane (0.09 mL, 0.44 mmol) in anhydrous THF (1 mL) was treated with *n*-BuLi (0.21 mL, 0.33 mmol) and stirred for 30 min at the same temperature. To this, a solution of **8** (70 mg, 0.11 mmol) in THF (1 mL) was introduced. After 1 h stirring, MeOTf (0.02 mL, 0.17 mmol) was added and the contents were stirred for additional 4 h at –78 °C. The reaction was quenched with sat. NH_4Cl solution and allowed to warm to rt. The contents were partitioned between water–EtOAc. The organic layer was separated and the aqueous layer extracted with EtOAc. Combined organic layer was washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. The crude was purified (230–400 silica gel, 10% EtOAc in pet ether) to procure lactone **4** (67 mg, 94%) as colorless solid by column chromatography. R_f = 0.5 (20% EtOAc in pet ether).

Characterization data of compound **4**: M.P. 116–117 °C; $[\alpha]^{25}_D$ = –60.9 (*c* 2.3, acetone); IR ($CHCl_3$) ν 2934, 2857, 1776, 1588, 1514, 1463, 1338, 1249, 1207, 1131, 914, 839, 782 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.62 (s, 2H), 6.20 (s, 2H), 3.77 (s, 6H), 3.67 (s, 6H), 2.86 (dq, *J* = 11.8, 6.7 Hz, 1H), 2.43 (dq, *J* = 11.8, 7.0 Hz, 1H), 1.29 (d, *J* = 7.0 Hz, 3H), 1.03 (d, *J* = 6.7 Hz, 3H), 1.01 (s, 9H), 0.99 (s, 9H), 0.13 (s, 6H), 0.11 (s, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ –4.7 (q, 4C), 13.2 (q), 16.2 (q), 18.6 (s), 18.7 (s), 25.7 (q, 6C), 41.1 (d), 46.2 (d), 55.7 (q, 2C), 56.0 (q, 2C), 91.0 (s), 104.1 (d, 2C), 104.7 (d, 2C), 132.7 (s), 133.7 (s), 134.5 (s), 135.4 (s), 150.9 (s, 2C), 151.2 (s, 2C), 178.7 (s) ppm; HRMS (m/z) calcd for $C_{34}H_{54}O_8Si_2Na$ 669.3255; found 669.3254.

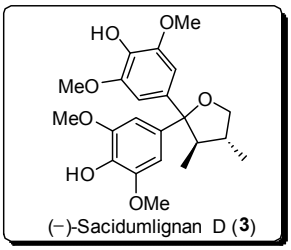


4,4'-diphenyl-*O-TBS*-tetrahydrofuran (15): To an ice cooled solution of lactone **4** (32 mg, 0.05 mmol) in THF (1 mL) was added LAH (6 mg, 0.15 mmol) slowly and stirred for 30 min at rt. Subsequently, the reaction mixture was quenched with sat. NH_4Cl solution, filtered through celite pad and the filtrate was partitioned between water–CH_2Cl_2. The organic layer was separated and the aqueous layer was extracted

with CH_2Cl_2. Combined organic layer was washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. The resulting crude diol was directly utilized in the next step without further purification.

A solution of above crude residue in CH_2Cl_2 (1 mL) was cooled to 0 °C and treated with 7 µL TFA. Within 5 minutes, the reaction was quenched with sat. $NaHCO_3$ solution. The layers were separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic layer was dried (Na_2SO_4), concentrated under reduced pressure and the resulting residue was purified by column chromatography (100–200 silica gel, 5% EtOAc in pet ether) to afford **15** (28 mg, 89%, 2 steps) as a colorless solid. R_f = 0.2 for reduction (20% EtOAc in pet ether), 0.8 for cyclization (20% EtOAc in pet ether).

Characterization data of compound **15**: M.P. 72–74 °C; $[\alpha]^{25}_D$ = –114.2 (*c* 1.8, acetone); IR ($CHCl_3$) ν 2957, 2930, 2857, 1586, 1511, 1463, 1412, 1333, 1249, 1183, 1130, 1040, 915, 838, 782 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.61 (s, 2H), 6.31 (s, 2H), 4.30 (t, *J* = 7.8 Hz, 1H), 3.76 (s, 6H), 3.67 (s, 6H), 3.48 (dd, *J* = 10.5, 8.3 Hz, 1H), 2.37 (dq, *J* = 10.6, 6.8 Hz, 1H), 2.03 (ddq, *J* = 13.6, 10.6, 7.1 Hz, 1H), 1.02 (d, *J* = 7.0 Hz, 3H), 1.01 (s, 9H), 0.99 (s, 9H), 0.83 (d, *J* = 6.8 Hz, 3H), 0.13 (s, 6H), 0.09 (s, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ –4.7 (q, 2C), –4.7 (q, 2C), 14.4 (q), 15.5 (q), 18.7(s) ,18.7 (s), 25.8 (q, 6C), 40.6 (d), 49.6 (d), 55.6 (q, 2C), 55.9 (q, 2C), 73.9 (t), 90.9 (s), 104.7 (d, 2C), 105.0 (d, 2C), 132.8 (s), 133.4 (s), 137.7 (s), 139.4 (s), 150.4 (s, 2C), 151.0 (s, 2C) ppm; HRMS (m/z) calcd for $C_{34}H_{56}O_7Si_2H$ 633.3643; found 633.3628.

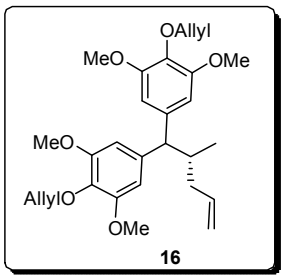


(−)-Sacidumlignan D (**3**)

(–)-Sacidumlignan D (3): At 0 °C, a solution of **16** (36 mg, 0.06 mmol) in THF (1 mL) was treated with TBAF (37 mg, 0.14 mmol) and stirred for 30 min. The reaction was quenched with sat. NH_4Cl solution and extracted with EtOAc. The combined organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was purified by column chromatography (100–200 silica, 40% EtOAc in pet ether) to obtain (–)-Sacidumlignan D (**3**) (22 mg, 96%) as white amorphous solid. R_f = 0.3 (50 % EtOAc in pet ether).

Characterization data of compound **3**: M.P. 150–152 °C; $[\alpha]^{25}_D$ = –138.2 (*c* 1.37, acetone); IR ($CHCl_3$) ν 3535, 3429, 3009, 2962, 2936, 2873, 2840, 1614, 1515, 1455, 1327, 1215, 1115,

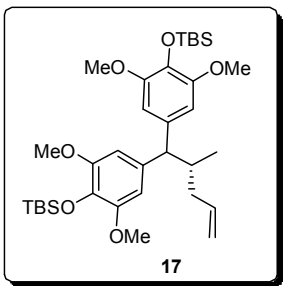
1050, 1008, 912, 840, 753, 666 cm^{-1}; ^1H NMR (400 MHz, Acetone-d_6) δ 7.17 (s, 1H), 7.06 (s, 1H), 6.78 (s, 2H), 6.53 (s, 2H), 4.26 (t, *J* = 7.7 Hz, 1H), 3.80 (s, 6H), 3.73 (s, 6H), 3.33 (dd, *J* = 10.1, 8.2 Hz, 1H), 2.42 (dq, *J* = 9.6, 6.9 Hz, 1H), 2.04–1.94 (m, 1H), 0.98 (d, *J* = 6.5 Hz, 3H), 0.86 (d, *J* = 6.9 Hz, 3H) ppm; ^{13}C NMR (100 MHz, Acetone-d_6) δ 15.4 (q), 17.0 (q), 42.3 (d), 51.1 (d), 56.9 (q, 2C), 57.0 (q, 2C), 74.2 (t), 91.5 (s), 106.0 (d, 2C), 106.4 (d, 2C), 135.7 (s), 136.2 (s), 137.1 (s), 139.4 (s), 148.0 (s, 2C), 148.4 (s, 2C) ppm; HRMS (m/z) calcd for $C_{22}H_{28}O_7H$ 405.1913; found 405.1900.



16

(R)-5,5'-(2-methylpent-4-ene-1,1-diyl)bis(2-(allyloxy)-1,3-dimethoxybenzene) (16): To a solution of **9** (100 mg, 0.2 mmol) in acetonitrile and CH_2Cl_2 (each 1 ml) was added triethylsilane (1.03 mmol) followed by $BF_3.Et_2O$ (1.03 mmol) at –42 ^oC and stirred for 2 h. After 2 h, the reaction mixture quenched with saturated $NaHCO_3$ solution and the organic layer was separated in CH_2Cl_2, concentrated in vacuum and loaded in the column (100–200 silica gel, 15% ethyl acetate/pet ether) to afford **16** (55 mg, 80%) and recovered starting material **9** (29 mg).

Characterization data of compound **16**: $[\alpha]^{24}_D$ = –3.4 (*c* 6.5, $CHCl_3$); IR ($CHCl_3$): 3013, 2959, 2937, 1590, 1503, 1421, 1326, 1217 992 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.84 (d, *J* = 6.5 Hz, 3H), 1.77 (dt, *J* = 16.6, 8.3 Hz, 1H), 2.13–2.19 (m, 1H), 2.23–2.30 (m, 1H), 3.36 (d, *J* = 10.8 Hz, 1H), 3.83 (s, 12H), 4.46–4.48 (m, 4H), 4.91–5.02 (m, 2H), 5.15–5.18 (m, 2H), 5.27–5.32 (m, 2H), 5.74–5.85 (m, 1H), 6.04–6.14 (m, 2H), 6.48 (s, 2H), 6.51 (s, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.05 (q), 37.09 (d), 39.33 (t), 56.17 (q, 4C), 59.01 (d), 74.12 (t, 2C), 105.23 (d, 4C), 116.19 (t), 117.37 (t, 2C), 134.60 (d, 2C), 135.17 (s), 135.23 (s), 136.84 (d), 139.82 (s), 139.91 (s), 153.18 (s, 2C), 153.26 (s, 2C) ppm; LCMS (*m/z*): 691.31 [M+Na].

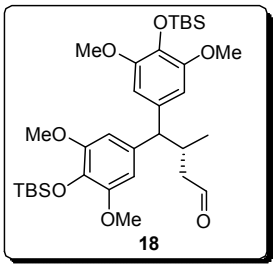


17

(R)-(((2-methylpent-4-ene-1,1-diyl)bis(2,6-dimethoxy-4,1-phenylene))bis(oxy))bis(tert-butyldimethylsilane) (17): Following the similar procedure used for synthesis of **13**, the *di-TBS* **17** (20 mg, 87%) was prepared from compound **16** (20 mg, 0.04 mmol).

Characterization data of compound **17**: $[\alpha]^{24}_D$ = –6.3 (*c* 5.9, $CHCl_3$); IR ($CHCl_3$): 2955, 2931, 2857, 1588, 1510, 1332, 1247, 1132, 914783 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.09 (s, 12H), 0.81 (d, *J* = 6.5 Hz, 3H), 0.98 (s, 18H), 1.66–1.81

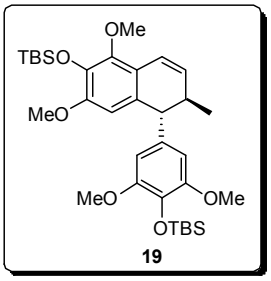
(m, 1H), 2.10–2.26 (m, 2H), 3.31 (d, J = 10.5 Hz, 1H), 3.75 (s, 12H), 4.87–4.99 (m, 2H), 5.68–5.88 (m, 1H), 6.42 (s, 2H), 6.45 (s, 2H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ –4.6 (q, 4C), 18.1 (q), 18.7 (s, 2C), 25.8 (q, 6C), 37.2 (d), 39.4 (t), 55.8 (q, 4C), 58.5 (d), 105.4 (d, 4C), 115.9 (t), 124.0 (s), 132.5 (s), 137.0 (s), 137.1 (d), 137.2 (s), 151.2 (s, 2C), 151.3 (s, 2C) ppm. LCMS (*m/z*): 639.40 [M+Na].



18

(R)-4,4-bis(4-((tert-butyldimethylsilyl)oxy)-3,5-dimethoxyphenyl)-3-methylbutanal (18): Following the similar procedure used for synthesis of lactol **14**, the aldehyde **18** (19 mg, 68%) was prepared from the *di-TBS* **17** (28 mg, 0.04 mmol).

Characterization data of compound **18**: $[\alpha]^{24}_D$ = +1.4 (*c* 3.4, $CHCl_3$); IR ($CHCl_3$): 2958, 2932, 2857, 1721, 1589, 1463, 1333, 1133, 910, 840 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.09 (s, 12H), 0.89 (d, J = 6.5 Hz, 3H), 0.98 (s, 18H), 2.19 (ddd, J = 17.1, 8.8, 2.1 Hz, 1H), 2.44 (dd, J = 17.1, 3.2 Hz, 1H), 2.75–2.79 (m, 1H), 3.36 (d, J = 11.0 Hz, 1H), 3.74 (s, 6H), 3.75 (s, 6H), 6.43 (s, 2H), 6.45 (s, 2H), 9.63 (br s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ –4.64 (q, 4C), 18.67 (s, 2C), 19.35 (q), 25.78 (q, 6C), 32.60 (d), 49.94 (t), 55.85 (q, 2C), 55.88 (q, 2C), 58.55 (d), 105.30 (d, 2C), 105.36 (d, 2C), 132.90 (s), 133.00 (s), 135.95 (s), 136.14 (s), 151.42 (s, 2C), 151.52 (s, 2C), 202.30 (d) ppm.

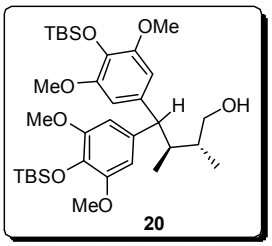


19

tert-Butyl(((5R,6R)-5-(4-((tert-butyldimethylsilyl)oxy)-3,5-dimethoxyphenyl)-1,3-dimethoxy-6-methyl-5,6-dihydronaphthalen-2-yl)oxy)dimethylsilane (19): To a solution of aldehyde **18** (20 mg, 0.03 mmol) in toluene (1 ml) was added *p*-toluene sulfonic acid (1 mg, 0.003 mmol). After 15 minutes, the reaction mixture was concentrated in vacuum and loaded in the column for purification (100–200 silica, 5% ethyl acetate/pet ether) to get the dihydronaphthalene **19** (16 mg, 82%).

Characterization data of compound **19**: $[\alpha]^{24}_D$ = +0.3 (*c* 6.7, $CHCl_3$); IR ($CHCl_3$): 2955, 2857, 1583, 1512, 1416, 1251, 1131, 916, 837 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.12 (s, 12H), 0.98–1.00 (m, 21H), 2.61–2.71 (m, 1H), 3.49–3.53 (m, 4H), 3.72 (s, 6H), 3.77 (s, 3H), 5.76 (dd, J = 9.8, 3.0 Hz, 1H), 6.03 (s, 1H), 6.37 (s, 2H), 6.69 (dd, J = 9.8, 2.1 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ –4.7 (q, 4C), 18.6 (s), 18.7 (s), 20.0 (q), 25.8 (q, 3C), 25.8 (q, 3C), 36.3 (d), 52.8 (d), 55.2 (q), 55.7 (q, 2C), 60.8 (q), 106.0 (d, 2C), 107.8 (d), 120.5 (d), 120.7 (s), 131.6 (s),

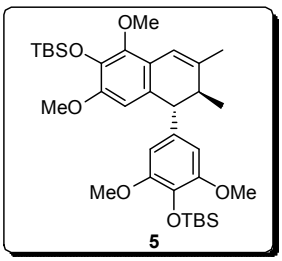
131.9 (d), 132.6 (s), 136.4 (s, 2C), 147.5 (s), 150.4 (s), 151.4 (s, 2C) ppm; LCMS (*m/z*): 623.39 [M+Na].



20

(2*R*,3*S*)-4,4-Bis(4-((*tert*-butyldimethylsilyl)oxy)-3,5-dimethoxyphenyl)-2,3-dimethylbutan-1-ol (20): The reduction of lactone **4** with LAH was carried out according to the procedure used for the preparation of compound **15**. After that, the crude residue was directly employed in the next step without further purification. At 0 ^{o}C, a solution of the above crude product (55 mg) in CH_2Cl_2 (1 mL) was treated slowly with Et_3SiH (0.07 mL, 0.43 mmol) followed by $BF_3.Et_2O$ (0.03 mL, 0.25 mmol) and stirred for 5 minutes before quenching with sat. $NaHCO_3$ solution and the aqueous layer was extracted with CH_2Cl_2. The combined organic layer was dried (Na_2SO_4), concentrated under reduced pressure and the crude was purified by column chromatography (100–200 silica gel, 25% EtOAc in pet ether) to afford the alcohol **20** (40 mg, 74%) as colorless oil and the compound **15** (6 mg, 11%). R_f = 0.4 for **20**, 0.7 for **15** (20 % EtOAc in pet ether).

Characterization data of compound **20**: $[\alpha]^{25}_{D}$ = –16.7 (*c* 3.4, acetone); IR ($CHCl_3$) ν 3450, 2956, 2934, 2857, 1588, 1508, 1465, 1421, 1330, 1248, 1127, 1037, 913, 834, 784 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ6.50 (s, 2H), 6.47 (s, 2H), 3.76 (s, 12H), 3.47 (dd, *J* = 10.6, 8.4 Hz, 1H), 3.44 (dd, *J* = 10.6, 6.4 Hz, 1H), 3.42 (d, *J* = 11.4 Hz, 1H), 2.50 (ddq, *J* = 11.4, 6.8, 2.1 Hz, 1H), 1.77–1.69 (m, 1H), 1.64 (br s, 1H), 0.99 (br s, 18H) , 0.75 (d, *J* = 6.9 Hz, 3H) , 0.65 (d, *J* = 6.8 Hz, 3H), 0.11 (br s, 6H), 0.10 (s, 6H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ –4.6 (q, 2C), –4.7 (q, 2C), 9.8 (q), 11.8 (q), 18.7 (s, 2C), 25.8 (q, 6C), 36.2 (d), 36.3 (d), 55.8 (q, 2C), 55.9 (q, 2C), 56.7 (d), 67.0 (t), 105.3 (d, 2C), 105.4 (d, 2C), 132.6 (s, 2C), 136.9 (s), 137.4 (s), 151.2 (s, 2C), 151.3 (s, 2C) ppm; HRMS (m/z) calcd for $C_{34}H_{58}O_7Si_2Na$ 657.3619; found 657.3571.

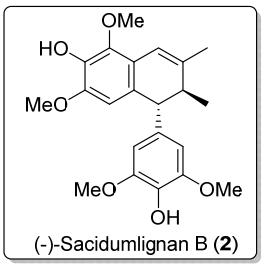


5

***tert*-Butyl(((5R,6S)-5-(4-((*tert*-butyldimethylsilyl)oxy)-3,5-dimethoxyphenyl)-1,3-dimethoxy-6,7-dimethyl-5,6-dihydronaphthalen-2-yl)oxy)dimethylsilane (5):** A suspension of **7** (35 mg, 0.06 mmol) and IBX (24 mg, 0.08 mmol) in EtOAc (5 mL) was refluxed for 1 h. The reaction mixture was cooled to room temperature and was filtered through celite. The resulting aldehyde **7** was dissolved in toluene (1 mL) and treated with *p*-TSA (0.5 mg, 0.002 mmol, 5 mol %). After stirring at rt for

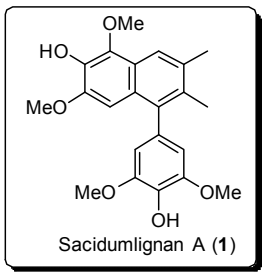
15 minutes, the reaction mixture was concentrated and the residue was purified by column chromatography (100–200 silica gel, 5% EtOAc in pet ether) to afford **5 (**27 mg, 80% in 2 steps**)** as a colorless syrup. R_f = 0.6 (10 % EtOAc in pet ether).

Characterization data of compound **5**: $[\alpha]^{25}_{D}$ = –45.1 (*c* 0.4, acetone); IR ($CHCl_3$) ν 2956, 2928, 2851, 1585, 1456, 1410, 1333, 1248, 1193, 1127, 1100, 941, 916, 834, 776 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 6.42 (d, *J* = 1.2 Hz, 1H), 6.29 (s, 1H), 6.23 (s, 2H), 3.78 (s, 3H), 3.67 (br s, 9H), 3.60 (d, *J* = 4.3 Hz, 1H), 2.38 (dq, *J* = 7.0, 4.3 Hz, 1H), 1.78 (d, *J* = 1.2 Hz, 3H), 1.05 (d, *J* = 7.0 Hz, 3H), 1.02 (s, 9H), 0.99 (s, 9H), 0.15 (d, *J* = 1.1 Hz, 6H), 0.10 (s, 6H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ –4.7 (q, 2C), –4.6 (q, 2C), 18.5 (q), 18.6 (s), 18.7 (s), 22.4 (q), 25.8 (q, 6C), 41.7 (d), 51.9 (d), 55.3 (q), 55.6 (q, 2C), 60.7 (q), 104.9 (d, 2C), 108.6 (d), 115.3 (d), 121.1 (s), 128.6 (s), 132.3 (s), 136.6 (s), 137.7 (s), 138.4 (s), 147.0 (s), 150.1 (s), 151.1 (s, 2C) ppm. HRMS (m/z) calcd for $C_{34}H_{54}O_6Si_2K$ 653.3096; found 653.3093.



Synthesis of (–)-Sacidumlignan B (2): The procedure used in the preparation of compound **3** has been followed in silyl deprotection of **5** (20 mg). Usual work up and purification by column chromatography gave (–)-Sacidumlignan B (**2**) (12 mg, 95%) as colorless solid. R_f = 0.5 (50% EtOAc in pet ether).

Characterization data of compound **2**: $[\alpha]^{25}_{D}$ = –65.9 (*c* 0.8, acetone); IR ($CHCl_3$) ν 3510, 3439, 2956, 2928, 2846, 1722, 1613, 1514, 1459, 1314, 1209, 1111, 757, 661 cm^{-1}; ^1H NMR (400 MHz, Acetone-d_6) δ 7.31 (s,1H), 6.95 (s, 1H), 6.50 (s, 1H), 6.46 (d, *J* = 1.2 Hz, 1H), 6.42 (s, 2H), 3.81 (s, 3H), 3.74 (s, 3H), 3.71 (s, 6H), 3.67 (d, *J* = 3.0 Hz, 1H), 2.41 (dq, *J* = 7.0, 3.0, 1H), 1.82 (d, *J* = 1.2 Hz, 3H), 1.05 (d, *J* = 7.0 Hz, 3H) ppm; ^{13}C NMR (100 MHz, Acetone-d_6) δ 18.9 (q), 22.7 (q), 42.5 (d), 52.0 (d), 52.0 (q), 56.4 (q, 2C), 60.9 (q), 105.9 (d, 2C), 109.4 (d), 116.1 (d), 121.4 (s), 127.1 (s), 135.1 (s), 137.1 (s), 138.8 (s), 139.1 (s), 143.9 (s), 147.8 (s), 148.3 (s, 2C) ppm; HRMS (m/z) calcd for $C_{22}H_{26}O_6Na$ 409.1627; found 409.1639.

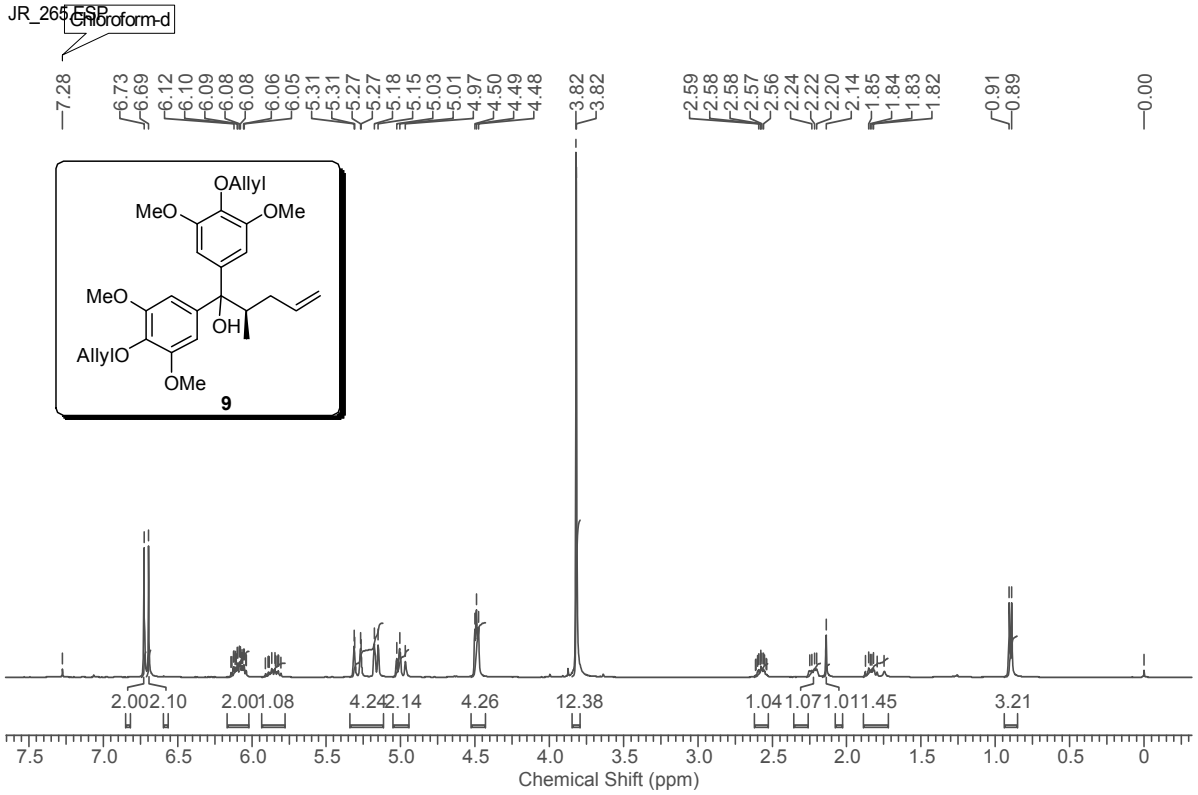


Sacidumlignan A (1): A solution of **5** (8 mg, 0.013 mmol**)** and DDQ (5 mg, 0.02 mmol) in CH_2Cl_2 (1 mL) were stirred at room temperature under argon atmosphere. After 5 minutes, TBAF (9 mg, 0.032 mmol) was added and stirred for 10 minutes and then quenched with sat. NH_4Cl solution. Usual work up followed by chromatographic purification (100–

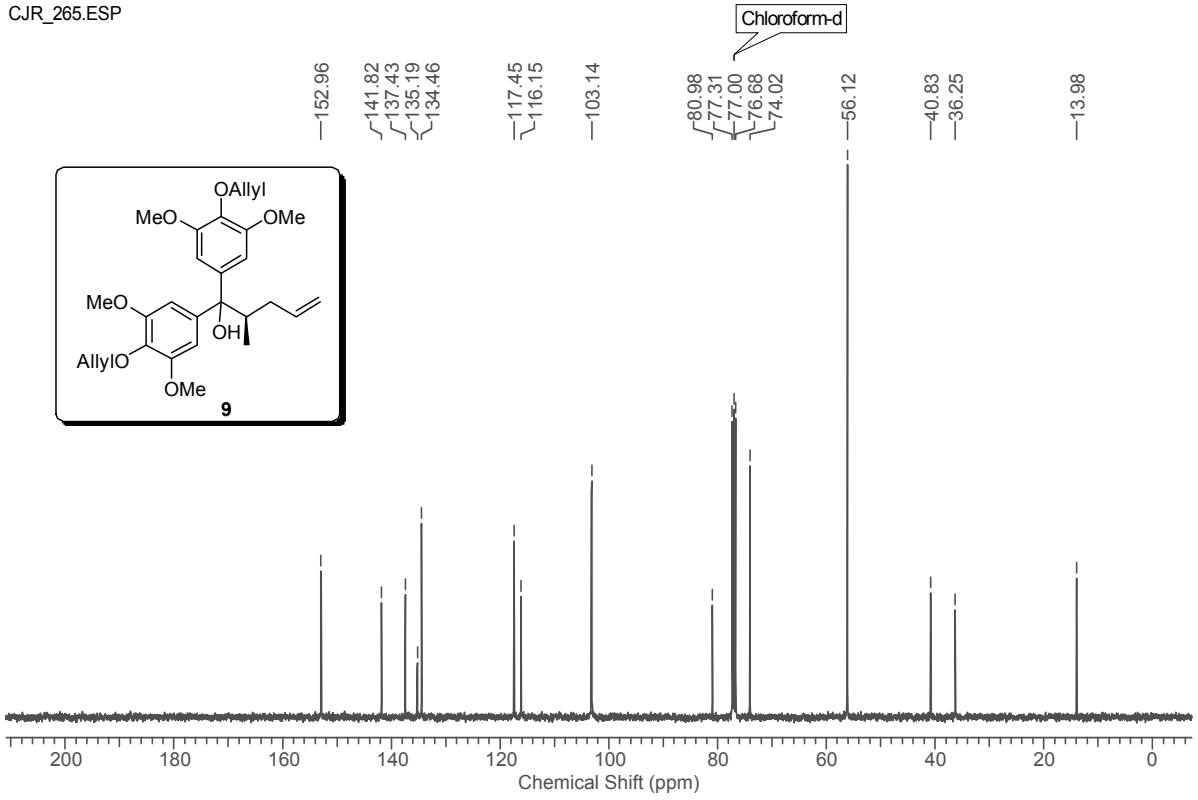
200 silica gel, 25% EtOAc in pet ether) gave Sacidumlignan A (**1**) (4 mg, 80%) as colorless solid. R_f = 0.5 (50% EtOAc in pet ether).

Characterization data of compound **1**: IR ($CHCl_3$) ν 3543, 3439, 2957, 2925, 2853, 1722, 1611, 1518, 1464, 1288, 1215, 1116, 911, 759 cm^{-1}; ^1H NMR (400 MHz, Acetone-d_6) δ 7.77 (s, 1H), 7.73 (s, 1H), 7.32 (s, 1H), 6.58 (s, 1H), 6.49 (s, 2H), 3.97 (s, 3H), 3.84 (s, 6H), 3.67 (s, 3H), 2.45 (s, 3H), 2.11 (s, 3H) ppm; ^{13}C NMR (100 MHz, Acetone-d_6) δ 17.6 (q), 21.4 (q), 55.9 (q), 56.7 (q, 2C), 60.7 (q), 101.8 (d), 106.2 (d, 2C), 120.5 (d), 123.9 (s), 127.4 (s), 131.7 (s), 131.8 (s), 133.7 (s), 135.7 (s), 138.1 (s), 138.7 (s), 140.7 (s), 148.9 (s, 2C), 149.1 (s) ppm; HRMS (m/z) calcd for $C_{22}H_{24}O_6Na$ 407.1471; found 407.1442.

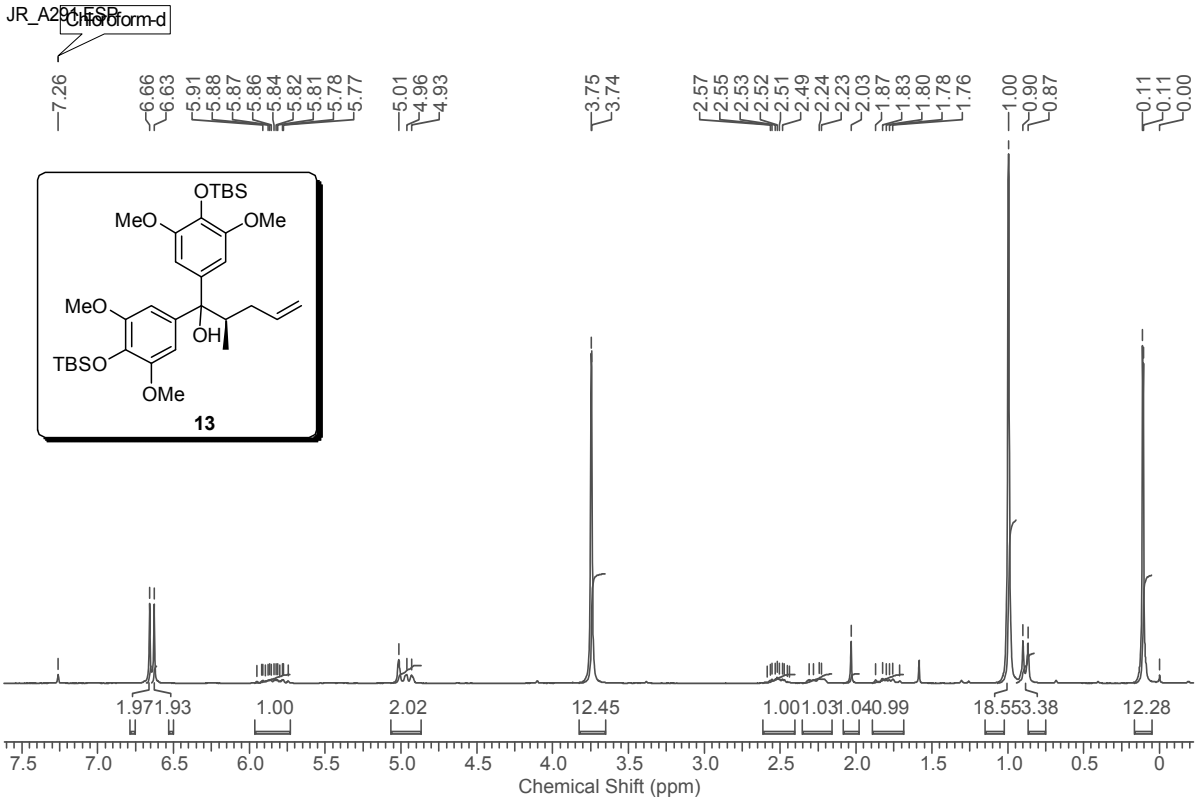
SPECTRA



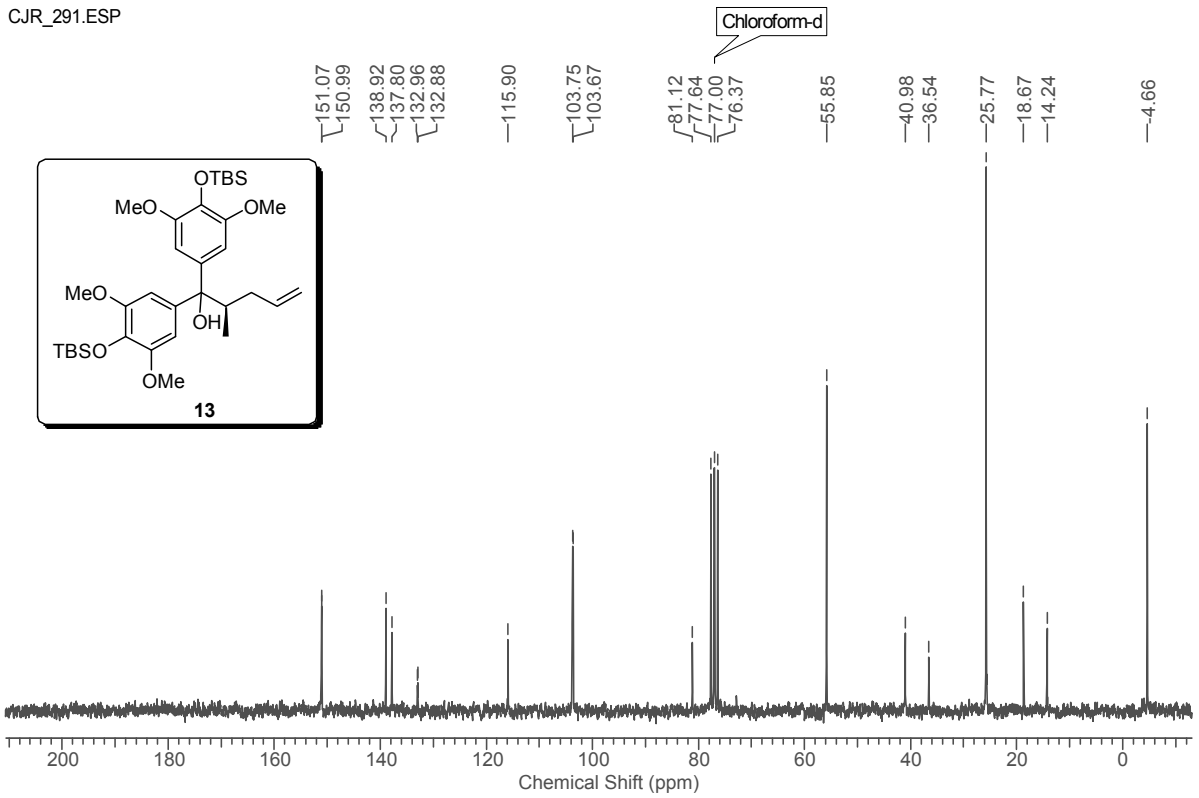
^{1}H NMR Spectrum of **9** in $CDCl_3$ (200 MHz)



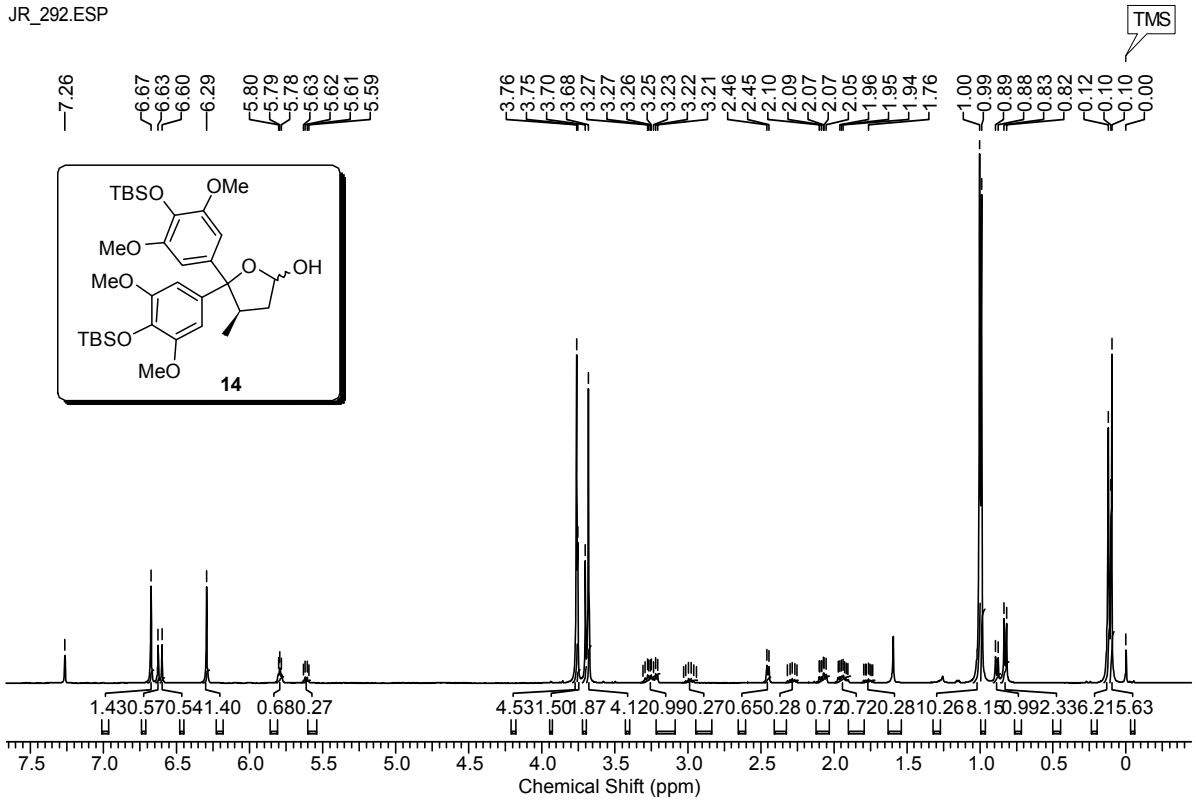
^{13}C NMR Spectrum of **9** in $CDCl_3$ (50 MHz)



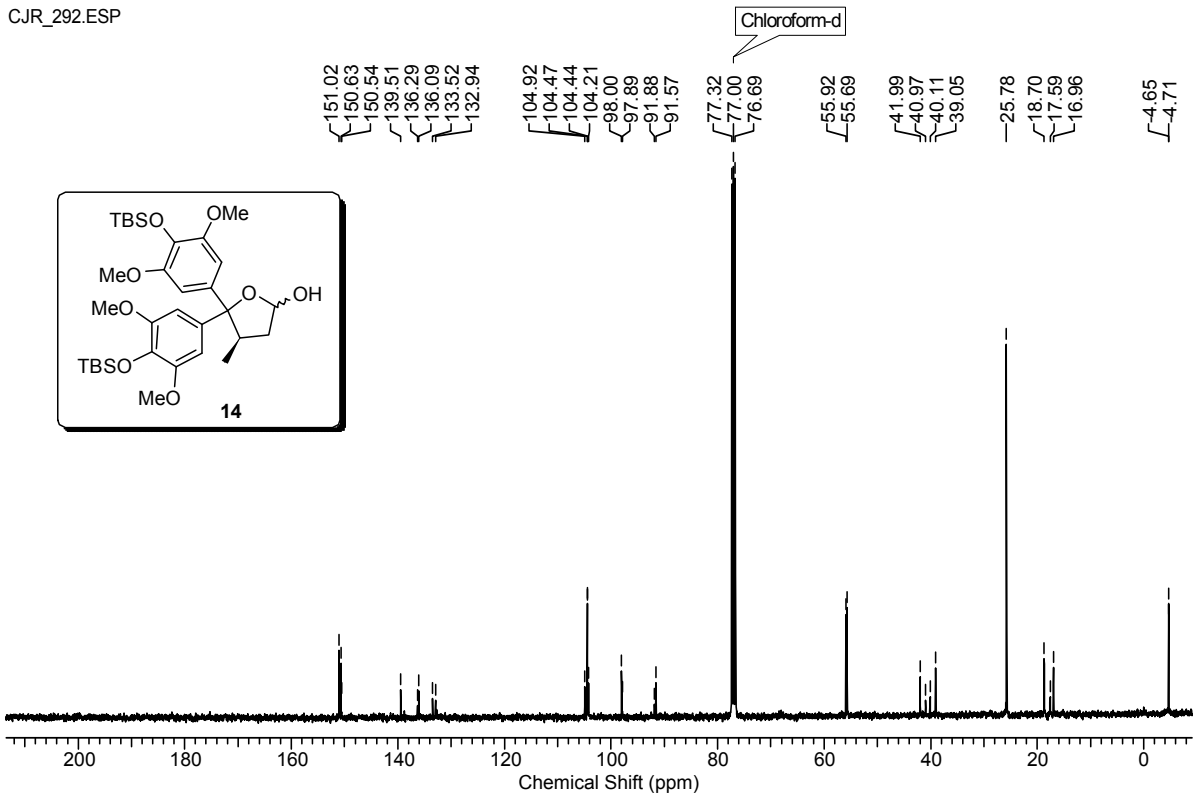
^{1}H NMR Spectrum of **13** in $CDCl_3$ (200 MHz)



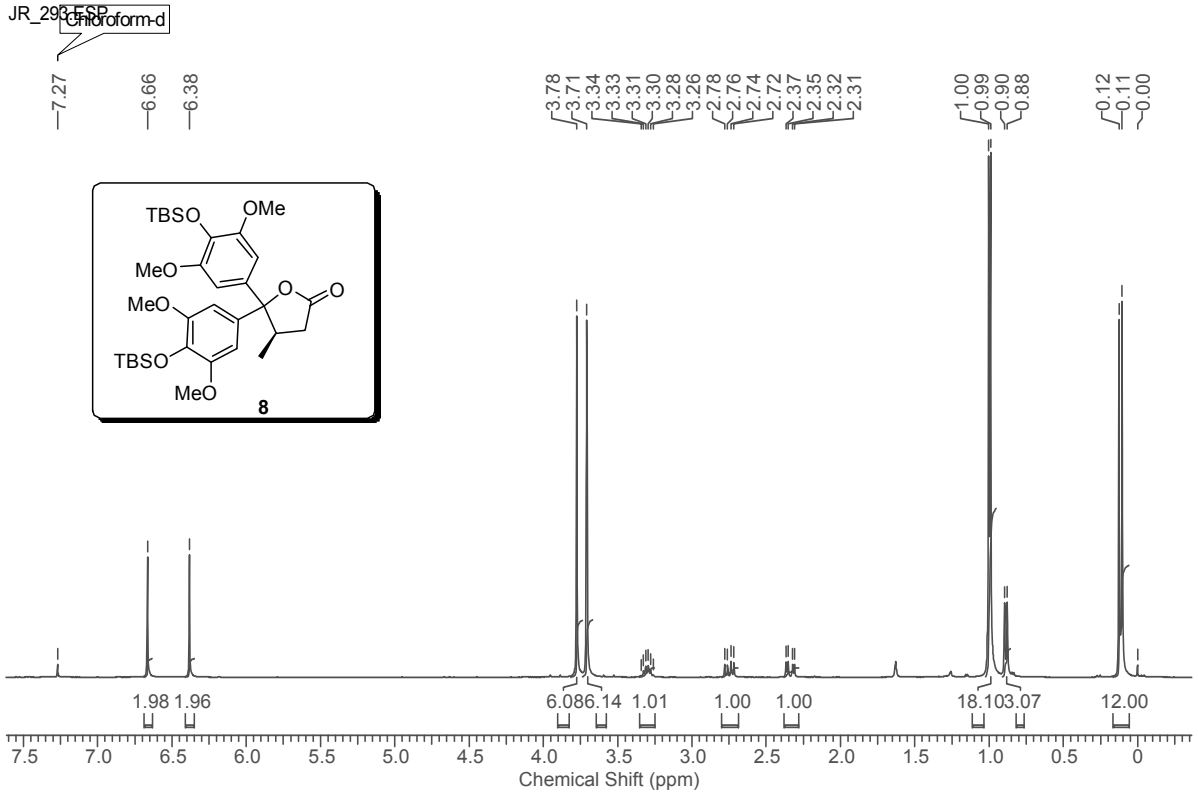
^{13}C NMR Spectrum of **13** in $CDCl_3$ (50 MHz)



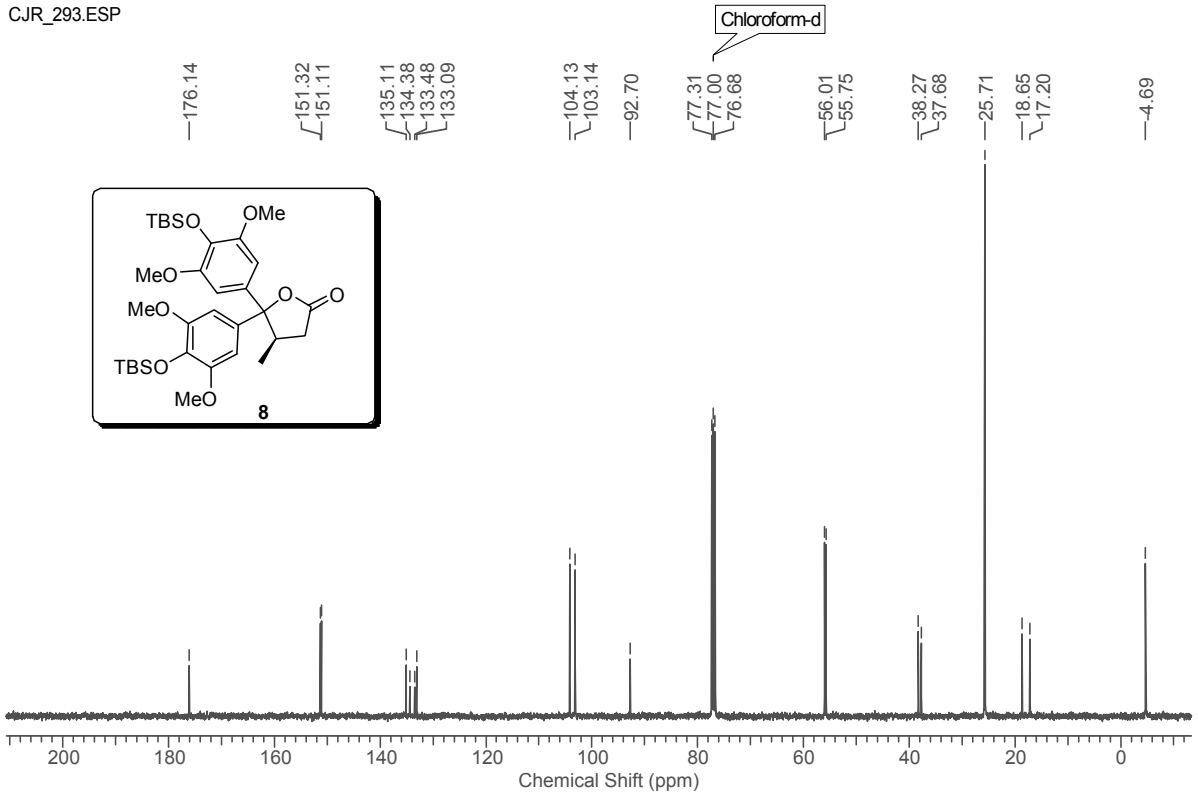
^{1}H NMR Spectrum of **14** in $CDCl_3$ (400 MHz)



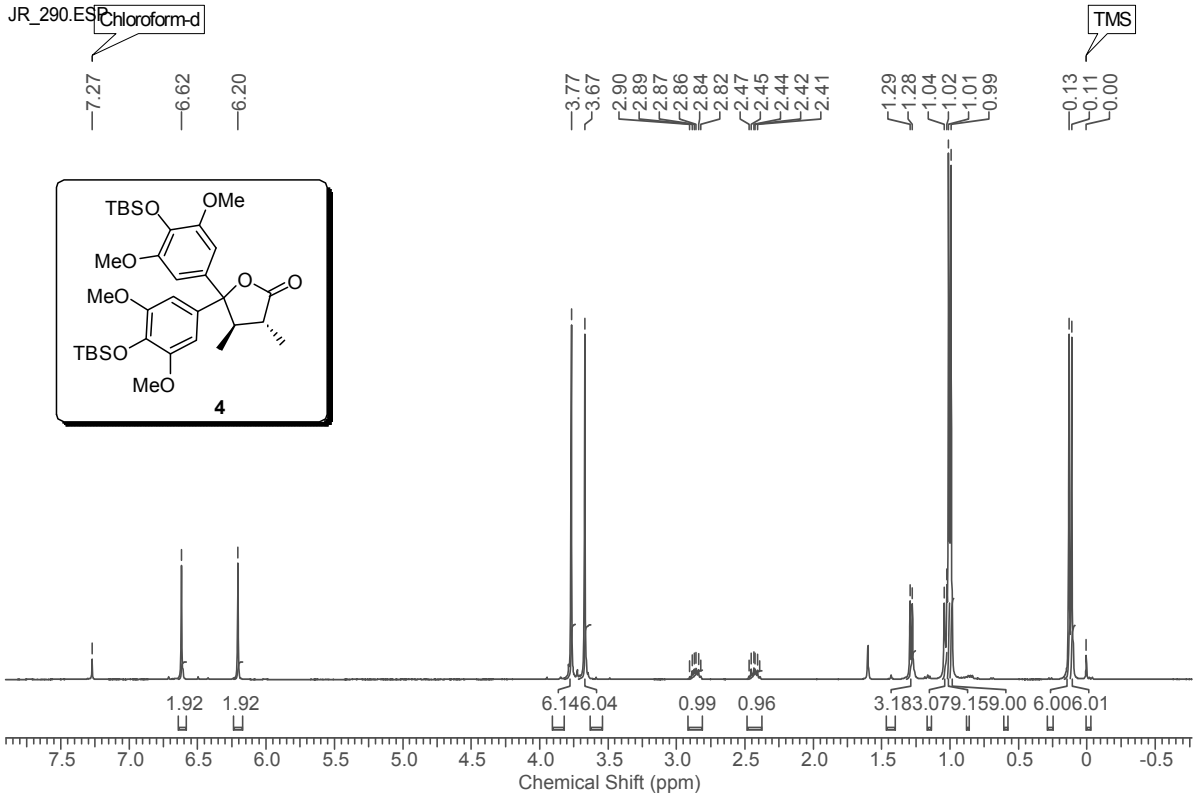
^{13}C NMR Spectrum of **14** in $CDCl_3$ (100 MHz)



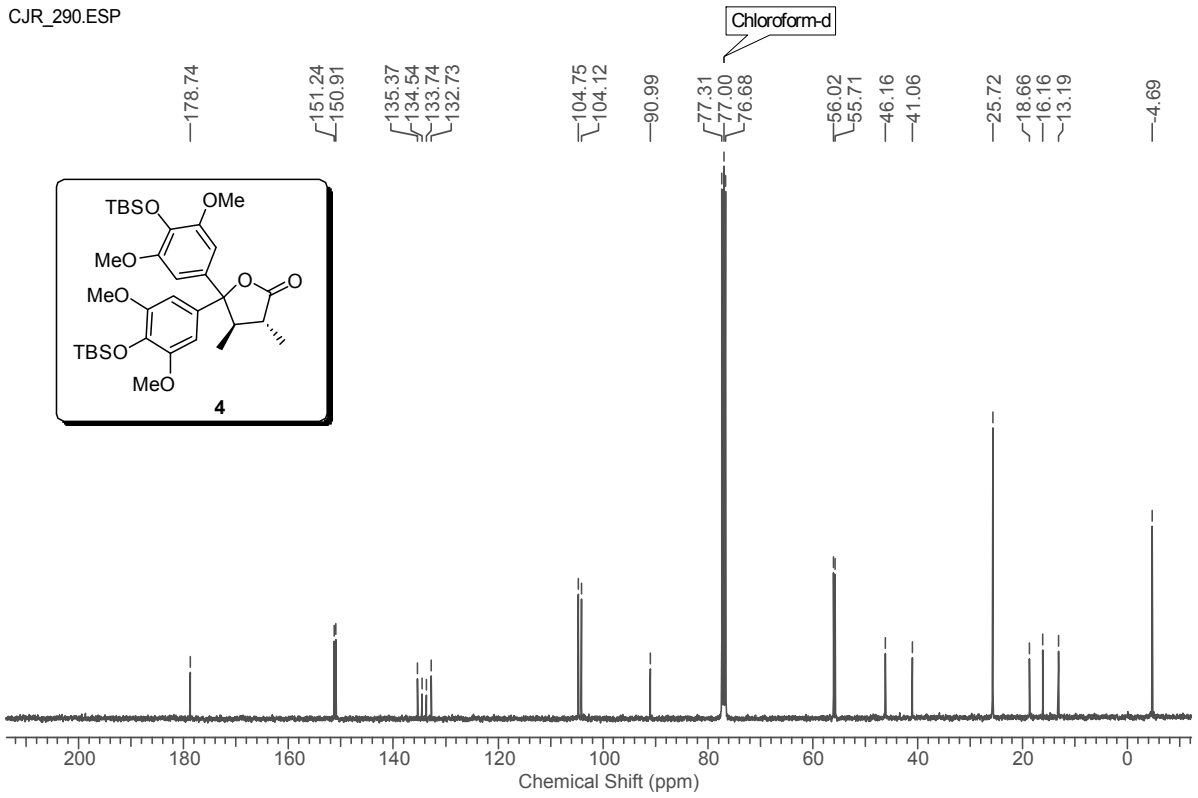
^{1}H NMR Spectrum of **8** in $CDCl_3$ (400 MHz)



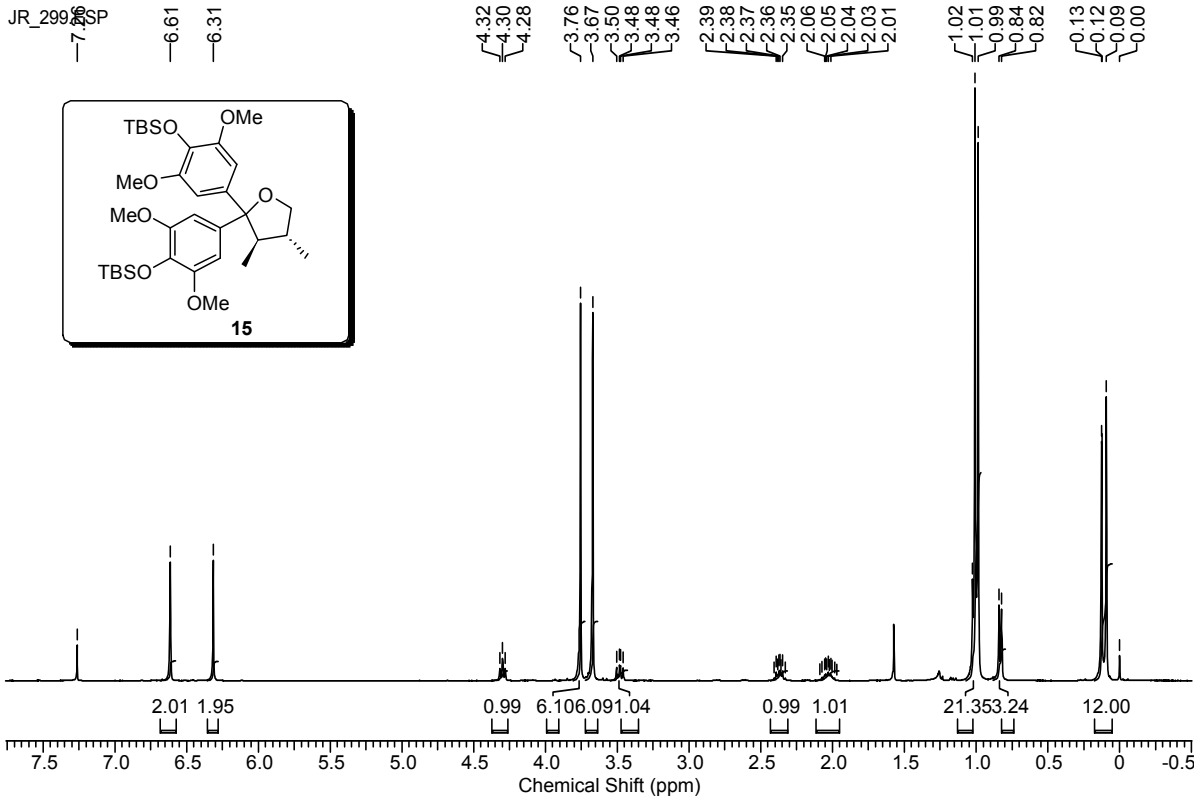
^{13}C NMR Spectrum of **8** in $CDCl_3$ (100 MHz)



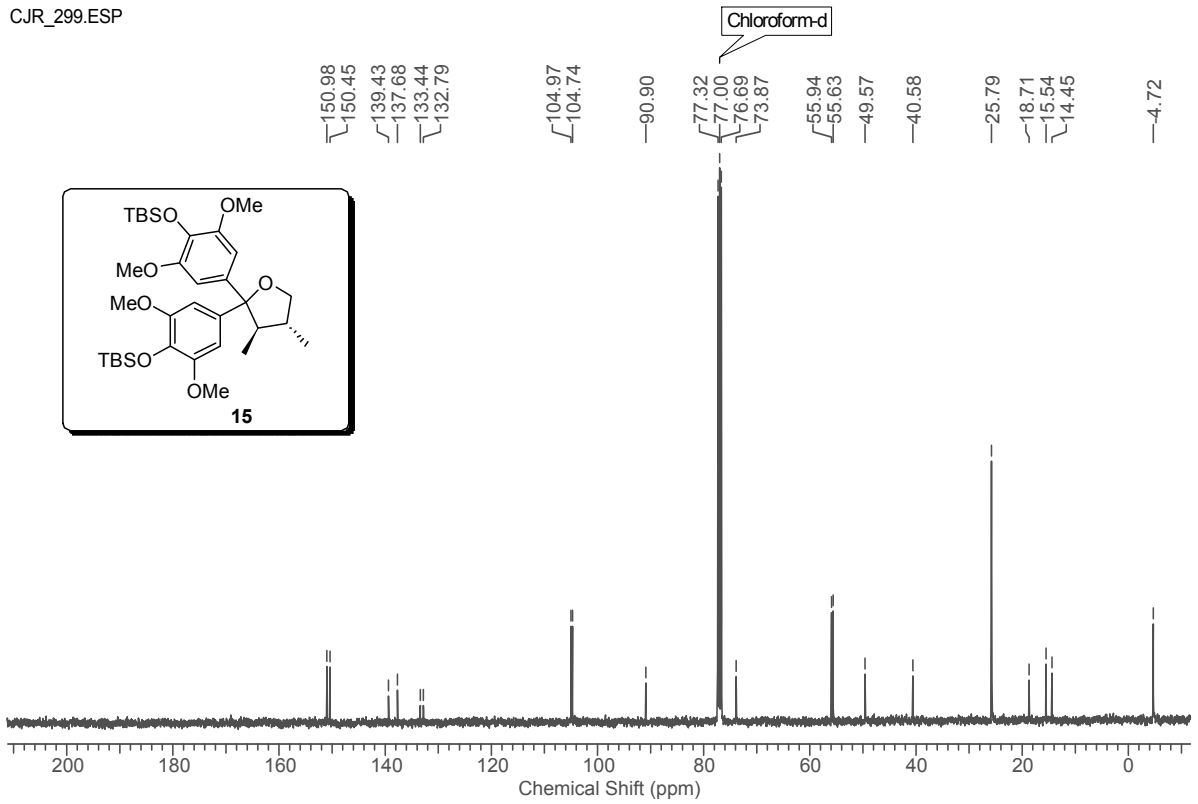
^{1}H NMR Spectrum of **4** in $CDCl_3$ (400 MHz)



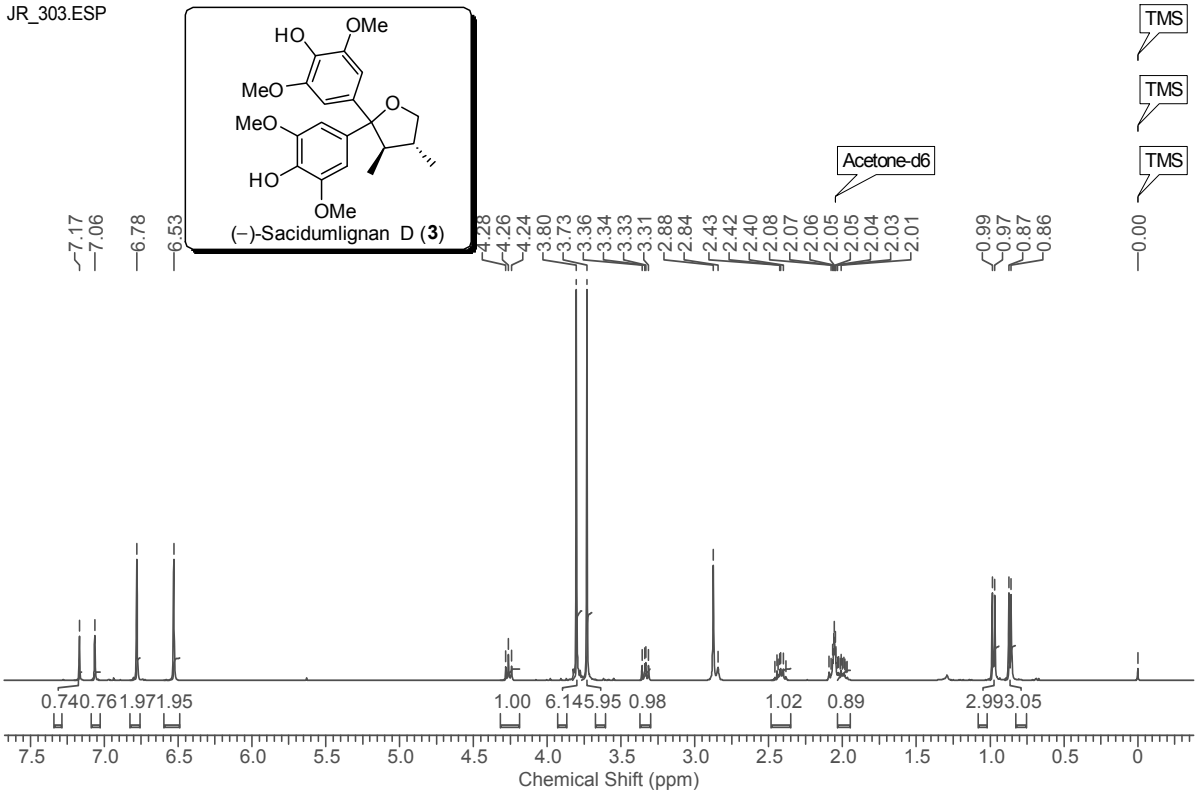
^{13}C NMR Spectrum of **4** in $CDCl_3$ (100 MHz)



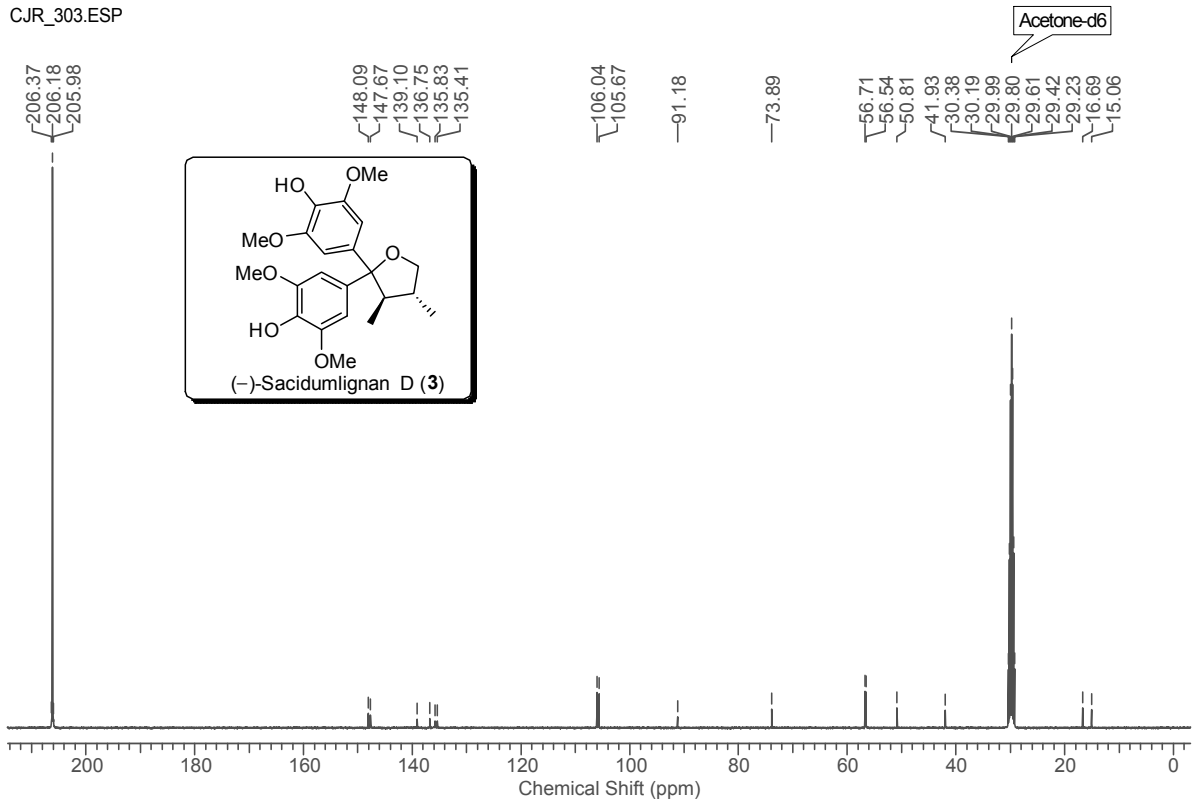
^{1}H NMR Spectrum of **15** in $CDCl_3$ (400 MHz)



^{13}C NMR Spectrum of **15** in $CDCl_3$ (100 MHz)



^{1}H NMR Spectrum of **3** in Acetone-d_6 (400 MHz)



^{13}C NMR Spectrum of **3** in Acetone-d_6 (100 MHz)

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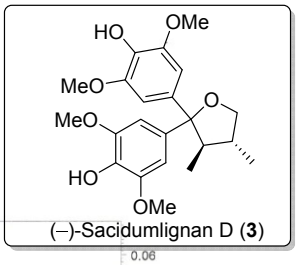
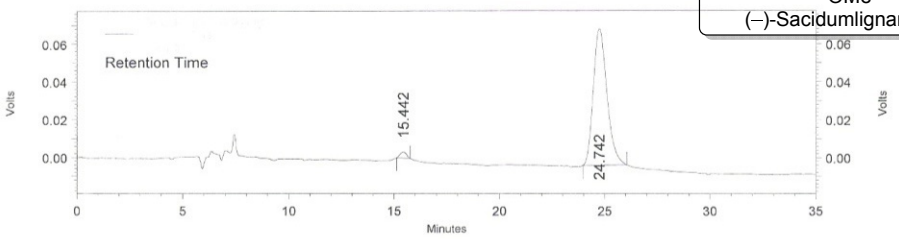
Printed: 4/21/11 3:54:34 PM
Sample Name JR-303-Chiral



(–)-Sacidumlignan D (**3**)

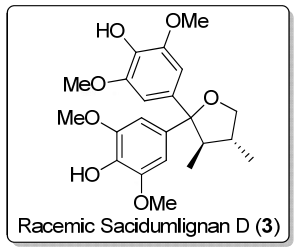


Detector A - 1 (254nm)

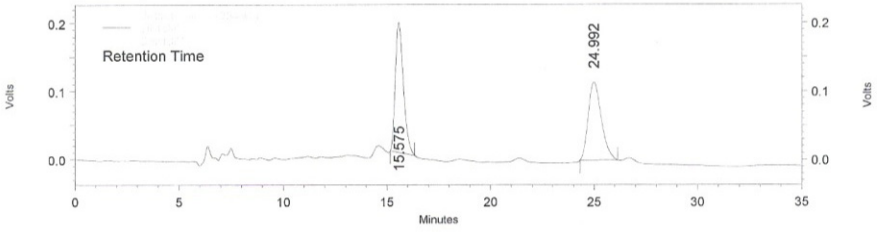
Retention Time	C Area	Area %
15.442	69053	2.074
24.742	3260147	97.926
Totals	3329200	100.000

Project Leader : Dr.C.V. RAMANA
Column :Kromasil 5-AmyCoat (250x4.6mm)
Mobile Phase :Ethanol:n-Hexane (40:60)
Wavelength : 254nm
Flow Rate : 0.5ml/min 44 kgf
Inj vol- :5ul
Kunte

