Novel Methods for the Stereoselective Synthesis of *C*-Glycosides from 2-Vinyloxymethyl Glycals

A thesis submitted for the degree of
DOCTOR OF PHILOSOPHY

by

Chalapala Sudharani

School of Chemistry
University of Hyderabad
Hyderabad-500 046

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To

All My teachers,

family and

friends

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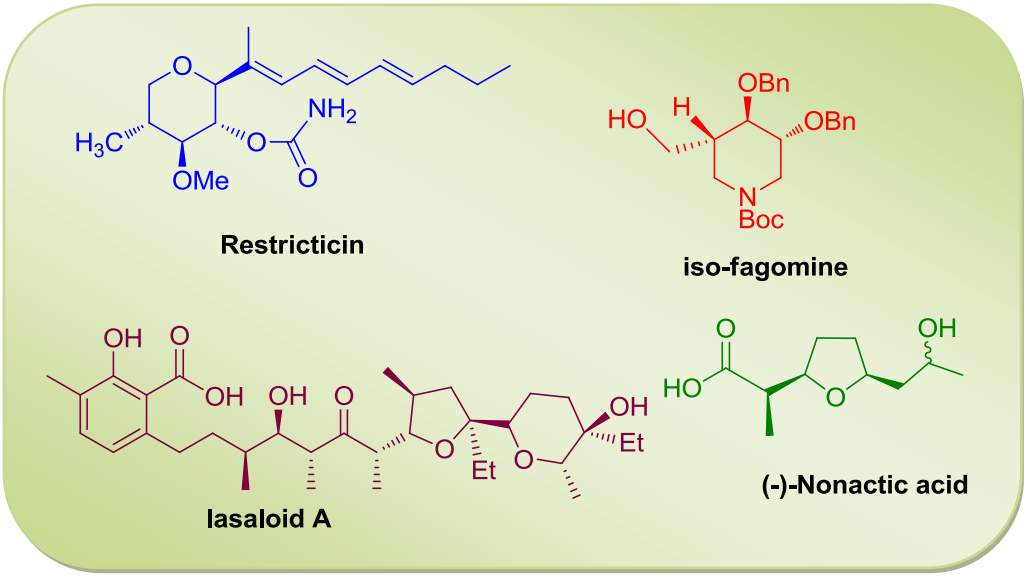
Introduction to the chemistry of *C*-1 and *C*-2 branched glycals



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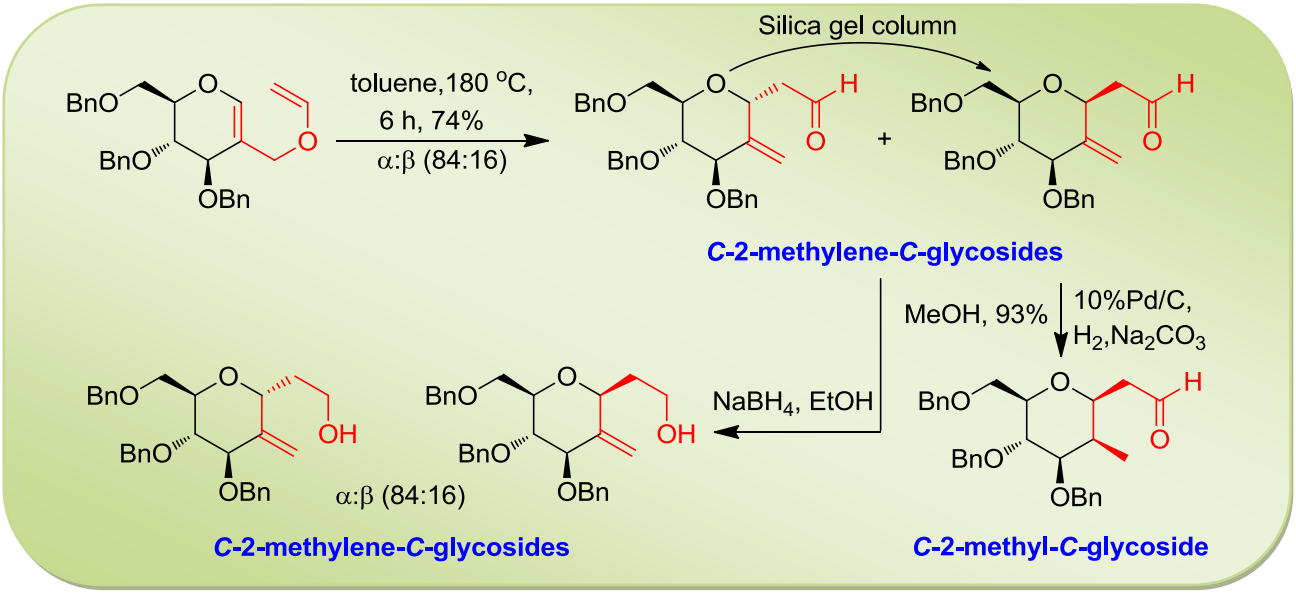

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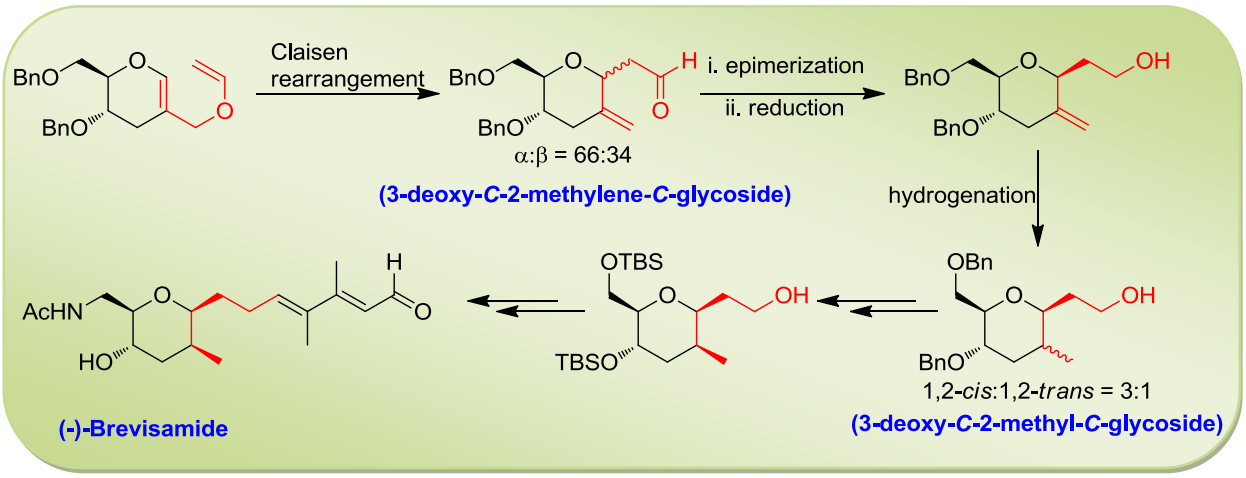

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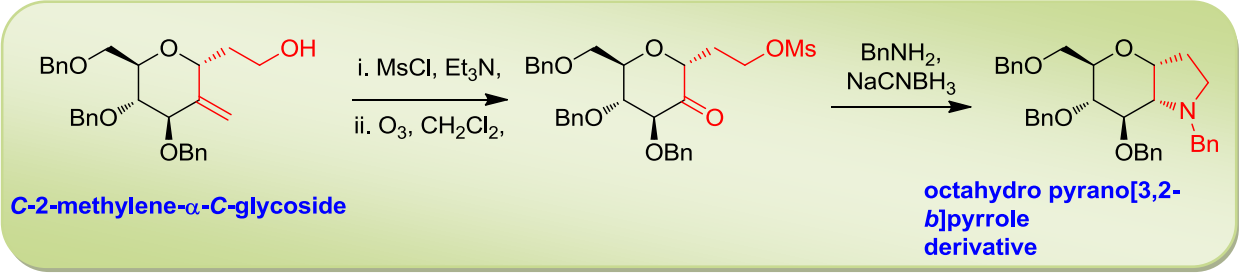

Statement

I hereby declare that, the overall material contained in this thesis is the outcome of research accomplished by me in the School of chemistry, University of Hyderabad, Hyderabad, India, under the supervision of Dr. Perali Ramu Sridhar.

In keeping with the general trend of reporting scientific observations, due acknowledgements have been made wherever the work described is based on the findings of other investigations. Any omission, which might have occurred by oversight or error, is regretted.

Sudharani Chalapala

University of Hyderabad
December, 2014

Dr. P. Ramu Sridhar
Assitant Professor
Work: 91-40-66794823
Fax: +91-40-23012460
e-mail:prssc@uohyd.ernet.in

School of Chemistry
University of Hyderabad
Prof. C. R. Rao Road
Gachibowli
Hyderabad-500046 India

Certificate

Certified that the work pertaining to the thesis entitled "Novel Methods for the Stereoselective Synthesis of *C*-Glycosides from 2-Vinyloxymethyl Glycals" has been carried out by Ms. Sudharani Chalapala under my supervision and that the aforementioned work has not been submitted elsewhere for obtaining degree.

Dr. Perali Ramu Sridhar
(Supervisor)

Dean
School of Chemistry
University of Hyderabad

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Sudharani Chalapala…

Hyderabad
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List of Abbreviations

Ac	acetyl
AIBN	azobis(isobutyro)nitrile
am	amyl
Anal.	analysis
aq.	aqueous
atm	atmosphere
Bn	benzyl
BnBr	benzyl bromide
BnOH	benzyl alcohol
Boc	tert-butoxy carbonyl
Bu	butyl
Calcd	calculated
CAN	ceric ammonium nitrate
CR	claisen rearrangement
CSA	camphor sulfonic acid
d	doublet
DCN	1,4-dicyanonaphthalene
dd	doublet of doublet
dt	doublet of doublet
DA	Donor–Acceptor
DAIB	diacetoxy iodobenzene
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCE	dicholorethane
DCM	dichloromethane
DDQ	2,3-dichloro-5,6-dicyano-*p*-benzoquinone
DIBAL	diisobutyl aluminium hydride
DIPEA	diisopropyl ethyl amine
DMAP	4-(dimethylamino) pyridine
DMDC	2-deoxy-2-methylidenecytidine
DMF	*N, N'*-dimethylformamide
DEAD	dibenzyl azodicarboxylate

DMP	dimethyl propane
DMPU	1,3-Dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone
DMSO	dimetyhl sulfoxide
EDA	ethyl diazo acetate
EI	electron ionization
EtOAc	Ethyl acetate
Ether	diethyl ether
Et	ethyl
equiv	equivalent
FAB	fast atom bombardment
FT	Fourier transform
g	gram(s)
GAA	glyco amino acid
h	hour(s)
HRMS	high-resolution mass spectrum
Hz	hertz
IR	infrared
KHMDS	potassium hexa methyl disilazide
LAH	lithium aluminium hydride
Lit	literature
LDA	lithium diisopropylamide
LHMDS	lithium hexamethyl disilazide
m	multiplet
MALDI	matrix-assisted laser desorption / ionization
MDA	methyl diazo acetate
Me	methyl
mg	milligram(s)
MHz	mega hertz
min	minute(s)
mL	milli liter
μL	micro liter
mmol	milli mole(s)
MOM	methoxy methyl
MS	molecular sieves

MsCl	methane sulfonyl chloride
NBS	*N*-bromo succinimide
NIS	*N*-iodo succinimide
NMR	nuclear magnetic resonance
ORTEP	Oak Ridge thermal ellipsoid plot
OTf	triflоromethane sulfonate
PDC	pyridinium dichromate
PET	photo induced electron transfer
Ph	phenyl
PPh_3	triphenyl phosphine
PPh_3.HBr	triphenyl phosphonium hydrobromide
ppm	parts per million
PTSA	p-toulene sulfonic acid
Py	pyridine
q	quartet
Q-Tof	quadrupole time-of-flight
RCM	ring-closing metathesis
RT or rt	room temperature
s	singlet
SIBX	Stabilized 2-iodoxybenzoic acid
t	triplet
TBAI	tetrabutyl ammonium iodide
TBAF	tetrabutyl ammonium fluoride
TBDPS	tert-butyl diphenyl silyl
TBS	tert-butyl dimethyl silyl
TBTU	*O*-benzotriazolyl-*N*-*N*-*N*$'$-*N*$'$-tetramethyluranium tetrafluoroborate
td	triplet of doublet
TEMPO	2,2,6,6-Tetramethylpiperidinyloxy
TFA	trifloro acetic acid
TFA	trifloro acetic anhydride
Tf_2NPh	*N*,*N*-Bis(trifluoromethylsulfonyl)aniline
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	tetramethylsilane

List of publications

1. An efficient synthesis of D-*ribo*-C_{18}-phytosphingosine and L-*arabino*-C_{18}-phytosphingosine from D-fructose.

   Ramu Sridhar Perali, Suresh Mandava, **Sudharani Chalapala**. *Tetrahedron* **2011**, *67*, 9283-9290.

2. Stereoselective synthesis of *C*-2-methylene and *C*-2-methyl-*C*-glycosides by Claisen rearrangement of 2-vinyloxymethyl glycals.

   Perali Ramu Sridhar, **Chalapala Sudharani**. *Rsc. Adv*. **2012**, *2*, 8596-8598.

3. A one-pot septanoside formation and glycosylation of acyclic dithioacetals derived from 1,2-cyclopropanated sugars.

   Patteti Venukumar, **Chalapala Sudharani**, Perali Ramu Sridhar. *Chem. Commun*. **2014**, *50*, 2218-2221.

4. Stereoselective Synthesis of *C*-2-Methylene and *C*-2-Methyl α- and β-*C*-Glycosides from 2-*C*-Branched Glycals: Formal Total Synthesis of (-)-Brevisamide.

   Chalapala Sudharani, Patteti Venukumar, Perali Ramu Sridhar. *Eur. J. Org. Chem* Accepted, DOI: 10.1002/ejoc.201403062.

5. Stereoselective synthesis of octahydropyrano[3,2-*b*]pyrroles as novel glycosidase inhibitors.

   Chalapala Sudharani, Bandi Ramakrishna, Perali Ramu Sridhar (manuscript to be communicated).

6. A one-pot Synthesis of β-*C*-Glyco Amino-acids.

   Bandi Ramakrishna, **Chalapala Sudharani**, Perali Ramu Sridhar (manuscript to be communicated).

7. The effect of capsaicin derivatives on tight-junction integrity of MDCK cells.

   Mathias Kaiser, **Sudharani Chalapala**, Ramu Sridhar Perali, Francisco M. Goycoolea (manuscript to be communicated).

Posters and flash presentations

1. **Chalapala Sudharani**, Perali Ramu Sridhar, Stereoselective synthesis of *C*-2-methylene and *C*-2-methyl-*C*-glycosides by Claisen rearrangement of 2-vinyloxymethyl glycals.

   Flash Presentation at "Chemfest-2013 (*In-house*)" held in February **2013**, School of Chemistry, *University of Hyderabad*, India.
2. **Chalapala Sudharani**, Perali Ramu Sridhar, Stereoselective synthesis of *C*-2-methylene and *C*-2-methyl-*C*-glycosides by Claisen rearrangement of 2-vinyloxymethyl glycals. Formal Total Synthesis of (-)-Brevisamide.

   Flash Presentation at 9th J-NOST conference, held in December **2013**, *Indian Institute of Science Education and Research*, Bhopal, India.
3. **Chalapala Sudharani**, Perali Ramu Sridhar, Stereoselective synthesis of *C*-2-methylene and *C*-2-methyl-*C*-glycosides by Claisen rearrangement of 2-vinyloxymethyl glycals. Formal Total Synthesis of (-)-Brevisamide.

   Poster Presentation at 27th International Carbohydrate Symposium, held in January **2014**, *Indian Institute of Science*, Bangalore, India.

Synopsis

The thesis entitled **"Novel Methods for the Stereoselective Synthesis of *C*-Glycosides from 2-Vinyloxymethyl Glycals"** is divided into four chapters.

Chapter 1

Introduction to the Chemistry of *C*-1 and *C*-2 branched glycals

This chapter mainly demonstrates the synthesis of *C*-1 branched glycals/*C*-glycosides and *C*-2 branched glycals along with their applications in synthetic organic chemistry. Importance and introduction of *C*-glycosides followed by various methods for the synthesis of *C*-glycosides, which mainly includes reactions of carbohydrate derived electrophilic glycosyl donors with *C*-nucleophiles, metal mediated synthesis of *C*-disaccharides. In addition to these, one of the versatile approaches for the preparation *C*-glycosides, the so called thermal rearrangements of glucal derived allyl vinyl ethers, was also mentioned. The application of methodologies developed for the synthesis of *C*-glycosides in the preparation of natural products possessing *C*-glycoside moiety like (-)-nonacticacid, lasaloid A *etc*. were also included in this section.

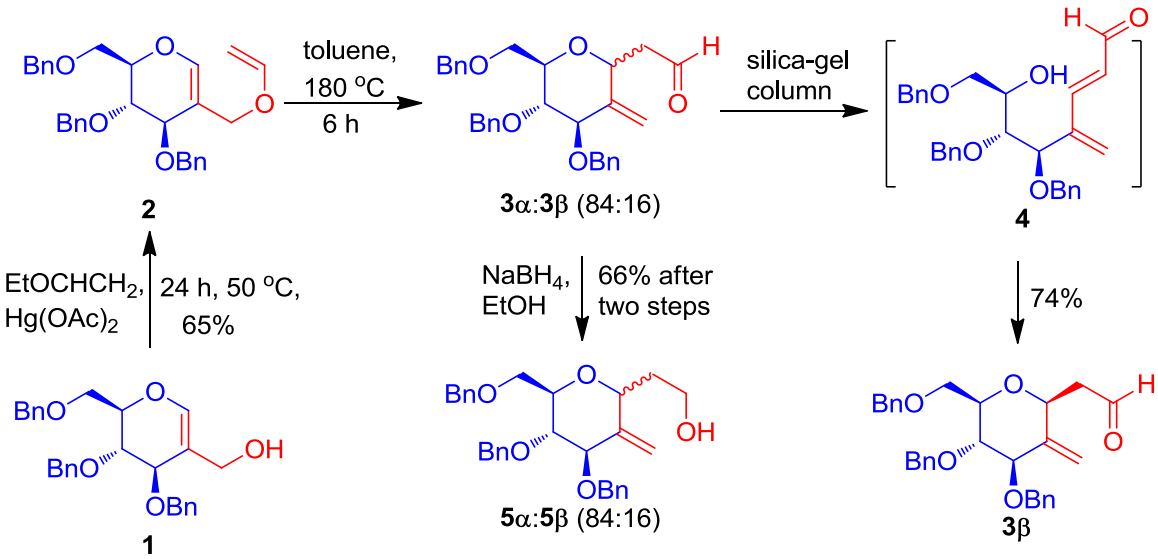
The next part of this chapter explains the synthesis and applications of 2-*C*-formyl glycals. Due to the presence of α,β-unsaturated carbonyl system, 2-*C*-formyl glycals has been considered as an important synthons for the various transformations. Synthesis of fused compounds from dienes derived from 2-*C*-formyl glycals, synthesis of *C*-glycosides and acyclo *C*-nucleosides were discussed. Reduction of the formyl glycal to 2-hydroxy methyl glycal, a versatile precursor for the preparation of *O*-, *C*-glycosides, pyranobenzopyrans synthesis, iminosugars and synthesis of ring contraction and expansions also exemplified briefly. Finally, schemes for the synthesis of *C*-2, *C*-3, *C*-4 and *C*-5 branched sugars through 3,3-sigmatropic rearrangement also explained.

Chapter 2

Stereo Selective Synthesis of *C*-2-Methylene and *C*-2-Methyl-*C*-Glycosides by Claisen Rearrangement of 2-Vinyloxymethyl Glycals

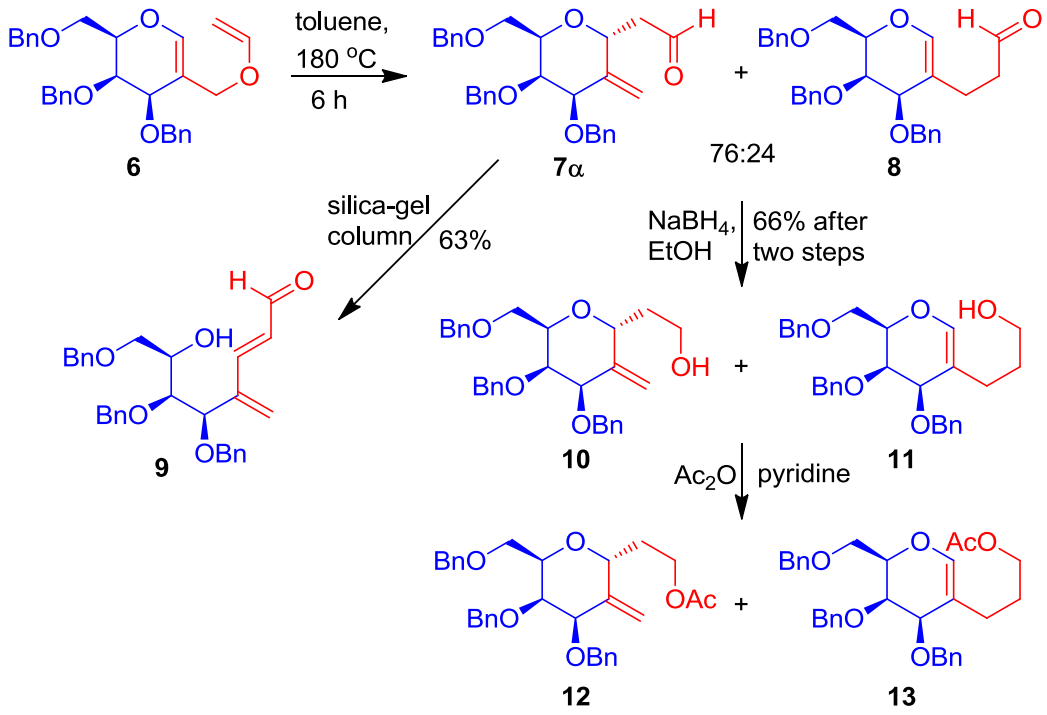
This chapter mainly deals with the stereoselective synthesis of *C*-2-methylene-α- and -β-*C*-glycosides by Claisen rearrangement (CR) of 2-vinyloxymethyl glycal derivatives. The application of this methodology was further extended by synthesizing the corresponding *C*-2-methyl *C*-glycosides.

The starting precursor, 2-vinyloxymethyl glucal, **2** was synthesized from alcohol **1** involving a transvinylation reaction with ethylvinyl ether in presence of mercuric acetate. When compound **2** was heated in a sealed tube at 180 ^{o}C for 6 h in toluene produced the expected *C*-2-methylene-*C*-glycosides **3α** and **3β** in 84:16 ratio, respectively. Interestingly, the α-anomer **3α** was found to be very unstable and converted to the β-anomer **3β** in the purification process using silica-gel column chromatography, probably *via* ring opening to form α,β-unsaturated aldehyde **4** followed by intramolecular *oxa*-Michael addition reaction. Whereas, direct reduction of crude aldehyde mixture (**3α** and **3β**) with $NaBH_4$/EtOH at -10 ^{o}C produced the corresponding alcohols **5α** and **5β** in 84:16 ratio respectively (Scheme 1).



Scheme 1: Claisen-rearrangement of 2-vinyloxymethyl glucal derivative.

We further applied this methodology to various 2-vinyloxymethyl-glycal derivatives. The Claisen rearrangement of galactose derived 2-vinyloxymethyl-glycal **6** provided a mixture of aldehyde **7α** as a single diastereomer along with unexpected aldehyde **8** in a ratio of 76:24 respectively. However, column chromatography of this mixture over silica-gel provided only the ring opened α,β-unsaturated aldehyde derivative **9**. A one-pot CR followed by reduction of the crude aldehyde provided alcohols **10** and **11**. Due to the difficulty in separation of this alcoholic mixture the crude product was acetylated to provide galactose derived *C*-2-methylene-*C*-glycoside **12** as a single diastereomer and *C*-2 alkylated galactal derivative **13** (Scheme 2).



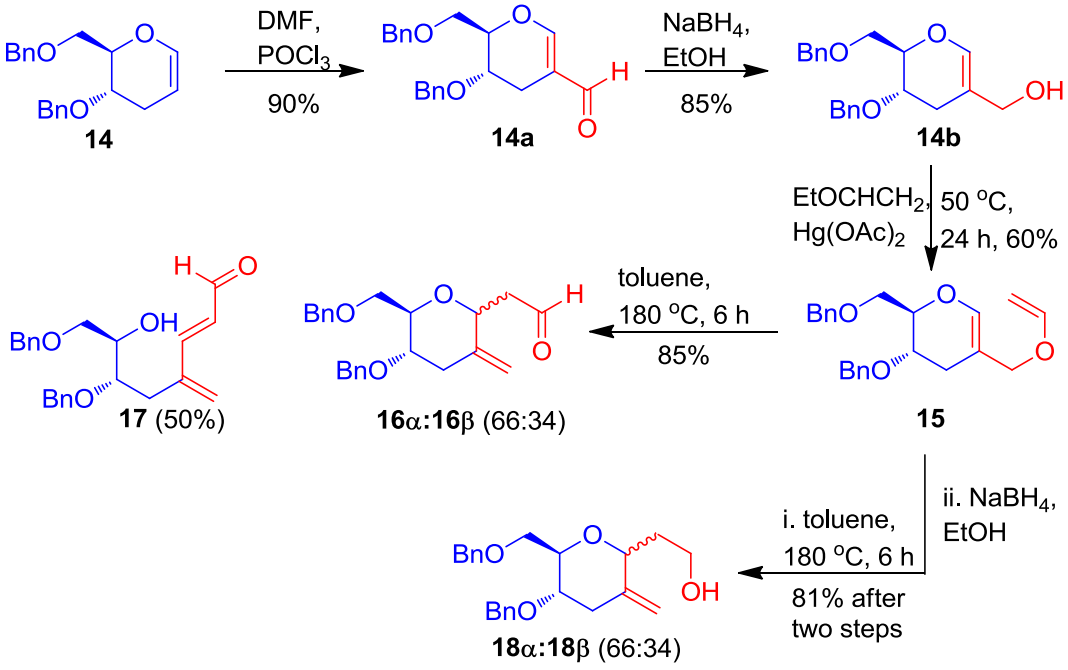
Scheme 2: Claisen-rearrangement of 2-vinyloxymethyl galactal derivative.

Chapter 3

Stereoselective synthesis of *C*-2-methylene and *C*-2-methyl α- and β-*C*-glycosides from 2-*C*-branched glycals: Formal total synthesis of (–)-brevisamide

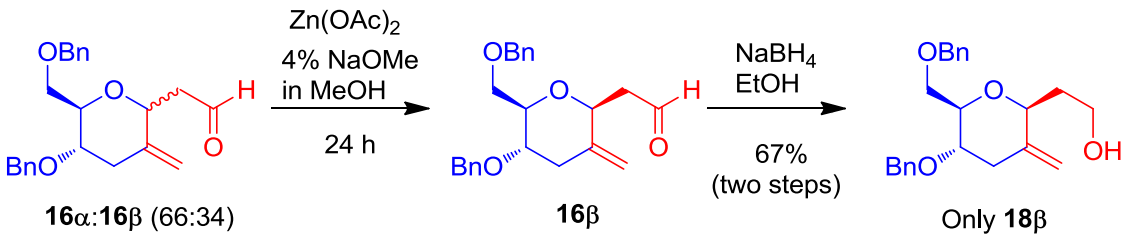
This chapter is mainly focused on the synthesis of deoxy-sugar based *C*-glycoside derivatives possessing methylene or methyl group at *C*-2 position, by employing Claisen rearrangement of 2-vinyloxy methyl deoxy-glycals as synthetic precursors. The method was found to be highly diastereoselective towards the formation of *C*-2-methylene α-*C*-glycosides.

The 3-deoxy 2-vinyloxymethyl glucal **15** was prepared from 3-deoxy glucal **14** in 3 steps, which was heated at 180 °C in toluene for 6 h provided *C*-2-methylene *C*-glycosides **16α**:**16β** in 66:34 ratio. During purification, α,β-unsaturated aldehyde derivative **17** was observed along with the unseparable **16α**:**16β**. On the otherhand direct reduction of crude aldehydic mixture with $NaBH_4$ provided the corresponding 3-deoxy *C*-2-methylene *C*-glycosides **18α**:**18β** in 66:34 ratio.



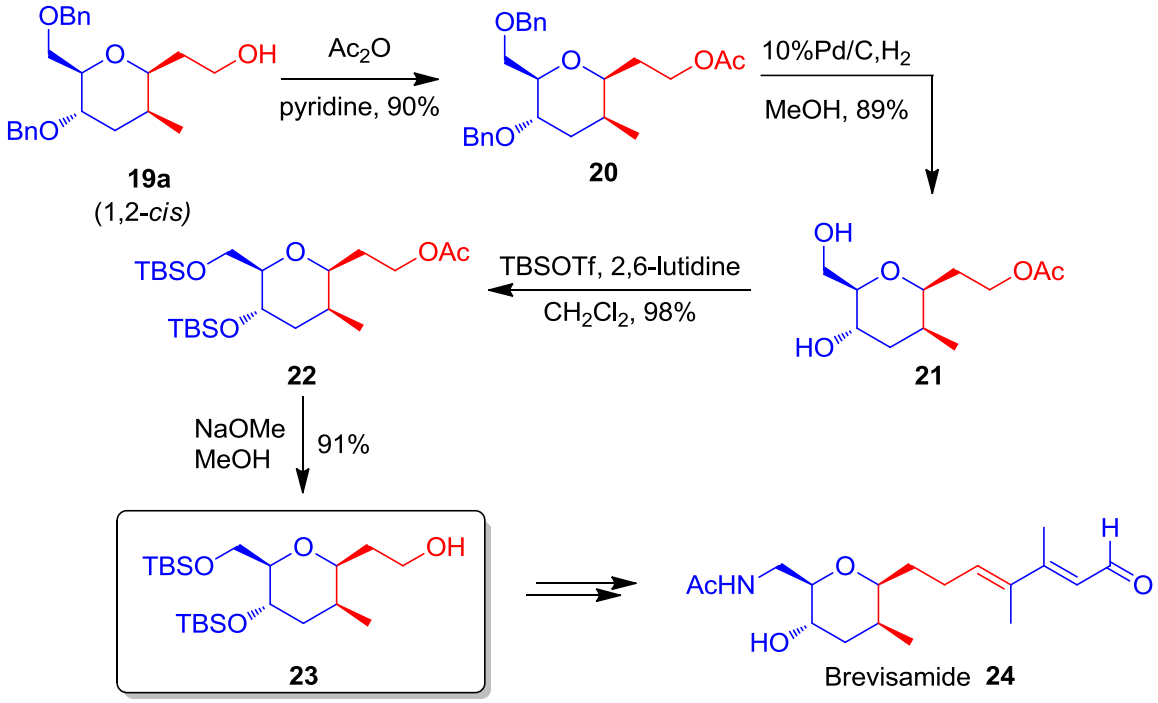
Scheme 3: Synthesis of 3-deoxy *C*-2-methlene-*C*-glycoside derivative.

The methodology was applied to other deoxy-2-vinyloxymethyl glycal derivatives. Further conversion of these major α-*C*-glycosides to pure β-*C*-glycosides using anhydrous zinc acetate and sodium methoxide in methanol.



Scheme 4: Epimerization of α-*C*-glycosides to β-*C*-glycosides.

The generality of the reaction is fully evaluated. The developed methodology has been successfully applied to the formal stereoselective total synthesis of (-)-brevisamide **24**, a monocyclic ether alkaloid isolated from *Karenia brevis* (Red tide dinoflagellate). Starting from *C*-2-methylene *C*-glycoside **18β**, chemoselective hydrogenation of **18β** with Pd/C, in H_2 atmosphere provided the corresponding 1,2-*cis*:1,2-*trans* *C*-2-methyl *C*-glycoside **19a** (1,2-



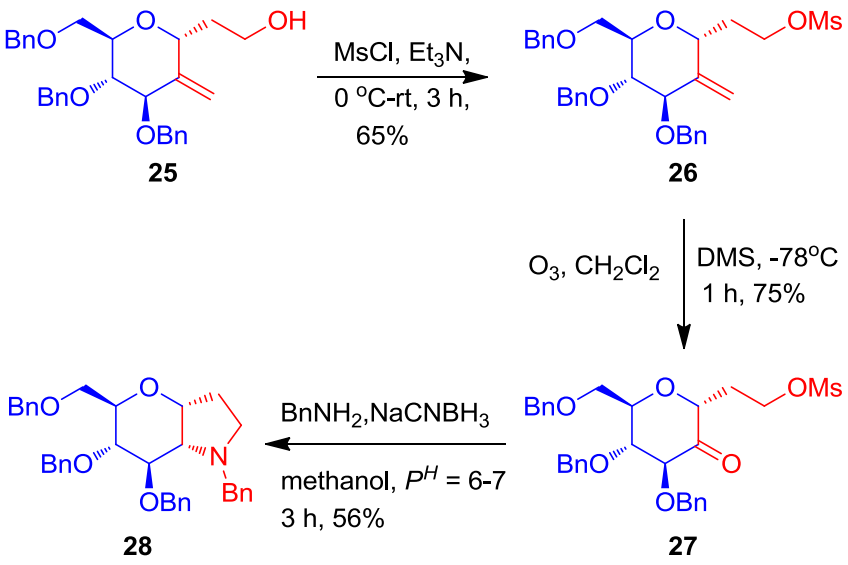
Scheme 5: Formal total synthesis of (–)-brevisamide.

(cis) and **19b** (1,2-*trans*) in 75:25 ratio. The hydroxyl function in alcohol **19a** was acetylated to give compound **20** which upon hydrogenolysis provided the diol **21**. TBS protection of both the hydroxyls using TBSOTf/2,6-lutidine in CH_2Cl_2 provided **22** which was subjected to Zemplén deacylation conditions provided the advanced intermediate **23** (Scheme 5).

Chapter 4

Stereoselective synthesis of octahydropyrano[3,2-*b*]pyrroles as novel glycosidase inhibitors

This chapter mainly describes the application of *C*-2-methylene-*C*-glycosides in the synthesis of fused bicyclic octahydropyrano[3,2-*b*]pyrrole derivatives. Mesylation of the compound **25** with mesylchloride and triethylamine in dichloromethane provided compound **26** in 65% yield. Ozonolysis of the compound **26** at -78 ^oC gave the compound **27** in 75% yield. One pot mesylate substitution and reductive amination with benzyl amine using sodiumcyanoborohydride afforded the *cis*-fused bicyclic octahydropyrano[3,2-*b*]pyrrole derivative **28** in 56% yield (Scheme 6). This methodology was further extended to a series of *C*-2-mthylene-*C*-glycoside units.

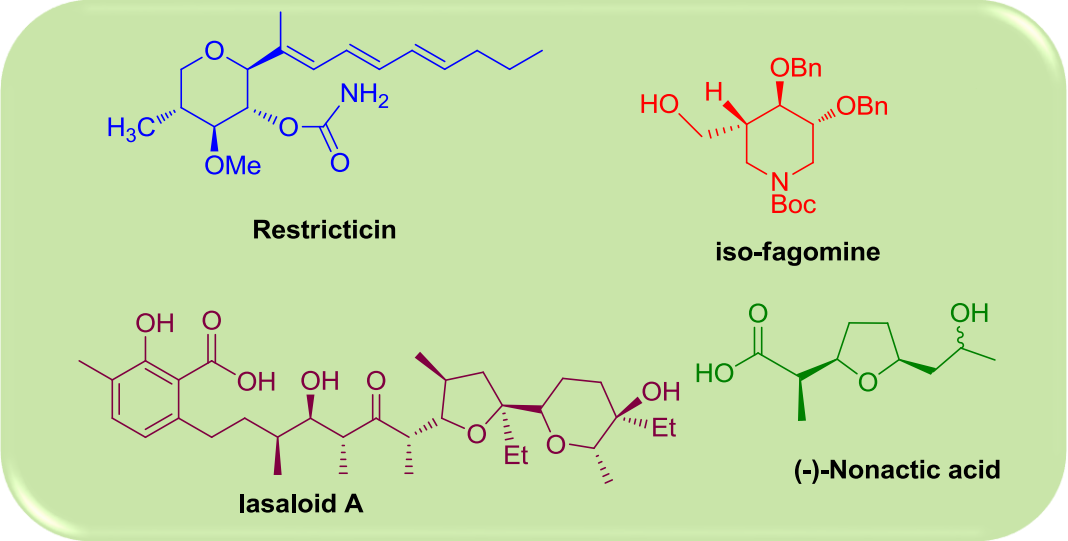


Scheme 6: Synthesis of fused bicyclic octahydro pyrano[3,2-*b*]pyrrole **28** from glucose derived *C*-2-methylene-*C*-glycoside **25**.

.

Introduction to the chemistry of *C*-1 and *C*-2 branched glycals

ABSTRACT: The present chapter mainly focus on the illustration of various synthetic methods in literature so far for *C*-1 branched glycals/*C*-glycosides and *C*-2 branched glycals along with their applications in the synthetic organic chemistry.



1.1 Carbohydrates

Carbohydrates are one of the ubiquitous chiral pool materials chosen by nature profoundly for energy storage. Most of the sugars are highly oxygenated and possess continuous stereo centres. Importantly, they are found as the building blocks of DNA and RNA. Moreover, many enzymes possess intrinsic glyco portion which helps in the proper folding of the protein to express its activity. Recently, there has been an intense interest in the synthesis of various mono, oligo and poly saccharides[1] including natural and unnatural sugars. Due to their presence from the origin of life, a number of protocols have been developed for the recognition of the different sugar units and several methodologies are established with large range of available protection/deprotection strategies, enabling high chemo selectivity, sensitivity and efficiency towards the higher ordered oligosaccharides.

Within the large and diverse field of synthetic carbohydrate chemistry, the stereo regulated formation of carbon-carbon bonds represents an important and highly demanding task. This problem has been widely addressed in connection with the total synthesis of natural products and the utilization of sugars as versatile chiral pool starting materials[2]. In the closure context of the carbohydrate research, extensive efforts have been directed towards the

synthesis of aza-sugars,[3a] imino-sugars,[3b] *C*-glycosides[4], carbasugars[5] and branched chain derivatives[6], both as naturally occurring compounds and as the potential mimics of biologically active glyco-structures.

1.2 *C*-1 branched sugars or *C*-glycosides

C-glycosides occur when the exocyclic oxygen atom in a glycoside is replaced by a carbon atom (Figure 1.1). Synthesis of these glycosides is quiet interesting due to their requirement as the therapeutic agents. The highly resistant glycosidic bond towards enzymatic and acidic hydrolysis increases the importance of the *C*-glycosides when compared to the *O*- or *N*-glycosides.

The core structure of the *C*-glycosides includes a sugar moiety as in the form of pyranose or furanose with aliphatic chain or aromatic ring as aglycon.

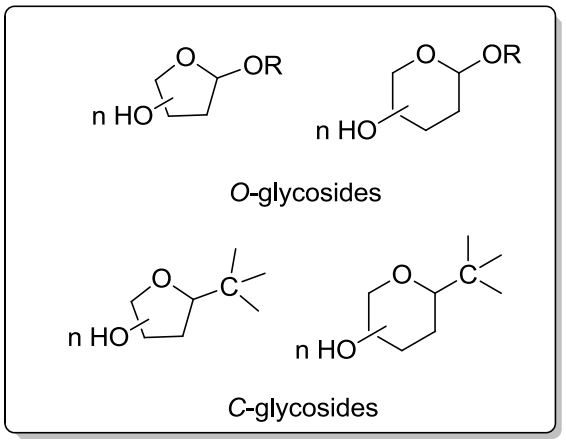
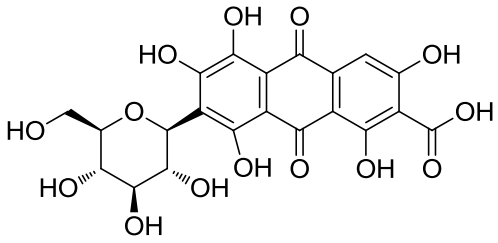
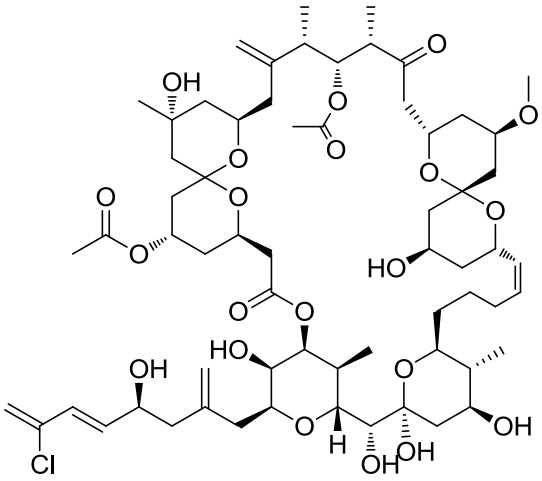


Figure 1.1: Schematic representation of *O*- and *C*-glycosides.

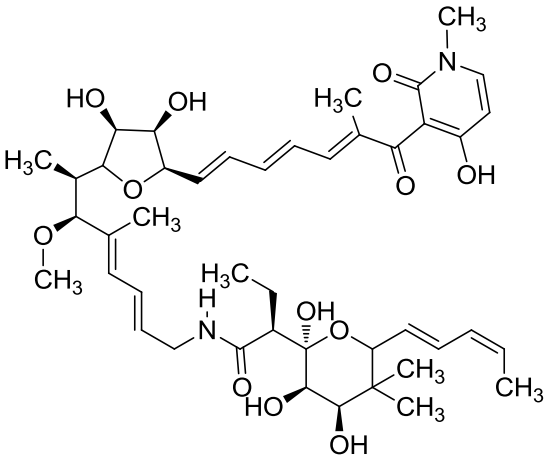
From the last three decades, scientists has put their immense attention towards the total synthesis of natural products containing *C*-glycosides. Some of the naturally occurring *C*-glycosides, which are isolated from plant genera with fully established structure based on physical methods, are aloin, carminic acid, saponarin, scoparin, *C*-glycosyl xanthones[8], flavonoid phytotoxins[7], and benzoquinone altromycin B[9] (Figure 1.2). Furthermore, previous efforts were also focused on the synthesis of complex *C*-glycosides with strong antibiotic activity. Specifically aurodox[10], lasalocid A[11], herbicidin[12] and the hyper functionalized molecules spongistatins[13] and polytoxin[14].



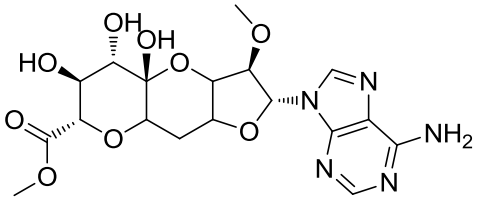
Carminic acid



Spongistatin



Aurodox



Herbicidine B

Figure 1.2: Some of the naturally occurring *C*-glycosides.

1.2.1 Synthetic approaches for the preparation of *C*-glycosides

Synthesis of *C*-glycosides has been previously reviewed by Postema, [4a,b] Levy,[4c] Sinay,[4g] Beau,[4d] and Nicotra.[4e] The common methods for the synthesis of *C*-glycosides are.,

- Reaction of electrophilic glycosyl donors with carbon nucleophile's
- Using glycosyl acetates
- From anomeric trichloroacetimidates
- Anomeric anions intermediates with carbon electrophiles
- Intermolecular free radical approaches
- Radical *C*-glycosylation with exomethylenic carbohydrates
- Metal mediated C-C bond formation
- Using Claisen rearrangements or Concerted reactions

- Wittig reaction of carbohydrate hemi-acetals
- Using Mitsunobu reaction
- Using Grubb's cross metathesis reaction
- Using Ramburg-Backlund rearrangement
- Free radical approaches
- The tether approach

Out of these, some of the most widely used protocols for *C*-glycoside synthesis were chosen and discussed in the following text.

1.2.2 Reaction of electrophilic glycosyl donors with carbon nucleophiles

Electrophilic reactions are one of the typical methods for the formation of *C*-glycosides due to the simplicity of reaction, straight forward accessibility and halfway stability. Carbohydrate synthons having an electrophilic anomeric centre are versatile building blocks for the *C*-glycosylation reactions. General electrophilic *C*-glycosyl donors are glycosyl halides **1**, sugar based lactones **2**, simple glycals **3** and 1,2-anhydro sugars **4** which are shown in Figure 1.3.

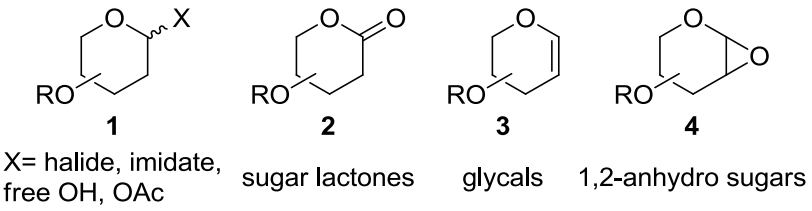
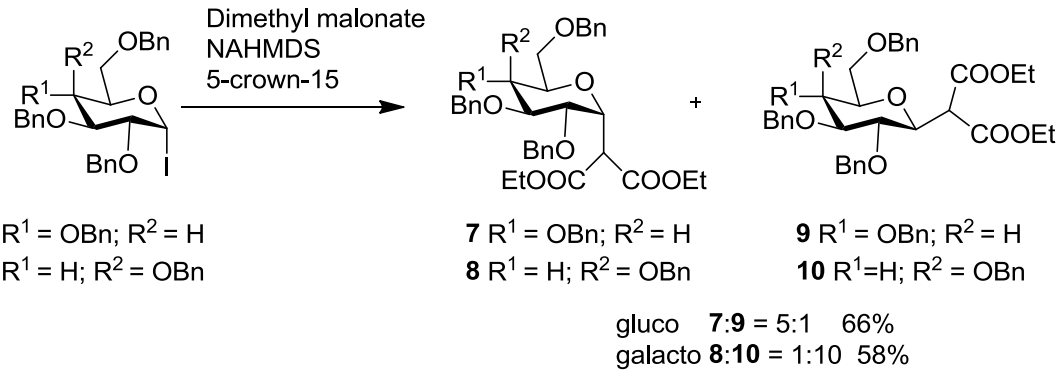


Figure 1.3: Some of the electrophilic *C*-glycoside donors.

1.2.2.1 From glycosyl halides

Metal chelation is one of the most common methods to activate glycosyl halides in glycosylation reaction. In general, the stereo chemical outcome of the glycosylation reaction is governed by a combination of effects including, neighbouring group, solvent and the metal catalyst. On the other hand, glycosyl halides can also be *C*-glycosylated under basic conditions. In these reactions, the nuecleophillic displacement of anomeric halide occurs in an S_N^2 fashion. In 1997, J. Gervay *et al*., synthesised *C*-glycosides by reaction of α-glycosyl iodides with stabilized anions, such as malonate anion [$^-CH(CO_2Et)_2$], that proceeds with inversion of configuration at anomeric centre, to give *C*-glycosides in good yield and with

high stereo selectivity. The reaction is noted to work well even in the absence of *C*-2 participating ester group.[15] The observed α-selectivity in the glucose derivative **7** is due to the *insitu* anomerization of α-iodide to β-iodide, which is highly reactive. Whereas for galactosyl iodide **6** which is considerably more reactive than its gluco equal **5** gives directly the S_N2 product **10** in good yield with more β-stereoselectivity (Scheme 1.1). Similar kind of reaction using α-D-glycopyranosyl iodide with tetra butyl ammonium cyanide provided a moderate yield of β-D-glycosyl cyanide, however, frequently it is accompanied by E-2 elimination giving glycal as the side product.[15]



5 R^1 = OBn; R^2 = H
6 R^1 = H; R^2 = OBn

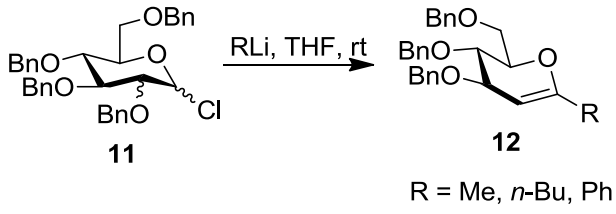
7 R^1 = OBn; R^2 = H
8 R^1 = H; R^2 = OBn

9 R^1 = OBn; R^2 = H
10 R^1=H; R^2 = OBn

gluco **7**:**9** = 5:1 66%
galacto **8**:**10** = 1:10 58%

Scheme 1.1: Synthesis of *C*-glycosides from glycosyl iodides.

C-glycals of type **12** are conveniently synthesized by treating the ether protected glycopyranosyl chlorides of type **11** with organolithium reagents (Scheme 1.2).[16]

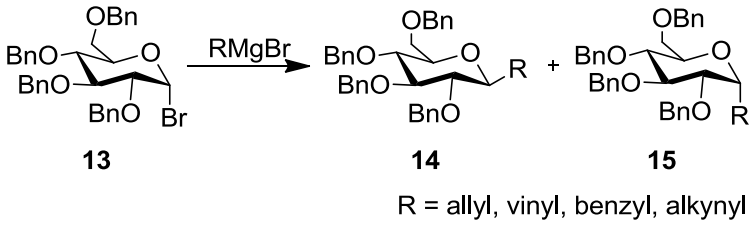


11 **12**

R = Me, *n*-Bu, Ph

Scheme 1.2: Synthesis of *C*-glycals from glycopyranosyl chlorides.

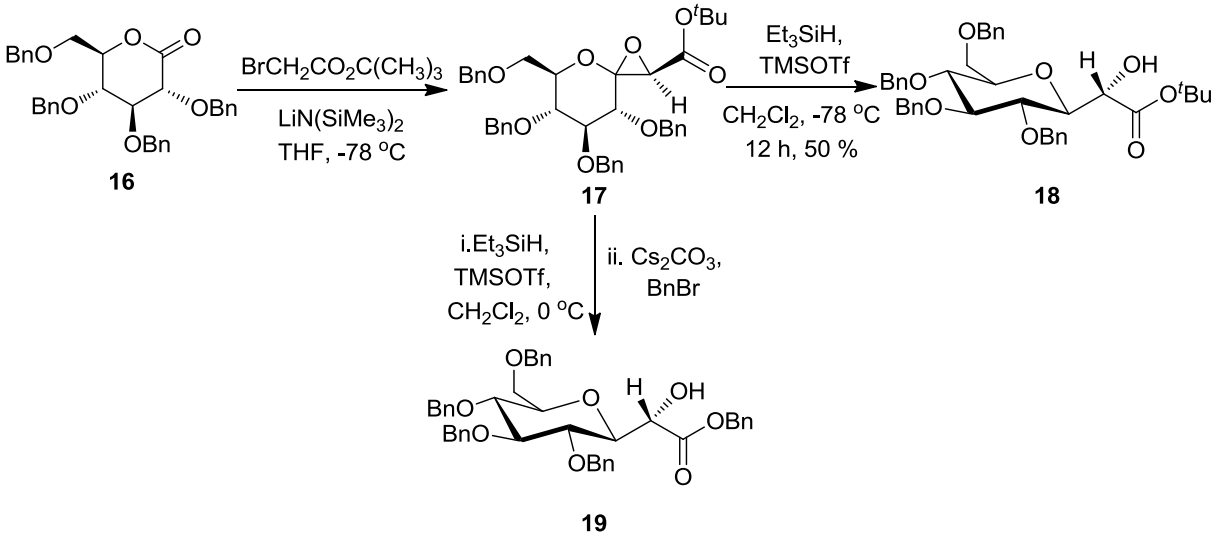
Grignard reagents, organozinc, organo cuprate and organotin have also been utilized for the *C*-glycosylation of anomeric halides, thus glycosyl bromide **13** was *C*-glycosylated with Grignard reagents gave the corresponding α-or β-*C*-glycosides **14** and **15** in different ratios, which mainly depends on protecting group at the glycosyl bromide (Scheme 1.3).[4c]



Scheme 1.3: Synthesis of *C*-glycosides from glycosyl bromides using Grignard reagents.

1.2.2.2 From sugar lactones

Sugar lactones, which are easily prepared by the oxidation of lactols, are useful substrates for the synthesis of *C*-glycosides. One way of synthesizing *C*-glycosides from sugar lactones is treatment of pyranose or furanose lactones with organolithium reagents. In 1995, R. H. Wightman and co-workers synthesized *C*-gluco furanosides from the corresponding furanose lactones.[17a] In an another report, Schweizer in 2001 had conveniently utilized the sugar δ-lactones for synthesis of *C*-glycosides[17b] and *C*-glyco aminoacids. In this



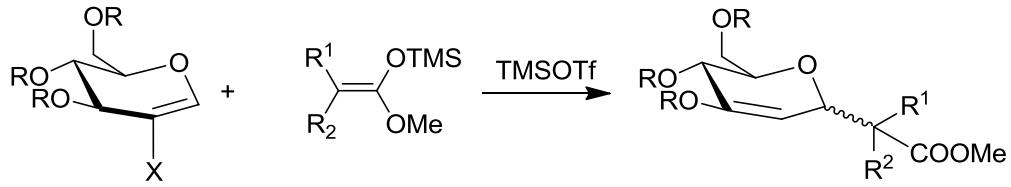
Scheme 1.4: Synthesis of *C*-glycosides from sugar lactones.

study, first they had converted the 2,3,4,6-tetra-*O*-benzyl-D-glucono-1,5-lactone **16** to the corresponding exocyclic epoxide **17** by using the enolate of *t*-butylbromoacetate, which was generated by using Lithium bis-(trimethlsilyl) amide/$[(CH_3)_3Si]_2NLi$ in THF at -78 °C. Later on opening of this oxirane with triethylsilane and TMSOTf at -78 °C gave the corresponding *C*-glycoside **18** in moderate yield. On the other hand, at 0 °C cleavage of ester group occurs and the resulting carboxyl group was converted to the benzylic ester using CS_2CO_3 and

benzyl bromide to provide *C*-glycoside **19** in 35 % yield. The same methodology was evaluated on various sugar derived lactones.

1.2.2.3 From *glycals*

The easy accessibility and versatile functionality of glycals also provides an advantageous method in *C*-glycoside synthesis. Csuk and co-workers reported the formation of 2,3-unsaturated *C*-glycosides, from glycals **20**, **21**, **22** and silyl ketene acetals **23**, **24**, after allylic rearrangement (Scheme 1.5).[18] While the benzoylated glucal **21** reacts with silyl ketene acetal **23** to give *C*-glycoside **27** in 98% yield, the 2,3,4,6-tetra-*O*-benzoyl-1,5-anhydro-D-arabino-hex-1-enitol **22** does not react under the same coupling conditions (disfavoured allylic rearrangement).



20 R = Ac; X = H
21 R = Bz; X = H
22 R = X = OBz

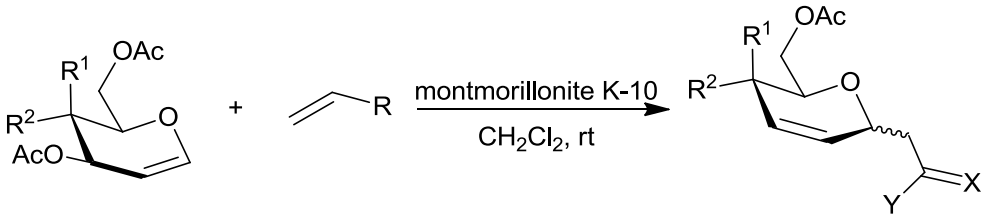
23 $R^1 = R^2$ = Me
24 $R^1 = R^2$ = Et

25 R = Ac; $R^1 = R^2$ = Me; 68%; α:β = 1:4
26 R = Ac; $R^1 = R^2$ = Et; 25%; only β
27 R = Bz; $R^1 = R^2$ = Me; 98%; α:β = 1:1.6

22 + **23** $\xrightarrow{\text{TMSOTf}}$ No reaction

Scheme 1.5: Synthesis of 2, 3-unsaturated *C*-glycosides from glycals and silyl ketene acetals.

An inexpensive and reusable acid clay, Montmorillonite K-10, has been reported to serve as an efficient catalyst for the *C*-glycosylation of glycals **20**, **28** with allylsilane **29** and



20 ; R^1 = H; R^2 = OAc; **29** ; R = CH_2TMS;
28 ; R^1 = OAc; R^2 = H **30** ; R = OTMS

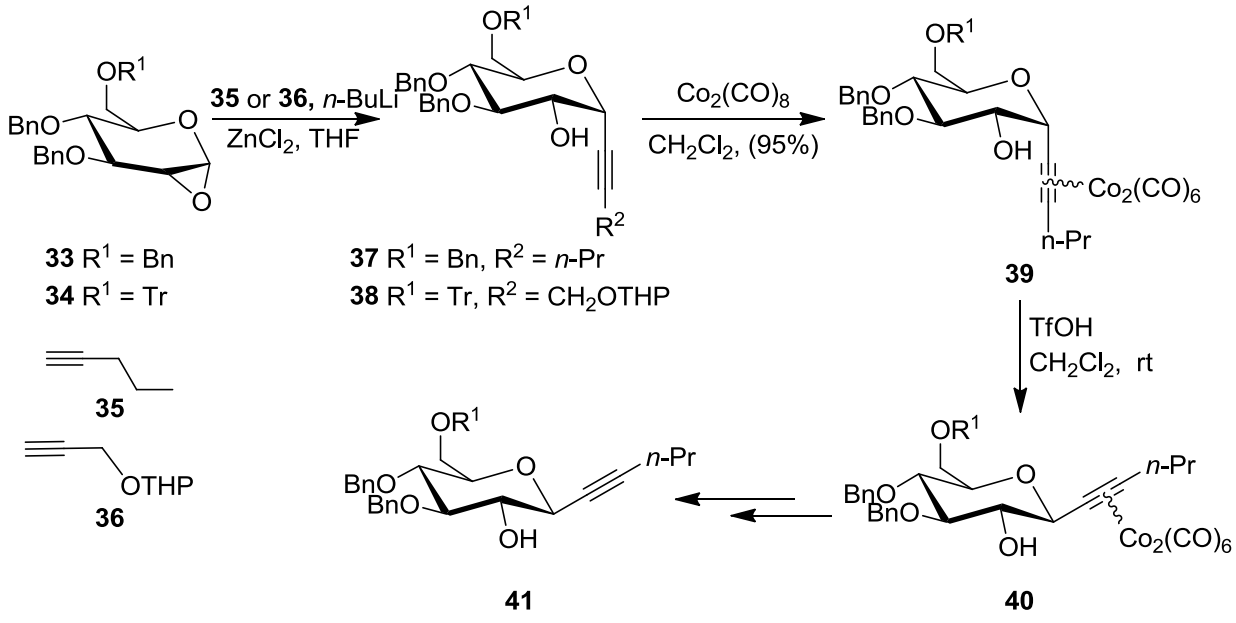
31; X = CH_2; Y = H
32; X = O; Y = H

Scheme 1.6: Synthesis of *C*-glycosides from glycals and silanes using montmorillonite K-10 as catalyst.

vinloxysilane **30** mainly giving α-products **31**and **32** (Scheme 1.6).[19]

1.2.2.4 From 1, 2-anhydrosugars

1, 2-Anhydro sugars are generally synthesized from glycals or glycosyl halides or *C*-2 tosylated sugars. Van Boom and co-workers[20a] reported the synthesis of *C*-glycosides (lithiated alkynyl derivatives) by using dialkyl /aryl cuprates in the presence of *n*-BuLi. The desired ring opening of 1,2-anhydro 3, 4, 6-tri-*O*-benzyl-α-D-glucopyranose **33** or 1,2-anhydro 3,4,-di-*O*-benzyl-6-*O*-trityl-α-D-glucopyranose **34** in the presence of zinc chloride with alkynyl nucleophile's like **35** or **36** proceeds with retention of configuration to afford α-*C*-(alkynyl) glycosides **37** or **38** respectively (Scheme 1.7). 1, 2-anhydro sugars are also excellent glycosyl donors in *O*-glycosidation reactions resulting in 1, 2-trans stereoselectivity.[20b, 20c] The high α-selectivity in **37** or **38** was rationalized based on the reaction mechanism and the epimerization of the α-*C*-glycoside **39** to β-*C*-glycoside **40** or **41** was also investigated.

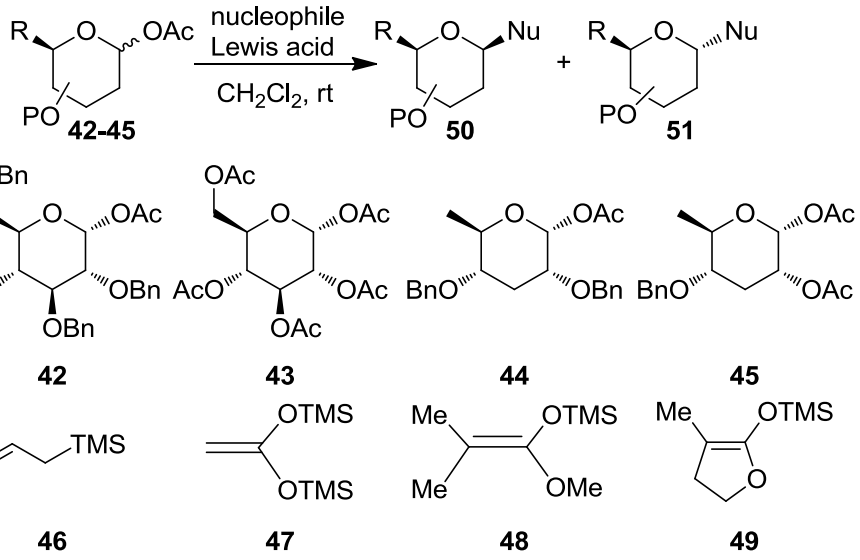


Scheme 1.7: Synthesis of α- and β-*C*-(alkynyl) glycosides from 1, 2-anhydrosugars.

1.2.3 From glycosyl acetates

Majority of glycosyl acetates react directly with allyl and vinyl silanes in the presence of Lewis acids (TMSOTf or $BF_3.Et_2O$) to provide α-*C*-glycosides in good yield (Table 1.1).[21] In 1997, Kishi and Minehan[22] used glycosyl acetates **42-45** and silyl ketene acetals **46-49** to attain *C*-glycosides **50** and **51**.The stereochemistry of the product mainly depends on the electronic and steric properties of the silyl ketene nucleophiles.

Table 1.1: The electronic effects of the silylketene acetal based nucleophiles.



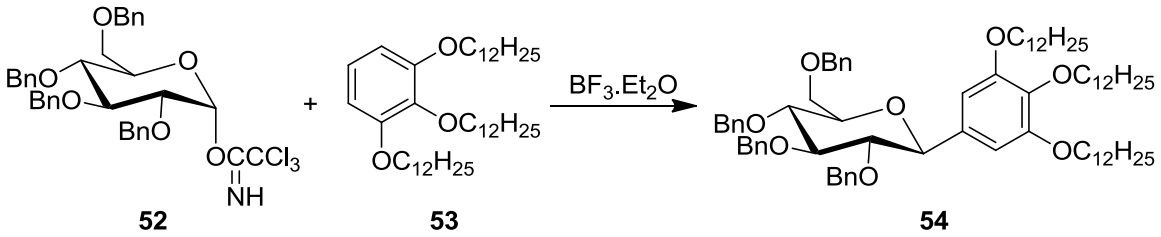
Substrate	Nucleophile	β:α	Yield %	Method	Substrate	Nucleophile	β:α	Yield %	Method
42	**46**	<1:10	55	A	**44**	**46**	<1:10	96	A
42	**47**	1.4:1	57	A	**44**	**47**	1.1:1	72	A
42	**48**	3:1	64	A	**44**	**48**	2:1	78	A
42	**49**	3:1	65	A	**44**	**49**	8:1	72	A
43	**46**	<1:10	50	B	**45**	**46**	<1:10	50	B
43	**47**	>10:1	47	B	**45**	**47**	>10:1	52	B
43	**48**	>10:1	53	B	**45**	**48**	>10:1	71	B
43	**49**	NR	....	B	**45**	**49**	>10:1	60	B

Method A: 1 eq of TMSOTf was used; Method B: 1 eq of TMSOTf and 9 eq of BF_3Et_2O were used.

These studies showed that the allyl silanes with lower nucleophilicity, afford α-*C*-glycosides whereas silyl ketene acetals mainly forms β-*C*-glycosides. An increase in the steric hindrance at the nucleophile's reaction terminus and also presence of a neighbouring group (such as OAc) on C-2 can also enormously increase the β-selectivity.

1.2.4 From anomeric trichloroacetimidates

Schmidt and co-workers[23] synthesised β-*C*-glycosides using anomeric trichloroacetimidates as glycosyl donors, particularly in aryl *C*-glycosylation reactions. Glycosyl imidate **52** was reacted with electron rich aromatic compounds, such as **53**, in the presence of $BF_3.Et_2O$ or TMSOTf, to afford the β-*C*-aryl glycoside **54** in a stereo selective fashion in good yield (Scheme 1.8).[24]



Scheme 1.8: Synthesis of β-*C*-aryl glycosides from anomeric trichloroacetimidates.

1.2.5 From anomeric anionic intermediates

The "umpolung" strategy is complementary to the electrophilic methods. Most of the applications, based on the deprotonation of the anomeric centre, rely on the use of lithiated glycosyl nucleophiles to prepare *C*-glycosides. Paulsen and co-workers[25] first reported the carbon elongation of open-chain carbohydrates by polarity inversion (umpolung) at the anomeric centre using dianions of hydroxylated 1,3-dithianes. This idea has more recently been applied to 1-nitronates **55**, lithiated 2-deoxysugars **56**, glycals **57** and dilithiated sugars **58** (Figure 1.4).

Kessler and co-workers[26] generated the α-dianion **60α** from the vicinal halohydrin **59** by treatment with *n*-BuLi and lithium naphthalenide, which was further treated with aldehydes to give the corresponding α-*C*-glycosides **61** and **62**. The synthesis of *C*-2-lithium

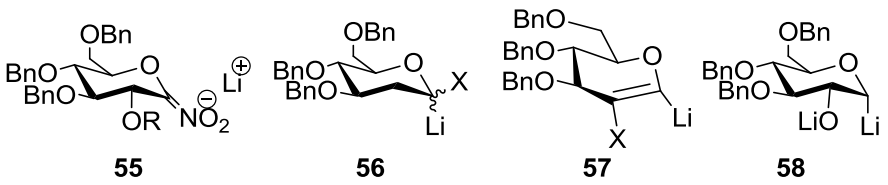
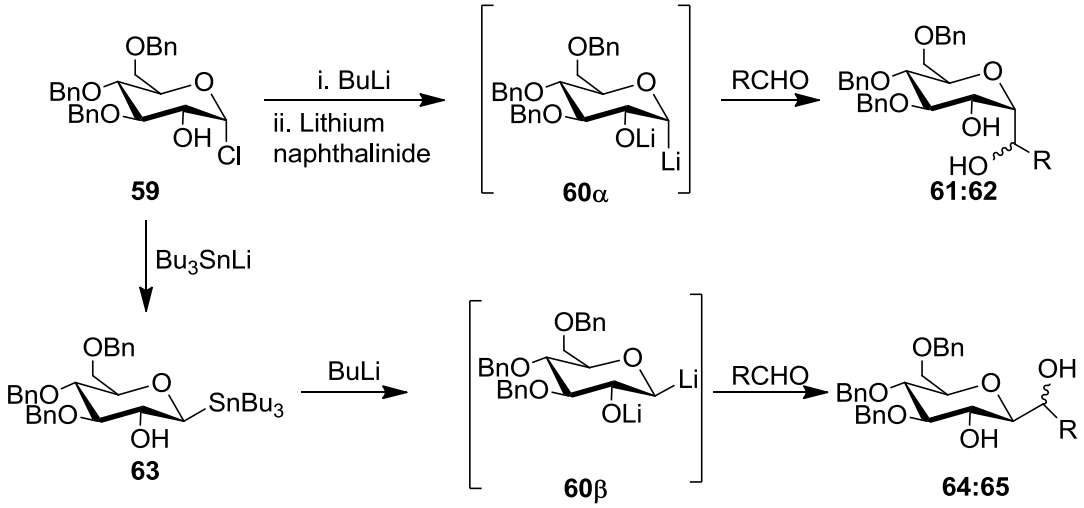
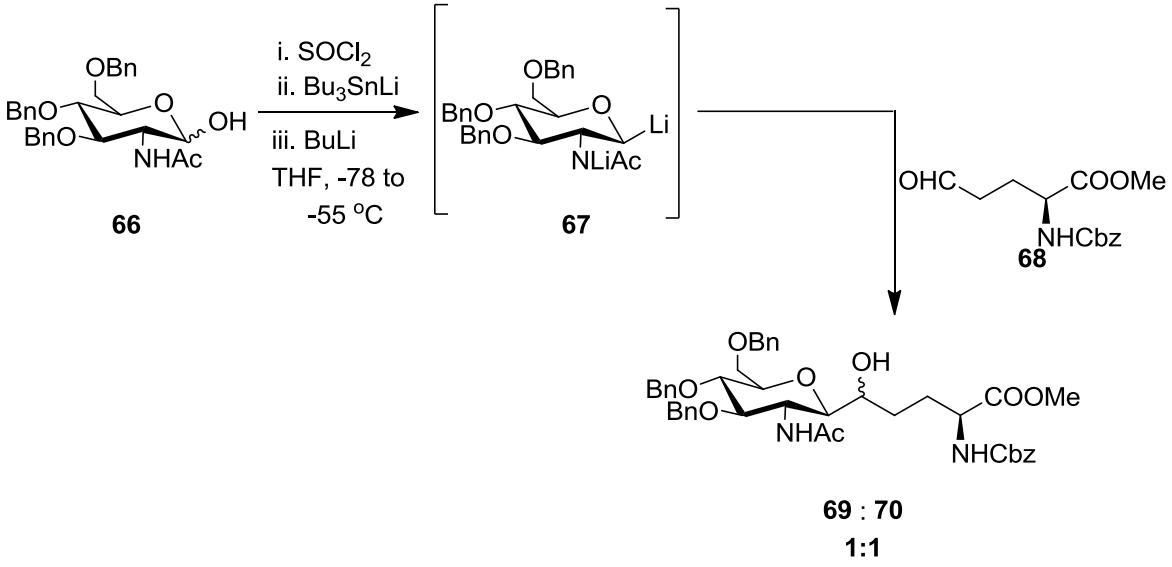


Figure 1.4: Anomeric anionic species used in *C*-glycosylation.

alkoxide effectively prevents 1, 2-elimination thus blocking the undesired glycal formation (Scheme 1.9). The lithiation of the corresponding β-glucosyl stannane **63** provides the β-dianion **60β,** which gave the corresponding β-*C*-glycosides **64** and **65**.



Scheme 1.9: 1, 2-dianion species used in *C*-glycosylation.



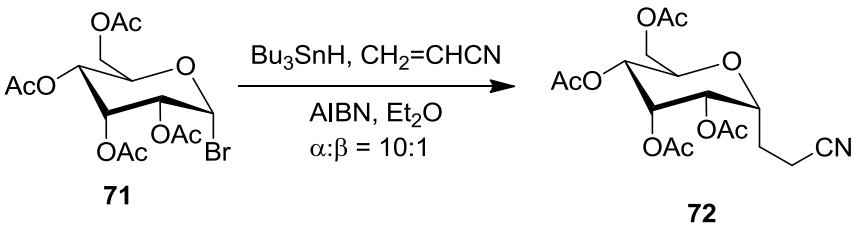
Scheme 1.10: Synthesis of *C*-glycopeptides.

The same approach has also been applied to amino sugars to prepare *C*-glycopeptides (Scheme 1.10).[27] The synthetic route comprises, generation of dianion **67** from compound **66** through deprotonation, substitution followed by transmetallation with BuLi. This compound **67** was treated with protected aminoacid **68** gave the corresponding *C*-glycopeptides **69** and **70** in 1:1 ratio.

1.2.6 Intermolecular free radical approaches

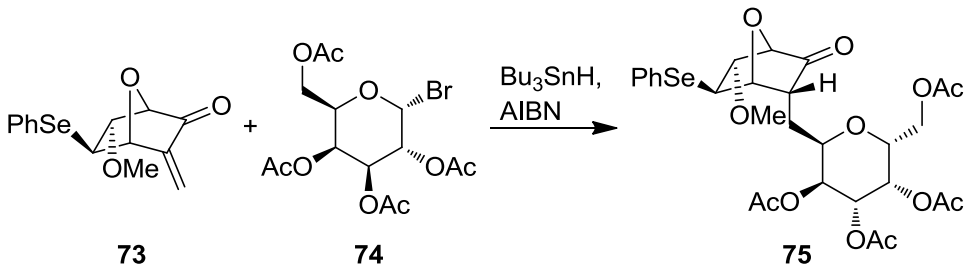
Alkoxyalkyl radicals behave like nucleophiles because of the high-lying HOMO which can interact with the LUMO of an electron poor alkene, for example maleic anhydride, acrolein, acrylonitrile, fumarodinitrile etc. could be used in the formation of a C-C bond. The presence of electron deactivating substituents in the alkene lowers the LUMO energy and increases the addition rate by reducing the HOMO-LUMO energy difference.[28] Thus the addition of a glycosyl radical to an electron poor olefin constitutes an interesting approach for the construction of *C*-glycosides or *C*-disaccharides.

The most commonly used method for radical *C*-glycosidation is the reaction of the radicals generated from glycosyl bromides like **71** with an electron deficient alkene[29a] in presence of tributyltin hydride and AIBN affords *C*-glycosides of type **72**. Later Schafer[29b] showed that vitamin B_{12} (in place of AIBN as radical initiator) together with Zn and NH_4Cl (as co-catalysts) improved the yield and stereo selectivity of radical *C*-glycosylation (Scheme 1.11).



Scheme 1.11: Synthesis of *C*-glycosides by intermolecular free radical approach.

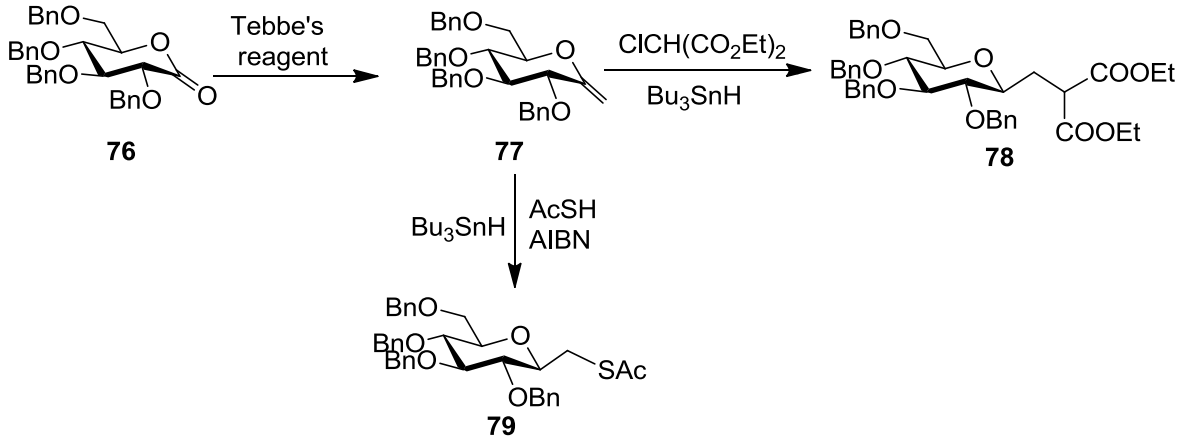
In 1995, Janine Cossy and his co-workers, [30] synthesised α-*C*-galactopyranosides of carbapentopyranoses using the similar protocol (Scheme 1.12). In this reaction, compound **73** with aceto bromo galactose **74** gave the corresponding 3–endo-[(α-D-galactopyranosyl)-methyl]-7-oxabicyclo[2, 2,1]heptan-2-ones **75** in good yield.



Scheme 1.12: Synthesis of α-*C*-galactopyranosides of carbapentopyranoses.

1.2.7 Radical *C*-glycosylation with exo methylenic carbohydrates

exo-Glyccal, obtained by reaction of the corresponding lactone **76** with Tebbe' s reagent gave compound **77**, this *exo*-methylenic compound **77** reacts with a malonyl radical to give the stable *C*-glycoside **78** with β-stereoselectivity based on the preferred configuration of the anomeric radical (Scheme1.13). Reaction of the same malonyl radical with *exo*-methylenic furanose gives the corresponding β-*C*-furanosides.[31] similarly, radical addition of thioacetic acid to compound **77** with AIBN initiator, generate β-*C*-glycosides **79** in good to excellent yields.[32]

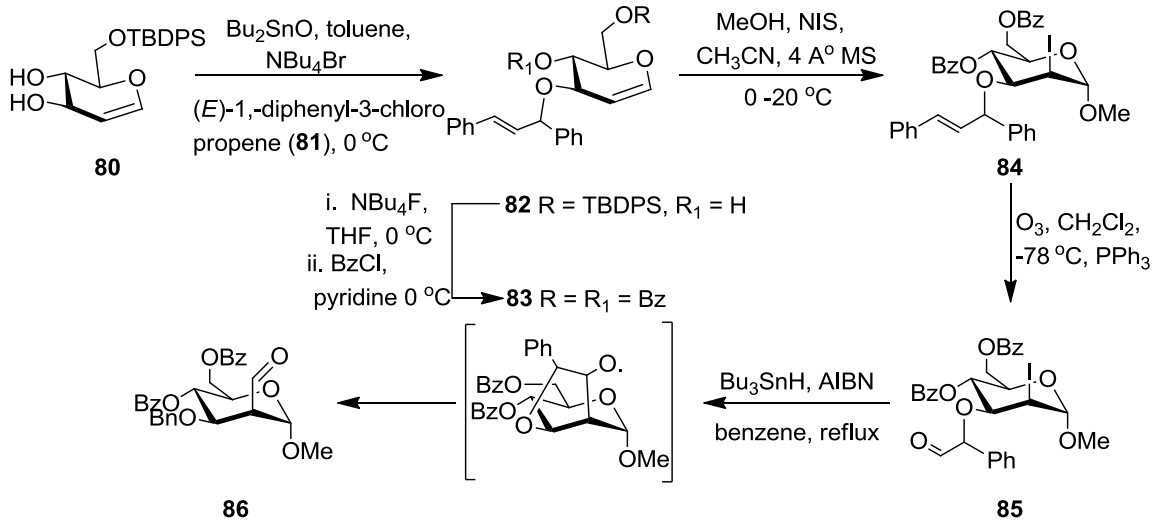


Scheme 1.13: Synthesis of *C*-glycosides from *exo*-glycals.

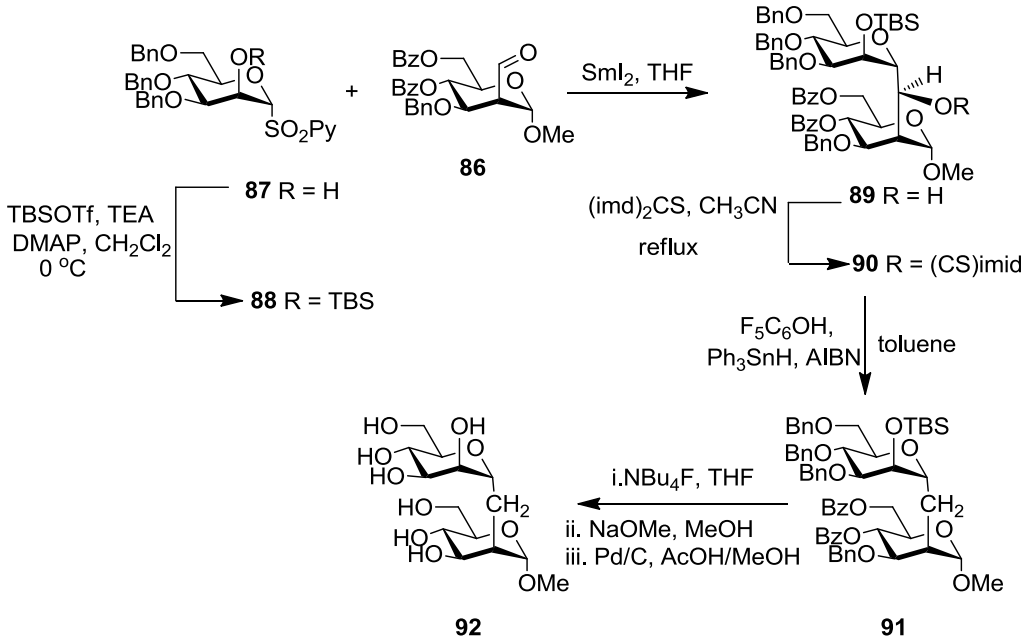
1.2.8 From metal mediated synthesis

In 1996, J. M. Beau *et al.*,[33] synthesised *C*-disaccharides, by employing samarium mediated *C*-glycosylation, especially methyl α-*C*-mannobioside **92**. Towards this, they have started their exploration by synthesising the aldehyde **86**, which was easily prepared from glucal **80.** Regioselective etherification of glucal **80** with allylic chloride **81** provided a diastereomeric mixture of allylic ether **82** in 68% yield. On deprotection of TBDPS group

and benzolylation of the obtained diol furnished glycal **83**. Iodoetherification of glycal **83** with *N*-iodosuccinimde lead to the iodo compound **84**, which upon ozonolysis followed by radical mediated reaction gave the corresponding *C*-2 branched aldehyde **86** having desired manno-configuration (Scheme 1.14). Coupling of the aldehyde **86** with pyridylsulfone **88** in presence of samarium iodide in THF led to the disaccharide **89**, which then transformed to thiocarbonyldiimidazole derivative **90,** which on radical mediated deoxygenation with tributyl tin hydride afforded disaccharide **91**. Finally, global deprotection of all the protecting groups gave the desired methyl-α-*C*-mannobioside **92** (Scheme 1.15) in good yield.



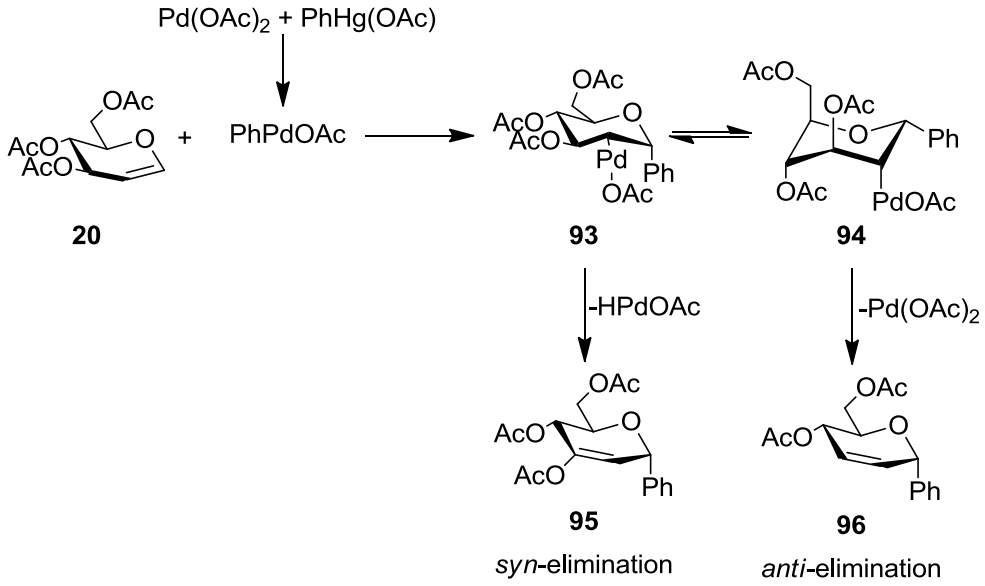
Scheme 1.14: Synthesis of 2-*C*-branched aldehyde from glucal.



Scheme 1.15: Synthesis of methyl-α-*C*-mannobioside.

1.2.81 Palladium mediated *C*-glycosylation

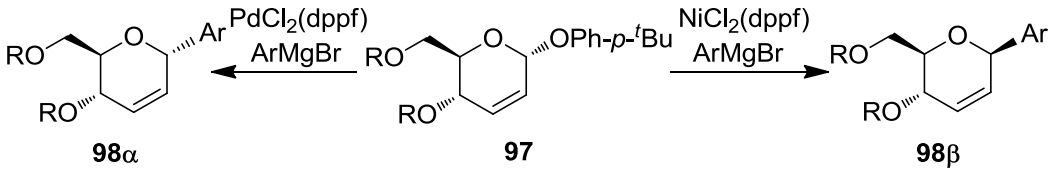
Coupling reaction between aryl or vinyl halide to an alkene in the presence of palladium catalyst is called the Heck-reaction. It has wide range of applications in synthetic organic chemistry. In 1998, Daves[34] had successfully applied the Heck reaction to carbohydrate derived moieties. In their synthetic route, 3,4,6-tri-*O*-acetyl-D-glucal **20** was treated with aryl palladium complex to give the corresponding *C*-aryl glycosides **95** and **96** through two different intermediates **93** and **94** in two reaction pathways. They have explained the regeoselectivity of the Heck type *C*-glycosylation through a plausible mechanism as shown in Scheme1.16. The stereo chemical outcome of this reaction is illustrated by the addition of aryl palladium complex on two faces of glycalic double bond in the formation of an organo palladium *π-complex.*



Scheme1.16: Palladium mediated synthesis of *C*-aryl glycosides.

In the last three decades, a number of research groups (Dunkerton and co-workers[35], Nicolaou and co-workers[36] utilized the stille cross coupling reaction to carbohydrate chemistry) synthesized *C*-glycosides using palladium-*π*-complexes. In addition to the palladium and samarium, other transition metal mediated *C*-glycosylation reactions were also reported by Sinou and co-workers[37]. Palladium catalyzed coupling of *p-tert*-butylphenyl-α-*O*-Δ^2-glycopyranoside **97** with various substituted arylmagnesium bromides provides stereospecifically the corresponding α-*C*-aryl-Δ^2-glycopyranosidecs of type **98α**. On the other

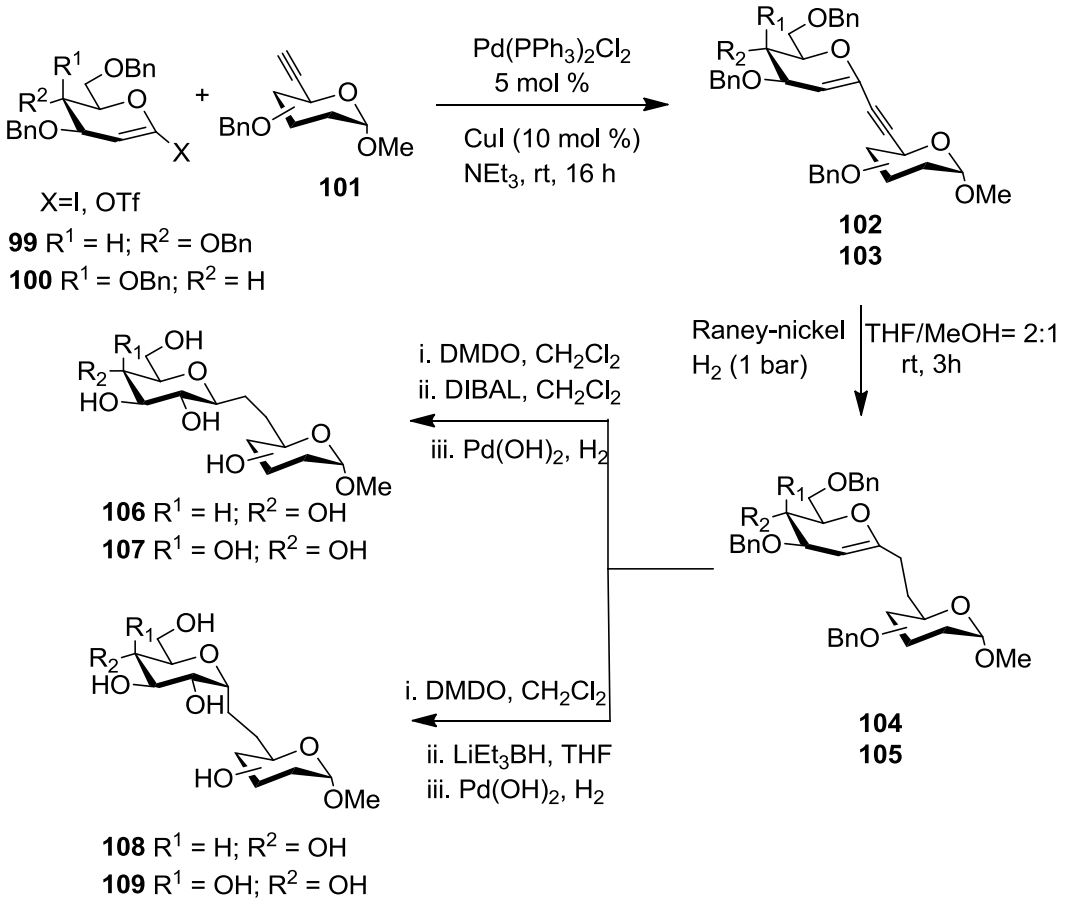
hand, the nickel mediated reaction provided the β-*C*-aryl glycosides of type **98β**. (Scheme1.17).



R = Bn, TBDMS, Ar = Ph, 2-OMePh, 4-OMePh, 3,4-(CH_2O_2)ph-, 2-MePh, 4-MePh, 4-ClPh, Bn

Scheme 1.17: Palladium and Nickel mediated *C*-aryl glycosylation.

In 2010, Daniel B. Werz and his co-workers, [38] synthesised (1→6)-linked *C*-glycosides (Scheme 1.18) using palladium catalysed coupling reaction. According to them,



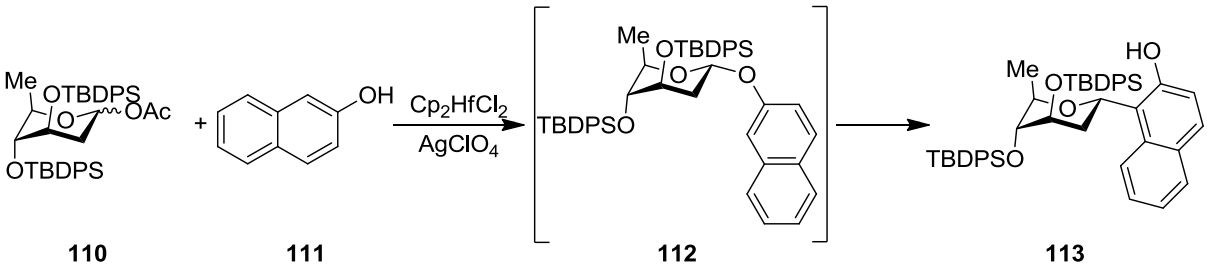
Scheme 1.18: Synthesis of (1→6)-Linked *C*-glycosides.

coupling of 1-iodo- or 1-triflato-glycals **99** or **100** with alkynyl glycoside **101** afforded the corresponding 1→6 linked alkynyl disaccharides **102** and **103**. Hydrogenation of the alkyne in **102** or **103** with Raney-nickel gave the resultant hydrogenated products **104** or **105**. Then epoxidation of compound **104** or **105** with DMDO, followed by reductive ring opening using different hydride sources provided the α- or β-*C*-glycosides **106-109** depending on the type of hydride source employed.

Later in 2013 the same group reported the preparation of more challenging *C*-glycosidic bonds and an accessible strategy to build α- and β-linked (1→2)-, (1→3)-, and (1→4)-*C*-disaccharides from 1-stannylglucals and exocyclic bromo olefins involving Stille cross coupling reaction.[39]

1.2.9 Conversion of *O*- to *C*-glycosides

The synthesis of *C*-aryl glycosides was explored by Suzuki and co-workers.[40a] This reaction usually goes through initial formation of an *O*-glycoside which rearranges to a *C*-glycoside in the presence of a Lewis acid. The yield and stereoselectivity of the *O*→*C*-glycosylation strongly depends on the reaction conditions like catalyst, temperature etc. Thus, glycosyl acetate **110** upon reaction with 2-naphthol **111** in the presence of Cp_2HfCl_2-$AgClO_4$ afforded the *C*-aryl glycoside **113** through the *O*-glycoside **112**(Scheme1.19).[40b]

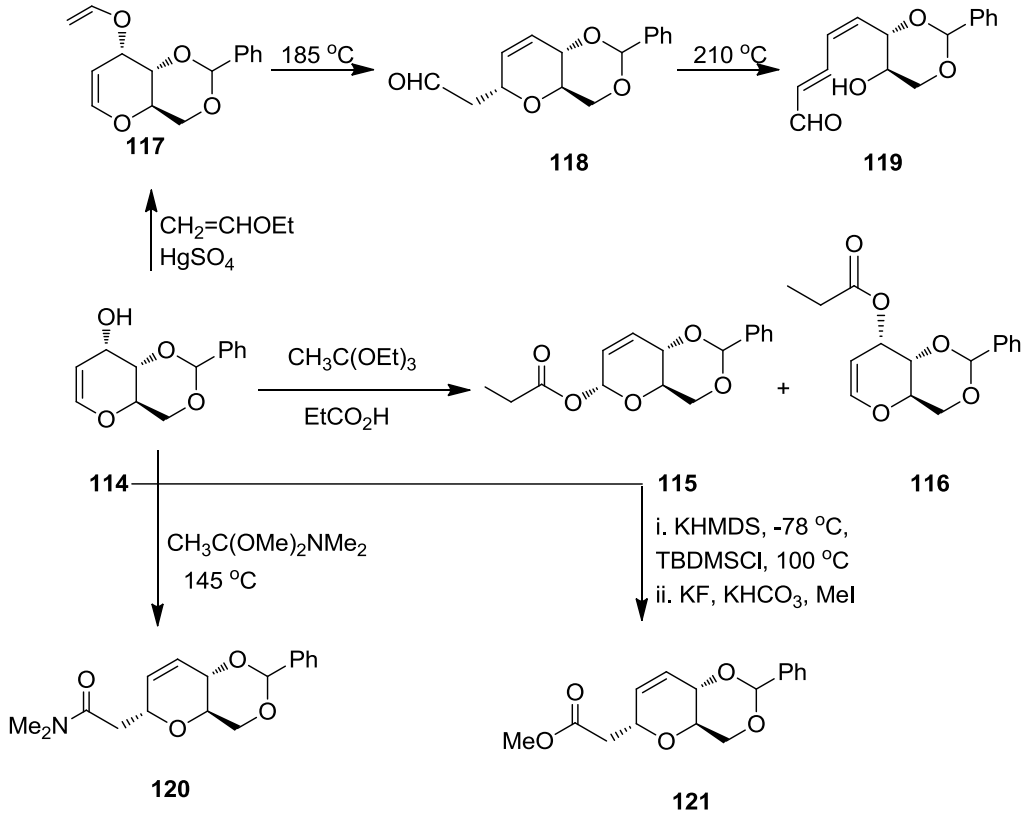


Scheme 1.19: Conversion of *O*→*C*-glycosides in presence of Lewis acids.

1.2.10 From Claisen rearrangement of glucal derived allyl-vinyl ethers

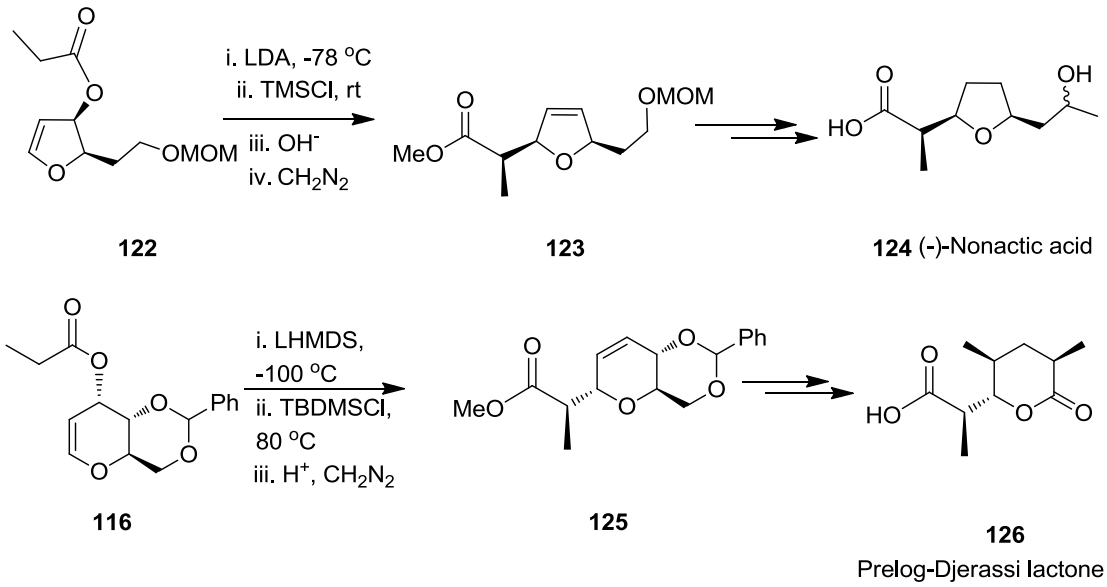
Towards the stereo selective synthesis of α-*C*-glyco-pyranosides, Fraser-Reid *et al*., explored the sigma tropic rearrangement of reactive intermediates derived from 4,6-*O*-benzylidene–D-allal **114**.[41] In the initial attempts to synthesize *C*-glycosides from the D-allal derived allylic alcohol **114** under Johnson orthoester Claisen rearrangement reaction conditions, undesired products **115** and **116** were obtained rather than the expected Claisen

rearrangement products. To avoid such side reactions, later they have made the vinyl ether **117** using $HgSO_4$ and ethyl vinyl ether, which upon heating at 185 ^oC provided the corresponding rearranged product **118,** whereas heating at 210 ^oC gave the ring opened unsaturated aldehyde derivative **119**. Alternatively, the most satisfying results were observed with Eschenmoser amide acetal procedure for the same allylic alcohol **114**, which gave the corresponding rearranged dimethylamide **120**. On the otherhand, subjecting the allylic alcohol **114** to form silyl ketene acetal followed by rearrangement and esterification, by Ireland and co-workers,[42] gave the expected *C*-glycoside **121**, however in a prolonged period of time (Scheme 1.20). It was found that the Ireland–Claisen rearrangement reaction works well with less-constrained furanose or pyranose derived allylic alcohols.



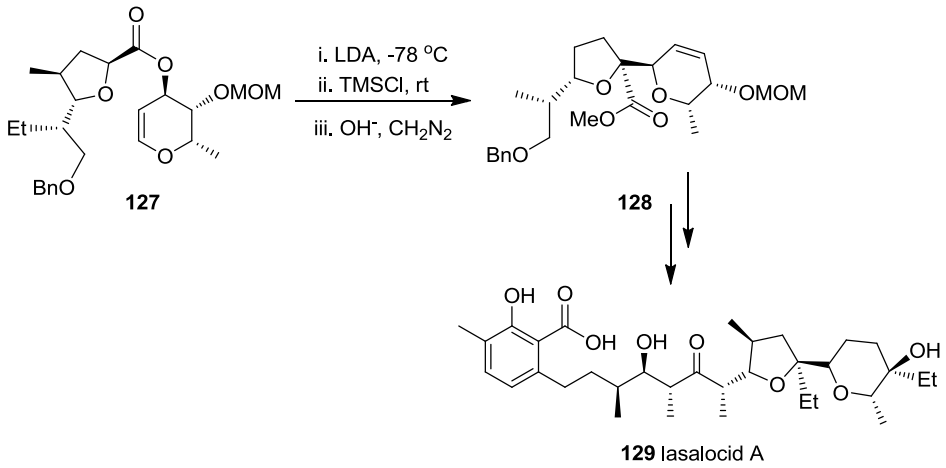
Scheme 1.20: The first glycal Claisen rearrangements by Fraser-Reid and Ireland.

A couple of *C*-glycoside derived natural products like (-)-nonactic acid **124**, (+)-nonactic acid and Prelog-Djerassi lactone **126** have been synthesized in a stereoselective fashion using the Ireland-Claisen rearrangement of corresponding furanoid and pyranoid glycal propionates **122** and **116** through intermediates **123** and **125** (Scheme 1.21).



Scheme 1.21: Synthesis of (-)-Nonactic acid and Prelog-Djerassi lactone through Ireland-Claisen rearrangement.

A variety of carbohydrate derived natural products like lasalocid A **129 (**by Ireland and co-workers) from compound **127** through **128** (Scheme 1.22),[43] indanomycin (by Ley *et al.*,[44]) in a Stereoselective fashion was achieved by utilizing the Claisen rearrangement of glycalesters.[45]

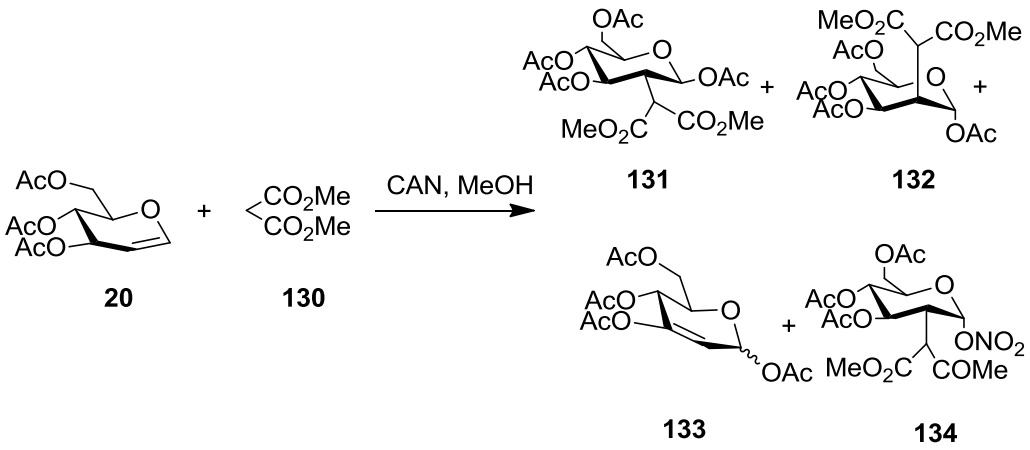


Scheme 1.22: Glycal Claisen rearrangement product as a key intermediate for the total synthesis of lasalocid A.

1.3. *C*-2 branched sugars

C-branched sugars are of current interest in carbohydrate chemistry. In the literature there are many methods available for the construction of *C*-glycosides but, formation of a C-C bond at positions other than the anomeric centre (at C-1) is somewhat challenging. Among the various methods available, cycloaddition, [46a] epoxidation, [46b] the addition of hetero atoms, [46c] and acid induced rearrangements[46d] are the most important reactions for the synthesis of 2-*C*-brached sugars.

In 1997, Linker[47]*et al*., developed a convenient method for the synthesis of 2-*C*-branched sugars **131** and **132** involving the radical addition of dimethyl malonate **130** on tri-*O*-acetyl-D-glucal **20** using manganese (III) or Cerium (IV) as radical generators. However, minor amount of the by-products **133** through the Ferrier rearrangement and 2-*C*-branched nitrate **134** through addition of ONO_2 radical**,** were also observed (Scheme 1.23). In this report, the authors also revealed that the cerium (IV) mediated radical addition gave higher stereo selectivity at lower temperatures when compared with manganese (III).



Scheme 1.23: Radical mediated synthesis of *C*-2-branched sugars.

One of the immediate precursor for the 2-*C*-branched sugars could be the 2-*C*-formyl glycal. In this regard, 2-*C*-formyl glycals are shown to be the important chiral pool substrates for chemo, regio, and Stereoselective glycosylation, nucleophilic addition/substitution and cycloaddition reactions. The presence of an α,β-unsaturated carbonyl system has extended the importance of 2-*C*-formyl glycals as potential synthons, which is evident from a number of reports which have been appeared in the literature from the last two decades. In addition, they have also been used for the synthesis of *C*-glycosides, homologated conjugated enals,

heterocyclic compounds, annulated glycopyranosides and also in total synthesis of some polyene compounds like "restricticin." Due to the wide applications of 2-*C*-formyl glycals as an important synthons in organic chemistry, their synthesis is quiet fascinating.

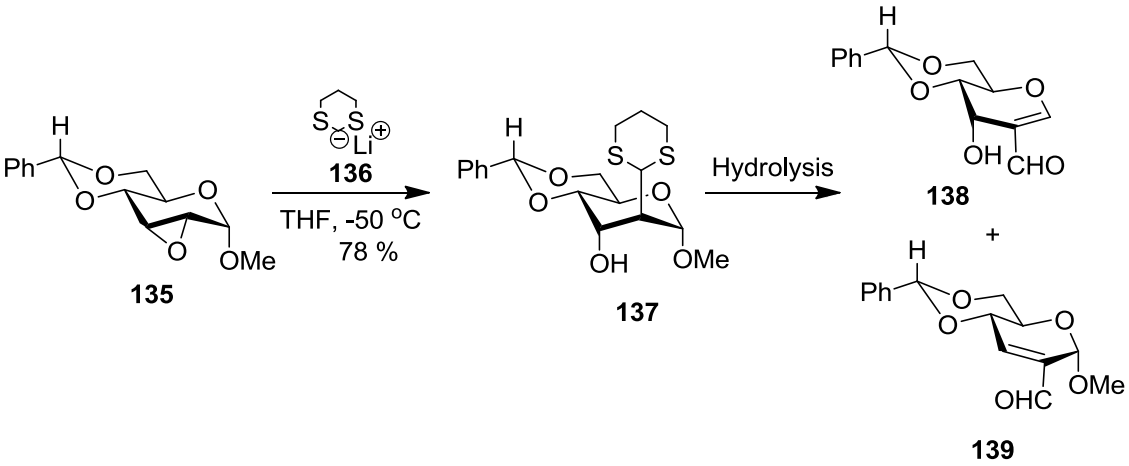
1.3.1 Synthesis of 2-*C*-formyl glycals

Some of the literature methods available to prepare 2-*C*-formyl glycals include,

- Synthesis by dithiane-based methodology
- Synthesis by the hydrolysis of sugar enol ethers
- Synthesis by Vilsmeier-Haack Reaction
- Synthesis by formyl group transfer

1.3.1.1 Synthesis by dithiane-based methodology

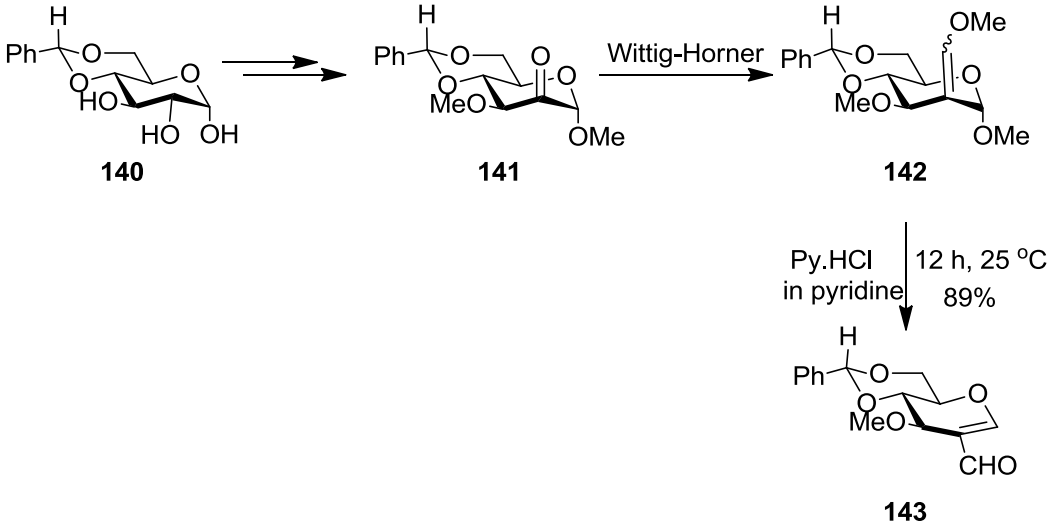
In 1982, Tietze *et al.*,[48a] reported the racemic synthesis of *C*-2-formyl glucal type compounds by means of hetero Diels-Alder reaction of malanodialdehyde.[48b] Later in 1988, Lukacs *et al.*,[48c] firstly synthesized 2-*C*-formyl glycals and revised their behaviour towards Diels-Alder reaction. Their synthetic method primarily involves the opening of epoxide ring of methyl 2, 3-anhydro-4,6-*O*-benzylidene-α-D-allopyranoside **135** with dithiane anion **136**, followed by oxidative removal of the dithiane group in dithioacetal **137** using ceric ammonium nitrate, resulting in the free aldehyde **138**. Using different hydrolysis conditions like MeI/$CaCO_3$, HgO/$HgCl_2$, MeCN/H_2O provided the mixture of aldehydes **138** and **139**. This methodology was used mainly for the synthesis of D-allal derived aldehyde **138** in high yields (Scheme 1.24).



Scheme 1.24: Dithiane based synthesis of 2-*C*-formyl glucals.

1.3.1.2 Synthesis by the hydrolysis of sugar enol ethers

In this protocol reported by Lukacs and co-workers,[48c] hemiacetals **140** was converted to the 2-keto derivative **141** which upon Witting-Horner reaction gave compound **142**, followed by mild acidic hydrolysis afforded the corresponding 2-*C*-formyl glucal **143** in high yield (Scheme1.25). This methodology was shown to be applicable to a variety of sugar derivatives.

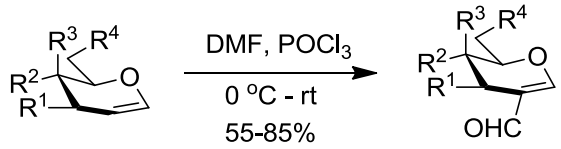


Scheme 1.25: Synthesis of 2-*C*-formyl glucal from hydrolysis of sugar enol ethers.

1.3.1.3 Synthesis by Vilsmeier-Haack Reaction

The Vilsmeier-Haack reaction is one of the best methods for the direct formylation of enol ethers, enolizable ketones, electron rich aromatic nuclei, and other active hydrogen compounds. Piancatelli and co-workers extended this reaction to the formylation of 5,6-dihydro-4*H*-pyran[49]. Later, in 1991 K. K. Balasubramanian *et al*., investigated this reaction

Table 1.2: Vilsmeier-Haack reaction of glycals.

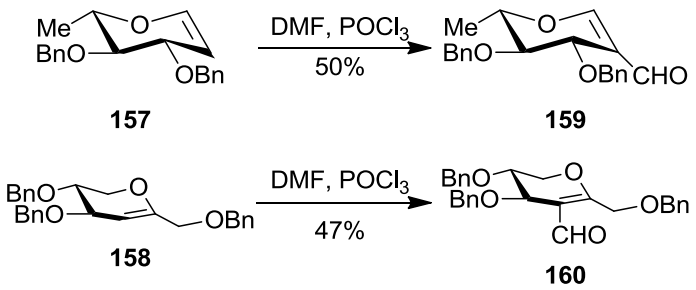


Entry	Glycal	R^1	R^2	R^3	R^4	Product	Time (h)	Yield (%)
1	**144**	OMe	OMe	H	OMe	**151**	4	60
2	**145**	OBn	OBn	H	OBn	**152**	8	55
3	**146**	OMe	H	OMe	OMe	**153**	8	80
4	**147**	OBn	H	OBn	OBn	**154**	8-9	85
5	**148**	OMe	H	OMe	OTr	**155**	8-9	72
6	**20**	OAc	OAc	H	OHAc	-	-	-
7	**149**	OMe	isopropilidene	H	-	-	-	-
8	**150**	OBn	N_3	H	OBn	**156**	4	44

Me = methyl; Bn = benzyl; Tr = trityl (triphenylmethyl); Ac = acetyl.

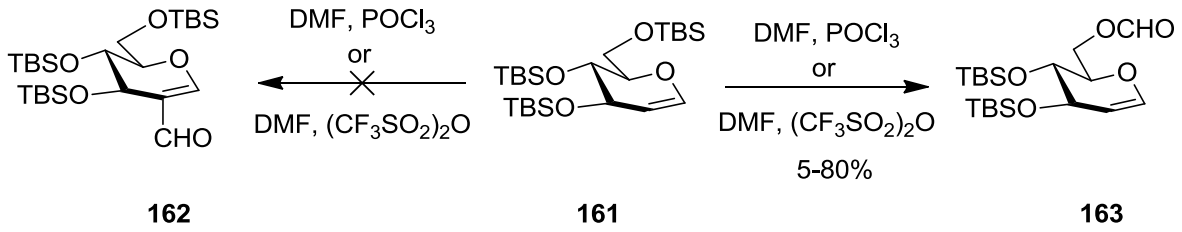
and extended its scope to carbohydrate derived cyclic enol ethers, also known as glycals, (Table1.2).[50] Thus, treatment of tri-*O*-methyl-D-glucal **144** under Vilsmeier-Haack conditions (DMF and $POCl_3$) gave the corresponding 2-*C*-formyl glucal **151** in 60% yield (Table 1.2, Entry 1). The reaction has been successfully applicable to other glycals (**145** – **150**) to obtain the corresponding 2-*C*-formyl glycals (**152**-**156**) as well. The observed yields are high in the case of *galactal* series than in *glucal* series (Table 1.2, entries 3-5). The methodology was also shown to be plausible even with the glycals possessing acid sensitive groups like trityl ethers. But the reaction failed in the case of glycals having isopropilidene and acetate protective groups.

In 2001 Lellouche[51] and co-workers used the combination of $(CF_3SO_2)_2O$.DMF instead of the Vilsmeier-Haack reagent ($POCl_3$/DMF) to synthesize 2-*C*-formyl glycals in good yield. Later, Peseke and co-workers extended this methodology to di-*O*-benzyl-L-rhamnal **157** and tri-*O*-benzyl-D-fructal **158** to obtain the corresponding 2-*C*-formyl glycals **159** and **160** in moderate yield (Scheme1.26).[52]



Scheme 1.26: Synthesis of di-*O*-benzyl 2-*C*-formyl –L-rhamnal and D-fructal.

Recently Feit and co-workers[53] applied Vilsmeier-Haack reaction to the disaccharide glycals. Lellouche and co-workers[51] studied the behaviour of silyl protected glycals under Vilsmeier-Haack formylation reaction conditions. According to them, tri-*O*-silyl glucal **161** upon reaction with Vilsmeier-Haack reagent, a selective deprotection of the primary silyl group followed by *O*-formylation resulting compound **163** and no *C*-formylation product **162** was observed (Scheme 1.27).

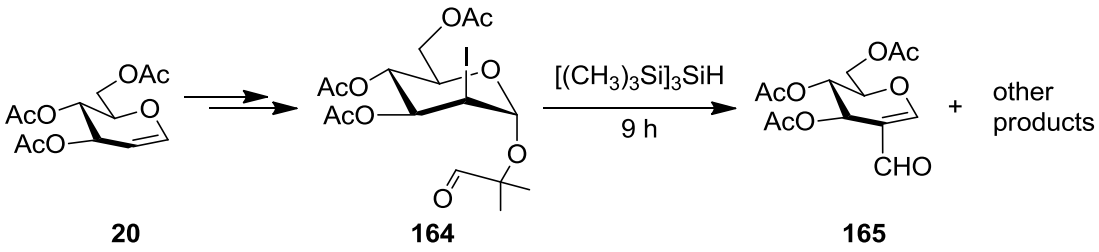


162 **161** **163**

Scheme 1.27: Formylation of silyl protected glycals.

1.3.1.4 Synthesis by formyl group transfer

Jung *et al.*, synthesized 2-*C*-formyl glycopyranosides by intramolecular radical initiated formyl group transfer affording the tri-*O*-acetyl-2-*C*-formyl-D-glucal **165** as the side product[54] from compound **164** using tris(trimethylsilyl)silane or tributylstannane as a reagent for radical formation (Scheme 1.28).



20 **164** **165**

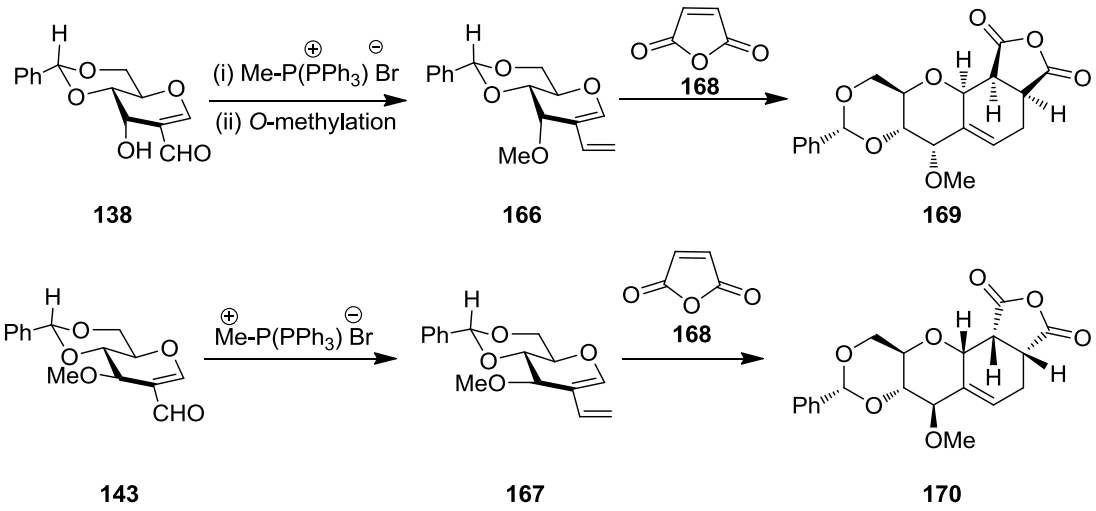
Scheme 1.28: Synthesis of 2-*C*-Formyl glucal by intramolecular formyl group transfer.

1.4 Synthetic applications of 2-*C*-formyl glycals

1.4.1 Synthesis of dienes from 2-*C*-formyl glycals and their Diels-Alder reactions

A new class of *C*-glycoside synthesis was developed by Lukacs *et al.*,[55] starting from 2-*C*-formyl glycals. Wittig olefination of 2-*C*-formyl glycals **138** and **143** provided the C-3

epimeric dienes **166** and **167**, which upon π facial selective Diels-Alder reaction with maleic anhydride **168** provided the corresponding adducts **169** and **170** respectively (Scheme1.29).

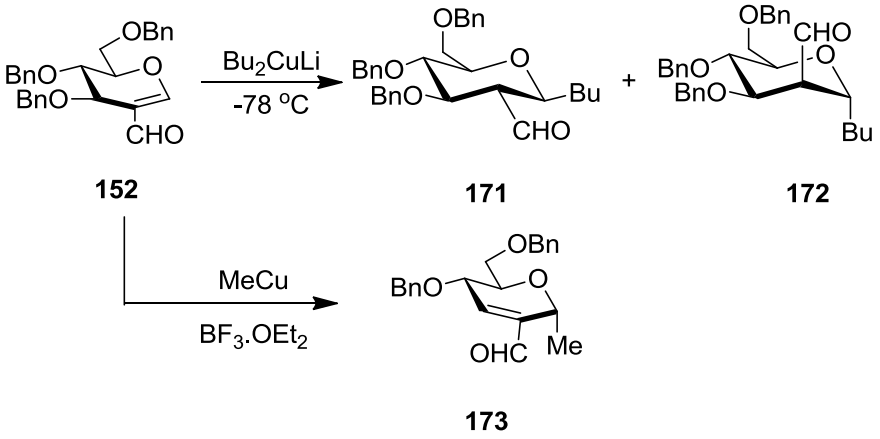


Scheme 1.29: Synthesis and Diels-Alder reaction of Carbohydrate dienes derived from 2-*C*-formyl glycals.

They have observed that the methoxy group at C-3 in the diene **166** and **167** exerts an anti-directing effect on the approach of the dienophile. But no such type of facial selectivity was observed if there is no alkoxy or any stereo directing group at C-3 position. Reaction also works well with linear acetylene dienophiles but not exclusively anti to the C-3 methoxy group. The synthesized annulated and benz annulated glycopyranosides have prospective biological importance.

1.4.2 Synthesis of *C*-glycosides using 2-*C*-formyl glucal with organo copper Reagents

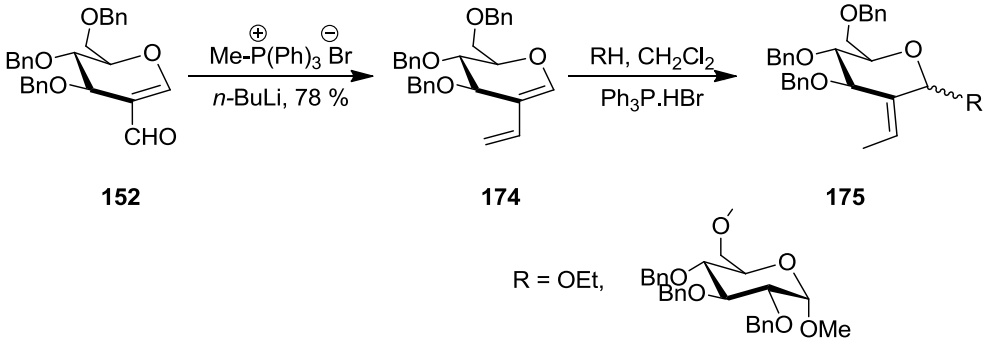
Cossy and co-workers had successfully performed a Michael-type addition reaction on 2-*C*-formyl glycals using organo-copper reagents.[56] The product of the reaction depends on the nature of the organo-copper reagent employed. As a consequence, addition of lithium dialkylcuprates to 2-*C*-formylglucal **152** resulted in a facile Michael addition reaction to provide the corresponding 2-*C*-formyl-*C*-glycosides **171** and **172**, the β-anomer **171** was found to be the major product. On the other hand, treatment of the same glucal **152** with alkylcopper reagent in the presence of $BF_3.OEt_2$ resulted in a carbon-Ferrier-type rearrangement provided the 2-*C*-formyl-2,3-unsaturated-α-*C*-glycoside **173** as the only product. This reaction was generalized for a variety of copper reagents (Scheme 1.30).



Scheme 1.30: *C*-glycosylation of 2-*C*-formyl glucal with organo-copper reagents.

1.4.3 Synthesis of 2-*C*-(β-methyl) methylene glycals

Feit and co-workers[53] used 2-*C*-ethenyl-D-glucal **174** for the synthesis of 2-*C*-(β-methyl) methylene glycals. Compound **174** was readily prepared by Wittig olefination of 2-*C*-formyl glucal **152** with triphenylphosphonium bromide in the presence of *n*-BuLi as a base. 2-*C*-ethenyl glycal **174** on treatment with alcohols (including sugar alcohols) in presence of triphenyl phosphonium bromide mediated electrophilic addition afforded the 2-*C*-(β-methyl) methylene glycosides of type **175** (Scheme 1.31).

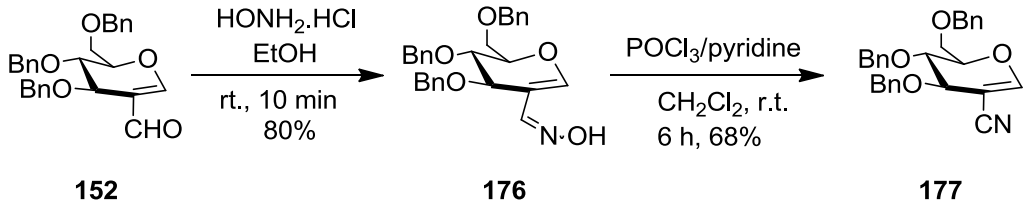


Scheme 1.31: Synthesis of 2-*C*-(β-methyl) methylene glycals from 2-*C*-formyl glucal.

1.4.4 Synthesis of 2-*C*-cyano glucal

In 2003, K. K. Balasubramanian and co-workers had synthesized the 2-*C*-cyano glucal **177** [57] from the 2-*C*-formyl glucal **152** in two steps. In their protocol, treatment of glucal with hydroxylamine hydrochloride in ethanol at room temperature afforded the corresponding oxime **176**, which was dehydrated to the 2-*C*-cyano glucal **177** by using $POCl_3$

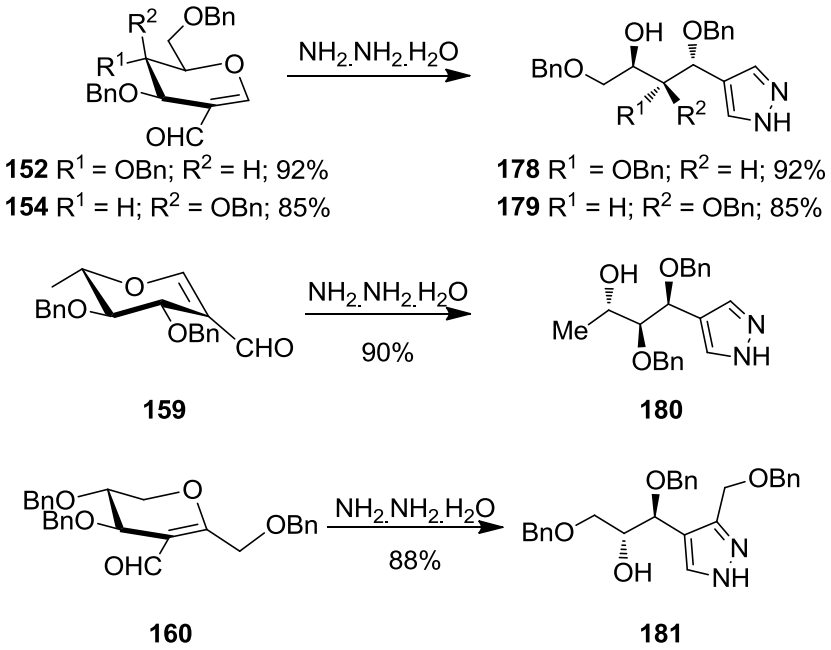
and pyridine (Scheme1.32). This was an alternate approach to the synthesis of 2-*C*-cyano glucal.[58] The synthesized 2-*C*-cyano glycals provides scope for further utilization of its chemical [59] and biological [60] properties (Scheme 1.32).



Scheme 1.32: Synthesis of 2-*C*-cyano glucal.

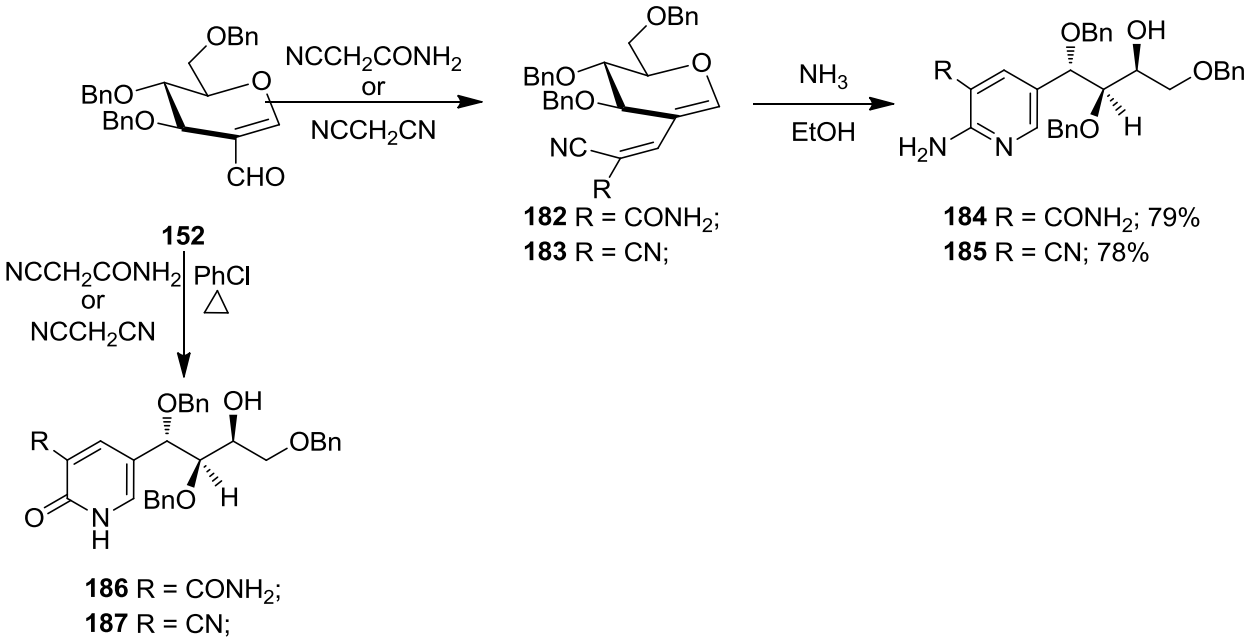
1.4.5 Synthesis of acyclo-*C*-nucleosides from 2-*C*-formyl glycals

C-nucleoside analogues with straight chain sugar moiety have been shown to possess important biological properties, [61] because of which there has been an immense attention in the synthesis of acyclo-*C*-nucleosides. Peseke and co-workers have synthesized a variety of acyclo-*C*-nucleosides from 2-*C*-formyl glycals.[62] Towards this, they treated 2-*C*-formyl glycals like **152**, **154**, **159** and **160** with hydrazine hydrate in refluxing ethanol afforded the corresponding C-(1H-pyrazol-4-yl)alditols **178**, **179**, **180** and **181** respectively in good yield (Scheme 1.33).[63]



Scheme 1.33: Synthesis of acyclo-*C*-nucleosides from 2-*C*-formyl glycals.

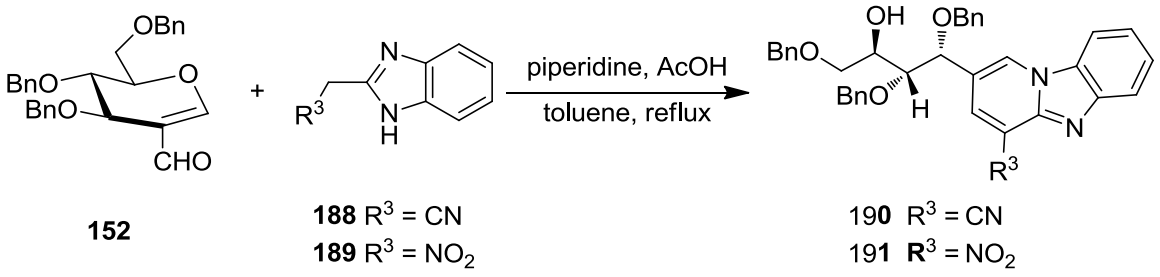
They also synthesized pyridine attached acyclo-*C*-nucleosides from 2-*C*-formyl glycals. For this 2-*C*-formyl glycal **152** was treated with malanonitrile or cyanoacetamide



Scheme 1.34: Synthesis of pyridine acyclo-*C*-nucleosides from 2-*C*-formyl glycals.

with pyridinium acetate as the catalyst, which gave the branched chain sugars **182** and **183**, which on exposure to ammonia in ethanol afforded the nicotinamide and nicotinonitrile derivatives **184** and **185** respectively (Scheme 1.34) [53, 62]. On the other hand, prolonged treatment of these formyl glycals with cyanoacetamide in the presence of pyridinium acetate provided the pyridone derivatives **186** and **187**.

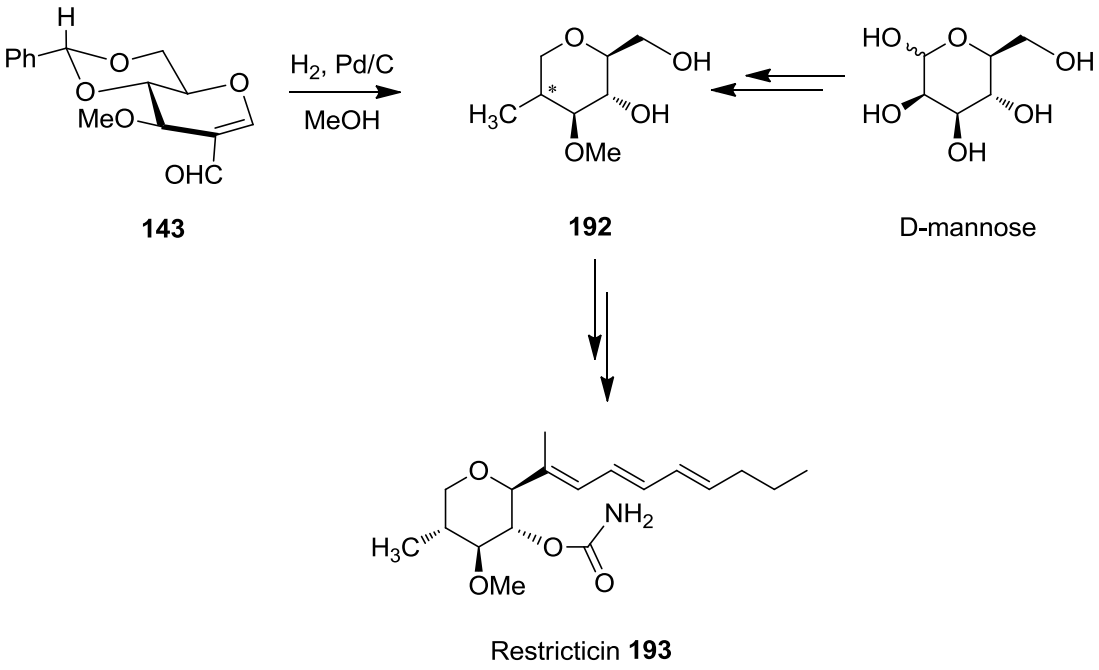
The methodology was further extended to the synthesis of polycyclic acyclo *C*-nucleosides. In this application, 2-*C*-formyl glucal **152** was treated with 2-benzimidazolylacetonitrile **188** or 2-nitromethylbenzimidazole **189** to furnish the 2-benzimi-



Scheme 1.35: Synthesis of polycyclic acyclo-*C*-nucleosides from 2-*C*-formyl glycals.

-dazolylacetonitrile **188** or 2-nitromethylbenzimidazole **189** to furnish the corresponding acyclo *C*-nucleosides **190** and **191** in moderate to 70-75% yield (Scheme 1.35).

1.4.6 Total synthesis of polyene antibiotic "Restricticin":



Scheme 1.36: Total synthesis of restricticin from 2-*C*-formyl glucal.

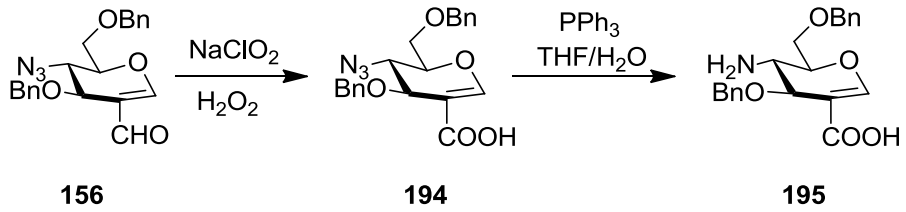
Restricticin **193**[63], is a polyenic antibiotic, isolated from fungi of the genus *Penicillium*. Jendrzejewski and co-workers had reported the first total synthesis of restricticin.[64] In their synthetic route, they utilised the 2-*C*-formyl glycal **143** which was subjected to hydrogenolysis conditions (Pd/C, H_2**)** to afford the 2-*C*-methyl sugar derivatives **192** in 93% yield. The same intermediate was also synthesized from D-mannose. But diastereomeric ratio is higher in the case of former procedure when compared to later one. A total synthesis of restricticin **193** from **192** was accomplished by a series of steps (Scheme 1.36).

1.4.7 Synthesis of γ-amino butyric acid (GABA) analogues

γ-Aminobutyric acid (GABA) is a neurotransmitter in the mammalian central nervous system which is necessary in maintaining the equilibrium between neuronal excitation and inhibition. Low levels of GABA result in many neurological disorders.[65] Hence, the synthesis of GABA analogues is continued to be an interesting area. Compounds which deactivate γ-

amino butyric acid aminotransferase, the enzyme that is responsible for the degradation of GABA, in order to supply high level of GABA which is necessary for the proper functioning of the brain are under extensive investigation.[66]

Synthesis of GABA analogues from carbohydrate moieties is quiet important due to their compatibility that was shown by Hindsgaul and co-workers.[67] Li *et al*, synthesized GABA analogues starting from 2-*C*-formyl-glycals.[68] Towards this, oxidation of the aldehyde in the 2-*C*-formyl-glycal **156** with $NaClO_2$ and H_2O_2 provided carboxylic acid **194**. Staudinger reduction of the azido group at the C-4 position in **194** afforded the corresponding carbohydrate derived γ-aminobutyric acid **195** (Scheme 1.37). They also synthesized molecules wherein the carboxyl group of **195** was replaced by tetrazole and acylamide moieties. They applied this methodology to both 3-azido derived glucal as well as galactal with benzyl and methoxy protecting groups.



156 **194** **195**

Scheme 1.37: Synthesis of carbohydrate derived γ-amino butyric acid (GABA) analogues.

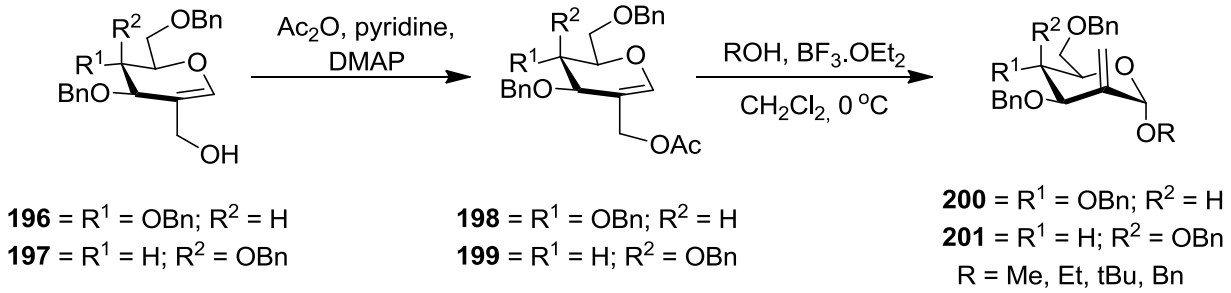
1.5 Synthetic applications of 2-*C*-hydroxymethyl glycals

2-*C*-hydroxymethyl glycals were easily synthesized by reduction of the corresponding 2-*C*-formyl glycals.

1.5.1 Synthesis of 2-*C*-methylene glycosides

The 2-*C*-methylene group is a significant structural unit present in molecules involved in mechanism based inactivation of the enzyme ribonucleotide diphosphate reductase.[69] Synthetically these are good synthons for the *C*-disaccharides preparation. K. K. Balasubramanian and co-workers first synthesized the 2-*C*-methylene glycosides from 2-*C*-formyl glycals.[70] Their synthetic route towards 2-*C*-methylene glycosides consists of reduction of the 2-*C*-formyl glycals **151** and **154** with sodium borohydride to obtain alcohols **196** and **197**, followed by acetylation with acetic anhydride resulted in 2-acetoxy methyl glycals **198** and **199**. Treatment of these acetates with an alcohol in the presence of $BF_3.OEt_2$

gave the corresponding 2-*C*-methylene glycosides **200** and **201** in good yields (Scheme 1.38) with α-anomer as the major isomer.

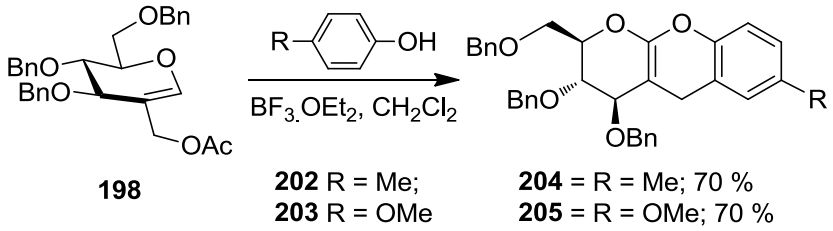


Scheme 1.38: $BF_3.Et_2O$ catalysed synthesis of 2-*C*-methylene glycosides.

Later in 2000, Vankar and co-workers[71] investigated the effect of different acid catalysts on the 2-acetoxy methyl glycals to improve the anomeric selectivity with alcohols and phenols. They have used acid catalysts like Nafion-H, Montmorillonite K-10, and $LiClO_4$, but they also observed the α-anomers as major products.

1.5.2 Synthesis of chiral pyranobenzopyrans

K. K. Balasubramanian *et al.*,[72a] reported the reaction of substituted phenols **202** and **203** with 2-*C*-acetoxy methyl glycal **198** in the presence of $BF_3.OEt_2$ providing chiral pyrano[2,3-b][1]benzoprans **204** and **205** in high yields via 2-*C*-methylene-*O*-aryl glycosides(which were not isolated) followed by tandem cyclisation. These compounds are regarded as annulated pyranosides with chiral centres (Scheme 1.39). (Pyranobenzopyrans with chiral centres are rare).



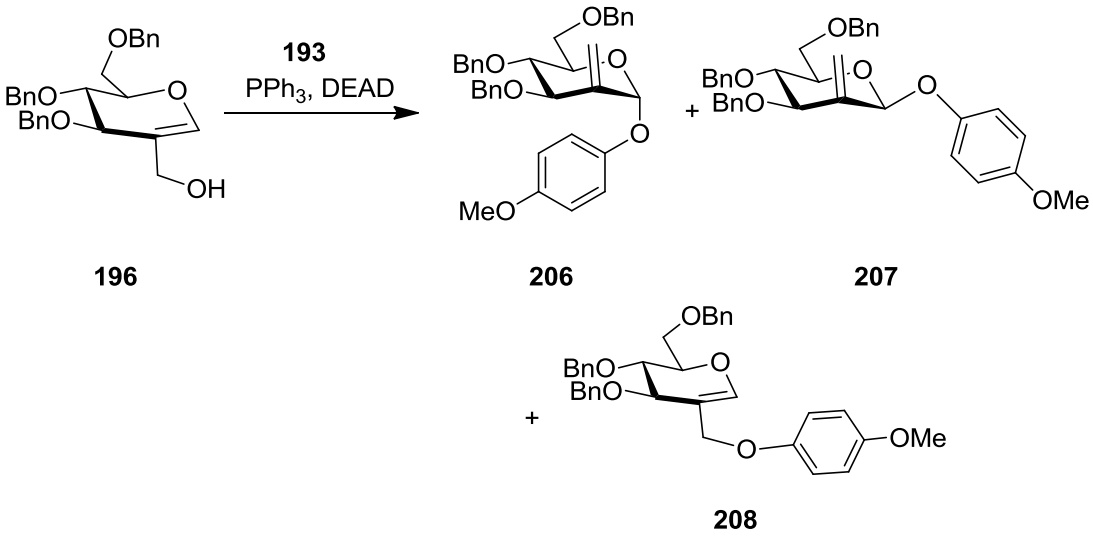
Scheme 1.39: Synthesis of chiral pyrano[2,3-*b*][1]benzopyrans.

Later Ghosh *et al.*, extended this reaction with β-naphthol by using $InCl_3$ as the catalyst. The reaction proceeded smoothly to give pyranonaphthopyrans[72b, 72c] in high yield.

This clearly indicates that $InCl_3$ is an efficient catalyst alternative to corrosive and moisture sensitive $BF_3.Et_2O$.

1.5.3 Synthesis of 2-*C*-methylene-*O*-aryl glycosides

Alternatively, 2-*C*-methylene-*O*-aryl glycosides were synthesized by using Mitsunobu reaction.[73] This methodology consists of reacting alcohol **196** with phenols under Mitsunobu reaction conditions to provide the corresponding 2-*C*-methylene-*O*-aryl glycosides as mixture of α- and β-anomers **206**, and **207** in different ratios, along with allyl aryl ether **208** as the minor product. In the case of galactal series, this reaction was found to be diastereo selective, affording only α-anomer (Scheme 1.40).

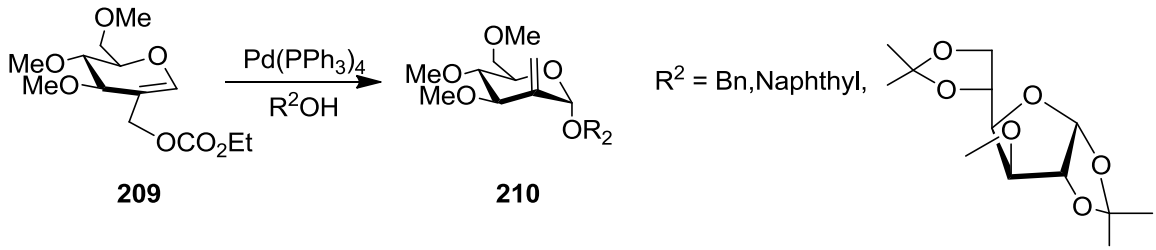


Scheme 1.40: Synthesis of 2-*C*-methylene-*O*-aryl glycosides by a Mitsunobu approach.

Later, in 2000, a stereo selective synthesis of 2-*C*-methylene–β-*O*-aryl glycosides from 2-*C*-acetoxy methyl galactal **199** was reported by Vankar's group[71]. They employed Nafion-H and $LiClO_4$ as catalysts for the Ferrier rearrangement of **199** with *p*-cresol and β-naphthol to afford the β-*O*-aryl glycosides stereo selectively in good yield. But, the method was not successful with parent phenol and also it was not extended to the *glucal* derivatives. The same reaction was also successful with Montmorillonite K-10. An interesting observation with Montmorillonite K-10 as catalyst was, the treatment of β-naphthol with **199** gave the corresponding β-*O*-aryl glycoside, whereas *p*-cresol, under the same conditions, yielded not the *O*-aryl glycoside, instead *C*-aryl glycoside in 62% yield.

Another stereo selective approach for the synthesis of 2-*C*-methylene-*O*-glycosides and *O*-aryl glycosides is by using palladium catalysts. The starting allylic carbonates **209** (which was prepared from the corresponding hydroxymethyl glucal derivative) underwent

smooth reactions with substituted phenols in the presence of $[Pd_2(dba)_3]$/dppb or $[Pd(PPh_3)_4]$ to provide the corresponding 2-*C*-methylene-*α*-*O*-aryl glycosides **210** exclusively.[71,73] The methodology also works well with aliphatic alcohols to give the corresponding α-*O*-alkyl glycosides (Scheme 1.41). The anomeric selectivity is due to the formation of *π*-allyl palladium complex from the β-face, followed by attack of nucleophile from the α-face. The regiospecific *O*-alkylation is in good agreement with the fact that alkylation occurs under electronic control in the *π*-allyl system bearing oxygen at one terminal. However, this reaction was investigated only in the glucal series.



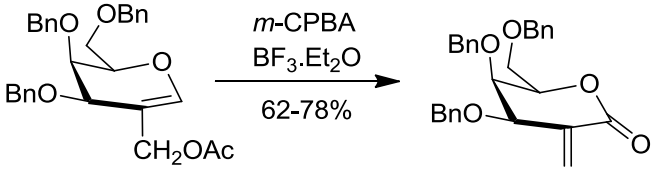
209 **210**

Scheme 1.41: Palladium-catalysed stereo selective synthesis of 2-*C*-methylene –α-*O*-glycosides.

Wolf *et al*., reported a similar kind of method for the synthesis of 2-*C*-methylene nucleosides by the condensation of a silylated base with a π-allyl palladium complex which was derived from 2-*C*-acetoxy methyl-furanoid glycal.[74]

1.5.4 Synthesis of α-methylene–δ-valerolactones

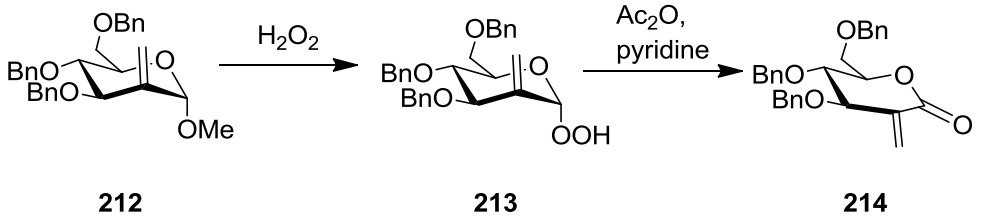
Vankar and co-workers have developed a synthetic route for the synthesis of α-methylene-δ-valerolactones.[71] Towards this, oxidation of the 2-*C*-acetoxy methyl galactal **199** with *m*-CPBA in the presence of $BF_3.Et_2O$ at -65 ^oC afforded the lactone **211** in good yield (Scheme 1.42).



199 **211**

Scheme 1.42: Synthesis of α-methylene-δ-valerolactones from 2-*C*-acetoxymethyl glycals.

Previously, Chmielewski and co-workers had synthesized the sugar based α-methylene-δ-valerolactones in two steps from the 2-*C*-methylene-α-*O*-methyl glycoside **212**. Anomeric oxidation of **212** with hydrogen peroxide afforded sugar hydro peroxide **213**, which on treatment with acetic anhydride/pyridine gave the lactone **214** in 81% yield (Scheme 1.43).[61]



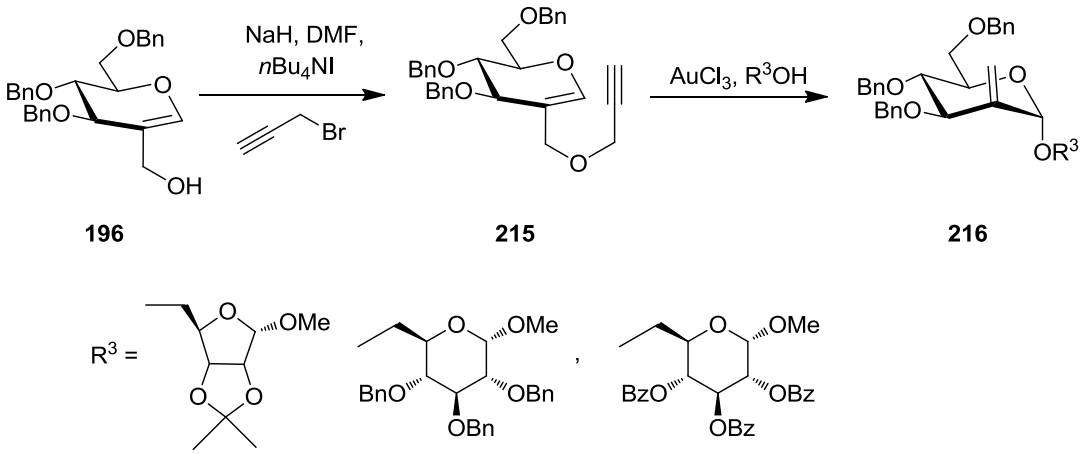
212 **213** **214**

Scheme 1.43: Synthesis of α-methylene-δ-valerolactones from 2-*C*-methylene glycosides

These lactones **211** and **214** have been used as precursors in the synthesis of *C*-disaccharides.[75] Chmielewski and co-workers utilized the above mentioned hydro peroxide **213** as chiral oxidant for the enantioselective epoxidation of the allylic alcohols, with enantiomeric excess (ee) range from 4-44%. They had also converted methyl aryl sulphides to the corresponding sulfoxides with 25% ee.

1.5.5 Ferrier rearrangement of 2-*C*-propargyloxymethyl-glycals

Hotha and co-workers synthesized 2-*C*-methylene glycosides by using gold catalyst ($AuCl_3$), by exploiting its alkynophilicity.[76] Their synthetic route involves the synthesis of 2-*C*-propargyloxymethyl-glucal **215** in two steps from 2-*C*-formyl glucal. Treatment of which



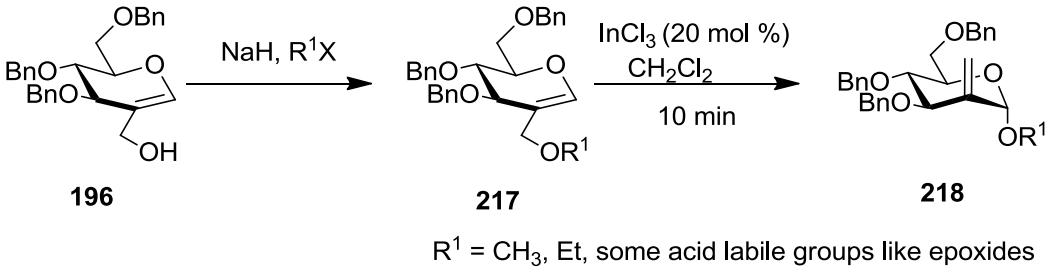
196 **215** **216**

Scheme 1.44: Ferrier rearrangement of 2-*C*-Propargyloxymethyl-glycals.

in the presence of catalytic amount of $AuCl_3$(5 mol %) with a variety of alcohols, including monosaccharides afforded the 2-*C*-methylene glycosides **216** through Ferrier rearrangement in good to moderate (60-72%) yield (Scheme 1.44). Only α-anomer was observed in this rearrangement.

1.5.6 1, 3-alkoxy migration reaction of 2-*C*-substituted glycal ethers

N. G. Ramesh and co-workers had developed a novel and rapid $InCl_3$ catalysed 1,3–alkoxy migration reaction leading to the stereoselective synthesis of 2-*C*-methylene-α-*O*-glycosides.[77] The starting substrate **217** was synthesized by direct etherification of 2-*C*-hydroxymethyl-glucal **196** with alkyl halides in the presence of sodium hydride as a base. Treatment of these alkoxy alkyl glucal derivatives of type **217** with $InCl_3$ (20 mol %), afforded the corresponding 2-*C*-methylene glycosides of type **218** through intramolecular 1,3-alkoxy migration in just 10 min in high yield (Scheme1.45). The reaction was highly stereoselective, only α-anomers were formed in all cases and also reaction works well with acid labile groups like epoxide and acetal groups. They also investigated the catalytic activity of different Lewis acids such as $ZnCl_2$, ceric ammonium nitrate, $BiCl_3$ and $BF_3.Et_2O$. Among these, $InCl_3$ was found to be the most suitable catalyst for this transformation. The methodology thus provides an alternative to the Ferrier rearrangement for the synthesis of 2-*C*-methylene glycosides. A plausible mechanism for the exclusive formation of α- anomer was confirmed based on AMI calculations and also involvement of anchimeric assistance of the C-6 benzyloxy group.



Scheme 1.45: 1, 3-Alkoxy migration approach to the synthesis of 2-*C*-methylene glycosides.

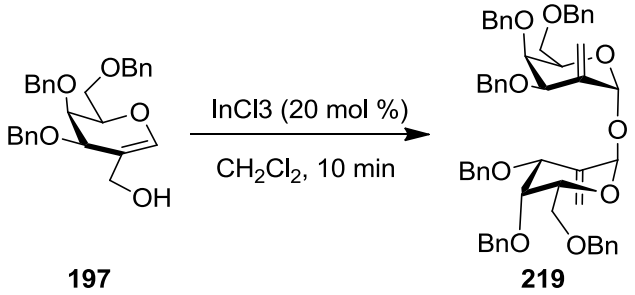
1.5.7 Direct allylic substitution of 2-*C*-hydroxymethyl-glycals

Later, the same reaction was carried out by the same group under Ferrier rearrangement conditions. $InCl_3$ was found to be efficient catalyst for the direct allylic

substitution of the hydroxy group of 2-*C*-hydroxy methyl glycals **196** and **197** by oxygenated nucleophile's to afford 2-*C*-methylene glycosides in good yields.[78a] The reaction requires only 5mol % of $InCl_3$, and completes in a short period of time (30 min). The methodology was also found to be very facile with a variety of alcohols including monosaccharides possessing acid labile groups and proceeds in high yields. Synthesis of 2-*C*-methylene glycosides can be achieved without protecting the hydroxymethyl group, which is the main asset of this methodology. Moreover, the reaction also works well in the presence of phenols to furnish 2-*C*-methylene-*O*-aryl glycosides in good yields. Consequent to this protocol, Bhagavathy and co-workers performed the same reaction with Montmorillonite K-10 as the catalyst. [78b]

1.5.8 Synthesis of an α,α-(1→1)-linked disaccharides

One of the interesting observations in the above mentioned methodology is, formation of a doubly unsaturated α,α-(1→1)-linked disaccharide **219** in just 30 min in a high yield, 80 % (Scheme 1.46). Formation of this unexpected disaccharide was explained by a suitable mechanism.[78a]



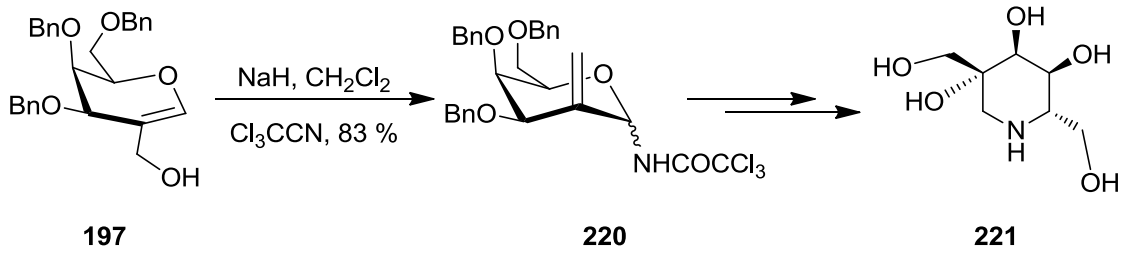
197 **219**

Scheme 1.46: Direct synthesis of α,α-(1→1)-linked disaccharide **209** through a domino process.

