Synthesis and Application of Spiro-Cyclopropanecarboxylated Sugars

A thesis submitted for the degree of
DOCTOR OF PHILOSOPHY

by

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To

All My beloved teachers,

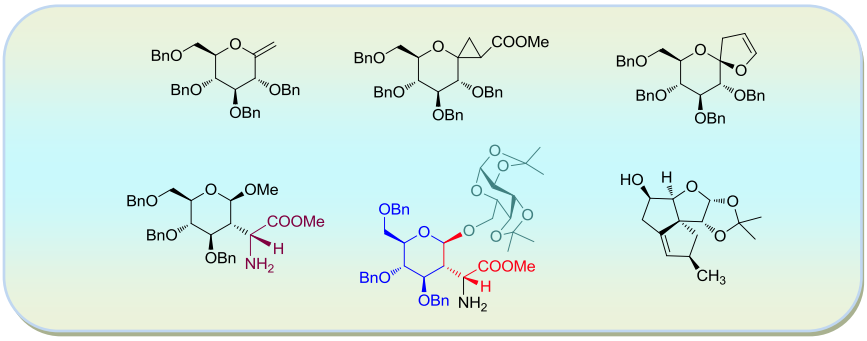
family members

friends and indian soldiers

Contents

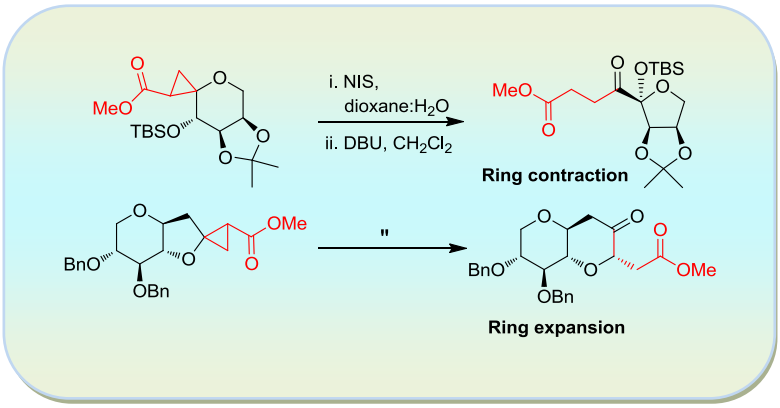
CHAPTER 1

An Introduction to the Chemistry of of spiro-cyclopropane carboxylated sugars.



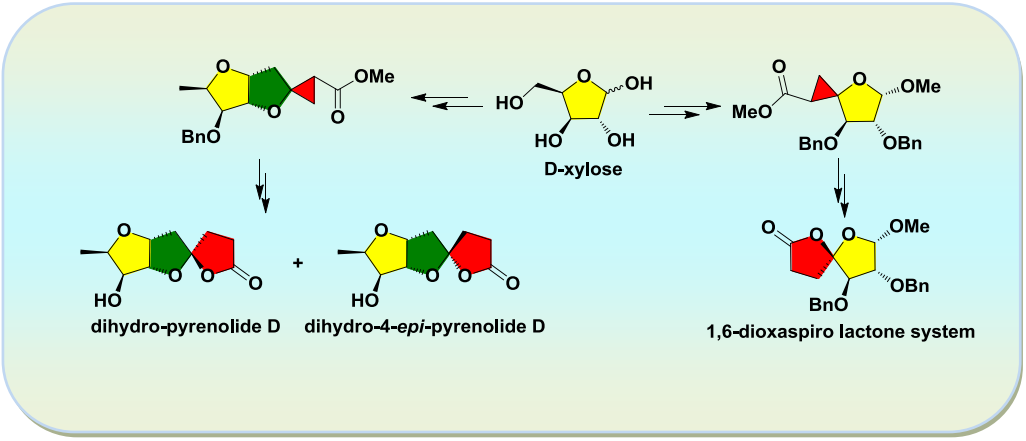
CHAPTER 2

Ring-Contraction *vs* Ring-Expansion Reactions of Spiro-Cyclopropanecarboxylated Sugars



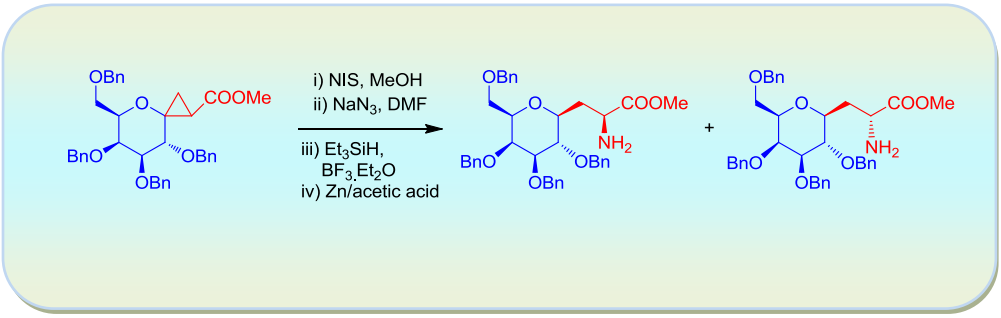
CHAPTER 3

Stereoselective synthesis of 1,6-dioxaspirolactones from spiro-cyclopropanecarboxylated sugars: Total synthesis of dihydro-pyrenolide D



CHAPTER 4

Synthesis of β-*C*-Glyco Amino-acids from spiro-cyclopropanecarboxylated sugars



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.

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Certificate

Certified that the work pertaining to the thesis entitled "Synthesis and Application of Spiro-Cyclopropanecarboxylated Sugars" has been carried out by Mr. Ramakrishna Bandi under my supervision and that the aforementioned work has not been submitted elsewhere for obtaining degree.

Dr. Perali Ramu Sridhar
(Supervisor)

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Ramakrishna

List of Abbreviations

Ac	acetyl
AIBN	azobis(isobutyro)nitrile
am	amyl
Anal.	analysis
aq.	aqueous
atm	atmosphere
Bn	benzyl
BnOH	benzyl alcohol
Boc	tert-butoxy carbonyl
BTEAC	benzyltriethylammonium chloride
Bu	butyl
Calcd	calculated
CAN	ceric ammonium nitrate
CSA	camphor sulfonic acid
d	doublet
DCN	1,4-dicyanonaphthalene
dd	doublet of doublet
dt	doublet of triplet
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
DIB	diacetoxyiodo benzene
DIBAL	diisobutyl aluminium hydride
DIPEA	diisopropyl ethyl amine
DMAP	4-(dimethylamino) pyridine
DMDC	2-deoxy-2-methylidenecytidine
DMDO	dimethyldioxirane
DMF	*N, N'*-dimethylformamide

DEAD	dibenzyl azodicarboxylate
DME	dimethoxy ethane
DMP	dimethyl propane
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
IDCP	iodonium-di(*s*-collidine)perchlorate
IR	infrared
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
ppm	parts per million
PPTS	pyridinium *p*-toluenesulfonate
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
td	triplet of doublet
TEMPO	2,2,6,6-Tetramethylpiperidinyloxy
TFA	trifloro acetic acid
TFA	trifloro acetic anhydride
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	tetramethylsilane
TMSOTf	trimethylsilyl trifluoromethane slufonate
TMU	tetramethylurea

List of publications

1. A convenient synthesis of L-ribose from D-fructose.
   Ramu Sridhar Perali, Suresh Mandava, **Ramakrishna Bandi**. *Tetrahedron* **2011**, 67, 4031-4035.

2. Ring-Contraction *vs* Ring-Expansion Reactions of Spiro-Cyclopropanecarboxylated Sugars.
   Bandi Ramakrishna, Perali Ramu Sridhar. *Org. Lett.* **2013**, *15*, 4474-4477.

3. Stereoselective synthesis of 1,6-dioxaspirolactones from spiro-cyclopropanecarboxylated sugars: Total synthesis of dihydro-pyrenolide D.

   Bandi Ramakrishna, Perali Ramu Sridhar. *RSC adv.* (in press).

4. Synthesis of β-*C*-Glyco Amino-acids from spiro-cyclopropanecarboxylated sugars.
   Bandi Ramakrishna, Chalapala Sudharani, Perali Ramu Sridhar (manuscript to be communicated).
5. Stereoselective synthesis of octahydropyrano[3,2-*b*]pyrroles as novel glycosidase inhibitors.
   Chalapala Sudharani, **Bandi Ramakrishna**, Perali Ramu Sridhar (manuscript to be communicated).

Posters and flash presentations

1. **Bandi Ramakrishna**, Perali Ramu Sridhar, Ring-Contraction *vs* Ring-Expansion Reactions of Spiro-Cyclopropanecarboxylated Sugars.
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2. **Bandi Ramakrishna**, Perali Ramu Sridhar, Ring-Contraction *vs* Ring-Expansion Reactions of Spiro-Cyclopropanecarboxylated Sugars.
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3. Participant at International Carbohydrate Symposium held in January **2014**, IISC Bangalore, India.

Synopsis

The thesis entitled **"Synthesis and Application of Spiro-Cyclopropanecarboxylated Sugars"** is divided into four chapters.

Chapter 1

An Introduction to the chemistry of spiro-cyclopropane-carboxylated sugars

This chapter mainly discuss the synthesis of *exo*-glycals from different sugar based scaffolds and its applications in the synthesis of *C*-glycosides and carbasugars. *exo*-glycals are very important synthetic intermediates in both carbohydrate synthesis as well as in total synthesis of natural products. In addition, they have been versatile starting materials for the synthesis of spiro-cyclopropanecarboxylated sugars. This chapter starts with a brief introduction about the glycals followed by synthesis of *exo*-glycals. Different protocols available for the incorporation of an *exo*-olefin on pyranose or furanose moiety are outlined in the chapter. Out of several methods for the synthesis of *exo*-glycals we have chosen two methods which have been used in the current research work are Petasis reagent mediated conversion of lactones to vinyl ether and 1,8- diazabicyclo[5.4.0]undec-7-ene (DBU) mediated dehydrohalogenation reaction.

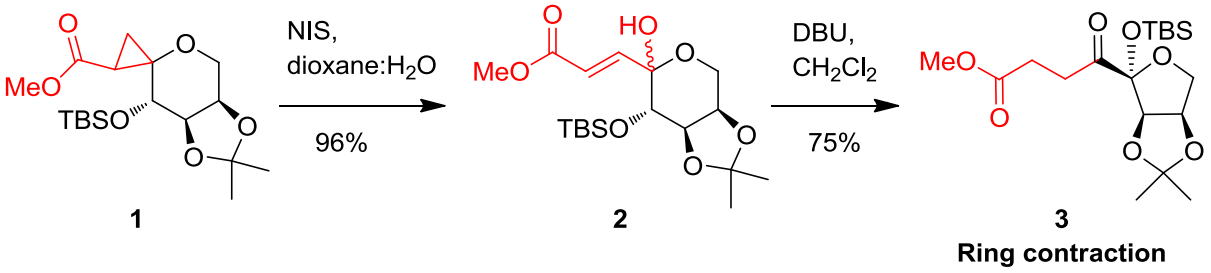
Like 1,2-cyclopropanated sugar derivatives, chemistry of spiro-cyclopropanated carbohydrate moieties are very important in synthetic organic chemistry. Sugar derived spiro-cyclopropanes are synthesized by cyclopropanation of the corresponding *exo*-glycals through metal catalysed reactions. Electrophilic ring opening of these donor-acceptor spiro-cyclopropane carboxylated sugars is a key reaction, applicable to the stereoselective total synthesis of various natural products like asteltoxin, pantolactone homolog, eremantholide A. Due to the ring strain in cyclopropane ring system these spiro-cyclopropanes acts as glycosidase inhibitors, and also useful in the synthesis of spiroketals, bicyclic and tricyclic systems. In comparison with *endo*-glycals, cyclopropanation of *exo*-glycals is not very much explored in the synthetic organic chemistry. To the best of our knowledge, stereoselective cyclopropanation of *exo*-glycals is still an unsolved problem.

Chapter 2

Ring-Contraction *vs* Ring-Expansion Reactions of Spiro-Cyclopropanecarboxylated Sugars

This chapter mainly describes the electrophilic ring-opening of spiro-cyclopropanecarboxylated sugars followed by reaction with 1,8- diazabicyclo[5.4.0]undec-7-ene that revealed an interesting ring-contraction and ring-expansion reactions depending on the substrate and the kind of hydroxyl protective group present adjacent to the spiro centre. A stereoselective method for accessing a new class of carbon chain extended keto-furanoses and *C*-glycosylated bicyclic compounds is reported.

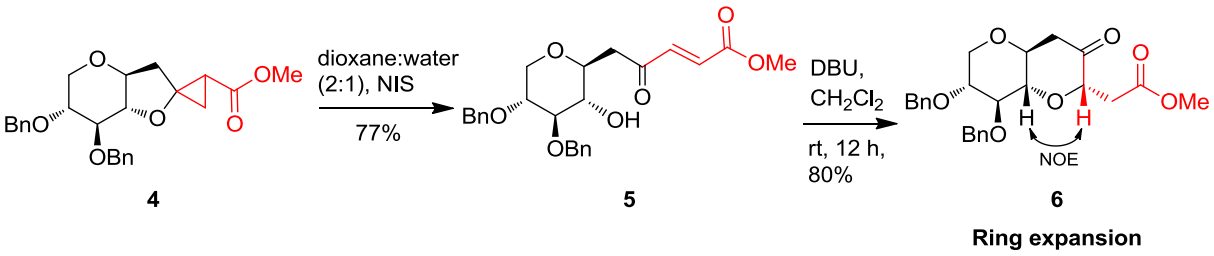
Spiro-cyclopropanecarboxylated sugar derivatives were prepared by cyclopropanation of various sugar derived protected *exo*-glycals with methyl diazoacetate (MDA) and catalytic amount of $Rh_2(OAc)_4$ in moderate yields and with good diastereoselectivity. *N*-Iodosuccinimide (NIS) mediated ring-opening of these spiro-cyclopropanecarboxylated sugar **1** (TBS group adjacent to the spirocenter) in dioxane/water provided the α,β-unsaturated ester **2** in excellent yield. Reaction of **2** with 1,8- diazabicyclo[5.4.0]undec-7-ene in CH_2Cl_2, at 0 °C gave the ring contracted product **3** in good yield as a single diastereomer. This methodology was successfully applied to various sugar derived (pyranose or furanose) spiro-cyclopropanecarboxylates to provide the corresponding hemiacetals in moderate to good yield (Scheme 1).



Scheme 1: Ring contraction reaction of spiro-cyclopropanecarboxylated sugar.

In addition to the ring contraction reaction, ring expansion reaction was also developed using fused bicyclic spiro-cyclopropanecarboxylated sugar derivatives. In this protocol electrophilic ring opening of the spiro-cyclopropane carboxylate **4** with *N*-iodosuccinimide

dioxane/water provided the ring opened α,β-unsaturated ester **5** which upon exposing to 1,8-diazabicyclo[5.4.0]undec-7-ene provided the ring-expanded bicyclic-pyrano[3,2-*b*]pyran derivative **6** as a single diastereomer (Scheme 2). This protocol was also successfully implemented to various fused bicyclic spiro-cyclopropanecarboxylated sugar derivatives to synthesize the corresponding bicyclic compounds.



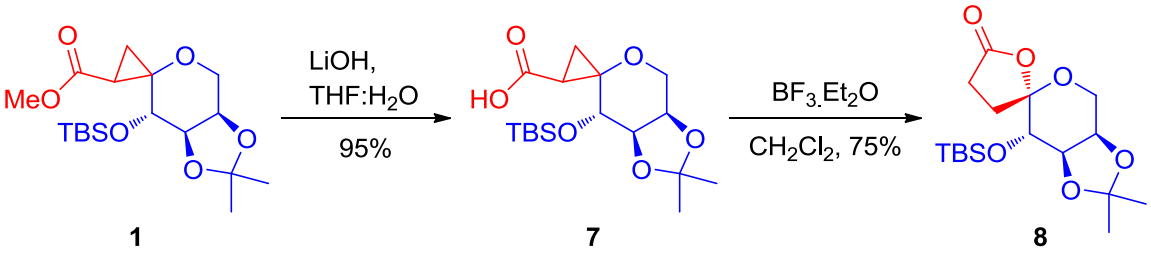
Scheme 2: Ring expansion reaction of fused bicyclic spiro-cyclopropanecarboxylated sugar.

Chapter 3

Stereoselective synthesis of 1,6-dioxaspirolactones from spiro-cyclopropanecarboxylated sugars: Total synthesis of dihydro-pyrenolide D

Chapter 3 mainly address the synthesis of a thermodynamically driven stereoselective synthesis of 1,6-dioxaspiro[4.n]decan-2-one systems (n = 4, 5) from spiro-cyclopropanecarboxylated sugar derivatives. The reaction involves a one-pot cyclopropane ring opening followed by cyclization to form γ-spiroketal γ-lactone moiety. The generality and the stereoselectivity of the reaction are examined by synthesizing a series of spirocyclic systems. A successful approach to the synthesis of saturated analogues of pyrenolide D is also revealed by the application of the current protocol particularly for the formation of crucial quaternary spiro centre of this molecule. These spiro systems are present in number of biologically active natural products like pyrenolide D, crassalactone D, *epi*-crassalactone D, cephalosporolide E and F, papyracillic acid A, B and C.

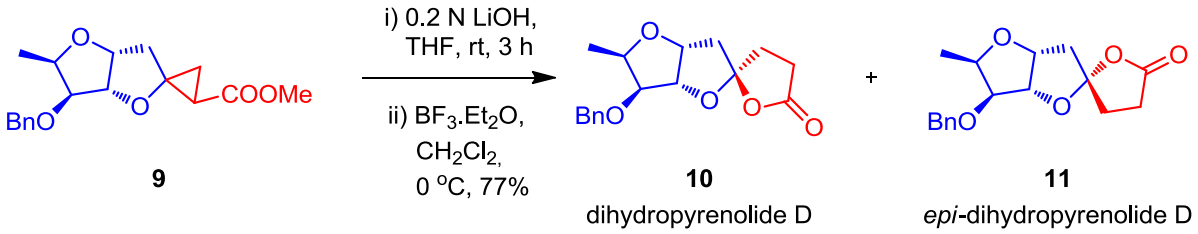
Our synthesis depart from fructose derived spiro-cyclopropanecarboxylated sugar **1** transformed into corresponding carboxylic acid **7** using lithium hydroxide (0.2 N), followed by treatment with boron trifluoride diethyl etherate at 0 ^{o}C to provide the spiro-lactone **8** as single diastereomer in 75% yield respectively (Scheme 3).



1 7 8

Scheme 3: Synthesis of spiro-lactone from spiro-cyclopropanecarboxylated sugar.

The above strategy was applied to various pyranose and furanose derived spiro-cyclopropanecarboxylated sugars to give the corresponding spiro-lactones in good yield. Further the methodology was extended to the synthesis of dihydropyrenolide D and epi-dihydropyrenolide D from xylose derived fused bicyclic spiro-cyclopropanecarboxylate (Scheme 4).



9 10 dihydropyrenolide D 11 *epi*-dihydropyrenolide D

Scheme 4: Synthesis of dihydropyrenolide D and *epi*-dihydropyrenolide D.

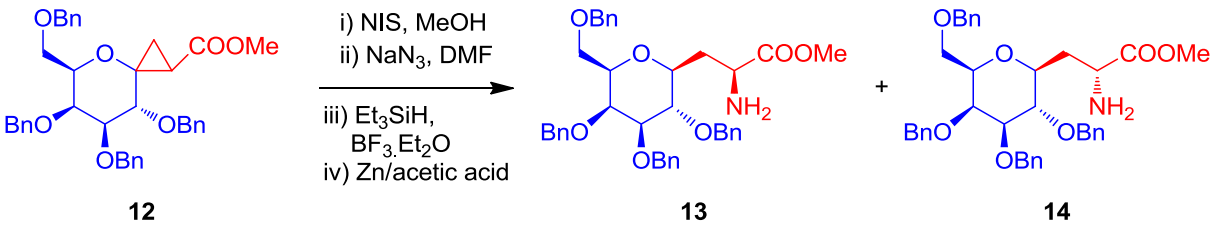
Chapter 4

Synthesis of β-*C*-Glyco Amino-acids from spiro-cyclopropanecarboxylated sugars

Chapter 4 summarizes synthesis of β-*C*-glycosyl α-amino acids from spiro-cyclopropane carboxylated sugars. Stereoselective synthesis of 1-*C*-branched glyco-amino acids involving *N*-iodosuccinimide mediated electrophilic ring opening of spiro-cyclopropane carboxylated sugar, followed by conversion of iodide to azide and then Staudinger reduction/Zn in acetic acid mediated conversion of azide to amine. Interestingly, some of the antibiotics possessing the glyco-amino acid subunit are found to be excellent antibiotics. For

example, furanose derived glyco-amino acids polyoxins, nikkomycins, and pyranose derived glyco-amino acids miharamycins, amipurymicin are some of the anti-biotic molecules isolated from bacterial cultures. In addition β-*C*-glycosidic amino acid structural units are present in the synthesis of β-*C*-galcer, β-*C*-glucer and its new β-aza-*C*-glycoside analogues, glycospingolipids. These are having *in vitro* and *in vivo* natural killer (NK) cell activity.

Electrophilic ring opening of spiro-cyclopropanecarboxylated sugar with *N*-iodosuccinimide in presence of methanol furnished the ring opened iodo-ketal as mixture of diastereomers. Substitution of the iodide with azide followed by removal of OMe with triethylsilane in presence of boron trifluoride diethyl etherate followed by reduction of the azide to amine using Zn/acetic acid provided the β-D-glycosyl α-amino acids **13** and **14** (Scheme 5). Further the developed methodology was extended to glucose and fructose derived spiro-cyclopropanecarboxylated sugars to furnish the corresponding glyco-amino acids in good yield.



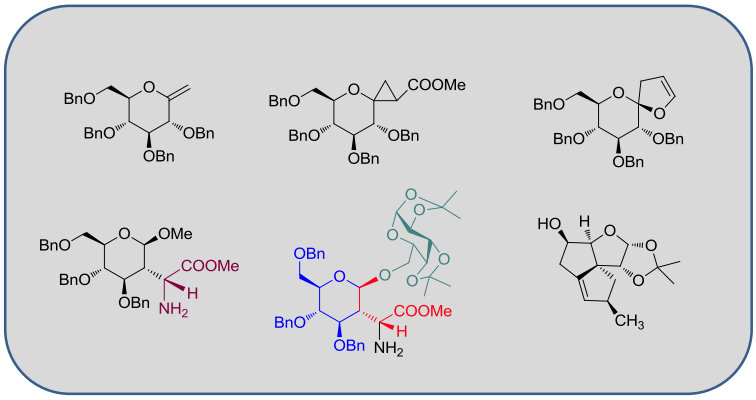
Scheme 5: Synthesis of β-*C*-galactosyl alanines.

Chapter 1

Introduction of Spiro-Cyclopropane Carboxylated Sugars

ABSRACT

This chapter mainly discuss the synthesis of *exo*-glycals from different sugar based scaffolds and its applications in the synthesis of *C*-glycosides, carbasugars. Further, synthesis of spiro-cyclopropane carboxylated sugars from the corresponding *exo*-cyclic olefin and their uses in the synthesis of various natural products are also described.



1.1 Carbohydrates

Optically active polyhydroxy aldehydes or ketones are generally called as carbohydrates. Carbohydrate chemistry is one of the important branch in organic as well as biological chemistry. In nature, a number of components are made up of carbohydrate derived products like food materials, medicines, agrochemicals, drugs, and antibiotics.[1] Carbohydrates are naturally occurring, readily available and inexpensive chiral pool reagents.

1.2 Glycals

Glycals are unsaturated pyranosides or cyclic enol ether derivatives of sugars having a double bond between carbon atoms one and two of the ring system. The nomenclature of

the D-glucal is "1,5-anhydro-2-deoxy-alken-1-enitol" and commonly used terminology is "glycal" for all sugars which are having double bond between 1 and 2 carbon atoms.[2] Glycals can be described in the form of pyranose (six-membered) or furanose (five-membered) rings, depending on the monosaccharide used as a starting material to synthesize the glycals. Glycals are classified into two types, one is *endo*-glycals **1** and the second one is *exo*-glycals **2,** although an extra carbon atom is involved (Figure 1.2). In *endo*-glycal the double bond is present within the ring, whereas in the *exo*-glycal the double bond is placed at anomeric position projecting outside with an additional carbon atom. The pyranose *endo*-glycal conformation has been well studied compare to the *exo*-glycal conformation.

According to the stability principle of Brown and coworkers[3] 6-membered ring having an *endo*-cyclic double bond is more stable than the *exo*-cyclic double bond. In contrast for 5-memebered rings, an *exo*-cyclic double bond stabilizes, and an *endo*-cyclic one disrupts, the ring. Thus stability principle has thus far been proved in the field of the carbocyclic olefins.

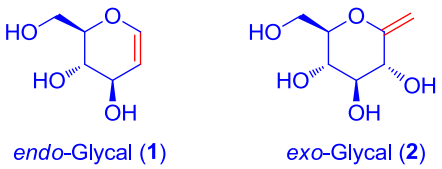
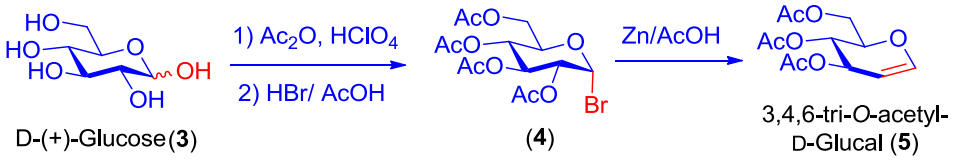


Figure 1.1: Structures of *exo*- and *endo*-glycals.

1.2.1 Synthesis of *endo*-cyclic glycals

Many methods are available for the synthesis of glycal, but the method reported by Fischer in 1913 is still one of the best methods that is used even today[4]. In the Fischer method, a tetraacetyl glycosyl halide **4**, prepared from D-glucose **3**, is treated with zinc dust in presence of acetic acid to eliminate the halide and the adjacent acetate to afford the corresponding glycal **5** (Scheme 1.1). A major disadvantage of the Fischer method is the instability of glycosyl halides of type **4** and some of them are very unstable to be isolated. Later, several advanced protocols are reported for the preparation of glycals[5] with practically simple procedures and high yield. *endo*-Glycals,[6] 1,2-unsaturated sugars, have been shown to be indispensable chiral synthons in the preparation of various biomolecules.



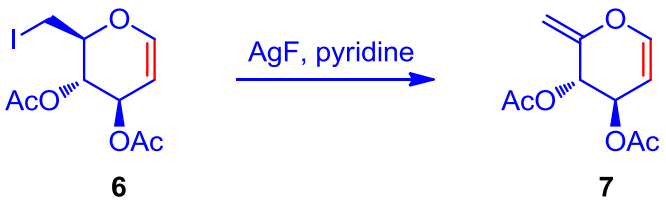
Scheme 1.1: Fischer's method for the first glycal synthesis.

1.2.2 Synthesis of *exo*-cyclic glycals

*e*xo-Glycals are unsaturated sugars that have an *exo*-cyclic olefin attached at the anomeric centre. Methylene *exo*-glycals,[7] often referred as *exo*-methylene sugars, are the simplest version of *exo*-glycals and have been employed widely to synthesize *C*-glycoside structures of biological interest. Methylene *exo*-glycals are very important synthetic intermediates in both carbohydrate synthesis and natural product synthesis, owing to the potential for further elaboration of the enol ether functionality. However, the chemistry of *exo*-glycals is very rare and tedious in comparison with the *endo*-glycals due to the stability and the difficulties associated with large scale production.

Several methods for the formation of carbon-carbon double bond at the anomeric centre or on 5th position in pyranoses have been reported in the literature. Two major starting materials for the synthesis of *exo*-olefins are 6-iodo hexopyranoses and pyranosyl δ-lactones. The first one involves, iodination of the primary alcohol (C-6 hydroxyl in hexo-pyranoses or C-5 hydroxyl in pento-furanoses) followed by elimination according to the well-established procedures using AgF[8] or DBU[9] to obtain the unsaturated sugars. In the second one, pyranosyl δ-lactones or furanosyl γ-lactones are olefinated with Tebbe reagent[10], Petasis reagent[11], Wittig olefination[12], Julia olefination[13] methods to insert the *exo*-olefin functionality. Apart from these protocols Bamford-Stevens rearrangement[14], Ramberg-Backlund rearrangement[15], oxidation of methyl phenyl selenium followed by elimination[16], Fischer-Zanch method[17], or by elimination reaction of the corresponding pyranoketosyl bromides, nucleophilic addition followed by dehydration[18] are also reported to access the *exo*-glycal derivatives.

In 1969, J. Kiss synthesized *exo*-cyclic olefin **7**[8] at 5,6 position from 3,4-di-*O*-acetyl-1,5-anhydro-2,6-dideoxy-6-iodo-D-arabino-hex-1-enitol **6**, using silver fluoride by the method of Helferich and Himmen (Scheme 1.2)[19].

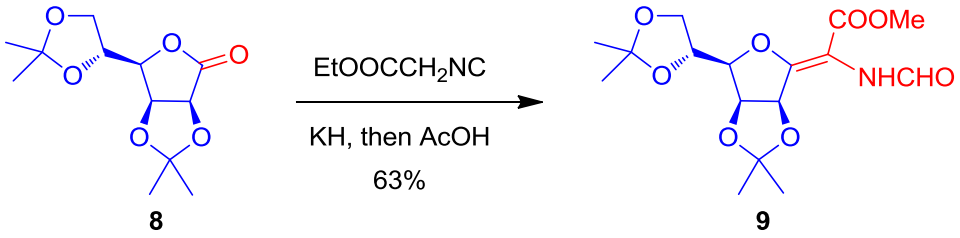


6 **7**

Scheme 1.2: Synthesis of *exo*-cyclic olefin along with *endo*-olefin.

1.2.2.1 Direct olefination methods

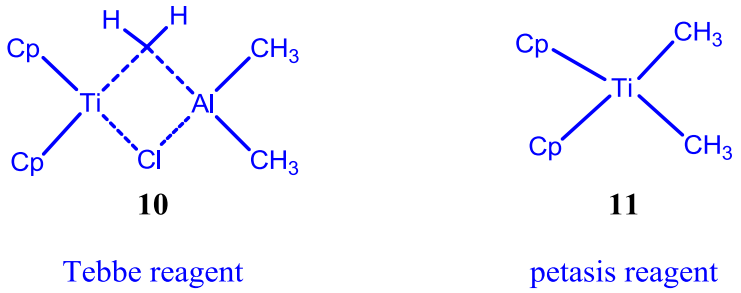
In 1975 Bischofberger *et al.*, reported the synthesis of *exo*-glycal **9** by the reaction of ethyl isocyanoacetate with mannose derived lactone **8**.[20] Hydrogenation of the olefin lead to anomeric *N*-formyl amino acids (Scheme 1.3). This is one of the key reaction developed for the olefination of carbohydrate lactone in an one-pot protocol. The use of lactones as starting compounds for direct formation of *exo*-glycals is attractive provided that a suitable and general reaction could be found.



8 **9**

Scheme 1.3: Synthesis of *exo*-cyclic olefin with ethyl isocyanoacetate.

1.2.2.1.1 With Tebbe reagent



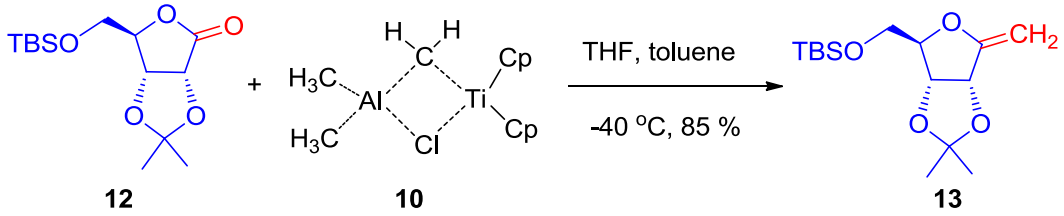
10 **11**

Tebbe reagent petasis reagent

Figure 1.2: Structures of Tebbe reagent and Petasis reagent.

Tebbe reagent (μ-chloro bis(cyclopentadienyl) (dimethylaluminium)-μ-methylenetitanium)[10] **10** (Figure 1.2) was well known for the methylenation of ketones and lactones. Methylenation of sugar lactones using Tebbe reagent was first disclosed by Wilcox

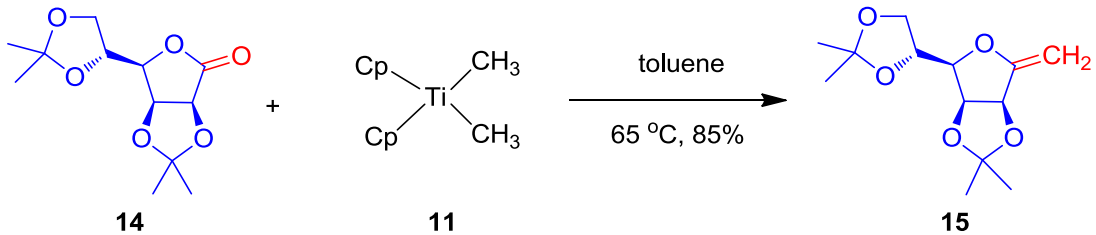
and co-workers in 1984. This led to interesting developments in carbohydrate chemsitry[21]. The ribono lactone **12** was treated with Tebbe reagent **10** at -40 °C to afford the methylene product **13** in 85% yield. This example established the validity of the Tebbe methylenation of sugar lactones.



Scheme 1.4: Synthesis of sugar derived *exo*-cyclic olefin with Tebbe reagent.

1.2.2.1.2 With petasis reagent

Due to the extreme sensitivity (methylenation of lactone) to air and moisture, tedious preparation as well as high costs of commercially available Tebbe's reagent, Glanzer and Csuk has introduced another alternative reagent to the titanocene methyledene complex for the methylenation of carbohydrate derived lactones,[22] the so called Petasis reagent[11] is a reasonably stable compound which can be prepared in large quantities and it can be stored at -20 °C in the dark without any significant decomposition, up to one week (so it's better to use before one week). Compared to Tebbe reagent, high yields were obtained using Petasis reagent. The reaction of 2,3:5,6-di-*O*-isopropylidene-D-mannono-1,4-lactone **14** with two equivalents of **11** in toluene at 65 °C for 24 hours afforded 85% of 2,5-anhydro1-deoxy-3,4:6,7-di-*O*-isopropylidene-D-manno-hept-1-enitol **15** (Scheme 1.5).



Scheme 1.5: Sythesis of *exo*-cyclic olefin with Tebbe reagent.

By using above protocol a series of carbohydrate derived exo-glycals **16**, **17**, **18**, **19** and **20** from the corresponding lactones have been synthesised (Figure 1.3).

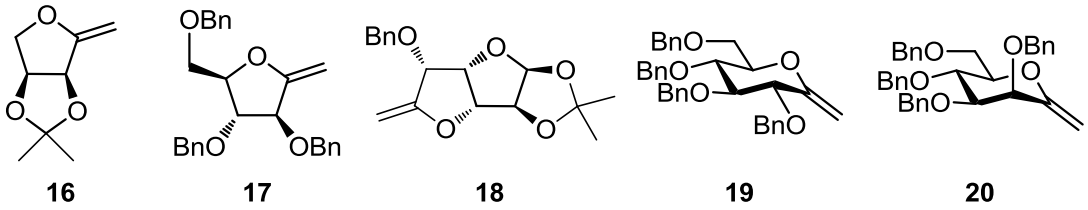
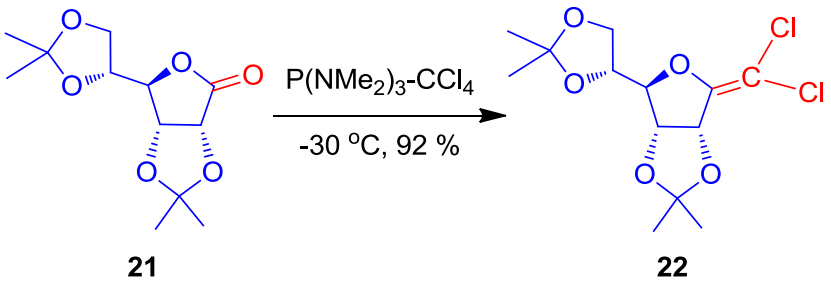


Figure 1.3: Structures of synthesized *exo*-glycals using Petasis reagent.

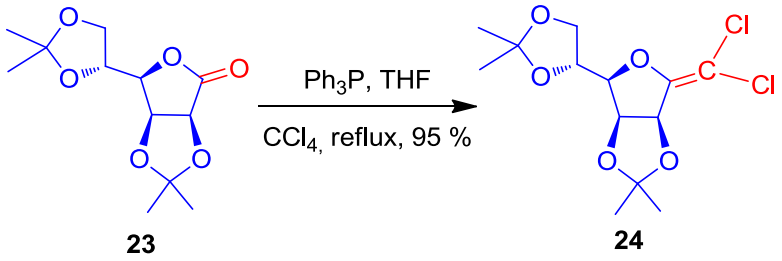
1.2.2.1.3 Wittig type olefination

Exo-dichloro methylene compounds also prepared from sugar derived γ- lactones by using phosphorus based reagents. In 1984 Chapleur developed Wittig type olefination of lactone **21** using tris(dimethylamino)phosphine-tetrachloromethane reagent system to give the corresponding dichloroolefination product **22** (Scheme 1.6).[23] This reagent is generally used at low temperature and also reacts with aldehydes and ketones to form germinal dichloroalkenes. .



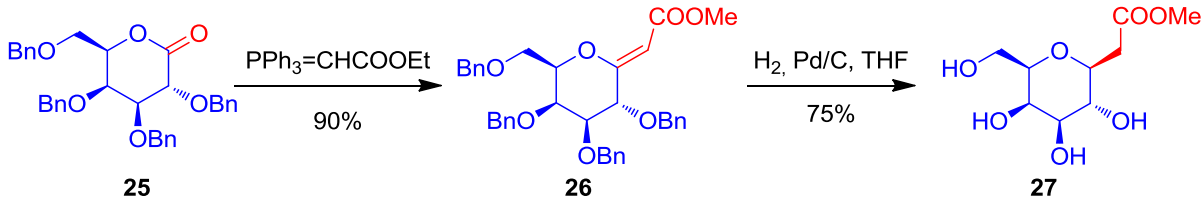
Scheme 1.6: dichloroolefination of lactones under Wittig type reaction conditions.

Later in 1994, Chapleur and Lakhrissi developed an efficient synthesis of dichloro olefins from lactones and acetates, using triphenylphosphine and carbontetrachloride. As shown in scheme 1.7, lactone **23** was converted to dichloralkene **24** in 95% yield. Compare to above method, Ph_3P and CCl_4 reacts cleanly by refluxing the reaction mixture in tetrahydrofuran with substituted γ- and δ-lactones and esters to afford the corresponding dichloro olefins in good yield (Scheme 1.7).[24]



Scheme 1.7: Dichloroolifenation of lactones using Ph_3P and CCl_4.

The Wittig reaction has also been widely employed for the synthesis of *C*-glycosides and amino *C*-glycosides. In these conversions the stabilised Wittig ylide was treated with lactols to provide α,β-unsaturated carbonyls which undergo spontaneous intramolecular hetero Michael addition to give *C*-glycosides.[24b] Although several methods are available for the synthesis of alkenyl ethers from lactones either by wittig reaction of ylide[24] or by using titanium based reagents,[21, 22] Juan Xie reported an efficient method for the synthesis of *C*-glycosides and amino *C*-glycosides by Wittig olefination of sugar lactones and further hydrogenation of the double bond. Reaction of the readily available perbenzylated galactonolactone **25** with 2 equivalents of ethoxycarbonylmethylene-(tryphenylphosporane) at reflux in toluene provided the *exo*-olefin derivative **26** in good yield. Compound **26** was stereoselectively transformed to the *C*-glycoside **27** by palladium mediated hydrogenation reaction[12] (Scheme 1.8).



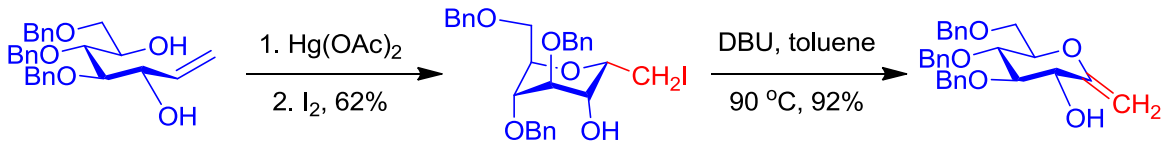
25 **26** **27**

Scheme 1.8: Synthesis of *exo*-cyclic olefin with Wittig reagent and *C*-glycoside formation.

1.2.2.2 Stepwise olefination methods

1.2.2.2.1 DBU mediated dehydrohalogenation

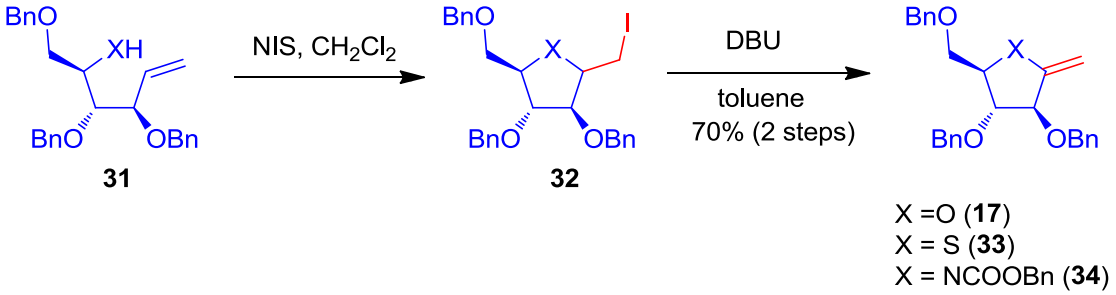
In 1994 Olivier R. Martin *et al*., synthesized *exo*-cyclic olefin **30** from 4,5,7-tri-*O*-benzyl-1,2-dideoxy-D-gluco-1-heptinol **28**. In this approach oxymercuration of **28** with $Hg(OAc)_2$ followed by iodine promoted cyclization resulted the formation of 2,6-anhydro-1,3,4,-tri-*O*-benzyl-1,2-dideoxy-D-gluco-1-heptinol **29** in 62% yield. DBU mediated dehydrohalogenation of compound **29** afforded the expected *exo*-glycal derivative **30** in high yield (Scheme 1.9).[9]



28 **29** **30**

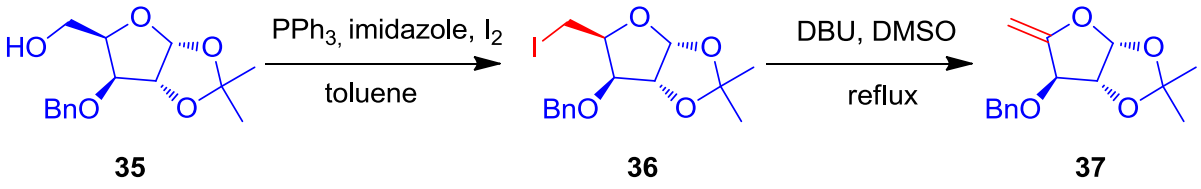
Scheme 1.9: Synthesis of *exo*-cyclic olefin by dehydrohalogenation with DBU.

In 2000 Martin and Tatibouet, developed the synthesis of *exo*-cyclic glycals[25] along with "heteroglycals", namely glycal analogues, with sulphur or nitrogen in the ring. In these results they started with 2,3,5-tri-*O*-benzyl-D-aurabinofuranose which upon Wittig olefination provided the hexenitol **31.** NIS mediated electrophilic cyclization of **31** gave the *C*-glycoside **32**, which upon reaction with DBU in toluene converted to *exo*-cyclic olefin **17** in moderate yield (Scheme 1.10). Interestingly other so called heteroglycals having sulphur or nitrogen atoms, compounds **33** and **34** in the ring were prepared by cyclization of the corresponding amino and thio derivatives by using the above protocol.



Scheme 1.10: Synthesis of *exo*-cyclic olefins having hetero atom.

Interestingly in the case of 1,2-isopropyledene xylose derivative **36**, synthesized from compound **35**, DBU-toluene mediated dehydrohalogenation did not proceed smoothly. This may be attributed due to the higher energy state of the bicyclic intermediate compared to the monocyclic compound. However, elimination reaction did proceed to form *exo*-olefin **37** using the more polar aprotic solvent, DMSO, under reflux conditions (Scheme 1.11).[26]

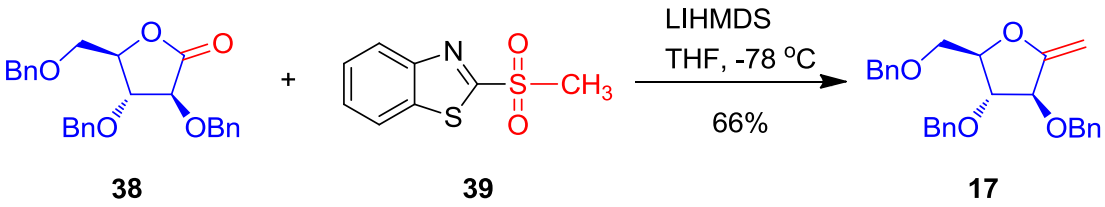


Scheme 1.11: Synthesis of *exo*-cyclic olefin with DBU, DMSO reflux condition.

1.2.2.2.3 Julia olefination

Julia olefination has been used extensively in the last decade for the construction of C=C bonds present in many natural products. This type of reaction is carried out using a heteroaryl sulfone and aldehyde, recently it has been extended to ketones and hemiacetals,

but Julia olefination has not been achieved with lactones. David Gueyard and co-workers synthesized *exo*-olefin **17** from lactone **38** using olefinating agent **39** involving a modified Julia-olefination protocol (Scheme 1.12).[13]

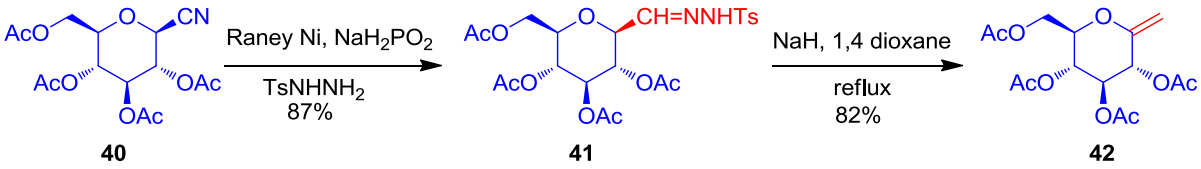


38 **39** **17**

Scheme 1.12: Synthesis of *exo*-cyclic olefin through Julia type olefination

1.2.2.2.4 Bamford-Stevens rearrangement

Somsák and co-workers reported a novel method for the preparation of *exo*-glycals[14] based on the generation of *C*-glycosylmethylene carbenes by application of the aprotic Bamford–Stevens reaction on tosylyhydrazones of 2,5- and 2,6-anhydroaldose derivatives followed by their spontaneous rearrangement. The reaction of acylated glycosyl cyanide **40** with Raney nickel-sodium hypophosphite in the presence of tosylhydrazine in acetic acid-water-pyridine solvent mixture provided an easy access to the tosylhydrazone of 2,6-anhydroaldose **41** in good yield. Compound **41** upon further reflux in 1,4 dioxane with sodium hydride provided *exo*-glycal **42** in 82% yield (Scheme 1.13).



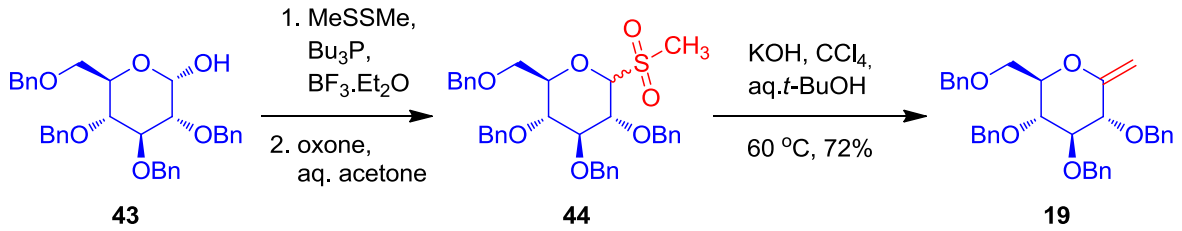
40 **41** **42**

Scheme 1.13: Synthesis of *exo*-cyclic olefin through Bamford-Stevens rearrangement.

1.2.2.2.2 Ramberg-Bäcklund rearrangement

In 1998 F. K. Griffin and co-workers synthesized *exo*-glycals from *S*-glycoside dioxides *via* the Meyers variant of the Ramberg-Bäcklund rearrangement.[15] This methodology was successfully applied to glucose, galactose, mannose, xylose, fucose, and ribose derivatives. For example lactol **43** was converted to **44** *via* the thioglycoside formation followed by oxone mediated oxidation. A one pot α-chlorination followed by

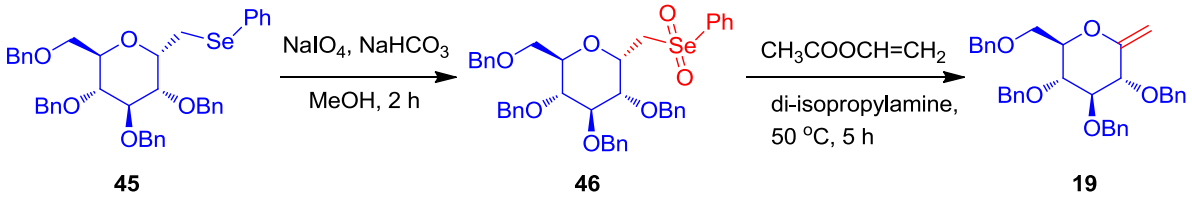
Ramberg-Bäcklund rearrangement of **44** using KOH in CCl_4 and aqueous *t*-BuOH provided the *exo*-glycal **19** in good yield (Scheme 1.14). These *exo*-methylene sugars are valuable synthetic intermediates in the synthesis of biologically active compounds, which can also be used as glycosidase inhibitors. The similar reaction has been employed to prepare novel *C*-glycosides, *C*-disaccharides as well.



Scheme 1.14: Synthesis of *exo*-cyclic olefin through Ramberg-Bäcklund rearrangement.

1.2.2.2.3 Synthesis of *exo*-glycal by using selenocyclisation-oxidation-elimination

In 1985 Sinay and co-workers synthesized *exo*-cyclic olefin by using selenium oxidation followed by subsequent one pot elimination. 2,6-Anhydro-3,4,5,7-tetra-*O*-benzyl-1-deoxy-l-phenylseIeno-D-glycero-D-idoheptitol **45** was oxidised with sodium periodate and sodium bicarbonate to give 2,6-anhydro-3,4,5,7-tetra-*O*-benzyl-l-deoxy-I-phenylseleninyl-D-glycero-D-ido-heptitol **46** in 97% yield. Base mediated elimination of **46** using vinyl acetate solvent and di-isopropylamine provided the corresponding *exo*-glycal 2,6-anhydro-3,4,5,7-tetra-*O*-benzyl-l-deoxy-D-gluco-hept-l-enitol **19** in 91% yield (Scheme 1.15).[16]

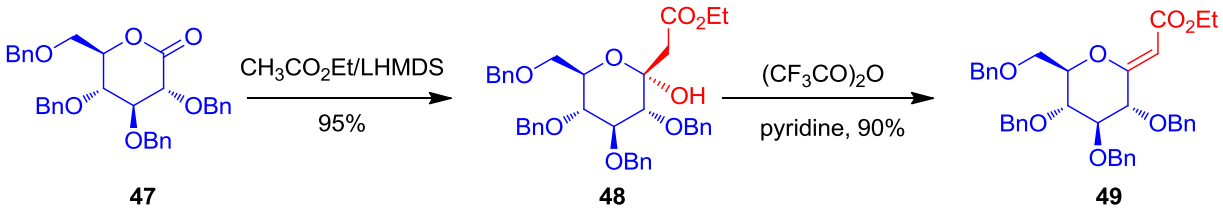


Scheme 1.15: Synthesis of *exo*-cyclic olefin by using selenoether-oxidation-elimination.

1.2.2.2.5 Nucleophilic addition followed by dehydration

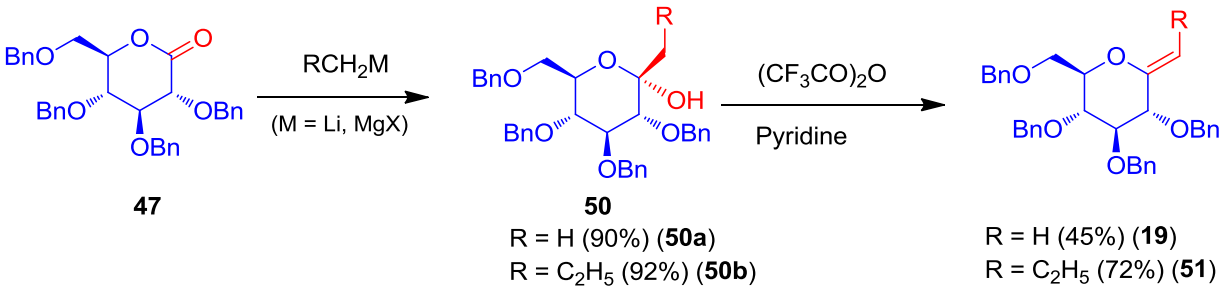
Substituted *exo*-glycals are useful in synthetic chemist and have been utilized as valuable glycosidase inhibitors and applied for the preparation of *C*-glycosides as well. Although 1-*exo*-methylene sugars have been synthesized according to known procedures including the methylenation of sugar lactones by Tebbe reagent, Petasis reagent and the elimination of pyranoketosyl bromides, there are no general methods to prepare substituted

or functionalized *exo*-glycals, except Wittig reaction. Hence Lin group demonstrated a novel approach to prepare *exo*-glycals.[27] The sugar lactone **47** was reacted with a variety of nucleophiles generated by different bases to give the pyranoketose of type **48**, which on dehydration with trifluoroacetic anhydrie afforded the *exo*-glycal **49** (Scheme 1.16). CH_3CO_2Et and LHMDS is the best nucleophile and base, respectively compare to other. There was preference to form mostly *Z*-isomers predominantly was observed.



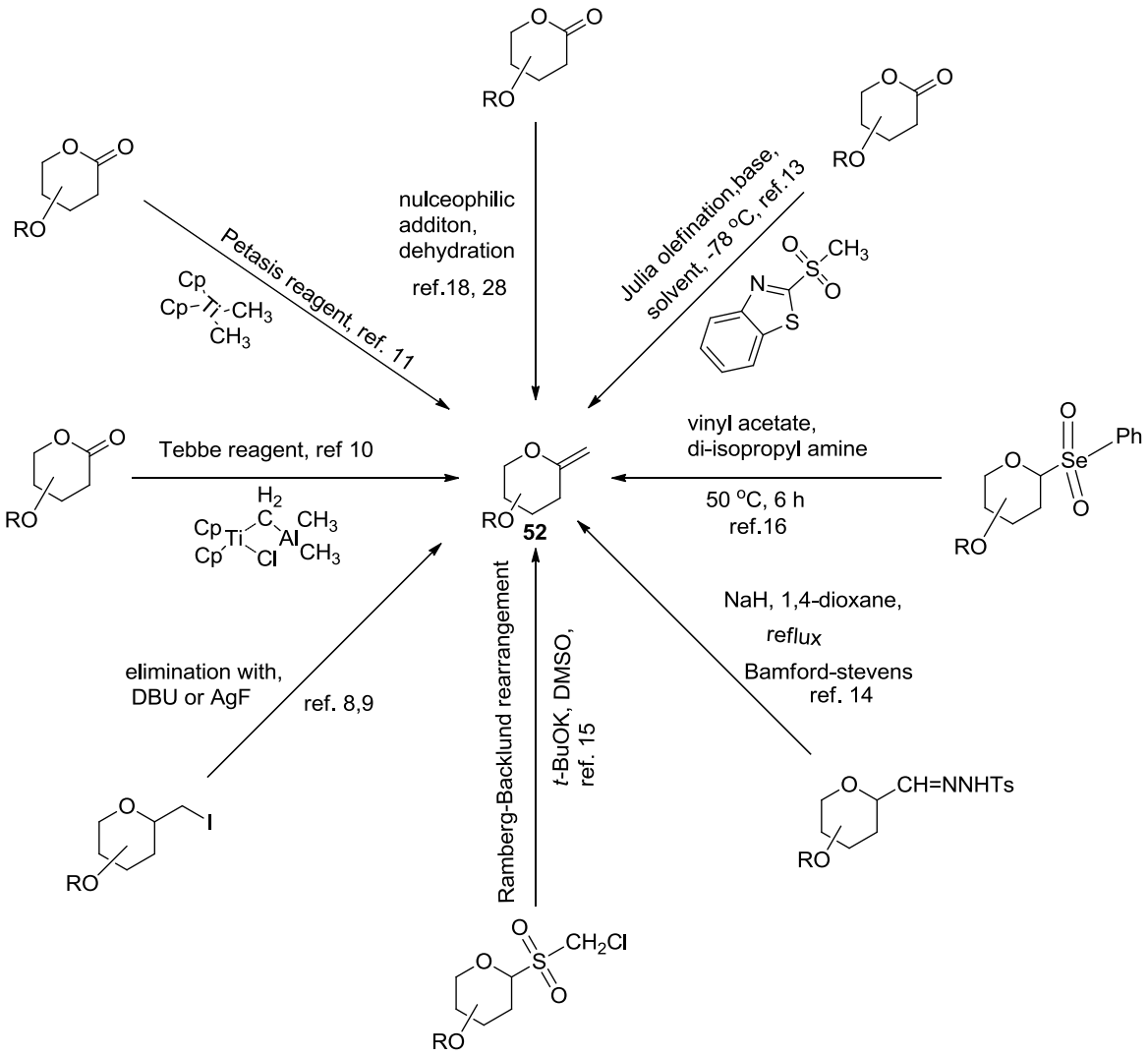
Scheme 1.16: Synthesis of conjugated *exo*-glycal through nucleophilic addition with base followed by dehydration.

In 2002 the same group reported a stereoselective method, exclusively for (*Z*)-isomers of *exo*-glycals,[18] with detailed study on product stereochemistry. The sugar lactone **47** was reacted with organolithium or Grignard reagents to give the pyranoketose, of type **50** which on further dehydration with trifluoroacetic anhydride and pyridine provided the substituted *exo*-glycal of type **51** as an exclusively (*Z*)-isomer (Scheme 1.17). This method was successfully applied to the galactose and mannose derivatives.



Scheme 1.17: Synthesis of *exo*-glycal through nucleophilic addition with organometallic reagents followed by dehydration.

In summary, several methods are available for the synthesis of *exo*-cyclic olefins from lactones, iodo compounds, nucleophilic additions etc., briefly which are shown in the given scheme 1.18.



Scheme 1.18: Overall methods for the synthesis of *exo*-cyclic glycals.

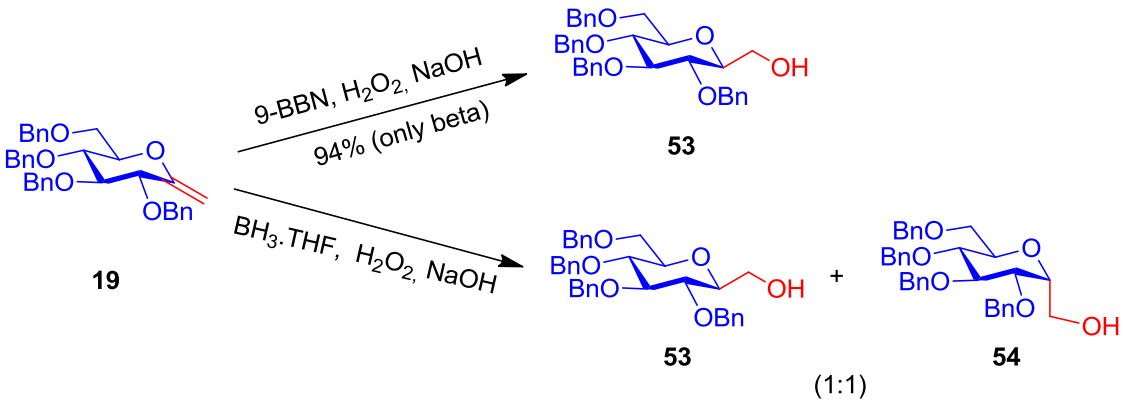
1.3 Applications of *exo*-cyclic glycals

The *exo*-glycals are excellent starting materials for the synthesis of spiro cyclopropane carboxylated sugars, which are further useful in the synthesis of spiroketals and various biologically active natural products. The *exo*-cyclic olefin at anomeric position of carbohydrates have attracted considerable attention, because of the increased interest in the use of simple sugars as chiral synthons for the synthesis of complex natural products including biologically active[28] *C*-glycosides, carbasugars etc. These *exo*-cyclic enol ethers possess good reactivity, mainly governed by the presence of the ring oxygen substituent, it is clear that electrophilic addition on this electron rich double bond would be facilitated by formation of a stabilized intermediate oxonium ion. So these double bonds are useful in *C*-

glycoside synthesis, *N*-glycosides, synthesis of ketoses and ketosides, carbasugars and new sugar based scaffolds and will provide highly advanced synthetic chiral intermediates in the synthesis of complex natural products.

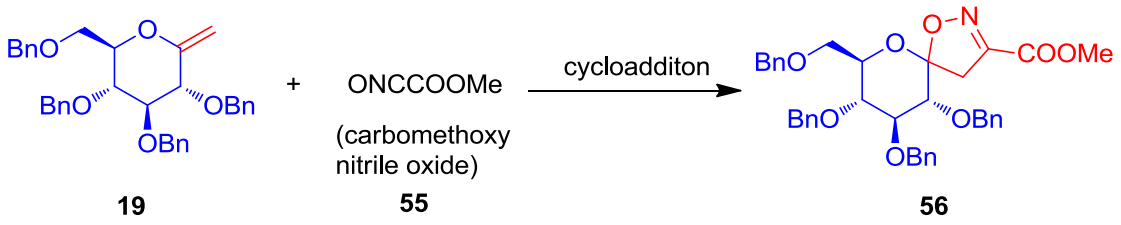
1.3.1 Synthesis of *C*-glycosyl compounds

Although there are large number of methods available to construct *C*-glycosyl derivatives, formation of *C*-glycoside from *exo*-glycal is one of the stereoselective protocol. For instance, hydroboration on *exo*-cyclic olefin is controlled by the other stereocentres present on the sugar template. For example hydroboration of **19** using 9-BBN gives exclusively the *β*-D-*C*-glucopyranosyl derivative **53** in 94% yield. However hydroboration with borane-THF complex yields as 1:1 mixture of α- and β- hydroxymethyl glucosides **53** and **54** (Scheme 1.19).[10c]



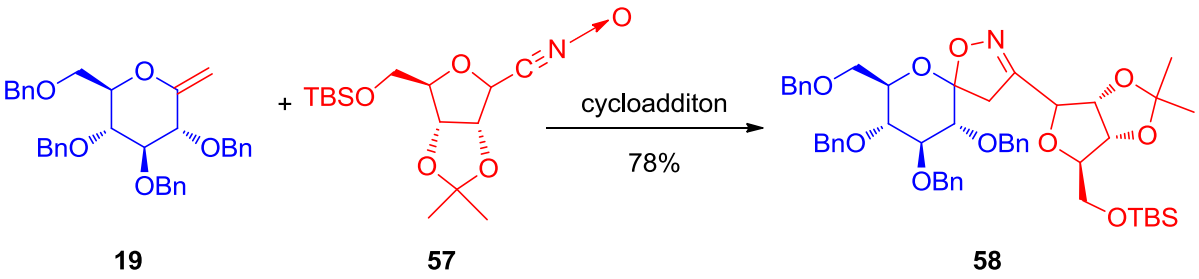
Scheme 1.19: Synthesis of *C*-methylene glycosides from *exo*-cyclic olefin.

The lack of reactivity of structurally related enol ethers in hetero Diels-Alder reactions has been well established. However *exo*-glycals does undergo very facile 1,3-dipolar cycloadditions. For example compound **19** reacts with carbomethoxy nitrile oxide **55** in a regio and stereospecific fashion and provides isoxazoline **56** (Scheme 1.20)[10c] in good yield.



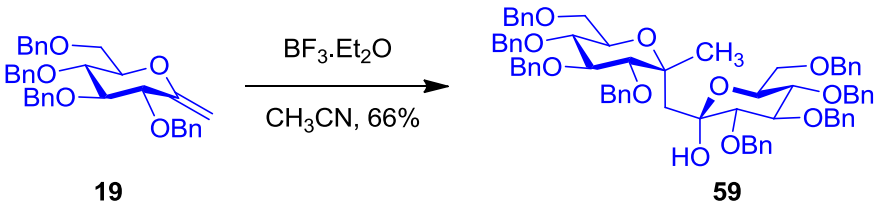
Scheme 1.20: Synthesis of isoxazoline from *exo*-cyclic olefin.

The important application of this methodology may be in the synthesis of extended sugar derivatives like *C*-linked polysaccharides. As a model for the synthesis of tunicamycin[29] dipolar cycloaddition of **19** with a ribose derived nitrile oxide **57**, under the typical Mukaiyama conditions isoxazoline **58** was formed as a single stereoisomer in 78% yield (Scheme 1.21).[10c]



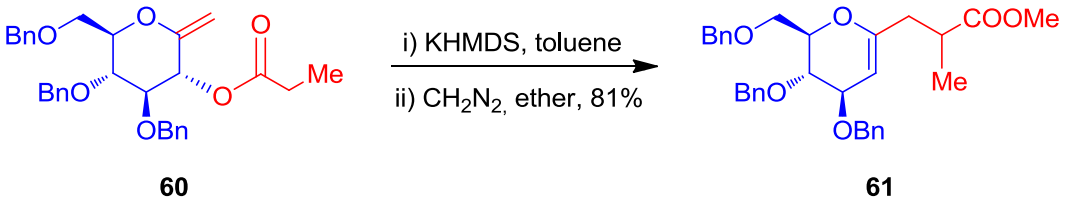
Scheme 1.21: Synthesis of sugar derived isoxazoline from *exo*-cyclic olefin.

exo-glycals, have been the key intermediates in the synthesis of *C*-glycosides. Nicotra et al., reported the Lewis acid mediated dimerization of compound **19** to give C-disaccharide **59**. This reaction proceeds (Scheme 1.22) *via* formation of an oxonium ion from **19**, attacked from α face by another molecule of **19** to give the *C*-glycoside **59** in 66% yield.[30]



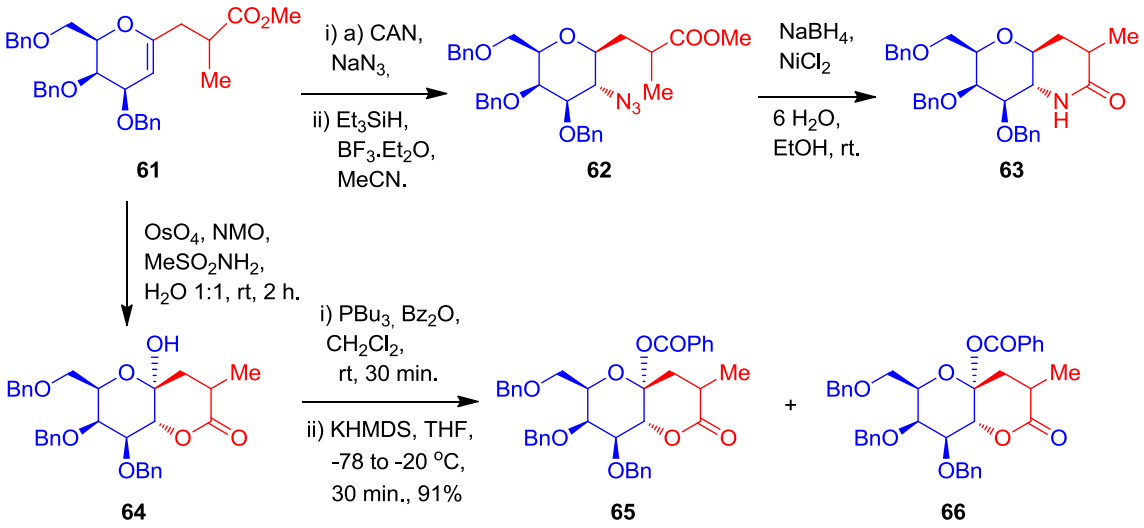
Scheme 1.22: Synthesis of *C*-disaccharides from *exo*-cyclic olefin.

In 1999, Langlois, synthesized *C*-glycosides[31] involving Ireland-Claisen rearrangement of *exo*-glycal derivatives. In this protocol compound **60** on treatment with KHMDS in toluene undergo Ireland-Claisen rearrangement to afford the corresponding the carboxylic acid that was esterfied with diazomethane to give the glycosylated product **61** (Scheme 1.23). Best results were obtained when potassium bis(trimethylsilyl)amide in toluene solution was used as a base and solvent, respectively, to form the enol intermediate.



Scheme 1.23: Synthesis of *C*-glycoside from *exo*-cyclic olefin.

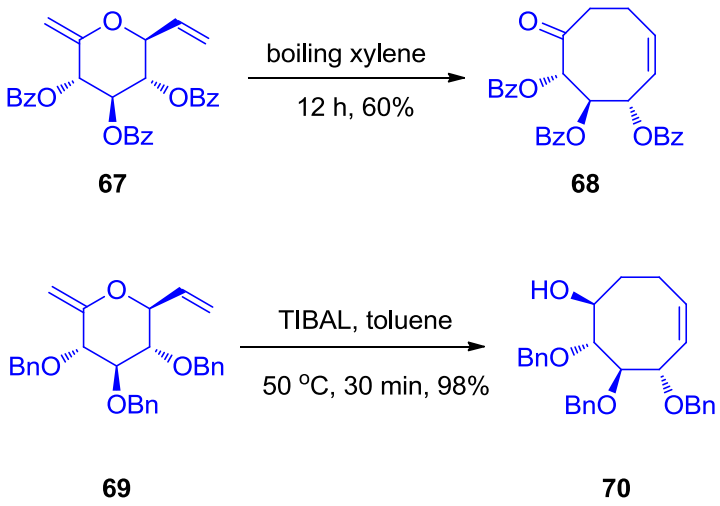
Compound **61** on treatment with ceric ammonium nitrate-sodium azide afforded an azido-nitrate intermediate, which on further reduction with triethyl silane provided the 2-azido *C*-glycoside **62**. Nickel borohydride mediated reduction of **62** resulted the formation of lactam derivative **63**. On the other hand dihydroxylation of compound **61** afforded smoothly lactone **64** in good yield. Esterification of the tertiary alcohol in **64** with benzoic anhydride and *tri*-n-butylphosphine led to ester derivatives **65** and **66** (Scheme 1.24). Deprotonation of the 35:65 mixture of diastereomeric esters **65:66** with KHMDS followed by reprotonation afforded **65:66** in an unoptimised 20:80 ratio.[31]



Scheme 1.24: Synthesis of bicyclic lactone.

In 2000 Sinay and co-workers, developed cyclooctanic carbasugars[32], which can be glycomimetics, potential therapeutic agents with various biological activities. For example *C*-glycoside mimics, acabose (Glycobay) and voglibose (Basen), are currently clinically useful therapeutic agents to control diabetes. Carbohydrates in which the *endo*-cyclic oxygen is replaced by a methylene group, pyranoses or furanoses, are called carbasugars. These glycomimics are attractive in the context of drug discovery because of their stability

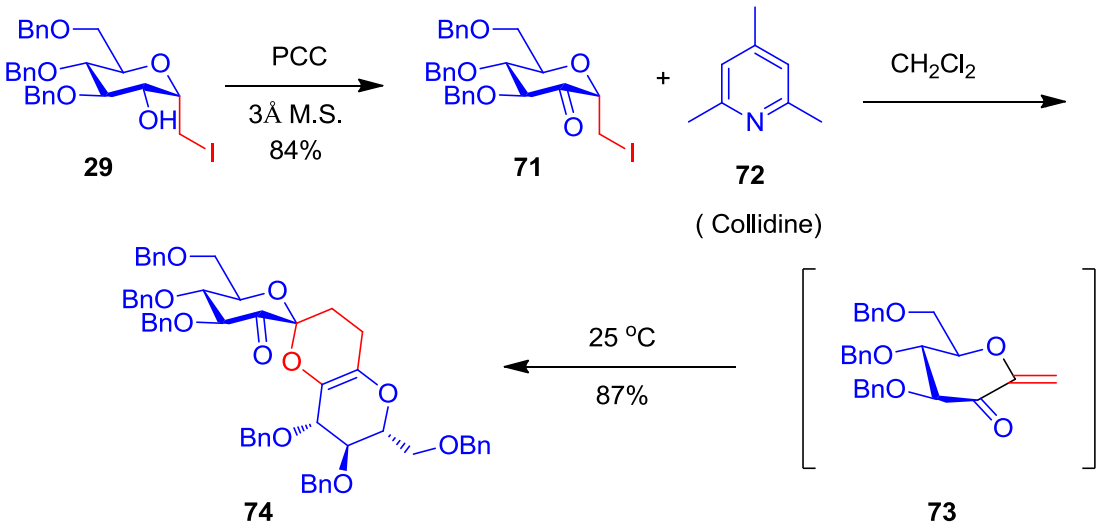
toward endogenous degradative enzymes as well as their interesting biological properties mainly as antibiotics and glycosidase inhibitors. 2-methylene-6-vinyl-tetrahydropyrans **67** and **69** undergo thermal or triisobutylaluminum (TIBAL) mediated Claisen rearrangement to afford the eight membered carbasugars **68** and **70** (Scheme 1.25).



67 **68** **69** **70**

Scheme 1.25: Synthesis of cyclooctanic carbasugars from *exo*-cyclic olefin.

Another application of the *exo*-cyclic olefin is cycloaddition reaction, oxidation of secondary alcohol to ketone in compound **29** with PCC gave the corresponding 2-keto deriv-



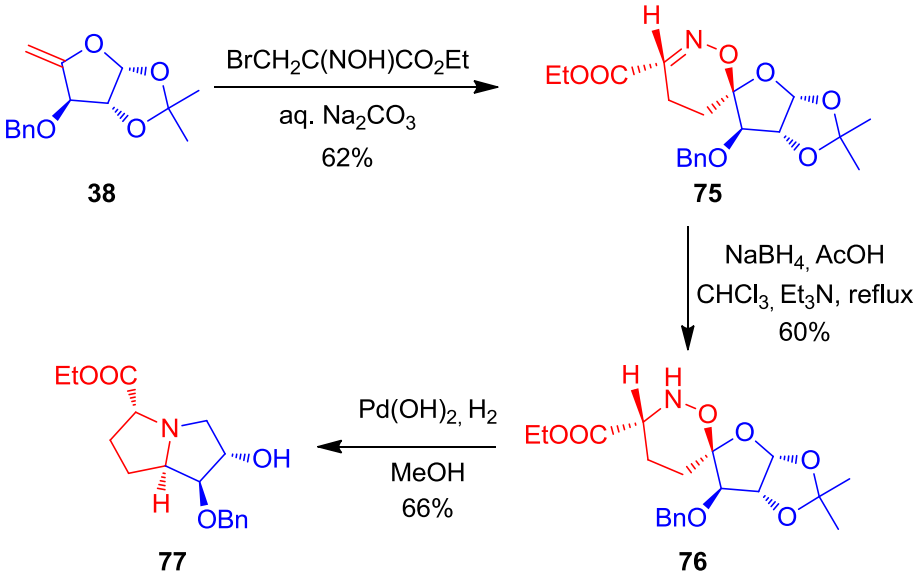
29 **71** **72** **73** **74**

Scheme 1.26: Synthesis of bicyclic adduct through cycloaddition reaction.

-ative **71**, which was subjected to collidine **72** in CH_2Cl_2 at room temperature. After 30 min, the reaction provided a single product **74** (Scheme 1.26). Formation of spiro-glycoside can be visualized via the (4+2) cycloaddition through compound **73**. Interestingly α,β-

unsaturated sugar derivative **73** was never observed and it was assumed that this compound must dimerize spontaneously as soon as it is formed.[9]

Alkaloids containing monosaccharides are widespread in plants and microorganisms. Among them pyrrolidines, pipperdines, pyrrolidizines are shown to exhibit glycosidase inhibitory activity and also they are potential therapeutic agents. It has been shown that inhibition of glycosidases is related to many diseases, such as viral and microbial infection, metastasis, diabetes and other metabolic disorders. In 2002 J. K. Gallos research group synthesized hydroxylated pyrrolizidines *via* hetero-Diels-Alder reaction involving *exo*-glycals as synthetic precursors. The addition of ethyl-2-nitrosoacrylate (insitu generated from oxime of ethyl bromopyruvate) to the *exo*-cyclic olefin **38** yielded the spiro cyclic product **75** in 62% yield. Reduction of the oxyme with sodim borohydride to give compound **76**, followed by hydrogenolysis provided the pyrrolidizine derivative **77** in 66% yiled (Scheme 1.27).[26]



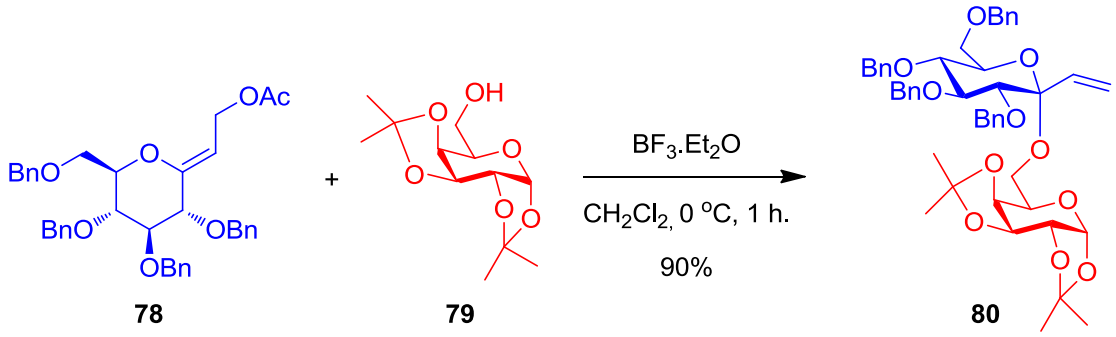
Scheme 1.27: Synthesis of pyrrolidizine derivative from *exo*-cyclic olefin.

1.3.2 Ferier reactions in *exo*-glycals

1.3.2.1 Glycoslyation of *exo*-glycals by Ferrier type reaction

exo-Glycals also have been used as glycosyl donors in traditional glycosylation reactions. In 2003 Lin et al., developed a Ferrier type rearrangement reaction, involving *exo*-glycals, to obtain C-1-branched disaccharides in a stereoselective manner.[33] Due to the driving force

of the Ferrier type rearrangement, the *exo*-glycals are highly reactive with various alcohols to afford glycosides and glyco conjugates with exclusive α-configuration at the anomeric centre. The obtained vinyl group in these glycosylation products can be further elaborated for general applications, including the synthesis of spiro derivatives. The *exo*-glycal which is already discussed earlier in the synthesis of *exo*-glycals, reacted with variety of alcohols in presence of $BF_3.Et_2O$ to give exclusively α-glycosidation products. For example treatment of compound **78** with galactose derived alcohol **79** in presence of Lewis acid, $BF_3.Et_2O$, afforded the glycosylated product **80** in 90% yield (Scheme 1.28).

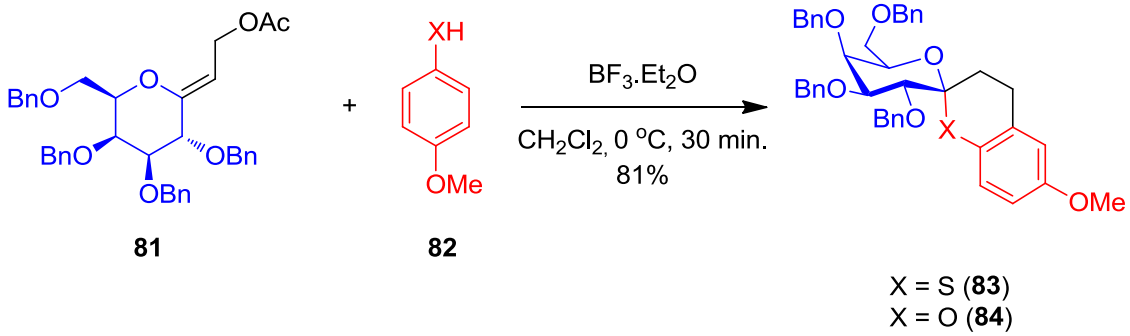


78 79 80

Scheme 1.28: synthesis of disaccharides from *exo*-glycals by using Ferrier-rearrangement.

1.3.2.2 Synthesis of 1,7-dioxaspiro[5.5]undecane by ferrier type reaction:

Lin group also extended this reaction to synthesize dioxaspiro systems,[34] these spiro systems are present in many important natural products. Apart from general methods, acid catalyzed cyclization, intramolecular hydrogen abstraction reaction, and ring-closing metathesis etc., which require moisture-sensitive starting materials, this method provided



81 82

X = S (**83**)
X = O (**84**)

Scheme 1.29: Synthesis of 1,7-dioxaspiro[5.5]undecane and 1-oxa-7-thiaspiro[5.5]undecane systems from *exo*-glycal.

a straight forward access for spiro-sugar derivatives in satisfactory yield. As shown in scheme 1.29, treatment of *exo*-glycal **81** with phenol derivatives **82** with 1.0 equiv of $BF_3.Et_2O$ in dichloromethane at 0 ^oC provided the dioxaspiroundecane systems **83** and **84** in good yield.

1.4 Cyclopropanation of Glycals

The cyclopropane was first discovered in 1881 by August Freund, by treating 1,3 dibromopropane with sodium to afford cyclopropane. Later it was synthesized by the W. H. Perkin in 1884 through attack of diethyl malonate dianion upon 1,2 dibromo ethane.[35] Due to ring strain these molecules can react like olefins and possess good reactivity. Cyclopropane ring is found in various biomolecules as well as in pharmaceutical drugs.

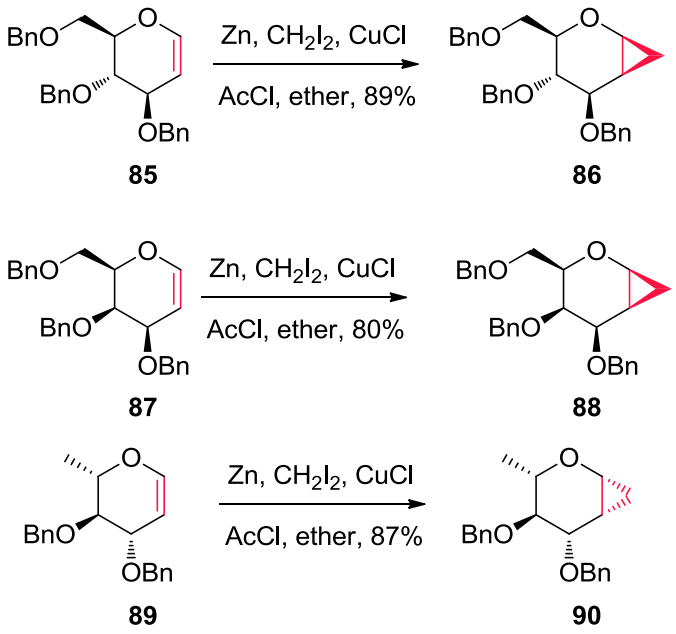
One of the most important advances in cyclopropane[36] chemistry over the last two decades has been the integration of cyclopropanes and carbohydrates, which are of great interest to chemists. The ring opening reactions of cyclopropanated carbohydrates have excellent potential for synthesis, due to the possibility to acquire diverse molecular architectures. The cyclopropanation of *endo* or *exo*-glycals affords unique bicyclic or spiro-cyclic structures combining the high reactivity of cyclopropanes together with the high optical purity and functional density associated with sugar derivatives.[37] The electron donating effect from the pyran ring oxygen conveniently helps one predict cyclopropane reactivity for accessing *C*-2 carbon branched glycosides as well as the *C*-1 functionalized carbohydrate mimics. By using this cyclopropanated carbohydrates, synthesis of natural products was also investigated.[38]

1.4.1 Synthesis of 1,2-cyclopropanated Glycals

1,2-Cyclopropanated sugars are very important in carbohydrate chemistry, which are very useful in glycosidation reactions, synthesis of glyco-amino acids, and preparation of septanosides through lewis acid mediated ring opening reactions, and synthesis of various natural products. Although several methods are available for the synthesis of 1,2 cyclopropanated sugars, which involves the addition of carbene to 1,2-unsaturated carbohydrates (commonly called as glycals or *endo*-glycals), mainly three methods are available, which are Simmons-Smith cyclopropanation, Mąkosza cyclopropanation/dihalocarbene cyclopropanation and transition-metal catalysed cyclopropanation using diazo compounds.

1.4.1.1 Simmons-Smith cyclopropanation

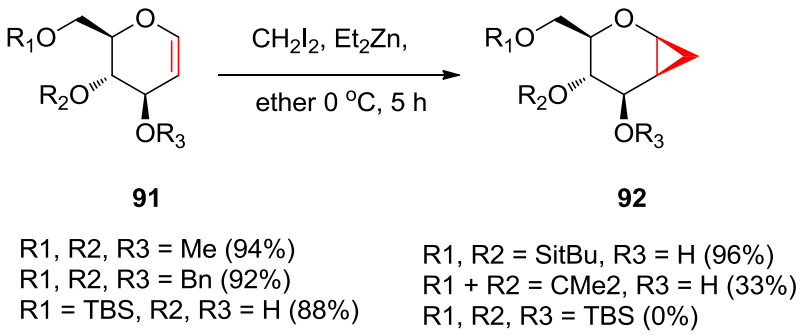
Cyclopropanation of olefins using diiodomethane in presence of Zn/Cu couple is called Simmons-Smith cyclopropanation reaction. In this reaction methylene free radical adds on both carbons of the alkene simultaneously. The Simmons-Smith reaction[39] is an efficient method for the stereospecific synthesis of cyclopropanes from alkenes. Cyclopropanation reactions under Simmons-Smith conditions are characteristically stereospecific and proceeds through a butterfly-type transition state. One of the major advantage of this reaction is its excellent chemoselectivity, since it is applicable to a variety of olefins, different functional groups such as enamines, enolethers (glycals type), esters, ketones, etc. are intact under the reaction conditions. In 1995, Nagarajan and co-workers provided the synthetic route for the cyclopropanation of a series of glycals by using the standard Simmons-Smith reaction conditions. In this report benzyl-protected glycals **85**, **87** and **89** were treated with CH_2I_2/Zn/CuCl in presence of acetyl chloride to obtain **86**, **88** and **91**, respectively, in excellent yields with high stereoselectivity (Scheme 1.31).[40]



Scheme 1.31: Simmons-Smith cyclopropanation of *endo*-glycals.

Later, synthesis of cyclopropanes was carried out using the Furukawa modification[41] of the Simmons-Smith reaction, in which zinc-copper couple is replaced with diethylzinc. This methodology provided moderate to excellent stereoselectivities and yields. However the use of the furukawa version involving diethylzinc is preferred when cyclopropanation of less nuecleophillic alkenes is required. These conditions are practically quite simple where one

can use diethylzinc and diiodomethane without purification. For instance glucals of type **91** upon exposer to diiodomethane in presence of diethylzinc provide the corresponding cyclopropanated sugars of type **92** in good yield. Interestingly, cyclopropanation of glycals in which the hydroxyls were protected with *tert*-butyldimethylsilyl (TBS) group were found to be unsuccessful, may due to the steric hindrance of bulky *tert*-butyldimethylsilyl group (Scheme 1.32).[42]



91

R1, R2, R3 = Me (94%)
R1, R2, R3 = Bn (92%)
R1 = TBS, R2, R3 = H (88%)

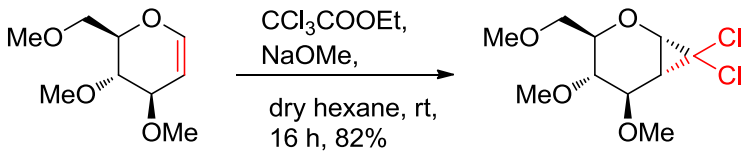
92

R1, R2 = SitBu, R3 = H (96%)
R1 + R2 = CMe2, R3 = H (33%)
R1, R2, R3 = TBS (0%)

Scheme 1.32: Synthesis of cyclopropanes using the Furukawa's method.

1.4.1.2 Mąkosza Cyclopropanation/Dihalocarbene Cyclopropanation

The Mąkosza or dihalocarbene method is also a very important and convenient method for the synthesis of dihalo cyclopropanated sugars that are readily converted into the higher membered sugars (septanosides), which can be useful synthons in derivatization reactions by utilizing the halogen functionality. In 1967, Brimacombe and his co-workers described the cyclopropanation of 3,4,6-tri-*O*-methyl-D-glucal **93** with dichlorocarbene, which was generated by the action of sodium methoxide on ethyl trichloroacetate, to give compound **94** in 82% yield (Scheme 1.33).[43]

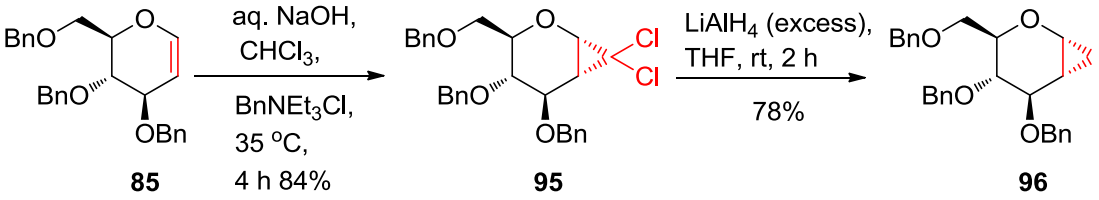


93 **94**

Scheme 1.33: Cyclopropanesugar derivative reported by Brimacombe.

In 1997, Nagarajan and co-workers reported the *trans*-cyclopropanation of benzyl-protected glycals by using biphasic Mąkosza cyclopropanation.[44] Thus treatment of 3,4,6-tri-*O*-benzyl-D-glucal **85** in $CHCl_3$, with 50% aqueous NaOH in the presence of catalytic amount of benzyltriethylammonium chloride provided the corresponding dichloro adduct **95** in 84%

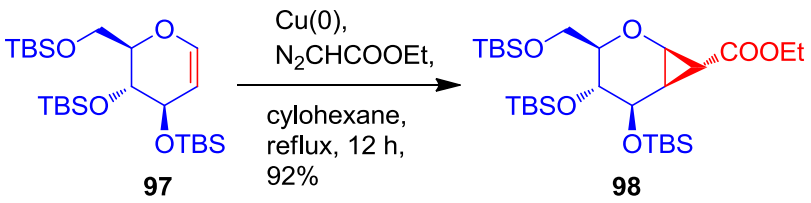
yield. Further dehalogenation of this adduct with $LiAlH_4$ in THF afforded the 1,2-cyclopropanated product **96** in good yield (Scheme 1.34).



Scheme 1.34: Synthesis of 1,2-cyclopropanated sugars using dihalocarbene method.

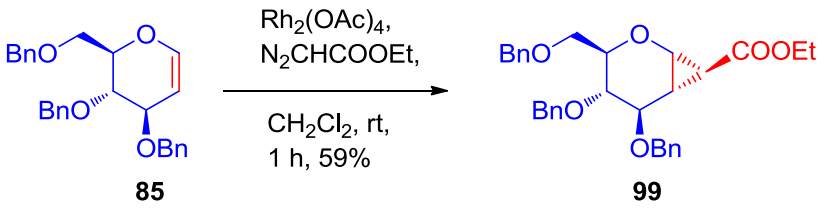
1.4.1.3 Diazoester cyclopropanation of glycals

The cyclopropanation of glycals by using transition metal-catalysed decomposition of diazoester is one of the most extensively studied reaction in carbohydrate chemistry. These cyclopropanated sugars have the selective functionality on the ring compare to Simmons-Smith and Mąkosza cyclopropanated sugars. In 1981 Fraser-Reid and co-workers first reported cyclopropanation of tri-*O*-*tert*-butyldimethylsilyl-D-glucal **97** with ethyldiazoacetate in presence of Cu powder, provided exclusively β-facial selectivity giving the *cis*-cyclopropane product **98** in 92% yield (Scheme 1.35).[45]



Scheme 1.35: Copper-mediated diazo-based cyclopropanation of glycal.

Hoberg and Claffey described the *trans*-cyclopropanation of glycals with ethyl diazoacetate (EDA), in which Cu(0) is replaced by catalytic amount of rhodium acetate (dimer) ($Rh_2(OAc)_4$).[46] Using this protocol different carbohydrate derived α-1,2-cyclopropanecarboxylated sugars were synthesized by treating the corresponding glycals with good diastereoselectivty. The α-facial selectivity of the products is completely governed by steric factors at *C*-3 substituent. This work was further supported by the van Boom and co-workers,[47] in which *trans*-cyclopropanation of glycals was achieved with EDA and $Rh_2(OAc)_4$ (Scheme 1.36). For example *trans*-cyclopropane **99** was synthesized by treating the 3,4,6-tri-*O*-benzyl-D-glucal **85** with ethyldiazoacetae in presence of 0.08 equivalents of $Rh_2(OAc)_4$, in 59% yield (Scheme 1.36).



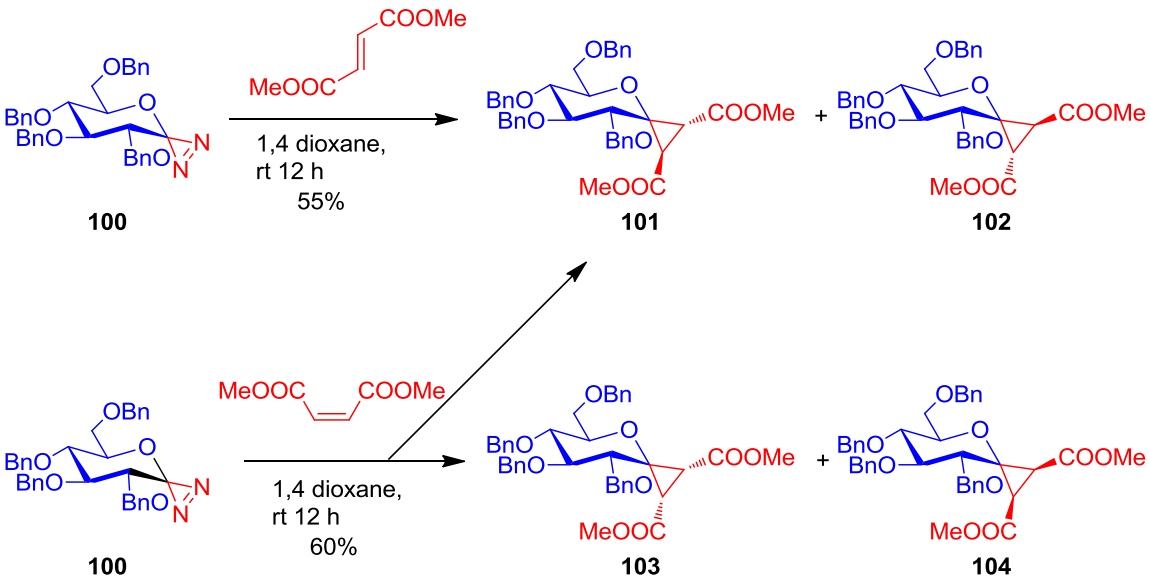
Scheme 1.36: Ethyl diazoacetate-mediated cyclopropanation using catalytic $Rh_2(OAc)_4$.

1.5 Cyclopropanation of *Exo*-Glycals

In comparison with *endo*-glycals, cyclopropanation of *exo*-glycals is not very much explored in the synthetic organic chemistry. To the best of our knowledge, stereoselective cyclopropanation of *exo*-glycals is still an unsolved problem. In principal, methods that could be used for the insertion of a carbene group on an *exo*-olefin can also should work on the *exo*-glycals to provide spiro-cyclopropanated derivatives. Thus, similar methods that have been used for the cyclopropanation of *endo*-glycals have been applied to *exo*-glycals as well. Apart from these some of the interesting methods particularly for spiro-cyclopropanated sugars have also been developed.

1.5.1 Synthesis of spirocyclopropane dicarboxylates from diazirine

In 1991 Andrea Vasella group synthesized spirocyclopropane[48] from sugar derived diazirine derivatives. The cycloaddition reaction between sugar derived diazirine **100** and

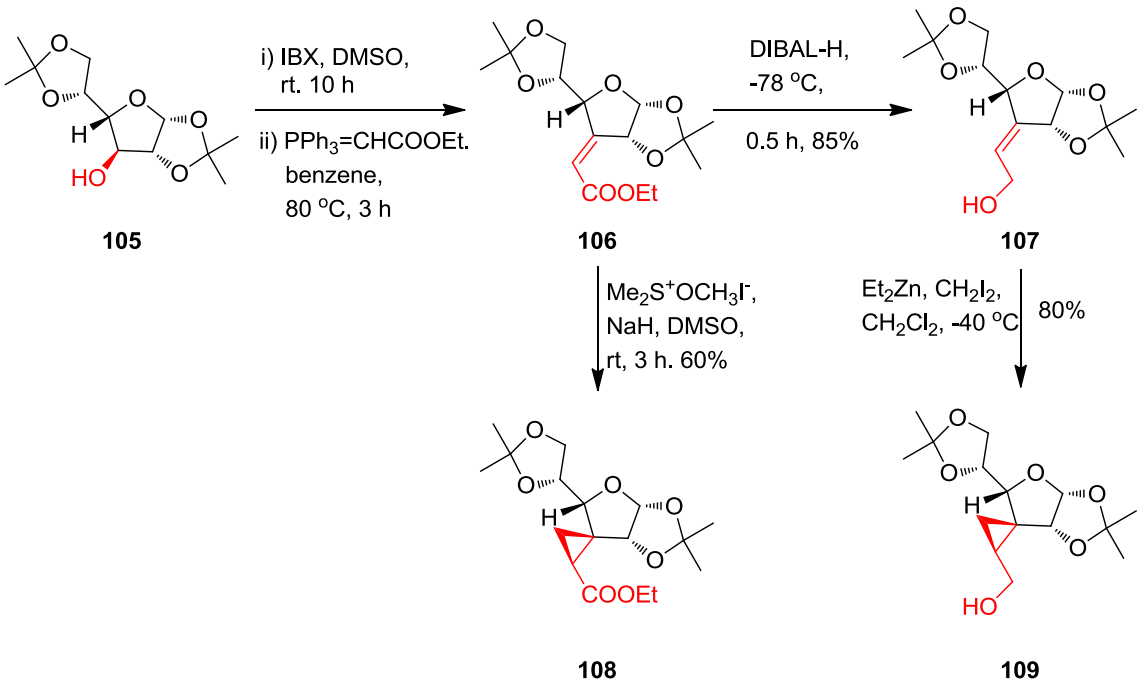


Scheme 1.37: Synthesis of spiro-cyclopropanes from diazirine.

excess dimethyl fumarate provided a diastereomeric mixture of spiro-cyclopropane dicarboxylates **101** and **102**, which are separated by using HPLC. On the other hand, using dimethyl maleate instead of dimethyl fumarate led to the formation of a mixture of four diastereomers **101**, **102**, **103**, **104** in 60% yield (Scheme 1.37).

1.5.2 3-Spiro-cyclopropane carboxylated sugars through Wittig reaction

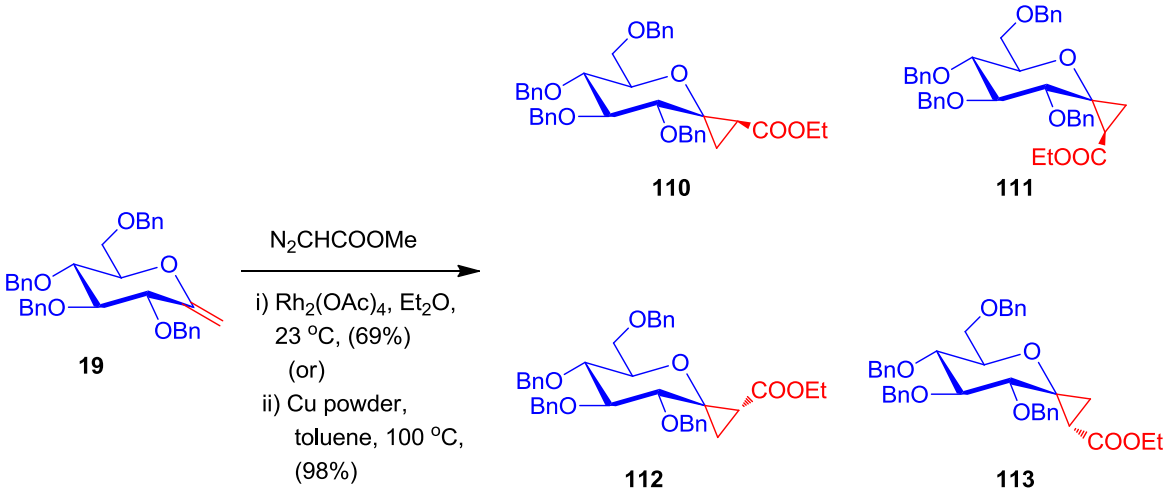
In 1998, Gurjar and co-workers synthesized 3-spiro-cyclopropane carboxylated sugars through Wittig reaction followed by cyclopropanation.[38] They started with 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose **105** was oxidised with IBX-DMSO and then the resulting ketone was treated with PPh_3=CHCOOEt in benzene under reflux to obtain α,β-unsaturated ester **106** in 70% yield (Scheme 1.38). Cyclopropanation of compound **106** with sulphur ylide (generated from Me_2SOCH_3I-NaH) in dry DMSO gave the insertion product **108** as single diastereomer in 60% yield. On the other hand unsaturated ester **106** was converted in to the allylic alcohol **107** followed by cyclopropanation with Furukawa modification of the Simmons-Smith reaction led to the formation of the corresponding *C*-3 spiro-cyclopropane **109** as a single diastereomer in good yield (Scheme 1.38).



Scheme 1.38: synthesis of *C*-3-spirocyclopropanecarboxylated furanose derivative.

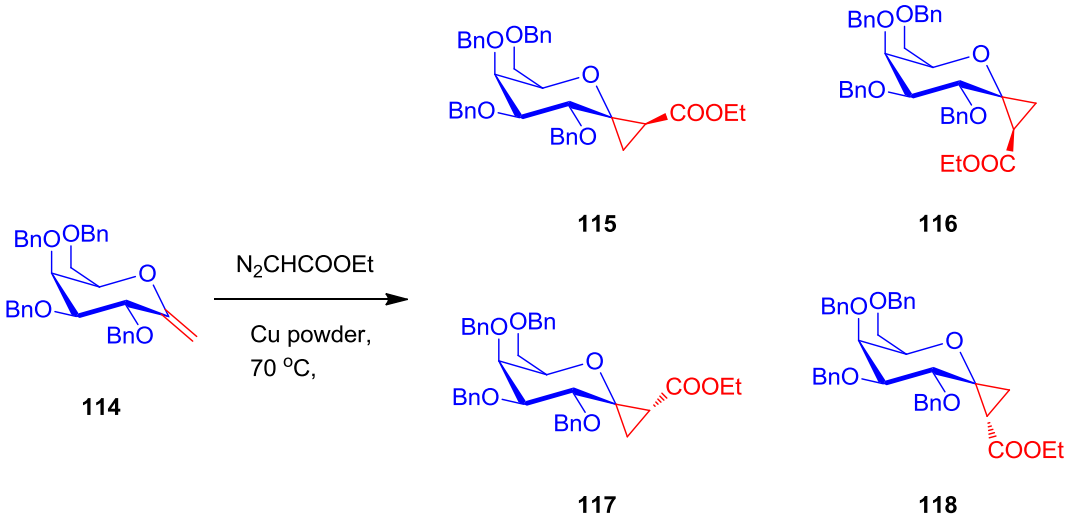
1.5.3 Diazoester cyclopropanation of *exo*- glycals

In 2003 Andrea Vasella and co-workers reported the synthesis of spiro-cyclopropane carboxylated sugars[49] from *exo*-glycals, as a possible glycosidase inhibitors. The enol ether was cyclopropanated with ethyl diazoacetate in the presence of Cu powder under reflux conditions in toluene.[50] Although the reaction worked very well with respect to the yield (93-98%) a mixture of diastereomers **110**-**113** in 3:1:3:2 ratio were obtained. It was also revealed that $Rh_2(OAc)_4$ catalysed cyclopropanation seems to require a large excess of diazoacetate to achieve reasonable yield (42-69%). Interestingly, the ratio of spirocyclopropane carboxylated sugars **110**-**113** depends on the choice of the solvent and temperature. The cyclopropanation progressed best when toluene solution of ethyldiazoacetate at below 25 °C was slowly added to a suspension of Cu powder in a toluene solution of **19** at 100 °C. The obtained diastereomeric products were separated by using crystallisation and HPLC with different solvent system to give compounds **110** (36%), **111** (12%), **112** (28%), **113** (18%) (Scheme 1.39).



Scheme 1.39: Synthesis of glucose derived *C*-1 spiro-cyclopropanecarboxylated sugar using rhodium acetate or Cu catalyst.

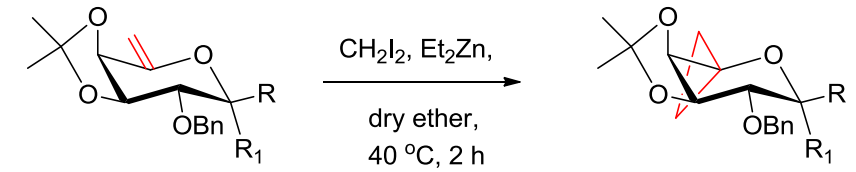
The above procedure has been successfully applied for the synthesis of galactose derived spiro-cyclopropanecarboxylated sugars. Cyclopropanation of **114** with excess ethyl diazoacetate in the presence of Cu powder (0.2 equiv) gave 91% of a mixture of the diastereomeric ethyl cyclopropanecarboxylates **115**-**118** with a ratio of 18:42:17:23 (Scheme 1.40).



Scheme 1.40: Synthesis of galactose derived *C*-1 spiro-cyclopropanecarboxylated sugar through metal catalyst.

1.5.4 Simmons-Smith cyclopropanation

Recently in 2008, Rescifina and Pistara group developed cyclopropanation of 5-methylene galactopyranosides[51] by dihalo, ethoxycarbonyl and substituted carbenes. The resulting spiro-cyclopropanated functionalized sugars are claimed to be very important as synthetic building blocks, glycosidase inhibitors and useful scaffolds as carbohydrate mimics. 5-Methylene galactopyranosides **119α**, **119β** were reacted with diethyl zinc and diiodomethane in dry diethyl ether and heated in a sealed vessel at 40 °C to obtain spiro-cyclic systems **120α, 120β** in nearly quantitative yield (Scheme 1.41).[52]



R = H, R_1 = OCH_3 (**119**α)
R = OCH_3, R_1 = H (**119**β)

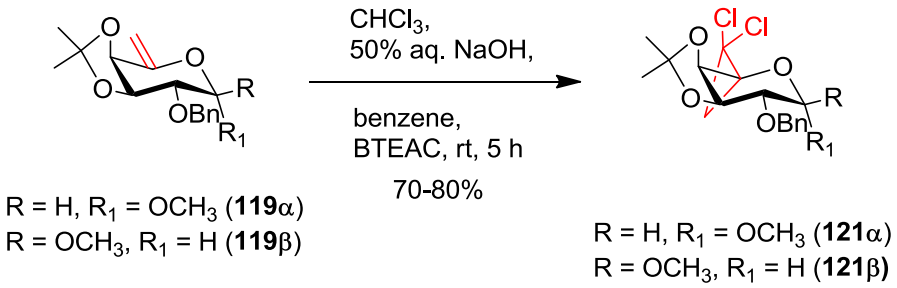
R = H, R_1 = OCH_3 (**120**α)
R = OCH_3, R_1 = H (**120β)**

Scheme 1.41: Synthesis of *C*-5-spiro-cyclopropanated hexoses.

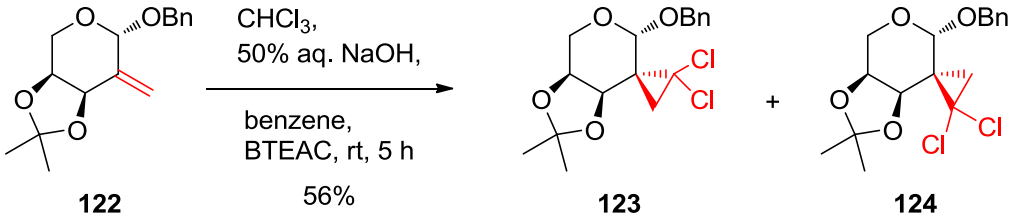
1.5.5 Mąkosza cyclopropanation

The dichloro cyclopropanation reactions were conducted in chloroform by adding 50% aqueous NaOH in the presence of benzyltriethylammonium chloride (BTEAC) as phase-transfer catalyst to obtain the *C*-5-spiro-dichlorocyclopropanated sugar derivatives, thus, *exo*-glycals **119α** and **119β** in chloroform were treated with 50% aq. sodium hydroxide in

presence of benzene and phase transfer catalyst to afford compounds **121α** and **121β** in good yield (Scheme 1.42).[52] A similar protocol was adopted to the cyclopropanation of *C*-2-methylene sugar **122** to prepare spiro derivatives **123** and **124** as a mixture of diastereomers (Scheme 1.43).[51]



Scheme 1.42: Synthesis of Mąkosza cyclopropanation.



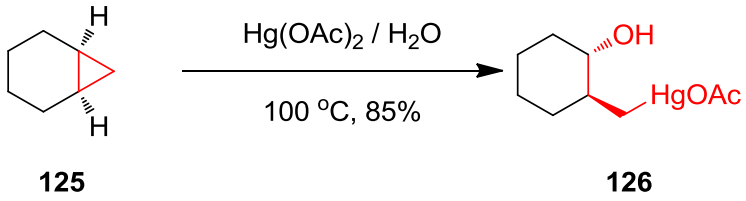
Scheme 1.43: Synthesis of Mąkosza cyclopropanation.

1.6 Applications of 1, 2 cyclopropanated sugars

Cyclopropanated compounds have been versatile synthetic intermediates in the synthesis of various functionalized cycloalkanes, acyclic compounds and biologically active compounds. Vicinal donor-acceptor cyclopropanes are particularly useful synthetic building blocks, because of the reactivity imparted to the cyclopropane by the substituent is amplified by a synergetic electron push-pull relationship. Due to the high stereoselectivity achieved in the case of *endo*-glycals a number of stereoselective transformations have been developed by using these chiral precursors. In this section we discuss the application of 1,2-cyclopropanated sugars in the synthesis of natural products, higher ordered sugars (septanosides) and transition metal catalysed reactions.

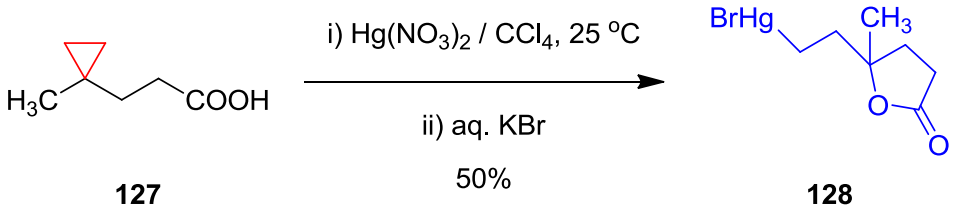
1.6.1 Ring–Opening of 1,2-Cyclopropanated Sugars

1,2-Cyclopropanated sugars are important synthetic intermediates in the synthesis of 2-*C*-branched glycosides, epothilone analogues, oligosaccharide synthesis and septanoside derivatives. In 1950 Dokl and co-workers first time reported the ring opening of norcarane **125** with mercuric acetate in presence of water at 100 °C to obtain the ring open compound **126** in 85% yield (Scheme 1.44).[53]



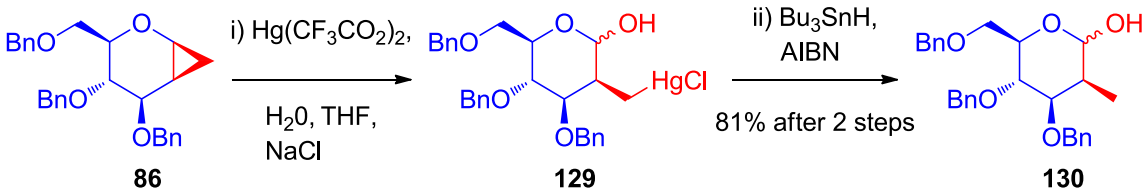
Scheme 1.44: Stereoselective cleavage of norcarane.

In 1983 John S. Hallock and his co-workers performed the studies pertaining to mercury-mediated lactonizations of unactivated cyclopropane derivatives.[54] Cyclopropane carboxylic acid **127** undergo ring opening with mercuric nitrate followed cyclization by addition of potassium bromide to provide the lactone **128** in 50% yield (Scheme 1.45).



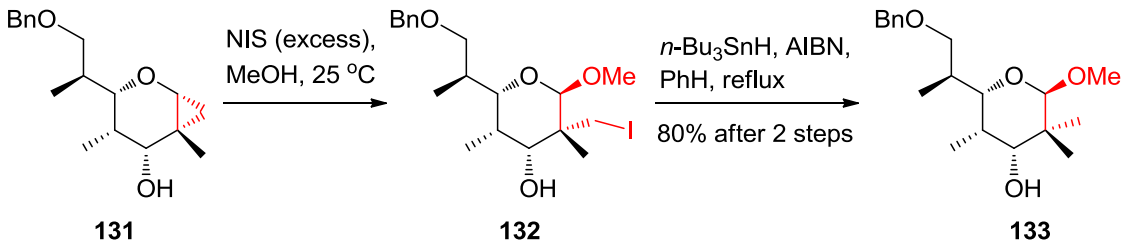
Scheme 1.45: Synthesis of lactone from unactivated cyclopropane carboxylic acid.

In this regard, in 1996 Heathcock and Scoot demonstrated the first example of mercury mediated ring-opening of 1,2-cyclopropanated sugar derivatives. Ring opening of 1,2-cyclopropanated sugar **86** with mercuric trifluoroacetate in presence of water provided an organomercurial compound **129** as a mixture of anomers. This upon reductive removal of mercury with tributyltin hydride and catalytic AIBN gave the 2-*C*-methyl carbohydrate **130** in good yield (Scheme 1.46).[55]



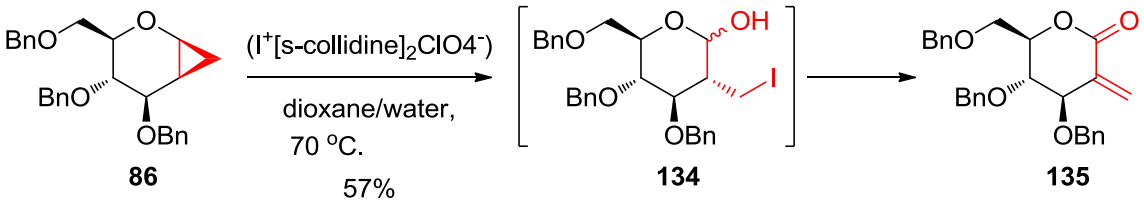
Scheme 1.46: Mercury-mediated ring-opening of 1,2-cyclopropanated sugar.

Interestingly, in 1996 Danishefsky and co-workers demonstrated a new strategy for the ring-opening of 1,2-cyclopropanated sugars in presence of excess *N*-iodosuccinimide (NIS) in methanol. Treatment of cyclopropanated sugar **131** with excess NIS in methanol provided the iodomethyl compound **132**, which upon reduced with tributyl tinhydride to give methyl glycoside **133** in 80% yield (Scheme 1.15).[56] The product **133** was further used in the synthesis of natural products, epothilone A and B (Scheme 1.47).[57]



Scheme 1.47: Ring-opening of 1,2-cyclopropanated sugar by using NIS and methanol.

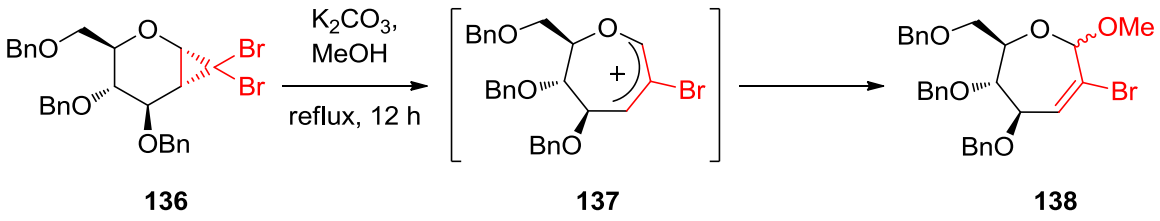
In 1997 Nagarajan and co-workers described a facile synthesis of chiral *α*-methylidene-δ-valerolactones. In this protocol 1,2-cyclopropanated sugars were reacted with iodonium-di(*s*-collidine)perchlorate (IDCP) to facilitate ring opening followed by dehydrohalogenation reaction in one-pot. Thus, ring-opening of 1,2-cyclopropanated sugar **86** by using IDCP in dioxane/water to form the intermediate hydroxyl-iodide **134** which undergo oxidation followed by elimination gave the required *α*- methylidene-δ-valerolactone **135** (Scheme 1.48) in 57% yield.[58]



Scheme 1.48: Synthesis of *α*-methylidene valerolactone from 1,2-cyclopropanated sugar.

In addition Nagarajan and co-workers reported solvolytic ring expansion of 1,2-dibromocyclopropnated sugars with potassium carbonate in methanol under reflux conditions to provide the corresponding chiral oxepins in good yield. Electrophilic ring opening (C1-C2) of 1,2-cyclopropanated sugar **136** with excess K_2CO_3 in methanol under

reflux provided the ring-expanded septanoside **138** as an anomeric mixture in 67% yield (Scheme 1.49)[44] *via* intermediate **137**.

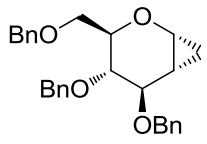
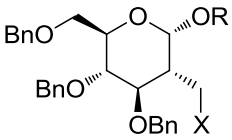
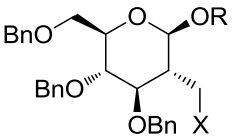


136 **137** **138**

Scheme 1.49: Synthesis of chiral oxepins through ring expansion of 1,2-dibromocyclopropanated sugar.

Electrophilic ring openings of simple cyclopropanes were carried out with different electrophiles to give different functionalized 2-deoxy-2-*C*-branced chain glycosides (table 1.1). Ring opening of cyclopropane **96** was carried out with hydrochloric acid in presence of methanol under refluxing condition to furnish the 3,4,6-tri-*O*-benzyl-2-deoxy-2-*C*-methyl-β-D-glucopyranoside **139** in 70% yield exclusively.[43] Adopting the similar protocol a series of 2-C-branched sugars **140** – **144** were synthesized by using different electrophiles and solvents.

Table 1.1: Ring opening of 1,2 cyclopropane sugars with different electrophiles.

Entry	Substrate	Reagent/solvent/time	product(s)	yield %
	 **96**		 	
1		HCl/MeOH/15d	R = CH_3 X = H	**139** **70**
2		NBS/MeOH/8h	R = CH_3 X = Br	**140** (20 : 80) **141** **72**
3		NIS/MeOH/12h	R = CH_3 X = I	**142** (20 : 80) **143** **86**
4		NBS/H_2O/8h	R = H X = Br	**144** **66**

1.6.2 Glyco-Amino Acids

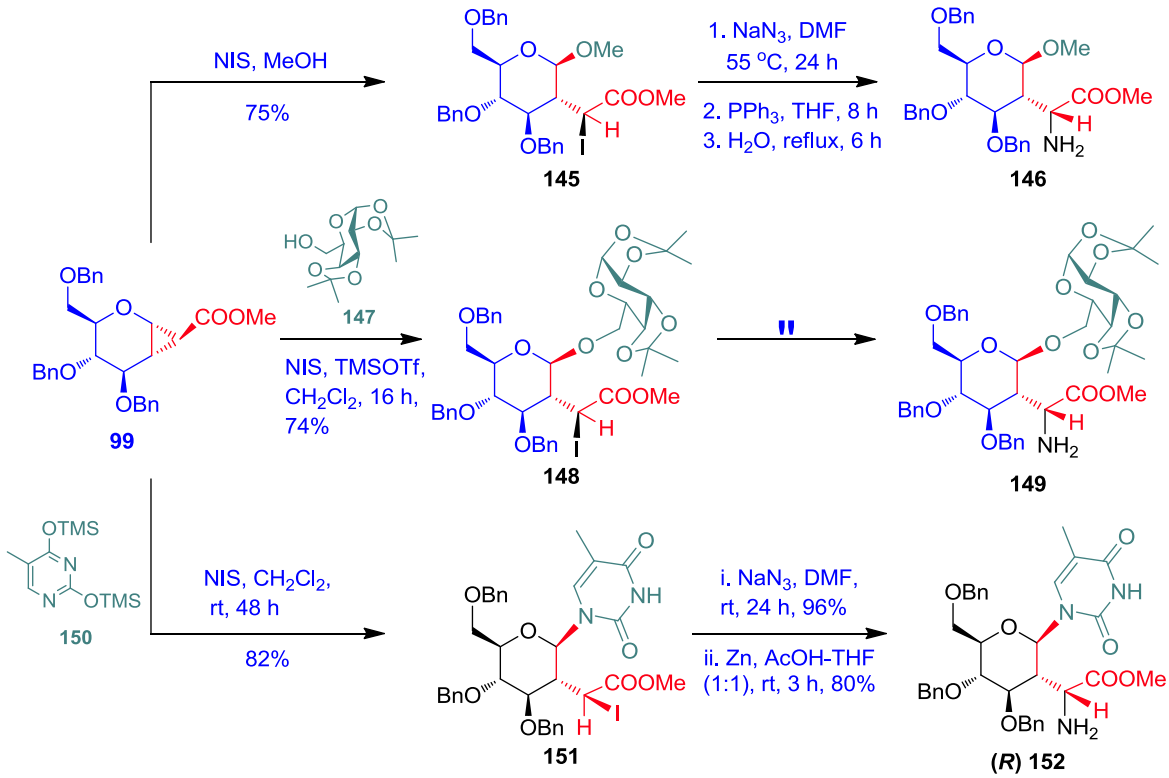
1.6.2.1 Synthesis of 2-*C*-Branched glyco-Amino Acids

1,2-cycopropane carboxylated sugars are used as synthons for the synthesis of glyco-amino acids, which are used in the synthesis of glycopeptide synthesis. In 2004, Chandrasekaran group developed an efficient methodology for the synthesis of 2-*C*-branched glyco-amino acids by ring opening of 1,2-cyclopropanated sugars. In their approach, 1,2 cyclopropane carboxylated sugar **99** undergo electrophilic ring opening with NIS/MeOH to get the compound **145** with 75% yield as a single diastereomer. Further treated with NaN_3 in presence DMF as solvent obtain the azido derivate, which on further reduction with PPh_3/THF/H_2O (Staudinger reaction) to get the amine **146** in 95% yield (Scheme 1.50).[59]

In 2009 Sridhar group applied this methodology for the synthesis of oligo glyco-amino acids.[60] For this they proceeded from 1,2 cyclopropanecarboxylate **99** as donor and acceptor **147** with NIS as the electrophile at 0 ^oC in acetonitrile or dichloromethane, under these conditions the reaction did not work even after stirring for 48 h. Due to less nucleophilicity of acceptor **147** for ring opening, they tried with trimethylsilyl trifluoromethanesulfonate (TMSOTf) as the promoter. So the glycosidation reaction between donor **99** and acceptor **147** with NIS and TMSOTf in dichloromethane at 0 ^oC provided the 2-*C*-branched disaccharide **148** in 74% yield. This was further converted to the disaccharide derived glyco-amino acid **149** in 96% yield (Scheme 1.50). These glyco-amino acids are claimed to mimic nucleoside antibiotics such as polyoxins, miharamycin, nikkomycin and amipurymicin.

In 2009 Chandrasekaran group, demonstrated synthesis of pyrimidine based unnatural pyranosyl *C*-2-branched glycol-amino acid nucleosides using NIS mediated ring-opening of 1,2-cyclopropanecarboxylated sugar derivatives. Electrophilic ring opening of 1,2 cyclopropane carboxylated sugar **99** with NIS and trimethylsilyl-activated thymine **150** in dichloromethane afforded the 2-*C*-branched iodocarboxylate with nucleobase **151** as a single diastereomer with *β*-configuration in 82% yield.[61] Which on further treated with NaN_3 in DMF to give the azido compound in 96% yield. Due to low yield of Staudinger reduction for conversion of azide to amine, they choose zinc-mediated reduction (Zn/AcOH-THF), was found to be the best, which gave the corresponding amine **152** in 80% yield (Scheme 1.50). The above methodology was also successfully extended to the synthesis of

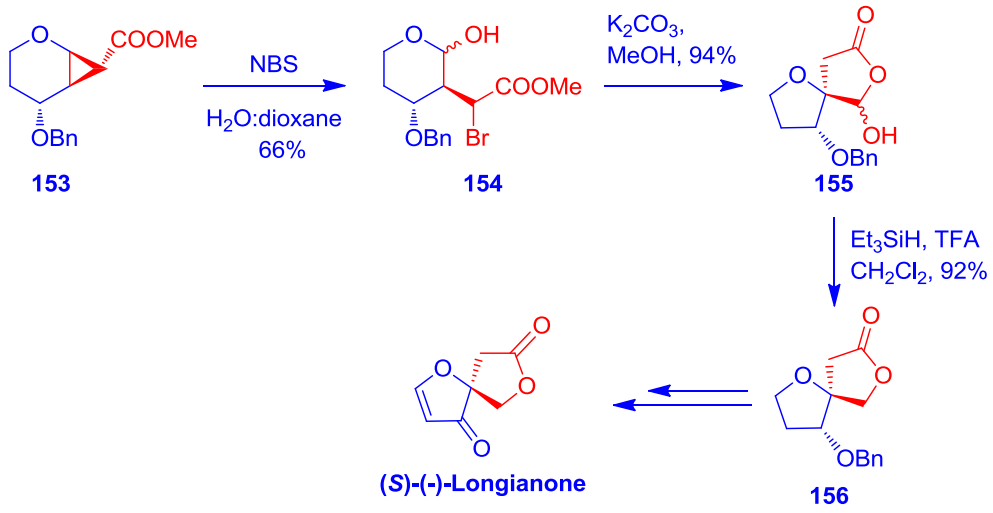
furanosyl nucleosides which are having potential applications in the development of nontoxic antifungal therapeutics.



Scheme 1.50: Synthesis of glyco-amino acids from 1,2-cycloporpane carboxylated sugars.

1.6.3 Synthesis of spiro-lactones

Recently, stereoselective synthesis of sugar fused *C*-spiro-glycosides[62] from 1,2-cyclopropanated sugars has been revealed from our laboratory. Electrophilic ring opening

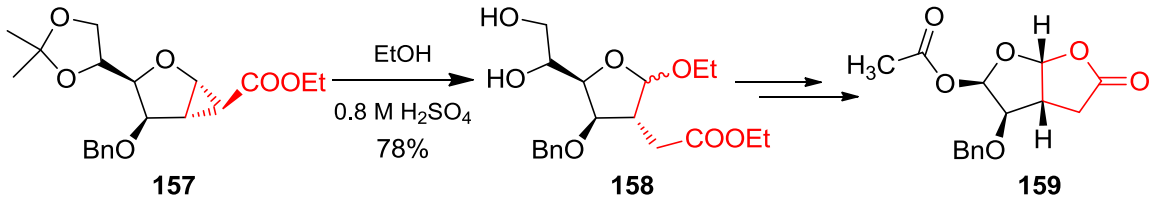


Scheme1.51: stereoselective synthesis of carbohydrate derived *C*-spiro-lactones from 1,2-cyclopropanecarboxylated sugar derivative.

of 1,2-cyclopropane carboxylated sugar **153** with NBS/H_2O:doxane system provided the corresponding α-bromo-γ-hydroxy carboxylate **154** in 66% yield. (Scheme 1.47). Interestingly, reacting compound **154** with K_2CO_3 in MeOH provided the spiro-cyclic lactol **155** involving a one-pot dehydrohalogenation, intramolecular hetero Michael addition (IHMA) followed by ester hydrolysis. Dehydroxylation of **155** with Et_3SiH/TFA in dichloromethane provided the spiro-lactone **156** in 92% yield. The methodology was further extended to the stereoselective total synthesis of (S)-(–)-Longianone (Scheme 1.51).[63]

1.6.4 Synthesis of Bicyclic systems

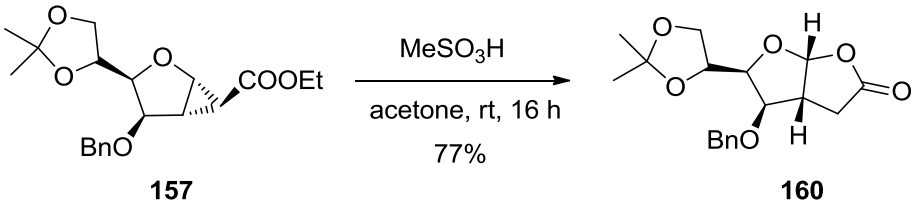
In 1999, research work on 1,2-cyclopropanecarboxylated by Theodorakis revealed an acid-mediated ring-opening followed by cyclization to form furo[2.3-b]furolactone ring systems that were present in norrisolide side chain.[64] According to this report, 1,2-cyclopropanecarboxylated sugar **157** upon reaction with dilute ethanolic solution of sulphuric acid lead to the formation of 2-*C*-branched furanose derivative **158**, which was later transformed into fused lactone **159** (Scheme 1.52) in two steps.



157 **158** **159**

Scheme 1.52: Enantioselective synthesis of the Norrisane side chain.

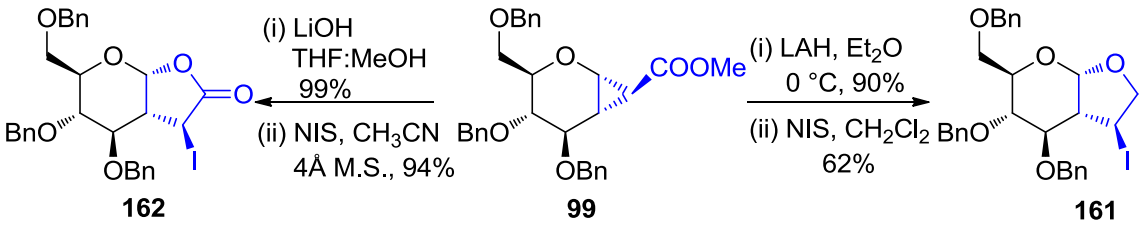
Subsequently, the same group developed a one-step protocol for the synthesis of linearly fused bicycle **160** from the 1,2-cyclopropanecarboxyalted sugar **157** using methanesulfonic acid in acetone (Scheme 1.53).[65] The methodology was successfully applied to various 1,2-cyclopropanated sugars to get the bicyclic lactones with high diastereoselectivty.



157 **160**

Scheme 1.53: Acid-mediated ring-opening of 1,2-cyclopropanecarboxylated sugars.

In 2007, Chandrasekaran and co-workers reported an efficient method for the synthesis of fused perhydrofuro[2,3-b]pyran[66] **161** involving a diastereoselective electrophilic ring-opening of 1,2-cyclopropanecarboxylated sugar derivative **99** (Scheme 1.54). This methodology has also been successfully applied to the synthesis of fused perhydrofuro[2,3-b]pyrano-γ-butyrolactone derivative **162** in good yield (Scheme 1.54). These bicyclic pyran or furan systems were useful in bio-active natural product synthesis.



Scheme 1.54: Formation of fused bicycles by ring-opening of 1,2-cyclopropanecarboxylated sugar derivative **99.**

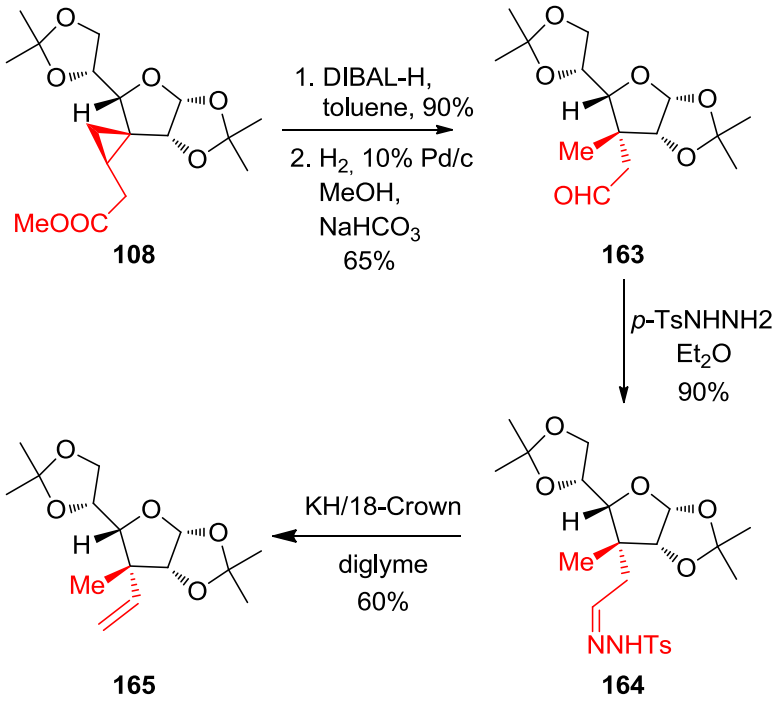
1.7 Applications of Spiro-cyclopropanated sugars

In compare with 1,2-cyclopropanated sugar derivatives, chemistry of spiro-cyclopropanated carbohydrate moieties is not much explored. One of the possible reason is the lack of stereoselective synthetic protocols for the preparation of carbohydrate derived enantiomerically pure spiro-cyclopropane systems. However, theoretically, most of the reactions performed by 1,2-cyclorpopane carboxylates can be applied in the case of spiro-cyclopropanecarboxylates, which can be obtained by the cyclopropanation of *exo*-glycals. Also, they can be useful synthons for the preparation of natural products like asteltoxin, pantolactone homolog, eremantholide A etc.[67] In general, the driving force for the reactions of fused or spiro-cyclopropane sugars is mainly the ring strain, that makes the cyclopropane ring to open in presence of an electrophilic and nuecleophillic reagents.

1.7.1 Synthesis of Spiro ring system

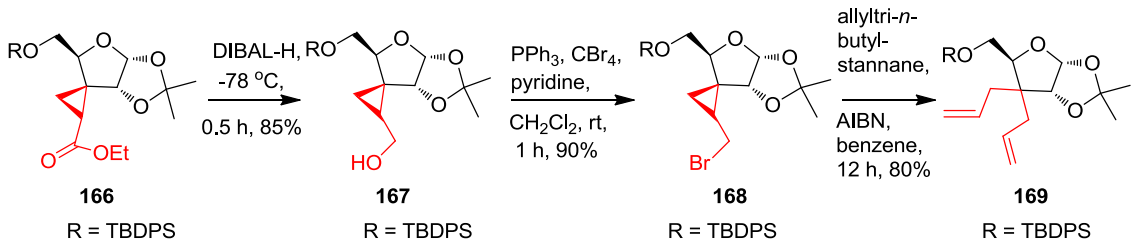
In 1998 Gurjar and co-workers reported synthesis of spiro-cyclopropane derivatives and their applications.[38] For example, Compound **109** which is already mentioned in the preparation of spiro-cyclopropanes, undergo reduction with DIBAL-H in presence of toluene to get the rather unstable aldehyde in 90% yield, which upon hydrogenation with 10% Pd/C at 60 psi, containing a catalytic amount of $NaHCO_3$ provided the aldehyde **163**.

The obtained compound was treated with *p*-tosylhydrazine in ether at room temperature to give the corresponding hydrazone derivative **164,** which upon heated under reflux with KH/18-Crown-6 in diglyme for 3 h to afford the required 3-*C* allyl derivative **165** in 60% yield (Scheme 1.55). 3-deoxy-l.2:5.6-di-*O*-isopropylidene-3-*C*-methyl-3-*C*-vinyl-α-D-a1lyl-furanose **165** has been identified as a versatile synthon for natural product synthesis asteltoxin.



Scheme 1.55: Synthesis of 3-*C* ally derivative from 3,3 spiro-cyclopropane.

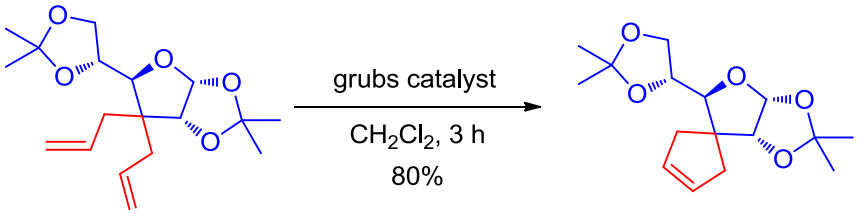
C-3 spiro-cyclopropane carboxylate sugars are excellent starting material for the synthesis of spiro cyclic ring at *C*-3 position which is already mentioned in the previous discussion. The compound **166** undergo reduction with DIBAL-H at -78 ^{o}C, to produce **167** in 85% yield. The obtained alcohol was treated with CBr_4-PPh_3 in CH_2Cl_2 at room temperature gave the bromo derivative **168** which on further reaction with allyl tri-*n*-butylstannane in the presence of catalytic amount of AIBN in refluxing benzene, provided dially compound **169** 72% overall yield (Scheme 1.56).[68] These gem-diallylic substituted carbohydrate synthons can be excellent precursors for the synthesis of spiro-ring systems.



166 R = TBDPS **167** R = TBDPS **168** R = TBDPS **169** R = TBDPS

Scheme 1.56: Synthesis of 3-*C* dially derivative from 3,3-spiro-cyclopropane.

The diallylic derivative **170** (Scheme 1.57), undergo ring closing metathesis reaction with Grubs catalyst in CH_2Cl_2 at room temperature to give the spirocyclic compound **171** in 80% yield as single diastereomer.[68]

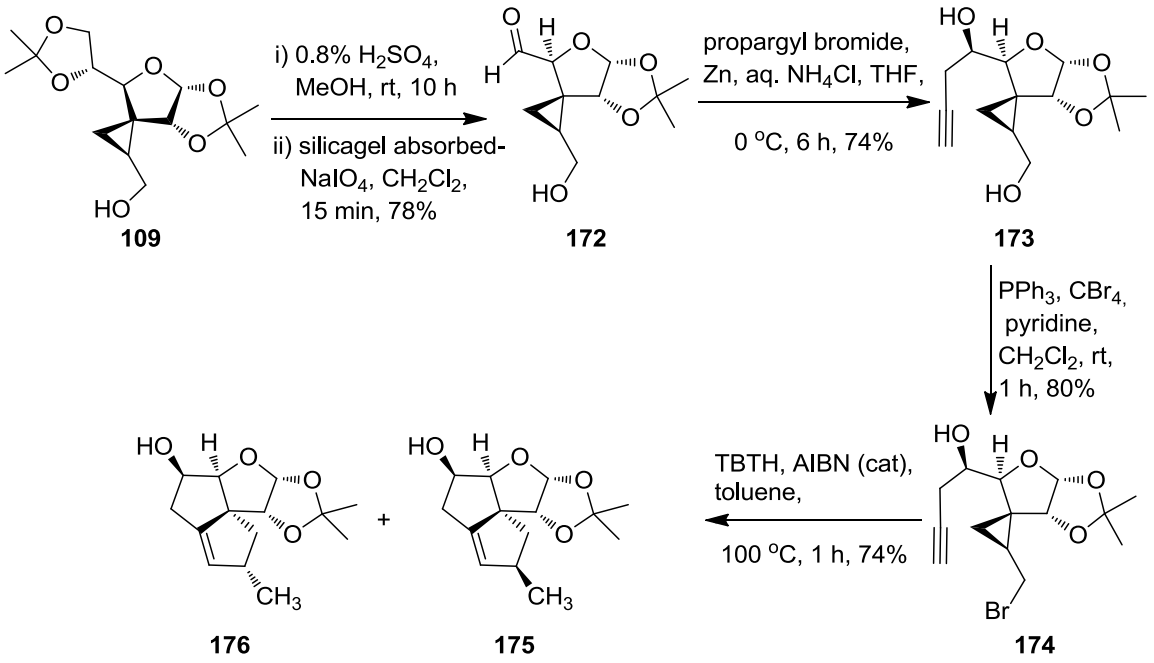


170 **171**

Scheme 1.57: Synthesis of Spiro ring system from dially derivative.

1.7.2 Synthesis of oxatriquinane system

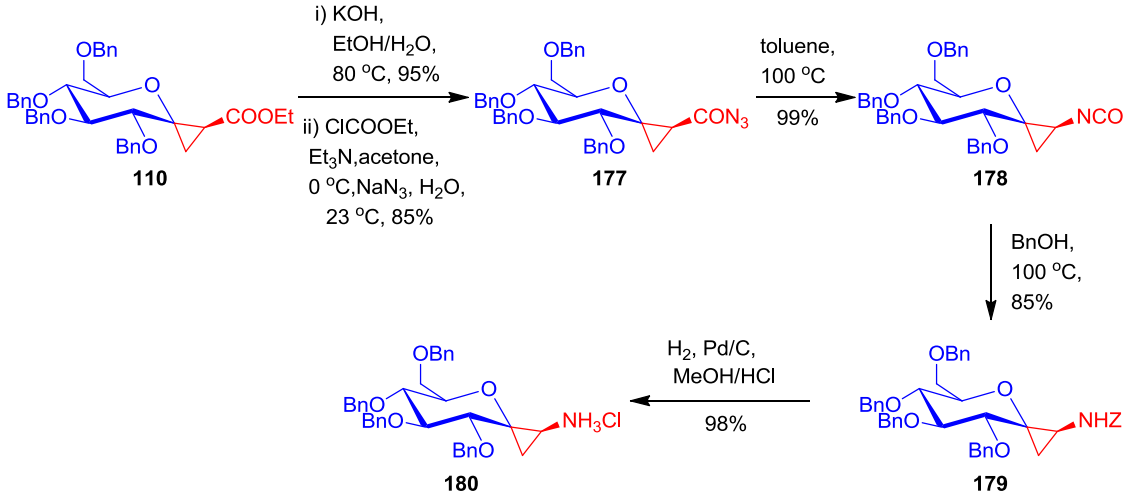
In 2001 Gurjar and co-workers synthesized a novel oxa-triquinane system through cascade radical cyclisation reactions on furanose-sugar system *via* tertiary radical formation from cyclopropylmethyl bromide with simultaneous release of ally group. These triquinane systems are associated with significant biological activity has necessitated development of many approaches for their synthesis. Compound **172** was obtained from compound **109** through regio selective deprotection and oxidative cleavage with $NaIO_4$, then immediately subjected with Barbier reaction under aqueous conditions with Zn and propargyl bromide to obtained the compound **173** in 74% yield. Conversion of alcohol to bromide using CBr_4-PPh_3 in dichloromethane, in the presence of pyridine at room temperature to form bromide **174** followed by radical reaction of **174** with tertiary butyl tinhydride (TBTH) and AIBN in dry toluene at 100 °C gave the triquinane derivatives **175** and **176** as mixtures of diastereomers with 8.5:1.5 in 74% yield (Scheme 1.55).[69]



Scheme 1.58: Synthesis of angularly fused oxa-triquinane derivatives.

1.7.3 Glycosidase inhibitors

The spiro-cyclopropyl amines[49] are also shown to mimic the glycosidase inhibitors. These compounds are prepared from the spiro-cyclopropanecarboxylated sugars. The spiro-cyclopropane **110** was hydrolysed by using KOH in ethanol/water and the resulting acid was transformed into the corresponding acylazide **177**. Heating this azide in toluene at 100 °C to undergo Schmidt rearrangement, and treatment of the resulting isocyanate 178 with BnOH

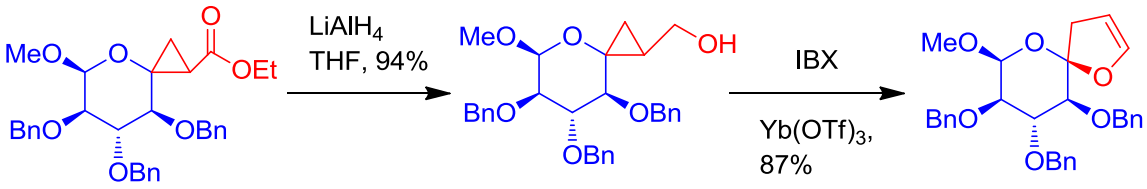


Scheme 1.59: Synthesis of glycosidase inhibitors from spiro-cyclopropanecarboxylated sugars.

provided the carbamate **179** (Z = $C_6H_5CH_2OCO$) in 85% yield. Finally, total deprotection led to the formation of spiro-cyclopropyl amine **180** in good yield (Scheme 1.59). Similarly this protocol could be utilized in the various spiro-cyclopropane carboxylated sugars for glycosidase inhibitors.

1.7.4 Synthesis of spiroketals

Another recent application of spiro-cyclopropanated sugars is the synthesis of spiroketals, involving a ring enlargement reaction. In 2009, Werz et al. synthesized [n,5]-spiroketals[70] from spiro-cyclopropane carboxylated sugars through reduction followed by oxidation with Lewis acid as $Yb(OTf)_3$. The spiroketal moiety is a characteristic architectural feature in simple as well as in complex natural products including insect pheromones and fungal toxins. A number of different spiroketal subunits have been observed in nature, and out of these most abundant are [6,6], [6,5], [5,5]-spiroketals. Spiro-cyclopropanecarboxylated sugar **181** was prepared from the corresponding *exo*-olefin. Reduction of **181** with $LiAlH_4$ provided the corresponding alcohol **182** in 94% yield. While oxidizing the alcohol function using hypervalent iodine reagents IBX in presence of Lewis acid $Yb(OTf)_3$, compound **182** produced [6,5]- spiroketal **183** in 87% yield (Scheme 1.60). This observation was extended to a series of other spiro-cyclopropanated systems.



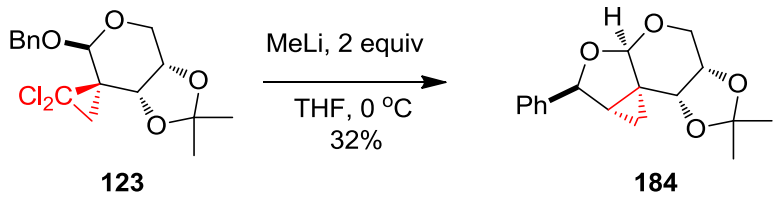
181 **182** **183**

Scheme 1.60: Synthesis of spiroketal from spiro-cyclopropane derivative.

1.7.5 Bicyclic compound from *C*-2 spiro cyclopropanes

The *C*-2 spiro cyclopropanated sugar[52] **123** which is already discussed earlier in spiro-cyclopropane synthesis, upon treatment with methyl lithium in THF at 0 ^oC led to an insertion reaction into the adjacent benzylic C-H bond, *via* a LiCl carbenoid intermediate, to afford compound **184** in low yield (Scheme 1.61). This cyclization may open a novel

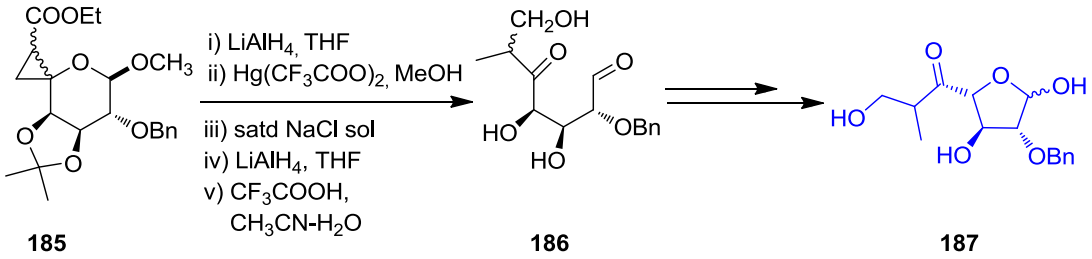
technologies in the formation of ring systems encountered in microline[71] and mycorbizzin[72] antibiotics.



Scheme 1.61: Synthesis of bicyclic system from *C*-2 spiro-cyclopropane derivative.

1.7.6 Synthesis of δ-dicarbonyl heptoses

Recently, Corsaro group demonstrated a new route to the synthesis of dideoxy δ-dicarbonyl heptoses from spiro-cyclopropanecarboxylated D-galactose derivative through the ring opening by a methoxymercuration-demercuarationprocedures.[73] Spiro-cyclopropanecarboxylated sugar **185** undergo reduction followed by ring opening with mercury mediated reagents to give dicarbonyl open chain compound **186** in good yield (Scheme 1.62). These natural dicarbonyl monosaccharides have been postulated as intermediates in the synthesis of cyclitols and are also useful synthetic intermediates in the preparation of high value added compounds such as iminosugars, carbasugars, and polyhydroxy cyclopentanes.

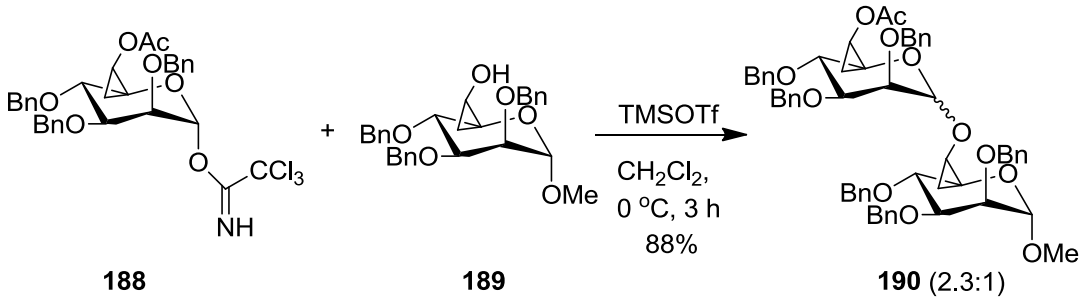


Scheme 1.62: Synthesis of δ-dicarbonyl heptoses from spiro-cyclopropane carboxylated derivative.

1.7.7 Glycosylation of cyclopropyl-modified mannose derivatives

In 2012 Werz *et al.*, developed a glycosylation[74] reaction between mannosyl-like spiro-annulated cyclopropane, at C-5, as donor and acceptors in presence of TMSOTf to give the corresponding di and tri saccharide compounds. Cyclopropane motifs have been widely used

to rigidify peptide sequences.[75] As shown in scheme 1.63, glycosidation between donor **188** and acceptor **189** in presence of TMSOTf formed the disaccharide compound **190** in 88% yield.



Scheme 1.63: Glycosylation reaction of cyclopropyl-modified mannosyl trichloroacetimidate.

1.8 References

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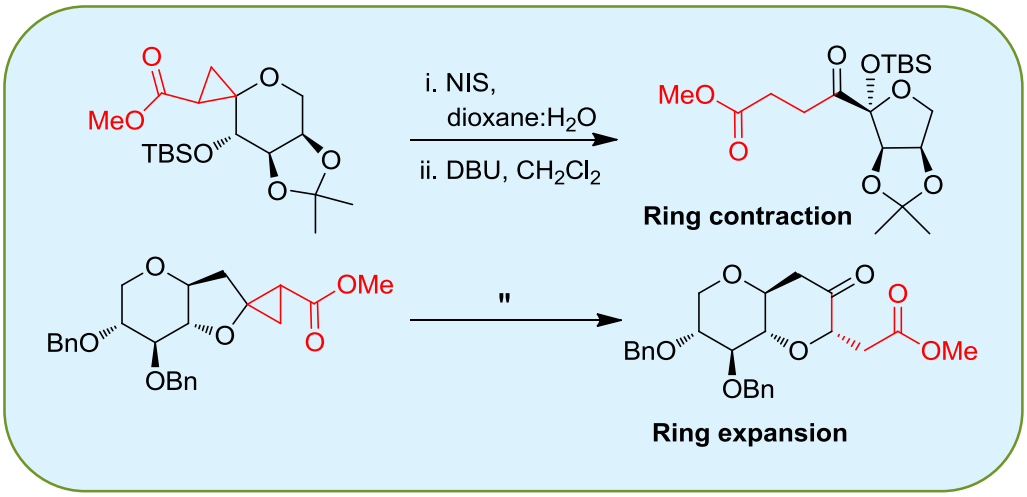
Chapter 2

Ring-Contraction *vs* Ring-Expansion Reactions of Spiro-Cyclopropanecarboxylated Sugars

ABSRACT

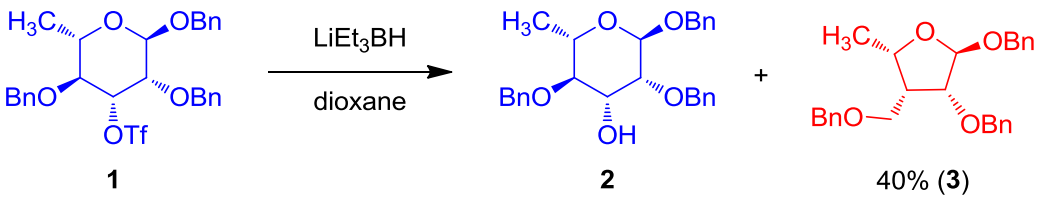
Electrophilic ring-opening of spiro-cyclopropanecarboxylated sugars followed by reaction with DBU revealed interesting ring-contraction and ring-expansion reactions depending on the substrate and the kind of hydroxyl protective group present adjacent to the spiro centre. A stereoselective method for accessing a new class of carbon chain extended keto-furanoses and C-glycosylated bicyclic compounds is reported.



2.1 Introduction

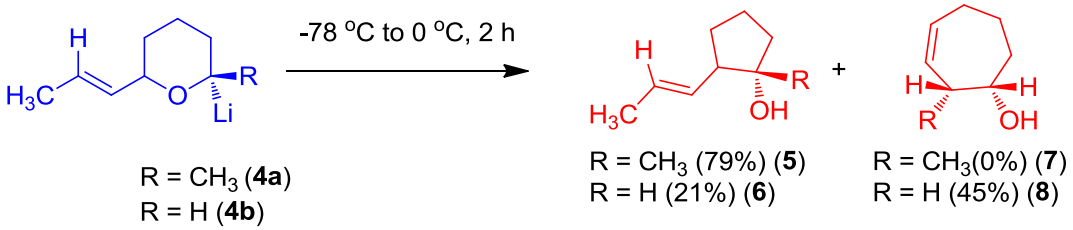
Carbohydrates are ubiquitous chiral resources whose chemistry has underpinned the discovery of many awe-inspiring and fascinating new transformations in chemistry and biology.[1] Apart from designed methodologies, quite a few surprising reactions/ rearrangements have emerged in "sugar chemistry", and some are even unusual.[2] In this context, ring-contraction[3] and ring-expansion[4] reactions involving carbohydrate derivatives are very significant. Ring contraction reactions of carbohydrate derived sugar moieties is one of the significant methods for constructing functional, enantiomerically pure carbocycles and conversion of pyranose to furanose ring will be an additional tool in the synthesis of biologically active compounds.