Shimadzu CLASS-VP V6.12 SP5
Method Name: C:\CLASS-VP\Method ch 2.met
Data Name: C:\CLASS-VP\Data\General\Gen1302
User: System
Acquired: 4/21/11 2:35:49 PM
Printed: 4/21/11 3:11:58 PM
Sample Name JR-RAC



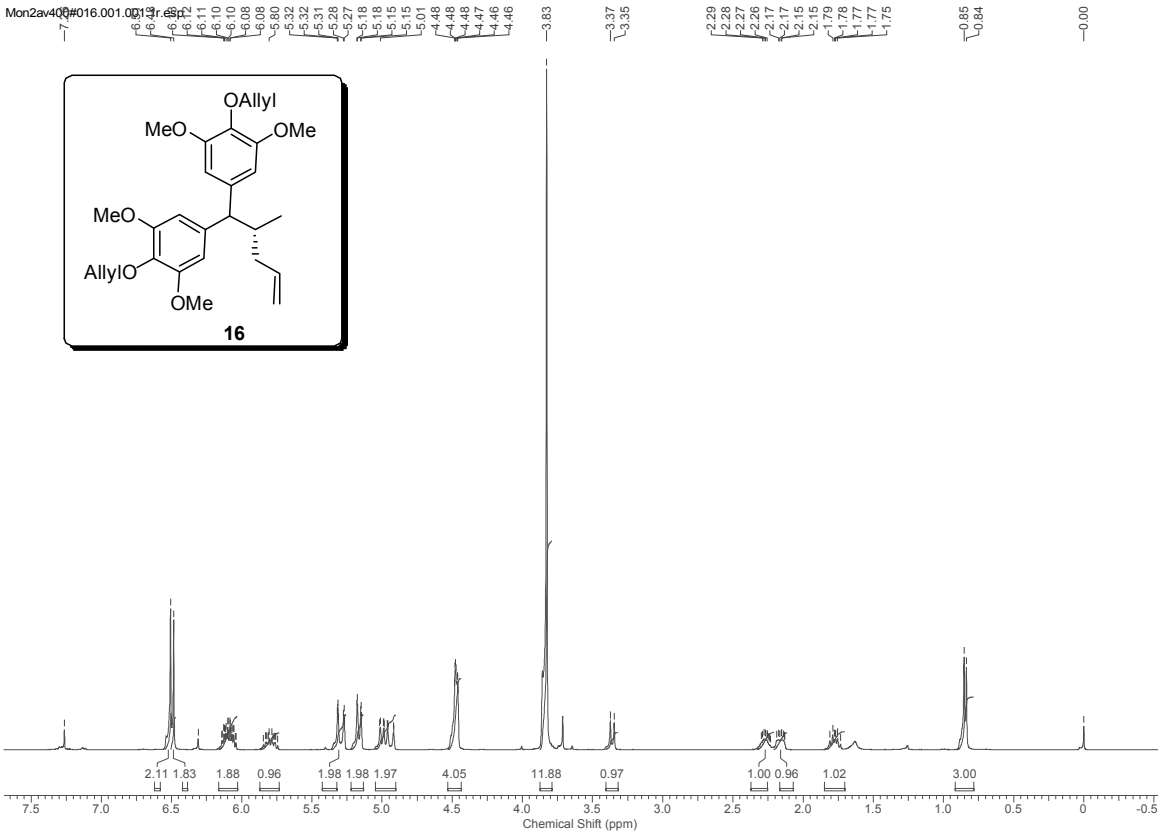
Racemic Sacidumlignan D (**3**)



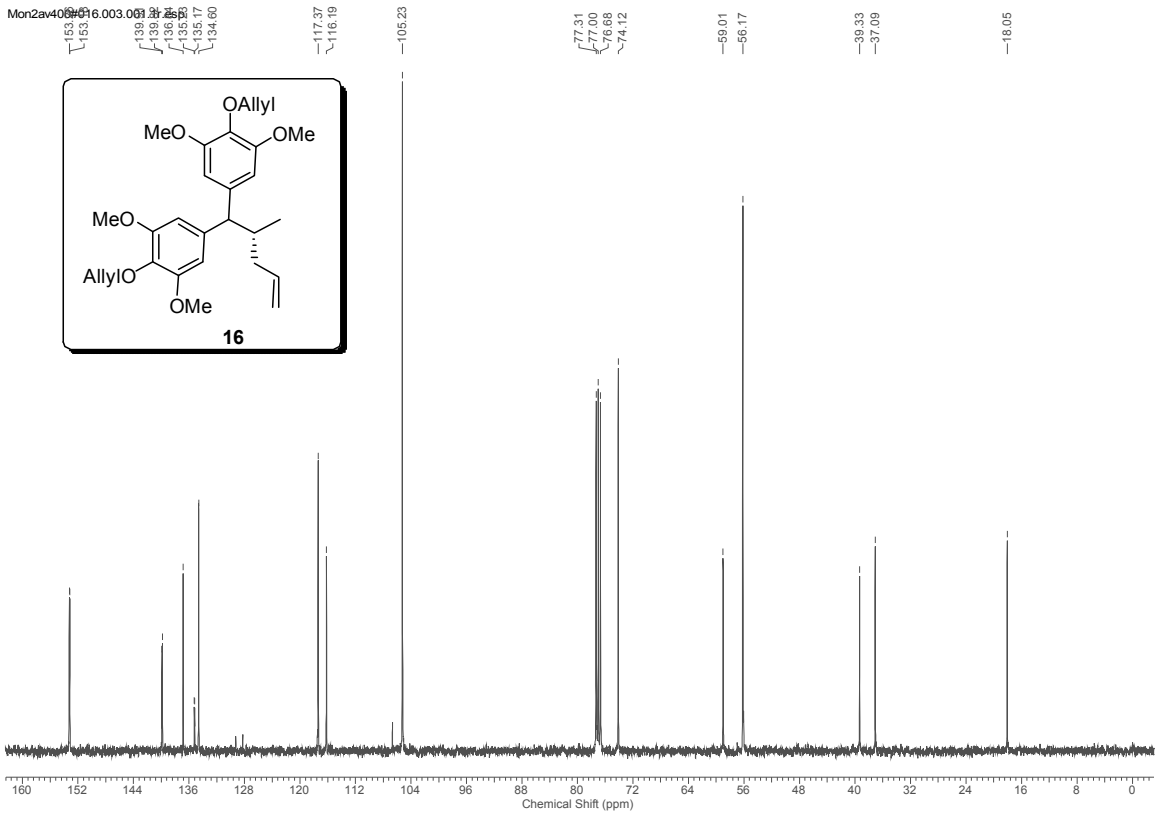
Detector A - 1 (254nm)

Retention Time	C Area	Area %
15.575	5139051	50.498
24.992	5037702	49.502
Totals	10176753	100.000

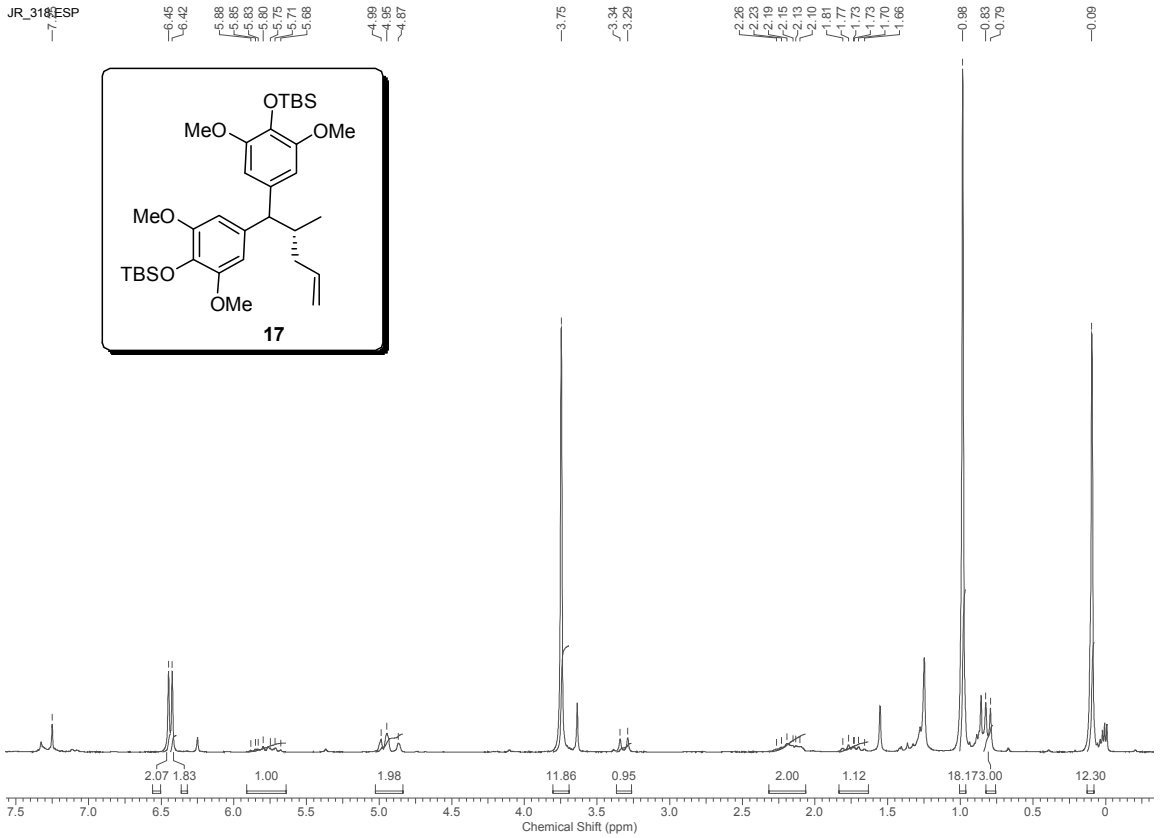
Project Leader : Dr.C.V. RAMANA
Column :Kromasil 5-AmyCoat (250x4.6mm)
Mobile Phase :Ethanol:n-Hexane (40:60)
Wavelength : 254nm
Flow Rate : 0.5ml/min 44 kgf
Inj vol- :5ul
Kunte



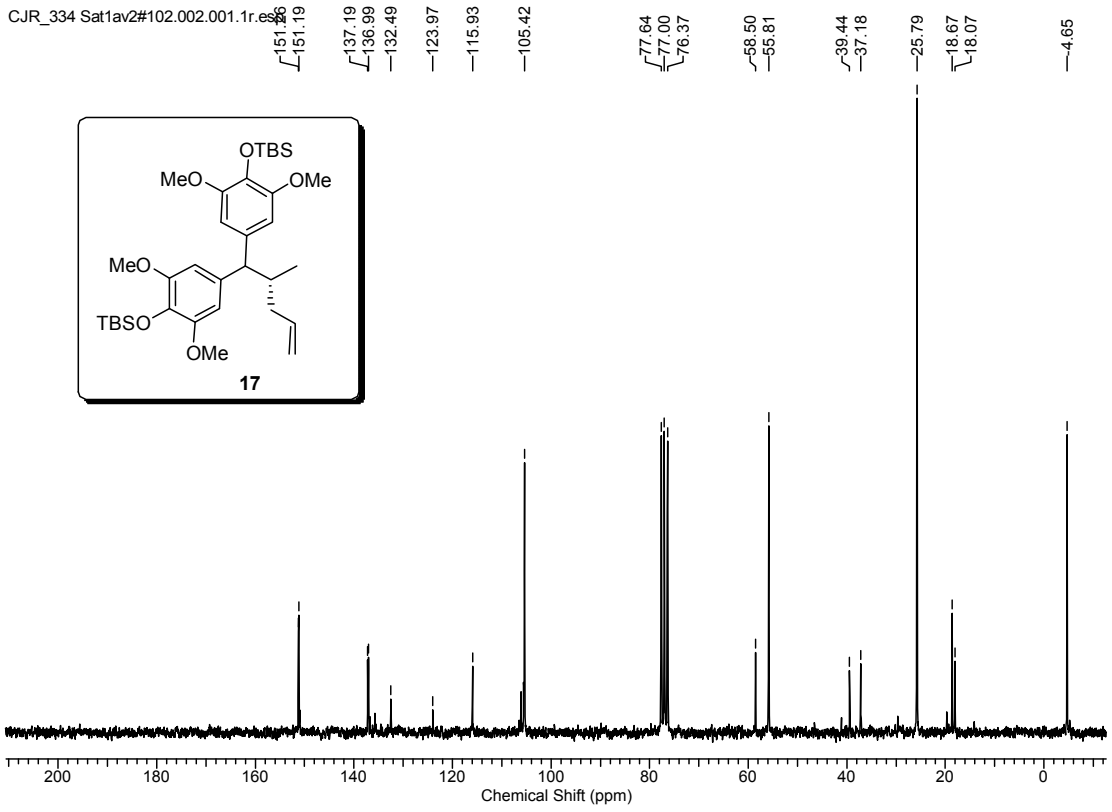
^{1}H NMR Spectrum of **16** in $CDCl_3$ (400 MHz)



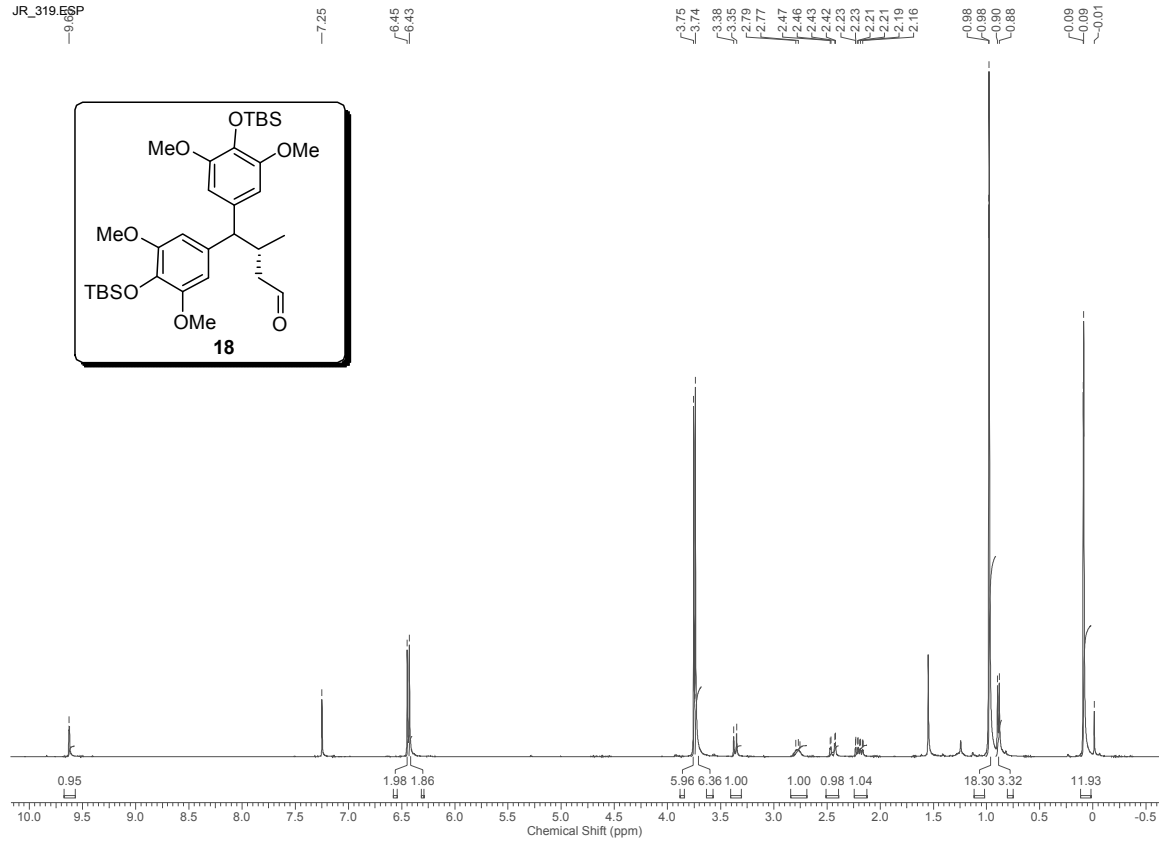
^{13}C NMR Spectrum of **16** in $CDCl_3$ (100 MHz)



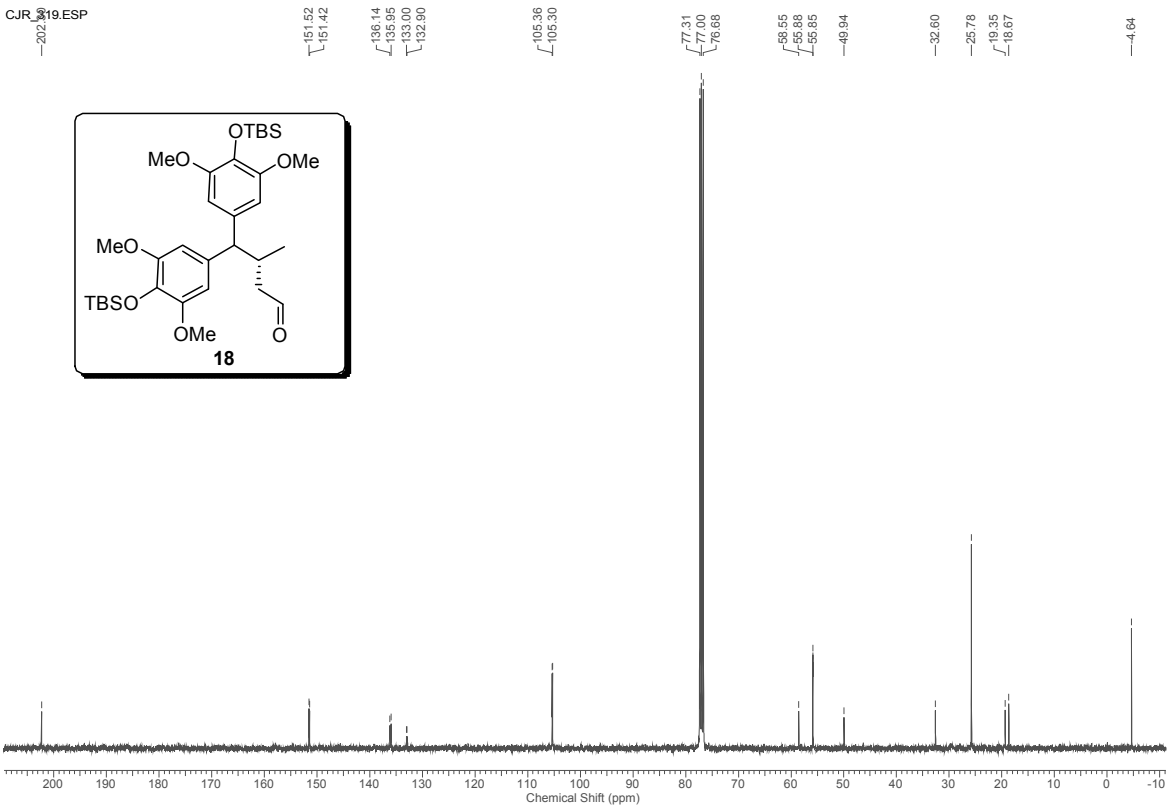
^{1}H NMR Spectrum of **17** in $CDCl_3$ (200 MHz)



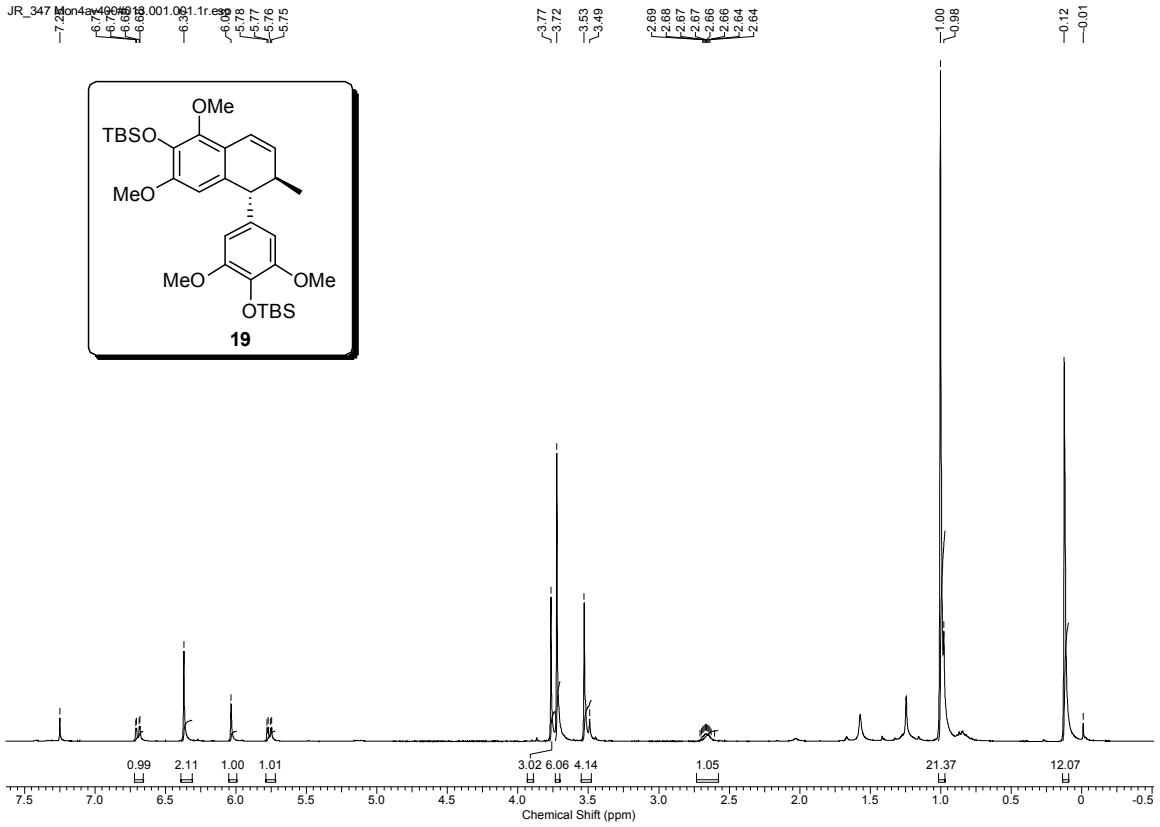
^{13}C NMR Spectrum of **17** in $CDCl_3$ (200 MHz)



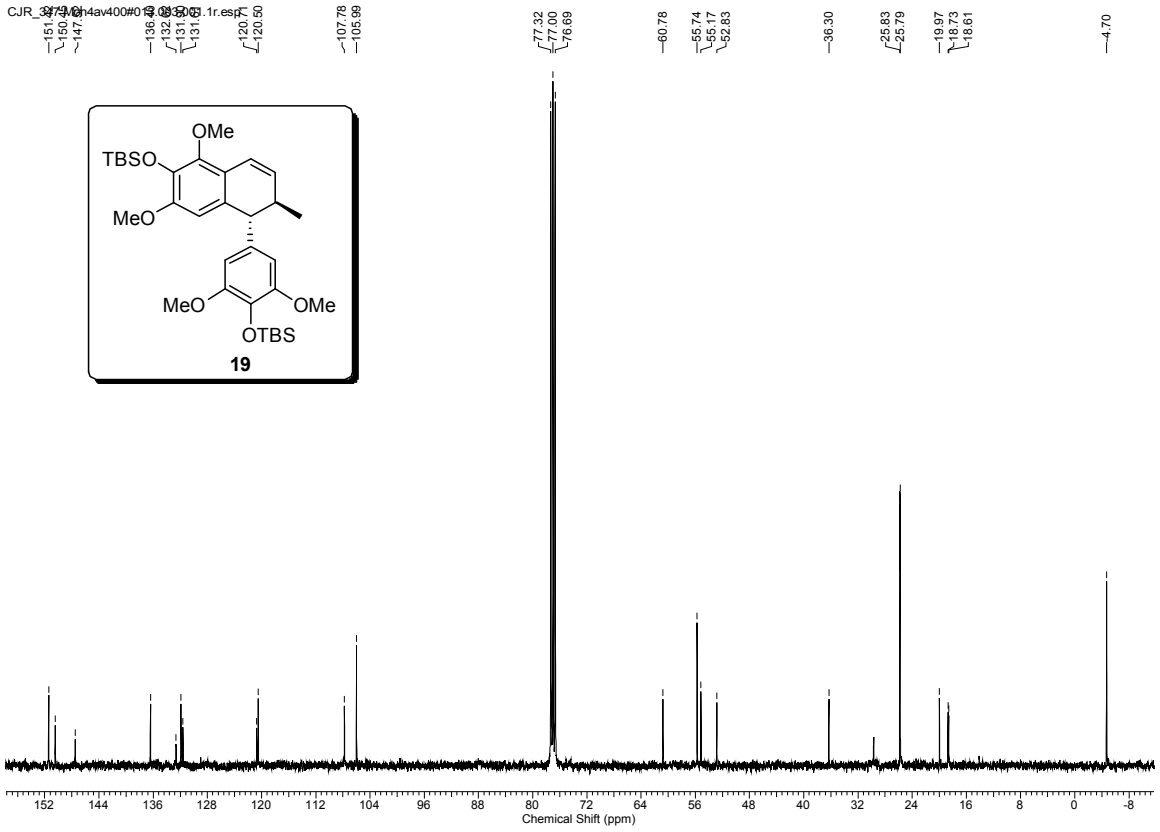
^{1}H NMR Spectrum of **18** in $CDCl_3$ (400 MHz)



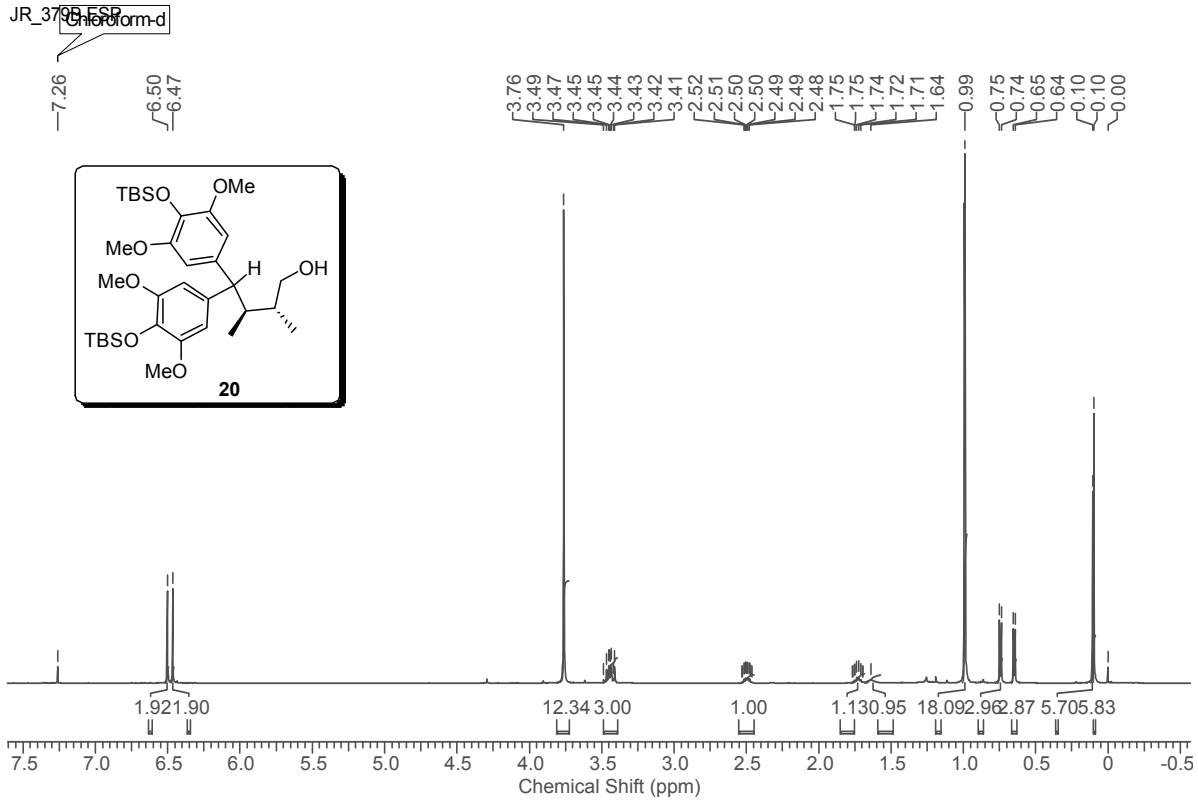
^{13}C NMR Spectrum of **18** in $CDCl_3$ (100 MHz)



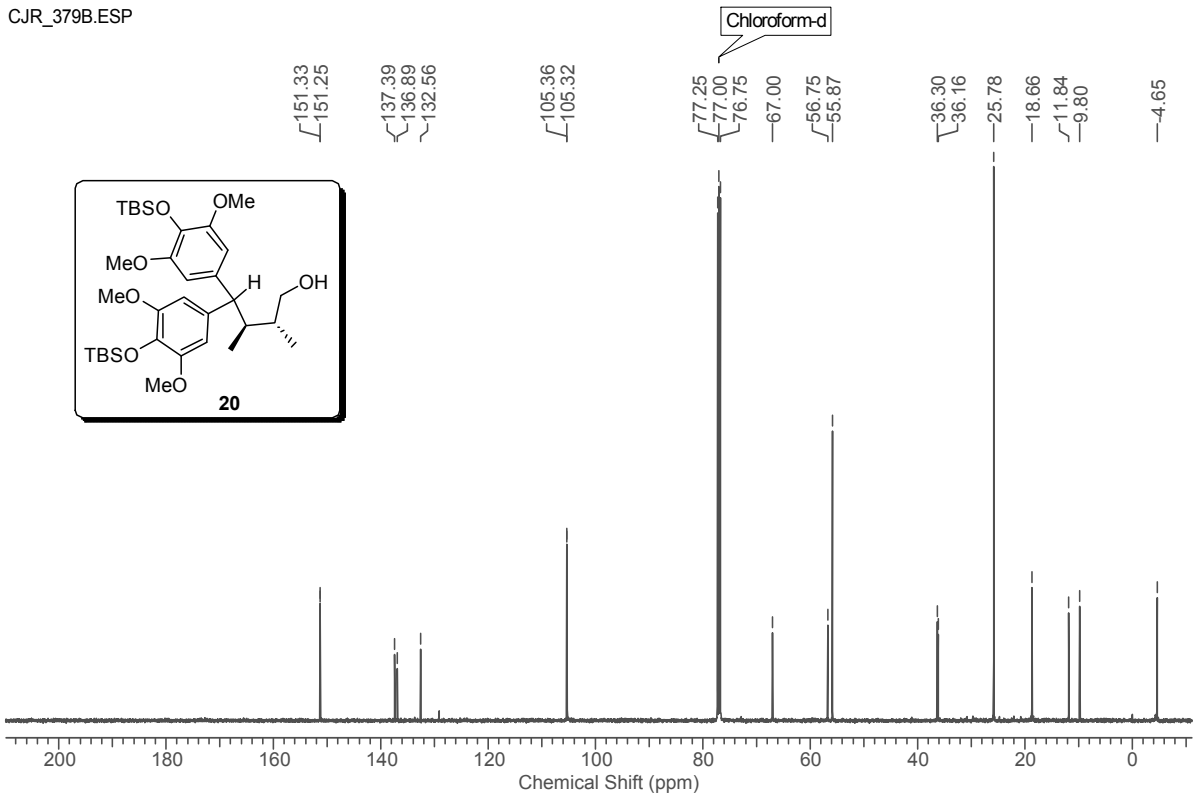
^{1}H NMR Spectrum of **19** in $CDCl_3$ (400 MHz)



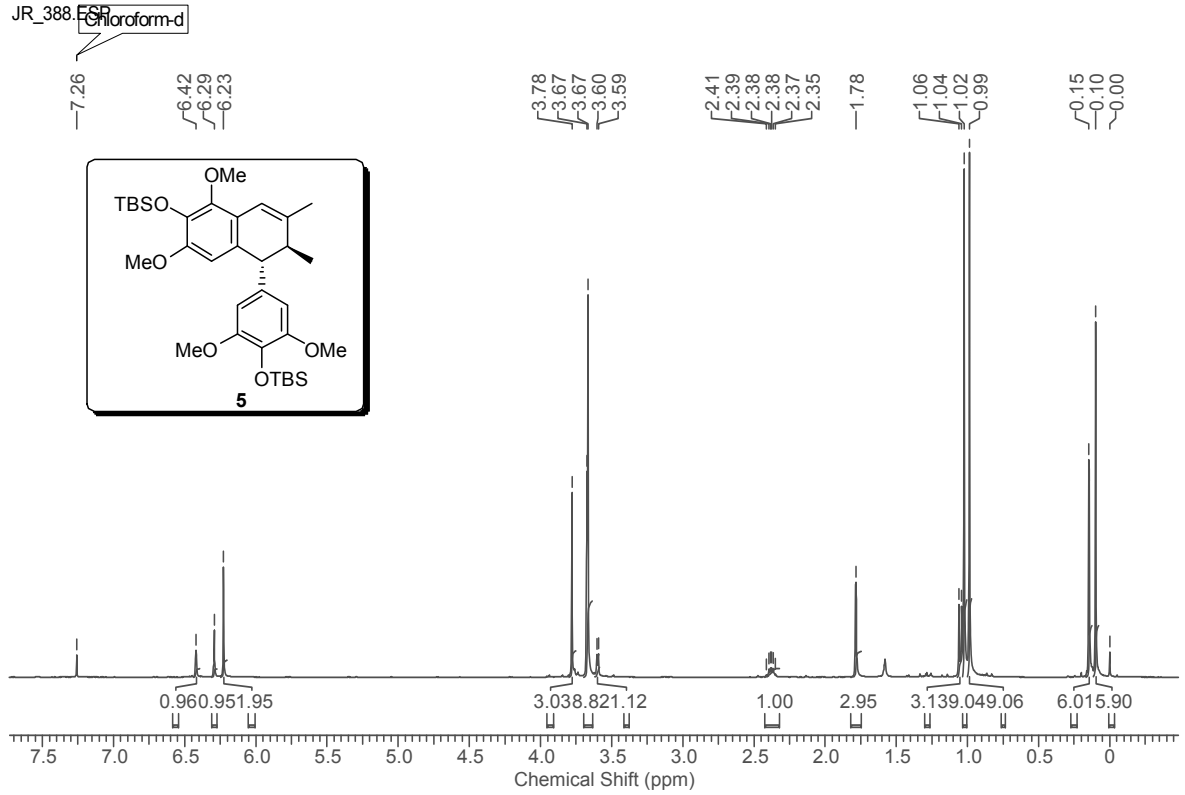
^{13}C NMR Spectrum of **19** in $CDCl_3$ (100 MHz)



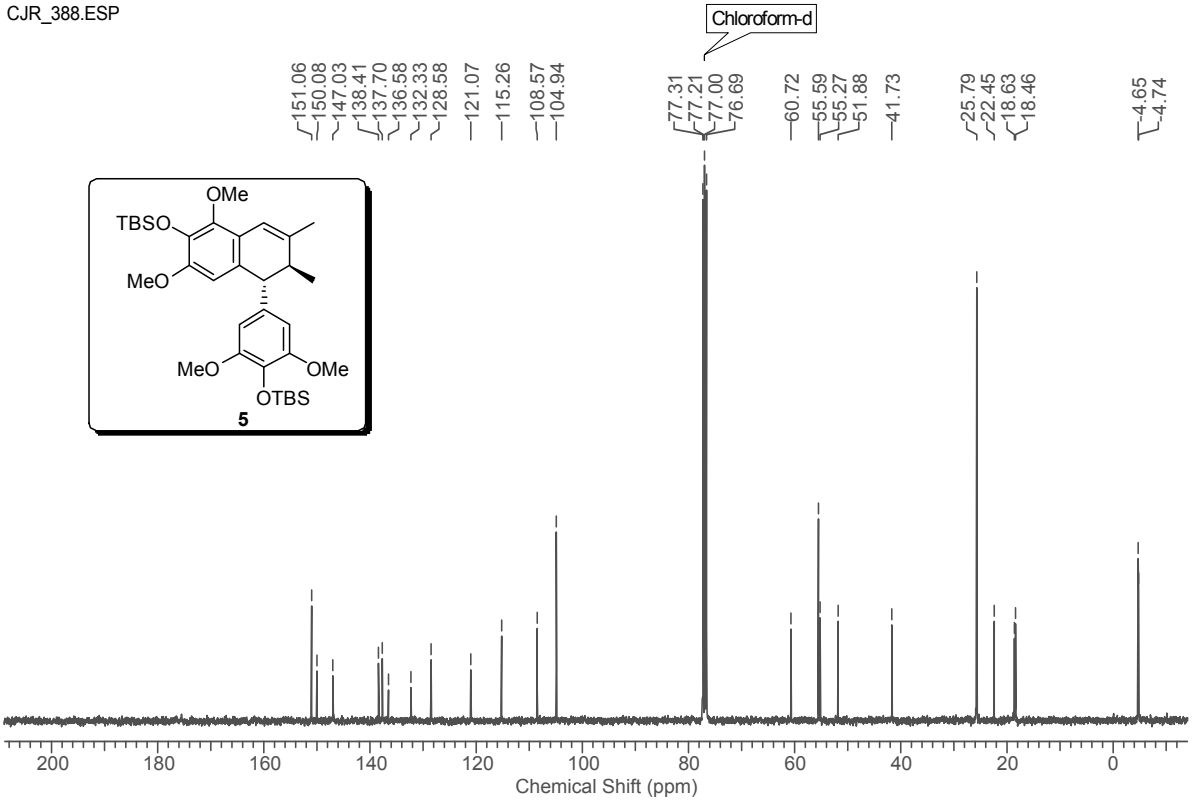
^{1}H NMR Spectrum of **20** in $CDCl_3$ (500 MHz)



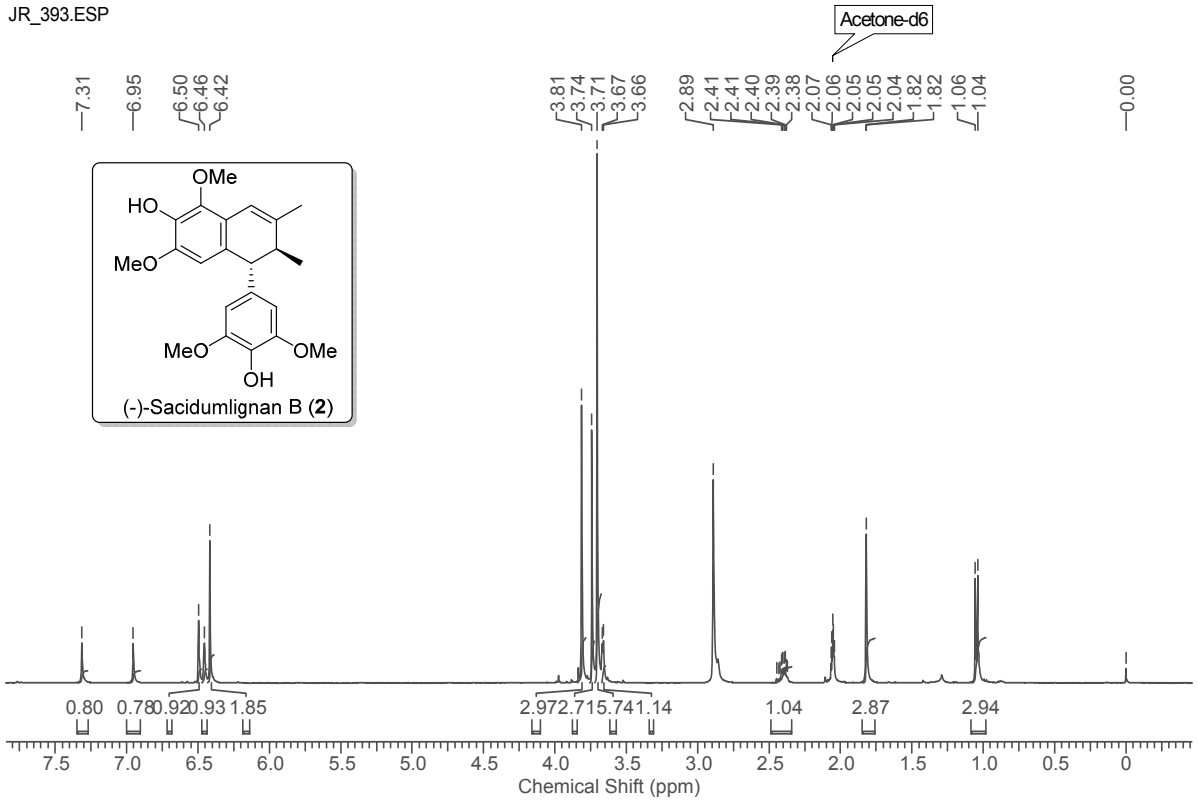
^{13}C NMR Spectrum of **20** in $CDCl_3$ (125 MHz)



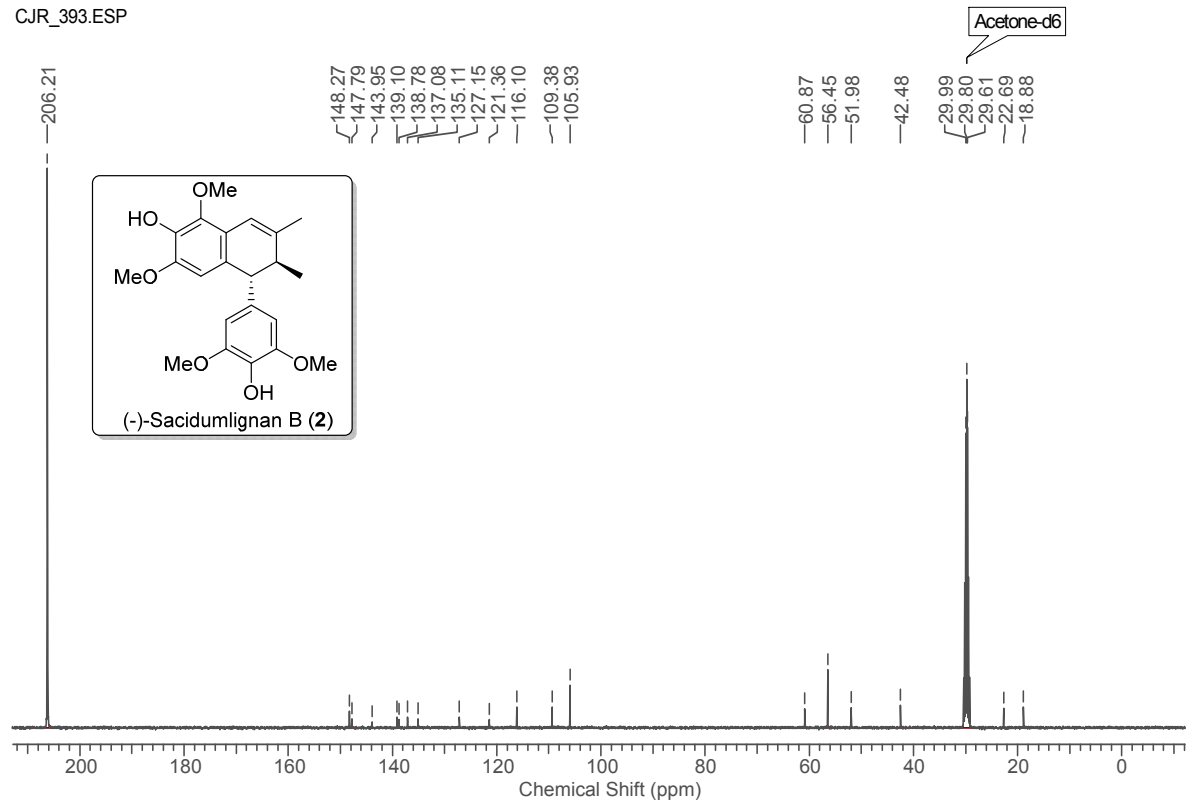
^{1}H NMR Spectrum of **5** in $CDCl_3$ (400 MHz)



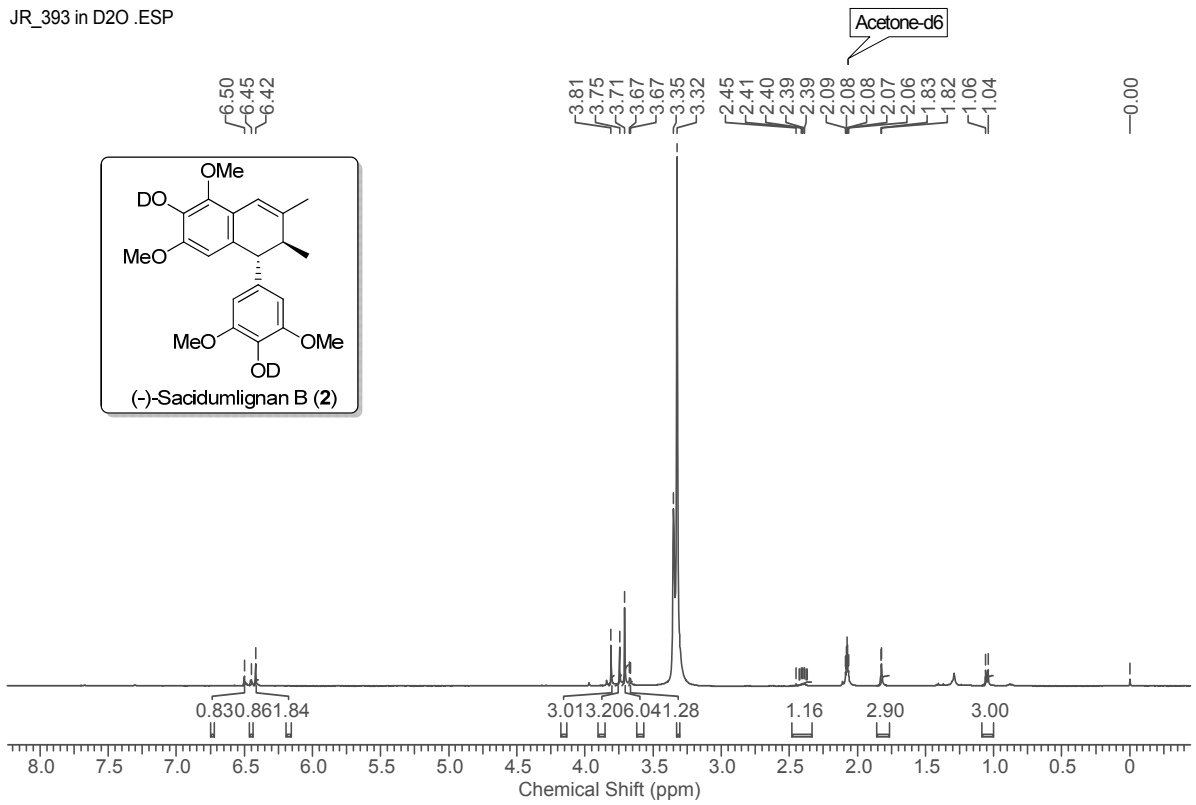
^{13}C NMR Spectrum of **5** in $CDCl_3$ (100 MHz)



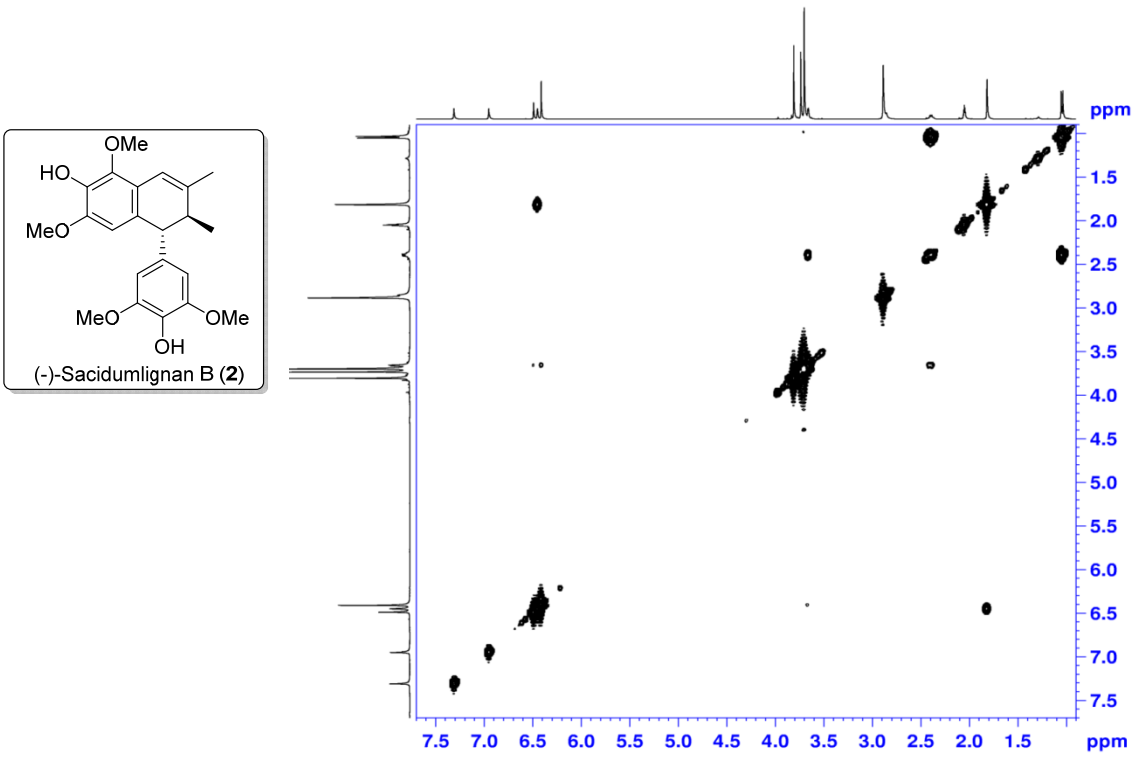
^{1}H NMR Spectrum of **2** in Acetone d_6 (400 MHz)



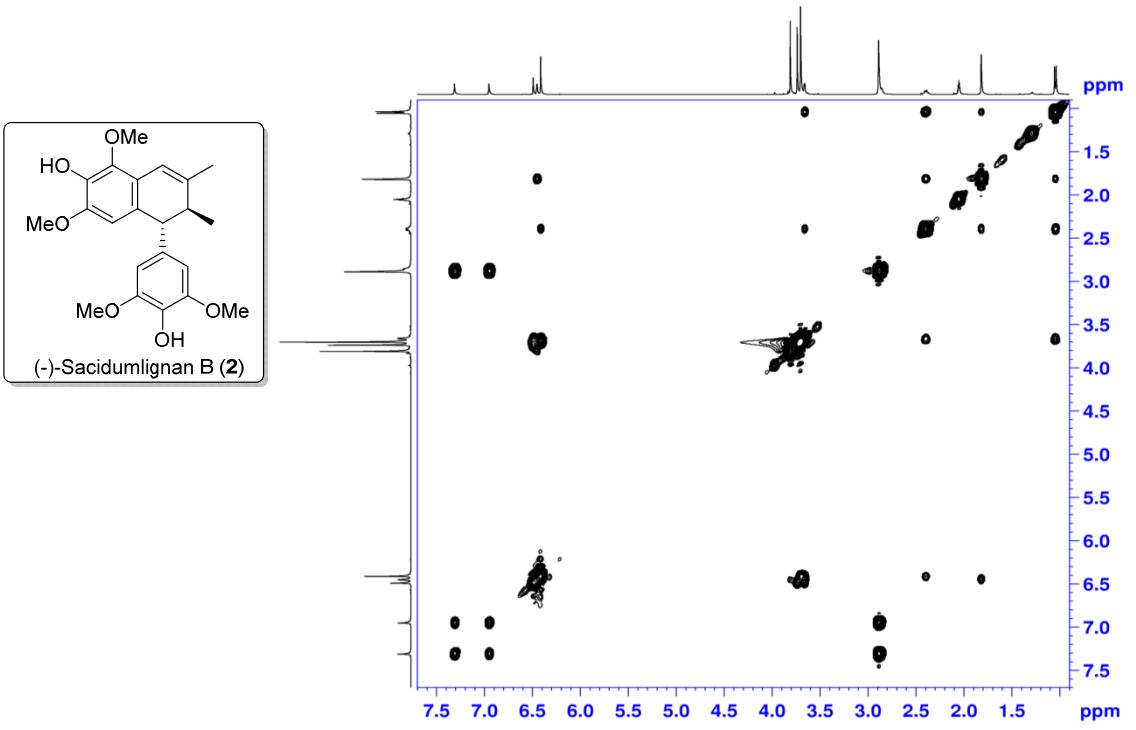
^{13}C NMR Spectrum of **2** in Acetone d_6 (100 MHz)



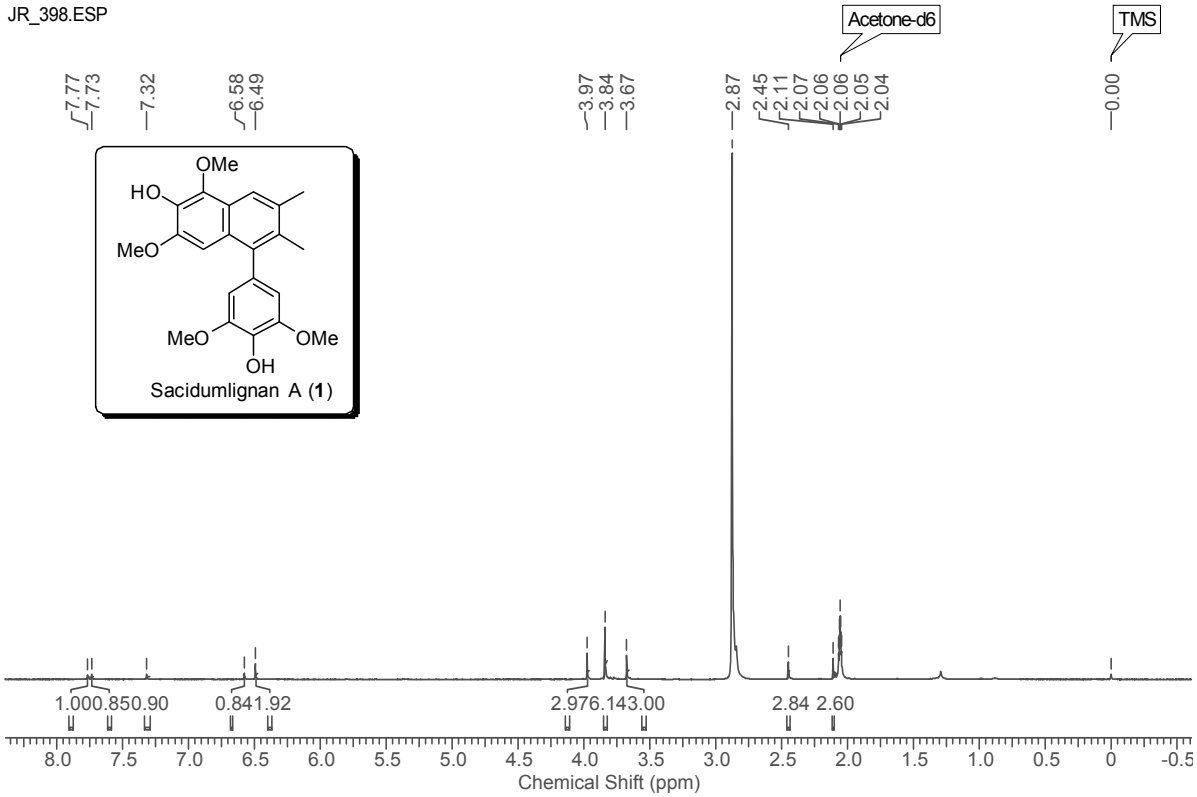
^{1}H NMR Spectrum of deuterated **2** in Acetone d_6 (400 MHz)



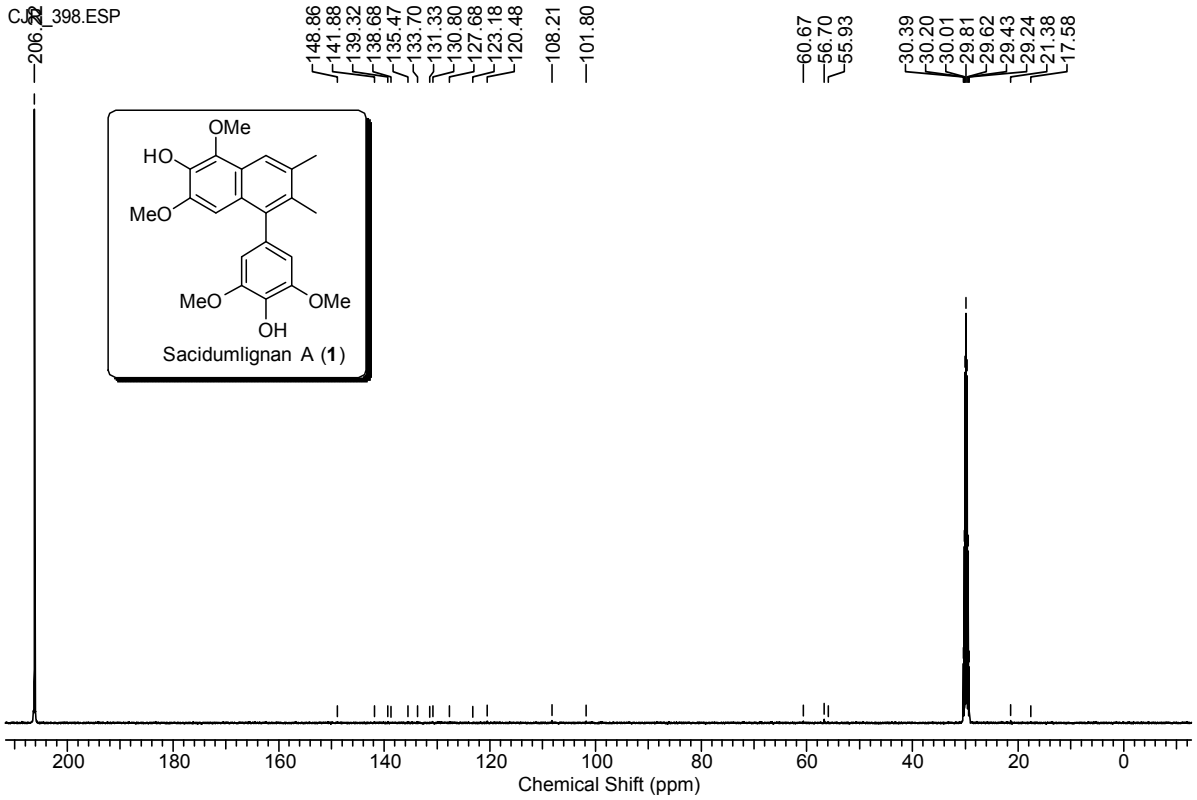
COSY Spectrum of **2** in Acetone-d_6



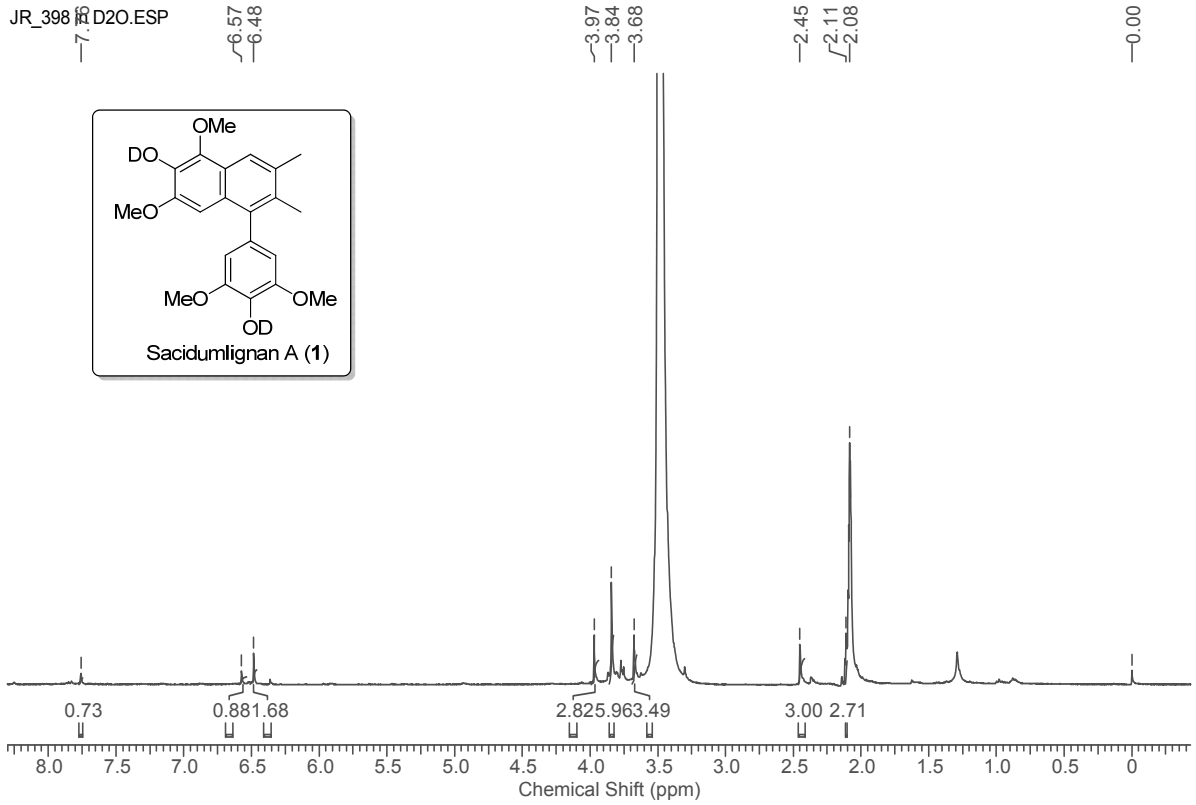
NOESY Spectrum of **2** in Acetone-d_6



^{1}H NMR Spectrum of **1** in Acetone-d_6 (400 MHz)



^{13}C NMR Spectrum of **1** in Acetone-d_6 (100 MHz)



^{1}H NMR Spectrum of deuteriated **1** in Acetone-d_6 (400 MHz)

REFERENCE

1. (a) Amit K. Sharma, *Bio-social Issues in Health*. New Delhi, India: Northern Book Centre. **2009**, 129. (b) D. Frawley, S. Ranade, Ayurveda, *Nature's Medicine Lotus Press* **2001**, 11.
2. W. M. Hearon, W. S. Macgregor, *Chem. Rev.* **1955**, *55*, 957.
3. (a) L. C. Vining, *Annual Review of Microbiology* **1990,** *44*, 395; (b) J. S. Dickschat, *Beilstein J. Org. Chem.* **2011***, 7*, 1620.
4. G. P. Moss, *Pure and Applied Chemistry* **2000,** *72*, 1493.
5. (a) S. Suzuki, T. Umezawa, M. Shimada, *Biosci., Biotechnol., Biochem.* **2002,** *66*, 1262; (b) T. Umezawa, T. Okunishi, M. Shimada, P. Canadian, A Paper In *Iswpc - 9th International Symposium on Wood and Pulping Chemistry - Oral Presentations*, **1997**, 41; (c) W. M. Kamil, P. M. Dewick, *Phytochemistry* **1986,** *25*, 2093; (d) W. M. Kamil, P. M. Dewick, *Phytochemistry* **1986,** *25*, 2089; (e) D. E. Jackson, P. M. Dewick, *Phytochemistry* **1984,** *23*, 1037; (f) D. E. Jackson, P. M. Dewick, *Phytochemistry* **1984,** *23*, 1029; (g) A. J. Broomhead, M. M. A. Rahman, P. M. Dewick, D. E. Jackson, J. A. Lucas, *Phytochemistry* **1991,** *30*, 1489.
6. D. C. D. Quiroz, S. B. Carmona, F. Bolívar, A. Escalante, *Research and Reports in Medicinal Chemistry* **2014**, *4*, 35.
7. (a) K. Mangathayaru, *Pharmacognosy*, *Pearson Education India* 2. (b) A. H. -Davis. History: From the Dawn of Civilization to the Present Day. Penguin. 53.
8. (a) A. Kato, Y. Hashimoto, *J. Nat. Prod.* **1979**, *42*, 159. (b) H. Achenbach, R. Waibel, I. Addae-Mensah, *Phytochemistry* **1983**, *22*, 749. (c) S. Nishibe, T. Fujimoto, M. Nose, T. Takeda, Y. Ogihara, G. Xu, *Phytochemistry* **1993**, *32*, 1579. (d) Y. Zhao, A. Nookandeh, B. Schneider, X. Sun, B. Schmitt, J. Stockigt, *J. Chromatogr. A* **1999**, *837*, 83.
9. Y. Damayanthi, J. W. Lown, *Current Medicinal Chemistry* **1998,** *5*, 205.
10. (a) J. B. Chang, Q. Wang, Y. F. Li, *Curr. Top. Med. Chem.* **2009,** *9*, 1660; (b) Y.-w. Choi, K. Kim, J.-y. Jo, H.-l. Kim, Y.-j. Lee, W.-j. Shin, S. J. Sacket, M. Han, D.-S. Im, *Acta Pharmacologica Sinica* **2008,** *29*, 1006; (c) K. Chen, Y. Kashiwada, D. C. Zhang, C. Q. Hu, J. Q. Jin, H. Nozaki, R. E. Kilkuskie, E. Tramontano, Y. C. Cheng, D. R. McPhail, A. T. McPhail, K. H. Lee, Q. Shi, *J. Nat. Prod.* **1992,** *55*, 340; (d) C. Q. Hu, K. Chen, Q. Shi, R. E. Kilkuskie, Y. C. Cheng, K. H. Lee, *J. Nat. Prod.* **1994,** *57*, 42; (e) T. Konoshima, I. Yasuda, Y. Kashiwada, L. M. Cosentino, K. H. Lee, *J. Nat. Prod.* **1995,** *58*, 1372; (f) D. F. Chen, S. X. Zhang, L. Xie, J. X. Xie, K. Chen, Y. Kashiwada, B. N. Zhou, P. Wang, L. M. Cosentino, K. H. Lee, *Bioorg. Med. Chem.*

1997, *5*, 1715; (g) L. W. Wang, T. Chen, H. X. Sun, Y. Xiong, C. X. Zhou, Y. Zhao, *Acta Crystallogr. Sect. E: Struct. Rep. Online* **2004,** *60*, 513.

11. (a) R. L. Arslanian, D. T. Bailey, M. C. Kent, S. L. Richheimer, K. R. Thornburg, D. W. Timmons, Q. Y. Zheng, *J. Nat. Prod.* **1995,** *58*, 583; (b) J. B. Chang, J. Reiner, J. X. Xie, *Chem. Rev.* **2005,** *105*, 4581.
12. A. F. Barrero, A. Haidour, M. M. Dorado, J. M. Cuerva, *Phytochemistry* **1996,** *41*, 605.
13. S. Yamauchi, Y. Hayashi, Y. Nakashima, T. Kirikihira, K. Yamada, T. Masuda, *J. Nat. Prod.* **2005,** *68*, 1459.
14. (a) G. C. Brophy, J. Mohandas, M. Slaytor, S. Sternhell; T. R. Watson, L. A. Wilson, *Tetrahedron Lett.* **1969**, *59* 5159. (b) O. L. Chapman, M. R. Engel, J. P. Springer, J. C. Clardy, *J. Am. Chem. Soc.* **1971,** *93*, 6696.
15. S. R. Angle, K. D. Turnbull, *J. Org. Chem.* **1993,** *58*, 5360.
16. (a) J. Sinkkonen, J. Liimatainen, M. Karonen, K. Wiinamaki, P. Eklund, R. Sjoholm, K. Pihlaja, *Angew. Chem. Int. Ed.* **2007,** *46*, 4148. (b) K. Yoshikawa, H. Kinoshita, S. Arihara, *J. Nat. Prod.* **1997,** *60*, 511.
17. C. L. Cardoso, I. Castro-Gamboa, G. M. Bergamini, A. J. Cavalheiro, D. H. S. Silva, M. N. Lopes, A. R. Araujo, M. Furlan, H. Verli, V.D. S. Bolzani, *J. Nat. Prod.* **2011,** *74*, 487.
18. A. R. Carroll, W. C. Taylor, *Aus. J. Chem.* **1991,** *44*, 1705.
19. (a) J. B. Johnson, E. A. Bercot, C. M. Williams, T. Rovis, *Angew. Chem. Int. Ed.* **2007,** *46*, 4514; (b) S. Mitra, S. R. Gurrala, R. S. Coleman, *J. Org. Chem.* **2007,** *72*, 8724; (c) R. S. Coleman, S. R. Gurrala, *Org. Lett.* **2004,** *6*, 4025.
20. S. P. Hong, M. C. McIntosh, *Org. Lett.* **2002,** *4*, 19.
21. M. K. Gurjar, J. Cherian, C. V. Ramana, *Org. Lett.* **2004,** *6*, 317.
22. M. K. Gurjar, B. Karumudi, C. V. Ramana, *J. Org. Chem.* **2005,** *70*, 9658.
23. S. H. Yu, M. J. Ferguson, R. McDonald, D. G. Hall, *J. Am. Chem. Soc.* **2005,** *127*, 12808.
24. L. S. Gan, S. P. Yang, C. Q. Fan, J. M. Yue, *J. Nat. Prod.* **2005,** *68*, 221.
25. X. Wei, L. Sheng-Hong, N. Zhi, Z. Hong-Jie, Z. Qin-Shi, L. Zhong-Wen, S. Han-Dong, *Acta Botanica Yunnanica* **2002**, *24*, 535.
26. S. K. Pandey, C. V. Ramana, *J. Org. Chem.* **2011,** *76*, 2315.
27. J.-J. Zhang, C.-S. Yan, Y. Peng, Z.-B. Luo, X.-B. Xu, Y.-W. Wang, *Org. Biomol. Chem.* **2013,** *11*, 2498.

