“Stereoselective Synthesis of Nitrogen Based Chiral Polyheterocycles”

Dissertation submitted

To

Sikkim University

In partial fulfillment of the requirements for the award of

Degree of Master of Philosophy

By

Ankit Thakuri

Department of Chemistry

School of Physical Sciences

February 2019

Declaration

I hereby declare that the work embodied in this dissertation entitled **"Stereoselective Synthesis of Nitrogen Based Chiral Polyheterocycles"** submitted to Sikkim University in partial fulfillment of the requirements for the award of the degree of **Master of Philosophy** in Chemistry is my original work and the content of this dissertation is based on the experiments which I have performed myself. This dissertation has not been submitted to any other University or Institution for the award of any degree or diploma.

Place: Ankit Thakuri

Date: Roll No: 17MPCH01

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Assistant Professor
Chemistry Department
Sikkim University

Certificate

This is to certify that the work presented in this dissertation, entitled **"Stereoselective Synthesis of Nitrogen Based Chiral Polyheterocycles"** submitted to Sikkim University in partial fulfilment of the award of the Degree of Master of Philosophy in Chemistry embodies the result of bona fide research work carried out by **Ankit Thakuri** under my supervision. No part of the dissertation has been submitted for any other degree, diploma, associate-ship or fellowship.

All the assistance and help received during the course of investigation have been duly acknowledged by him.

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Place:

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“Stereoselective Synthesis of Nitrogen Based Chiral Polyheterocycles”

Submitted by

Ankit Thakuri

Under the supervision

of

Dr. Biswajit Gopal Roy

Department of Chemistry

School of Physical Science

Signature of the Student

Countersigned by Head of Department

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Date:

Place: Ankit Thakuri

Abbreviations and Acronyms

Ac	Acetyl
AcOH	Acetic Acid
aq	Aqueous
Ar	Aromatic
Bu	Butyl group
Bn	Benzyl group
Boc	tert-butylcarboxy group
$CDCl_3$	Deuterated chloroform
COSY	Homonuclear correlation spectroscopy
DCM	Dichloromethane
dd	Doublet of doublet
DDQ	2,-3-Dichloro5,6-dicyano-p-benzoquinone
DMAP	N,N-dimethylaminopyridine
DMF	Dimethylformamide
DMSO	Dimethyl sulfoxide
DNA	Deoxyribonucleic Acid
Et	Ethyl group
FTIR	Fourier Transform Infra-red Spectroscopy
HMQC	Heteronuclear Multiple Quantum Correlation
INC	Intramolecular Nitrone Cycloaddition
IR	Infra-red
m	Multiplet
MeCN	Acetonitrile
MsCl	Methanesulfonyl chloride

NMR	Nuclear Magnetic Resonence
NOESY	Nuclear Overhauser effect spectroscopy
PCC	Pyridinium Chlorochromate
Ph	Phenyl group
PTC	Phase Transfer Catalyst
s	Singlet
TBAB	Tetrabutylammonium bromide
TBS	Tributylsilyl group
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMS	Trimethylsilyl group
TsCl	Tosyl chloride
Ts	p-Toulenesuphonyl group

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1.1 Introduction

Nitrogen containing chiral polyheterocycles are one of the most frequently encountered chemical entities in natural products and in contemporary drug molecules [1]. Many of natural products and compounds derived from natural products with anti-cancer [2], antimalarial [3] and cytotoxic [4] properties have been found to contain several polyheterocyclic structures with multiple heteroatoms [5] (Fig. 1). In 2017 the Center for Drug Evaluation and Research (CDER) [5] approved 46 drugs, of which 19 (41%) contained a heterocyclic ring as an active ingredient.

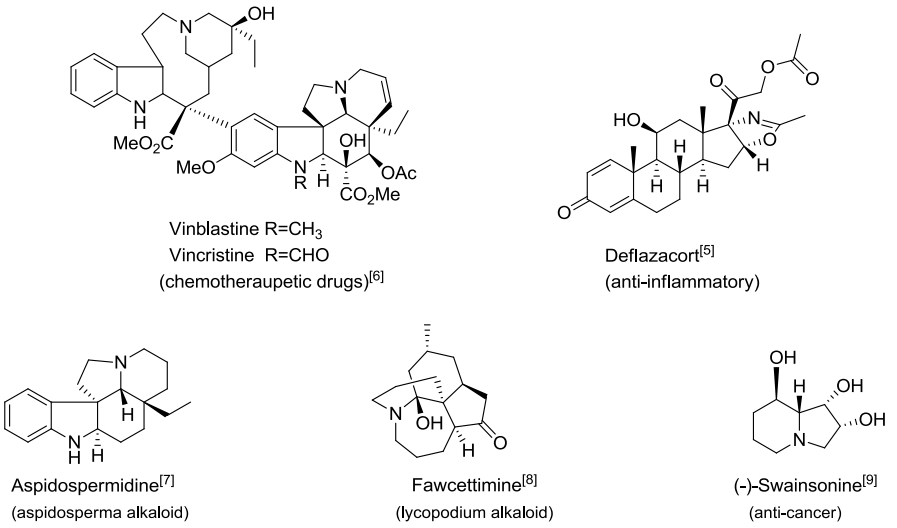


Fig. 1: Examples of some of the current drugs with nitrogen containing chiral polyheterocycles.

Chiral polyheterocycles with more rigidity have inflexible three-dimensional orientations of functional groups that can perturb biomolecules such as proteins and DNA to modulate and alter their function. As a result of their inflexibility and rigid structure, chiral polyheterocycles can bind more effectively and selectively than planar molecules. Synthesis of chiral polyheterocycles from carbohydrates as starting materials can generate highly rigid and inflexible moieties that can be used for gene modulation. Chirality in multiple sites of a molecule provide a selective binding advantage in three dimensional biological systems and bring huge diversity in their bioactivity.

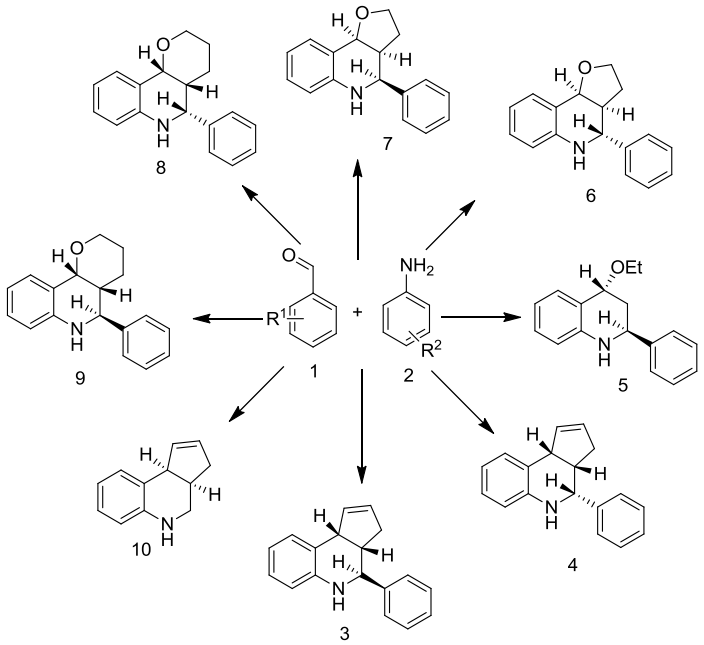
Synthesis of such complex polyheterocyclic structures while maintaining the chirality is a difficult task to achieve. The isolation and purification of chiral polyheterocycles from natural products is a tedious and time-consuming process as they are present in

very low concentration and the separation techniques to be used as equally difficult and challenging. Often the methods employed for stereoselective synthesis require expensive chiral reagents, chiral catalysts or chiral auxiliaries, and hence increase the number of steps and the time required for purification of stereoisomers. Therefore, stereoselective synthesis using inexpensive and easily available chiral pool could be an effective way for synthesis of such chiral polyheterocycles. Being one of the cheapest available chiral pool, D-glucose [10], with its four easily functionalizable stereocentres and a prochiral centre is one of the most preferred starting materials. This dissertation deals with synthesis of several highly complex *N*-containing chiral polyheterocycles using the inexpensive chiral pool of D-glucose.

2.1 Literature Review

Chiral polyheterocycles containing nitrogen as one of the heteroatoms have attracted the attention of various synthetic and medicinal chemists owing to their huge importance in the pharmaceutical industry. Some of the relevant recent synthesis of such compounds have been summarized below.

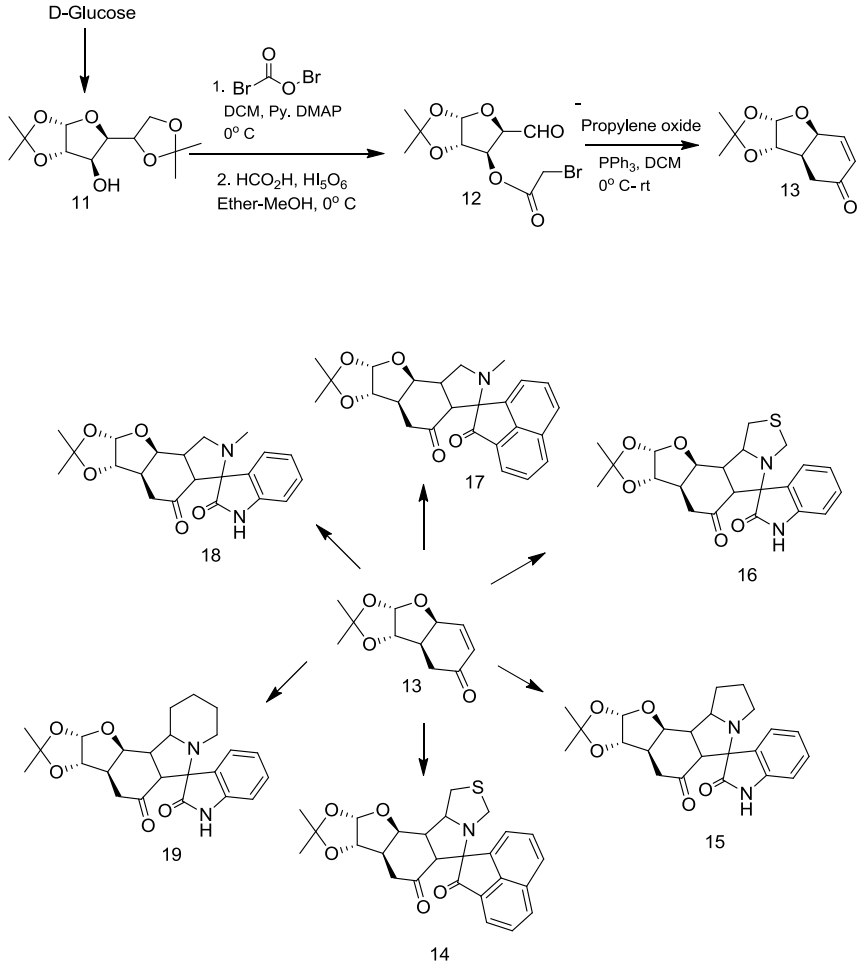
Kumar *et.al*[11] reported the synthesis of tetrahydroquinoline analogues through diversity-oriented synthesis using the natural carbohydrate derived solid acid catalyst via multicomponent aza-Diels Alder reaction. The Diels Alder reaction was carried out between an imine (generated in situ from the aromatic amine and the aldehyde) with a dienophile in acetonitrile in a diastereoselective manner. The use of water in place of acetonitrile as a solvent reversed the diastereoselectivity of the Diels Alder reaction.



Scheme 1: Quinoline analogues prepare by using cellulose sulfuric acid as a catalyst.

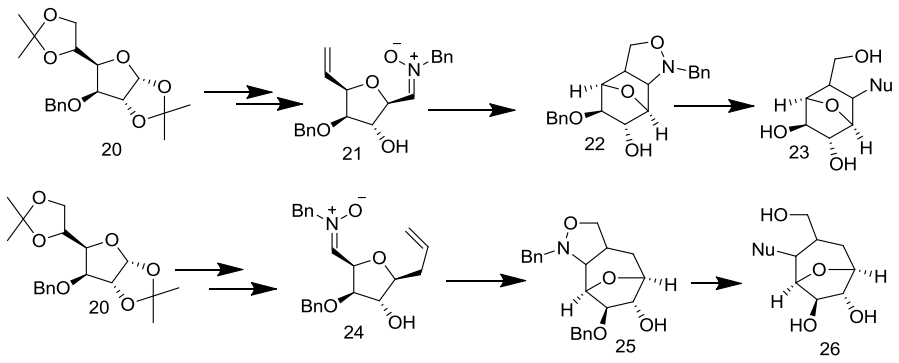
The synthesis of glucosylspiro-oxindole derivatives via cycloaddition of azomethine ylides was reported by Prasanna *et.al*[12]. They used chiral D-Glucose as a precursor to generate the substrate required for cycloaddition. The reaction proceeds via 1-3 dipolar cycloaddition between the azomethine ylide and the synthesized precursor. The azomethine ylide was generated from isatin and acenaphthoquinone using sarcosine.

The ylides were trapped by the sugar derivative to give glucosylspiro-oxindole derivatives.



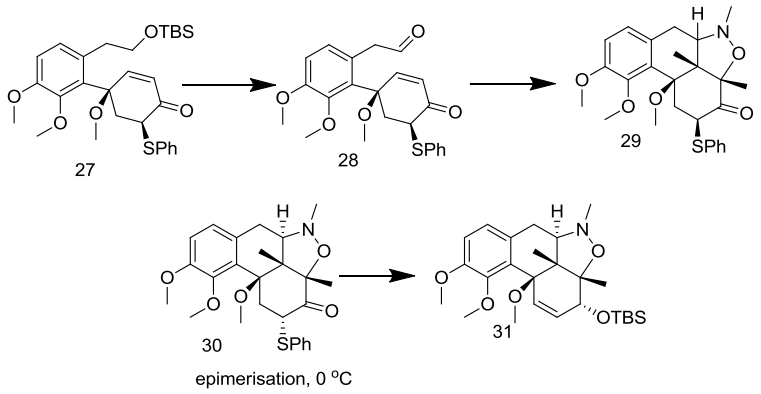
Scheme 2: Synthesis of glucosylspiro-oxindole derivatives

Ghosh *et.al.*[13] strategized and performed the synthesis of locked nucleosides from 1,2:5,6-di-*O*-isopropylidene-*α*-D-glucofuranose. Intramolecular nitrone condensation was performed on glucose derived substrates carrying an allyl group at C-1 and an enose nitrone at C-5 or an aldehyde nitrone at C-1 and a vinyl group at C-4 to obtain tricyclic compounds. These tricyclic systems were then converted to bicyclic nucleosides.



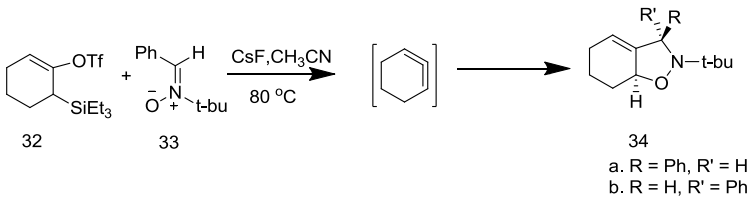
Scheme 3: Synthesis of locked nucleosides.

Raustchek *et.al.*[14] utilized the intramolecular nitrone cycloaddition for the formation of the phenanthrene ring which followed by sulphoxide elimination led to a key intermediate for the synthesis codeine from isovanillin. They used intramolecular nitrone addition as a tool for the formation of a polyheterocyclic ring.



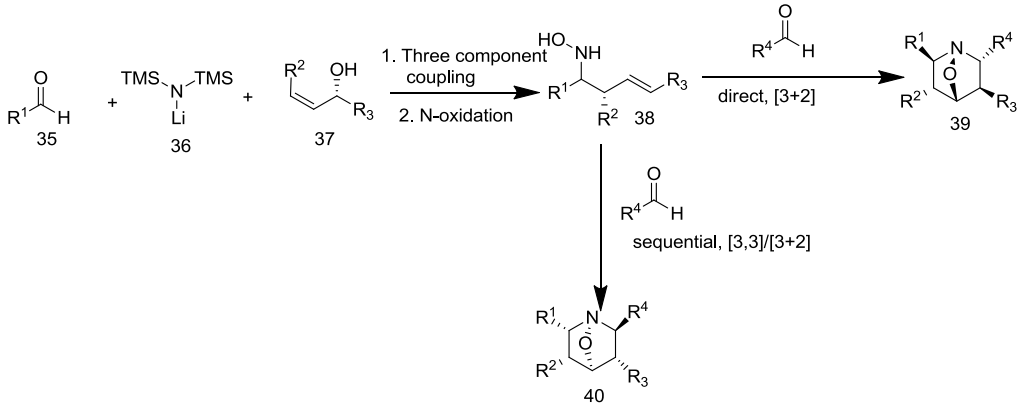
Scheme 4: Synthesis codeine via intramolecular nitrone cycloaddition.

Barber *et.al.*[15] reported the 1,3 dipolar cycloaddition of 1,2-cyclohexadiene. 1,2-cyclohexadiene as generated in situ under mild conditions and trapped with nitrones to give isoxazolidine product. The reactions occurred regioselectively and exhibited a notable endo preference resulting in the formation of two new bonds and two stereogenic centres.



Scheme 5: Synthesis of polyheterocycle from 1,2-cyclohexadiene

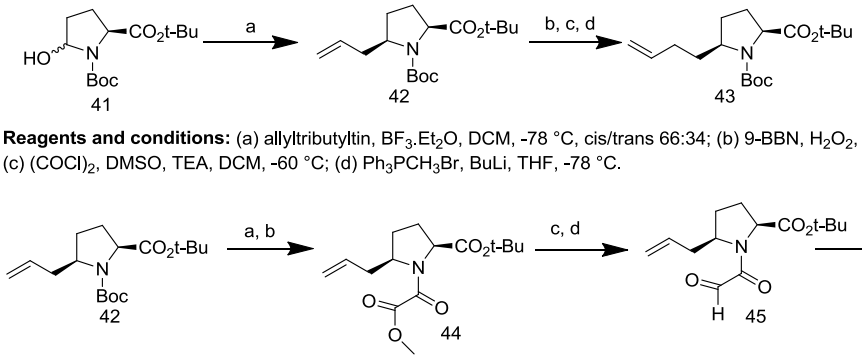
A convergent and stereodivergent pathway to highly substituted 1-aza-7-oxabicyclo[2.2.1]heptanes was performed and reported by Yang *et.al.*[16]. The synthesis was carried out by three component coupling involving allylic alcohol, aldehydes and LiHMDS to produce stereodefined primary allylic amines. N-oxidation followed by condensation with formaldehyde generated densely functionalized nitrones whose intramolecular cyclisation can be controlled to deliver one of two distinct skeletons. Stereochemistry was controlled from the control of the nitrone geometry and selective portioning of the reaction between [3+2] cycloaddition and tandem [3,3] rearrangement followed by [3+2] cycloaddition.



Scheme 6: Convergent route to 1-aza-7-oxabicyclo[2.2.1]heptanes.

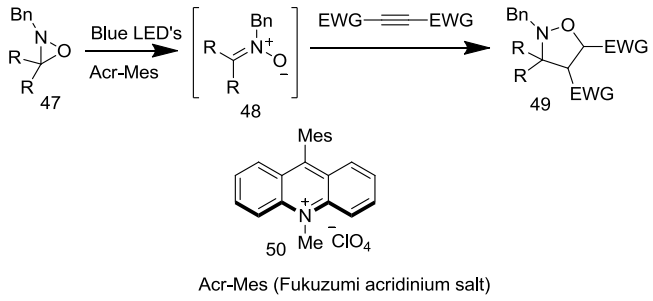
An efficient synthesis of functionalized azabicycloalkane amino acids from substituted prolines was accounted by Manzoni *et.al.*[17]. They proceeded by preparation of cis- and trans-5-substituted prolines. The formed substrates were subjected to selective removal of the tert-butoxcarbonyl group followed by treatment with methyl chloroxaacetate to yield an ester. The ester was converted to an aldehyde by subsequent reduction and Swern oxidation. On treatment with benzylhydroxylamine hydrochloride in presence

of sodium bicarbonate, the aldehyde yielded nitrones which underwent highly regio and stereoselective cycloaddition to form azabicycloalkane amino acids.



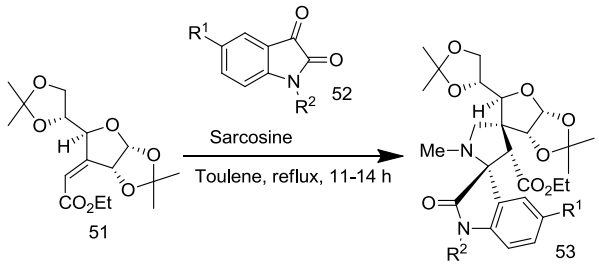
Scheme 7: Synthesis of functionalized azabicycloalkane amino acids.

Jang *et.al.*[18] envisioned and performed the synthesis of 4-isoxazolines via visible light photoredox catalysis. The oxarizidine moiety on irradiation with blue LEDs in presence of Fukuzumi acridinium salt generated nitrones followed by cyclization with electron deficient alkynes to give 4-isoxazolines. They performed controlled experiments to reveal that both light and acridinium salt were necessary for the cycloaddition to occur. Optimizing the reaction conditions they reported the 34 examples with up to 90 % yield.



Scheme 8: Visible-light photoredox catalyzed [3+2] cycloaddition.

Barman *et.al.*[19] reported the formation of bi-spiroheterocycles from carbohydrate-derived precursors. The synthesis was achieved by cycloaddition between a sugar-derived exocyclic olefin with a non-stabilised azomethine ylide generated in situ by condensation of a 1,2-diketone with an *N*-substituted amino acid such as sarcosine or proline.



Scheme 9: Synthesis of bi-spiroheterocycles**.**

2.2 Aims and Objectives

Due to the huge importance of *N*-containing chiral polyheterocycles inexpensive synthesis of more number of such molecules with structural diversity is highly desirable. Towards that we have started with the following objectives.

i. Stereoselective synthesis of nitrogen-based chiral polyheterocycles using D-glucose.
ii. To use intramolecular nitrone condensation (INC) as a synthetic tool for achieving structural diversity through cyclisation and incorporation of nitrogen atom in the chiral polyheterocycles.
iii. Structure elucidation of synthesized polyheterocycles and stereochemistries of the newly generated chiral centers using various spectroscopic techniques like NMR spectroscopy, Mass spectrometry, FTIR spectroscopy etc.
iv. Confirmation of stereochemical orientation of the generated polyheterocycles through X-ray crystallography wherever possible.

3.1 Synthetic strategy

D-Glucose was converted into a room temperature stable solid derivative, 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose, which was utilized as a starting material for the synthesis of *N*-containing chiral polyheterocycles. The strategy involved

(i) the incorporation of an *O*-isoprenyl group at C-3 by treating the glucose derivative with 3,3-dimethylallylbromide in a mixture of dichloromethane and aqueous sodium hydroxide in presence of a phase transfer catalyst. Conversion of the 1,2-isopropylidene protection to an aldehyde and its subsequent treatment with benzylhydroxylamine should lead to generation of a nitrone. The formed compound with an olefinic bond and nitrone could be easily by applying heat forming an *N*-containing polyheterocycle.