1.5.9 Synthesis of azasugars

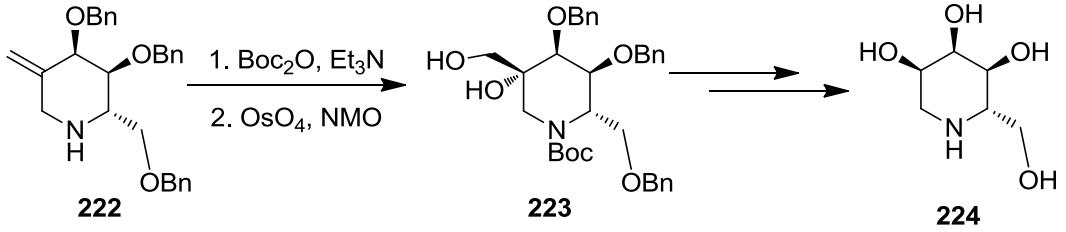
Azasugars are very important compounds having stereo chemical and structural resemblance to natural sugars but, biological properties differ from them. Their selective inhibition of a range of glycosidases collectively encouraging the discovery of some azasugar based drugs, which has driven organic chemists to develop novel synthetic strategies for the natural and unnatural azasugars. Recently, Vankar and co-workers developed a new route for the synthesis of azasugars from 2-*C*-formyl glycals through aza-Claisen rearrangement as the key step. Their synthetic route involves trichloroacetamides as precursor for the preparation

of aza-sugar derivatives. The synthesis begins with 2-hydroxymethyl glycal **197**, which upon reaction with trichloroacetonitrile in presence of NaH provided the trichloracetimidate which undergo a facile *insitu* aza-Claisen rearrangement to afford directly 2-*C*-methylene-*N*-glucoside[79a] **220** in one step. They utilized these 2-*C*-methylene-*N*-glucosides for further synthesis of natural and unnatural azasugars. These amides were subjected to a sequence of steps to provide the C-2 homo analogue of 1-deoxy nojirimycin **221** (Scheme 1.47).



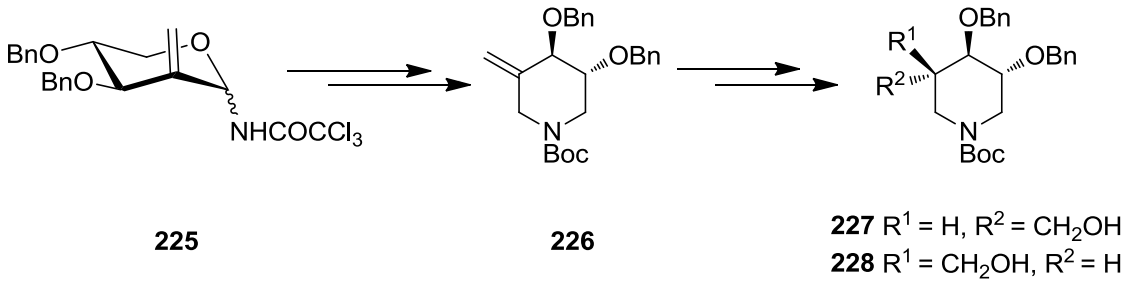
Scheme 1.47: Synthesis of azasugars from 2-*C*-methylene-*N*-glucosides.

They also synthesized L-allo- deoxynojirimycin **224** using the precursor **222**. Towards this, protection of amine as Boc with Boc_2O, followed by dihydroxylation gave diol **223**. Oxidative cleavage of the diol, followed by stereo selective reduction of the ketone and finally global deprotection gave the L-allo-1-deoxynojirimycin **224** (Scheme 1.48).



Scheme 1.48: Synthesis of L-allo-deoxynojirimucin

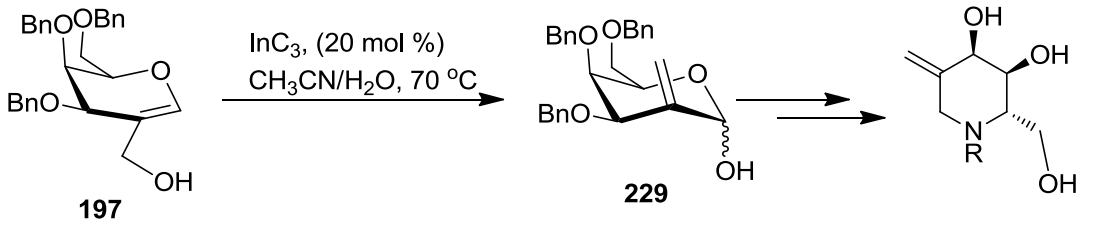
Further, a synthetic route for the β-glucosidase inhibitor which was previously designed by Bols *et al*., was also synthesised by the Vankar group. Towards this, D-xylal derived trichloroacetamide **225** was employed for the construction of piperidine ring **226**, which was prepared by using the same procedure described for **221**. Hydroboration of the exocyclic methylene in **226** by using 9-borabyclo [3.3.1] nonane (9-BBN) and subsequent deprotection resulted in the formation of iso-fagomine (**227**) and 5-*epi*-iso-fagomine (**228**) in 8:2 ratio, respectively (Scheme 1.49).[79b]



225 **226** **227** R^1 = H, R^2 = CH_2OH
228 R^1 = CH_2OH, R^2 = H

Scheme 1.49: Synthesis of isofagomine and 5-*epi*-isofagomine

N. G. Ramesh and co-workers also developed an alternate route towards the synthesis of unsaturated azasugars such as **230** and **231**. The key reaction in their synthesis was a 1, 3-transposition of the hydroxyl group in **197** by using $InCl_3/CH_3CN/H_2O$ as an efficient catalyst-solvent combination. Thus treatment of 2-*C*-hydroxymethyl-galactal **197** with $InCl_3$ (20 mol %) in a mixture of CH_3CN/H_2O (9:1) at 70 ^oC led to the facile transposition of the allylic hydroxyl group, which resulted in the formation of 2-*C*-methylene hexose **229**. Reduction of **229** with $NaBH_4$ followed by treatment of resulting diol with MsCl afforded dimesylate. The obtained dimesylate was treated with a variety of primary amines, affording piperidine derivatives **230** and **231** through double nucleophilic substitutions reaction (Scheme 1.50).[80]



197 **229**

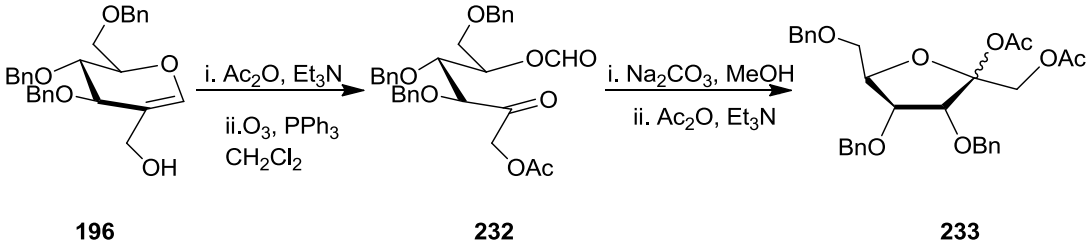
230 R = Bn, 82 %
231 R = Bu, 92 %

Scheme 1.50: Synthesis of 2-*C*-methylene azasugars through a double nucleophilic substitution reaction.

1.5.10 Synthesis of D-fructofuranose from 2-*C*-formyl-glucal

K. K. Balasubramanian and co-workers reported the conversion of an aldopyranose to a ketohexo furanose *via* a novel [6+1-1] strategy.[81] Their synthetic route involves conversion of the compound **196** to acetate **198** in two steps by using literature protocol. Then ozonolysis

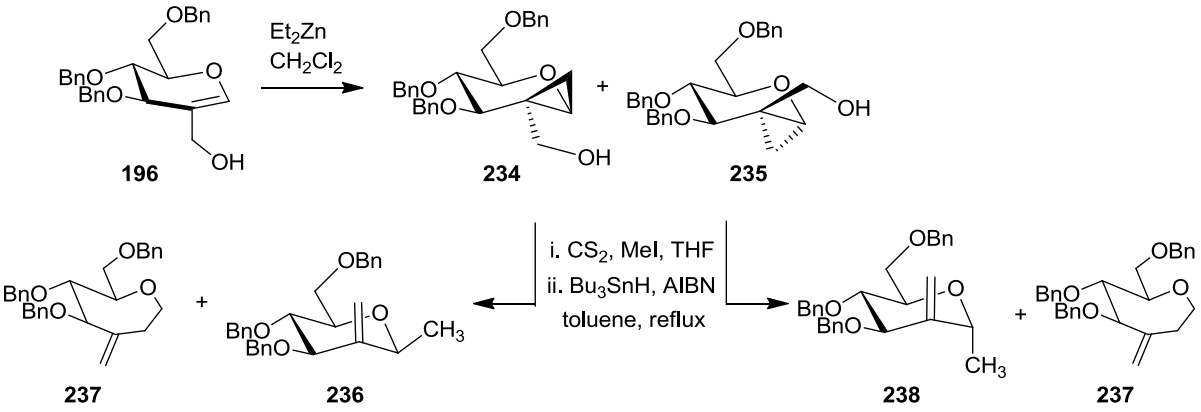
of the enol ether double bond of **198** gave the keto ester **232**. Base hydrolysis of the ester groups in **232** resulted in concomitant cyclization to give the protected ketohexo furanose derivative, which was characterized as diacetate **233** after acetylation (Scheme 1.51).



Scheme 1.51: Synthesis of functionalized ketohexofuranose from 2-*C*-formyl-glucal.

1.5.11 Radical ring opening of 1, 2-cyclopropanated derivatives derived from 2-*C*-formyl-glucal

Using the 2-hydroxymethylglucal derived cyclopropanes **234** and **235**, Kar and co-workers[82] reported the synthesis of 2-*C*-methylene-*C*-methyl glycosides **236** and **238** and an oxepane derivative **237** through Bu_3SnH-mediated radical reaction. Thus, cyclopropyl derivatives **234** and **235** were synthesized from 2-hydroxymethylglucal derivative **196** using Simmons-Smith cyclopropanation reaction conditions (Et_2Zn/CH_2I_2). Further alcohol **234** was converted into xanthate by using known procedures, followed by Bu_3SnH-mediated radical ring opening of the cyclopropyl ring, resulted in the formation of the 2-*C*-methylene-β-*C*-methyl glycoside **236** along with oxepane derivative **237** in an almost 1:1 ratio (Scheme 1.52). In a similar fashion, cyclopropyl derivative **235** afforded 2-*C*-methylene-α-*C*-methyl glycoside **238** along with oxepane derivative **237**.



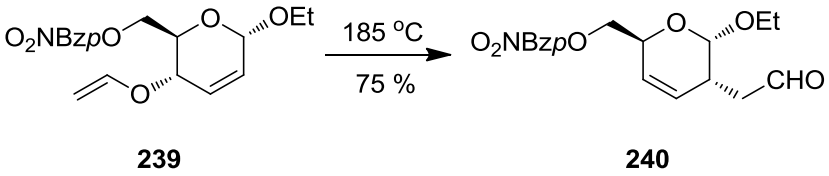
Scheme 1.52: Synthesis of 2-*C*-methylene-*C*-methyl glycosides and an oxepane derivative.

In addition to the above mentioned protocols for the synthesis of *C*-branched sugars, Claisen rearrangement of carbohydrate derived allyl vinyl and allyl aryl ethers provides *C*-branched sugars at various positions of pyranose ring.

1.6 Synthesis of *C*-2, *C*-3, *C*-4 and *C*-5 branched sugars using 3,3-sigmatropic rearrangement

1.6.1 *C*-2 branched sugars

The products obtained by Ferrier rearrangement of *endo*-glycals with nucleophiles have been used as starting materials for the synthesis of *C*-2 branched sugars. Interestingly, this was the first Claisen rearrangement in carbohydrate chemistry reported by Ferrier and Vethaviyasar.[83] Their synthetic approach involves, heating of 2,3-unsaturated allyl vinyl ether **239** at 185 °C, which gave the corresponding *C*-2-branched aldehyde **240** in 75 % yield..

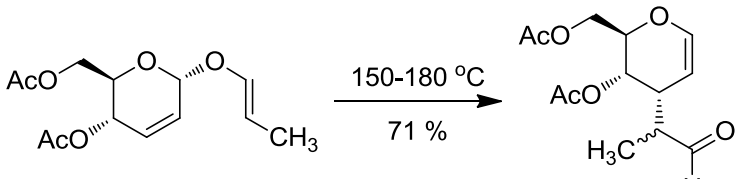


239 **240**

Scheme 1.53: Synthesis of *C*-2-branched sugars using Claisen rearrangement of allyl vinyl ether.

1.6.2 *C*-3 branched sugars

Synthesis of *C*-3 branched sugars with the involvement of anomeric position were described by Heyns and Hohlweg, [84] de Raadt and Ferrier, [85] Descotes and co-workers.[86] Among those, Ferrier approach involves heating of the propenyl glycoside **241** at 150-180 °C



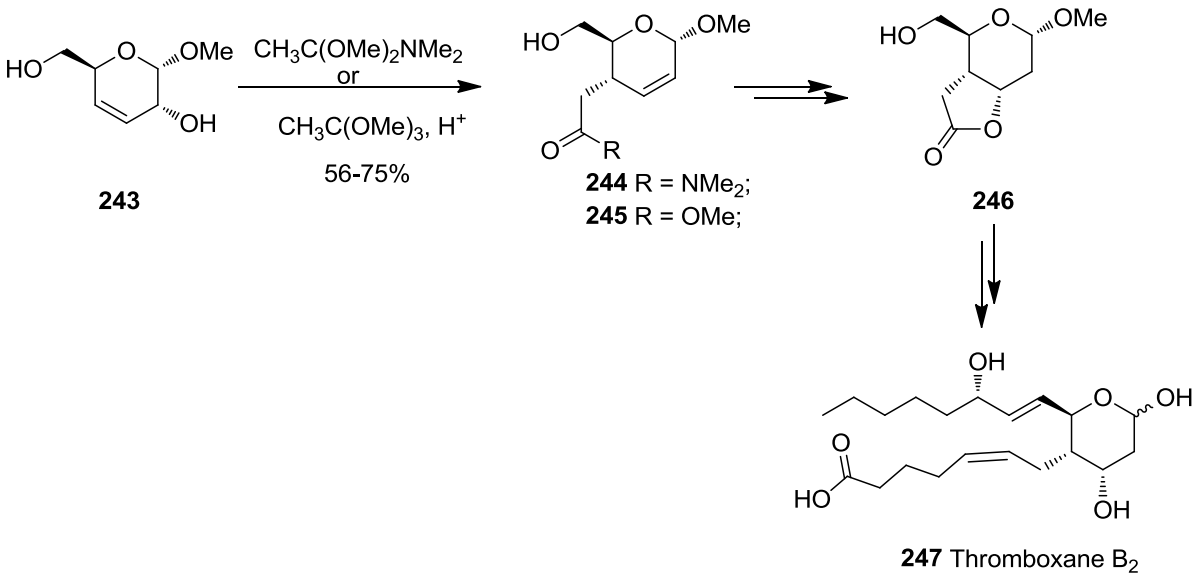
241 **242**

Scheme 1.54: Synthesis of *C*-3-branched sugars using Claisen rearrangement of propenyl glycoside.

to provide the corresponding 3-*C*-branched sugar derivative **242** in 71 % yield (Scheme 1.54). Later, K. K. Balasubramanian and co-workers [87] extended the same protocol to phenyl glycosides.

1.6.3 *C*-4 branched sugars

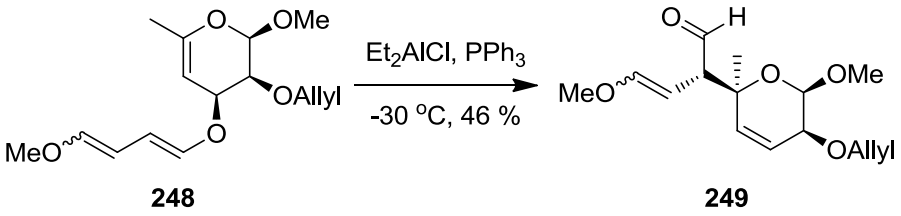
Conversion of 3,4-unsaturated glycosides to *C*-4 branched sugar derivatives through Claisen rearrangement was first described independently by Corey *et al*.,[88] and Hernandez.[89] Their synthetic approach involves the conversion of allylic alcohol **243** to the respective amide **244** or ester **245** using Eschenmoser amide acetal or Johnson orthoester rearrangements, respectively. Corey and co-workers further converted this amide or ester to corresponding lactone **246,** which was utilized previously for the total synthesis of thromboxane B_2 **247** (Scheme 1.55). Later, Fleet and co-workers [90] utilized the same approach for the synthesis of (*S*)-quinuclidinol.



Scheme 1.55: Synthesis of *C*-4-branched sugars using Eschenmoser amide acetal and Johnson orthoester rearrangements.

1.6.4 *C*-5 branched sugars

Vatele *et al*, synthesized the *C*-5 branched sugar **249** [91] by utilizing the Claisen rearrangement of 4,5-unsaturated glycoside **248** (Scheme 1.56) with the aim of total synthesis of antibiotic and antitumour agent nogalomycin.



248 **249**

Scheme 1.56: Synthesis of *C*-5 branched sugars by Claisen rearrangement of 4,5-unsaturated sugars.

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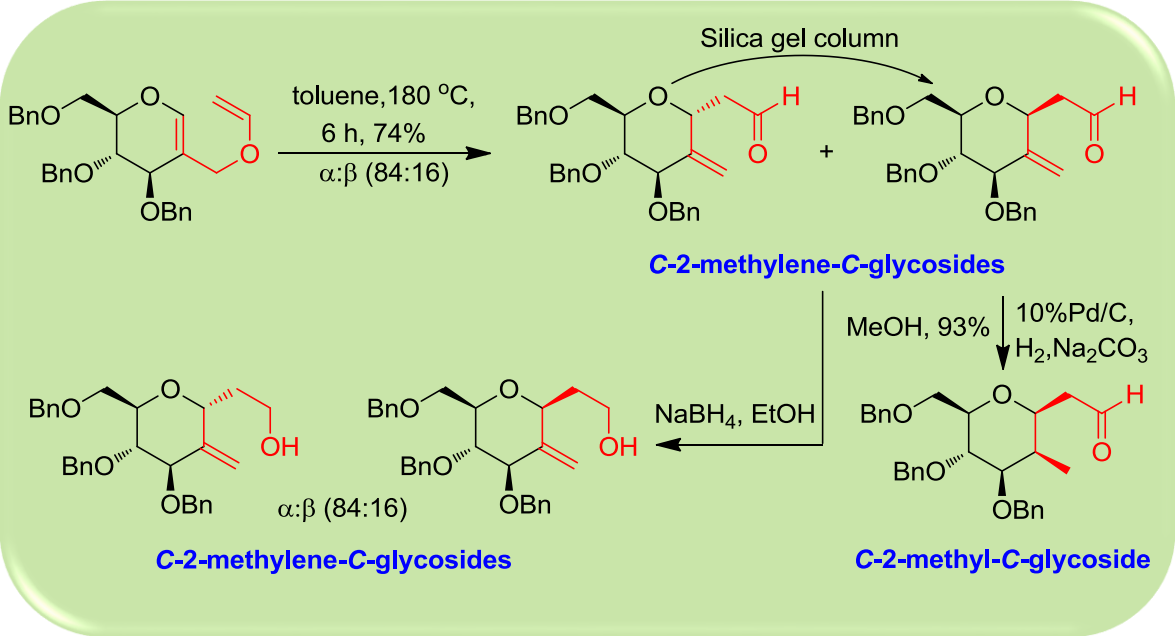
Stereoselective Synthesis of *C*-2-Methylene and *C*-2-Methyl-*C*-Glycosides by Claisen Rearrangement of 2-Vinyloxymethyl Glycal

ABSTRACT: This chapter describes an efficient methodology for the stereoselective synthesis of *C*-2-methylene-α- and -β-*C*-glycosides by Claisen rearrangement of 2-vinyloxymethyl glycal derivatives with a plausible mechanism for the formation of α-selective-*C*-glycoside along with the extended methodology to the high diastereoselective synthesis of *C*-2-methyl-*C*-glycosides.



2.1 Introduction

Carbon branched sugars, in which the hydroxyl groups on pyranose/furanose ring is replaced with carbon are widely present in a number of natural products. Notably, *C*-2-methyl analogues of nucleosides have shown potential inhibitory activity against hepatitis C viral RNA replication.[1] On the other hand, *C*-2-methylene- and *C*-2-methyl-*C*-glycoside derivatives exist ubiquitously in nature as subunits of several highly bioactive natural products such as spliceostatins, spongistatins, phorboxazoles, brevenal, brevetoxin, gambieric acids and

halichondrins *etc*.,(Figure 2.1). One of the widely used approaches for stereoselective construction of *C*-glycosides is Claisen or Ireland-Claisen rearrangement[2] of glucal derived allyl vinyl ethers that has been discussed extensively in the literature.[3,4] A portion of this is conferred in the introduction chapter (Chapter 1). Due to the intriguing features of the Claisen-[3,3]-sigmatropic rearrangement reaction, it has been utilized to provide key intermediates for the total synthesis of a number of natural products possessing *C*-2,[5] *C*-3,[6] *C*-4,[7] *C*-5[8] carbon branched carbohydrate framework.

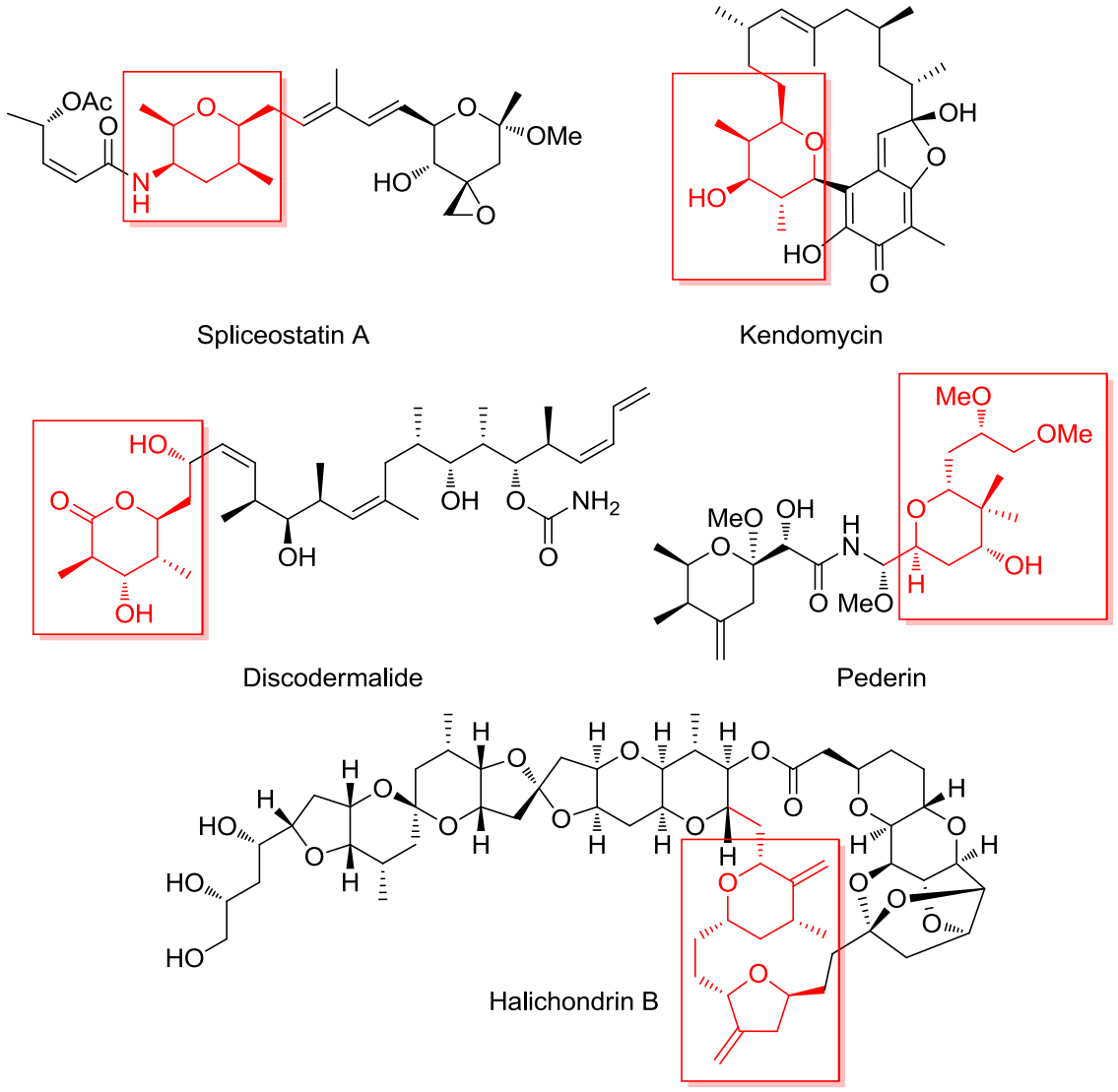
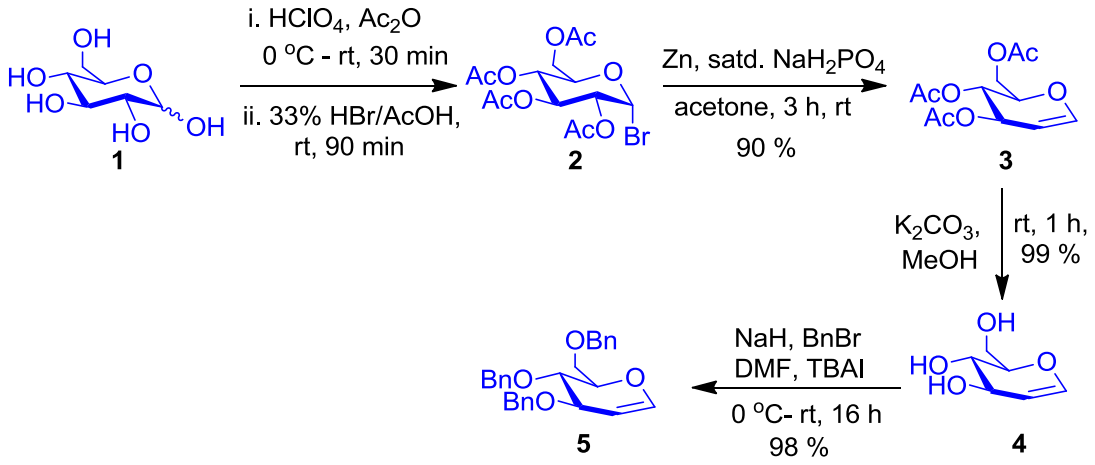


Figure 2.1: Some of the Bio active natural products containing *C*-2-methylene and *C*-2-methyl *C*-glycosides.

Surprisingly, all the reported Claisen rearrangement (CR) reactions involving carbohydrate moieties with *endo*-cyclic allyl alcohol include at least one chiral centre in the rearrangement sequence, which directs the stereochemical course of the newly generated stereocentres. In our interest towards the stereoselective synthesis of *C*-branched sugars,[9] we envisaged that CR of glycal derived ally vinyl moieties might provide a straight forward access to the formation of *C*-2-methylene-*C*-glycosides, intern offer an access to the preparation of 2-*C*-branched-*C*-glycosides. Even though, no chiral centre is involved in the rearrangement sequence, we anticipated the reaction to proceed in a stereoselective fashion due to the concerted nature, highly organized transition state in CR reactions and the influence of additional stereocentres in the molecule. Chemoselective hydrogenation of *C*-2-methylene group further provides an efficient route for the diastereoselective preparation of *C*-2-methyl-*C*-glycosides.

2.2 Results and Discussion

2-*C*-formyl glycals used in the present chapter, were prepared from the readily available carbohydrates (D-glucose, D-galactose, L-rhamnose, D-xylose, D-arabinose and L-arabinose) by using the previously reported literature protocols.[10] The conversion of D-glucose to D-glucal was conducted by adopting the methodology pioneered by Fisher[11] and refined by others.[12] The peracetylation of D-glucose **1** with acetic anhydride and catalytic perchloric acid gave the clear solution of penta-*O*-acetyl-D-glucose, which was directly treated with hydrobromide in acetic acid to provide the 2,3,4,6-tetra-*O*-acetyl-D-glycosyl bromide **2**.

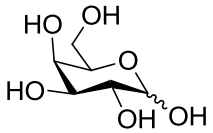
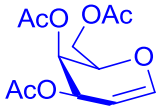
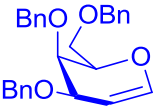
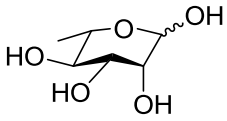
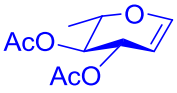
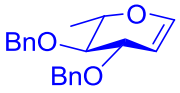
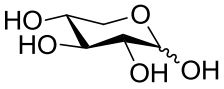
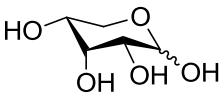
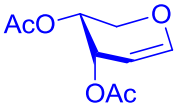
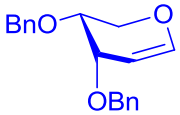
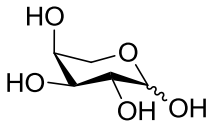
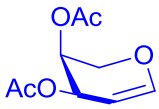
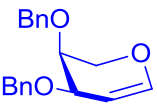


Scheme 2.1: Preparation of the 3, 4, 6-tri-*O*-benzyl-D-glucal from the D-glucose.

The reductive elimination of **2** with Zinc and saturated NaH_2PO_4 gave the 3,4,6-tri-*O*-acetyl-D-glucal **3** in good yield.[13] To incorporate the appropriate protecting groups in **3**, acetyl groups were deprotected using K_2CO_3 in methanol to give D-glucal **4,**[14] which upon benzylation with benzyl bromide and sodium hydride to provide the 3,4,6-tri-*O*-benzyl-D-glucal **5** (Scheme 2.1).

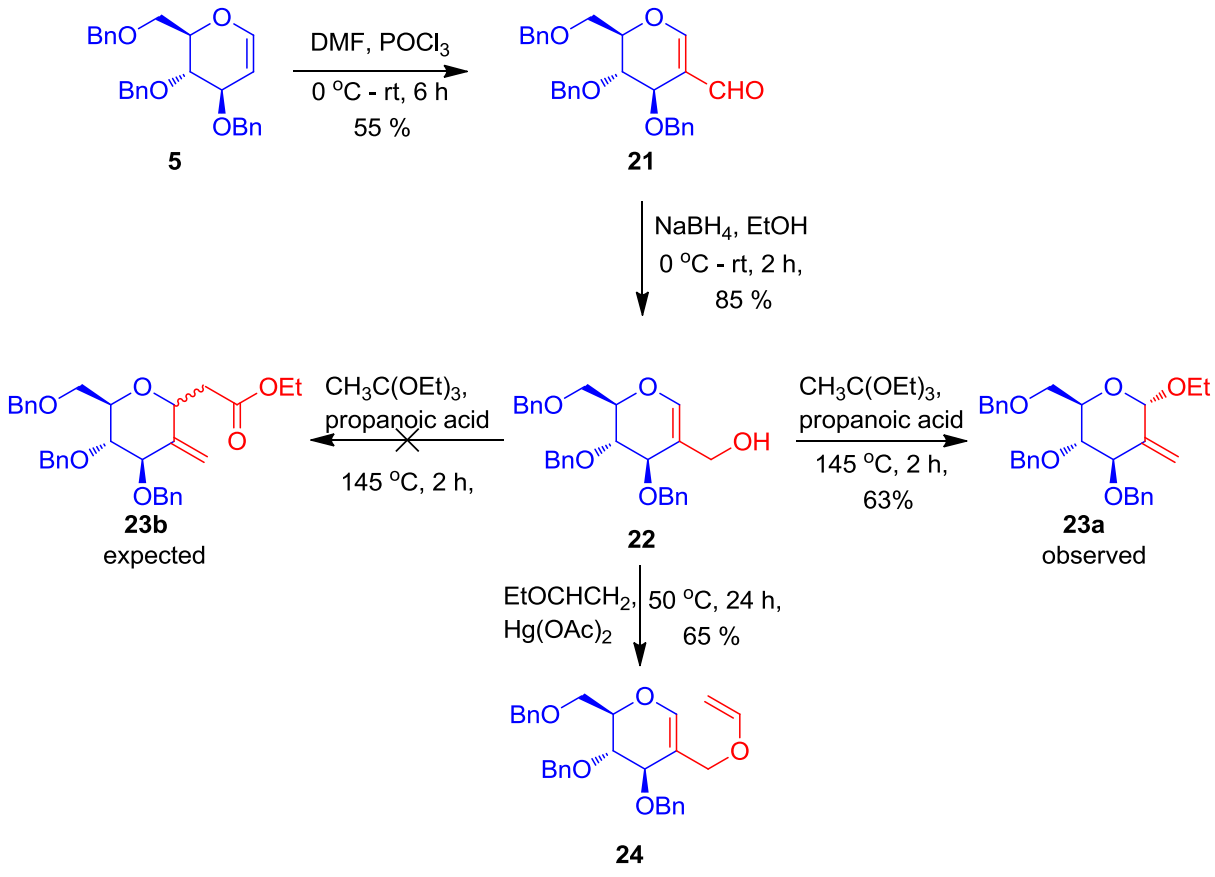
Similarly, using the above protocol 3,4,6-tri-*O*-benzyl-D-galactal **8** and 3, 4-di-*O*-benzyl-L-rhamnal **11**, 3, 4-di-*O*-benzyl-D-xylal **14**, 3, 4-di-*O*-benzyl-D-arabinal **17** and 3,4-di-*O*-benzyl-L-arabinal **20** were synthesized in good yields from the D-galactose **6**, L-rhamnose **9**, D-xylose **12**, D-arabinose **15** and L-arabinose **18** *via* the tri and di acetyl glycals **7**, **10**, **13**, **16** and **19**, respectively (Table 2.1). These five protected glycals were used as substrates for the Vilsmeier-Haack formylation reaction.

Table 2.1: Synthesis of protected glycals from the corresponding sugar precursors.

entry	carbohydrate	peracetyl glycal (%)[a]	perbenzyl glycal (%)[a]
1	 **6**	 **7** (81 %)	 **8** (98 %)
2	 **9**	 **10** (87 %)	 **11** (95 %)
3	 **12**	 **13** (76 %)	 **14** (97 %)
4	 **15**	 **16** (90%)	 **17** (96 %)
5	 **18**	 **19** (90 %)	 **20** (96 %)

[a] Yield refers to pure isolated products after two steps.

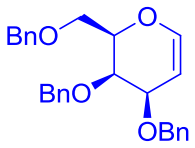
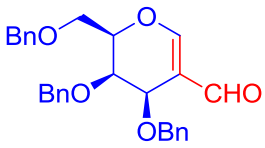
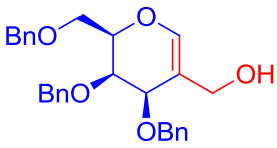
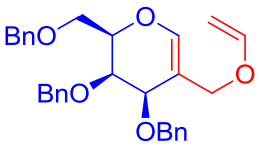
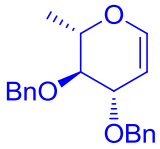
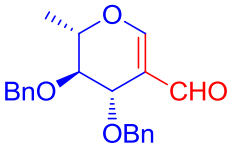
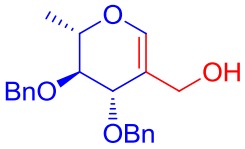
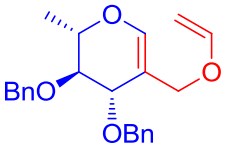
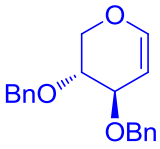
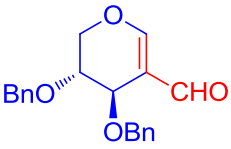
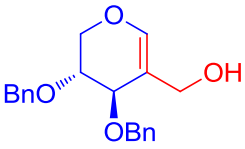
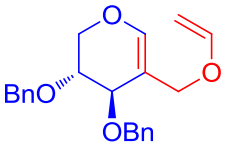
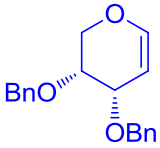
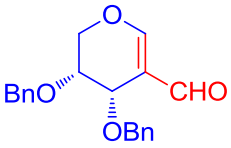
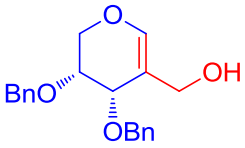
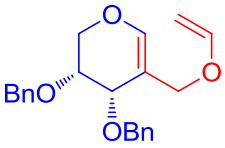
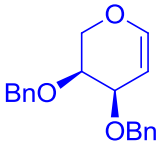
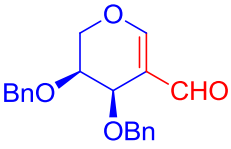
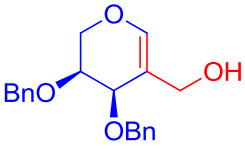
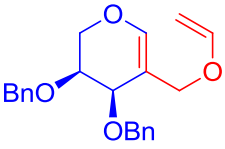
Thus, formylation of 3,4,6-tri-*O*-benzyl-D-glucal under Vilsmeier-Haack conditions ($POCl_3$, DMF)[10a] gave the corresponding (2*R*,3*S*,4*R*)-3,4-bis(benzyloxy)-2-((benzyloxy)methyl)-3,4-dihydro-2*H*-pyran-5-carbaldehyde **21** in 55 % yield. Reduction of the aldehyde function with sodiumborohydride in ethanol gave the corresponding alcohol ((2*R*,3*S*,4*R*)-3,4-bis(benzyloxy)-2-((benzyloxy)methyl)-3,4-dihydro-2*H*-pyran-5-yl)methanol **22**[15] in 85 % yield. Initially, we had attempted Johnsonorthoester rearrangement on **22** with triethylorthoacetate and propionic acid as catalyst by heating at 145 °C for 2 h but, unfortunately the expected orthoester rearranged product **23b** was not observed instead, simple *C*-2-methylene-*O*-glycoside **23a** was obtained in 63% yield. So, in an alternative protocol for the synthesis of *C*-glycoside skeleton, compound **22** was transvinylated with catalytic amount of $Hg(OAc)_2$ in ethylvinyl ether to obtain the required precursor 2-vinyloxymethyl glucal derivative **24**[16, 17] in 65 % yield (Scheme 2.2).



Scheme 2.2: Synthesis of 2-vinyloxymethyl glucal.

In a similar fashion Vilsmeier-Haack formylation of glycal derivatives **8**, **11**, **14**, **17** and **20** provided the 2-*C*-formyl glycals **25**, **28**, **31**, **34** and **37** in moderate yield. Further conversion of these aldehydes to the alcohols **26**, **29**, **32**, **35** and **38** followed by $Hg(OAc)_2$ catalyzed vinylation provided the glucal derived allylvinyl ethers **27**, **30**, **33**, **36** and **39**, respectively in good yield (Table 2.2).

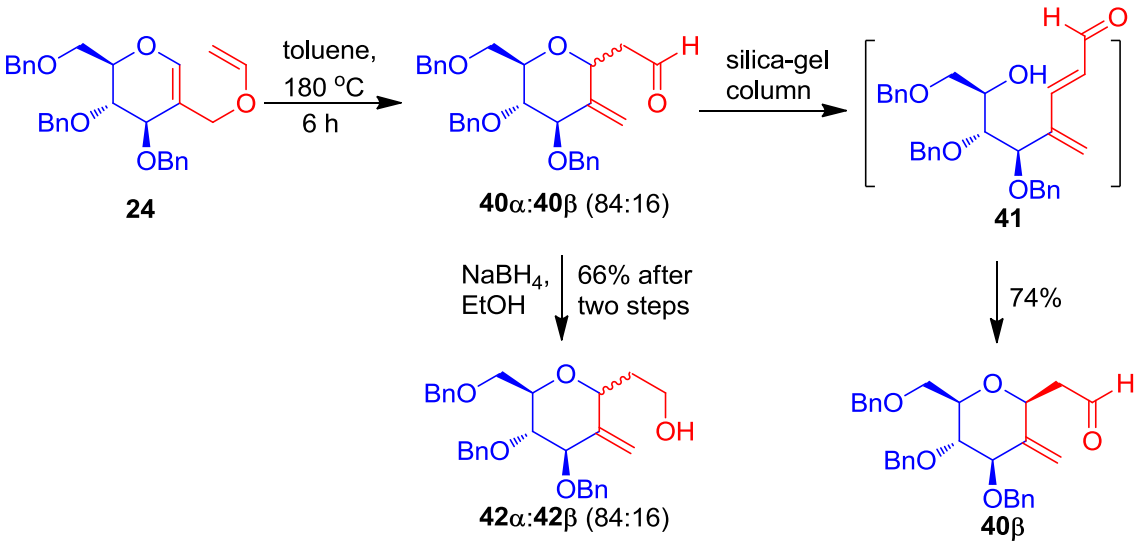
Table 2.2: Synthesis of 2-vinyloxymethyl glycal derivatives.

entry	glycal	2-*C*-formyl glycal (%)[a]	2-hydroxymethyl glycal (%)[a]	2-vinyloxymethyl glycal (%)[a]
1	 **8**	 **25** (85 %)	 **26** (85 %)	 **27** (61%)
2	 **11**	 **28** (50 %)	 **29** (82 %)	 **30** (63 %)
3	 **14**	 **31** (44 %)	 **32** (80 %)	 **33** (54 %)
4	 **17**	 **34** (73 %)	 **35** (80 %)	 **36** (50 %)
5	 **20**	 **37** (73 %)	 **38** (80 %)	 **39** (50 %)

[a]Yield refers to pure and isolated products.

2.2.1 Synthesis of *C*-glycosides from 2-vinyloxymethyl glucal

After having a series of glycal derived allyl-vinyl ethers, we focused our attention to implement the Claisen rearrangement reaction on these precursors. Thus, a solution of compound **24** in toluene was heated in a sealed tube at 180 °C for 6 h.[16] The reaction produced the expected *C*-2-methylene-*C*-glycosides **40α** and **40β** in 84:16 ratio, respectively.[17,18] Interestingly, the α-anomer **40α** was found to be very unstable and converted to the β-anomer **40β**[19] in the purification process using silicagel column chromatography, probably *via* ring opening to form α,β-unsaturated aldehyde **41** followed by intramolecular *oxa*-Michael addition reaction. Whereas, direct reduction of the obtained crude aldehyde mixture (**40α** and **40β**) with $NaBH_4$/EtOH at -10 °C produced the corresponding alcohols **42α** and **42β** in 84:16 ratio, respectively (Scheme 2.3).



Scheme 2.3: Claisen-rearrangement of 2-vinyloxymethyl glucal derivative.

2.2.2 Plausible mechanism for the formation of *C*-glycosides

The formation of major α-*C*-glycoside can be explained by considering the following facts. (a) Due to the vinylogous anomeric effect,[20] an oxocarbenium ion formation can be visualized during the course of the rearrangement. (b) The electrostatic stabilization of oxocarbenium ion by C-3 and C-4 alkoxy groups assume pseudo axial positions in their half chair conformation.[21] (c) The nucleophilic attack on six membered ring oxocarbenium ion occur

through chair like transition state preferably along axial trajectory.[22] Thus, for both the possible conformations, $^{5}H_{4}$ **24a** and $^{4}H_{5}$ **24b**, the CR will have an early transition state with bond breaking well in advanced with respect to bond making that may lead to the formation of ionic resonance structures **43a** and **43b**. For transition state **43a**, the approach of nucleophilic carbon on to oxocarbenium ion along the stereochemically preferred axial trajectory endure *syn*-pentane interaction[23] that builds up between the nucleophile and substituent on C-5 as well as smaller *syn*-butanol[24] interaction with substituent on C-3. Due to these interactions, the transition state **43a** *via* $^{5}H_{4}$ is destabilized compared to the transition state **43b** *via* $^{4}H_{5}$ in the reaction coordinate. As a result, the formation of *C*-2-methylene-α-*C*-glycoside **40α** is major through the lowest-energy transition sate, namely *via* $^{4}H_{5}$.

However, compound **40α** suffer with 1,3-diaxial interaction, that drives to form α,β-unsaturated aldehyde derivative **41** which might further undergo intramolecular *oxa*-Michael addition reaction to give stable *C*-2-methylene-β-*C*-glycoside **40β** during the purification process (Figure 2.2). On the other hand, the direct reduction of the crude aldehyde mixture provides the corresponding *C*-2-methylene-*C*-glycosides **42α** and **42β** in 84:16 ratio respectively, reflecting the ratio in the crude aldehyde mixture.

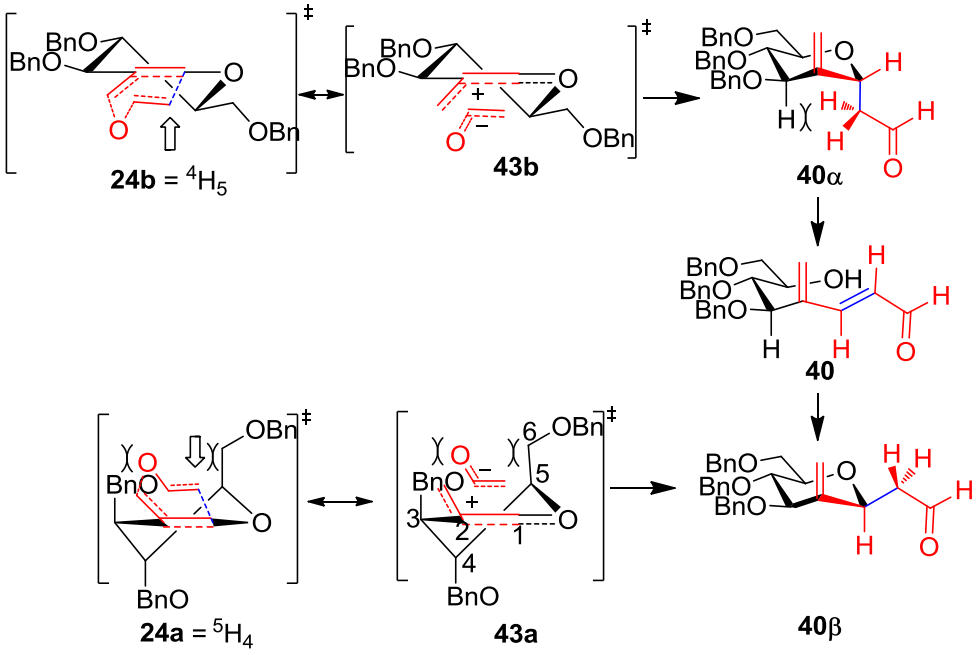


Figure 2.2: Proposed mechanism for the Claisen rearrangement of 2-Vinyloxymethyl glucal derivative.

2.2.3 Stereochemical assignment of *C*-2-methylene-*C*-glycosides

The structure of the C-2 methylene-C-glycosides was assigned based on the 2D NMR studies. In the case of β-*C*-glycoside **40**β, the stereochemistry at C-1 position was confirmed by observing a strong NOE correlation between axial C-1 proton with axial C-5 proton and axial C-3 proton (1,3-diaxial interactions). Where as in the case of α-*C*-glycoside **42**α, the stereochemistry at C-1 was confirmed based on the strong NOE correlation between C-1 proton with one of the proton present at C-6 and also CH_2 protons (C-7) with axial C-5 and C-3 protons (Figure 2.3).

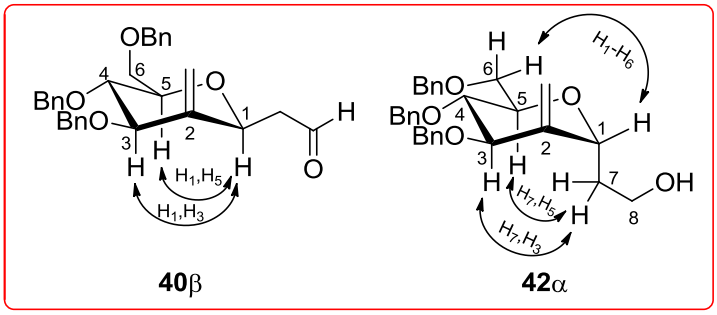
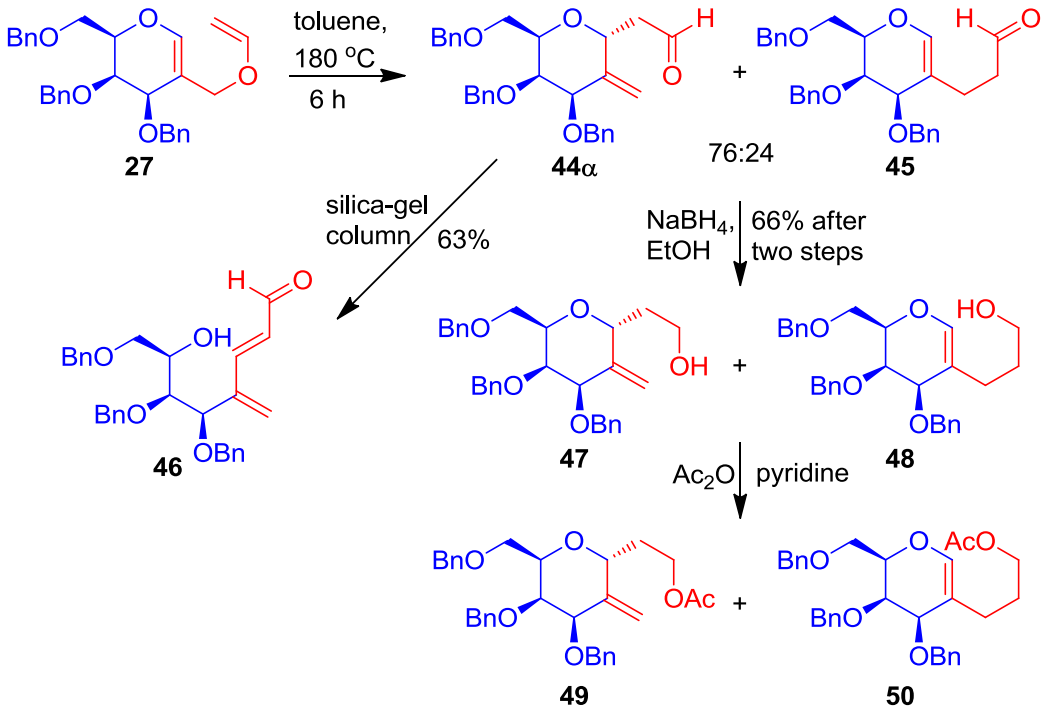


Figure 2.3: Assignment of the stereochemistry of C-2-methylene α- and β-*C*-glycosides.

Interestingly, galactose derived vinyl ether **27** upon CR provided a mixture of aldehyde **44**α as a single diastereomer along with unexpected aldehyde **45** in a ratio of 76:24 respectively. However, column chromatography of this mixture over silicagel provided only the ring opened α,β-unsaturated aldehyde derivative **46**.[25] A one-pot CR followed by reduction of the crude aldehyde provided alcohols **47** and **48**. Due to the difficulty in separation of this alcoholic mixture, the crude product was acetylated to provide galactose derived *C*-2-methylene-*C*-glycoside **49** as a single diastereomer along with the *C*-2 alkylated galactal derivative **50** (Scheme 2.4).

The observation of unexpected aldehyde **45** supports the formation of fully separated ionic resonance structures in the proposed mechanism. As can be expected, the transition state **27a** with $^5H_4$ conformation will lead to the ionic resonance structure **51a**. The nucleophilic attack



Scheme 2.4: Claisen-rearrangement of 2-vinyloxymethyl galactal derivative.

at anomeric position (path a) *via* **51a** suffers with higher steric strain that prohibits the formation of *C*-2-methylene-β-*C*-glycoside **44β**. On the other hand, nucleophilic attack at less hindered site through a (1, 3)-sigmatropic rearrangement (path b) leads to the formation of aldehyde **45** (Figure 2.4). This reaction provides ample evidence about the formation of ionic resonance structure in the Claisen rearrangement reaction along with the concerted mechanism.

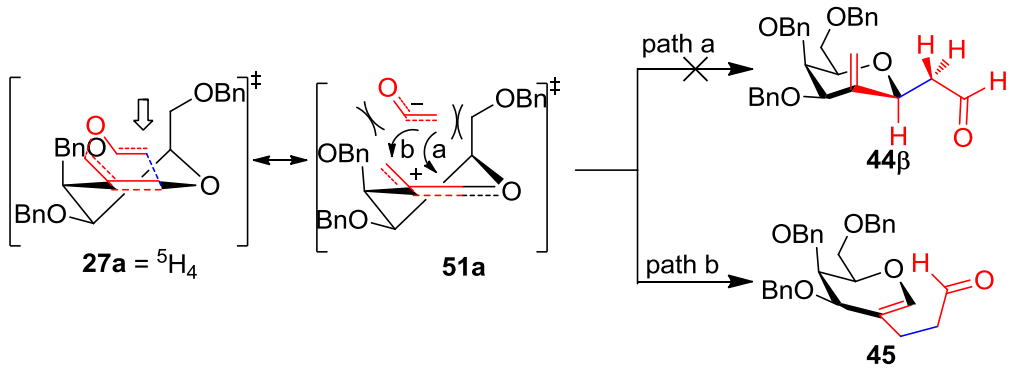
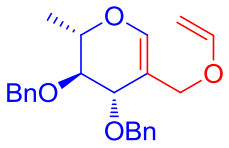
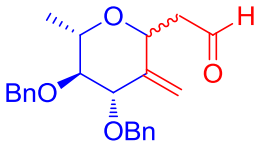
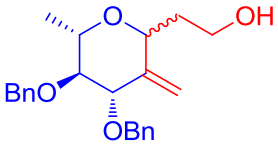
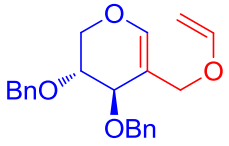
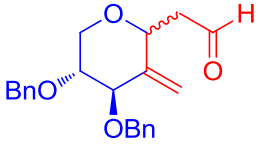
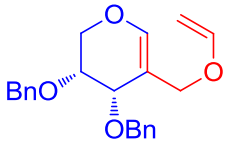
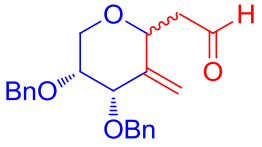
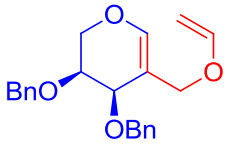
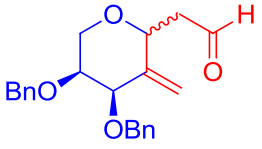


Figure 2.4: Proposed mechanism for the unexpected formation of C-2-alkyl galactal derivative **45** under Claisen rearrangement reaction conditions.

The generality of the reaction has been proved successfully by applying to a number of 2-vinyloxymethyl-glycal derivatives. Thus, rhamnal derived allylvinyl ether **30** upon CR provided the corresponding C-2-methylene-*C*-glycosides **52α** and **52β** in 87:13 ratio, respectively in good yield (Table 2.1, entry 1). Again, a similar kind of anomerization mentioned in the case of **40α** was observed while carrying out the purification over silicagel leading to the formation of **52β** as a single diastereomer.

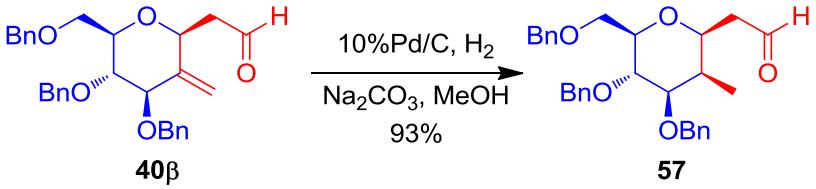
Table 2.3: Synthesis of *C*-2-methylene-*C*-glycosides.

entry	vinyl ether	*C*-2-methylene *C*-glycoside (%)[a]	α:β ratio
1	 **30**	 **52**α:**52**β (88)[b]	87:13
2	**30**	 **53**α:**53**β (85)[c]	87:13
3	 **33**	 **54**α:**54**β (73)	50:50
4	 **36**	 **55**α:**55**β (73)	50:50
5	 **39**	 **56**α:**56**β (72)	50:50

[a]Yield represents pure and isolated products. [b]The mixture upon column chromatogrphy provided only 51β as a single diastereomer. [c]The vinyl ether was subjected to CR and the obtained crude product was directly reduced with $NaBH_4$/EtOH.

2.2.4 Synthesis of *C*-2-methyl-*C*-glycosides

The importance of the methodology was further enhanced by applying it to synthesize a series of *C*-2-methyl-*C*-glycosides. Thus, *C*-2-methylene-β-*C*-glycoside **40β** was hydrogenated with 10%Pd/C, H_2 in MeOH in presence of Na_2CO_3[26] to provide *C*-2-methyl-β-*C*-glycoside **57** as a single diastereomer in excellent yield, 93% (Scheme 2.5).



40β **57**

Scheme 2.5: Synthesis of glucose derived *C*-2-methyl-β-*C*-glycoside.

2.2.5 Stereochemical assignment of *C*-2-methyl *C*-glycosides

The 1,2-*cis* and 1,2-*trans* relationship in *C*-2-methyl-*C*-glycoside **57** was confirmed by 2D NMR experiments. The 1,2-*cis* configuration in compound **57** was confirmed by observing the NOE between three 1,3-diaxial which are present at C-1, C-3 and C-5 positions (Figure 2.5).

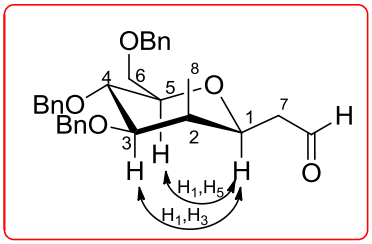
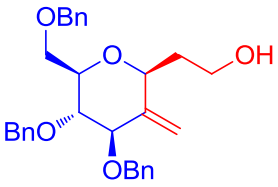
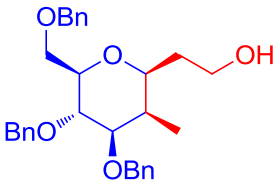
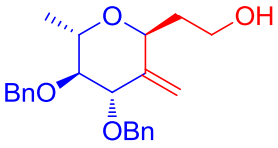
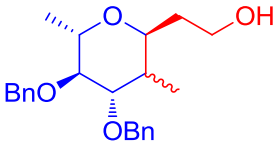
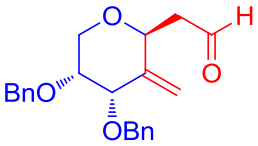
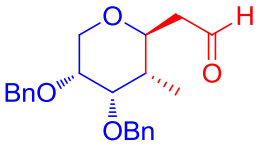
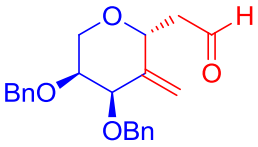
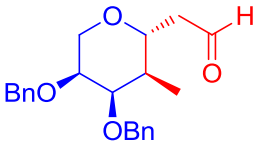


Figure 2.5: Assignment of stereochemistry of *C*-2 methyl group of α- and β-*C*-glycosides.

Further, application of the selective hydrogenation protocol to other C-2-methylene-*C*-glycosides **42β, 53α, 55α** and **56α** also provided *C*-2-methyl-*C*-glycosides **58-61** in excellent yield with very high diastereoselectivity (Table 2.4).

Table 2.4: Synthesis of *C*-2-methyl-*C*-glycosides.

entry	C-2-methylene *C*-glycoside	*C*-2-methyl *C*-glycoside (%)[a]	1,2-*cis*:1,2-*trans*
1	 **42**β	 **58**(75)	100:0
2	 **53**α	 **59**(92)	15:85
3	 **55**α	 **60** (58)	0:100
4	 **56**α	 **61** (67)	0:100

[a]Yield represents to pure and isolated products.

2.3 Summary and conclusion

In conclusion, an efficient methodology for the stereoselective synthesis of C-2-methylene-*C*-glycosides as well as *C*-2-methyl-*C*-glycosides was developed. Importantly, the method is applicable to synthesize α- as well as β-*C*-glycosides in a stereoselective fashion. This novel method may provide an easy access to the synthesis of natural products possessing carbon branched sugar subunits.

2. 4 Experimental Section

2.4.1 Materials and Methods

Chemicals and solvents were purchased from the local suppliers and Sigma-Aldrich®chemical company. Solvents were used in the reactions after distilled over the dehydrating agents. All the reactions were carried out underN_2or Ar conditions and monitored by the thin layer chromatography (TLC) using silica-gel on aluminum plates (GF_{254}) by charring with 5% (v/v) H_2SO_4 in methanol or by phosphomolybdic acid (PMA) stain or by ultra violet (UV)detection. Silica-gel (100-200 mesh) was used for column chromatography to purify the all the compounds. ^1H, ^{13}C, DEPT spectra were recorded on Bruker® 400 Avance MHz spectrometer in $CDCl_3$. ^1H NMR chemical shifts were reported in parts per million (ppm) (δ) with TMS as an internal standard (δ 0.00) and ^{13}C NMR were reported in chemical shifts with solvent reference ($CDCl_3$, δ 77.00).Infrared (IR) spectra were recorded with a JASCO FT/IR-5300 pulse Fourier transform infrared spectrometer. High resolution mass spectra (HRMS) were recorded with a Bruker maXis ESI-TOF spectrometer.

2.4.2 General Experimental Procedures and Spectral Data

(2.4.2.1) General procedure for the preparation of 2-*C*-formyl glycal derivatives:

To a solution of dry DMF (2 mL) and $POCl_3$ (3 mmol) at 0 ^oC was added a precooled solution of glycal (1 mmol) in of dry DMF (2 mL) dropwise for about 30 min. The mixture was allowed to stir for 5-6 h at room temperature. After complete disappearance of starting material (by TLC) the reaction was quenched with aq $NaHCO_3$ (sat) solution and diluted with diethylether. The organic layer was separated and the aqueous layer was extracted with diethyl ether. The combined ether layers were washed with brine solution, dried over anhydrous Na_2SO_4 and concentrated. The crude thus obtained was purified by column chromatography to yield 2-*C*-formyl glycal derivatives as pale yellow coloured gummy compounds in 60-80% yield.

(2.4.2.2) General procedure for the preparation of 2-hydroxymethyl glycal derivatives:

To a stirred solution of 2-*C*-formyl glycal (1 mmol) in dry ethanol (4 mL) at 0^oC, was added solid $NaBH_4$ (1.5 mmol) and the stirring was continued for 3 h. After completion of the reaction (by TLC), it was quenched with saturated NH_4Cl solution. Ethanol was evaporated

under reduced pressure and aqueous suspension was extracted with dichloromethane (2x50mL). The combined organic layers were washed with water, brine solution, dried over anhydrous $NaSO_4$and concentrated. The obtained crude product was purified by silica-gel column chromatography to give 2-hydroxymethyl glycal derivatives in 85-95 % yield.

(2.4.2.3) General procedure for the preparation of 2-vynyloxymethyl glycal derivatives:

A mixture of primary alcohol (0.2 mmol), ethyl vinyl ether (3 mL, freshly distilled over sodium) and mercuric acetate (0.05 mmol) was stirred at reflux under an argon atmosphere. After 24 h the reaction was cooled to RT, and acetic acid (2.98 μL) was added and stirring was continued for 3h at RT. The mixture was diluted with an equal volume of hexane and washed with 5% aqueous KOH (2 X 5 mL), water (3 X 5 mL), with brine solution and concentrated under reduced pressure. The residue was purified using basic alumina to afford 2-vinyloxymethyl glycal derivatives as colourless gummy liquid in 45-60 % yield.

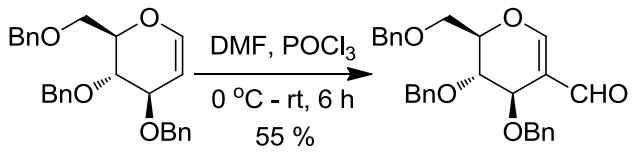
(2.4.2.4) General procedure for Claisen rearrangement reaction:

A solution of 2-vinyloxymethyl glycal derivative (1 mmol) in toluene (15 mL), was heated at 180-185 ^oC in sealed tube for 5-6 h. Cooling the reaction followed by evaporation of toluene over rotary evaporator and purification over silica-gel provided the *C*-2-methylene-*C*-glycoside derivatives in 60-80 % yield.

(2.4.2.5) General procedure for Selective hydrogenation of olefin:

To a stirred solution of olefin (0.2 mmol) in methanol (5 mL) was added Na_2CO_3, (0.2 mmol), 10% Pd/C (10 mg). The mixture was stirred for 4h under H_2 atmosphere. After completion of the reaction (by TLC) the suspension was filtered through a pad of Celite and concentrated *in vacuo* to afford the corresponding C-2-methyl-*C*-glycoside derivative as oil in 90-95% yield.

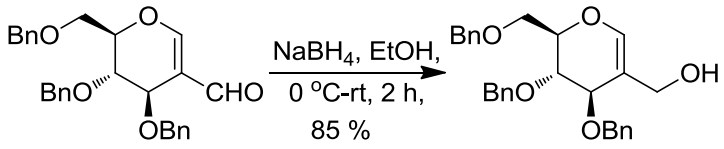
(2.4.2.6) (2*R*,3*S*,4*R*)-3,4-bis(benzyloxy)-2-((benzyloxy)methyl)-3,4-dihydro-2*H*-pyran-5carbaldehyde (21):



5 **21**

Compound **21** was synthesized using the 3, 4, 6-tri-*O*-benzyl-D-glucal **5** (2.0 g, 4.807 mmol), $POCl_3$ (14.423 mmol, 1.34 mL) in dimethylformamide according to the procedure in **(2.4.2.1)**. The crude product was purified by silica-gel column chromatography with ethyl acetate/hexane (3:7) to provide the **21** as a ight yellow oil (55 % yield).

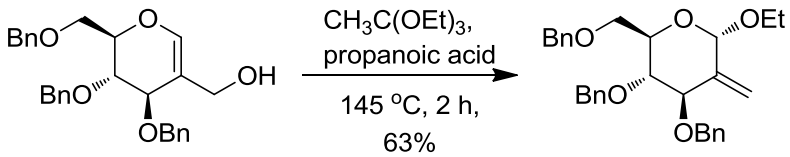
(2.4.2.7) ((2*R*,3*S*,4*R*)-3,4-bis(benzyloxy)-2-((benzyloxy)methyl)-3,4-dihydro-2*H*-pyran-5-yl)methanol (22):



21 **22**

Compound **22** was synthesized using the 2-*C*-formyl glucal **21** (1.0 g, 2.25 mmol), $NaBH_4$ (127 mg, 3.37 mmol,) in ethanol according to the procedure in **(2.4.2.2)**. The crude product was purified by silica-gel column chromatography with ethyl acetate/hexane (4:6) to provide the **22** as light yellow oil (85 % yield).

(2.4.2.8) (2*R*,3*S*,4*R*)-3,4-bis(benzyloxy)-2-((benzyloxy)methyl)-6-ethoxy-5-methylenetetrahydro-2*H*-pyran (23a):



22 **23a**

Allylic alcohol **22** (100 mg, 0.22 mmol), triethylorthoacetate (2.24 mmol, 0.4 mL), and propanoic acid (0.022 mmol, 1.66 µL) were combined in a round bottom flask equipped with magnetic stirring and a short path distillation apparatus. The mixture was heated at 145 °C for 2

h. The reaction mixture was diluted with ether and extracted with 10% HCl, Saturated $NaHCO_3$, water and brine. The resulting organic layer was dried over anhydrous Na_2SO_4, filtered and evaporated under reduced pressure, flash chromatography on silica-gel afforded product **23a** in 63% yield (67 mg). R_f = 0.56 (20% Ethylacetate/hexanes).

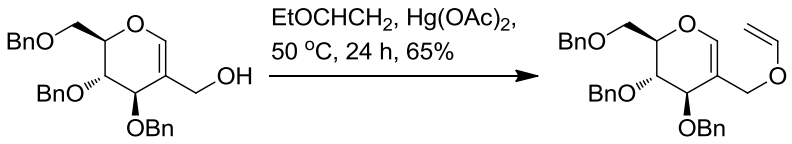
^{1}H (400 MHz, $CDCl_3$): δ 7.17-7.43 (m, 15H), 5.32 (s, 1H), 5.20 (s, 1H), 5.18 (s, 1H), 4.89 (d, *J* = 10.8 Hz, 1H), 4.79 (d, *J* = 11.2 Hz, 1H), 4.73 (d, *J* = 11.2 Hz, 1H), 4.65 (d, *J* = 12.4 Hz, 1H), 4.53 (d, *J* = 6.4 Hz, 1H), 4.48 (q, *J* = 15.6 Hz, 2H), 3.97 (m, 1H), 3.74-3.81 (m, 2H), 3.69-3.72 (dd, *J* = 2.0 Hz, *J* = 10.8 Hz, 1H), 3.62 (t, *J* = 9.2 Hz, 1H), 3.52 (m, 1H), 1.24 (t, *J* = 7.2 Hz, 3H). ppm.

^{13}C (100 MHz, $CDCl_3$): δ 142.5, 138.3, 138.3, 138.1, 128.4, 128.3, 128.3, 127.9, 127.8, 127.7, 127.6, 127.6, 110.3, 101.1, 81.3, 80.0, 75.0, 73.4, 73.4, 71.4, 68.8, 62.6, 15.0 ppm.

Low-resolution MS(EI): m/z: 474 (M^+).

HRMS (ESI) calcd for $C_{30}H_{34}O_5$+Na 497.2304, found 497.2305.

(2.4.2.9) (2*R*,3*S*,4*R*)-3,4-bis(benzyloxy)-2-((benzyloxy)methyl)-5-((vinyloxy)methyl)-3,4-dihydro-2*H*-pyran (24):



22 24

Compound **24** was synthesized using the 2-hydroxymethyl glucal **22** (0.8 g, 1.79 mmol), $Hg(OAc)_2$ (159 mg, 0.50 mmol,) in ethylvinylether according to the procedure in **(2.4.2.3)**. The crude product was purified by basic alumina column chromatography with ethyl acetate/hexane (1:9) to provide the **24** as colourless oil (65 % yield).

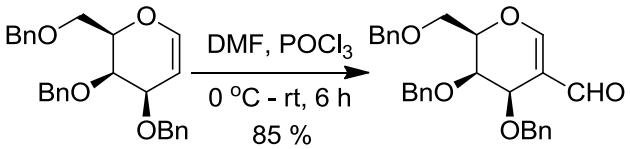
^{1}H (500 MHz, $CDCl_3$): δ 7.30-7.38 (m, 15H), 6.56 (s, 1H), 6.49 (dd, 1H, *J* = 7 Hz, *J* = 14.5 Hz), 4.82 (d, 1H, *J* = 13 Hz), 4.69 (d, 1H, *J* = 11 Hz), 4.68 (d, 1H, *J* = 11.5 Hz), 4.60 (d, 1H, *J* = 12.5 Hz), 4.58 (s, 2H), 4.44 (d, 1H, *J* = 11 Hz), 4.25-4.30 (m, 3H), 4.07 (dd, 1H, *J* = 2 Hz, *J* = 7 Hz), 4.00 (d, 1H, *J* = 11 Hz), 3.97 (dd, 1H, *J* = 5.5 Hz, *J* = 7 Hz), 3.84 (dd, 1H, *J* = 5.5 Hz, *J* = 11 Hz), 3.76 (dd, 1H, *J* = 3.5 Hz, *J* = 11 Hz) ppm.

^{13}C (125 MHz, $CDCl_3$): δ 151.2, 144.1, 138.1, 137.9, 137.9, 128.4, 128.3, 128.3, 128.1, 127.9, 127.8, 127.7, 127.6, 127.6, 127.5, 109.1, 87.2, 76.7, 74.5, 74.0, 73.3, 73.1, 72.8, 68.1, 66.2 ppm.

Low-resolution MS(EI): m/z: 472 (M^+).

HRMS (ESI) calcd for $C_{30}H_{32}O_5$+Na 495.2148, found 495.2148.

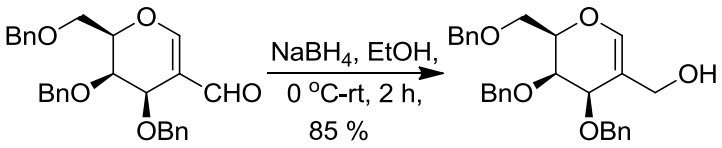
(2.4.2.10) (2*R*,3*R*,4*R*)-3,4-bis(benzyloxy)-2-((benzyloxy)methyl)-3,4-dihydro-2*H*-pyran-5-carbaldehyde (25):



8 **25**

Compound **25** was synthesized using the 3, 4, 6-tri-*O*-benzyl-D-galactal **8** (2.0 g, 4.807 mmol), $POCl_3$ (14.423 mmol, 1.34 mL) in dimethylformamide according to the procedure in **(2.4.2.1)**. The crude product was purified by silica-gel column chromatography with ethyl acetate/hexane (3:7) to provide the **25** as light yellow oil (85 % yield).

(2.4.2.11) ((2*R*,3*R*,4*R*)-3,4-bis(benzyloxy)-2-((benzyloxy)methyl)-3,4-dihydro-2*H*-pyran-5-yl)methanol (26):



25 **26**

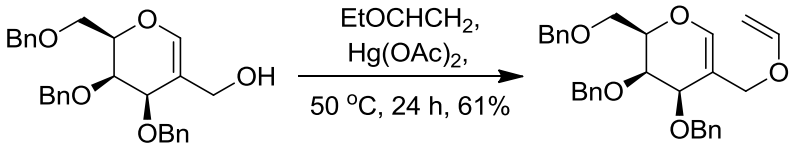
Compound **26** was synthesized using the 2-*C*-formyl glucal **25** (1.6 g, 3.62 mmol), $NaBH_4$ (205 mg, 5.44 mmol,) in ethanol according to the procedure in **(2.4.2.2)**. The crude product was purified by silica-gel column chromatography with ethyl acetate/hexane (4:6) to provide the **26** as light yellow oil (85 % yield).

^{1}H (400 MHz, $CDCl_3$): δ 7.34-7.42, (m, 15H), 6.46 (s, 1H), 4.89 (d, 1H, *J* = 11.6 Hz), 4.88 (d, 1H, 11.6 Hz), 4.72 (d, 1H, *J* = 12 Hz), 4.66 (d, 1H, *J* = 11.6 Hz), 4.61 (d, 1H, *J* = 11.6 Hz), 4.51 (d, 1H, *J* = 12 Hz), 4.40 (d, 1H, *J* = 2.4 Hz), 4.31 (bs, 1H), 4.17 (d, 1H, *J* = 11.6 Hz), 4.02-4.09

(m, 2H), 3.88 (dd, 1H, *J* = 7.2 Hz, *J* = 10 Hz), 3.80 (dd, 1H, *J* = 5.2 Hz, *J* = 10 Hz), 2.37 (bs, 1H) ppm.

^{13}C (100 MHz, CDCl$_3$):δ 142.3, 137.9, 137.6, 128.2, 128.1, 127.6, 127.5, 127.5, 112.0, 75.3, 72.1, 73.0, 72.7, 72.3, 71.1, 67.8, 61.0 ppm.

(2.4.2.12) (2R,3R,4R)-3,4-bis(benzyloxy)-2-((benzyloxy)methyl)-5-((vinyloxy)methyl)-3,4-dihydro-2H-pyran (27):



26 **27**

Compound **27** was synthesized using the 2-hydroxymethyl galactal **26** (1.0 g, 2.24 mmol), $Hg(OAc)_2$ (199 mg, 0.62 mmol,) in ethylvinylether according to the procedure in **(2.4.2.3)**. The crude product was purified by basic alumina column chromatography with ethyl acetate/hexane (1:9) to provide the **27** as colourless oil (61 % yield).

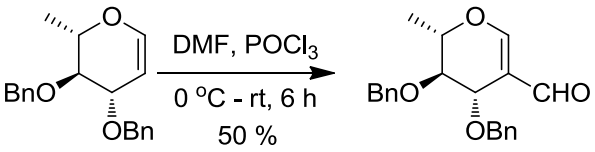
^{1}H (400 MHz, CDCl$_3$): δ 7.30-7.34, (m, 15H), 6.45 (s, 1H), 6.42 (dd, 1H, *J* = 6.8 Hz, *J* = 14.4 Hz), 4.84 (d, 1H, *J* = 11.6 Hz), 4.77 (d, 1H, *J* = 11.6 Hz), 4.64 (d, 1H, *J* = 11.6 Hz), 4.64 (d, 1H, *J* = 11.6 Hz), 4.51 (d, 1H, *J* = 12 Hz), 4.45 (d, 1H, *J* = 11.6 Hz), 4.42 (d, 1H, *J* = 12 Hz), 4.21-4.29 (m, 3H), 3.99-4.09 (m, 3H), 3.79 (dd, 1H, *J* = 7.6 Hz, *J* = 10 Hz), 3.68 (dd, 1H, *J* = 4.8 Hz, *J* = 10 Hz) ppm.

^{13}C (100 MHz, CDCl$_3$): δ 151.4, 143.8, 138.4, 138.2, 138.0, 128.4, 128.0, 127.9, 127.9, 109.3, 87.3, 75.9, 73.4, 71.2, 68.1, 66.4 ppm.

Low-resolution MS (EI): m/z: 472 (M^+).

HRMS (ESI) calcd for $C_{30}H_{32}O_5$+Na 495.2148, found 295.2148.

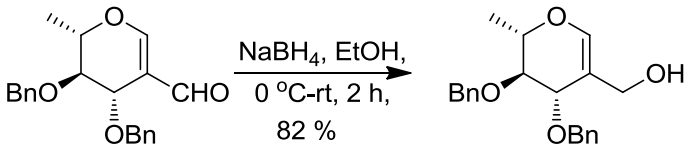
(2.4.2.13) (2*S*,3*S*,4*S*)-3,4-bis(benzyloxy)-2-methyl-3,4-dihydro-2*H*-pyran-5-carbaldehyde (28):



11 **28**

Compound **28** was synthesized using the 3, 4,-di-*O*-benzyl-L-rhamnal **11** (2.0 g, 6.47 mmol), $POCl_3$ (19.41 mmol, 1.80 mL) in dimethylformamide according to the procedure in **(2.4.2.1)**. The crude product was purified by silica-gel column chromatography with ethyl acetate/hexane (2:8) to provide the **28** as colourless oil (50 % yield).

(2.4.2.14) ((2*S*,3*S*,4*S*)-3,4-bis(benzyloxy)-2-methyl-3,4-dihydro-2*H*-pyran-5-yl)methanol (29):



28 **29**

Compound **29** was synthesized using the 2-*C*-formylrhamnal **28** (1.0 g, 2.95 mmol), $NaBH_4$ (167 mg, 4.43 mmol,) in ethanol according to the procedure in **(2.4.2.2)**. The crude product was purified by silica-gel column chromatography with ethyl acetate/hexane (3:7) to provide the **29** as a white solid (82 % yield).

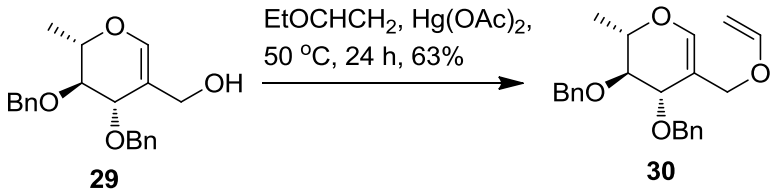
^{1}H (400 MHz, $CDCl_3$): δ 7.23-7.34 (m, 10H), 6.41 (s, 1H), 4.64-4.77 (m, 4H), 4.25 (d, 1H, *J* = 4.4 Hz), 4.06-4.11 (m, 2H), 3.96 (d, 1H, *J* = 12 Hz), 3.57 (t, 1H, *J* = 11.6 Hz), 1.35 (d,3H, *J* = 6.4 Hz) ppm.

^{13}C (100 MHz, $CDCl_3$): δ 143.4, 138.0, 137.8, 128.5, 127.9, 127.8, 112.0, 79.1, 76.2, 73.5, 73.4, 72.9, 61.7, 16.8 ppm.

Low-resolution MS (EI): m/z: 340 (M^+).

HRMS (ESI) calcd for $C_{30}H_{32}O_5$+Na 363.1572, found 363.1570.

(2.4.2.15) (2*S*,3*S*,4*S*)-3,4-bis(benzyloxy)-2-methyl-5-((vinyloxy)methyl)-3,4-dihydro-2*H*-pyran (30):



Compound **30** was synthesized using the 2-hydroxymethyl rhamnal **29** (0.8 g, 2.35 mmol), $Hg(OAc)_2$ (209 mg, 0.65 mmol,) in ethylvinylether according to the procedure in **(2.4.2.3)**. The crude product was purified by basic alumina column chromatography with ethyl acetate/hexane (1:9) to provide the **30** as colourless oil (63 % yield).

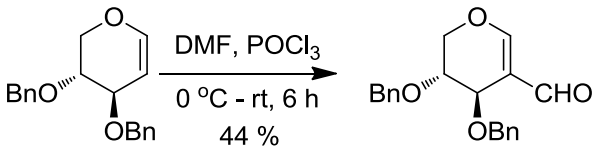
^{1}H (400 MHz, $CDCl_3$): δ 7.30-6.37 (m, 10H), 6.48 (dd, 1H, *J* = 6.4 Hz, *J* = 14.4 Hz), 4.82 (d, 1H, *J* = 11.2 Hz), 4.71 (d, 1H, *J* = 11.2 Hz), 4.69 (d, 1H, *J* = 11.2 Hz), 4.64 (d, 1H, *J* = 11.2 Hz), 4.44 (d, 1H, *J* = 11.2 Hz), 4.24-4.28 (m, 2H), 4.12 (m, 1H), 4.05 (dd, 1H, *J* = 2 Hz, *J* = 6.8 Hz), 3.97 (d, 1H, *J* = 10.8 Hz), 3.56 (dd, 1H, *J* = 4 Hz, *J* = 7.6 Hz), 1.38 (d, 3H, *J* = 6.4 Hz) ppm.

^{13}C (100 MHz, $CDCl_3$): δ 151.3, 144.4, 138.3, 138.0, 128.5, 128.4, 128.4, 128.0, 127.9, 127.7, 109.4, 87.3, 79.3, 75.5, 74.2, 73.7, 73.2, 66.1, 17.1 ppm .

Low-resolution MS (EI): m/z: 366 (M^+).

HRMS (ESI) calcd for $C_{23}H_{26}O_4$+Na 389.1729, found 389.1729.

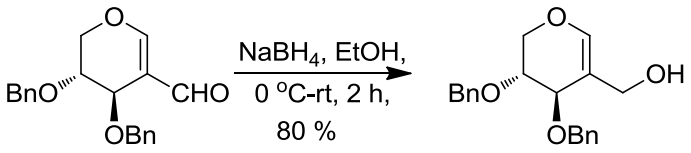
(2.4.2.16) (3*R*,4*R*)-3,4-bis(benzyloxy)-3,4-dihydro-2*H*-pyran-5-carbaldehyde (31):



Compound **31** was synthesized using the 3, 4,-di-*O*-benzyl-D-xylal **14** (3.3 g, 11.13 mmol), $POCl_3$ (33.41 mmol, 3.00 mL) in dimethylformamide according to the procedure in

(2.4.2.1). The crude product was purified by silica-gel column chromatography with ethyl acetate/hexane (2:8) to provide the **31** as colourless oil (44 % yield).

(2.4.2.17) ((3*R*,4*R*)-3,4-bis(benzyloxy)-3,4-dihydro-2*H*-pyran-5-yl)methanol (32):



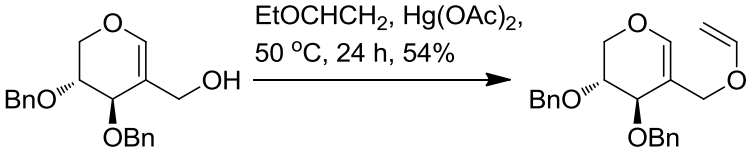
31 **32**

Compound **32** was synthesized using the 2-*C*-formyl xylal **31** (1.5 g, 4.62 mmol), $NaBH_4$ (262 mg, 6.94 mmol,) in ethanol according to the procedure in **(2.4.2.2)**. The crudeproduct was purified by silica-gel column chromatography with ethyl acetate/hexane (3:7) to provide the **32** as colourless oil (80 % yield).

^{1}H (400 MHz, $CDCl_3$): δ 7.30-7.39 (m, 10H), 6.61 (s, 1H), 4.66 (d, 1H, J= 12.4 Hz), 4.63 (d, 2H, *J* = 11.2 Hz), 4.57 (d, 1H, *J* = 11.6 Hz), 4.15-4.10 (m, 1H), 4.08 (d, 1H, *J* = 12 Hz), 3.97-4.01 (m, 2H), 3.90 (dd, 1H, *J* = 1.6 Hz, *J* = 12 Hz), 3.71 (m, 1H), 2.10 (bs, 1H) ppm.

^{13}C (125 MHz, $CDCl_3$): δ 145.0, 137.8, 137.6, 128.4, 128.2, 127.9, 127.8, 127.7, 111.3, 71.7, 71.6, 70.9, 70.6, 63.4, 62.4 ppm.

(2.4.2.18) (3*R*,4*R*)-3,4-bis(benzyloxy)-5-((vinyloxy)methyl)-3,4-dihydro-2*H*-pyran (33):



32 **33**

Compound **33** was synthesized using the 2-hydroxymethyl rhamnal **32** (0.8 g, 2.45 mmol), $Hg(OAc)_2$ (218 mg, 0.68 mmol,) in ethylvinylether according to the procedure in **(2.4.2.3)**. The crude product was purified by basic alumina column chromatography with ethyl acetate/hexane (1:9) to provide the **33** as colourless oil (54 % yield).

^{1}H (400 MHz, $CDCl_3$): δ 7.24-7.29 (m, 10H), 6.60 (s, 1H), 6.39 (dd, 1H, *J* = 6.8 Hz, 14 Hz), 4.57 (bs, 2H), 4.54 (d, 1H, *J* = 11.6 Hz), 4.47 (d, 1H, *J* = 11.6 Hz), 4.25 (d, 1H, *J* = 7.2 Hz),

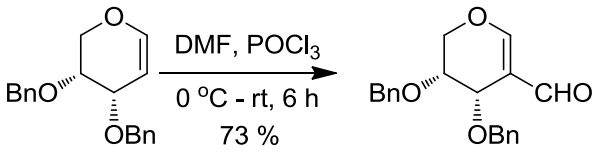
4.17 (d, 1H, *J* = 14.4 Hz), 4.12 (d, 1H, *J* = 11.6 Hz), 3.96-3.98 (m, 2H), 3.86-3.93 (m, 2H), 3.64 (s, 1H) ppm.

^{13}C (100 MHz, $CDCl_3$): δ 151.4, 146.1, 138.1, 137.9, 128.5, 128.5, 128.0, 127.9, 127.8, 108.0, 87.0, 71.9, 71.7, 71.0, 69.5, 67.2, 63.9 ppm.

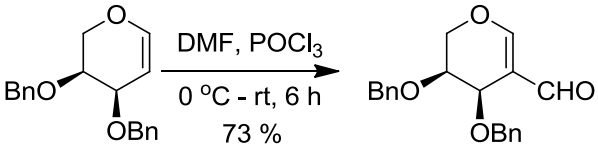
Low-resolution MS (EI): m/z: 352 (M^+).

HRMS (ESI) calcd for $C_{22}H_{24}O_4$+Na 375.1573, found 375.1573.

(2.4.2.19) (3*R*,4*S*)-3,4-bis(benzyloxy)-3,4-dihydro-2*H*-pyran-5-carbaldehyde (34) and (3*S*,4*R*)-3,4-bis(benzyloxy)-3,4-dihydro-2*H*-pyran-5-carbaldehyde (37):



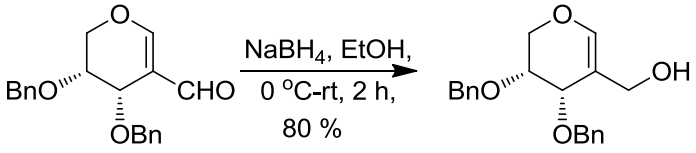
17 **34**



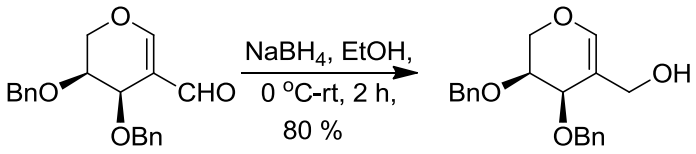
20 **37**

Compound **34** and **37** was synthesized using the 3, 4,-di-*O*-benzyl-D-arabinal **17** and3, 4,-di-*O*-benzyl-L-arabinal **20** (2.0 g, 6.75 mmol), $POCl_3$ (20.27 mmol, 1.88 mL) in dimethylformamide according to the procedure in **(2.4.2.1)**. The crude product was purified by silica-gel column chromatography with ethyl acetate/hexane (2:8) to provide the **34** and **37** as colourless oil (73 % yield).

(2.4.2.20) ((3*R*,4*S*)-3,4-bis(benzyloxy)-3,4-dihydro-2*H*-pyran-5-yl)methanol (35) and ((3*S*,4*R*)-3,4-bis(benzyloxy)-3,4-dihydro-2*H*-pyran-5-yl)methanol (38):



34 **35**



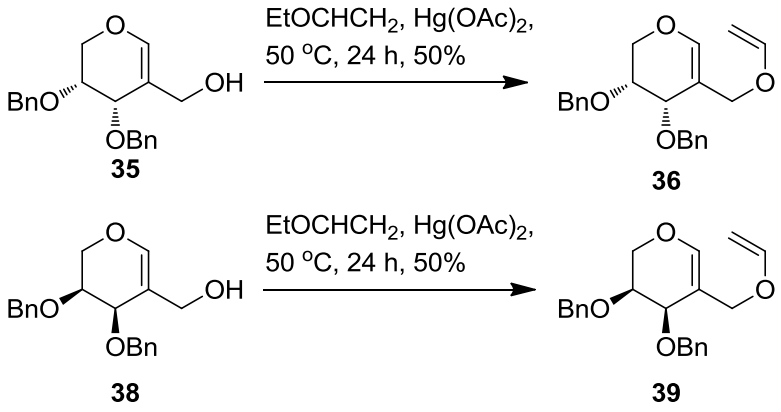
37 **38**

Compound **35** and **38** was synthesized using the 2-*C*-formyl-D-arabinal **34** and2-*C*-formyl-L-arabinal **37** (1.0 g, 3.08 mmol), $NaBH_4$ (175 mg, 4.62 mmol,) in ethanol according to the procedure in **(2.4.2.2)**. The crude product was purified by silica-gel column chromatography with ethyl acetate/hexane (3:7) to provide the **35** and **38** as colourless oil (80 % yield).

^{1}H (400 MHz, $CDCl_3$): δ 7.26-7.37, (m, 10H), 6.41 (s, 1H), 4.94 (d, 1H, *J* = 11.6 Hz), 4.70 (bs, 2H), 4.65 (d, 1H, *J* = 11.2 Hz), 4.23 (d, 1H, *J* = 2.8 Hz), 3.92-4.03 (m, 4H), 3.78-3.82 (m, 1H) ppm.

^{13}C (100 MHz, $CDCl_3$): δ 144.6, 138.5, 137.9, 128.5, 128.4, 128.2, 127.8, 127.7, 127.5, 111.7, 74.1, 73.7, 71.5, 69.6, 62.7, 61.7 ppm.

(2.4.2.21) (3*R*,4*S*)-3,4-bis(benzyloxy)-5-((vinyloxy)methyl)-3,4-dihydro-2*H*-pyran (36) and (3*S*,4*R*)-3,4-bis(benzyloxy)-5-((vinyloxy)methyl)-3,4-dihydro-2*H*-pyran (39):



35 **36**

38 **39**

Compounds **36** and **39** was synthesized using the 2-hydroxymethyl-D-arabinal **35** and 2-hydroxymethyl-L-arabinal **38** (0.8 g, 2.45 mmol), $Hg(OAc)_2$ (218 mg, 0.68 mmol,) in ethylvinylether according to the procedure in **(2.4.2.3)**. The crude product was purified by basic alumina column chromatography with ethyl acetate/hexane (1:9) to provide the **36** and **39** as colourless oil (50 % yield).

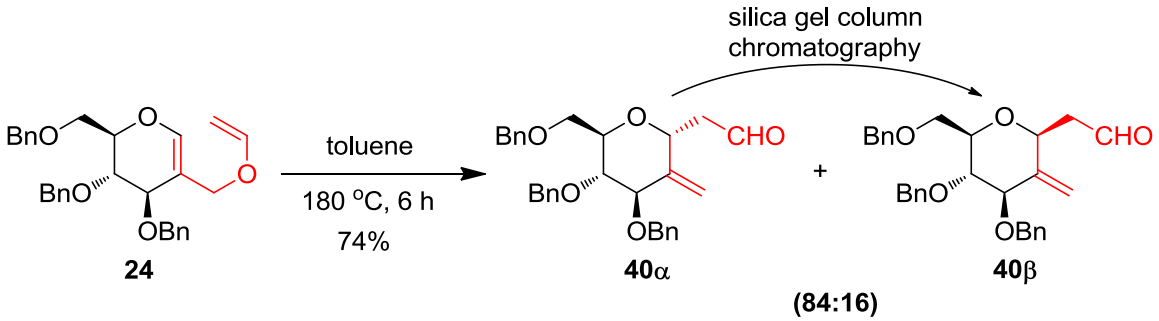
^{1}H (400 MHz, $CDCl_3$): δ 7.27-7.37, (m, 10H), 6.46 (s, 1H), 6.36 (dd, 1H, *J* = 6.8 Hz, *J* = 14 Hz), 4.91 (d, 1H, *J* = 11.6 Hz), 4.72 (d, 1H, *J* = 12 Hz), 4.68 (d, 1H, 11.2 Hz), 4.65 (d, 1H, *J* = 11.6 Hz),4.17-4.35 (m, 3H), 4.93-4.06 (m, 4H), 3.80-3.85 (m, 1H) ppm.

^{13}C (100 MHz, $CDCl_3$): δ 151.3, 138.6, 137.9, 128.5, 128.3, 128.2, 127.9, 127.7, 127.6, 108.6, 87.2, 74.4, 74.0, 71.7, 68.7, 66.5, 62.9 ppm.

Low-resolution MS (EI): m/z: 352 (M^+).

HRMS (ESI) calcd for $C_{22}H_{24}O_4$+Na 375.1573, found 375.1573.

(2.4.2.22) 2-((2*S*,4*R*,5*S*,6*R*)-4,5-bis(benzyloxy)-6-((benzyloxy)methyl)-3-methylenetetrahydro-2*H*-pyran-2-yl)acetaldehyde (40*α* and 40β):



Compound **40*α*, 40β** was synthesized using the 2-vinyloxymethyl glucal **24** (0.3 g, 0.63 mmol), in toluene according to the procedure in **(2.4.2.4)**. The crude product was purified by silica-gel column chromatography with ethylacetate/hexane (2:8) to provide the **40**β as colourless oil (74 % yield).

Compound 40α: Unable to isolate in pure form due to its anomerization to the more stable **40β.**

Compound 40β:

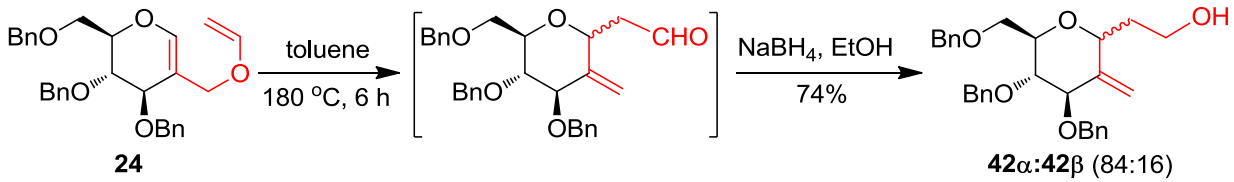
^{1}H (500 MHz, $CDCl_3$): δ 9.86 (s, 1H), 7.18-7.40 (m, 15H), 5.37 (s, 1H), 4.98 (s, 1H), 4.88 (d, 1H, *J* = 11 Hz), 4.78 (d, 1H, *J* = 11.5 Hz), 4.71 (d, 1H, *J* = 11.5 Hz), 4.59 (d, 1H, *J* = 12.5 Hz), 4.54 (d, 1H, *J* = 11 Hz), 4.52 (d, 1H, *J* = 12 Hz), 4.34 (dd, 1H, *J* = 5.5 Hz, *J* = 7.5 Hz), 4.11 (d, 1H, *J* = 8 Hz), 3.67-3.72 (m, 2H), 3.63-3.64 (m, 1H), 3.56 (t, 1H, *J* = 9 Hz), 2.93 (ddd, 1H, *J* = 2 Hz, *J* = 7.5 Hz, *J* = 16.5 Hz), 2.82 (dd, 1H, *J* = 5 Hz, *J* = 16.5 Hz) ppm.

^{13}C (125 MHz, $CDCl_3$): δ 200.5, 143.3, 138.1, 138.1, 138.0, 128.5, 128.4, 128.3, 127.9, 127.8, 127.7, 127.6, 108.1, 84.2, 79.8, 79.3, 74.8, 73.4, 73.3, 72.6, 69.1, 45.3 ppm.

Low-resolution MS (EI): m/z: 473 (M^++1).

HRMS (ESI) calcd for $C_{30}H_{32}O_5$+Na 495.2148, found 495.2148.

(2.4.2.23) 2-((4*R*,5*S*,6*R*)-4,5-bis(benzyloxy)-6-((benzyloxy)methyl)-3-methylenetetrahydro-2*H*-pyran-2-yl)ethanol (42α and 42β):



24 **42α:42β** (84:16)

Compound **42*α*, 42β** was synthesized using the 2-vinyloxymethyl glucal **24** (0.3 g, 0.63 mmol), in toluene according to the procedure in **(2.4.2.4)**. The crude product was further reduced with $NaBH_4$ (59 mg, 1.57 mmol) in ethanol at -10 °C, according to the procedure in **(2.4.2.2)** purified by silica-gel column chromatography with ethyl acetate/hexane (4:6) to provide the **42**α and **42**β in 84:16 ratio as a colourless oil (74 % yield).

Compound 42*α*:

^{1}H (500 MHz, $CDCl_3$): δ 7.18-7.38 (m, 15H), 5.25 (s, 1H), 5.11 (s, 1H), 4.79 (d, 1H, *J* = 11.0 Hz), 4.72 (d, 1H, *J* = 11.5 Hz), 4.63 (d, 1H, *J* = 11.5 Hz),4.60 (dd, 1H, *J* = 5.5 Hz, *J* = 9.5 Hz), 4.58 (d, 1H, *J* = 12.0 Hz), 4.52 (d, 1H, *J* = 10 Hz), 4.48 (d, 1H, *J* = 11.5 Hz), 4.20 (d, 1H, *J* = 7.0 Hz), 3.92-3.95 (m, 1H), 3.81-3.84 (m, 2H), 3.63-3.64 (m, 2H), 3.46 (dd, 1H, *J* = 7.0 Hz, *J* = 8.5 Hz), 2.62 (bs, 1H), 2.16-2.24 (m, 1H), 1.72-1.77 (m, 1H) ppm.

^{13}C (125 MHz, $CDCl_3$): δ 144.0, 138.0, 137.9, 128.4, 128.3, 127.9, 127.8, 127.7, 127.7, 111.0, 80.9, 80.1, 77.0, 73.9, 73.4, 73.0, 72.7, 69.4, 61.1, 33.2 ppm.

Low-resolution MS (EI): m/z: 474 (M^+).

HRMS (ESI) calcd for $C_{30}H_{34}O_5$+Na 497.2304, found 497.2304.

Compound 42β:

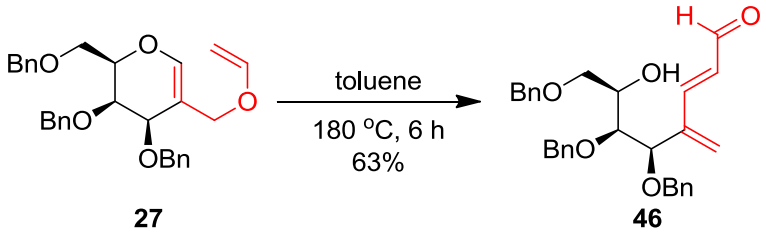
^{1}H (500 MHz, $CDCl_3$): δ 7.19-7.42 (m, 15H), 5.34 (s, 1H), 5.09 (s, 1H), 4.89 (d, 1H, *J* = 10.5 Hz), 4.78 (d, 1H, *J* = 11.5 Hz), 4.69 (d, 1H, *J* = 11.5 Hz),4.57 (d, 1H, *J* = 12.0 Hz), 4.53 (d, 1H, *J* = 11.0 Hz), 4.52 (d, 1H, *J* = 12.0 Hz),4.07(d, 1H, *J* = 8.5 Hz), 4.00 (dd, 1H, *J* = 2.5 Hz, *J* = 10.0 Hz), 3.89 (t, 2H, *J* = 5.0 Hz), 3.70 (dd, 1H, *J* = 2.0 Hz, *J* = 7.0 Hz), 3.65 (ddd, 1H, *J* = 2.0 Hz, *J* = 6.0 Hz, *J* = 9.0 Hz), 3.57-3.61 (m, 2H), 3.46 (t, 1H, *J* = 9.0 Hz), 2.83 (bs, 1H), 2.06-2.12 (m, 1H), 1.94-1.99 (m, 1H) ppm.

^{13}C (125 MHz, $CDCl_3$): δ 144.1, 138.1, 138.0, 138.0, 128.5, 1284, 128.3, 127.9, 127.8, 127.7, 127.6, 107.7, 84.3, 80.2, 78.8, 74.8, 73.4, 73.2, 69.6, 61.2, 33.4 ppm.

Low-resolution MS (EI): m/z: 474 (M^+).

HRMS (ESI) calcd for $C_{30}H_{34}O_5$+Na 497.2304, found 497.2304.

(2.4.2.24) 2-(5*R*,6*S*,7*R*,*E*)-5,6,8-tris(benzyloxy)-7-hydroxy-4-methyleneoct-2-enal (46):



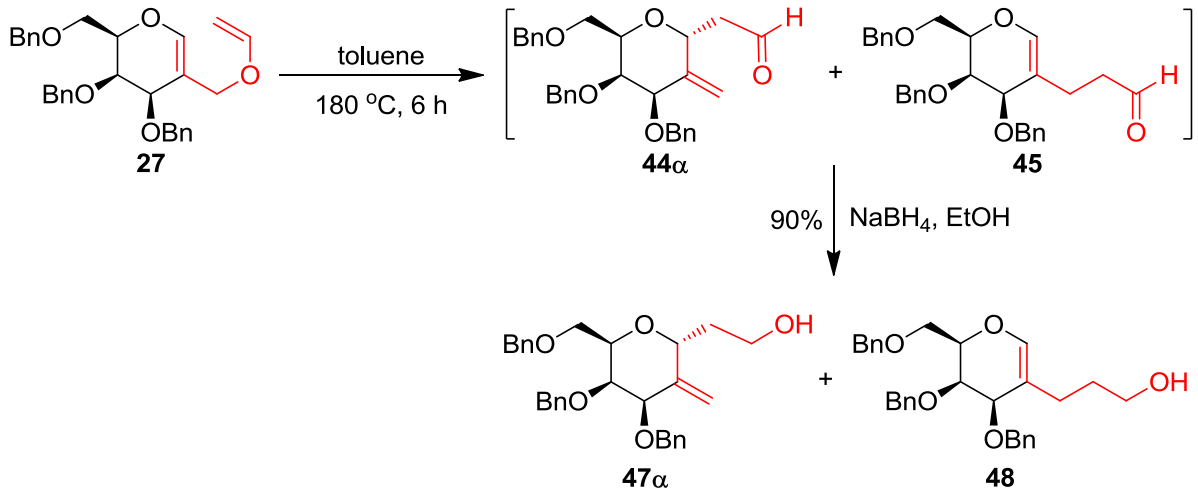
27 **46**

Compound **46** was synthesized using the 2-vinyloxymethyl galactal **27** (0.2 g, 0.42 mmol), in toluene according to the procedure in **(2.4.2.4)**. The crude product was purified by silica-gel column chromatography with ethyl acetate/hexane (3:7) to provide the **46** as colourless oil (63 % yield).

^{1}H (400 MHz, $CDCl_3$): δ 9.52 (d, 1H, *J* = 7.6 Hz), 7.26-7.38 (m, 15H), 7.12 (d, 1H, *J* = 16 Hz), 6.46 (dd, 1H, *J* = 7.6 Hz, *J* = 16 Hz), 5.84 (s, 1H), 5. 80 (s, 1H), 4.55 (d, 1H, *J* = 12 Hz), 4.53 (d, 1H, *J* = 11.6 Hz), 4.49 (d, 1H, *J* = 12 Hz), 4.37-4.40 (m, 3H), 4.32 (d, 1H, *J* = 11.6 Hz), 4.16 (m, 1H), 3.69 (dd, 1H, *J* = 1.6 Hz, *J* = 8 Hz), 3.56 (dd, 1H, *J* = 6 Hz, *J* = 9.6 Hz), 3.49 (dd, 1H, *J* = 6.4 Hz, *J* = 9.6 Hz), 2.64 (d, 1H, *J* = 7.6 Hz) ppm.

^{13}C (100 MHz, $CDCl_3$): δ 194.1, 151.3, 142.4, 137.8, 137.4, 137.2, 129.9, 128.5, 128.4, 128.3, 128.2, 128.0, 128.0, 127.8, 126.9, 79.1, 78.7, 74.1, 73.4, 71.0, 70.9, 69.2 ppm.

(2.4.2.25) 2-((2R,4R,5R,6R)-4,5-bis(benzyloxy)-6-((benzyloxy)methyl)-3-methylenetetrahydro-2H-pyran-2-yl)ethanol(46α) and 3-((2R,3R,4R)-3,4-bis(benzyloxy)-2-((benzyloxy)methyl)-3,4-dihydro-2H-pyran-5-yl)propan-1-ol (48):



Compound **47α** and **48** was synthesized using the 2-vinyloxymethyl galactal **27** (0.6 g, 1.27 mmol), in toluene according to the procedure in **(2.4.2.4)**. The crude product was further reduced with $NaBH_4$ (72 mg, 1.90 mmol) in ethanol at -10 °C, according to the procedure in **(2.4.2.2)** purified by silica-gel column chromatography with ethyl acetate/hexane (4:6) to provide the **47**α and **48** in 74:26 ratio as a colourless oil (90 % yield after two steps).

Compound 47α:

^{1}H (500 MHz, $CDCl_3$): δ 7.27-7.37 (m, 15H), 5.26 (s, 1H), 5.15 (s, 1H), 4.79 (d, 1H, *J* = 12.0 Hz), 4.66 (d, 1H, *J* = 12.5 Hz), 4.58-4.61 (m, 2H), 4.53 (d, 2H, *J* = 12.5 Hz), 4.49 (d, 1H, *J* = 12.0 Hz), 4.28 (s, 1H, 4.13-4.16 (m, 1H), 3.91 (dd, 1H, *J* = 8.0 Hz, *J* = 10.0 Hz), 3.80-3.83 (m, 3H), 3.51 (dd, 1H, *J* = 4.0 Hz, *J* = 10.5 Hz), 2.79 (bs, 1H), 2.03-2.10 (m, 1H), 1.71-1.76 (m, 1H) ppm.

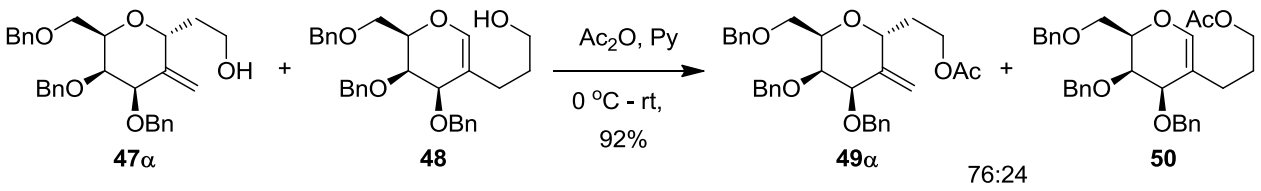
^{13}C (125 MHz, $CDCl_3$): δ 143.1, 138.3, 138.1, 137.9, 128.4, 128.3, 128.2, 128.1, 127.8, 127.7, 127.6, 127.3, 111.3, 78.1, 75.7, 74.3, 73.4, 72.8, 72.7, 71.0, 68.7, 61.1, 33.1 ppm.

Low-resolution MS (EI): m/z: 474 (M^+).

HRMS (ESI) calcd for $C_{30}H_{34}O_5$+Na 497.2304, found 297.2304.

Compound 48: Compound **48** was not obtained in pure form and it was isolated along with compound **47**α.

(2.4.2.26) 2-((2*R*,4*R*,5*R*,6*R*)-4,5-bis(benzyloxy)-6-((benzyloxy)methyl)-3-methylenetetrahydro-2*H*-pyran-2-yl)ethyl acetate (49α) and 3-((2*R*,3*R*,4*R*)-3,4-bis(benzyloxy)-2-((benzyloxy)methyl)-3,4-dihydro-2*H*-pyran-5-yl)propyl acetate (50):



Compounds **49**α and **50** was synthesized using the mixture of **47**α and **48** (0.4 g, 0.84 mmol), in pyridine (4 mL) and acetic anhydride (4.2 mmol, 0.4 mL) at 0 °C-room temperature for about 4 h. After completion of the starting material by checking TLC, pyridine was evaporated with rotary evaporator, the crude was dissolved in dichloromethane, organic layer was washed with aqueous copper sulphate solution, then with water and finally with brine, dried over anhydrous sodium sulphate, solvent was removed under vacuum, the obtained crude was chromatographed using silica-gel with hexane/ethyl acetate (8:2) to provide the **49**α and **50** in 76:24 ratio as a colourless oil (92 % yield).

Compound 49α:

^{1}H (500 MHz, $CDCl_3$): δ 7.23-7. 34 (m, 15H), 5.30 (s, 1H), 5.12 (s, 1H), 4.83 (d, 1H, *J* =12.0 Hz,), 4.64 (d, 1H, *J* = 12.5 Hz), 4.61 (d, 1H, *J* = 12.0 Hz), 4.55 (d, 1H, *J* = 12.0 Hz), 4.46-4.50 (m, 2H), 4.42 (d, 1H, *J* = 11.5 Hz), 4.09-4.17 (m, 3H), 3.96-3.98 (td, 1H,*J* = 2.0 Hz, *J* = 6 Hz), 3.89 (s, 1H), 3.67 (dd, 1H, *J* =6.5 Hz, *J* =10 Hz), 3.61 (dd, 1H, *J* =6 Hz, *J* = 10 Hz), 2.00-2.09 (m, 1H), 2.01 (s, 3H), 1.84-1.91 (m, 1H) ppm.

^{13}C (125 MHz, $CDCl_3$): δ 170.9, 142.5, 138.5, 138.2, 128.4, 128.3, 128.1, 127.8, 127.6, 127.6, 127.5, 127.2, 111.2, 78.1, 75.5, 73.4, 73.3, 73.2, 72.8, 71.2, 68.8, 61.3, 30.1, 20.9 ppm.

Low-resolution MS (EI): m/z: 516 (M^+).

HRMS (ESI) calcd for $C_{32}H_{36}O_6$+Na 539.2410, found 539.2410.

Compound 50:

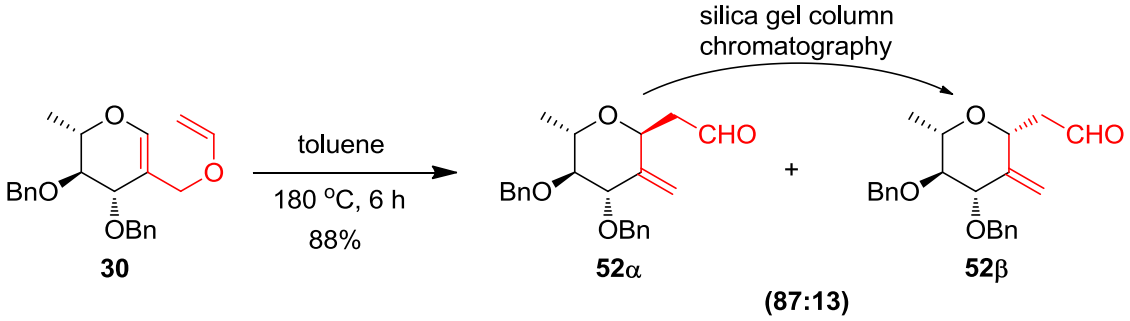
^{1}H (500 MHz, $CDCl_3$): δ 7. 25-7. 36 (m, 15H), 6.14 (s, 1H), 4.81 (s, 1H), 4.79 (s, 1H), 4.64 (d, 1H, *J* =12.0 Hz,), 4.53 (d, 1H, *J* =12.0 Hz), 4.51 (d, 1H, *J* = 11.5 Hz), 4.43 (d, 1H, *J* = 11.5 Hz),4.20-4.22 (m, 1H), 4.08 (d, 1H, *J* = 4.0 Hz), 3.95-4.01 (m, 3H), 3.79 (dd, 1H, *J* = 7.5 Hz, *J* = 10.5 Hz), 3.69 (dd, 1H, *J* = 5.0 Hz, *J* = 10.5 Hz), 2.10-2.18 (m, 1H), 2.00 (s, 3H), 1.91-1.97 (m, 1H), 1.55-1.65 (m, 2H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 171.0, 139.5, 138.4, 138.3, 138.1, 128.3, 127.9, 127.7, 127.7, 127.6, 127.6, 111.2, 75.2, 73.4, 73.1, 72.9, 72.7, 71.5, 68.2, 64.0, 27.2, 25.4, 20.9 ppm.

Low-resolution MS (EI): m/z: 516 (M^+).

HRMS (ESI) calcd for $C_{32}H_{36}O_6$+Na 539.2410, found 539.2410.

(2.4.2.27) 2-((2*R*,4*S*,5*S*,6*S*)-4,5-bis(benzyloxy)-6-methyl-3-methylenetetrahydro-2*H*-pyran-2-yl)acetaldehyde (52β):



Compound **52β** was synthesized using the 2-vinyloxymethyl-L-rhamanal **30** (0.5 g, 1.36 mmol), in toluene according to the procedure in **(2.4.2.4)**. The crude product was purified by silica-gel column chromatography with ethyl acetate/hexane (2:8) to provide the **52**β as a colourless gum (88 % yield).

Compound 52β:

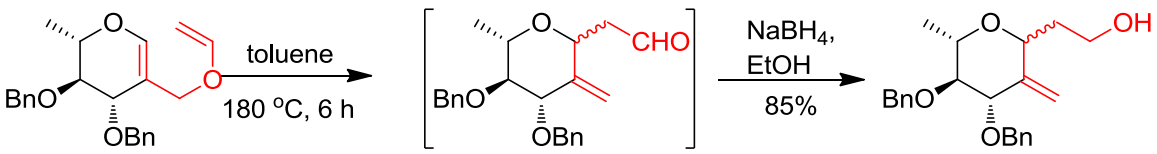
^{1}H (500 MHz, $CDCl_3$): δ 9.83 (t, 1H, *J* = 2.5 Hz), 7.29-7.39 (m, 10H), 5.33 (d, 1H, *J* = 1.5 Hz), 4.94 (d, 1H, *J* = 1.5 Hz), 4.76 (d, 1H, *J* = 11.5 Hz), 4.69 (d, 1H, *J* = 11.5 Hz), 4.63 (d, 1H, *J* = 11 Hz), 4.29 (dd, 1H, *J* = 5 Hz, *J* = 8 Hz), 4.06 (dt, 1H, *J* = 1.5 Hz, *J* = 8.5 Hz), 3.54 (dd, 1H, *J* = 6 Hz, *J* = 9 Hz), 3.13 (t, 1H, *J* = 9 Hz), 2.82 (ddd, 1H, *J* = 2.5 Hz, *J* = 8 Hz, *J* = 16.5 Hz), 2.75 (ddd, 1H, *J* = 2 Hz, *J* = 5 Hz, *J* = 16.5 Hz), 1.26 (d, 3H, *J* = 6 Hz) ppm.

^{13}C (125 MHz, $CDCl_3$): δ 200.6, 144.0, 138.2, 138.0, 128.5, 128.4, 128.0, 127.7, 107.6, 85.6, 84.1, 75.7, 75.1, 73.3, 72.3, 45.3, 18.3 ppm.

Low-resolution MS (EI): m/z: 366 (M^+).

HRMS (ESI) calcd for $C_{23}H_{26}O_4$+Na 389.1729, found 389.1729.

(2.4.2.28) 2-((4*S*,5*S*,6*S*)-4,5-bis(benzyloxy)-6-methyl-3-methylenetetrahydro-2*H*-pyran-2-yl)ethanol (53α and 53β):



Compound **53α, 53β** was synthesized using the 2-vinyloxymethyl rhamnal **30** (0.25 g, 0.68 mmol), in toluene according to the procedure in **(2.4.2.4)**. The crude product was further reduced with $NaBH_4$ (38 mg, 1.02 mmol) in ethanol at -10 °C, according to the procedure in **(2.4.2.2)** purified by silica-gel column chromatography with ethyl acetate/hexane (4:6) to provide the **53**α and **53**β in 87:13 ratio as a white solid (85 % yield).

Compound 53α:

^{1}H (400 MHz, $CDCl_3$): δ 7.30-7.41 (m, 10H), 5.26 (s, 1H), 5. 10 (s, 1H), 4.88(d, 1H, *J* = 11.2 Hz), 4.74 (d, 1H, *J* = 11.6 Hz), 4.67 (d, 1H, *J* = 11.6 Hz), 4.63 (d, 1H, *J* = 11.2 Hz), 4.53 (dd, 1H, *J* = 4.8 Hz, *J* = 9.6 Hz), 4.20 (d, 1H, *J* = 7.6 Hz), 3.77-3.83 (m, 3H), 3.21 (t, H, *J* = 8.4 Hz), 2.12-2.18 (m, 1H), 1.73-1.80 (m, 1H) ppm.

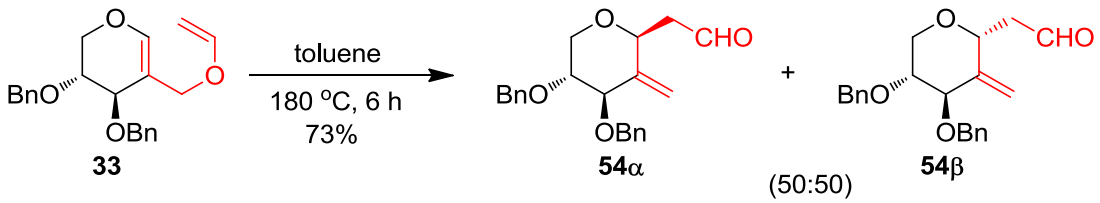
^{13}C (100 MHz, $CDCl_3$): δ 144.5, 138.2, 138.1, 128.5, 128.4, 128.0, 127.8, 127.7, 110.4, 85.5, 80.9, 76.4, 74.5, 72.8, 69.8, 60.6, 33.2, 18.5 ppm.

Low-resolution MS (EI): m/z: 368 (M^+).

HRMS(ESI) calcd for $C_{23}H_{28}O_4$+Na 391.1886, found 391.1885.

Compound 53β: Not able to resolve in column chromatography and obtained along with **53α**.

(2.4.2.29) 2-((2*R*,4*R*,5*R*)-4,5-bis(benzyloxy)-3-methylenetetrahydro-2*H*-pyran-2-yl)acetaldehyde compound with 2-((2*S*,4*R*,5*R*)-4,5-bis(benzyloxy)-3-methylenetetrahydro-2*H*-pyran-2-yl)acetaldehyde (1:1) (54):



Compound **54** was synthesized using the 2-vinyloxymethyl-D-xylal **33** (0.4 g, 1.13 mmol), in toluene according to the procedure in **(2.4.2.4)**. The crude product was purified by

silica-gel column chromatography with ethyl acetate/hexane (2:8) to provide the **54**β as a colourless gum (73 % yield).

Compound 54α: Not resolved in column chromatography and obtained along with **54**β.

Compound 54β:

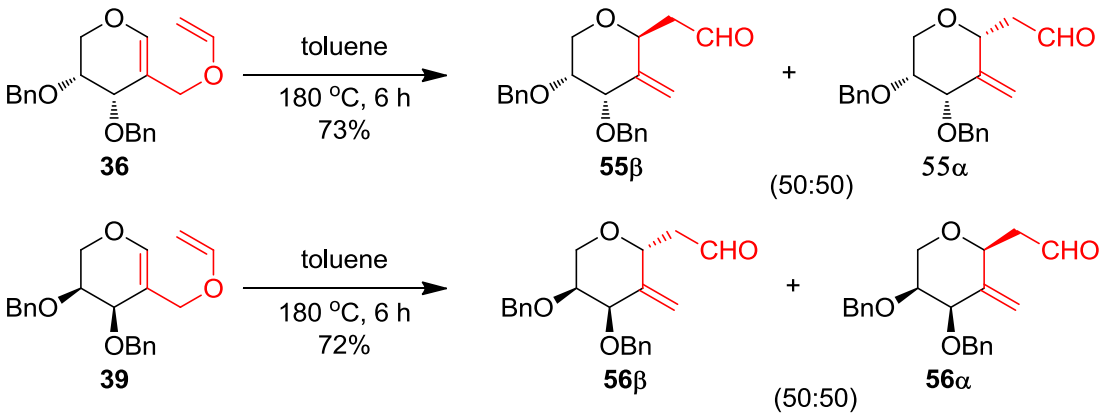
^{1}H (500 MHz, $CDCl_3$): δ 9.84 (t, 1H, *J* = 2 Hz), 7.27-7.36 (m, 10H), 5.14 (s, 1H), 5.12 (s, 1H), 4.66 (dd, 1H, *J* = 4.5 Hz, *J* = 8 Hz), 4.55-4.67 (m, 3H), 4.33 (d, 1H, *J* = 12 Hz), 3.91-4.01 (m, 3H), 3.55-3.56 (m, 1H), 2.85 (ddd, 1H, *J* = 2.5 Hz, *J* = 8.5 Hz, *J* = 16.5 Hz), 2.74 (ddd, 1H, *J* = 1.5 Hz, *J* = 4.5 Hz, *J* = 16.5 Hz) ppm.

^{13}C (125 MHz, $CDCl_3$): δ 200.4, 142.9, 138.2, 128.4, 127.8, 109.6, 82.5, 79.2, 73.2, 73.1, 73.0, 67.4, 45.3 ppm.

Low-resolution MS (EI): m/z: 352 (M^+).

HRMS (ESI) calcd for $C_{22}H_{24}O_4$+Na 375.1573, found 375.1573.

(2.4.2.30) 2-((2*R*,4*S*,5*R*)-4,5-bis(benzyloxy)-3-methylenetetrahydro-2*H*-pyran-2-yl)acetaldehyde compound with 2-((2*S*,4*S*,5*R*)-4,5-bis(benzyloxy)-3-methylenetetrahydro-2*H*-pyran-2-yl)acetaldehyde (1:1) (55α:55β) and 2-((2*R*,4*R*,5*S*)-4,5-bis(benzyloxy)-3-methylenetetrahydro-2*H*-pyran-2-yl)acetaldehyde compound with 2-((2*S*,4*R*,5*S*)-4,5-bis(benzyloxy)-3-methylenetetrahydro-2*H*-pyran-2-yl)acetaldehyde (1:1) (56α:56β):



Compounds **55α, 55β** was synthesized using the 2-vinyloxymethyl-D-arabinal **36** (0.5 g, 1.42 mmol), in toluene according to the procedure in **(2.4.2.4)**. The crude product was purified

by silica-gel column chromatography with ethyl acetate/hexane (2:8) to provide the **55**α and **55**β as a colourless gum (73 % yield).

Compound **56α, 56β** was synthesized using the 2-vinyloxymethyl-L-arabinal **39** (0.5 g, 1.42 mmol), in toluene according to the procedure in **(2.4.2.4)**. The crude product was purified by silica-gel column chromatography with ethyl acetate/hexane (2:8) to provide the **56**α and **56**β as a colourless gum (72 % yield).

Compounds 55β and 56β:

^{1}H (500 MHz, $CDCl_3$): δ 9.79 (dd, 1H, *J* = 2.0 Hz, *J* = 3 Hz), 7.28-7.39 (m, 10H), 5.04 (s, 1H), 4.99 (s, 1H), 4.67 (d, 1H, *J* = 12.5 Hz),4.60 (t, 1H, *J* = 7 Hz),4.58 (d, 1H, *J* = 12 Hz), 4.49 (d, 1H, *J* = 12.0 Hz), 4.42 (d, 1H, *J* = 12.5 Hz), 4.21 (d, 1H, *J* = 3.0 Hz), 3.96 (t, 1H, *J* = 11 Hz),3.83 (dd, 1H, *J* = 5 Hz, *J* = 11 Hz), 3.57 (ddd, 1H, *J* = 3 Hz, *J* = 5.0 Hz, *J* = 10.5 Hz), 2.67-2.70 (m, 2H) ppm.

^{13}C (125 MHz, $CDCl_3$): δ 200.7, 142.8, 138.0, 128.4, 128.3, 127.9, 127.7, 127.6, 127.5, 113.7, 76.9, 76.0, 70.7, 69.4, 69.2, 65.0, 44.8 ppm.

Low-resolution MS (EI): m/z: 352 (M^+).

HRMS (ESI) calcd for $C_{22}H_{24}O_4$+Na 375.1573, found 375.1573.

Compound 55α and 56α:

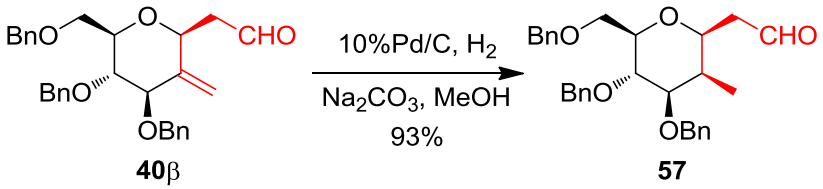
^{1}H (400 MHz, $CDCl_3$): δ 9.81 (t, 1H, *J* = 2 Hz), 7.27-7.35 (m, 10H), 5.33 (s, 1H), 5.11 (s, 1H), 4.68 (s, 2H), 4.64 (d, 1H, *J* = 12.4 Hz),4.49 (d, 1H, *J* = 12.4 Hz), 4.44 (dd, 1H, *J* = 4.8 Hz, *J* = 8 Hz), 4.06-4.07 (m, 1H), 4.03 (dd, 1H, *J* = 5.2 Hz, *J* = 12.4 Hz), 3.70-3.72 (m, 1H), 3.56 (dd, 1H, *J* = 2.4 Hz, *J* = 12 Hz), 3.07 (ddd, 2 Hz, *J* = 8.4 Hz, *J* = 16.8 Hz), 2.81 (ddd, 1H, *J* = 2 Hz, *J* = 8.4 Hz, *J* = 16.8 Hz) ppm.

^{13}C (100 MHz, $CDCl_3$): δ 200.7, 141.8, 138.2, 137.9, 128.4, 128.3, 127.9, 127.8, 127.8, 127.6, 127.5, 111.7, 78.1, 74.5, 73.0, 71.2, 70.5, 64.8, 45.5 ppm.

Low-resolution MS (EI): m/z: 352 (M^+).

HRMS (ESI) calcd for $C_{22}H_{24}O_4$+Na 375.1573, found 375.1573.

(2.4.2.31) 2-((2*S*,3*R*,4*R*,5*S*,6*R*)-4,5-bis(benzyloxy)-6-((benzyloxy)methyl)-3-methyltetrahydro-2*H*-pyran-2-yl)acetaldehyde (57):



40β **57**

Compound **57** was synthesized using the compound **40**β (0.2 g, 0.42 mmol), Na_2CO_3 (134 mg, 1.27 mmol) in methanol according to the procedure in **(2.4.2.5)**. The crude product was purified by silica-gel column chromatography with ethyl acetate/hexane (2:8) to provide the **57** as a colourless gum (93 % yield).

Compound 57:

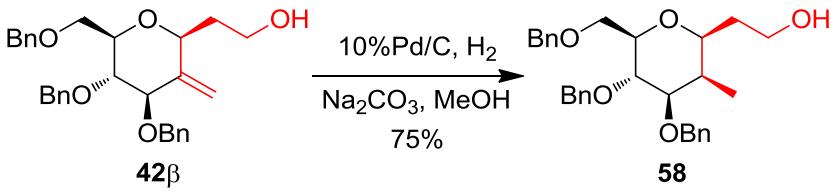
^{1}H (400 MHz, $CDCl_3$): δ 9.82 (t, 1H, *J* = 1.6 Hz), 7.19-7.41 (m, 15H), 4.90 (d, 1H, *J* = 10.8 Hz), 4.70 (d, 1H, *J* = 11.6 Hz), 4.57 (d, 1H, *J* = 11.6 Hz), 4.56 (d, 1H, *J* = 11.6 Hz), 4.53 (d, 1H, *J* = 12.0 Hz), 4.49 (d, 1H, *J* = 12.0 Hz), 4.01-4.04 (m, 1H), 3.66-3.76 (m, 4H), 3.46 (dt, 1H, *J* = 2.8 H, *J* = 9.6 Hz), 2.77 (dd, 1H, *J* = 8.8 Hz, *J* = 16.0 Hz), 2.50 (dd, 1H, *J* = 4.4 Hz, *J* = 16.0 Hz), 2.25-2.28 (m, 1H), 1.05 (d, 3H, *J* = 7.2 Hz) ppm.

^{13}C (100 MHz, $CDCl_3$): δ 200.8, 138.5, 138.4, 138.3, 128.4, 128.3, 128.0, 127.9, 127.6, 83.8, 79.7, 75.1, 74.0, 73.4, 73.3, 70.8, 69.3, 46.4, 35.9, 6.5 ppm.

Low-resolution MS(EI): m/z: 474 (M^+).

HRMS (ESI) calcd for $C_{30}H_{34}O_5$+Na 497.2304, Found: 497.2304.

(2.4.2.32) 2-((2*S*,3*R*,4*R*,5*S*,6*R*)-4,5-bis(benzyloxy)-6-((benzyloxy)methyl)-3-methyltetrahydro-2*H*-pyran-2-yl)ethanol (58):



42β **58**

Compound **58** was synthesized using the compound **42**β (0.15 g, 0.31 mmol), Na_2CO_3 (101 mg, 0.95 mmol) in methanol according to the procedure in **(2.4.2.5)**. The crude product was purified by silica-gel column chromatography with ethyl acetate/hexane (4:6) to provide the **58** as a colourless gum (75 % yield).

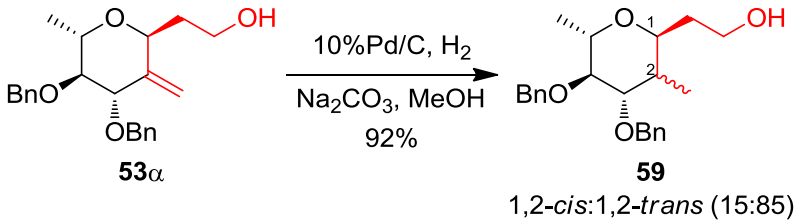
^{1}H (500 MHz, $CDCl_3$): δ 7.20-7.40 (m, 15H), 4.89 (d, 1H, *J* = 11.0 Hz), 4.69 (d, 1H, *J* = 11.5 Hz), 4.59 (d, 1H, *J* = 12.0 Hz), 4.55 (d, 1H, *J* = 11.5 Hz), 4.54 (d, 1H, *J* = 12.0 Hz), 4.50 (d, 1H, *J* = 11.0 Hz), 3.81-3.83 (m, 2H), 3.65-3.72 (m, 3H), 3.63 (dd, 1H, *J* = 6.0 Hz, *J* = 11.5 Hz), 3.57 (t, 1H, *J* = 9.5 Hz), 3.47 (ddd, 1H, *J* = 2.0 Hz, *J* = 6.0 Hz, *J* = 9.5 Hz), 2.66 (bs, 1H), 2.17-2.20 (m, 1H), 2.01-2.06 (m, 1H), 1.53-1.56 (m, 1H), 1.05 (d, 3H, *J* = 7.0 Hz) ppm.

^{13}C (100 MHz, $CDCl_3$): δ 138.5, 138.4, 138.2, 128.4, 128.3, 128.3, 128.0, 127.7, 127.6, 127.5, 127.5, 83.9, 79.3, 78.9, 75.0, 74.5, 73.3, 70.6, 69.7, 61.9, 36.6, 34.5, 6.6 ppm.

Low-resolution MS(EI): m/z: 476 (M^+).

HRMS (ESI) calcd for $C_{30}H_{36}O_5$+Na 499.2461, Found: 499.2461.

(2.4.2.33) 2-((2*S*,4*S*,5*S*,6*S*)-4,5-bis(benzyloxy)-3,6-dimethyltetrahydro-2*H*-pyran-2-yl)ethanol (59):



53α **59**

1,2-*cis*:1,2-*trans* (15:85)

Compound **59** was synthesized using the compound **53**α (0.2 g, 0.54 mmol), Na_2CO_3 (172 mg, 1.63 mmol) in methanol according to the procedure in **(2.4.2.5)**. The crude product was purified by silica-gel column chromatography with ethyl acetate/hexane (3:7) to provide the **59** as white solid (92 % yield).

Compound 59 (for 1,2-*trans* compound**)**:

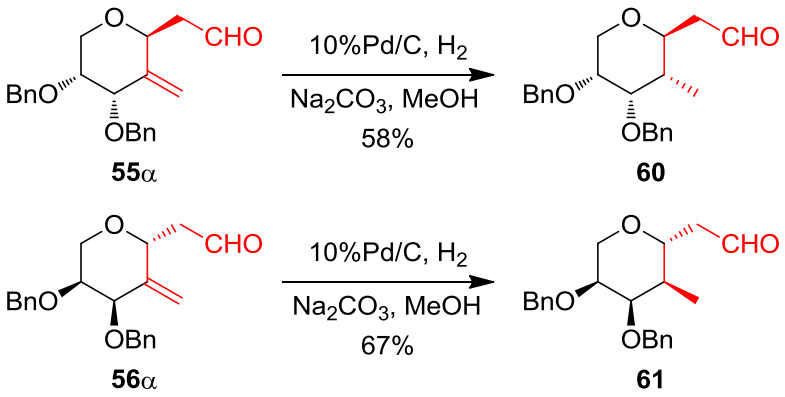
^{1}H (400 MHz, $CDCl_3$): δ 7.28-7.37 (m, 10H), 4.4.72 (d, 1H, *J* = 11.6 Hz), 4.59 (d, 1H, *J* = 11.6 Hz), 4.58 (d, 1H, *J* = 12.0 Hz), 4.53 (d, 1H, *J* = 12.0 Hz), 3.85-3.95 (m, 2H), 3.78 (t, 2H, *J* = 6.0 Hz), 3.66 (dd, 1H, *J* = 4.4 Hz, *J* = 5.6 Hz), 3.35 (t, 1H, *J* = 5.6 Hz), 2.07-2.11 (m, 1H), 1.96-1.99 (m, 1H), 1.65-1.70 (m, 1H), 1.35 (d, 3H, *J* = 6.8 Hz), 1.05 (d, 1H, *J* = 7.2 Hz) ppm.

^{13}C (100 MHz, $CDCl_3$): δ 138.4, 138.4, 128.5, 128.4, 128.3, 127.9, 127.8, 127.7, 78.9, 77.8, 74.2, 73.3, 71.6, 69.8, 61.4, 35.6, 33.3, 17.8, 13.5 ppm.

Low-resolution MS (EI): m/z: 370 (M^+).

HRMS (ESI) calcd for $C_{23}H_{30}O_4$+Na 393.2042, found 393.2046.

(2.4.2.34) 2-((2*S*,3*S*,4*S*,5*R*)-4,5-bis(benzyloxy)-3-methyltetrahydro-2*H*-pyran-2-yl)acetaldehyde (60) and 2-((2*R*,3*R*,4*R*,5*S*)-4,5-bis(benzyloxy)-3-methyltetrahydro-2*H*-pyran-2-yl)acetaldehyde (61):



Compound **60** was synthesized using the compound **55**α (0.1 g, 0.28 mmol), Na_2CO_3 (90 mg, 0.85 mmol) in methanol according to the procedure in **(2.4.2.5)**. The crude product was purified by silica-gel column chromatography with ethyl acetate/hexane (2:8) to provide the **60** as white solid (58 % yield).

Compound **61** was synthesized using the compound **56**α (0.1 g, 0.28 mmol), Na_2CO_3 (90 mg, 0.85 mmol) in methanol according to the procedure in **(2.4.2.5)**. The crude product was purified by silica-gel column chromatography with ethyl acetate/hexane (2:8) to provide the **61** as white solid (67 % yield).

Compounds 60 and 61:

^{1}H (500 MHz, $CDCl_3$): δ 9.76 (dd, 1H, *J* = 1.5 Hz, *J* = 4.0 Hz), 7.29-7.40 (m, 10H), 5.03 (d, 1H, *J* = 11.5 Hz), 4.60-4.65 (m, 3H), 3.99 (td, 1H, *J* = 3.0 Hz, *J* = 9.5 Hz), 3.79-3.85 (m, 3H), 3.59 (ddd, 1H, *J* = 2.5 Hz, *J* = 7.0 Hz, *J* = 9.0 Hz),2.54 (ddd, 1H, *J* = 1.5 Hz, *J* = 3.5 Hz, *J* = 15.5 Hz), 2.32 (ddd, 1H, *J* = 3.5 Hz, *J* = 9.5 Hz, *J* = 15.5 Hz), 1.58-1.62 (m, 1H), 0.94 (d, 3H, *J* = 7.0 Hz) ppm.

^{13}C (125 MHz, $CDCl_3$): δ 201.8, 139.1, 138.4, 128.5, 128.4, 128.2, 127.8, 127.7, 127.5, 127.4, 127.3, 77.6, 74.7, 72.7, 71.3, 64.5, 46.8, 40.2, 14.0 ppm.

Low-resolution MS (EI): m/z: 354 (M^+).

HRMS (ESI) calcd for $C_{22}H_{26}O_4$+Na 377.1729, found 377.1729.