In 1980 Vince Pozsgay reported formation of ring contracted compound **3 (40%)**, along with pyranose **2** by reacting benzyl 2,4-di-*O*-benzyl-3-*O*-trifluoromethanesulfonyl-α-L-rhamnopyranoside **1** with lithium triethylborohydride in dioxane (Scheme 2.1).[3l]



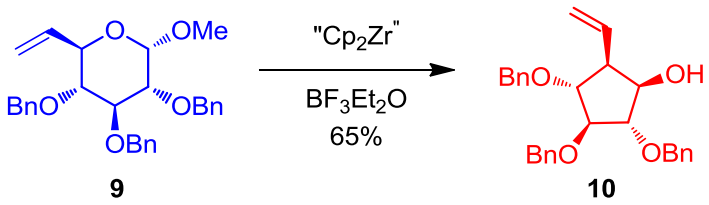
Scheme 2.1: Ring contraction by carbon participation in a hexopyranoside ring.

Later in 1992 Theodore Cohen group reported the stereochemical analysis of 1,2-and 2,3-wittig rearrangement reaction. 2,3 rearrangement requires a trans outlook of the two substituents in a 2-lithio-6-vinyltetrahydropyran, and both rearrangements undergo inversion of configuration at the lithium-bearing carbon atom, which are involving through radical mechanism. 2-lithio-6-vinyltetrahydropyran type **4** at low temperature undergo ring contraction as well as ring expansion to give products **5-8** through 1,2 and 2,3 rearrangements. The amount of formation of products were depends on the alkyl group present on the lithium-bearing chiral carbon (Scheme 2.2).[3a]



Scheme 2.2: Ring contraction and Ring expansion reaction through Wittig rearrangement.

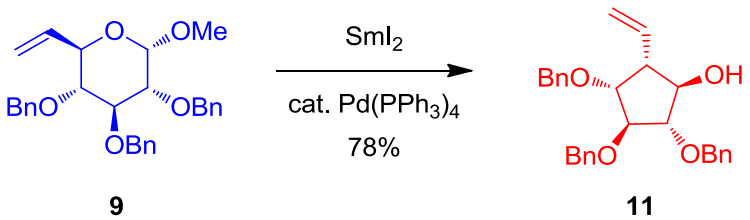
In 1993 Yuji Hanjawa and co-workers developed an efficient and highly diastereoselective zirconium-mediated ring contraction of carbohydrative derivatives to carbocycles. In this report, a ring contraction reaction was observed by treating 5-vinyl pyranoside **9** with "Cp_2Zr" and $BF_3.Et_2O$ in THF producing the corresponding carbocycle **10** in 65% yield (Scheme 2.3). This methodology was successfully applied to various vinyl carbohydrate derivatives for carbocycles synthesis. In all the products *cis* stereochemistry was observed between the hydroxyl and vinyl group present on cyclopentane derivatives of type 10.[3b, 3d]



9 **10**

Scheme 2.3: Ring contraction reaction of carbohydrate derivative by using zirconium reagent.

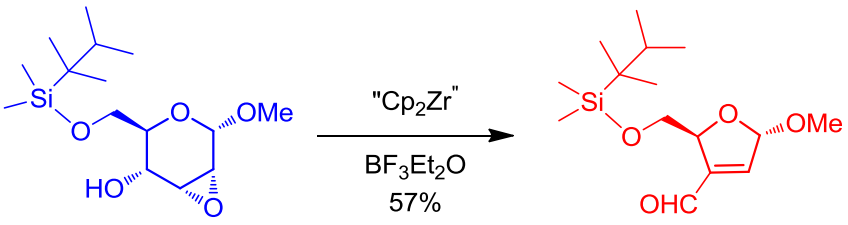
Beatriz Lopez implemented a new strategy for conversion of carbohydrate structure into a functionalized carbocycle. Treatment of 5-vinylpyranosides **9** with samarium iodide and catalytic amount of $Pd(PPh_3)_4$ results in the formation of 2-vinylcyclopentanol **11** in 78% yield (Scheme 2.4).[3f] The generality of this reaction is the preferred trans-relationship observed between the newly generated stereocenters which is opposite to the other methodologies. On the other hand treatment of this compound with zirconocene and $BF_3.Et_2O$, which is already mentioned above in scheme 2.3, undergo ring-contraction to afford *cis*-2-vinylcyclopentanols. In this method (SmI_2) high yields were obtained when compare to other reported protocols.



9 **11**

Scheme 2.4: Synthesis of 2-vinylcyclopentanols by SmI_2/Pd(0)-mediated carbohydrate ring-contraction.

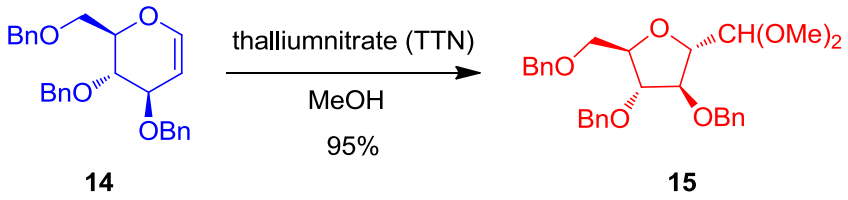
Magnusson and Ponten reported ring contraction reactions of epoxycyclohexanes and epoxycyclohexenols to cyclopentane- and cyclopentenecarboxaldehydes respectively. These are versatile starting materials for the synthesis of a number of terpenes. Epoxycyclohexane **12** undergo ring contraction with LiBr and tetramethylurea (TMU) in refluxing toluene for 10 min. to provide the α,β-unsaturated furanosidic aldehyde **13** in 57%yield.[3k] These are useful in the synthesis of enantiomerically pure tetrahydrofuran-type natural products.[3m]



12 **13**

Scheme 2.5: Ring contraction of epoxyhexopyranosides to α,β-unsaturated five-membered ring aldehyde.

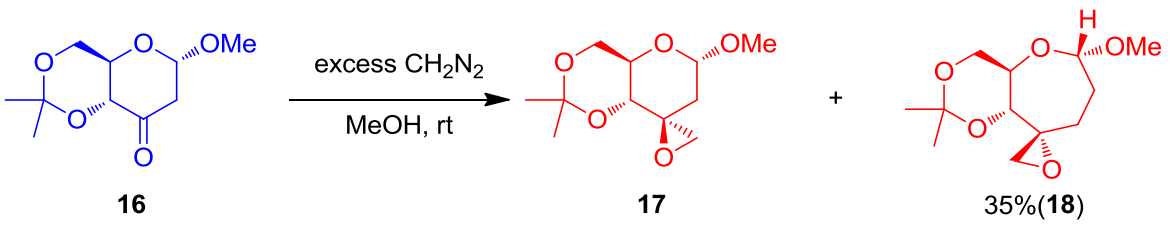
In 1998 Giovanni Piancatelli group reported a general method for ring contraction reaction of pyranose derivative to the corresponding furanose derivative. Treatment of tri benzyl glucal **14** with thallium(III) nitrate in methanol at 35 ^{o}C, gave the highly substituted, enantiomerically pure tetrahydrofuran dimethylacetal **15** in high yield (Scheme 2.6).[3g] This ring contraction reaction was successfully applied to various mono-glycals and perbenzylated glycosyl-glycals.



14 **15**

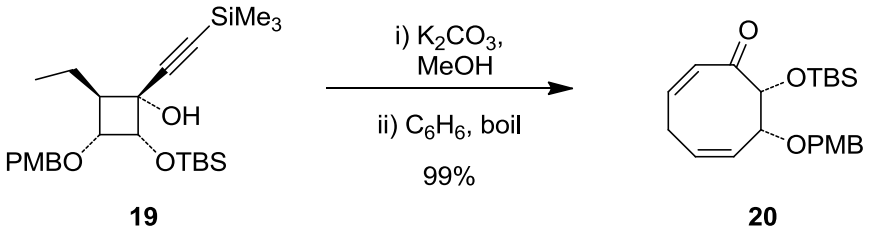
Scheme 2.6: Stereoselective synthesis of tetrahydrofurans from tribenzyl-glucal.

In contrast to ring-contraction reactions, very few reports of the conversion of carbohydrates into the corresponding ring-expanded versions are also revealed in the literature. In 1966 Williams and his co-workers developed a method for ring expansion of pyranose derivative to corresponding septanoside derivative. In their report methyl 4,6-*O*-bezylidene-2-deoxy-3-keto-α-D-*erythro*-hexopyranoside **16** in methanol was treated with excess amount of diazomethane in ether at room temperature to obtain the ring expanded product **18** in 35% yield along with pyranose epoxide **17** (Scheme 2.7).[4a]



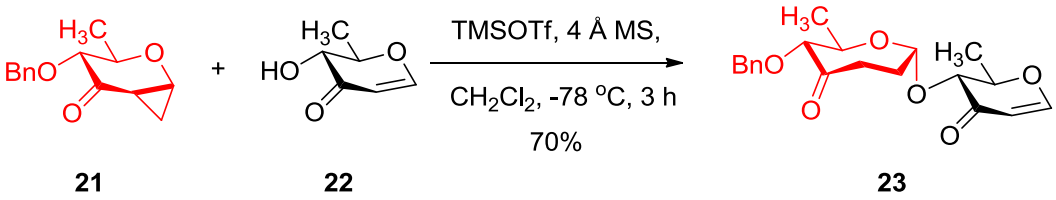
Scheme 2.7: Ring expansion reaction of glycoside from pyranoside ring.

Carbohydrates also have been the precursors to cyclooctene polyols and carbasugars. Zhang and Paquette reported an enantioselective route from carbohydrates to cyclooctane polyols. Ring expansion of cyclobutane derivative **19** was reported to occur under mild basic conditions to provide the eight membered ring **20** in excellent yield (Scheme 2.8),[5, 3b] Further hydroxylation of the obtained cyclooctene derivatives paved the way to the synthesis of cyclooctane polyols. The stating materials for synthesis of cyclobutane derivatives type **19** were prepared from D-glucose or D-arabinose through zirconium mediated ring contraction and 3,3-sigmatropic rearrangement.



Scheme 2.8: Synthesis of cyclooctadienone ring from cyclobutane derivative.

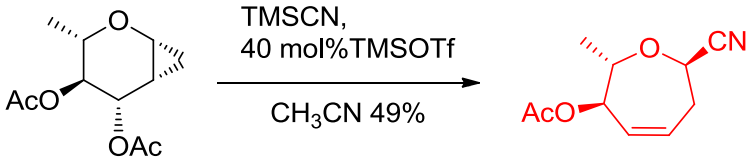
In 2012 our group developed a TMSOTf-mediated one-pot ring expansion-glycosylation reaction of 3-oxo-1,2-cyclopropanated sugar derivatives. In our approach, 1,2-cyclopropanated sugars were used as glycosyl donors and carbohydrate *O*-nucleophiles as acceptors for the construction of septano-oligosaccharides. Thus, glycosylation reaction between 1,2-cyclopropanated sugar **21** as a glycosyl donor and rhamnal derived alcohol **22** as an acceptor in presence of TMSOTf in dichloromethane provided the corresponding ring expanded septano disaccharide **23** as a single diastereomer in good yield (Scheme 2.9).[6] This methodology was useful in the synthesis of various sugar derived septano-disaccharides and septano-oligosaccharides.



21 **22** **23**

Scheme 2.9: Synthesis of septano di-saccharide through ring expansion of 1,2-cyclopropanated sugar.

Hoberg group developed a method for the synthesis of highly functionalized seven membered ring systems which are present in natural products such as isolaurepinnacin and rogioloxepane A having variety of biologically activities. According to this protocol, L-rhamnose derived cyclopropane **24** in presence of lewis acid TMSOTf and TMSCN in acetonitrile undergoes the ring expansion reaction providing the septanoside **25** in 49% yield (Scheme 2.10).[7] In presence of lewis acid oxonium ion (breaking of C1-C2 carbon) was formed by ring opening of cyclopropane sugar followed by attack of nucleophile (CN^-) to give the ring expanded product as oxepane. For optimisation of this reaction they used different lewis acids and different solvents, out of all TMSOTf and acetonitrile were found to be the best and effective catalyst and solvent, respectively.

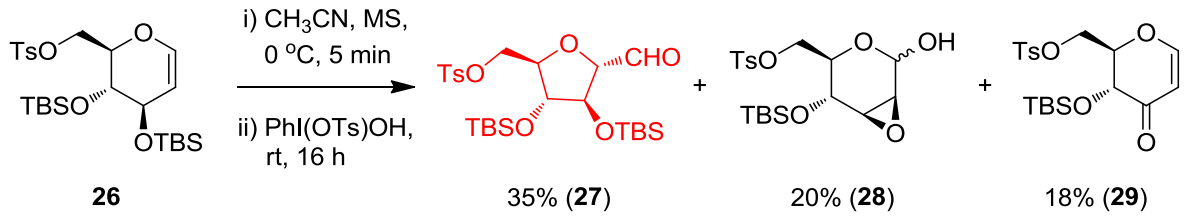


24 **25**

Scheme 2.10: Formation of septanoside ring by ring-expansion of cyclopropane using lewis acid.

Out of several published protocols, the ring-contraction of α-trifluoromethanesulfonylated aldonolactones[8] and Kirschning's hypervalent iodine-mediated oxidative ring-contraction of glycals[9] to formyl glycosyl analogues are noteworthy. This reaction was carried out by reacting glucal derivative **26** with PhI(OTs)OH in presence of acetonitrile and molecular sieves to give the corresponding ring contracted product **27** in 35% yield, along with side products **28** and **29**.[10] Gin *et al.*,[11] cleverly implemented the I^{III} mediated ring-contraction of a glycal as a key step in his first total synthesis of (+)-pyrenolide D. However, the application of such ring-

contraction reactions, and the conversion of pyranoses to *C*-branched furanoses, in the stereoselective total synthesis of complex natural products have been very scarce.[12]



26 35% (**27**) 20% (**28**) 18% (**29**)

Scheme 2.11: Ring contraction reaction of glucal derivative by using hypervalent iodine reagent.

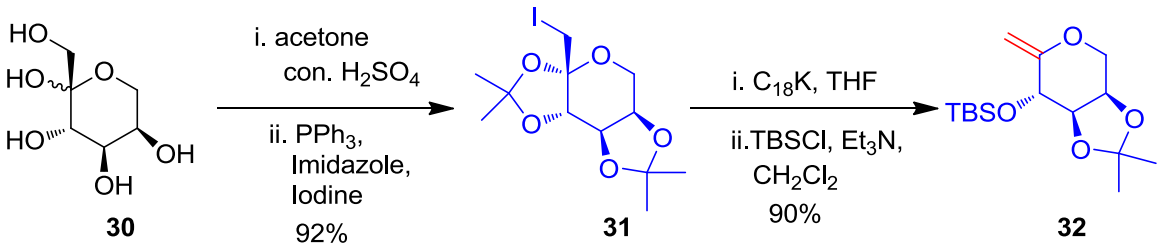
The classical Achmatowicz[13] reaction involving the rearrangement of furfuryl alcohol derivatives to dihydropyran systems has been used successfully in total synthesis[14] as well as in combinatorial chemistry.[15] Ring-expansion through the formation of a cyclopropane has been effectively utilized to synthesize 7-membered oxygen heterocycles, oxepines, as well as septanosides.[16] 1,2-cyclopropanated sugar derivatives have also been converted to the corresponding ring-contracted counterparts.[17] Very recently, spiroannulated donor-acceptor cyclopropane derivatives were successfully converted to [n,5]-spiroketals (n = 5,6) via ring enlargement of the cyclopropane moiety.[18] However, to the best of our knowledge, ring-expansion of a furanose derivative to a *C*-glycosylated pyranose has not been reported in the literature. In continuation of our investigations on the application of cyclopropanated sugar motifs [6, 19] in the preparation of novel chiral architectures, and in the total synthesis of natural products, herein we disclose an interesting ring-contraction reaction of spiro-cyclopropanecarboxylated sugar scaffolds to give keto-furanose derivatives, as well as a ring-expansion methodology for the diastereoselective synthesis of sugar-fused bicyclic systems.

2.2 Results and Discussion

2.2.1 Synthesis of exo-cyclic glycals

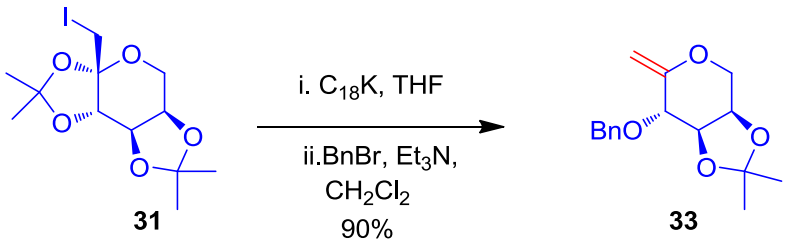
Exo-cyclic glycals are synthetic precursors for the synthesis of spiro-cyclopropane carboxylated sugars. Sugar derived (glucose, fructose, rhamnal, xylose, arabinose, ribose) lactones and iodo compounds are versatile starting materials for the preparation of *exo*-cyclic olefins. We began the synthesis of *exo*-glycals starting from D-fructose **30**. Stirring a suspension of **30** in acetone in presence of catalytic concentrated sulphuric acid provided the

2,3:4,5-di-*O*-isopropilidene-β-D-fructopyranose, that was treated with iodine, triphenylphosphine and imidazole to provide the corresponding 1-deoxy-1-iodo-2,3:4,5-di-*O*-isopropylidene-β-D-fructopyranose **31** in 92% yield. A one-pot $C_{18}K$ mediated olefin formation followed by TBS protection of the generated hydroxyl group led to the formation of *exo*-glycal **32** in 90% yield (Scheme 2.12). [20]



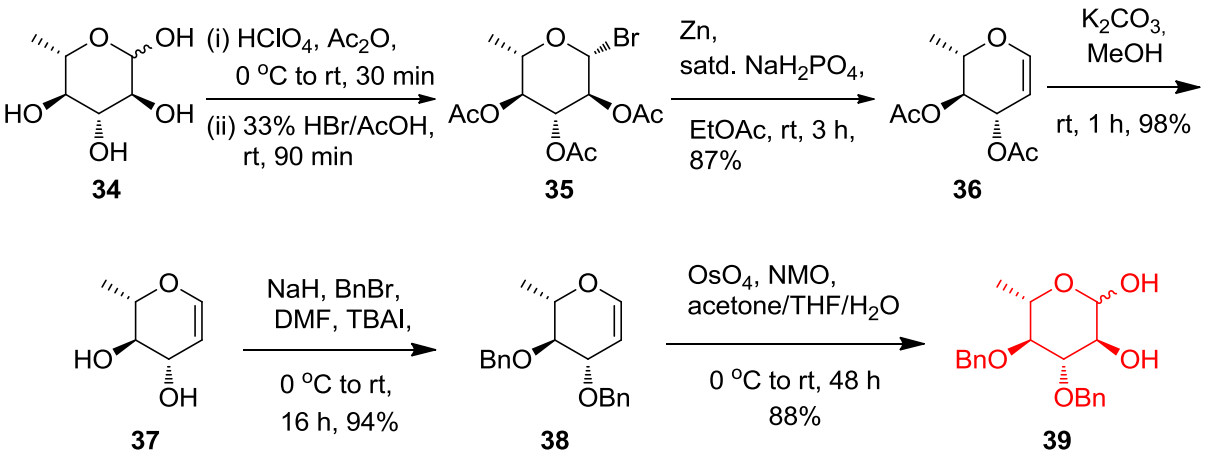
Scheme 2.12: Synthesis of *exo*-cyclic olefin (adjacent to the OTBS group) from fructose.

By using above procedure benzyl protected *exo*-cyclic olefin **33** was also prepared from compound **31** by exposing it to $C_{18}K$ in THF followed by addition of benzyl bromide in presence of triethylamine at 0 ^{o}C (Scheme 2.13).



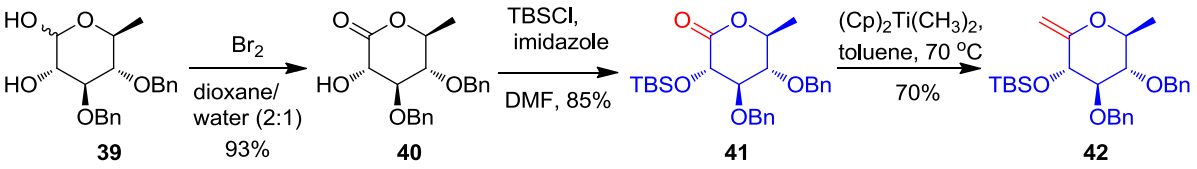
Scheme 2.13: Synthesis of *exo*-cyclic olefin (adjacent to the OBn group) from fructose.

A different protocol was followed for the preparation of L-rhamnol derived *exo*-glycal. Initially, L-rhamnose was converted to L-rhamnal using refined Fisher[21-23] The peracetylation of L-rhamnose **35** with acetic anhydride in presence of catalytic perchloric acid gave a clear solution of tetra-*O*-acetyl-L-rhamnose, which was directly treated in the same flask with 33% hydrobromic acid in acetic acid to provide the tri-*O*-acetyl-bromo-L-rhamnoside **35**. Reductive elimination of this with zinc and saturated NaH_2PO_4 gave the 3,4-di-*O*-acetyl-L-rhamnal **36** in good yield.[23] To incorporate the stable protecting groups in **36**, acetyl groups were deprotected using K_2CO_3 in methanol[24] to give 3,4-dihydroxy L-rhamnal **37**, which upon benzylation with benzyl bromide and sodium hydride provided the 3,4-di-*O*-benzyl-L-rhamnal **38** (Scheme 2.3) in 94% yield. Dihydroxylation of rhamnal **38** with OsO_4, and NMO provided the hemiacetal **39** in good yield (Scheme 2.14).[25]



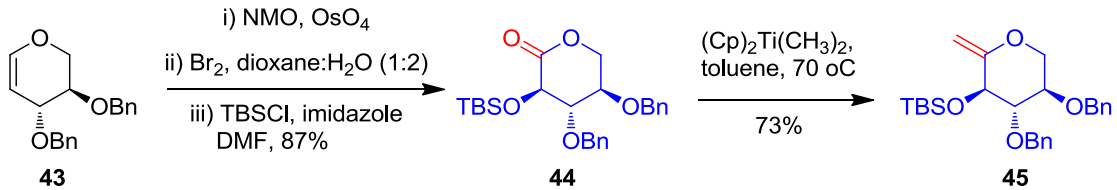
Scheme 2.14: Preparation of the 1,2-dihydroxy 3,4-di-*O*-benzyl-L-rhamnal from L-rhamnose.

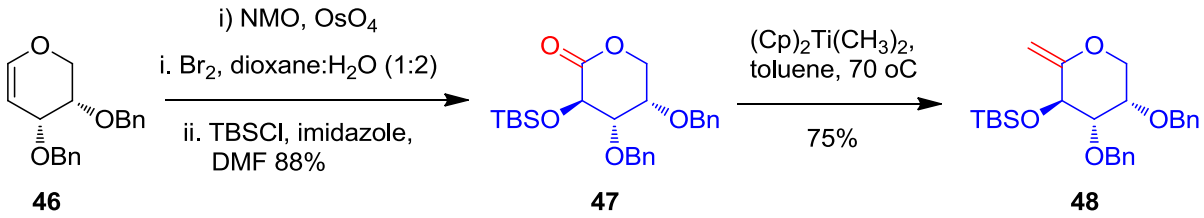
Selective oxidation of hemiacetal **39** by using bromine, dioxane-water followed by quenching the reaction with $BaCO_3$ afforded the hydroxy lactone **40**.[26] TBS protection of the secondary alcohol in 40 using TBSCl, imidazole in dimethylformamide provided the lactone **41** in 85% yield. Exposing the lactone **41** Petasis reagent[27] in toluene gave the *exo*-glycals **42** in 70% yield (Scheme 2.15).



Scheme 2.15: Synthesis of *exo*-cyclic olefin adjacent to the OTBS group from L-rhamnose.

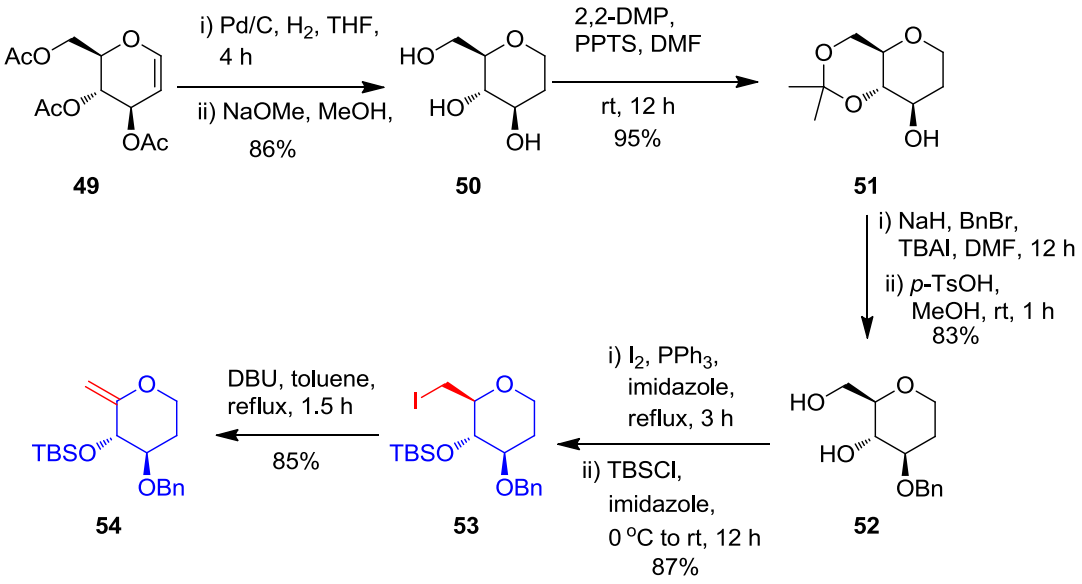
Adopting the above two protocols, **45** and **48** were synthesized from D-xylose and L-arabinose *via* intermediate lactones **44** and **47** which intern were synthesized from D-xylal **43** and L-arabinal **46** (Scheme 2.16).





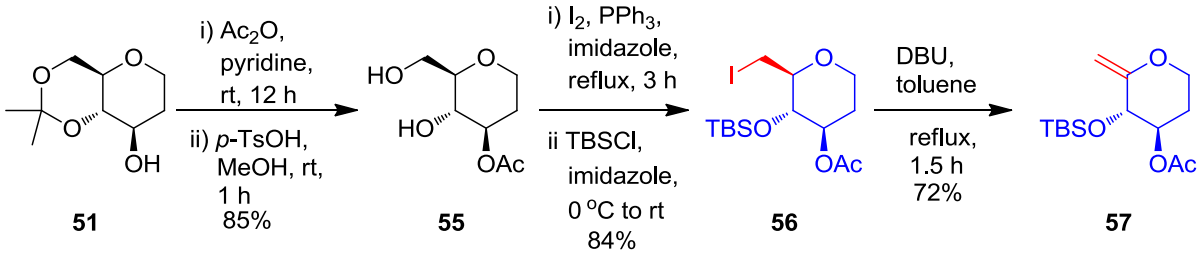
Scheme 2.16: Synthesis of *exo*-cyclic olefins (45 and 48) adjacent to the OTBS group from D-xylose and L- arabinose.

Towards the investigation of the effect of substituents on pyranose ring we planned to synthesize a series of deoxysugar derived *exo*-glycal derivatives. Thus, triacetyl glucal **49** was hydrogenated and the acetate were deprotected to get the triol **50**. Regioselective protection of 4-OH and 6-OH hydroxyls using 2,2-dimethoxypropane (DMP) in presence of catalytic PPTS provided the acetonide **51**. Benzylation of the 3-OH followed by deprotection of the acetonide afforded the corresponding 4,6-diol **52** in good yield.[28] Iodination[29] of the primary hydroxyl followed by protection of the secondary alcohol with TBS gave the iodide **53** which upon dehydrohalogenation with 1,8- diazabicyclo[5.4.0]undec-7-ene (DBU) in toluene[30] provided the *exo*-cyclic olefin **54** in 85% yield (Scheme 2.17).



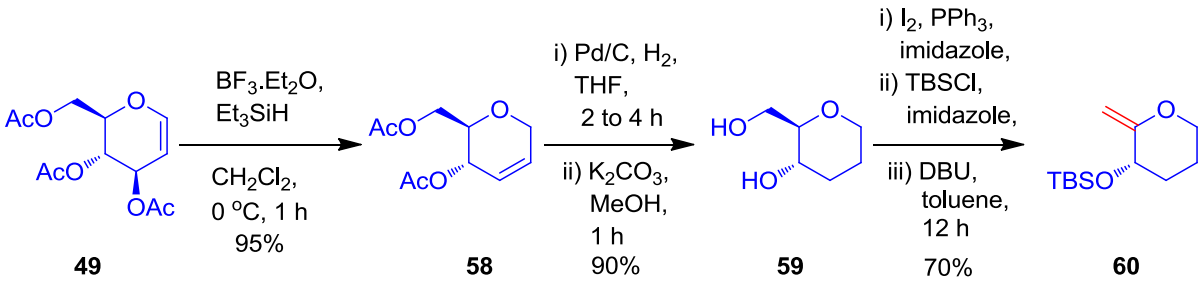
Scheme 2.17: Synthesis of 1,2 dideoxy *exo*-cyclic olefin from D-glucose.

On the other hand, acetylation of the secondary hydroxyl group in compound **51** with acetic anhydride in pyridine[31] and subsequent deprotection of the acetonide with *p*-toluene sulphonic acid in methanol afforded compound **55**. Substitution of the primary hydroxyl with iodide followed by TBS protection of the secondary alcohol, to give compound **56**, and finally dehydrohalogenation with DBU furnished the *exo*-glycal derivative **57** in 72% yield (Scheme 2.18).



Scheme 2.18: Synthesis of 1,2-dideoxy *exo*-cyclic olefin from D-glucose.

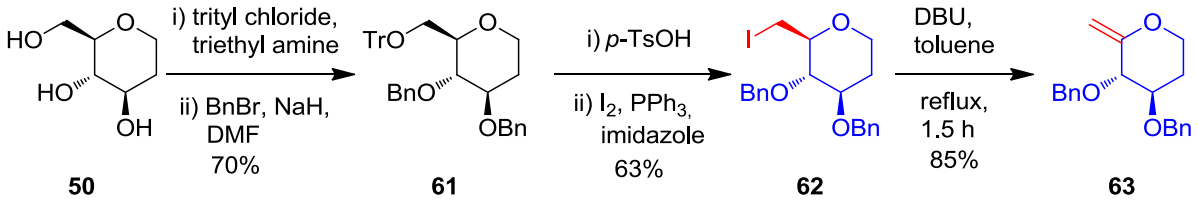
Towards the preparation of 1,2,3-trideoxy exo-glycal, compound **49** was subjected to Ferrier rearrangement with triethylsilane using borontrifluoride etherate as a Lewis acid[32] to give alkene **58**, which on further hydrogenation followed by hydrolysis afforded the diol **59** in good yield. Conversion of the primary alcohol in **59** to olefin and protection of secondary alcohol with TBS to obtain *exo*-glycal **60** was achieved by following the protocol described previously (Scheme 2.19).



Scheme 2.19: Synthesis of 1,2,3-trideoxy *exo*-cyclic olefin from D-glucose.

1,2-dihydroglucal **50** was also converted to the benzyl protected *exo*-glycal **63**. In this process, primary hydroxyl in **50** was selectively protected with Trityl group using trityl chloride and treiethylamine[33], then benzylation of the rest of the hydroxyls with benzyl bromide and sodium hydride gave compound **61**. Deprotection of trityl group using *p*-toluenesulphonic in methanol

followed by iodination provided the iodide **62** which was converted to the *exo*-glycal **63** by applying the previous synthetic procedure (Scheme 2.20).

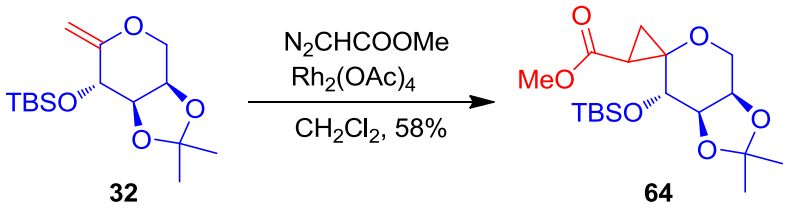


50 **61** **62** **63**

Scheme 2.20: Synthesis of 1,2-di-deoxy *exo*-cyclic olefin from D-glucose.

2.2.2 Synthesis of spiro-cyclopropane carboxylated sugars

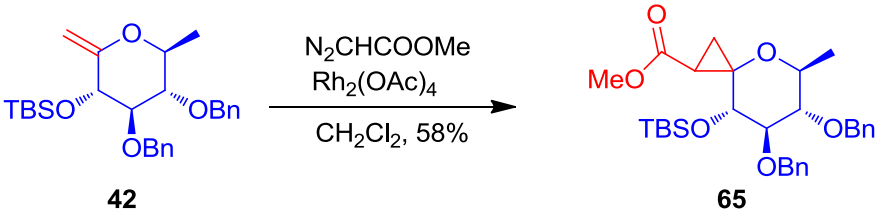
All the spiro-cyclopropane carboxylated sugars were prepared from the corresponding *exo*-cyclic olefin through Rhodium acetate catalysed cyclopropanation methodology using methyldiazoacetate as a reagent. Cyclopropanation of exocyclic-glycal[34] **32** using methyldiazoacetate in CH_2Cl_2 under catalytic $Rh_2(OAc)_4$ conditions provided the spiro-cyclopropane derivative **64** as a mixture of diastereomers[35] in 58% yield (Scheme 2.21).



32 **64**

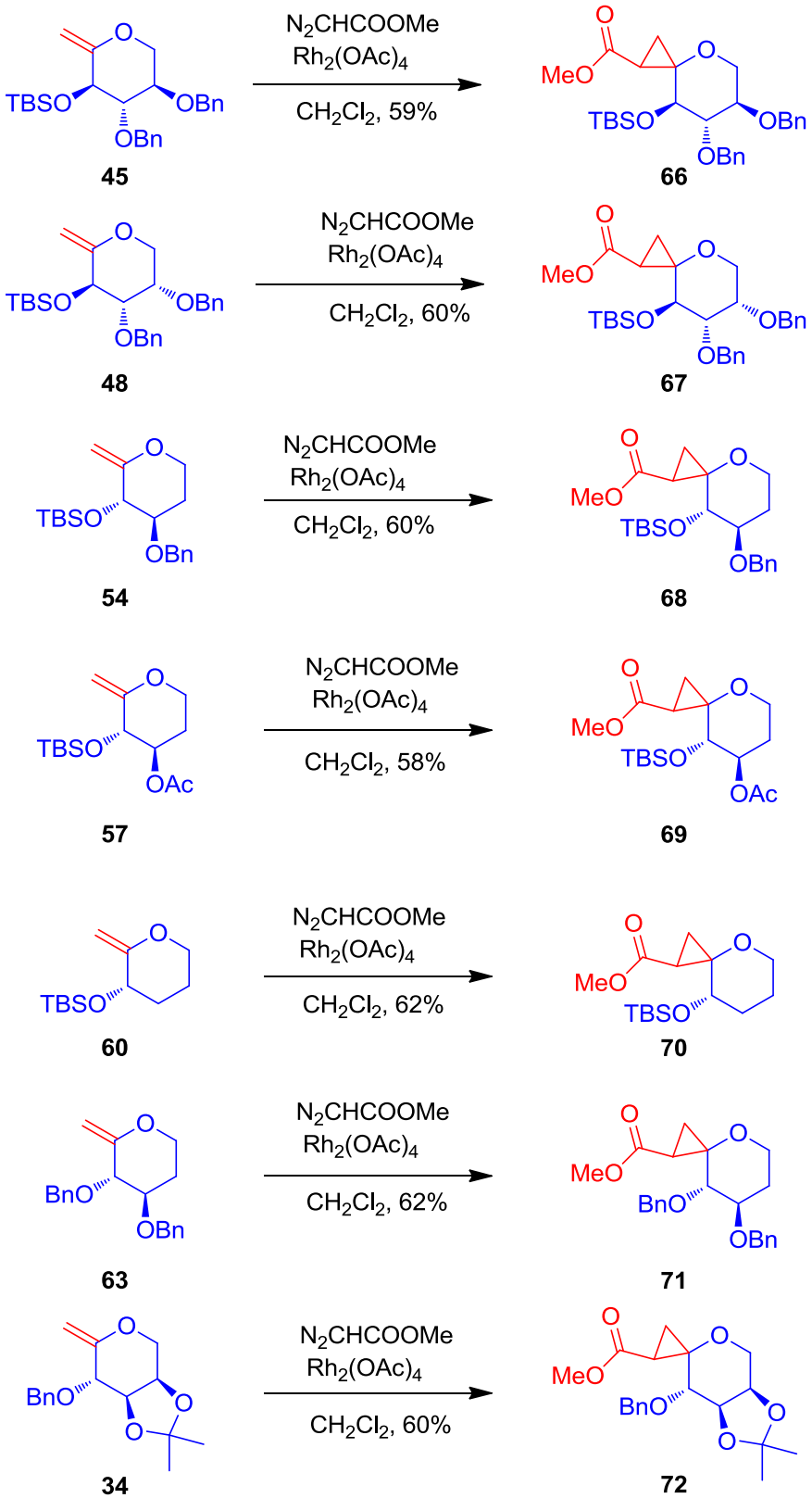
Scheme 2.21: Synthesis of spiro-cyclopropanecarboxylated sugar from *exo*-glycal.

By using the above protocol we synthesised various cyclopropane carboxylated sugars, **65-72**, from the corresponding *exo*-glycals, **42**, **45**, **48**, **54**, **57**, **60**, **63** and **34** respectively (Scheme 2.22).



42 **65**

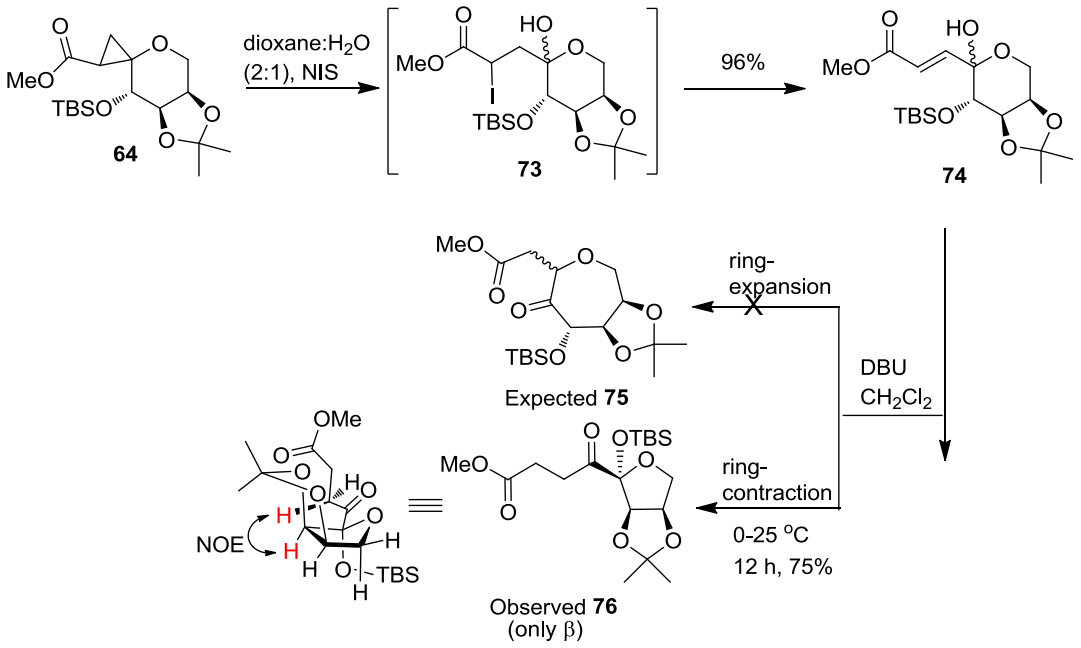
(Continuation)



Scheme 2.22: Synthesis of spiro-cyclopropanecarboxylated sugars 65-72 from various *exo*-glycals.

2.2.3 Ring contraction reaction of spiro-cyclopropanecarboxylated sugar

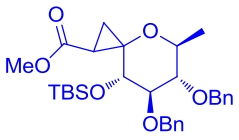
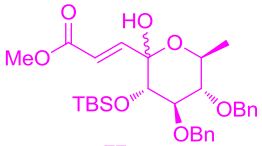
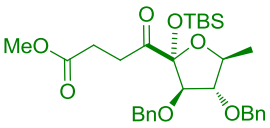
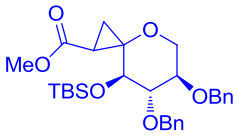
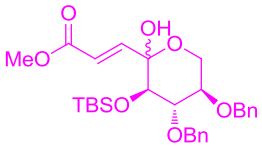
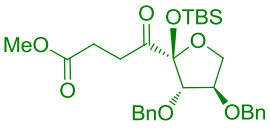
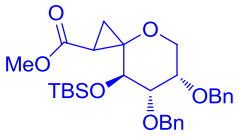
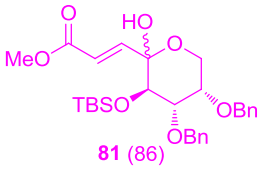
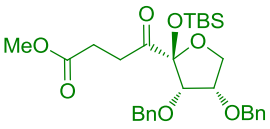
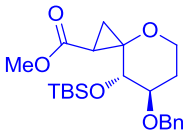
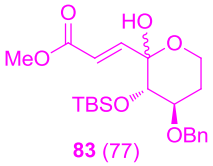
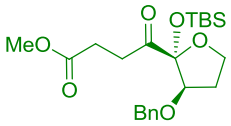
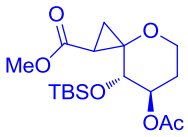
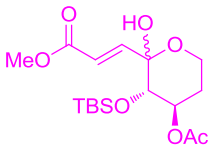
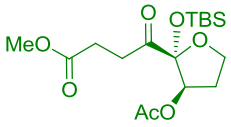
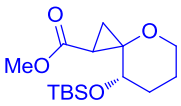
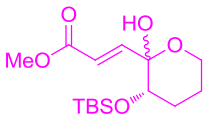
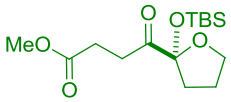
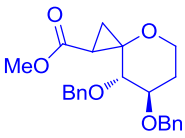
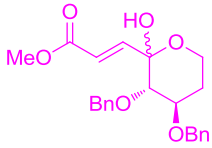
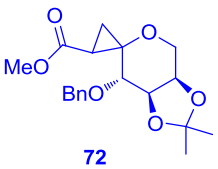
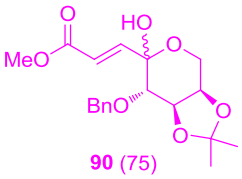
Electrophilic ring-opening of the donor-acceptor cyclopropane **64** with *N*-iodosuccinimide (NIS) in dioxane:water[36] (2:1) provided the α,β-unsaturated ester **74**, through the formation of the iodo-alcohol **73** followed by dehydrohalogenation, in excellent yield. We assumed that compound **74,** under basic conditions, would undergo an intramolecular hetero Michael addition (IHMA) reaction and provide the septanoside derivative **75**. Interestingly, treatment of compound **74** with DBU in CH_2Cl_2 provided **76** as single diastereomer**.** Detailed spectral analysis revealed that the product was a keto-furanose derivative **76** instead of a septanoside **75** (Scheme 2.23). The structure of compound **76**, and stereochemistry at the newly formed quaternary centre, were assigned by observing the NOE between the pseudo-equatorial hydrogen and the methylene group adjacent to the carbonyl group.



Scheme 2.23: Ring-expansion *vs* ring-contraction of a spiroannulated sugar derivative.

The generality of this serendipitous ring-contraction reaction, was investigated by applying it to a series of spiro-cyclopropanecarboxylated sugar derivatives. Thus, compound **65** (table 2.1) was subjected to NIS mediated solvolytic ring-opening to give α,β-unsaturated ester **77** which, upon reaction with DBU in CH_2Cl_2, gave the furanoside **78** as a 1:1 mixture of diastereomers. Similarly, spiro-compounds **66**, **67**, **68**, **69** and **70** upon NIS mediated ring-opening, provided the hemiketals **79**, **81**, **83**, **85** and **87** respectively. Reaction of these hemi ketals with DBU

Table 2.1: Electrophilic ring-opening followed by ring-contraction reaction of spiro-cyclopropanecarboxylated sugar derivatives.

entry	spiro-cyclopropane carboxylate	α,β-unsaturated ester (%)[a]	product[b] (%)[a] (α:β)
1	 **65**	 **77** (80)	 **78** (78) (1:1)
2	 **66**	 **79** (88)	 **80** (78) (4:1)
3	 **67**	 **81** (86)	 **82** (72) (1:4)
4	 **68**	 **83** (77)	 **84** (80) (0:100)
5	 **69**	 **85** (73)	 **86** (65) (30:70)
6	 **70**	 **87** (76)	 **88** (85)[c]
7	 **71**	 **89** (75)	[d]
8	 **72**	 **90** (75)	[d]

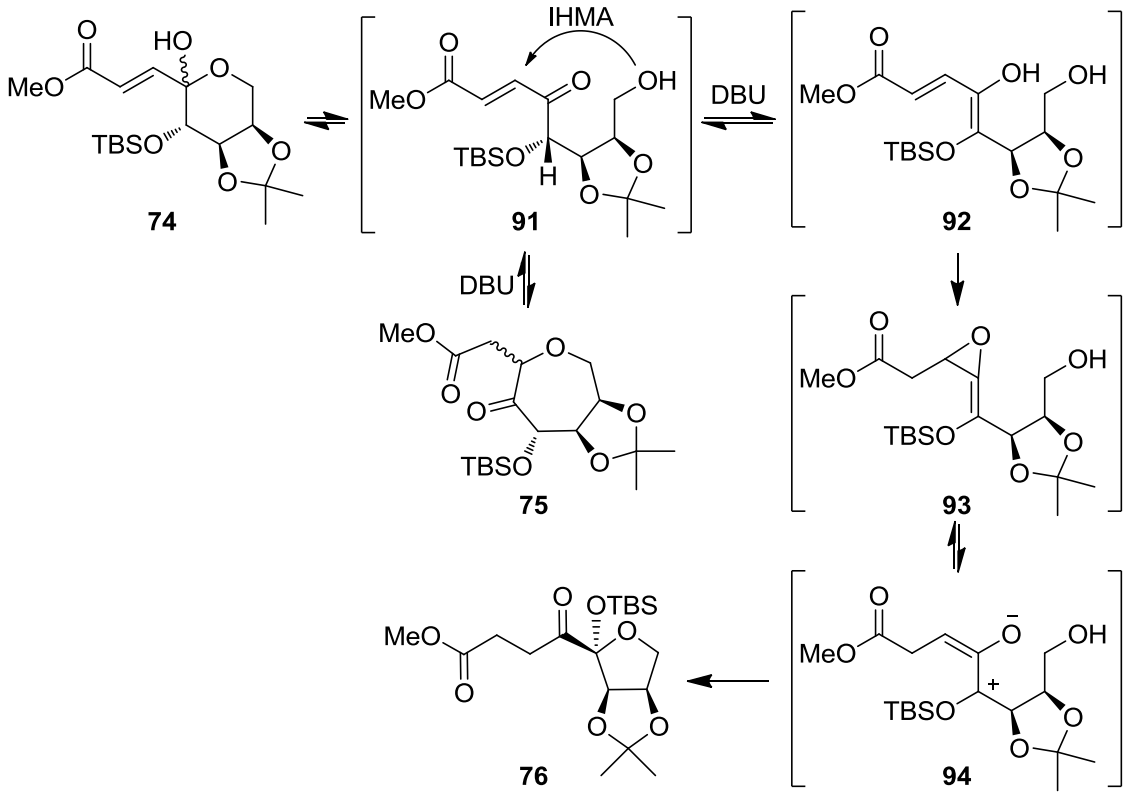
[a]Yield refers pure and isolated products. [b]Major diastereomer is represented. [c] Obtained in 30% ee (by HPLC). Stereochemistry at anomeric centre was not assigned. [d]No product was observed and the starting material was recovered.

resulted the formation of *C*-glycosylated keto-furanose derivatives **80**, **82**, **84, 86** and **88** in good yield and stereoselectivity (Table 2.1, entries 2 to 6). These compounds can serve as excellent synthons for the preparation of bistetrahydrofuran derivatives particularly present in annonaceous acetogenins[37] by selective reduction of the ketone to the alcohol followed by lactonization, as well as furan-annulated spiro-cyclic natural products.[38] Further, anomeric deoxygenation could provide an access to the preparation of *C*-glycoside derivatives.

Implementation of the electrophilic ring-opening reaction on spiroannulated compounds **71** and **72**, in which the protecting group adjacent to the spirocentre was a benzyl group, provided the hemiketals **89** and **90** respectively in good yield. However, treating these compounds with DBU gave neither ring-contracted nor ring-expanded product even after an extended period of time (~3 days) (Table 2.1, entries 7 and 8).

2.2.4 Proposed Mechanism

Based on the above observations, a plausible mechanism is proposed for the formation of the ring-contracted keto-furanoside **76** from the pyranosyl hemiketal **74**. It is believed that cyclic hemiketal **74** exists in equilibrium with hydroxy ketone **91** that likely can undergo intramolecular hetero Michael addition to give ring-expanded septanose **75**. However under the reaction conditions **75** can undergo a reverse Michael addition reaction to give **91**, to set up an equilibrium between **75** and **91**. On the other hand, ketone **91**, under basic conditions, can undergo enolization to form the corresponding enol **92**. Baldwin et al.,[39] reported that enols of type **92** may form favourable allene epoxides instead of cyclopropanone intermediate, which is commonly observed in the classical Favorskii rearrangement.[40] Thus, we assumed that enol **92** could convert to the allene epoxide **93** and this could eventually open to give the planar dipole intermediate **94**.[41] Finally, an intramolecular addition of *O*-nucleophile at the carbocation would provide the ring-contracted furanose derivative **76** (Scheme 2.24). Based on this, we believe that the conversion of hemiketal **74** to keto furanoside **76** depends on the formation of allene epoxide **93**. The driving force for the formation of intermediate **93** may be a consequence of the steric hindrance in intermediate enol **92**. Thus, the presence of a bulky silyloxy group on the enolic carbon might push the enol **92** to form the allene epoxide **93**. On the other hand, when the silyloxy group was replaced with a benzyloxy group (Table 2.1, entries 7 and 8), whereas the steric hindrance would be lower for an OBn compared to an OTBS, the reaction did not proceed further to form the corresponding keto furanoside derivative.

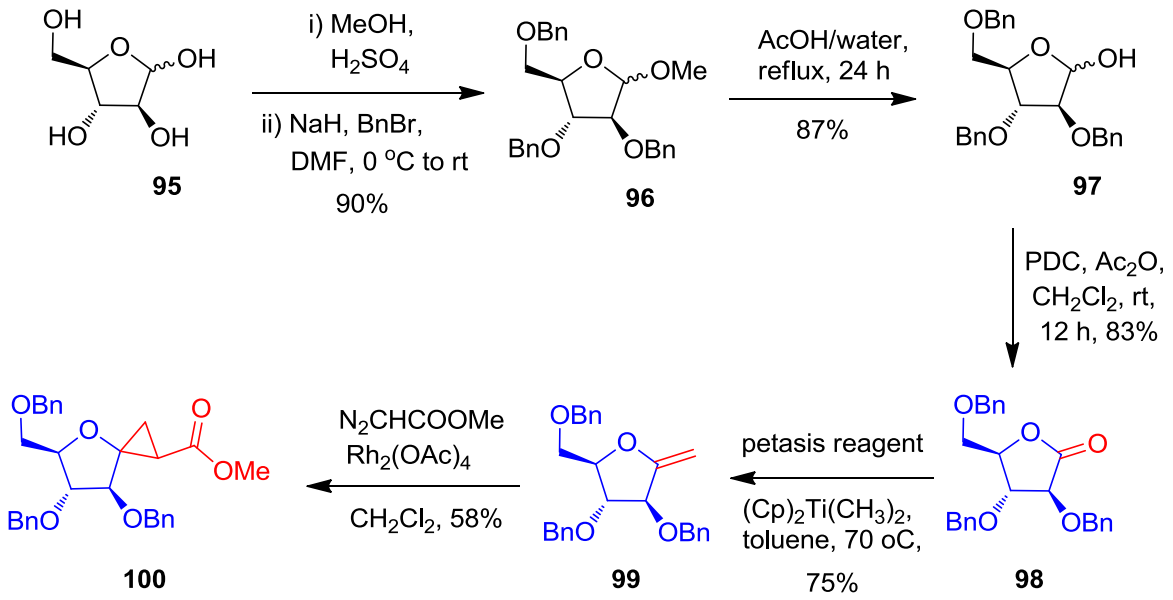


Scheme 2.24: proposed mechanism for the ring-contraction reaction of spiro-cyclopropanecarboxylated sugar.

2.2.4 Ring expansion reactions

2.2.4.1 Synthesis of furanose derived spiro-cyclopropane carboxylated sugars

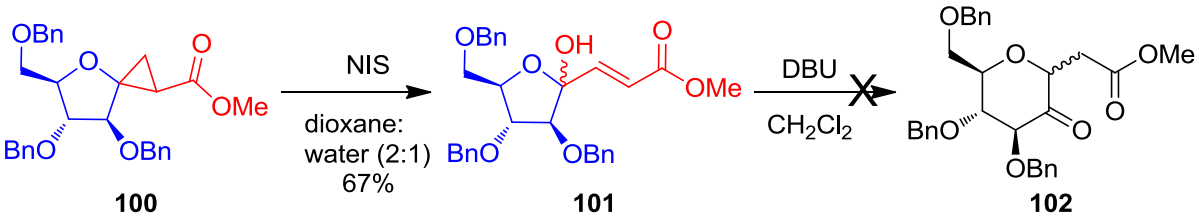
To test the developed methodology in case of five membered rings, our further efforts were focused on the synthesis furan derived spiro-cyclopropane carboxylated sugars from the corresponding *exo*-glycals. In this direction, methyl 2,3,5-tribenzyl-D-arabinofuranose **96** was prepared from D-arabinose **95** by anomeric methylation with MeOH, and catalytic amount of con. sulphuric acid[42] and further benzylation of the rest of the alcohols using benzyl bromide and NaH. Hydorlysis of the acetal in **96** using acetic acid/water under reflux provided hemiacetal **97** as mixture of anomers in good yield.[43] Oxidation of this with pyridinium dichromate (PDC) and acetic anhydride[44] provided the arabino lactone **98**. Finally olefination of the lactone using Petasis reagent provided *exo*-cyclic olefin **99**, which upon cyclopropanation with methyl diazoacetate under catalytic $Rh_2(OAc)_4$ conditions provided the spiro-cyclopropane carboxylated sugar **100** in good yield (Scheme 2.25).



Scheme 2.25: Synthesis of furanose derived spiro-cyclopropanecarboxylate sugar.

2.2.4.2 Ring expansion of spiro-cyclopropane carboxylated sugar

Keeping the previous experience with respect to the pyranose derived spiro-cyclopropanecarboxylated sugars in mind, we envisaged that replacing the spiroannulated pyran with a furan moiety might give the five membered hemi-ketal, upon NIS mediated ring-opening, which could then undergo a ring-expansion to a pyran derivative. Thus, compound **100** was subjected to electrophilic ring-opening to give the furanosyl-hemiketal **101** in 67% yield. However, compound **101** did not provide the expected ring expansion product **102** in presence of DBU (Scheme 2.26).



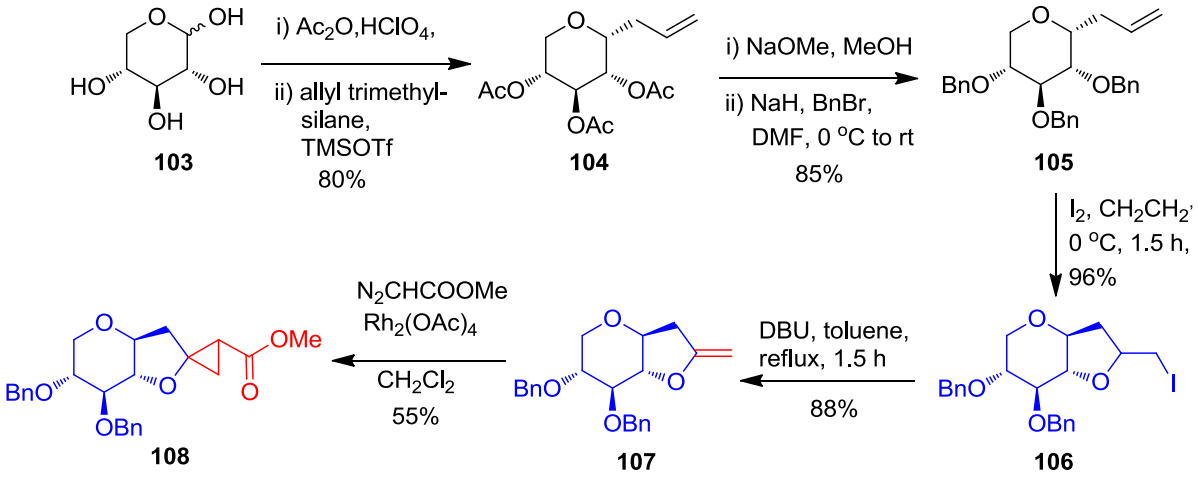
Scheme 2.26: Ring expansion of furanose derived spiro-cyclopropane carboxylated sugar.

The reason for the lack of reactivity of compound **101** is certainly due to its higher stability in the furanose form compared to the keto-pyranose **102**. Hence, we speculated that, decreasing

the flexibility of furanose-hemiketal might give rise to the ring-expansion product. So we planned to synthesize fused bicyclic spiro-cyclopropanecarboxylated sugars.

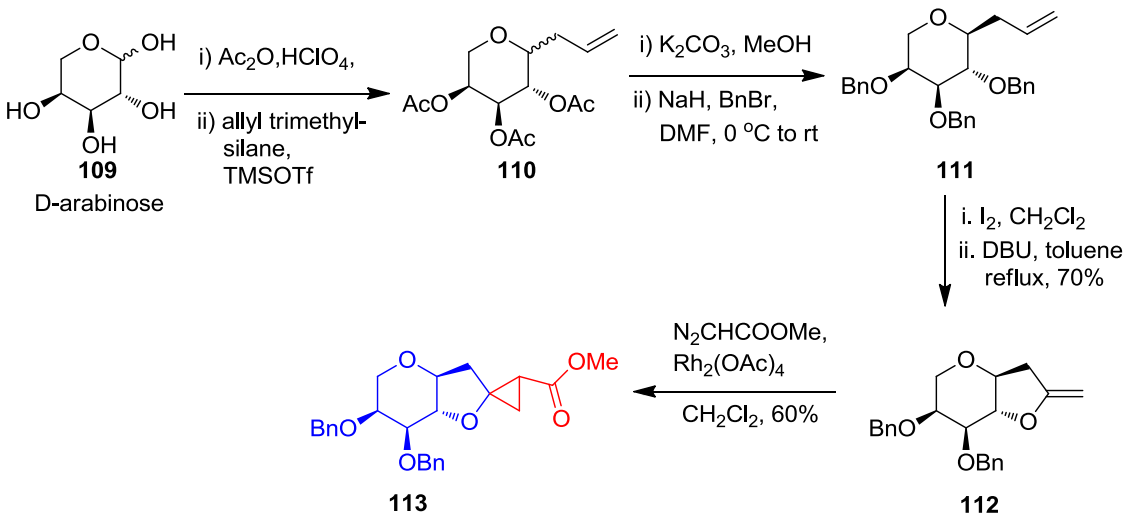
2.2.4.3 Synthesis of fused bicyclic spiro-cyclopropanecarboxylated sugars

Accordingly our synthesis started from commercially available D-xylose **103**. Peracetylation of D-xylose with perchloric acid, followed by allylation with allytrimethylsilane[45] provided *C*-glycoside derivative **104**. Potassium carbonate mediated deacetylation of **104**, subsequent benzylation with BnBr and NaH gave 1-allyl-2,3,4-tri-*O*-benzy-β-D-xylopyranose l**05** in good yield. Iodine mediated cyclization[46] of compound **105**, resulted the formation of bicyclic compound **106**, which was subjected to DBU mediated dehydrohalogenation to give olefin **107** in good yield. Spiro-cyclopropanecarboxylated fused bicycle **108** (Scheme 2.16) was synthesized by cyclopropanation of the *exo*-cyclic vinyl-ether **107** with methyldiazoacetate and rhodium acetate in dichloromethane in 55% yield (Scheme 2.27).



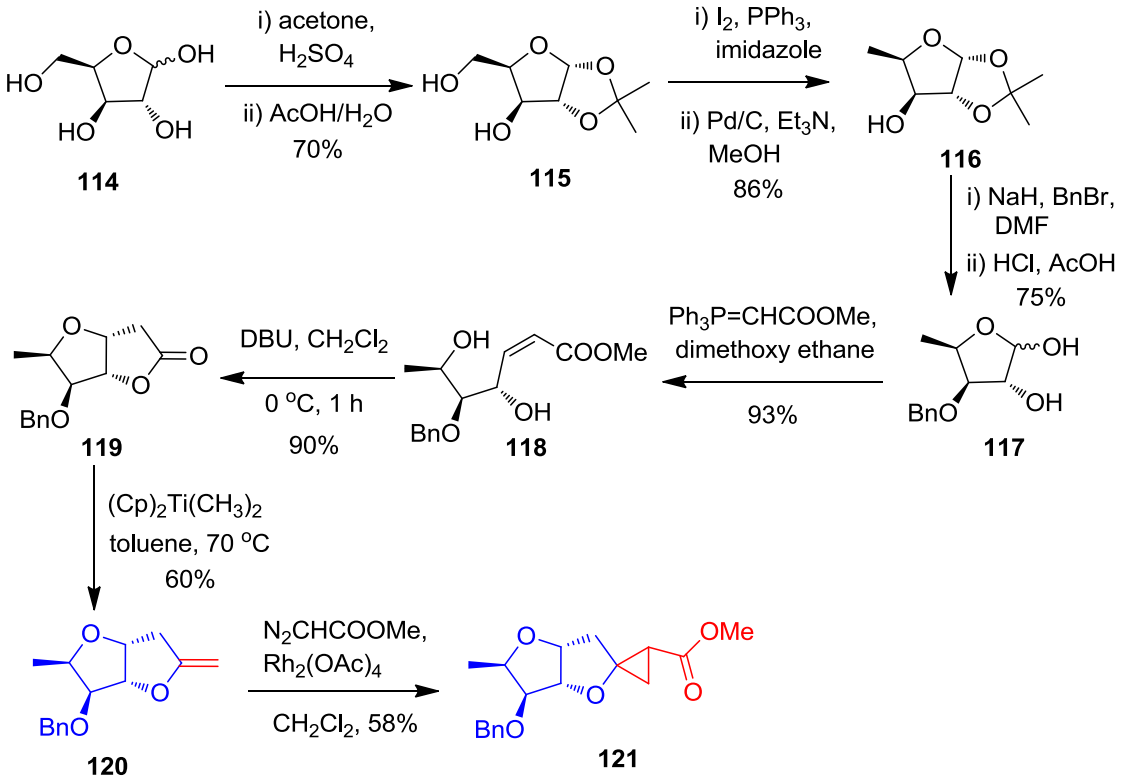
Scheme 2.27: Synthesis of fused bicyclic spiro-cyclopropanecarboxylated sugar from D-xylose.

In a similar fashion fused bicyclic spiro-cyclopropanecarboxylated sugar **113** was synthesized from D- arabinose **109** via the formation of tri-acetyl C-glycoside **110**, tri-benzyl *C*-glycoside **111** and *exo*-cyclic vinylether **112** (Scheme 2.28). Cyclopropanation of vinylether with methyldiazoacetate catalytic amount of rhodium acetate in dichloromethane to provide the fused bicyclic spiro-cyclopropanecarboxylated sugar **113** in 60% yield. These fused spiro systems are further useful in ring expansion reaction, which were discussed in below schemes.



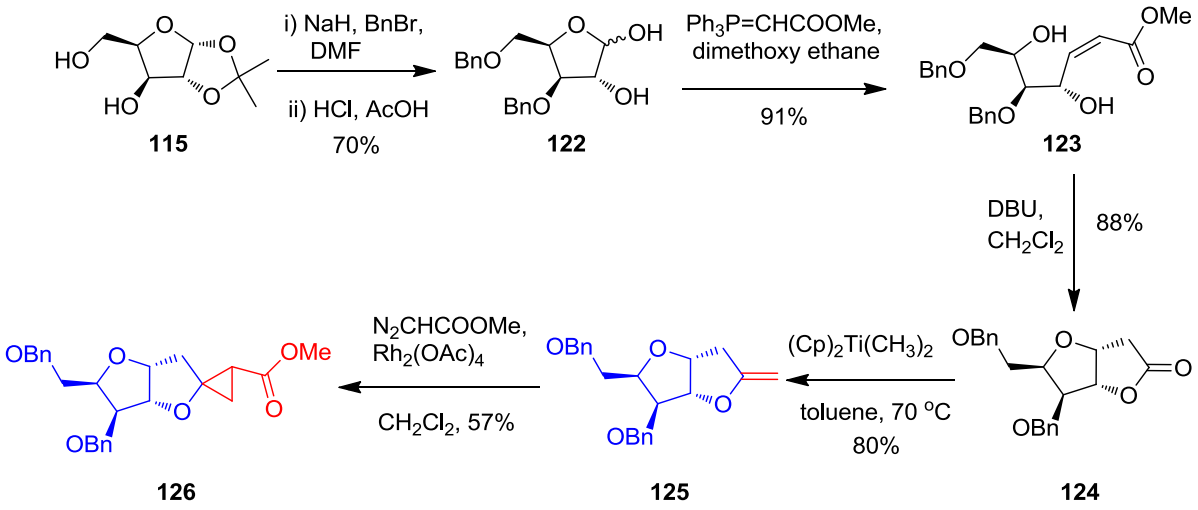
Scheme 2.28: Synthesis of fused bicyclic spiro-cyclopropanecarboxylated sugar from D-arabinose.

Another interesting two more bicyclic spiro-cyclopropanecarboxylated sugars were synthesized from D-xylose. Diacetonide protection of D-xylose **114,** with acetone in presence of 18 N sulphuric acid to provide the corresponding 1,2:3,5-diacetonide-D-xylose, which upon selective deprotection of acetonide [47] at 3,5 position with AcOH/H_2O gave the mono acetonide compound **115**. Conversion of primary hydroxyl to the corresponding iodide using iodine, PPh_3 and imidazole, subsequent palladium/carbon catalyzed dehalogenation with H_2 in methanol[48] afforded the compound **116** in good yield. Towards the formation of bicyclic lactone, benzylation of secondary hydroxyl group in 116 with NaH and BnBr followed by deprotection of acetonide with HCl and acetic acid[49] to give the corresponding diol **117**, which upon treated with methoxy carbonyl methylene triphenylphophorane[50] in dry dimethoxy ethane (DME) gave the α,β-unsaturated ester **118**, instead of cyclized lactone **119 (**only small amount of lactone was obtained with this Wittig reagent) (Scheme 2.29). However, for complete conversion we treated compound **118** with DBU in dichloromethane at 0 °C, and all the ring opened unsaturated ester was completely converted to the required bicyclic lactone **119** in good yield. Finally this lactone was transferred to the *exo*-cyclic vinyl-ether **120** by using Petasis reagent, which on further cyclopropanation with above established protocol afforded the bicyclic spiro-cyclopropanecarboxylated sugar **121** in 58% yield (Scheme 2.29).



Scheme 2.29: Synthesis of fused bicyclic spiro-cyclopropanecarboxylated sugar from D-xylose.

Mono acetonide **115** was also used to make another bicyclic spiro-cyclopropanecarboxylated sugar derivative according to the scheme 2.30. In this sequence, **115** was benzylated and then the acetonide was deprotected using HCl, AcOH to afford hemiacetal **122** in 70% yield. Wittig

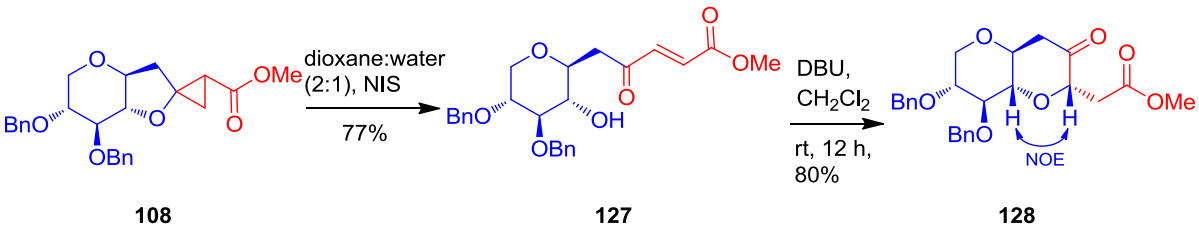


Scheme 2.30: Synthesis of fused bicyclic spiro-cyclopropanecarboxylated sugar from D-xylose.

olefination of **122**, to give unsaturated ester **123**, followed by DBU mediated cyclization reaction provided the bicyclic lactone **124**. Olefination of the lactone to *exo*-cyclic vinyl ether **125** and cyclopropanation of this double bond provided the By using above procedures (scheme 2.29) spiro-cyclopropanecarboxylated sugar **126** was synthesized from ring opened hydroxy α,β-unsaturated ester **123** with known procedures.

2.2.4.4 Stereoselective synthesis of fused pyrano or furo[3,2-b]pyrans

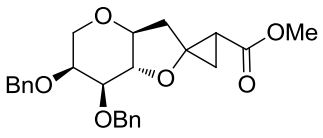
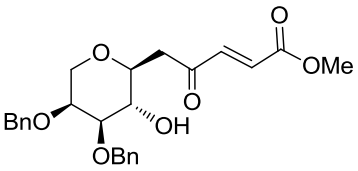
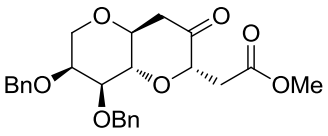
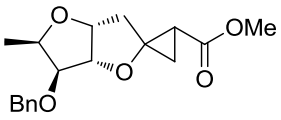
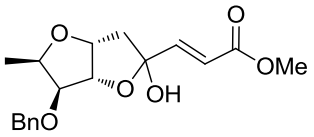
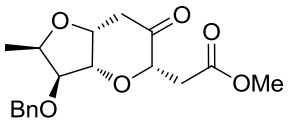
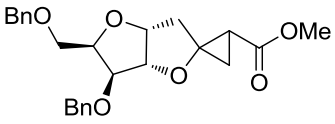
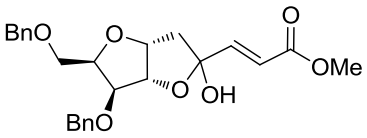
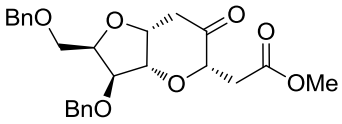
Exposure of compound **108** to NIS resulted in *C*-glycoside **127** which, upon reaction with DBU, provided the expected ring-expanded bicyclic-pyrano[3,2-b]pyran derivative **128** as a single diastereomer. The stereochemistry at the newly formed chiral centre was assigned from the NOE between the 1,3-diaxial hydrogen atoms present in bicycle **128** (Scheme 2.31).



Scheme 2.31: Ring-expansion of spiro-cyclopropanecarboxylated sugar derivative

Similarly, the spiroannulated sugar derivative **113**, upon electrophilic ring-opening, provided the *C*-glycoside **129** which smoothly ring-expanded to the bicyclo-pyrano[3,2-b]pyran derivative **130** in excellent yield upon exposure to DBU (Table 2.2, entry 1). On the other hand, reaction of cyclopropanecarboxylated furo[3,2-b]furan derivatives **121** and **126** with NIS provided exclusively the bicyclic hemiketals **131** and **133**. However, in presence of DBU these hemiketals, furnished the expected ring-expansion products **132** and **134** respectively, in good yield. This type of bicyclo-tetrahydrofuro or pyrano[3,2-b]pyran ringsystems are present in a number of bioactive natural products.[51] The present ring-expansion methodology will provide a straightforward access to this kind of bicyclic architecture from inexpensive sugar-based raw materials.

Table 2.2: Stereoselective synthesis of fused pyrano or furo[3,2-b]pyrans from spiro-cyclopropanecarboxylated sugar derivatives.

entry	spiro-cyclopropane carboxylate	α,β-unsaturated ester (%)a	product (%)a,b
1	 **113**	 **129** (75)	 **130** (84)
2	 **121**	 **131** (82)	 **132** (70)
3	 **126**	 **133** (85)	 **134** (70)

[a]Yield refers pure and isolated products. [b]Only a single diastereomer was obtained.

2.3 Conclusion:

In conclusion, an interesting ring-contraction of spiro-cyclopropanecarboxylated sugar derivatives to keto-furanoses, involving NIS mediated electrophilic ring opening followed by a DBU mediated cyclisation reaction, has been discovered. The generality of this methodology was investigated and a plausible mechanism for the process was proposed. Additionally, a ring-expansion protocol for the diastereoselective synthesis of fused pyrano or furo[3,2-b]pyran frameworks has been developed. Further investigations and applications of this methodology in the synthesis of bioactive natural products are in progress.

2.4 Experimental section

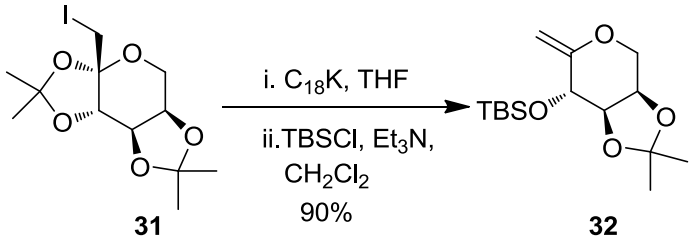
2.4.1 General Information

All the reactions were carried out under nitrogen or argon 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. All the chemicals were purchased from local suppliers and Sigma-Aldrich Chemicals Company. Solvents used in the reactions were distilled over dehydrated agents. Silica-gel (100-200 mesh) was used for column chromatography. ^{1}H, ^{13}C, DEPT, COSY, NOESY spectra were recorded on Bruker 400 MHz and 500 MHz spectrometer in $CDCl_3$. ^{1}H NMR chemical shifts were reported in ppm (δ) with TMS as internal standard (δ 0.00) and ^{13}C NMR were reported in chemical shifts with solvent reference ($CDCl_3$, δ 77.00). High resolution mass spectra (HRMS) were obtained in the ESI mode.

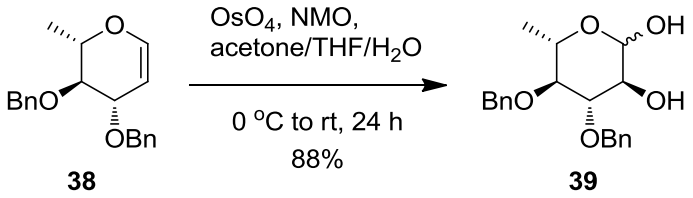
2.4.2 Experimental Procedures and spectral data

(2.4.2.1) *tert*-butyl(((3a*R*,7*S*,7a*R*)-2,2-dimethyl-6-methylenetetrahydro-3a*H*-[1,3]dioxolo[4,5-c]pyran-7-yl)oxy)dimethylsilane:



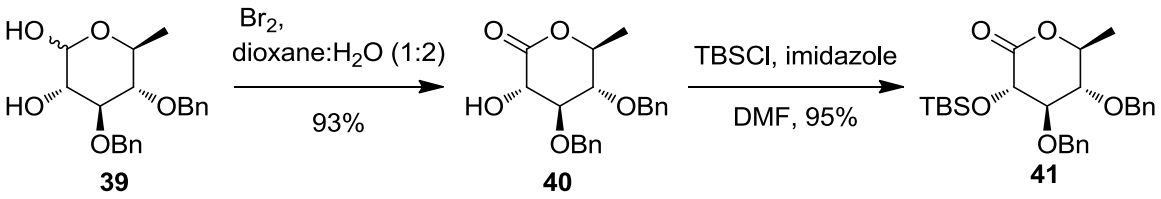
To a stirred suspension of $C_{18}K$ (22.2 mmol) in THF (40 mL) was added a solution of 1-deoxy-1-iodo-2,3:4,5-di-*O*-isopropylidene-β-D-fructopyranose[1] **31** (3.70 g, 10.0 mmol) under argon at 0 °C. After 10 min *tert*-butyldimethylsilyl chloride (3.0 g, 20 mmol) was added and the stirring was continued for further 15 min at same temperature. After completion of reaction triethyl amine (7 mL, 50 mmol) was added to quench the reaction and the suspension was filtered and the filtrate was concentrated and the obtained residue was subjected to column chromatography to give 2,6-anhydro-3-*O*-*tert*-butyldimethylsilyl-1-deoxy-4,5-*O*-isopropylidene-D-arabino-hex-1-enitol **32** (2.7 g) in 90% yield. **^{1}H NMR (400 MHz, $CDCl_3$)**: δ 4.39 (s, 1H), 4.32-4.37 (m, 1H), 4.35 (s, 1H), 4.22 (dd, 1H, *J* = 2.8 Hz, *J* = 7.6 Hz), 4.18 (bs, 1H), 4.11 (d, 1H, *J* = 2.8 Hz), 4.06 (s, 1H), 4.02 (dd, 1H, *J* = 2.0 Hz, *J* = 12.4 z), 1.44 (s, 3H), 1.31 (s, 3H), 0.85 (s, 9H), 0.09 (s, 3H), 0.07 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 160.4, 109.7, 90.5, 74.9, 72.4, 70.0, 63.9, 26.3, 25.9, 24.4, 17.9, -4.6, -5.0. **HRMS (ESI)** calcd for $C_{15}H_{28}O_4Si$+H 301.1835, found 301.1837.

(2.4.2.2) (3*S*,4*S*,5*S*,6*S*)-4,5-bis(benzyloxy)-6-methyltetrahydro-2*H*-pyran-2,3-diol:



To a stirred sollution of rhamnal **38** (2.89 g, 9.32 mmol) and N-methylmorpholine-N-oxide (1.417 g, 12.11 mmol) in a mixture of acetone (17 mL), tetrahydrofuran (6 mL), and water (3.5 mL) at 0 °C, was added osmium tetraoxide (54.46 mg, 12.11 mmol) in two portions over 10 minutes. The resulting mixture was allowed to warm to come to rt over 1 h and then stirred for 24 h. After completion of the reaction confirmed b TLC analysis (40% EA/Hexane) was cooled to 0 °C, and carefully quenched with saturated sodum thiosulfhate (10 mL) stirred for 30 minutes and then filtered through a pad of silicagel on celite. The layers were seperated and aqueous layer were extract with ethyl acetate (3 x 50 mL). The combined organic extracts were washed with saturated sodium thiosulfate, brine and dried over Na_2SO_4. The crude prodct was purified by column chromatography to afford the dihyroxy compound **39** (2.9 g) in 88% yiled as mixture of anomeric diastereomers.

(2.4.2.3) (3*S*,4*R*,5*S*,6*S*)-4,5-bis(benzyloxy)-3-((*tert*-butyldimethylsilyl)oxy)-6-methyltetrahydro-2*H*-pyran-2-one:

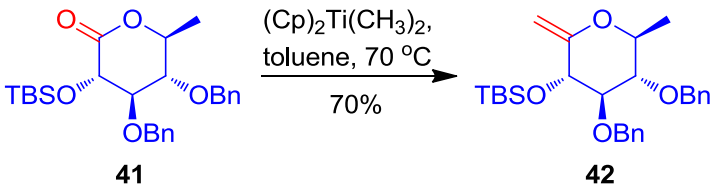


To a solution of 3,4-di-*O*-benzyl-L-arabinopyranose **39** (2.0 g, 6.06 mmol) in dioxane/H_2O 1:2 (70 mL) was added $BaCO_3$ (1.62 g, 8.24 mmol). The mixture was cooled to 0 °C, and bromine (1.73 mL, 46.70 mmol) was added drop wise. The reaction mixture was stirred for 1.5 h in the dark while allowing it to reach 25 °C. The mixture was then cooled to 0 °C again and neutralized with Na_2CO_3. To destroy the bromine, $Na_2S_2O_3$ was added until a white precipitate was formed. The reaction mixture was filtered over celite, and the solvents were evaporated. The residue was dissolved in EtOAc and washed with brine, dried over $MgSO_4$, filtered, and concentrated, Column chromatography with EtOAc/Hexane 1:1 gave 3,4-di-*O*-benzyl-L-arabinolactone **40** (1.85 g) in 93% yield. **^{1}H NMR (400 MHz, $CDCl_3$)**: δ 7.22-7.46 (m, 10H), 4.68-4.85 (m, 5H),

4.44-4.48 (m, 1H), 4.14-4.17 (m, 1H), 3.92-3.98 (m, 1H), 3.79-3.87 (m, 1H). **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 172.9, 137.6, 137.3, 131.6, 129.3, 128.5, 127.8, 77.9, 72.5, 72.2, 72.0, 70.3, 68.6. **HRMS (ESI)** calcd for $C_{19}H_{20}O_5$+Na 351.1208, found 351.1205.

To a solution of 3,4-di-*O*-benzyl-L-arabinolactone **40** (1.5 g, 4.57 mmol) in DMF (10 mL) at 0 °C was added imidazole (1.55 g, 22.86 mmol) followed by *tert*-butyldimethylsilyl chloride (1.72 g, 11.42 mmol). The reaction mixture was stirred for overnight at room temperature. DMF was removed under vacuum, and to the residue was added CH_2Cl_2 (80 mL) and water (100 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 20 mL). The combined organic layers were washed with water and brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by silica column chromatography with EtOAc/hexane to afford 3,4-di-*O*-benzyl-2-*O*-*tert*-butyldimethylsilyl-L-arabinolactone **41** (1.9 g) in 95% yield. **^{1}H NMR (400 MHz, $CDCl_3$)**: δ 7.31-7.36 (m, 10H), 4.67-4.68 (m, 4H), 4.50 (d, 1H, *J* = 8.0 Hz), 4.38 (dd, 1H, *J* = 4.4 Hz, *J* = 12.0 Hz), 4.09 (dd, 1H, *J* = 2.8 Hz, *J* = 12.0 Hz), 3.96-3.97 (m, 1H), 3.76 (dd, 1H, *J* = 2.0 Hz, *J* = 8.0 Hz), 0.91 (s, 9H), 0.18 (s, 3H), 0.14 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 170.5, 137.7, 137.4, 128.5, 128.4, 128.0, 127.9, 127.8, 78.6, 72.7, 71.9, 71.1, 71.0, 67.1, 25.7, 18.3, -4.7, -5.3. **HRMS (ESI)** calcd for $C_{25}H_{34}O_5Si$+Na 465.2073, found 465.2063.

(2.4.2.4) (((3*S*,4*R*,5*S*,6*S*)-4,5-bis(benzyloxy)-6-methyl-2-methylenetetrahydro-2*H*-pyran-3-yl)oxy)(*tert*-butyl)dimethylsilane:

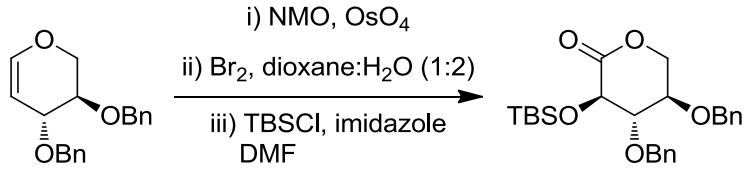


41 **42**

3,4-di-*O*-benzyl-2-*O*-*tert*-butyldimethylsilyl-L-arabinolactone **41** (1.0 g, 2.26 mmol) was dissolved in dry toluene (15 mL) and dimethyl titanocene (3.76 mL of a 20% w/w solution in toluene, 4.52 mmol) was added slowly at room temperature, then the reaction mixture stirred in the dark for 24 h (or until TLC showed disappearance of the starting material) at 70 ^{0}C under argon. The brown reaction mixture was concentrated, and the remaining syrup after dilution with a minimum amount of toluene subjected to column chromatography, on neutral alumina using hexane/ethyl acetate (containing 1% triethylamine) to give the methylenated product **42** (0.75 g) in 70% yield. **^{1}H NMR (400 MHz, $CDCl_3$)**: δ 7.27-7.37 (m, 10H), 4.68 (s, 4H), 4.64

(s, 1H), 4.56 (s, 1H), 4.37 (d, 1H, *J* = 7.2 Hz), 4.03 (dd, 1H, *J* = 5.2 Hz, *J* = 10.8 Hz), 3.89-3.92 (m, 1H), 3.63 (dd, 1H, *J* = 3.2 Hz, *J* = 10.8 Hz), 3.52 (dd, 1H, *J* = 3.2 Hz, *J* = 7.6 Hz), 0.88 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 160.1, 138.5, 138.2, 128.4, 128.3, 127.8, 127.7, 127.5, 95.5, 79.7, 72.7, 72.5, 71.8, 69.9, 67.9, 25.8, 18.1, -4.8, -4.9. **HRMS (ESI)** calcd for $C_{26}H_{36}O_4Si$+Na 463.2281, found 463.2287.

(2.4.2.5) (3*R*,4*S*,5*R*)-4,5-bis(benzyloxy)-3-((*tert*-butyldimethylsilyl)oxy)tetrahydro-2*H*-pyran-2-one :



43 80% **44**

Compound **44** was obtained from compound **43** (4.2 g, 14.18 mmol) in three steps by following the procedure described for compound **41** (2.4.2.3). The crude products were separated by silica-gel column chromatography (ethyl acetate in hexane 2:8) to afford the required lactone in 80% yield.

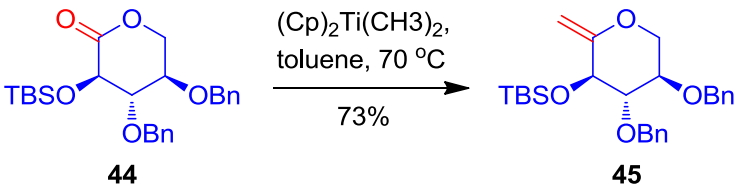
Data for second step (Selective oxidation of anomeric alcohol):

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.20-7.36 (m, 10H), 4.81 (d, 1H, *J* = 12.0 Hz), 4.65 (d, 1H, *J* = 11.6 Hz), 4.56 (d, 1H, *J* = 11.6 Hz), 4.49 (d, 1H, *J* = 11.6 Hz), 4.43-4.45 (m, 1H), 4.35-4.38 (m, 2H), 3.77-3.79 (m, 2H). **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 173.1, 137.3, 136.8, 128.6, 128.5, 128.1, 128.0, 127.8, 82.0, 75.0, 72.3, 72.1, 70.4, 66.2. **HRMS (ESI)** calcd for $C_{19}H_{20}O_5$+Na 351.1208, found 351.1210.

Data for third step(TBS protection):

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32-7.37 (m, 10H), 4.69 (d, 1H, *J* = 11.6 Hz), 4.59 (d, 1H, *J* = 11.6 Hz), 4.56 (d, 1H, *J* = 11.6 Hz), 4.48 (d, 1H, *J* = 11.6 Hz), 4.39-4.43 (m, 1H), 4.28-4.34 (m, 2H), 3.76-3.79 (m, 2H), 0.95 (s, 9H), 0.19 (s, 3H), 0.11 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 170.6, 137.3, 137.1, 128.5, 128.5, 128.0, 127.7, 83.5, 75.3, 72.9, 70.5, 65.2, 25.7, 18.3, -4.6, -5.3. **HRMS (ESI)** calcd for $C_{25}H_{34}O_5Si$+Na 465.2073, found 465.2072.

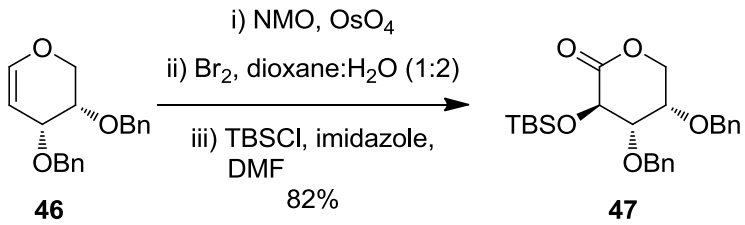
(2.4.2.6) (((3*R*,4*S*,5*R*)-4,5-bis(benzyloxy)-2-methylenetetrahydro-2*H*-pyran-3-yl)oxy)(*tert*-butyl)dimethylsilane:



44 **45**

The compound **45** was synthesized from compound **44** (1.2 g, 2.7 mmol) and dimethyl titanocene (4.5 mL of a 20% w/w solution in toluene, 5.4 mmol) by following the same procedure in **42** (2.4.2.4). The reaction mixture was stirred for 24 h at room temperature. Crude product was purified by silica-gel column chromatography (EtOAc in hexane 1:9) to provide the exocyclic-olefin 4**5** (0.87) as a pale yellow gum (73% yield). **^{1}H NMR (400 MHz, CDCl$_3$)**: δ 7.31-4.37 (m, 10H), 4.85(d, 2H, *J* = 3.2 Hz), 4.67-4.72 (m, 3H), 4.63 (dd, 1H, *J* = 2.8 Hz, *J* = 11.6 Hz), 4.07-4.10 (m, 2H), 3.71-3.77 (m, 1H), 3.48-3.54 (m, 2H), 0.98 (s, 9H), 0.11 (s, 6H). **^{13}C NMR (100 MHz, CDCl$_3$)**: δ 159.9, 138.6, 138.1, 128.4, 128.3, 127.8, 127.7, 127.5, 93.5, 85.4, 77.9, 74.6, 72.9, 72.0, 68.0, 25.8, 18.1, -4.6, -4.8. **HRMS (ESI)** calcd for $C_{26}H_{36}O_4Si$+H 441.2461, found 441.2462.

(2.4.2.7) (3*R*,4*S*,5*S*)-4,5-bis(benzyloxy)-3-((*tert*-butyldimethylsilyl)oxy)tetrahydro-2*H*-pyran-2-one:



46 **47**

Compound **47** was obtained from compound **46** (4.0 g, 13.51 mmol) in three steps following the procedure described for compound **41** (2.4.2.3). The crude products were separated by silica-gel column chromatography to afford the lactone in 82% yield.

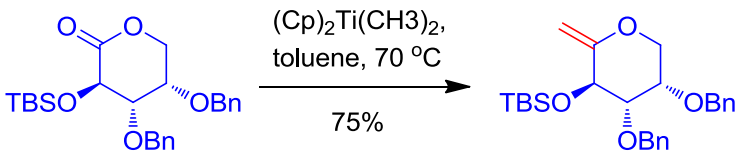
Data for second step (Selective oxidation of anomeric alcohol):

^{1}H NMR (400 MHz, CDCl$_3$): δ 7.22-7.46 (m, 10H), 4.68-4.85 (m, 5H), 4.44-4.48 (m, 1H), 4.14-4.17 (m, 1H), 3.92-3.98 (m, 1H), 3.79-3.87 (m, 1H). **^{13}C NMR (100 MHz, CDCl$_3$)**: δ 172.9, 137.6, 137.3, 131.6, 129.3, 128.5, 127.8, 77.9, 72.5, 72.2, 72.0, 70.3, 68.6. **HRMS (ESI)** calcd for $C_{19}H_{20}O_5$+Na 351.1208, found 351.1205.

Data for third step(TBS protection):

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31-7.36 (m, 10H), 4.67-4.68 (m, 4H), 4.50 (d, 1H, *J* = 8.0 Hz), 4.38 (dd, 1H, *J* = 4.4 Hz, *J* = 12.0 Hz), 4.09 (dd, 1H, *J* = 2.8 Hz, *J* = 12.0 Hz), 3.96-3.97 (m, 1H), 3.76 (dd, 1H, *J* = 2.0 Hz, *J* = 8.0 Hz), 0.91 (s, 9H), 0.18 (s, 3H), 0.14 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 170.5, 137.7, 137.4, 128.5, 128.4, 128.0, 127.9, 127.8, 78.6, 72.7, 71.9, 71.1, 71.0, 67.1, 25.7, 18.3, -4.7, -5.3. **HRMS (ESI)** calcd for $C_{25}H_{34}O_5Si$+Na 465.2073, found 465.2063.

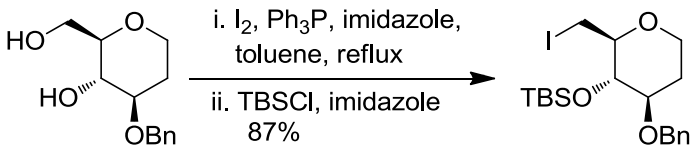
(2.4.2.8) (((3*R*,4*S*,5*S*)-4,5-bis(benzyloxy)-2-methylenetetrahydro-2*H*-pyran-3-yl)oxy)(*tert*-butyl)dimethylsilane :



47 **48**

The compound **48** was synthesized from compound **47** (1.0 g, 2.26 mmol) and dimethyl titanocene (3.76 mL of a 20% w/w solution in toluene, 4.52 mmol) by following the same procedure in compound **42** (2.4.2.4). The reaction mixture was stirred in the dark for 24 h at room temperature. Crude product was purified by silica-gel column chromatography (EtOAc in hexane 1:9) to provide the exocyclic-olefin **48** (750 mg) as a pale yellow gum (75% yield). **^{1}H NMR (400 MHz, $CDCl_3$)**: δ 7.27-7.37 (m, 10H), 4.68 (s, 4H), 4.64 (s, 1H), 4.56 (s, 1H), 4.37 (d, 1H, *J* = 7.2 Hz), 4.03 (dd, 1H, *J* = 5.2 Hz, *J* = 10.8 Hz), 3.89-3.92 (m, 1H), 3.63 (dd, 1H, *J* = 3.2 Hz, *J* = 10.8 Hz), 3.52 (dd, 1H, *J* = 3.2 Hz, *J* = 7.6 Hz), 0.88 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 160.1, 138.5, 138.2, 128.4, 128.3, 127.8, 127.7, 127.5, 95.5, 79.7, 72.7, 72.5, 71.8, 69.9, 67.9, 25.8, 18.1, -4.8, -4.9. HRMS (ESI) calcd for $C_{26}H_{36}O_4Si$+Na 463.2281, found 463.2287.

(2.4.2.9) (((2*S*,3*S*,4*R*)-4-(benzyloxy)-2-(iodomethyl)tetrahydro-2*H*-pyran-3-yl)oxy)(*tert*-butyl)dimethylsilane:

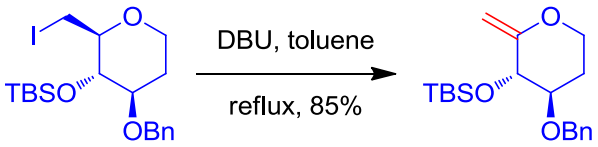


52 **53**

To a solution of 1,2-dideoxy-3-*O*-benzyl-D-glucopyranose **52** (3.5 g, 14.69 mmol) was dissolved in toluene (90 mL) and triphenylphosphine (11.55 g, 44.08 mmol), imidazole (2.86 g, 44.08 mmol) were added. Then iodine (7.46 g, 29.38 mmol) was added slowly over a period of 30 min. The reaction mixture was heated at reflux for 6 h. When the reaction is completed it was brought to 25 ^{o}C and saturated $NaHCO_3$ was added, until the solution becomes clear. Then iodine was added slowly until the organic phase becomes coloured. Sodium thiosulphate was added until decolourisation occurs. The mixture was transferred to a separating funnel and the organic phase was diluted with Ethyl acetate. The organic phase was washed with water dried over anhydrous Na_2SO_4, concentrated, followed by column chromatography afforded 1,2,6-trideoxy-3-*O*-benzyl-6-iodo-D-glucopyranose (4.7 g) in 92% yield. **^{1}H NMR (400 MHz, $CDCl_3$)**: δ 7.32-7.37 (m, 5H), 4.68 (d, 1H, *J* = 11.6 Hz), 4.50 (d, 1H, *J* = 11.6 Hz), 4.02 (dd, 1H, *J* = 4.0 Hz, *J* = 11.2 Hz), 3.54 (dd, 1H, *J* = 2.0 Hz, *J* = 10.4 Hz), 3.44-3.49 (m, 2H), 3.34-3.41 (m, 2H), 3.14 (bs, 1H), 2.90-2.94 (m, 1H), 2.06 (d, 1H, *J* = 12.4 Hz), 1.64 (ddd, 1H, *J* = 4.8 Hz, *J* = 12.4 Hz, *J* = 24.0 Hz). **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 138.1, 128.6, 128.0, 127.8, 80.1, 78.2, 74.4, 70.8, 65.6, 30.5, 8.4. **HRMS (ESI)** calcd for $C_{13}H_{18}IO_3$+H 349.0301, found 349.0301.

To a solution of above 1,2,6-trideoxy-3-*O*-benzyl-6-iodo-D-glucopyranose (3.0 g, 8.62 mmol) in DMF (10 mL) at 0 °C was added imidazole (1.76 g, 25.86 mmol) followed by *tert*-butyldimethylsilyl chloride (3.24 g, 21.55 mmol). The reaction mixture was stirred for overnight at 25 ^{o}C. DMF was removed under vacuum, and the residue was diluted with CH_2Cl_2 and water. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 70 mL). The combined organic layers were washed with water and brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The obtained residue was purified by silica column chromatography with EtOAc/hexane to afford 1,2,6-trideoxy-3-*O*-benzyl-4-*O*-*tert*-butyldimethylsilyl-6-iodo-D-glucopyranose **53** (3.8 g) in 95% yield. **^{1}H NMR (400 MHz, $CDCl_3$)**: δ 7.27-7.32 (m, 5H), 4.62 (d, 1H, *J* = 11.6 Hz), 4.48 (d, 1H, *J* = 11.6 Hz), 4.01 (ddd, 1H, *J* = 2.0 Hz, *J* = 4.8 Hz, *J* = 12.4 Hz), 3.56 (dd, 1H, *J* = 2.8 Hz, *J* = 10.0 Hz), 3.41-3.49 (m, 3H), 3.37 (dd, 1H, *J* = 4.8 Hz, *J* = 10.0 Hz), 2.87-2.91 (m, 1H), 2.06-2.11 (m, 1H), 1.55-1.65 (m, 1H), 0.88 (s, 9H), 0.13 (s, 3H), 0.05 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 138.4, 128.2, 127.6, 127.5, 80.5, 79.2, 75.3, 70.5, 65.3, 30.7, 26.1, 18.3, 9.4, -3.7, -4.5. **HRMS (ESI)** calcd for $C_{19}H_{31}IO_3Si$+Na 485.0985, found 485.0984.

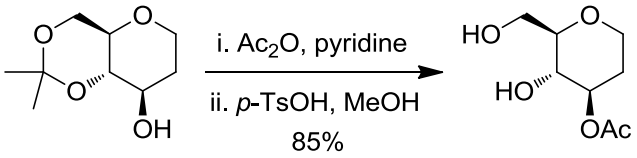
(2.4.2.10) (((3*S*,4*R*)-4-(benzyloxy)-2-methylenetetrahydro-2*H*-pyran-3-yl)oxy)(*tert*-butyl)dimethylsilane:



53 **54**

DBU (4.85 mL, 32.43 mmol) was added slowly for a period of 10 min to a solution of 1,2,6-trideoxy-3-*O*-benzyl-4-*O*-*tert*-butyldimethylsilyl-6-iodo-D-glucopyranose **53** (3.0 g, 6.48 mmol) in toluene (30 mL). The mixture was refluxed for 90 min. After completion of reaction the mixture was diluted with ethyl acetate and water. The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were dried and filtered. Evaporation of solvent followed by flash column chromatography provided the exocyclic vinyl ether **54** (1.86 g) in 85% yield. **^{1}H NMR (400 MHz, $CDCl_3$)**: δ 7.30-7.38 (m, 5H), 4.65-4.66 (m, 4H), 4.05-4.09(m, 2H), 3.61 (t, 1H, *J* = 10.8 Hz), 3.46-3.49 (m, 1H), 2.11-2.15 (m, 1H), 1.79-1.83 (m, 1H), 0.98 (s, 9H), 0.13 (s, 3H), 0.12 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 160.9, 138.5, 128.2, 127.6, 127.4, 94.2, 79.1, 72.7, 71.6, 66.4, 29.9, 25.9, 18.1, -4.7, -4.9. **HRMS (ESI)** calcd for $C_{19}H_{30}O_3Si$+Na 357.1862, found 357.1865.

(2.4.2.11) (2*R*,3*S*,4*R*)-3-hydroxy-2-(hydroxymethyl)tetrahydro-2*H*-pyran-4-yl acetate :



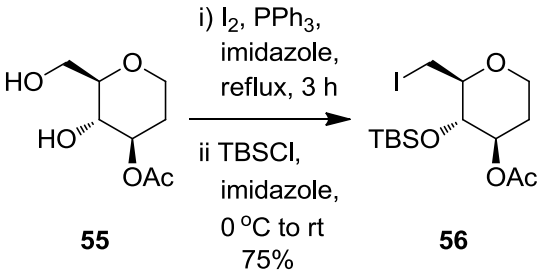
51 **55**

To a solution of 1,2-dideoxy-4,6-*O*-isopropylidine-D-glucopyranose **51** (3.5g, 18.61 mmol) in pyridine (35 mL) was added acetic anhydride (3.5 mL, 37.23 mmol) at 0 °C. The mixture was stirred for overnight at room temperature. Pyridine was removed under reduced pressure and the obtained residue was taken in CH_2Cl_2 (100 mL). The solution was transferred into a separating funnel and washed with aqueous $CuSO_4$ solution followed by brine, dried over anhydrous Na_2SO_4 and filtered to afford 1,2-dideoxy-3-*O*-acetyl-4,6-*O*-isopropylidine-D-glucopyranose (4.0 g) in 93% yield. This material was used directly in the next step without further purification. **^{1}H NMR (400 MHz, $CDCl_3$)**: δ 4.78-4.81 (m, 1H), 3.87 (ddd, 1H, *J* = 1.6

Hz, *J* = 5.2 Hz, *J* = 12.0 Hz), 3.79-3.83 (m, 1H), 3.62 (dt, 1H, *J* = 10.8 Hz, *J* = 18.0 Hz), 3.50 (dt, 1H, *J* = 2.0 Hz, *J* = 12.0 Hz), 3.17-3.21 (m, 1H), 2.01 (s, 3H), 1.43 (s, 3H), 1.32 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 170.4, 99.6, 72.9, 72.7, 71.4, 65.8, 62.2, 60.2, 31.5, 29.0, 21.1, 19.0. **HRMS (ESI)** calcd for $C_{11}H_{18}O_5$+Na 253.1052, found 253.1054.

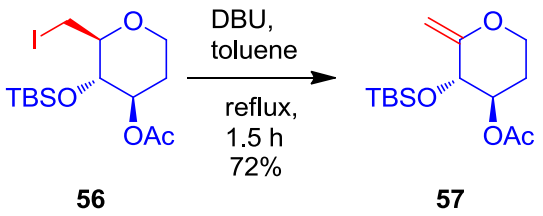
The above isopropylidene acetate (3.8 g, 12.16 mmol) was dissolved in MeOH (40 mL) and treated with *p*-toluenesulfonic acid (0.57 g, 3.04 mmol) at 25 °C. The mixture was stirred for 1 h. Removal of solvent and purification of the crude product over silica gel column chromatography provided 1,2-dideoxy-3-*O*-acetyl-D-glucopyranose **55** (2.90 g) in 92% yield.

(2.4.2.12) (2*S*,3*S*,4*R*)-3-((*tert*-butyldimethylsilyl)oxy)-2-(iodomethyl)tetrahydro-2*H*-pyran-4-yl acetate.



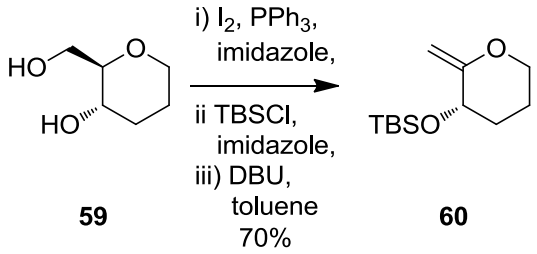
The compound **56** was synthesized from 1,2-dideoxy-3-*O*-acetyl-D-glucopyranose **55** (1.2 g, 6.31 mmol) by following the same procedure in **53** (2.4.2.9). Crude product was purified by silica-gel column chromatography (EtOAc in hexane 1:9) to provide the iodo compound **56** in 75% yield. **^{1}H NMR (400 MHz, $CDCl_3$)**: δ 4.70-4.76 (m, 1H), 3.96 (dd, 1H, *J* = 4.8 Hz, *J* = 11.6 Hz), 3.49-3.57 (m, 3H), 3.35 (dd, 1H, *J* = 4.8 Hz, *J* = 10.4 Hz), 2.83-2.87 (m, 1H), 2.83-2.87 (m, 1H), 2.11-2.15 (m, 1H), 2.06 (s, 3H), 1.60 (ddd, 1H, *J* = 4.8 Hz, *J* = 12.4 Hz, *J* = 24.4 Hz), 0.85 (s, 9H), 0.17 (s, 3H), 0.09 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 170.3, 78.7, 75.7, 73.5, 65.0, 31.0, 25.7, 21.5, 18.1, 9.1, -4.1, -4.1. **HRMS (ESI)** calcd for $C_{14}H_{27}O_4Si$+Na 437.0621, found 437.0621.

(2.4.2.13) (3*S*,4*R*)-3-((*tert*-butyldimethylsilyl)oxy)-2-methylenetetrahydro-2*H*-pyran-4-yl acetate:



The compound **57** was synthesized from compound 1,2,6-trideoxy-3-*O*-acetyl-4-*O*-*tert*-butyldimethylsilyl-6-iodo-D-glucopyranose **56** (0.90 g, 2.17 mmol) and DBU (1.62 mL, 10.86 mmol) in toluene (10 mL) by following the procedure described for compound **54** (2.4.2.10). The crude product was separated by flash column chromatography provided the exocyclic vinyl ether **57** (0.45 g) in 72% yield. **^{1}H NMR (400 MHz, CDCl$_3$)**: δ 4.72-4.74 (m, 1H), 4.61 (s, 2H), 3.96-4.03 (m, 2H), 3.62 (dt, 1H, *J* = 2.8 Hz, *J* = 11.2 Hz), 2.13-2.17 (m, 1H), 2.03 (s, 3H), 1.74-1.77 (m, 1H), 0.87 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H). **^{13}C NMR (100 MHz, CDCl$_3$)**: δ 170.0, 160.2, 95.1, 74.1, 70.9, 66.4, 30.0, 25.6, 21.2, 18.0, -4.8, -4.9. **HRMS (ESI)** calcd for $C_{14}H_{26}O_4Si$+H 287.1679, found 287.1677.

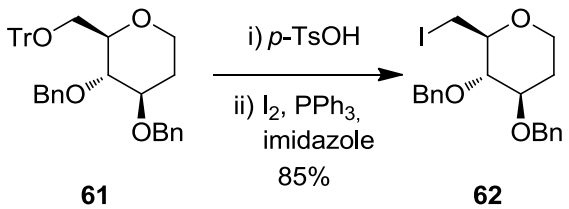
2.4.2.14 (*S*)-*tert*-butyldimethyl((2-methylenetetrahydro-2*H*-pyran-3-yl)oxy)silane:



59 **60**

The compound **60** was synthesized from compound **59** (1.0 g, 7.57 mmol) by following the procedure described for compounds **53** (2.4.2.9) and **54** (2.4.2.10). The crude product was separated by flash column chromatography provided the exocyclic vinyl ether **60** (1.2 g) in 70% yield. **^{1}H NMR (400 MHz, CDCl$_3$)**: δ 4.51 (s, 1H), 4.49 (s, 1H), 4.07 (dd, 1H, *J* = 4.8 Hz, *J* = 9.6 Hz), 3.95-3.99 (m, 1H), 3.61-3.67 (m, 1H), 2.10-2.13 (m, 1H), 1.95-1.99 (m, 1H), 1.81-1.88 (m, 2H), 0.92 (s, 9H), 0.12 (s, 3H), 0.09 (s, 3H). **^{13}C NMR (100 MHz, CDCl$_3$)**: δ 163.1, 91.5, 69.8, 68.2, 33.4, 25.7, 24.1, 18.1, -4.9, -4.9. **HRMS (ESI)** calcd for $C_{12}H_{24}O_2Si$+H 229.1624, found 229.1624.

(2.4.2.15) (2*S*,3*S*,4*R*)-3,4-bis(benzyloxy)-2-(iodomethyl)tetrahydro-2*H*-pyran:



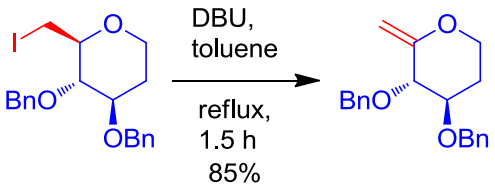
61 **62**

To a stirred solution of compound **61** (6.3 g, 8.92 mmol) and *p*-TsOH in dichloromethane/methanol (1:2) was stirred for overnight. After complete deprotection of the

trityl group, solvent was evaporated under reduced pressure and crude product was dissolved in dichloromethane, taken into the separating funnel, washed with water (2 x 100 mL), aq. 10% Na_2CO_3 (100 mL), and aq. NaCl solution (100 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated under reduced pressure. The crude product was purified by column chromatography on silica-gel to obtain the 1,2-dideoxy-3,4-di-*O*-benzyl-D-glucopyranose in 95% yield.

The above 1,2-dideoxy-3,4-di-*O*-benzyl-D-glucopyranose (2.0 g, 6.09 mmol) was dissolved in toluene (50 mL) and to this triphenylphosphine (4.79 g,18.29 mmol), imidazole (1.18 g, 18.27 mmol) were added. Then iodine (3.09 g, 12.18 mmol) was added slowly over a period of 30 min. The reaction mixture was stirred at reflux temperature for 6 h. When the reaction is completed (monitored by TLC) it was brought to 25 ^oC and saturated aqueous $NaHCO_3$ was added, until the solution becomes clear. While stirring iodine was added slowly until the organic phase becomes coloured. Sodium thiosulphate was added until decolourisation occurs. The mixture was transferred to a separating funnel and diluted with ethyl acetate. The organic phase was separated, washed with water, dried over anhydrous Na_2SO_4, concentrated. Purification of the crude product over column chromatography afforded 1,2-dideoxy-3,4-di-*O*-benzyl-6-deody-6-iodo-D-glucopyranose **62** (2.2 g) in 90% yield. **^{1}H NMR (400 MHz, $CDCl_3$)**: δ 7.33-7.38 (m, 10H), 5.06 (d, 1H, *J* = 10.8 Hz), 4.78 (d, 1H, *J* = 10.8 Hz), 4.74 (d, 1H, *J* = 12.0 Hz), 4.64 (d, 1H, *J* = 11.6Hz), 4.04 (dd, 1H, *J* = 4.0 Hz, *J* = 11.2 Hz), 3.68-3.74 (m, 1H), 3.54 (dd, 1H, *J* = 2.4 Hz, *J* = 10.8 Hz), 3.43-3.48 (m, 2H), 3.41 (t, 1H, *J* = 8.8 Hz), 2.95-2.97 (m, 1H), 2.11-2.15 (m, 1H), 1.71-1.77 (m, 1H). **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 138.3, 128.5, 128.1, 127.9, 127.7, 82.0, 80.7, 77.9, 75.5, 71.3, 65.5, 31.4, 8.6. **HRMS (ESI)** calcd for $C_{20}H_{23}IO_3$+Na 461.0590, found 461.0596.

(2.4.2.16) (3*S*,4*R*)-3,4-bis(benzyloxy)-2-methylenetetrahydro-2*H*-pyran:

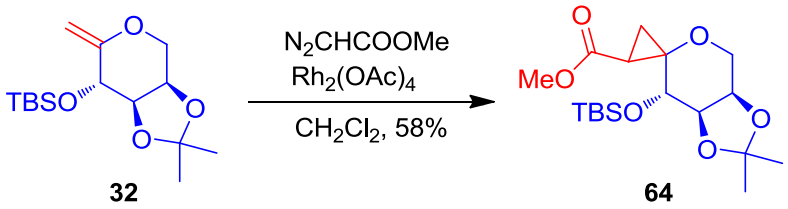


62 **63**

To a solution of 1,2-dideoxy-3,4-di-*O*-benzyl-6-deoxy-6-iodo-D-glucopyranose **62** (1.5 g, 3.42 mmol) in toluene(15 mL) at 0 ^oC was added DBU (1.28 mL, 8.56 mmol), drop wise over a period of 10 min. The reaction mixture was brought to 25 ^oC and heated at reflux for 1.5 h.

After completion of the reaction, the mixture was diluted with ethyl acetate. The solution was taken into a separating funnel and washed with water, dried over anhydrous Na_2SO_4, concentrated and the obtained residue was purified by column chromatography to give the exocyclic-olefin **63** (1.2 g) in 85% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33-7.41 (m, 10H), 4.59-4.81 (m, 6H), 4.09-4.15 (m, 1H), 3.93 (d, 1H, *J* = 5.6 Hz), 3.81-3.87 (m, 1H), 3.76-3.80 (m, 1H), 2.24-2.31 (m, 1H), 1.81-1.88 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.6, 138.3, 138.1, 128.3, 127.7, 127.7, 127.5, 127.4, 96.2, 77.5, 76.2, 71.4, 71.3, 65.4, 28.5. HRMS (ESI) calcd for $C_{20}H_{22}O_3$+H 311.1647, found 311.1647.

(2.4.2.17) (3a*R*,7*S*,7a*R*)-methyl 7-((*tert*-butyldimethylsilyl)oxy)-2,2-dimethyltetrahydrospiro[[1,3]dioxolo[4,5-*c*]pyran-6,1'-cyclopropane]-2'-carboxylate:



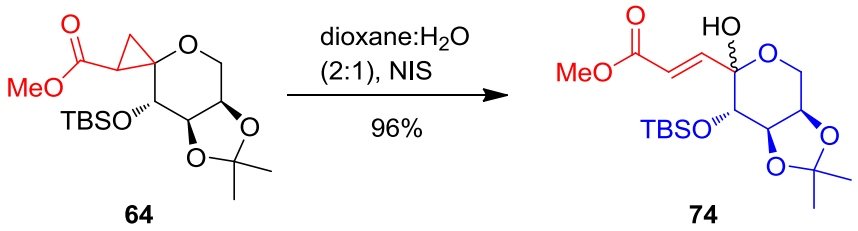
32 **64**

To a stirred suspension of exocyclic-glycal **32** (2.6 g, 8.66 mmol) and $Rh_2(OAc)_4$ (76.0 mg, 0.17 mmol) in anhydrous CH_2Cl_2 (20 mL) was added drop wise, over a period of 1 h, a solution of methyl diazoacetate (2.4 mL, 25.98 mmol) in CH_2Cl_2 (80 mL). After completion of the reaction, the reaction mixture was concentrated in *vacuo* and the obtained crude product was purified by silica gel column chromatography (eluent: 10-20% EtOAc in Hexane) to give desired spiro-cyclopropanecarboxylate **64** (1.86 g) in 58% yield as a mixture of diastereomers. Interestingly we separated one of the diastereomer from mixture of diastereomers.

Diastereomer 1: **^{1}H NMR (400 MHz, $CDCl_3$)**: δ 4.34-4.38 (m, 1H), 4.15 (d, 1H, *J* = 2.0 Hz), 4.10 (dd, 1H, *J* = 2.0 Hz, *J* = 5.2 Hz), 3.90 (dd, 1H, *J* = 6.4 Hz, *J* = 11.6 Hz), 3.67(s, 3H), 3.43 (dd, 1H, *J* = 8.4 Hz, *J* = 11.6 Hz), 1.95 (dd, 1H, *J* = 7.6 Hz, *J* = 9.2 Hz), 1.46 (s, 3H), 1.35-1.40 (m, 2H), 1.32 (s, 3H), 0.90 (s, 9H), 0.13 (s, 3H), 0.12 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 172.0, 109.6, 75.7, 69.1, 66.4, 65.7, 65.5, 51.7, 27.5, 26.8, 26.0, 25.8, 19.0, 18.0, -4.4, -4.8. **HRMS (ESI)** calcd for $C_{18}H_{32}O_6Si$+Na 395.1866, found 395.1866.

Note: All the spiro-cyclopropane carboxylated sugars **65** to **72** (table 2.1) synthesized by the following procedure described for compound **64** (2.4.2.17), as an inseparable mixture of diastereomers.

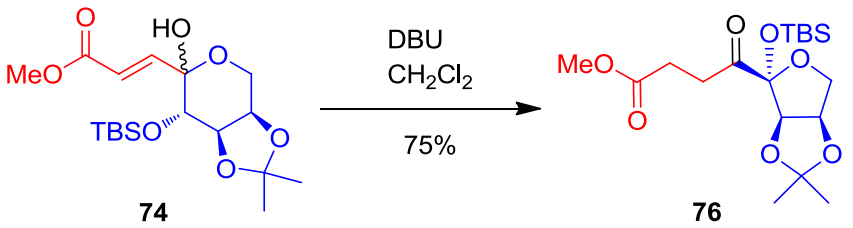
(2.4.2.18) (*E*)-methyl 3-((3a*R*,7*S*,7a*R*)-7-((*tert*-butyldimethylsilyl)oxy)-6-hydroxy-2,2-dimethyltetrahydro-3a*H*-[1,3]dioxolo[4,5-c]pyran-6-yl)acrylate:



64 **74**

To a stirred solution of spiro-cyclopropanecarboxylated sugar **64** (200 mg, 0.53 mmol) in 1,4-dioxane:water (2:1, 9 mL) was added *N*-iodosuccinimide (144 mg, 0.64 mmol) at 0 °C. The reaction was warmed slowly to room temperature over a period of 1 h and stirred for overnight. Upon completion of the reaction (TLC), the mixture was concentrated to half of its volume in *vacuo* and diluted with CH_2Cl_2 (20 mL). The organic layer was separated and aqueous phase was extracted with CH_2Cl_2 (2 x 10 mL). The combined organic layers were washed with aqueous saturated sodium thiosulphate solution for decolourization, dried over anhydrous Na_2SO_4, filtered and concentrated. The crude product was purified by column chromatogram on silica gel (eluent: 30-40% EtOAc in Hexane) to obtain the α,β-unsaturated ester **74** (208 mg) in 96% yield. **^{1}H NMR (400 MHz, $CDCl_3$)**: δ 6.92 (d, 1H, *J* = 15.6Hz), 6.25 (d, 1H, *J* = 15.6 Hz), 4.23-4.25 (m, 1H), 4.16-4.19 (m, 2H), 3.99 (d, 1H, *J* = 13.2 Hz), 3.76 (s, 3H), 3.69 (d, 1H, *J* = 5.6 Hz), 3.42 (s, 1H), 1.54 (s, 3H), 1.38 (s, 3H), 0.92 (s, 9H), 0.17 (s, 3H), 0.09 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 166.6, 146.7, 122.3, 109.4, 95.1, 76.4, 73.3, 72.8, 60.3, 51.7, 27.5, 25.9, 25.7, 18.0, -4.3, -5.0. **HRMS (ESI)** calcd for $C_{18}H_{32}O_7Si$+Na 411.1815, found 411.1815.

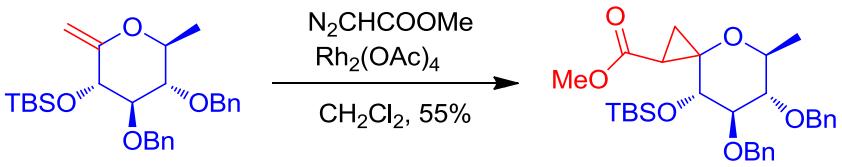
(2.4.2.19) Methyl 4-((3a*R*,4*R*,6a*R*)-4-((*tert*-butyldimethylsilyl)oxy)-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxol-4-yl)-4-oxobutanoate:



74 **76**

To a stirred solution of α,β-unsaturated ester **74** (100 mg, 0.25 mmol) in CH_2Cl_2 (5 mL) was added 1,8-diazabicyclcoundec-7-ene (DBU) (76.8 μL, 0.51 mmol) at 0 °C and the reaction mixture was stirred overnight at room temperature. After completion of the reaction, the solvent was evaporated and purified by column chromatography on silica gel (eluent: 10-20%) to obtain the ring-contraction product **76** (75 mg) in 75% yield as single diastereomer. **^{1}H NMR (400 MHz, $CDCl_3$)**: δ 4.87 (dd, 1H, *J* = 3.6 Hz, *J* = 6.0 Hz), 4.62 (d, 1H, *J* = 6.0 Hz), 4.17 (d, 1H, *J* = 10.4 Hz), 4.05 (dd, 1H, *J* = 3.6 Hz, *J* = 10.4 Hz), 3.70 (s, 3H), 3.05-3.09 (m, 2H), 2.57-2.62 (m, 2H), 1.44 (s, 3H), 1.27 (s, 3H), 0.90 (s, 9H), 0.07 (s, 3H), 0.05 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 204.7, 173.1, 112.8, 107.3, 88.3, 79.9, 72.5, 51.7, 35.0, 27.6, 25.8, 25.6, 24.4, 17.9, -3.4, -4.1. **HRMS (ESI)** calcd for $C_{18}H_{32}O_7Si$+Na 411.1815, found 411.1813.

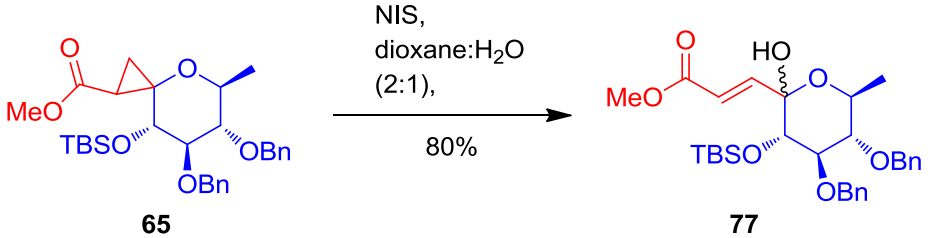
(2.4.2.20) (5*S*,6*S*,7*R*,8*S*)-methyl 6,7-bis(benzyloxy)-8-((*tert*-butyldimethylsilyl)oxy)-5-methyl-4-oxaspiro[2.5]octane-1-carboxylate:



42 **65**

The methylenated product **42** (250 mg, 0.55 mmol), methyl diazoacetate (0.16 mL, 1.65 mmol), $Rh_2(OAc)_4$ (4.86 mg, 0.01 mmol) was cyclopropanated according to the procedure described for compound **64** (2.4.2.17) to obtain spiro-cyclopropanecarboxylate **65** (160 mg) in 55% yield as a mixture of diastereomers. HRMS (ESI) calcd for $C_{30}H_{42}O_6Si$+Na 549.2648, found 549.2651.

(2.4.2.21) (*E*)-methyl 3-((3*S*,4*R*,5*S*,6*S*)-4,5-bis(benzyloxy)-3-((*tert*-butyldimethylsilyl)oxy)-2-hydroxy-6-methyltetrahydro-2*H*-pyran-2-yl)acrylate:

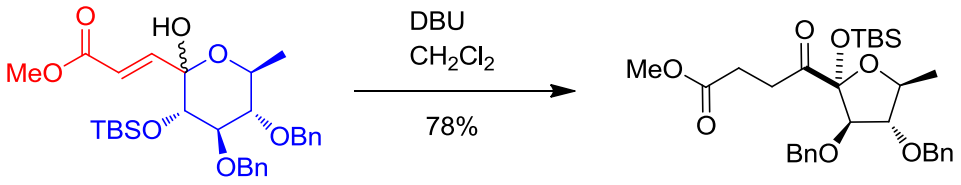


65 **77**

Compound **77** was synthesized from **65** (70 mg, 0.133 mmol), NIS (36 mg, 0.16 mmol) by following the procedure described for compound **74** (2.4.2.18). Yield 80% (56 mg). Only one

major anomer was obtained. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.18-7.33 (m, 10H), 6.83 (d, 1H, *J* = 15.6 Hz), 6.26 (d, 1H, *J* = 15.6 Hz), 4.98 (s, 1H, *J* = 10.8 Hz), 4.79 (d, 1H, *J* = 11.6 Hz), 4.76 (d, 1H, *J* = 11.6 Hz), 4.62 (d, 1H, *J* = 10.8 Hz), 4.03-4.07 (m, 1H), 3.75 (s, 3H), 3.69 (d, 1H, *J* = 8.8 Hz), 3.62 (d, 1H, *J* = 8.8 Hz), 3.23 (t, 1H, *J* = 10.2 Hz), 0.87 (s, 9H), 0.01 (s, 3H), -0.01 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.5, 147.1, 138.6, 137.8, 128.4, 128.2, 127.9, 127.8, 127.2, 126.7, 122.6, 95.9, 84.2, 82.7, 75.9, 75.1, 75.1, 68.6, 51.7, 25.9, 17.9, 14.1, -3.8, -4.3. HRMS (ESI) calcd for $C_{30}H_{42}O_7Si$+Na 565.2597, found 565.2597.

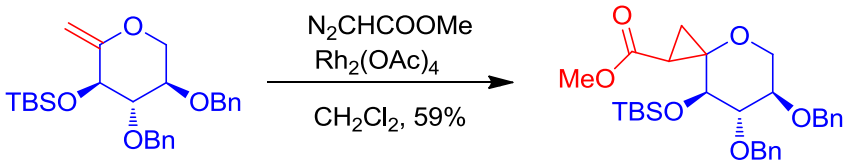
(2.4.2.22) methyl 4-((2*R*,3*R*,4*S*,5*S*)-3,4-bis(benzyloxy)-2-((*tert*-butyldimethylsilyl)oxy)-5-methyltetrahydrofuran-2-yl)-4-oxobutanoate:



77 **78**

Compound **78** was synthesized from **77** (50 mg, 0.092 mmol), DBU (13.8 µL, 0.092 mmol) by following procedure described for compound **76** (2.4.2.19). Yield 78% (39 mg). This compound was obtained as an inseparable mixture of diastereomers. HRMS (ESI) calcd for $C_{30}H_{42}O_7Si$+H 543.2778, found 543.2775.

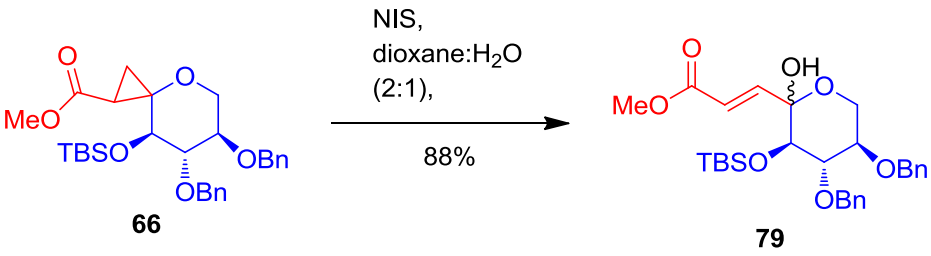
(2.4.2.23) (6*R*,7*S*,8*R*)-methyl 6,7-bis(benzyloxy)-8-((*tert*-butyldimethylsilyl)oxy)-4-oxaspiro[2.5]octane-1-carboxylate:



45 **66**

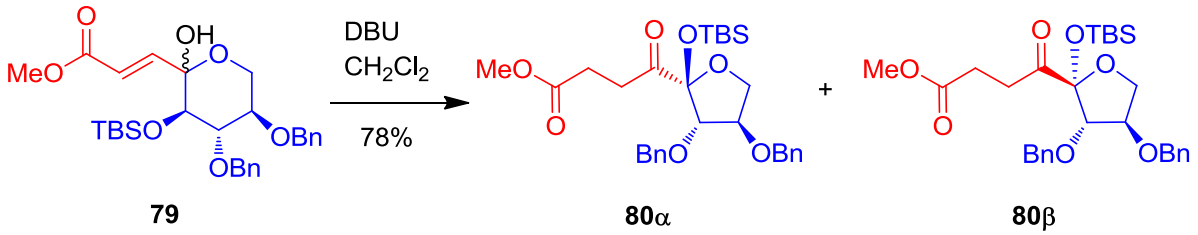
The exo-cyclcic methylenated product **45** (0.8 g, 1.81 mmol), methyl diazoacetate (0.5 mL, 5.45 mmol), $Rh_2(OAc)_4$ (16 mg, 0.036 mmol) was cyclopropanated following the procedure described for compound **64** (2.4.2.17) to obtain spiro-cyclopropanecarboxylate **66** (0.55 g) as a mixture of diastereomers in 59% yield. HRMS (ESI) calcd for $C_{29}H_{40}O_6Si$+Na 535.2492, found 535.2492.

(2.4.2.24) (*E*)-methyl 3-((3*R*,4*S*,5*R*)-4,5-bis(benzyloxy)-3-((*tert*-butyldimethylsilyl)oxy)-2-hydroxytetrahydro-2*H*-pyran-2-yl)acrylate:



Compound **79** was synthesized from **66** (100 mg, 0.195 mmol), NIS (52 mg, 0.23 mmol) by following the procedure described for compound **74** (2.4.2.18). Yield 88% (90 mg). Only one major anomer was obtained. **^{1}H NMR (400 MHz, $CDCl_3$)**: δ 7.25-7.33 (m, 10H), 6.82 (d, 1H, *J* = 15.6 Hz), 6.24 (d, 1H, *J* = 15.6 Hz), 5.05 (d, 1H, J =11.2 Hz), 4.74 (d, 1H, *J* = 11.6 Hz), 4.61 (s, 2H), 3.79-3.81 (m, 2H), 3.75 (s, 3H), 3.65-3.67 (m, 2H), 3.56 (d, 1H, *J* = 8.4 Hz), 3.36 (bs, 1H), 0.88 (s, 9H), 0.01 (s, 3H), 0.00 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 166.4, 146.9, 138.7, 137.9, 128.4, 128.2, 127.9, 127.8, 127.3, 122.8, 96.2, 82.1, 78.5, 75.5, 75.2, 73.0, 61.0, 51.8, 25.9, 17.9, -3.8, -4.4. **HRMS (ESI)** calcd for $C_{29}H_{40}O_7Si$+Na 551.2441, found 551.2441.

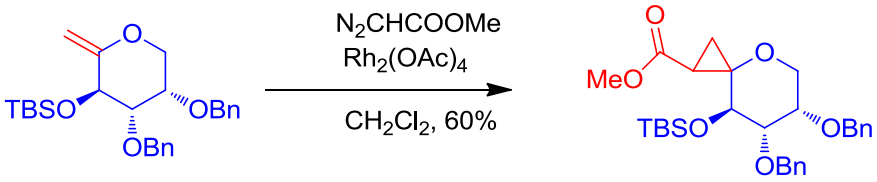
(2.4.2.25) methyl 4-((2*S*,3*S*,4*R*)-3,4-bis(benzyloxy)-2-((*tert*-butyldimethylsilyl)oxy)tetrahydrofuran-2-yl)-4-oxobutanoate and methyl 4-((2*R*,3*S*,4*R*)-3,4-bis(benzyloxy)-2-((*tert*-butyldimethylsilyl)oxy)tetrahydrofuran-2-yl)-4-oxobutanoate:



Compound **80α** and **80β** was synthesized from **79** (50 mg, 0.094 mmol), DBU (28.11 µL, 0.19 mmol)), following the procedure described for compound **76** (2.4.2.19). Yield 78% (39 mg). Obtained as mixture of diastereomers **80α** and **80β** in 80:20 ratio, accordingly. **80α: ^{1}H NMR (400 MHz, $CDCl_3$)**: δ 7.26-7.37 (m, 10H), 4.75 (d, 1H, *J* = 12.0 Hz), 4.57 (d, 1H, *J* = 12.0 Hz), 4.46 (d, 1H, *J* = 12.0 Hz), 4.43 (d, 1H, *J* = 12.0 Hz), 4.31 (dd, 1H, *J* = 1.2 Hz, *J* = 2.4 Hz), 4.17-4.26 (m, 2H), 3.83-3.87 (m, 1H), 3.68 (s, 3H), 2.98-3.03 (m, 2H), 2.56-2.61 (m, 2H), 0.95 (s, 9H), 0.18 (s, 3H), 0.11 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 206.7, 173.0, 138.0,

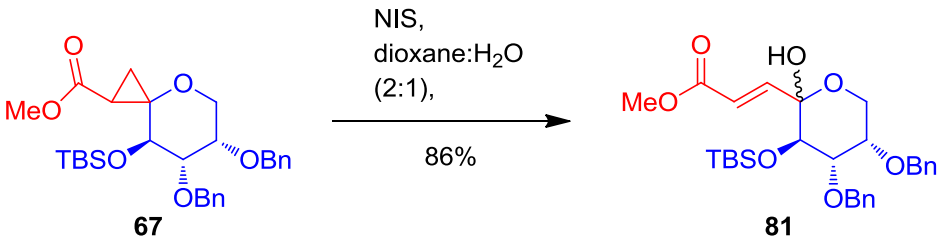
137.6, 129.4, 128.4, 128.3, 127.9, 127.9, 127.8, 127.6, 105.0, 83.5, 82.3, 72.3, 71.6, 69.9, 51.7, 31.5, 27.6, 25.8, 18.1, -3.1, -3.3. HRMS (ESI) calcd for $C_{29}H_{40}O_7Si$+Na 551.2441, found 551.2439. **80β: ^{1}H NMR (400 MHz, $CDCl_3$)**: δ 7.26-7.39 (m, 10H), 4.42-4.54 (m, 4H), 4.32-4.37(m, 1H), 4.11-4.19 (m, 2H), 4.05-4.08 (m, 1H), 4.67 (s, 3H), 2.99 (t, 2H, *J* = 7.2 Hz), 2.49 -2.54 (m, 2H), 0.91 (s, 9H), 0.09 (s, 3H), 0.05 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 206.6, 173.1, 137.6, 137.1, 128.4, 128.3, 128.2, 127.9, 127.9, 127.8, 127.6, 107.3, 90.5, 81.8, 72.6, 72.2, 71.9, 51.6, 34.7, 27.7, 25.7, 17.9, -3.4, -3.8. **HRMS (ESI)** calcd for $C_{29}H_{40}O_7Si$+Na 551.2441, found 551.2439.

(2.4.2.26) (6*S*,7*S*,8*R*)-methyl 6,7-bis(benzyloxy)-8-((*tert*-butyldimethylsilyl)oxy)-4-oxaspiro[2.5]octane-1-carboxylate:



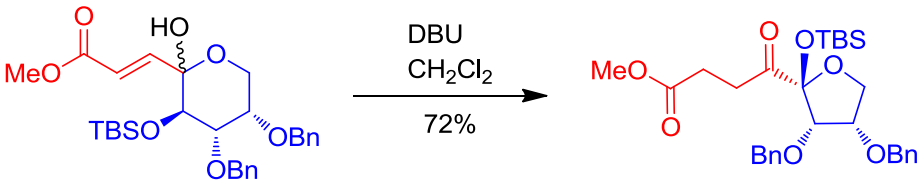
The methylenated product **48** (300 mg, 0.68 mmol), methyl diazoacetate (0.19 mL, 2.04 mmol), $Rh_2(OAc)_4$ (5.9 mg, 0.013 mmol) was cyclopropanated by following the procedure described for compound **64** (2.4.2.17) to afford spiro-cyclopropanecarboxylate **67** as a mixture of diastereomers (210 mg) in 60% yield. **HRMS (ESI)** calcd for $C_{29}H_{40}O_6Si$+Na 535.2492, found 535.2494.

(2.4.2.27) (*E*)-methyl 3-((3*R*,4*S*,5*S*)-4,5-bis(benzyloxy)-3-((*tert*-butyldimethylsilyl)oxy)-2-hydroxytetrahydro-2*H*-pyran-2-yl)acrylate:



Compound **81** was synthesized from **67** (85 mg, 0.166 mmol), NIS (44 mg, 0.20 mmol), by following the procedure described for compound **74** (2.4.2.18). Yield 86% (74 mg). This compound was obtained as an inseparable anomeric mixture. **HRMS (ESI)** calcd for $C_{29}H_{40}O_7Si$+Na 551.2441, found 551.2441.

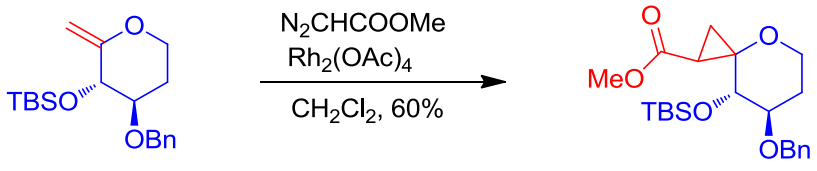
(2.4.2.28) methyl 4-((2*S*,3*S*,4*S*)-3,4-bis(benzyloxy)-2-((*tert*-butyldimethylsilyl)oxy)tetrahydrofuran-2-yl)-4-oxobutanoate:



81 **82β**

Compound **82** was synthesized from **81** (45 mg, 0.085 mmol), DBU (127 µL, 0.085 mmol) by following the procedure described for compound **76** (2.4.2.19). Yield 72% (32 mg). This compound was obtained as a mixture of diastereomers **82α** and **82β** in 20:80 ratio, accordingly. However, only **82β** was able to be obtained as a pure compound after chromatography, where as **82α** was obtained as an inseparable mixture along with **82β**. **82β: ^{1}H NMR (500 MHz, $CDCl_3$)**: δ 7.27-7.36 (m, 10H), 4.67 (d, 1H, *J* = 12 Hz), 4.64 (d, 1H, *J* = 12 Hz), 4.55 (d, 1H, *J* = 11.5 Hz), 4.54 (d, 1H, *J* = 11.5 Hz), 4.30 (dt, 1H, *J* = 6.0 Hz, *J* = 4.0 Hz), 4.11-4.17 (m, 2H), 4.02 (d, 1H, *J* = 4.5 Hz), 3.65 (s, 3H), 3.14 (ddd, 1H, *J* = 6.5 Hz, *J* = 7.0 Hz, *J* = 19.5 Hz), 3.03 (dt, 1H, *J* = 7.0 Hz, *J* = 19.5 Hz), 2.52 (dt, 1H, *J* = 7.5 Hz, *J* = 16.5 Hz), 2.40 (dt, 1H, *J* = 6.5 Hz, *J* = 16.5 Hz), 0.87 (s, 9H), 0.04 (s, 3H), 0.01 (s, 3H). **^{13}C NMR (125 MHz, $CDCl_3$)**: δ 206.9, 173.2, 137.6, 137.6, 128.4, 128.3, 127.9, 127.7, 106.9, 85.4, 77.9, 73.5, 72.8, 70.5, 51.6, 34.9, 27.7, 25.6, 17.8, -3.7, -4.0. **HRMS (ESI)** calcd for $C_{29}H_{40}O_7Si$+Na 551.2441, found 551.2441.

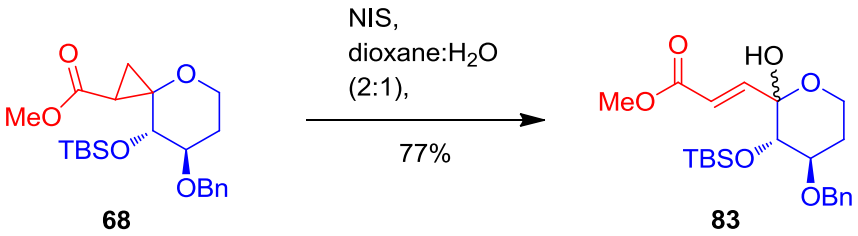
(2.4.2.29) (7*R*,8*S*)-methyl 7-(benzyloxy)-8-((*tert*-butyldimethylsilyl)oxy)-4-oxaspiro[2.5]octane-1-carboxylate:



54 **68**

Cyclopropanation of above vinyl ether **54** (1.3 g, 3.88 mmol), methyl diazoacetate (1.07 mL, 11.65 mmol), $Rh_2(OAc)_4$ (34 mg, 0.07 mmol) following the procedure described for compound **64** (2.4.2.17) to obtain spiro-cyclopropanecarboxylate **68** (0.95 g) in 60% yield as a mixture of diastereomers. HRMS (ESI) calcd for $C_{22}H_{34}O_5Si$+Na 429.2073, found 429.2074.

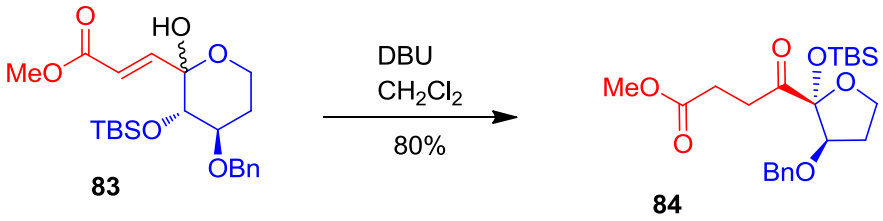
(2.4.2.30) (*E*)-methyl 3-((3*S*,4*R*)-4-(benzyloxy)-3-((*tert*-butyldimethylsilyl)oxy)-2-hydroxytetrahydro-2*H*-pyran-2-yl)acrylate:



68 **83**

Compound **83** was synthesized from **68** (200 mg, 0.49 mmol), NIS (132 mg, 0.59 mmol), following the procedure described for compound **74** (2.4.2.18). Yield 77% (160 mg). This compound was obtained as an inseparable mixture of anomers. HRMS (ESI) calcd for $C_{22}H_{34}O_6Si$+Na 445.2022, found 445.2023.

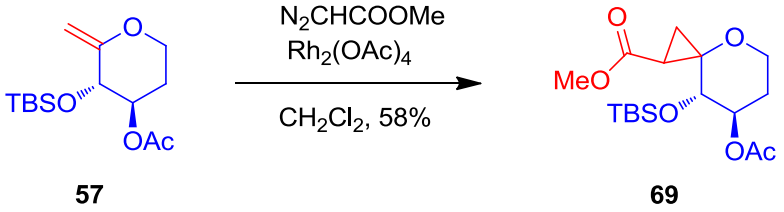
(2.4.2.31) methyl 4-((2*R*,3*R*)-3-(benzyloxy)-2-((*tert*-butyldimethylsilyl)oxy)tetrahydrofuran-2-yl)-4-oxobutanoate:



83 **84**

Compound **84** was synthesized from **83** (100 mg, 0.23 mmol), DBU (42.4 µL, 0.28 mmol) by following the procedure described for compound **76** (2.4.2.19). Yield 80% (80 mg). This compound was obtained as a single diastereomer **84β**. **^{1}H NMR (400 MHz, $CDCl_3$)**: δ 7.27-7.33 (m, 5H), 4.68 (d, 1H, *J* = 12.0 Hz), 4.43 (d, 1H, *J* = 12.0 Hz), 4.22 (t, 1H, *J* = 7.2 Hz), 4.13 (td, 1H, *J* = 4.8 Hz, *J* = 8 Hz), 3.85 (dt, 1H, *J* = 8.4 Hz, *J* = 7.2 Hz), 3.68 (s, 3H), 2.94-3.01 (m, 2H), 2.60 (dt, 1H, *J* = 2 Hz, *J* = 6.4 Hz), 2.17-2.23 (m, 1H), 2.09-2.15 (m, 1H), 0.95 (s, 9H), 0.18 (s, 3H), 0.13 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 207.4, 173.1, 138.2, 128.2, 127.6, 127.5, 104.4, 79.5, 72.0, 65.8, 51.7, 31.8, 31.1, 27.6, 25.9, 18.1, -3.1, -3.2. **HRMS (ESI)** calcd for $C_{22}H_{34}O_6Si$+Na 445.2022, found 445.2025.

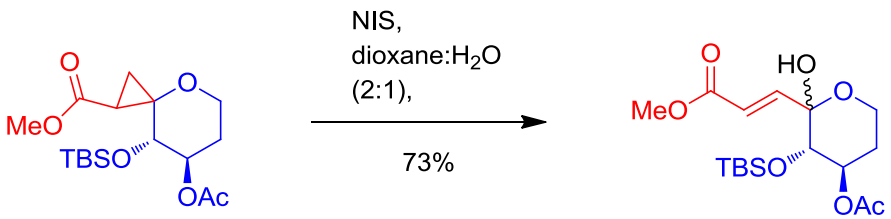
(2.4.2.32) (7*R*,8*S*)-methyl 7-acetoxy-8-((*tert*-butyldimethylsilyl)oxy)-4-oxaspiro[2.5]octane-1-carboxylate:



57 **69**

Cyclopropanation of above vinyl ether **57** (500 mg, 1.74 mmol) following the procedure described for compound **64** (2.4.2.17) provided spiro-cyclopropanecarboxylate **69** (290 mg) in 58% yield as a mixture of diastereomers. **HRMS (ESI)** calcd for $C_{17}H_{30}O_6Si$+Na 381.1709, found 381.1711.

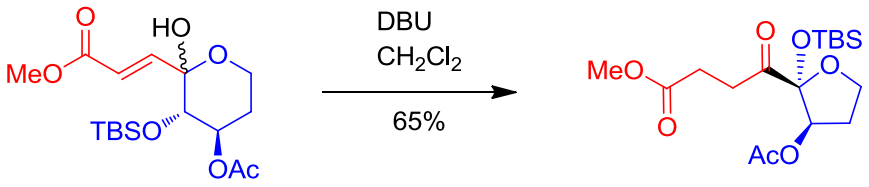
(2.4.2.33) (*E*)-methyl 3-((3*S*,4*R*)-4-acetoxy-3-((*tert*-butyldimethylsilyl)oxy)-2-hydroxytetrahydro-2*H*-pyran-2-yl)acrylate:



69 **85**

Compound **85** was synthesized from **69** (55 mg, 0.153 mmol), NIS (41 mg, 0.18 mmol) by following the procedure described for compound **74** (2.4.2.18). Yield 73% (41 mg). Only one major anomer was obtained. **^{1}H NMR (400 MHz, $CDCl_3$)**: δ 6.86 (d, 1H, *J* = 15.6 Hz), 6.25 (d, 1H, *J* = 15.6 Hz), 4.95-4.99 (m, 1H), 4.04 (dt, 1H, *J* = 1.6 Hz, *J* = 12.4 Hz), 3.71-3.80 (m, 5H), 3.62 (d, 1H, *J* = 8.8 Hz), 3.26 (bs, 1H), 2.08 (s, 3H), 1.59-1.67 (m, 1H), 0.92-0.97 (m, 1H), 0.86 (s, 9H), 0.08 (s, 3H), 0.05 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 170.2, 166.4, 146.7, 122.8, 96.5, 74.2, 72.5, 58.8, 51.8, 25.7, 21.4, 17.9, -3.9, -4.1. **HRMS (ESI)** calcd for $C_{17}H_{30}O_7Si$+Na 397.1658, found 397.1658.

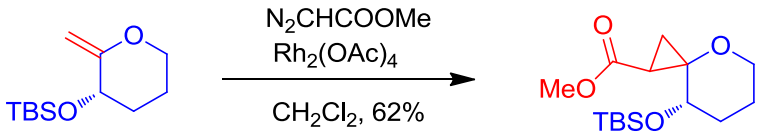
(2.4.2.34) methyl 4-((2*R*,3*R*)-3-acetoxy-2-((*tert*-butyldimethylsilyl)oxy)tetrahydrofuran-2-yl)-4-oxobutanoate:



85 **86**

Compound **86** was synthesized from **85** (20 mg, 0.053 mmol), DBU (9.58 µL) by following the procedure described for compound **76** (2.4.2.19). Yield 65% (14 mg). This compound was obtained as an inseparable mixture of diastereomers, α:β, in 30:70 ratio, respectively. **HRMS (ESI)** calcd for $C_{17}H_{30}O_7Si$+Na 397.1658, found 397.1660.

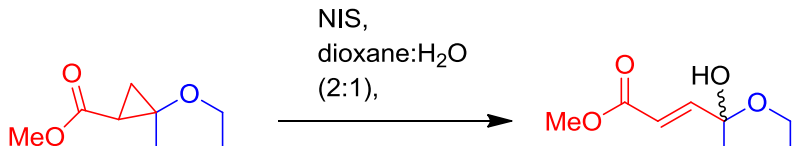
(2.4.2.35) (8*S*)-methyl 8-((*tert*-butyldimethylsilyl)oxy)-4-oxaspiro[2.5]octane-1-carboxylate:



60 **70**

Cyclopropanation of above vinyl ether **60** (1.1 g, 4.82 mmol), methyl diazoacetate (1.34 mL, 14.4 mmol), $Rh_2(OAc)_4$ (42 mg, 0.09 mmol) following the procedure described for compound **64** (2.4.2.17) to afford spiro-cyclopropanecarboxylate **70** (0.9 g, 62% yield) as a mixture of diastereomers. **HRMS (ESI)** calcd for $C_{15}H_{28}O_4Si$+Na 323.1655, found 323.1657.

(2.4.2.36) (*E*)-methyl 3-((3*S*)-3-((*tert*-butyldimethylsilyl)oxy)-2-hydroxytetrahydro-2*H*-pyran-2-yl)acrylate:

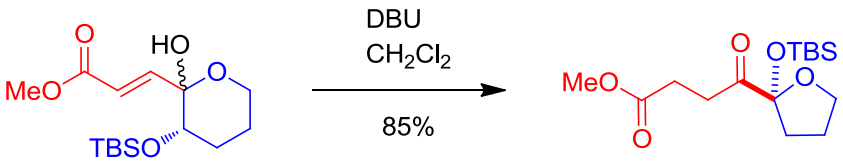


70 **87**

Compound **87** was synthesized from **70** (40 mg, 0.133 mmol), NIS (36 mg, 0.16 mmol) following the procedure described for compound **74** (2.4.2.18). Yield 76% (32 mg). This

compound was obtained as an inseparable anomeric mixture. **HRMS (ESI)** calcd for $C_{15}H_{28}O_5Si+H$ 317.1784, found 317.1787.

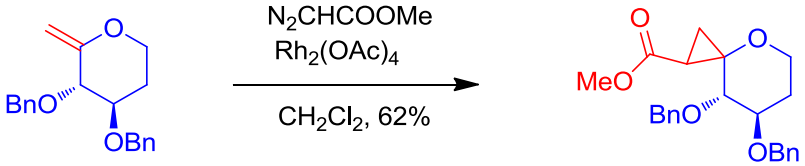
(2.4.2.37) (*R*)-methyl 4-(2-((*tert*-butyldimethylsilyl)oxy)tetrahydrofuran-2-yl)-4-oxobutanoate:



87 **88**

Compound **88** was synthesized from **87** (20 mg, 0.066 mmol), DBU (12 µL) following the procedure described for compound **76** (2.4.2.19). Yield 85% (17 mg). $([\alpha]_D^{25}$ -13 (C =1.8, $CHCl_3$), based on HPLC it was observed that compound **88** was obtained with 30% ee). The stereochemistry at quaternary centre was not assigned). **^{1}H NMR (400 MHz, $CDCl_3$)**: δ 4.15 (td, 1H, *J* = 4.4 Hz, *J* = 8.4 Hz), 3.94 (dt, 1H, *J* = 8.0 Hz, *J* = 6.4 Hz), 3.68 (s, 3H), 2.94 (td, 2H, *J* = 4.0 Hz, *J* = 6.8 Hz), 2.61 (t, 2H, *J* = 6.8 Hz), 2.18-2.25 (m, 1H), 2.05-2.12 (m, 1H), 1.95-1.99 (m, 2H), 0.90 (s, 9H), 0.10 (s, 3H), 0.09 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 206.5, 173.2, 107.3, 69.7, 51.7, 36.6, 31.7, 27.6, 25.7, 24.7, 17.9, -3.5, -3.6. **HRMS (ESI)** calcd for $C_{15}H_{28}O_5Si+H$ 317.1784, found 317.1785.

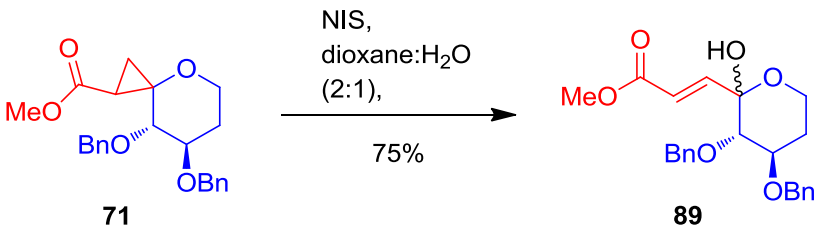
(2.4.2.38) (7*R*,8*S*)-methyl 7,8-bis(benzyloxy)-4-oxaspiro[2.5]octane-1-carboxylate:



63 **71**

Cyclopropantion of above exocyclic-olefin **63** (835 mg, 2.69 mmol), methyl diazoacetate (0.74 mL, 8.08 mmol), $Rh_2(OAc)_4$ (23 mg, 0.05 mmol) by following the procedure described for compound **64** (2.4.2.17) to obtain spiro-cyclopropanecarboxylate **71** (637 mg) in 62% yield as a mixture of diastereomers. **HRMS (ESI)** calcd for $C_{23}H_{26}O_5+Na$ 405.1678, found 405.1675.

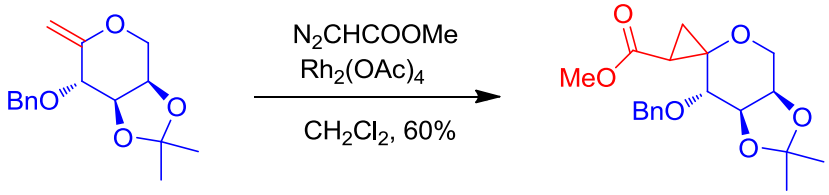
(2.4.2.39) (*E*)-methyl 3-((3*S*,4*R*)-3,4-bis(benzyloxy)-2-hydroxytetrahydro-2*H*-pyran-2-yl)acrylate:



71 **89**

Compound **89** was synthesized from **71** (200 mg, 0.52 mmol), NIS (140 mg, 0.62 mmol) following the procedure described for compound **74** (2.4.2.18). Yield 75%. This compound was obtained as an inseparable mixture of anomers. **HRMS (ESI)** calcd for $C_{23}H_{26}O_6$+Na 421.1627, found 421.1623.

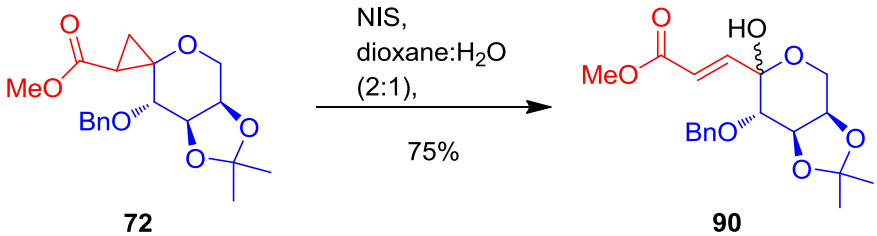
(2.4.2.40) (3a*R*,7*S*,7a*R*)-methyl 7-(benzyloxy)-2,2-dimethyltetrahydrospiro[[1,3]dioxolo[4,5-c]pyran-6,1'-cyclopropane]-2'-carboxylate:



34 **72**

Compound **72** was synthesized from cyclopropanation of 2,6-anhydro-3-*O*-benzyl-1-deoxy-4,5-*O*-isopropylidene-D-arabino-hex-1-enitol **34**, (520 mg, 1.88 mmol), methyl diazoacetate (0.51 mL, 5.6 mmol), $Rh_2(OAc)_4$ (16 mg, 0.037 mmol) following the procedure described for compound **64** (2.4.2.17). Yield 60% (377 mg). This compound was obtained as an inseparable mixture of diastereomers. **HRMS (ESI)** calcd for $C_{19}H_{24}O_6$+Na 371.1471, found 371.1471.