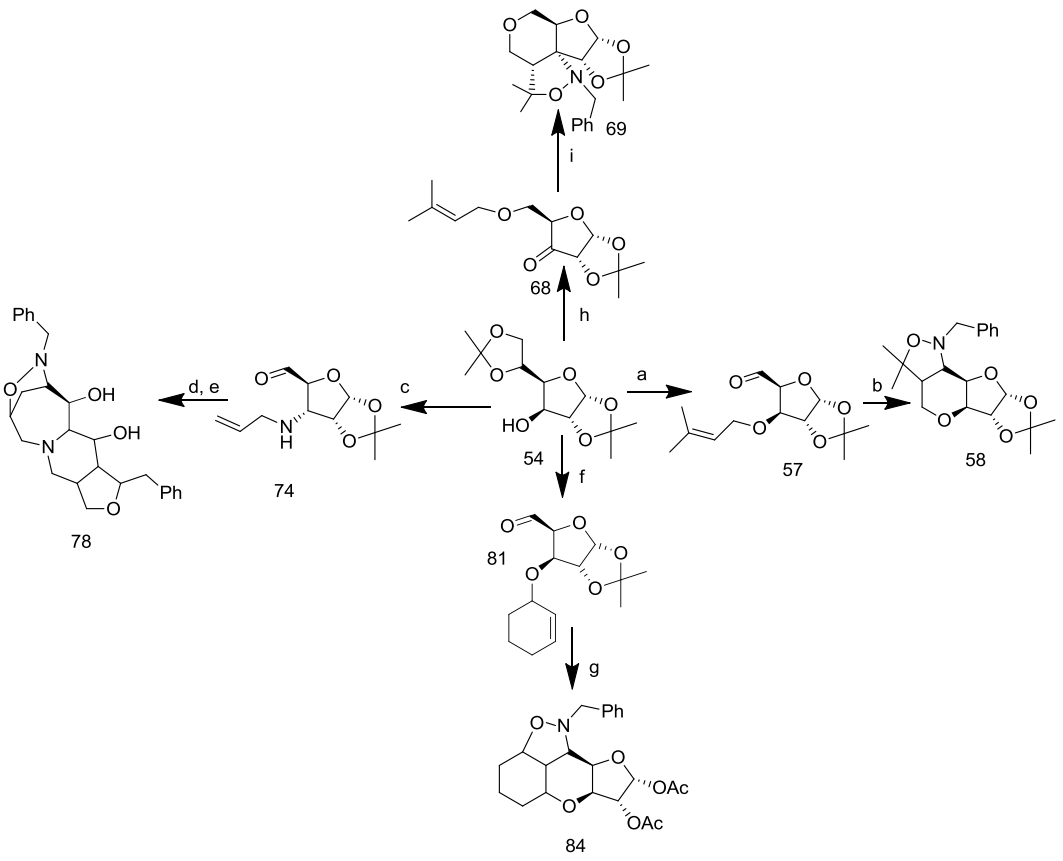
(ii) The protection of the hydroxyl group at C-3 of by 4-methoxybenzylchloride could enable us to incorporate the *O*-isoprenyl group at C-5 position of **54**. Subsequent deprotection of the 4-methoxybenzylgroup and oxidation of the hydroxyl group should form of **68**. Refluxing **68** with benzylhydroxylamine should lead to the formation of a complex chiral polyheterocycle.

(iii) Compound **54** can easily be converted to **74** in four simple steps. The cyclisation of **74** can be conveniently brought about by refluxing it with benzylhydroxylamine to yield **75**. *N*-allylation of the polycycle **75** and the removal of 1,2-isopropylidene protection will generate a polyheterocycle with an olefinic bond and an aldehyde. Cyclisation of this masked aldehyde in hemiacetal on INC reaction with benzylhydroxylamine should form a highly rigid polyheterocycle containing three nitrogen atoms.

(iv) Using 3-bromocyclohexene an *O*-cyclohexenyl group can be incorporated at C-3 of **54**. Generation of nitrone at C-5 aldehyde should spontaneously cyclize to form fused *N*-containing chiral polyheterocycle.

3.1.1 Synthetic route

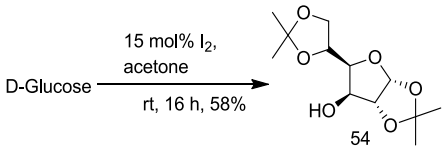
The following synthetic route was devised for synthesis of polyheterocycles **58**, **69**, **78** and **84**



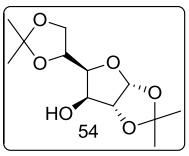
Reagents and conditions: (a) 50% NaOH, TBAB, 3,3-dimethylallylbromide,dicholoromethane, rt, 24 h; 75% AcOH, rt, 24 h; $NaIO_4$, methanol, 0 ^oC, 30 min; (b) Benzylhydroxylamine, ethanol, reflux, 8 h; (c) Pyridinium chlorochromate,dry dicholoromethane, Molecular sieves 3 ^oA, 24 h; allylamine,dry dichloromethane, rt, 24 h; $NaBH_4$, methanol, 0 ^oC-rt, 18 h; $NaIO_4$, methanol, 0 ^oC, 30 min; (d) Benzylhydroxylamine, ethanol, reflux, 8 h; (e) NaH, allylbromide, dry THF, rt; 8% H_2SO_4, acetonitrile/water; benzylhydroxylamine, ethanol, reflux, 8 h; (f) 50% NaOH, TBAB, 3-bromocyclohexene,dicholoromethane, rt, 24 h; 75 % AcOH, rt, 24 h; $NaIO_4$, methanol, 0 ^oC, 30 min; (g) Benzylhydroxylamine, ethanol, reflux, 8 h; 4 % H_2SO_4, acetonitrile/water; acetic anhydride, DMAP, pyridine, 8 h; (h) 50% NaOH, TBAB, 4-methoxybenzylchloride, dicholoromethane, rt, 24 h; 75 % AcOH, rt, 24 h; $NaIO_4$, methanol, 0 ^oC, 30 min; $NaBH_4$, methanol, 0 ^oC-rt, 4 h; 50% NaOH, TBAB, 3,3-dimethyl allylbromide,dicholoromethane, rt, 24 h; DDQ, 20:1 DCM/H_2O, rt, 3 h; Pyridinium chlorochromate,dry dicholoromethane, Molecular sieves 3 ^oA, 12 h; (i) Benzylhydroxylamine, ethanol, reflux, 8 h

Scheme 10: Synthetic route for synthesis of various *N*-containing chiral polyheterocycles.

3.2 Synthesis of 1,2:5,6-di-*O*-isopropylidene-*α*-D-glucofuranose[20]



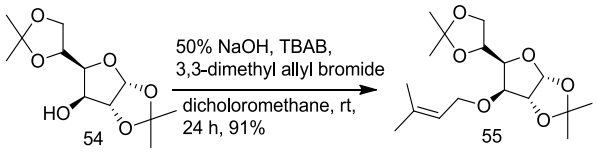
D-Glucose (10.00 g, 55.50 mmol) was stirred in acetone (600 ml) and 15 mol% iodines (2.10 g) was added to the solution. The mixture was then stirred at room temperature for 16 h. Saturated aqueous sodium thiosulphate was added until purple color disappeared and the solution was immediately concentrated and extracted with dichloromethane. The combined organic extracts were washed with water and brine, passed over anhydrous sodium sulphate and concentrated under reduced pressure to obtain 1,2:5,6-di-*O*-isopropylidene-*α*-D-glucofuranose as a white solid (8.50 g, 58%).



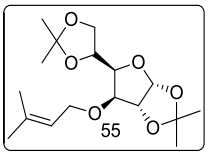
^{1}H NMR ($CDCl_3$, 400MHz): δ ppm 5.93 (d, 1H, *J* = 3.6 Hz), 4.52 (d, 1H, *J* = 3.6 Hz), 4.32 (m, 2H), 4.15 (dd, 1H, *J* = 6.4, 8.4 Hz), 4.05 (dd, 1H, *J* =2.4, 7.6), 3.98 (dd, 1H, *J* = 5.2, 8.8 Hz), 2.98 (s.1H), 1.49 (s, 3H), 1.44 (s, 3H), 1.36 (s, 3H), 1.31 (s, 3H).

^{13}C NMR ($CDCl_3$, 100MHz): δ ppm 111.8 (C), 109.6 (C), 105.2 (CH), 85.5 (CH), 81.0 (CH), 75.0 (CH), 73.3 (CH), 67.6 (CH_2), 26.8 (CH_3), 26.7 (CH_3), 26.1 (CH_3), 25.1 (CH_3).

3.3 Synthesis of (5aS,5bR,8aR,9aR)-1-benzyl-3,3,7,7-tetramethyloctahydro-1H-[1,3]dioxolo [4'',5'':4',5']furo[2',3':5,6]pyrano[4,3-c]isoxazole (58)

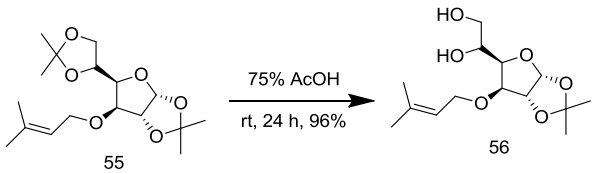


A solution of 1,2:5,6-di-*O*-isopropylidene-*α*-D-glucofuranose (4.00 g, 15.30 mmol) in dichloromethane (DCM) was prepared. An aqueous solution of 50% sodium hydroxide (NaOH) was to the solution and vigorously stirred for 10 minutes. To the mixture 10 mol% tetrabutylammoniumbromide (0.49 g) was added which was followed by 3,3 dimethylallylbromide (2.20 ml, 16.90 mmol). The reaction mixture was allowed to stir for 24 h at room temperature while the progress of the reaction was monitored by thin layer chromatography. After completion of the reaction the organic layer was separated using a separating funnel, washed with brine and dried over anhydrous sodium sulphate. The solution was then evaporated under reduced pressure to obtain the crude product. The product was purified using column chromatography to obtain an oily liquid **55** (4.60 g, 91%).



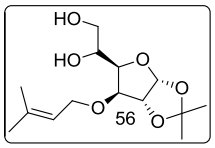
^{1}H NMR ($CDCl_3$, 400MHz): δ ppm 5.84 (d, 1H, *J* = 3.6 Hz), 5.29 (t, 1H, *J* = 5.6 Hz), 4.51 (d, 1H, *J* = 4 Hz), 4.27 (dd, 1H, *J* = 1.6 Hz, 6 Hz), 4.09-4.04 (m, 3H), 3.94 (dd, 1H, *J* = 6 Hz, 8 Hz), 3.88 (d, 1H, *J* = 3.2 Hz), 1.72 (s, 3H), 1.65 (s, 3H), 1.46 (s, 3H), 1.39 (s, 3H), 1.32 (s, 3H), 1.29 (s, 3H).

^{13}C NMR ($CDCl_3$, 100MHz): δ ppm 137.6 (C), 120.5 (CH), 111.5 (C), 108.8 (C), 105.1 (CH), 82.9 (CH), 81.1 (CH), 80.8 (CH), 72.4 (CH), 67.2 (CH_2), 66.9 (CH_2), 26.7 (CH_3), 26.7 (CH_3), 26.1 (CH_3), 25.7 (CH_3), 25.3 (CH_3), 17.9 (CH_3).



An aqueous solution of 75% acetic acid (40 ml) was prepared and compound **55** (3.0 g, 9.10 mmol) was dissolved in the solution. The reaction mixture was then allowed to stir at room temperature for 24 h. Upon completion of the reaction (confirmed by thin layer

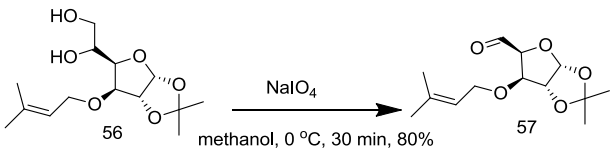
chromatography), the solvent was evaporated under reduced pressure via azeotropic distillation with toluene to obtain compound **56** as an oily liquid (2.50 g, 96%).



^{1}H NMR ($CDCl_3$, 400MHz): δ ppm 5.94 (d, 1H, *J* = 4 Hz), 5.34 (t, 1H, *J* = 5.6 Hz), 4.60 (d, 1H, *J* = 3.6 Hz), 4.27-4.07 (m, 2H), 4.04-4.02 (m, 3H), 3.84 (dd, 1H, *J* = 3.6 Hz, 11.6 Hz), 3.73 (dd, 1H, *J* = 6 Hz, 11.2 Hz), 2.32 (s, 2H), 1.77 (s, 3H), 1.71 (s, 3H), 1.50 (s, 3H), 1.34 (s, 3H).

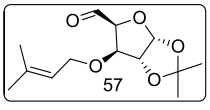
^{13}C NMR ($CDCl_3$, 100MHz): δ ppm 138.3 (C), 120.0 (CH), 111.6 (C), 104.9 (CH), 82.2 (CH), 81.4 (CH), 79.6 (CH), 69.1 (CH), 66.6 (CH_2), 64.1 (CH_2), 26.5 (CH_3), 26.1 (CH_3), 25.7 (CH_3), 18.0 (CH_3).

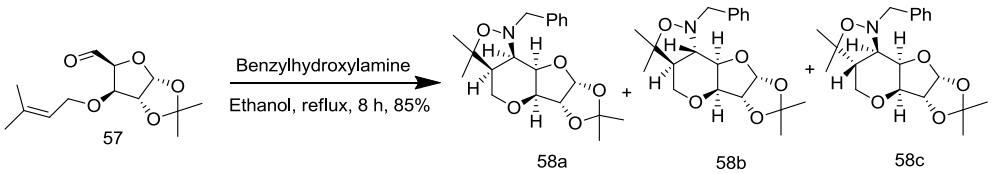
FTIR Spectrum: ν_{max}(neat/cm^{-1}): 3918, 2934, 1452, 1294.



Compound **56** (2.40 g, 8.30 mmol) was dissolved in methanol and cooled to 0 °C in an ice bath. To the cooled solution an aqueous solution of sodium metaperiodate (1.80 g, 9.60 mmol) was added slowly to the solution while continuously stirring. The reaction mixture was allowed to stir for 30 minutes, monitoring the progress via thin layer chromatography. The precipitate then formed was filtered with a Buchner funnel, methanol was evaporated under reduced pressure and the residue was extracted with dichloromethane (3 x 15 ml). The obtained extract was dried over anhydrous sodium sulphate and evaporated to procure the aldehyde (1.70 g, 80%).

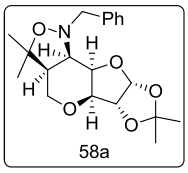
FTIR Spectrum: ν_{max}(neat/cm^{-1}): 2922, 1728, 1456, 1215.





The aldehyde, compound **57** (0.50 g, 1.90 mmol) was dissolved in ethanol and allowed to stir. To it benzylhydroxylamine (0.30 g, 2.40 mmol) was added. The solution was the set in an oil bath and refluxed for 8 h. After completion of the reaction (confirmed by thin layer chromatography) the solvent was evaporated and the crude product was purified via column chromatography. This reaction provided three chiral polyheterocycles **58a** (0.24 g, 34%), **58b** (0.11 g, 16%) and **58c** (0.35 g, 35%).

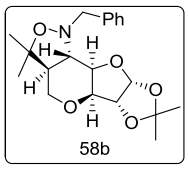
(3aS,5aS,5bR,8aR,9aR,9bR)-1-benzyl-3,3,7,7-tetramethyloctahydro-1H-[1,3]dioxolo [4'',5'':4',5']furo[2',3':5,6]pyrano[4,3-c]isoxazole.



^{1}H NMR ($CDCl_3$, 400MHz): δ ppm 7.42 -7.25 (m, 5H), 5.83 (d, 1H, *J* = 3.6 Hz), 4.49 (d, 1H, *J* = 3.6 Hz), 4.25 (d, 1H, *J* = 9.6 Hz), 4.11 (d, 1H, *J* = 9.6 Hz), 3.96 (s, 1H), 3.82 (dd, 1H, *J* = 5.6 Hz, 11.2 Hz), 3.65 (d, 2H, *J* = 5.6 Hz), 3.60 (t, 1H, *J* = 11.6 Hz), 2.44 (dt, 1H, *J* = 5.2 Hz, 11.6 Hz), 1.33 (s, 3H), 1.31 (s, 3H), 1.29 (s, 3H), 1.17 (s, 3H).

^{13}C NMR ($CDCl_3$, 100MHz): δ ppm 136.8 (C), 129.1 (CH), 128.4 (CH), 127.5 (CH), 111.6 (C), 104.2 (CH), 83.6 (CH), 80.6 (CH), 77.4 (C), 73.8 (CH), 64.3 (CH_2), 64.0 (CH_2), 63.65 (CH), 45.59 (CH), 29.8 (CH_3), 26.6 (CH_3), 26.1 (CH_3), 21.8 (CH_3).

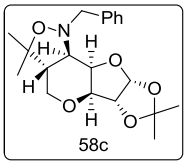
(3aR,5aS,5bR,8aR,9aR,9bR)-1-benzyl-3,3,7,7-tetramethyloctahydro-1H-[1,3]dioxolo [4'',5'':4',5']furo[2',3':5,6]pyrano[4,3-c]isoxazole.



^{1}H NMR ($CDCl_3$, 400MHz): δ ppm 7.44-7.26 (m, 5H), 6.00 (d, 1H, *J* = 3.6 Hz), 4.60 (dd, 1H, *J* = 4 Hz, 6 Hz), 4.58 (d, 1H, *J* = 4 Hz), 4.36 (d, 1H, *J* = 14.8 Hz), 4.04 (d, 1H, *J* = 3.6 Hz), 3.96 (d, 1H, *J* = 8.4 Hz), 3.91 (d, 1H, *J* = 14.8 Hz), 3.80 (t, 1H, *J* = 10 Hz), 3.05 (dd, 1H, *J* = 5.6 Hz, 12.8 Hz), 2.50 (dt, 1H, *J* = 8 Hz, 16 Hz), 1.50 (s, 3H), 1.35 (s, 3H), 1.31 (s, 3H), 1.27 (s, 3H).

^{13}C NMR ($CDCl_3$, 100MHz): δ ppm 137.2 (C), 129.51 (CH), 128.1 (CH), 127.1 (CH), 112.2 (C), 106.3 (CH), 83.8 (CH), 82.2 (CH), 79.9 (CH), 79.2 (C), 69.1 (CH), 65.0 (CH_2), 62.0 (CH_2), 49.1 (CH), 28.7 (CH_3), 27.37 (CH_3), 26.83 (CH_3), 24.80 (CH_3).

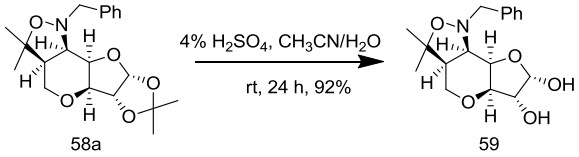
(3aR,5aS,5bR,8aR,9aR,9bR)-1-benzyl-3,3,7,7-tetramethyloctahydro-1H-[1,3]dioxolo [4'',5'':4',5']furo[2',3':5,6]pyrano[4,3-c]isoxazole



58c

^{1}H NMR ($CDCl_3$, 400MHz): δ ppm 7.23-7.44 (m, 5H), 5.92 (d, 1H, *J* = 3.6 Hz), 4.39 (d, 1H, *J* = 3.2 Hz), 4.33 (d, 1H, *J* = 13.2 Hz), 4.00 (d, 1H, *J* = 13.2 Hz), 3.94 (d, 1H, *J* = 8 Hz), 3.84 (s, 1H), 3.77 (s, 1H), 3.37 (t, 1H, *J* = 10.8 Hz), 2.86 (s, 1H), 2.65 (t, 1H, *J* = 8.4 Hz), 1.32 (s, 3H), 1.28 (s, 3H), 1.26 (s, 3H), 1.09 (s, 3H).

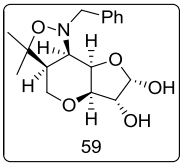
^{13}C NMR ($CDCl_3$, 100MHz): δ ppm 135 (C), 129.3(CH), 129.0 (CH), 128.4 (CH), 128.3 (CH), 127.5 (CH), 111.6 (C), 105.2 (CH), 82.5 (CH), 78.9 (CH), 78.4 (CH), 77.4 (C), 74.5 (CH), 68.2 (CH), 66.5 (CH_2), 63.1 (CH_2), 47.8 (CH), 27.7 (CH_3), 26.5 (CH_3), 26.1 (CH_3), 24.8 (CH_3).



58a 59

Compound **58a** (0.30 g, 0.83 mmol) was dissolved in an acidic solution of 4% sulphuric acid in acetonitrile and water. The mixture was allowed to stir at room temperature for 24 h. After completion of the reaction, verified by thin layer chromatography, the acidic solution was neutralised by calcium carbonate, filtered to remove the precipitate and the filtrate was evaporated. The residue was dissolved in dichloromethane and passed through sodium sulphate to remove any traces of water and dried to obtain **59** (0.24 g, 92%).

The formed compound **59** is in hemiacetal form which can easily undergo anomerisation changing the stereochemistry of the –OH group at C-1 carbon resulting in formation of two anomers which is evident by the twin peaks present in ^{1}HNMR and ^{13}CNMR.

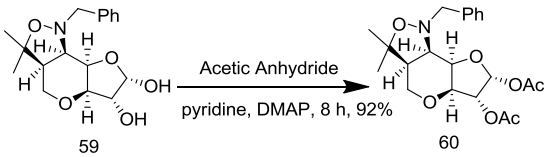


59

^{1}H NMR ($CDCl_3$, 400MHz): δ ppm 7.40-7.26 (m, 5H), 4.20 (t, 1H, *J* = 5.6 Hz), 4.17-4.14 (m, 1H), 4.10 (t, 2H, *J* = 13.6 Hz), 3.88 (dd, 2H, *J* = 5.6 Hz, 11.2 Hz) , 3.81 (dd, 1H, *J* = 5.6 Hz, 11.2 Hz), 3.66-

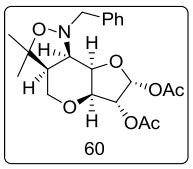
3.59 (m, 2H), 2.43 (dt, 1H, *J* = 3.2 Hz, 12 Hz), 1.66 (s, 2H), 1.30 (s, 3H), 1.17 (s, 3H).

^{13}C NMR ($CDCl_3$, 100MHz): δ ppm 136.8 (C), 129.2 (CH), 129.1 (CH), 128.6 (CH), 127.5 (CH), 127.4 (CH), 96.7 (CH), 80.7 (CH), 80.6 (CH),79.0 (C), 77.7 (CH), 63.9 (CH_2), 63.9 (CH_2), 63.4 (CH_2), 63.3 (CH_2), 45.4 (CH), 45.3 (CH), 29.7 (CH_3), 21.9 (CH_3).