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17. A one-pot ortho ester-Claisen (Johnson-Claisen) rearrangement of **22** was unsuccessful and provided undesired **23a** in 63% yield.
18. The ratio was calculated by taking crude ^{1}H NMR and integrating the aldehyde peaks. The stereochemistry at anomeric centre was established by considering the products ratio in later stage.
19. The configuration at anomeric centre was assigned by NOE experiment.
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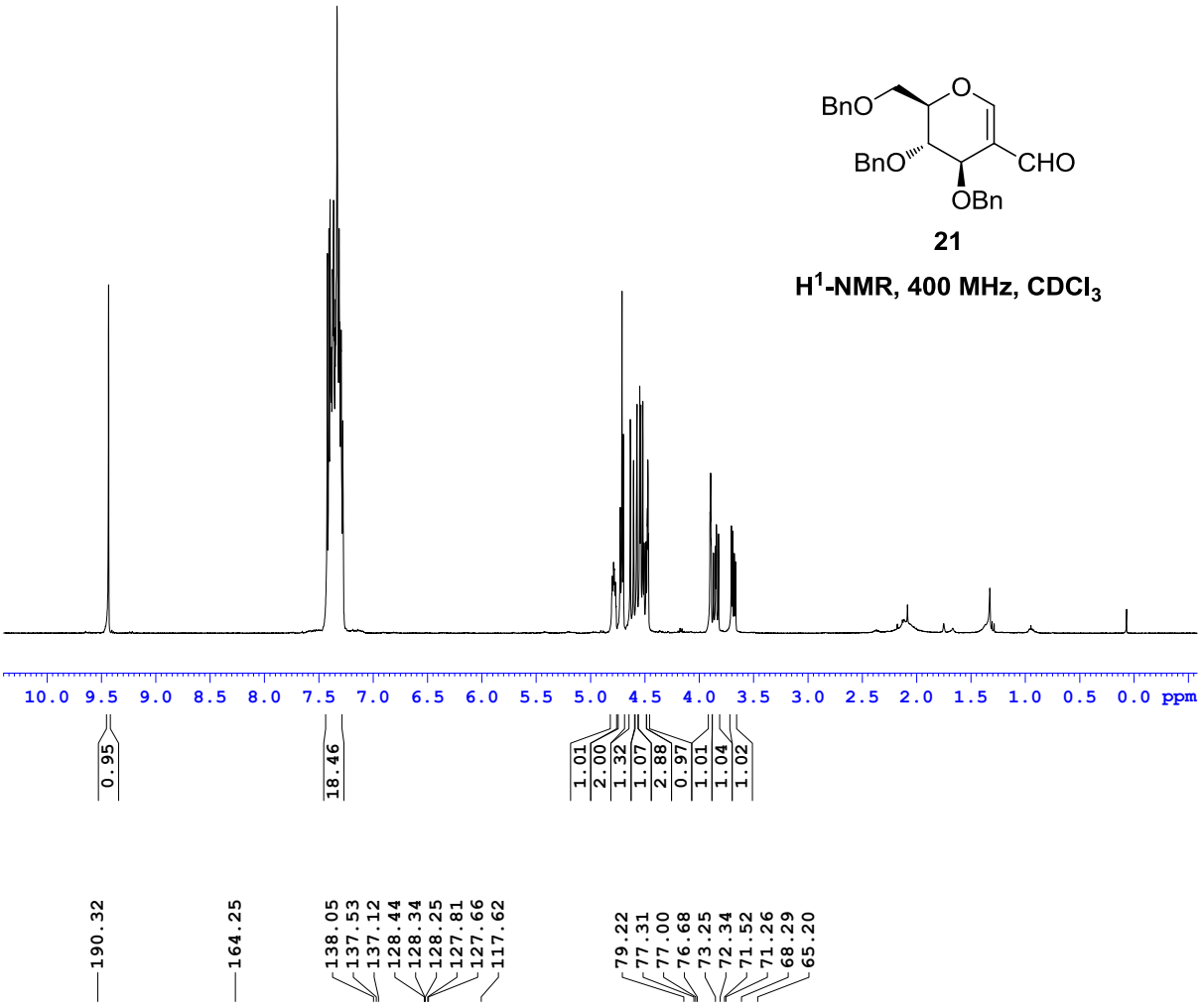
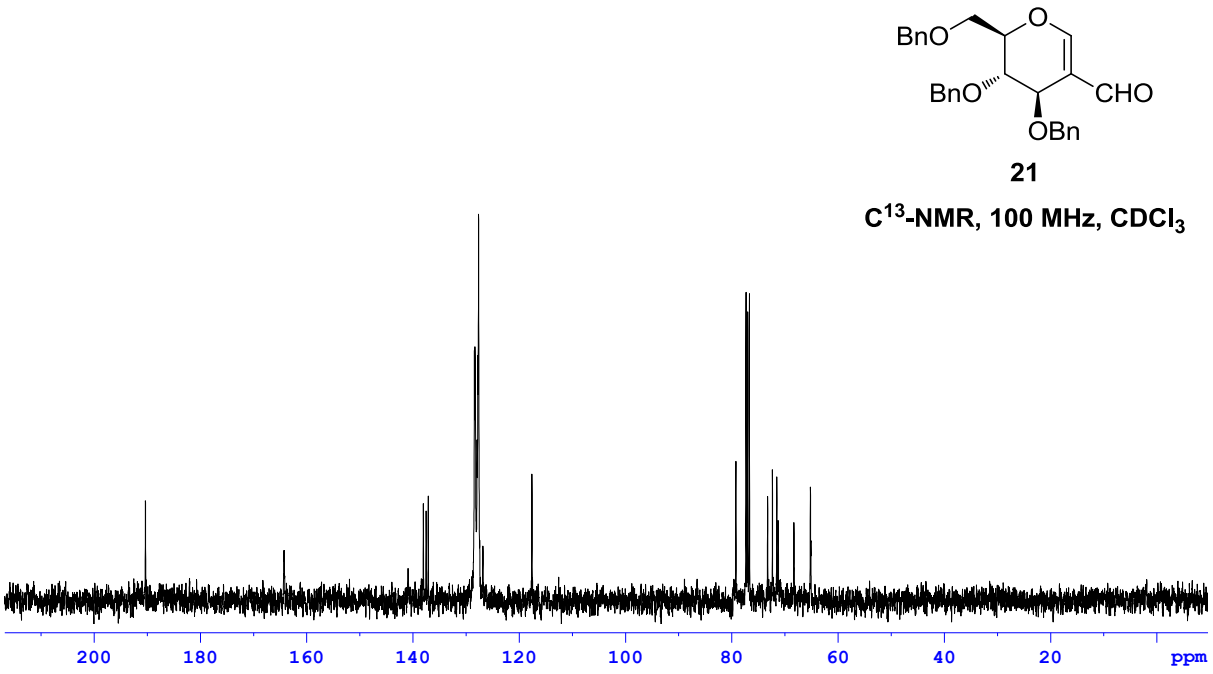


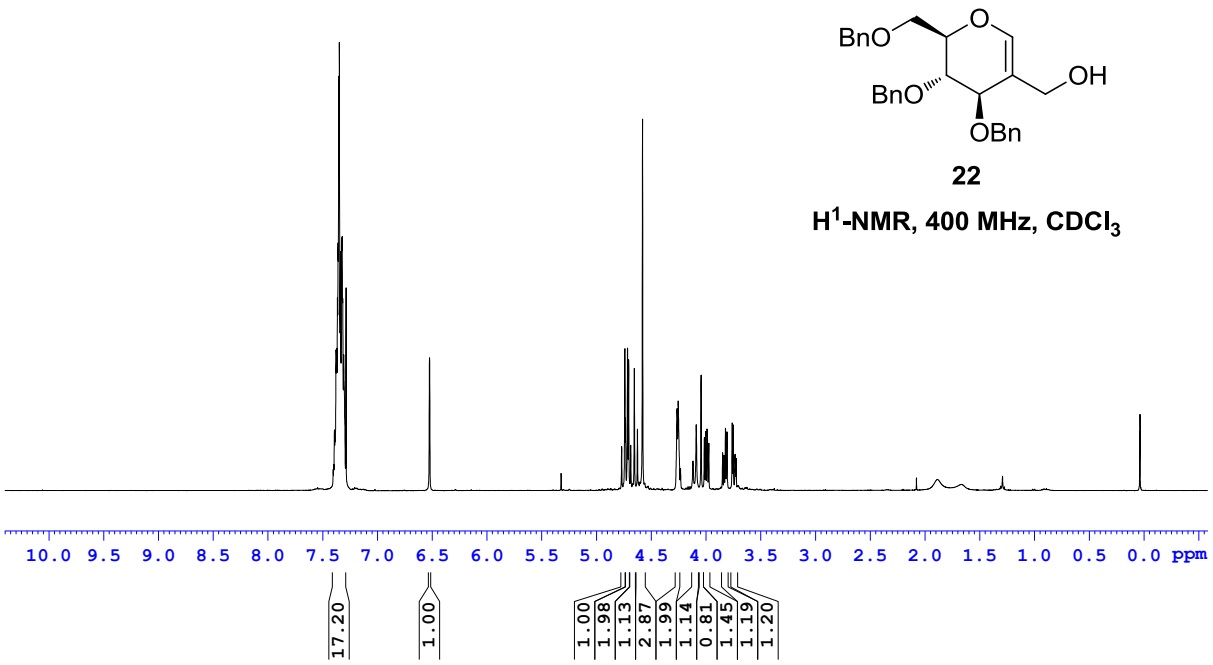
21

H^1-NMR, 400 MHz, $CDCl_3$



21

C^{13}-NMR, 100 MHz, $CDCl_3$



22

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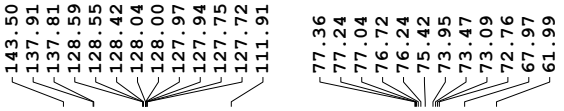
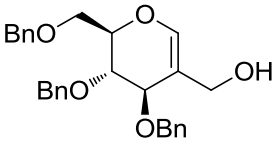
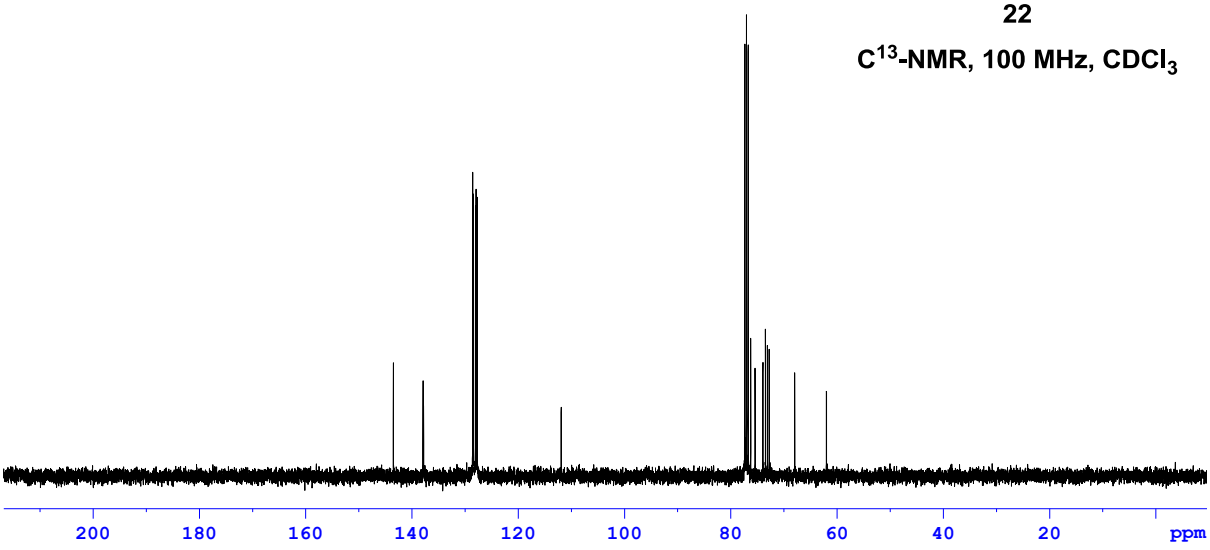
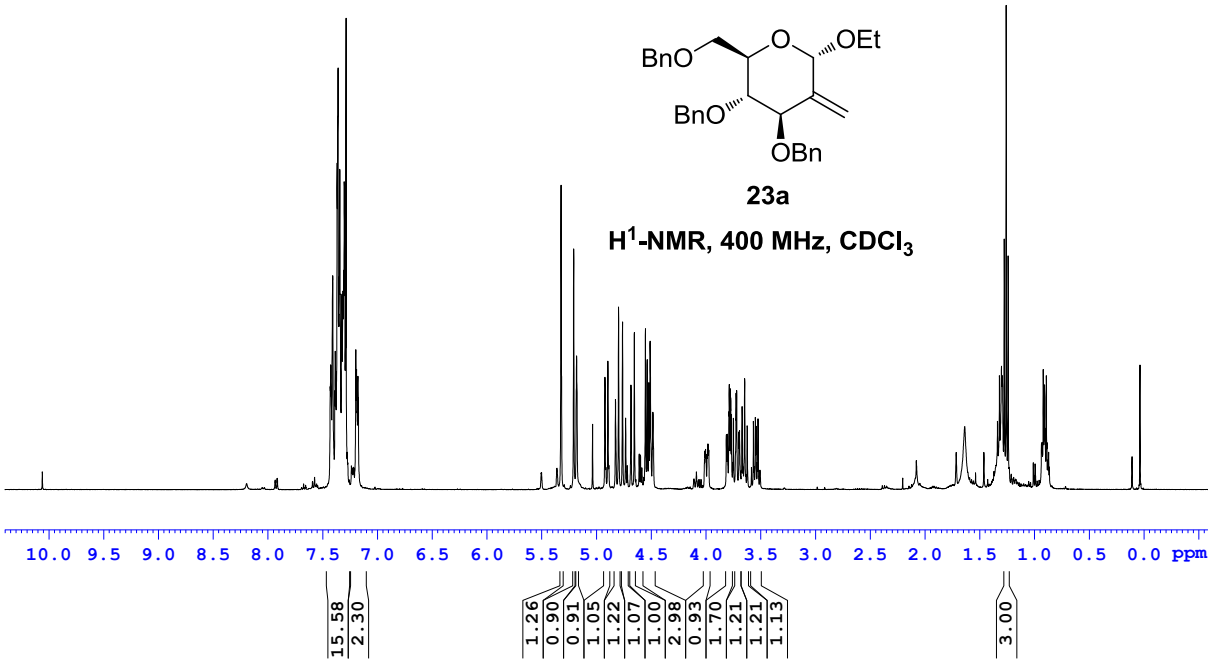




22

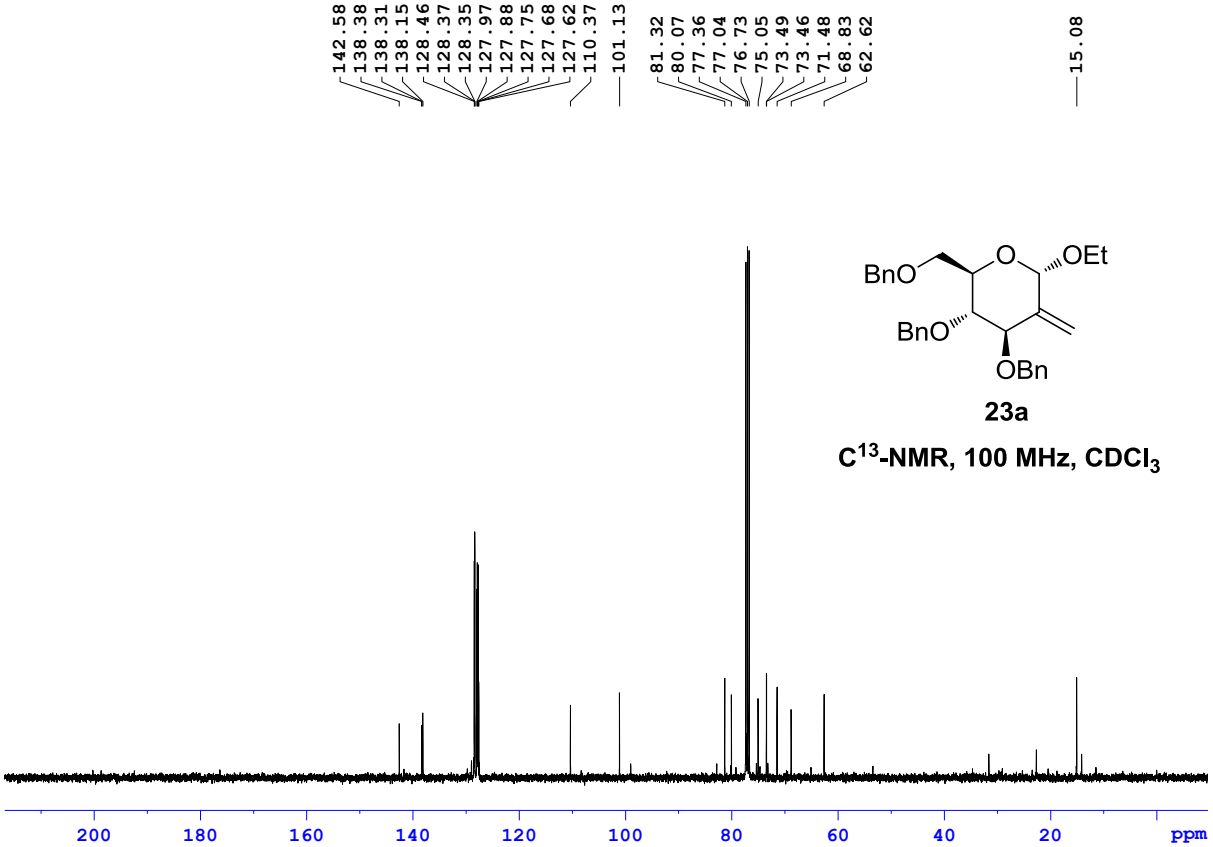
C^{13}-NMR, 100 MHz, $CDCl_3$





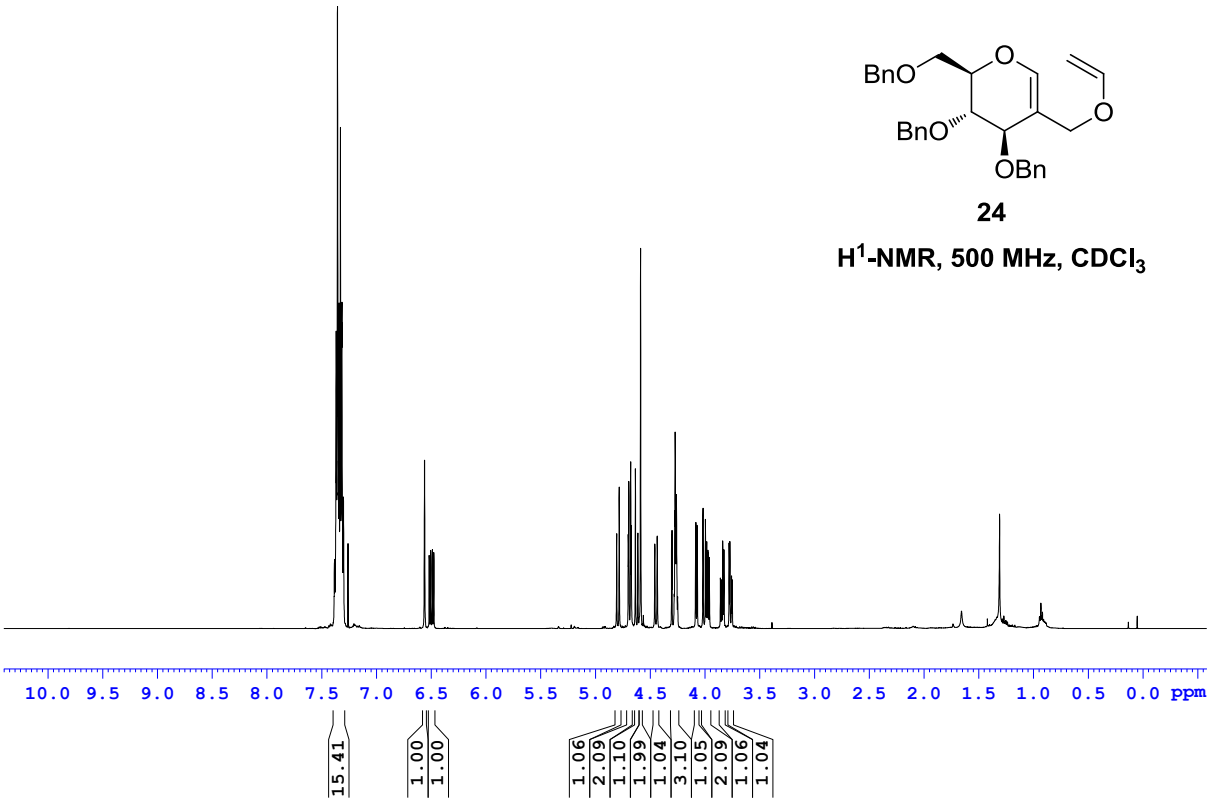
23a

H^1-NMR, 400 MHz, $CDCl_3$



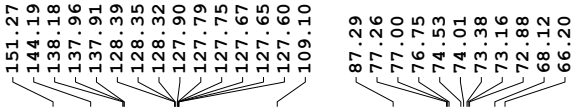
23a

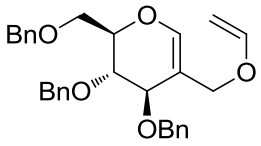
C^{13}-NMR, 100 MHz, $CDCl_3$



24

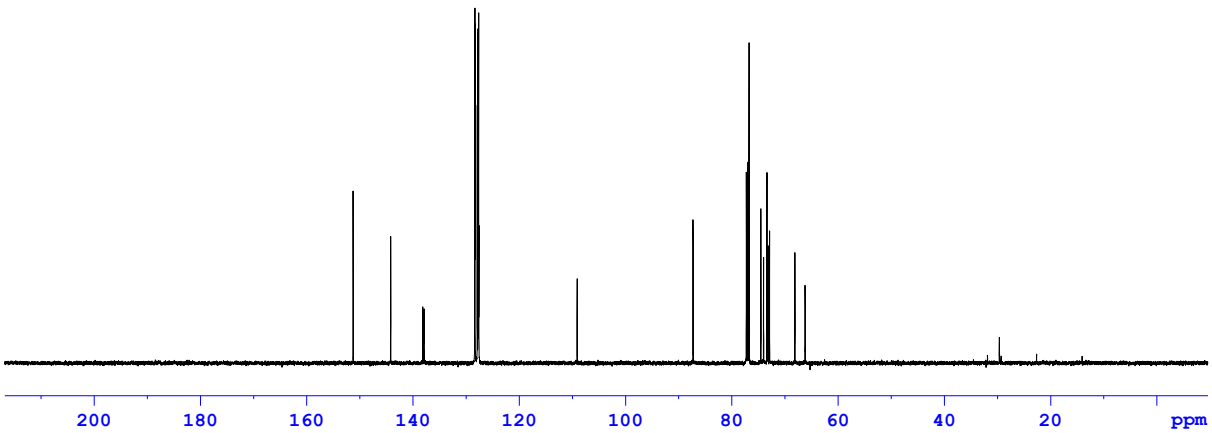
H^1-NMR, 500 MHz, $CDCl_3$

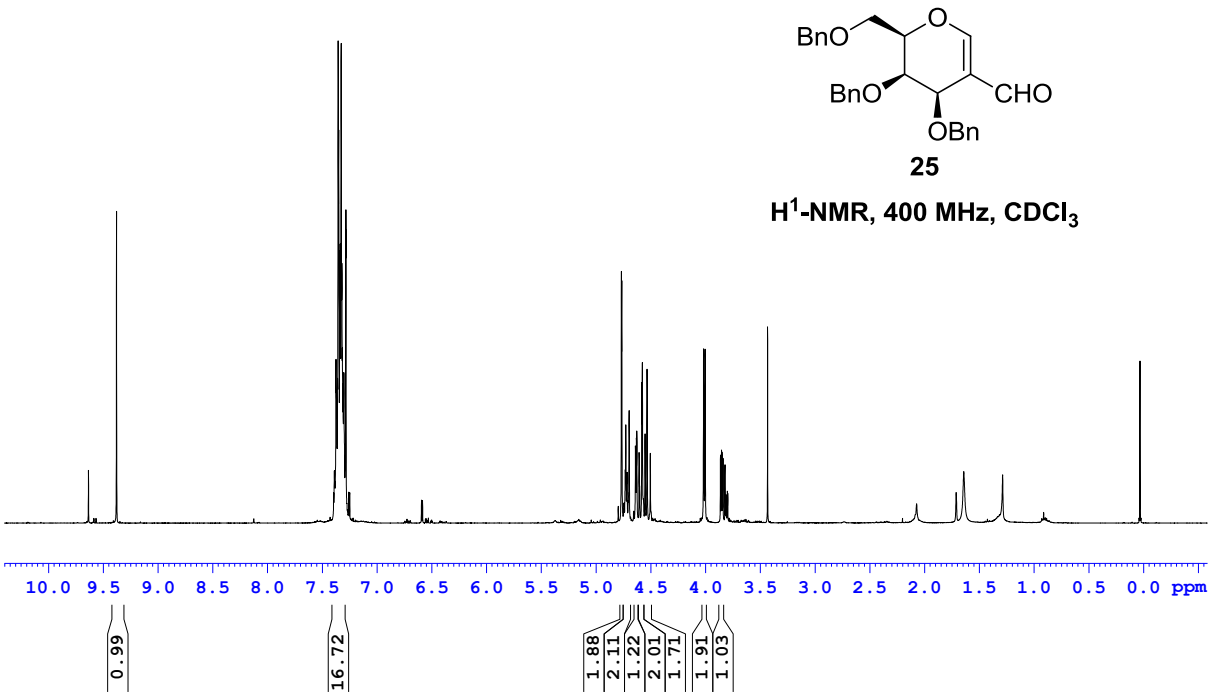




24

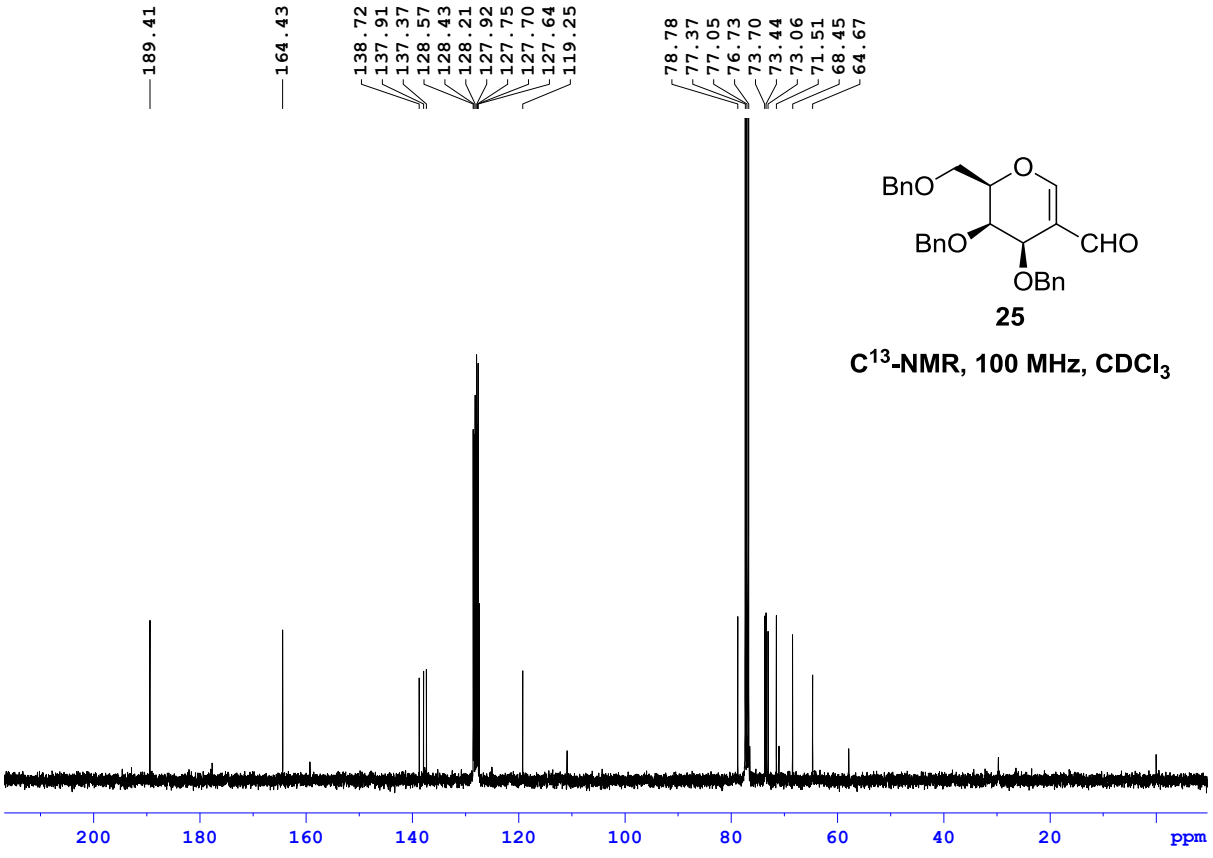
C^{13}-NMR, 125 MHz, $CDCl_3$





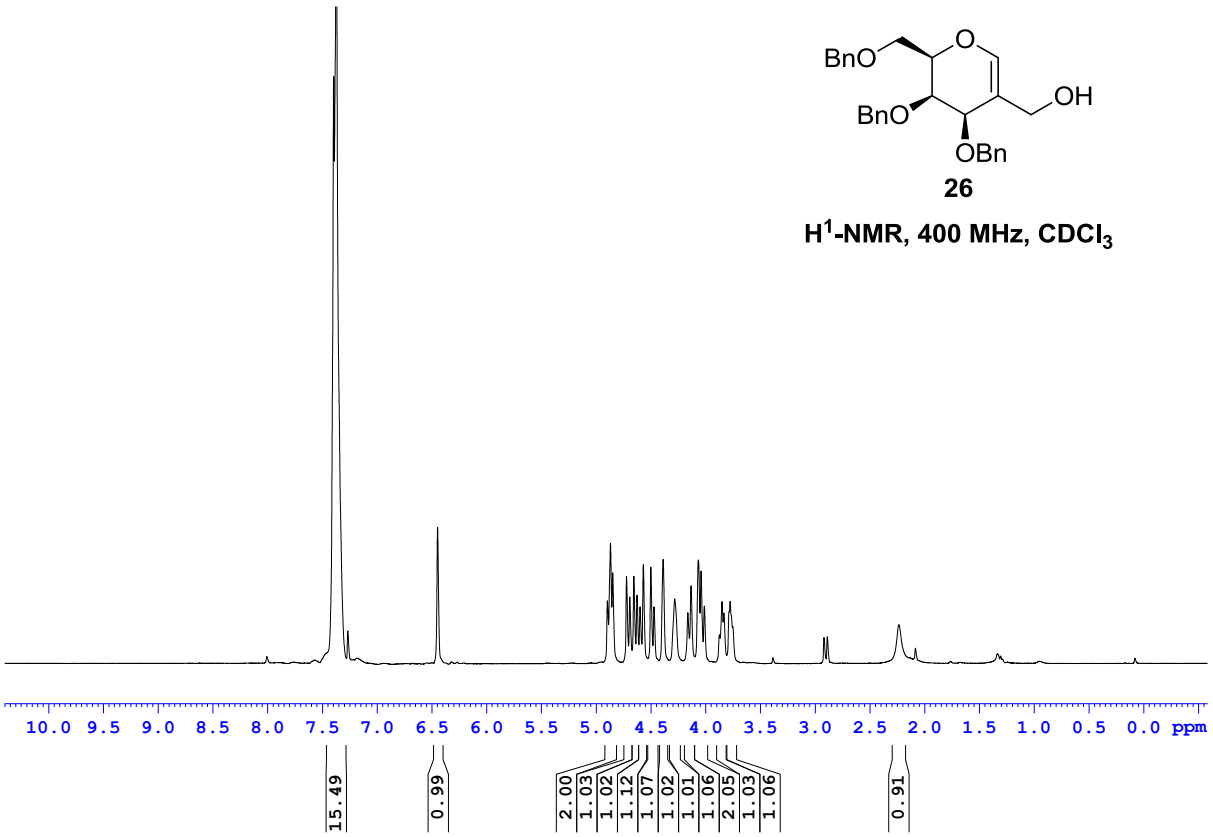
25

H^1-NMR, 400 MHz, $CDCl_3$



25

C^{13}-NMR, 100 MHz, $CDCl_3$



26

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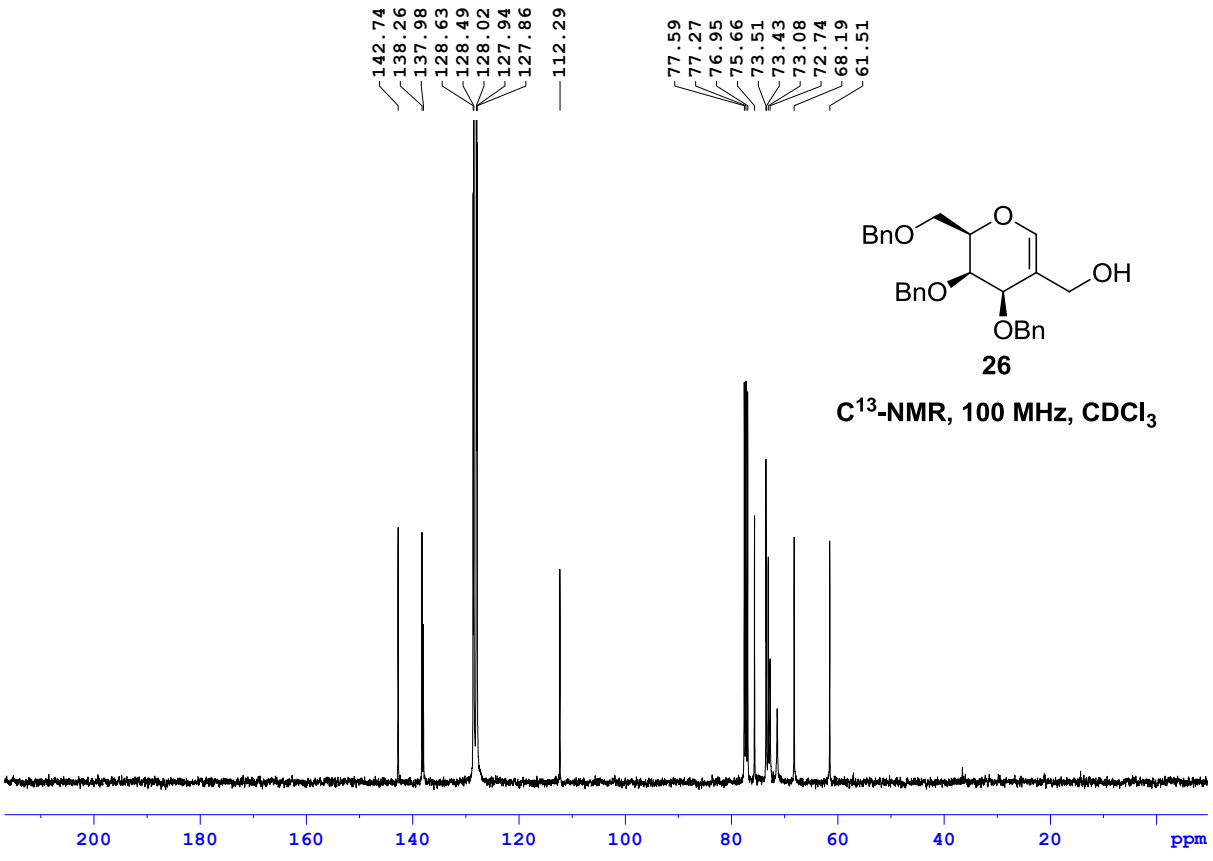

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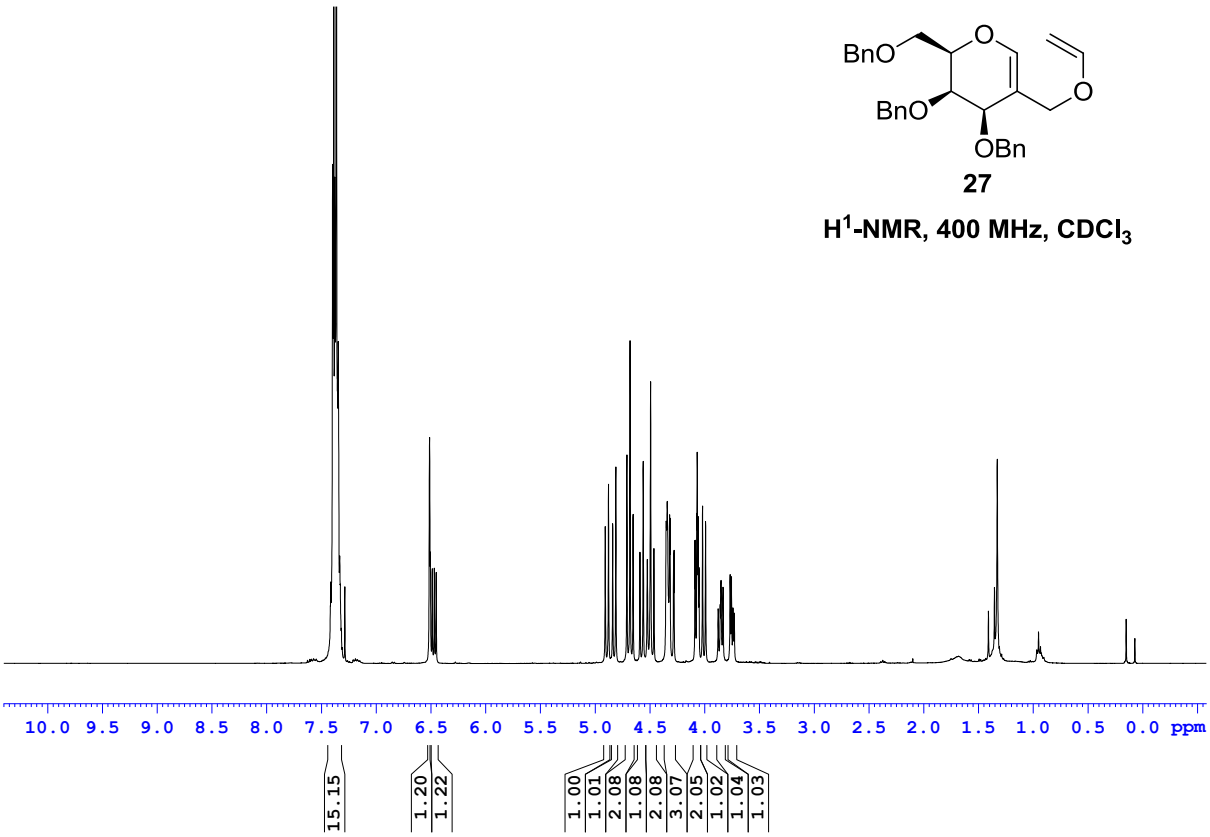

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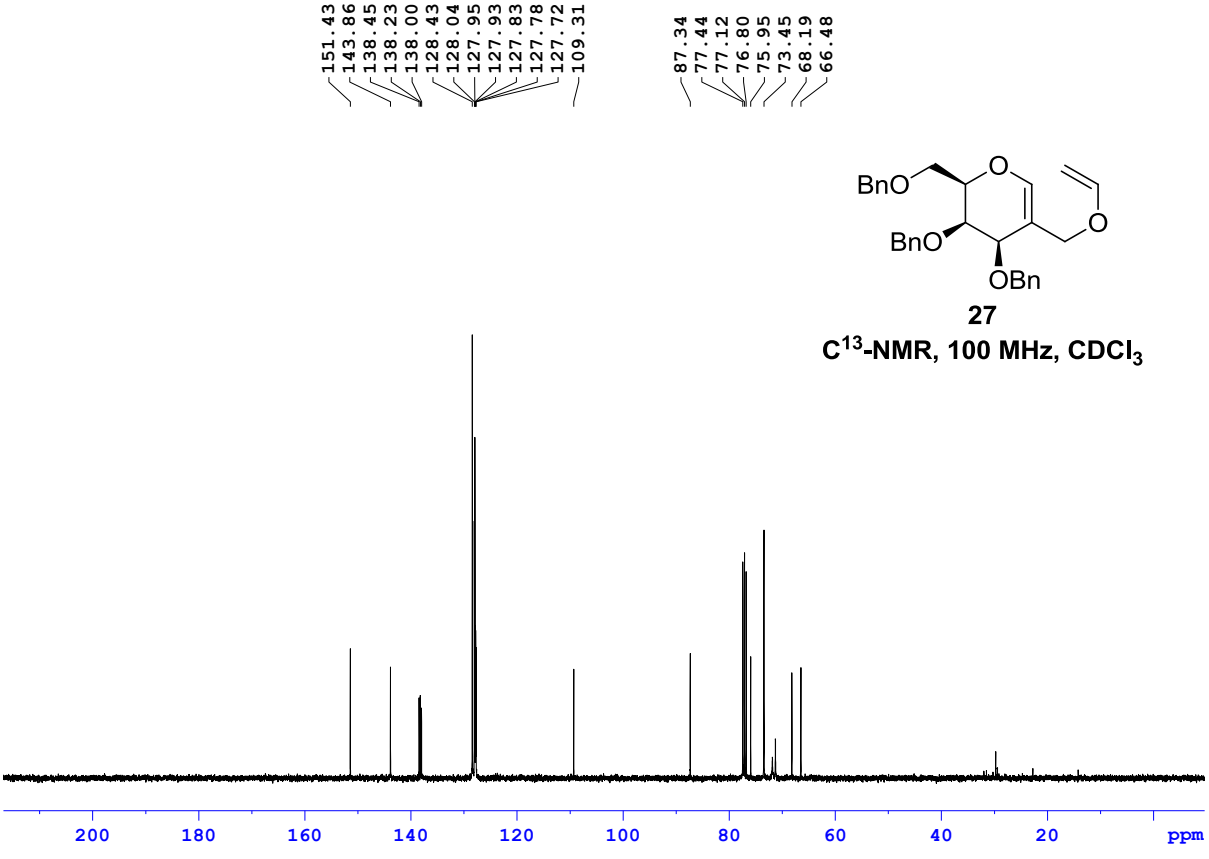

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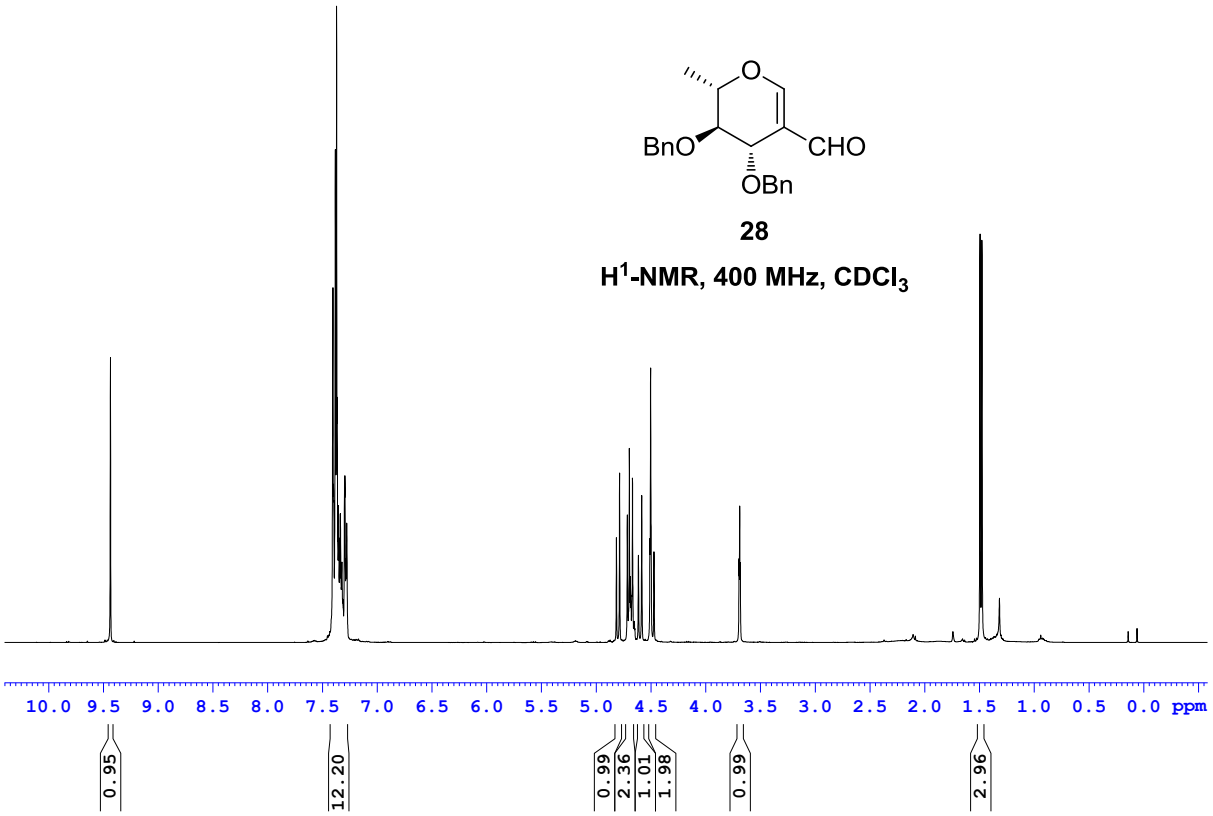

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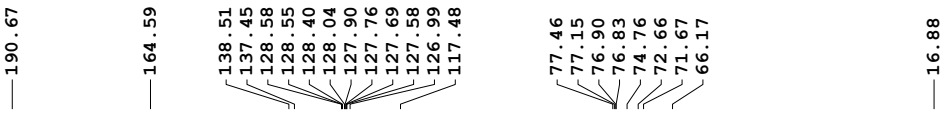

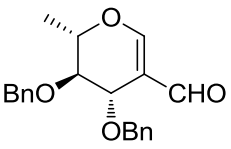

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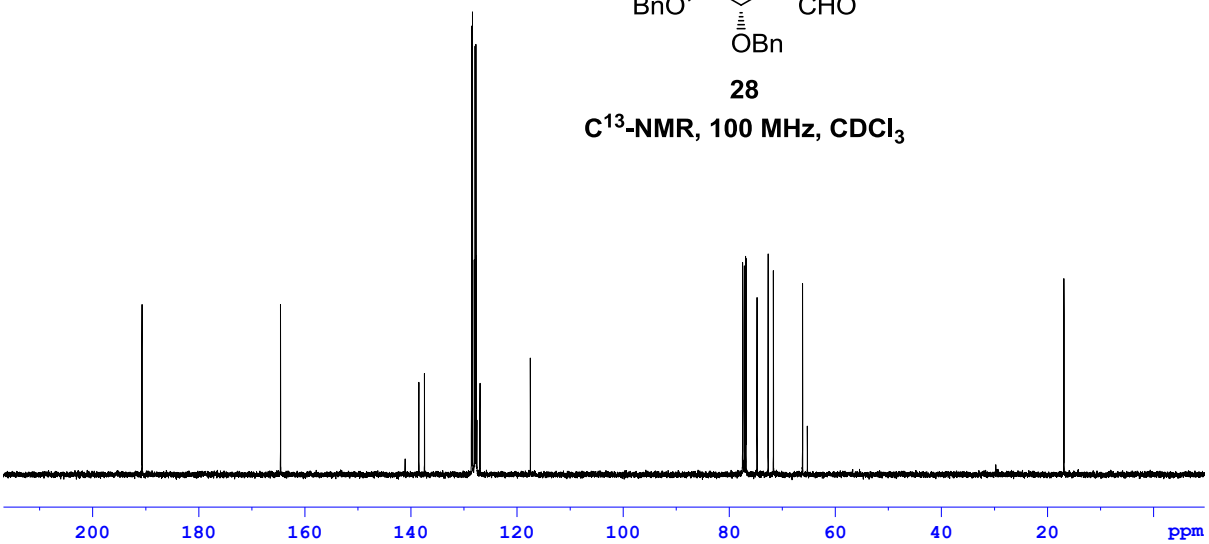

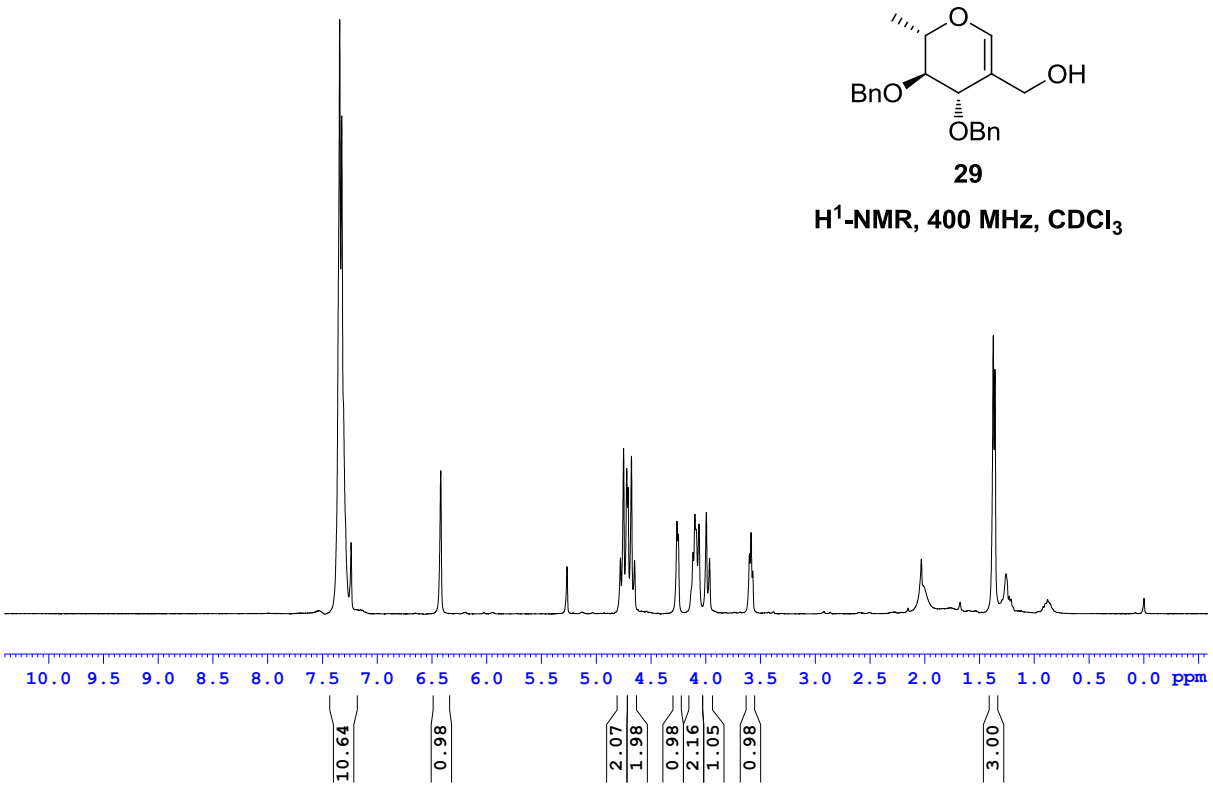

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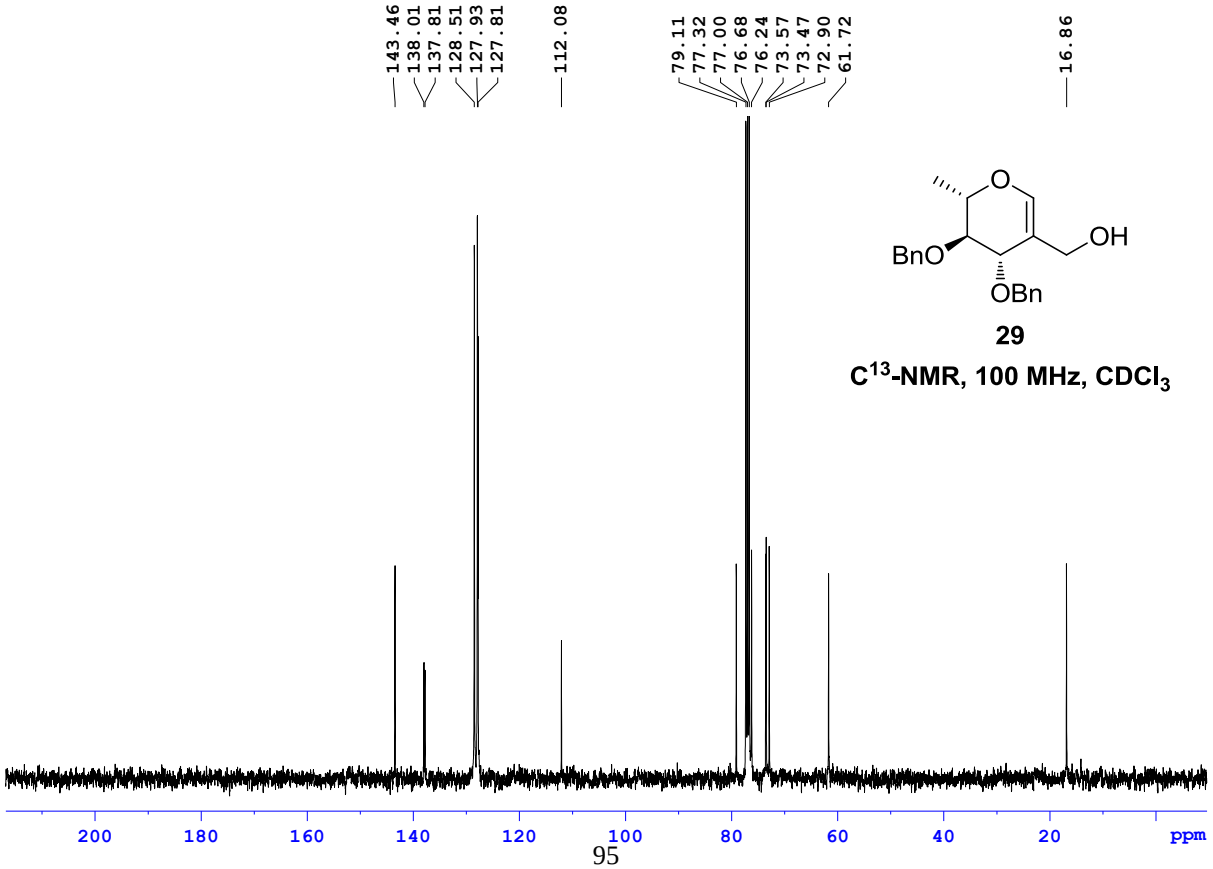

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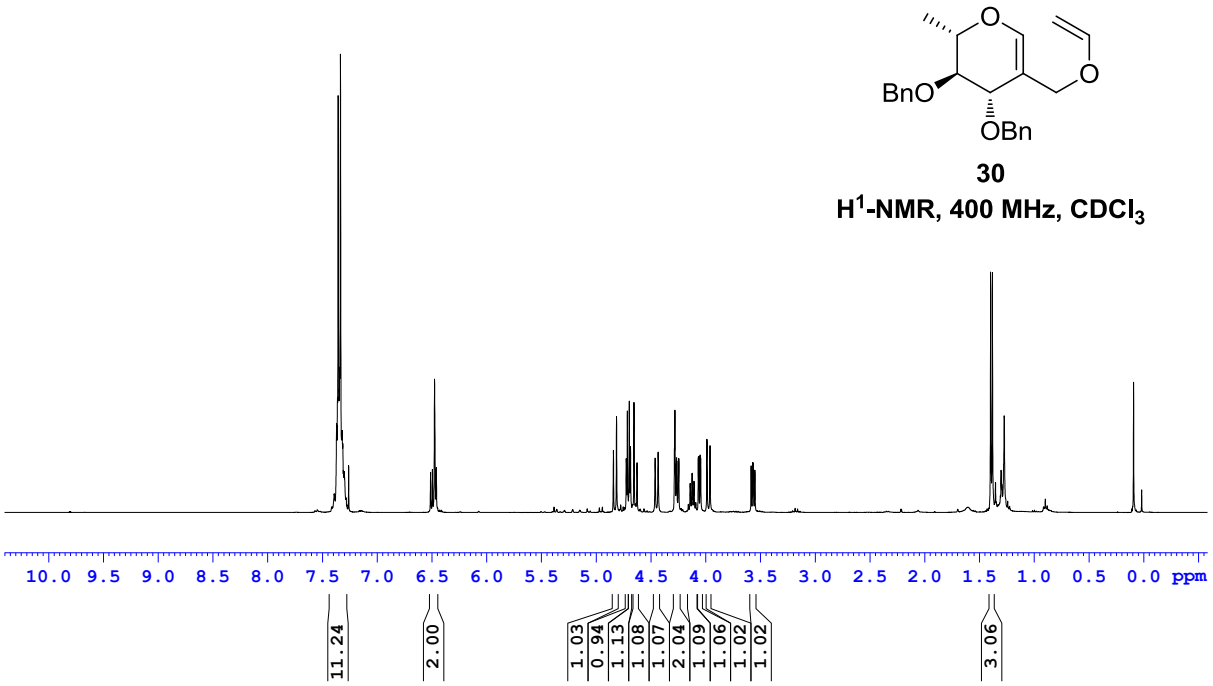

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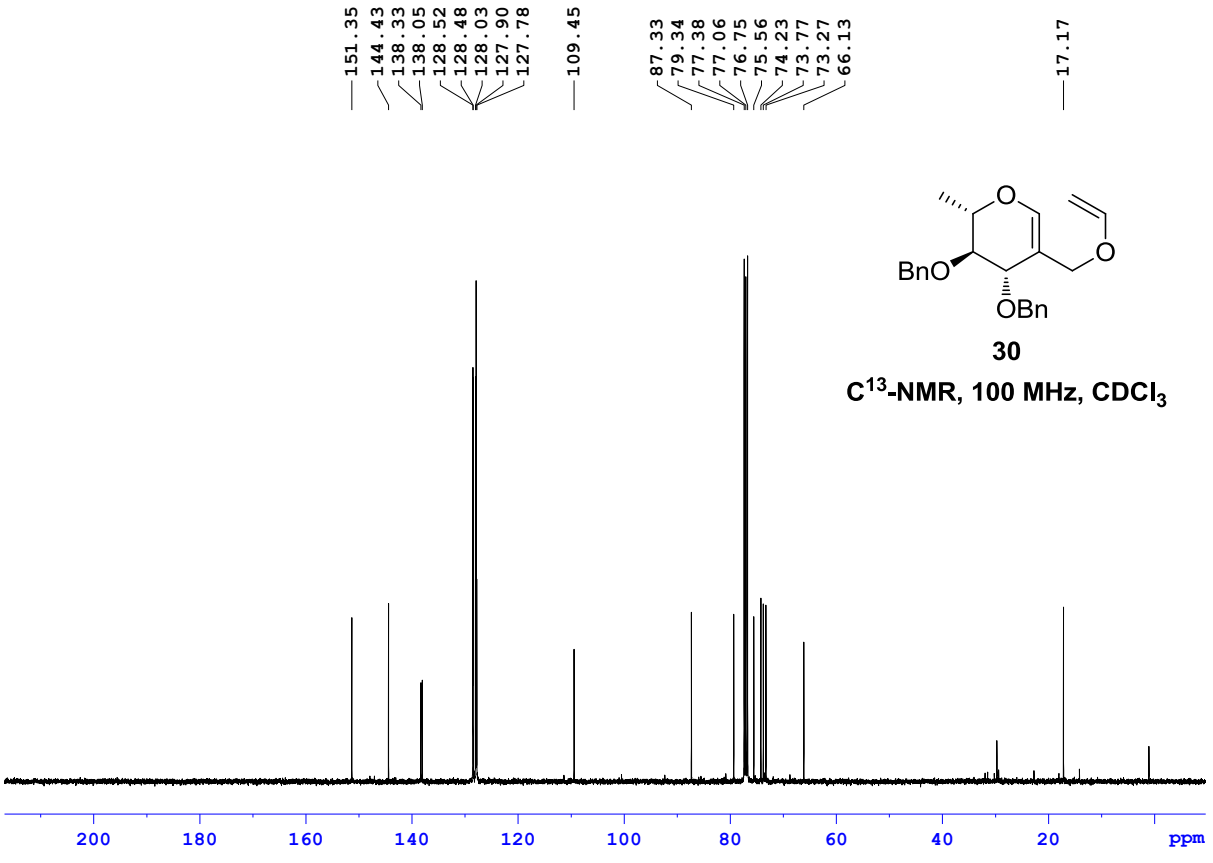

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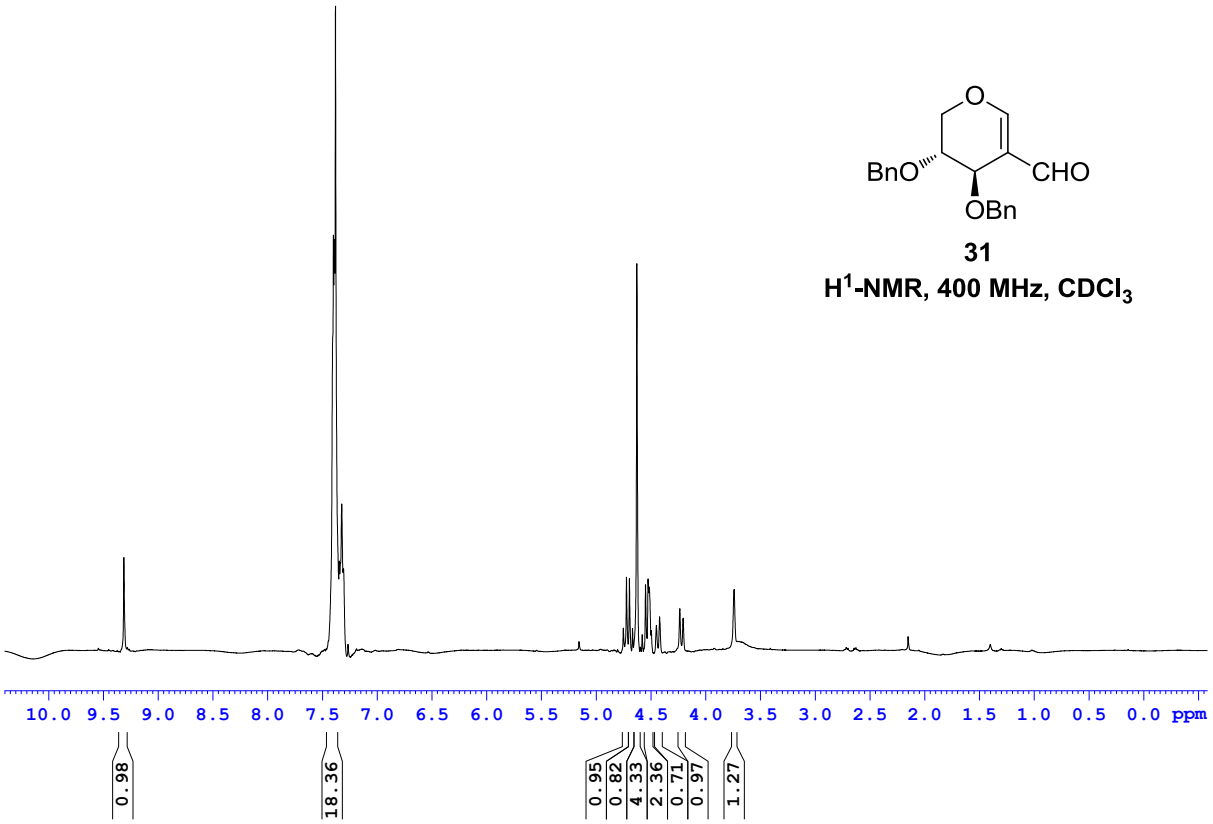

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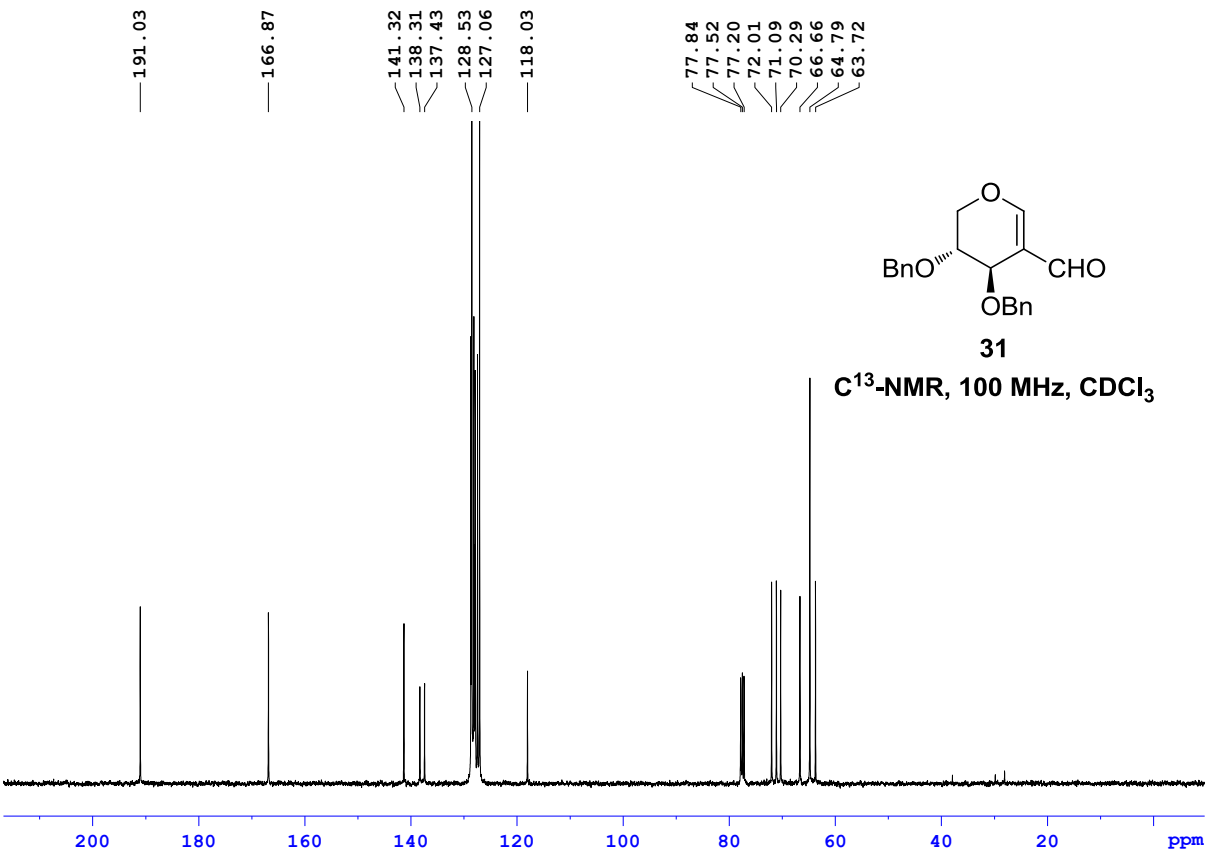

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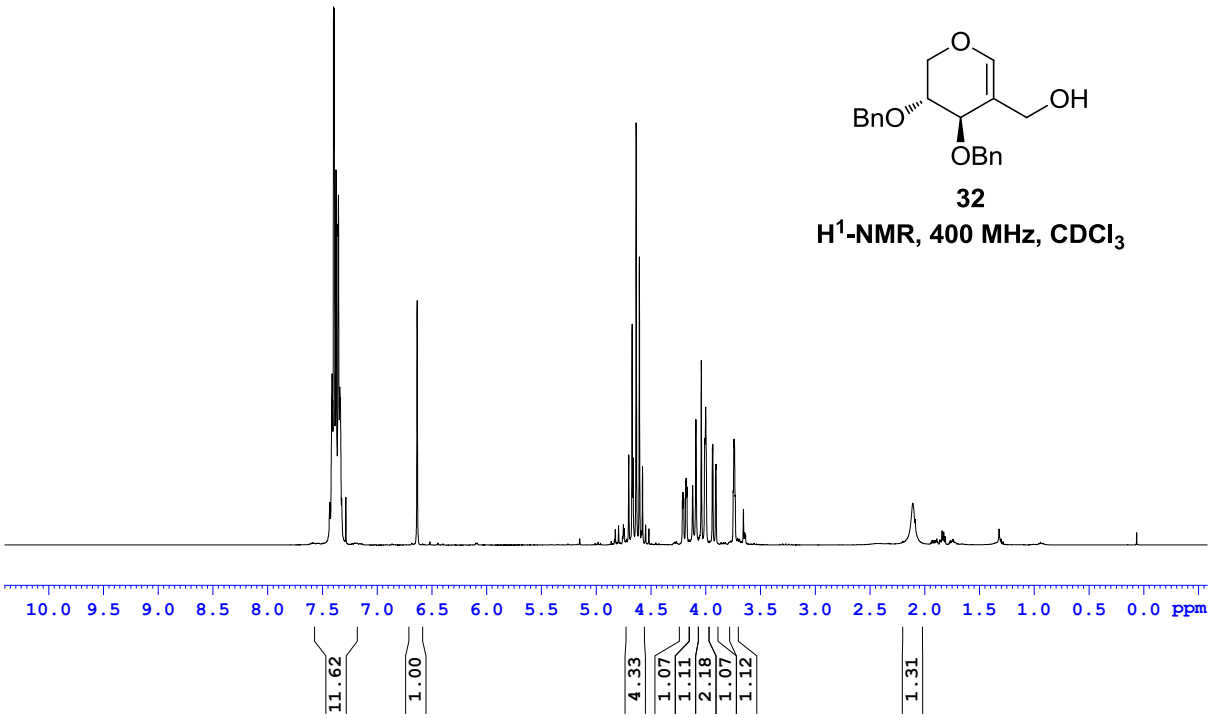

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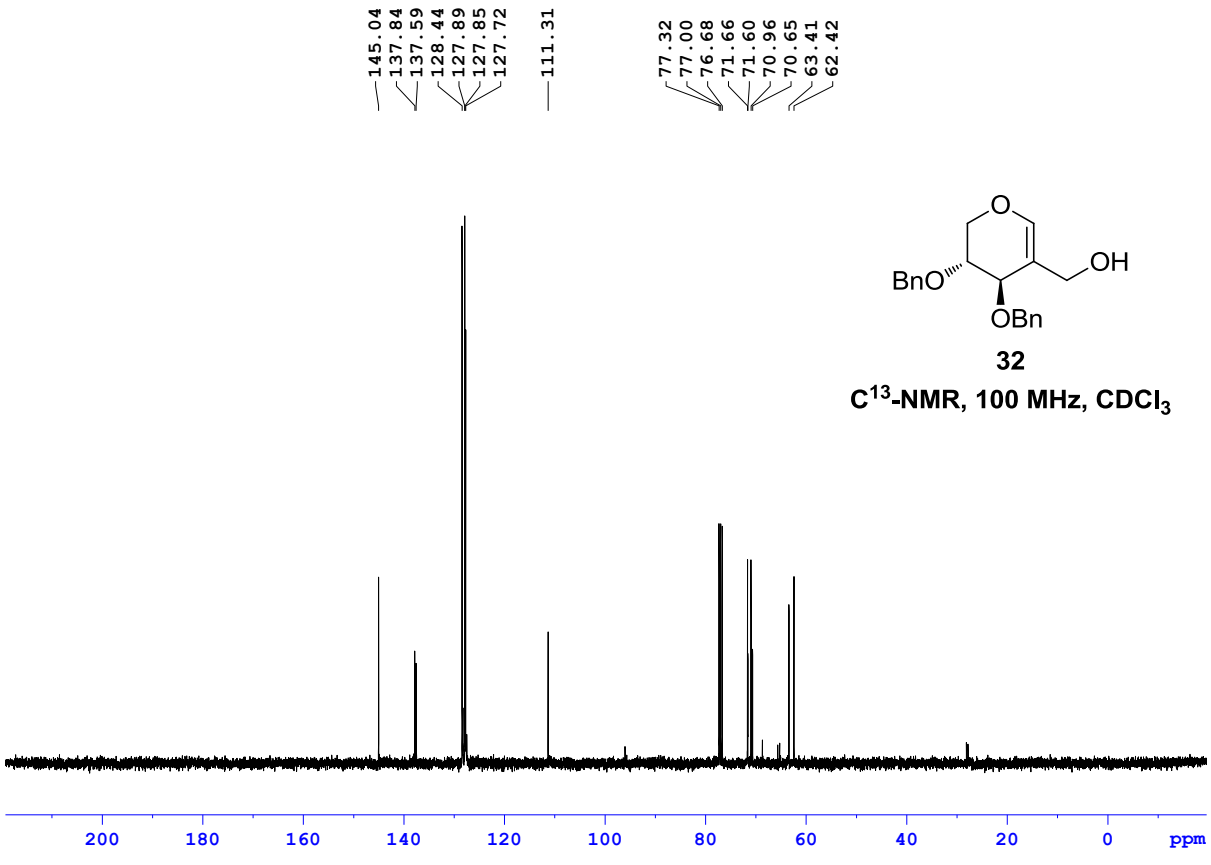

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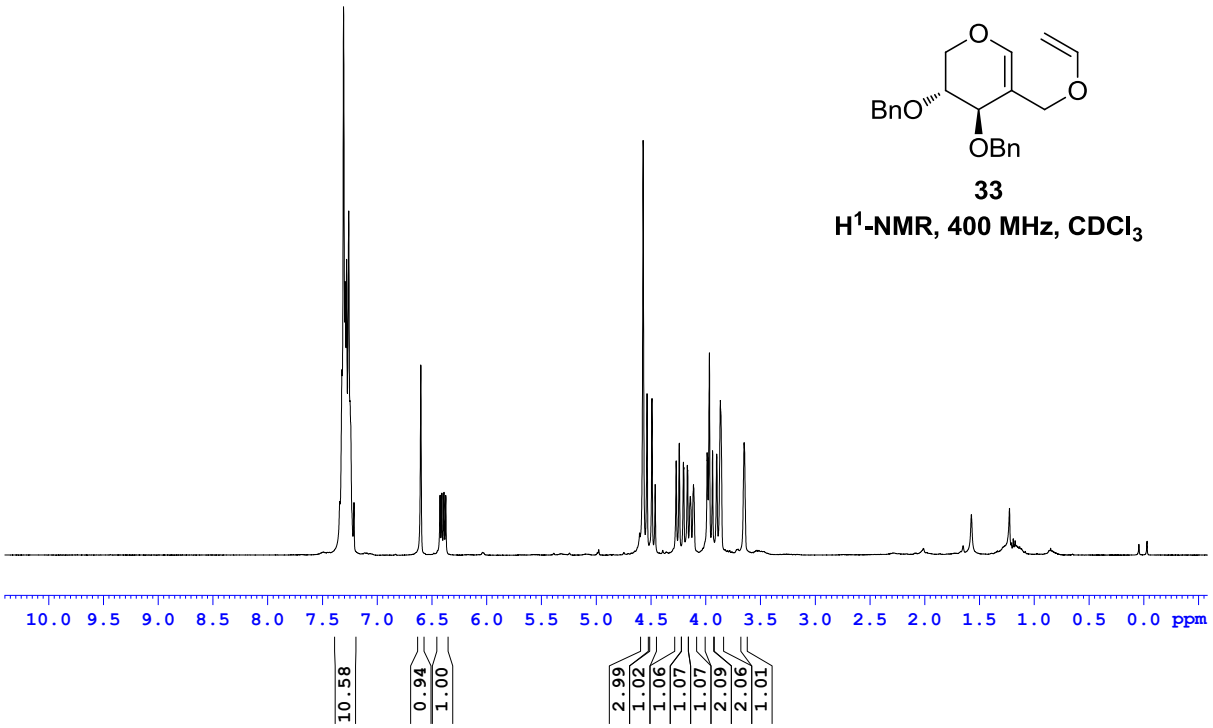

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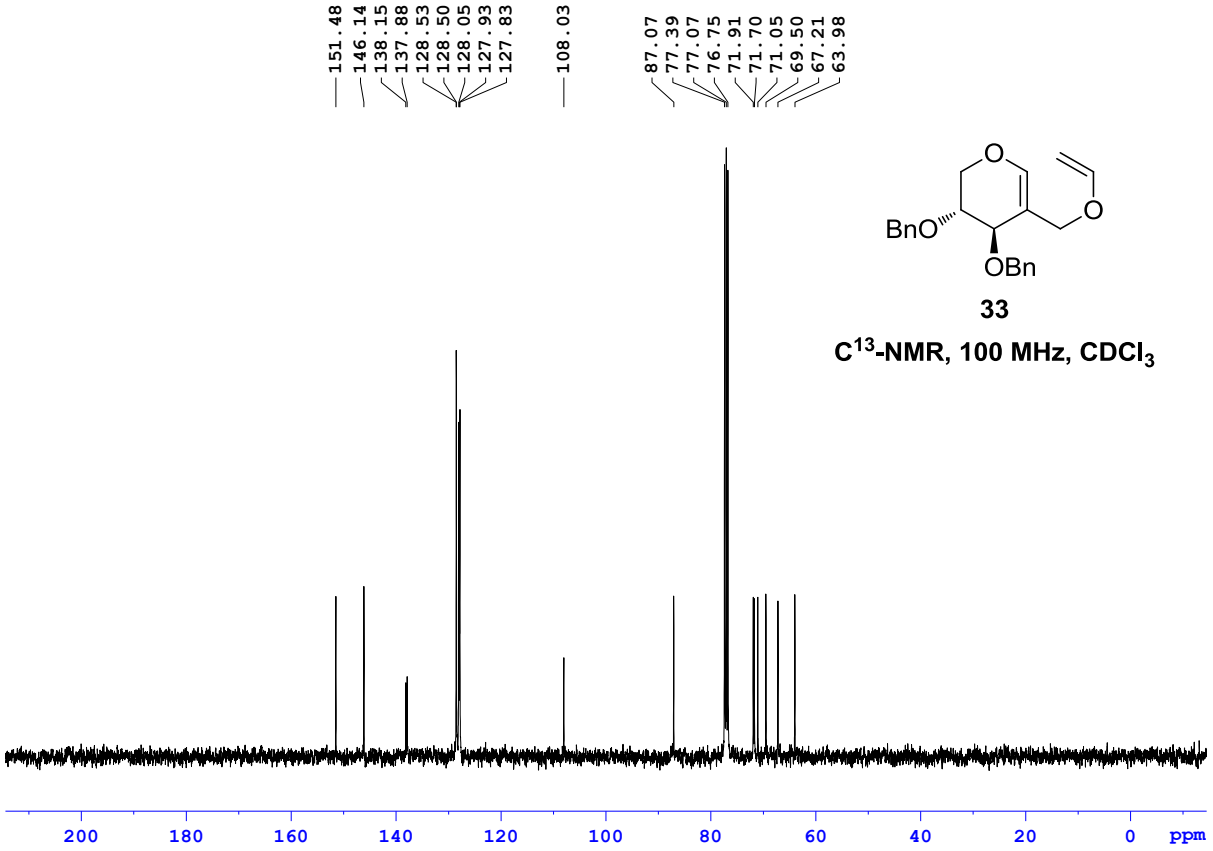

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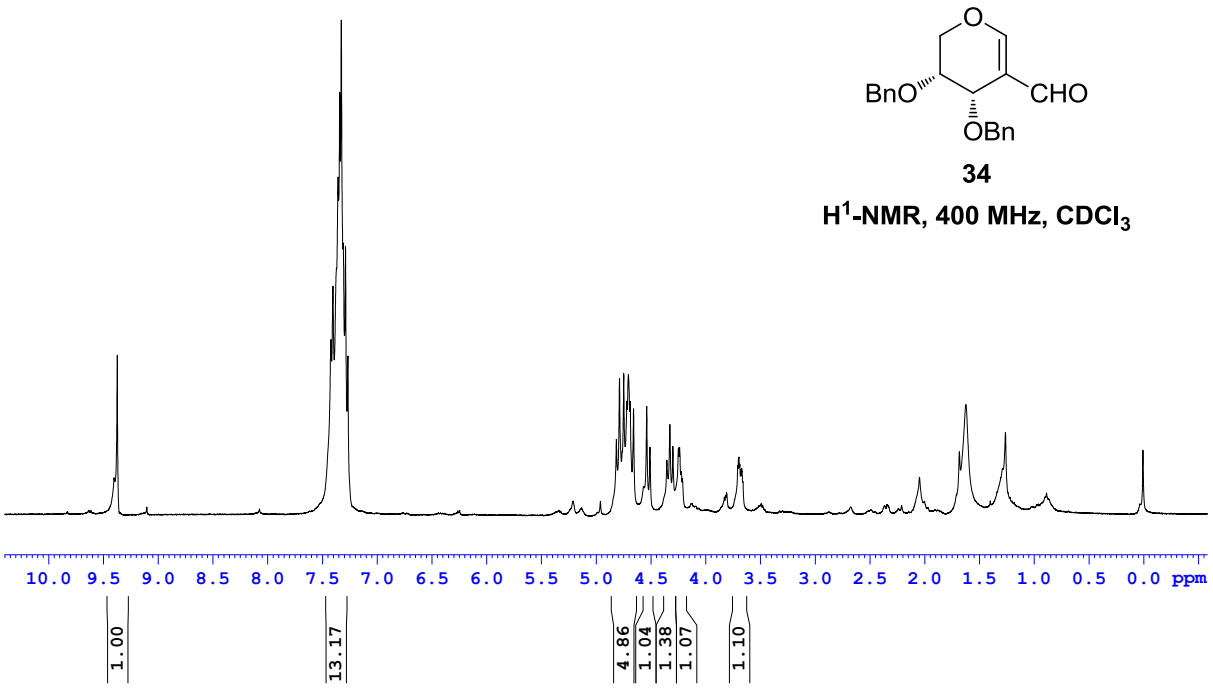

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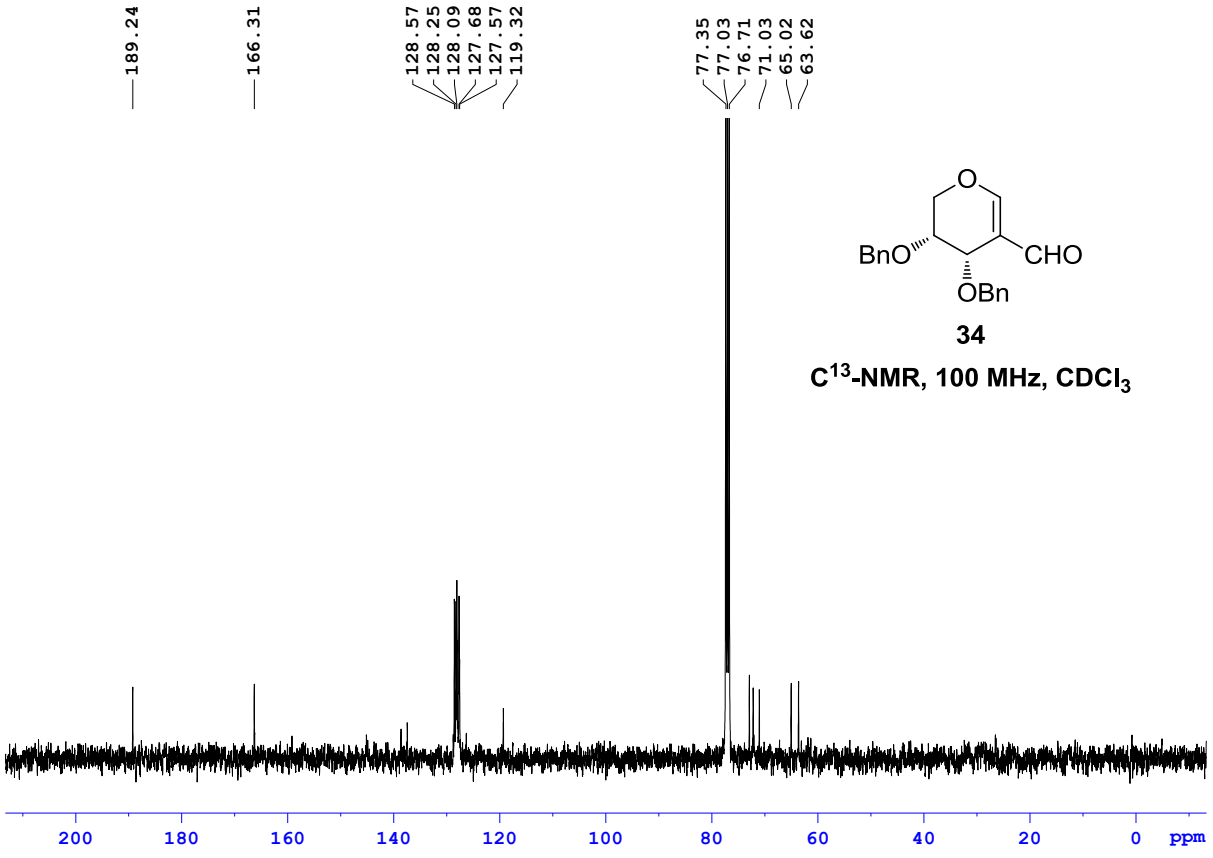
H^1-NMR, 400 MHz, $CDCl_3$



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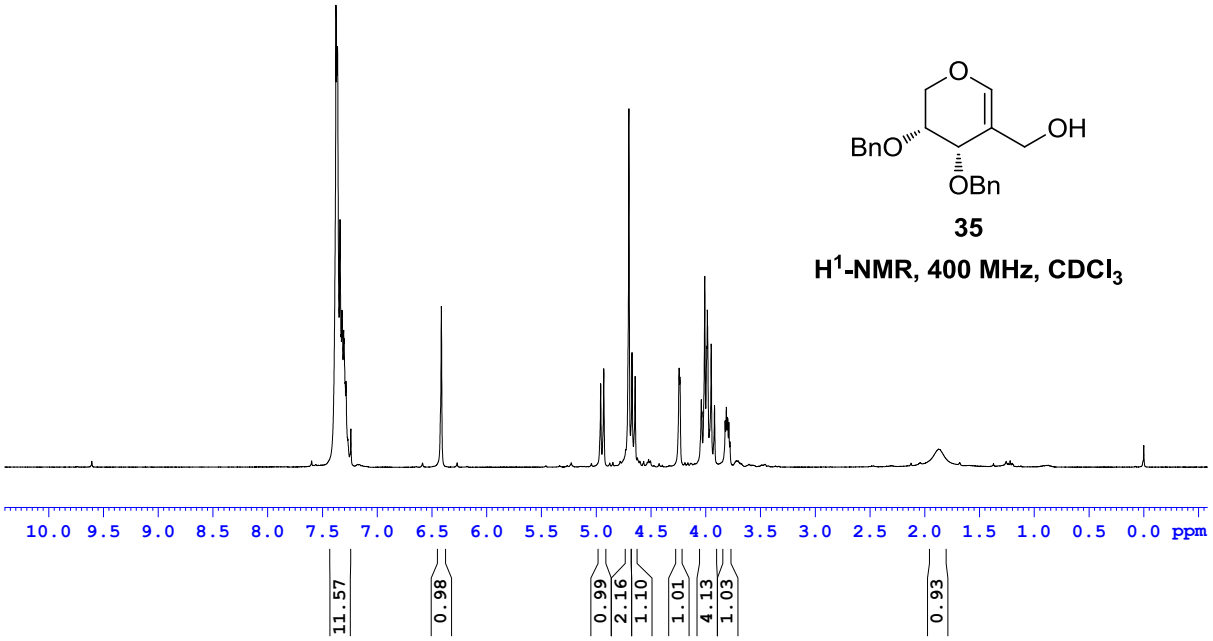

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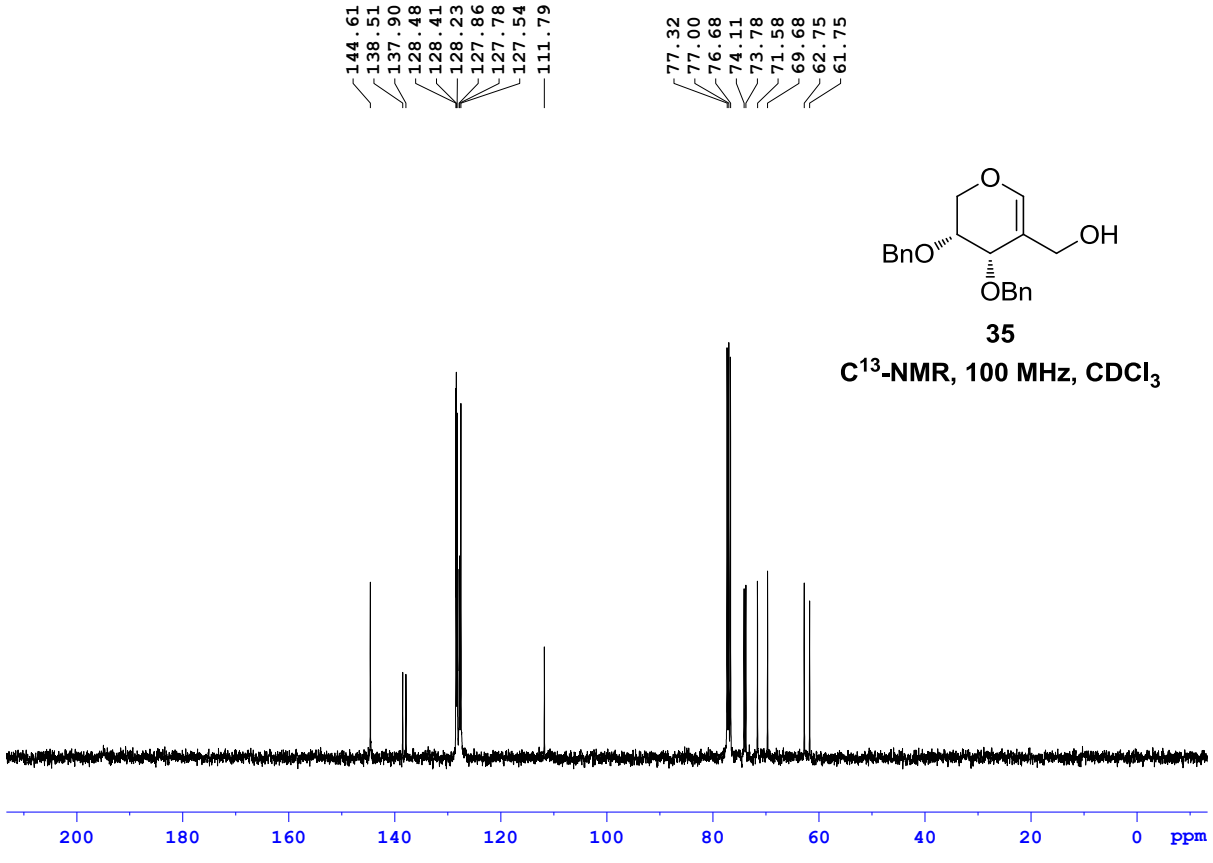

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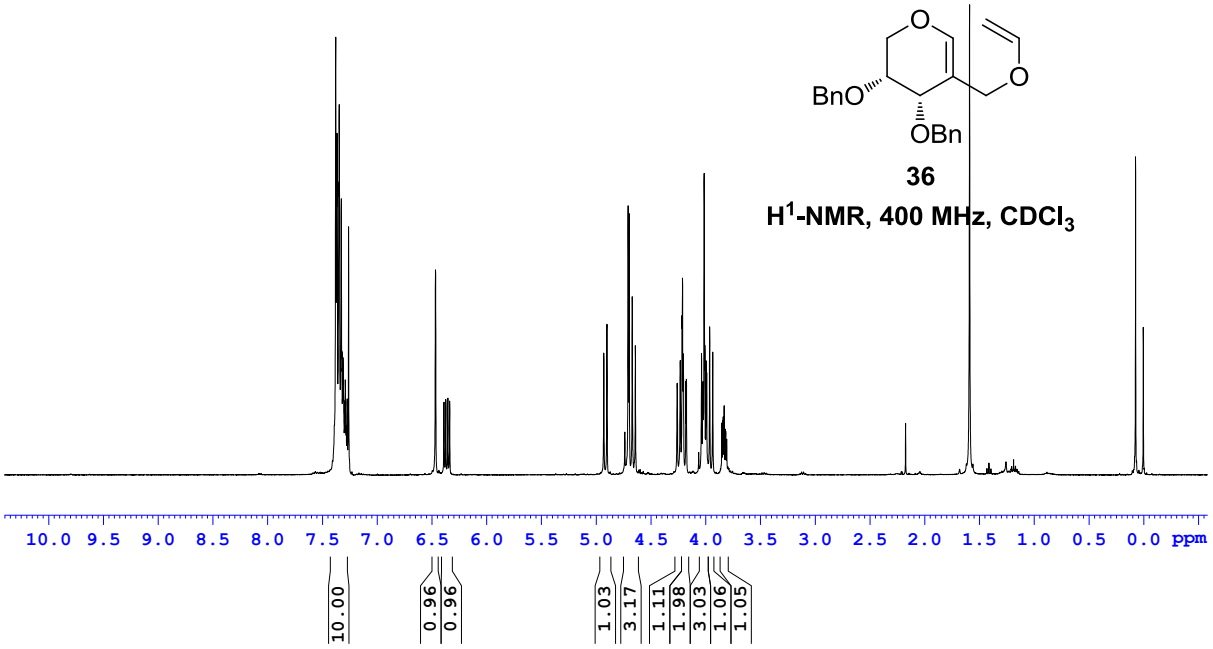

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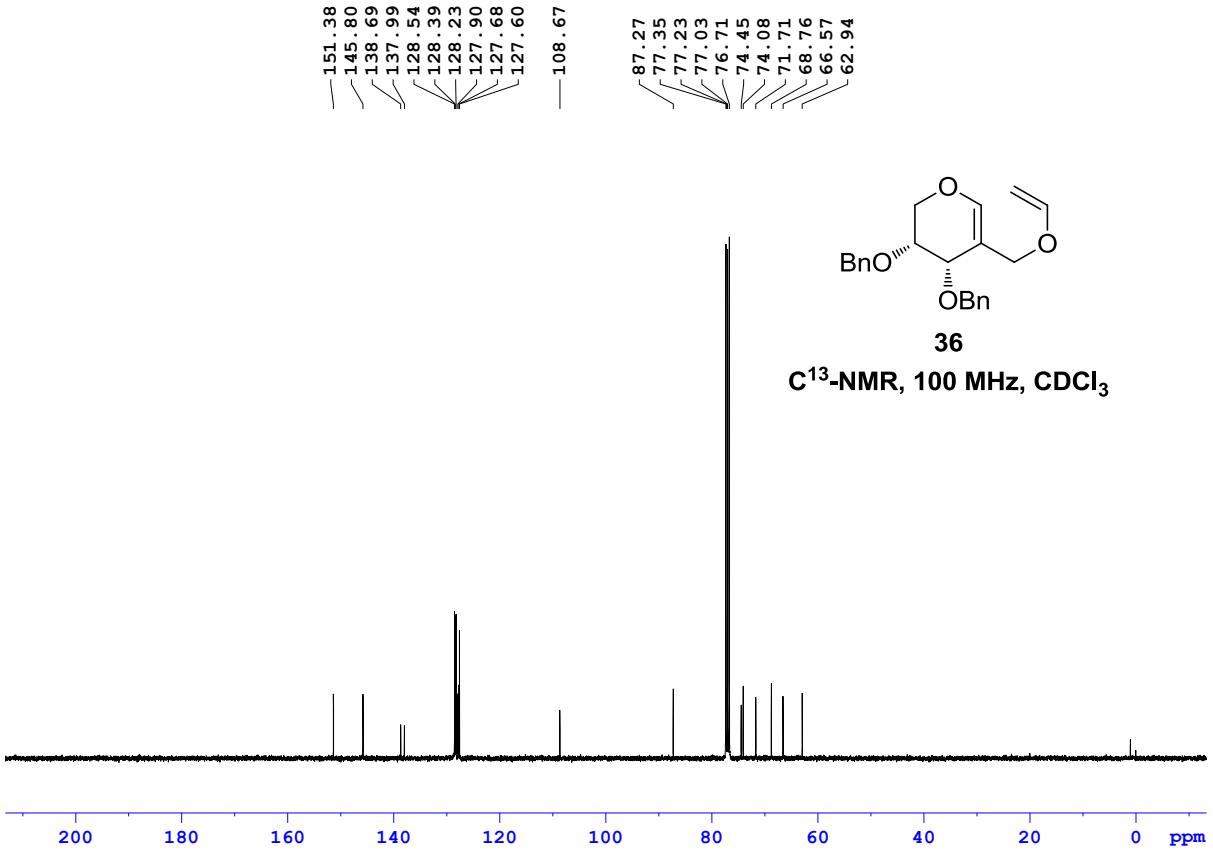

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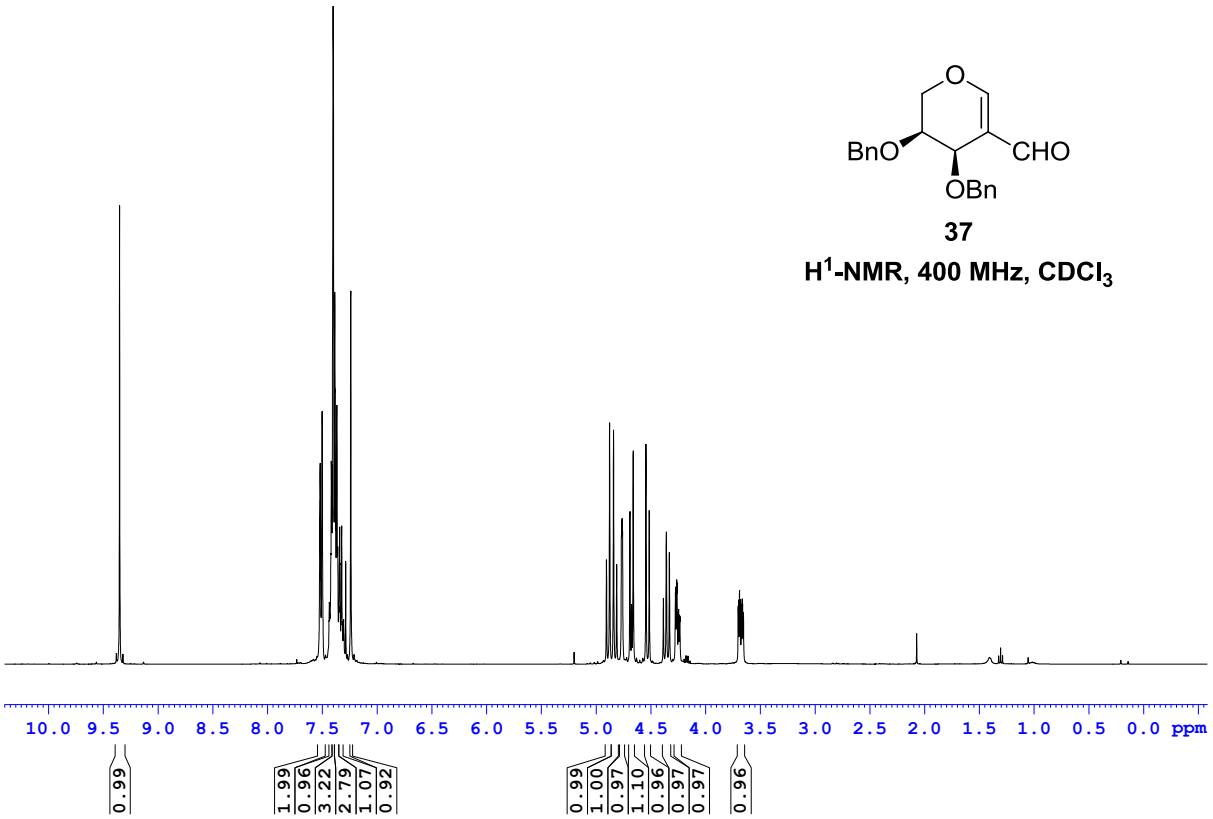
C^{13}-NMR, 100 MHz, $CDCl_3$



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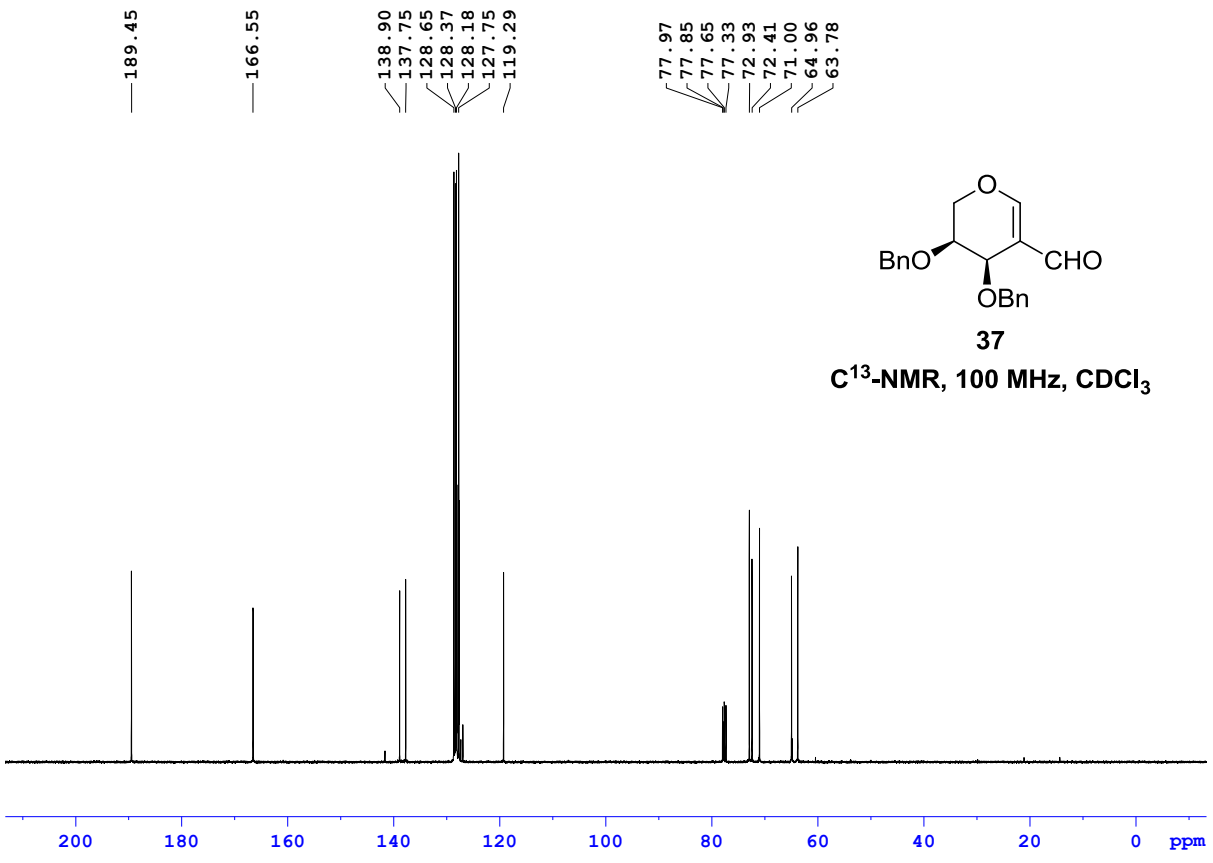
H^1-NMR, 400 MHz, $CDCl_3$



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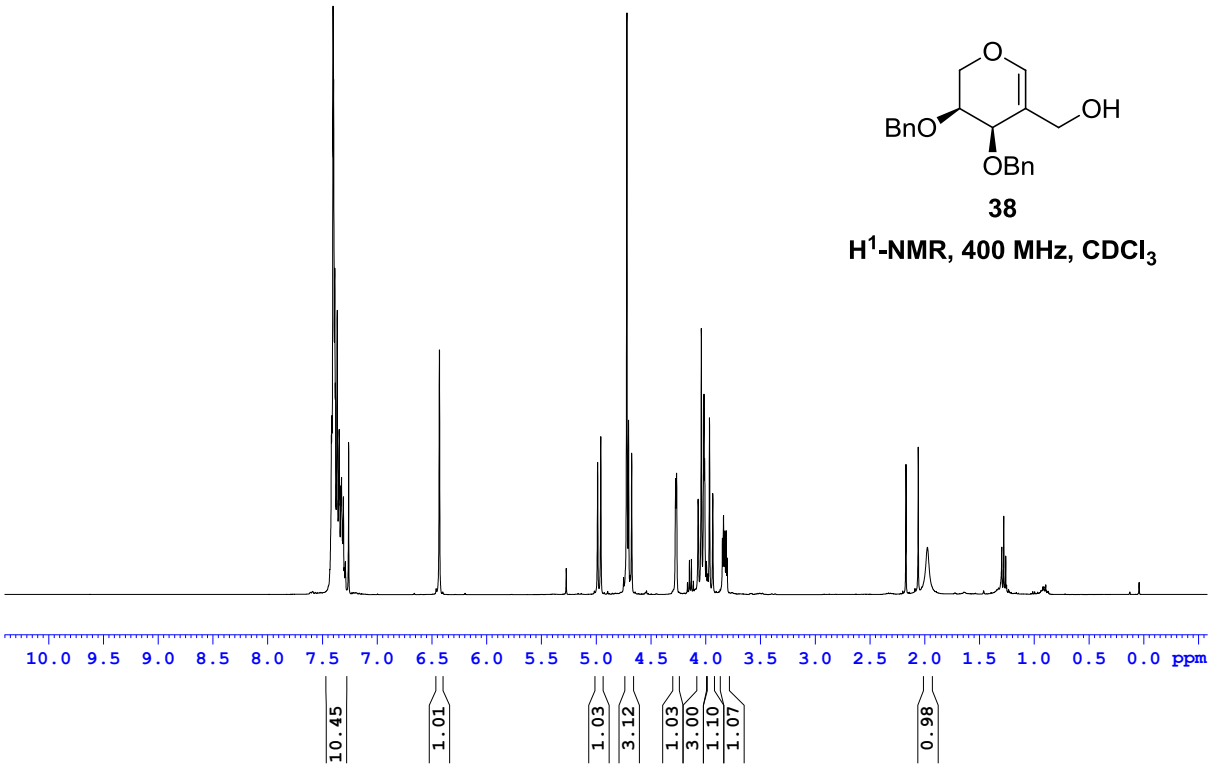
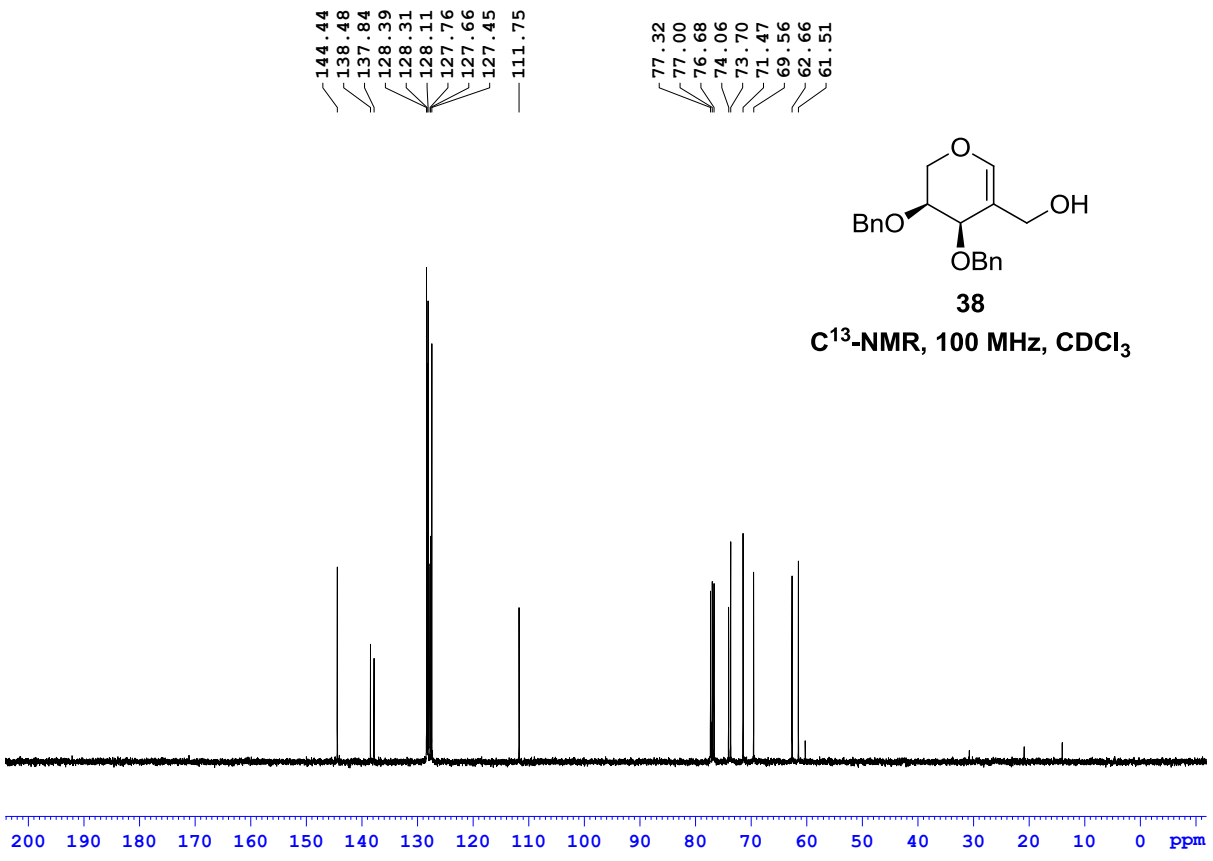
C^{13}-NMR, 100 MHz, $CDCl_3$