28. For acid-mediated dehydrative cyclization leading to dihydronaphthalenes, (a) D. F. Taber, W. Tian, *J. Org. Chem.* **2008**, *73*, 7560; (b) T. D. E Vicente, M. J. Villa, *Heterocycles* **1998**, *48*, 243; (c) F. Salmon-Legagneur, G. Poulain, *Bull. Soc. Chim. Fr.* **1964**, 1318.
29. (a) D. A. Evans, M. D. Ennis, D. J. Mathre, *J. Am. Chem. Soc.* **1982**, *104*, 1737; b) T. E. Smith, D. P. Richardson, G. A. Truran, K. Belecki, *M.* Onishi, *J. Chem. Educ.* **2008**, *85*, 695.
30. (a) R. Karaman, I. T. Badejo, J. L. Fry, *J. Am. Chem. Soc.* **1989**, *111*, 6450; (b) H. D. Zook, J. March, D. F. Smith, *J. Am. Chem. Soc.* **1959**, *81*, 1617; (c) S. Ibrahim, K. J. Msayib, C. I. F. Watt, J. M. Wilson, *J. Chem. Soc., Perkin Trans. 2* **1992**, 1703.
31. (a) F. Garrohelion, A. Merzouk, F. Guibe, *J. Org. Chem.* **1993**, *58*, 6109; (b) P. J. Harrington, J. D. Brown, T. Foderaro, R. C. Hughes, *Org. Process Res. Dev.* **2004**, *8*, 86.
32. W. S. Yu, Y. Mei, Y. Kang, Z. M. Hua, Z. D. Jin, *Org. Lett.* **2004**, *6*, 3217.
33. (a) V. Balogh, M. Golfier, M. Fetizon, *J. Org. Chem.* **1971**, *36*, 1339; (b) C. V. Ramana, S. B. Suryawanshi, R. G. Gonnade, *J. Org. Chem.* **2009**, *74*, 2842.
34. (a) S. Yamauchi, M. Okazaki, K. Akiyama, T. Sugahara, T. Kishida, T. Kashiwagi, *Org. Biomol. Chem.* **2005**, *3*, 1670; (b) F. Allais, T. J. L. Pla, P.-H. Ducrot, *Synthesis* **2011**, 1456.
35. (a) V. Gevorgyan, M. Rubin, S. Benson, J. X. Liu, Y. Yamamoto, *J. Org. Chem.* **2000**, *65*, 6179; (b) M. Orfanopoulos, I. Smonou, *Synth. Commun.* **1988**, *18*, 833; (c) J. L. Fry, M. Orfanopoulos, M. G. Adlington, W. R. Dittman, S. B. Silverman, *J. Org. Chem.* **1978**, *43*, 374; (d) M G. Adlington, M. Orfanopoulos, J. L. Fry, *Tetrahedron Lett.* **1976**, *17*, 2955.
36. Selected references on acid-mediated dehydrative cyclization leading to quinolinone and dihydroisoquinolines: (a) J. R. Butler, C. Wang, J. W. Bian, J. M. Ready, *J. Am. Chem. Soc.* **2011**, *133*, 9956; (b) E. R. Walker, S. Y. Leung, A. G. M. Barrett, *Tetrahedron Lett.* **2005**, *46*, 6537.
37. (a) J. D. More, N. S. Finney, *Org. Lett.* 2002, *4*, 3001; (b) T. Wirth, *Angew. Chem., Int. Ed.* **2001**, *40*, 2812; (c) M. Frigerio, M. Santagostino, S. Sputore, G. Palmisano, *J. Org. Chem.* **1995**, *60*, 7272; (d) M. Frigerio, M. Santagostino, *Tetrahedron Lett.* **1994**, *35*, 8019.
38. For various other methods used in the synthesis of aryldihydronaphthalene lignans, see: (a) C. E. Rye, D. Barker, *J. Org. Chem.* **2011**, *76*, 6636; (b) T. Assoumatine, P.

K. Datta, T. S. Hooper, B. L. Yvon, J. L. Charlton, *J. Org. Chem.* **2004**, *69*, 4140; (c) B. L. Yvon, P. K. Datta, T. N. Le, J. L. Charlton, *Synthesis* **2001**, 1556; (d) S. I. Yoshida, T. Ogiku, H. Ohmizu, T. Iwasaki, *Synlett* **1994**, 895; (e) S. Kadota, K. Tsubono, K. Makino, M. Takeshita, T. Kikuchi, *Tetrahedron. Lett.* **1987**, *28*, 2857.

39. D. Walker, J. D. Hiebert, *Chem. Rev.* **1967**, *67*, 153.

CHAPTER II:

Stereoselective Synthesis of *C*-disaccharides

INTRODUCTION

Carbohydrates called "hydrates of carbon" are ubiquitous in biological systems and perform several activities in living organisms. These mainly store energy in the form of starch and glycogen and are also utilized for the synthesis of the structural components of the plant in the form of cellulose and chitin in arthropods. Apart from this, their role in cell recognition, embryogenesis, inflammation, fertilization, the reproduction of cells and their organization into specific tissues, hormone activities, viral and bacterial infections, neuronal development, tumor cell metastasis, and host-pathogen recognitions are highly important for medicinal chemists and biologists.[1] In biochemistry, these are termed as saccharides and are classified as mono-, di-, oligo-, and polysaccharide depending on the number of repeating units. It has proved itself as a very important class of biomolecules, although it remains under the least exploited area among the biomolecules, viz. nucleic acids, proteins, and carbohydrates. The syntheses of carbohydrates pose a great challenge for synthetic chemistry as they possess a high level of complex structure with different conformations and a wide spectrum of functional groups. Because of their hydrophilicity and complex nature, they are hardly taken for drug discovery.[2] The binding affinity of carbohydrates with their receptors is very weak due to lack of charged moieties and hydrophobic interactions. However, experts believe that some of the potential problems can be solved by the use of the carbohydrates analogues.[3]

The carbohydrates synthesis and their metabolism are primarily organized by two types of enzymes viz. glycosyl transferases and glycosidases or glycosyl hydrolases.[4] Glycosyl transferases are the enzymes that are engaged for the biosynthesis of the complex carbohydrates through glycosidic linkages. These are mainly responsible for the catalysis of the transfer of a monosaccharide unit from a glycosyl donor to a glycosyl acceptor. The glycosyl acceptor could be a carbohydrate, protein, lipid, or nucleic acid. During transfer, they 'retain' or 'invert' the stereochemistry of the glycosidic donor's anomeric bond. The inversion mechanism follows the Walden inversion to furnish α to β or β to α anomer, whereas the retention mechanism is still a matter of debate. An orthogonal associative mechanism has been put forward, which suggests a single nucleophilic attack from a non-linear angle. But glycosidases, on the other hand, do the reverse. They trim the complex oligosaccharides to small oligomers and monosaccharides by the hydrolysis of the glycosidic bond. They even degrade biomass such as cellulose. These enzymes are extensively distributed in nature found in all domains of life. This large assembly of enzymes are now branded as "amylase". These were first investigated by Payen and Persoz in 1833.[5] The

amylases are of two types: endohydralase or α-amylase and exohydralase or β-amylase. α-amylase break α bonds of α-linked polysaccharides ramdomly, such as starch and glycogen to monosaccharides such as glucose and oligosaccharides such as maltose whereas β-amylase attack the polysaccharides from the non-reducing end to produce oligosaccharides. Like glycosyl transferase, both inversion and retention mechanism works for the hydrolysis of the glycosyl –O– bond. β-Amylase releases β-maltose units from the non-reducing end by hydrolyzing the α-1,4-glucosidic linkages of the starch through an inversion mechanism. Nevertheless, sometimes these valuable amylases create complexity in the development of carbohydrate as drug candidates. [6] As a result, the hetero-atomic glycosidic bonds of the drugs get cleaved like in starch, and glycogen hydrolysis, consequently, they get decomposed before doing their job. Therefore, the development of stable carbohydrate analogues (carbohydrate mimetics) is urgently essential.

All the carbohydrate mimetics are classified into 2 types, depending on the position of the modification are the core modification and linkage modification. When the core oxygen of a saccharide unit is replaced by nitrogen, sulfur, or carbon, then the sugars are called iminosugar, thiasugar, and carbasugar respectively. On the contrary, modifications in linkage by nitrogen, sulfur, or carbon are termed as *N*-glycosides, *S*-glycosides, and *C*-glycosides. Besides these other modifications linked with the change in functional group, ring size, peptoidic bond, spiro glycosides and sugar chromans are known. Among the crucial modifications, the *C*-glycosides are defined as the most imperative analogues by providing inert glycosidic bond towards chemical and enzymatic hydrolysis. This mimetic have completely identical properties with their natural counterparts except in the difference of their conformation.

C-glycosides are the carbon counterpart of natural *O*-glycosides. These are also termed as pseudosaccharides. A disaccharide containing a carbon linkage unit (methylene group) instead of oxygen, called *C*-disaccharide, is inert towards chemo-enzymatic hydrolysis. They someway lack behind an anomeric effect, and it is a matter of debate in current days whether the *O*-disaccharide is replaced by *C*-glycoside or not. Till date, it is still unknown whether a *C*-disaccharide is a safe replacement of *O*-disaccharide or not. However, there some analogues have proven therapeutic utilities in the treatment of AIDS, cancer, diabetes etc. Eribulin is an anticancer drug marketed by Eisai Co, a macrocyclic ketone analogue of the natural product Halicondrin B that contains a *C*-disaccharide unit.[7] On the other hand, several pharmacologically

active natural products hold the *C*-glycosidic linkage. The selected examples include Halichondrin B, Tunicamycin, Showdomycin, and Vancomycin.[8] Apart from this, the *C*-glycosides are also observed with an aromatic aglycon in several flavonoids, for e.g. Isoschaftoside, Spinosin, Luteolin-6-*C*-apioside-8-*C*-glucoside (Figure S2.1).[9]

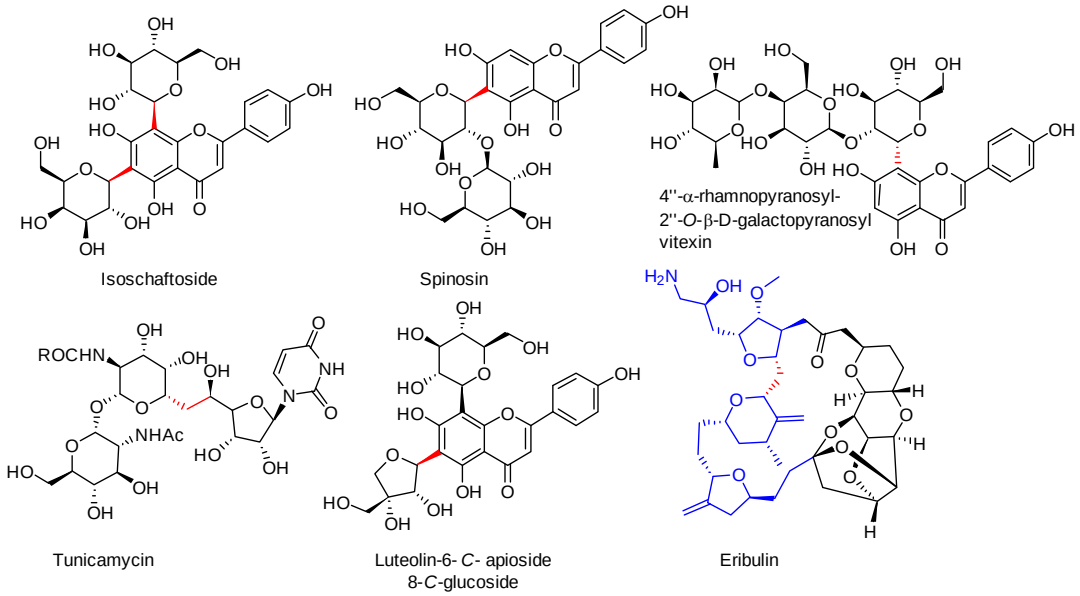


Figure S2.1. Representative natural products having *C*-glycoside linkages

In 1983, Sinay and Rouzaud first reported the synthesis of *C*-disaccharide.[10] After that several groups addressed the synthesis of different *C*-glycosides in the past focusing mainly on [1→3]-, [1→4]-, and [1→6]-linkages.[11–13] Lots of modular and robust approaches with respect to *C*-glycosidic linkage have been documented for diverse building blocks to mimic the natural products. However, mild, modular and general approaches are still rare. The methods known can be divided into 2 types:

a) Intermolecular *C*-glycoside Preparation

b) Intramolecular *C*-glycoside Preparation

Intermolecular C-glycoside Preparation: The glycosidic donor (electrophile) and glycosidic acceptor (nucleophile) exist in different substrates. Representative examples are the nitro-aldol reaction approach by Martin, the carbon-Ferrier reaction approach by Osborn, the Wittig olefination approach by Dondoni, the epoxide- alkyne reaction approach by Boom etc.

Intramolecular *C*-glycoside Preparation: The glycosidic donor (electrophile) and glycosidic acceptor (nucleophile) exist in the same substrates. Representative examples are the Ramberg-Backlund rearrangement by Taylor, the oxidation-reduction approach by Armstrong, intramolecular epoxide-alcohol reaction by Kishi etc. Other reaction approaches include the ring closing metathesis (RCM), illustrated by Postema which is intramolecular in nature. All the approaches are briefly discussed below.

Most of the *C*-glycoside synthesis after 1983 relied on simple acid-base chemistry, or radical chemistry using Bu_3SnH. The advances in transition metal chemistry in the 21th century guided new directions for generating the reactive intermediates under mild condition. As a result, the complexity associated with classical glycoside preparation, such as functional group tolerance, became relieved and good selectivity of anomeric ratio in the preparation of complex oligomers was observed. However, the electrophilic reactions using classical methods are widely encountered due to the easy accessibility of the electrophilic sugars such as lactones, glycals, 1,2-anhydrosugars, halides, imidates etc. Conversely, the *C*-glycosylation through the anomeric anionic species was also investigated. This is done by the highly basic lithiated bases. This technique is also called "umpolung" as a carbanion is generated near to the ring oxygen. For radical *C*-glycosylations, the leaving groups such as sulfonates, phosphates, and halides are used frequently to liberate free radicals at the anomeric centre. Samarium iodide is a popular radical initiator *via* one- and two- electron transfer processes for the *C*-glycosylation. The commonly used cationic, anionic, and radical precursors are shown below.

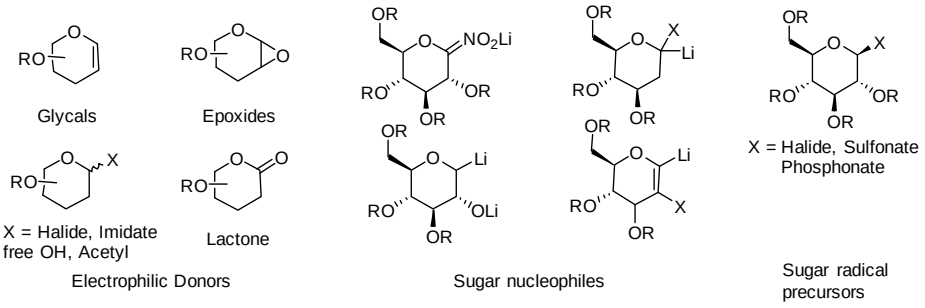
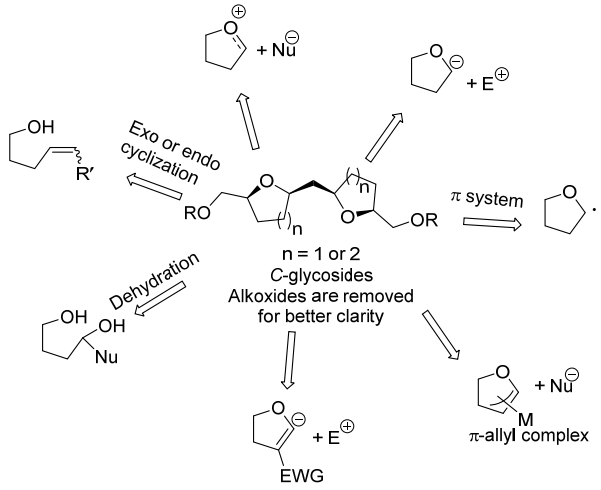


Figure S2.2. Various sugar derived electrophiles, nucleophiles, and radical precursors

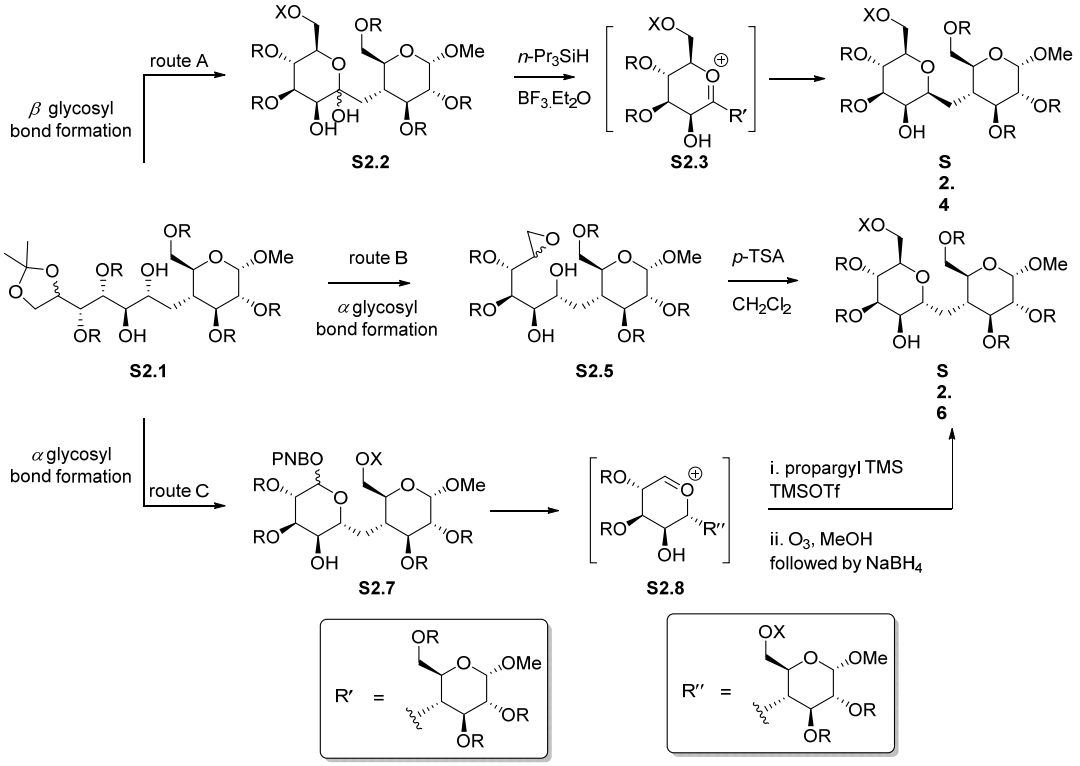
An overview of the literature reported methods for the synthesis of *C*-glycosides are depicted below. The synthesized disaccharides were retrosynthetically disconnected to the respective synthons and their coupling partners. The reactions usually involved in glycosylation are, a) addition of nucleophile to oxocarbenium species, b) addition of electrophile to anionic

anomeric species, c) radical coupling, d) metal catalyzed addition of nucleophile to the π-allyl system, e) Henry reaction, f) cycloisomerization by metal or Lewis acid etc.



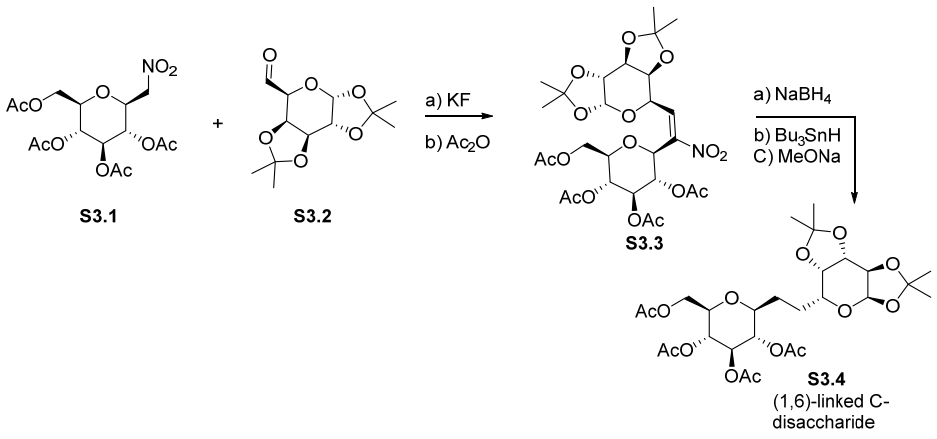
Scheme S2.1. Salient features of the methods used for the *C*-disaccharide synthesis

Kishi's Synthesis of [1→4]-Linked *C*-Disaccharides (1992): To study the conformational properties, the *C*-cellobioside **S2.4** with [1→4]-*β*-linkage and *C*-maltoside **S2.6** with a [1→4]-*α*-linkage have been synthesized by Kishi. Three different synthetic approaches have been employed in this context. The higher sugar precursor **S2.1** has been employed for the preparation of the key intermediates **S2.2**, **S2.5**, and **S2.7** of these three routes A – C. The routes A and C were characterized by the attack of a nucleophilic on pyranose oxycarbenium cation. The route A involved the axial attack of a hydride nucleophile to the oxycarbenium cation **S2.3**, whereas attack of a carbon nucleophile equatorially on the oxycarbenium cation **S2.8** in route C furnished the [1→4]-linked *C*-disaccharides. Reductive cleavage of the intermediate acetal in route A was done with *n*-$Pr_3SiH/BF_3 \cdot Et_2O$, which is being treated as one of the important factors in the present context. The route B, however, implied the Bronsted acid-catalyzed intramolecular epoxide opening by the pendant alcohol. This method is usually applied for the construction of tetrahydrofuran and tetrahydropyran ring systems. The flexibility of the synthesis was beautifully explained by synthesizing both the [1→4]-*α*- and [1→4]-*β*-linked *C*-disaccharides of the pyran-pyran combination.[14–15]



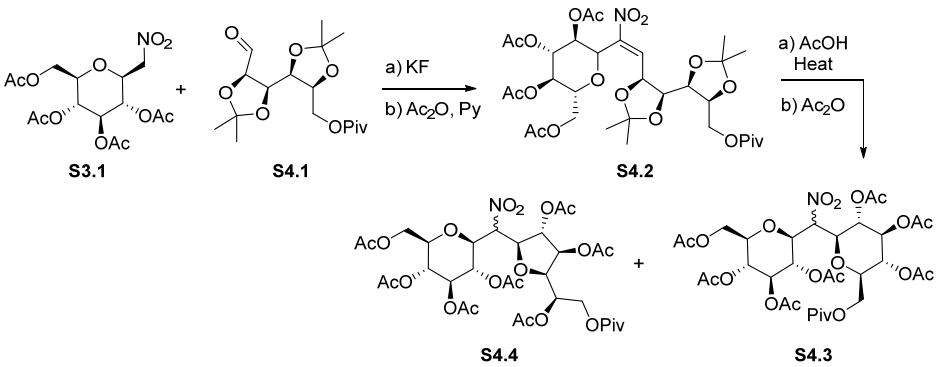
Scheme S2.2. Nucleophilic addition-deoxygenation strategy for *C*-disaccharides

Martin's Synthesis of [1→6]- and [1→1]-Linked *C*-Disaccharides (1993): Martin has reported a fluoride ion-mediated nitro-aldol reaction for the synthesis of *C*-disaccharides in six steps. They combined a nitronate anion derived from a glycosyl nitromethane with hexodialdose in the presence of potassium fluoride. The obtained nitro aldol was later dehydrated in the presence of acetic anhydride. Nucleophilic hydrogenation carried out with $NaBH_4$ followed by the radical denitration using Bu_3SnH afforded [1→6]-linked *C*-disaccharide having pyran-pyran combination.[12k]



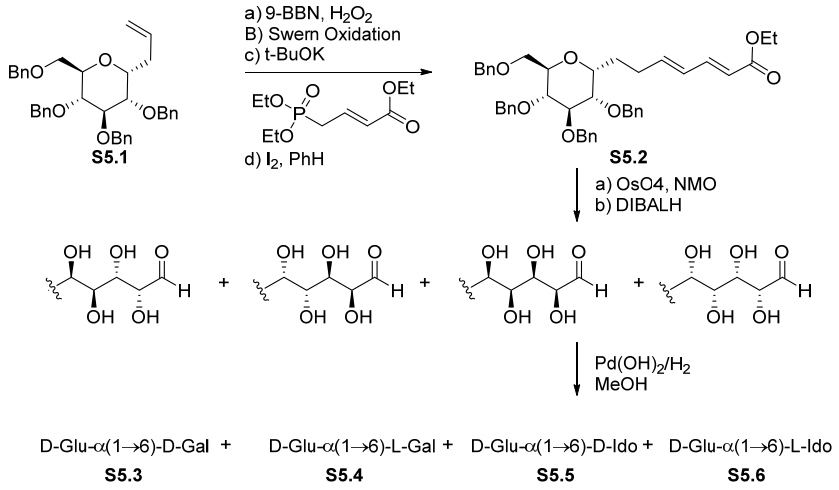
Scheme S2.3. Nitro-aldol condensation for [1→6]-linked *C*-disaccharides

Trehalose analogues (*β*-D-Glc-[1→1]-*β*-D-Glc were also synthesized using the same protocol just by altering the aldehyde partner. The deprotection of nitro aldol condensed product ended with the protected [1→1]-*C*-disaccharides in the presence of acetic acid under heating conditions. This ring formation harnesses an intramolecular Michael addition to produce two very valuable *C*-disaccharides having a pyran-pyran and a pyran-furan combination. Methods to prepare the [1→1]-linked *C*-disaccharides are very rare. However, this simple protocol easily solved this fundamental problem.



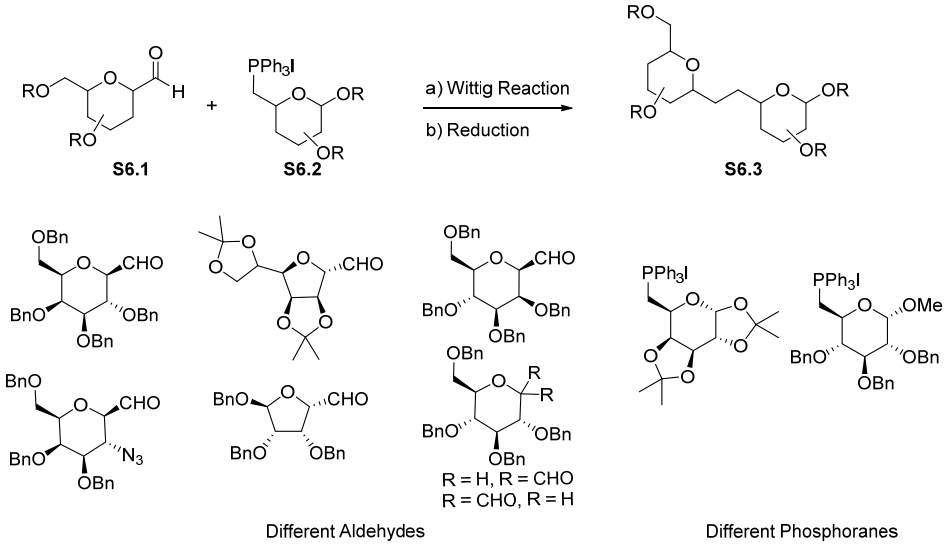
Scheme S2.4. Nitro-aldol condensation for [1→1]-linked *C*-disaccharides

Armstrong's Synthesis of [1→6]-Linked *C*-Disaccharides (1994): Armstrong's synthesis of *C*-disaccharides is based on oxidation and reduction protocol. The strategy, however, established well the stereochemistry of four *C*-disaccharides containing D and L sugars from a single precursor. C1 homologated diene ester monosaccharide was readily obtained from the *α*-*C*-1-allyl tetrabenzyl glucopyranose through a sequence of simple functional group transformations. The hydroxylation of olefins in OsO_4, the reduction of ester to aldehyde by DIBALH and, finally, global deprotection of benzyl ether, led to the manufacture of a mixture of four separable diastereomers. It must be noted here that all the *C*-disaccharides produced possess the pyran-pyran combination, two of which are L-configured [1→6]-disaccharides.[14l]



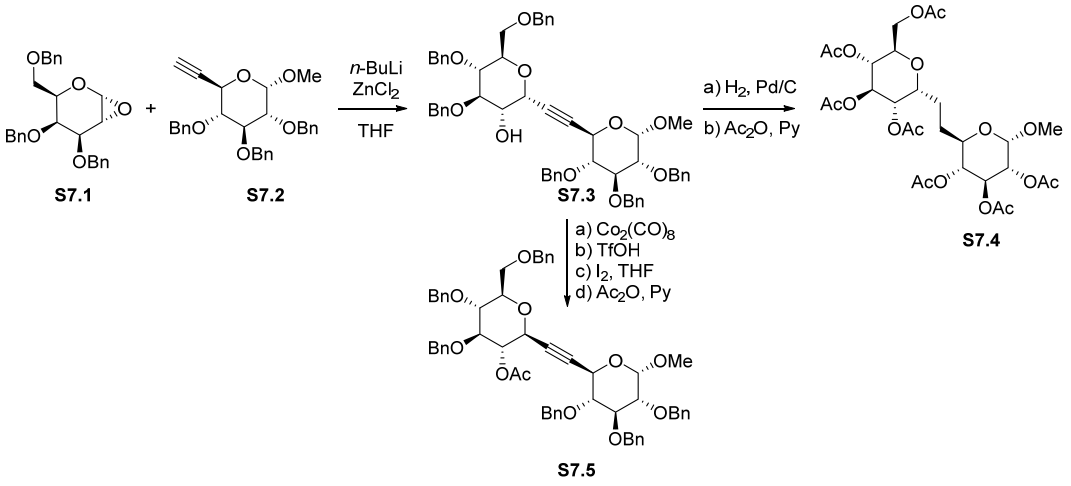
Scheme S2.5. Oxidation-reduction approach for [1→6]-linked *C*-disaccharides

Dondoni's Synthesis of [1→6]-Linked *C*-Disaccharides (1997): The Wittig reaction has been pretty well exploited by Dondoni in the context of *C*-oligosaccharide synthesis. The synthesis of *α*- and *β*-D-[1→6]-*C*-disaccharides from formyl *C*-glycofuranosides, pyranosides with gluco- and galactopyranose 6-phosphoranes was thoroughly exploited. The protected *C*-disaccharides with olefin at the centre obtained by the Wittig reaction were subsequently reduced undercatalytic hydrogenation method. Various pyran-pyran and pyran-furan combinations of [1→6]-linked *C*-disaccharides were reported.[13g]



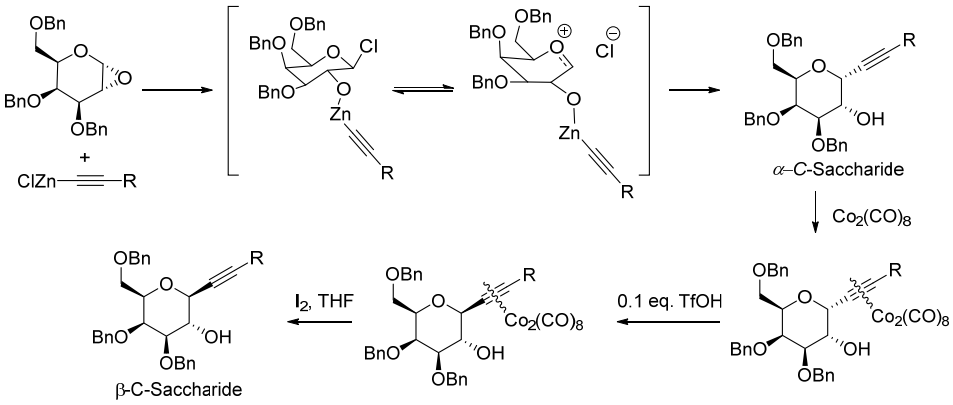
Scheme S2.6. Wittig olefination for [1→6]-linked *C*-disaccharides

Boom's Synthesis of [1→6]-Linked *C*-Disaccharides (1997): In the year 1997, Boom and co-workers reportedly synthesized the *α*-*C*-(alkynyl)-glycosides *via* the ring-opening of *α*-[1→2]-anhydrosugar by C6 ethynyl glucopyranose. The alkynyl derivative was lithiated with *n*-butyl lithium followed by addition to anhydrosugar in the presence of zinc chloride, and proceeded with retention of configuration to produce the *α*-anomer. The complete catalytic hydrogenation produced the *α*-*C*-disaccharide. However, the anomeric centre of the *α*-*C*-(alkynyl)-glycosides was inverted by the coordination with octacarbonyldicobalt and subsequent treatment with 0.1 equivalent of triflic acid followed by iodine. In this way both *α*- and *β*-[1→6]-linked *C*-disaccharides with pyran-pyran combination were synthesized.[14q]



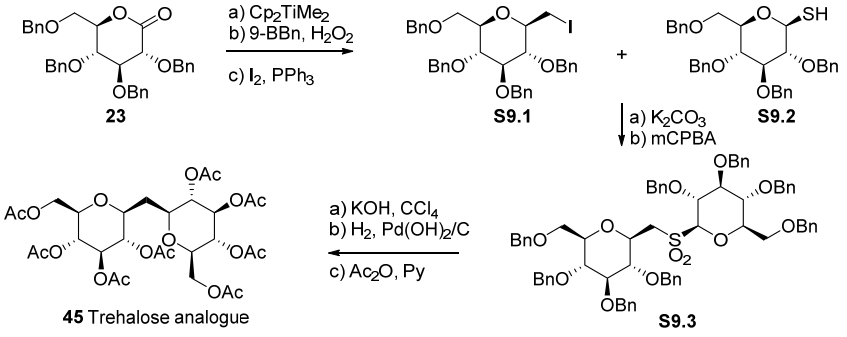
Scheme S2.7. Nucleophilic epoxide opening approach for [1→6]-linked *C*-disaccharides

The retention of configuration is believed to proceed *via* the formation of alkynyl zinc chloride which opens the epoxide after zinc-oxygen coordination. The ion-pair mechanism advances through a concerted manner to produce the *α*-anomer. The conversion of *α*-anomer to the thermodynamically stable *β*-anomer was facilitated by a Bronsted acid mediated ring opening of alkynyl cobalt.



Scheme S2.8. Mechanism for the anomeric selectivity

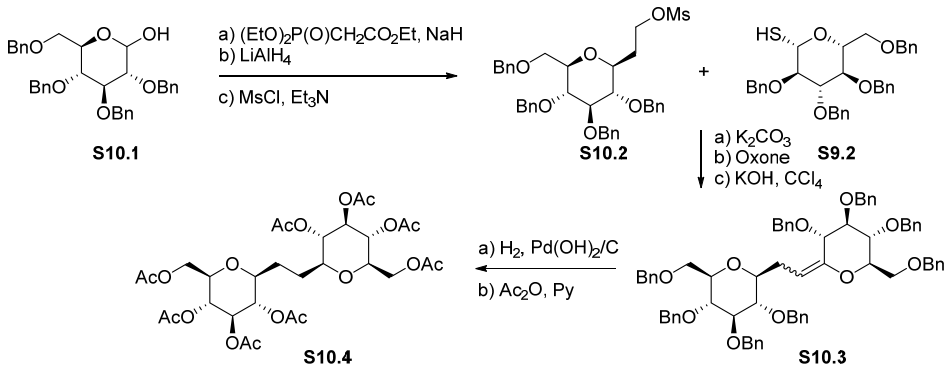
Taylor's Synthesis of [1→1]-, [1→6]-Linked *C*-Disaccharides (1999): Richard J. K. Taylor and co-workers focused on the use of Ramberg-Backlund rearrangement of *S*-glycoside dioxides in the synthesis of *C*-trehalose, a higher homologue of *C*-trehalose, and methyl *C*-gentiobioside. The trehalose analogue synthesis started with the known *gluco*-configured lactone. The lactone was converted to its methylene iodide by simple organic transformations such as Tebbe olefination, hydroboration-oxidation and iodination. The coupling of thiol and alkyl iodide was carried out in the presence of K_2CO_3, and successive oxidation with *m*-chloroperbenzoic acid produced the Ramberg-Backlund rearrangement precursor. The treatment of mineral base, potassium hydroxide followed by hydrogenation and peracetylation furnished the acetylated form of *β*,*β*-linked [1→1]-*C*-disaccharide.[15h]



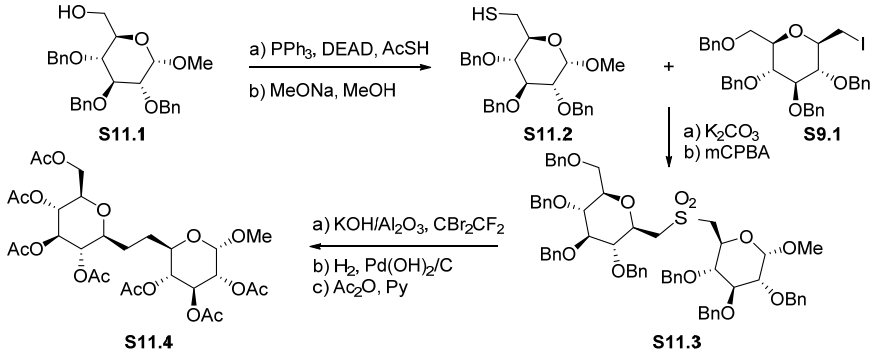
Scheme S2.9. Trehalose analogues synthesis

Similarly, the synthesis of the higher homologue of *C*-trehalose analogue (Scheme S2.10) and methyl *C*-gentiobioside (Scheme S2.11) were carried out by employing the same analogy. The known *gluco*-lactol and 6-hydroxy free methyl glucopyranoside have been used as starting

materials for these vital syntheses. The former deals with the synthesis of a [1→1]-linked homologue disaccharides, whereas later [1→6]-linked disaccharides have been synthesized. It is noteworthy to say here that the synthesis is a general scheme for the pyran-pyran combination *C*-disaccharide.



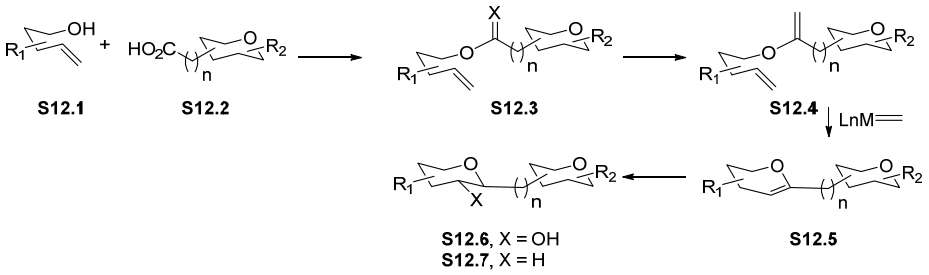
Scheme S2.10. Synthesis of homologue of *C*-trehalose analogue



Scheme S2.11. Synthesis of analogue of methyl *C*-gentiobioside

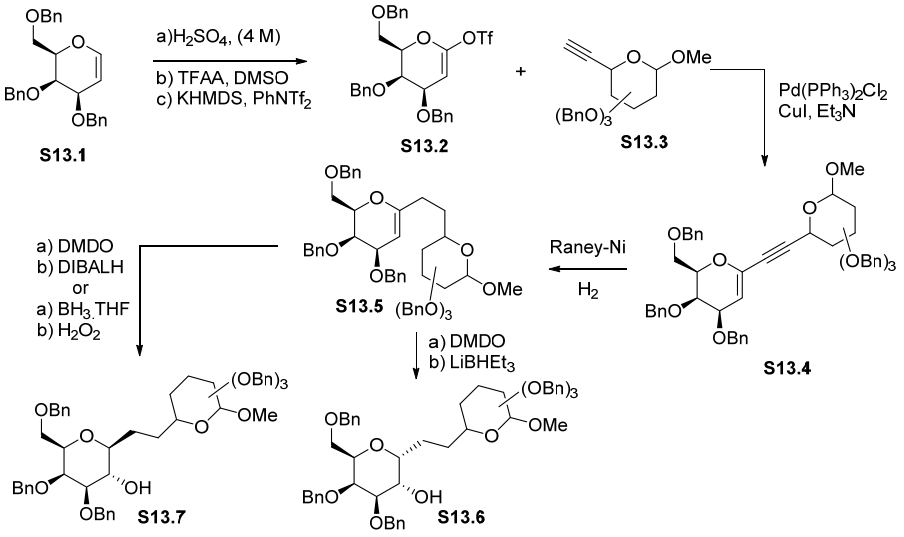
Postema's Unified Approach to all possible linked *C*-disaccharides (2001): At the advent of 21th century, a new synthetic technique was handsomely introduced by Postema for the synthesis of *C*-disaccharides with all possible linkages. This is the first ever general report to address this concern. Keck allylation and ring-closing metathesis (RCM) are the key transformations employed in this regard. The RCM was carried with the Grubb's 2nd generation and Shrock's catalysts. At the first observation, the yield was substantially low (41%) in cyclization, which is because of the decomposition of the product during purification, but this problem was solved later by using the RCM and hydroboration-oxidation in one pot (64%), one after other. This approach started with the esterification of a suitable carbohydrate-based acid **S12.2** with olefin

alcohol **S12.1** and subsequent methylenation of the ester and RCM to give the glycal **S12.5**. The functionalization of the double bond produced the *β*-*C*-disaccharides **S12.6** or **S12.7**.[11g]



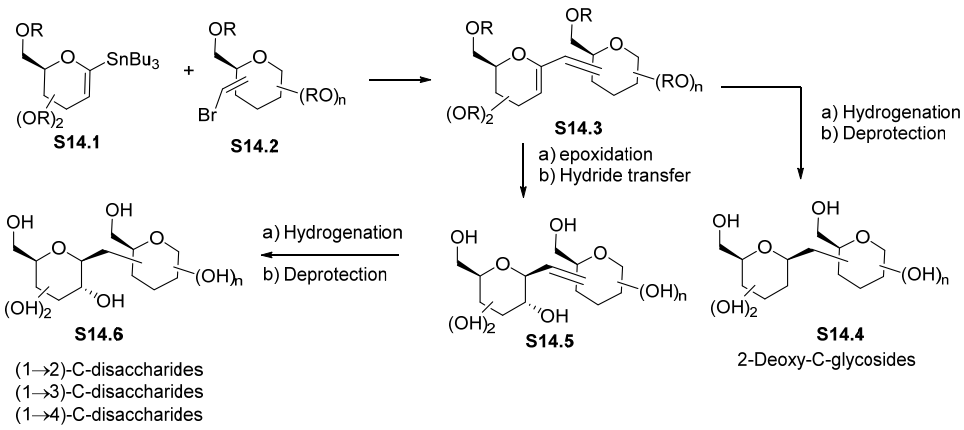
Scheme S2.12. RCM approach for all possible linked *C*-disaccharides

Werz's 1st Approach for the Synthesis of [1→6]-Linked *C*-Disaccharide (2010): In 2010, Werz and co-workers presented a Pd-catalyzed Sonogashira-Hagihara reaction for the synthesis of both *α*, and *β*-[1→6]-linked *C*-disaccharides by the coupling of 1-iodo- or 1-triflato-glycals with alkynyl glycosides. The formed triple bond was reduced selectively in the presence of Raney nickel and hydrogen. To install the native hydroxyl group at the 2-position, the oxygenations were done in face-selective fashion which, in turn, actually generated the *α*-, and *β*-anomers. The oxygenations were generally planned through two step processes, involving epoxidation with DMDO followed by nucleophilic reduction either with DIBALH or $LiBHEt_3$. The DIBALH led to the formation of the *β*-anomer, whereas $LiBHEt_3$ ended with the *α*-anomer. Other methods included the hydroboration and oxidation to furnish the *β*-product. A number of *C*-disaccharides were illustrated by varying both the glycal (D-glucose, D-mannose, D-galactose derivatives) and alkyne parts (D-glucose, D-mannose, D-galactose derivatives). This coupling method emphasized the synthesis of only pyran-pyran combination disaccharides.[12b]



Scheme S2.13. Sonogashira-Hagihara approach for [1→6]-linked *C*-disaccharide

Werz's 2nd Approach for the Synthesis of 2-Deoxy-*C*-glycosides and [1→2]-, [1→3]-, and [1→4]-Linked *C*-disaccharide (2013): This 2nd Generation approach of Werz was fairly similar to the 1st Generation approach except that the Sonogashira coupling has been now replaced with a Stille coupling [change of the glycal (tributyltin instead of triflato or iodo group) and vinyl bromide instead of alkyne]. The stannyl glycals and exocyclic bromoolefins were rapidly accessed from the corresponding precursors. The present Stille coupling strategy appeared to be more efficient and flexible than the first strategy, as it assures more possible linked products. On the other hand, this method repeatedly used the same oxidation-reduction strategy developed during the 1st method. However, both the approaches are limited to the synthesis of *C*-disaccharides with a pyran-pyran combination. No pyran-furan or furan-furan combination of *C*-disaccharides was indicated.[12a]



Scheme S2.14. Stille coupling for various *C*-disaccharides

RESULT AND DISCUSSION

Carbohydrates are an important class of biomolecules that play a crucial role in various biological processes. Inflammation, intercellular and host-pathogen recognition are some of the key biological process, to name a few, which are mediated by carbohydrate epitopes. Glycosidases and glycosyl transferases are two important classes of enzymes that are responsible for the synthesis and manipulation of complex carbohydrates that have been identified as potential targets for developing new drugs for various types of diseases.[6] Thus, the development of carbohydrate analogues which are stable towards these enzymes has multi-faceted advantages. The *C*-glycosides/*C*-saccharides, which entail methylene substitution for the anomeric oxygen, are isosteric mimics of their *O*-glycoside counterparts that offer a great deal of stability without substantial conformational amendment. The *C*-disaccharides, also known as pseudodisaccharides, attracted a great deal of attention from a synthetic as well as biological point of view because of their hydrolytic stability and potent inhibitory properties against enzymes such as disaccharidases of the digestive track. Some analogues have proved to be of use in the therapeutic strategies for the treatment of cancer, AIDS and diabetes, which clearly indicate the need for the *C*-disaccharides.

Our attention on the *C*-disaccharides synthesis has been drawn while dealing with the synthesis of Aflastatin A.[16] The alkynone-cycloisomerization has been employed as the key reaction for the synthesis of the *C*-glycosidic unit present in this natural product. During our model studies, we have found that the intermediate glycals resulting from the alkynol cycloisomerization are unstable and hydrolyze readily to the corresponding hemiacetals, if proper care has not been taken. Taken together with the well-established Kishi's strategy[14–15] for the synthesis of *C*-glycosides that we have discussed earlier, we have reasoned that a combination of metal-catalyzed alkynol-cycloisomerization/Et_3SiH-$BF_3 \cdot Et_2O$ induced reductive cleavage of intermediate acetals[17] in one-pot could provide a simple approach for the synthesis of *C*-disaccharides. We have come up with this idea while designing a retrosynthetic pathway for the recently isolated complex natural product Zooxanthellamide D (ZAD-D).[18]

Zooxanthellamide D was isolated by Ojika in 2007 from a cultured marine microalgae i.e. dinoflagellate of the genus *Symbiodinium*. It is a long-chain polyhydroxy polyene amide having a C_{22}-acid part and a C_{32}-amine part, decorated with six isolated butadiene chromophores and three tetrahydropyran rings. ZAD-D showed moderate cytotoxicity against two human tumor cell lines–A431 vulval-derived epidermoid carcinoma and Nakata oral squamous cell carcinoma. ZAD-D was characterized by the presence of a 2,2'-bipyran moiety having D-*gluco* and D-*ribo*

configurations. The relative stereochemistry was assigned partly by 1D and 2D NMR studies. The *nOe* correlations in ROESY helped to find the relative spatial arrangements of the hydroxyl functionality in the C(11)–C(21) fragment containing the tetrahydropyran rings. It is the only observation of the presence of a perhydro 2,2'-bipyran system in all of the Zooxanthellamides. This fact, taken together with our current interest on *C*-glycosides synthesis, has driven us to find a novel protocol for the construction of this challenging C(11)–C(21) bis-pyran core of the ZAD-D.

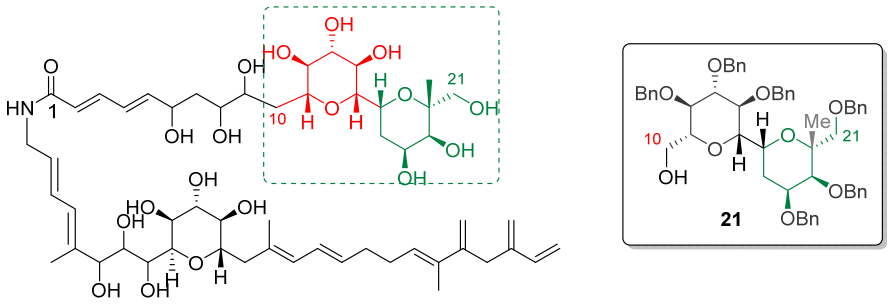
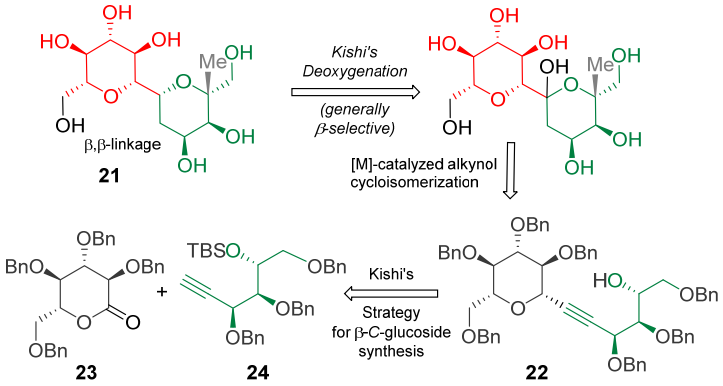


Figure 2.1. The structure of Zooxanthellamide D and the targeted key 2,2'-bipyran unit

As shown in Figure 2.1, we have intended to develop a protocol for the synthesis of the 2,2'-bipyran **21** by projecting a two-step sequence that comprises the cycloisomerization of alkynol **22** and Kishi's deoxygenation. In the field of alkynol cycloisomerization, the role of palladium and gold complexes is exceptionally significant. This is because palladium and gold tolerate a wide spectrum of functional groups and facilitate unique transformations that are difficult to accomplish by classical methods and importantly, they proceed under mild reaction conditions. The total synthesis of Bryostatin 16 by Trost[19] is a notable example of functional group tolerance that used the gold catalyzed alkynol cycloisomerization technique for the synthesis of the tetrahydropyran unit.

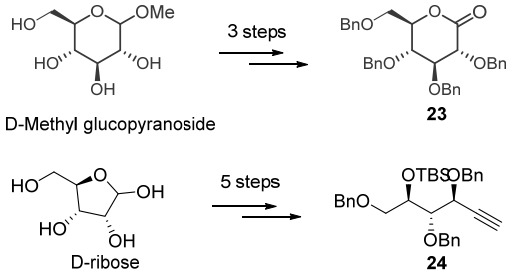
Coming to the synthesis of key alkynol **22**, having a pre-existing THP moiety that disposes the key alkynol, we admired Kishi's two-stage strategy of *C*-glycoside synthesis involving the addition of a sugar alkyne to a furano/pyrano lactone and subsequent reductive deoxygenation. The alkyne was adorned with a secondary alcohol derived from the D-ribose and likewise D-*gluco*-configured lactone was elegantly selected for the union of the key fragment.



Scheme 2.1. The intended approach for the 2,2'-bipyran **21**

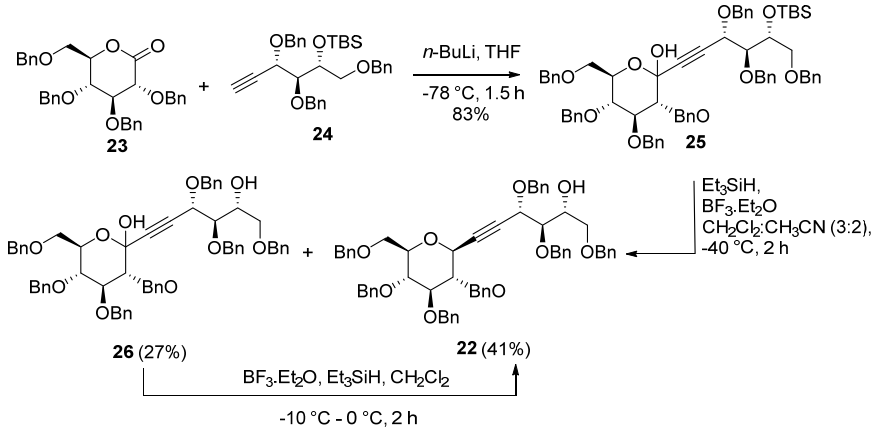
After strategizing the key transformations, the next important concern is about the regioselectivity of the alkynol cycloisomerization. Two possible modes of ring closures 5-*exo*-dig and 6-*endo*-dig are possible. However, according to Baldwin's Rule,[20] the mode of cyclization not only depends on the number of atoms in the newly formed ring but the electronic and stereochemical factors of the surrounding substituents play a decisive role in determining the outcome. The proposed alkynol **22** is highly rich in oxygenated functionality. Based upon our previous experience with sugar alkynol cycloisomerization and especially the exclusive 6-*endo*-dig cyclization that we have noticed in the synthesis of the *C*-glycoside portion of Aflastatin A, we were optimistic about the cyclization of **22** in a desired fashion. When exhaustive dry conditions are not employed for the cyclization, the resulting enol ether was expected to hydrolyze to a hemiacetals, the Kishi's deoxygenation (using $Et_3SiH/BF_3{\cdot}Et_2O$) of which is expected to deliver the *C*-glycoside with the desired *β*-selectivity.[11o,14m,14p]

Synthesis of the Key Alkynol: Having set the objective of synthesizing **21**, our journey in this context started with the preparation of the known intermediates **23**[13g] and **24**[16b] from their respective starting materials D-glucose and D-ribose respectively. The lactone **23** was synthesized in 3 steps from methyl glucopyranoside following the established procedures. Similarly, the ribose derived alkynol **24** was synthesized in 5 steps from the D-ribose following the procedure developed by Vasella's group.[16d]



Scheme 2.2. Known reactive intermediates

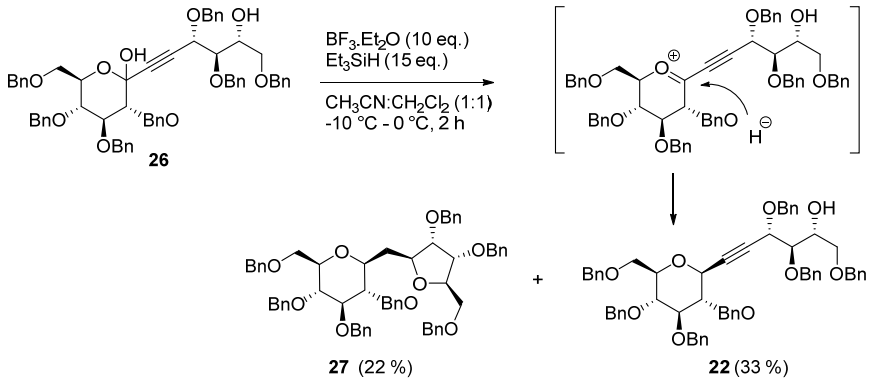
Next, the lithiation of the D-ribose derived alkyne **24** in THF at –78 °C followed by addition of D-glucose derived lactone **23** generated an inseparable mixture of hemiacetal **25** in 83% yield. The proton NMR peaks of both anomers were so overlapped that they were unable to distinguish except the missing of the alkyne doublet proton at δ 2.42. As it happened, each peak became double in the ^{13}C NMR. The mass spectrometry thus confirmed the required mass with two peaks at 1091 (M+Na) and 1107 (M+K). It was then subjected for the reductive-deoxygenation by using 5 eq. triethylsilane and 2 eq. of $BF_3 \cdot Et_2O$ at –40 °C in CH_2Cl_2 and CH_3CN (3:2 ratio). During reductive deoxygenation, the TBS ether was also found to cleave to furnish the required alkynol **22** which is β-configured (41%) along with an inseparable mixture of diol **25** (27%) in substantial amounts.



Scheme 2.3. Synthesis of alkynol **22**

Later the diol **26** was re-deoxygenated at a little elevated temperature (–10 to 0 °C) by using excess of triethylsilane (15 eq.) and $BF_3 \cdot Et_2O$ (10 eq.) to achieve the alkynol **22** exclusively. The deoxygenated product was completely characterized by the physical and spectroscopic techniques. The appearance of a doublet at δ 5.10 with a coupling constant J =

10.5 Hz corresponding to an anomeric proton and 35 protons at the aromatic region in ^{1}H NMR spectrum of **22** were the initial indications for the synthesis of alkynol. Similarly, the presence of 19 non aromatic carbons from δ 68.6 to 85.9 including two alkyne carbons at δ 82.0 and 84.9 and seven phenyl carbon singlets of benzyl groups in the ^{13}C NMR spectrum of **22** confirmed the alkynol structure. The large coupling constant of the anomeric proton indicated the β-disaccharide formation. Furthermore, HRMS supported the expected structure.



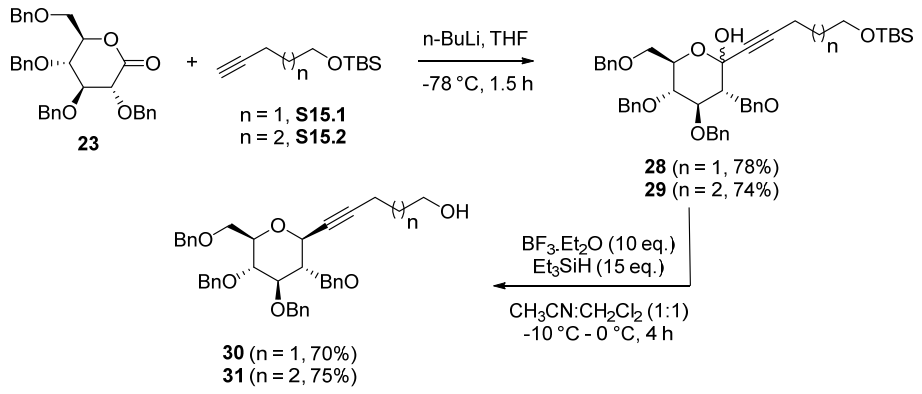
Scheme 2.4. The outcome of Kishi's deoxygenation of hemiacetal **26** in the presence of excess reagents

When examining the possibility of getting exclusively **22** from the hemiacetal **26** at a little elevated temperature (–10 to 0 °C) in the presence of excess Lewis acid (10 eq.) and excess reducing agent (15 eq.), quite surprisingly, a 22% of a novel product **27** was liberated along with the required alkynol **22** (33 %). Curiously, when analyzed, at the first instant, it seemed to be a novel disaccharide having a challenging pyran/fuan combination with [1→1]-linkage. The absence of an alkyne carbon C–C triple bond (known from ^{13}C NMR) and the presence of a newly formed methylene group –CH_2– (known from both ^{1}H &^{13}C NMR) strongly indicated a new discovery. Additionally, the HRMS validated the suspected structure as a novel disaccharide.

This unexpected result probably occurred due to the cycloisomerization. We hypothesized that the attack of the secondary alcohol to the polarized alkyne in the presence of Lewis acid ($BF_3.Et_2O$) is the origin for the *exo*-enol ether. Then, the unstable exocyclic enol ether might have hydrolyzed in the presence of trace water molecules to hemiketals followed by its deoxygenation. The water was expected as a contaminant during the $BF_3.Et_2O$ addition.

Without much thinking about its mechanism, we tried to explore the validity of the methodology for other substrates.

For that the *C*-glycosyl donor was replaced by TBS protected hex-5-yn-1-ol and pent-4-yn-1-ol and the same reaction sequence with the tetrabenzyl D-glucolactone **23** was repeated. The nucleophilic addition reactions were proceeded smoothly to provide the requisite hemiacetals **28** and **29**. Like the previous reaction, the results were concurrent with having inseparable anomeric mixtures. After complete characterization, they were made ready to put in the similar reaction conditions as described above. The deoxygenation of hemiacetals **28** and **29** was performed with excess Lewis acid and excess reducing agent. Unfortunately, we could not realize any sign of cyclized product after repeating and varying the reaction conditions (such as temperature, time, amount of acid and reducing agent). The alkynol products **30** and **31** were seen to be intact as such even after the use of 20 eq. of acid, elevated temperature up to 25 °C, and time up to 3 days.

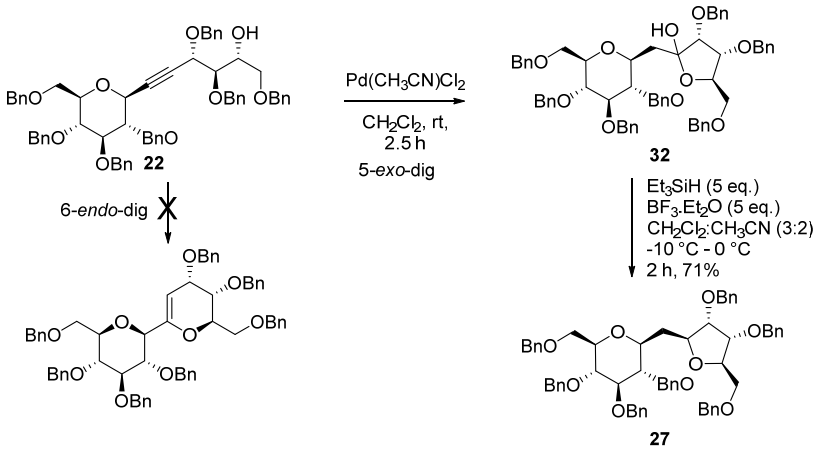


Scheme 2.5. Synthesis of pentyne and hexyne derived alkynol

Without any ray of hope, this unusual transformation (Lewis acid catalysed cycloisomerization) was stopped for some time and focus was shifted on the main objective of conducting the metal-catalyzed alkynol cycloisomerization of **22** and subsequent Kishi's deoxygenation.

Attempts to Construct the Bipyran Moiety through Cycloisomerization: Initially, the cycloisomerization of the sugar alkynol was intended to be pursued with transition metal catalysis such as with palladium, gold and platinum complexes. Considering the availability and cost, the most moisture stable, cheap and popular palladium complexes such as $Pd(CH_3CN)_2Cl_2$

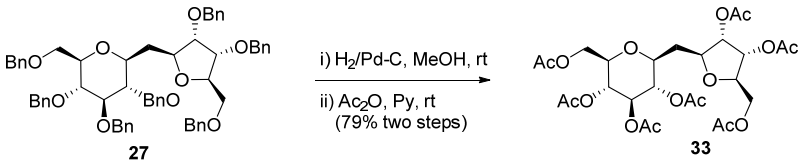
and $Pd(PhCN)_2Cl_2$ were chosen. This is because the electrophilic Pd(II) complexes generally bind to the *sp* hybridized carbon of alkyne to set up η^2-electrophilic complexes that are facile to nucleophilic attack. Towards the cycloisomerization, the alkynol **22** was added to the $Pd(CH_3CN)_2Cl_2$ in CH_2Cl_2 at room temperature for 2.5 h. The reaction underwent efficiently and probably through a low energy transient species which was, however, not an interest of choice at the beginning. The conclusion was ruined with a hemiacetals **32** as a mixture of anomers.



Scheme 2.6. Attempt to construct the 2,2'-bipyran moiety

The structure of the hemiacetal **32** could not be detailed at the beginning because of its complex proton NMR pattern. It was looking like a mixture of products. In order to understand its character, it was submitted for mass spectrometry. The HRMS data confirmed it as a water added product. A multiplet for the methylene $-CH_2-$ protons was seen to resonate at the high field region of the ^1H NMR spectrum of hemiacetals **32**. Therefore, the suspect went towards the 5-*exo*-dig cyclization of alkyne by the alcohol. Furthermore, the anomeric carbon peaks of the newly generated stereo-center appeared at δ 103.1 and 106.9 in the ^{13}C NMR spectrum of hemiacetals **32**. The hemiacetal was subjected for deoxygenation in order to gain more information regarding the nature of cyclization. The reduction led to a benzyl protected disaccharide **27** (which was obtained as a side product during the deoxygenation to prepare the alkynol under forced conditions) as a sole product under the established conditions. This involves addition of triethylsilane (5 eq.) followed by $BF_3.Et_2O$ (5 eq.) to the hemiketals **32** in CH_2Cl_2:CH_3CN (3:2) at –10 °C for 2 h. However, a little change in the ratio of addition of acid and reducing agent or change in temperature from 0 to –40 °C would not affect the yield (71%) of the reaction much.

The obtained benzyl protected [1→1]-linked *C*-disaccharide **27** connected by a methyl –CH_2– group is a rare example of its kind. There are very few methods found in the literature for particular ring synthesis (6-membered). Those are very limited and no general method is available. However, this was characterized easily by both ^{1}H and ^{13}C NMR and of course HRMS. Evidently, the furan ring was formed as four doublet peaks observed in the lower field region (δ 80.8, 81.2, 82.4, and 87.2) of the ^{13}C NMR spectrum of **27**. Obviously, the methylene group –CH_2– was rationalized from both ^{1}H and ^{13}C NMR. In order to make the NMR spectra less complicated, it was further converted to its peracetate **33** following a sequence of hydrogenation of the benzyl ethers with molecular hydrogen in the presence of Pd-C and subsequent acetylation with acetic anhydride and pyridine.



Scheme 2.7. Peracetylation of *C*-disaccharide

The final heptaacetate **33** that resulted was the simplified version of the heptabenzylated *C*-disaccharide **27**. The important aspect in carbohydrate chemistry is always to know the relative stereochemistry between the substituents and, of course, the linkages, as they matter in determining the interaction with the pathogens or enzyme. For that reason, the carbohydrate chemist usually inquires into the nature of the anomer and the path followed by the reactive intermediates after glycosylation. Hence, obviously, we opted to analyze the configuration of the newly born stereocenter with the aid of 2D NMR method. The n*O*e technique was then exploited to establish the relative configuration of the anomeric protons (C1**H** and C1'**H**). As expected, there was a strong n*O*e interaction observed between the two protons to confirm a β-linkage. The present disaccharide was elucidated as a β, β-linked *C*-disaccharide containing a pyran-furan system.

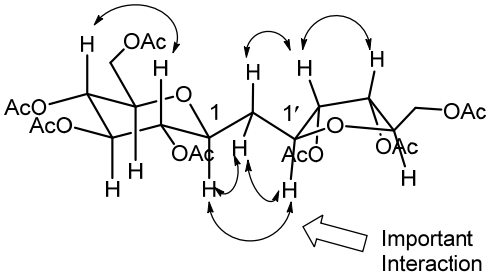


Figure 2.2. n*O*e interactions

Mechanism for the Origin of Stereoselectivity

The oxocarbenium species of both 5- and 6-membered ring systems exhibit similar selectivity pattern during nucleophilic addition. It is really tough to find the stereochemical models for 5-membered systems as the conformational inter-conversions are faster than six-membered rings. However, attack of a nucleophile on the oxocarbenium species of the conformationally constrained 5-membered ring generally occurred from inside of the envelope selectively to form a staggered product.[21]

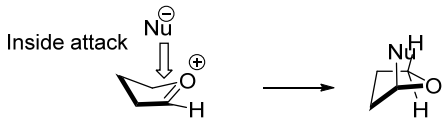


Figure 2.3. Approach of a nucleophile towards five-membered ring

The inside attack normally avoids most of the gauche interactions. However, this does not always taken place as it depends on the bulkiness of the substituent pattern around different positions in the ring. In the present context, the C-2 position is mono substituted and its stereo-electronic nature actually contributes to the selectivity. In Figure 2.4, there are two possible transition states (conformers) **A** and **B** having envelope geometry set for hydride attacks that uphold the equilibrium. The transient species **A** is addressed with one pseudoequitorial and two pseudoaxial benzyloxy groups. On the other hand, the transient species **B** possesses two pseudoequitorial and one pseudoaxialbenzyloxy groups. If the steric factor is taken to account, probably, the oxocarbenium ion **B** would be the major species in the equilibrium. However in reality, the situation is different. The stability of the conformer **A** is enhanced by hyperconjugation. Hence, the overlap of the pseudoaxial σ_{C-H} bond at C2 with the vacant orbital of the oxocarbenium ion (probably π^*) is the important parameter that dominates. This electronic

interaction leads to the attack of a hydride nucleophile pseudoaxially at the concave surface of the oxocarbenium ion to produce a *β*-configured disaccharide.

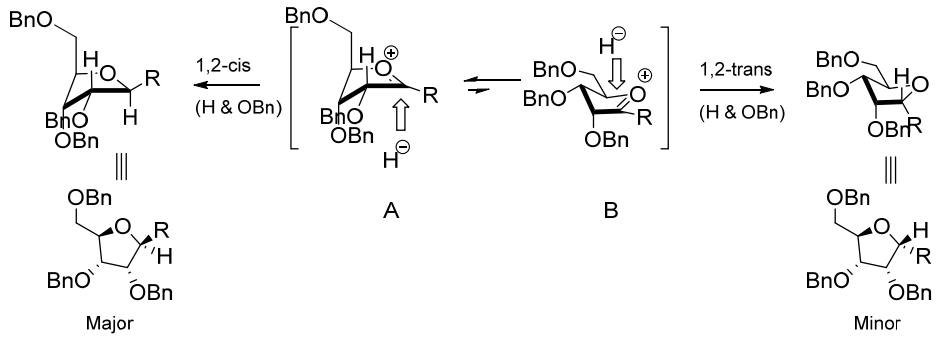


Figure 2.4. Mechanism of deoxygenation

On the other hand, as an inside attack on the pseudoaxial conformer **B** is destabilized by a gauche interaction and provides the least selectivity for the 1,2-trans product. In reality, we never observed any 1,2-trans product (H & OBn). In other words, no *α*-linked product was likely to be formed during the deoxygenation.

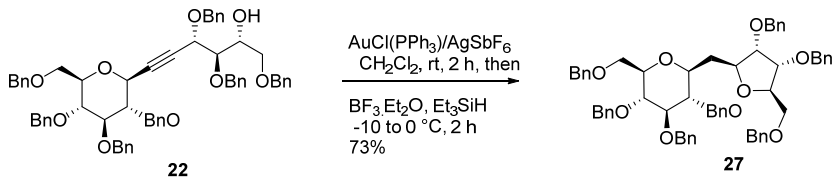
Catalyst Screening for Alkynol Cycloisomerization: So far, the discussion has been about the synthesis of an undesired product liberated exclusively during the cycloisomerization which, of course, was not our primary concern. Therefore, in order to set a proper catalytic system for the concerned cyclization, different palladium complexes were attempted at the beginning. The results were concurrent with the preceding result (i.e. furan with a *β*-linkage) with all palladium complexes screened except the yield. The $Pd(CH_3CN)_2Cl_2$ gave the best 5-*exo*-dig results in comparison to $Pd(OAc)_2$, and $Pd(PhCN)_2Cl_2$ in terms of yield. With no knowledge about the electronic influence of the ring system and/or the substituent pattern (steric factor), we again proceeded to investigate the outcome with other acetylenophilic catalysts. By the way, the front runners next to palladium were the gold catalysts. The Au(III) and Au(I) were selected for the judgment. The treatment of the same alkynol **22** with $AuBr_3$ and $AuCl_3$ complexes ended with complex reaction mixtures whereas a reactive gold(I)-antimony complex generated *in situ* from the $AuCl(PPh_3)/AgSbF_6$ in CH_2Cl_2 repeated the past result (5-*exo*-dig fashion) with better yield. Nevertheless, it must be mentioned here that the $AuCl(PPh_3)/AgSbF_6$ catalytic system is the best for the alkynol cycloisomerization in the current circumstance (Table 2.1).