59 60

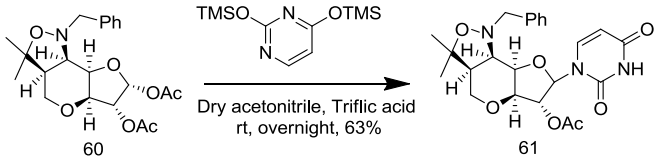
To a solution of compound **59** (0.20 g, 0.62 mmol) in pyridine, a catalytic amount of N,N-dimethylaminopyridine (DMAP) was added, followed by acetic anhydride (0.09 ml, 1.30 mmol). The reaction mixture was allowed to stir at room temperature for 8 h monitoring the progress via thin layer chromatography. Upon completion of the reaction, pyridine was evaporated under reduced pressure by azeotropic distillation with toluene to procure crude product. The crude was dissolved in dichloromethane washed with water, brine and dried over sodium sulphate. The filtrate was then evaporated and the product was purified by column chromatography to obtain pure product **60** (0.23 g, 92%).



60

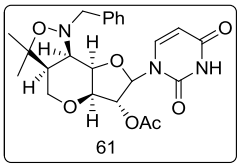
^{1}H NMR ($CDCl_3$, 400MHz): δ ppm 7.42-7.30 (m, 5H), 6.40 (d, 1H, *J* = 3.6 Hz), 5.21 (d, 1H, *J* = 4.8 Hz), 4.15 (d, 2H, *J* = 2.8 Hz), 4.12 (s, 1H), 3.92 (s, 1H), 3.86 (dd, 1H, *J* = 5.6 Hz, 11.2 Hz), 3.65 (d, 1H, *J* = 5.2 Hz), 3.59 (t, 1H, *J* = 11.2 Hz), 2.49 (dt, 1H, *J* = 5.6 Hz, 11.6 Hz), 2.12 (s, 3H), 2.07 (s, 3H), 1.31 (s, 3H), 1.271 (s, 3H).

^{13}C NMR ($CDCl_3$, 100MHz): δ ppm 169.3 (C=O), 137.1 (C), 128.9 (CH), 128.3 (CH), 127.3 (CH), 94.2 (CH), 77.3 (C), 74. 5 (CH), 71.8 (CH), 65.1 (CH), 63.8 (CH_2), 63.3 (CH_2), 45.3 (CH), 29.7 (CH_3), 29.5 (CH_3), 20.9 (CH_3), 20.4 (CH_3).



60 61

Uracil (0.20 g, 0.49 mmol) was refluxed with hexamethyldisilagen in presence of catalytic amount of trimethylsilylchloride for 6 h. The solution was then evaporated under reduced pressure to procure a white powder of 2,4-bis((trimethylsilyl)oxy)pyrimidine. Compound **60** (0.10 g, 0.24 mmol) was then dissolved in dry acetonitrile and added to the 2,4-bis((trimethylsilyl)oxy)pyrimidine. Triflic acid was added to the mixture and the solution was allowed to stir at room temperature overnight. Upon completion of the reaction, verified by thin layer chromatography, the acid was neutralised by sodium hydrogen carbonate and filtered to remove the precipitate. The filtrate was evaporated under pressure and extracted with ethyl acetate (3 x 15 ml), dried over sodium sulphate. The extract was evaporated and subjected to column chromatography to obtain the product **61** (0.14 g, 63%).

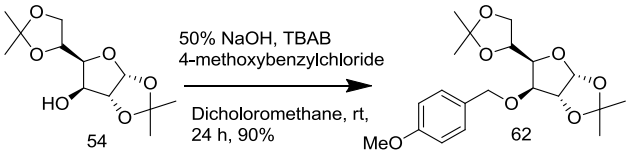


61

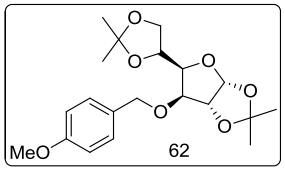
^{1}H NMR ($CDCl_3$, 400MHz): δ ppm 9.25 (s, 1H), 7.70 (d, 1H, *J* = 8 Hz), 7.42-7.34 (m, 5H), 7.32 (d, 1H, *J* = 8 Hz), 5.80 (d, 1H, *J* = 8 Hz), 4.99 (s, 1H), 4.21 (d, 1H, *J* = 14 Hz), 4.15 (d, 1H, *J* = 13.6 Hz), 3.99 (s, 1H), 3.96 (d, 1H, *J* = 5.6 Hz), 3.72 (d, 1H, *J* = 12 Hz), 3.69 (d, 1H, *J* = 6 Hz), 3.65 (s, 1H), 2.48 (dt, 1H, *J* = 6 Hz, 12 Hz), 2.12 (s, 3H), 1.31 (s, 3H), 1.26 (s, 3H).

^{13}C NMR ($CDCl_3$, 100MHz): δ ppm 169.2 (C), 162.4 (C), 149.9 (C), 140.7 (CH), 136.7 (C), 129.0 (CH), 128.4 (CH), 127.6 (CH), 103.4 (CH), 87.8 (CH), 80.8 (CH), 80.6 (C), 76.6 (CH), 75.5 (CH), 64.4 (CH), 63.4 (CH_2), 63.4 (CH_2), 62.6 (CH_2), 45.3 M(CH), 27.2 (CH_3), 26.7 (CH_3), 26.7 (CH_3), 22.6 (CH_3).

3.4 Synthesis of (6aS,7aR,10aR)-1-benzyl-3,3,9,9- tetramethyloctahydro[1,3] [dioxolo [4'',5'':4',5']furo[3',2':4,5]pyrano[4,3-c]isoxazole (69)

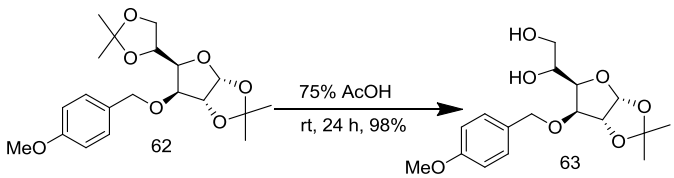


An aqueous solution of 50% sodium hydroxide was added to a solution of compound **54** (3.00 g, 11.50 mmol) in dichloromethane while vigorously stirring. After 10 minutes tetrabutylammoniumbromide (0.37 g, 1.15 mmol) was added to it followed by 4-methoxybenzylchloride (1.80 g, 12.60 mmol). The mixture was allowed to stir for 24 h. after completion of the reaction, verified by thin layer chromatography, the organic layer was separated using a separating funnel washed with water, brine and dried over sodium sulphate. The extract was evaporated under reduced pressure and purified using column chromatography to obtain pure compound **62** (3.80 g, 90 %).



^{1}H NMR ($CDCl_3$, 400MHz): δ ppm 7.26 (d, 2H, *J* = 8.4 Hz), 6.87 (d, 2H, *J* = 8.4 Hz), 5.88 (d, 1H, *J* = 3.2 Hz), 4.6 (d, 1H, *J* = 11.6 Hz), 4.58 (s, 1H), 4.53 (t, 1H, *J* = 11.2 Hz), 4.33 (dd, 1H, *J* = 6.4 Hz, 6.8 Hz), 4.14 (dd, 1H, *J* = 2.8 Hz, 7.6 Hz), 4.09 (dd, 1H, *J* = 6.4 Hz, 8 Hz), 4.00 (s, 2H), 3.78 (s, 3H), 1.48 (s, 3H), 1.42 (s, 3H), 1.37 (s, 3H), 1.30 (s, 3H).

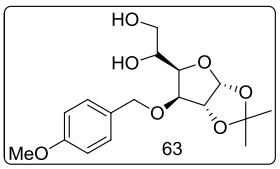
^{13}C NMR ($CDCl_3$, 100MHz): δ ppm 159.3 (C), 129.6 (CH), 129.5 (CH), 129.3 (C), 114.0 (CH), 113.7 (CH), 111.7 (C), 108.9 (C), 105.2 (CH), 82.6 (CH), 82.1 (CH), 81.4 (CH), 72.5 (CH_2), 72.0 (CH), 67.2 (CH_2), 55.2 (CH_3), 26.8 (CH_3), 26.7 (CH_3), 26.2 (CH_3), 25.4 (CH_3).



An aqueous solution of 75% acetic acid (40 ml) was prepared and compound **62** (3.50 g, 9.50 mmol) was dissolved in the solution. The reaction mixture was then allowed to

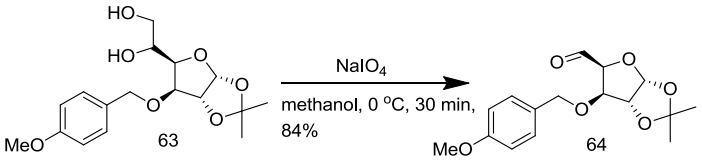
stir at room temperature for 24 h. Upon completion of the reaction (confirmed by thin layer chromatography), the solvent was evaporated under reduced pressure via azeotropic distillation with toluene to obtain compound **63** as an oily liquid (3.05 g, 98%).

^{1}H NMR ($CDCl_3$, 400MHz): δ ppm 7.27 (d, 2H, *J* = 8 Hz), 6.89 (d, 2H, *J* = 8.4 Hz), 5.93 (d, 1H, *J* = 4 Hz), 4.65 (d, 1H, *J* = 11.6 Hz), 4.61 (d, 1H, *J* = 3.6 Hz), 4.49 (d, 1H, *J* = 11.6 Hz), 4.13-4.08 (m, 2H), 4.00 (s, 1H), 3.80 (s, 3H), 3.78 (s, 1H), 3.68 (dd, 1H, *J* = 5.6 Hz, 11.6 Hz), 2.87 (s, 2H), 1.48 (s, 3H), 1.28 (s, 3H).



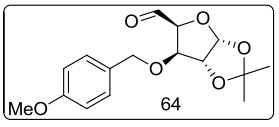
^{13}C NMR ($CDCl_3$, 100MHz): δ ppm 159.5 (C), 129.6 (CH), 129.2 (C), 114.0 (CH), 111.7 (C), 105.7 (CH), 82.1 (CH), 81.4 (CH), 79.8 (CH), 71.7 (CH_2), 69.2 (CH_2), 64.2 (CH_2), 55.2 (CH_3), 26.6 (CH_3), 26.2 (CH_3).

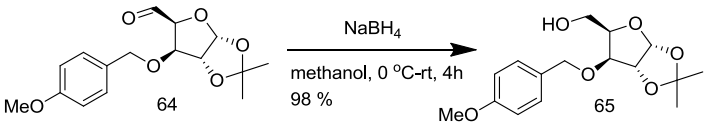
FTIR Spectrum: ν_{max} (neat/cm^{-1}) 3445, 2935, 1612, 1246.



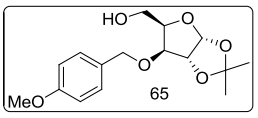
Compound **63** (2.50 g, 7.60 mmol) was dissolved in methanol and cooled to 0 °C in an ice bath. To the cooled solution an aqueous solution of sodium metaperiodate (1.80 g, 8.40 mmol) was added slowly to the solution while continuously stirring. The reaction mixture was allowed to stir for 30 minutes, monitoring the progress via thin layer chromatography. The precipitate then formed was filtered with a Buchner funnel, methanol was evaporated under reduced pressure and the residue was extracted with dichloromethane (3 x 15 ml). The obtained extract was dried over anhydrous sodium sulphate (Na_2SO_4) and evaporated to procure the aldehyde **64** (1.90 g, 84%).

FTIR Spectrum: ν_{max} (neat/cm^{-1}) 2935, 1737, 1374.



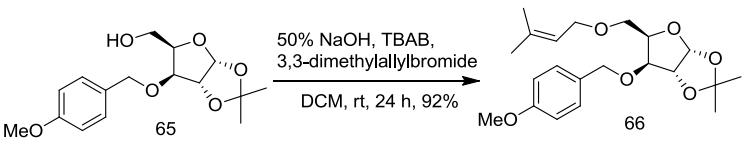


A methanolic solution of compound **64** (1.50 g, 5.10 mmol) was cooled to 0 ^{o}C and to it sodium borohydride (0.20 g, 5.60 mmol) was slowly added while stirring continuously. After 20 minutes the reaction mixture was slowly brought to room temperature and left to stir for 4 h. upon confirming the completion of the reaction via thin layer chromatography the solvent was evaporated and the residue was dissolved with dichloromethane. The solution was then washed with water, brine and passed through sodium sulphate. The extract was dried to obtain compound **65** (1.49 g, 98%).

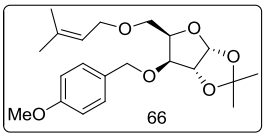


^{1}H NMR ($CDCl_3$, 400MHz): δ ppm 7.27 (d, 2H, *J* = 9.6 Hz), 6.91 (d, 2H, *J* = 8.8 Hz), 6.01 (d, 1H, *J* = 4 Hz), 4.68 (d, 1H, *J* = 11.6 Hz), 4.65 (d, 1H, *J* = 3.6 Hz), 4.43 (d, 1H, *J* = 11.6 Hz), 4.28 (dd, 1H, *J* = 4.8 Hz, 8.4 Hz), 4.02 (d, 1H, *J* = 3.6 Hz), 3.96-3.91 (m, 1H), 3.87 (dd, 1H, *J* = 4.4 Hz, 8 Hz), 3.83 (s, 3H), 2.20 (dd, 1H, *J* = 3.6 Hz, 8.8 Hz), 1.50 (s, 3H), 1.35 (s, 3H).

^{13}C NMR ($CDCl_3$, 100MHz): δ ppm 159.2 (C), 129.4 (CH), 129.3 (C), 114.0 (CH), 111.7 (C), 105.7 (CH), 82.5 (CH), 82.4 (CH), 79.4 (CH), 71.5 (CH_2), 61.0 (CH_2), 55.3 (CH_3), 26.8 (CH_3), 26.3 (CH_3).

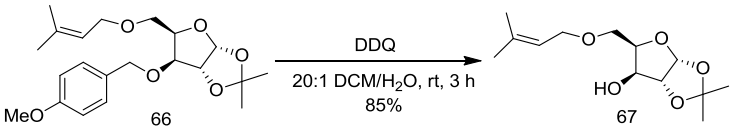


An aqueous solution of 50 % sodium hydroxide was added to a solution of compound **65** (1.20 g, 4.05 mmol) in dichloromethane while vigorously stirring. After 10 minutes tetrabutylammoniumbromide (0.13 g, 0.40 mmol) was added to it followed by 3,3-dimethylallylbromide (0.57 ml, 4.4 mmol). The mixture was allowed to stir for 24 h. after completion of the reaction, verified by thin layer chromatography, the organic layer was separated using a separating funnel washed with water, brine and dried over sodium sulphate. The extract was evaporated under reduced pressure and purified using column chromatography to obtain pure compound **66** (1.3 g, 92%).

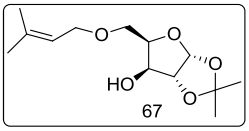


^{1}H NMR ($CDCl_3$, 400MHz): δ ppm 7.24 (d, 2H, *J* = 8.4 Hz), 6.82 (d, 2H, *J* = 8.4 Hz), 5.93 (d, 1H, *J* = 3.6 Hz), 5.35 (t, 1H, *J* = 6.8 Hz), 4.61 (d, 1H, *J* = 4.6 Hz), 4.59 (d, 1H, *J* = 4 Hz), 4.47 (d, 1H, *J* = 11.6 Hz), 4.36 (dd, 1H, *J* = 3.6 Hz, 6 Hz), 4.02 (dd, 2H, *J* = 6.8 Hz, 14.8 Hz), 3.96 (d, 1H, *J* = 3.2 Hz), 3.81 (s, 3H), 3.68 (d, 2H, *J* = 6 Hz), 1.75 (s, 3H), 1.68 (s, 3H), 1.48 (s, 3H), 1.31 (s, 3H).

^{13}C NMR ($CDCl_3$, 100MHz): δ ppm 159.5 (C), 137.2 (C), 129.8 (CH), 129.4 (CH), 121.1 (CH), 114.0 (CH), 111.7 (CH), 105.2 (CH), 82.6 (CH), 81.4 (CH), 79.4 (CH), 71.5 (CH_2), 67.9 (CH_2), 67.3 (CH_2), 55.4 (CH_3), 26.9 (CH_3), 26.5 (CH_3), 26.0 (CH_3), 18.2 (CH_3).

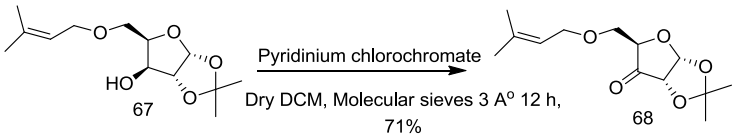


Compound **66** (1.00 g, 2.74 mmol) was dissolved in a mixture of 20:1 dichloromethane and water. While continuously stirring 2,3-dichloro-5,6-dicyano-p-benzoquinone (0.72 g, 3.10 mmol) was added to the mixture and the solution was allowed to stir for 3 h. Upon verifying the completion of the reaction by tin layer chromatography the mixture was quenched with saturated solution of sodium hydrogen carbonate and the organic layer was separated using a separating funnel. The organic layer was washed with water, brine and passed over sodium sulphate. The extract was then dried and purified via column chromatography to obtain pure product (0.60 g, 85%).



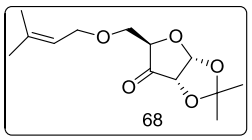
^{1}H NMR ($CDCl_3$, 400MHz): δ ppm 6.00 (d, 1H, *J* = 3.6 Hz), 5.34 (t, 1H, *J* = 6.8 Hz), 4.54 (d, 1H, *J* = 3.6 Hz), 4.31 (s, 1H), 4.24 (d, 1H, *J* = 3.2 Hz), 4.08 (dd, 2H, *J* = 6.8 Hz, 14.4 Hz), 4.00 (s, 1H), 3.95 (d, 1H, *J* = 4 Hz), 3.92 (d, 1H, *J* = 2.8 Hz), 1.76 (s, 3H), 1.69 (s, 3H), 1.50 (s, 3H), 1.34 (s, 3H).

^{13}C NMR ($CDCl_3$, 100MHz): δ ppm 136.9 (C), 120.0 (CH), 111.5 (CH), 104.8 (CH), 88.1 (CH), 85.4 (CH), 77.9 (CH), 68.4 (CH_2), 67.9 (CH_2), 26.7 (CH_3), 26.1 (CH_3), 25.7 (CH_3), 18.4 (CH_3).

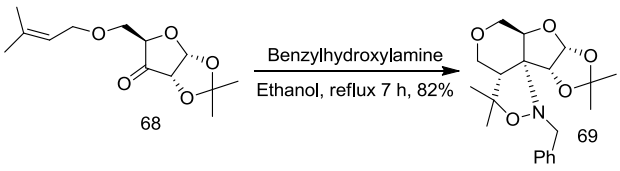


In a moisture free round bottomed flask compound **67** (0.50 g, 1.90 mmol) was taken and dissolved in dry dichloromethane. To the solution molecular sieves 3 A^0 (preheated and cooled) was added and kept on stirring. After 5 minutes pyridinium chlorochromate (0.39 g, 2.90 mmol) was added and the reaction mixture was allowed to stir for 12 h. The completion of the reaction was verified by thin layer chromatography and the product was purified via column chromatography acquiring **68** (0.35 g, 71%).

^{13}C NMR ($CDCl_3$, 100MHz): δ ppm 210.1 (C), 137.5 (C), 127.0 (CH), 114.0 (CH), 104.3 (CH), 79.9 (CH), 76.5 (CH_2), 69.4 (CH_2), 68.0 (CH_2), 27.5 (CH_3), 26.9 (CH_3), 26.4 (CH_3), 18.0 (CH_3).

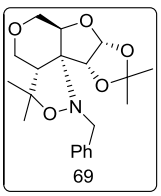


FTIR Spectrum: ν_{max} (neat/cm^{-1}) 2988, 2934, 1774, 1515, 1453, 1079.



The ketone **68** (0.20 g, 0.78 mmol) was dissolved in ethanol and benzylhydroxylamine (0.10 g, 8.60 mmol) was added to the solution. The solution was allowed to reflux for 7 h while the progress of the reaction was monitored by thin layer chromatography. After completion of the reaction the solvent was dried and the crude was purified to obtain compound **69** (0.23 g, 82%).

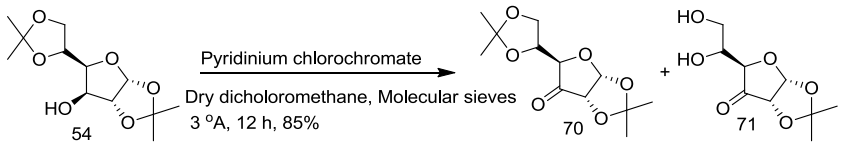
(6aS,7aR,10aR)-1-benzyl-3,3,9,9-tetramethyloctahydro-[1,3]dioxolo[4'',5'':4',5']furo[3',2':4,5] pyrano[4,3-c]isoxazole.



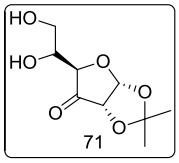
^1H NMR ($CDCl_3$, 400MHz): δ ppm 7.50-7.36 (m, 5H), 6.08 (d, 1H, *J* = 4.4 Hz), 5.37 (d, 1H, *J* = 13.2 Hz), 5.24 (s, 1H), 5.18 (dd, 2H, *J* = 1.6 Hz, 4.4 Hz), 5.09 (s, 1H), 5.05 (s, 1 H), 4.10 (dd, 1H, *J* = 2 Hz, 10 Hz), 3.93 (dt, 2H, *J* = 11.6 Hz, 16.8 Hz), 3.57 (dd, 1H, *J* = 2 Hz, 10 Hz), 1.73 (s, 3H), 1.69 (s, 3H), 1.48 (s, 3H), 1.45 (s, 3H).

^{13}C NMR ($CDCl_3$, 100MHz): δ ppm 136.4 (C), 129.2 (CH), 128.4 (CH), 120.9 (CH), 113.9 (C), 105.3 (CH), 80.1 (CH), 77.3 (CH), 71.2 (C), 68.1 (CH_2), 68.0 (CH_2), 63.9 (CH_2), 29.7 (CH), 27.6 (CH_3), 27.5 (CH_3), 25.7 (CH_3), 18.0 (CH_3).

3.5 Synthesis of (10S,11S,11aR)-1,9-dibenzyldodecahydro-7,10-[3',4':4,5] pyrido[2,1-e][1,2,6]oxadiazocine-11,12-diol (78).

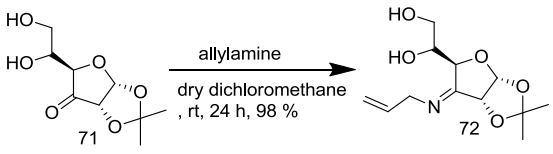


The oxidation of 1,2:5,6-di-*O*-isopropylidiene-α-D-glucofuranose (**54**) was carried out using the same procedure used for the oxidation of compound **67**. Upon completion (verified by thin layer chromatography) the product was purified via column chromatography. After purification two products were obtained which were identified as **70** and **71** (85%).