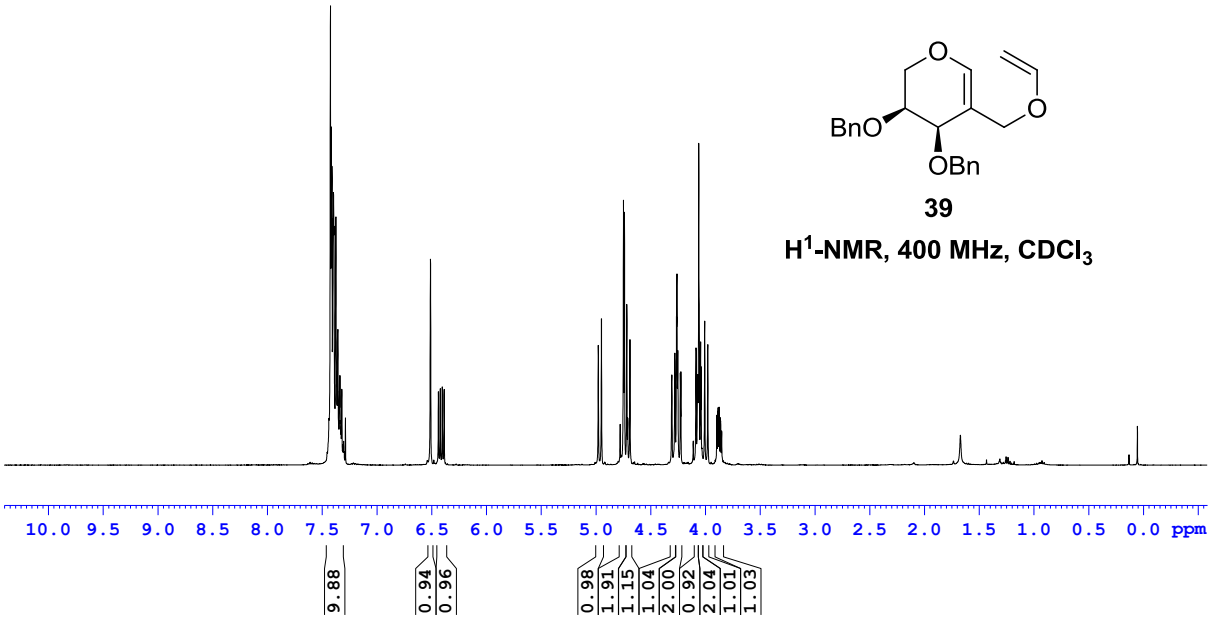
38

H^1-NMR, 400 MHz, $CDCl_3$



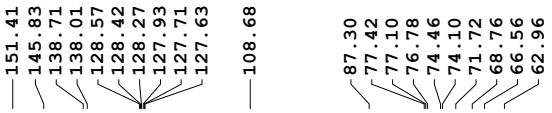
38

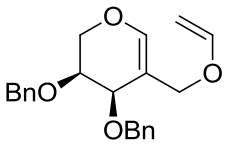
C^{13}-NMR, 100 MHz, $CDCl_3$



39

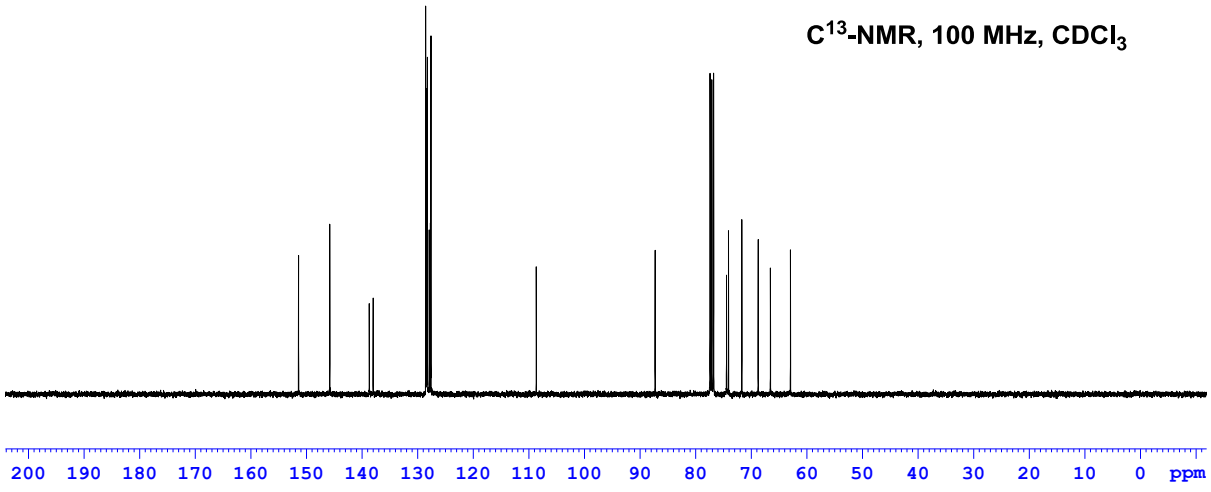
H^1-NMR, 400 MHz, $CDCl_3$

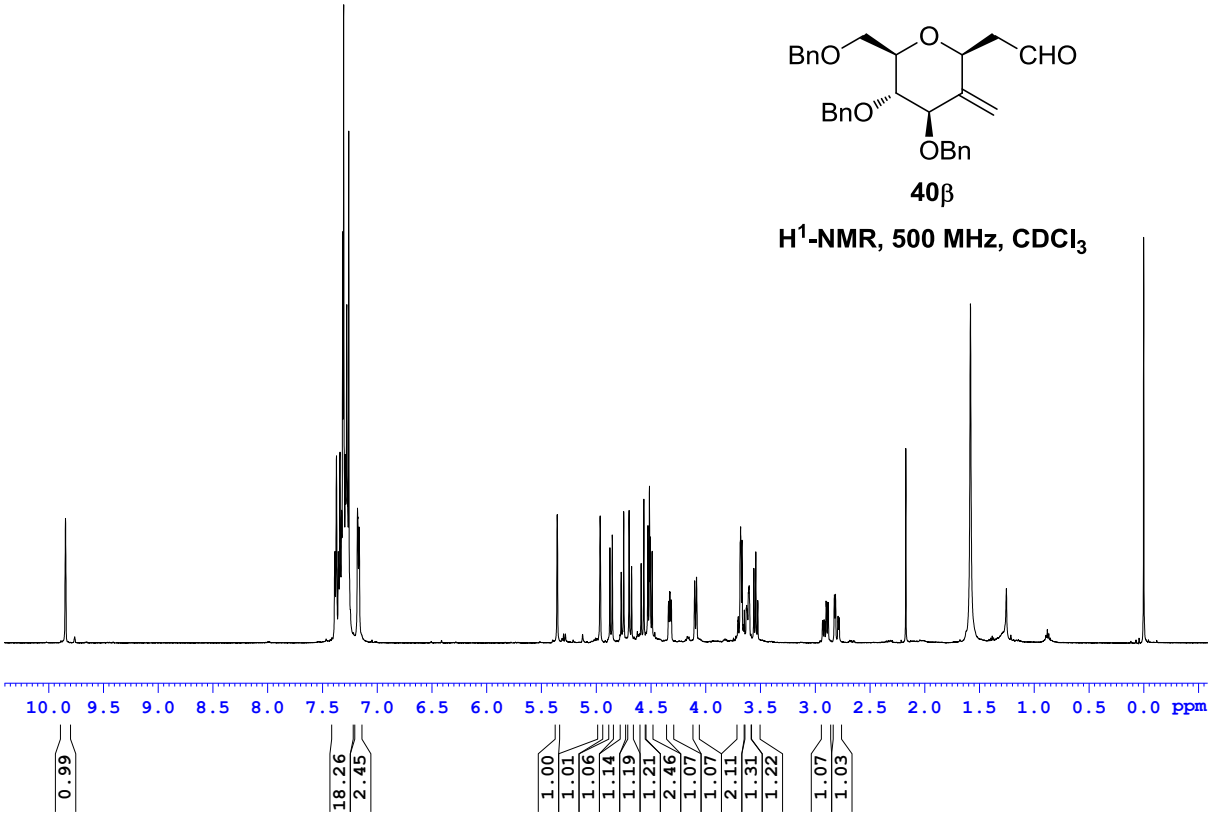




39

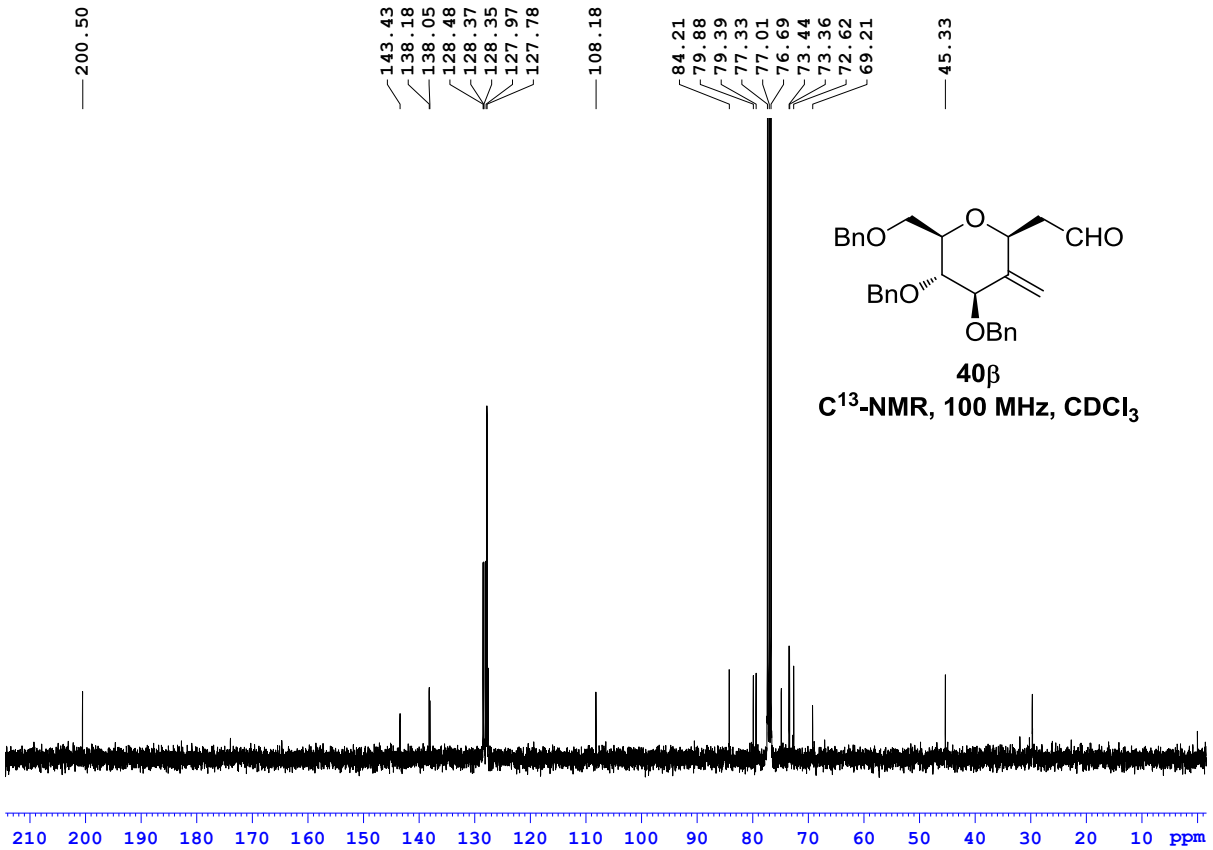
C^{13}-NMR, 100 MHz, $CDCl_3$





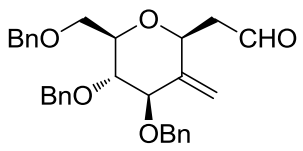
40β

H^1-NMR, 500 MHz, $CDCl_3$



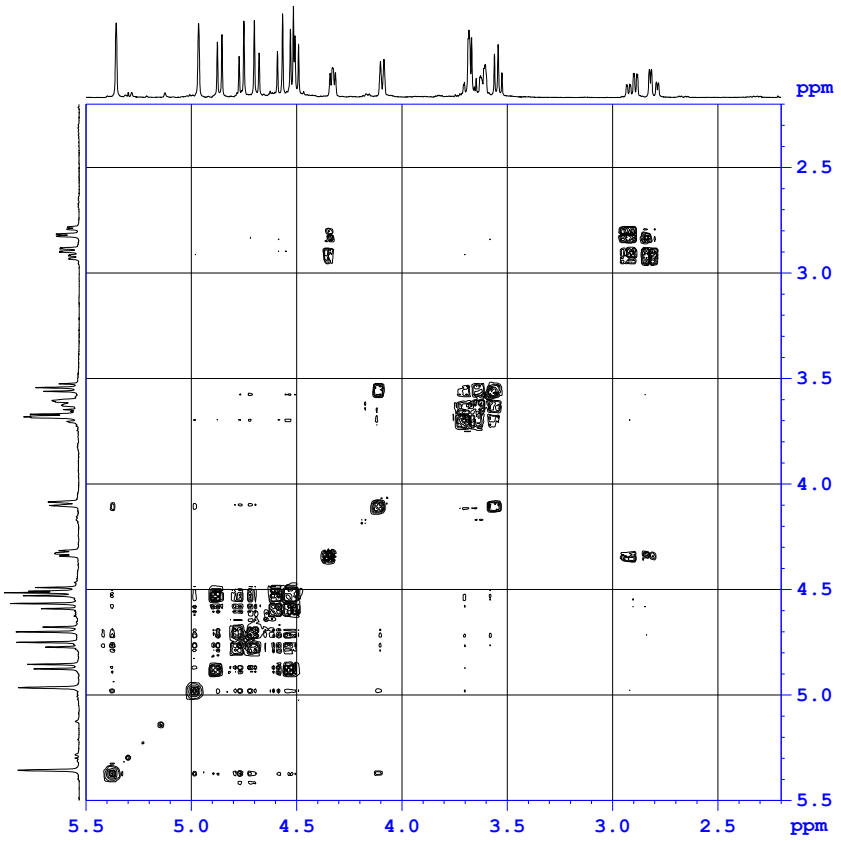
40β

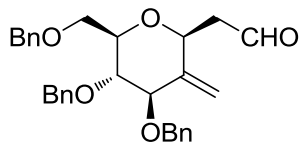
C^{13}-NMR, 100 MHz, $CDCl_3$



40β

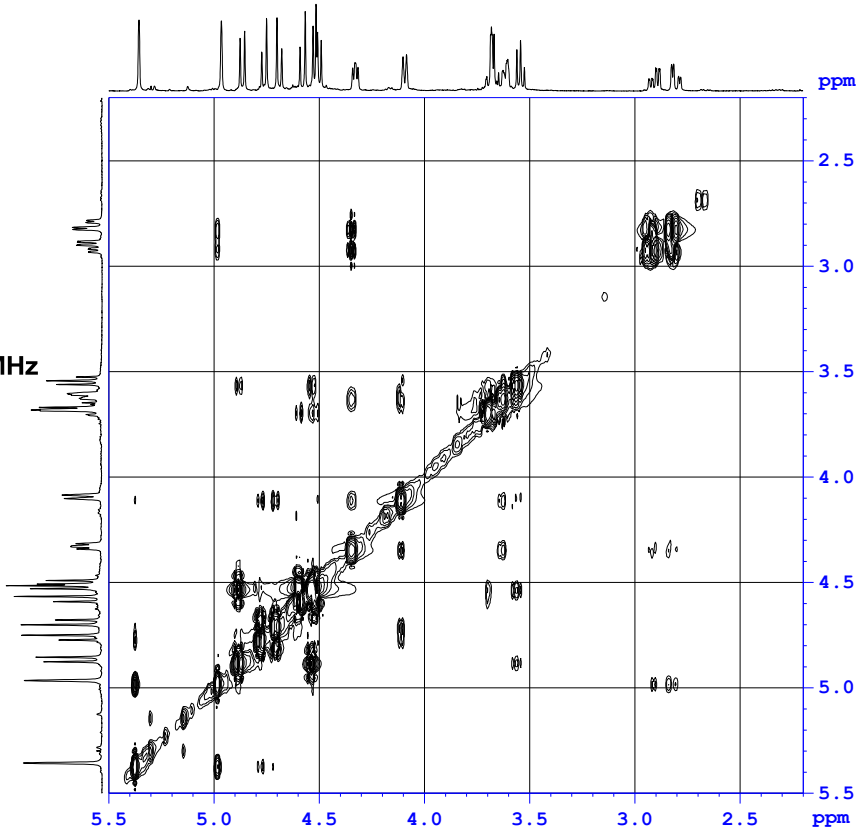
H^1-H^1-COSY NMR, 500 MHz

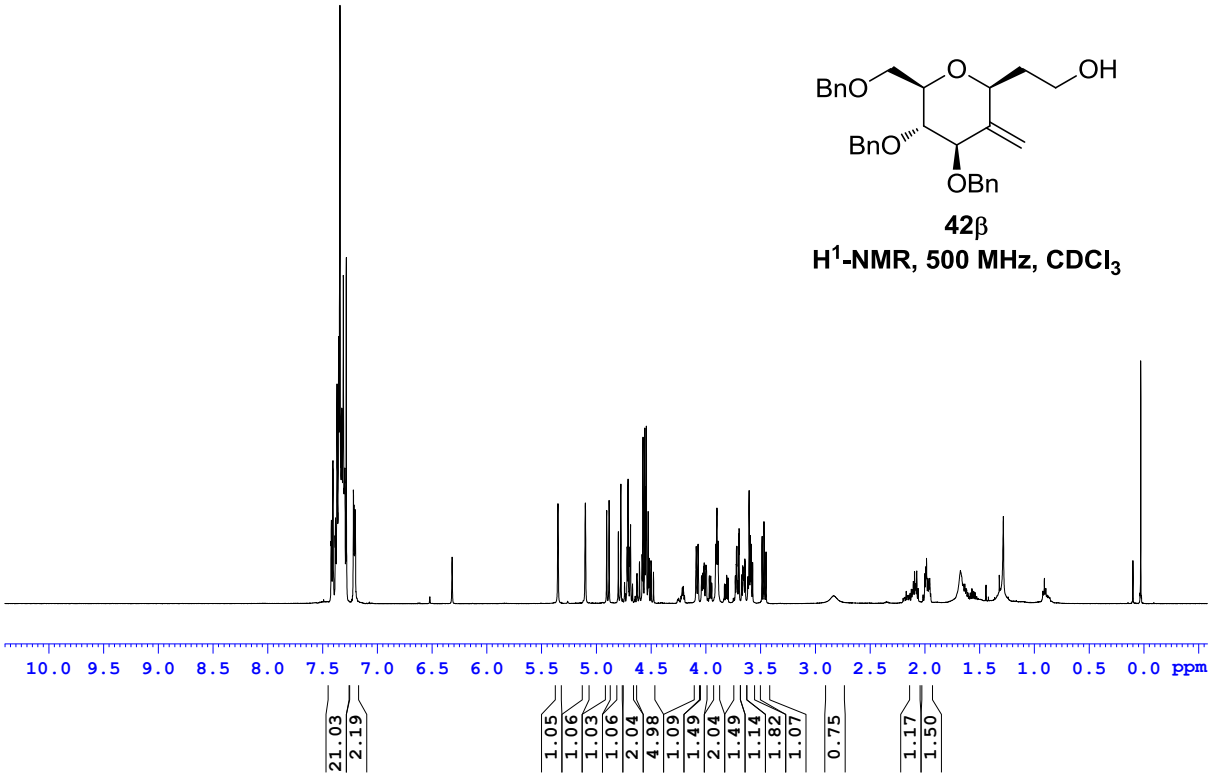




40β

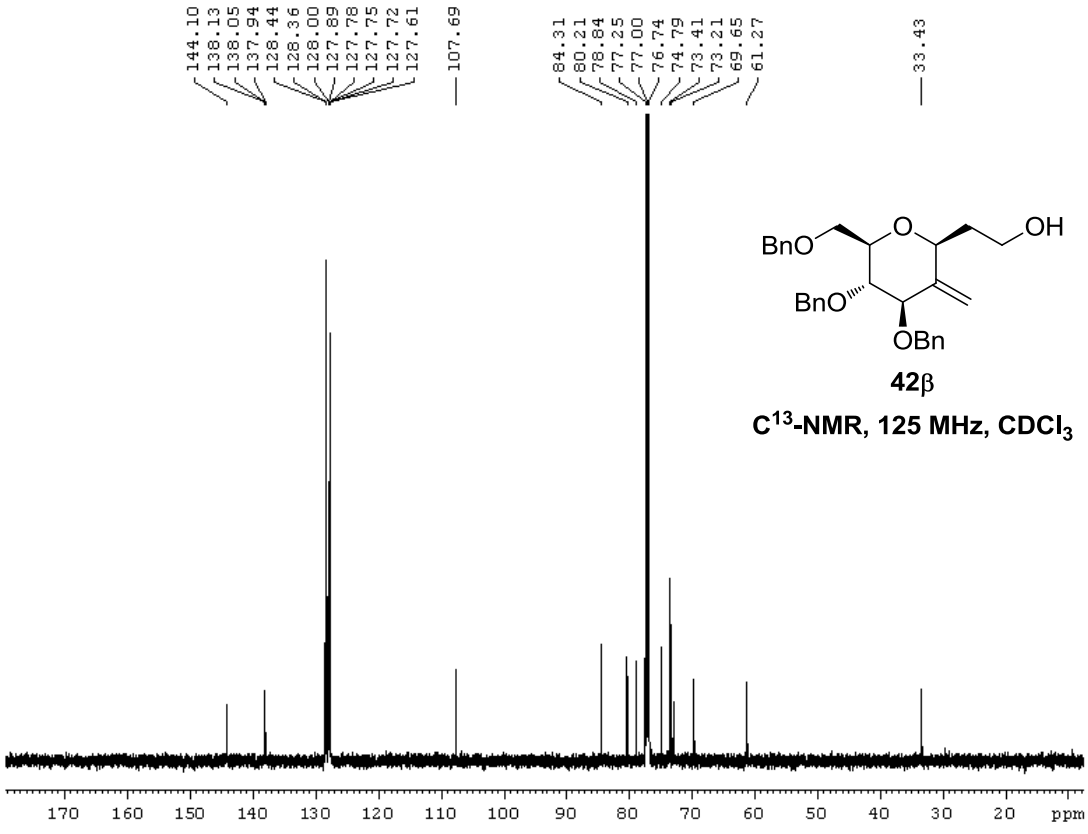
H^1-H^1-NOESY NMR, 500 MHz





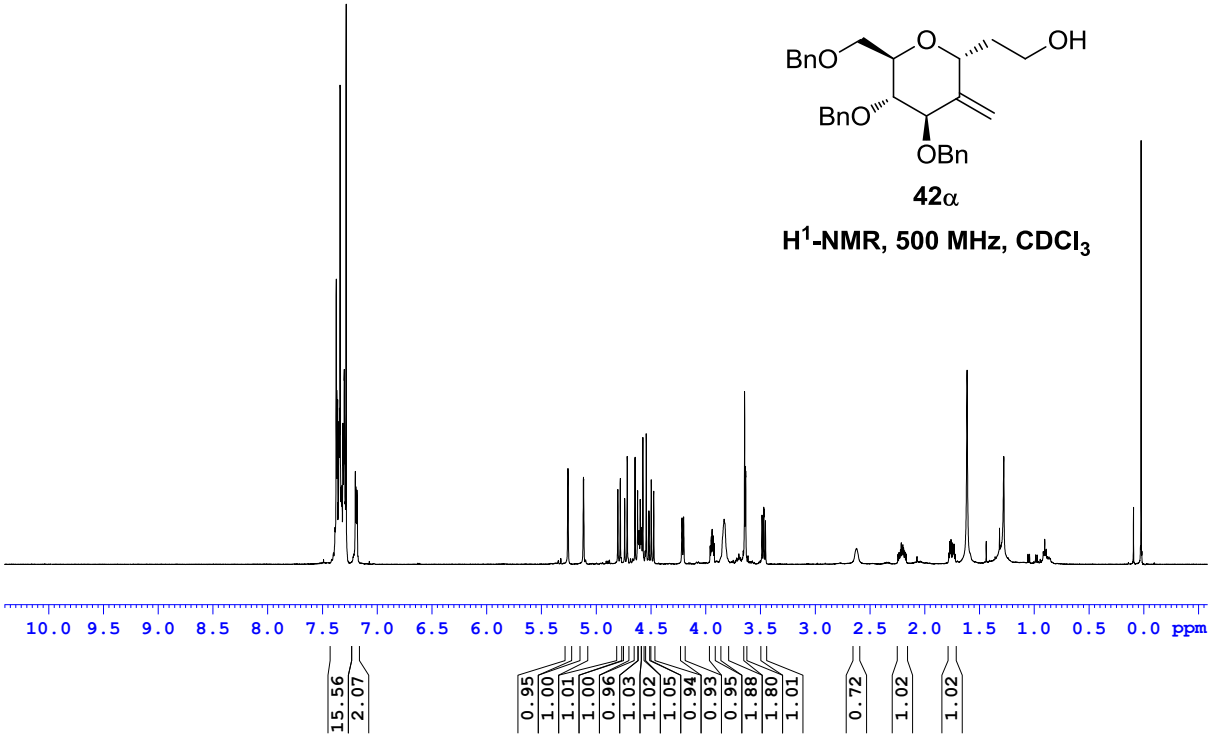
42β

H^1-NMR, 500 MHz, $CDCl_3$



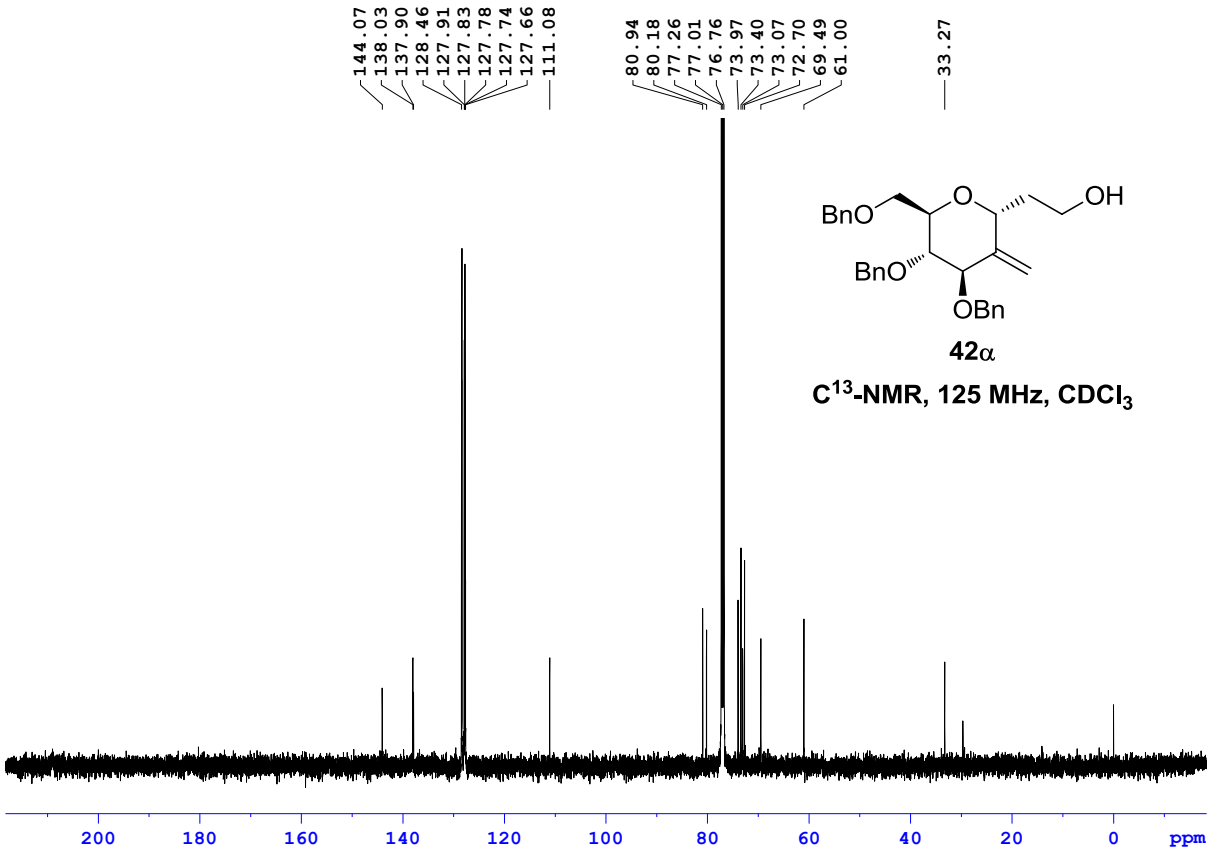
42β

C^{13}-NMR, 125 MHz, $CDCl_3$



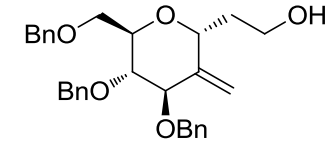
42α

H^1-NMR, 500 MHz, $CDCl_3$



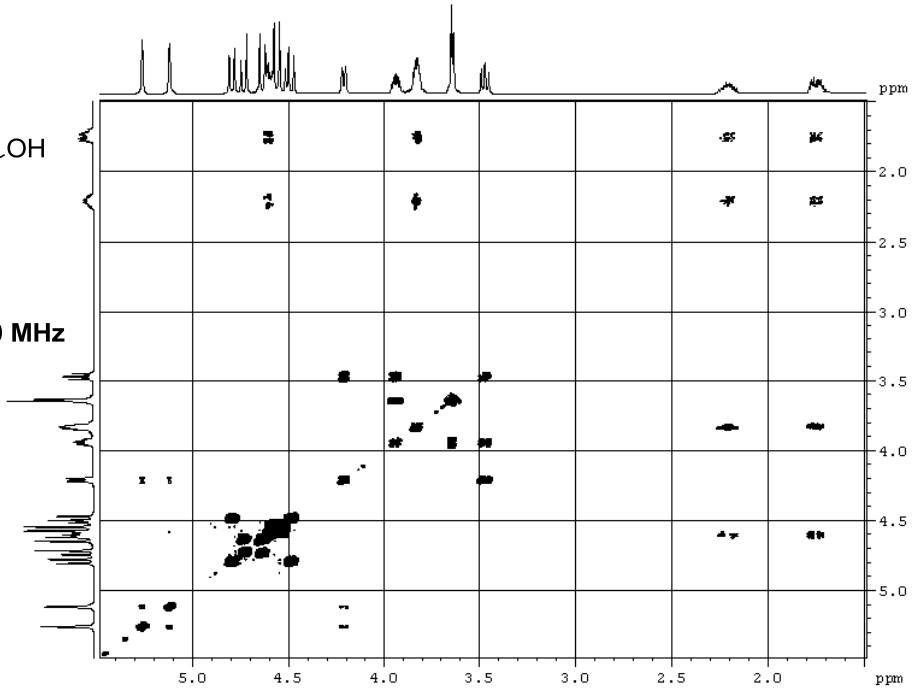
42α

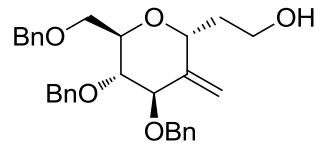
C^{13}-NMR, 125 MHz, $CDCl_3$



42α

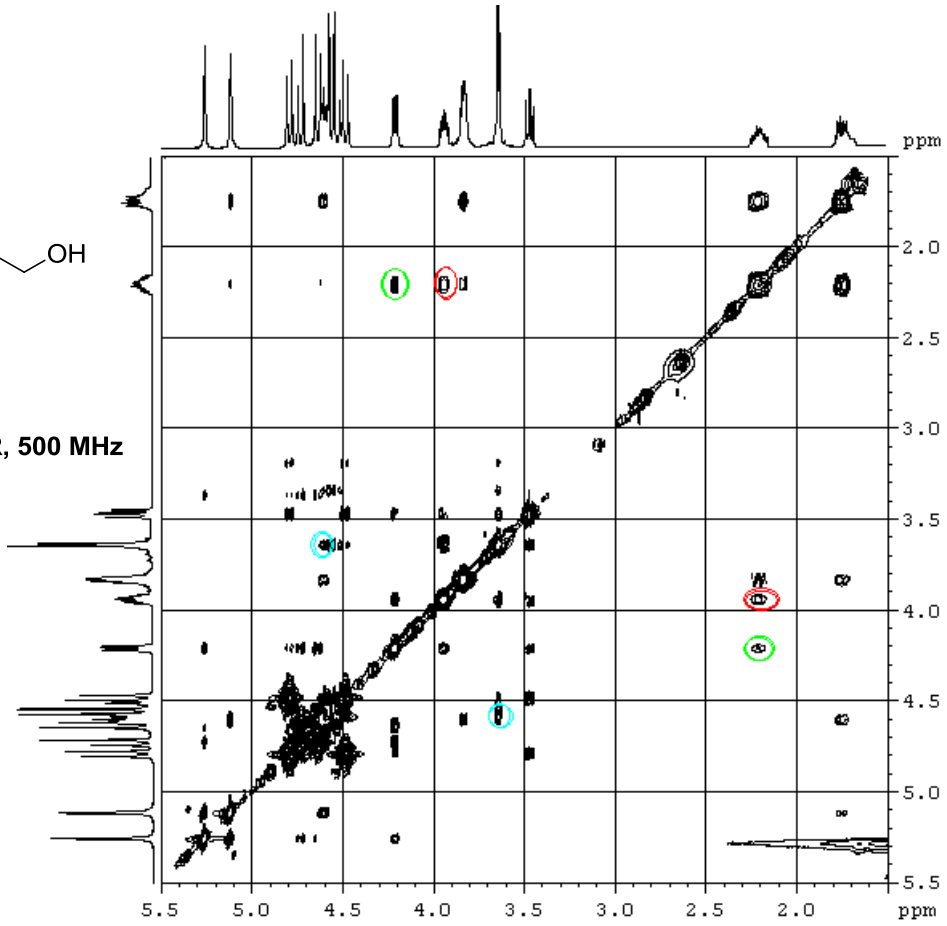
H^1-H^1-COSY NMR, 500 MHz

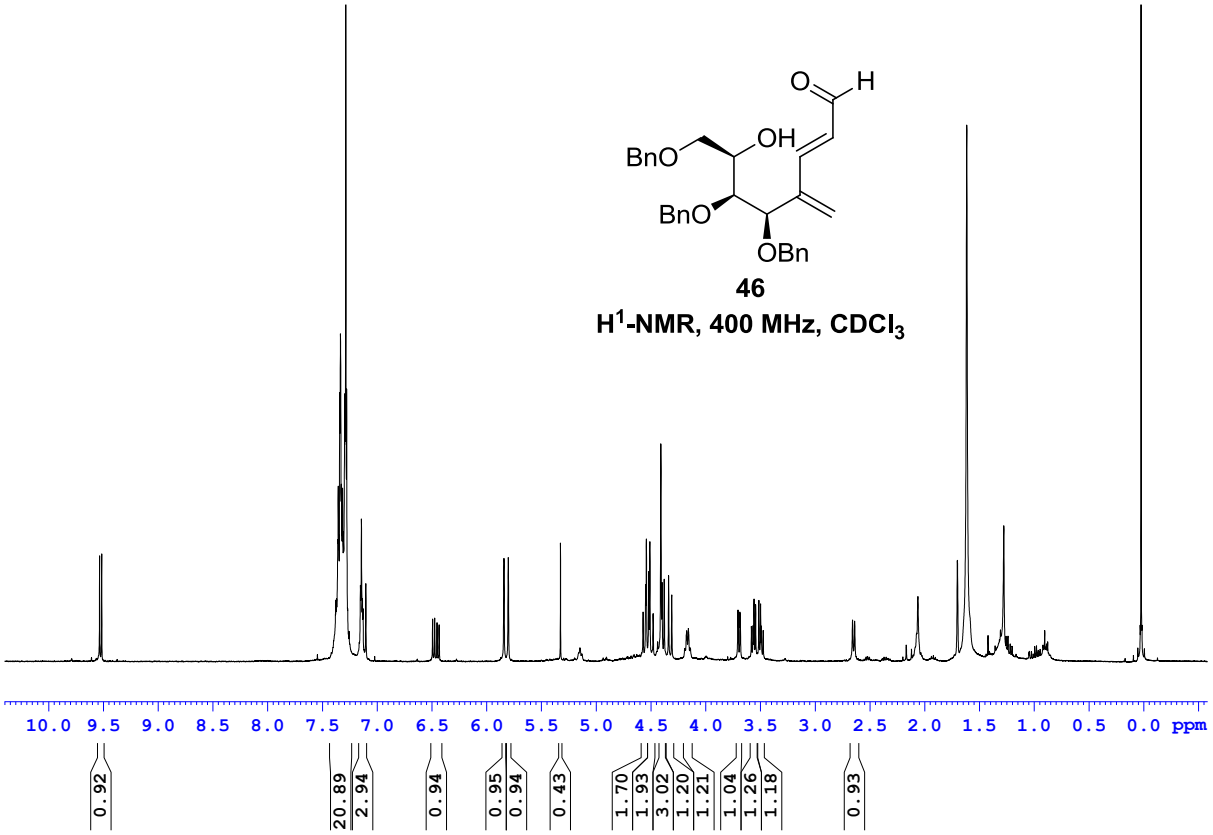




42α

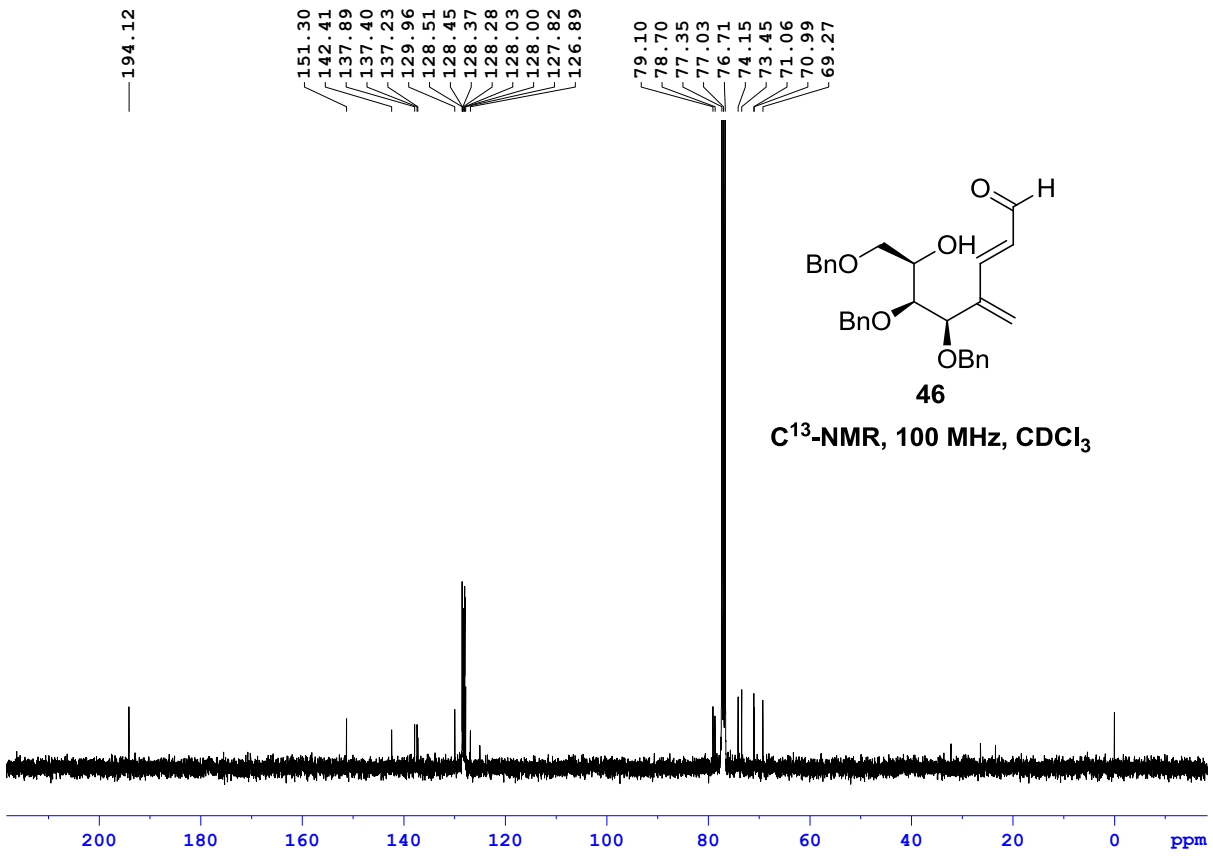
H^1-H^1-NOESY NMR, 500 MHz





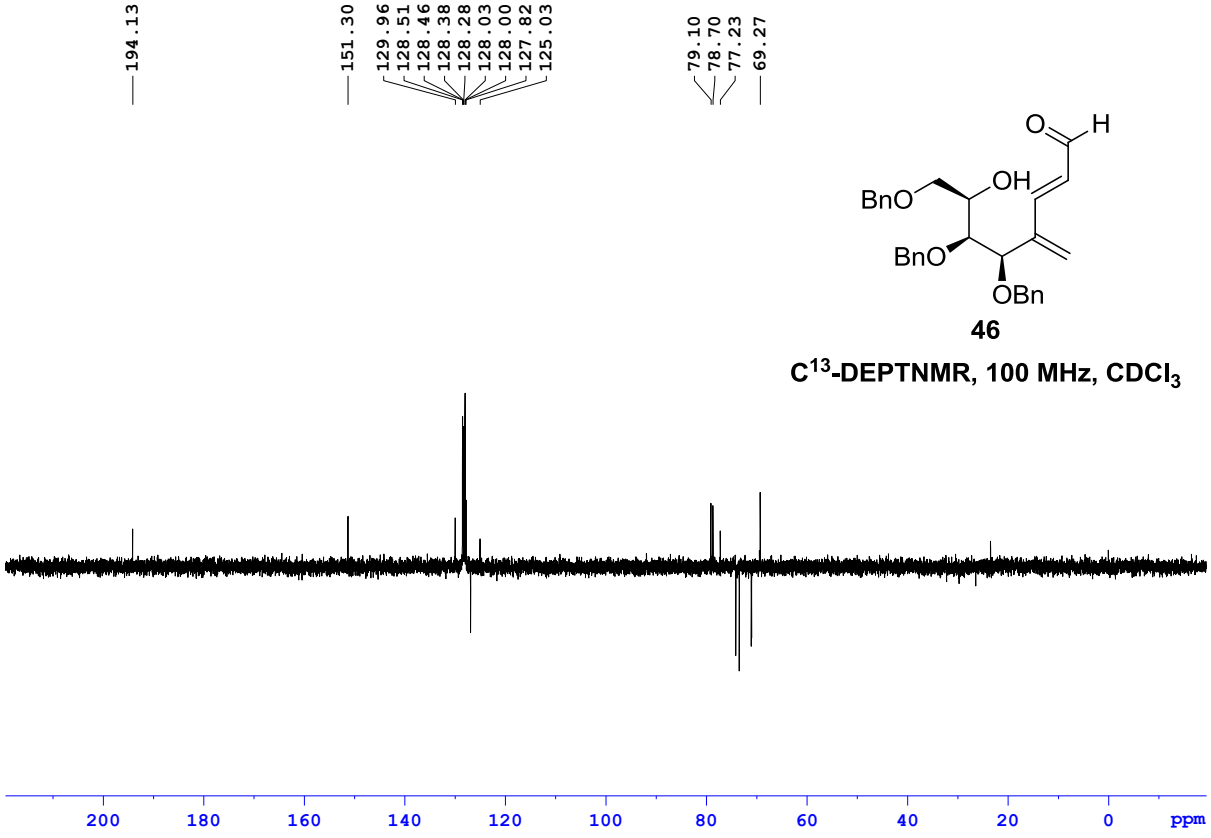
46

H^1-NMR, 400 MHz, $CDCl_3$



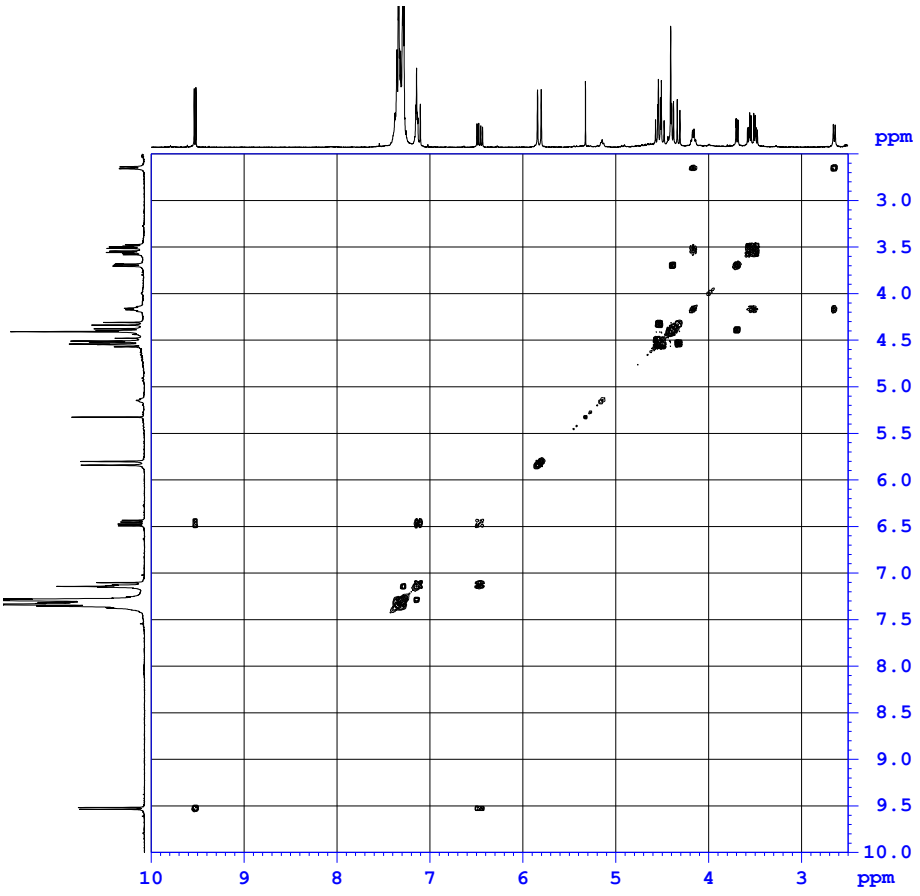
46

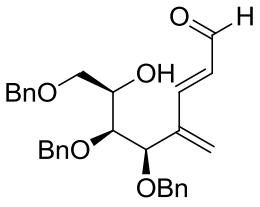
C^{13}-NMR, 100 MHz, $CDCl_3$



46

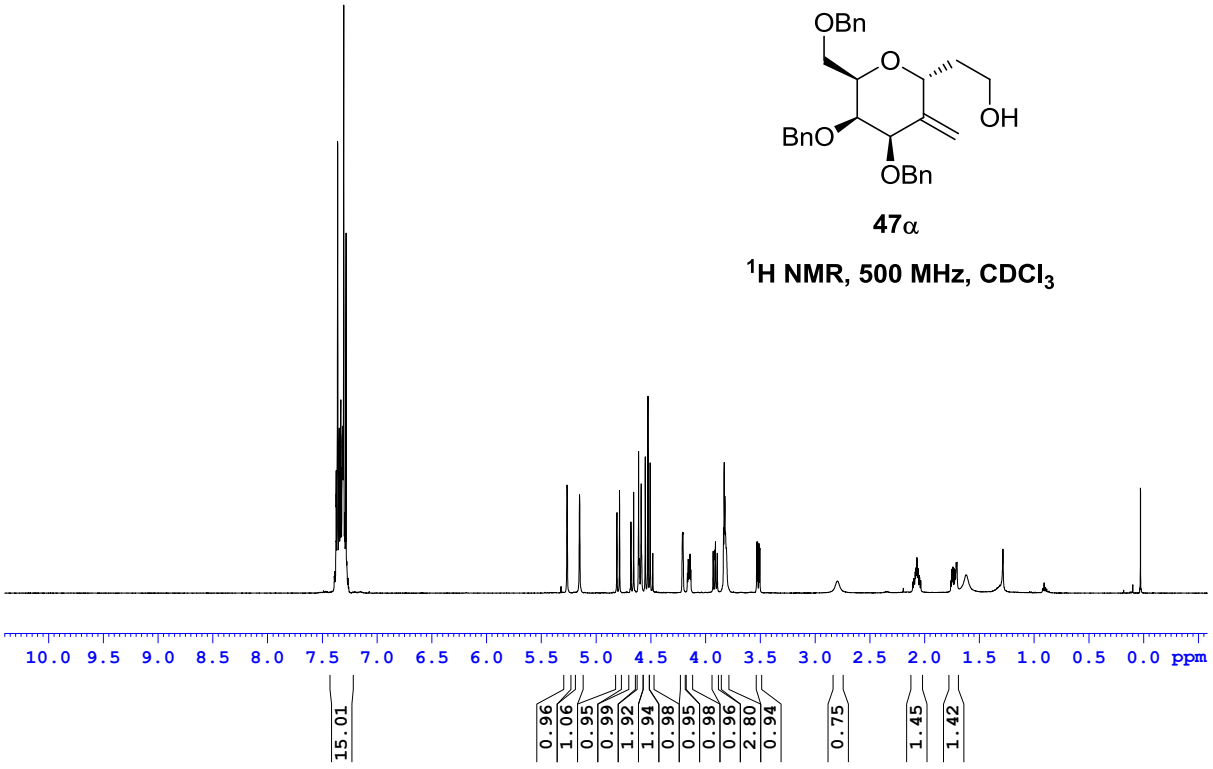
C^{13}-DEPTNMR, 100 MHz, $CDCl_3$





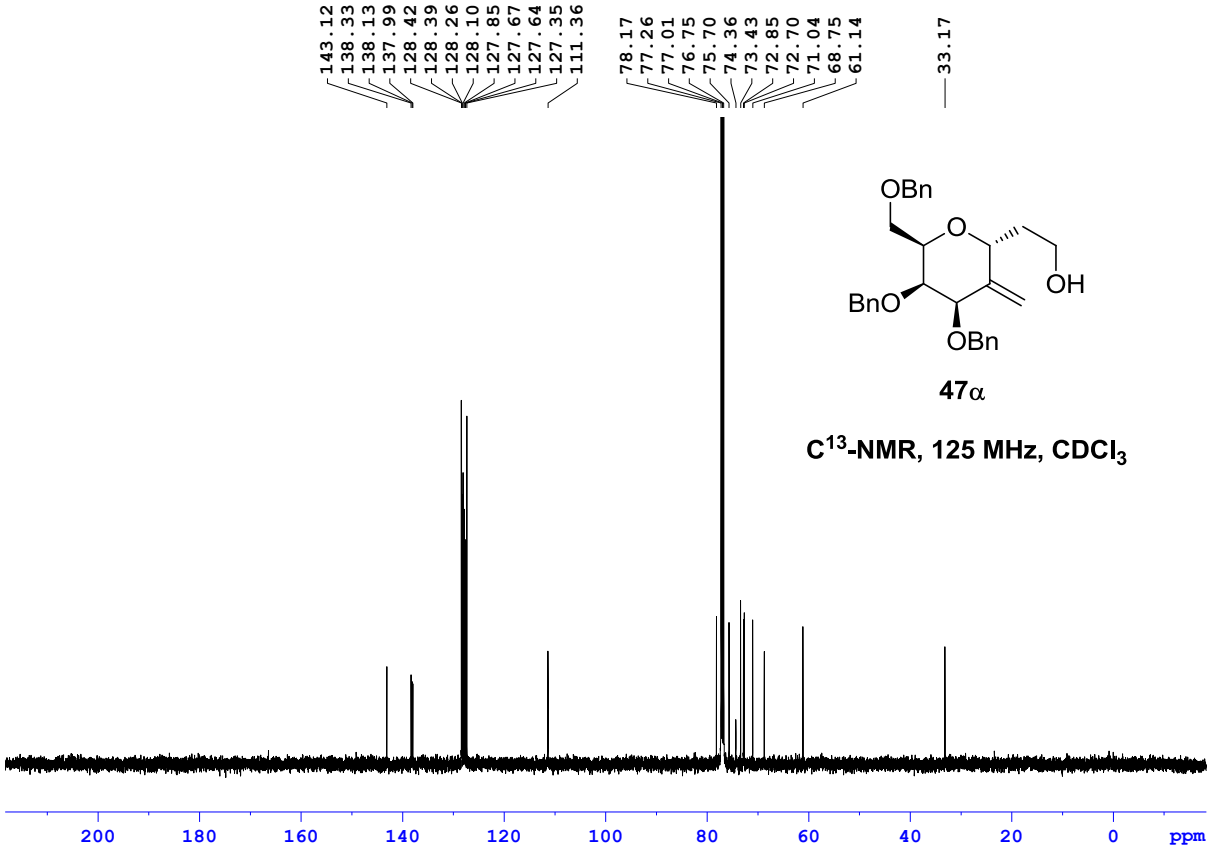
46

H^1-H^1-COSY NMR, 400 MHz



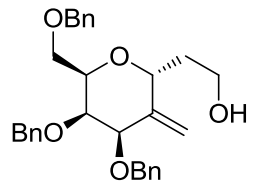
47α

^{1}H NMR, 500 MHz, $CDCl_3$



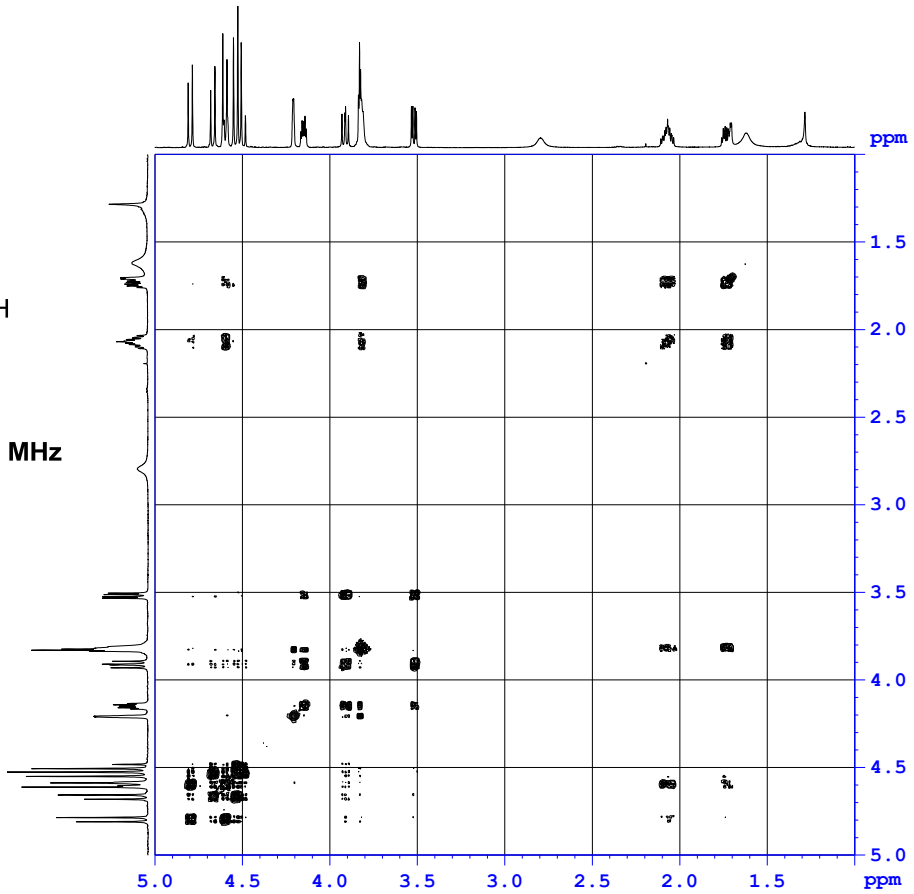
47α

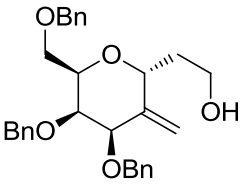
C^{13}-NMR, 125 MHz, $CDCl_3$



47α

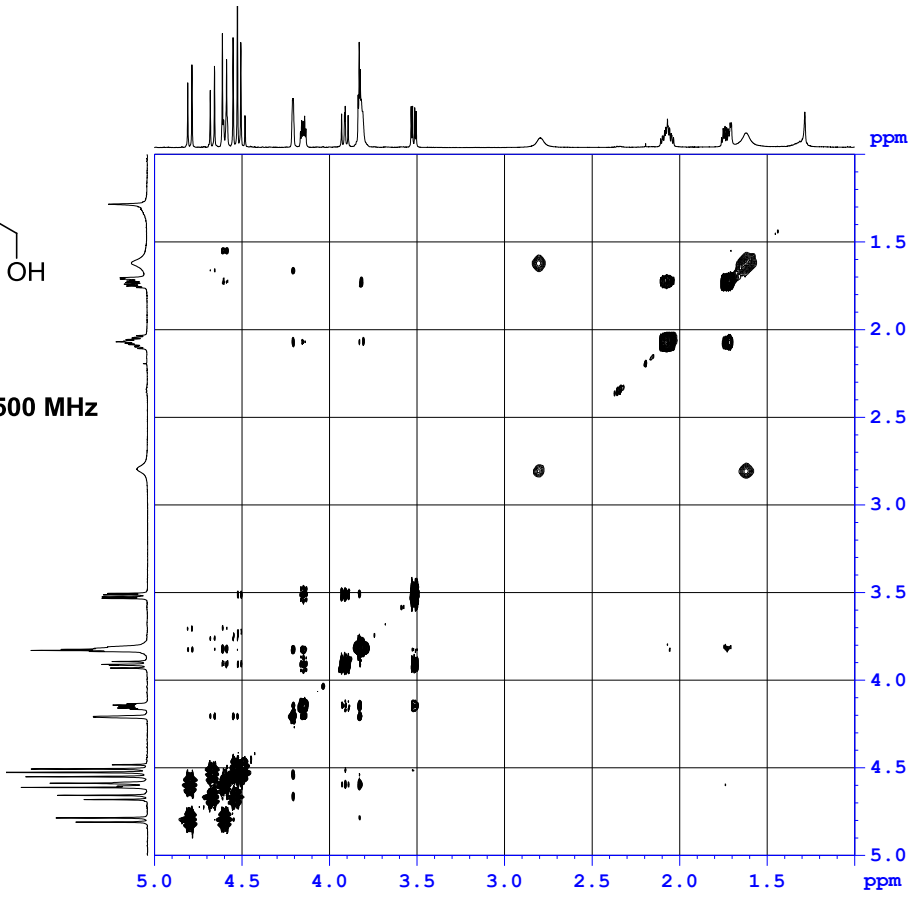
H^1-H^1-COSY NMR, 500 MHz

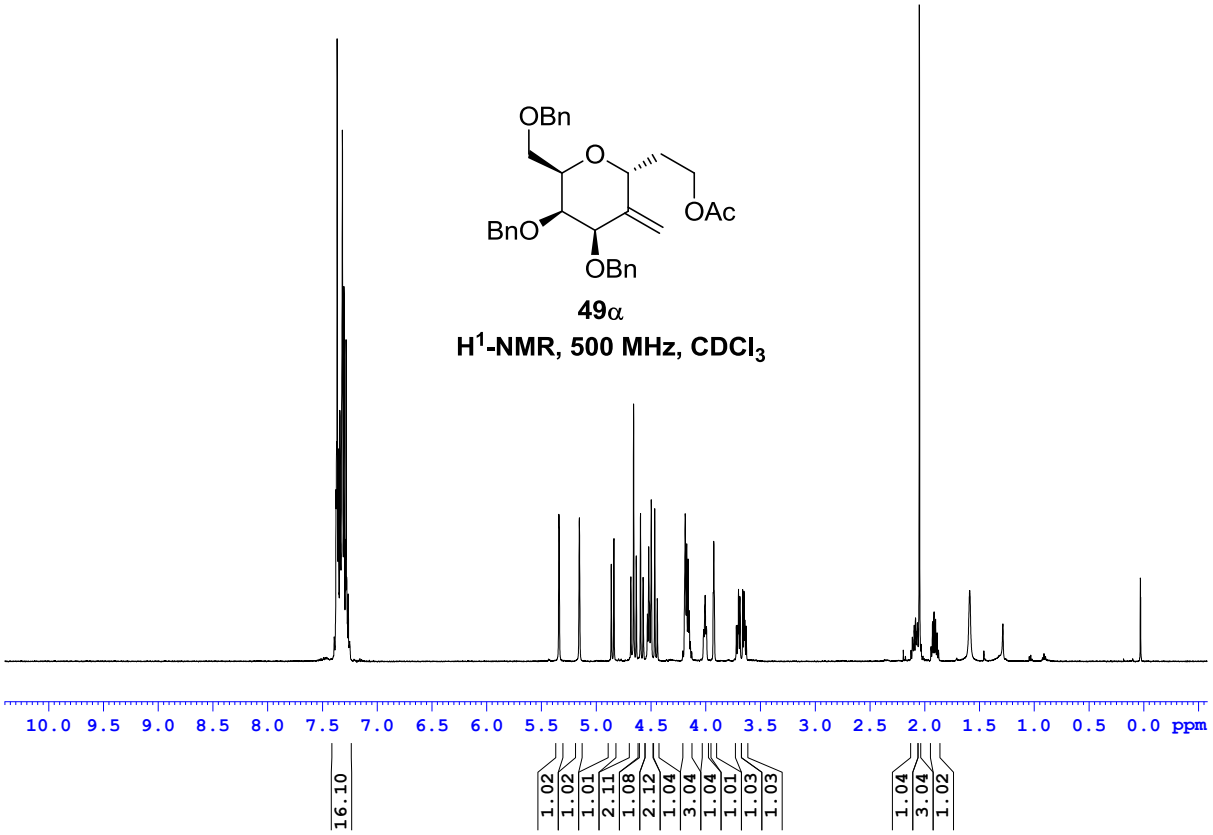




47α

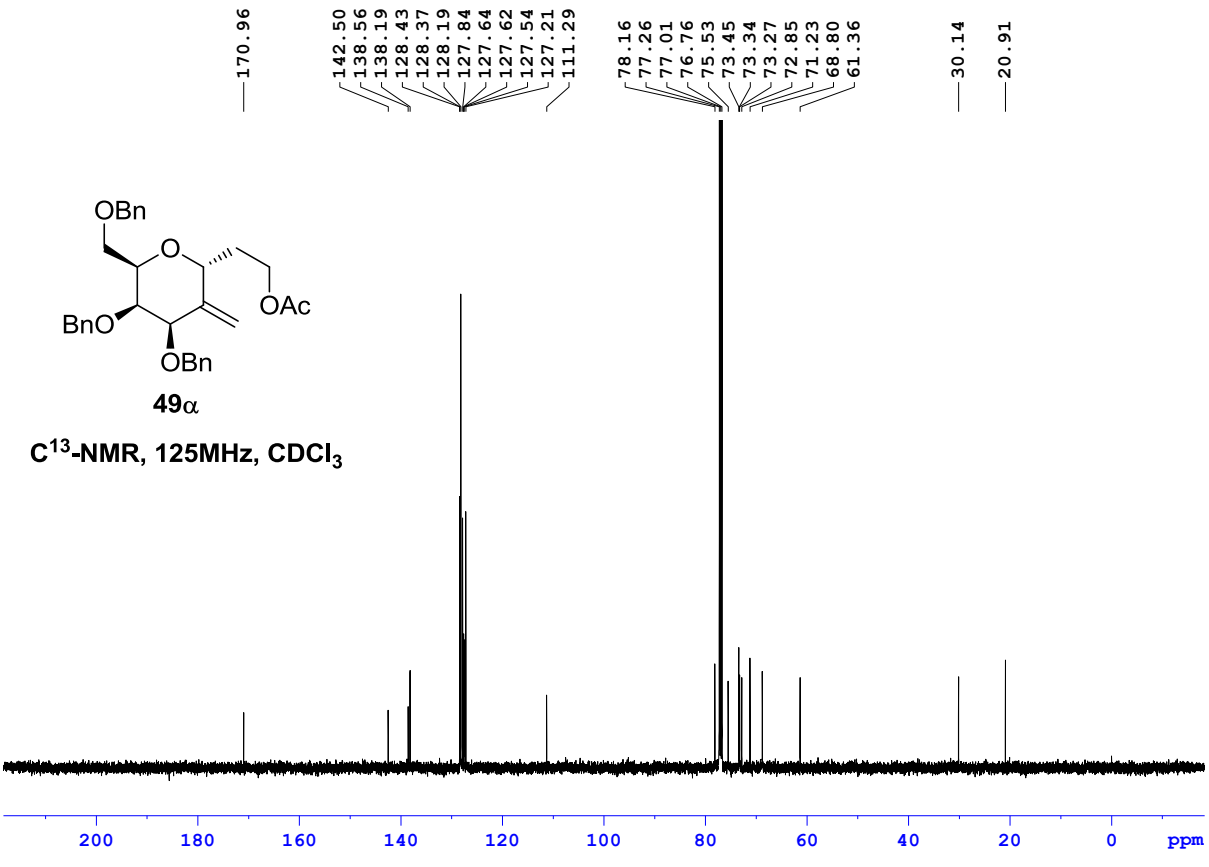
H^1-H^1-NOEY NMR, 500 MHz





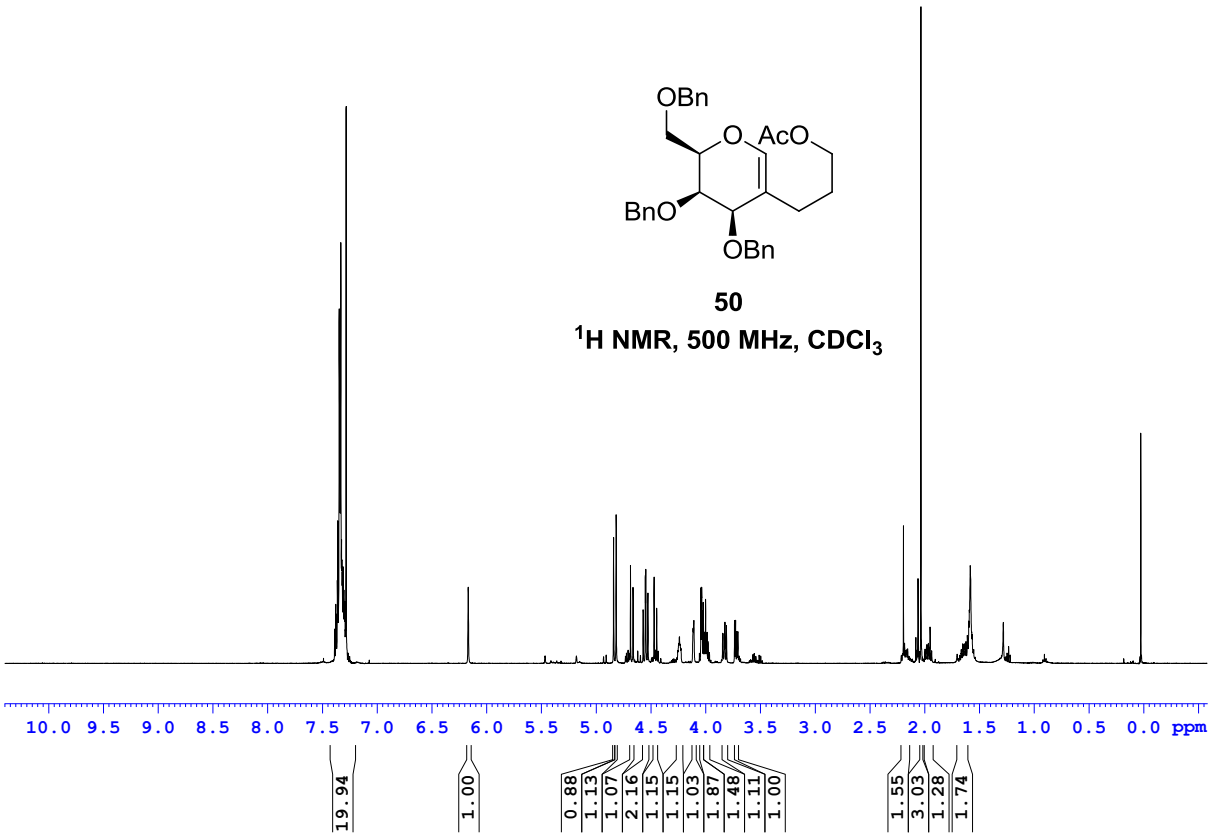
49α

H^1-NMR, 500 MHz, $CDCl_3$



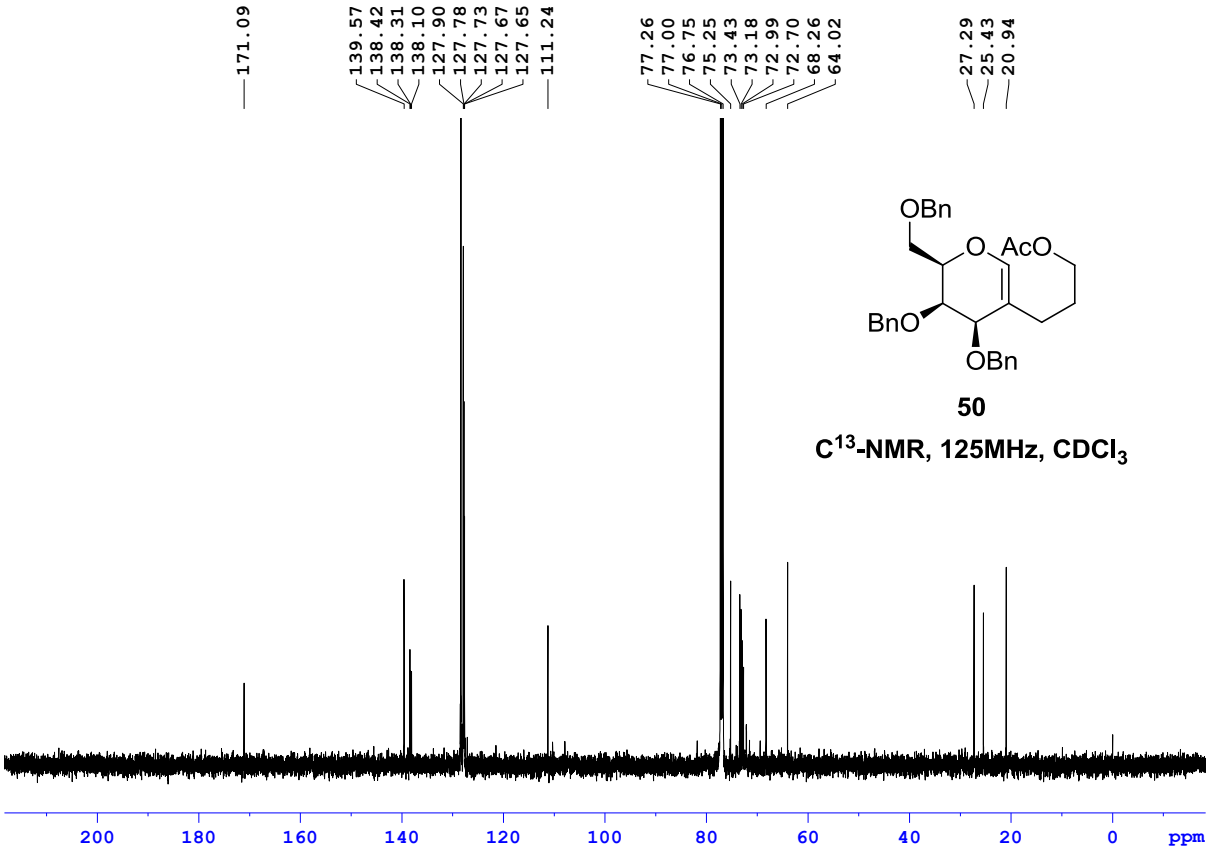
49α

C^{13}-NMR, 125MHz, $CDCl_3$



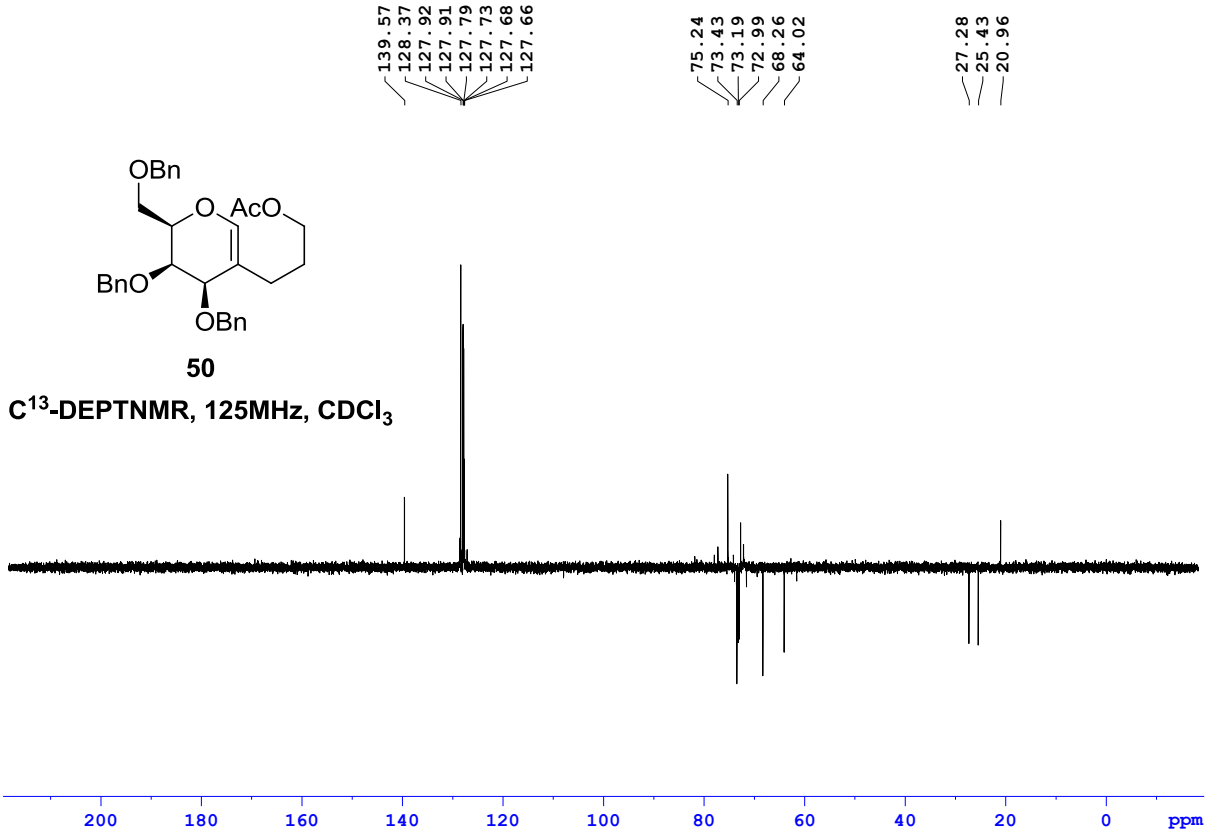
50

^{1}H NMR, 500 MHz, $CDCl_3$



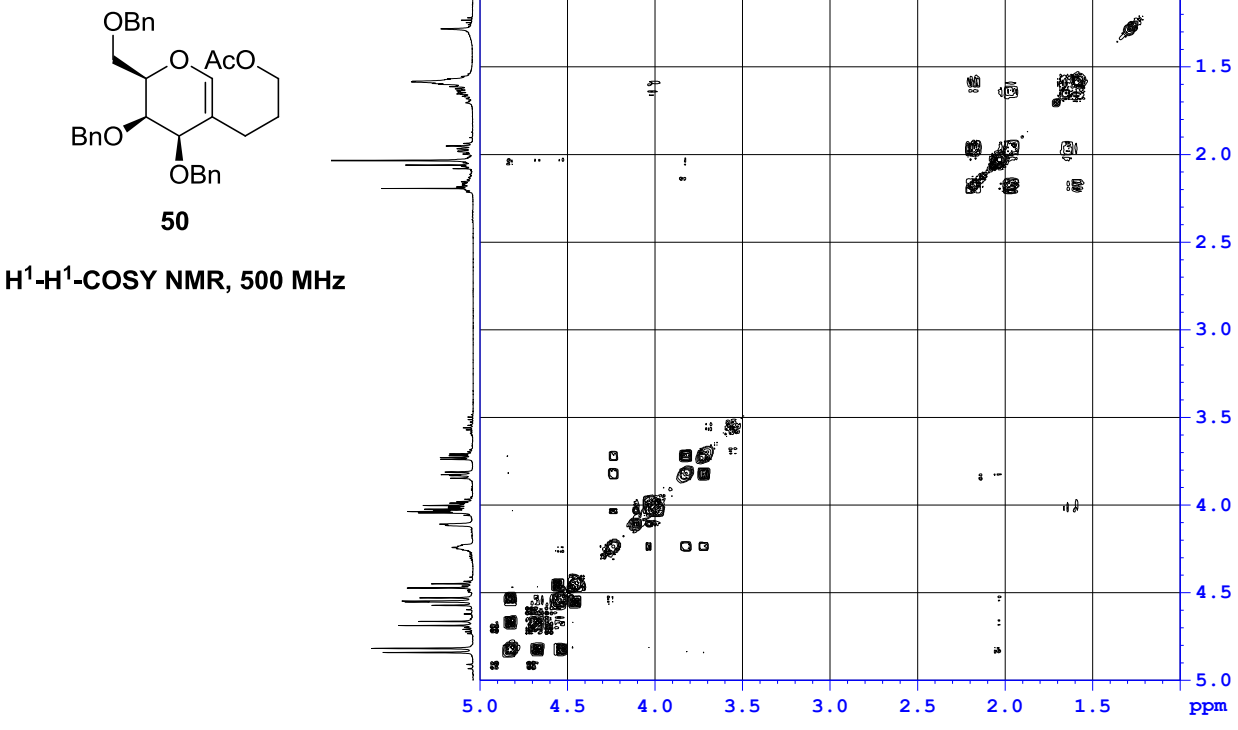
50

C^{13}-NMR, 125MHz, $CDCl_3$



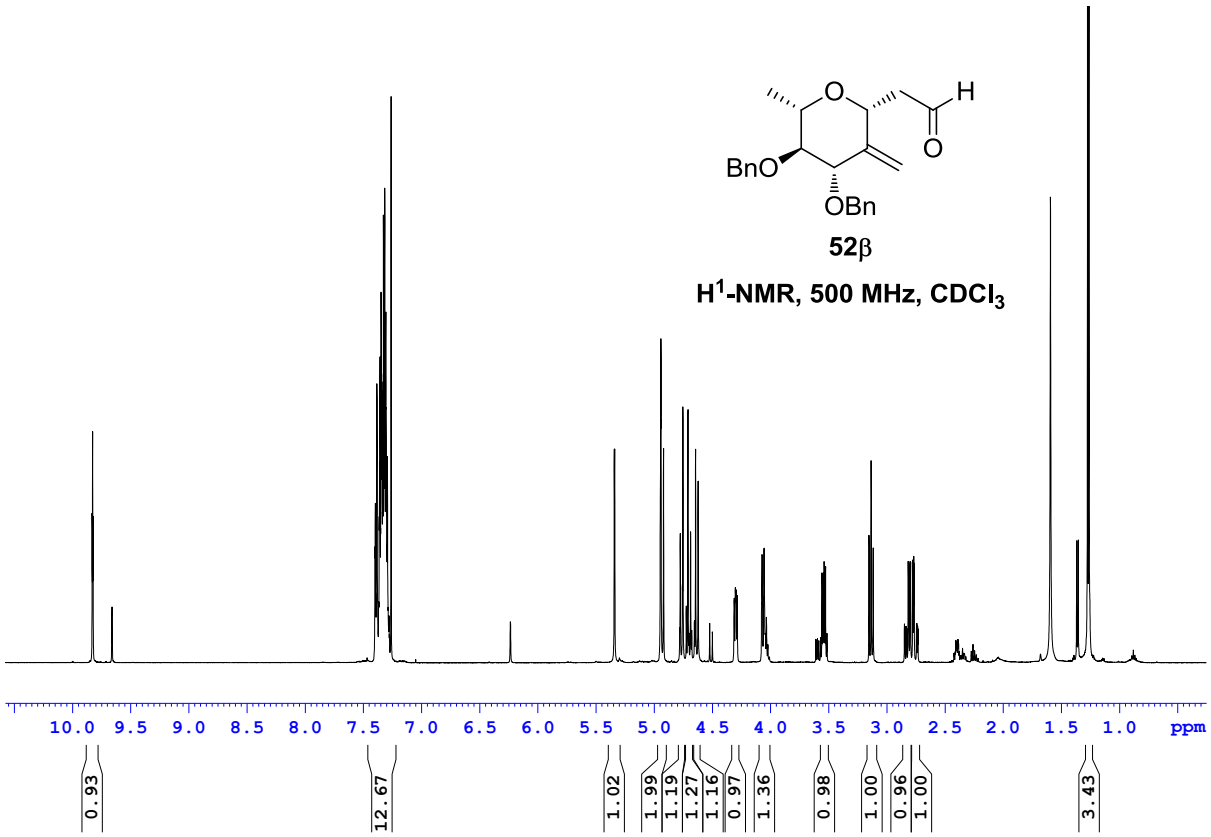
50

C^{13}-DEPTNMR, 125MHz, $CDCl_3$



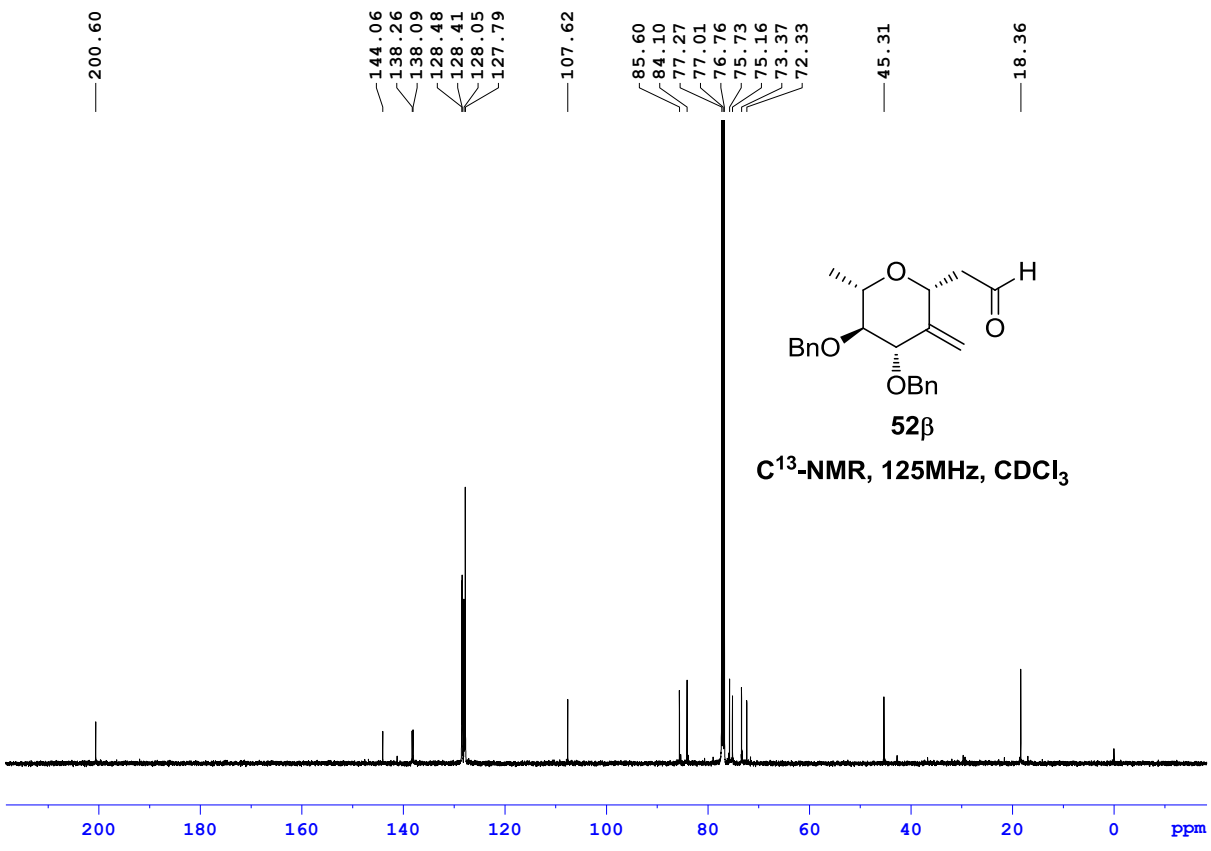
50

H^1-H^1-COSY NMR, 500 MHz



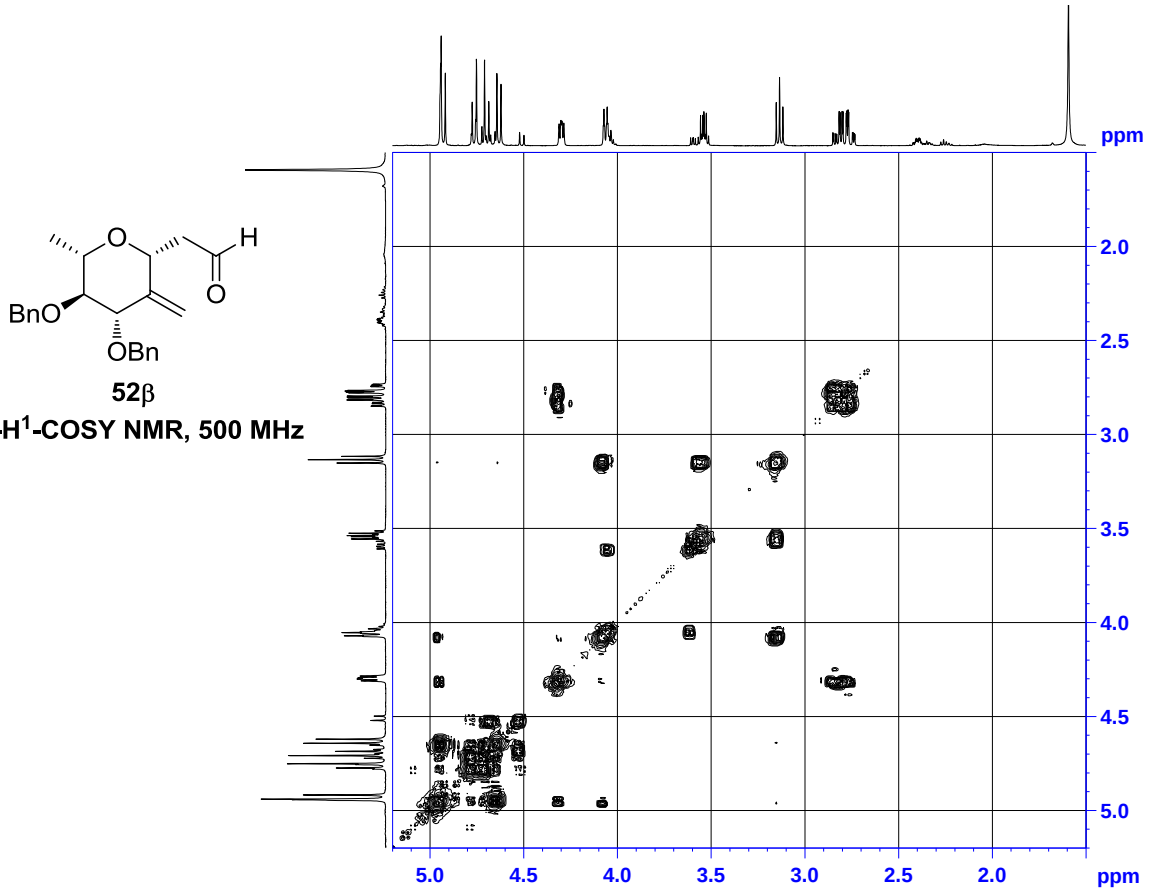
52β

H^1-NMR, 500 MHz, $CDCl_3$



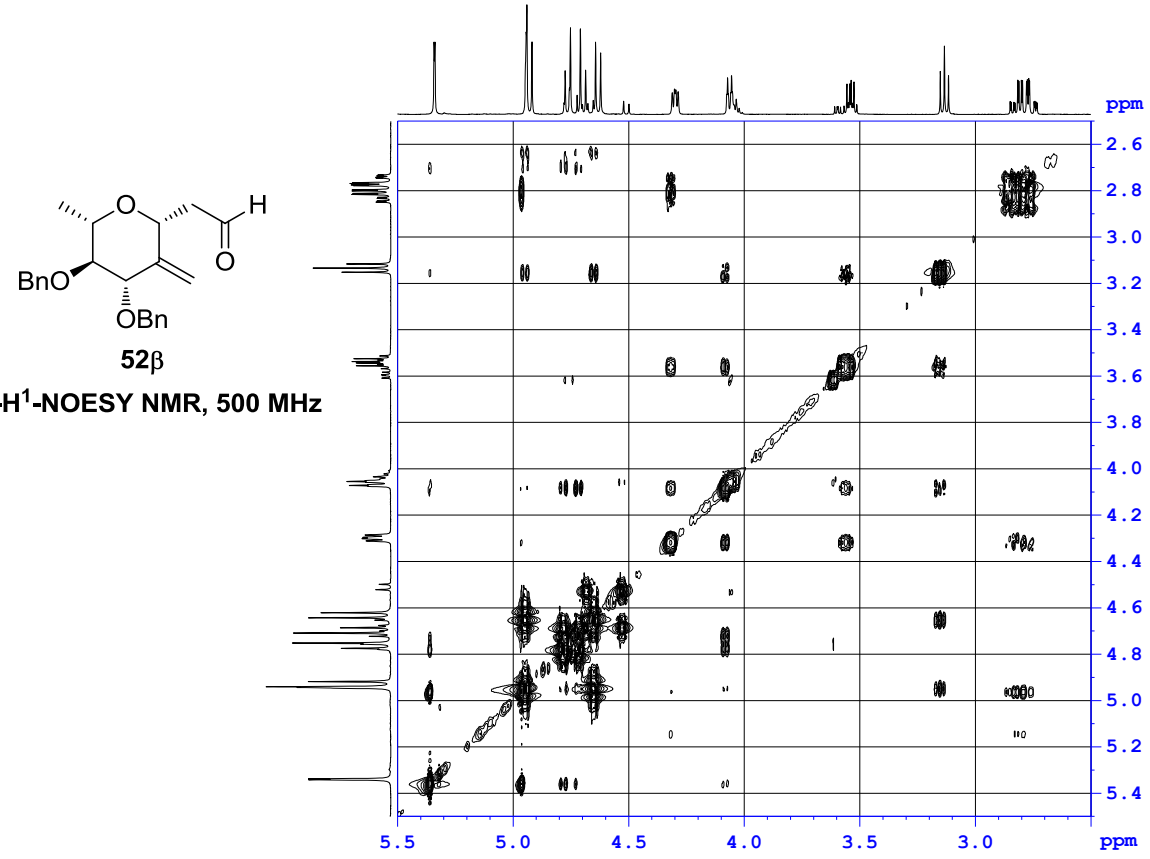
52β

C^{13}-NMR, 125MHz, $CDCl_3$



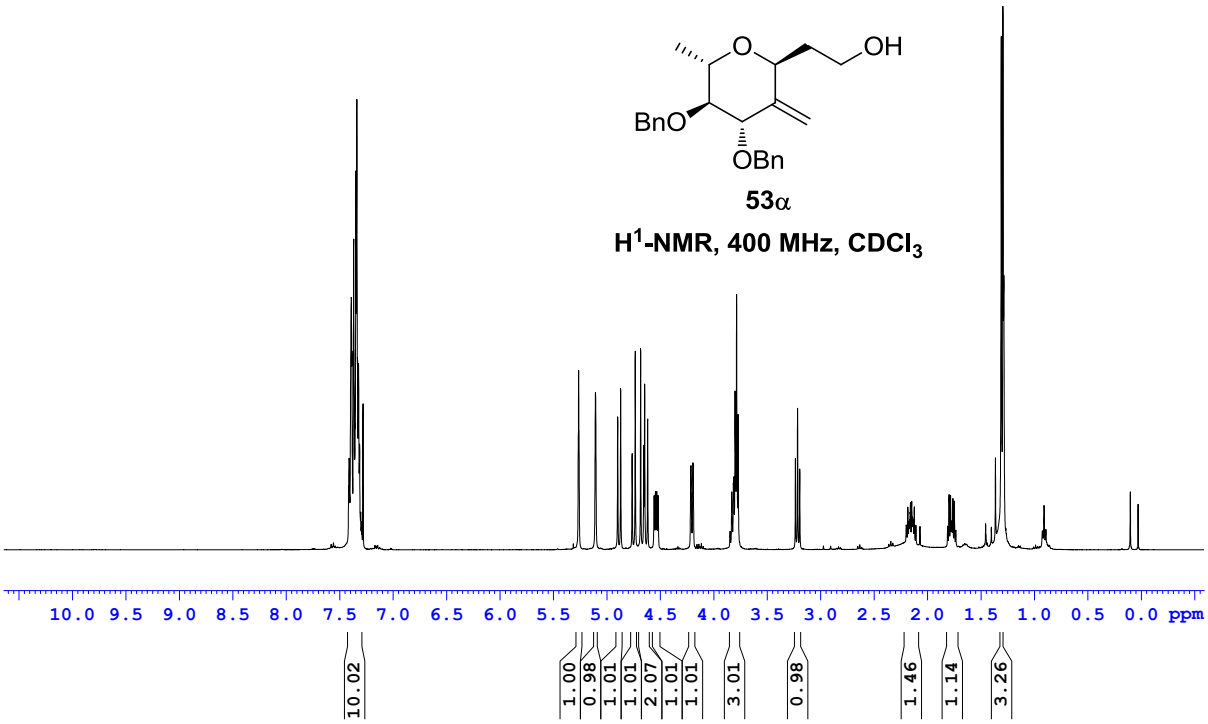
52β

H^1-H^1-COSY NMR, 500 MHz



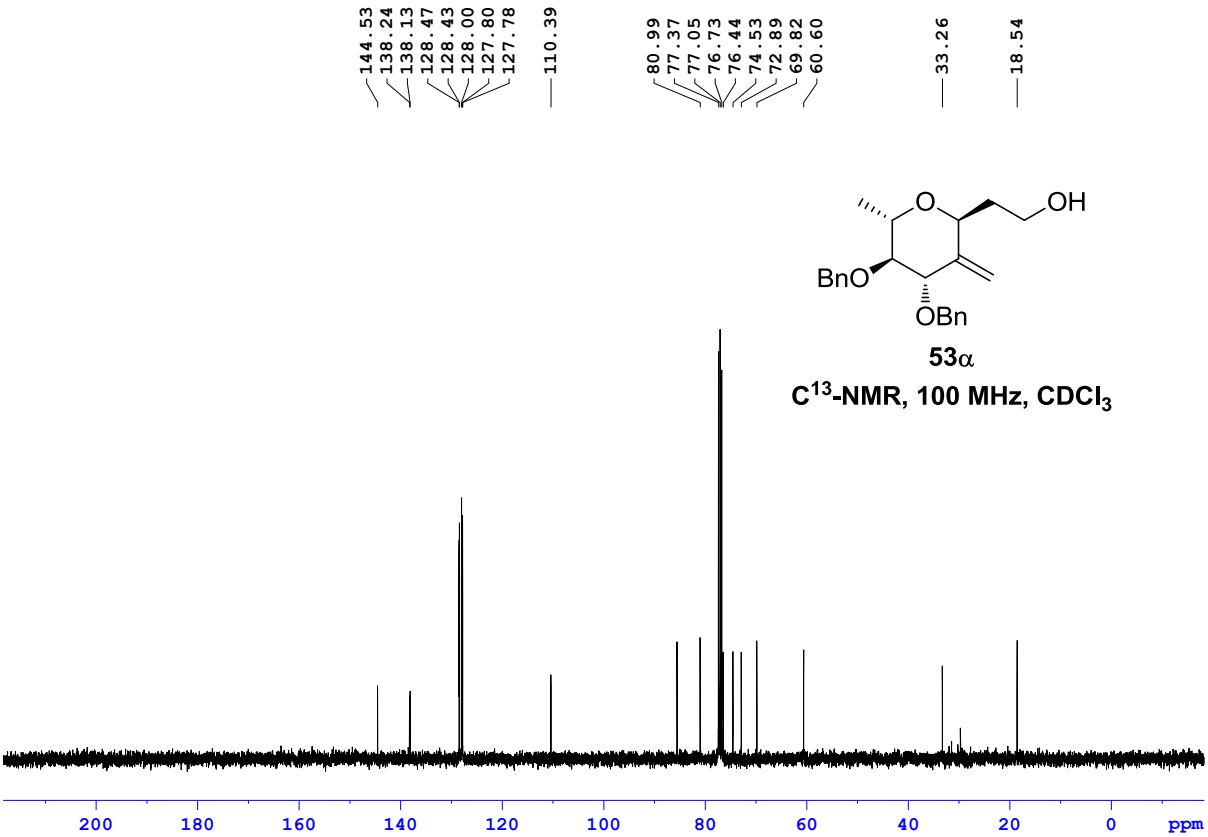
52β

H^1-H^1-NOESY NMR, 500 MHz



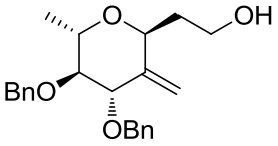
53α

H^1-NMR, 400 MHz, $CDCl_3$



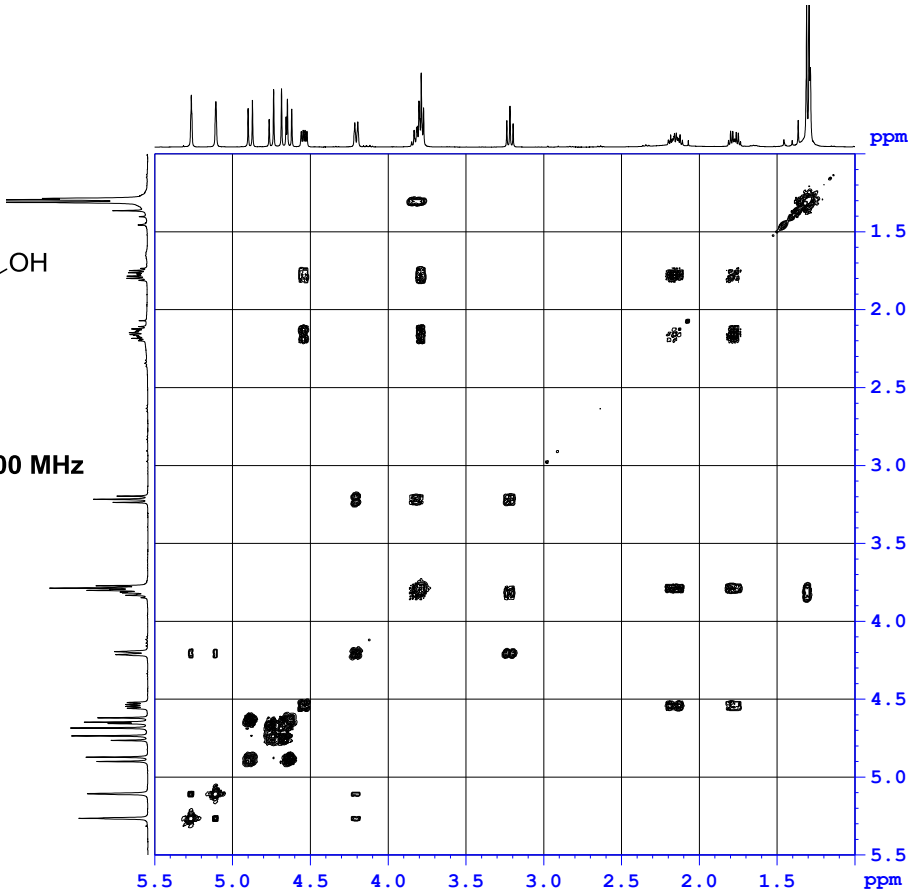
53α

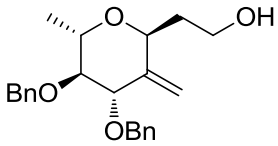
C^{13}-NMR, 100 MHz, $CDCl_3$



53α

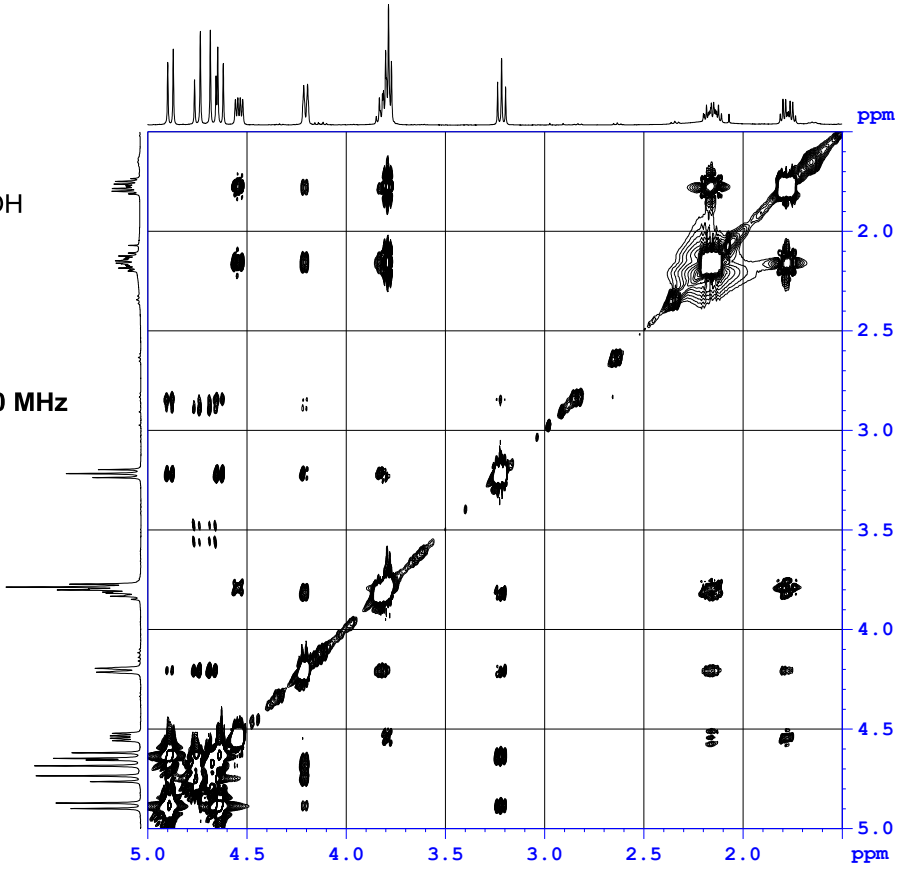
H^1-H^1-COSY NMR, 400 MHz

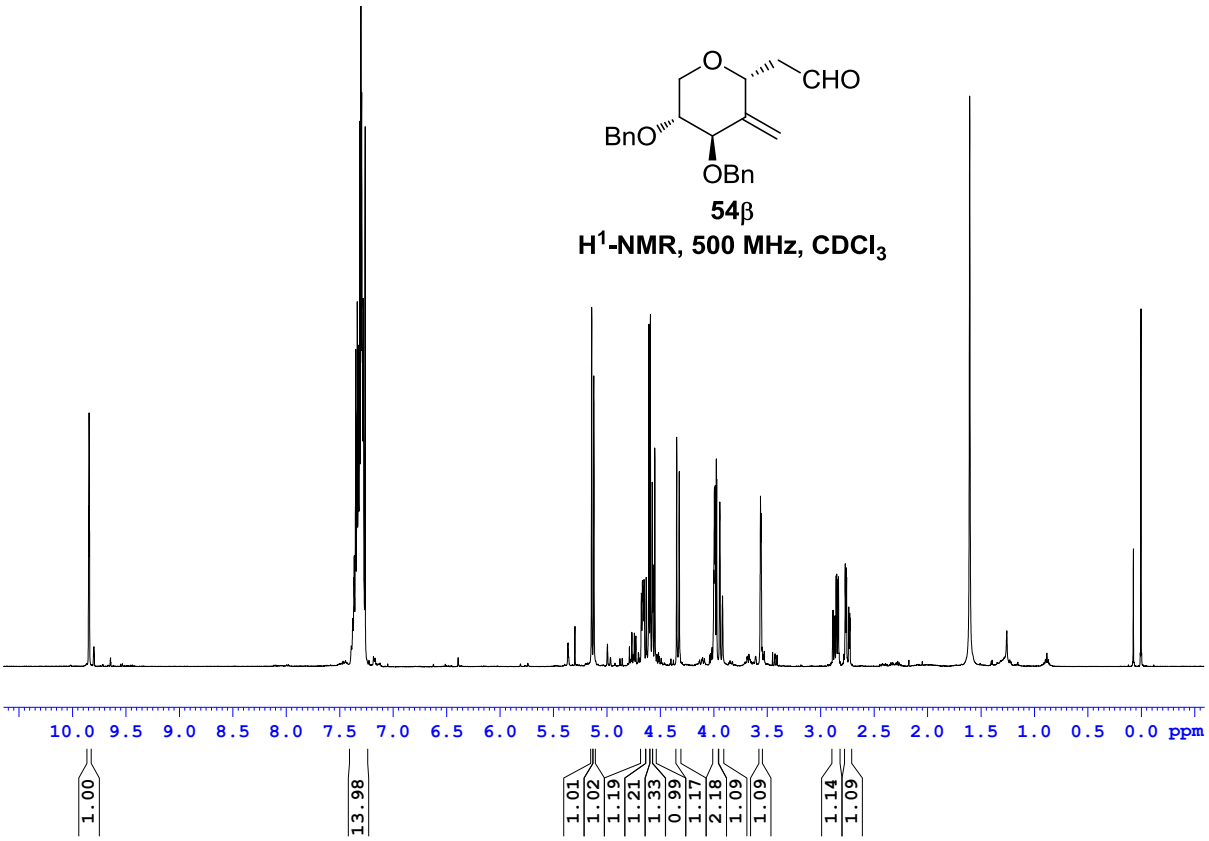




53α

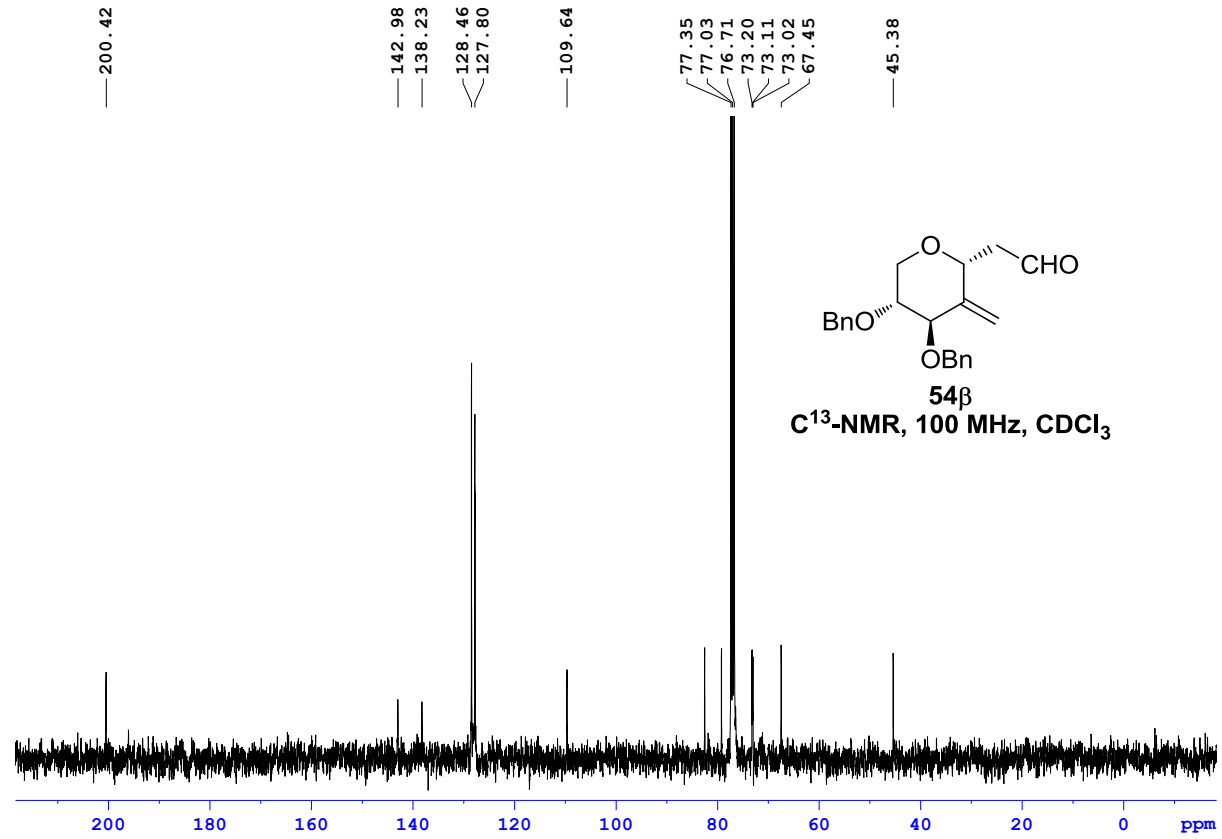
H^1-H^1-NOESY NMR, 400 MHz





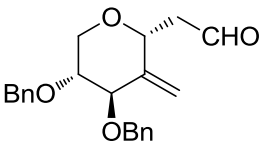
54β

H^1-NMR, 500 MHz, $CDCl_3$



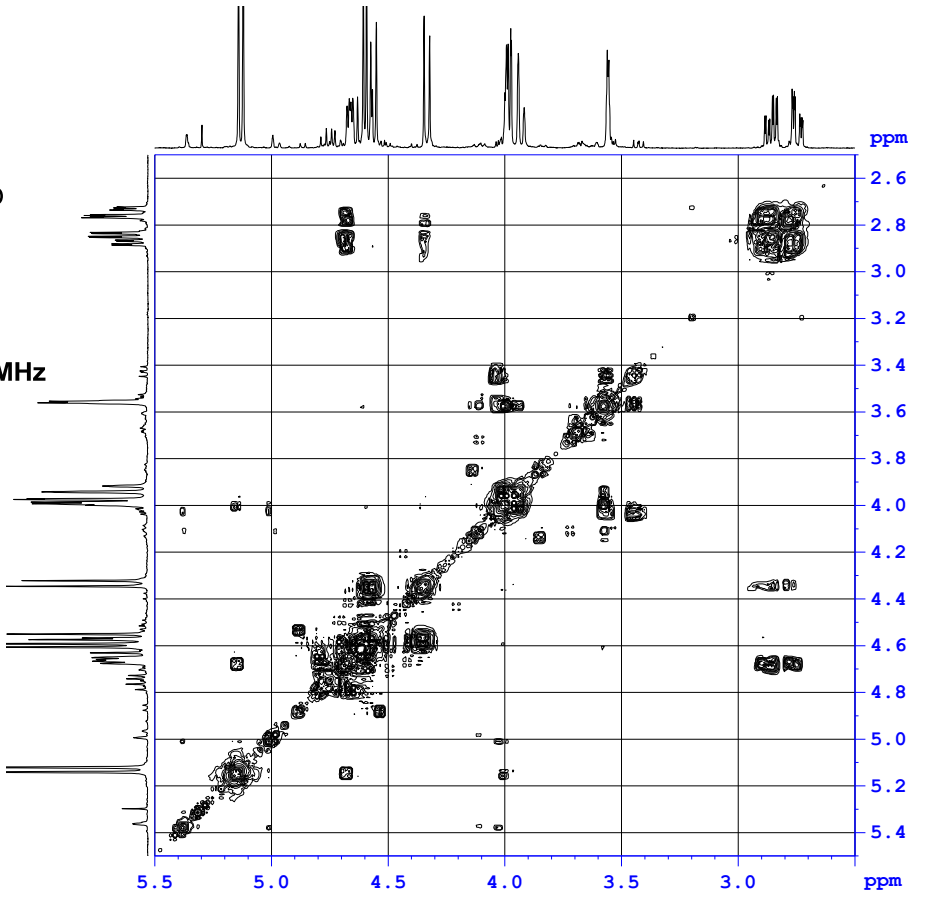
54β

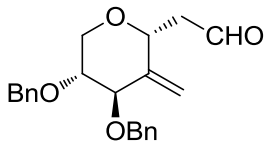
C^{13}-NMR, 100 MHz, $CDCl_3$



54β

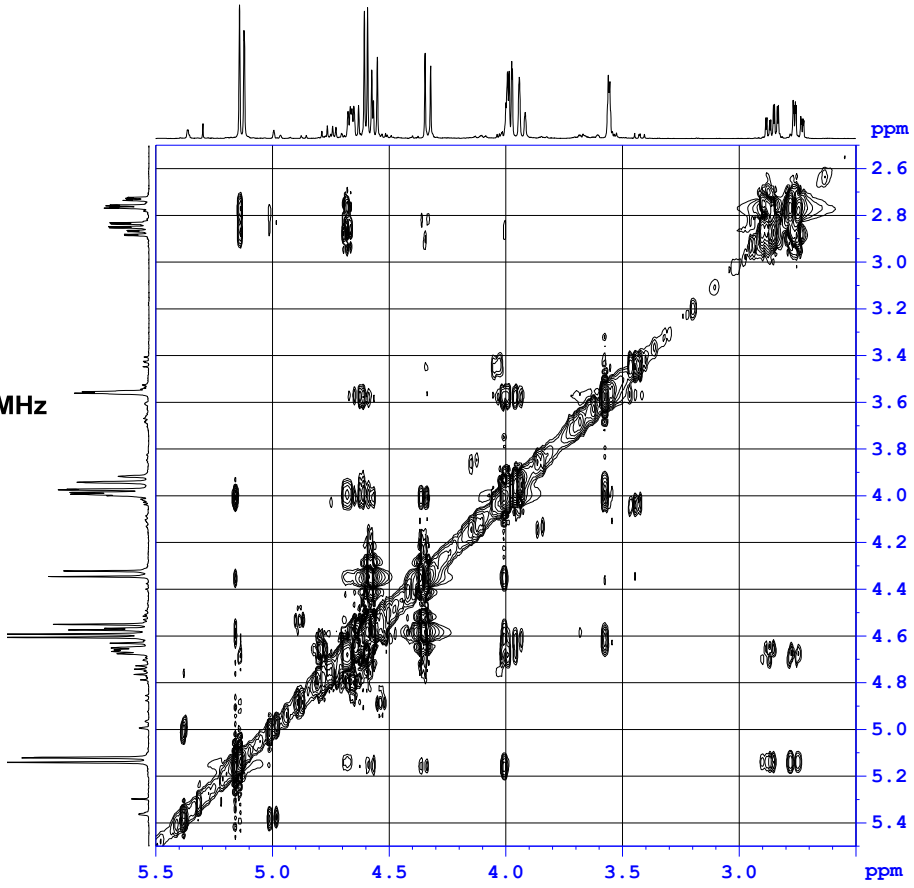
H^1-H^1-COSY NMR, 500 MHz

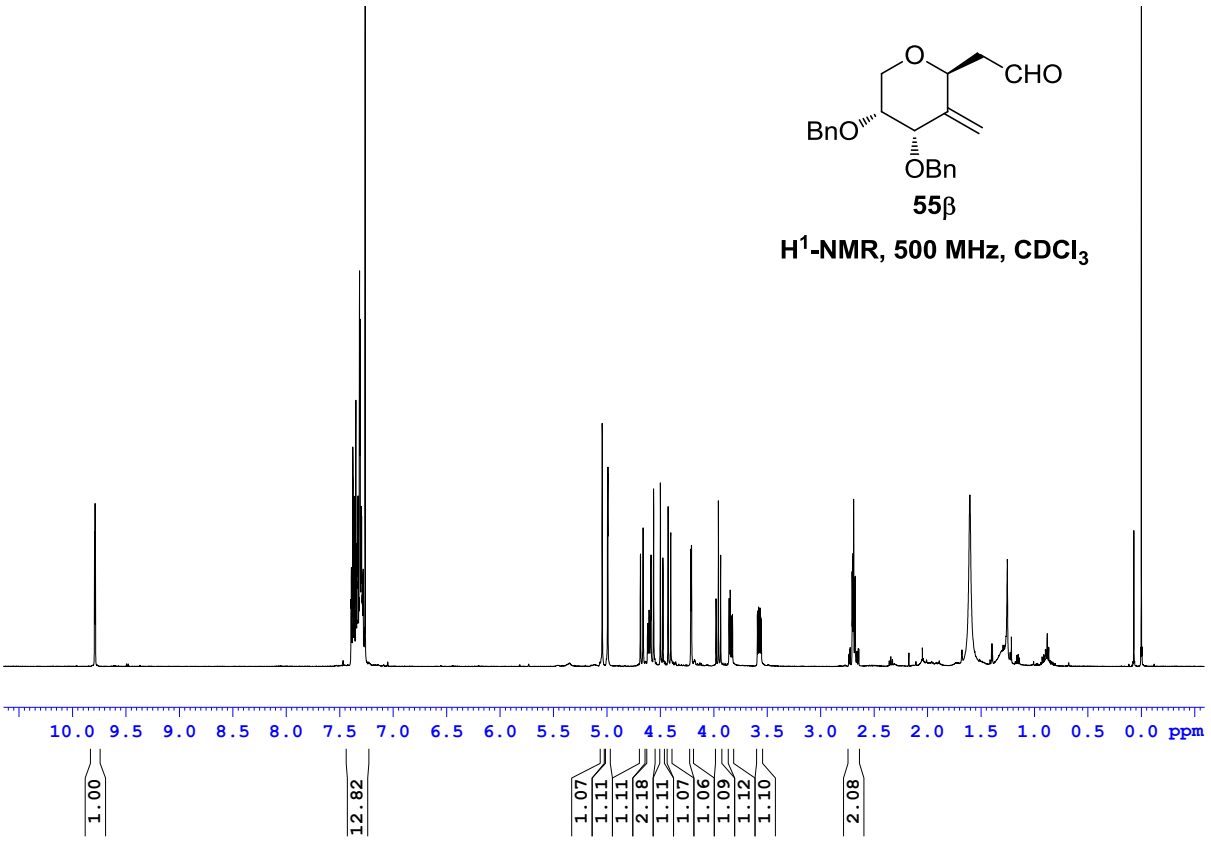




54β

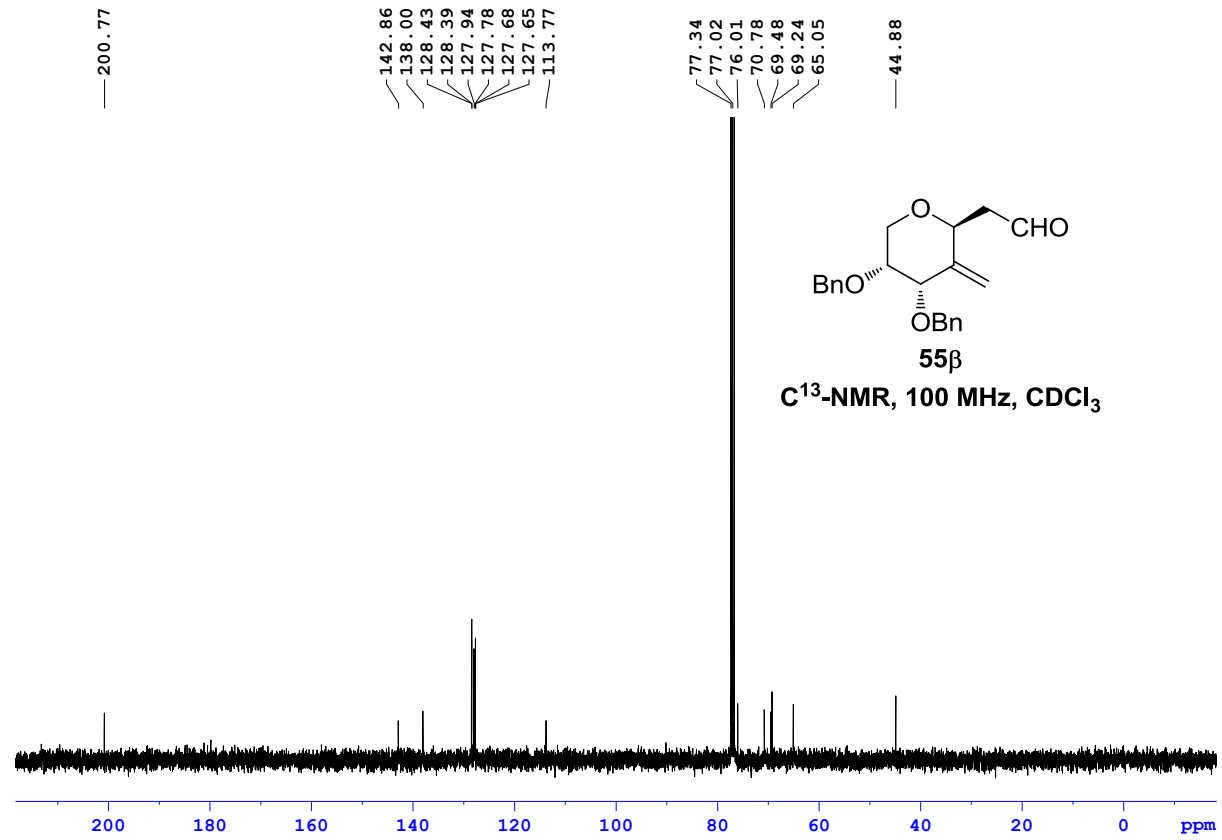
H^1-H^1-NOESY NMR, 500 MHz





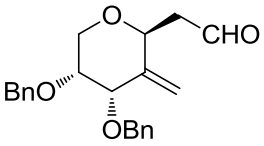
55β

H^1-NMR, 500 MHz, $CDCl_3$



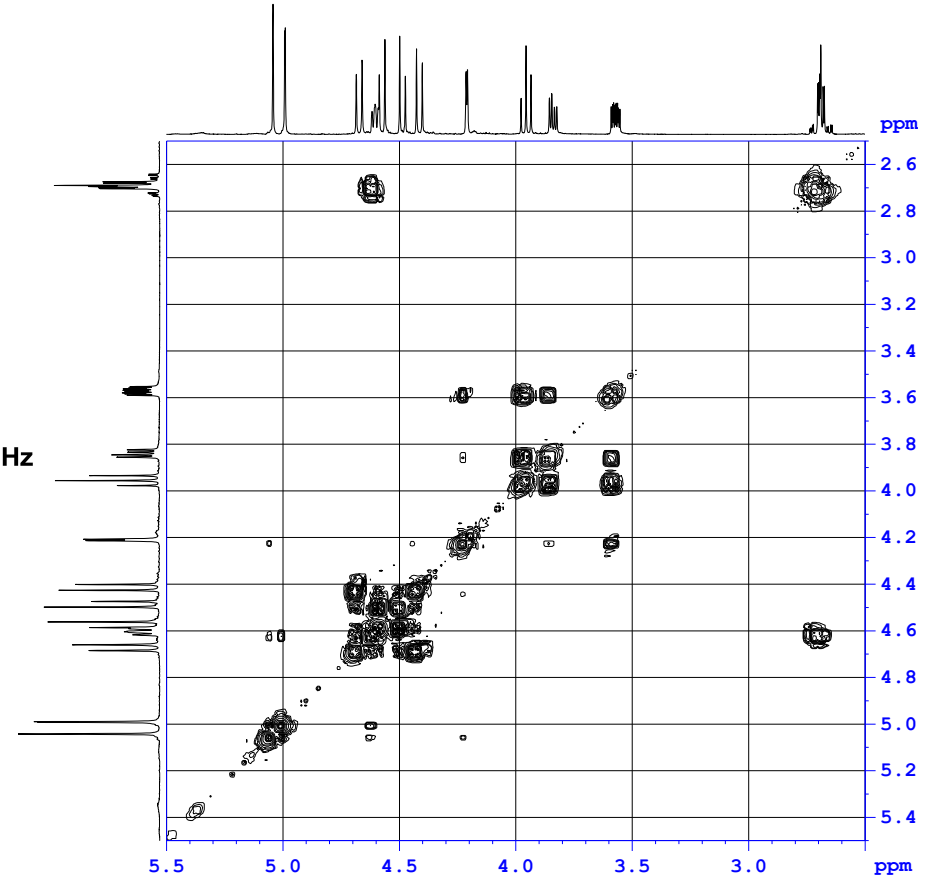
55β

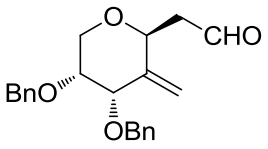
C^{13}-NMR, 100 MHz, $CDCl_3$



55β

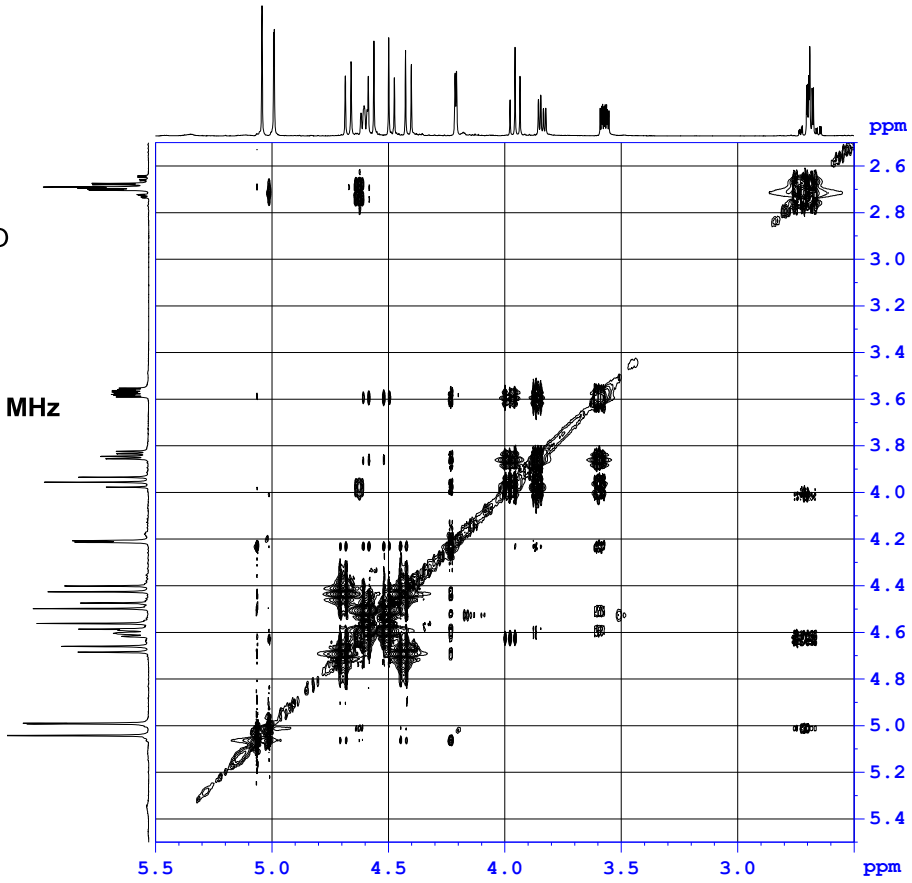
H^1-H^1-COSY NMR, 500 MHz

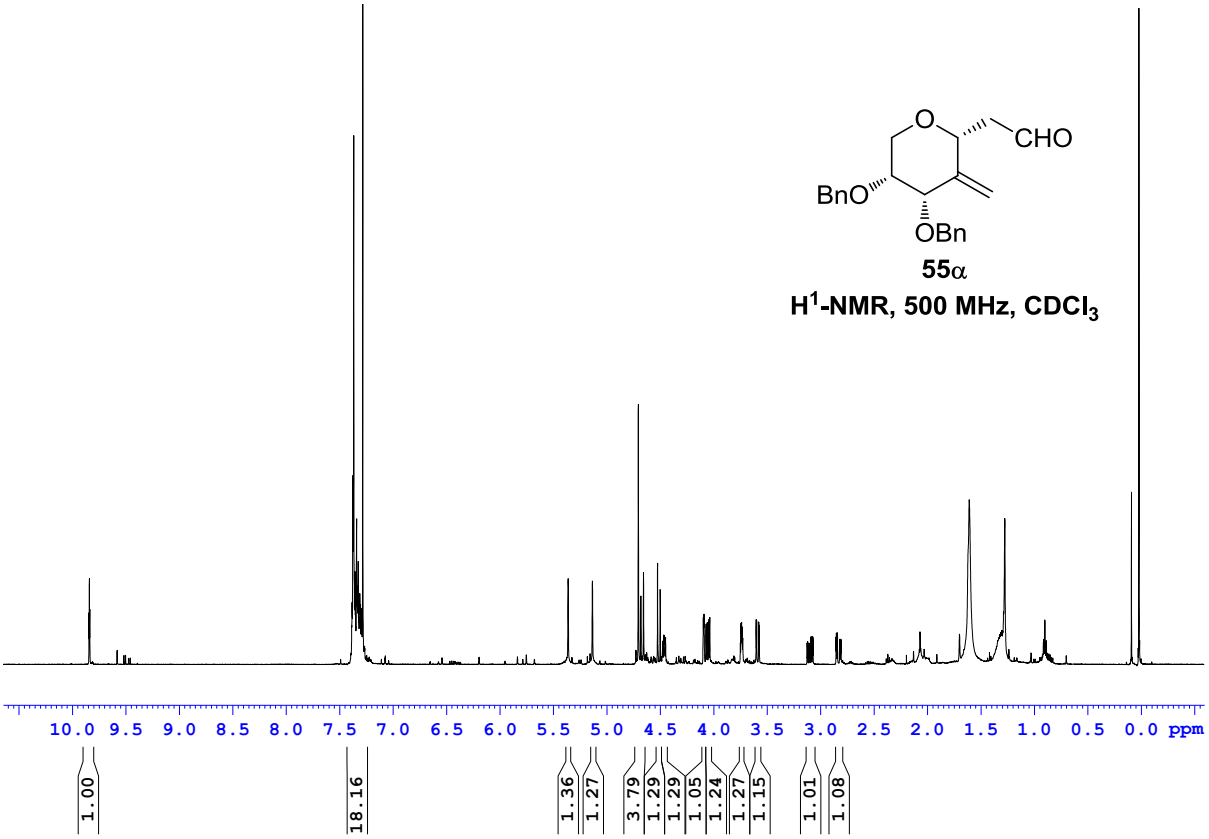




55β

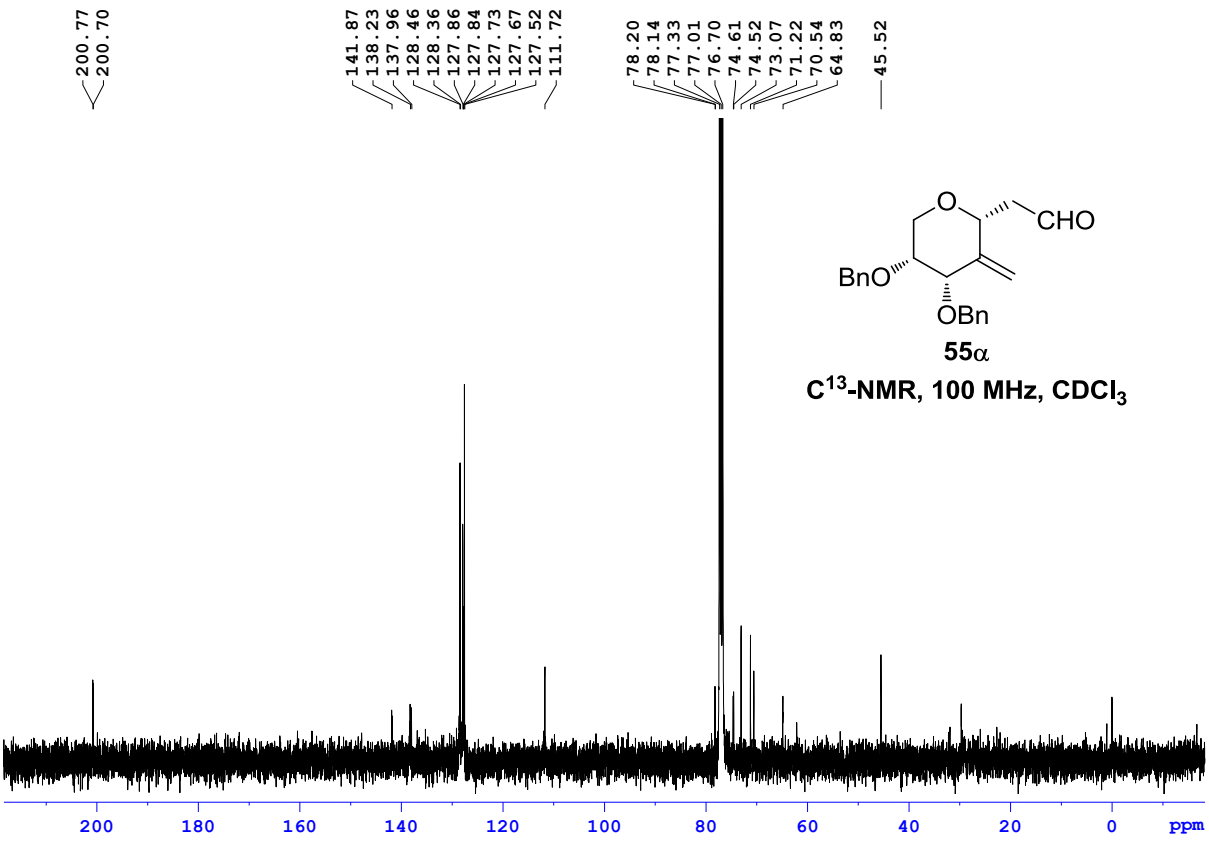
H^1-H^1-NOESY NMR, 500 MHz





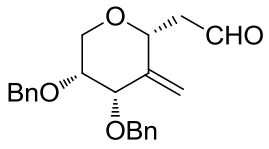
55α

H^1-NMR, 500 MHz, $CDCl_3$



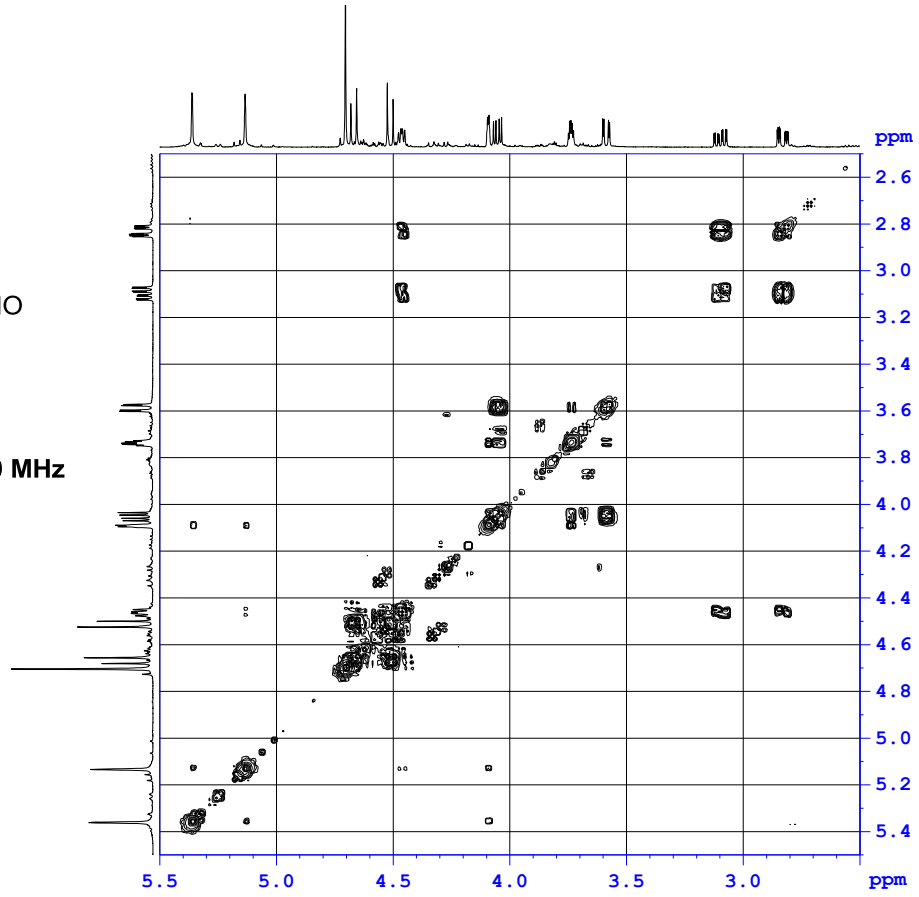
55α

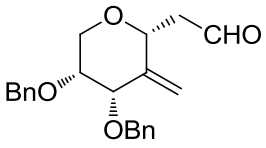
C^{13}-NMR, 100 MHz, $CDCl_3$



55α

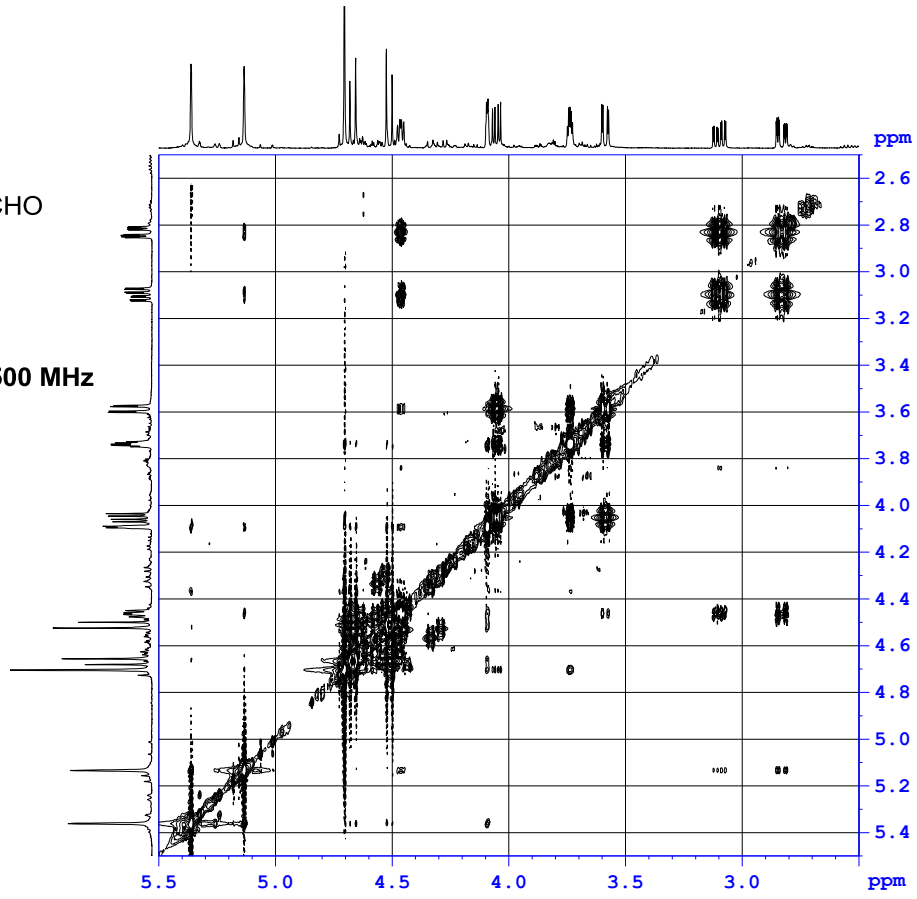
H^1-H^1-COSY NMR, 500 MHz

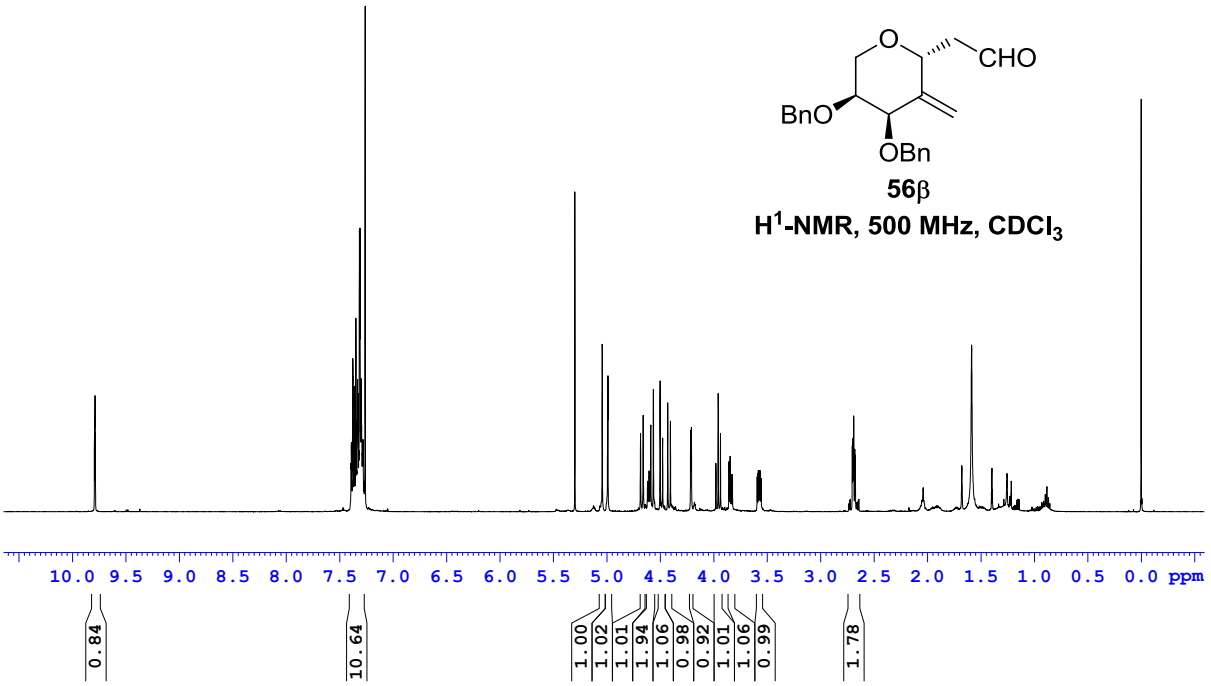




55α

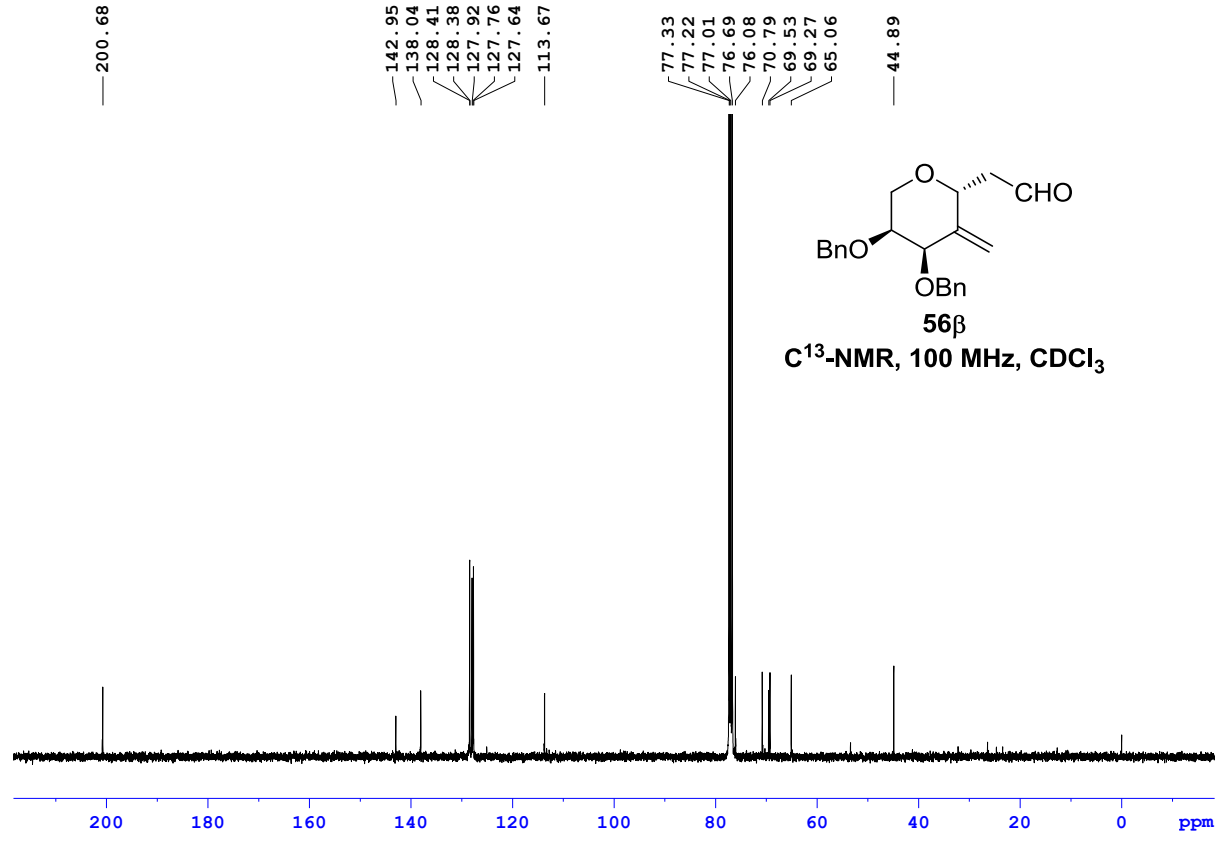
H^1-H^1-NOESY NMR, 500 MHz





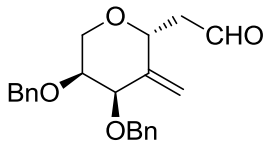
56β

H^1-NMR, 500 MHz, $CDCl_3$



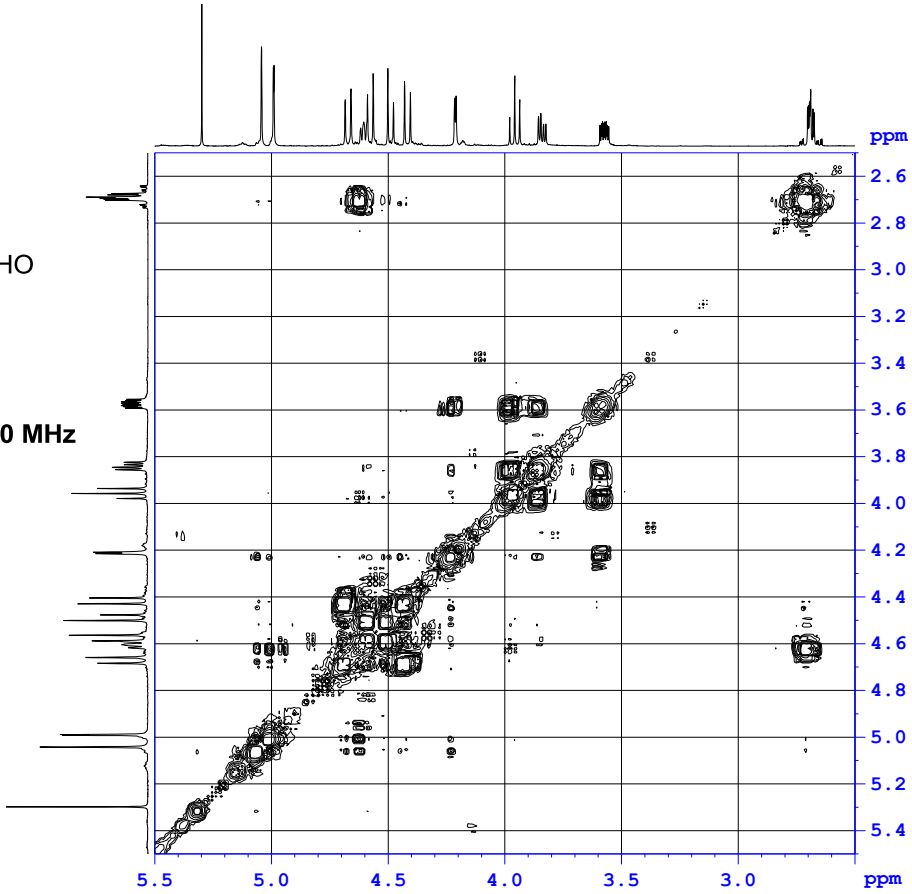
56β

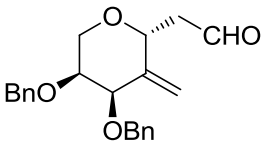
C^{13}-NMR, 100 MHz, $CDCl_3$



56β

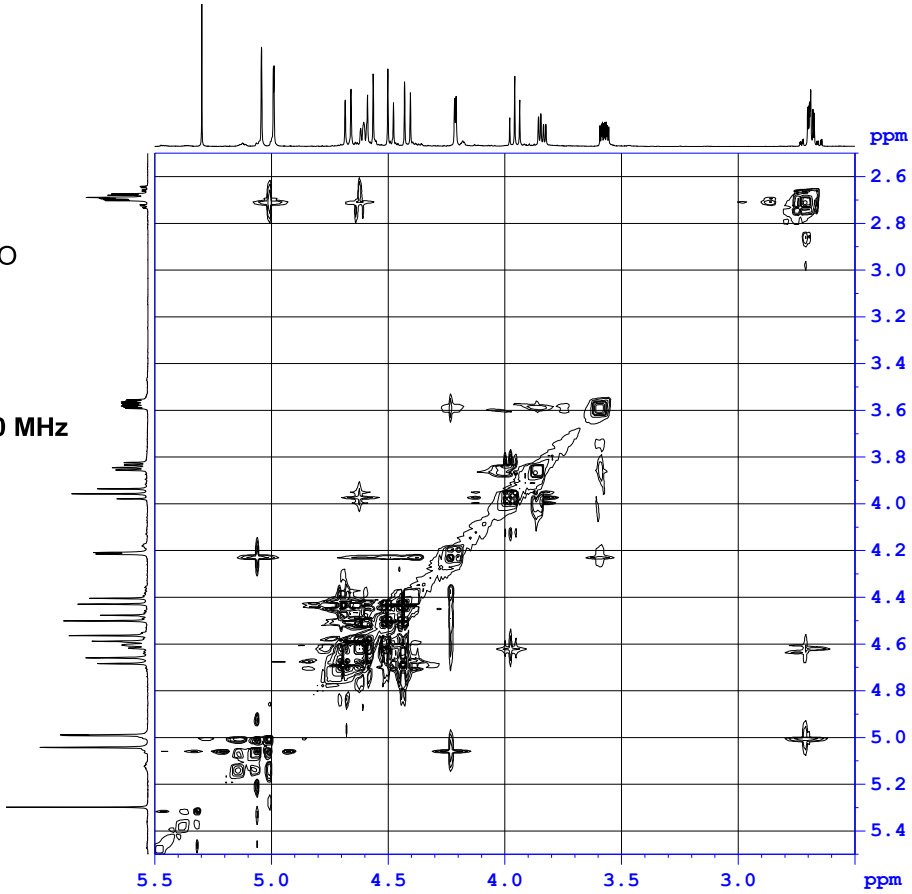
H^1-H^1-COSY NMR, 500 MHz

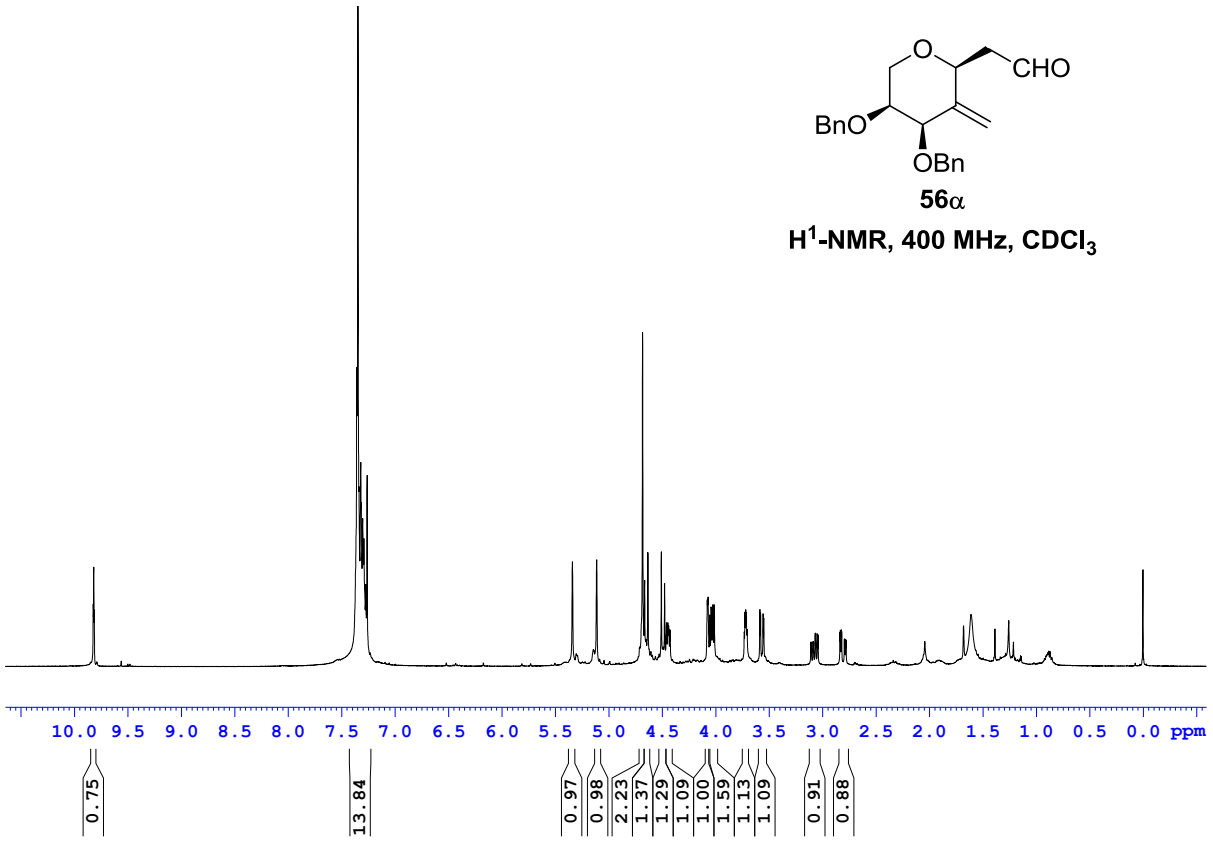




56β

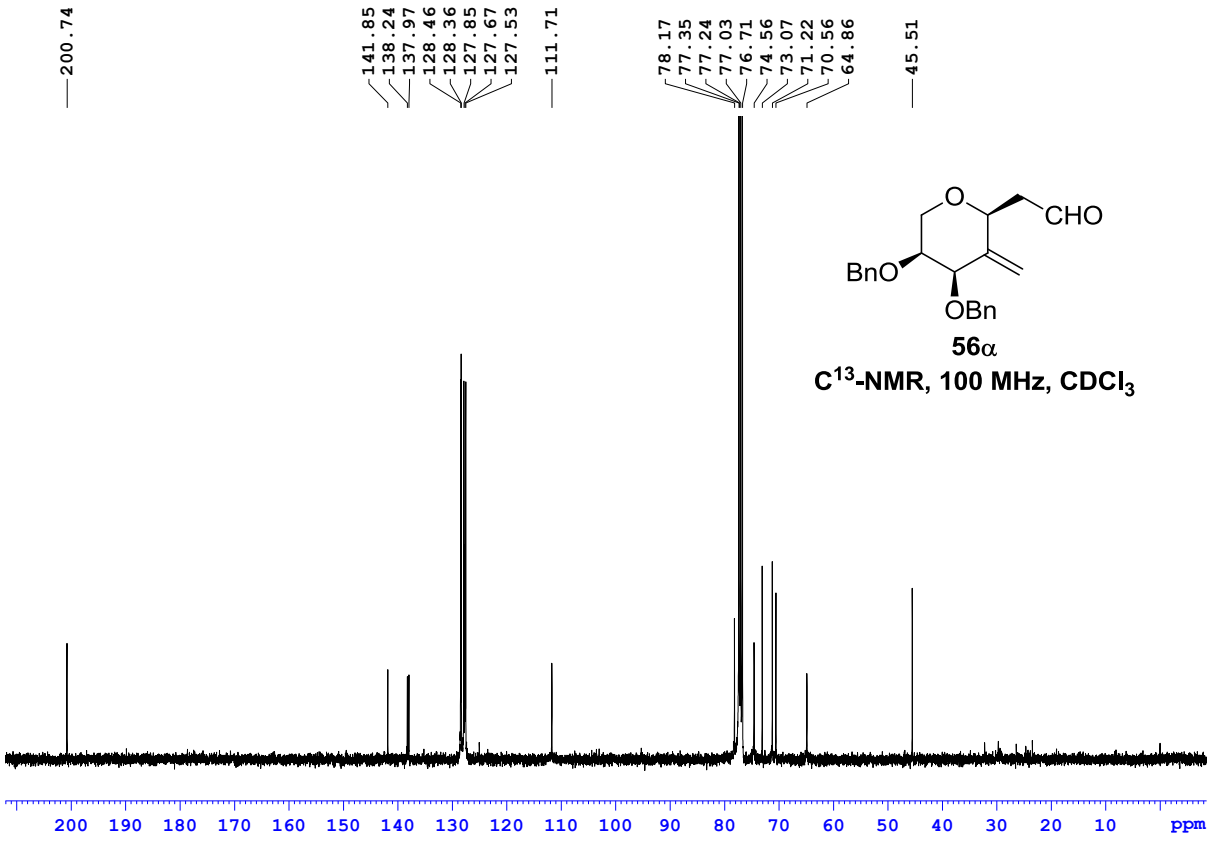
H^1-H^1-NOESY NMR, 500 MHz





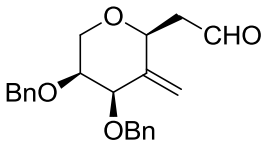
56α

H^1-NMR, 400 MHz, $CDCl_3$



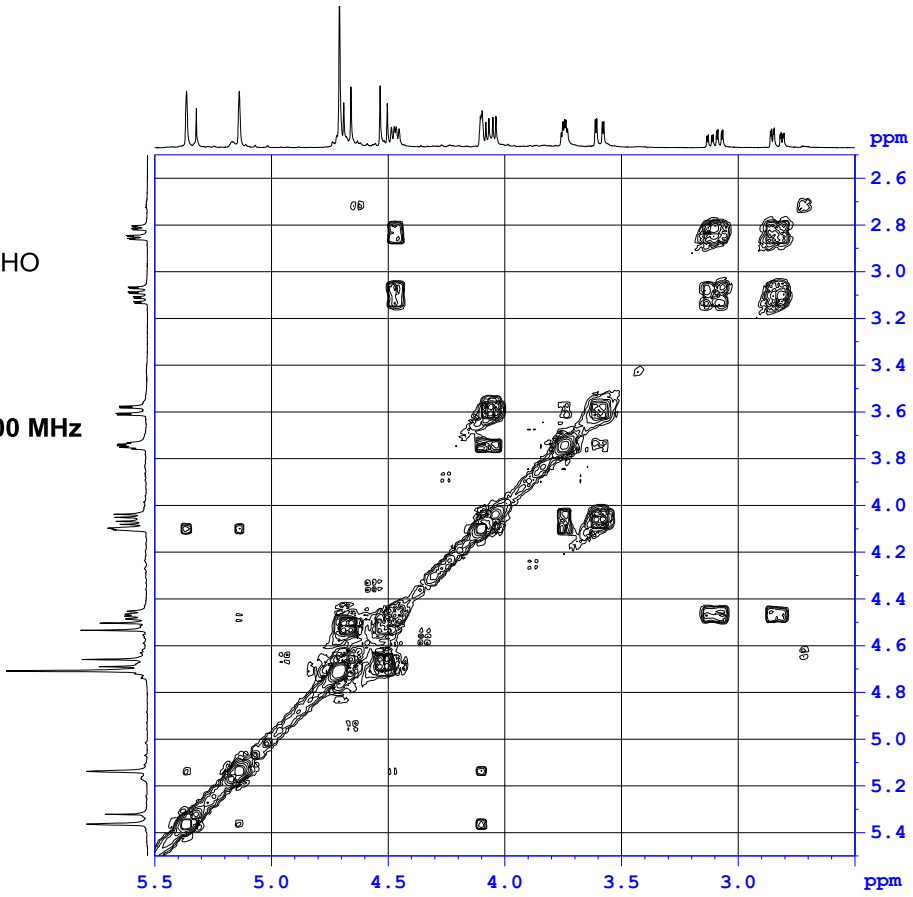
56α

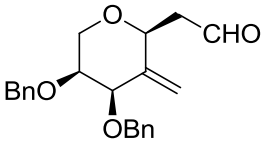
C^{13}-NMR, 100 MHz, $CDCl_3$



56α

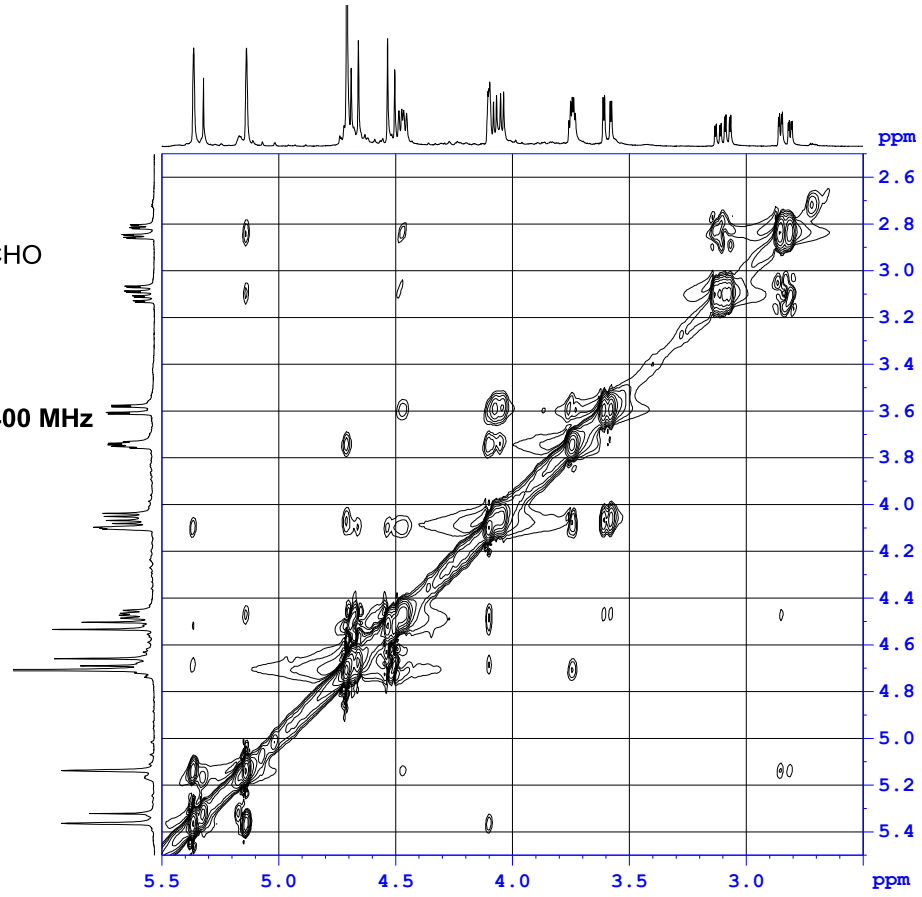
H^1-H^1-COSY NMR, 400 MHz

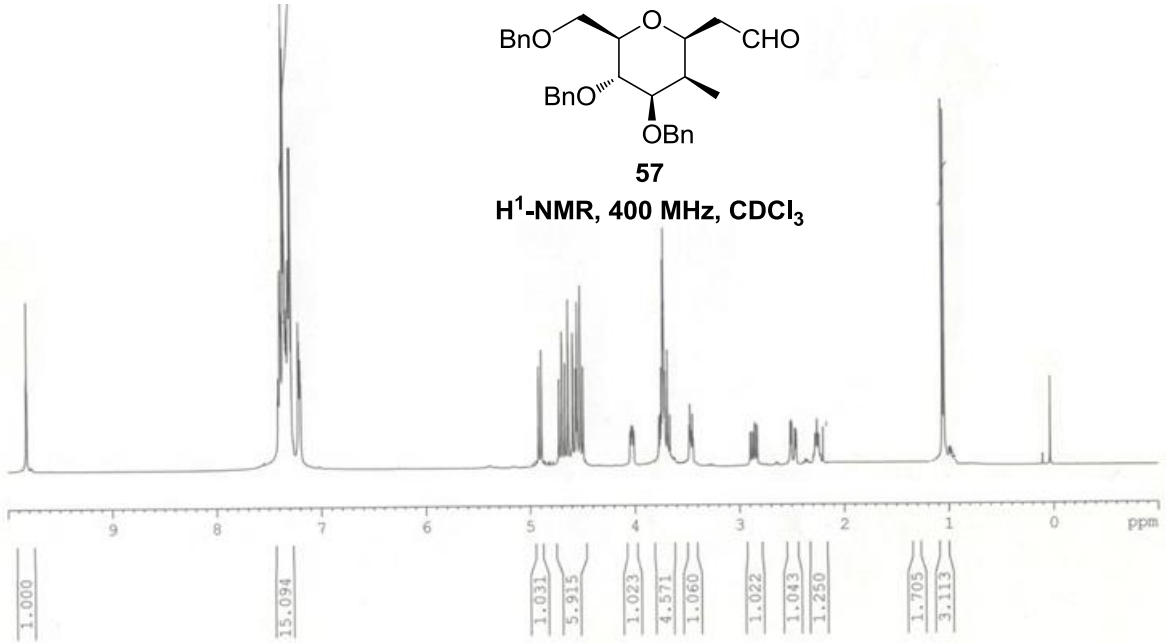




56α

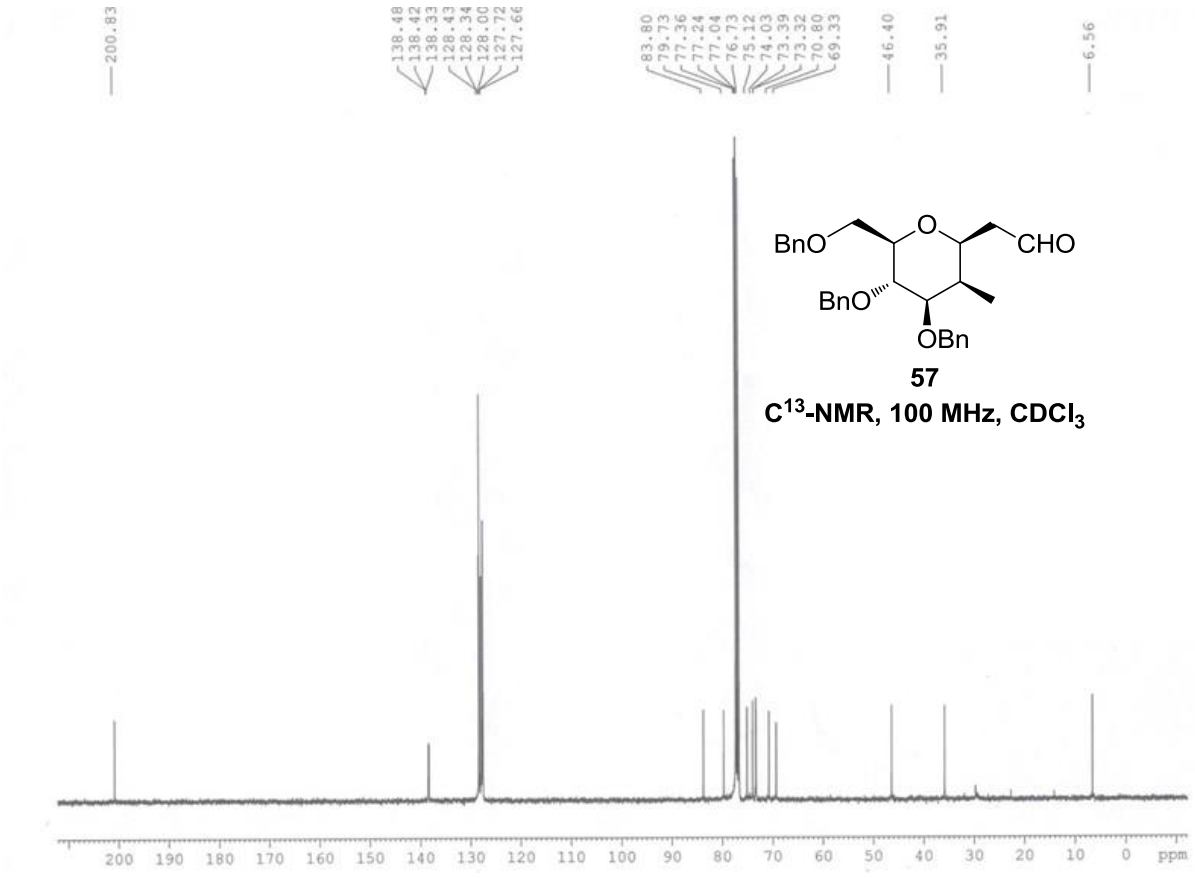
H^1-H^1-NOESY NMR, 400 MHz





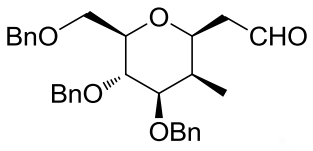
57

H^1-NMR, 400 MHz, $CDCl_3$



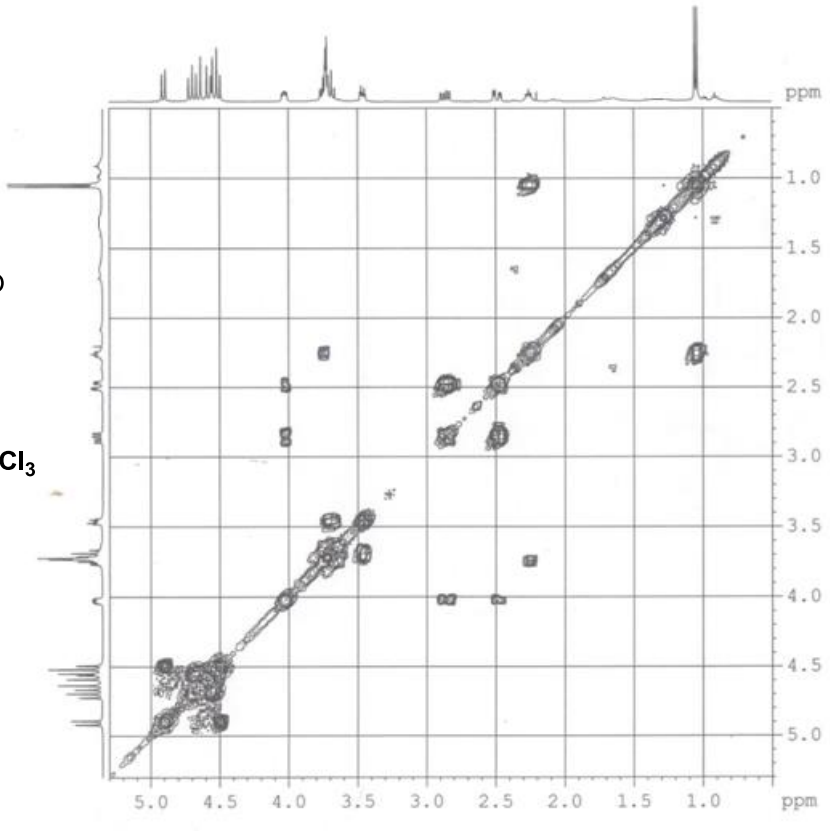
57

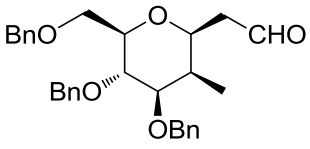
C^{13}-NMR, 100 MHz, $CDCl_3$



57

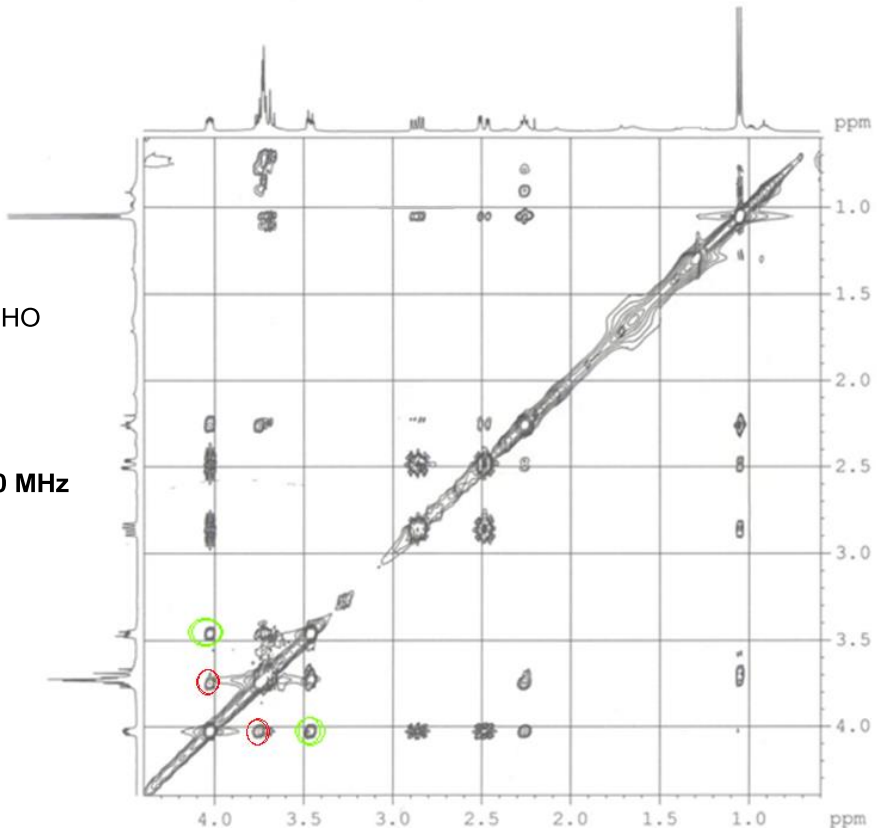
^{1}H-^{1}H COSY, 400 MHz, $CDCl_3$

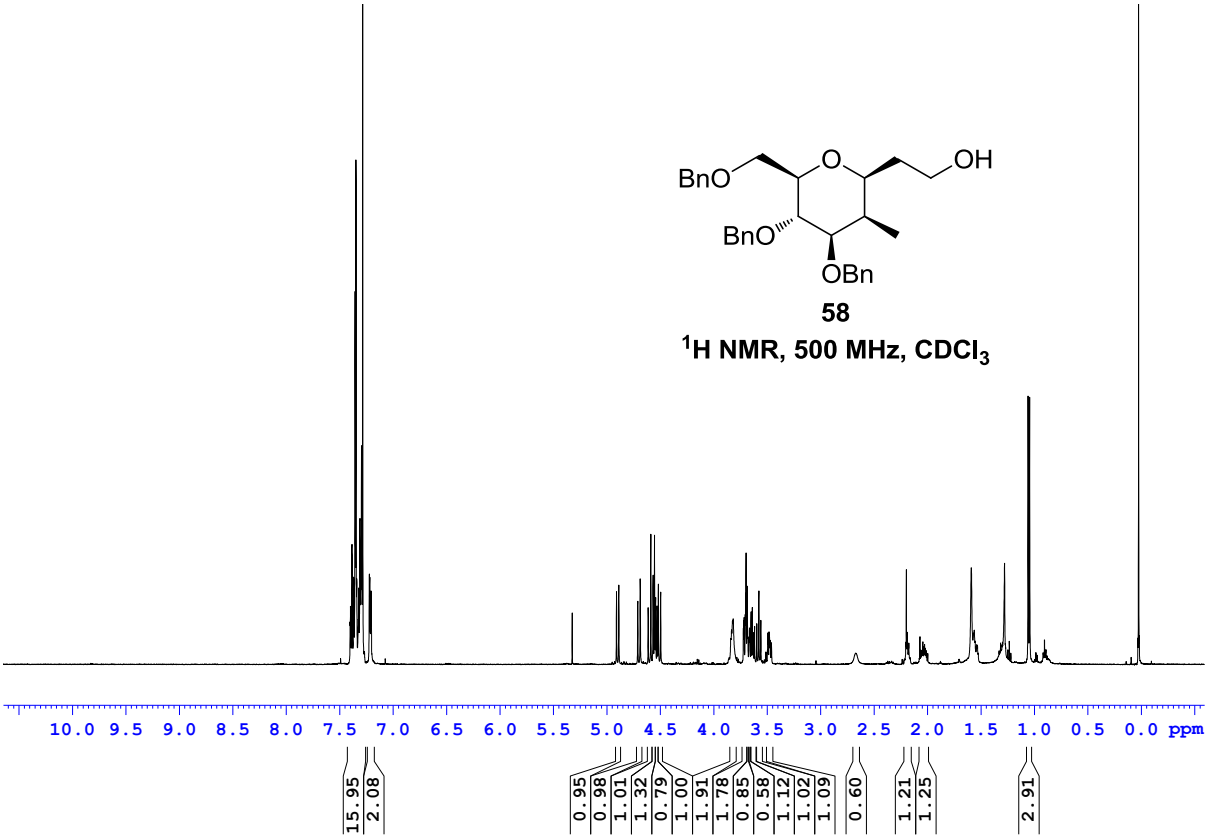




57

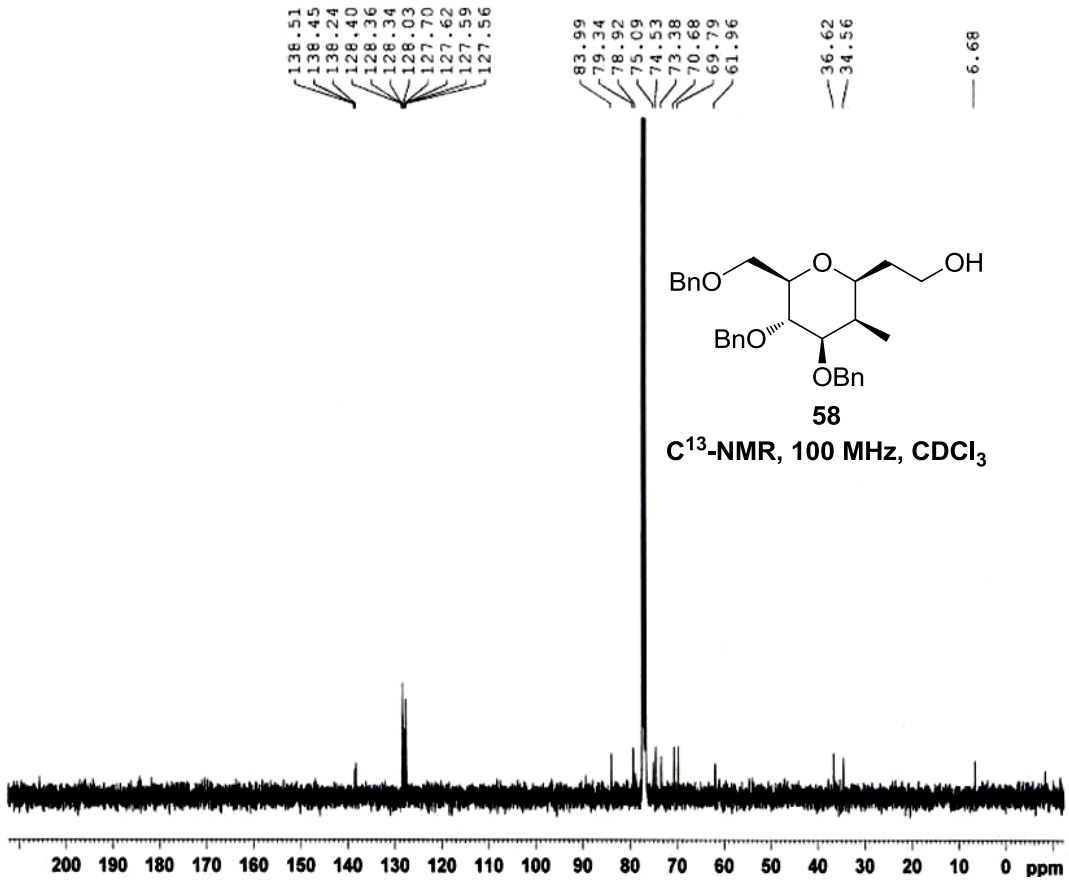
H^{1}-H^{1}-NOESY NMR, 400 MHz





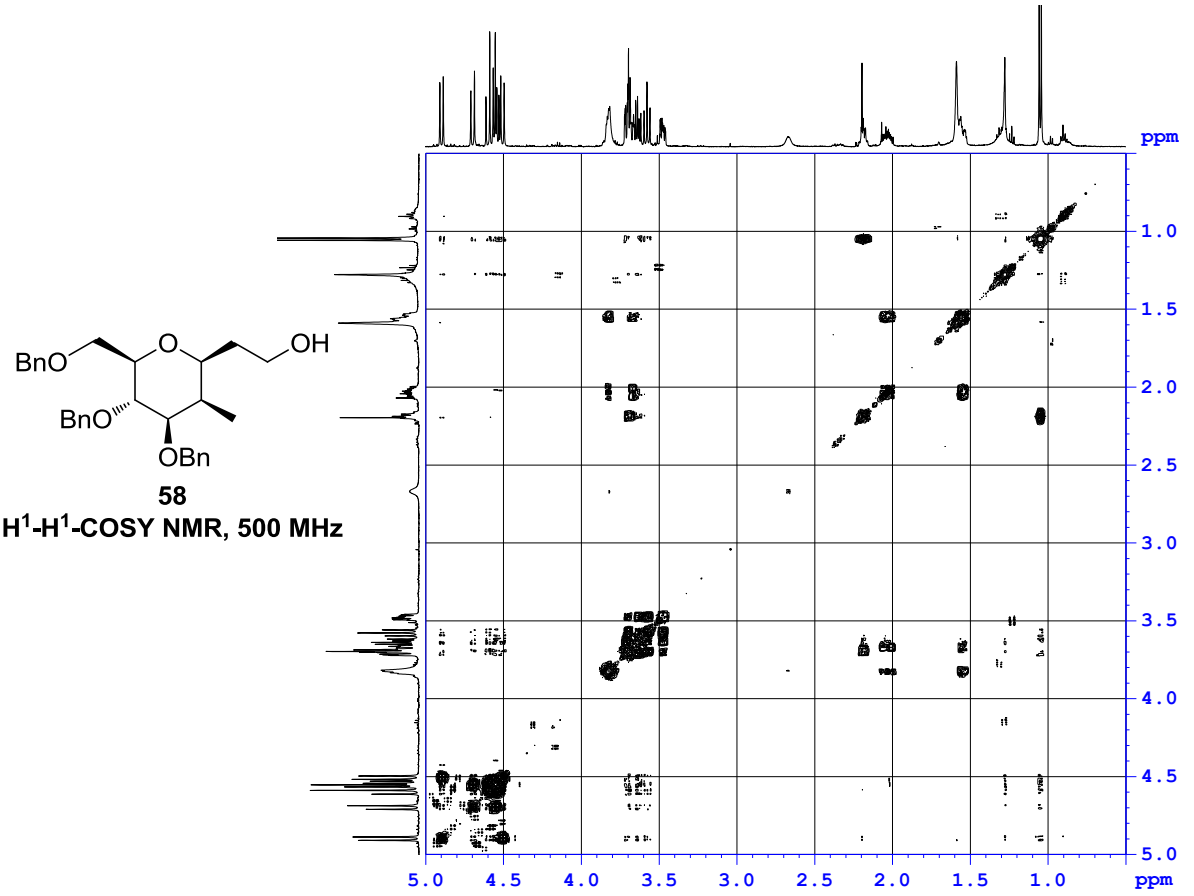
58

^{1}H NMR, 500 MHz, $CDCl_3$



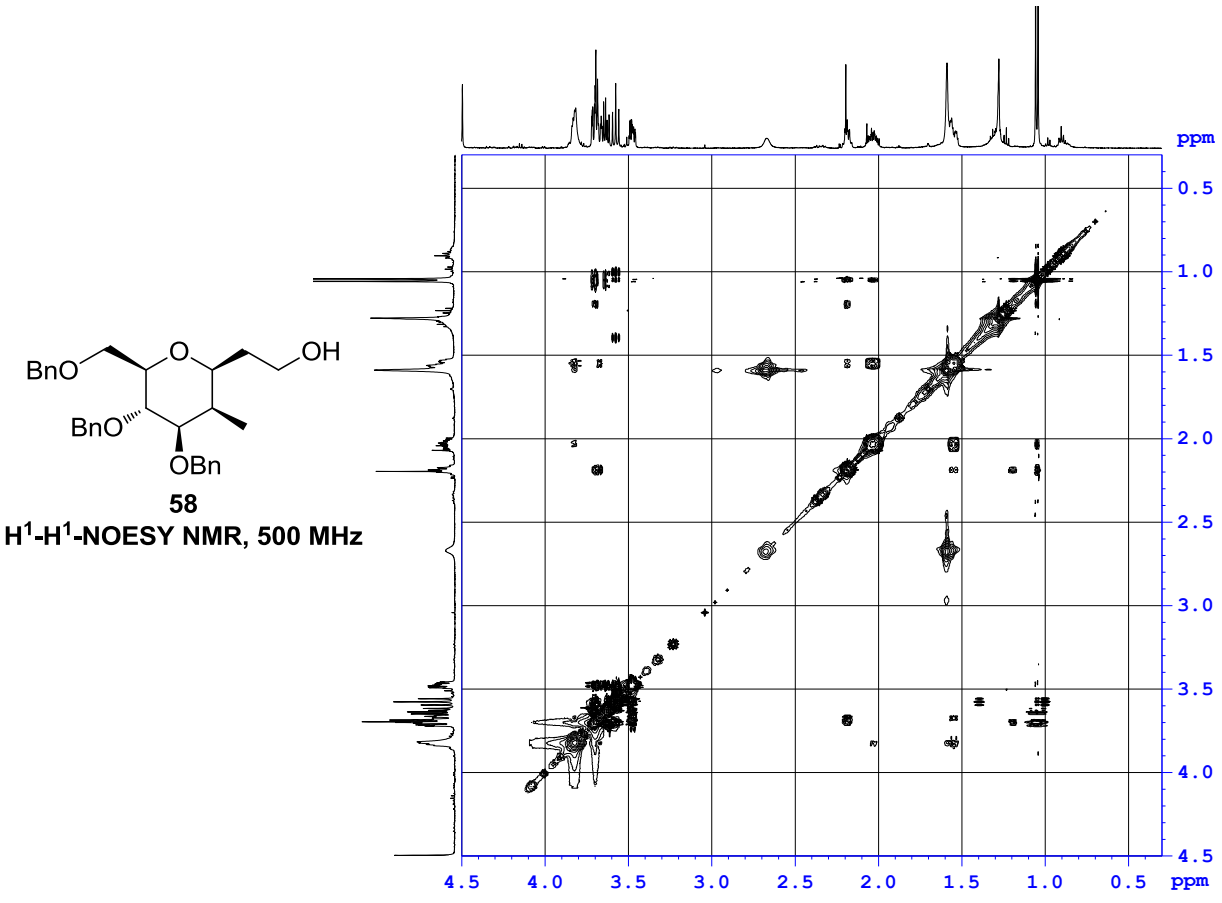
58

C^{13}-NMR, 100 MHz, $CDCl_3$



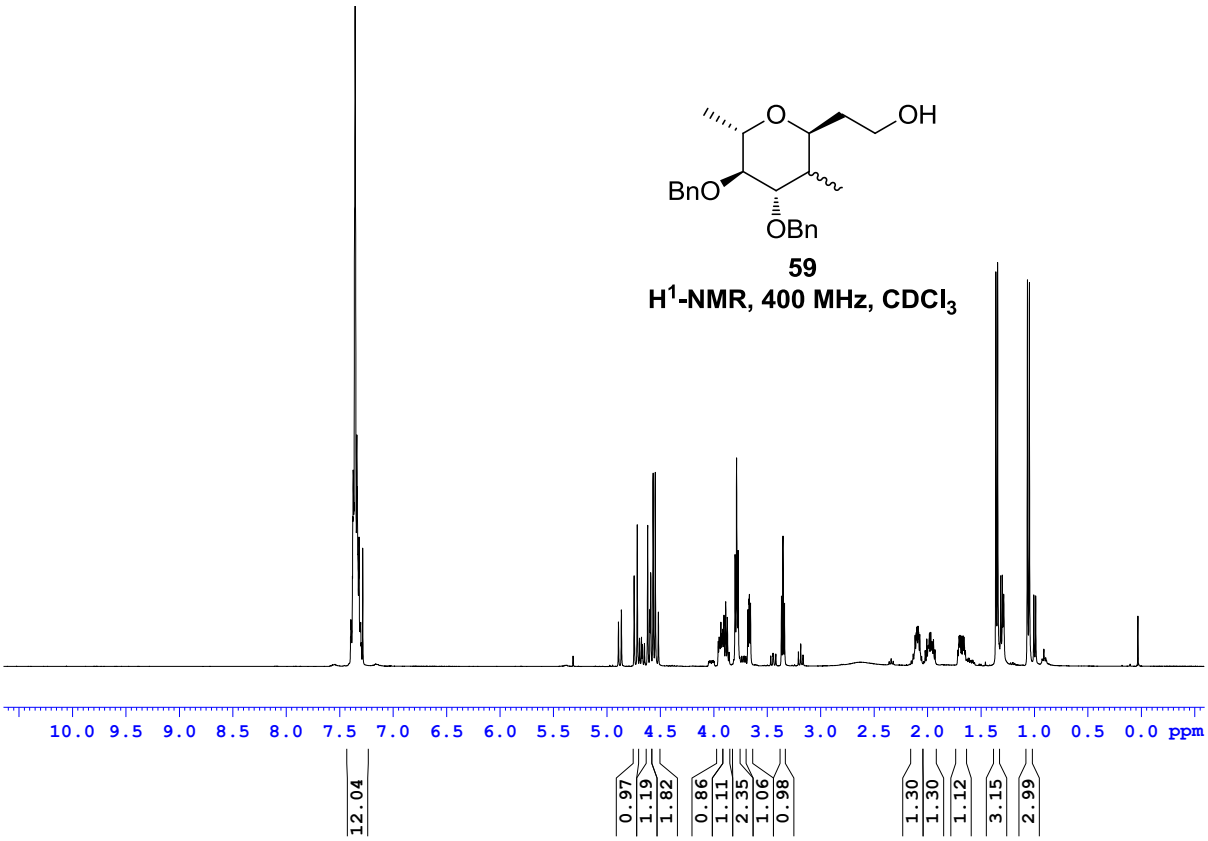
58

H^1-H^1-COSY NMR, 500 MHz



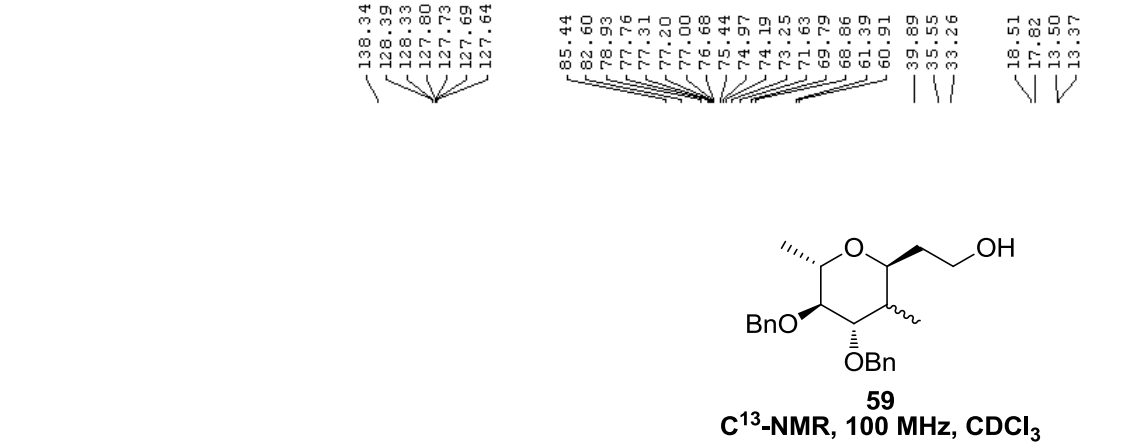
58

H^1-H^1-NOESY NMR, 500 MHz



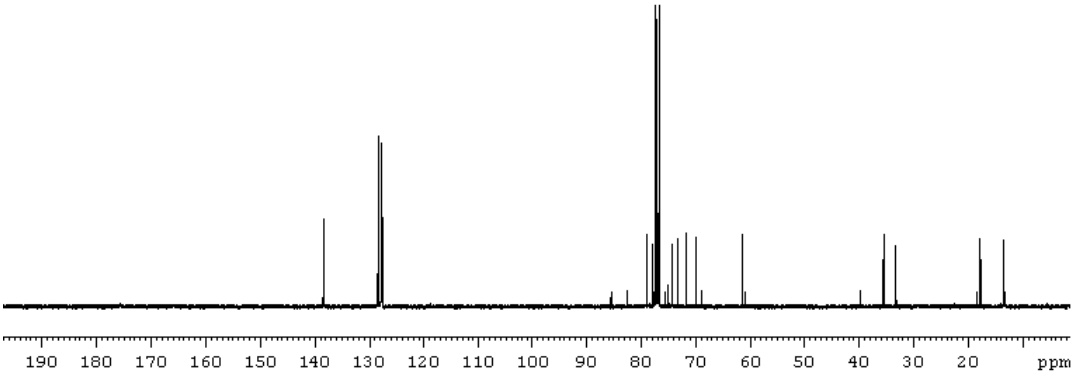
59

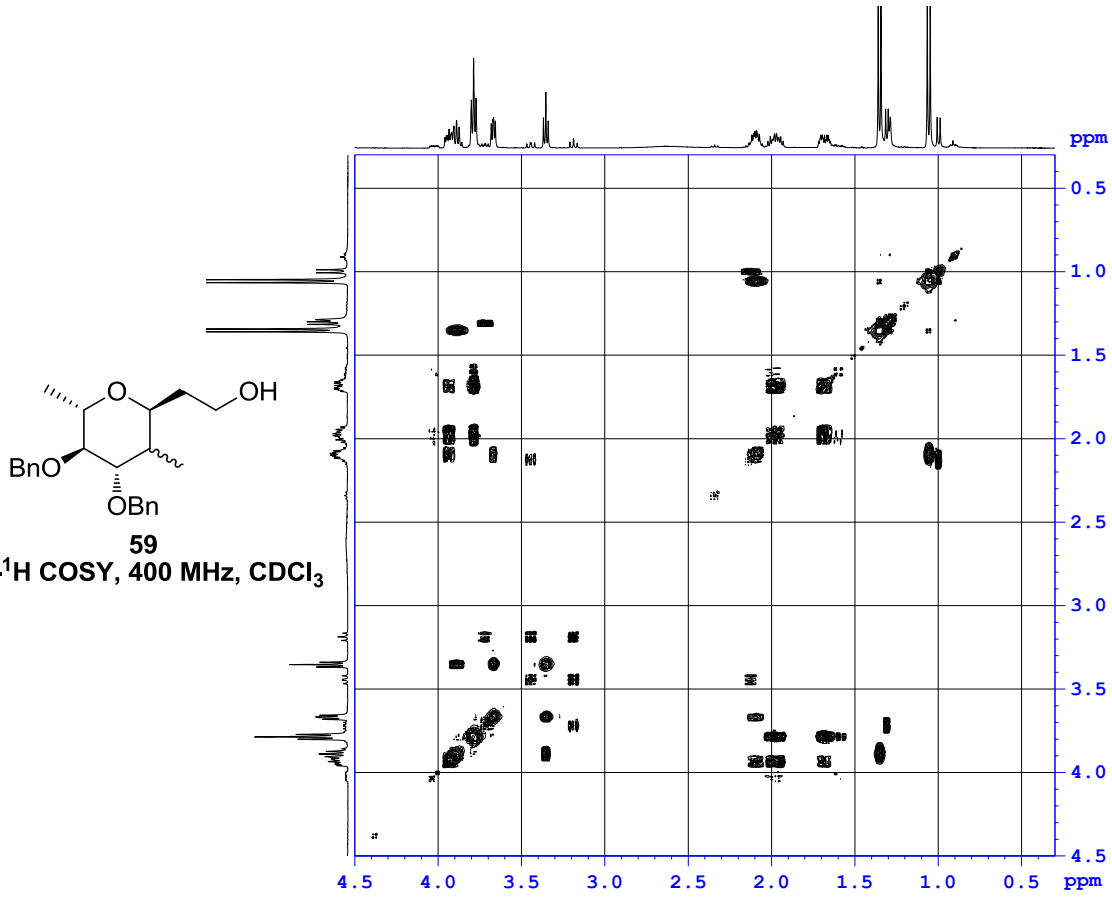
H^1-NMR, 400 MHz, $CDCl_3$



59

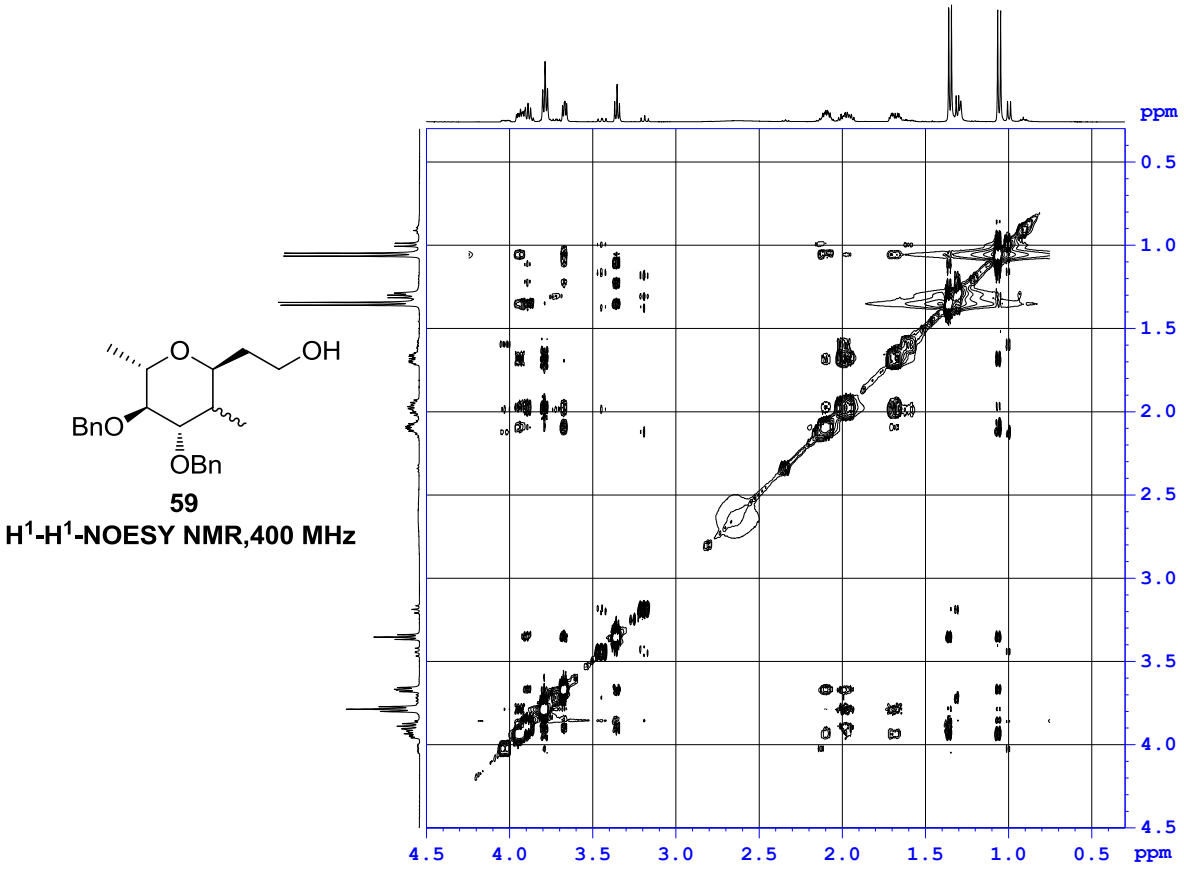
C^{13}-NMR, 100 MHz, $CDCl_3$





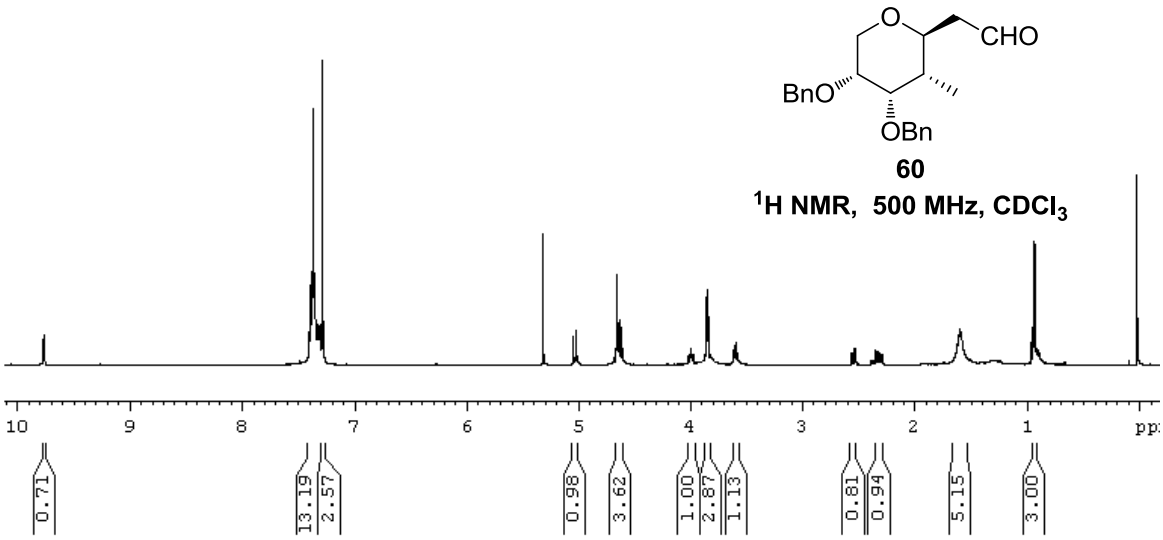
59

^{1}H-^{1}H COSY, 400 MHz, $CDCl_3$



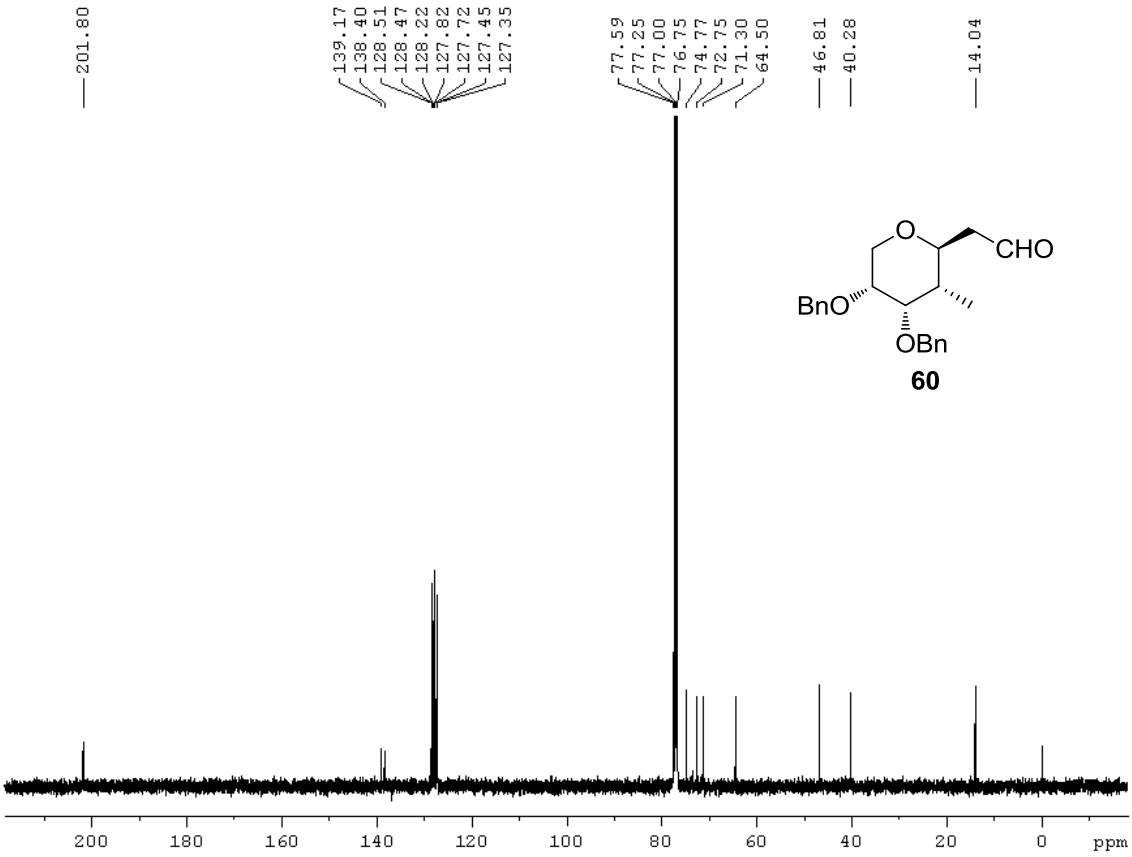
59

H^1-H^1-NOESY NMR,400 MHz



60

^{1}H NMR, 500 MHz, $CDCl_3$



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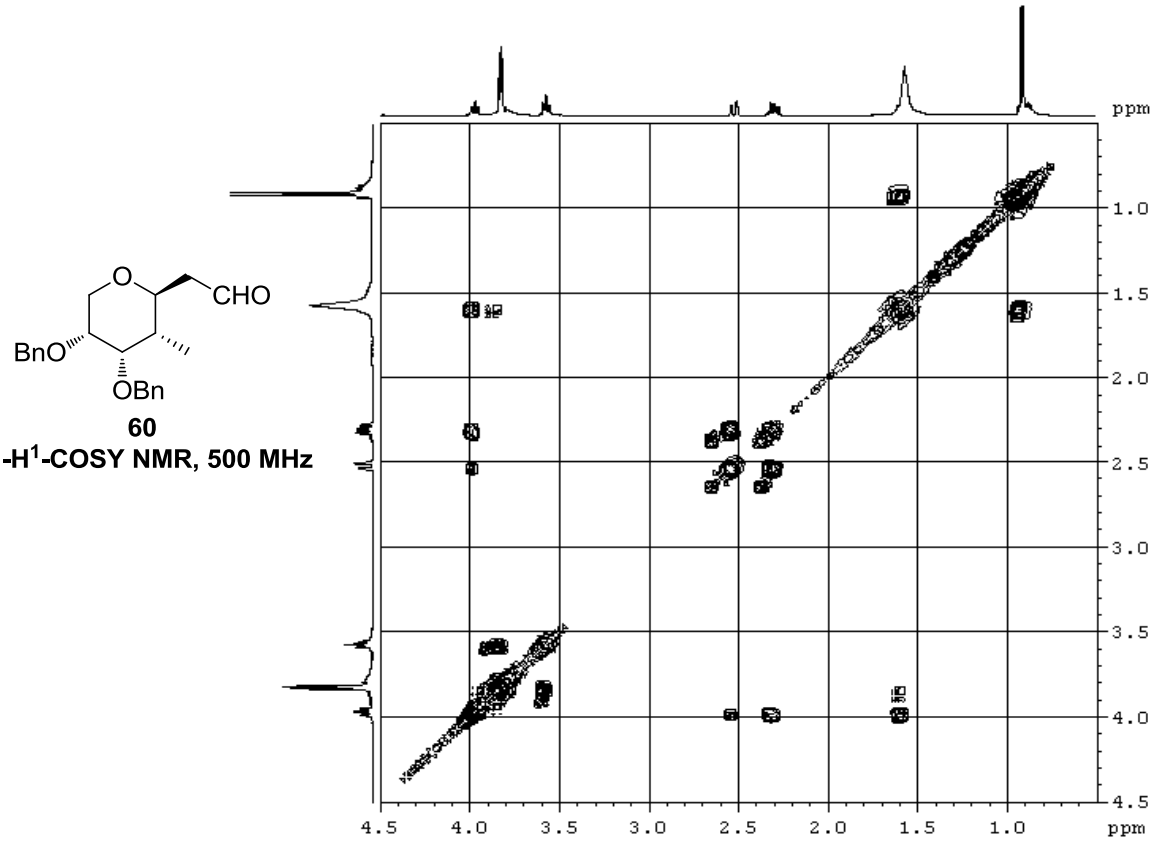
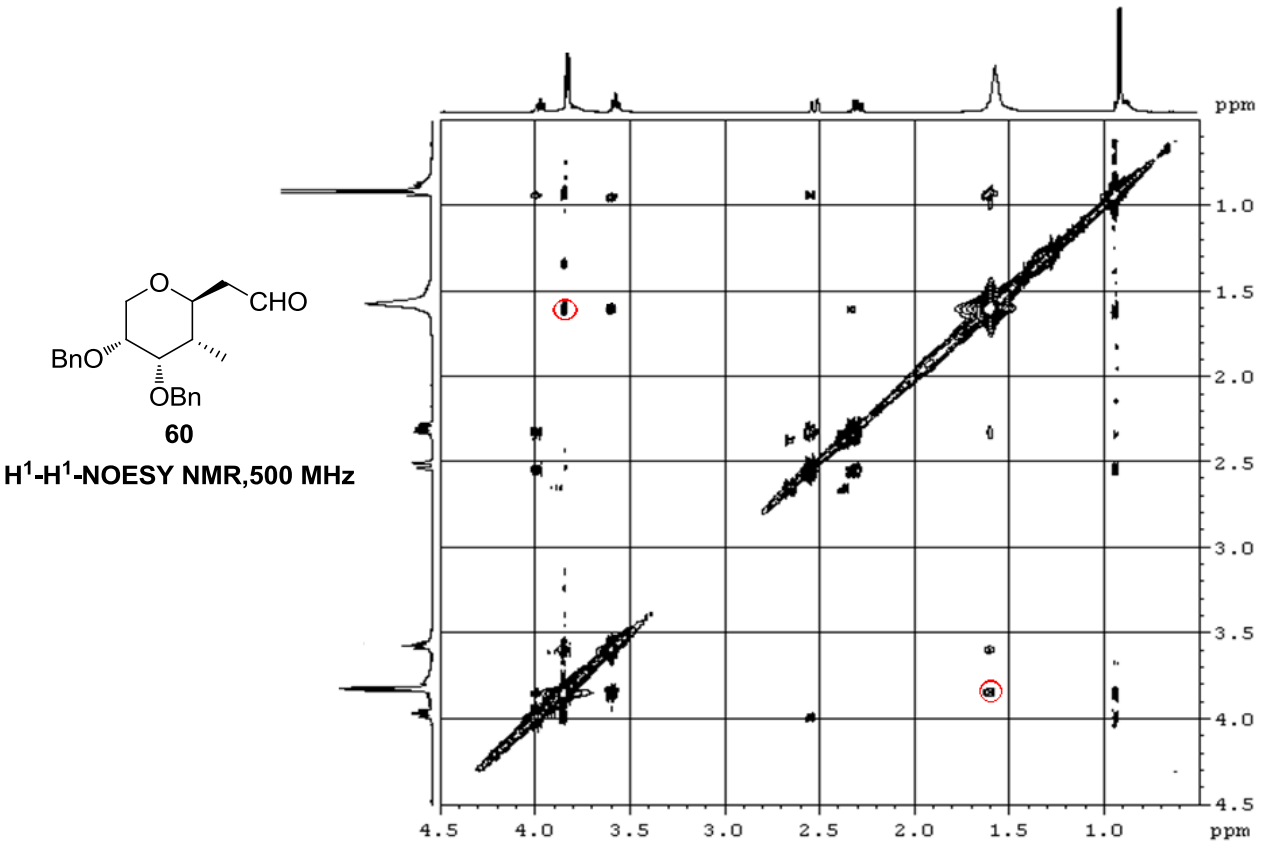


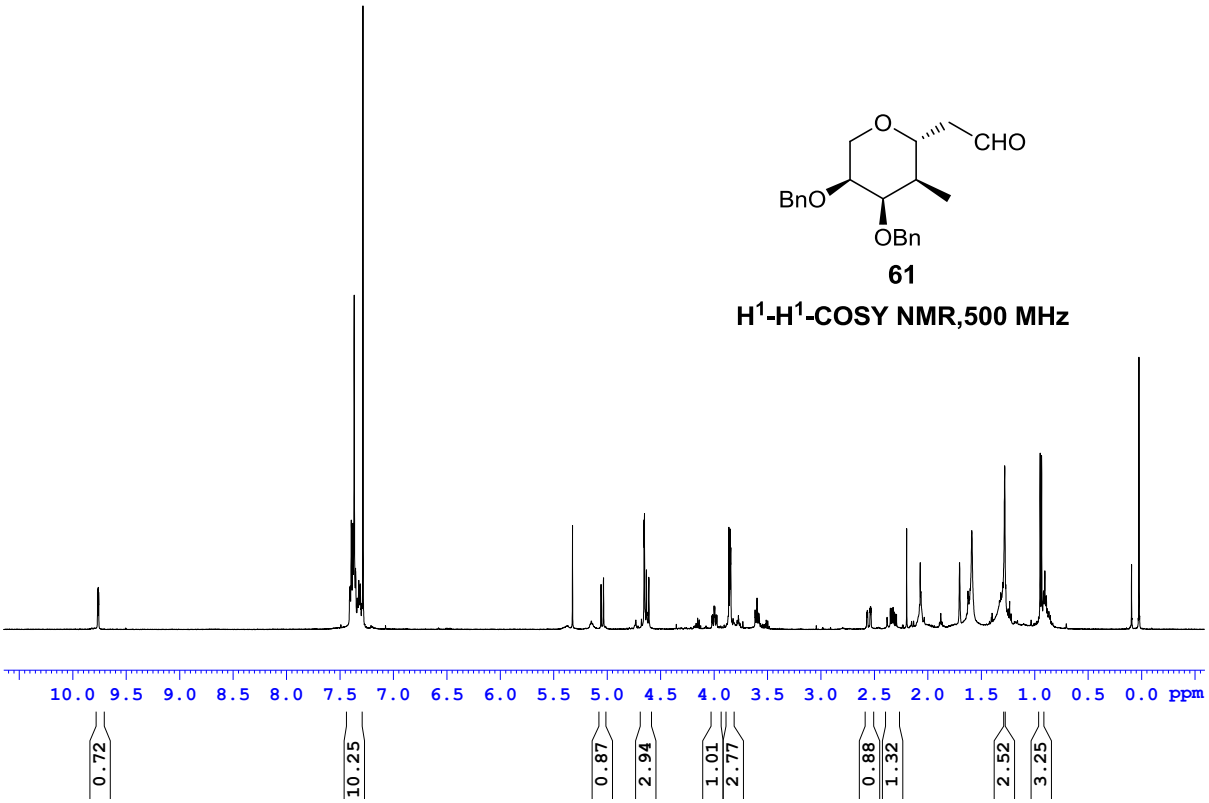
60

H^1-H^1-COSY NMR, 500 MHz



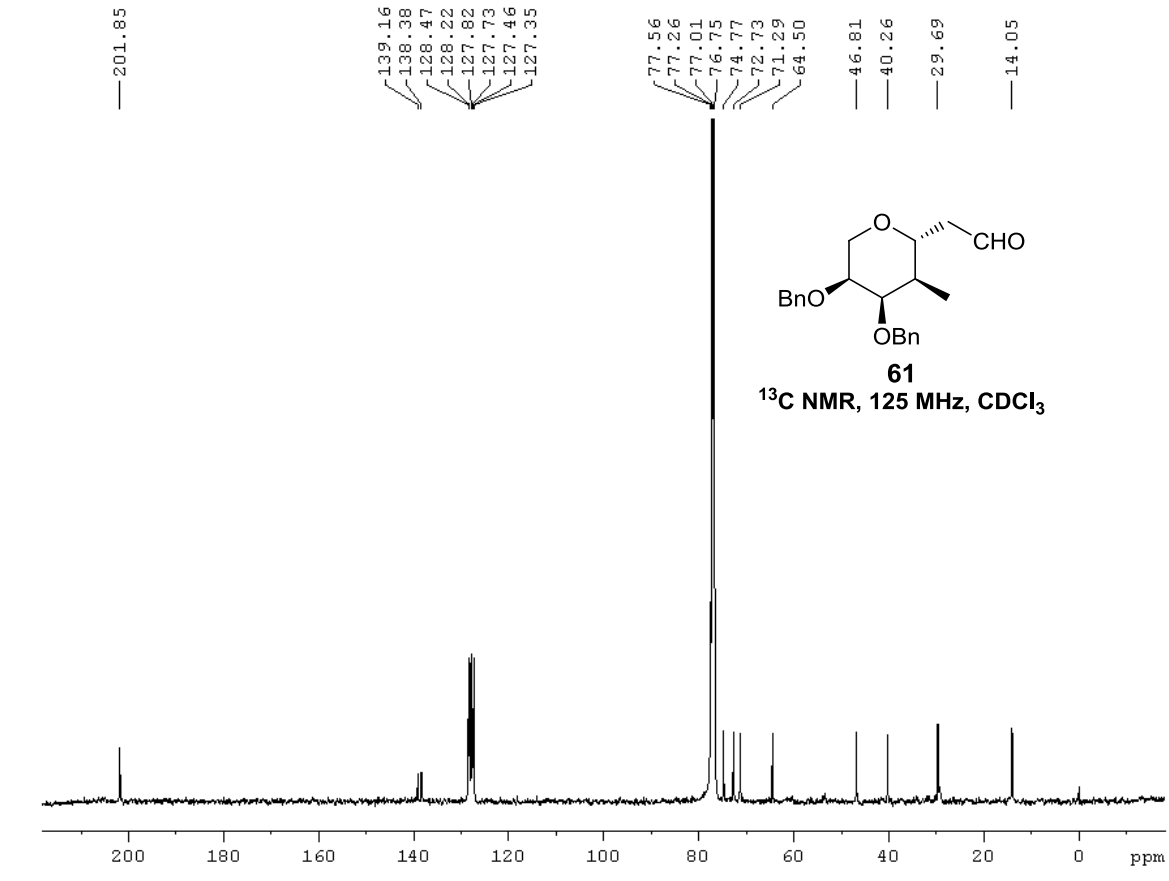
60

H^1-H^1-NOESY NMR,500 MHz



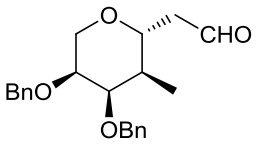
61

H^1-H^1-COSY NMR,500 MHz



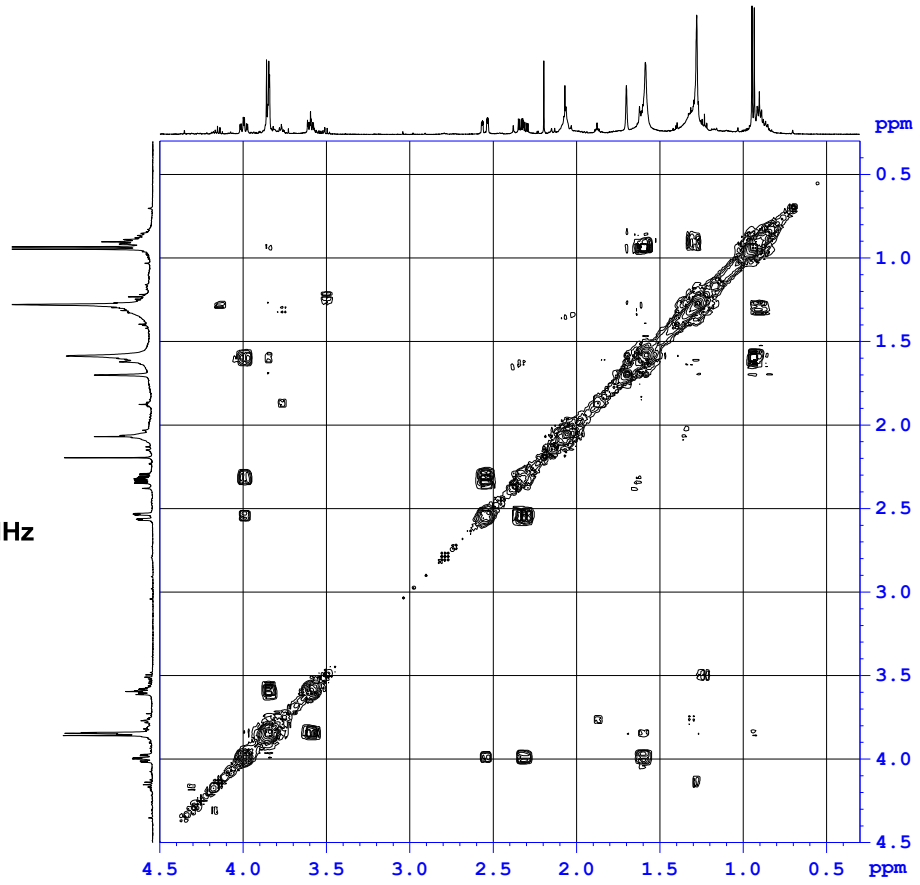
61

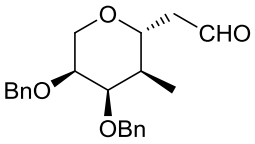
^{13}C NMR, 125 MHz, $CDCl_3$



61

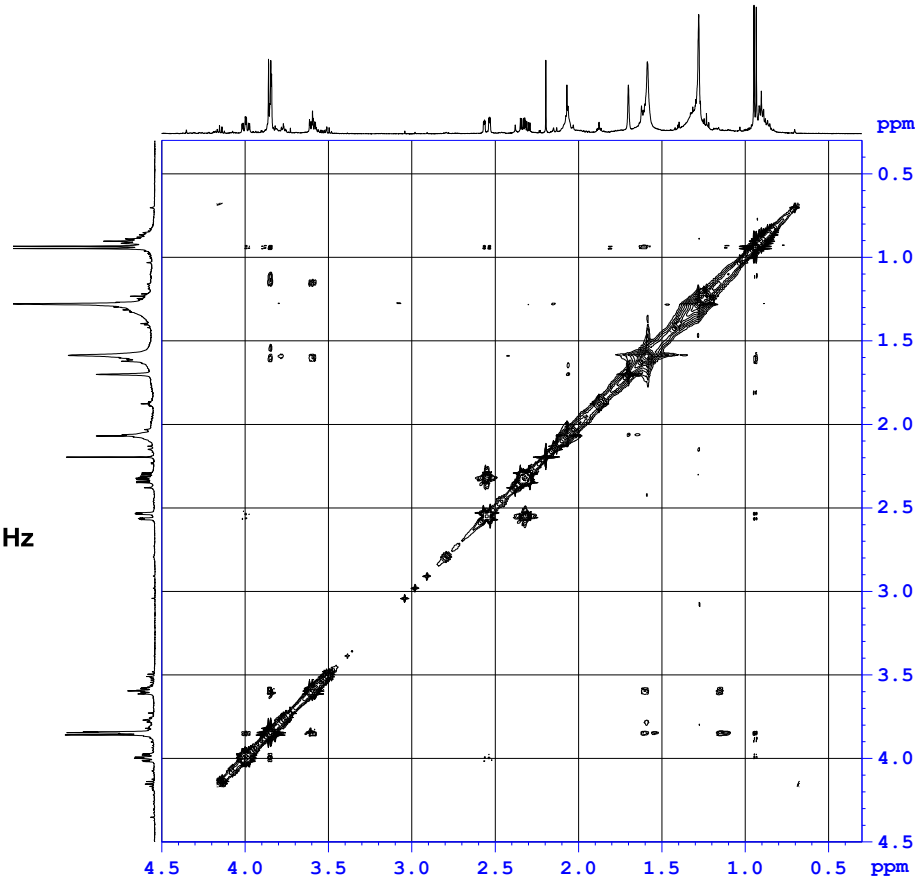
H^1-H^1-COSY NMR,500 MHz





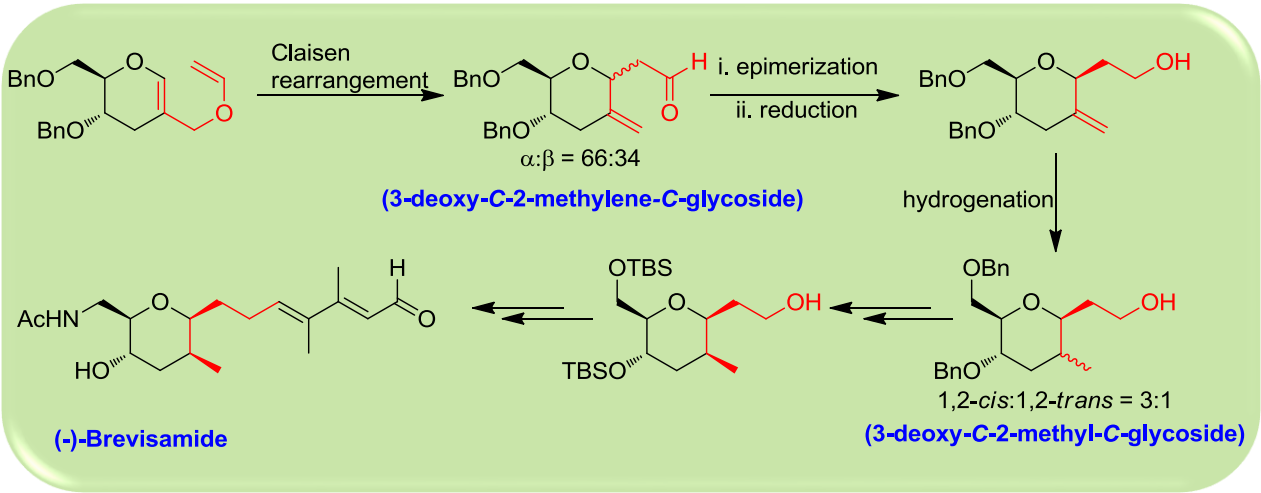
61

H^1-H^1-NOESY NMR,500 MHz



Stereoselective synthesis of *C*-2-methylene and *C*-2-methyl α- and β-*C*-glycosides from 2-*C*-branched glycals: Formal total synthesis of (−)-brevisamide

ABSTRACT: Stereoselective synthesis of deoxy *C*-glycoside derivatives possessing methylene or methyl group at *C*-2 position was investigated by employing Claisen rearrangement of 2-vinyloxy methyl deoxy-glycals as synthetic precursors. The method was found to be highly diastereoselective towards the formation of *C*-2-methylene α-*C*-glycosides. Complimentary to this protocol, a Zn (II) mediated anomerization of α-*C*-glycosides to β-*C*-glycosides is also revealed to obtain diastereomerically pure *C*-2-methylene β-*C*-glycosides. The generality of the reaction is fully evaluated. The developed methodology has been successfully applied to the formal stereoselective total synthesis of (-)-brevisamide, a monocyclic ether alkaloid isolated from *Kareniabrevis* (Red tide dinoflagellate).