Sr. No.	Catalyst	Time	%Yield
1	$Pd(CH_3CN)_2Cl_2$	2 h	68%
2	$Pd(PhCN)_2Cl_2$	2.5 h	61%
3	$Pd(OAc)_2$	3 h	46%
4	$AuBr_3$	0.5 h	--
5	$AuCl_3$	0.5 h	--
6	$AuCl(PPh_3)/AgSbF_6$	2 h	77%

Table 2.1. Screening of different catalyst for cycloisomerization

Realization of One-Pot Alkynol Cycloisomerization-Deoxygenation as a New *C*-glycoside Synthetic Tool:

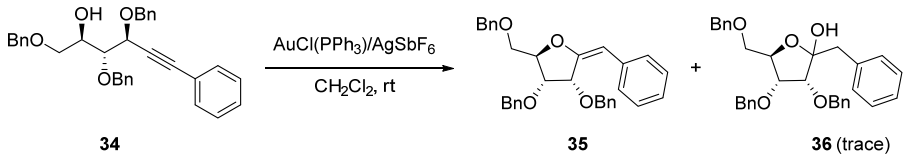
At this point, we took a pause to think and recap the whole story– the tried to accumulate. A new ray of hope had entered at some point in our minds. We figured out our incapability to achieve the target. But at the same time, a new destiny had appeared. We realized the obtained one carbon linked disaccharide as a serendipitous discovery. The literature survey then revealed that there is no general method available for the [1→1]-linked *C*-disaccharide synthesis. With this idea in mind, we tried to bring some change in the synthetic strategy and follow the step economy rule so as to increase the efficiency. To do so, the cycloisomerization and deoxygenation reactions were performed in one pot one after the other (Scheme 2.8).



Scheme 2.8. One-pot cycloisomerization and deoxygenation

The reactions progressed smoothly. However, there was never seen any significant improvement in yield, though it reduced somewhat the time and labor. The optimum conditions involve addition of $AuCl(PPh_3)$ catalyst followed by $AgSbF_6$ to the alkynol in CH_2Cl_2, with stirring at rt for 2 h. The reaction was protected with aluminum foil to avoid light. After complete consumption of the starting material, the reaction mixture was cooled to –10 °C. Thereafter, Et_3SiH followed by $BF_3.Et_2O$ was charged and the system was stirred for additional 2 h. We must note a point here that the hydrolysis of the exo-enol ether took place due to the moisture content because of the highly hygroscopic silver co-catalyst or contamination with

moisture during catalyst addition. The reaction in ordinary CH_2Cl_2 also provided the same result. However, the rate of hydrolysis varies from substrate to substrate. Like the above substrate, some of the substrates were facile to hydrolysis even after strict dry reaction conditions were maintained. In some occasions, the un-hydrolyzed *exo*-enol ethers were captured with the hydrolyzed product. The conjugation of phenyl ring with the enol ether led to the gain of extra stability in the preparation of benzyl *C*-disaccharides. Alkynol for this purpose was obtained from the Sonogashira reaction of the *ribo*-derived alkyne and iodo benzene which furnished a mixture of un-hydrolyzed and hydrolyzed (trace) product.



Scheme 2.9. Recovery of stable enol-ether along with hydrolyzed product

We already alleged that these kinds of *C*-disaccharide synthesis are scarce in literature. By understanding the importance, the problem associated in synthesis and moreover, their natural abundance in natural products, an effort has been taken to generalize.

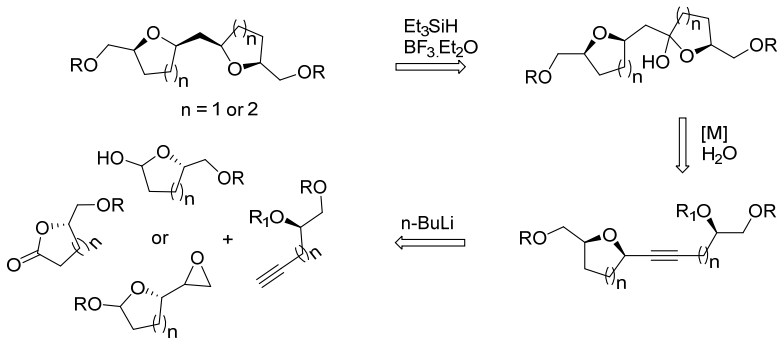
Importance of the Present Protocol

The current protocol accommodates an intramolecular *C*-glycoside synthesis category. It emphasizes the importance of transition metal catalysis and proves its power by establishing a novel synthetic strategy for one carbon *β,β*-linked C-glycoside analogues of non-reducing disaccharides. We set an alcohol as a nucleophile and alkyne as an electrophile in the effect of electrophilic Pd and Au catalysts to produce an ideal system for cycloisomerization. Gratifyingly, it worked completely in a regioselective fashion whereas the other major part of the methodology i.e. deoxygenation, concluded stereoselectively. The syntheses of the stable *C*-glycosidic mimics of oligosaccharides such as the *C*-disaccharides pose several challenges, such as pre functionalization of both the sugar units, the need for a reliable method for the coupling of the densely functionalized sugar units, as well as methods that address the desired anomeric configuration. Sinaÿ and Rouzaud have reported the first synthesis of a *C*-disaccharide in 1983. Since then, various approaches have been developed for the synthesis of C-disaccharides, which, in general, are target-specific and require specially designed building blocks. Methods that are

general, use simple building blocks and require minimal revision of the synthetic plan and/or starting materials are highly sought in the area of *C*-saccharides synthesis and some elegant approaches have been published recently.

A few reports have been acknowledged for the synthesis of a one carbon [1→1]-linked glucopyranose unit. However, there is no such report documented for their pyran-furan or furan-furan combination. We, therefore, deliberately tried to extend this novel protocol towards the missing *C*-disaccharides just by altering the electrophilic and nucleophilic components (Scheme 2.10). In order to see the validity of the methodology, three simple reaction approaches were selected to fuse the components to facilitate the key alkynols. For that, readily available lactone, lactol and epoxide were chosen as electrophilic components. In the same way, alkynes were derived from the respective D-ribose, D-arabinose, and D-galactose. The approaches for the synthesis of the key alkynols are:

a) addition of alkyne to lactone
b) addition of alkyne to lactol
c) addition of alkyne to epoxide

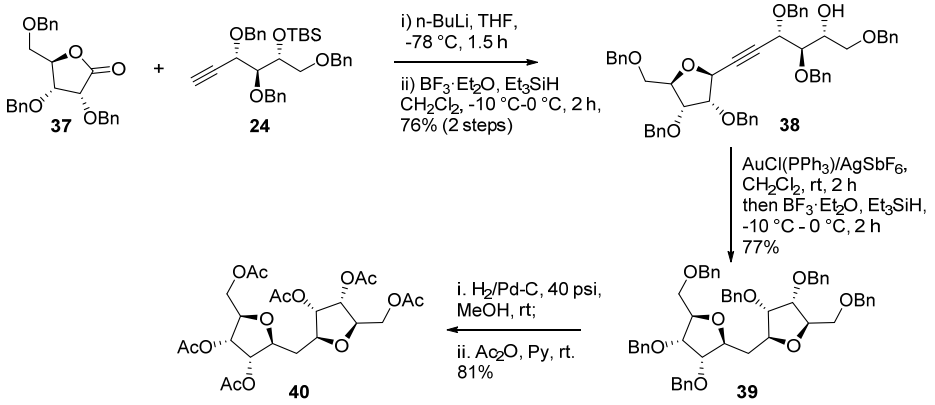


Scheme 2.10. Design of *C*-disaccharides

Both the first and second approaches were employed to solve the most challenging problem by synthesizing the [1→1]-linked *C*-glycoside analogues of the non-reducing disaccharides, whereas the third deals with the [1→6]-linked glycoside.

Addition of Alkyne to Lactone: This approach followed the Kishi's protocol, which involves the addition of a sugar alkyne to a D-furano/pyrano lactone and subsequent reductive deoxygenation to achieve the alkynol unit. Here, we demonstrated the real flexibility in terms of

ring size so that any of the sugar derived lactone and of alkynes of different chain lengths can be handled. For that, D-glucose and D-ribose derived lactone were taken initially as the primary electrophile whereas D-ribose and D-arabinose derived alkynes served as nucleophiles. The story of D-gluco-configured lactone **23** with D-ribose derived alkyne **24** has already been discussed. Thereafter, we introduced the addition of the known D-ribose derived lactone **37** and alkyne **24** like in the earlier discussion. This time, the lactone-alkyne added product was deoxygenated at elevated temperatures (–10 to 0 °C) to avoid the complications in the separation of the number of products. The same reaction sequences were followed to achieve a C_2-symmetric disaccharide **39**. Appearance of a characteristic peak at δ 1.71 in ^{1}HNMR as triplet with coupling constant (*J*) 6.6 Hz for two methylene protons –C**H$_2$**– confirmed the symmetry and the expected disaccharide. The methylene carbon –**C**H$_2$– was further confirmed from ^{13}CNMR: it resonated at δ 38.6 as triplet. As usual, the disaccharide protected as benzyl ether was transformed to its acetate form for clarifying the configuration. This is the only example of a **furan-furan** combination *C*-disaccharide having [1→1]-linkage.

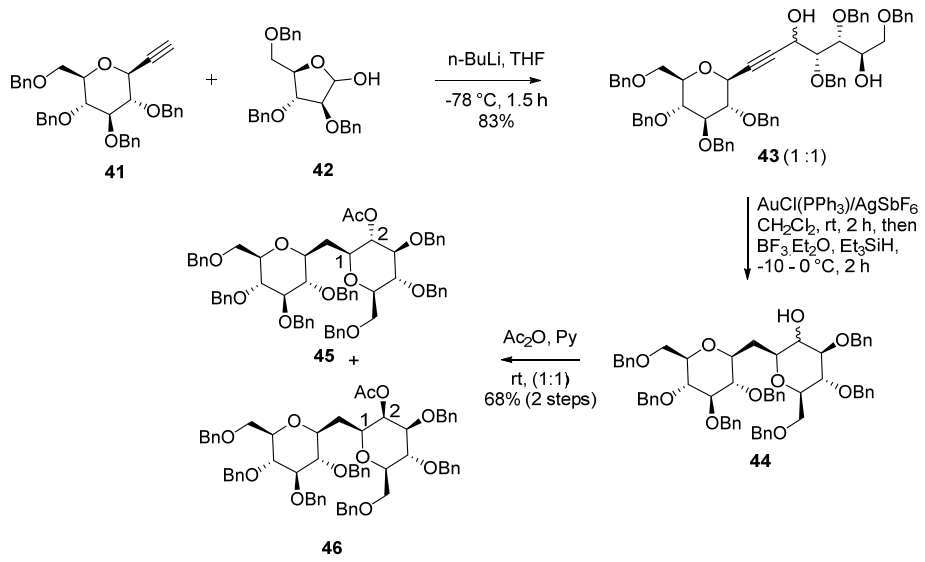


Scheme 2.11. Synthesis of C_2-Symmetric *C*-disaccharide

The methodology, however, is well suited when there is a change in the ring size of the electrophile (lactone). To check both the feasibility and stereo-electronic effect during deoxygenation, we modified the stereochemistry at the C3 position of the alkyne. A C3 inverted D-ribose alkyne (i.e. D-arabinose derived alkyne) was taken into consideration. Unlike the previous results, two disaccharides were obtained during the deoxygenation with the ratio β:α=2:3. The obtained β, β- and β, α-linkages could be explained by the envelope mechanism of

the oxocarbenium ion. However, the detail of this alkynol cycloisomerization is not a part of this thesis.

2nd Approach Comprising the Addition of Alkyne to Lactol[22a,22b] – Synthesis of Trehalose Analogue: Having designed a workable methodology, it was further extended for the [1→1]-linked *C*-disaccharides having a **pyran-pyran** unit. The similar units were previously reported by Martin using the Henry reaction, Taylor using the Ramberg-Backlund reaction, and Postema by the RCM. In the current work, we tailored a C1-ethynyl *β*-C-glucoside **41**[22c] with a D-tribenzylarabinolactol **42**[22d] at –78 °C in THF using *n*-BuLi as base to achieve a 1:1 inseparable mixture of alkynol **43** in 83% yield. The mixture was then set for the one-pot cycloisomerization-deoxygenation under standardized conditions. The benefit of this process was that, for instance, another inseparable diastereomeric mixture of *C*-disaccharides **44** was identified. For easy separation and recognition of the product obtained, the hydroxyl group in **44** was esterified with acetate and this, in turn, provided a good separation of the diastereomers and also a good splitting pattern of the characteristic protons in ^{1}H NMR and also distinguished both the C2 epimers **45** and **46**.



Scheme 2.12. Synthesis of Trehalose analogue **45**

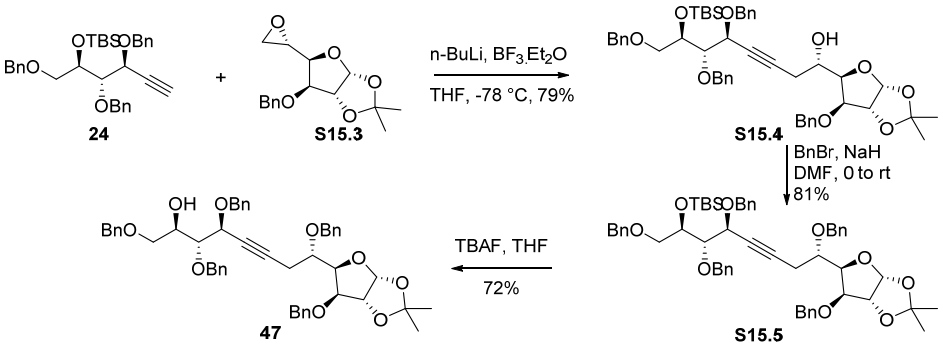
Although poor diastereoselectivity is the disadvantage of the methodology, it opened access to the synthesis of two epimers having [1→1]-linked *C*-disaccharides, one of which is a trehalose analogue **45**. These two epimers were easily distinguished from their coupling

constants at the C2–H. The C2–H in **45** has interacted axially with C1 and C3 axial protons, experiencing a similar spin environment leading to a triplet (J = 9.4 Hz). On the other hand, two equatorial-axial interactions furnished a doublet of doublet (J = 2.7, 2.8 Hz) for the C–H of **46**, which indicates that the former is a *β*-D-*gluco*-configured and the later is a *β*-*manno*-configured pyranoside.

The trehalose is an important non-reducing sugar having *α*[1→1]-linked *O*-disaccharide formed by two *α*-D-glucopyranose units. It is synthesized by fungi, bacteria, invertebrate animals (not by mammals), and plants. This is also synthesized by *M. tuberculosis* through three independent pathways and found in the outer portion of the mycobacterial cell envelope. Their cell envelope has so strong a permeability barrier that most of foreign substances like drugs and probes face difficulties in reaching the bacterial cytoplasm. Consequently, a suitable drug or probe is barely achieved. Davis and coworkers[23] have recently proposed a model that can be used as a probe to study the internal mechanism happening inside the cell of the *M. tuberculosis*. For that, they made the analogues of trehalose and labeled the same with Fluorescein Isothiocyanate (FITC-trehalose). By the way, there is no carbon analogue of trehalose tested to study the cell wall of the *M. tuberculosis* till to date. We believe that the present synthetic strategy will help to synthesize a variety of analogues and some among them may play a crucial role for studying the cell wall of the bacteria and ultimately the requisite drug could be developed.

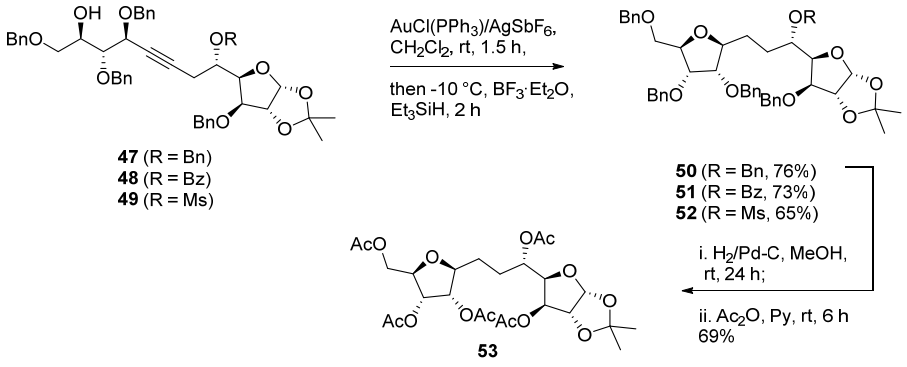
Addition of Alkyne to Epoxide:[24a] In order to predict whether this protocol is only limited to [1→1]-linked *C*-disaccharide or goes beyond that, the synthesis of [1→6]-linked *C*-disaccharides were focused upon thereafter. In nature, the [1→6]-linked *O*-polysaccharides in the form of amylopectin and glycogen are widely spread for the storage of energy. Literally, the number of methods for the synthesis of [1→6]-linked *C*-disaccharides is huge. As discussed earlier, Martin's nitro-aldol, Armstrong's oxidation-reduction, Dondoni's Wittig olefination, Boom's nucleophilic epoxide by alkyne, Taylor's Ramberg-Backlund, Postema's RCM, and Werz's Sonogashira-Hagihara approaches are the popular examples. The requisite alkynol for this purpose was planned to be synthesized *via* an epoxide-alkyne coupling. A 5,6-anhydrohexofuranose derivative was opted for as an epoxide partner having an *α*-geometry. The epoxide was synthesized in 6 steps from the D-glucose, which was earlier reported by our group in the Aflastatin fragment synthesis.[16] An acid catalyzed nucleophilic reaction was carried out between the known epoxide and the D-*ribo* derived alkyne **24** at –78 °C. At lower temperature,

the TBS protecting group survived under acidic conditions. The obtained alcohol was later subjected for benzyl protection with benzyl bromide and sodium hydride at room temperature. The cleavage of TBS ether in presence of TBAF or catalytic *p*-TSA in methanol furnished the requisite alkynol for [1→6]-linked *C*-disaccharides synthesis.



Scheme 2.13. Synthesis of alkynol for [1→6]-combination

Initially, the epoxide opened alcohol protected with benzyl ether **47,** was taken to test the feasibility of the reaction. The alkynol **47** was subjected for the one-pot cycloisomerization-deoxygenation to provide 76%. Without any trouble, it again concluded in the 5-*exo*-dig opening product **50**. The product **50** was rationalized easily by finding the four methylene protons –2C**H**$_2$– which resonated at δ 1.63–1.72 as multiplet in ^{1}HNMR spectrum. Their carbons resonated at δ 29.6 and 27.4 in the upper field region of the ^{13}CNMR spectrum. The ring size was confirmed by both the ^{1}H and ^{13}C NMR spectra, and the glycosidic bond (β-linked) was characterized by the n*O*e interactions from the 2D NMR after debenzylation followed by peracetylation.

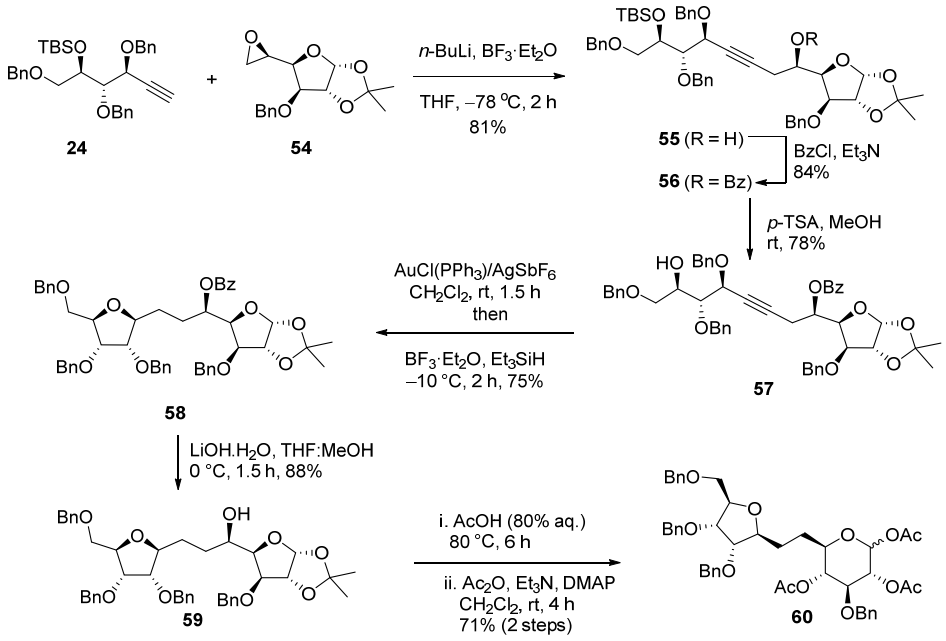


Scheme 2.14. Synthesis of *C*-disaccharide for [1→6]-combination

Next, the job was to check the regioselectivity with diverse protecting groups as well as their survival in the presence of different reactive species during the cycloisomerization-deoxygenation (Scheme 2.14). Accordingly, the C5-OH was protected with acid and base labile protecting groups (such as mesyl, benzoyl). The OH was actually kept different from the rest of the *O*-protecting group as the plan was for it to take part in ring expansion and for other purposes in the future. The key reaction for all the substrates associated with different protecting groups progressed without any crisis. All the compounds involved in the synthesis were clearly verified by means of physical and spectroscopic techniques. Similar variations in chemical shifts and coupling constants were observed in both benzoylate **51** and the mesylate **52** *C*-disaccharides like benzyl counterparts.

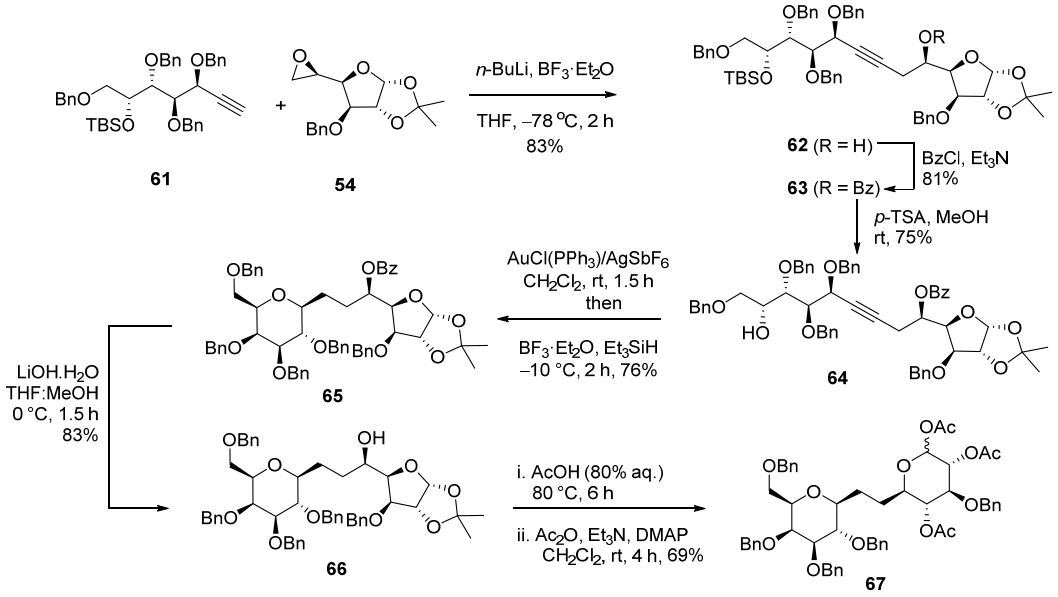
This approach was again repeated by inverting the stereochemistry of the epoxide to check the regioselectivity and the actual aim was to synthesize the natural D-*gluco*-configured [1→6]-linked *C*-disaccharides. For that, a *gluco*-configured 5,6-epoxide **54**[24b] and ribose alkyne **24** as the coupling partners were taken. At –78 °C, the ribose derived alkyne was lithiated in *n*-BuLi followed by the addition of epoxide **54** in THF was added in acidic condition ($BF_3.Et_2O$) to afford the alcohol **55**. They were esterified with benzoyl chloride, and triethyl amine in CH_2Cl_2. The silyl ether was then hydrolyzed with *p*-TSA and methanol to have the vital alkynol **57** for the [1→6]-combination. The key reaction was carried out in a similar fashion to get the 5-*exo*-dig opening furan derivative as the sole product **58**. Like the *α*-derived alkynol, it also has no effect on the regio- and stereoselectivity. All the compounds were analyzed by comparing with the spectra of the corresponding intermediates obtained in the *α*-epoxide derived alkynol. The saponification of the benzoyl ester **58** with lithium hydroxide was then set for ring expansion. The secondary alcohol **59** that resulted was easily recognized from the missing of the benzoyl group and the merging of its *α*-proton to the ring protons in the ^{1}H NMR. This proton was distinctly resonated at δ 5.52 (dt, J = 7.8, 3.3 Hz) when the benzoyl group was intact. The cleavage of acetonide was conducted in 80% aqueous acetic acid at 80 °C for 6 h. Without any characterization, the intermediate product was subjected for acetylation to yield a triacetate **60** as a mixture of 1:1 inseparable anomers. The ring expansion was identified by watching the anomeric carbon peaks at δ 92.2 and 89.4 and protons at δ 6.28 (d, J = 3.7 Hz) and 5.60 (d, J = 8.2 Hz). The expansion was also carried out by *p*-TSA in methanol to obtain a similar mixture of

1:1 inseparable *O*-methyl glycosides. Thus, this way, it confers a combination of **furan-pyran** [1→6]-linked *C*-disaccharides.



Scheme 2.15. Synthesis of [1→6]-linked *C*-disaccharide with pyran-furan combination

To test the impact of an elevated alkynol chain length on the outcome of cycloisomerization, the choice was made for a one carbon homologation of the present alkyne **61** but having a D-galacto-configuration. The same reaction sequence was repeated to procure good to excellent yields. Like previous results, no new observation was realized. Cycloisomerization and deoxygenation were seen to occur in the same manner to render the 6-*exo*-dig cyclization product as a single product. All the compounds were easily characterized from the experience gained as discussed earlier. This result elucidated a **pyran-pyran** combination of [1→6]-linked *C*-disaccharide.



Scheme 2.16. Synthesis of [1→6]-linked *C*-disaccharide with pyran-pyran combination

Discussion about the Factors Responsible for the Regioselectivity during the Alkynol Cycloisomerization: According to Baldwin's rule[20], the regioselectivity during cyclization not only depends on the number of atoms in the chain but also on the stereo-electronic factors imposed by the substituents. In the present context, about nine alkynols having different stereo-electronic environments were employed. To determine whether the outcome of cycloisomerization is concurrent or not, the stereochemistry at the alkyne partner was inverted. Two different alkynes derived from D-ribose and D-arabinose were selected at the beginning for the coupling with the D-*gluco*-configured lactone and the transformations of both alkynols **22** and **I** (Figure 2.5) ended with a single product in the regioselective sense (5-*exo*-dig). Later, a similar alkynol possessing one carbon homologation and 1:1 mixture of both epimers obtained from C1-ethynyl *β*-C-glucoside and D-arabino lactol furnished a 6-*exo*-dig product (alkynol **43**). The next five alkynols contained a similar alkyne partner **24** but differed in the electrophilic partners (lactone **37** and epoxide **54**) to produce one product (5-*exo*-dig) in each case (alkynol **38**, **47**, **48**, **49**, & **57**). In order to see any change of the stereo-electronic effect, the protecting groups (MsO, BnO, BzO) at the homo-propargylic position were altered, but no different result was seen to appear (alkynol **47**, **48**, and **49**). Similarly, the final alkynol **64** possessing a homologated alkyne (D-galacto-configured) having more benzyl substituents also delivered a single product (6-*exo*-dig). After a comparison of all the alkynols, it appears that the outcome of the cycloisomerization doesn't depend much on the stereoelectronic effects imposed by the

substituents around the nucleophilic partner. This means that the substituents on the other end of the alkyne must have some influence on the result. Indeed, we have demonstrated this earlier, especially when competition is between the 5-*exo* vs 6-*endo*. But unfortunately, in the present case, the substituents present on the other side of the alkynes have little variation of the electronic influence that can have an impact on the alkyne (all furanosyl or pyranosyl units) or in effect they had no influence on the outcome.

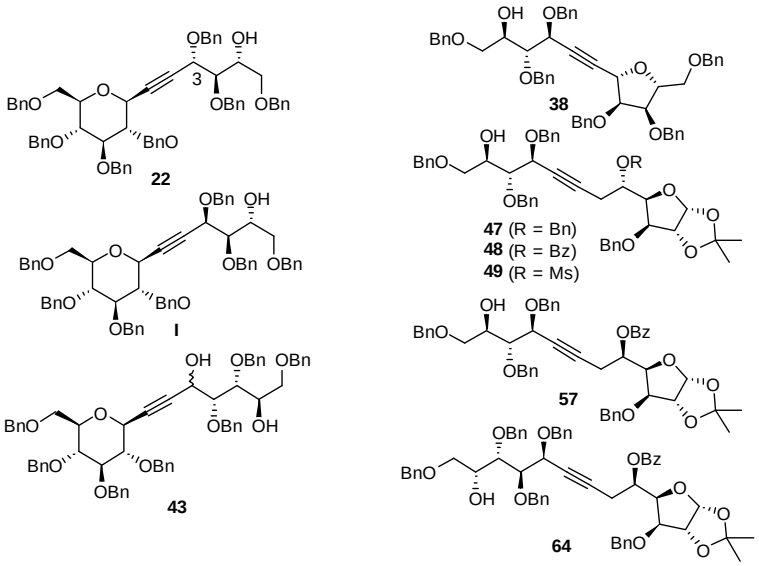
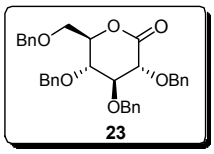


Figure 2.5. Different alkynols used for cycloisomerization

Conclusion

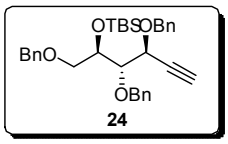
In conclusion, a one-pot intramolecular gold-catalyzed nucleophilic addition across the alkyne and Kishi's deoxygenation protocol has been amply illustrated for the synthesis of [1→1]- and [1→6]-*β*-linked *C*-disaccharides. This highly efficient and general methodology has been developed to access all possible pyran-pyran, furan-furan and pyran-furan combinations. Furthermore, the story behind this is lucidly described from the Zooxanthellamide D to *C*-disaccharide. The extension of this protocol for the syntheses of other [1,n]-linked *C*-disaccharides is currently under progress.

EXPERIMENTAL



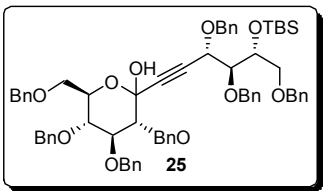
Synthesis of lactone 23: The lactone **23** was synthesized by following the literature reported procedure.

Characterization data of compound **23**: $[\alpha]_D^{25}$ +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) ppm.



Synthesis of alkyne 24: The alkyne **24** was synthesized by following the literature reported procedure.

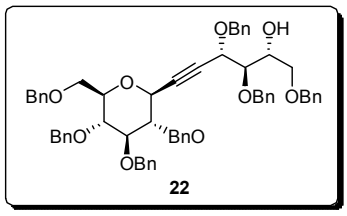
Characterization data of compound **24**: ^1H NMR ($CDCl_3$, 400 MHz) δ 0.02 (s, 3H), 0.03 (s, 3H), 0.85 (s, 9H), 2.52 (d, J = 2.1 Hz, 1H), 3.55 (dd, J = 5.3, 10.0 Hz, 1H), 3.72 (dd, J = 4.4, 10.0 Hz, 1H), 3.80 (dd, J = 4.2, 6.2 Hz, 1H), 4.27 (dd, J = 4.6, 9.5 Hz, 1H), 4.41 (dd, J = 2.1, 6.2 Hz, 1H), 4.46 (d, J = 12.0 Hz, 1H), 4.50 (d, J = 12.0 Hz, 1H), 4.75 (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), 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).



Synthesis of hemiketal 25: To a solution of alkyne **24** (300 Mg, 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 **23** (200 mg, 0.4 mmol) in THF (5 mL) was added slowly and stirred for 3 h. After complete consumption of starting material, the reaction mixture was quenched with saturated solution of ammonium chloride (10 mL) at –78 °C and partitioned between ethyl acetate (100 mL) and water (30 mL). Organic layer was separated, dried (Na_2SO_4) and evaporated under reduced pressure. The resulting crude was purified by

column chromatography (100–200 mesh silica gel, 1:3 ethyl acetate/petroleum ether) to procure pure product **25** (330 mg, 83%) as thin oil.

Characterization data of compound **25:** IR ($CHCl_3$): 3436, 2930, 1605, 1498, 1047, 745, 696 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 0.01 (s, 3H), 0.04 (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) ppm; ^{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), 127.5 (d), 127.6 (d), 127.7 (d), 127.7 (d), 127.7 (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), 137.8 (s), 138.0 (s), 138.1 (s), 138.2 (s), 138.4 (s), 138.5 (s), 138.6 (s), 138.7 (s) ppm; LCMS (*m/z*): 1091.06 (100% $[M+Na]^+$), 1107.22 (60% $[M+K]^+$).

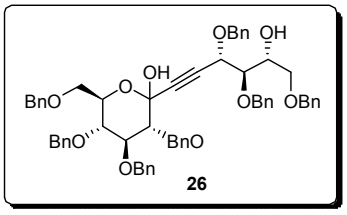


22

Synthesis of alkynol 22: Triethylsilane (170 mg, 0.23 mL, 1.49 mmol) was added to a solution of compound **25** (320 mg, 0.3 mmol) in CH_2Cl_2 (10 mL) at 0 °C under argon atmosphere and stirred for 5 min. The reaction mixture was cooled to –40 °C and treated slowly with a solution of $BF_3.Et_2O$ (210 mg, 0.18 mL, 1.5 mmol) in CH_2Cl_2 (1 mL) and allowed to stir at same temperature for 1.5 h. After complete consumption of starting material, the reaction mixture was quenched with saturated $NaHCO_3$ (5 mL) at –40 °C. The reaction mixture was portioned between ethyl acetate (50 mL) and water (20 mL). The organic layer was washed with saturated $NaHCO_3$ (20 mL), water (20 mL), brine (15 mL), dried (Na_2SO_4) 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 **22** (110 mg, 41%) and compound **26** (82 mg, 27%).

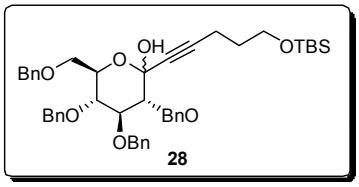
Characterization data of compound **22***:* Colourless gum; $[\alpha]_D^{25}$ +39.0 (*c* 1.8, $CHCl_3$); IR ($CHCl_3$): 3401, 2930, 1555, 1496, 1028, 742, 679 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 3.47–3.49 (m, 1H), 3.59 (dd, *J* = 5.7, 9.7 Hz, 1H), 3.65 (dd, *J* = 3.2, 9.7 Hz, 1H), 3.66–3.70

(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) ppm; ^{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), 127.6 (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) ppm; HRMS: calcd for $C_{61}H_{62}O_9Na$ ([M+Na]$^+$) 961.4292, found 961.4279.



26

Characterization data of compound **26**: Colourless gum; IR ($CHCl_3$): 3414, 2932, 1580, 1480, 1070, 765, 698 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) ppm; ^{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), 71.4 (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), 75.7 (t), 75.7 (t), 75.7 (t), 77.3 (d), 77.6 (d), 80.0 (d), 80.4 (d), 80.4 (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), 127.6 (d), 127.6 (d), 127.6 (d), 127.7 (d), 127.7 (d), 127.8 (d), 127.8 (d), 127.9 (d), 127.9 (d), 128.0 (d), 128.1 (d), 128.2 (d), 127.2 (d), 128.3 (d), 128.3 (d), 128.3 (d), 128.4 (d), 128.4 (d), 137.4 (s), 137.5 (s), 137.7 (s), 137.8 (s), 137.8 (s), 137.9 (s), 138.0 (s), 138.10 (s), 138.13 (s), 138.2 (s), 138.6 (s) ppm; HRMS: calcd for $C_{61}H_{62}O_{10}$ ([M+Na]$^+$) 977.4241, found 977.4223.

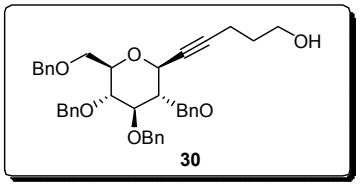


28

Synthesis of hemiacetals 28: Following the similar procedure used for synthesis of hemiketals **25**, the hemiketals **28** (320 mg, 78%) was assembled from lactone **23** (300 mg, 0.56 mmol) and alkyne **S15.1** (165 mg, 0.83

mmol).

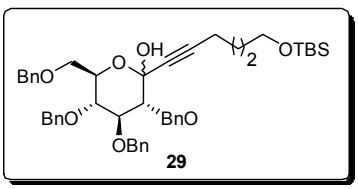
Characterization data of compound **28**: IR ($CHCl_3$): 3412, 2928, 2858, 1728, 1453, 1258, 1070, 835 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ 0.01 (s, 6H), 0.85 (s, 9H), 1.70 (sextet, J = 6.6 Hz, 2H), 2.29 (t, J = 7.4 Hz, 1H), 2.34 (t, J = 7.2 Hz, 1H), 3.58–4.02 (m, 8H), 4.41 (m, 4H), 4.71–5.03 (m, 5H), 7.08–7.16 (m, 2H), 7.22–7.39 (m, 18H) ppm. ^{13}C NMR ($CDCl_3$, 50 MHz): δ –5.4 (q), 15.2 (t), 15.2 (t), 18.2 (s), 25.9 (q), 31.3 (t), 31.5 (t), 61.5 (t), 61.6 (t), 68.6 (t), 68.6 (t), 71.7 (d), 73.4 (t), 74.0 (d), 74.6 (t), 74.9 (t), 75.1 (t), 75.7 (t), 75.8 (t), 77.5 (d), 77.7 (d), 79.7 (q), 82.5 (d), 83.7 (d), 84.2 (d), 84.3 (d), 84.8 (s), 89.1 (s), 91.6 (s), 95.5 (s), 127.5 (d), 127.5 (d), 127.6 (d, 2C), 127.7 (d), 127.8 (d), 127.9 (d), 128.0 (d), 128.2 (d, 2C), 128.3 (d), 137.9 (s), 138.0 (s), 138.1 (s, 2C), 138.6 (s), 138.7 (s) ppm; HRMS: calcd for $C_{45}H_{56}O_7SiNa$ ($[M+Na]^+$) 759.3693, found 759.3671.



30

Synthesis of alkynol 30: Following the similar procedure used for synthesis of alkynol **22**, the alkynol **30** (58 mg, 70%) was prepared from hemiketals **28** (100 mg, 0.14 mmol).

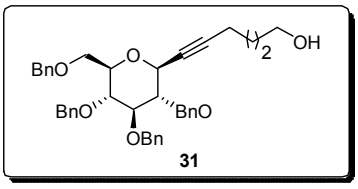
Characterization data of compound **30**: Colourless gum; $[\alpha]_D^{25}$ +2.05 (*c* 3.4, $CHCl_3$); IR ($CHCl_3$): 3464, 2925, 2868, 1454, 1360, 1093, 1066, 752 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ 1.66–1.80 (m, 3H), 2.35 (dt, J = 1.9, 7.1 Hz, 2H), 3.38–3.46 (m, 1H), 3.55–3.77 (m, 7H), 4.02–4.06 (m, 1H), 4.48–4.54 (m, 2H), 4.61 (d, J = 12.2 Hz, 1H), 4.78–4.84 (m, 3H), 4.91 (d, J = 11.0 Hz, 1H), 4.99 (d, J = 10.7 Hz, 1H), 7.09–7.14 (m, 2H), 7.23–7.37 (m, 18H) ppm. ^{13}C NMR ($CDCl_3$, 50 MHz): δ 15.4 (t), 30.9 (t), 61.3 (t), 68.7 (t), 70.0 (d), 73.4 (t), 75.0 (t), 75.2 (t), 75.6 (t), 77.6 (d), 78.8 (d), 82.5 (d), 85.9 (d), 86.1 (s, 2C), 127.6 (d, 2C), 127.7 (d, 3C), 127.8 (d, 2C), 127.9 (d, 4C), 128.3 (d, 4C), 128.3 (d, 5C), 137.9 (s), 137.9 (s), 138.1 (s), 138.4 (s) ppm; HRMS: calcd for $C_{39}H_{42}O_6Na$ ($[M+Na]^+$) 629.2879, found 629.2845.



29

Synthesis of hemiacetals 29: Following the similar procedure used for synthesis of hemiketals **25**, the hemiketals **29** (310 mg, 74%) was assembled from lactone **23** (300 mg, 0.56 mmol) and alkyne **S15.2** (177 mg, 0.83 mmol).

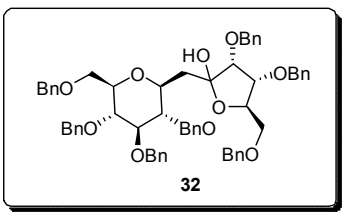
Characterization data of compound **29**: IR ($CHCl_3$): 3392, 2929, 2859, 14154, 1216, 1090, 755 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ 0.00–0.01 (m, 6H), 0.85–0.86 (m, 9H), 1.53–1.63 (m, 5H), 2.20–2.32 (m, 2H), 3.43–3.71 (m, 6H), 3.76–4.03 (m, 2H), 4.45–4.73 (m, 4H), 4.77–5.04 (m, 4H), 7.09–7.14 (m, 2H), 7.23–7.36 (m, 18H) ppm; ^{13}C NMR ($CDCl_3$, 50 MHz): δ –5.3 (q), 18.3 (s), 18.5 (t), 24.6 (t), 24.8 (t), 25.9 (q), 31.8 (t), 32.0 (t), 62.4 (t), 62.5 (t), 68.5 (t), 68.6 (t), 71.7 (d), 73.4 (t), 74.0 (d), 74.6 (t), 74.9 (t), 75.1 (t), 75.7 (t), 75.8 (t), 77.5 (d), 77.7 (d), 79.8 (s), 82.5 (d), 83.8 (d), 83.9 (d), 84.2 (d), 84.3 (d), 85.0 (s), 89.4 (s), 91.6 (s), 95.5 (s), 127.4 (d), 127.6 (d), 127.6 (d), 127.8 (d), 127.8 (d), 127.9 (d), 128.0 (d), 128.0 (d), 128.1 (d), 128.2 (d), 128.3 (d), 138.0 (s), 138.0 (s), 138.1 (s), 138.1 (s), 138.3 (s), 138.6 (s), 138.6 (s), 138.7 (s) ppm; HRMS: calcd for $C_{46}H_{58}O_7SiNa$ ($[M+Na]^+$) 773.3850, found 773.3821.



31

Synthesis of alkynol 31: Following the similar procedure used for synthesis of alkynol **22**, the alkynol **31** (62 mg, 75%) was prepared from hemiketals **29** (100 mg, 0.13 mmol).

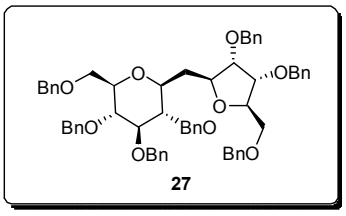
Characterization data of compound **31**: Colourless gum; $[\alpha]_D^{25}$ +3.7 (*c* 2.25, $CHCl_3$); IR ($CHCl_3$): 3458, 2925, 2862, 1729, 1496, 1454, 1094, 1066 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ 1.53–1.66 (m, 4H), 1.81–1.82 (m, 1H), 2.28 (dt, *J* = 1.9, 6.6 Hz, 2H), 3.40–3.46 (m, 1H), 3.55–3.72 (m, 7H), 4.02–4.07 (m, 1H), 4.52 (d, *J* = 11.9 Hz, 2H), 4.61 (d, *J* = 12.1 Hz, 1H), 4.78–4.88 (m, 3H), 4.90 (d, *J* = 11.0 Hz, 1H), 5.0 (d, *J* = 10.7 Hz 1H), 7.09–7.14 (m, 2H), 7.23–7.36 (m, 18H) ppm; ^{13}C NMR ($CDCl_3$, 50 MHz): δ 18.7 (t), 24.5 (t), 31.8 (t), 62.2 (t), 68.8 (t), 70.1 (d), 73.4 (t), 75.0 (t), 75.2 (t), 75.6 (t), 77.6 (d), 78.8 (d), 82.5 (d), 86.0 (d), 86.5 (s, 2C), 127.6 (d, 3C), 127.7 (d, 4C), 127.9 (d, 5C), 128.3 (8C), 137.9 (s), 138.0 (s), 138.2 (s), 138.5 (s) ppm; HRMS: calcd for $C_{40}H_{44}O_6Na$ ($[M+Na]^+$) 643.3036, found 643.3000.



32

Synthesis of hemiacetals 32: To a solution of alkynol **22** (50 mg, 53 mmol) in anhydrous CH_2Cl_2 (2 mL) was added $AgSbF_6$ (2.6 mg, 5.3 μmol), $AuCl(PPh_3)$ (1.8 mg, 5.3 μmol) and stirred for 2 h at rt. The solvent was evaporated under reduced pressure and the crude was purified by column chromatography (230–400 mesh silica gel, 1:3 ethyl acetate/petroleum ether) to isolate pure product **32** (39 mg, 77%).

Characterization data of compound **32:** Colourless gum; IR ($CHCl_3$): 3370, 2927, 2855, 1552, 1466, 1071, 755, 685 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) ppm; ^{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), 127.7 (d), 127.8 (d), 127.9 (d), 128.0 (d), 128.1 (d), 128.3 (d), 128.4 (d), 137.8 (s), 137.8 (s), 137.9 (s), 137.9 (s), 138.0 (s), 138.0 (s), 138.1 (s), 138.2 (s), 138.4 (s), 138.5 (s), 138.5 (s) ppm; LCMS (*m/z*): 979.20 [M+Na] .



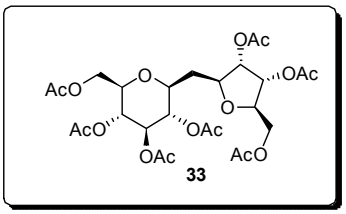
27

Synthesis of *C*-disaccharides 27: To a solution of acetal **32** (20 mg, 22 μmol) in CH_2Cl_2 (1 mL) at 0 °C under argon atmosphere was added triethylsilane (12 mg, 110 μmol) followed by addition of $BF_3.Et_2O$ (15 mg, 110 μmol) at –10 °C and allowed to warm up to 0 °C. Stirring was continued at 0 °C for 2.5 h. The reaction mixture was quenched with saturated $NaHCO_3$ at 0 °C and subjected for usual workup. Purification of the resulting crude by column chromatography (230–400 mesh silica gel, 1:4 ethyl acetate/petroleum ether) gave compound **27** (14 mg, 71%).

Characterization data of compound **27:** Colourless gum; $[\alpha]_D^{25}$ 4.1 (*c* 1.3, $CHCl_3$); IR ($CHCl_3$): 2930, 2855, 1560, 1419, 1080, 731, 668 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) ppm; ^{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), 74.9 (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) ppm; HRMS: calcd for $C_{61}H_{64}O_9Na$ ($[M+Na]^+$) 963.4448, found 963.4436.

Disaccharide **27** can also be prepared by using one-pot cycloisomerization-reduction protocol.

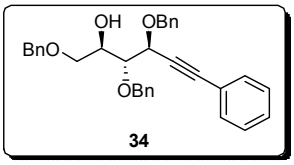
Procedure A- General Procedure for one-pot cycloisomerization/Et_3SiH-BF_3Et_2O reduction: To a solution of alkynol (1 eq.) in CH_2Cl_2, $AgSbF_6$ (10 mol%) and $AuCl(PPh_3)$ (10 mol%) were added sequentially at room temperature. Reaction container was covered with silver foil and stirred for 2 h. After consumption of starting material on TLC, reaction mixture was cooled to –10 °C and treated with triethylsilane (15 eq.) followed by $BF_3.Et_2O$ (10 eq.). After stirring for 2 h at 0 °C, reaction mixture was quenched by adding $NaHCO_3$ solution and extracted with CH_2Cl_2 and water. Organic layer dried over Na_2SO_4 and evaporated under reduced pressure. Crude was purified by column chromatography (230–400 mesh silica gel) to afford pure disaccharide with good yields.



33

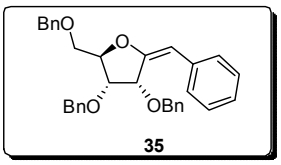
Synthesis of compound 33: A suspension of compound **27** (13 mg) and Pd-C (10%, 4 mg) in methanol (2 mL) was stirred at room temperature under H_2 atmosphere (40 psi) for 48 h. After disappearance of starting material on TLC, reaction mixture was filtered through *Celite* pad and the *Celite* pad was washed repeatedly with methanol. Combined 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 6 h. The crude product was isolated by removal of solvent 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 **33** (7 mg, 79%).

Characterization data of compound **33:** $[\alpha]_D^{25}$ +2.8 (*c* 1.3, $CHCl_3$); IR ($CHCl_3$): 2929, 2858, 1738, 1536, 1471, 1073, 728, 691 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) ppm; ^{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) ppm; HRMS: calcd for $C_{26}H_{36}O_{16}Na$ ($[M+Na]^+$) 627.1901, found 627.1885.



Synthesis of alkynol 34: A solution of D-ribo derived alkyne (100 mg, 0.24 mmol) and iodo benzene (106 mg, 0.48 mmol) in DMF (3 ml) was degassed in argon for 15 minutes followed by $Pd(PPh_3)_4$ (14 mg, 0.01 mmol), CuI (5 mg, 0.02 mmol), and $CsCO_3$ (157 mg, 0.48 mmol) was added. After addition the reaction mixture was again degassed and stirred overnight. The reaction mixture was quenched with water and organic layer was separated in ethyl acetate, concentrated in vaccum and loaded in the column (230–400 mesh silica gel, 1:4 ethyl acetate/petroleum ether) to give alkynol **34** (95 mg, 80%).

Characterization data of compound **34**: ^{1}H NMR ($CDCl_3$, 200 MHz): δ 2.72 (d, J = 5.1 Hz, 1H), 3.59–3.72 (m, 2H), 3.87 (dd, J = 4.2, 7.4 Hz, 1H), 3.99–4.09 (m, 1H), 4.47 (d, J = 11.8 Hz, 1H), 4.54 (d, J = 11.8 Hz, 1H), 4.59 (d, J = 11.8 Hz, 1H), 4.65 (d, J = 11.7 Hz, 1H), 4.74 (d, J = 4.2 Hz, 1H), 4.95 (d, J = 11.8 Hz, 1H), 4.96 (d, J = 11.3 Hz, 1H), 7.25–7.40 (m, 18H), 7.43–7.48 (m, 2H) ppm; ^{13}C NMR ($CDCl_3$, 50 MHz): δ 70.8 (t), 71.0 (d), 71.1 (t), 71.7 (d), 73.4 (t), 74.1 (t), 80.6 (d), 85.4 (s), 87.7 (s), 122.6 (s), 127.6 (d, 2C), 127.7 (d, 3C), 127.8 (d, 2C), 127.9 (d, 2C), 128.1 (d, 2C), 128.2 (d, 4C), 128.4 (d, 4C), 131.9 (d), 137.6 (s), 138.0 (s), 138.3 (s) ppm; LCMS: calcd for $C_{33}H_{32}O_4Na$ ($[M+Na]^+$) 515.21, found 515.18 (100%).

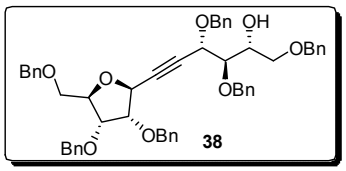


Synthesis of enol ether 35: To a solution of alkynol **34** (50 mg, 0.1 mmol) in dry CH_2Cl_2 was added $AuCl(PPh_3)$ (3 mg, 0.005 mmol) followed by $AgSbF_6$ (2 mg, 0.005 mmol) [or $PdCH_3CN)_2Cl_2$ 1 mg, 0.005 mmol] at room temperature and stirred for 5 h. The reaction mixture was directly concentrated in vaccum and loaded in the column (230–400 mesh silica gel, 1:9 ethyl acetate/petroleum ether) to afford pure product **35** (28 mg, 56%).

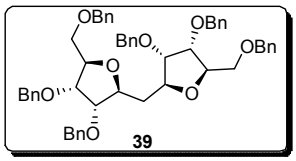
Characterization data of compound **35**: $[\alpha]^{24}_D$ = +0.7 (*c* 3.8, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz): IR ($CHCl_3$): 3031, 2924, 1727, 1496, 1454, 1097, 1027, 750 cm^{-1}; δ 3.65 (dd, J = 4.3, 11.3 Hz, 1H), 3.81 (dd, J = 2.8, 11.3 Hz, 1H), 4.06 (dd, J = 4.7, 7.1 Hz, 1H), 4.32 (d, J = 4.7 Hz, 1H), 4.49–4.64 (m, 5H), 4.68–4.82 (m, 2H), 5.43 (s, 1H), 7.11–7.19 (m, 1H), 7.25–7.41 (m, 17H), 7.60–7.64 (m, 2H) ppm; ^{13}C NMR ($CDCl_3$, 50 MHz): δ 69.0 (t), 70.0 (t), 72.0 (t), 73.3 (t), 76.3 (d), 76.6 (d), 83.0 (d), 102.9 (d), 125.8 (d), 127.5 (d), 127.6 (d), 127.8 (d), 127.9 (d), 128.0 (d, 2C), 128.1 (d, 2C), 128.1 (d, 2C), 128.2 (d, 2C), 128.4 (d,

2C), 128.4 (d, 2C), 128.4 (d, 2C), 128.4 (d, 2C), 135.5 (s), 137.5 (s), 137.8 (s), 153.4 (s) ppm; LCMS: calcd for $C_{33}H_{32}O_4Na$ ([M+Na]$^+$) 515.21, found 515.13 (100%).

Synthesis of alkynol 38: Following the similar procedure used for synthesis of compound **22**, the alkynol **38** (297 mg, 76%) was assembled from lactone **37** (200 mg, 0.48 mmol) and alkyne **24** (380 mg, 0.72 mmol).

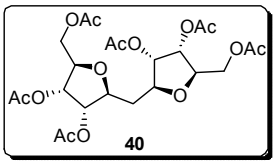


Characterization data of compound **38***:* $[\alpha]^{24}_D$ = +42.8 (*c* 1.3, $CHCl_3$); IR ($CHCl_3$): 3435, 2924, 2856, 1528, 1431, 1096, 736, 697 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.60 (bs, 1H), 3.52 (dd, *J* = 4.3, 15.9 Hz, 1H), 3.55–3.59 (m, 2H), 3.63 (dd, *J* = 3.2, 9.7 Hz, 1H), 3.77 (dd, *J* = 3.8, 7.6 Hz, 1H), 3.91 (m, 1H), 3.97–4.01 (m, 2H), 4.20 (dd, *J* = 4.5, 8.9 Hz, 1H), 4.42–4.47 (m, 3H), 4.48–4.53 (m, 3H), 4.54 (d, *J* = 12.1 Hz, 1H), 4.55–4.57 (m, 2H), 4.60 (d, *J* = 11.9 Hz, 1H), 4.68 (d, *J* = 12.1 Hz, 1H), 4.74–4.77 (m, 1H), 4.83 (d, *J* = 12.2 Hz, 1H), 4.86 (d, *J* = 11.7 Hz, 1H), 7.23–7.34 (m, 30H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 70.1 (t), 70.7 (d), 70.8 (t), 71.0 (t), 71.1 (d), 71.3 (d), 72.2 (t), 72.2 (t), 73.3 (t, 2C), 74.0 (t), 78.1 (d), 80.4 (d), 81.3 (d), 81.9 (d), 83.0 (s), 85.4 (s), 127.5 (d, 2C), 127.5 (d, 2C), 127.6 (d, 3C), 127.7 (d, 2C), 127.7 (d, 2C), 127.7 (d, 2C), 127.8 (d, 5C), 127.9 (d, 2C), 128.0 (d, 2C), 128.2 (d, 3C), 128.3 (d, 5C), 137.6 (d, 2C), 137.7 (d), 137.9 (d), 138.1 (d), 138.3 (d) ppm; HRMS: calcd for $C_{53}H_{54}O_8Na$ ([M+Na]$^+$) 841.3716, found 841.3702.



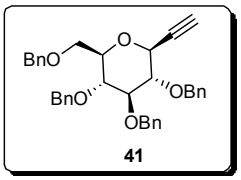
Synthesis of *C*-disaccharide 39: The *C*-disaccharide **39** (81 mg, 77%) was isolated as pale yellow thick oil from alkynol **38** (105 mg, 0.13 mmol) using a general procedure A.

Characterization data of compound **39***:* $[\alpha]^{24}_D$ = +22.5 (*c* 1.7, $CHCl_3$); IR ($CHCl_3$): 2923, 2854, 1496, 1454, 1216, 1122, 758, 697 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.71 (t, *J* = 6.6 Hz, 2H), 3.42–3.44 (m, 4H), 3.66 (t, *J* = 5.4 Hz, 1H), 3.88 (d, *J* = 5.1 Hz, 1H), 3.90 (d, *J* = 5.1 Hz, 1H), 4.13–4.25 (m, 4H), 4.35–4.58 (m, 13H), 7.22–7.35 (m, 30H) ppm; ^{13}C NMR ($CDCl_3$, 50 MHz): 38.6 (t), 70.3 (t, 2C), 71.7 (t, 2C), 71.7 (t, 2C), 73.4 (t, 2C), 77.4 (d, 2C), 78.5 (d, 2C), 80.9 (d, 2C), 81.0 (d, 2C), 127.5 (d, 5C), 127.6 (d, 4C), 127.6 (d, 3C), 127.7 (d, 2C), 127.9 (d, 4C), 128.0 (d, 4C), 128.3 (d, 8C), 138.0 (s, 2C), 138.1 (s, 2C), 138.3 (s, 2C) ppm; HRMS: calcd for $C_{53}H_{56}O_8K$ ([M+K]$^+$) 859.3712, found 859.3798.



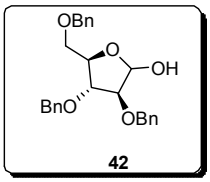
Synthesis of acetate 40: Employing the similar procedure used for the synthesis of acetate **33**, acetate **40** (15 mg, 81%) was prepared from benzyl ether **39** (30 mg, 36 μmol).

Characterization data of compound **40***:* $[\alpha]_D^{25}$ +18.4 (*c* 1.83, $CHCl_3$); IR ($CHCl_3$): 2931, 2861, 1729, 1469, 1071, 728, 673 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.71 (s, 3H), 1.74 (s, 3H), 1.77 (s, 3H); 1.81–1.85 (m, 2H), 4.10–4.23 (m, 2H), 4.31–4.35 (m, 1H), 4.40–4.47 (m, 1H), 5.16 (t, *J* = 5.9 Hz, 1H), 5.35–5.39 (m, 1H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): 20.0 (q), 20.1 (q), 20.2 (q), 37.8 (t), 63.6 (t), 72.2 (d), 74.9 (d), 77.8 (d), 79.7 (d), 169.3 (s), 169.4 (s), 169.8 (s) ppm; HRMS: calcd for $C_{23}H_{32}O_{14}Na$ ($[M+Na]^+$) 555.1690, found 555.1676.



Synthesis of alkyne 41: The alkyne **41** was synthesized by following the literature reported procedure.

Characterization data of compound **41**: ^1H NMR ($CDCl_3$, 200 MHz): δ 2.60 (d, *J* = 2.1 Hz, 1H), 3.48–3.51 (m, 1H), 3.64–3.83 (m, 5H), 4.07–4.13 (m, 1H), 4.58 (d, *J* = 11.5 Hz, 2H), 4.68 (d, *J* = 12.1 Hz, 1H), 4.84–4.91 (m, 3H), 4.97 (d, *J* = 10.9 Hz, 1H), 5.06 (d, *J* = 10.4 Hz, 1H), 7.15–7.22 (m, 2H), 7.30–7.41 (m, 18H) ppm.

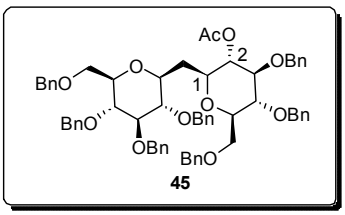


Synthesis of lactol 42: The lactol **42** was synthesized by following the literature reported procedure.

Characterization data of compound **42**: ^1H NMR ($CDCl_3$, 200 MHz): δ 3.29 (d, *J* = 7.8 Hz, 0.5H), 3.51–3.69 (m, 2H), 3.92–4.09 (m, 2H), 4.11–4.23 (m, 1H), 4.47–4.74 (m, 6.8H), 5.34–5.46 (m, 1H), 7.28–7.42 (m, 15H) ppm.

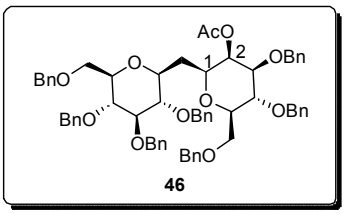
Synthesis of *C*-disaccharides 45 & 46: To the solution of alkyne **41** (98 mg, 178 μmol) in anhydrous THF (3 mL) was slowly added a solution of *n*-BuLi in hexane (0.1 mL, 178 μmol) at –78 °C. After stirring for 30 min at same temperature, a solution of lactol **42** (50 mg, 119 μmol) in THF (1 mL) was added slowly and stirring was continued for 2.5 h. The reaction mixture was quenched with saturated solution of ammonium chloride (1 mL) at –78 °C and extracted with ethyl acetate (10 mL) and water (3 mL). The separated organic layer was concentrated under reduced pressure to afford crude product (120 mg) which was purified by column chromatography (100–200 silica gel, 1:9 ethyl acetate/petroleum ether) to isolate a diastereomeric mixture of compound **43** (95 mg, 83%, dr = 1:1). The one-pot

alkynol cycloisomerization/reductive-deoxygenation of **43** (45 mg, 46 μmol) gave the two diastereomeric *C*-disaccharides **45** (16 mg, 34%) and **46** (16 mg, 34%).



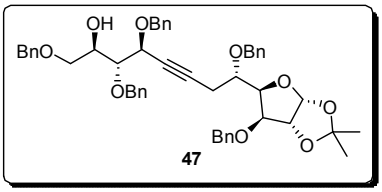
45

Characterization data of compound **45**: $[\alpha]_D^{25}$ +1.29 (*c* 0.4, $CHCl_3$); IR ($CHCl_3$) 2923, 2863, 1732, 1461, 1088, 728, 664 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.44 (ddd, *J* = 1.9, 4.8, 12.7 Hz, 1H), 1.93 (s, 3H), 1.95–2.00 (m, 1H), 3.22 (t, *J* = 9.2 Hz, 1H), 3.33 (dt, *J* = 2.9, 9.5 Hz, 1H), 3.38 (ddd, *J* = 2.1, 3.6, 9.4 Hz, 1H), 3.53–3.70 (m, 10H), 4.51 (d, *J* = 12.1 Hz, 1H), 4.54 (d, *J* = 13.3 Hz, 1H), 4.56–4.60 (m, 4H), 4.64 (d, *J* = 11.0 Hz, 1H), 4.69 (d, *J* = 11.4 Hz, 1H), 4.77–4.83 (m, 4H), 4.86 (dd, *J* = 9.3, 9.4 Hz, 1H), 4.89–4.92 (m, 2H), 7.16–7.34 (m, 35H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz) δ 21.1 (q), 34.0 (t), 68.7 (t), 68.9 (t), 73.2 (t), 73.3 (t), 73.6 (d), 74.2 (d), 74.7 (d), 74.8 (t), 74.9 (t), 75.1 (t, 2C), 75.5 (t), 78.4 (d), 78.5 (d), 78.7 (d), 79.1 (d), 81.9 (d), 84.7 (d), 87.3 (d), 127.5 (d), 127.6 (d, 4C), 127.7 (d, 5C), 127.8 (d, 7C), 127.9 (d, 2C), 128.3 (d, 2C), 128.3 (d, 8C), 128.4 (d, 6C), 137.9 (s), 138.1 (s), 138.1 (s), 138.2 (s), 138.3 (s), 138.4 (s), 138.6 (s), 170.0 (s) ppm; HRMS: calcd for $C_{64}H_{72}O_{11}N$ ($[M+NH_4]^+$) 1030.5100, found 1030.5106.



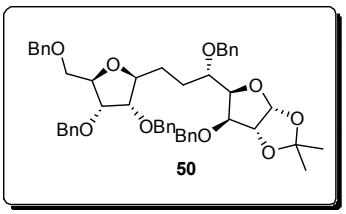
46

Characterization data of compound **46**: $[\alpha]_D^{25}$ –2.7 (*c* 0.3, $CHCl_3$); IR ($CHCl_3$) 2925, 2857, 1738, 1454, 1098, 732, 657 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.73–1.78 (m, 1H), 1.87–1.93 (m, 1H), 2.10 (s, 3H), 3.28–3.38 (m, 1H), 3.61–3.68 (m, 6H), 3.69–3.77 (m, 3H), 3.85 (dd, *J* = 8.8, 9.3 Hz, 1H), 4.21 (dt, *J* = 1.9, 7.3 Hz, 1H), 4.41–4.47 (m, 4H), 4.56 (d, *J* = 12.7 Hz, 1H), 4.58 (d, *J* = 17.6 Hz, 1H), 4.60 (d, *J* = 7.6 Hz, 1H), 4.61 (d, *J* = 7.2 Hz, 1H), 4.63 (d, *J* = 2.7 Hz, 1H), 4.81 (d, *J* = 8.6 Hz, 1H), 4.83 (d, *J* = 8.6 Hz, 1H), 4.88 (d, *J* = 11.2 Hz, 1H), 4.91 (d, *J* = 10.6 Hz, 1H), 4.93 (d, *J* = 10.6 Hz, 1H), 5.29 (dd, *J* = 2.7, 2.8 Hz, 1H), 7.16–7.32 (m, 35H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz) δ 21.2 (q), 31.2 (t), 68.8 (t), 69.2 (t), 69.9 (d), 71.7 (t), 73.0 (d), 73.3 (d), 73.38 (t), 73.4 (t), 74.5 (d), 74.7 (t), 74.9 (t), 75.0 (t), 75.5 (t), 76.5 (d), 77.8 (d), 78.3 (d), 78.8 (d), 81.1 (d), 87.3 (d), 127.5 (d, 3C), 127.6 (d), 127.7 (d, 2C), 127.75 (d, 4C), 127.80 (d, 5C), 127.9 (d, 2C), 128.1 (d, 3C), 128.2 (d, 3C), 128.3 (d, 3C), 128.4 (d, 3C), 128.4 (d, 4C), 128.5 (d, 2C), 137.8 (s), 138.0 (s), 138.1 (s), 138.2 (s), 138.3 (s), 138.5 (s), 138.5 (s), 170.5 (s) ppm; HRMS: calcd for $C_{64}H_{72}O_{11}N$ ($[M+NH_4]^+$) 1030.5100, found 1030.5103.



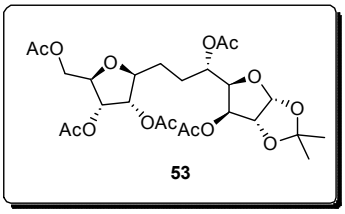
Synthesis of alkynol 47: The alkynol **47** was synthesized by following the literature reported procedure.

Characterization data of compound **47**: ^{1}H 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) ppm.



Synthesis of *C*-disaccharide 50: The *C*-disaccharide **50** (76 mg, 76%) was prepared from alkynol **47** (100 mg, 0.12 mmol) employing procedure A.

Characterization data of compound **50***:* $[\alpha]^{24}_D$ = –67.7 (*c* 0.1, $CHCl_3$); IR ($CHCl_3$): 2925, 2855, 1603, 1455, 1373, 1075, 1027, 696 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.32 (s, 3H), 1.49 (s, 3H), 1.63–1.72 (m, 4H), 3.43–3.52 (m, 3H), 3.74–3.86 (m, 3H), 3.90–3.99 (m, 1H), 4.10 (q, J = 4.4 Hz, 1H), 4.19 (dd, J = 3.2, 8.2 Hz, 1H), 4.35–4.61 (m, 10H), 4.89 (d, J = 11.5 Hz, 1H), 5.99 (d, J = 3.9 Hz, 1H), 7.24–7.34 (m, 25H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 26.3 (q), 26.7 (q), 27.4 (t), 29.6 (t), 70.5 (t), 71.7 (t), 71.8 (t), 71.9 (t), 73.3 (t), 73.4 (t), 77.6 (d), 77.7 (d), 80.5 (d), 81.0 (d), 81.1 (d), 81.5 (d), 82.6 (d), 84.2 (d), 105.1 (d), 111.5 (s), 127.2 (d), 127.5 (d, 3C), 127.7 (d), 127.7 (d), 127.8 (d, 4C), 127.9 (d, 2C), 128.0 (d, 2C), 128.1 (d, 2C), 128.2 (d), 128.3 (d, 3C)128.3 (d, 3C), 128.5 (d, 2C), 137.2 (s), 137.9 (s), 138.0 (s), 138.1 (s), 139.2 (s) ppm; HRMS: calcd for $C_{50}H_{57}O_9$ ([M+H]$^+$) 801.3997, found 801.3998.

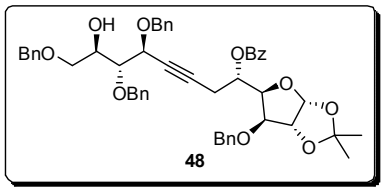


Synthesis of acetate 53: Acetylation of compound **50** (30 mg, 0.04 mmol) was carried out to afford acetate **53** (14 mg, 69%) *via* similar procedure used for synthesis of acetate **33**.