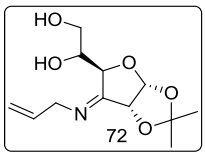
^{1}H NMR ($CDCl_3$, 400MHz): δ ppm 5.99 (d, 1H, *J* = 3.2 Hz), 4.51 (t, 1H, *J* = 5.2 Hz), 4.45 (s, 2H), 4.30 (d, 1H, *J* = 6.8 Hz), 3.81 (dd, 1H, *J* = 6 Hz, 9.2 Hz), 3.60 (s, 1H), 2.49 (s, 1H), 1.60 (s, 3H), 1.39 (s, 3H).

^{13}C NMR ($CDCl_3$, 100MHz): δ ppm 208.2 (C), 114.0 (C), 107.0 (CH), 84.3 (CH), 82.7 (CH), 74.2 (CH), 71.0 (CH_2), 27.2 (CH_3).



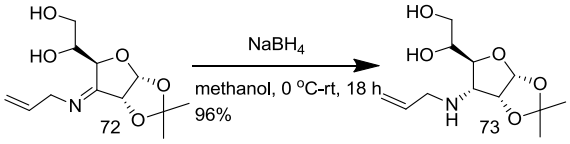
In an oven dried round bottomed flask, fitted with a guard tube filled with anhydrous calcium chloride, compound **71** (4.00 g, 18.30 mmol) was dissolved in dry dichloromethane. While stirring continuously allyl amine (1.40 ml, 22.00 mmol) was added and the solution was allowed to stir for 24 h. The solution was evaporated after

verifying the completion of the reaction via thin layer chromatography to procure **72** (4.60 g, 98%).

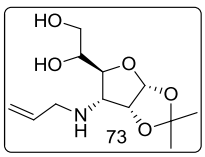


^{1}H NMR ($CDCl_3$, 400MHz): δ ppm 5.93 (d, 1H, *J* = 3.6 Hz), 5.92 (m, 1H), 5.25 (dd, 1H, *J* = 1.6 Hz, 17.2 Hz), 5.10 (dd, 1H, *J* = 1.6 Hz, 17.2 Hz), 4.52 (d, 1H, *J* = 3.6 Hz), 4.46 (q, 1H, *J* = 5.6 Hz), 4.33 (d, 1H, *J* = 4.8 Hz), 4.24 (dd, 1H, *J* = 6.8 Hz, 9.2 Hz), 3.69 (dd, 1H, *J* = 6 Hz, 9.2 Hz), 3.32 (d, 2H, *J* = 4.8 Hz), 2.07 (s, 2H), 1.57 (s, 3H), 1.39 (s, 3H).

^{13}C NMR ($CDCl_3$, 100MHz): δ ppm 136.8 (CH), 115.7 (CH_2), 113.6 (C), 106.9 (C), 103.4 (CH), 84.5 (CH), 82.7 (CH), 73.7 (CH), 72.1 (CH_2), 45.3 (CH_2), 27.6 (CH_3), 27.0 (CH_3).

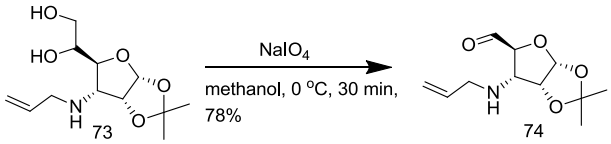


The reduction of compound **72** (4.00 g, 15.50 mmol) was carried out using afore mentioned procedure in the synthesis of **65**. The obtained product **73** (3.90 g, 96%) was sufficiently pure to proceed without purification.

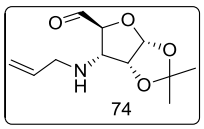


^{1}H NMR ($CDCl_3$, 400MHz): δ ppm 5.91 (m, 1H), 5.87 (d, 1H, *J* = 3.6 Hz), 5.27 (d, 1H, *J* = 16 Hz), 5.19 (d, 1H, *J* = 10 Hz), 4.65 (t, 1H, *J* = 4 Hz), 4.03 (d, 1H, *J* = 2.8 Hz), 3.76 (t, 1H, *J* = 2.8 Hz), 3.74 (d, 1H, *J* = 3.2 Hz), 3.45 (dd, 1H, *J* = 6.4 Hz, 13.6 Hz), 3.26 (dd, 1H, *J* = 6.4 Hz, 13.6 Hz), 3.20 (dd, 1H, *J* = 4.4 Hz, 9.6 Hz), 1.55 (s, 3H), 1.38 (s, 3H).

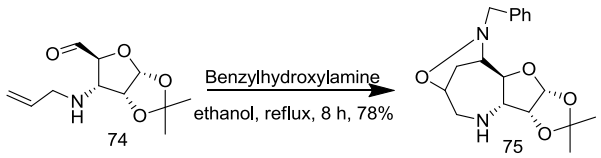
^{13}C NMR ($CDCl_3$, 100MHz): δ ppm 135.0 (CH), 117.7 (CH_2), 112.2 (C), 104.5 (CH), 81.3 (CH), 70.4 (CH), 62.9 (CH), 58.8 (CH_2), 50.2 (CH_2), 26.5 (CH_3), 26.4 (CH_3).



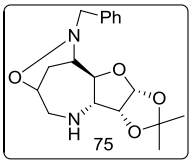
Compound **73** (3.50 g, 13.50 mmol) was subjected to oxidative cleavage by sodium metaperiodate following the procedure mentioned in the synthesis of **57**. Compound **74** was isolated as an oily colourless viscous liquid (2.40 g, 78%).



FTIR spectrum: v_{max} (neat/cm^{-1}) 3333, 2986, 2935, 1666.

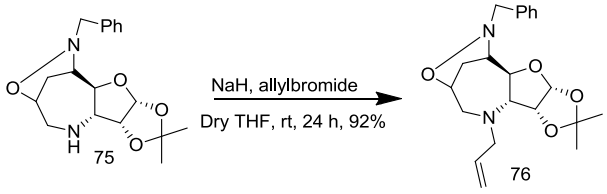


The aldehyde **74** (2.30 g, 10.10 mmol) was dissolved in ethanol (40 ml) and allowed to stir before adding benzylhydroxylamine (1.49 g, 12.10 mmol). The mixture was set into reflux for 8 h while the progress of the reaction was monitored by thin layer chromatography. After completion ethanol was dried off and the crude was purified to procure the adduct **75**[21] as a yellowish oily liquid (2.60 g, 78%).



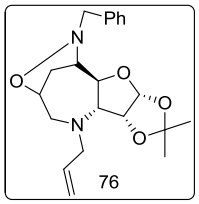
^{1}H NMR ($CDCl_3$, 400MHz): δ ppm 7.39-7.23 (m, 5H), 5.80 (d, 1H, *J* = 3.6 Hz), 5.49 (d, 1H, *J* = 2.4 Hz), 4.52 (d, 1H, *J* =3.6 Hz), 4.09 (s, 1H), 4.04 (d, 1H, *J* = 13.2 Hz), 3.86 (d, 1H, *J* = 13.2 Hz), 3.75 (dd, 1H, *J* = 2 Hz, 3.6 Hz), 3.52 (dd, 1H, *J* = 2.4 Hz, 10 Hz), 3.41 (dd, 1H, *J* = 4 Hz, 10 Hz), 3.11 (d, 1H, *J* = 14.8 Hz), 2.76 (dd, 1H, *J* = 3.2 Hz, 14.8 Hz), 2.47-2.37 (m, 1H), 1.88 (d, 1H, *J* = 13.2 Hz), 1.53 (s, 3H), 1.36 (s, 3H).

^{13}C NMR ($CDCl_3$, 100MHz): δ ppm 136.9 (C), 129.0 (CH), 128.4 (CH), 127.4 (CH), 112.1 (C), 104.5 (CH), 80.65 (CH), 79.5 (CH), 78.1 (CH), 62.7 (CH), 61.1 (CH_2), 68.2 (CH), 50.9 (CH_2), 29.7 (CH_2), 26.2 (CH_3), 25.9 (CH_3).



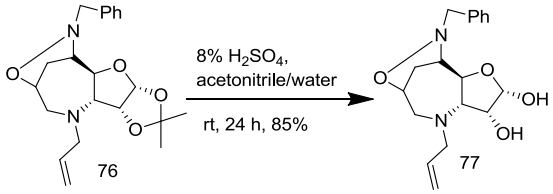
Compound **75** (2.50 g, 7.50 mmol) was taken in a round bottomed flask under inert atmosphere and dissolved in anhydrous tetrahydrofuran. To the solution sodium

hydride (60 % in silicon oil) was slowly added while continuously stirring until evolution of hydrogen ceased. The mixture was allowed to stir for 30 minutes. Allylbromide (0.70 ml, 8.20 mmol) was added and allowed to stir for 24 h. Upon completion of the reaction confirmed by thin layer chromatography, the mixture was quenched with water and filtered via Buchner funnel filled with celite filter. The filtrate was evaporated and the residue was extracted with dichloromethane (3 x 20 ml), washed with water, brine and passed over sodium sulphate to remove any traces of water. The extract was then evaporated under reduced under pressure and subjected to column chromatography to procure **76** (2.60 g, 92%).

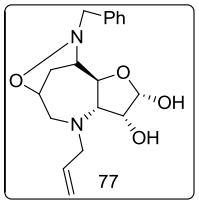


^{1}H NMR ($CDCl_3$, 400MHz): δ ppm 7.38-7.26 (m, 5H), 5.92 (m, 1H), 5.81 (d, 1H, *J* = 3.6 Hz), 5.23 (s, 1H), 5.20 (d, 1H, *J* = 1.6 Hz), 4.70 (d, 1H, *J* = 3.6 Hz), 4.62 (d, 1H, *J* = 8.8 Hz), 4.08 (d, 1H, *J* = 13.2 Hz), 3.92-3.85 (m, 2H), 3.77 (dd, 1H, *J* = 2.4 Hz, 7.2 Hz), 3.53 (d, 1H, *J* = 6.4 Hz), 3.14 (dd, 1H, *J* = 3.6 Hz, 9.2 Hz), 2.78 (t, 1H, *J* = 3.6 Hz), 2.33-2.29 (m, 1H), 2.17 (d, 1H, *J* = 12.4 Hz), 1.58 (s, 3H), 1.31 (s, 3H).

^{13}C NMR ($CDCl_3$, 100MHz): δ ppm 136.9 (C), 134.5 (C), 129.0 (CH), 128.4 (CH), 127.3 (CH), 118.2 (CH_2), 112.3 (C), 103.9 (CH), 80.09 (CH), 79.3 (CH), 76.7 (CH), 63.5 (CH), 62.5 (CH), 61.2 (CH_2), 58.5 (CH_2), 57.3 (CH_2), 28.9 (CH_2), 26.7 (CH_3), 26.1 (CH_3).

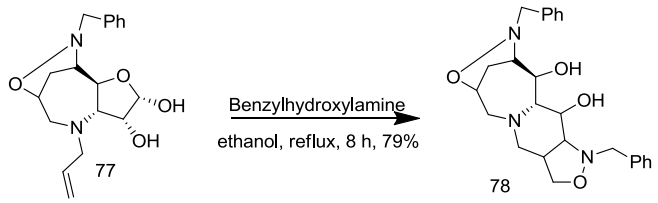


Compound **76** (2.50, 6.72 mmol) g was dissolved in an acidic solution of 8 % sulphuric acid in acetonitrile and water. The solution was allowed to stir for 24 h. The completion of the reaction was confirmed by thin layer chromatograph. The solution was then neutralised by calcium carbonate and filtered via a Buchner funnel. The filtrate was dried off and the residue was dissolved in dichloromethane which was then passed over sodium

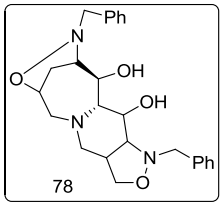


sulphate. The solution was then evaporated under reduced pressure to acquire compound **77** (1.90 g, 86 %).

FTIR Spectrum: ν_{max} (neat)/cm^{-1} 3355, 2923, 2853, 1659, 1557, 1047.



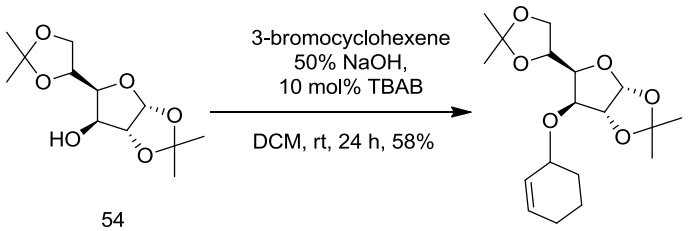
A solution of compound **77** (0.50 g, 1.50 mmol) in ethanol was prepared. The solution was allowed to stir and benzylhydroxylamine (0.20 g, 1.60 mmol) was added. The mixture was then set into reflux for 8 h. The progress of the reaction was monitored by thin layer chromatography. After completion ethanol was dried off and the crude product was subjected to column chromatography to acquire pure compound **78** as a white amorphous solid (0.52 g, 79%).



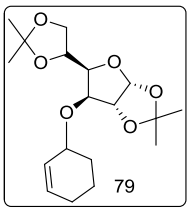
^{1}H NMR ($CDCl_3$, 400MHz): δ ppm 7.43-7.31 (m, 10H), 4.67 (dd, 1H, *J* = 4.4 Hz, 8.4 Hz), 4.30 (s, 1H), 4.12-4.07 (m, 2H), 4.02 (d, 1H, *J* = 7.2 Hz), 3.76 (d, 1H, *J* = 12.8 Hz), 3.51 (dd, 1H, *J* = 6.8 Hz, 8.4 Hz), 3.46 (dd, 1H, *J* = 4 Hz, 6.8 Hz), 3.41 (s, 1H), 3.15 (t, 1H, *J* = 10 Hz), 3.03 (s, 2H), 3.00-2.92 (m, 2H), 2.85 (d, 1H, *J* = 10 Hz), 2.85 (d, 1H, *J* = 10 Hz), 2.74 (d, 1H, *J* = 12.8 Hz), 2.67 (d, 1H, *J* = 11.6 Hz), 2.57-2.52 (m, 3H), 2.36 (dd, 1H, *J* = 8 Hz, 12 Hz).

^{13}C NMR ($CDCl_3$, 100MHz): δ ppm 137.1 (C), 137.0 (C), 129.2 (CH), 129.0 (CH), 128.8 (CH), 128.6 (CH), 127.9 (CH), 127.7 (CH), 77.6 (CH), 70.2 (CH_2), 69.9 (CH), 67.3 (CH), 66.8 (CH), 63.3 (CH), 62.8 (CH), 62.2 (CH2), 61.9 (CH_2), 60.9 (CH_2), 51.0 (CH_2), 43.1 (CH), 29.8 (CH_2).

3.6 Synthesis of (6aS,7R,8R,9aR,9bS)-1-benzyldodecahydrofuro[3',2':2,3]chromeno[4,5-cd]isoxazole-7,8-diyl diacetate (84).

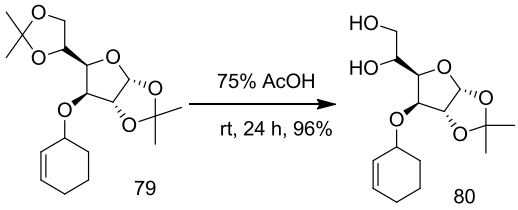


1,2:5,6-*O*-isoproplyidene-α-D-glucofuranose (2.00 g, 7.68 mmol) was dissolved in 30 ml of dichloromethane and an aqueous solution of 50 % sodium hydroxide was added while stirring vigorously. 15 mins later tetrabutylammoniumbromide (0.59 g, 0.77 mmol) was added to the mixture and after 5 mins 3–bromocyclohexene (1.36 g, 8.45 mmol) was added. The mixture was left to stir continuously for 24 hours. The mixture was transferred to separating funnel and distilled water was added to it, the product was extracted with dichloromethane (3 x20 ml). The combined extract was washed with brine, passed through anhydrous sodium sulphate and evaporated. The crude was chromatographed over silica gel to obtain oily colorless viscous liquid (1.50 g, 58%).

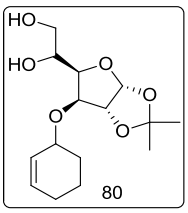


^{1}HNMR ($CDCl_3$, 400MHz): δ ppm 5.93 (d, 1H, *J* = 3.6 Hz), 5.85 (m, 1H,), 5.76 (t like, 1H, *J* = 10 Hz , *J* = 12.4 Hz), 4.52 (d, 1H, *J* = 3.6 Hz), 4.32 (m, 2H), 4.15 (dd, 1H, J = 6.4, 8.4 Hz), 4.05 (dd, 1H, *J* =2.4, 7.6), 3.98 (dd, 1H, *J* = 5.2, 8.8 Hz), 1.96 (m, 2H), 1.79 (m, 4H), 1.69 (m, 1H), 1.49 (s, 3H), 1.44 (s, 3H), 1.36 (s, 3H), 1.31 (s, 3H).

^{13}C NMR ($CDCl_3$, 100MHz): δ ppm 131.6 (CH), 127.8 (CH), 112.8 (CH), 109.5 (C), 103.8 (CH), 78.8 (CH), 78.1(CH), 77.7 (CH), 75.9 (CH), 73.4 (CH), 64.8 (CH_2), 29.4 (CH_2), 28.0 (CH_2), 26.8 (CH_3), 26.5 (CH_3), 25.1 (CH_3), 25.0 (CH_3), 19.8 (CH_2).



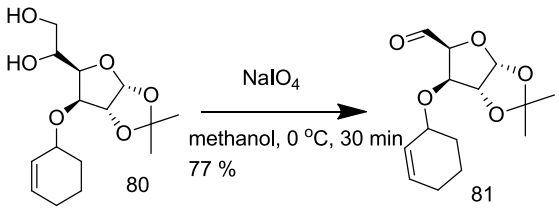
The compound **79** (1.00 g, 2.85 mmol) was subjected to selective deprotection following the procedure mentioned in the synthesis of **56**. Compound **80** was obtained as a viscous oily liquid (0.85 g, 96%).



^{1}HNMR ($CDCl_3$, 400MHz): δ ppm 5.93 (d, 1H, *J* = 3.6 Hz), 5.85 (m, 1H,), 5.76 (t like, 1H, *J* = 10 Hz, *J* = 12.4 Hz), 4.52 (d, 1H, *J* = 3.6 Hz), 4.32 (m, 2H), 4.15 (dd, 1H, J = 6.4, 8.4 Hz), 4.05 (dd, 1H, *J* =2.4, 7.6), 3.98 (dd, 1H, *J* = 5.2, 8.8 Hz), 1.96 (m, 2H), 1.79 (m, 4H), 1.69 (m, 1H), 1.49 (s, 3H), 1.44 (s, 3H).

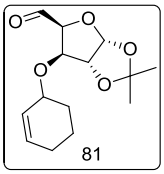
^{13}C NMR ($CDCl_3$, 100MHz): δ ppm 133.0 (CH), 127.0 (CH), 111.7 (CH), 105.1 (CH), 83.1 (CH), 80.4 (CH), 79.9 (CH), 71.8 (CH), 69.7 (CH_2), 64.5 (CH_2), 29.4 (CH_2), 27.9 (CH_2), 26.2 (CH_3), 25.1 (CH_3), 19.8 (CH_2).

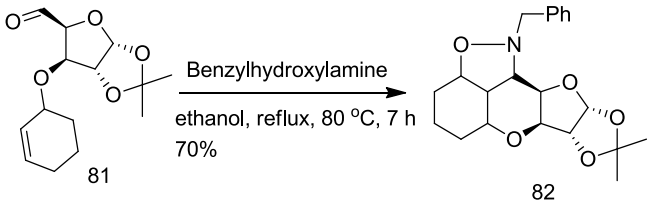
FTIR spectrum: ν_{max} (neat/cm^{-1}) 3425, 2986, 1454, 1080.



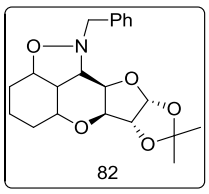
Compound **80** (0.80 g, 2.80 mmol) was subjected to oxidative cleavage by sodium metaperiodate following the procedure mentioned in the synthesis of **57**. Compound **81** was isolated as an oily colourless viscous liquid (0.55 g, 78 %).

FTIR spectrum: ν_{max} (neat/cm^{-1}) 2987, 1736, 1454, 1072.



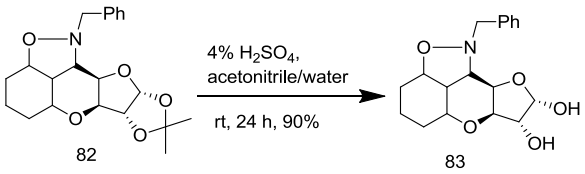


Compound **81** (0.50 g, 1.8 mmol) was dissolved in ethanol. To it benzylhydroxylamine (0.25 g, 2.0 mmol) was added. The mixture was set into reflux and the reaction progress was monitored via thin layer chromatography. After completion of the reaction the solvent was evaporated and the crude product was purified by column chromatography to obtain compound **82**[22] as a yellowish solid (0.48 g, 70%).



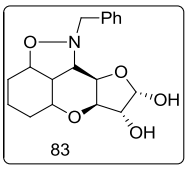
^{1}HNMR (CDCl3, 400MHz): δ ppm 7.4 (m, 5H), 6.32 (d, *J* = 4.0 Hz), 4.61 (d, *J* = 2.8 Hz), 4.6 (d, *J* = 4.4 Hz, 1H), 4.42 (d, *J* = 14.4 Hz, 1H), 4.19 (m, 2H), 4.14 (d, *J* = 3.6 Hz, 1H), 3.92 (d, *J* = 14.4 Hz, 1H), 3.06 (dd, *J* = 5.6, 13.2 Hz, 1H), 2.76 (m, 1H), 1.97 (m, 2H), 1.58 (s, 3H), 1.52 (s, 3H), 1.32 (m, 2H).

^{13}C NMR ($CDCl_3$, 100MHz): δ ppm 137.3 (C), 129.4 (CH), 128.3 (CH), 127.3 (CH), 112.1 (C), 106.4 (CH), 83.7 (CH), 83.1 (CH), 80.2 (CH), 75.2 (CH), 73.2 (CH), 66.2 (CH), 63.0 (CH_2), 42.7 (CH), 31.5 (CH_2), 29.0 (CH_2), 27.3 (CH_3), 26.7 (CH_3), 19.0 (CH_2).



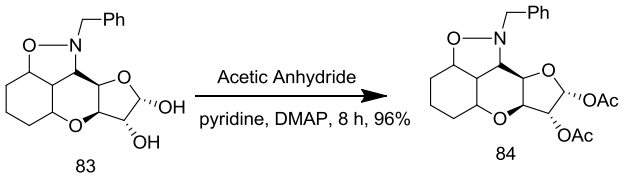
Compound **82** (0.3 g, 0.80 mmol) was deprotected in acidic media following afore mentioned procedure in the synthesis of **59**. Compound **83** was obtained as an oily viscous colorless liquid (0.24 g, 92 %).