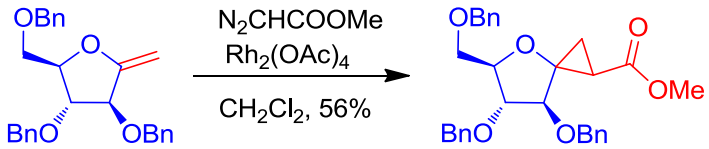
(2.4.2.41) (*E*)-methyl 3-((3a*R*,7*S*,7a*R*)-7-(benzyloxy)-6-hydroxy-2,2-dimethyltetrahydro-3a*H*-[1,3]dioxolo[4,5-c]pyran-6-yl)acrylate:



72 **90**

Compound **90** was synthesized from **72** (200 mg, 0.59 mmol), NIS (161 mg, 0.71 mmol) by following the procedure described for compound **74** (2.4.2.18). Yield 75% (162 mg). Only one major anomer was obtained. **^{1}H NMR (400 MHz, $CDCl_3$)**: δ 7.25-7.35 (m, 5H), 6.91 (d, 1H, *J* = 15.6 Hz), 6.19 (d, 1H, *J* = 16.0 Hz), 4.83 (d, 1H, *J* = 11.6 Hz), 4.63 (d, 1H, *J* = 11.6 Hz), 4.39 (t, 1H, *J* = 6.4 Hz), 4.20 (dd, 1H, *J* = 2.0 Hz, *J* = 6.0 Hz), 4.15 (dd, 1H, *J* = 2.4 Hz, *J* = 13.2 Hz), 3.98 (d, 1H, *J* = 13.6 Hz), 3.73 (s, 3H), 3.41 (d, 1H, *J* = 6.4 Hz), 1.46 (s, 3H), 1.36 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 166.6, 146.2, 137.1, 128.3, 128.0, 127.9, 127.8, 122.2, 109.1, 95.1, 78.5, 76.2, 73.4, 73.1, 59.8, 51.7, 27.6, 26.0. **HRMS (ESI)** calcd for $C_{19}H_{24}O_7$+Na 387.1420, found 387.1419.

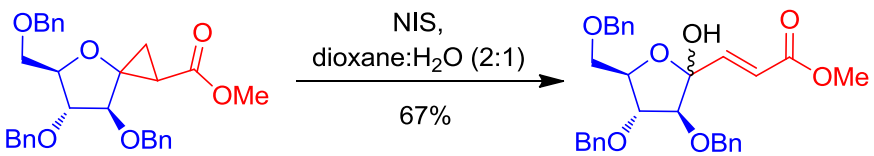
(2.4.2.42) (5*R*,6*R*,7*S*)-methyl 6,7-bis(benzyloxy)-5-((benzyloxy)methyl)-4-oxaspiro[2.4]heptane-1-carboxylate:



99 **100**

Compound **100** was synthesized from 2,5-anhydro-3,4,6-tri-*O*-benzyl-1-deoxy-D-arabino-hex-1-enitol **99** (1.35 g, 3.22 mmol), methyl diazoacetate (0.89 mL, 9.68 mmol), $Rh_2(OAc)_4$ (28 mg, 0.064 mmol) following the procedure described for compound **64** (2.4.2.17). Yield 56% (870 mg). This compound was obtained as a mixture of diastereomers, **HRMS (ESI)** calcd for $C_{30}H_{32}O_6$+Na 511.2097, found 511.2096.

(2.4.2.43) (*E*)-methyl 3-((3*S*,4*R*,5*R*)-3,4-bis(benzyloxy)-5-((benzyloxy)methyl)-2-hydroxytetrahydrofuran-2-yl)acrylate:

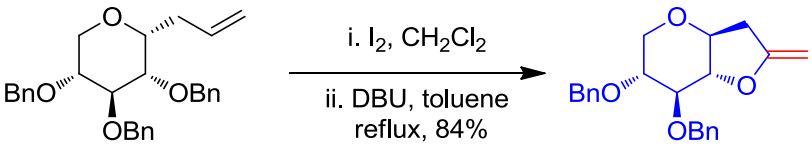


100 **101**

Compound **101** was synthesised from **100** (290 mg, 0.59 mmol), NIS (159 mg, 0.71 mmol) by following the porcedure described for compound **74** (2.4.2.18). Yield 67% (200 mg). This

compound was obtained as an inseparable mixture of anomers. HRMS (ESI) calcd for $C_{30}H_{32}O_7$+Na 527.2046, found 527.2047.

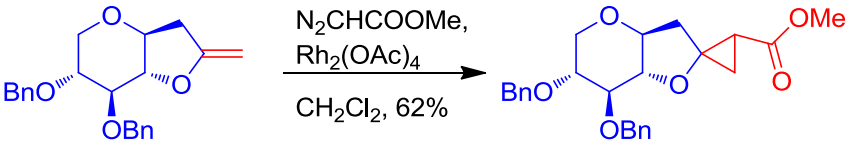
(2.4.2.44) (3a*S*,6*R*,7*S*,7a*S*)-6,7-bis(benzyloxy)-2-methylenehexahydro-2*H*-furo[3,2-*b*]pyran:



105 **107**

To a stirred solution of 1-allyl-2,3,4-tri-*O*-benzyl-β-D-xylopyranose **105** (3.0 g, 6.7 mmol) in dry CH_2Cl_2 (30 mL) at 0 °C was added iodine (3.43 g, 13.50 mmol). After completion of reaction (~30 min, monitored by TLC) aqueous $Na_2S_2O_3$ was added and the mixture was stirred until the mixture become colourless. The organic layer was separated and dried over anhydrous Na_2SO_4 and filtered, evaporation of the solvent followed by column chromatography provided the bicyclic iodoether as a colourless gum. The crude product was dissolved in toluene (30 mL) and cooled to 0 °C. DBU (2.1 mL, 14.06 mmol) was added slowly for a period of 10 min and the reaction mixture was allowed to room temperature. The solution was refluxed for 90 min. After completion of reaction the mixture was diluted with ethyl acetate and water. The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were dried and filtered. Removal of solvent followed by flash column chromatography provided the vinyl ether **107** (2.03 g) in 84% yield as a colourless gum which solidified upon refrigeration. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30 - 7.46 (m, 10H), 4.98 (d, 1H, *J* = 11.6 Hz), 4.85 (d, 1H, *J* = 11.6 Hz), 4.80 (d, 1H, *J* = 11.6 Hz), 4.67 (d, 1H, *J* = 11.6 Hz), 4.43 (s, 1H), 4.04-4.09 (m, 2H), 3.75 – 3.79 (m, 1H), 3.64-3.70 (m, 2H), 3.50-3.57 (m, 1H), 3.42 (t, 1H, *J* = 10.4 Hz), 2.78 (dd, 1H, *J* = 6.8 Hz, *J* = 14.4 Hz), 2.56-2.53 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.7, 138.4, 138.0, 128.6, 128.3, 128.2, 127.8, 127.7, 127.5, 84.1, 82.8, 78.2, 77.5, 74.3, 73.2, 70.3, 33.5. HRMS (ESI) calcd for $C_{22}H_{24}O_4$+Na 375.1572, found 375.1573.

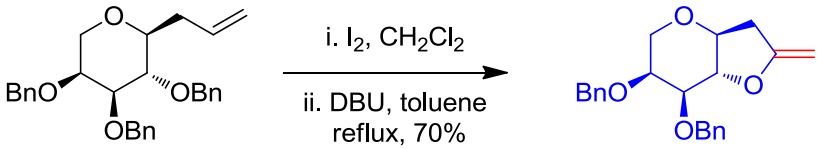
(2.4.2.45) (3a'*S*,6'*R*,7'*S*,7a'*S*)-methyl 6',7'-bis(benzyloxy)hexahydrospiro[cyclopropane-1,2'-furo[3,2-*b*]pyran]-2-carboxylate:



107 **108**

Compound **108** was synthesized from **107** (667 mg, 1.89 mmol), methyl diazoacetate (0.52 mL, 5.67 mmol), $Rh_2(OAc)_4$ (16.0 mg, 0.037 mmol) by following the procedure described for compound **64** (2.4.2.17). Yield 62% (495 mg). This compound was obtained as an inseparable mixture of diastereomers. HRMS (ESI) calcd for $C_{25}H_{28}O_6$+Na 447.1784, found 447.1785.

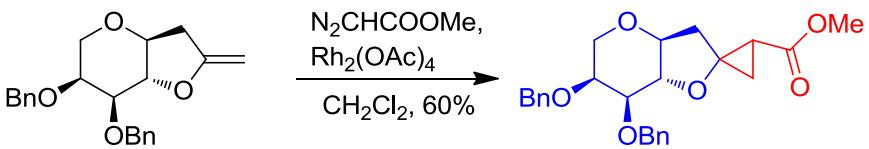
(2.4.2.46) (3a*S*,6*S*,7*S*,7a*S*)-6,7-bis(benzyloxy)-2-methylenehexahydro-2*H*-furo[3,2-*b*]pyran:



111 **112**

The synthesis of vinyl ether **112** was prepared starting from 1-allyl-2,3,4-tri-*O*-benzyl-α-L-arabinopyranose **111** following the procedure described for compound **107** (2.4.2.44). Yield 70%. **^{1}H NMR (400 MHz, $CDCl_3$)**: δ 7.32 - 7.45 (m, 10H), 4.89 (d, 1H, *J* = 12.4 Hz), 4.81 (s, 1H), 4.80 (s, 1H), 4.70 (d, 1H, *J* = 12.4 Hz), 4.47 (s, 1H), 4.28 (t, 1H, *J* = 9.6 Hz), 4.17 (dd, 1H, *J* = 2.0 Hz, *J* = 12.4 Hz), 4.07 (s, 1H), 3.83-3.84 (m, 1H), 3.73 (dd, 1H, *J* = 3.6 Hz, *J* = 10.4 Hz), 3.48 (dd, 1H, *J* = 1.6 Hz, *J* = 12.4 Hz), 3.33-3.43 (m, 1H), 2.82 (dd, 1H, *J* = 7.2 Hz, *J* = 14.8 Hz), 2.71-2.79 (m, 1H). **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 159.0, 138.4, 138.2, 128.6, 128.4, 128.4, 128.0, 127.8, 127.7, 127.5, 83.9, 81.2, 80.4, 79.0, 74.3, 72.7, 71.6, 70.9, 33.7. **HRMS (ESI)** calcd for $C_{22}H_{24}O_4$+Na 375.1572, found 375.1576.

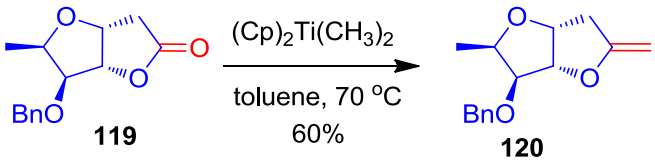
(2.4.2.47) (3a'*S*,6'*S*,7'*S*,7a'*S*)-methyl 6',7'-bis(benzyloxy)hexahydrospiro[cyclopropane-1,2'-furo[3,2-*b*]pyran]-2-carboxylate:



112 **113**

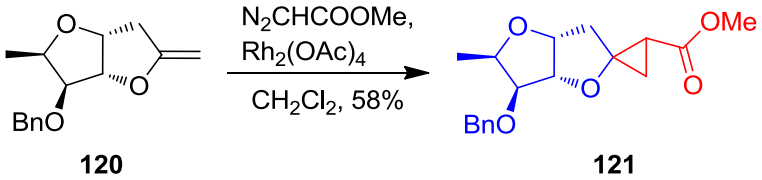
The ovinyl ether **112** (400 mg, 1.13 mmol), methyl diazoacetate (0.31 mL, 3.4 mmol), $Rh_2(OAc)_4$ (10.0 mg, 0.022 mmol) was cyclopropanated to give **113** (289 mg) following the procedure described for compound **64** (2.4.2.17). Yield 60%. This compound was obtained as a diasteremeric mixture. HRMS (ESI) calcd for $C_{25}H_{28}O_6$+Na 447.1784, found 447.1781.

(2.4.2.48) (2*R*,3*S*,3a*S*,6a*R*)-3-(benzyloxy)-2-methyl-5-methylenehexahydrofuro[3,2-*b*]furan:



3,6-anhydro-5-*O*-benzyl-2,7-di-deoxy-D-ido-heptono-2,4-lactone **119** (2.5 g, 10 mmol) was dissolved in dry toluene (50 mL) and dimethyl titanocene (16.64 mL of a 20% w/w solution in toluene, 20 mmol) was added slowly at room temperature, then the reaction mixture stirred in the dark for 24 h or until TLC showed disappearance of the starting material at 70 ^{0}C under argon. The brown reaction mixture was concentrated, and the remaining syrup after dilution with a minimum amount of toluene subjected to column chromatography, on neutral alumina using hexane/ethyl acetate (containing 1% triethylamine) to give the methylenated product **120** (1.5 g) in 60% yield. **^{1}H NMR (400 MHz, $CDCl_3$)**: δ 7.26 - 7.36 (m, 5H), 4.80-4.83 (m, 2H), 4.70 (d, 1H, *J* = 12.0 Hz), 4.57 (d, 1H, *J* = 12.0 Hz), 4.25 (s, 1H), 4.10-4.12 (m, 1H), 4.86 (d, 2H, *J* = 11.2 Hz), 2.69 (bs, 2H), 1.27 (d, 3H, *J* = 6.0 Hz). **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 161.9, 137.8, 128.4, 127.9, 127.6, 88.3, 83.1, 81.3, 79.7, 77.0, 72.2, 37.1, 13.8. **HRMS (ESI)** calcd for $C_{15}H_{18}O_3$+Na 269.1154, found 269.1152.

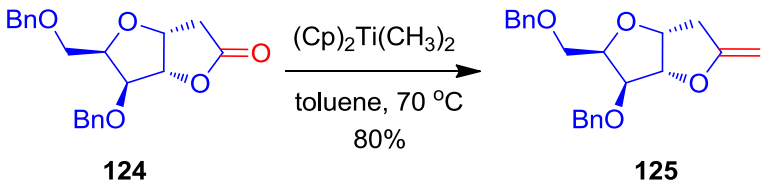
(2.4.2.49) (3a'*R*,5'*R*,6'*S*,6a'*S*)-methyl 6'-(benzyloxy)-5'-methyltetrahydro-3'*H*-spiro[cyclopropane-1,2'-furo[3,2-*b*]furan]-2-carboxylate:



The obtained methylenated product **120** (200 mg, 0.81 mmol), methyl diazoacetate (0.24 mL, 2.43 mmol), $Rh_2(OAc)_4$ (7.1 mg, 0.016 mmol) was cyclopropanated following the procedure

described for compound **64** (2.4.2.17) to obtain spiro-cyclopropanecarboxylate **121** (150 mg) in 58% yield as a diastereomeric mixture. HRMS (ESI) calcd for $C_{18}H_{22}O_5$+Na 341.1365, found 341.1368.

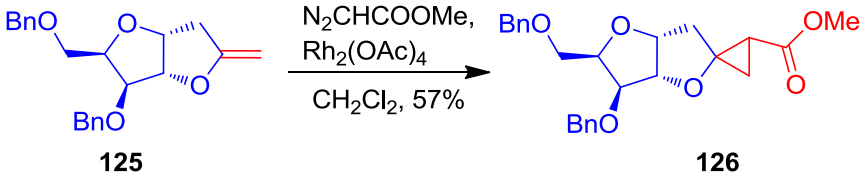
(2.4.2.50) (2*R*,3*S*,3a*S*,6a*R*)-3-(benzyloxy)-2-((benzyloxy)methyl)-5-methylenehexahydrofuro[3,2-*b*]furan:



124 **125**

3,6-anhydro-5,7-di-*O*-benzyl-2-deoxy-D-ido-heptono-2,4-lactone **124** (1 g, 2.8 mmol) was methylenation with peatasis reagent (4.68 mL of a 20% w/w solution in toluene, 5.6 mmol) to give methylenated product **125** following the procedure described for compound **120** (2.4.2.48) in 80% yield (0.80 g). **^{13}C NMR (100 MHz, CDCl$_3$)**: δ 161.6, 138.1, 137.6, 128.5, 128.3, 127.9, 127.8, 127.6, 87.8, 82.3, 81.7, 80.5, 80.2, 73.5, 72.4, 68.2, 37.0. **HRMS (ESI)** calcd for $C_{22}H_{24}O_4$+Na 375.1572, found 375.1573.

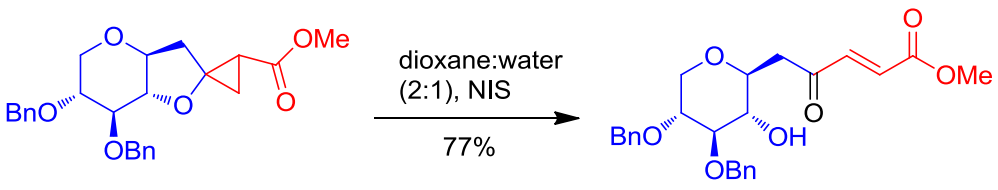
(2.4.2.51) (3a'*R*,5'*R*,6'*S*,6a'*S*)-methyl 6'-(benzyloxy)-5'-((benzyloxy)methyl)tetrahydro-3'*H*-spiro[cyclopropane-1,2'-furo[3,2-*b*]furan]-2-carboxylate:



125 **126**

The obtained vinyl ether **125** (750 mg, 2.13 mmol), methy diazoacetate (0.62 mL, 6.39 mmol) and rhodium acetate (18.8 mg, 0.042 mmol) was cyclopropanated by following the procedure described for compound **64** (2.4.2.17) to obtian a diastereomeric mixture of spiro-cyclopropanecarboxylate **126** (520 mg) in 57% yield. **HRMS (ESI)** calcd for $C_{18}H_{22}O_5$+Na 341.1365, found 341.1365.

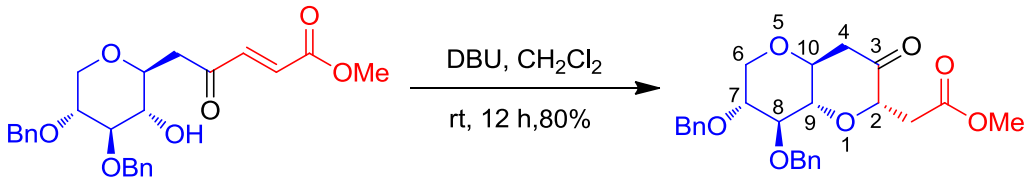
(2.4.2.52) (*E*)-methyl 5-((2*S*,3*S*,4*R*,5*R*)-4,5-bis(benzyloxy)-3-hydroxytetrahydro-2*H*-pyran-2-yl)-4-oxopent-2-enoate:



108 **127**

Compound **127** was synthesized from **108** (160 mg, 0.37 mmol) and NIS (101 mg, 0.45 mmol) in dioxane: water (2:1) (6 mL) by following the procedure described for compound **74** (2.4.2.18). Yield 77% (123 mg). **^{1}H NMR (400 MHz, $CDCl_3$)**: δ 7.32-7.39 (m, 10H), 7.10 (d, 1H, *J* = 16.0 Hz), 6.69 (d, 1H, *J* = 16.0 Hz), 5.04 (d, 1H, *J* = 11.6 Hz), 4.73 (d, 1H, *J* = 11.6 Hz), 4.69 (d, 1H, *J* = 11.6 Hz), 4.63 (d, 1H, *J* = 11.6 Hz), 3.97 (dd, 1H, *J* = 5.2 Hz, *J* = 11.6 Hz), 3.82 (s, 3H), 3.71 (dt, 1H, *J* = 3.2 Hz, *J* = 9.2 Hz), 3.58-3.64 (m, 1H), 3.45 (t, 1H, *J* = 8.8 Hz), 3.30 (t, 1H, *J* = 9.2 Hz), 3.25 (t, 1H, *J* = 11.2 Hz), 3.06 (dd, 1H, *J* = 4.0 Hz, *J* = 16.0 Hz), 2.78 (dd, 1H, *J* = 8.4 Hz, *J* = 16.0 Hz). **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 197.4, 165.9, 139.7, 138.4, 137.9, 130.7, 128.6, 128.5, 128.0, 127.9, 127.8, 85.1, 78.3, 75.9, 75.1, 73.0, 73.0, 68.0, 52.3, 44.0. **HRMS (ESI)** calcd for $C_{25}H_{28}O_7$+Na 463.1733, found 463.1734.

(2.4.2.53) Methyl 2-((2*S*,4a*S*,7*R*,8*S*,8a*S*)-7,8-bis(benzyloxy)-3-oxooctahydropyrano[3,2-b]pyran-2-yl)acetate:

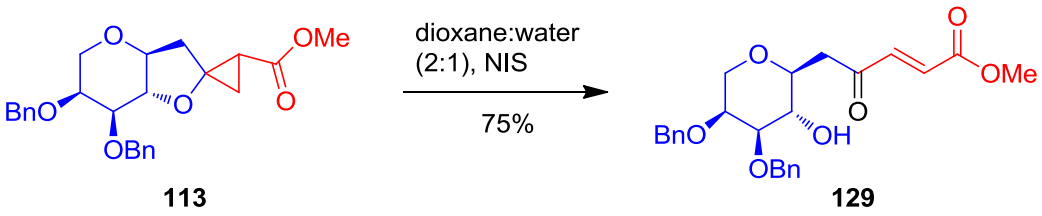


127 **128**

To a stirred solution of α,β-unsaturated ester **127** (100 mg, 0.22 mmol) and in CH_2Cl_2 (5 mL) was added 1,8-diazabicyclcoundec-7-ene (68 µL, 0.45 mmol) at 0 °C and the reaction mixture was stirred for 1 h at same temperature. After completion of the reaction, the solvent was evaporated and purified by column chromatography on silica gel (eluent: 10-20%) to obtain the ring-expanded product **128** (80 mg) in 80% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31 - 7.41 (m, 10H, phenyl), 4.90 (d, 1H, *J* = 11.2 Hz, PhC*H*), 4.81 (d, 2H, *J* = 11.2 Hz, PhCH_2), 4.67 (d, 1H, *J* = 11.2 Hz, PhC*H*), 4.26 (dd, 1H, *J* = 4.8 Hz, *J* = 6.8 Hz, *H*-2), 4.00 (dd, 1H, *J* = 4.8 Hz, *J* = 11.6 Hz, *H*-6_a), 3.69 (s, 3H, OCH_3), 3.59-3.69 (m, 2H, *H*-7, *H*-8), 3.47-3.54 (m, 2H, *H*-9, *H*-10), 3.30 (t, 1H, *J* = 10.4 Hz, *H*-6_b), 3.01 (dd, 1H, *J* = 4.8 Hz, *J* = 16.0 Hz, *H*-4a), 2.92 (dd, 1H, *J* = 4.4 Hz, *J* = 16.0 Hz, *H*-11a), 2.74 (dd, 1H, *J* = 6.4 Hz, *J* = 16.4 Hz, *H*-11b),

2.48 (dd, 1H, *J* = 10.4 Hz, *J* = 16.0 Hz, *H*-4b). ^{13}C NMR (100 MHz, $CDCl_3$): δ 203.9, 170.9, 138.6, 138.1, 128.4, 128.3, 127.9, 127.8, 127.6, 82.8, 81.1, 79.2, 77.2, 75.0, 74.3, 73.8, 68.5, 52.0, 44.5, 35.4. HRMS (ESI) calcd for $C_{25}H_{28}O_7$+Na 463.1733, found 463.1736.

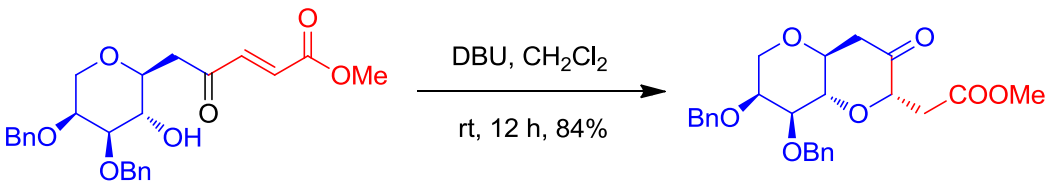
(2.4.2.54) (*E*)-methyl 5-((2*S*,3*S*,4*R*,5*S*)-4,5-bis(benzyloxy)-3-hydroxytetrahydro-2*H*-pyran-2-yl)-4-oxopent-2-enoate:



113 **129**

Compound **129** was synthesized from **113** (54 mg, 0.127 mmol) and NIS (34.2 mg, 0.15 mmol) in dioxane: water (2:1) (3 ml) following the procedure described for the preparation of compound **74** (2.4.2.18). Yield 75% (40 mg). **^{1}H NMR (400 MHz, $CDCl_3$)**: δ 7.31 - 7.40 (m, 10H), 7.12 (d, 1H, *J* = 16.0 Hz), 6.71 (d, 1H, *J* = 16.0 Hz), 4.77 (d, 1H, *J* = 6.0 Hz), 4.75 (s, 1H), 4.63 (d, 1H, *J* = 11.6 Hz), 4.59 (d, 1H, *J* = 12.4 Hz), 4.40 (d, 1H, *J* = 11.6 Hz), 4.09 (dd, 1H, *J* = 2.0 Hz, *J* = 12.8 Hz), 3.81-3.87 (m, 4H), 3.77 (dd, 1H, *J* = 2.8 Hz, *J* = 6.4 Hz), 3.73 (dd, 1H, *J* = 2.8 Hz, *J* = 9.2 Hz), 3.40 (dd, 1H, *J* = 3.2 Hz, *J* = 9.2 Hz), 3.39 (dd, 1H, *J* = 0.8 Hz, *J* = 12.8 Hz), 3.13 (dd, 1H, *J* = 3.2 Hz, *J* = 16.4 Hz), 2.95 (dd, 1H, *J* = 8.4 Hz, *J* = 16.0 Hz), 2.42 (bs, 1H). **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 197.6, 166.0, 139.8, 137.9, 137.6, 130.6, 128.6, 128.4, 128.0, 127.9, 127.8, 82.1, 76.1, 71.7, 71.2, 71.0, 69.8, 67.1, 52.3, 44.0. **HRMS (ESI)** calcd for $C_{25}H_{28}O_7$+Na 463.1733, found 463.1730.

(2.4.2.55) methyl 2-((2*S*,4a*S*,7*S*,8*S*,8a*S*)-7,8-bis(benzyloxy)-3-oxooctahydropyrano[3,2-b]pyran-2-yl)acetate:

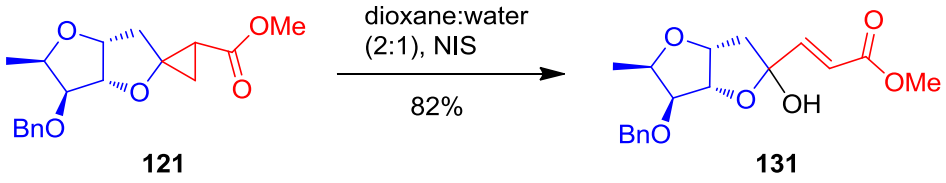


129 **130**

Compound **130** was synthesized from **129** (20 mg, 0.045 mmol) and DBU (8.15 µL, 0.054 mmol) in dichloromethane (2 mL) by following the procedure described for the preparation of compound **128** (2.4.2.53). Yield 84%. **^{1}H NMR (400 MHz, $CDCl_3$)**: δ 7.30-7.44 (m, 10H),

4.82 (d, 1H, *J* = 12.4 Hz), 4.78 (d, 1H, *J* = 12.4 Hz), 4.76 (d, 1H, *J* = 12.4 Hz), 4.66 (d, 1H, *J* = 12.4 Hz), 4.31 (dd, 1H, *J* = 4.8 Hz, *J* = 6.4 Hz), 4.07 (dd, 1H, *J* = 2.0 Hz, *J* = 12.8 Hz), 4.04 (t, 1H, *J* = 9.6 Hz), 3.80 (bs, 1H), 3.71 (s, 3H), 3.55 (dd, 1H, *J* = 3.2 Hz, *J* = 9.6 Hz), 3.43-3.49 (m, 1H), 3.40 (d, 1H, *J* = 12.8 Hz), 3.03 (dd, 1H, *J* = 5.6 Hz, *J* = 16.0 Hz), 2.92 (dd, 1H, *J* = 4.8 Hz, *J* = 16.4 Hz), 2.79 (dd, 1H, *J* = 6.4 Hz, *J* = 16.4 Hz), 2.66 (dd, 1H, *J* = 11.2 Hz, *J* = 16.0 Hz). **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 204.4, 170.8, 138.4, 138.1, 128.4, 128.3, 128.0, 127.7, 127.6, 127.5, 79.6, 79.1, 78.1, 74.8, 73.8, 72.5, 72.0, 68.4, 51.9, 44.4, 35.6. **HRMS (ESI)** calcd for $C_{25}H_{28}O_7$+Na 463.1733, found 463.1732.

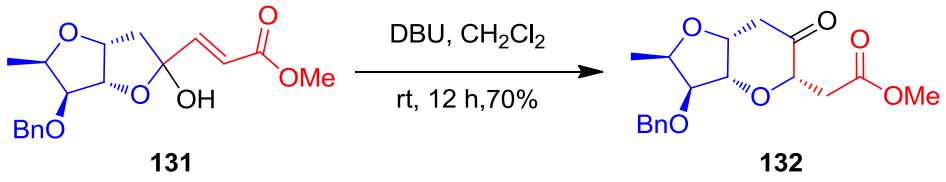
(2.4.2.56) (*E*)-methyl 3-((3a*R*,5*R*,6*S*,6a*S*)-6-(benzyloxy)-2-hydroxy-5-methylhexahydrofuro[3,2-b]furan-2-yl)acrylate:



121 **131**

Compound **131** was synthesized from compound **121** (60 mg, 0.188) and NIS (50.73 mg, 0.22 mmol) in dioxane: water (2:1) (3 ml) by following the procedure described for compound **74** (2.4.2.18). Yield 82%. This compound was obtained as an inseparable anomeric mixture. **HRMS (ESI)** calcd for $C_{18}H_{22}O_6$+Na 357.1314, found 357.1310.

(2.4.2.57) Methyl 2-((2*R*,3*S*,3a*S*,5*S*,7a*R*)-3-(benzyloxy)-2-methyl-6-oxohexahydro-2*H*-furo[3,2-*b*]pyran-5-yl)acetate:

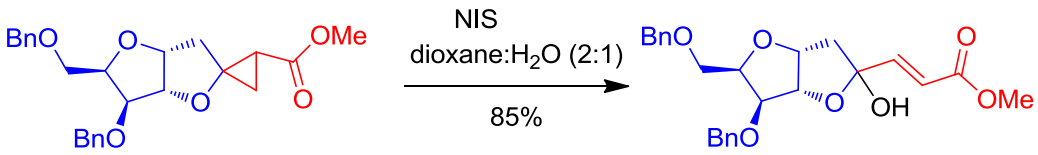


131 **132**

Compound **132** was synthesized from **131** (20 mg, 0.060 mmol) and DBU (11 µL, 0.718 mmol) in dichloromethane (2 mL) following the procedure described for compound **128** (2.4.2.53). Yield 70% (14 mg). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36-7.38 (m, 5H), 4.73 (d, 1H, *J* = 12 Hz), 4.57 (d, 1H, *J* = 12 Hz), 4.54-4.57 (m, 1H), 4.32 (dd, 1H, *J* = 4.0 Hz, *J* = 6.4 Hz), 4.27 (d, 1H, *J* = 4.0 Hz), 4.05 (dd, 1H, *J* = 4.4 Hz, *J* = 6.4 Hz), 3.93 (d, 1H, *J* = 3.2 Hz), 3.72 (s,

3H), 3.92 (dd, 1H, *J* = 6.8 Hz, *J* = 15.6 Hz), 2.78-2.88 (m, 2H), 2.73 (dd, 1H, *J* = 6.4 Hz, *J* = 16 Hz), 1.31 (d, 3H, *J* = 6.4 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 208.3, 170.5, 137.7, 128.4, 127.8, 127.5, 84.0, 81.5, 78.1, 75.7, 74.7, 72.0, 52.0, 41.0, 35.8, 13.8. HRMS (ESI) calcd for $C_{18}H_{22}O_6$+Na 357.1314, found 357.1313.

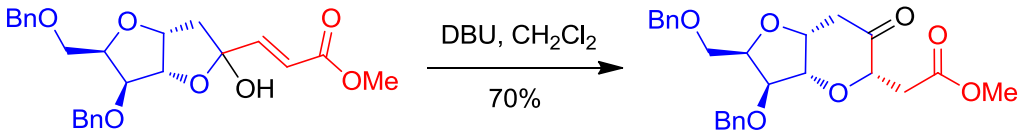
(2.4.2.58) (*E*)-methyl 3-((3a*R*,5*R*,6*S*,6a*S*)-6-(benzyloxy)-5-((benzyloxy)methyl)-2-hydroxyhexahydrofuro[3,2-*b*]furan-2-yl)acrylate:



126 **133**

Compound **133** was synthesized from **126** (85 mg, 0.2 mmol), NIS (54 mg, 0.24 mmol) in dioxane/water (2:1) (4 mL) following the procedure described for compound **74** (2.4.2.18). Yield 85% (75 mg). This compound was obtained as an inseparable anomeric mixture. HRMS (ESI) calcd for $C_{25}H_{28}O_7$+Na 463.1733, found 463.1733.

(2.4.2.59) methyl 2-((2*R*,3*S*,3a*S*,5*S*,7a*R*)-3-(benzyloxy)-2-((benzyloxy)methyl)-6-oxohexahydro-2*H*-furo[3,2-*b*]pyran-5-yl)acetate:



133 **134**

Compound **134** was synthesized from **133** (30 mg, 0.068 mmol) and DBU (12 µL, 0.081 mmol) in dichloromethane (2 mL) by following the procedure described for compound **128** (2.4.2.53). Yield 70% (20 mg). **^{1}H NMR (400 MHz, $CDCl_3$)**: δ 7.29-7.37 (m, 10H), 4.64 (d, 1H, *J* = 12 Hz), 4.63 (d, 1H, *J* = 12 Hz), 5.59-4.62 (m, 1H), 4.56 (d, 1H, *J* = 12 Hz), 4.53 (d, 1H, *J* = 12 Hz), 4.38-4.42 (m, 1H), 4.28 (dd, 1H, *J* = 1.6 Hz, *J* = 4.4 Hz), 4.15 (dd, 1H, *J* = 1.2 Hz, *J* = 4.4 Hz), 4.10 (dd, 1H, *J* = 4.4 Hz, *J* = 6.4 Hz), 3.68-3.76 (m, 5H), 2.94 (dd, 1H, *J* = 6 Hz, *J* = 15.6 Hz), 2.87 (dd, 1H, *J* = 4.4 Hz, *J* = 16.8 Hz), 2.80 (dd, 1H, *J* = 6.4 Hz, *J* = 15.6 Hz), 2.69 (dd, 1H, *J* = 6.8 Hz, *J* = 16.8 Hz). **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 207.4, 170.6, 138.1, 137.6, 128.4, 128.3, 127.8, 127.7, 127.6, 127.5, 83.1, 80.8, 78.9, 78.0, 75.6, 73.5, 72.4, 68.2, 52.0, 41.1, 35.6. **HRMS (ESI)** calcd for $C_{25}H_{28}O_7$+Na 463.1733, found 463.1745.

2.5 References

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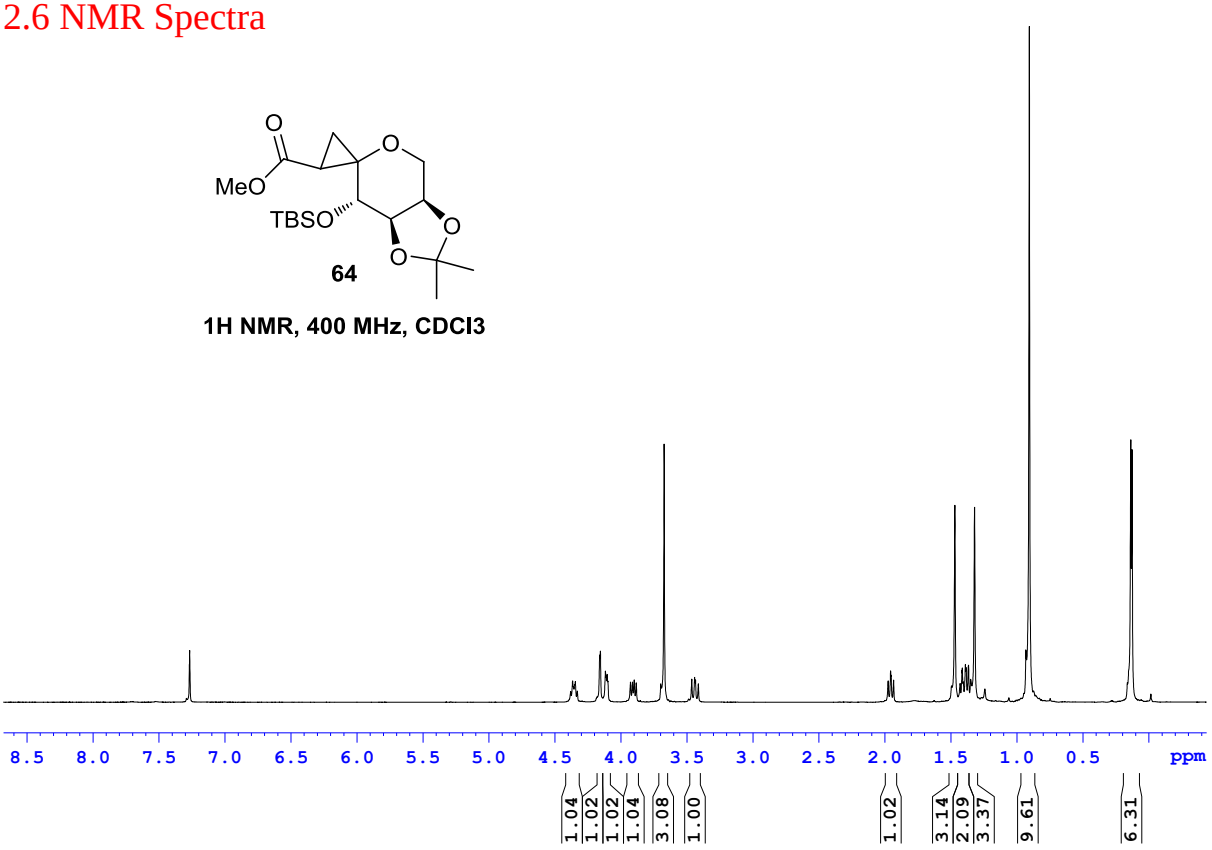
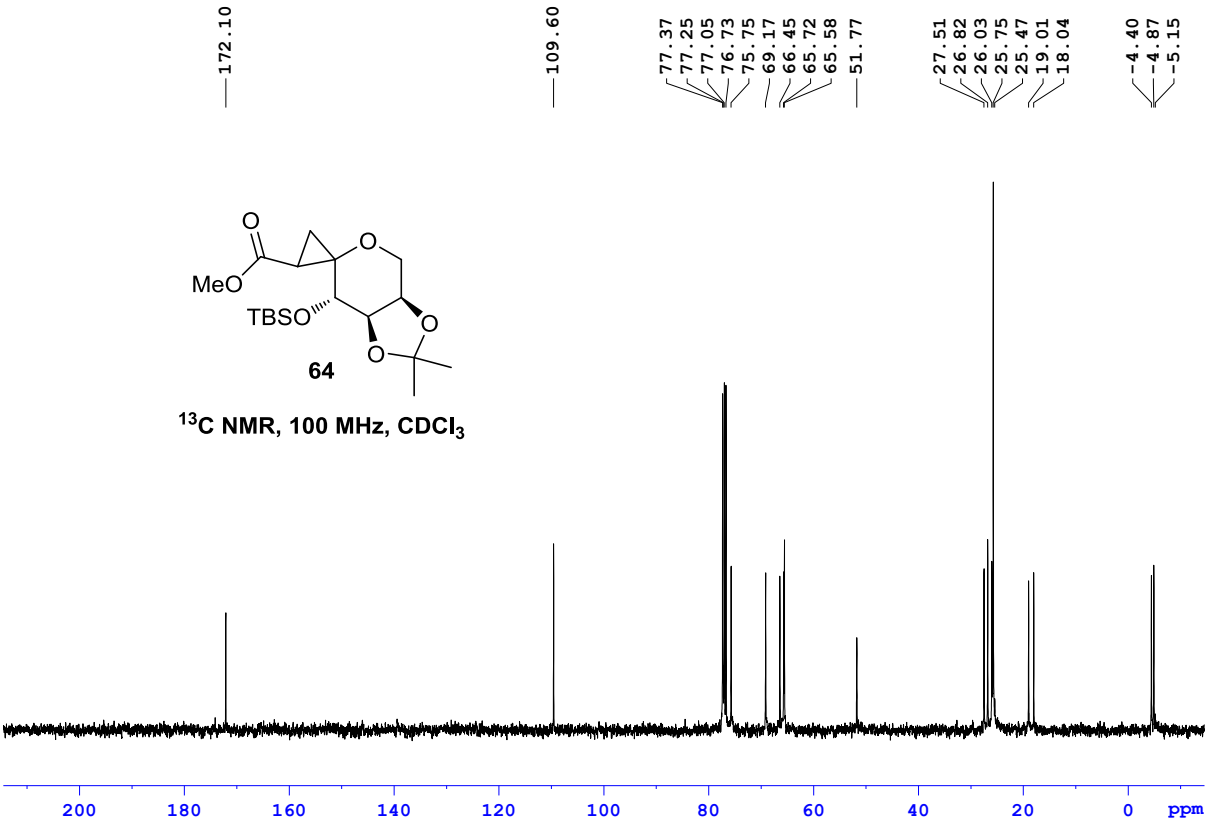
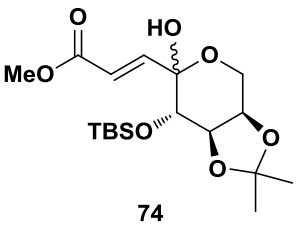
2.6 NMR Spectra

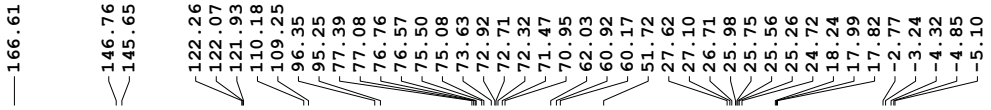


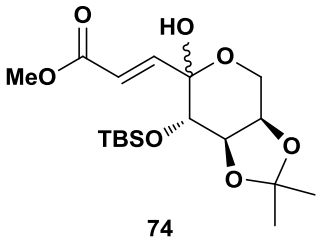




74

1H NMR, 400 MHz, $CDCl_3$





74

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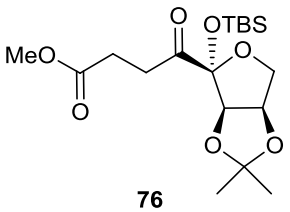

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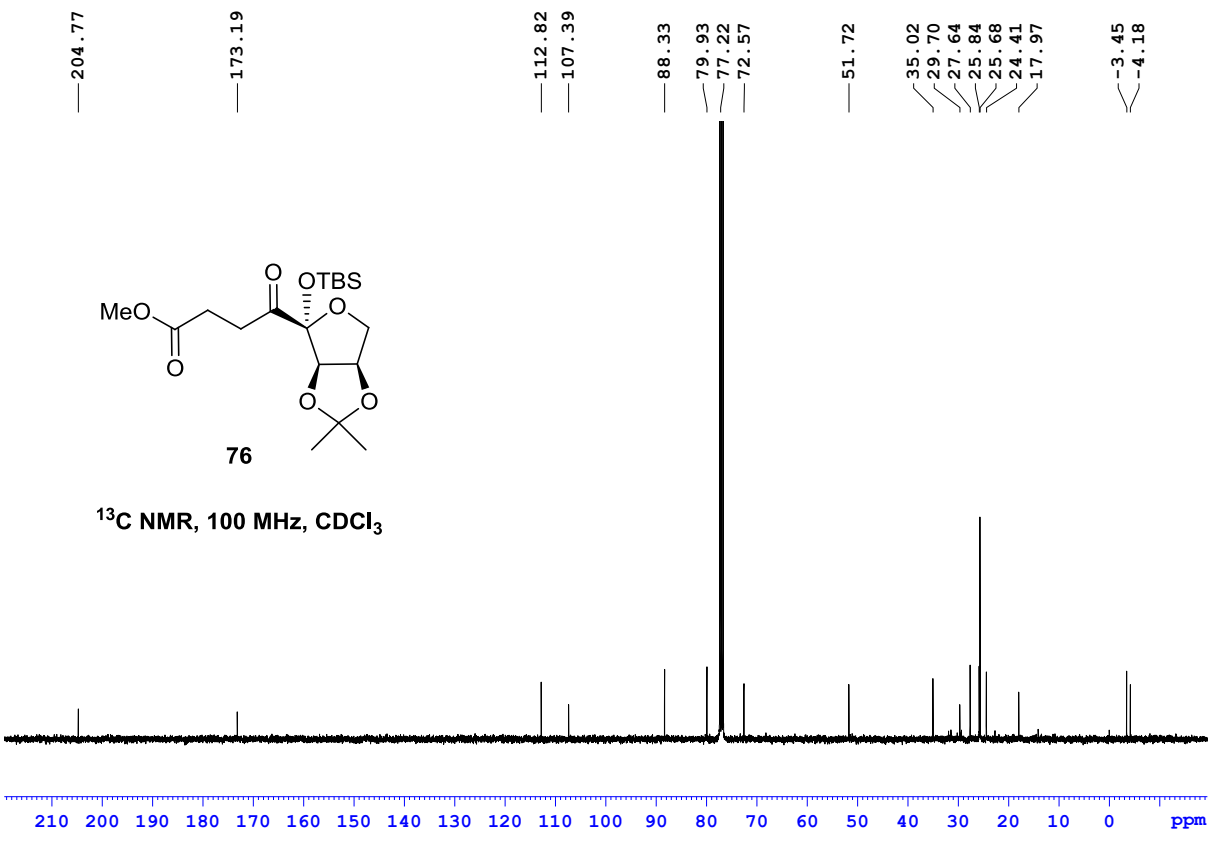

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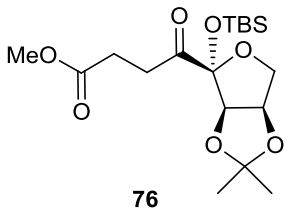

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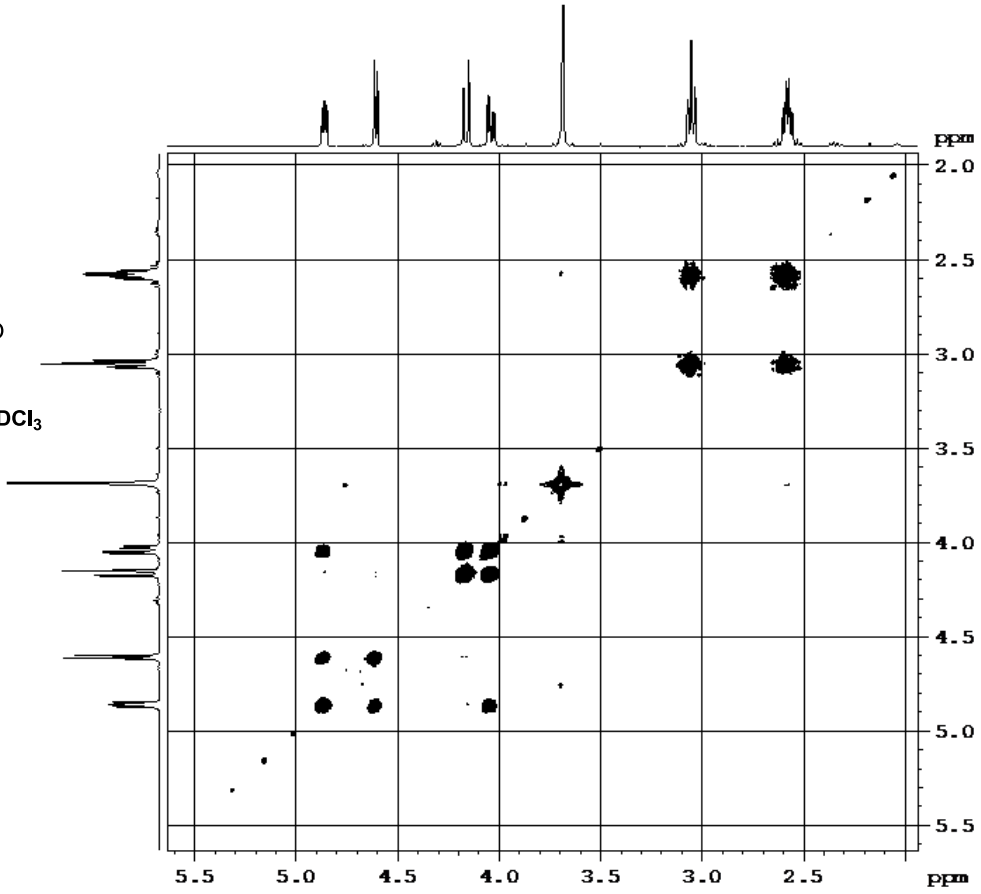
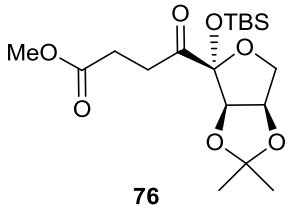
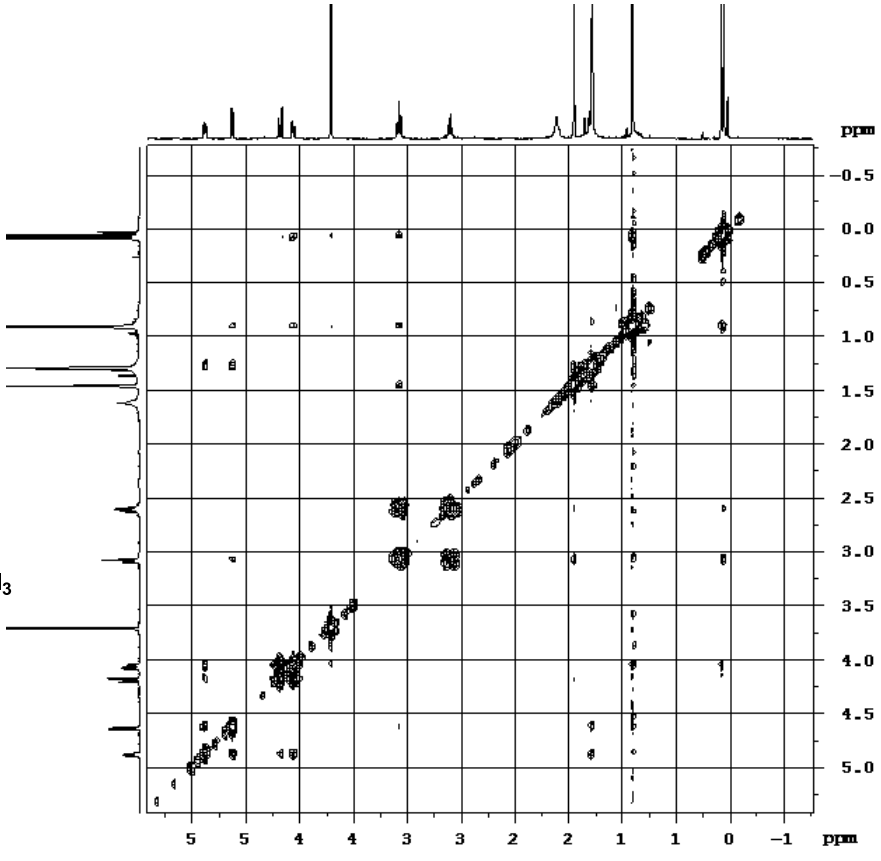
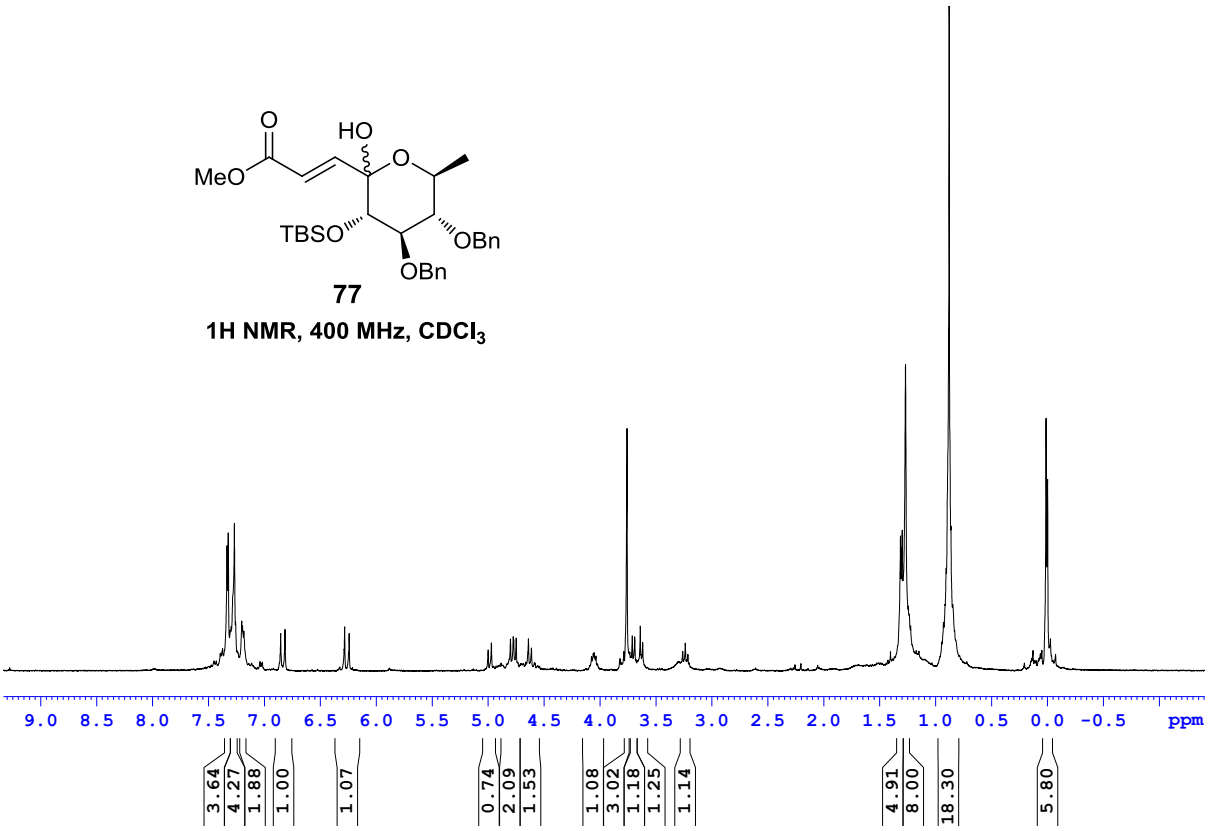




76

^{1}H-^{1}H NOESY NMR, 400 MHz, $CDCl_3$





77

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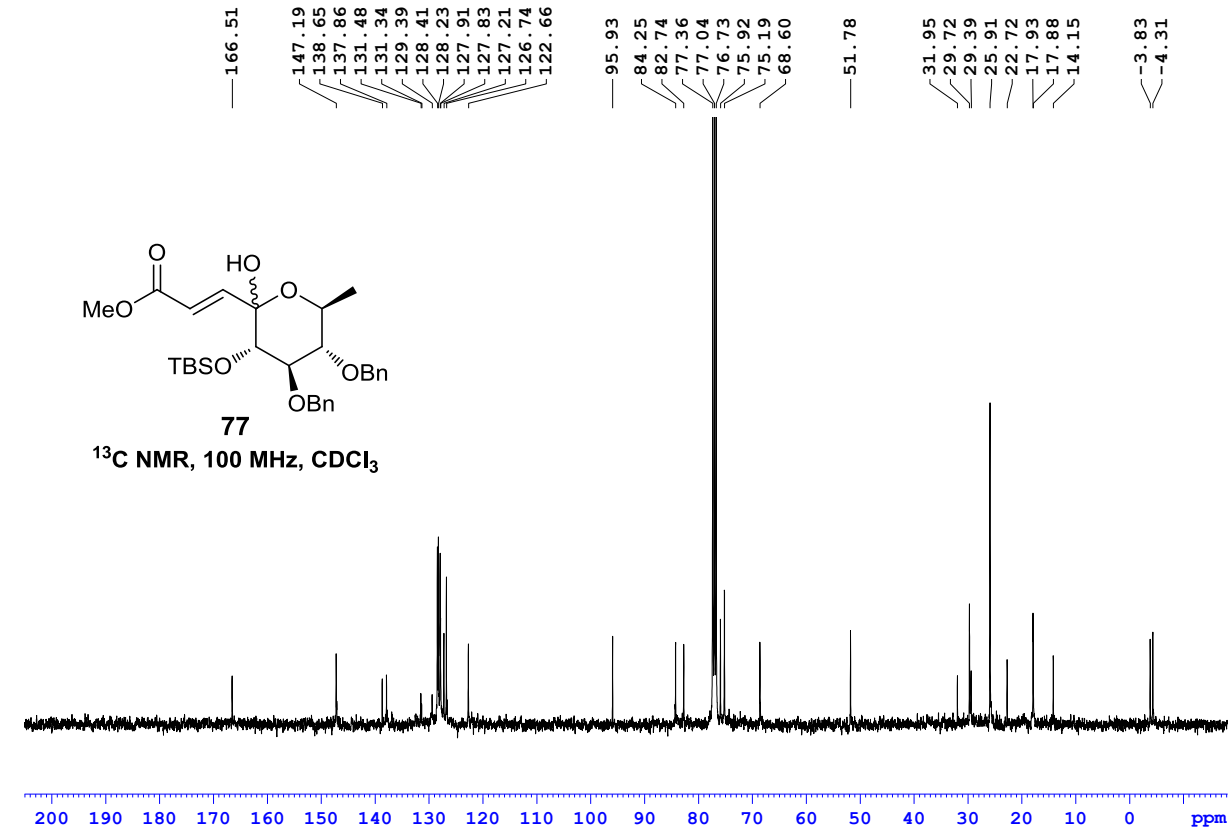

77

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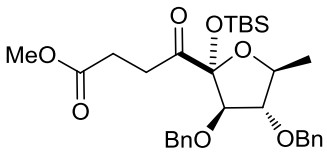

78

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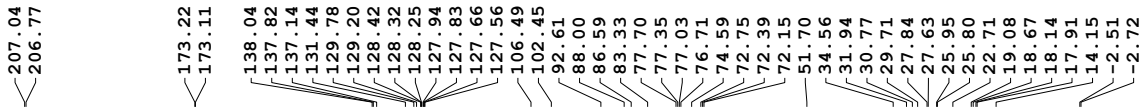

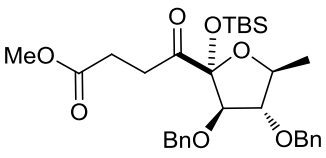

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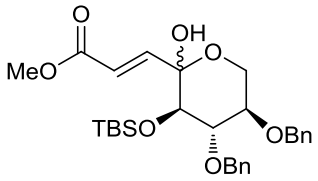

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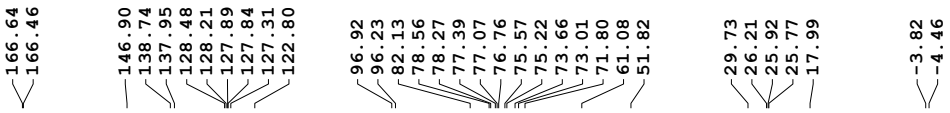

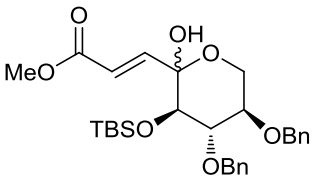

79

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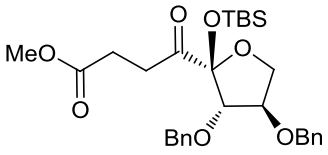
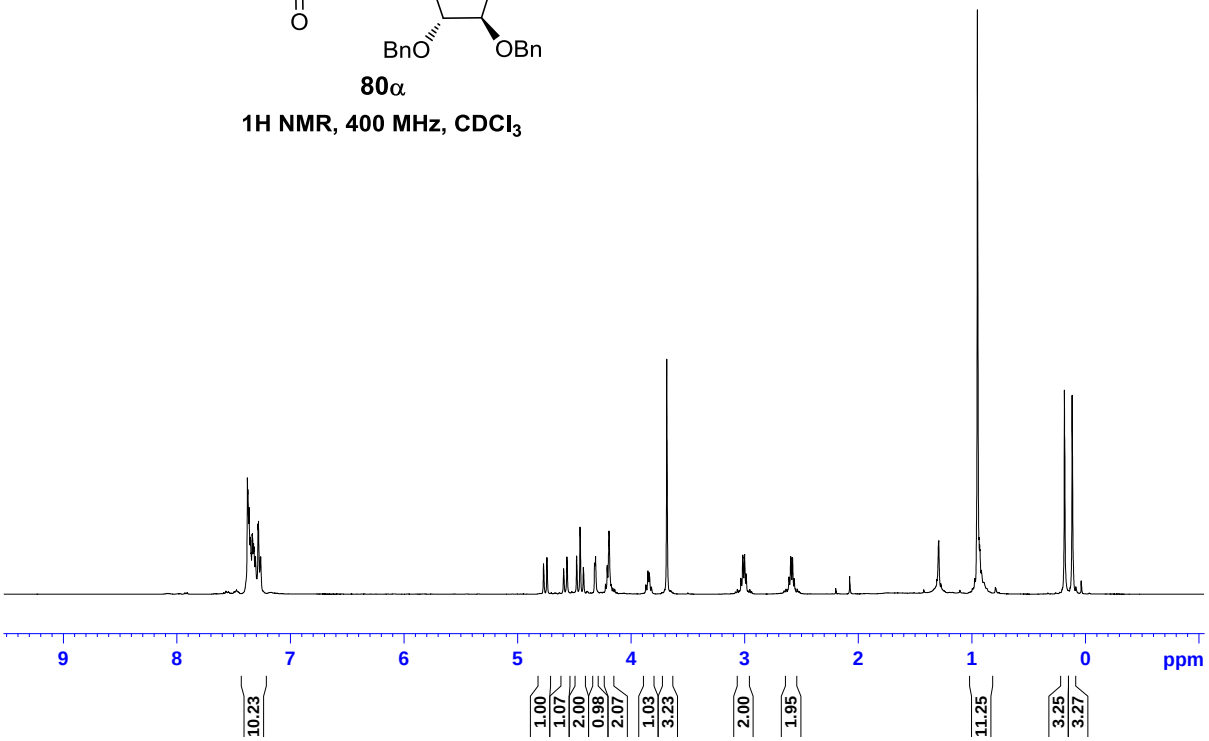
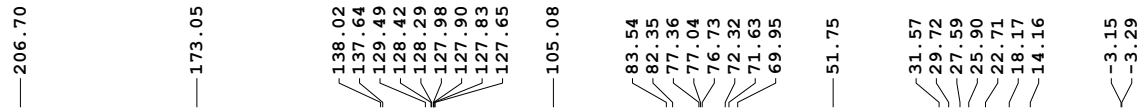
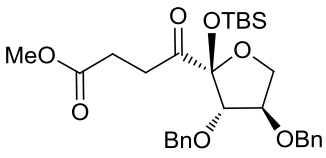


80α

1H NMR, 400 MHz, $CDCl_3$

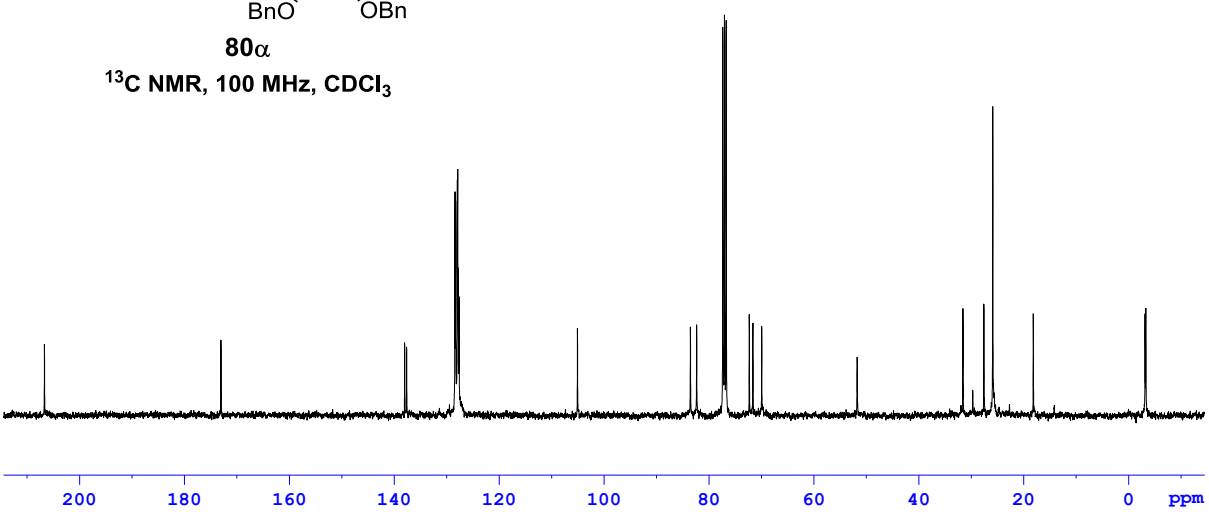


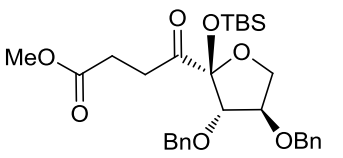




80α

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





80α

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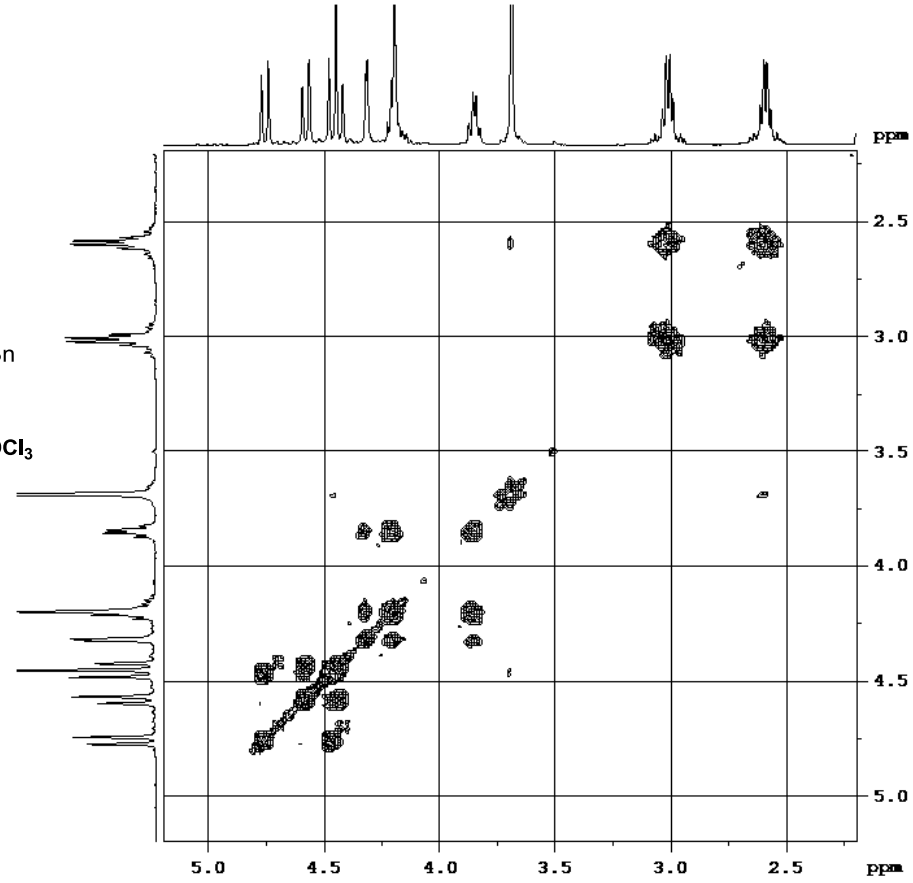
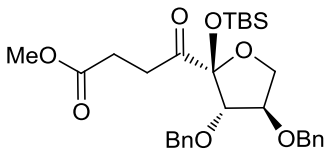
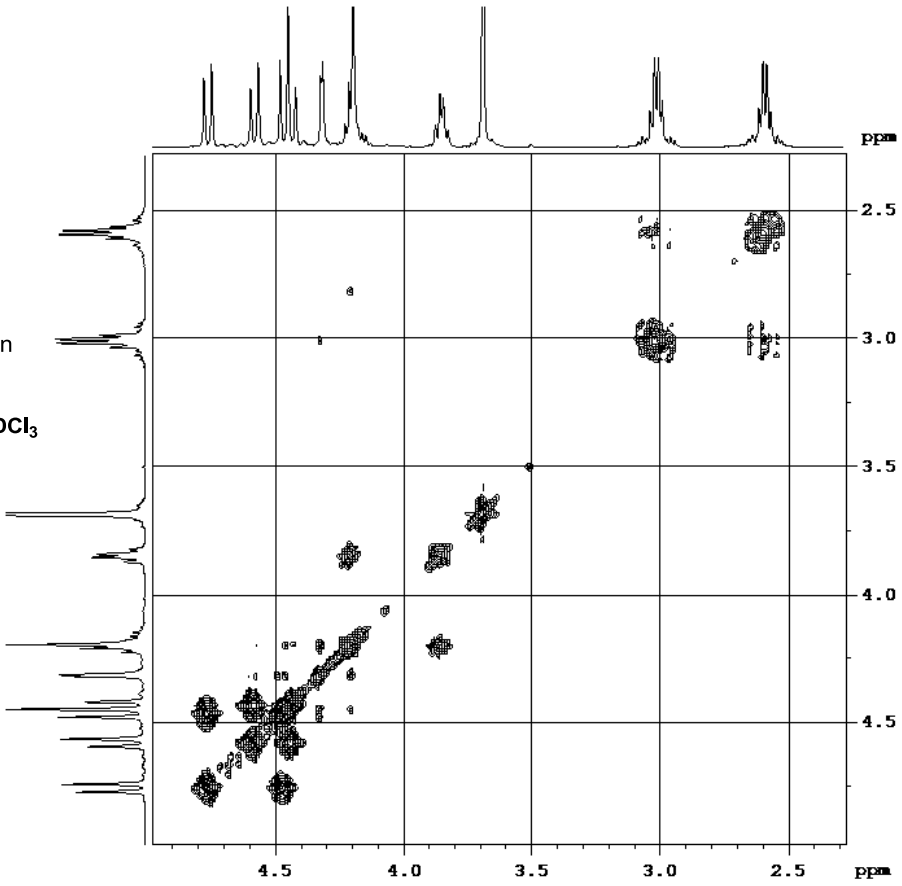
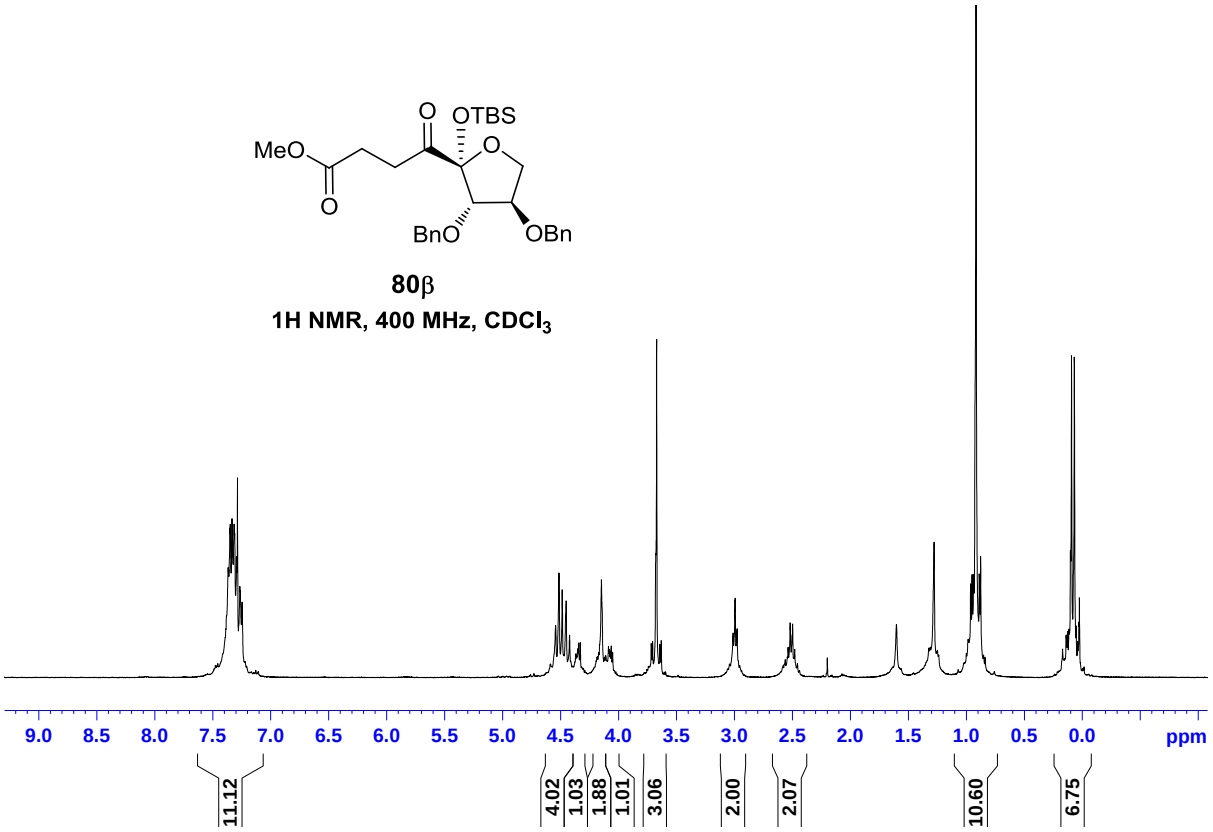




80α

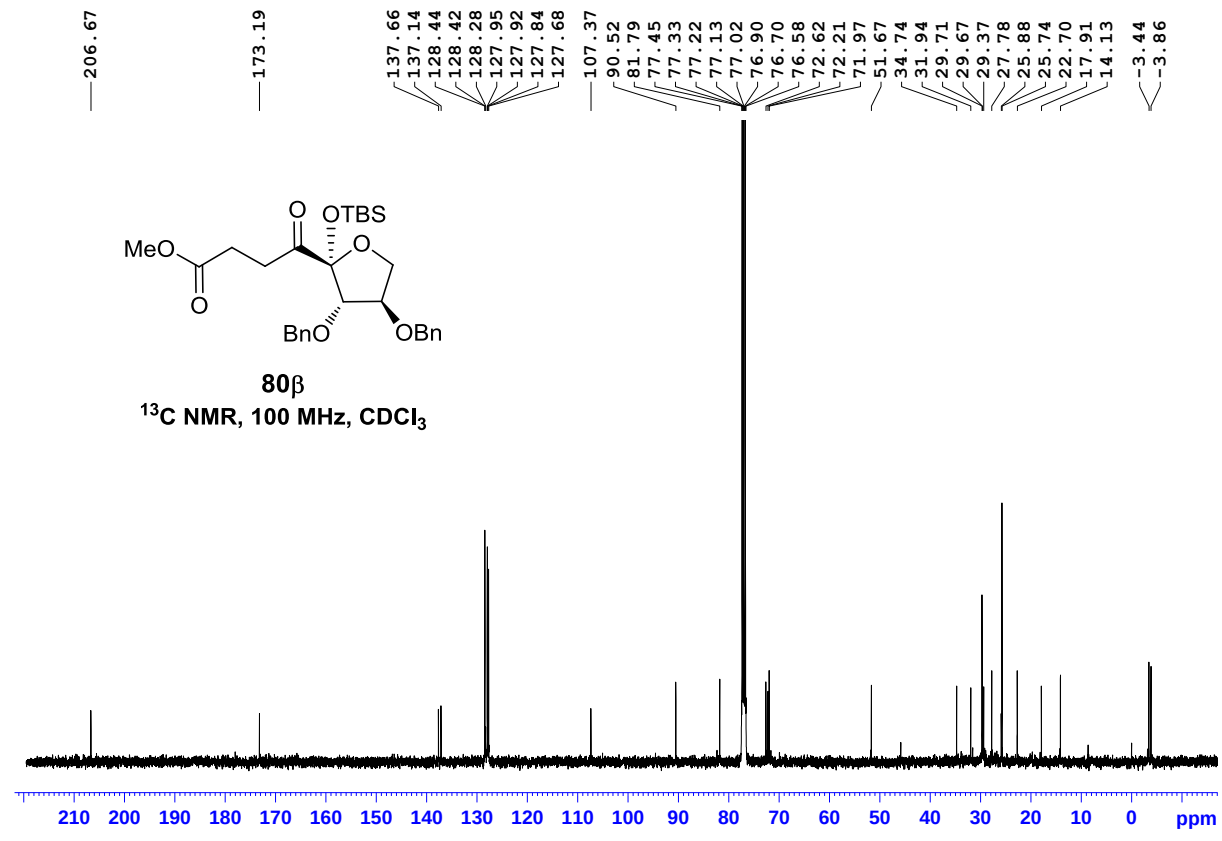
^{1}H-^{1}H NOESY NMR, 400 MHz, $CDCl_3$





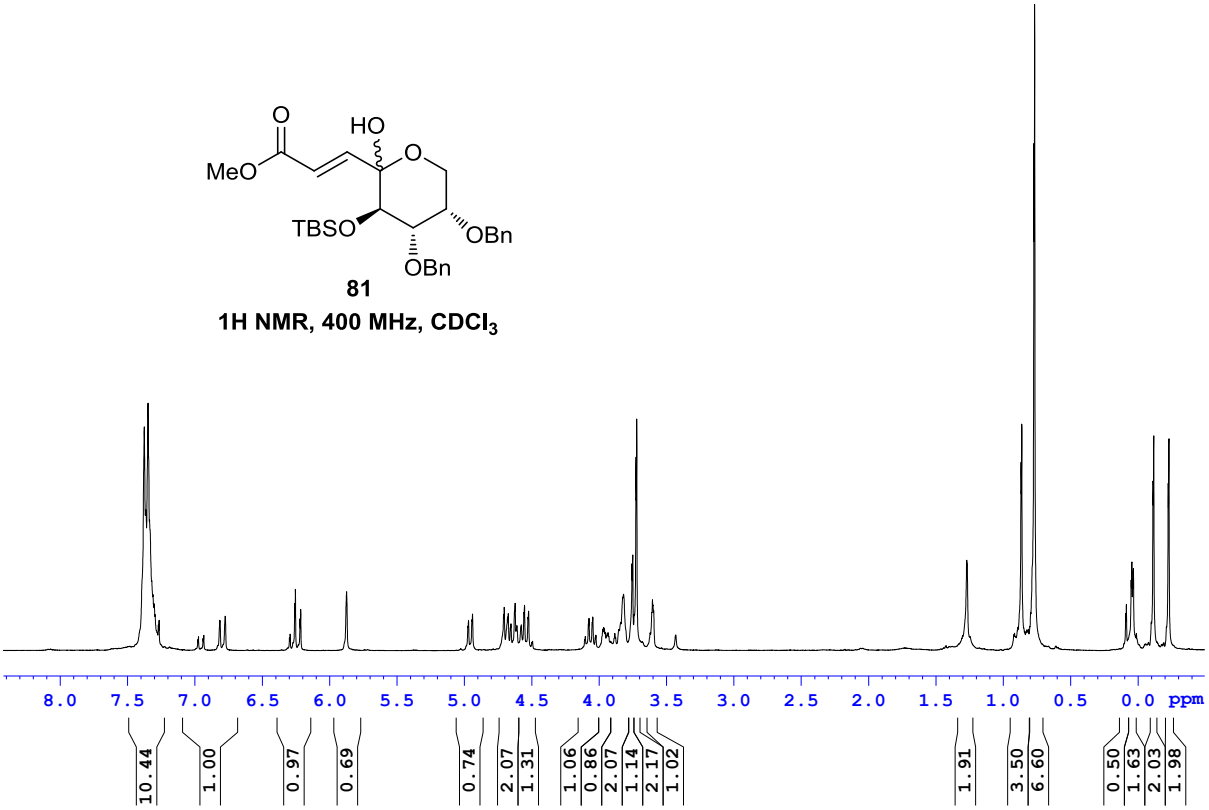
80β

1H NMR, 400 MHz, $CDCl_3$



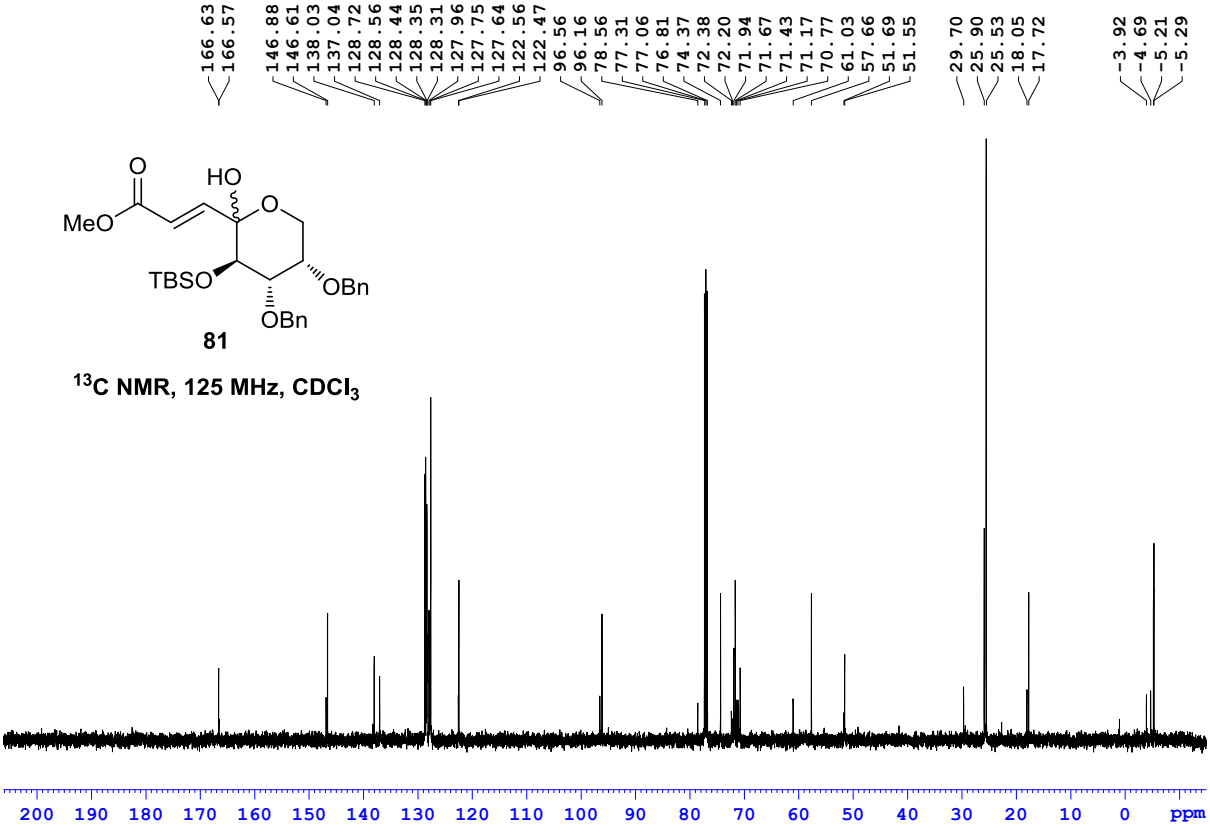
80β

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



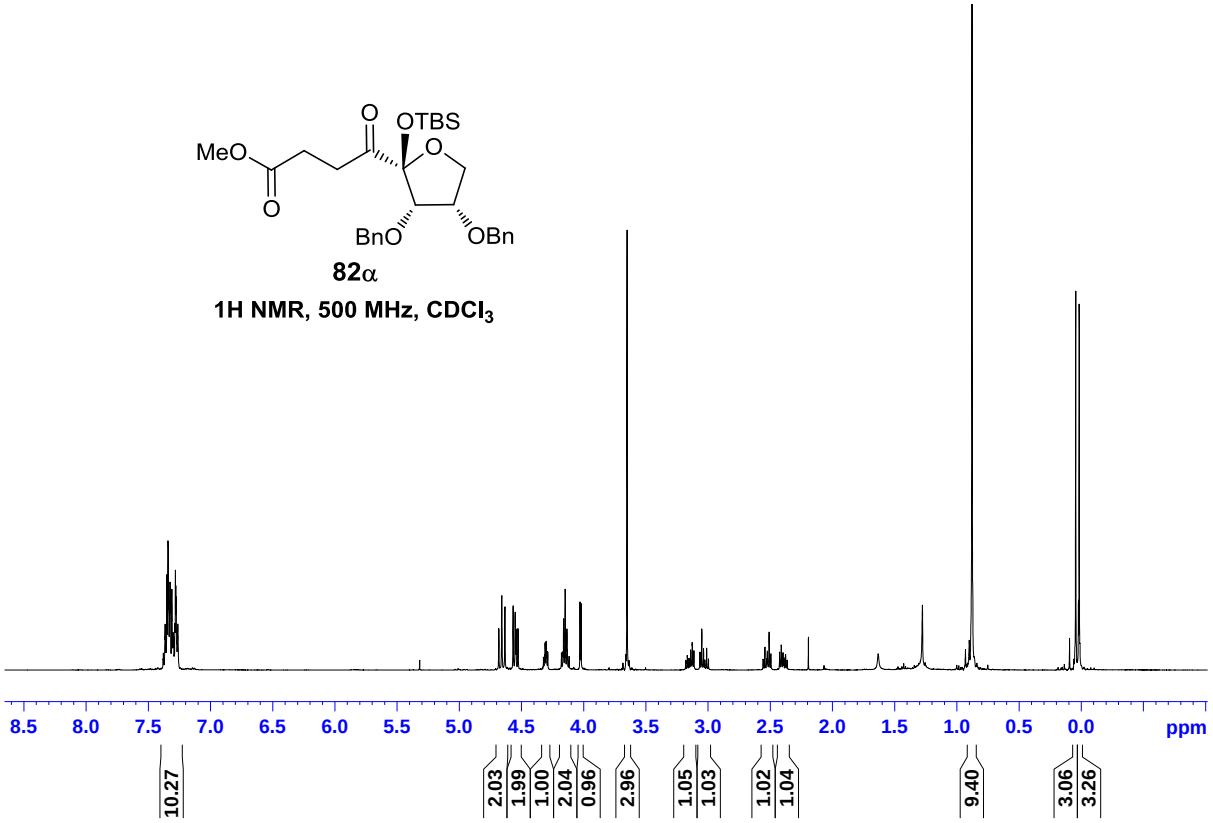
81

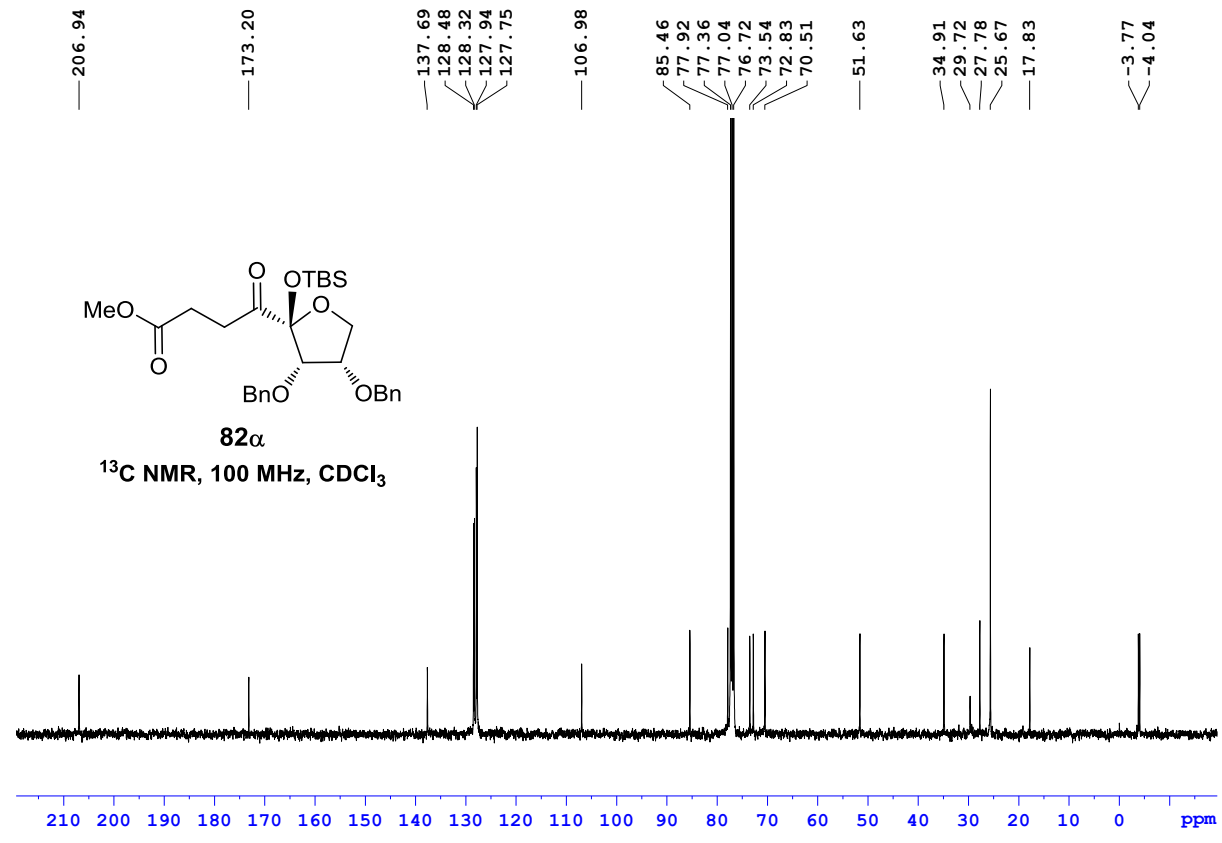
1H NMR, 400 MHz, $CDCl_3$

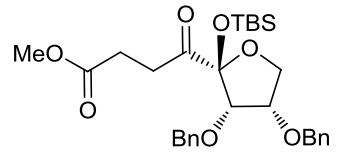


81

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

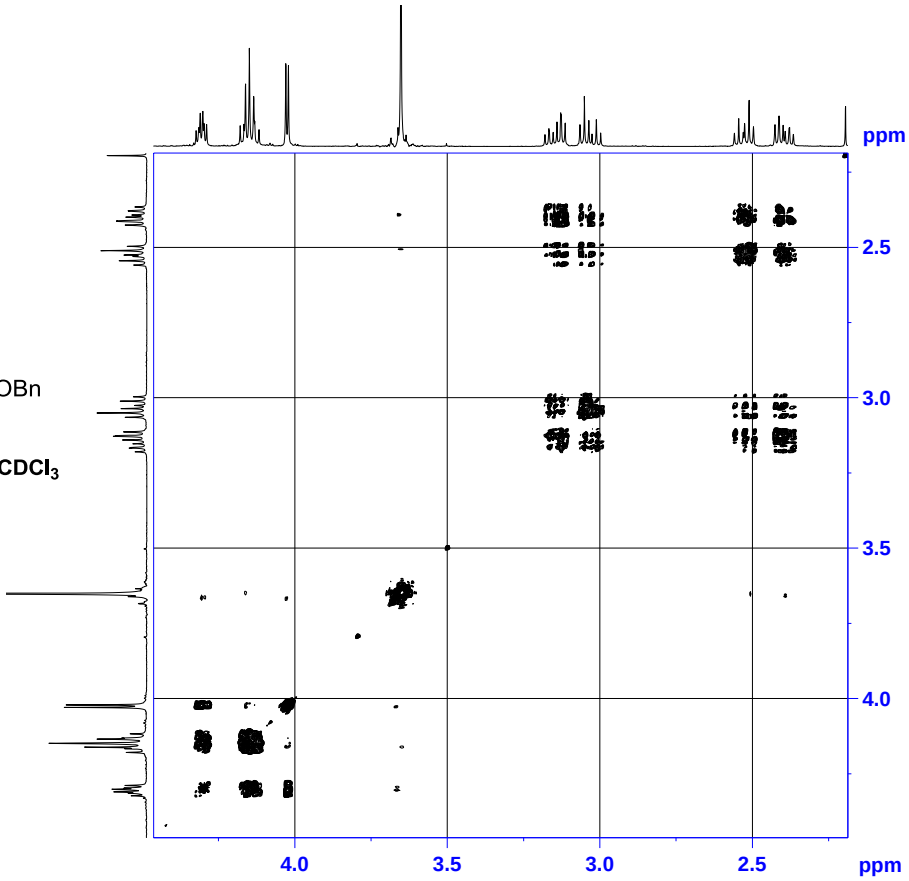

MeO
O
OTBS
O
BnO
OBn
82α
1H NMR, 500 MHz, CDCl3
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm
10.27
2.03
1.99
1.00
2.04
0.96
2.96
1.05
1.03
1.02
1.04
9.40
3.06
3.26

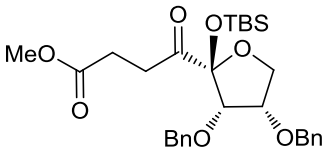

206.94
173.20
137.69
128.48
128.32
127.94
127.75
106.98
85.46
77.92
77.36
77.04
76.72
73.54
72.83
70.51
51.63
34.91
29.72
27.78
25.67
17.83
-3.77
-4.04
MeO
O
OTBS
O
BnO
OBn
82α
13C NMR, 100 MHz, CDCl3
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm



82α

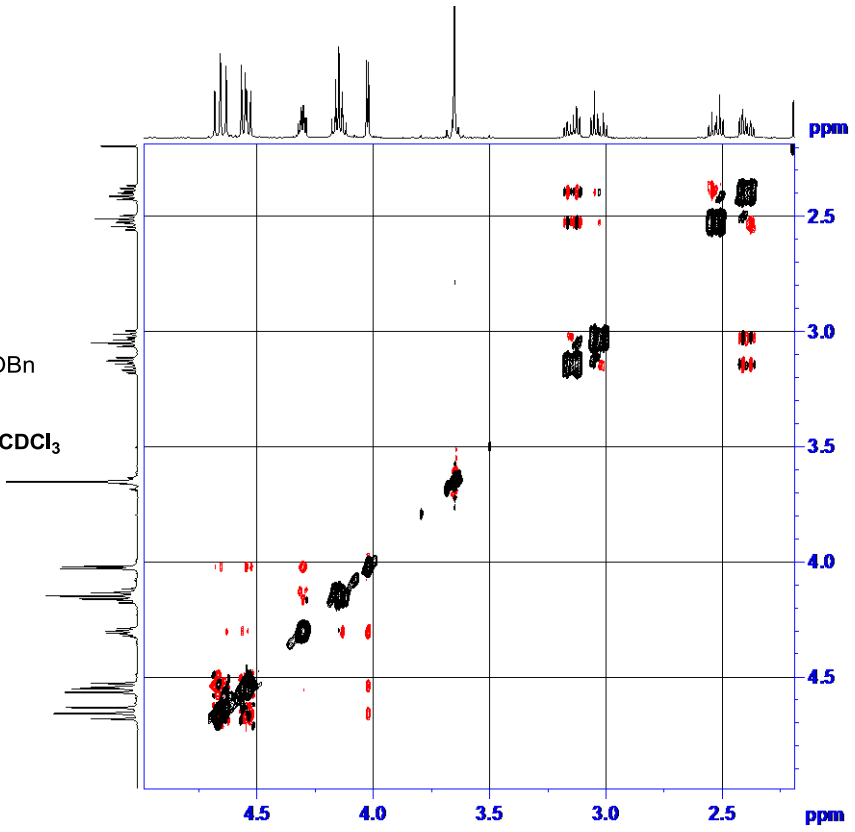
^{1}H-^{1}H COSY NMR, 500 MHz, $CDCl_3$

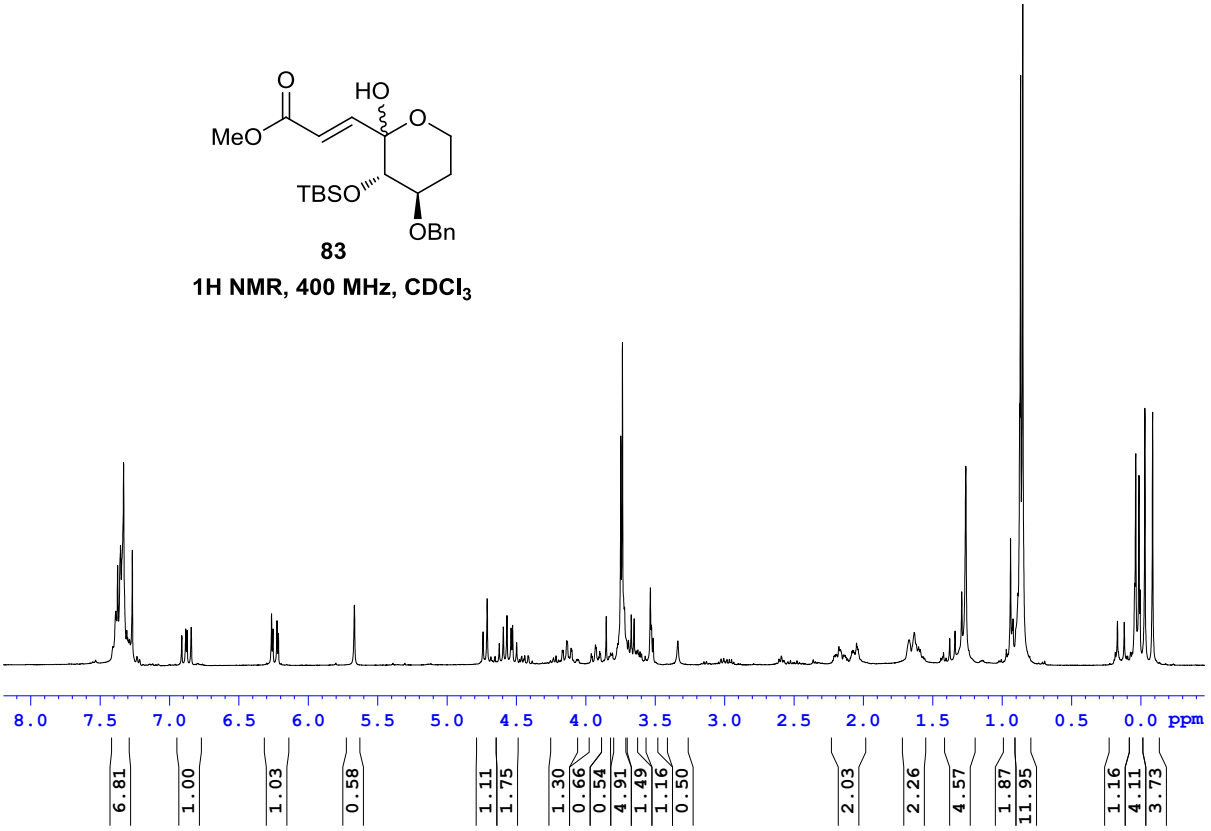




82α

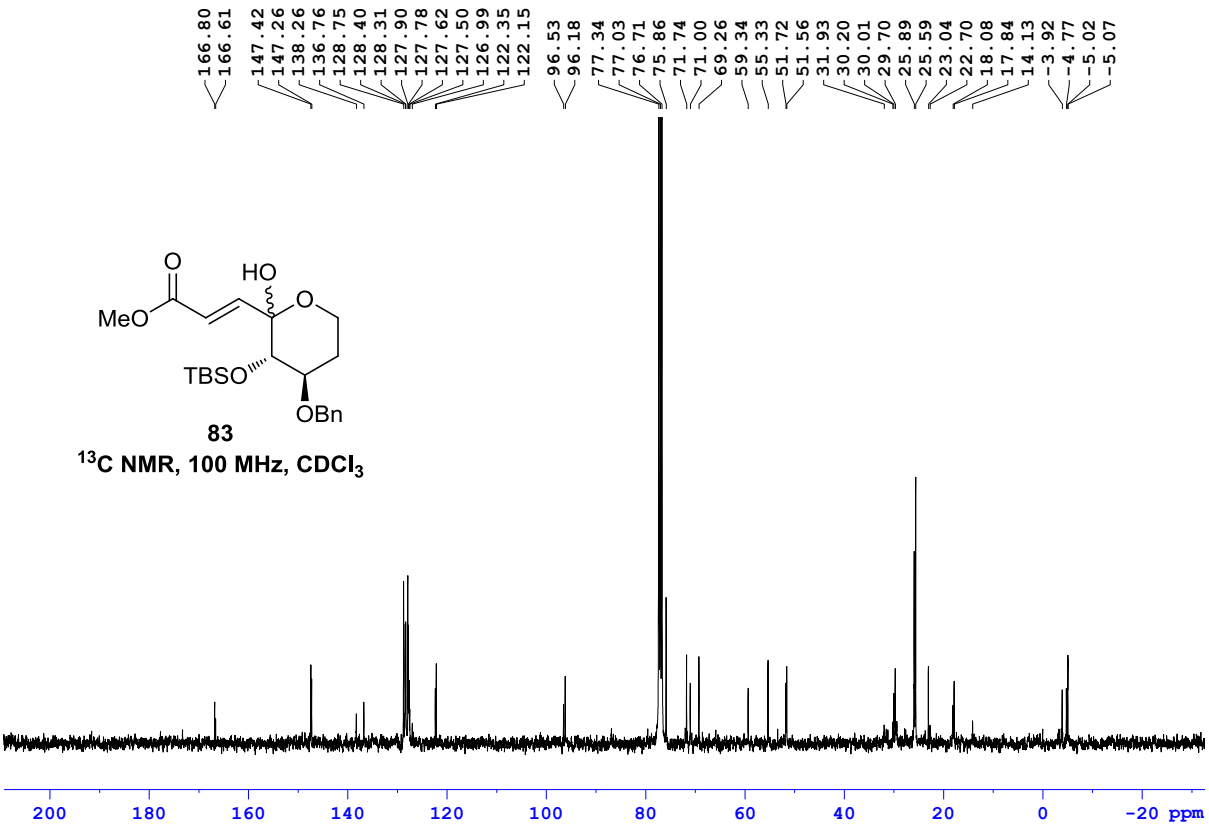
^{1}H-^{1}H NOESY NMR, 500 MHz, $CDCl_3$





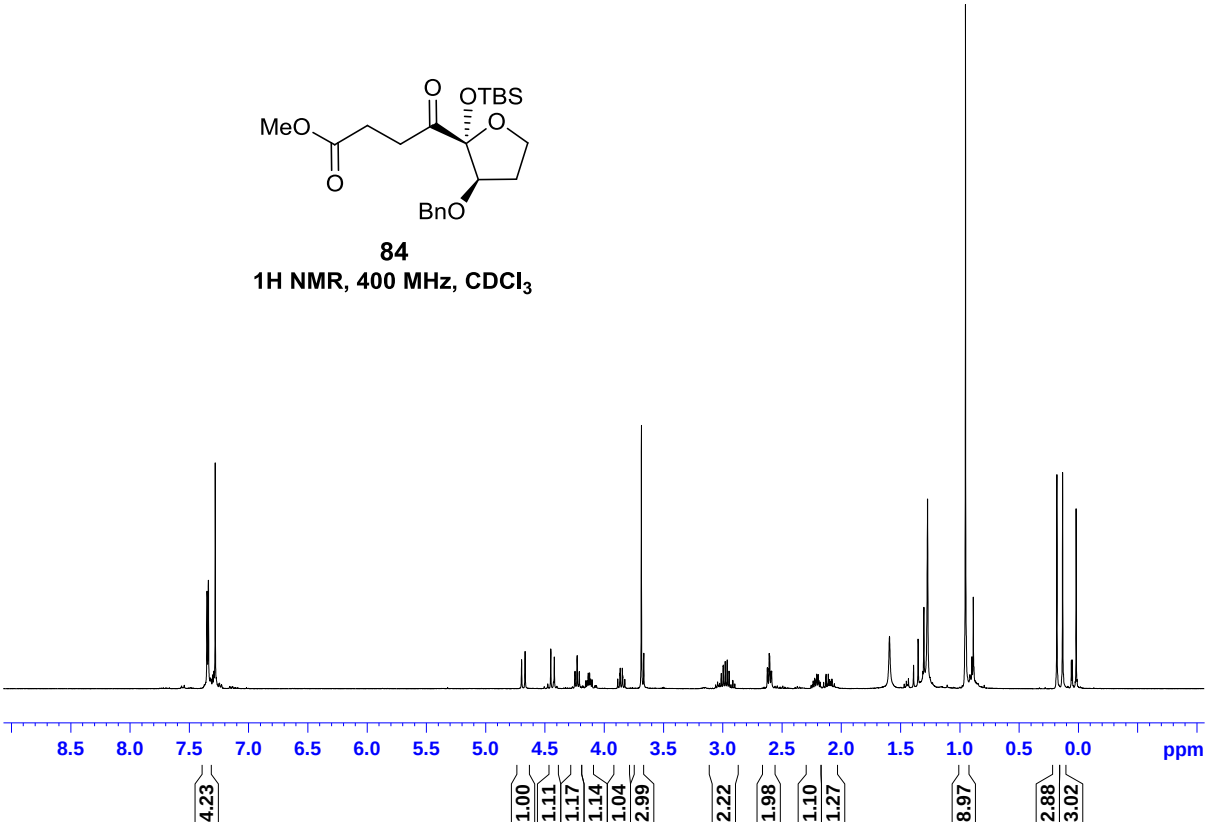
83

1H NMR, 400 MHz, $CDCl_3$



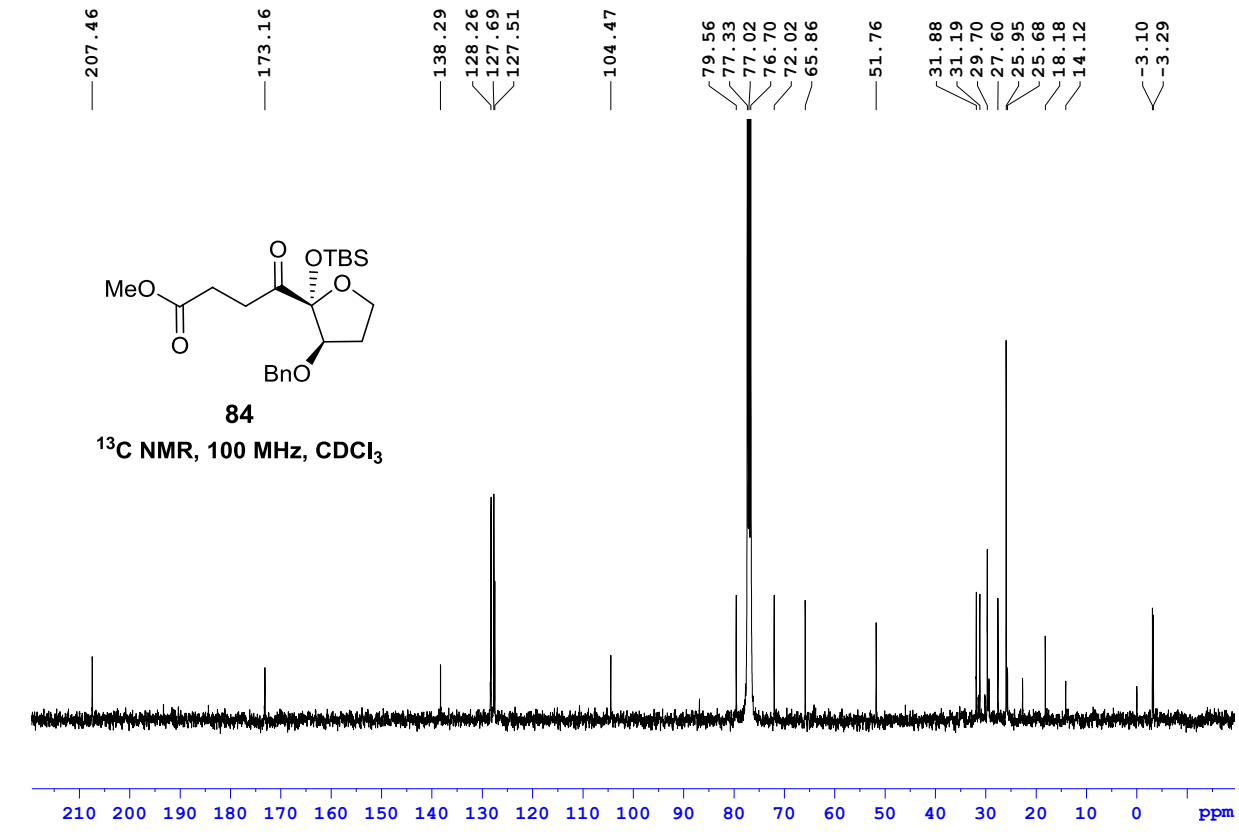
83

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



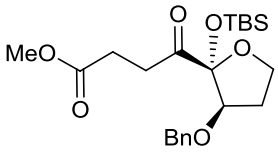
84

1H NMR, 400 MHz, $CDCl_3$



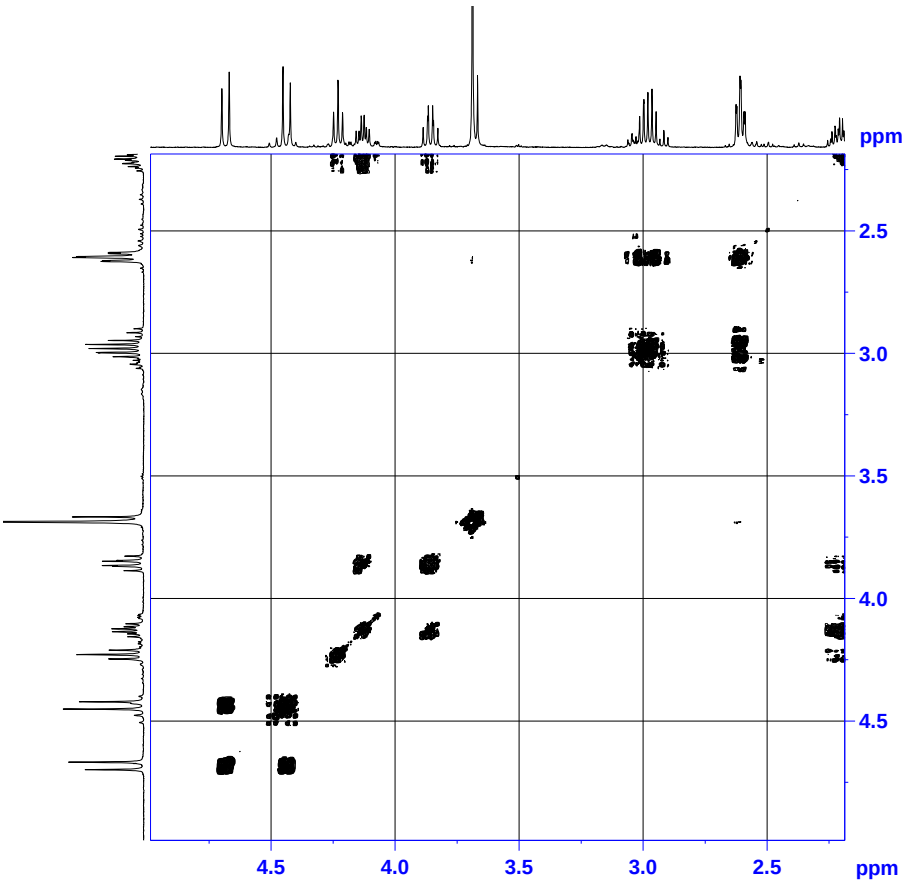
84

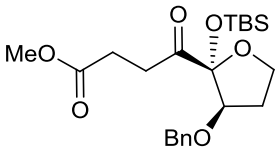
^{13}C NMR, 100 MHz, $CDCl_3$



84

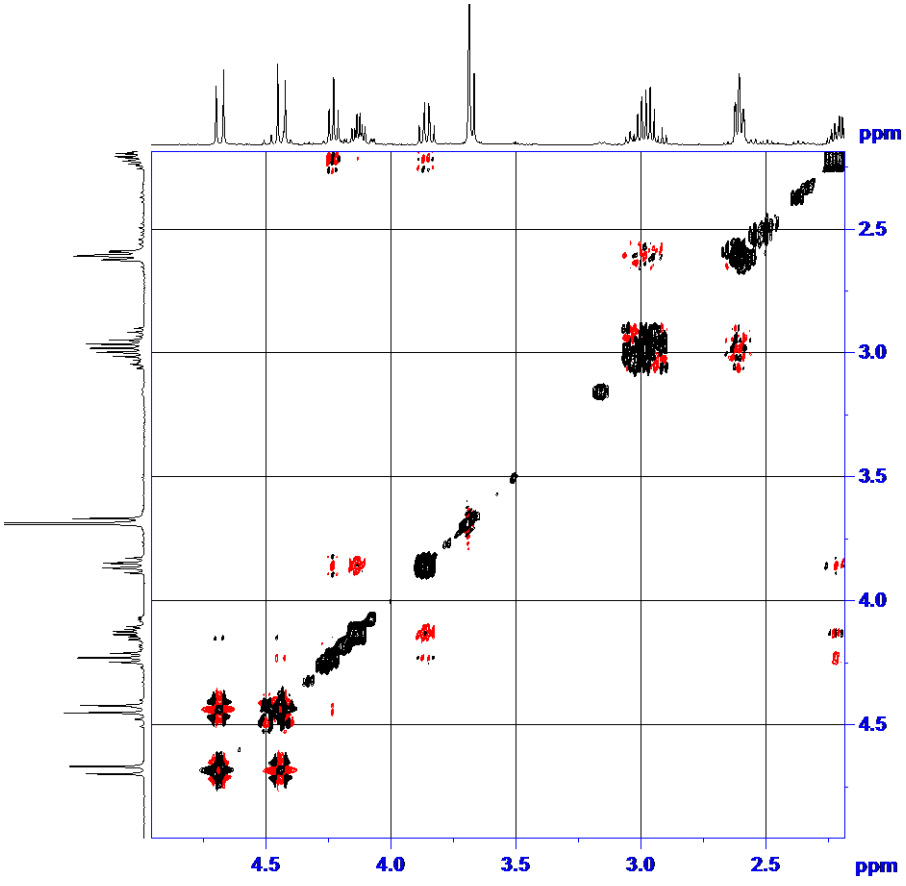
^{1}H-^{1}H COSY NMR, 400 MHz, $CDCl_3$

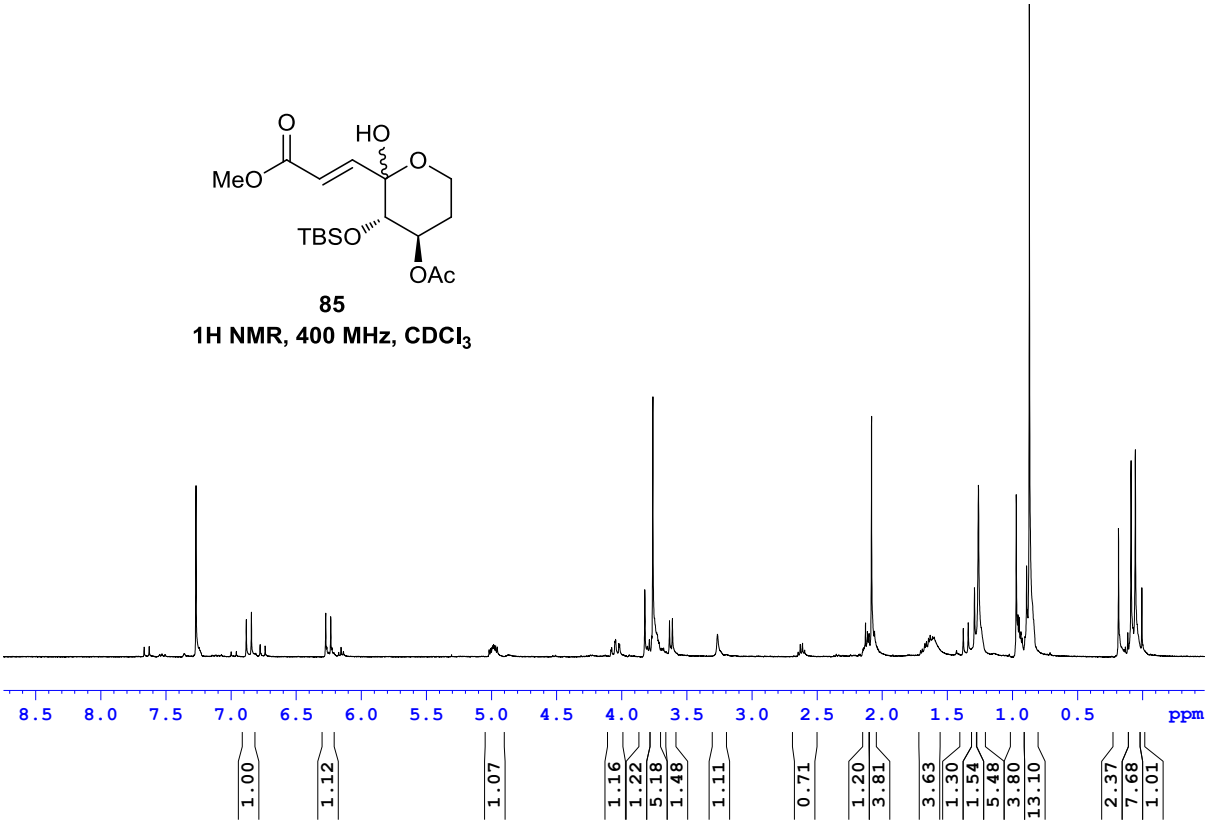




84

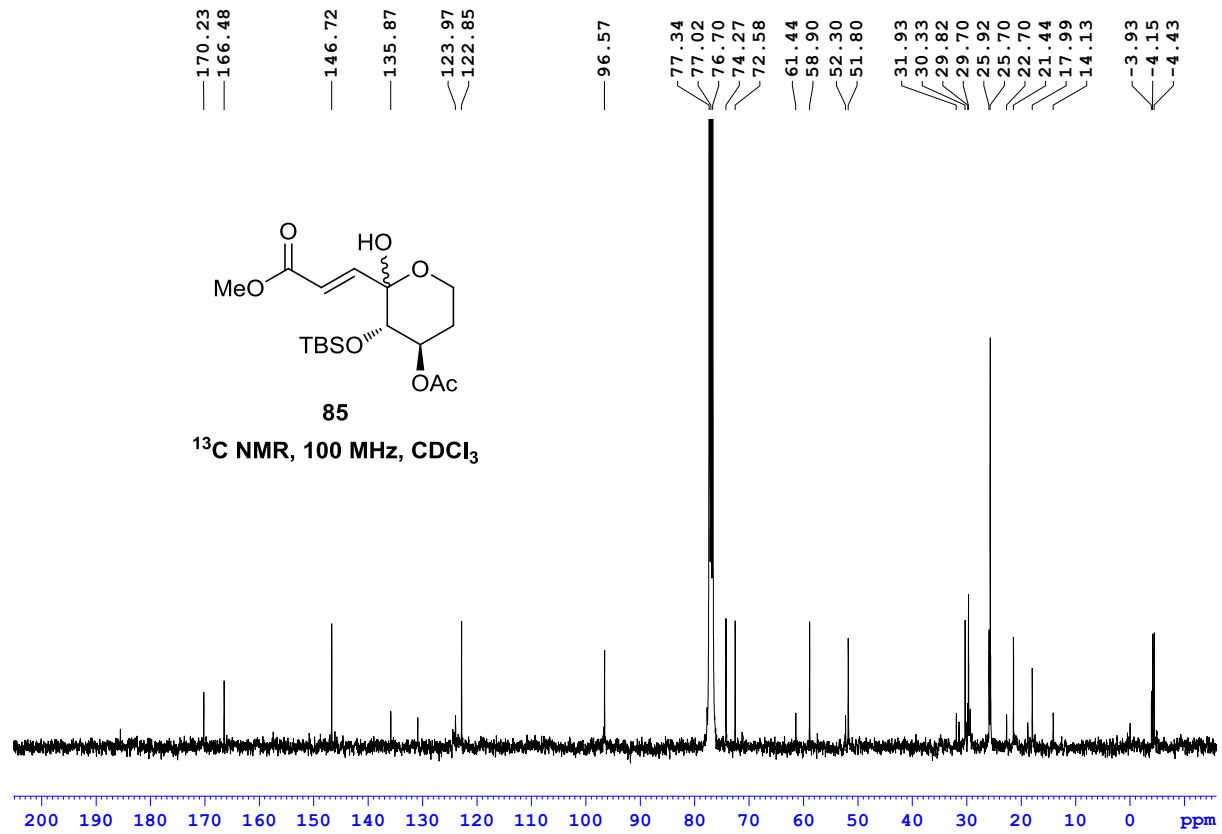
^{1}H-^{1}H NOESY NMR, 400 MHz, $CDCl_3$





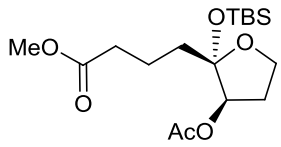
85

1H NMR, 400 MHz, $CDCl_3$



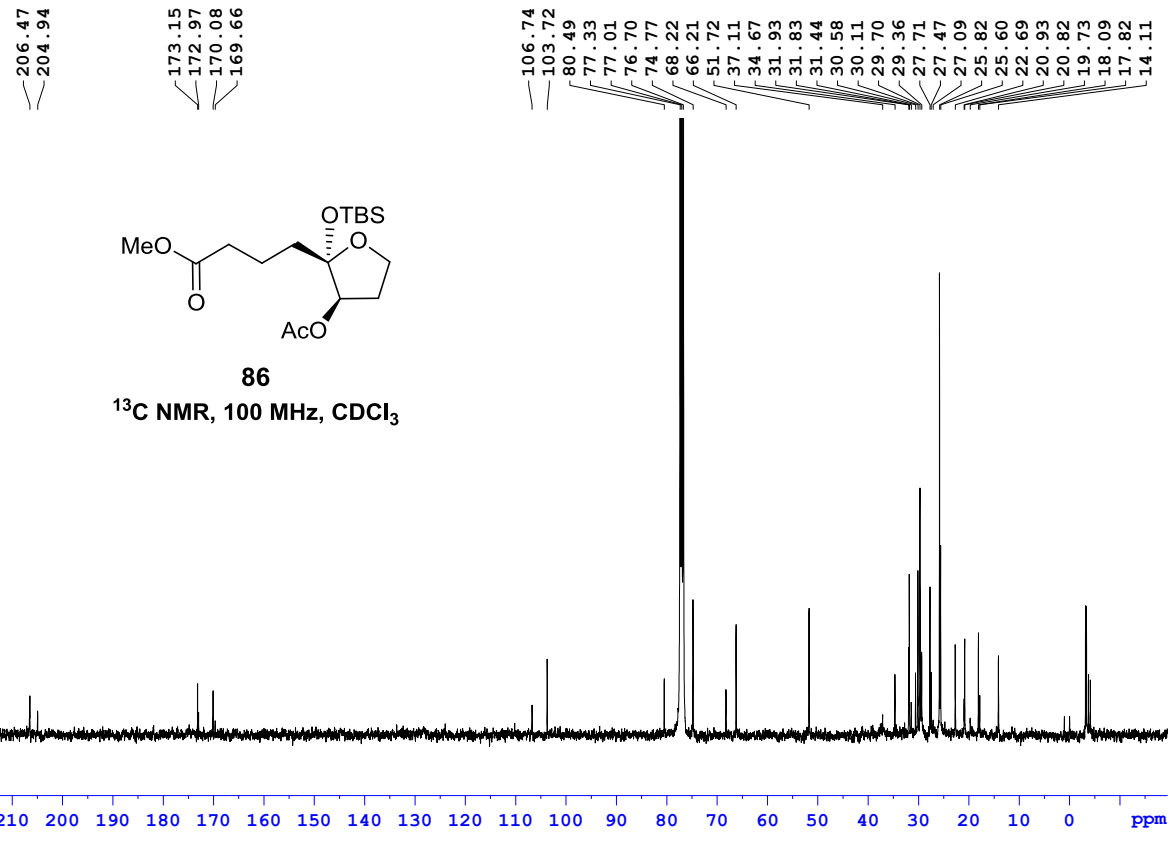
85

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



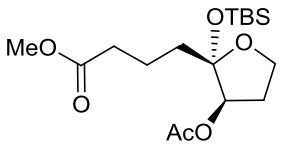
86

1H NMR, 400 MHz, $CDCl_3$



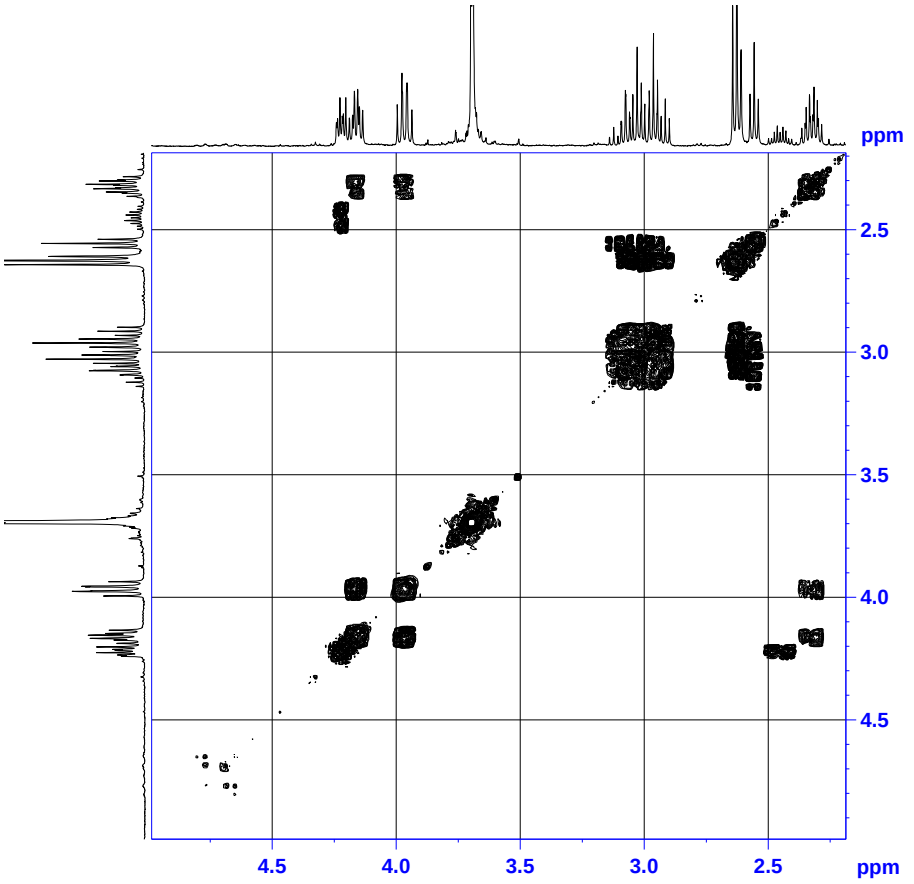
86

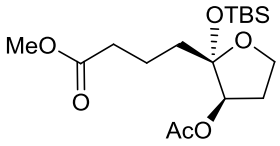
^{13}C NMR, 100 MHz, $CDCl_3$



86

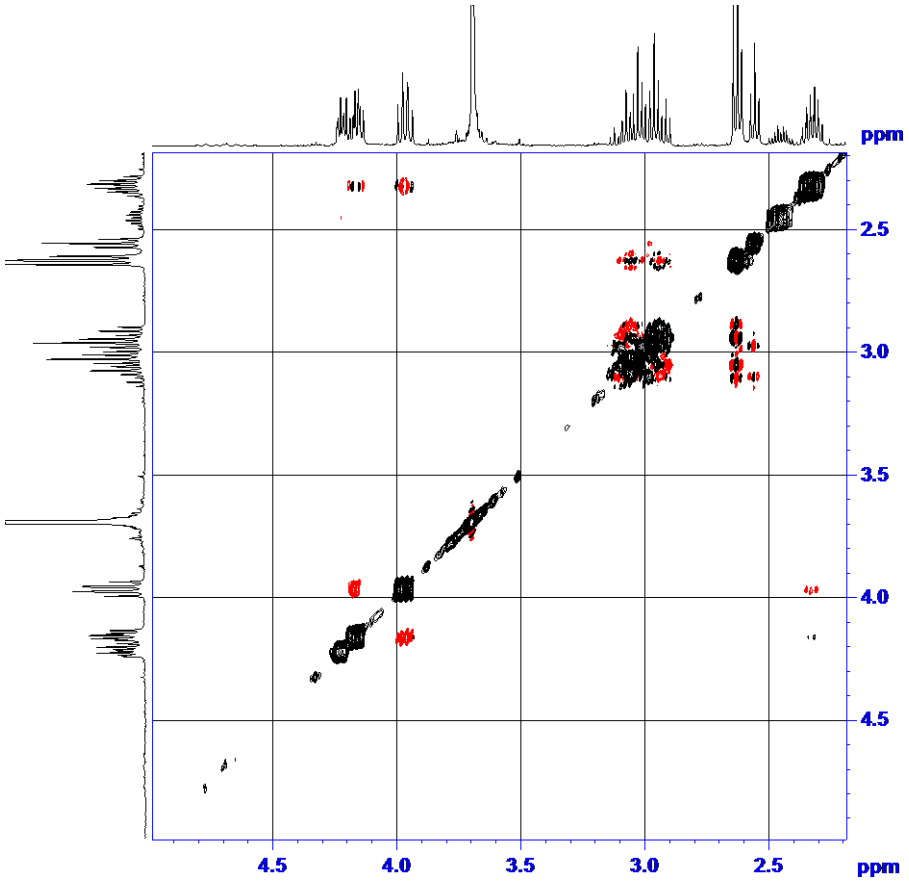
^{1}H-^{1}H COSY NMR, 400 MHz, $CDCl_3$

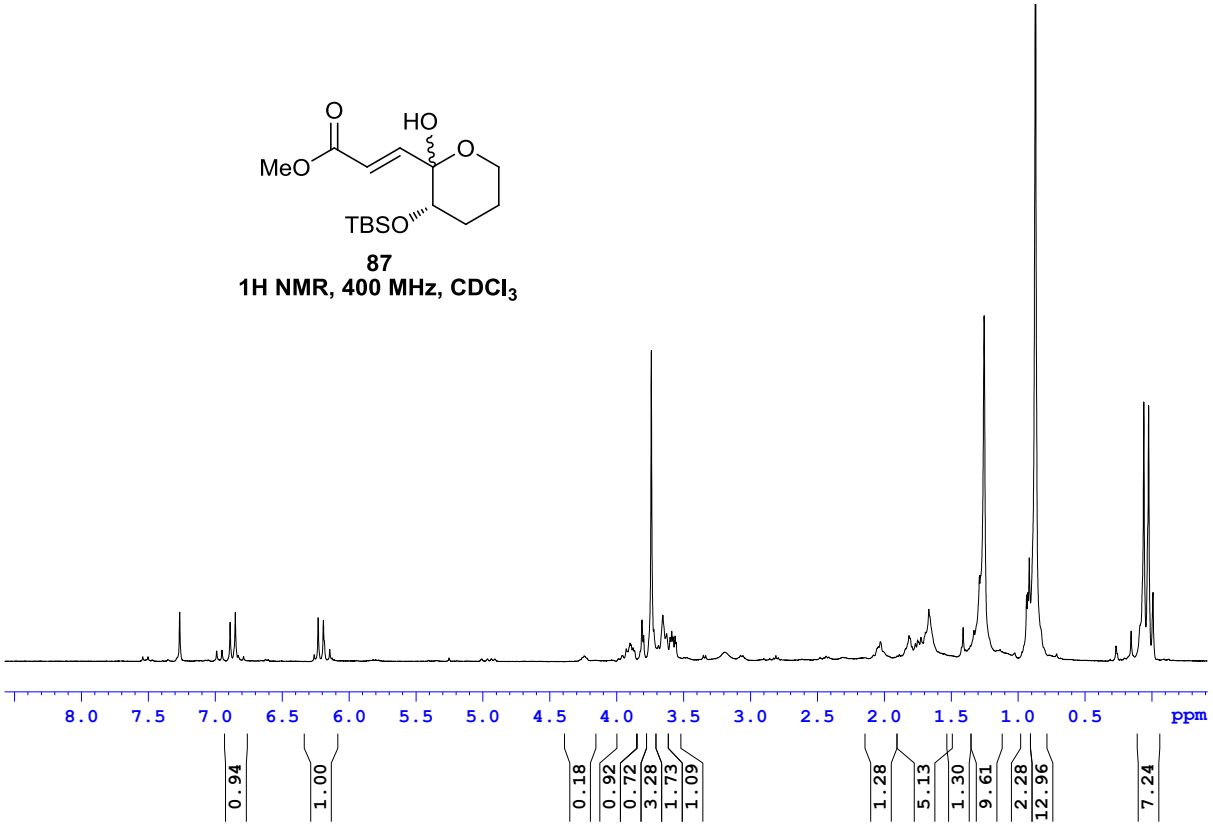




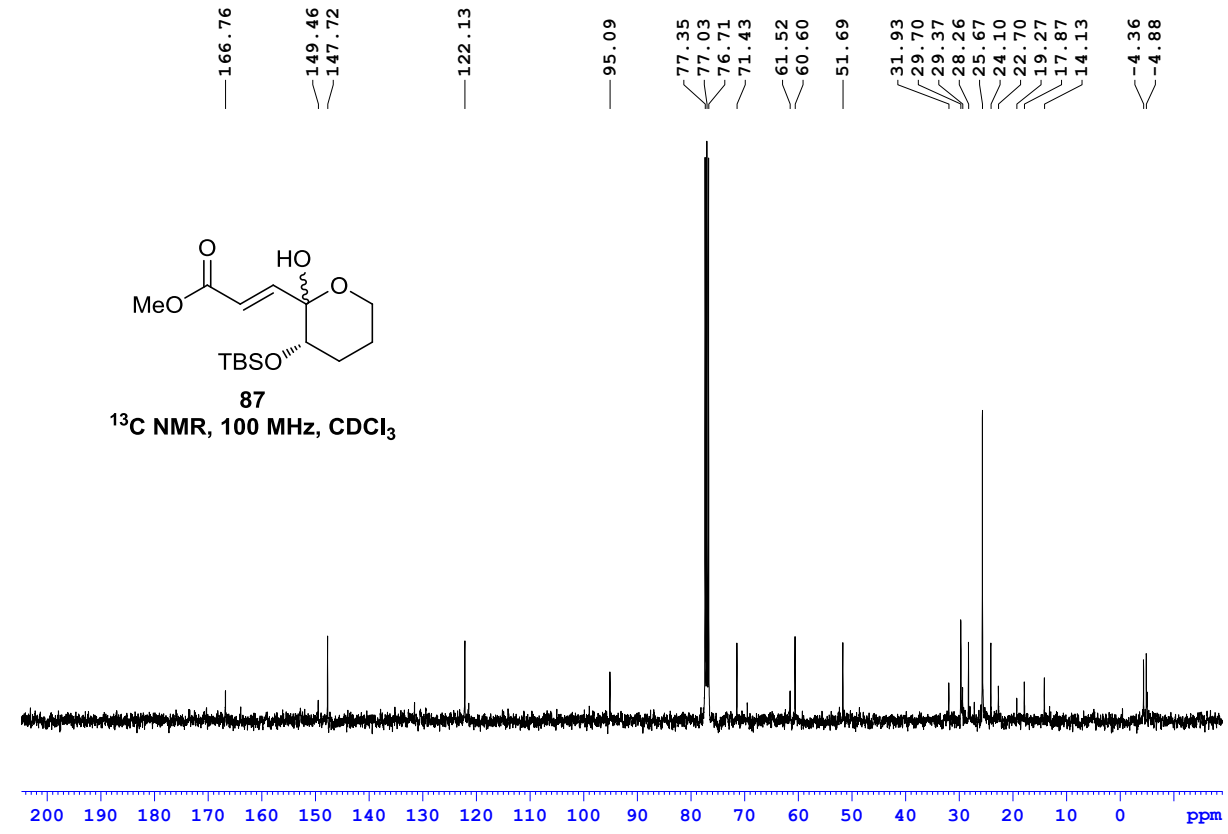
86

^{1}H-^{1}H NOESY NMR, 400 MHz, $CDCl_3$

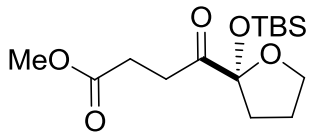




87
1H NMR, 400 MHz, $CDCl_3$

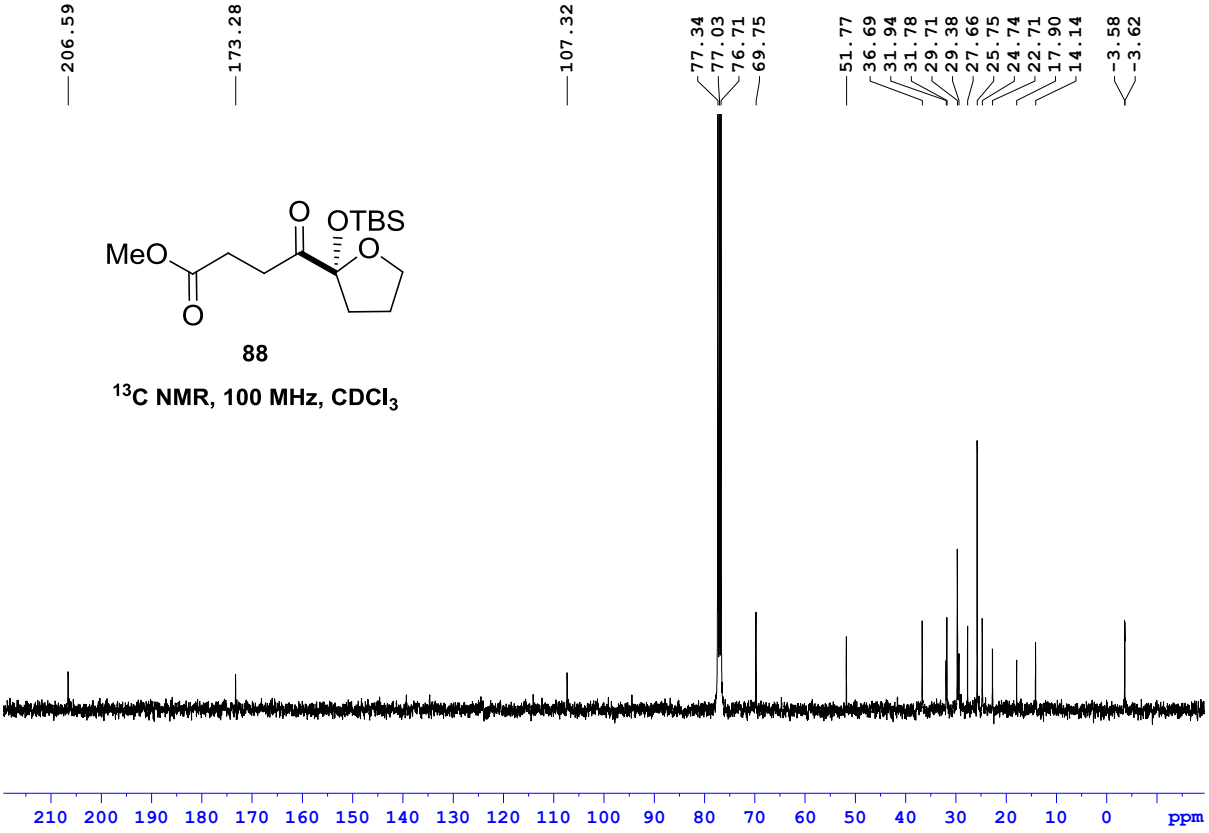


87
^{13}C NMR, 100 MHz, $CDCl_3$



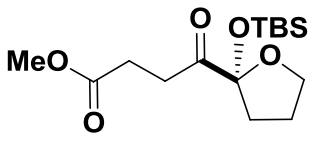
88

^{1}H NMR, 400 MHz, $CDCl_3$



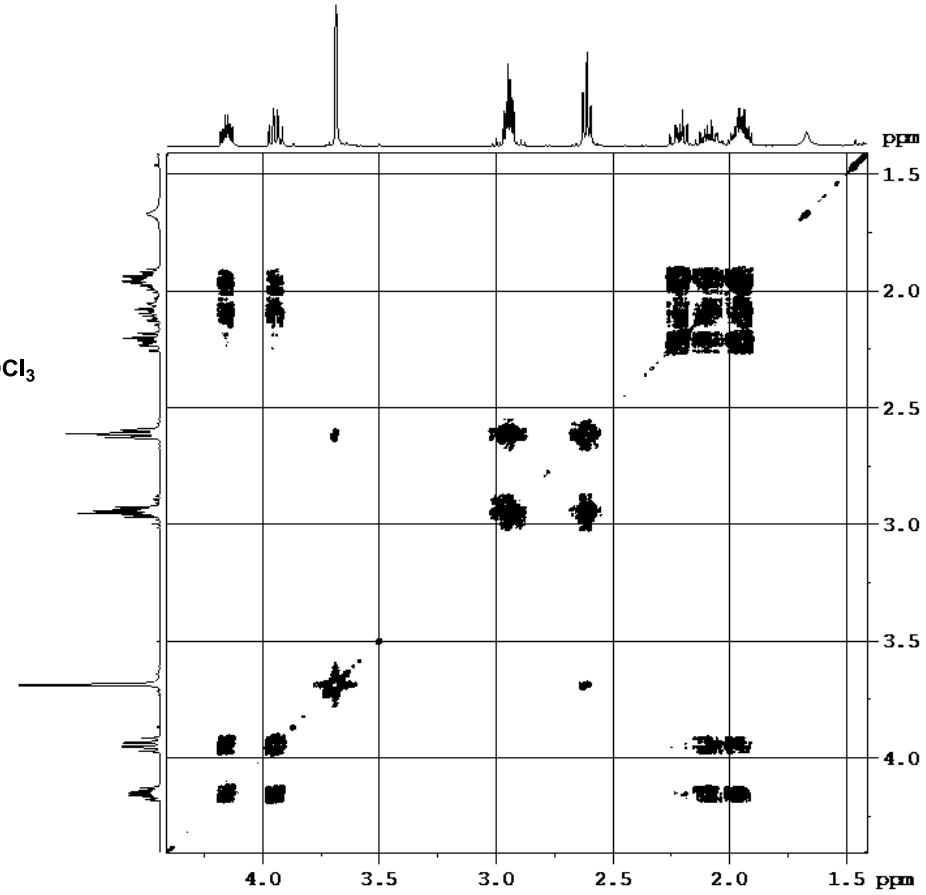
88

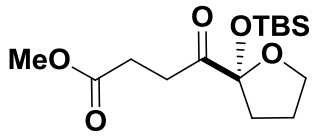
^{13}C NMR, 100 MHz, $CDCl_3$



88

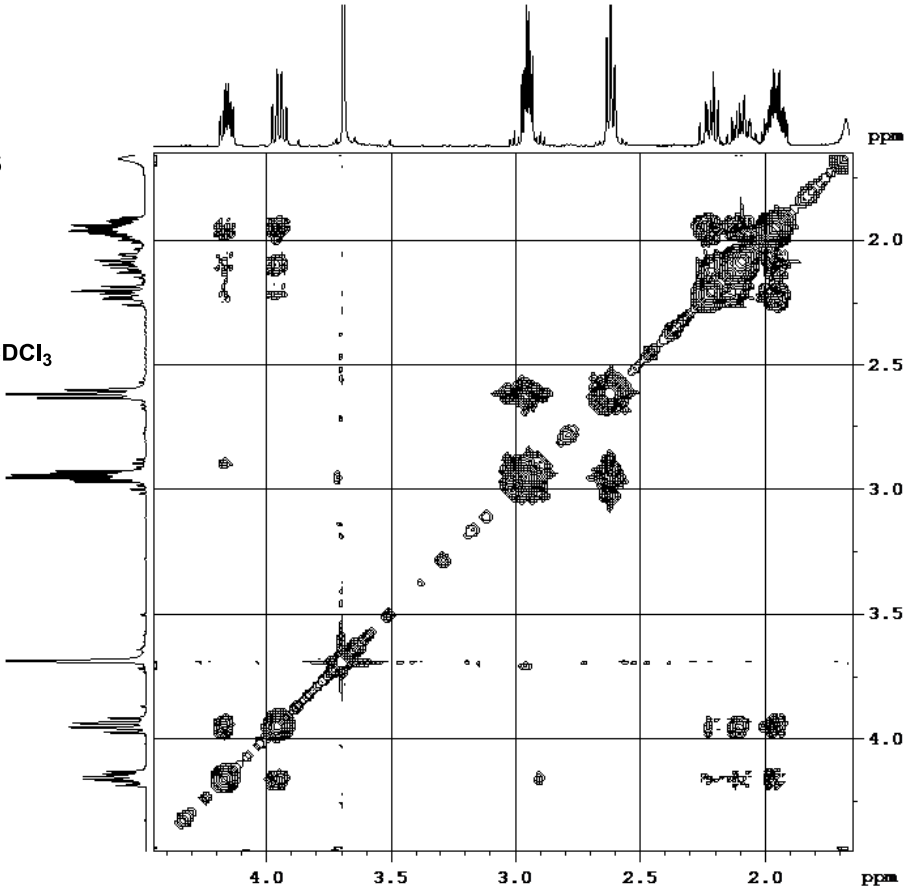
^{1}H-^{1}H COSY NMR, 400 MHz, $CDCl_3$

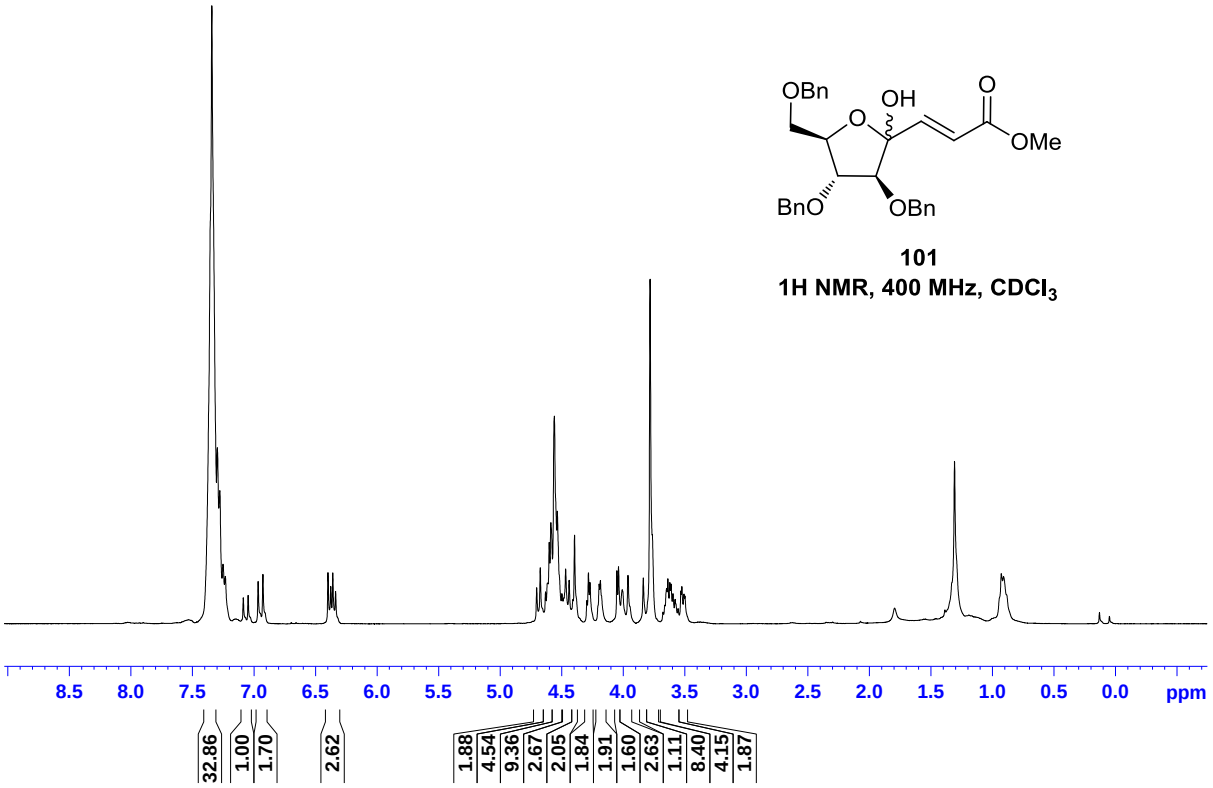




88

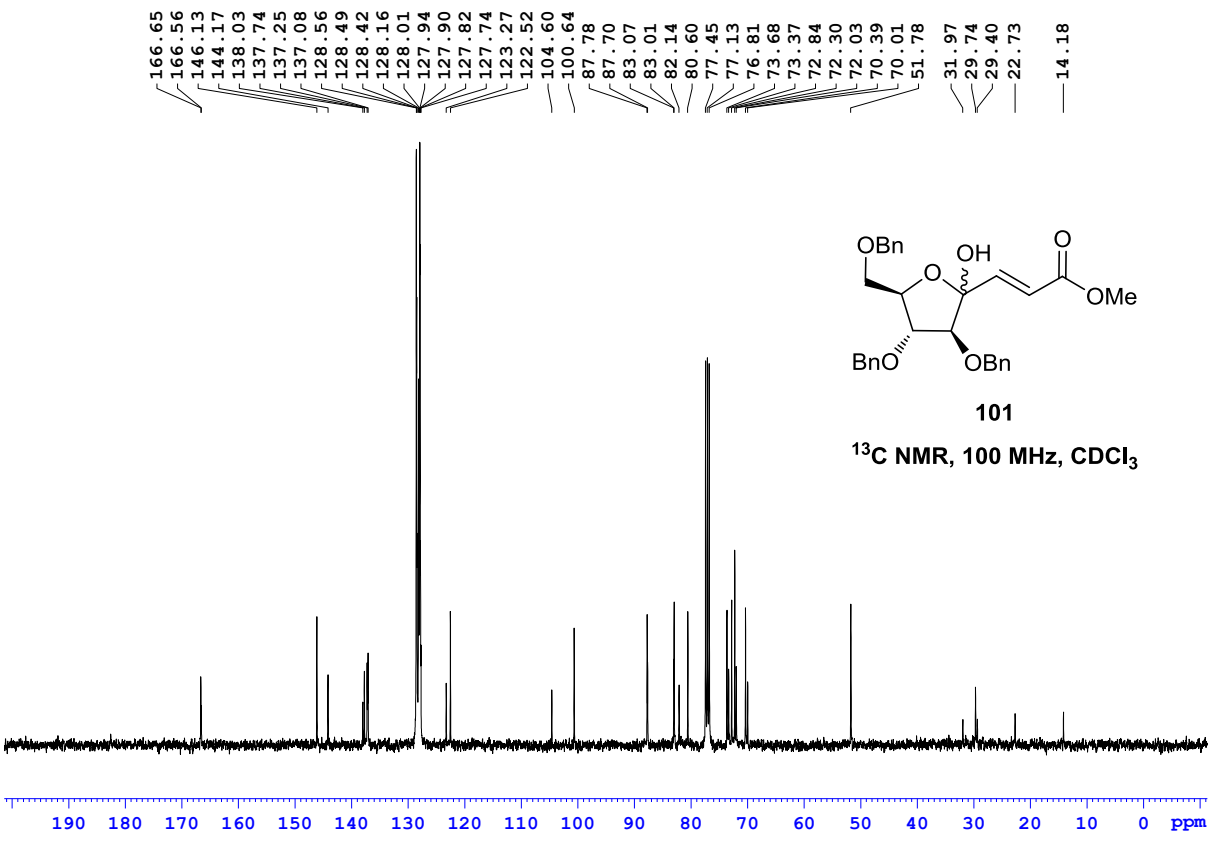
^{1}H-^{1}H NOESY NMR, 400 MHz, $CDCl_3$