Characterization data of compound **53**: $[\alpha]^{24}_D$ = –15.8 (*c* 0.4, $CHCl_3$); IR ($CHCl_3$): 2854, 1746, 1374, 1228, 1022, 739, 655 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.31 (s, 3H), 1.52 (s, 3H), 1.58–1.69 (m, 4H), 2.07–2.11 (m, 15H), 3.93–3.96 (m, 1H), 4.10–4.11 (m, 2H), 4.24–4.30 (m, 2H), 4.49 (d, J = 3.7 Hz, 1H), 4.88 (t, J = 5.9 Hz, 1H), 5.09 (t, J = 5.3 Hz, 1H), 5.15 (d, J = 3.2 Hz, 1H), 5.23–5.26 (m, 1H), 5.91 (d, J = 3.7 Hz, 1H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz): δ 20.6 (q), 20.6 (q), 20.7 (q), 20.8 (q), 21.2 (q),

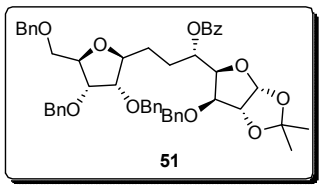
26.2 (d), 26.4 (t), 26.7 (d), 28.6 (t), 63.6 (t), 70.3 (d), 71.6 (d), 74.1 (d), 76.3 (d), 79.0 (d), 79.9 (d), 78.0 (d), 83.6 (d), 104.6 (d), 112.2 (s), 169.8 (s), 169.8 (s), 169.9 (s), 170.5 (s), 170.6 (s) ppm; HRMS: calcd for $C_{25}H_{36}O_{14}Na$ ($[M+Na]^+$) 583.1997, found 583.2000.

Synthesis of alkynol 48: To an ordinary methanolic solution (3 mL) of corresponding TBS compound (70 mg, 0.07 mmol) was added *p*-TSA.H_2O (14 mg, 0.07 mmol) at room temperature and stirred for about 12 h. After the completion of reaction, the reation mixture was directly concentrated in rotavapour and loaded in the column (100–200 silica gel, 15% ethyl acetate in petroleum ether) to obtain pure product **48** (50 mg, 81%). This synthesis was also followed according to literature procedure.



48

Characterization data of compound **48**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.31 (s, 3H), 1.45 (s, 3H), 2.54 (ddd, J = 1.9, 4.9, 17.5 Hz, 1H), 2.78 (ddd, J = 1.9, 4.3, 17.5 Hz, 1H), 3.52 (dd, J = 5.6, 9.7 Hz, 1H), 3.58 (dd, J = 3.0, 9.7 Hz, 1H), 3.72 (dd, J = 3.5, 7.8 Hz, 1H), 3.86 (ddd, J = 3.0, 5.6, 7.8 Hz, 1H), 4.09 (d, J = 3.6 Hz, 1H), 4.41 (d, J = 11.6 Hz, 2H), 4.46 (d, J = 10.0 Hz, 2 H), 4.49–4.50 (m, 1H), 4.54 (d, J = 11.5 Hz, 1H), 4.65–4.69 (m, 3H), 4.81 (d, J = 11.6 Hz, 1H), 4.82 (d, J = 11.4 Hz, 1H), 5.55 (dt, J = 4.9, 8.0 Hz, 1H), 5.99 (d, J = 3.9 Hz, 1H), 7.20 –7.34 (m, 20H), 7.45–7.49 (m, 2H), 8.02 (dd, J = 1.2, 8.2 Hz, 2H), 8.10 (dd, J = 1.2, 8.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 21.3 (t), 26.3 (q), 26.9 (q), 70.5 (d), 70.6 (d), 70.8 (t), 70.9 (t), 71.4 (d), 71.6 (t), 73.3 (t), 73.9 (t), 78.4 (s), 80.3 (d), 80.3 (d), 81.7 (d), 82.0 (d), 82.9 (s), 105.2 (d), 111.9 (s), 127.5 (d), 127.6 (d), 127.7 (d), 127.8 (d, 2C), 127.8 (d, 2C), 128.1 (d, 2C), 128.2 (d, 2C), 128.2 (d, 2C), 128.3 (d, 2C), 128.4 (d, 2C), 128.5 (d), 128.6 (d, 2C), 129.9 (d, 2C), 130.1 (s), 130.2 (d), 132.8 (d), 133.7 (d), 136.8 (s), 137.7 (s), 138.0 (s), 138.4 (s), 165.8 (s) ppm; HRMS: calcd for $C_{50}H_{53}O_{10}$ ($[M+H]^+$) 813.3639, found 813.3633.

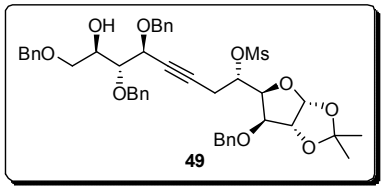


51

Synthesis of *C*-disaccharide 51: The *C*-disaccharide **51** (29 mg, 73 %) was successfully prepared from alkynol **48** (40 mg, 0.05 mmol) by following procedure A.

Characterization data of compound **51**: $[\alpha]^{24}_D$ = –33.4 (*c* 0.7, $CHCl_3$); IR ($CHCl_3$): 2925, 1453, 1271, 1106, 1026, 697 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.31 (s, 3H), 1.49 (s, 3H), 1.61–1.83 (m, 4H), 3.42 (d, J = 4.5, 2H), 3.47 (t, J = 5.9 Hz, 1H), 3.80 (t, J = 5.0 Hz, 1H), 3.89–3.94 (m, 1H), 3.92 (d, J = 3.5, 1H), 4.09 (q, J = 4.5 Hz, 1H), 4.29 (dd, J = 3.5, 8.3 Hz, 1H), 4.40 (d, J = 11.8 Hz, 1H), 4.41 (d, J = 11.8 Hz, 1H),

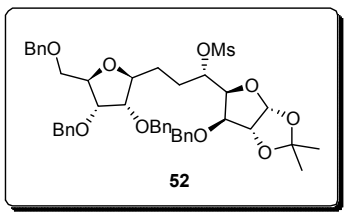
4.46–4.52 (m, 5H), 4.60–4.64 (m, 2H), 5.62 (dt, *J* = 2.9, 8.3 Hz, 1H), 5.95 (d, *J* = 3.9 Hz, 1H), 7.23–7.30 (m, 20H), 7.37–7.41 (m, 2H), 7.50–7.54 (m, 1H), 8.02–8.04 (m, 2H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 26.3 (q), 26.8 (q), 27.3 (t), 29.5 (t), 70.4 (t), 71.6 (t), 71.7 (t), 71.8 (t), 72.3 (d), 73.3 (t), 77.5 (d), 80.5 (d), 80.8 (d), 81.1 (d), 81.4 (d), 81.9 (d), 82.0 (d), 105.0 (d), 111.6 (s), 127.5 (d, 2C), 127.7 (d, 2C), 127.7 (d, 2C), 127.8 (d, 2C), 127.8 (d, 2C), 128.0 (d, 2C), 128.0 (d, 2C), 128.2 (d, 2C), 128.3 (d, 2C), 128.3 (d, 2C), 128.5 (d, 2C), 129.8 (d, 2C), 130.5 (s), 132.7 (d), 137.0 (s), 137.9 (s), 137.9 (s), 138.1 (s), 166.0 (s) ppm; HRMS: calcd for $C_{50}H_{55}O_{10}$ ($[M+H]^+$) 815.3790, found 815.3789.



49

Synthesis of alkynol 49: The alkynol **49** (25 mg, 68%) was synthesized by following the synthesis of alkynol **48.**

Characterization data of compound **49**: $[\alpha]^{24}_D$ = +35.5 (*c* , 0.3, $CHCl_3$); IR ($CHCl_3$): 3525, 2924, 2855, 1454, 1361, 1176, 1074, 698 cm^{-1}. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.30 (s, 3H), 1.41 (s, 3H), 2.51 (ddd, *J* = 1.8, 5.2, 17.7 Hz, 1H), 2.68–2.69 (m, 1H), 2.72 (ddd, *J* = 1.8, 3.7, 17.7 Hz, 1H), 3.06 (s, 3H), 3.59 (dd, *J* = 5.7, 9.7 Hz, 1H), 3.65 (dd, *J* = 2.9, 9.7 Hz, 1H), 3.76 (dd, *J* = 3.4, 8.0 Hz, 1H), 3.90–3.95 (m, 1H), 4.04 (d, *J* = 3.4 Hz, 1H), 4.36 (d, *J* = 11.6 Hz, 1H), 4.46–4.50 (m, 3H), 4.52 (d, *J* = 11.9 Hz, 1H), 4.55–4.56 (m, 1H), 4.58 (d, *J* = 11.3 Hz, 2H), 4.62 (d, *J* = 3.7 Hz, 1H), 4.85 (d, *J* = 7.6 Hz, 1H), 4.88 (d, *J* = 7.3 Hz, 1H), 4.91 (ddd, *J* = 3.7, 5.2, 8.7 Hz, 1H), 5.95 (d, *J* = 3.7 Hz, 1H), 7.24–7.37 (m, 20 H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz) δ 22.6 (t), 26.3 (q), 26.7 (q), 38.6 (q), 70.6 (d), 71.0 (t), 71.0 (t), 71.3 (d), 71.7 (t), 73.3 (t), 74.0 (t), 79.3 (d), 79.4 (s), 80.4 (d), 80.5 (d), 81.1 (d), 81.5 (s), 81.7 (d), 105.0 (d), 112.2 (s), 127.5 (d), 127.6 (d), 127.7 (d), 127.8 (d, 2C), 127.9 (d, 2C), 128.0 (d, 2C), 128.1 (d, 2C), 128.2 (d, 2C), 128.3 (d, 2C), 128.4 (d, 2C), 128.4 (d), 128.7 (d, 2C), 136.3 (s), 137.8 (s), 138.1 (s), 138.4 (s) ppm; HRMS: calcd for $C_{44}H_{51}O_{11}S$ ($[M+H]^+$) 787.3152, found 787.3141.

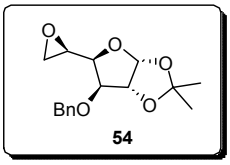


52

Synthesis of *C*-disaccharide 52: The *C*-disaccharide **52** (13 mg, 65%) was successfully prepared from alkynol **49** (20 mg, 0.02 mmol) by following procedure A.

Characterization data of compound **52**: $[\alpha]^{24}_D$ = –7.4 (*c* 2.9, $CHCl_3$); IR ($CHCl_3$): 2925, 2856, 1454, 1353, 1173. 1075, 698 cm^{-1}. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.31 (s, 3H), 1.48 (s, 3H), 1.64–1.79 (m, 4H), 3.12 (s, 3H), 3.45 (d, *J* = 4.4 Hz, 2H), 3.58 (t, *J* = 5.6 Hz, 1H), 3.81–3.86 (m, 2H), 3.89–3.95 (m, 1H), 4.12 (dd, *J* = 4.5, 9.0

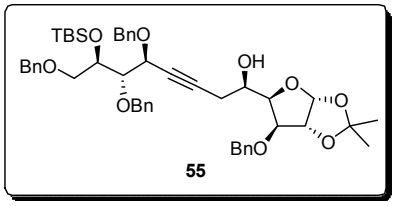
Hz, 1H), 4.20 (dd, *J* = 3.14, 9.0 Hz, 1H), 4.37 (d, *J* = 11.6 Hz, 1H), 4.50–4.60 (m, 8H), 4.85–4.94 (m, 1H), 5.94 (d, *J* = 3.8 Hz, 1H), 7.29–7.35 (m, 20H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz) δ 26.2 (q), 26.7 (q), 27.6 (t), 29.3 (t), 38.8 (q), 70.5 (t), 71.8 (t), 71.9 (t), 71.9 (t), 73.3 (t), 77.7 (d), 80.4 (d), 80.8 (d), 81.0 (d), 81.4 (d), 81.6 (d), 81.6 (d), 82.7 (d), 104.9 (d), 112.0 (s), 127.6 (d), 127.6 (d, 2C), 127.7 (d), 127.7 (d), 127.9 (d, 2C), 128.0 (d, 2C), 128.1 (d, 2C), 128.3 (d, 3C), 128.4 (d, 4C), 128.7 (d, 2C), 136.5 (s), 137.9 (s, 2C), 138.2 (s) ppm; HRMS: calcd for $C_{44}H_{53}O_{11}S$ ($[M+H]^+$) 788.3309, found 789.3296.



54

Synthesis of epoxide 54: The epoxide **54** was synthesized by following the literature reported procedure.

Characterization data of compound **54**: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.31 (s, 3H), 1.46 (s, 3H), 2.79 (dd, *J* = 2.6, 5.1 Hz, 1H), 2.93 (dd, *J* = 3.9, 5.1 Hz, 1H), 3.31 (ddd, J = 2.6, 3.9, 7.1 Hz, 1H), 3.76 (dd, *J* = 3.2, 7.1 Hz, 1H), 4.08 (d, *J* = 3.2 Hz, 1H), 4.64 (d, *J* = 3.7 Hz, 1H), 4.66 (d, *J* = 11.9 Hz, 1H), 4.74 (d, *J* = 11.9 Hz, 1H), 5.95 (d, *J* = 3.7 Hz, 1H), 7.29–7.37 (m, 5H) ppm.

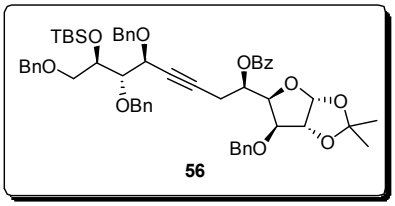


55

Synthesis of alkynol 55: At −78 °C, a solution of alkyne **24** (2.4 g, 4.5 mmol) in anhydrous THF (15 mL) was treated with *n*-BuLi (2.8 mL, 1.6 M in hexane, 4.5 mmol) and stirred for 20 min. Then to this reaction contents, a solution of $BF_3.Et_2O$ (598 mg, 4.2 mmol) was introduced and stirring was continued at same temperature for 20 min. After that, a solution of epoxide **54** (440 mg, 1.5 mmol) in anhydrous THF (4 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 (2 mL) and partitioned between ethyl acetate (80 mL) and water (20 mL). The organic layer was washed with brine (20 mL), dried (Na_2SO_4) and evaporated under reduced pressure. The crude compound was purified by column chromatography (silica 230–400 mesh, 2.5:7.5 ethyl acetate/petroleum ether) to afford compound **55** (1.0 g, 81% yield) as colorless syrup.

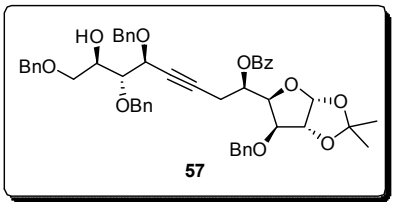
Characterization data of compound **55**: $[\alpha]^{24}_D$ = +33.0 (*c* 1.7, $CHCl_3$); IR ($CHCl_3$): 3501, 2928, 2856, 1454, 1252, 1076, 1027, 835, 736, 697 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.01 (s, 6H), 0.81 (s, 9H), 1.30 (s, 3H), 1.43 (s, 3H), 2.56 (ddd, *J* = 1.6, 6.7, 17.1 Hz, 1H), 2.72 (ddd, *J* = 1.7, 4.1, 17.1 Hz, 1H), 3.54 (dd, *J* = 4.7, 10.1 Hz, 1H), 3.58 (dd, *J* = 3.1, 10.1 Hz, 1H), 3.82 (dd, *J* = 3.8, 6.9 Hz, 1H), 3.96 (ddd, *J* = 3.1, 4.7, 7.2 Hz, 1H), 4.06–4.09 (m,

2H), 4.11 (dd, *J* = 2.8, 8.1 Hz, 1H), 4.44–4.50 (m, 4H), 4.56 (d, *J* = 11.8 Hz, 1H), 4.58 (d, *J* = 3.8 Hz, 1H), 4.64 (d, *J* = 11.8 Hz, 1H), 4.68 (d, *J* = 11.5 Hz, 1H), 4.82 (d, *J* = 11.9 Hz, 1H), 4.90 (d, *J* = 11.5 Hz, 1H), 5.92 (d, *J* = 3.8 Hz, 1H), 7.24–7.35 (m, 20H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ –5.0 (q), –4.3 (q), 18.0 (s), 25.4 (t), 25.8 (q, 3C), 26.3 (q), 26.8 (q), 67.2 (d), 70.8 (t), 71.1 (d), 71.8 (t), 72.1 (d), 72.3 (t), 73.2 (t), 74.3 (t), 79.6 (s), 81.5 (d), 81.7 (d), 81.7 (d), 82.5 (d), 83.9 (s), 105.1 (d), 111.7 (s), 127.4 (d, 2C), 127.6 (d), 127.7 (d, 2C), 127.8 (d, 2C), 127.9 (d, 2C), 128.0 (d, 3C), 128.2 (d, 4C), 128.3 (d, 2C), 128.5 (d, 2C), 137.3 (s), 137.8 (s), 138.3 (s), 138.6 (s) ppm; HRMS: calcd for $C_{49}H_{66}O_9N$ ($[M+NH_4]^+$) 840.4501, found 840.4505.



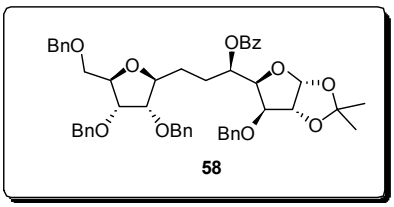
Synthesis of benzoate 56: A solution of compound **55** (500 mg, 0.60 mmol) in anhydrous CH_2Cl_2 (5 mL) was treated with triethyl amine (0.1 mL, 0.79 mmol) followed by benzoyl chloride (0.08 mL, 0.66 mmol) at 0 °C for 1.5 h. Then reaction mixture was diluted with 50 mL CH_2Cl_2, washed sequentially with water (10 mL) and brine (10 mL). The organic layer dried (Na_2SO_4) and evaporated under reduced pressure. The crude compound obtained was purified by column chromatography to isolate benzoate **56** (472 mg, 84%) as pale yellow gum.

Characterization data of compound **56**: $[\alpha]^{24}_D$ = –6.8 (*c* 1.8, $CHCl_3$); IR ($CHCl_3$): 2828, 2856, 1724, 1585, 1496, 1453, 1273, 1111, 1075, 1027, 835, 698 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.00 (s, 3H), 0.02 (s, 3H), 0.83 (s, 9H), 1.38 (s, 3H), 1.52 (s, 3H), 2.96 (ddd, *J* = 1.5, 4.6, 17.6 Hz, 1H), 3.20 (ddd, *J* = 1.6, 3.9, 17.6 Hz, 1H), 3.47–3.59 (m, 2H), 3.79 (dd, *J* = 4.6, 6.3 Hz, 1H), 3.98–4.05 (m, 1H), 4.10 (d, *J* = 3.1 Hz, 1H), 4.39–4.45 (m, 5H), 4.57–4.82 (m, 5H), 4.95 (d, *J* = 11.5 Hz, 1H), 5.54 (dt, *J* = 4.1, 8.6 Hz, 1H), 6.02 (d, *J* = 3.6 Hz, 1H), 7.16–8.00 (m, 25H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ –5.0 (q), –4.4 (q), 18.0 (s), 21.9 (t), 25.8 (q, 3C), 26.3 (q), 26.9 (q), 68.9 (d), 70.5 (t), 70.9 (d), 71.8 (t), 72.1 (t), 72.1 (d), 73.2 (t), 74.2 (t), 78.7 (s), 79.3 (d), 80.8 (d), 81.6 (d), 82.0 (d), 82.8 (s), 105.3 (d), 112.0 (s), 127.2 (d), 127.3 (d), 127.6 (d, 2C), 127.9 (d, 3C), 127.9 (d, 2C), 128.0 (d, 3C), 128.1 (d, 3C), 128.1 (d, 4C), 128.3 (d, 2C), 128.3 (d, 2C), 129.7 (d), 130.0 (s), 132.9 (d), 136.7 (s), 138.0 (s), 138.5 (s), 138.9 (s), 165.1 (s) ppm; HRMS: calcd for $C_{56}H_{67}O_{10}Si$ ($[M+H]^+$) 927.4498, found 927.4472.



Synthesis of alkynol 57: To an ice cooled solution of TBS ether **56** (500 mg, 0.54 mmol) in anhydrous THF (5 mL) was added a solution of TBAF (211 mg, 0.81 mmol) [or *p*-TSA (5 mol%) in MeOH] in anhydrous THF (2 mL) under argon atmosphere and allowed to stir at room temperature for 4 h. Reaction mixture was concentrated and the residue was purified by column chromatography (230–400 mesh silica gel, 1:4 ethyl acetate/petroleum ether) to afford compound **57** (342 mg, 78% yield) as a colorless gum.

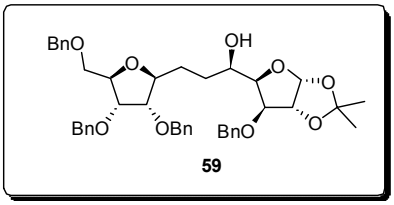
Characterization data of compound **57**: $[\alpha]^{24}_{D}$ = –3.0 (*c* 1.0, $CHCl_3$); IR ($CHCl_3$): 3504, 2926, 2866, 1722, 1496, 1453, 1273, 1112, 1074, 1027, 698 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 1.32 (s, 3H), 1.47 (s, 3H), 2.70 (bs, 1H), 2.86 (ddd, *J* = 1.7, 4.9, 17.6 Hz, 1H), 3.09 (ddd, *J* = 2.0, 4.0, 17.6 Hz, 1H), 3.52 (dd, *J* = 5.7, 9.7 Hz, 1H), 3.57 (dd, *J* = 3.1, 9.7 Hz, 1H), 3.70 (dd, *J* = 4.0, 7.6 Hz, 1H), 3.89–3.93 (m, 1H), 4.02 (d, *J* = 3.2 Hz, 1H), 4.36 (d, *J* = 11.5 Hz, 1H), 4.36 (d, *J* = 11.6 Hz, 1H), 4.42–4.48 (m, 3H), 4.54 (bd, *J* = 11.7 Hz, 2H), 4.63 (d, *J* = 3.7 Hz, 1H), 4.65 (dd, *J* = 3.2, 8.8 Hz, 1H), 4.77 (d, *J* = 11.6 Hz, 1H), 4.84 (d, *J* = 11.5 Hz, 1H), 5.51 (dt, *J* = 4.4, 8.8 Hz, 1H), 5.95 (d, *J* = 3.7 Hz, 1H), 7.07–7.32 (m, 22H), 7.48–7.50 (m, 1H), 7.92–7.93 (m, 2H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz): δ 22.0 (t), 26.3 (q), 26.9 (q), 68.7 (d), 70.7 (t), 70.8 (d), 70.9 (t), 71.4 (d), 72.1 (t), 73.3 (t), 73.9 (t), 78.3 (s), 79.3 (d), 80.3 (d), 80.7 (d), 81.9 (d), 83.3 (s), 105.2 (d), 112.0 (s), 127.4 (d), 127.5 (d), 127.6 (d), 127.8 (d, 2C), 127.8 (d, 2C), 127.9 (d), 128.0 (d, 5C), 128.2 (d, 2C), 128.2 (d, 2C), 128.3 (d, 5C), 129.7 (d, 2C), 129.9 (s), 133.0 (d), 136.7 (s), 137.7 (s), 138.1 (s), 138.4 (s), 165.1 (s) ppm; HRMS: calcd for $C_{50}H_{53}O_{10}$ ($[M+H]^+$) 813.3633, found 813.3629.



Synthesis of *C*-disaccharide 58: The *C*-disaccharide **58** (75 mg, 75%) was prepared from alkynol **57** (100 mg, 0.13 mmol) employing procedure A.

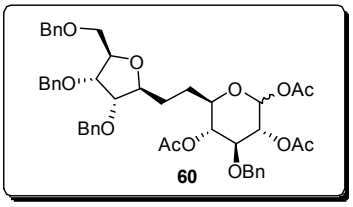
Characterization data of compound **58**: $[\alpha]^{24}_{D}$ = –31.9 (*c* 1.0, $CHCl_3$); IR ($CHCl_3$): 2926, 2865, 1721, 1453, 1269, 1112, 1026, 698 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.32 (s, 3H), 1.51 (s, 3H), 1.64–1.89 (m, 3H), 2.15–2.23 (m, 1H), 3.46 (d, *J* = 4.5 Hz, 2H), 3.56 (t, *J* = 5.8 Hz, 1H), 3.82 (t, *J* = 5.1 Hz, 1H), 3.95–3.99 (m, 2H), 4.13 (dt, *J* = 4.6, 9.2 Hz, 1H), 4.33–4.35 (m, 2H), 4.44 (d, *J* = 11.8 Hz, 1H), 4.48–4.52 (m, 6H), 4.59 (d, *J* = 3.8 Hz, 1H), 5.52 (dt, *J* = 3.6, 8.0 Hz, 1H), 5.92 (d, *J* = 3.8 Hz, 1H), 7.14–7.33 (m, 20H), 7.39–7.43 (m, 2H), 7.54–7.57 (m, 1H), 7.97–7.99 (m, 2H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 26.2 (q), 26.9 (q), 28.2 (t), 29.0 (t), 70.4 (t), 71.0 (d), 71.7 (t), 71.9 (t),

72.1 (t), 73.3 (t), 77.6 (d), 80.7 (d, 2C), 80.9 (d), 81.0 (d), 81.2 (d), 81.8 (d), 105.2 (d), 111.7 (s), 127.5 (d), 127.6 (d, 3C), 127.6 (d), 127.8 (d), 127.9 (d, 2C), 128.0 (d, 4C), 128.3 (d, 5C), 128.3 (d, 5C), 129.6 (d, 2C), 130.2 (s), 132.9 (d), 136.8 (s), 137.9 (s), 137.9 (s), 138.2 (s), 165.3 (s) ppm; HRMS: calcd for $C_{50}H_{55}O_{10}$ ($[M+H]^+$) 815.3790, found 815.3790.



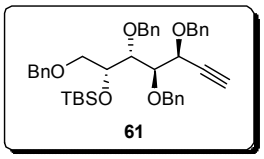
Synthesis of alcohol 59: To a solution of the benzoate **58** (55 mg, 0.07 mmol) in THF:MeOH (2:1, 3 mL), was added $LiOH.H_2O$ (28 mg, 0.7 mmol) at room temperature and stirred for 15 h. Then reaction solvent was evaporated directly under reduced pressure and crude was purified by column chromatography (230–400 silica gel, 1:3 ethyl acetate/petroleum ether) to procure the alcohol **59** (42 mg, 88%).

Characterization data of compound **59**: $[\alpha]^{24}_D$ = –47.7 (*c* 0.3, $CHCl_3$); IR ($CHCl_3$): 3412, 2925, 1602, 1455, 1215, 1074, 1027, 733, 696 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.31 (s, 3H), 1.46 (s, 3H), 1.51–1.56 (m, 2H), 1.85–1.88 (m, 2H), 2.93 (bs, 1H), 3.44–3.51 (m, 2H), 3.58 (t, *J* = 5.8 Hz, 1H), 3.89 (t, *J* = 5.1 Hz, 1H), 3.97–4.08 (m, 4H), 4.16 (dt, *J* = 4.3, 4.5 Hz, 1H), 4.47 (d, *J* = 12.2 Hz, 1H), 4.48–4.59 (m, 6H), 4.60 (d, *J* = 3.8 Hz, 1H), 4.70 (d, *J* = 11.7 Hz, 1H), 5.94 (d, *J* = 3.8 Hz, 1H), 7.26–7.34 (m, 20H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 26.3 (q), 26.8 (q), 29.5 (t), 31.1 (t), 68.6 (d), 70.0 (t), 71.8 (t), 72.0 (t), 72.2 (t), 73.4 (t), 77.2 (d), 80.8 (d), 81.1 (d), 81.3 (d), 82.2 (d, 2C), 82.4 (d), 105.1 (d), 111.5 (s), 127.7 (d, 3C), 127.7 (d, 2C), 127.9 (d, 2C), 127.9 (d, 2C), 128.1 (d, 2C), 128.1 (d), 128.3 (d, 3C), 128.4 (d, 3C), 128.6 (d, 2C), 137.3 (s), 137.9 (s, 2C), 138.0 (s) ppm; HRMS: calcd for $C_{43}H_{51}O_9$ ($[M+H]^+$) 711.3528, found 711.3528.



Synthesis of *C*-disaccharides 60: A solution of acetonide derivative **59** (35 mg, 0.05 mmol) in acetic acid (4 mL) and water (1 mL) was stirred at 85 °C for 8 h. Then the reaction contents were evaporated under reduced pressure. The traces acetic acid and water were removed by co-evaporation with toluene (3 x 3 mL). The crude product thus obtained was dissolved in pyridine (0.5 mL) and treated with acetic anhydride (0.5 mL) at 0 °C to rt for 4 h. The reaction contents were removed by co-evaporation with toluene on rotavapour under reduced pressure. The crude was purified by column chromatography (230–400 silica gel, 1:4 ethyl acetate/petroleum ether) to afford 1:1 anomeric mixture of **60** (28 mg, 71%) as colourless thick oil.

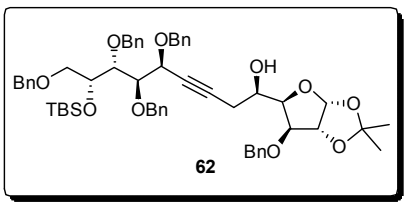
Characterization data of compound **60**: [α:β = 1:1]; IR ($CHCl_3$): 2925, 1752, 1523, 1369, 1220, 1042, 769, 685 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 1.44–1.53 (m, 4H), 1.70–1.84 (m, 4H), 1.95 (s, 3H), 1.96 (s, 3H), 2.00 (s, 3H), 2.01 (s, 3H), 2.08 (s, 3H), 2.14 (s, 3H), 3.49 (dd, *J* = 4.5, 9.8 Hz, 4H), 3.56 (t, *J* = 5.9 Hz, 2H), 3.70 (t, *J* = 9.4 Hz, 1H), 3.79–3.83 (m, 1H), 3.88 (dd, *J* = 5.2, 9.8 Hz, 2H), 3.90–3.94 (m, 3H), 4.16–4.19 (m, 2H), 4.48–4.64 (m, 16H), 4.71 (d, *J* = 11.8 Hz, 1H), 4.96 (t, *J* = 10.0 Hz, 1H), 4.96 (t, *J* = 9.5 Hz), 5.04 (dd, *J* = 3.7, 10.0 Hz, 1H), 5.14 (dd, *J* = 8.3, 9.5 Hz, 1H), 5.60 (d, *J* = 8.3 Hz, 1H), 6.28 (d, *J* = 3.7 Hz, 1H), 7.25–7.27 (m, 2H), 7.31–7.37 (m, 38H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz): δ 20.6 (q), 20.7 (q), 20.8 (q), 20.8 (q), 20.9 (q), 20.9 (q), 27.4 (t), 27.7 (t), 29.2 (t), 29.7 (t), 70.5 (t), 70.5 (t), 71.5 (d), 71.7 (t, 2C), 71.8 (d), 71.9 (t), 71.9 (t), 72.6 (d), 72.6 (d), 73.4 (t, 2C), 73.9 (t), 74.5 (t), 74.6 (d), 77.2 (d, 2C), 77.5 (d), 77.5 (d), 80.3 (d), 80.7 (d), 80.8 (d), 81.0 (d), 81.0 (d), 81.1 (d), 81.3 (d), 89.4 (d), 92.2 (d), 127.4 (d, 2C), 127.6 (d, 5C), 127.7 (d, 5C), 127.8 (d, 3C), 127.8 (d), 127.9 (d, 2C), 128.0 (d, 2C), 128.1 (d, 2C), 128.1 (d, 2C), 128.3 (d, 5C), 128.3 (d, 5C), 128.4 (d, 4C), 128.4 (d, 2C), 137.7 (s), 137.8 (s), 137.9 (s, 2C), 137.9 (s), 138.1 (s), 138.2 (s), 138.3 (s), 168.9 (s), 169.1 (s), 169.2 (s), 169.4 (s), 169.4 (s), 169.6 (s) ppm; HRMS: calcd for $C_{46}H_{56}O_{12}N$ ($[M+NH_4]^+$) 814.3797, found 814.3798.



61

Synthesis of alkyne 61: The alkyne **61** was synthesized in 8 steps from methyl D-galactopyranoside by following the literature reported procedure.

^1H NMR ($CDCl_3$, 400 MHz): δ 0.06 (s, 3H), 0.10 (s, 3H), 0.90 (s, 9H), 2.60 (d, *J* = 2.0 Hz, 1H), 3.79–3.87 (m, 2H), 3.92–3.94 (m, 1H), 4.42–4.47 (m, 2H), 4.50–4.62 (m, 4H), 4.70–4.79 (m, 3H), 4.83 (d, *J* = 11.5 Hz, 1H), 4.84 (d, *J* = 11.2 Hz, 1H), 7.29–7.41 (m, 20H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ –4.8 (q),–4.7 (q), 18.0 (s), 25.8 (q, 3C), 70.7 (d), 71.3 (t), 71.6 (t), 71.9 (d), 73.0 (t, 2C), 75.8 (s), 75.9 (t), 81.5 (d), 81.6 (s), 86.1 (d), 127.2 (d, 2C), 127.3 (d, 2C), 127.5 (d), 127.6 (d, 2C), 127.7 (d), 127.7 (d), 127.9 (d, 2C), 128.0 (d, 2C), 128.1 (d, 2C), 128.1 (d), 128.2 (d, 4C), 138.0 (s), 138.7 (s), 138.9 (s), 139.0 (s) ppm.

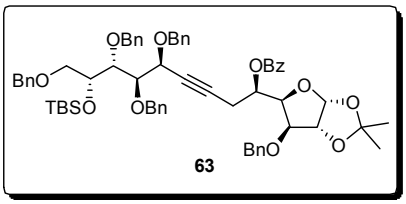


62

Synthesis of alcohol 62: The compound **62** (803 mg, 83%) was prepared from epoxide **54** (300 mg, 1.03 mmol) and alkyne **61** (2.0 gm, 3.08 mmol) following similar procedure used for preparation of compound **55**.

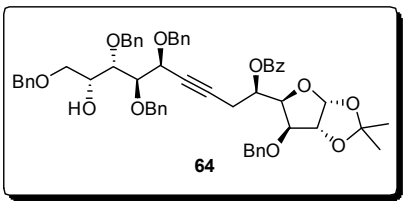
Characterization data of compound **62**: $[\alpha]^{24}_D$ = +5.4 (*c* 1.1, $CHCl_3$); IR ($CHCl_3$): 3467, 2928, 2856, 1951, 1496, 1454, 1373, 1252, 1075, 1027, 697

cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ ^1H NMR ($CDCl_3$, 500 MHz) δ 0.03 (s, 3H), 0.07 (s, 3H), 0.88 (s, 9H), 1.34 (s, 3H), 1.48 (s, 3H), 2.49–2.55 (m, 1H), 2.66–2.73 (m, 1H), 3.76–3.80 (m, 2H), 3.86–3.91 (m, 2H), 4.08–4.12 (m, 3H), 4.39–4.43 (m, 2H), 4.50 (d, J = 12.1 Hz, 1H), 4.54–4.58 (m, 3H), 4.63 (d, J = 3.9 Hz, 1H), 4.64–4.73 (m, 4H), 4.80 (d, J = 11.1 Hz, 1H), 4.82 (d, J = 11.1 Hz, 1H), 5.95 (d, J = 3.8 Hz, 1H), 7.26–7.36 (m, 25H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz): δ –4.8 (q), –4.6 (q), 18.0 (s), 25.3 (t), 25.9 (q, 3C), 26.3 (q), 26.9 (q), 67.3 (d), 71.0 (d), 71.2 (t), 71.4 (t), 72.2 (t), 72.3 (d), 72.8 (t), 73.0 (t), 75.6 (t), 80.3 (s), 81.3 (d), 81.6 (d), 81.7 (d), 82.4 (d), 84.3 (s), 86.0 (d), 105.1 (d), 111.8 (s), 127.2 (d, 2C), 127.3 (d), 127.4 (d), 127.5 (d, 2C), 127.6 (d, 2C), 127.7 (d, 2C), 127.8 (d, 2C), 127.9 (d, 2C), 128.0 (d, 2C), 128.1 (d, 3C), 128.2 (d, 2C), 128.2 (d, 2C), 128.6 (d, 2C), 137.3 (s), 138.3 (s), 138.6 (s), 139.0 (s), 139.1 (s) ppm; HRMS: calcd for $C_{57}H_{74}O_{10}NSi$ ($[M+NH_4]^+$) 960.5077, found 960.5079.



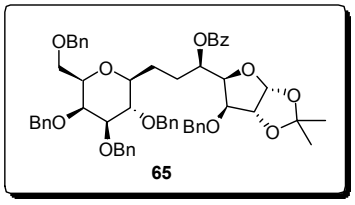
Synthesis of benzoate 63: Applying similar procedure for synthesis of compound **56**, benzoate **63** (450 mg, 81%) was prepared from alcohol **62** (500 mg, 0.53 mmol).

Characterization data of compound **63**: $[\alpha]^{24}_D$ = –19.5 (*c* 0.8, $CHCl_3$); IR ($CHCl_3$): 2926, 1725, 1602, 1454, 1272, 1112, 1027, 836, 697 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 0.03 (s, 3H), 0.09 (s, 3H), 0.91 (s, 9H), 1.35 (s, 3H), 1.42 (s, 3H), 2.93 (ddd, J = 1.7, 5.1, 17.5 Hz, 1H), 3.14 (ddd, J = 1.8, 3.7, 17.5 Hz, 1H), 3.79 (dd, J = 2.4, 8.4 Hz, 1H), 3.81–3.85 (m, 2H), 3.91 (d, J = 9.0 Hz, 1H), 4.12 (d, J = 3.1 Hz, 1H), 4.43–4.54 (m, 5H), 4.59–4.66 (m, 4H), 4.68–4.75 (m, 3H), 4.81 (d, J = 11.6 Hz, 1H), 4.86 (d, J = 11.3 Hz, 1H), 5.59 (ddd, J = 3.7, 5.1, 8.8 Hz, 1H), 6.04 (d, J = 3.6 Hz, 1H), 7.19–7.30 (m, 8H), 7.32–7.40 (m, 19H), 7.56–7.59 (m, 1H), 7.97–8.00 (m, 2H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz) δ –4.8 (q), –4.7 (q), 18.0 (s), 22.0 (t), 25.8 (q, 3C), 26.4 (q), 27.0 (q), 68.8 (d), 70.7 (t), 70.7 (d), 71.6 (t), 71.9 (d), 72.2 (t), 72.8 (t), 72.9 (t), 75.6 (t), 79.4 (d), 80.1 (s), 80.9 (d), 81.3 (d), 82.0 (d), 83.1 (s), 86.1 (d), 105.3 (d), 112.1 (s), 127.0 (d), 127.1 (d), 127.2 (d), 127.2 (d), 127.3 (d), 127.3 (d), 127.5 (d, 2C), 127.6 (d, 2C), 127.7 (d, 2C), 127.8 (d, 2C), 127.9 (d), 128.0 (d, 2C), 128.0 (d, 2C), 128.0 (d, 3C), 128.2 (d, 2C), 128.3 (d, 3C), 129.7 (d, 2C), 129.8 (s), 133.0 (d), 136.7 (s), 138.4 (s), 138.8 (s), 139.0 (s), 139.2 (s), 165.0 (s) ppm; HRMS: calcd for $C_{64}H_{78}O_{11}NSi$ ($[M+NH_4]^+$) 1064.5339, found 1064.5344.



Synthesis of alkynol 64: The alkynol **64** (319 mg, 75%) was synthesized from TBS ether **63** (480 mg, 0.45 mmol) following similar procedure used for the preparation of compound **57**.

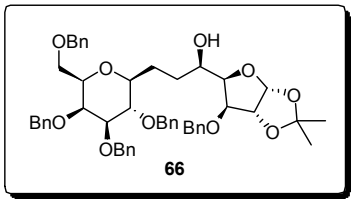
Characterization data of compound **64**: $[\alpha]^{24}_{D}$ = –42.5 (*c* 1.5, $CHCl_3$); IR ($CHCl_3$): 3401, 2924, 1722, 1601, 1454, 1272, 1114, 1072, 698 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 1.31 (s, 3H), 1.46 (s, 3H), 2.85 (ddd, *J* = 1.8, 4.8, 17.5 Hz, 1H), 3.07 (ddd, *J* = 1.9, 3.8, 17.5 Hz, 1H), 3.65 (dd, *J* = 4.5, 10.3 Hz, 1H), 3.68–3.71 (m, 2H), 3.87 (dt, *J* = 1.3, 4.2 Hz, 1H), 3.93 (dd, *J* = 1.3, 8.5 Hz, 1H), 4.03 (d, *J* = 3.2 Hz, 1H), 4.36 (d, *J* = 11.5 Hz, 1H), 4.37 (d, *J* = 12.1 Hz, 1H), 4.40 (d, *J* = 11.8 Hz, 1H), 4.43 (d, *J* = 11.5 Hz, 1H), 4.46 (bs, 3H), 4.54 (d, *J* = 11.6 Hz, 1H), 4.62–4.64 (m, 2H), 4.69 (d, *J* = 11.6 Hz, 1H), 4.77 (d, *J* = 11.7 Hz, 1H), 4.80 (d, *J* = 11.5 Hz, 1H), 5.49 (dt, *J* = 4.4, 8.9 Hz, 1H), 5.95 (d, *J* = 3.7 Hz, 1H), 7.09–7.17 (m, 4H), 7.20–7.32 (m, 23H), 7.48 (t, *J* = 7.5 Hz, 1H), 7.91–7.93 (m, 2H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz): δ 22.0 (t), 26.3 (q), 27.0 (q), 68.6 (d), 68.7 (d), 70.7 (t), 71.3 (d), 71.8 (t), 72.17 (t), 72.5 (t), 73.3 (t), 73.7 (t), 76.2 (d), 79.1 (s), 79.5 (d), 80.0 (d), 80.8 (d), 82.0 (d), 83.5 (s), 105.3 (d), 112.1 (s), 127.4 (d, 2C), 127.5 (d), 127.6 (d, 3C), 127.7 (d, 2C), 127.9 (d), 127.9 (d, 2C), 128.0 (d, 2C), 128.1 (d, 2C), 128.2 (d, 4C), 128.2 (d, 2C), 128.3 (d, 3C), 128.3 (d, 3C), 129.7 (d, 2C), 129.8 (s), 133.0 (d), 136.7 (s), 137.6 (s), 138.2 (s), 138.3 (s), 138.7 (s), 165.0 (s) ppm; HRMS: calcd for $C_{58}H_{64}O_{11}N$ ($[M+NH_4]^+$) 950.4474, found 950.4479.



Synthesis of disaccharide 40: The *C*-disaccharide **65** (167 mg, 76%) was prepared from alkynol **64** (220 mg, 0.23 mmol) using procedure A.

Characterization data of compound **65**: $[\alpha]^{24}_{D}$ = –31.8 (*c* 2.5, $CHCl_3$); IR ($CHCl_3$): 2925, 2857, 1722, 1454, 1269, 1111, 1027, 692 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 1.32 (s, 3H), 1.51 (s, 3H), 1.69–1.75 (m, 1H), 1.79–1.86 (m, 2H), 2.16–2.22 (m, 1H), 3.64 (dd, *J* = 4.2, 14.6 Hz, 1H), 3.66 (dd, *J* = 5.0, 14.6 Hz, 1H), 3.68–3.72 (m, 1H), 3.78 (dd, *J* = 3.5, 4.7 Hz, 1H), 3.83–4.01 (m, 2H), 4.03 (dd, *J* = 4.2, 4.7 Hz, 1H), 4.09 (dd, *J* = 3.4, 5.0 Hz, 1H), 4.31–4.39 (m, 4H), 4.42–4.47 (m, 4H), 4.50 (d, *J* = 11.6 Hz, 1H), 4.56 (d, *J* = 11.9 Hz, 1H), 4.58 (d, *J* = 3.8 Hz, 1H), 4.74 (d, *J* = 11.9 Hz, 1H), 5.51–5.55 (m, 1H), 5.92 (d, *J* = 3.8 Hz, 1H), 7.13–7.32 (m, 25H), 7.38 (t, *J* = 7.6 Hz, 2H), 7.54 (t, *J* = 7.3 Hz, 1H), 7.96–7.98 (m, 2H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz): δ 26.2 (q), 26.9 (q), 28.1 (t), 28.3 (t), 70.9 (d), 71.0 (t), 71.6 (t), 71.8 (t), 72.1 (t), 73.0 (t), 73.3 (t), 77.7

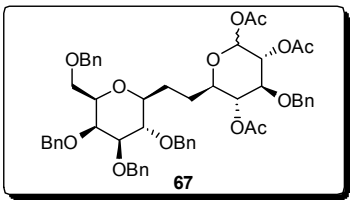
(d), 80.6 (d), 81.2 (d), 81.8 (d), 82.0 (d, 2C), 84.5 (d), 88.0 (d), 105.2 (d), 111.7 (s), 127.4 (d, 2C), 127.5 (d), 127.6 (d, 2C), 127.6 (d, 2C), 127.7 (d, 2C), 127.8 (d), 128.0 (d, 2C), 128.2 (d, 4C), 128.3 (d, 6C), 128.3 (d, 5C), 129.6 (d, 2C), 130.2 (s), 132.9 (d), 136.9 (s), 138.0 (s), 138.1 (s), 138.3 (s), 138.6 (s), 165.2 (s) ppm; HRMS: calcd for $C_{58}H_{63}O_{11}$ ($[M+H]^+$) 935.4365, found 935.4365.



66

Synthesis of alcohol 41: The alcohol **66** (73 mg, 83%) was synthesized from compound **65** (100 mg, 0.1 mmol) employing similar procedure used for the preparation of compound **59**.

Characterization data of compound **66**: $[\alpha]^{24}_{D}$ = –34.4 (*c* 0.8, $CHCl_3$); IR ($CHCl_3$): 3435, 2926, 2861, 1496, 1454, 1373, 1215, 1074, 1027, 736, 697 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 1.32 (s, 3H), 1.47 (s, 3H), 1.48–1.52 (m, 1H), 1.68–1.77 (m, 1H), 1.82–1.89 (m, 2H), 2.75 (d, *J* = 5.8 Hz, 1H), 3.63–3.68 (m, 2H), 3.72 (dd, *J* = 4.6, 9.8 Hz, 1H), 3.80 (dd, *J* = 3.5, 5.1 Hz, 1H), 3.93–3.99 (m, 2H), 4.01–4.05 (m, 1H), 4.07 (d, *J* = 3.0 Hz, 1H), 4.09–4.11 (m, 1H), 4.13 (dd, *J* = 3.4, 4.8 Hz, 1H), 4.35–4.51 (m, 6H), 4.53 (d, *J* = 12.0 Hz, 1H), 4.57 (d, *J* = 11.9 Hz, 1H), 4.60 (d, *J* = 3.9 Hz, 1H), 4.70 (d, *J* = 11.9 Hz, 1H), 4.75 (d, *J* = 11.9 Hz, 1H), 5.94 (d, *J* = 3.9 Hz, 1H), 7.21–7.24 (m, 3H), 7.27–7.34 (m, 22H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz): δ 26.3 (q), 26.8 (q), 29.1 (t), 30.9 (t), 68.9 (d), 70.7 (t), 71.8 (t), 71.9 (t), 72.0 (t), 73.0 (t), 73.4 (t), 77.7 (d), 82.1 (d), 82.1 (d), 82.1 (d), 82.2 (d), 82.4 (d), 84.5 (d), 88.0 (d), 105.1 (d), 111.6 (s), 127.5 (d, 2C), 127.6 (d, 2C), 127.6 (d, 2C), 127.6 (d), 127.7 (d), 127.7 (d, 2C), 127.9 (d, 2C), 128.2 (d, 3C), 128.2 (d, 2C), 128.3 (d, 2C), 128.4 (d, 4C), 128.6 (d, 2C), 137.2 (s), 137.9 (s), 138.0 (s), 138.3 (s), 138.5 (s) ppm; HRMS: calcd for $C_{51}H_{59}O_{10}$ ($[M+H]^+$) 831.4103, found 831.4102.

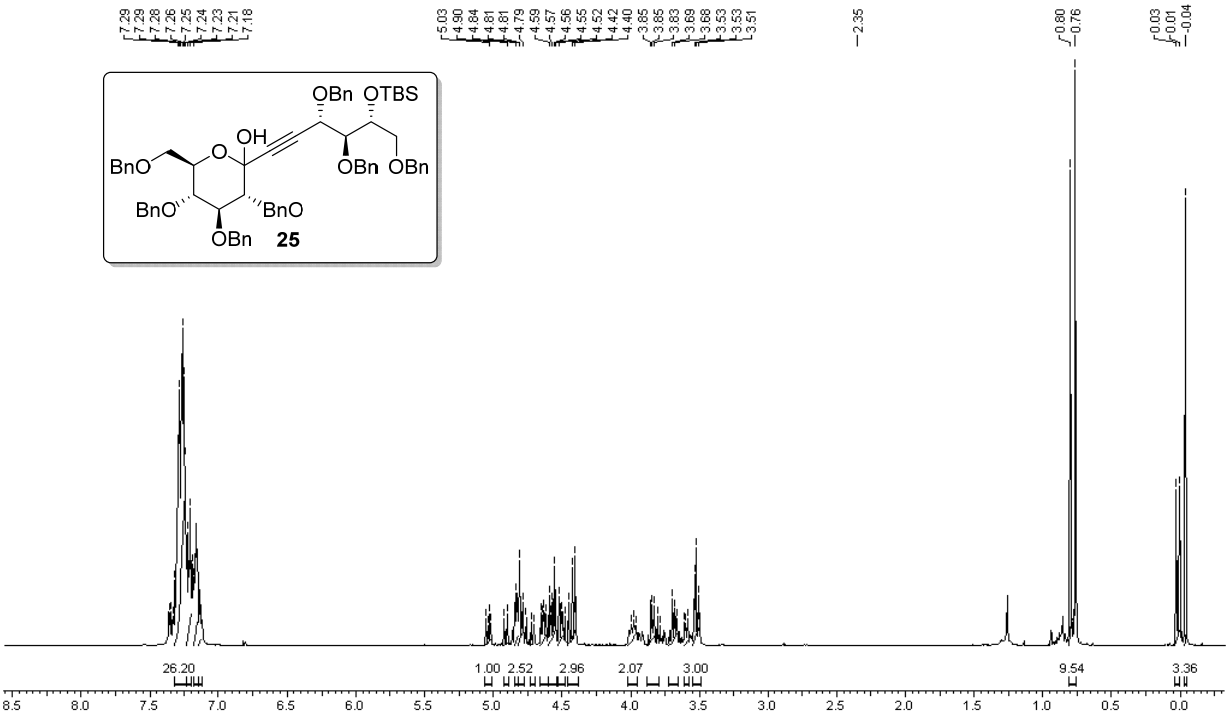


67

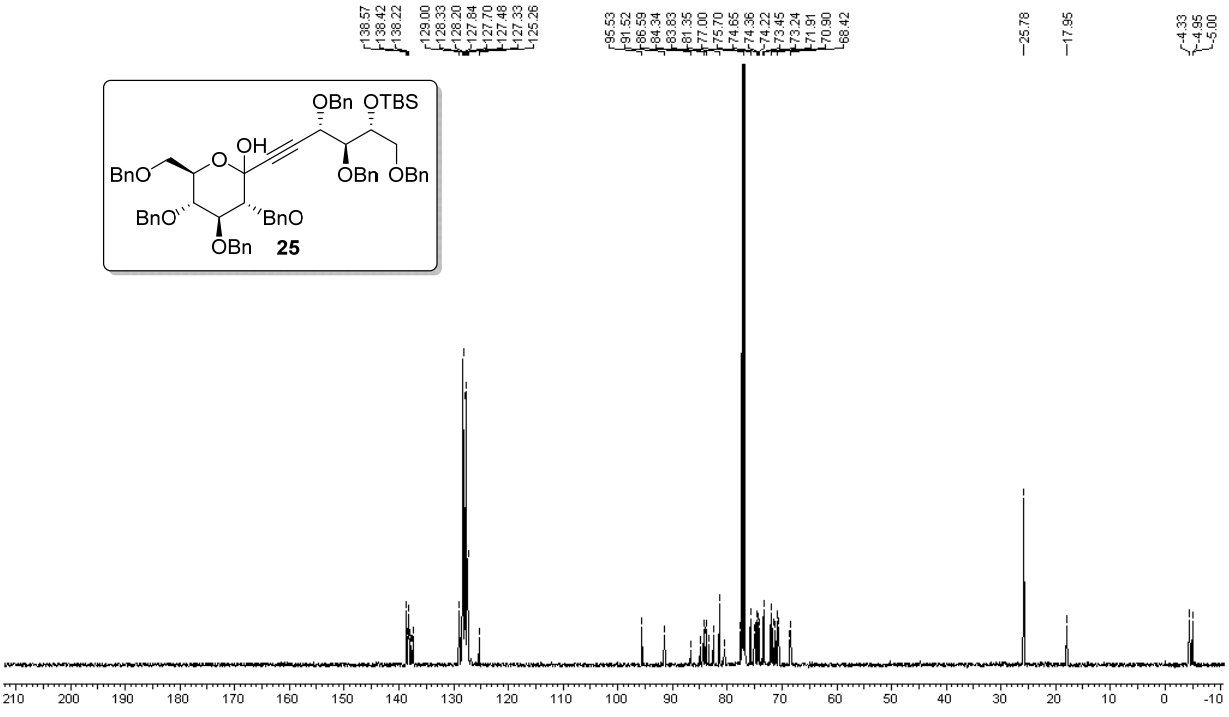
Synthesis of *C*-disaccharide 67: A solution of acetonide derivative **66** (25 mg, 0.03 mmol) in acetic acid (4 mL) and water (1 mL) was stirred at 85 °C for 12 h. Then the reaction contents were evaporated under reduced pressure. The traces acetic acid and water were removed by co-evaporation with toluene (3 x 2 mL). The crude product thus obtained was dissolved in pyridine (0.5 mL) and treated with acetic anhydride (0.5 mL) at 0 °C to rt for 4 h. The reaction contents were removed by co-evaporation with toluene on rotavapour under reduced pressure. The crude was purified by column chromatography (230–400 silica gel, 1:4 ethyl acetate/petroleum ether) to afford 1:1 anomeric mixture of **67** (19 mg, 69%) as colourless thick oil.

Characterization data of compound **67**: [α:β = 1:1]; IR ($CHCl_3$): 2925, 2868, 1755, 1496, 1454, 1368, 1219, 1071, 738, 681 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 138–1.47 (m, 2H), 1.59–1.64 (m, 2H), 1.69–1.77 (m, 4H), 1.91 (s, 3H), 1.92 (s, 3H), 1.96 (s, 3H), 1.98 (s, 3H), 2.05 (s, 3H), 2.11 (s, 3H), 3.47–3.57 (m, 2H), 3.59–3.68 (m, 6H), 3.72 (dd, J = 4.6, 9.2 Hz, 2H), 3.75–3.85 (m, 4H), 3.87–3.99 (m, 4H), 4.04–4.13 (m, 4H), 4.32–4.39 (m, 4H), 4.40–4.49 (m, 10H), 4.51–4.59 (m, 4H), 4.61 (bd, J = 4.3 Hz, 2H), 4.69 (d, J = 11.9 Hz, 2H), 4.73 (d, J = 11.8 Hz, 1H), 4.76 (d, J = 11.8 Hz, 1H), 4.94 (t, J = 9.7 Hz, 2H), 5.02 (dd, J = 3.7, 10.0 Hz, 1H), 5.12 (dd, J = 8.4, 9.3 Hz, 1H), 5.59 (d, J = 8.3 Hz, 1H), 6.26 (d, J = 3.8 Hz, 1H), 7.21–7.24 (m, 10 H), 7.27–7.34 (m, 40H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz): δ 20.6 (q), 20.7 (q), 20.8 (q), 20.8 (q), 20.8 (q), 20.9 (q), 27.6 (t), 27.9 (t), 28.6 (t), 28.7 (t), 70.8 (t), 70.9 (t), 71.6 (t), 71.7 (t), 71.7 (d), 71.8 (t, 2C), 71.9 (d), 72.7 (d, 2C), 73.1 (t, 2C), 73.4 (t, 2C), 74.0 (t), 74.6 (t), 74.7 (d), 77.2 (d), 77.3 (d), 77.7 (d, 2C), 80.3 (d), 82.1 (d), 82.3 (d, 2C), 82.4 (d), 84.6 (d), 84.6 (d), 88.2 (d), 88.3 (d), 89.4 (d), 92.2 (d), 127.3 (d), 127.4 (d), 127.5 (d), 127.5 (d, 3C), 127.6 (d, 4C), 127.6 (d, 3C), 127.7 (d, 4C), 127.7 (d, 3C), 127.7 (d, 5C), 127.8 (d), 128.0 (d), 128.1 (d, 3C), 128.2 (d, 2C), 128.3 (d), 128.3 (d, 5C), 128.4 (d, 5C), 128.4 (d, 5C), 128.4 (d, 2C), 137.8 (s), 137.9 (s, 2C), 138.0 (s, 2C), 138.1 (s), 138.3 (s), 138.3 (s), 138.6 (s), 138.6 (s), 169.0 (s), 169.1 (s), 169.2 (s), 169.4 (s, 2C), 169.6 (s) ppm; HRMS: calcd for $C_{54}H_{64}O_{13}N$ ($[M+NH_4]^+$) 934.4372, found 934.4373.

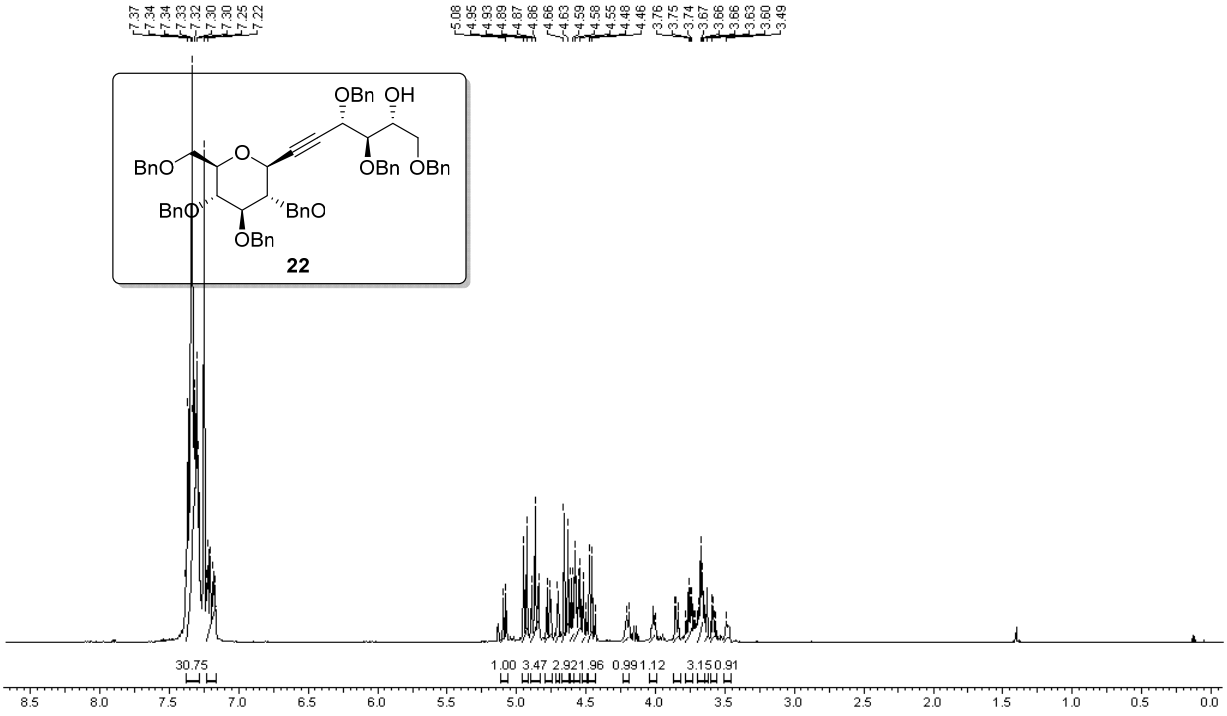
SPECTRA



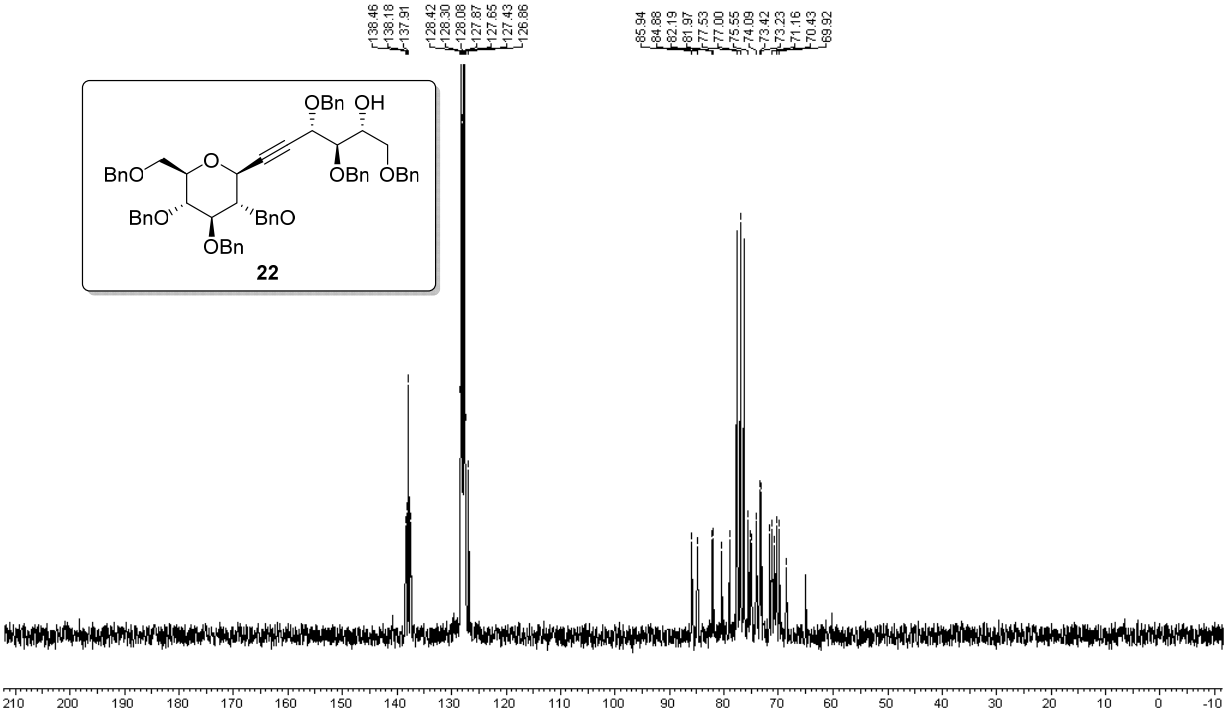
^{1}H NMR Spectrum of **25** in $CDCl_3$ (500 MHz)



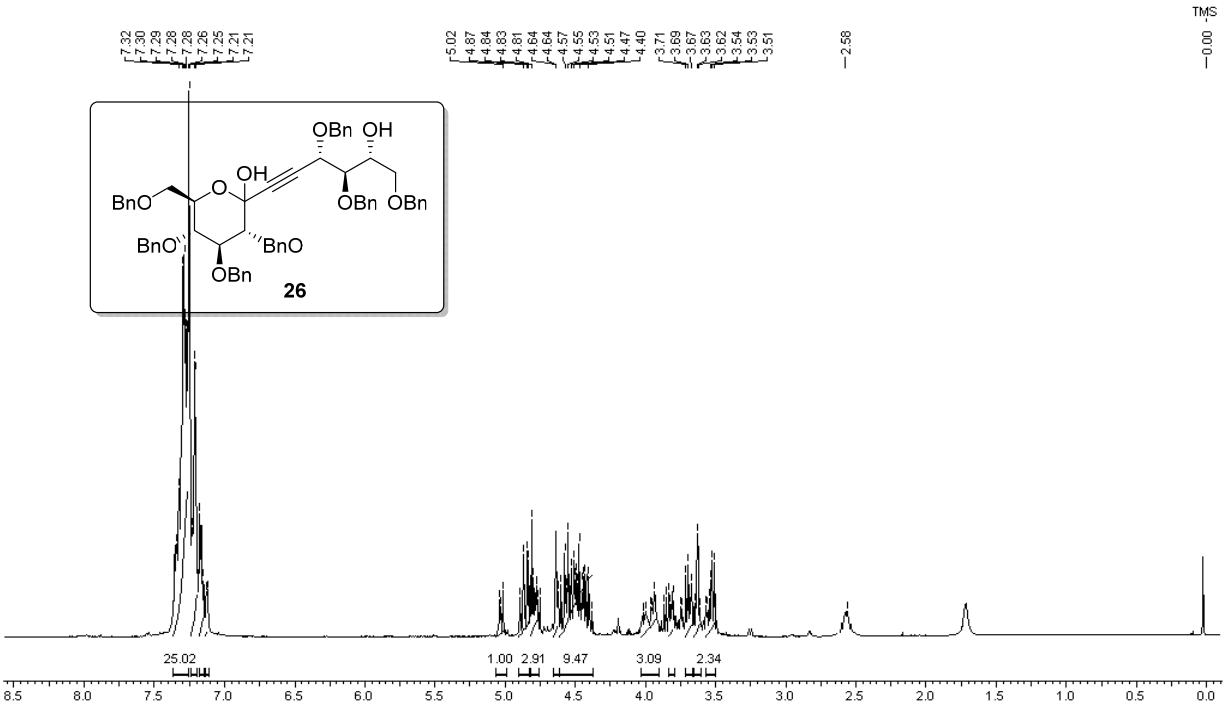
^{13}C NMR Spectrum of **25** in $CDCl_3$ (125 MHz)



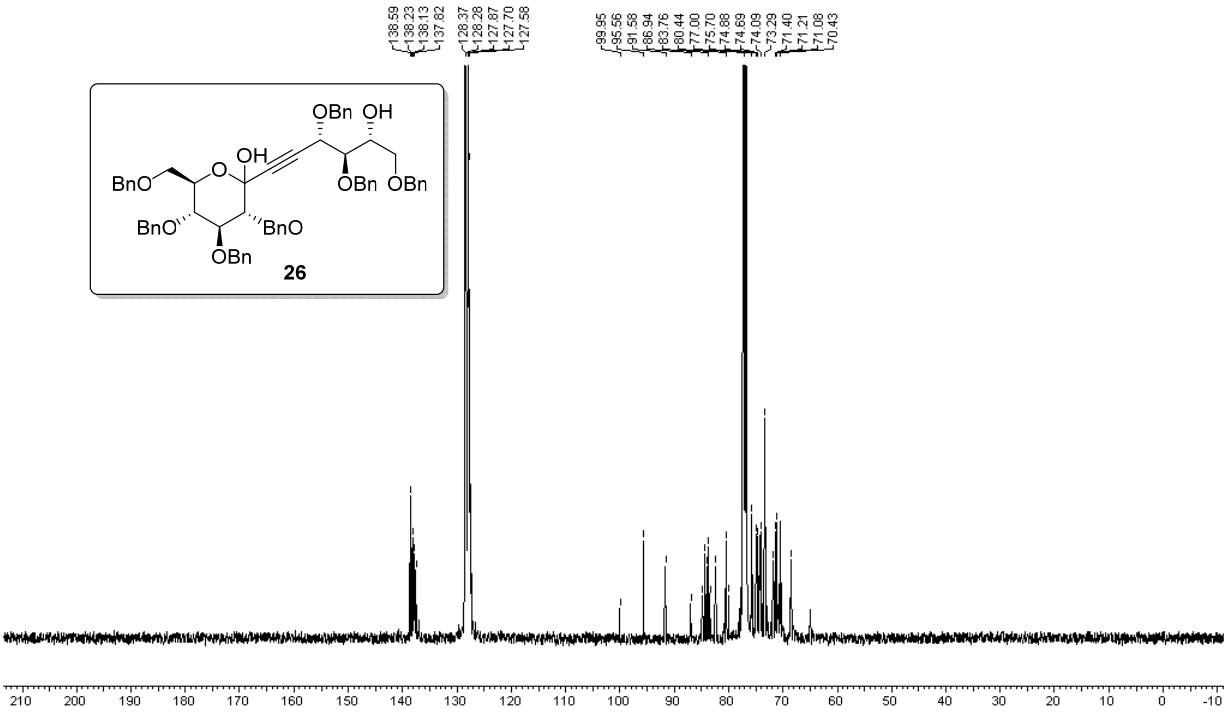
^{1}H NMR Spectrum of **22** in $CDCl_3$ (400 MHz)



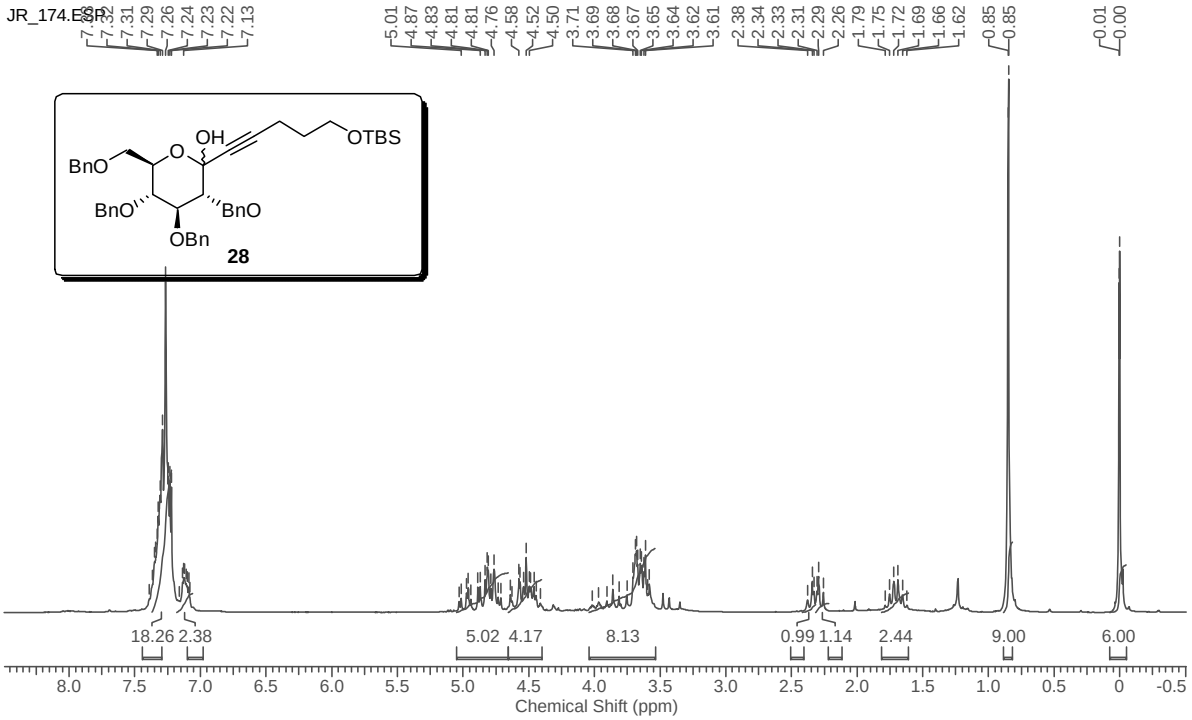
^{13}C NMR Spectrum of **22** in $CDCl_3$ (100 MHz)