The formed compound **83** is in hemiacetal form which can easily undergo anomerisation changing the stereochemistry of the –OH group at C-1 carbon resulting in formation of two anomers which is evident by the twin peaks present in ^{1}HNMR and ^{13}CNMR.



^{1}HNMR (CDCl3, 400MHz): δ ppm 7.44-7.23 (m, 5H), 5.28 (d, 1H, *J* = 18 Hz), 4.52 (s, 2H), 4.39 (d, 1H, *J* = 14.4 Hz), 4.17-4.09 (m, 2H), 4.02 (s, 1H), 3.94 (dd, 2H, *J* = 4.8 Hz, 9.6 Hz), 3.02 (dd, 1H, *J* = 4.8 Hz, 9.6 Hz), 2.55 (dt, 1H, *J* = 8.4 Hz, 13.2 Hz), 2.06 (m, 1H), 1.94 (s, 1H), 1.60 (s, 1H), 1.27-1.22 (m, 2H), 1.02 (m, 2H).

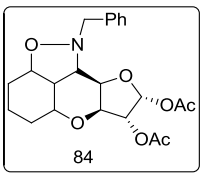
^{13}C NMR ($CDCl_3$, 100MHz): δ ppm 136.3 (C), 129.8 (CH), 128.2 (CH), 127.5 (CH), 96.2 (CH), 81.5 (CH), 79.8 (CH), 77.4 (CH), 75.4 (CH), 72.2 (CH), 66.6 (CH), 64.4 (CH_2), 42.7 (CH), 31.4 (CH_2), 29.2 (CH_2), 18.6 (CH_2).



83 84

The acetylation of compound **83** (0.20 g, 0.60 mmol) was achieved following the procedure in the synthesis of **60**. Compound **84** was obtained as a white amorphous solid (0.24 g, 96%).

The acetylated product **84** is synthesized from **83** which anomerises rapidly. Therefore acetylation also yields two anomers that could not be separated via column chromatography owing to their very similar polar nature.



84

^{1}HNMR (CDCl3, 400MHz): δ ppm 7.42 (d, 2H, *J* = 7.2 Hz), 7.36-7.27 (m, 3H), 6.56 (d, 1H, *J* = 9.6 Hz), 5.81 (d, 1H, *J* = 9.6 Hz), 5.09 (d, 1H, *J* = 10.4 Hz), 4.46 (m, 2H), 4.23 (dd, 2H, *J* = 8.8 Hz, 16.8 Hz), 4.18 (m, 2H), 3.00 (dd, 1H, *J* = 6.4 Hz, 13.2 Hz), 2.70 (dt, 1H, *J* = 8 Hz, 13.6 Hz), 2.13 (s, 3H), 2.02 (s, 3H), 1.18-1.02 (m, 4H).

^{13}C NMR ($CDCl_3$, 100MHz): δ ppm 169.7 (C), 169.3 (C), 136.3 (C), 129.9 (CH), 128.2 (CH), 127.3 (CH), 95.9 (CH), 83.6 (CH), 82.6 (CH), 78.8 (CH), 78.2 (CH), 76.2 (CH), 74.7 (CH), 65.1 (CH), 62.1 (CH_2), 42.4 (CH), 31.3 (CH_2), 29.4 (CH_2), 20.9 (CH_3), 18.7 (CH_3).

4.1 Results and Discussions

The synthesis of 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose **54** was achieved via a reported procedure[20] using iodine as a catalyst and acetone to protect D-Glucose. The ^{1}HNMR and ^{13}CNMR spectrum of **54** corroborated to the reported spectrum

The hydroxyl group at C-3 of **54** was subjected to *O*-dimethylallylation with 3,3-dimethylallylbromide and aqueous sodium hydroxide solution with tetrabutylammoniumbromide as the phase transfer catalyst. The allylation of the hydroxyl group at C-3 by 3,3-dimethylallyl group was confirmed by the disappearance of the broad singlet at δ 2.98 ppm in ^{1}HNMR spectrum. The appearance of two singlets at δ 1.65 and 1.72 ppm for 3 protons each correspond to the protons of two methyl peaks of the isoprenyl group. A triplet at δ 5.29 ppm represents the proton attached to the olefinic of the isoprenyl. In ^{13}CNMR spectrum two peaks at δ 137.6 and 120.5 ppm represent two olefinic carbons of the isoprenyl group. The appearance of two peaks at δ 25.3 and 17.9 ppm representing the two methyl peaks of isoprenyl group also confirmed the formation of **55**. Selective deprotection by mild acid of the thermodynamically less stable 5,6-isoprpylidene protection of **55** led to the formation of a diol **56**. The formation of **56** was confirmed by the disappearance of two singlets at δ 1.32 and 1.29 ppm in the ^{1}HNMR spectrum. The appearance of a singlet at δ 2.32 ppm for two protons, one for each hydroxyl group also supported the formation of the diol. In ^{13}CNMR spectrum the absence of peaks at δ 108.8 ppm representing the quaternary carbon and at δ 26.7 and 26.1 ppm representing the methyl groups of the 5,6-isopropylidene protection respectively also supported the formation of **56**. A broad peak at 3418 cm^{-1} in the FTIR spectrum also confirmed the conversion of **55** to diol. Compound **56** was subjected to oxidative cleavage by sodium metaperiodate which resulted in the formation of the aldehyde **57**. The formation of the aldehyde was confirmed by the presence of the characteristic aldehyde peak at 1728 cm^{-1} in FTIR spectrum and a peak at δ 210.3 ppm in ^{13}CNMR spectrum. When compound **57** was refluxed with benzylhydroxylamine in ethanol, three spots were observed in the thin layer chromatography which indicated the generation of three new products. After purification and isolation these three products were characterized using ^{1}HNMR, ^{13}CNMR and single crystal XRD. The disappearance of a triplet δ 5.34 ppm reflected the absence of a carbon-carbon double bond. The appearance of a multiplet from δ 7.4 to 7.2 ppm in ^{1}HNMR spectrum confirmed incorporation of singly substituted benzene

ring in all three products. Along with the multiplet the presence of two doublets at δ 4.25 and 4.12 ppm for **58a**, δ 4.36 and 3.91 ppm for **58b**, δ 4.33 and 4.00 ppm for **58c** confirmed the addition of *N*-benzyl group. The presence of a doublet of triplet at δ 2.44 ppm for **58a**, δ2.50 ppm for **58b** and δ2.65 ppm for **58c** representing one proton in each of the three products suggested the formation of a cyclized structure. The fact is also supported by the appearance of a triplet at δ 3.60 ppm for **58a**, δ 3.80 ppm for **58b** and δ 3.37 ppm for **58c** corresponding to one proton . In ^{13}CNMR the absence of a peak at δ 120.9 ppm for a double bonded carbon suggested the disappearance of the double bond. Further the appearance of peaks near δ 129, 128, 127 and 66 ppm corresponding to the *N*-benzyl group confirmed the formation **58a**, **58b**, and **58c**. The single crystal X-ray diffraction studies revealed that generation of different products was not due to the region selectivity of nitrone cycloaddition but due to the difference in stereochemistry of mode of addition of the isoxazolidine ring with the pyran ring as shown in figure below.

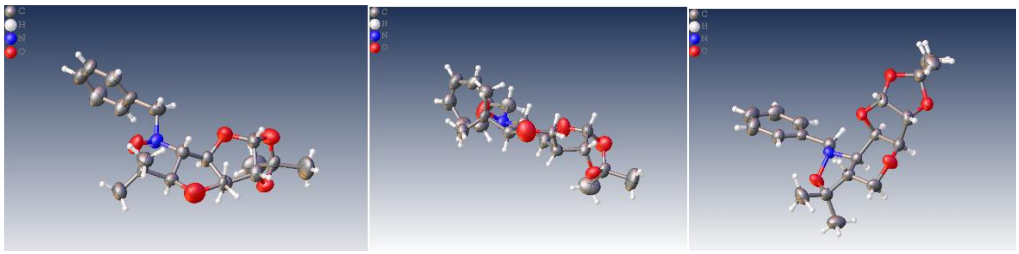


Fig. 2: ORTEP diagrams of compounds **58a**, **58b** and **58c**

Further modification of the cyclized adduct **58a** was performed to bring further structural diversity. Deprotection of the 1,2-isoprpopylidene protection of compound **58a** with 4% sulphuric acid in acetonitrile and water led to the formation of **59**. The disappearance of two methyl singlets corresponding to 1,2-isoprpopylidene protection at δ 1.32 and 1.31 ppm in ^{1}HNMR spectrum confirmed the formation of **59**. Also the absence of a peak at δ 5.83 ppm representing the proton at C-1 further confirmed the information. Two ^{13}CNMR peaks at δ 26.6 and 26.1 ppm representing the two carbon of the methyl peaks of the 1,2-isoprpopylidene protection were absent. Corresponding to their absence the peak at δ 111.6 ppm representing the quaternary carbon of the protection was also noted. Compound **59** contains a hemiacetal ring which can rapidly anomerise, a phenomenon that causes the hydroxyl group at C-1 to rapidly change its stereochemistry. This results in the formation of two anomers showing twin peaks in both ^{1}HNMR and^{13}CNMR spectrum. Acetylation of the two hydroxyl group of

compound **59** with acetic anhydride in pyridine along with catalytic 4,4-dimethylaminopyridine was found to successful as indicated by the ^{1}HNMR and ^{13}CNMR data. The appearance of two new singlets at δ2.12 and 2.02 ppm in the ^{1}HNMR spectrum for six protons of the two methyl groups of the acetyl protection confirmed the formation of **60**. The presence of a new peak at δ 169.3 ppm in ^{13}CNMR spectrum for C=O and two peaks at δ 29.7 and 29.5 ppm for the two methyl carbons assured that compound **60** was formed. The synthesis of nucleoside analogue of **58a** was achieved by treating compound **60** with 2,4-bis((trimethylsilyl)oxy)pyrimidine (formed by refluxing uracil with hexamethyldisilagen with trimethylsilyl chloride as catalyst) and triflic acid. The formation of the nucleoside analogue **61** was confirmed by the presence of new peaks at δ 9.25 ppm in ^{1}HNMR spectrum corresponding to the single proton of the –NH group and at δ 7.70 and 5.80 ppm for one proton each representing the two hydrogen of the carbon-carbon double bond of the uracil moiety. The disappearance of a singlet at δ 2.02 ppm for three protons associated with the methyl group of acetyl protection also suggested the formation of the nucleoside analogue. In ^{13}CNMR spectrum the two new peaks at δ 162.4 and 149.9 for two carbonyl carbons (one for each C=O group of the uracil ring) was observed. Further the appearance of two more peaks at δ 140.7 and 103.4 ppm corresponding to two CH groups of the carbon-carbon double bond confirmed the formation of **61**.

The hydroxyl group of C-3 carbon of **54** was protected by 4-methoxybenzyl group to form compound **62.** The success of the reaction was confirmed by the disappearance of the singlet at δ 2.98 ppm in ^{1}HNMR spectrum. The presence of two doublets at δ 7.26 and 6.87 ppm, characteristic of a para substituted phenyl ring also supported the success of the synthesis. A singlet at δ 3.78 ppm for three protons characteristic of an *O*-methyl group also confirmed the incorporation. The formation was also supported by the presence of peaks at δ 159.3, 129.6, 129.3, and 113.7 ppm in ^{13}CNMR, characteristic of a para substituted phenyl ring. A singlet at δ 55.2 ppm corresponding to the *O*-methyl group also confirmed the formation of **62.** Selective deprotection of 5,6-isopropylidene protetion **62** resulted in the formation of diol **63.** The disappearance of two singlets at δ 1.42 and 1.37 ppm in ^{1}HNMR confirmed the removal of the methyl peaks of 5,6-isopropylidene protetion. A broad singlet at δ 2.87 for two protons verified the formation of the diol. The absence of a peak at nδ 108.9 ppm in ^{13}CNMR corresponding to the tertiary carbon of the protection, and the disappearance of two peaks at δ 26.8

and 26.7 ppm for two methyl peaks of the protection also confirmed the formation of **63**. The conversion of the diol to aldehyde **64** by subjecting **63** to oxidative cleavage was confirmed by the presence of a characteristic peak at 1737 cm^{-1} in the FTIR spectrum. The reduction of the aldehyde was carried out using sodium borohydride. The formation of **65** was confirmed by the presence of a peak at δ 2.20 ppm in ^{1}HNMR spectrum. The absence any characteristic peak of an aldehyde was also noted. Compound **65** was allylated with 3,3-dimethyallylbromide using sodium hydroxide solution as a base and tetrabutylammoniumbromide as a phase transfer catalyst. This resulted in the formation of **66** which was confirmed by the presence of a triplet at δ 5.35 ppm in ^{1}HNMR for one proton representing the hydrogen of CH group of the olefinic carbon of the isoprenyl group. The appearance of two new peaks at δ 1.75 and 1.68 ppm for six protons corresponding to the methyl groups of the dimethylallyl group also verified its formation. In ^{13}CNMR the presence of a peak at δ 137.2 ppm for the quaternary carbon and δ 121.1 ppm for the CH carbon of the double bond was noted. This coupled with the appearance of two peaks δ 26.0 and 18.2 ppm confirmed the formation of **66**. Deprotection of the 4-methoxybenzyl group was perfomed using 2,3-dichloro-5,6-dicyano-p-benzoquinone which resulted in formation of **67**. Its formation was confirmed by the absence of the characteristic doublets at δ 7.24 and 6.82 ppm for the phenyl ring and δ 3.81 ppm for the *O*-methyl group in ^{1}HNMR spectrum. The disappearance of peaks at δ 159.5, 129.8, 129.4 and 114.7 ppm for the carbons of the phenyl ring and at δ 55.4 ppm for the carbon of the *O*-methyl group was also noted in the ^{13}CNMR spectrum. These data contributed in the confirmation of formation of **67**. The hydroxyl group at C-3 carbon of **67** was oxidized to ketone by pyridiniumchlorochromate (PCC) to obtain **68** whose formation was confirmed by the presence of a peak at δ 210.1 ppm in the ^{13}CNMR and a characteristic peak at 1736 cm^{-1} in FTIR spectrum. Refluxing compound **68** with benzylhydroxylamine in ethanol led to the formation of **69**. The disappearance of a peak at δ 210.1 ppm in the ^{13}CNMR spectrum and the appearance of peaks at δ 129.2, 129.0 and 128.4 ppm suggested the presence of a phenyl ring. The presence of a multiplet at δ 7.50-7.36 ppm for five protons along with a doublet at δ 5.37 ppm ^{1}HNMR confirmed the presence of benzyl group. The appearance of a doublet of triplet at δ 3.93 ppm and a doublet of doublet at δ 3.57 ppm indicated the formation of a cyclized product **69**. The NOESY spectrum of compound **69** showed cross peaks between protons at δ 7.5-7.4 ppm representing the protons of the phenyl ring and at δ 1.7-1.5 ppm corresponding to the protons of four

methyl peaks indicating that the phenyl ring and the methyl peaks are oriented in the same direction in space. The information from the NOESY spectrum confirmed that the newly formed isoxazolidine ring has the same orientation as that of the 1,2-isopropylidene ring.

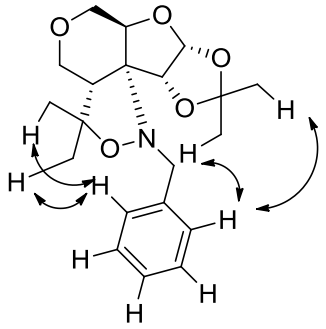


Fig. 3: Spatial interaction of the protons as seen in NOESY spectrum

The oxidation of hydroxyl group at C-3 of compound **54** by pyridiniumchlorochromate (PCC) and its subsequent purification led to the formation of 5,6-deprocteted ketone **71**. The formation of the deprotected ketone was characterized by the appearance of peak at δ 210.1 ppm in the ^{13}CNMR and the disappearance of two singlets at δ 1.36 and 1.31 ppm for six protons representing the two methyl peaks of the 5,6-protection in ^{1}HNMR. The treatment of ketone to allylamine in dry dichloromethane led to formation of compound **72**. The confirmation of its formation was provided by the presence of a multiplet at δ 5.92 ppm for one proton and two doublets of doublets at δ 5.23 and 5.10 ppm each for one proton in ^{1}HNMR. On reduction by sodium borohydride compound **72** yielded a secondary amine **73**. The formation of **73** was confirmed by the presence of two doublets of doublets at δ 3.26 and 3.20 ppm for one proton each corresponding to a proton at C-3 carbon and a NH proton respectively. The presence of a new peak at δ 62.9 ppm for a CH carbon in ^{13}CNMR also confirmed the formation of **73.** Conversion of the diol to aldehyde via oxidative cleavage led to formation of an aldehyde **74.** The presence of a characteristic aldehyde peak at 1666 cm^{-1} in the FTIR spectrum confirmed its formation. The aldehyde **74** was refluxed with benzylhydroxylamine in ethanol leading to synthesis of a seven membered bridged heterocycle **75**[21]. The formation of the heterocycle was confirmed by presence of a multiplet at δ 2.47 ppm for one proton and a doublet at δ 1.88 ppm for one proton in the ^{1}HNMR. The presence of a multiplet at δ 7.39-7.23 ppm for five protons along with two doublets at δ 4.04 and 3.86 ppm confirmed the incorporation of benzyl group. In ^{13}CNMR the presence of peaks at δ

136.9, 129.0, 128.4 and 127.4 ppm indicated the presence of benzyl group. The presence of a peak at δ 29.7 ppm corresponding to the bridge-head carbon was also noted. Allylation of the -NH proton of **75** was carried out using sodium hydride as a base in dry tetrahydrofuran and treating with allylbromide. The successful formation of the allylated product **76** was confirmed by the presence of a multiplet for one proton at δ 5.92 ppm (characteristic of an allyl group) in ^{1}HNMR spectrum. The appearance of two peaks at δ 134.5 and 118.2 ppm ^{13}CNMR spectrum representing the two carbons of the double bond also verified the formation of **76.** Deprotection of compound **76** with 8% sulphuric acid in acetonitrile and water led to the formation of the hemiacetal **77**, showing characteristic peaks at 3355 and 1659 cm^{-1} in the FTIR spectrum. The formed hemiacetal was refluxed with benzylhydroxylamine in ethanol, which led to formation of polyheterocycle **78**. The disappearance of a multiplet at δ 5.92 ppm ^{1}HNMR spectrum for one proton (characteristic of allyl peak) suggested the formation of the compound. Multiplet at δ7.40-7.30 ppm for ten protons suggested the presence of two phenyl rings. The presence of a doublet of doublet at δ 2.36 ppm for one proton suggested the presence of only one bridge-head in the heterocycle. The indication therefore predicted the presence of a fused system along with a bridge-head. The presence of a fused system is also supported by the ^{13}CNMR spectrum. At δ 28.6 ppm a single for the bridge-head carbon is noted and a peak δ 43.1 ppm corresponds to the carbon fused to nitrogen of the azepane ring. All the above facts indicate the formation of a heterocycle with newly formed six membered ring fused to the previously formed seven membered bridged heterocycle.

The –OH group at C-3 Carbon of **54** was subjected to cyclic allylation with 3-bromocyclohexene to obtain **79**. The formation of **79** was confirmed by the disappearance of hydroxyl peak at δ 2.98 ppm in ^{1}HNMR spectrum and the appearance of characteristic peak for allylic proton at δ 5.76 and a pair doublet of doublets at δ 5.85 and 5.87 ppm. The appearance of multiple peaks in the region δ 1.5- 2.1 ppm further confirmed the formation of **79**. Selective deprotection of 5,6 position of compound **79** yielded compound **80**. The formation of compound **80** was confirmed by the presence of two instead of four 3H singlets for methyl groups between δ 1.3 and 1.5 ppm in ^{1}HNMR spectrum. Oxidative cleavage by sodium metaperiodate of the diol **80** resulted in formation of compound **81**. Compound **81** was refluxed with benzylhydroxylamine in ethanol to compound **82**[22]. The absence of the characteristic peak for allylic double

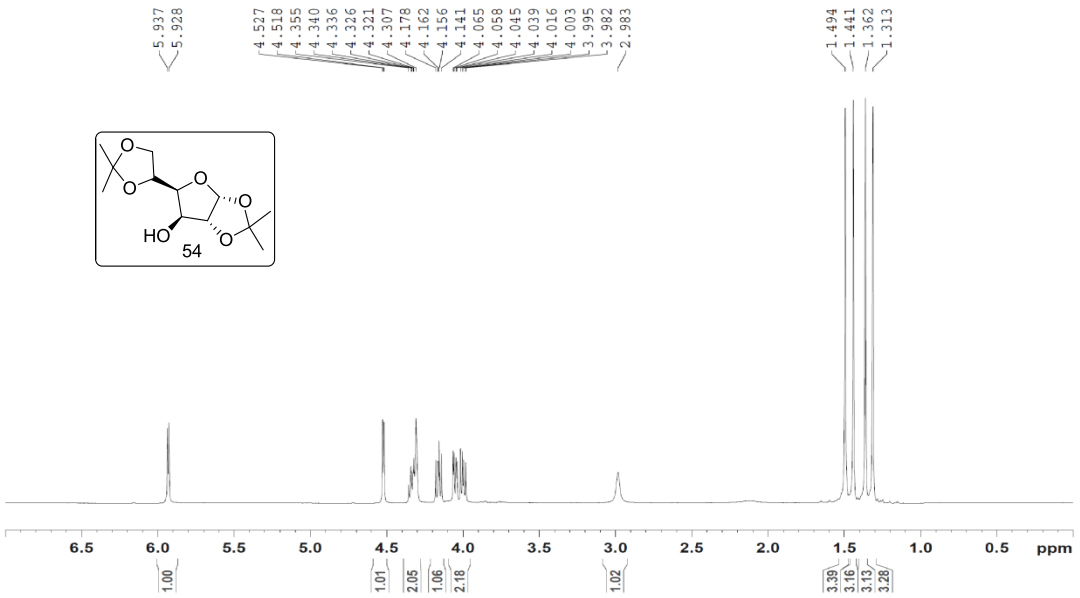
bond at δ 5.85 and 5.87 ppm ^{1}HNMR spectrum confirmed the formation of **82.** Further the presence of multiplet at δ 2.7 ppm , a doublet of doublet at δ 3.05 ppm (J = 5.6, 13.2 Hz) and a doublet at δ 4.1 and 4.4 ppm (J = 14.4 Hz) in ^{1}HNMR. The formation of compound **82** is further confirmed by the presence of a multiplet at δ 7.5 ppm, a characteristic peak of phenyl moiety ^{1}HNMR spectrum. The deprotection of **82** in acidic medium led to the formation of **83** a hemiacetal. The formation of **83** was confirmed by the absence of two singlets at δ 1.35 and δ 1.29 ppm in the ^{1}HNMR spectrum. Further the disappearance of a doublet at δ 5.91 (J = 3.6 Hz), characteristic of a proton at C-1 was also noted. The absence of two peaks at δ 27.5 and 26.5 ppm in the ^{13}CNMR spectrum also corroborated the formation of **83**. Acetylation of compound **83** by treating with acetic anhydride led to the formation of **84.** The presence of two singlets at δ 2.13 and 2.02 ppm for six protons in the ^{1}HNMR spectrum corresponding to the methyl groups of the acetyl protection suggested formation of the product. In ^{13}CNMR spectrum the presence of two peaks at δ 169.7 and 169.3 ppm representing the carbonyl carbon of the two acetyl groups and two peaks at δ 20.9 and 18.7 ppm for the carbon of methyl groups of the acetyl protection confirmed the formation of **84**.