3.1 Introduction

Many microorganisms produce *C*-branched-*C*-glycoside derived natural products exhibiting extremely high bio-activity.[1] Very often these compounds are produced particularly a line of defense against their predators. Among them, *C*-glycosides possessing a methyl or methylene group at *C*-2-position frequently exists as subunit in these highly bioactive natural products, for example, brevenal, brevetoxin, eribulin, gambieric acids, halichondrins, (+)-lasono-

-lide, phorboxazoles, spliceostatins and spongistatins *etc.*, (Figure 3.1) possess deoxy *C*-2-methyl/*C*-2-methylene-*C*-glycopyranoside subunit. In general, most of the reported chemical synthesis of these scaffolds involves an achiral starting material to assemble the carbon-branched *C*-glycoside unit. Although, the highly abundant carbohydrates could be the closest chiral pool starting materials for the synthesis of these complex architectures, stereoselective incorporation of a carbon branch, at *C*-2[2], *C*-3[3] or *C*-4[4] position on a *C*-glycoside is particularly difficult.[5] Even though, several methods have been reported in the literature for the synthesis of normal *C*-glycosides,[6] general protocols to synthesize *C*-2 branched *C*-glycosides are very scarce.[2-4]

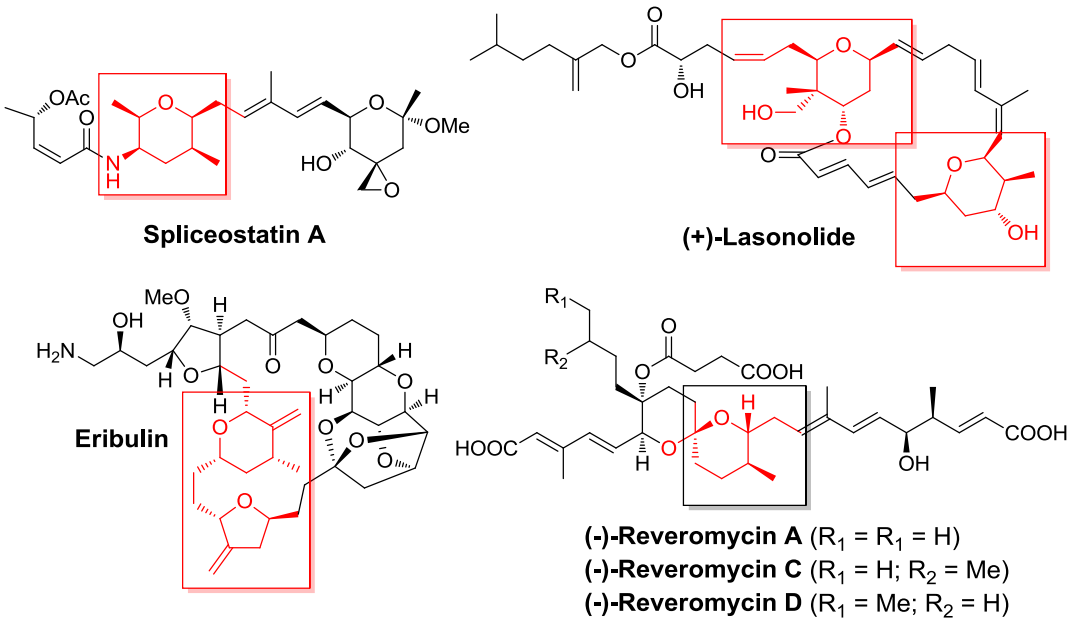


Figure 3.1: Some of the natural products possessing *C*-2-methylene/*C*-2-methyl *C*-glycoside subunits.

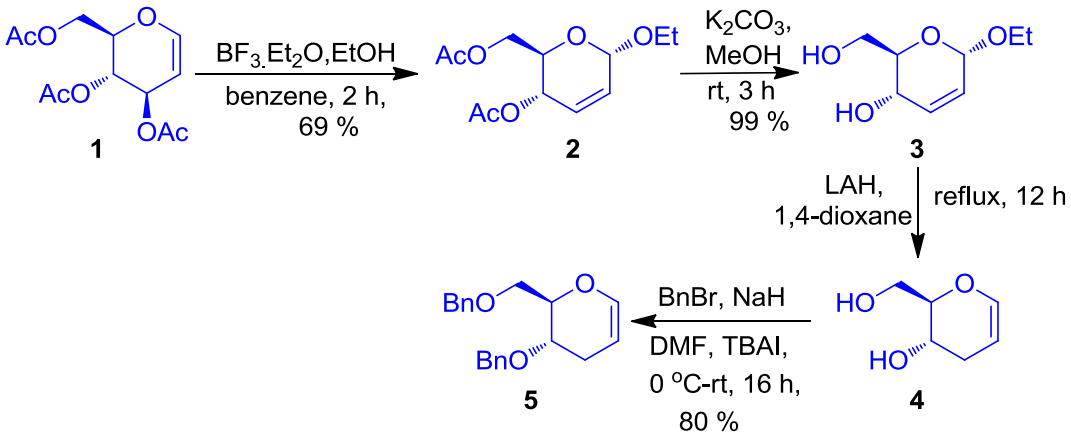
One of the common approaches for the stereoselective formation of *C*-glycosides is *via* Claisen or Ireland-Claisen rearrangement[7] of glucal derived ally vinyl ethers.[8] This reaction was studied extensively for 3-*O*-vinyl glycal derivatives to obtain *C*-glycosides of 2,3-glycals.[9] In continuation of our investigations towards the synthesis of *C*-branched sugars[10], we recently reported the Claisen rearrangement of 2-vinyloxymethyl glycal derivatives to provide an access to the construction of *C*-2-methylene and *C*-2-methyl *C*-glycosides in a stereoselective fashion.[11] However, this protocol provides an access to the synthesis of *C*-2-branched α-*C*-glycosides as

major products. Herein, we report our further investigations particularly in the case of 2-vinyloxymethyl glycals derived from deoxy-sugars as well as the conversion of *C*-2-methylene α-*C*-glycosides to the corresponding β-*C*-glycosides. Further, we also report the application of the developed methodology towards the formal stereoselective total synthesis of (–)-brevisamide.

3.2 Results and Discussion

3.2.1 Synthesis of deoxy-glycals

The 3-deoxy 4,6-di-*O*-benzyl-D-glucal was prepared from 3,4,6-tri-*O*-acetyl-D-glucal **1** in four steps. Thus, Ferrier rearrangement of the 3,4,6-tri-*O*-acetyl-D-glucal **1** with $BF_3.Et_2O$, using ethanol in benzene for 2 h at room temperature gave the 2,3-unsaturated compound **2**[12] in 69% yield, the acetate groups of **2** was deprotected using K_2CO_3 in methanol at room temperature to give the diol **3**[13] in 99% yield. Reductive rearrangement of the compound **3** using

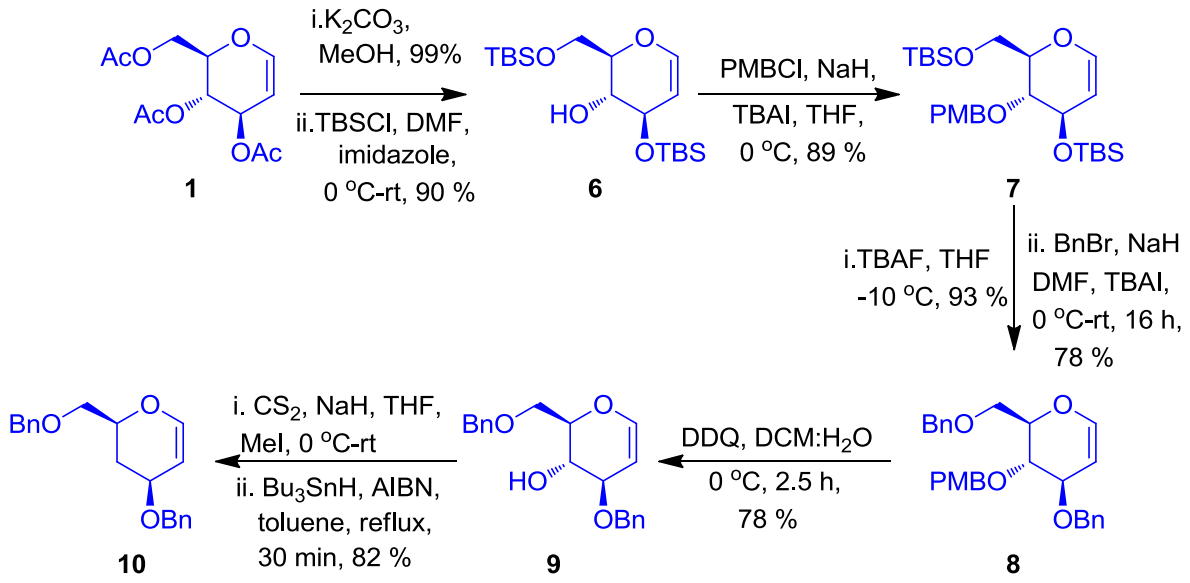


Scheme 3.1: Synthesis of 3-deoxy-4,6-di-*O*-bezyl-D-glucal.

LAH in dioxane under refluxing conditions provided 3-deoxy glucal **4**,[14] which was benzylated to obtain the desired 3-deoxy 4,6-di-*O*-benzyl-D-glucal **5**[14] in 80 % yield (Scheme 3.1).

Synthesis of 4-deoxy-3,6-di-*O*-benzyl-D-glucal **10** was also prepared from glucal **1** in a sequence of steps showed in scheme 3.2. Initial deacetylation of **1** with K_2CO_3 in methanol gave the corresponding triol, which was selectively protected with TBSCl using imidazole in DMF provided 3,6-di-*O*-*tert*-butyldimethylsilyl glucal **6** in 90 % yield. Compound **6** was

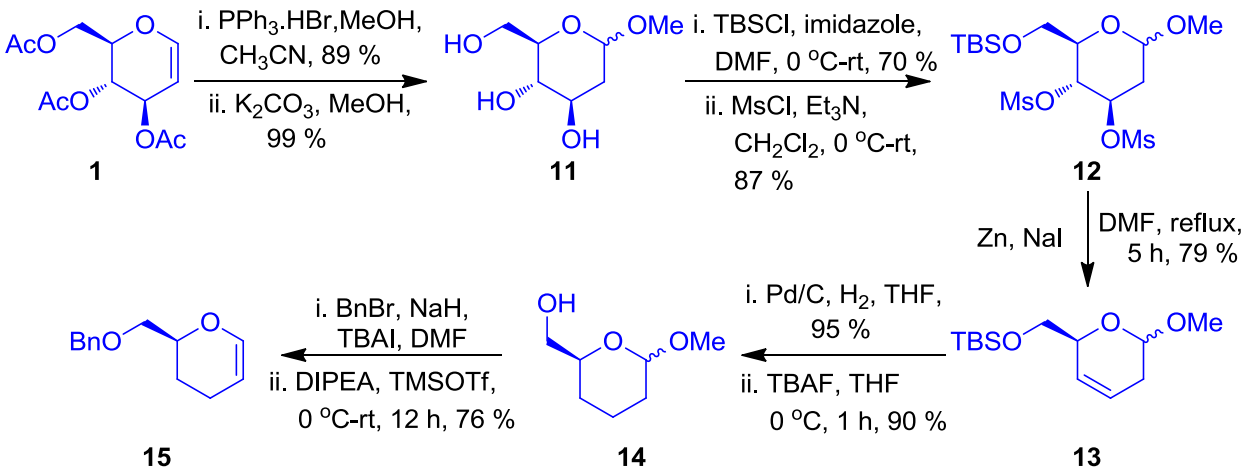
converted to PMB ether **7** using PMBCl, NaH in THF in 89 % yield. Further TBS deprotection of **7** with TBAF in THF followed by benzylation afforded compound **8** in 78 % yield after two steps. Deprotection of PMB ether with DDQ gave the compound **9** [15] in 78 % yield. Subjecting compound **9** to Barton-Mc Combie deoxygenation [16] reaction provided 4-deoxy-3,6-di-*O*-benzyl-D-glucal **10** in 82% yield after two steps (Scheme 3.2).



Scheme 3.2: Synthesis of 4-deoxy-3,6-di-*O*-bezyl-D-glucal.

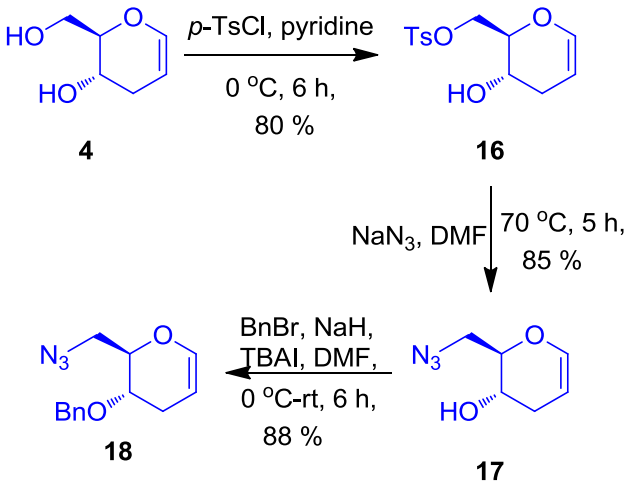
Synthesis of 3,4-dideoxy-6-*O*-benzyl-D-glucal was initiated from glucal **1** in 9 steps. Compound **1** was treated with catalytic amount of triphenylphosphonium bromide, methanol in acetonitrile to give the corresponding glycoside[17] as a mixture of anomers in 9:1 ratio in 89 % yield. Deprotection of acetates using K_2CO_3 in methanol provided triol **11** in 99 % yield. Selective protection of the primary alcohol in compound **11** with 1 eq of TBSCl, imidazole, in DMF gave corresponding the corresponding TBS protected glucoside in 70 % yield. Further mesylation of both the secondary alcohols with methane sulphonyl chloride provided compound **12**[18] in 87 % yield. Zinc mediated elimination of dimesylate using NaI in refluxing DMF for 5 h gave the corresponding 3,4-unsaturated glucoside **13**[18] in 79 % yield. Compound **13** was hydrogenated with Pd/C under H_2 atmosphere gave the hydrogenated compound in 95 % yield, followed by TBS deprotecion with TBAF gave the compound **14** in 90 % yield. Benzylation of

the hydroxyl group followed by elimination using DIPEA and TMSOTf provided 3,4-dideoxy-6-*O*-benzyl-D-glucal **15** in 76 % yield[19] (Scheme 3.3).



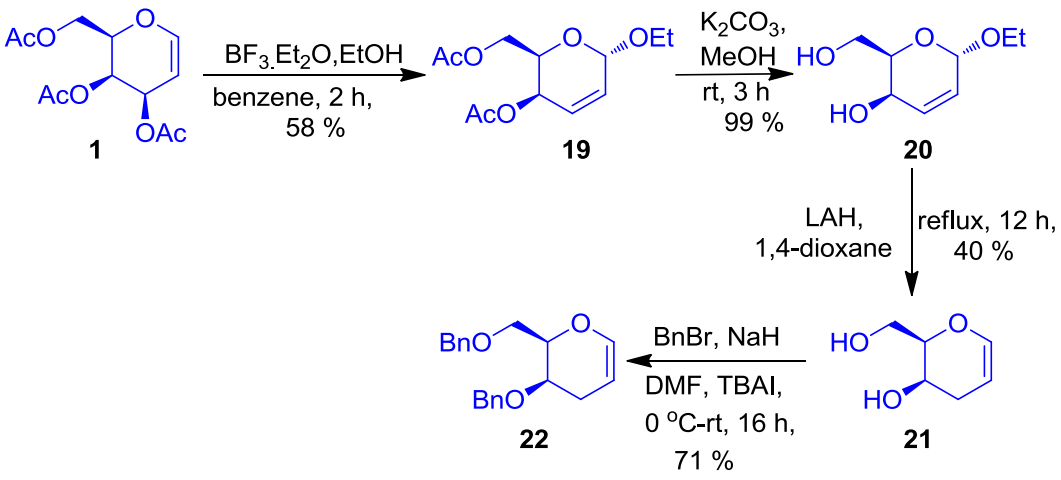
Scheme 3.3: Synthesis of 3,4-dideoxy-6-*O*-benzyl-D-glucal.

3-deoxy-6-azido-4-*O*-benzyl-D-glucal **18** was synthesized from 3-deoxy-glucal **4**. Selective tosylation of primary alcohol in compound **4** using *p*-toluenesulphonyl chloride in pyridine at 0 °C for 6 h gave the tosylate **16** in 80 % yield. Azidation of compound **16** with sodium azide in DMF at 70 °C for 5 h provided compound **17** in 85 % yield. Benzylation of secondary alcohol present in compound **17** provided 3-deoxy-6-azido-4-*O*-benzyl-D-glucal **18** in 88 % yield (Scheme 3.4).



Scheme 3.4: Synthesis of 3-deoxy-6-azido, 4-*O*-benzyl-D-glucal.

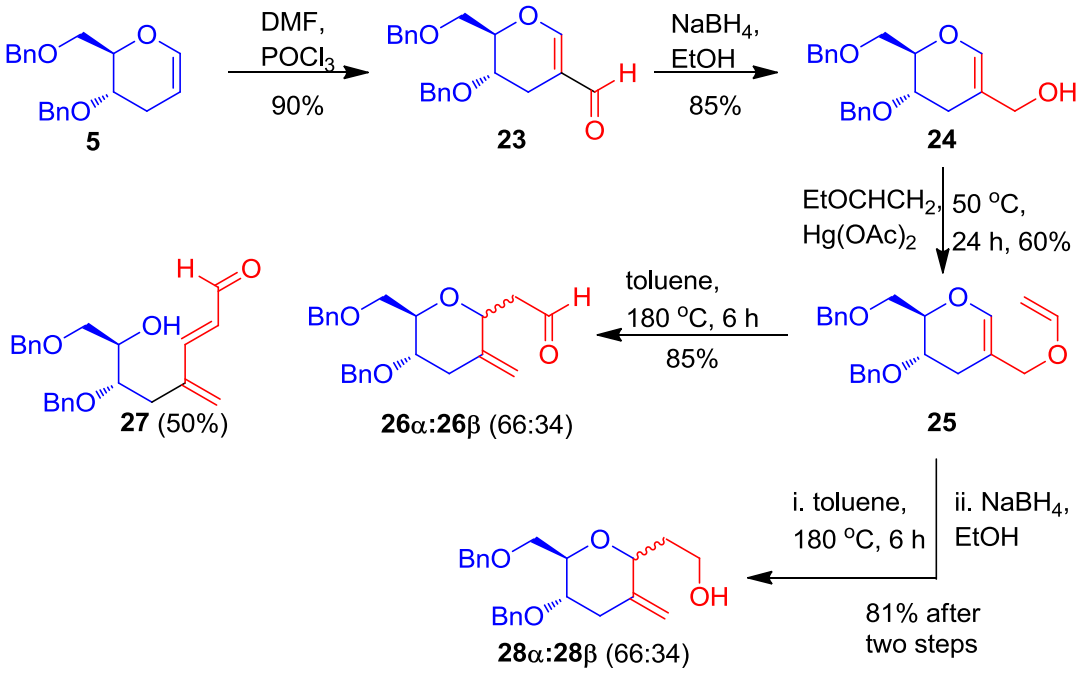
3-deoxy-4,6-di-*O*-benzyl-D-galactal **22** was synthesized from tri-*O*-acetyl-D-galactal *via* the formation of diacetate **19**, diol **20** and 3-deoxy galactal **21** according to the protocol described earlier for the preparation of **5** (Scheme 3.5).[14]



Scheme 3.5: Synthesis of 3-deoxy-4,6-di- *O*-bezyl-D-galactal.

3.2.2 Synthesis of *C*-glycosides from 3-deoxy derived 2-vinyloxymethyl glucal

To obtain the deoxy sugar derived 2-vinyloxymethyl glucal **25**, 3-deoxy-4,6-di-*O*-benzyl-D-glucal **5**[20] was formylated[21] using *N*,*N*-dimethylformamide (DMF), $POCl_3$ to give 3-deoxy-2-formyl-4,6-di-*O*-benzyl-D-glucal **23** [22], which upon reduction with $NaBH_4$ in EtOH provided 3-deoxy 2-hydroxymethyl-4,6-di-*O*-benzyl-D-glucal **24**.[23] Vinylation of **24** using catalytic mercuric acetate, in ethyl vinyl ether provided the required 3-deoxy-2-vinyloxymethyl-4,6-di-*O*-benzyl-D-glucal **25** in 60% yield. Compound **25** upon heating at 180 °C for 6 h in a sealed tube smoothly underwent the Claisen rearrangement and provided a mixture of 3-deoxy-*C*-2-methylene *C*-glycosides **26α** and **26β** in 66:34 ratio, respectively.[24] However, column chromatography of the obtained mixture over silica gel provided an inseparable mixture of **26α** and **26β** in 66:34 ratio, respectively in 35% yield, along with the ring opened α,β-unsaturated aldehyde derivative **27** in 50% yield.[25] Interestingly, direct reduction of crude mixture (**26α**, **26β**) that is obtained after Claisen rearrangement, with $NaBH_4$/EtOH at -10 °C produced the corresponding alcohols **28α** and **28β** in 66:34 ratio, respectively, in good yield and no reduction product derived from **27** was



Scheme 3.6: Synthesis of 3-deoxy *C*-2-methylene *C*-glycoside derivative.

observed (Scheme 3.6). These two anomers were easily separated by silica gel column chromatography.

3.2.3 Stereo chemical assignment of *C*-2-methylene-*C*-glycosides

The stereochemistry at the anomeric position was determined by 2D NOESY experiments. In the case of α-*C*-glycoside **28**α, a strong NOE correlation was observed between the axial CH_2 (C-7 protons) and the axial C-5 proton (1,3-diaxial interaction). On the otherhand, for β-*C*-glycoside **28**β, an NOE correlation was observed between the three axial hydrogen atoms present at C-1, C-3 and C-5 (see Figure 3.1).

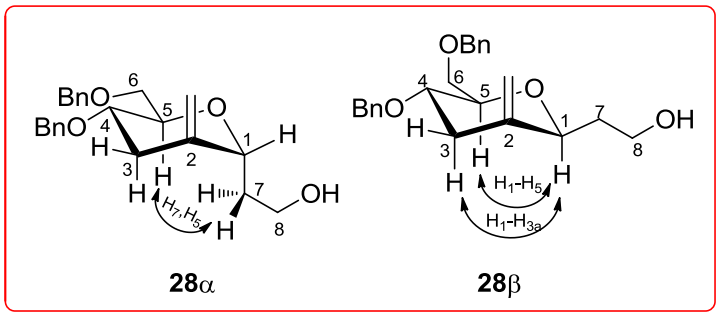
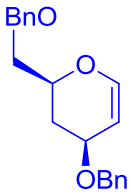
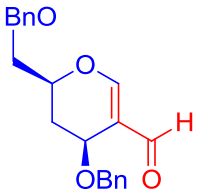
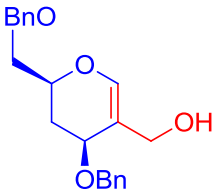
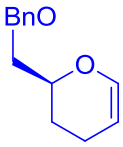
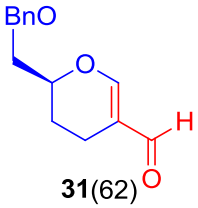
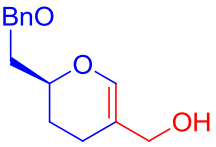
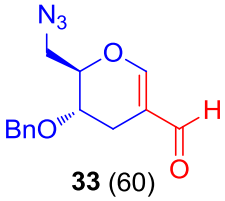
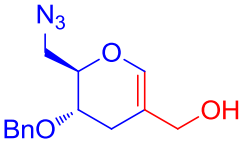
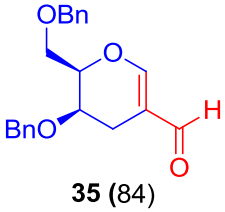
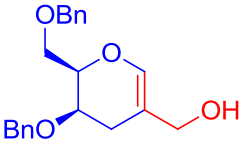


Figure 3.2: Assignment of the stereochemistry of *C*-2-methylene α-and β-*C*-glycosides.

Encouraged with this result, we further applied this methodology to other deoxy-2-vinyloxymethyl glycal derivatives. Towards this, initially formylation of 4-deoxy-3,6-di-*O*-benzyl-D-glucal **10** under Vilsmeier-Haack formylation reaction conditions provided 2-*C*-formyl glucal **29**. Reduction of **29** with $NaBH_4$ in EtOH gave the corresponding alcohol **30** in good yield. Using the above procedure other deoxy glycals **15**, **18** and **22** were converted to the corresponding 2-hydroxymethyl glycals **32**, **34** and **36** through 2-*C*-formyl glycals **31**, **33** and **35** in good to excellent yields (Table 3.1).

Table 3.1: Synthesis of deoxy sugar derived 2-hydroxymethyl glycals.

entry	deoxy glycal	deoxy 2-*C*-formyl glycal (%)[a]	2-hydroxymethyl glycal derivative(%)[a]
1	 **10**	 **29** (40)	 **30** (85)
2	 **15**	 **31**(62)	 **32** (80)
3	 **18**	 **33** (60)	 **34** (87)
4	 **22**	 **35** (84)	 **36** (70)

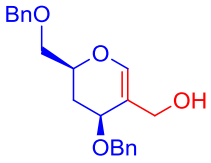
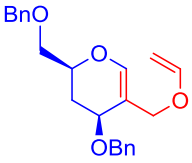
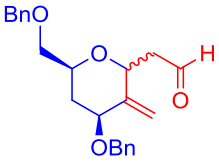
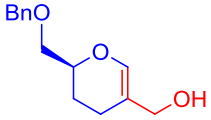
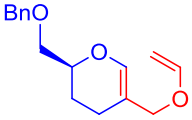
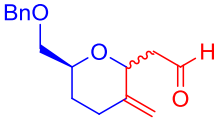
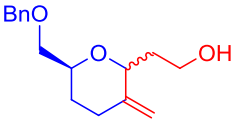
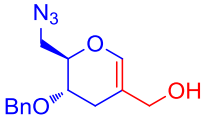
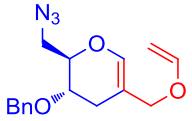
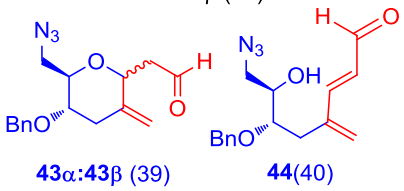
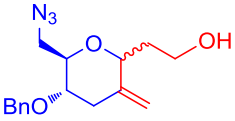
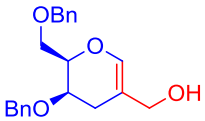
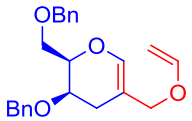
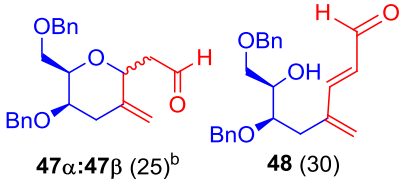
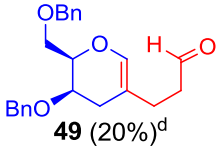
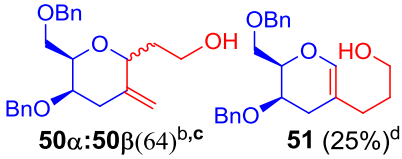
[a]Yield refers to pure isolated products.

Later, 4-deoxy-2-hydroxymethyl-3,6-di-*O*-benzyl-D-glucal **30** was vinylated to give the corresponding vinyl ether **37**. Claisen rearrangement of **37** provided the 4-deoxy-*C*-2-methylene *C*-glycosides **38α** and **38β** in 90:10 ratio, respectively. Similarly, 3,4-dideoxy vinyl ether **39**, derived from 2-hydroxymethyl glycal **32**, upon Claisen rearrangement provided the *C*-2-methylene-*C*-glycosides **40α** and **40β** in 83:17 ratio, respectively, in good yield and treatment of the aldehyde mixture **40α** and **40β** with $NaBH_4$ provided the *C*-2-methylene *C*-glycosides **41α** and **41β**, in 83:17 ratio, respectively. Vinyl ether **42**, synthesized by vinylation of azido alcohol **34**, upon Claisen rearrangement followed by column chromatography provided a mixture of *C*-2-methylene *C*-glycosides **43α** and **43β**, in 72:28 ratio respectively, along with the corresponding ring opened α,β-unsaturated aldehyde derivative **44** (Table 3.2, entry 4). Conversely, direct reduction of the crude product obtained after Claisen rearrangement of **42** provided a mixture of 3-deoxy-*C*-2-methylene *C*-glycosides **45α**:**45β** (72:28), respectively in good yield (Table 3.2, entry 5). On the other hand, Vinyl ether **46**, synthesized by vinylation of alcohol **36** upon Claisen rearrangement followed by column chromatography, provided a mixture of *C*-2-methylene *C*-glycosides **47α** and **47β** in 70:30 ratio respectively, along with the corresponding ring opened α,β-unsaturated aldehyde derivative **48** and 1,3-sigmatropic rearrangement product **49** (Table 3.2, entry 6). Whereas, direct reduction of the crude product after Claisen rearrangement of **46** provided a mixture of 3-deoxy-*C*-2-methylene *C*-glycosides **50α**:**50β** (70:30) and corresponding alcohol **51** through 1,3-sigmatropic rearrangement. These results suggest that, the equatorial -OBn at *C*-4 (shown in compound **25** and **42**) strongly influences the product stability and particularly increases the β-*C*-glycoside formation.

3.2.4 Epimerization of α-*C*-glycosides to β-*C*-glycosides

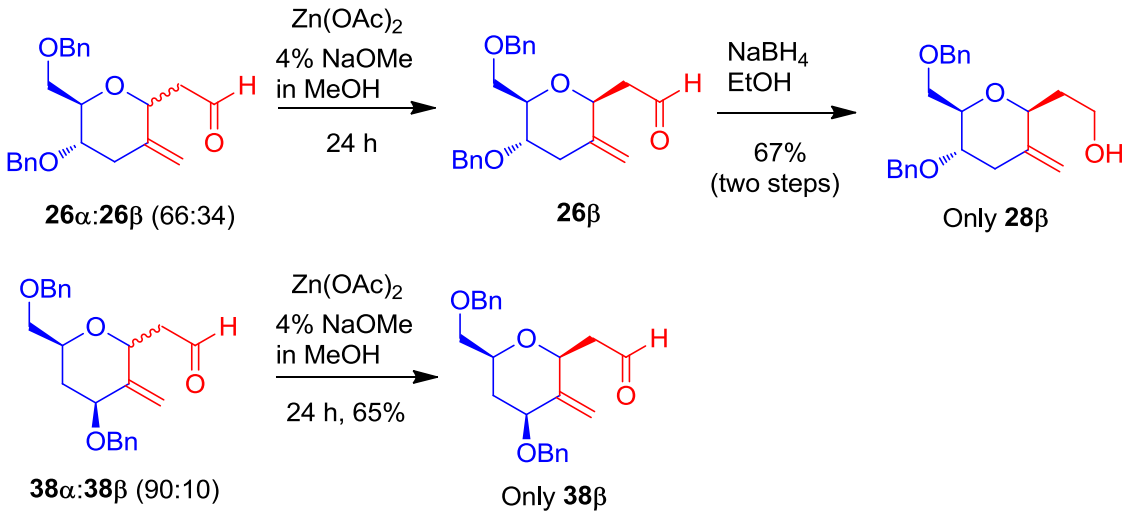
As all the above Claisen rearrangement reactions provided the *C*-2-methylene α-*C*-glycosides as major products, we further focused our attention to convert the obtained α-*C*-glycosides to their β-*C*-anomers. Towards this, we attempted the Zinc (II) mediated epimerization of 2′-carbonylalkyl-α-*C*-glycosides.[26] Thus, the mixture (**26α** and **26β**) obtained after Claisen rearrangement of **25** was directly treated with $Zn(OAc)_2$ in NaOMe/MeOH. To our privilege, *C*-1 epimerization has occurred smoothly and the anomeric mixture was completely converted to the β-*C*-glycoside **26β**.[27] Further reduction of **26β** with $NaBH_4$ provided the diaster-

Table 3.2: Synthesis of deoxysugar derived *C*-2-methylene-*C*-glycosides.

entry	2-hydroxymethyl glycal derivative	vinyl ether (%)[a]	*C*-2 methylene *C*-glycoside (%)[a]	α:β ratio
1	 **30**	 **37** (74)	 **38**α:**38**β (65)	90:10
2	 **32**	 **39** (65)	 **40**α:**40**β (75)[b]	83:17
3	**32**	**39**	 **41**α:**41**β (69)[c]	83:17
4	 **34**	 **42** (66)	 **43**α:**43**β (39) **44**(40)	72:28
5	**34**	**42**	 **45**α:**45**β (75)[c]	72:28
6	 **36**	 **46** (50)	 **47**α:**47**β (25)[b] **48** (30)  **49** (20%)[d]	70:30
7	**36**	**46**	 **50**α:**50**β(64)[b,c] **51** (25%)[d]	70:30

[a]Yield refers to pure and isolated products. [b] Obtained as an inseparable mixture. [c] The vinyl ether was subjected to Claisen rearrangement and the obtained crude product was directly reduced with $NaBH_4$/EtOH.[d] Obtained along with *C*-glycosides.

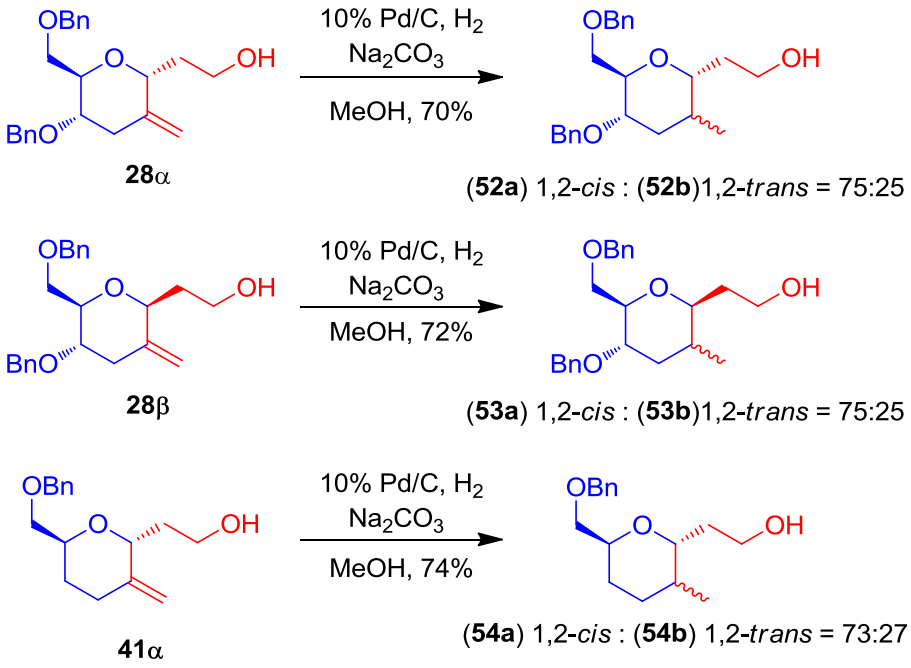
-eomerically pure alcohol **28β**. Application of the similar protocol to the mixture of anomers **38α** and **38β** lead to the formation of pure β-*C*-glycoside **38β,** as a single diastereomer (Scheme 3.7).



Scheme 3.7: Epimerization of α-*C*-glycosides to β-*C*-glycosides.

3.2.5 Synthesis of *C*-2-methyl-*C*-glycosides

To escalate the significance of the developed methodology, we further evaluated by applying it to synthesize a series of deoxy-*C*-2-methyl-*C*-glycosides. Towards this, *C*-2-methylene-*C*-glycoside **28α** was subjected to selective hydrogenation with 10% Pd/C under hydrogen atmosphere in presence of Na_2CO_3 as a catalyst-poison.[28] This reaction provided *C*-2-methyl-*C*-glycosides **52a** and **52b** in 70% yield as a mixture of 1,2-*cis* and 1,2-*trans* diastereomers in 75:25 ratio, respectively. Similarly, *C*-2-methylene *C*-glycosides **28β** and **41α** upon hydrogenation provided **53a**, **53b** (75:25) and **54a**, **54b** (73:27) as 1,2-*cis* and 1,2-*trans* *C*-2-methyl-*C*-glycosides respectively (Scheme 3.8).



Scheme 3.8: Synthesis of *C*-2-methyl *C*-glycosides.

3.2.6 Stereo chemical assignment of *C*-2-methyl-*C*-glycosides

The 1,2-*cis* and 1,2-*trans* relationship with respect to the C-1- and C-2-branched glycosides was assigned by observing the NOE correlation in 2D NOESY experiment. The protons of the C-2 methyl group of 1,2-*cis*diastereomer **52a** showed an NOE correlation with the α-C-7 protons, whereas the C-2 methyl group of β-C-glycoside **53a** had an NOE correlation with the C-4 proton, which is in an axial orientation (see Figure 3.3).

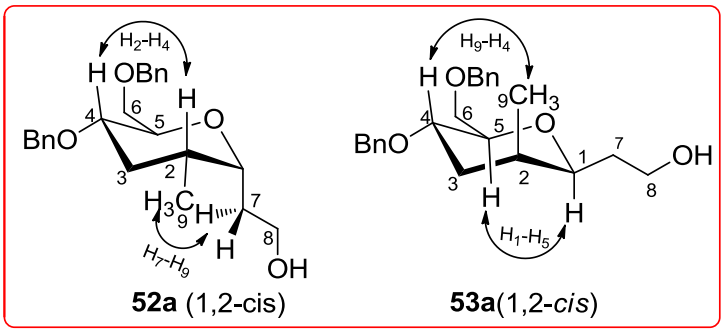
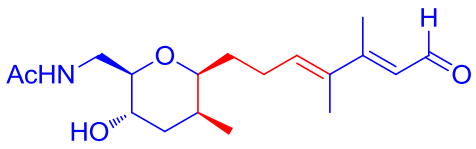


Figure 3.3: Assignment of the stereochemistry of *C*-2 methyl group of α- and β-*C*-glycosides.

3.2.7 Application of the developed methodology towards the total synthesis of (-)-brevisamide

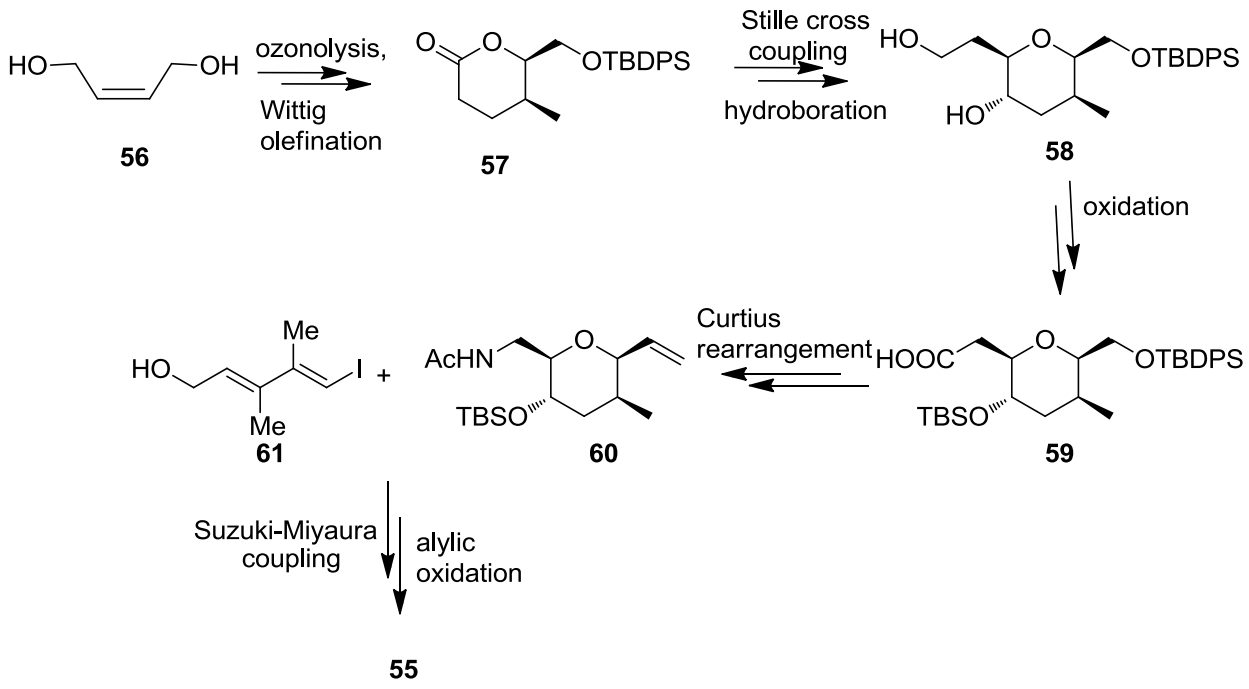
3.2.7.1 Previous methods for the total synthesis of (-)-brevisamide

As we formerly mentioned, a number of natural products possessing *C*-2-methylene or *C*-2-methyl-*C*-glycoside core structure are having potent biological activity. Synthesis of a natural product with the proposed methodology could intensify its importance in synthetic organic chemistry. In this direction, we have chosen (–)-brevisamide **55**, a marine cyclic ether alkaloid, first isolated by Wright and co-workers in 2008 from cultures of *Karenia Brevis*.[29]



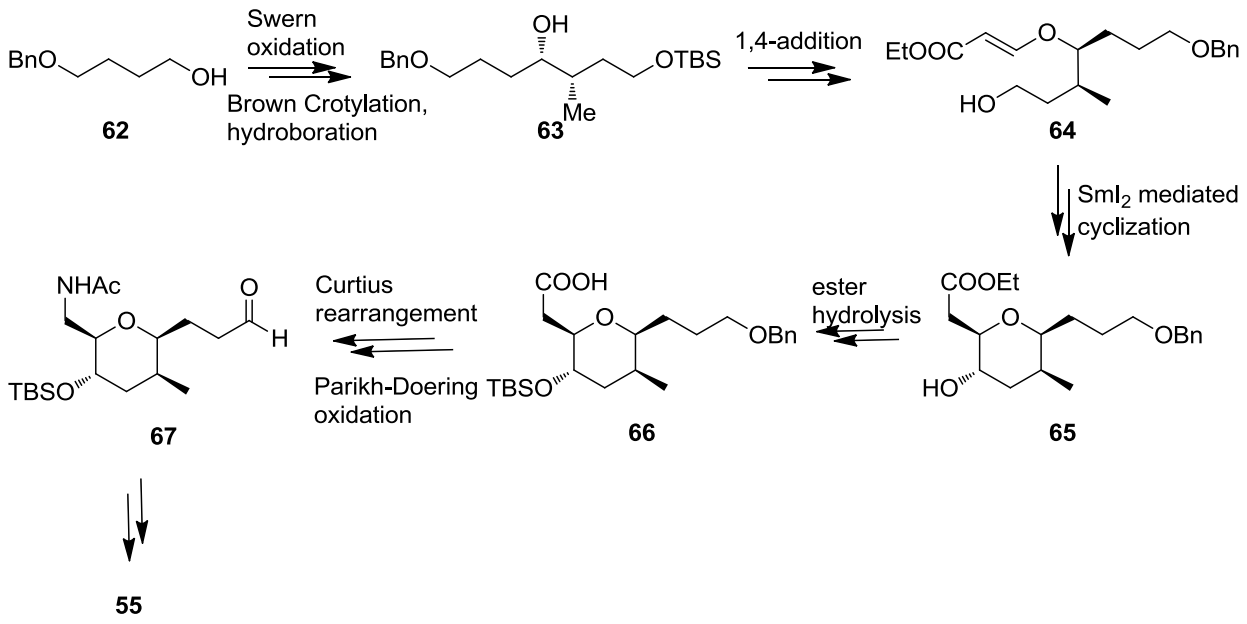
(-)-Brevisamide 55

The first total synthesis and characterization of (–)-brevisamide **55** was reported by the Satake and co-workers.[30] Their synthetic route involves the formation of tetrahydropyran **57** from *cis*-2-butene-1,4-diol **56** in 7 steps. Later **57** was converted to ketene acetaltriflate by using Tf_2NPh in DMPU in presence of KHMDS, this was subjected to stille cross coupling with vinyl tributylstannane (CH_2=CHSn-*n*-Bu_3) followed by hydroboration provided **58**. Further, secondary alcohol present in **58** was converted to TBS ether using TBSCl, then oxidation of primary alcohol to carboxylic acid using TEMPO afforded **59**. Curtius rearrangement and acetylation of **59** followed by selective deprotection of TBDPS using TBAF, oxidation of resulting alcohol followed by wittig olefination with methyltriphenylphosphoniumbromide provided alkene **60**. Finally, **60** was subjected to Suzuki-Miyaura cross-coupling with iodide **61** (which was also prepared from **56** in 7 steps) using $PdCl_2$(dppf) followed by deprotection of silyl ethers and allylic oxidation with MnO_2 provided brevisamide **55** (Scheme 3.10).



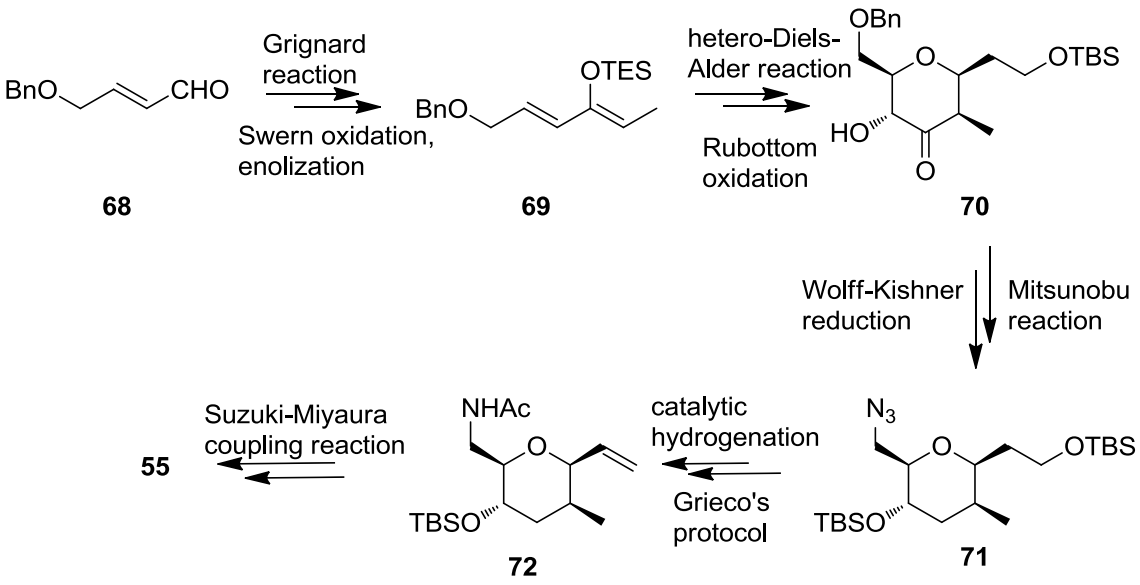
Scheme 3.10: Total synthesis of brevisamide by M. Satake and K. Tachibana.

In 2009, the second total synthesis was reported by Lindsley and co-workers[31] from mono benzyl protected 1,4-butane diol **62**. In this approach, they have started with the Swern oxidation of the alcohol **62**, and the obtained aldehyde was converted to homoallylic alcohol using Brown crotylation to furnish a single diastereomer. This was subjected to hydroboration followed by chemoselective protection of alcohol as TBS ether afforded **63**. Compound **63** was treated with ethylpropiolate, followed by TBS deprotection using HCl in methanol provided **64**. The alcohol in **64** was oxidised to aldehyde under Swern oxidation conditions and SmI_2 mediated cyclization afforded the tetra substituted pyran **65**. Protection of alcohol with TBSCl followed by ester hydrolysis gave **66**. Curtius rearrangement of **66**, acetylation with acetic anhydride, hydrogenolysis of benzyl ether and Parikh–Doering oxidation provided aldehyde **67**. The Horner-Wadsworth-Emmons olefination of **67** with (*E*)-ethyl 4-(diethoxyphosphoryl)-3-methylpent-2-enoate, followed by formation of diene, reduction of ester with DIBAL-H, deprotection of TBS and MnO_2 mediated allylic oxidation of the alcohol delivered brevisamide **55** (Scheme 3.11).



Scheme 3.11: Total synthesis of brevisamide by Lindsley.

In the same year, A. K. Ghosh*et al*., [32] synthesized (–)-brevisamide **55** from unsaturated aldehyde **68**. Grignard addition of ethyl magnesium bromide on aldehyde **68** followed by Swern oxidation afforded enone, that was enolized to get the diene **69**. Jacobsen's asymmetric catalytic hetero-Diels-Alder reaction of **69** with 3-((*tert*-butyldimethylsilyl)oxy)propanal using Jacobsen's chromium catalyst for 7 days provided pyran ring and Rubottom oxidation of which with *m*-chloroperbenzoicacid gave the ketone **70**. A modified Wolf-Kishner reduction of the ketone with tosylhydrazide, followed by reduction of the hydrazide with $NaCNBH_3$ and treatment of the obtained hydrazine with NaOAc in EtOH afforded deoxygenated product. The secondary alcohol in deoxy compound was protected as TBS ether with TBSOTf, followed by hydrogenolysis and Mitsunobu reaction of primary alcohol with hydrazoic acid provided compound **71**. Reduction of the azide by catalytic hydrogenation followed by acetylation of the amine with acetic anhydride, selective deprotection of the primary TBS under Grieco's protocol gave alkene **72**. Suzuki-Miyaura coupling reaction of alkene **72** with *tert*-butyl(((2*E*,4*E*)-5-iodo-3,4-dimethylpenta-2,4-dien-1-yl)oxy)dimethylsilane, followed by hydroboration, desilylation and oxidation afforded **55** (Scheme 3.12).

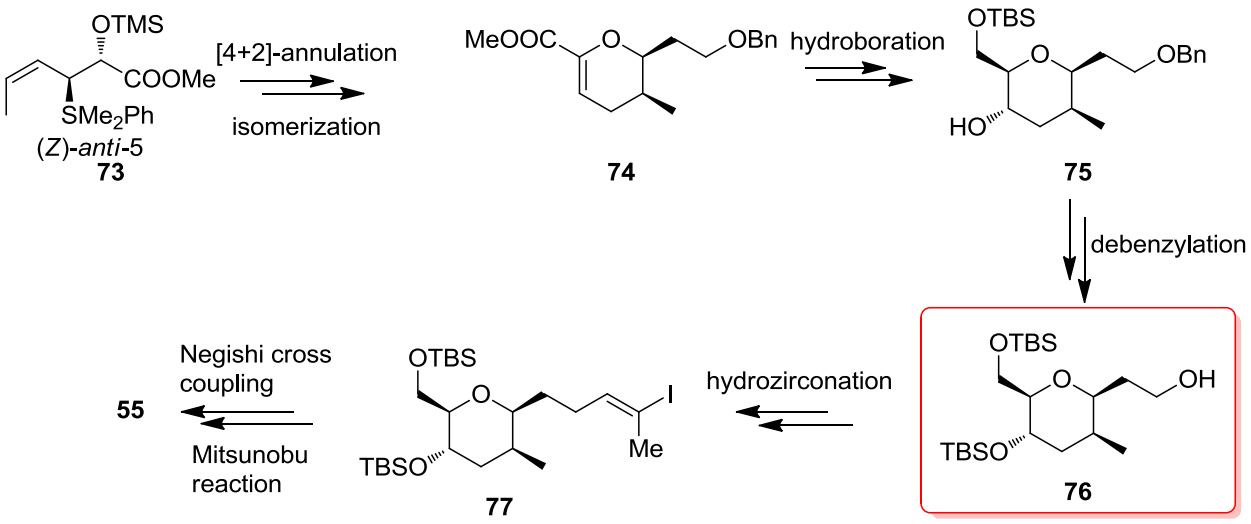


Scheme 3.12: Total synthesis of brevisamide by A. K. Ghosh.

Later, Panek and co-workers[33] synthesized (-)-brevisamide using (4+2) annulation as the key step. Their approach started from (4+2) annulation of (*Z*)-crotylsilane **73** with 3-(benzyloxy) propanal provided pyran ring, DBU mediated isomerization of olefin gave the required trisubstituted pyran **74**. Reduction of ester with LAH, protection of the resulting alcohol as TBS ether and hydroboration afforded compound **75**. The secondary alcohol in **75** was converted to TBS ether with TBSOTf followed by hydrogenolysis provided **76** in high yield. To install the alkene side chain, primary alcohol was activated with triflic anhydride, which was treated with propynyllithium at -78 ^{o}C and finally hydrozirconation provided iodide **77**. The iodide **77** was treated with (*E*)-*tert*-butyl((3-iodobut-2-en-1-yl)oxy)diphenylsilane under modified Negishi cross coupling conditions, followed by a sequence of steps provided **55** in good yield (Scheme 3.12).

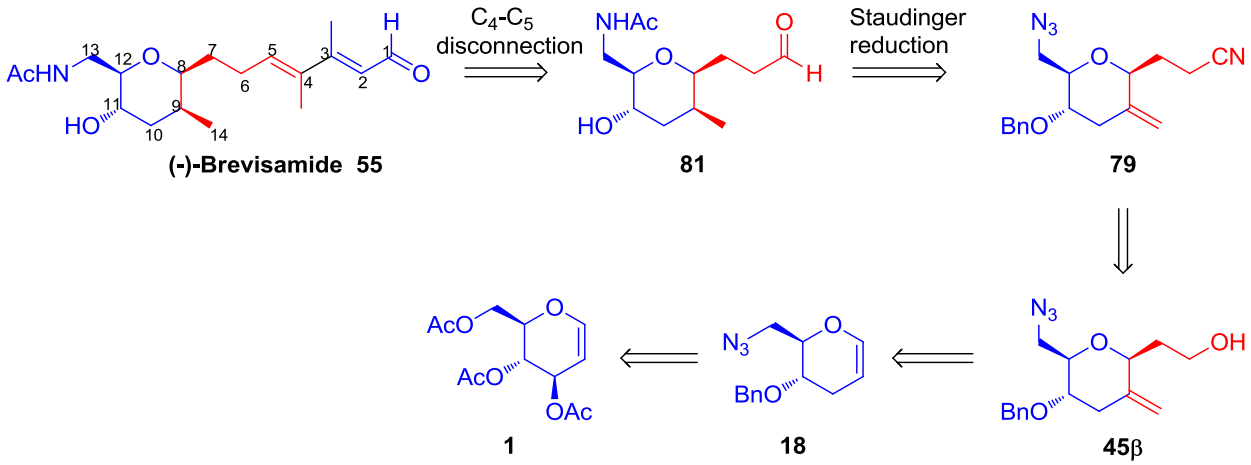
3.2.7.2 Attempted total synthesis of (-)-brevisamide from our approach

Initially, we planned to synthesize (-)-brevisamide from compound **45β**. Our retro synthetic analysis of (-)-brevisamide is shown in scheme 3.13. Disconnection of C-4-C-5 bond in **55** leads to the aldehyde **81,** which could be obtained by functional group transformation of **79** using Staudinger reduction, hydrogenation and reduction of cyanide with DIBAl-H. Compound



Scheme 3.12: Total synthesis of brevisamide by J. S. Panek.

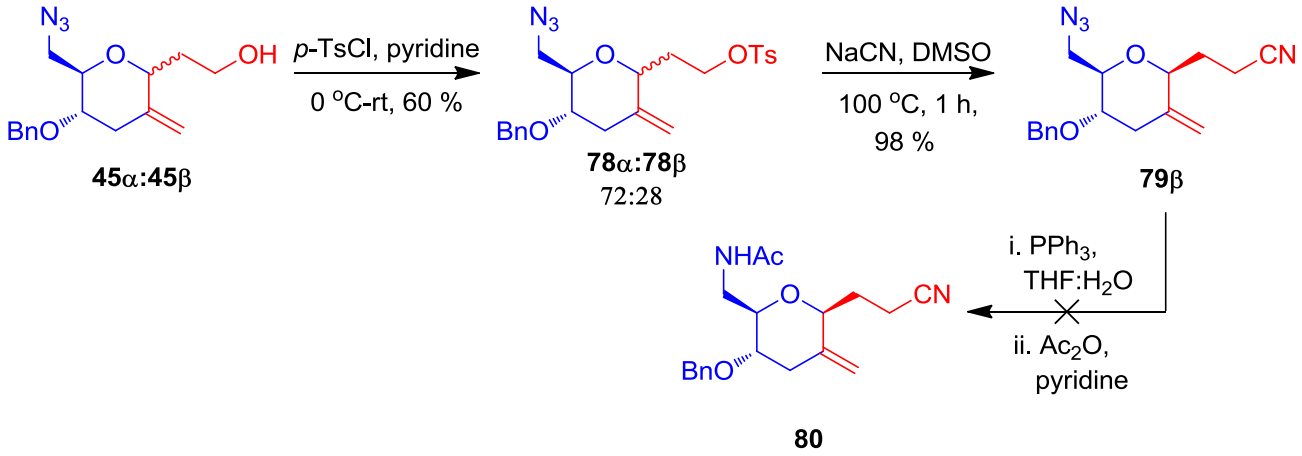
79 was planned to synthesise from **45β**, by means of using protection/substitution protocol. As showed previously, compound **45β** could be obtained from azido glycal **18**, which intern could be synthesized from tri-*O*-acetyl-D-glucal **1** (Scheme 3.13).



Scheme 3.13: Retrosynthetic analysis of (-)-brevisamide.

As per the retro synthetic analysis, we began the synthesis of (-)-brevisamide **55** from the anomeric mixture of **45α** and **45β**. Synthesis of this mixture has been explained previously in table 3.4. Thus, the anomeric mixture of **45α** and **45β** was tosylated using tosylchloride in

pyridine at 0 °C for 5 h to obtain **78α**:**78β** in 72:28 ratio. Substitution of tosyl group with cyanide using sodium cyanide in DMSO at 100 °C afforded **79α** and **79β**, which were able to separate using silica-gel column chromatography and also structure was confirmed based on 2D-NMR experiments. However, when compound **79β** was subjected to Staudinger reduction (PPh_3, THF/H_2O) followed by acetylation with acetic anhydride did not provide the desired compound **80** (Scheme 3.14). In addition to this, formation of **79β** as minor isomer in the Claisen rearrangement reaction made us to reinvestigate the synthetic protocol.



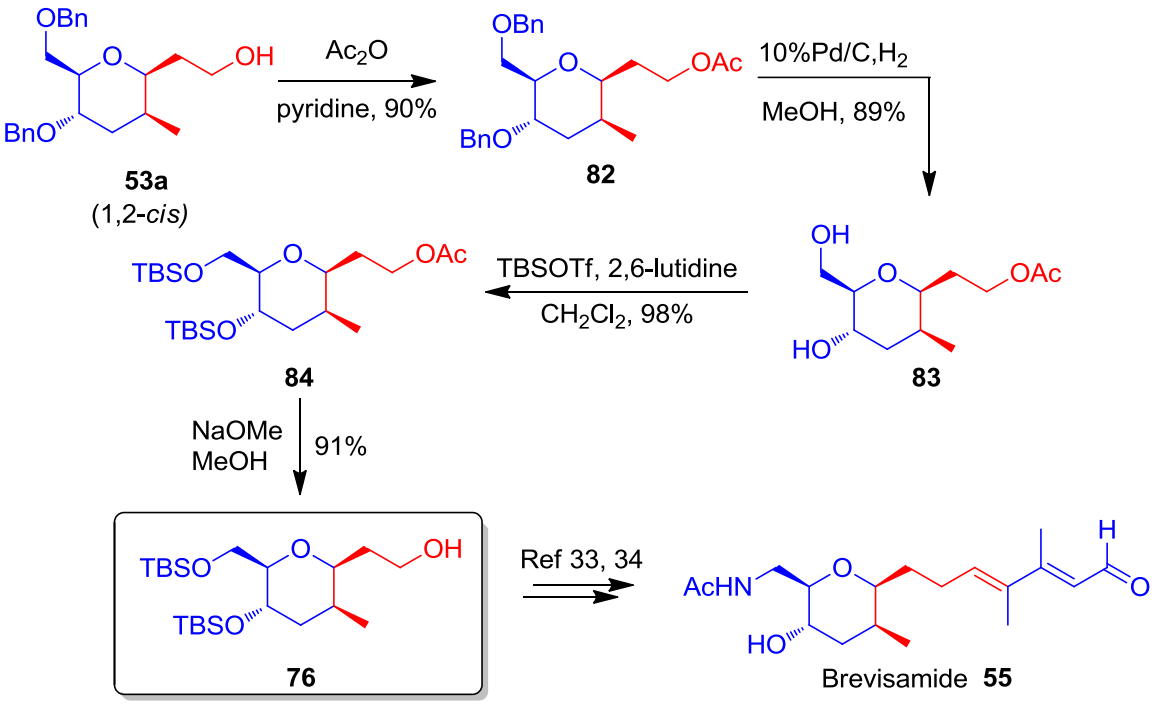
Scheme 3.14: Synthesis of compound **79β**.

3.2.7.3 Formal total synthesis of (-)-brevisamide from our approach

In the revised approach, alcohol **53a** was chosen as starting material**.** The hydroxyl function in alcohol **53a** was acetylated to give compound **82** which upon hydrogenolysis provided the diol **83**. TBS protection of both the hydroxyls using TBSOTf/2,6-lutidine in CH_2Cl_2 provided **84,** which was subjected to Zemplén deacylation conditions provided the advanced intermediate **76**.[33,34] Compound **76** was used recently for the total synthesis of (–)-brevisamide **55** (Scheme 3.15).

3.3 Summary and Conclusions

In conclusion, a general methodology has been developed for the synthesis of deoxygenated *C*-2-methylene-*C*-glycosides by Claisen rearrangement of 2-vinyloxymethyl glycal derivatives. Importantly, the method is applicable to synthesize *C*-2-methylene α- as well



Scheme 3.15: Formal total synthesis of (–)-brevisamide.

as β-*C*-glycosides in a stereoselective fashion. The generality and stereoselectivity of the rearrangement reaction is evaluated. The methodology is also extended to deoxysugar derived *C*-2-methyl-*C*-glycosides by selective hydrogenation of *C*-2-methylene functionality. It is worth to mention that, most of these compounds can serve as key intermediates in the synthesis of several bioactive natural products. The application of the methodology was further extended to the preparation of an advanced intermediate involved in the total synthesis of (–)-brevisamide. Further, application of this methodology for the total synthesis of complex natural products possessing these structural features are under progress.

3.4 Experimental Section

3.4.1 Materials and Methods

All the chemicals were purchased from Carbosynth, Merck and Sigma-Aldrich Chemical Companies and were of the highest purity. The reactions were carried out under an inert atmosphere and monitored by thin-layer chromatography (TLC) using silica gel GF_{254} plates

with detection by charring with 5% (v/v) H_2SO_4 in methanol or by phosphomolybdic acid (PMA) stain or by ultra violet (UV) detection unless otherwise mentioned. Dimethyl formamide, ethanol, ethylvinylether, toluene, methanol, dichloromethane, dimethylsulphoxide, pyridine and $POCl_3$ used in the reactions were distilled from dehydrating agents prior to use. Silica gel (100-200) was used for column chromatography. ^1H, ^{13}C, DEPT, COSY, NOESY spectra were recorded with Bruker 400 MHz or 500 MHz spectrometers in $CDCl_3$. ^1H NMR chemical shifts are reported in ppm (δ) with TMS as internal standard (δ = 0.00 ppm); ^{13}C NMR data are reported in chemical shifts with solvent reference ($CDCl_3$, δ = 77.00 ppm). IR spectra were recorded with a JASCO FT/IR-5300 spectrometer. High-resolution mass spectra were recorded with a BrukermaXis ESI-TOF spectrometer.

3.4.2 Experimental Procedures and Spectral Data

(3.4.2.1) General procedure for the preparation of 2-*C*-formyl glycal derivatives

To a solution of dry DMF (2 mL) and $POCl_3$ (3 mmol) at 0 ^oC was added a precooled solution of glycal (1 mmol) in of dry DMF (2 mL) dropwise for about 30 min. The mixture was allowed to stir for 5-6 h at room temperature. After complete disappearance of starting material (by TLC) the reaction was quenched with aqueous $NaHCO_3$ (sat) solution and diluted with diethylether. The organic layer was separated and the aqueous layer was extracted with diethyl ether. The combined ether layers were washed with brine solution, dried over anhydrous $Na_2SO_4$and concentrated. The crude thus obtained was purified by column chromatography to yield 2-*C*-formyl glycal derivatives as pale yellow colored gummy compounds in 40-84% yield.

(3.4.2.2) General procedure for the preparation of 2-hydroxymethyl glycal derivatives

To a stirred solution of 2-*C*-formyl glycal (1.0 mmol) in dry ethanol (4 mL) at 0^oC, was added solid $NaBH_4$ (1.5 mmol) and the stirring was continued for 3 h. After completion of the reaction (by TLC), it was quenched with saturated NH_4Cl solution. Ethanol was evaporated under reduced pressure and aqueous suspension was extracted with dichloromethane (2x50mL). The combined organic layers were washed with water, brine solution, dried over anhydrous $NaSO_4$and concentrated. The obtained crude product was purified by silica-gel column chromatography to give 2-hydroxymethyl glycal derivatives in 70-85% yield.

(3.4.2.3) General procedure for the preparation of 2-vynyloxymethyl glycal derivatives

A mixture of primary alcohol (0.2 mmol), ethyl vinyl ether (3 mL, freshly distilled over sodium) and mercuric acetate (0.05 mmol) was stirred at reflux under an argon atmosphere. After 24 h the reaction was cooled to RT, and acetic acid(2.98 μL) was added and stirring was continued for 3h at RT. The mixture was diluted with an equal volume of hexane and washed with 5% aqueous KOH (2 X 5 mL), water (3 X 5 mL), with brine solution and concentrated under reduced pressure. The residue was purified using basic alumina to afford 2-vinyloxymethyl glycal derivatives as colorless gummy liquid in 50-74% yield.

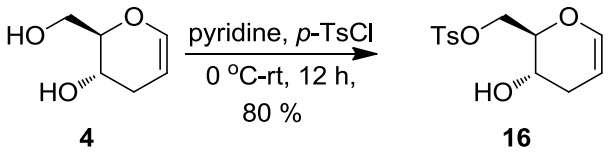
(3.4.2.4) General procedure for Claisen rearrangement reaction

A solution of 2-vinyloxymethyl glycal derivative (1 mmol) in toluene (15 mL), was heated at 180-185 ^{o}C in sealed tube for 5-6 h. Cooling the reaction followed by evaporation of toluene over rotary evaporator and purification over silica-gel provided the *C*-2-methylene-*C*-glycoside derivatives in 65-75 % yield.

(3.4.2.5) General procedure for Selective hydrogenation of olefin

To a stirred solution of olefin (0.2 mmol) in methanol (5 mL) was added Na_2CO_3, (0.2 mmol), 10% Pd/C (10 mg). The mixture was stirred for 4h under H_2 atmosphere. After completion of the reaction (by TLC) the suspension was filtered through a pad of celite and concentrated *in vacuo* to afford the corresponding *C*-2-methyl-*C*-glycoside derivative as oil in 70-74% yield.

(3.4.2.6) ((2*R*,3*S*)-3-hydroxy-3,4-dihydro-2*H*-pyran-2-yl)methyl 4-methylbenzenesulfonate (16):



4 **16**

To a stirred solution of compound **4** (800 mg, 6.151 mmol) in dry pyridine (10 mL), p-toluenesulphonyl chloride (1.4 g, 7.381 mmol) was added at 0 ^{o}C, slowly reaction was warmed to room temperature and stirring was continued for 12 h. After completion of the reaction,

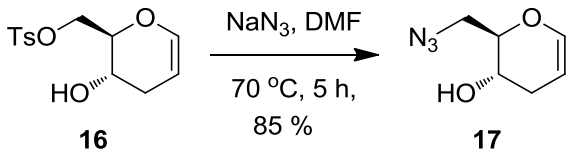
pyridine was removed under vacuum, the obtained crude product was dissolved in 200 mL of dichloromethane, the resulting organic layer was washed with aqueous copper sulphate solution, followed by brine, dried over anhydrous sodium sulfate, filter and evaporation of the solvent through rotary evaporator, and the residue was purified through silica gel column chromatography in 80 % yield (1.4 g), R_f = 0.5 in 40 % Ethylacetate/hexanes.

^{1}H (400 MHz, $CDCl_3$): δ 7.75 (d, *J* = 1.6 Hz, 2H), 7.31 (d, *J* = 8 Hz, 2H), 6.16 (d, *J* = 2 Hz, 1H), 4.58-4.62 (m, 1H), 4.31 (dd, *J* = 15.6 Hz, *J* = 10.8 Hz, 1H)4.22 (dd, *J* = 2.4 Hz, *J* = 11.2 Hz, 1H), 3.86 (t, J = 8 Hz, 1H), 3.71-3.75 (m, 1H), 3.19 (d, *J* = 4 Hz, 1H), 2.40 (s, 3H), 2.24-2.29 (m, 1H), 1.96-2.02 (m, 1H) ppm.

^{13}C (100 MHz, $CDCl_3$): δ 145.2, 142.6, 142.4, 132.3, 129.9, 127.9, 98.3, 76.3, 68.7, 62.9, 28.8, 21.6ppm.

Low-resolution MS(EI): m/z: 284 (M^+).

(3.4.2.7) (2*R*,3*S*)-2-(azidomethyl)-3,4-dihydro-2*H*-pyran-3-ol (17):



16 **17**

To a stirred solution of compound **16** (1.2 g, 4.22 mmol) in dry DMF (7 mL), sodium azide (2.7 g, 42.2 mmol) was added at room temperature, then stirring was continued for 5 h at 70 °C. After completion of the reaction DMF was removed through high vacuum, residue was dissolved in dichloromethane, organic layer was washed with water, brine and filtered, the filterate was evaporated using rotary evaporator, followed by purification with silica gel column chromatography provided the compound **17** in 85 % (550 mg) yield. R_f = 0.5 in 30 % Ethylacetate/hexanes).

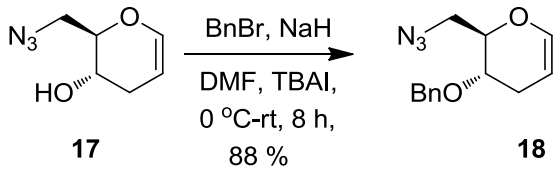
^{1}H (400 MHz, $CDCl_3$): δ 6.32 (d, *J* = 0.8 Hz, 1H), 4.67-4.71 (m, 1H), 3.80 (dd, *J* = 4.4 Hz, *J* = 9.6 Hz, 1H), 3.76-3.79 (m, 1H), 3.52-3.59 (m, 2H), 2.82 (s, 1H), 2.30-2.36 (m, 1H), 2.02-2.09 (m, 1H) ppm.

^{13}C (100 MHz, $CDCl_3$): δ 142.5, 98.2, 77.6, 64.3, 51.1, 28.9 ppm.

Low-resolution MS(EI): m/z: 155 (M^+).

IR(neat): $\tilde{\nu}_{max}$ = 3414, 2103, 1656 cm^{-1}.

(3.4.2.8) (2*R*, 3*S*)-2-(azidomethyl)-3-(benzyloxy)-3,4-dihydro-2*H*-pyran (18):



To a stirred solution of compound **17** (500 mg, 3.22 mmol) in dry DMF under an inert atmosphere, NaH (60 %, 6.45 mmol, 154 mg) was added slowly at 0 °C. After, continuous stirring for a further 30 min at 0 °C, benzyl bromide (6.44 mmol, 0.78 mL) and TBAI (cat) were added and the mixture was stirred at rt for overnight. The reaction was quenched with slow addition of cold water followed by extraction with dichloromethane provided compound, which was purified using silica gel column chromatography gave the pure **18** in 88 % yield (700 mg). R_f = 0.5 in 10 % Ethylacetate/hexanes.

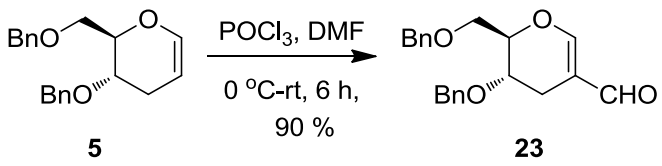
^{1}H (400 MHz, $CDCl_3$): δ 7.40-7.51 (m, 5H), 6.45-6.46 (d, *J* = 4.0 Hz, 1H), 4.74-4.80 (m, 2H), 4.60-4.3 (d, *J* = 11.6 Hz, 1H), 3.93-3.97 (m, 1H), 3.80-3.84 (m, 1H), 3.70 (dd, *J* = 2.4 Hz, 13.2 Hz, 1H), 3.61-3.66 (dd, *J* = 5.2 Hz, *J* = 12.8 Hz, 1H), 2.51-2.56 (m, 1H), 2.16-2.22 (m, 1H) ppm.

^{13}C (100 MHz, $CDCl_3$): δ 142.6, 137.7, 128.3, 127.7, 127.4, 97.8, 76.4, 71.9, 70.7, 51.1, 26.4 ppm.

Low-resolution MS(EI): m/z: 245 (M^+).

IR (neat): $\tilde{\nu}_{max}$ = 3013, 2105, 1654 cm^{-1}.

(3.4.2.9) (2*R*,3*S*)-3-(benzyloxy)-2-((benzyloxy) methyl)-3,4-dihydro-2*H*-pyran-5-carbaldehyde (23):



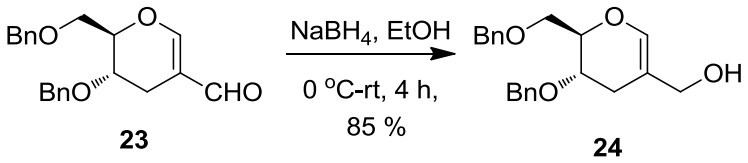
Compound **23** was synthesized using the 3-deoxy 4, 6-di-*O*-benzyl-D-glucal **5** (5.0 g, 16.129 mmol), $POCl_3$ (48.387 mmol, 7.4 mL) in dimethylformamide according to the procedure in **(3.4.2.1)**. The crude product was purified by silica-gel column chromatography with ethyl acetate/hexane (2:8) to provide the **23** as light yellow oil (90 % yield). R_f = 0.52 (EtOAc/hexanes, 30%).

^{1}H (400 MHz, $CDCl_3$): δ 9.29 (s, 1H), 7.29-7.38 (m, 11H), 4.50-4.69 (m, 4H), 4.19-4.23 (m, 1H), 3.81-3.86 (m, 1H), 3.77-3.79 (m, 2H), 2.69 (dd, 1H, *J* = 16.0 Hz, *J* = 4.8 Hz), 2.26 (dd, 1H, *J* = 16.4 Hz, *J* = 7.6 Hz) ppm.

^{13}C (100 MHz, $CDCl_3$): δ 189.5, 163.2, 137.3, 137.3, 128.1, 127.4, 127.4, 116.5, 79.0, 73.2, 70.5, 68.1, 68.0, 22.4 ppm.

Low-resolution MS(EI): m/z: 338 (M^+).

(3.4.2.10) ((2*R*,3*S*)-3-(benzyloxy)-2-((benzyloxy)methyl)-3,4-dihydro-2*H*-pyran-5-yl)methanol (24):



23 **24**

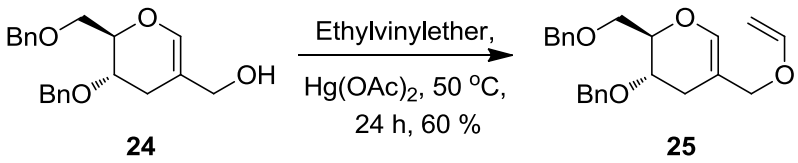
Compound **24** was synthesized using the 2-*C*-formyl glucal **23** (4.8 g, 14.201 mmol), $NaBH_4$ (536 mg, 14.201 mmol,) in ethanol according to the procedure in **(3.4.2.2)**. The crude product was purified by silica-gel column chromatography with ethyl acetate/hexane (4:6) to provide the **24** as light yellow oil (85 % yield). R_f = 0.5 (EtOAc/hexanes, 40%).

^{1}H (400 MHz, $CDCl_3$): δ 7.25-7.38, (m, 10H), 6.46 (s, 1H), 4.69 (d, 1H, *J* = 11.6 Hz), 4.65 (d, 1H, *J* = 12 Hz), 4.60 (d, 1H, *J* = 12 Hz), 4.55 (d, 1H, *J* = 11.6 Hz), 3.93-3.98 (m, 3H), 3.83-3.89 (m, 1H), 3.80 (d, 2H, *J* = 4 Hz), 2.75 (bs, 1H), 2.53 (dd, 1H, *J* = 5.6 Hz, *J* = 16.4 Hz), 2.22 (dd, 1H, *J* = 7.6 Hz, *J* = 16.4 Hz) ppm.

^{13}C (100 MHz, $CDCl_3$): δ 140.1, 137.6, 137.5, 127.9, 127.8, 127.3, 127.2, 109.8, 76.4, 72.9, 70.4, 69.7, 68.3, 62.7, 27.1 ppm.

Low-resolution MS(EI): m/z: 340 (M^+).

(3.4.2.11) (2*R*,3*S*)-3-(benzyloxy)-2-((benzyloxy)methyl)-5-((vinyloxy)methyl)-3,4-dihydro-2*H*-pyran (25):



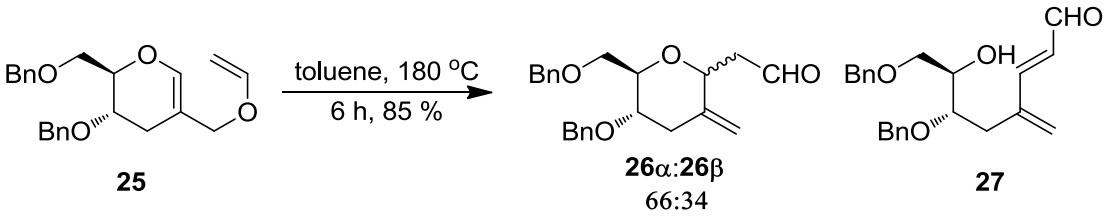
Compound **25** was synthesized using the 3-deoxy-2-hydroxymethyl glucal **24** (4.8 g, 14.117 mmol), $Hg(OAc)_2$ (1.0 g, 3.24 mmol,) in ethylvinylether according to the procedure in **(3.4.2.3)**. The crude product was purified by basic alumina column chromatography with ethyl acetate/hexane (1:9) to provide the **25** as colourless oil (60 % yield). R_f = 0.64 (EtOAc/hexanes, 10%).

^{1}H (500 MHz, $CDCl_3$): δ 7.27-7.34 (m, 10H), 6.51 (s, 1H), 6.44 (dd, 1H, *J* = 7.0 Hz, *J* = 14.0 Hz), 4.67 (d, 1H, *J* = 11.5 Hz), 4.62 (d, 1H, *J* = 12.5 Hz), 4.57 (d, 1H, *J* = 12.0 Hz), 4.52 (d, 1H, *J* = 12.0 Hz), 4.24 (dd, 1H, *J* = 2.0 Hz, *J* = 14.0 Hz), 4.08 (s, 2H), 4.02 (dd, 1H, *J* = 2.0 Hz, *J* = 7.0 Hz), 3.91-3.94 (m, 1H), 3.84 (td, 1H, *J* = 5.5 Hz, *J* = 8.0 Hz), 3.77-3.78 (m, 2H), 2.49 (dd, 1H, *J* = 5.5 Hz, *J* = 16.0 Hz), 2.17 (dd, 1H, *J* = 8.0 Hz, *J* = 16.0 Hz) ppm.

^{13}C (125 MHz, $CDCl_3$):δ 151.3, 142.4, 138.1, 138.0, 128.4, 128.3, 127.8, 127.7, 127.6, 106.6, 87.3, 76.8, 73.5, 71.0, 70.0, 69.4, 68.8, 28.0 ppm.

Low-resolution MS (EI): m/z: 366 (M^+).

(3.4.2.12) 2-((5*S*,6*R*)-5-(benzyloxy)-6-((benzyloxy)methyl)-3-methylenetetrahydro-2*H*-pyran-2-yl)acetaldehyde(26*α*:26β) and (6*S*,7*R*,*E*)-6,8-bis(benzyloxy)-7-hydroxy-4-methyleneoct-2-enal (27):



Compound **26** was synthesized using the 3-deoxy-2-vinyloxymethyl glucal **25** (0.5g, 1.366 mmol), in toluene according to the procedure in **(3.4.2.4)**. The crude product was purified by silica-gel column chromatography with ethyl acetate/hexane (2:8) to provide the **26α, 26β**as mixture along with **27**as colourless oil (85 % yield). R_f = 0.52 for **26α**, **26β**, 0.36 for **27**(EtOAc/hexanes, 20%).

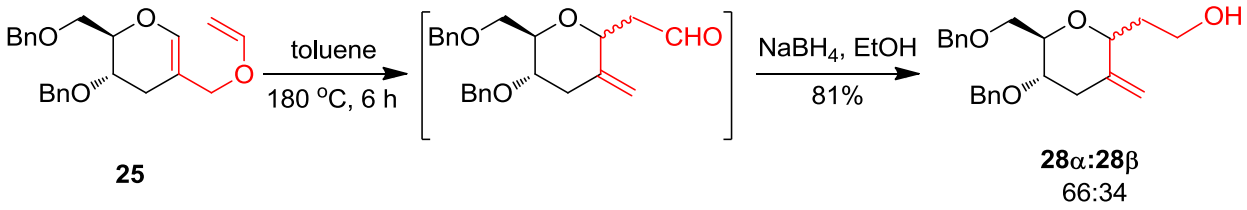
Compound 27:

^{1}H (400 MHz, CDCl$_3$): 9.58 (d, 1H, *J* = 7.6 Hz), 7.21-7.38 (m, 10H), 7.11 (d, 1H, *J* = 16.0 Hz), 6.28 (dd, 1H, *J* = 7.6 Hz, *J* = 16.0 Hz), 5.60 (d, 2H, *J* = 6.8 Hz), 4.57 (s, 2H), 4.48 (s, 2H), 3.84-3.88 (m, 1H), 3.60-3.68 (m, 2H), 2.71 (dd, 1H, *J* = 2.8 Hz, *J* = 14.4 Hz), 2.52 (dd, 1H, *J* = 8.8 Hz, *J* = 14.8 Hz) ppm.

^{13}C (100 MHz, CDCl$_3$): δ 194.0, 154.4, 141.9, 137.8, 137.6, 129.1, 128.5, 128.3, 128.1, 128.0, 127.9, 127.9, 127.8, 78.1, 73.5, 73.1, 71.9, 70.6, 33.6 ppm.

Low-resolution MS (EI): m/z: 366 (M^+).

(3.4.2.13) 2-((5*S*,6*R*)-5-(benzyloxy)-6-((benzyloxy)methyl)-3-methylenetetrahydro-2*H*-pyran-2-yl)ethanol (28):



25

28α:28β
66:34

Compound **28α**, **28β** was synthesized using the 2-vinyloxymethyl glucal **25** (1.5 g, 4.09 mmol), in toluene according to the procedure in **(3.4.2.4)**. The crude product was further reduced with $NaBH_4$ (154 mg, 4.09 mmol) in ethanol at -10 °C, according to the procedure in **(3.4.2.2)** purified by silica-gel column chromatography with ethyl acetate/hexane (4:6) to provide the **28**α and **28**β in 66:34 ratioas a colourless oil (81 % yield). R_f = 0.61 for **28α** and 0.62 for **28β** (EtOAc/hexanes, 40%).

(3.4.2.14) 2-((2*R*,5*S*,6*R*)-5-(benzyloxy)-6-((benzyloxy)methyl)-3-methylenetetrahydro-2*H*-pyran-2-yl)ethanol (28α):

^{1}H (400 MHz, $CDCl_3$): δ 7.25-7.36 (m, 10H), 4.89 (s, 1H), 4.87 (s, 1H), 4.62 (d, 1H, *J* = 12.4 Hz), 4.55 (d, 1H, *J* = 12 Hz), 4.41-4.44 (m, 2H), 3.88-3.93 (m, 1H), 3.82-3.85 (m, 2H), 3.76 (dd, 1H, *J* = 2.4 Hz, *J* = 6.4 Hz), 3.59 (dd, 1H, *J* = 6.8 Hz, *J* = 10.8 Hz), 3.43-3.49 (m, 1H), 2.76 (dd, 1H, *J* = 4.8 Hz, *J* = 13.2 Hz), 2.70 (bs, 1H), 2.41 (dd, 1H, *J* = 11.2 Hz, *J* = 12.8 Hz), 2.29-2.33 (m, 2H), 1.63-1.68 (m, 2H) ppm.

^{13}C (100 MHz, $CDCl_3$): δ 143.6, 138.1, 138.0, 128.4, 128.3 127.8, 127.7, 127.6, 127.6, 111.0, 77.6, 75.0, 73.4, 72.3, 70.8, 69.8, 61.1, 34.9, 33.0 ppm.

HRMS (ESI) calcd for $C_{23}H_{28}O_4$+Na 391.1886; found 391.1886.

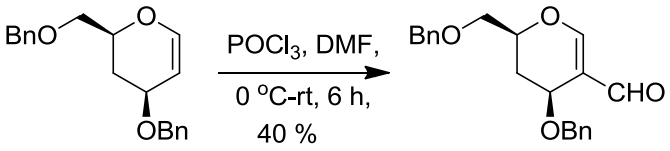
(3.4.2.15) 2-((2*S*,5*S*,6*R*)-5-(benzyloxy)-6-((benzyloxy)methyl)-3-methylenetetrahydro-2*H*-pyran-2-yl)ethanol (28β):

^{1}H (400 MHz, $CDCl_3$): δ 7.26-7.36 (m, 10H), 4.90 (s, 1H), 4.87 (s, 1H), 4.63 (d, 1H, *J* = 11.6 Hz), 4.53-4.58 (m, 2H), 4.44 (d, 1H, *J* = 11.6 Hz), 4.06 (t, 1H, *J* = 6.4 Hz), 3.89 (m, 2H), 3.77 (dd, 1H, *J* = 2 Hz, *J* = 10 Hz), 3.56-3.65 (m, 2H), 3.47-3.51 (m, 1H), 3.12 (bs, 1H), 2.88 (dd, 1H, *J* = 5.2 Hz, *J* = 13.2 Hz), 2.27 (dd, 1H, *J* = 7.6 Hz, *J* = 13.2 Hz), 1.95-2.00 (m, 2H) ppm.

^{13}C (100 MHz, $CDCl_3$): δ 143.6, 138.1, 138.0, 128.4, 128.4, 127.8, 127.7, 127.7, 127.6, 109.4, 79.9, 78.9, 74.7, 73.4, 71.0, 69.9, 61.5, 38.5, 33.4 ppm.

HRMS (ESI) calcd for $C_{23}H_{28}O_4$+Na 391.1886; found 391.1886.

(3.4.2.16) (2*S*,4*S*)-4-(benzyloxy)-2-((benzyloxy)methyl)-3,4-dihydro-2*H*-pyran-5-carbaldehyde (29):



10 **29**

Compound **29** was synthesized using the 4-deoxy 3, 6-di-*O*-benzyl-D-glucal **10** (4.0 g, 16.129 mmol), $POCl_3$ (48.387 mmol, 7.4 mL) in dimethylformamide according to the procedure in **(3.4.2.1)**. The crude product was purified by silica-gel column chromatography with ethyl

acetate/hexane (2:8) to provide the **29** as light yellow oil (40 % yield). R_f = 0.50 (EtOAc/hexanes, 30%).

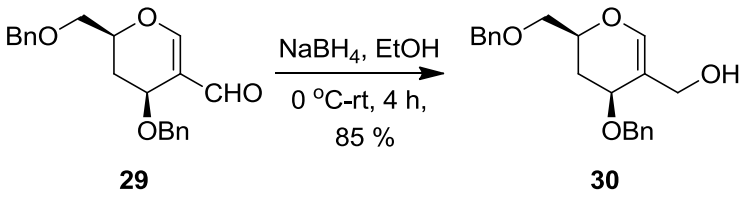
^{1}H (400 MHz, $CDCl_3$): δ 9.33 (s, 1H), 7.26-7.37 (m, 11H), 4.69(t, *J* = 3.2 Hz, 1H), 4.56 (dd, *J* = 13.2 Hz, *J* = 12 Hz, 2H), 4.47 (dd, *J* = 12 Hz, *J* = 16.8 Hz, 2H), 3.92 (dd, *J* = 8.4 Hz, *J* = 10.8 Hz, 1H), 3.58 (dd, *J* = 3.6 Hz, *J* = 10.8 Hz, 1H), 2.16 (m, *J* = 2.4 Hz, *J* = 14.8 Hz, 1H), 1.89-1.98 (m, 1H) ppm.

^{13}C (100 MHz, $CDCl_3$): δ 189.9, 165.1, 138.5, 137.7, 128.4, 128.3, 127.8, 127.6, 119.5, 73.4, 71.7, 71.7, 71.1, 62.9, 28.2 ppm.

HRMS (ESI) calcd for $C_{21}H_{23}O_4$ 339.1596; found 339.1595.

IR (neat): $\tilde{\nu}_{max}$ 3063, 3030, 2926, 1715, 1616, 1501 cm^{-1}.

(3.4.2.17) ((2*S*,4*S*)-4-(benzyloxy)-2-((benzyloxy)methyl)-3,4-dihydro-2*H*-pyran-5-yl)methanol (30):



29 **30**

Compound **30** was synthesized using the 4-deoxy-2-*C*-formyl glucal **29** (1.6 g, 4.73 mmol), $NaBH_4$ (178 mg, 4.73 mmol,) in ethanol according to the procedure in **(3.4.2.2)**. The crude product was purified by silica-gel column chromatography with ethyl acetate/hexane (4:6) to provide the **30** as light yellow oil in 85 % yield (1.28 g). R_f = 0.5 (EtOAc/hexanes, 40%).

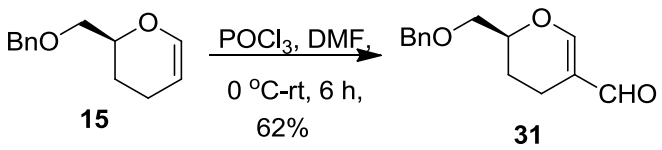
$[\alpha]_D^{25}$ = +47 (c = 0.37, $CHCl_3$).

^{1}H (400 MHz , $CDCl_3$) : δ 7.26-7.36 (m, 10H), 6.51 (s, 1H), 4.68 (d, 1H, *J* = 11.6 Hz), 4.49-4.62 (m, 3H), 4.33 (t, 1H, *J* = 7.2 Hz), 4.15-4.21 (m, 1H), 4.02 (q, 2H, *J* = 12 Hz), 3.67 (dd, 1H, *J* = 6.4 Hz, *J* = 10 Hz), 3.55 (dd, 1H, *J* = 4.4 Hz, *J* = 10.4 Hz), 2.33 (bs, 1H), 2.22-2.27, (m, 1H), 1.88-1.96 (m, 1H) ppm.

^{13}C (100 MHz, $CDCl_3$): δ 144.4, 137.9, 137.8, 128.5, 128.4, 127.9, 127.8, 113.5, 73.7, 73.5, 71.5, 71.1, 70.8, 62.3, 30.0 ppm.

HRMS (ESI) Calcd for $C_{21}H_{24}O_4$+Na 363.1573; found 363.1571.

(3.4.2.18) (*S*)-2-((benzyloxy)methyl)-3,4-dihydro-2*H*-pyran-5-carbaldehyde (31):



Compound **29** was synthesized using the 3,4-dideoxy-6-*O*-benzyl-D-glucal **15** (2.0 g, 9.80 mmol), $POCl_3$ (29.411 mmol, 2.7 mL) in dimethylformamide according to the procedure in **(3.4.2.1)**. The crude product was purified by silica-gel column chromatography with ethyl acetate/hexane (2:8) to provide the **31** as light yellow oil in 62 % yield (1.5 g). R_f = 0.50 (EtOAc/hexanes, 20%).

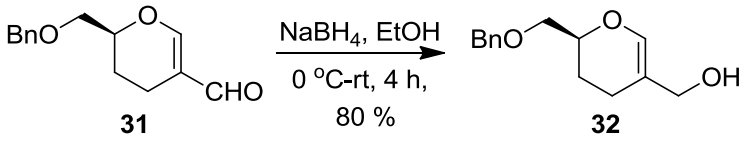
$[\alpha]_D^{25}$ = +83.171 (c = 1.0, $CHCl_3$).

^{1}H (400 MHz , $CDCl_3$) : δ 9.23 (s, 1H), 7.28-7.36 (m, 6H), 4.60 (dd, *J* = 12 Hz, *J* = 13.6 Hz, 2H), 4.20-4.24 (m, 1H), 3.59-3.67 (m, 1H), 2.35-2.41 (m, 1H), 2.14-2.19 (m, 1H), 1.91-1.96 (m, 1H), 1.65-1.73 (m,1H) ppm.

^{13}C (100 MHz, $CDCl_3$): δ 190.3, 164.6, 137.6, 128.5, 127.8, 127.7, 119.3, 77.6, 73.5, 71.4, 22.5, 16.3 ppm.

HRMS (ESI) Calcd for $C_{14}H_{17}O_3$233.1178; found 233.1168.

(3.4.2.19) (*S*)- (2-((benzyloxy)methyl)-3,4-dihydro-2*H*-pyran-5-yl)methanol (32):



Compound **32** was synthesized using the 3,4-dideoxy-2-*C*-formyl glucal **31** (1.4 g, 6.03 mmol), $NaBH_4$ (229 mg, 6.03 mmol,) in ethanol according to the procedure in **(3.4.2.2)**. The

crude product was purified by silica-gel column chromatography with ethyl acetate/hexane (4:6) to provide the **32** as light yellow oil in 80 % yield (1.10 g). R_f = 0.52 (EtOAc/hexanes, 40%).

$[\alpha]_D^{25}$ = +51 (c = 0.29, $CHCl_3$).

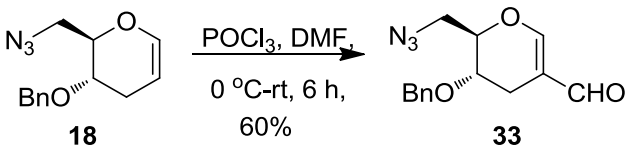
^{1}H (400 MHz, $CDCl_3$): δ 7.31-7.36 (m, 5H), 6.50 (s, 1H), 4.57 (t, 2H, *J* = 0.4 Hz), 3.96-3.99 (m, 3H), 3.56 (t, 2H, *J* = 5.6 Hz), 2.09-2.17 (m, 3H), 1.90-1.94 (m, 1H), 1.72-1.74 (m, 1H) ppm.

^{13}C (100 MHz, $CDCl_3$): δ 141.6, 138.0, 128.4, 127.7, 127.7, 112.7, 74.1, 73.4, 72.2, 64.3, 24.0, 20.8 ppm.

HRMS (ESI) Calcd for $C_{14}H_{18}O_3$ 234.1256; found 234.1259.

IR (neat): $\tilde{\nu}_{max}$ 3419, 2854, 1671 cm^{-1}.

(3.4.2.20) (2*R*,3*S*)-2-(azidomethyl)-3-(benzyloxy)-3,4-dihydro-2*H*-pyran-5-carbaldehyde (33):



Compound **33** was synthesized using the 3-deoxy-6-azido-4-*O*-benzyl-D-glucal **18** (4.0 g, 16.32 mmol), $POCl_3$ (48.97 mmol, 4.56 mL) in dimethylformamide according to the procedure in **(3.4.2.1)**. The crude product was purified by silica-gel column chromatography with ethyl acetate/hexane (2:8) to provide the **33** as light yellow oil in 60 % yield (2.7 g). R_f = 0.51 (EtOAc/hexanes, 20%).

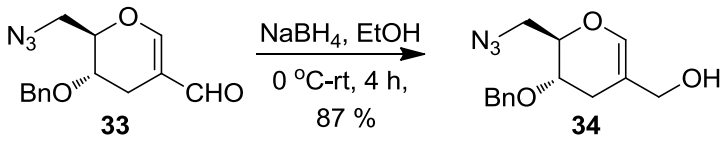
^{1}H (400 MHz, $CDCl_3$): δ 9.33 (s, 1H), 7.29-7.36 (m, 6H), 4.70 (d, *J* = 11.2 Hz, 1H), 4.50-4.53 (d, *J* = 11.6 Hz, 1H), 4.07 (d, *J* = 3.6 Hz, 1H), 3.68 (dd, *J* = 8.0 Hz, *J* = 12.8 Hz, 2H), 3.57 (dd, *J* = 4.8 Hz, *J* = 13.2 Hz, 1H), 2.86 (dd, *J* = 4.8 Hz, *J* = 16.0 Hz, 1H), 2.14 (dd, *J* = 9.2 Hz, *J* = 16.4 Hz, 1H) ppm.

^{13}C (100 MHz, $CDCl_3$): δ 189.5, 162.6, 136.9, 128.4, 128.0, 127.8, 117.2, 78.9, 70.7, 68.7, 50.6, 22.9 ppm.

HRMS (ESI) Calcd for $C_{14}H_{16}N_3O_3$ 274.1192; found 274.1190.

IR (neat): $\tilde{\nu}_{max}$ 3013, 2105, 1710, 1654 cm^{-1}.

(3.4.2.21) ((2*R*,3*S*)-2-(azidomethyl)-3-(benzyloxy)-3,4-dihydro-2*H*-pyran-5-yl)methanol (34):



Compound **33** was synthesized using the 6-azido-3-deoxy-2-*C*-formyl glucal **33** (2.5 g, 9.15 mmol), $NaBH_4$ (348 mg, 9.15 mmol,) in ethanol according to the procedure in **(3.4.2.2)**. The crude product was purified by silica-gel column chromatography with ethyl acetate/hexane (3:7) to provide the **34** as light yellow oil in 87 % yield (2.1 g). R_f = 0.67 (EtOAc/hexanes, 30%).

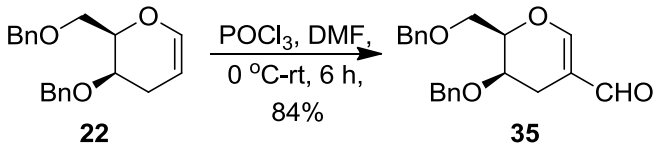
^{1}H (400 MHz, $CDCl_3$): δ 7.33-7.41, (m, 5H), 6.46 (s, 1H), 4.72 (d, 1H, *J* = 12.4 Hz), 4.56 (d, 1H, *J* = 11.6 Hz), 4.00 (s, 2H), 3.84-3.87 (m, 1H), 3.74-3.80 (m, 1H), 3.64 (dd, 1H, *J* = 2.8 Hz, *J* = 13.2 Hz), 3.55 (dd, 1H, *J* = 5.2 Hz, *J* = 12.8 Hz), 2.62 (dd, 1H, *J* = 6.0 Hz, *J* = 16.0 Hz), 2.21 (dd, 1H, *J* = 8.4 Hz, *J* = 16.0 Hz) ppm.

^{13}C (100 MHz, $CDCl_3$): δ 140.6, 137.7, 128.5, 127.9, 127.8, 110.7, 76.4, 70.9, 70.6, 63.4, 51.1, 27.9 ppm.

HRMS (ESI) calcd for $C_{14}H_{17}N_3O_3$+Na 298.1168; found 298.1168.

IR (neat): $\tilde{\nu}_{max}$3433, 3013, 2107, 1654 cm^{-1}.

(3.4.2.22) (2*R*,3*R*)-3-(benzyloxy)-2-((benzyloxy)methyl)-3,4-dihydro-2*H*-pyran-5-carbaldehyde (35)



Compound **35** was synthesized using the 3-deoxy-6-azido-4-*O*-benzyl-D-glucal **18** (2.0 g, 6.45 mmol), $POCl_3$ (19.35 mmol, 1.8 mL) in dimethylformamide according to the procedure in

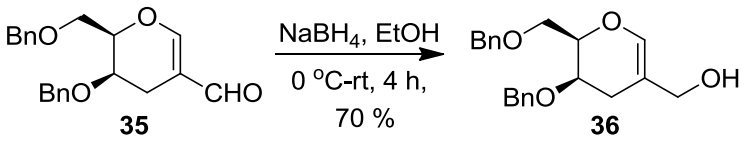
(3.4.2.1). The crude product was purified by silica-gel column chromatography with ethyl acetate/hexane (3:7) to provide the **35** as light yellow oil in 84 % yield (1.7 g). R_f = 0.52 (EtOAc/hexanes, 20%).

^{1}H (400 MHz, $CDCl_3$): δ 9.32 (s, 1H), 7.26-7.35 (m, 11H), 4.63 (d, *J* = 12.0 Hz, 1H), 4.57 (d, *J* = 11.6 Hz, 1H), 4.49 (d, *J* = 11.6 Hz, 1H), 4.40 (d, *J* = 12.0 Hz, 1H), 4.22 (t, *J* = 5.2 Hz, 1H), 3.95 (s, 1H), 3.79 (dd, *J* = 7.2 Hz, *J* = 10.0 Hz, 1H), 3.71 (dd, *J* = 5.2 Hz, *J* = 10.0 Hz, 1H), 2.68 (d, *J* = 17.2 Hz, 1H), 2.22 (d, *J* = 17.6 Hz, 1H) ppm.

^{13}C (100 MHz, $CDCl_3$): δ 190.3, 163.9, 137.4, 137.3, 128.3, 127.7, 127.6, 116.5, 78.4, 73.4, 70.7, 68.4, 67.4, 20.9 ppm.

Low-resolution MS(EI): m/z: 338 (M^+).

(3.4.2.23) ((2*R*,3*R*)-3-(benzyloxy)-2-((benzyloxy)methyl)-3,4-dihydro-2*H*-pyran-5-yl)methanol (36):



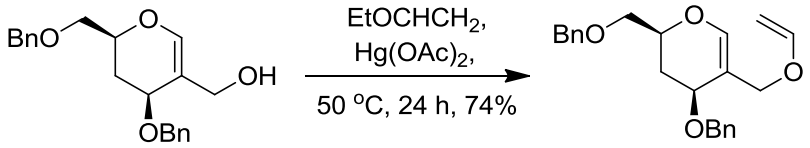
Compound **36** was synthesized using the 6-azido-3-deoxy-2-*C*-formyl glucal**35** (1.6 g, 4.73 mmol), $NaBH_4$ (179 mg, 4.73 mmol,) in ethanol according to the procedure in **(3.4.2.2)**. The crude product was purified by silica-gel column chromatography with ethyl acetate/hexane (4:6) to provide the **36** as a light yellow oil in 70 % yield (1.15 g).R_f = 0.5(EtOAc/hexanes, 40%).

^{1}H (400 MHz, $CDCl_3$): δ 7.31-7.37 (m, 10H), 6.51 (s, 1H), 4.67 (d, *J* = 12.4 Hz, 1H), 4.58 (d, *J* = 12.0 Hz, 1H), 4.49 (dd, *J* = 5.2 Hz, *J* = 12.0 Hz, 2H), 4.05 (t, *J* = 16 Hz 1H), 3.93 (dd, *J* = 1.2 Hz, *J* = 11.2 Hz, 3H), 3.73 (dd, *J* = 6.8 Hz, *J* = 10.0 Hz, 1H), 3.66 (dd, *J* = 5.6 Hz, *J* = 9.6 Hz, 1H), 2.30 (d, *J* = 3.6 Hz, 2H) ppm.

^{13}C (100 MHz, $CDCl_3$): δ 141.0, 138.1, 137.9, 128.4, 127.9, 127.8, 127.8, 127.7, 110.2, 75.3, 73.4, 71.1, 69.5, 68.8, 64.0, 25.7 ppm.

Low-resolution MS(EI): m/z: 340 (M^+).

(3.4.2.24) (2*S*,4*S*)-4-(benzyloxy)-2-((benzyloxy)methyl)-5-((vinyloxy)methyl)-3,4-dihydro-2*H*-pyran (37):



30 **37**

Compound **37** was synthesized using the 4-deoxy-2-hydroxymethyl glucal **30** (1.2 g, 3.52 mmol), $Hg(OAc)_2$ (258 mg, 0.81 mmol,) in ethylvinylether according to the procedure in **(3.4.2.3)**. The crude product was purified by basic alumina column chromatography with ethyl acetate/hexane (1:9) to provide the **37** as colourless oil in 74 % yield (0.95 g). R_f = 0.5 (EtOAc/hexanes, 10%).

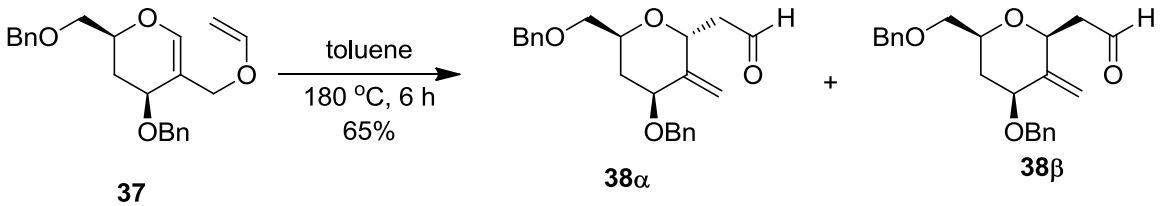
$[\alpha]_D^{25}$ = +35.748 (c = 0.353, $CHCl_3$).

^{1}H (400 MHz , $CDCl_3$) : δ 7.26-7.35 (m, 10H), 6.53 (s, 1H), 6.42 (dd, 1H, *J* = 6.8 Hz, *J* = 14.4 Hz), 4.48-4.64 (m, 5H), 4.23-4.27 (m, 2H), 4.01 (dd, 1H, *J* = 1.6 Hz, *J* = 6.8 Hz), 3.92 (d, 1H, *J* = 10.8 Hz), 3.68 (dd, 1H, *J* = 6.8 Hz, *J* = 10.4 Hz), 3.54 (dd, 1H, *J* = 4.4 Hz, *J* = 10.4 Hz), 2.16-2.22 (m, 1H), 1.88-1.96 (m, 1H) ppm.

^{13}C (100 MHz, $CDCl_3$): δ 151.5, 145.1, 138.3, 137.9, 128.4, 128.3, 127.7, 127.7,127.6, 110.9, 87.1, 74.0, 73.4, 71.5, 71.0, 68.3, 66.5, 29.7 ppm.

HRMS (ESI) Calcd for $C_{23}H_{26}O_4$+Na389.1729; found 389.1729.

(3.4.2.25) 2-((2*R*,4*S*,6*S*)-4-(benzyloxy)-6-((benzyloxy)methyl)-3-methylenetetrahydro-2*H*-pyran-2-yl)acetaldehyde (38α) and 2-((2*S*,4*S*,6*S*)-4-(benzyloxy)-6-((benzyloxy)methyl)-3-methylenetetrahydro-2*H*-pyran-2-yl)acetaldehyde (38β):



37 **38α** **38β**

90:10

Compounds **38α** and **38β** were obtained from **37** (0.8 g 2.18 mmol) by following the procedure **(3.4.2.4)**, yield 65% (0.520 g), R_f = 0.6 (EtOAc/hexanes, 30%), as **90:10** diastereomeric ratio, only **38α** was able to purify using silica gel column chromatography.

Compound 38α:

^{1}H (400 MHz , CDCl$_3$): δ 9.75-9.76 (q, 1H), 7.27-7.35 (m, 10H), 5.23 (s, 1H), 5.03 (s, 1H), 4.96 (dd, 1H, *J* = 5.6 Hz, *J* = 14.4 Hz), 4.51-4.60 (m, 4H), 4.10 (dd, 1H, *J* = 4.8 Hz, *J* = 9.2 Hz), 4.00-4.06 (m, 1H), 3.67 (dd, 1H, *J* = 6.4 Hz, *J* = 10.4 Hz), 3.45 (dd, 1H, *J* = 4.4 Hz, *J* = 10 Hz), 2.83 (ddd, 1H, *J* = 3.2 Hz, *J* = 8.8 Hz, *J* = 16 Hz), 2.59 (ddd, 1H, *J* = 2.0 Hz, *J* = 6.0 Hz, *J* = 16 Hz), 2.16 (dt, 1H, *J* = 4.4 Hz, *J* = 12.8 Hz), 1.57 (m, 1H) ppm.

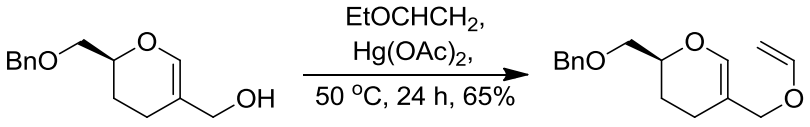
^{13}C (100 MHz, CDCl$_3$): δ 200.1, 144.4, 138.2, 138.1, 128.4, 128.3, 127.7, 127.6, 127.3, 110.1, 74.2, 73.3, 71.9, 71.4, 70.5, 70.2, 53.4, 45.6, 35.8 ppm.

HRMS (ESI) Calcd for $C_{23}H_{27}O_4$+H 367.1909; found 367.1908.

Compound 38β:

This compound was not resolved in the column chromatography and obtained along with **38α**.

(3.4.2.26) (*S*)-2-((benzyloxy)methyl)-5-((vinyloxy)methyl)-3,4-dihydro-2*H*-pyran (39):



32 **39**

Compound **39** was synthesized using the 3,4-dideoxy-2-hydroxymethyl glucal **32** (1.0 g, 4.27 mmol), $Hg(OAc)_2$ (312 mg, 0.98 mmol,) in ethylvinylether according to the procedure in **(3.4.2.3)**. The crude product was purified by basic alumina column chromatography with ethyl acetate/hexane (1:9) to provide the **39** as colourless oil in 65 % yield (0.72 g). R_f = 0.7 (EtOAc/hexanes, 10%).

$[\alpha]_D^{25}$ = +45 (c = 1.0, $CHCl_3$).

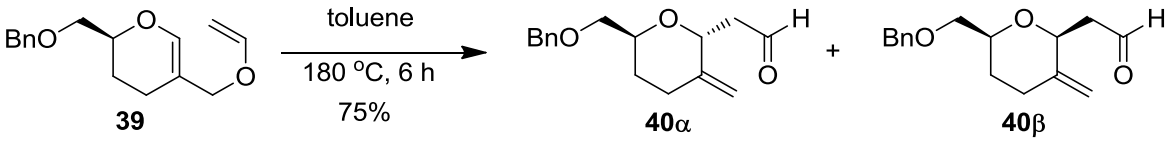
IR (neat): $\tilde{\nu}_{max}$ 3024, 2920, 1671, 1638, 1616 cm^{-1}.

^{1}H (400 MHz , $CDCl_3$): δ 7.28-7.38 (m, 5H), 6.56 (s, 1H), 6.44 (q, 1H, *J* = 6.8 Hz, *J* = 14.4 Hz), 4.57 (q, 2H, *J* = 12 Hz, *J* = 17.2 Hz), 4.23 (dd, 1H, *J* = 1.6 Hz, *J* = 14 Hz), 4.04-4.07 (m, 2H), 4.03 (d, 1H, *J* = 2 Hz), 4.01 (d, 1H, *J* = 2 Hz), 3.54-3.64 (m, 2H), 2.14-2.19 (m, 1H), 2.06-2.11 (m, 1H), 1.89-1.96 (m, 1H), 1.71-1.79 (m, 1H) ppm.

^{13}C (100 MHz, $CDCl_3$): δ 151.4, 143.1, 138.0, 128.4, 127.7, 108.9, 87.0, 74.2, 73.4, 72.1, 70.1, 23.9, 21.1 ppm.

HRMS (ESI) Calcd for $C_{16}H_{20}O_3$+Na 283.1310; found 283.1327.

(3.4.2.27) 2-((6*S*)-6-((benzyloxy)methyl)-3-methylenetetrahydro-2*H*-pyran-2-yl)acetaldehyde (40α:40β):

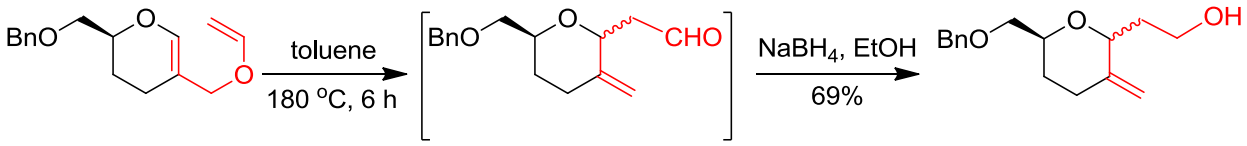


39 **40α** **40β**

Compounds **40α** and **40β** were obtained from **39** (0.4 g, 1.53 mmol)by following the procedure **(3.4.2.4)**, yield 75% (0.3 g), R_f = 0.4 (EtOAc/hexanes, 20%), as **83:17** diastereomeric ratio.These compounds were obtained as an inseparable mixture of **40α** and **40β** (please see the spectra).

HRMS (ESI) Calcd for $C_{16}H_{20}O_3$ 283.1310; found 283.1219.

(3.4.2.28) 2-((6*S*)-6-((benzyloxy)methyl)-3-methylenetetrahydro-2*H*-pyran-2-yl)ethanol (41α and 41β):



39 **41α:41β** 83:17

Compound **41α** and **41β** were synthesized from **39** (0.4 g, 1.53 mmol) by following the procedure described for compound **28α** and**28β**, yield 69% (0.28 g), R_f = 0.4 (EtOAc/hexanes, 40% for **41α**). Compound **41β** was unable to isolate during column chromatogrsphy.

Compound 41α:

$[\alpha]_D^{25}$ = +17 (*c* = 1.0, $CHCl_3$).

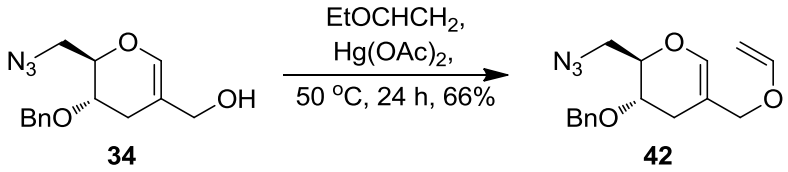
^{1}H (400 MHz , $CDCl_3$): δ 7.25-7.35 (m, 5H), 4.79 (s, 1H), 4.77 (s, 1H), 4.50 (q,1H, *J* = 26.8 Hz,) 4.44 (dd, 1H, *J* = 4.4 Hz, *J* = 10.8 Hz), 4.04-4.10 (m, 1H), 3.84-3.89 (m, 2H), 3.76-3.82 (m, 2H), 3.38-3.46 (m, 2H), 2.37-2.46 (m, 1H), 2.28-2.36 (m, 2H), 1.67-1.73 (m, 1H), 1.51-1.58 (m, 1H), 1.36-1.47 (m, 1H) ppm.

^{13}C (100 MHz, $CDCl_3$): δ 145.4, 137.8, 128.2, 127.4, 109.1, 78.2, 73.2, 72.8, 68.6, 61.2, 33.2, 29.0, 28.1 ppm.

HRMS (ESI) Calcd for $C_{16}H_{20}O_3$+H 285.1467; found 285.1455.

IR (neat): $\tilde{\nu}_{max}$ 3446, 2920, 1654, 1457 cm^{-1}.

(3.4.2.29) (2*R*,3*S*)-2-(azidomethyl)-3-(benzyloxy)-5-((vinyloxy)methyl)-3,4-dihydro-2*H*-pyran (42):



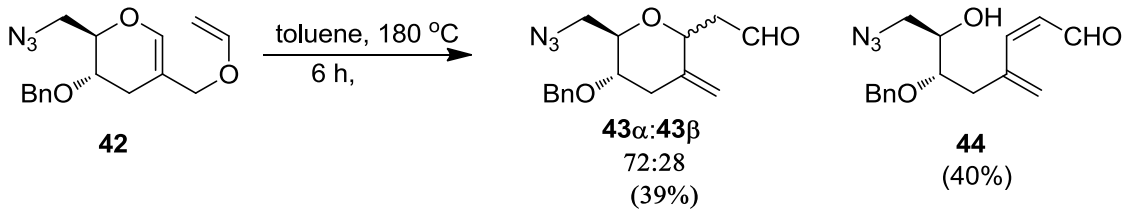
Compound **42** was synthesized using the 6-azidi-3-deoxy-2-hydroxymethyl glucal **34** (2.0 g, 7.27 mmol), $Hg(OAc)_2$ (531 mg, 1.67 mmol) in ethylvinylether according to the procedure in **(3.4.2.3)**. The crude product was purified by basic alumina column chromatography with ethyl acetate/hexane (0.5:9.5) to provide the **42** as colourless oil in 66 % yield (1.35 g). R_f = 0.65 (EtOAc/hexanes, 5%).

^{1}H (400 MHz, $CDCl_3$): δ 7.32-7.39, (m, 5H), 6.50 (s, 1H), 6.46 (dd, 1H, *J* = 6.8 Hz, *J* = 14.4 Hz), 4.71 (d, 1H, *J* = 11.2 Hz), 4.53 (d, 1H, *J* = 11.2 Hz), 4.25 (dd, 1H, *J* = 2.0 Hz, *J* = 14.4 Hz), 4.09 (s, 2H), 4.05 (dd, 1H, *J* = 2.0 Hz, *J* = 6.8 Hz), 3.84-3.87 (m, 1H), 3.76-3.80 (m, 1H), 3.65 (dd, 1H, *J* = 2.4 Hz, *J* = 13.2 Hz), 3.55 (dd, 1H, *J* = 5.2 Hz, *J* = 12.8 Hz) ppm.

^{13}C (100 MHz, $CDCl_3$): δ 151.2, 142.0, 137.6, 128.5, 127.9, 127.8, 107.1, 87.4, 76.6, 70.9, 70.4, 69.0, 51.1, 28.2 ppm.

Low-resolution MS(EI): m/z: 301 (M^+).

(3.4.2.30) 2-((2*R*,5*S*,6*S*)-5-azido-6-((benzyloxy)methyl)-3-methylenetetrahydro-2*H*-pyran-2-yl)acetaldehyde (43*α*), 2-((2*S*,5*S*,6*S*)-5-azido-6-((benzyloxy)methyl)-3-methylenetetrahydro-2*H*-pyran-2-yl)acetaldehyde (43β) and (6*S*,7*S*,*Z*)-6-azido-8-(benzyloxy)-7-hydroxy-4-methyleneoct-2-enal (44):



42

43α:**43**β
72:28
(39%)

44
(40%)

Compound **43** and **44** were synthesized using the 6-azido-3-deoxy-2-vinyloxymethyl glucal **42** (250 mg, 0.83 mmol), in toluene according to the procedure in **(3.4.2.4)**. The crude product was purified by silica-gel column chromatography with ethyl acetate/hexane (2:8) to provide the **43*α*** along with **44** as colourless oil.

Compound 43*α*:

yield 39%, R_f = 0.6 (EtOAc/hexanes, 30%).

^{1}H (400 MHz, $CDCl_3$): δ 9.86 (t, 1H, *J* = 2.0 Hz), 7.32-7.40, (m, 5H), 4.97 (s, 1H), 4.80 (s, 1H), 4.67 (d, 1H, *J* = 11.6 Hz), 4.47 (d, 1H, *J* = 11.6 Hz), 4.40 (t, 1H, *J* = 6.4 Hz), 3.65 (dtd, 1H, *J* = 2.4 Hz, *J* = 6.0 Hz, *J* = 11.2 Hz), 3.55 (dd, 1H, *J* = 2.4 Hz, *J* = 13.2 Hz), 3.42-3.48 (m, 1H), 3.37 (dd, 1H, *J* = 6.0 Hz, *J* = 13.2 Hz), 2.97 (dd, 1H, *J* = 4.8 Hz, *J* = 12.8 Hz), 2.79 (dd, 2H, *J* = 2.4 Hz, *J* = 6.4 Hz), 2.30 (dd, 1H, *J* = 11.6 Hz, *J* = 12.8 Hz) ppm.

^{13}C (100 MHz, $CDCl_3$): δ 200.6, 142.3, 137.7, 128.5, 127.9, 127.8, 110.5, 80.2, 74.8, 73.7, 71.0, 51.6, 45.2, 38.4 ppm.

Low-resolution MS(EI): m/z: 301 (M^+).

Compound 43β: This compound was observed only in the crude NMR. However it was not detected after the column chromatography.

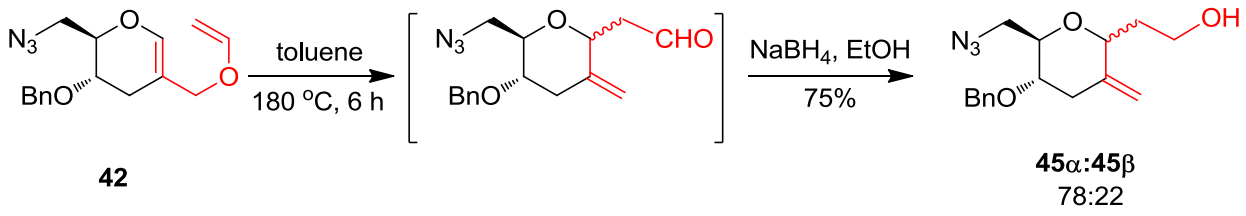
Compound 44: (this compound was observed only while purifying compound **43α** and **43β** over silica gel) yield 40%, R_f = 0.5 (EtOAc/hexanes, 30%).

^{1}H (400 MHz, $CDCl_3$): δ 9.59 (d, 1H, *J* = 7.6 Hz), 7.29-7.38, (m, 5H), 7.14 (d, 1H, *J* = 15.6 Hz), 6.26 (dd, 1H, *J* = 7.6 Hz, *J* = 16 Hz), 5.63 (d, 2H, *J* = 14.4 Hz), 4.54 (d, 2H, *J* = 5.2 Hz), 3.81-3.83 (m, 1H), 3.60-3.65 (m, 1H), 3.50 (d, 2H, *J* = 5.6 Hz), 2.66 (dd, 1H, *J* = 3.2 Hz, *J* = 13.6 Hz), 2.57 (dd, 1H, *J* = 8.4 Hz, *J* = 14.4 Hz), 2.29 (bs, 1H) ppm.

^{13}C (100 MHz, $CDCl_3$): δ 193.9, 154.0, 141.4, 137.4, 129.2, 128.5, 128.1, 128.0, 78.3, 73.2, 71.9, 53.4, 33.2 ppm.

Low-resolution MS(EI): m/z: 301 (M^+).

(3.4.2.31) 2-((5*S*,6*S*)-5-azido-6-((benzyloxy)methyl)-3-methylenetetrahydro-2*H*-pyran-2-yl)ethanol (45α,45β):

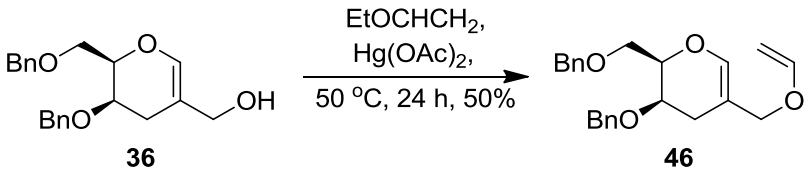


42 **45α:45β** 78:22

Compound **45** was synthesized using the 6-azido-3-deoxy-2-vinyloxymethyl glucal **42** (1.0 g, 3.32 mmol), in toluene according to the procedure in **(3.4.2.4)**. The crude product was further reduced with $NaBH_4$ (126 mg, 3.32 mmol) in ethanol at -10 °C, according to the procedure in **(3.4.2.2)** purified by silica-gel column chromatography with ethyl acetate/hexane (3:7) to provide the **45**αand **45**β as inseparable mixture in 78:22 ratio as a colorless oil (75 % yield, 0.75 g). R_f = 0.65 for **45α** and 0.66 for **45β** (EtOAc/hexanes, 30%) (see spectra).

HRMS (ESI) Calcd for $C_{16}H_{21}N_3NaO_3$ 326.1481; found 326.1479.

(3.4.2.32) (2*R*,3*R*)-3-(benzyloxy)-2-((benzyloxy)methyl)-5-((vinyloxy)methyl)-3,4-dihydro-2*H*-pyran (46):



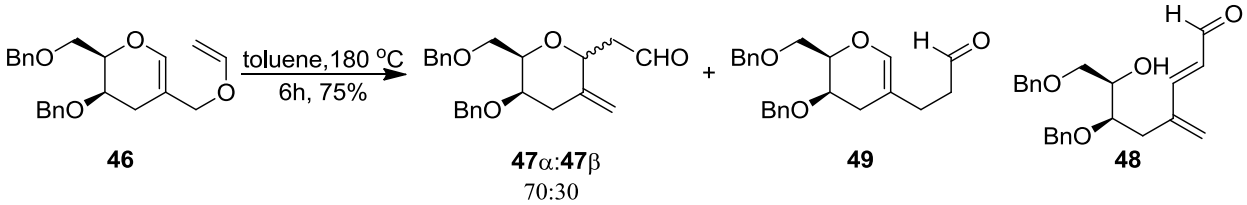
Compound **46** was synthesized using the 3-deoxy-2-hydroxymethyl galactal **36** (1.1 g, 3.23 mmol), $Hg(OAc)_2$ (232 mg, 0.74 mmol,) in ethylvinylether according to the procedure in **(3.4.2.3)**. The crude product was purified by basic alumina column chromatography with ethyl acetate/hexane (1:10) to provide the **46** as colourless oil in 50 % yield (0.6 g). R_f = 0.64 (EtOAc/hexanes, 10%).

^{1}H (400 MHz, $CDCl_3$): δ 7.26-7.37 (m, 10), 6.56 (s, 1H), 6.43 (dd, *J* = 6.8 z, *J* = 14.4 Hz, 1H), 4.66 (d, *J* = 12.4 Hz, 1H), 4.57 (d, *J* = 11.6 Hz, 1H), 4.48 (d, *J* = 12.4 Hz, 2H), 4.24 (dd, *J* = 1.2 Hz, *J* = 14.0 Hz, 1H), 4.09 (d, *J* = 2.4 Hz, 3H), 4.02 (dd, *J* = 1.6 Hz, *J* = 6.8 Hz, 1H), 3.92 (s, 1H), 3.72 (dd, *J* = 7.6 Hz, *J* = 9.6 Hz, 1H), 3.66 (dd, *J* = 5.6 Hz, *J* = 10.0 Hz, 1H), 2.21 (m, 2H) ppm.

^{13}C (100 MHz, $CDCl_3$): δ 151.2, 142.4, 138.1, 137.9, 128.4, 127.9, 127.8, 127.7, 127.7, 106.5, 87.4, 75.4, 73.5, 71.0, 69.9, 69.2, 68.7, 26.0 ppm.

Low-resolution MS(EI): m/z: 366 (M^+).

(3.4.2.33) 2-((2*R*,5*R*,6*R*)-5-(benzyloxy)-6-((benzyloxy)methyl)-3-methylenetetrahydro-2*H*-pyran-2-yl)acetaldehyde (47*α*), 2-((2*S*,5*R*,6*R*)-5-(benzyloxy)-6-((benzyloxy)methyl)-3-methylenetetrahydro-2*H*-pyran-2-yl)acetaldehyde (47β),3-((2*R*,3*R*)-3-(benzyloxy)-2-((benzyloxy)methyl)-3,4-dihydro-2*H*-pyran-5-yl)propanal (49) and (6*R*,7*R*,*E*)-6,8-bis(benzyloxy)-7-hydroxy-4-methyleneoct-2-enal (48):



Compound **47α, 47β**, **48** and **49** were synthesized using the 3-deoxy-2-vinyloxymethyl galactal **46** (0.2 g, 0.54 mmol), in toluene according to the procedure in **(3.4.2.4)**. The crude product was purified by silica-gel column chromatography with ethyl acetate/hexane (2:8) to provide the mixture of **47α**, **47β** along with **49** in 45% yield and also pure ring opened product **48** in 30% yield. R_f = 0.51 for **47α**, 0.52 for **47β**, 0.52 for **48** in ethylacetate /hexanes 20%.

Compound 48:

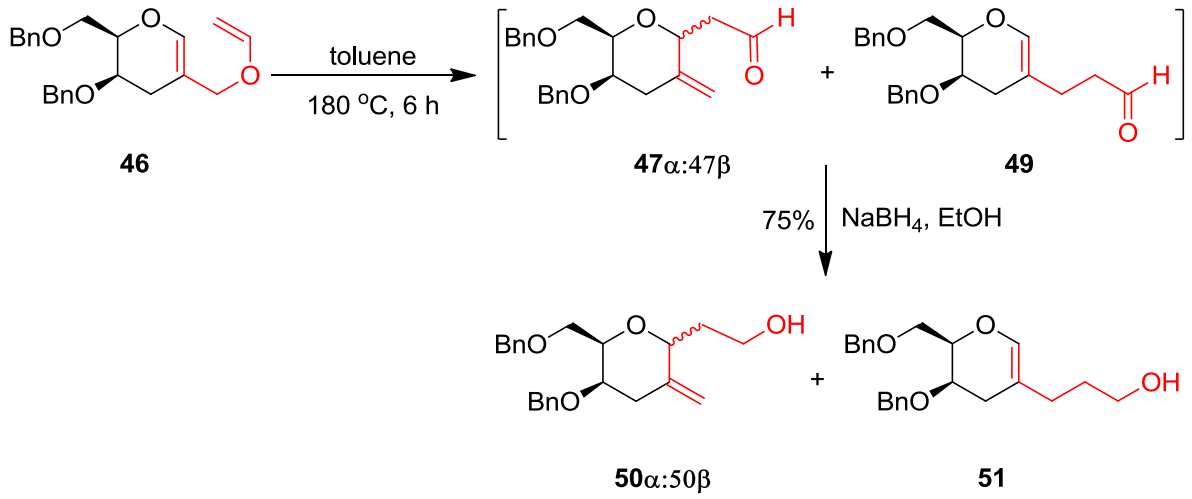
Yield = 30%, R_f = 0.4 in ethyl acetate/hexanes 20%.

^{1}H (500 MHz, CDCl$_3$): δ 9.58 (d, *J* = 7.5 Hz, 1H), 7.25-7.38 (m, 10H), 7.09 (d, *J* = 16.0 Hz, 1H), 6.22 (dd, *J* = 7.5 Hz, J = 16.0 Hz, 1H), 5.60 (d, *J* = 7.0 Hz, 2H), 4.48-4.58 (m, 6H), 3.79 (t, *J* = 7.5 Hz, 1H), 3.69-3.73 (m, 1H), 3.55 (dd, *J* = 6.0 Hz, *J* = 9.5 Hz, 1H), 3.51 (dd, *J* = 5.5 Hz, *J* = 9.5 Hz, 1H), 2.64 (m, 1H), 2.54 (dd, *J* = 7.5 Hz, *J* = 14.0 Hz, 1H) ppm.

^{13}C (125 MHz, CDCl$_3$): δ 193.8, 153.9, 141.6, 137.8, 137.8, 129.0, 128.4, 128.4, 128.3, 128.0, 127.9, 127.8, 127.8, 73.5, 73.1, 71.0, 70.9, 33.2, 29.6 ppm.

Low-resolution MS(EI): m/z: 366 (M^+).

(3.4.2.34) 2-((2*R*,5*R*,6*R*)-5-(benzyloxy)-6-((benzyloxy)methyl)-3-methylenetetrahydro-2*H*-pyran-2-yl)ethanol (50α),2-((2*S*,5*R*,6*R*)-5-(benzyloxy)-6-((benzyloxy)methyl)-3-methylenetetrahydro-2*H*-pyran-2-yl)ethanol (50β) and 3-((2*R*,3*R*)-3-(benzyloxy)-2-((benzyloxy)methyl)-3,4-dihydro-2*H*-pyran-5-yl)propan-1-ol (51):



Compound **50α, 50β** and **51** was synthesized using the 3-deoxy-2-vinyloxymethyl galactal **46** (0.35 g, 0.95 mmol), in toluene according to the procedure in **(3.4.2.4)**. The crude product was further reduced with $NaBH_4$ (36 mg, 0.95 mmol) in ethanol at -10 ^oC, according to the procedure in **(3.4.2.2)** purified by silica-gel column chromatography with ethyl acetate/hexane (4:6) to provide of **50α**:**50β** in 70:30 and **51** as minor, which are inseparable in column chromatography. (75 % yield after two steps).

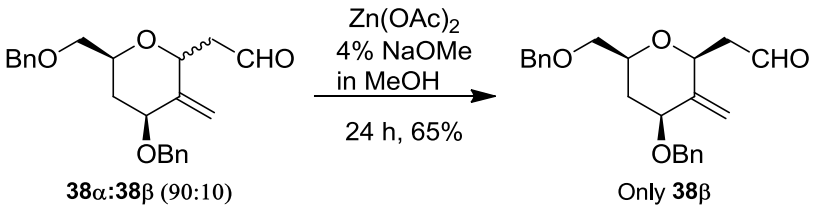
HRMS (ESI) Calcd for $C_{23}H_{28}NaO_4$ 391.1865; found 391.1861.

(3.4.2.35) Zn (II) mediated anomerization of α-*C*-glycoside to β-*C*-glycoside:

2-((5*S*,6*R*)-5-(benzyloxy)-6-((benzyloxy)methyl)-3-methylenetetrahydro-2*H*-pyran-2-yl)ethanol (28β):

To a solution of crude **26α**:**26β** (0.1 g, 0.27 mmol) in 4% NaOMe/MeOH (3 mL) anhydrous $Zn(OAc)_2$ (249 mg, 1.36 mmol) was added at 25 ^oC and continued stirring for a period of 24 h. After complete disappearance of the α-*C*-glycoside (by TLC), the reaction mixture was neutralized slowly with AcOH. The suspension was filtered through a pad of celite and the filter cake was washed with ethylacetate (50 mL). The filtrate was washed with water, brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to provide crude **26β** as colour less gum that was used in the next step without further purification (attempts to purify **26β** were unsuccessful). The obtained crude **26β** (75% (crude)) was immediately taken in dry ethanol (3 mL) and treated with $NaBH_4$ (15 mg, 0.40 mmol) at 0^oC. Stirring was continued for 3 h. After complete disappearance of starting material the reaction was quenched by the addition of aq. NH_4Cl (saturated). Ethanol was removed under reduced pressure and the obtained residue was taken in CH_2Cl_2 (50 mL). The resulting solution was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to obtain crude β-*C*-glycoside. Purification of the crude over silica gel column chromatography provided pure **28β** (67 mg, 67%) as a colour less gum. R_f = 0.62 (EtOAc/hexanes, 40%).

(3.4.2.36) 2-((2*S*,4*S*,6*S*)-4-(benzyloxy)-6-((benzyloxy)methyl)-3-methylenetetrahydro-2*H*-pyran-2-yl)acetaldehyde (38β):



38α:38β (90:10) Only **38β**

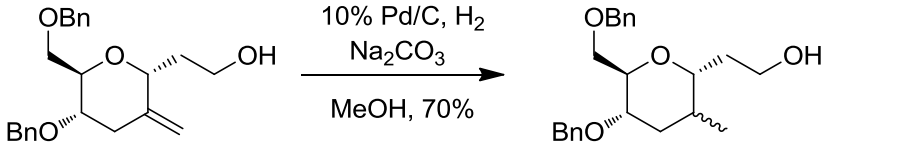
Compound **38β** was synthesized using **38α**:**38β** mixture (0.1 g, 0.27 mmol), in toluene according to the procedure described for **26β**. The crude product purified by silica-gel column chromatography with ethyl acetate/toluene (3:7) to provide **38**β as the single diastereomer in 65 % yield (65 mg). R_f = 0.64 (EtOAc/toluene, 30%).

^{1}H (400 MHz , CDCl$_3$): δ 9.82 (t, 1H, *J* = 1.6 Hz), 7.26-7.36 (m, 10H), 5.36 (d, 1H, *J* = 2 Hz), 4.89 (s, 1H), 4.61-4.68 (m, 2H), 4.51-4.57 (m, 2H), 4.27 (t, 1H, *J* = 6 Hz), 4.00 (dd, 1H, *J* = 4.8 Hz, *J* = 11.2 Hz), 3.79 (m, 1H), 3.50 (dd, 1H, *J* = 5.2 Hz, *J* = 10.8 Hz), 3.45 (dd, 1H, *J* = 8.8 Hz, *J* = 16 Hz), 2.76-2.87 (m, 2H), 2.17 (ddd, 1H, *J* = 1.6 Hz, *J* = 4 Hz, *J* = 11.2 Hz), 1.42 (m, 1H) ppm.

^{13}C (100 MHz, CDCl$_3$): δ 200.8, 145.5, 138.3, 138.1, 128.4, 128.4, 127.7, 127.3, 106.4, 75.4, 73.4, 72.8, 71.0, 60.4, 45.3, 37.1ppm.

HRMS (ESI) Calcd for $C_{23}H_{27}O_4$+H 367.1909; found 367.1908.

(3.4.2.37) 2-((2*R*,3*R*,5*S*,6*R*)-5-(benzyloxy)-6-((benzyloxy)methyl)-3-methyltetrahydro-2*H*-pyran-2-yl)ethanol (52a) and 2-((2*R*,3*S*,5*S*,6*R*)-5-(benzyloxy)-6-((benzyloxy)methyl)-3-methyltetrahydro-2*H*-pyran-2-yl)ethanol (52b):



28α (**52a**) 1,2-*cis* : (**52b**)1,2-*trans* = 75:25

Compound **52a, 52b** was synthesized using the compound **28α** (0.2 g, 0.42 mmol), Na_2CO_3 (134 mg, 1.27 mmol) in methanol according to the procedure in **(3.4.2.5)**. The crude product was purified by silica-gel column chromatography with ethyl acetate/hexane (2:8) to

provide the **(52a**) 1,2-*cis* : **(52b**) 1,2-*trans* in 75:25 ratio as a colourless gum (70 % yield). R_f = 0.64 (EtOAc/hexanes, 40%).

Compound 52a:

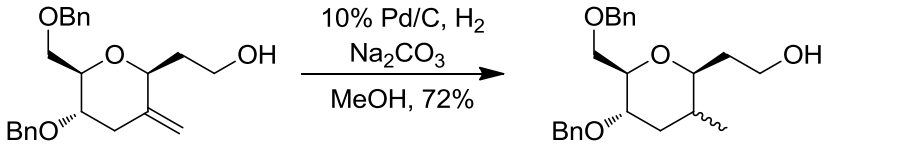
^{1}H (500 MHz, $CDCl_3$): δ 7.24-7.36 (m, 10H), 4.63 (d, 1H, *J* = 12.0 Hz), 4.62 (d, 1H, *J* = 11.5 Hz), 4.56 (d, 1H, *J* = 12.5 Hz), 4.40 (d, 1H, *J* = 11.5 Hz), 3.99-4.03 (m, 1H), 3.85-3.87 (m, 2H), 3.78-3.80 (m, 2H), 3.58 (dd, 1H, *J* = 7.0 Hz, *J* = 10.5 Hz), 3.36-3.41 (m, 1H), 2.78 (bs, 1H), 2.06-2.21 (m, 3H), 1.35-1.47 (m, 2H), 0.90 (d, 3H, *J* = 7.0 Hz) ppm.

^{13}C (125 MHz, $CDCl_3$): δ 138.4, 138.2, 128.4, 128.3, 127.7, 127.6, 127.5, 77.2, 74.1, 73.5, 71.8, 70.6, 70.2, 61.7, 32.9, 32.8, 26.2, 17.1 ppm.

HRMS (ESI) calcd for $C_{23}H_{30}O_4$+Na 393.2042; found 393.2042.

Compound 52b: This compound was not resolved in column chromatography and obtained along with **52a**.

(3.4.2.38) 2-((2*S*,3*S*,5*S*,6*R*)-5-(benzyloxy)-6-((benzyloxy)methyl)-3-methyltetrahydro-2*H*-pyran-2-yl)ethanol (53a) 2-((2*S*,3*R*,5*S*,6*R*)-5-(benzyloxy)-6-((benzyloxy)methyl)-3-methyltetrahydro-2*H*-pyran-2-yl)ethanol (53b):



28β (**53a**) 1,2-*cis* : (**53b**)1,2-*trans* = 75:25

Compound **53a**, **53b** was synthesized using the compound **28β** (0.5 g, 1.35 mmol), Na_2CO_3 (432 mg, 4.07 mmol) in methanol according to the procedure in **(3.4.2.5)**. The crude product was purified by silica-gel column chromatography with ethyl acetate/hexane (4:6) to provide the (**53a)** 1,2-*cis* : (**53b)** 1,2-*trans* in 75:25 ratio as a colourless gumin70 % yield (360 mg). For **53a** R_f = 0.66 (EtOAc/hexanes, 40%).

Compound 53a:

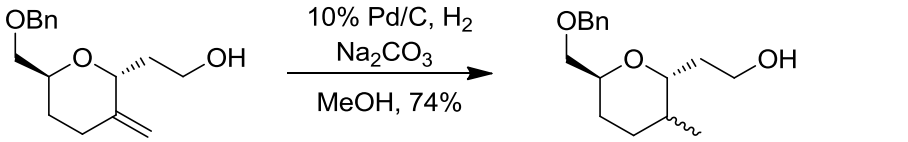
^{1}H (500 MHz, $CDCl_3$): δ 7.24-7.35 (m, 10H), 4.60 (d, 1H, *J* = 12.0 Hz), 4.57 (d, 1H, *J* = 11.5 Hz), 4.55 (d, 1H, *J* = 12.0 Hz), 4.39 (d, 1H, *J* = 11.5 Hz), 3.80-3.86 (m, 2H), 3.77 (dd, 1H, *J* = 1.5 H, *J* = 11.0 Hz), 3.73 (dt, 1H, *J* = 2.5 Hz, *J* = 10.5 Hz), 3.60 (dd, 1H, *J* = 6.5 Hz, *J* = 10.5 Hz), 3.50-3.53 (m, 2H), 2.11-2.14 (m, 1H), 1.87-1.92 (m, 2H), 1.47-1.52 (m, 2H), 1.00 (d, 3H, *J* = 7.5 Hz) ppm.

^{13}C (125 MHz, $CDCl_3$): δ 138.4, 138.3, 128.3, 127.7, 127.6, 127.6, 127.5, 80.9, 80.8, 73.4, 71.0, 70.3, 70.1, 62.3, 36.9, 34.7, 33.1, 13.0 ppm.

HRMS (ESI) calcd for $C_{23}H_{30}O_4$+Na 393.2042; found 393.2042.

Compound 53b: This compound was not resolved in column chromatography and obtained along with **53a**.

(3.4.2.39) 2-((2*R*,3*R*,6*S*)-6-((benzyloxy)methyl)-3-methyltetrahydro-2*H*-pyran-2-yl)ethanol (54a) and 2-((2*R*,3*S*,6*S*)-6-((benzyloxy)methyl)-3-methyltetrahydro-2*H*-pyran-2-yl)ethanol (54b):

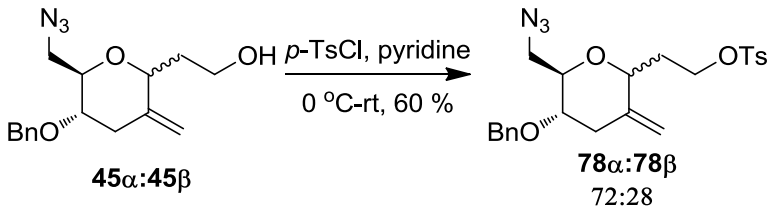


41α (**54a**) 1,2-*cis* : (**54b**) 1,2-*trans* = 73:27

Compounds **54a** and **54b** were synthesized using the compound **41α** (110 mg, 0.41 mmol), Na_2CO_3 (130 mg, 1.23 mmol) in methanol according to the procedure in **(3.4.2.5)**. The crude mixture was not resolved in silica-gel column chromatography with ethyl acetate/hexane (4:6), in 74 % yield (82 mg). For **54a** R_f = 0.44 (EtOAc/hexanes, for **54b** 0.45, 40%).

HRMS (ESI) Calcd for $C_{16}H_{24}O_3$+H 265.1805; found 265.1804.

(3.4.2.40) 2-((2*R*,5*S*,6*R*)-6-(azidomethyl)-5-(benzyloxy)-3-methylenetetrahydro-2*H*-pyran-2-yl)ethyl 4-methylbenzenesulfonate (78α) and 2-((2*S*,5*S*,6*R*)-6-(azidomethyl)-5-(benzyloxy)-3-methylenetetrahydro-2*H*-pyran-2-yl)ethyl 4-methylbenzenesulfonate (78β):



45α:45β **78α:78β** 72:28

Compound **78α**, **78β** was synthesized from **45** (mixture).To a stirred solution of compound **45** (0.5 g, 1.65 mmol) in dry pyridine (5 mL) at 0 °C, *p*-toluene sulphonylchloride was added and stirring was continued for 5 h at room temperature, after completion of the reaction pyridine was removed through high vacuum, the obtained crude was dissolved in dichloromethane (2x200 mL), washed with aqueous copper sulphate solution then water, brine and dried over anhydrous Na_2SO_4, evaporation followed by column chromatography provided **78α** and **78β** as pure compounds in 60% yield (**78α** = 324 mg, **78β** = 126 mg). For **78**α R_f = 0.62 in 20% Ethylacetate/hexanes, For **78**β R_f = 0.61 in 20% Ethylacetate/hexanes.

Compound 78α:

^{1}H (500 MHz, $CDCl_3$): δ 7.18 (dd, *J* = 1.5 Hz, *J* = 6.5 Hz, 2H),7.35-7.38 (m, 2H), 7.28-7.33 (m, 5H), 4.88 (s, 1H), 4.85 (s, 1H), 4.62 (d, *J* = 11.5 Hz, 1H), 4.43 (d, *J* = 11.5 Hz, 1H), 4.29 (q, *J* = 6.0 Hz, 1H), 4.09-4.14 (m, 2H), 3.55 (m, 1H), 3.40 (dd, *J* = 2.5 Hz, *J* = 13.0 Hz, 1H), 3.35 (m, 1H), 3.31 (dd, *J* = 6.0 Hz, *J* = 12.5 Hz, 1H), 2.75 (dd, *J* = 5.0 Hz, *J* = 13.0 Hz, 1H), 2.46 (s, 3H), 2.21-2.28 (m, 2H), 1.86-1.93 (m, 1H) ppm.

^{13}C (125 MHz, $CDCl_3$): δ 144.8, 141.8, 137.7, 132.9, 129.8, 128.5, 127.9, 127.7, 112.5, 75.1, 74.2, 72.2, 70.9, 66.9, 51.8, 34.4, 29.9, 21.6 ppm.

HRMS (ESI) calcd for $C_{23}H_{27}N_3O_5S$+Na 480.1569; found 480.1565.

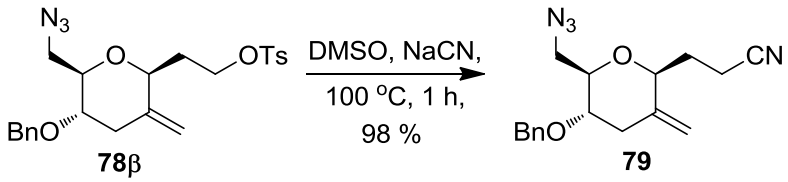
Compound 78β:

^{1}H (500 MHz, $CDCl_3$): δ 7.81 (dd, *J* =1.5 Hz, *J* = 6.5 Hz, 2H), 7.35-7.39 (m, 2H), 7.28-7.33 (m,5H), 4.90 (s, 1H), 4.81 (s, 1H), 4.63 (d, *J* = 11.0 Hz, 1H), 4.42 (d, *J* = 11.5 Hz, 1H), 4.42-4.29 (m,2H), 3.89 (d, *J* = 9.5 Hz, 1H), 3.43-3.46 (m,1H), 3.34-3.39 (m, 2H), 3.26 (dd, *J* = 5.0 Hz, *J* = 13.0 Hz, 1H), 2.88 (dd, *J* = 5.0 Hz, *J* = 13.0 Hz, 1H), 2.46 (s, 3H), 2.17-2.23 (m, 2H), 1.85-1.91 (m, 1H) ppm.

^{13}C (125 MHz, $CDCl_3$): δ 144.7, 142.8, 137.7, 132.8, 129.8, 128.5, 127.9, 127.7, 109.8, 79.9, 75.1, 73.6, 70.9, 67.2, 51.8, 38.5, 31.0, 21.6 ppm.

HRMS (ESI) calcd for $C_{23}H_{27}N_3O_5S$+Na 480.1569; found 480.1567.

(3.4.2.41) 3-((2*S*,5*S*,6*R*)-6-(azidomethyl)-5-(benzyloxy)-3-methylenetetrahydro-2*H*-pyran-2-yl)propanenitrile (79):



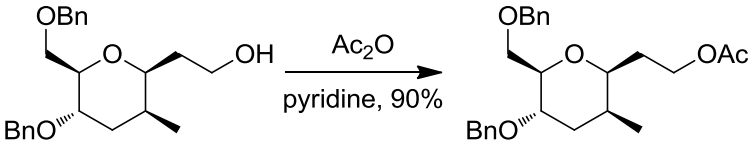
Compound **79** was synthesized from **78β**. To a stirred solution of compound **78β** (0.11 g, 0.24 mmol) in dry DMSO (3 mL) at room temperature, sodium cyanide was added and stirring was continued for 1 h at 100 °C, after completion of the reaction reaction mixture was dissolved in diethyl ether (30 mL) washed with water, brine and dried over anhydrous Na_2SO_4, evaporation followed by column chromatography provided **79** in 98% yield (73 mg). R_f = 0.5 in 20% Ethylacetate/hexanes.

^{1}H (500 MHz, $CDCl_3$): δ 7.28-7.39 (m, 5H), 4.96 (s, 1H), 4.87 (s, 1H), 4.65 (d, *J* = 11.5 Hz, 1H), 4.45 (d, *J* = 11.5 Hz, 1H), 3.94 (d, *J* = 9.0 Hz, 1H), 3.60-3.64 (m, 1H), 3.50 (dd, *J* = 2.0 Hz, *J* = 13.0 Hz, 1H), 3.39-3.44 (m, 1H), 3.34 (dd, *J* = 6.5 Hz, *J* = 13.0 Hz, 1H), 2.90 (dd, *J* = 4.5 Hz, *J* = 13.0 Hz, 1H), 2.58 (dd, J = 11.5 Hz, *J* = 19.5 Hz, 2H), 2.25 (q, *J* = 11.0 Hz, 1H), 2.11-2.17 (m, 1H), 1.94- 2.00 (m, 1H) ppm.