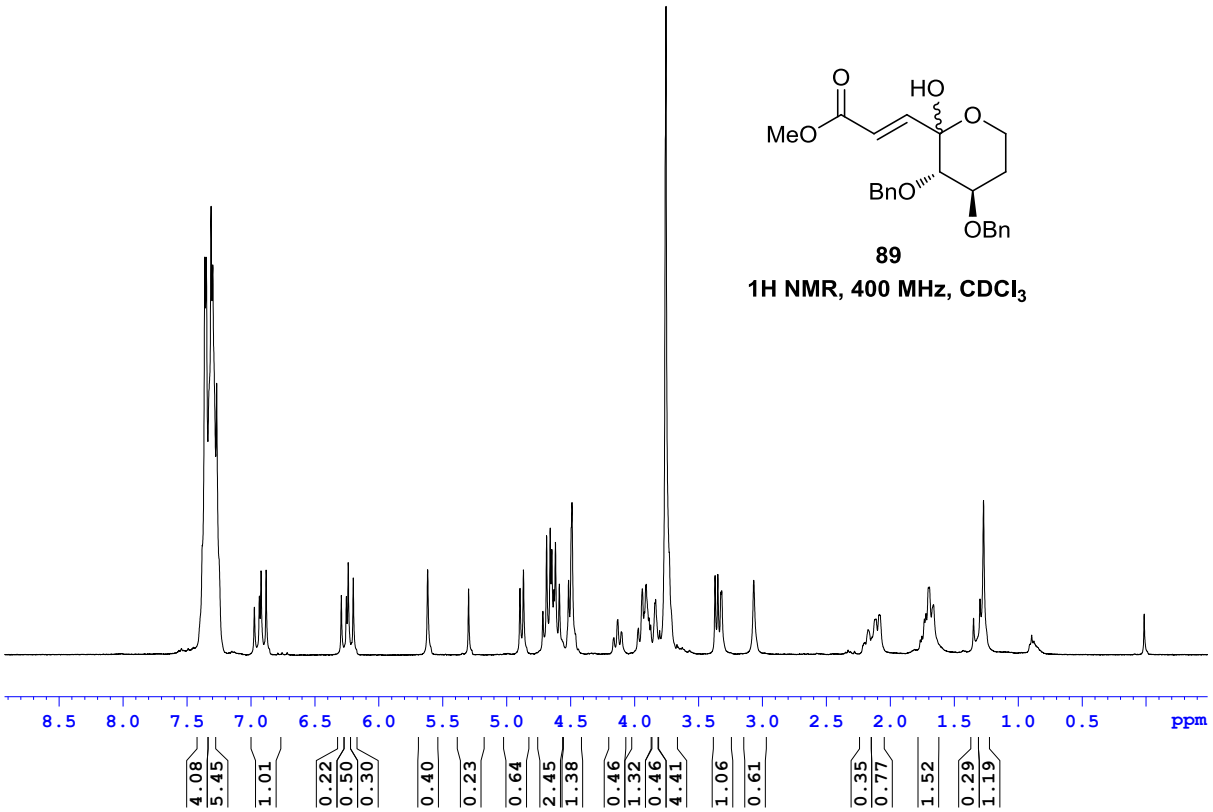
101

1H NMR, 400 MHz, $CDCl_3$



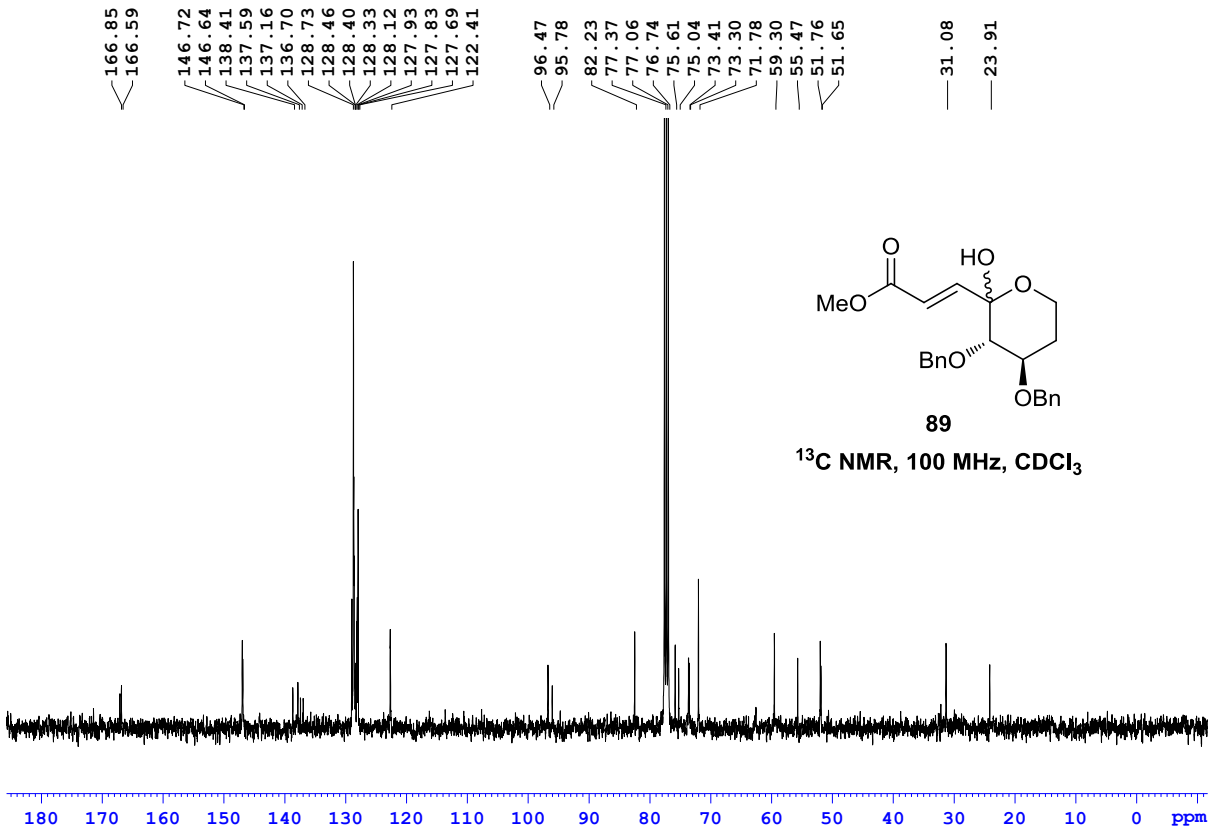
101

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



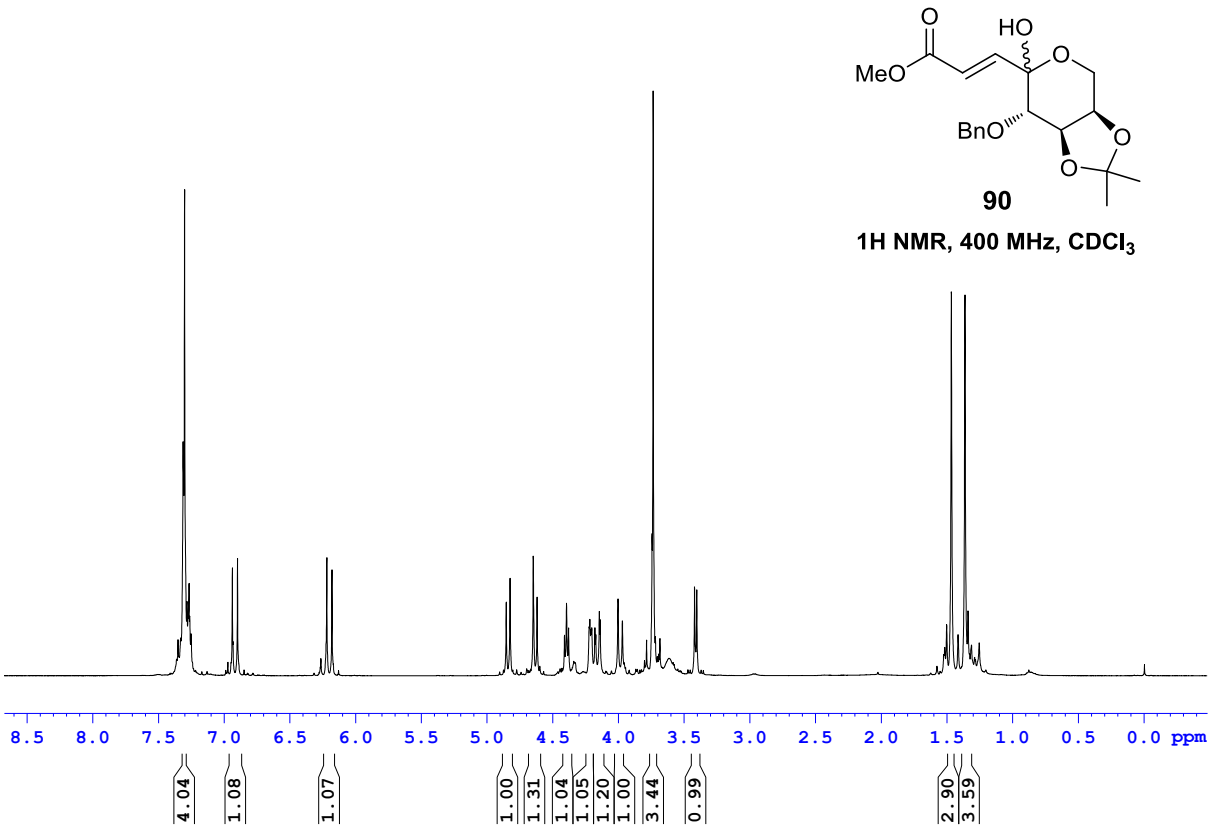
89

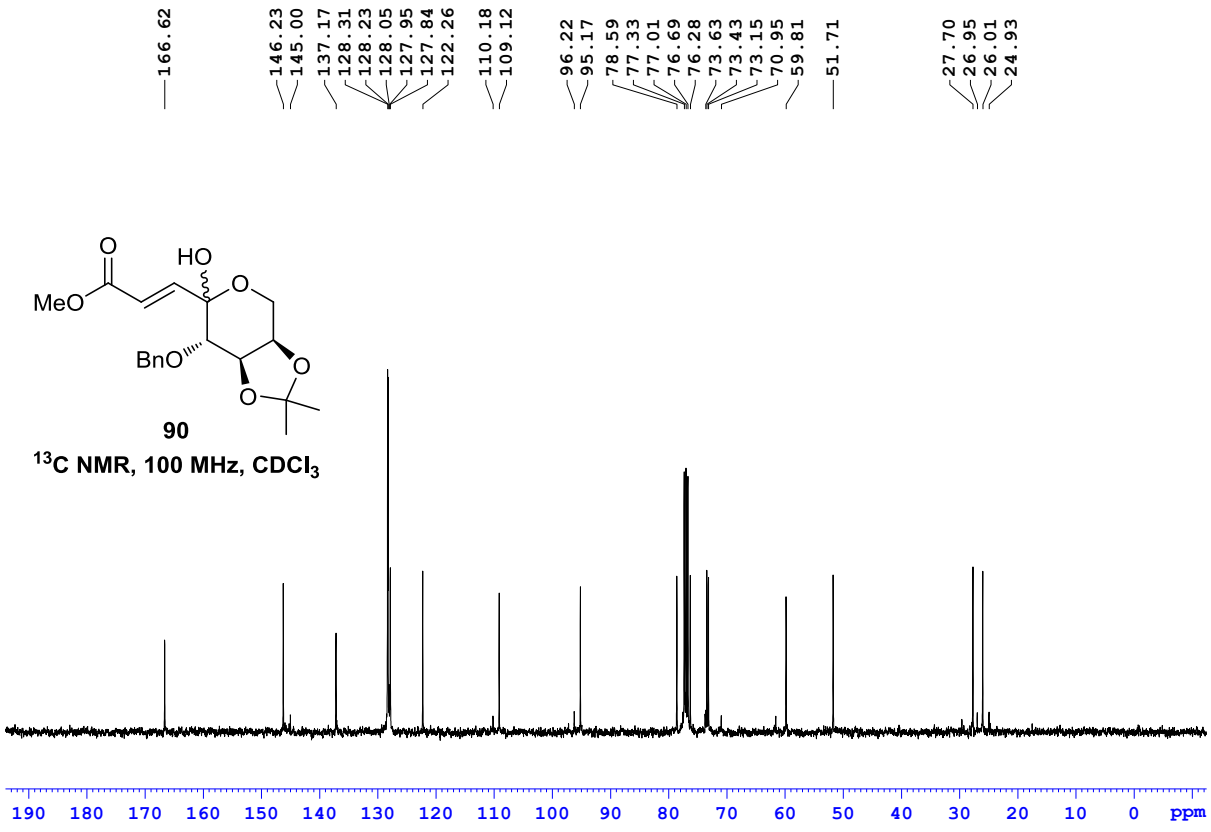
1H NMR, 400 MHz, $CDCl_3$

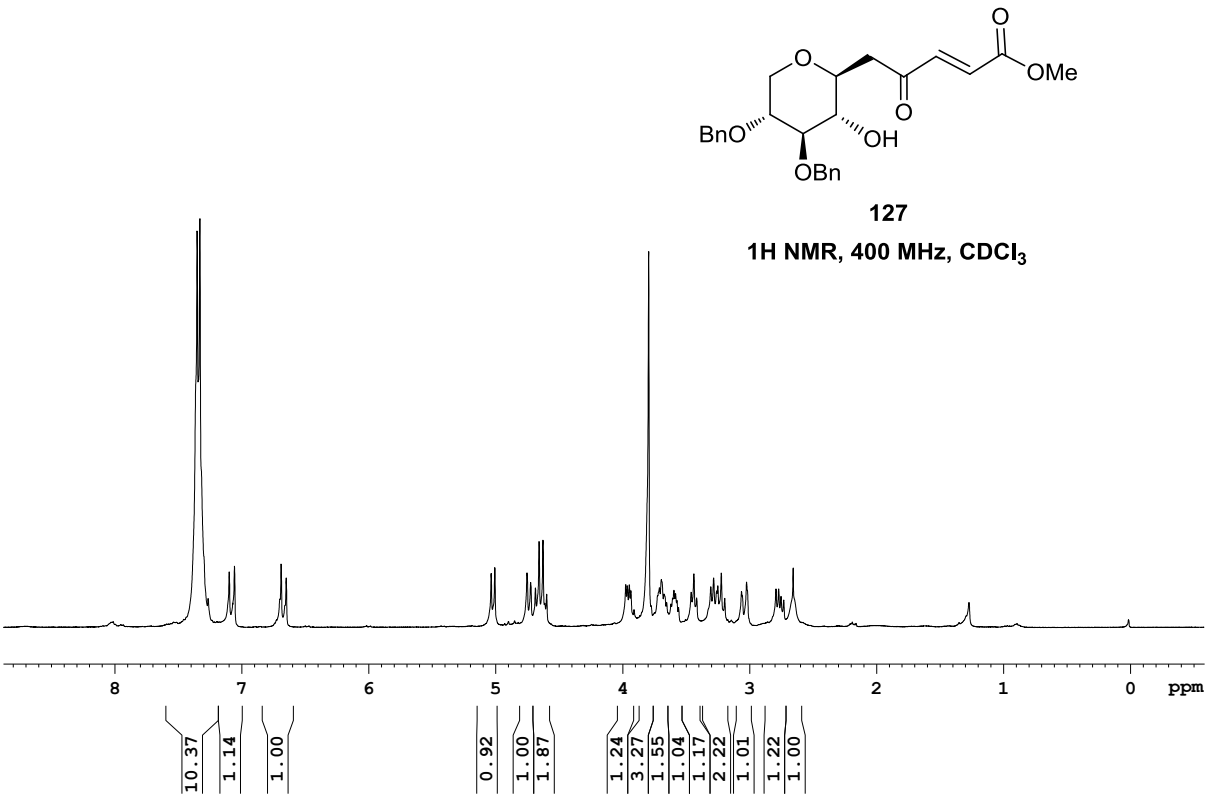


89

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

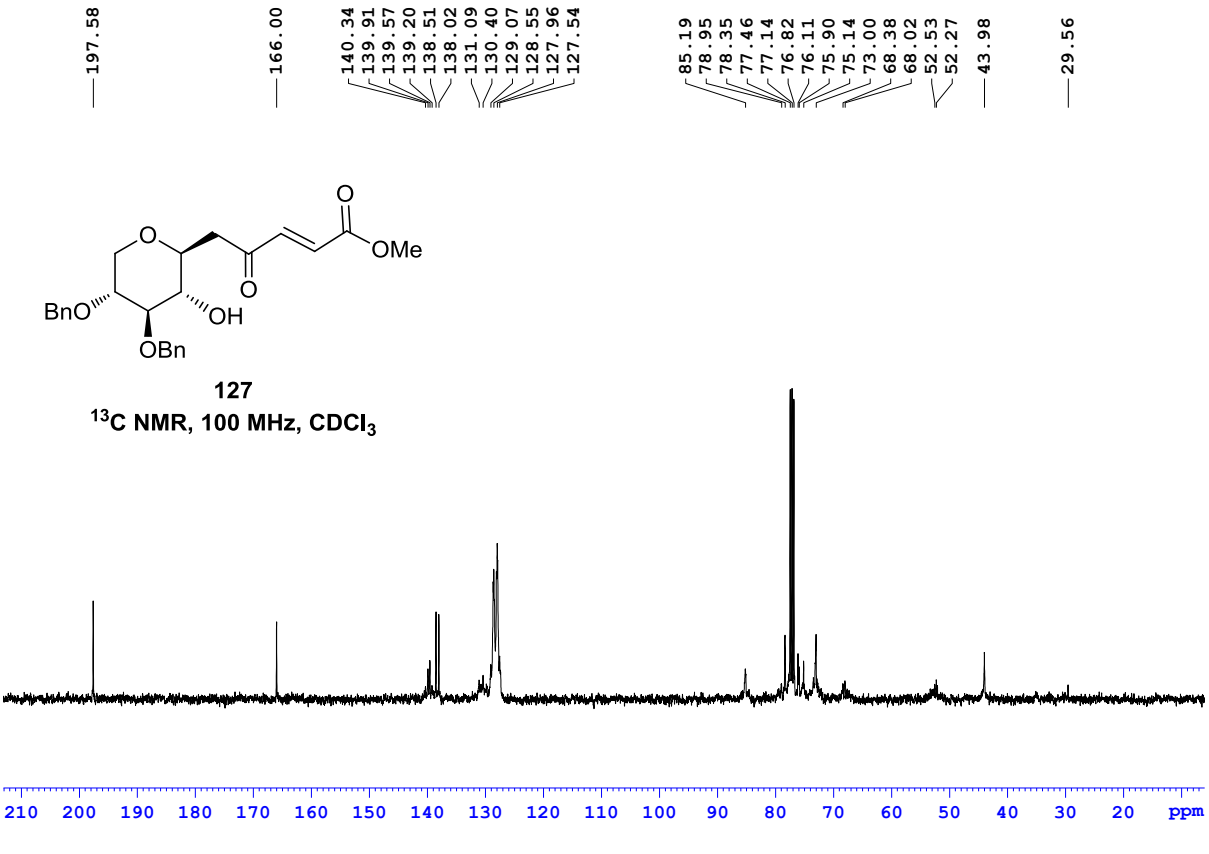

MeO
HO
BnO
90
1H NMR, 400 MHz, CDCl3
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm
4.04 1.08 1.07 1.00 1.31 1.04 1.05 1.20 1.00 3.44 0.99 2.90 3.59


166.62
146.23 145.00 137.17 128.31 128.23 128.05 127.95 127.84 122.26
110.18 109.12
96.22 95.17 78.59 77.33 77.01 76.69 76.28 73.63 73.43 73.15 70.95 59.81
51.71
27.70 26.95 26.01 24.93
MeO
HO
BnO
90
13C NMR, 100 MHz, CDCl3
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm



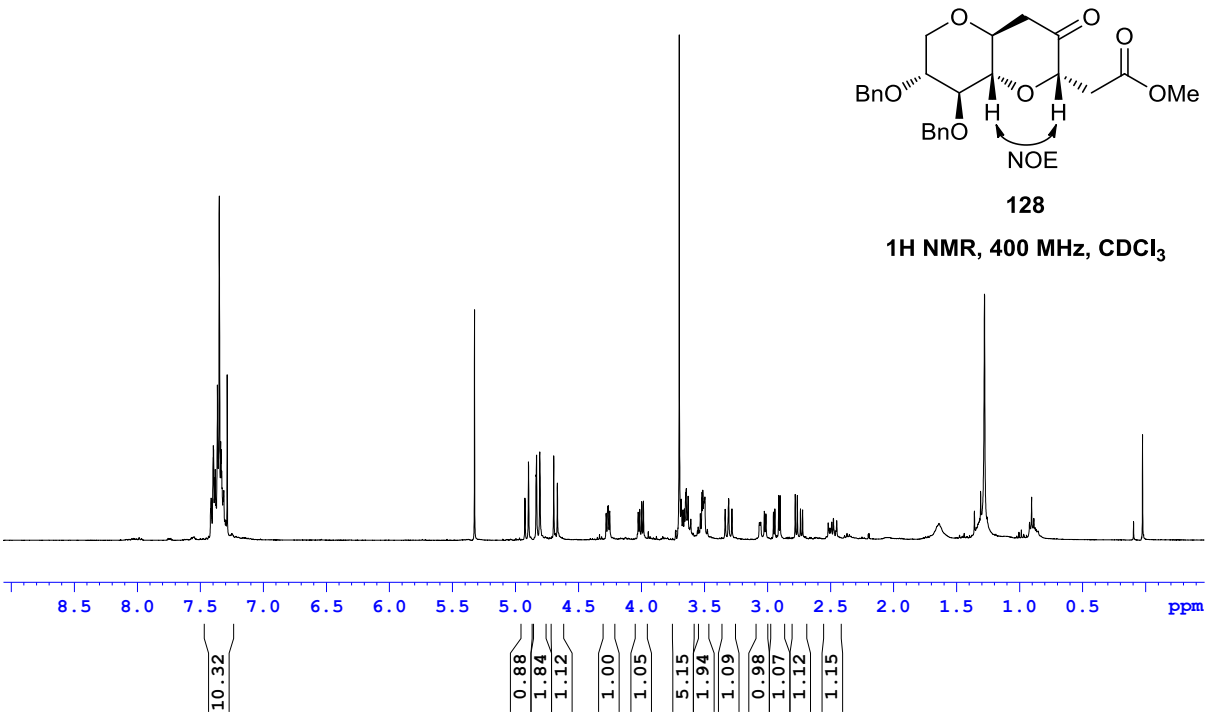
127

1H NMR, 400 MHz, $CDCl_3$



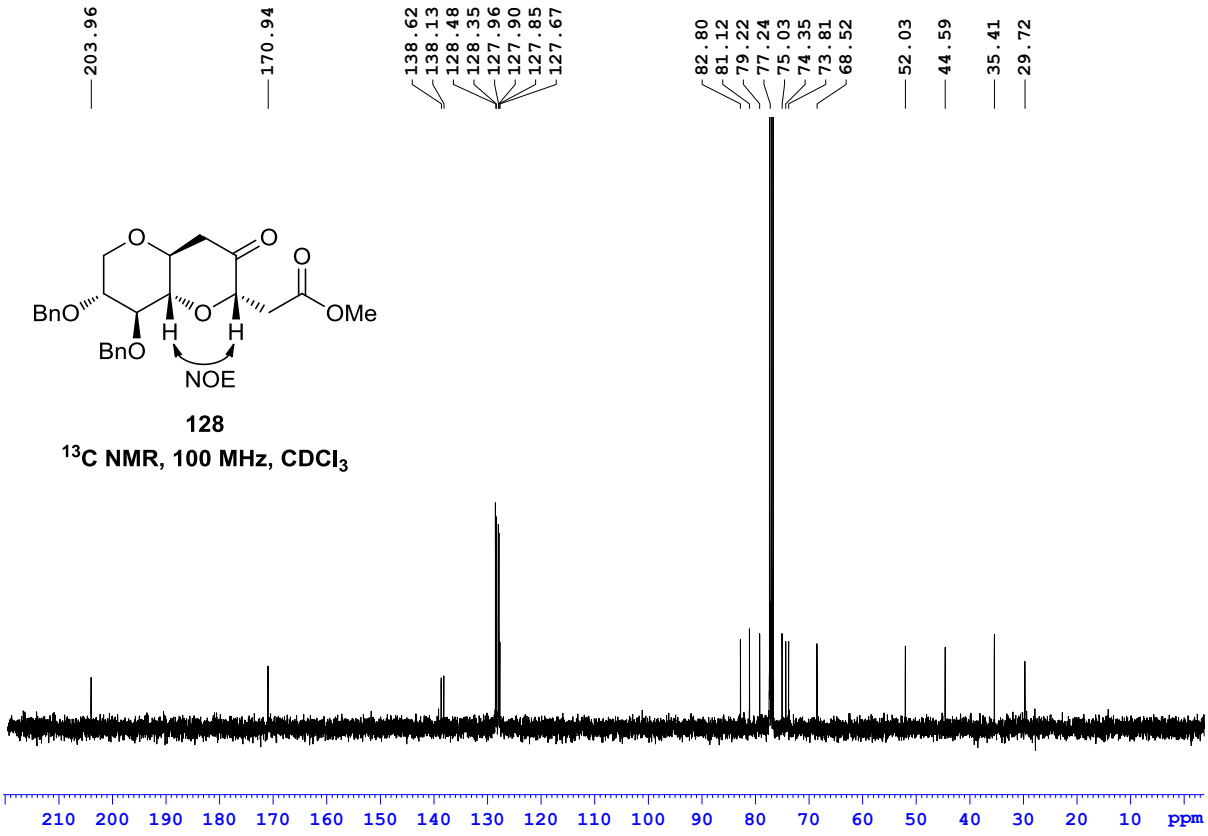
127

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



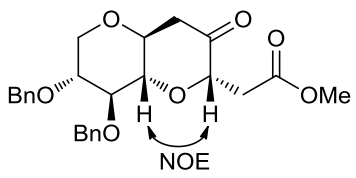
128

1H NMR, 400 MHz, $CDCl_3$



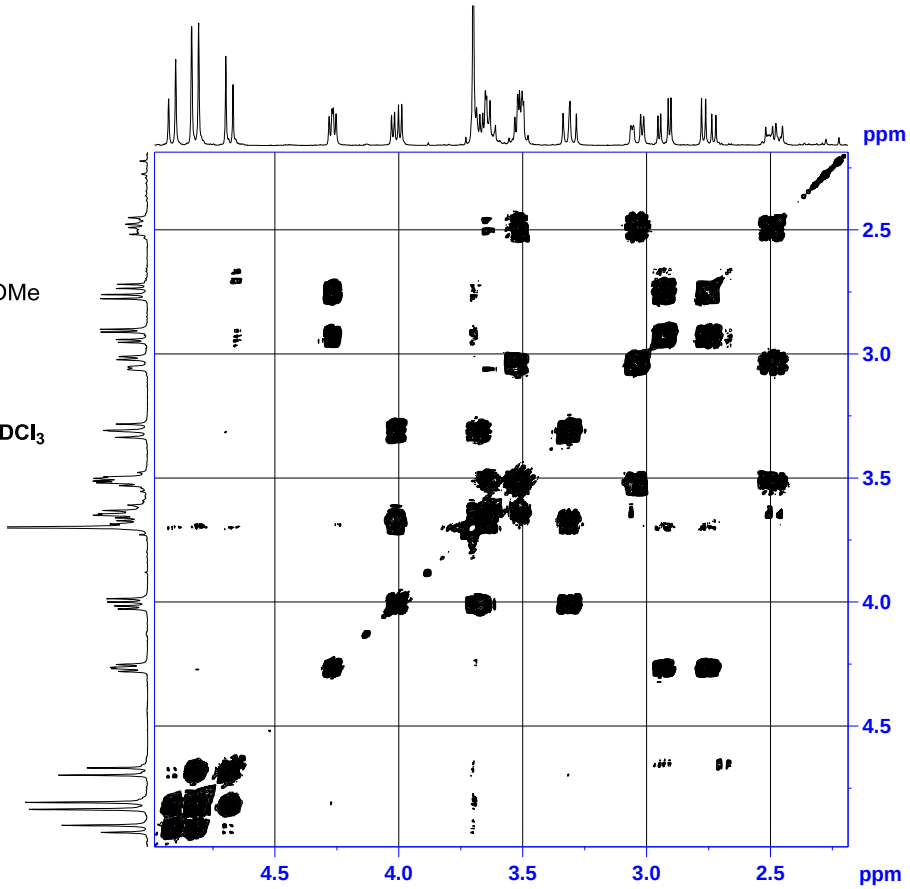
128

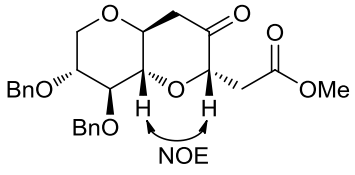
^{13}C NMR, 100 MHz, $CDCl_3$



128

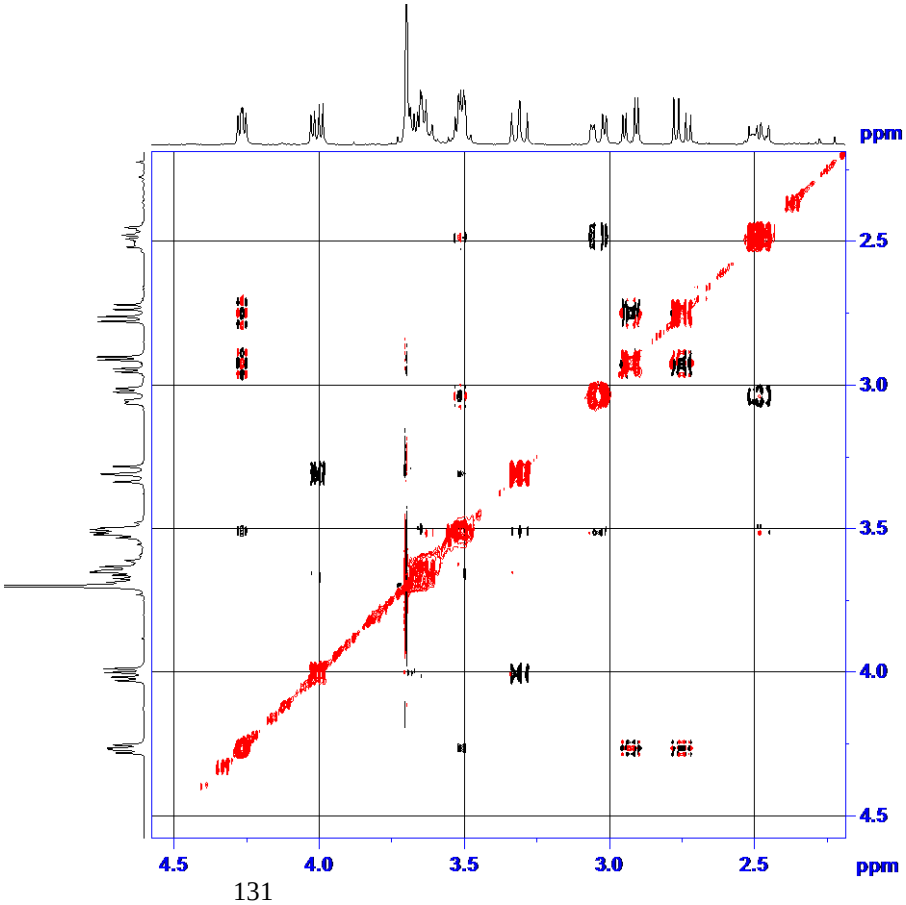
^{1}H-^{1}H COSY NMR, 400 MHz, $CDCl_3$

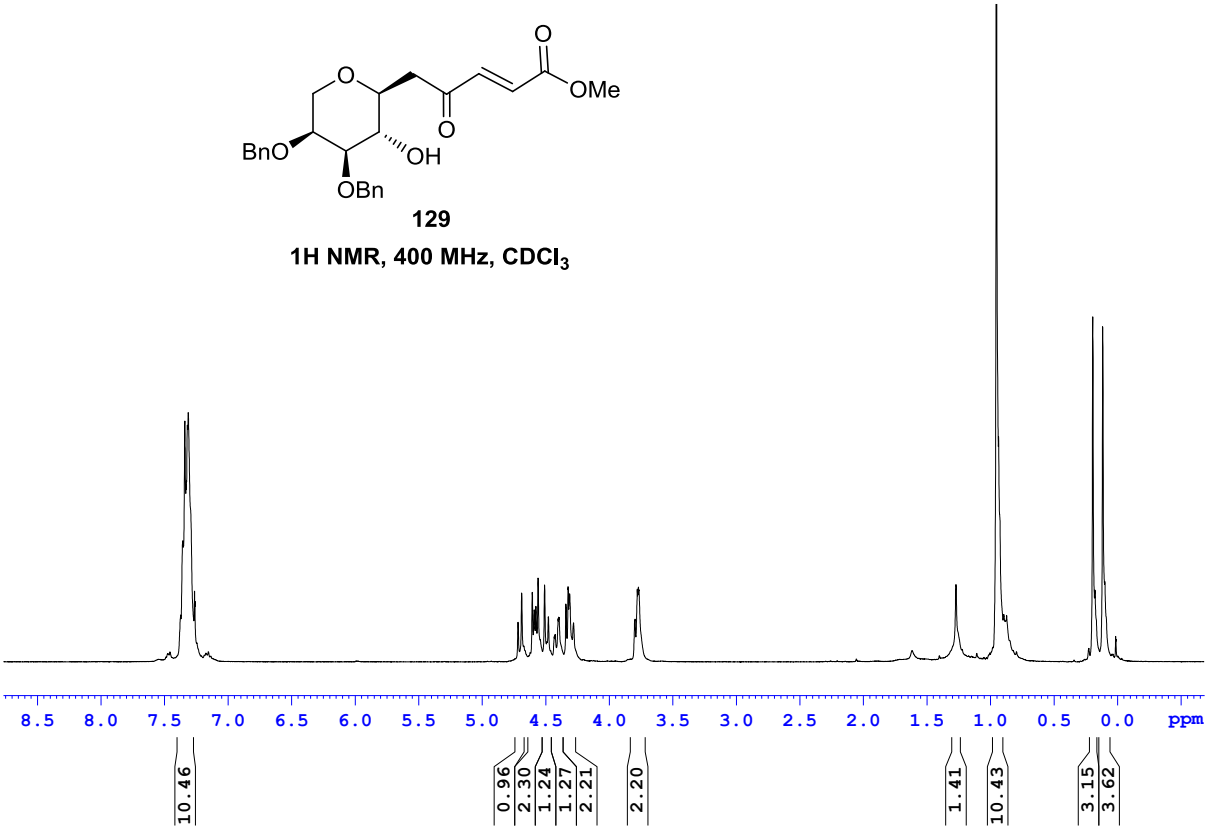




128

^{1}H-^{1}H NOESY NMR, 400 MHz, $CDCl_3$





129

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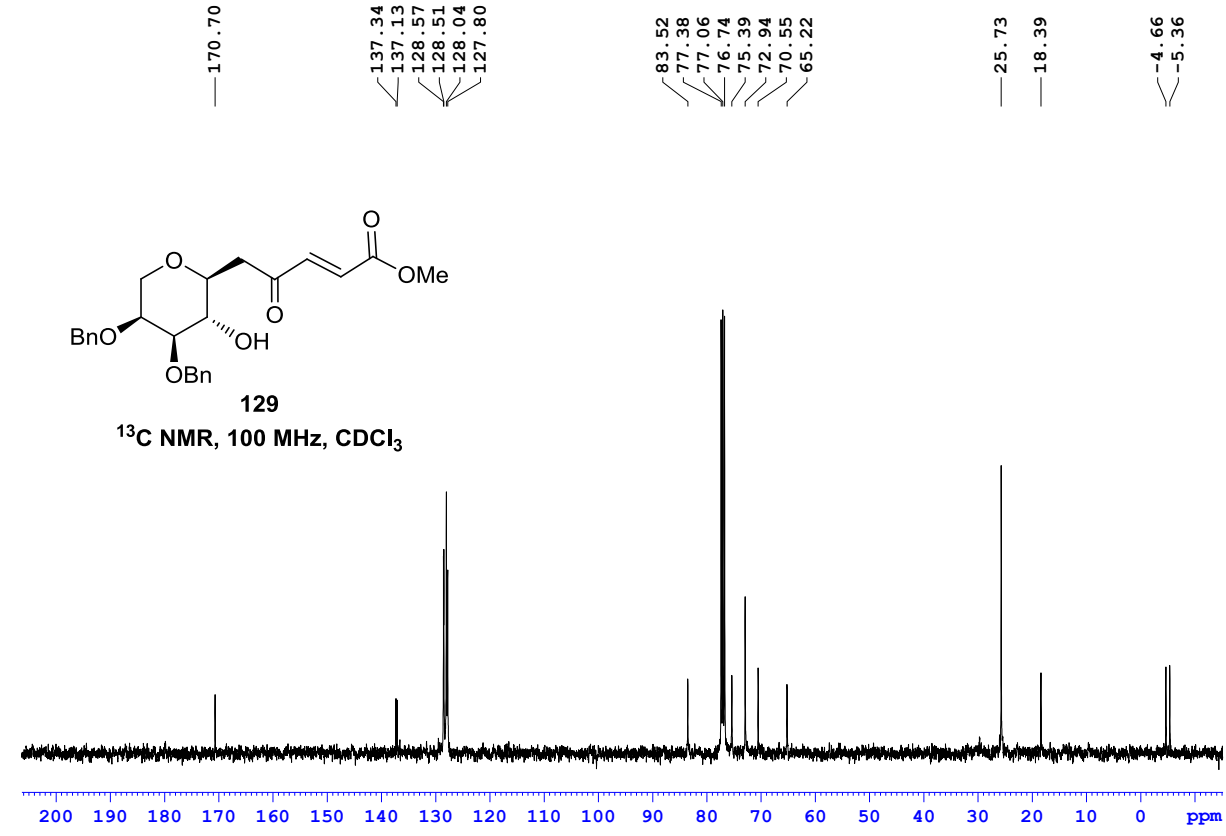

129

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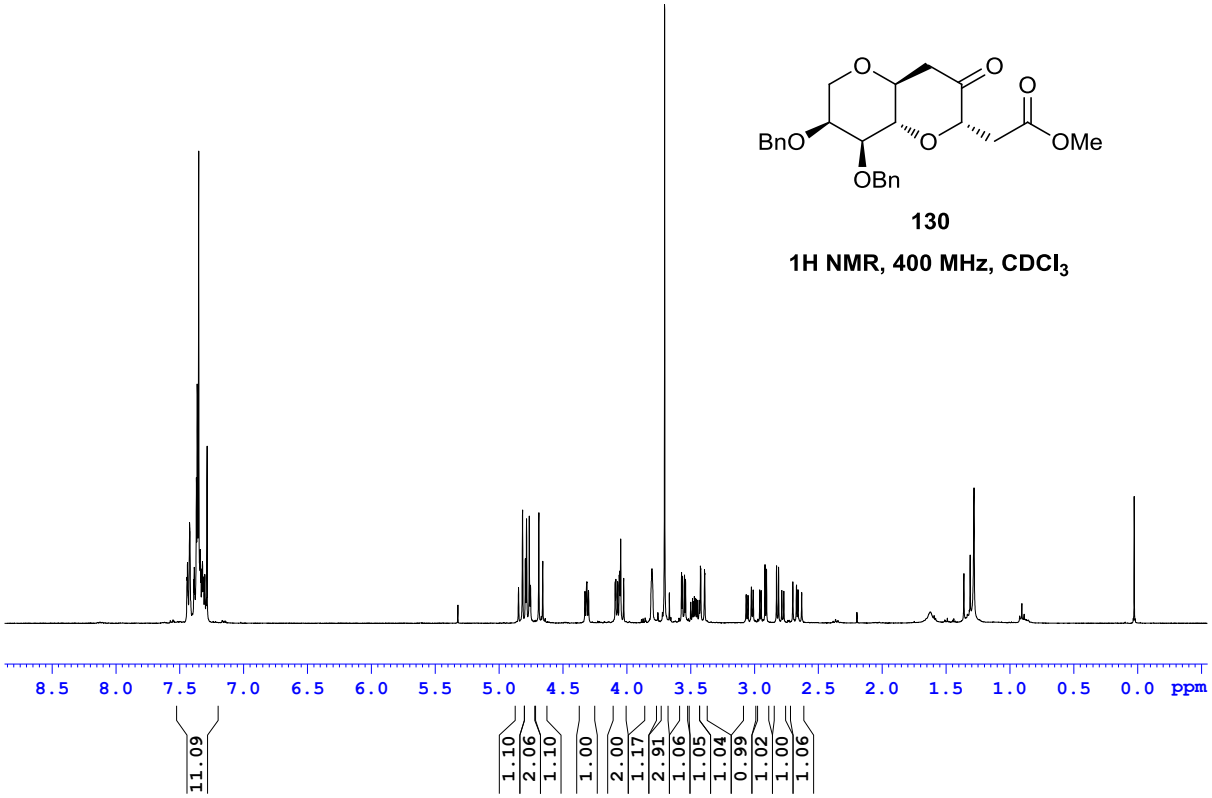
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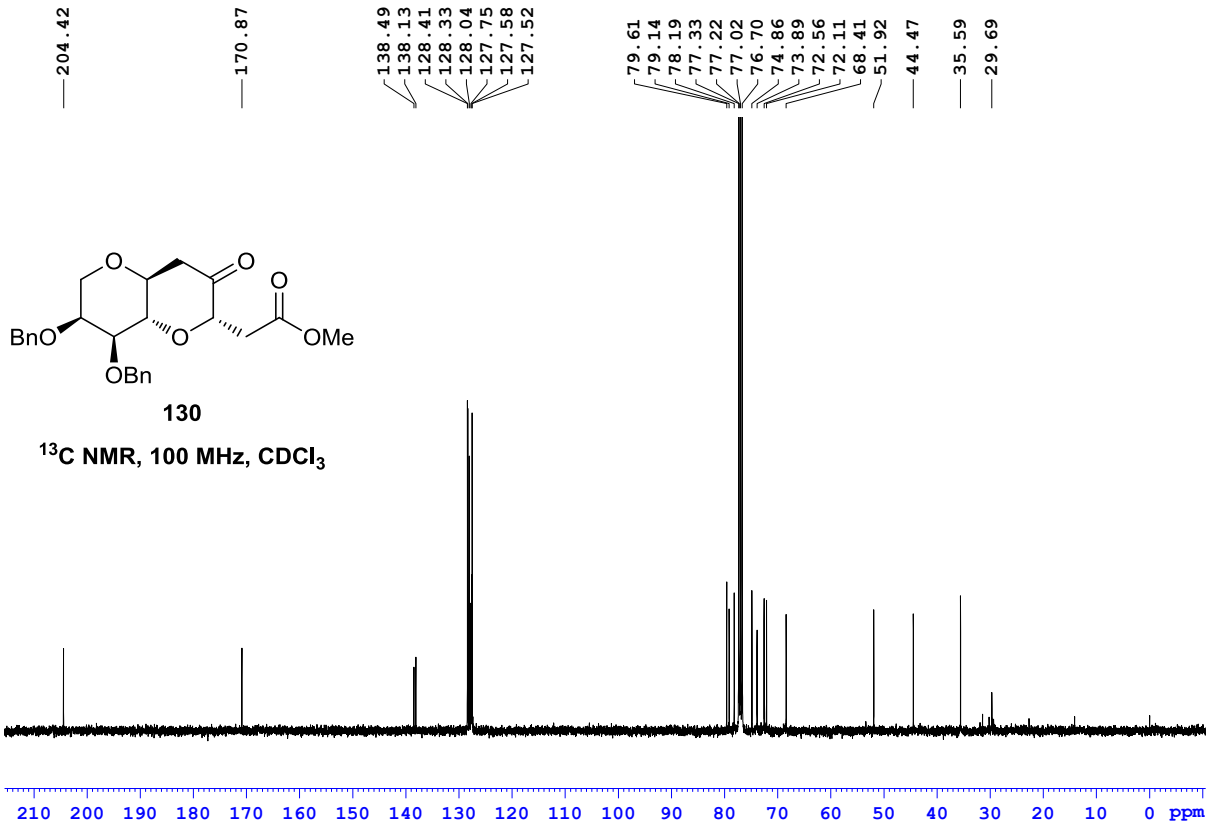
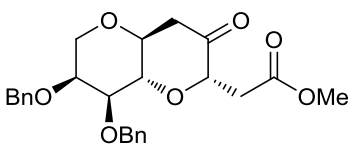
OBn
O
OMe
130
1H NMR, 400 MHz, CDCl3
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm
11.09
1.10 2.06 1.10 1.00 2.00 1.17 2.91 1.06 1.05 1.04 0.99 1.02 1.00 1.06


204.42
170.87
138.49 138.13 128.41 128.33 128.04 127.75 127.58 127.52
79.61 79.14 78.19 77.33 77.22 77.02 76.70 74.86 73.89 72.56 72.11 68.41
51.92
44.47
35.59
29.69
BnO
OBn
O
OMe
130
13C NMR, 100 MHz, CDCl3
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm



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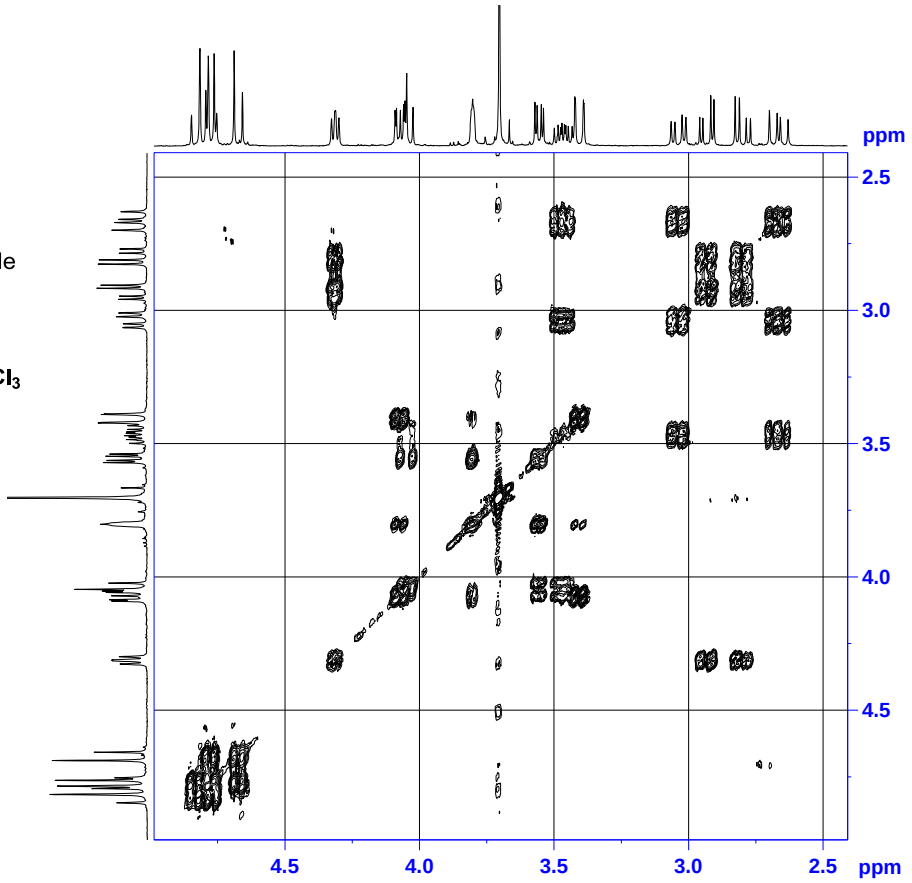

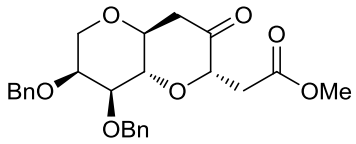

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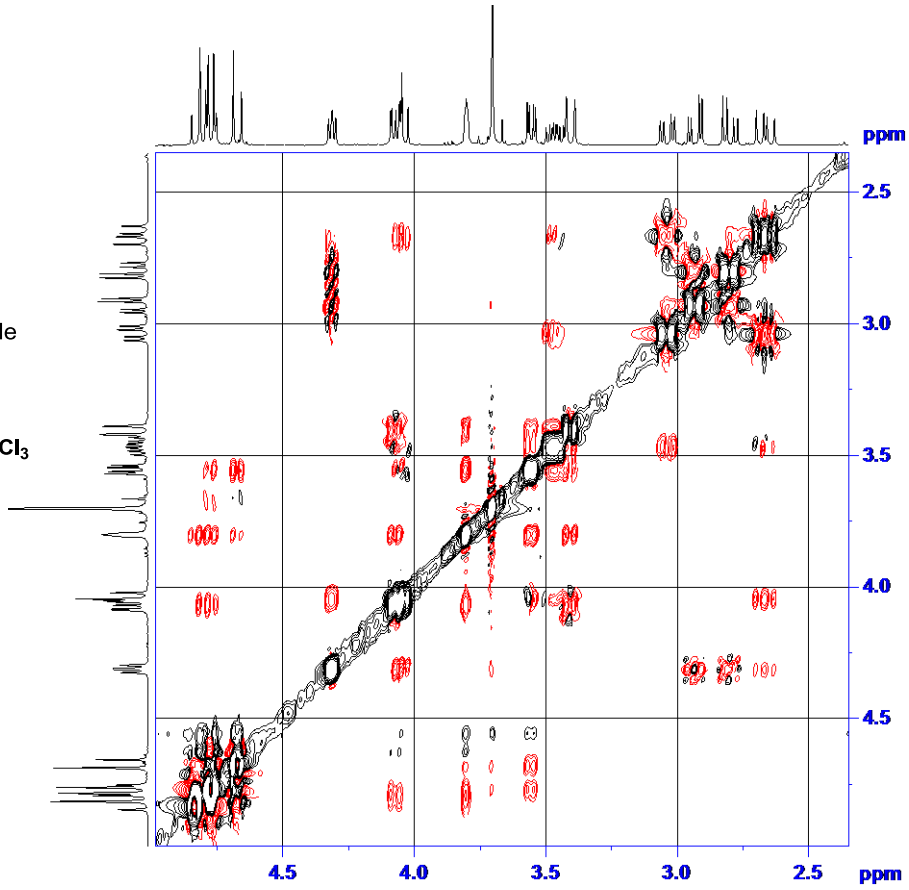

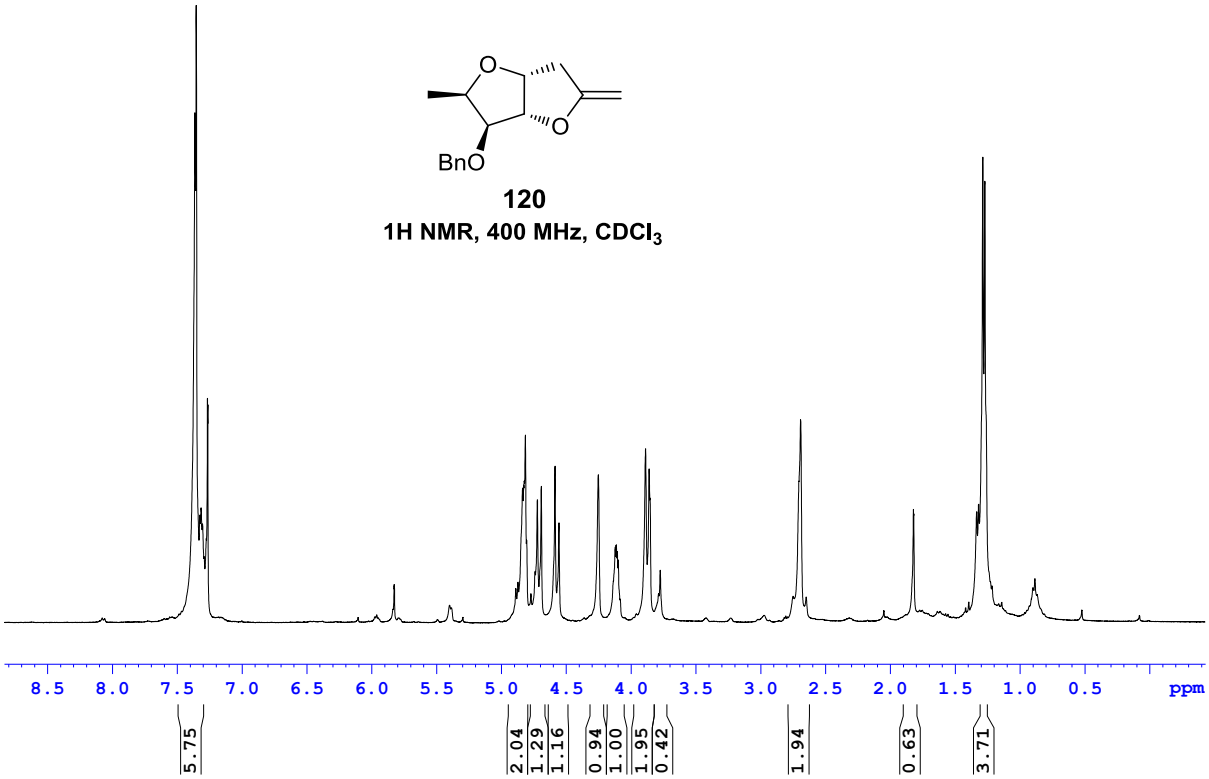

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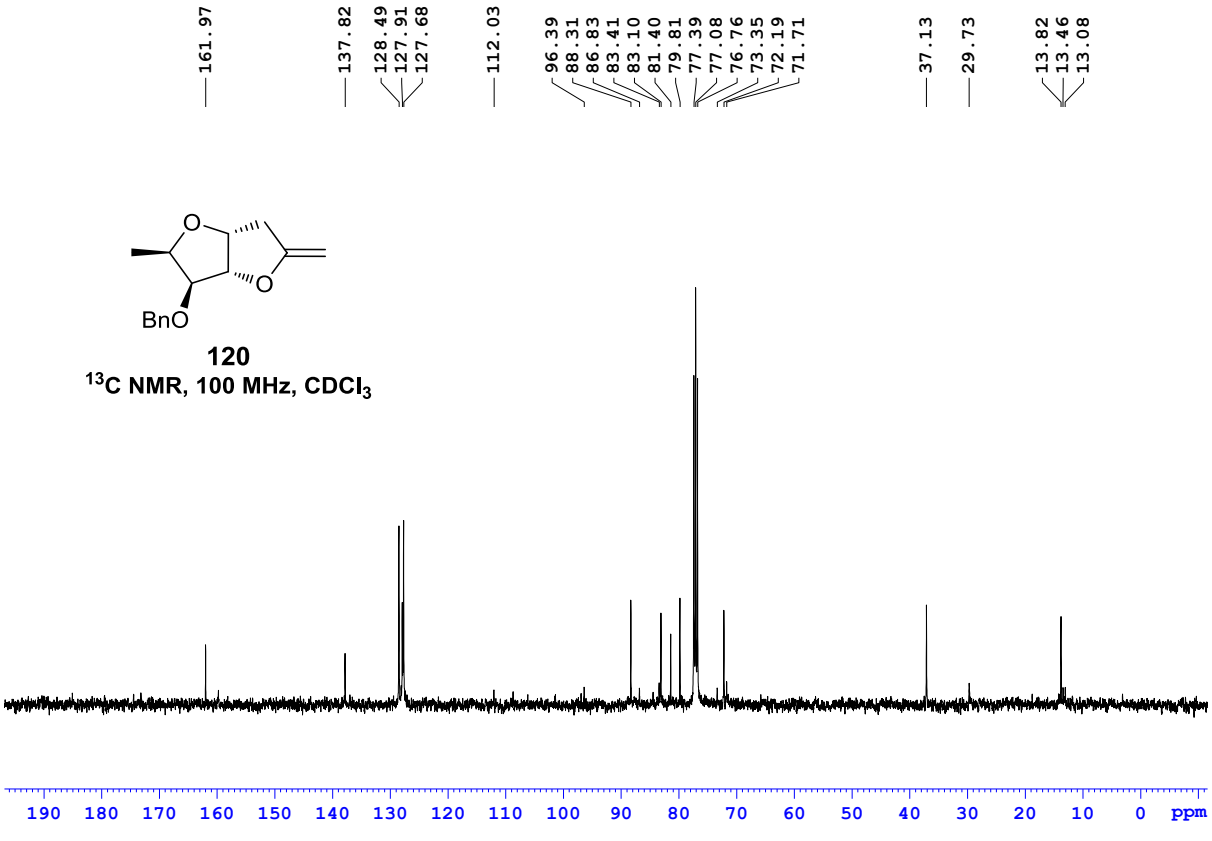
1H NMR, 400 MHz, $CDCl_3$



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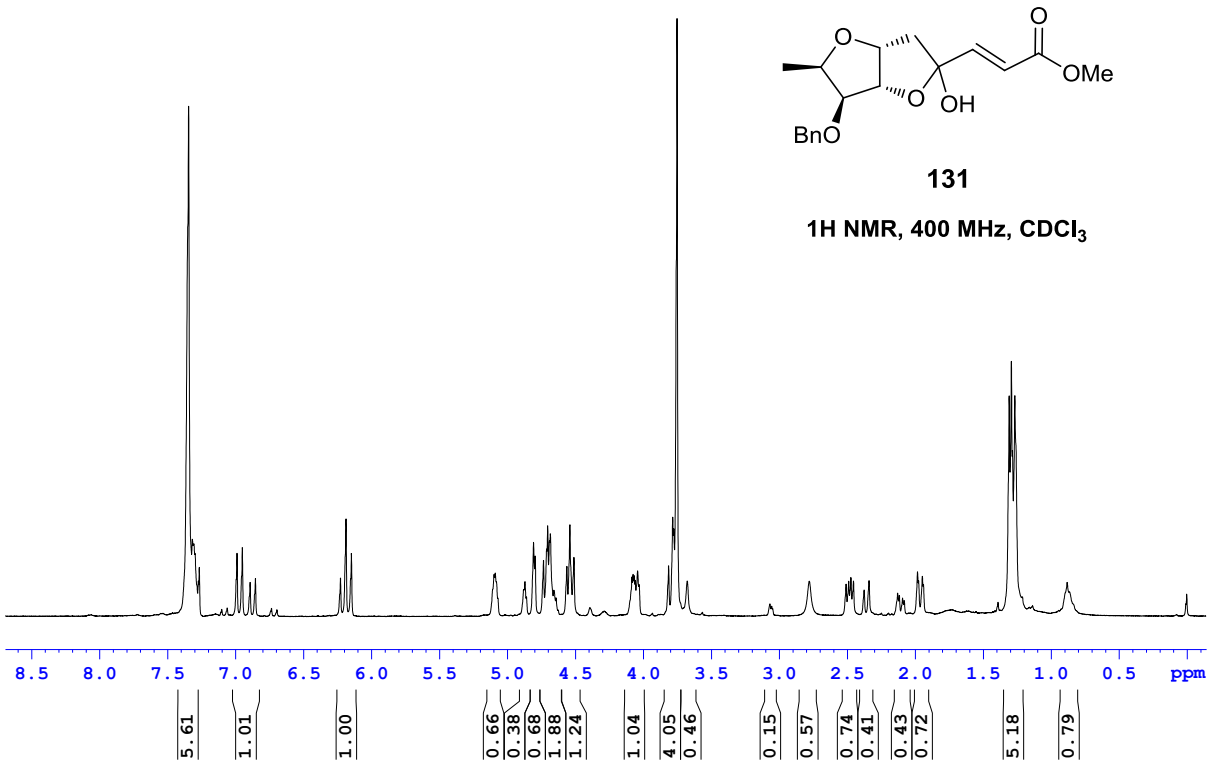

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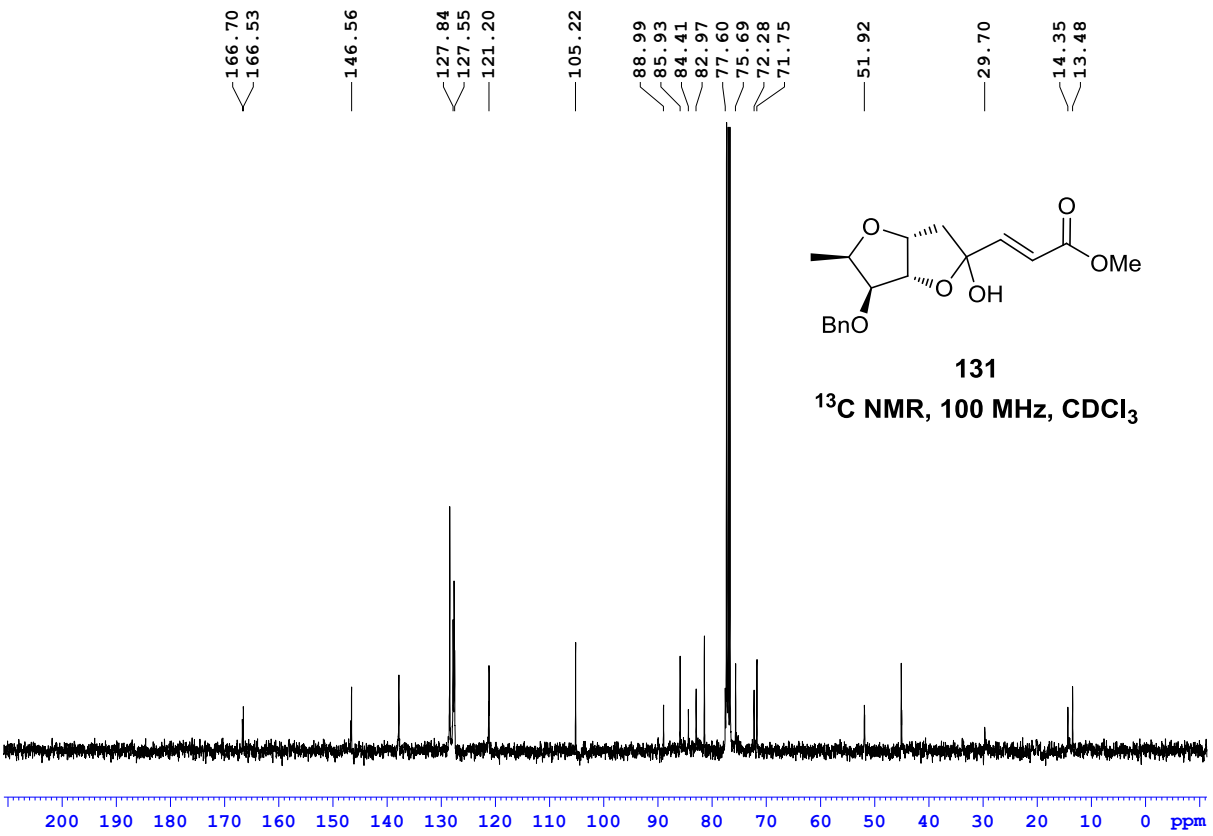

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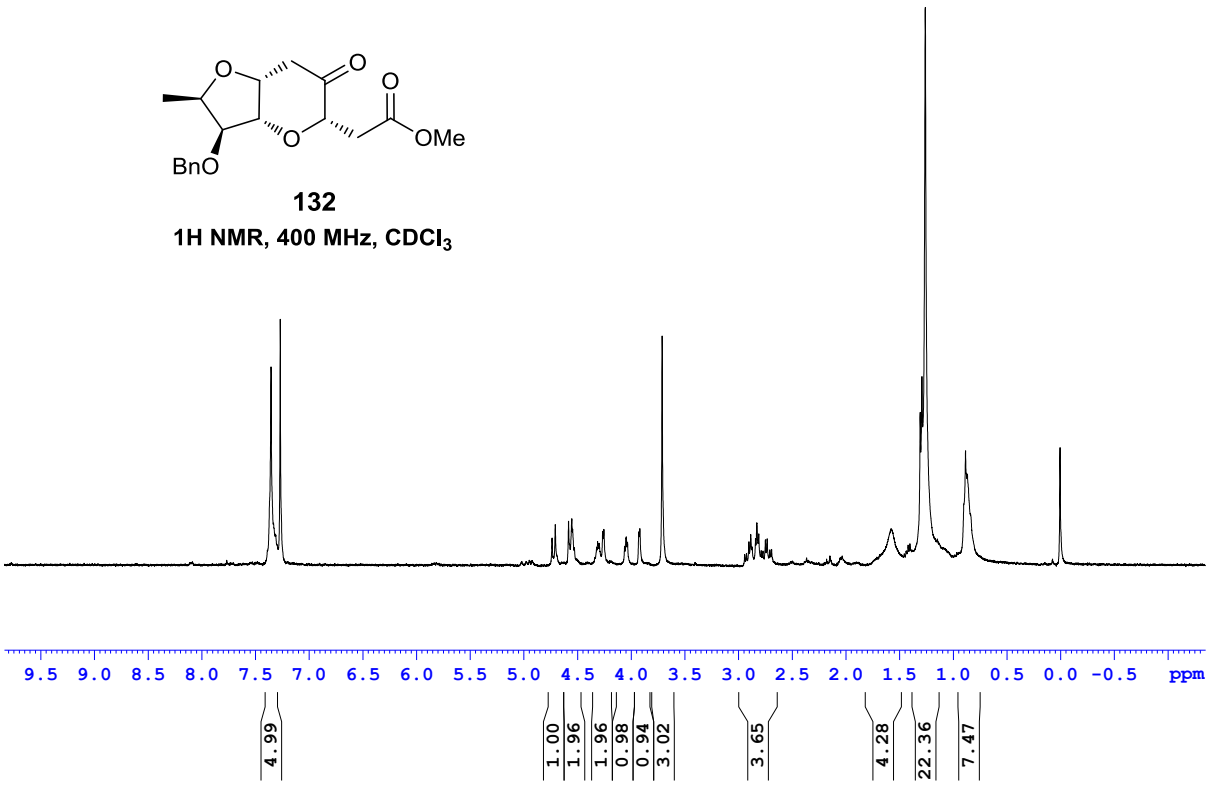

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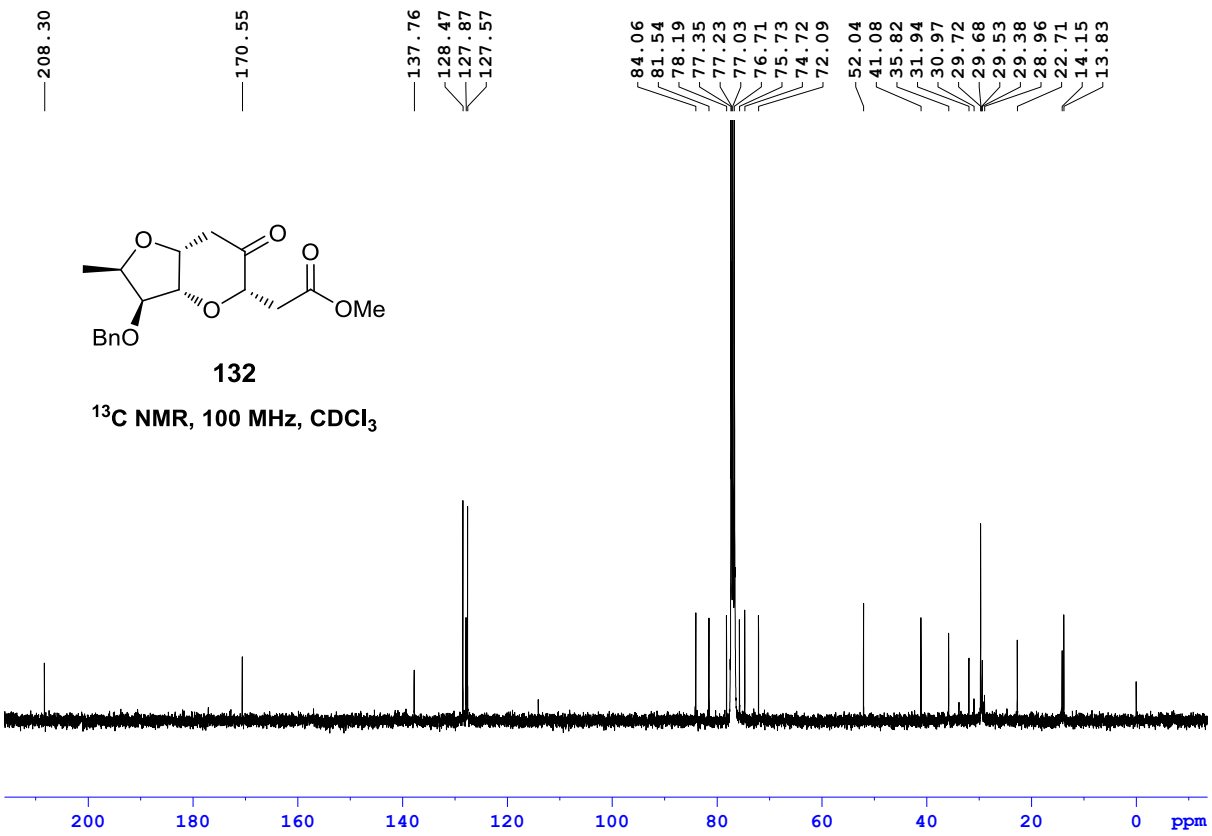

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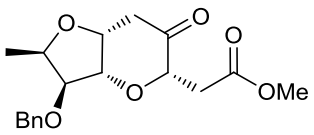

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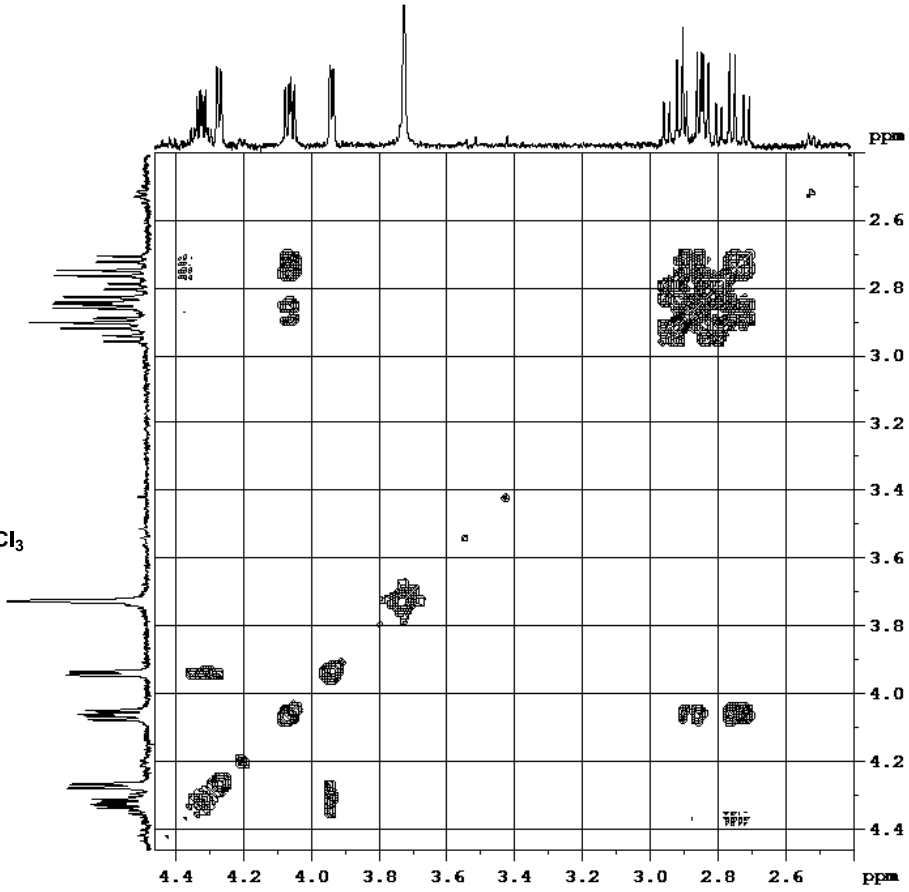

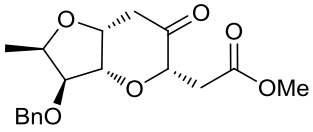

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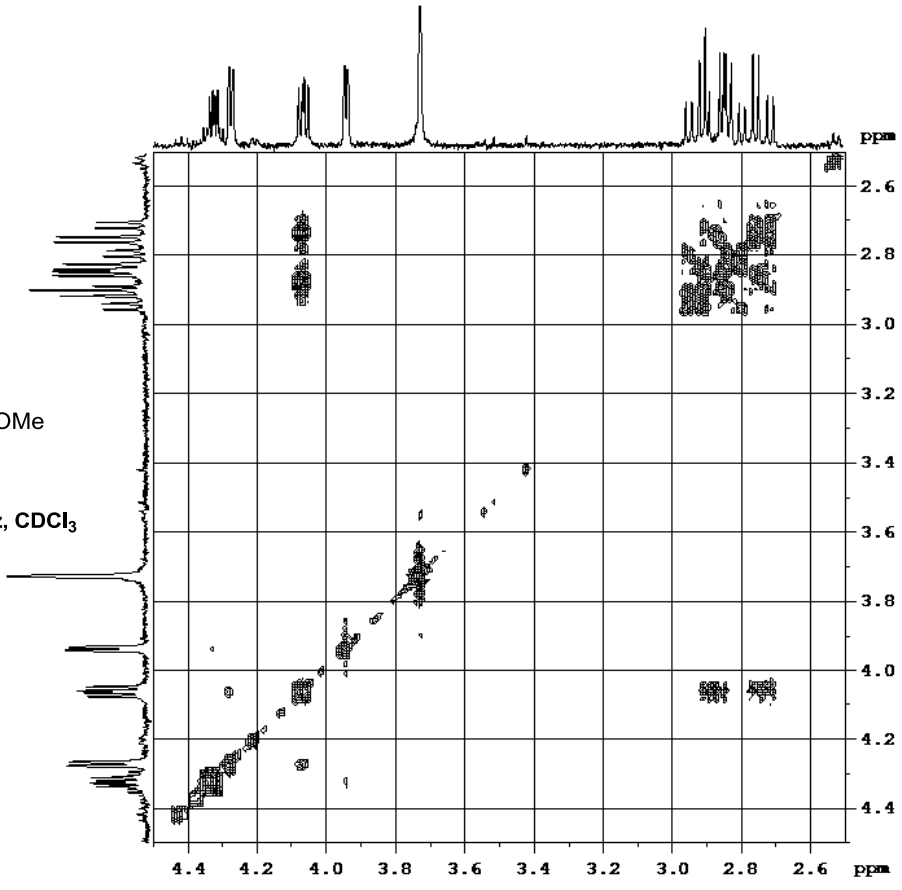
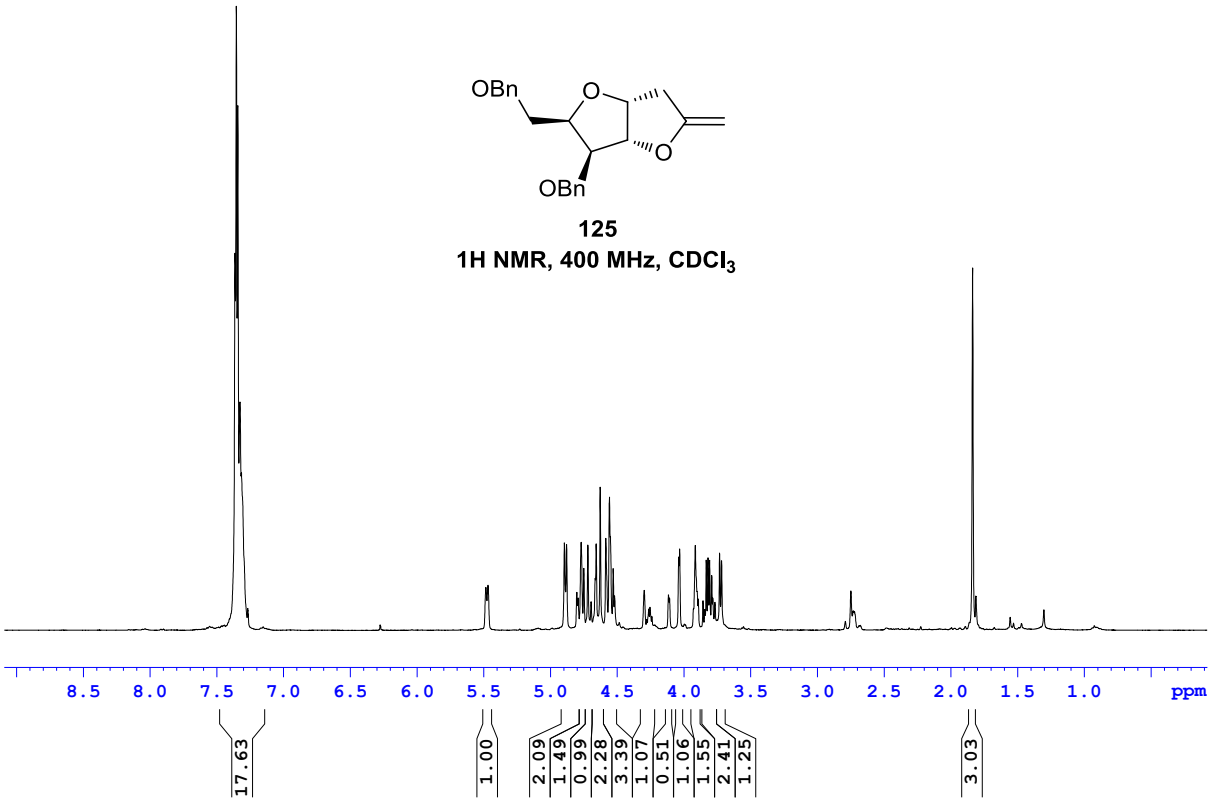
^{1}H-^{1}H NOESY NMR, 400 MHz, $CDCl_3$




OBn
O
O
OBn
125
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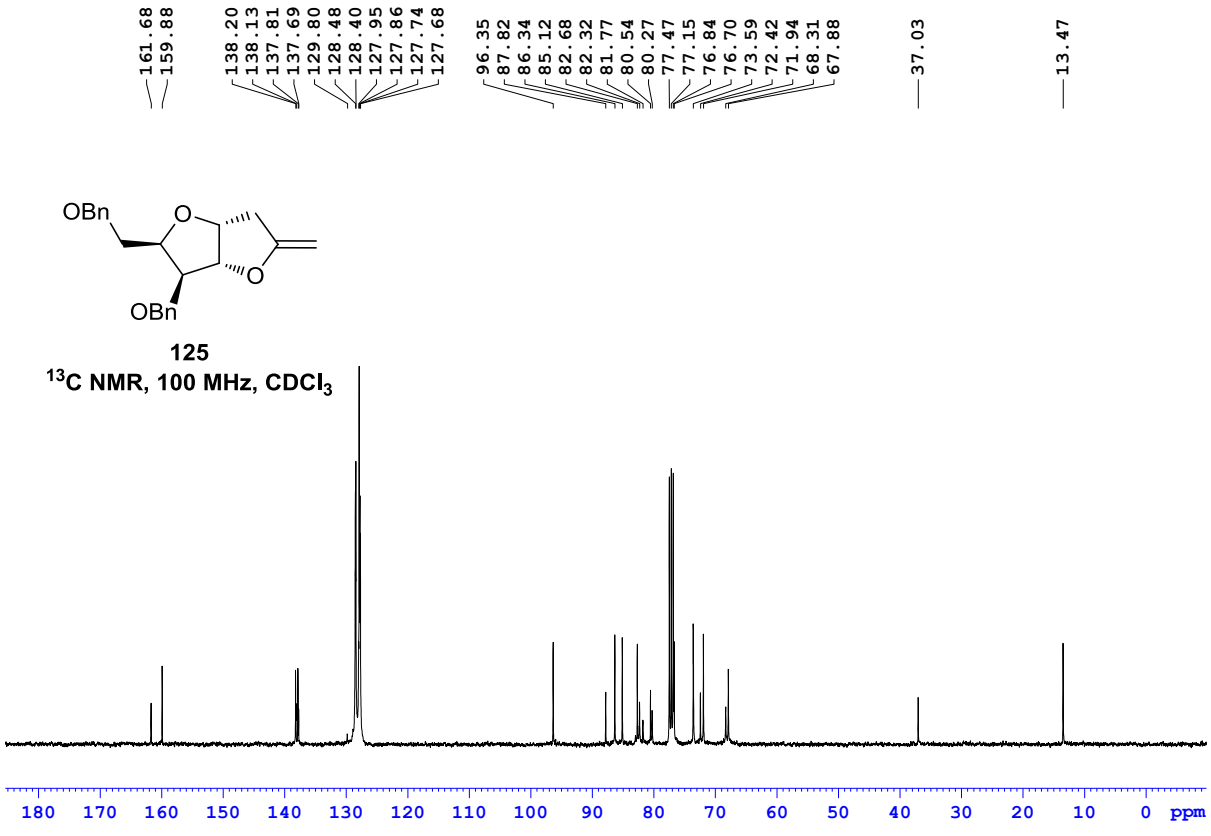
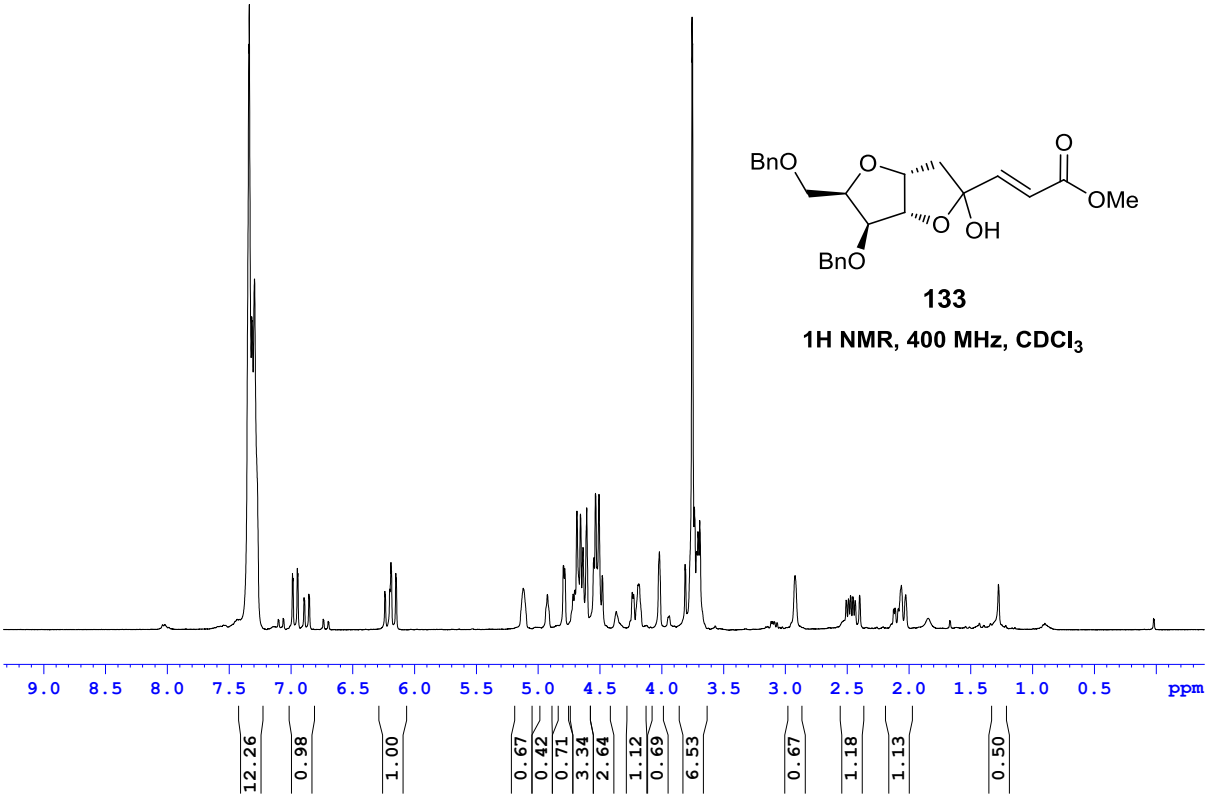
17.63
1.00
2.09
1.49
0.99
2.28
3.39
1.07
0.51
1.06
1.55
2.41
1.25
3.03


161.68
159.88
138.20
138.13
137.81
137.69
129.80
128.48
128.40
127.95
127.86
127.74
127.68
96.35
87.82
86.34
85.12
82.68
82.32
81.77
80.54
80.27
77.47
77.15
76.84
76.70
73.59
72.42
71.94
68.31
67.88
37.03
13.47
OBn
O
O
OBn
125
13C NMR, 100 MHz, CDCl3
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm



133

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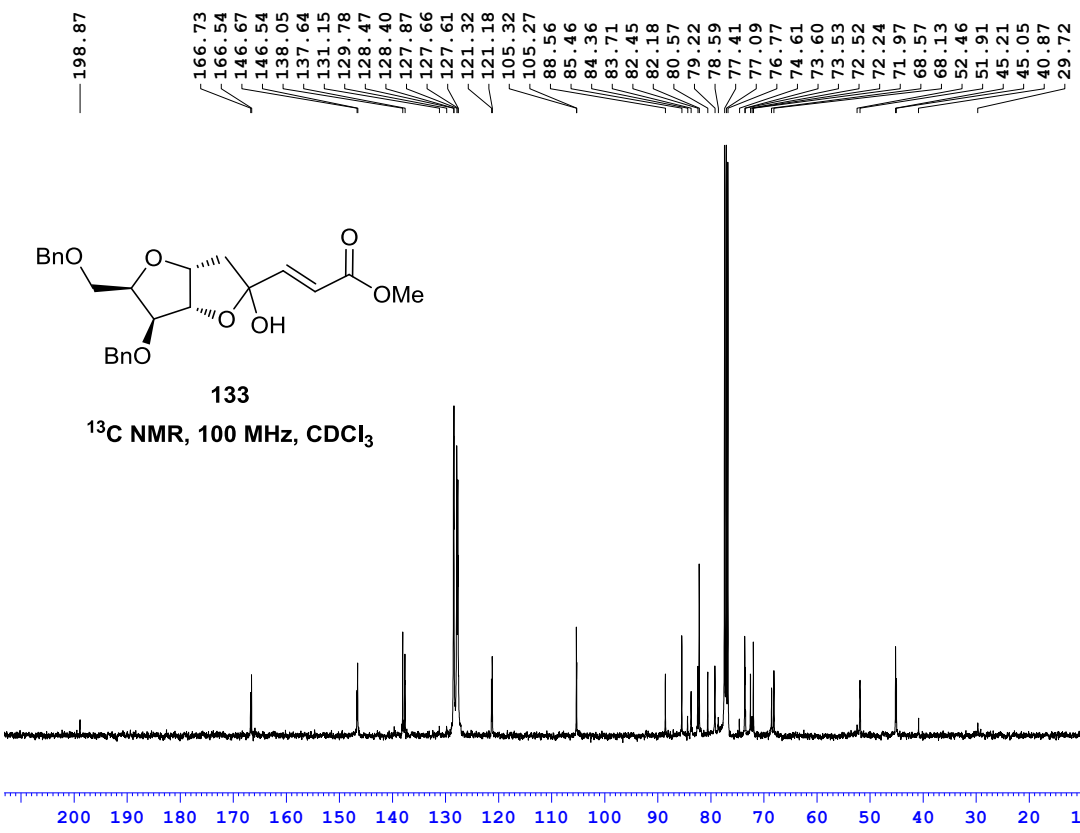

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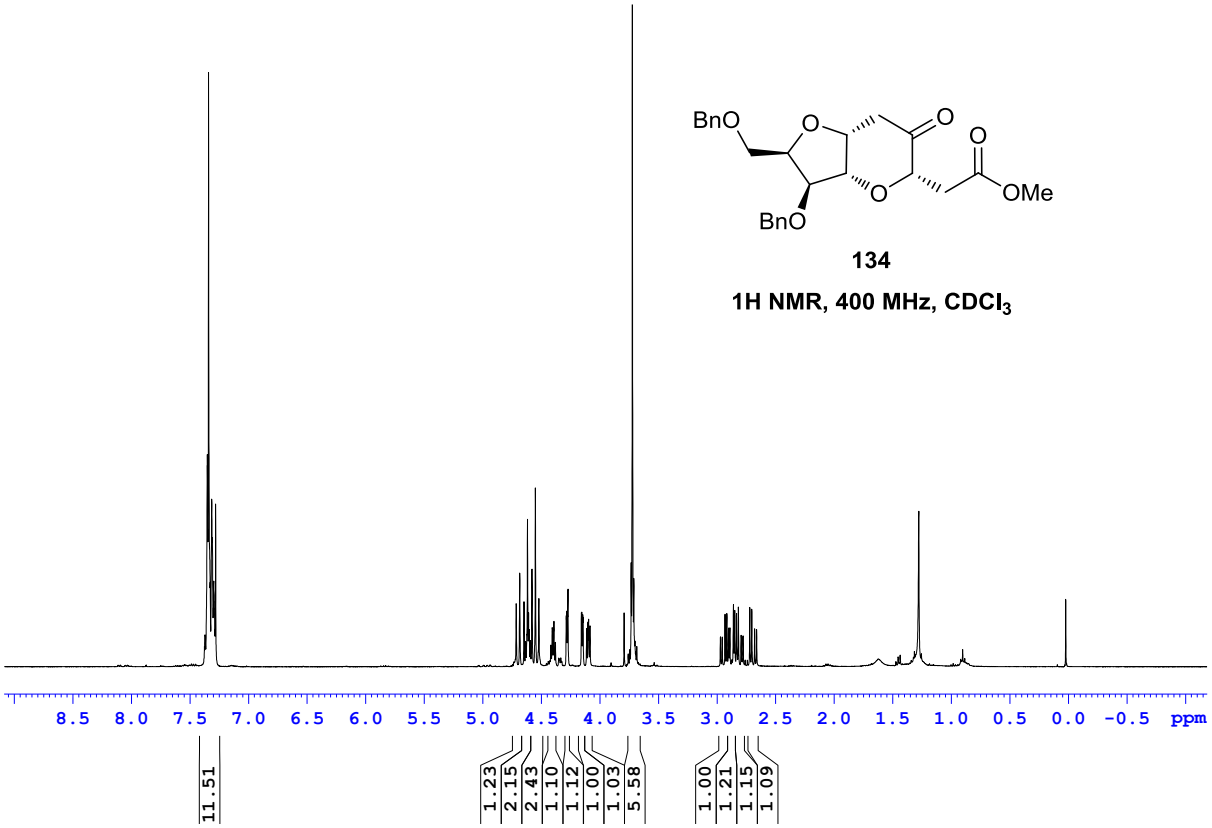

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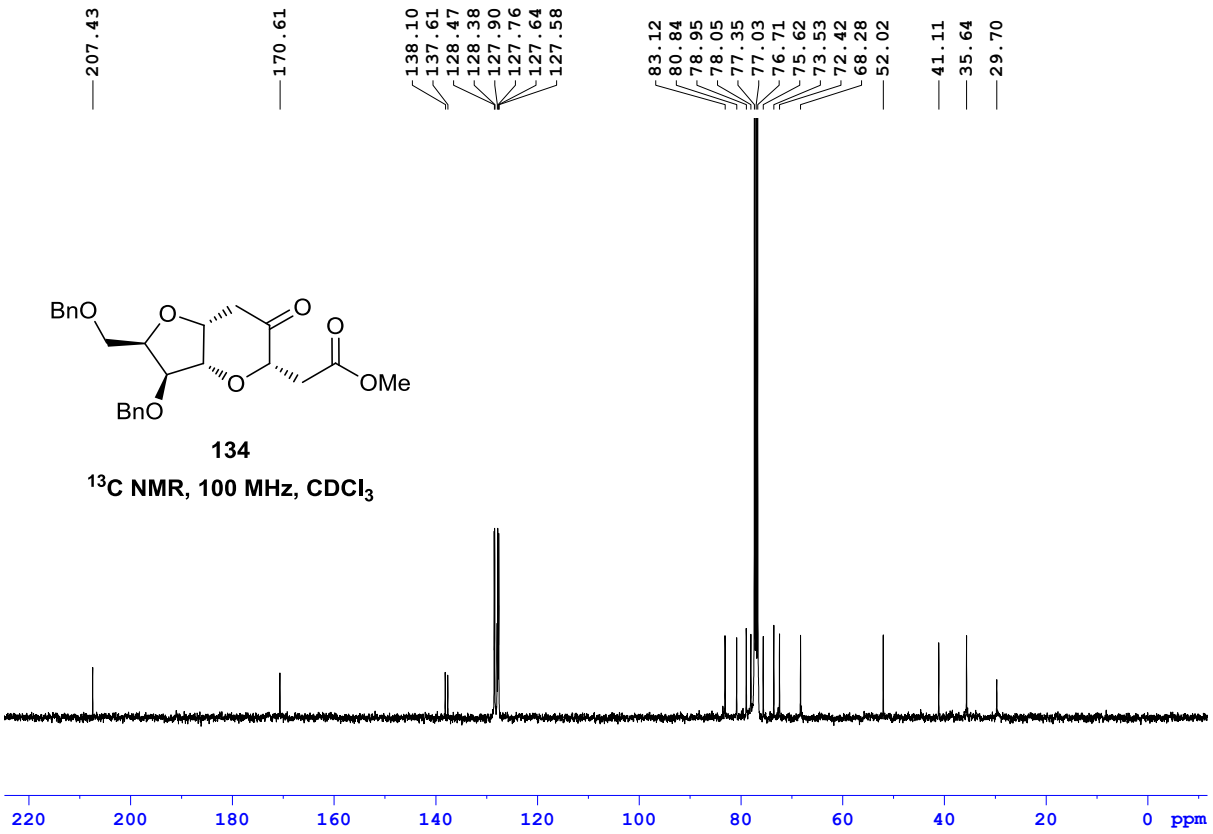
1H NMR, 400 MHz, $CDCl_3$



134

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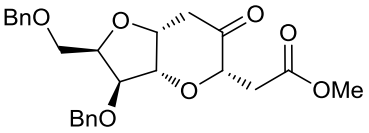

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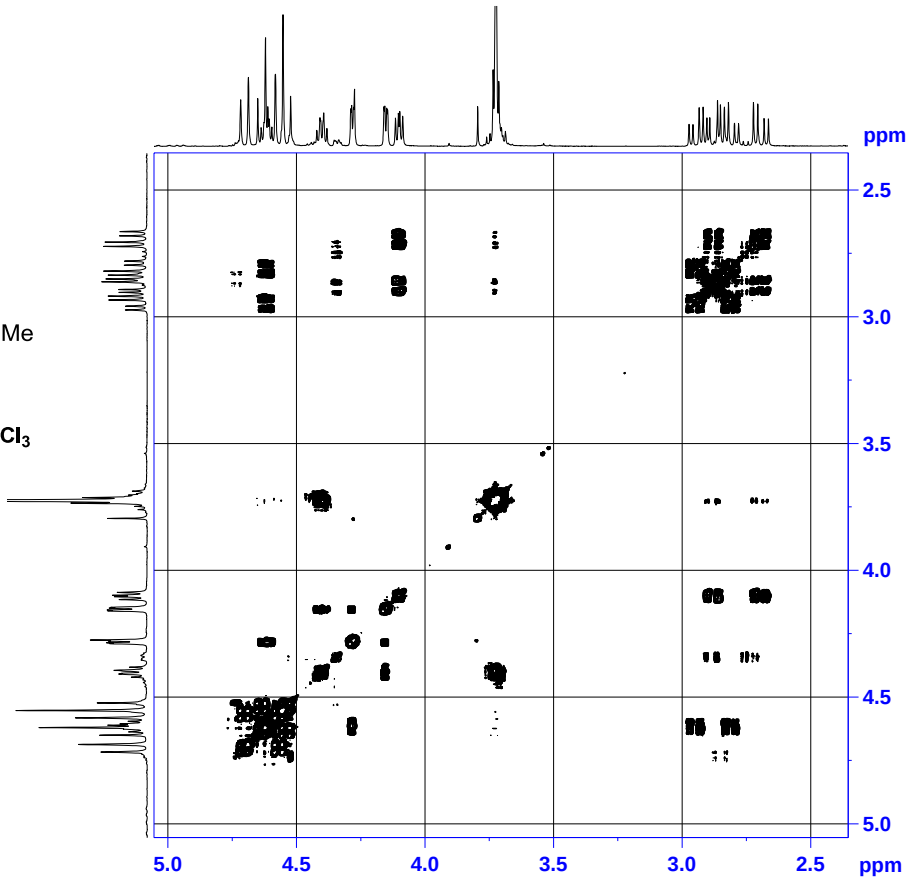
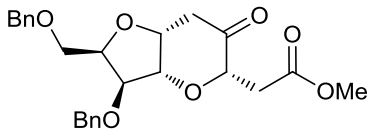
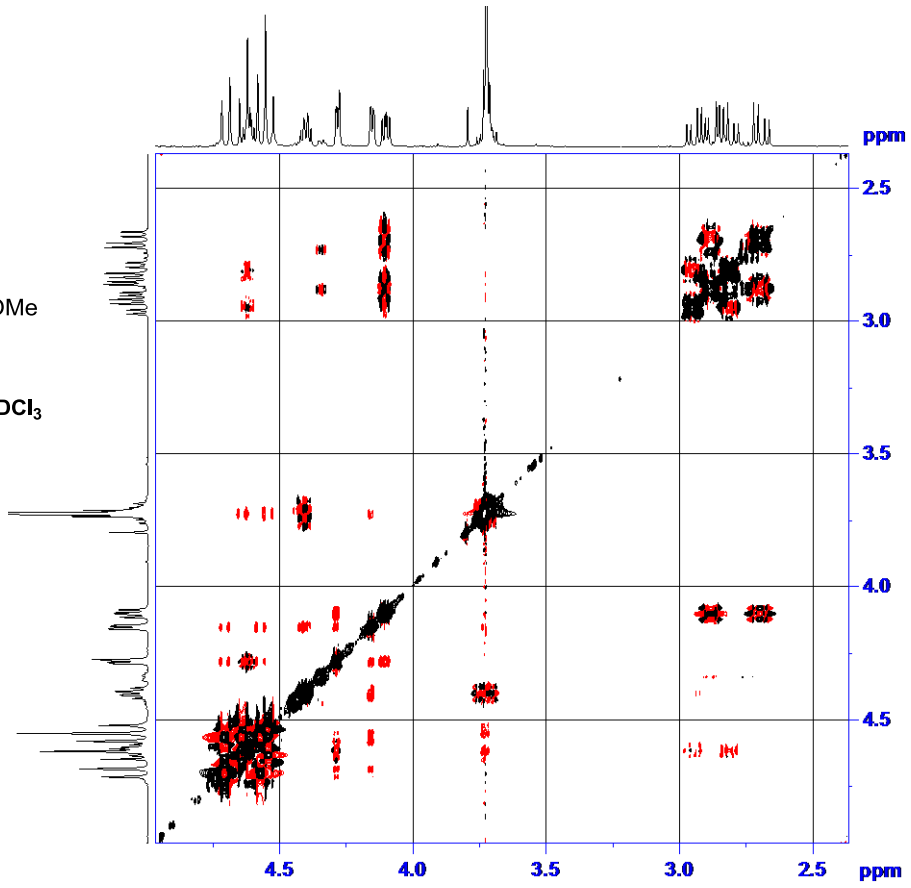
^{1}H-^{1}H COSY NMR, 400 MHz, $CDCl_3$





134

^{1}H-^{1}H NOESY NMR, 400 MHz, $CDCl_3$

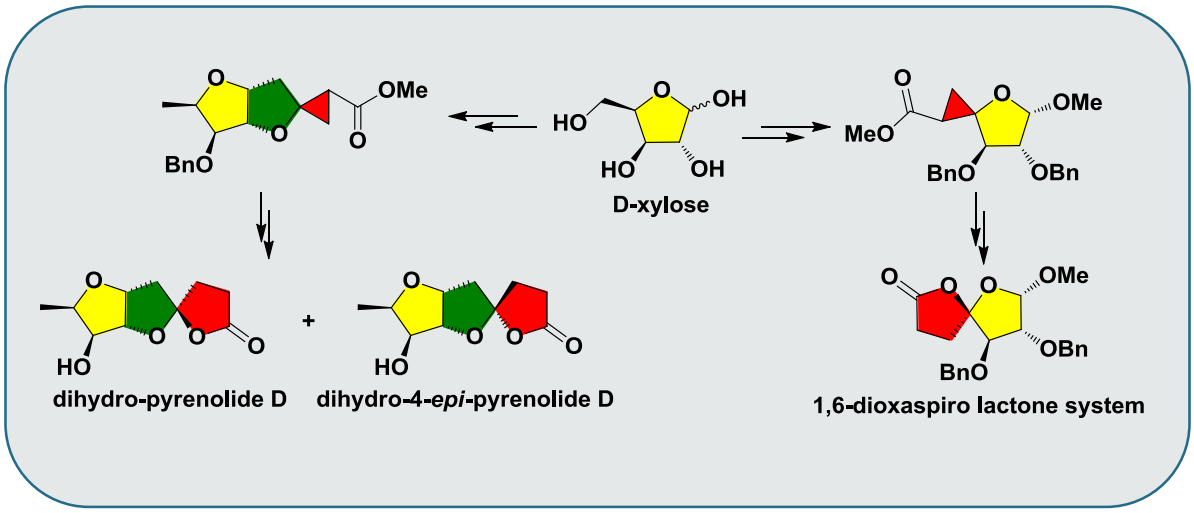


Chapter 3

Stereoselective synthesis of 1,6-dioxaspirolactones from spiro-cyclopropanecarboxylated sugars: Total synthesis of dihydro-pyrenolide D

Abstract

A thermodynamically driven stereoselective synthesis of 1,6-dioxaspiro[4.n]decan-2-one systems (n = 4, 5) is accomplished from spiro-cyclopropanecarboxylated sugar derivatives. The reaction involves a one-pot cyclopropane ring opening followed by cyclization to form γ-spiroketal γ-lactone moiety. The generality and the stereoselectivity of the reaction are examined by synthesizing a series of spirocyclic systems. A successful approach to the synthesis of saturated analogues of pyrenolide D is also revealed by the application of the current protocol particularly for the formation of crucial quaternary spiro centre of this molecule.



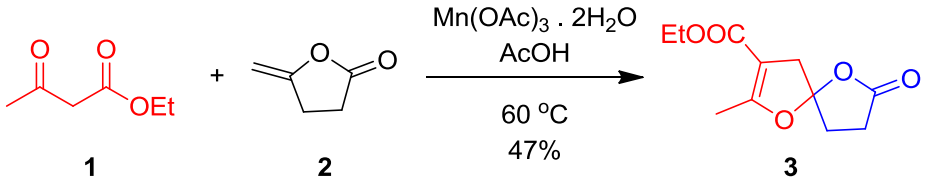
3.1 Introduction

1,6-dioxaspiro system, particularly in the form of spiroketal[1] or spirolactone,[2] is one of the intriguing structural unit present in a number of highly bioactive natural products.[3] For example, marine toxins like azaspiracids,[4] pinnatoxins,[5] pteriatoxins,[6] spongistatins[7] and spirolides[8] etc. possess the spiroketal moiety as the core structure. Interestingly, some of the spiroketal subunits were found to retain the biological activity that was exhibited by the parent natural product.[9] The traditional method for the spiroketal synthesis involves an acid catalyzed ketalization of a dihydroxy ketone precursor, which often produces the thermodynamic product in which there is a profound preference for the carbon-oxygen bond at spirocenter in a bis-diaxial C-O conformation.[10] Alternatively, oxidative radical cyclization is another brilliant approach that provides an access to the kinetically controlled preparation of spiroketals.[11] Recently Werz *et al.* reported an interesting spiroketalization of spiro-cyclopropanated carbohydrate derivatives involving IBX/Yb(OTf)$_3$ mediated one-pot oxidative ring-opening and cyclization reaction.[12]

Although several methods have been reported for the synthesis of spiroketals, the stereoselective protocols for the preparation of spiro-lactones (γ-spiroketal γ-lactones) are very scarce.[13] In addition, spiro-lactones are also an excellent synthons for the preparation of spiroketals[14] as well as for further functional group modifications. Apart from directed protocols,[15] photolytic oxidative cyclization of sugar derived nononamides[16] and gold phosphate-catalyzed one-pot three component coupling reaction of alkynols, anilines and glyoxylic acid towards the preparation of spirolactones[17] are recently revealed. Some of the spiroketals are briefly discussed in the below paragraph.

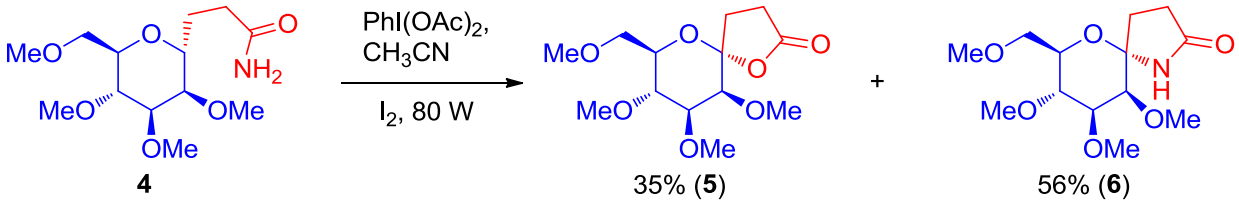
3.1.1Synthetic Methods for the preparation of spiro-lactones:

In 1993 Mellor and Mohammed developed a simple method for the construction of oxa-spiro-lactones by using manganese(III) acetate dihydrate prompted addition to *exo*-cyclic enol lactones. These spirolactone systems are present in naturally occurring spirooxabovolide, α-levantenolide and grindelistrictic acid, having important pheromonal and antibiotic activity. Treatment of ethyl acetoacetate **1** with lactone **2** in presence of manganese acetate afforded the spiro-lactone **3** in 45% yield *via* radical mechanism (Scheme 3.1).[13a] This methodology was also successfully applied to the six-membered lactones to afford the corresponding spiro-lactones.



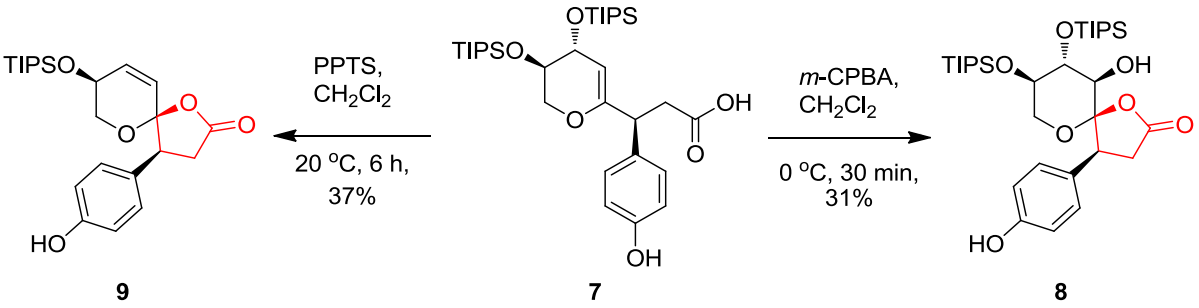
Scheme 3.1: Synthesis of spiro-lactone by using manganese acetate.

In 2005 Suarez and his co-workers synthesized 1,6-dioxaspiro[4.4]nonan-2-one (spiro-lactone) and 1-oxa-6-azaspiro[4.4]nonan-7-one (spiro-lactam) systems from glycosyl amides through *N*-radical mechanism followed by intramolecular hydrogen abstraction. This *N*-radical was generated by the hemolytic cleavage of iodo-amide, which is in situ prepared by the reaction of amide with diacetoxyiodo benzene (DIB) in presence of iodine, under irradiation with 80 W tungsten filament lamp at room temperature. Treatment of glycosyl amide **4** with diacetoxyiodo benzene and iodine in acetonitrile furnished the mixture of spiro-lactone **5** and spiro-lactam **6** in 4:6 ratio (Scheme 3.2).[16] These two products were obtained by *O*- and *N*-cyclisation of carbenium and oxacarbonium intermediate by intramolecular hydrogen abstraction, respectively.



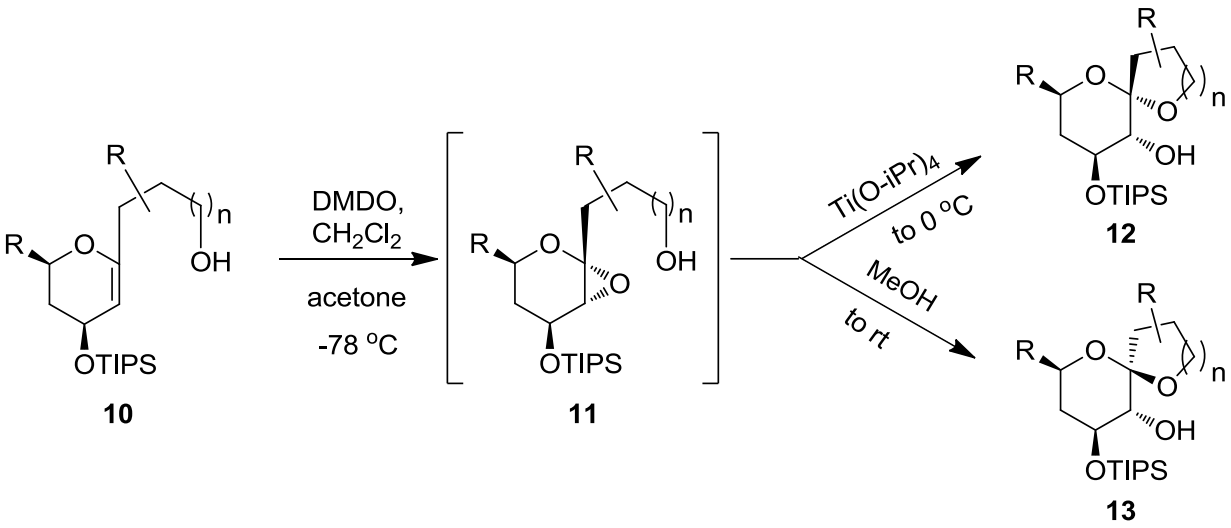
Scheme 3.2: Synthesis of spiro-lactone and spiro-lactam by using nuecleophillic cyclization of amide.

Recently (2010) synthesis of *ent*-sawaranospirolides C and D was first reported by Robertson group by using spiro-cyclization of glycal derivative. Treatment of glycal derivative **7** with *meta*-chloroperbenzoicacid in dichloromethane at 0 °C, provided spirolactone **8** with 31% yield. On the other hand when it was treated with pyridinium *p*-toluenesulfonate (PPTS) in dichloromethane at 20 °C provided the corresponding spiro-lactone **9** in 37% yield (Scheme 3.3).[2b] From these two spiro-lactones they synthesized *ent*-sawaranospirolides C and D in two steps by using suitable reagents. In this method the only drawback is lower yields were obtained in the synthesis of spiro-lactones.



Scheme 3.3: Synthesis of spiro-lactone systems from glycal derivative.

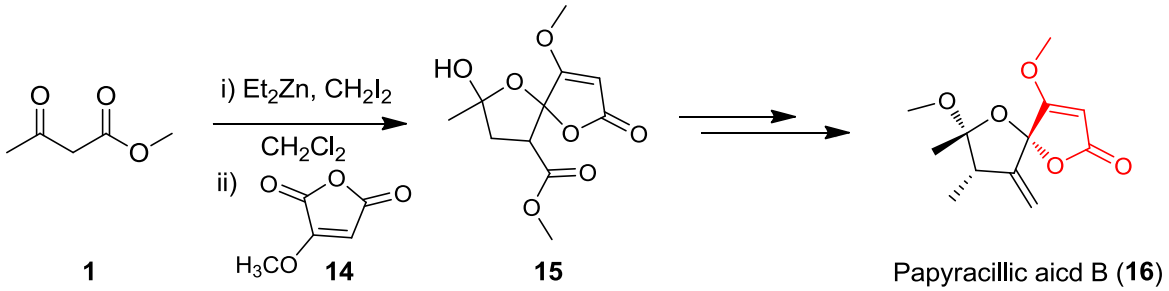
In 2011 Derek S. Tan and his co-workers developed a stereoselective synthesis of spiro-ketals[18] *via* MeOH mediated ring-opening spiro-cyclisation of glycal epoxide. These spiro ketal motifs are present in number of biologically active natural products. Epoxidation of glycal derivative **10** with dimethyldioxirane (DMDO) in dichloromethane and acetone at low temperature provided the corresponding epoxide intermediate **11**. In presence of Ti(O-^{i}Pr)$_4$ catalyst, glycal epoxide underwent spiro-cyclization reaction to afford the C1-epimeric spiroketal **12** with retention of configuration at anomeric carbon. Where as in the case of methanol catalyzed reaction, the ring opening of glycal-epoxide followed by spiro-cyclization *via* hydrogen bonding catalysis to form the spiroketal **13** with inversion of configuration was observed (Scheme 3.4).



Scheme 3.4: Stereoselective synthesis of spiro-ketals from glycal-epoxide.

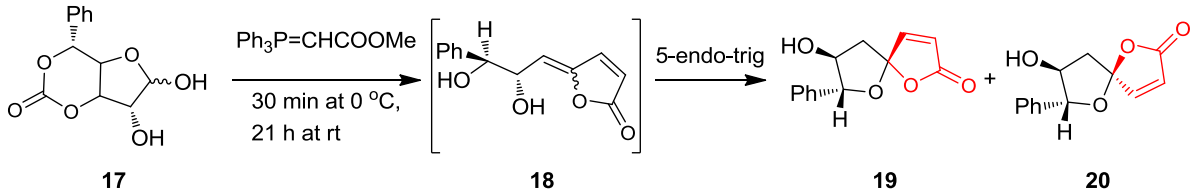
In 2012 Zercher and Mazzone developed a method for chain extension acylation reaction and successfully applied this methodology to natural product based spiro-fused cyclic ketals such as papyracillic acid B and 4-*epi*-papyracillic acid B, 4-*epi*-papyracillic acid C. Exposure of

methyl acetoacetate **1** with furukawa-modified carbenoid to get the organometallic intermediate, which on further subjected with 3-methoxymaleic anhydride **14** to provide the corresponding spiro-fused cyclic ketal **15** respectively. From this they have synthesized papyracillic acid B **16** in three steps (Scheme 3.5).[19]



Scheme 3.5: Synthesis of spiro-fused cyclic ketal by using tandem chain extension acylation reaction.

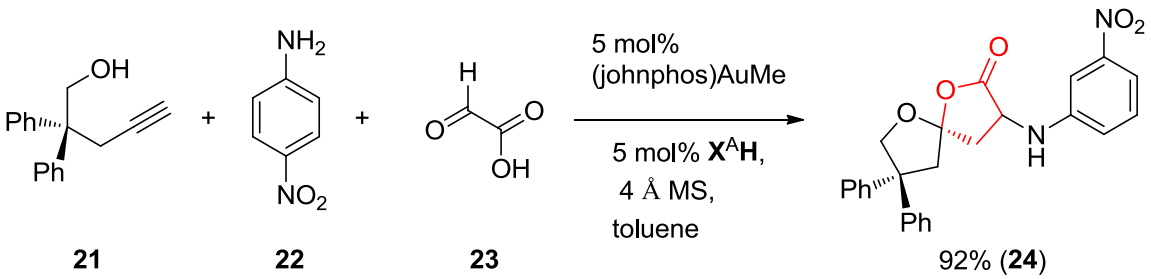
In 2012 Bogdanovic and his co-workers invented a method for the synthesis of spiro-lactones which are related to biologically active natural products such as goniobutenolides A and B, crassalctone D and 4-*epi*-crassalactone D. Spiro-lactones **19** and **20** were synthesized by treatment of lactol **17** under *Z*- selective Wittig olefination conditions to get the intermediate **18**, which undergo spiro-cyclization through 5-*endo*-trig ring closure process (Scheme 3.6).[20] These styryl lactones are exhibited potent cytotoxic activities, antiproliferative activities and selective antitumor agents.



Scheme 3.6: Synthesis of cytotoxic styryl lactones from D-glucose.

In 2013 Rodriguez developed a new method for construction of enantioselective synthesis of spiro-acetals by coupling reaction between alkynols, anilines and glyoxylic acid through gold-phosphate catalyzed reaction. Coupling reaction between alkynol **21**, 4-nitro aniline **22** and glyoxalic acid **23** in presence of gold-phosphate provided the spiro-acetal **24** in 92% yield (Scheme 3.7).[17] In this regard two intermediates, *exo*-cyclic enol formed from alkynol, and

imine was formed by condensation reaction between amine and aldehyde in situ, undergo (3+2) cycloaddition reaction to give [5,5]-spiroacetal.



Scheme 3.7: Synthesis of spiroacetals by using aurum-phosphate catalyzed coupling reaction.

In continuation of our investigation towards the application of cyclopropanecarboxylated sugars in the stereoselective synthesis of bicycilc architectures,[21] herein we report a general methodology for the preparation of carbohydrate derived 1,6-dioxa[n,5]-spiroketal butyrolactones (n = 5, 6) involving a one-pot ring expansion and cyclization reaction of sugar derived donor-acceptor spiro-cyclopropanecarboxylicacids.[22] Further, the developed methodology was successfully utilized to the total synthesis of 2,3-dihydro-pyrenolide D and 2,3-dihydro-4-*epi*-pyrenolide D.

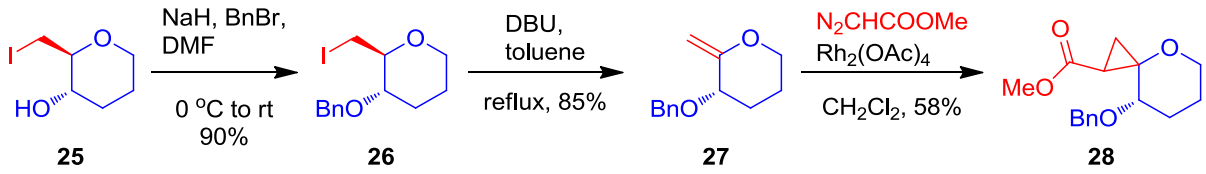
3.2 Results and Discussion

3.2.1 Synthesis of pyranose derived spiro-cyclopropanecarboxylated sugars

Spiro-cyclopropanecarboxylated sugars are useful in the synthesis of spiroketals and glycosyl inhibitors and various natural products. In this chapter we synthesized spiro-lactones from various spiro-cyclopropanecarboxylated sugars. The synthesis of carbohydrate derived donor-acceptor cyclopropanecarboxylate was planned starting from the *exo*-glycals. The synthesis of donor-acceptor spiro-cyclopropanecarboxylates has been discussed in the previous chapter. However, a couple of them (which are not mentioned previously) are briefly discussed here.

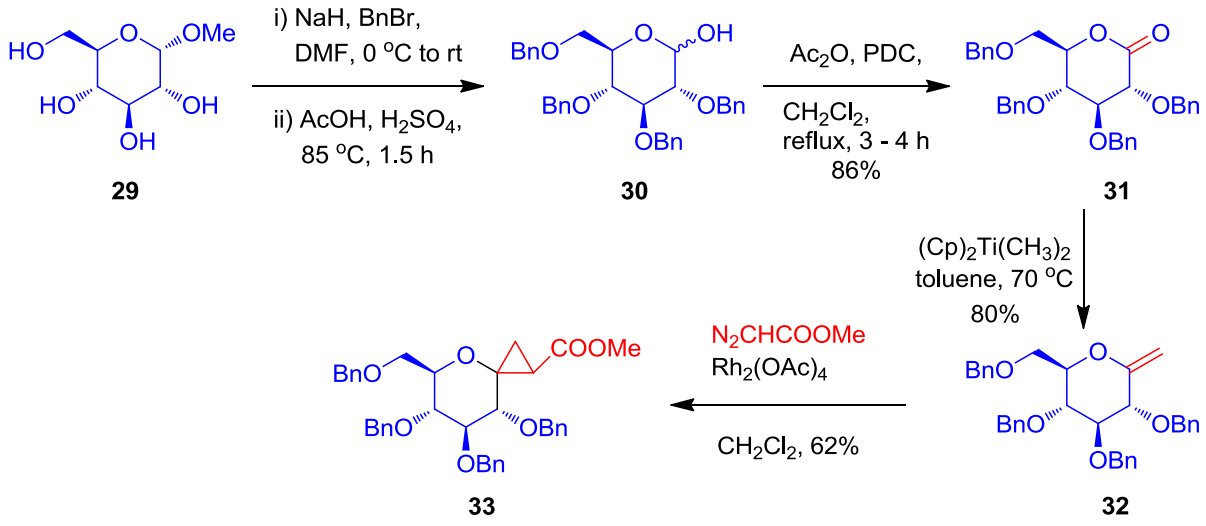
Glucose derived C-5-spiro-cyclopropanecarboxylated sugar **28** was prepared from 1,2,3,6-tetradeoxy-6-iodo-D-glucopyranose **25** which is already discussed in chapter 2 (scheme 2.8). Reaction of **25** with NaH and benzyl bromide provided the 1,2,3,6-tetradeoxy-6-iodo-4-*O*-benzyl-D-glucopyranose **26** in 90% yield. Dehydrohalogenation[23] of compound **26** with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) afforded the *exo*-cyclic vinyl ether **27** in 85% yield, finally $Rh_2(OAc)_4$ catalyzed cyclopropanation of *exo*-glycal[24] **27** using methyldiazoacetate

provided the spiro-cyclopropanecarboxylate **28** as a mixture of diastereomers in 58% yield (Scheme 3.8).



Scheme 3.8: Synthesis of 1,2,3,4-*tetra*-deoxy-spiro-cyclopropanecarboxylated sugar 28.

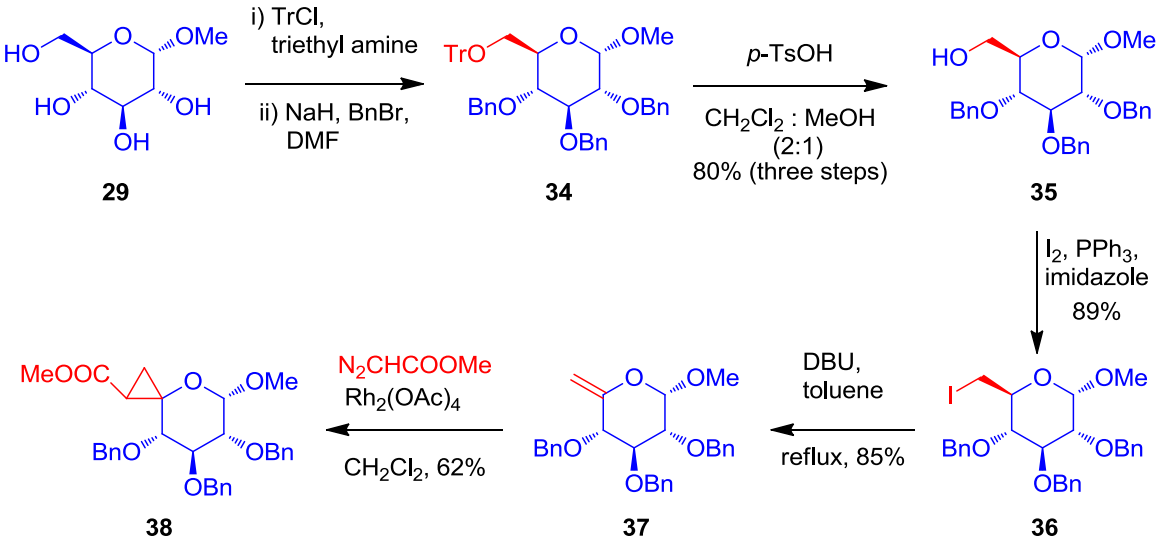
Synthesis of C-1 spiro-cyclopropanecarboxylated sugar **33** was started from methyl α-D-glucopyranoside **29**. Perbenzylation of **29** followed be acid mediated hydrolysis of the acetal provided the[25] 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose **30** in good yield. Oxidation of this anomeric alcohol with PDC and acetic anhydride[26] gave the lactone **31** and olefination[27] of this lactone with cyclopentadienyl dimethyl titanocene, followed by cyclopropanation with methyldiazoacetate in presence of rhodium acetate afforded the spiro-cyclopropanecarboxylated sugar **33** in 62% yield (Scheme 3.9).



Scheme 3.9: Synthesis of C-1 spiro-cyclopropanecarboxylated sugar 33.

Another interesting C-5 spiro-cyclopropanecarboxylated sugar preparation was started from methyl α-D-glucopyranoside **29**, in which first primary alcohol was selectively converted to trityl group with trityl chloride and treiethylamine, then benzylation with NaH and benzyl bromide to afford the compound **34** in good yield. Deprotection of the trityl group with para-toluenesulfonic acid[28] in dichloromethane and methanol gave the primary alcohol **35**, which

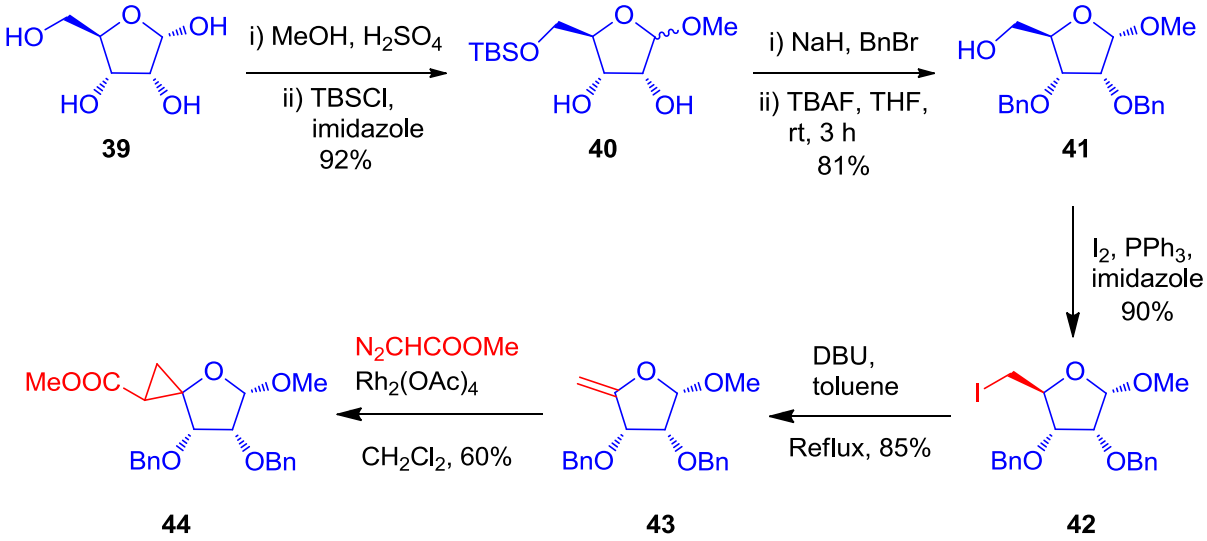
on further transformed into the primary iodide with iodine, imidazole, and triphenyl phosphine in toluene reflux method,[29] followed by elimination with DBU[23] to provide the *exo*-cyclic olefin **37** in 85% yield. Finally cyclopropanation of this exo-glycal with known procedure provided the spiro-cyclopropanecarboxylated sugar **38** in 62% yield. (Scheme 3.10).



Scheme 3.10: Synthesis of C 5-spiro-cyclopropanecarboxylated sugar 38 from methyl α-D-glucose.

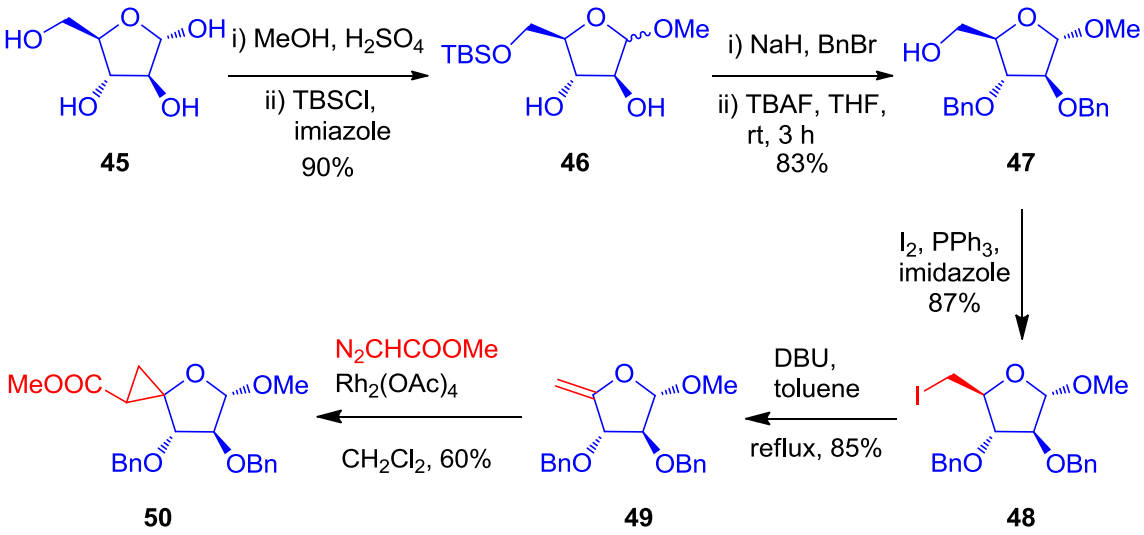
3.2.2 Synthesis of furanose derived spiro-cyclopropanecarboxylated sugars

To demonstrate the generality of the reaction, a series of furanose derived donor-acceptor spiro-cyclopropanecarboxylated sugars were also synthesized using commercially available sugars such as D-ribose, D-arabinose, L-arabinose and D-xylose. First we started with D-ribose **39**, which on treatment with MeOH, and catalytic amount of con. sulphuric acid[30] provided the methyl D-ribofuranose. Protection of the primary alcohol with TBSCl gave dihydroxy compound **40**. Benzylation of compound **40**, followed by deprotection of TBS group with tetra butyl ammonium fluoride (TBAF) in tetrahydrofuran gave the corresponding primary alcohol **41** in good yield. *Exo*-glycal **43**[31] was obtained from **41** by iodination, to give **42**, followed by dehydrohalogenation with DBU[23] in toluene according to the known procedures. Finally spiro-cyclopropanecarboxylate **44** was obtained by the cyclopropanation of *exo*-glycal **43** with methyldiazoacetate by using previously reported protocol (Scheme 3.11).



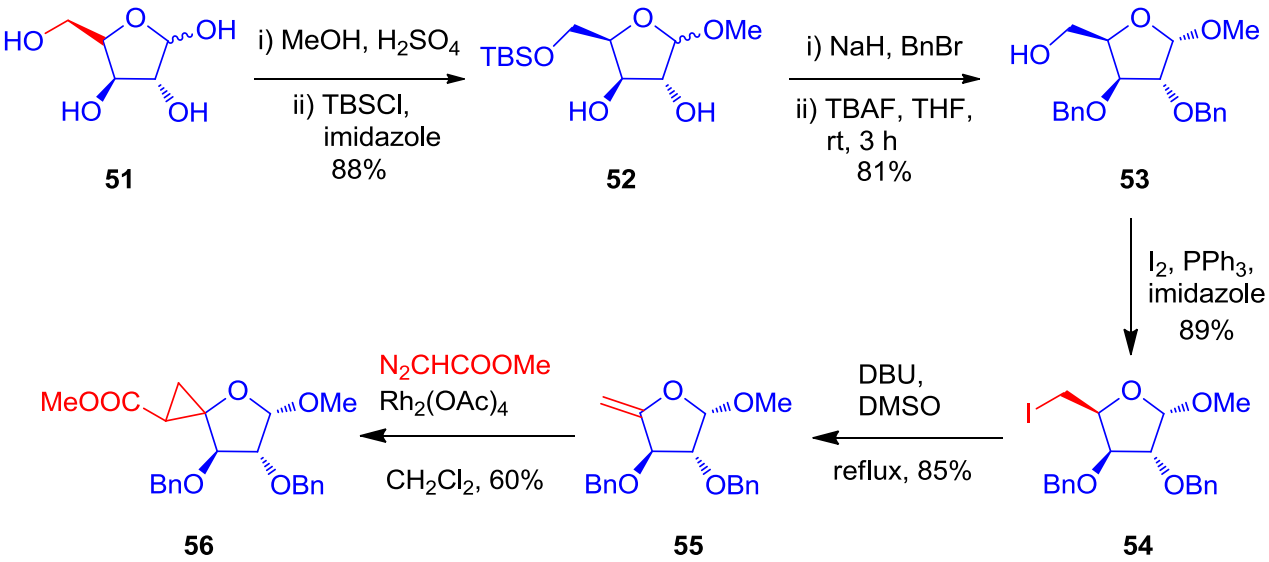
Scheme 3.11: Synthesis of furanose derived spiro-cyclopropanecarboxylated sugar 44 from D-ribose.

Similarly furanose derived C 4-spiro-cyclopropanecarboxylated sugar **50** was synthesized from D-arabinose *via* synthesizing the **46-49** according to the above protocol. Cyclopropanation of *exo*-glycal **49** with methyldiazoacetate in presence of rhodium acetate provided the corresponding spiro-cyclopropanecarboxylated sugar **50** in 62% yield (Scheme 3.12).



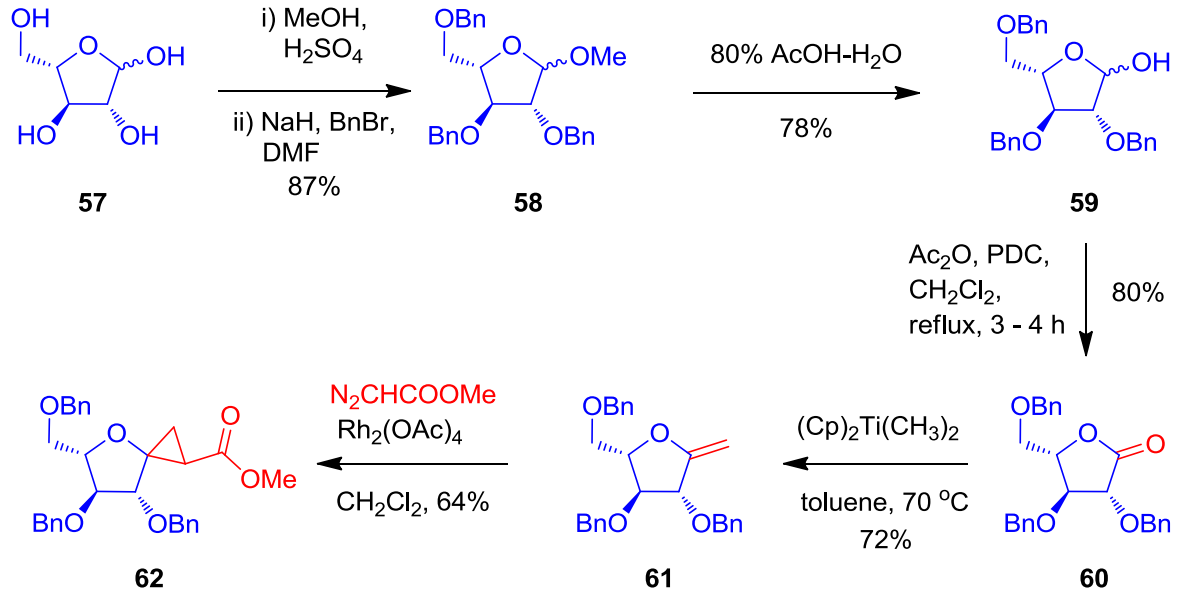
Scheme 3.12: Synthesis of furanose derived spiro-cyclopropanecarboxylated sugar 50 from D-arabinose.

Similarly Compound **54** was synthesized from D-xylose by using above known procedures (Scheme 3.13). In the case of D-xylose, 3rd and 4th positions are placed at same plane, due to this under DBU and toluene reflux conditions elimination did not occur. Thus, treatment of compound **54** with DBU and DMSO under reflux condition[32] provided the corresponding *exo*-cyclic olefin **55** in 85% yield. Finally cyclopropanation of *exo*-cyclic olefin with known procedure gave the spiro-cyclopropanecarboxylated sugar **56** in 60% yield (Scheme 3.13).



Scheme 3.13: Synthesis of furanose derived C 4-spiro-cyclopropanecarboxylated sugar 56 D-xylose.

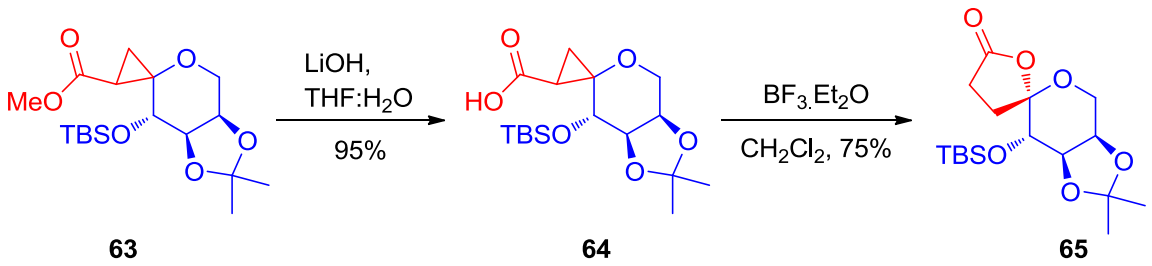
Furanose derived C-1-spiro-cyalopropane carboxylated sugar **62** was synthesized from L-arabinose. Glycosylation of L-arabinose **57** with methanol and sulphuric acid[29] followed by benzylation with NaH and benzyl bromide in DMF afforded methyl 2,3,5-tribenzyl-arabinofuranoside **58** as mixture of anomers. Hydrolysis of acetal with acetic acid/water[33] to provide the 2,3,5-tri-*O*-benzyl L-arabinose **59**,[34] and oxidation with PDC and acetic anhydride[26] gave the lactone **60** in good yield. *exo*-Glycal **61** was synthesized by treatment of lactone **60** with Petasis reagent in toluene[27] at 70 °C. Cyclopropanation of the obtained *exo*-glycal **61** with methyldiazoacetate in presence of rhodium acetate afforded the spiro-cyclopropanecarboxylated sugar **62** in 64% yield (Scheme 3.14).



Scheme 3.14: Synthesis of furanose derived C 1-spiro-cyclopropanecarboxylated sugar **62**. From L-arabinose.

3.2.3 Synthesis of spiro-lactones from spiro-cyclopropanecarboxylic acids

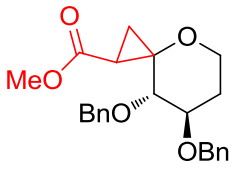
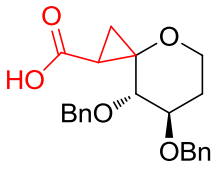
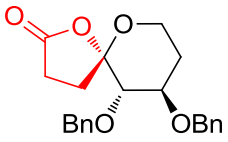
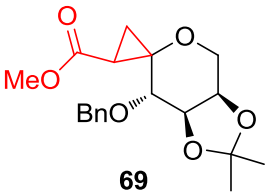
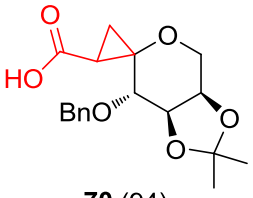
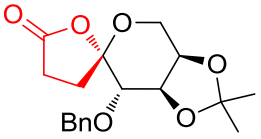
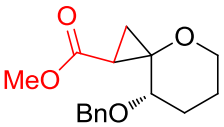
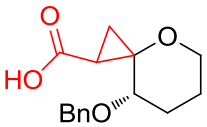
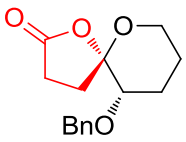
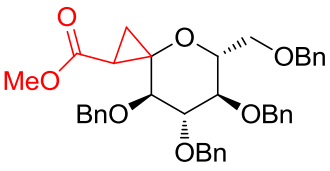
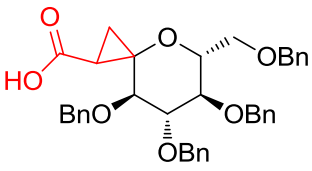
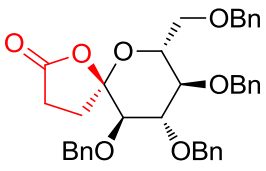
In contrast to the 1,2-cyclopropane carboxylated sugars which have been shown to undergo ring-opening followed by cyclization reaction,[35] direct exposure of spiro-cyclopropanecarboxylate **63** (Scheme 2.21) to a series of Lewis acids did not provide the expected spirolactone **65**. This might be attributed due to the higher stability and lower strain of spiro-cyclopropanecarboxylate, when compared to linearly fused systems. We assumed that, converting the cyclopropanecarboxylate to the corresponding carboxylic acid will increase the electrophilicity of the carbonyl group and facilitate the cyclopropane ring opening. Thus, ester **63** was hydrolyzed[36] to give spiro-cyclopropanecarboxylic acid **64** and reacted with catalytic $BF_3.Et_2O$. Under these conditions, **64** underwent a facile one-pot ring-opening and cyclization reaction to provide the expected spirolactone **65** as a single diastereomer (Scheme 3.15). The formation of a single diastereomer clearly indicates the existence of oxonium ion intermediate which is eventually trapped by the carboxylic acid, minimizing the anomeric effect of both the rings that provide the thermodynamically more stable spirocyclic system. The stereochemistry at the spirocenter was unambiguously assigned by 2D NOESY experiment.



Scheme 3.15: Synthesis of spiro-lactone from spiro-cyclopropanecarboxylated sugar.

Encouraged with this results the generality of the reaction was investigated by applying it to a number of sugar derived spiro-cyclopropanecarboxylic acids. Spiro-cyclopropanecarboxylated sugars **66** and **69** were prepared from D-glucose and D-fructose, respectively (Scheme 2.22).

Table 3.1. Stereoselective synthesis of pyranose derived 1,6-dioxaspiro[4.5]decan-2-one systems.

entry	spiro-cyclopropane carboxylate	spiro-cyclopropane carboxylic acid (%)[a]	spirolactones (%)[a]
1	 **66**	 **67** (93%)	 **68** (80%)
2	 **69**	 **70** (94)	 **71** (85)
3	 **28**	 **72** (95)	 **73** (85) (55:45)[b]
4	 **33**	 **74** (95)	 **75** (70)

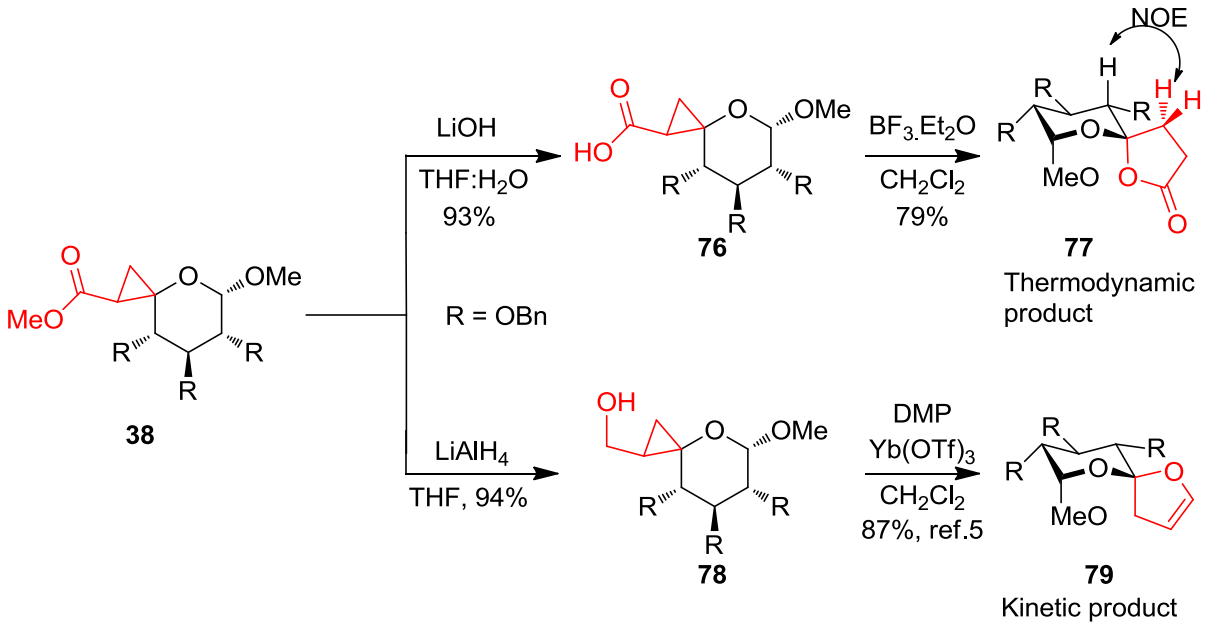
[a] Yield refers to pure and isolated products. [b] Major diastereomer is represented.

Thus, a series of pyranose fused cyclopropanecarboxylated sugar derivatives **66**, **69** and **28** were subjected to the base hydrolysis to obtain the corresponding spiro-cyclopropanecarboxylic acids **67**, **70** and **72**, respectively, in excellent yield. Subjecting these acid derivatives to the $BF_3.Et_2O$ mediated ring-opening cyclization reaction provided the sugar derived 1,6,-dioxaspirolactones **68**, **71** and **73**, respectively, in good yield. In the all ring-opening and cyclization reactions we observed the formation of thermodynamically more stable spirolactone as the only product, except in the case of spirolactone **73** in which a 55:45 ratio of thermodynamic *vs* kinetic product formation was observed (Table 3.1, entry 1-3).

Towards the application of this methodology to fully substituted hexose derived spiro-cyclic systems, glucose based donor-acceptor cyclopropanecarboxylated compounds **33** and **38** were hydrolysed to obtain the corresponding acids **74** (Table 3.1, entry 4) and **76** (Scheme 3.16) which were upon exposure to $BF_3.Et_2O$ lead to the formation of 1,6-dioxaspiro[4.5]decan-2-one systems **75** and **77** as single diastereomers.

3.2.3.1 Comparison between Thermodynamic *vs* kietic products

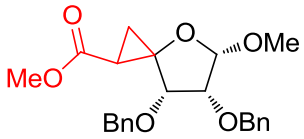
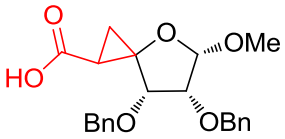
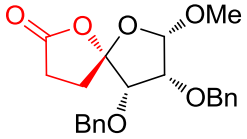
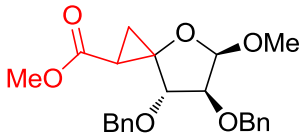
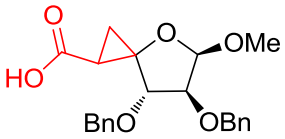
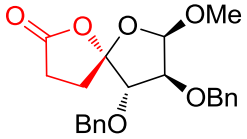
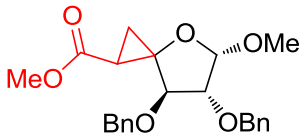
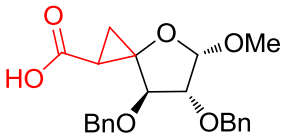
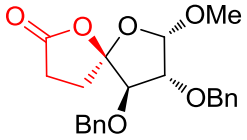
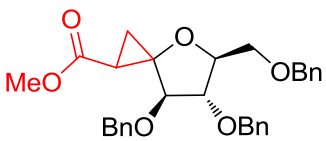
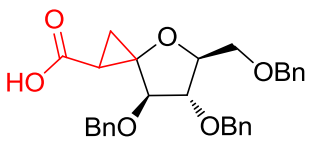
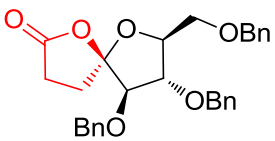
Interestingly, Werz *et al.* recently reported[12] a similar kind of reaction using the spiro-cyclopropanated sugar derivative **78** which involve an oxidative ring expansion that provided the kinetic product **79** as a single diastereomer (Scheme 3.16). On the other hand in the present work ring-opening followed by cyclization reaction, thermodynamic product **77** was formed exclusively. Thus, these methodologies are very advantageous to synthesize spiro-cyclic systems possessing bis-diaxial C-O conformation as well as spiroketals that do not reside in the bis-diaxial C-O conformation (ex: in pectinotoxin).



Scheme 3.16: Synthesis of thermodynamic *vs* kinetic spiroketals.

The methodology was further evaluated in the case of furanose derived fused spiro-cyclopropanecarboxylic acids. Thus, spiro-cyclopropanecarboxylates **44**, **50**, **56** and **62** were hydrolyzed to obtain furanose fused spiro-cyclopropanecarboxylic acids **80**, **82**, **84** and **86**, respectively (Table 3.2 entry 1-4). Reaction of these acids with $BF_3.Et_2O$ provided the 1,6-dioxaspiro[4.4]nonan-2-one motifs **81**, **83**, **85** and **87** as single diastereomers in good yield. Interestingly in all the five-membered derived spiro-compounds the oxygen of the lactone was found to have a 1,2-*syn* relationship. These observations indicate that the stereocentre adjacent to the spirocenter has profound influence on the conformation of the intermediate oxonium ion and eventually the stereochemistry of the 1,6-dioxaspiro system.

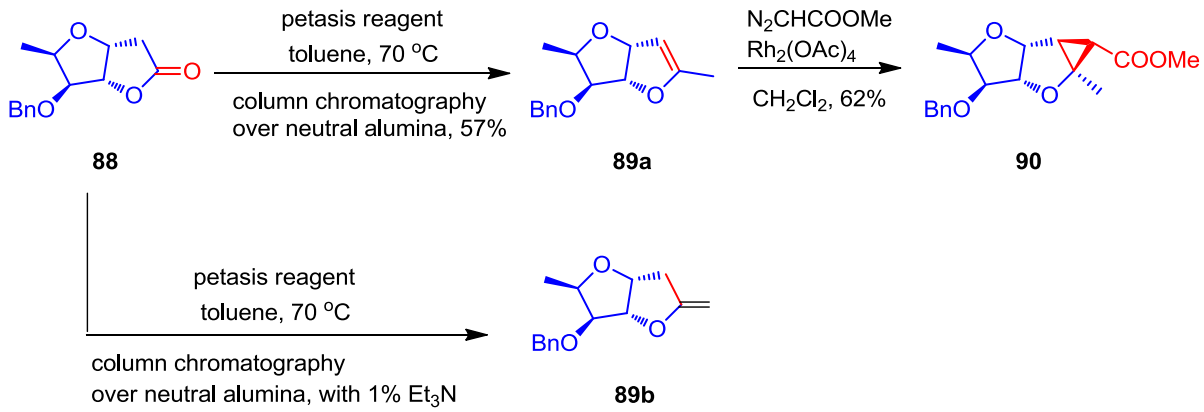
Table 3.2. Stereoselective synthesis of furanose derived 1,6-dioxaspiro[4.4]nonan-2-one systems.

entry	spiro-cyclopropane carboxylate	spiro-cyclopropane carboxylic acid (%)[a]	spirolactones (%)[a]
1	 **44**	 **80** (96)	 **81** (80)
2	 **50**	 **82** (93)	 **83** (80)
3	 **56**	 **84** (91)	 **85** (79)
4	 **62**	 **86** (94)	 **87** (72)

[a] Yield refers to pure and isolated products

3.2.4 Synthesis of linearly fused tricyclic spiro-cyclopropanecarboxylated sugar

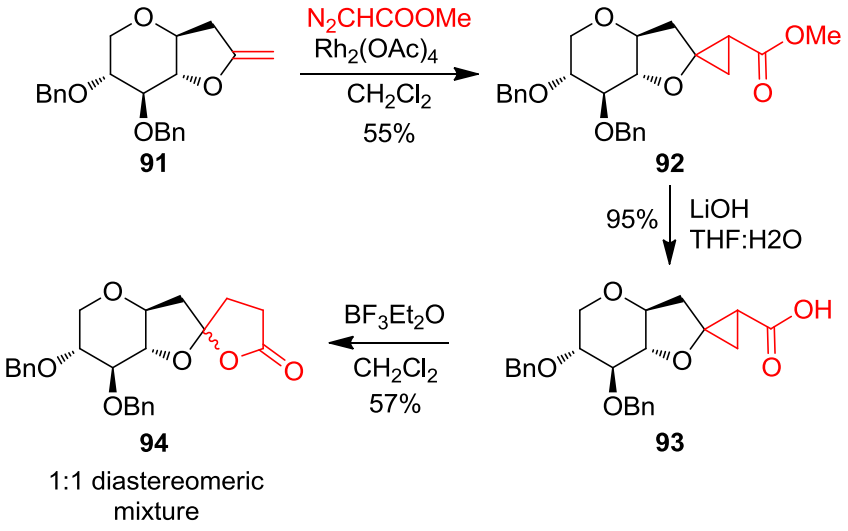
To investigate the further applications of this methodology spiro-cyclopropanecarboxylate sugar **90** was prepared from bicyclic lactone **88**. This bicyclic lactone **88** was discussed in chapter 2 (Scheme 2.29). Treatment of lactone **88** with cyclopentadienyl dimethyl titanocene in toluene at 70 ^{o}C, for 24 h in dark gave the corresponding *exo*-cyclic olefin, which on purification by column chromatography over neutral alumina without adding triethylamine provided the unsaturated product **89a** in 57% yield. However, *exo*-cyclic olefin **89b** was obtained if when the column has done in presence of triethylamine. Finally cyclopropanation of compound **89a** with methyldiazoacetate and rhodium acetate in dichloromethane to afford the linearly fused bicyclic spiro-cyclopropanecarboxylated sugar **90** in 62% yield (Scheme 3.17).



Scheme 3.17: Synthesis of linearly fused bicyclic spiro-cyclopropanecarboxylate sugar 90.

3.2.5 Synthesis of fused tricyclic spiro-lactone system

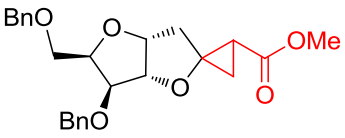
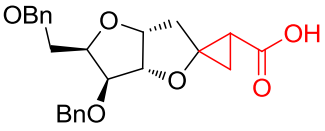
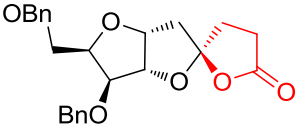
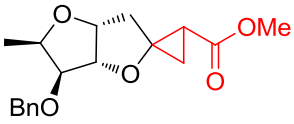
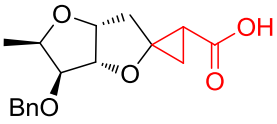
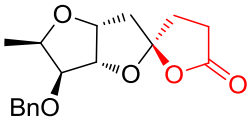
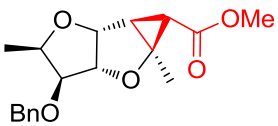
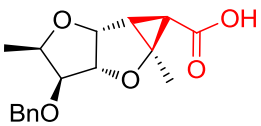
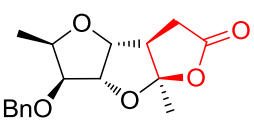
To examine the application of this methodology in bicyclic systems, *exo*-olefin **91** (discussed in chapter 2, Scheme 2.27), was cyclopropanated to give tricyclic cyclopropanecarboxylate **92,** which upon base hydrolysis provided the corresponding carboxylic acid **93**. $BF_3.Et_2O$ mediated ring-opening and cyclization of **93** provided the tricyclic spirolactone **94** as a 1:1 diastereomeric mixture (Scheme 3.18) in moderate yield.



Scheme 3.18: Synthesis of tricyclic spiro system possessing spirolactone moiety.

Application of the similar protocol on spiro-cyclopropanecarboxylic acids **96** and **99**, synthesized from esters **95** and **98**, provided the spiro-lactones **97a** and **97b** (8:7) and **100a** and **100b** (3:2), respectively (Table 3.2, entry 1 and 2). The lower diastereoselectivity in these reactions might be due to the lack of stereocentre adjacent to the spirocenter.

Table 3.2 Synthesis of fused tricyclic spiro-systems

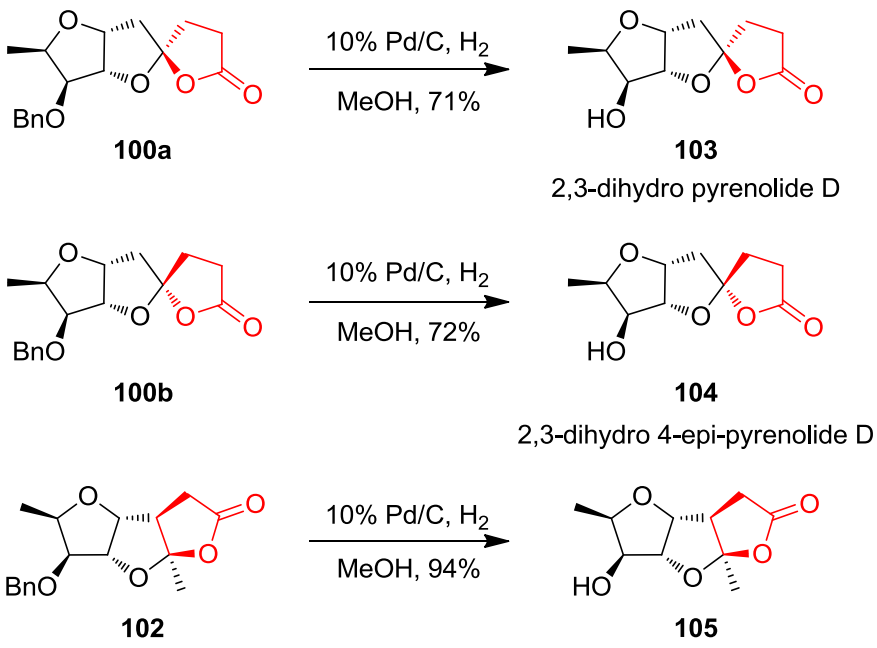
entry	spiro-cyclopropane carboxylate	spiro-cyclopropane carboxylic acid (%)[a]	spiro-lactone (%)[a]
1	 **95**	 **96** (92)	 **97a**:**97b** (8:7), (75)[b]
2	 **98**	 **99** (74)	 **100a**:**100b** (3:2), (77)[b]
3	 **90**	 **101** (95)	 **102** (83)

[a] Yield refers to pure and isolated products. [b] Major diastereomer is represented

The methodology is also equally applicable to the synthesis of fused lactones that has been shown by synthesizing the cyclopropanecarboxylic acid **101**, prepared from **90**,[37] and treating with $BF_3.Et_2O$ to give linearly fused tricyclic lactone **102** as a single diastereomer (Table 3.2, entry 3).

Note: Synthesis of spiro-cyclopropanecarboxylated sugars **95** and **98** were discussed in chapter 2 (Scheme 2.29 and Scheme 2.30).

To enhance the significance of the developed methodology we planned to synthesize the analogues of a bio-active spirolactone containing natural product pyrenolide D[38] (IC_{50} = 4 μg/mL against HL-60). Thus, purified spiro-lactones **100a** and **100b** were treated with 10% Pd/C under hydrogen atmosphere to give the 2,3-dihydro-pyrenolide D **103**, and 2,3-dihydro-4-*epi*-pyrenolide D **104**. Surprisingly to the best of our knowledge, the synthesis of dihydro-pyrenolides **103** and **104** has not been reported to date. We assume that the biological activity of these compounds would reveal the importance of the unsaturated lactone moiety in the natural product pyrenolide D. Similarly hydrogenolysis of compound **102** provided the fused tricyclic lactone **105** (Scheme 3.18).



Scheme 3.18: Synthesis of pyrenolide D analogues and linearly fused tricyclic lactone.

3.3 Conclusion

In conclusion, a stereoselective protocol for the construction of spiro[6.5] and spiro[5.5]lactone using a diastereomeric mixture of carbohydrate derived spiro-cyclopropanecarboxylates was revealed. The generality of the reaction was investigated by applying the methodology to synthesize a variety of spirocyclic systems. In all the spiro-lactones that were synthesized it was observed that there is a pronounced effect of the stereocentre adjacent to the anomeric position which directs the chirality of emerging spirocentre. This methodology was also further applied to synthesize a series of tricyclic spiro[furan-2,2'-furo[3,2-b]furan] ring systems. A successful application of the developed methodology was shown by synthesizing dihydro-pyrenolide D and dihydro-4-*epi*-pyrenolide D. Exploitation of this protocol in the total synthesis of bioactive natural products and the investigation of controlling the stereochemistry at the spirocentre are in progress.