The compounds synthesized in various steps were purified via column chromatography. The progress and completion of the reactions were monitored and confirmed by thin layer chromatography. All the formed compounds and intermediates were characterized by ^{1}HNMR, ^{13}CNMR, FTIR, single crystal XRD etc. wherever necessary. The ortep diagrams of the crystal were solved and obtained using OLEX2 (v.1.2)[23].

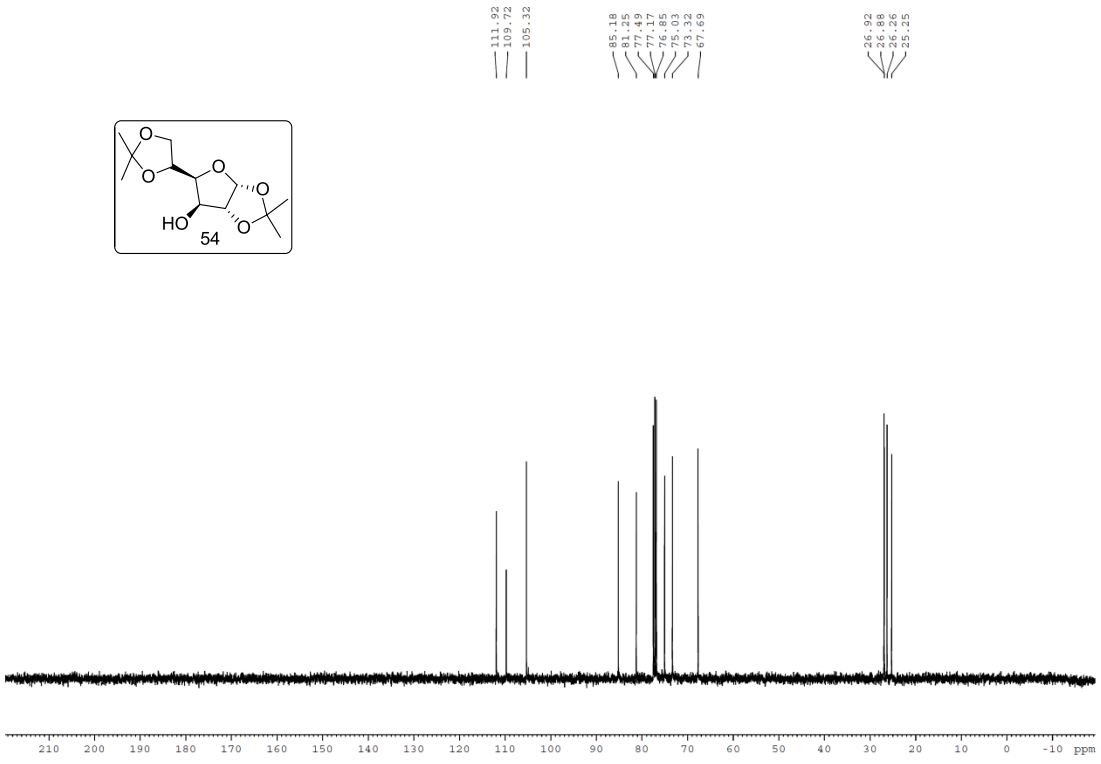
5.1 Conclusion and Future prospects

Seven different complex nitrogen containing chiral polyheterocycles have been successfully using simple nitrone cycloaddition as a synthetic tool. The stereochemistry of the newly generated chiral centers was unequivocally determined using 2-D NMR spectroscopy and single crystal X-ray diffraction. Some of the chiral polyheterocycles have been subsequently modified to nucleosides. Further synthesis and diversification of the generated nitrogen containing polyheterocycles are in progress in our laboratory.

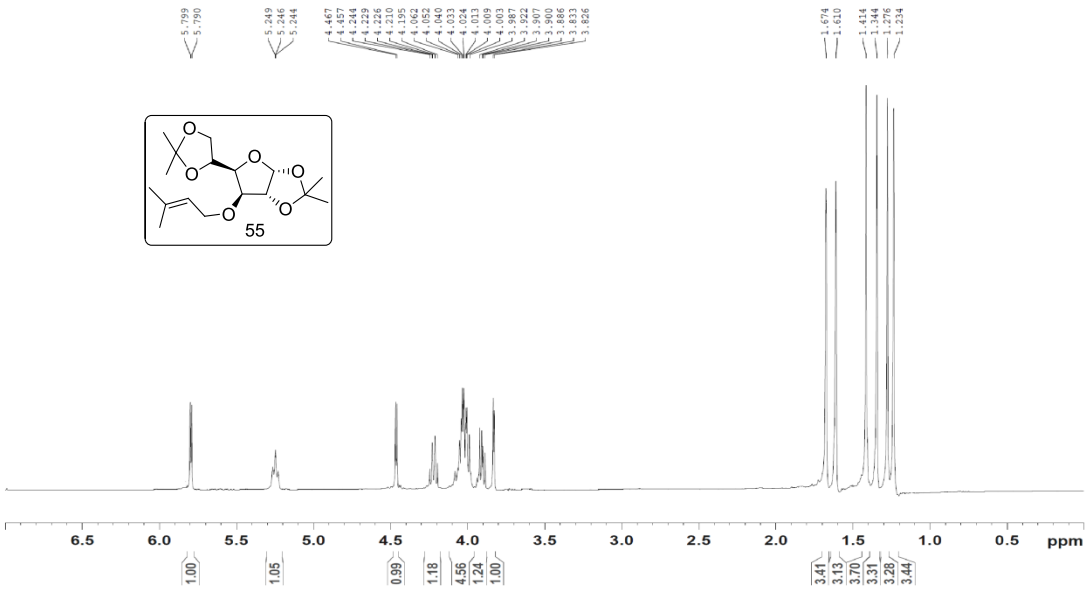
5.2 Spectra



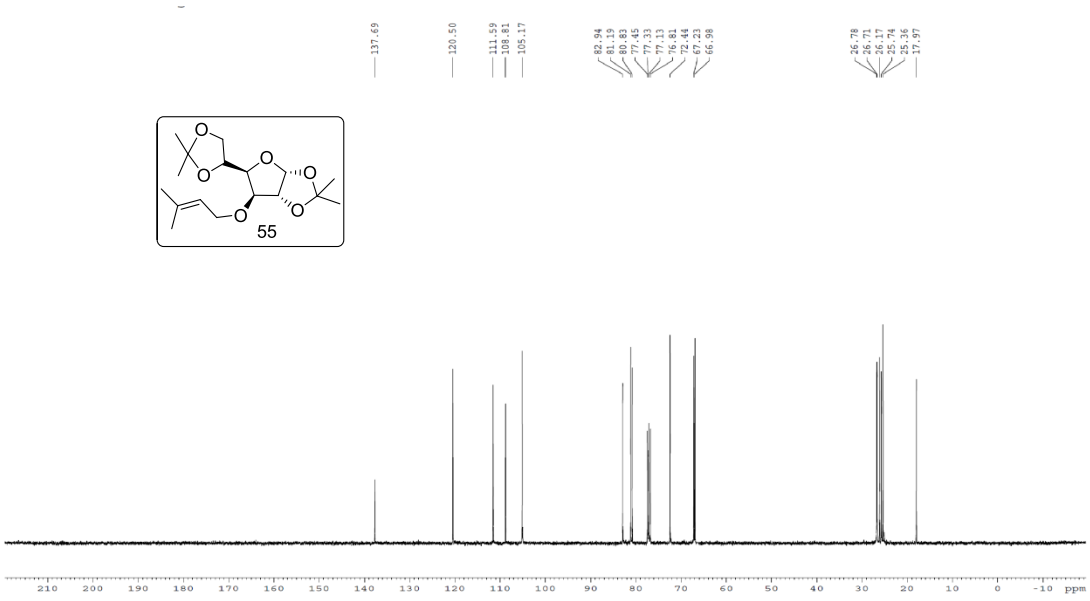
^{1}H NMR ($CDCl_3$, 400MHz) Spectrum of Compound 54



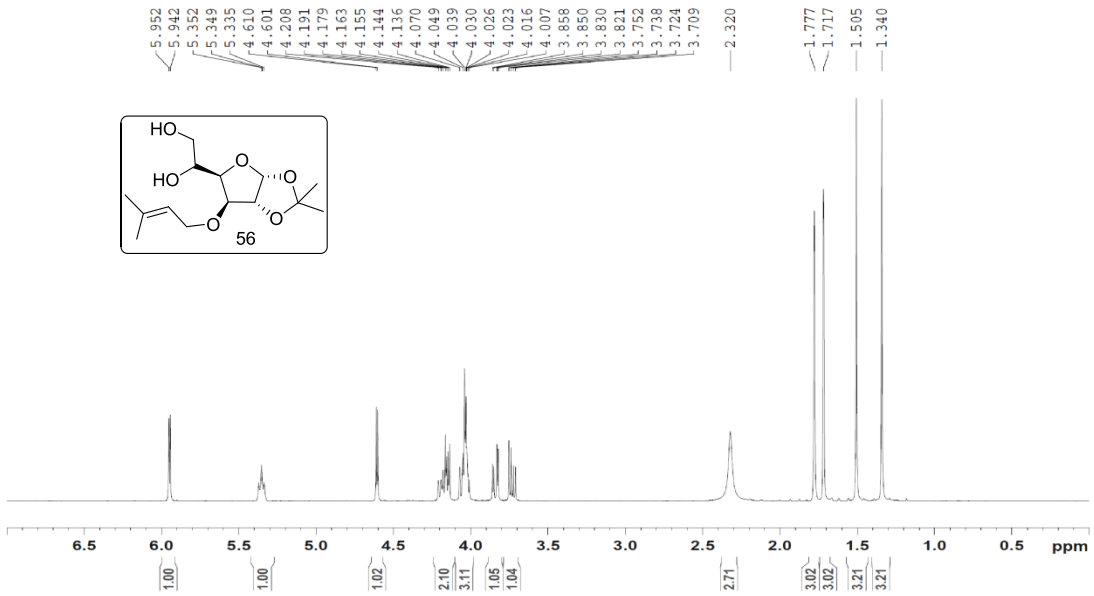
^{13}C NMR ($CDCl_3$, 100MHz) Spectrum of Compound 54



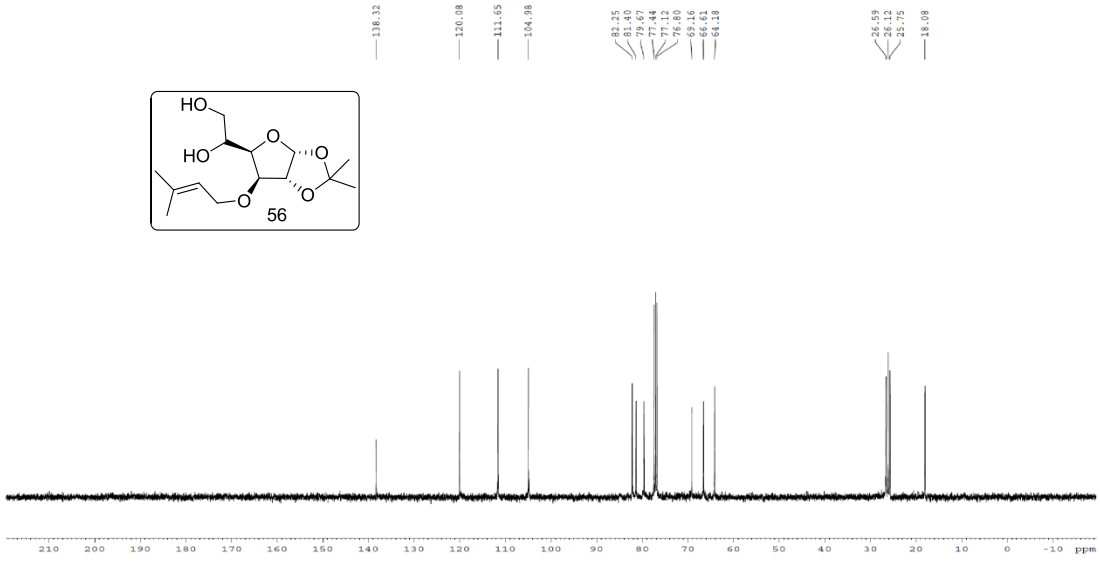
^{1}H NMR ($CDCl_3$, 400MHz) Spectrum of Compound 55



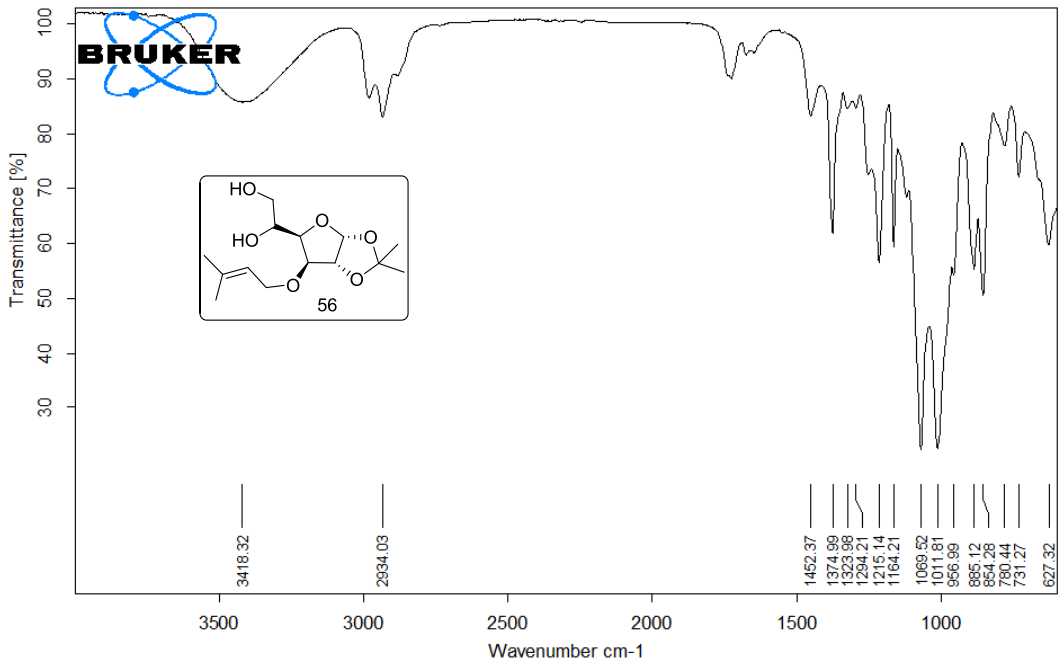
^{13}C NMR ($CDCl_3$, 100MHz) Spectrum of Compound 55



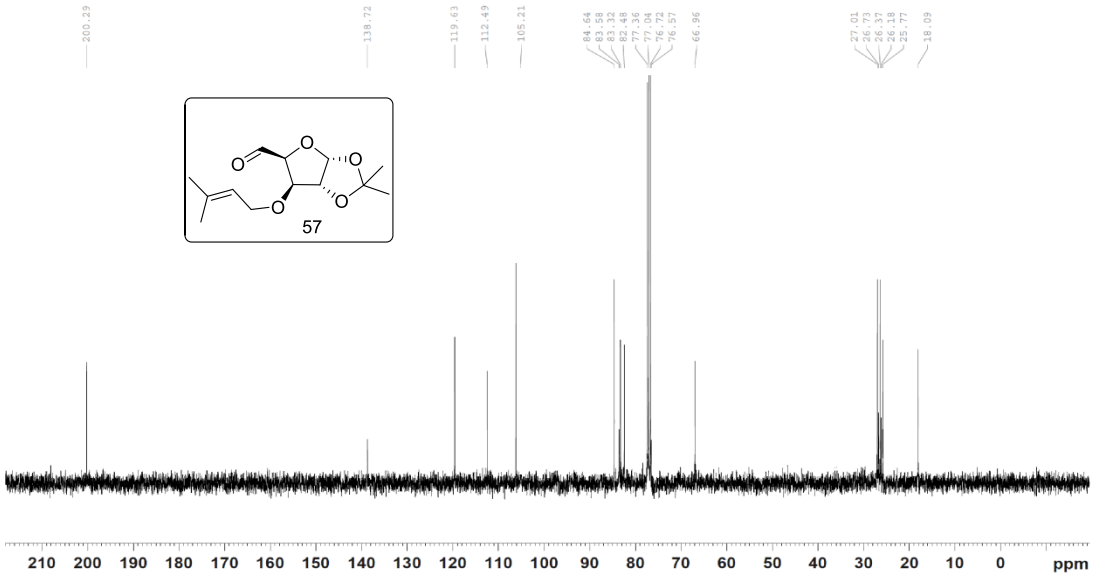
^{1}H NMR ($CDCl_3$, 400MHz) Spectrum of Compound 56



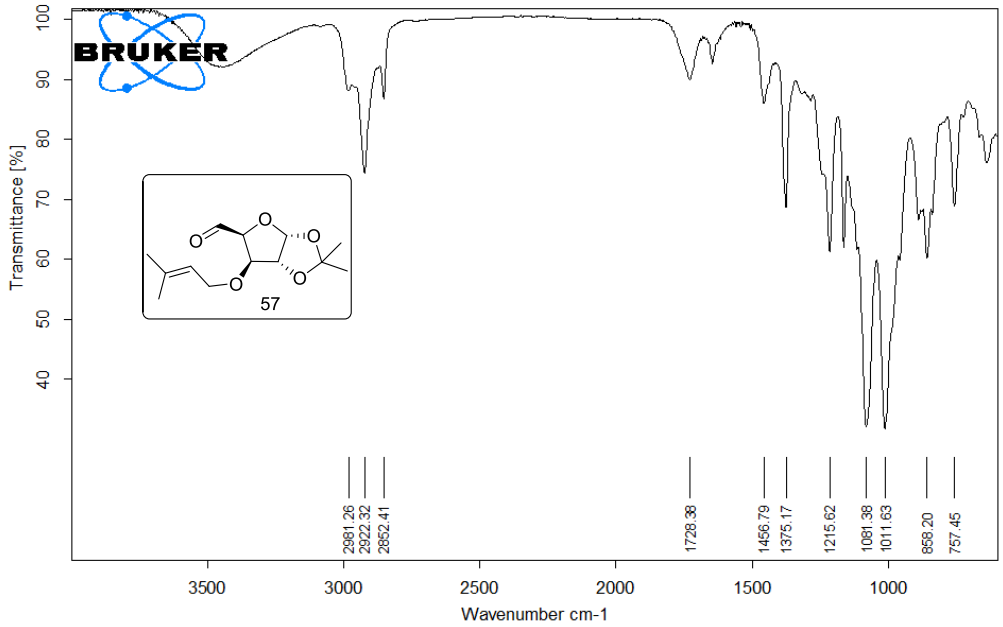
^{13}C NMR ($CDCl_3$, 100MHz) Spectrum of Compound 56



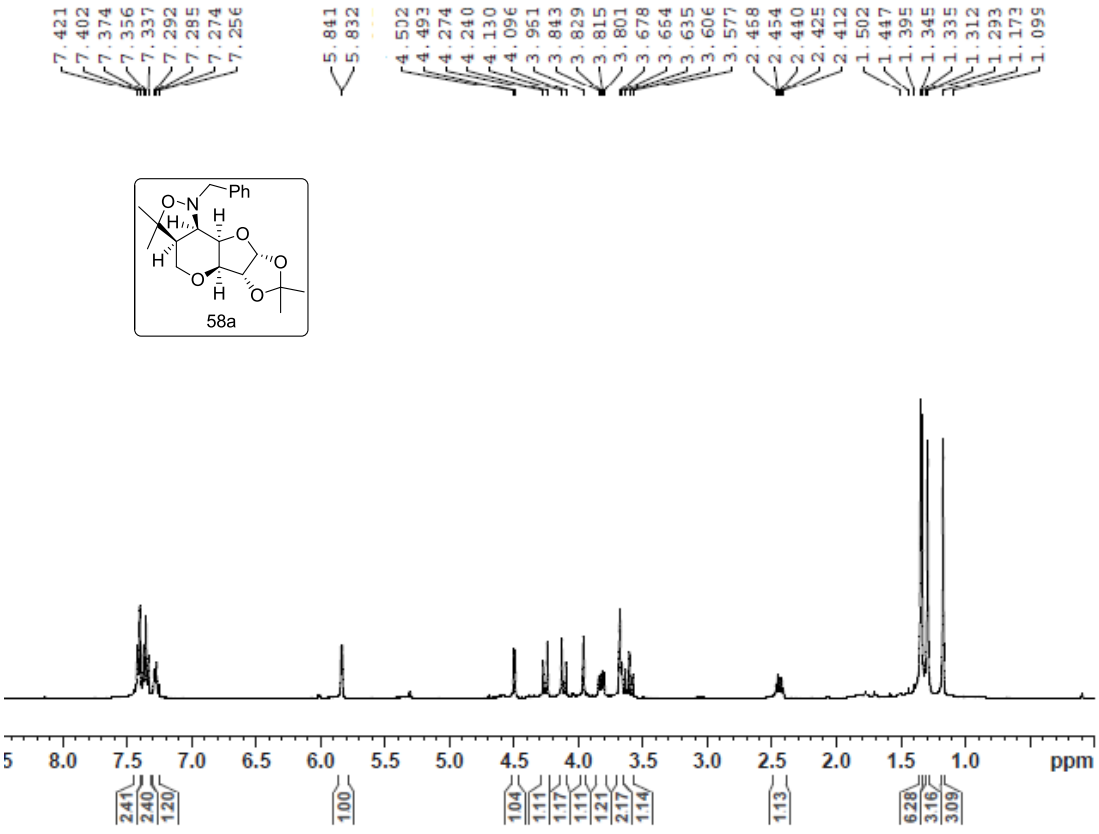
FTIR Spectrum: ν_{max} (neat)/cm^{-1} of Compound 56