^{13}C (125 MHz, $CDCl_3$): δ 142.5, 137.7, 128.5, 127.9, 127.7, 119.5, 110.1, 80.1, 75.6, 75.0, 70.9, 51.9, 38.3, 27.5, 13.5 ppm.

HRMS (ESI) calcd for $C_{17}H_{20}N_4O_2$+H31.1665; found 313.1657.

(3.4.2.42) 2-((2*S*, 3*S*, 5*S*, 6*R*)-5-(benzyloxy)-6-((benzyloxy) methyl)-3-methyltetrahydro-2*H*-pyran-2-yl)ethyl acetate (82):



53a (1,2-*cis*) **82**

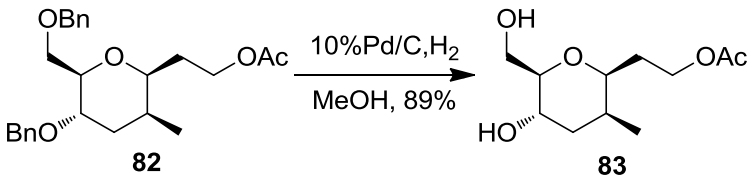
Acetic anhydride (359 µL, 3.80 mmol) was added slowly at 0 °C to a solution of **53a** (0.35 g, 0.95 mmol) in dry pyridine (7 mL). After stirring for 4 h at room temperature, pyridine was evaporated under reduced pressure and the obtained residue was dissolved in CH_2Cl_2 (50 mL). The obtained solution was washed with aqueous copper sulphate solution, water, brine and dried over anhydrous Na_2SO_4. Evaporation of the solvent followed by purification of the crude product over silica-gel column chromatography gave **82** (0.31 g, 90%) as a colour less oil. R_f = 0.65 (EtOAc/hexanes, 20%).

^{1}H (400 MHz, $CDCl_3$): δ 7.25-7.35 (m, 10H), 4.66 (d, 1H, *J* = 12.4 Hz), 4.56 (d, 2H, *J* = 12 Hz), 4.40 (d, 1H, *J* = 11.2 Hz), 4.13-4.23 (m, 2H), 3.76 (dd, 1H, *J* = 2.0 Hz, *J* = 10.8 Hz), 3.71 (dd, 1H, *J* = 4.8 Hz, *J* = 10.8 Hz), 3.59-3.66 (m, 1H), 3.55-3.58 (m, 1H), 3.39 (ddd, 1H, *J* = 2.0 Hz, *J* = 4.8 Hz, *J* = 9.6 Hz), 2.14 (ddd, 1H, *J* = 2.4 Hz, *J* = 4.4 Hz, *J* = 12.4 Hz), 2.06 (s, 3H), 1.85-1.94 (m, 2H), 1.64-1.72 (m, 2H), 0.99 (d, 3H, *J* = 7.2 Hz) ppm.

^{13}C (100 MHz, $CDCl_3$): δ 171.1, 138.6, 138.5, 128.3 128.2, 127.7, 127.5, 127.4, 81.3, 76.4, 73.4, 71.0, 69.9, 69.8, 62.0, 37.0, 32.6, 32.0, 21.0, 12.7 ppm.

HRMS (ESI) calcd for $C_{25}H_{32}O_5$+Na 435.2148; found 435.2144.

(3.4.2.43) 2-((2*S*,3*S*,5*S*,6*R*)-5-hydroxy-6-(hydroxymethyl)-3-methyltetrahydro-2*H*-pyran-2-yl)ethyl acetate (83):



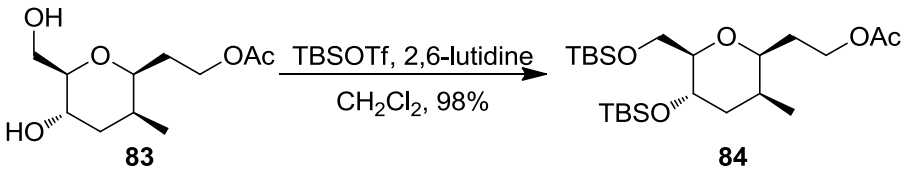
82 **83**

To a solution of ester **82** (240 mg, 0.58 mmol) in MeOH (8 mL) was added 10% Pd/C (20 mg). The reaction mixture was stirred for 24 h under H_2 atmosphere then filtered through a pad of celite and concentrated *in vacuo.* Purification of this residue by column chromatography over silica gel afforded compound **83** (120 mg, 89%) as a colour less oil. R_f = 0.5 (MeOH/$CHCl_3$, 5%).

^{1}H (400 MHz, $CDCl_3$): δ 4.17 (dd, 1H, *J* = 6.0 Hz, *J* = 7.2 Hz), 3.83 (td, 1H, *J* = 4.0 Hz, *J* = 7.6 Hz), 3.77 (dd, 2H, *J* = 4.8 Hz, *J* = 11.6 Hz), 3.56-3.58 (m, 1H), 3.16-3.18 (m, 1H), 2.06 (s, 3H), 1.98-2.03 (m, 1H), 1.77-1.90 (m, 2H), 1.65-1.67 (m, 2H), 0.98 (d, 3H, *J* = 7.2 Hz) ppm.

^{13}C (100 MHz, $CDCl_3$): δ 171.1, 82.0, 76.2, 63.9, 63.5, 61.7, 40.1, 32.8, 31.9, 21.0, 12.6 ppm. **HRMS** (ESI) calcd for $C_{11}H_{20}O_5$+Na 255.1209; found 255.1209.

(3.4.2.44) 2-((2*S*, 3*S*, 5*S*, 6*R*)-5-((tert-butyldimethylsilyl)oxy)-6-(((tert-butyldimethylsilyl)oxy)methyl)-3-methyltetrahydro-2*H*-pyran-2-yl)ethyl acetate (84):



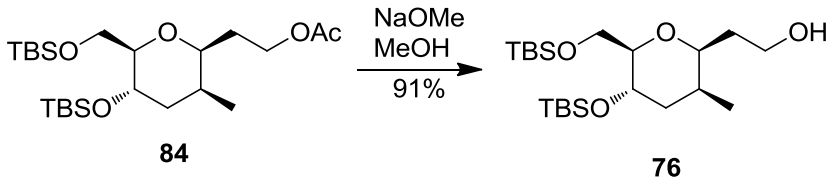
A solution of diol **83** (100 mg, 0.43 mmol) and 2, 6-lutidine (399.25 µL, 3.44 mmol) in dry CH_2Cl_2 (8 mL) was cooled to -78 ^{o}C, *tert*-butyldimethylsilyltirfluoromethanesulfonate (TBSOTf) (395 µL, 1.72 mmol) was added at the same temperature and the reaction mixture was allowed to warm to 0 ^{o}C over a period of 1 h. After completion of the reaction (by TLC) the reaction mixture was diluted with CH_2Cl_2 (30 mL), washed with water, brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to obtain crude product as an oil. Purification of the crude product over silica gel provided compound **84** (195 mg, 98%) as a colorless oil. R_f = 0.5 (EtOAc/hexanes, 5%).

^{1}H (400 MHz, $CDCl_3$): δ 4.14-4.19 (m, 2H), 3.72-3.81 (m, 3H), 3.53 (ddd, 1H, *J* = 2.4 Hz, *J* = 3.6 Hz, *J* = 10.6 Hz), 3.04 (ddd, 1H, *J* = 2.4 Hz, *J* = 4.4 Hz, *J* = 10.2 Hz), 2.06 (s, 3H), 1.76-1.90 (m, 3H), 1.54-1.67 (m, 2H), 0.96 (d, 3H, *J* = 6.8 Hz), 0.90 (s, 9H), 0.88 (s, 9H), 0.07 (s, 6H), 0.06 (s, 6H) ppm.

^{13}C (100 MHz, $CDCl_3$): δ 171.1, 83.5, 75.7, 62.8, 62.7, 62.1, 40.9, 33.0, 32.0, 25.8, 25.7, 21.0, 18.3, 17.9, 12.6, -4.3, -4.9, -5.0, -5.2 ppm.

HRMS (ESI) calcd for $C_{23}H_{48}O_5Si_2$+Na 483.2938; found 483.2938.

(3.4.2.45) 2-((2*S*,3*S*,5*S*,6*R*)-5-((tert-butyldimethylsilyl)oxy)-6-(((tert-butyldimethylsilyl)oxy)methyl)-3-methyltetrahydro-2*H*-pyran-2-yl)ethanol (76):



84 **76**

A solution of compound **84** (150 mg, 0.33 mmol) in dry MeOH (6 mL), was added catalytic amount of sodium methoxide at 25 °C, stirring was continued for 1 h. After completion of reaction the p^H of the reaction was brought to neutral by careful addition of amberlite IR 120 acidic resin. The suspension was filtered, concentrated and the obtained crude product was purified by column chromatography over silica gel to give alcohol **76** (130 mg, 91%) as a colour less oil. R_f = 0.5 (EtOAc/hexanes, 10%).

^{1}H (400 MHz, $CDCl_3$): δ 3.71-3.85 (m, 3H), 3.61-3.71 (m, 3H), 3.19 (ddd, 1H, *J* = 2.4 Hz, *J* = 6.4 Hz, *J* = 10.2 Hz), 1.81-1.88 (m, 3H), 1.61 (td, 1H, *J* = 4.4 Hz, *J* = 11.2 Hz), 1.38-1.41 (m, 1H), 0.99 (d, 3H, *J* = 7.2 Hz), 0.90 (s, 9H), 0.87 (s, 9H), 0.06 (s, 6H), 0.05 (s, 6H) ppm.

^{13}C (100 MHz, $CDCl_3$): δ 83.6, 81.4, 63.2, 63.2, 62.9, 40.9, 34.4, 33.5, 25.9, 25.7, 18.3, 17.9, 13.0, -4.1, -4.9, -5.3, -5.4 ppm.

HRMS (ESI) calcd for $C_{21}H_{46}O_4Si_2$+Na 441.2833; found 441.2833.

3.5 References

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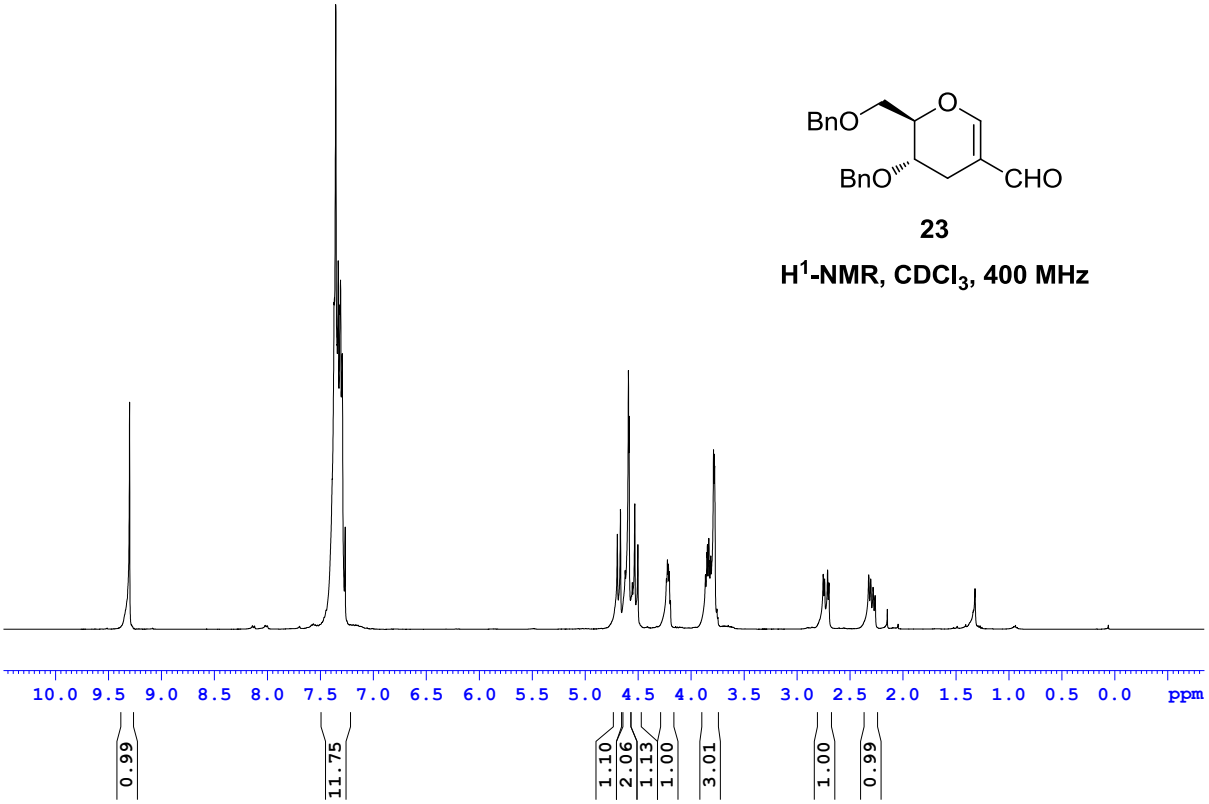
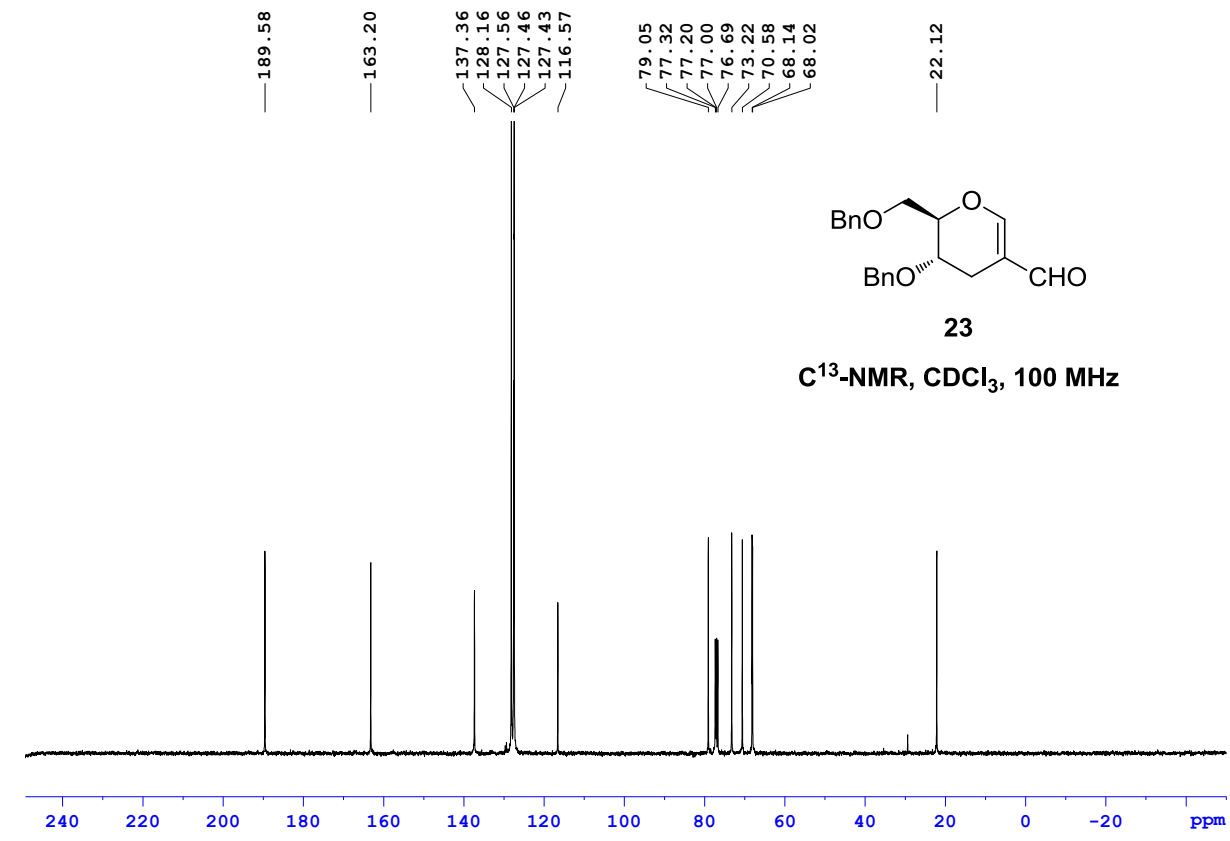


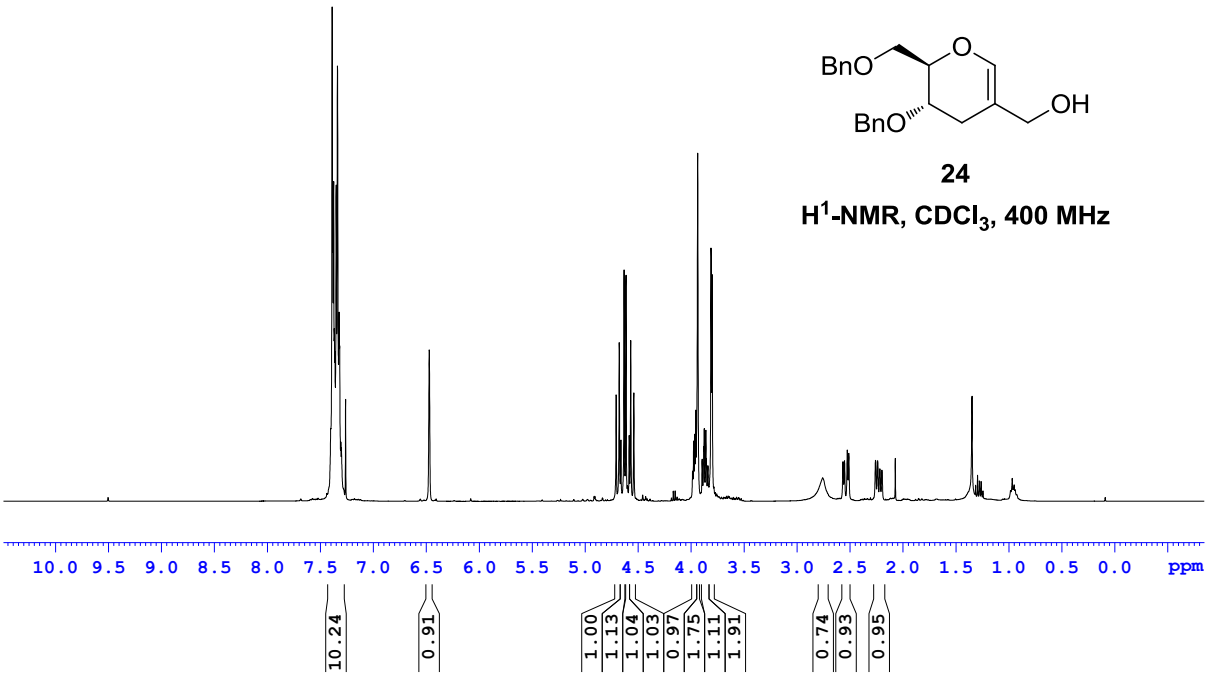
23

H^1-NMR, $CDCl_3$, 400 MHz



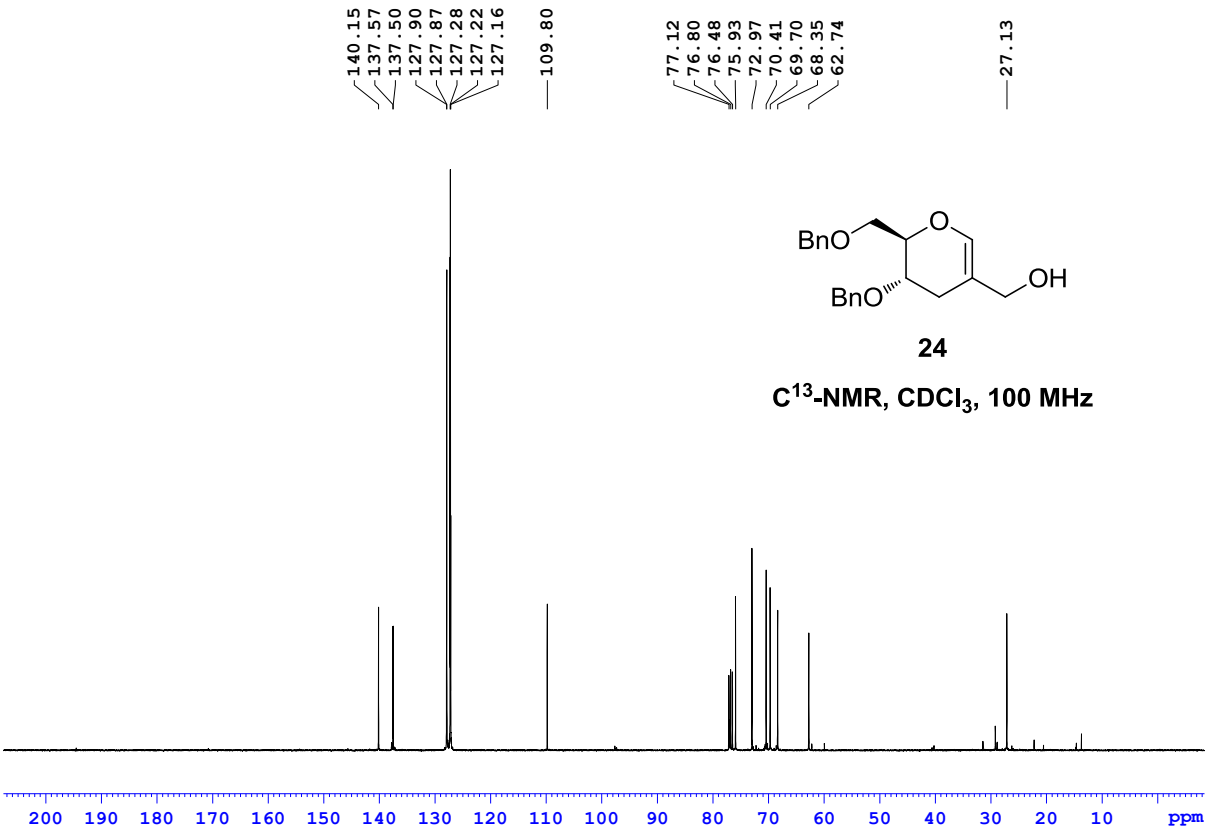
23

C^{13}-NMR, $CDCl_3$, 100 MHz



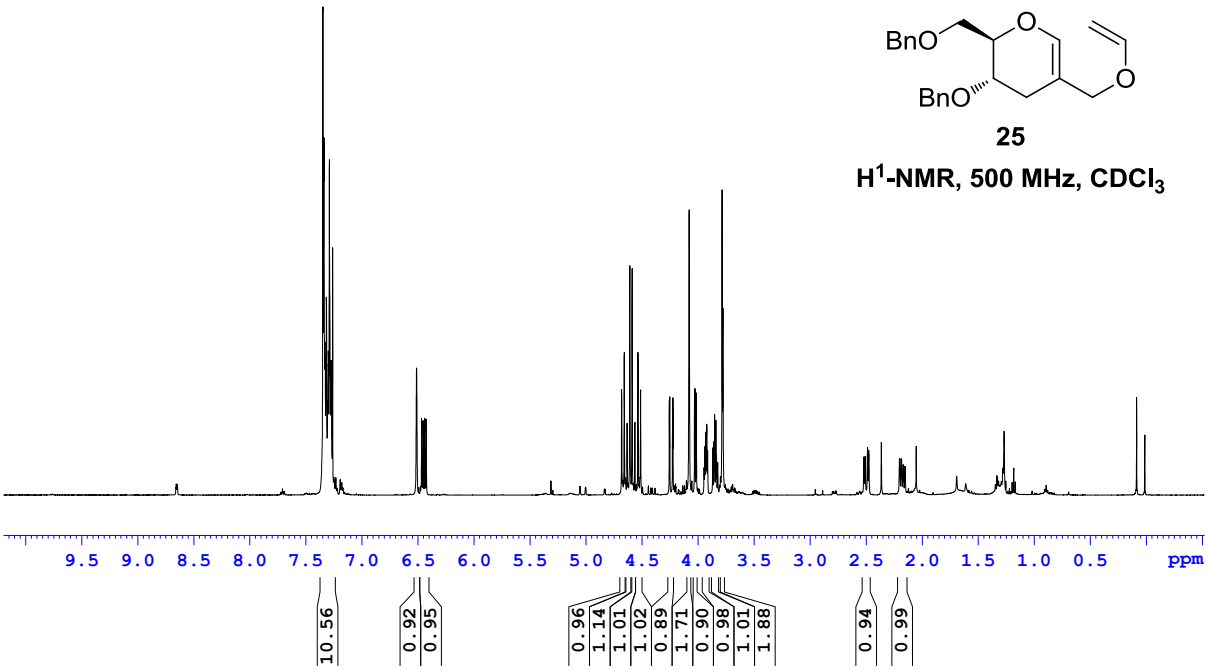
24

H^1-NMR, $CDCl_3$, 400 MHz



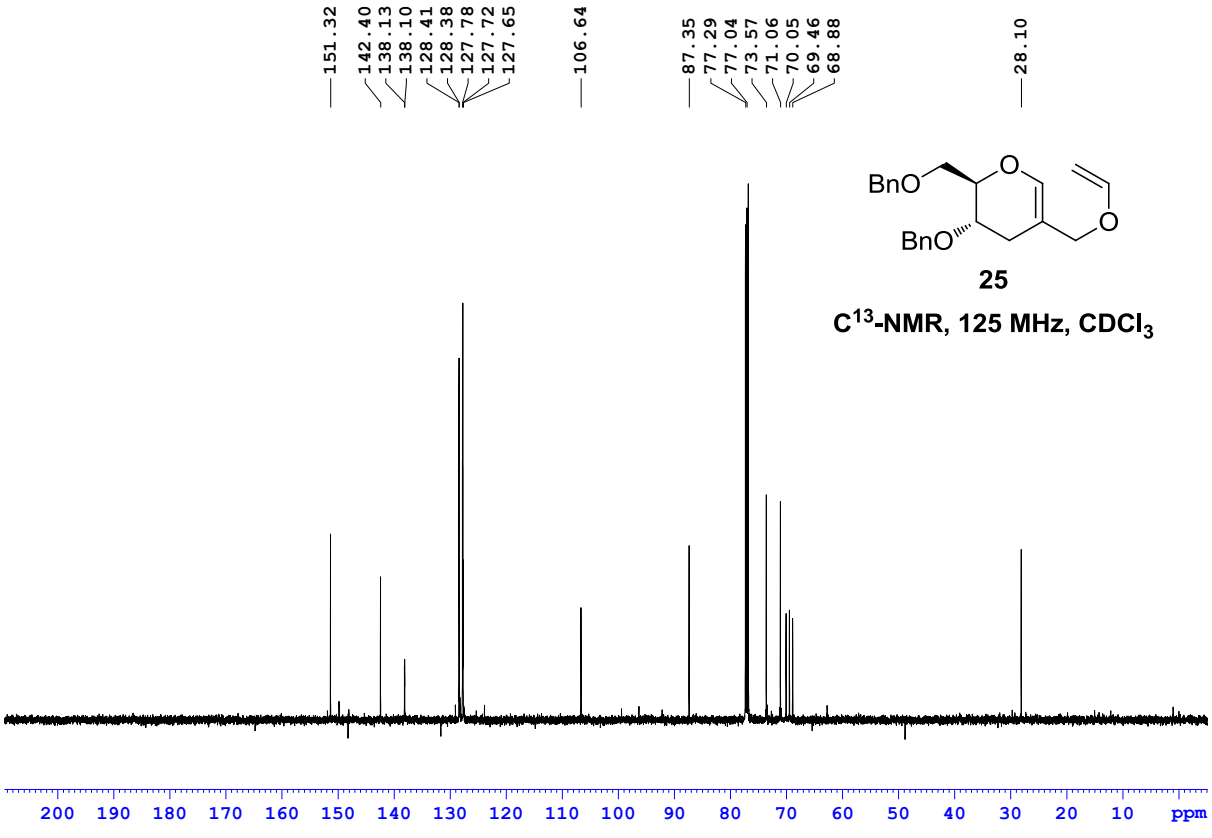
24

C^{13}-NMR, $CDCl_3$, 100 MHz



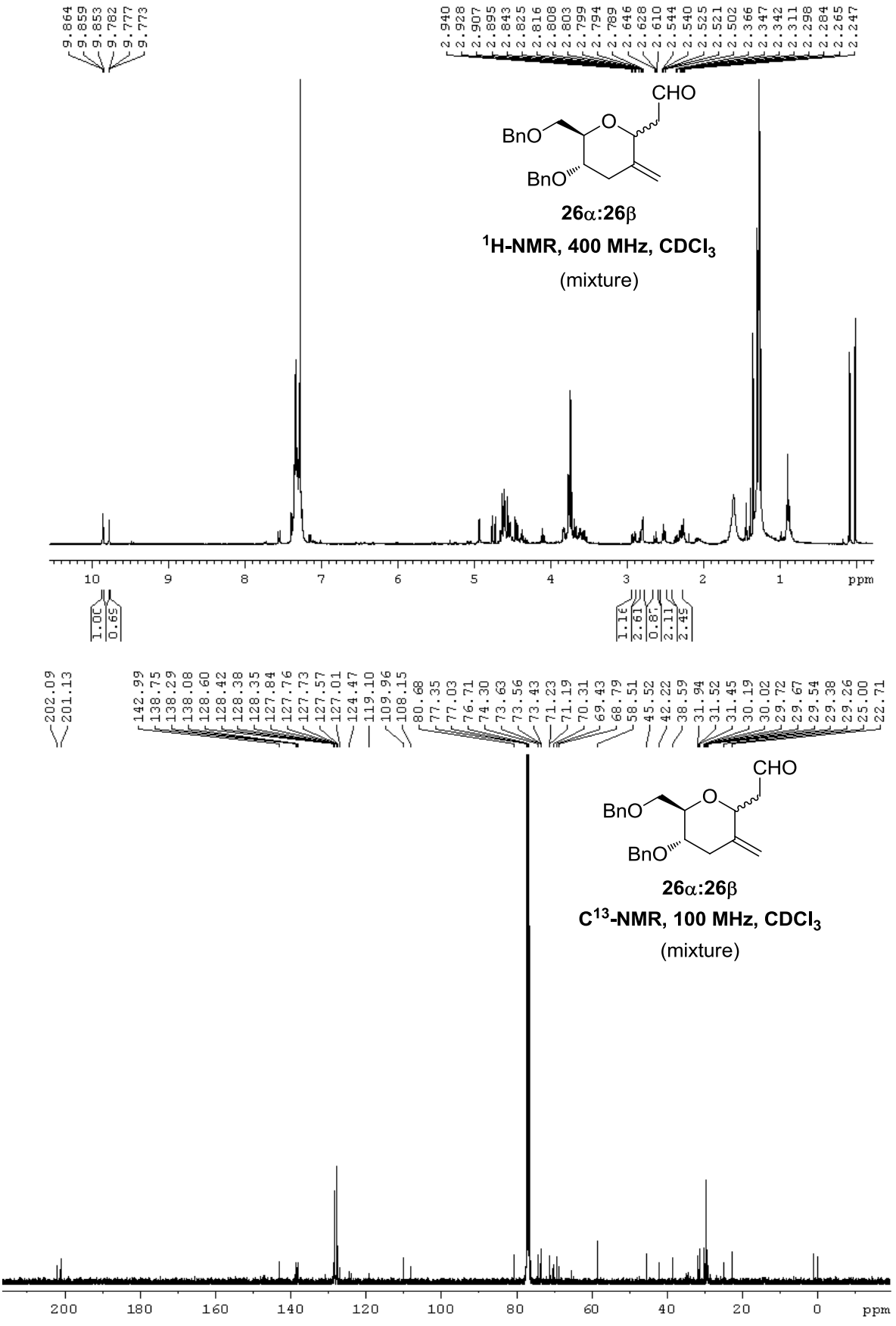
25

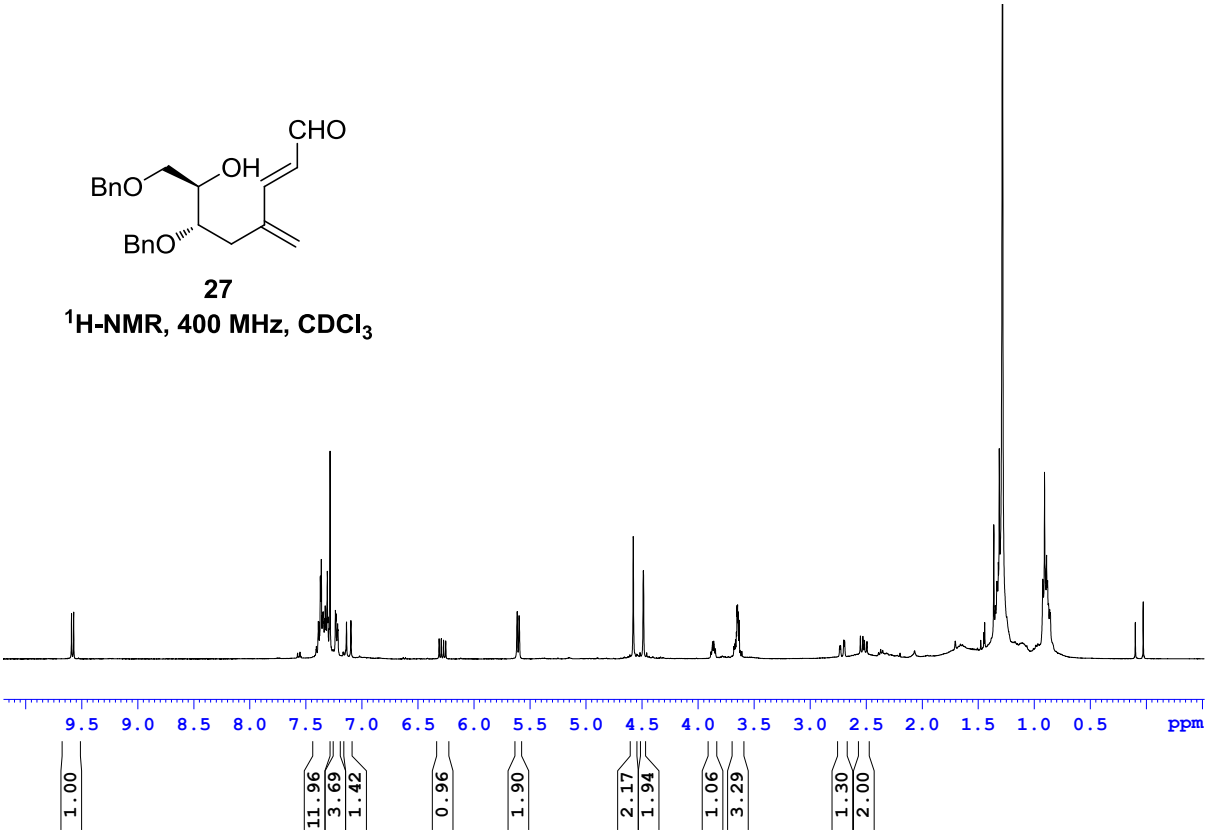
H^1-NMR, 500 MHz, $CDCl_3$



25

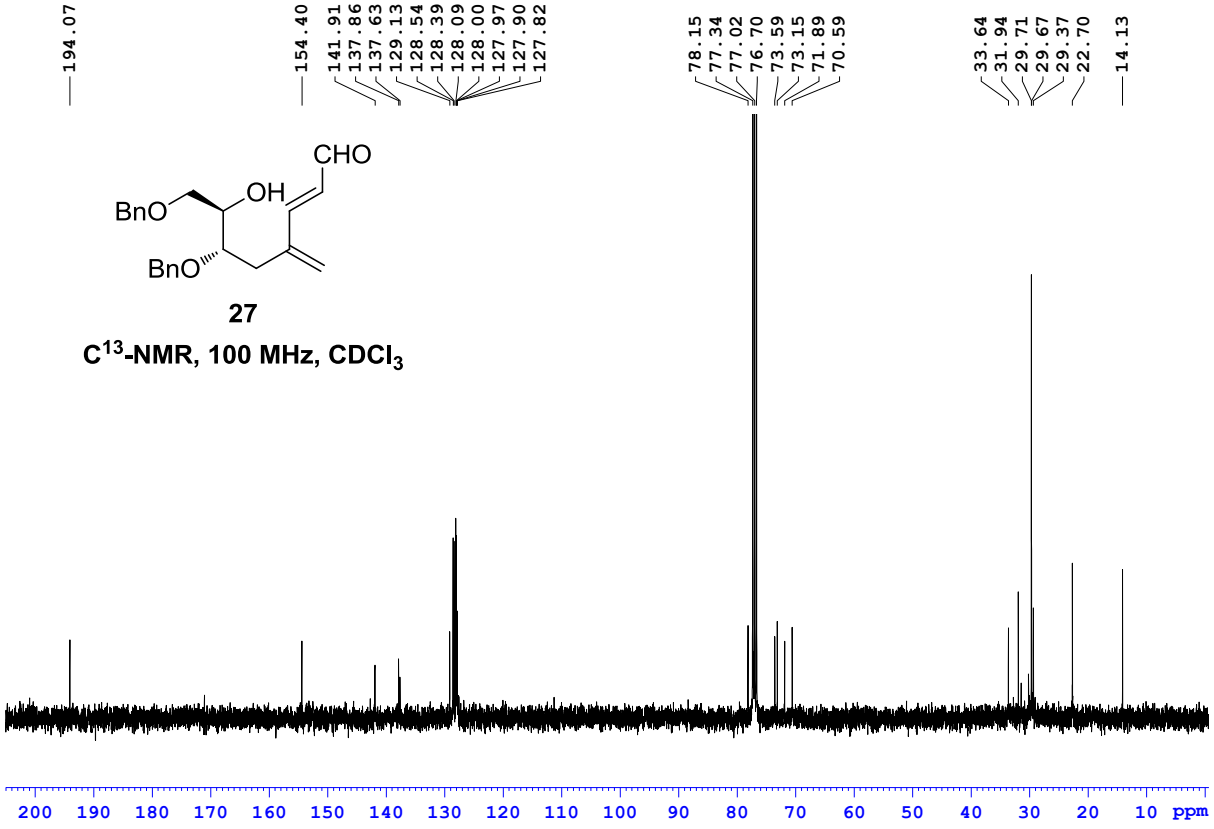
C^{13}-NMR, 125 MHz, $CDCl_3$


9.864
9.859
9.853
9.782
9.777
9.773
2.940
2.928
2.907
2.895
2.843
2.825
2.816
2.808
2.803
2.799
2.794
2.789
2.646
2.628
2.610
2.544
2.540
2.525
2.521
2.502
2.366
2.347
2.342
2.311
2.298
2.284
2.265
2.247
CHO
BnO
O
BnO
26α:26β
1H-NMR, 400 MHz, CDCl3
(mixture)
10
9
8
7
6
5
4
3
2
1
ppm
1.00
0.65
1.16
2.61
0.87
2.11
2.45
202.09
201.13
142.99
138.75
138.29
138.08
128.60
128.42
128.38
128.35
127.84
127.76
127.73
127.57
127.01
124.47
119.10
109.96
108.15
80.68
77.35
77.03
76.71
74.30
73.63
73.56
73.43
71.23
71.19
70.31
69.43
68.79
58.51
45.52
42.22
38.59
31.94
31.52
31.45
30.19
30.02
29.72
29.67
29.54
29.38
29.26
25.00
22.71
CHO
BnO
O
BnO
26α:26β
C13-NMR, 100 MHz, CDCl3
(mixture)
200
180
160
140
120
100
80
60
40
20
0
ppm



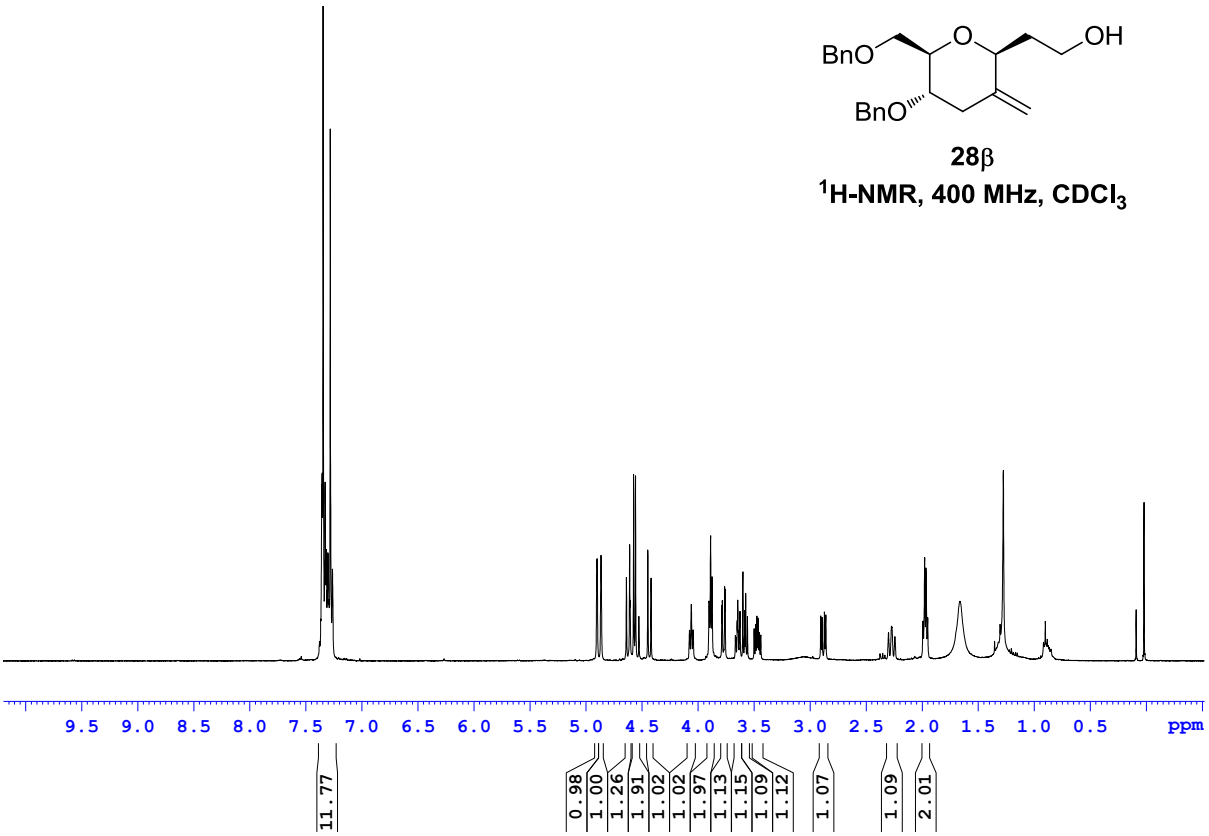
27

^{1}H-NMR, 400 MHz, $CDCl_3$



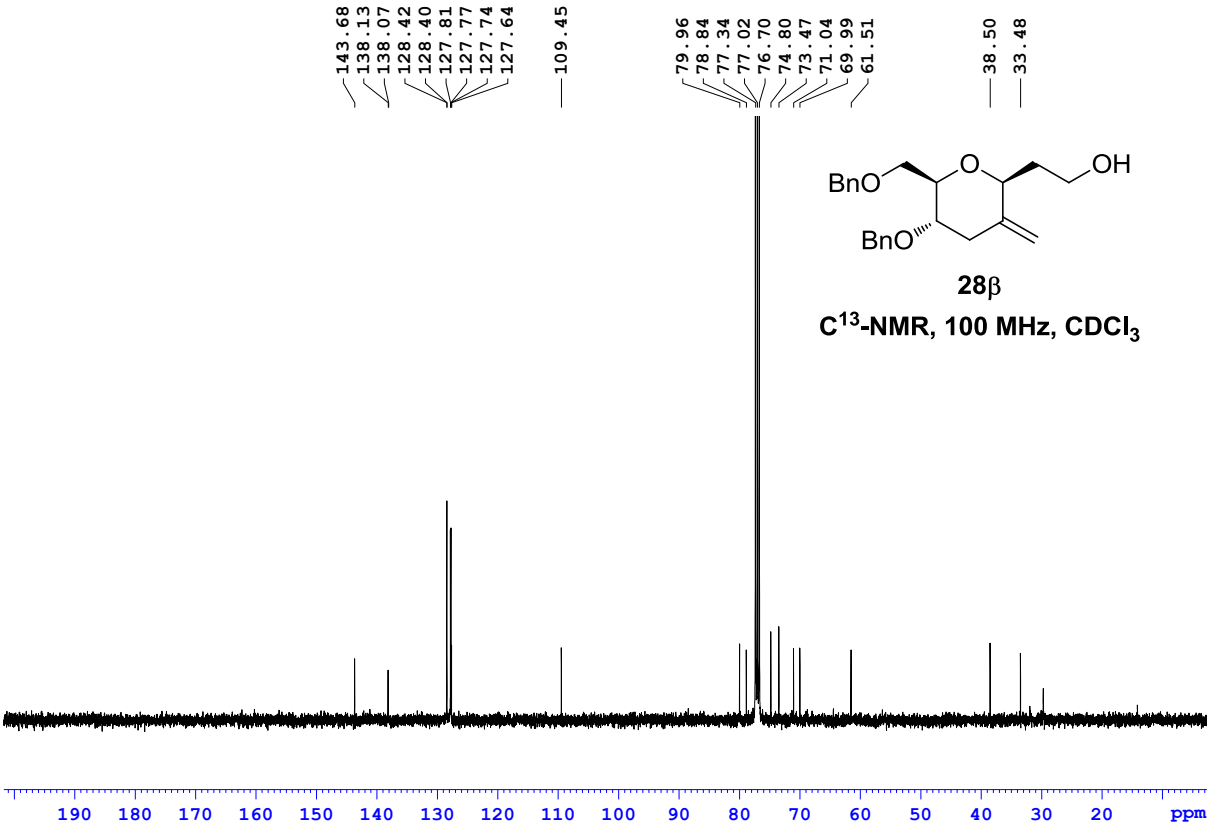
27

C^{13}-NMR, 100 MHz, $CDCl_3$



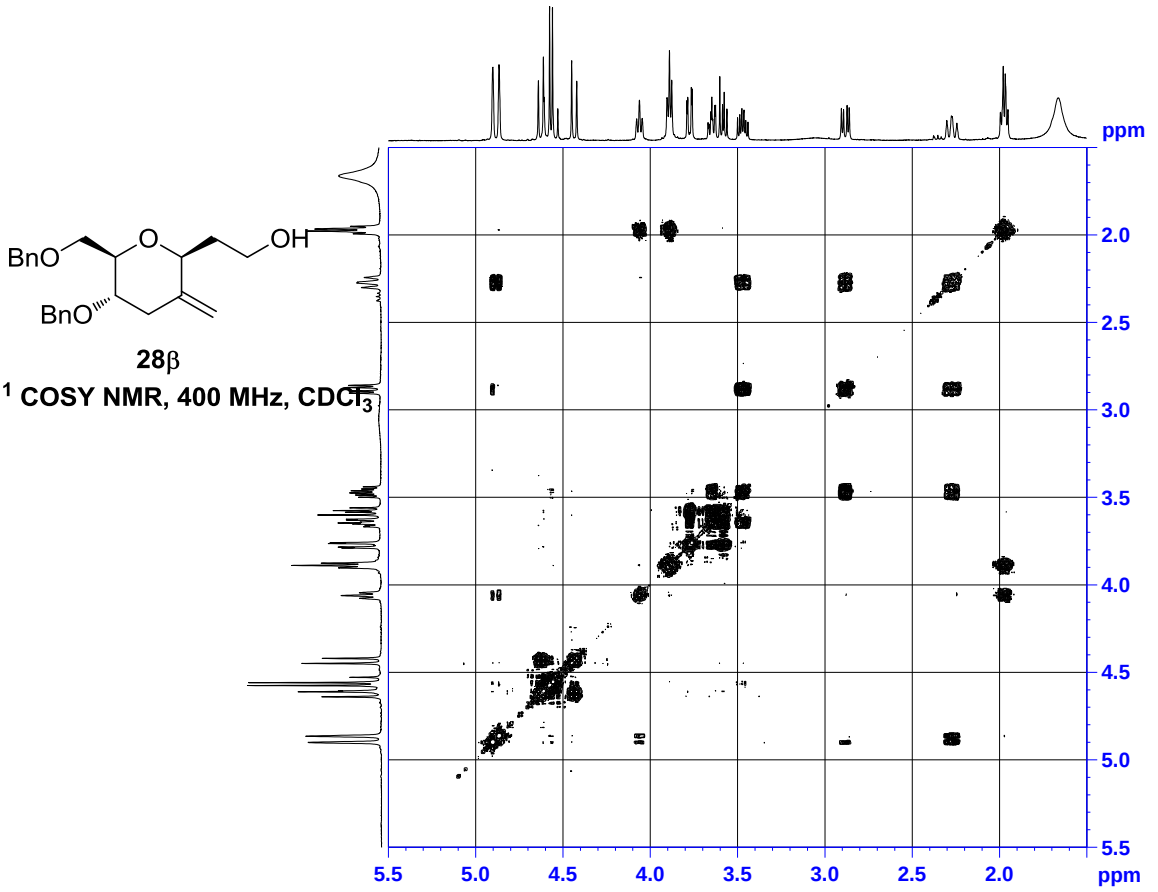
28β

^{1}H-NMR, 400 MHz, $CDCl_3$



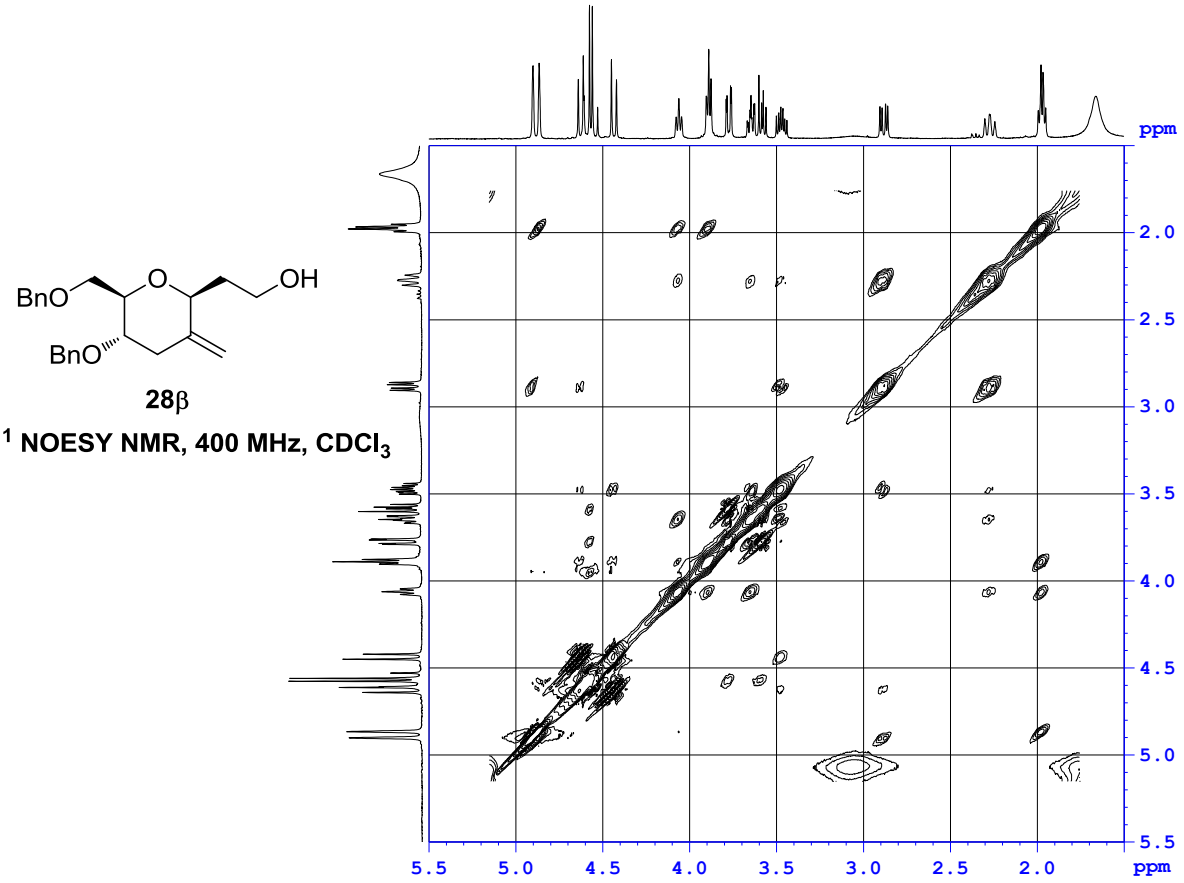
28β

C^{13}-NMR, 100 MHz, $CDCl_3$



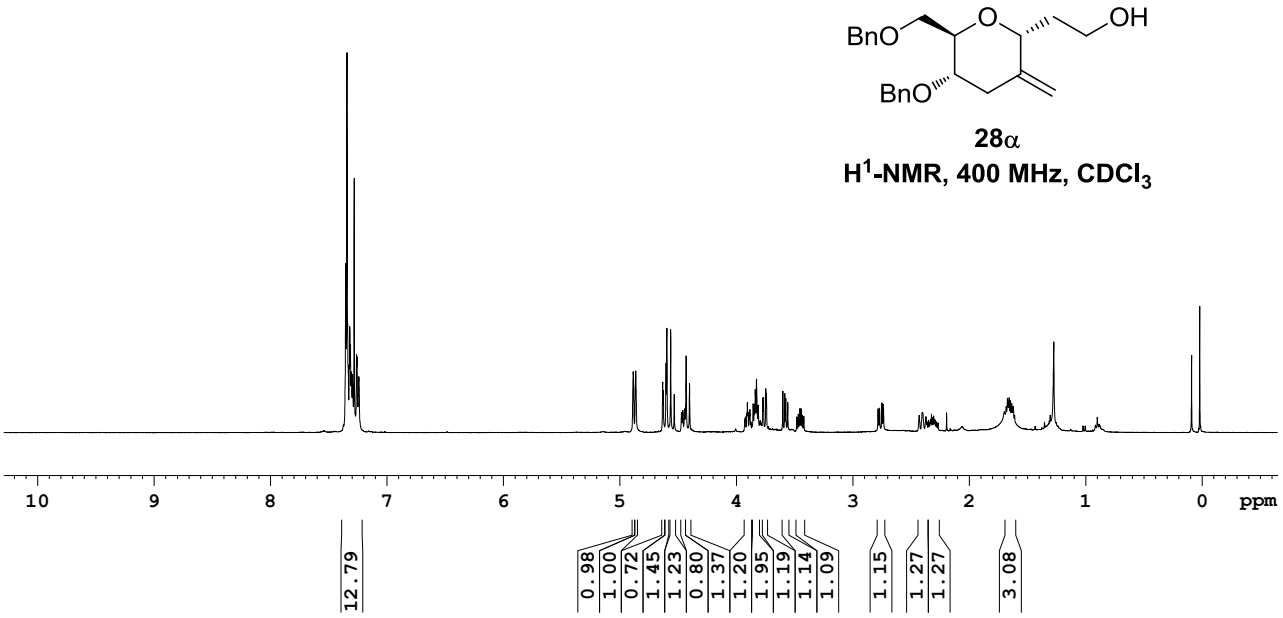
28β

H^1-H^1 COSY NMR, 400 MHz, $CDCl_3$



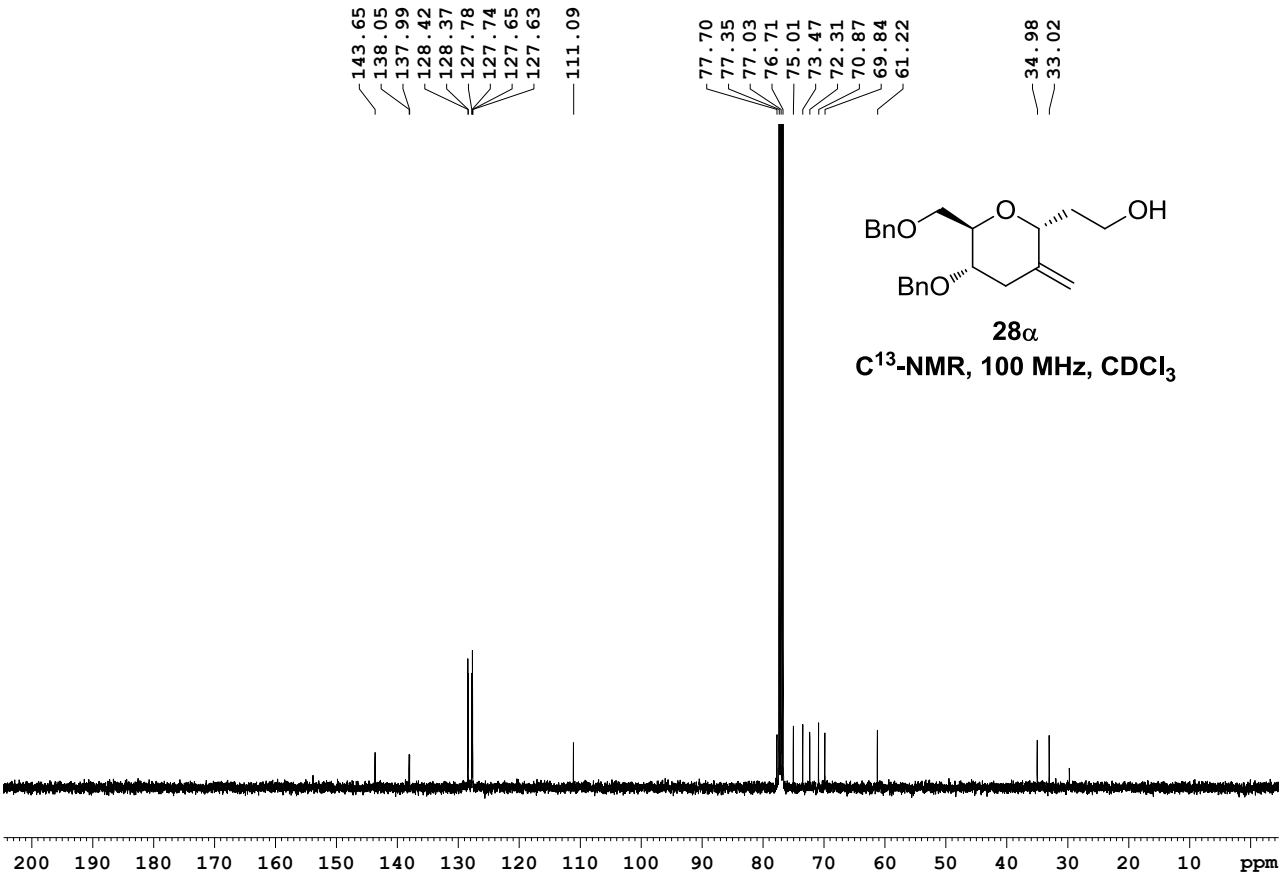
28β

H^1-H^1 NOESY NMR, 400 MHz, $CDCl_3$



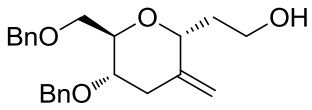
28α

H^1-NMR, 400 MHz, $CDCl_3$



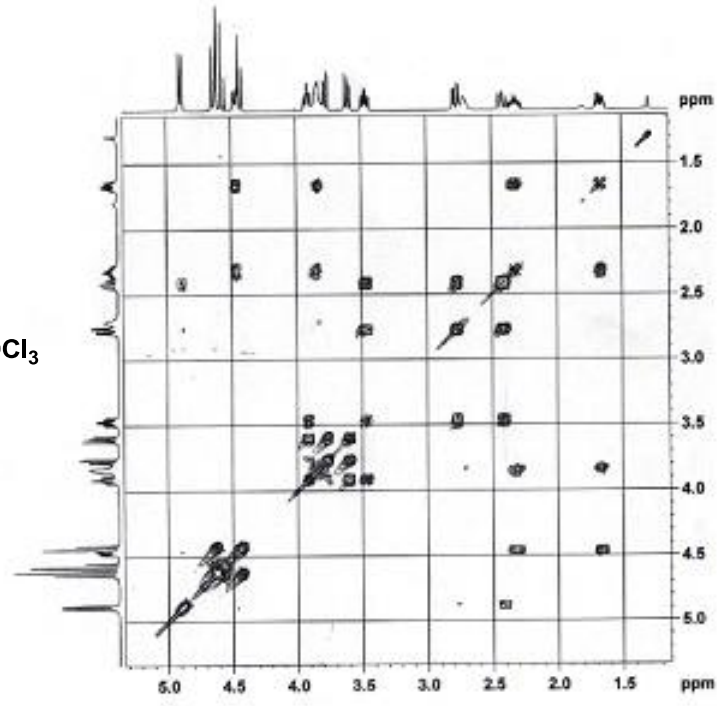
28α

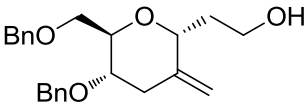
C^{13}-NMR, 100 MHz, $CDCl_3$



28α

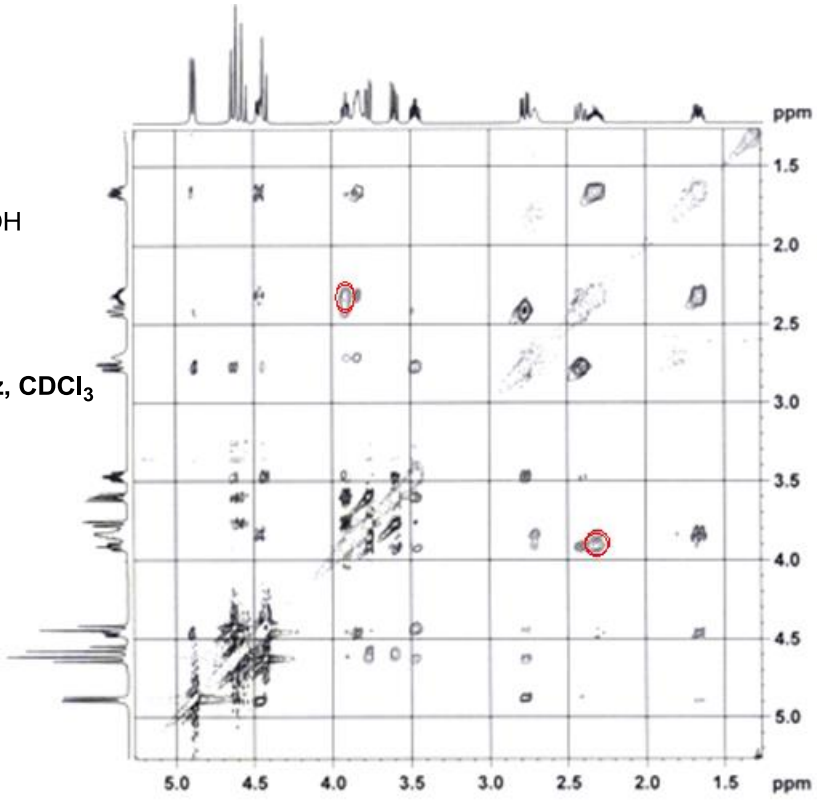
H^1-H^1 COSY NMR, 400 MHz, $CDCl_3$

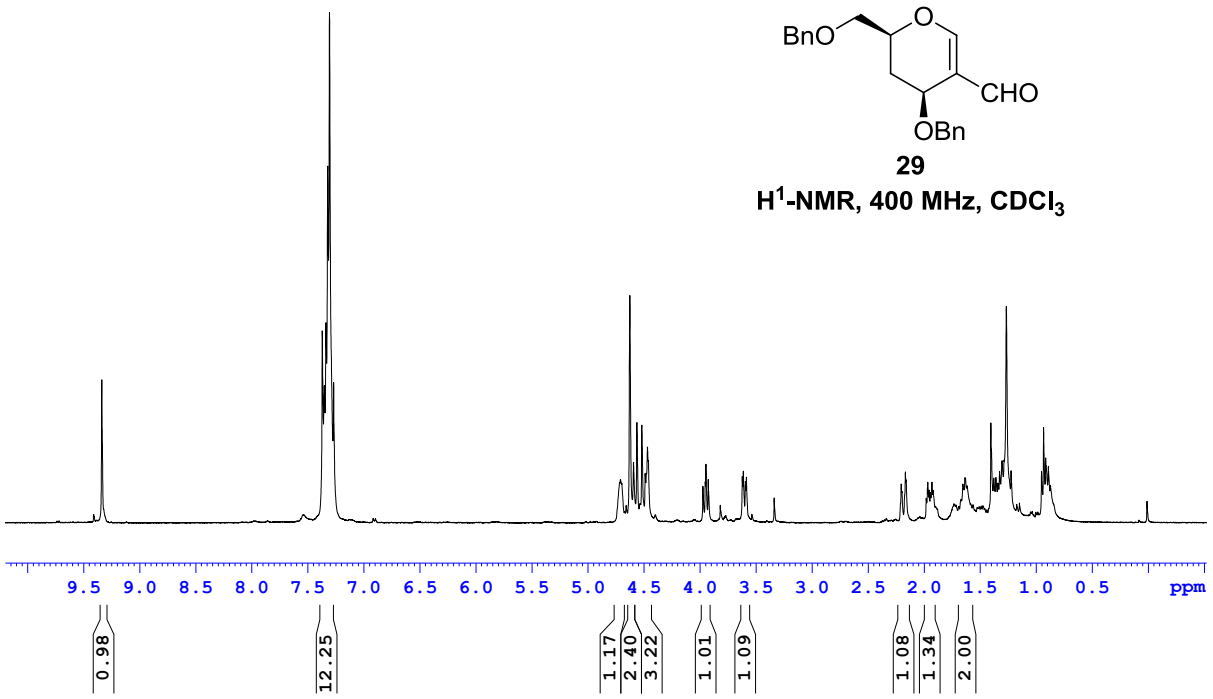




28α

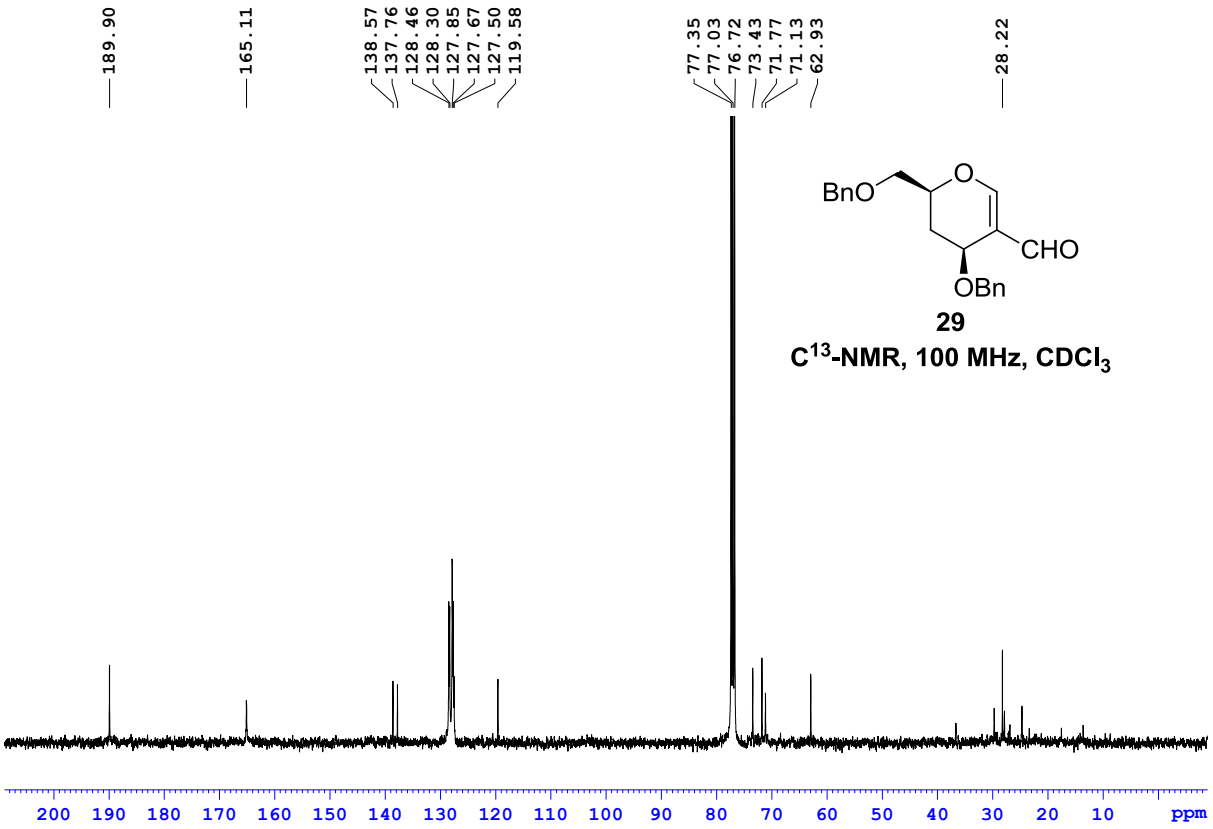
H^1-H^1 NOESY NMR, 400 MHz, $CDCl_3$





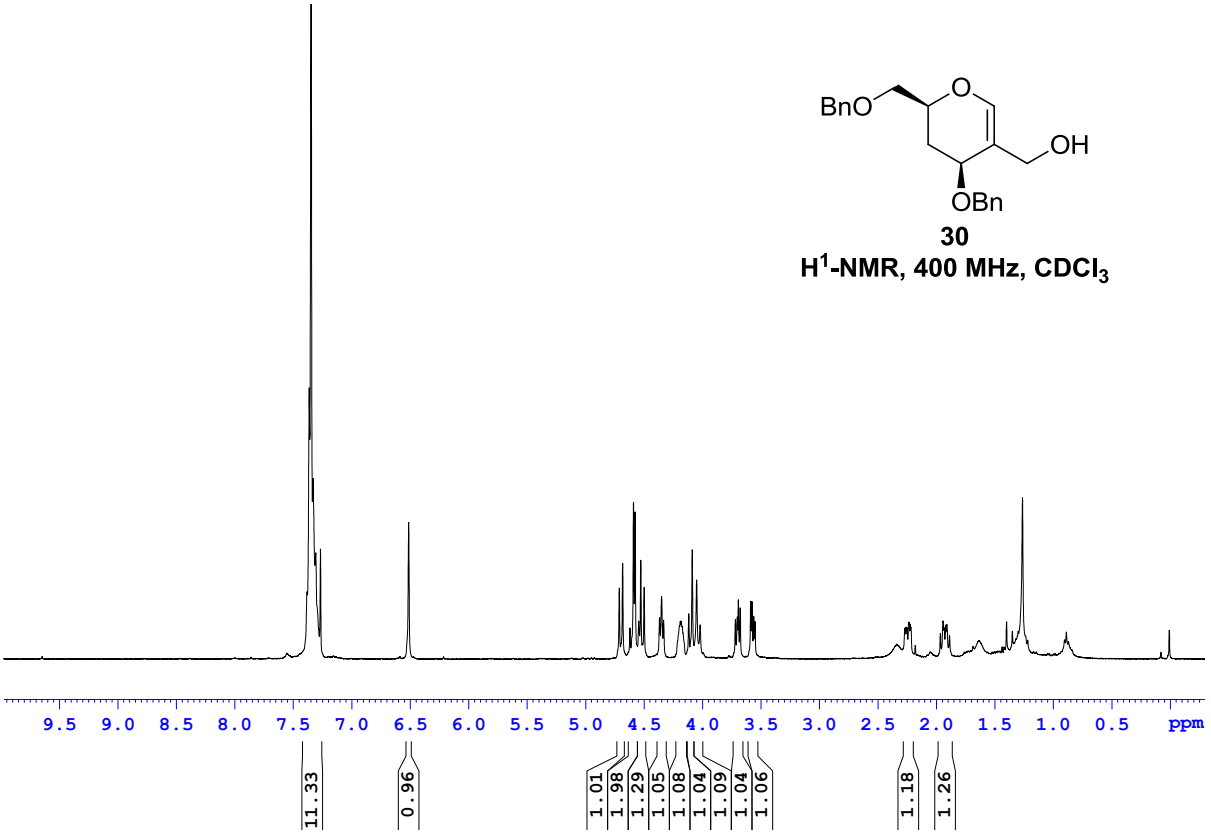
29

H^1-NMR, 400 MHz, $CDCl_3$



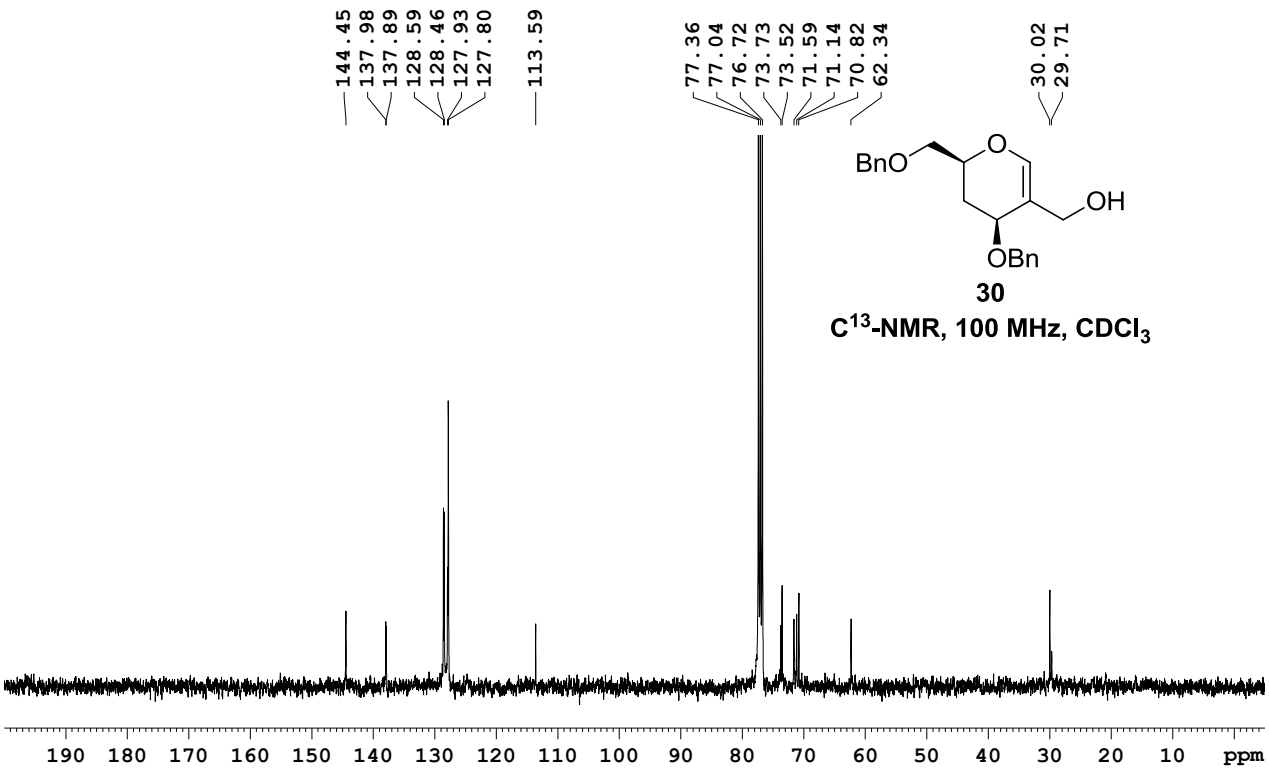
29

C^{13}-NMR, 100 MHz, $CDCl_3$



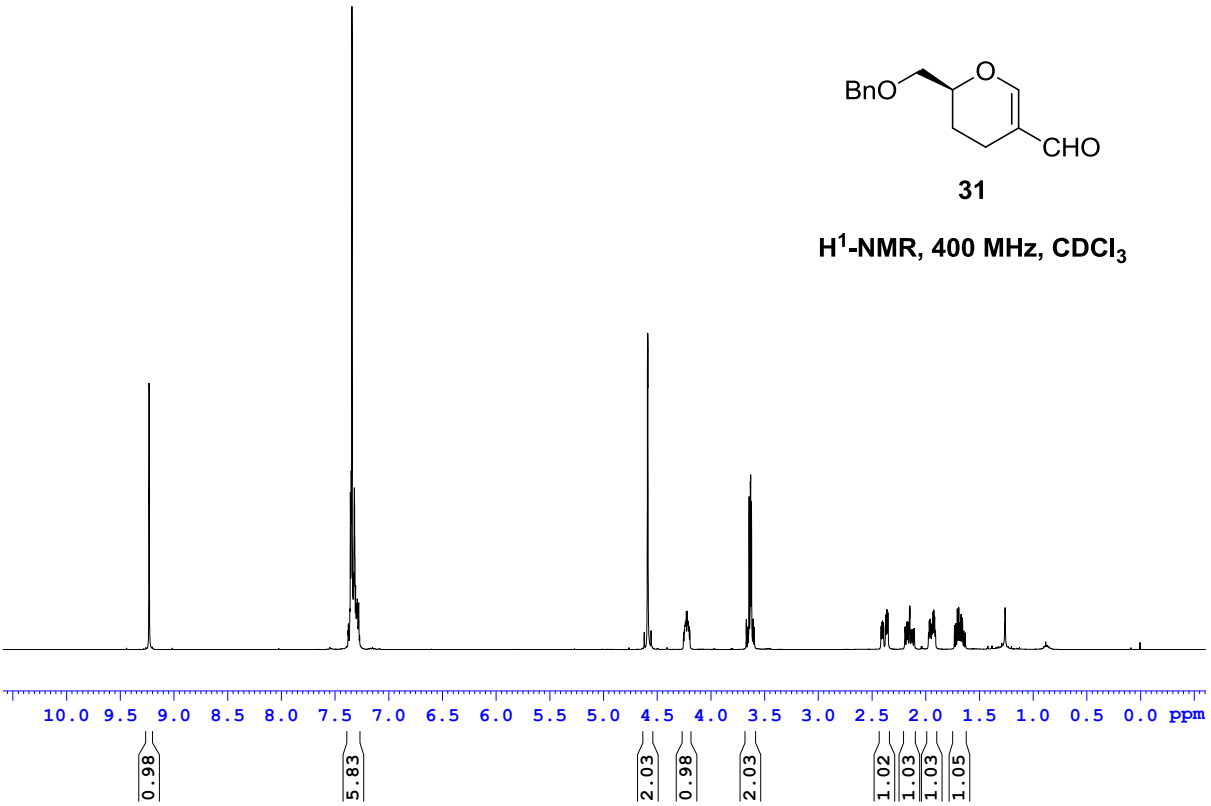
30

H^1-NMR, 400 MHz, $CDCl_3$



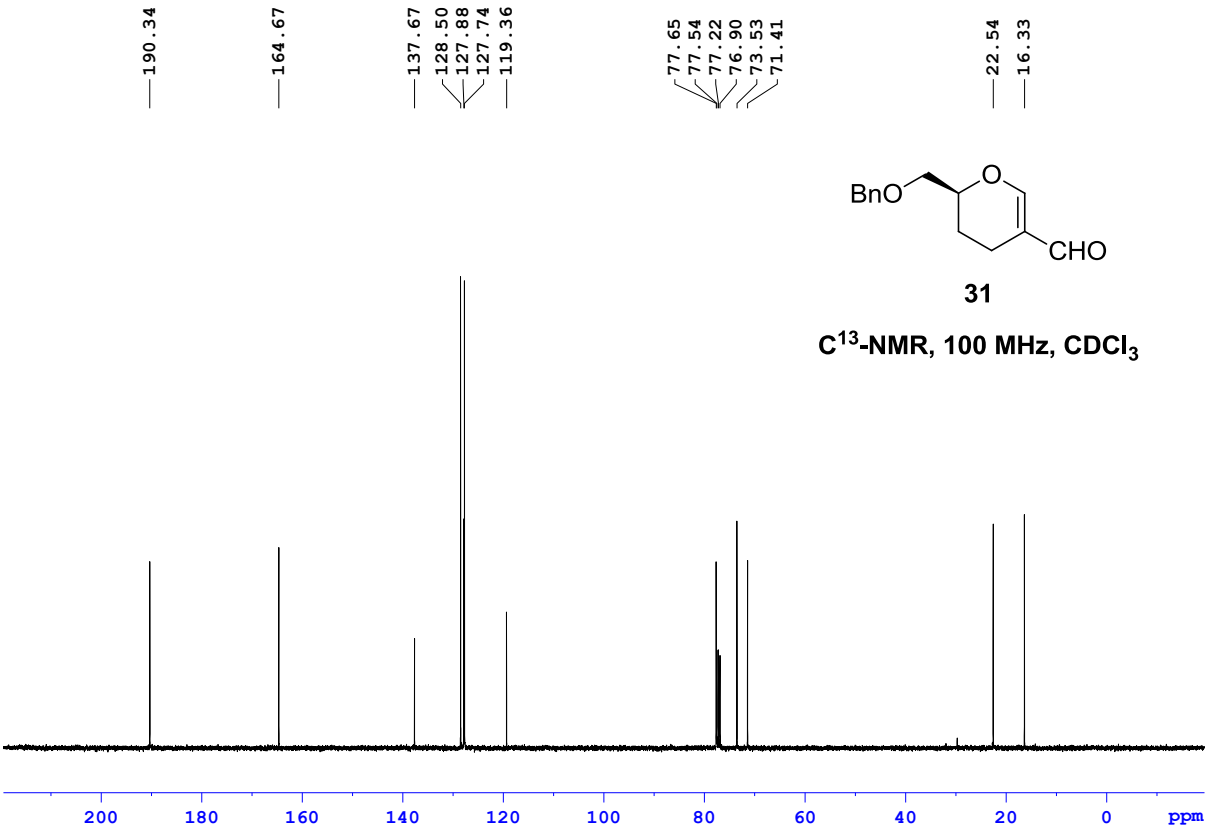
30

C^{13}-NMR, 100 MHz, $CDCl_3$



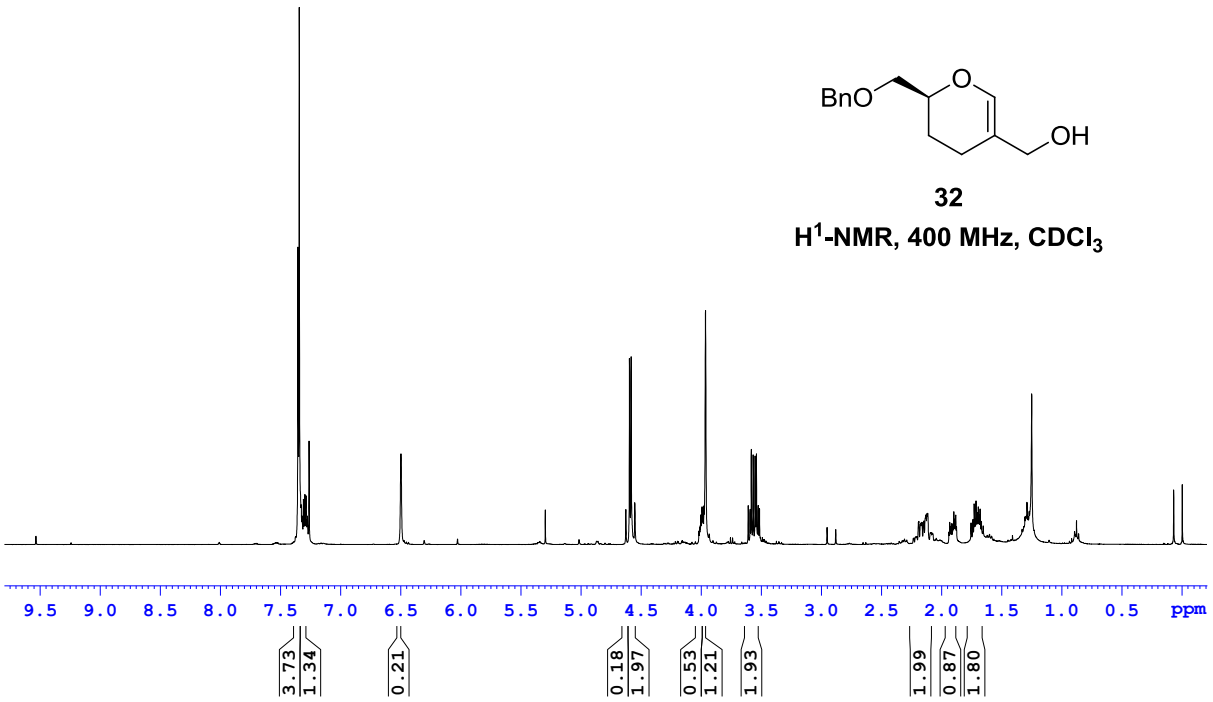
31

H^1-NMR, 400 MHz, $CDCl_3$



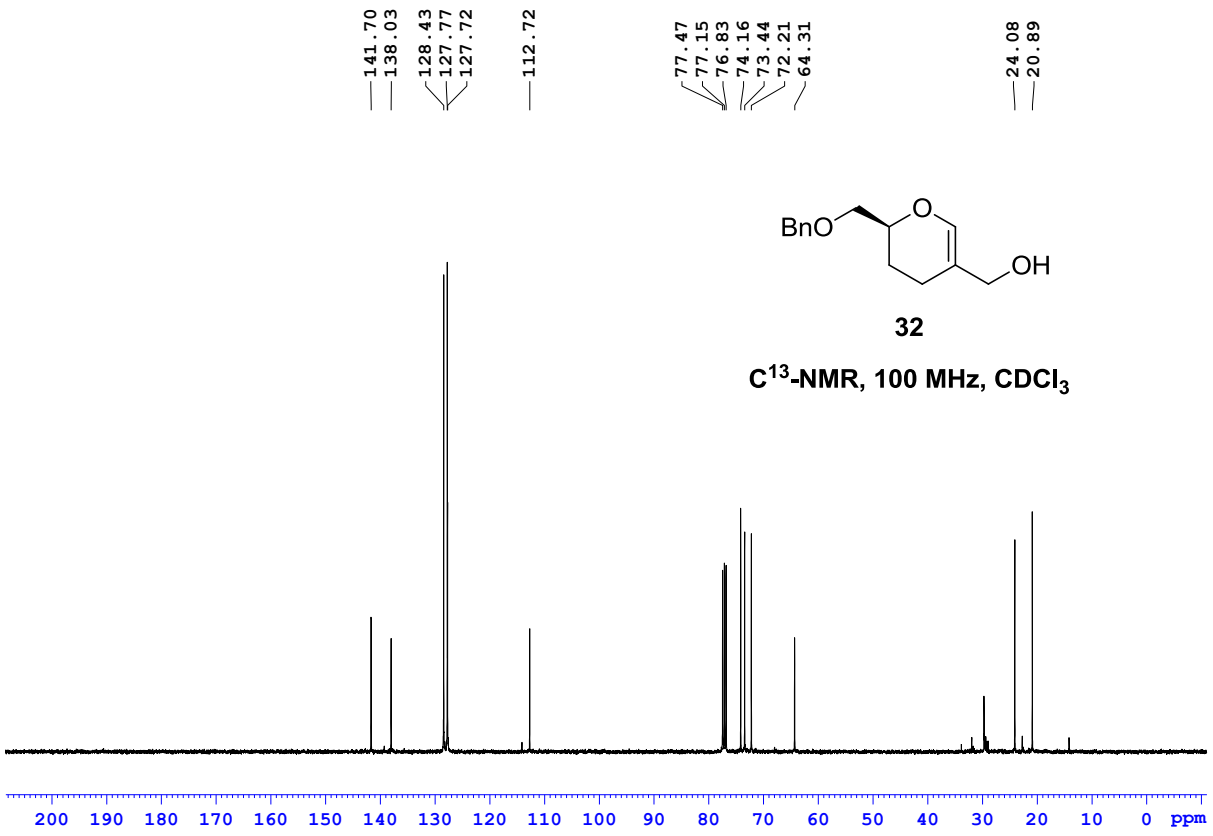
31

C^{13}-NMR, 100 MHz, $CDCl_3$



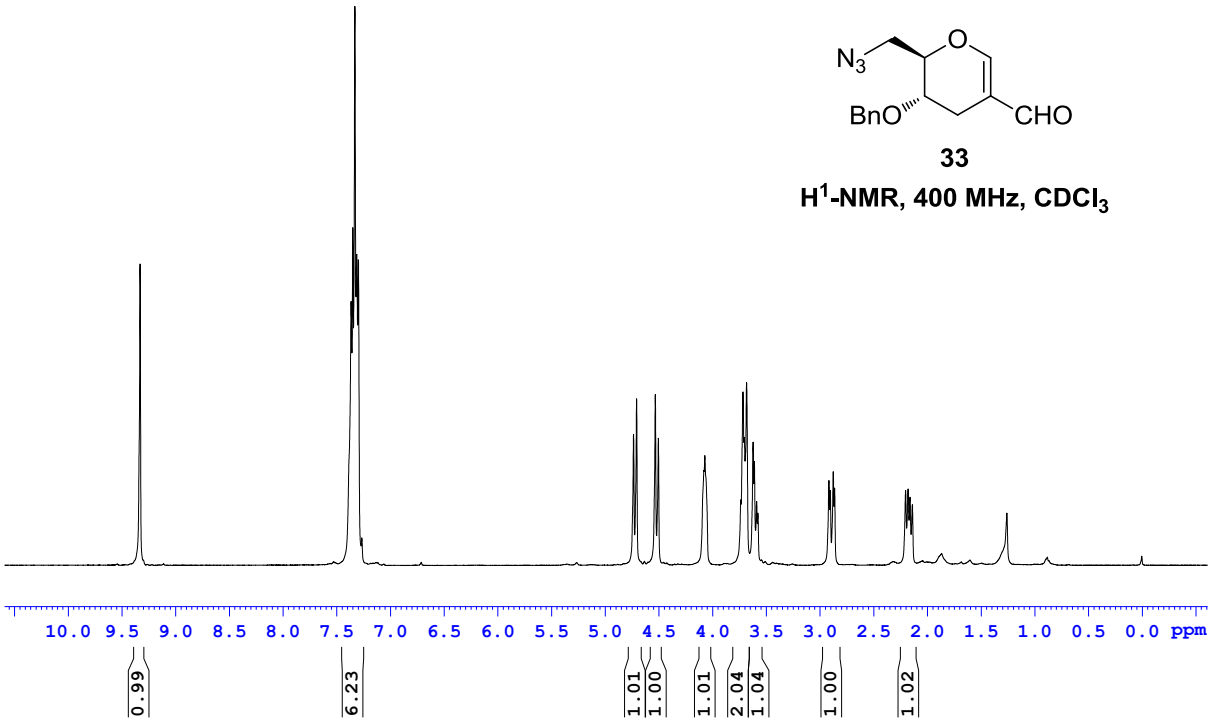
32

H^1-NMR, 400 MHz, $CDCl_3$



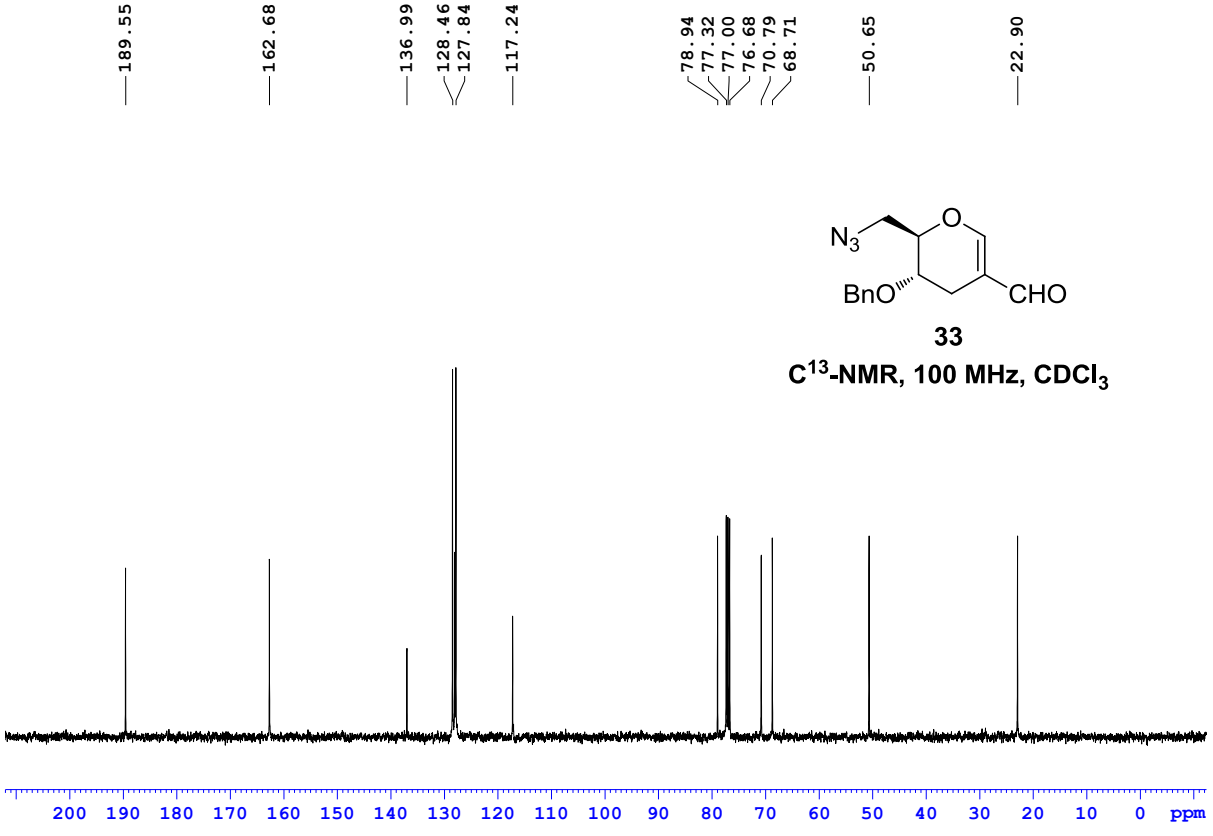
32

C^{13}-NMR, 100 MHz, $CDCl_3$



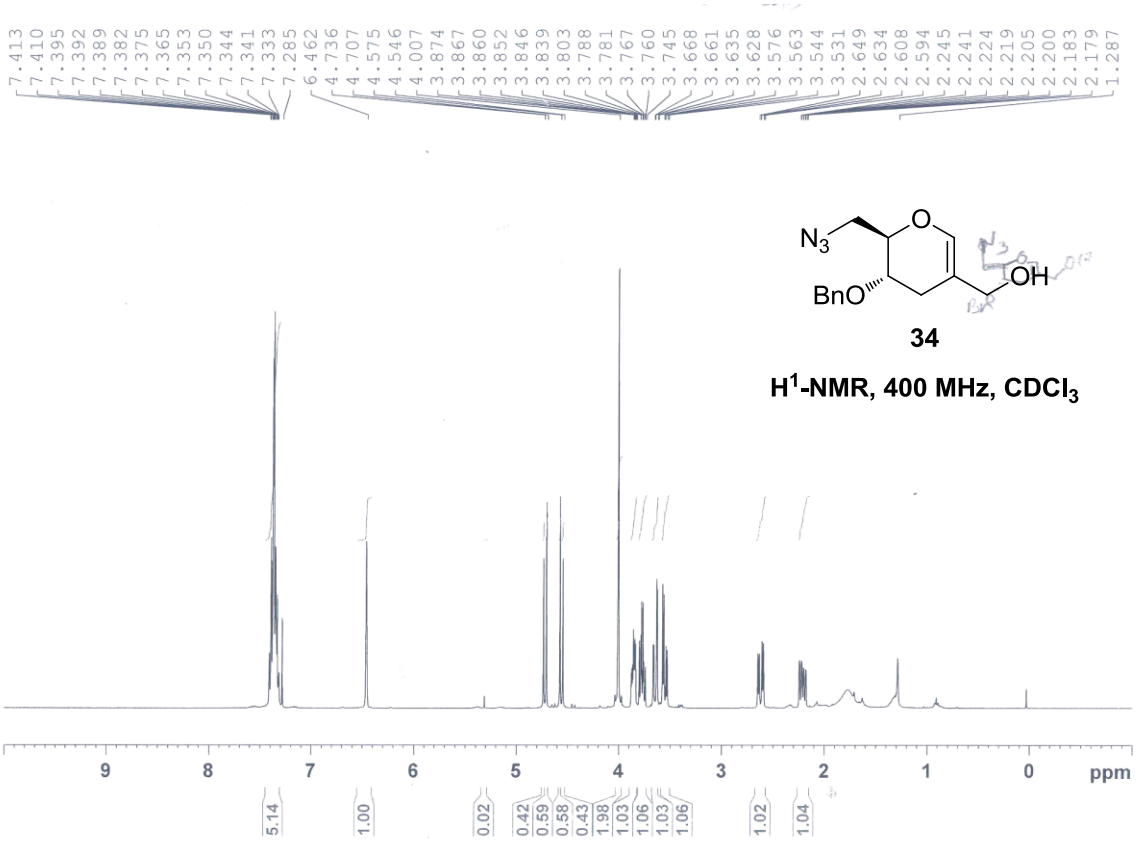
33

H^1-NMR, 400 MHz, $CDCl_3$



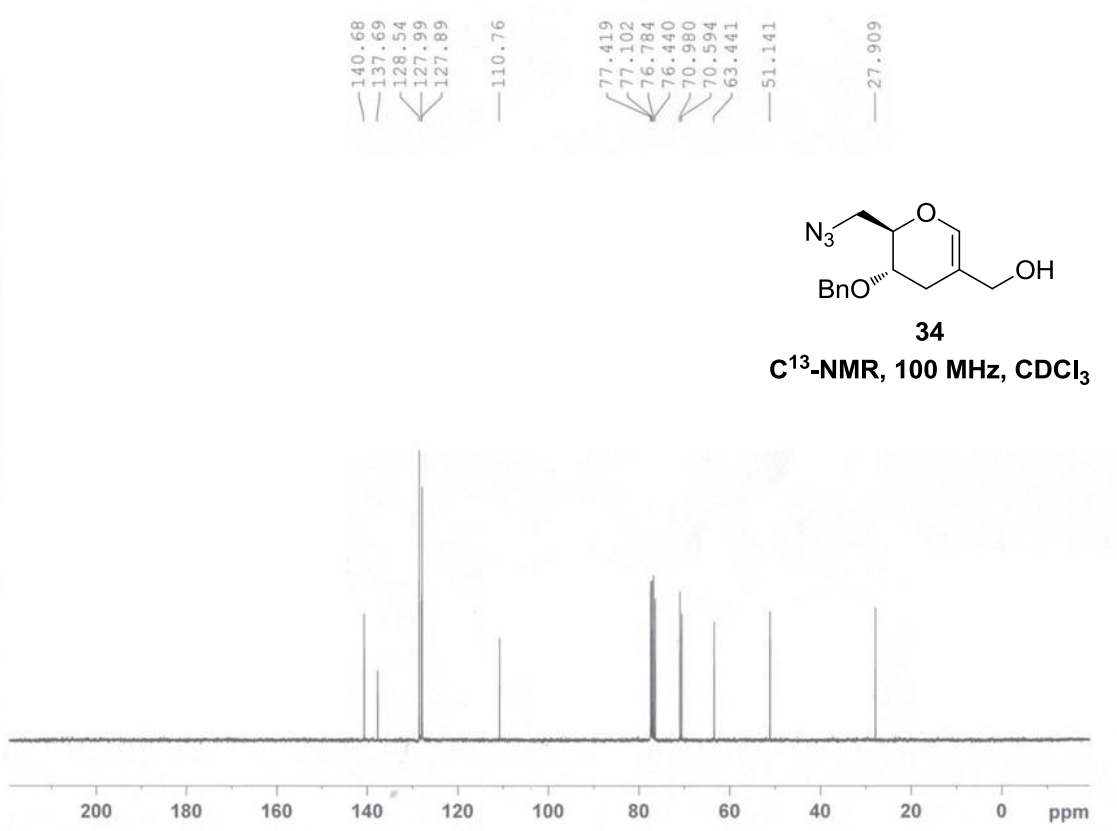
33

C^{13}-NMR, 100 MHz, $CDCl_3$



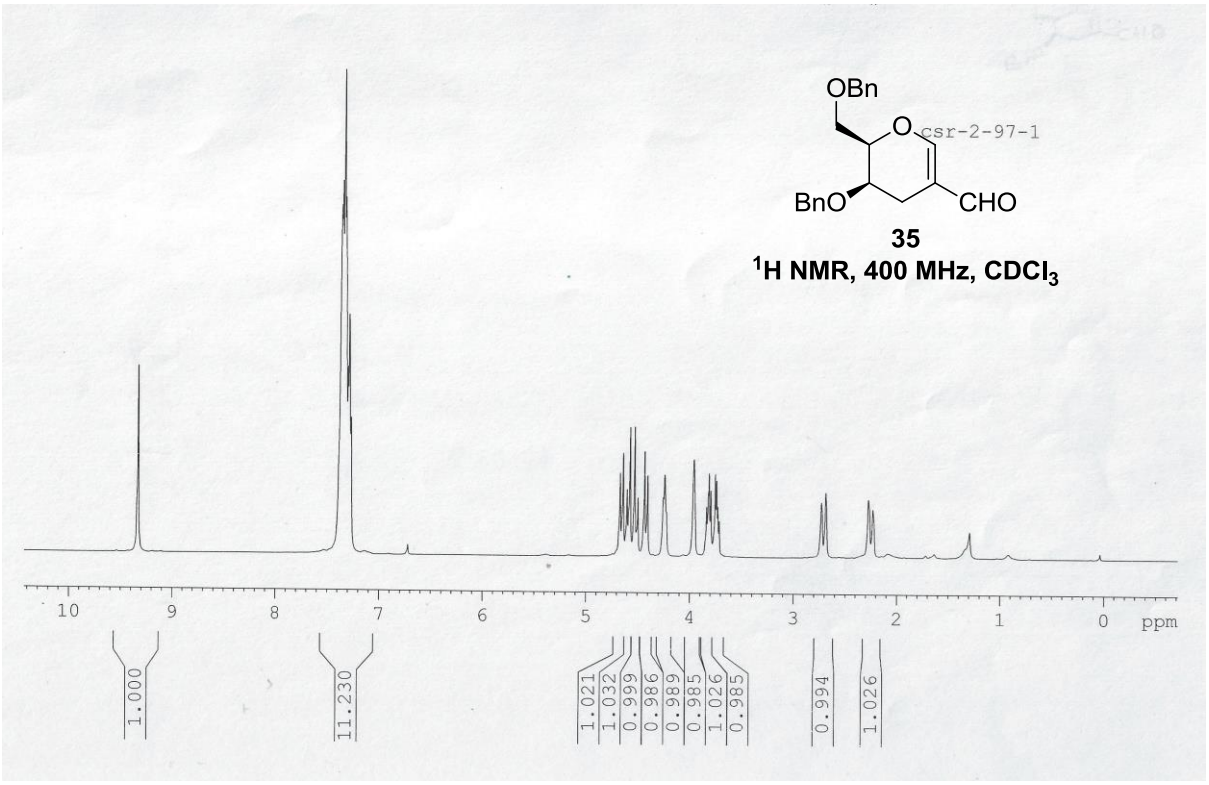
34

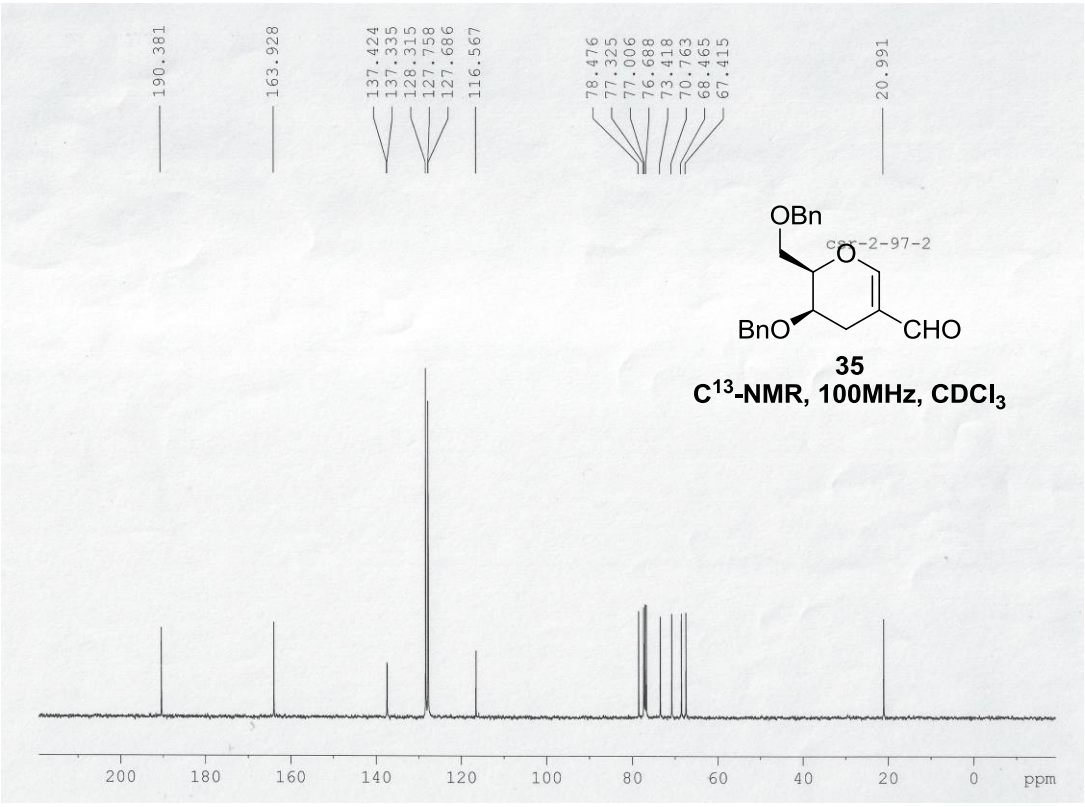
H^1-NMR, 400 MHz, $CDCl_3$

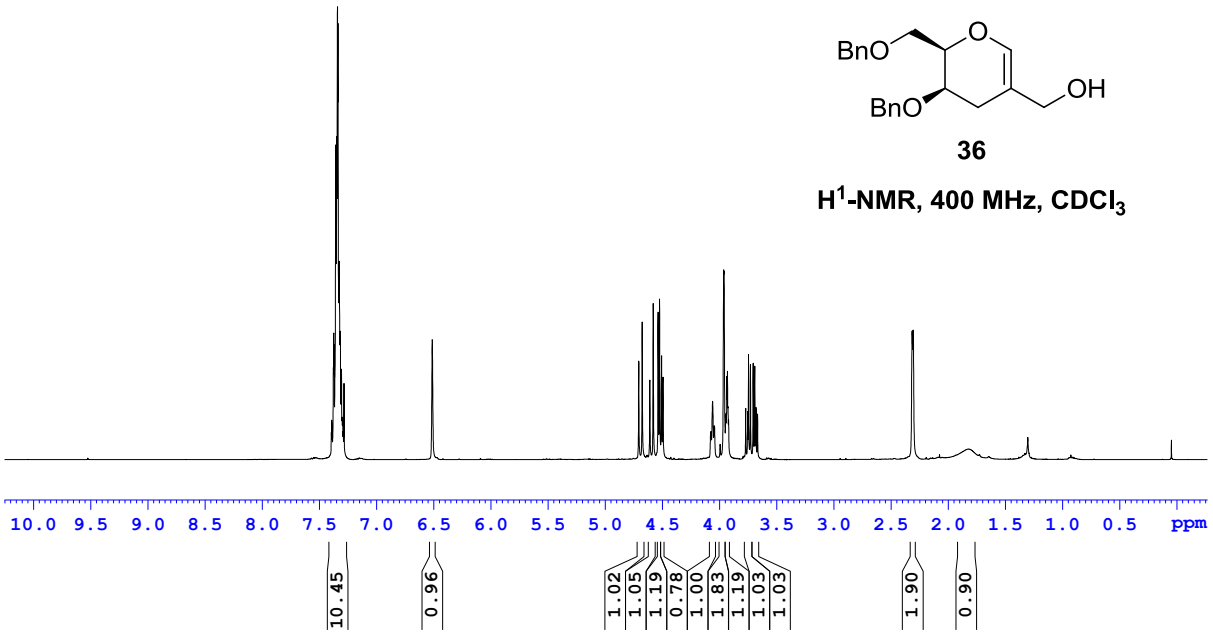


34

C^{13}-NMR, 100 MHz, $CDCl_3$

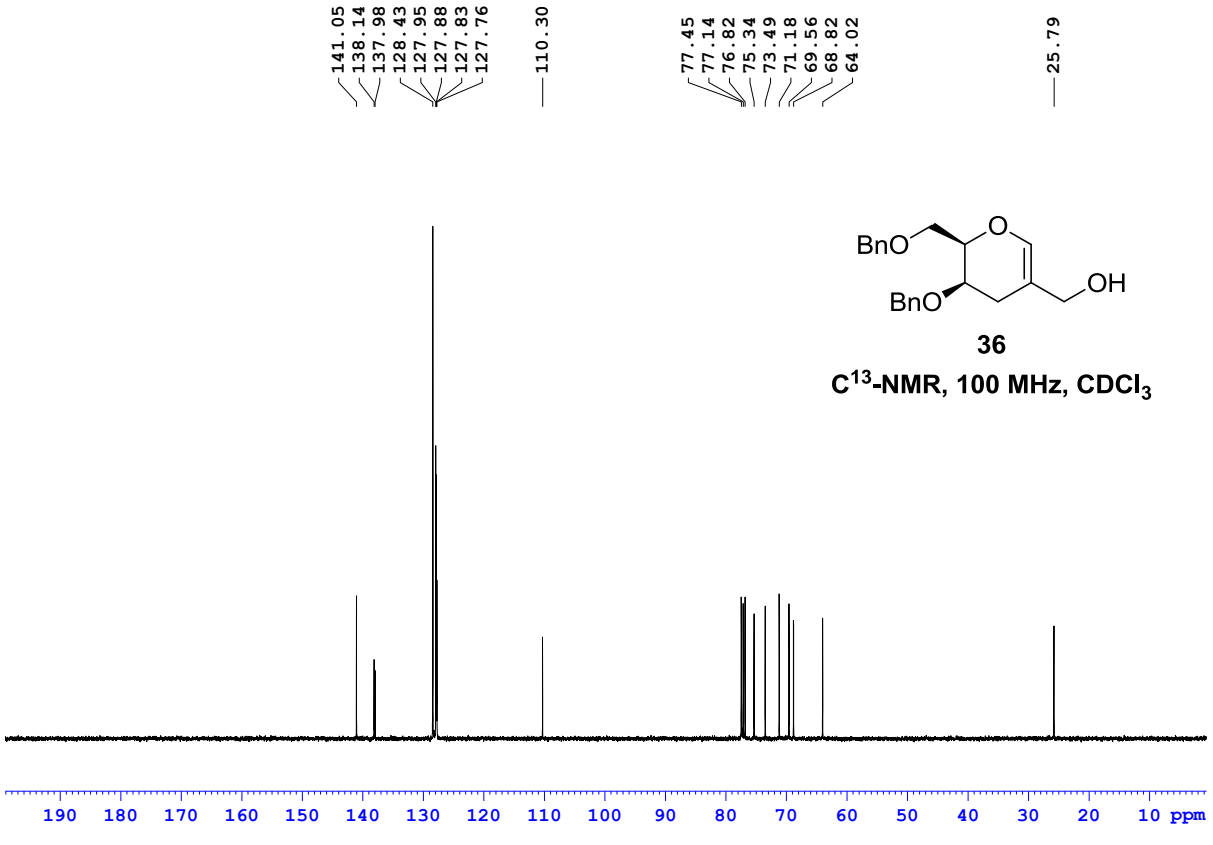

OBn
O
csr-2-97-1
BnO
CHO
35
1H NMR, 400 MHz, CDCl3
10
9
8
7
6
5
4
3
2
1
0
ppm
1.000
11.230
1.021
1.032
0.999
0.986
0.989
0.985
1.026
0.985
0.994
1.026


190.381
163.928
137.424
137.335
128.315
127.758
127.686
116.567
78.476
77.325
77.006
76.688
73.418
70.763
68.465
67.415
20.991
OBn
csr-2-97-2
O
BnO
CHO
35
C13-NMR, 100MHz, CDCl3
200
180
160
140
120
100
80
60
40
20
0
ppm



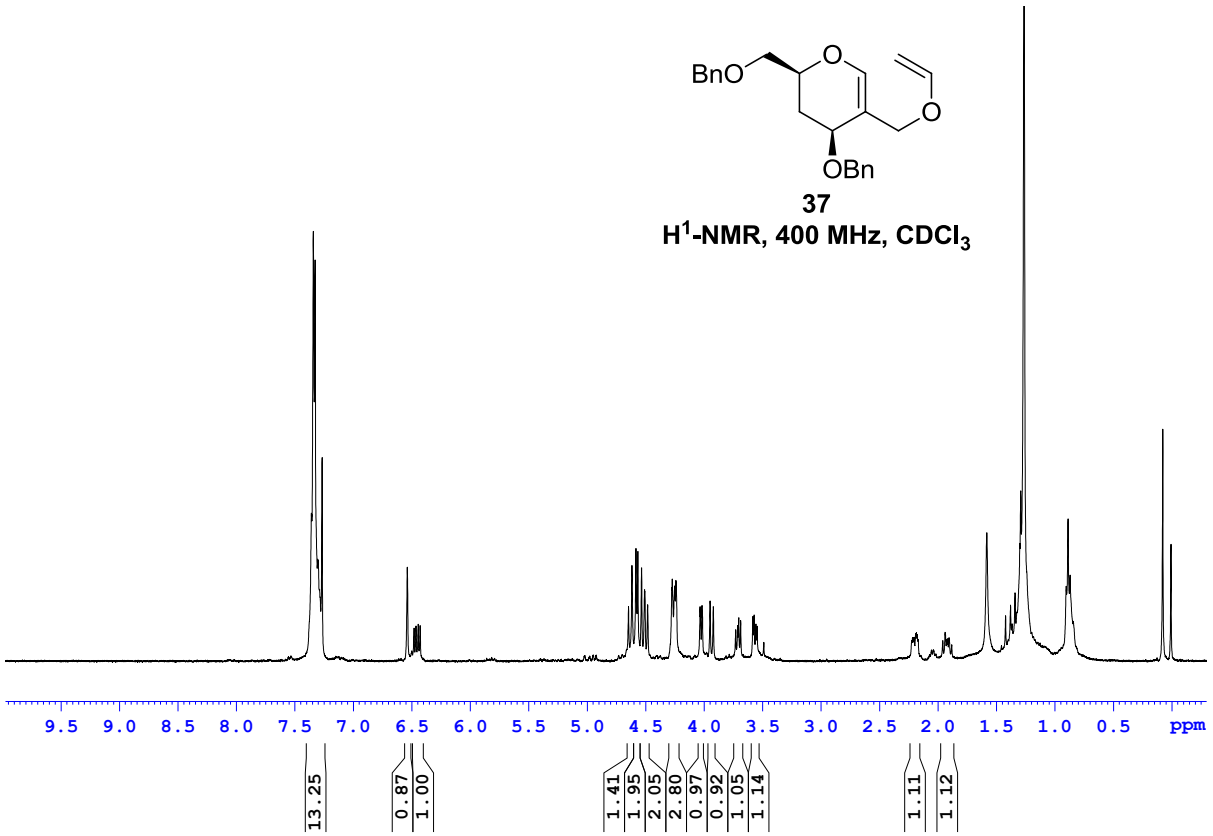
36

H^1-NMR, 400 MHz, $CDCl_3$



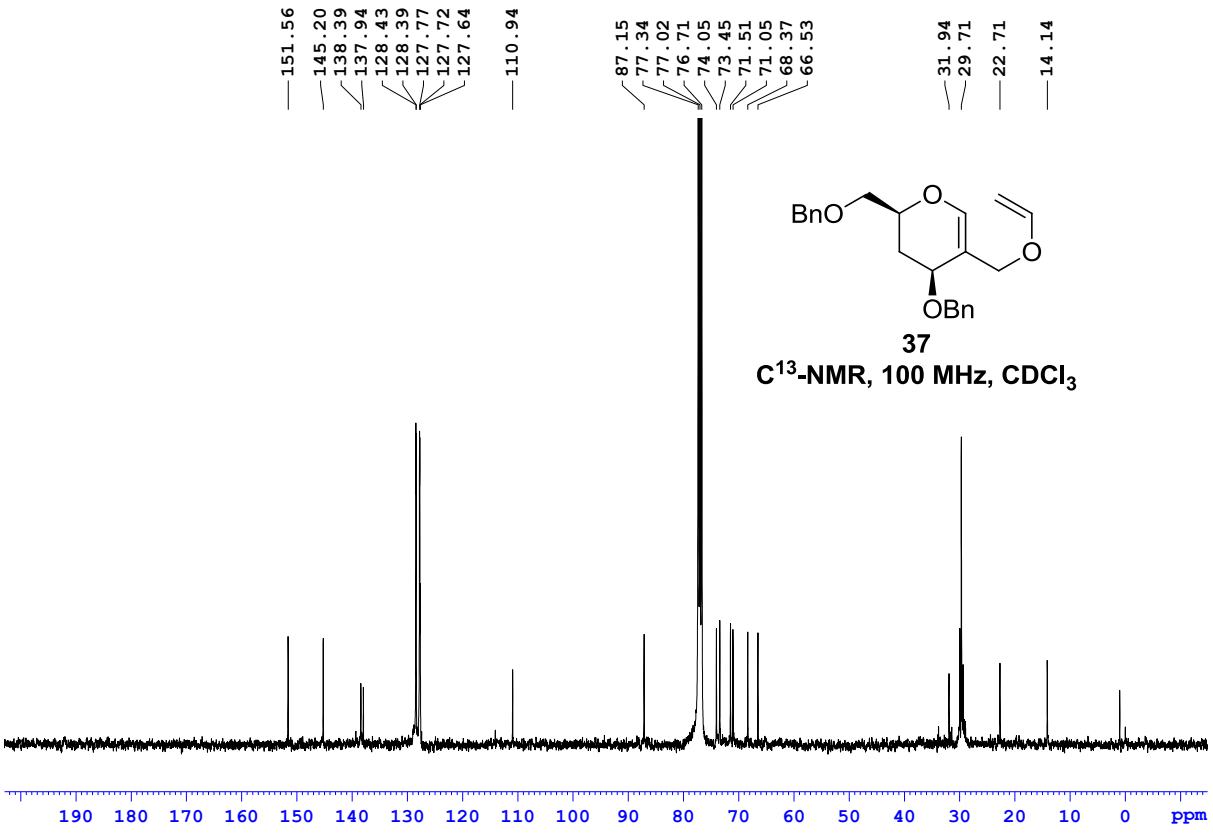
36

C^{13}-NMR, 100 MHz, $CDCl_3$



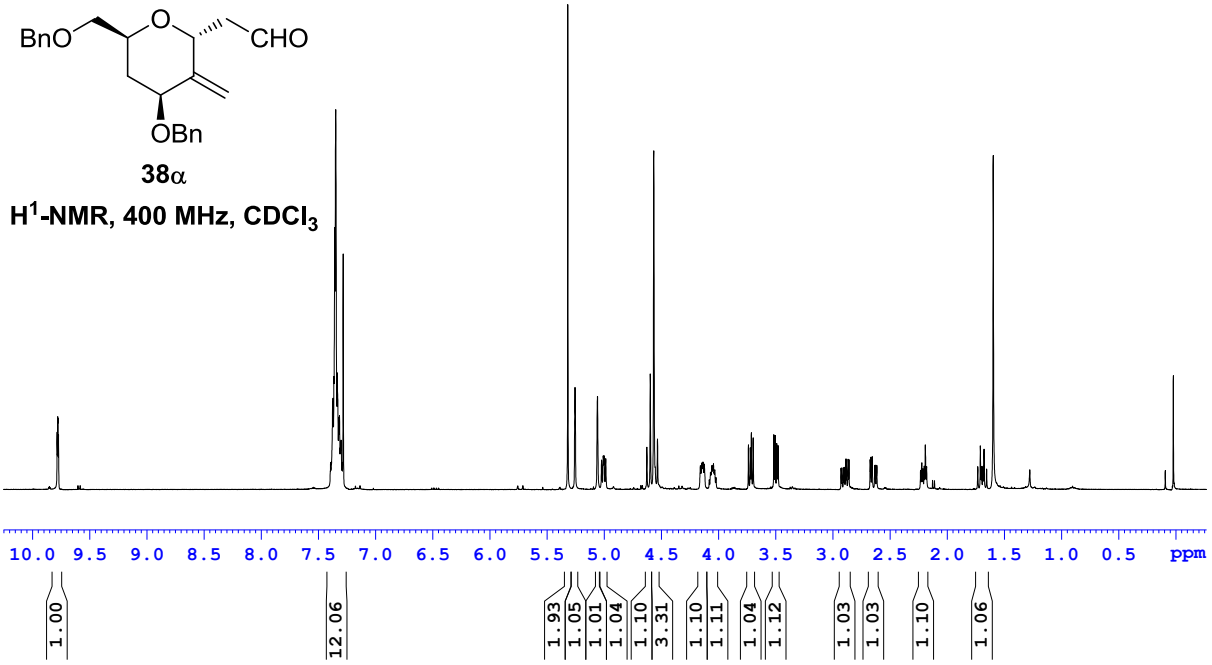
37

H^1-NMR, 400 MHz, $CDCl_3$



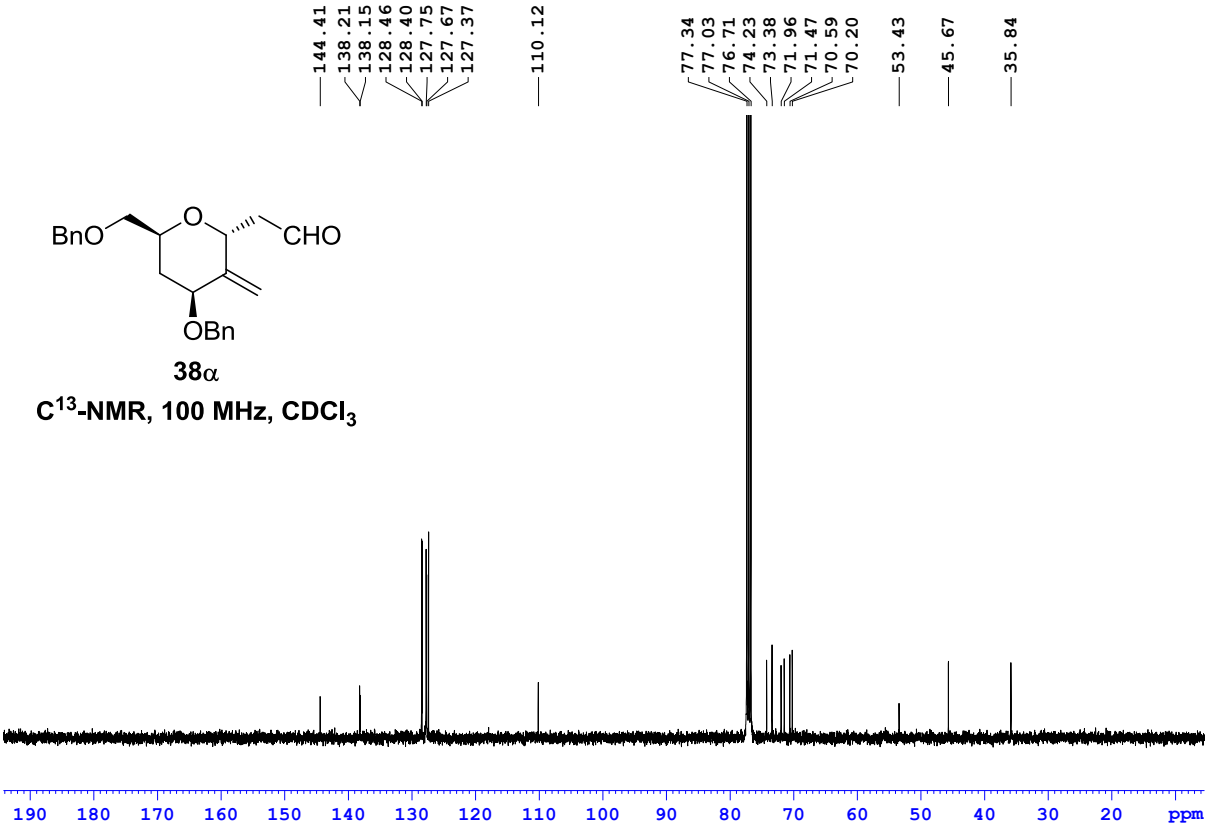
37

C^{13}-NMR, 100 MHz, $CDCl_3$



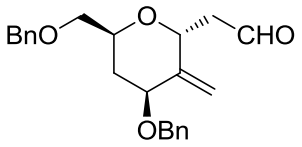
38α

H^1-NMR, 400 MHz, $CDCl_3$



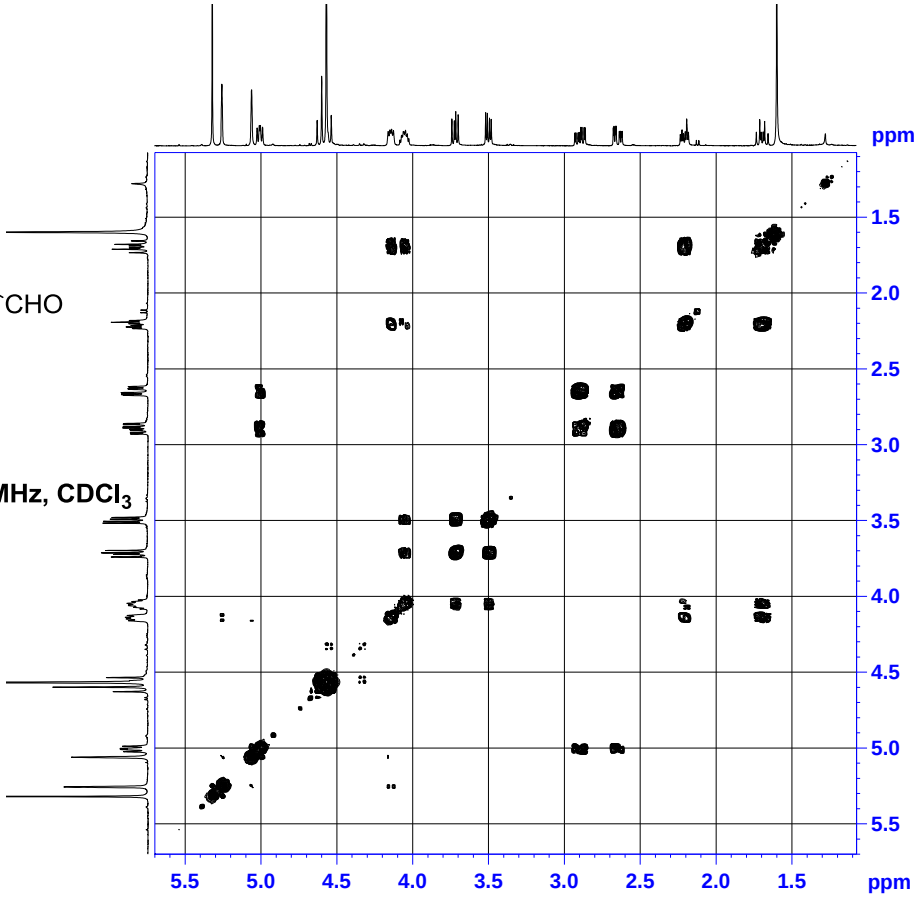
38α

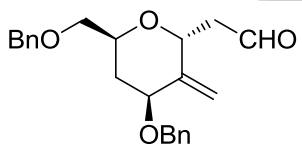
C^{13}-NMR, 100 MHz, $CDCl_3$



38α

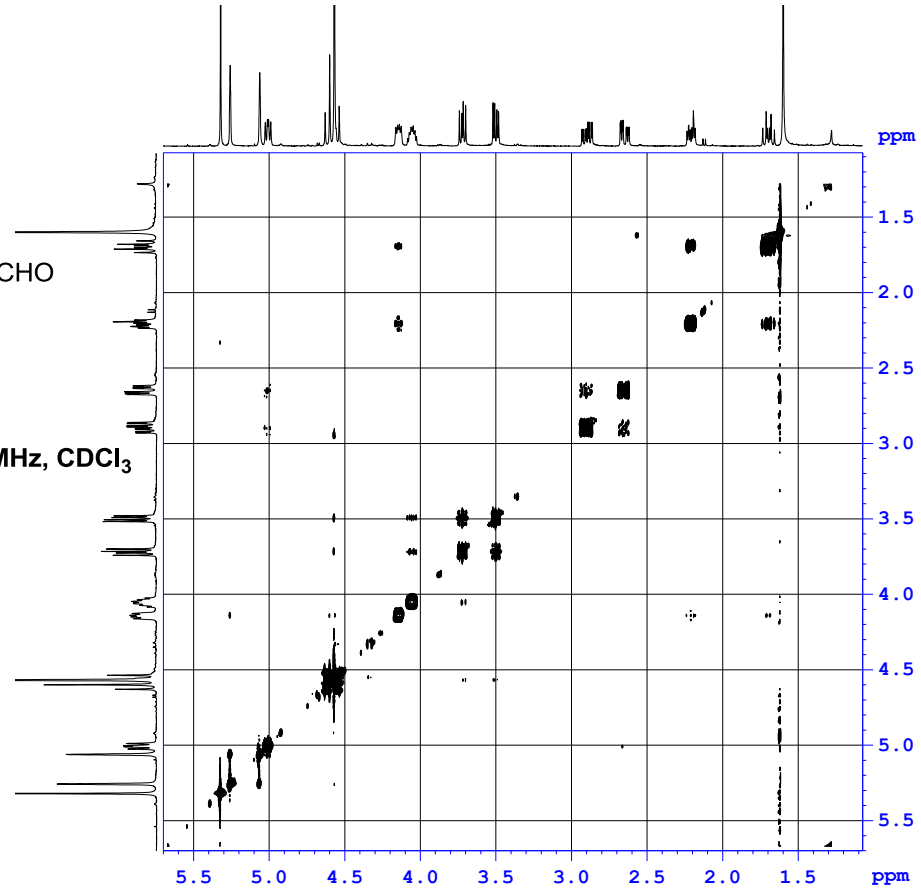
H^1-H^1 COSY NMR, 400 MHz, $CDCl_3$

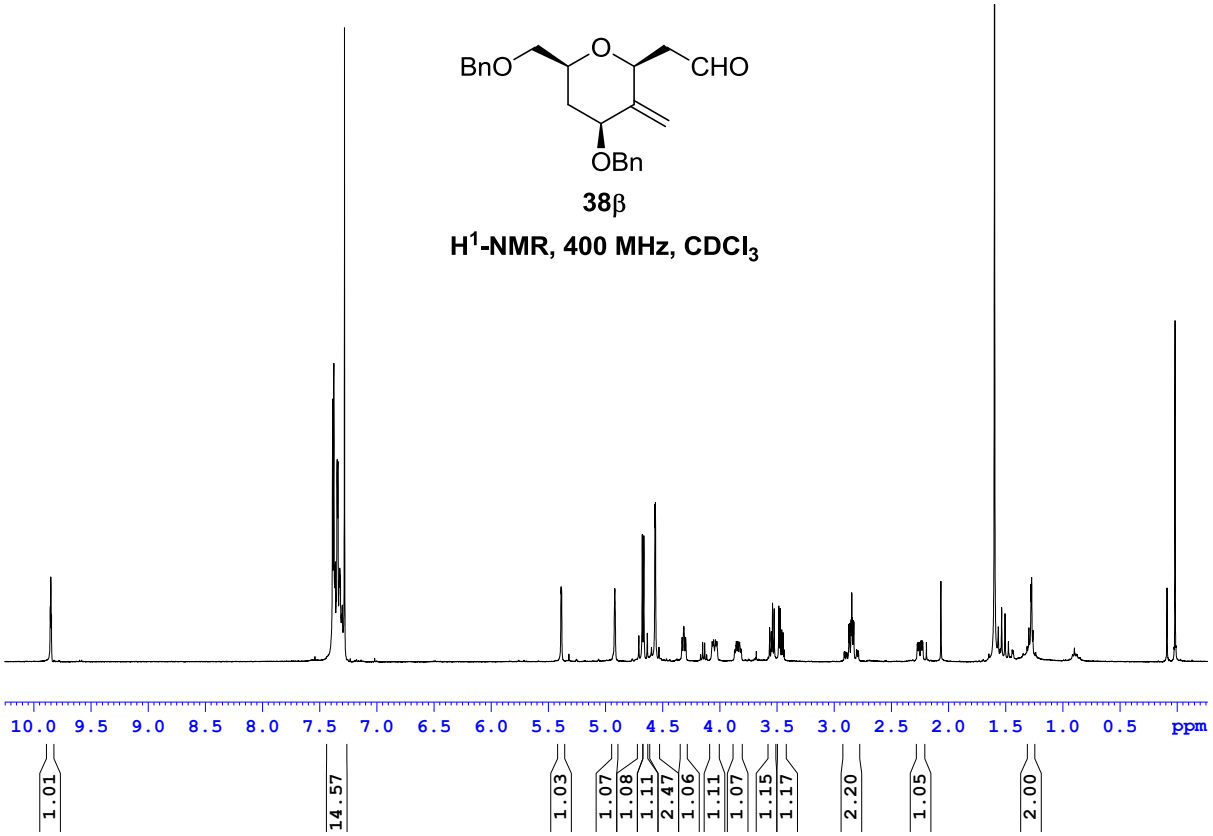




38α

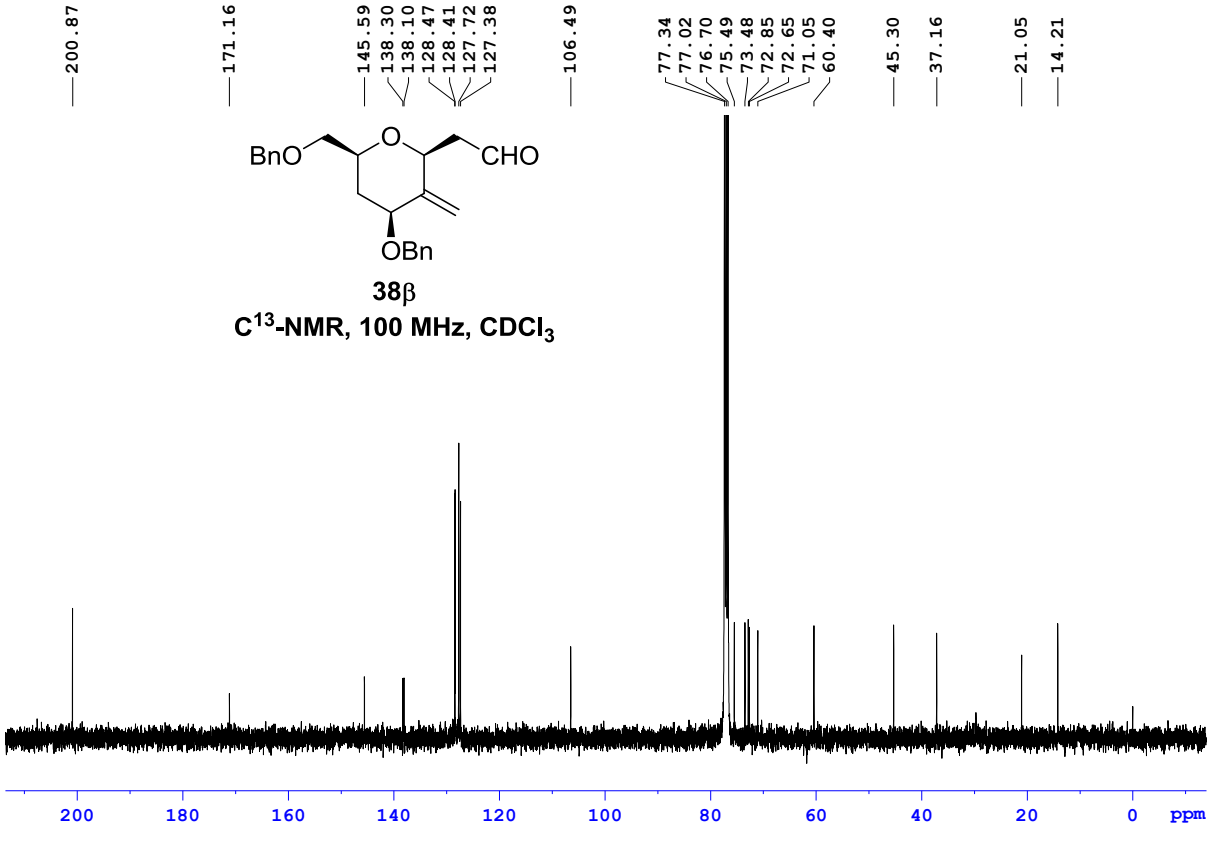
H^1-H^1 NOESY NMR, 400 MHz, $CDCl_3$





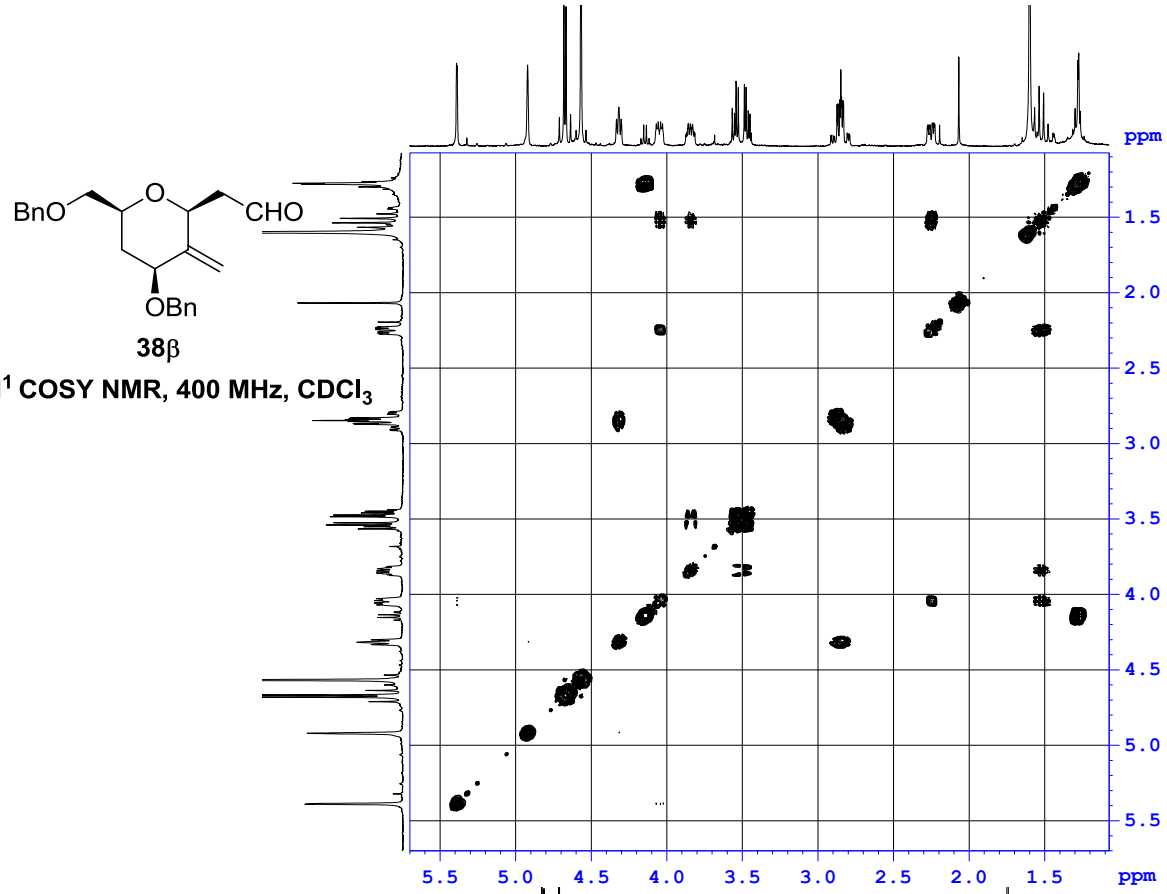
38β

H^1-NMR, 400 MHz, $CDCl_3$



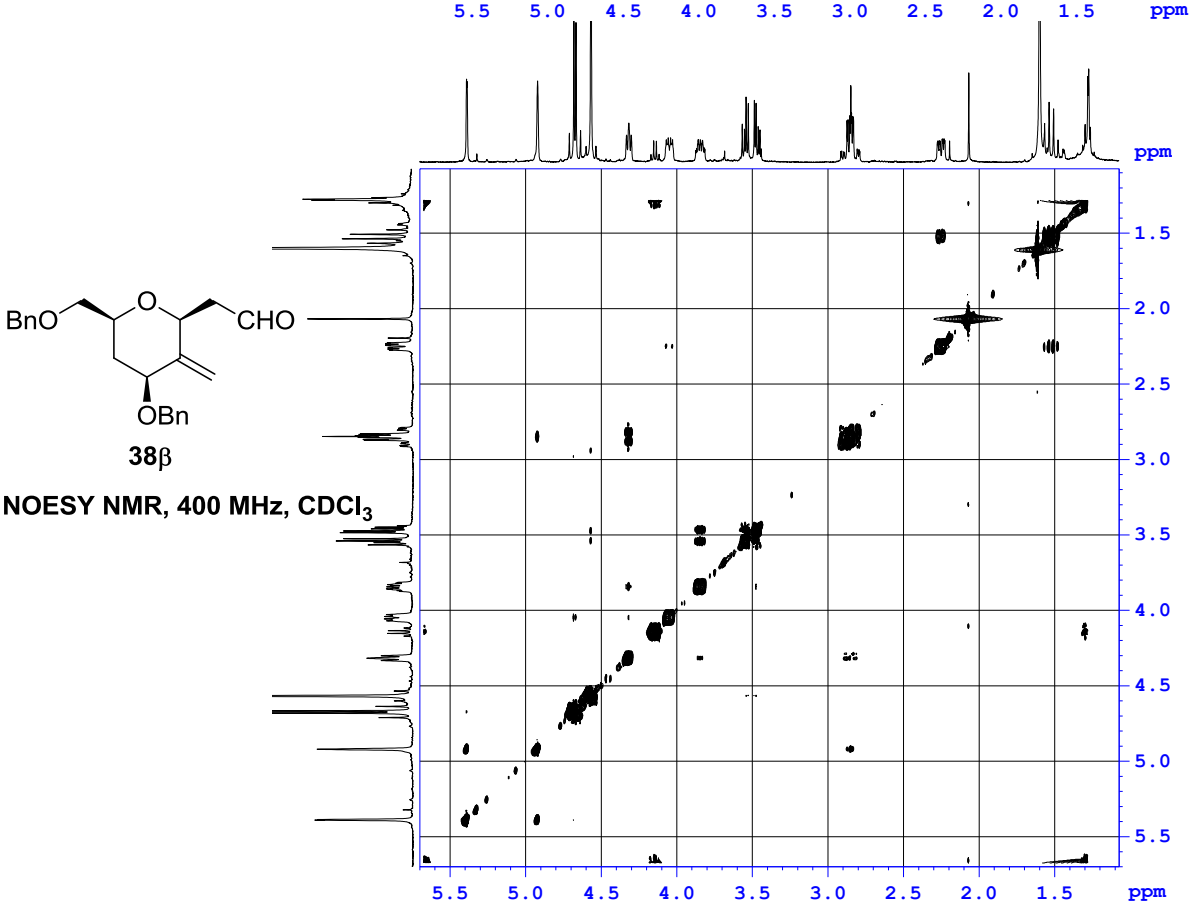
38β

C^{13}-NMR, 100 MHz, $CDCl_3$



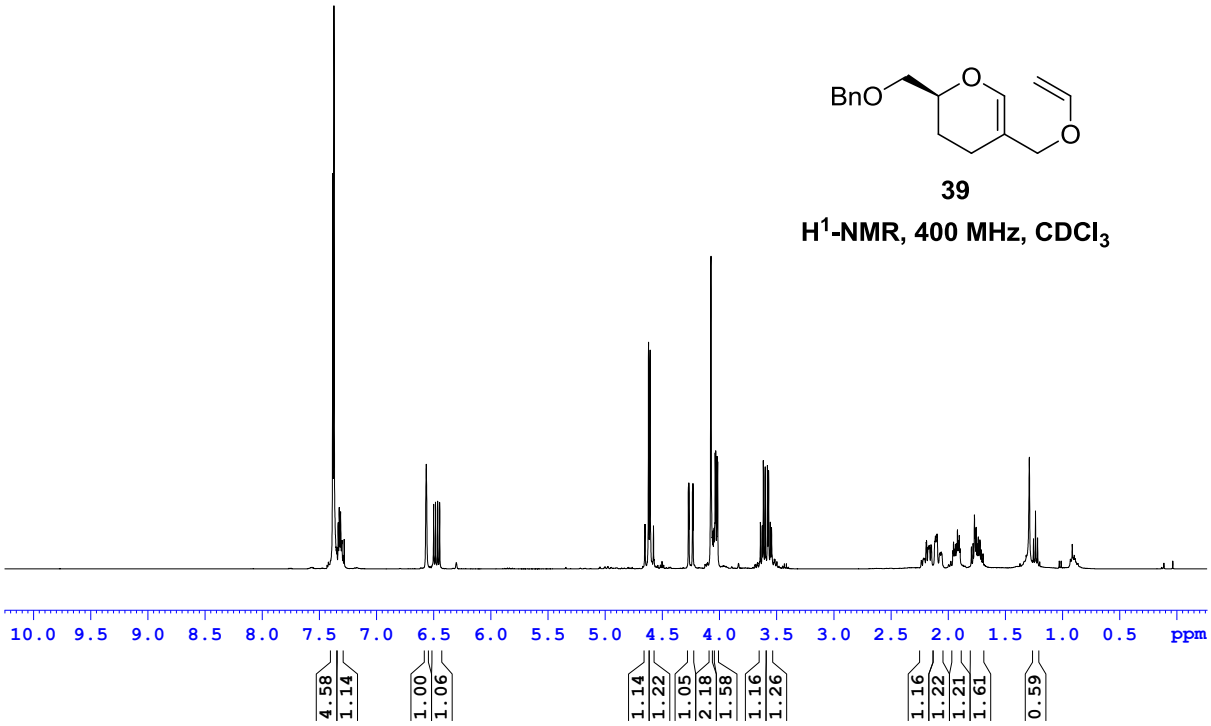
38β

H^1-H^1 COSY NMR, 400 MHz, $CDCl_3$



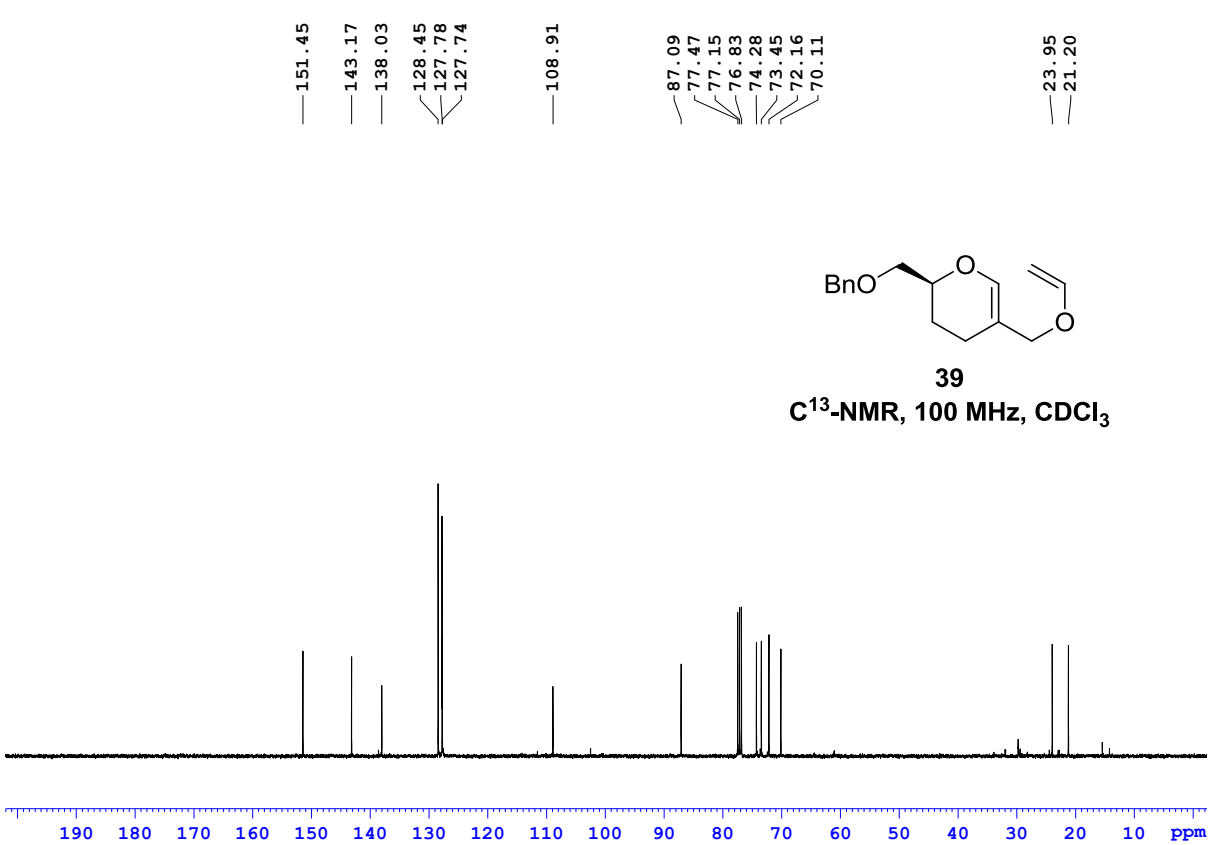
38β

H^1-H^1 NOESY NMR, 400 MHz, $CDCl_3$



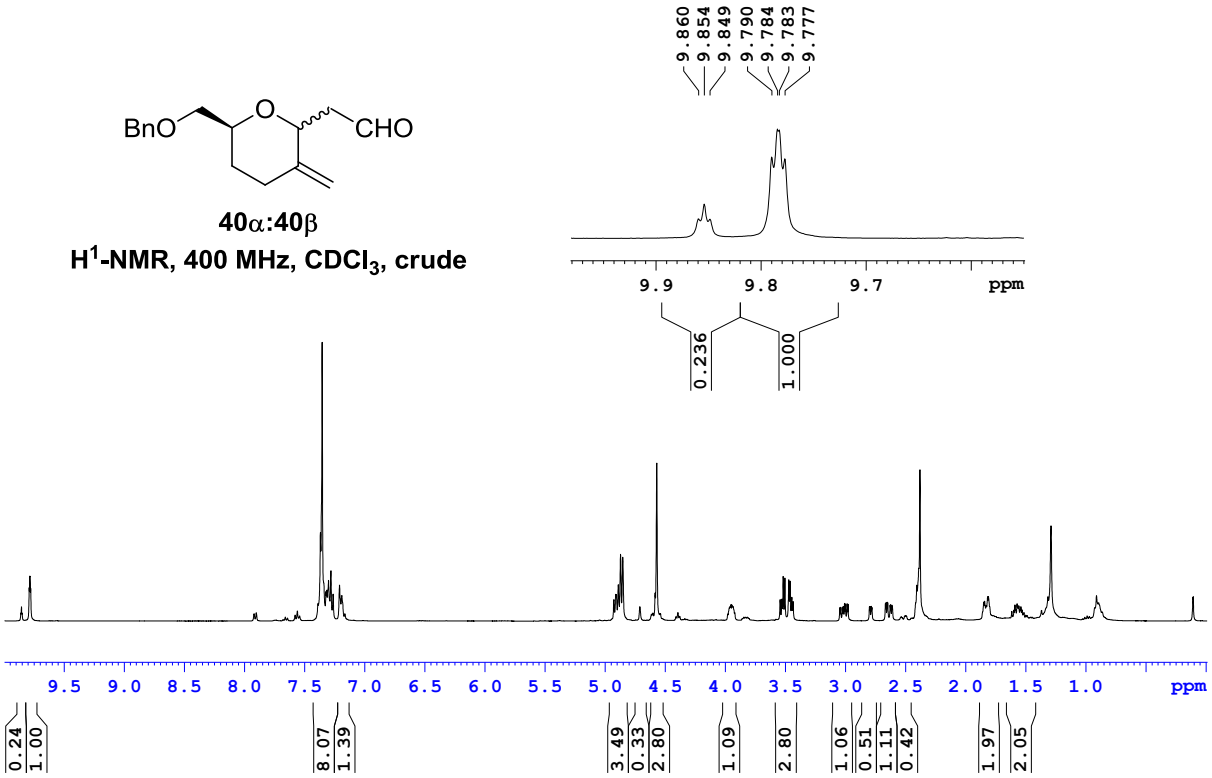
39

H^1-NMR, 400 MHz, $CDCl_3$



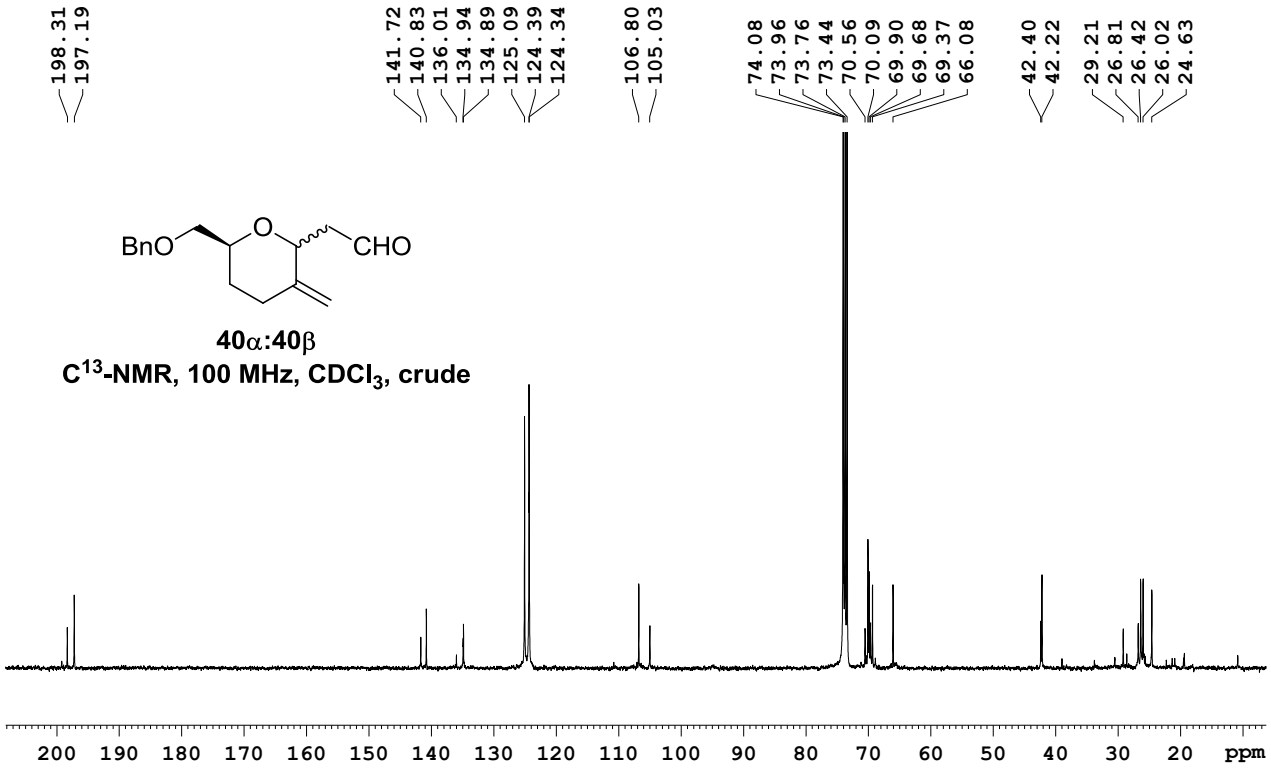
39

C^{13}-NMR, 100 MHz, $CDCl_3$



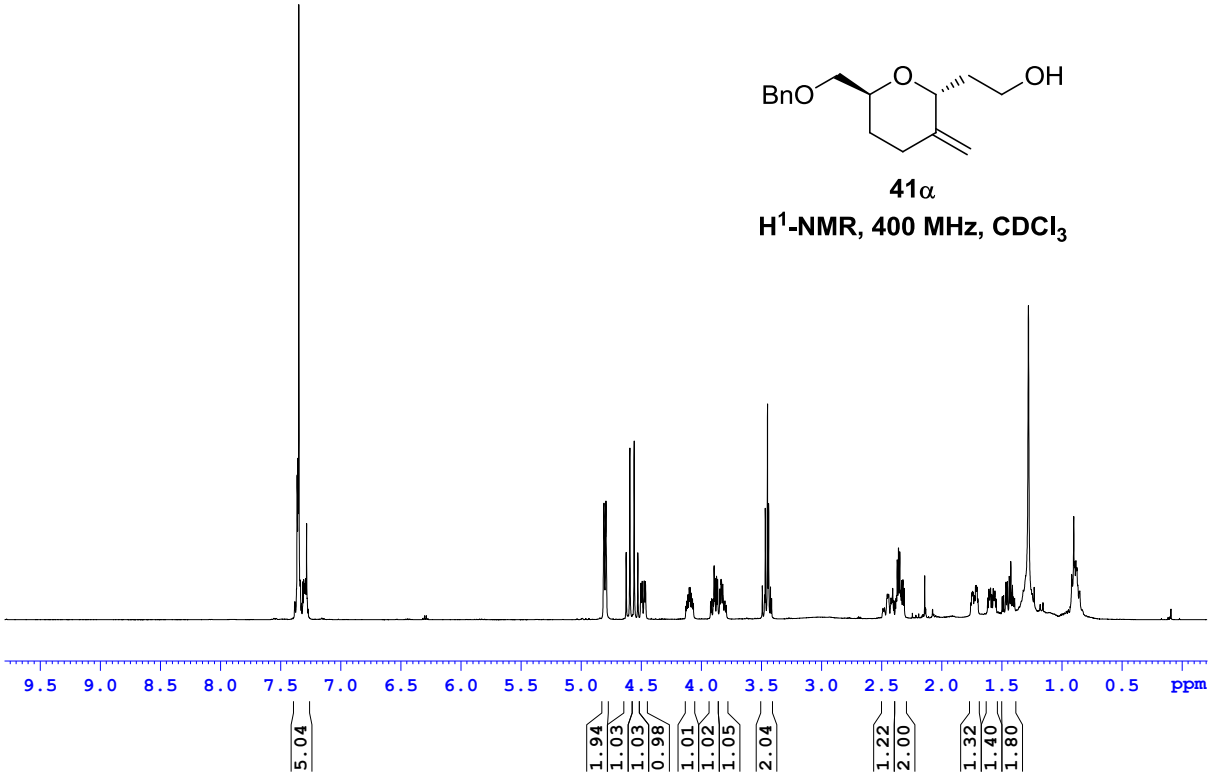
40α:40β

H[1]-NMR, 400 MHz, $CDCl_3$, crude



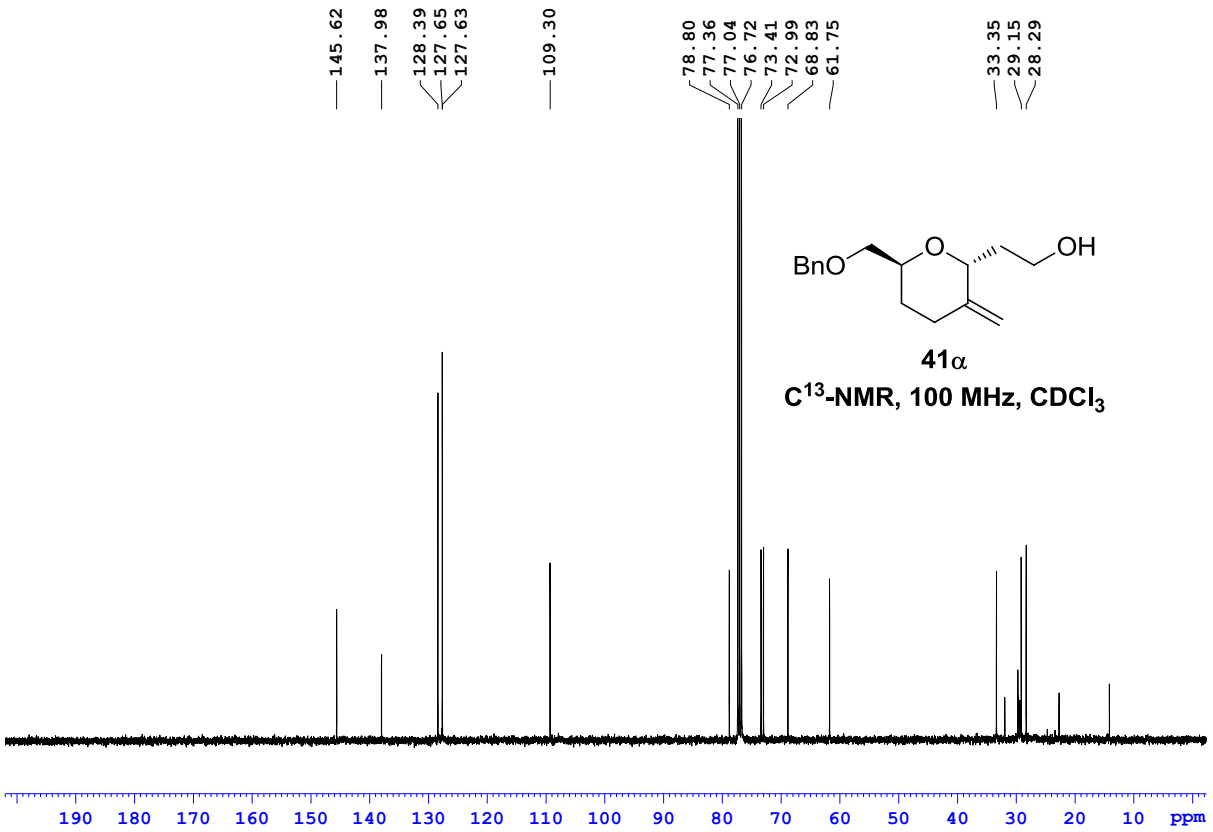
40α:40β

C[13]-NMR, 100 MHz, $CDCl_3$, crude



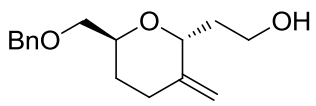
41α

H^1-NMR, 400 MHz, $CDCl_3$



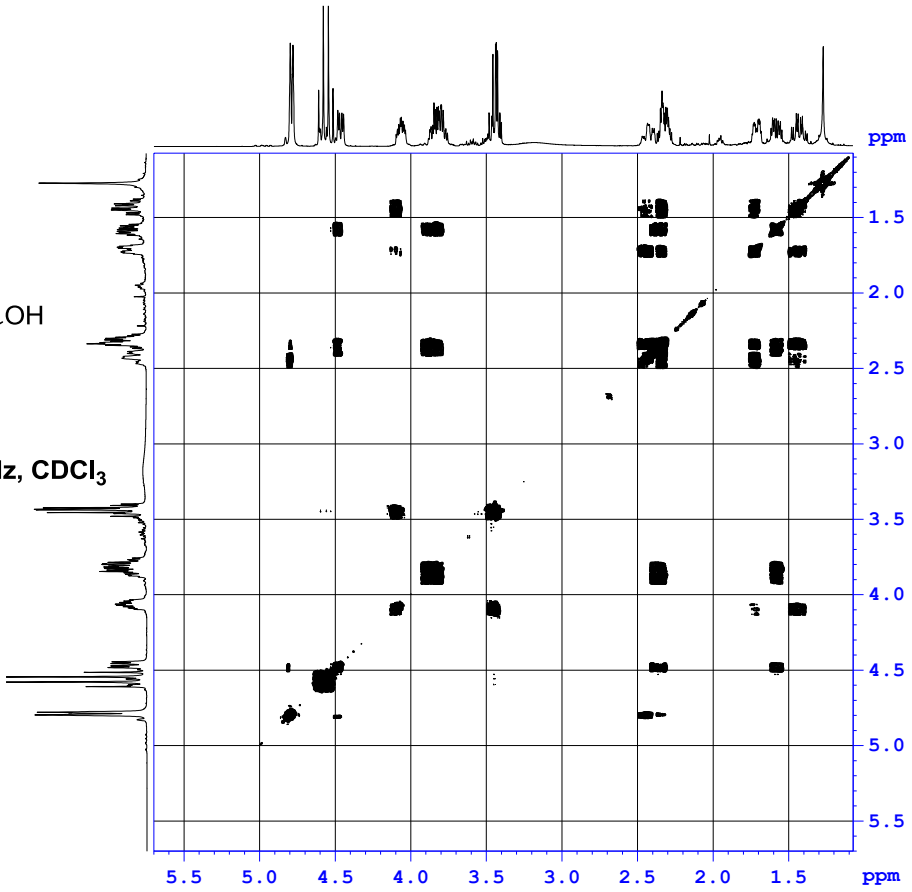
41α

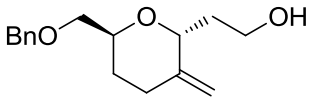
C^{13}-NMR, 100 MHz, $CDCl_3$



41α

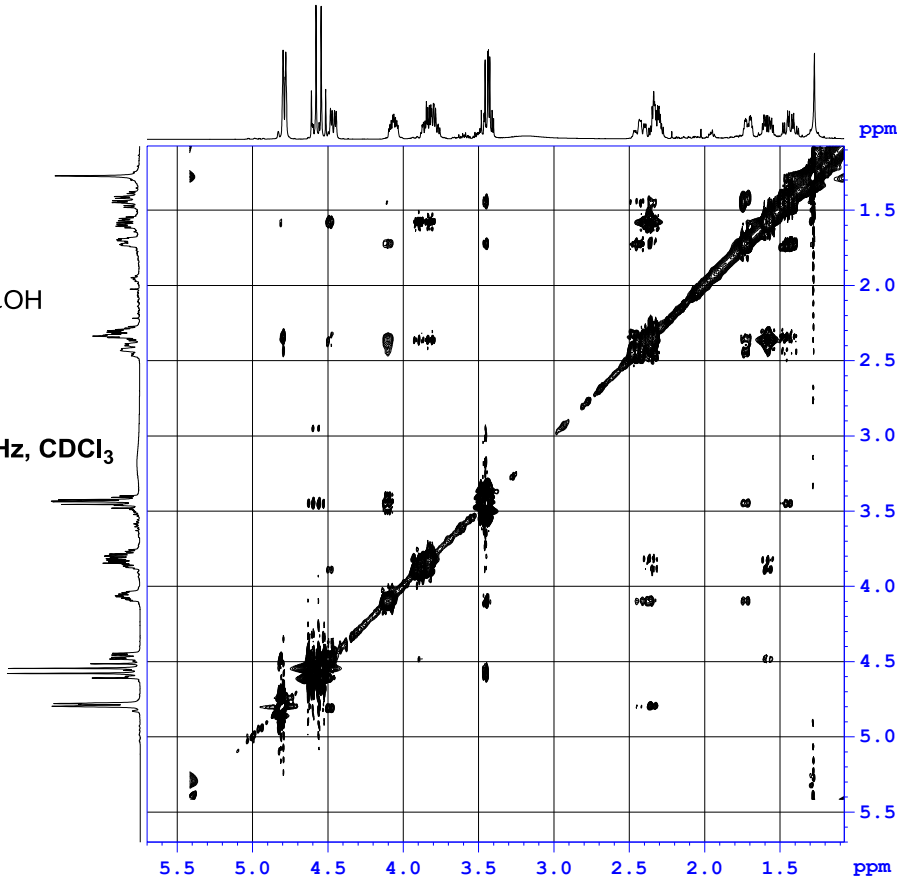
H^1-H^1 COSY NMR, 400 MHz, $CDCl_3$

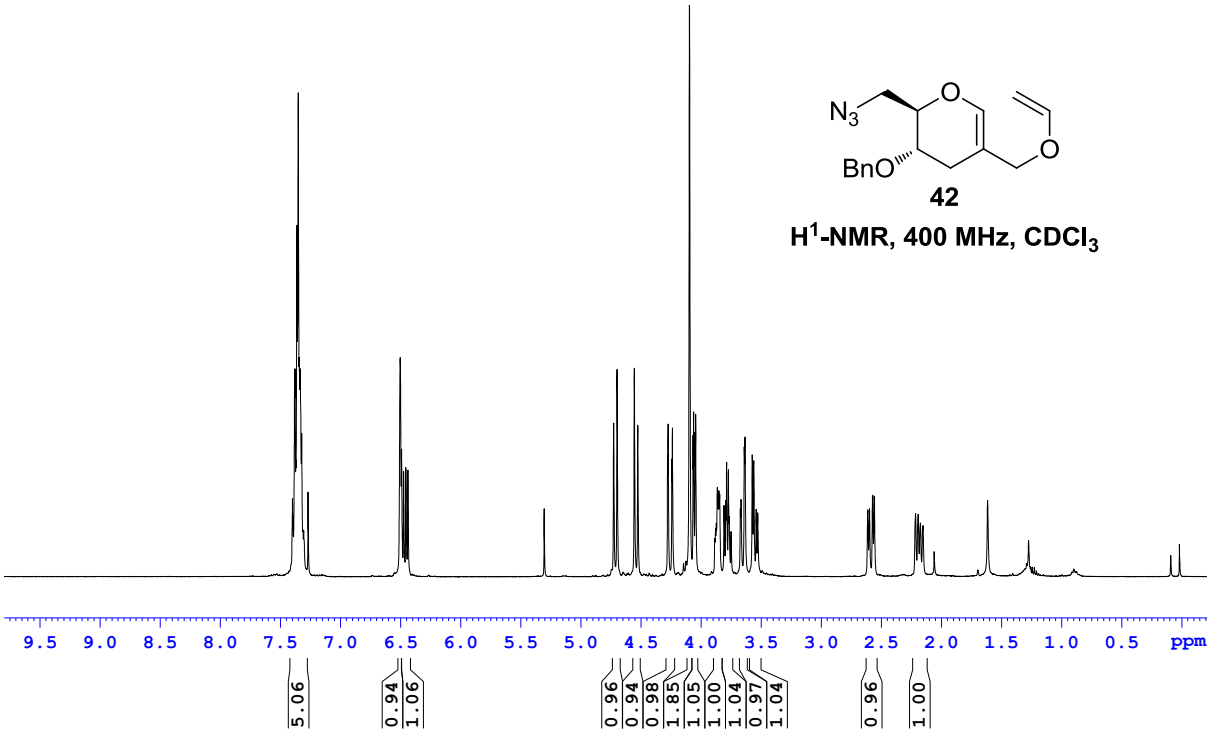


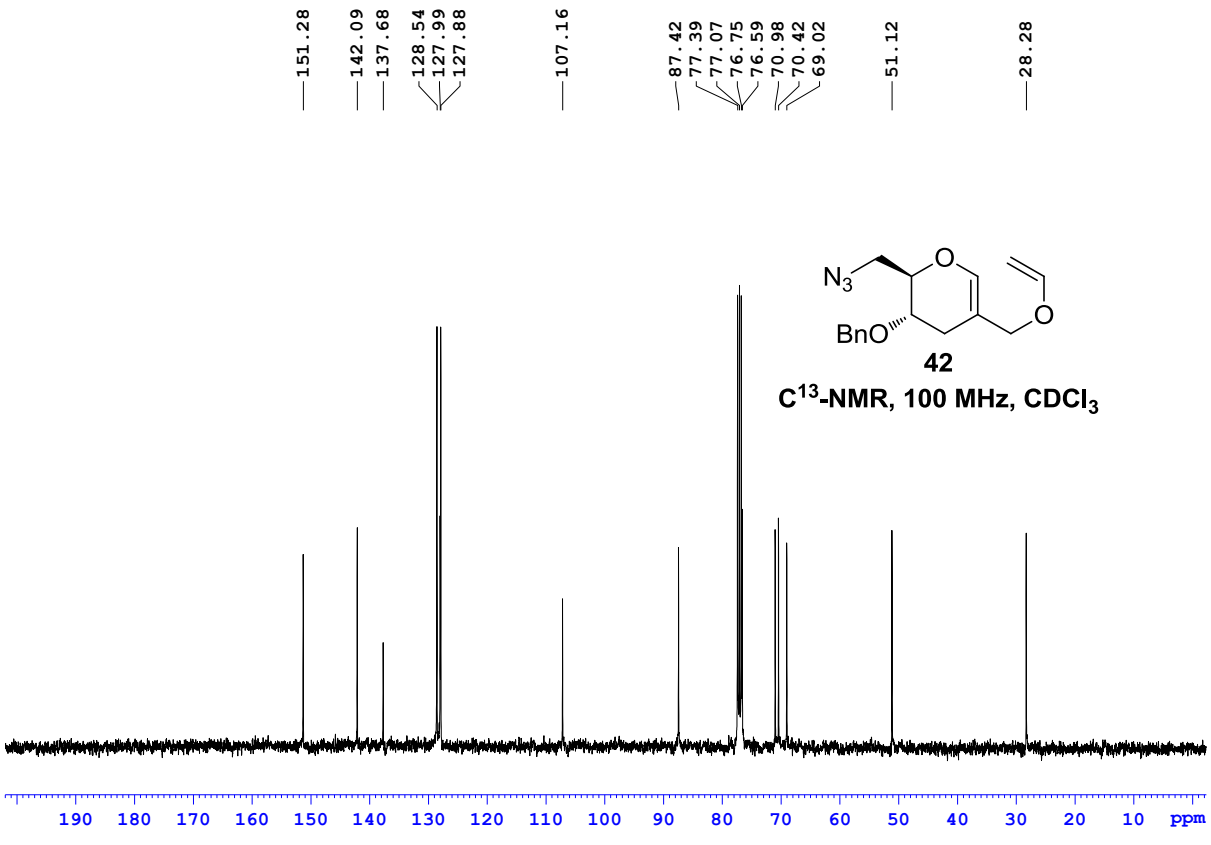


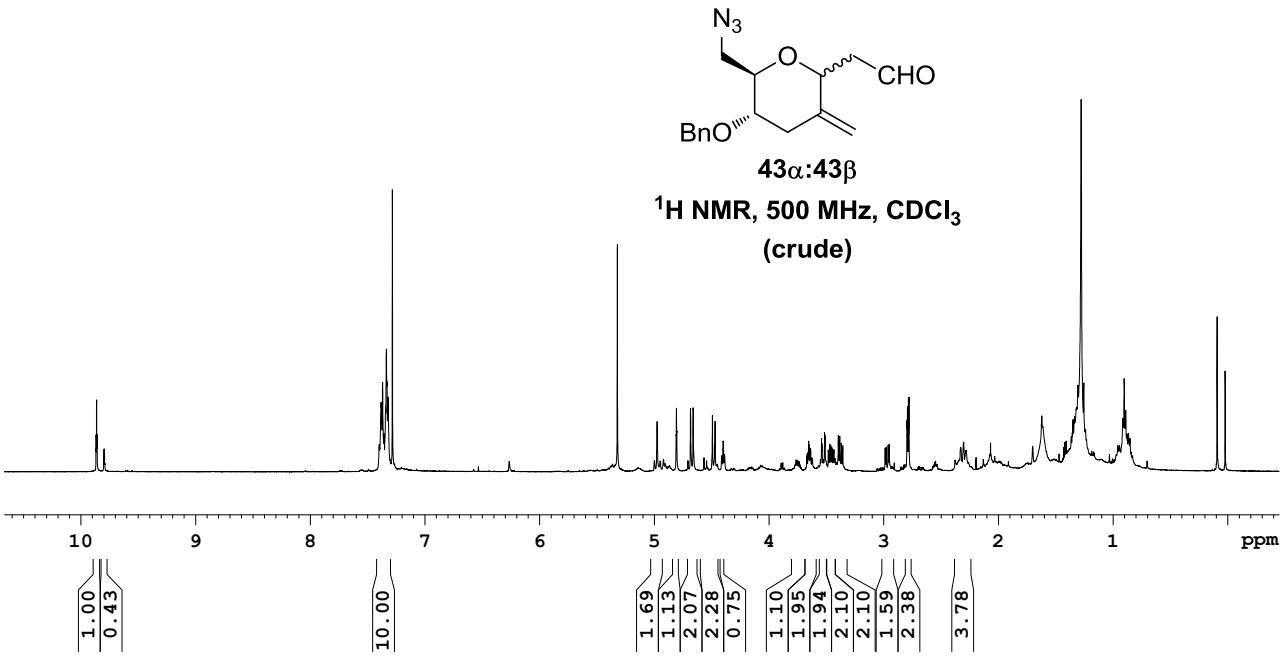
41α

H^1-H^1 NOESY NMR, 400 MHz, $CDCl_3$




N3
O
BnO
O
42
H1-NMR, 400 MHz, CDCl3
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
5.06
0.94
1.06
0.96
0.94
0.98
1.85
1.05
1.00
1.04
0.97
1.04
0.96
1.00