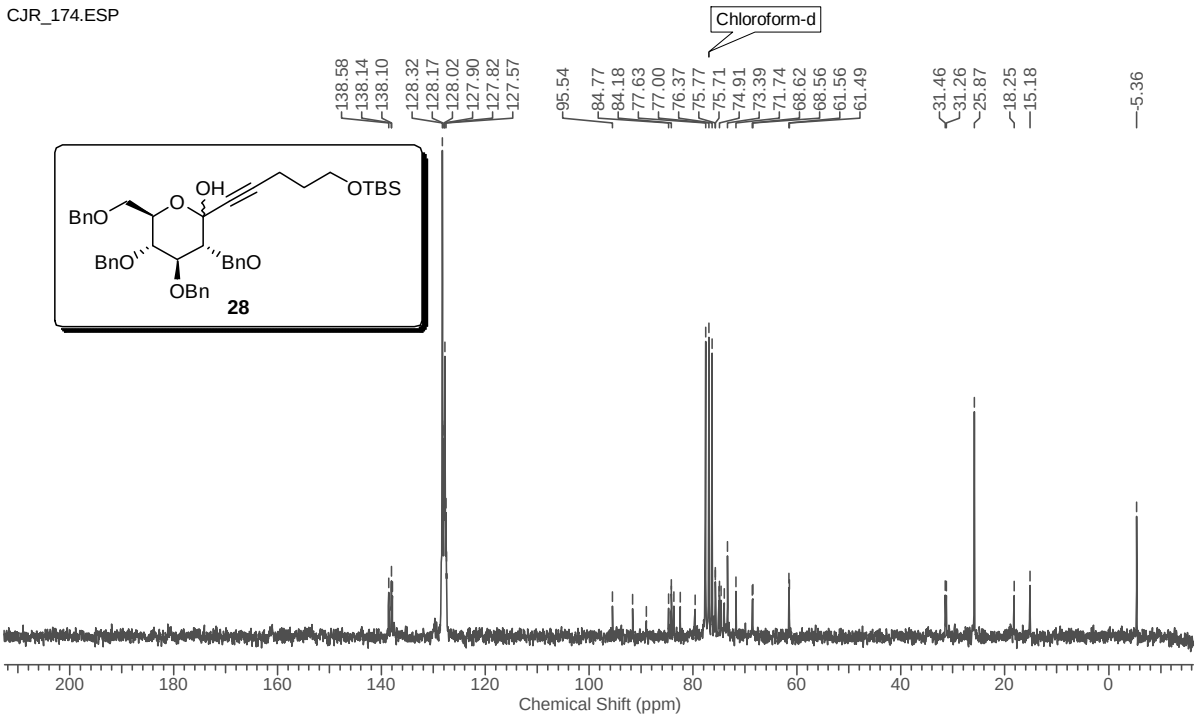
^{1}H NMR Spectrum of **26** in $CDCl_3$ (500 MHz)



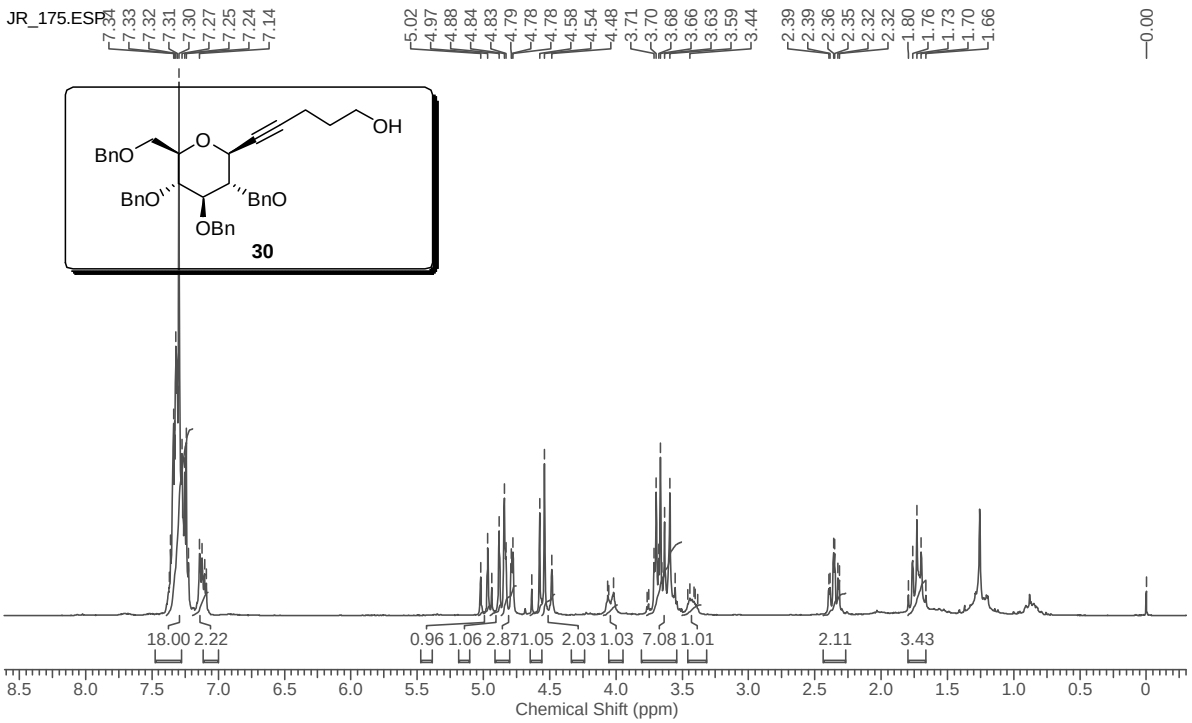
^{13}C NMR Spectrum of **26** in $CDCl_3$ (125 MHz)



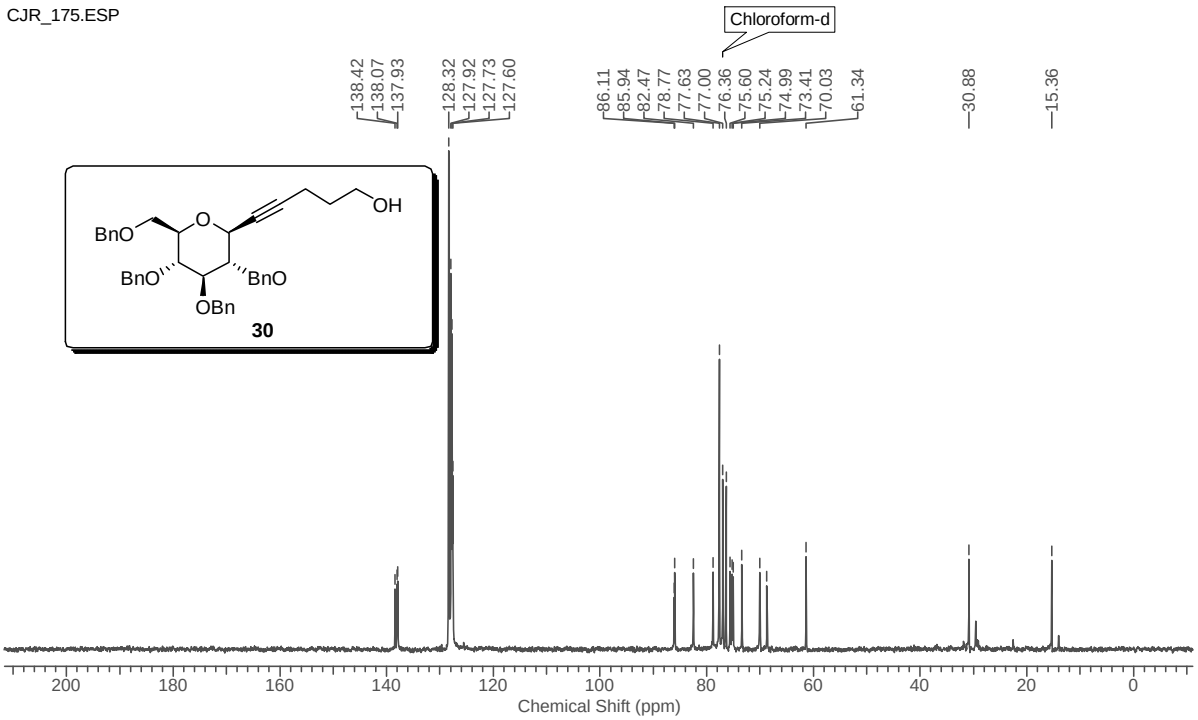
^{1}H NMR Spectrum of **28** in $CDCl_3$ (200 MHz)



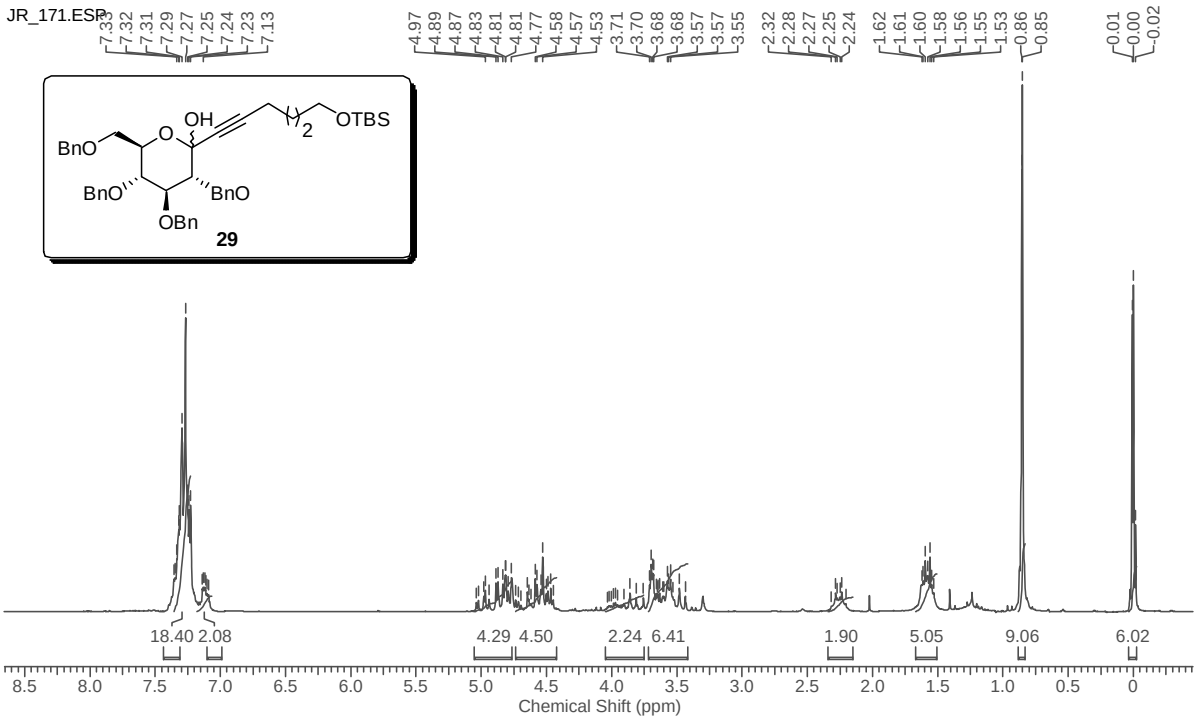
^{13}C NMR Spectrum of **28** in $CDCl_3$ (50 MHz)



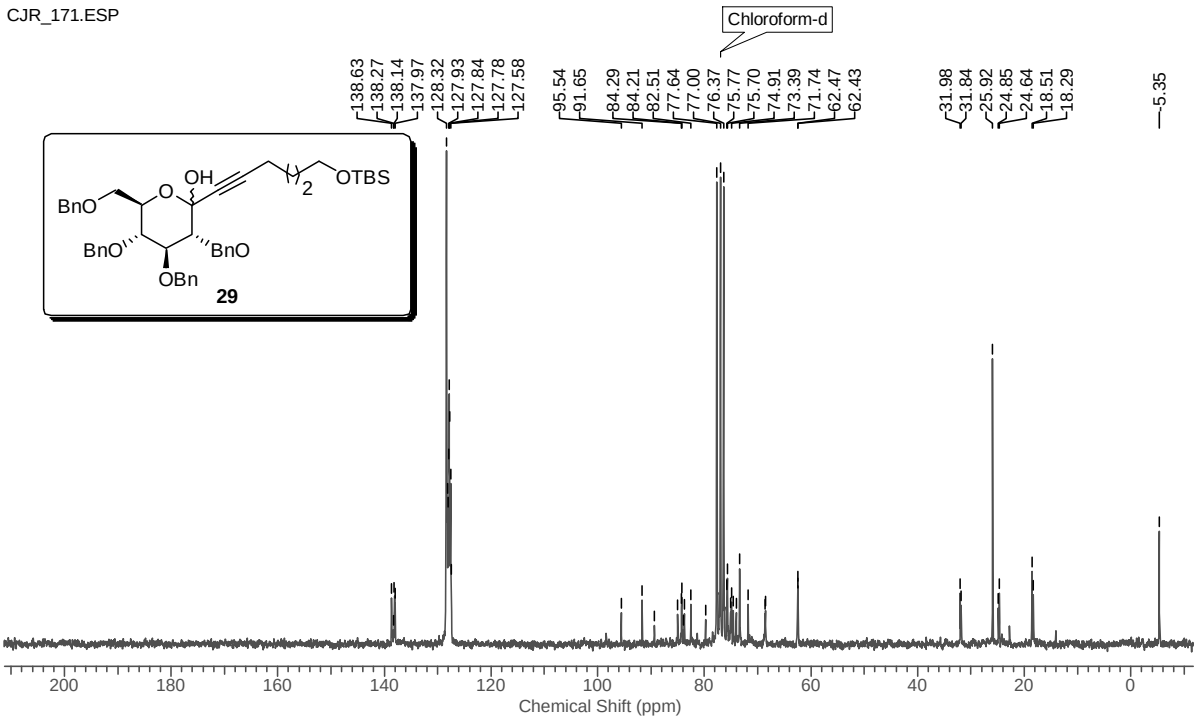
^{1}H NMR Spectrum of **30** in $CDCl_3$ (200 MHz)



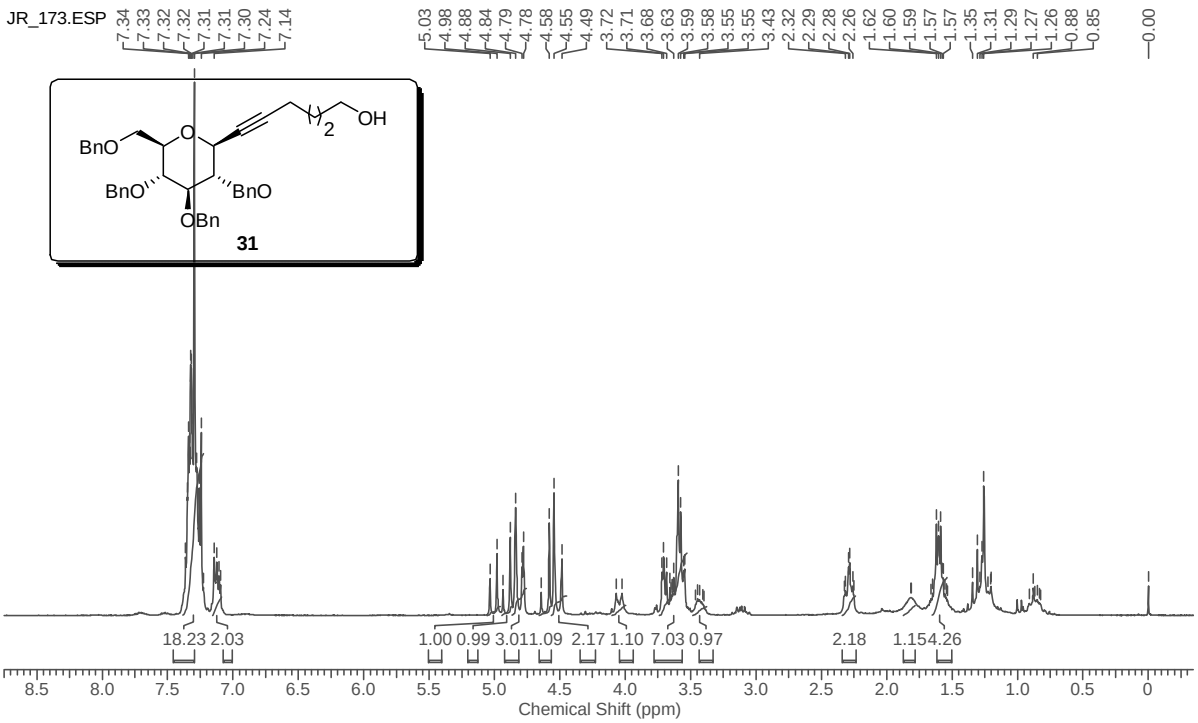
^{13}C NMR Spectrum of **30** in $CDCl_3$ (50 MHz)



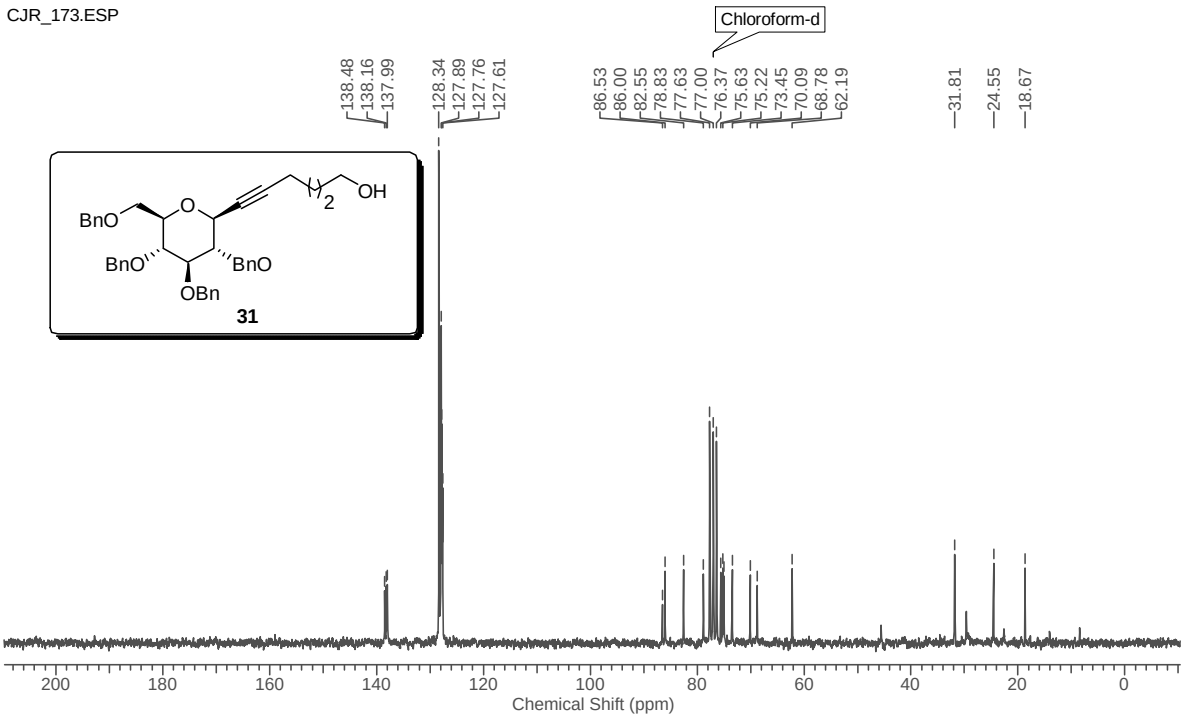
^{1}H NMR Spectrum of **29** in $CDCl_3$ (200 MHz)



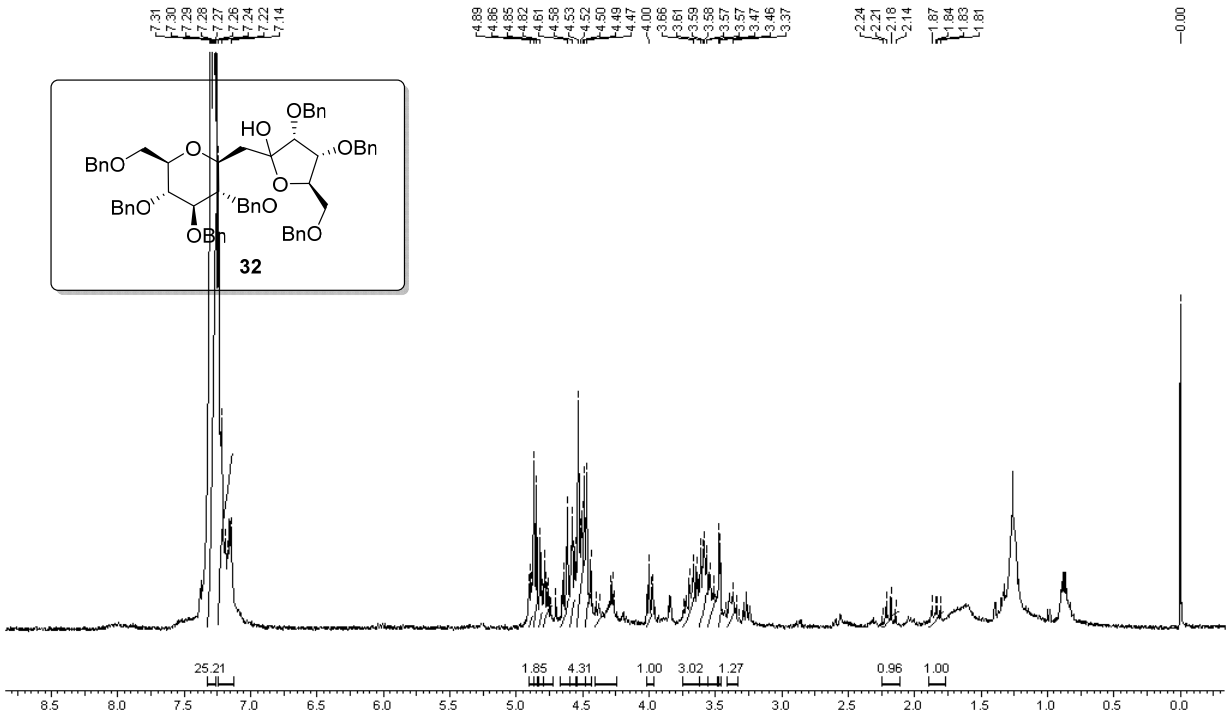
^{13}C NMR Spectrum of **29** in $CDCl_3$ (50 MHz)



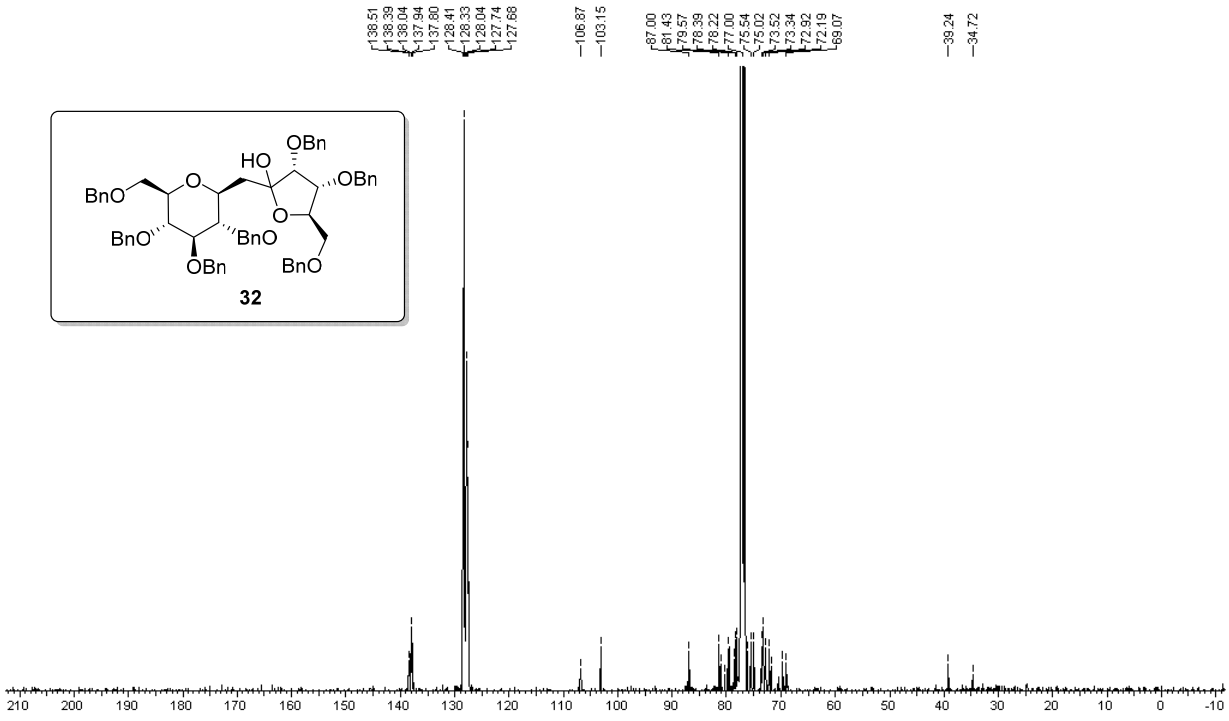
^{1}H NMR Spectrum of **31** in $CDCl_3$ (200 MHz)



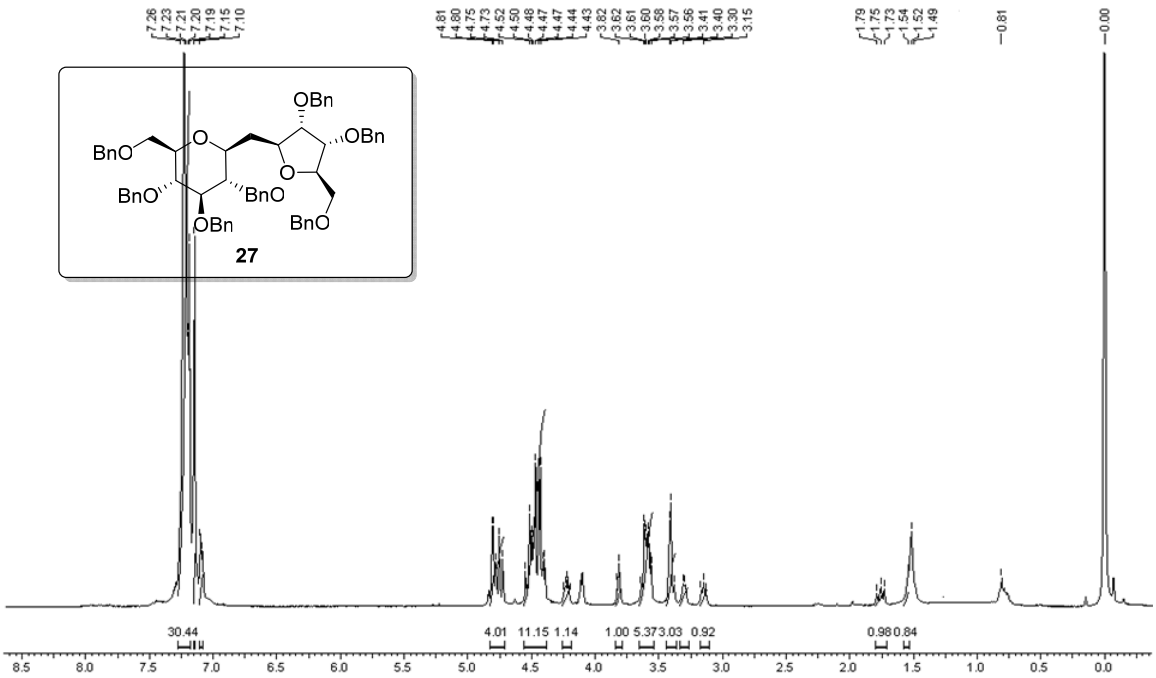
^{13}C NMR Spectrum of **31** in $CDCl_3$ (50 MHz)



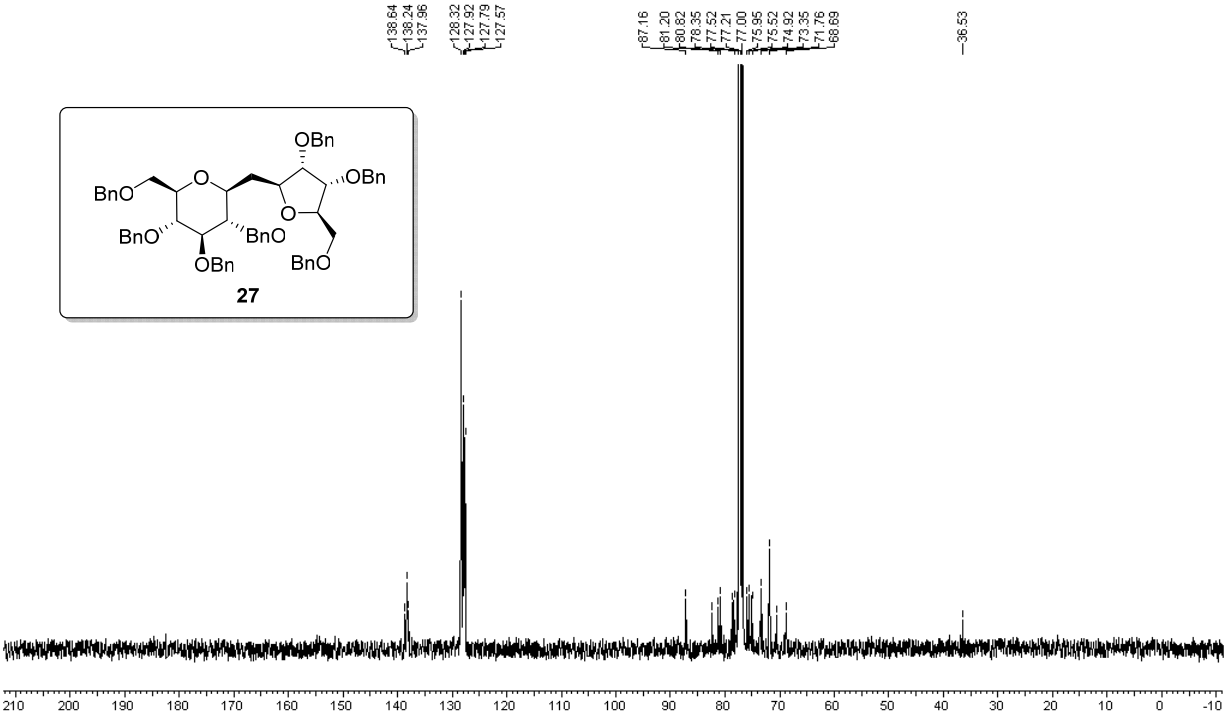
^{1}H NMR Spectrum of **32** in $CDCl_3$ (500 MHz)



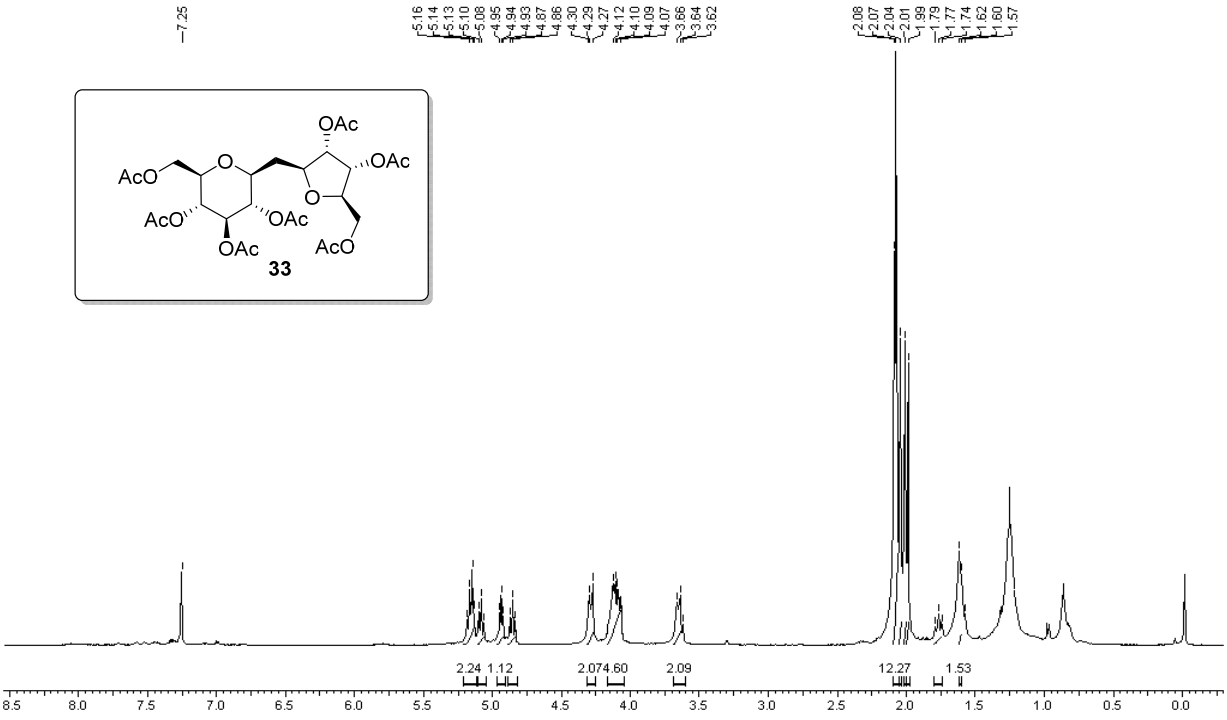
^{13}C NMR Spectrum of **32** in $CDCl_3$ (125 MHz)



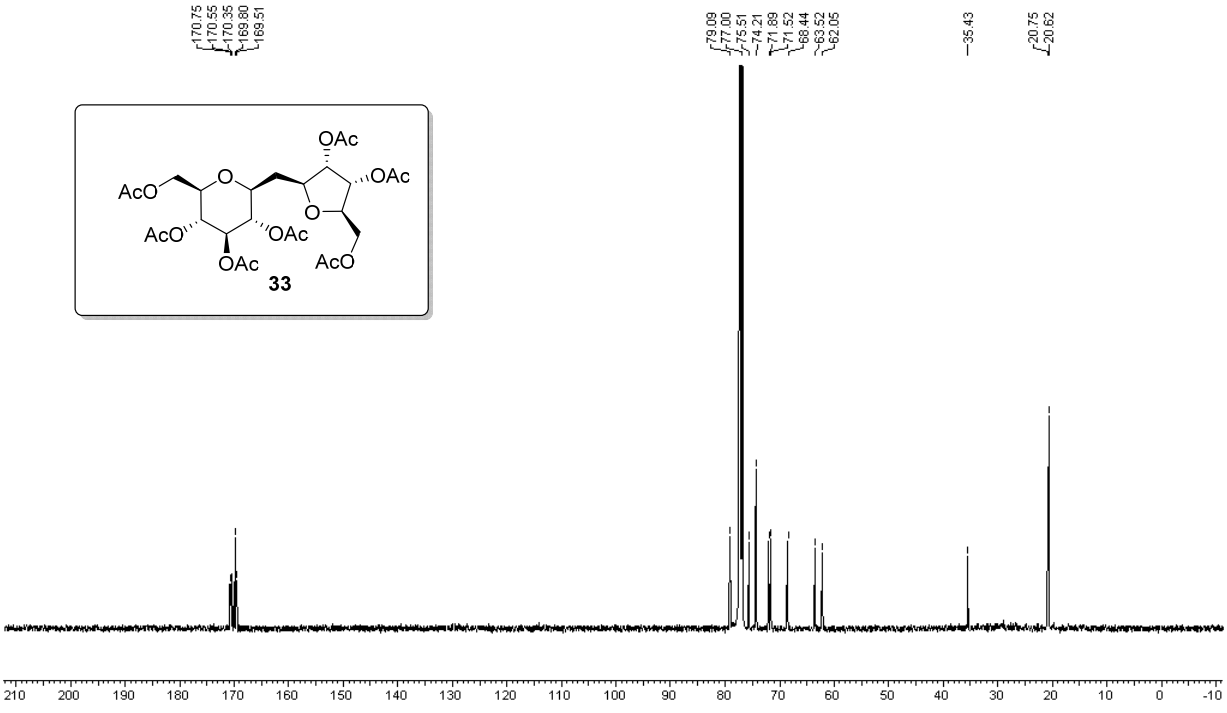
^{1}H NMR Spectrum of **27** in $CDCl_3$ (500 MHz)



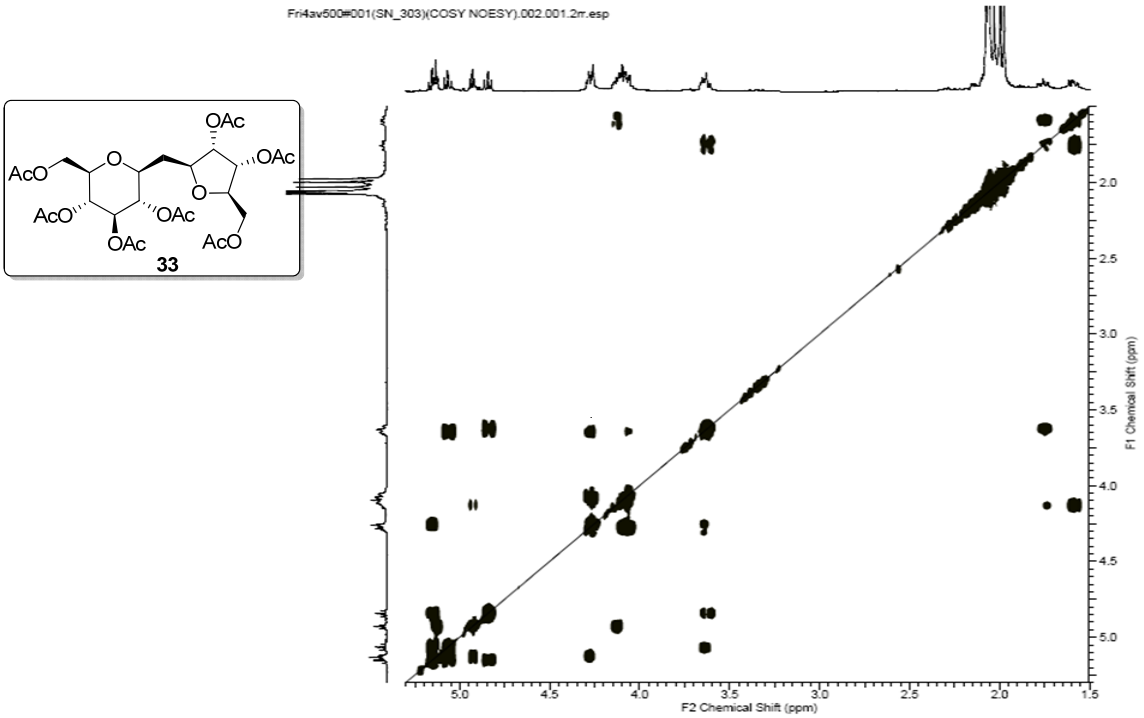
^{13}C NMR Spectrum of **27** in $CDCl_3$ (125 MHz)



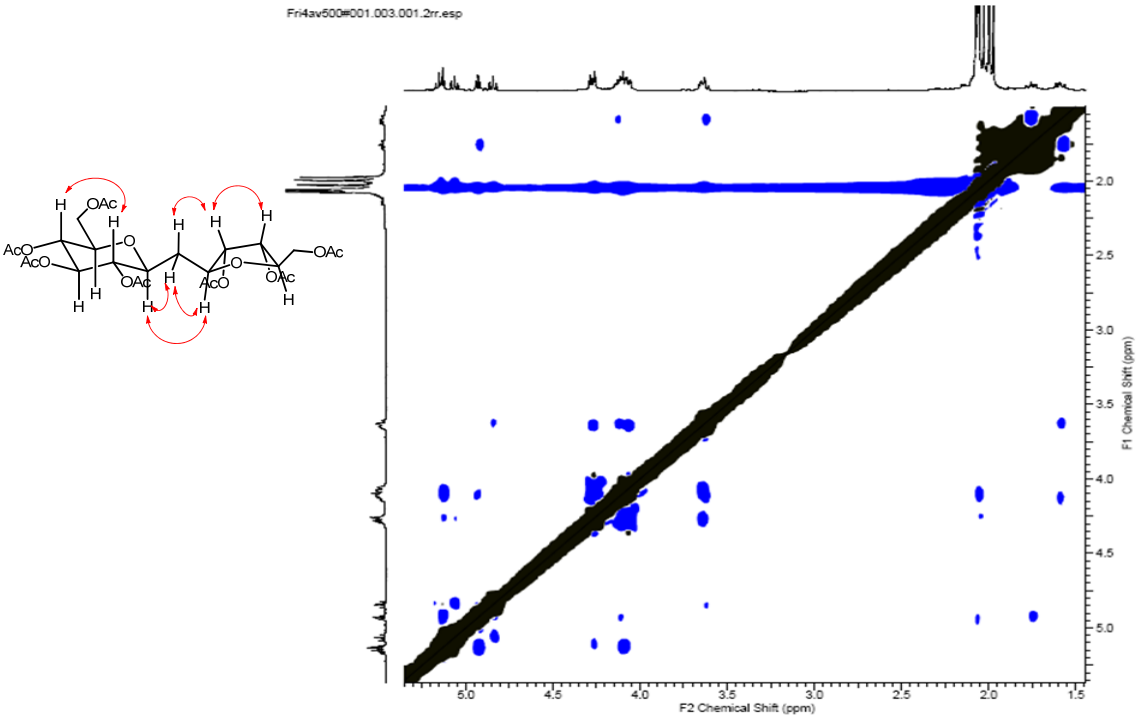
^{1}H NMR Spectrum of **33** in $CDCl_3$ (500 MHz)



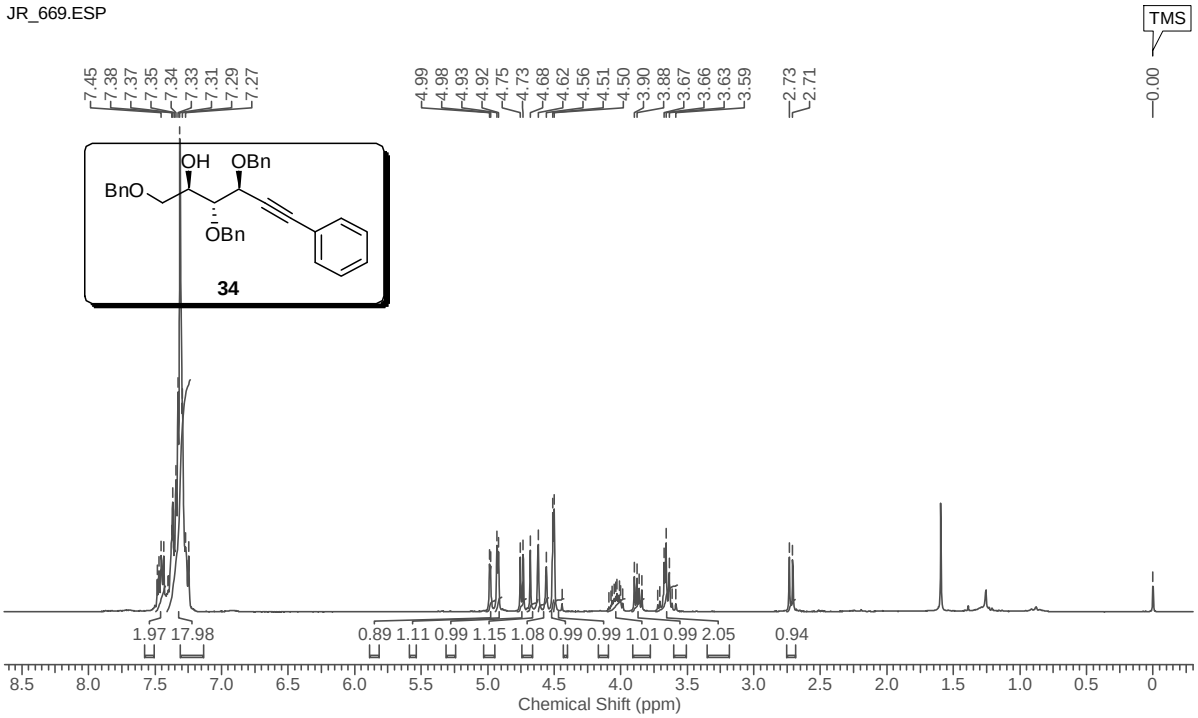
^{13}C NMR Spectrum of **33** in $CDCl_3$ (125 MHz)



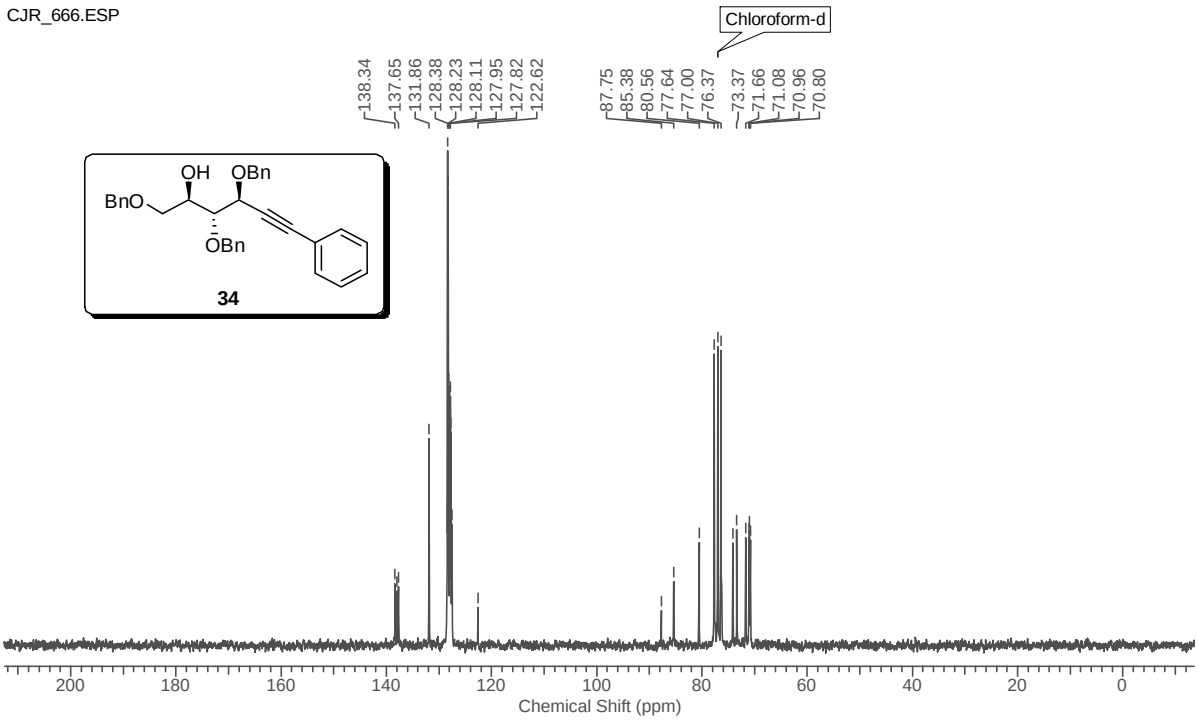
COSY Spectrum of **33** in $CDCl_3$ (500 MHz)



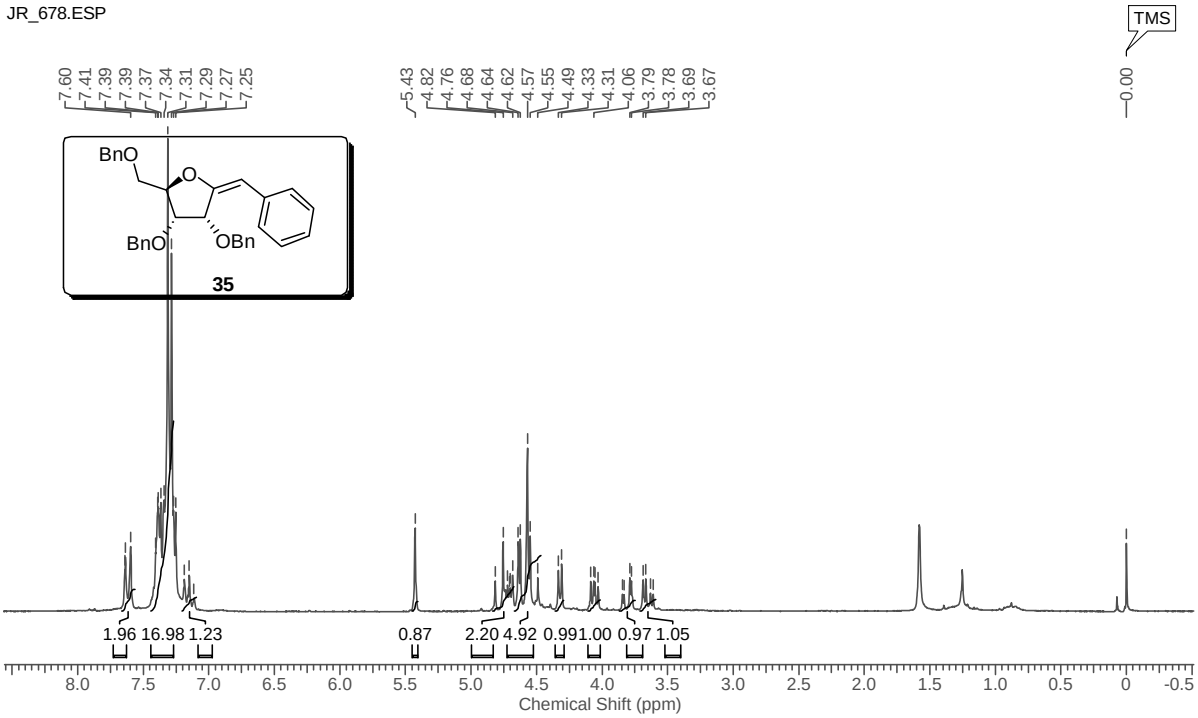
NOESY Spectrum of **33** in $CDCl_3$ (500 MHz)



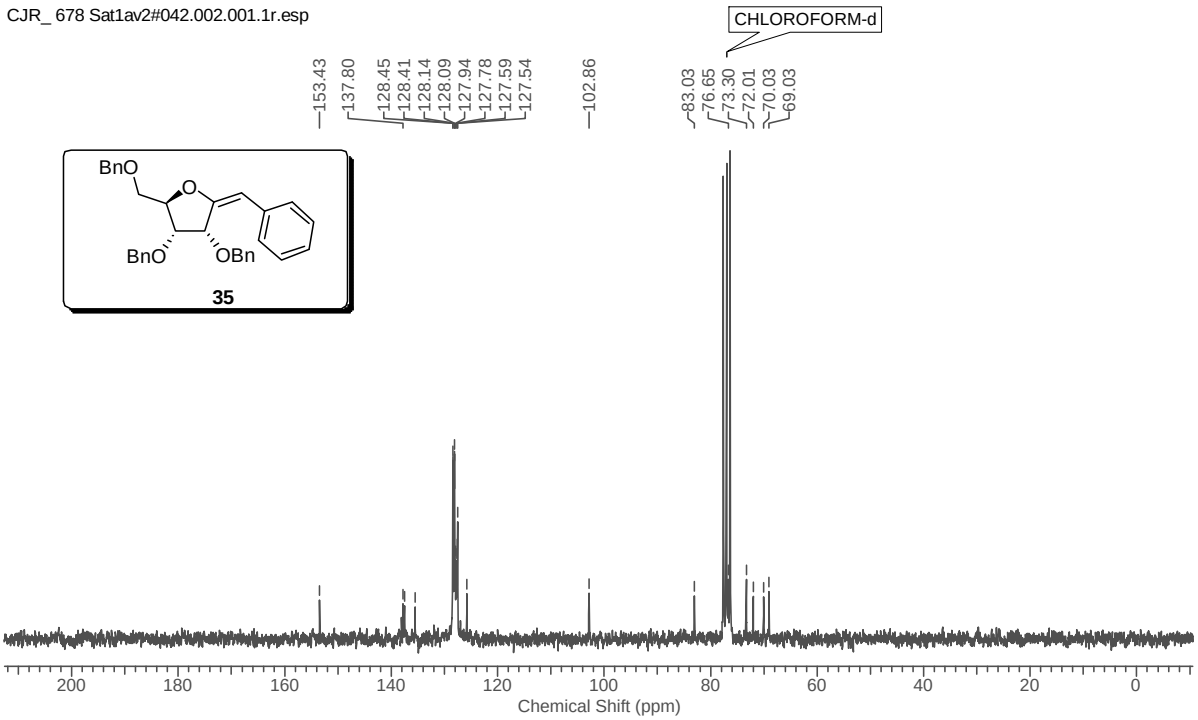
^{1}H NMR Spectrum of **34** in $CDCl_3$ (200 MHz)



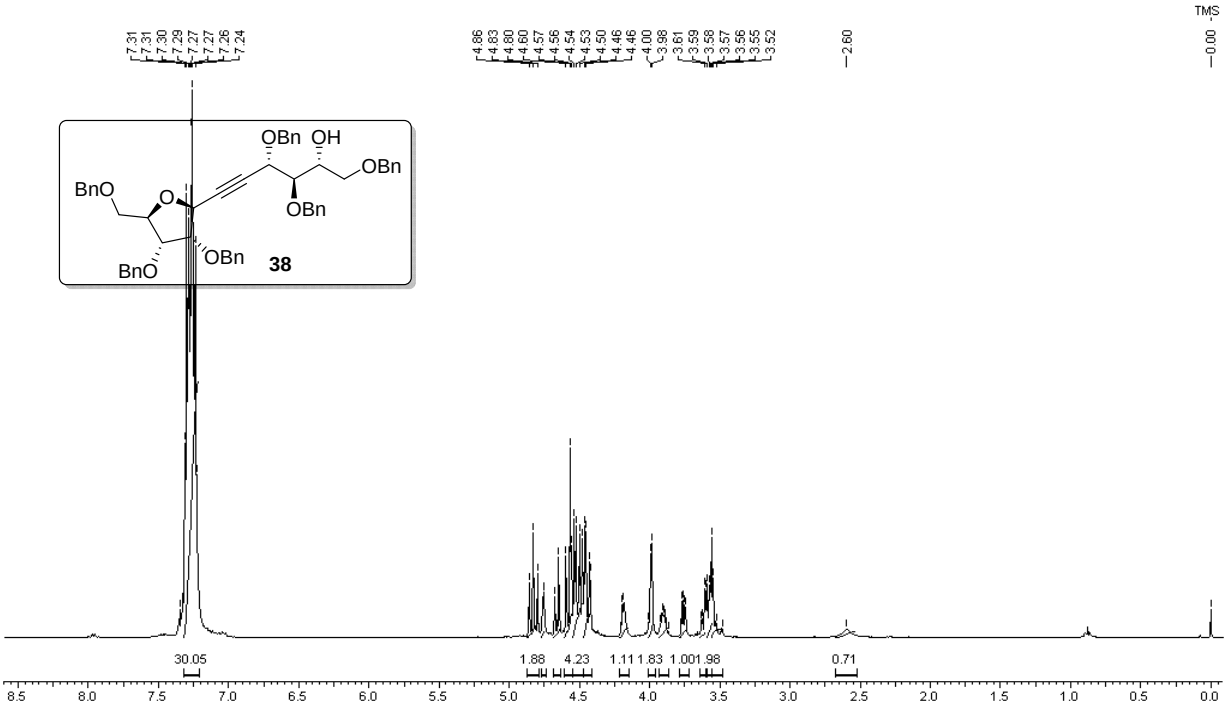
^{13}C NMR Spectrum of **34** in $CDCl_3$ (50 MHz)



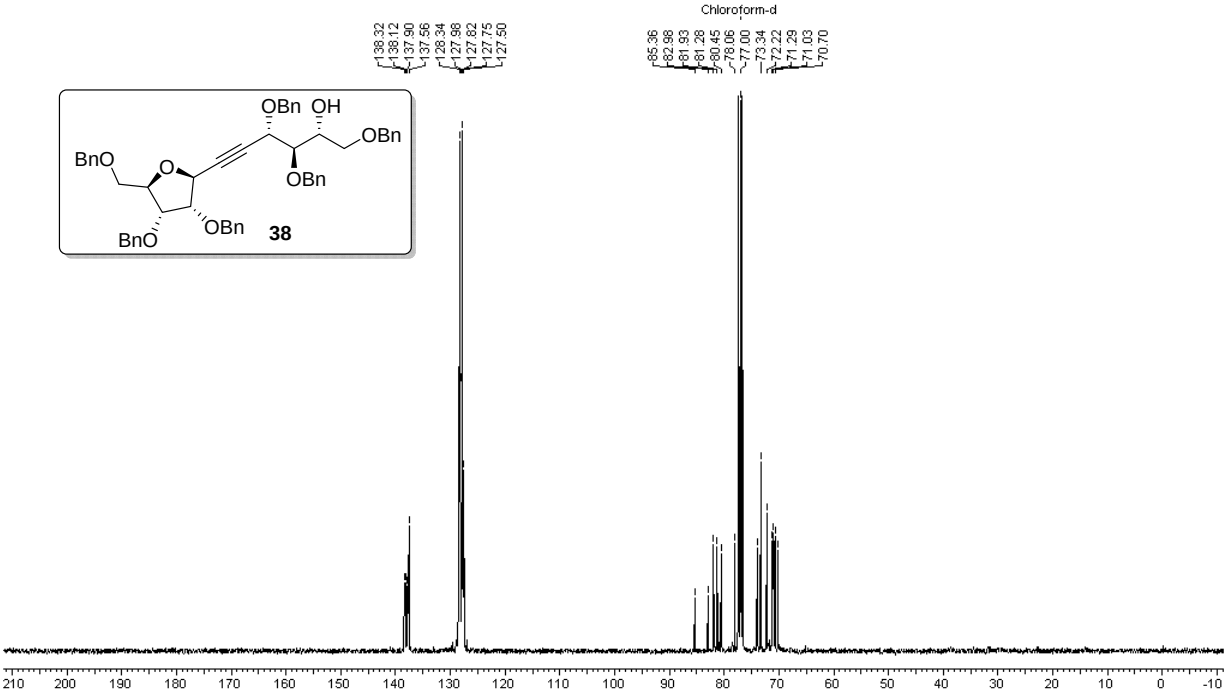
^{1}H NMR Spectrum of **35** in $CDCl_3$ (200 MHz)



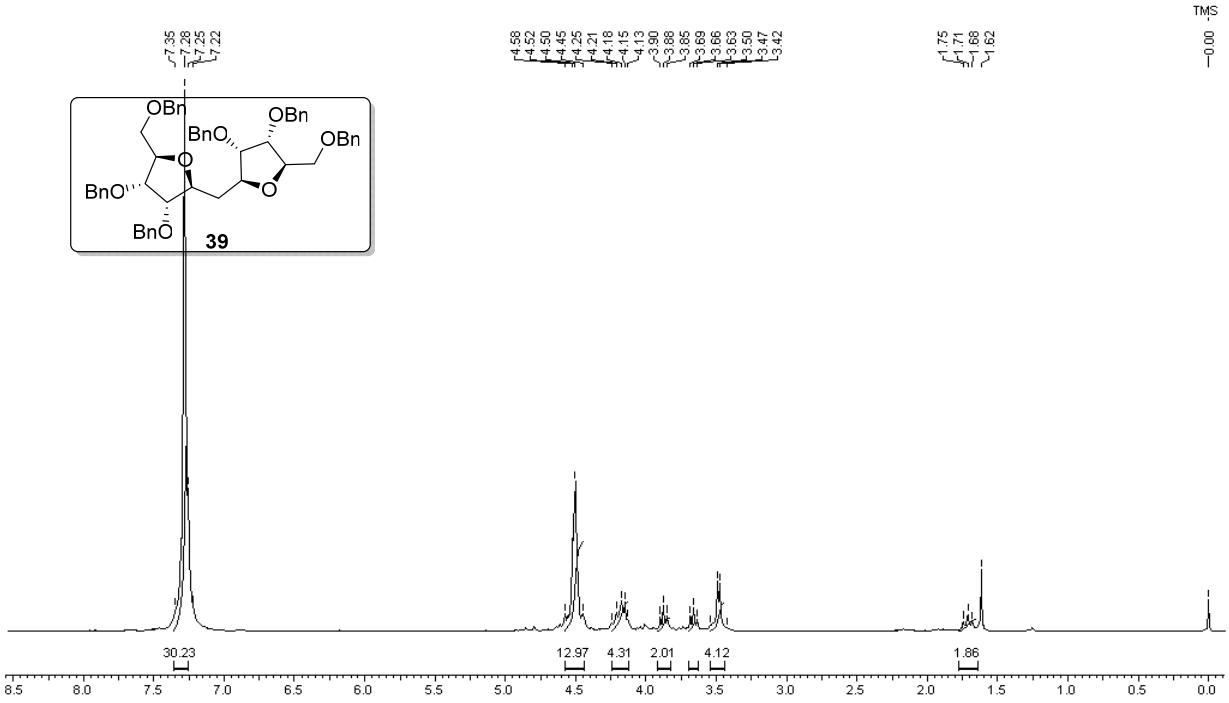
^{13}C NMR Spectrum of **35** in $CDCl_3$ (50 MHz)



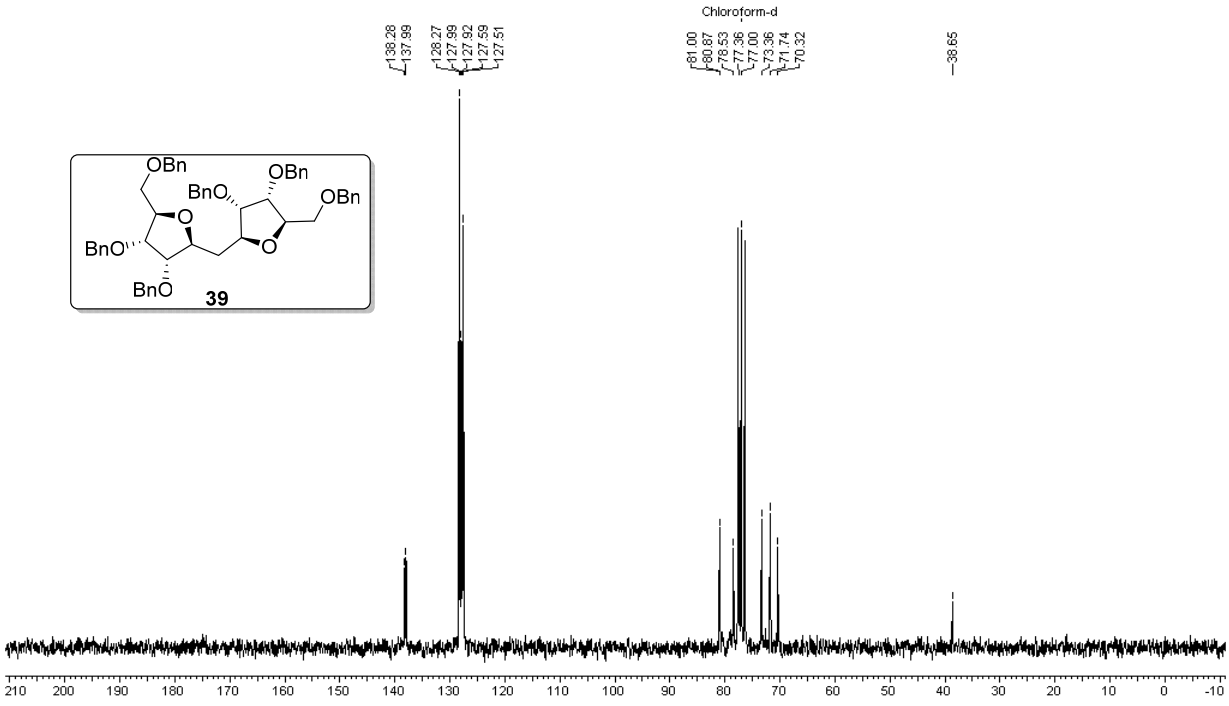
^{1}H NMR Spectrum of **38** in $CDCl_3$ (400 MHz)



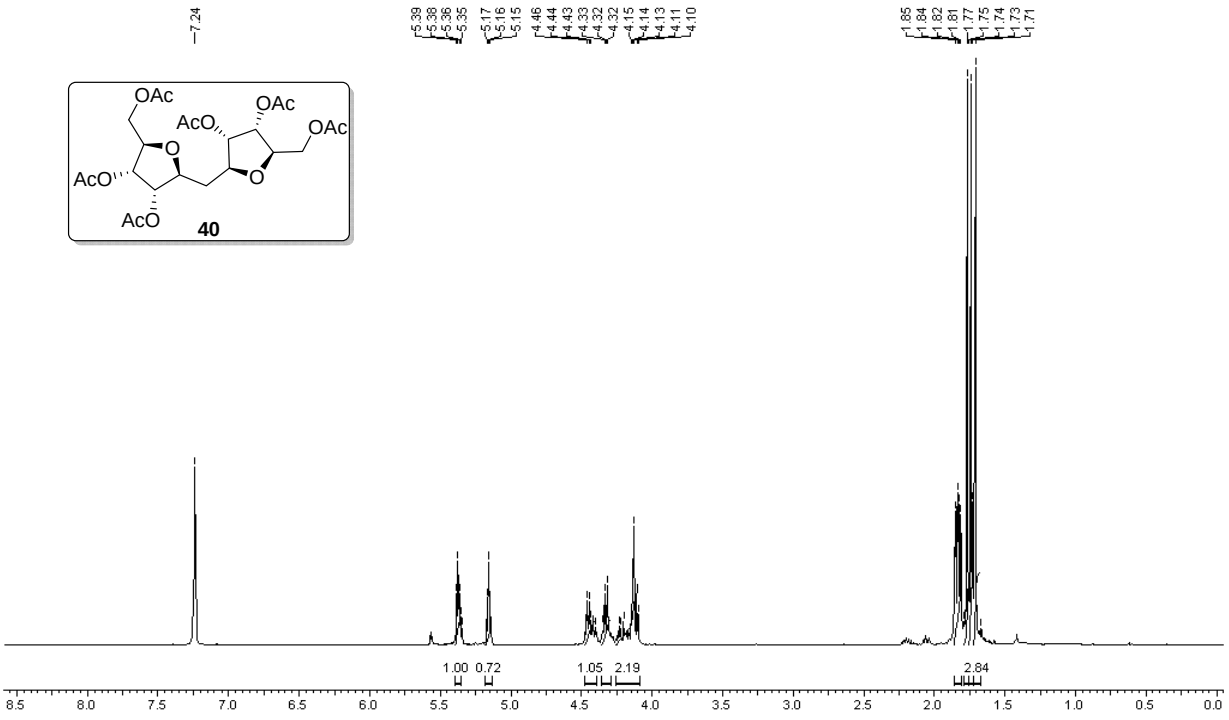
^{13}C NMR Spectrum of **38** in $CDCl_3$ (100 MHz)



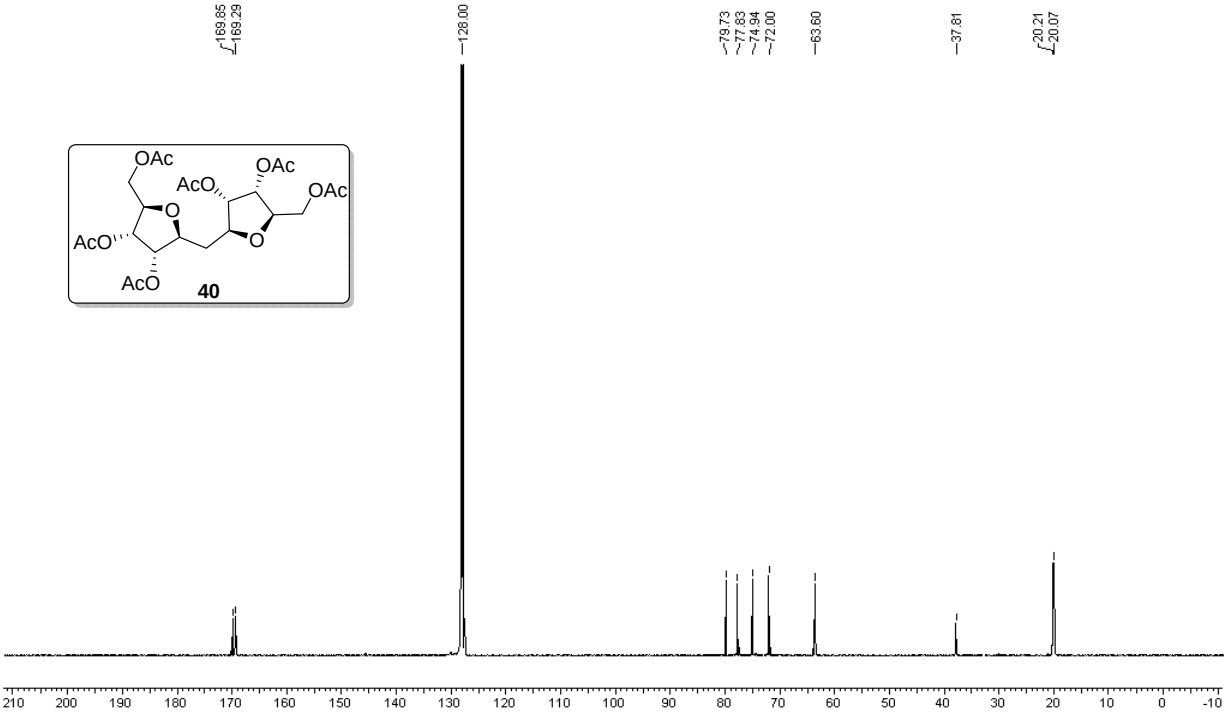
^{1}H NMR Spectrum of **39** in $CDCl_3$ (200 MHz)



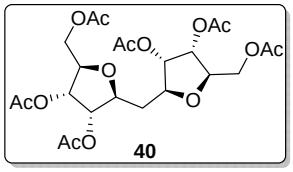
^{13}C NMR Spectrum of **39** in $CDCl_3$ (50 MHz)