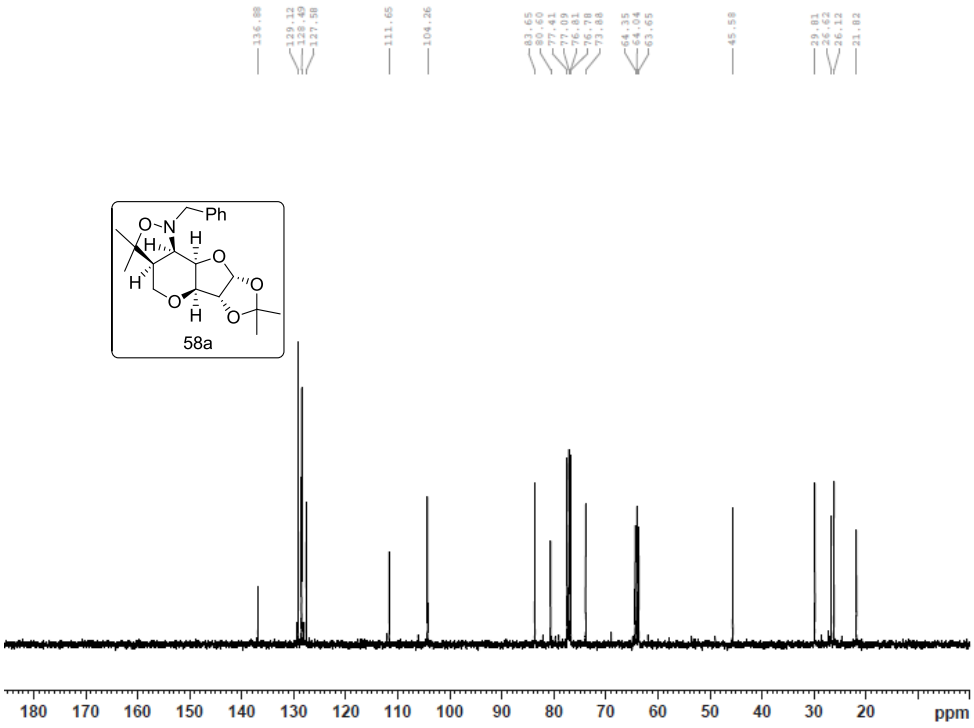
^{13}C NMR ($CDCl_3$, 100MHz) Spectrum of Compound 57



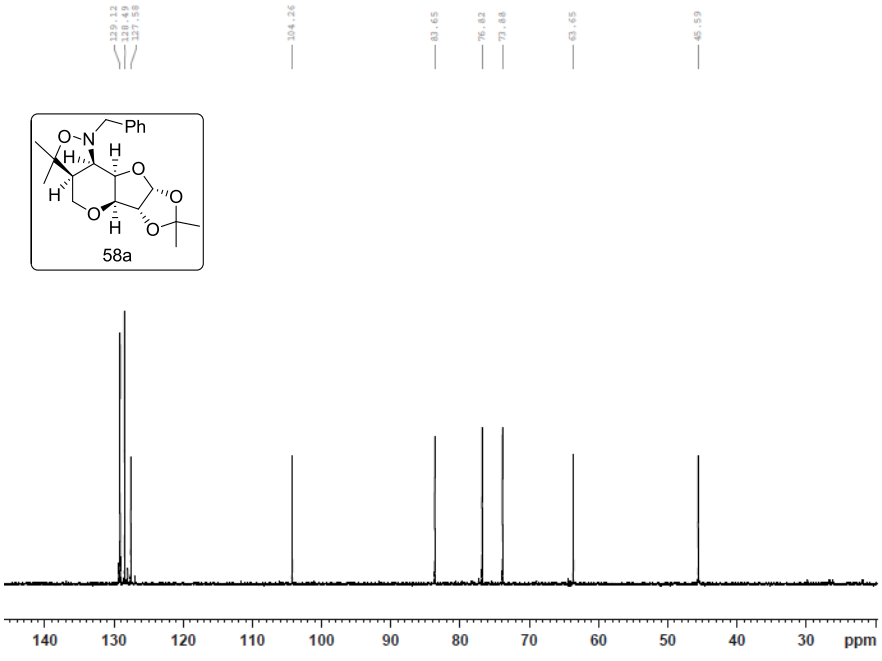
FTIR Spectrum: ν_{max} (neat)/cm^{-1} of Compound 57



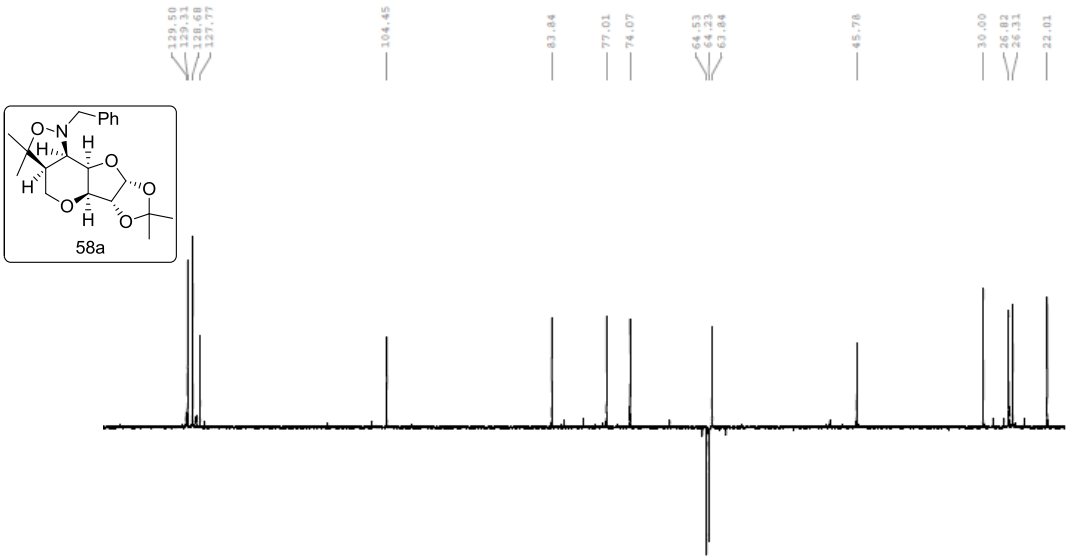
^{1}H NMR ($CDCl_3$, 400MHz) Spectrum of Compound 58a



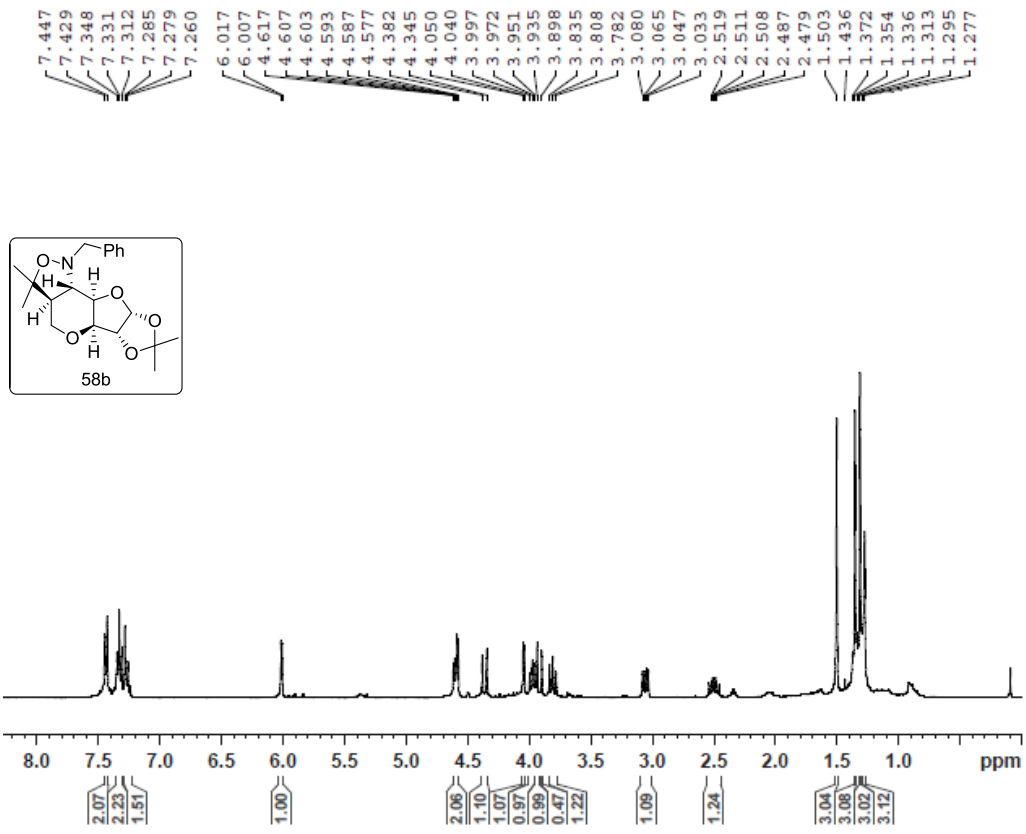
^{13}C NMR ($CDCl_3$, 100MHz) Spectrum of Compound 58a



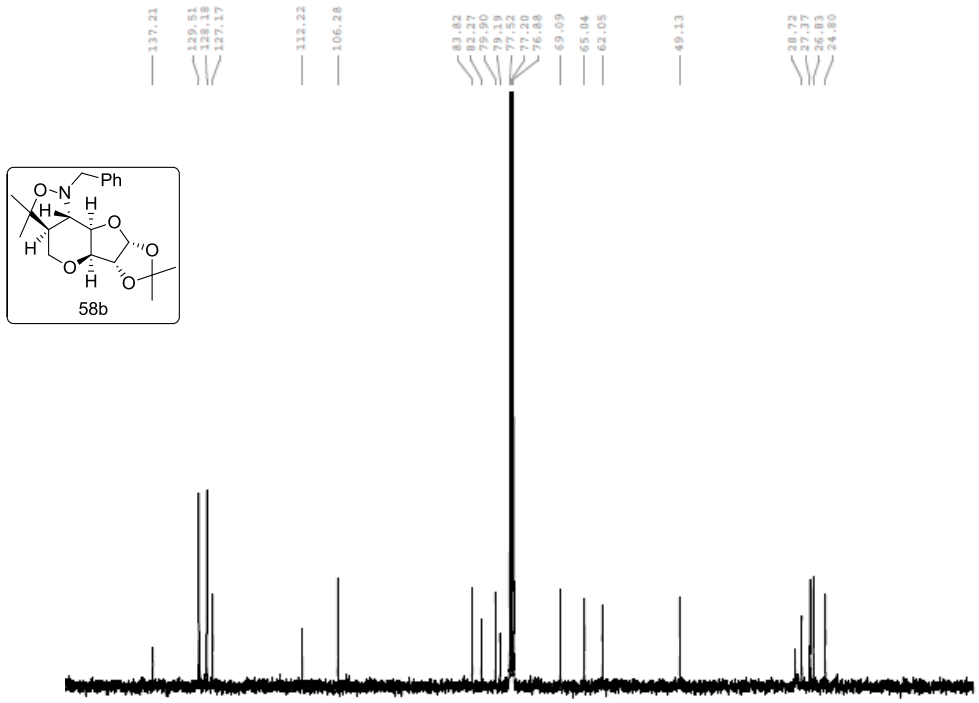
DEPT 90 ($CDCl_3$, 100MHz) Spectrum of Compound 58a



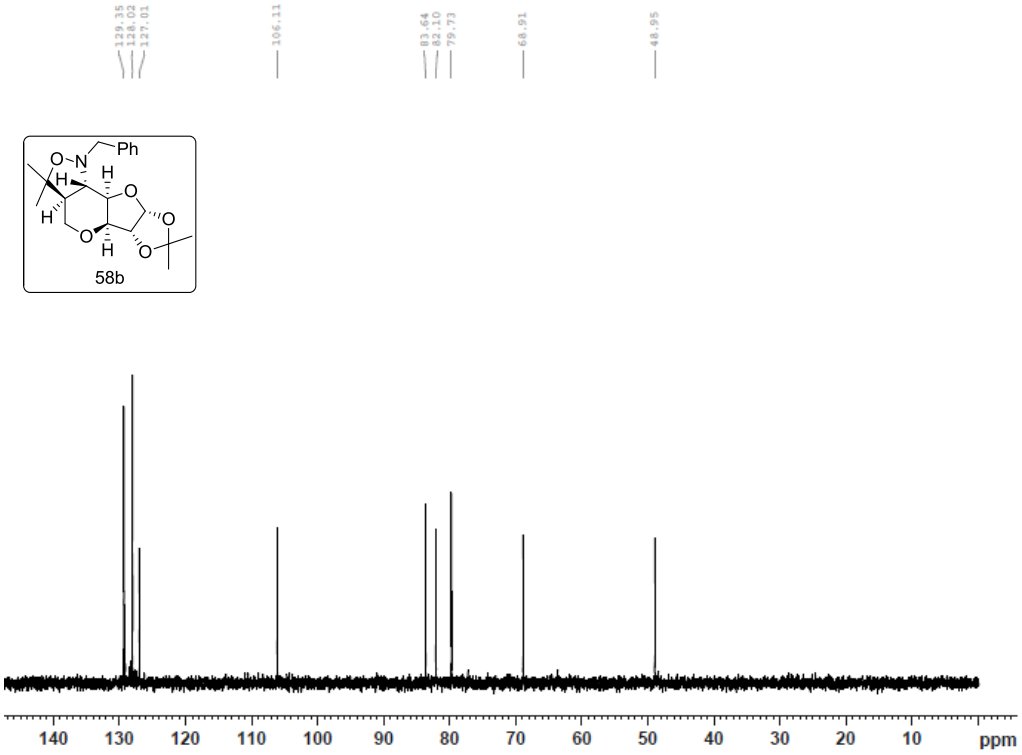
DEPT 135 ($CDCl_3$, 100MHz) Spectrum of Compound 58a



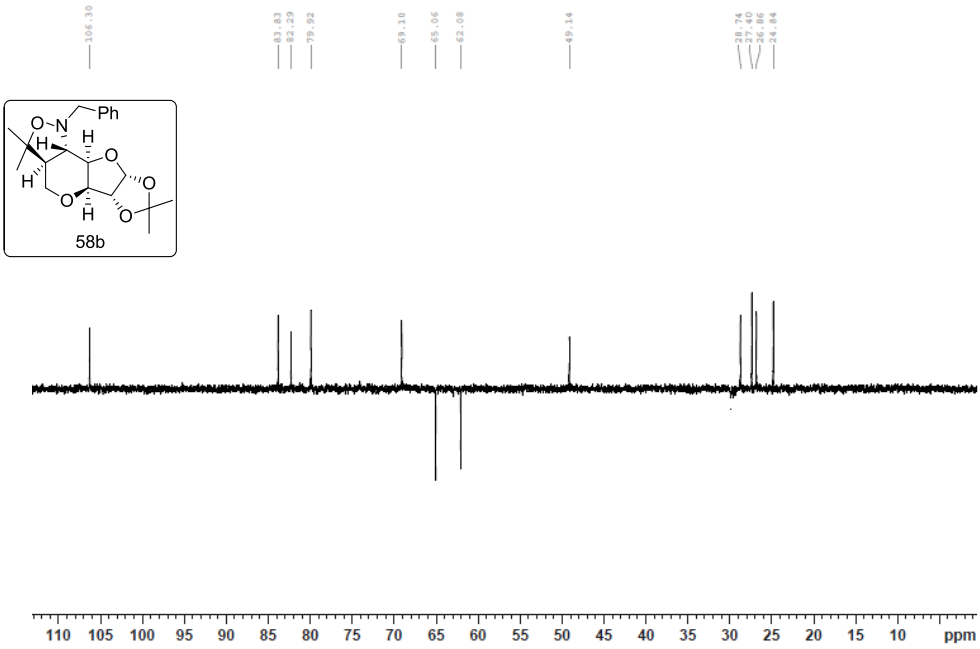
^{1}H NMR ($CDCl_3$, 400MHz) Spectrum of Compound 58b



^{13}C NMR ($CDCl_3$, 100MHz) Spectrum of Compound 58b



DEPT 90 ($CDCl_3$, 100MHz) Spectrum of Compound 58b



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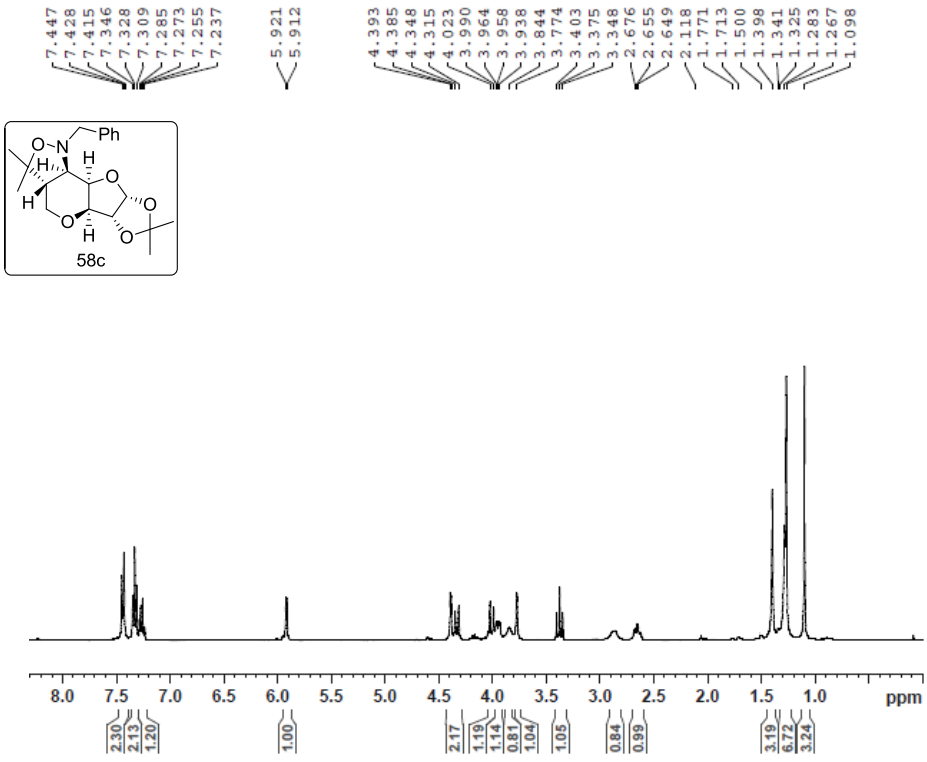
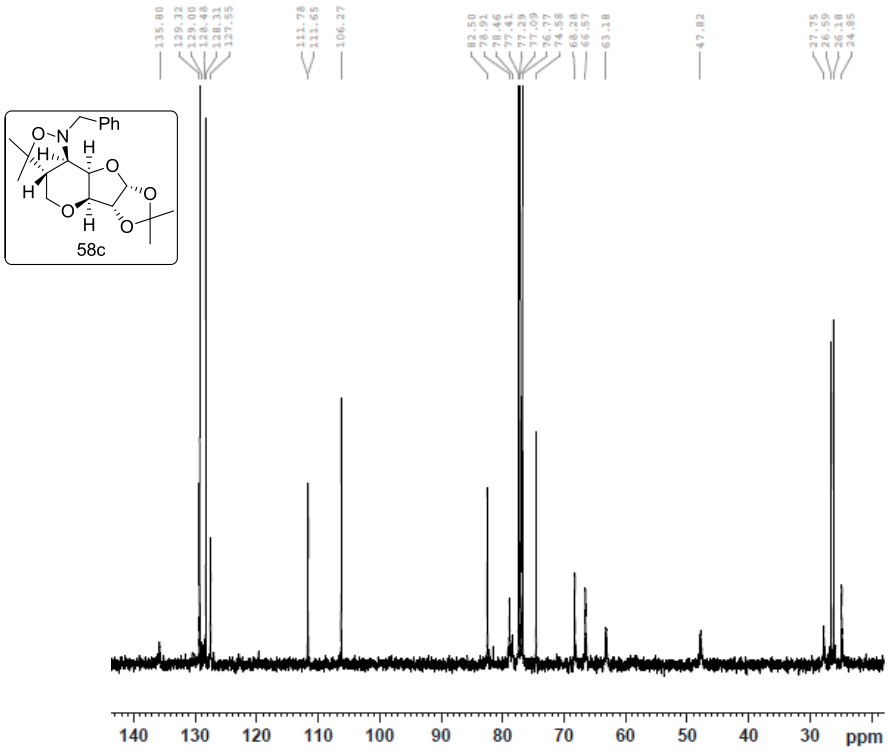
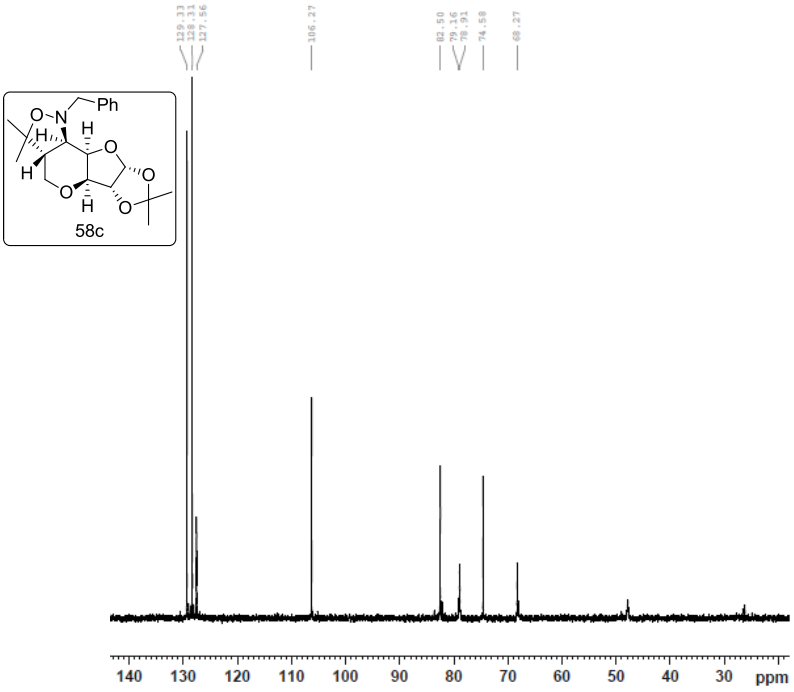