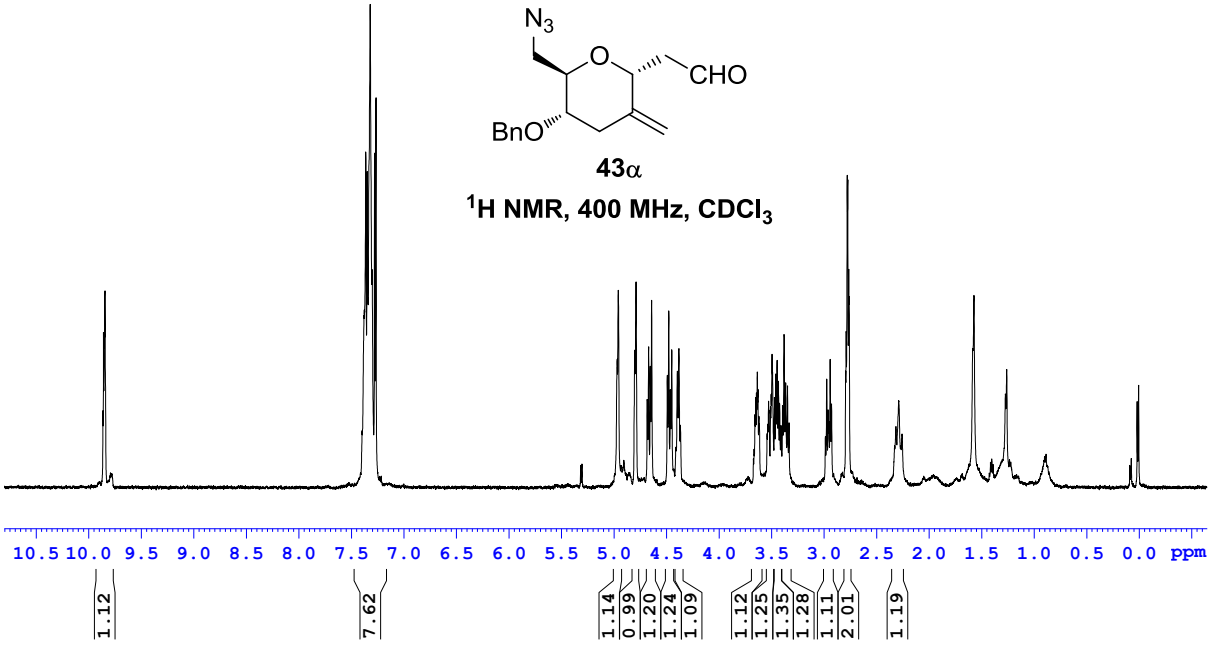

151.28
142.09
137.68
128.54
127.99
127.88
107.16
87.42
77.39
77.07
76.75
76.59
70.98
70.42
69.02
51.12
28.28
N3
O
BnO
O
42
C13-NMR, 100 MHz, CDCl3
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm



43α:43β

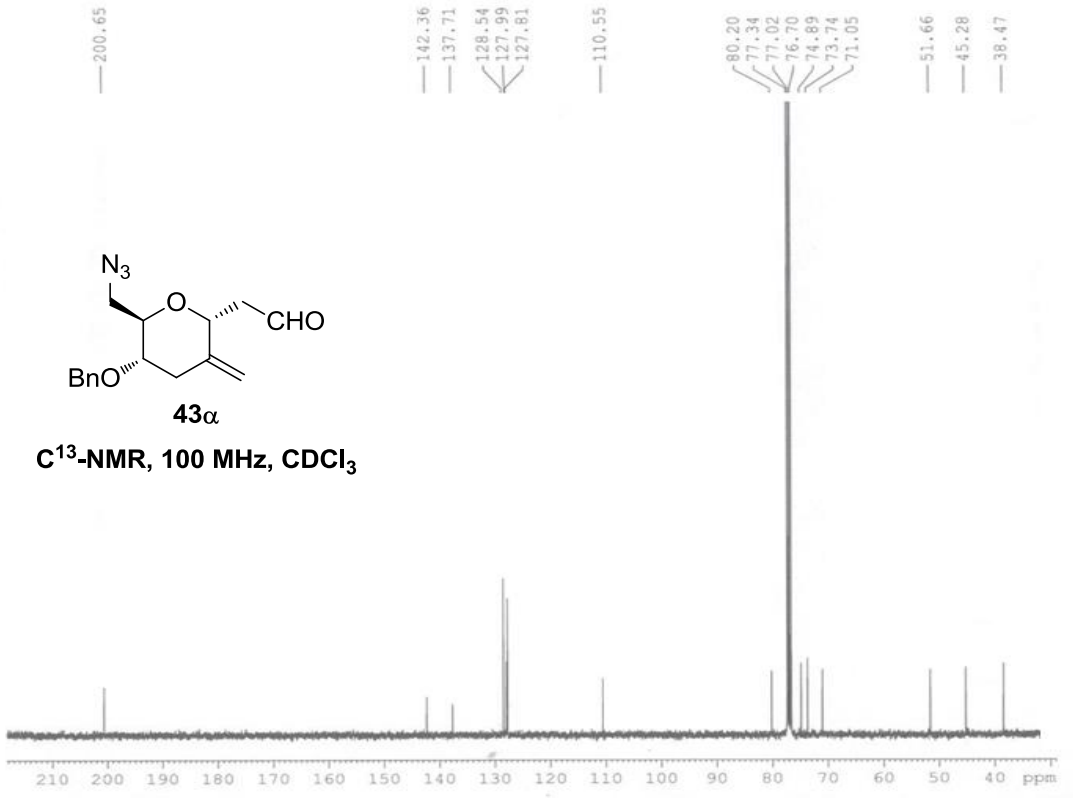
^{1}H NMR, 500 MHz, $CDCl_3$

(crude)



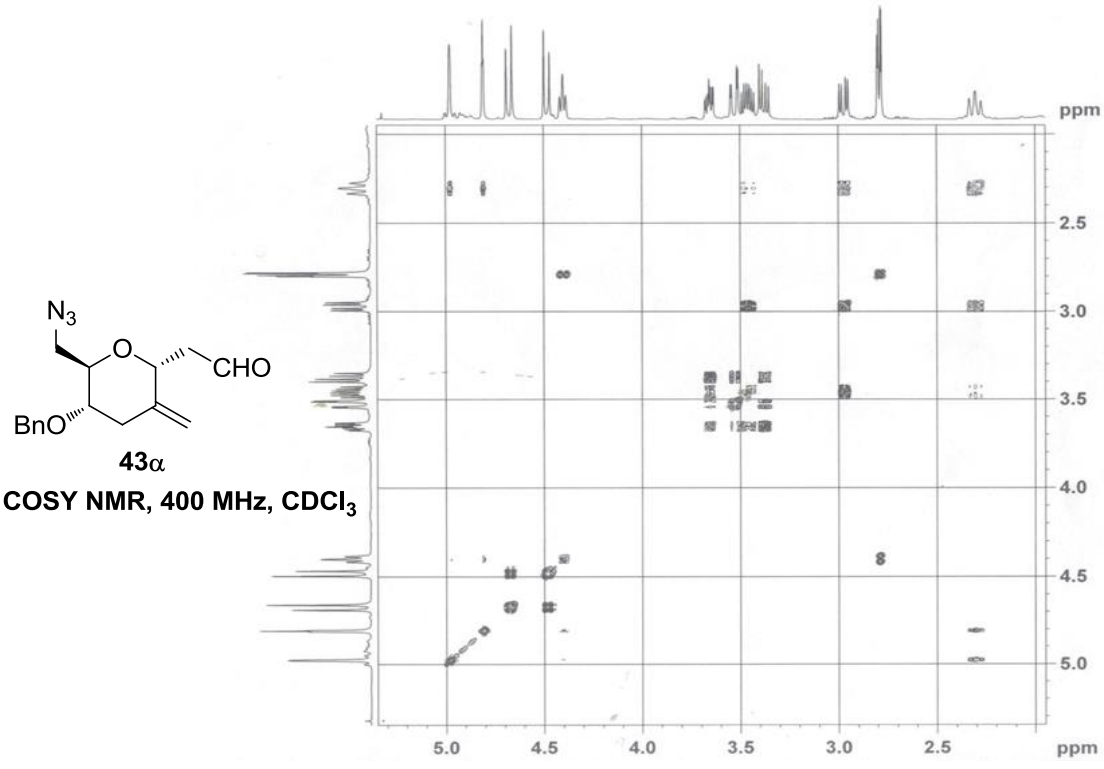
43α

^{1}H NMR, 400 MHz, $CDCl_3$



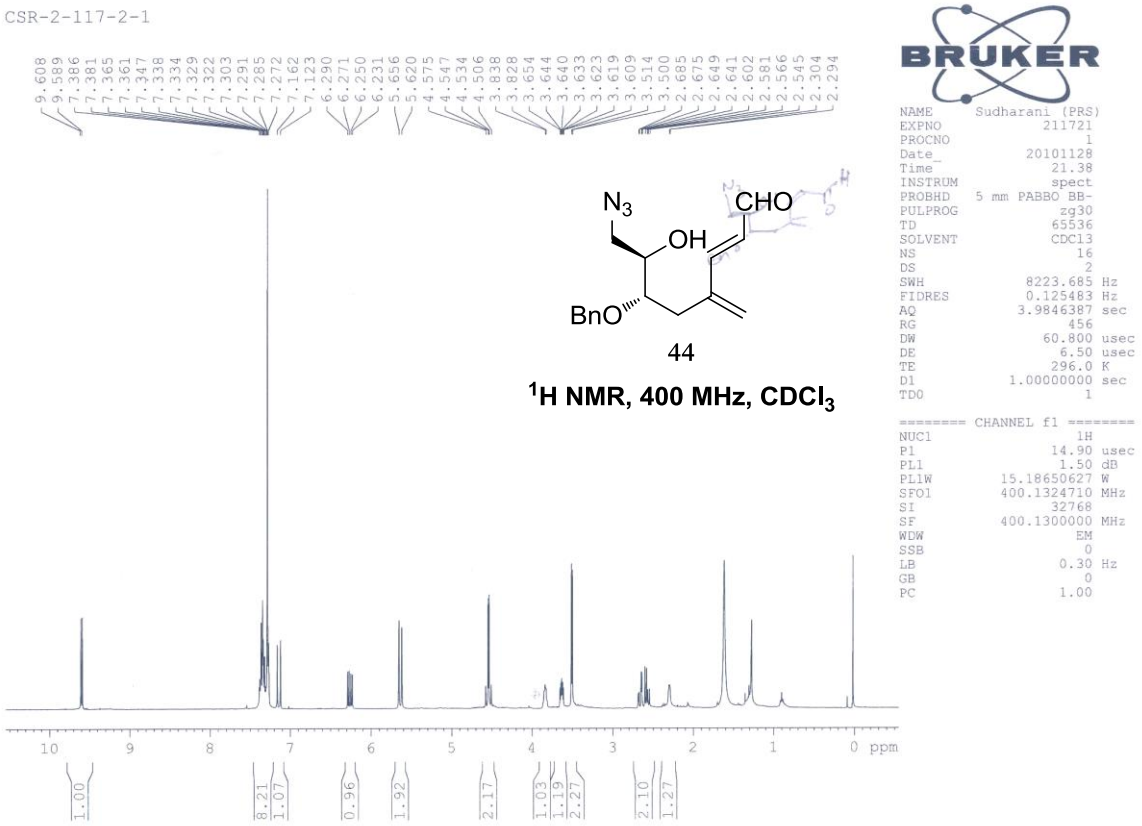
43α

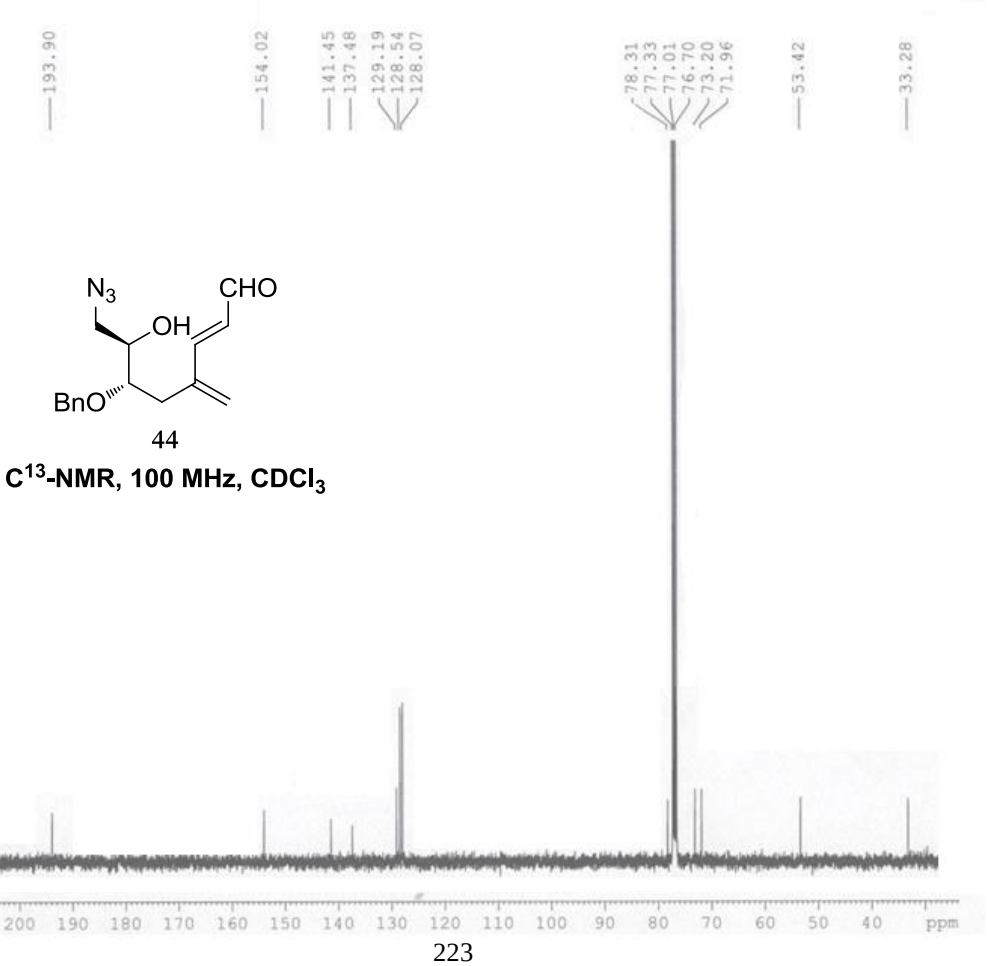
C^{13}-NMR, 100 MHz, $CDCl_3$

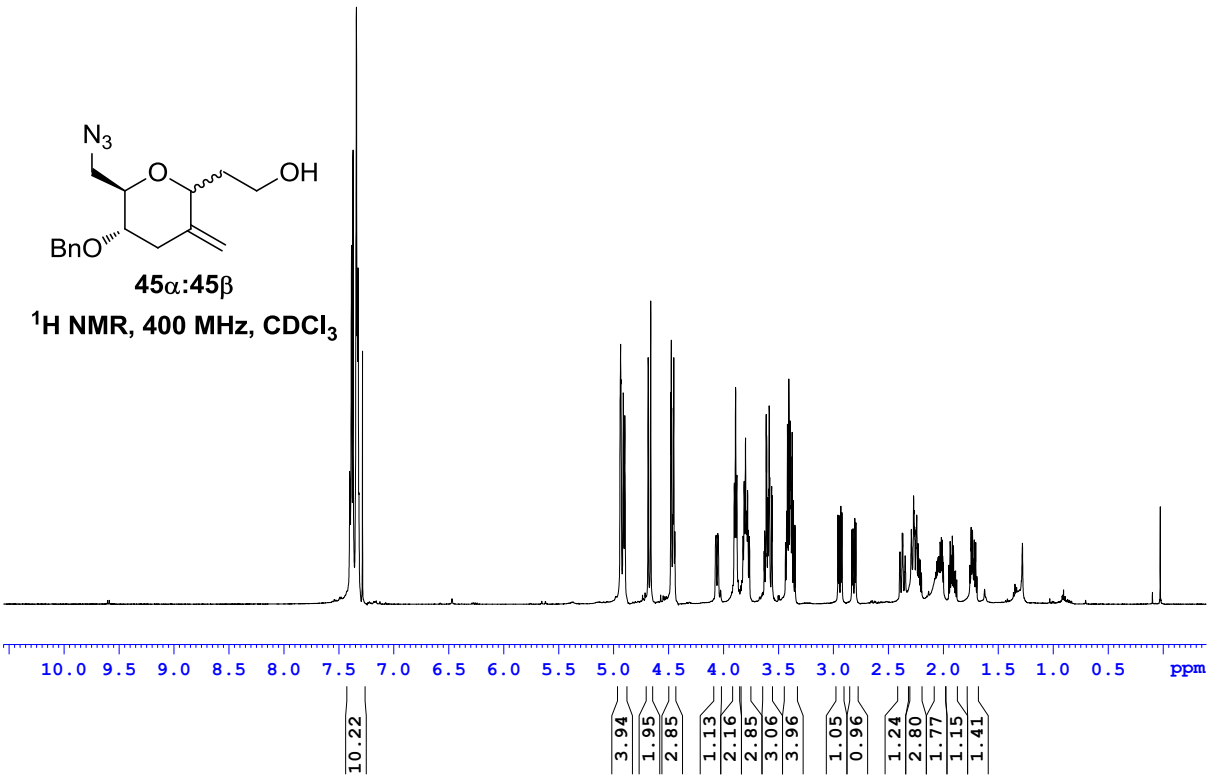


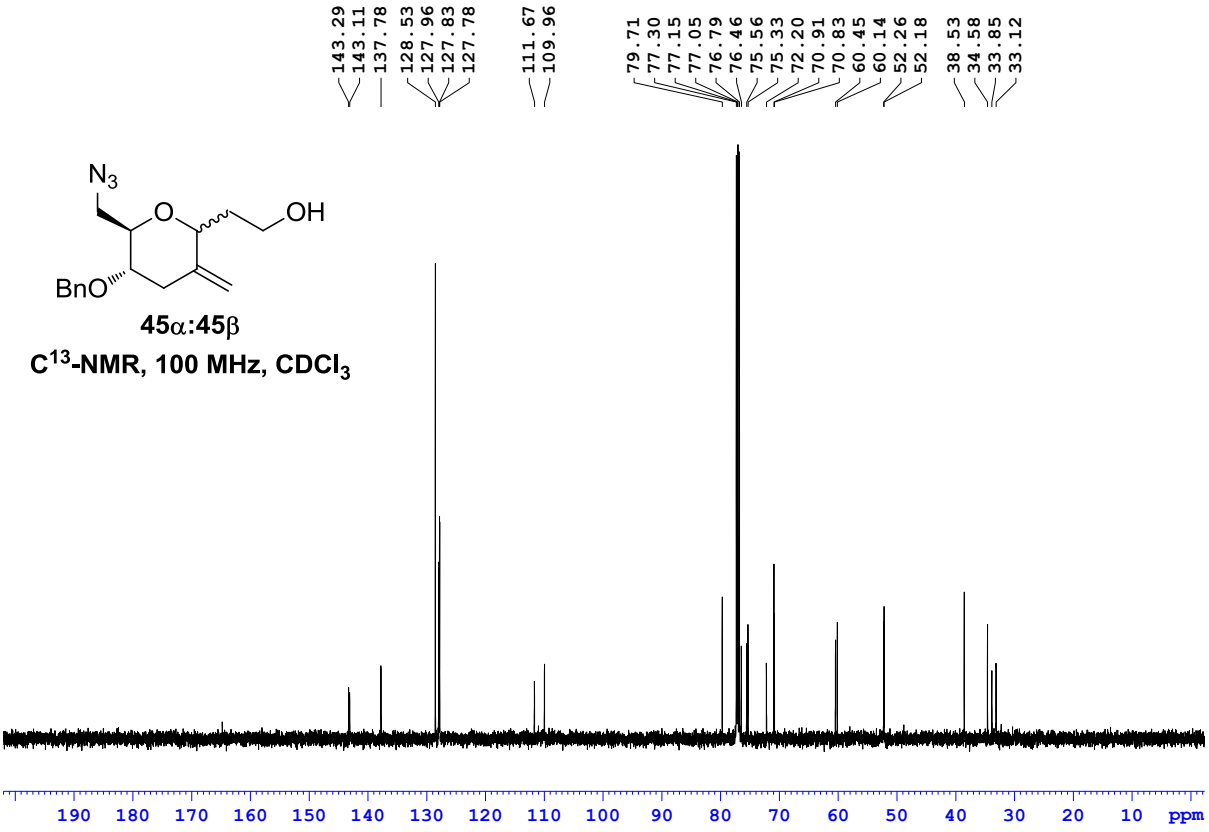
43α

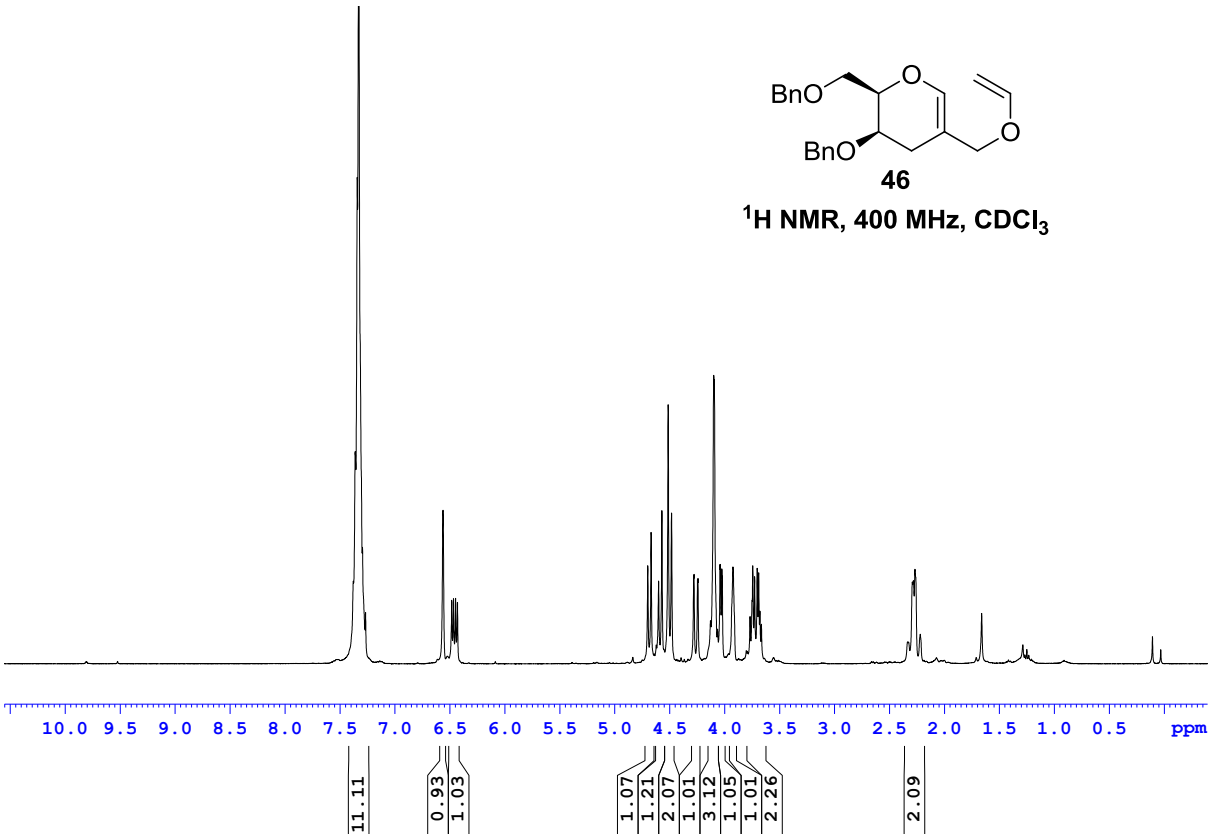
H^1-H^1 COSY NMR, 400 MHz, $CDCl_3$

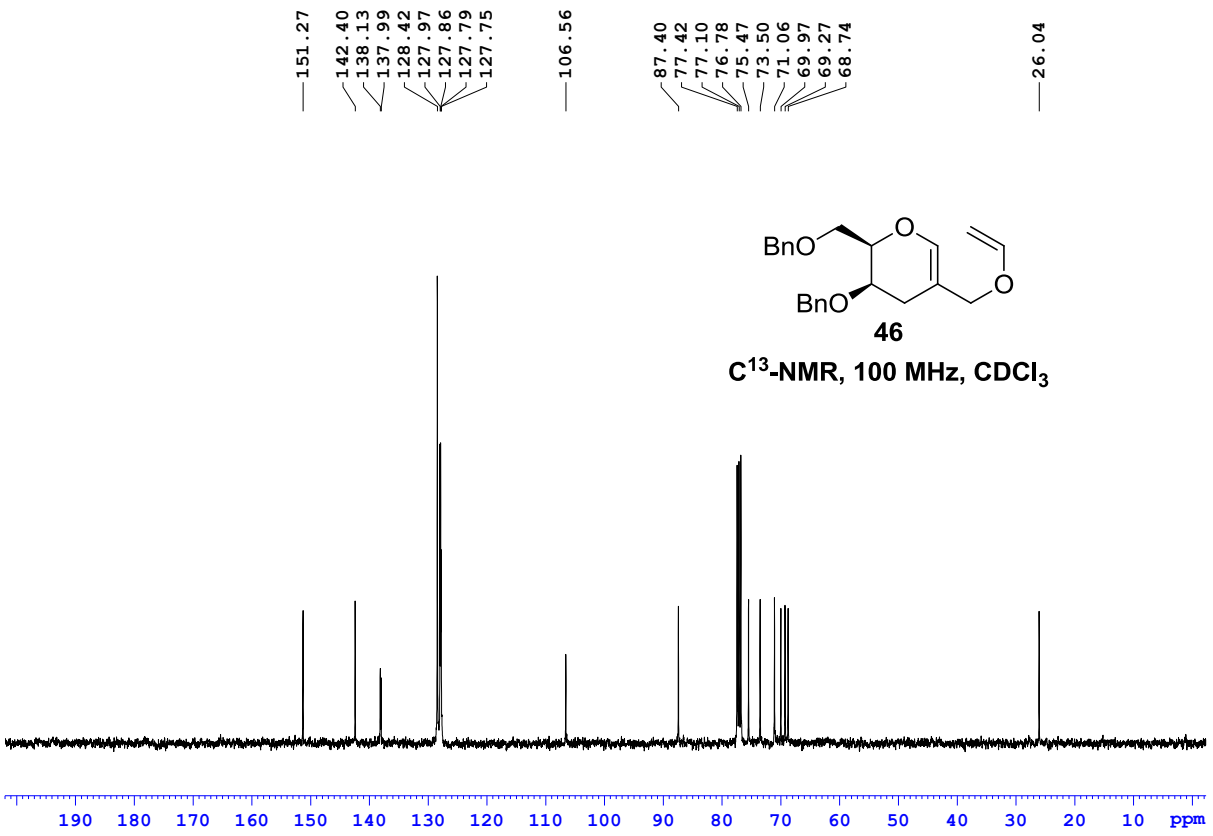

CSR-2-117-2-1
9.608 9.589 7.386 7.381 7.365 7.361 7.347 7.338 7.334 7.329 7.322 7.303 7.291 7.285 7.272 7.162 7.123 6.290 6.271 6.250 6.231 5.656 5.620 4.575 4.547 4.534 4.506 3.838 3.828 3.654 3.644 3.640 3.633 3.623 3.619 3.609 3.514 3.500 2.685 2.675 2.649 2.641 2.602 2.581 2.566 2.545 2.304 2.294
N3
CHO
OH
BnO
44
1H NMR, 400 MHz, CDCl3
BRUKER
NAME Sudharani (PRS)
EXPNO 211721
PROCNO 1
Date_ 20101128
Time 21.38
INSTRUM spect
PROBHD 5 mm PABBO BB-
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 8223.685 Hz
FIDRES 0.125483 Hz
AQ 3.9846387 sec
RG 456
DW 60.800 usec
DE 6.50 usec
TE 296.0 K
D1 1.00000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 1H
P1 14.90 usec
PL1 1.50 dB
PL1W 15.18650627 W
SFO1 400.1324710 MHz
SI 32768
SF 400.1300000 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
10 9 8 7 6 5 4 3 2 1 0 ppm
1.00 8.21 1.07 0.96 1.92 2.17 1.03 1.19 2.27 2.10 1.27

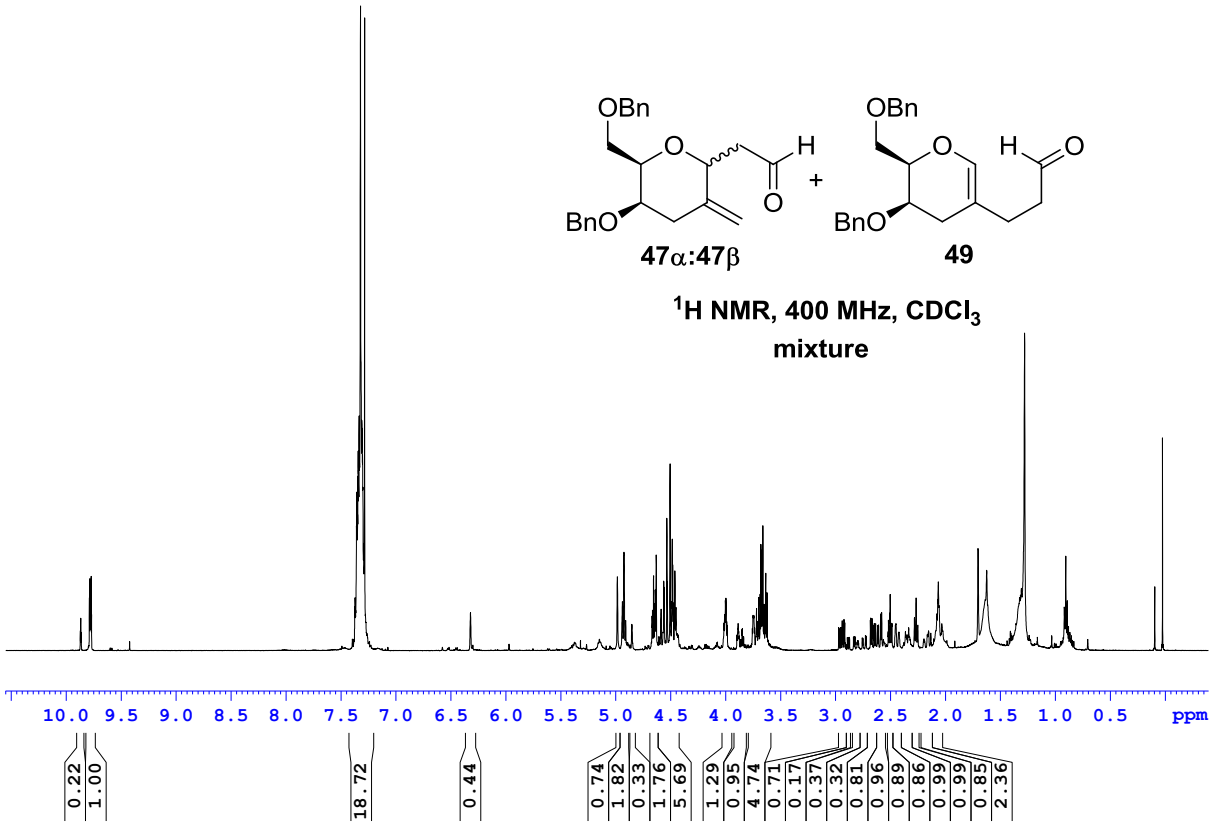

193.90
154.02
141.45
137.48
129.19
128.54
128.07
78.31
77.33
77.01
76.70
73.20
71.96
53.42
33.28
N3
CHO
OH
BnO
44
C13-NMR, 100 MHz, CDCl3
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 ppm

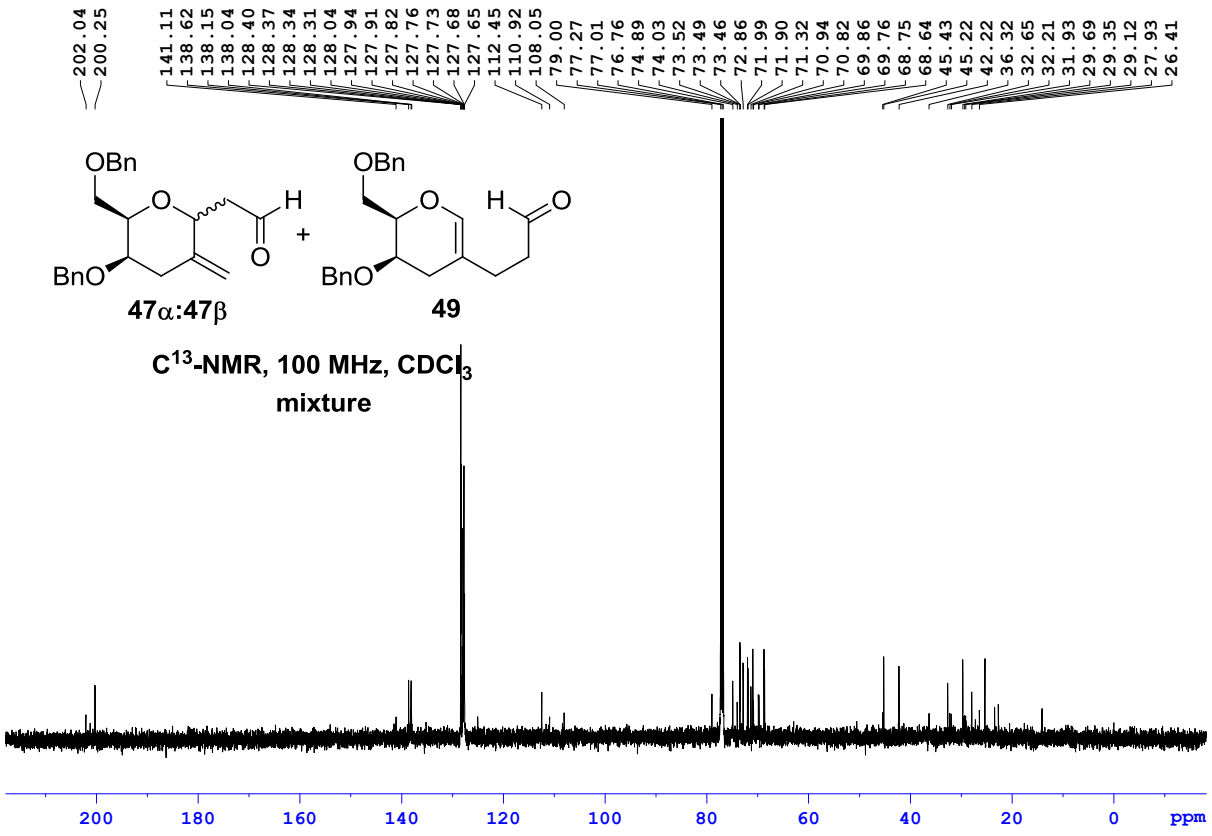

N3
O
OH
BnO
45α:45β
1H NMR, 400 MHz, CDCl3
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
10.22
3.94
1.95
2.85
1.13
2.16
2.85
3.06
3.96
1.05
0.96
1.24
2.80
1.77
1.15
1.41

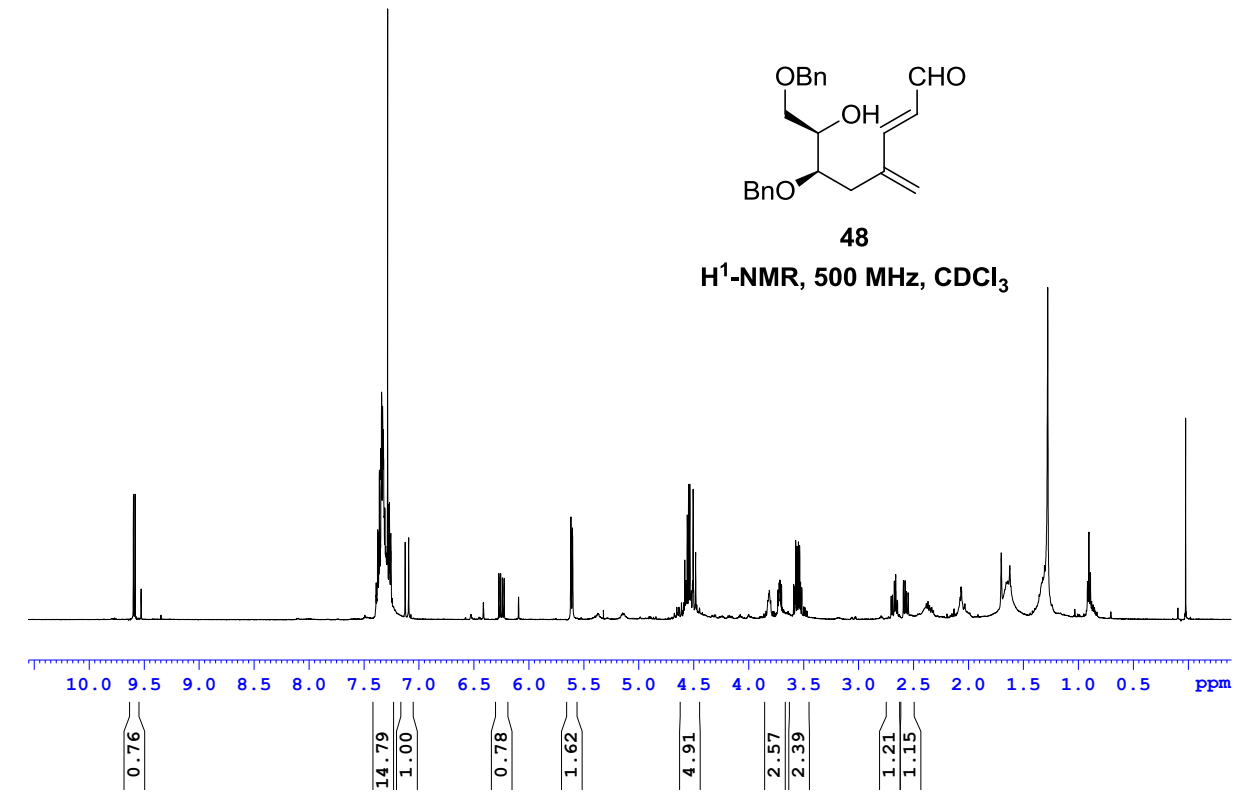

143.29
143.11
137.78
128.53
127.96
127.83
127.78
111.67
109.96
79.71
77.30
77.15
77.05
76.79
76.46
75.56
75.33
72.20
70.91
70.83
60.45
60.14
52.26
52.18
38.53
34.58
33.85
33.12
N3
O
OH
BnO
45α:45β
C13-NMR, 100 MHz, CDCl3
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm


BnO
BnO
O
O
46
1H NMR, 400 MHz, CDCl3
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
11.11
0.93
1.03
1.07
1.21
2.07
1.01
3.12
1.05
1.01
2.26
2.09


151.27
142.40
138.13
137.99
128.42
127.97
127.86
127.79
127.75
106.56
87.40
77.42
77.10
76.78
75.47
73.50
71.06
69.97
69.27
68.74
26.04
BnO
BnO
O
O
46
C13-NMR, 100 MHz, CDCl3
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

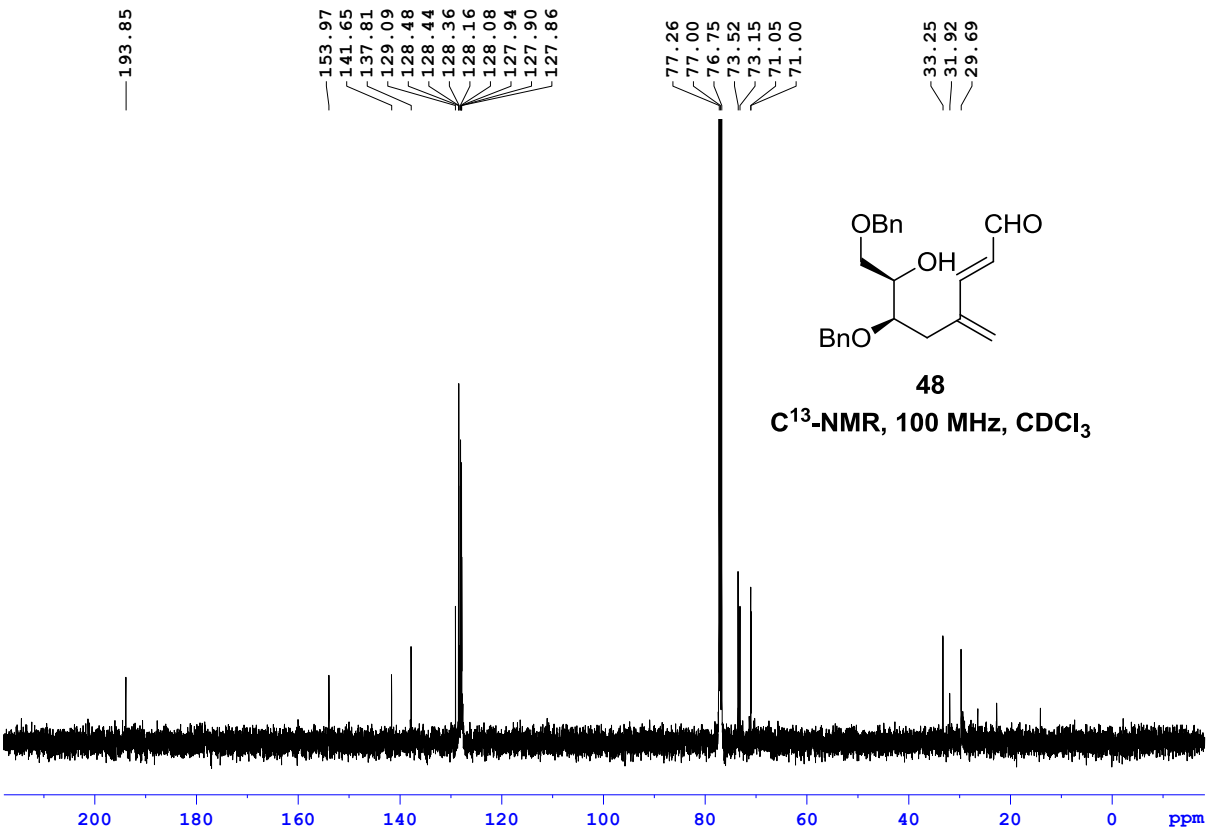

OBn
O
H
O
BnO
+
OBn
O
H
O
BnO
47α:47β
49
^{1}H NMR, 400 MHz, CDCl$_3$
mixture
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
0.22
1.00
18.72
0.44
0.74
1.82
0.33
1.76
5.69
1.29
0.95
4.74
0.71
0.17
0.37
0.32
0.81
0.96
0.89
0.86
0.99
0.99
0.85
2.36


202.04
200.25
141.11
138.62
138.15
138.04
128.40
128.37
128.34
128.31
128.04
127.94
127.91
127.82
127.76
127.73
127.68
127.65
112.45
110.92
108.05
79.00
77.27
77.01
76.76
74.89
74.03
73.52
73.49
73.46
72.86
71.99
71.90
71.32
70.94
70.82
69.86
69.76
68.75
68.64
45.43
45.22
42.22
36.32
32.65
32.21
31.93
29.69
29.35
29.12
27.93
26.41
OBn
O
H
O
BnO
+
OBn
O
H
O
BnO
47α:47β
49
C^{13}-NMR, 100 MHz, CDCl$_3$
mixture
200 180 160 140 120 100 80 60 40 20 0 ppm



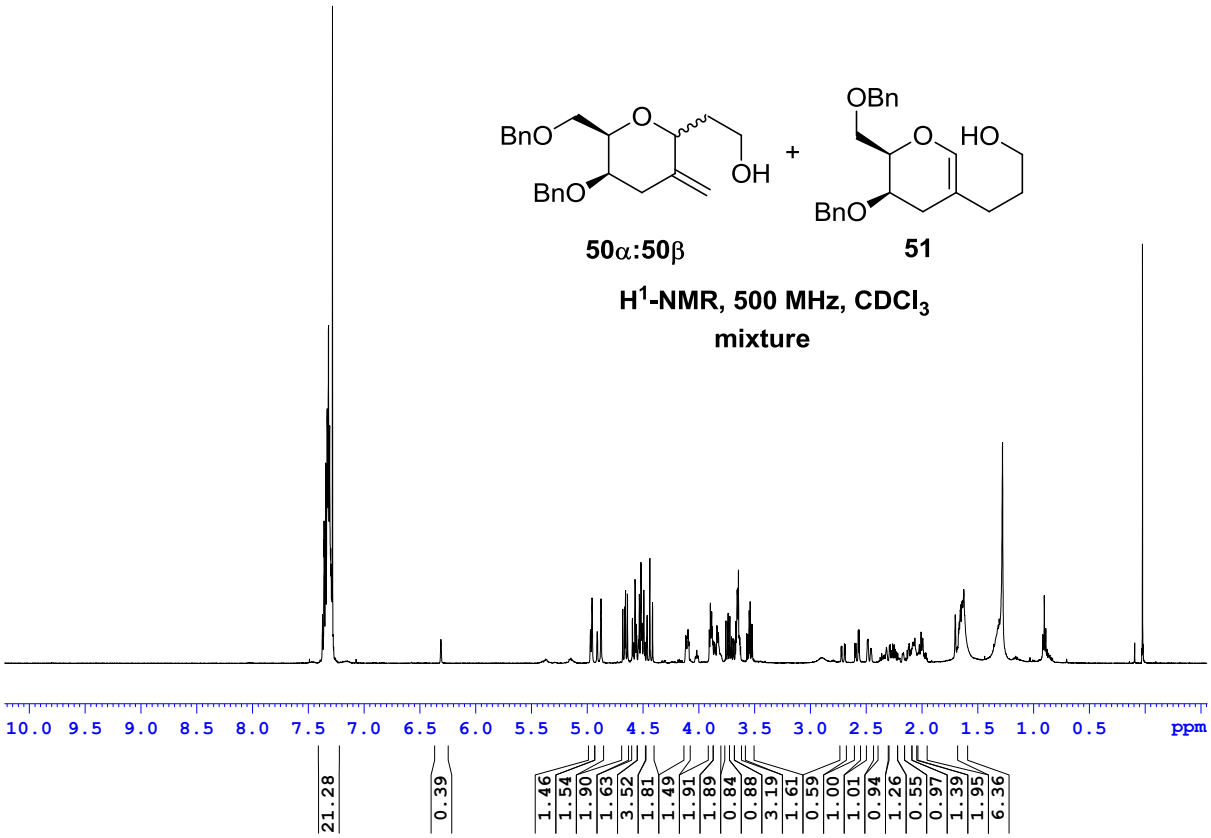
48

H^1-NMR, 500 MHz, $CDCl_3$



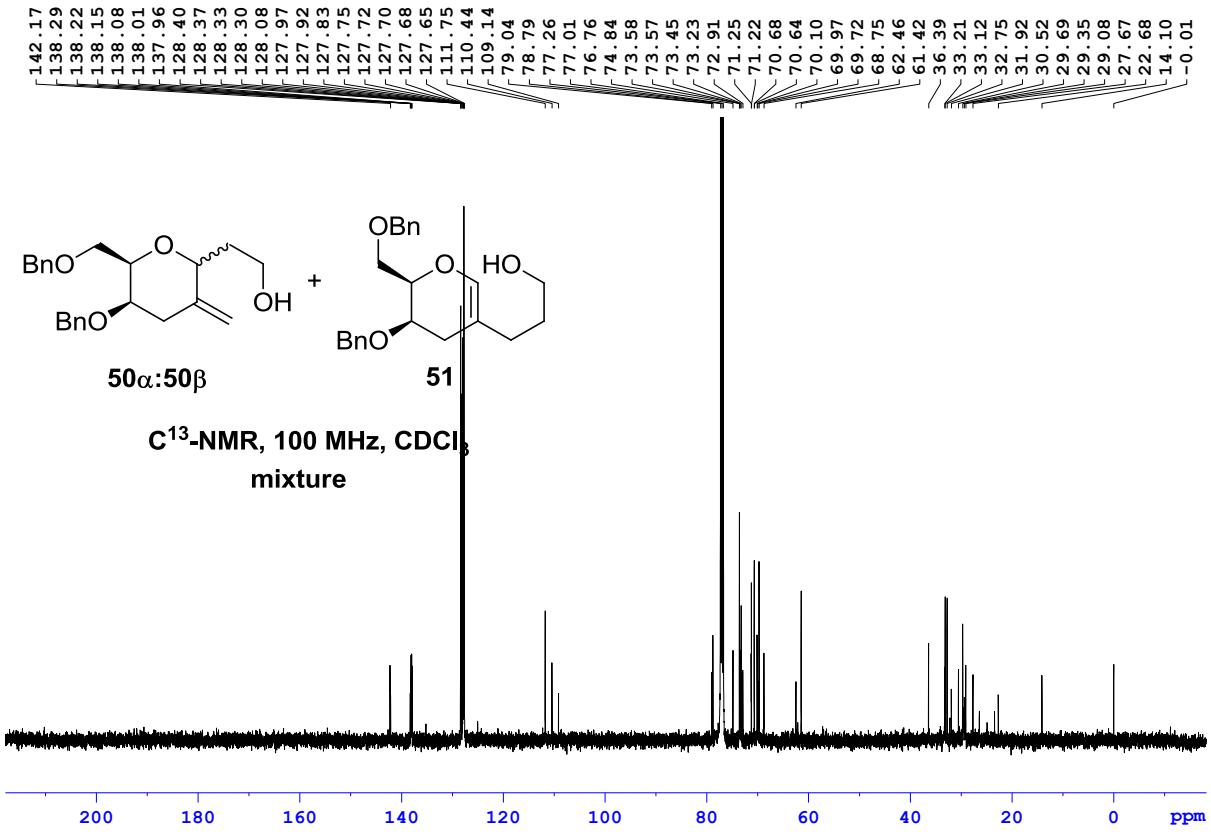
48

C^{13}-NMR, 100 MHz, $CDCl_3$



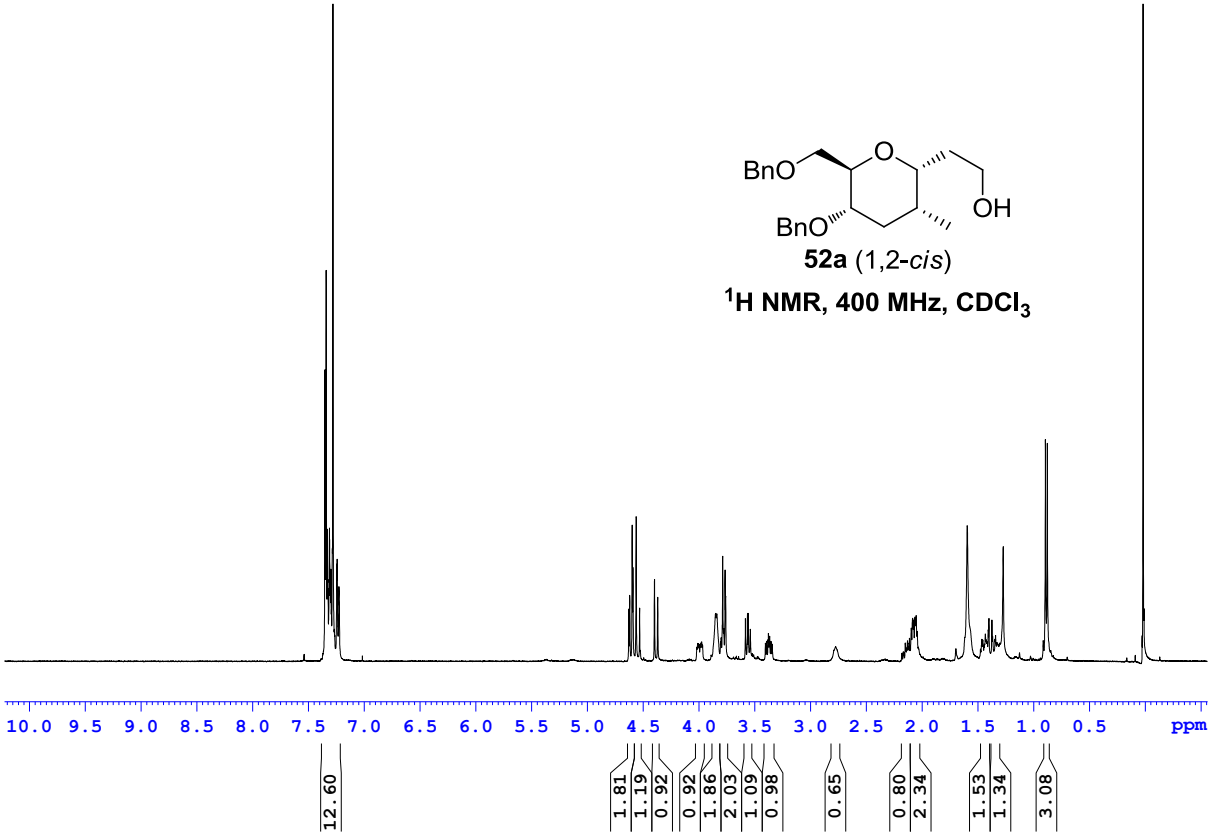
50α:50β **51**

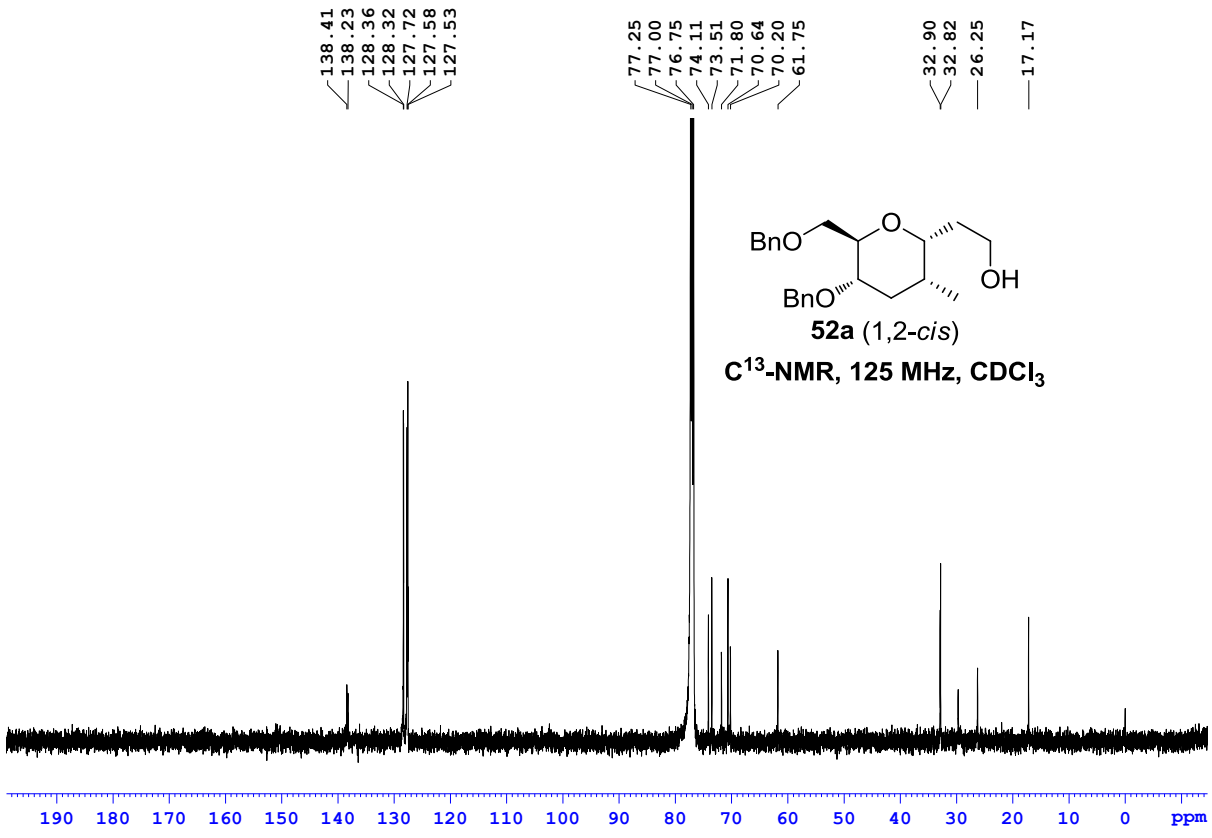
H[1]-NMR, 500 MHz, $CDCl_3$
mixture

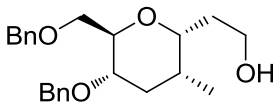


50α:50β **51**

C[13]-NMR, 100 MHz, $CDCl_3$
mixture

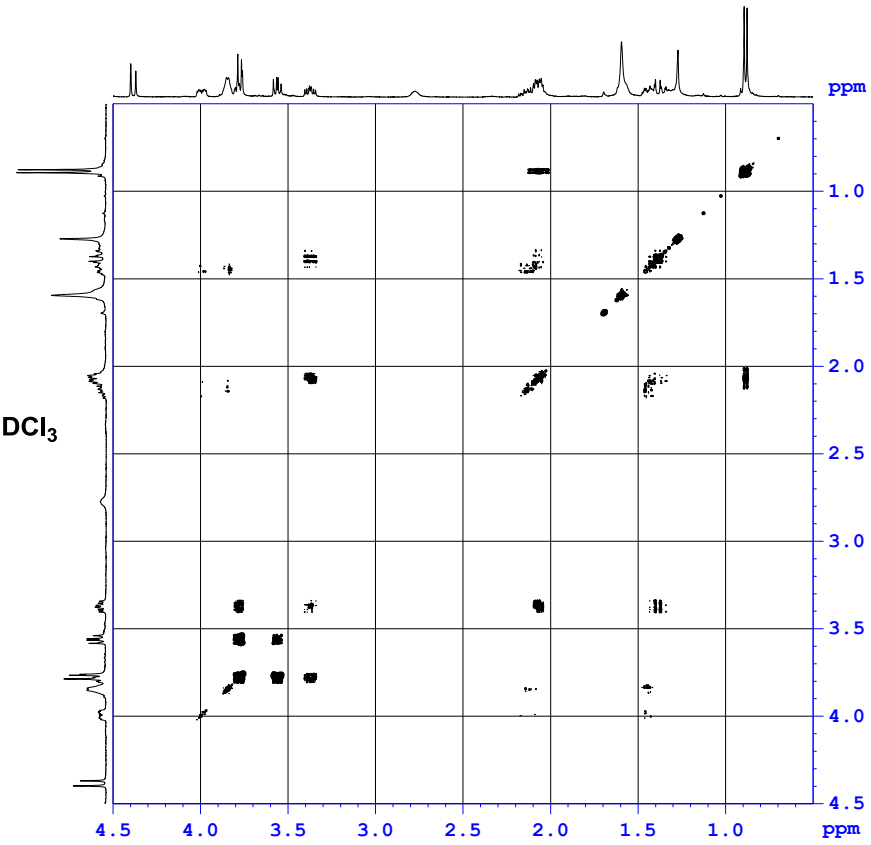

BnO
O
OH
BnO
52a (1,2-cis)
1H NMR, 400 MHz, CDCl3
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
12.60
1.81
1.19
0.92
0.92
1.86
2.03
1.09
0.98
0.65
0.80
2.34
1.53
1.34
3.08

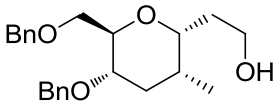

138.41
138.23
128.36
128.32
127.72
127.58
127.53
77.25
77.00
76.75
74.11
73.51
71.80
70.64
70.20
61.75
32.90
32.82
26.25
17.17
BnO
O
OH
BnO
52a (1,2-cis)
C13-NMR, 125 MHz, CDCl3
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm



52a (1,2-*cis*)

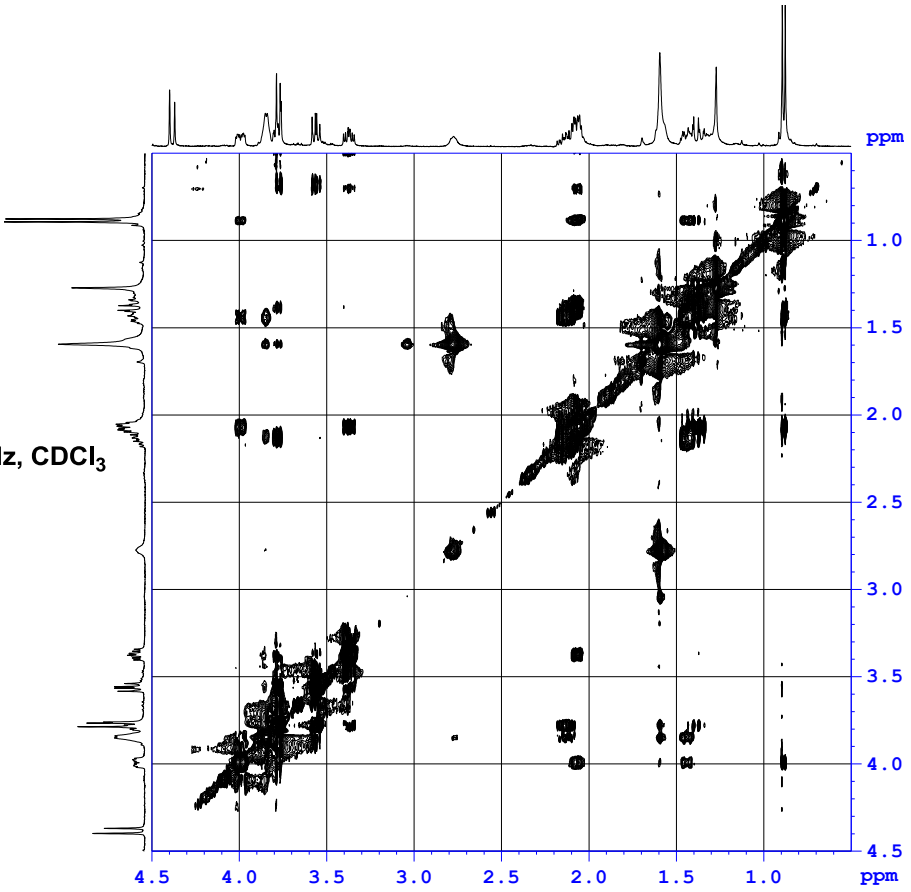
H^1-H^1 COSY NMR, 400 MHz, $CDCl_3$

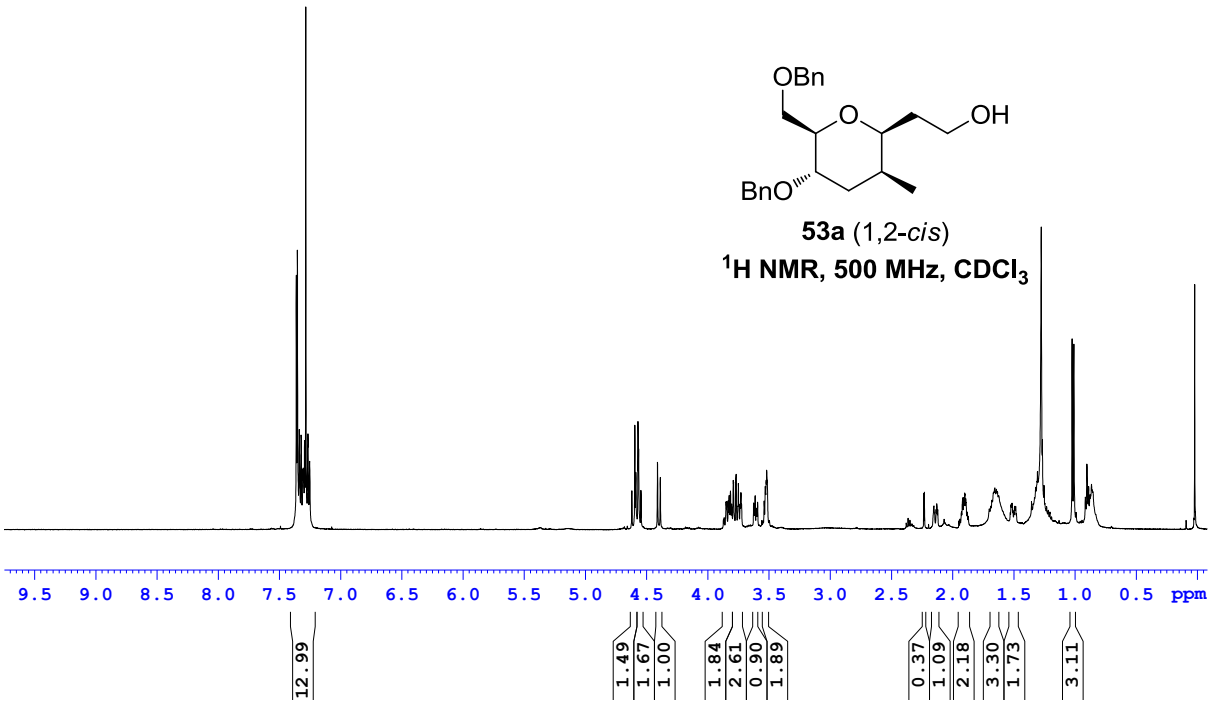




52a (1,2-*cis*)

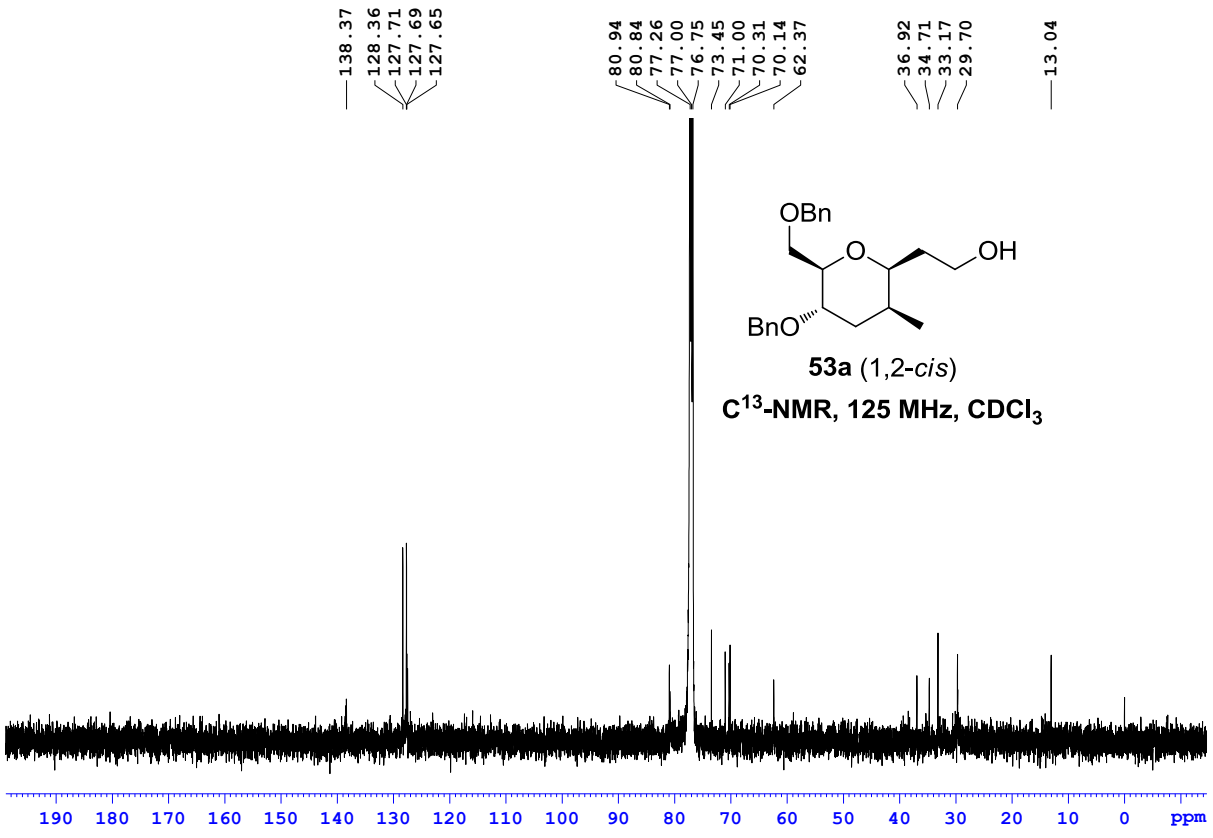
H^1-H^1 NOESY NMR, 400 MHz, $CDCl_3$





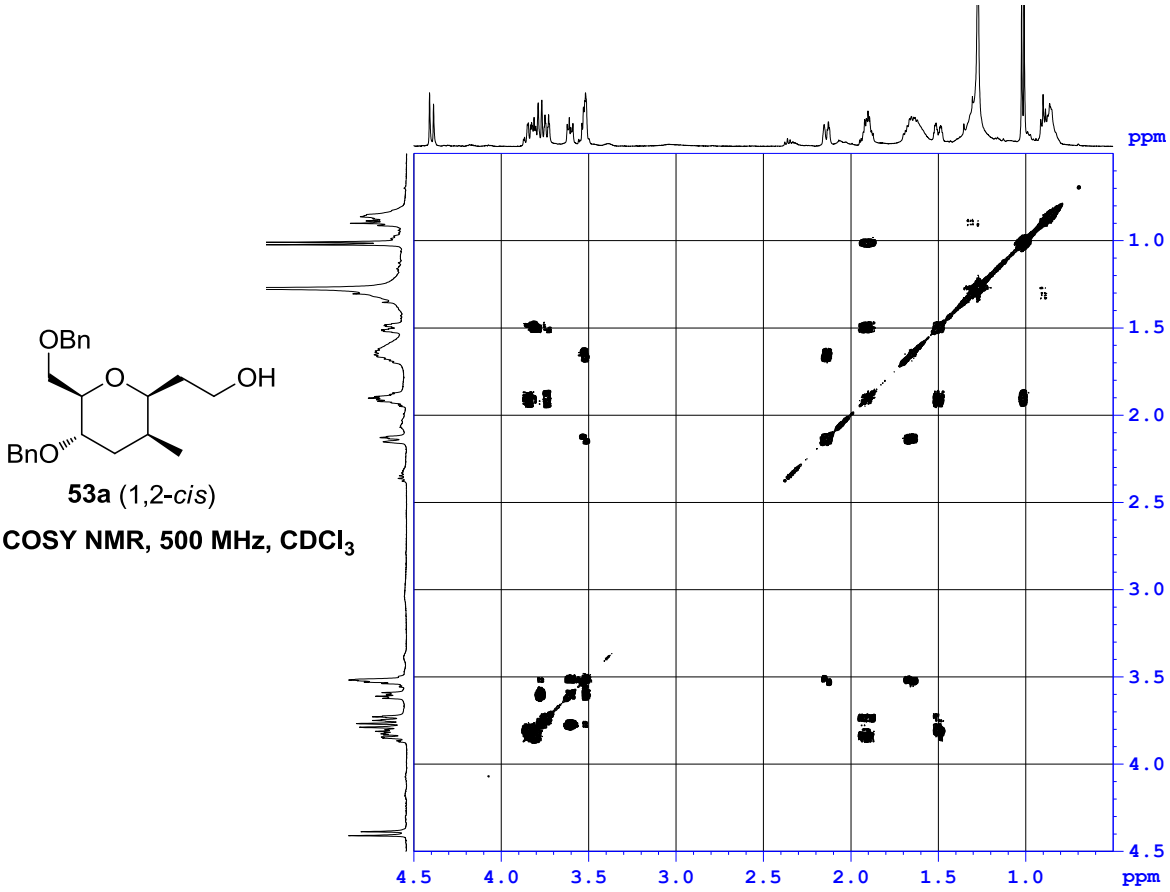
53a (1,2-*cis*)

^{1}H NMR, 500 MHz, $CDCl_3$



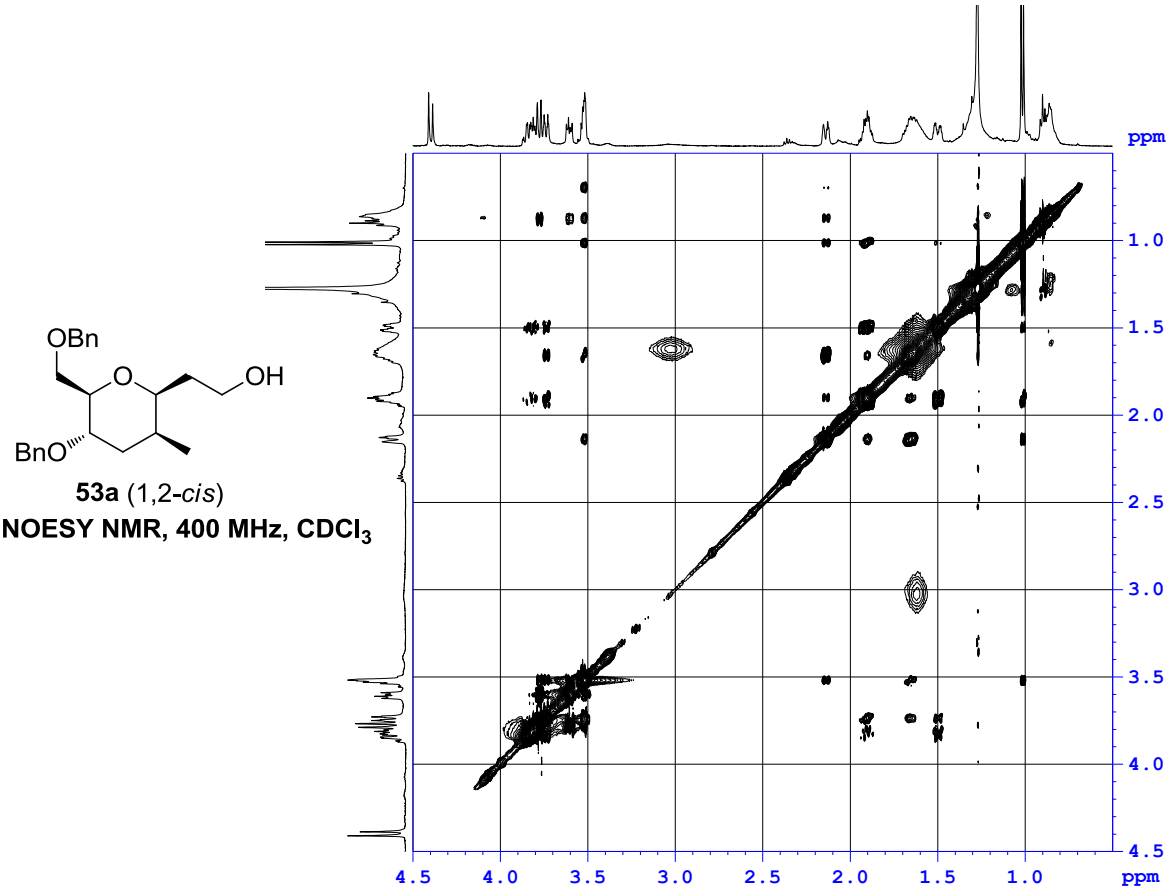
53a (1,2-*cis*)

C^{13}-NMR, 125 MHz, $CDCl_3$



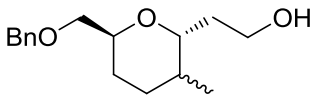
53a (1,2-*cis*)

H^1-H^1 COSY NMR, 500 MHz, $CDCl_3$



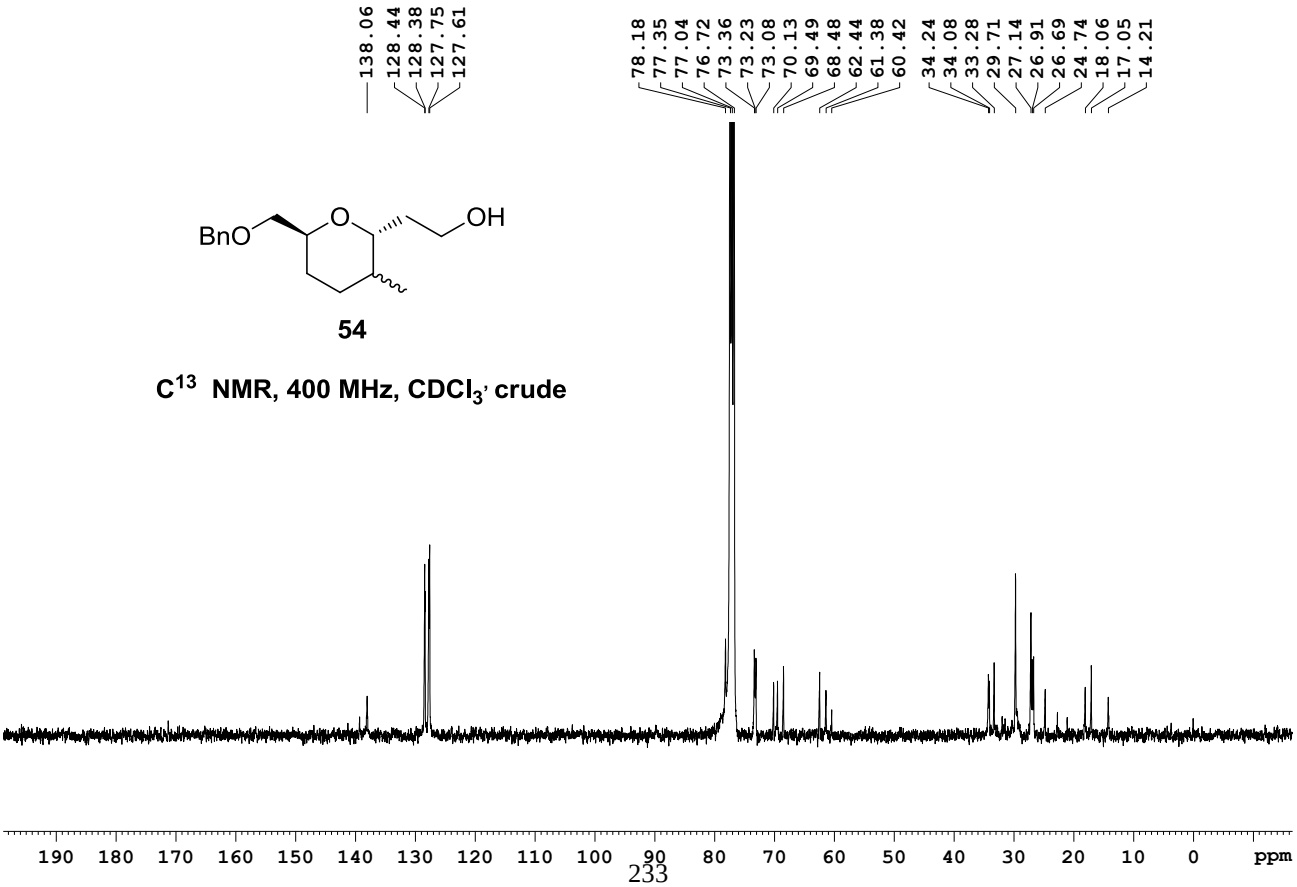
53a (1,2-*cis*)

H^1-H^1 NOESY NMR, 400 MHz, $CDCl_3$



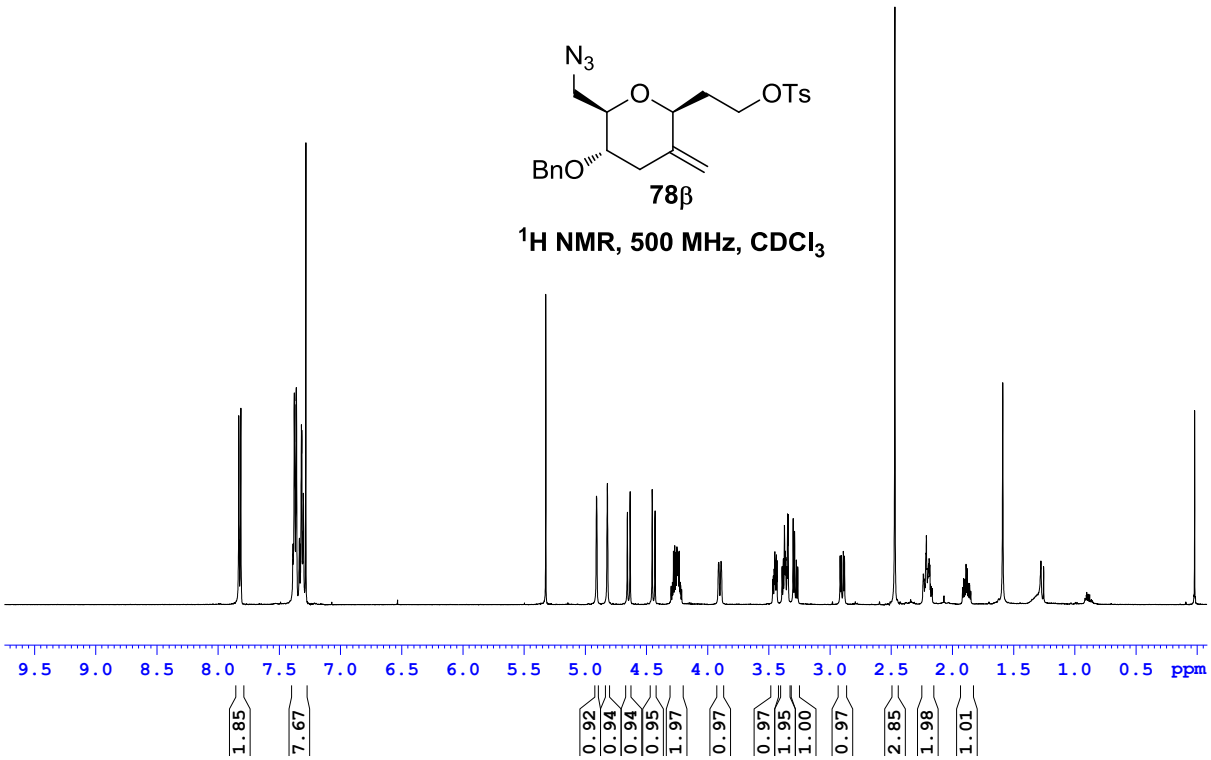
54

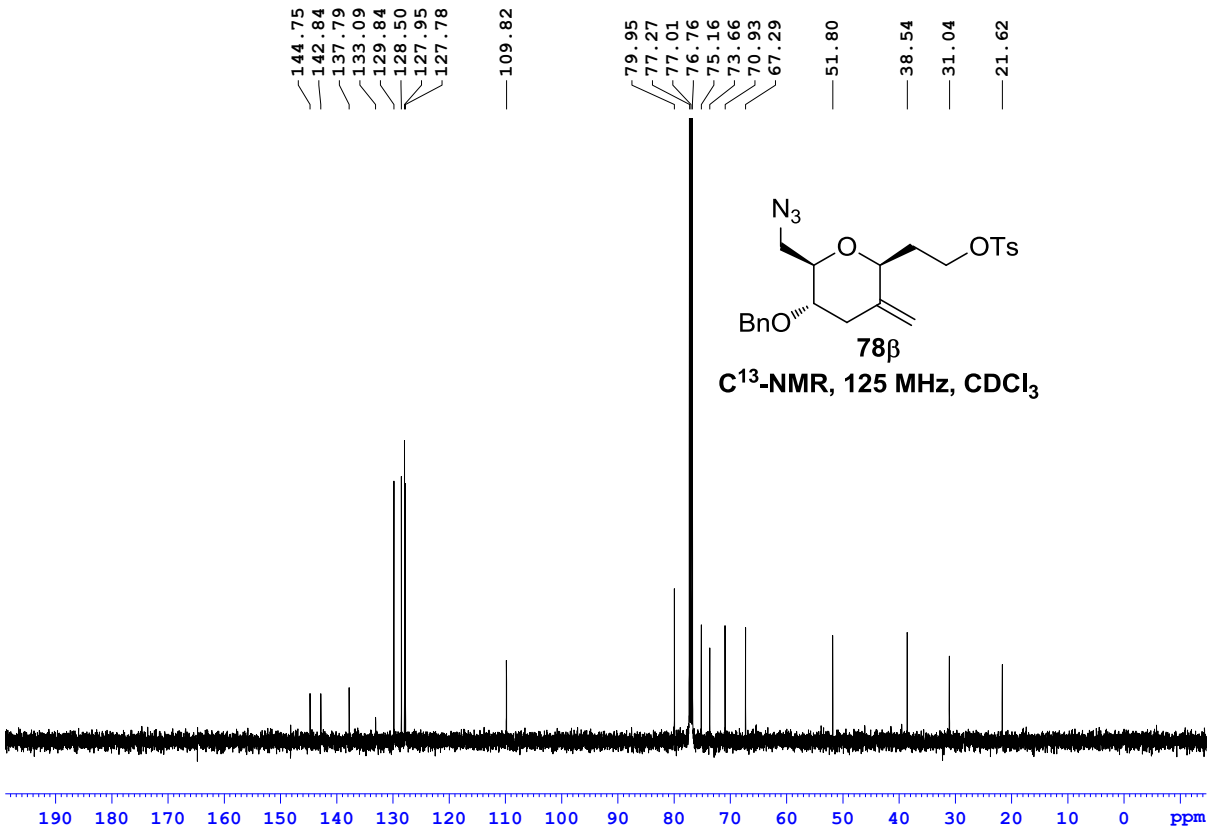
H^1 NMR, 400 MHz, $CDCl_3$, crude

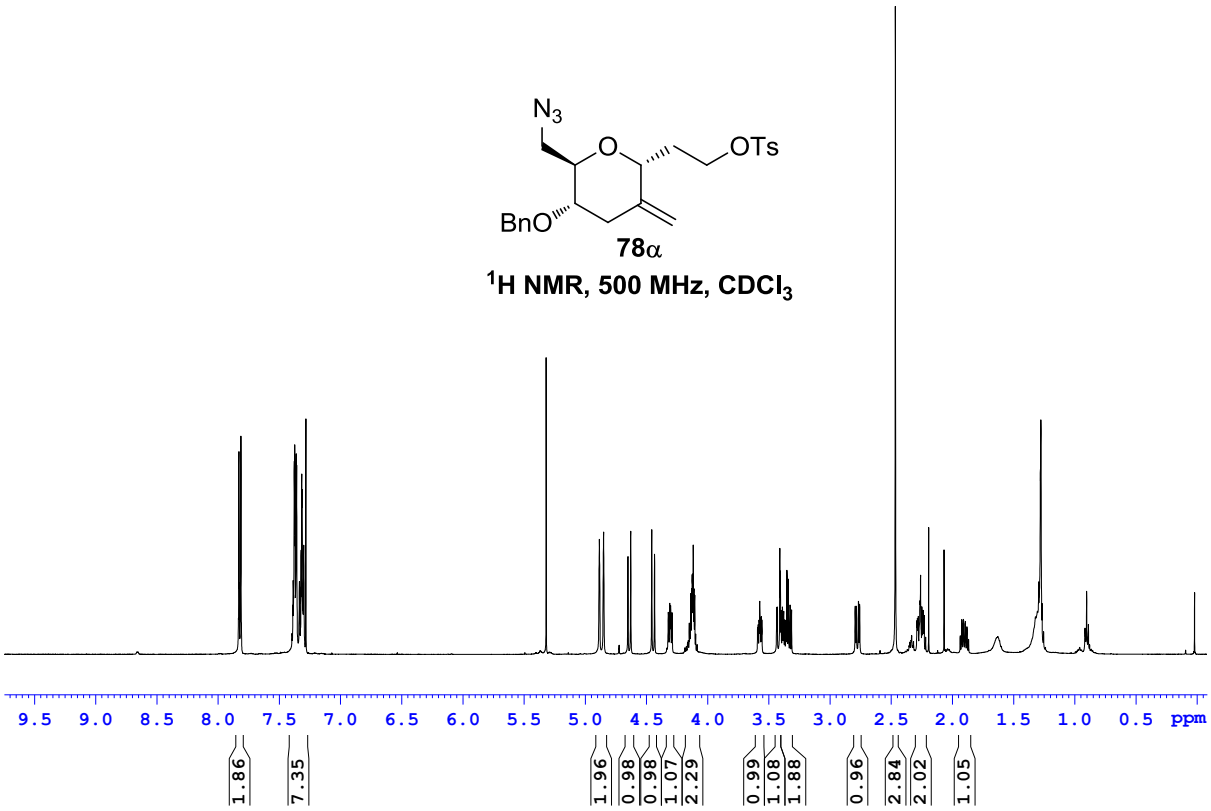


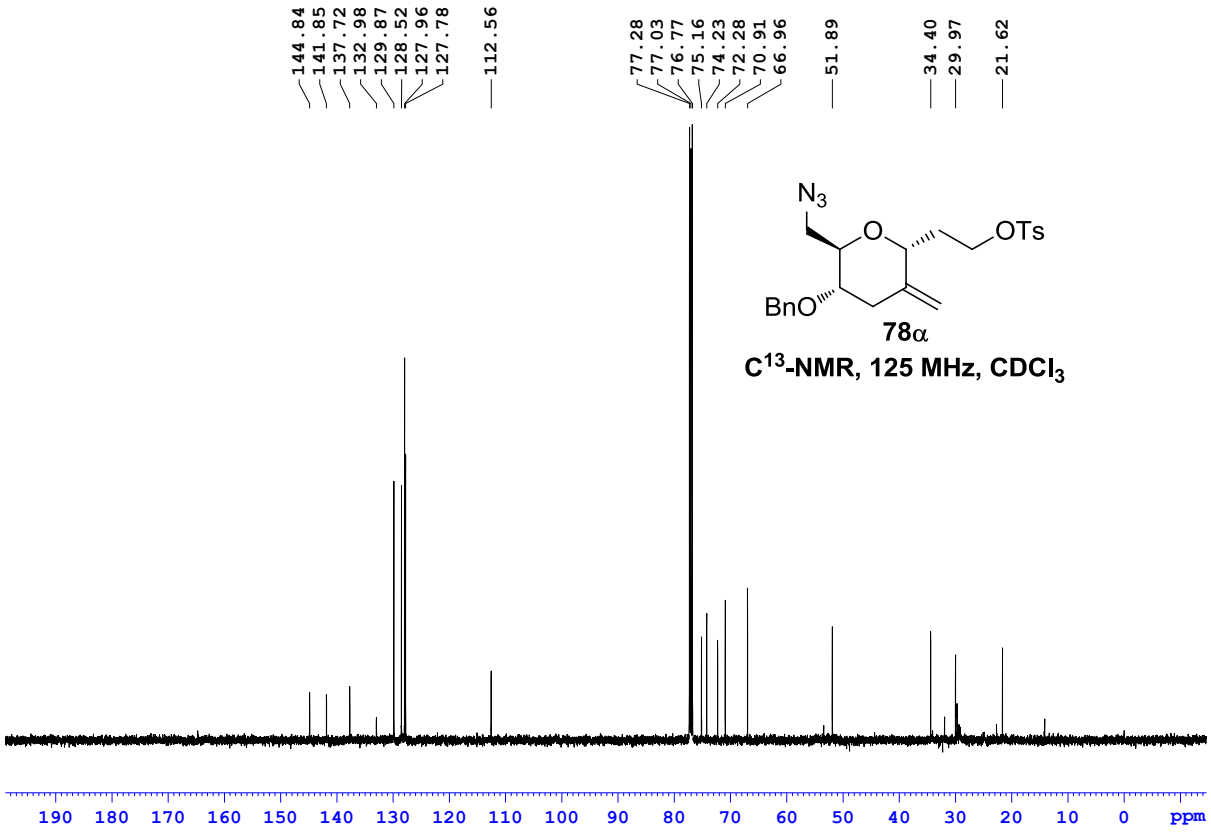
54

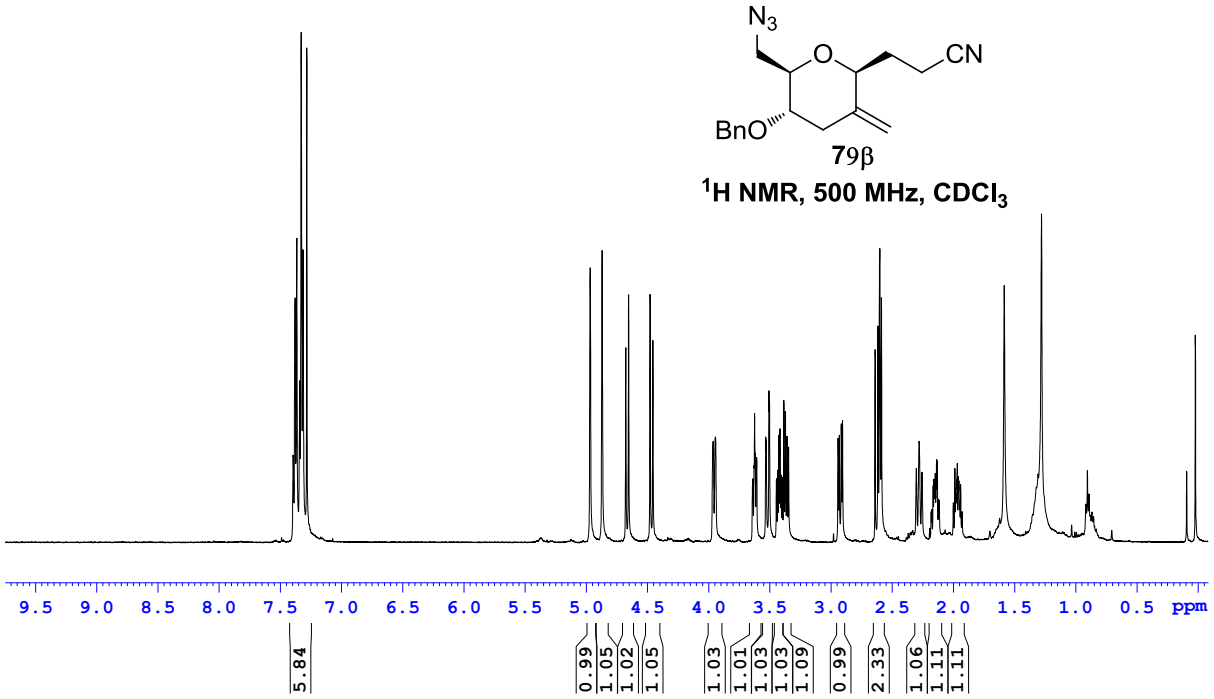
C^{13} NMR, 400 MHz, $CDCl_3$, crude

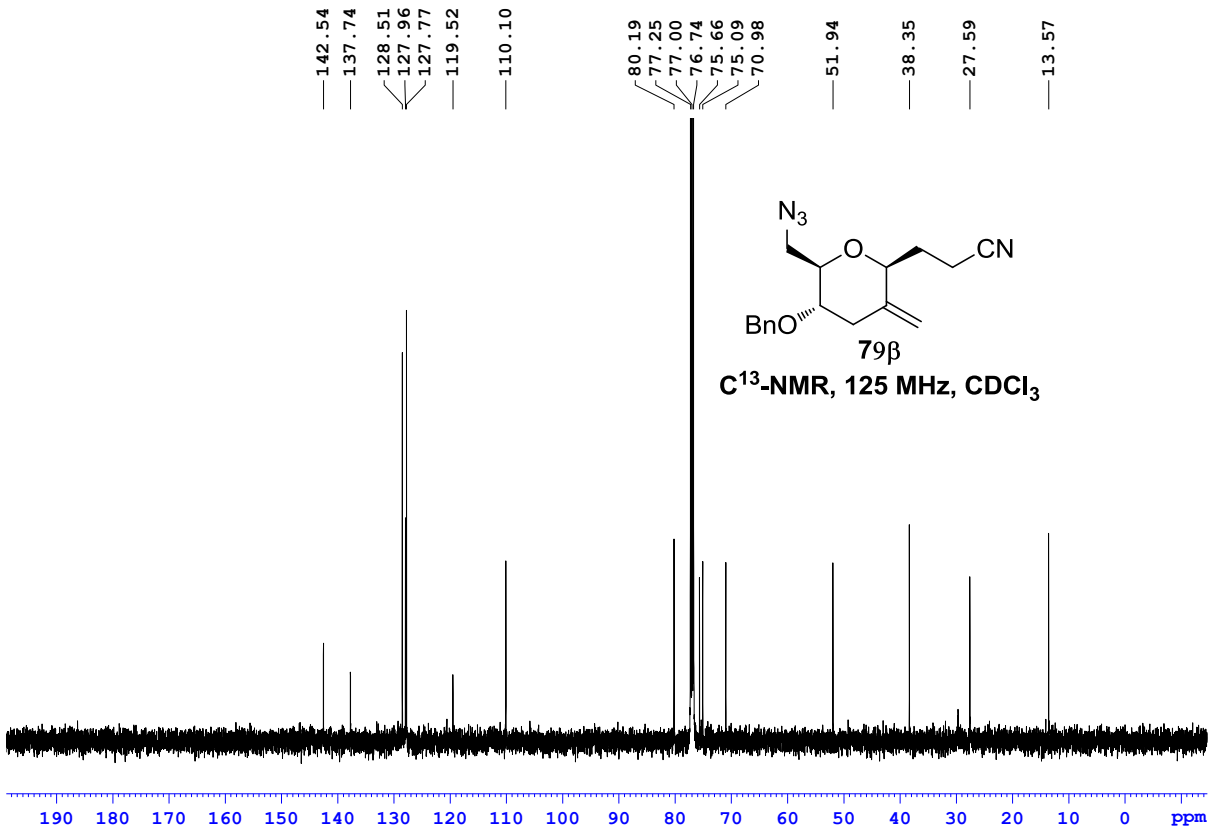

N3
O
OTs
BnO
78β
1H NMR, 500 MHz, CDCl3
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
1.85
7.67
0.92
0.94
0.94
0.95
1.97
0.97
0.97
1.95
1.00
0.97
2.85
1.98
1.01

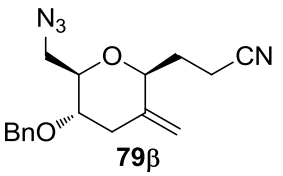

144.75
142.84
137.79
133.09
129.84
128.50
127.95
127.78
109.82
79.95
77.27
77.01
76.76
75.16
73.66
70.93
67.29
51.80
38.54
31.04
21.62
N3
O
OTs
BnO
78β
C13-NMR, 125 MHz, CDCl3
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm


N3
O
OTs
BnO
78α
1H NMR, 500 MHz, CDCl3
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
1.86
7.35
1.96
0.98
0.98
1.07
2.29
0.99
1.08
1.88
0.96
2.84
2.02
1.05


144.84
141.85
137.72
132.98
129.87
128.52
127.96
127.78
112.56
77.28
77.03
76.77
75.16
74.23
72.28
70.91
66.96
51.89
34.40
29.97
21.62
N3
O
OTs
BnO
78α
C13-NMR, 125 MHz, CDCl3
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

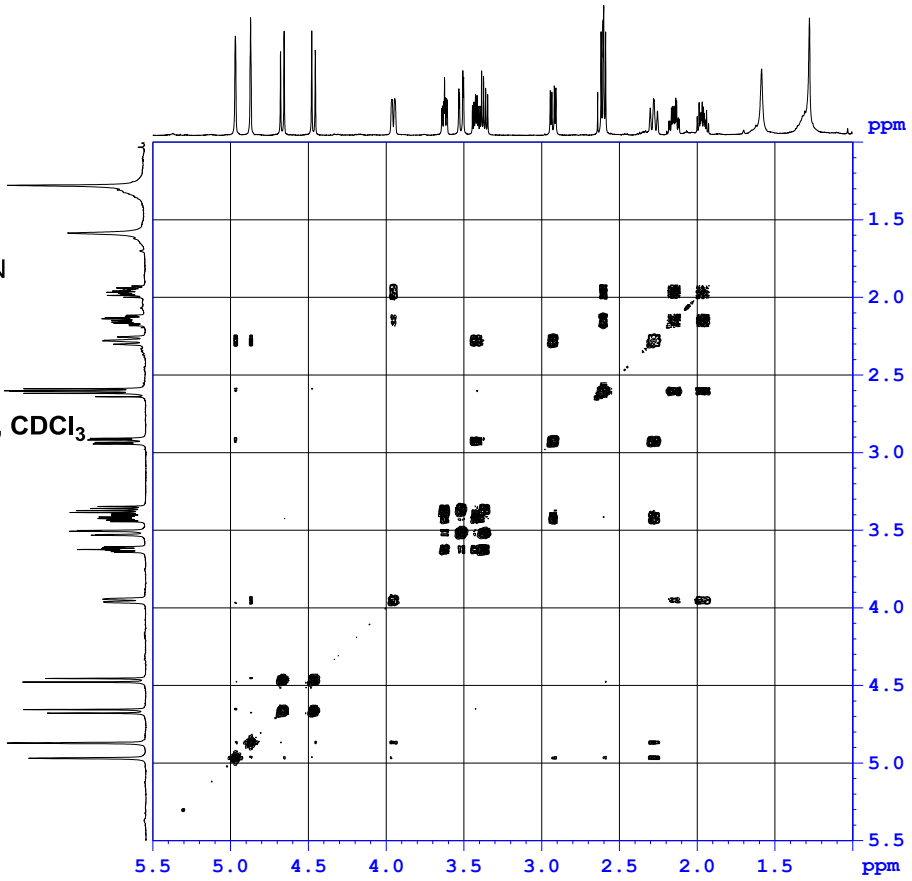

N3
O
CN
BnO
79β
1H NMR, 500 MHz, CDCl3
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
5.84
0.99
1.05
1.02
1.05
1.03
1.01
1.03
1.03
1.09
0.99
2.33
1.06
1.11
1.11

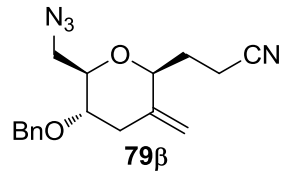

142.54
137.74
128.51
127.96
127.77
119.52
110.10
80.19
77.25
77.00
76.74
75.66
75.09
70.98
51.94
38.35
27.59
13.57
N3
O
CN
BnO
79β
C13-NMR, 125 MHz, CDCl3
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm



79β

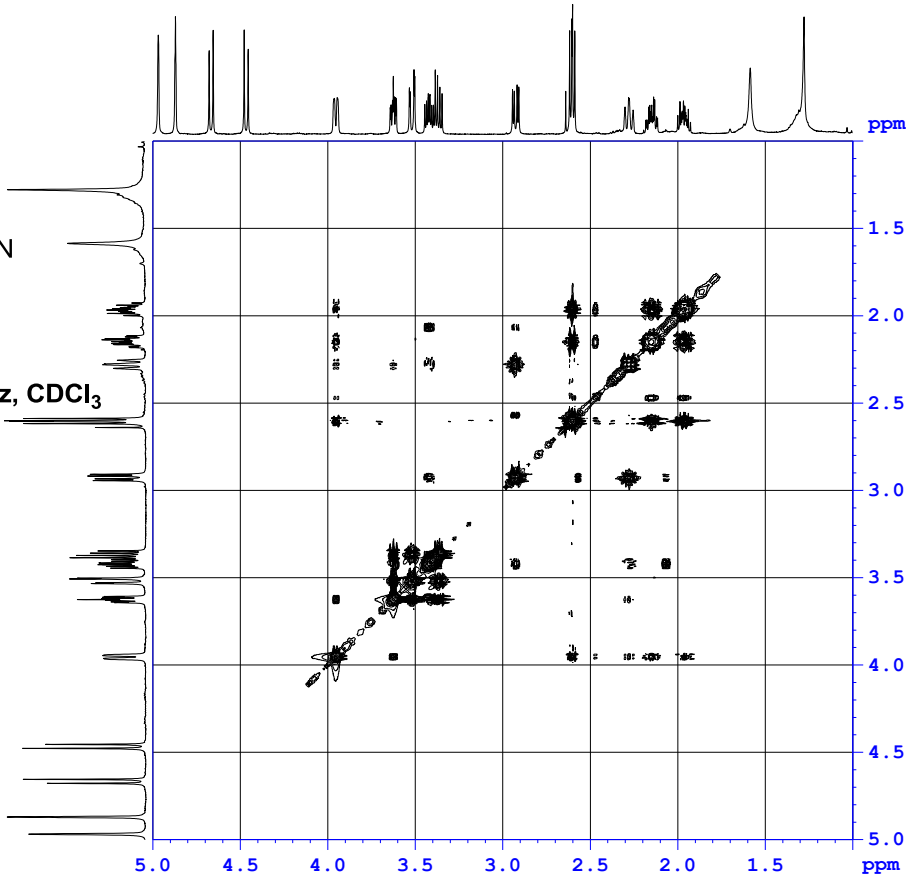
H^1-H^1 COSY NMR, 500 MHz, $CDCl_3$

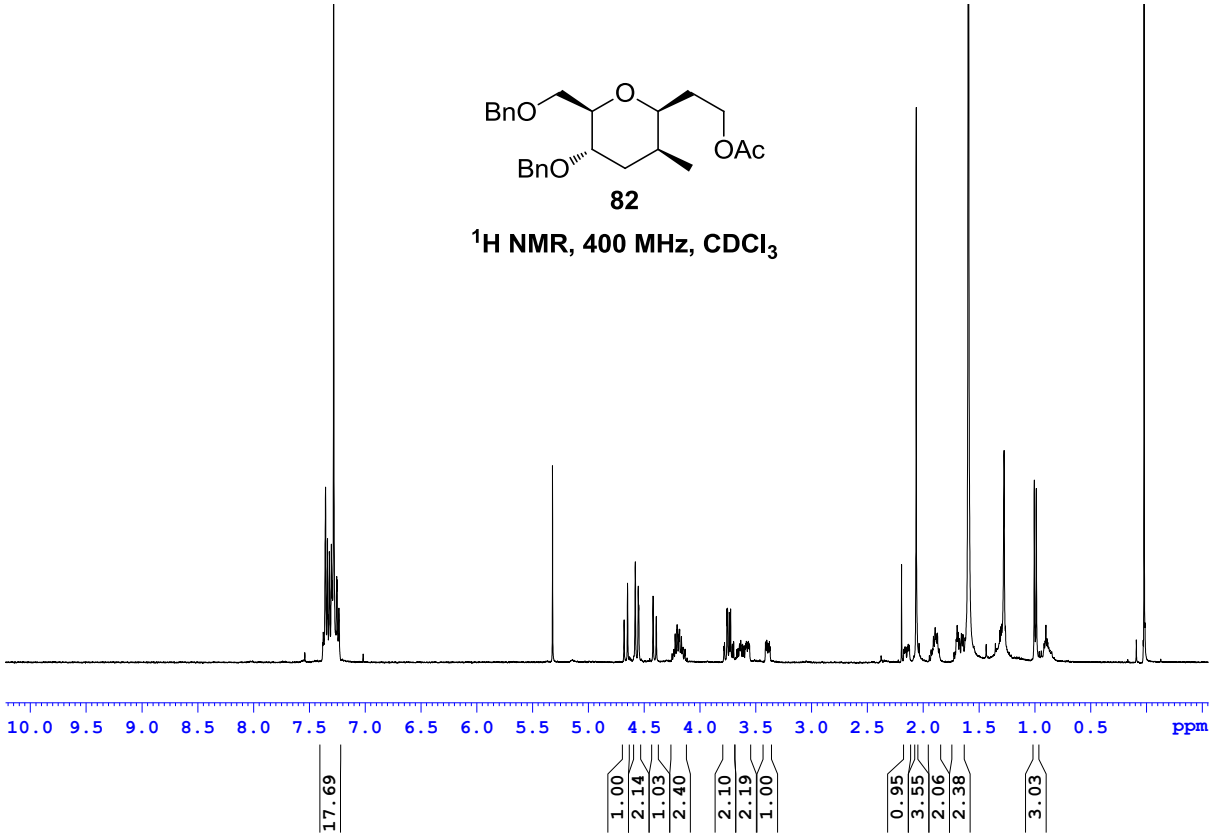


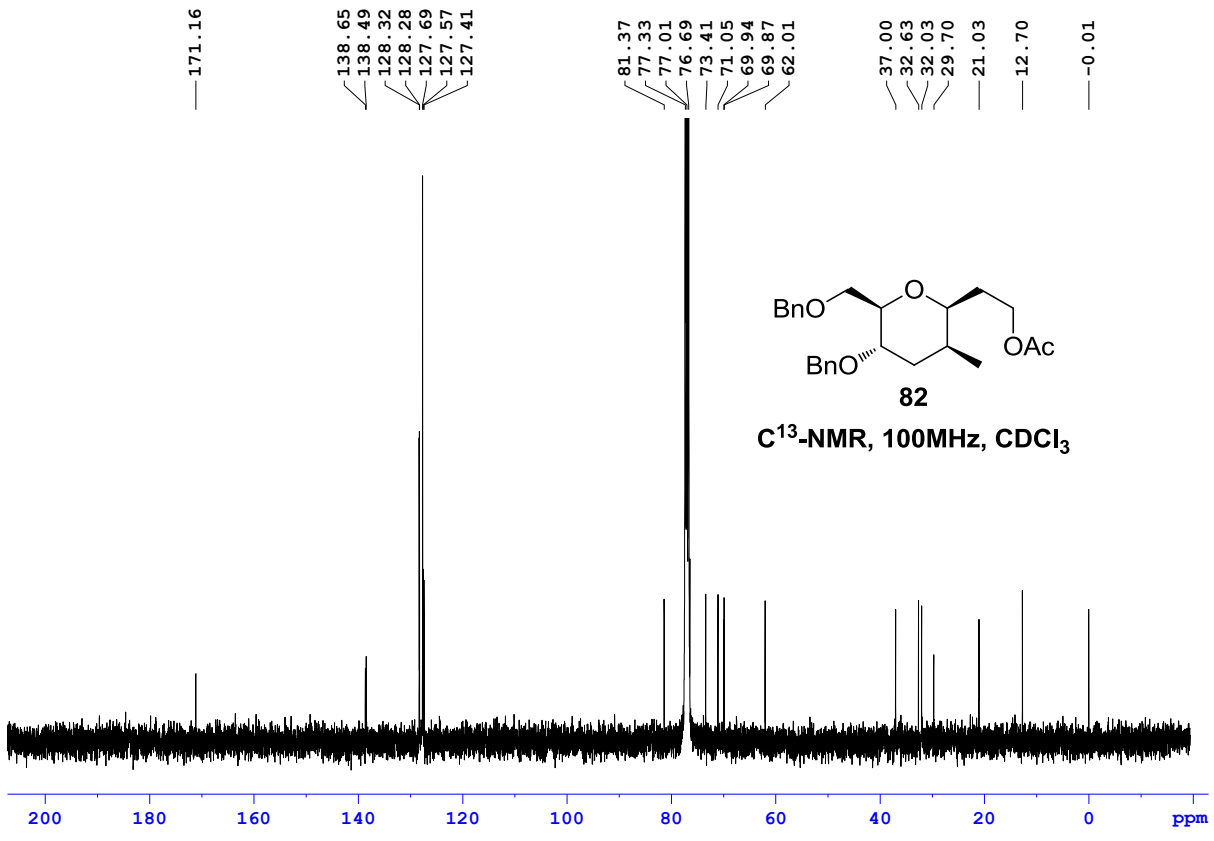


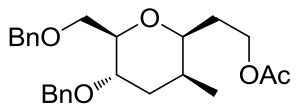
79β

H^1-H^1 NOESY NMR, 400 MHz, $CDCl_3$



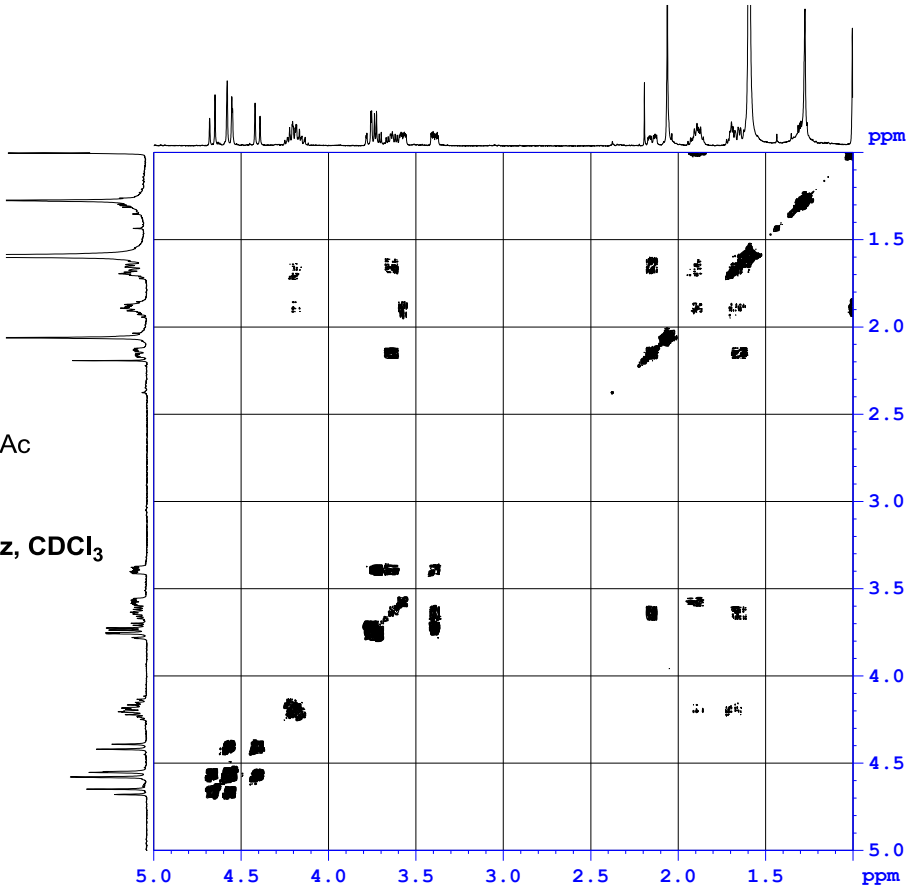

BnO
O
OAc
BnO
82
1H NMR, 400 MHz, CDCl3
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
17.69
1.00
2.14
1.03
2.40
2.10
2.19
1.00
0.95
3.55
2.06
2.38
3.03

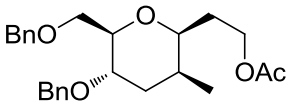

171.16
138.65
138.49
128.32
128.28
127.69
127.57
127.41
81.37
77.33
77.01
76.69
73.41
71.05
69.94
69.87
62.01
37.00
32.63
32.03
29.70
21.03
12.70
-0.01
BnO
O
OAc
BnO
82
C13-NMR, 100MHz, CDCl3
200 180 160 140 120 100 80 60 40 20 0 ppm



82

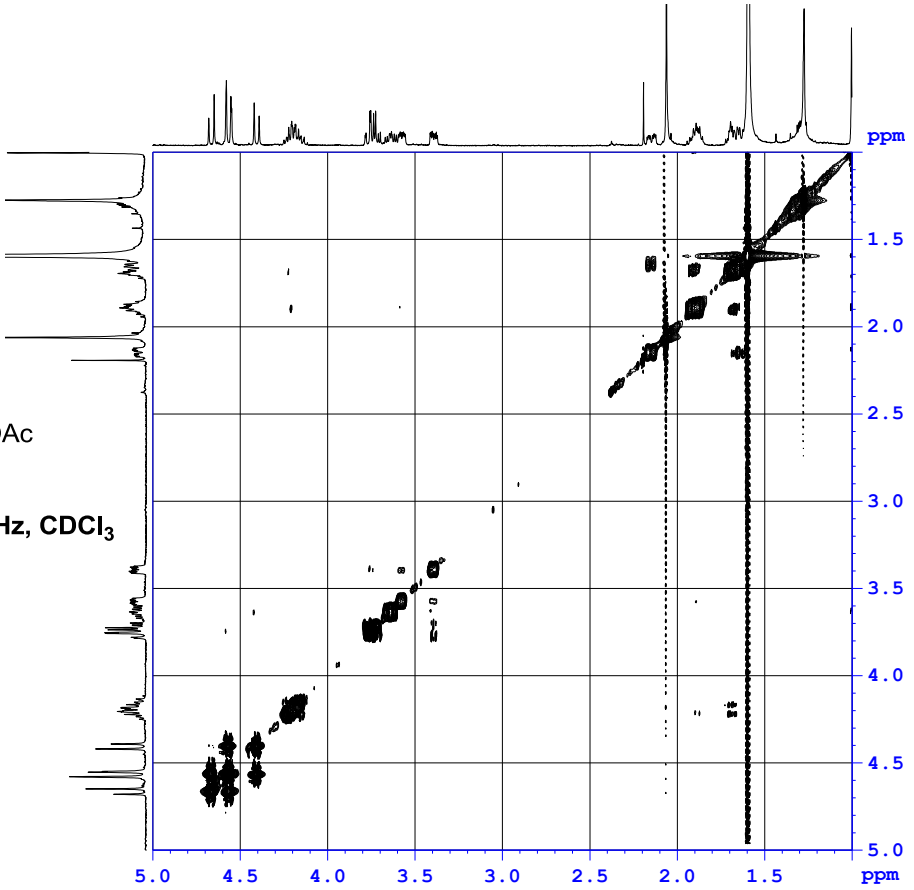
H^1-H^1 COSY NMR, 400 MHz, $CDCl_3$

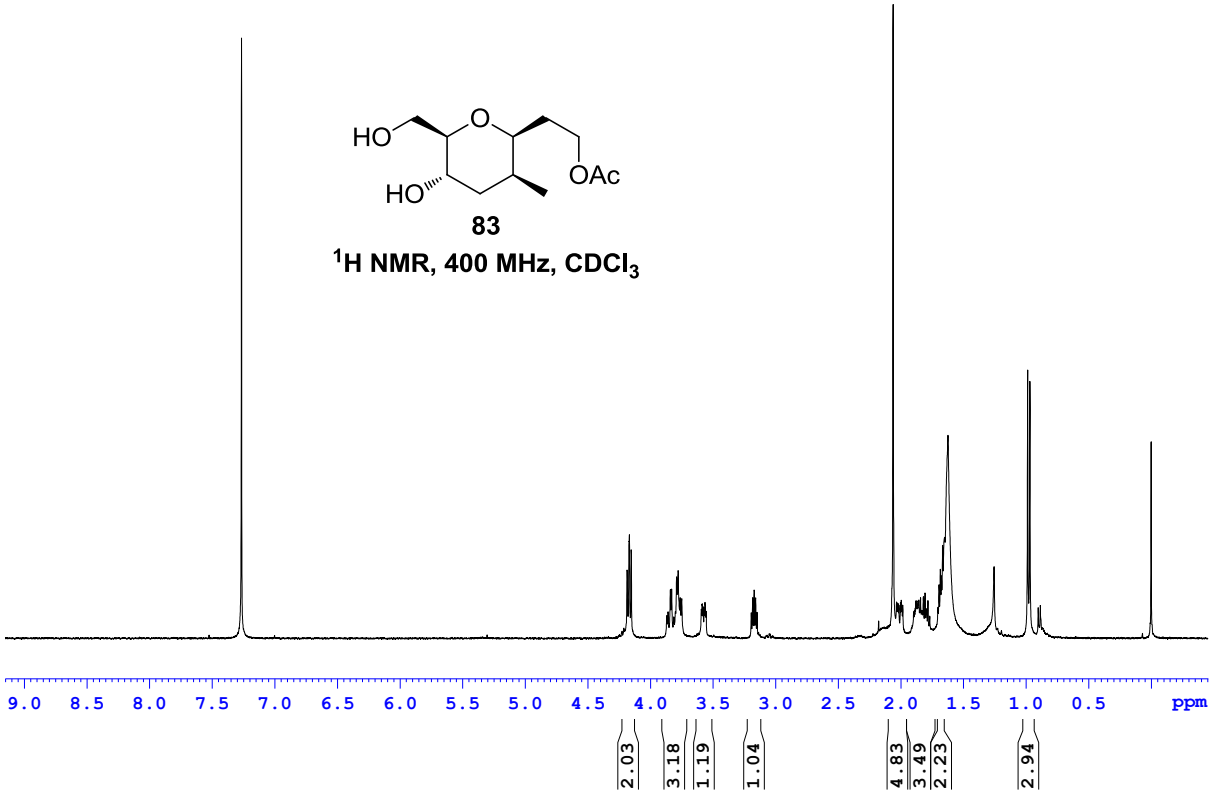




82

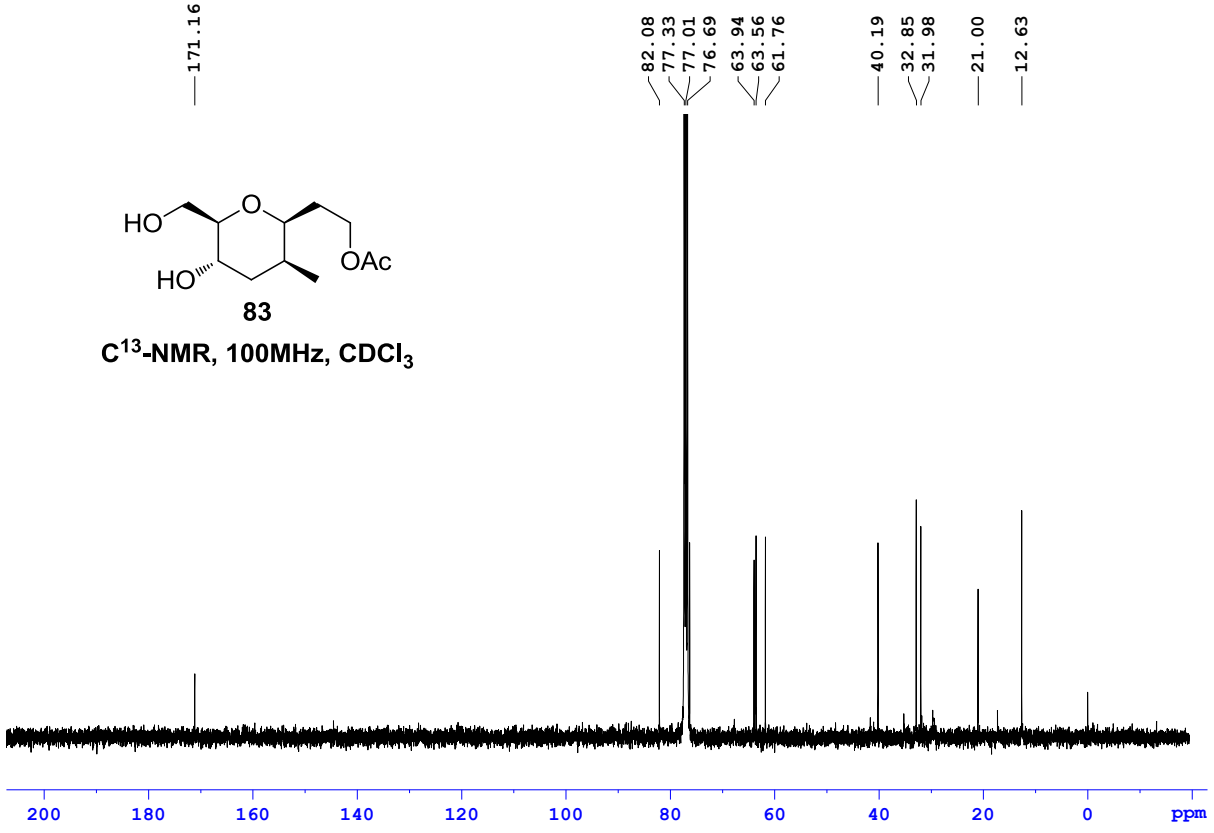
H^1-H^1 NOESY NMR, 400 MHz, $CDCl_3$





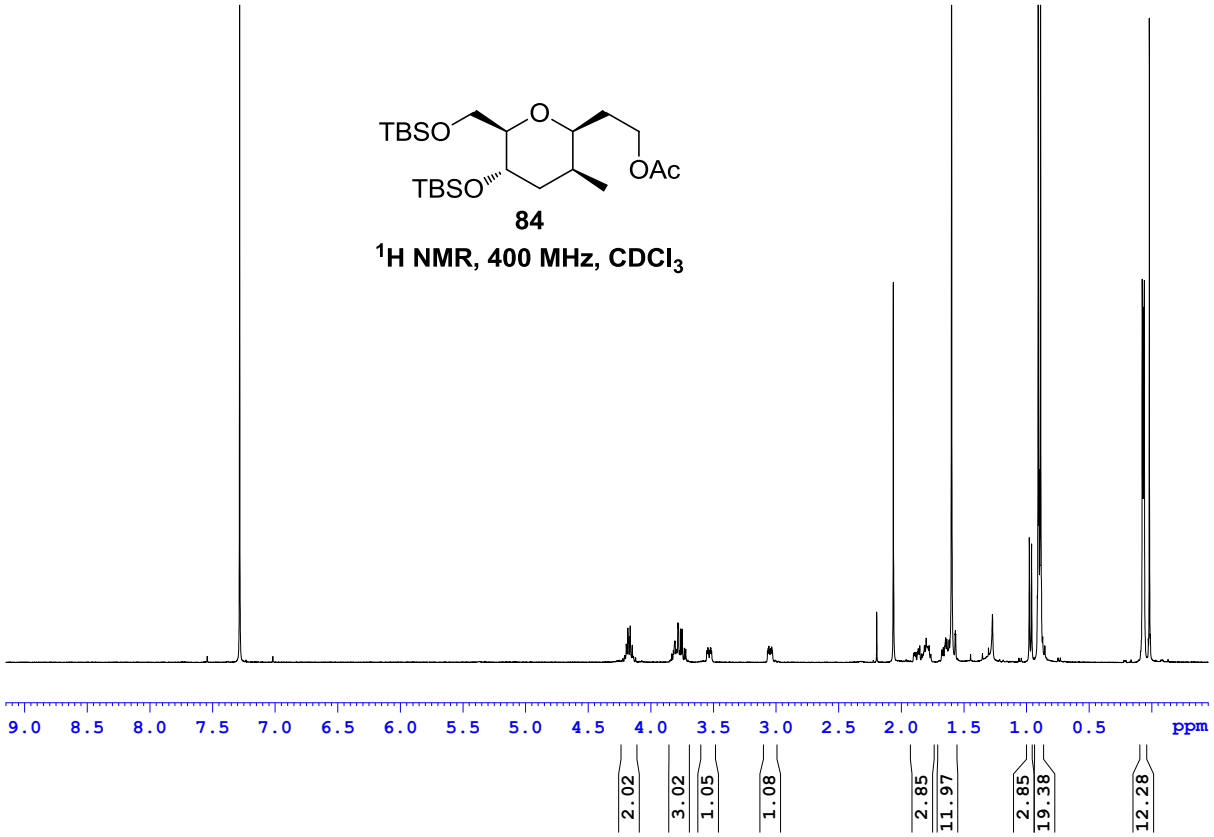
83

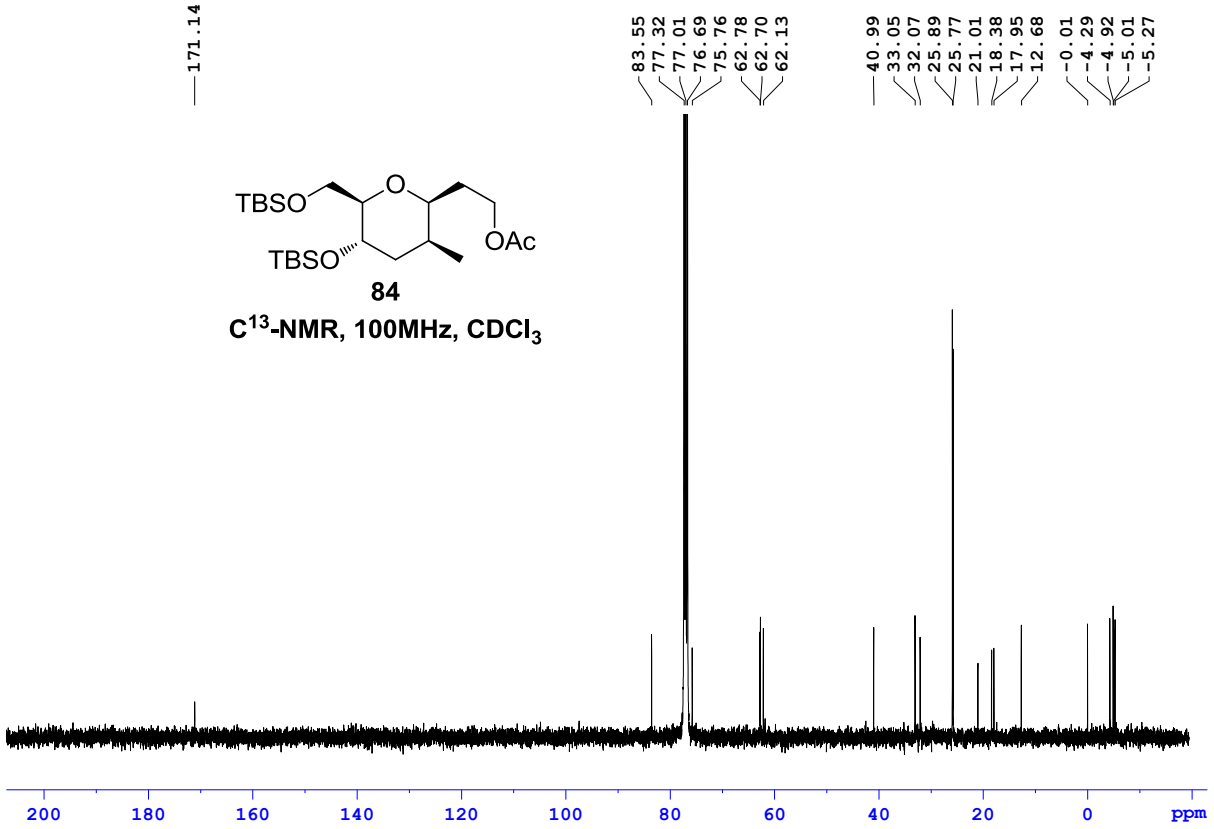
^{1}H NMR, 400 MHz, $CDCl_3$

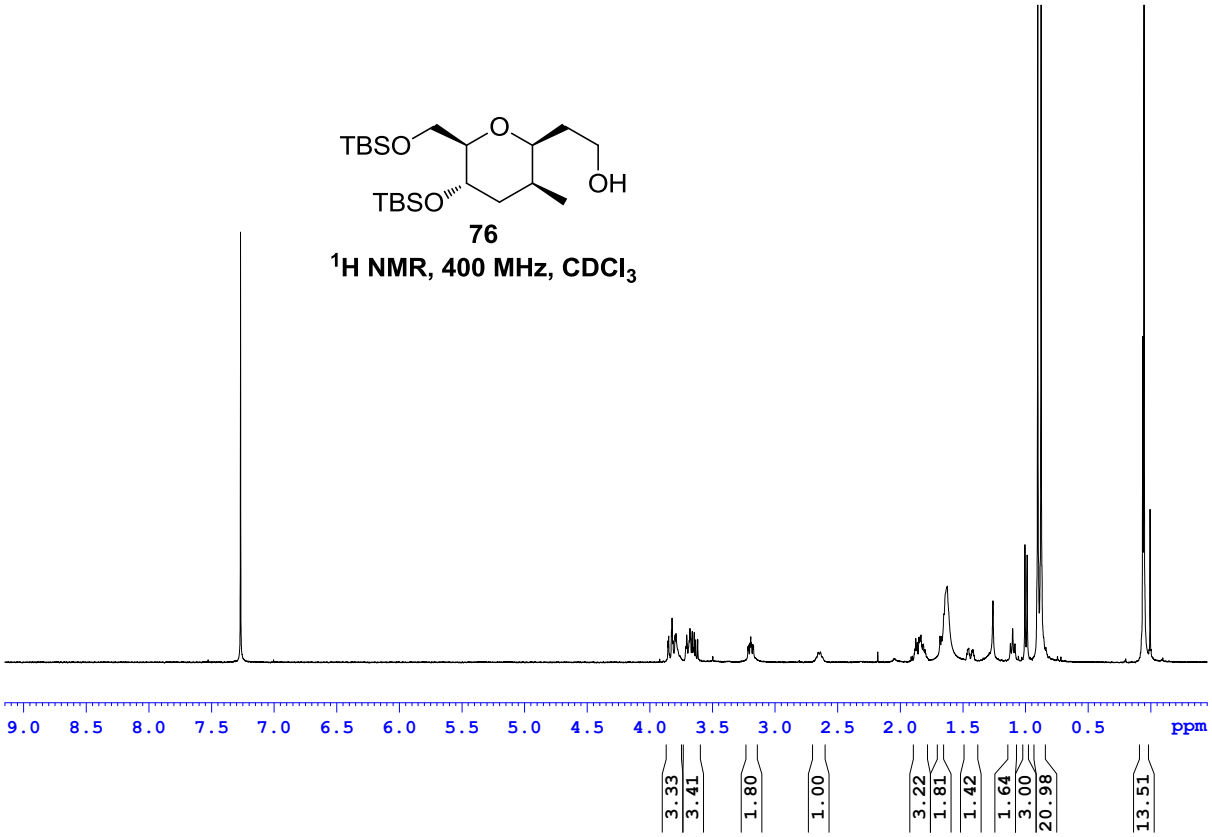


83

C^{13}-NMR, 100MHz, $CDCl_3$

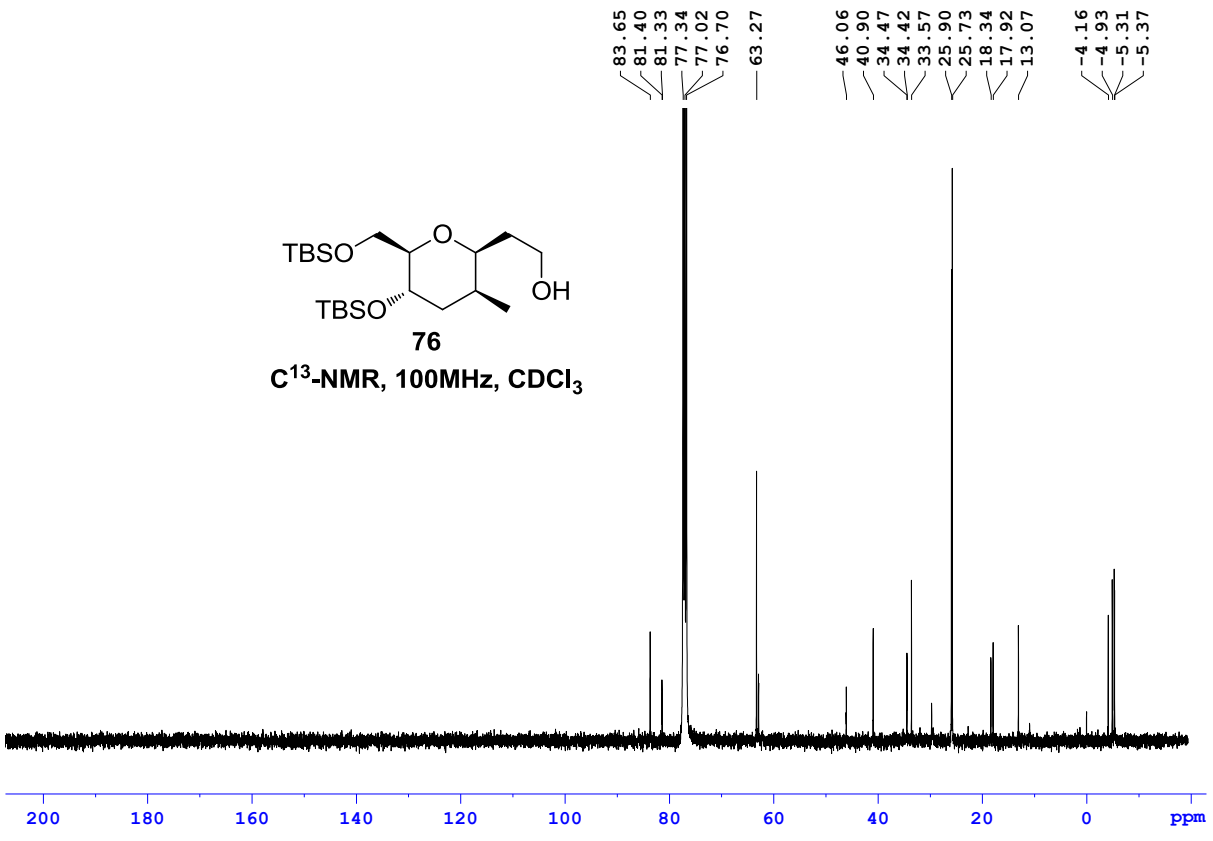

TBSO
O
OAc
TBSO
84
^{1}H NMR, 400 MHz, CDCl$_3$
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
2.02
3.02
1.05
1.08
2.85
11.97
2.85
19.38
12.28


171.14
83.55
77.32
77.01
76.69
75.76
62.78
62.70
62.13
40.99
33.05
32.07
25.89
25.77
21.01
18.38
17.95
12.68
-0.01
-4.29
-4.92
-5.01
-5.27
TBSO
O
OAc
TBSO
84
C^{13}-NMR, 100MHz, CDCl$_3$
200 180 160 140 120 100 80 60 40 20 0 ppm



76

^{1}H NMR, 400 MHz, $CDCl_3$

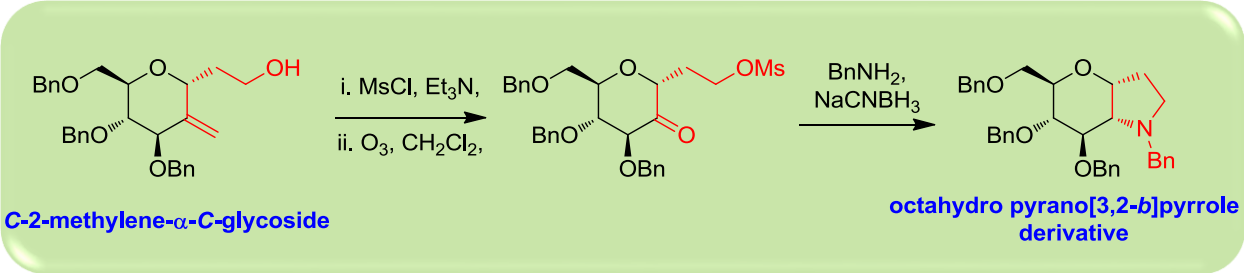


76

C^{13}-NMR, 100MHz, $CDCl_3$

Stereoselective synthesis of octahydropyrano[3,2-*b*]pyrroles as novel glycosidase inhibitors

ABSTRACT: The application of *C*-2-methylene-*C*-glycosides in the synthesis of fused bicyclic octahydropyrano[3,2-*b*]pyrrole scaffold is investigated. The reaction involves the activation of alcohol present in *C*-2-methylene-*C*-glycoside with methanesulfonyl chloride followed by ozonolysis of the exo-olifin and a one-pot mesylate substitution and reductive amination with primary amine (benzyl amine). The methodology was evaluated by synthesizing a series of carbohydrate derived octahydropyrano[3,2-*b*]pyrrole moieties.