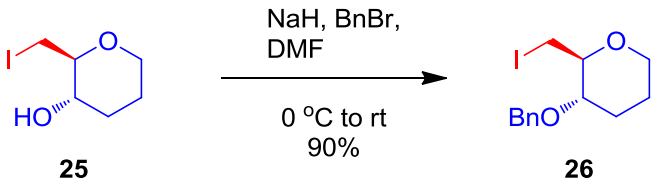
3.4 Experimental section

3.4.1 General Information

All the reactions were carried out under nitrogen or argon 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. All the chemicals were purchased from local suppliers and Sigma-Aldrich Chemicals Company. Solvents used in the reactions were distilled over dehydrating agents. Dry toluene was prepared by using sodium and benzophenone. Silica-gel (100-200 mesh) and neutral alumina were used for column chromatography. ^{1}H, ^{13}C, DEPT, COSY, NOESY spectra were recorded on Bruker 400 MHz and 500 MHz spectrometer in $CDCl_3$. ^{1}H NMR chemical shifts were reported in ppm (δ) with TMS as 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. Optical rotation was recorded on a Rudolph autopol IV polarimeter.

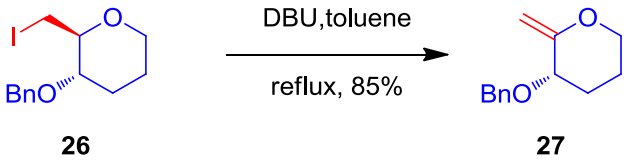
3.4.2 Experimental Procedures and spectral data

(3.4.1.1) (2*S*,3*S*)-3-(benzyloxy)-2-(iodomethyl)tetrahydro-2*H*-pyran:



To a stirred solution of sodium hydride (0.79 g, 19.82 mmol) in DMF (10 mL) at 0 °C was added a solution of compound **25** (2.4 g, 9.91 mmol) in DMF (30 mL) over a period of 10 min and the mixture was stirred for another 30 min. Benzyl bromide (1.77 mL, 14.86 mmol) was added drop wise to the reaction mixture for a period of 10 min and then TBAI (100 mg) was added. The reaction mixture was allowed to stir at room temperature for overnight. After completion of the reaction, water (20 mL) was added slowly and the reaction mixture was extracted with diethyl ether (3 x 50 mL). The combined organic extracts were washed with water (50 mL) and saturated aq. NaCl (50 mL), dried over anhydrous Na_2SO_4, concentrated under reduced pressure and purified by column chromatography EtOAc/hexane (1:9) to afford the 1,2,3,5-tetra deoxy-5-iodo-4-*O*-benzyl glucopyranose derivative **26** (2.9 g,) in 90% yield as a colourless gum.

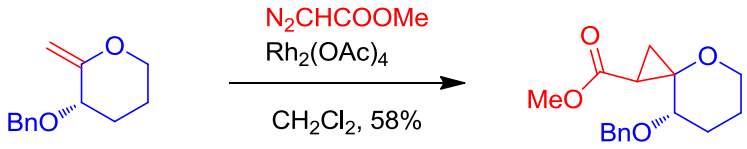
(3.4.1.2) (*S*)-3-(benzyloxy)-2-methylenetetrahydro-2*H*-pyran:



To a solution of (3*S*)-3-(benzyloxy)-2-(iodomethyl)tetrahydro-2*H*-pyran **26** (8.0 g, 24 mmol) in toluene (100 mL) at 0 °C was added DBU (9 mL, 60.24 mmol), drop wise over a period of 10 min. The reaction mixture was brought to 25 °C and heated at reflux for 1.5 h. After completion of the reaction, the mixture was diluted with ethyl acetate. The solution was taken into a separating funnel and washed with water, brine, dried over anhydrous Na_2SO_4, concentrated and the obtained residue was purified by column chromatography in EtOAc/hexane (1:9) to give the *exo*-cyclic olefin **27** (4.2 g) as a colourless liquid in 85% yield.

IR (neat): ν_{max} 2958, 2920, 2849, 1720, 1452, 1364, 1271, 1172, 1117, 1035, 723 cm^{-1}. **^{1}H NMR (400 MHz, $CDCl_3$)**: δ 7.29-7.39 (m, 5H), 4.70 (dd, 1H, *J* = 2.8 Hz, *J* = 12.0 Hz), 4.65 (d, 1H, *J* = 3.2 Hz), 4.46 (dd, 1H, *J* = 2.8 Hz, *J* = 12.0 Hz), 4.40 (d, 1H, *J* = 2.8 Hz), 4.00-4.06 (m, 1H), 3.81-3.87 (m, 2H), 2.06-2.14 (m, 1H), 1.93-1.98 (m, 2H), 1.58-1.66 (m, 1H). **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 158.4, 138.6, 128.3, 127.9, 127.6, 127.5, 94.6, 73.4, 70.0, 69.2, 29.5, 21.7. **HRMS (ESI)** calcd for $C_{13}H_{16}O_2$+H 205.1229, found 205.1227.

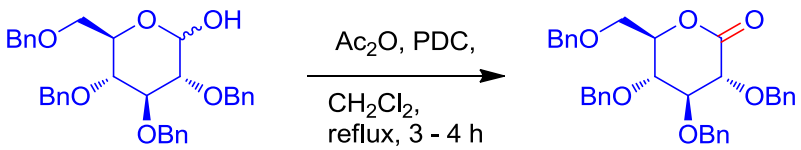
(3.4.1.3) (8*S*)-methyl 8-(benzyloxy)-4-oxaspiro[2.5]octane-1-carboxylate:



27 **28**

To a stirred suspension of *exo*-cyclic glycal **27** (1.0 g, 4.9 mmol), methyl diazoacetate (1.36 mL, 14.7 mmol) and $Rh_2(OAc)_4$ (43.0 mg, 0.098 mmol) in anhydrous CH_2Cl_2 (20 mL), a solution of methyl diazoacetate (1.36 mL, 14.70 mmol) in CH_2Cl_2 (40 mL) was added drop wise, over a period of 1 h, After completion of the reaction, the reaction mixture was concentrated in *vacuo* and the obtained crude product was purified by silica-gel column chromatography (eluent: 10-20% EtOAc in Hexane) to give desired spiro-cyclopropanecarboxylate **28** (0.78 g) in 58% yield as a mixture of diastereomers. **IR (neat)**: ν_{max} 3057, 3019, 2958, 2838, 1726, 1490, 1430, 1358, 1265, 1254, 1194, 1156, 1073, 882, 739, 706 cm^{-1}. **HRMS (ESI)** calcd for $C_{16}H_{20}O_4$+H 277.1440, found 277.1443.

(3.4.1.4) (3*R*,4*S*,5*R*,6*R*)-3,4,5-tris(benzyloxy)-6-((benzyloxy)methyl)tetrahydro-2*H*-pyran-2-one:

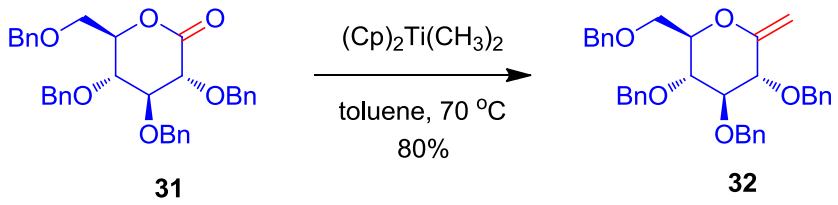


30 **31**

To a stirred solution of pyridinium dichromate (PDC) (2.57 g, 6.84 mmol) and acetic anhydride (2.90 mL, 30.90 mmol) in dry dichloromethane (15 mL) was added 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose **30** in dry dichloromethane (40 mL) under argon at room temperature. The resulting mixture was stirred under reflux until complete conversion (3 to 4 h), after complete

conversion by checking TLC it was cooled to room temperature and solvent was removed in *vacuo*, then diethyl ether was added to the solid residue and the mixture was filtered over sintered funnel. After washing residue and funnel with ether 2 to 3 times, the obtained crude product was purified by silica-gel column chromatography in EtOAc/hexane (2:8) to give the lactone **31** in 87% yield.

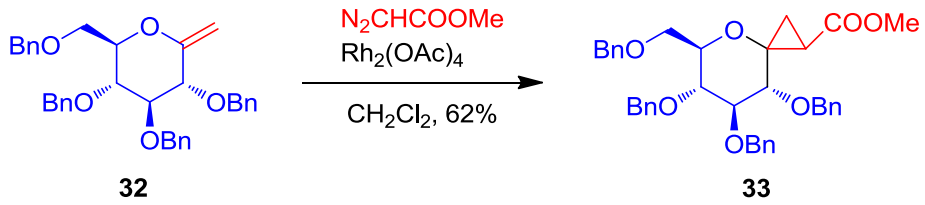
(3.4.1.5) (2*R*,3*R*,4*S*,5*R*)-3,4,5-tris(benzyloxy)-2-((benzyloxy)methyl)-6-methylenetetrahydro-2H-pyran:



31 **32**

2,3,4,6-tetra-*O*-benzyl-D-gluconolactone **31** (2.0 g, 3.71 mmol) was dissolved in dry toluene (20 mL) and dimethyl titanocene (6.16 mL of a 20% w/w solution in toluene, 7.43 mmol) was added slowly at room temperature, then the reaction mixture stirred in the dark for 24 h (or until TLC showed disappearance of the starting material) at 70 ^{0}C under argon. The brown reaction mixture was concentrated, and the remaining syrup after dilution with a minimum amount of toluene subjected to column chromatography, on silica-gel column chromatography using hexane/ethyl acetate (containing 1% triethylamine) to give the methylenated product **32** (1.6 g) in 80% yield.

(3.4.1.6) (5*R*,6*R*,7*S*,8*R*)-methyl 6,7,8-tris(benzyloxy)-5-((benzyloxy)methyl)-4-oxaspiro[2.5]octane-1-carboxylate:

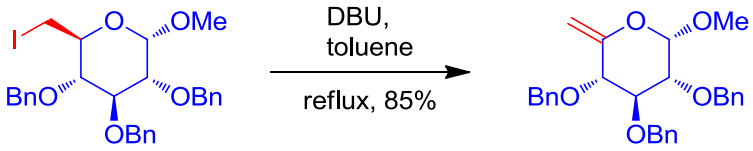


32 **33**

Compound **33** was synthesized using 2,6-Anhydro-3,4,5,7-tetra-*O*-benzyl-1-deoxy-D-glucohept-1-enitol **32** (500 mg, 0.93 mmol) methyl diazoacetate (0.26 mL, 2.79 mmol) and $Rh_2(OAc)_4$ (4.1 mg, 0.01 mmol) by following the procedure described for compound **28**

(3.4.1.3). The obtained crude product was purified by silica-el column chromatography in 20% EA/hexane to give spiro-cyclopropane carboxylate sugar **33** (351 mg) in 62% yield. **IR** (neat): ν_{max} max 3091, 3056, 3029, 2942, 2869, 1736, 1627, 1496, 1453, 1343, 1249, 1210, 1164, 1094, 1066, 1025, 913, 844, 822 cm^{-1}. **HRMS (ESI)** calcd for $C_{38}H_{40}O_7$+Na 631.2672, found 631.2672.

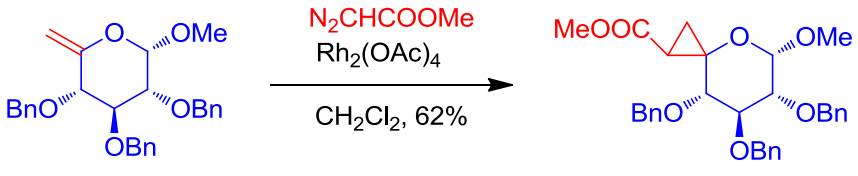
(3.4.1.7) (2*S*,3*R*,4*S*,5*S*)-3,4,5-tris(benzyloxy)-2-methoxy-6-methylenetetrahydro-2*H*-pyran:



36 **37**

To a solution of methyl 6-deoxy-6-iodo-2,3,4-tri-*O*-benzyl-α-D-glucopyranoside **36** (4.0 g, 6.96 mmol) in toluene (60 mL) at 0 °C was added DBU (3.12 mL, 20.90 mmol), drop wise over a period of 10 min. The reaction mixture was brought to 25 °C and heated at reflux for 1.5 h. After completion of the reaction, the mixture was diluted with ethyl acetate. The solution was taken into a separating funnel and washed with water, brine, dried over anhydrous Na_2SO_4, concentrated and the obtained residue was purified by silica-gel column chromatography to give methyl 2,3,4-tri-*O*-benzyl-α-D-xylo-hex-5-enopyranoside **37** (2.65 g, 85%) as a colourless semisolid. **IR (neat)**: ν_{max} 3068, 3035, 2920, 1731, 1501, 1452, 1353, 1090, 1024, 734, 701 cm^{-1}. **^{1}H NMR (400 MHz, $CDCl_3$)**: δ 7.27-7.39 (m, 15H), 4.92 (d, 1H, *J* = 10.4 Hz), 4.89 (s, 1H), 4.88 (d, 1H, *J* = 10.8 Hz), 4.84 (d, 1H, *J* = 12.0 Hz), 4.79 (d, 2H, *J* = 2.4 Hz), 4.72 (d, 1H, *J* = 0.8 Hz), 4.69 (d, 1H, *J* = 12.0 Hz), 4.64 (d, 1H, *J* = 3.2 Hz), 3.99 (t, 1H, *J* = 9.2 Hz), 3.91 (dt, 1H, *J* = 0.8 Hz, *J* = 8.8 Hz), 3.62 (dd, 1H, *J* = 3.2 Hz, *J* = 9.2 Hz), 3.44 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 153.6, 138.6, 138.0, 137.9, 128.5, 128.4, 128.1, 128.0, 127.9, 127.8, 127.7, 127.6, 99.0, 96.9, 81.2, 79.5, 79.2, 75.8, 74.5, 73.6, 55.4. **HRMS (ESI)** calcd for $C_{28}H_{30}O_5$+H 447.2171, found 447.2173.

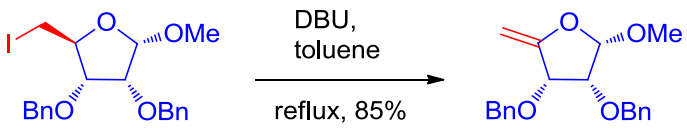
(3.4.1.8) (5*S*,6*R*,7*S*,8*S*)-methyl 6,7,8-tris(benzyloxy)-5-methoxy-4-oxaspiro[2.5]octane-1-carboxylate:



37 **38**

To a stirred suspension of methyl 2,3,4-tri-*O*-benzyl-α-D-*xylo*-hex-5-enopyranoside **37** (1.1 g, 2.46 mmol) and $Rh_2(OAc)_4$ (10.8 mg, 0.02 mmol) in anhydrous CH_2Cl_2 (20 mL) was added drop wise, over a period of 1 h, a solution of methyl diazoacetate (0.68 mL, 7.39 mmol) in CH_2Cl_2 (40 mL). After completion of the reaction, the reaction mixture was concentrated in *vacuo* and the obtained crude product was purified by silica gel column chromatography (eluent: 10-20% EtOAc in Hexane) to give desired spiro-cyclopropanecarboxylate **38** (0.80 g, 62%) as a mixture of diastereomers. **IR (neat)**: ν_{max} 3084, 3057, 3029, 2920, 2854, 1719, 1500, 1451, 1358, 1199, 1166, 1051, 914, 739, 695 cm^{-1}. **HRMS (ESI)** calcd for $C_{31}H_{34}O_7$+Na 541.2202, found 541.2204.

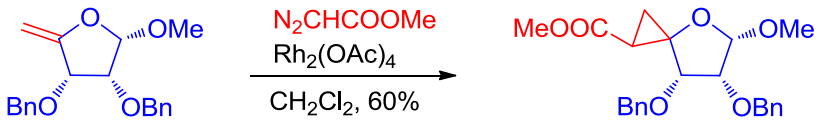
(3.4.1.9) (2*S*,3*R*,4*S*)-3,4-bis(benzyloxy)-2-methoxy-5-methylenetetrahydrofuran:



42 **43**

To a solution of methyl 5-deoxy-5-iodo-2,3-di-*O*-benzyl-α-D-rybofuranoside **42** (1.3 g, 2.38 mmol) in toluene (15 mL) at 0 °C was added DBU (0.89 mL, 5.97 mmol), drop wise over a period of 10 min. The reaction mixture was brought to 25 °C and heated at reflux for 1.5 h. After completion of the reaction (by monitoring TLC), the mixture was diluted with ethyl acetate (50 mL). The solution was taken into a separating funnel and washed with water, brine, dried over anhydrous Na_2SO_4, concentrated and the obtained residue was purified by column chromatography to give methyl 5-deoxy-2,3-di-*O*-benzyl-α-D-erythro-pent-4-eno-furanoside **43** (0.66 g, 85%) as a colourless liquid. **IR (neat)**: ν_{max} 3090, 3068, 3035, 2926, 2865, 1720, 1501, 1457, 1353, 1112, 1024, 745, 695 cm-1. **1H NMR (400 MHz, $CDCl_3$)**: δ 7.32-7.40 (m, 10H), 5.16 (d, 1H, J = 2.0 Hz), 4.66 (d, 2H, J = 2.8 Hz), 4.63 (d, 2H, J = 3.6 Hz), 4.55 (s, 1H), 4.39 (d, 1H, J = 4.8 Hz), 4.28 (s, 1H), 3.84 (dd, 1H, J = 2.4 Hz, J = 4.8), 3.45 (s, 3H). **13C NMR (100 MHz, $CDCl_3$)**: δ 158.5, 137.6, 137.4, 128.5, 128.1, 128.0, 127.9, 106.8, 85.0, 78.7, 75.9, 72.2, 71.5, 56.5. **HRMS (ESI)** calcd for $C_{20}H_{22}O_4$+H 327.1596, found 327.1593.

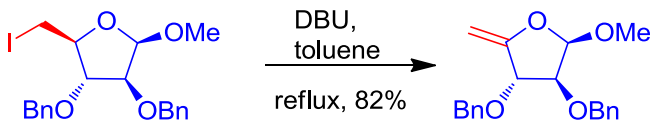
(3.4.1.10) (5*S*,6*R*,7*S*)-methyl 6,7-bis(benzyloxy)-5-methoxy-4-oxaspiro[2.4]heptane-1-carboxylate:



43 **44**

The above methylenated product **43** (0.326 g, 1 mmol), methyl diazoacetate (0.27 mL, 3 mmol) and $Rh_2(OAc)_4$ (8.8 mg, 0.02 mmol) was cyclopropanated following the procedure described for compound **28** (3.4.1.3), to obtain the spiro-cyclopropanecarboxylate **44** (0.24 g, 60%) as a mixture of diastereomers. **IR (neat)**: ν_{max} 3095, 3068, 3035, 2953, 2925, 1725, 1495, 1456, 1374, 1325, 1215, 1155, 739, 706 cm^{-1}. **HRMS (ESI)** calcd for $C_{23}H_{26}O_6$+H 399.1808, found 399.1809.

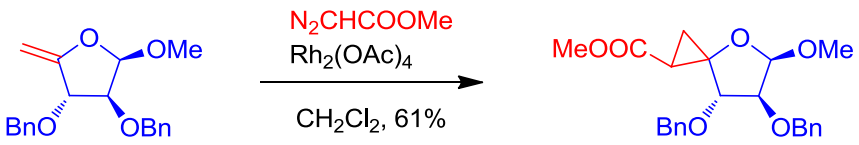
(3.4.1.11) (2*R*,3*S*,4*S*)-3,4-bis(benzyloxy)-2-methoxy-5-methylenetetrahydrofuran:



48 **49**

To a solution of methyl 5-deoxy-5-iodo-2,3-di-*O*-benzyl-β-D-arabinofuranoside **48** (1.8 g, 3.47 mmol) in toluene (20 mL) at 0 °C was added DBU (1.46 mL, 10.42 mmol), drop wise over a period of 10 min. The reaction mixture was brought to 25 °C and heated at reflux for 1.5 h. After completion of the reaction, the mixture was diluted with ethyl acetate, taken into a separating funnel and washed with water, dried over anhydrous Na_2SO_4, concentrated and the obtained residue was purified by silica gel column chromatography to give the *exo*-cyclic-olefin **49** (0.93 g, 82%) as colourless liquid. **IR (neat)**: ν_{max} 3084, 3068, 3030, 2931, 2876, 1715, 1501, 1457, 1358, 1210, 1112, 1024, 739, 706 cm^{-1}. **^{1}H NMR (400 MHz, $CDCl_3$)**: δ 7.32-7.39 (m, 10H), 5.11 (d, 1H, *J* = 1.6 Hz), 4.70 (s, 2H), 4.62 (d, 1H, *J* = 11.6 Hz), 4.61 (t, 1H, *J* = 2.0 Hz), 4.57 (d, 1H, *J* = 11.6 Hz), 4.39 (m, 1H), 4.29 (t, 1H, *J* = 1.6 Hz), 4.03 (dd, 1H, *J* = 2.0 Hz, *J* = 3.2 Hz), 3.24 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 159.6, 137.6, 137.2, 128.5, 128.5, 128.0, 127.9, 127.8, 108.3, 86.4, 84.9, 79.7, 72.0, 71.2, 56.2. **HRMS (ESI)** calcd for $C_{20}H_{22}O_4$+H 327.1596, found 327.1596.

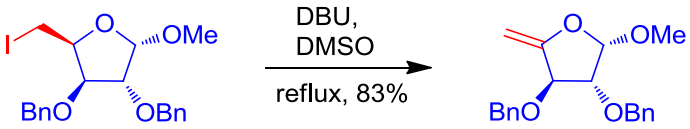
(3.4.1.12) (5*R*,6*S*,7*S*)-methyl 6,7-bis(benzyloxy)-5-methoxy-4-oxaspiro[2.4]heptane-1-carboxylate:



49 **50**

The above obtained methylenated product **49** (600 mg 1.84 mmol), methyl diazoacetate (0.51 mL, 5.52 mmol) and $Rh_2(OAc)_4$ (8.1 mg, 0.02 mmol) was cyclopropanated by following the procedure described for compound **28** (3.4.1.3), to obtain the spiro-cyclopropanecarboxylate **50** (450 mg) in 61% yield as a mixture of diastereomers. **IR (neat)**: ν_{max} 3057, 3035, 2953, 2920, 2848, 1719, 1500, 1456, 1440, 1380, 1265, 1199, 1155, 1100, 739, 700 cm^{-1}. **HRMS (ESI)** calcd for $C_{23}H_{26}O_6$+H 399.1808, found 399.1808.

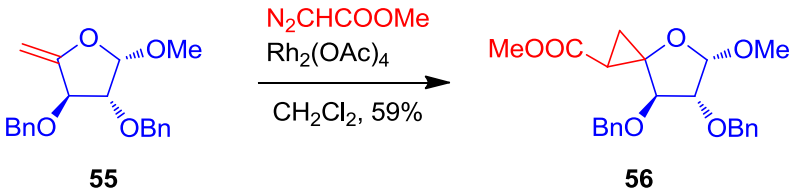
(3.4.1.13) (2*S*,3*R*,4*R*)-3,4-bis(benzyloxy)-2-methoxy-5-ethylenetetrahydrofuran:



54 **55**

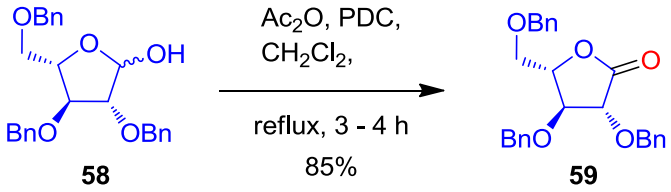
To a solution of methyl 5-deoxy-5-iodo-2,3-di-*O*-benzyl-α-D-xylofuranoside **54** (0.80 g, 1.47 mmol) in dimethyl sulfoxide (DMSO) (12 mL) at 0 °C was added DBU (0.54 mL, 3.67 mmol), drop wise over a period of 5 min. The reaction mixture was brought to 25 °C and heated at reflux for 3 h in presence of 3 Å molecular sieves. After completion of the reaction, water (20 mL) was added and the reaction mixture was extracted with diethyl ether. The solution was taken into a separating funnel and washed with water, brine and dried over anhydrous Na_2SO_4, concentrated and the obtained residue was purified by column chromatography to give methyl 5-deoxy-2,3-di-*O*-benzyl-α-D-*threo*-pent-4-eno-furanoside **55** (0.40 g, 83%) as a colourless liquid. **IR (neat)**: ν_{max} 3057, 3024, 2926, 2871, 1731, 1704, 1660, 1501, 1452, 1205, 1090, 734, 706 cm^{-1}. **^{1}H NMR (400 MHz, $CDCl_3$)**: δ 7.31-7.41 (m, 10H), 5.13 (d, 1H, *J* = 2.0 Hz), 4.70 (s, 2H), 4.62 (d, 1H, *J* = 11.6 Hz), 4.61 (t, 1H, *J* = 2.0 Hz), 4.57 (d, 1H, *J* = 11.6 Hz), 4.39 (m, 1H), 4.29 (t, 1H, *J* = 1.6 Hz), 4.03 (dd, 1H, *J* = 2.0 Hz, *J* = 3.2 Hz), 3.24 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 159.6, 137.6, 137.2, 128.5, 128.5, 128.0, 128.0, 127.9, 108.3, 86.4, 85.0, 79.7, 72.0, 71.2, 56.3. **HRMS (ESI)** calcd for $C_{20}H_{22}O_4$+H 327.1596, found 327.1592.

(3.4.1.14) (5*S*,6*R*,7*R*)-methyl 6,7-bis(benzyloxy)-5-methoxy-4-oxaspiro[2.4]heptane-1-carboxylate:



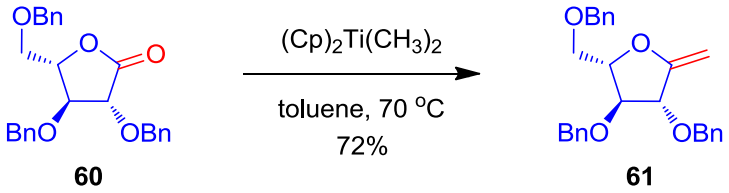
The above methylenated product **55** (270 mg, 0.82 mmol), methyl diazoacetate (0.23 mL, 2.48 mmol) and $Rh_2(OAc)_4$ (7.2 mg, 0.016 mmol) was cyclopropanated following the procedure described for compound **28** (3.4.1.3), to obtain spiro-cyclopropanecarboxylate **56** (195 mg, 59%) as a mixture of diastereomers. **IR (neat)**: ν_{max} 3062, 3029, 2920, 2854, 1741, 1500, 1451, 1369, 1265, 1100, 1018, 739, 700 cm^{-1}. **HRMS (ESI)** calcd for $C_{23}H_{26}O_6$+Na 421.1627, found 421.1626.

(3.4.1.15) (3*R*,4*S*,5*S*)-3,4-bis(benzyloxy)-5-((benzyloxy)methyl)dihydrofuran-2(3*H*)-one:



To a stirred solution of pyridinium dichromate (PDC) (2.64 g, 7.03 mmol) and acetic anhydride (3.0 mL, 31.79 mmol) in dry dichloromethane (16 mL) was added 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose **58** (4 g, 9.51 mmol), in dry dichloromethane (40 mL) under argon at room temperature. The resulting mixture was stirred under reflux until complete conversion (3 to 4 h), after complete conversion by checking TLC it was cooled to room temperature and solvent was removed in *vacuo*, then diethyl ether was added to the solid residue and the mixture was filtered over sintered funnel. After washing residue and funnel with ether 2 to 3 times, the obtained crude product was purified by silica-gel column chromatography in EtOAc/hexane (2:8) to give the lactone **59** in 85% yield.

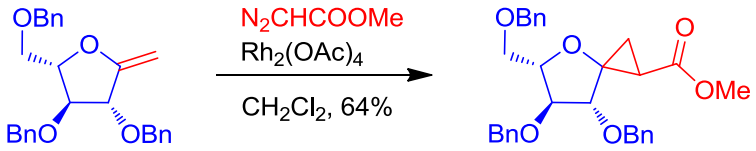
(3.4.1.16) (2*S*,3*S*,4*R*)-3,4-bis(benzyloxy)-2-((benzyloxy)methyl)-5-methylenetetrahydrofuran:



60 **61**

2,3,5-tri-*O*-benzyl-L-arabinoic acid γ-lactone **60** (1.0 g, 2.39 mmol) was dissolved in dry toluene (20 mL) and cyclopentadienyl dimethyl titanocene (4.0 mL of 20% w/w solution in toluene) was added slowly at room temperature, then the reaction mixture was stirred in the dark at 70 °C under argon for 24 h or until TLC showed disappearance of the starting material. The brown reaction mixture was concentrated, and subjected to silica-gel column chromatography, using hexane/ethyl acetate (containing 1% triethylamine) to give the corresponding exo-cyclic enol ether product **61** (0.72 g, 72%) as a colourless liquid. IR (neat): ν_{max} 3066, 3028, 2936, 2875, 2249, 1723, 1496, 1453, 1350, 1271, 1205, 1089, 1026, 906, 726 cm-1. **^{1}H NMR (400 MHz, $CDCl_3$)**: δ 7.29-7.33 (m, 15 H), 4.64-4.76 (m, 4H), 4.58-4.61 (m, 2H), 4.46-4.50 (m, 2H), 4.09-4.10 (m, 1H), 4.01-4.05 (m, 2H), 3.81-3.83 (m, 1H), 3.75-3.77 (m, 1H). 13C NMR (100 MHz, CDCl3): δ 155.9, 138.5, 138.2, 138.1, 128.4, 128.4, 127.7, 127.7, 97.9, 76.9, 76.2, 72.6, 72.5, 71.6, 71.4, 66.9. **HRMS (ESI)** calcd for $C_{27}H_{28}O_4$+H 417.2066, found 417.2062.

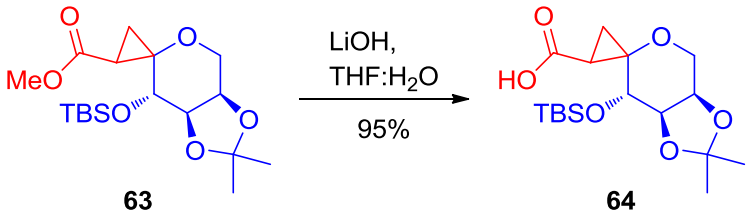
(3.4.1.17) (5*S*,6*S*,7*R*)-methyl 6,7-bis(benzyloxy)-5-((benzyloxy)methyl)-4-oxaspiro[2.4]heptane-1-carboxylate:



61 **62**

The obtained methylenated product **61** (570 mg 1.36 mmol), methyl diazoacetate (0.37 mL, 4.09 mmol) and $Rh_2(OAc)_4$ (12 mg, 0.027 mmol) was cyclopropanated by following the procedure described for compound **28** (3.4.1.3), to provide spiro-cyclopropanecarboxylate **62** (425 mg, 64%) as a mixture of diastereomers. **IR (neat)**: ν_{max} 2923, 2852, 1722, 1496, 1453, 1364, 1264, 1209, 1164, 1071, 1027, 888, 843, 804, 733 cm^{-1}. **HRMS (ESI)** calcd for $C_{30}H_{32}O_6$+Na 511.2097, found 511.2100.

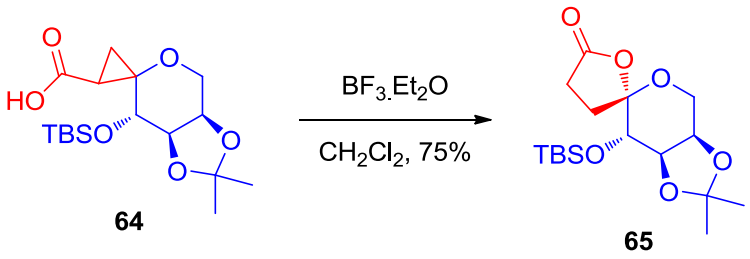
(3.4.1.18) (3a*R*,7*S*,7a*R*)-7-((tert-butyldimethylsilyl)oxy)-2,2-dimethyltetrahydrospiro[[1,3]dioxolo[4,5-*c*]pyran-6,1'-cyclopropane]-2'-carboxylic acid:



63 **64**

To a stirred solution of spiro-cyclopropanecarboxylated sugar **63** (400 mg, 1.07 mmol) in THF (10 mL), aqueous 0.2N LiOH (5.3 mL) was added. The reaction mixture was stirred for 3 h at room temperature, then poured into water, neutralized with 1N HCl, (2 mL) and extracted with ethyl acetate (2 x 50 mL). The combined organic layers were washed with water (100 mL), brine (100 mL), and dried over anhydrous Na_2SO_4, filtered and concentrated in *vacuo*. The obtained crude product was further purified by the silica-gel column chromatography in ethyl acetate/hexane (1:1) provided carboxylic acid **64** (365 mg) in 95% yield as a mixture of diastereomers. **IR (neat)**: ν_{max} 2980, 2964, 2925, 2865, 1703, 1451, 1380, 1248, 1122, 1002, 832, 782 cm^{-1}. **HRMS (ESI)** calcd for $C_{17}H_{30}O_6Si$+Na 381.1709, found 381.1710.

(3.4.1.19) (2'*S*,3a*R*,7*S*,7a*R*)-7-((tert-butyldimethylsilyl)oxy)-2,2-dimethyltetrahydro-3'*H*-spiro[[1,3]dioxolo[4,5-*c*]pyran-6,2'-furan]-5'(4'*H*)-one:

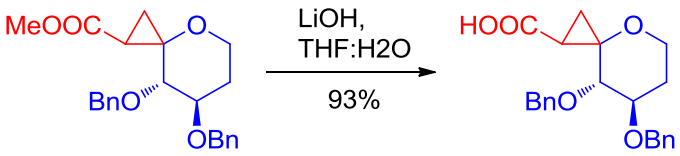


64 **65**

To a cooled (0 ^oC) solution of spiro-cyclopropanecarboxylic acid **64** (80 mg, 0.22 mmol) in dry dichloromethane (4 mL), was added borontrifluoride-diethyletherate ($BF_3.Et_2O$) (5.4 µL, 0.04 mmol). The reaction mixture was stirred for 1 h while allowing the temperature to come to 25 ^oC. During the reaction, the colour was changed to pale red colour. After completion of the reaction (monitored by TLC), it was quenched with triethylamine. Removal of solvent under reduced pressure followed by silica-gel column chromatography afforded compound **65** (60 mg, 75%) as a colourless solid. **IR (neat):** ν_{max} 2975, 2942, 2931, 2881, 2848, 1774, 1385, 1243, 1210, 1122, 1078, 1056, 914, 848, 788 cm^{-1}. **^{1}H NMR (400 MHz, $CDCl_3$)**: δ 4.24-4.26

(m,1H), 4.18 (t, 1H, *J* = 2.8 Hz), 4.15 (t, 1H, *J* = 3.2 Hz), 4.08 (d, 1H, *J* = 13.6 Hz), 3.68 (d, 1H, *J* = 6.8 Hz), 2.65-2.74 (m, 1H), 2.43-2.59 (m, 2H), 2.10 (ddd, 1H, *J* = 3.2 Hz, *J* = 9.2 Hz, *J* = 14.0 Hz), 1.55 (s, 3H), 1.37 (s, 3H), 0.88 (s, 9H), 0.19 (s, 3H), 0.12 (s, 3H). **^{13}C NMR (100 MHz, CDCl$_3$)**: δ 175.7, 109.1, 108.3, 77.1, 74.2, 73.2, 61.9, 29.8, 28.2, 27.8, 26.2, 25.7, 18.0, -3.8, -5.2. **HRMS (ESI)** calcd for $C_{17}H_{30}O_6Si$+Na 381.1709, found 381.1712. $[\alpha]_D^{25}$ = -90.2 (*c* = 1.0, $CHCl_3$).

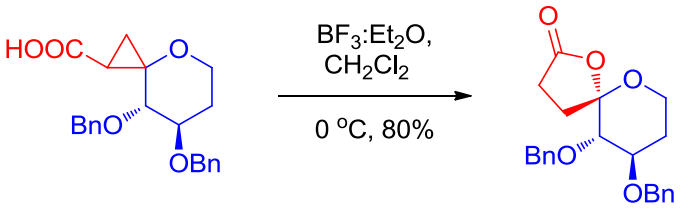
(3.4.1.20) (7*R*,8*S*)-7,8-bis(benzyloxy)-4-oxaspiro[2.5]octane-1-carboxylic acid:



66 **67**

Spiro-cyclopropanecarboxylate sugar **66** (342 mg, 0.89 mmol), and 0.2 N LiOH (4.8 mL, 1.79 mmol) undergo hydrolysis according to the procedure described for compound **64** (3.4.1.18), to provide the corresponding spiro-cyclopropanecarboxylic acid **67** (300 mg) in 93% Yield as mixture of diastereomers. **IR (neat)**: ν_{max} 3029, 2925, 2870, 1725, 1692, 1456, 1210, 1100, 1067, 744, 700 cm^{-1}. **HRMS (ESI)** calcd for $C_{22}H_{24}O_5$+Na 391.1521, found 391.1521.

(3.4.1.21) (9*R*,10*S*)-9,10-bis(benzyloxy)-1,6-dioxaspiro[4.5]decan-2-one:

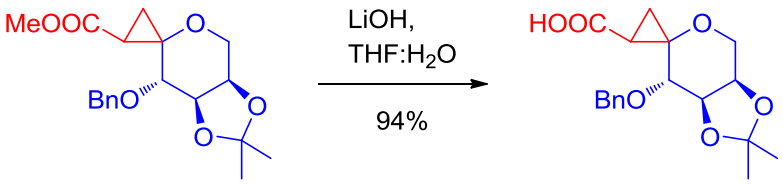


67 **68**

Compound **68** was synthesized using **67** (100 mg, 0.16 mmol) and $BF_3.Et_2O$ (6.7 µL, 0.05 mmol) in dichloromethane (3 mL) following the procedure described for compound **65** (3.4.1.19). The obtained crude product was purified by silica-gel column chromatography in ethyl acetate/hexane (2:8) to provide the spiro-lactone **68** in 80% yield as a single diastereomer. **IR (neat)**: ν_{max} 3024, 2920, 1780, 1456, 1363, 1215, 1095, 908, 733, 700 cm^{-1}. **^{1}H NMR (500 MHz, CDCl$_3$)**: δ 7.28-7.36 (m, 10H), 5.06 (d, 1H, *J* = 11.5 Hz), 4.71 (d, 1H, *J* = 6.0 Hz), 4.69 (d, 1H, *J* = 3.0 Hz), 4.62 (d, 1H, *J* = 11.5 Hz), 3.99 (ddd, 1H, *J* = 5.0 Hz, *J* = 9.5 Hz, *J* = 14.0

Hz), 3.82-3.89 (m, 1H), 3.76 (ddd, 1H, *J* = 1.5 Hz, *J* = 5.5 Hz, *J* = 12.0 Hz), 3.42 (d, 1H, *J* = 9.5 Hz), 2.54-2.61 (m, 1H), 2.48 (ddd, 1H, *J* = 6.0 Hz, *J* = 10.5 Hz, *J* = 18.0 Hz), 2.21 (ddd, 1H, *J* = 7.0 Hz, *J* = 10.0 Hz, *J* = 17.0 Hz), 2.11-2.15 (m, 1H), 1.95 (ddd, 1H, *J* = 5.5 Hz, *J* = 10.0 Hz, *J* = 15.5 Hz), 1.71-1.79 (m, 1H). **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 175.8, 138.2, 137.9, 128.4, 127.8, 127.7, 109.1, 81.7, 77.5, 75.2, 71.8, 61.4, 31.1, 30.8, 28.4. **HRMS (ESI)** calcd for $C_{22}H_{24}O_5$+Na 391.1521, found 391.1522. $[\alpha]_D^{25}$ = -71.7 (*c* = 1.0, $CHCl_3$).

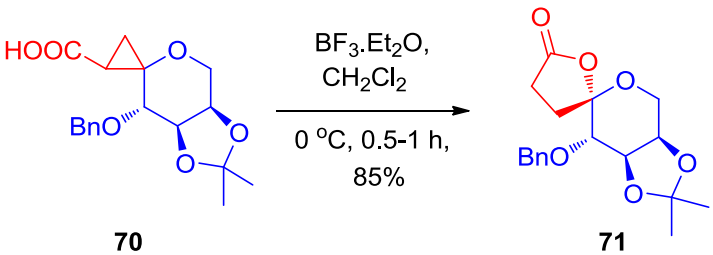
(3.4.1.22) (3a*R*,7*S*,7a*R*)-7-(benzyloxy)-2,2-dimethyltetrahydrospiro[[1,3]dioxolo[4,5-*c*]pyran-6,1'-cyclopropane]-2'-carboxylic acid:



69 **70**

Compound **70** was synthesized using the spiro-cyclopropanecarboxylate sugar **69** (320 mg, 0.95 mmol) and 0.2 N LiOH (4.79 mL, 0.95 mmol) by following the procedure described for compound **64** (3.4.1.18). The obtained crude product was purified by silica-gel column chromatography in ethyl acetate/hexane (1:1) to provide the spiro-cyclopropanecarboxylic acid **70** (290 mg) in 94% yield as a mixture of diastereomers. **IR (neat)**: ν_{max} 2985, 2925, 1703, 1456, 1385, 1221, 1111, 1084, 848, 744, 706 cm^{-1}. **HRMS (ESI)** calcd for $C_{18}H_{22}O_6$+Na 357.1314, found 357.1312.

(3.4.1.23) (2'*S*,3a*R*,7*S*,7a*R*)-7-(benzyloxy)-2,2-dimethyltetrahydro-3'*H*-spiro[[1,3]dioxolo[4,5-*c*]pyran-6,2'-furan]-5'(4'*H*)-one:

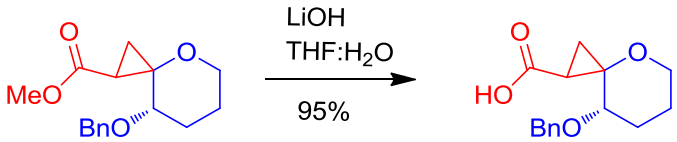


70 **71**

Compound **71** was synthesized using spiro-cyclopropanecarboxylic acid **70** (100 mg, 0.30 mmol) and $BF_3.Et_2O$ (7.4 mL) in dichloromethane (3 mL) following the procedure described for compound **65** (3.4.1.19). The obtained crude product was purified by silica-gel column chromatography in ethyl acetate/hexane (20-30%) to provide the spiro-lactone **71** in 85% yield

as a single diastereomer. **IR (neat)**: ν_{max} 3030, 2986, 2931, 2871, 2849, 1780, 1457, 1375, 1205, 1117, 1084, 909, 745 cm^{-1}. **^{1}H NMR (500 MHz, $CDCl_3$)**: δ 7.29-7.34 (m, 5H), 4.96 (d, 1H, *J* = 12.0 Hz), 4.66 (d, 1H, *J* = 12.0 Hz), 4.43 (dd, 1H, *J* = 5.5 Hz, *J* = 7.0 Hz), 4.27 (ddd, 1H, *J* = 1.0 Hz, *J* = 3.0 Hz, *J* = 5.5 Hz), 4.16 (dd, 1H, *J* = 3.0 Hz, *J* = 13.5 Hz), 4.08 (d, 1H, *J* = 13.5 Hz), 3.51 (d, 1H, *J* = 7.5 Hz), 2.51-2.65 (m, 2H), 2.36 (ddd, 1H, *J* = 7.5 Hz, *J* = 10.0 Hz, *J* = 17.5 Hz), 2.01 (ddd, 1H, *J* = 5.0 Hz, *J* = 10.0 Hz, *J* = 15.5 Hz), 1.54 (s, 3H), 1.39 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 175.6, 137.6, 128.4, 128.0, 127.9, 109.3, 107.4, 78.1, 77.1, 73.2, 72.7, 61.9, 30.3, 28.2, 28.1, 26.2. **HRMS (ESI)** calcd for $C_{18}H_{22}O_6$+Na 357.1314, found 357.1315. $[\alpha]_D^{25}$ = -71.5 (*c* = 1.0, $CHCl_3$).

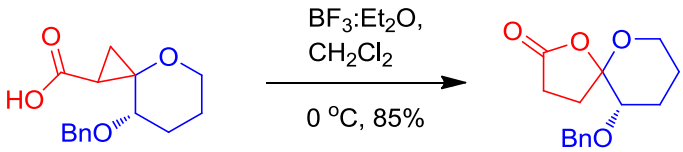
(3.4.1.24) (8*S*)-8-(benzyloxy)-4-oxaspiro[2.5]octane-1-carboxylic acid:



28 **72**

Compound **72** was synthesized using the spiro-cyclopropanecarboxylate sugar **28** (200 mg, 0.72 mmol) and 0.2 N LiOH (3.62 mL, 0.72 mmol) by following the procedure described for compound **64** (3.4.1.18). The obtained crude product was purified by silica-gel column chromatography in ethyl acetate/hexane (1:1) to provide the spiro-cyclopropanecarboxylic acid **72** (180 mg) in 95% yield as a mixture of diastereomers. **IR (neat)**: ν_{max} 3063, 3030, 2926, 1742, 1506, 1452, 1358, 1227, 1079, 1024, 745, 690 cm^{-1}. **HRMS (ESI)** calcd for $C_{15}H_{18}O_4$+H 263.1283, found 263.1280.

(3.4.1.25) (10*S*)-10-(benzyloxy)-1,6-dioxaspiro[4.5]decan-2-one:

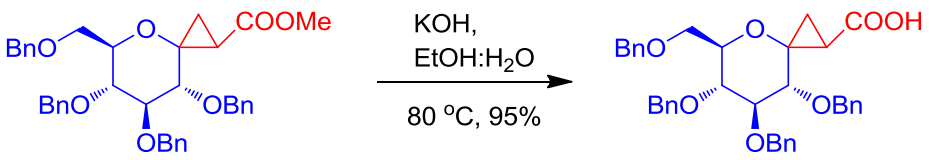


72 **73**

Compound **73** was synthesized using spiro-cyclopropanecarboxylic acid **72** (35 mg, 0.13) and $BF_3.Et_2O$ (3.3 µL, 0.02 mmol) in dichloromethane (2 mL) following the procedure described for compound **65** (3.4.1.19). The crude product was purified by silica-gel column

chromatography in ethyl acetate/hexane (2:8) to obtain the spiro-lactone **73** (30 mg) in 85% yield as an inseparable mixture of *S*,*S* and *R*,*S* diastereomers in 55:45 ratio respectively. **IR (neat)**: ν_{max} 3063, 3024, 2942, 2887, 1786, 1501, 1457, 1358, 1271, 1221, 1194, 1095, 1063, 909, 734, 701 cm^{-1}. **HRMS (ESI)** calcd for $C_{15}H_{18}O_4$+H 263.1283, found 263.1282.

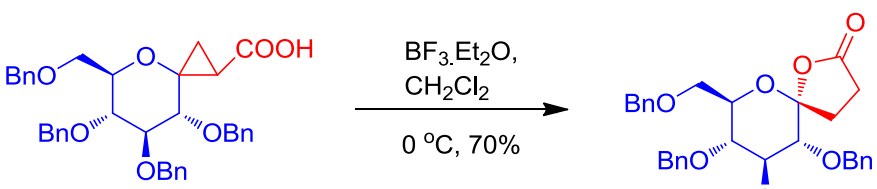
(3.4.1.26) (5*R*,6*R*,7*S*,8*R*)-6,7,8-tris(benzyloxy)-5-((benzyloxy)methyl)-4-oxaspiro[2.5]octane-1-carboxylic acid:



33 **74**

To a stirred solution of spiro-cyclopropanecarboxylated sugar **33** (350 mg, 0.574 mmol) in EtOH/H_2O (15 mL, 2:1) was added KOH (226 mg, 4.04 mmol) and the mixture was stirred at 80 °C for 2 h, after completion of the reaction (by TLC), 1/3 of the solvent was removed in *vacuo* at 50 °C. The obtained suspension was diluted with H_2O (60 mL), and extracted with ethyl acetate (100 mL). The aqueous phase was acidified with 1N HCl, and the solution was extracted with ethyl acetate (2 × 50 mL). The combined organic layers were washed with brine solution (50 mL), dried over anhydrous Na_2SO_4. Evaporation of the solvent under reduced pressure provided the crude product which was purified by the silica-gel column chromatography to obtain the spiro-cyclopropanecarboxylic acid **74** (324 mg, 95%) as a colourless thick oil in mixture of diastereomers. **IR (neat)**: ν_{max} 3085, 3056, 3029, 2920, 2863, 1696, 1496, 1453, 1360, 1205, 1094, 1026, 911 cm^{-1}. **HRMS (ESI)** calcd for $C_{37}H_{38}O_7$+Na 617.2515, found 617.2517.

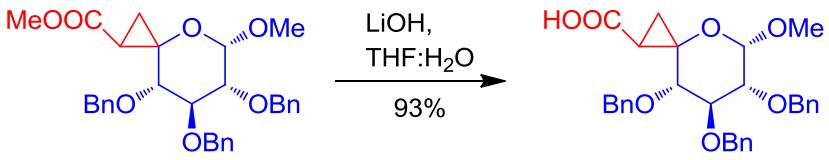
(3.4.1.27) (5*R*,7*R*,8*R*,9*S*,10*R*)-8,9,10-tris(benzyloxy)-7-((benzyloxy)methyl)-1,6-dioxaspiro[4.5]decan-2-one:



74 **75**

To a cooled (0 °C) solution of spiro-cyclopropanecarboxylic acid **74** (100 mg, 0.16 mmol) in dry dichloromethane (5 mL) was added $BF_3.Et_2O$ (20.5 µL, 0.16 mmol) and the mixture was stirred for 5 h at the room temperature. After completion of the reaction (by checking TLC), the reaction was quenched by the addition of triethylamine. The reaction mixture was concentrated under reduced pressure, followed by silica-gel column chromatography afforded the spiro-lactone **75** (70 mg, 70%) as colourless solid. **IR (neat)**: ν_{max} 3090, 3063, 3030, 2926, 2865, 1780, 1501, 1452, 1364, 1265, 1210, 1106, 909, 734, 701 cm^{-1}. **^{1}H NMR (400 MHz, $CDCl_3$)**: δ 7.28-7.39 (m, 20H), 5.05 (d, 1H, *J* = 11.6 Hz), 4.96 (d, 1H, *J* = 4.8 Hz), 4.77 (d, 1H, *J* = 11.6 Hz), 4.74 (s, 1H), 4.73 (d, 1H, *J* = 12.0 Hz), 4.64 (d, 1H, *J* = 11.2 Hz), 4.50 (d, 1H, *J* = 12.0 Hz), 4.46 (d, 1H, *J* = 12.0 Hz), 4.14 (t, 1H, *J* = 6.8 Hz), 3.97-4.09 (m, 3H), 3.51-3.60 (m, 2H), 2.45-2.63 (m, 2H), 2.19 (ddd, 1H, *J* = 7.2 Hz, *J* = 11.6 Hz, *J* = 16.8 Hz), 2.05 (ddd, 1H, *J* = 6.4 Hz, *J* = 10.4 Hz, *J* = 16.4 Hz). **^{13}C NMR (100 MHz, $CDCl_3$)**: 175.7, 138.4, 138.0, 137.8, 137.8, 128.5, 128.3, 128.2, 127.9, 127.8, 127.7, 127.6, 108.9, 80.9, 77.5, 75.3, 74.8, 74.2, 73.4, 72.9, 72.6, 68.2, 30.7, 28.5. **HRMS (ESI)** calcd for $C_{37}H_{38}O_7$+Na 617.2515, found 617.2518. $[\alpha]_D^{25}$ = +28.1 (*c* = 1.0, $CHCl_3$).

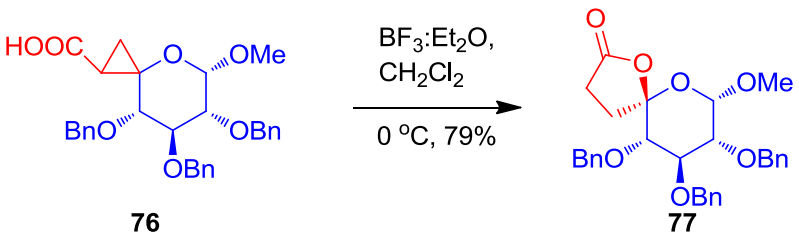
(3.4.1.28) (5*S*,6*R*,7*S*,8*S*)-6,7,8-tris(benzyloxy)-5-methoxy-4-oxaspiro[2.5]octane-1-carboxylic acid:



38 **76**

Compound **76** was synthesized using the spiro-cyclopropanecarboxylate sugar **38** (220 mg, 0.42 mmol) and 0.2 N LiOH (2.12 mL, 0.42 mmol) by following the procedure described for compound **64** (3.4.1.18). The obtained crude product was purified by silica-gel column chromatography in ethyl acetate/hexane (1:1) to provide the spiro-cyclopropanecarboxylic acid **76** (200 mg) in 93% yield as a mixture of diastereomers. **IR (neat)**: ν_{max} 3062, 3024, 2920, 2859, 1698, 1495, 1451, 1358, 1166, 1100, 1056, 733, 695 cm^{-1}. **HRMS (ESI)** calcd for $C_{30}H_{32}O_7$+Na 527.2046, found 527.2045.

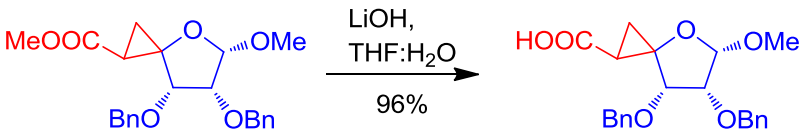
(3.4.1.29) (5*R*,7*S*,8*R*,9*R*,10*S*)-8,9,10-tris(benzyloxy)-7-methoxy-1,6-dioxaspiro[4.5]decan-2-one:



76 **77**

Compound **77** was synthesized using spiro-cyclopropanecarboxylic acid **76** (100 mg, 0.19 mmol) and $BF_3.Et_2O$ (5 µL, 0.04 mmol) in dichloromethane (3 mL) following the procedure described for compound **65** (3.4.1.19). The crude product was purified by silica-gel column chromatography in ethyl acetate/hexane (2:8) to obtain the spiro-lactone **77** (79 mg) in 79% yield. **IR (neat)**: ν_{max} 3057, 3024, 2926, 2849, 1786, 1495, 1457, 1358, 1221, 1073, 915, 739, 701 cm^{-1}. **^{1}H NMR (400 MHz, $CDCl_3$)**: δ 7.27-7.36 (m, 15H), 5.00 (d, 1H, *J* = 11.6 Hz), 4.94 (d, 1H, *J* = 10.8 Hz), 4.93 (d, 1H, *J* = 11.2 Hz), 4.78-4.80 (m, 2H,), (4.74 (d, 1H, *J* = 11.6 Hz), 4.68 (d, 1H, *J* = 11.6 Hz), 4.01 (t, 1H, *J* = 9.6 Hz), 3.54 (s, 3H), 3.47-3.52 (m, 2H), 2.46-2.66 (m, 2H), 2.04-2.16 (m, 2H). **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 175.2, 138.4, 138.2, 137.5, 128.5, 128.4, 128.3, 128.0, 127.9, 127.8, 127.6, 106.5, 102.1, 82.0, 80.9, 80.2, 76.0, 75.3, 74.6, 57.6, 30.6, 28.1. **HRMS (ESI)** calcd for $C_{30}H_{32}O_7$+Na 527.2046, found 527.2048. $[\alpha]_D^{25}$ = -15.9 (C = 1.0, $CHCl_3$).

(3.4.1.30) (5*S*,6*R*,7*S*)-6,7-bis(benzyloxy)-5-methoxy-4-oxaspiro[2.4]heptane-1-carboxylic acid:

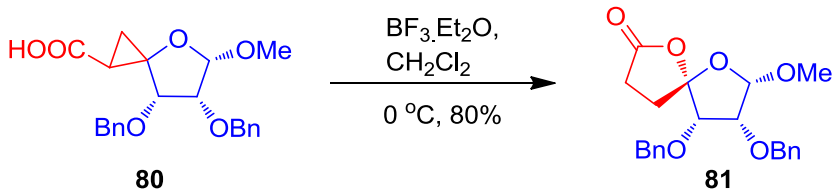


44 **80**

Compound **80** was synthesized using the spiro-cyclopropanecarboxylate sugar **44** (200 mg, 0.5 mmol) and 0.2 N LiOH (2.25 mL, 0.5 mmol) by following the procedure described for compound **64** (3.4.1.18). The obtained crude product was purified by silica-gel column chromatography in ethyl acetate/hexane (1:1) to provide the spiro-cyclopropanecarboxylic acid **80** (180 mg) in 96% yield as a mixture of diastereomers. **IR (neat)**: ν_{max} 3035, 2920, 2859,

1703, 1451, 1407, 1265, 1210, 1150, 1111, 1040, 739, 695 cm^{-1}. **HRMS (ESI)** calcd for $C_{22}H_{24}O_6$+Na 407.1471, found 407.1473.

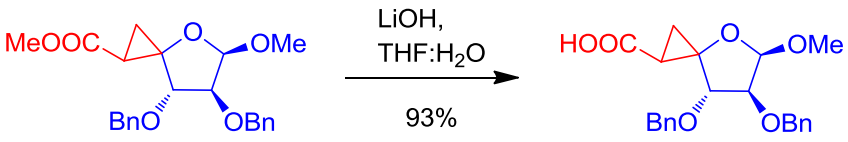
(3.4.1.31) (5*S*,7*S*,8*R*,9*S*)-8,9-bis(benzyloxy)-7-methoxy-1,6-dioxaspiro[4.4]nonan-2-one:



80 **81**

Compound **81** was synthesized using spiro-cyclopropanecarboxylic acid **80** (100 mg, 0.26 mmol) and $BF_3.Et_2O$ (6.4 µL, 0.05 mmol) in dichloromethane (3 mL) following the procedure described for compound **65** (3.4.1.19). The crude product was purified by silica-gel column chromatography in ethyl acetate/hexane (2:8) to obtain the spiro-lactone **81** in 80% yield. **IR (neat)**: ν_{max} 3068, 3035, 2920, 2860, 1786, 1731, 1501, 1452, 1265, 1030, 882, 739, 695 cm^{-1}. **^{1}H NMR (500 MHz, $CDCl_3$)**: δ 7.31-7.39 (m, 10H), 5.00 (d, 1H, *J* = 1.5 Hz), 4.71 (d, 1H, *J* = 12.5 Hz), 4.67 (s, 1H), 4.63 (d, 1H, *J* = 12.0 Hz), 4.57 (d, 1H, *J* = 12.0 Hz), 4.32 (d, 1H, *J* = 4.5 Hz), 4.00 (dd, 1H, *J* = 1.5 Hz, *J* = 4.5 Hz), 3.39 (s, 3H), 2.67-2.76 (m, 2H), 2.49 (ddd, 1H, *J* = 8.5 Hz, *J* = 13.0 Hz, *J* = 17.5 Hz), 2.18-2.24 (m, 1H). **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 175.6, 137.5, 137.2, 128.5, 128.5, 127.9, 127.8, 127.7, 115.4, 106.3, 81.3, 80.3, 73.3, 72.6, 55.6, 29.6, 28.1. **HRMS (ESI)** calcd for $C_{22}H_{24}O_6$+Na 407.1471, found 407.1474. $[\alpha]_D^{25}$ = +21.6 (*c* = 0.78, $CHCl_3$).

(3.4.1.32) (5*R*,6*S*,7*S*)-6,7-bis(benzyloxy)-5-methoxy-4-oxaspiro[2.4]heptane-1-carboxylic acid:

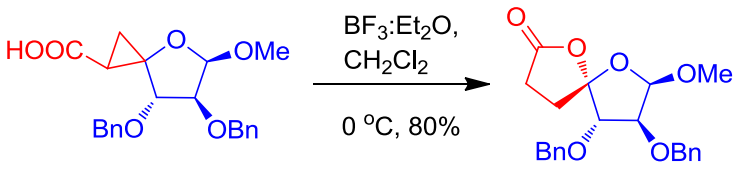


50 **82**

Compound **82** was synthesized using the spiro-cyclopropanecarboxylate sugar **50** (100 mg, 0.25 mmol) and 0.2 N LiOH (2.5 mL, 0.5 mmol) by following the procedure described for compound **64** (3.4.1.18). The obtained crude product was purified by silica-gel column chromatography in ethyl acetate/hexane (1:1) to provide the spiro-cyclopropanecarboxylic acid **82** (90 mg) in 93% yield as a mixture of diastereomers. **IR (neat)**: ν_{max} 3068, 3029, 2920, 2859,

1703, 1500, 1456, 1270, 1210, 1100, 1029, 952, 733, 700 cm^{-1}. **HRMS (ESI)** calcd for $C_{22}H_{24}O_6$+H 385.1651, found 385.1654.

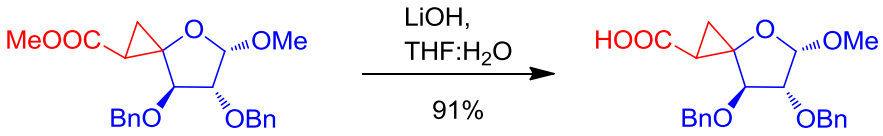
(3.4.1.33) (5*S*,7*R*,8*S*,9*S*)-8,9-bis(benzyloxy)-7-methoxy-1,6-dioxaspiro[4.4]nonan-2-one:



82 **83**

Compound **83** was synthesized using spiro-cyclopropanecarboxylic acid **82** (50 mg, 0.13 mmol) and $BF_3.Et_2O$ (3.2 µL) in dichloromethane (2 mL) following the procedure described for compound **65** (3.4.1.19). The crude product was purified by silica-gel column chromatography in ethyl acetate/hexane (2:8) to obtain the spiro-lactone **83** (40 mg) in 80% yield. **IR (neat)**: ν_{max} 3084, 3057, 3030, 2920, 2854, 1780, 1501, 1452, 1369, 1210, 904, 739, 701 cm^{-1}. **^{1}H NMR (400 MHz, $CDCl_3$)**: δ 7.28-7.37 (m, 10H), 4.92 (d, 1H, *J* = 3.6 Hz), 4.79 (d, 1H, *J* = 12.0 Hz), 4.64 (d, 1H, *J* = 6.0 Hz), 4.61 (d, 1H, *J* = 6.8 Hz), 4.55 (d, 1H, *J* = 12.0 Hz), 4.24 (dd, 1H, *J* = 3.6 Hz, *J* = 7.6 Hz), 3.94 (d, 1H, *J* = 7.6 Hz), 3.39 (s, 3H), 2.44-2.66 (m, 2H), 2.15-2.20 (m, 2H). **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 174.8, 137.4, 137.3, 128.5, 128.1, 127.9, 127.8, 111.4, 108.1, 85.7, 83.8, 72.7, 72.4, 55.9, 29.9, 28.2. **HRMS (ESI)** calcd for $C_{22}H_{24}O_6$+Na 407.1471, found 407.1472. $[\alpha]_D^{25}$ = +14.9 (*c* = 0.76, $CHCl_3$).

(3.4.1.34) (5*S*,6*R*,7*R*)-6,7-bis(benzyloxy)-5-methoxy-4-oxaspiro[2.4]heptane-1-carboxylic acid:

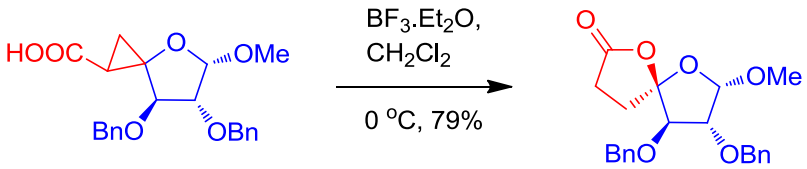


56 **84**

Compound **84** was synthesized using the spiro-cyclopropanecarboxylate sugar **56** (100 mg, 0.25 mmol) and 0.2 N LiOH (2.5 mL, 0.5 mmol) by following the procedure described for compound **64** (3.4.1.18). The obtained crude product was purified by silica-gel column chromatography in ethyl acetate/hexane (1:1) to provide the spiro-cyclopropanecarboxylic acid **84** (88 mg) in 91% yield as a mixture of diastereomers. **IR (neat)**: ν_{max} 3029, 2920, 2848, 1698,

1500, 1451, 1407, 1308, 1210, 1095, 1023, 952, 739, 695 cm^{-1}. **HRMS (ESI)** calcd for $C_{22}H_{24}O_6$+Na 407.1471, found 407.1472.

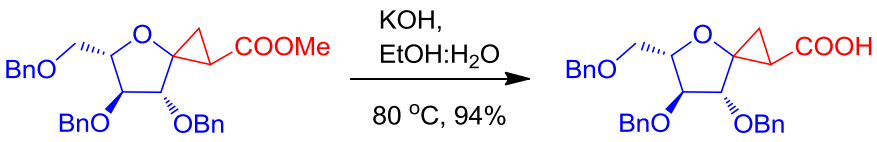
(3.4.1.35) (5*R*,7*S*,8*R*,9*R*)-8,9-bis(benzyloxy)-7-methoxy-1,6-dioxaspiro[4.4]nonan-2-one:



84 **85**

Compound **85** was synthesized using spiro-cyclopropanecarboxylic acid **84** (20 mg, 0.05 mmol) and $BF_3.Et_2O$ (1.3 µL, 0.01 mmol) in dichloromethane (2 mL) following the procedure described for compound **65** (3.4.1.19). The crude product was purified by silica-gel column chromatography in ethyl acetate/hexane (2:8) to obtain the spiro-lactone **85** (16 mg) in 79% yield. **IR (neat)**: ν_{max} 3029, 2920, 2848, 1785, 1730, 1643, 1451, 1402, 1248, 1084, 908, 739, 695 cm^{-1}. **^{1}H NMR (400 MHz, $CDCl_3$)**: δ 7.29-7.41 (m, 10H), 4.94 (d, 1H, *J* = 3.6 Hz), 4.82 (d, 1H, *J* = 12.0 Hz), 4.66 (d, 1H, *J* = 6.0 Hz), 4.63 (d, 1H, *J* = 7.2 Hz), 4.57 (d, 1H, *J* = 11.6 Hz), 4.26 (dd, 1H, *J* = 3.6 Hz, *J* = 7.6 Hz), 3.96 (d, 1H, *J* = 7.2 Hz), 3.41 (s, 3H), 2.60-2.68 (m, 1H), 2.44-2.55 (m, 1H), 2.16-2.22 (m, 2H). **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 174.7, 137.4, 137.3, 128.4, 128.1, 127.9, 111.4, 108.1, 85.7, 83.8, 72.7, 72.4, 55.9, 29.9, 28.2. **HRMS (ESI)** calcd for $C_{22}H_{24}O_6$+Na 407.1471, found 407.1471. $[\alpha]_D^{25}$ = -10.3 (*c* = 0.73, $CHCl_3$).

(3.4.1.36) (5*S*,6*S*,7*R*)-6,7-bis(benzyloxy)-5-((benzyloxy)methyl)-4-oxaspiro[2.4]heptane-1-carboxylic acid:

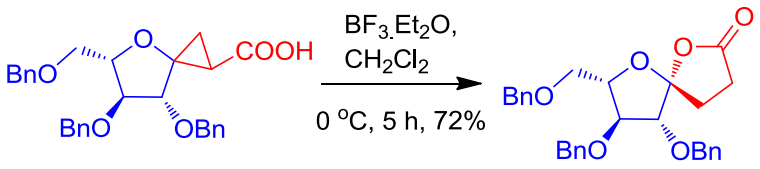


62 **86**

To a solution of spiro-cyclopropanecarboxylated sugar **62** (200 mg, 0.41 mmol) in EtOH/H_2O (10 mL, 2:1) was added KOH (161 mg, 2.88 mmol) at room temperature, and the reaction mixture was stirred at 80 °C for 2 h. After completion of the reaction (by TLC) 1/3 of the solvent was removed in *vacuo*. The obtained residue was diluted with water (40 mL), and once extracted with ethyl acetate (50 mL). The aqueous phase was acidified with 1N HCl and extracted with ethyl acetate (3 × 50 mL). The combined organic layers were washed with brine

solution (100 mL), dried over Na_2SO_4, and evaporated. The obtained crude product was purified by the silica-gel column chromatography to furnish the spiro-cyclopropanecarboxylic acid **86** (183 mg, 94%). **IR (neat)**: ν_{max} 3059, 3018, 2926, 2853, 1693, 1496, 1453, 1317, 1264, 1186, 1069, 1026, 882 cm^{-1}. **HRMS (ESI)** calcd for $C_{29}H_{30}O_6$+Na 497.1940, found 497.1945.

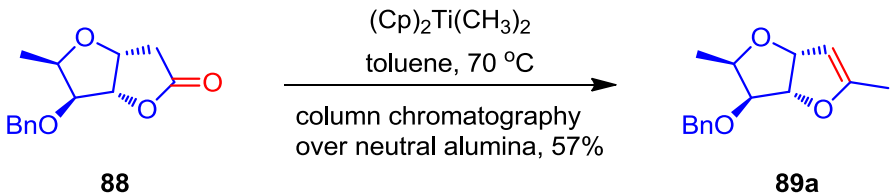
(3.4.1.37) (5*R*,7*S*,8*S*,9*R*)-8,9-bis(benzyloxy)-7-((benzyloxy)methyl)-1,6-dioxaspiro[4.4]nonan-2-one:



86 **87**

To a cooled (0 °C) solution of spiro-cyclopropanecarboxylic acid **86** (30 mg, 0.06 mmol) in dry dichloromethane (3 mL) was added $BF_3.Et_2O$ (7.76 µL, 0.06 mmol) and stirred the reaction mixture for 5 h at the room temperature. After completion of the reaction by checking TLC, the reaction mixture was quenched by addition of triethylamine, then concentrated by using rotary evaporator. Purification of the obtained residue over silica-gel column chromatography gave the spirolactone **87** (22 mg, 72%) as a single diastereomer. **IR (neat)**: ν_{max} 2922, 2853, 1781, 1741, 1602, 1496, 1453, 1365, 1263, 1208, 1124, 1095, 1051, 1027, 910, 858, 801, 737 cm^{-1}. **^{1}H NMR (400 MHz, $CDCl_3$)**: δ 7.28-7.43 (m, 15H), 5.09 (d, 1H, *J* = 11.6 Hz), 4.79 (d, 1H, *J* = 12.4 Hz), 4.74 (d, 1H, *J* = 12.4 Hz), 4.73 (d, 1H, *J* = 11.6 Hz), 4.66 (d, 1H, *J* = 12 Hz), 4.63 (d, 1H, *J* = 12 Hz), 4.04 (d, 1H, *J* = 9.6 Hz), 4.00 (dd, 1H, *J* = 2.8 Hz, *J* = 10.0 Hz), 3.89 (dd, 1H, *J* = 1.6 Hz, *J* = 12.4 Hz), 3.84 (d, 1H, *J* = 1.6 Hz), 3.81 (d, 1H, *J* = 12.8 Hz), 2.57-2.66 (m, 2H), 2.26 (ddd, 1H, *J* = 7.2 Hz, *J* = 10.0 Hz, *J* = 17.2 Hz), 2.09 (ddd, 1H, *J* = 5.6 Hz, *J* = 10.4 Hz, *J* = 16.0 Hz). **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 175.7, 138.0, 128.4, 127.9, 127.8, 109.2, 79.4, 77.6, 75.5, 73.2, 72.2, 71.8, 63.7, 30.7, 28.4. **HRMS (ESI)** calcd for $C_{29}H_{30}O_6$+Na 497.1940, found 497.1942. $[\alpha]_D^{25}$ = +57.5 (*c* = 1.0, $CHCl_3$).

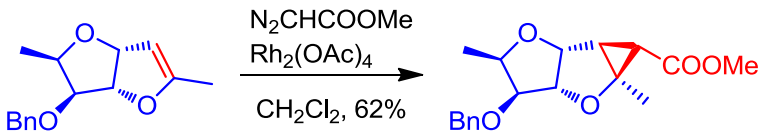
(3.4.1.38) (2*R*,3*S*,3a*S*,6a*R*)-3-(benzyloxy)-2,5-dimethyl-2,3,3a,6a-tetrahydrofuro[3,2-*b*]furan:



88 **89a**

3,6-anhydro-5-*O*-benzyl-2,7-di-deoxy-D-ido-heptono-2,4-lactone **88** (3.5 g, 14.11 mmol) was dissolved in dry toluene (70 mL) and cyclopentadienyl dimethyl titanocene (23.48 mL of a 20% w/w solution in toluene) was added slowly at room temperature, then the reaction mixture was stirred in the dark at 70 °C under argon for a period of 24 h or until TLC showed disappearance of the starting material. The brown reaction mixture was concentrated, and subjected to column chromatography using neutral alumina in hexane/ethyl acetate without adding triethylamine to give the unsaturated methyl product **89a** (2.0 g, 57%). (If the column has done in presence of triethylamine, methylenated product was obtained). **IR (neat)**: ν_{max} 2958, 2926, 2849, 1736, 1671, 1463, 1391, 1205, 1079, 1024, 734 cm^{-1}. **^{1}H NMR (400 MHz, $CDCl_3$)**: δ 7.27-7.37 (m, 5H), 5.39 (d, 1H, *J* = 6.0 Hz), 4.88 (d, 1H, *J* = 6.8 Hz), 4.72-4.77 (m, 2H), 4.57 (dd, 1H, *J* = 2.0 Hz, *J* = 12.4 Hz), 3.78-3.81 (m, 2H), 1.82 (s, 3H), 1.33 (d, 3H, *J* = 2.4 Hz). **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 159.7, 137.9, 128.4, 127.8, 127.7, 96.4, 86.8, 84.4, 83.4, 73.3, 71.7, 13.4, 13.0. **HRMS (ESI)** calcd for $C_{15}H_{18}O_3$+Na 269.1154, found 269.1155.

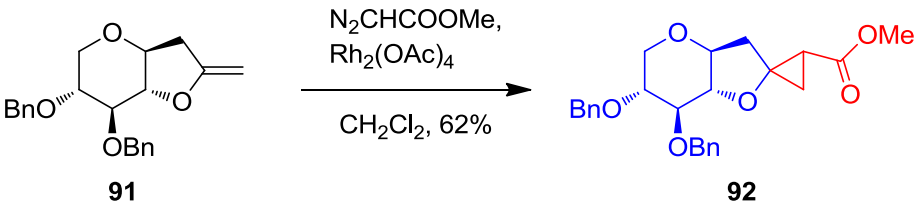
(3.4.1.39) (2*R*,3*S*,3a*S*,4a*S*,5*R*,5a*R*,5b*R*)-methyl 3-(benzyloxy)-2,4*a*-dimethylhexahydro-2*H*-cyclopropa[*b*]furo[2,3-*d*]furan-5-carboxylate:



89 **90**

To a stirred suspension of *endo*-cyclic olefin **89** (1.0 g, 4.06 mmol), methyl diazoacetate (1.12 mL, 12.18 mL) and $Rh_2(OAc)_4$ (35.0 mg, 0.081 mmol) in anhydrous CH_2Cl_2 (20 mL) was added drop wise, over a period of 1 h, a solution of methyl diazoacetate (1.12 mL, 12.18 mmol) in CH_2Cl_2 (40 mL). After completion of the reaction, the reaction mixture was concentrated in *vacuo* and the obtained crude product was purified by silica gel column chromatography (eluent: 10-20% EtOAc in Hexane) to give desired spiro-cyclopropanecarboxylate **90** (0.80 g, 62%) as a mixture of diastereomers. **IR (neat)**: ν_{max} 3057, 2926, 2860, 1731, 1446, 1331, 1216, 1156, 1079, 854, 734 cm^{-1}. **HRMS (ESI)** calcd for $C_{18}H_{22}O_5$+Na 341.1365, found 341.1364.

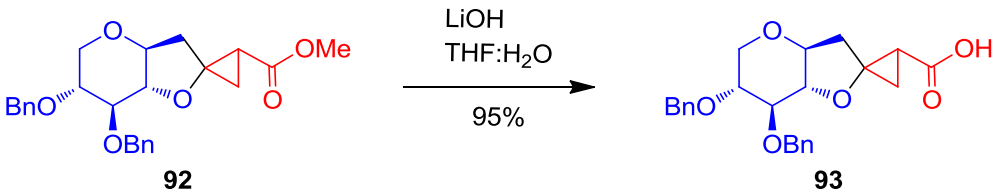
(3.4.1.40) (3a'*S*,6'*R*,7'*S*,7a'*S*)-methyl 6',7'-bis(benzyloxy)hexahydrospiro[cyclopropane-1,2'-furo[3,2-*b*]pyran]-2-carboxylate:



91 **92**

Compound **92** was synthesized using **91** (667 mg, 1.89 mmol), methyl diazoacetate (0.52 mL, 5.67 mmol), $Rh_2(OAc)_4$ (16.0 mg, 0.037 mmol) by following the procedure described for compound **28** (3.4.1.3). Yield 62% (495 mg). This compound was obtained as an inseparable mixture of diastereomers. **IR (neat)**: ν_{max} 3084, 3062, 3024, 2953, 2876, 1736, 1500, 1445, 1374, 848, 744, 700. **HRMS (ESI)** calcd for $C_{25}H_{28}O_6$+Na 447.1784, found 447.1785.

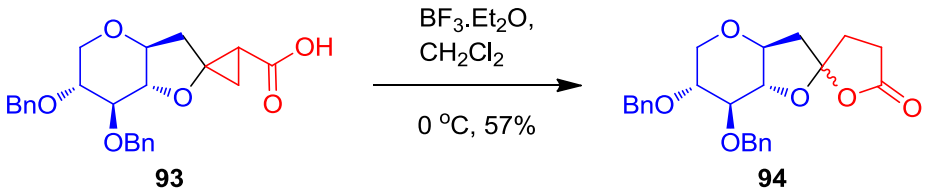
(3.4.1.41) (3a'*S*,6'*R*,7'*S*,7a'*S*)-6',7'-bis(benzyloxy)hexahydrospiro[cyclopropane-1,2'-furo[3,2*b*]pyran]-2-carboxylic acid:



92 **93**

Compound **93** was synthesized using the spiro-cyclopropanecarboxylate sugar **92** (168 mg, 0.39 mmol) and 0.2 N LiOH (3.96 mL, 0.79 mmol) by following the procedure described for compound **64** (3.4.1.18). The obtained crude product was purified by silica-gel column chromatography in ethyl acetate/hexane (2:1) to provide the spiro-cyclopropanecarboxylic acid **93** (155mg) in 95% yield as a mixture of diastereomers. **IR (neat)**: ν_{max} 3063, 3024, 2926, 2854, 1726, 1682, 1501, 1452, 1413, 1128, 1101, 1056, 914, 843, 728, 701 cm^{-1}. **HRMS (ESI)** calcd for $C_{24}H_{26}O_6$+Na 433.1627, found 433.1626.

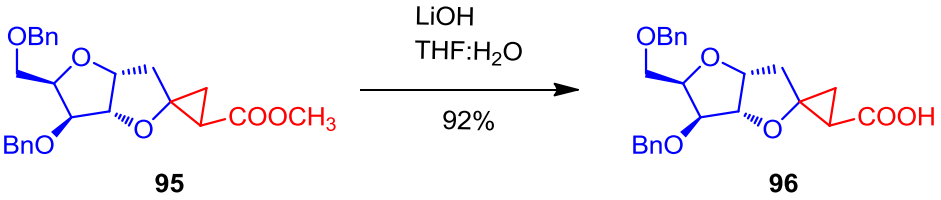
(3.4.1.42) (3a'*S*,6'*R*,7'*S*,7a'*S*)-6',7'-bis(benzyloxy)hexahydro-3*H*-spiro[furan-2,2'-furo[3,2-b]pyran]-5(4*H*)-one:



93 **94**

Compound **94** was synthesized using spiro-cyclopropanecarboxylic acid **93** (90 mg, 0.21 mmol) and $BF_3.Et_2O$ (55 µL, 0.43 mmol) in dichloromethane (4 mL) following the procedure described for compound **65** (3.4.1.19). The crude product was purified by silica-gel column chromatography in ethyl acetate/hexane (4:6) to obtain the spiro-lactone **94** (51 mg) in 57% yield as 1:1 mixture of diastereomers. **IR (neat)**: ν_{max} 3084, 3062, 3029, 2920, 2854, 1780, 1500, 1456, 1281, 1144, 1095, 1045, 903, 744, 695 cm^{-1}. **HRMS (ESI)** calcd for $C_{24}H_{26}O_6$+Na 433.1627, found 433.1629.

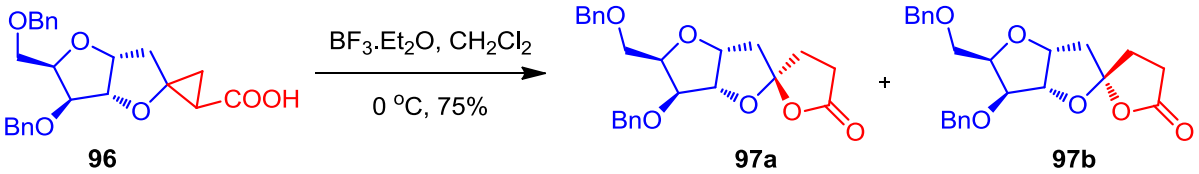
(3.4.1.43) (3a'*R*,5'*R*,6'*S*,6a'*S*)-6'-(benzyloxy)-5'-((benzyloxy)methyl)tetrahydro-3'*H*-spiro[cyclopropane-1,2'-furo[3,2-*b*]furan]-2-carboxylic acid:



95 **96**

Compound **96** was synthesized using the spiro-cyclopropanecarboxylate sugar **95** (200 mg, 0.47 mmol) and 0.2 N LiOH (4.7 mL, 0.94 mmol) by following the procedure described for compound **64** (3.4.1.18). The obtained crude product was purified by silica-gel column chromatography in ethyl acetate/hexane (2:1) to provide the spiro-cyclopropanecarboxylic acid **96** (178 mg) in 92% yield as a mixture of diastereomers. **IR (neat)**: ν_{max} 3068, 3035, 2931, 2865, 1786, 1682, 1490, 1452, 1216, 1073, 1030, 909, 838, 739 cm^{-1}. **HRMS (ESI)** calcd for $C_{24}H_{26}O_6$+Na 433.1627, found 433.1628.

(3.4.1.44) (2*R*,3a'*R*,5'*R*,6'*S*,6a'*S*)-6'-(benzyloxy)-5'-((benzyloxy)methyl)tetrahydro-3*H*,3'*H*-spiro[furan-2,2'-furo[3,2-*b*]furan]-5(4*H*)-one (97*a*) and (2*S*,3a'*R*,5'*R*,6'*S*,6a'*S*)-6'-(benzyloxy)-5'-((benzyloxy)methyl)tetrahydro-3*H*,3'*H*-spiro[furan-2,2'-furo[3,2-*b*]furan]-5(4*H*)-one (97*b*):



96 **97a** **97b**

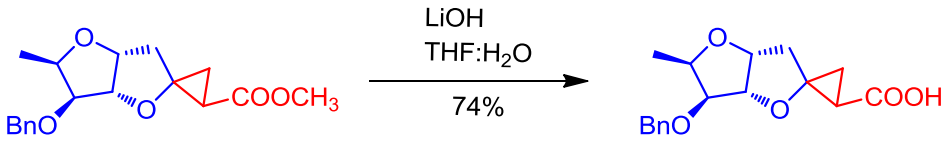
Compounds **97a** and **97b** were synthesized using spiro-cyclopropanecarboxylic acid **96** (100 mg, 0.243) and $BF_3.Et_2O$ (6.0 µL, 0.048 mmol) in dichloromethane (4 mL) following the procedure described for compound **65** (3.4.1.19). The crude product was purified by silica-gel

column chromatography in ethyl acetate/hexane (3:7) to obtain the spiro-lactones **97a** and **97b** in 75% yield with 7:8 ratio respectively.

Data for compound 97a: **IR (neat)**: ν_{max} 3062, 3024, 2953, 2914, 2859, 1785, 1725, 1456, 1270, 1078, 897, 744, 689 cm^{-1}. **^{1}H NMR (400 MHz, $CDCl_3$)**: δ 7.28-7.36 (m, 10H), 5.06-5.09 (m, 1H), 4.76 (d, 1H, *J* = 4.8 Hz), 4.66 (dd, 2H, *J* = 12.0 Hz, *J* = 20.4 Hz), 4.53(d, 1H, *J* = 12 Hz), 4.49 (d, 1H, *J* = 12.0 Hz), 4.20-4.22 (m, 1H), 4.00 (d, 1H, *J* = 3.2 Hz), 3.74 (d, 1H, *J* = 2.8 Hz), 3.73 (d, 1H, *J* = 4.0 Hz), 2.67-2.82 (m, 2H), 2.54 (ddd, 1H, *J* = 4.4 Hz, *J* = 7.6 Hz, *J* = 18.0 Hz), 2.34-2.38 (m, 2H), 2.17-2.21 (m, 1H). **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 175.6, 137.9, 137.4, 128.5, 128.4, 127.9, 127.8, 127.7, 116.7, 86.2, 81.6, 81.0, 79.4, 73.6, 71.9, 68.1, 43.5, 31.4, 28.7. **HRMS (ESI)** calcd for $C_{24}H_{26}O_6$+Na 433.1627, found 433.1627. $[\alpha]_D^{25}$ = -11.2 (*c* = 1.0, $CHCl_3$).

Data for compound 97b: **IR (neat)**: ν_{max} 3068, 3029, 2920, 2865, 1774, 1725, 1500, 1451, 1352, 1265, 1193, 1078, 908, 733, 706 cm^{-1}. **^{1}H NMR (400 MHz, $CDCl_3$)**: δ 7.28-7.35 (m, 10H), 4.98 (t, 1H, *J* = 5.6 Hz), 4.78 (d, 1H, *J* = 4.8 Hz), 4.68 (q, 1H, *J* = 5.2 Hz), 4.66 (d, 1H, *J* = 12.0 Hz), 4.62 (d, 1H, *J* = 12.0 Hz), 4.54 (d, 2H, *J* = 12.0 Hz), 4.14 (d, 1H, *J* = 5.2 Hz), 3.69 (d, 2H, *J* = 5.6 Hz), 2.71-2.80 (m, 1H), 2.62 (d, 1H, *J* = 15.2 Hz), 2.52 (ddd, 1H, *J* = 4.4 Hz, *J* = 8.0 Hz, *J* = 18.0 Hz), 2.27-2.37 (m, 2H), 2.15-2.20 (m, 1H). **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 175.6, 137.9, 137.4, 128.5, 128.4, 127.9, 127.8, 127.7, 116.7, 86.2, 81.6, 81.0, 79.4, 73.6, 71.9, 68.1, 43.5, 31.4, 28.7. **HRMS (ESI)** calcd for $C_{24}H_{26}O_6$+Na 433.1627, found 433.1628. $[\alpha]_D^{25}$ = -5.7 (*c* = 0.85, $CHCl_3$).

(3.4.1.45) (3a'*R*,5'*R*,6'*S*,6a'*S*)-6'-(benzyloxy)-5'-methyltetrahydro-3'*H*-spiro[cyclopropane-1,2'-furo[3,2-*b*]furan]-2-carboxylic acid:

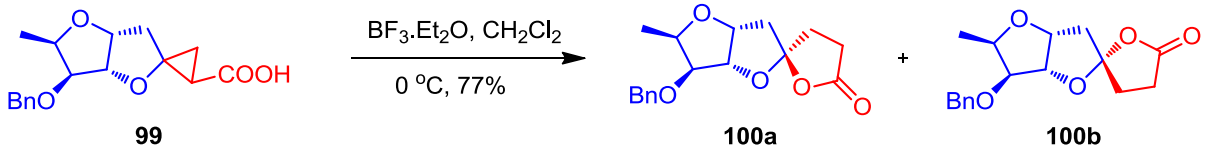


98 **99**

Compound **99** was synthesized using the spiro-cyclopropanecarboxylate sugar **98** (430 mg, 1.35 mmol) and 0.2 N LiOH (13.5 mL, 2.70 mmol) by following the procedure described for compound **64** (3.4.1.18). The obtained crude product was purified by silica-gel column chromatography in ethyl acetate/hexane (1:1) to provide the spiro-cyclopropanecarboxylic acid **99** (304 mg) in 74% yield as a mixture of diastereomers. **IR (neat)**: ν_{max} 3030, 2926, 2854,

1780, 1720, 1682, 1446, 1347, 1271, 1178, 1084, 1079, 909, 739, 701 cm^{-1}. **HRMS (ESI)** calcd for $C_{17}H_{20}O_5$+H 305.1389, found 305.1388.

(3.4.1.46) (2*R*,3a'*R*,5'*R*,6'*S*,6a'*S*)-6'-(benzyloxy)-5'-methyltetrahydro-3*H*,3'*H*-spiro[furan-2,2'-furo[3,2-*b*]furan]-5(4*H*)-one (100*a*) and (2*S*,3a'*R*,5'*R*,6'*S*,6a'*S*)-6'-(benzyloxy)-5'-methyltetrahydro-3*H*,3'*H*-spiro[furan-2,2'-furo[3,2-*b*]furan]-5(4*H*)-one (100*b*).

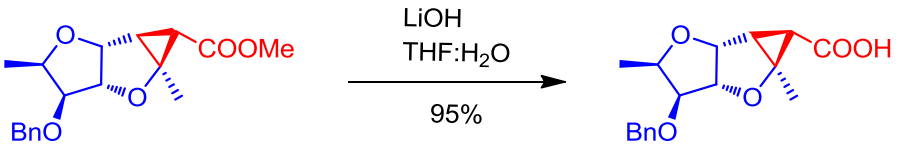


Compounds **100a** and **100b** were synthesized using spiro-cyclopropanecarboxylic acid **99** (65 mg, 0.21 mmol) and $BF_3.Et_2O$ (5.2 µL, 0.04 mmol) in dichloromethane (3 mL) following the procedure described for compound **65** (3.4.1.19). The crude product was purified by silica-gel column chromatography in ethyl acetate/hexane (3:7) to obtain the spiro-lactones **100a** and **100b** in 77% yield with 3:2 ratio respectively.

Data for compound 100a: **IR (neat)**: ν_{max} 3057, 3030, 2926, 2871, 1780, 1452, 1347, 1090, 1057, 898, 739, 701 cm^{-1}. **^{1}H NMR (400 MHz, $CDCl_3$)**: δ 7.29-7.35 (m, 5H), 5.01-5.04 (m,1H), 4.75 (d, 1H, *J* = 5.2 Hz), 4.71 (d, 1H, *J* = 12.0 Hz), 4.50 (d, 1H, *J* = 12.0 Hz), 4.07-409 (m, 1H), 3.75 (d, 1H, *J* = 3.6 Hz), 2.65-2.80 (m, 2H), 2.53 (ddd, 1H, *J* = 4.4 Hz, *J* = 7.6 Hz, *J* = 17.6 Hz), 2.32-2.37 (m, 2H), 2.08 (dd, 1H, *J* = 4.0 Hz, *J* = 14.8 Hz), 1.30 (d, 3H, *J* = 6.4 Hz). **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 175.6, 137.6, 128.4, 127.8, 127.6, 116.6, 86.7, 82.4, 80.3, 75.8, 71.7, 43.5, 31.2, 28.7, 13.4. **HRMS (ESI)** calcd for $C_{17}H_{20}O_5$+Na 327.1208, found 327.1208. $[\alpha]_D^{25}$ = -9.6 (*c* = 1.0, $CHCl_3$).

Data for compound 100b: **IR (neat)**: ν_{max} 3068, 3030, 2931, 1780, 1495, 1457, 1347, 1189, 1073, 904, 838, 745, 706 cm^{-1}. **^{1}H NMR (400 MHz, $CDCl_3$)**: δ 7.29-7.35 (m, 5H), 5.02-5.29 (m, 1H), 4.75 (d, 1H, *J* = 5.2 Hz), 4.71 (d, 1H, *J* = 12.4 Hz), 4.49 (d, 1H, *J* = 12.4 Hz), 4.03-4.14 (m, 1H), 3.74 (d, 1H, *J* = 3.2 Hz), 2.65-2.80 (m, 2H), 2.53 (ddd, 1H, *J* = 4.8 Hz, *J* = 7.6 Hz, *J* = 18.0 Hz), 2.32-2.37 (m, 2H), 2.08 (dd, 1H, *J* = 4.0 Hz, *J* = 14.8 Hz), 1.30 (d, 3H, *J* = 6.0 Hz). **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 175.7, 137.8, 128.4, 127.8, 127.5, 116.4, 89.8, 84.0, 80.2, 76.5, 72.1, 44.3, 33.1, 28.6, 14.0. **HRMS (ESI)** calcd for $C_{17}H_{20}O_5$+Na 327.1208, found 327.1211. $[\alpha]_D^{25}$ = -8.3 (*c* = 1.0, $CHCl_3$).

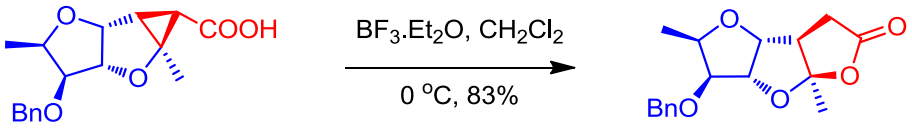
(3.4.1.47) (2*R*,3*S*,3a*S*,4a*S*,5*R*,5a*R*,5b*R*)-3-(benzyloxy)-2,4a-dimethylhexahydro-2*H*-cyclopropa[*b*]furo[2,3-*d*]furan-5-carboxylic acid:



90 **101**

Compound **101** was synthesized using the spiro-cyclopropanecarboxylate sugar **90** (300 mg, 0.94 mmol) and 0.2 N LiOH (4.7 mL, 0.94 mmol) by following the procedure described for compound **64** (3.4.1.18). The obtained crude product was purified by silica-gel column chromatography in ethyl acetate/hexane (1:1) to provide the spiro-cyclopropanecarboxylic acid **101** (250 mg) in 95% yield. **IR (neat)**: ν_{max} 3063, 3030, 2926, 2865, 1720, 1687, 1463, 1331, 1227, 1084, 860, 734 cm^{-1}. **^{1}H NMR (400 MHz, $CDCl_3$)**: δ 7.28-7.35 (m, 5H), 5.82 (d, 1H, *J* = 6.0 Hz), 4.94 (d, 1H, *J* = 4.8 Hz), 4.65 (d, 1H, *J* = 12.0 Hz), 4.49 (d, 1H, *J* = 12.4 Hz), 4.29 (d, 1H, *J* = 4.4 Hz), 4.09 (d, 1H, *J* = 4.0 Hz), 3.68 (s, 1H), 2.26 (d, 1H, *J* = 4.0 Hz), 1.64 (s, 3H), 1.31 (d, 3H, *J* = 6.0 Hz), 0.88 (t, 1H, *J* = 5.2 Hz). **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 175.6, 137.7, 128.4, 127.9, 127.6, 85.7, 84.3, 83.5, 76.4, 74.1, 71.9, 34.2, 27.9, 13.5, 13.3. **HRMS (ESI)** calcd for $C_{17}H_{20}O_5$+Na 327.1208, found 327.1206.

(3.4.1.48) (2*R*,3*S*,3a*S*,4a*R*,7a*R*,7b*R*)-3-(benzyloxy)-2,4a-dimethylhexahydrodifuro[2,3-b:2',3'-*d*]furan-6(2*H*)-one:

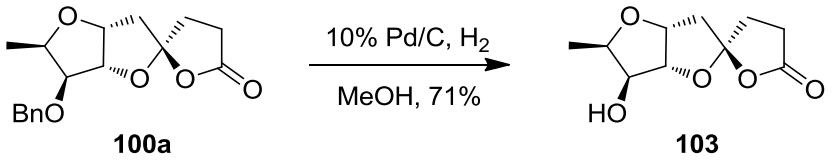


101 **102**

Compound **102** was synthesized using spiro-cyclopropanecarboxylic acid **101** (200 mg, 0.65 mmol) and $BF_3.Et_2O$ (16.23 µl, 0.13 mmol) in dichloromethane (6 mL) following the procedure described for compound **65** (3.4.1.19). The crude product was purified by silica-gel column chromatography in ethyl acetate/hexane (3:7) to obtain the linearly fused tricyclic lactone **102** (165 mg) in 83% yield. **IR (neat)**: ν_{max} 3068, 3024, 2931, 2849, 1775, 1501, 1446, 1386, 1243, 1090, 1030, 909, 843, 728 cm^{-1}. **^{1}H NMR (500 MHz, $CDCl_3$)**: δ 7.29-7.36 (m, 5H), 4.76 (d,

1H, *J* = 4.0 Hz), 4.69 (d, 1H, *J* = 12.0 Hz), 4.55 (d, 1H, *J* = 4.0 Hz), 4.53 (d, 1H, *J* = 12.0 Hz), 4.23-4.27 (m, 1H), 3.91 (d, 1H, *J* = 3.5 Hz), 2.96 (dd, 1H, *J* = 11.0 Hz, *J* = 18.5 Hz), 2.88 (dd, 1H, *J* = 2.5 Hz, *J* = 11.0 Hz), 2.60 (dd, 1H, *J* = 3.0 Hz, *J* = 18.5 Hz), 1.68 (s, 3H), 1.29 (d, 3H, *J* = 6.5 Hz). **^{13}C NMR (125 MHz, CDCl$_3$)**: δ 173.5, 137.4, 128.5, 127.9, 127.6, 118.2, 88.1, 86.1, 82.1, 72.2, 51.1, 33.8, 24.0, 13.8. **HRMS (ESI)** calcd for $C_{17}H_{20}O_5$+Na 327.1208, found 327.1210. $[\alpha]_D^{25}$ = -44.1 (*c* = 1.0, $CHCl_3$).

(3.4.1.49) (2*R*,3a'*R*,5'*R*,6'*S*,6a'*R*)-6'-hydroxy-5'-methyltetrahydro-3H,3'*H*-spiro[furan-2,2'-furo[3,2-*b*]furan]-5(4*H*)-one:

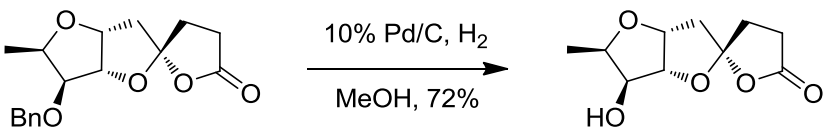


100a **103**

2,3-dihydro pyrenolide D

To a stirred solution of compound **100a** (40 mg, 0.13 mmol), in MeOH (5 mL) was hydrogenated over 10% Pd/C (5 mg), under hydrogen atmosphere for 4 h at 25 °C. The catalyst was filtered off and the filtrate was concentrated. The crude product was purified by silica-gel column chromatography using hexane/ethyl acetate (containing 1% triethylamine) to give 2,3-dihydro-pyrenolide D **103** (20 mg, 71%) as colourless solid. **IR (neat)**: ν_{max} 3424, 2942, 2871, 1780, 1649, 1446, 1194, 1052, 898, 816 cm^{-1}. **^{1}H NMR (400 MHz, CDCl$_3$)**: δ 5.01-5.05 (m, 1H), 4.63 (d, 1H, *J* = 5.2 Hz), 4.02-4.08 (m, 2H), 2.68-2.83 (m, 2H), 2.55 (ddd, 1H, *J* = 3.2 Hz, *J* = 8.8 Hz, *J* = 17.6 Hz), 2.34-2.43 (m, 2H), 2.10 (dd, 1H, *J* = 4.0 Hz, *J* = 14.8 Hz), 1.30 (d, 3H, *J* = 6.0 Hz). **^{13}C NMR (100 MHz, CDCl$_3$)**: δ 175.7, 116.6, 89.4, 79.9, 76.0, 75.4, 43.4, 31.1, 28.7, 12.8. **HRMS (ESI)** calcd for $C_{10}H_{14}O_5$+Na 237.0739, found 237.0741. $[\alpha]_D^{25}$ = +10.1 (*c* = 1.0, $CHCl_3$).

(3.4.1.50) (2*S*,3a'*R*,5'*R*,6'*S*,6a'*R*)-6'-hydroxy-5'-methyltetrahydro-3*H*,3'*H*-spiro[furan-2,2'-furo[3,2-*b*]furan]-5(4*H*)-one:

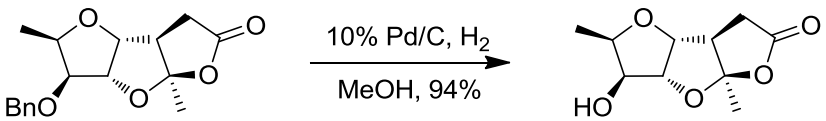


100b **104**

2,3-dihydro 4-*epi*-pyrenolide D

To a stirred solution of compound **100b** (20 mg, 0.06 mmol), in MeOH (3 ml) was hydrogenated over 10% Pd/C (4 mg) under hydrogen atmosphere for 4 h at 25 °C. The catalyst was filtered off and the filtrate was concentrated. The crude product was purified by silica-gel column chromatography using hexane/ethyl acetate (containing 1% triethylamine) to give the 4-*epi*-2,3-dihydro-pyrenolide D **104** (10 mg, 72%) as colourless solid. **IR (neat)**: ν_{max} 3419, 2936, 2871, 1764, 1736, 1643, 1441, 1276, 1194, 1057, 893, 816 cm^{-1}. **^{1}H NMR (400 MHz, $CDCl_3$)**: δ 4.93 (t, 1H, *J* = 5.6 Hz), 4.68 (d, 1H, *J* = 4.8 Hz), 4.59-4.66 (m, 1H), 4.11 (d, 1H, *J* = 2.8 Hz), 2.77 (dt, 1H, *J* = 10.0 Hz, *J* = 17.6 Hz), 2.60 (d, 1H, *J* = 15.2 Hz), 2.53 (ddd, 1H, *J* = 4.4 Hz, *J* = 6.8 Hz, *J* = 17.6 Hz), 2.34 (dd, 1H, *J* = 3.2 Hz, *J* = 10.0 Hz), 2.32 (d, 1H, *J* = 10.0 Hz), 2.18-2.25 (m, 1H), 1.27 (d, 3H, *J* = 6.4 Hz). **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 175.8, 116.5, 92.2, 80.2, 77.1, 76.4, 44.3, 33.2, 28.6, 13.4. **HRMS (ESI)** calcd for $C_{10}H_{14}O_5$+Na 237.0739, found 237.0739. $[\alpha]_D^{25}$ = +6.1 (*c* = 1.0, $CHCl_3$).

(3.4.1.51) (2*R*,3*S*,3a*R*,4a*R*,7a*R*,7b*R*)-3-hydroxy-2,4a-dimethylhexahydrodifuro[2,3-*b*:2',3'-*d*]furan-6(2*H*)-one:



102 **105**

To a stirred solution of compound **102** (30 mg, 0.09 mmol), in MeOH (4 mL) was hydrogenated over 10% Pd/C (5 mg) under hydrogen atmosphere for 4 h at 25°C. The catalyst was filtered off and the filtrate was concentrated. The crude product was purified by silica-gel column chromatography using hexane/ethyl acetate (containing 1% triethylamine) to give the product **105** (20 mg, 94%) as colourless solid. **IR (neat)**: ν_{max} 3424, 2926, 2865, 2854, 1775, 1501, 1452, 1386, 1249, 1084, 1035, 920, 838, 734, 701 cm^{-1}. **^{1}H NMR (400 MHz, $CDCl_3$)**: δ 4.63 (d, 1H, *J* = 4.60 Hz), 4.56 (d, 1H, *J* = 3.6 Hz), 4.17-4.23 (m, 2H), 2.97 (dd, 1H, *J* = 10.8 Hz, *J* = 18.4 Hz), 2.87(dd, 1H, *J* = 2.4 Hz, *J* = 10.8 Hz), 2.61 (dd, 1H, *J* = 2.8 Hz, *J* = 18.4 Hz), 2.23 (d, 1H, *J* = 4.8 Hz), 1.68 (s, 3H), 1.28 (d, 3H, *J* = 6.0 Hz). **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 173.7, 118.4, 88.7, 87.9, 77.4, 75.6, 51.2, 33.9, 24.0, 13.2. **HRMS (ESI)** calcd for $C_{10}H_{14}O_5$+Na 237.0739, found 237.0735. $[\alpha]_D^{25}$ = -11.9 (*c* = 1.0, $CHCl_3$).

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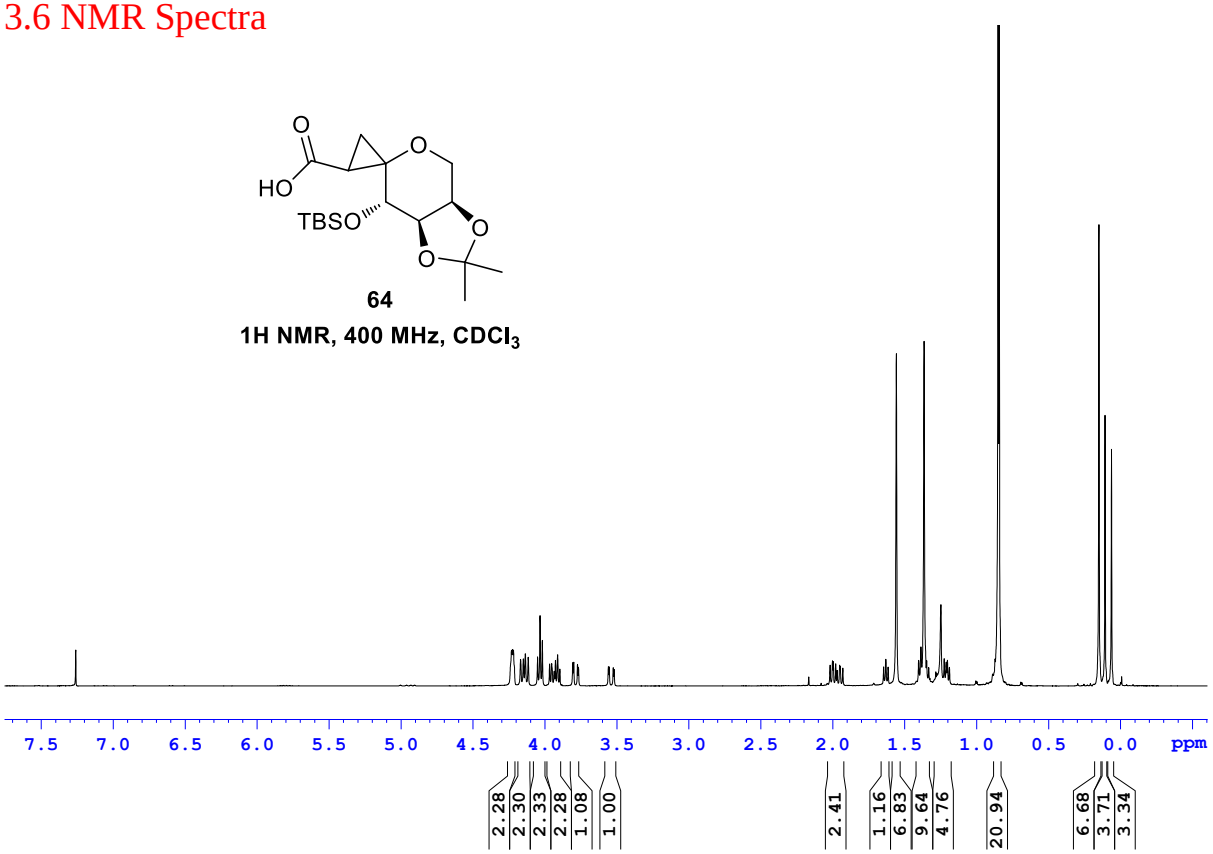
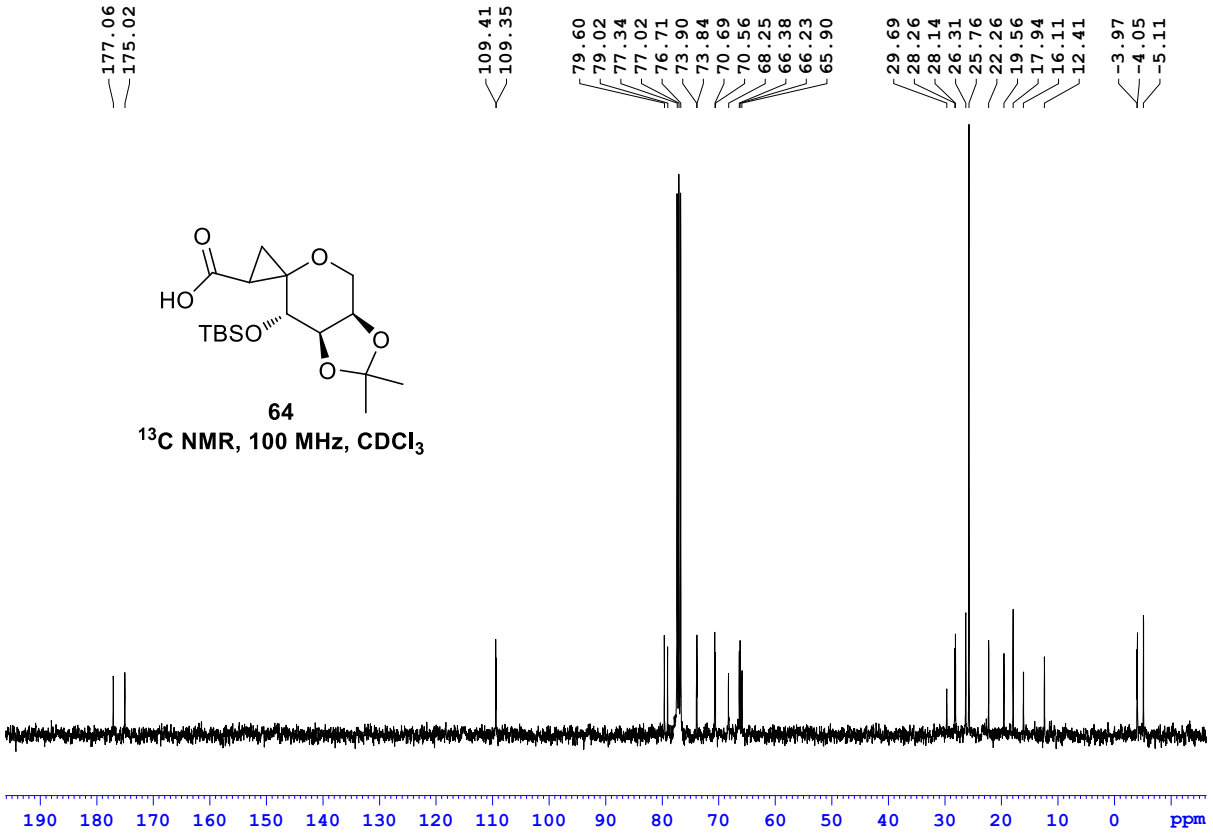
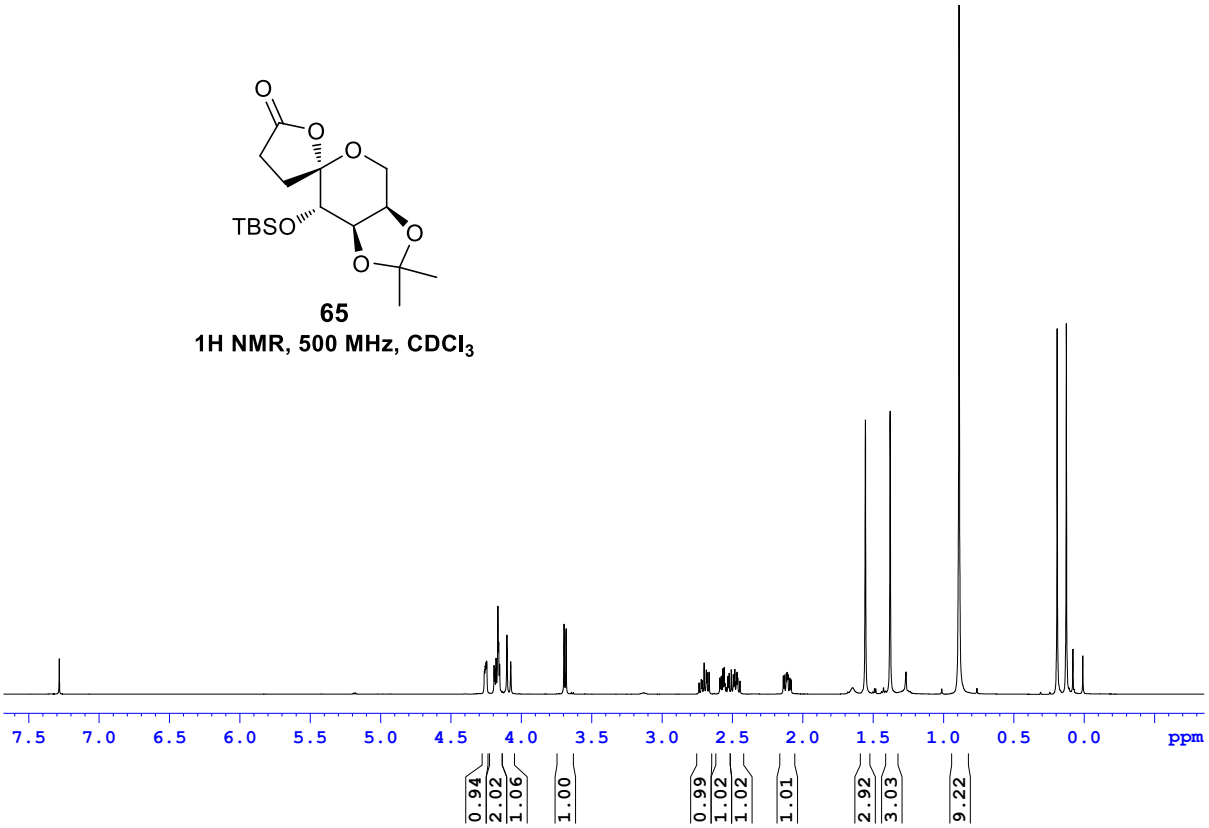
37. Compound **90** was obtained by cyclopropanation of the corresponding *endo*-glycal, which was obtained by the isomerization of *exo*-glycal precursor for the synthesis of **98** under chromatographic purification over neutral alumina. Please see the experimental section.
38. For isolation: a) Nukina, M.; Hirota, H.; *Biosci. Biotech. Biochem.* **1992**, *56*, 1158-1159. For total synthesis: b) Engstrom, K. M.; Mendoza, M. R.; Navarro-Villalobos, M.; Gin, D. Y. *Angew. Chem. Int. Ed.* **2001**, *40*, 1128-1130. For synthesis of analogues, see: (c) Robertson, J.; Stevens, K.; Naud, S. *Synlett.* **2008**, 2083-2086

3.6 NMR Spectra

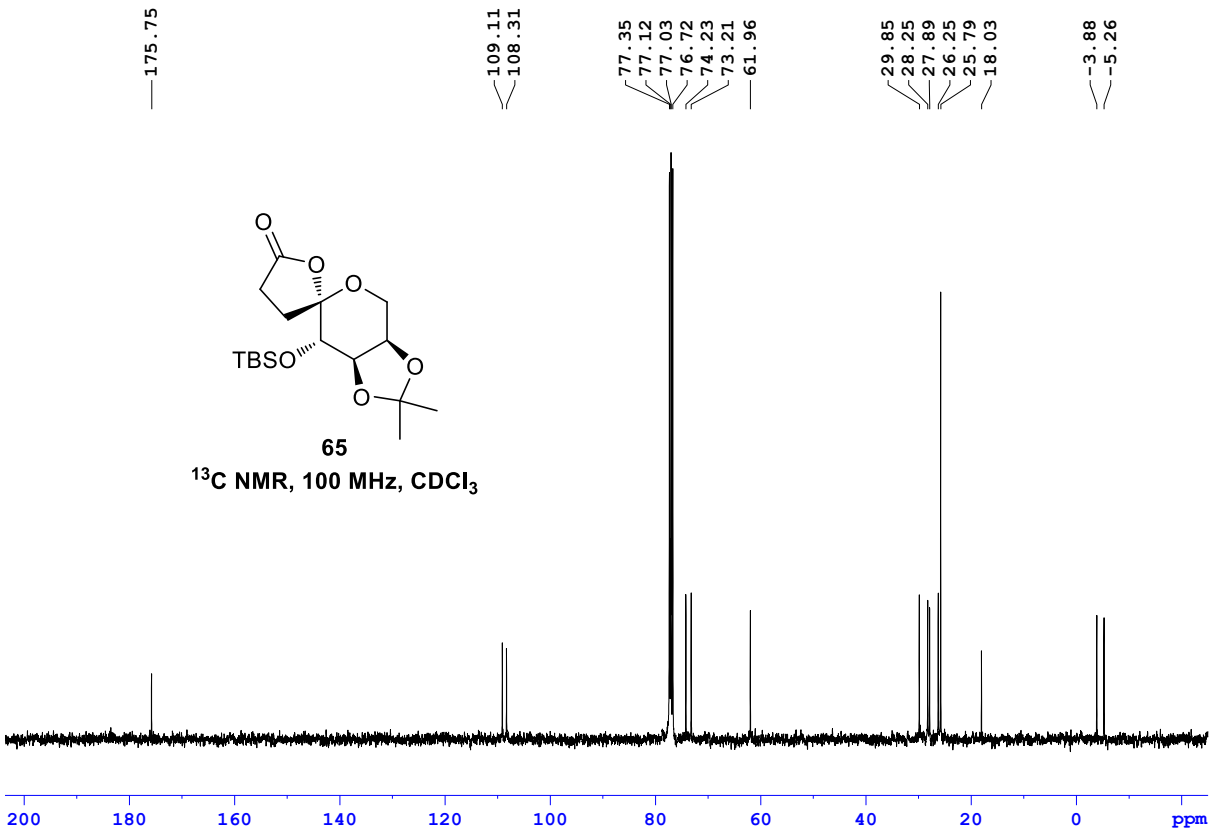






65

1H NMR, 500 MHz, $CDCl_3$



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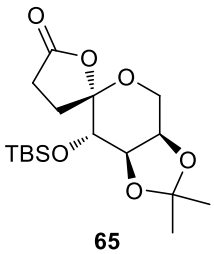
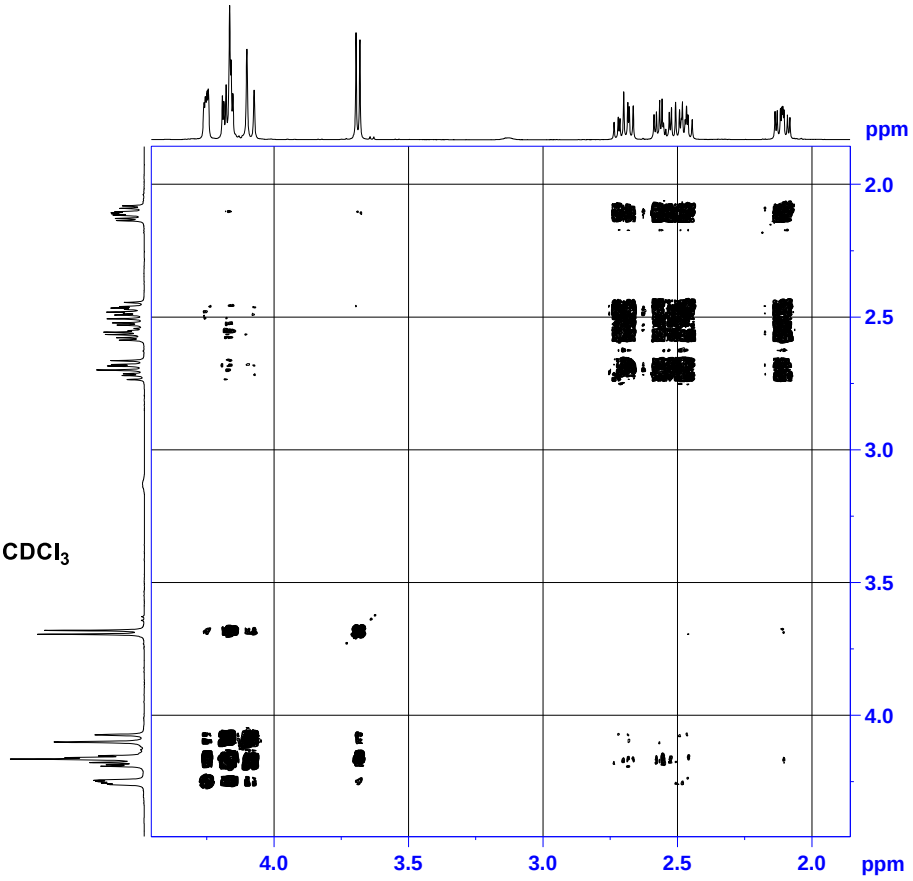
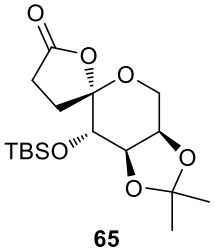
^{13}C NMR, 100 MHz, $CDCl_3$



65

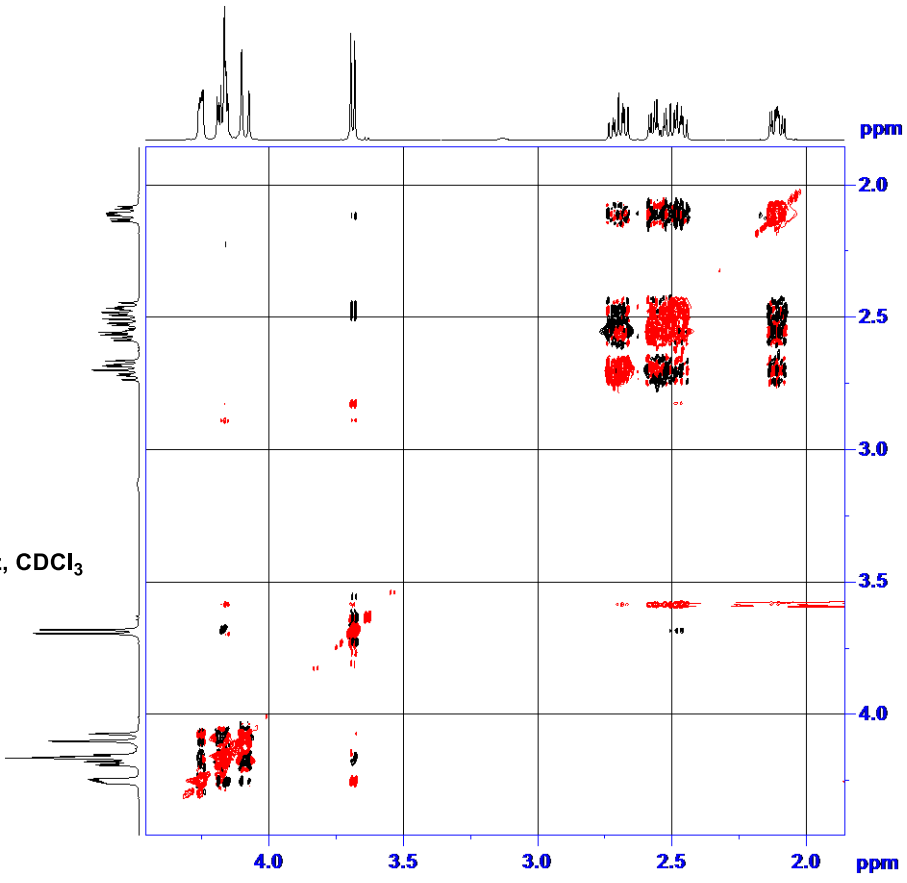
^{1}H-^{1}H COSY NMR, 500 MHz, $CDCl_3$

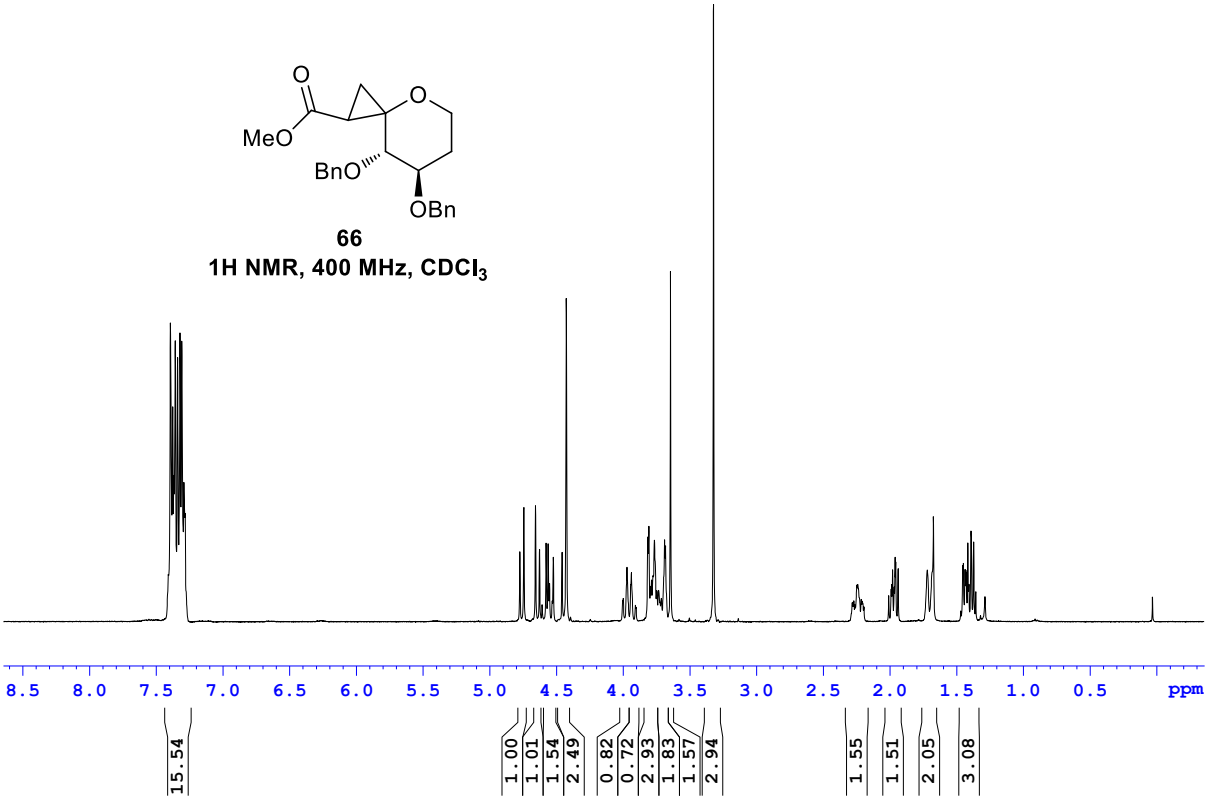


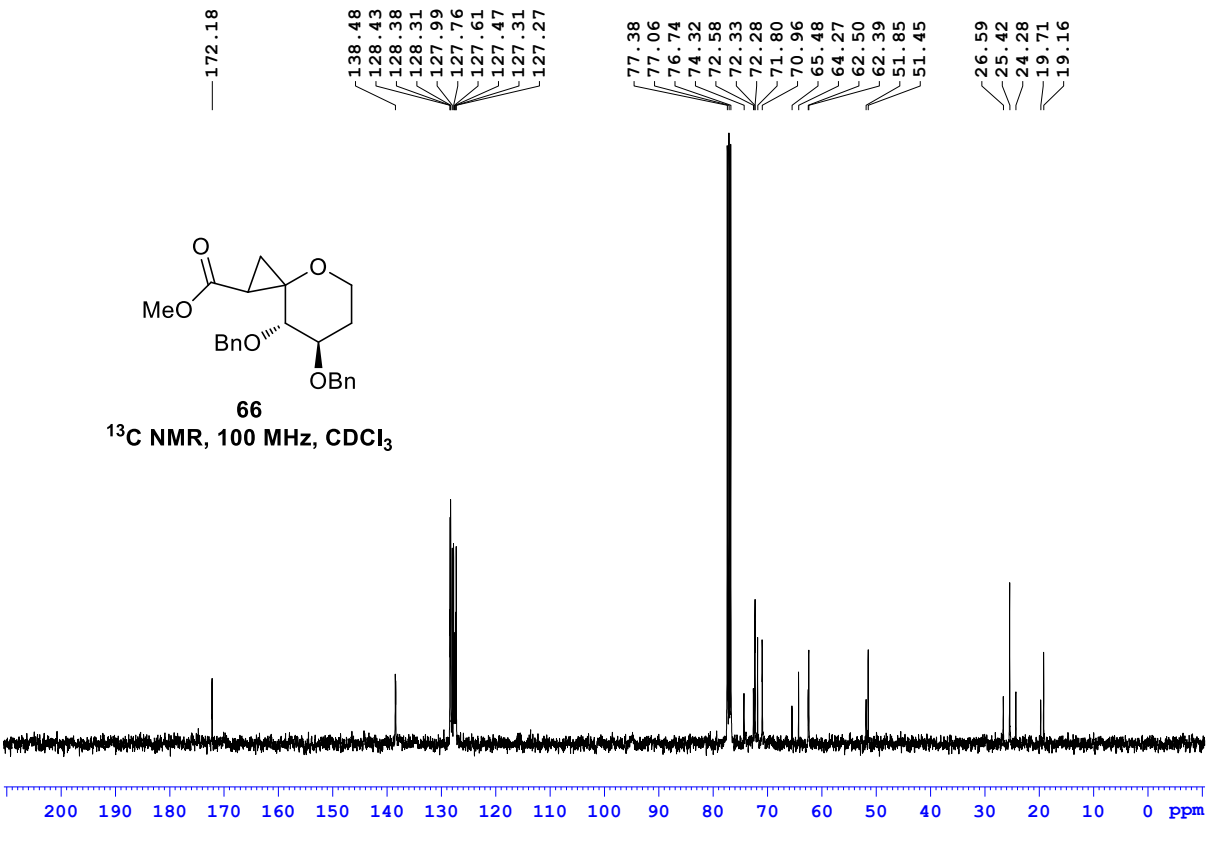


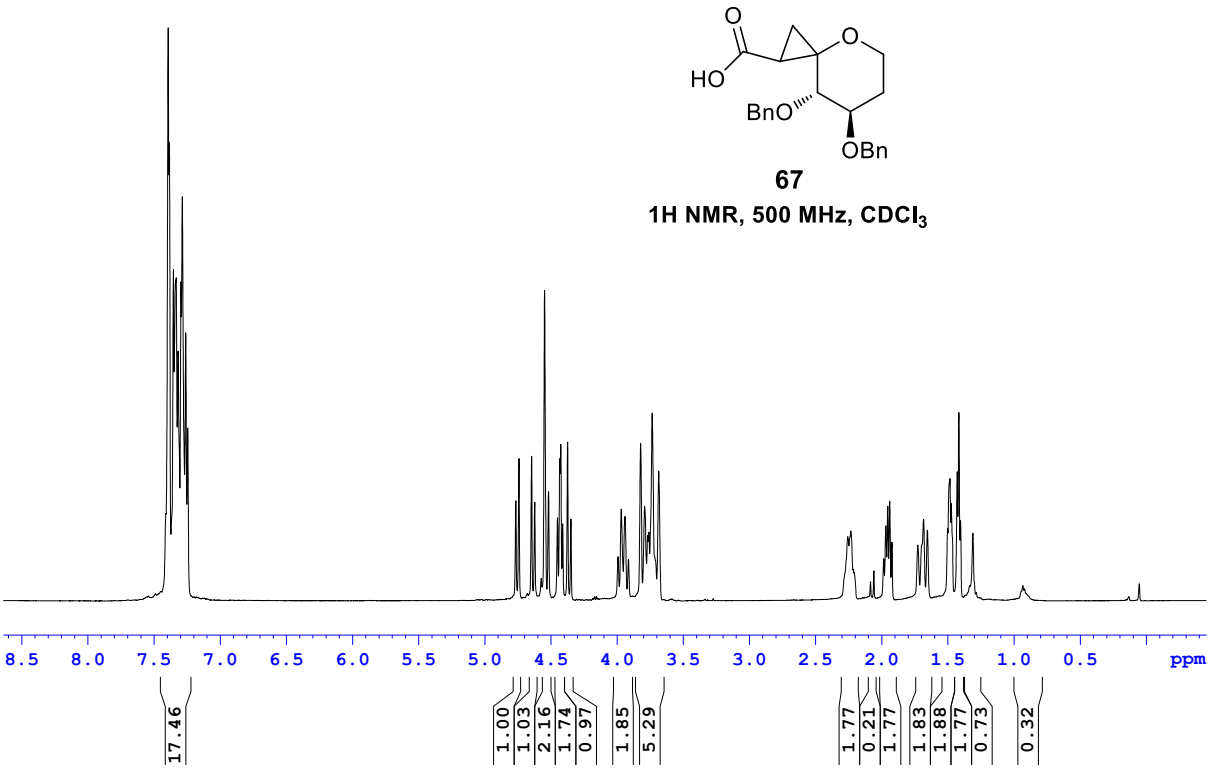
65

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



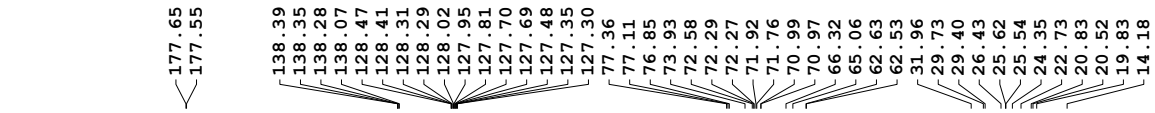

MeO
BnO
OBn
66
1H NMR, 400 MHz, CDCl3
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
15.54
1.00 1.01 1.54 2.49
0.82 0.72 2.93 1.83 1.57 2.94
1.55 1.51 2.05 3.08

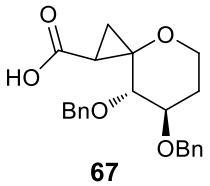

172.18
138.48 128.43 128.38 128.31 127.99 127.76 127.61 127.47 127.31 127.27
77.38 77.06 76.74 74.32 72.58 72.33 72.28 71.80 70.96 65.48 64.27 62.50 62.39 51.85 51.45
26.59 25.42 24.28 19.71 19.16
MeO
BnO
OBn
66
13C NMR, 100 MHz, CDCl3
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm



67

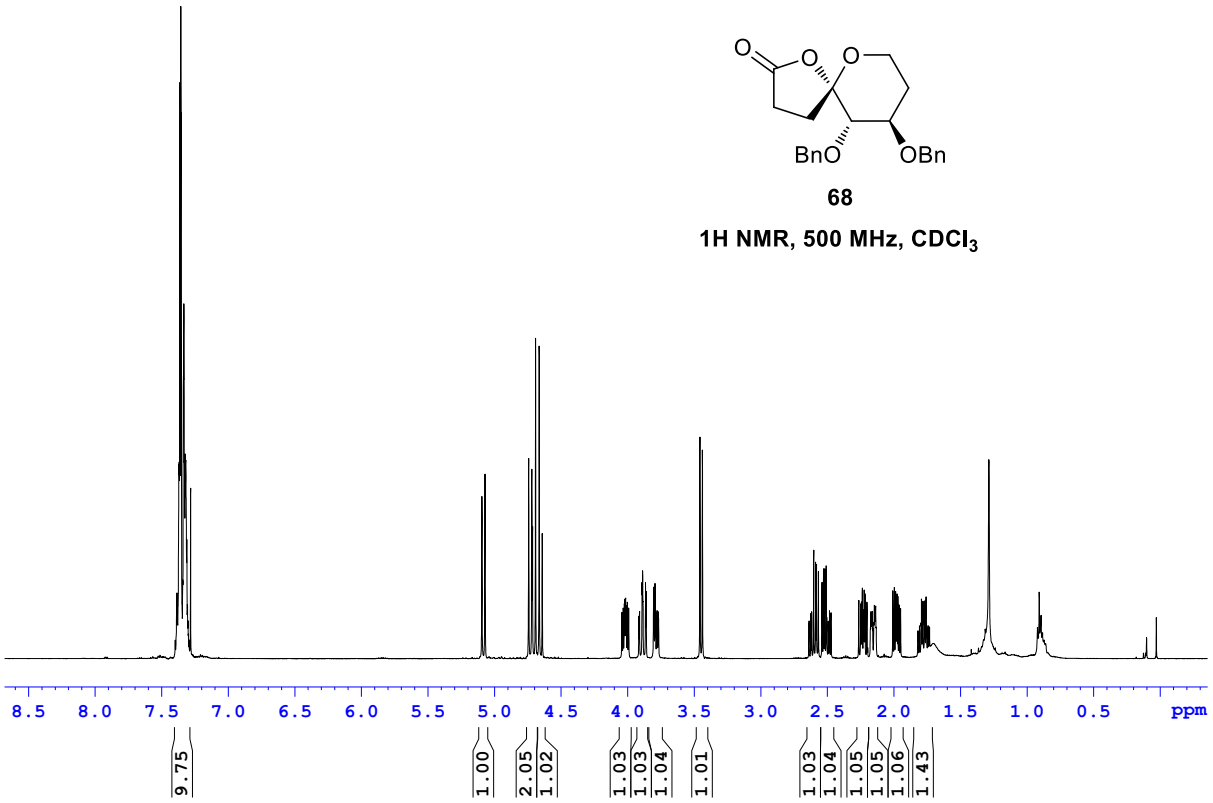
1H NMR, 500 MHz, $CDCl_3$

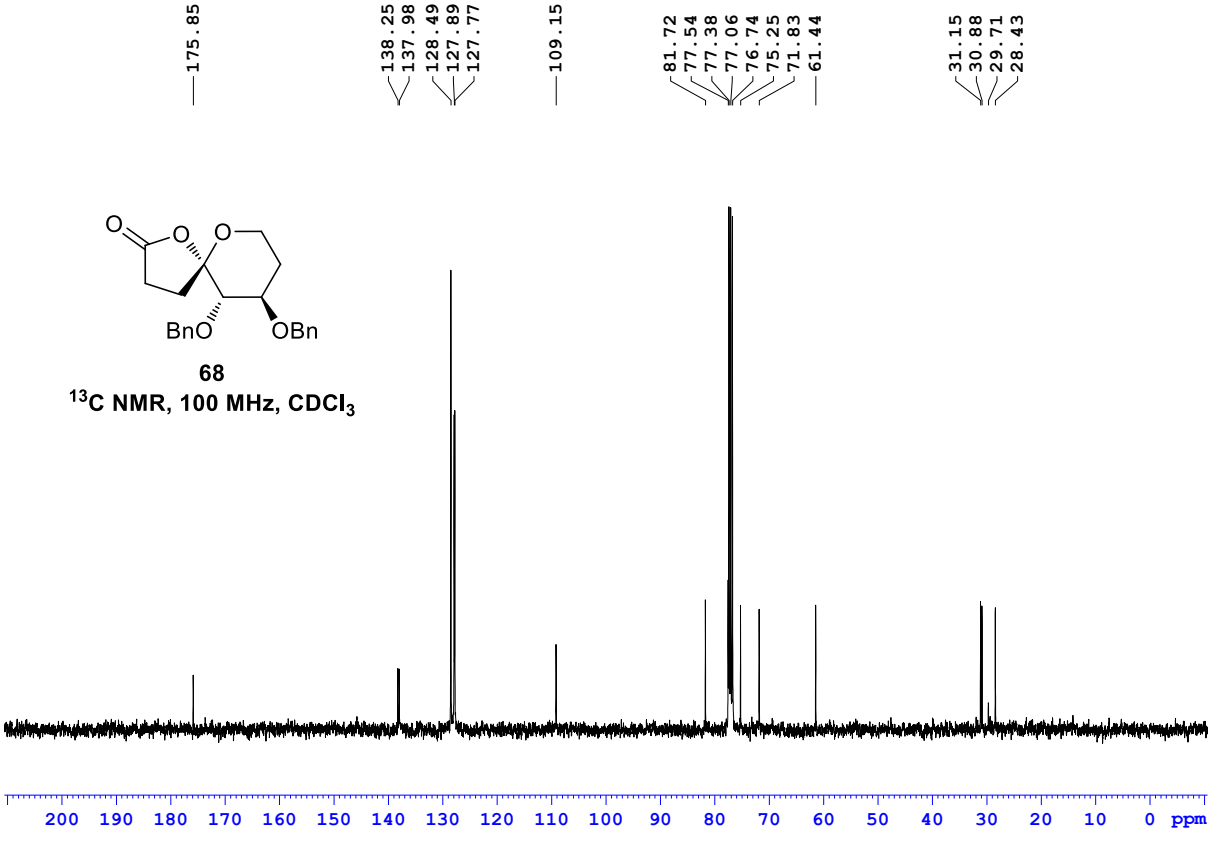


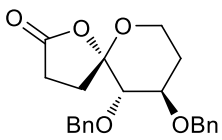


67

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

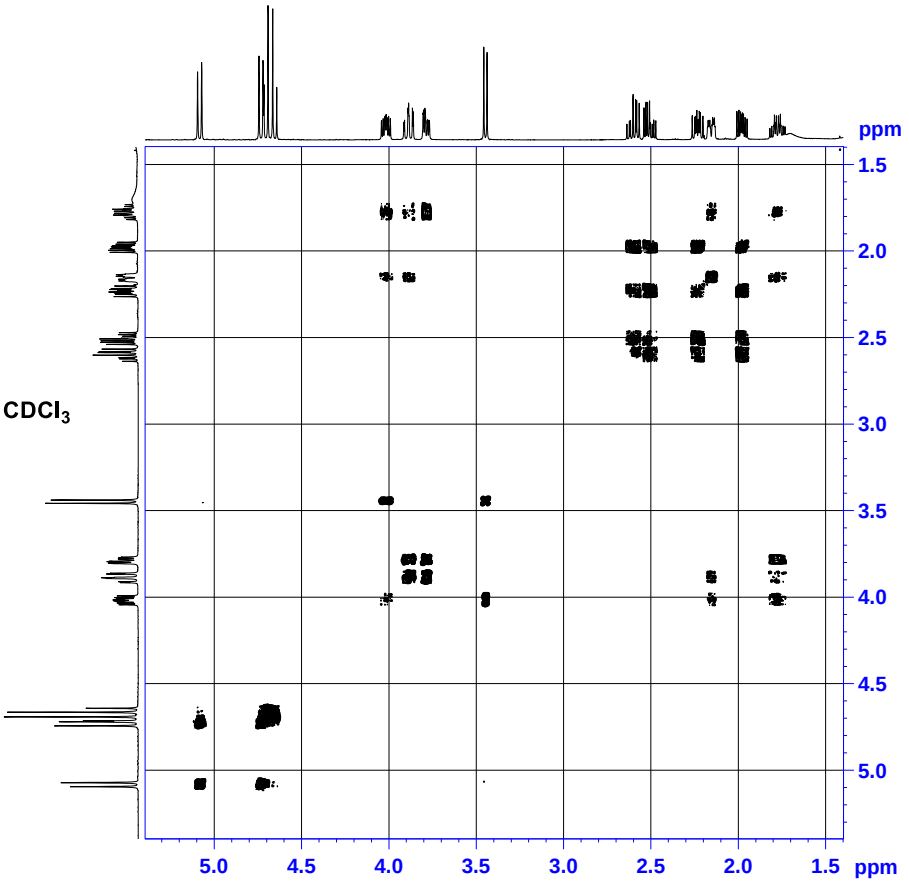

BnO
OBn
68
1H NMR, 500 MHz, CDCl3
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
9.75
1.00
2.05
1.02
1.03
1.03
1.04
1.01
1.03
1.04
1.05
1.05
1.06
1.43

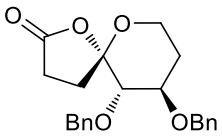

175.85
138.25
137.98
128.49
127.89
127.77
109.15
81.72
77.54
77.38
77.06
76.74
75.25
71.83
61.44
31.15
30.88
29.71
28.43
BnO
OBn
68
13C NMR, 100 MHz, CDCl3
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm



68

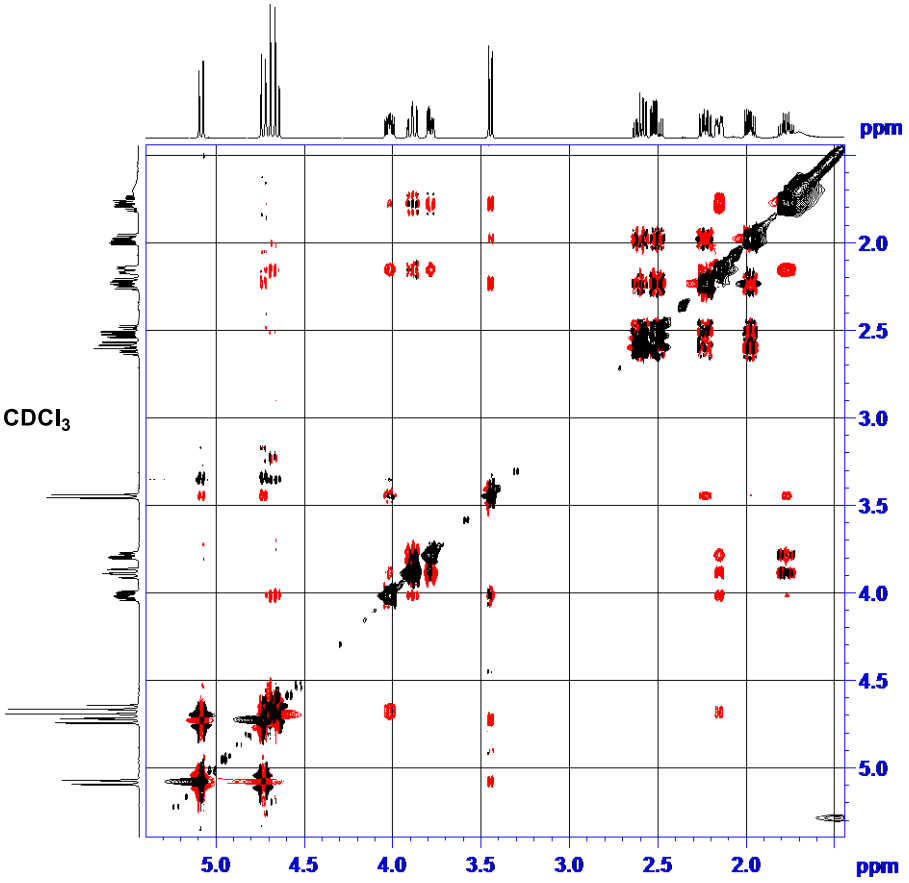
^{1}H-^{1}H COSY NMR, 500 MHz, $CDCl_3$

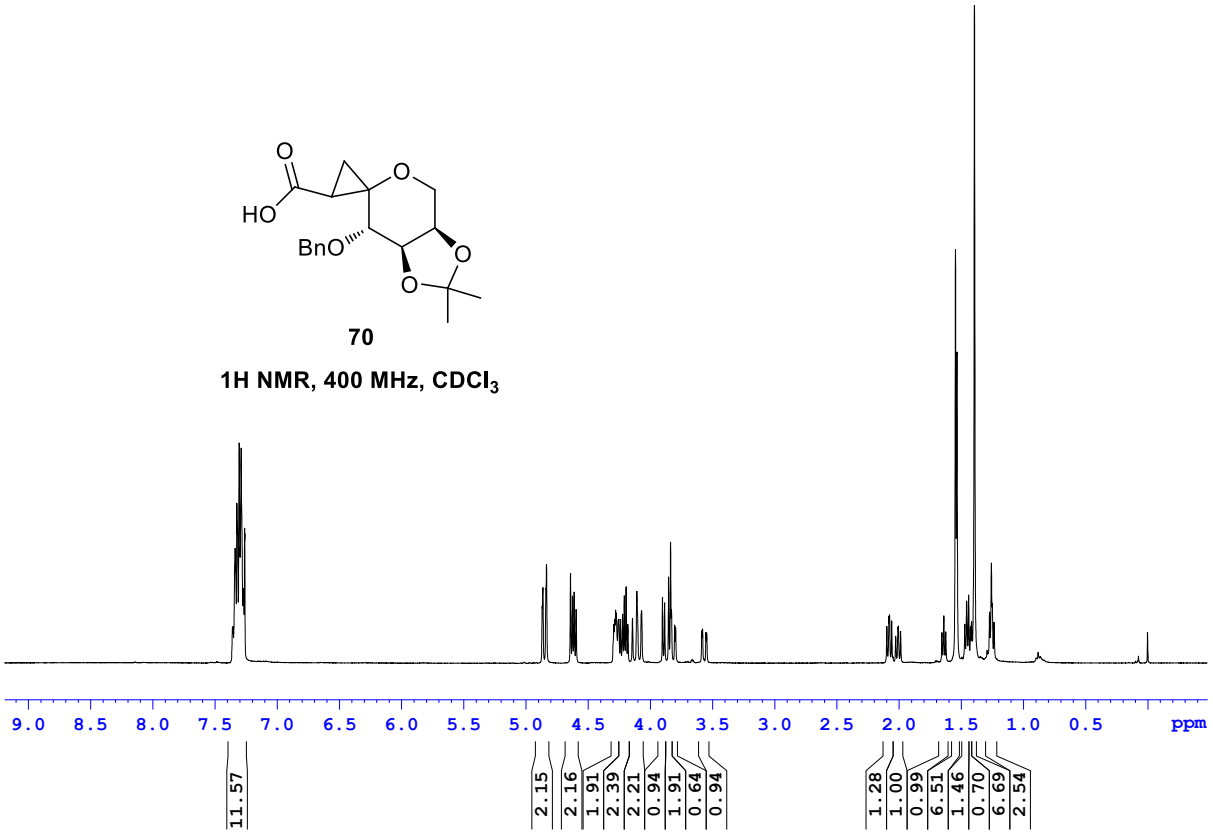




68

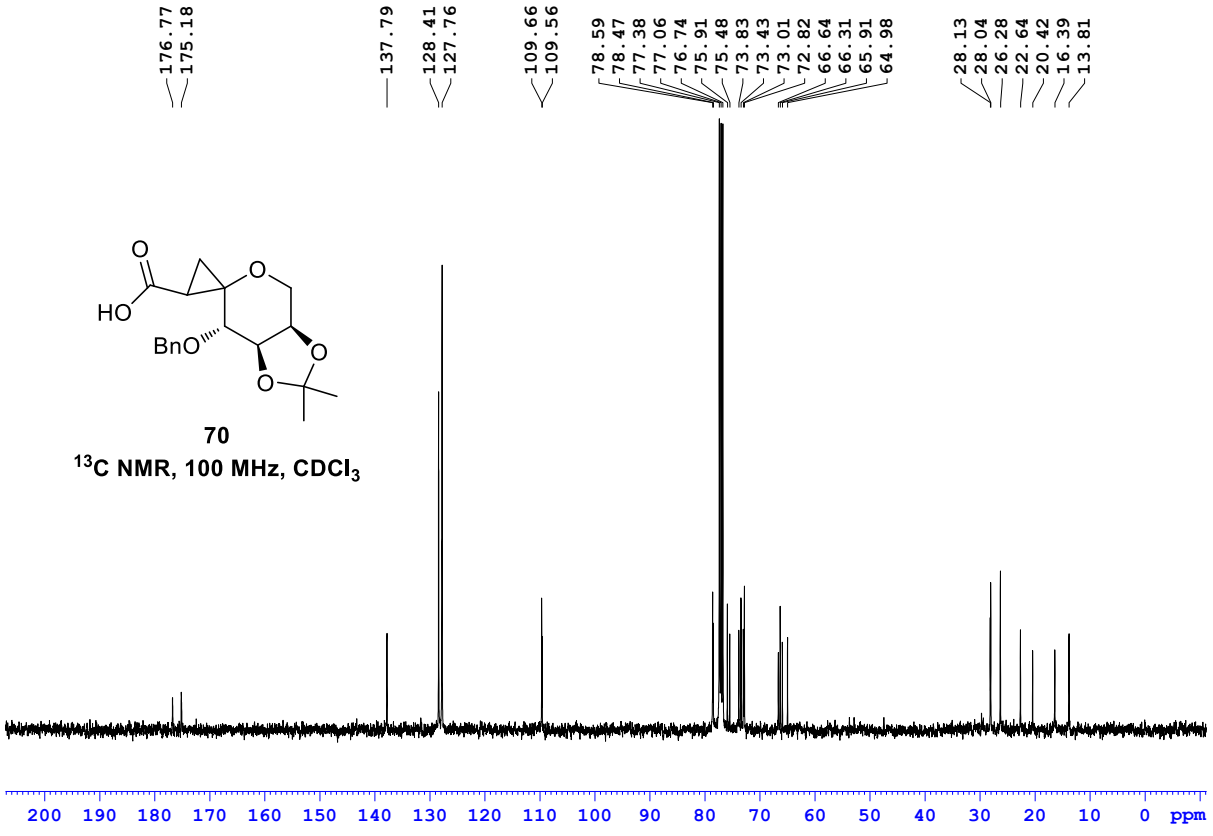
^{1}H-^{1}H NOESY NMR, 500 MHz, $CDCl_3$