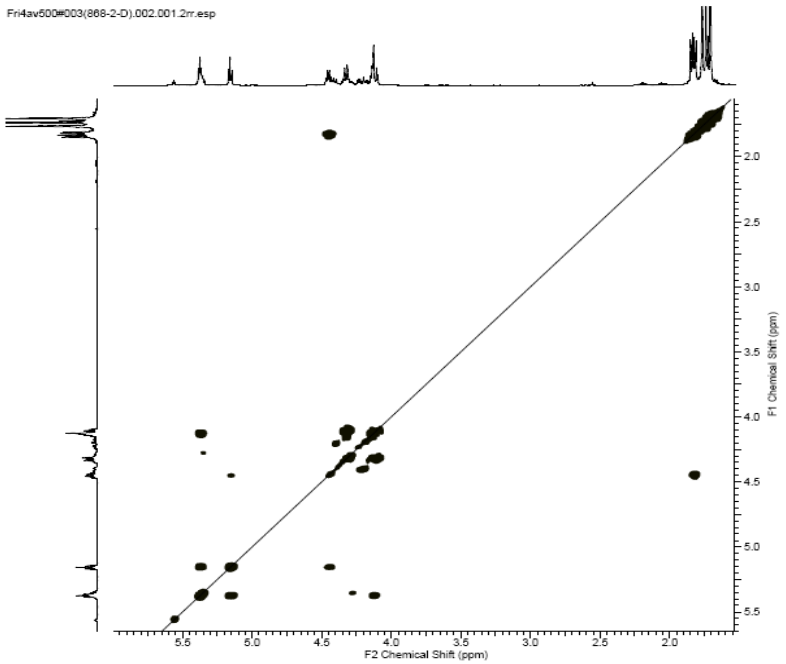


^{1}H NMR Spectrum of **40** in $CDCl_3$ (400 MHz)

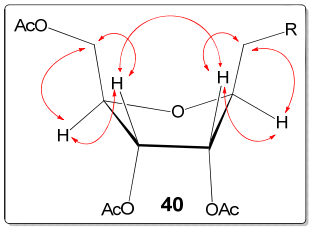


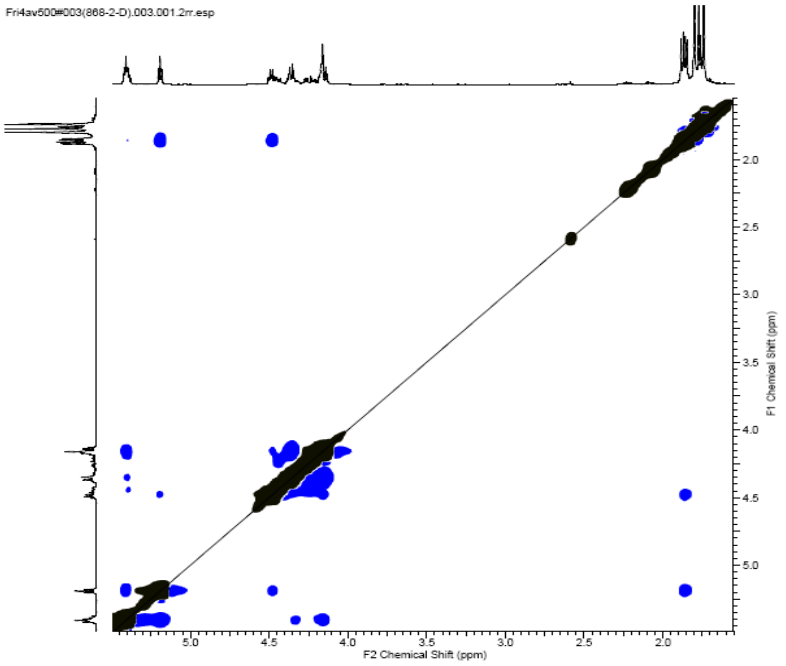
^{13}C NMR Spectrum of **40** in $CDCl_3$ (100 MHz)



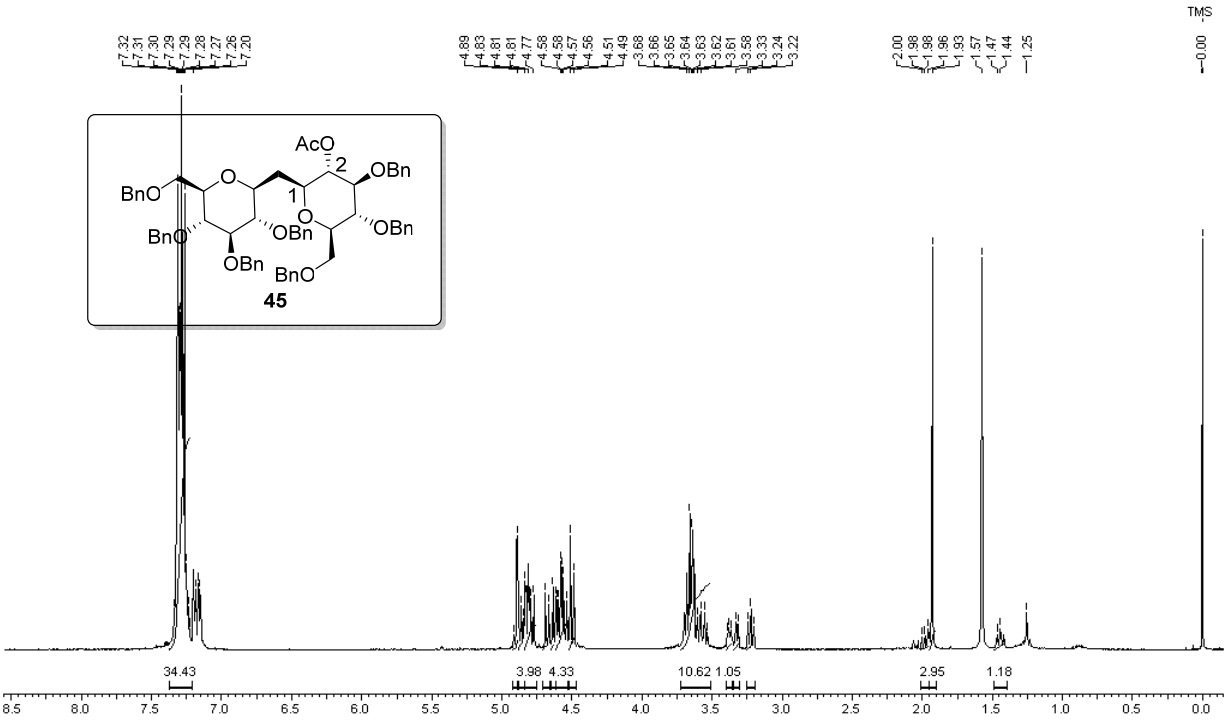


COSY Spectrum of **40** in $CDCl_3$ (400 MHz)

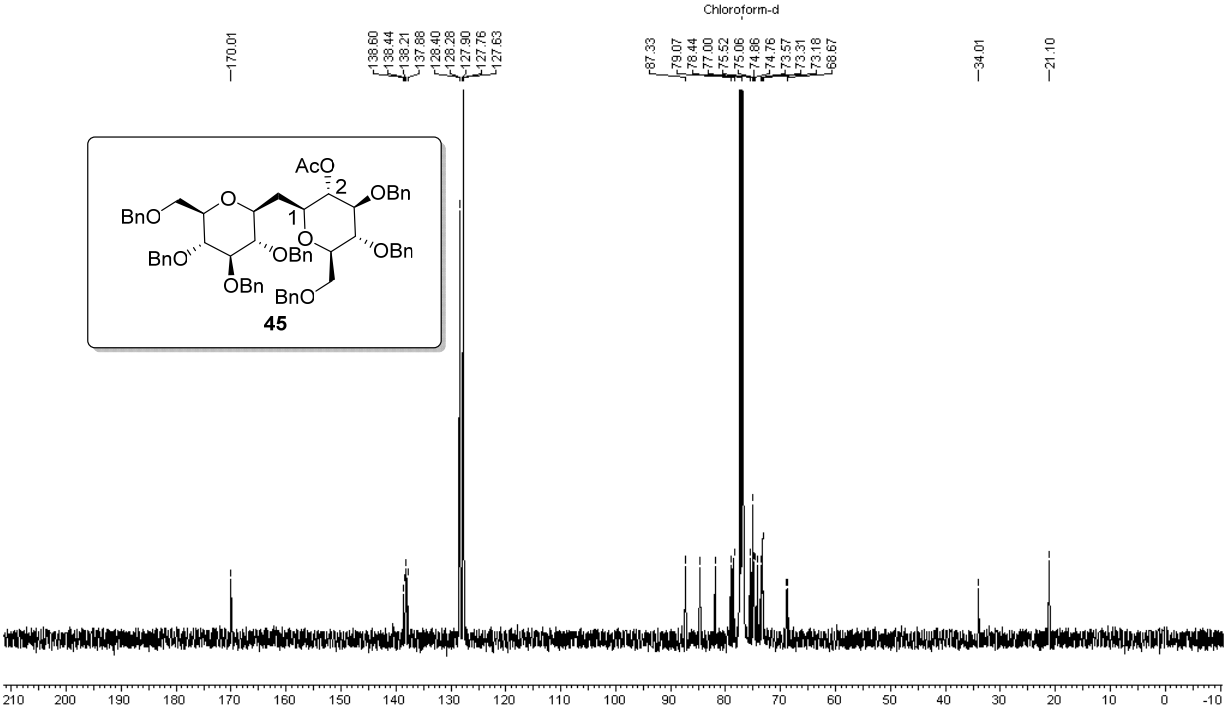




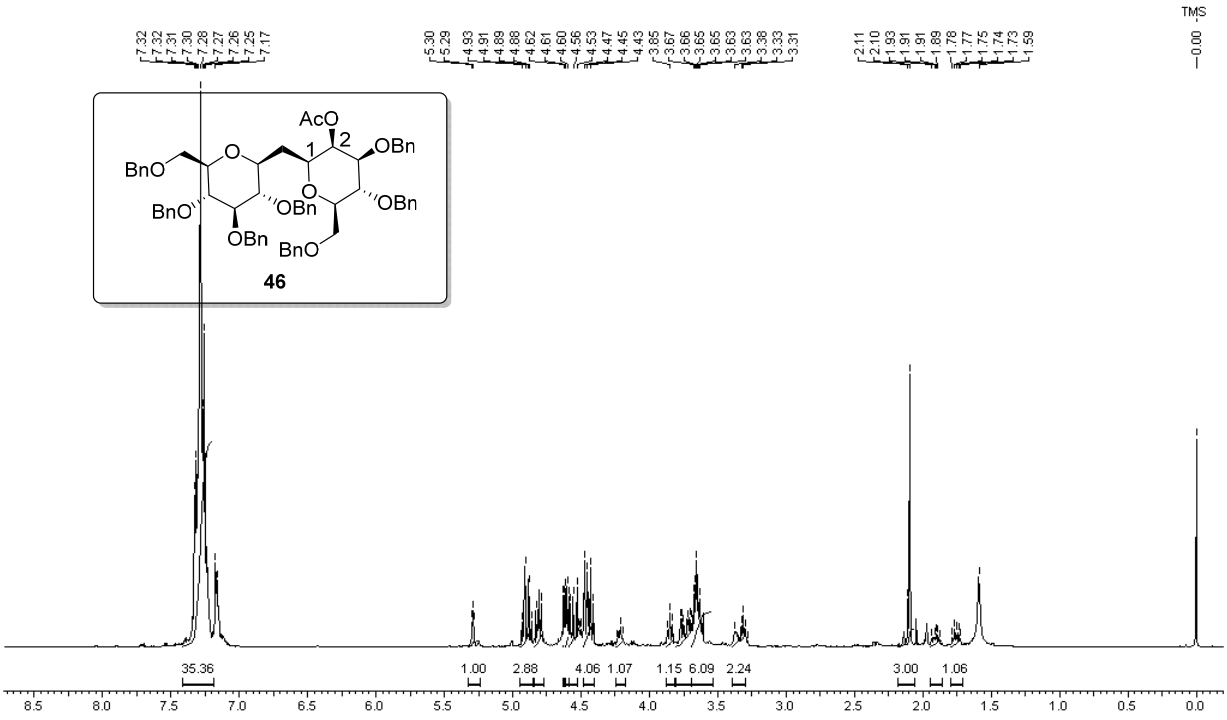
NOESY Spectrum of **40** in $CDCl_3$ (400 MHz)



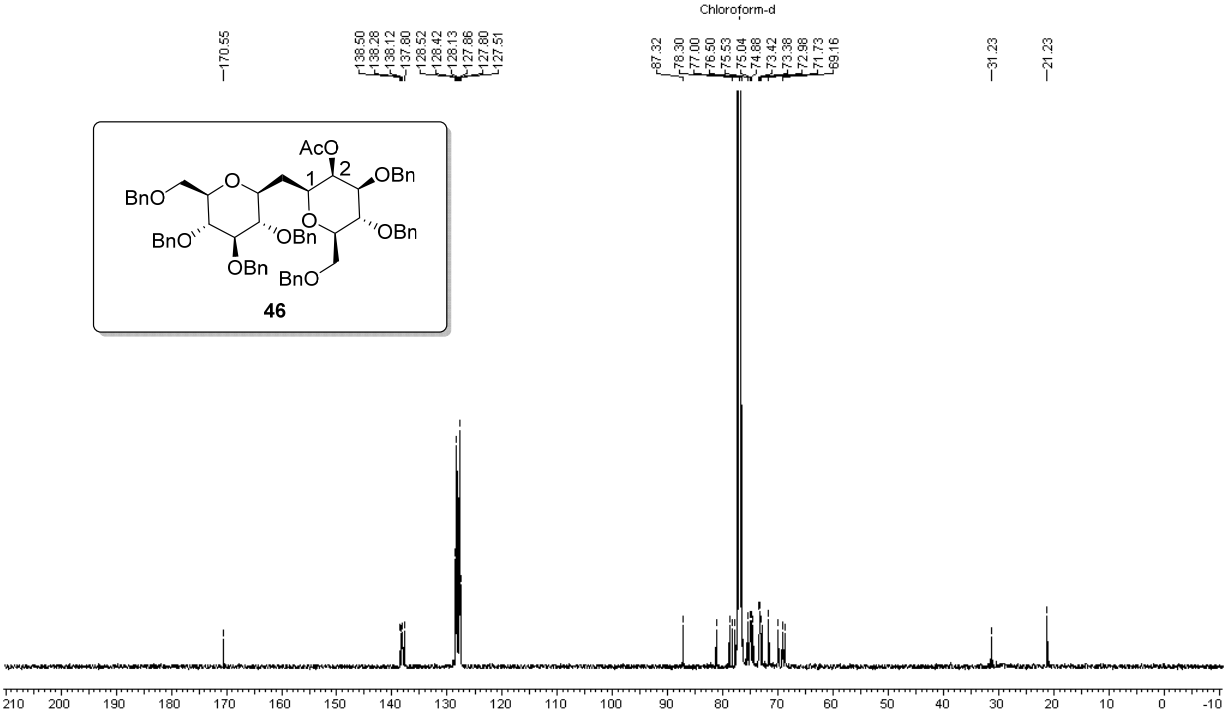
^{1}H NMR Spectrum of **45** in $CDCl_3$ (500 MHz)



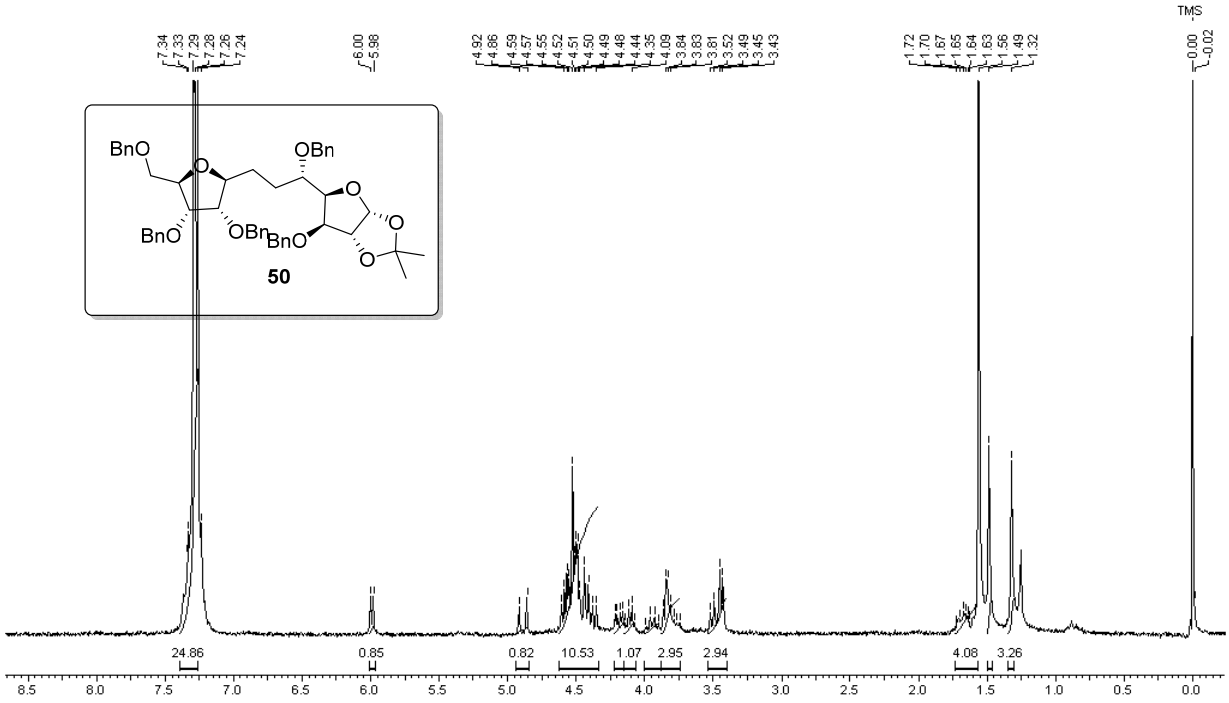
^{13}C NMR Spectrum of **45** in $CDCl_3$ (125 MHz)



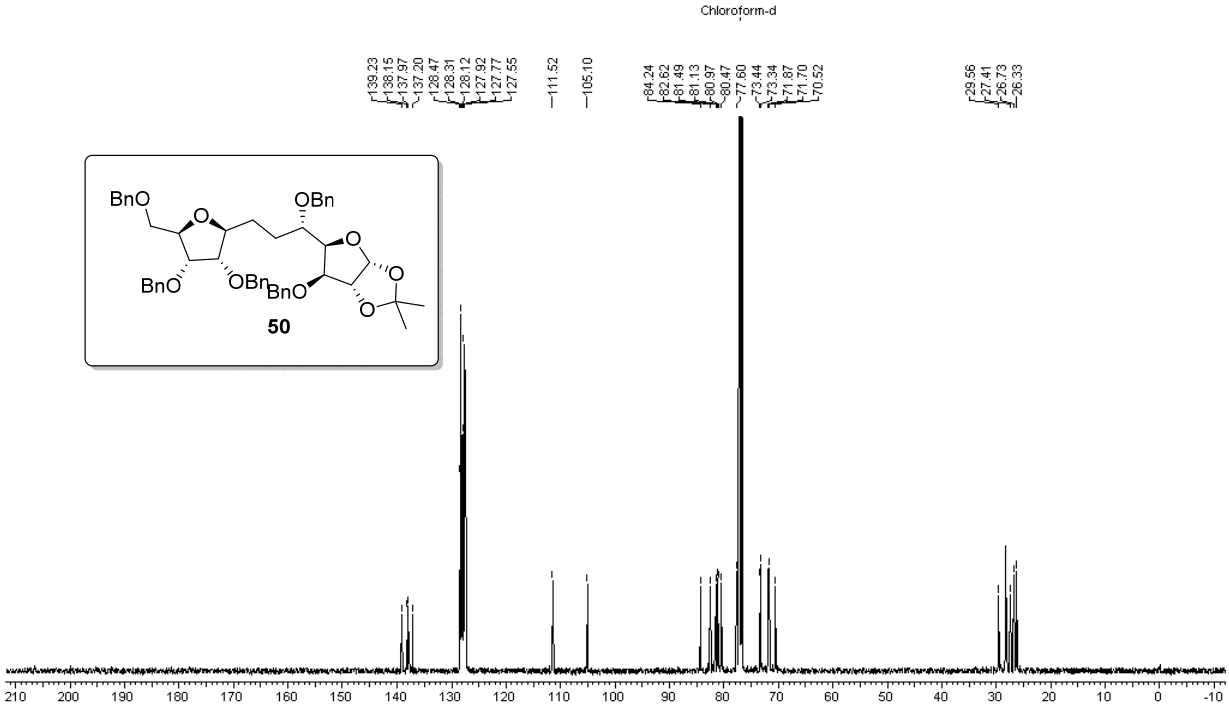
^{1}H NMR Spectrum of **46** in $CDCl_3$ (500 MHz)



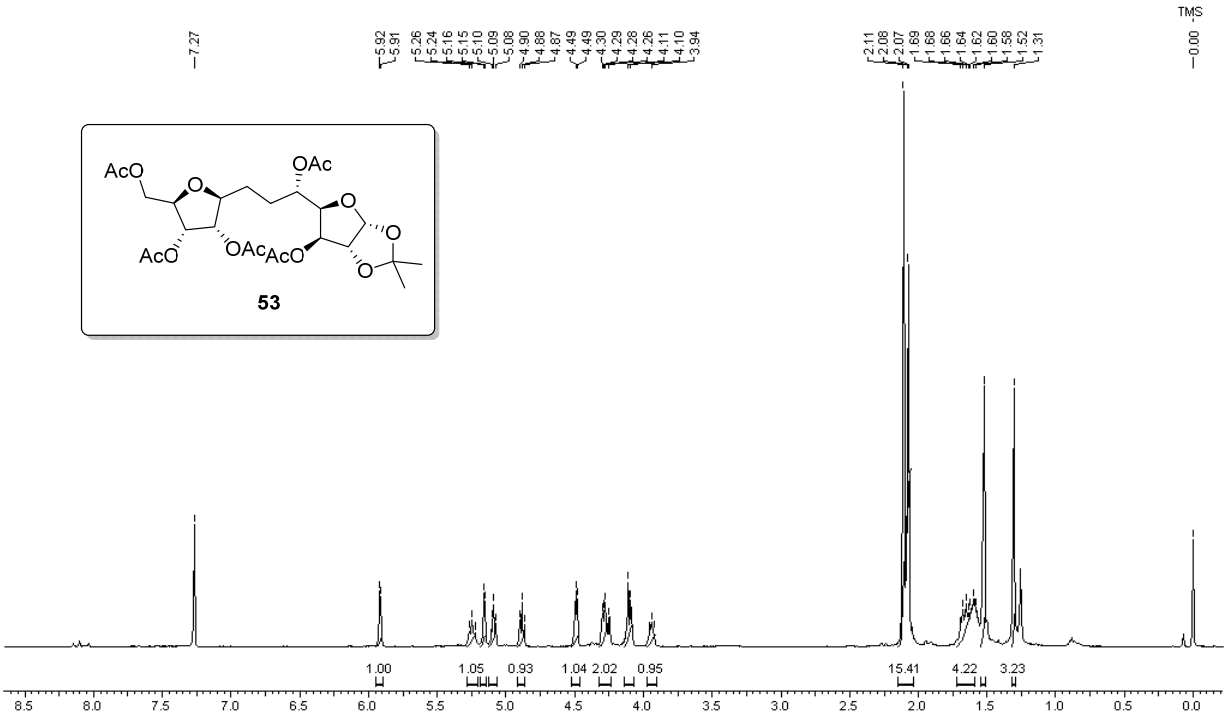
^{13}C NMR Spectrum of **46** in $CDCl_3$ (125 MHz)



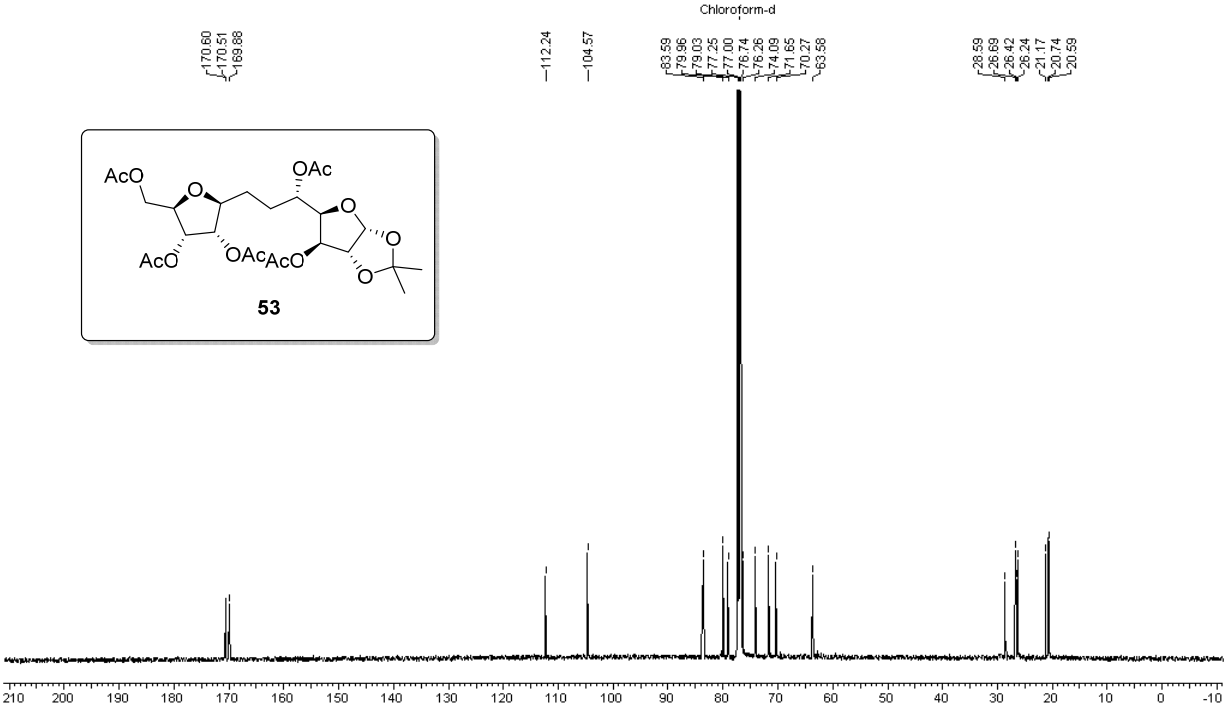
^{1}H NMR Spectrum of **50** in $CDCl_3$ (400 MHz)



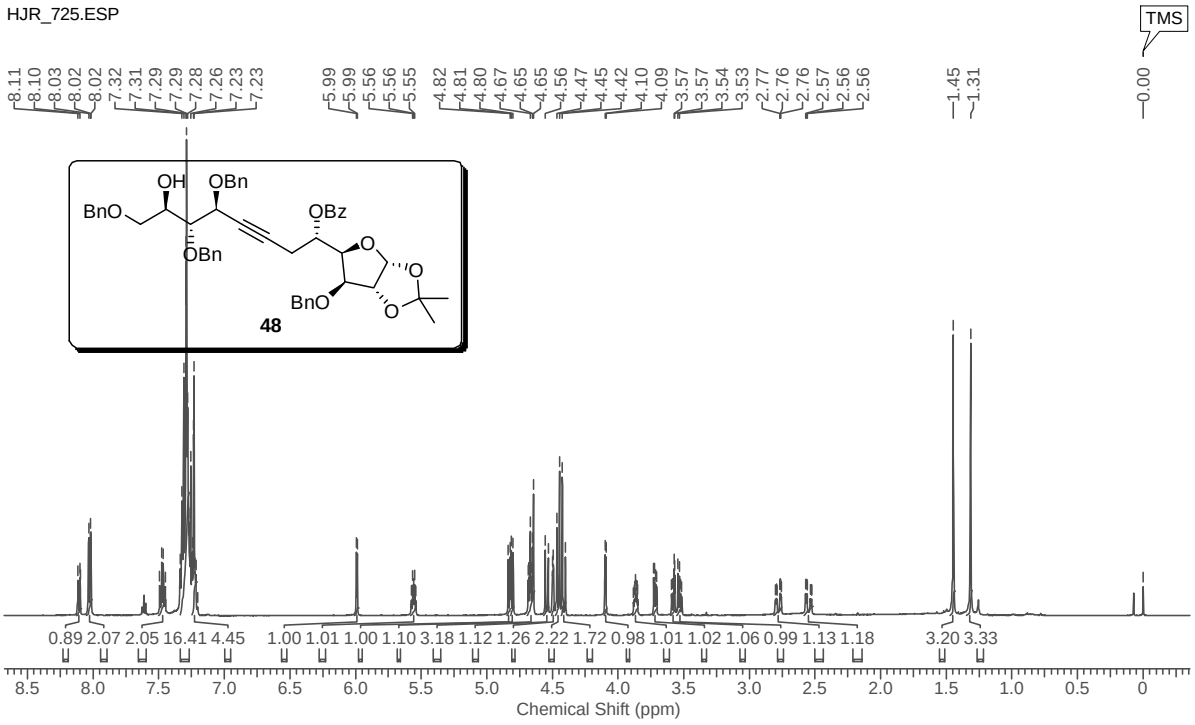
^{13}C NMR Spectrum of **50** in $CDCl_3$ (100 MHz)



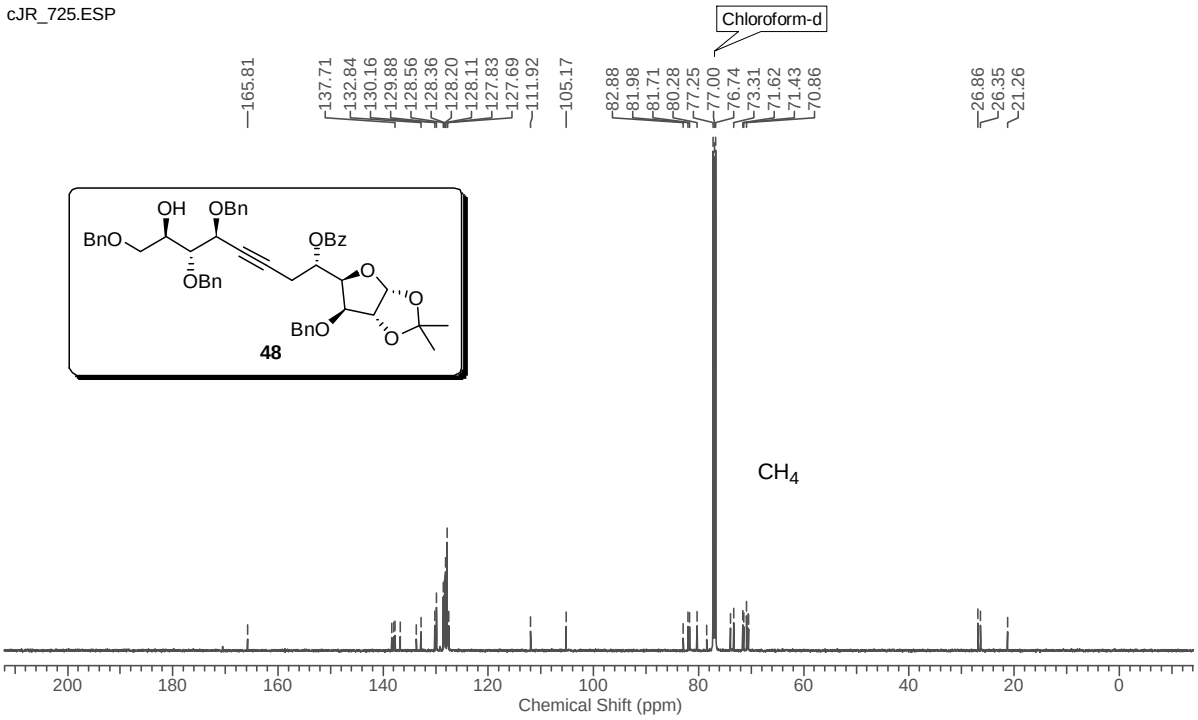
^{1}H NMR Spectrum of **53** in $CDCl_3$ (500 MHz)



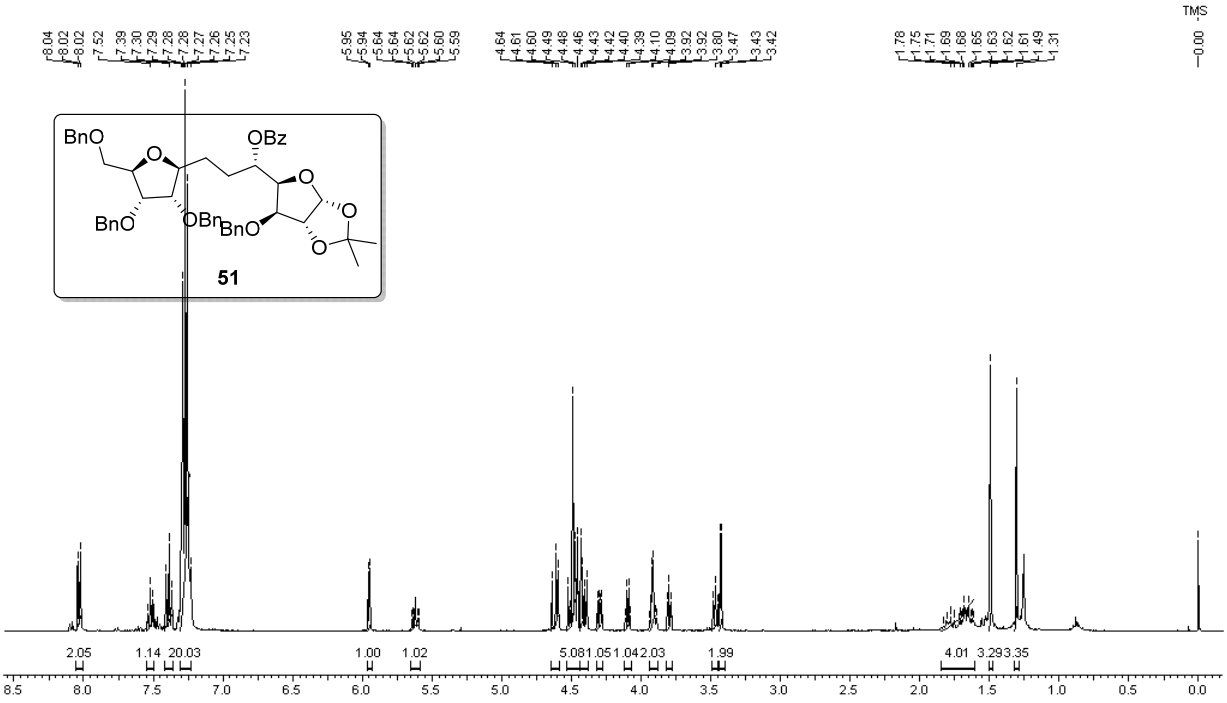
^{13}C NMR Spectrum of **53** in $CDCl_3$ (125 MHz)



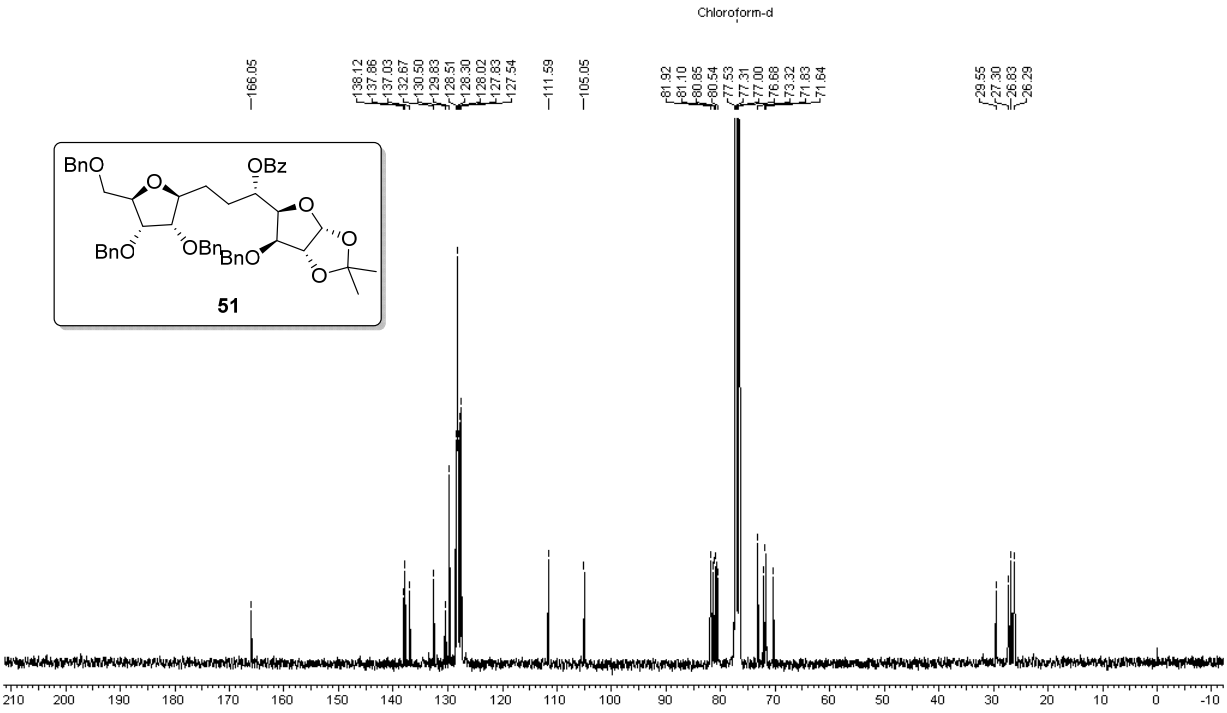
^{1}H NMR Spectrum of **48** in $CDCl_3$ (400 MHz)



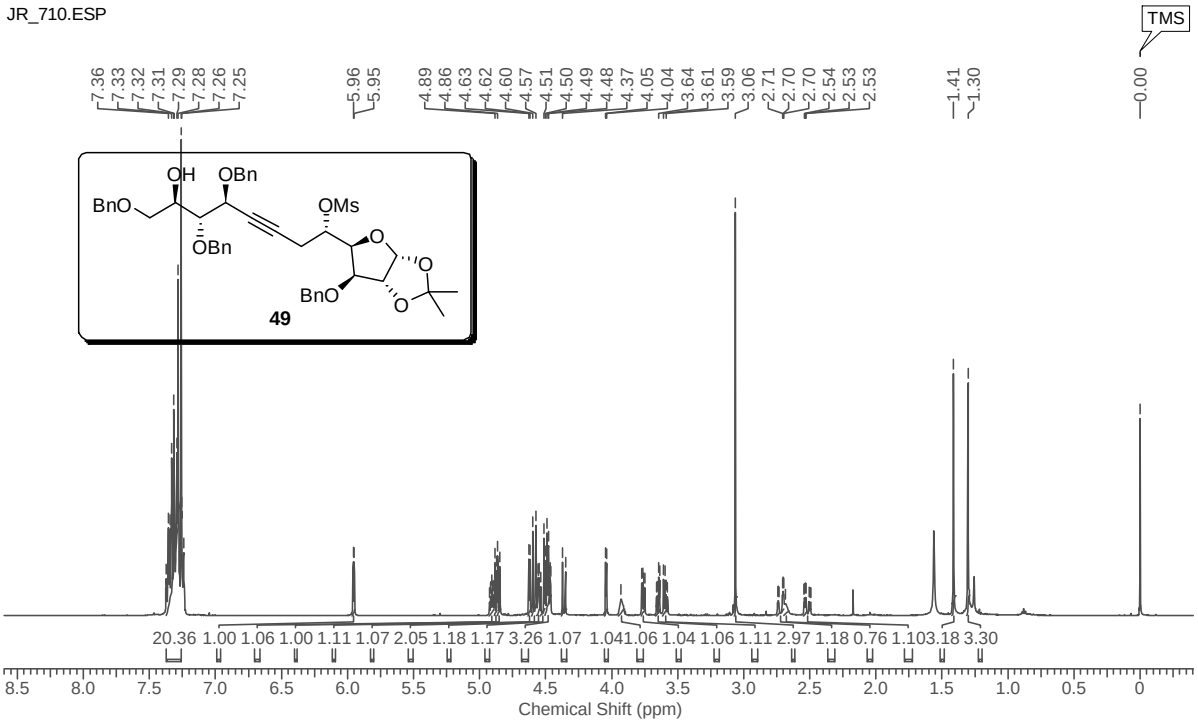
^{13}C NMR Spectrum of **48** in $CDCl_3$ (100 MHz)



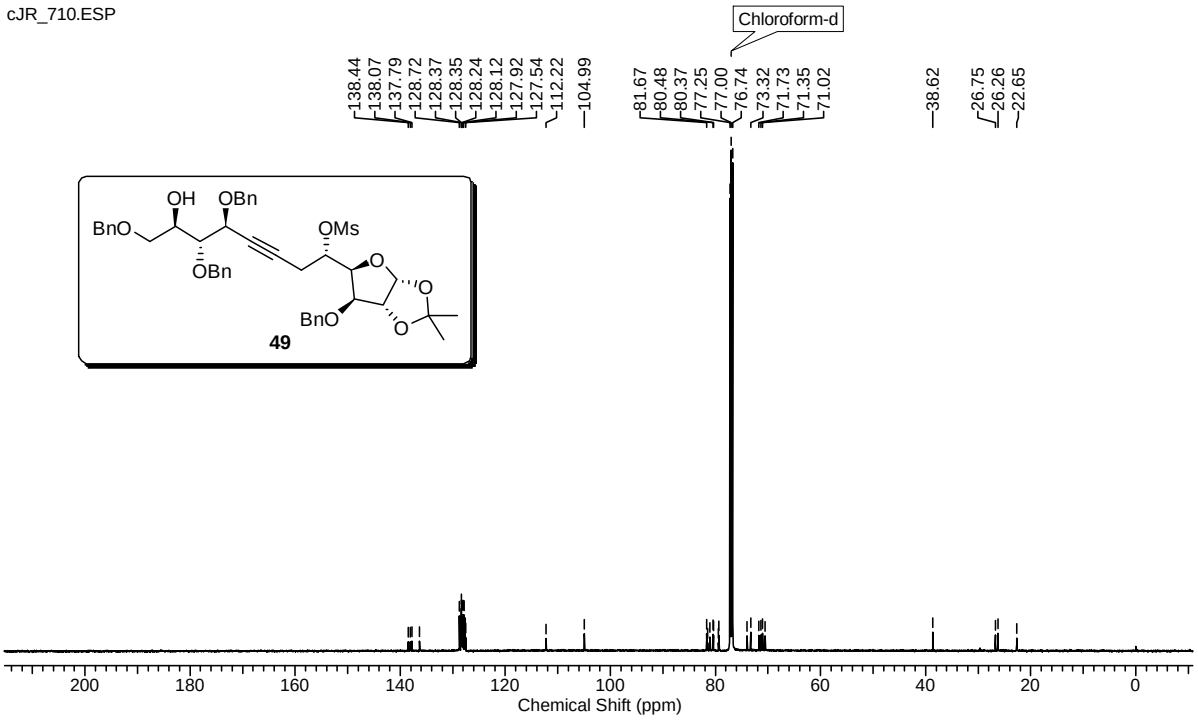
^{1}H NMR Spectrum of **51** in $CDCl_3$ (400 MHz)



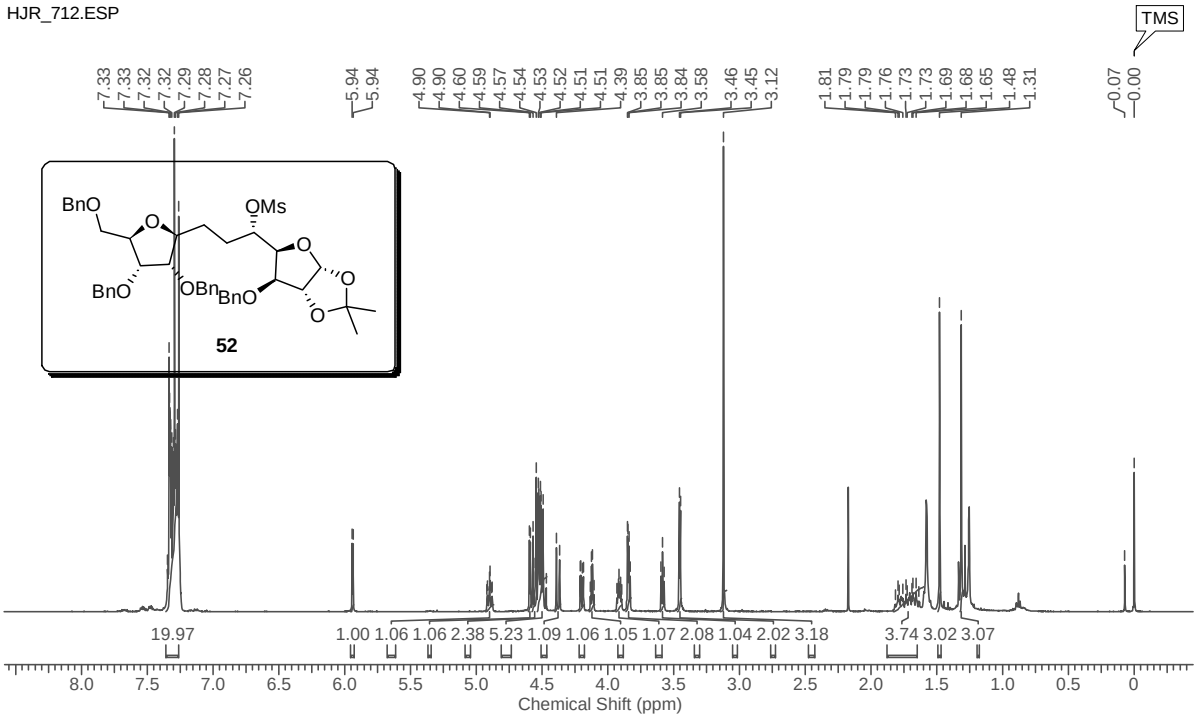
^{13}C NMR Spectrum of **51** in $CDCl_3$ (100 MHz)



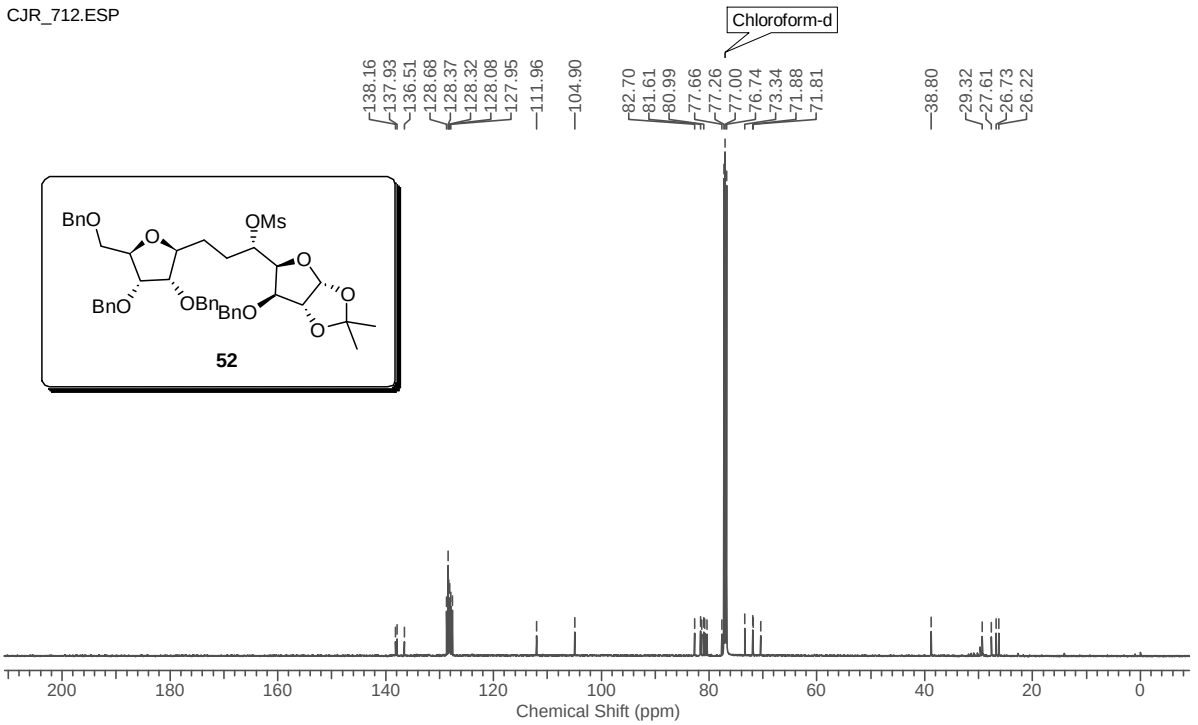
^{1}H NMR Spectrum of **49** in $CDCl_3$ (500 MHz)



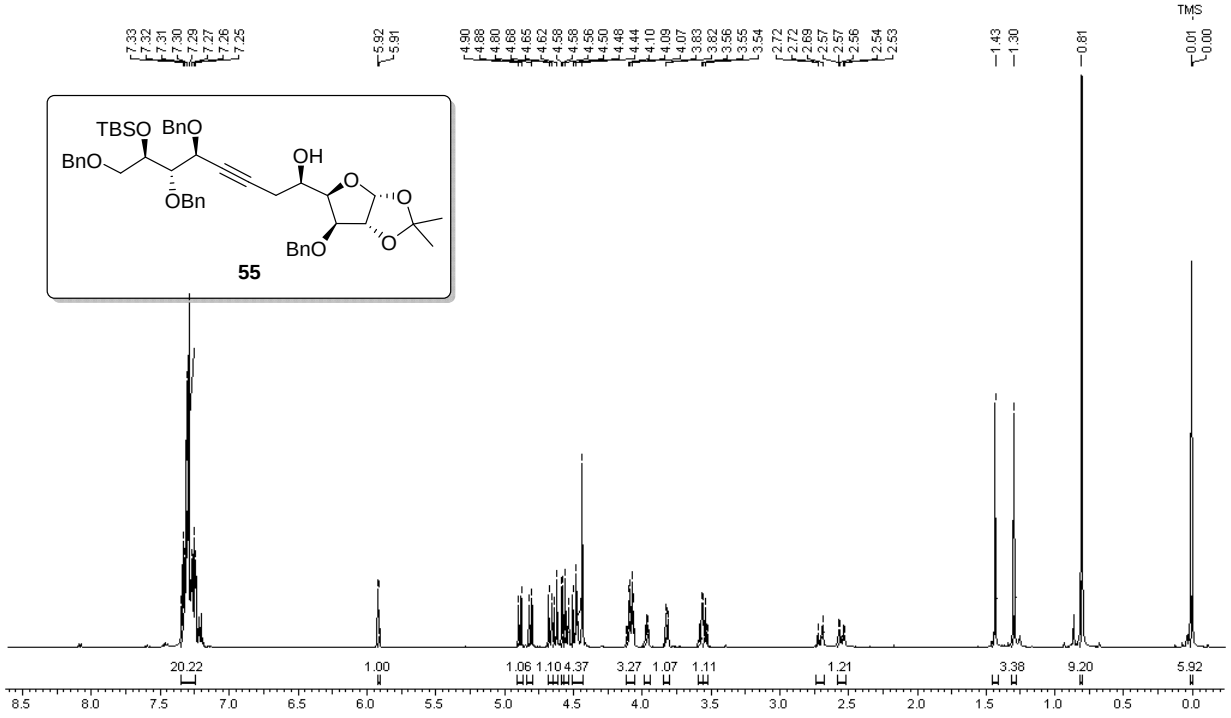
^{13}C NMR Spectrum of **49** in $CDCl_3$ (125 MHz)



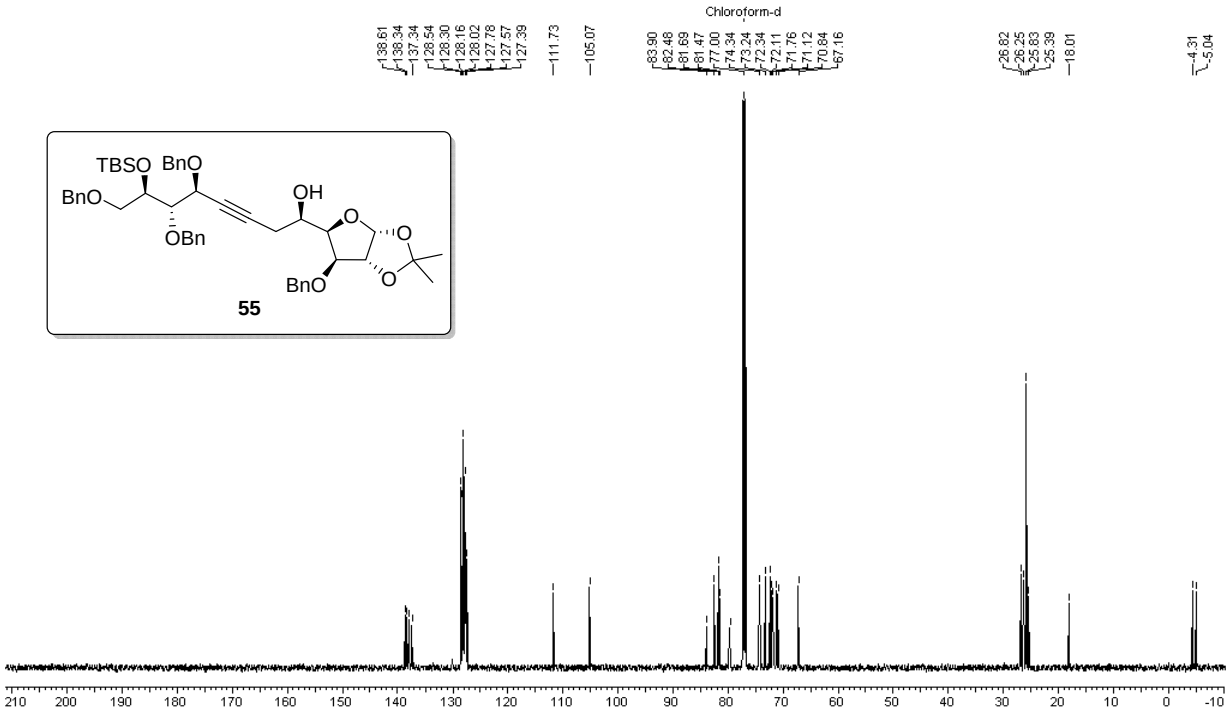
^{1}H NMR Spectrum of **52** in $CDCl_3$ (500 MHz)



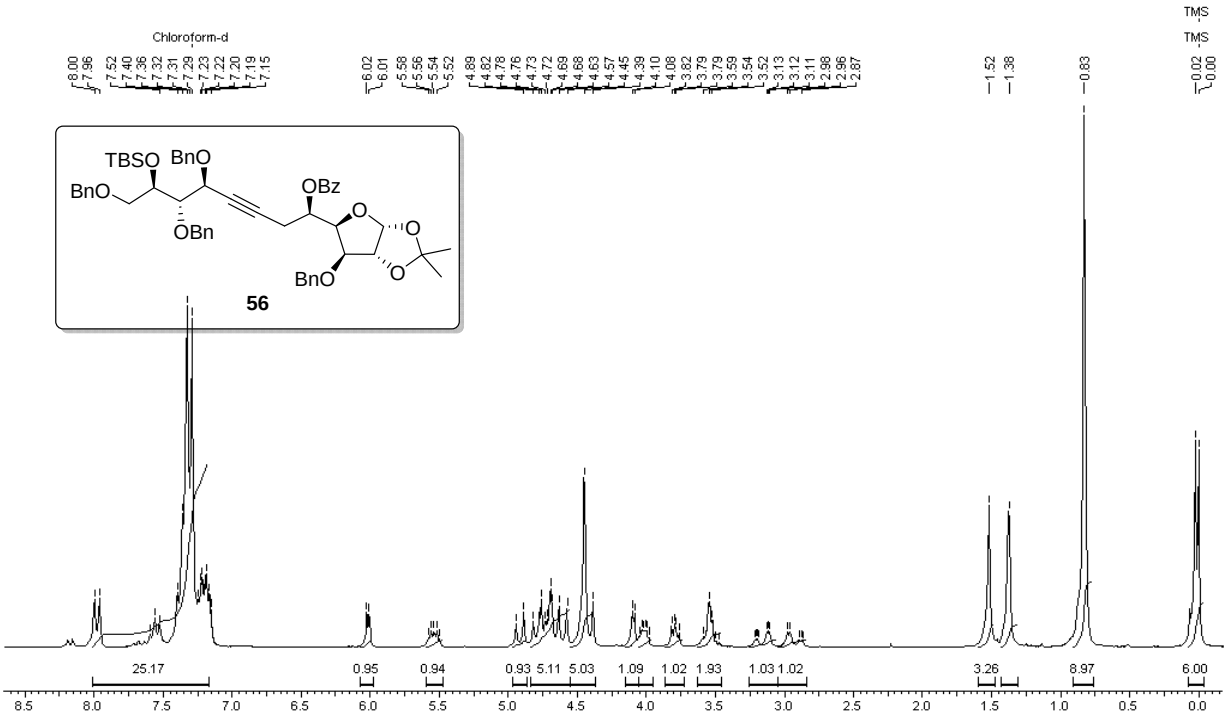
^{13}C NMR Spectrum of **52** in $CDCl_3$ (125 MHz)



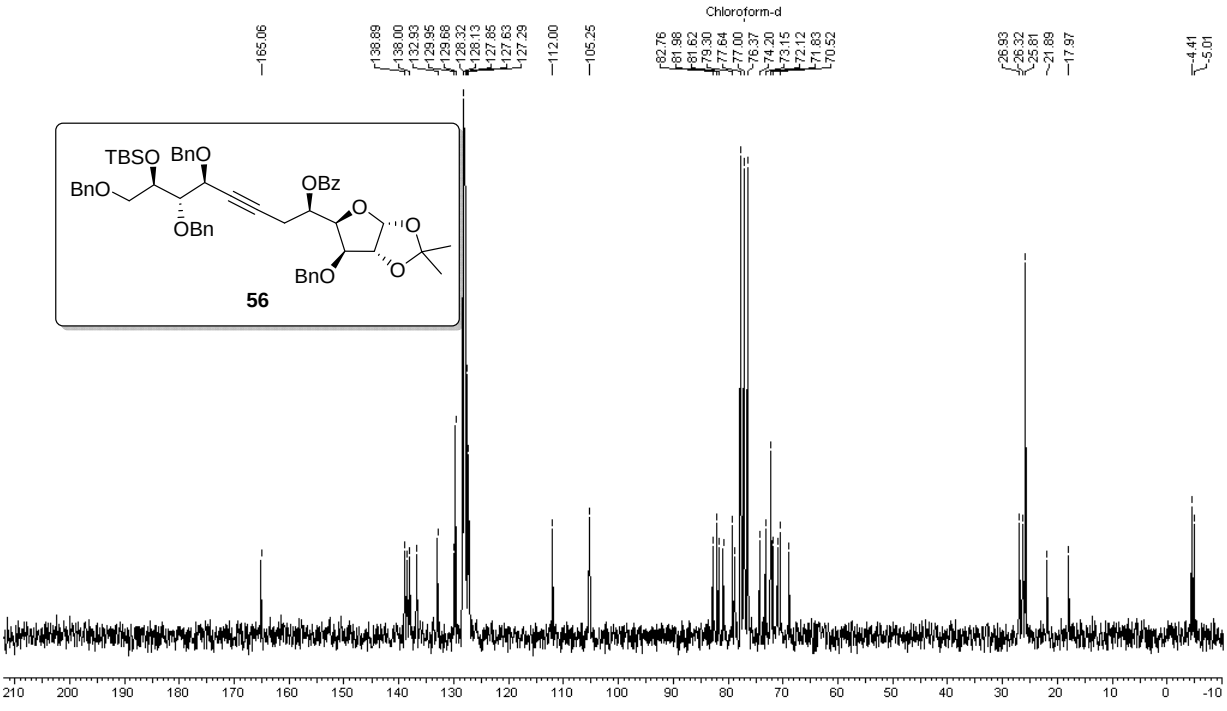
^{1}H NMR Spectrum of **55** in $CDCl_3$ (400 MHz)



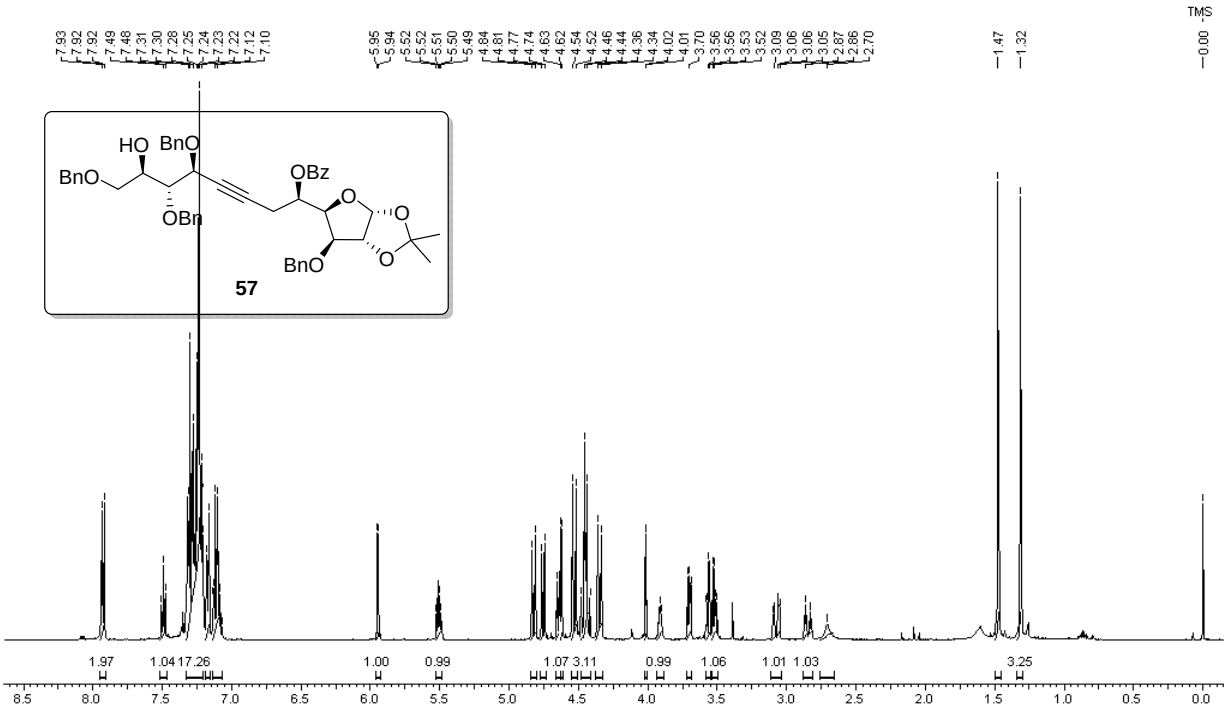
^{13}C NMR Spectrum of **55** in $CDCl_3$ (100 MHz)



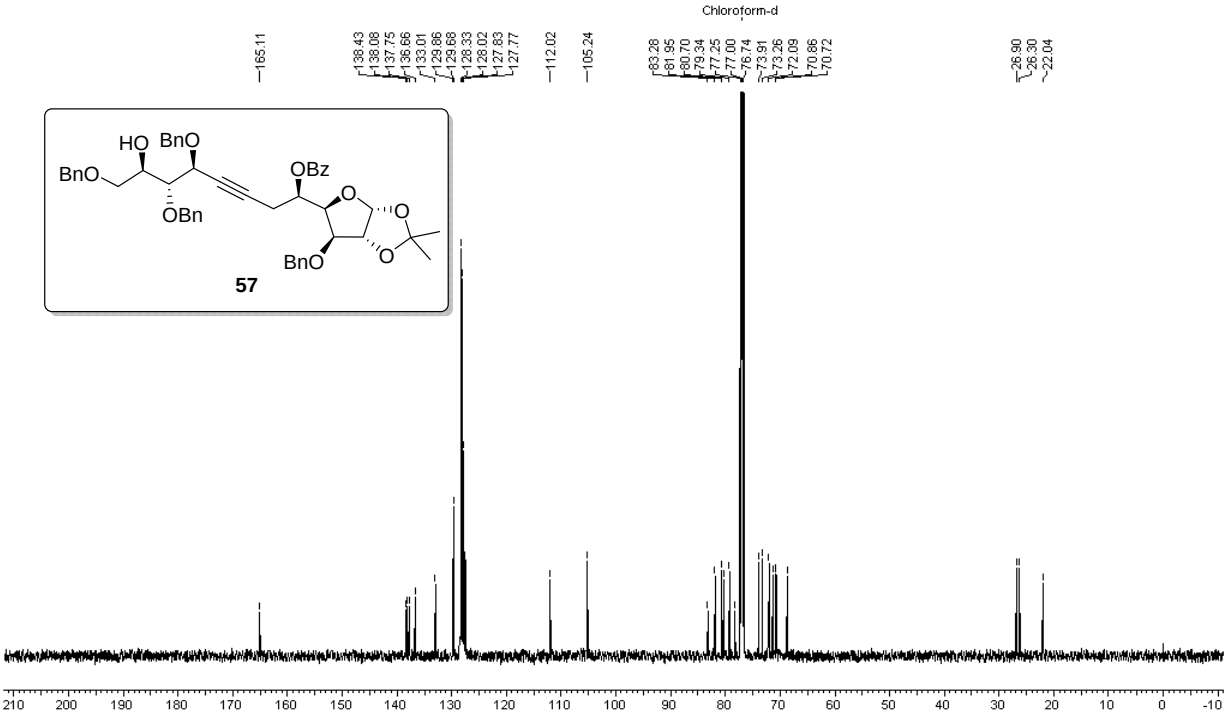
^{1}H NMR Spectrum of **56** in $CDCl_3$ (400 MHz)



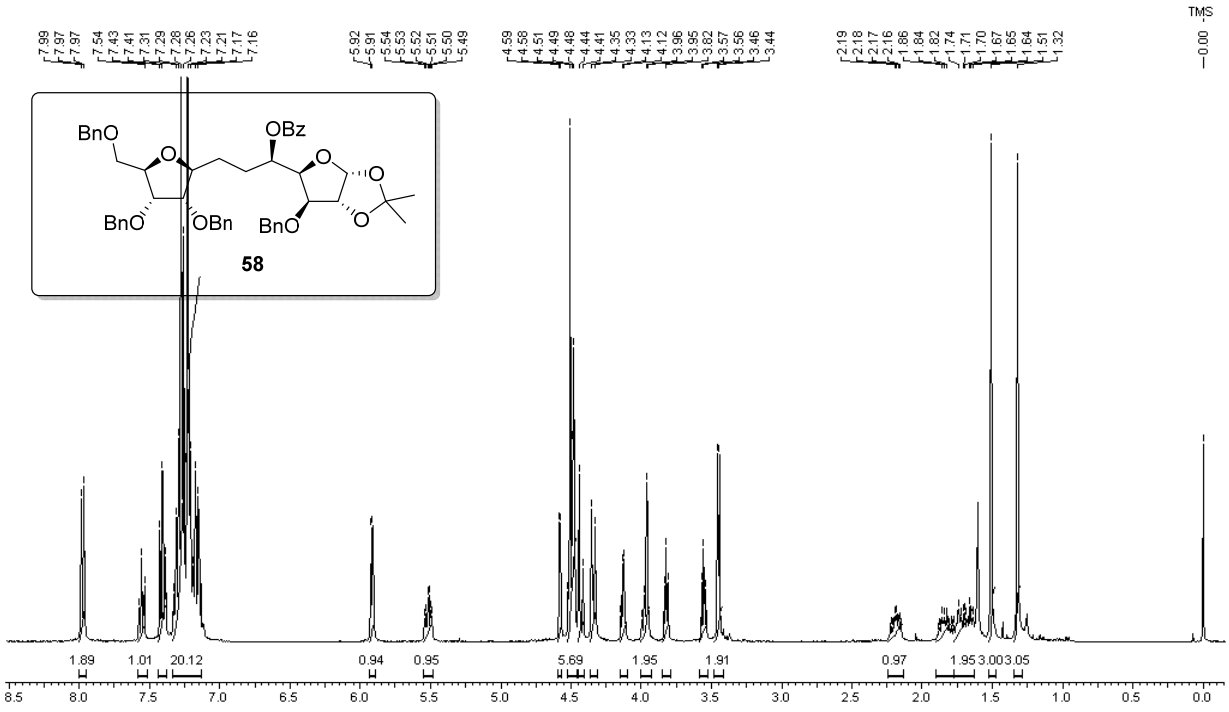
^{13}C NMR Spectrum of **56** in $CDCl_3$ (100 MHz)



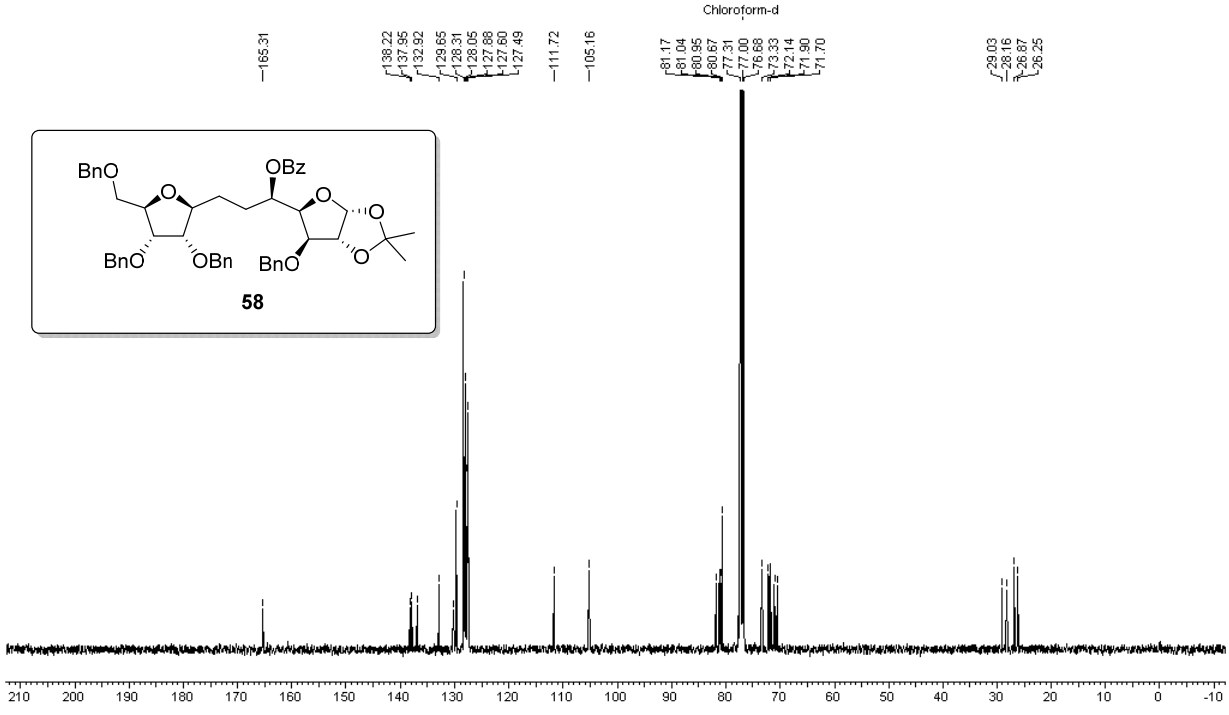
^{1}H NMR Spectrum of **57** in $CDCl_3$ (500 MHz)