4.1 Introduction

Mimicking natural glycans is the one of the intellectual way of misleading microorganisms and enzymes. Under this category, iminosugars, in which the endocycic oxygen is replaced by nitrogen are most attractive class of carbohydrate mimics reported so far. The origin goes back to ancient traditional chinese phyto medicine. Haarlem oil, the first medication produced on an industrial scale in 17th century was recommended for the treatment of diabetes and whitening the skin. One of the major constituent of haarlem oil is extract from the leaves Morus alba, known as white mulberry, which an extremely rich source of imino sugars. The renaissance of iminosugars came from the isolation of deoxy-nojiromycin (DNJ) from natural sources and finding it as an α-glucosidase inhibitor by Bayer Chemists in 1976. At present many iminosugars were designed and synthesised such as seven or eight membered iminoalditols, Conformationally constrained analogues of imino sugars and complex glycoconjugate mimetics. Scope has been extended to inhibit a number of enzymes such as glycosyltransferases, glycogen phosphorylases, nucleosides-processing enzymes, metalloproteinases. One of the most spectacular breakthroughs is the discovery that reversible competitive inhibitors could positively

influence the folding state of abnormal glycosidases, thus preventing their destruction by quality control in the endoplasmic reticulum (ER) and endoplasmic reticulum associated degradation. Chemical chaperone therapy is now under clinical trials with a DNJ analogue for the treatment of Fabry disease. (Gaucher Disease: a severe lysosoamal storage disorder). Apart from DNJ, it's analogues like *N*-butyl deoxy-nojiromycin (Glyset) and *N*-2-hydroxymetyl nojiromycin (Zavesca) are currently in the market for treatment of diabetes and gaucher diseases, respectively (Figure 4.1).

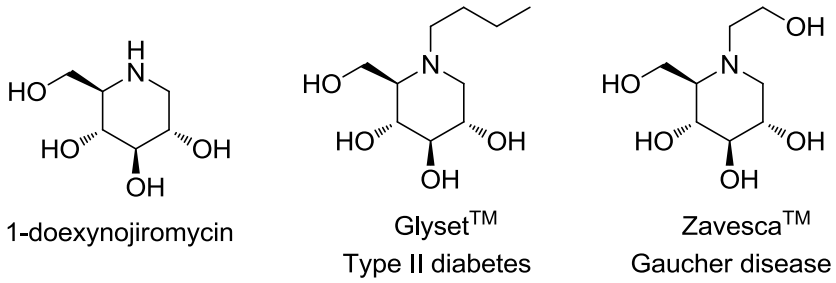


Figure 4.1: Imino-sugars in the treatment of diabetes and gaucher disease.

Due to the remarkable biological properties, like glycosidase inhibitor activities of the iminosugars (aza-sugars), their synthesis [1,2,3] is quiet interesting and challenging from 1960's onwards. Inhibitory activity of imino sugars was enhanced by morphological change in the skeleton of simple mono cyclic imino sugars into fused ones. A number of bicyclic iminosugars were synthesized and their glycosidase inhibitory activities has been reported. Out of these castanospermine, a potent inhibitor of lysosomal α-glucosidase and disturbs the lysosomal catabolism, australine, causarine, α-glycosidase inhibitors, and swainsonine, an α-mannosidase inhibitor, are noteworthy (Figure 4.2). [4]

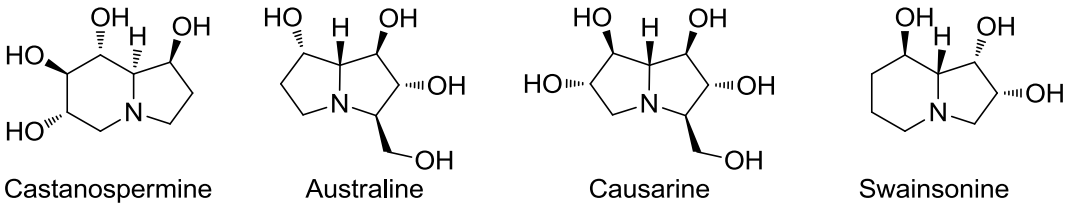
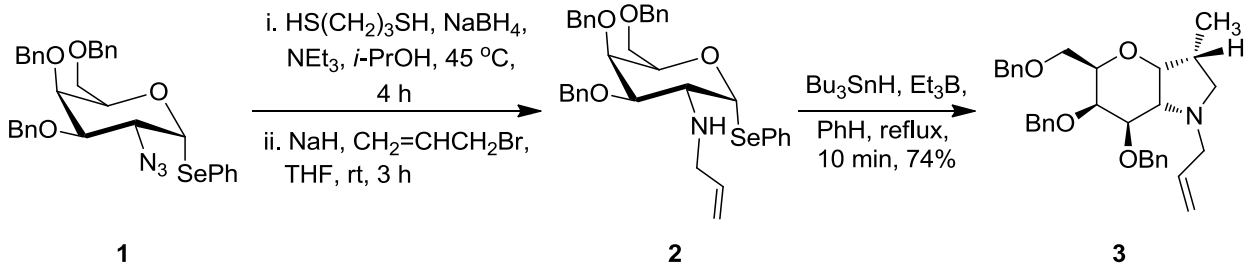


Figure 4.2: Some of the fused bicyclic imino sugar glycosidase inhibitors.

However, glycosidase inhibitory activity of fused compounds of 2-amino-*C*-glycosides is very unusual due to the lack of synthetic methods. To the best of our knowledge, there are very few reports for the synthesis of these fused heterocyclic compounds [5] as well as 2-amino-*C*-glycosides.[6]

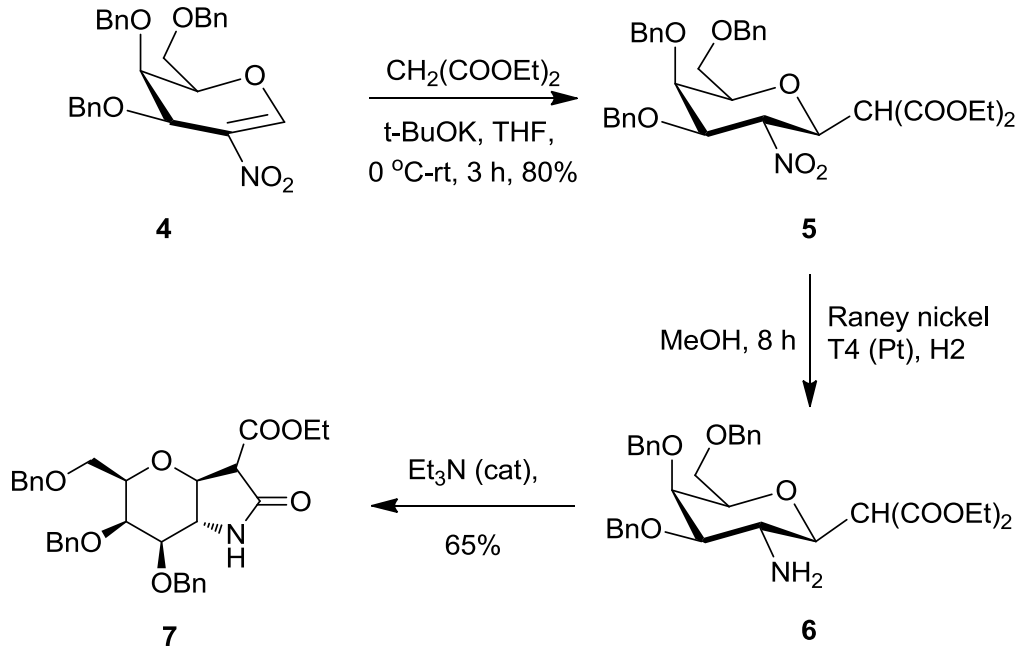
Earlier in 1996, Czernecki *et al*., synthesized the fused carbohydrate based octahydropyrano[3,2-*b*]pyrrole derivatives by using radical cyclization of 2-deoxy-2-allylamino seleno-glycosides.[7] Their synthetic route comprises, the preparation of mono-*N*-allylated galactosamine derivative **2** by reduction of phenyl 2-azido-3,4,6-tri-*O*-benzyl-2-deoxy-α-D-1-seleno galacto pyranoside **1**. Treatment of **2** with *n*-Bu_3SnH in the presence of triethylborane in benzene under reflux conditions provided fused bicyclic compound **3** as a single diastereomer in 74% yield (Scheme 4.1). The reaction was to work equally well with gluco pyranoside and di-allylated compounds.



1 **2** **3**

Scheme 4.1: Synthesis of 2-Amino-2-deoxy-α-D-*C*-galactopyranoside by radical cyclization.

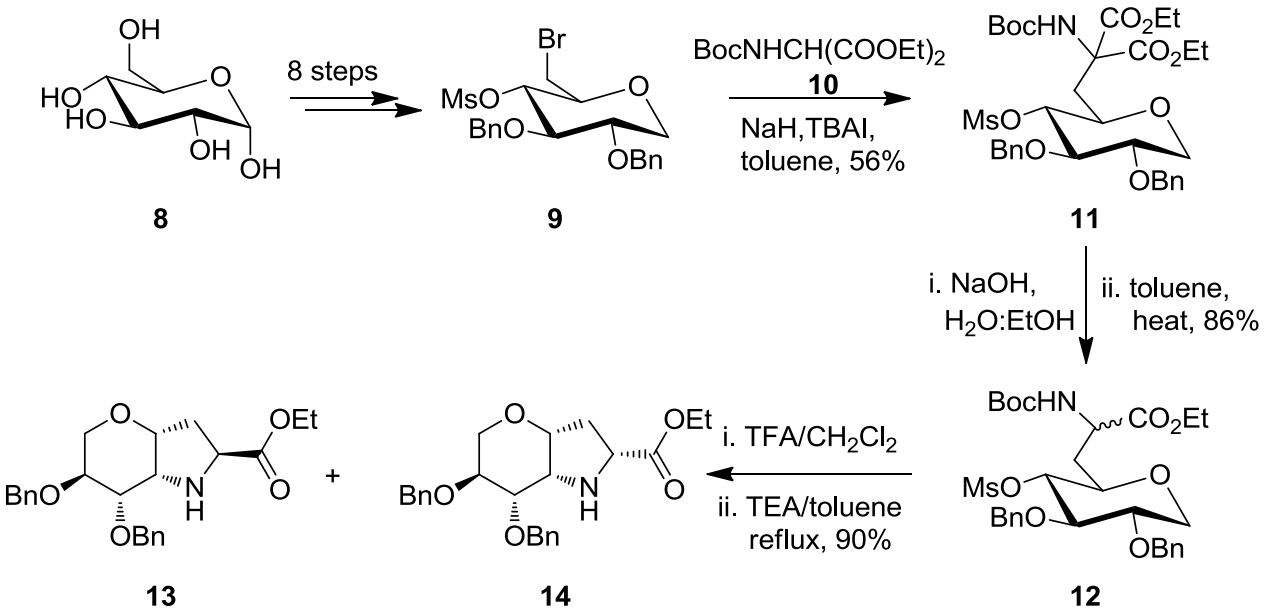
In 2002, Vankar *et al*., synthesized octahydropyrano[3,2-*b*]pyrrole derivatives using 2-nitroglycals as synthetic precursors.[6b] In this approach, Michael-addition of diethyl malonate on 3,4,6-tri-*O*-benzyl-2-nitro-D-galactal **4** in presence of *t*-BuOK as a base in THF provided exclusively the β-*C*-glycoside **5** in 80% yield. Reduction of nitro group in compound **5** with Raney nickel T4/H_2 afforded amine **6**. The crude amine intermediate **6** was further treated with Et_3N to afford the corresponding bicyclic *trans* fused lactam **7** in 65% yield. However, attempts to convert *trans* fused lactams to *cis* fused lactams under basic (DBU) conditions did not provided the expected anomerization product (Scheme 4.2). Same group in 2008 prepared from 1,2-anhydro sugars.[8]



Scheme 4.2: Synthesis of bicyclic lactam **7** from 2-nitro galactal derivative.

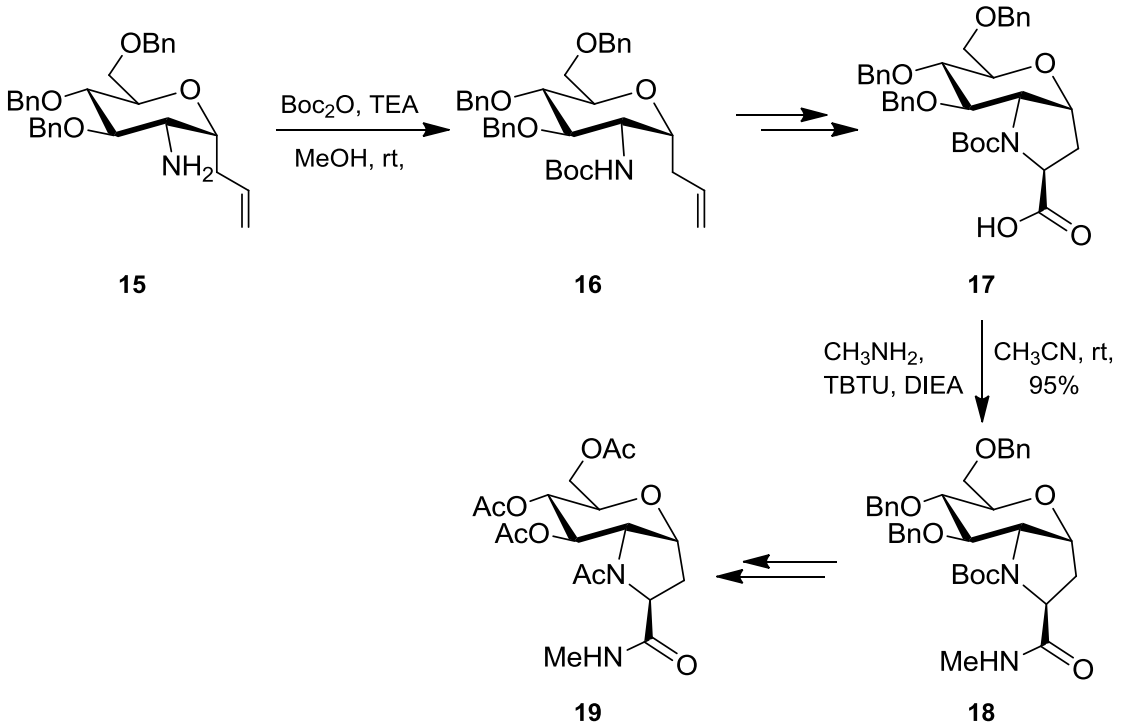
Later, Wang and co-workers, [9] in 2005 synthesized (6*R*,7*R*)-ethyl 6,7-bis(benzyloxy)octahydropyrano[3,2-*b*]pyrrole-2-carboxylate from glucose. Initially they have synthesized 6-bromo 4-mesylate derivative **9** from D-glucose **8** in 8 steps. Later it was treated with *N*-Boc protected diethyl aminomalonate **10** in presence of NaH, TBAI in toluene provided the alkylation product **11** in 56% yield. Mono decarboxylation of **11** with NaOH in Water-Ethanol mixture, followed by refluxing in toluene gave the diastereomeric mixture of **12** in 86% yield. Deprotection of Boc with TFA and intramolecular substitution of mesylate with the generated amine using TEA furnished the expected fused bicyclic products **13** and **14** in 90% yield (Scheme 4.3).

In 2007, Suárez and co-workers[10] synthesized substituted octahydropyrano[3,2-*b*]pyrrole derivatives by using an intramolecular hydrogen atom transfer reaction of phosphoramidyl and carbamoyl radicals. In the same year Schweizer and co-workers synthesized these fused bicyclic compounds from 2-Amino-*C*-glycosides.[11] In their methodology glucose derived 2-amino-*C*-glycoside **15**, which was synthesized in seven steps from 2,3,4,6-tetra-*O*-benzyl-D-



Scheme 4.3: Synthesis of aeruginosin analogues **13** and **14** from D-glucose.

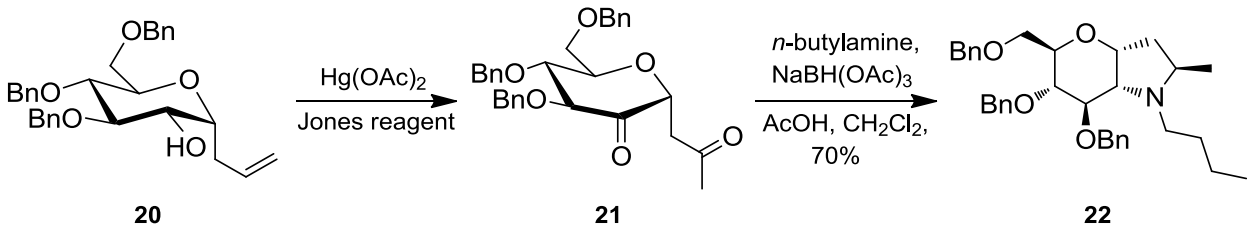
glucopyranose in 40% overall yield was used as a starting material. The amine in **15** was protected with Boc to furnish the Boc protected compound **16**. This was subjected to a sequence



Scheme 4.4: Synthesis of *N*-Acetyl-Glcopro *N*'-Methylamides.

of steps (aminoiodocyclization, tricyclic carbamate formation followed by jones oxidation) to provide the *N*-Boc-Glcpro H carboxylic acid **17**. The obtained carboxylic acid was coupled with methyl amine in presence of *O*-benzotriazolyl-*N*-*N*-*N*'-*N*'-tetramethyluranium tetrafluoroborate (TBTU) to furnish compound **18** in 95% yield. Deprotection of Boc followed by acetylation, hydrogenolysis and acetylation provided the expected compound **19** in quantitative yield (Scheme 4.4). Very recently they have also done the computational studies of these synthesized octahydropyrano[3,2-*b*]pyrrole derivatives.[12]

Very recently, Shao and co-workers[13] synthesized pyrrole fused bicyclic compounds from α-allyl-*C*-glycosides of type **20** involving reductive amination as the key step. The required 1,4-dicarbonyl precursor **21** for the reductive amination reaction was procured from **20** by $Hg(OAc)_2$ mediated oxidation of olefin to methyl ketone and subsequent oxidation of 2-OH to ketone under jones oxidation conditions. Subjecting compound **21** to reductive amination reaction using *n*-butylamine, $NaBH(OAc)_3$ and AcOH in CH_2Cl_2 provided the bicyclic compound **22** in 70% yield (Scheme 4.5). However, this methodology was restricted only to glucose derivative.



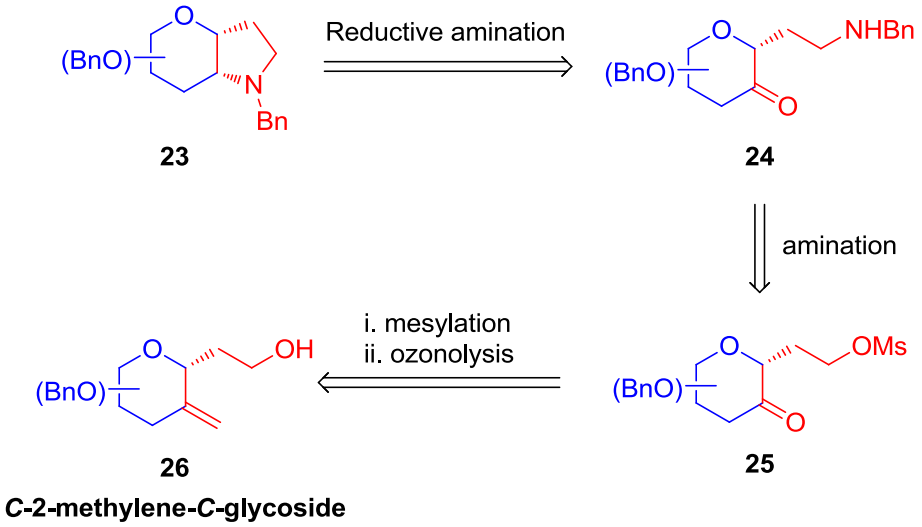
20 **21** **22**

Scheme 4.5: Synthesis of glucose derived octahydropyrano[3,2-*b*]pyrrole.

In continuation of our research in the synthesis and application of carbon branched sugars towards the construction of novel molecular architectures, we attempted to synthesize octahydro-pyrano[3,2-*b*]pyrrole systems starting from *C*-2-methylene-*C*-glycosides, which were previously prepared in our research laboratory. [14]

The retrosynthetic analysis for stereselecitve preparation of carbohydrate derived octahydropyrano[3,2-*b*]pyrrole systems from *C*-2-methylene-*C*-glycosides is presented in scheme 4.6. The pyran fused tetrahydropyrrole unit **23** could be obtained by the reductive

amination of amino ketone **24**, which could be synthesized from the keto mesylate **25**. The keto group in **25** could be incorporated by ozonolysis of the *C*-2-methylene group in **26**.

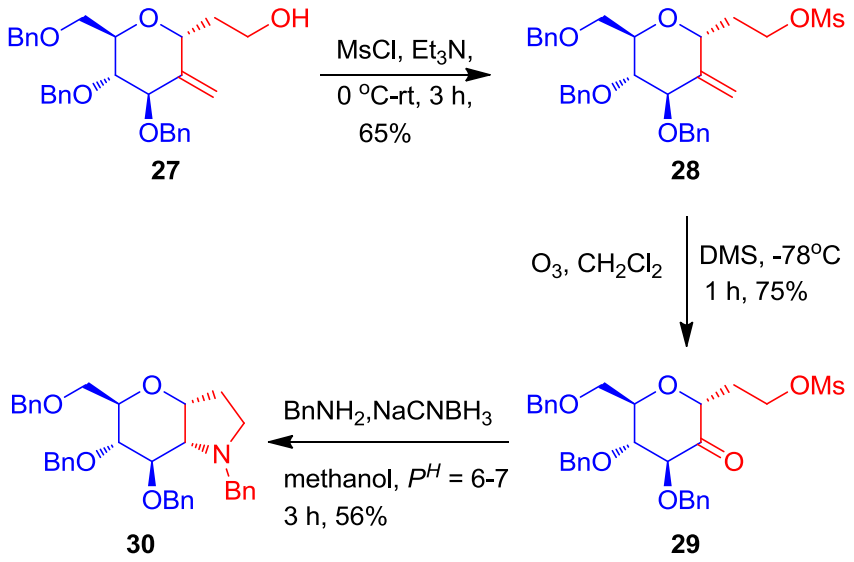


Scheme 4.6: Retrosynthetic analysis for the stereoselective formation of octahydro pyrano[3,2-*b*]pyrrole systems from *C*-2-methylene-*C*-glycosides.

4.2 Results and discussion

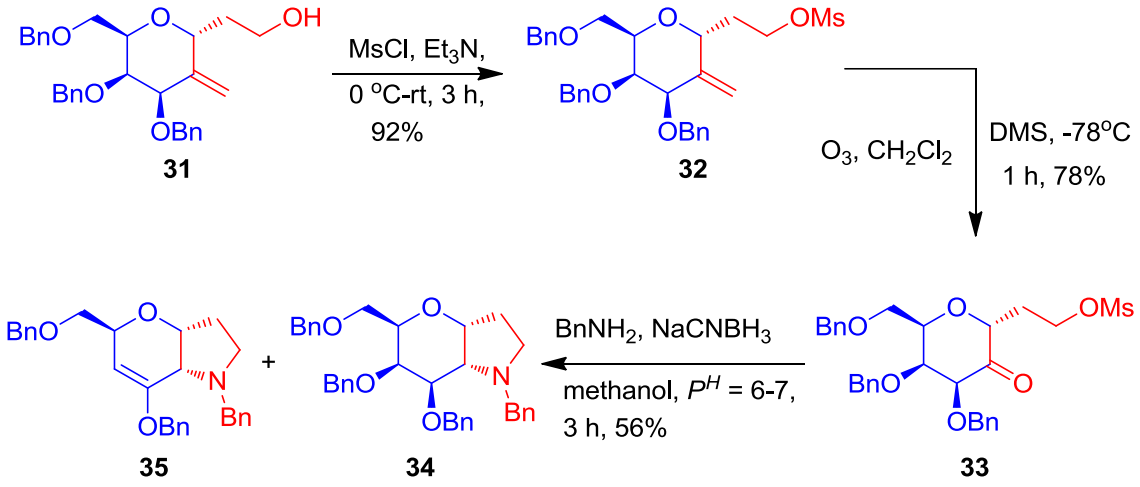
4.2.1. Synthesis of glucal derived octahydropyrano[3,2-*b*]pyrroles

The synthesis of *C*-2-methylene-*C*-glycosides **27**, **31**, **36** and **40** has been explained in chapter-2. Towards the preparation of carbohydrate derived octahydropyrano[3,2-*b*]pyrrole systems, compound **27** was mesylated using methanesulfonyl chloride and triethylamine in dichloromethane to obtain compound **28** in 65% yield. Ozonolysis of compound **28** at -78 ^{o}C gave the compound **29** in 75% yield. A one pot substitution of the mesylated with benzylamine and an intermolecular reductive amination reaction of **29** using sodiumcyanoborohydride afforded the *cis*-fused bicyclic iminosugar **30**[15] in 56% yield (Scheme 4.7).



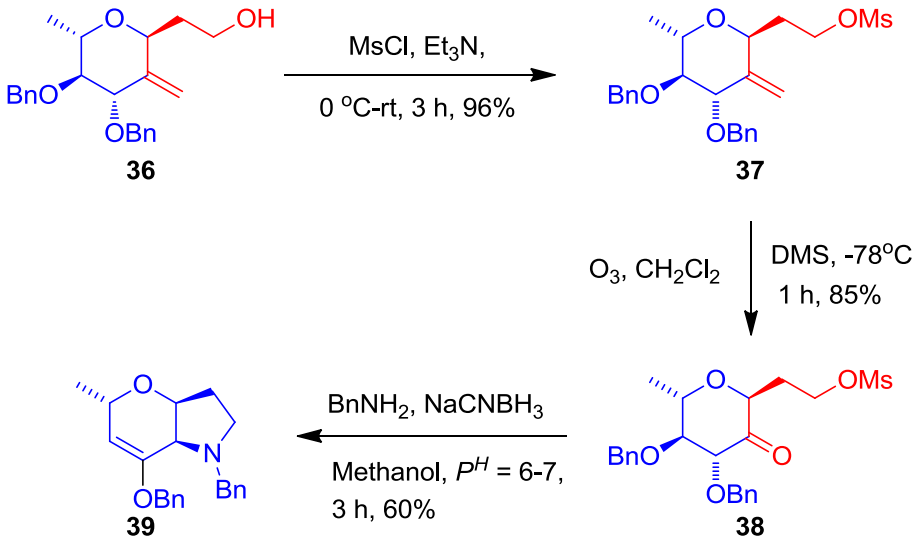
Scheme 4.7: Synthesis of fused imnosugar **30** from glucose derived *C*-2-methylene-*C*-glycoside **27**.

In a similar fashion, mesylation of the galactose derived *C*-2-methylene-*C*-glycoside **31** with mesylchloride and triethylamine in dichloromethane provided compound **32** in 92% yield. Ozonolysis of the compound **32** at -78 °C gave keto mesylate **33** in 78% yield. However, the one-pot substitution and reductive amination reation of compound **33** using benzyl amine and sodiumcyanoborohydride, respectively, afforded a mixture of pyranose fused pyrroles **34** and **35**[16] in 56% yield (Scheme 4.8).



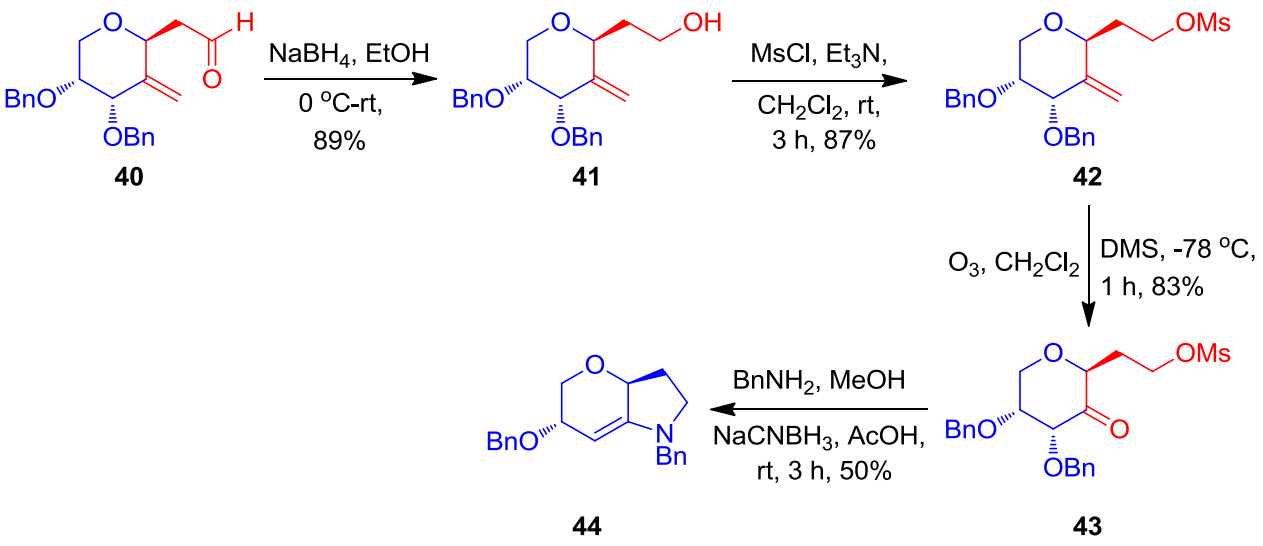
Scheme 4.8: Synthesis of fused iminosugars **34** and elimination product **35** from galactose derived *C*-2-methylene-*C*-glycoside **31**.

Surprised with the formation of the byproduct, the methodology was further extended to few other *C*-2-methylene-*C*-glycoside units. Thus, mesylation of the L-rhamnose derived *C*-2-methylene-α-*C*-glycoside **36** with mesylchloride and triethylamine in dichloromethane gave mesylate **37** in 96% yield. Ozonolysis of the exo-cyclic olefin in **37** at -78 ^{o}C for 1 h gave the ketone **38** in 85% yield. A simultaneous substitution of the mesylate and reductive amination reaction with benzyl amine in presence of sodiumcyanoborohydride afforded the elimination product **39** in 60% yield (Scheme 4.9).



Scheme 4.9: Synthesis of fused iminosugar **39** from L-rhamnose derived *C*-2-methylene-*C*-glycoside **36**.

Towards the application of the developed reaction in pyranose pentose sugars, D-arabinose derived *C*-2-methylene-*C*-glycoside **40** was reduced to the corresponding alcohol **41**. Mesylation of this alcohol to give mesylation **42** followed by ozolnoysis provided the keto-mesylate **43** in good yield. The one-pot substitution and reductive amination of the compound **43** using benzyl amine and sodium cyano borohydride, respectively, afforded the elimination product **44** in 50% yield (Scheme 4.10).



Scheme 4.10: Synthesis of fused iminosugar **44** from D-arabinose derived *C*-2-methylene-*C*-glycoside **40**.

4.3 Conclusion

A convenient methodology for the preparation of carbohydrate derived octahydropyrano[3,2-*b*]pyrrole scaffolds from *C*-2-methylene-*C*-glycosides is reported. The methodology provides an easy access to a variety of the pyranose fused pyrrole ring systems in a setreoselecitve fashion. Further synthesis of an array of these molecules and their assays against glycosidases is in progress.

4.4 Experimental data

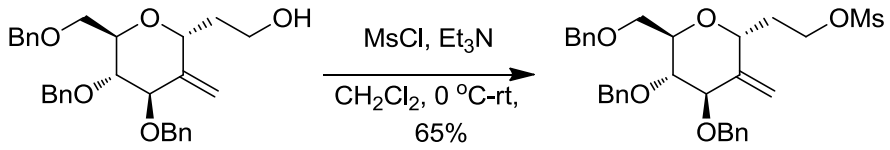
4.4.1 Materials and Methods

All the chemicals were purchased from Carbosynth, Merck and Sigma-Aldrich Chemical Companies and were of the highest purity. The reactions were carried out under an inert atmosphere and monitored by thin-layer chromatography (TLC) using silica gel GF_{254} plates with detection by charring with 5% (v/v) H_2SO_4 in methanol or by phosphomolybdic acid (PMA) stain or by ultra violet (UV) detection unless otherwise mentioned. Dimethyl formamide, ethanol, ethylvinylether, toluene, methanol, dichloromethane, dimethylsulfoxide, pyridine and $POCl_3$ used in the reactions were distilled from dehydrating agents prior to use. Silica gel (100-200) was used for column chromatography. ^1H, ^{13}C, DEPT, COSY, NOESY spectra were

recorded with Bruker 400 MHz or 500 MHz spectrometers in $CDCl_3$. ^1H NMR chemical shifts are reported in ppm (δ) with TMS as internal standard (δ = 0.00 ppm); ^{13}C NMR data are reported in chemical shifts with solvent reference ($CDCl_3$, δ = 77.00 ppm). IR spectra were recorded with a JASCO FT/IR-5300 spectrometer. High-resolution mass spectra were recorded with a Bruker maXis ESI-TOF spectrometer.

4.4.2 Experimental procedures and Spectral data

(4.4.2.1) 2-((2*R*,4*R*,5*S*,6*R*)-4,5-bis(benzyloxy)-6-((benzyloxy)methyl)-3-methylenetetrahydro-2*H*-pyran-2-yl)ethyl methanesulfonate (28):



27 **28**

To a stirred solution of compound **27** (0.563 g, 1.18 mmol) in dry dichloromethane (15 mL), triethylamine (2.97 mmol, 0.43 mL) and methane sulfonyl chloride (2.37 mmol, 0.19 mL) was added at 0 °C, then reaction was slowly warmed to room temperature, stirring was continued for 3 h at room temperature, after completion of the reaction, reaction mixture was diluted with water and extracted 3 times (3x150 mL) with dichloromethane, the resulting organic layer was washed with brine and dried over anhydrous sodium sulfate, evaporation followed by column chromatography using silica-gel provided compound **28** in 65% yield (370 mg). R_f = 0.52 in 40% Ethylacetate/hexanes.

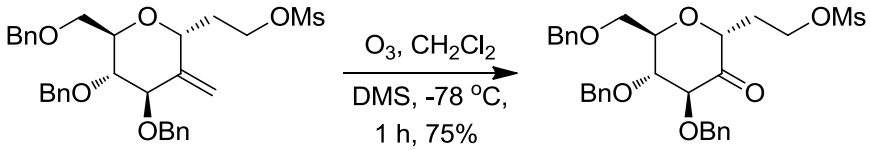
IR (neat): $\tilde{\nu}_{max}/cm^{-1}$ 3063, 3030, 2920, 1495, 1457, 1353, 1172.

^{1}H (400 MHz, $CDCl_3$): δ 7.18-7.36 (m, 15H), 5.29 (s, 1H), 5.12 (s, 1H), 4.79 (d, *J* = 11.2 Hz, 1H), 4.71 (d, *J* = 11.6 Hz, 1H), 4.63 (d, *J* = 11.6 Hz, 1H), 4.55 (d, *J* = 12.4 Hz, 1H),4.48-4.53 (m, 3H), 4.28 (m, 2H), 4.17 (d, *J* = 7.2 Hz, 1H), 3.76-3.79 (m, 1H), 3.63-3.66 (m, 2H), 3.50 (t, *J* = 8.0 Hz, 1H), 2.94 (s, 3H), 2.21-2.29 (m, 1H), 1.97-2.06 (m, 1H) ppm.

^{13}C (100 MHz, $CDCl_3$): δ 143.0, 138.0, 137.9, 128.4, 128.4, 127.9, 127.8, 111.6, 80.7, 80.0, 74.2, 73.5, 73.4, 72.9, 69.4, 66.6, 36.9, 30.4 ppm.

HRMS (ESI) calcd for $C_{31}H_{36}O_7S$+Na 575.2079; found 575.2075.

(4.4.2.2) 2-((2*R*,4*S*,5*R*,6*R*)-4,5-bis(benzyloxy)-6-((benzyloxy)methyl)-3-oxotetrahydro-2*H*-pyran-2-yl)ethyl methanesulfonate (29):



28 **29**

Compound **28** (0.350 g, 0.63 mmol) in dry dichloromethane (15 mL) was treated with O_3 at -78 ^oC until the solution become light blue in color (~1 h). Subsequently DMS was added and the reaction mixture was allowed to warm up to room temperature. The reaction mixture was diluted with dichloromethane (20 mL) concentrated under reduced pressure, purified by column chromatography over silica gel using 3:7 Ethylacetate/hexanes provided compound **29** in 75% yield (0.26 g). R_f = 0.4 in 30% Ethylacetate/hexanes.

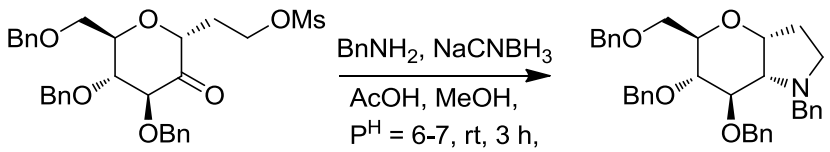
IR (neat): $\tilde{\nu}_{max}/cm^{-1}$ 2909, 2871, 1742, 1457, 1358.

^{1}H (400 MHz, $CDCl_3$): δ 7.19-7.40 (m, 15H), 4.94 (d, *J* = 11.2 Hz, 1H), 4.79 (d, *J* = 11.6 Hz, 1H), 4.63 (d, *J* = 11.6 Hz, 1H), 4.44-4.51 (m, 3H), 4.36-4.41 (m, 2H), 4.32-4.35 (m, 2H), 3.98-4.03 (m, 1H), 3.89-3.95 (m, 1H), 3.61 (dd, *J* = 2.8 Hz, *J* = 10.8 Hz, 1H), 3.52 (dd, *J* = 4.8 Hz, *J* = 10.8 Hz, 1H), 2.90 (s, 3H), 2.13-2.21 (m, 1H), 2.02-2.11 (m, 1H) ppm.

^{13}C (100 MHz, $CDCl_3$): δ 208.3, 137.6, 137.5, 137.4, 128.4, 128.2, 128.1, 127.9, 127.8, 127.7, 84.0, 76.7, 76.1, 76.0, 74.2, 74.0, 73.4, 69.8, 65.4, 37.2, 30.0 ppm.

HRMS (ESI) calcd for $C_{30}H_{35}O_8S$ 555.2053; found 555.2057.

(4.4.2.3) (3a*R*,5*R*,6*S*,7*R*)-1-benzyl-6,7-bis(benzyloxy)-5-((benzyloxy)methyl) octahydro-pyrano[3,2-*b*]pyrrole (30):



29 **30**

To a stirred solution of 29 (0.1 g, 0.18 mmol) in dry methanol (4 mL) benzyl amine (0.21 mmol, 24 µL) was added at room temperature, stirring was continued for 1 h, then 0.5 equivalents of acetic acid (0.09 mmol, 5 µL) and $NaCNBH_3$ (0.30 mmol, 19 mg) were added, additional stirring for 3 h at room temperature, followed by quenching with 2 mL of 1 N NaOH, extracted with ether, ether layer was dried over anhydrous Na_2SO_4, evaporation and purification over silica-gel chromatography provided compound **30** in 56% yield (55 mg). R_f = 0.6 in 30% Ethylacetae/hexanes.

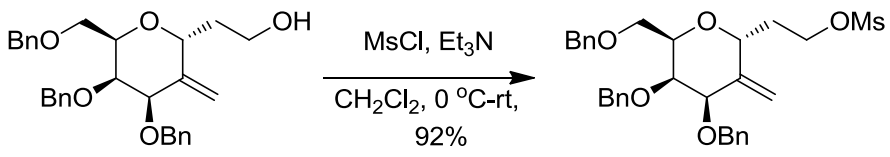
IR (neat): $\tilde{\nu}_{max}/cm^{-1}$ 3063, 2958, 2931, 2849, 1726, 1490, 1457, 1276.

^{1}H (400 MHz, $CDCl_3$): δ 7.20-7.37 (m, 20 H), 4.88 (d, *J* = 11.6 Hz, 1H), 4.77 (d, *J* = 11.6 Hz, 1H), 4.68 (d, *J* = 11.2 Hz, 1H), 4.57 (d, *J* = 12.8 Hz, 2H), 4.45 (dd, *J* = 12.0 Hz, *J* = 16.8 Hz, 2H), 4.17 (d, *J* = 13.2 Hz, 1H), 3.96-4.00 (m, 1H), 3.90 (t, *J* = 6.0 Hz, 1H), 3.67 (t, *J* = 7.2 Hz, 1H), 3.62 (d, *J* = 3.6 Hz, 1H), 3.32 (d, *J* = 12.8 Hz, 1H), 2.93 (t, *J* = 7.6 Hz, 1H), 2.72 (t, *J* = 6.4 Hz, 1H), 2.05 (m, 2H), 1.80 (m, 1H), 1.62 (m, 1H) ppm.

^{13}C (100 MHz, $CDCl_3$): δ 138.4, 138.2, 138.2, 128.8, 128.5, 128.4, 128.3, 128.1, 127.9, 127.8, 127.7, 127.6, 127.5, 127.0, 80.8, 77.6, 77.2, 74.9, 74.0, 73.5, 73.4, 73.3, 70.2, 67.1, 59.2, 51.5, 30.0 ppm.

HRMS (ESI) calcd for $C_{36}H_{39}O_4$+Na 572.2777; found 572.2760.

(4.4.2.4) 2-((2*R*,4*R*,5*R*,6*R*)-4,5-bis(benzyloxy)-6-((benzyloxy)methyl)-3-methylenetetrahydro-2*H*-pyran-2-yl)ethyl methanesulfonate (32):



31 **32**

To a stirred solution of compound **31** (1.4 g, 2.90 mmol) in dry dichloromethane (20 mL), triethylamine (7.26 mmol, 1.0 mL) and methane sulfonyl chloride (5.81 mmol, 0.44 mL) was added at 0 °C, then reaction was slowly warmed to room temperature, stirring was

continued for 3 h at room temperature, after completion of the reaction, reaction mixture was diluted with water and extracted 3 times (3x200 mL) with dichloromethane, the resulting organic layer was washed with brine and dried over anhydrous sodium sulfate, evaporation followed by column chromatography using silica-gel provided compound **32** in 92% yield (1.5 g). R_f = 0.52 in 40% Ethylacetate/hexanes.

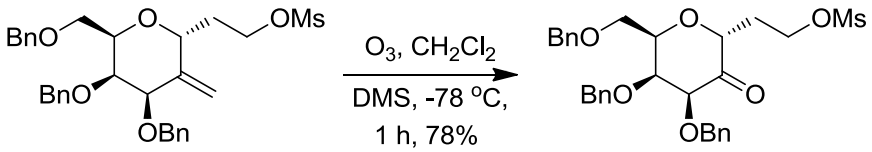
IR (neat): $\tilde{\nu}_{max}/cm^{-1}$ 3030, 2865, 1495, 1457, 1358, 1172.

^{1}H (400 MHz, $CDCl_3$): δ 7.28-7.36 (m, 15H), 5.34 (s, 1H), 5.17 (s, 1H), 4.80 (dd, *J* = 2.0 Hz, *J* = 11.6 Hz, 1H), 4.65 (dd, *J* = 2.0 Hz, *J* = 12.0 Hz, 1H), 4.60 (dd, *J* = 2.4 Hz, *J* = 12.4 Hz, 1H), 4.54-4.58 (m, 3H), 4.46 (m, 2H), 4.29 (t, *J* = 4.4 Hz, 2H), 4.17 (s, 1H), 3.96 (dd, *J* = 2.4 Hz, *J* = 4.4 Hz, 1H), 3.86 (d, *J* = 2.4 Hz, 1H), 3.74 (dt, *J* = 2.0 Hz, J = 9.6 Hz, *J* = 17.2 Hz, 1H), 3.53 (m, 1H), 3.10 (s, 3H), 2.12 (m, 1H), 1.97 (m, 1H) ppm.

^{13}C (100 MHz, $CDCl_3$): δ 142.0, 138.3, 138.0, 138.0, 128.5, 128.4, 128.2, 127.8, 127.7, 127.3, 111.9, 77.8, 75.4, 73.4, 73.1, 72.9, 71.6, 71.2, 69.0, 67.0, 36.8, 31.5 ppm.

HRMS (ESI) calcd for $C_{31}H_{36}O_7S$+H 553.2260; found 553.2255.

(4.4.2.5) 2-((2*R*,4*S*,5*S*,6*R*)-4,5-bis(benzyloxy)-6-((benzyloxy)methyl)-3-oxotetrahydro-2*H*-pyran-2-yl)ethyl methanesulfonate (33):



32 **33**

Compound **32** (1.4 g, 2.90 mmol) in dry dichloromethane (25 mL) was treated with O_3 at -78 °C until the solution become light blue in color (1 h). Subsequently DMS was added and the reaction mixture was allowed to warm up to room temperature. The reaction mixture was diluted with dichloromethane (20 mL) concentrated under reduced pressure, purified by column chromatography over silica gel using 4:6 Ethylacetate/hexanes provided compound **33** in 78% yield (1.1 g). R_f = 0.5 in 40% Ethylacetate/hexanes.

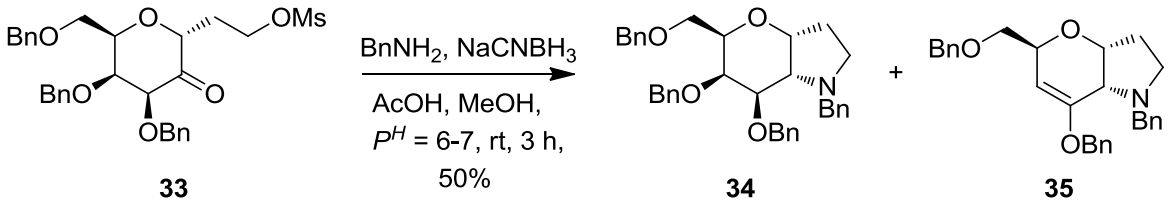
IR (neat): $\tilde{\nu}_{max}/cm^{-1}$ 3030, 2909, 1742, 1457, 1358, 1172.

^{1}H (400 MHz, $CDCl_3$): δ 7.23-7.40 (m, 15H), 4.98 (d, *J* = 12.0 Hz, 1H), 4.88 (d, *J* = 11.6 Hz, 1H), 4.57-4.63 (m, 3H), 4.52 (dd, *J* = 5.2 Hz, *J* = 8.0 Hz, 2H), 4.29-4.39 (m, 5H), 3.65 (dd, *J* = 6.8 Hz, *J* = 10.0 Hz, 1H), 3.59 (dd, *J* = 6.0 Hz, *J* = 10.0 Hz, 1H), 2.94 (s, 3H), 2.22-2.30 (m, 1H), 2.06-2.15 (m, 1H) ppm.

^{13}C (100 MHz, $CDCl_3$): δ 208.4, 137.8, 137.7, 137.5, 128.5, 128.5, 128.3, 128.1, 127.9, 127.8, 127.7, 82.3, 76.0, 74.8, 74.4, 73.5, 73.0, 67.5, 65.8, 37.2, 29.9 ppm.

HRMS (ESI) calcd for $C_{30}H_{35}O_8S$ 555.2053; found 555.2049.

(4.4.2.6) (3a*R*,5*R*,6*R*,7*R*)-1-benzyl-6,7-bis(benzyloxy)-5-((benzyloxy)methyl)octahydropyrano[3,2-*b*]pyrrole (34) and (3a*R*,5*S*,7a*S*)-1-benzyl-7-(benzyloxy)-5-((benzyloxy)methyl)-1,2,3,3a,5,7a-hexahydropyrano[3,2-*b*]pyrrole (35):

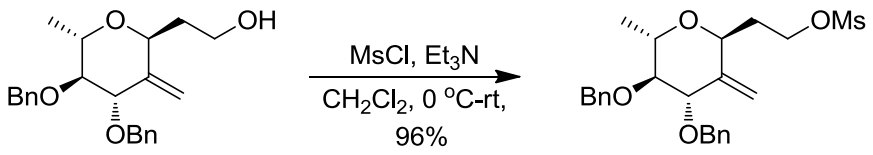


33 **34** **35**

To a stirred solution of **33** (0.5 g, 0.90 mmol) in dry methanol (7 mL) benzyl amine (1.08 mmol, 118 µL) was added at room temperature, stirring was continued for 1 h, then 0.5 equivalents of acetic acid (0.45 mmol, 25 µL) and $NaCNBH_3$ (1.53 mmol, 96 mg) were added, additional stirring for 3 h at room temperature, followed by quenching with 10 mL of 1 N NaOH, extracted with ether, ether layer was dried over anhydrous Na_2SO_4, evaporation and purification over silica-gel chromatography provided mixture of compounds **34** and **35** in 50% yield (240 mg). R_f = 0.61 for **34** and 0.62 for **35** in 30% Ethylacetae/hexanes.

IR (neat): $\tilde{\nu}_{max}/cm^{-1}$ 3057, 3030, 2920, 2860, 1665, 1495, 1095.

(4.4.2.7) 2-((2*S*,4*S*,5*S*,6*S*)-4,5-bis(benzyloxy)-6-methyl-3-methylenetetrahydro-2*H*-pyran-2-yl)ethyl methanesulfonate (37):



36 **37**

To a stirred solution of compound **36** (0.99 g, 2.69 mmol) in dry dichloromethane (10 mL), triethylamine (6.7 mmol, 0.93 mL) and methane sulfonyl chloride (5.38 mmol, 0.41 mL) was added at 0 °C, then reaction was slowly warmed to room temperature, stirring was continued for 3 h at room temperature, after completion of the reaction, reaction mixture was diluted with water and extracted 3 times (3x100 mL) with dichloromethane, the resulting organic layer was washed with brine and dried over anhydrous sodium sulfate, evaporation followed by column chromatography using silica-gel provided compound **37** in 96% yield (1.5 g). R_f = 0.6 in 40% Ethylacetate/hexanes.

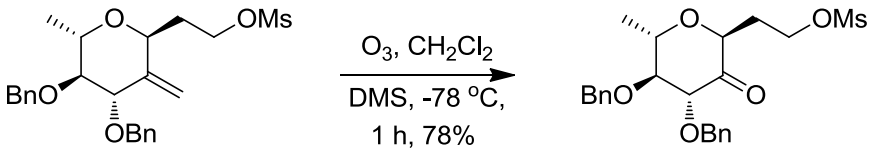
IR (neat): $\tilde{\nu}_{max}/cm^{-1}$ 3090, 3057, 2926, 1501, 1463, 1358, 1172, 1112.

^{1}H (500 MHz, $CDCl_3$): δ 7.29-7.36 (m, 10H), 5.28 (s, 1H), 5.10 (s, 1H), 4.84 (d, *J* = 11.0 Hz, 1H), 4.70 (d, *J* = 11.5 Hz, 1H), 4.63 (d, *J* = 11.5 Hz, 1H), 4.59 (d, *J* = 11.0 Hz, 1H), 4.42 (dd, *J* = 5.5 Hz, *J* = 10.0 Hz, 1H), 4.25-4.33 (m, 2H), 4.13 (d, *J* = 7.5 Hz, 1H), 3.67-3.73 (m, 1H), 3.17 (t, *J* = 8.0 Hz, 1H), 3.01 (s, 3H), 2.20-2.27 (m, 1H), 1.97-2.04 (m 1H), 1.27 (d, *J* = 6.5 Hz, 3H) ppm.

^{13}C (100 MHz, $CDCl_3$): δ 143.4, 138.1, 137.9, 128.5, 128.4, 128.0, 127.8, 111.2, 85.3, 80.6, 76.3, 74.6, 73.5, 72.9, 69.8, 66.6, 37.2, 30.5, 18.5 ppm.

HRMS (ESI) calcd for $C_{24}H_{31}O_6S$ 447.1841; found 447.1835.

(4.4.2.8) 2-((2*S*,4*R*,5*S*,6*S*)-4,5-bis(benzyloxy)-6-methyl-3-oxotetrahydro-2*H*-pyran-2-yl)ethyl methanesulfonate (38):



37 **38**

Compound **37** (1.1 g, 2.46 mmol) in dry dichloromethane (15 mL) was treated with O_3 at -78 ^oC until the solution become light blue in color (1 h). Subsequently DMS was added and the reaction mixture was allowed to warm up to room temperature. The reaction mixture was diluted with dichloromethane (20 mL) concentrated under reduced pressure, purified by column chromatography over silica gel using 4:6 Ethylacetate/hexanes provided compound **38** in 85% yield (0.94 g). R_f = 0.52 in 40% Ethylacetate/hexanes.

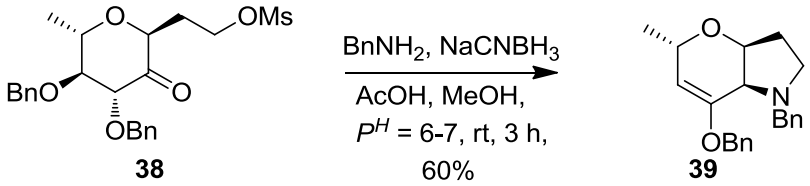
IR (neat): $\tilde{\nu}_{max}/cm^{-1}$ 3068, 2975, 2931, 1731, 1632, 1457, 1353, 1260, 1200.

^{1}H (400 MHz, $CDCl_3$): δ 7.26-7.44 (m, 10H), 4.95 (d, *J* = 11.6 Hz, 1H), 4.83 (d, *J* = 11.2 Hz, 1H), 4.60 (t, *J* = 12.0 Hz, 2H), 4.37 (d, *J* = 8.8 Hz, 1H), 4.29 (dd, *J* = 4.8 Hz, *J* = 10.0 Hz, 2H), 4.19 (t, *J* = 7.2 Hz, 1H), 4.01 (t, *J* = 6.8 Hz, 1H), 3.49 (t, J = 8.0 Hz, 1H), 2.98 (s, 3H), 2.12-2.16 (m, 2H), 1.31 (d, J = 6.4 Hz, 3H) ppm.

^{13}C (100 MHz, $CDCl_3$): δ 207.6, 137.7, 137.5, 128.5, 128.2, 128.1, 128.0, 128.0, 83.8, 83.6, 75.2, 74.4, 73.9, 71.8, 65.6, 37.2, 29.3, 18.1 ppm.

HRMS (ESI) calcd for $C_{23}H_{29}O_7S$ 449.1634; found 449.1635.

(4.4.2.9) (3a*S*,5*S*,7a*R*)-1-benzyl-7-(benzyloxy)-5-methyl-1,2,3,3a,5,7a-hexahydropyrano[3,2-*b*]pyrrole (39):



To a stirred solution of **38** (0.51 g, 1.15 mmol) in dry methanol (8 mL) benzyl amine (1.38 mmol, 150 µL) was added at room temperature, stirring was continued for 1 h, then 0.5 equivalents of acetic acid (0.57 mmol, 34 µL) and $NaCNBH_3$ (1.95 mmol, 121 mg) were added, additional stirring for 3 h at room temperature, followed by quenching with 10 mL of 1 N NaOH, extracted with ether, ether layer was dried over anhydrous Na_2SO_4, evaporation and purification over silica-gel chromatography provided compound **39** in 60% yield (230 mg). R_f = 0.52 in 30% Ethylacetae/hexanes.

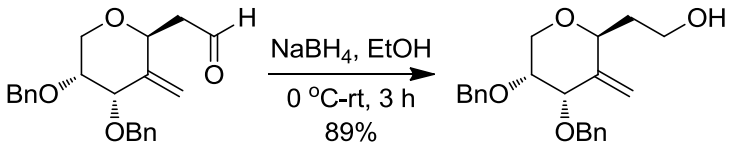
IR (neat): $\tilde{\nu}_{max}/cm^{-1}$ 3063, 3030, 2969, 2926, 2789, 1665, 1495, 1452, 1364.

^{1}H (400 MHz, $CDCl_3$): δ 7.23-7.37 (m, 10H), 4.91 (d, *J* = 2.8 Hz, 1H), 4.77 (dd, *J* = 11.2 Hz, J = 18.4 Hz, 2H), 4.55-4.59 (m, 1H), 4.41 (dd, *J* = 6.4 Hz, *J* = 12.0 Hz, 1H), 4.34 (d, *J* = 13.2Hz, 1H), 3.58 (d, *J* = 13.2 Hz, 1H), 2.96-3.01 (m, 1H), 2.90 (d, *J* = 5.6 Hz, 1H), 2.19 (dd, *J* = 9.2 Hz, *J* = 18.0 Hz, 1H), 2.03-2.12 (m, 1H), 1.87-1.95 (m, 1H), 1.28 (d, *J* = 1.6 Hz, 3H) ppm.

^{13}C (100 MHz, $CDCl_3$): δ 153.3, 138.7, 136.9, 129.4, 128.4, 128.0, 127.8, 127.5, 126.7, 101.3, 72.8, 68.9, 66.9, 61.2, 59.1, 50.7, 29.7, 21.0 ppm.

HRMS (ESI) calcd for $C_{22}H_{25}NO_2$+Na 358.1783; found 358.1779.

(4.4.2.10) 2-((2*S*,4*S*,5*R*)-4,5-bis(benzyloxy)-3-methylenetetrahydro-2*H*-pyran-2-yl)ethanol (41):



40 **41**

To a stirred solution of compound **40** (500 mg, 1.41 mmol) in dry ethanol (7 mL) at 0 °C, was added solid $NaBH_4$ (53 mg, 1.41 mmol) and the stirring was continued for 3 h. After completion of the reaction (by TLC), it was quenched with saturated NH_4Cl solution. Ethanol was evaporated under reduced pressure and aqueous suspension was extracted with dichloromethane (2x75 mL). The combined organic layers were washed with water, brine solution, dried over anhydrous $NaSO_4$ and concentrated. The obtained crude product was purified by silica-gel column chromatography to give corresponding alcohol **41** in 89% yield (450 mg). R_f = 0.52 in 40% Ethylacetate/hexanes.

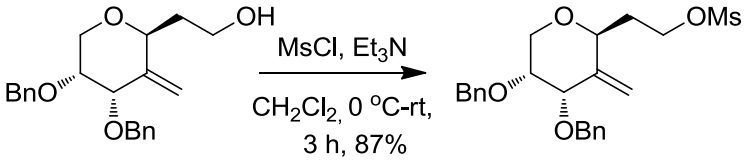
IR (neat): $\tilde{\nu}_{max}/cm^{-1}$ 3430, 2964, 2920, 1632, 1457, 1200.

^{1}H (400 MHz, $CDCl_3$): δ 7.26-7.37 (m, 10H), 5.07 (s, 1H), 4.98 (s, 1H), 4.61 (d, *J* = 12.4 Hz, 1H), 4.53 (d, *J* = 12.0 Hz, 1H), 4.43 (d, *J* = 12.4 Hz, 1H), 4.35 (d, *J* = 12.4 Hz, 1H), 4.20 (d, *J* = 7.2 Hz, 1H), 4.16 (s, 1H), 3.89 (t, *J* = 10.4 Hz, 1H), 3.76-3.85 (m, 3H), 3.52-3.57 (m, 1H), 2.88 (bs, 1H), 1.81-1.91 (m, 2H) ppm.

^{13}C (100 MHz, $CDCl_3$): δ 143.6, 138.2, 138.1, 128.4, 128.4, 128.4, 127.9, 127.7, 127.7, 127.6, 113.6, 77.1, 76.1, 73.1, 70.7, 69.3, 64.9, 60.7, 33.1 ppm.

HRMS (ESI) calcd for $C_{22}H_{26}O_4$+Na 377.1729 found 377.1721.

(4.4.2.11) 2-((2*S*,4*S*,5*R*)-4,5-bis(benzyloxy)-3-methylenetetrahydro-2*H*-pyran-2-yl)ethyl methanesulfonate (42):



41 **42**

To a stirred solution of compound **41** (0.46 g, 1.31 mmol) in dry dichloromethane (7 mL), triethylamine (3.29 mmol, 0.45 mL) and methane sulfonyl chloride (2.63 mmol, 0.2 mL) was added at 0 °C, then reaction was slowly warmed to room temperature, stirring was continued for 3 h at room temperature, after completion of the reaction, reaction mixture was diluted with water and extracted 3 times (3x75 mL) with dichloromethane, the resulting organic layer was washed with brine and dried over anhydrous sodium sulfate, evaporation followed by column chromatography using silica-gel provided compound **42** in 87% yield (0.5 g). R_f = 0.51 in 30% Ethylacetate/hexanes.

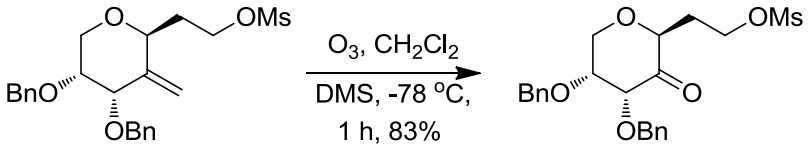
IR (neat): $\tilde{\nu}_{max}/cm^{-1}$ 3030, 2931, 2876, 1742, 1495, 1452, 1353, 1172.

^{1}H (400 MHz, $CDCl_3$): δ 7.26-7.39 (m, 10H), 5.08 (s, 1H), 5.04 (s, 1H), 4.64 (d, *J* = 12.4 Hz, 1H), 4.56 (d, *J* = 12.0 Hz, 1H), 4.46 (d, *J* = 12.0 Hz, 1H), 4.38-4.41 (m, 3H), 4.19 (d, *J* = 2.8 Hz, 1H), 4.14 (dd, *J* = 4.0 Hz, *J* = 10.8 Hz, 1H), 3.88 (d, *J* = 10.4 Hz, 1H), 3.81-3.86 (m, 1H), 3.53-3.58 (m, 1H), 3.12 (s, 1H), 3.00 (s, 3H), 2.15-2.23 (m, 1H), 1.90-1.99 (m, 1H) ppm.

^{13}C (100 MHz, $CDCl_3$): δ 143.3, 138.0, 128.4, 127.9, 127.6, 113.3, 76.1, 70.7, 69.4, 69.3, 67.1, 64.9, 37.1, 31.5, 30.7 ppm.

HRMS (ESI) calcd for $C_{23}H_{28}O_6$+Na 455.1504; found 455.1509.

(4.4.2.12) 2-((2*S*,4*R*,5*R*)-4,5-bis(benzyloxy)-3-oxotetrahydro-2*H*-pyran-2-yl)ethyl methanesulfonate (43):



42 **43**

Compound **42** (0.3 g, 0.69 mmol) in dry dichloromethane (10 mL) was treated with O_3 at -78 °C until the solution become light blue in color (1 h). Subsequently DMS was added and the reaction mixture was allowed to warm up to room temperature. The reaction mixture was diluted with dichloromethane (10 mL) concentrated under reduced pressure, purified by column chromatography over silica gel using 4:6 Ethylacetate/hexanes provided compound **43** in 83% yield (0.25 g). R_f = 0.4 in 40% Ethylacetate/hexanes.

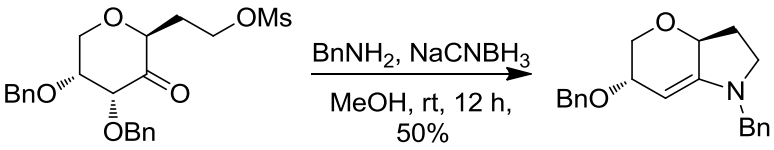
IR (neat): $\tilde{\nu}_{max}/cm^{-1}$ 2926, 2865, 1731, 1254, 1194.

^{1}H (400 MHz, $CDCl_3$): δ 7.26-7.35 (m, 10H), 5.13 (s, 1H), 4.89 (d, *J* = 12.4 Hz, 1H), 4.72 (dd, *J* = 12.4 Hz, *J* = 18.4 Hz, 2H), 4.54 (d, *J* = 12.4 Hz, 1H), 4.34-4.40 (m, 2H), 4.18 (dd, *J* = 2.8 Hz, *J* = 14.4 Hz, 2H), 4.10 (dd, *J* = 2.0 Hz, *J* = 12.8 Hz, 1H), 4.00 (dd, *J* = 3.6 Hz, *J* = 8.4 Hz, 1H), 3.75 (dd, *J* = 0.8 Hz, *J* = 12.4 Hz, 1H), 2.98 (s, 3H), 2.32-2.35 (m, 1H), 2.11-2.17 (m, 1H) ppm.

^{13}C (100 MHz, $CDCl_3$): δ 203.4, 137.7, 137.3, 128.5, 128.4, 128.0, 127.8, 127.7, 82.1, 78.1, 77.6, 72.3, 72.1, 67.8, 66.4, 37.1, 28.5 ppm.

HRMS (ESI) calcd for $C_{23}H_{28}O_6$+Na 435.1477; found 435.1470.

(4.4.2.13) (3a*S*,6*S*)-1-benzyl-6-(benzyloxy)-1,2,3,3a,5,6-hexahydropyrano[3,2-*b*]pyrrole (44):



43 **44**

To a stirred solution of **43** (0.3 g, 0.69 mmol) in dry methanol (5 mL) benzyl amine (0.82 mmol, 90 µL) was added at room temperature, stirring was continued for 1 h, then 0.5 equivalents of acetic acid (0.34 mmol, 20 µL) and $NaCNBH_3$ (1.17 mmol, 73 mg) were added, additional stirring for 12 h at room temperature, followed by quenching with 4 mL of 1N NaOH, extracted with ether, ether layer was dried over anhydrous Na_2SO_4, evaporation and purification over silica-gel column chromatography provided compound **44** in 50% yield (110 mg). R_f = 0.53 in 30% Ethylacetae/hexanes.

IR (neat): $\tilde{\nu}_{max}/cm^{-1}$ 3030, 2926, 2854, 1726, 1676, 1501, 1463, 1265, 1106.

^{1}H (400 MHz, $CDCl_3$): δ 7.26-7.42 (m, 5H), 5.06 (dd, *J* = 1.6 Hz, *J* = 4.8 Hz, 1H), 4.94 (d, *J* = 12.0 Hz, 1H), 4.87 (d, *J* = 12.0 Hz, 1H), 4.36 (d, *J* = 4.8 Hz, 1H), 4.25 (dd, *J* = 4.8 Hz, *J* = 8.8 Hz, 1H), 4.23 (d, *J* = 1.2 Hz, 1H), 4.18 (dd, *J* = 3.6 Hz, J = 8.4 Hz, 1H), 2.46-2.55 (m, 1H), 2.18-2.24 (m, 1H) ppm.

^{13}C (100 MHz, $CDCl_3$): δ 146.5, 135.8, 128.6, 128.0, 127.1, 117.4, 99.0, 81.6, 75.9, 69.8, 68.4, 64.3, 32.1 ppm.

HRMS (ESI) calcd for $C_{21}H_{24}NO_2$ 322.1807; found 322.1805.

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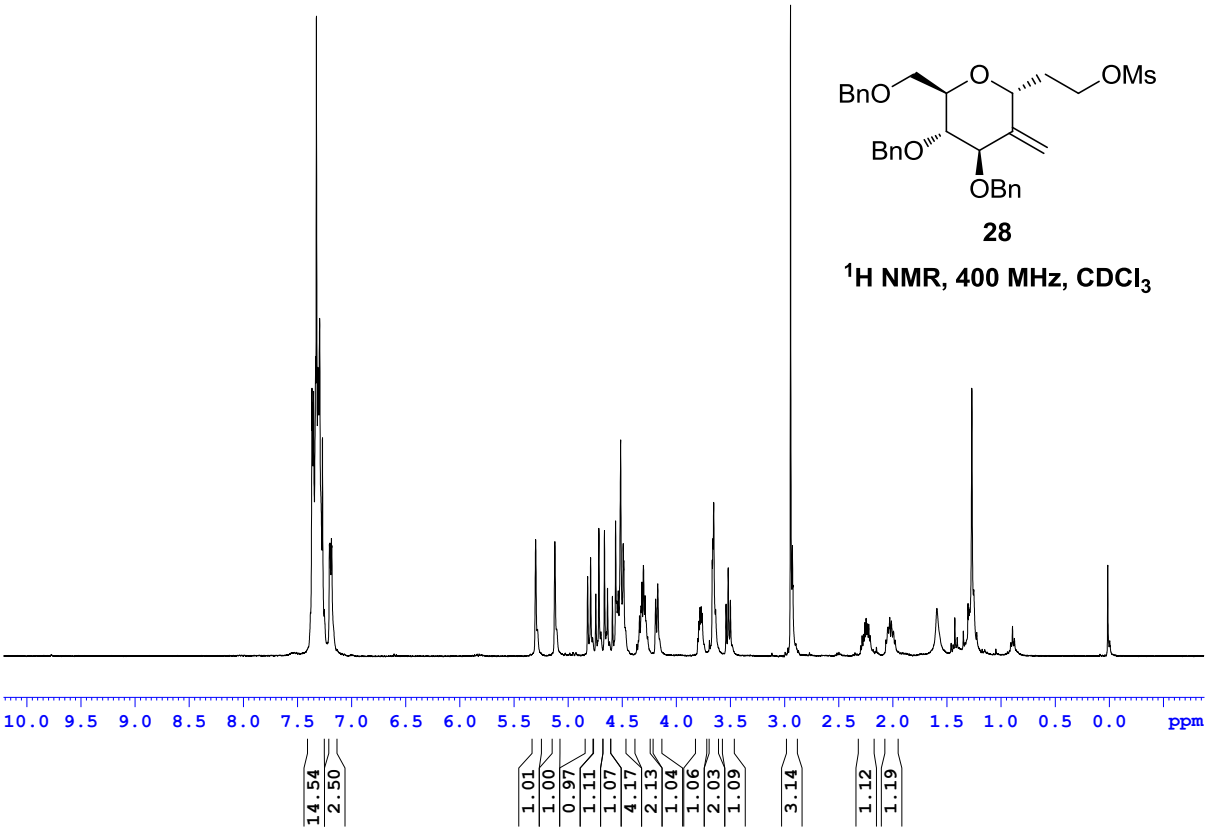
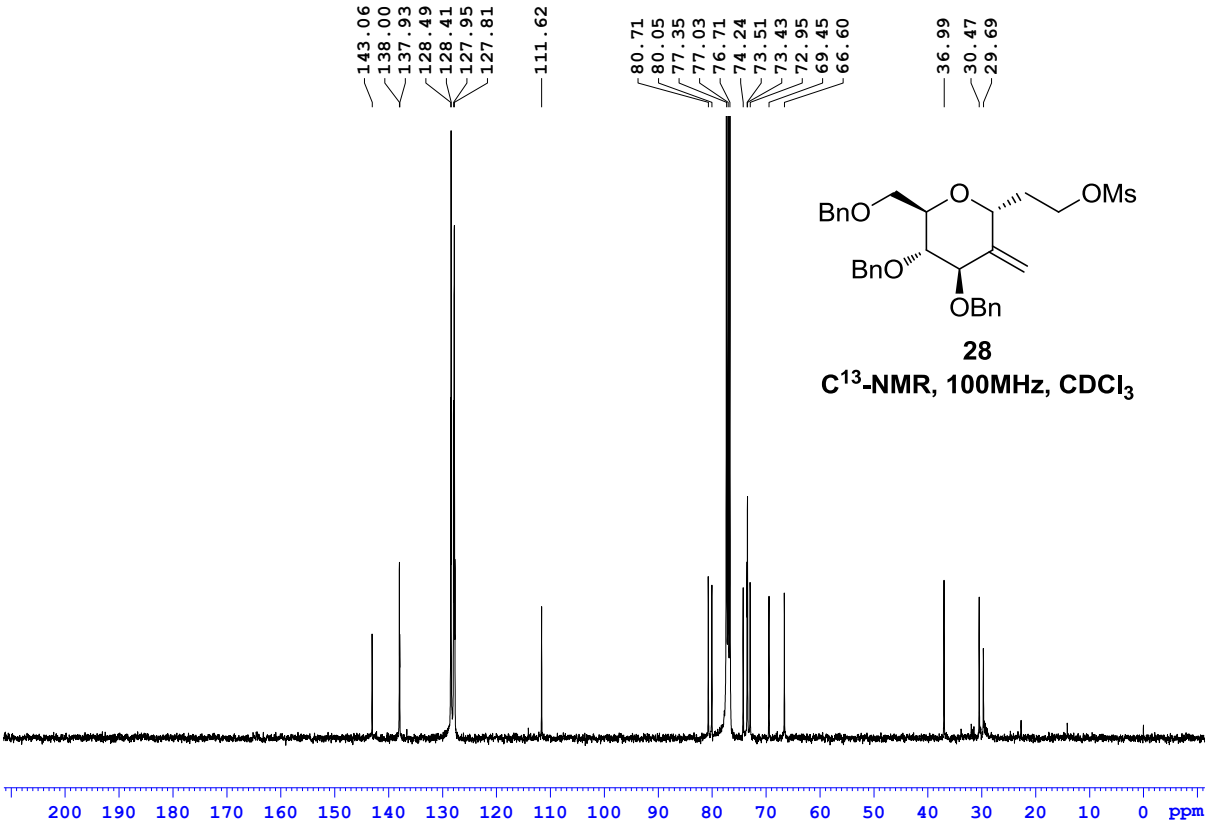
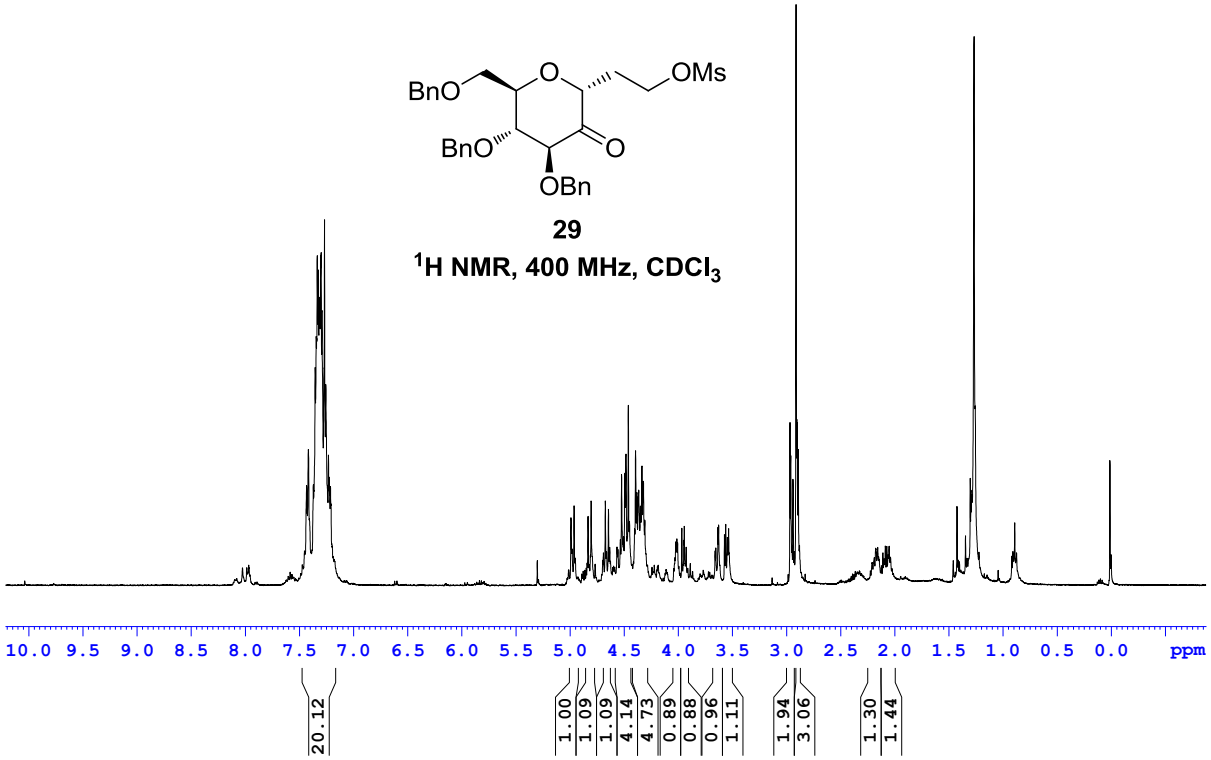
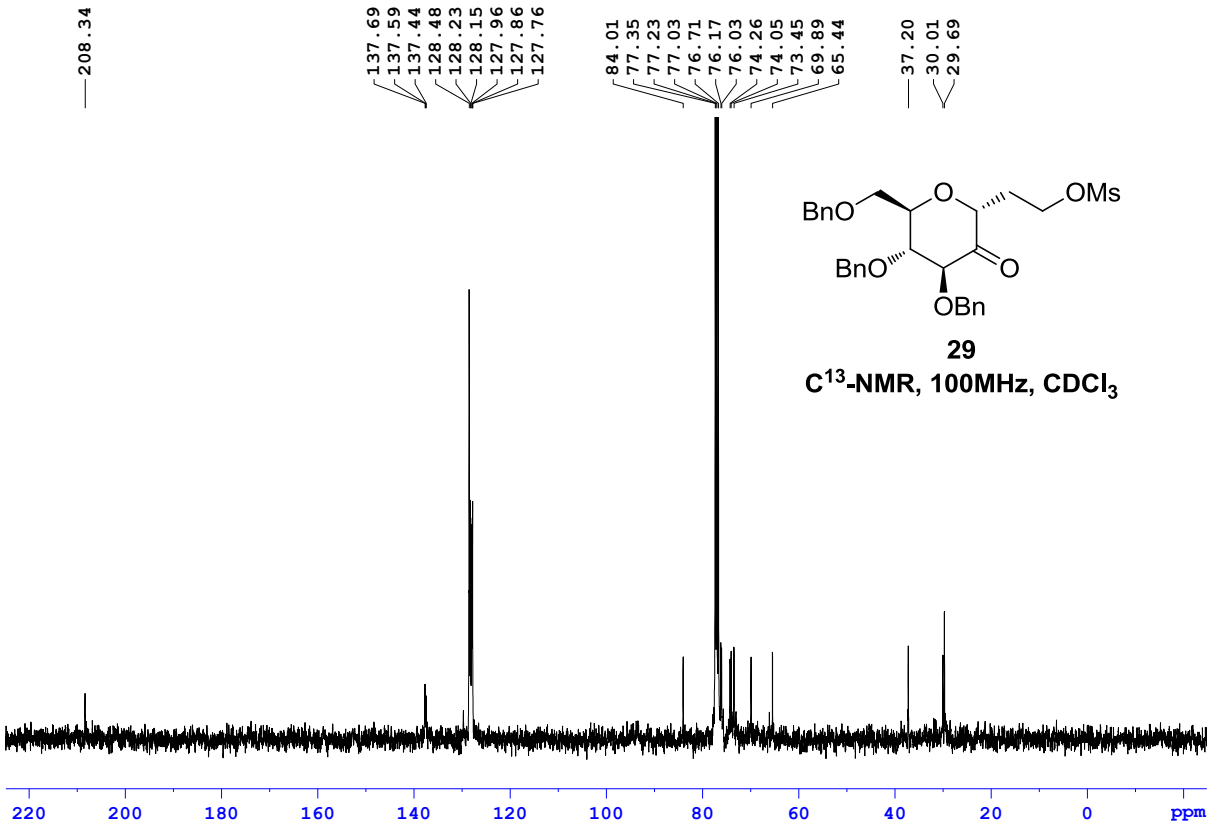

BnO
O
OMs
BnO
OBn
28
1H NMR, 400 MHz, CDCl3
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm
14.54
2.50
1.01
1.00
0.97
1.11
1.07
4.17
2.13
1.04
1.06
2.03
1.09
3.14
1.12
1.19


143.06
138.00
137.93
128.49
128.41
127.95
127.81
111.62
80.71
80.05
77.35
77.03
76.71
74.24
73.51
73.43
72.95
69.45
66.60
36.99
30.47
29.69
BnO
O
OMs
BnO
OBn
28
C13-NMR, 100MHz, CDCl3
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm



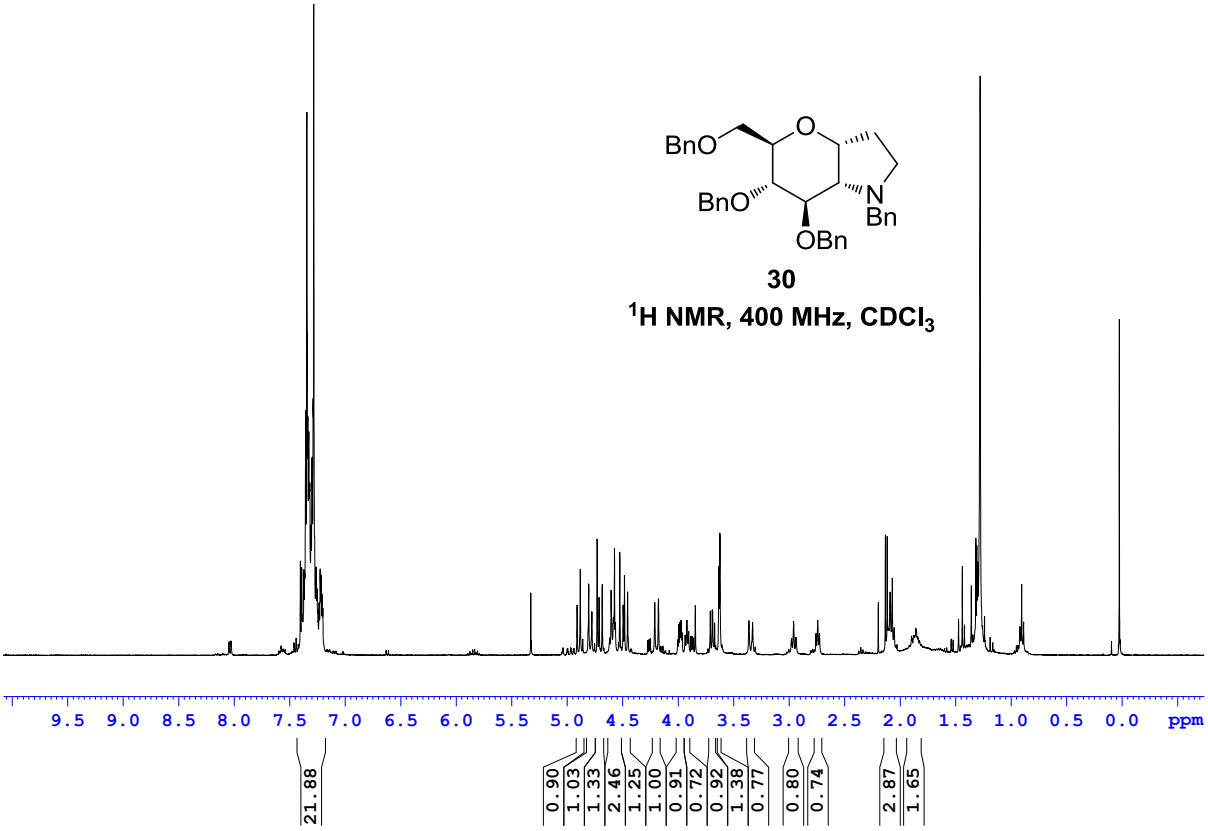
29

^{1}H NMR, 400 MHz, $CDCl_3$



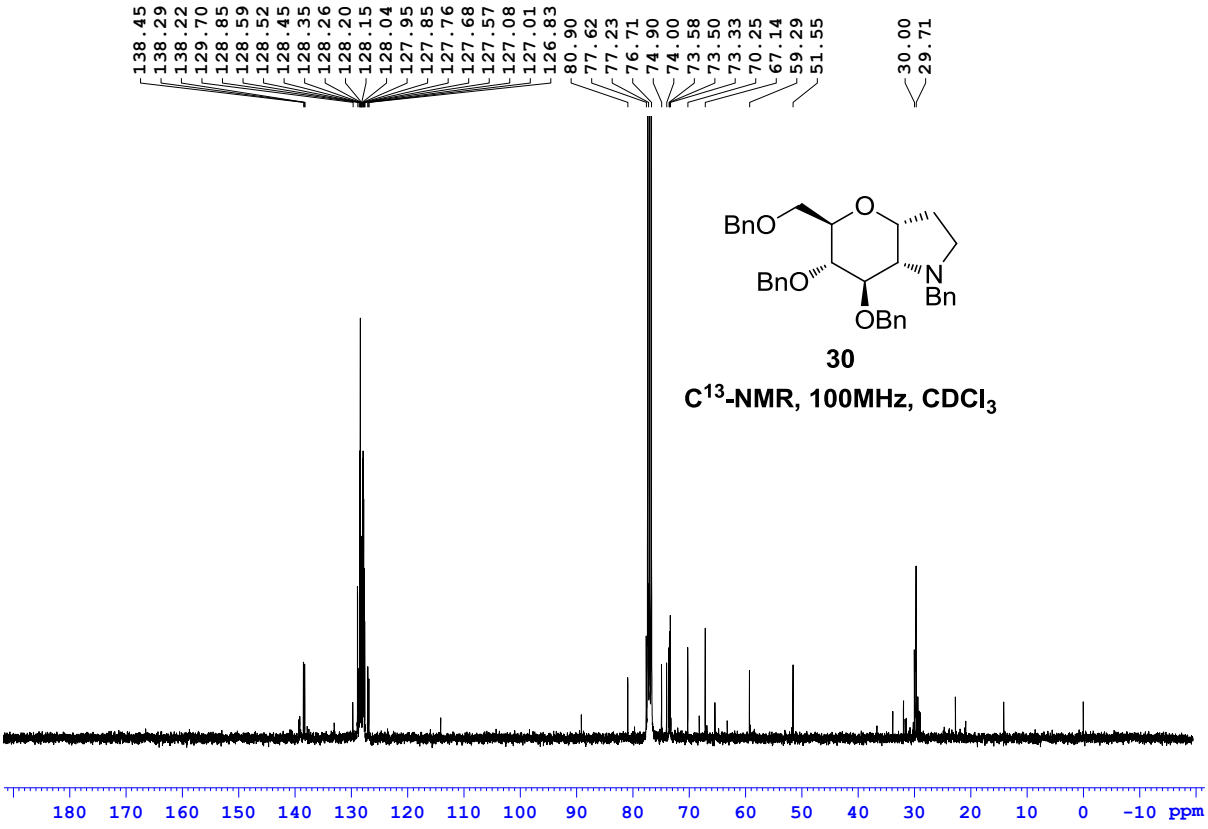
29

C^{13}-NMR, 100MHz, $CDCl_3$



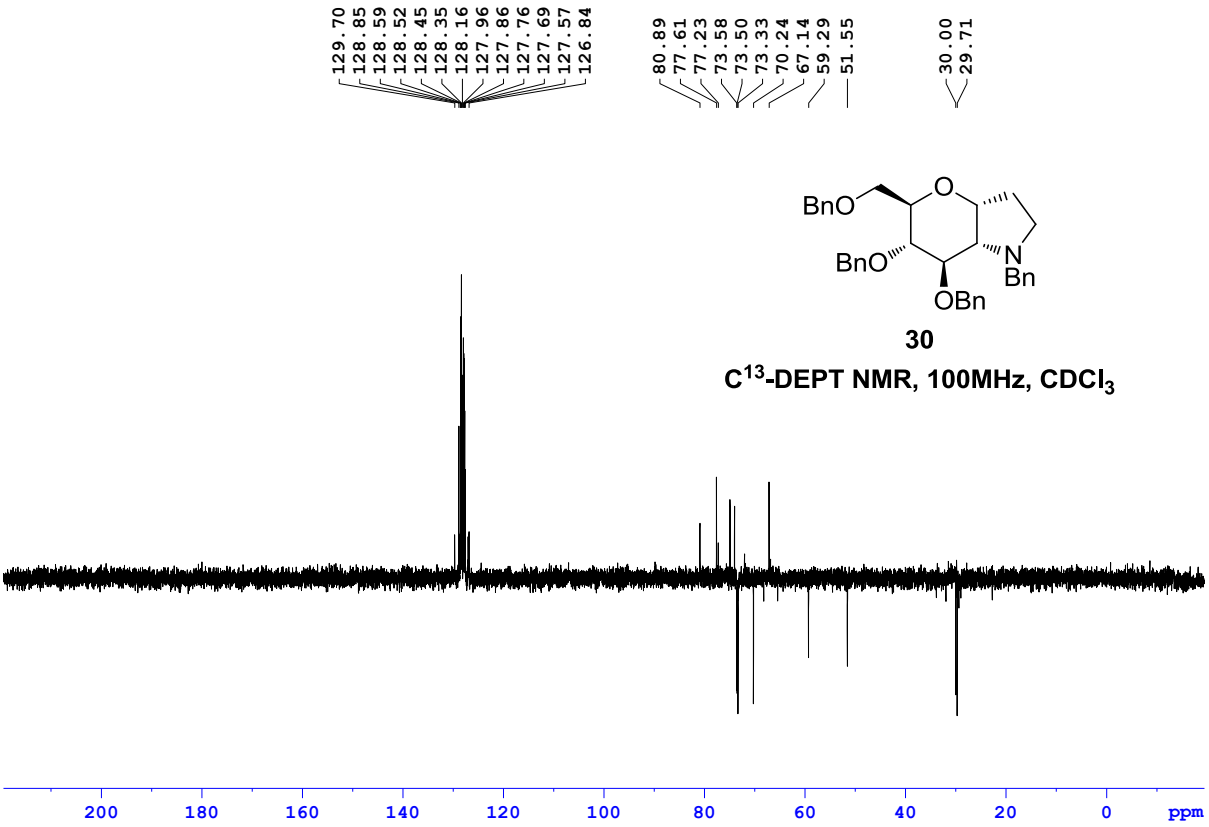
30

^{1}H NMR, 400 MHz, $CDCl_3$



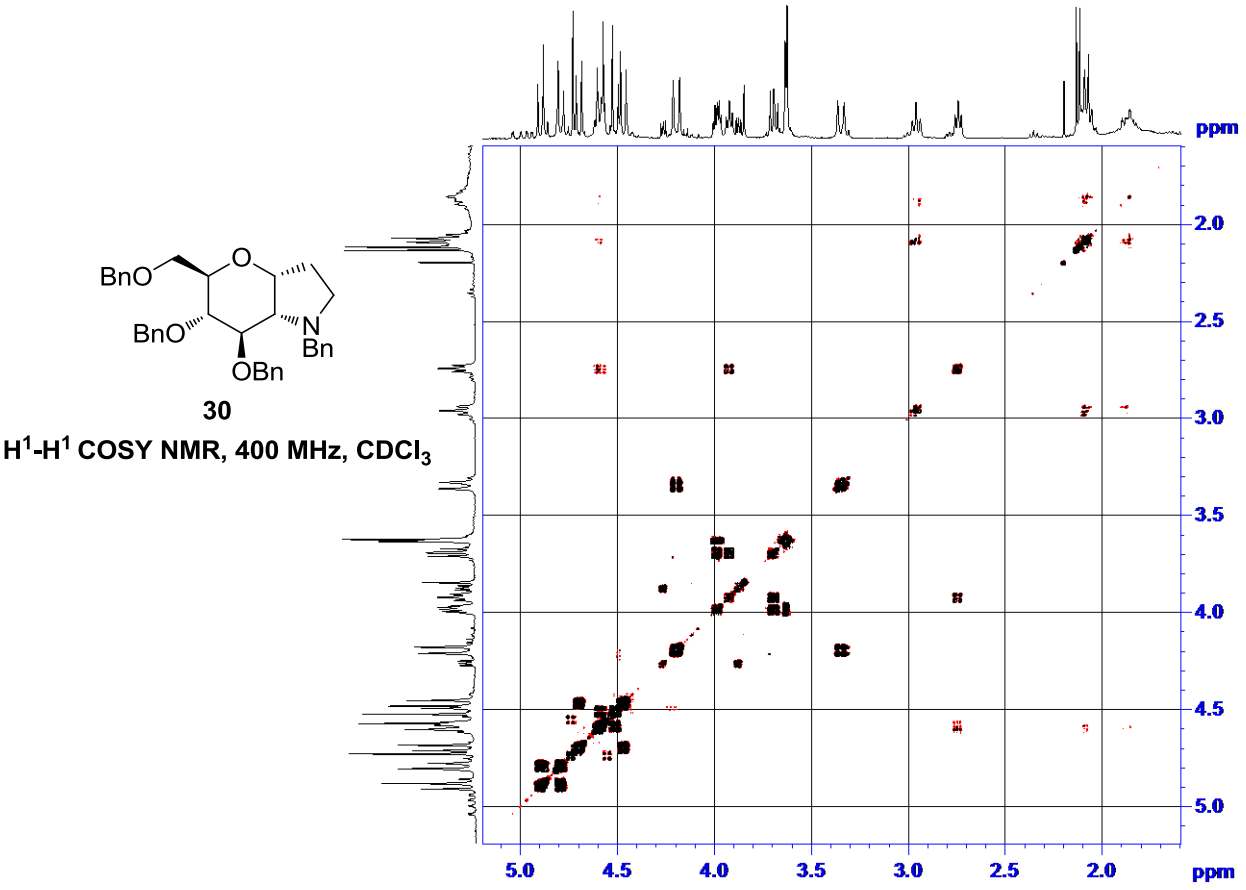
30

C^{13}-NMR, 100MHz, $CDCl_3$



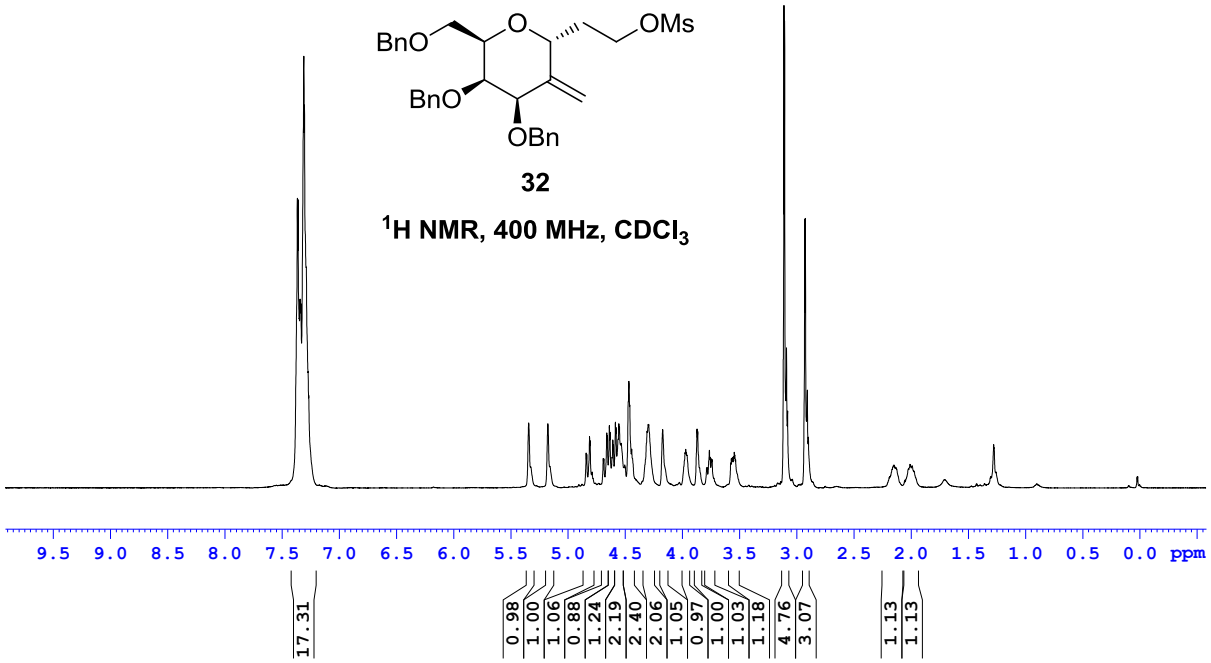
30

C^{13}-DEPT NMR, 100MHz, $CDCl_3$



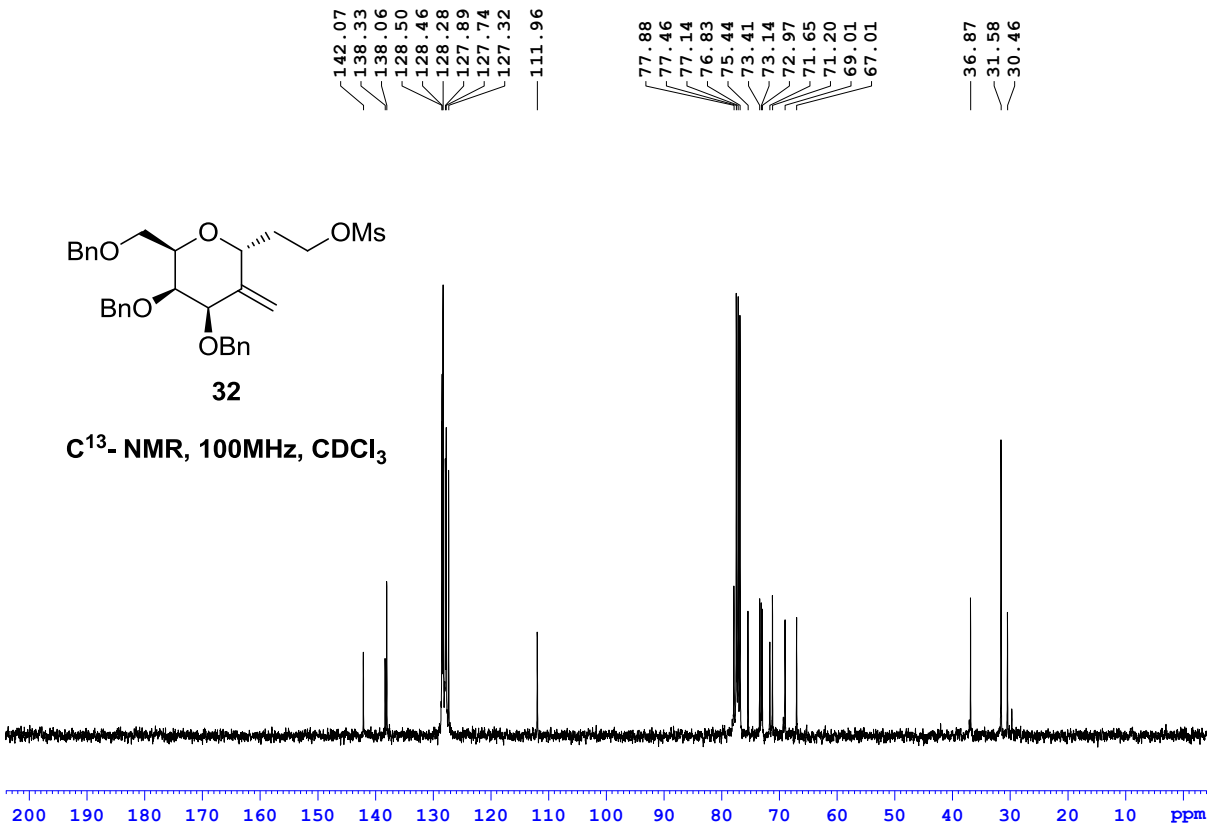
30

H^1-H^1 COSY NMR, 400 MHz, $CDCl_3$



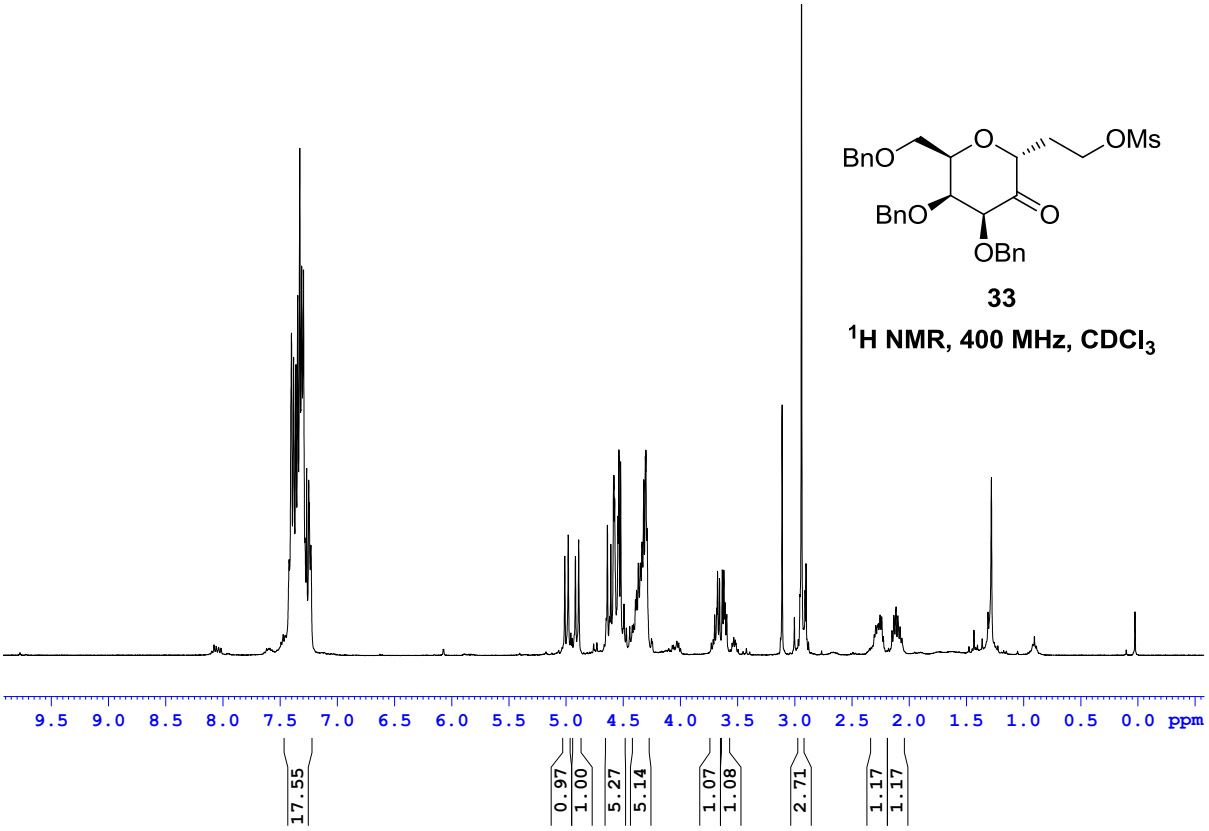
32

^{1}H NMR, 400 MHz, $CDCl_3$



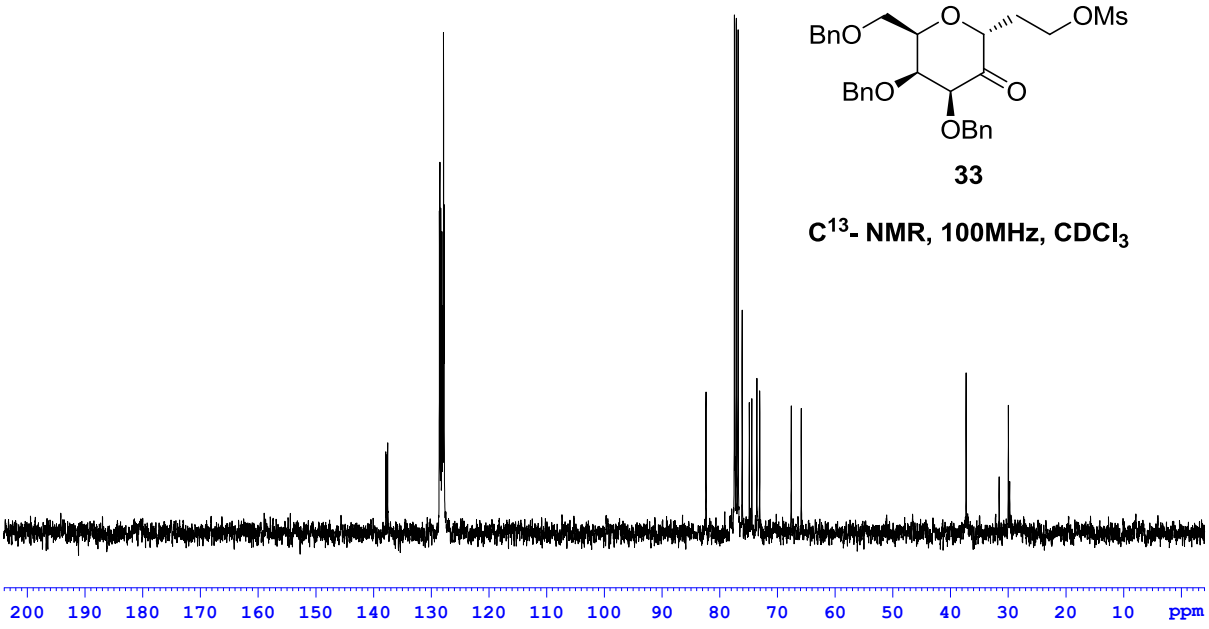
32

C^{13}- NMR, 100MHz, $CDCl_3$



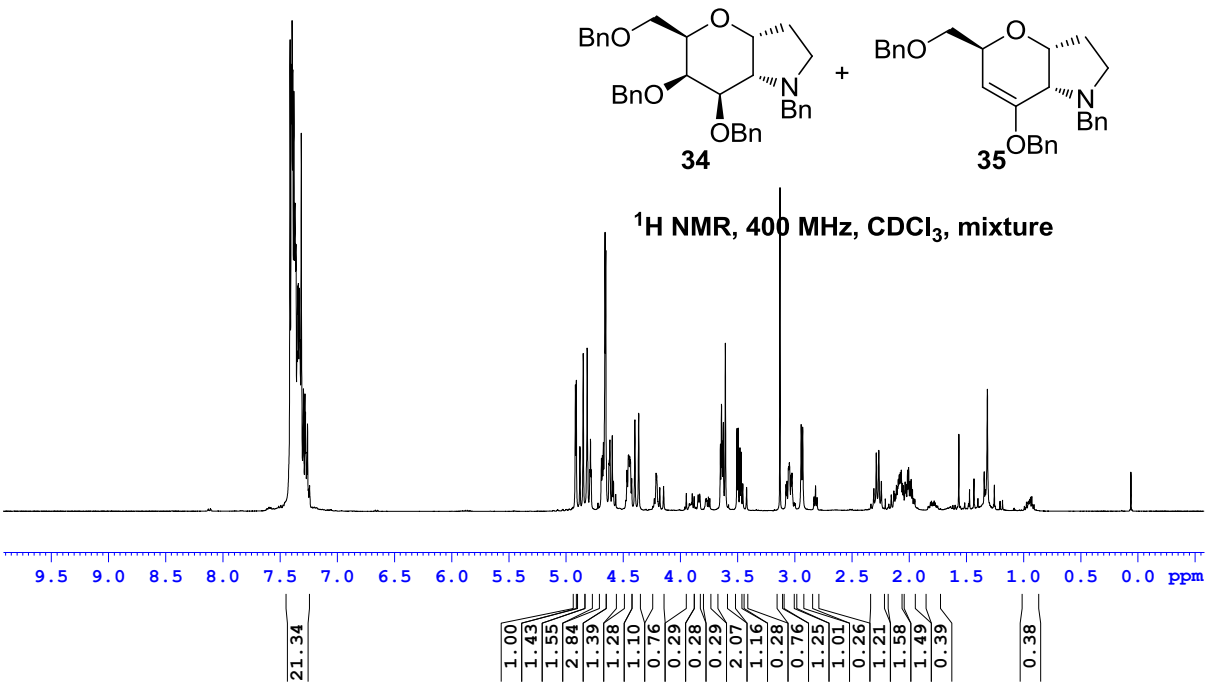
33

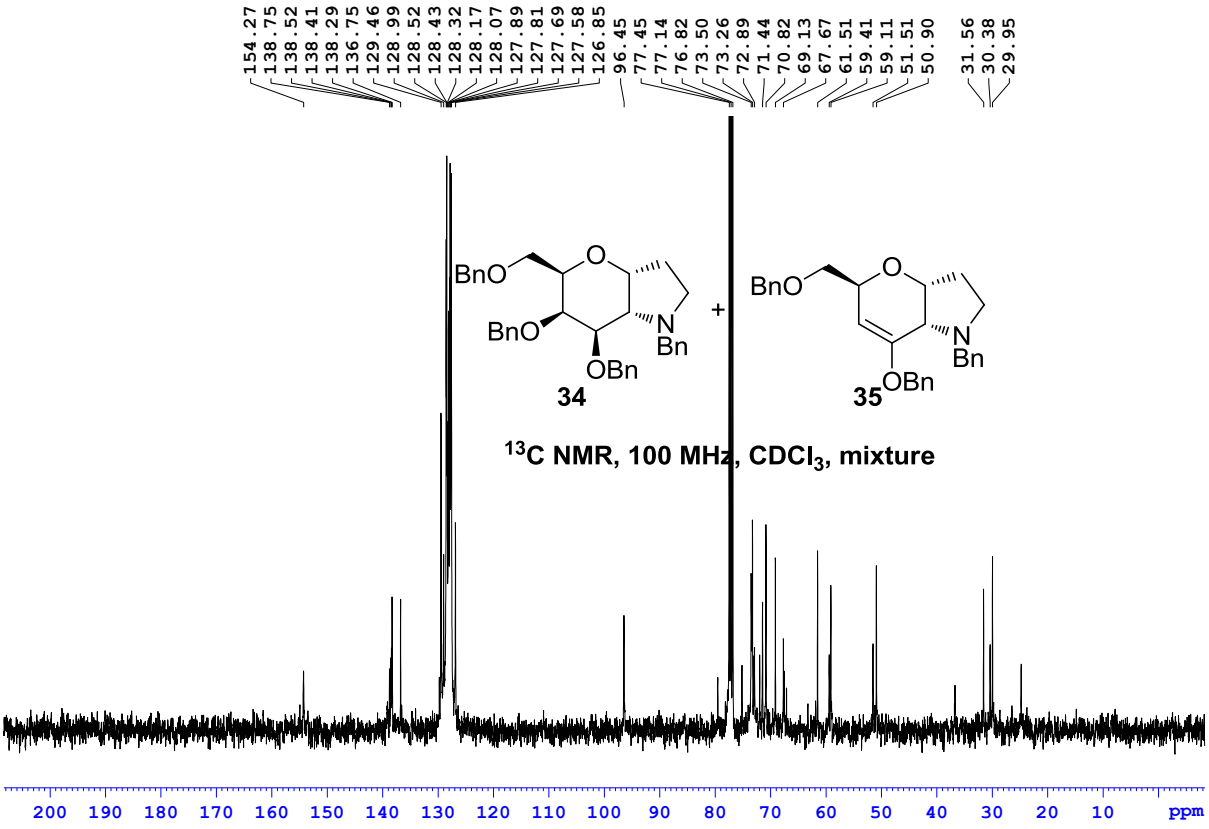
^{1}H NMR, 400 MHz, $CDCl_3$

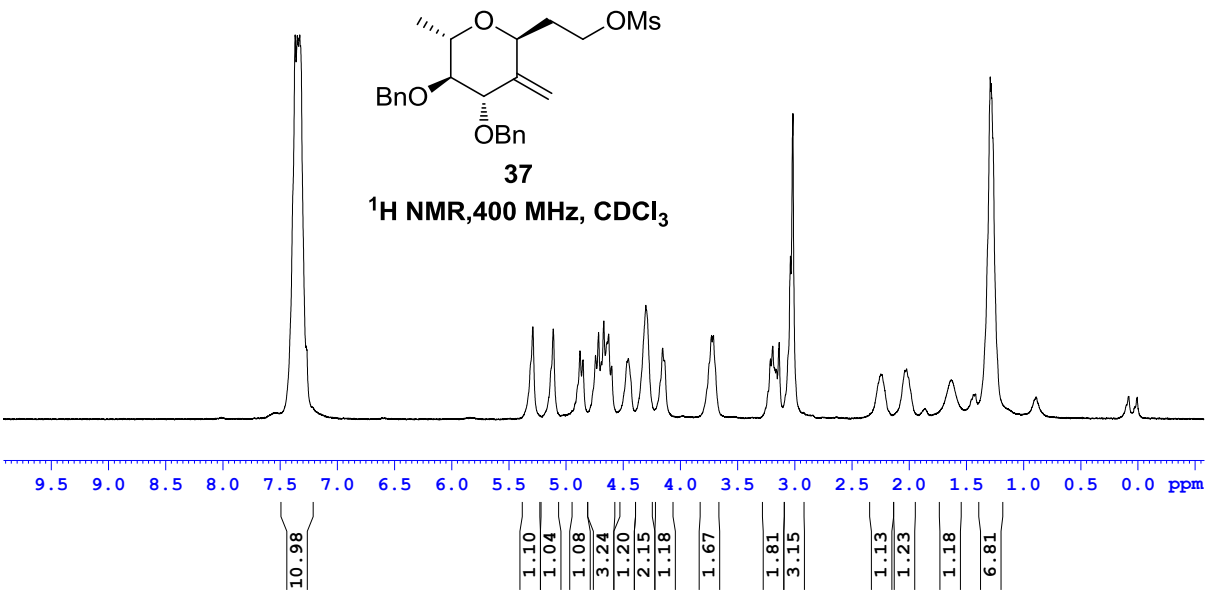


33

C^{13}- NMR, 100MHz, $CDCl_3$

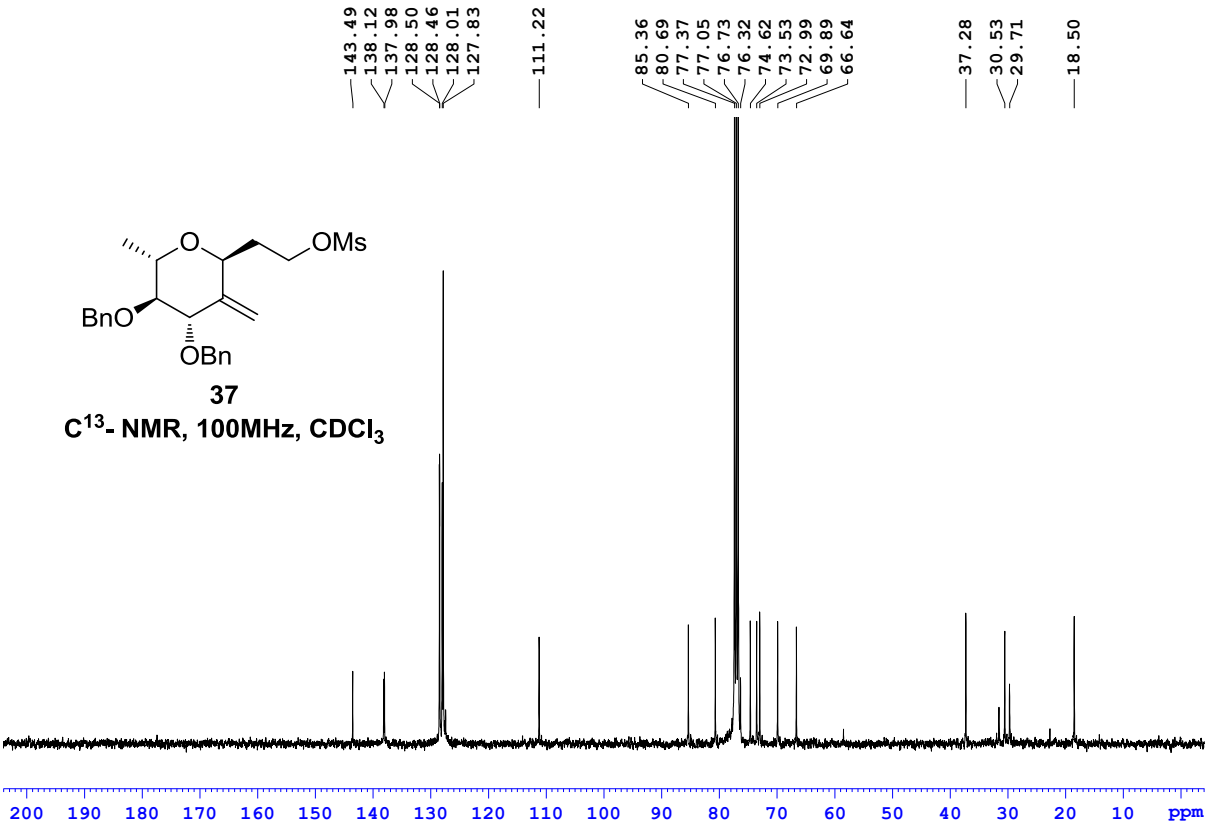

BnO
BnO
OBn
N
Bn
34
+
BnO
OBn
N
Bn
35
1H NMR, 400 MHz, CDCl3, mixture
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm
21.34
1.00 1.43 1.55 2.84 1.39 1.28 1.10 0.76 0.29 0.28 0.29 2.07 1.16 0.28 0.76 1.25 1.01 0.26 1.21 1.58 1.49 0.39
0.38


154.27 138.75 138.52 138.41 138.29 136.75 129.46 128.99 128.52 128.43 128.32 128.17 128.07 127.89 127.81 127.69 127.58 126.85 96.45 77.45 77.14 76.82 73.50 73.26 72.89 71.44 70.82 69.13 67.67 61.51 59.41 59.11 51.51 50.90 31.56 30.38 29.95
BnO
BnO
OBn
N
Bn
34
+
BnO
OBn
N
Bn
35
13C NMR, 100 MHz, CDCl3, mixture
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm



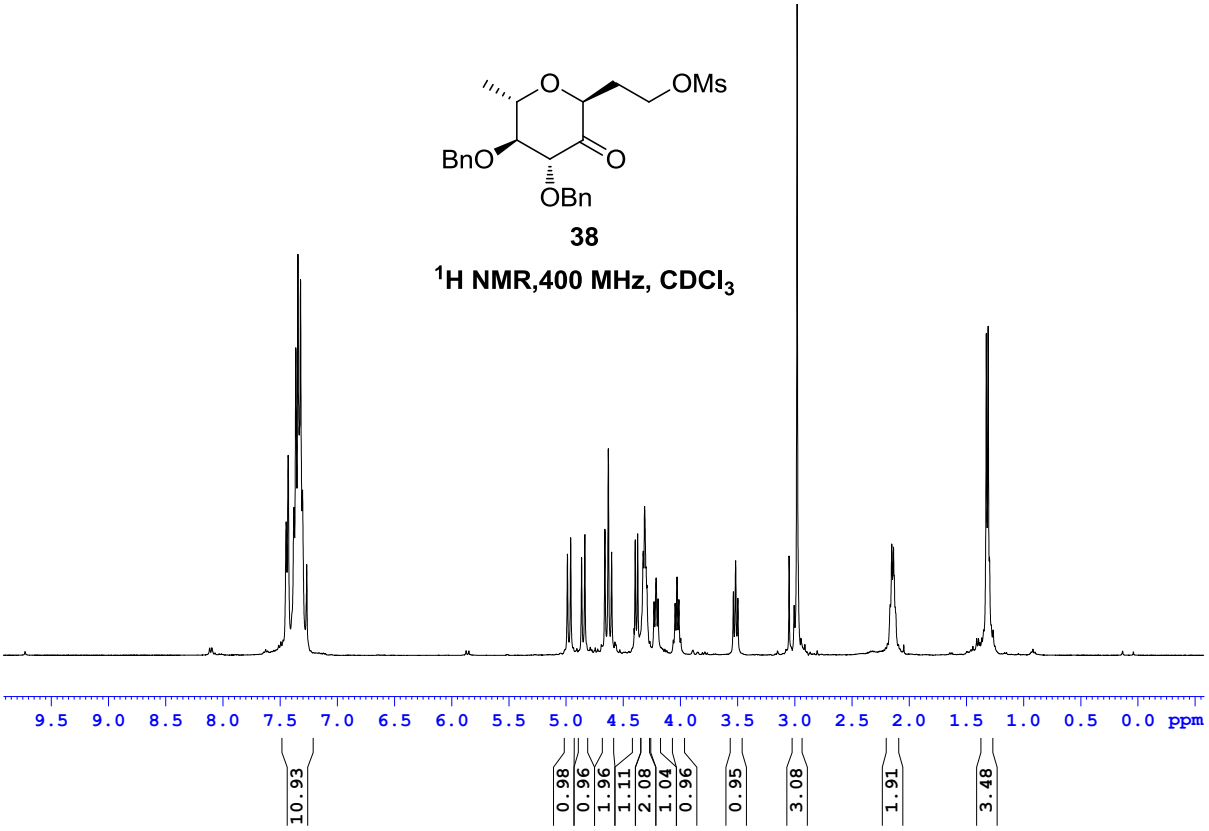
37

^{1}H NMR,400 MHz, $CDCl_3$



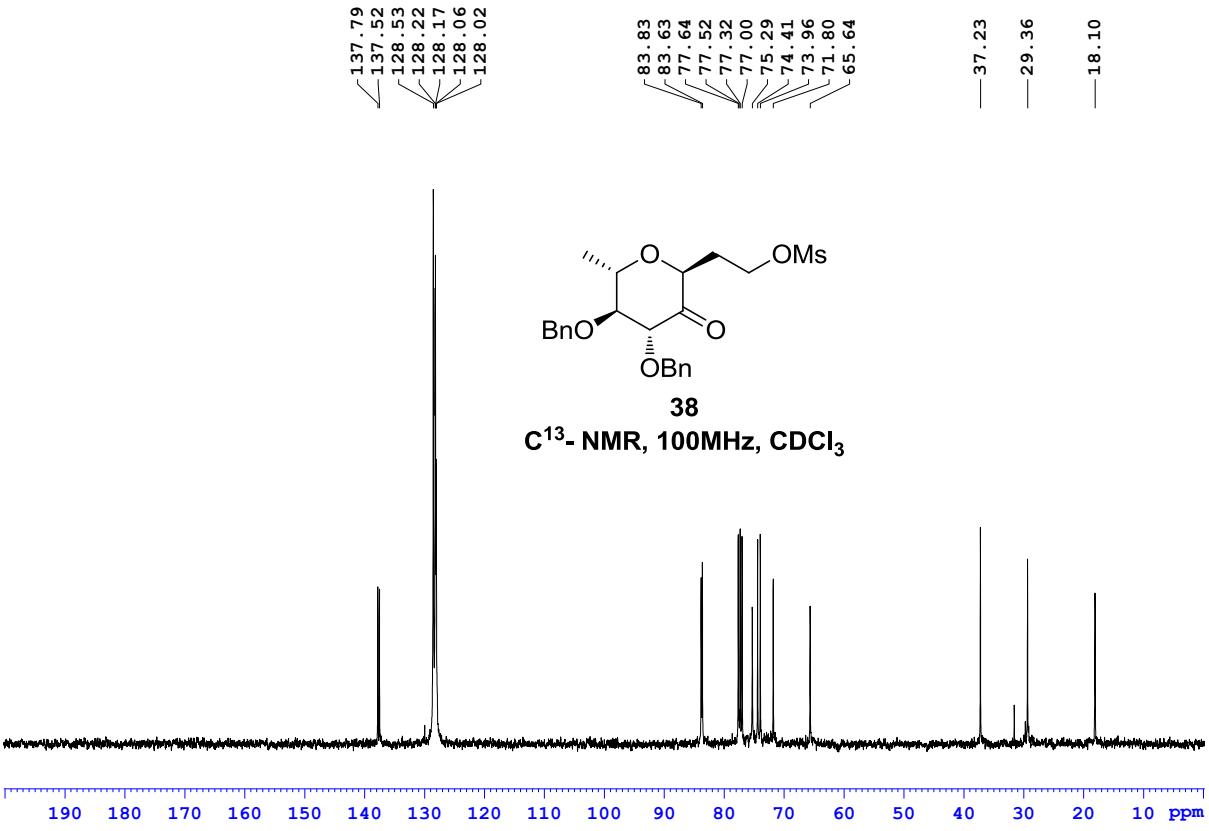
37

C^{13}- NMR, 100MHz, $CDCl_3$



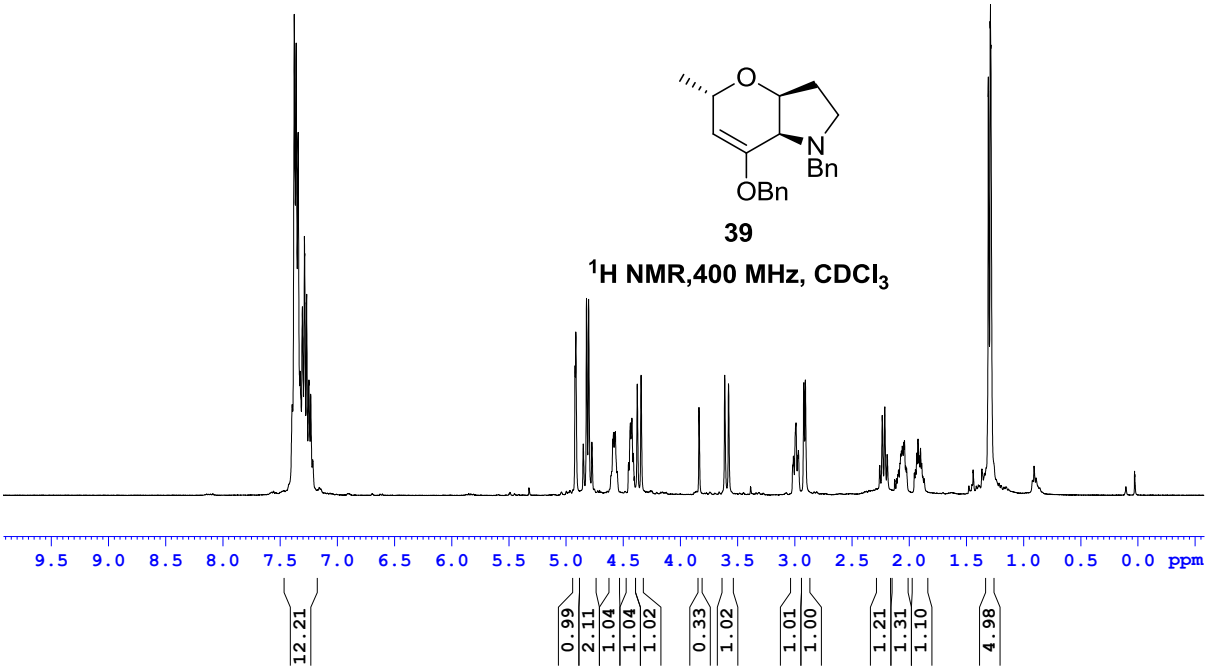
38

^{1}H NMR,400 MHz, $CDCl_3$



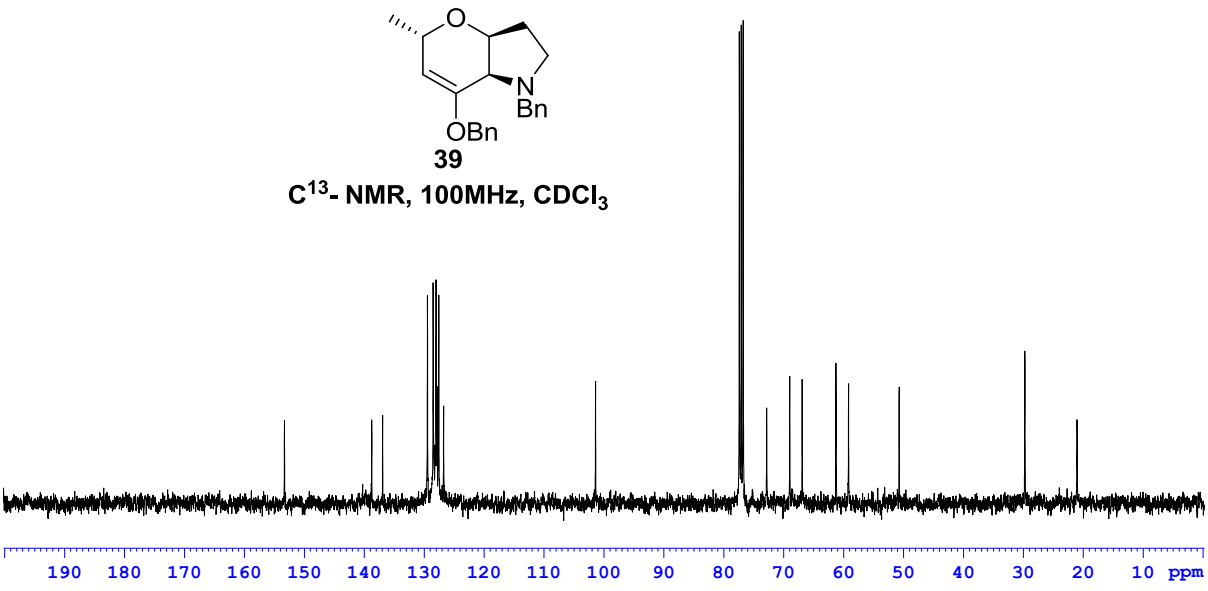
38

C^{13}- NMR, 100MHz, $CDCl_3$



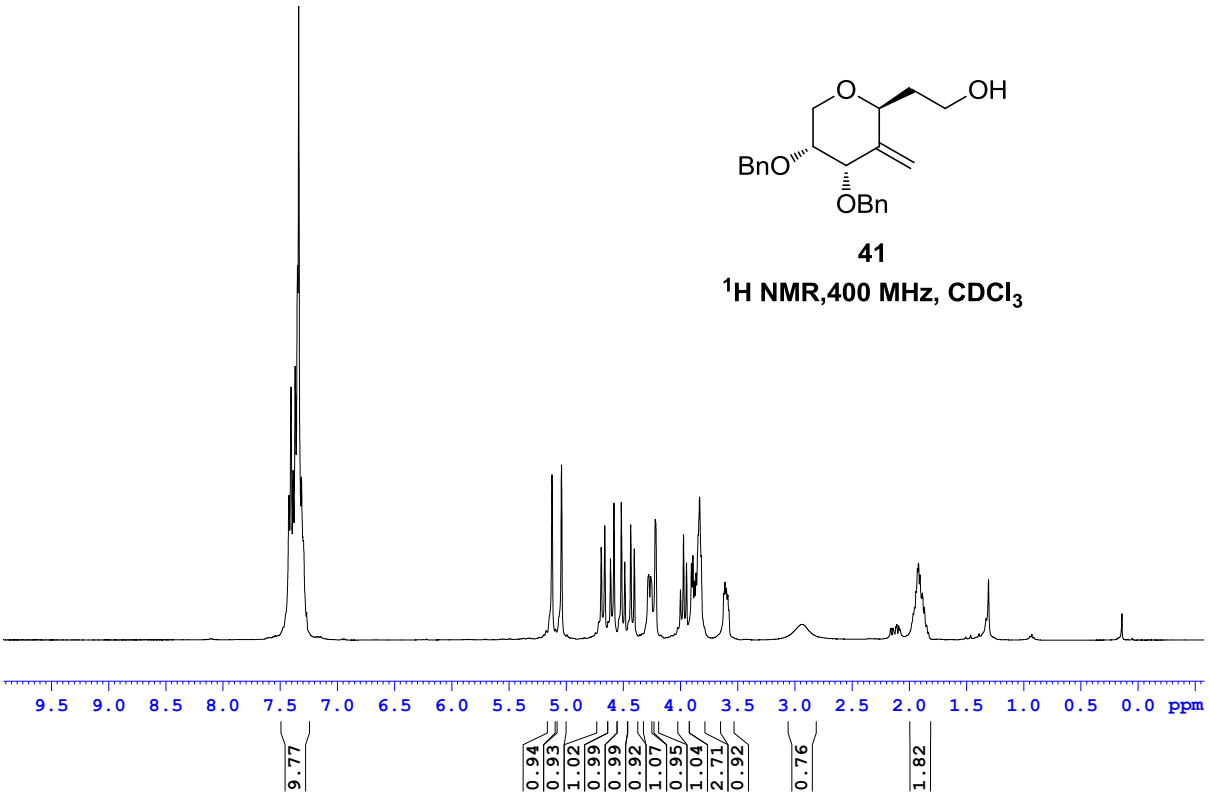
39

^{1}H NMR,400 MHz, $CDCl_3$



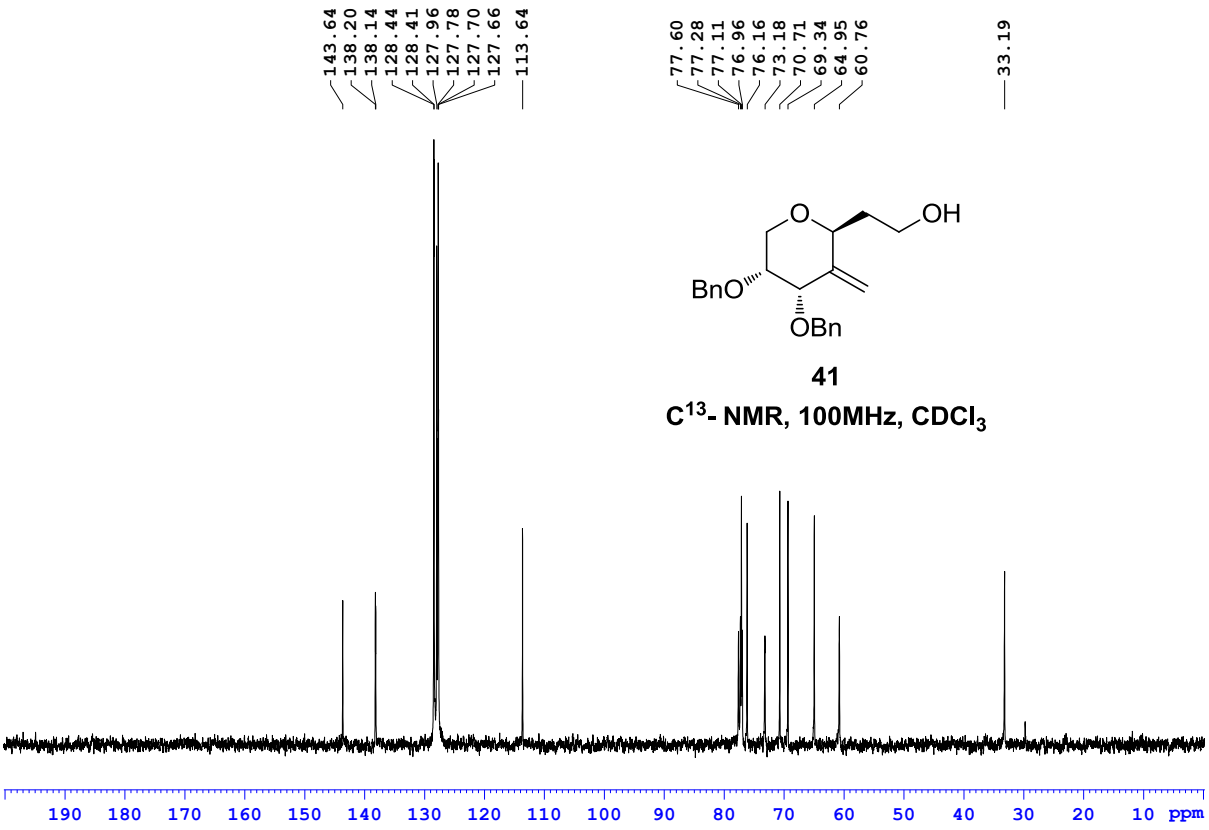
39

C^{13}- NMR, 100MHz, $CDCl_3$



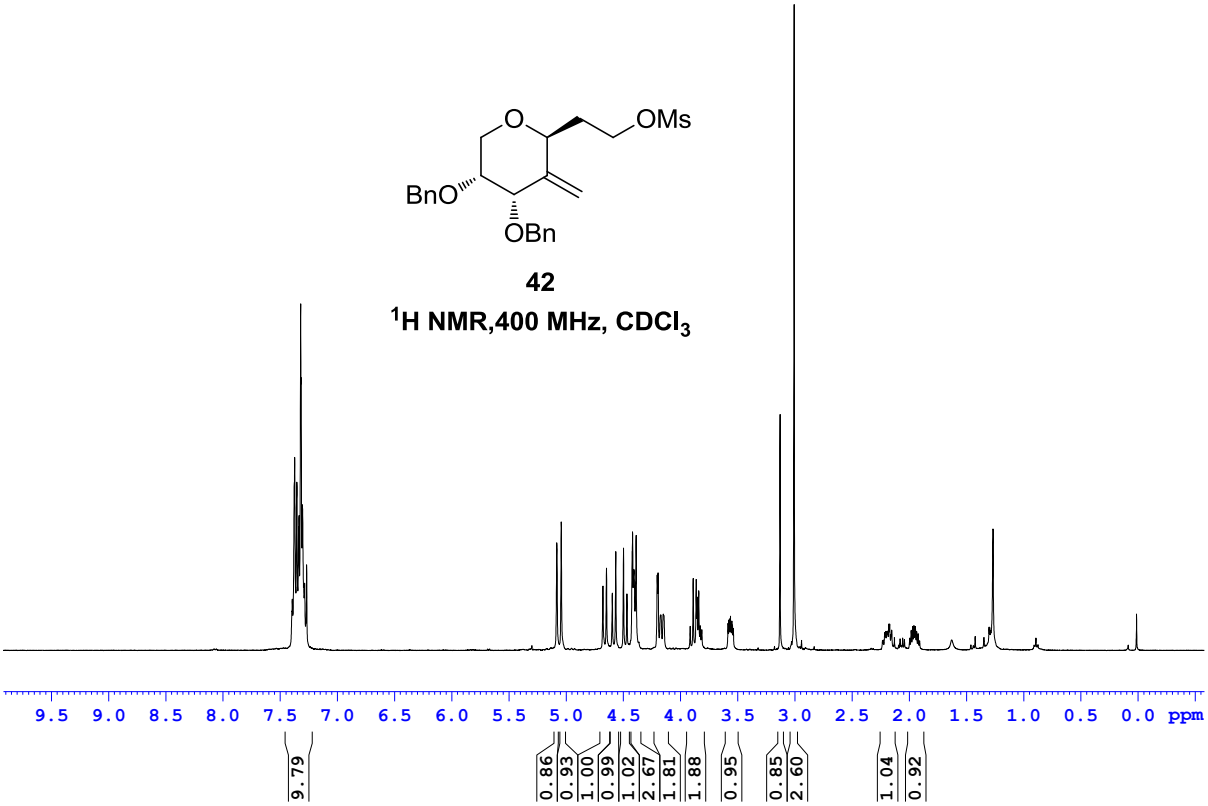
41

^{1}H NMR,400 MHz, $CDCl_3$



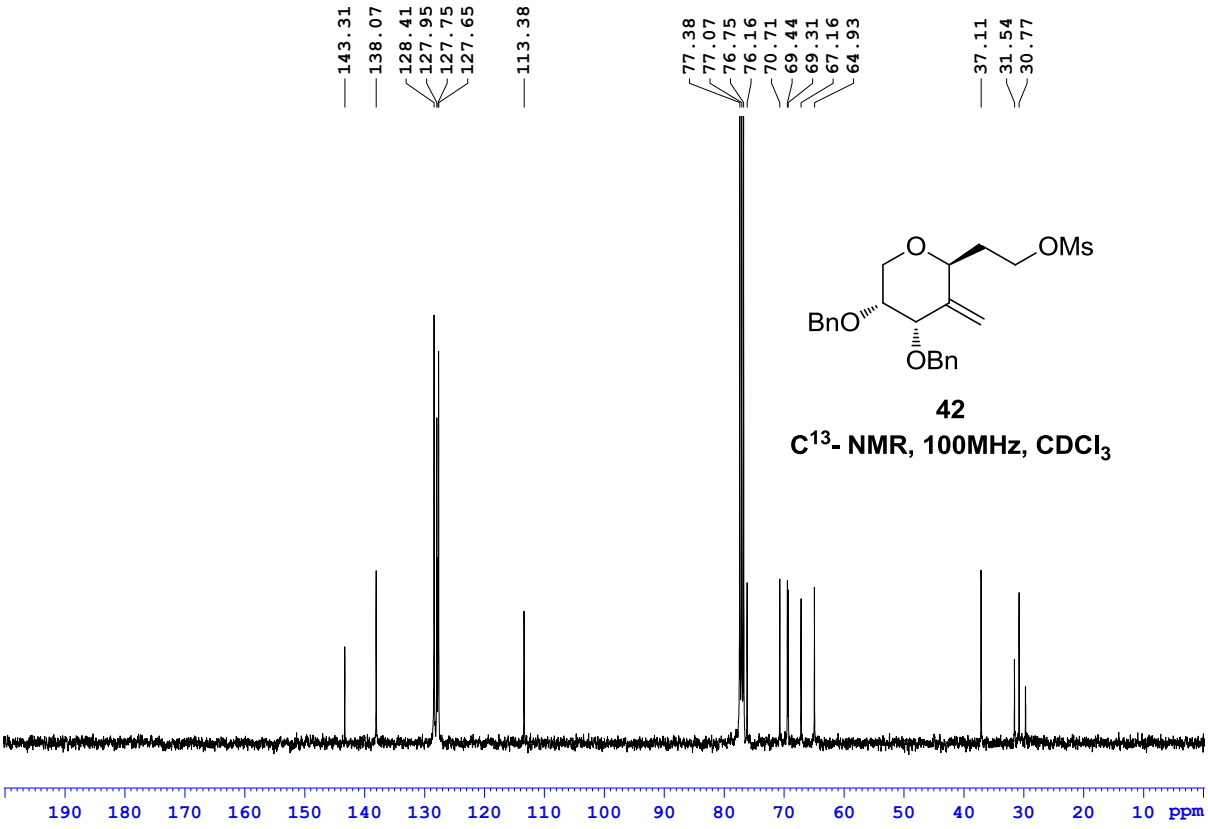
41

C^{13}- NMR, 100MHz, $CDCl_3$



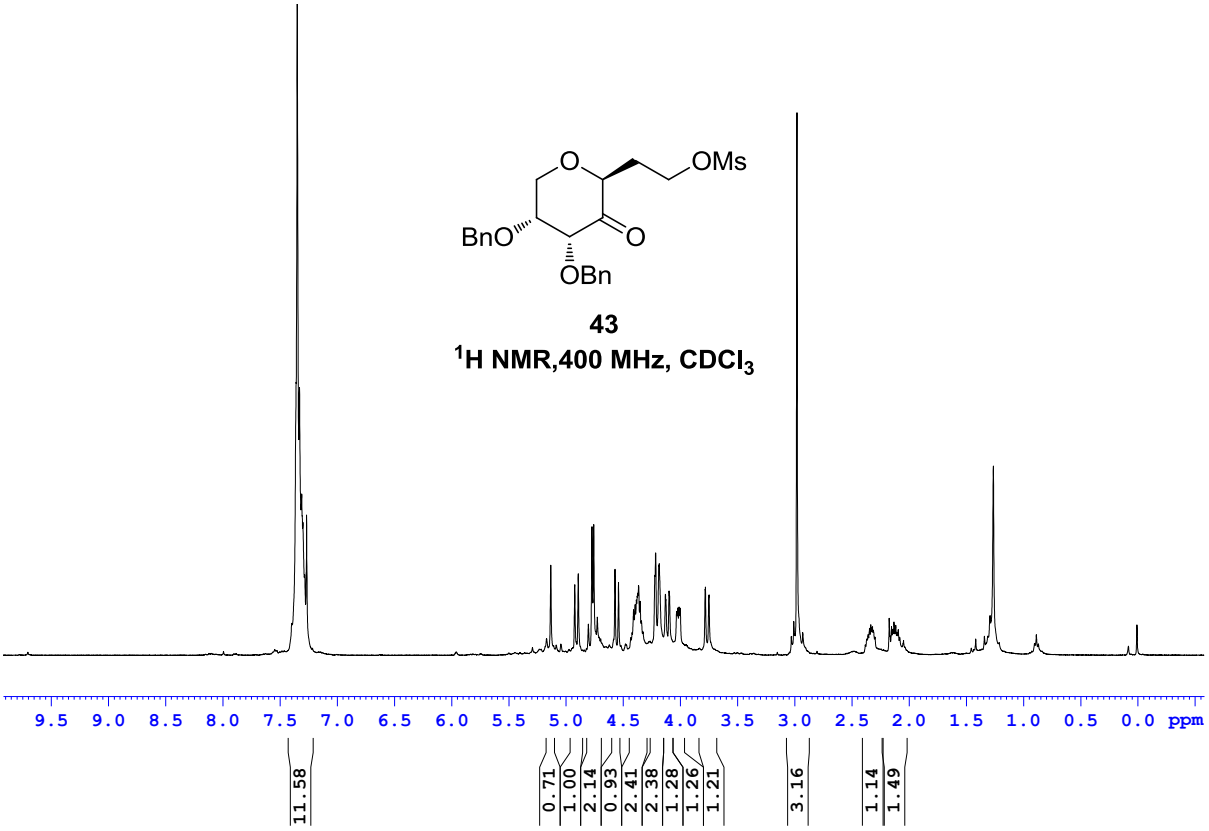
42

^{1}H NMR,400 MHz, $CDCl_3$



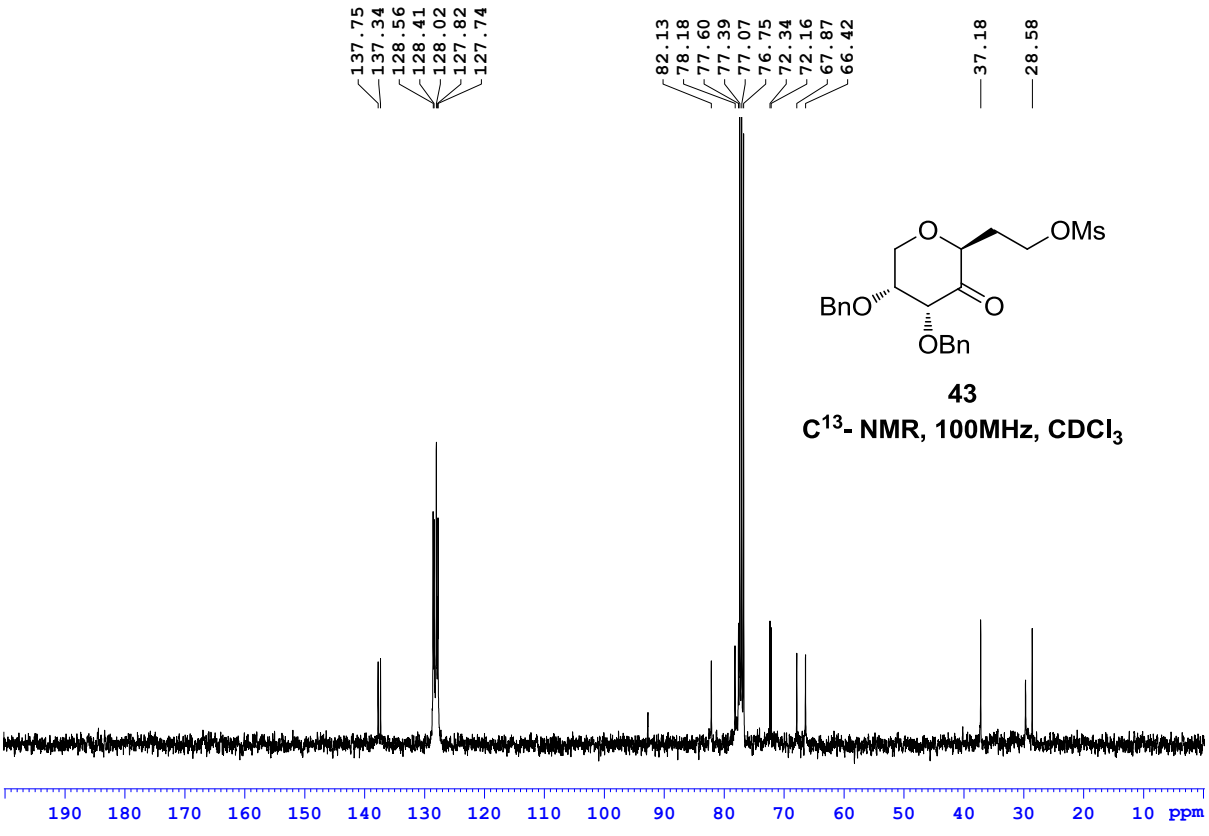
42

C^{13}- NMR, 100MHz, $CDCl_3$



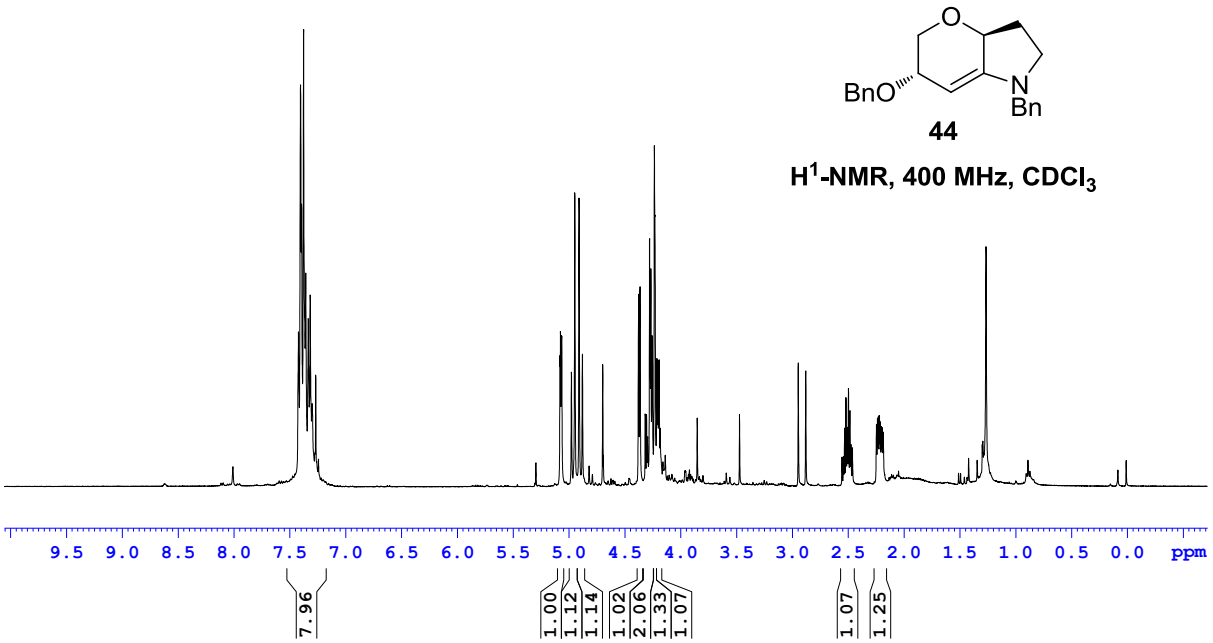
43

^{1}H NMR,400 MHz, $CDCl_3$



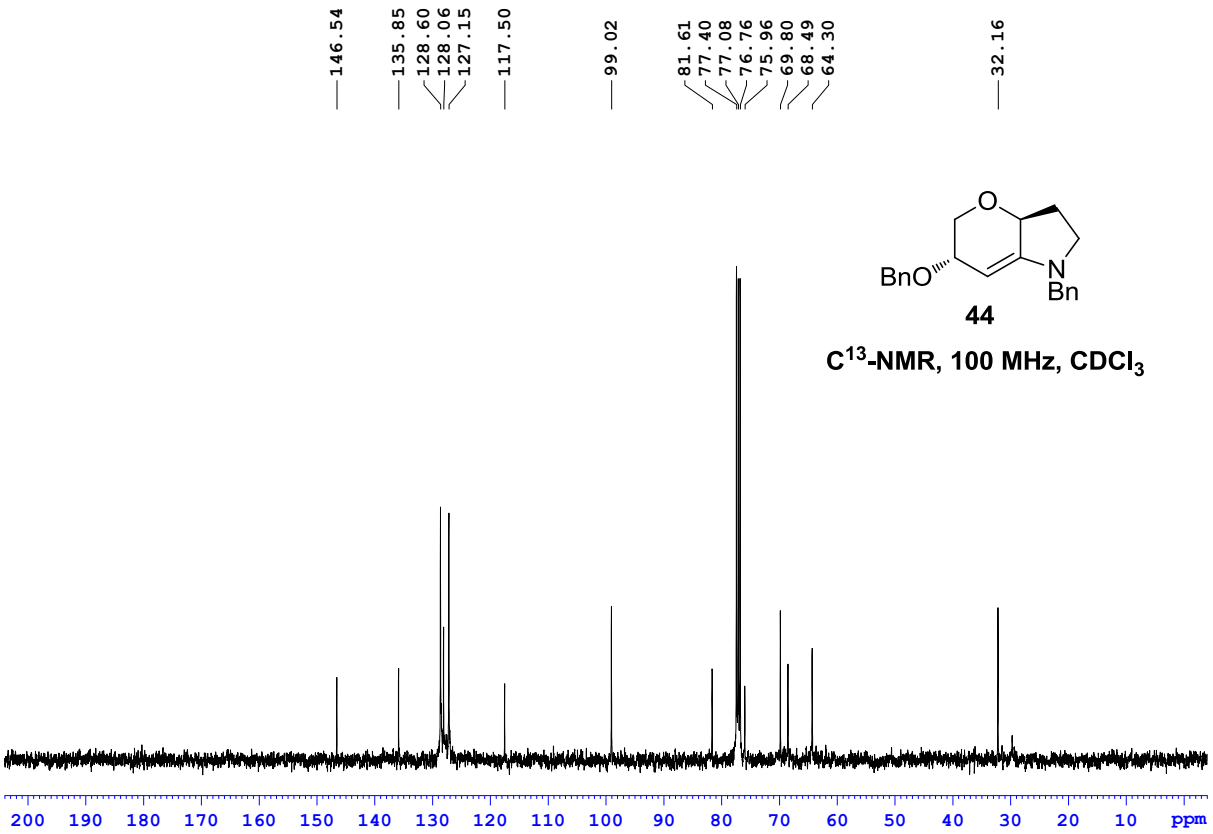
43

C^{13}- NMR, 100MHz, $CDCl_3$



44

H^1-NMR, 400 MHz, $CDCl_3$



44

C^{13}-NMR, 100 MHz, $CDCl_3$