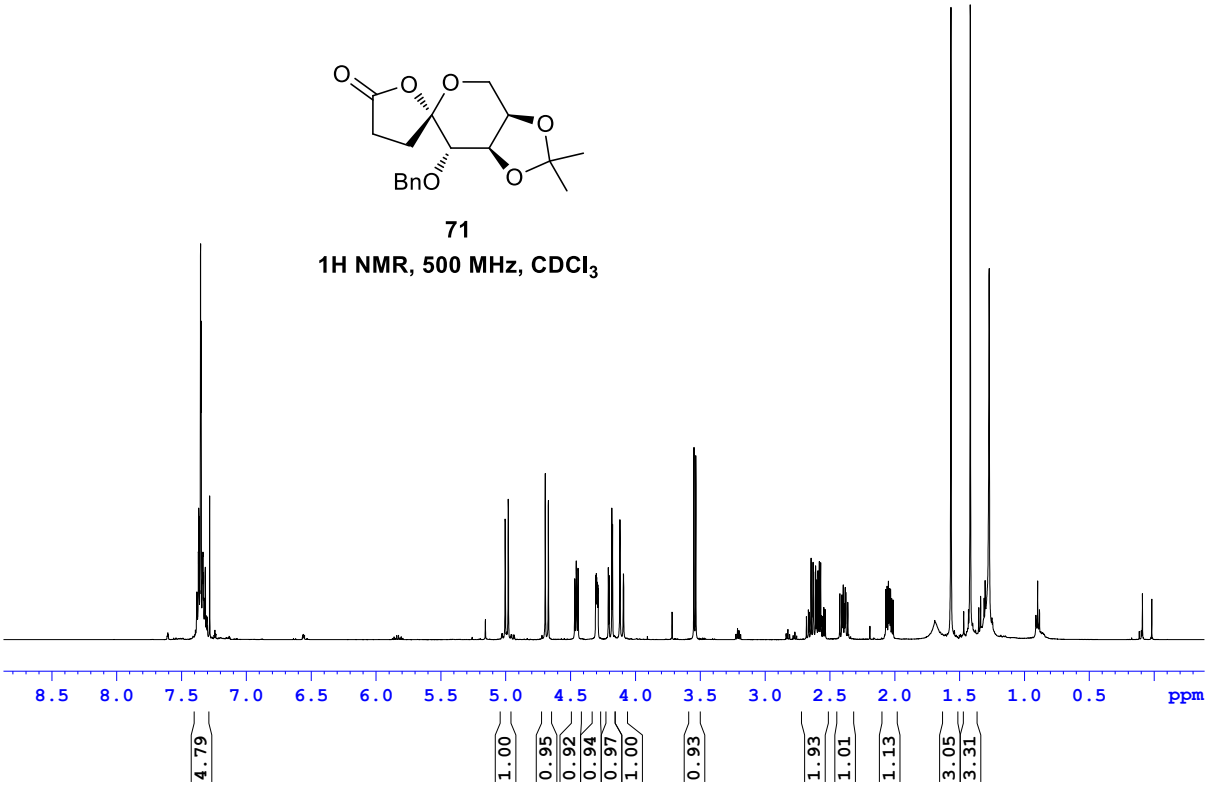
70

1H NMR, 400 MHz, $CDCl_3$



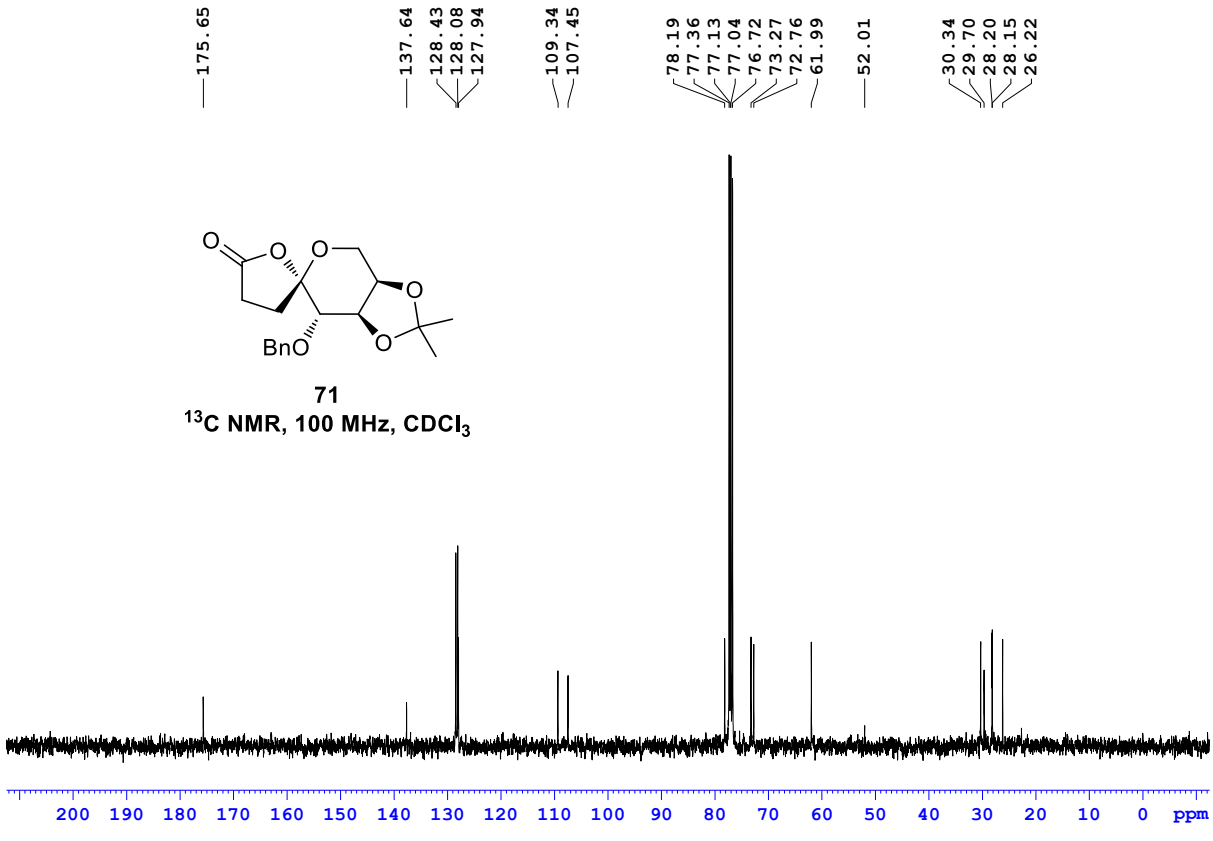
70

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



71

1H NMR, 500 MHz, $CDCl_3$



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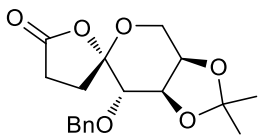
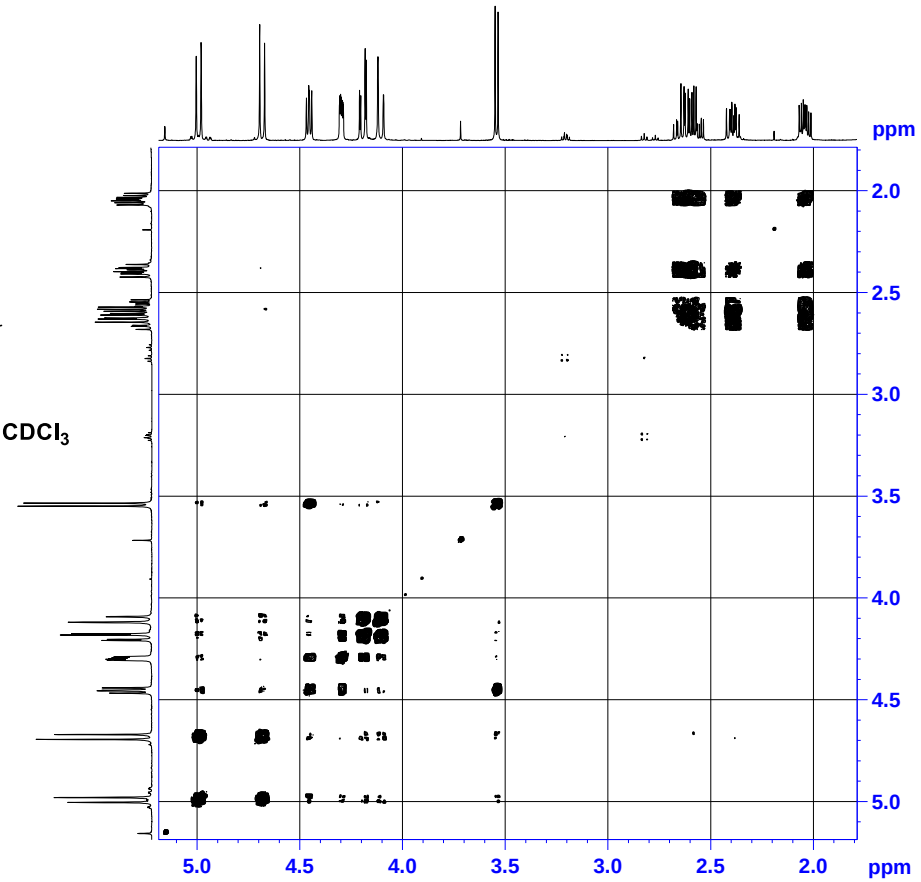
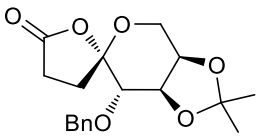


71

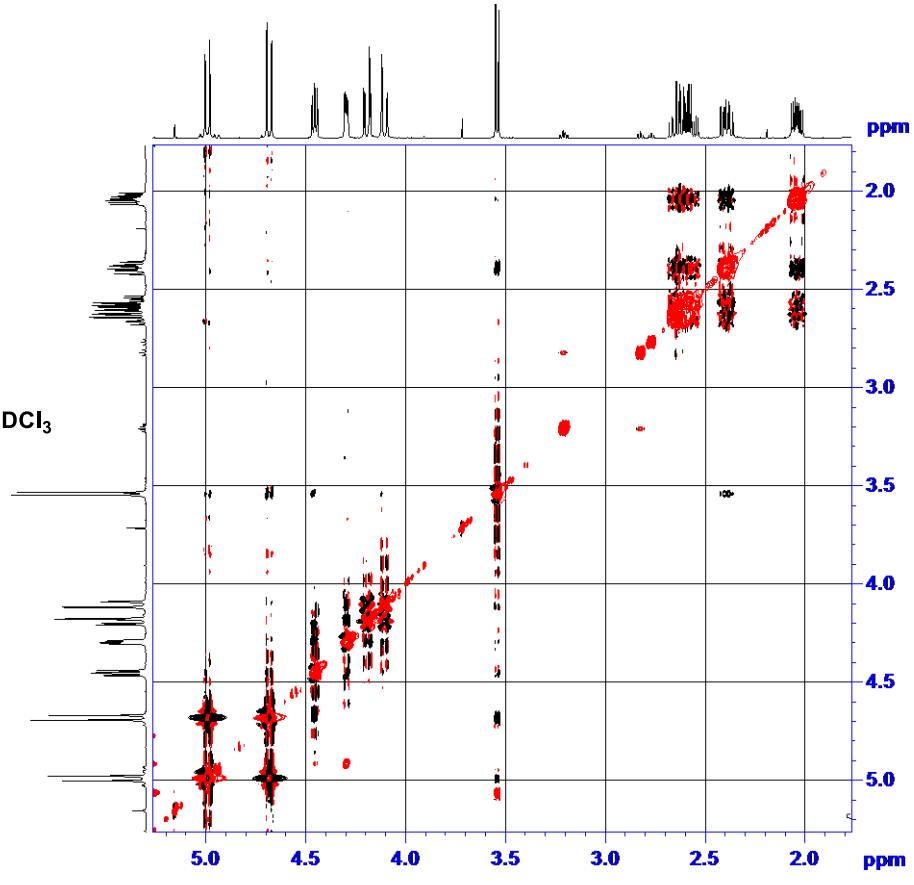
^{1}H-^{1}H COSY NMR, 500 MHz, $CDCl_3$

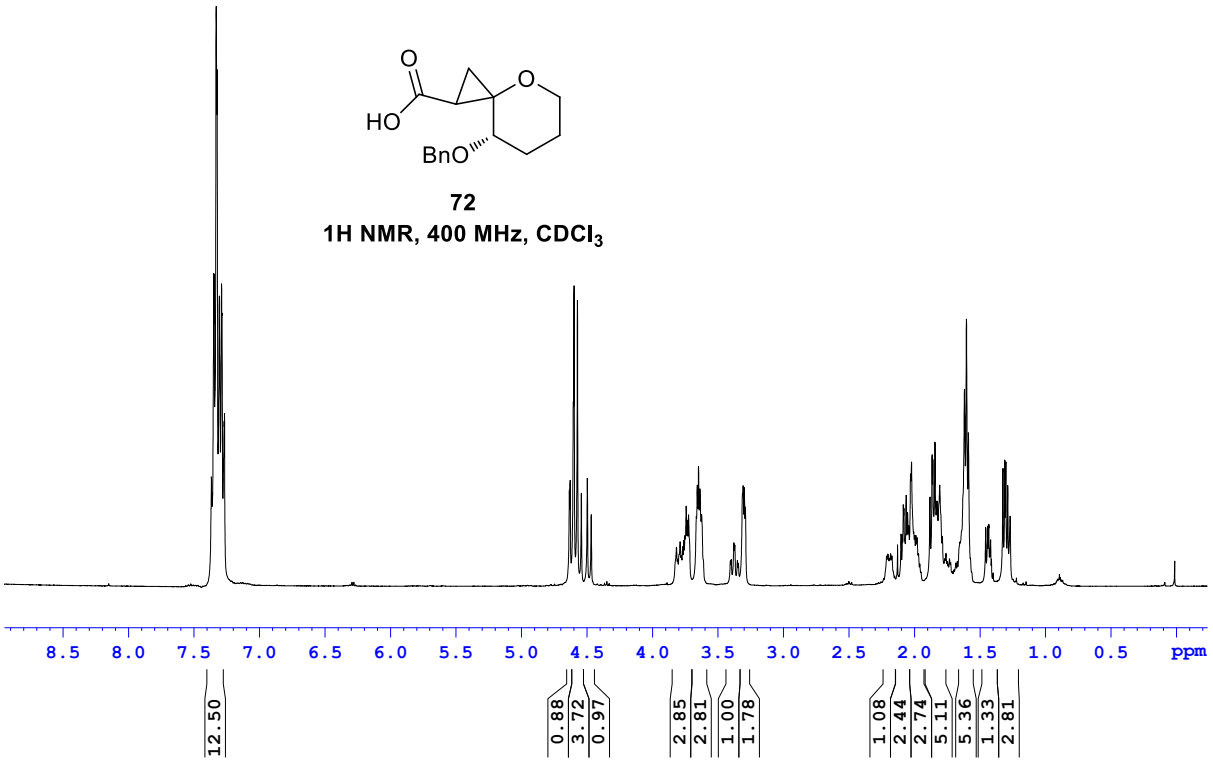




71

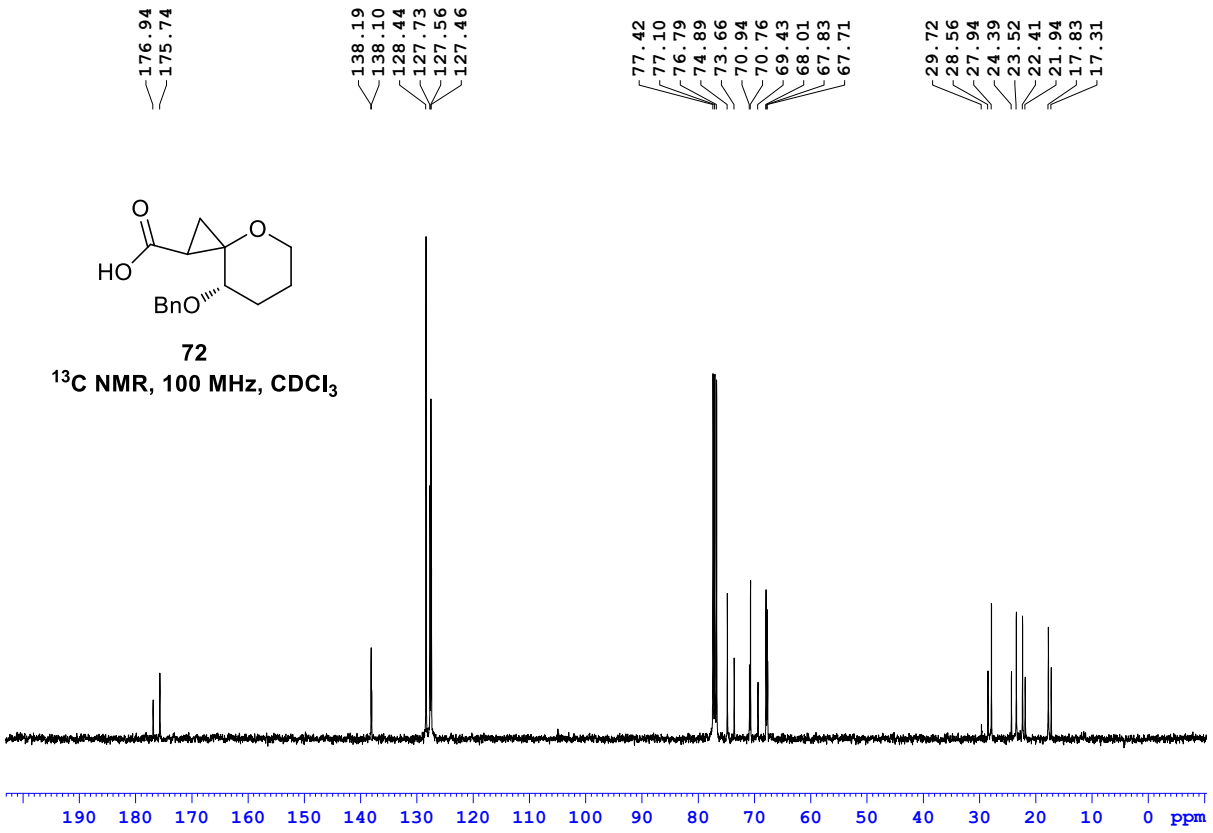
^{1}H-^{1}H NOESY NMR, 500 MHz, $CDCl_3$





72

1H NMR, 400 MHz, $CDCl_3$



72

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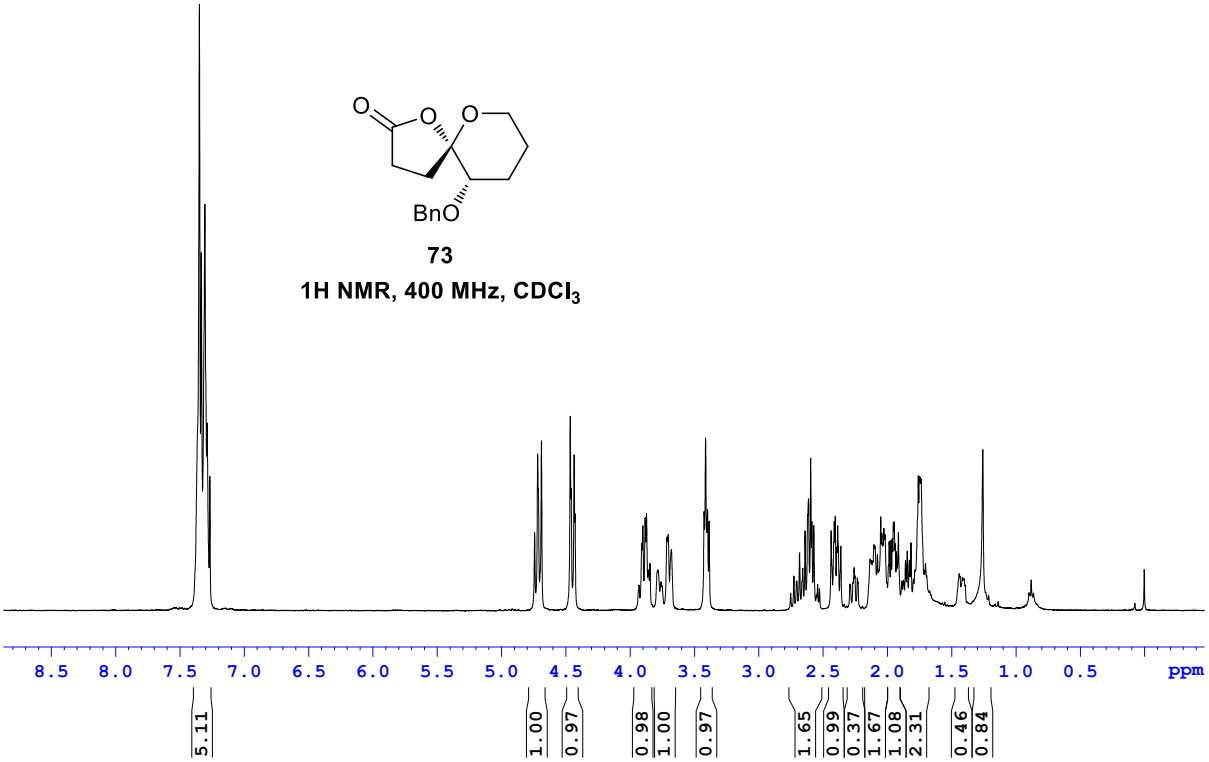
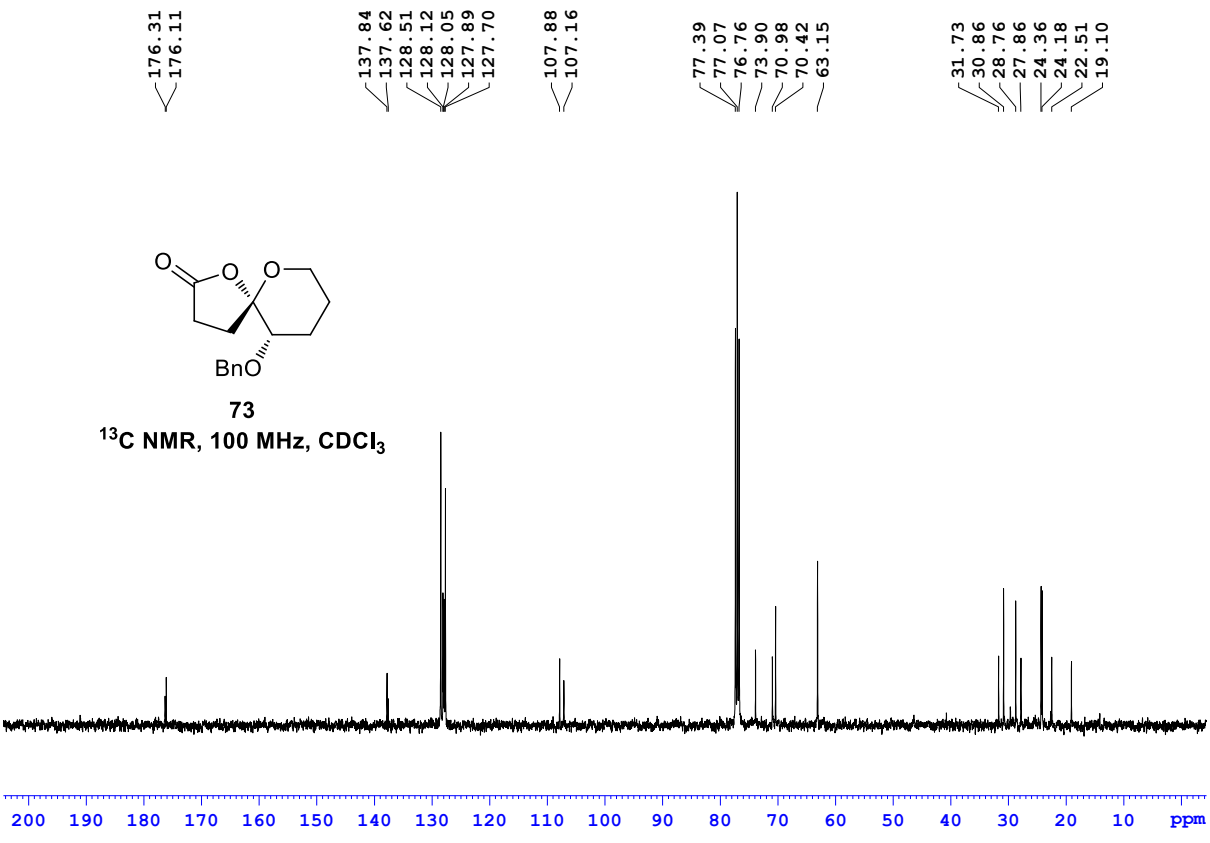


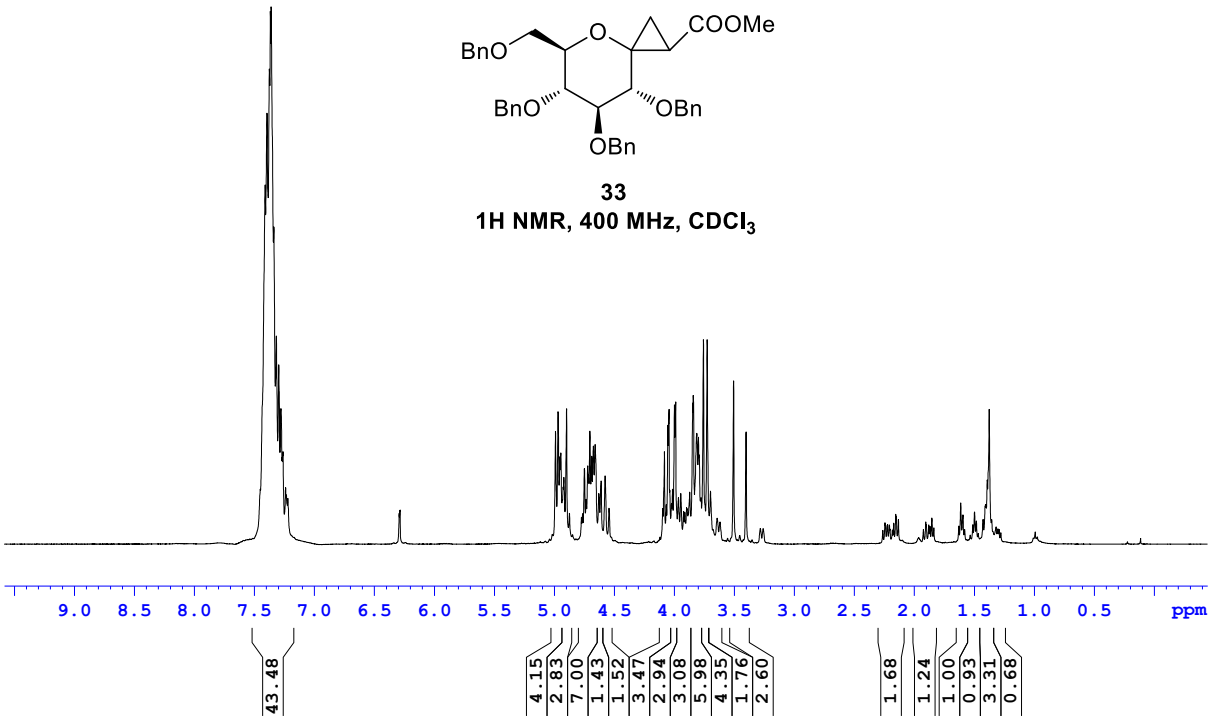
73

1H NMR, 400 MHz, $CDCl_3$

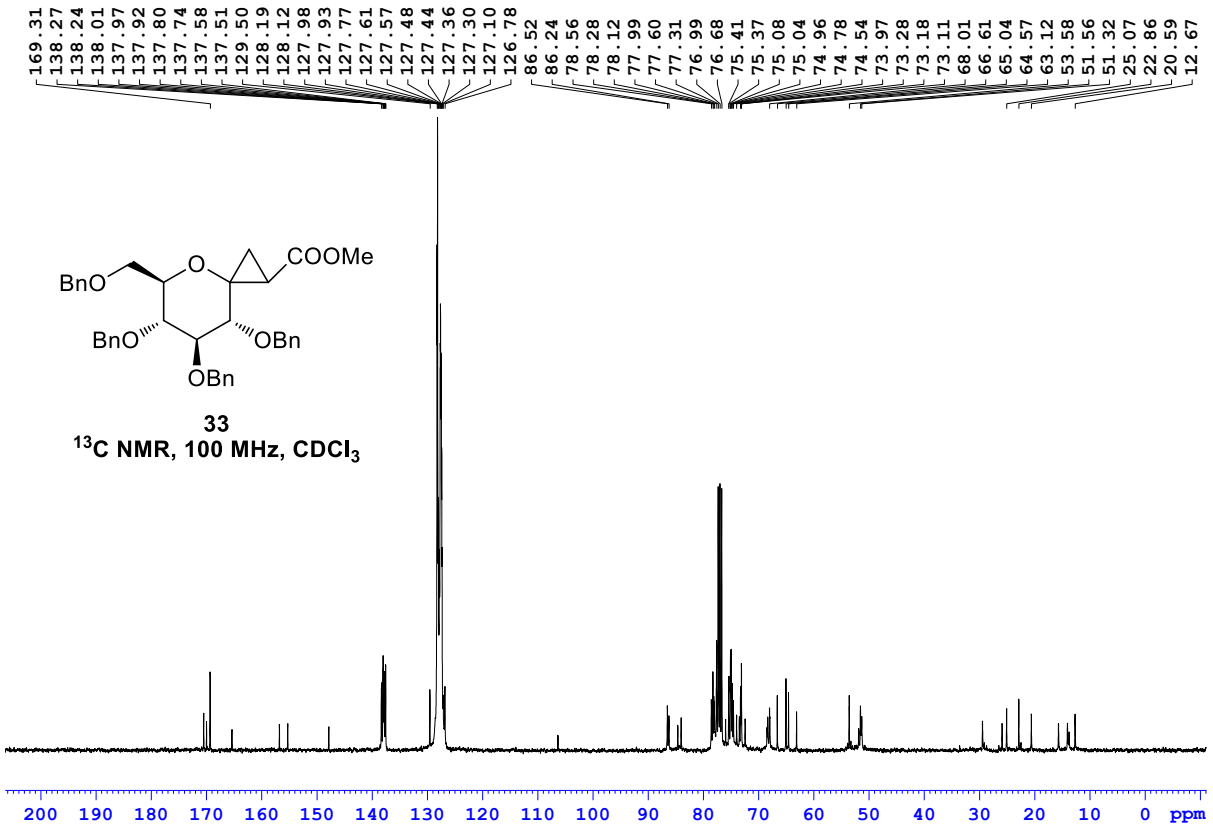


73

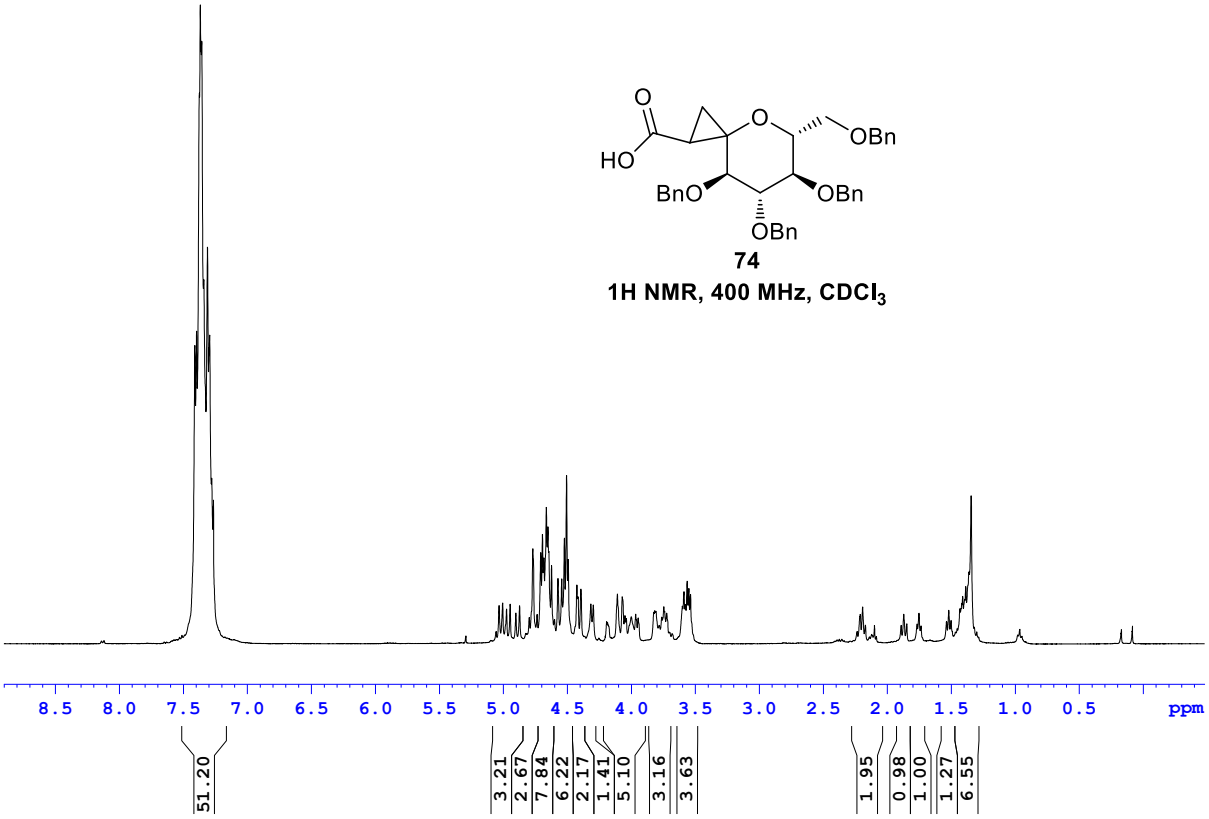
^{13}C NMR, 100 MHz, $CDCl_3$



33
1H NMR, 400 MHz, $CDCl_3$

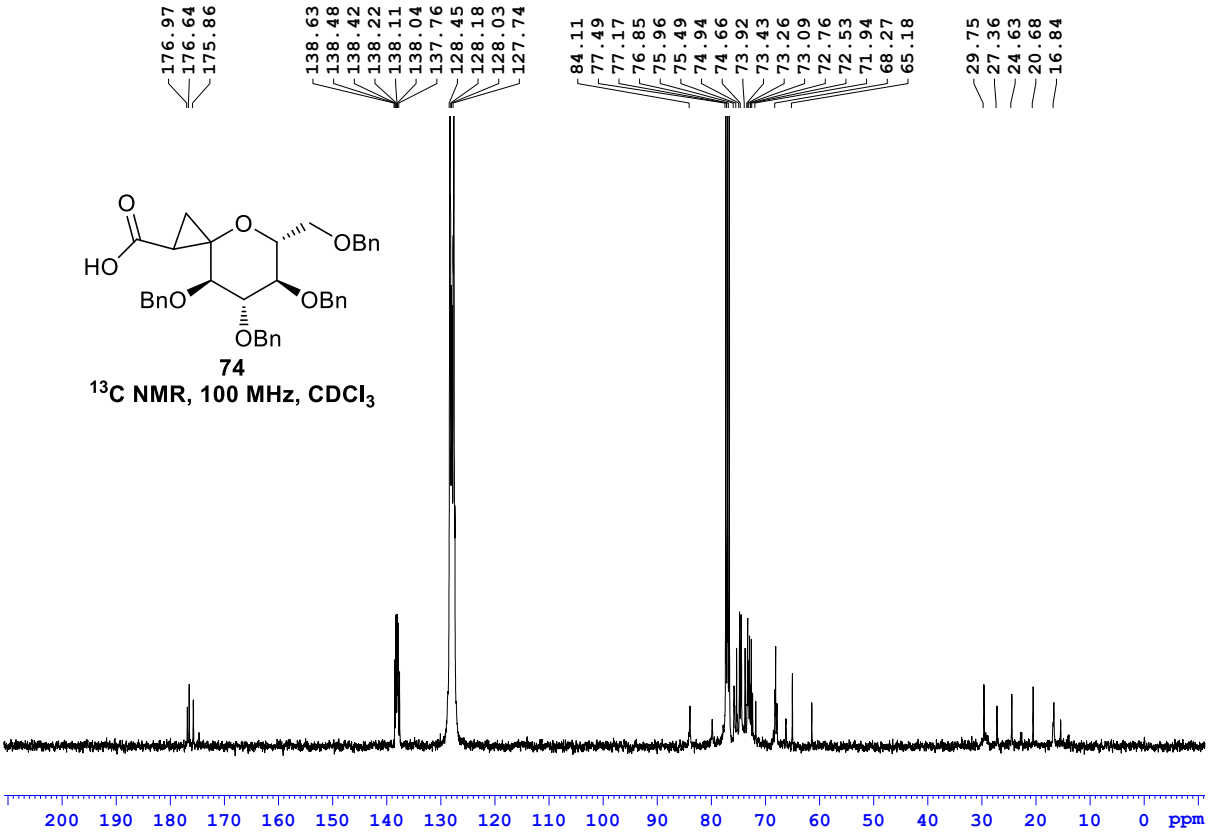


33
^{13}C NMR, 100 MHz, $CDCl_3$



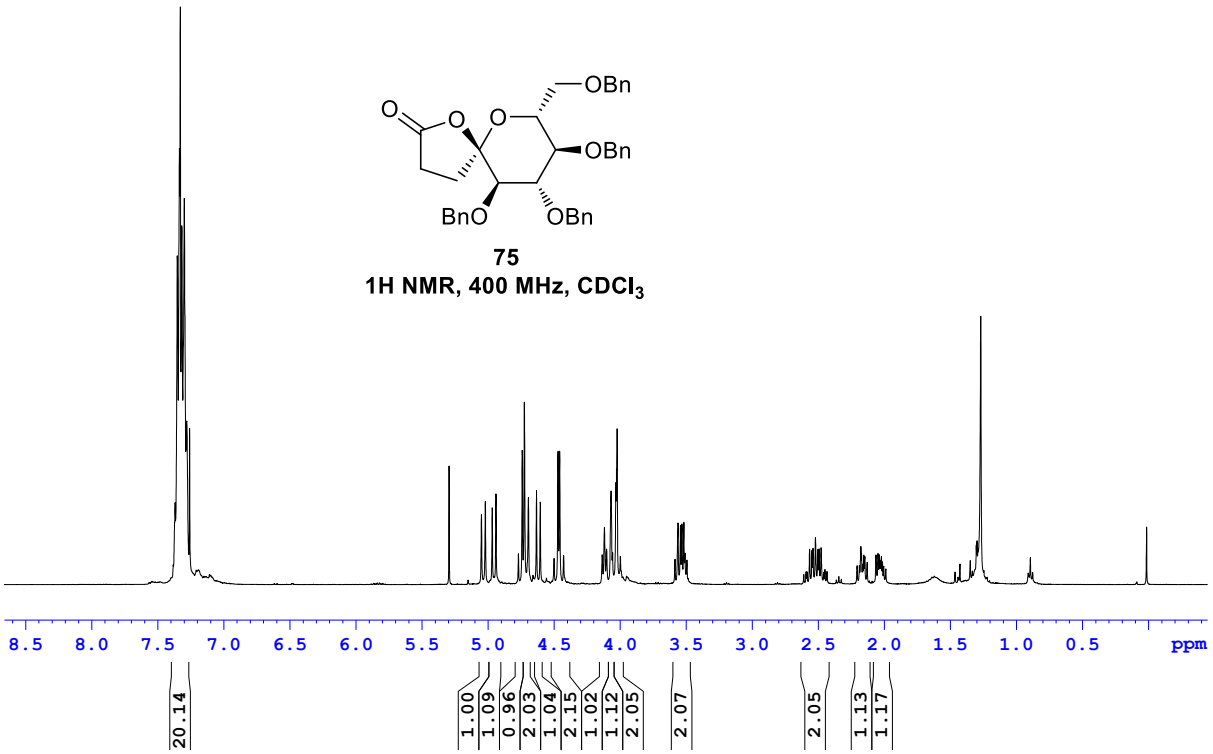
74

1H NMR, 400 MHz, $CDCl_3$



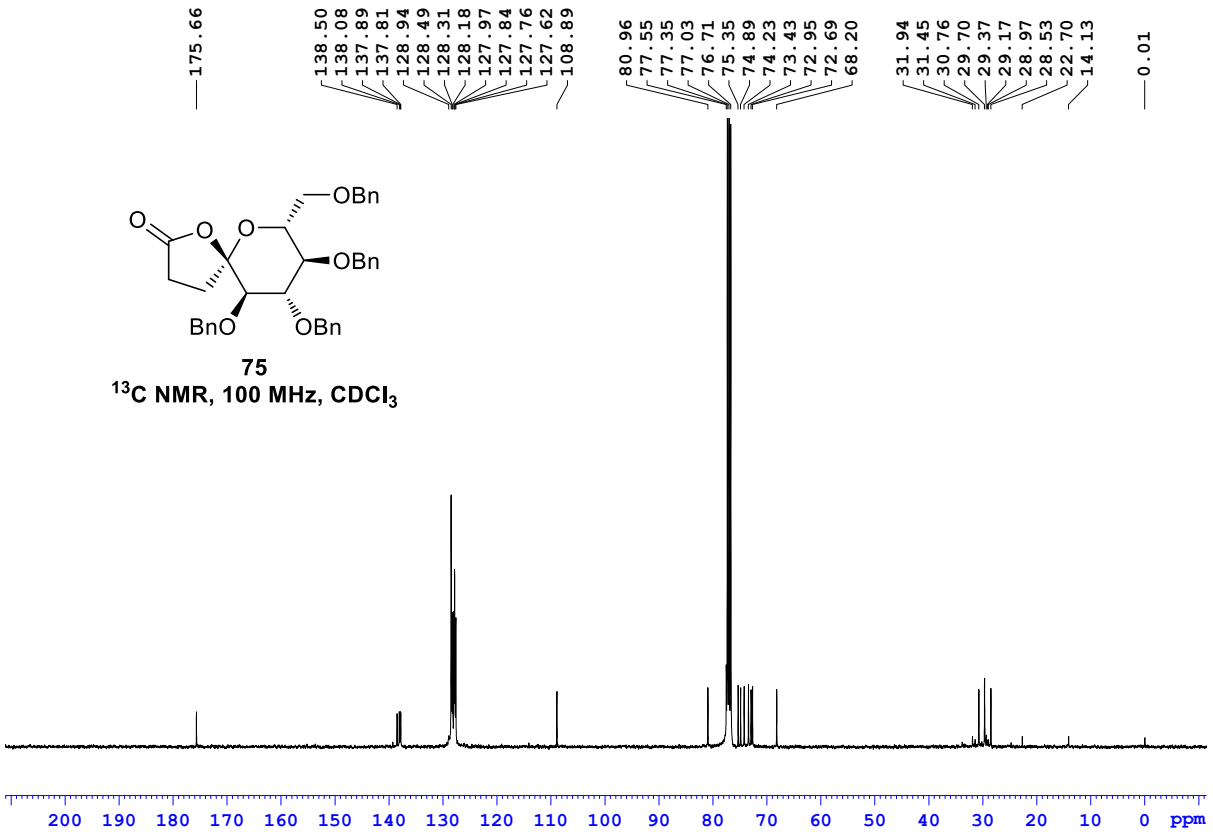
74

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



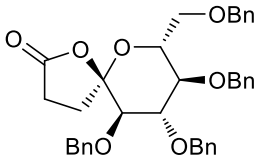
75

1H NMR, 400 MHz, $CDCl_3$



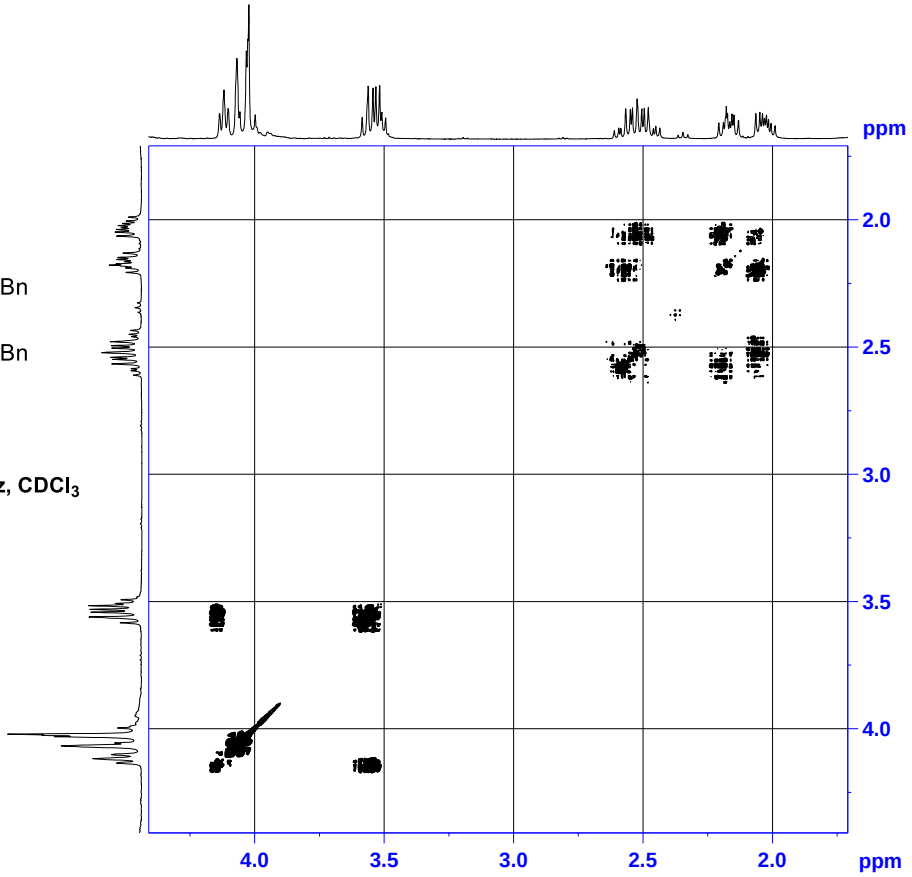
75

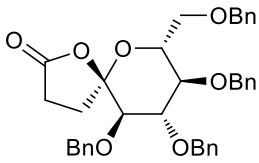
^{13}C NMR, 100 MHz, $CDCl_3$



75

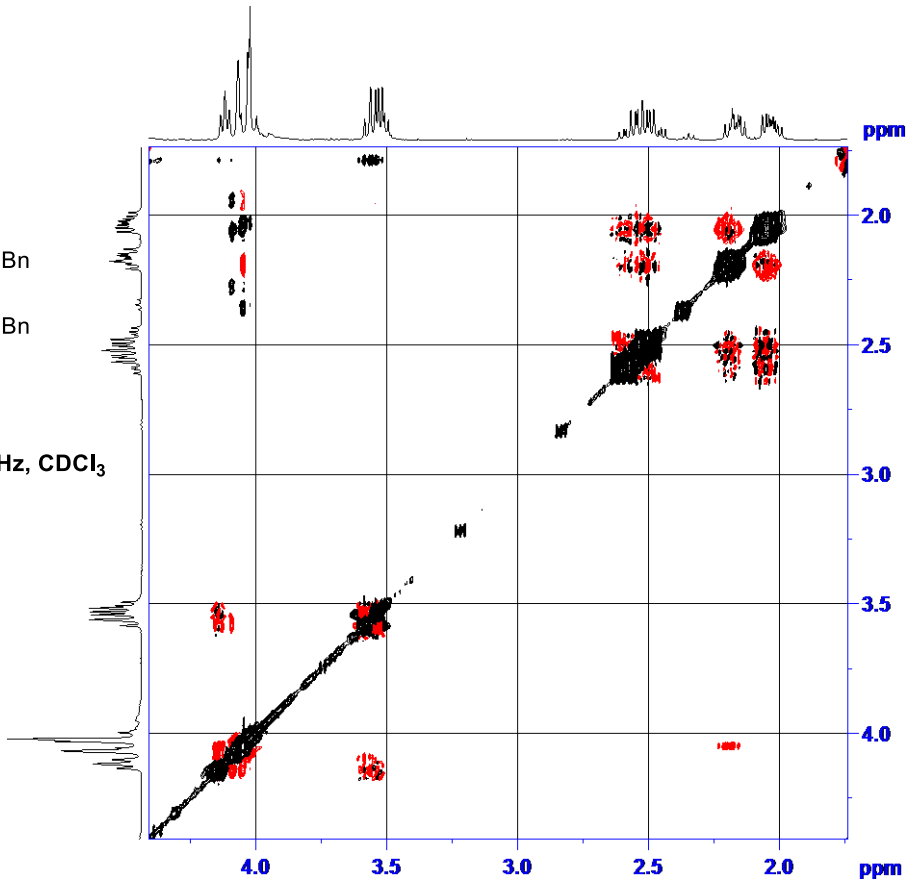
^{1}H-^{1}H COSY NMR, 400 MHz, $CDCl_3$

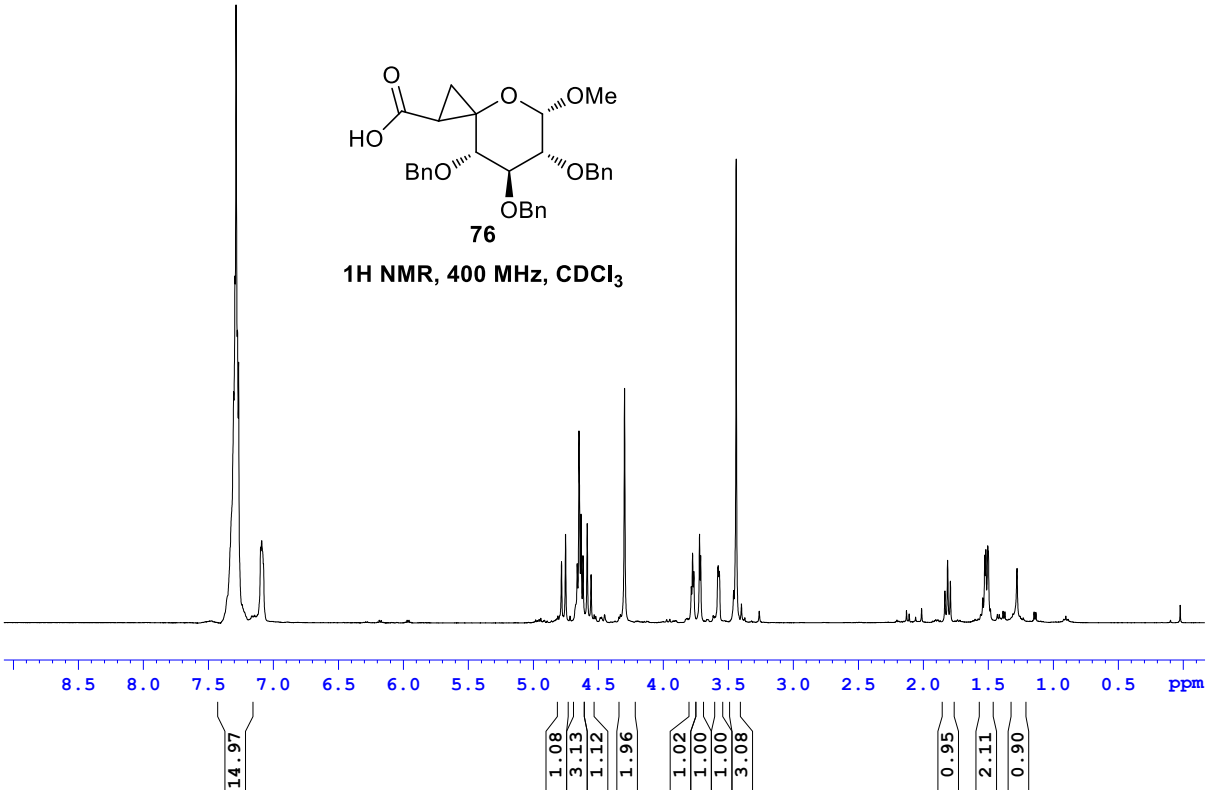


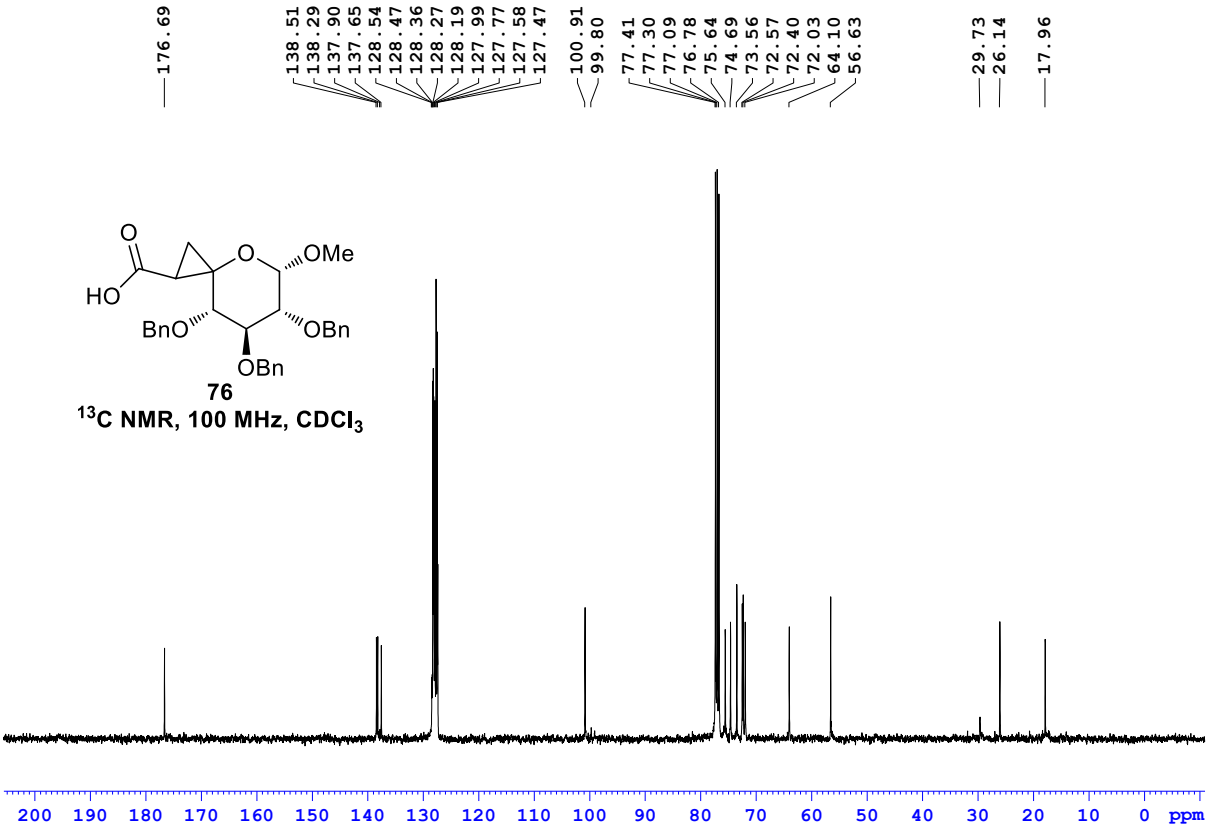


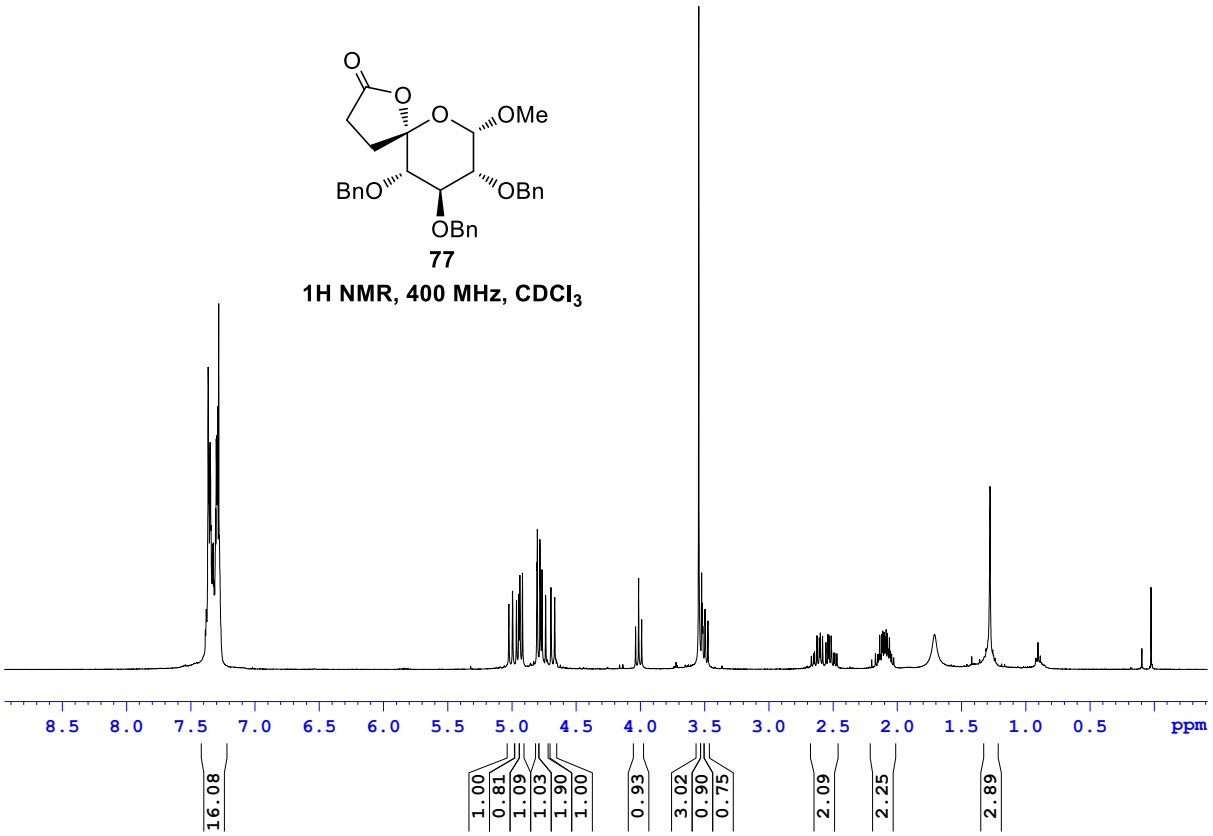
75

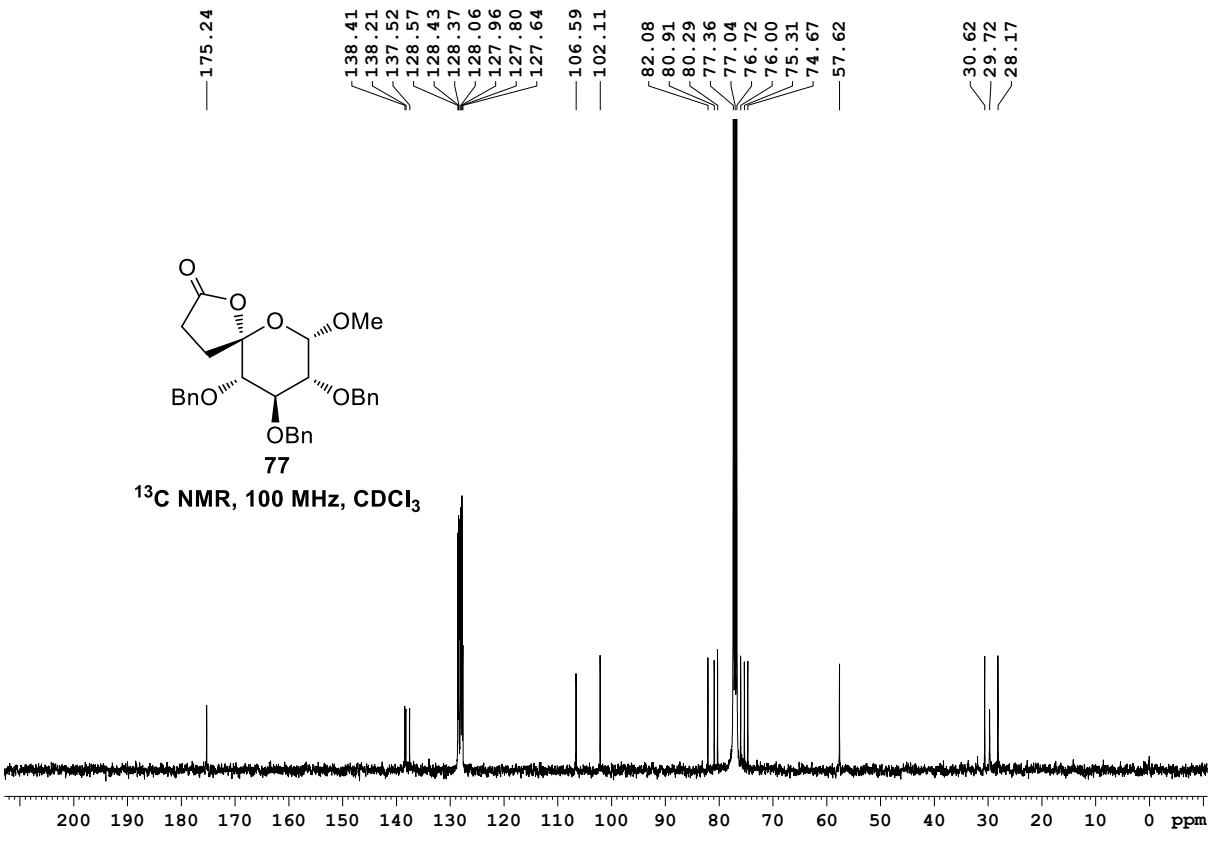
^{1}H-^{1}H NOESY NMR, 400 MHz, $CDCl_3$

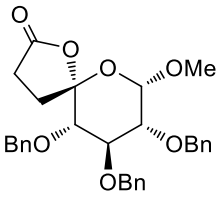



O
HO
O
OMe
BnO
OBn
OBn
76
1H NMR, 400 MHz, CDCl3
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
14.97
1.08
3.13
1.12
1.96
1.02
1.00
1.00
3.08
0.95
2.11
0.90


176.69
138.51
138.29
137.90
137.65
128.54
128.47
128.36
128.27
128.19
127.99
127.77
127.58
127.47
100.91
99.80
77.41
77.30
77.09
76.78
75.64
74.69
73.56
72.57
72.40
72.03
64.10
56.63
29.73
26.14
17.96
O
HO
O
OMe
BnO
OBn
OBn
76
13C NMR, 100 MHz, CDCl3
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

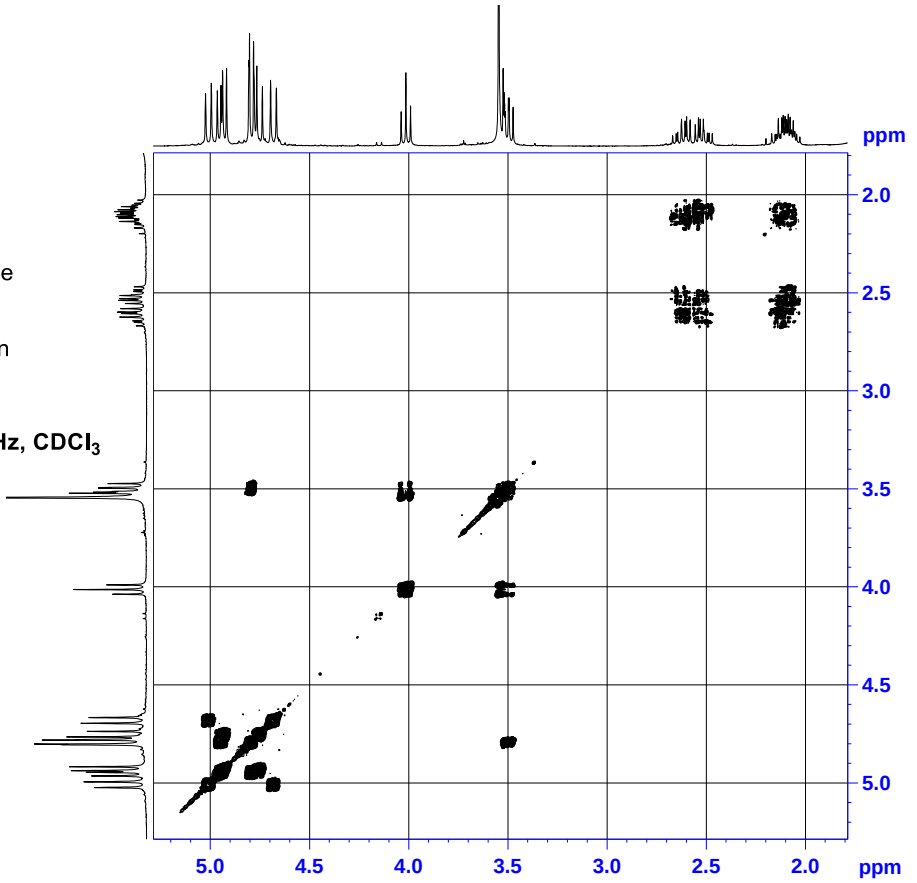

77
1H NMR, 400 MHz, CDCl3
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
16.08
1.00 0.81 1.09 1.03 1.90 1.00
0.93
3.02 0.90 0.75
2.09
2.25
2.89

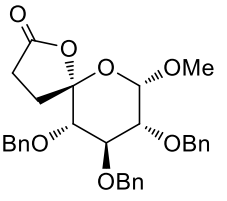

175.24
138.41 138.21 137.52 128.57 128.43 128.37 128.06 127.96 127.80 127.64
106.59 102.11
82.08 80.91 80.29 77.36 77.04 76.72 76.00 75.31 74.67
57.62
30.62 29.72 28.17
77
13C NMR, 100 MHz, CDCl3
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm



77

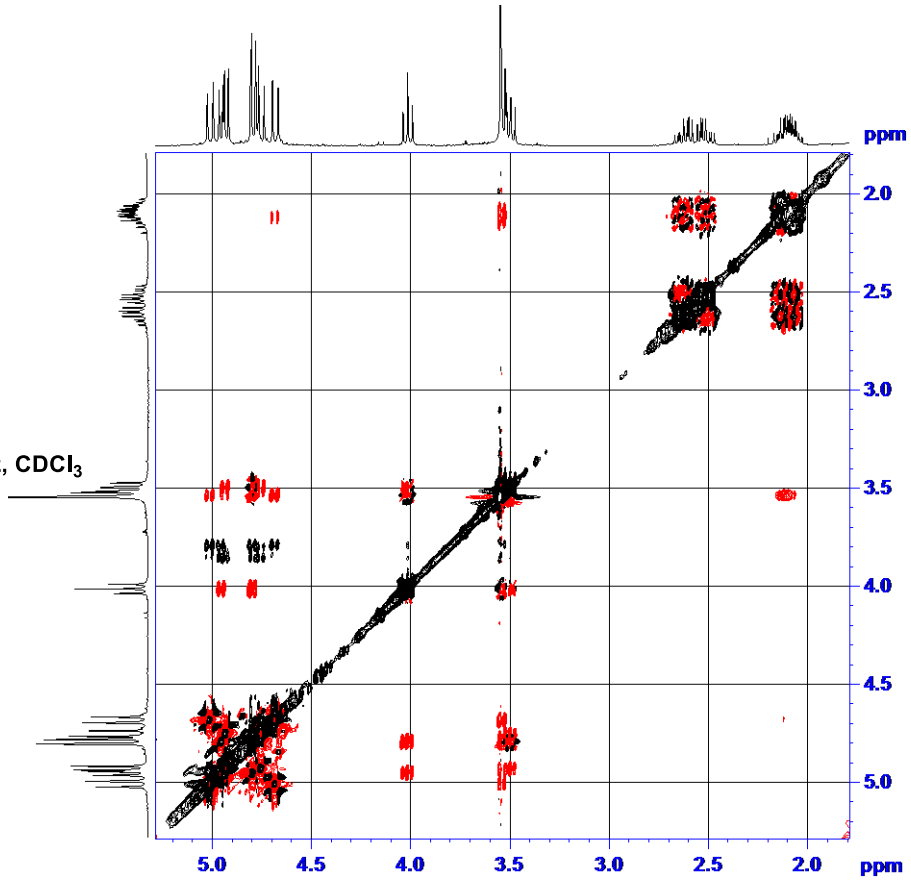
^{1}H-^{1}H COSY NMR, 400 MHz, $CDCl_3$

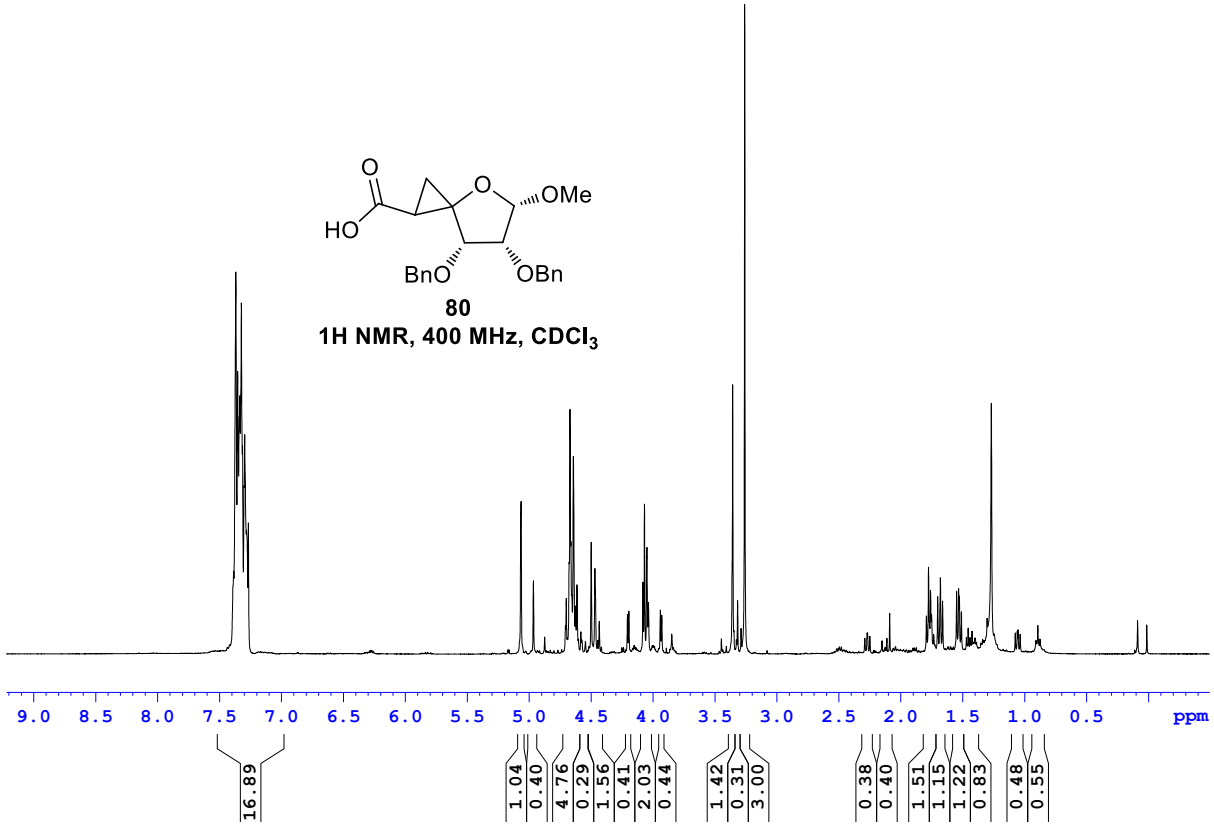




77

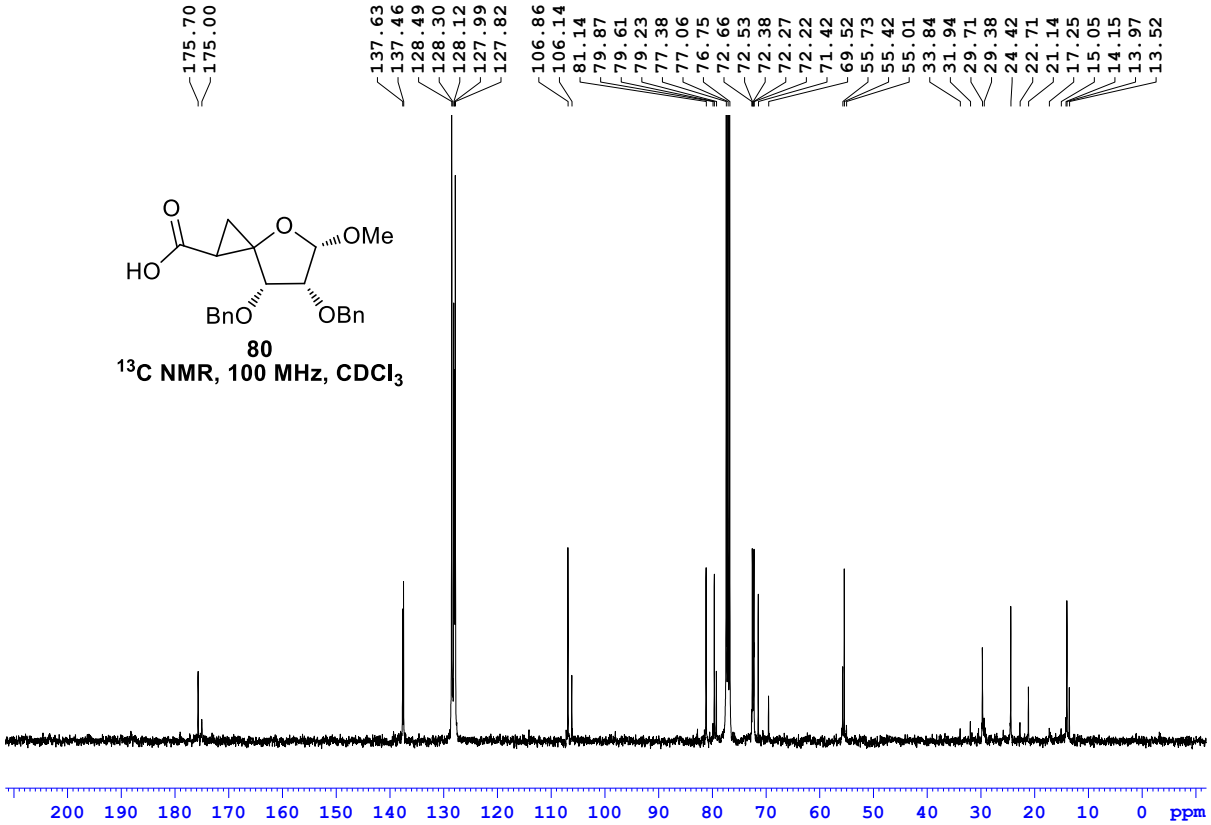
^{1}H-^{1}H NOESY NMR, 400 MHz, $CDCl_3$





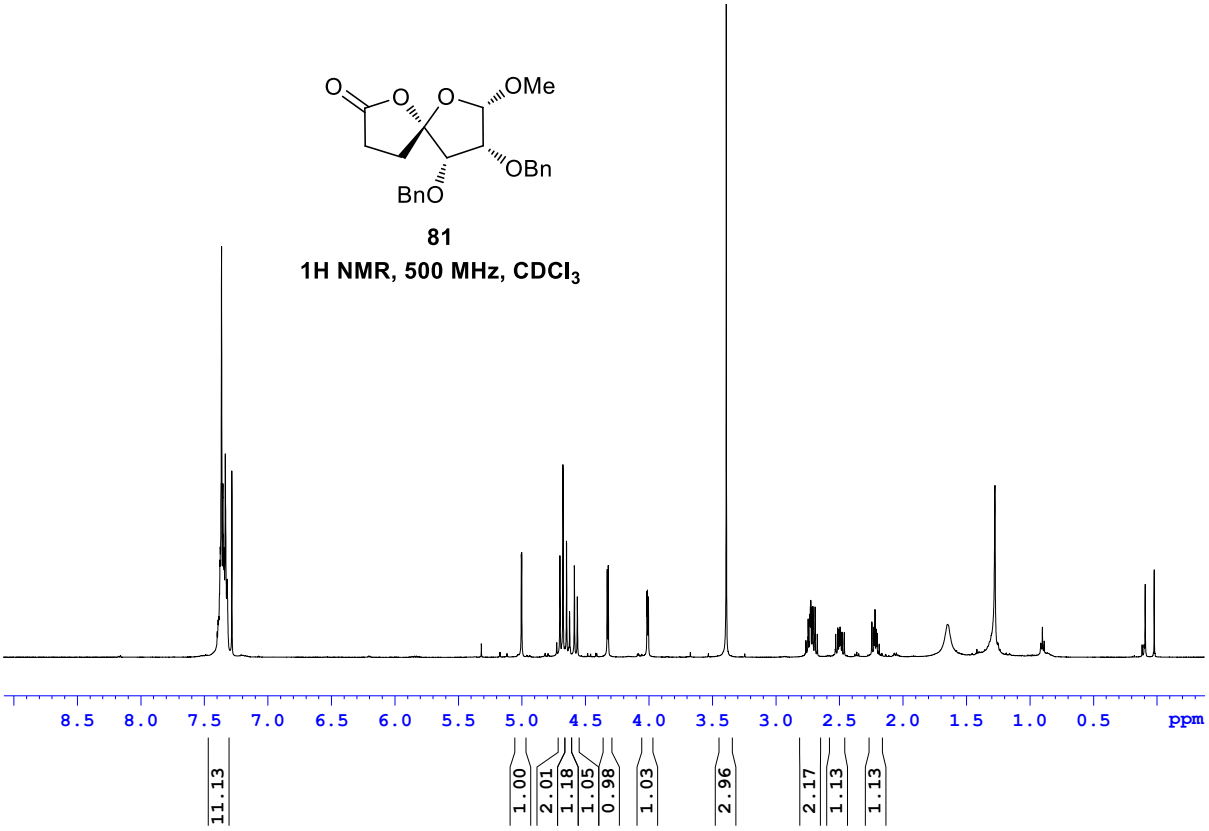
80

1H NMR, 400 MHz, $CDCl_3$



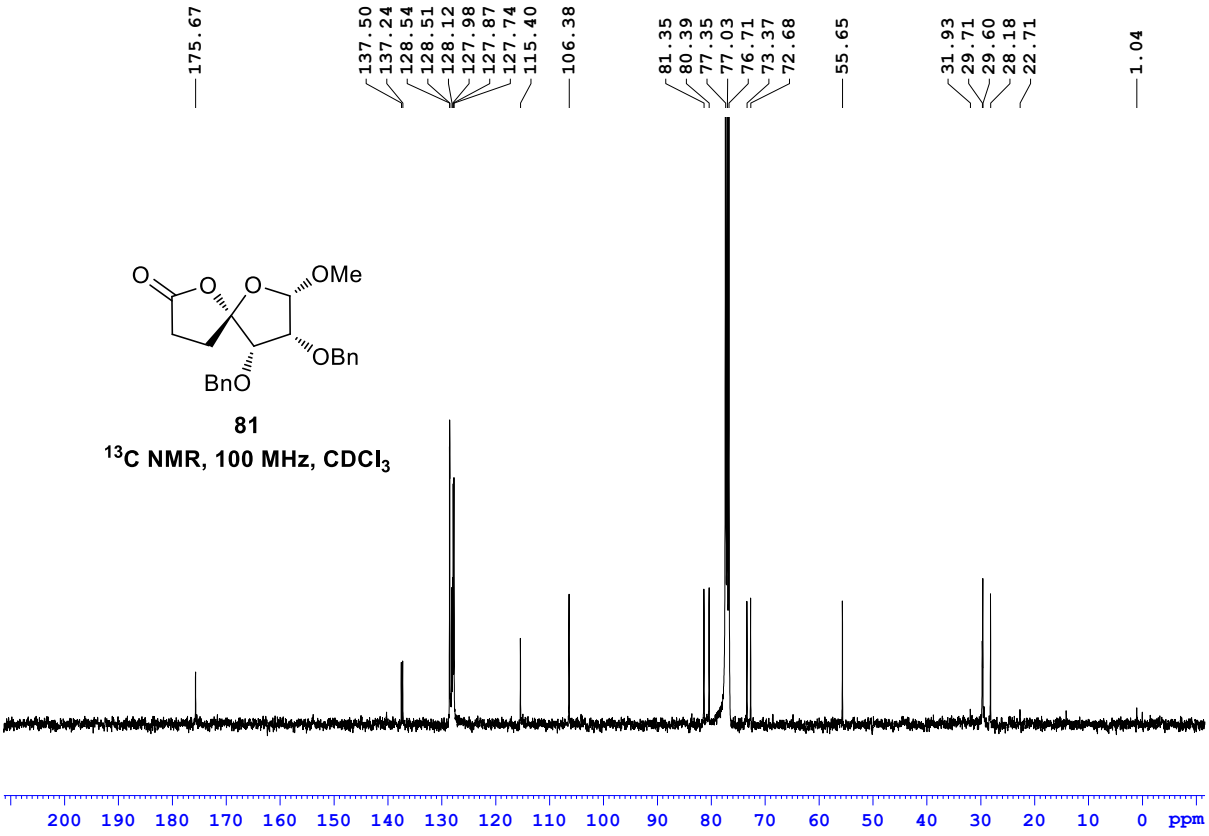
80

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



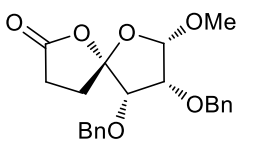
81

1H NMR, 500 MHz, $CDCl_3$



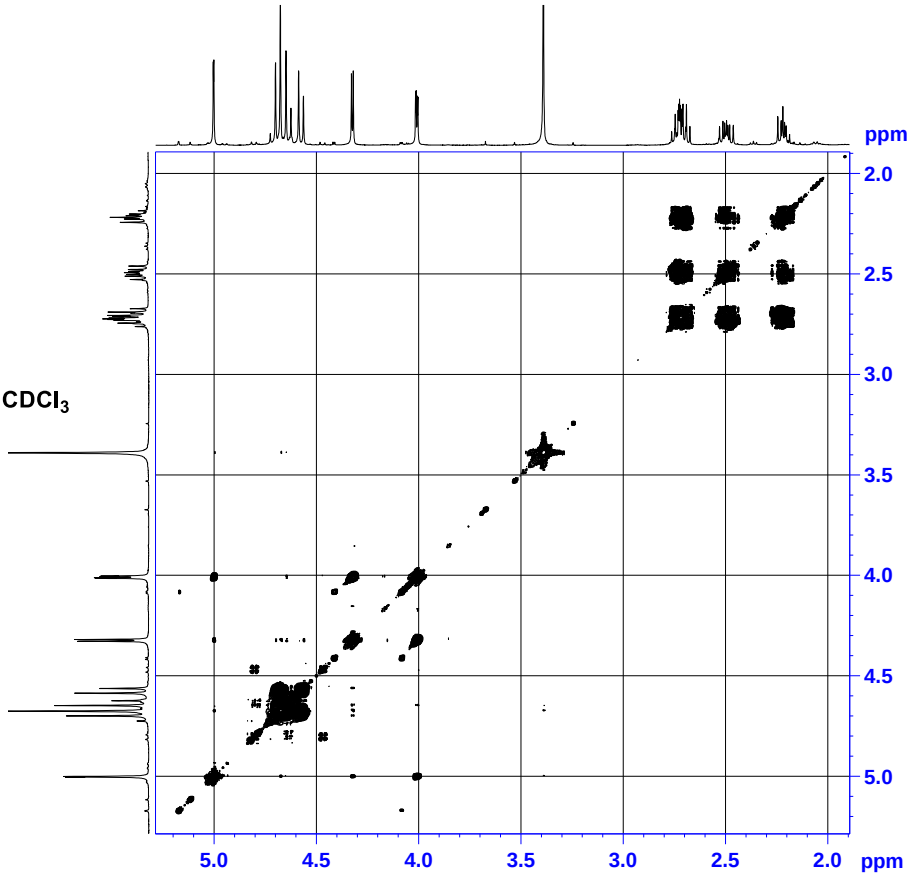
81

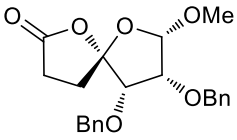
^{13}C NMR, 100 MHz, $CDCl_3$



81

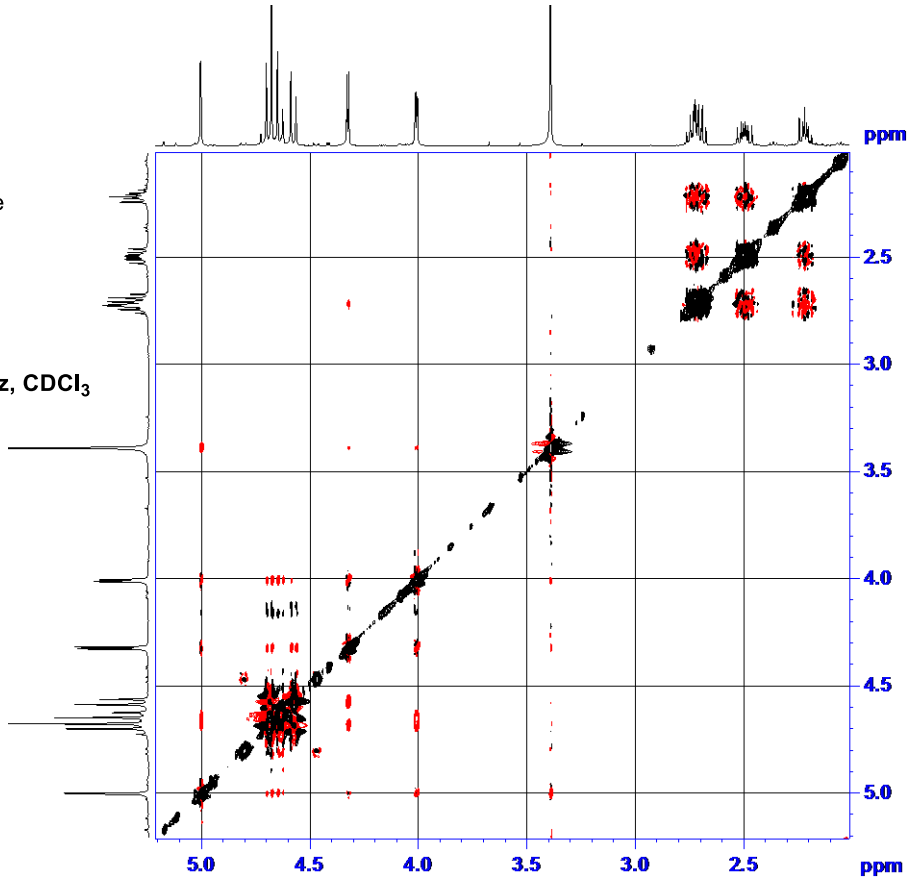
^{1}H-^{1}H COSY NMR, 500 MHz, $CDCl_3$

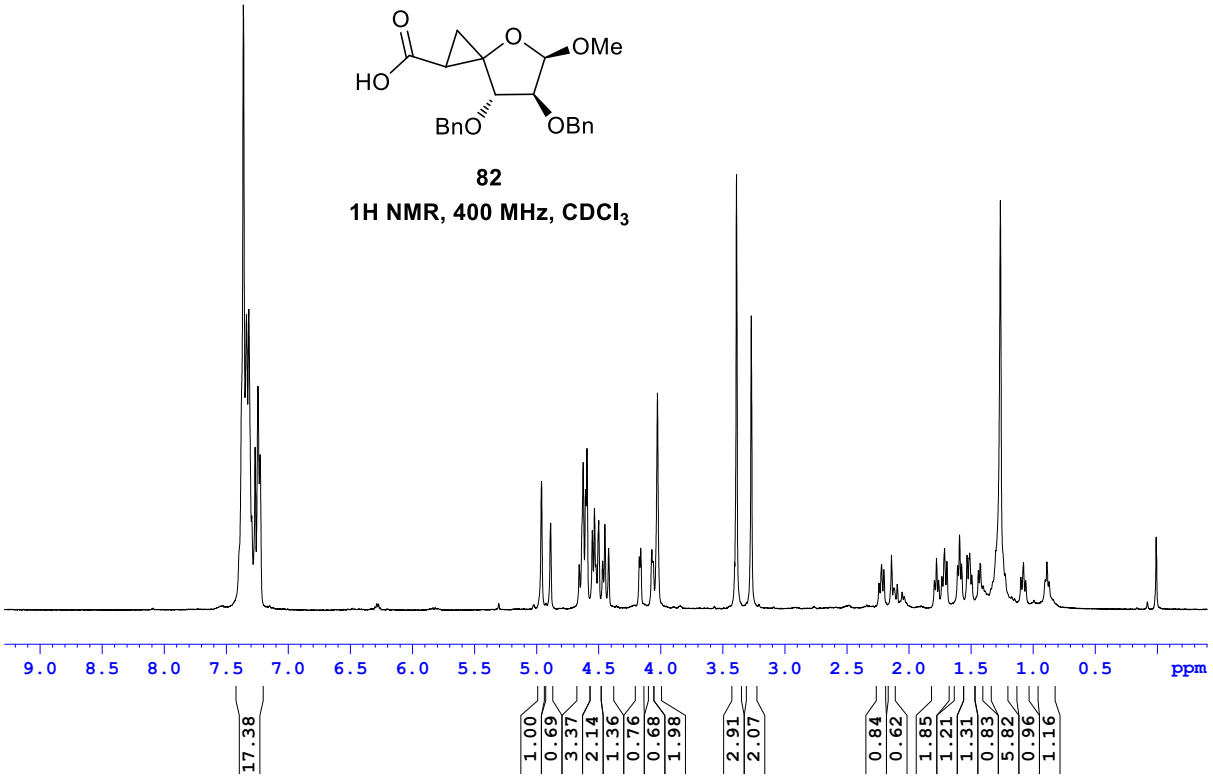




81

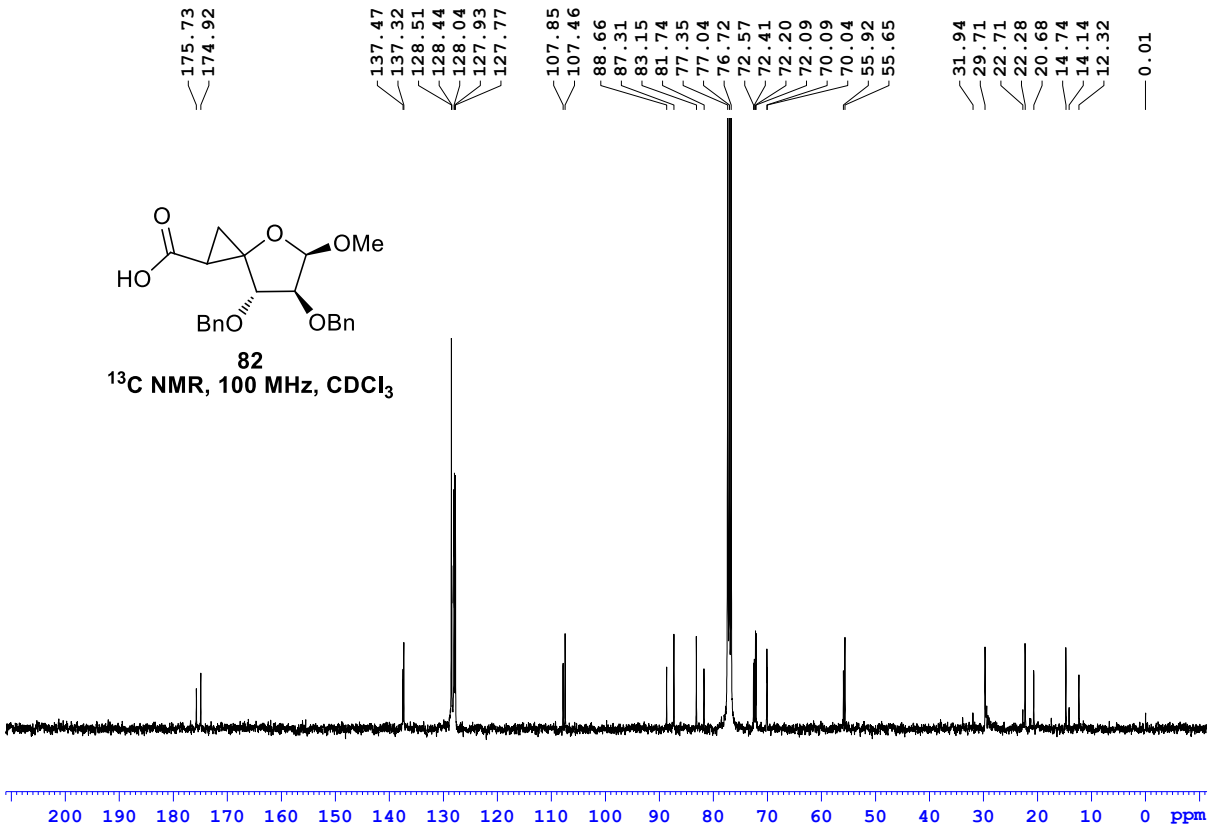
^{1}H-^{1}H NOESY NMR, 500 MHz, $CDCl_3$





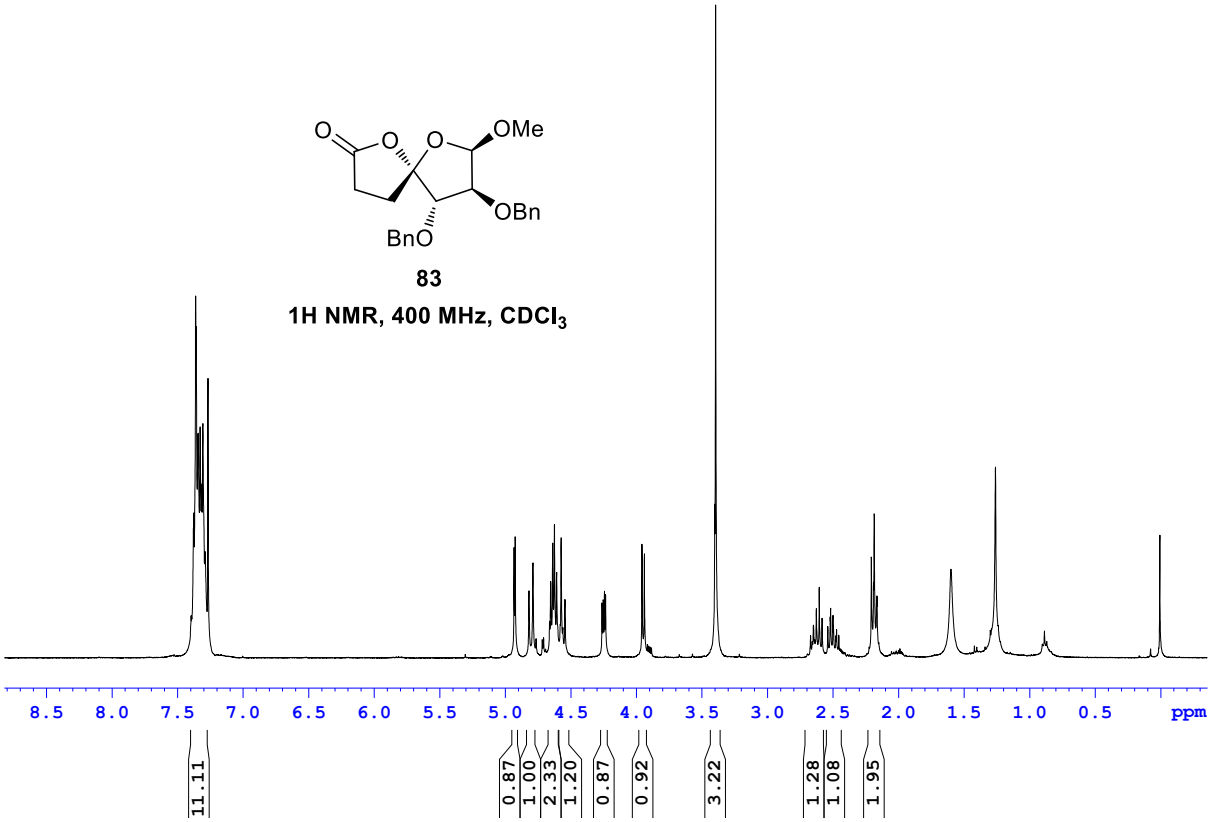
82

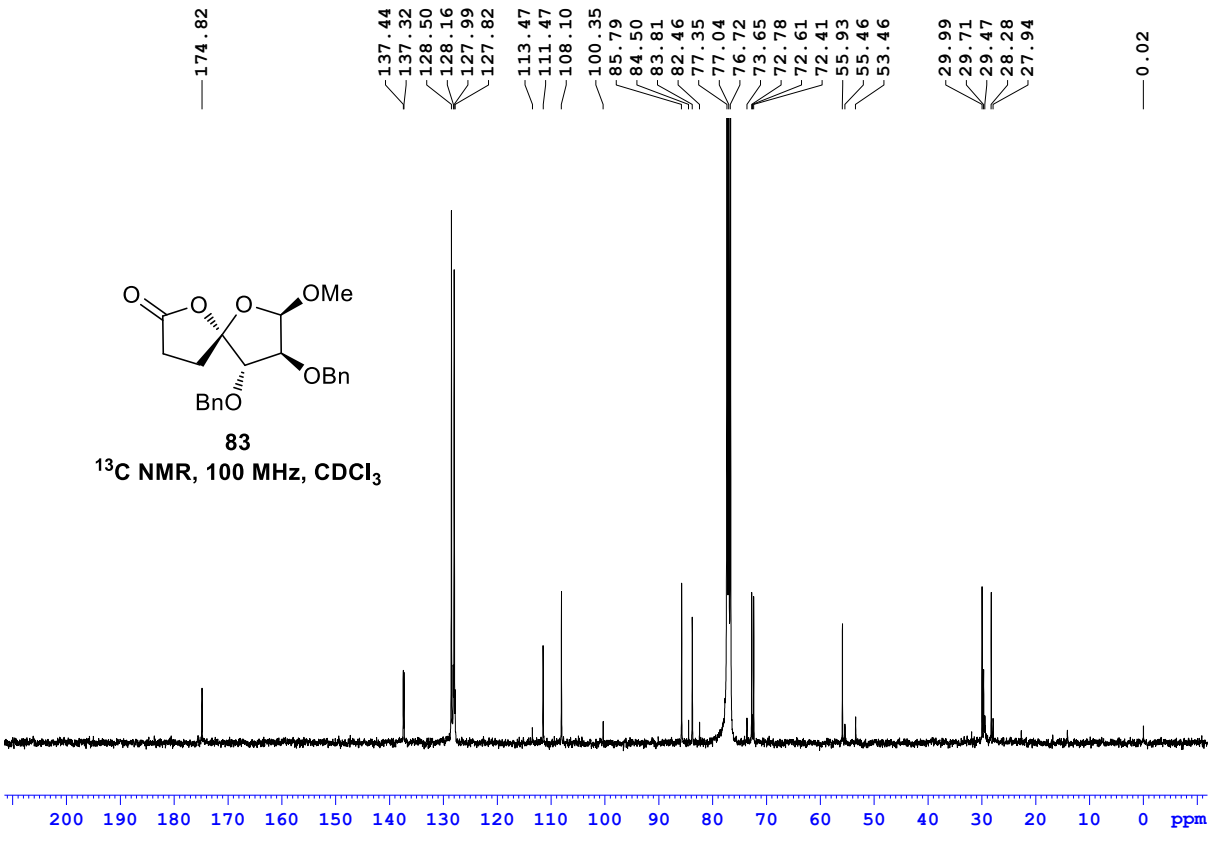
1H NMR, 400 MHz, $CDCl_3$

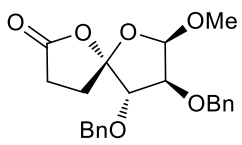


82

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

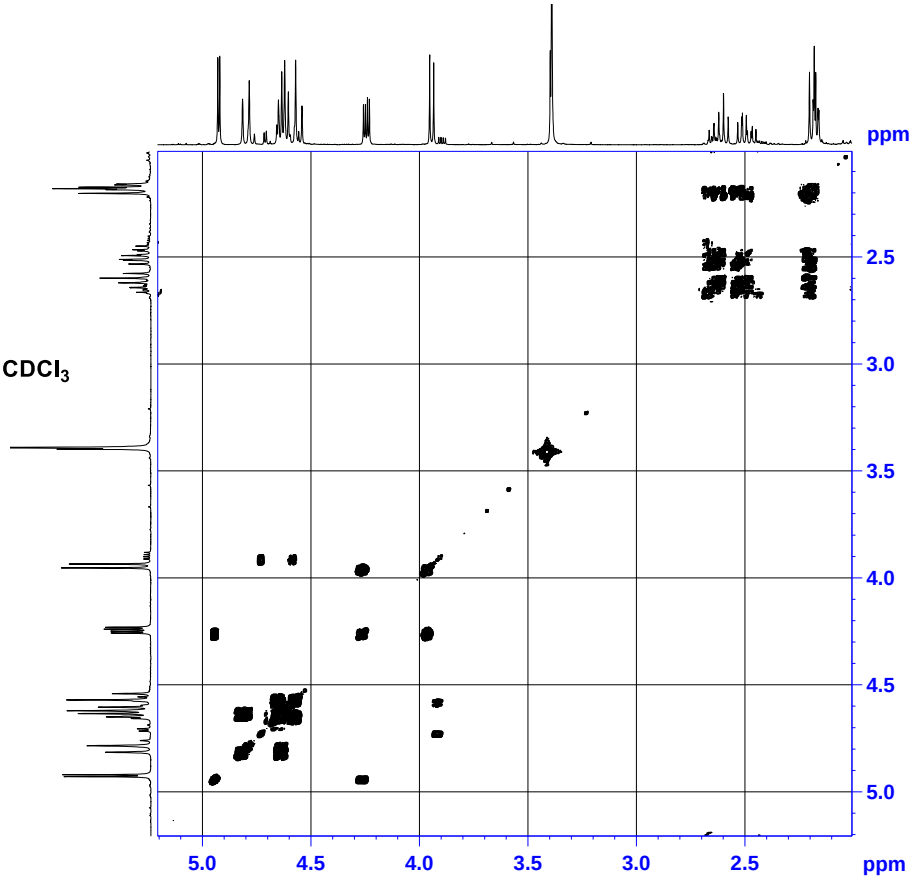

OMe
OBn
BnO
83
1H NMR, 400 MHz, CDCl3
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
11.11
0.87
1.00
2.33
1.20
0.87
0.92
3.22
1.28
1.08
1.95

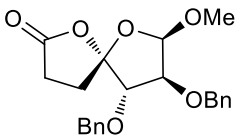

174.82
137.44
137.32
128.50
128.16
127.99
127.82
113.47
111.47
108.10
100.35
85.79
84.50
83.81
82.46
77.35
77.04
76.72
73.65
72.78
72.61
72.41
55.93
55.46
53.46
29.99
29.71
29.47
28.28
27.94
0.02
OMe
OBn
BnO
83
13C NMR, 100 MHz, CDCl3
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm



83

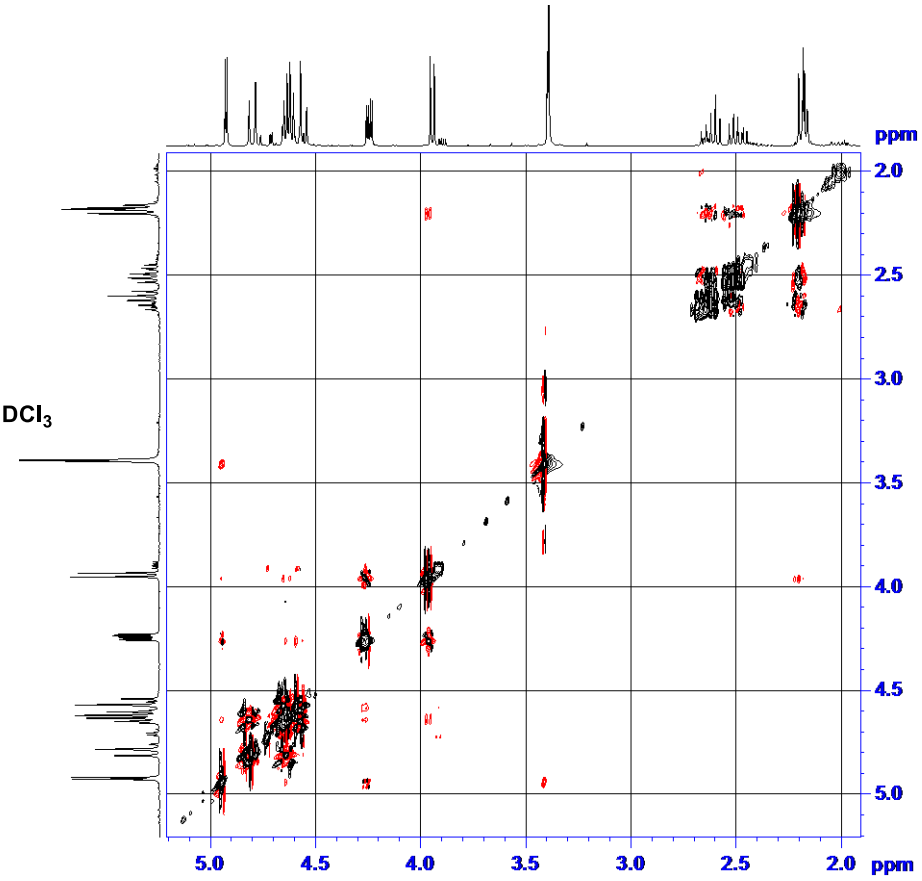
^{1}H-^{1}H COSY NMR, 400 MHz, $CDCl_3$

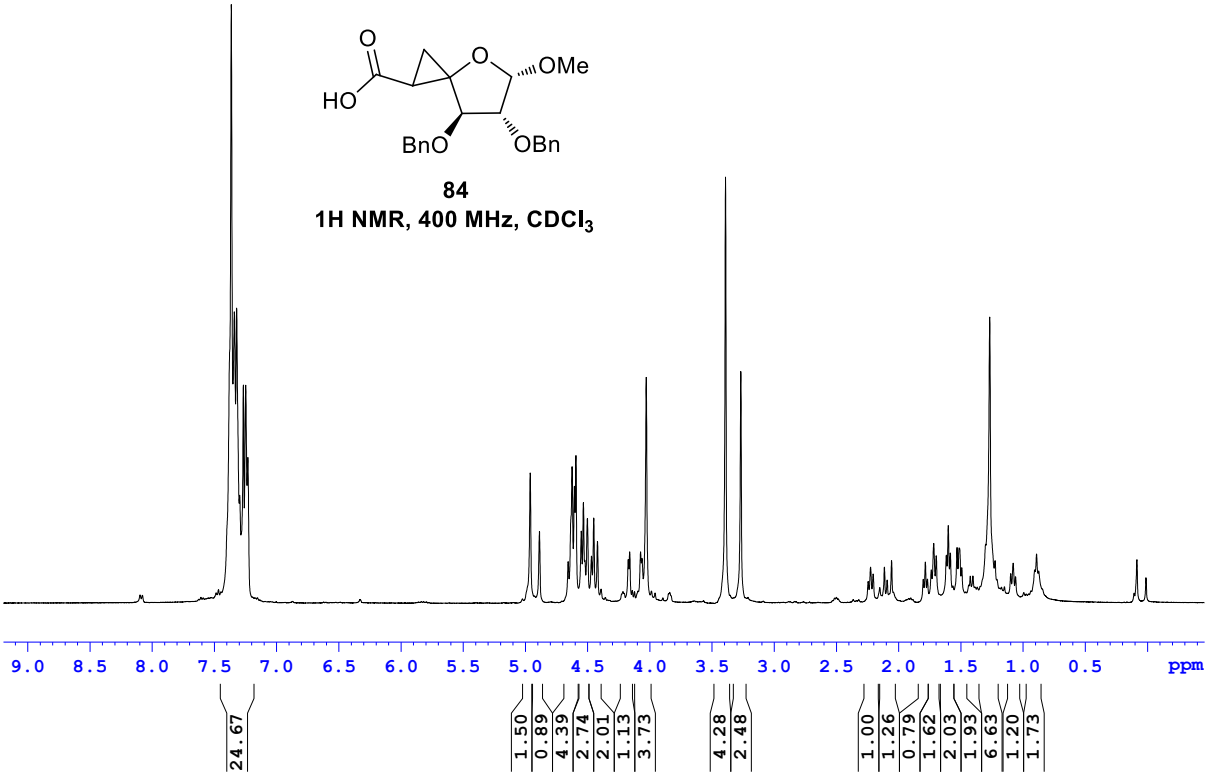




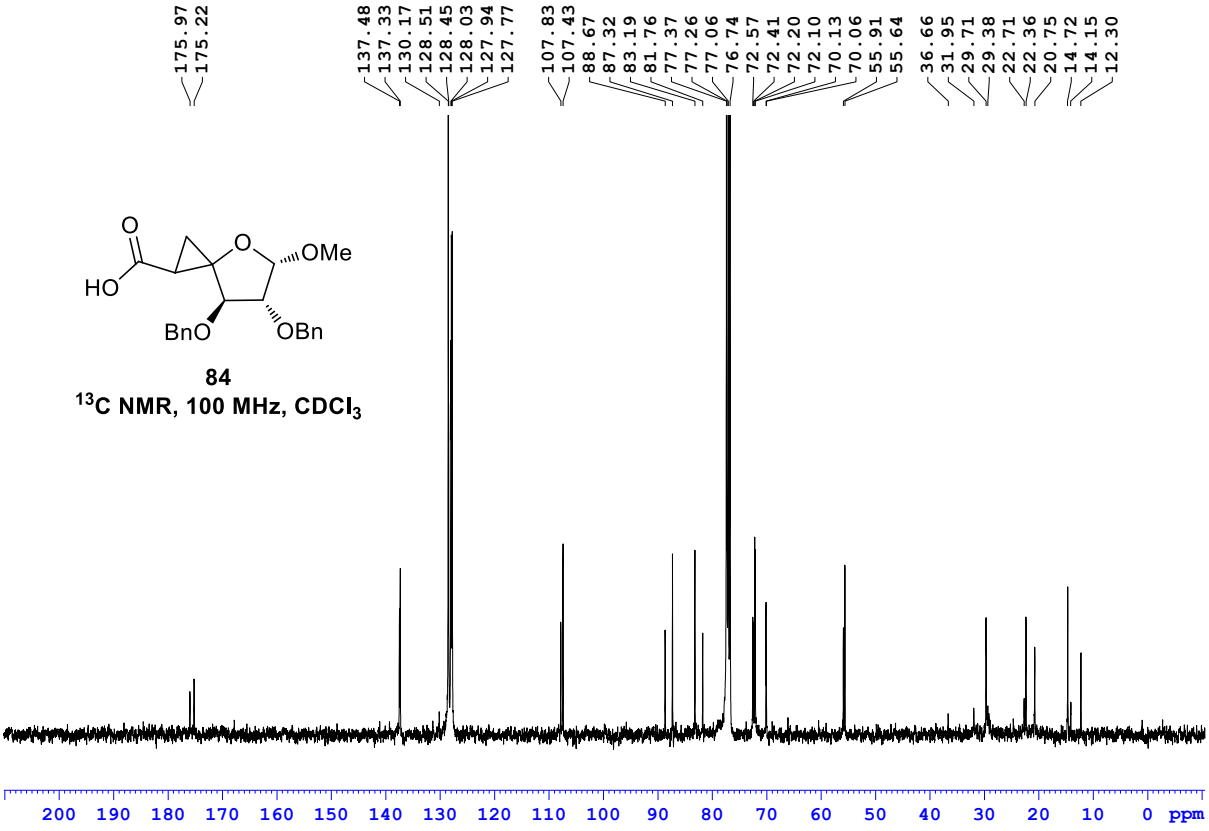
83

^{1}H-^{1}H NOESY NMR, 400 MHz, $CDCl_3$

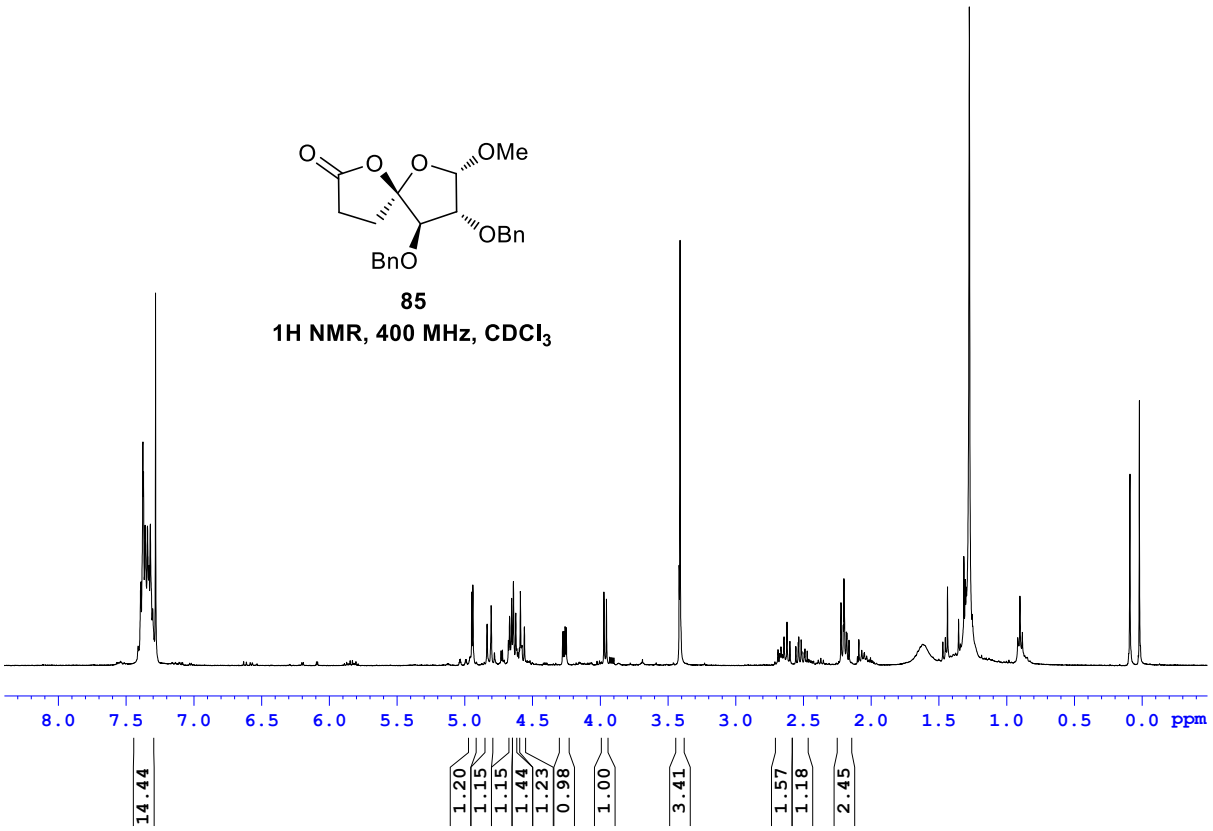


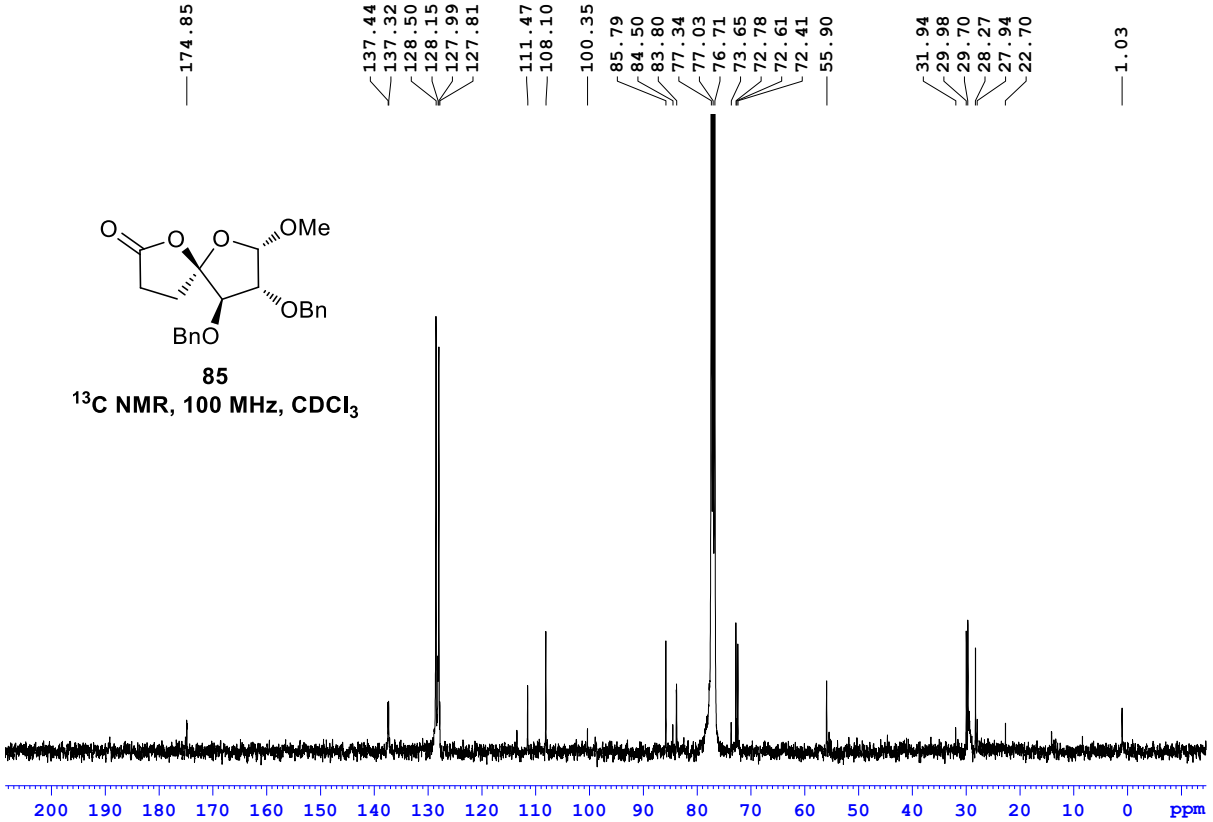


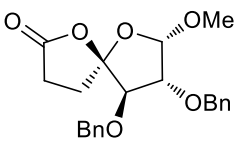
84
1H NMR, 400 MHz, $CDCl_3$



84
^{13}C NMR, 100 MHz, $CDCl_3$

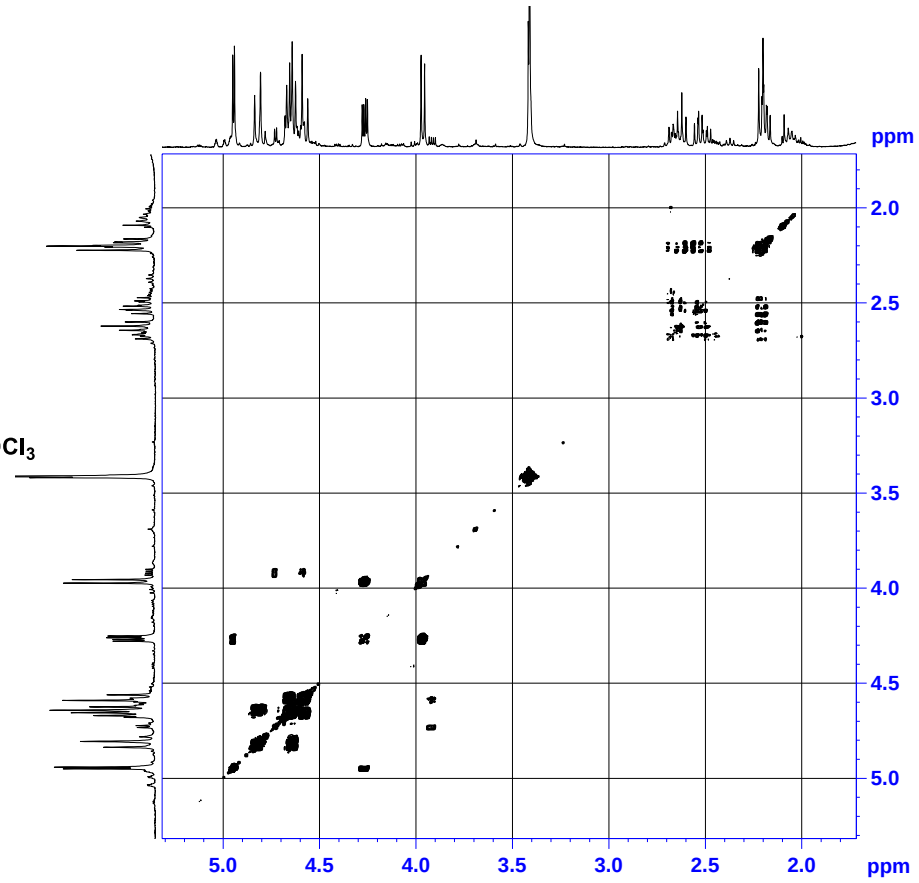

OMe
OBn
BnO
85
1H NMR, 400 MHz, CDCl3
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm
14.44
1.20
1.15
1.15
1.44
1.23
0.98
1.00
3.41
1.57
1.18
2.45

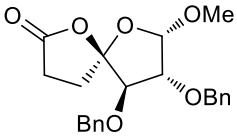

174.85
137.44
137.32
128.50
128.15
127.99
127.81
111.47
108.10
100.35
85.79
84.50
83.80
77.34
77.03
76.71
73.65
72.78
72.61
72.41
55.90
31.94
29.98
29.70
28.27
27.94
22.70
1.03
OMe
OBn
BnO
85
13C NMR, 100 MHz, CDCl3
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm



85

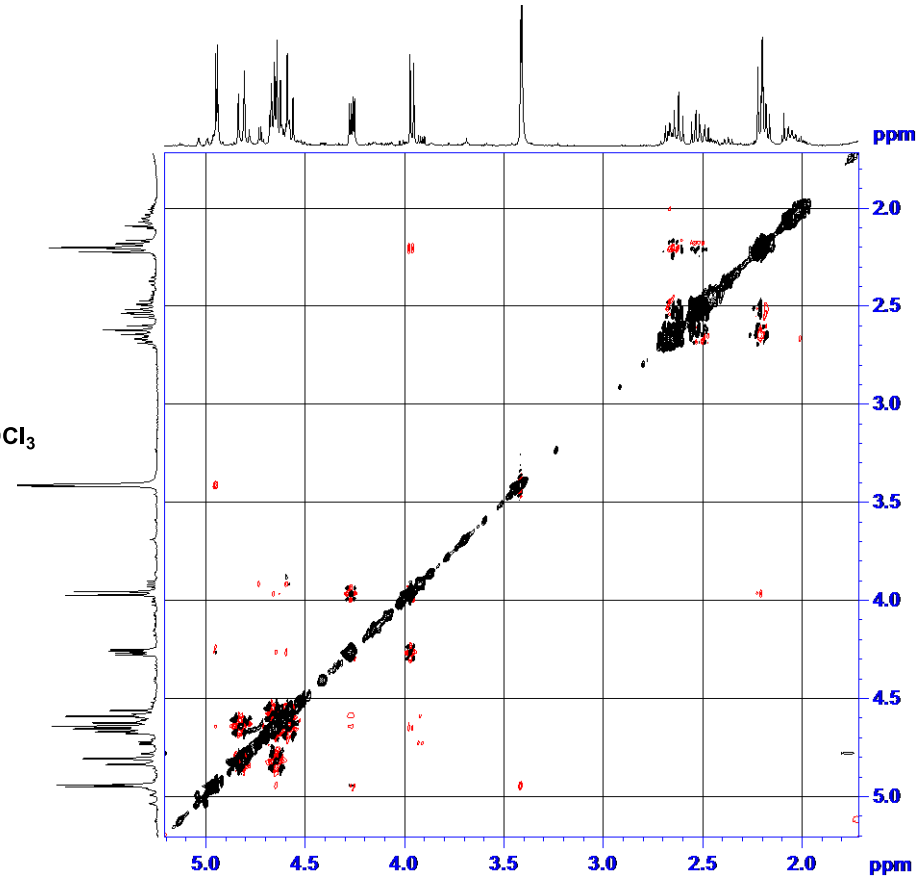
^{1}H-^{1}H COSY NMR, 400 MHz, $CDCl_3$

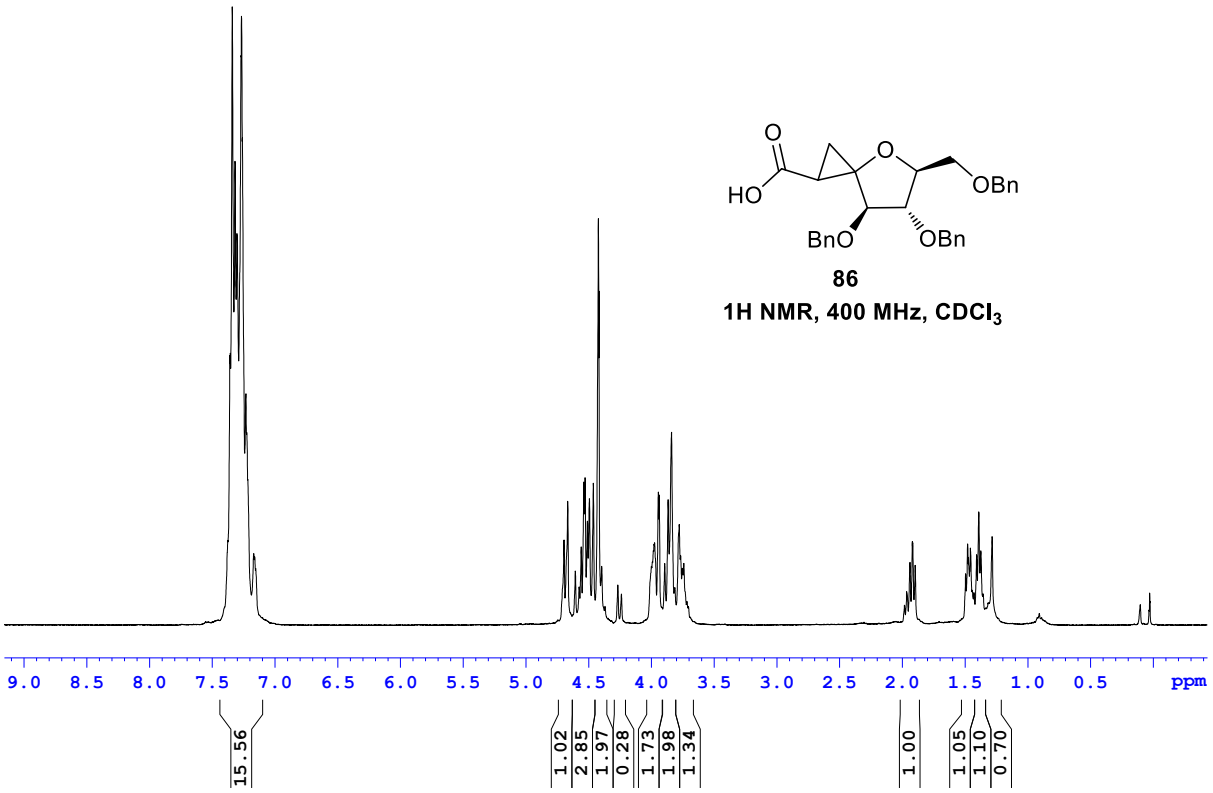




85

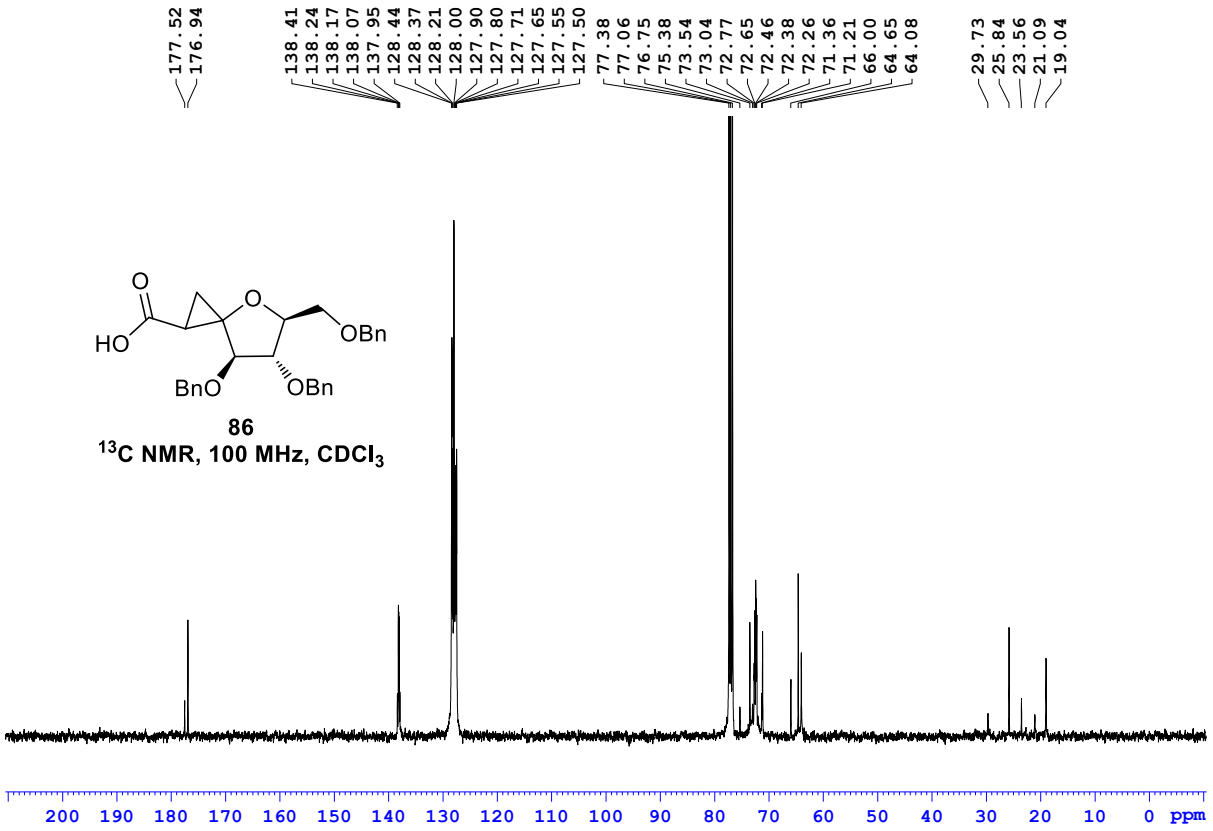
^{1}H-^{1}H NOESY NMR, 400 MHz, $CDCl_3$





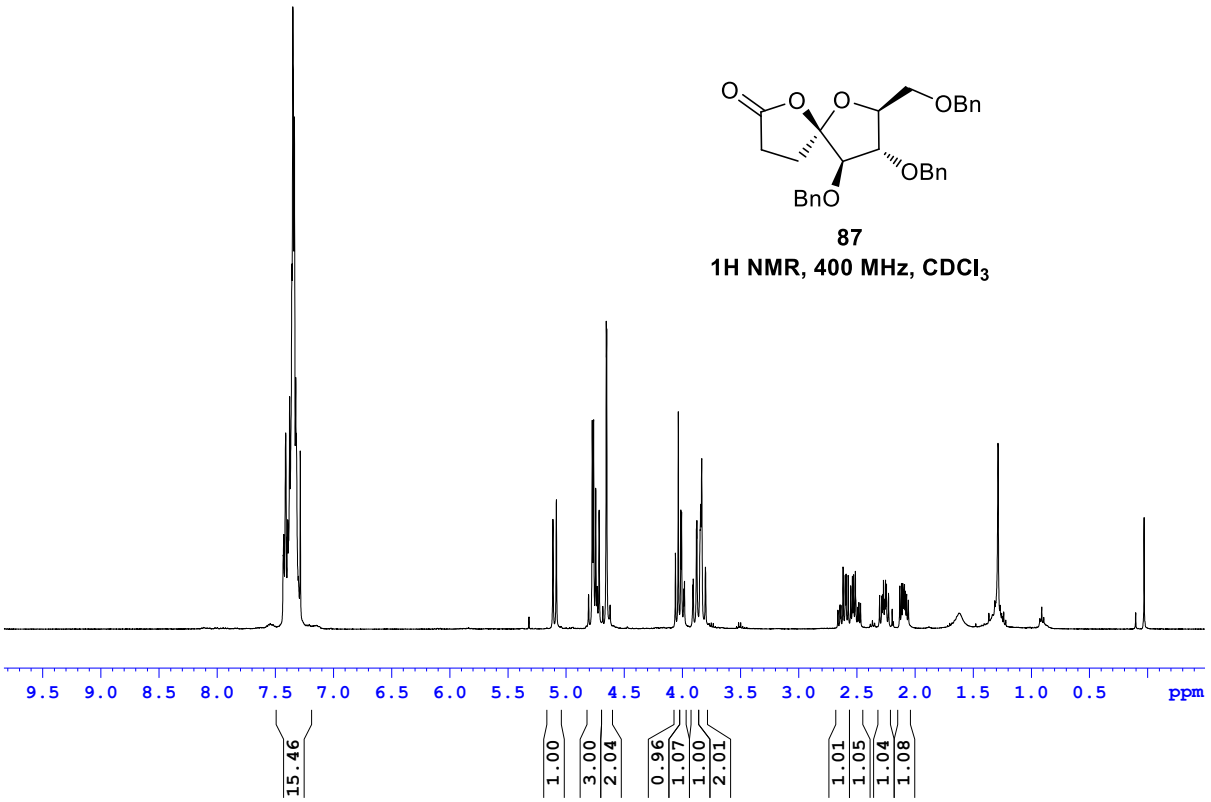
86

1H NMR, 400 MHz, $CDCl_3$



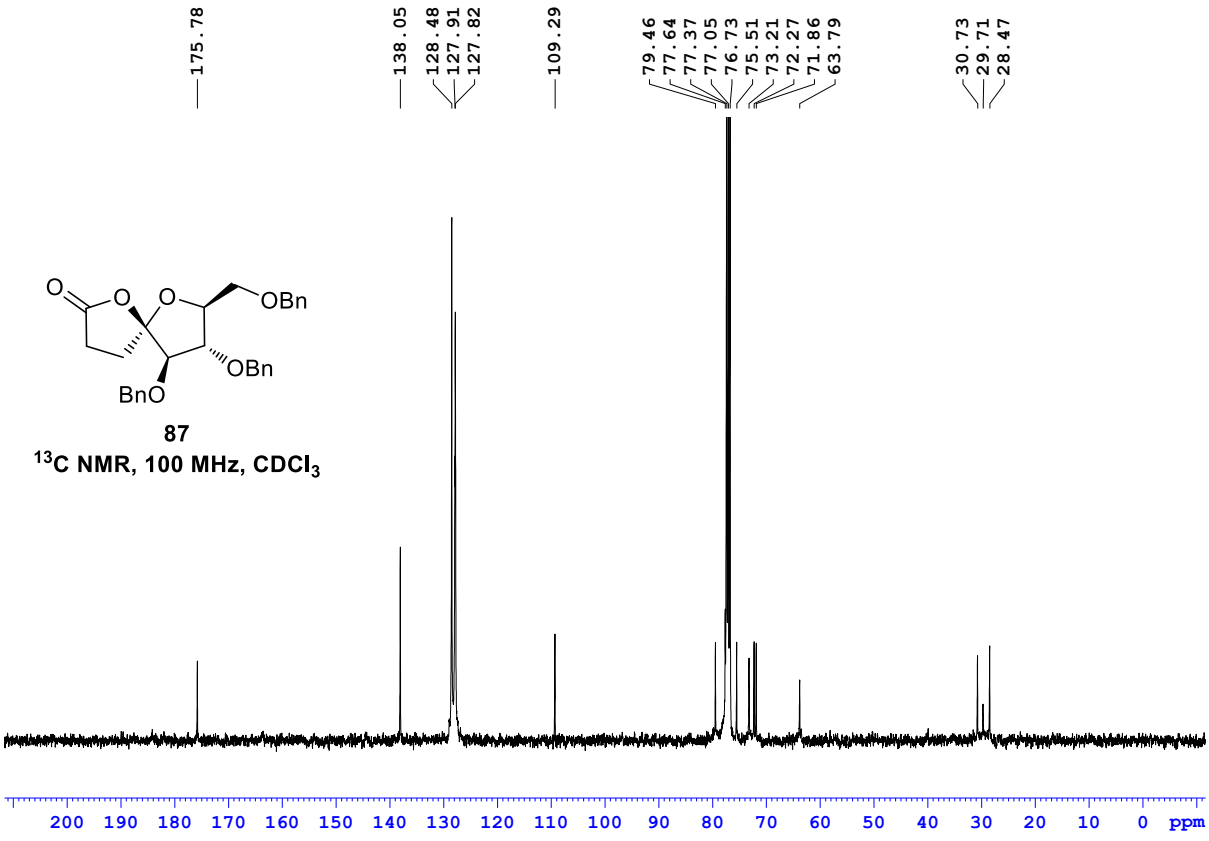
86

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



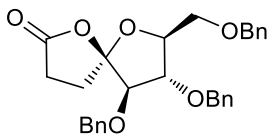
87

1H NMR, 400 MHz, $CDCl_3$



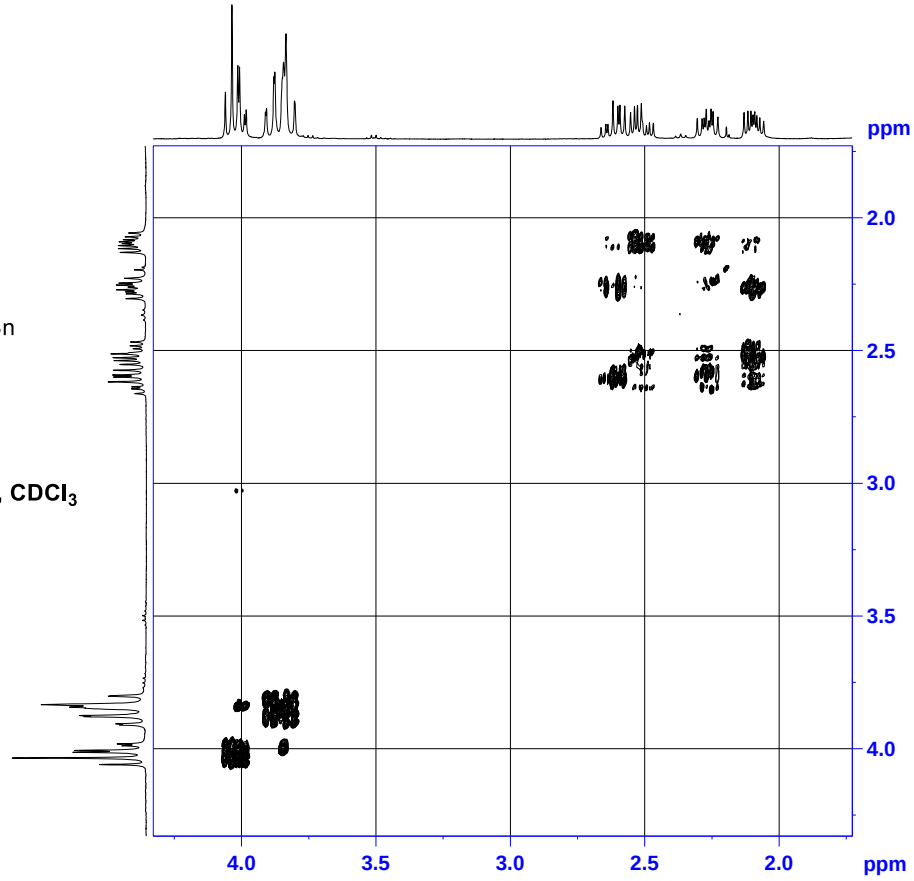
87

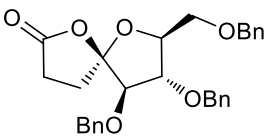
^{13}C NMR, 100 MHz, $CDCl_3$



87

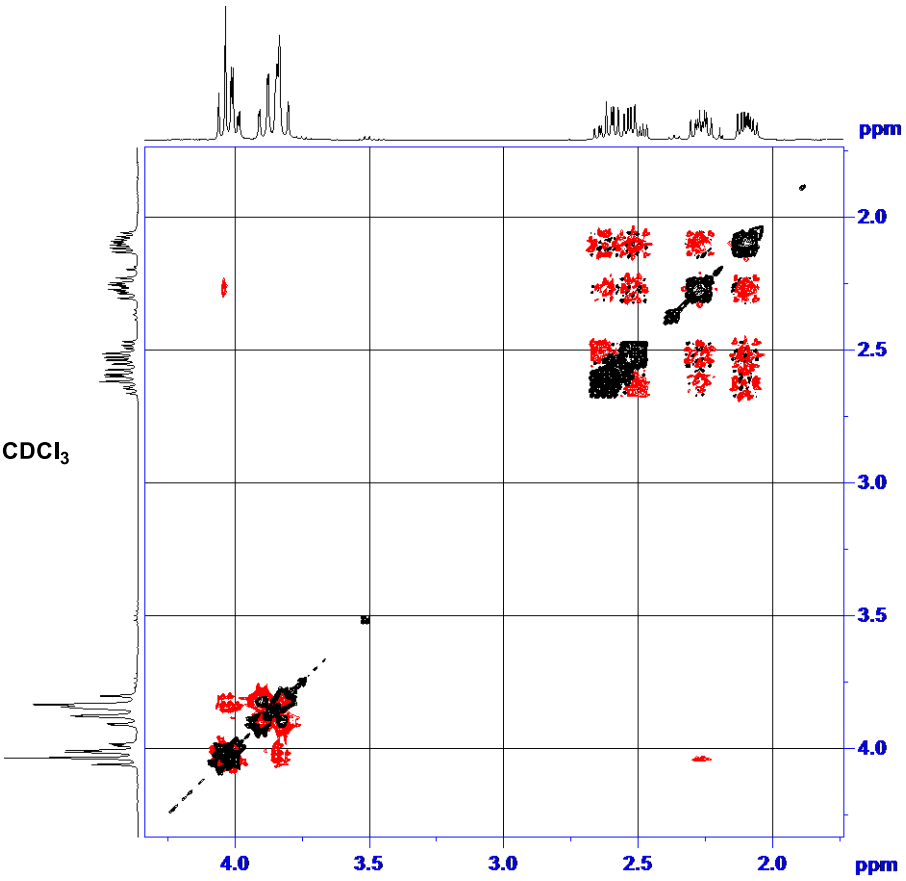
^{1}H-^{1}H COSY NMR, 400 MHz, $CDCl_3$

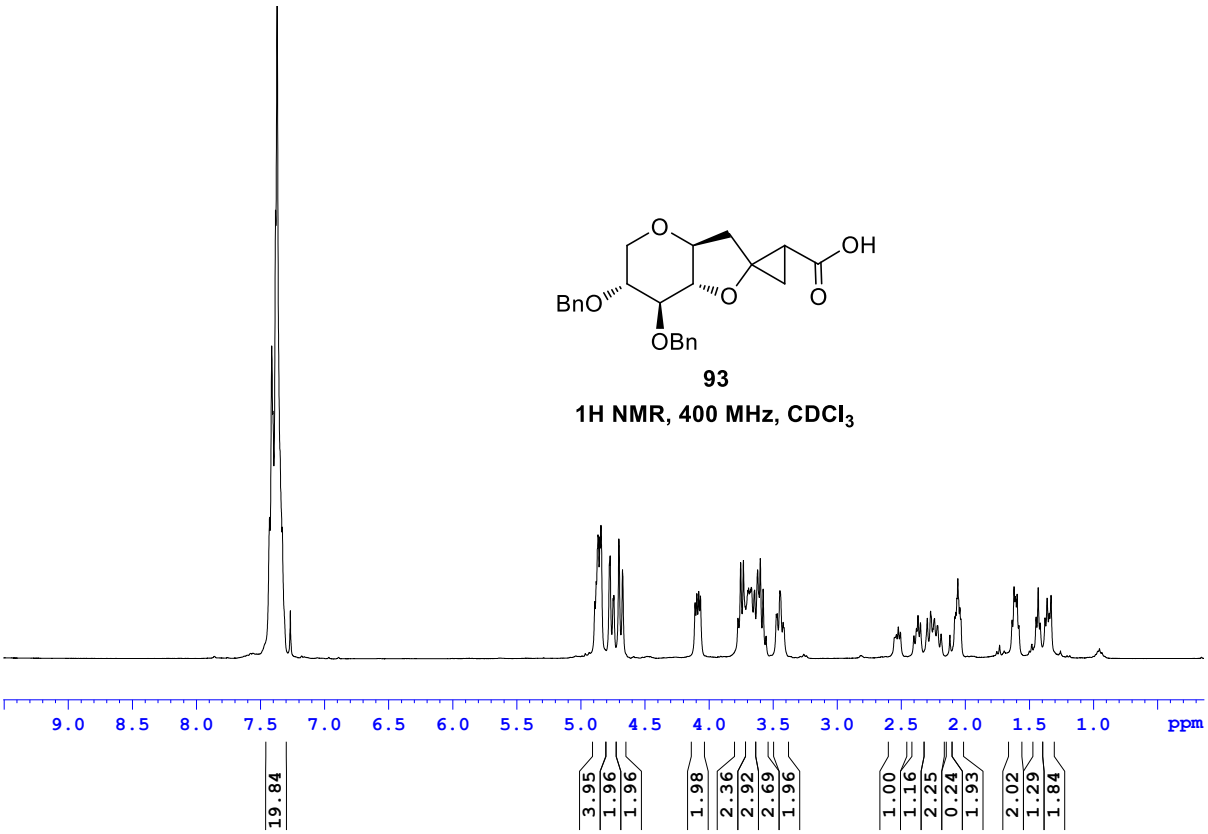




87

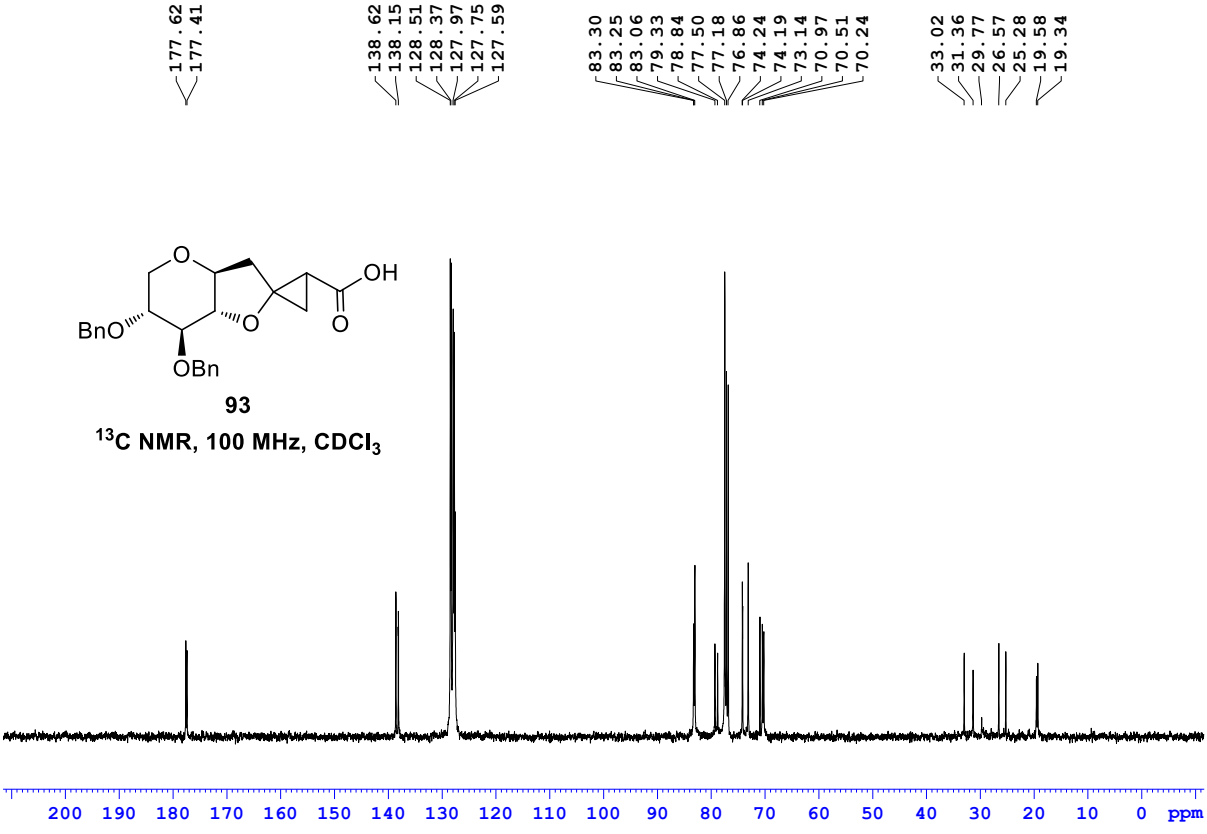
^{1}H-^{1}H NOESY NMR, 400 MHz, $CDCl_3$





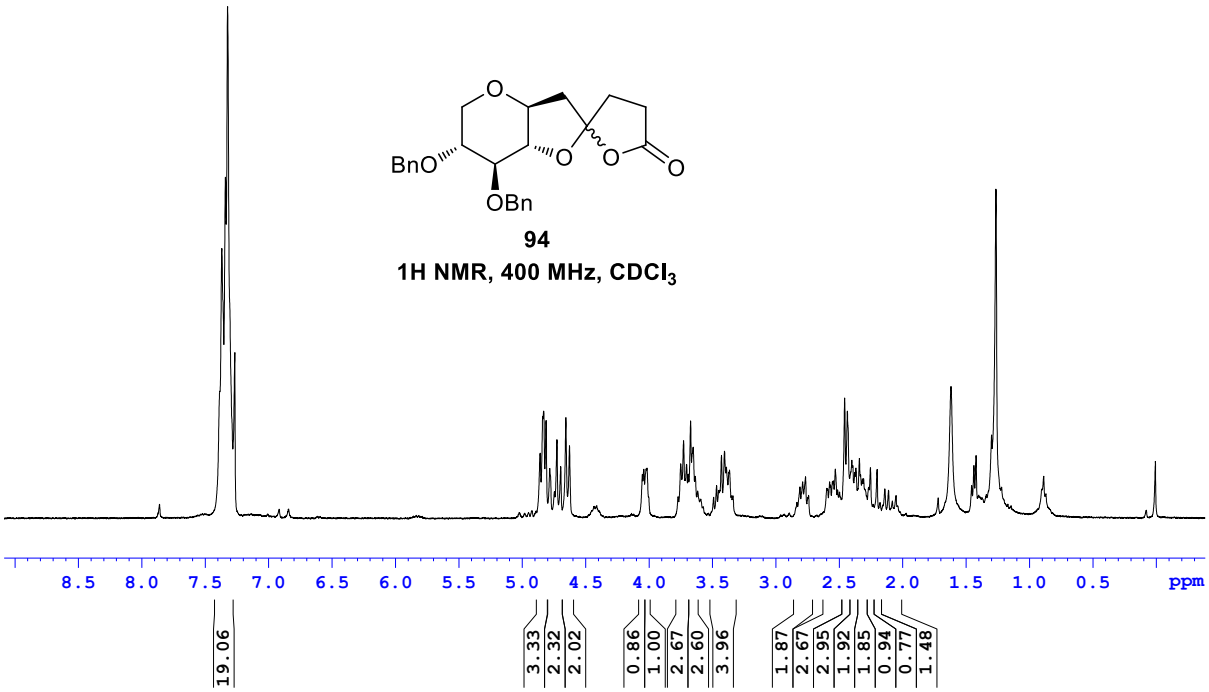
93

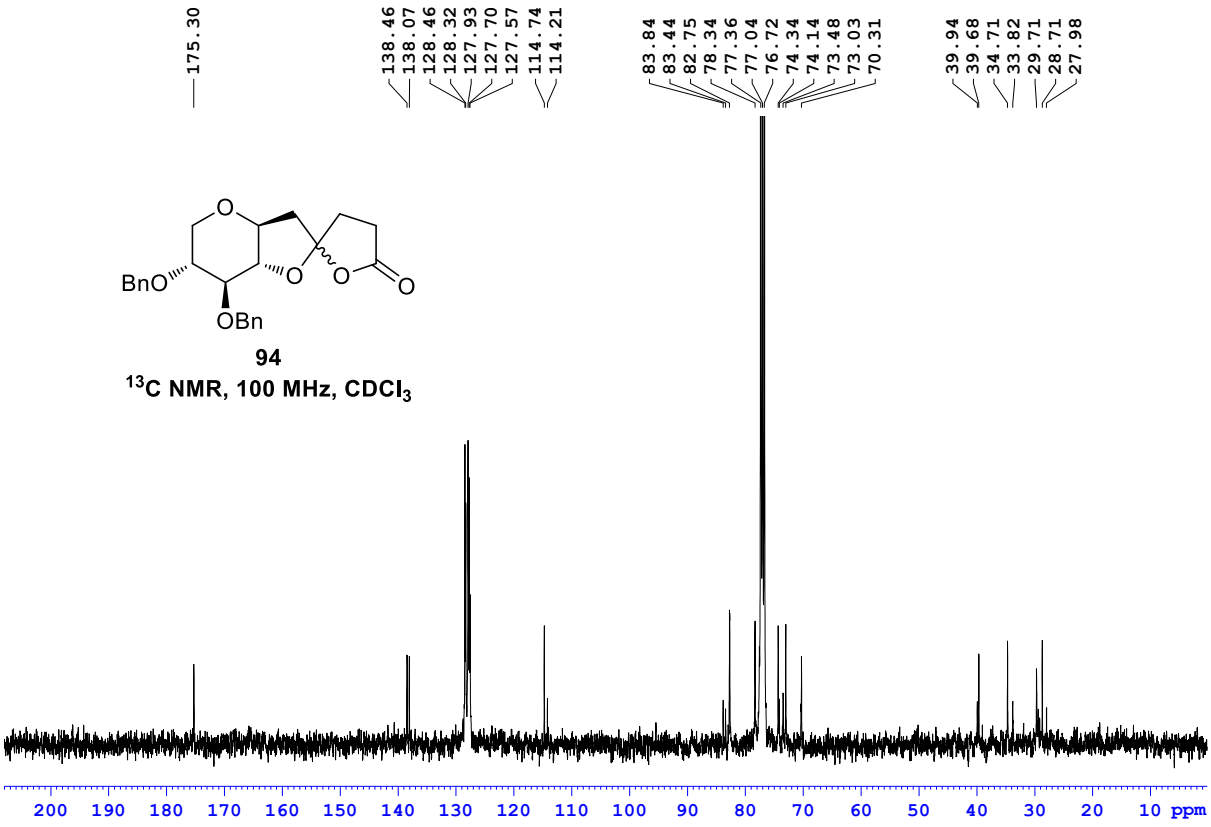
1H NMR, 400 MHz, $CDCl_3$

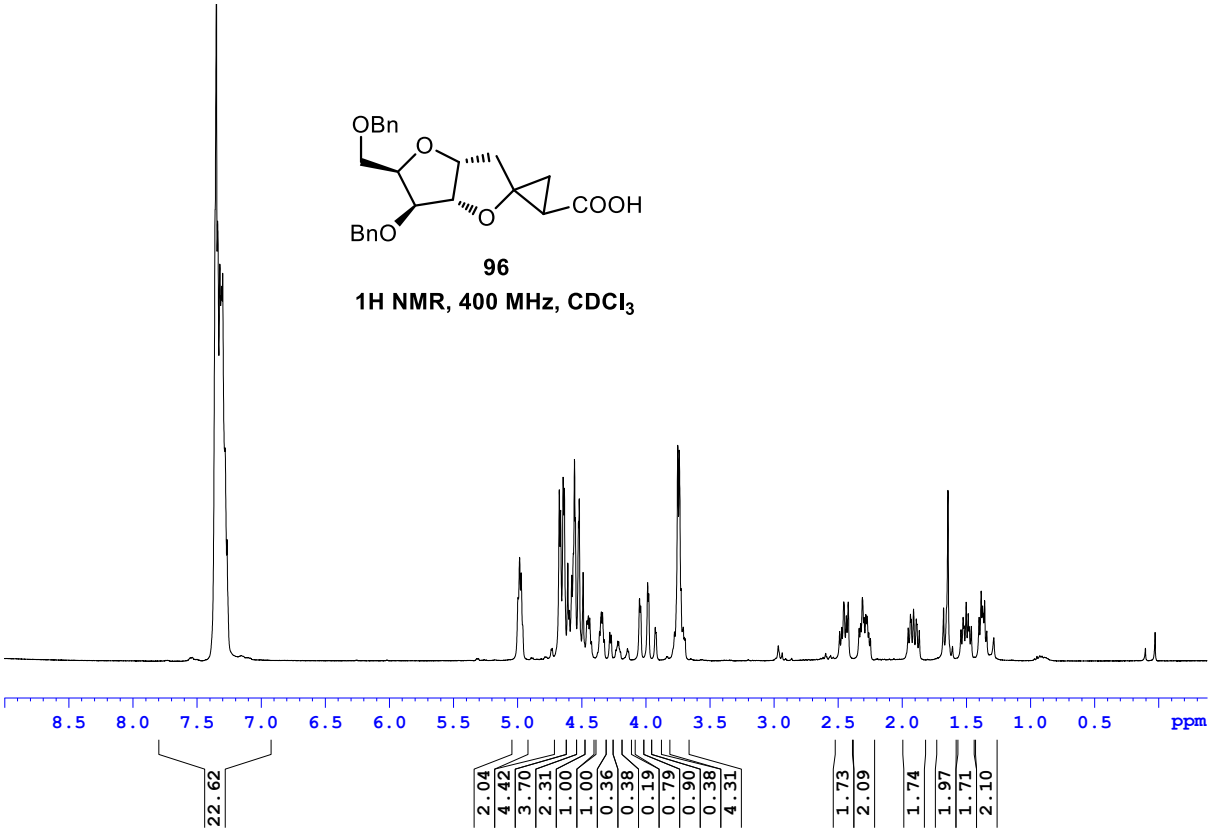


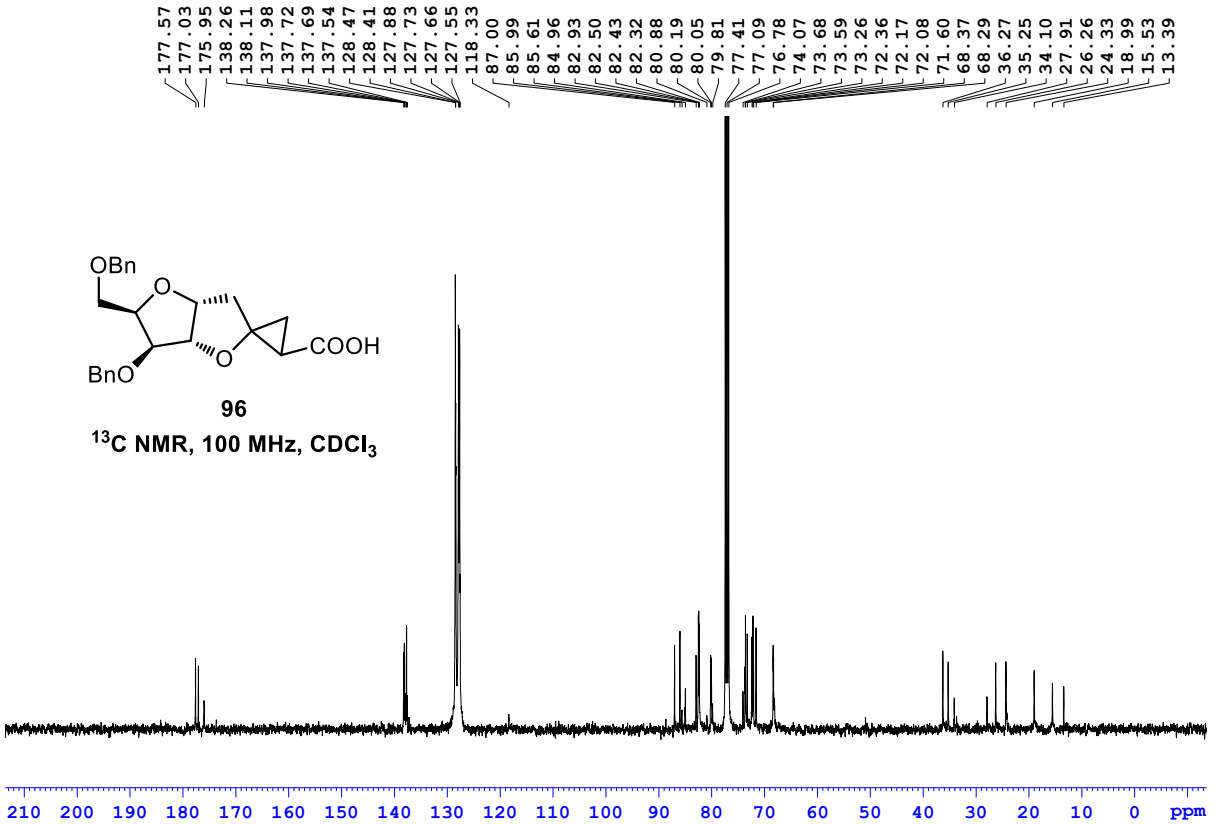
93

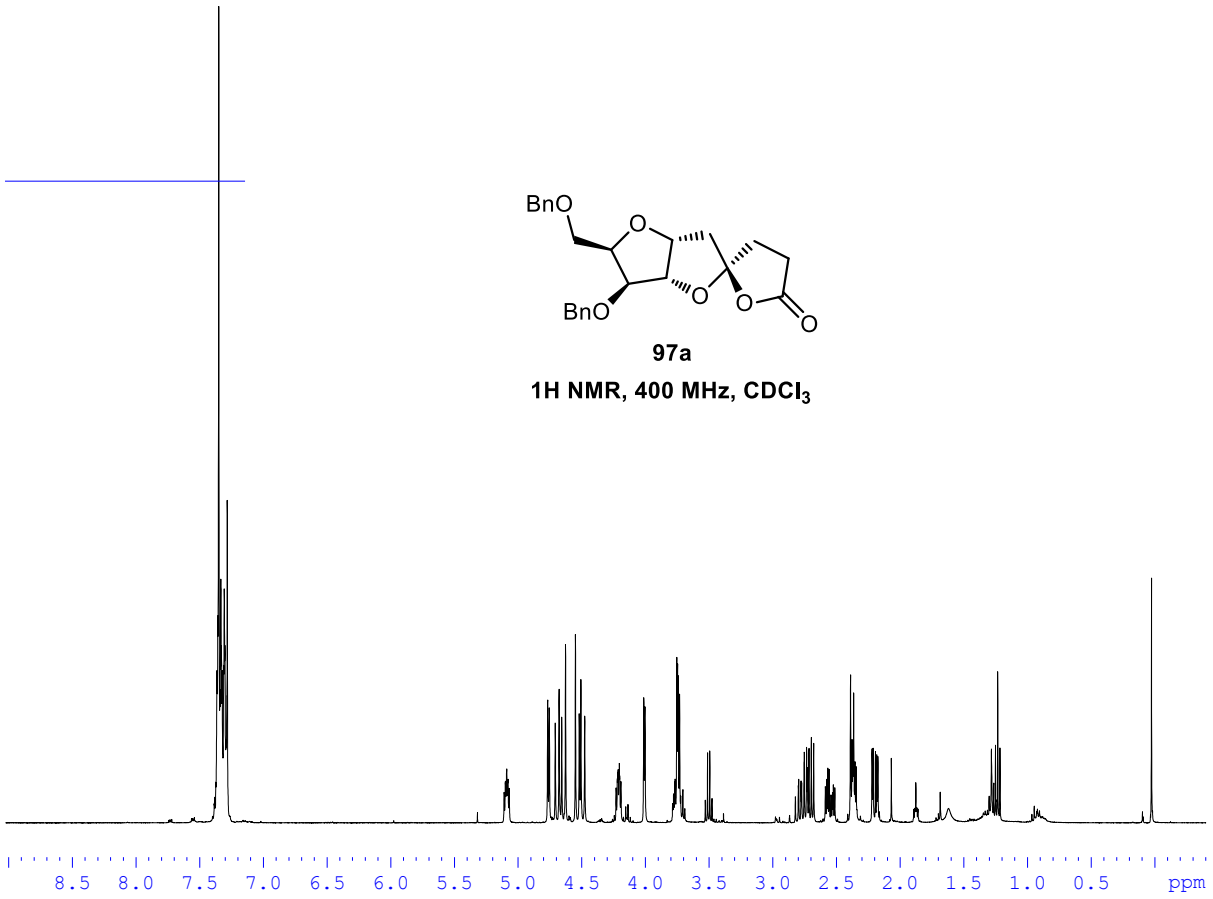
^{13}C NMR, 100 MHz, $CDCl_3$


BnO
OBn
O
O
O
O
94
1H NMR, 400 MHz, CDCl3
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
19.06
3.33 2.32 2.02
0.86 1.00 2.67 2.60 3.96
1.87 2.67 2.95 1.92 1.85 0.94 0.77 1.48