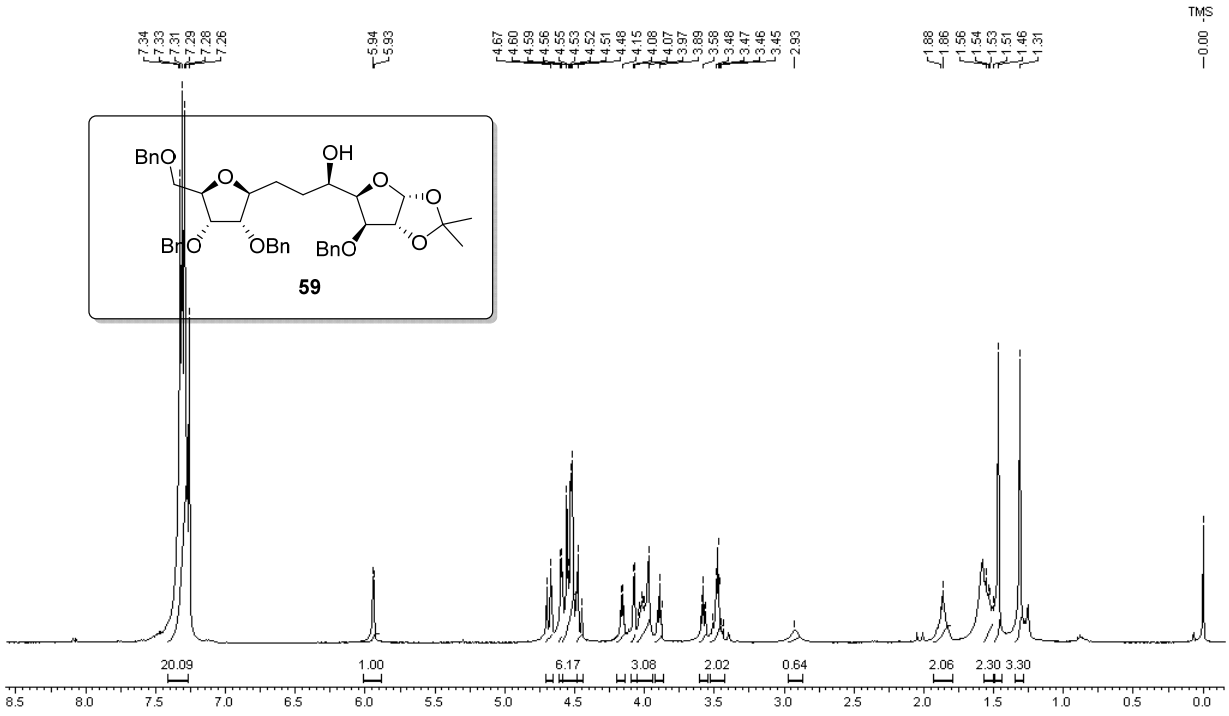
^{13}C NMR Spectrum of **57** in $CDCl_3$ (125 MHz)



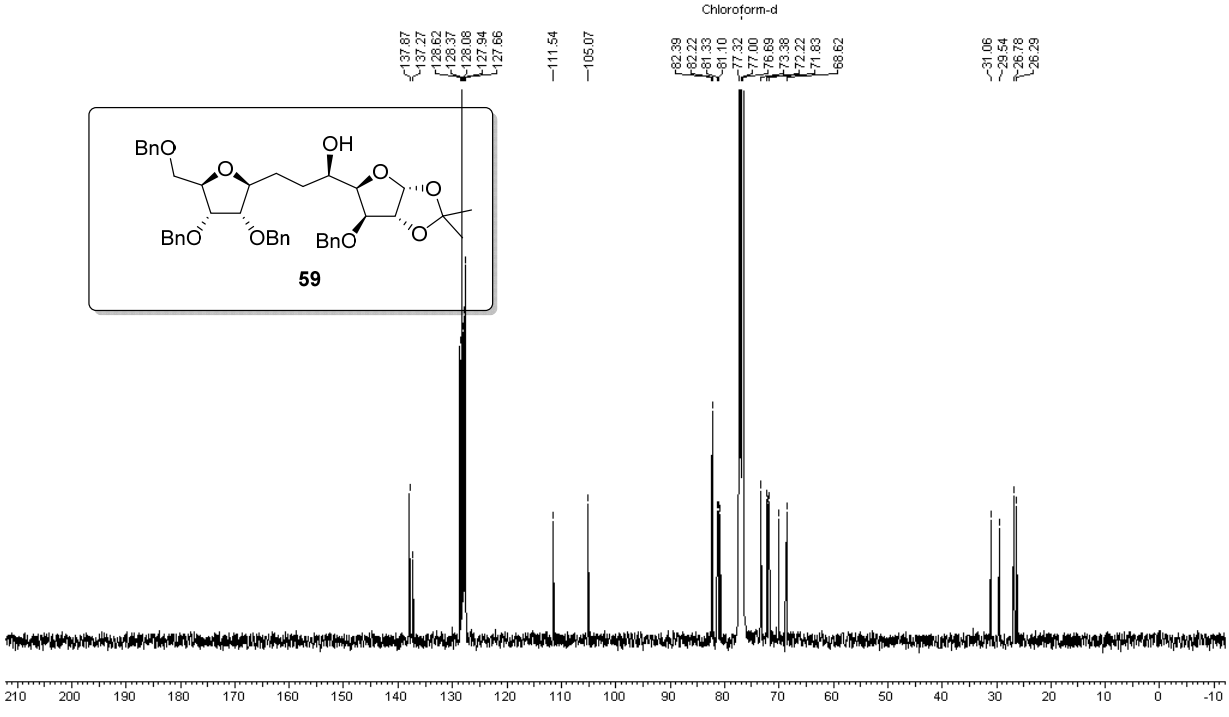
^{1}H NMR Spectrum of **58** in $CDCl_3$ (400 MHz)



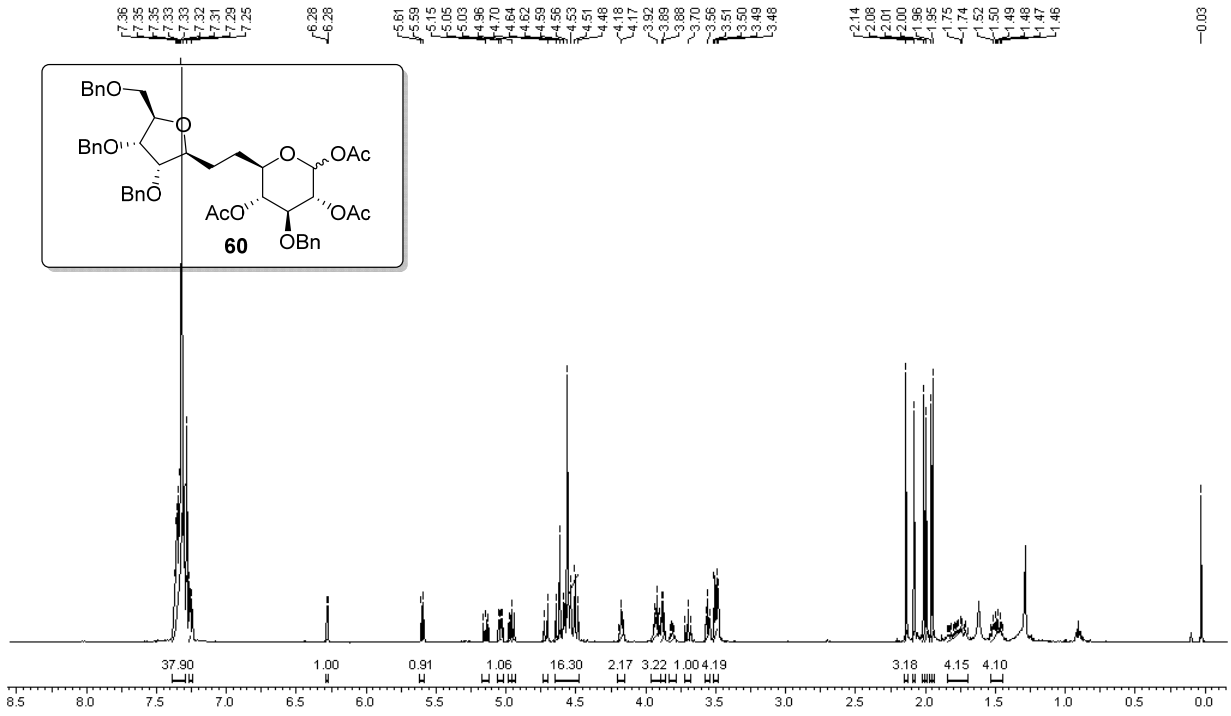
^{13}C NMR Spectrum of **58** in $CDCl_3$ (100 MHz)



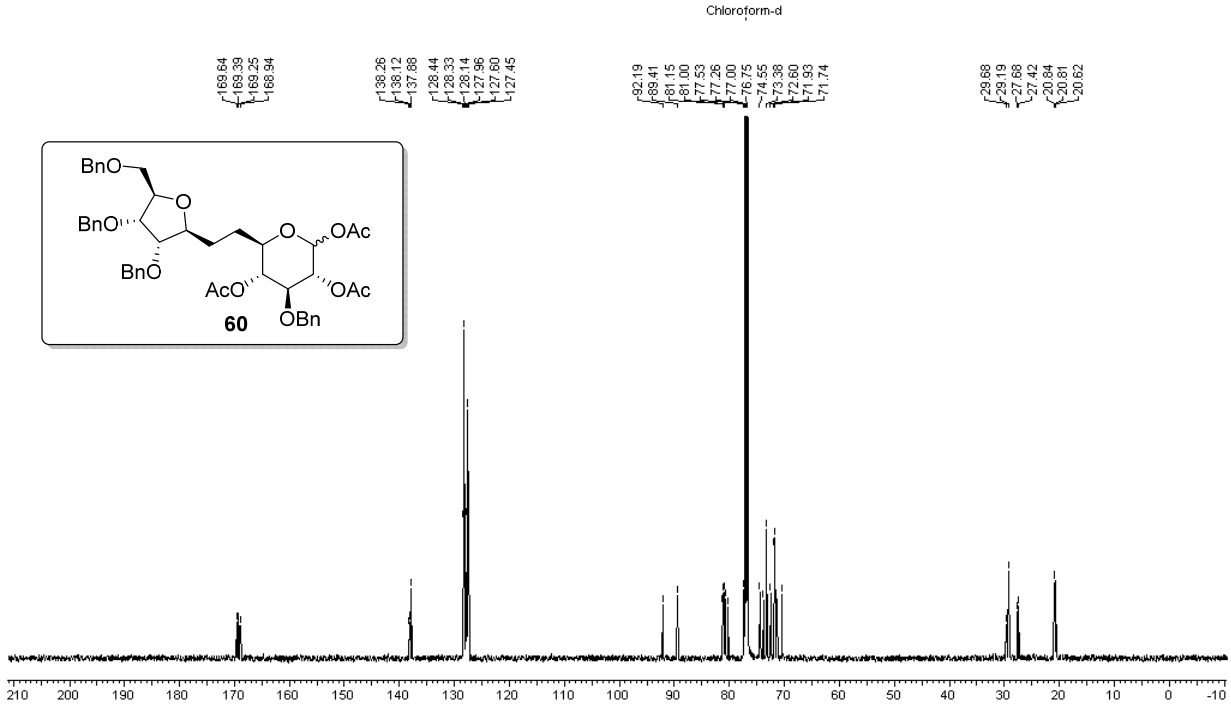
^{1}H NMR Spectrum of **59** in $CDCl_3$ (400 MHz)



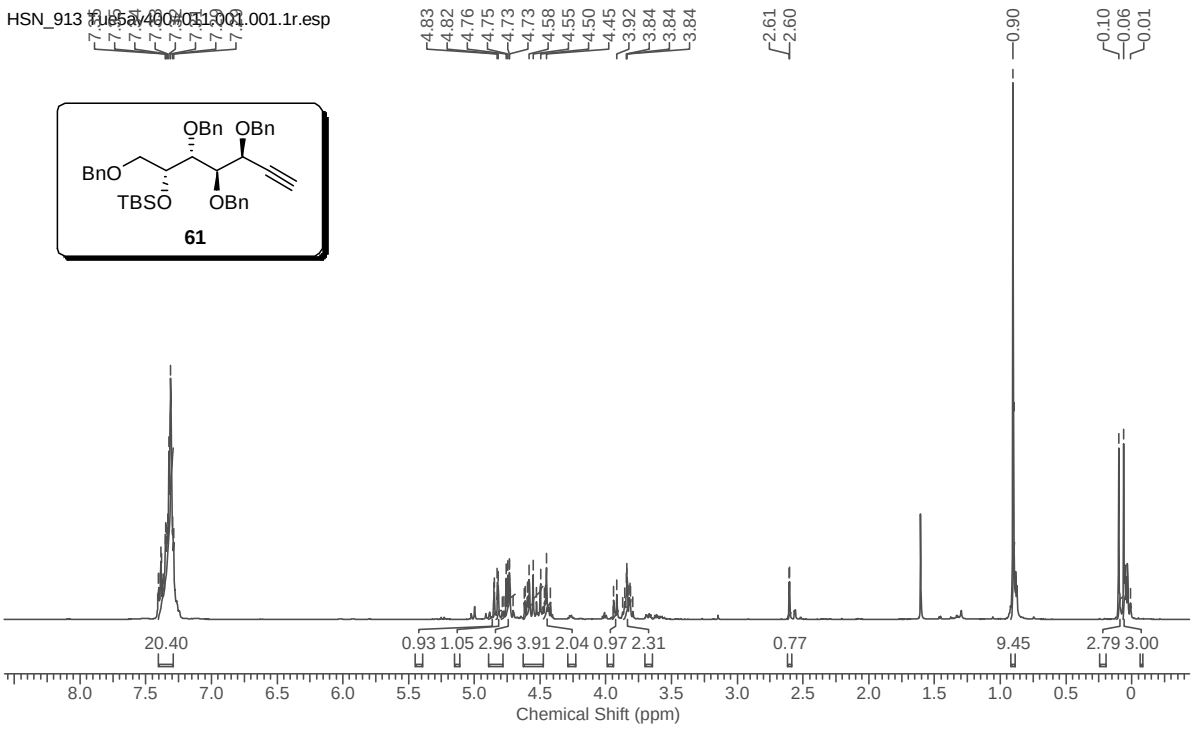
^{13}C NMR Spectrum of **59** in $CDCl_3$ (100 MHz)



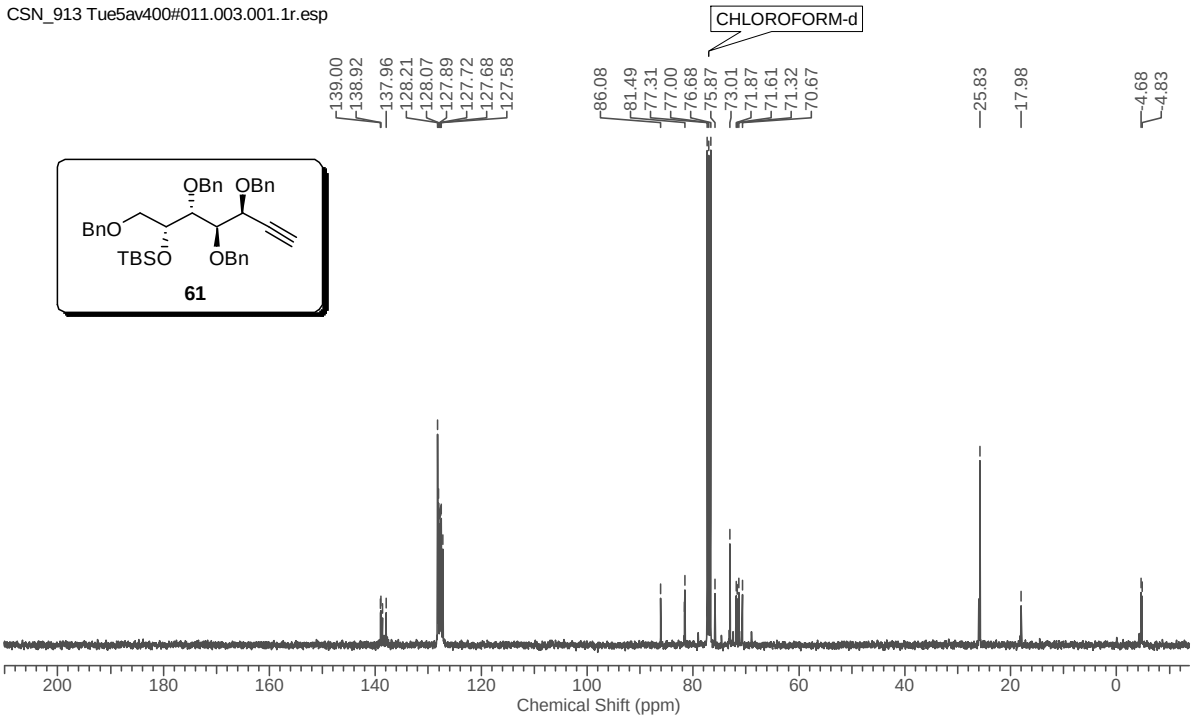
^{1}H NMR Spectrum of **60** in $CDCl_3$ (500 MHz)



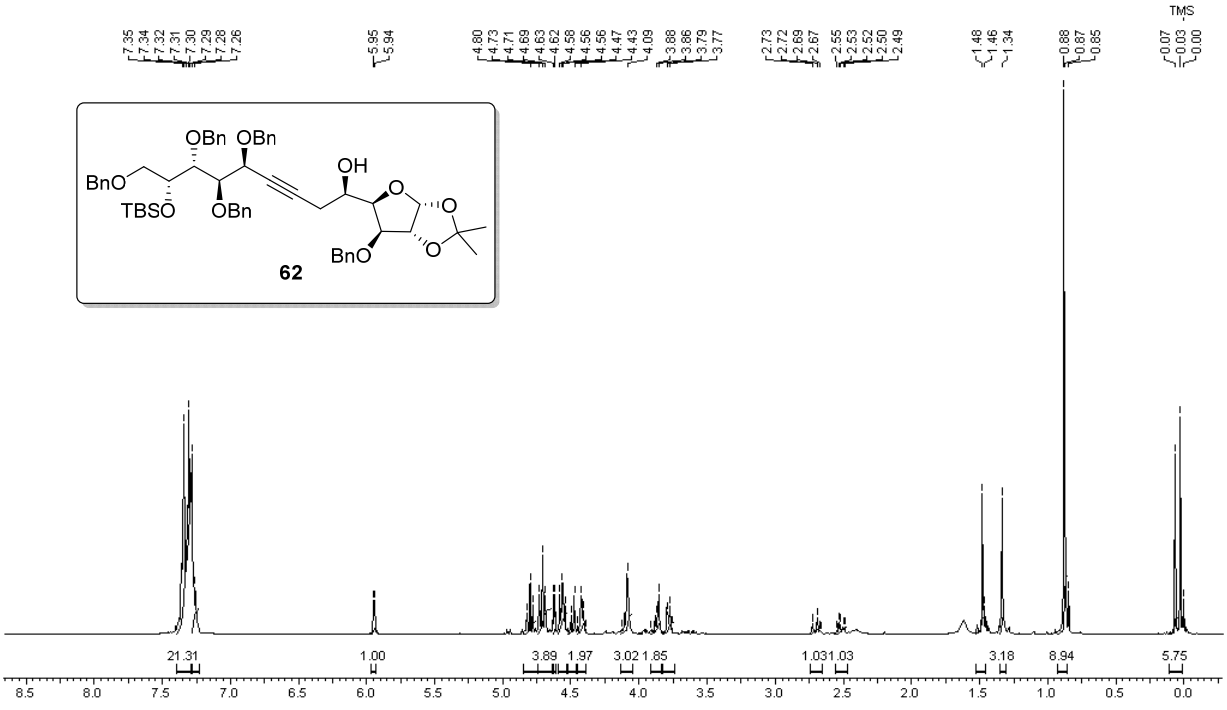
^{13}C NMR Spectrum of **60** in $CDCl_3$ (125 MHz)



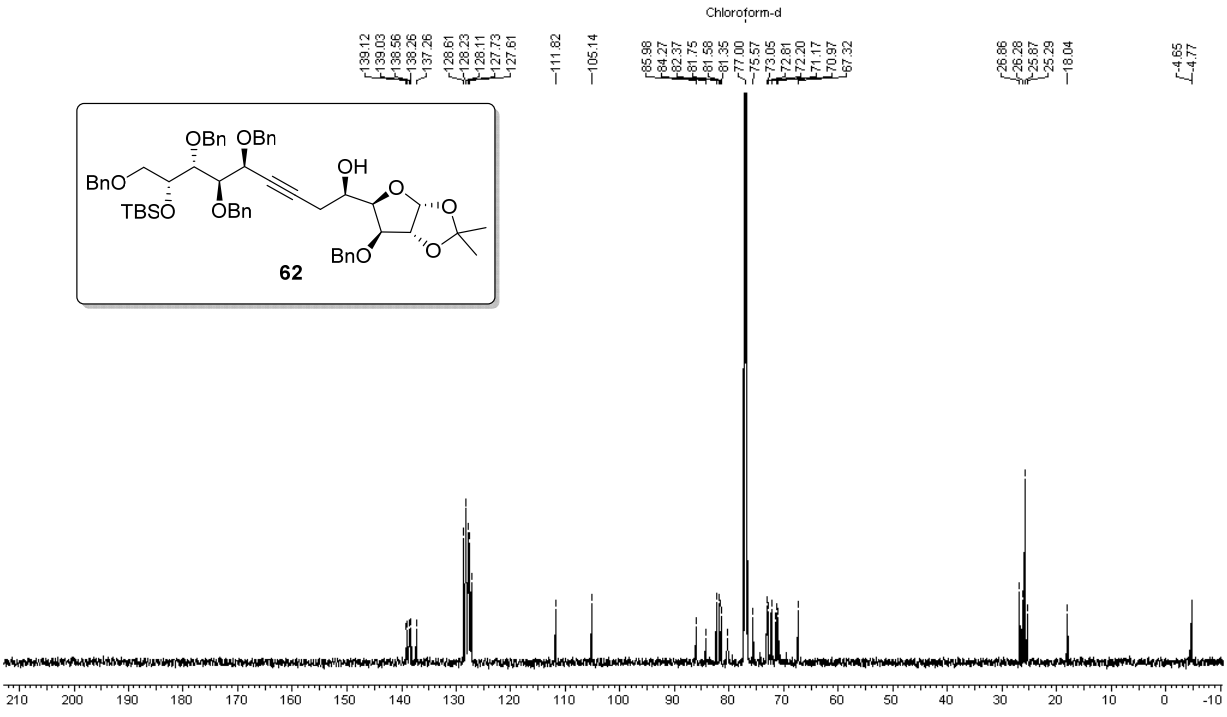
^{1}H NMR Spectrum of **61** in $CDCl_3$ (400 MHz)



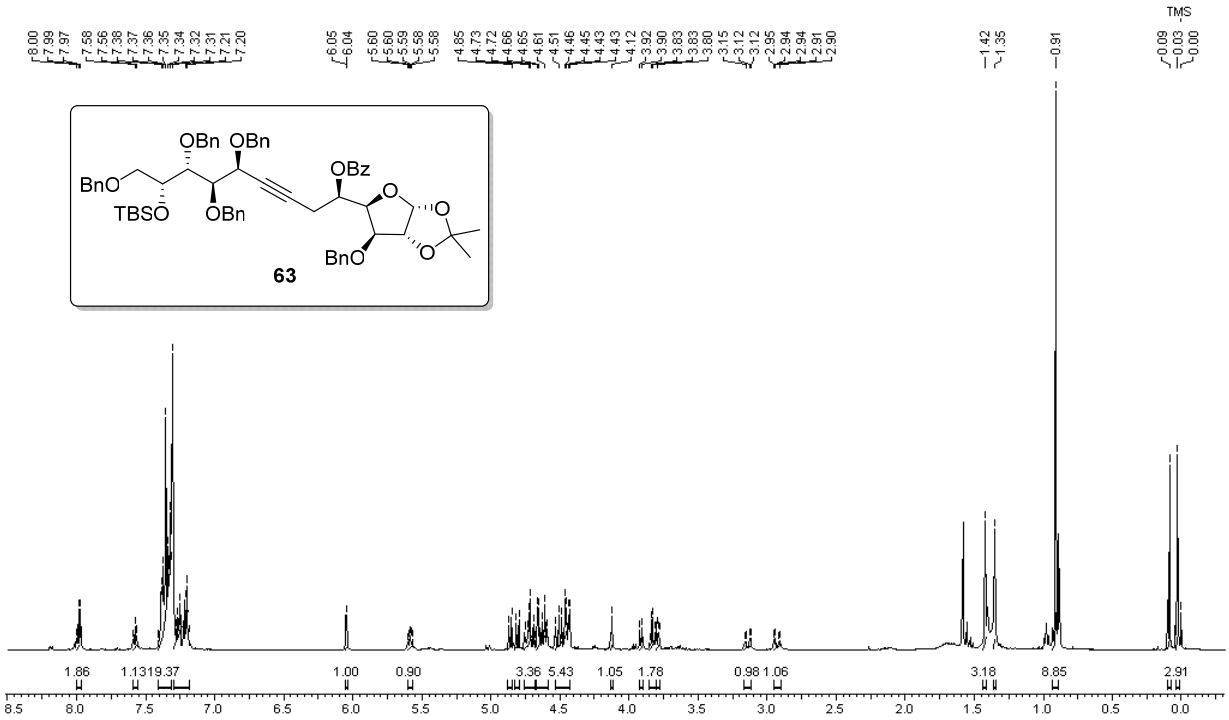
^{13}C NMR Spectrum of **61** in $CDCl_3$ (100 MHz)



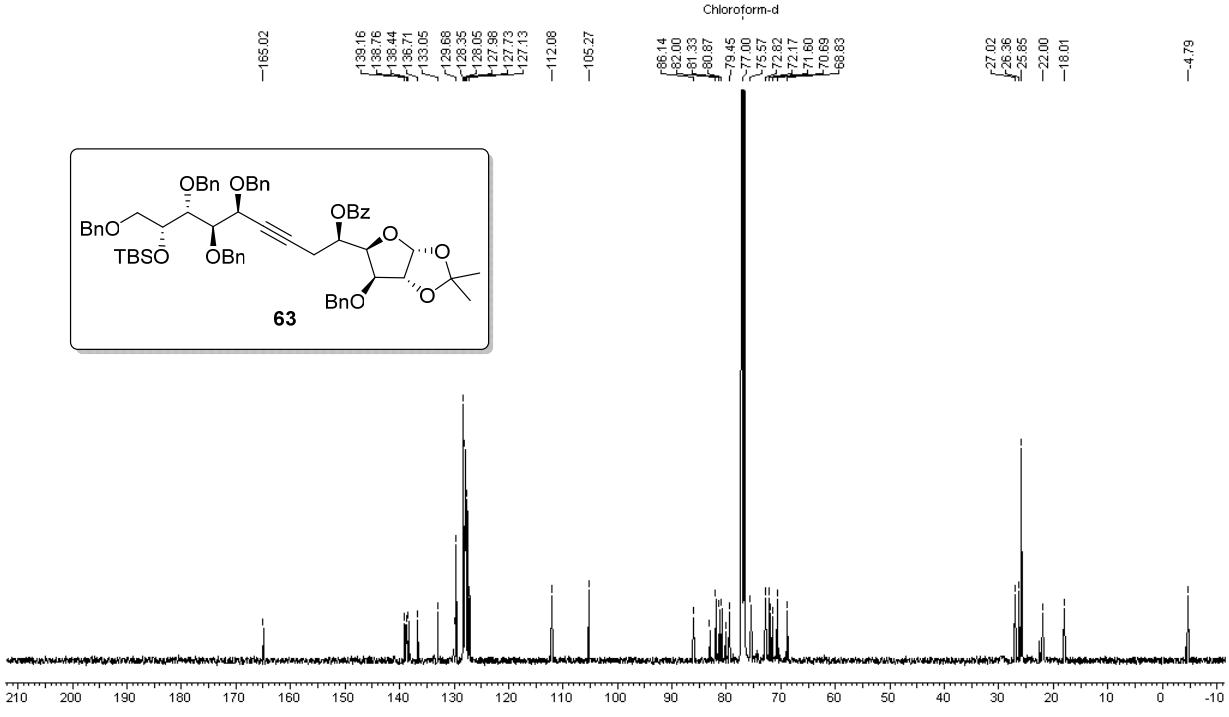
^{1}H NMR Spectrum of **62** in $CDCl_3$ (500 MHz)



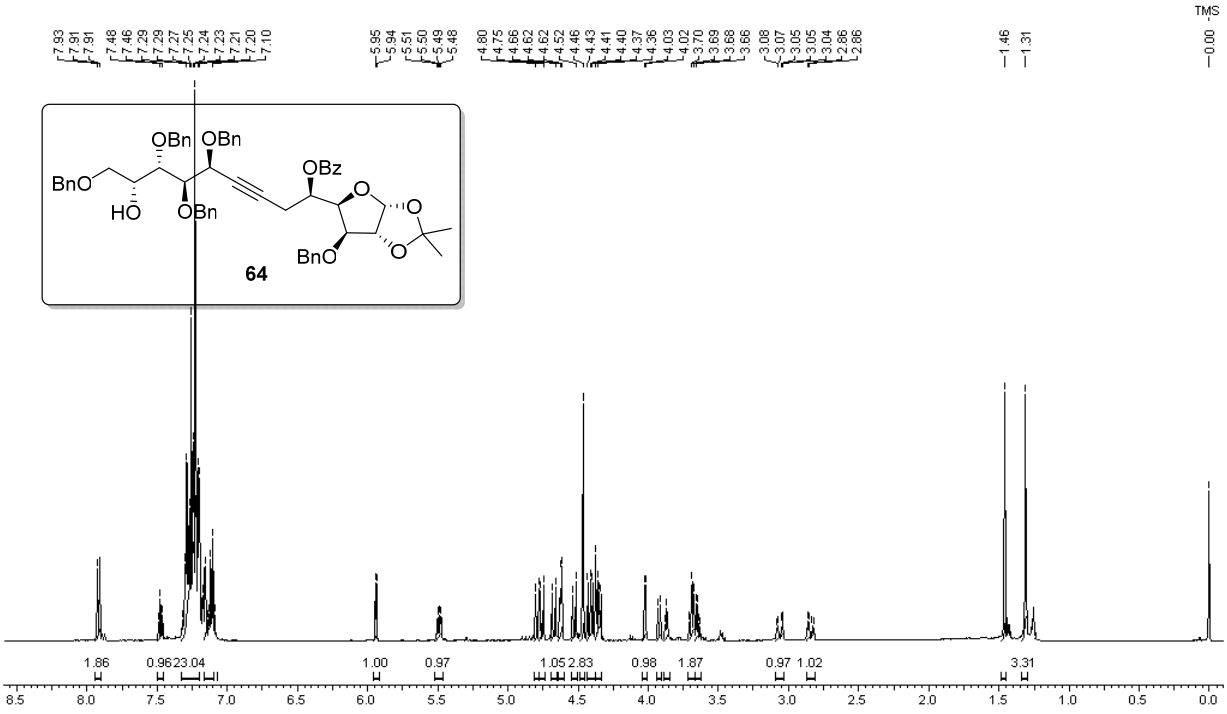
^{13}C NMR Spectrum of **62** in $CDCl_3$ (125 MHz)



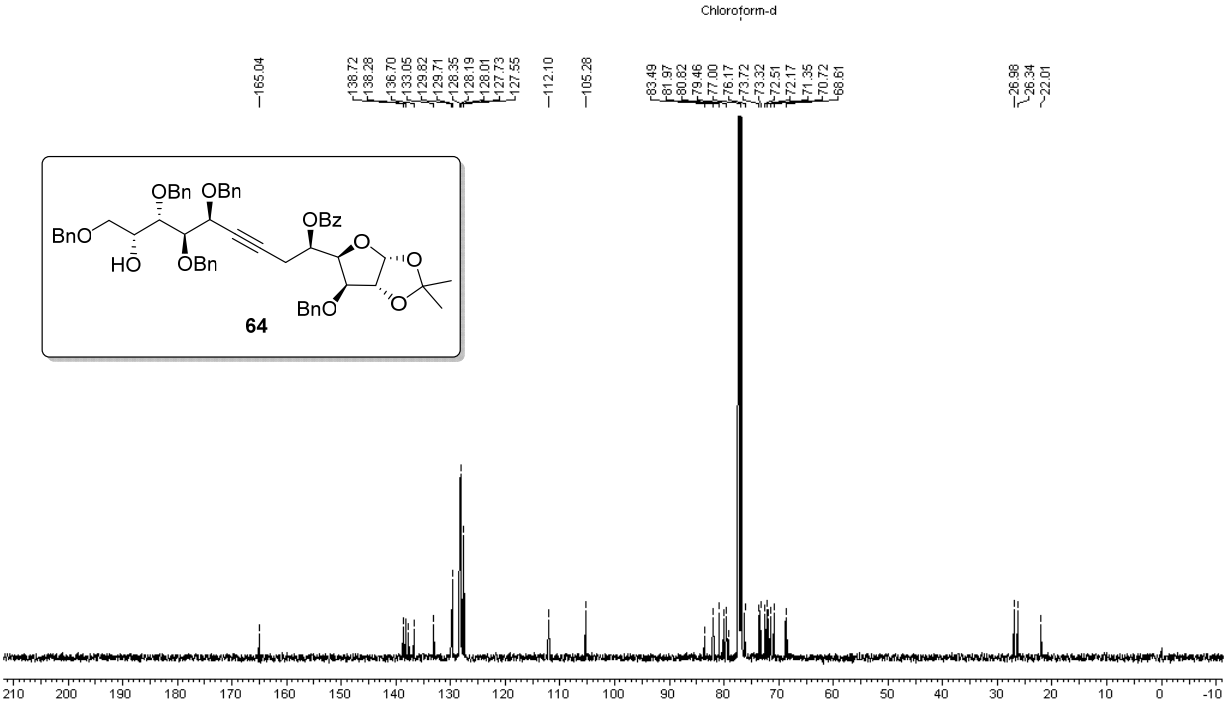
^{1}H NMR Spectrum of **63** in $CDCl_3$ (500 MHz)



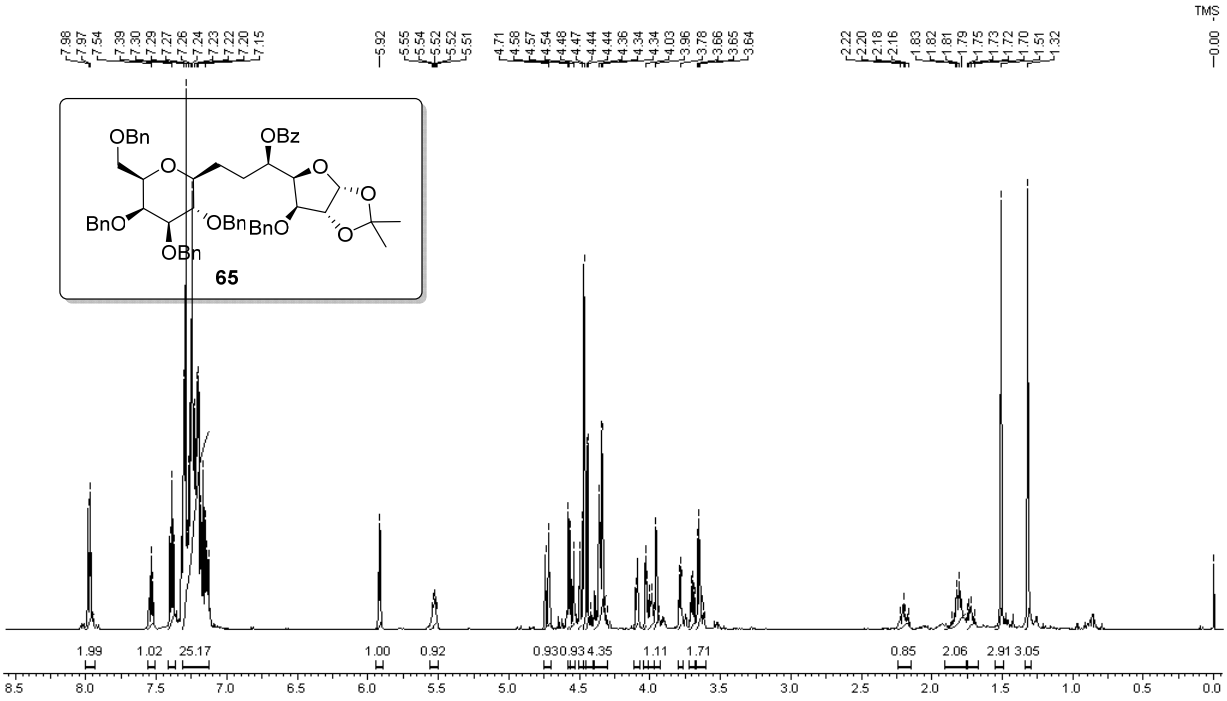
^{13}C NMR Spectrum of **63** in $CDCl_3$ (125 MHz)



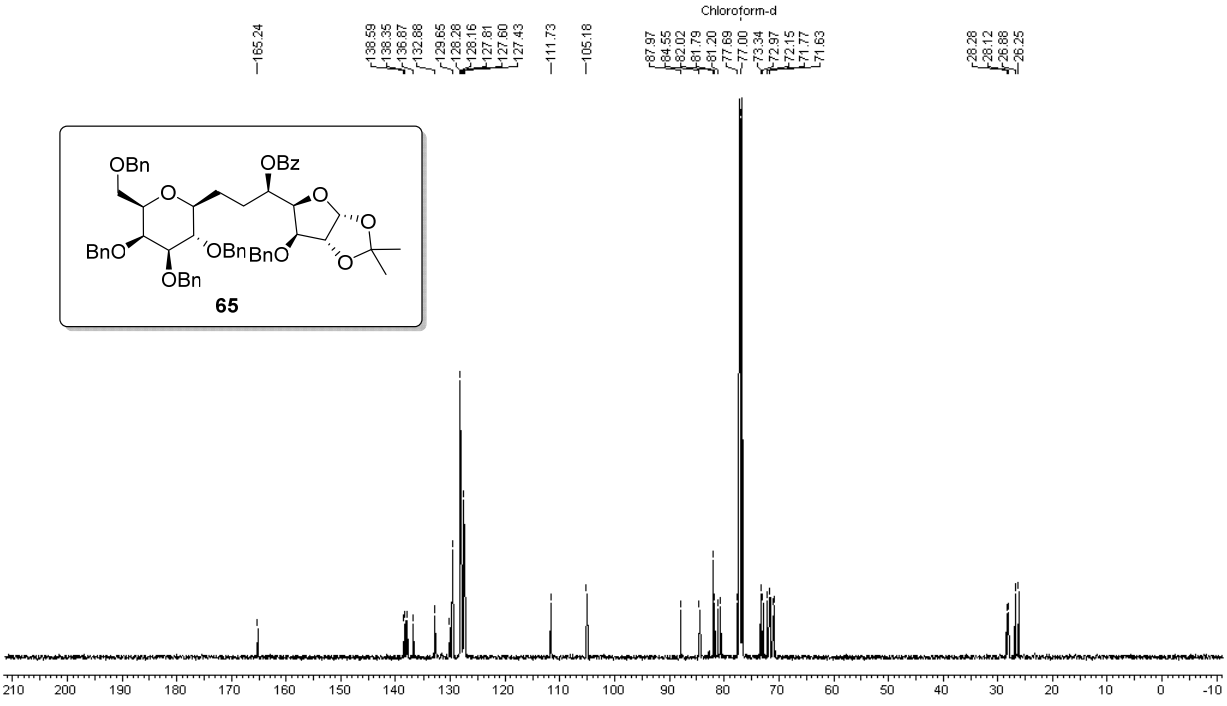
^{1}H NMR Spectrum of **64** in $CDCl_3$ (500 MHz)



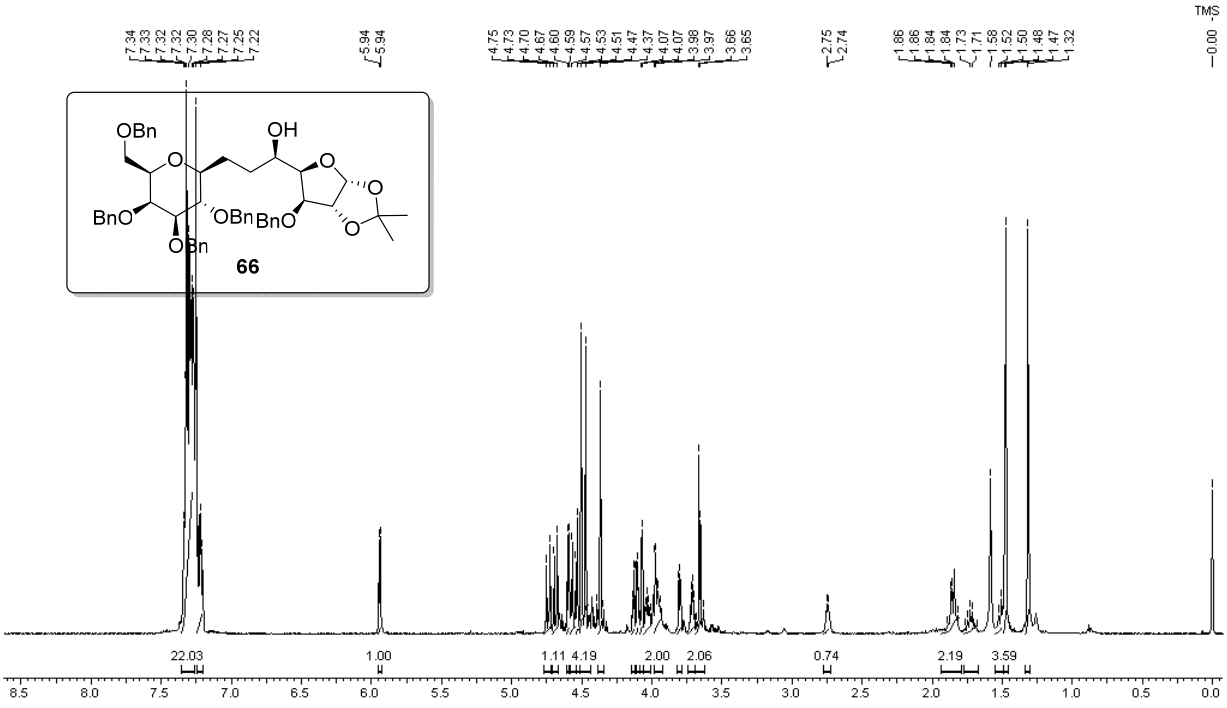
^{13}C NMR Spectrum of **64** in $CDCl_3$ (125 MHz)



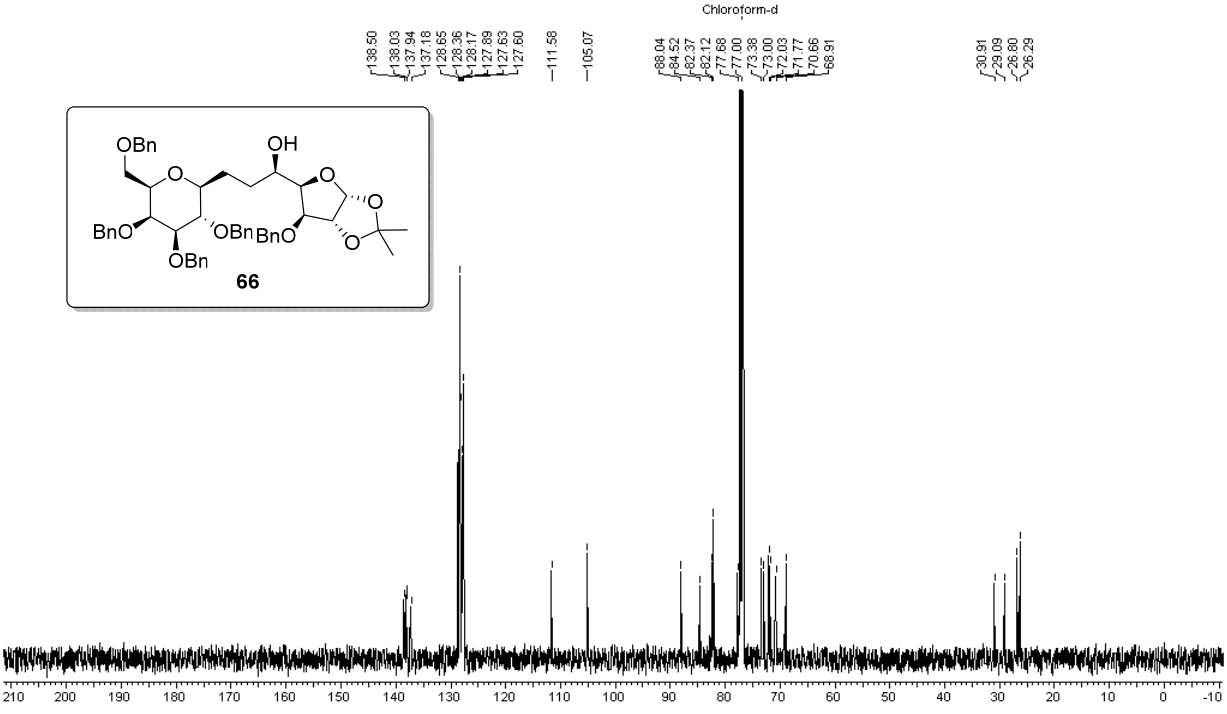
^{1}H NMR Spectrum of **65** in $CDCl_3$ (500 MHz)



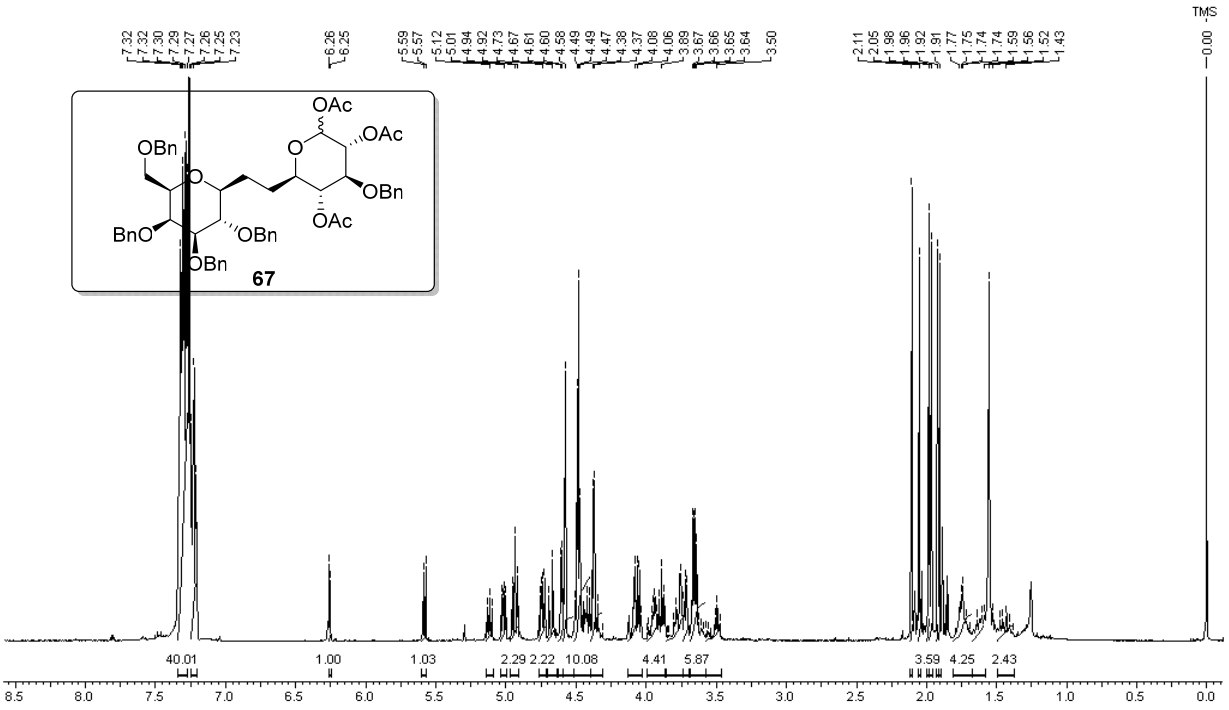
^{13}C NMR Spectrum of **65** in $CDCl_3$ (125 MHz)



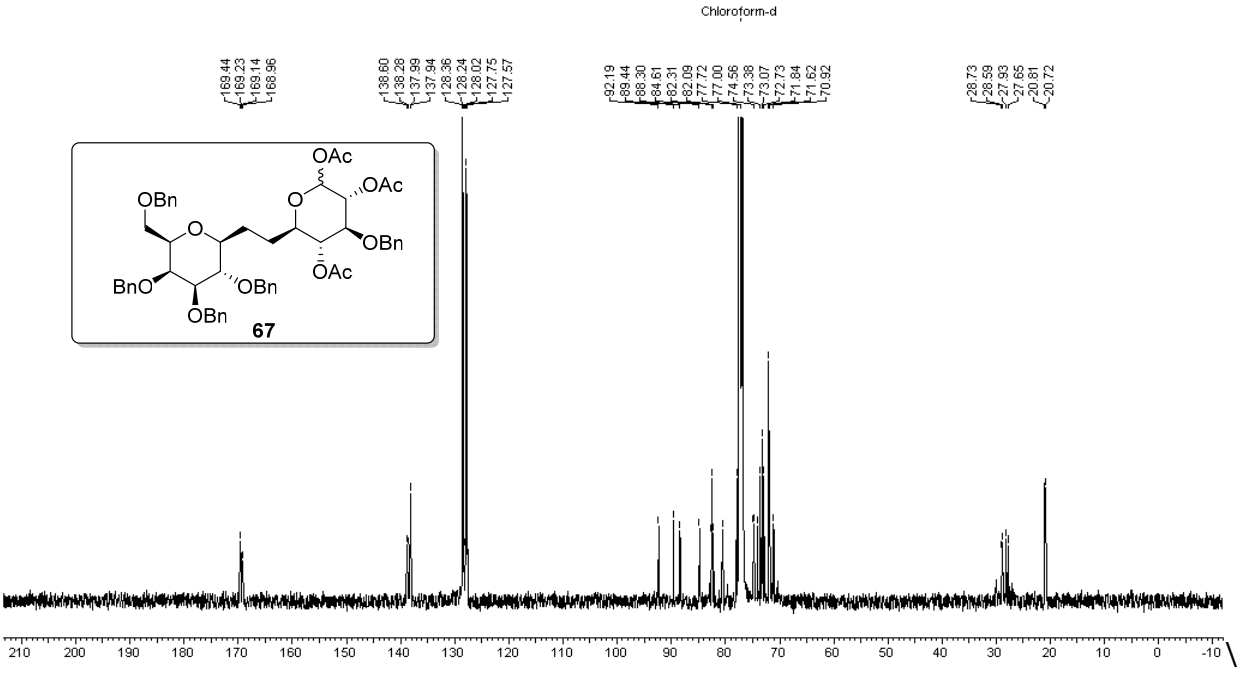
^{1}H NMR Spectrum of **66** in $CDCl_3$ (500 MHz)



^{13}C NMR Spectrum of **66** in $CDCl_3$ (125 MHz)



^{1}H NMR Spectrum of **67** in $CDCl_3$ (500 MHz)



^{13}C NMR Spectrum of **67** in $CDCl_3$ (**125** MHz)

REFERENCE

1. a) L. L. Kiessling, R. A. Splain, *Ann. Rev. Biochem.* **2010**, *79*, 619; b) Essentials of Glycobiology (Eds.: A. Varki, R. D. Cummins, J. D. Esko, H. P. Freeze, P. Stanley, C. R. Bertozzi, G. W. Hart, M. E. Etzle), 2nd ed., Cold Spring Harbor Laboratory Press, **2009**.
2. a) H. J. M. Gijsen, L. Qiao, W. Fitz, C. H. Wong, *Chem. Rev.* **1996**, *96*, 443. (b) D. C. Koester, A. Holkenbrink, D. B. Werz, Synthesis-Stuttgart **2010**, 3217.
3. a) P. Sears, C. H. Wong, *Angew. Chem. Int. Ed.* **1999**, *38*, 2301. b) H. J. M. Gijsen, L. Qiao, W. Fitz, C. H. Wong, Chem. Rev. **1996**, *96*, 443.
4. a) P. Bojarova, V. Kren, *Trends Biotechnol.* **2009**, *27*, 199; b) L. L. Lairson, B. Henrissat, G. J. Davies, S. G. Withers, *Ann. Rev. Biochem*. **2008**, *77*, 521.
5. A. Payen, J.-F. Persoz; *Annales de Chimie et de Physique*. **1833**. *53*, 73.
6. a) J. L. Treadway, P. Mendys, D. J. Hoover, *Expert Opin. Investig. Drugs* **2001**, *10*, 439; b) N. Zitzmann, A. S. Mehta, S. Carrouee, T. D. Butters, F. M. Platt, J. McCauley, B. S. Blumberg, R. A. Dwek, T. M. Block, *Proc. Natl. Acad. Sci. USA* **1999**, *96*, 11878; c) J. E. Groopman, *Rev. Infect. Dis.* **1990**, *12*, 908; d) E. Truscheit, I. Hillebrand, B. Junge, L. Muller, W. Puls, D. Schmidt, *Prog. Clin. Biochem. Med*. **1988**, *7*, 17.
7. a) Y. Hirata, D. Uemura, *Pure Appl. Chem.* **1986**, *58*. 701. b) M. J. Towle, K.A. Salvato, J. Budrow, B.F. Wels, G. Kuznetsov, K.K. Aalfs, S. Welsh, W. Zheng, B.M. Seletsky, M.H. Palme, G.J. Habgood, L.A. Singer, L.V. Dipietro, Y. Wang, J.J. Chen, D.A. Quincy, A. Davis, K. Yoshimatsu, Y. Kishi, M.J. Yu, B.A. Littlefield, *Cancer Res.* **2001**, *61*, 1013.
8. a) Takatsuk. A, K. Arima, G. Tamura, *Journal of Antibiotics* **1971**, *24*, 215. b) T. Sudo, K. Onodera, *J. of Cell. Physio.* **1979**, *101*, 149. c) T. Boettcher, S. A. Sieber, *J. Am. Chem. Soc.* **2010**, *132*, 6964. d) P.M. Small, H.F. Chambers. *Antimicrob. Agents Chemother*. **1990**, *34*, 1227.
9. a) A. M. Hooper, M. K. Tsanuo, K. Chamberlain, K. Tittcomb, J. Scholes, A. Hassanali, Z. R. Khan, J. A. Pickett, *Phytochemistry* **2010**, *71*, 904. b) L.-E. Wang, Y.-J. Bai, X.-R. Shi, X.-Y. Cui, S.-Y. Cui, F. Zhang, Q.-Y. Zhang, Y.-Y. Zhao, Y.-H. Zhang, *Pharmacology Biochemistry and Behavior* **2008**, *90*, 399.
10. D. Rouzaud, P. Sinay, *J. Chem. Soc. Chem. Comm.* **1983**, 1353.
11. a) T. Watanabe, G. Hirai, M. Kato, D. Hashizume, T. Miyagi, M. Sodeoka, *Org. Lett.* **2008**, *10*, 4167; b) G. Hirai, T. Watanabe, K. Yamaguchi, T. Miyagi, M. Sodeoka, *J. Am. Chem. Soc.* **2007**, *129*, 15420; c) R. J. K. Taylor, G. D. McAllister, R. W. Franck,

Carbohydr. Res. **2006**, *341*, 1298; d) X. L. Li, X. M. Xu, J. Tian, Y. X. Li, *Chinese J. Chem.* **2005**, *23*, 1564; e) P. Stepanek, O. Vich, L. Werner, L. Kiezo, H. Dvorakova, P. Vojtisek, Coll. Czech. *Chem. Comm.* **2005**, *70*, 1411; f) X. J. Yuan, R. J. Linhardt, *Curr. Top. Med. Chem.* **2005**, *5*, 1393; g) J. L. Piper, M. H. D. Postema, *J. Org. Chem.* **2004**, *69*, 7395; h) R. Demange, L. Awad, P. Vogel, *Tetrahedron: Asymmetry* **2004**, *15*, 3573; i) P. Stepanek, O. Vich, L. Kniezo, H. Dvorakova, P. Vojtisek, *Tetrahedron: Asymmetry* **2004**, *15*, 1033; j) R. W. Denton, D. R. Mootoo, *J. Carbohydr. Chem.* **2003**, *22*, 671; k) B. Patro, R. R. Schmidt, *J. Carbohydr. Chem.* **2000**, *19*, 817; l) B. A. Johns, Y. T. Pan, A. D. Elbein, C. R. Johnson, *J. Am. Chem. Soc.* **1997**, *119*, 4856; m) H. Streicher, A. Geyer, R. R. Schmidt, *Chem. Eur. J.* **1996**, *2*, 502; n) A. T. Khan, P. Sharma, R. R. Schmidt, *J. Carbohydr. Chem.* **1995**, *14*, 1353; o) W. Yuan, S. A. Babirad, Y. Kishi, *J. Org. Chem.* **1992**, *57*, 468; p) R. Preuss, R. R. Schmidt, *J. Carbohydr. Chem.* **1991**, *10*, 887; q) R. R. Schmidt, R. Preuss, *Tetrahedron Lett.* **1989**, *30*, 3409; r) B. Giese, M. Hoch, C. Lamberth, R. R. Schmidt, *Tetrahedron Lett.* **1988**, *29*, 1375; s) *Angew. Chem. Int. Ed.* **1986**, *25*, 450.

12. a) D. C. Koester, E. Kriemen, D. B. Werz, *Angew. Chem. Int. Ed.* **2013**, *52*, 2985; b) D. C. Koester, M. Leibeling, R. Neufeld, D. B. Werz, *Org. Lett.* **2010**, *12*, 3934; c) M. H. D. Postema, J. L. Piper, V. Komanduri, L. Liu, *Angew. Chem. Int. Ed.* **2004**, *43*, 2915; d) M. H. D. Postema, J. L. Piper, L. Liu, J. Shen, M. Faust, P. Andreana, *J. Org. Chem.* **2003**, *68*, 4748; e) Z. Abdallah, G. Doisneau, J.-M. Beau, *Angew. Chem. Int. Ed.* **2003**, *42*, 5209; f) L. M. Mikkelsen, S. L. Krintel, J. Jimenez-Barbero, T. Skrydstrup, *J. Org. Chem.* **2002**, *67*, 6297; g) L. Liu, H. D. Postema, *J. Am. Chem. Soc.* **2001**, *123*, 8602; h) N. Miquel, G. Doisneau, J.-M. Beau, *Angew. Chem. Int. Ed.* **2000**, *39*, 4111; i) D. Maz_as, T. Skrydstrup, J.-M. Beau, *Angew. Chem. Int. Ed.* **1995**, *34*, 909; j) D. Maz_as, T. Skrydstrup, O. Doumeix, J.-M. Beau, *Angew. Chem. Int. Ed.* **1994**, *33*, 1383; k) O. R. Martin, W. Lai, *J. Org. Chem.* **1993**, *58*, 176.
13. a) R. S. Patil, K. M. Ahire, C. V. Ramana, *Tetrahedron Lett.* **2012**, *53*, 6347; b) A. K. Pathak, V. Pathak, J. R. Riordan, W. J. Suling, S. S. Gurcha, G. S. Besra, R. C. Reynolds, Bioorg. *Med. Chem. Lett.* **2007**, *17*, 4527; c) G. X. Chang, T. L. Lowary, *Tetrahedron Lett.* **2006**, *47*, 4561; d) T. Aslam, M. G. G. Fuchs, A. Le Formal, R. H. Wightman, *Tetrahedron Lett.* **2005**, *46*, 3249; e) G. D. McAllister, D. E. Paterson, R. J. K. Taylor, *Angew. Chem. Int. Ed.* **2003**, *42*, 1387; f) J. L. McCartney, C. T. Meta, R. M. Cicchillo,

M. D. Bernardina, T. R. Wagner, P. Norris, *J. Org. Chem.* **2003**, *68*, 10152; g) A. Dondoni, A. Marra, *Tetrahedron Lett.* **2003**, *44*, 4067; g) P. Bowles, S. J. Brenek, S. Caron, N. M. Do, M. T. Drexler, S. Duan, P. Dube, E. C. Hansen, B. P. Jones, K. N. Jones, T. A. Ljubicic, T. W. Makowski, J. Mustakis, J. D. Nelson, M. Olivier, Z. Peng, H. H. Perfect, D. W. Place, J. A. Ragan, J. J. Salisbury, C. L. Stanchina, B. C. Vanderplas, M. E. Webster, R. M. Weekly, *Org. Process Res. Dev.* **2013**, *18*, 66.

14. Some selected references for synthesis of *C*-glycosides employing $Et_3SiH/BF_3{\cdot}Et_2O$ reductive deoxygenation: a) C. V. S. Kumar, V. G. Puranik, C. V. Ramana, *Chem. Eur. J.* **2012**, *18*, 9601; b) M. Imamura, K. Nakanishi, T. Suzuki, K. Ikegai, R. Shiraki, T. Ogiyama, T. Murakami, E. Kurosaki, A. Noda, Y. Kobayashi, M. Yokota, T. Koide, K. Kosakai, Y. Ohkura, M. Takeuchi, H. Tomiyama, M. Ohta, *Bioorg. Med. Chem.* **2012**, *20*, 3263; c) P. P. Deshpande, J. Singh, A. Pullockaran, T. Kissick, B. A. Ellsworth, J. Z. Gougoutas, J. Dimarco, M. Fakes, M. Reyes, C. Lai, H. Lobinger, T. Denzel, P. Ermann, G. Crispino, M. Randazzo, Z. Gao, R. Randazzo, M. Lindrud, V. Rosso, F. Buono, W. W. Doubleday, S. Leun, P. Richberg, D. Hughes, W. N. Washburn, W. Meng, K. J. Volk, R. H. Mueller, *Org. Process Res. Dev.* **2012**, *16*, 577; d) P. Patel, C. V. Ramana, *J. Org. Chem.* **2012**, *77*, 10509; e) G. Hernandez-Torres, M. Carmen Carreno, A. Urbano, F. Colobert, *Chem. Eur. J.* **2011**, *17*, 1283; f) P. P. Deshpande, B. A. Ellsworth, F. G. Buono, A. Pullockaran, J. Singh, T. P. Kissick, M.-H. Huang, H. Lobinger, T. Denzel, R. H. Mueller, *J. Org. Chem.* **2007**, *72*, 9746; g) J. M. MacDougall, X. D. Zhang, W. E. Polgar, T. V. Khroyan, L. Toll, J. R. Cashman, Bioorg. *Med. Chem. Lett.* **2005**, *15*, 1583; h) M. Terauchi, H. Abe, A. Matsuda, S. Shuto, *Org. Lett.* **2004**, *6*, 3751; i) E. Brenna, C. Fuganti, P. Grasselli, S. Serra, S. Zambotti, *Chem. Eur. J.* **2002**, *8*, 1872; j) K. Murty, A. Vasella, *Helv. Chim. Acta* **2001**, *84*, 939; k) Y. C. Xin, Y. M. Zhang, J. M. Mallet, C. P. J. Glaudemans, P. Sina, *Eur. J. Org. Chem.* **1999**, *471*; l) D. P. Sutherlin, R. W. Armstrong, *Tetrahedron Lett.* **1993**, *34*, 4897; m) W. Yuan, S. A. Babirad, Y. Kishi, *J. Org. Chem.* **1992**, *57*, 468; n) S. Czernecki, G. Ville, *J. Org. Chem.* **1989**, *54*, 610; o) J. M. Lancelin, P. H. A. Zollo, P. Sinay, *Tetrahedron Lett.* **1983**, *24*, 4833; p) M. D. Lewis, J. K. Cha, Y. Kishi, *J. Am. Chem. Soc.* **1982**, *104*, 4976. q) M. A. Leeuwenburgh, C. M. Timmers, G. A. vanderMarel, J. H. vanBoom, J. M. Mallet, P. G. Sinay, *Tetrahedron Lett.* **1997**, *38*, 6251.

15. Selected references on $Et_3SiH/BF_3{\cdot}Et_2O$ reductive deoxygenation in synthesis of tetrahydropyrans (other than sugars): a) S. Diaz-Oltra, C. A. Angulo-Pachon, J. Murga, E. Falomir, M. Carda, J. Alberto Marco, *Chem. Eur. J.* **2011**, *17*, 675; b) T. Oishi, T. Imaizumi, M. Murata, *Chem. Lett.* **2010**, *39*, 108; c) H. Fuwa, M. Sasaki, *Org. Lett.* **2010**, *12*, 584; d) J. D. Carrick, M. P. Jennings, *Org. Lett.* **2009**, *11*, 769; e) A. B. Smith, III, C. Sfouggatakis, C. A. Risatti, J. B. Sperry, W. Zhu, V. A. Doughty, T. Tomioka, D. B. Gotchev, C. S. Bennett, S. Sakamoto, O. Atasoylu, S. Shirakami, D. Bauer, M. Takeuchi, J. Koyanagi, Y. Sakamoto, *Tetrahedron* **2009**, *65*, 6489; f) C. G. Dong, J. A. Henderson, Y. Kaburagi, T. Sasaki, D.-S. Kim, J. T. Kim, D. Urabe, H. Guo, Y. Kishi, *J. Am. Chem. Soc.* **2009**, *131*, 15642; g) A. B. Smith, III, T. Tomioka, C. A. Risatti, J. B. Sperry, C. Sfouggatakis, *Org. Lett.* **2008**, *10*, 4359; h) R. Kartika, R. E. Taylor, *Angew. Chem. Int. Ed.* **2007**, *46*, 6874; i) D. A. Evans, P. H. Carter, E. M. Carreira, A. B. Charette, J. A. Prunet, M. Lautens, *J. Am. Chem. Soc.* **1999**, *121*, 7540.
16. a) S. B. Narute, C. V. Ramana, *Tetrahedron* **2013**, *69*, 1830; b) S. B. Narute, N. C. Kiran, C. V. Ramana, *Org. Biomol. Chem.* **2011**, *9*, 5469; c) C. V. Ramana, B. Induvadana, B. Srinivas, K. Yadagiri, M. N. Deshmukh, R. G. Gonnade, *Tetrahedron* **2009**, *65*, 9819; d) M. Xu, Z. Miao, B. Bernet, A. Vasella, *Helv. Chim. Acta*, **2005**, *88*, 2918.
17. a) J. A. Palmes, A. Aponick, *Synthesis* **2012**, *44*, 3699; b) A. Corma, A. Leyva-Perez, M. J. Sabater, *Chem. Rev.* **2011**, *111*, 1657; c) B. Biannic, A. Aponick, *Eur. J. Org. Chem.* **2011**, 6605; d) X. Du, F. Song, Y. Lu, H. Chen, Y. Liu, *Tetrahedron* **2009**, *65*, 1839; e) B. M. Trost, G. Dong, *Nature* **2008**, *456*, 485; f) H. Harkat, J.-M. Weibel, P. Pale, *Tetrahedron Lett.* **2007**, *48*, 1439; g) J. Muzart, *Tetrahedron* **2005**, *61*, 5955; h) Y. H. Liu, F. J. Song, Z. Q. Song, M. N. Liu, B. Yan, *Org. Lett.* **2005**, *7*, 5409; i) G. Zeni, R. C. Larock, *Chem. Rev.* **2004**, *104*, 2285; j) A. S. K. Hashmi, L. Schwarz, J. H. Choi, T. M. Frost, *Angew. Chem. Int. Ed.* **2000**, *39*, 2285; k) K. Utimoto, *Pure Appl. Chem.* **1983**, *55*, 1845.
18. T. Fukatsu, K.-i. Onodera, Y. Ohta, Y. Oba, H. Nakamura, T. Shintani, Y. Yoshioka, T. Okamoto, M. ten Lohuis, D. J. Miller, M. Kawachi, M. Ojika, *J. Nat. Prod.* **2007**, *70*, 407.
19. B. M. Trost, G. Dong, *Nature* **2008**, *456*, 485.
20. J. E. Baldwin, *J. Chem. Soc.*, *Chem. Commun.* **1976**, 734.

21. a) K. Krohn, H. Heins, K. Wielckens, *J. Med. Chem.* **1992**, *35*, 511; b) E. Calzada, C. A. Clarke, C. Roussinbouchard, R. H. Wightman, *J. Chem. Soc. Perkin Trans. 1* **1995**, 517. c) C. H. Larsen, B. H. Ridgway, J. T. Shaw, D. M. Smith, K. A. Woerpel, *J. Am. Chem. Soc.* **2005**, *127*, 10879.
22. a) J. G. Buchanan, A. R. Edgar, M. J. Power, J. Chem. Soc. Perkin Trans. 1 **1974**, 1943; b) D. Horton, J. B. Hughes, J. M. Tronchet, *Chem. Comm.* **1965**, 481; c) A. Yepremyan, T. G. Minehan, *Org. Biomol. Chem.*, **2012**, *10*, 5194; d) J. Zeng, S. Vedachalam, S. Xiang, X.-W. Liu, *Org. Lett.* **2011**, *13*, 42.
23. K. M. Backus, H. L. Boshoff, C. S. Barry, O. Boutureira, M. K. Patel, F. D'Hooge, S. S. Lee, L. E. Via, K. Tahlan, C. E. Barry, III, B. G. Davis, *Nature Chemical Biology* **2011** *7*, 228.
24. a) M. Yamaguchi, I. Hirao, *Tetrahedron Lett.* **1983**, *24*, 391; b) A. Hussain, S. K. Yousuf, D. K. Sharma, L. M. Rao, B. Singh, D. Mukherjee, *Tetrahedron* **2013**, *69*, 5517.

List of Publication

1. "Total Synthesis of (−)-Sacidumlignans B and D" Jeetendra Kumar Rout, C. V. Ramana, *J. Org. Chem.* **2012**, *77*, 1566−1571
2. "Synthesis of *C*-Disaccharides through a One-Pot Alkynol Cycloisomerization-Reductive Deoxygenation" Sachin B. Narute, Jeetendra Kumar Rout, Chepuri V. Ramana, *Chem. Eur. J*. **2013**, *19*, 15109 – 15114
3. "Studies toward the Synthesis of Cytospolide E" Paresh M. Vadhadiya, Jeetendra Kumar Rout, Chepuri V. Ramana (Manuscript under Preparation).