175.30
138.46 138.07 128.46 128.32 127.93 127.70 127.57 114.74 114.21
83.84 83.44 82.75 78.34 77.36 77.04 76.72 74.34 74.14 73.48 73.03 70.31
39.94 39.68 34.71 33.82 29.71 28.71 27.98
BnO
OBn
O
O
O
O
94
13C NMR, 100 MHz, CDCl3
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

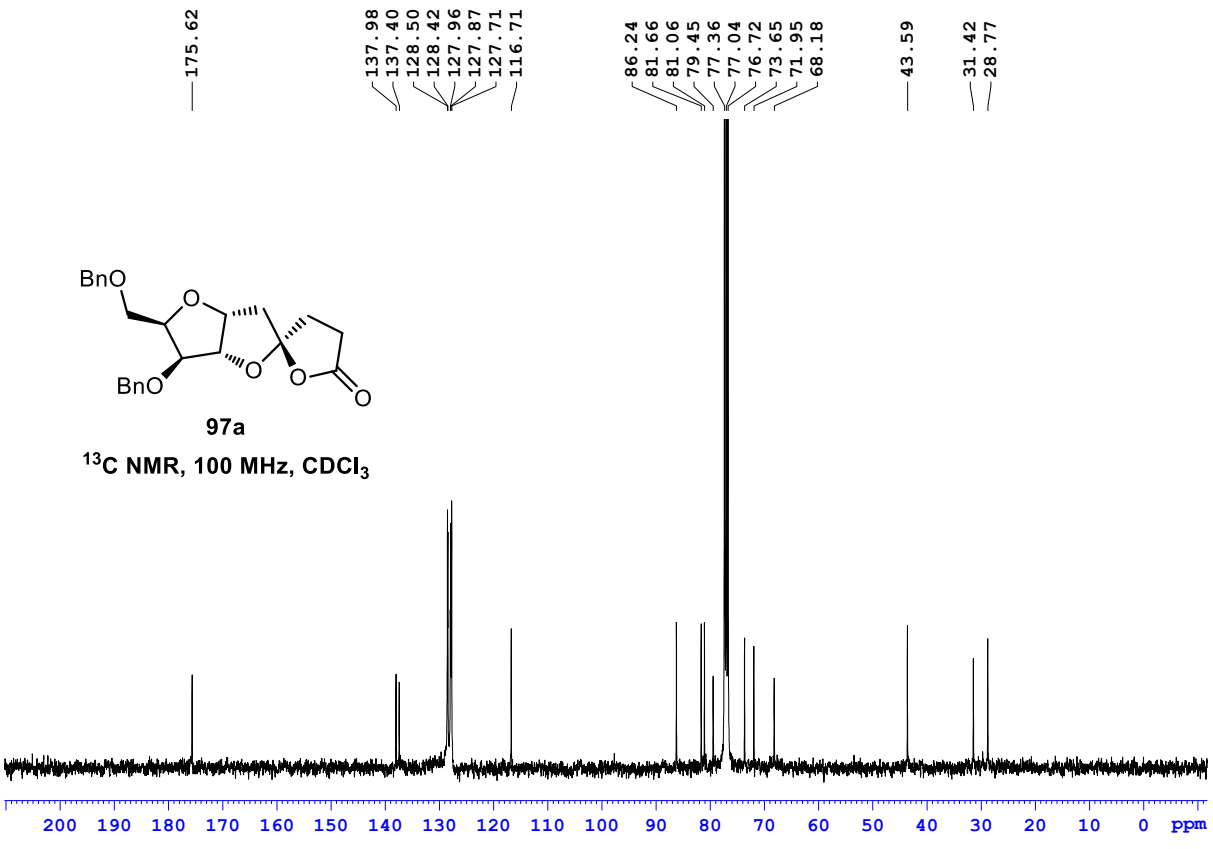

OBn
BnO
O
O
COOH
96
1H NMR, 400 MHz, CDCl3
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
22.62
2.04 4.42 3.70 2.31 1.00 1.00 0.36 0.38 0.19 0.79 0.90 0.38 4.31
1.73 2.09 1.74 1.97 1.71 2.10


177.57 177.03 175.95 138.26 138.11 137.98 137.72 137.69 137.54 128.47 128.41 127.88 127.73 127.66 127.55 118.33 87.00 85.99 85.61 84.96 82.93 82.50 82.43 82.32 80.88 80.19 80.05 79.81 77.41 77.09 76.78 74.07 73.68 73.59 73.26 72.36 72.17 72.08 71.60 68.37 68.29 36.27 35.25 34.10 27.91 26.26 24.33 18.99 15.53 13.39
OBn
BnO
O
O
COOH
96
13C NMR, 100 MHz, CDCl3
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm



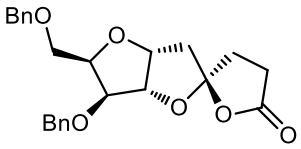
97a

1H NMR, 400 MHz, $CDCl_3$



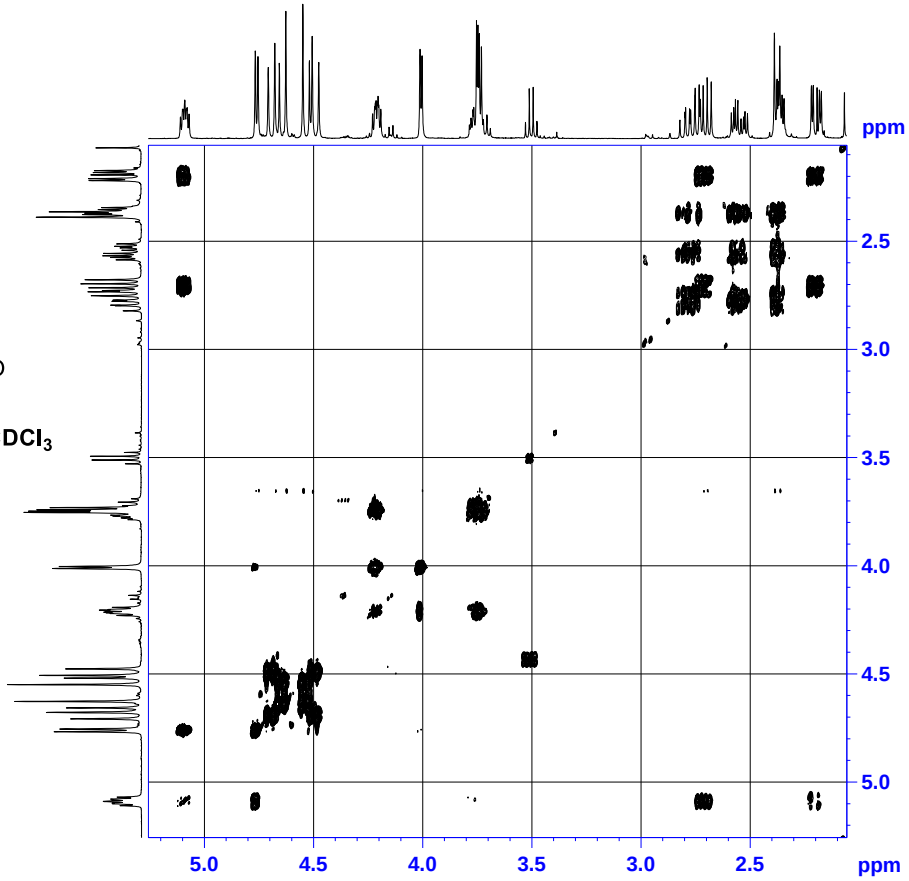
97a

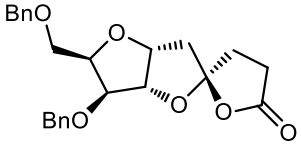
^{13}C NMR, 100 MHz, $CDCl_3$



97a

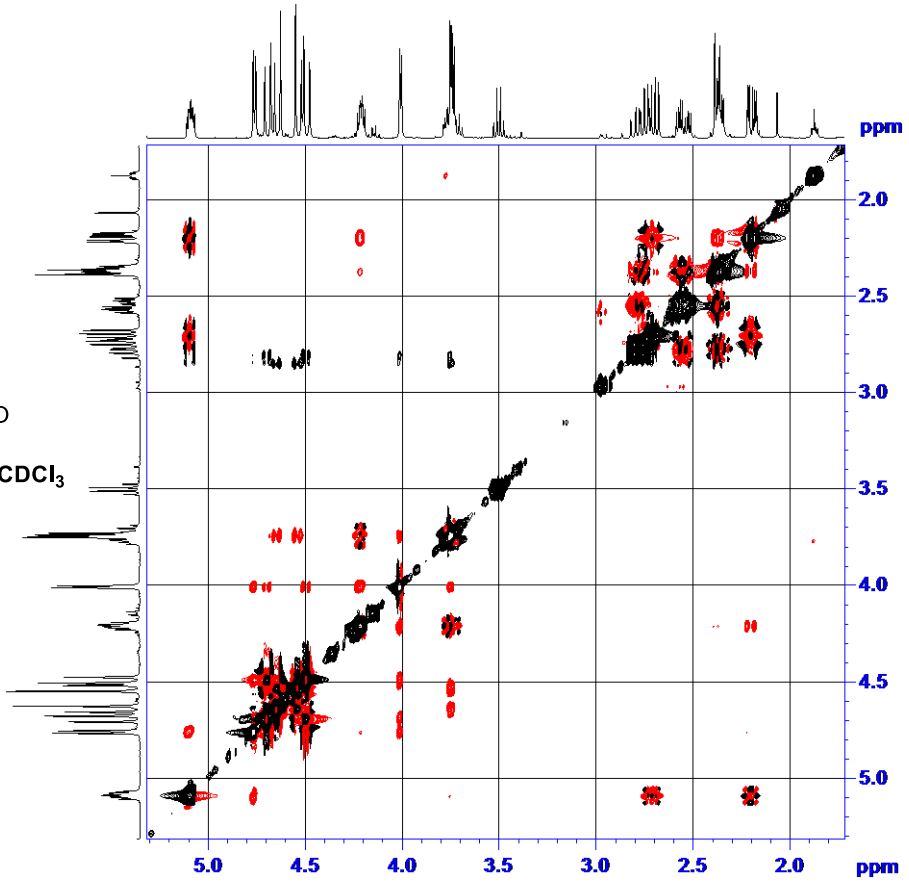
^{1}H-^{1}H COSY NMR, 400 MHz, $CDCl_3$

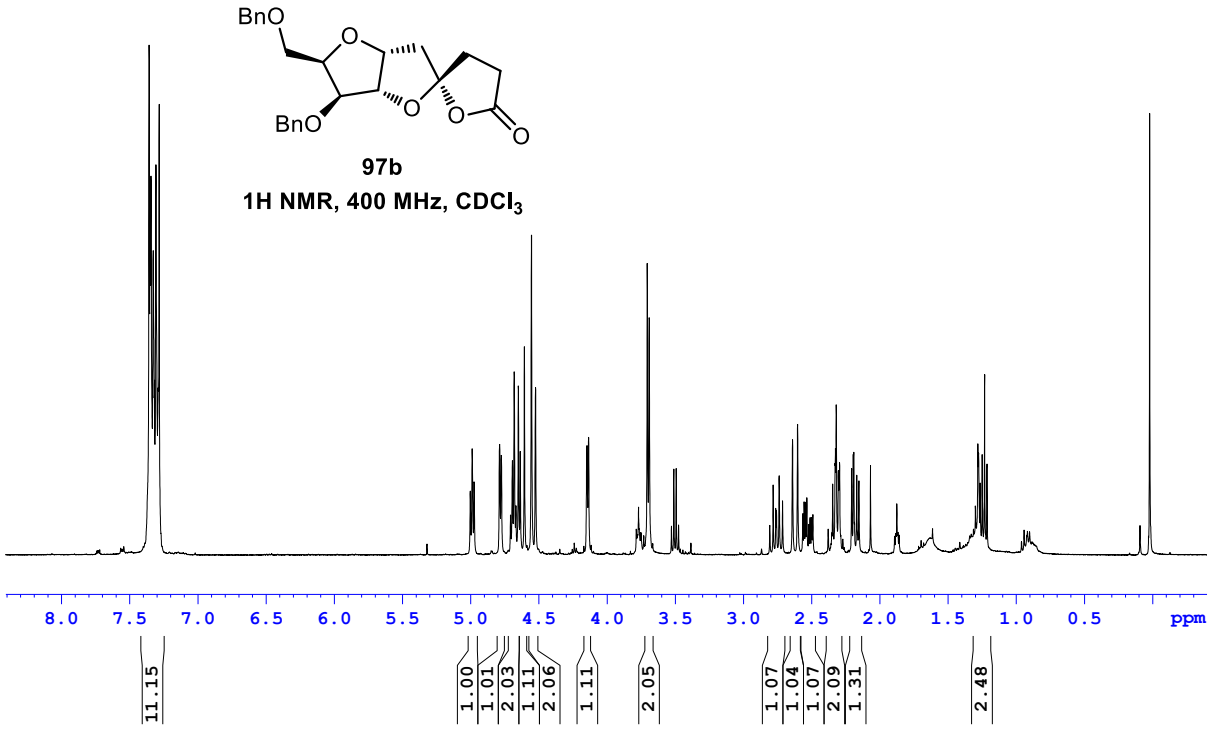


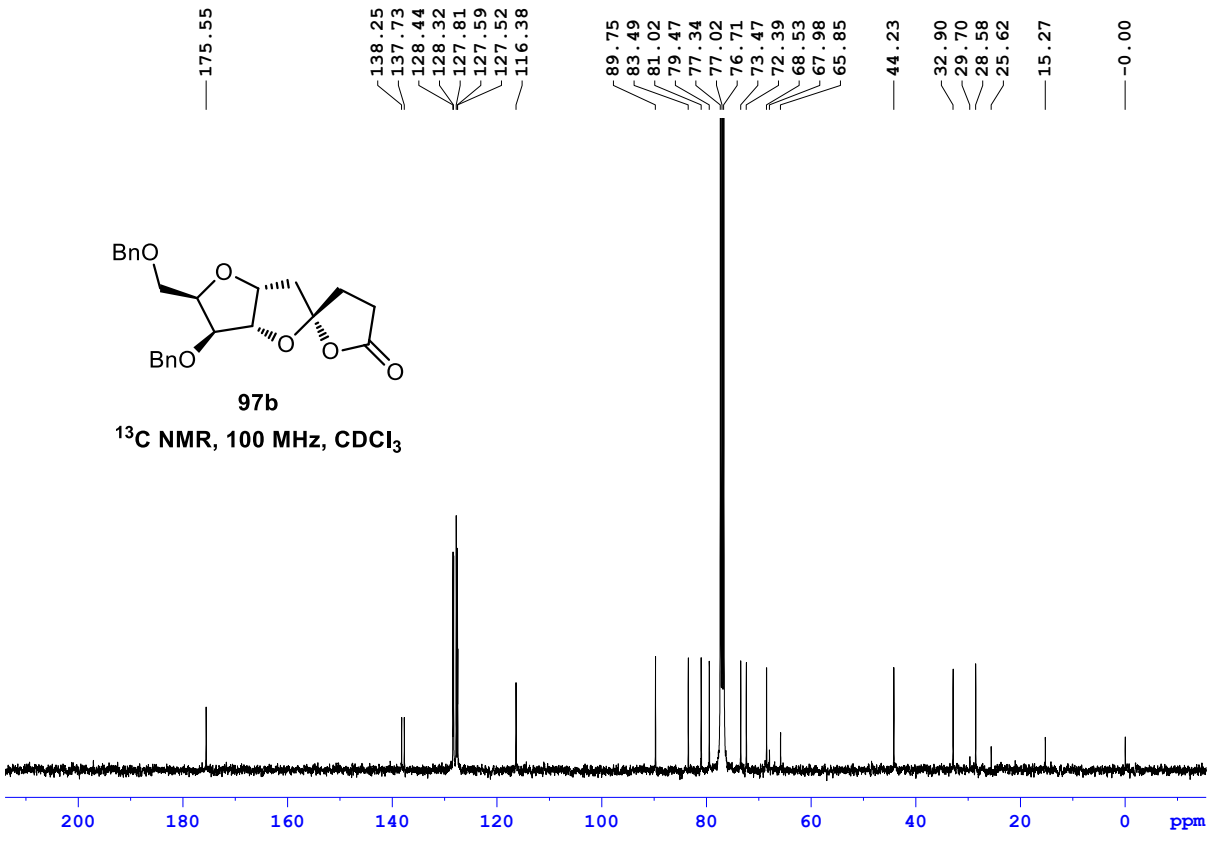


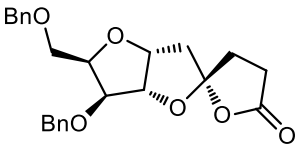
97a

^{1}H-^{1}H NOESY NMR, 400 MHz, $CDCl_3$



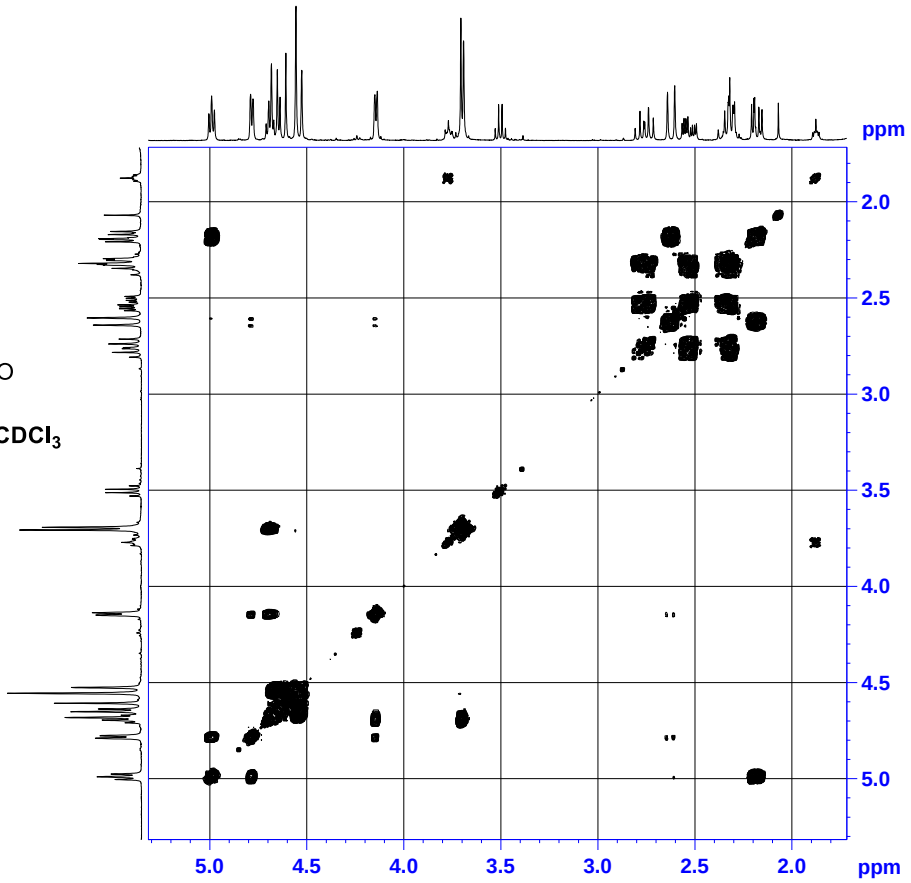

BnO
BnO
O
O
O
O
97b
1H NMR, 400 MHz, CDCl3
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
11.15
1.00
1.01
2.03
1.11
2.06
1.11
2.05
1.07
1.04
1.07
2.09
1.31
2.48

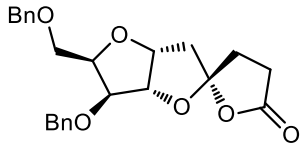

175.55
138.25
137.73
128.44
128.32
127.81
127.59
127.52
116.38
89.75
83.49
81.02
79.47
77.34
77.02
76.71
73.47
72.39
68.53
67.98
65.85
44.23
32.90
29.70
28.58
25.62
15.27
-0.00
BnO
BnO
O
O
O
O
97b
13C NMR, 100 MHz, CDCl3
200 180 160 140 120 100 80 60 40 20 0 ppm



97b

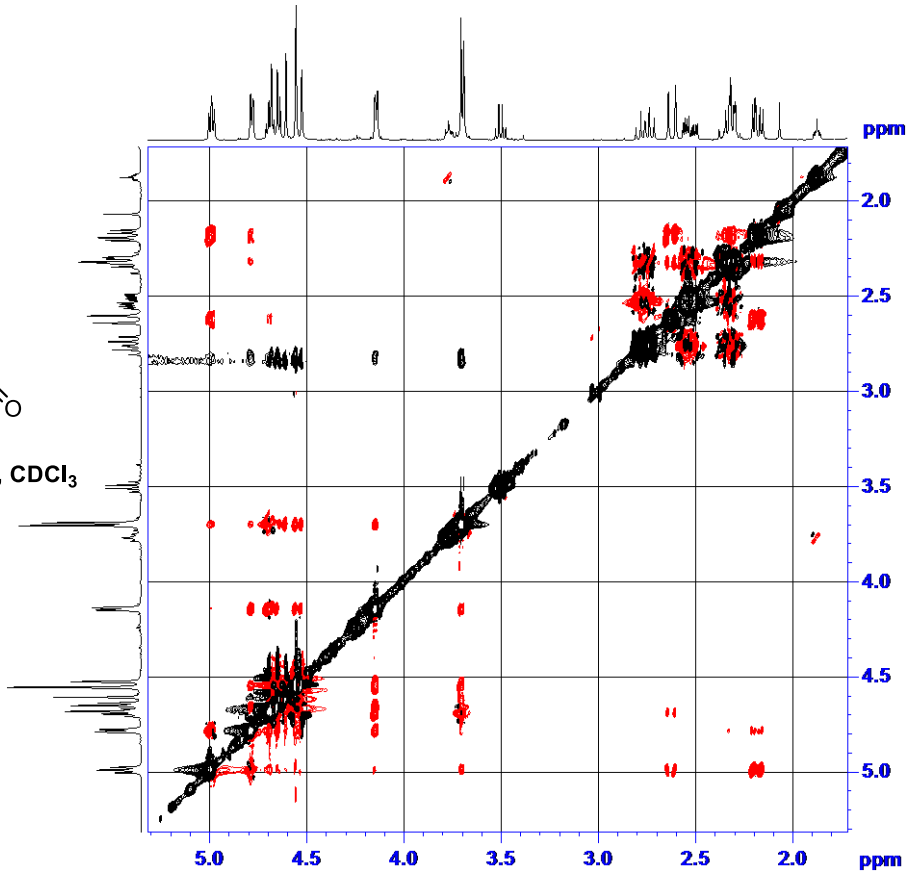
^{1}H-^{1}H COSY NMR, 400 MHz, $CDCl_3$

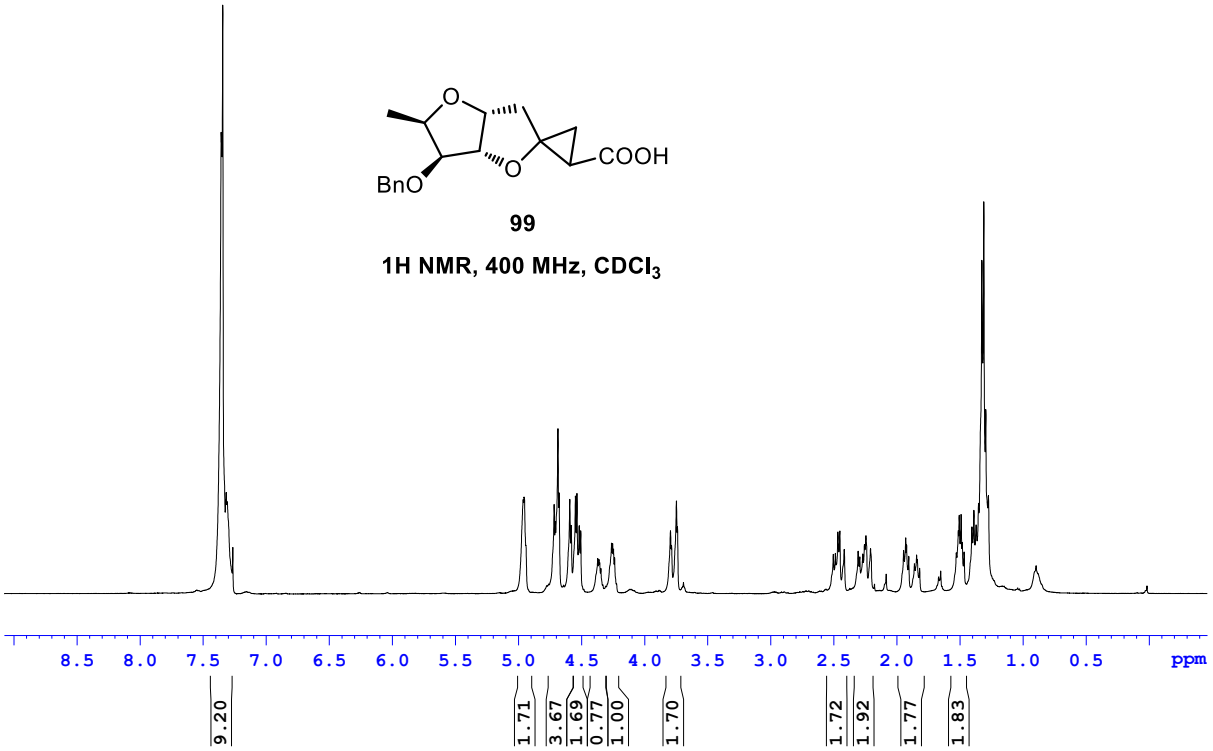


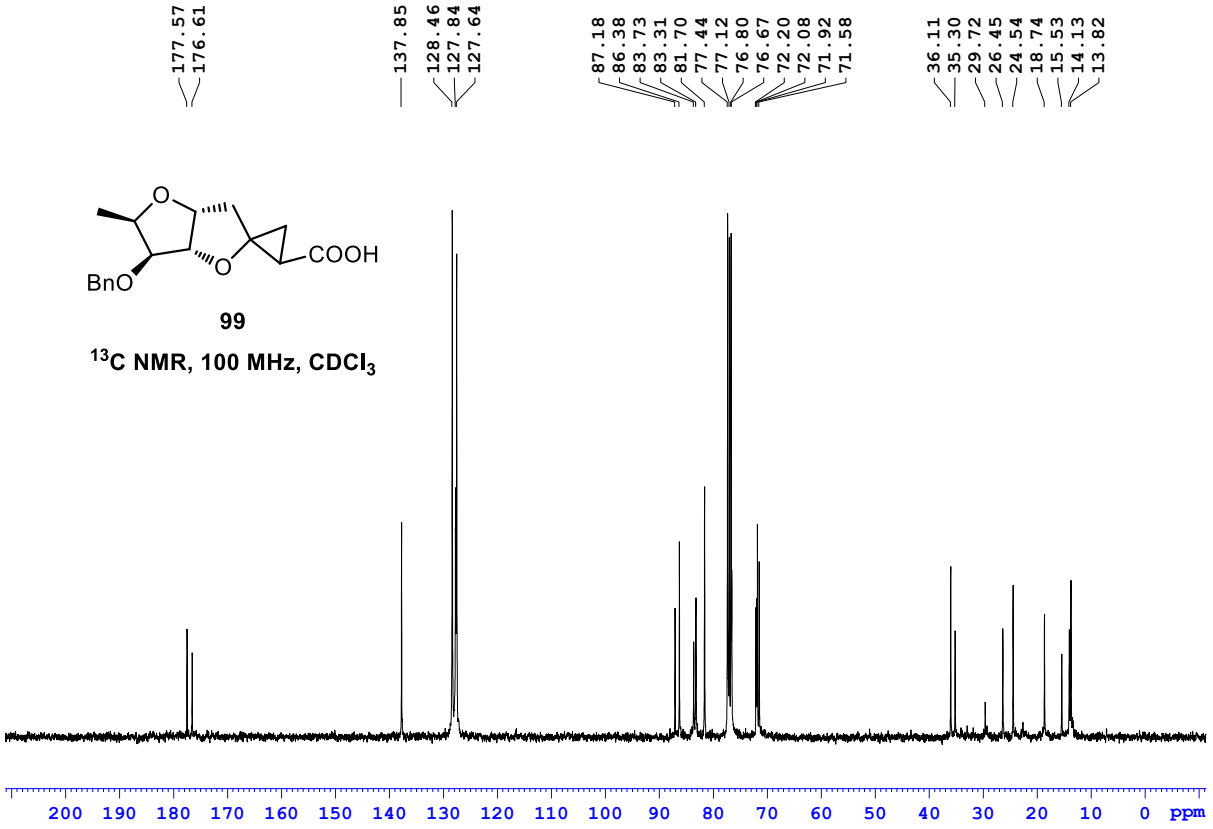


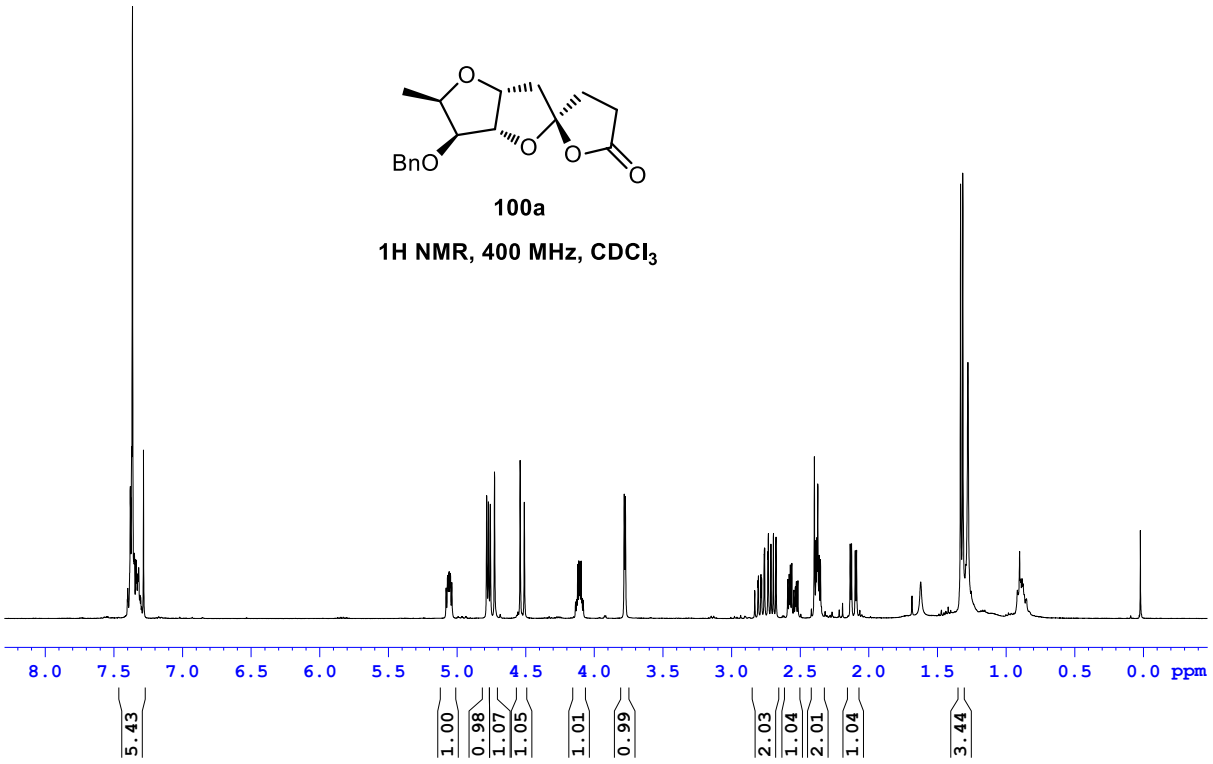
97b

^{1}H-^{1}H NOESY NMR, 400 MHz, $CDCl_3$



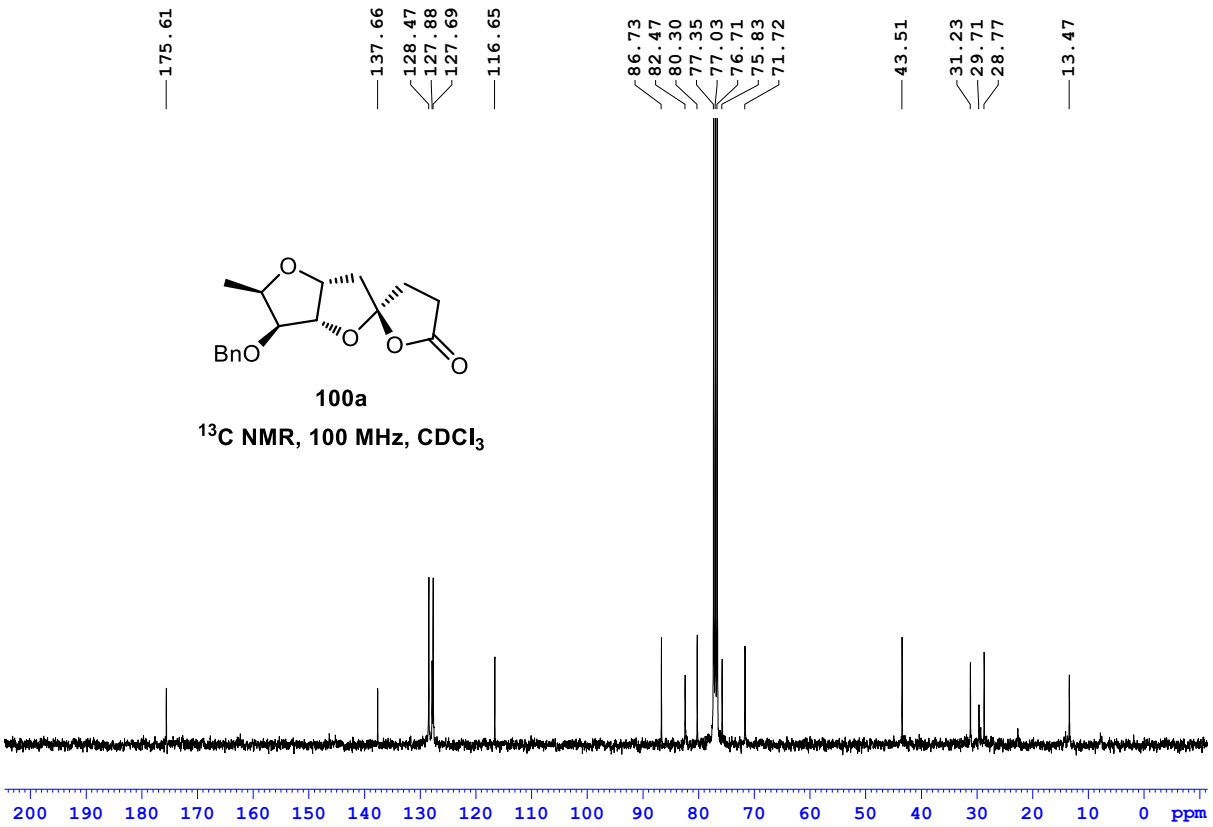

BnO
O
O
COOH
99
1H NMR, 400 MHz, CDCl3
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
9.20
1.71
3.67
1.69
0.77
1.00
1.70
1.72
1.92
1.77
1.83


177.57
176.61
137.85
128.46
127.84
127.64
87.18
86.38
83.73
83.31
81.70
77.44
77.12
76.80
76.67
72.20
72.08
71.92
71.58
36.11
35.30
29.72
26.45
24.54
18.74
15.53
14.13
13.82
BnO
O
O
COOH
99
13C NMR, 100 MHz, CDCl3
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm



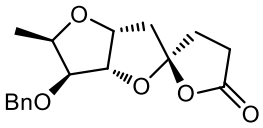
100a

1H NMR, 400 MHz, $CDCl_3$



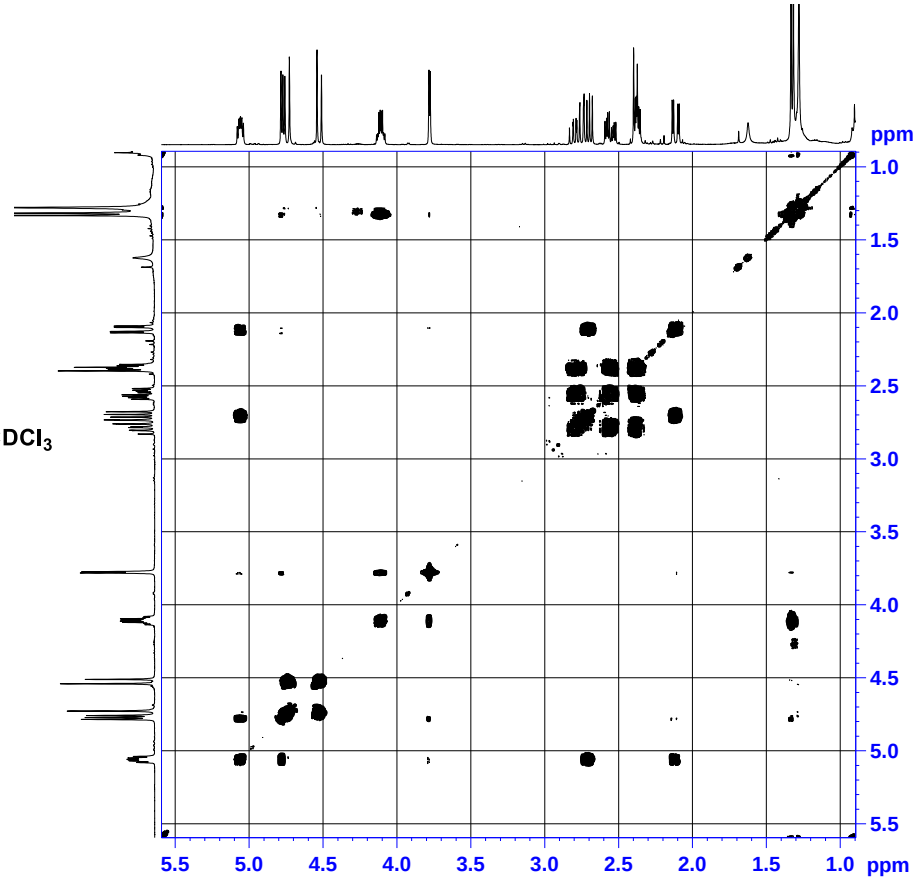
100a

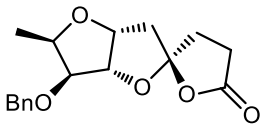
^{13}C NMR, 100 MHz, $CDCl_3$



100a

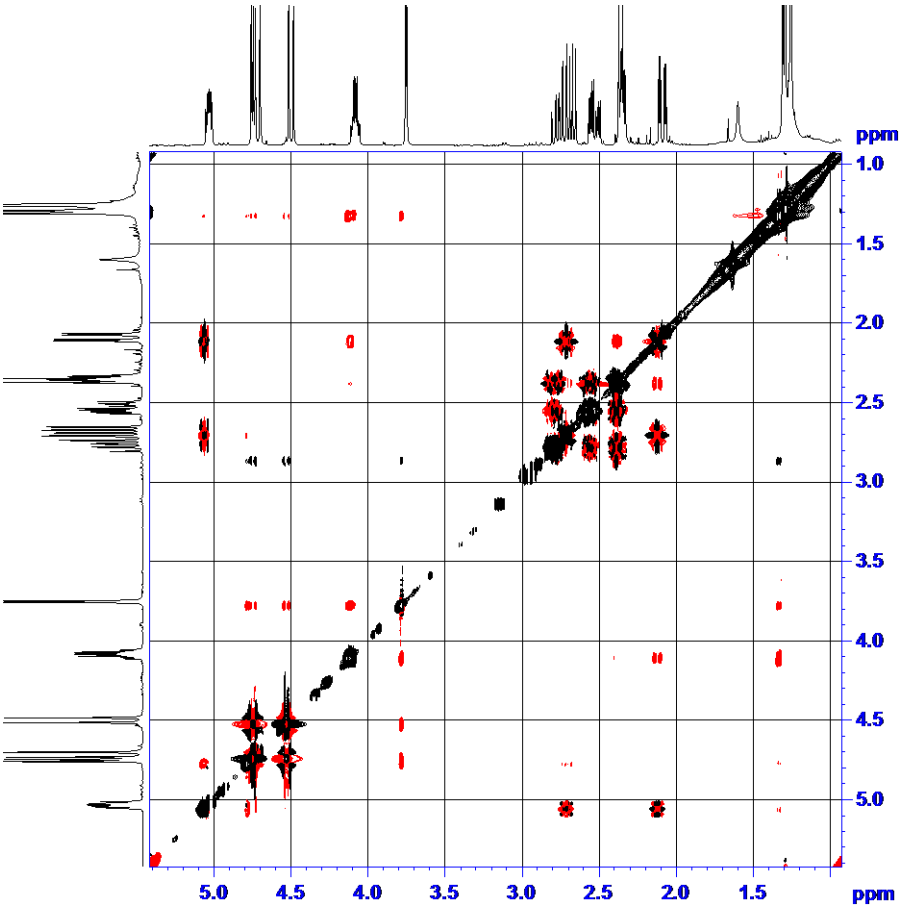
^{1}H-^{1}H COSY NMR, 400 MHz, $CDCl_3$

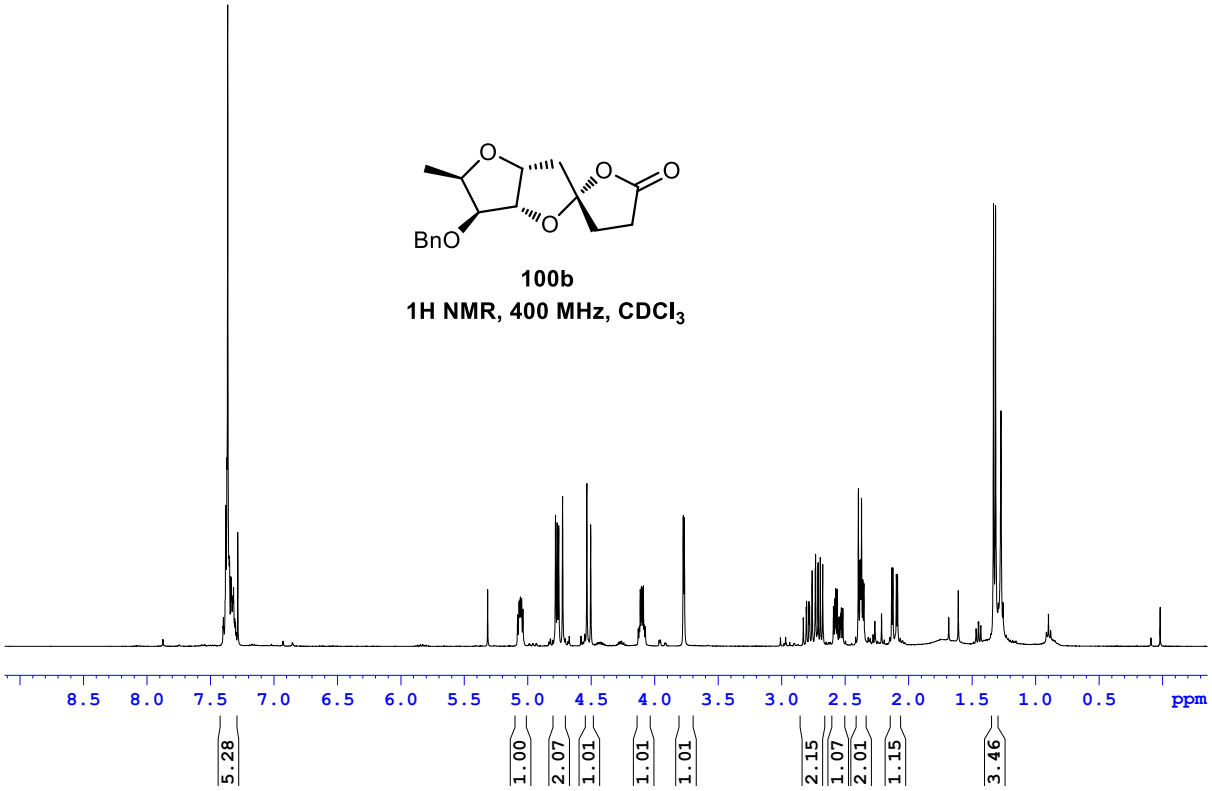




100a

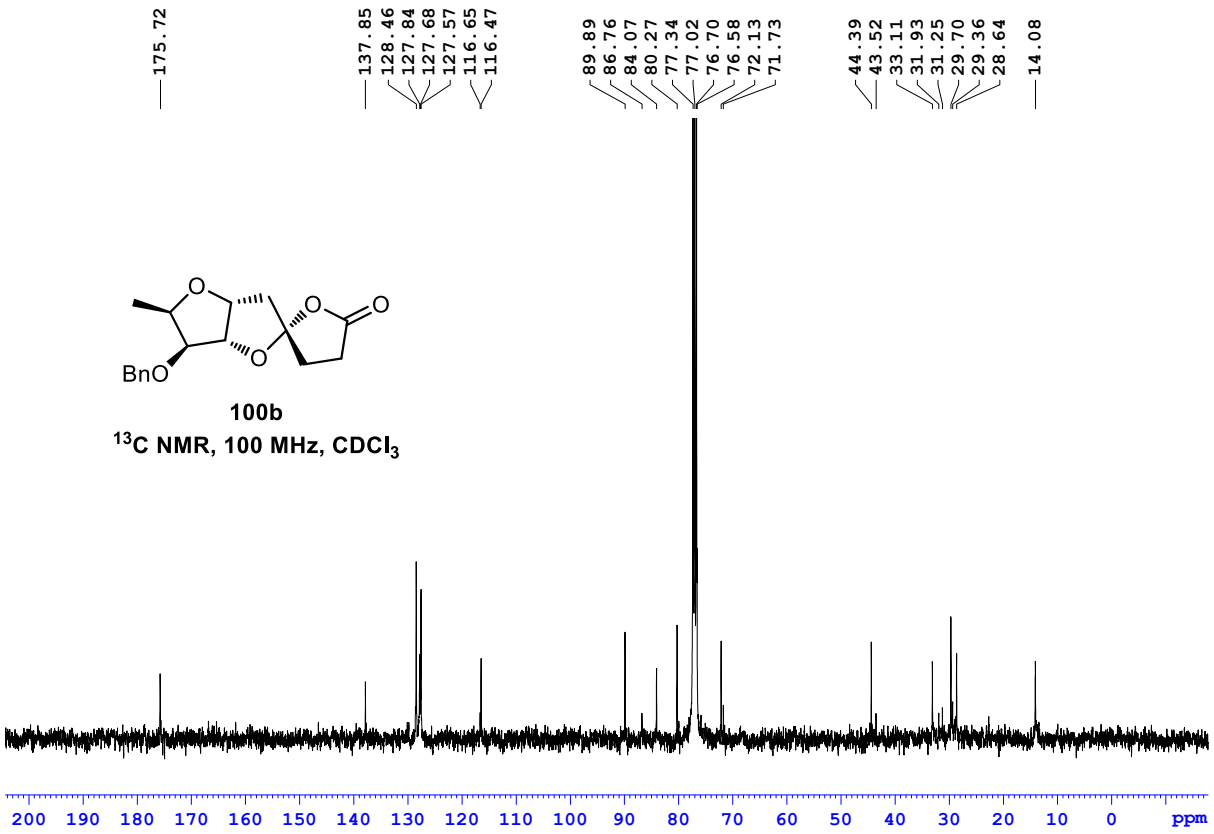
^{1}H-^{1}H NOESY NMR, 400 MHz, $CDCl_3$





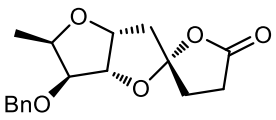
100b

1H NMR, 400 MHz, $CDCl_3$



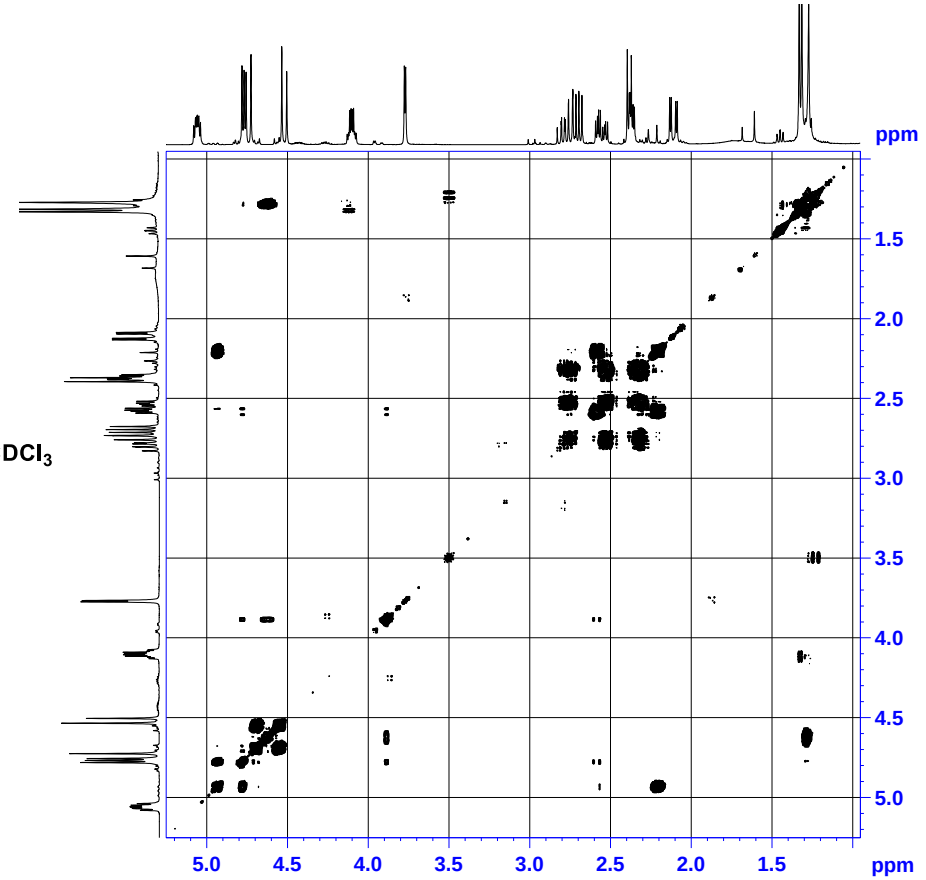
100b

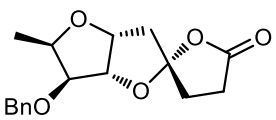
^{13}C NMR, 100 MHz, $CDCl_3$



100b

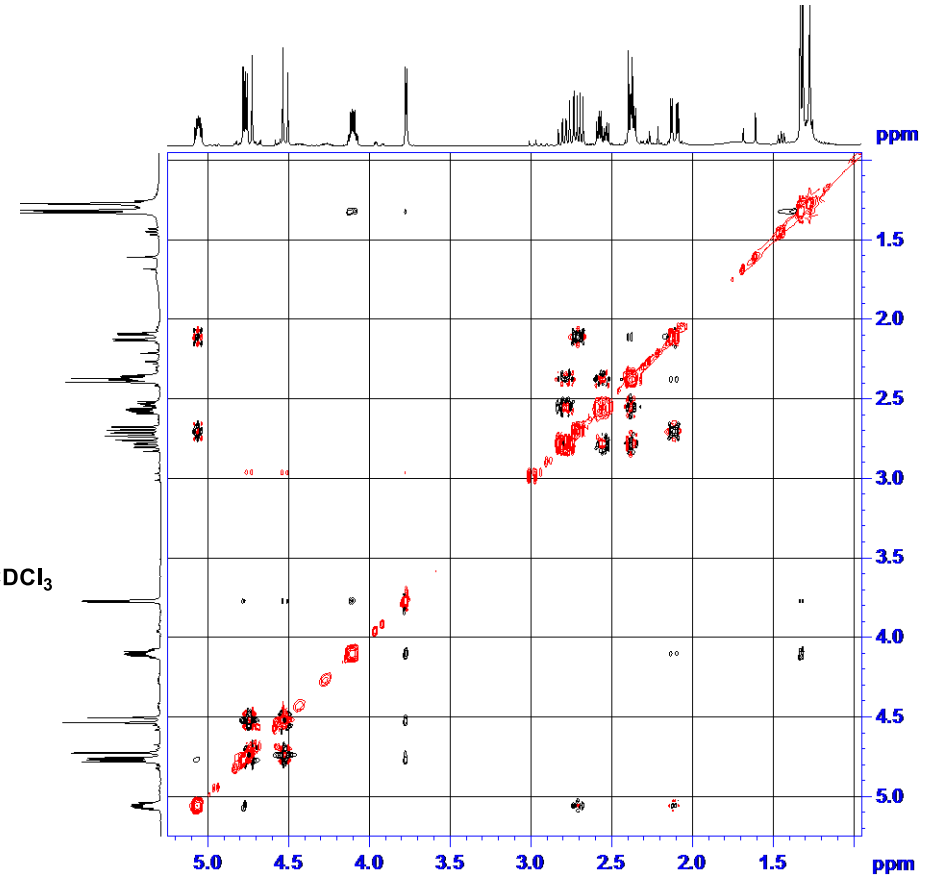
^{1}H-^{1}H COSY NMR, 400 MHz, $CDCl_3$

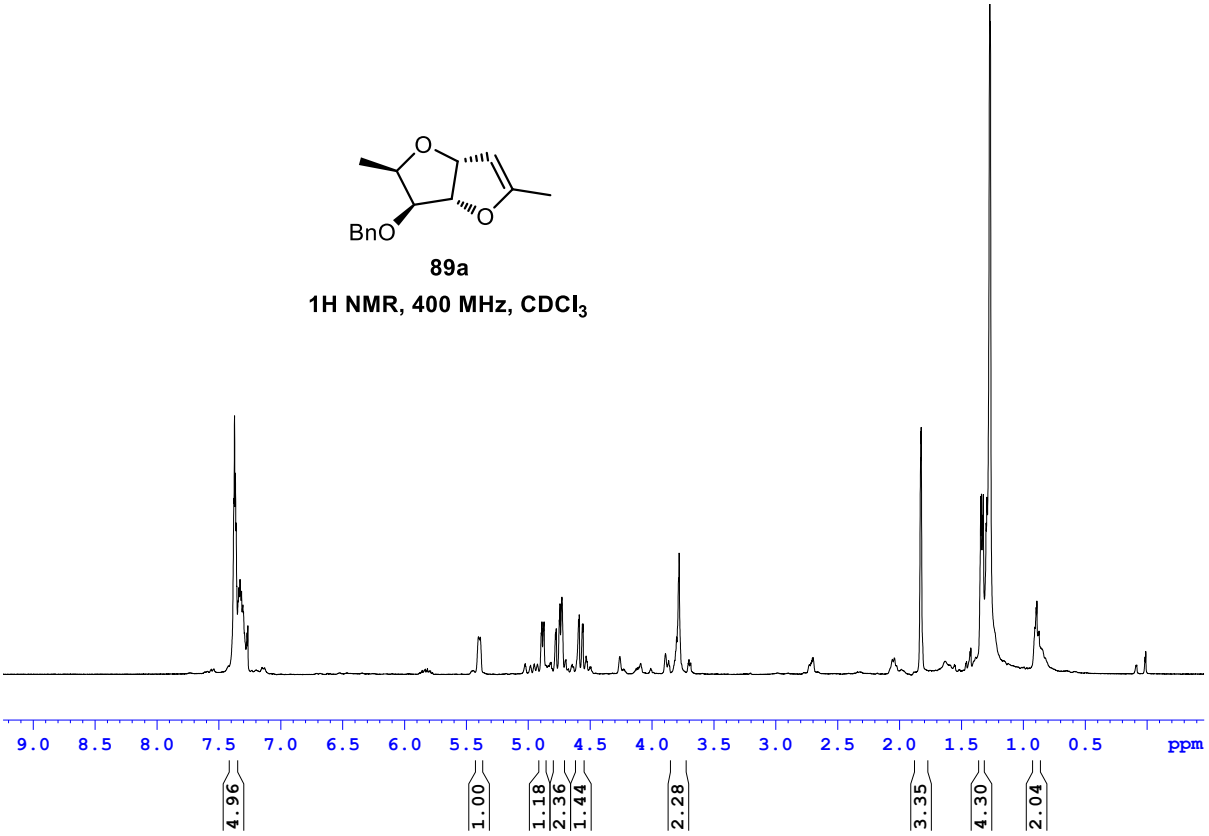




100b

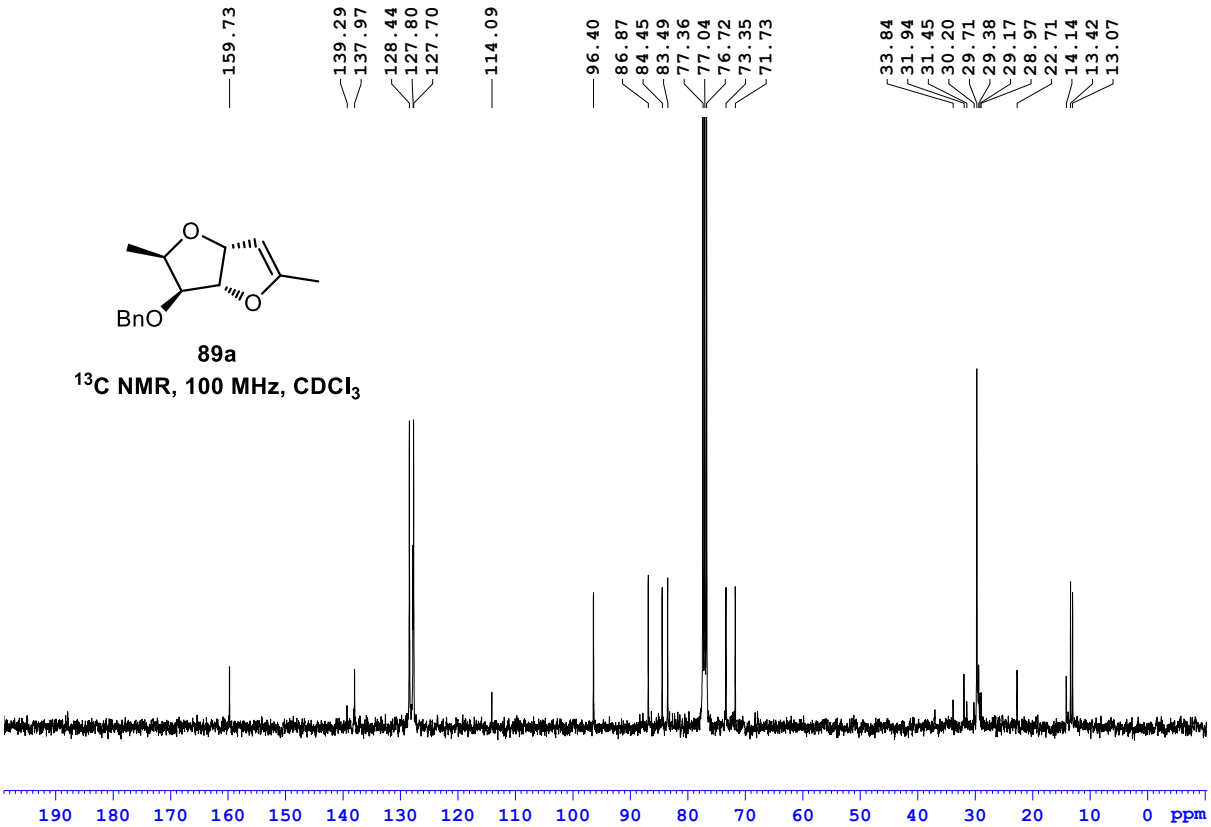
^{1}H-^{1}H NOESY NMR, 400 MHz, $CDCl_3$





89a

1H NMR, 400 MHz, $CDCl_3$



89a

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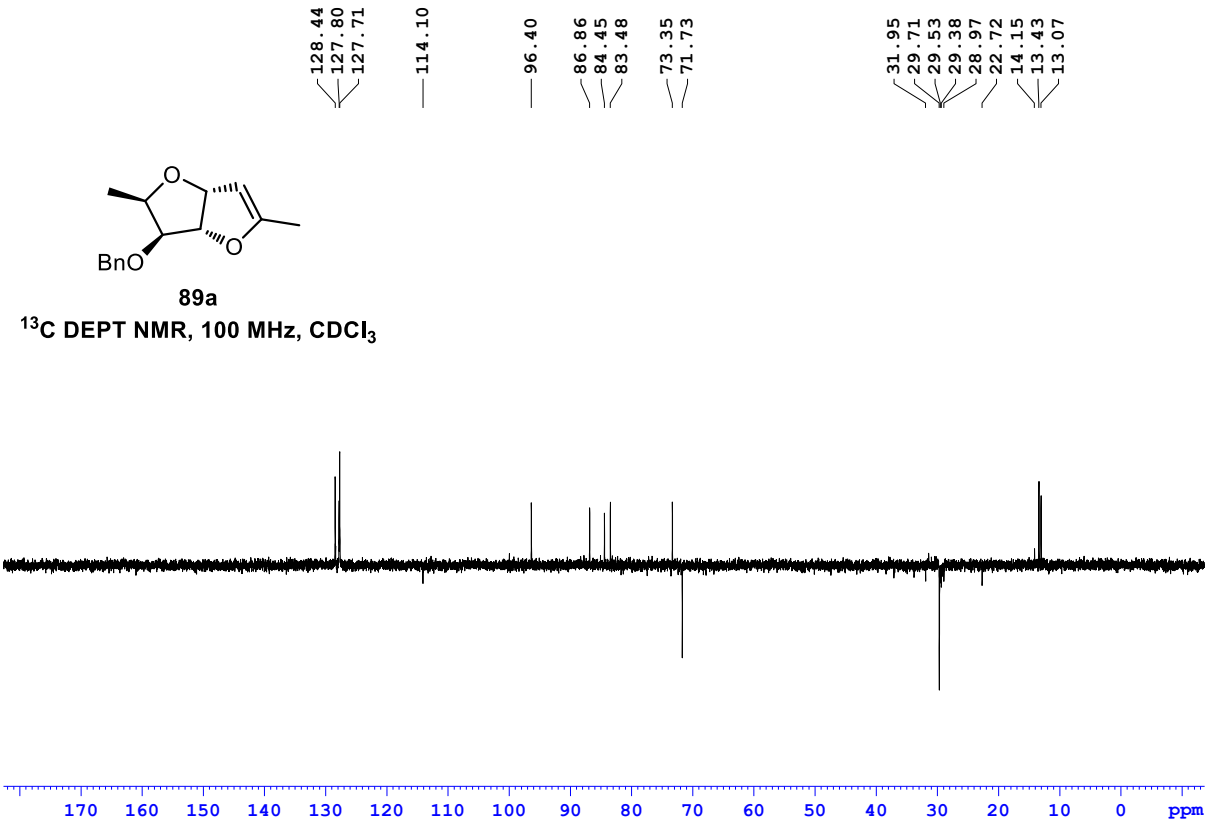
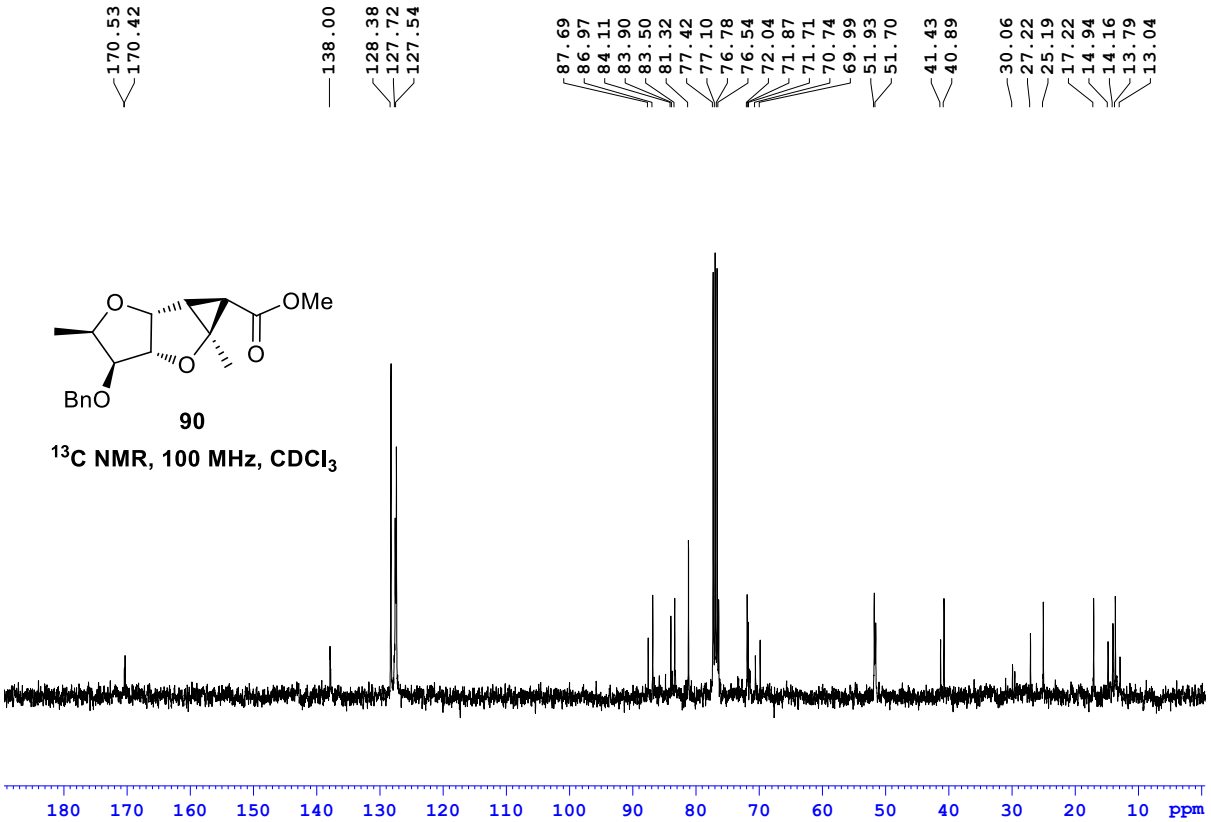


89a

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



90

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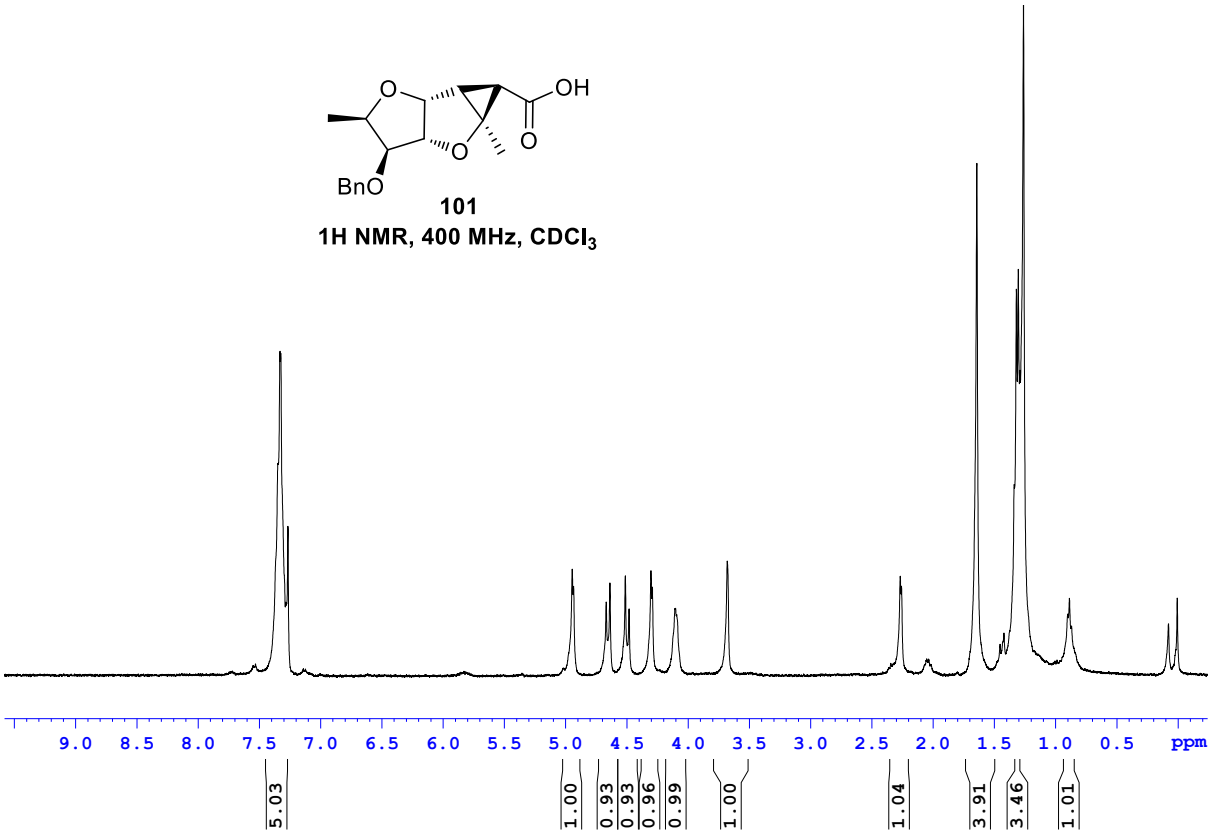

101

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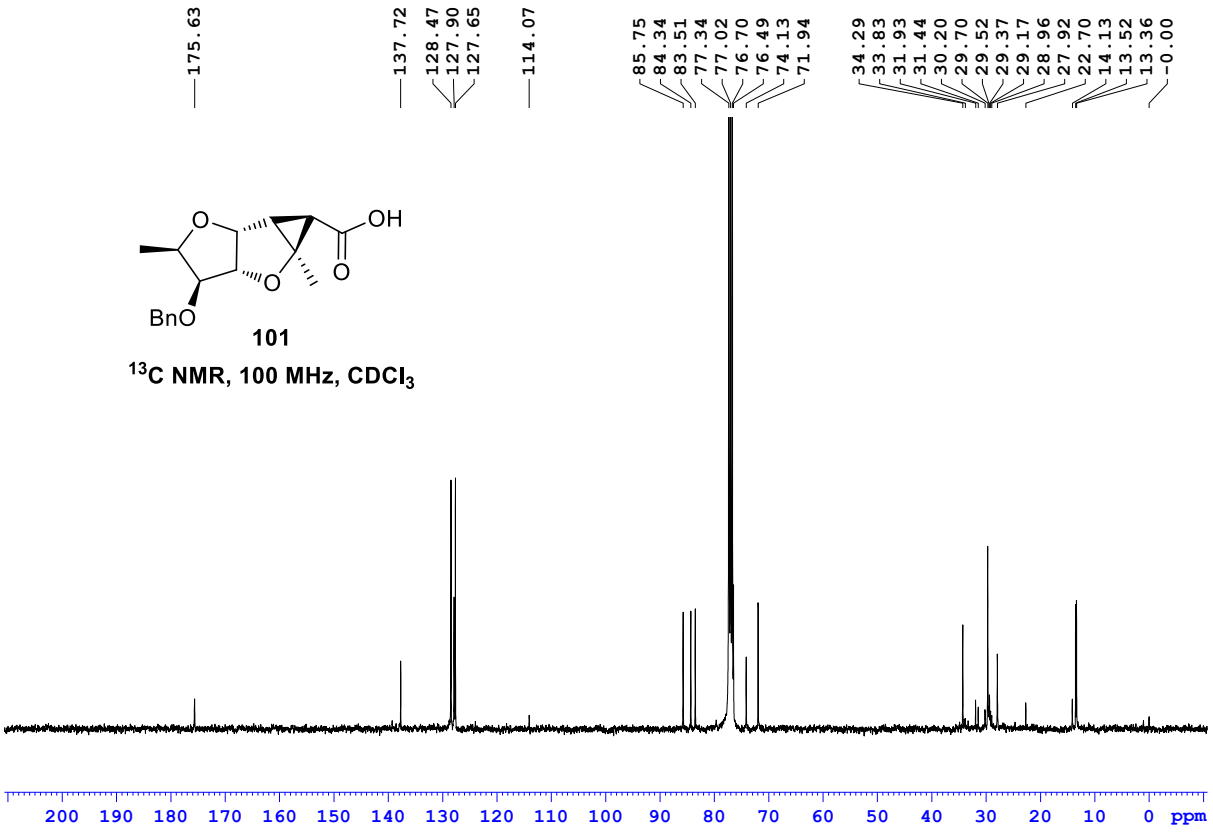

101

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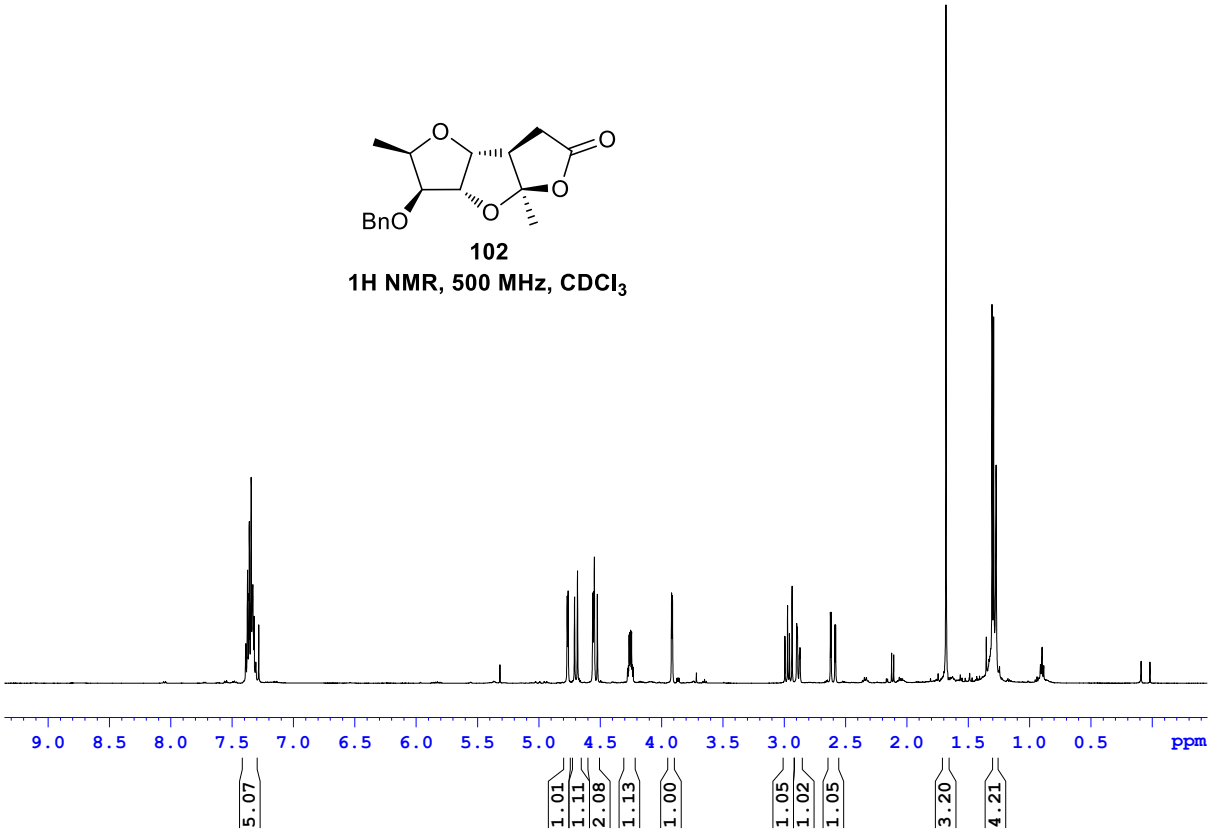

102

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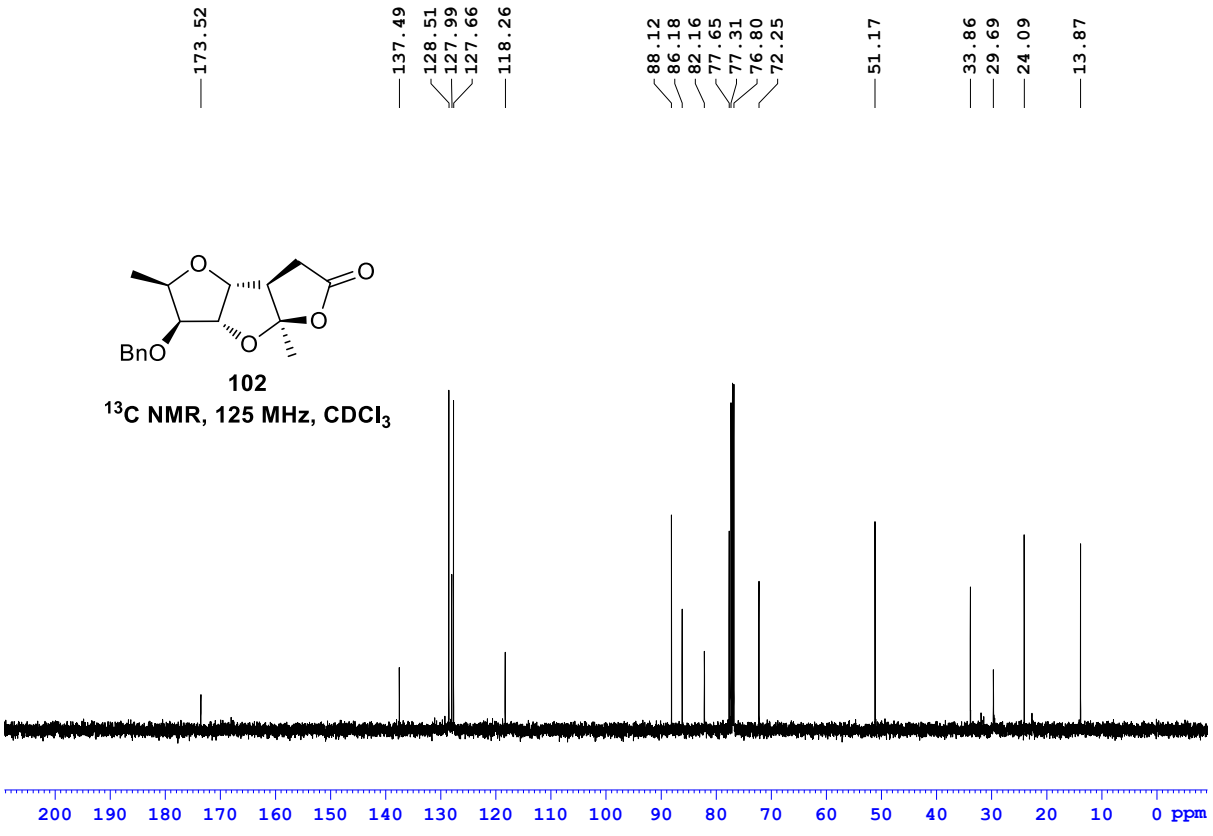

102

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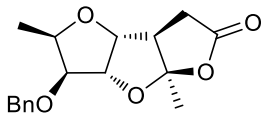
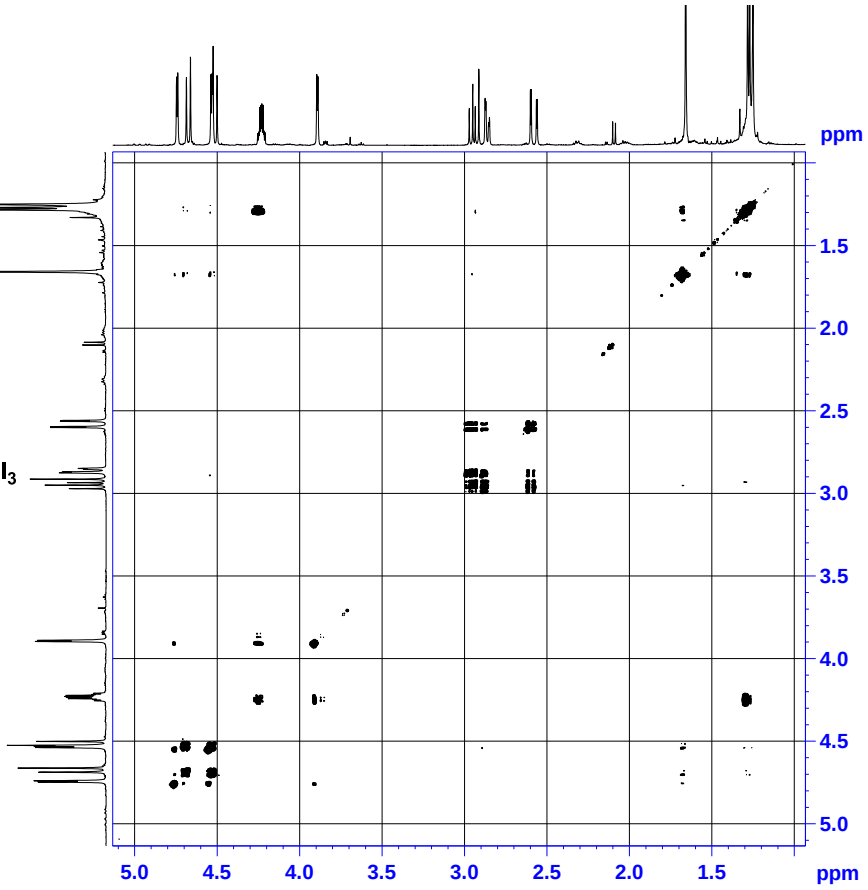
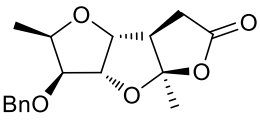


102

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





102

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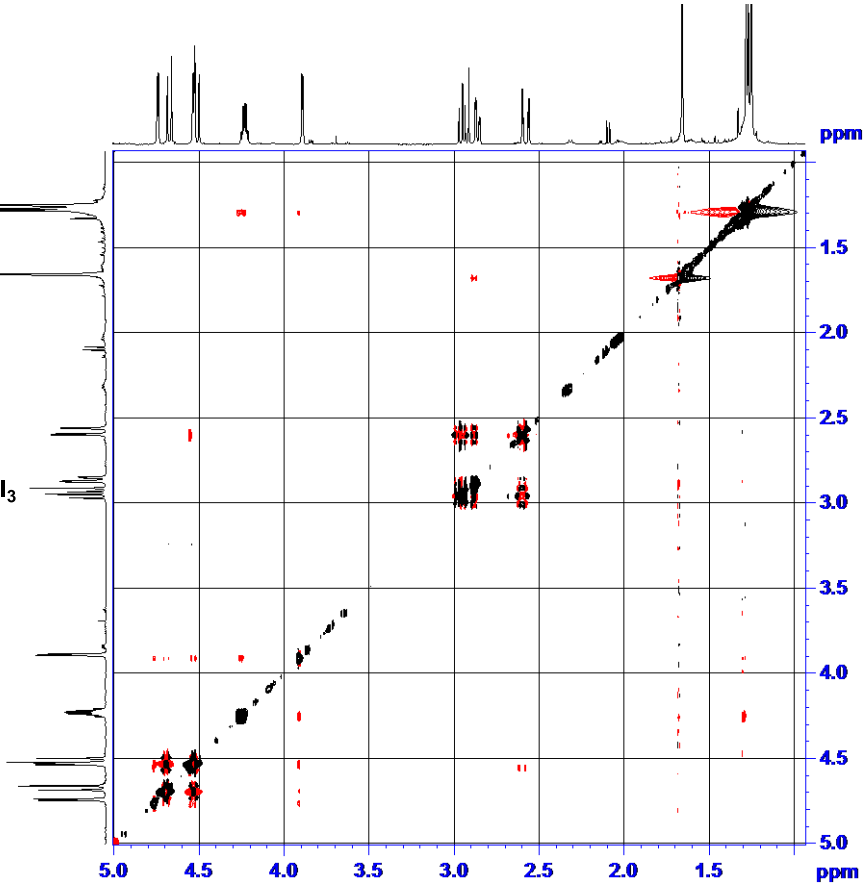
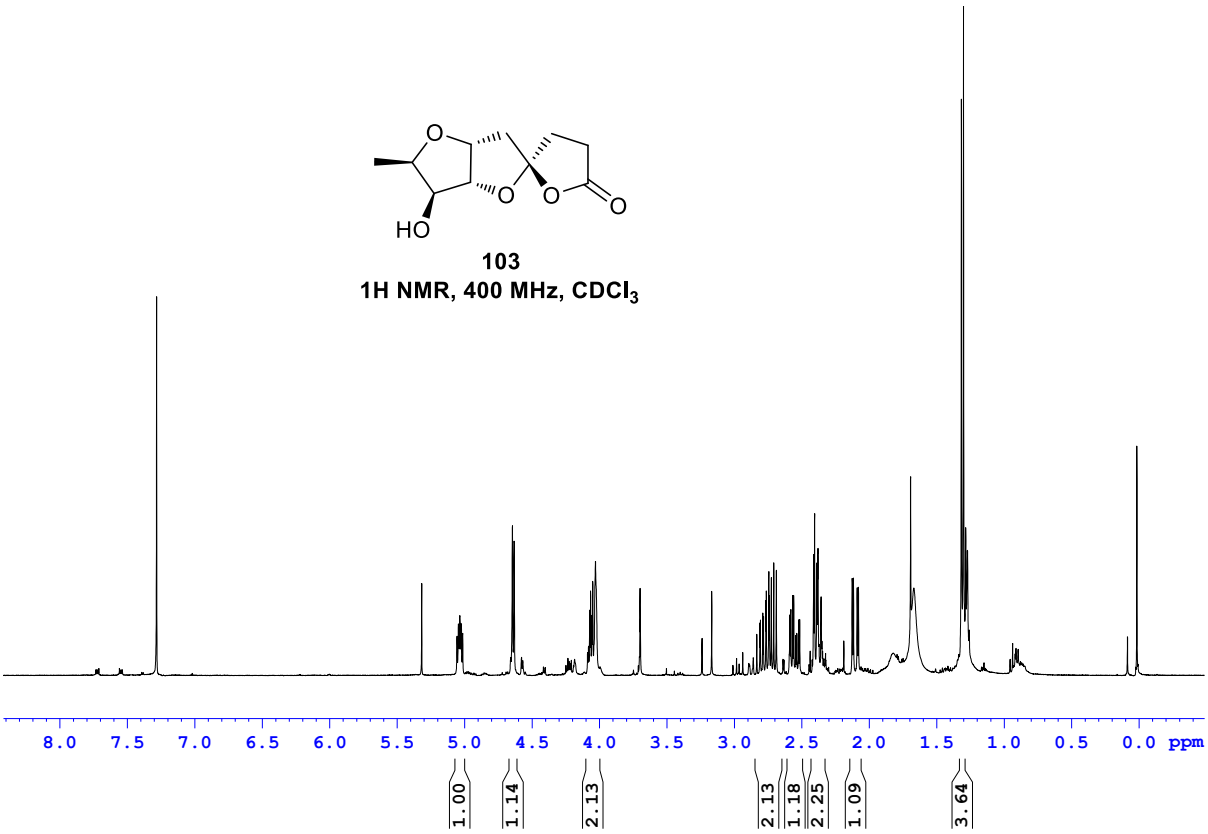
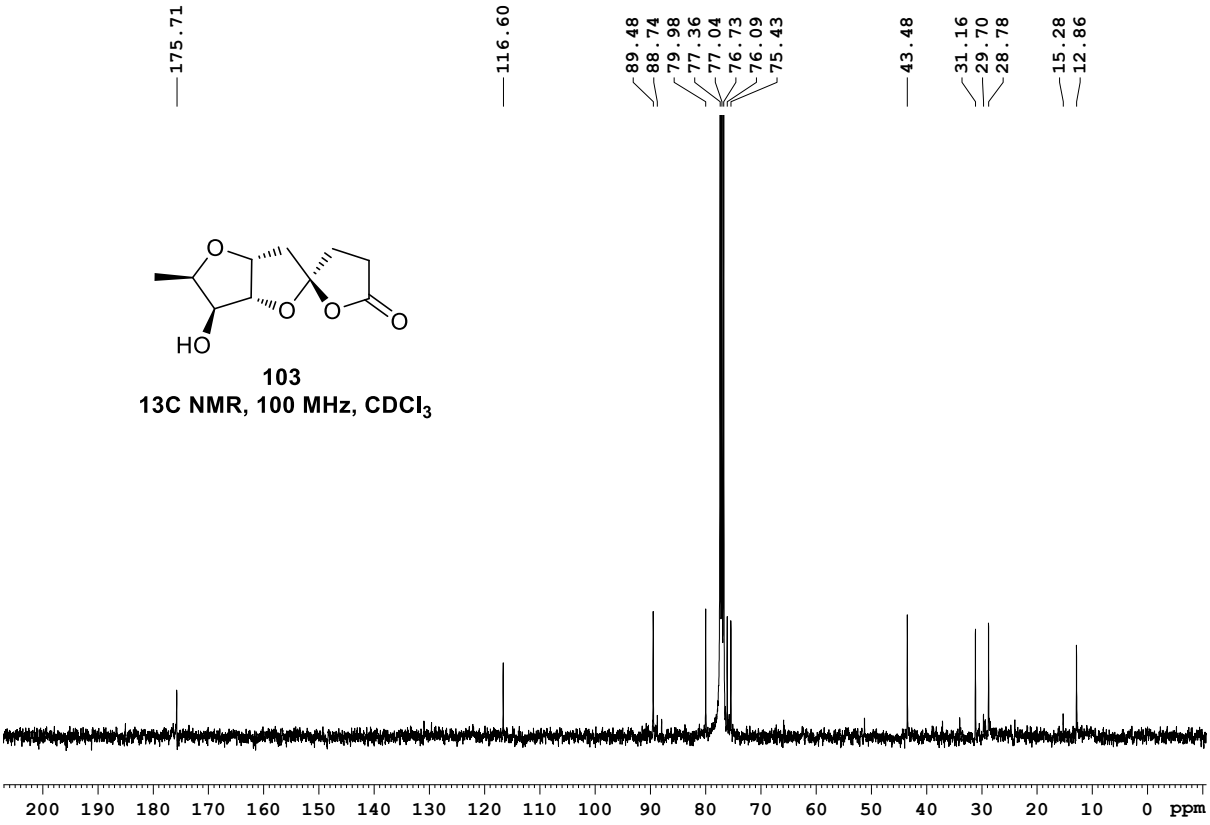
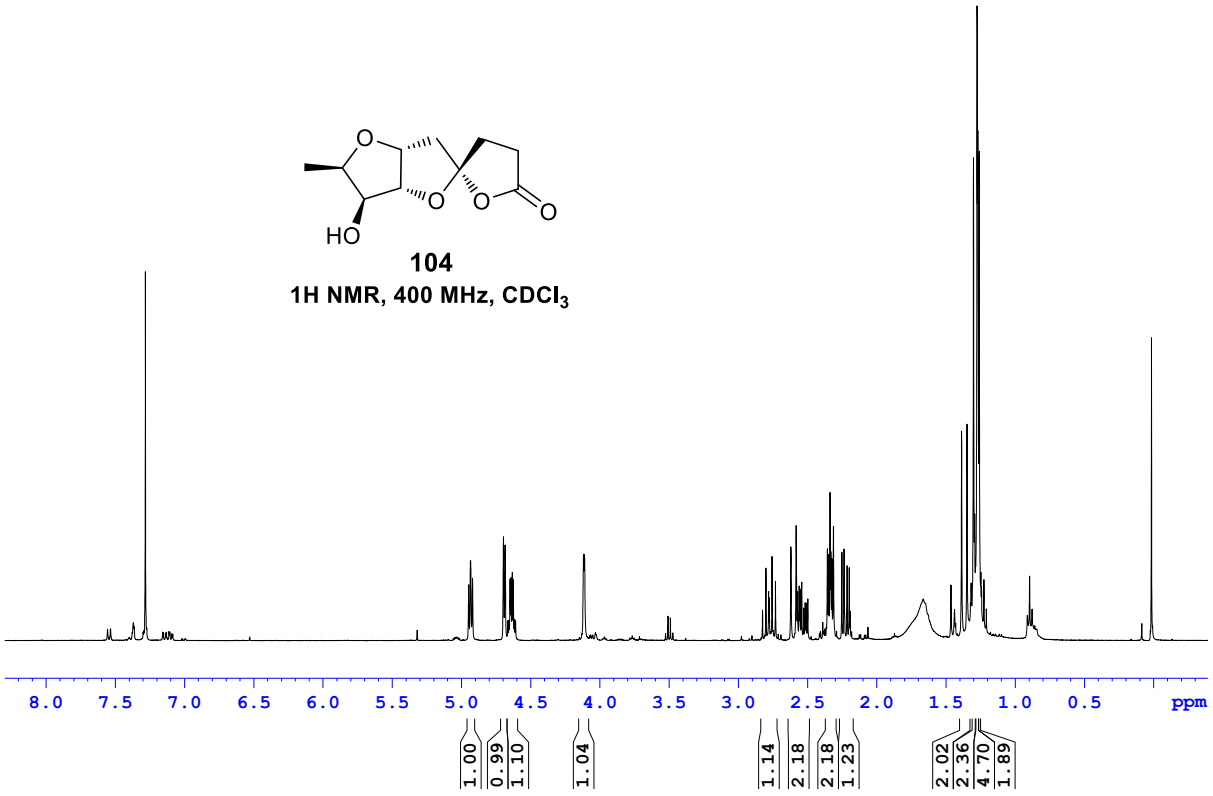




103
1H NMR, 400 MHz, $CDCl_3$

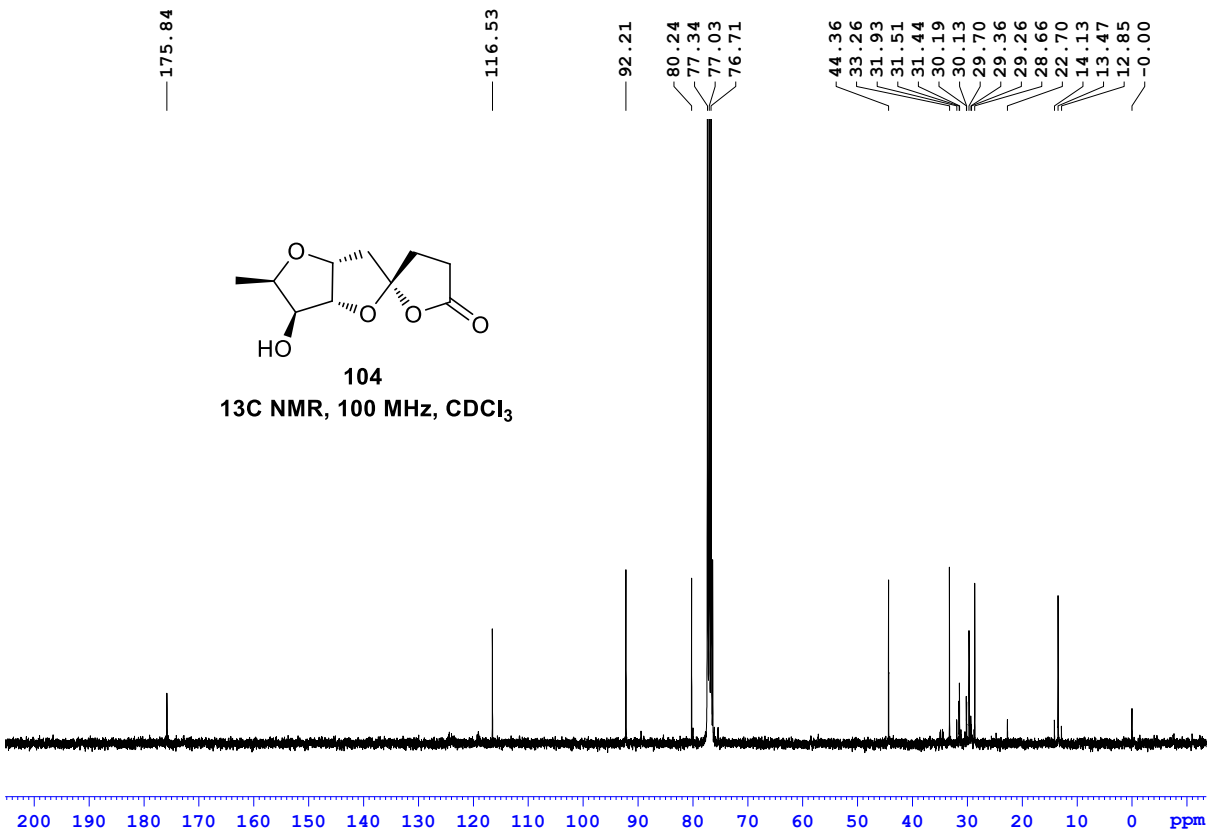


103
13C NMR, 100 MHz, $CDCl_3$



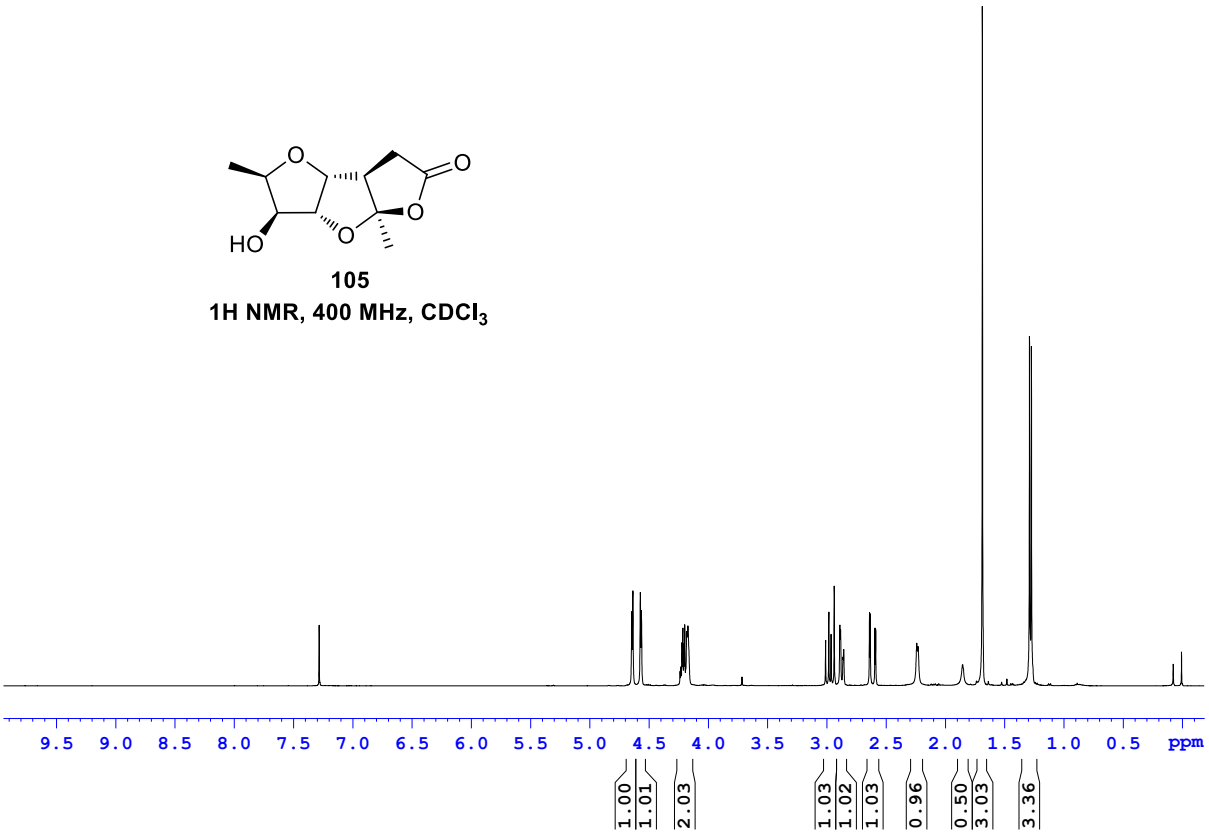
104

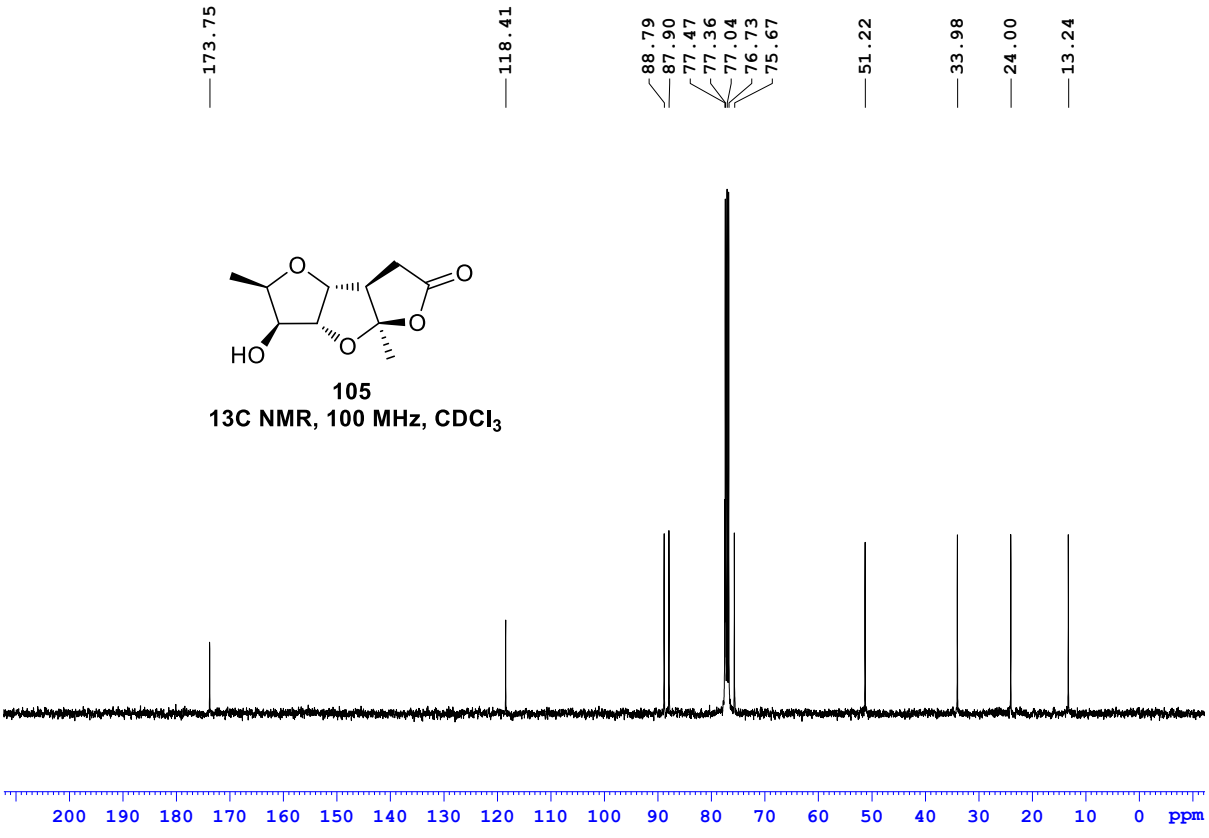
1H NMR, 400 MHz, $CDCl_3$



104

13C NMR, 100 MHz, $CDCl_3$

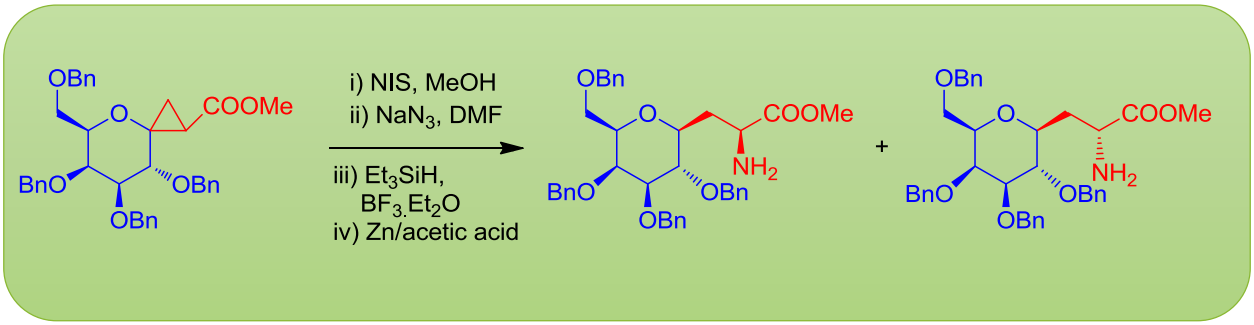

HO
O
O
O
O
105
1H NMR, 400 MHz, CDCl3
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
1.00
1.01
2.03
1.03
1.02
1.03
0.96
0.50
3.03
3.36


173.75
118.41
88.79
87.90
77.47
77.36
77.04
76.73
75.67
51.22
33.98
24.00
13.24
HO
O
O
O
O
105
13C NMR, 100 MHz, CDCl3
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

Chapter 4

Synthesis of β-*C*-Glyco Amino-acids from spiro-cyclopropanecarboxylated sugar

Abstract: stereoselective synthesis of 1-*C*-branched glyco-amino acids involving NIS mediated electrophilic ring opening of spiro-cyclopropanecarboxylated sugar, followed by conversion of iodide to azide and then Staudinger reduction/Zn in acetic acid mediated conversion of azide to amine.



4.1 Introduction

Sugar amino acids in which the amino acid subunit is directly attached to the sugar through a C-C band are called glyco-amino acids. Possessing the structural units of two major bio polymers, proteins and carbohydrates, polymers of glyco-amino acids are expected to exhibit the properties of both the biologically important macromolecules. Although the incorporation of an amine and acid functional groups on the sugar moiety through a hetero atom linker is studied extensively, stereoselective synthesis of glyco-amino acids is very scarce. Interestingly, some of the antibiotics possessing the glyco-amino acid subunit are found to be excellent antibiotics. For example, furanose derived glyco-amino acids polyoxins,[1] nikkomycins[2] (Figure 4.1) and pyranose derived glyco-amino acids amipurymicin and miharamycins[3] are some of the anti-biotic molecules isolated from bacterial cultures (Figure 4.2).

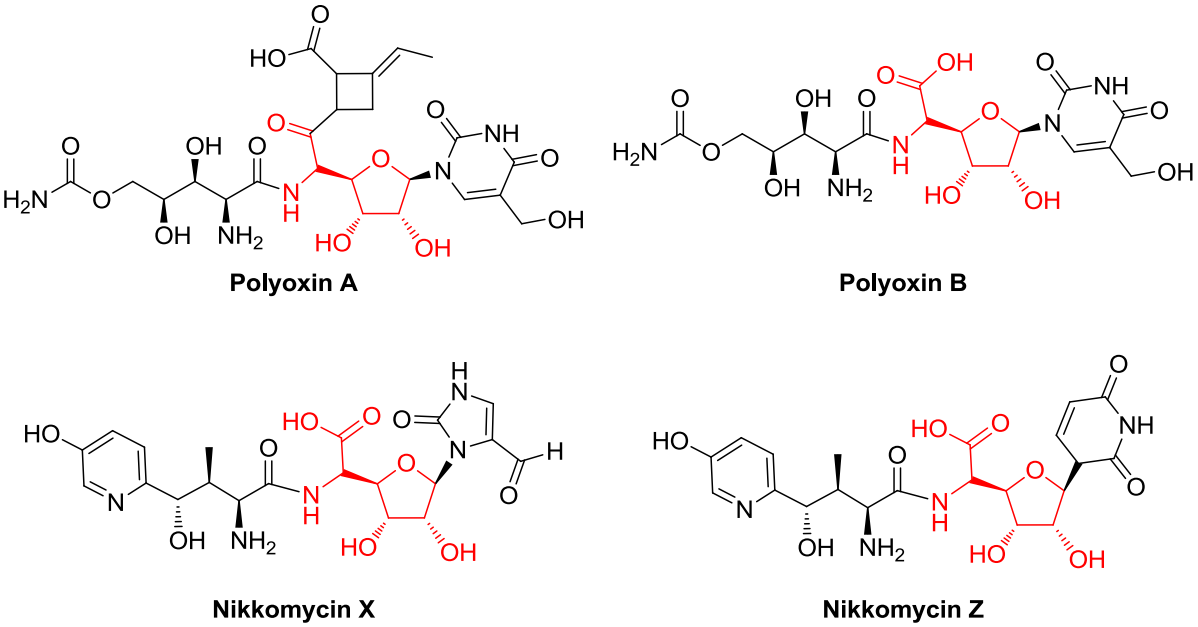


Figure 4.1: Furanose derived glyco-amino acid antibiotics

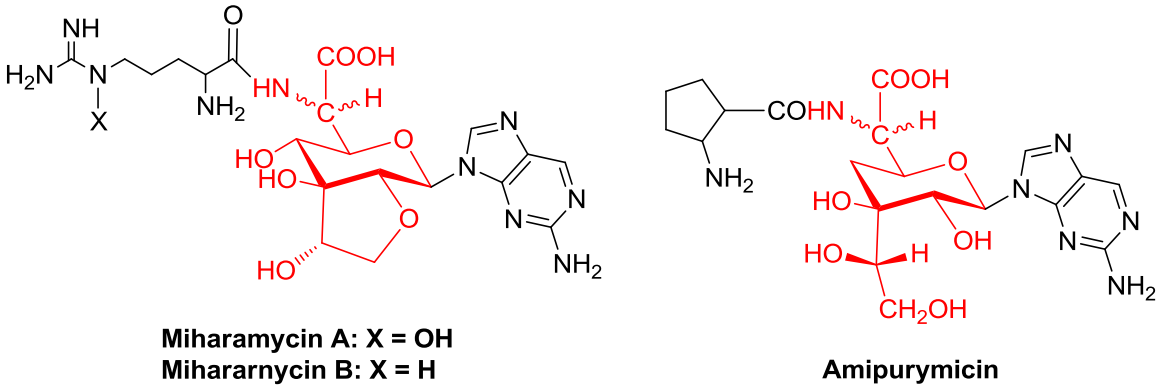


Figure 4.2: Pyranose derived glyco-amino acid antibiotics

Further the amino acid moiety attached to the sugar unit in glyco-amino acid can be further functionalized in to amino alcohols. Several highly bioactive compounds possessing the amino alcohol function on the sugar unit are reported in the literature. β-*C*-glycosidic amino acid structural units are present in the synthesis of β-*C*-galcer (Figure 3), β-*C*-glucer and its new β-aza-*C*-glycoside analogues,[4] and glycospingolipids[5]. These acts as potential inhibitors for HIV,

as well as antisolid tumour activity and various biological, therapeutic properties.[6] α-, β-galactosylceramide (Galcer), and α-, β-glucosylceramide (Glucer) having in vitro and in vivo natural killer (NK) cell activity.[7] α-galcer[8] possess stronger suppressive activity[9] than its β-type to enhancing the effects on NK cell activity. In glycosyl ceramides, the combination between sugar and ceramide plays an important role in antitumor activity as well as enhancing effect on NK cell activity of Galcers.

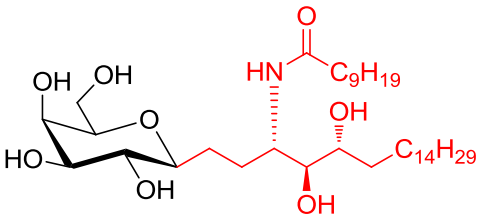
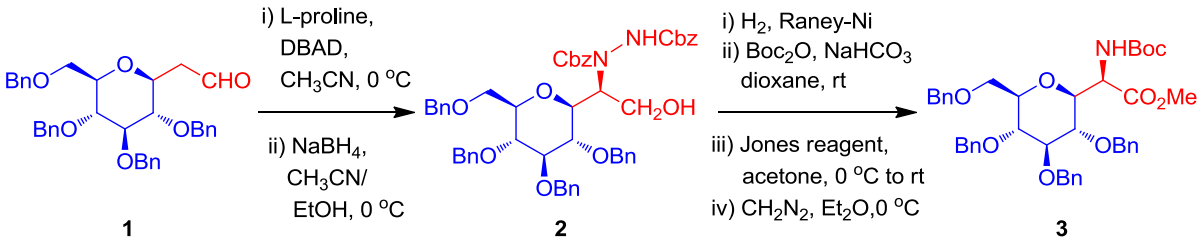


Figure 3: Molecular structure of β-*C*-galactosyl ceramide.

Even though large number of reports are available for the synthesis of α-linked *C*-glycosylated amino acids,[10] methods for the β-linked glycosyl amino acids are very scarce. These are also equally important in glyco-peptide synthesis,[11] as well as glycoprotein and glycolipid[12] synthesis. The importance of non-natural *C*-glycosyl α-amino acids[13] are mainly as building blocks for co-translational modification of natural glycopeptides and glycoproteins. On the other hand *C*-glycosyl α-amino acids are ability to withstand biological process of hydrolysis and having high chemical stability and also accepted as potential glycosidase inhibitors.

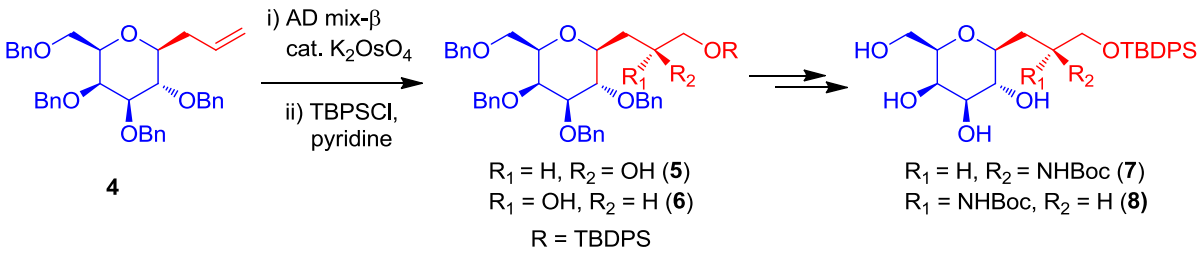
In 2008 Dondoni group demonstrated a general method for the synthesis of β-*C*-glycosyl α-amino acids[14] by using proline catalysed electrophilic α-amination reaction between *C*-glycosylalkyl aldehydes. In this method they have used an organocatalytic-reaction for asymmetric synthesis of carbon-linked sugar amino acids, such as *C*-glycosyl alanines, glycines, and methylene isosters of serines. The advantage of this method is inexpensive chiral catalyst, such as proline, and asymmetric α-hydrazination of glycosyl alky aldehydes with dibenzyl azodicarboxylate (DBAD) which is a simple and convenient method. Glucose derived methylene aldehyde **1** was converted to compound **2** using L-proline catalysed addition of carbanion on DBAD followed by reduction of the aldehyde with sodium borohydride. Subjecting alcohol **2** with H_2, Raney-nickel for hydrogenation and protection of the free amine with $(Boc)_2O$ provided the *N*-Boc protected amino alcohol which was oxidised to acid using

jones reagent followed by esterification of the obtained acid with diazomethane provided the NHBoc protected 1-β-*C*-glycosyl α-amino acid derivative **3** in good yield (Scheme 4.1).



Scheme 4.1: Synthesis of β-*C*-glycosyl α-amino acid.

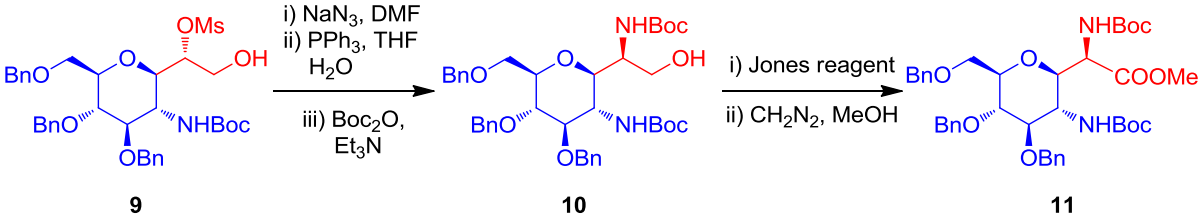
Recently Kulkarni and co-workers reported the synthesis of β-*C*-galactosyl D- and L-alanines[15] through stereoselective Grignard reaction of glycosyl iodides, Sharpless asymmetric dihydroxylation as key steps to functionalize the anomeric alkyl group. β-*C*-galactopyranoside **4** was prepared from 2,3,4,6-tetra-*O*-benzyl β-D-galactopyranosyl acetate involving TMSI mediated formation of glycosyl iodide followed by an SN_2 reaction with 2.0 M allylmagnesiumchloride in THF. Sharpless asymmetric dihydroxylation of **4** with using AD mix-β provided an inseparable diastereomeric mixture of diol **5** and **6**. Selective protection of the primary alcohols in **5** and **6** with TBDPS followed by conversion of the secondary alcohol to NHBoc provided the protected β-*C*-galactosyl amino alcohols **7** and **8** (Scheme 4.2).



Scheme 4.2: Synthesis of β-*C*-galactosyl D- and L- alanines.

In 2006, Y. D. Vankar group developed an interesting methodology for the synthesis of 2-deoxy-2-amino-β-*C*-glycosyl glycines and 2-deoxy-2-amino-β-*C*-glycosyl alanines[16] from D-galactose. These compounds are valuable synthons for the construction of artificial glycopeptides and the additional amino group present at C-2 position could be utilized to build the branched oligomeric peptides. In this protocol treatment of compound **9** with sodium azide provided the corresponding azide *via* SN_2 substitution reaction, which undergo Staudinger

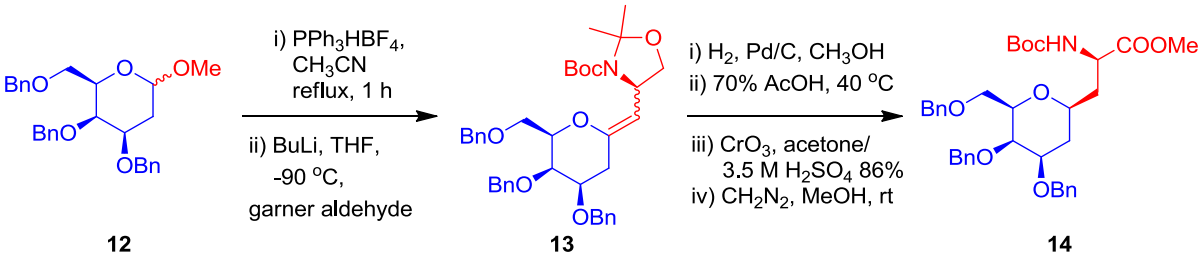
reaction followed by protection of the resulting amino group with Boc_2O afforded the compound **10** in good yield. Finally, oxidation of primary alcohol with jones reagent to give the corresponding acid, which upon esterification with diazomethane provided 2-deoxy-2-amino-*C*-glycosyl glycine **11** in 68% yield (Scheme 4.3). By using similar protocol they have also synthesized 2-deoxy-2-amino-*C*-glycosyl alanine from D-galactose.



9 **10** **11**

Scheme 4.3: Synthesis of 2-deoxy-2-amino-β-*C*-glycosyl glycine **11**.

In 1999, Lieberknecht synthesized *β*-(3,4,6-tri-*O*-benzyl -2-deoxy-β-D-galactopyranosyl)-*N*-*tert*-butoxycarbonyl-D-alanine from D-galactose.[17] Treatment of methyl 3,4,6-tri-*O*-benzyl -2-deoxy-*β*-D-galactopyranoside with hydrogentriphenylphophonium tetrafluoroborate (Wittig reaction) in acetonitrile gave the phosphonium salt in 1:1 (α:β) ratio, which upon reaction with garner aldehyde in presence of *n*-BuLi afforded the *exo*-cyclic enolether **13**. Hydrogenation of unsaturated olefin with Pd/C under hydrogen atmosphere followed by deprotection of acetal with 70% acetic acid provided the ring opened NHBoc methylene alcohol. Finally oxidation of primary alcohol with Jones reagent followed by esterification of the obtained acid with diazomethane in methanol gave the β-*C*-galactosyl D-alanine **14** in good yield (Scheme 4.4).



12 **13** **14**

Scheme 4.4: Synthesis of 2-deoxy β-*C*-galactosyl alanine 14.

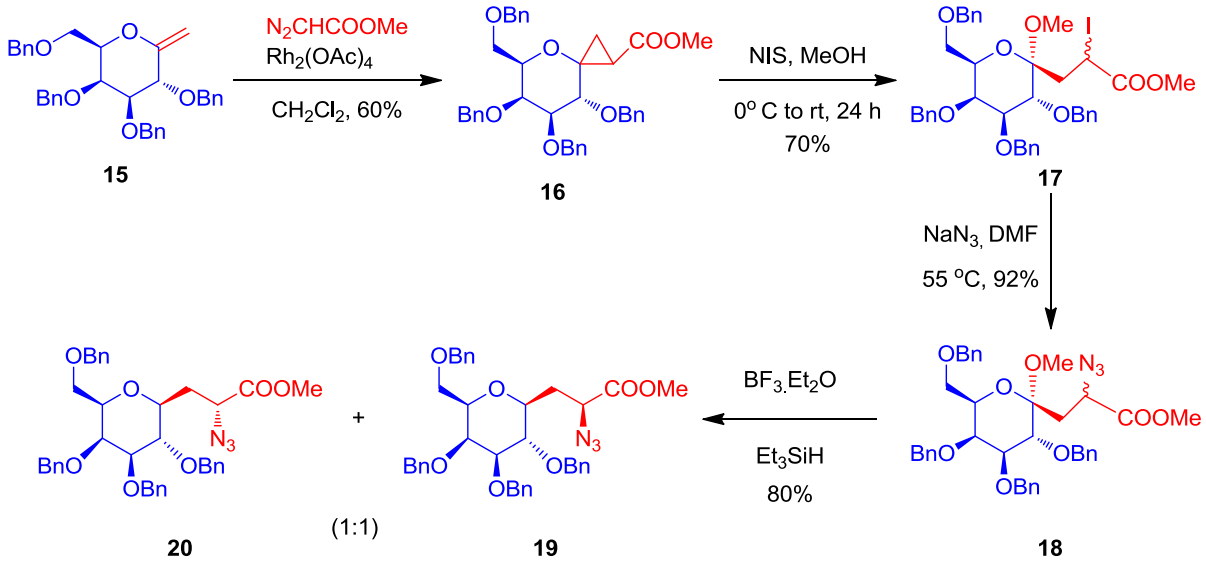
In continuation of our research work in the synthesis of glyco-amino acid derivatives, herein we report a simple and concise method for the stereoselective synthesis of β-*C*-glycosyl α-amino acids *via* electrophilic ring opening of spiro-cyclopropanecarboxylated sugars with NIS, followed by substitution of the iodide with azide and reduction of the azide with Zn/acetic

acid or using Staudinger reduction. These glycosyl α-amino acids are useful in the synthesis of building blocks for the preparation of stable *N*-linked glycopeptides and glycoprotein analogues which are unaffected by *O* or *N*-glycosidase as well as acidic hydrolysis. Interestingly, in comparison to the previous methods in which asymmetric catalysis was used, the present method is more advantageous with respect to the convenience and highly selective.

4.2 Results and Discussions

4.2.1 Synthesis of anomeric β-*C*-glycosyl α-amino acids

All the spiro-cyclopropanecarboxylated sugar precursors for the synthesis of glyco amino acids were prepared from the corresponding *exo*-glycals.[18] Our initial efforts were focused on galactose derived *exo*-cyclic olefin **15**. Rhodium acetate catalysed cyclopropanation[19] of **15** with methyldiazoacetate in dichloromethane provided the spiro-cyclopropanecarboxylated sugar **16** in 60% yield, as a mixture of diastereomers. *N*-iodosuccinimide (NIS) mediated electrophilic ring opening of this spiro system in methanol solvent[20] provided the ring opened methoxy iodo-carboxylate **17** as mixture of diastereomers. Interestingly, it was observed that the obtained diastereomeric mixture consists of only two compounds, in spite of the formation of two new chiral centres. Conversion of the resulting iodide to azide using sodium azide in DMF gave the azido carboxylate **18** again as a mixture of two diastereomers. Compounds **17** and **18** as mixture of diastereomers, could not separate on silica-gel column chromatography. However, removal of OMe in compound **18** by exposing

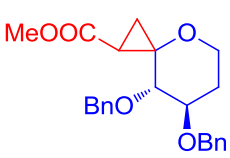
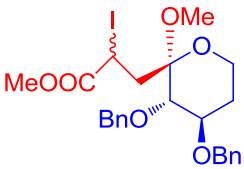
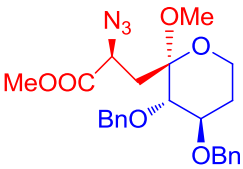
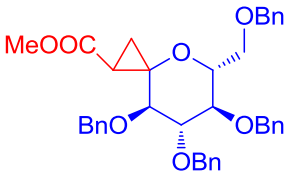
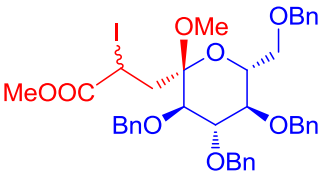
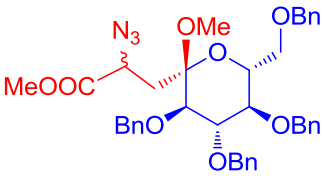
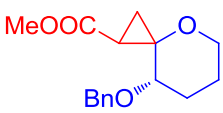
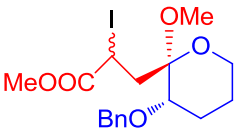
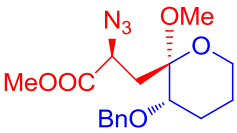
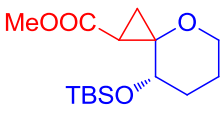
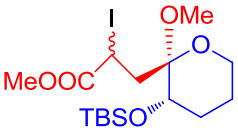
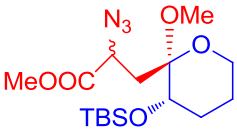
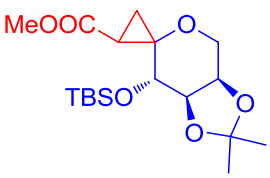
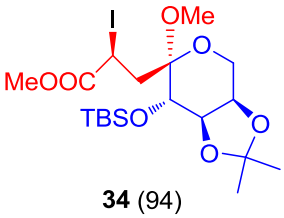
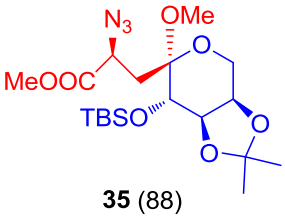


Scheme 4.5: Synthesis of galactose derived azido carboxylates **19** and **20**.

it to triethyl silane and $BF_3.Et_2O$[21] afforded the mixture of diastereomers **19** and **20** in 80% yield, which could be separated by silica-gel column chromatography in 10-15% ethyl acetate/hexane (Scheme 4.5).

The generality of the developed methodology was extended to the synthesis of a series of carbohydrate derived spiro-cyclopropanecarboxylated sugar derivatives. Thus, spiro-cyclopropanecarboxylated sugars **21**, **24**, **27** and **30** were synthesised by the cyclopropanation

Table 1. Synthesis of β-*C*-glycoside derivatives of α-azido esters

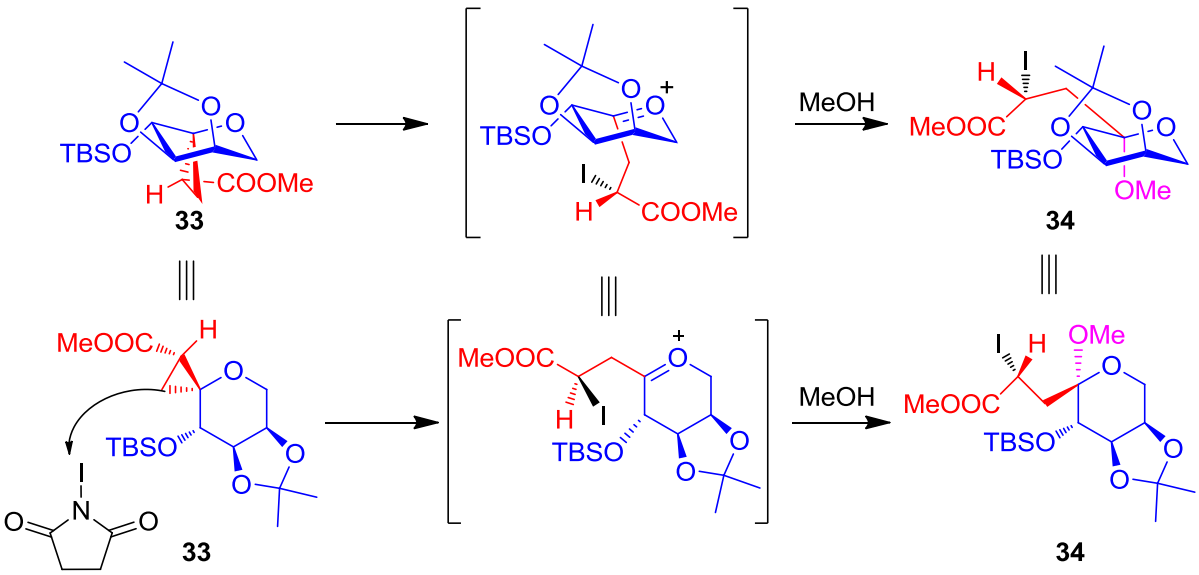
entry	spiro-cyclopropane carboxylate	β-*C*-glycosyl Iodide (%)[a]	β-*C*-glycosyl azide (%)[a]
1	 **21**	 **22** (73)	 **23** (70)
2	 **24**	 **25** (72)	 **26** (92)
3	 **27**	 **28**(57)	 **29** (78)
4	 **30**	 **31**(70)	 **32**(78)
5	 **33**	 **34** (94)	 **35** (88)

[a]Yield refers to pure and isolated compounds.

of the corresponding *exo*-glycals with methyl diazoacetate under rhodium acetate catalysis (chapter 2, Scheme 2.21). These spiro-cyclic donor-acceptor cyclopropane derivatives were subjected to NIS mediated electrophilic ring opening in methanol to obtain β-*C*-glycoside derivatives **22**, **25**, **28** and **31** as a mixture of two diastereomers. All the iodides were further converted to the corresponding azides **23**, **26**, **29** and **32** using sodium azide in DMF (Table 4.1, entries 1-4). Interestingly, in the case of iodides **22** and **28** the substitution reaction to give the corresponding azides, **23** and **29**, went in peculiar fashion that lead to the formation of single diastereomer respectively (Table 4.1, entries 1 and 3). Where as in other cases the azide was found to be a mixture of two diastereomers. To investigate the mechanism of the reaction, spiro-cyclopropane carboxylated sugar **33** was synthesised in a stereoselective fashion and subjected to electrophilic ring opening with NIS in methanol to give iodide **34** as a single diastereomer. SN_2 on this iodide with sodium azide provided the diastereomerically pure β-*C*-glycoside derived azido-ester **35** (Table 1, entry 5). This clearly implies that the ring opening of spiro-cyclopropane carboxylate undergoes through the formation of oxonium ion which will be trapped with the solvent methanol leading to the formation of 34.

4.2.2 Proposed mechanism

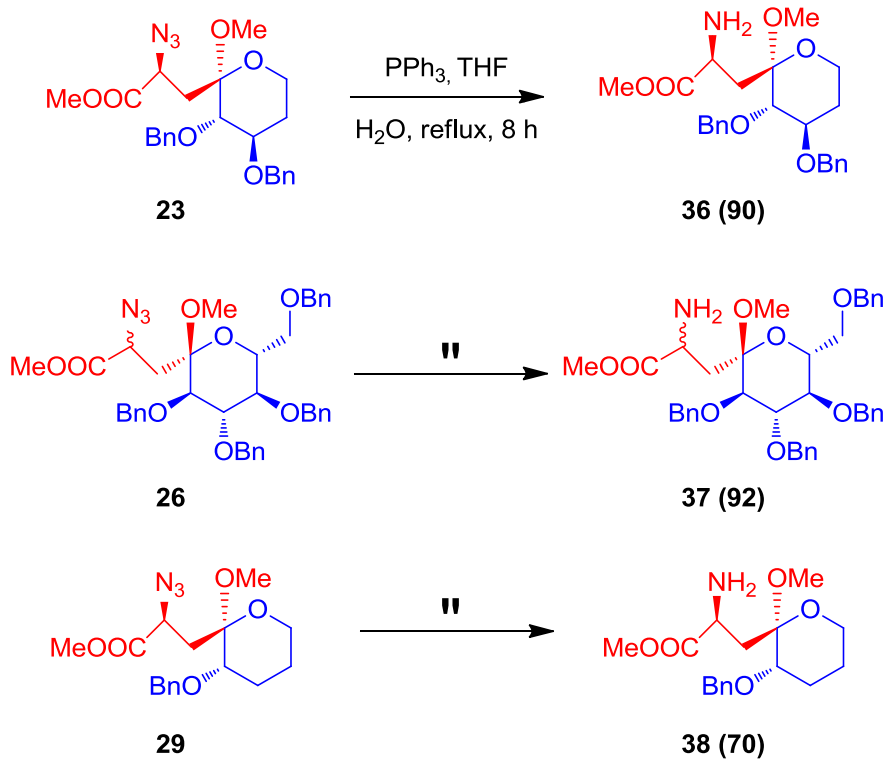
Based on the above observation a mechanism is proposed for the ring opening of spiro-cyclopropane carboxylate. As shown in the scheme 4.6 the electrophilic ring opening of the



Scheme 4.6: Proposed mechanism for the stereoselective formation of of β-*C*-glycoside.

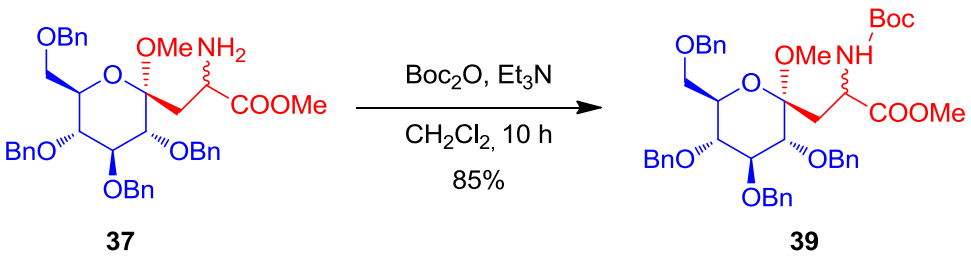
donor-acceptor cyclopropane **33** with iodinium ion occurs *via* an edge attack through a less hindered site to give the oxonium ion intermediate. This intermediate will be trapped by the solvent methanol to give the thermodynamically stable glycoside **34** having the OMe group on axial orientation.

After having a series of azides in hand we further proceeded to reduce the azides to the corresponding amines to achieve the 1-C-branched glyco-amino acid derivatives. Thus, azides **23**, **26** and **29** were subjected to Staudinger reduction (Ph_3P, THF and then addition of water after 5 h and refluxed for 3 h), all the azides gave the corresponding amines **36**, **37** and **38** in good yield (Scheme 4.7).



Scheme 4.7: Synthesis of 1-*C*-branched glyco-amino acids

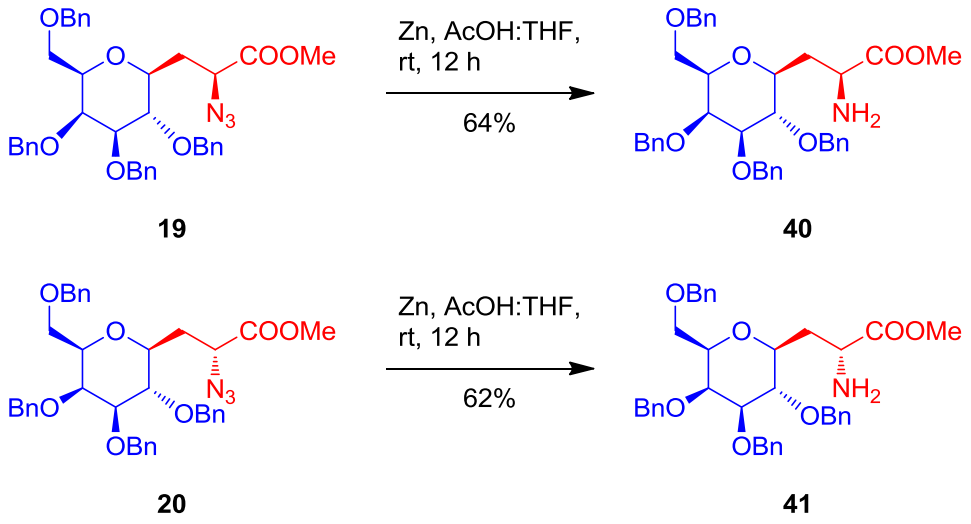
However, in some cases it become very difficult to resolve the triphenylphosphine oxide from the product amine. In those cases the obtained free amine was converted to the corresponding Boc protected derivative (Scheme 4.8).



37 **39**

Scheme 4.8: Synthesis of Boc protected 1-C-branched glyco-amino acid derivative.

Towards the synthesis of β-1-*C*-glycosyl α-amino acids, azides **19** and **20** were subjected to Staudinger reaction conditions (PPh_3/H_2O/THF) to obtain the β-1-*C*-glycosyl α-amino acids. Although this reaction proceeded smoothly we were not able to purify the compound due to the traces of triphenylphosphine oxide impurity that is also eluting along with the product. To overcome this difficulty, we choose Zn/acetic acid mediated reduction protocol. Thus, treatment of compounds **19** and **20** with Zn, acetic acid/tetrahydrofuran[22] at room temperature for 12 h, to our delight, afforded the β-*C*-galactosyl α-amino acids **39** and **49** in moderate yields as pure diastereomers (Scheme 4.9). The stereochemistry at the newly formed stereocentres was assigned by comparing the NMR spectra as well as the optical rotation with the reported literature.[12]



19 **40**

20 **41**

Scheme 4.9: Stereoselective synthesis of β-*C*-galactosyl α-amino acids.

4.3 Conclusion

A stereoselective method for the synthesis of β-1-*C*-glycosyl α-amino acids form spiro-cyclopropane carboxylated sugars is developed. The generality and the selectivity of the reaction was investigated. Conversion of these hybrid sugars to glyco-peptides and peptide-

glycals is under progress. A tentative mechanism is proposed for the ring-opening of the spiro-cyclopropanecarboxylated sugar derivative is proposed. The mechanistic details and the use of these amino acid ligated carbohydrates in the synthesis of novel molecular architectures are in progress.

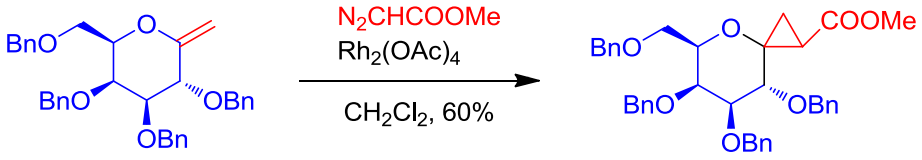
4.4 Experimental section

4.4.1 General Information

All the reactions were carried out under nitrogen or argon 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. All the chemicals were purchased from local suppliers and Sigma-Aldrich Chemicals Company. Solvents used in the reactions were distilled over dehydrating agents. Dry toluene was prepared by using sodium and benzophenone. Silica-gel (100-200 mesh) and neutral alumina were used for column chromatography. ^1H, ^{13}C, DEPT, COSY, NOESY spectra were recorded on Bruker 400 MHz and 500 MHz spectrometer in $CDCl_3$. ^1H NMR chemical shifts were reported in ppm (δ) with TMS as 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.

4.4.2 Experimental Procedures and spectral data

(4.4.1.1) (5*R*,6*S*,7*S*,8*R*)-methyl 6,7,8-tris(benzyloxy)-5-((benzyloxy)methyl)-4-oxaspiro[2.5]octane-1-carboxylate:

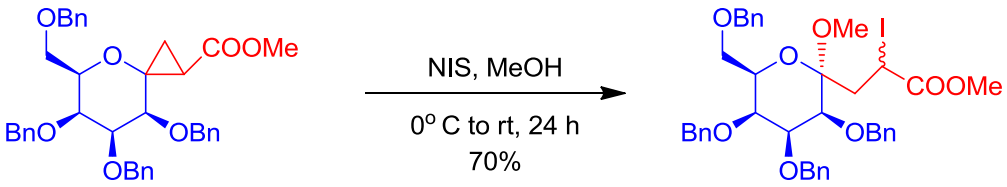


15 **16**

To a stirred suspension of *exo*-glycal **15** (4.4 g, 8.20 mmol), and $Rh_2(OAc)_4$ (72 mg, 0.16 mmol) in anhydrous CH_2Cl_2 (30 mL) was added drop wise, over a period of 1 h, a solution of methyl diazoacetate (2.28 mL, 24.6 mmol) in CH_2Cl_2 (70 mL). After completion of the reaction, the

reaction mixture was concentrated in *vacuo* and the obtained crude product was purified by silica gel column chromatography (eluent: 10-20% EtOAc in Hexane) to give desired spiro-cyclopropanecarboxylate **16** (2.9 g, 60%) as a mixture of diastereomers. **IR (neat)**: ν_{max} 3063, 3030, 2947, 2871, 1736, 1495, 1452, 1364, 1282, 1210, 1167, 1095, 1030, 734 cm^{-1}. **HRMS (ESI)** calcd for $C_{38}H_{40}O_7$+Na 631.2672, found 631.2670.

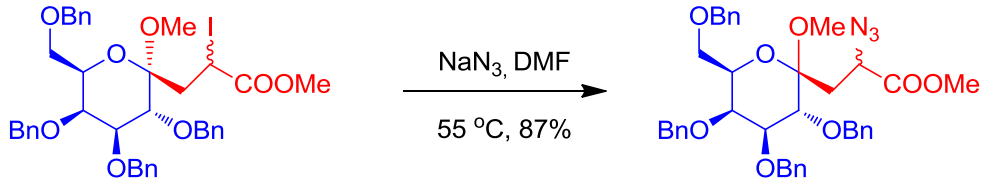
(4.4.1.2) methyl 2-iodo-3-((2*S*,3*S*,4*S*,5*S*,6*R*)-3,4,5-tris(benzyloxy)-6-((benzyloxy)methyl)-2-methoxytetrahydro-2*H*-pyran-2-yl)propanoate:



16 **17**

To a stirred solution of galactose derived spiro-cyclopropane carboxylate sugar **16** (3.3 g, 5.42 mmol) in 20 ml of methanol at 0 °C under nitrogen was added *N*-iodo succinimide (NIS) (1.45 g, 6.5 mmol) and stirring the reaction mixture for 24 h at room temperature. After complete conversion of the starting material by confirming the TLC quench with saturated sodium thiosulfate and usual work up with dichloromethane (3 x 100 mL). Finally the organic layer was washed with water and brine solution, concentrating on rotary evaporator the crude product was purified by silica-gel column chromatography to afford the ring opened iodo-carboxylate **17** (2.9 g) as mixture of diastereomers in 70% yield. **IR (neat)**: ν_{max} 3063, 3030, 2920, 2849, 1742, 1501, 1452, 1358, 1265, 1210, 1095, 734 cm^{-1}. **HRMS (ESI)** calcd for $C_{39}H_{43}IO_8$+Na 789.1900, found 789.1904.

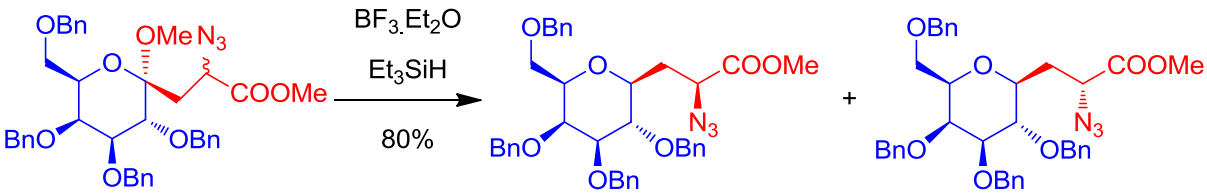
(4.4.1.3) methyl 2-azido-3-((3*S*,4*S*,5*S*,6*R*)-3,4,5-tris(benzyloxy)-6-((benzyloxy)methyl)-2-methoxytetrahydro-2*H*-pyran-2-yl)propanoate:



17 **18**

To a stirred solution of iodo-carboxylate **17** (2.6 g, 3.39 mmol), in 10 mL of dimethyl formamide (DMF) was added sodium azide (1.10 g, 16.95 mmol) in two portions, and stirred the reaction mixture at 55 ^{o}C for 24 h. after completion the reaction mixture by checking TLC, remove the DMF by rota vapour, extract with dichloromethane, washed with water and brine, dried over anhydrous $MgSO_4$. The obtained crude product was purified by silica-gel column-chromatography in 20% ethyl acetate/hexane to provide the corresponding azido carboxylate **18** (2.0 g) as mixture of diastereomers in good yield. **IR (neat)**: ν_{max} 3084, 3068, 3024, 2915, 2871, 2104, 1742, 1495, 1463, 1358, 1271, 1090, 1052, 739, 695. **HRMS (ESI)** calcd for $C_{39}H_{43}N_3O_8$+Na 704.2948, found 704.2945.

(4.4.1.4) (*S*)-methyl 2-azido-3-((2*S*,3*R*,4*R*,5*S*,6*R*)-3,4,5-tris(benzyloxy)-6-((benzyloxy)methyl)tetrahydro-2*H*-pyran-2-yl)propanoate and (*R*)-methyl 2-azido-3-((2*S*,3*R*,4*R*,5*S*,6*R*)-3,4,5-tris(benzyloxy)-6-((benzyloxy)methyl)tetrahydro-2*H*-pyran-2-yl)propanoate:



18 **19** **20**

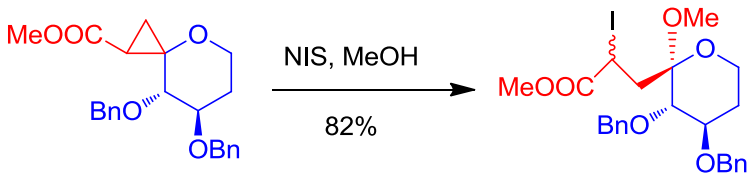
To a solution of azido carboxylate **18** (700 mg, 1.02 mmol) in dry dichloromethane (10 mL) added freshly distilled triethyl silane (3.25 mL, 20.55 mmol) and the reaction mixture was cooled to -78 ^{o}C, then freshly distilled $BF_3.Et_2O$ (1.29 mL, 10.30 mmol) was added drop wise over a period of 10 minutes via syringe. The reaction was warmed in to -50 ^{o}C, and allow to stir for an additional 4 h, after completion of the reaction by checking TLC the reaction mixture was quenched by the 10 ml of saturated aqueous solution of $NaHCO_3$. The mixture was poured in to separating funnel and extracted 3 times with dichloromethane. The combined organic layer was washed with water and brine solution, dried over anhydrous Na_2SO_4 and concentrated, the crude products were separated by silica-gel column chromatography in 10-20% ethyl acetate/hexane to afford the de-methoxy azido carboxylate derivatives **19** and **20** in good yield.

Data for compound **19**: **IR (neat)**: ν_{max} 3085, 3066, 3030, 2923, 2854, 2111, 1743, 1496, 1454, 1436, 1363, 1264, 1206, 1155, 1100, 1027, 910, 808 cm^{-1}. **^{1}H NMR (400 MHz, $CDCl_3$)**: δ

7.28-7.40 (m, 20H), 4.99 (d, 1H, *J* = 4.8 Hz), 4.96 (d, 1H, *J* = 5.2 Hz), 4.78 (d, 1H, *J* = 12.0 Hz), 4.69 (dd, 2H, *J* = 6.4 Hz, *J* = 13.6 Hz), 4.65 (d, 1H, *J* = 2.8 Hz), 4.47 (q, 1H, *J* = 12.0 Hz), 4.17 (dd, 1H, *J* = 3.2 Hz, *J* = 11.2 Hz), 4.05 (d, 1H, *J* = 2.4 Hz), 3.76 (s, 3H), 3.70 (1H, *J* = 9.2 Hz), 3.65 (1H, *J* = 2.4 Hz, *J* = 9.2 Hz), 3.55-3.59 (m, 3H), 3.45 (m, 1H), 2.2 (m, 1H), 1.96 (m, 1H). **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 171.9, 138.6, 138.2, 138.2, 137.9, 128.4, 128.4, 128.4, 128.3, 128.2, 128.0, 127.9, 127.8, 127.7, 127.6, 127.6, 84.7, 78.5, 76.9, 75.3, 74.7, 73.7, 73.5, 72.3, 68.7, 58.6, 52.5, 33.9. **HRMS (ESI)** calcd for $C_{38}H_{41}N_3O_7$+Na 674.2842, found 674.2841.

Data for compound **20**: **IR (neat)**: ν_{max} 3066, 3030, 2923, 2853, 2106, 1743, 1541, 1496, 1454, 1362, 1287, 1265, 1207, 1156, 1101, 1027, 909, 818 cm^{-1}. **^{1}H NMR (400 MHz, $CDCl_3$)**: δ 7.28-7.37 (m, 20H), 4.96 (dd, 2H, *J* = 9.6 Hz, *J* = 11.2 Hz), 4.75 (d, 1H, *J* = 11.6 Hz), 4.67 (d, 2H, *J* = 10.8 Hz), 4.62 (d, 1H, *J* = 11.6 Hz), 4.44 (q, 2H, *J* = 12.0 Hz), 4.10 (dd, 1H, *J* = 5.2 Hz, J = 7.6 Hz), 4.01 (d, 1H, *J* = 2.8 Hz), 3.71 (s, 3H), 3.60 (dd, 1H, *J* = 2.8 Hz, *J* = 9.2 Hz), 3.53 (m, 3H), 3.39 (m, 1H), 2.34 (ddd, 1H, *J* = 2.8 Hz, *J* = 7.2 Hz, *J* = 14.0 Hz), 1.96 (m, 1H). **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 170.7, 138.7, 138.2, 138.1, 137.9, 128.4, 128.4, 128.2, 128.1, 128.0, 127.9, 127.8, 127.7, 127.6, 84.7, 78.1, 76.8, 75.7, 75.3, 74.6, 73.6, 73.5, 72.2, 68.5, 59.0, 52.4, 33.8. **HRMS (ESI)** calcd for $C_{38}H_{41}N_3O_7$+Na 674.2842, found 674.2842.

(4.4.1.5) methyl 3-((2*R*,3*S*,4*R*)-3,4-bis(benzyloxy)-2-methoxytetrahydro-2*H*-pyran-2-yl)-2-iodopropanoate:

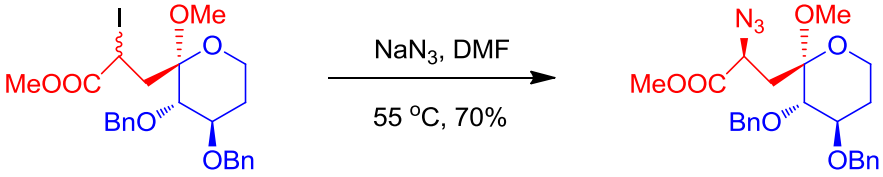


21 **22**

To a stirred solution of glucose derived spiro-cyclopropane carboxylate sugar **21** (870 mg, 2.27 mmol) in 15 ml of methanol at 0 ^oC under nitrogen was added *N*-iodo succinimide (NIS) (614 mg, 2.73 mmol) and stirring the reaction mixture for 24 h at room temperature. After complete conversion of the starting material by confirming the TLC quench with saturated sodium thiosulfate and usual work up with dichloromethane (3 x 100 mL). Finally the organic layer was washed with water and brine solution, concentrating on rotary evaporator the crude product was purified by silica-gel column chromatography to afford the ring opened iodo-carboxylate

22 (1.0 g) as mixture of diastereomers in 82% yield. **IR (neat)**: ν_{max} 3063, 3030, 2953, 2882, 1736, 1495, 1452, 1435, 1364, 1260, 1200, 1167, 1095, 734, cm-1. **HRMS (ESI)** calcd for $C_{24}H_{29}IO_6$+Na 563.0907, found 563.0909.

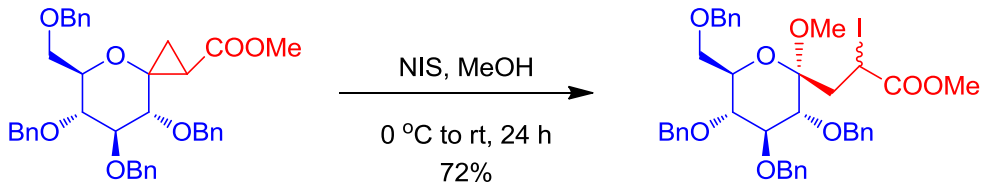
(4.4.1.6) (*S*)-methyl 2-azido-3-((2*R*,3*S*,4*R*)-3,4-bis(benzyloxy)-2-methoxytetrahydro-2*H*-pyran-2-yl)propanoate:



22 **23**

To a stirred solution of iodo-carboxylate **22** (830 mg, 1.53 mmol), in 10 mL of dimethyl formamide (DMF) was added sodium azide (500 mg, 7.68 mmol) in two portions, and stirred the reaction mixture at 55 °C for 24 h. after completion the reaction mixture by checking TLC, remove the DMF by rota vapour, extract with dichloromethane, washed with water and brine, dried over anhydrous $MgSO_4$. The obtained crude product was purified by silica-gel column chromatography in 20% ethyl acetate/hexane to provide the corresponding azido carboxylate **23** (489 mg) in good yield. **IR (neat)**: ν_{max} 3090, 3068, 3035, 2926, 2865, 1720, 1501, 1457, 1353, 1112, 1024, 745, 695 cm-1. **^{1}H NMR (500 MHz, $CDCl_3$)**: δ 7.28-7.39 (m, 10 H), 5.06 (d, 1H, *J* = 11.5 Hz), 4.82 (d, 1H, *J* = 11.5 Hz), 4.67 (q, 2H, *J* = 11.5 Hz), 4.01-4.07 (m, 1H), 3.76-3.79 (m, 1H), 3.74 (s, 3H), 3.58-3.64 (m, 2H), 3.49-3.54 (m, 1H), 3.24 (s, 3H), 2.33 (dd, 1H, *J* = 6.5 Hz, *J* = 14.5 Hz), 2.09 (ddd, 2H, *J* = 7.5 Hz, *J* = 14.5 Hz, *J* = 21.5 Hz), 1.66 (ddd, 1H, *J* = 5.5 Hz, *J* = 13.0 Hz, *J* = 24.5 Hz). **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 170.6, 138.4, 138.2, 128.4, 128.3, 128.3, 128.2, 127.6, 127.5, 100.3, 80.7, 76.6, 75.0, 71.6, 59.0, 58.3, 52.4, 47.5, 32.6, 31.4. **HRMS (ESI)** calcd for $C_{24}H_{29}N_3O_6$+Na 478.1954, found 478.1954.

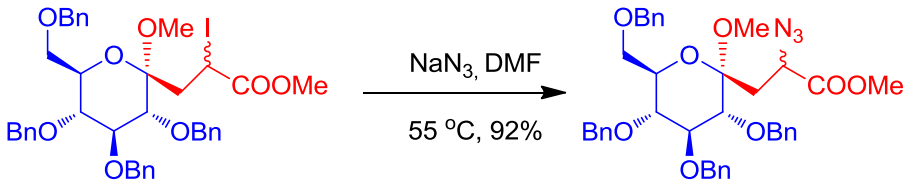
(4.4.1.7) methyl 2-iodo-3-((2*S*,3*R*,4*S*,5*R*,6*R*)-3,4,5-tris(benzyloxy)-6-((benzyloxy)methyl)-2-methoxytetrahydro-2*H*-pyran-2-yl)propanoate:



24 **25**

To a stirred solution of glucose derived spiro-cyclopropanecarboxylate sugar **24** (2.0 g, 3.28 mmol) in 20 ml of methanol at 0 ^{o}C under nitrogen was added *N*-iodosuccinimide (NIS) (0.88 g, 3.94 mmol) and stirring the reaction mixture for 24 h at room temperature. After complete conversion of the starting material by confirming the TLC quench with saturated sodium thiosulfate and usual work up with dichloromethane (3 x 100 mL). Finally the organic layer was washed with water and brine solution, concentrating on rotary evaporator the crude product was purified by silica-gel column chromatography to afford the ring opened iodo-carboxylate **25** (1.8 g) as mixture of diastereomers in 72% yield. **IR (neat)**: ν_{max} 3062, 3035, 2920, 2865, 1747, 1632, 1500, 1451, 1363, 1254, 1210, 1056, 739, 700 cm-1. **HRMS (ESI)** calcd for $C_{39}H_{43}IO_8$+Na 789.1900, found 789.1902.

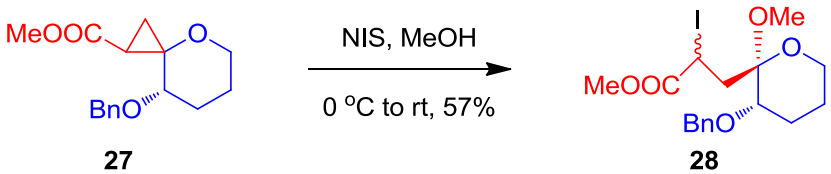
(4.4.1.8) methyl 2-azido-3-((2*S*,3*S*,4*S*,5*R*,6*R*)-3,4,5-tris(benzyloxy)-6-((benzyloxy)methyl)-2-methoxytetrahydro-2*H*-pyran-2-yl)propanoate:



25 **26**

To a stirred solution of iodo-carboxylate **25** (1.0 g, 1.39 mmol), in 10 mL of dimethyl formamide (DMF) was added sodium azide (0.45 g, 6.98 mmol) in two portions, and stirred the reaction mixture at 55 ^{o}C for 24 h. after completion the reaction mixture by checking TLC, remove the DMF by rota vapour, extract with dichloromethane, washed with water and brine, dried over anhydrous $MgSO_4$. The obtained crude product was purified by silica-gel column chromatography in 20% ethyl acetate/hexane to provide the corresponding azido carboxylate **26** (0.82 g) as mixture of diastereomers in good yield. **IR (neat)**: ν_{max} 3095, 3063, 3024, 2926, 2854, 2109, 1747, 1501, 1457, 1364, 1282, 1205, 1095, 1063, 739, 701cm-1. **HRMS (ESI)** calcd for $C_{39}H_{43}N_3O_8$+Na 704.2948, found 704.2951.

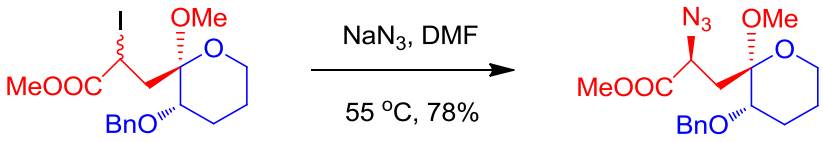
(4.4.1.9) methyl 3-((2*R*,3*S*)-3-(benzyloxy)-2-methoxytetrahydro-2*H*-pyran-2-yl)-2-iodopropanoate:



27 **28**

To a stirred solution of galactose derived spiro-cyclopropane carboxylate sugar **27** (290 mg, 1.05 mmol) in 5 ml of methanol at 0 ^{o}C under nitrogen was added *N*-iodo succinimide (NIS) (283 mg, 1.26 mmol) and stirring the reaction mixture for 24 h at room temperature. After complete conversion of the starting material by confirming the TLC quench with saturated sodium thiosulfate and usual work up with dichloromethane (3 x 100 mL). Finally the organic layer was washed with water and brine solution, concentrating on rotary evaporator the crude product was purified by silica-gel column chromatography to afford the ring opened iodo-carboxylate **28** (260 mg) as mixture of diastereomers in 57% yield. **IR (neat)**: ν_{max} 3084, 3068, 3024, 2953, 2882, 1731, 1600, 1495, 1457, 1435, 1364, 1315, 1260, 1210, 887, 821, 739, 701 cm-1. **HRMS (ESI)** calcd for $C_{17}H_{23}IO_5$+Na 457.0488, found 457.0489.

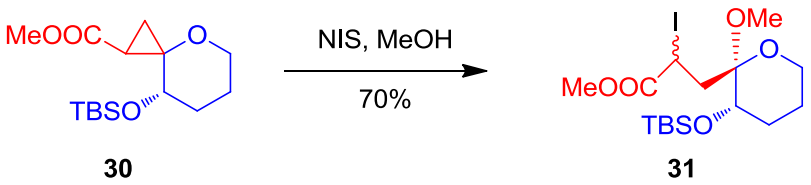
(4.4.1.10) (*S*)-methyl 2-azido-3-((2*R*,3*S*)-3-(benzyloxy)-2-methoxytetrahydro-2*H*-pyran-2-yl)propanoate:



28 **29**

To a stirred solution of iodo-carboxylate **28** (240 mg, 0.68 mmol), in 4 mL of dimethyl formamide (DMF) was added sodium azide (223 mg, 3.43 mmol) in two portions, and stirred the reaction mixture at 55 ^{o}C for 24 h. after completion the reaction mixture by checking TLC, remove the DMF by rota vapour, extract with dichloromethane, washed with water and brine, dried over anhydrous $MgSO_4$. The obtained crude product was purified by silica-gel column chromatography in 20% ethyl acetate/hexane to provide the corresponding azido carboxylate **29** (150 mg) as mixture of diastereomers in good yield. **IR (neat)**: ν_{max} 3035, 2953, 2871, 2109, 1742, 1627, 1495, 1435, 1353, 1287, 1210, 1112, 1084, 898, 745, 701 cm-1. **^{1}H NMR (400 MHz, $CDCl_3$)**: δ 7.27-7.31 (m, 5H), 4.67 (d, 1H, *J* = 11.6 Hz), 4.45 (d, 1H, *J* = 12.0 Hz), 3.82 (dd, 1H, *J* = 4.0 Hz, *J* = 7.6 Hz), 3.73 (s, 3H), 3.48-3.55 (m, 2H), 3.45 (dd, 1H, *J* = 4.8 Hz, *J* = 11.2 Hz), 3.27 (s, 3H), 2.42 (dd, 1H, *J* = 4.0 Hz, *J* = 14.8 Hz), 2.16 (dd, 1H, *J* = 8.4 Hz, *J* = 15.2 Hz), 1.92-1.99 (m, 1H), 1.77-1.92 (m, 1H), 1.56-1.66 (m, 2H). **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 170.7, 137.9, 137.8, 128.2, 128.0, 128.0, 127.6, 98.5, 76.6, 70.4, 60.6, 58.1, 52.3, 47.6, 33.7, 24.6, 22.9. **HRMS (ESI)** calcd for $C_{17}H_{23}N_3O_5$+Na 372.1535, found 372.1536.

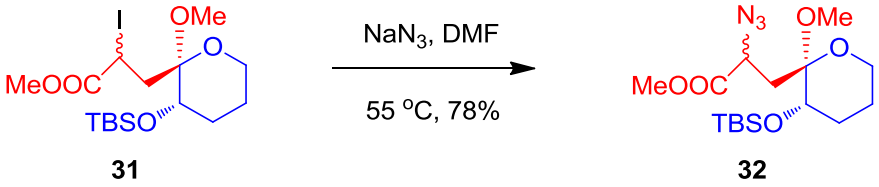
(4.4.1.11) methyl 3-((2*R*,3*S*)-3-((*tert*-butyldimethylsilyl)oxy)-2-methoxytetrahydro-2*H*-pyran-2-yl)-2-iodopropanoate:



30 **31**

To a stirred solution of glucose derived spiro-cyclopropane carboxylate sugar **30** (290 mg, 0.96 mmol) in 5 ml of methanol at 0 ^{o}C under nitrogen was added *N*-iodo succinimide (NIS) (260 mg, 1.15 mmol) and stirring the reaction mixture for 24 h at room temperature. After complete conversion of the starting material by confirming the TLC quench with saturated sodium thiosulfate and usual work up with dichloromethane (3 x 100 mL). Finally the organic layer was washed with water and brine solution, concentrating on rotary evaporator the crude product was purified by silica-gel column chromatography to afford the ring opened iodo-carboxylate **31** (310 mg) as mixture of diastereomers in 70% yield. **IR (neat)**: ν_{max} 2953, 2926, 2854, 1742, 1468, 1435, 1364, 1249, 1117, 1079, 838, 778 cm-1. **HRMS (ESI)** calcd for $C_{16}H_{31}IO_5Si$+Na 481.0883, found 481.0887.

(4.4.1.12) methyl 2-azido-3-((2*R*,3*S*)-3-((*tert*-butyldimethylsilyl)oxy)-2-methoxytetrahydro-2*H*-pyran-2-yl)propanoate:

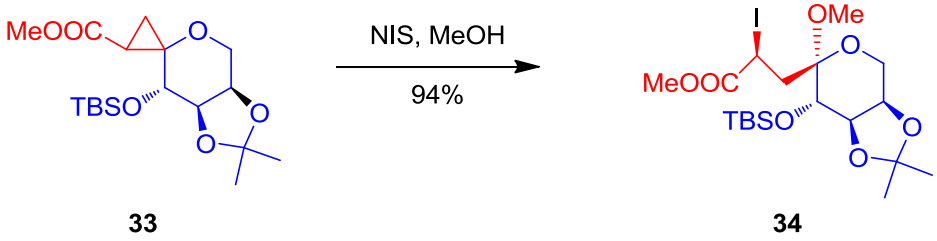


31 **32**

To a stirred solution of iodo-carboxylate **31** (280 mg, 0.61 mmol), in 5 mL of dimethyl formamide (DMF) was added sodium azide (198 mg, 3.05 mmol) in two portions, and stirred the reaction mixture at 55 ^{o}C for 24 h. after completion the reaction mixture by checking TLC, remove the DMF by rota vapour, extract with dichloromethane, washed with water and brine, dried over anhydrous $MgSO_4$. The obtained crude product was purified by silica-gel column chromatography in 20% ethyl acetate/hexane to provide the corresponding azido carboxylate **32** (177 mg) as mixture of diastereomers in 78% yield. **IR (neat)**: ν_{max} 2947, 2931, 2860, 2104,

1747, 1468, 1441, 1358, 1254, 1117, 843, 772 cm-1. **HRMS (ESI)** calcd for $C_{16}H_{31}N_3O_5Si$+Na 396.1931, found 396.1930.

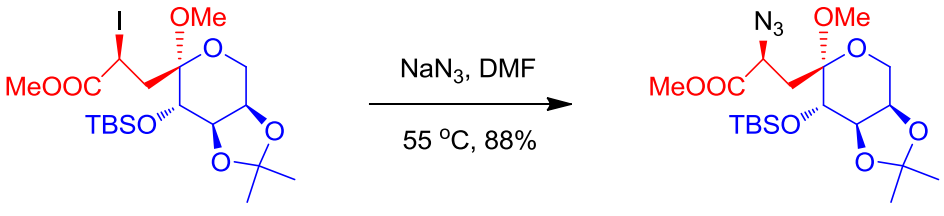
(4.4.1.13) (*S*)-methyl 3-((3a*R*,6*R*,7*S*,7a*R*)-7-((*tert*-butyldimethylsilyl)oxy)-6-methoxy-2,2-dimethyltetrahydro-3aH-[1,3]dioxolo[4,5-c]pyran-6-yl)-2-iodopropanoate



33 **34**

To a stirred solution of galactose derived spiro-cyclopropane carboxylate sugar **33** (120 mg, 0.32 mmol) in 4 ml of methanol at 0 °C under nitrogen was added *N*-iodo succinimide (NIS) (87 mg, 0.38 mmol) and stirring the reaction mixture for 24 h at room temperature. After complete conversion of the starting material by confirming the TLC quench with saturated sodium thiosulfate and usual work up with dichloromethane (3 x 100 mL). Finally the organic layer was washed with water and brine solution, concentrating on rotary evaporator the crude product was purified by silica-gel column chromatography to afford the ring opened iodo-carboxylate **34** (160 mg) as mixture of diastereomers in 94% yield. **IR (neat)**: ν_{max} 2931, 2865, 1742, 1457, 1435, 1364, 1249, 1221, 1128, 1079, 843, 778, 673 cm-1. **^{1}H NMR (400 MHz, $CDCl_3$)**: δ 4.49 (dd, 1H, *J* = 3.6 Hz, *J* = 10.8 Hz), 4.15-4.18 (m, 1H), 4.06 (dd, 1H, *J* = 6.0 Hz, *J* = 6.8 Hz), 3.75-3.86 (m, 2H), 3.71 (s, 3H), 3.59 (d, 1H, *J* = 7.2 Hz), 3.27 (s, 3H), 2.82 (dd, 1H, *J* = 10.8 Hz, *J* = 15.2 Hz), 2.52 (dd, 1H, *J* = 4.0 Hz, *J* = 15.6 Hz), 1.49 (s, 3H), 1.31 (s, 3H), 0.90 (s, 9H), 0.16 (s, 6H). **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 172.1, 108.6, 100.6, 75.8, 73.3, 60.4, 52.7, 49.8, 40.9, 28.12, 26.2, 25.9, 18.2, 13.8, -3.8, -5.1. **HRMS (ESI)** calcd for $C_{19}H_{35}IO_7Si$+Na 553.1094, found 553.1095.

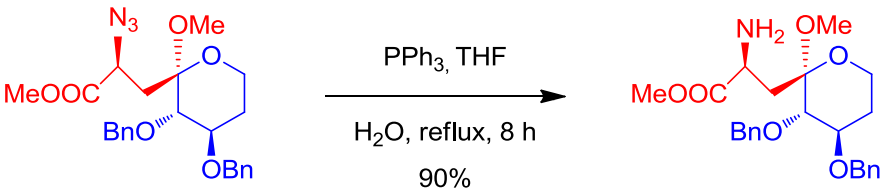
(4.4.1.14) (*S*)-methyl 2-azido-3-((3a*R*,6*R*,7*S*,7a*R*)-7-((*tert*-butyldimethylsilyl)oxy)-6-methoxy-2,2-dimethyltetrahydro-3a*H*-[1,3]dioxolo[4,5-*c*]pyran-6-yl)propanoate



34 **35**

To a stirred solution of iodo-carboxylate **34** (150 mg, 0.28 mmol), in 4 mL of dimethylformamide (DMF) was added sodium azide (91 mg, 1.41 mmol) in two portions, and stirred the reaction mixture at 55 ^{o}C for 24 h. after completion the reaction mixture by checking TLC, remove the DMF by rota vapour, extract with dichloromethane, washed with water and brine, dried over anhydrous $MgSO_4$. The obtained crude product was purified by silica-gel column chromatography in 20% ethyl acetate/hexane to provide the corresponding azido carboxylate **35** (110 mg) as mixture of diastereomers in 88% yield. **IR (neat)**: ν_{max} 2988, 2958, 2926, 2860, 2098, 1747, 1457, 1430, 1375, 1366, 1243, 1123, 1084, 1063, 1019, 942, 838, 772 cm-1. **^{1}H NMR (400 MHz, $CDCl_3$)**: δ 4.18-4.20 (m, 1H), 4.09 (t, 1H, *J* = 7.2 Hz), 3.95 (t, 1H, *J* = 7.6 Hz), 3.87 (d, 1H, *J* = 13.2 Hz), 3.51 (d, 1H, *J* = 7.2 Hz), 3.77 (s, 3H), 3.24 (s, 3H), 2.37 (dd, 1H, *J* = 7.6 Hz, *J* = 13.6 Hz), 2.16 (dd, 1H, *J* = 6.8 Hz, J = 14.0 Hz), 1.52 (s, 3H), 1.32 (s, 3H), 0.89 (s, 9H), 0.16 (s, 3H), 0.13 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 170.8, 108.6, 99.7, 76.7, 73.6, 73.4, 60.4, 58.0, 52.6, 48.6, 33.0, 28.1, 26.2, 25.9. **HRMS (ESI)** calcd for $C_{19}H_{35}N_3O_7Si$+Na 468.2142, found 468.2142.

(4.4.1.15) (*S*)-methyl 2-amino-3-((2*R*,3*S*,4*R*)-3,4-bis(benzyloxy)-2-methoxytetrahydro-2*H*-pyran-2-yl)propanoate:

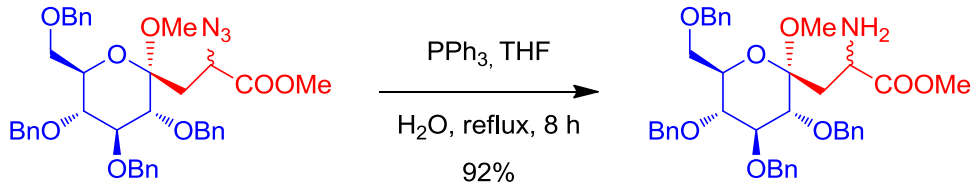


23 **36**

Triphenyl phosphine (26 mg, 0.09 mmol) was added to a solution of azide **23** (45 mg, 0.09 mmol) in dry THF (2 mL) under nitrogen condition, the solution was stirred for 8 h, after complete formation of iminophosphorane was confirmed by TLC, at this stage water was added and solution was refluxed for 6 h. The reaction mixture was washed with brine solution and extracted with chloroform. The organic extract was dried over anhydrous Na_2SO_4 and evaporated to dryness. The crude product was purified by silica-gel column chromatography using 90% ethyl acetate/hexane to afford the amine **36** (38 mg) in 90% yield as single diastereomer. **IR (neat)**: ν_{max} 3402, 3057, 3024, 2953, 2920, 2854, 1736, 1501, 1452, 1441, 1358, 1260, 1200, 1128, 1101, 1046, 739 cm-1. **^{1}H NMR (500 MHz, $CDCl_3$)**: δ 7.28-7.38 (m, 10H), 5.04 (d, 1H, *J* = 11.5 Hz), 4.82 (d, 1H, *J* = 11.5 Hz), 4.66 (q, 2H, *J* = 11.5 Hz), 3.98-4.03 (m, 1H), 3.66 (s, 3H), 3.58 (dd, 1H, *J* = 5.5 Hz, *J* = 12.5 Hz), 3.51 (dd, 1H, *J* = 2.5 Hz, *J* = 13.5

Hz), 3.25 (t, 1H, *J* = 7.0 Hz), 3.22 (s, 3H), 2.15 (dd, 1H, *J* = 7.5 Hz, *J* = 14.5 Hz), 2.05 (dt, 1H, *J* = 2.5 Hz, *J* = 13.0 Hz), 1.92 (dd, 1H, *J* = 6.5 Hz, J = 14.0 Hz), 1.76 (bs, 2H), 1.62 (ddd, 1H, *J* = 5.5 Hz, *J* = 13.0 Hz, *J* = 24.5 Hz), 1.37 (d, 1H, *J* = 38.0 Hz). **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 176.0, 138.6, 138.5, 128.3, 128.3, 128.2, 127.5, 127.4, 127.4, 80.8, 77.6, 74.7, 71.5, 58.8, 51.5, 50.8, 47.5, 37.0, 31.3. **HRMS (ESI)** calcd for $C_{24}H_{31}NO_6$+H 430.2230, found 430.2230.

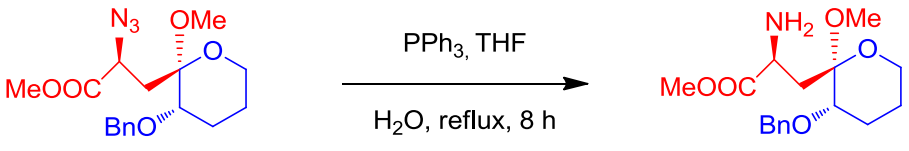
(4.4.1.16) methyl 2-amino-3-((2*S*,3*S*,4*S*,5*R*,6*R*)-3,4,5-tris(benzyloxy)-6-((benzyloxy)methyl)-2-methoxytetrahydro-2*H*-pyran-2-yl)propanoate:



26 **37**

Triphenyl phosphine (31 mg, 0.11 mmol) was added to a solution of azide **26** (80 mg, 0.11 mmol) in dry THF (3 mL) under nitrogen condition, the solution was stirred for 8 h, after complete formation of iminophosphorane was confirmed by TLC, at this stage water was added and solution was refluxed for 6 h. The reaction mixture was washed with brine solution and extracted with chloroform. The organic extract was dried over anhydrous Na_2SO_4 and evaporated to dryness. The crude product was purified by column chromatography in silica-gel column chromatography using 80% ethyl acetate/hexane to afford the amine **37** (70 mg) as mixture of diastereomers. **IR (neat)**: ν_{max} 3050, 3031, 2925, 2850, 1738, 1496, 1453, 1437, 1362, 1264, 1119, 1087, 1027 cm-1. **HRMS (ESI)** calcd for $C_{39}H_{45}NO_6$+H 656.3223, found 656.3222.

(4.4.1.17) (*S*)-methyl 2-amino-3-((2*R*,3*S*)-3-(benzyloxy)-2-methoxytetrahydro-2*H*-pyran-2-yl)propanoate:

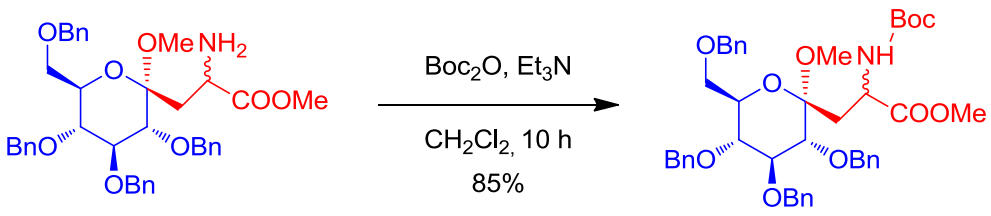


29 **38**

Triphenylphosphine (52 mg, 0.20 mmol) was added to a solution of azide **29** (70 mg, 0.20 mmol) in dry THF (3 mL) under nitrogen condition, the solution was stirred for 8 h, after

complete formation of iminophosphorane was confirmed by TLC, at this stage water was added and solution was refluxed for 6 h. The reaction mixture was washed with brine solution and extracted with chloroform. The organic extract was dried over anhydrous Na_2SO_4 and evaporated to dryness. The crude product was purified by column chromatography in silica-gel column chromatography using 80% ethyl acetate/hexane to afford the amine **38** as single diastereomer. **IR (neat)**: ν_{max} 3353, 3057, 2947, 2920, 2849, 1742, 1676, 1435, 1265, 1183, 1117, 1084, 909, 734 cm-1. **HRMS (ESI)** calcd for $C_{17}H_{25}NO_5$+Na 346.1630, found 346.1630.

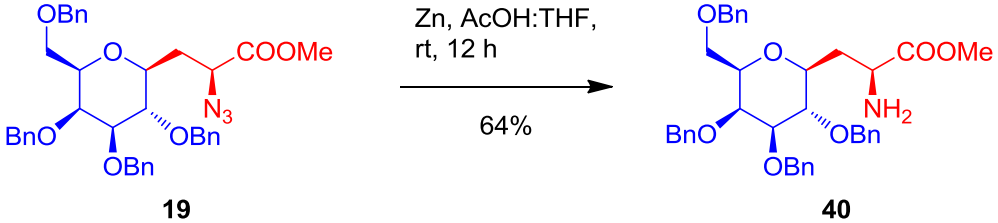
(4.4.1.18) methyl 2-((*tert*-butoxycarbonyl)amino)-3-((2*S*,3*R*,4*S*,5*R*,6*R*)-3,4,5-tris(benzyloxy)-6-((benzyloxy)methyl)-2-methoxytetrahydro-2*H*-pyran-2-yl)propanoate:



37 **39**

To a stirred solution of glyco-amino acid **37** (65 mg, 0.10 mmol) in dichloromethane (2 mL) was added triethylamine (42 µL, 0.30 mmol) and Boc_2O (124 µL, 0.60 mmol) drop wise over a period of 5 minutes and the reaction mixture was stirred for 10 h. after complete disappearance of starting material the reaction mixture was concentrated in *vacuo*, and extracted ethyl acetate, and washed with water, brine, dried over anhydrous Na_2SO_4. The obtained organic layer was concentrated over rota vapour and purified by silica-gel column chromatography in 30% ethyl acetate/hexane to obtain the N-protected Boc compound **39** (63 mg) in 85% yield as mixture of diastereomers. **IR (neat)**: ν_{max} 3050, 3031, 2925, 2850, 1752, 1709, 1496, 1453, 1365, 1264, 1207, 1161, 1066, 1027 cm-1. **HRMS (ESI)** calcd for $C_{44}H_{53}NO_{10}$+Na 778.3567, found 778.3565.

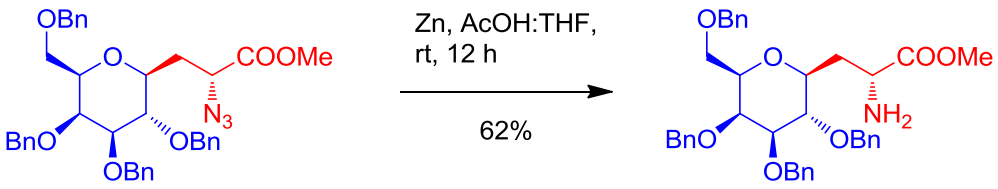
(4.4.1.19) (*S*)-methyl 2-amino-3-((2*S*,3*R*,4*R*,5S,6R)-3,4,5-tris(benzyloxy)-6-((benzyloxy)methyl)tetrahydro-2*H*-pyran-2-yl)propanoate:



19 **40**

To a stirred solution of azide **19** (30 mg, 0.04 mmol) in 3 mL of AcOH/THF (1:1), Zn dust (3.0 mg, 0.04 mmol) was added and the reaction mixture was stirred for 12 h at room temperature. After completion of the reaction, Zn was removed by filtration, then solvent was removed under vacuum followed by dilution with 10 mL of ethyl acetate. The organic layer was thoroughly washed with saturated $NaHCO_3$ solution, water and brine solution, dried over anhydrous Na_2SO_4, and concentrated. The crude product was separated by silica-gel column chromatography (adding 1% triethylamine) in ethyl acetate/hexane (1:1) to furnish the sugar derived glyco amino acid **40** (15 mg) in 64% yield. **IR (neat)**: ν_{max} 2920, 2854, 1742, 1463, 1364, 1276, 1123, 734, 695 cm^{-1}. **^{1}H NMR (500 MHz, $CDCl_3$)**: δ 7.26-7.34 (m, 20H), 4.95 (d, 1H, *J* = 4.0 Hz), 4.92 (d, 1H, *J* = 5.0 Hz), 4.74 (d, 1H, *J* = 11.5 Hz), 4.66 (d, 1H, *J* = 11.5 Hz), 4.62 (dd, 1H, *J* = 2.0 Hz, *J* = 11.0 Hz), 4.43 (q, 2H, *J* = 11.5 Hz), 3.98 (d, 1H, *J* = 3.0 Hz), 3.68-3.70 (m, 1H), 3.67 (s, 3H), 3.61 (dd, 1H, *J* = 2.5 Hz, *J* = 9.0 Hz), 3.47-3.55 (m, 4H), 2.28-2.33 (m, 1H), 1.98-2.07 (m, 1H), 1.95 (ddd, 2H, *J* = 2.0 Hz, *J* = 5.5 Hz, *J* = 9.0 Hz), 1.70 (bs, 2H). **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 176.6, 138.6, 138.2, 137.9, 128.4, 128.3, 128.2, 128.2, 128.0, 127.9, 127.7, 127.6, 127.5, 84.7, 78.6, 77.2, 76.1, 75.3, 74.5, 73.7, 73.4, 72.3, 68.9, 51.9, 51.2, 36.3. **HRMS (ESI)** calcd for $C_{38}H_{43}NO_7$+Na 648.2937, found 648.2936.

(4.4.1.20) (*R*)-methyl 2-amino-3-((2*S*,3*R*,4*R*,5*S*,6*R*)-3,4,5-tris(benzyloxy)-6-((benzyloxy)methyl)tetrahydro-2*H*-pyran-2-yl)propanoate:



20 **41**

Compound **41** was synthesized using azido carboxylate **20** (25mg, 0.03 mmol), Zn (2.5 mg, 0.03 mmol) and acetic acid/tetrahydrofuran (1:1) (2 mL) following the procedure described for compound **40** (4.4.1.19). The crude product was purified by silica-gel column chromatography in ethyl acetate/hexane (1:1) to obtain sugar derived glyco amino acid **41** (15.0 mg) in 60% yield. **IR (neat)**: ν_{max} 2958, 2926, 2854, 1742, 1452, 1369, 1265, 1112, 728, 701 cm^{-1}. **^{1}H NMR (500 MHz, $CDCl_3$)**: δ 7.27-7.36 (m, 20H), 4.95 (d, 1H, *J* = 5.0 Hz), 4.92 (d, 1H, *J* = 5.5 Hz), 4.74 (d, 1H, *J* = 11.5 Hz), 4.67 (d, 1H, *J* = 7.0 Hz), 4.64 (d, 1H, *J* = 6.5 Hz), 4.60 (d, 1H, *J* = 19.0 Hz), 4.45 (d, 1H, *J* = 11.5 Hz), 4.40 (d, 1H, *J* = 11.5 Hz), 3.97 (d, 1H, *J* = 2.5 Hz),

3.67-3.71 (m, 2H), 3.66 (s, 3H), 3.58 (dd, 1H, *J* = 2.5 Hz, *J* = 9.0 Hz), 3.50-3.55 (m, 3H), 3.41 (dt, 1H, *J* = 7.5 Hz, *J* = 9.5 Hz, *J* = 19.0 Hz), 2.29 (ddd, 1H, *J* = 2.0 Hz, *J* = 5.5 Hz, *J* = 14.0 Hz), 2.02 (bs, 2H), 1.78 (ddd, 1H, *J* = 6.5 Hz, *J* = 9.5 Hz, *J* = 15.5 Hz). **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 175.5, 138.7, 138.2, 137.8, 128.4, 128.3, 128.2, 128.1, 127.9, 127.8, 127.7, 127.6, 127.5, 84.6, 78.7, 77.5, 76.8, 75.4, 74.5, 73.7, 73.5, 72.2, 68.8, 52.4, 51.9. 37.0. **HRMS (ESI)** calcd for $C_{38}H_{43}NO_7$+Na 648.2937, found 648.2935.

4.5 References

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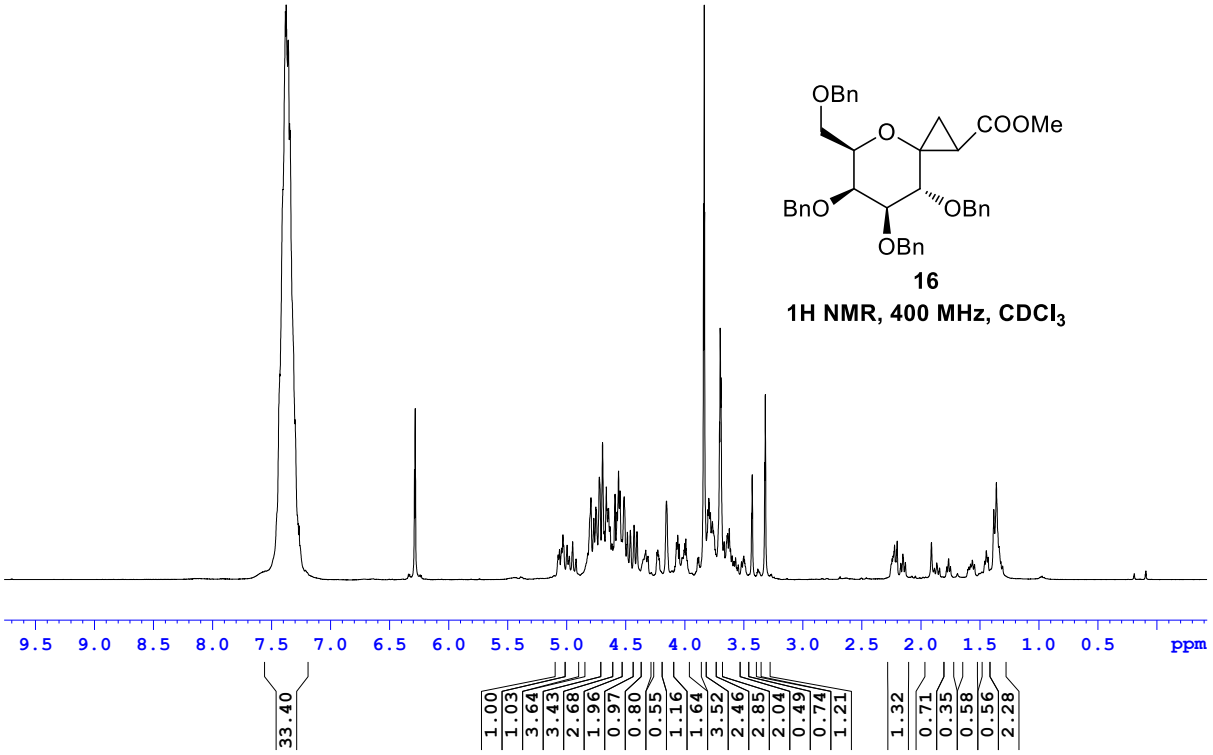
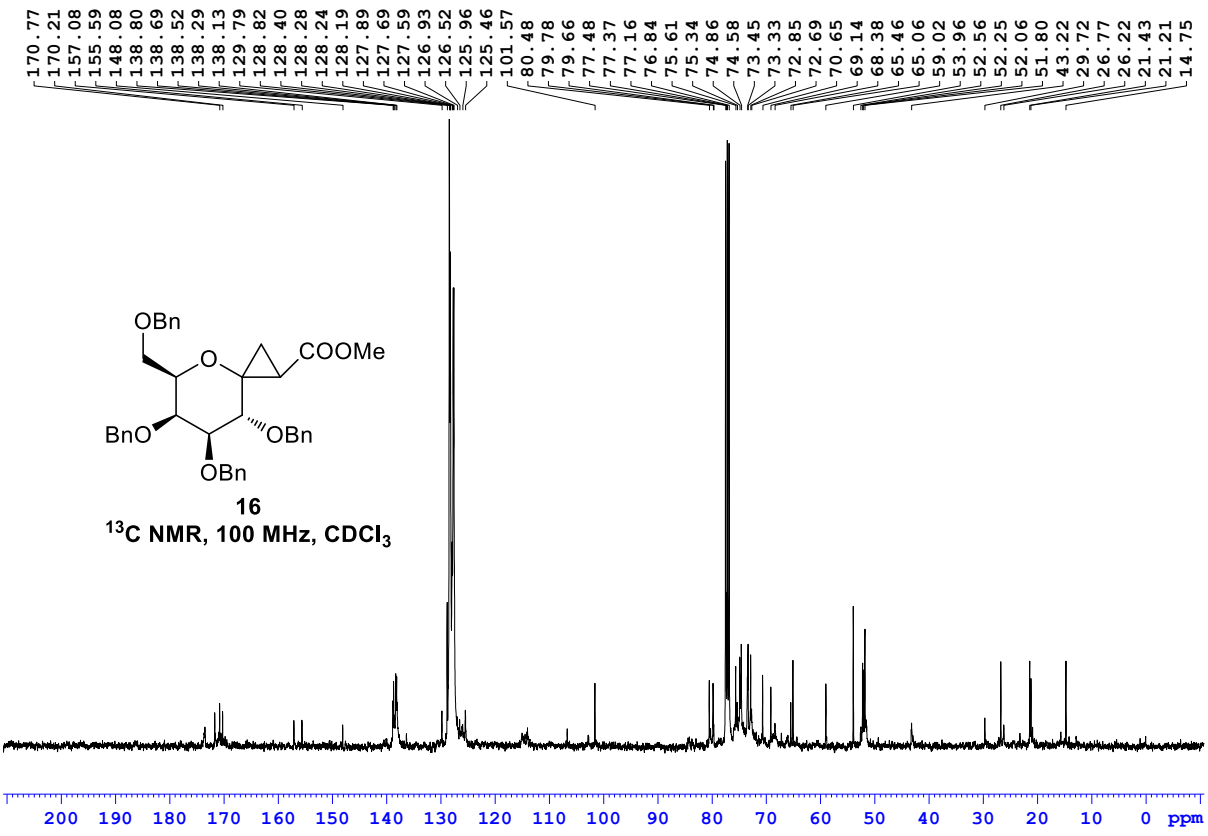
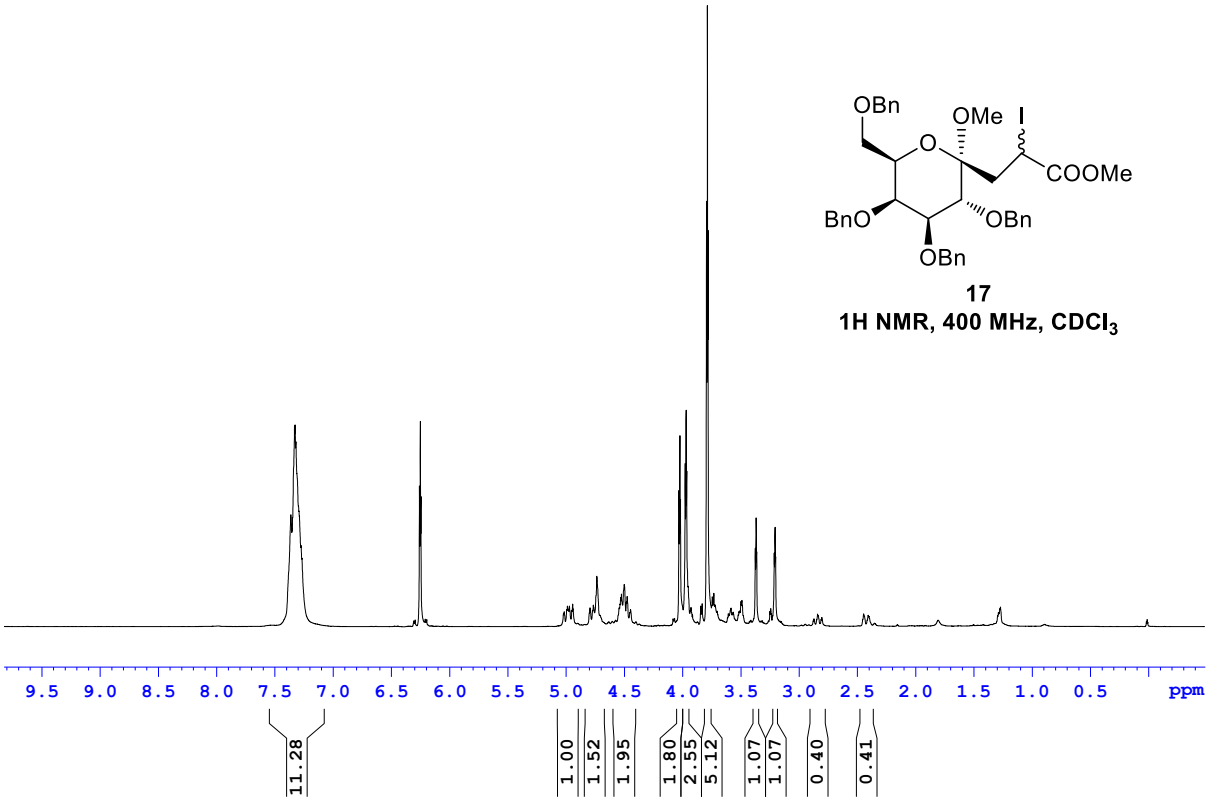
4.6 NMR Spectra

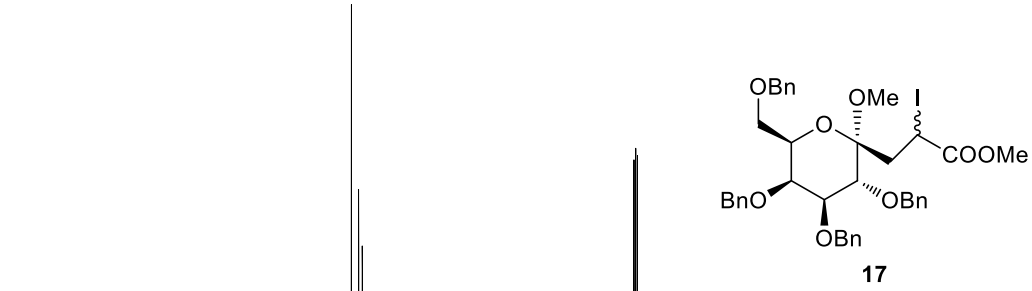






17

1H NMR, 400 MHz, $CDCl_3$



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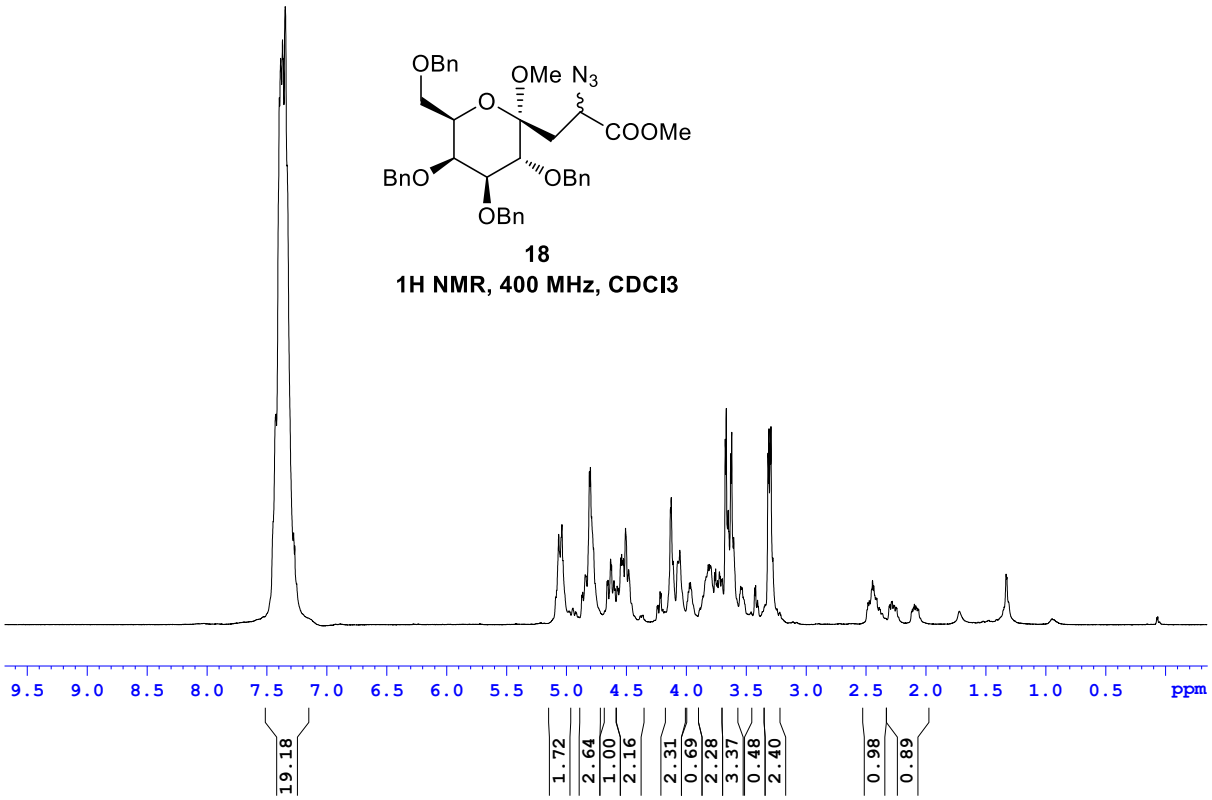

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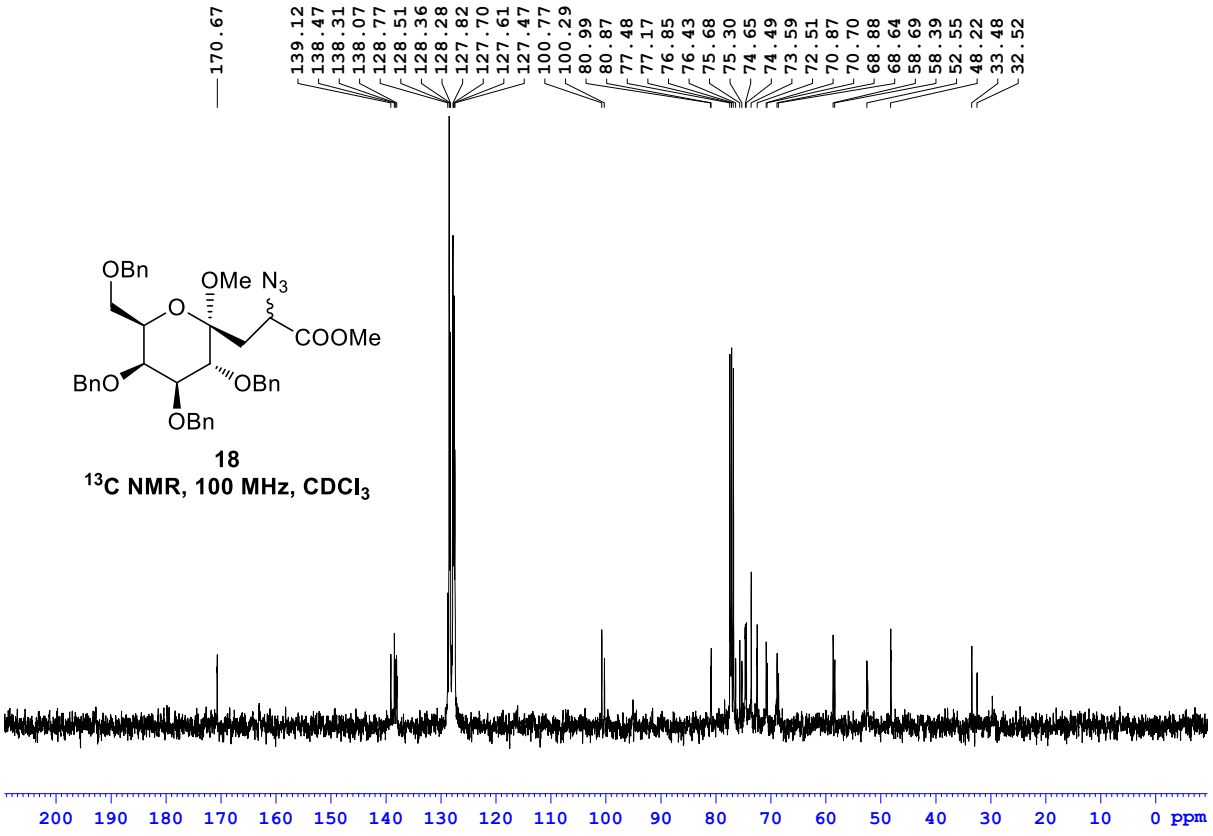

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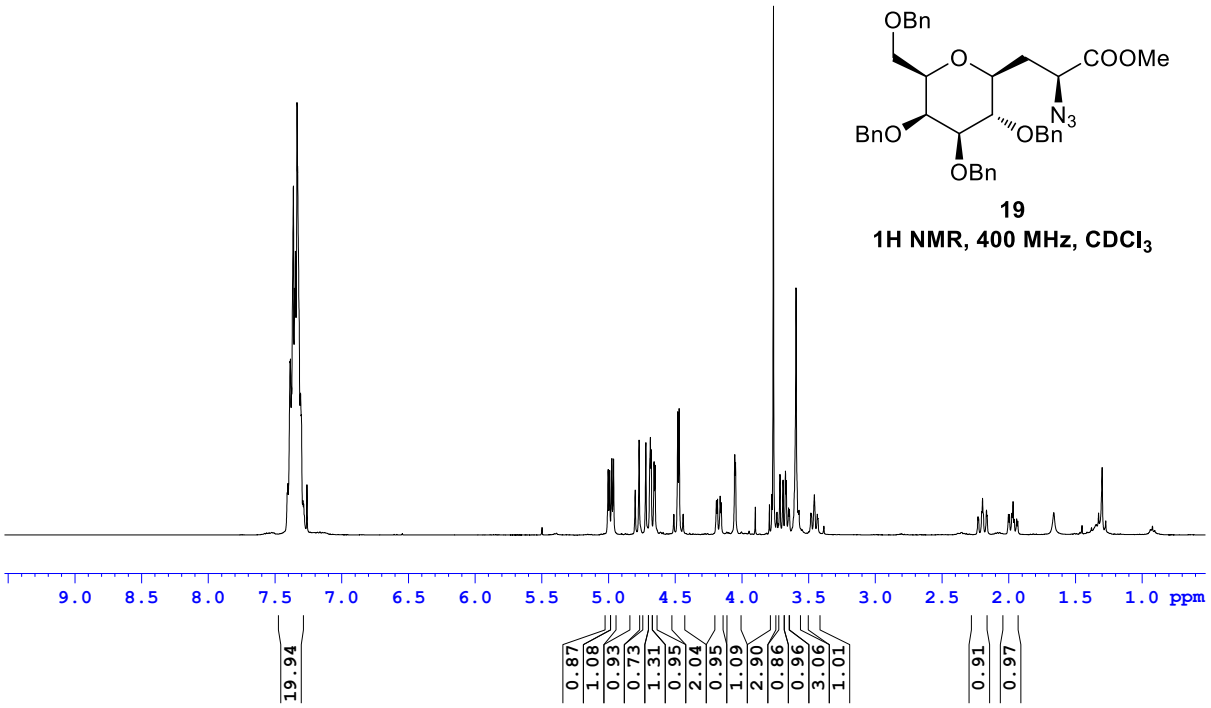

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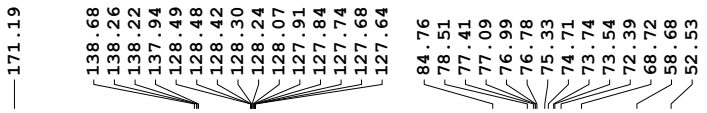

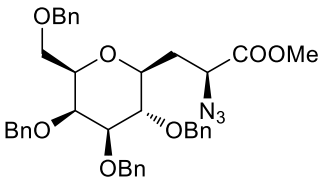

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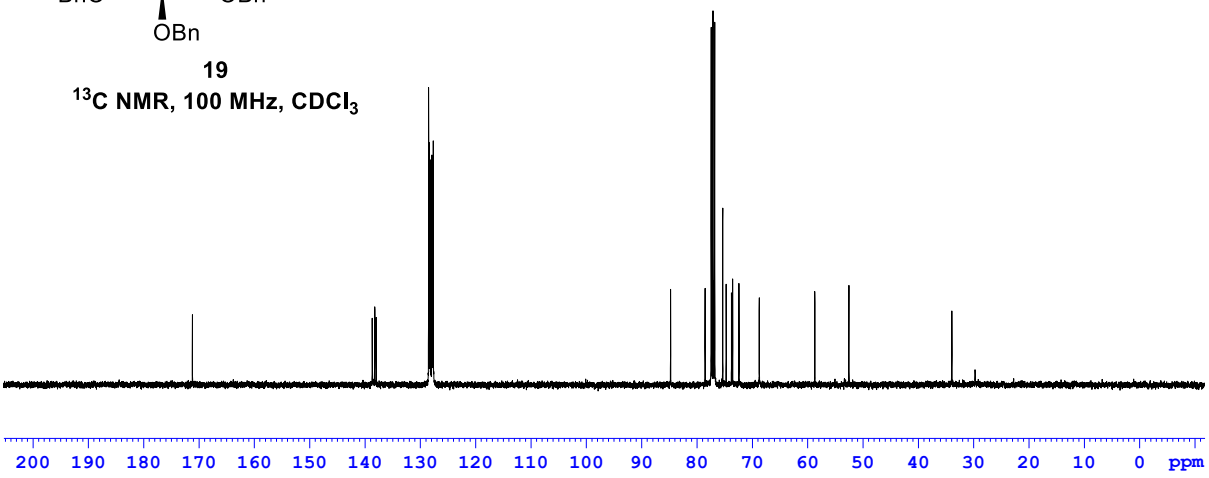

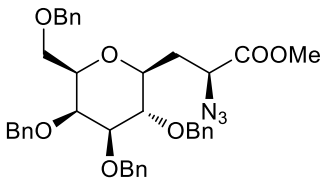

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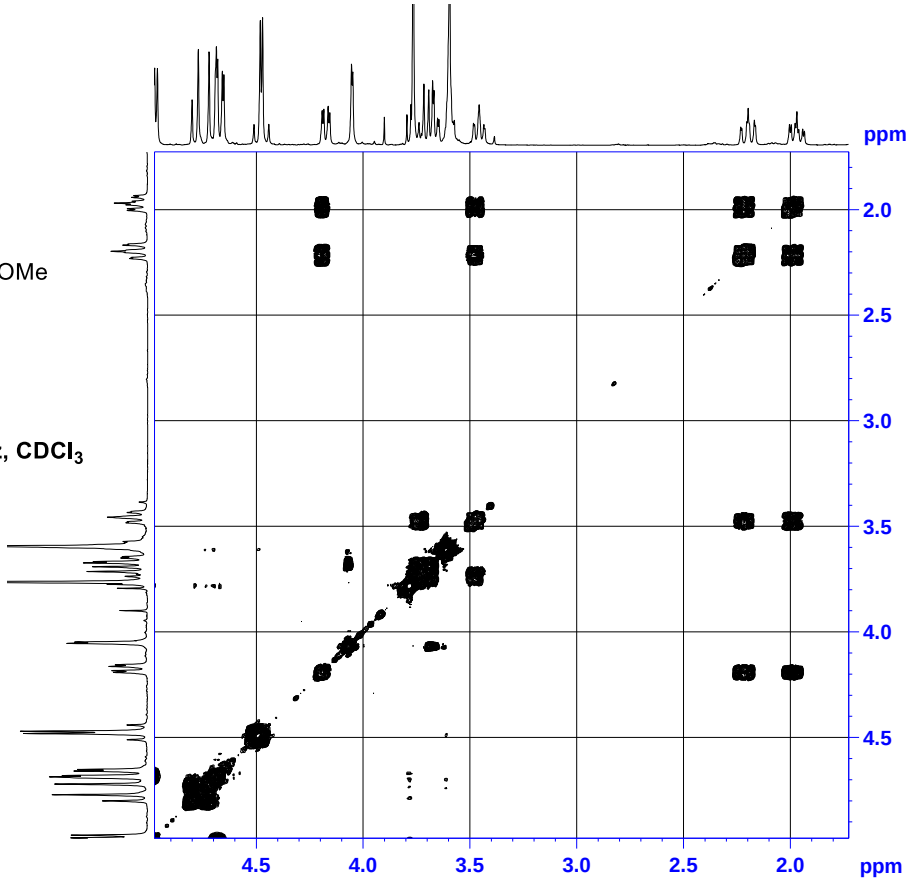

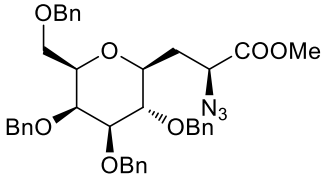

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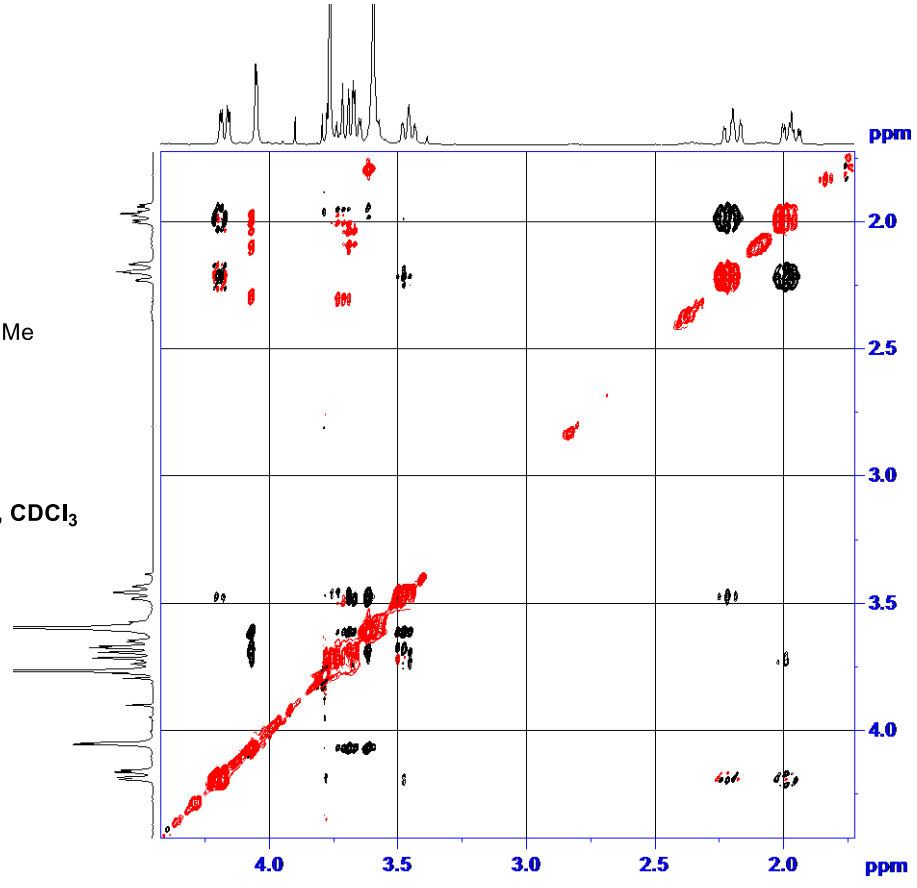

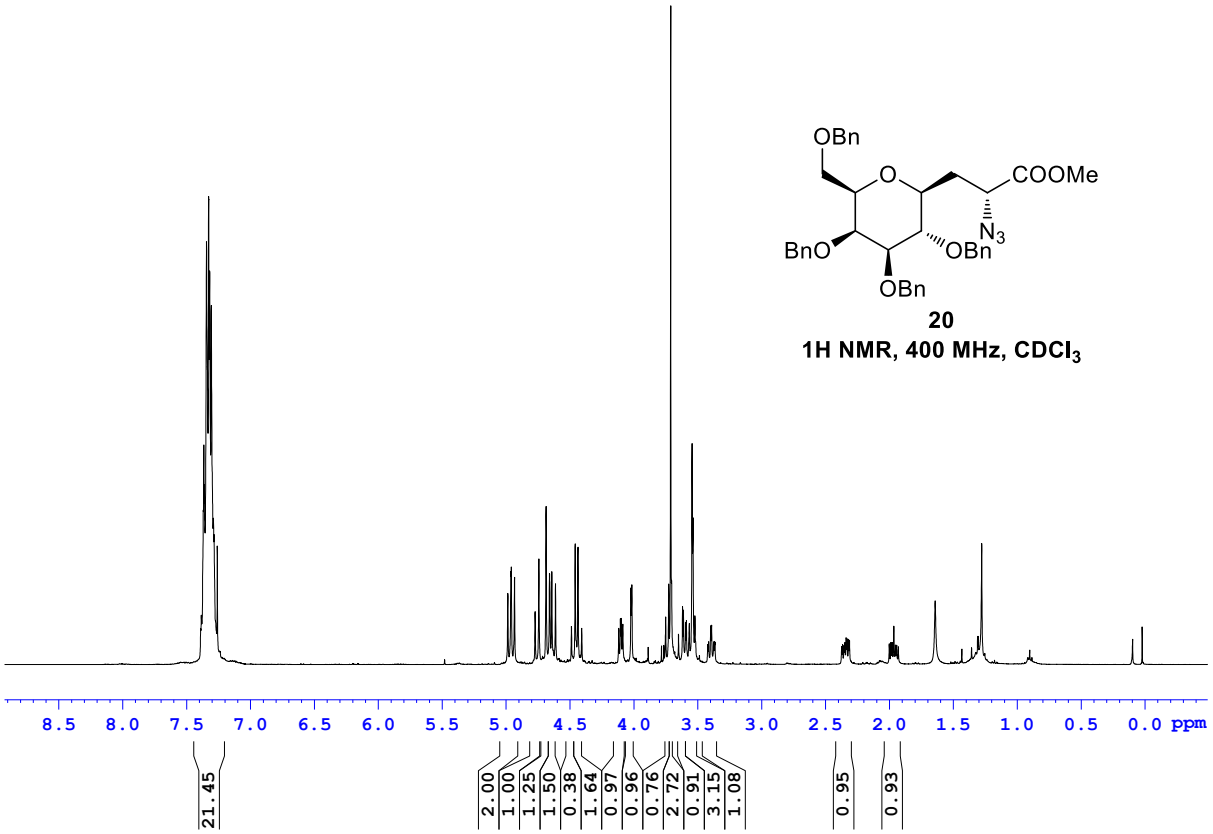

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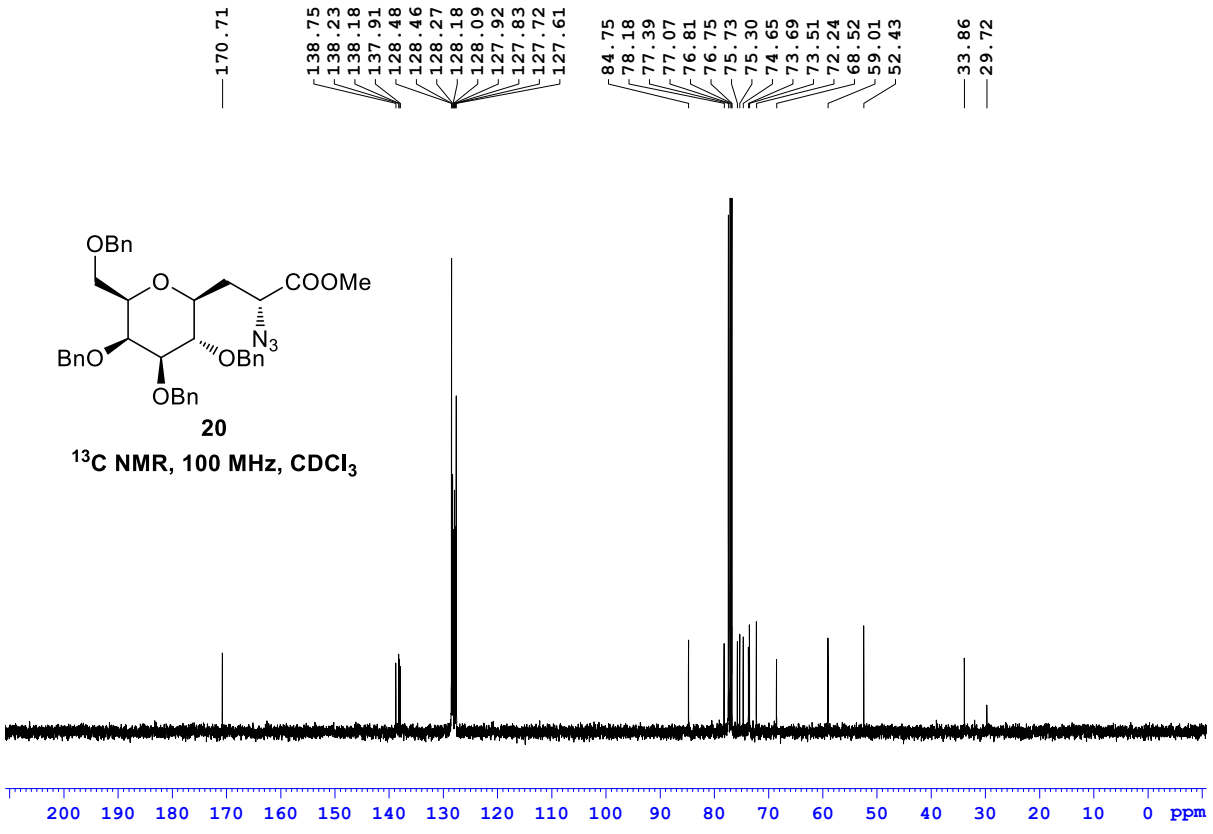

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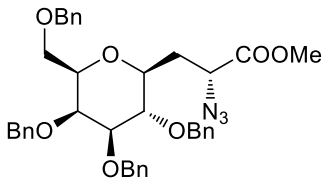

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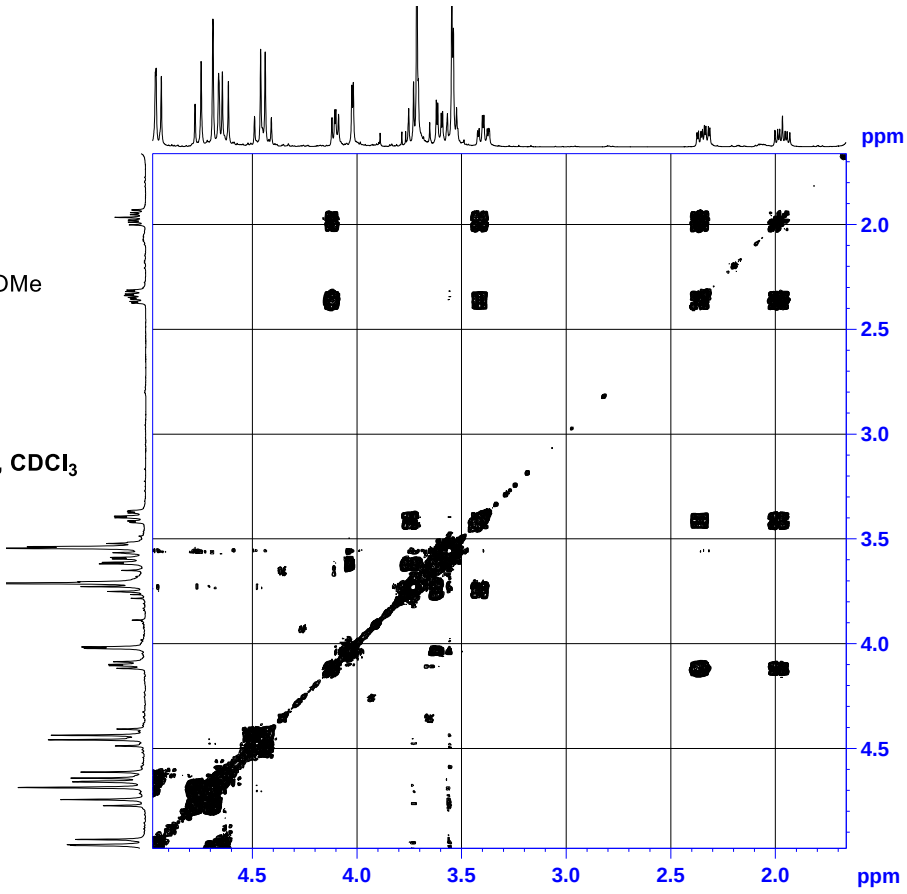

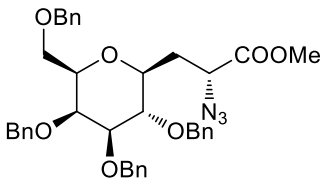

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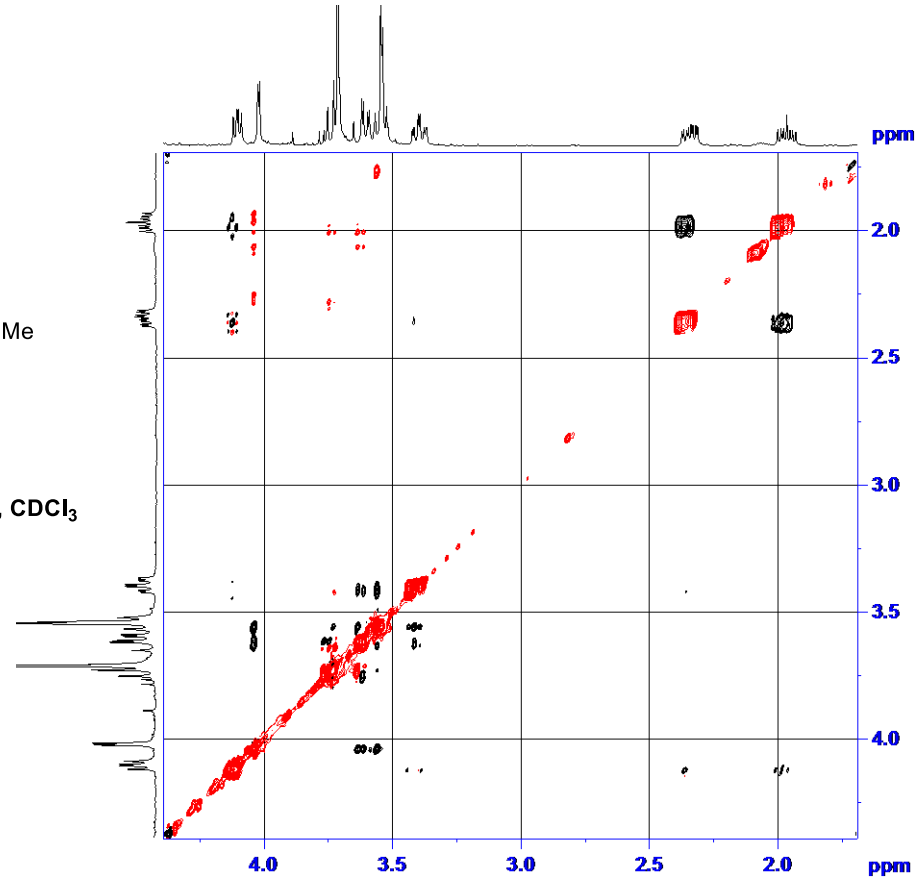

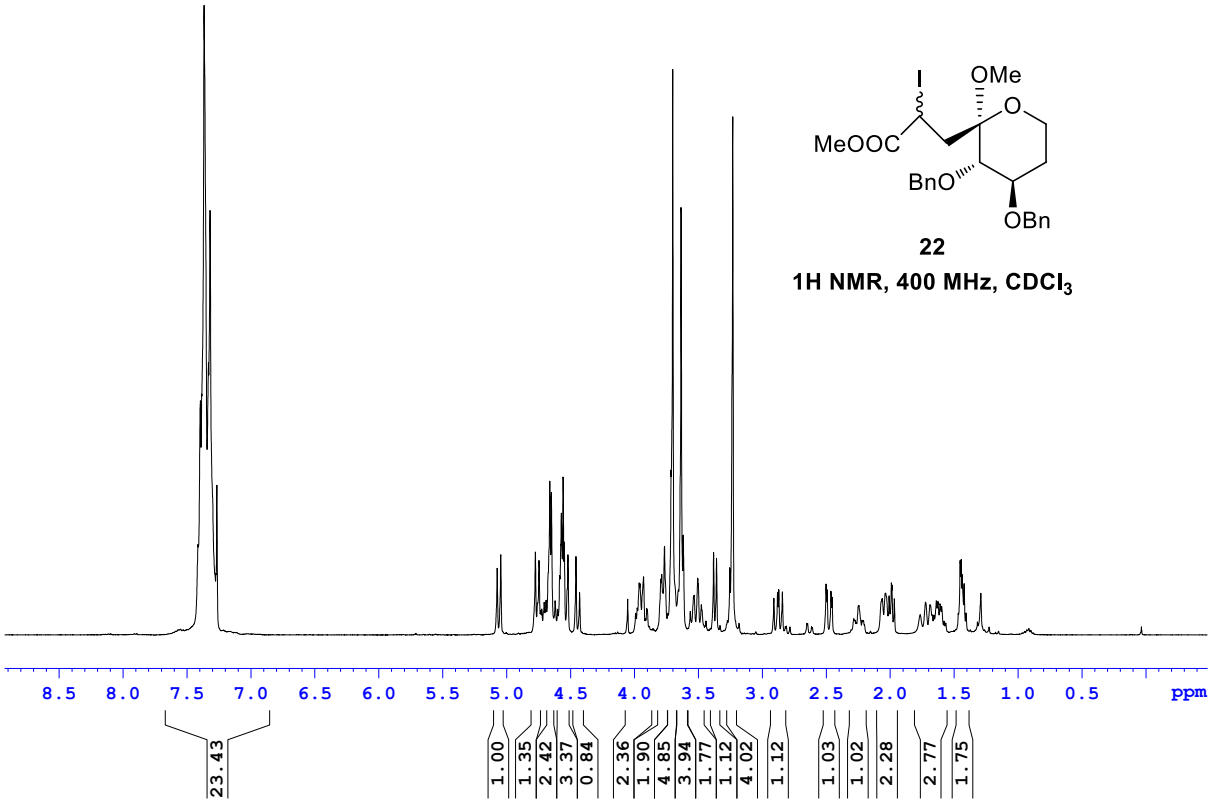

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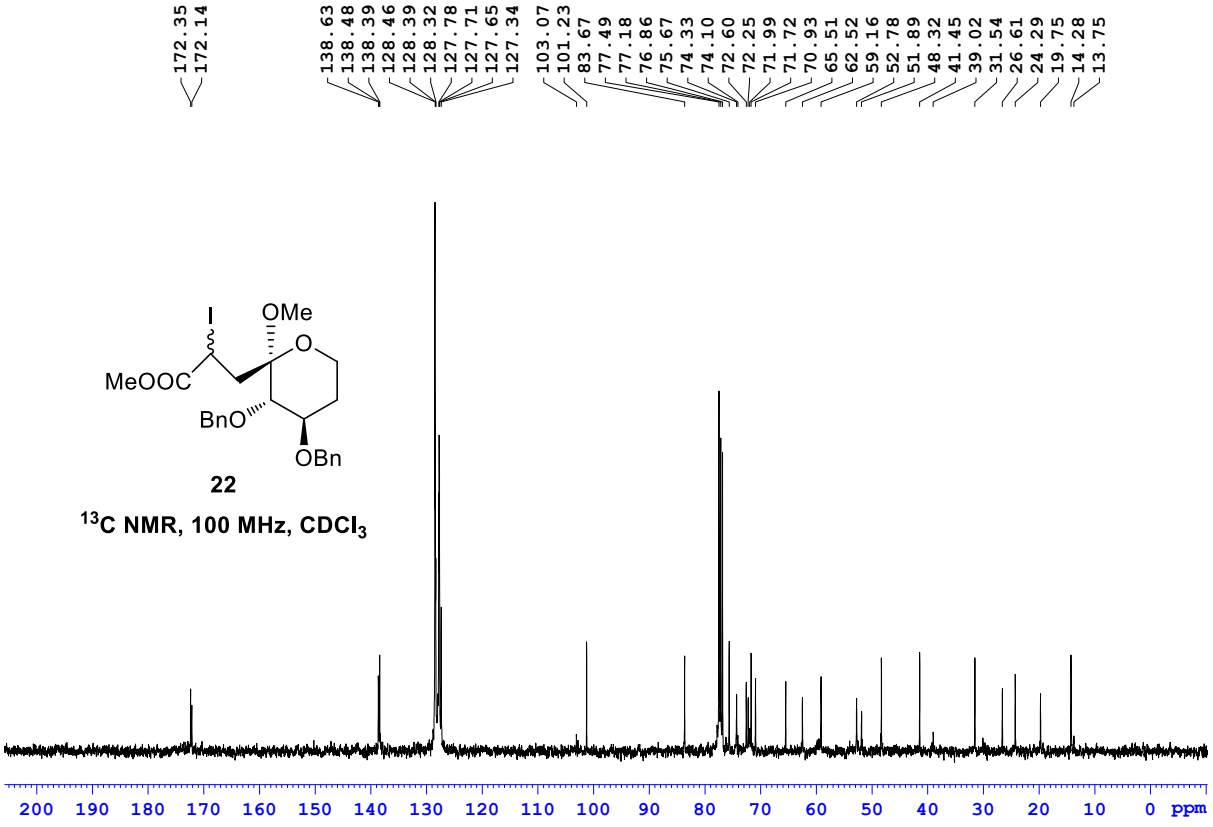
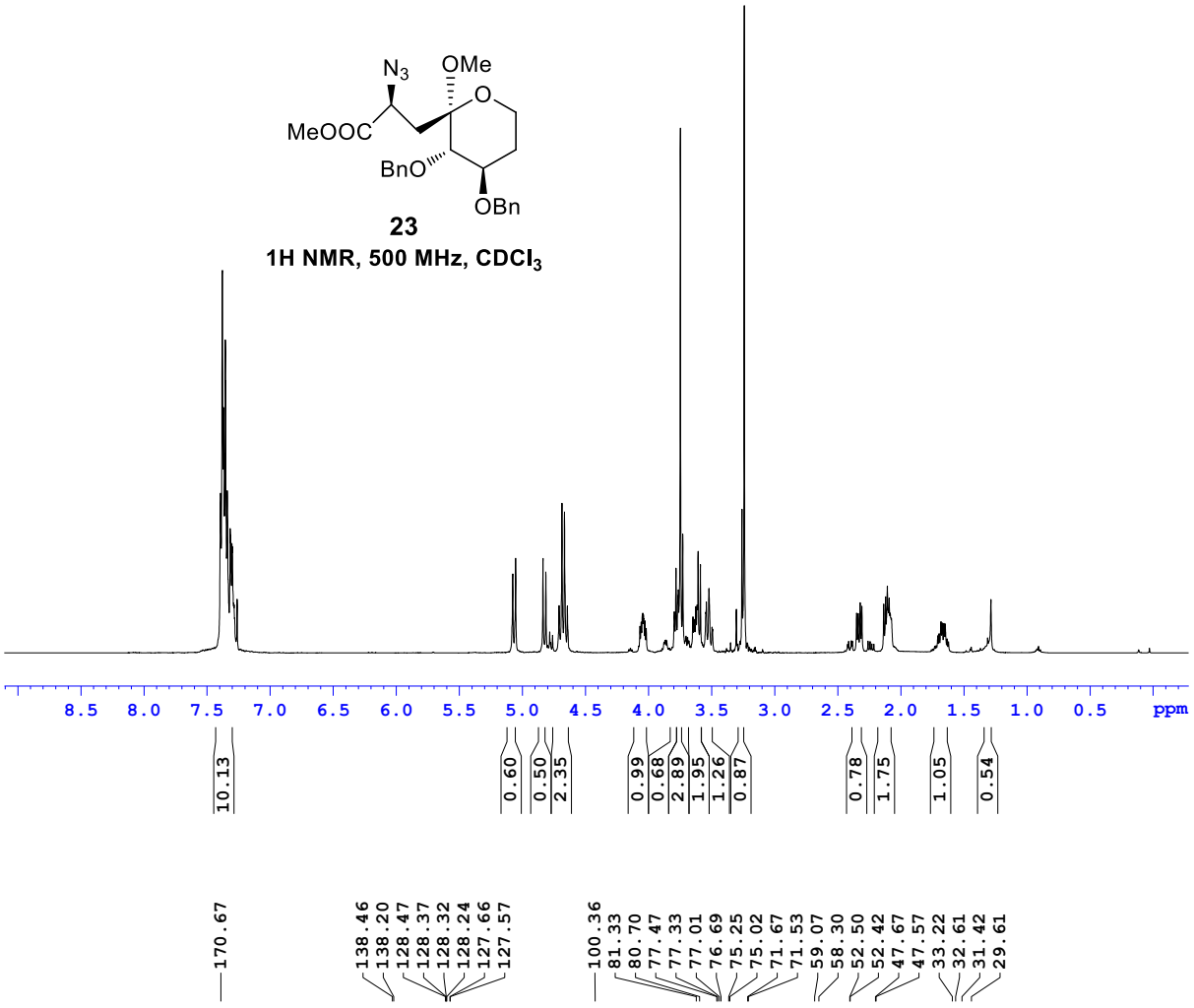
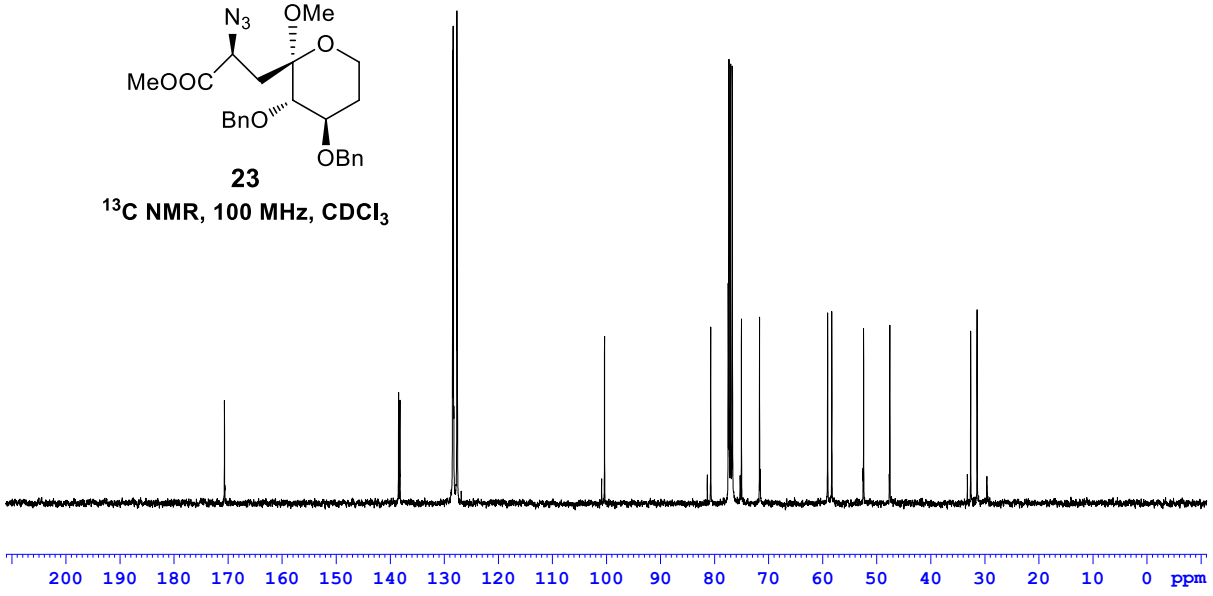
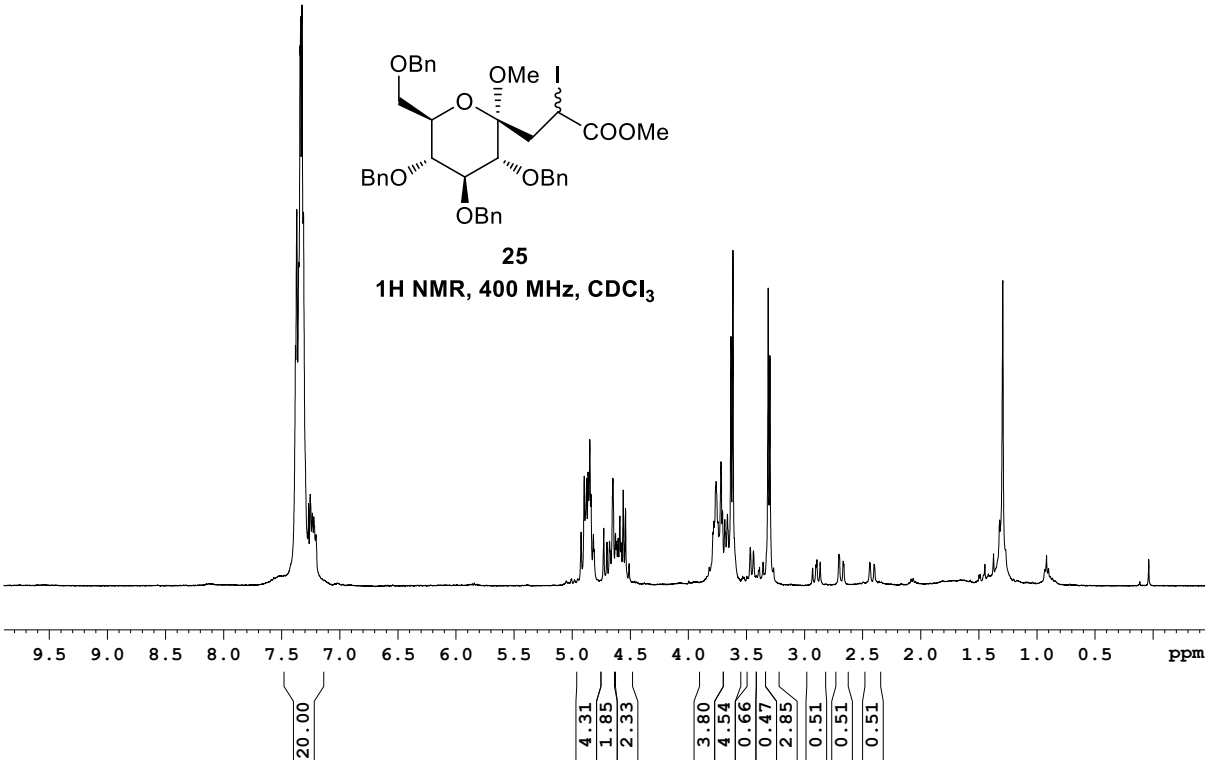


22

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

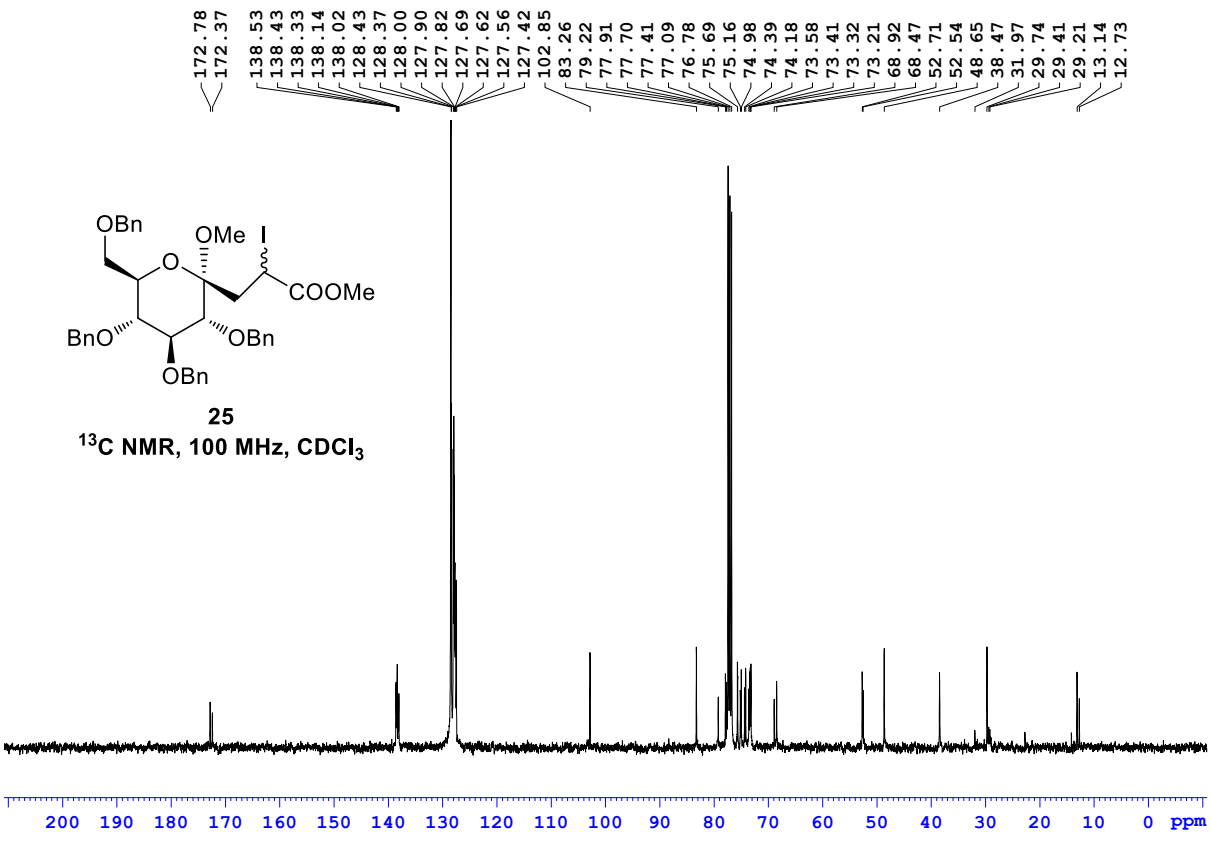

N3
OMe
MeOOC
O
BnO
OBn
23
1H NMR, 500 MHz, CDCl3
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
10.13
0.60
0.50
2.35
0.99
0.68
2.89
1.95
1.26
0.87
0.78
1.75
1.05
0.54
170.67
138.46
138.20
128.47
128.37
128.32
128.24
127.66
127.57
100.36
81.33
80.70
77.47
77.33
77.01
76.69
75.25
75.02
71.67
71.53
59.07
58.30
52.50
52.42
47.67
47.57
33.22
32.61
31.42
29.61


N3
OMe
MeOOC
O
BnO
OBn
23
13C NMR, 100 MHz, CDCl3
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm



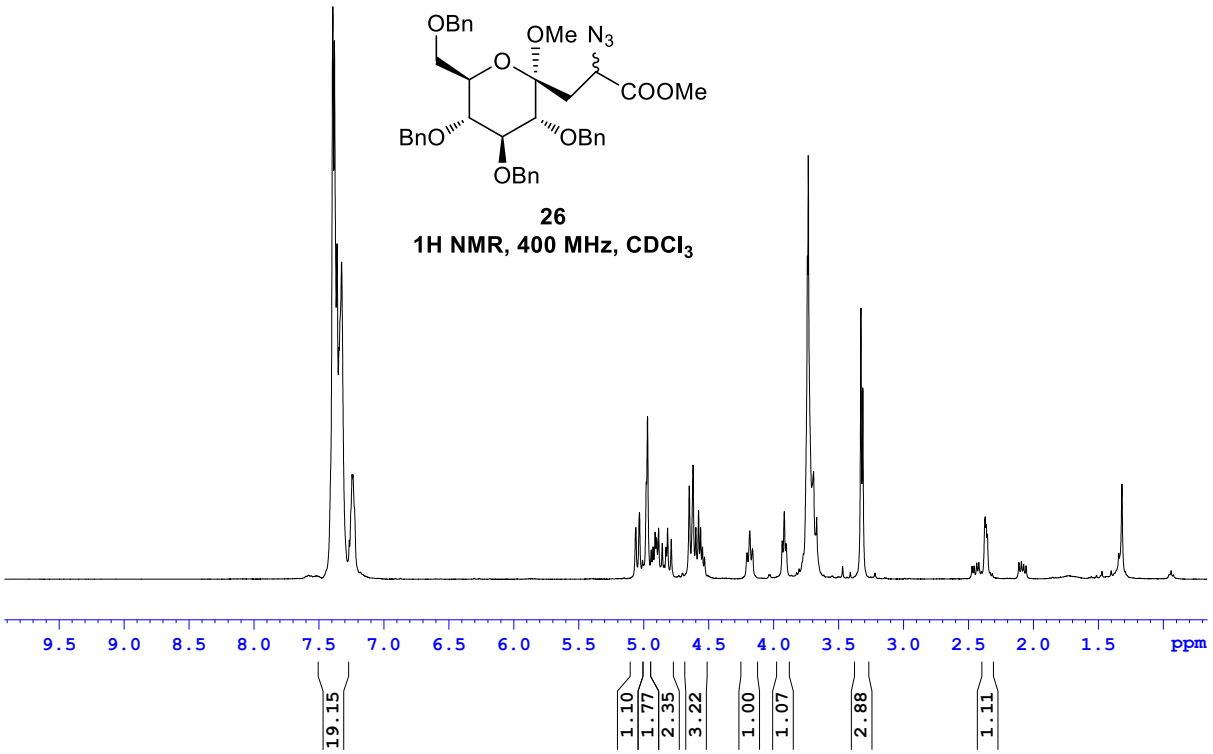
25

1H NMR, 400 MHz, $CDCl_3$

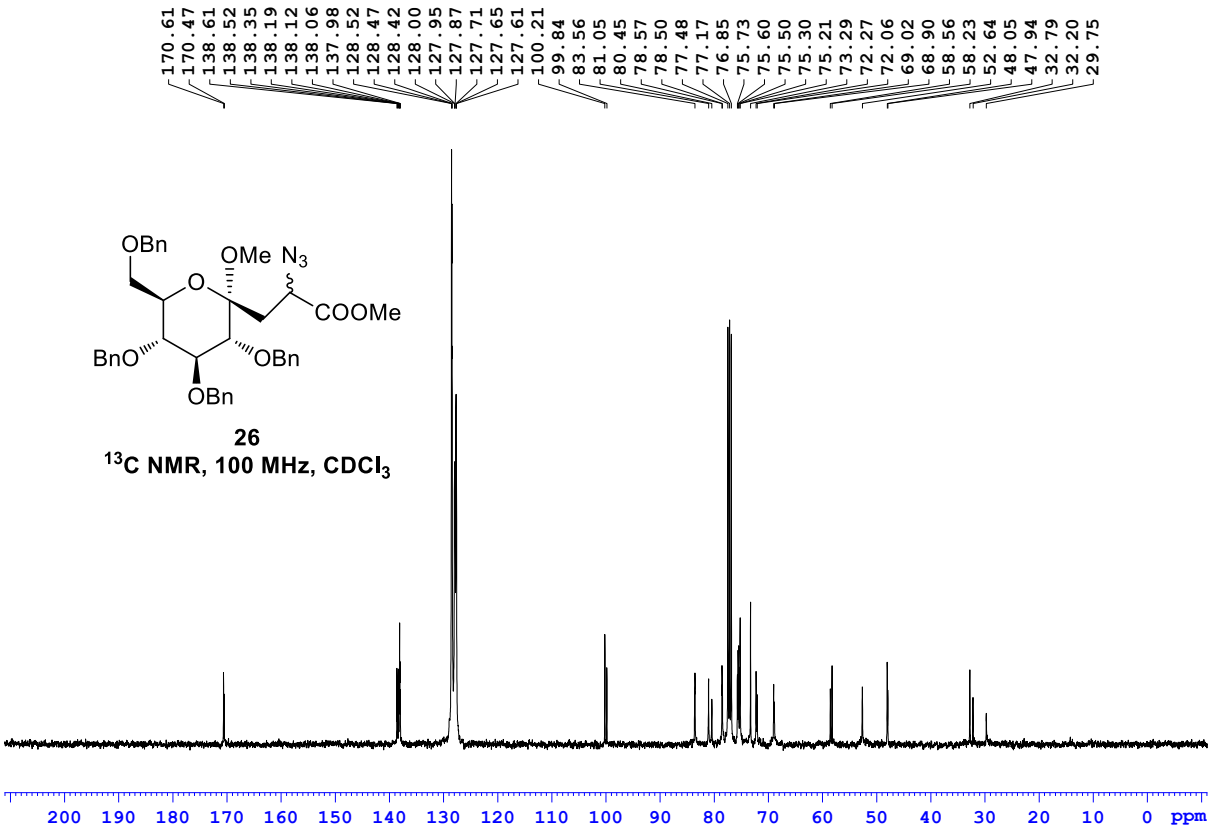


25

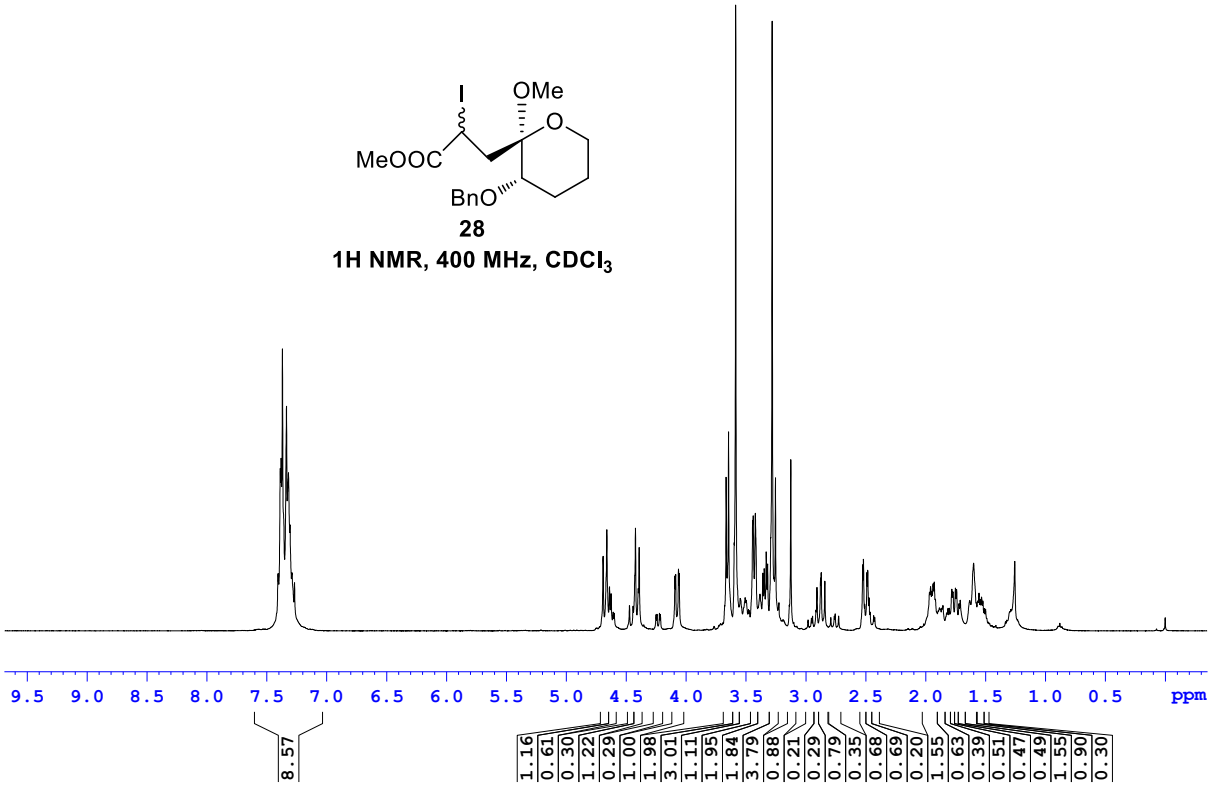
^{13}C NMR, 100 MHz, $CDCl_3$

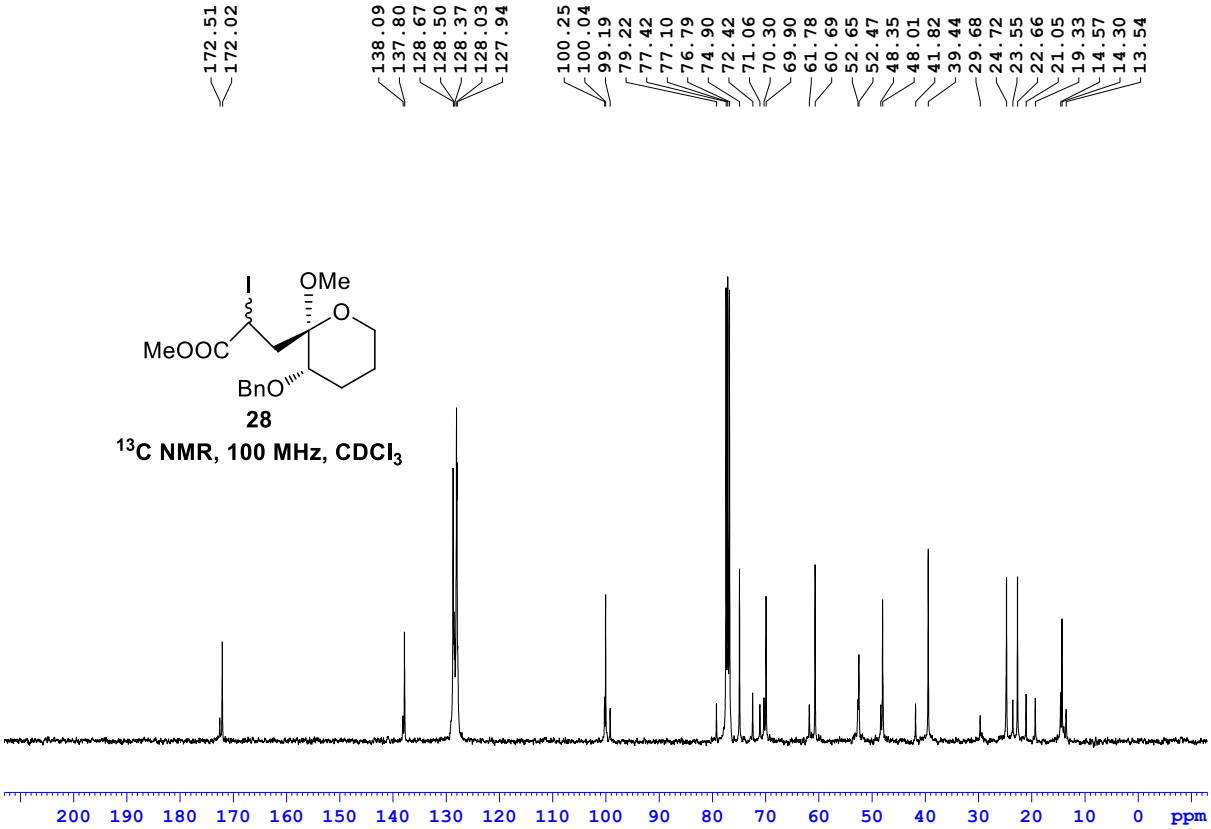


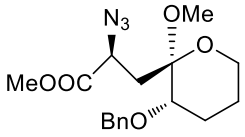
26
1H NMR, 400 MHz, $CDCl_3$



26
^{13}C NMR, 100 MHz, $CDCl_3$

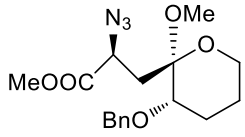

OMe
O
MeOOC
BnO
28
1H NMR, 400 MHz, CDCl3
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
8.57
1.16 0.61 0.30 1.22 0.29 1.00 1.98 3.01 1.11 1.95 1.84 3.79 0.88 0.21 0.29 0.79 0.35 0.68 0.69 0.20 1.55 0.63 0.39 0.51 0.47 0.49 1.55 0.90 0.30


172.51 172.02
138.09 137.80 128.67 128.50 128.37 128.03 127.94
100.25 100.04 99.19 79.22 77.42 77.10 76.79 74.90 72.42 71.06 70.30 69.90 61.78 60.69 52.65 52.47 48.35 48.01 41.82 39.44 29.68 24.72 23.55 22.66 21.05 19.33 14.57 14.30 13.54
OMe
O
MeOOC
BnO
28
13C NMR, 100 MHz, CDCl3
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm



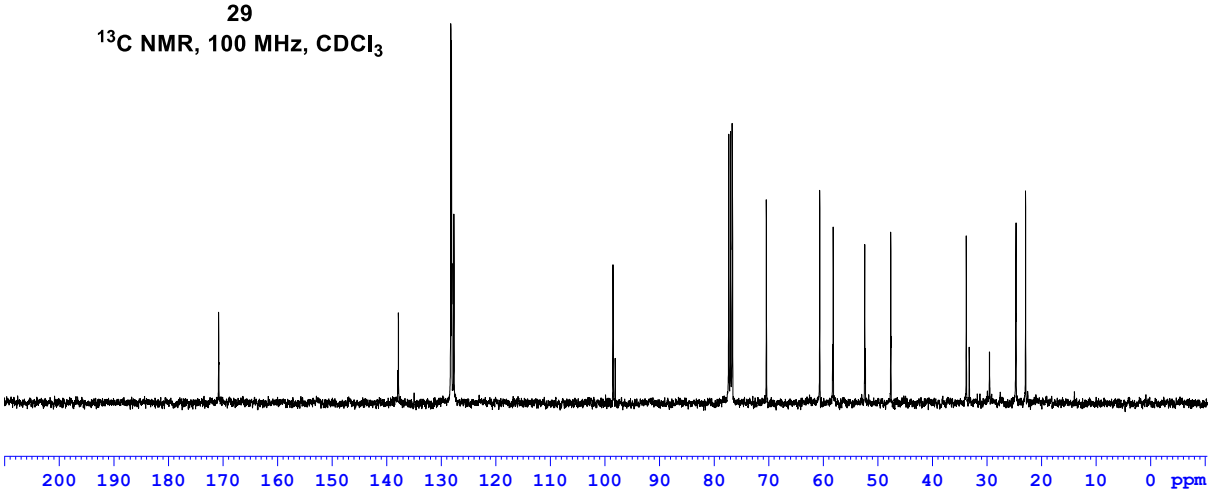
29

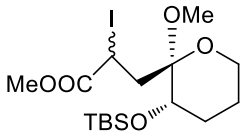
1H NMR, 400 MHz, $CDCl_3$



29

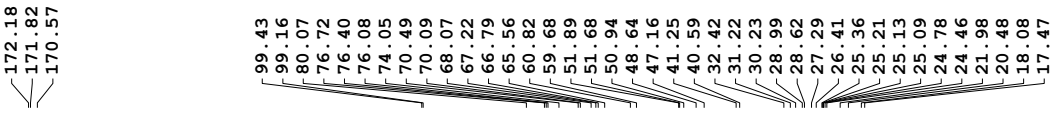
^{13}C NMR, 100 MHz, $CDCl_3$

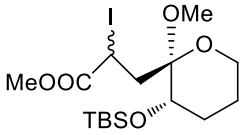




31

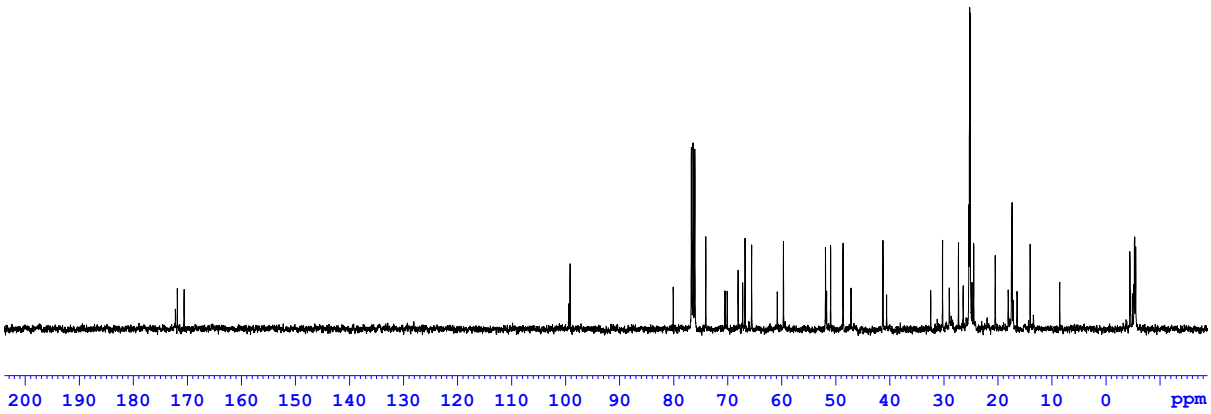
1H NMR, 400 MHz, $CDCl_3$

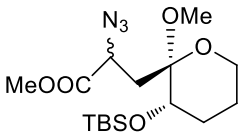




31

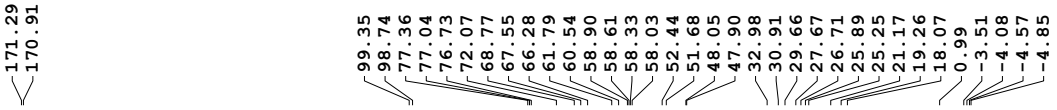
^{13}C NMR, 100 MHz, $CDCl_3$

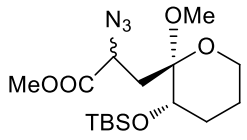




32

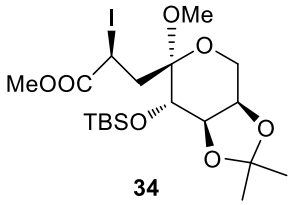
1H NMR, 400 MHz, $CDCl_3$





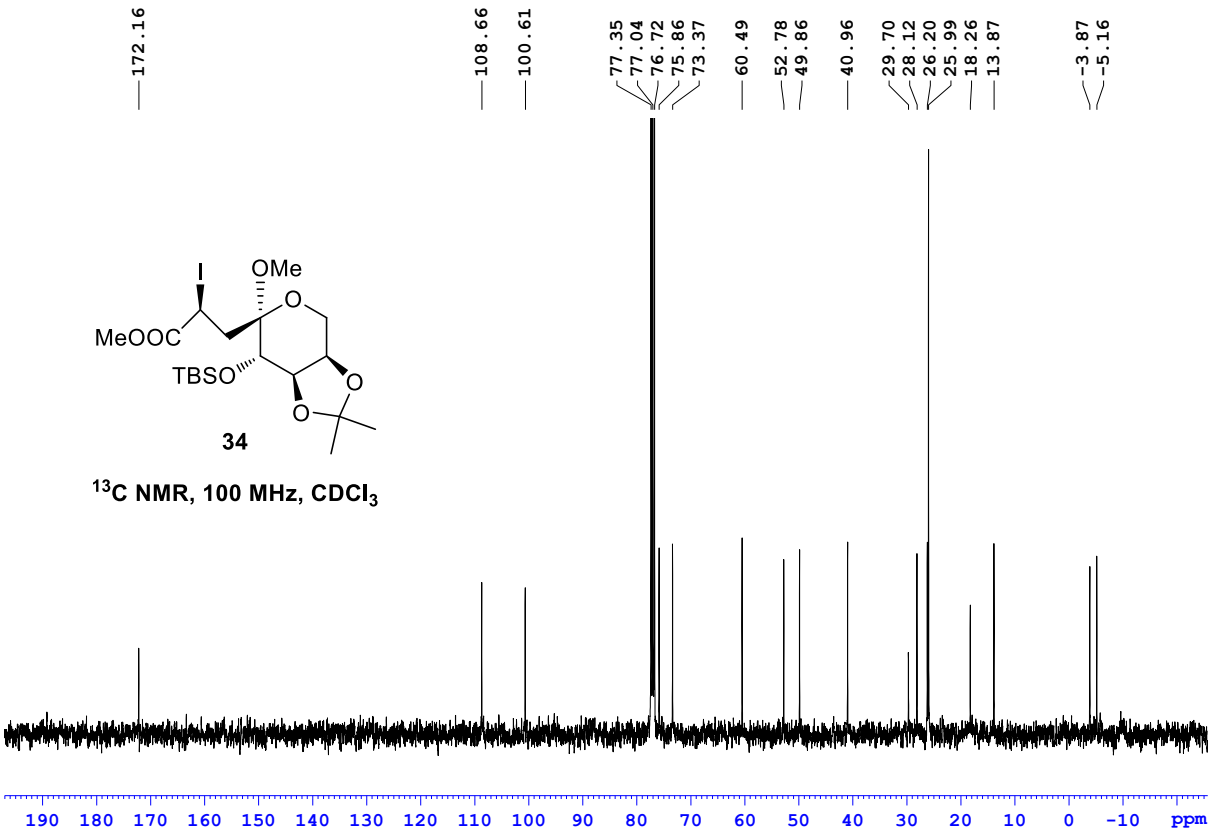
32

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



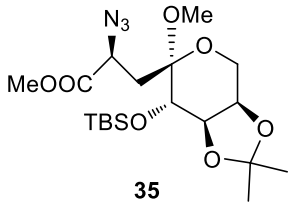
34

1H NMR, 400 MHz, $CDCl_3$



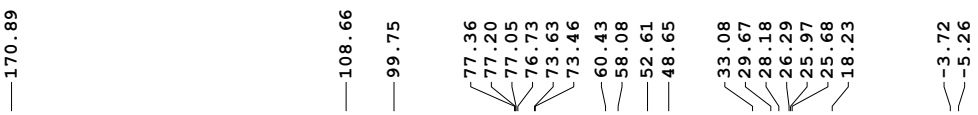
34

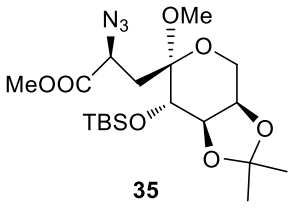
^{13}C NMR, 100 MHz, $CDCl_3$



35

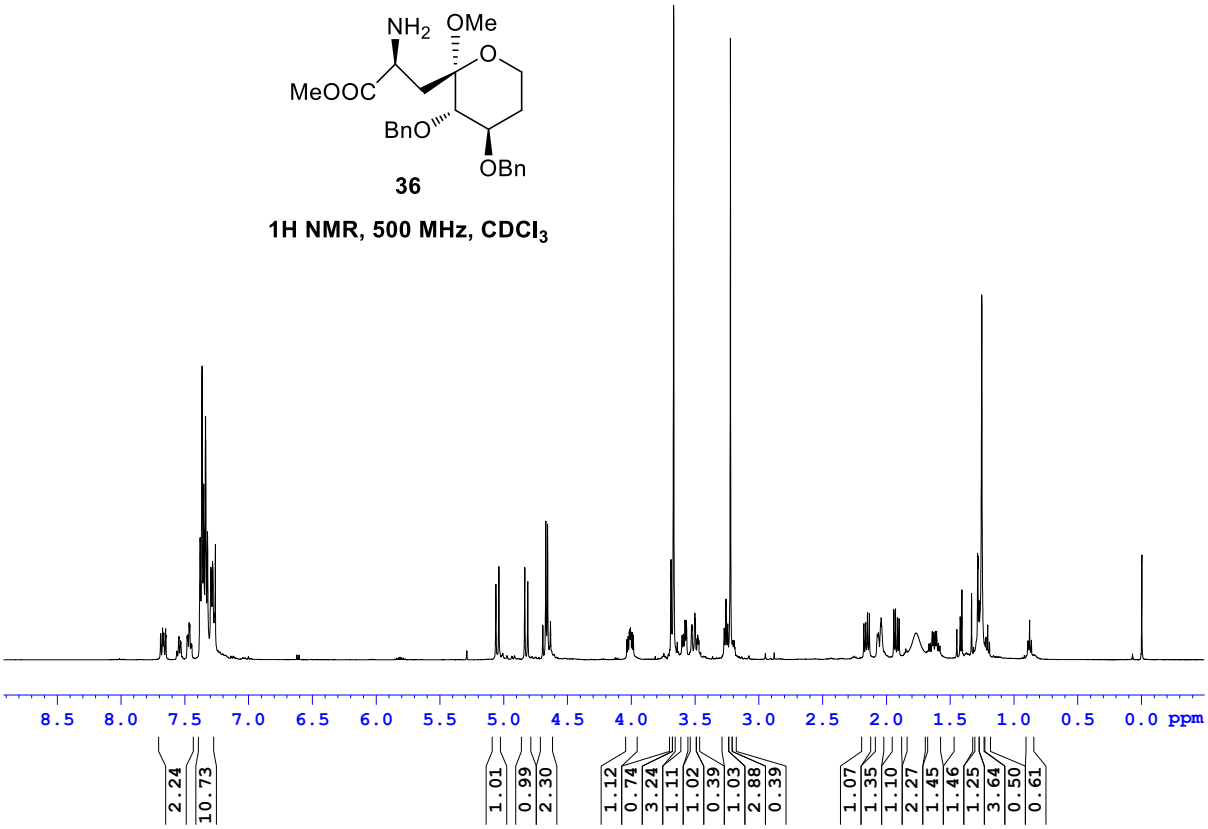
1H NMR, 400 MHz, $CDCl_3$

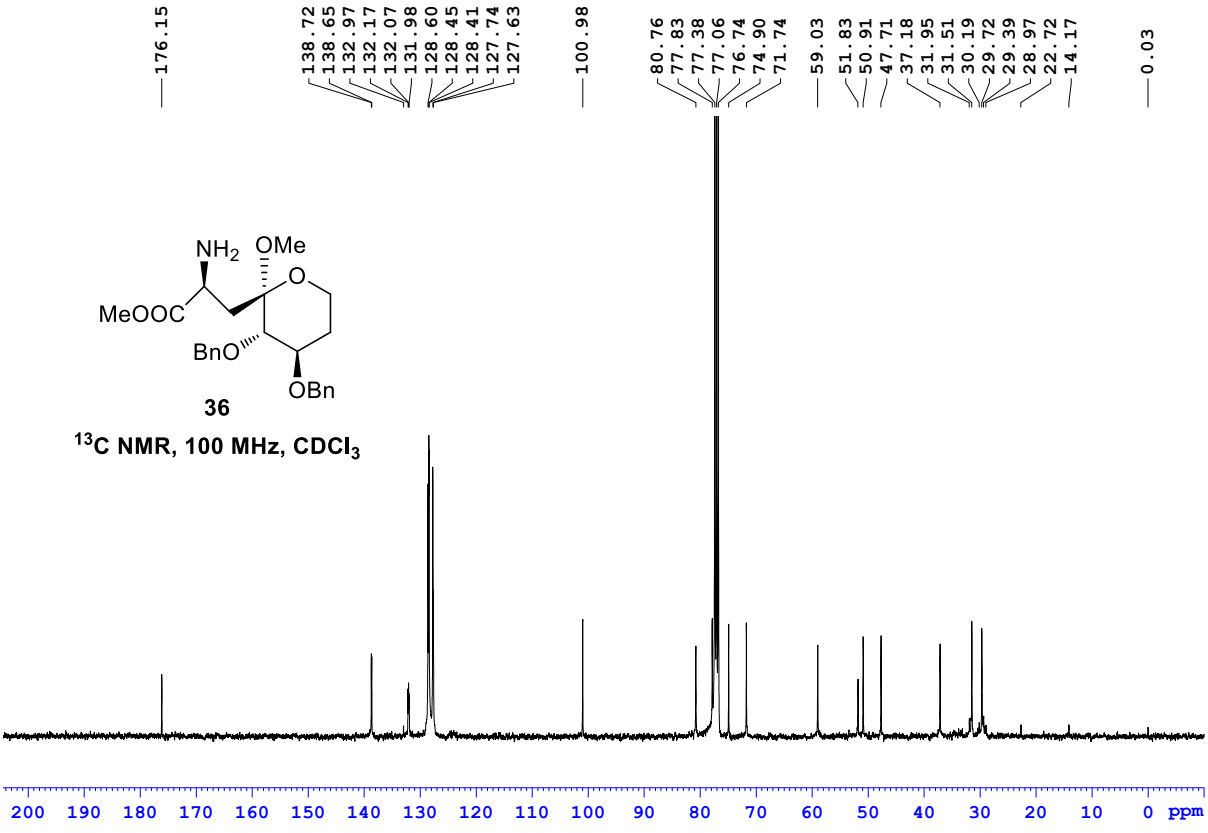


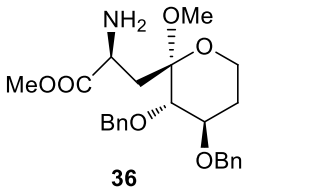


35

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

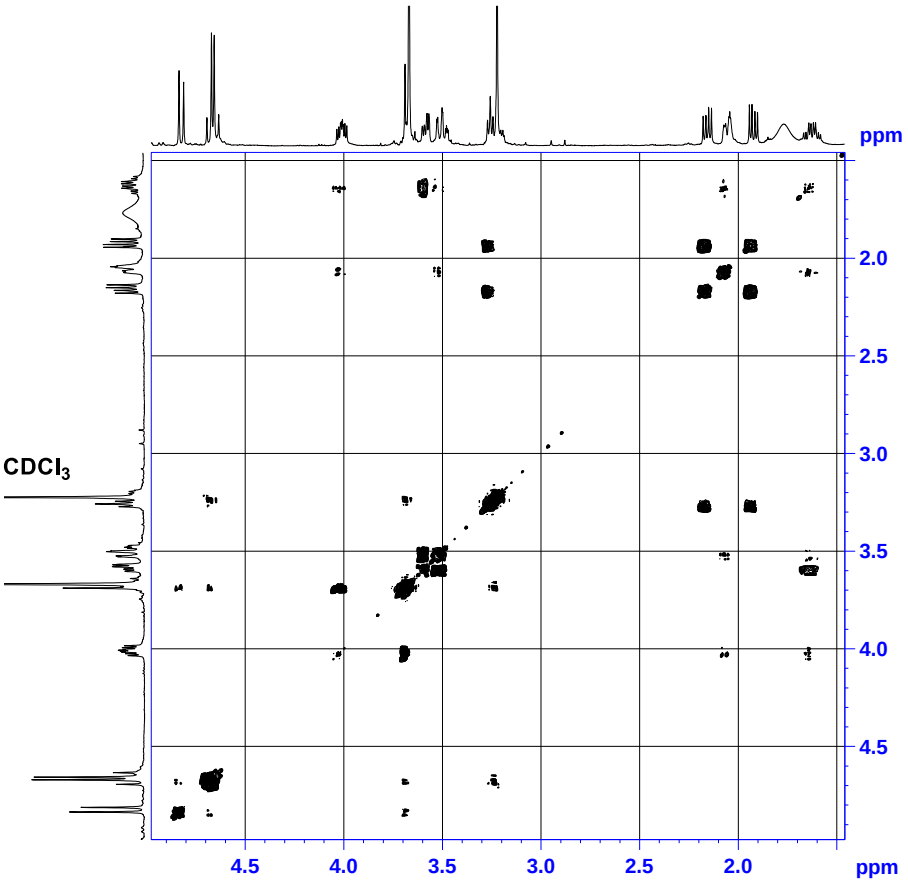

NH2
OMe
O
MeOOC
BnO
OBn
36
1H NMR, 500 MHz, CDCl3
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm
2.24 10.73 1.01 0.99 2.30 1.12 0.74 3.24 1.11 1.02 0.39 1.03 2.88 0.39 1.07 1.35 1.10 2.27 1.45 1.46 1.25 3.64 0.50 0.61

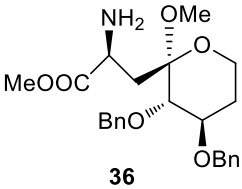

176.15
138.72 138.65 132.97 132.17 132.07 131.98 128.60 128.45 128.41 127.74 127.63
100.98
80.76 77.83 77.38 77.06 76.74 74.90 71.74
59.03
51.83 50.91 47.71 37.18 31.95 31.51 30.19 29.72 29.39 28.97 22.72 14.17
0.03
NH2
OMe
O
MeOOC
BnO
OBn
36
13C NMR, 100 MHz, CDCl3
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm



36

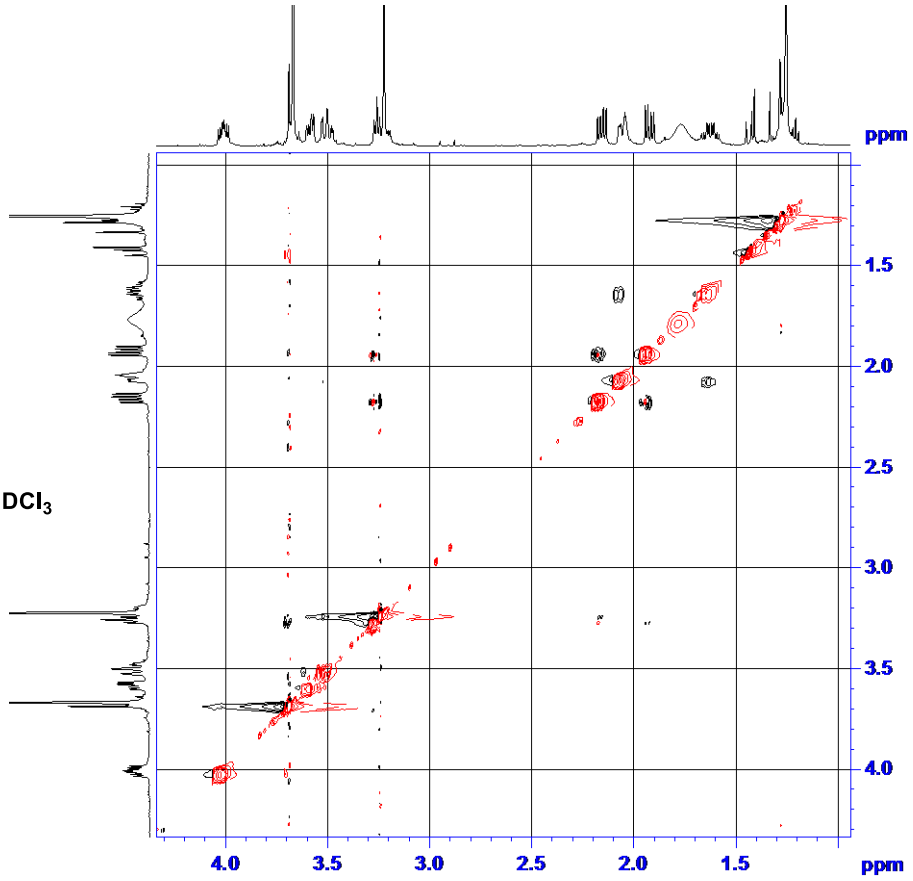
^{1}H-^{1}H COSY NMR, 500 MHz, $CDCl_3$

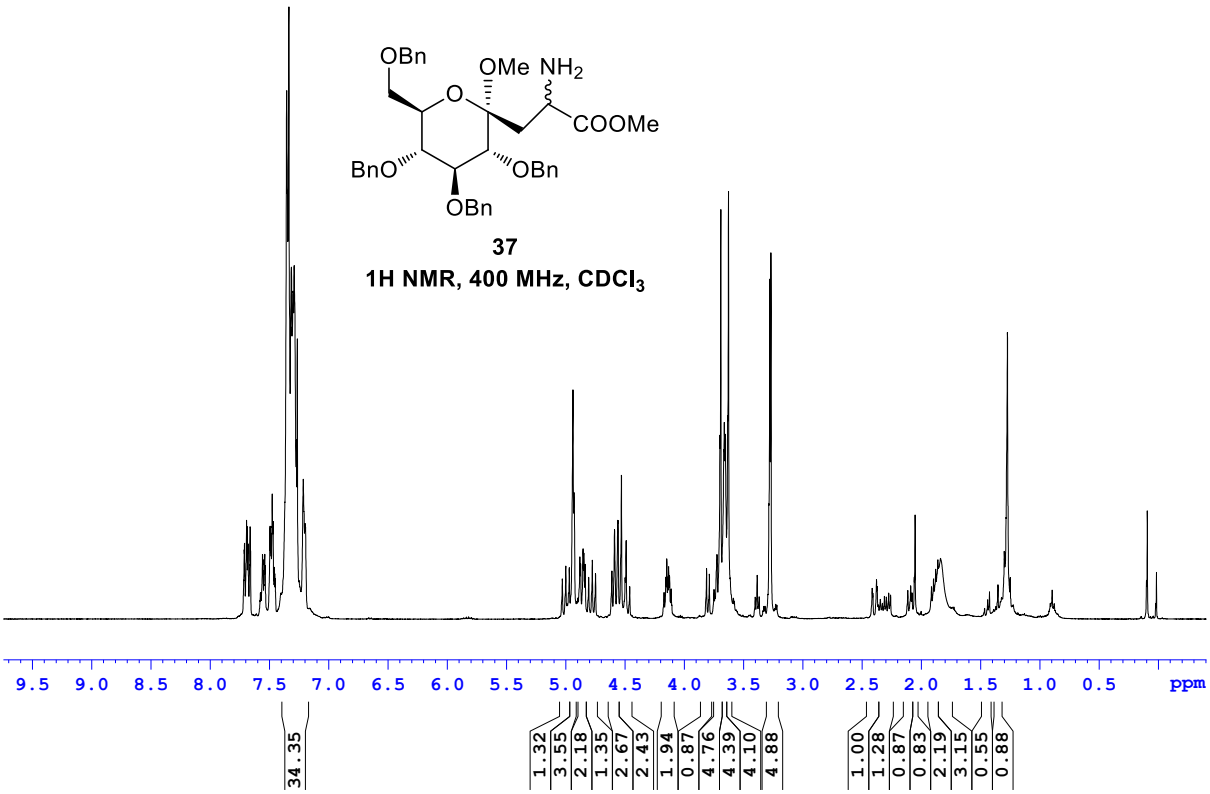




36

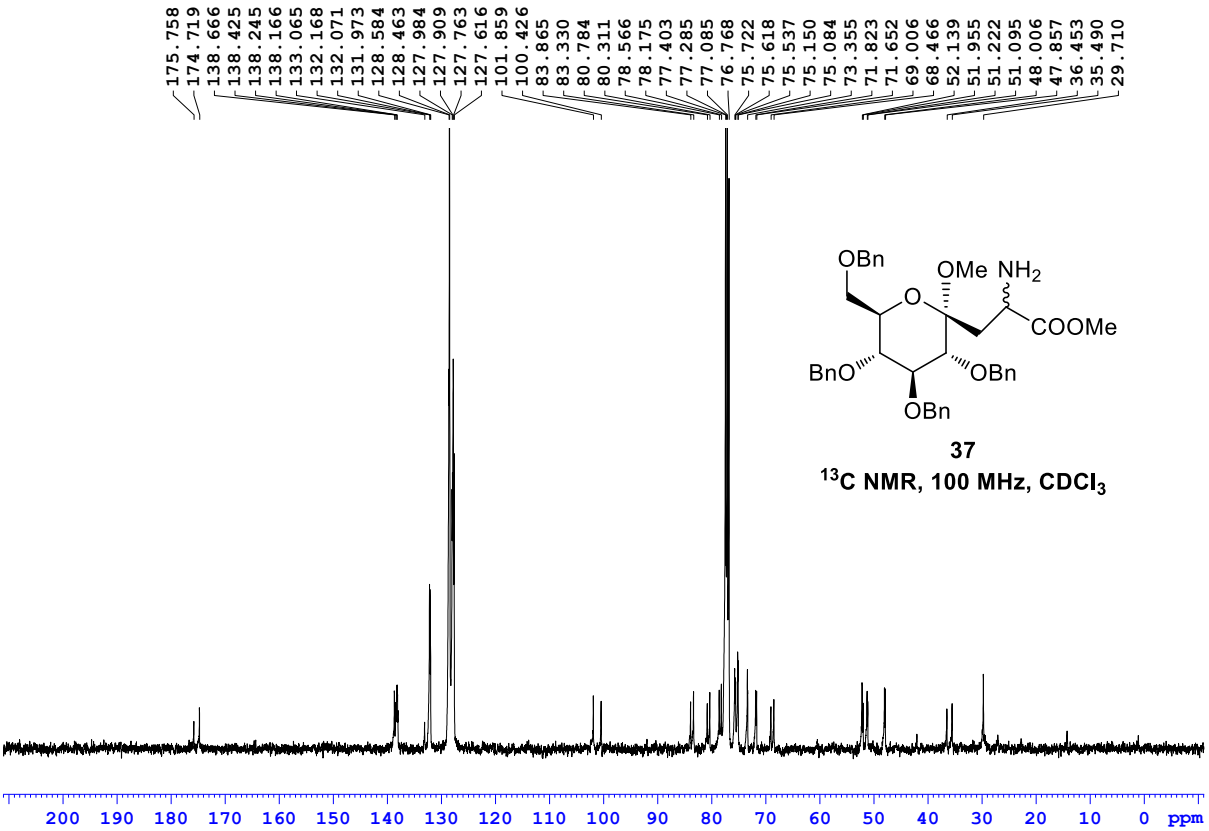
^{1}H-^{1}H NOESY NMR, 500 MHz, $CDCl_3$





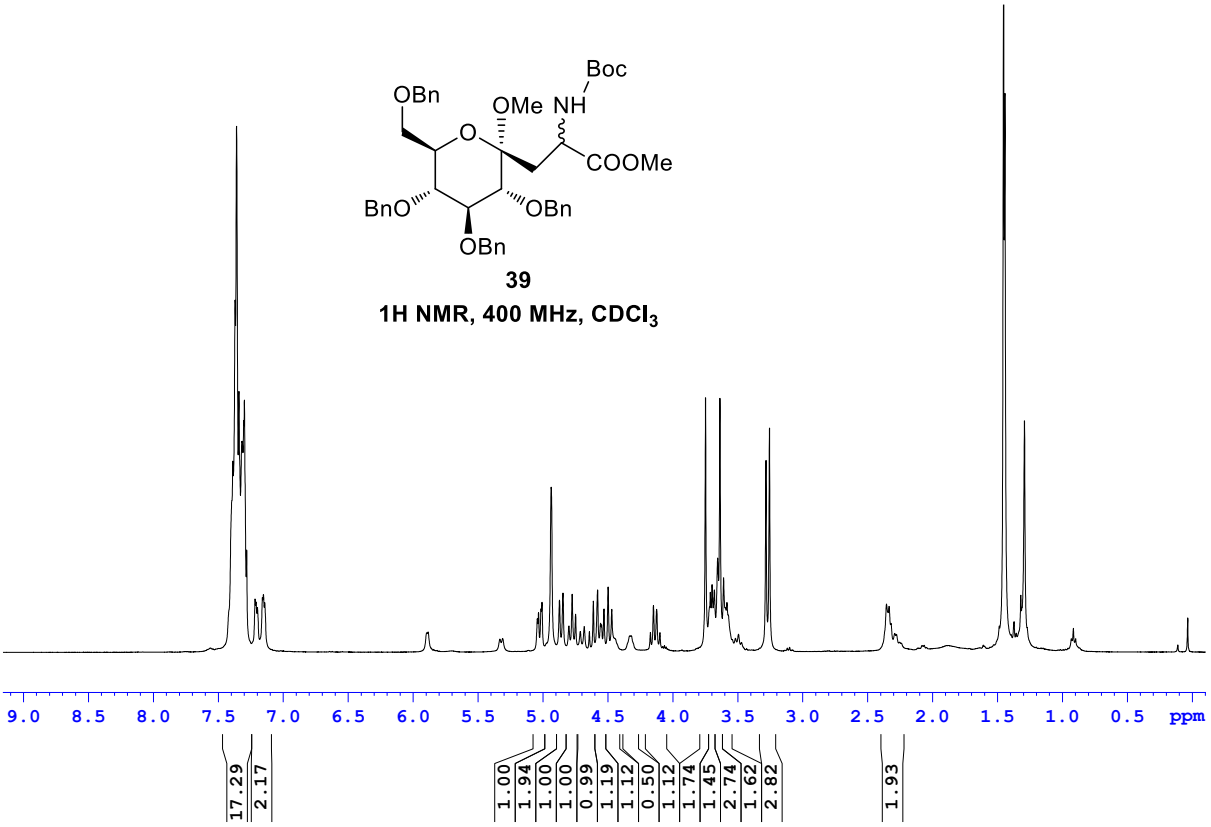
37

1H NMR, 400 MHz, $CDCl_3$



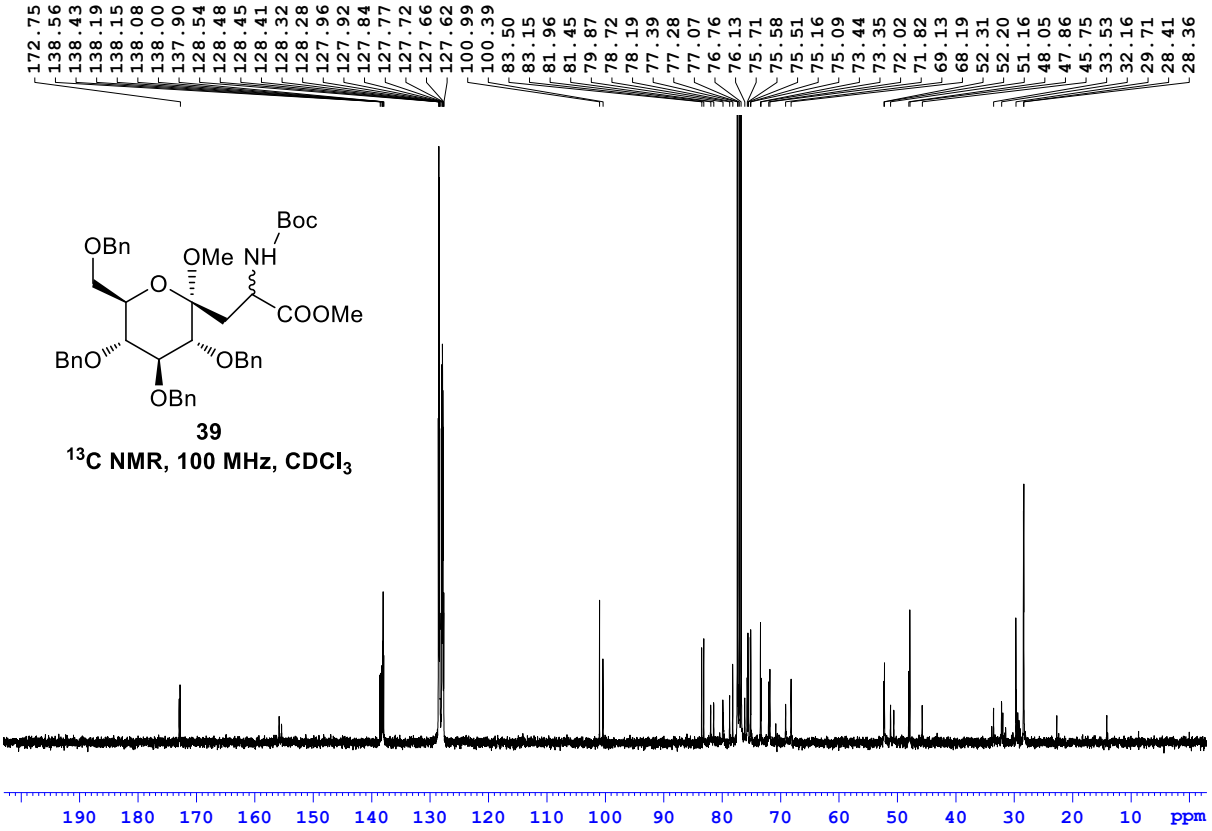
37

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



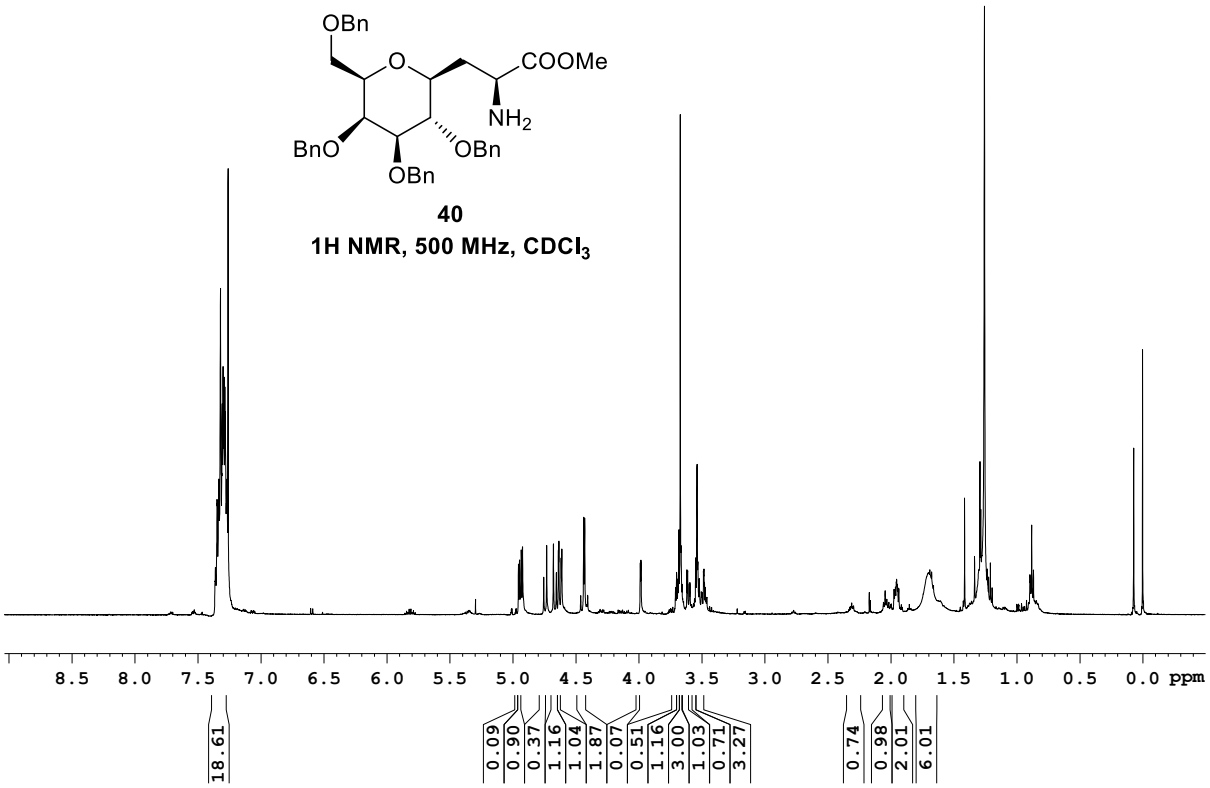
39

1H NMR, 400 MHz, $CDCl_3$



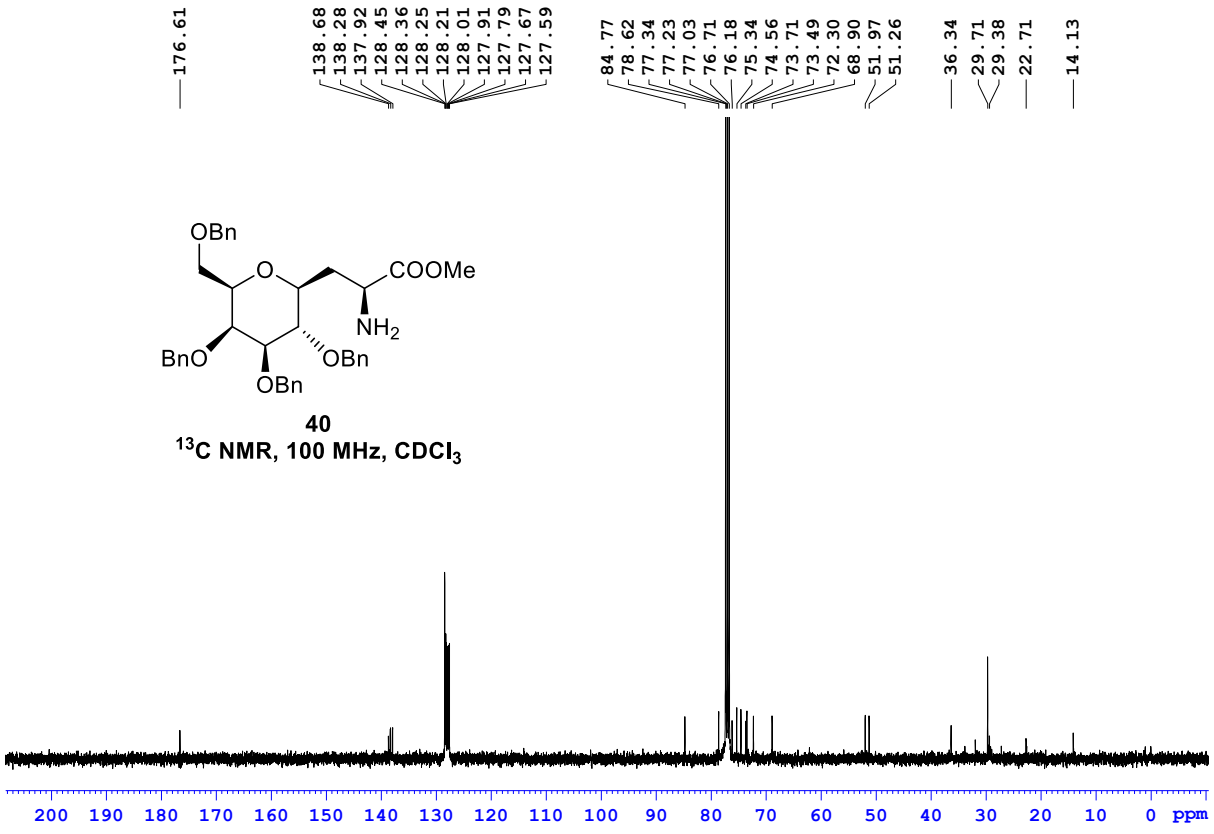
39

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



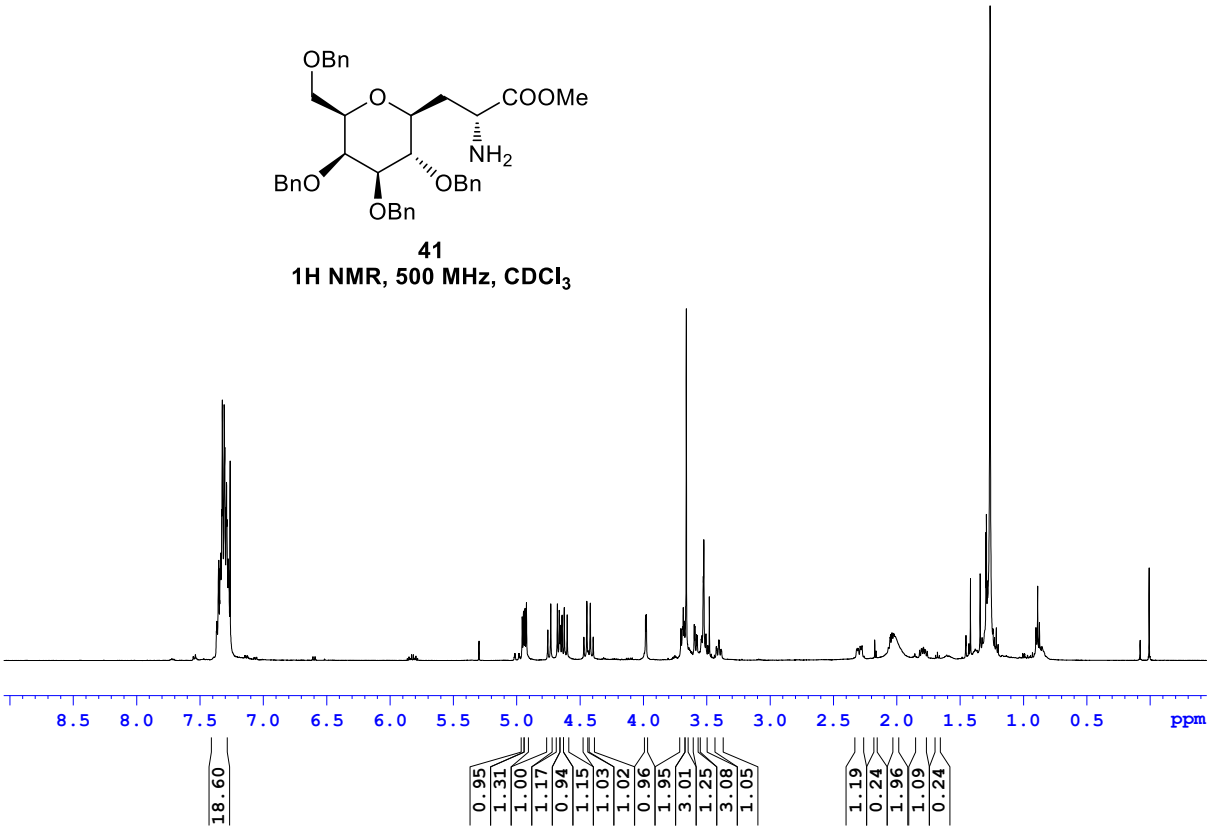
40

1H NMR, 500 MHz, $CDCl_3$

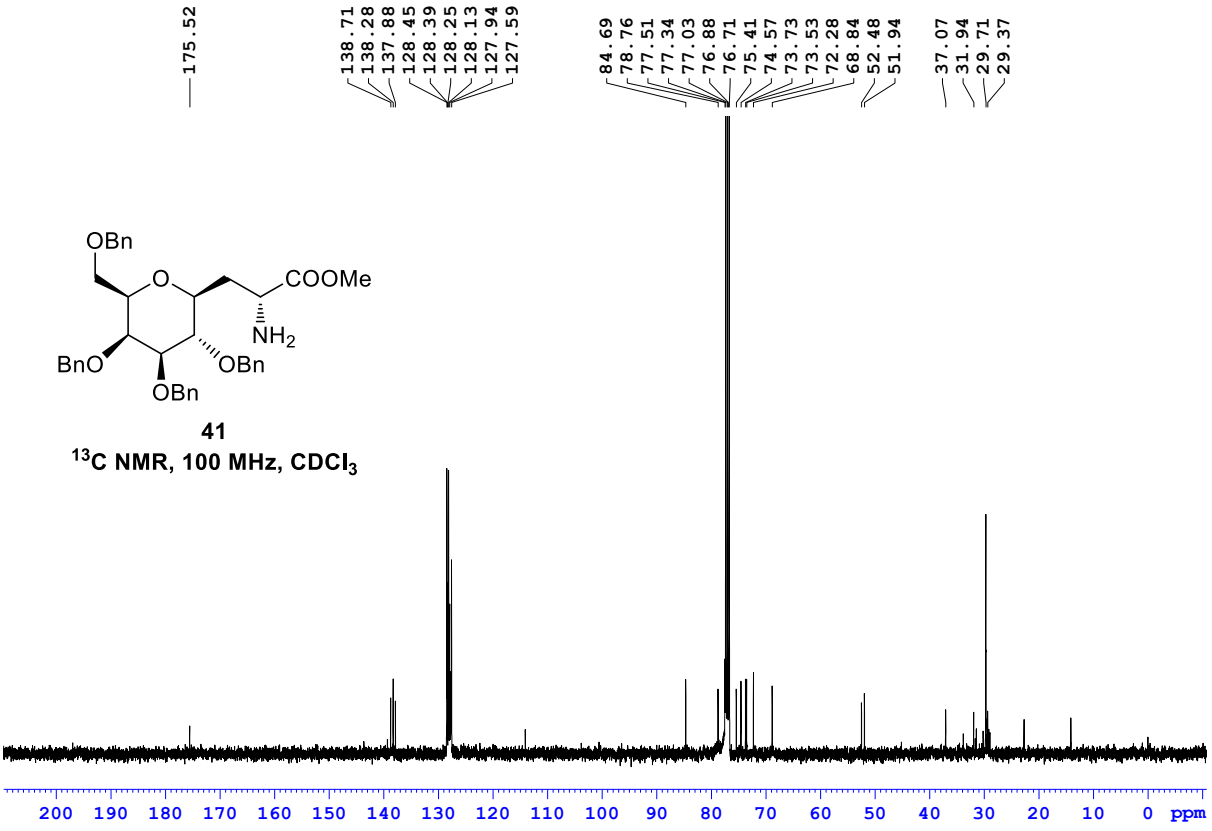


40

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



41
1H NMR, 500 MHz, $CDCl_3$



41
^{13}C NMR, 100 MHz, $CDCl_3$