^{1}H NMR ($CDCl_3$, 400MHz) Spectrum of Compound 58c



^{13}C NMR ($CDCl_3$, 100MHz) Spectrum of Compound 58c



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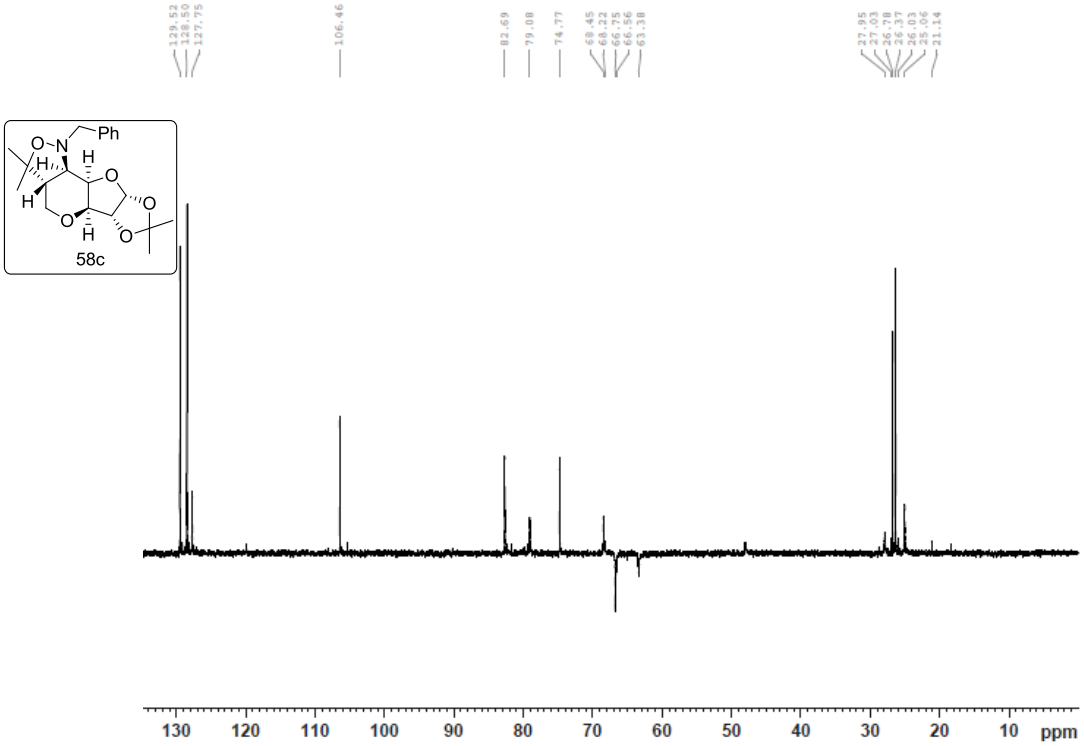
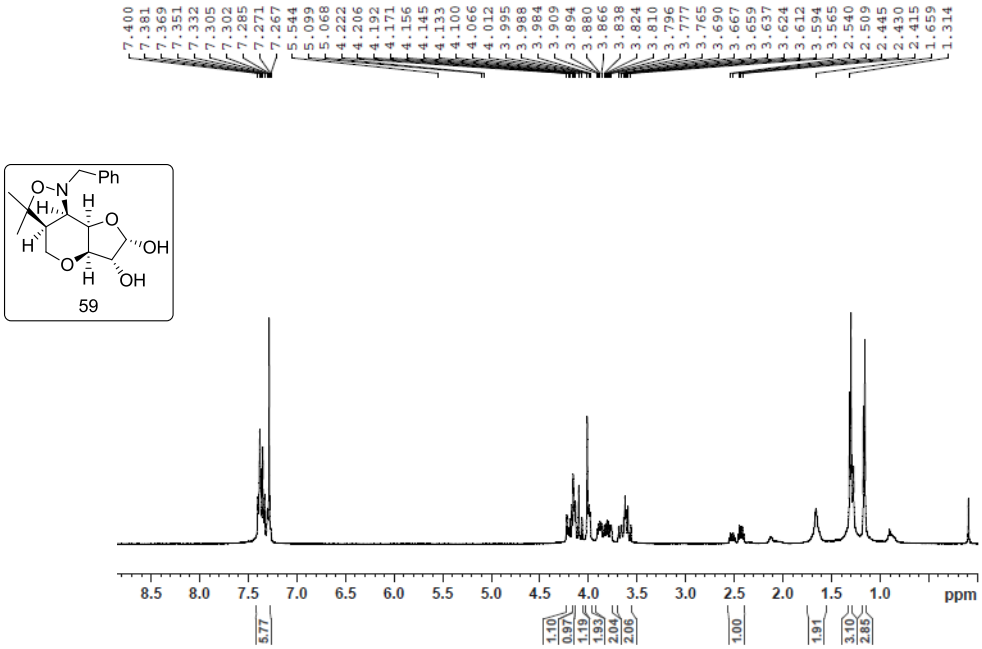
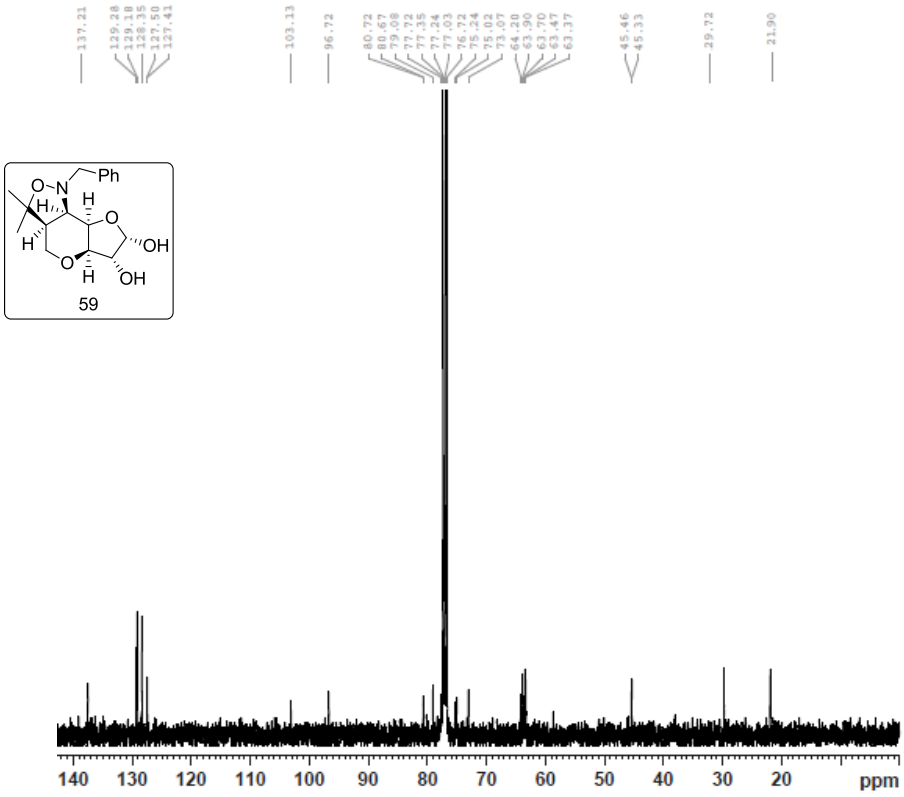


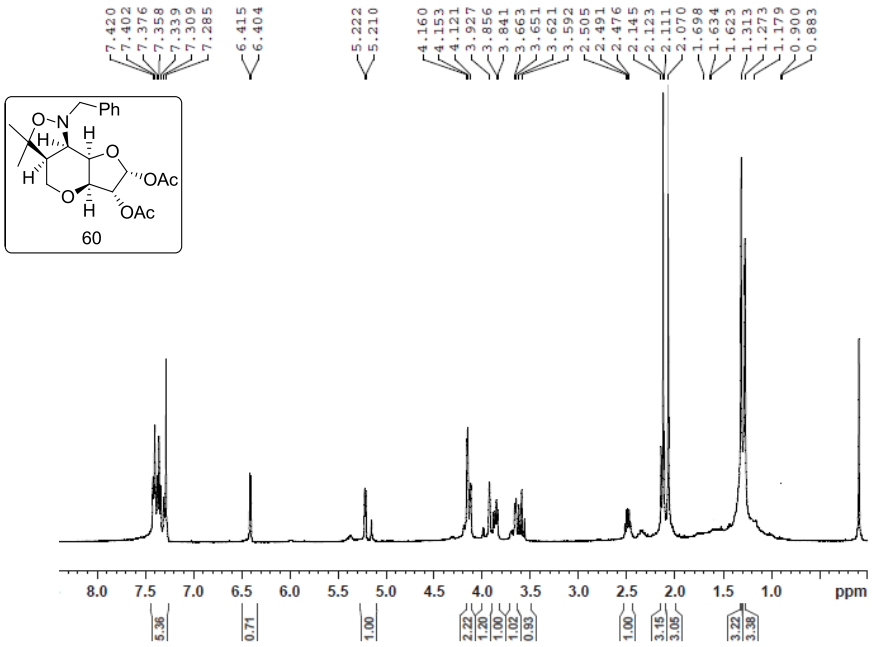
DEPT 135 ($CDCl_3$, 100MHz) Spectrum of Compound 58c



^{1}H NMR ($CDCl_3$, 400MHz) Spectrum of Compound 59



^{13}C NMR ($CDCl_3$, 100MHz) Spectrum of Compound 59



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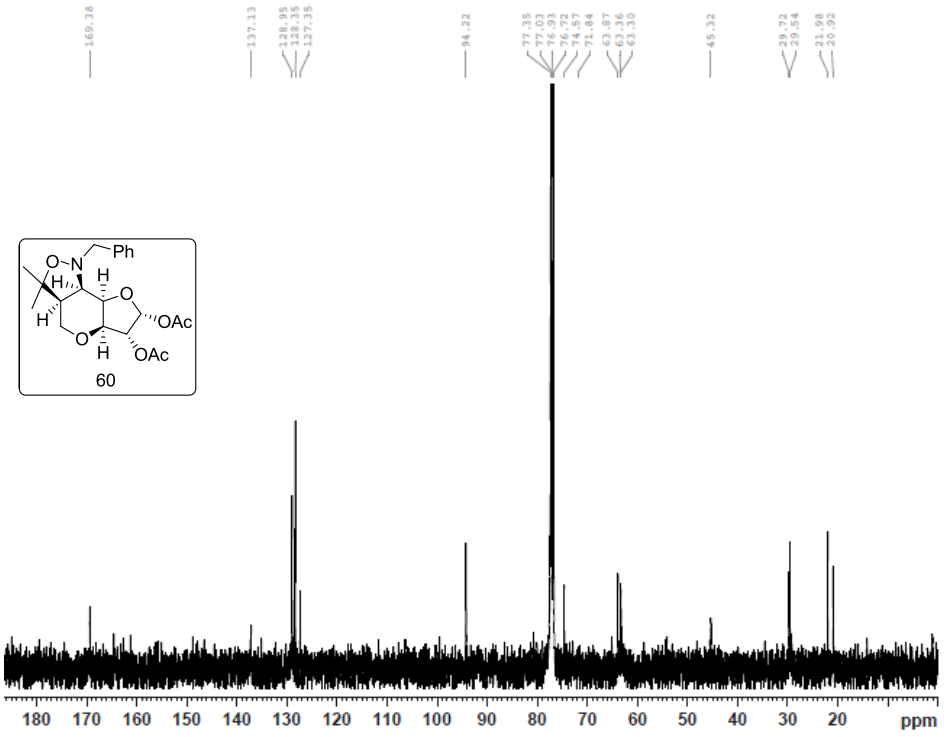

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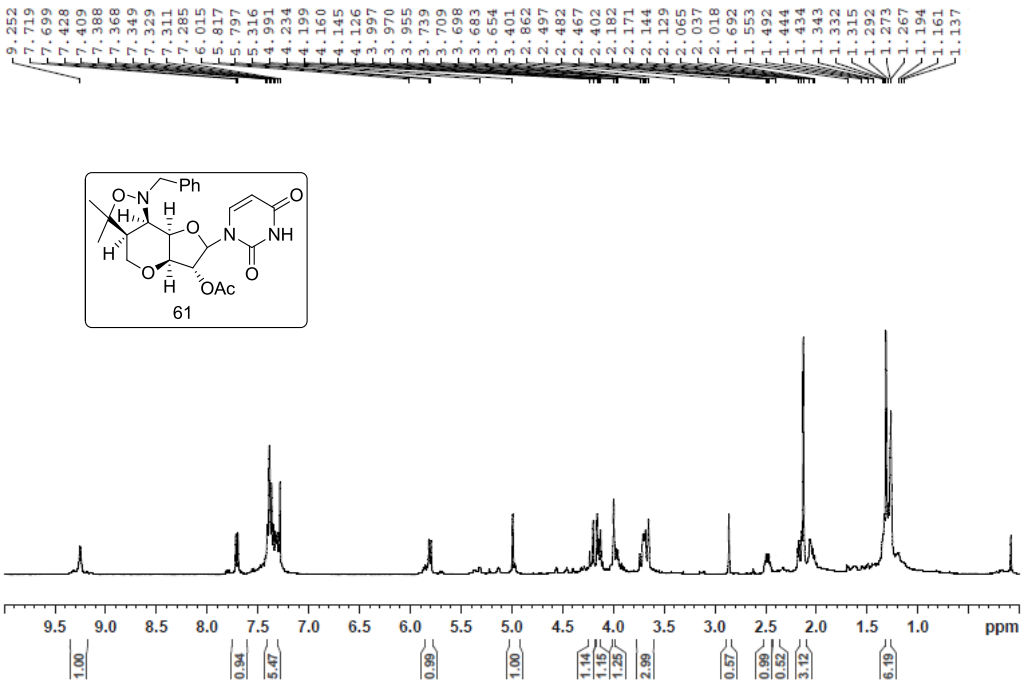

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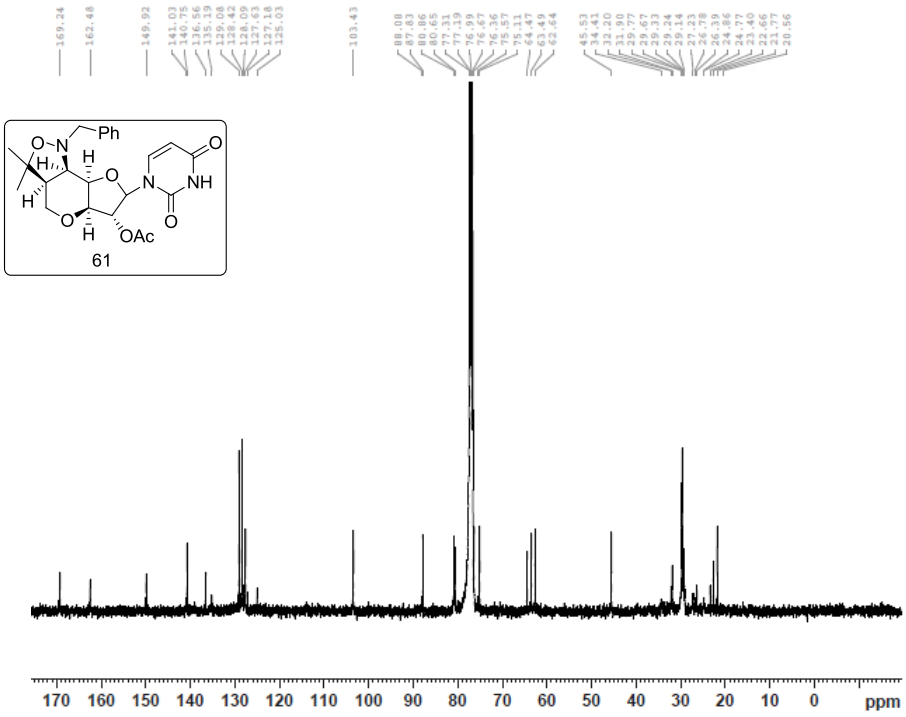

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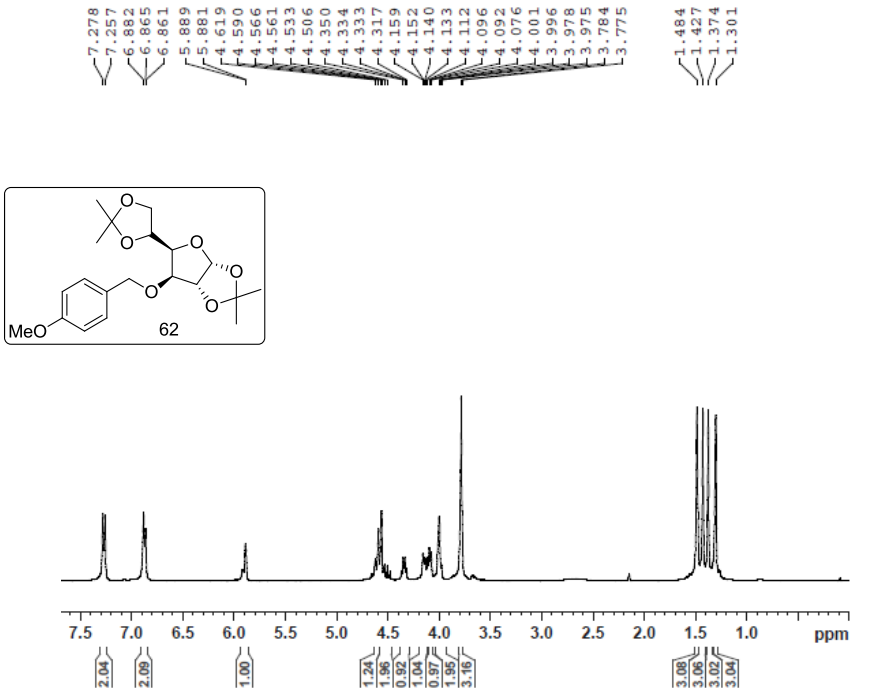

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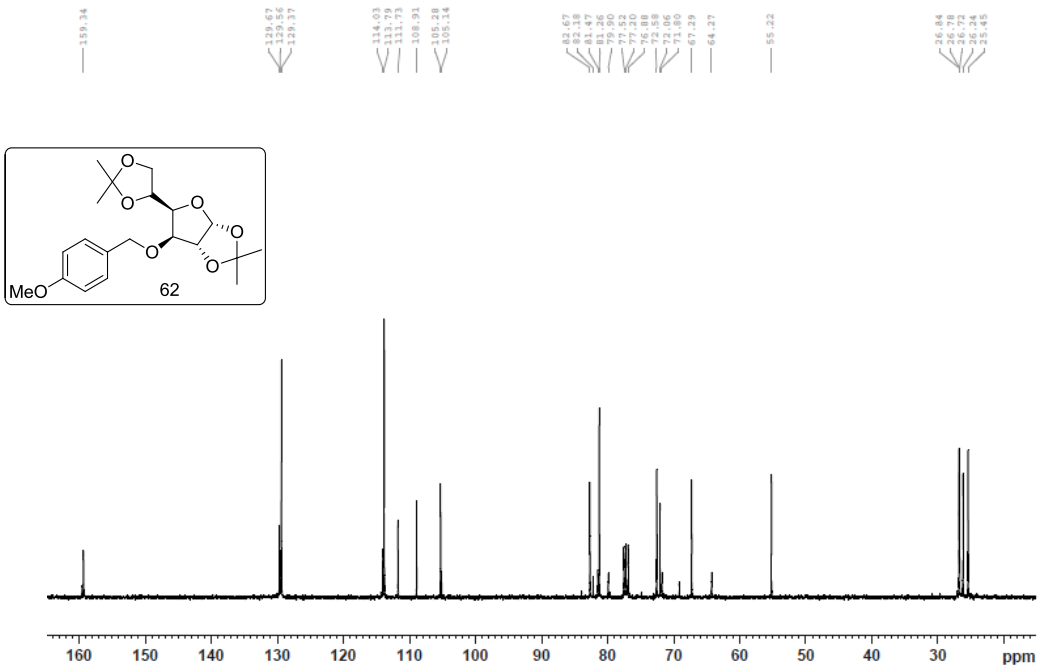

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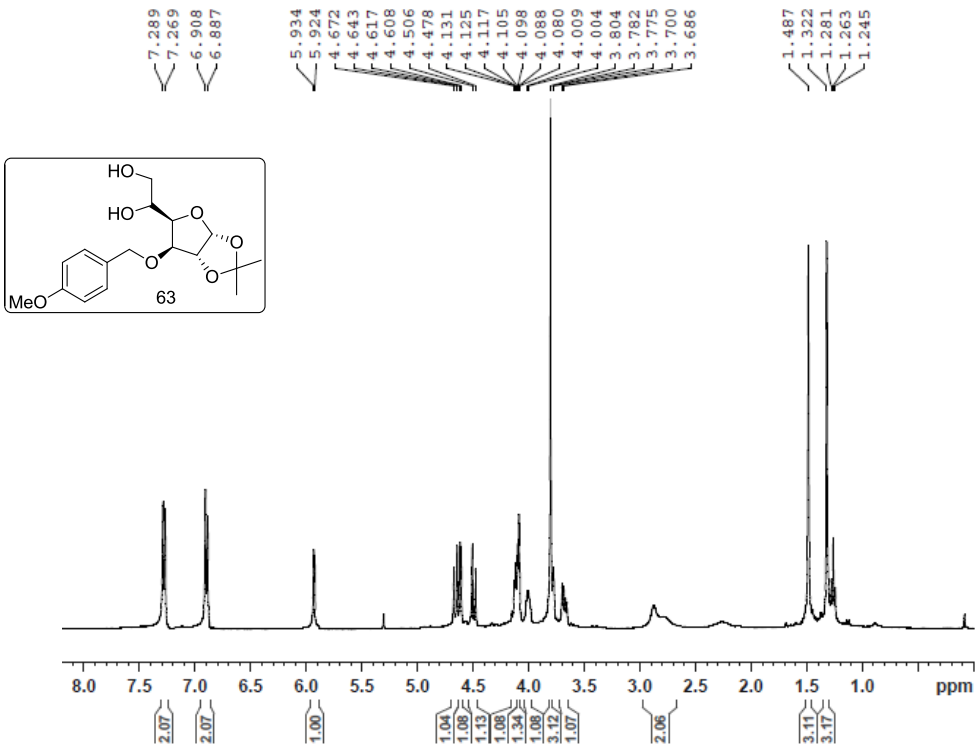

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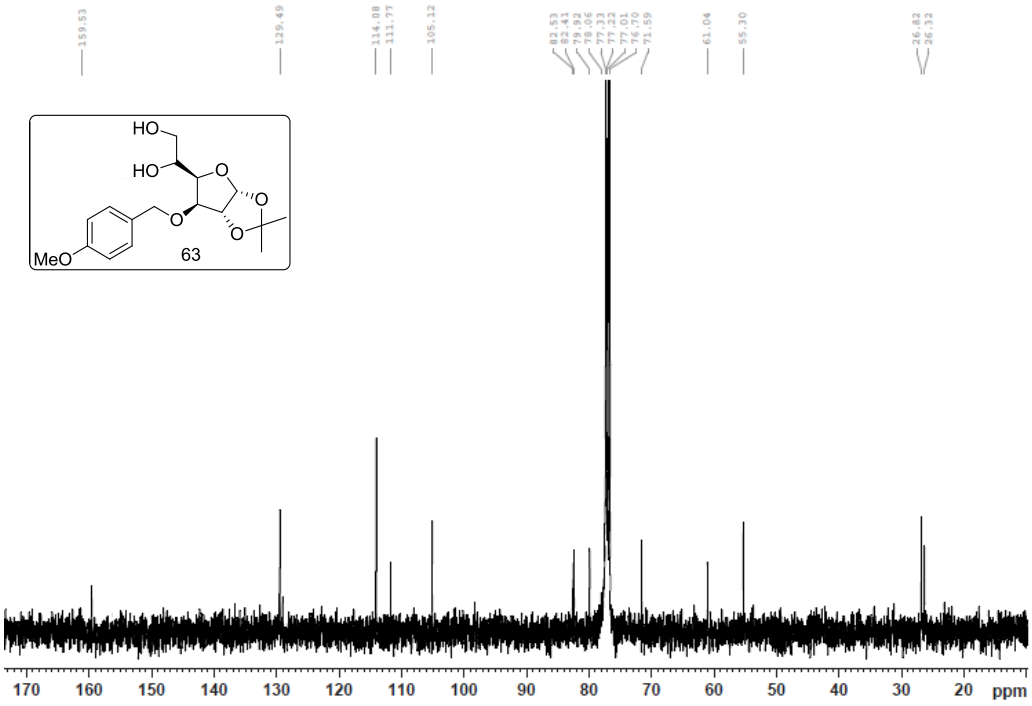

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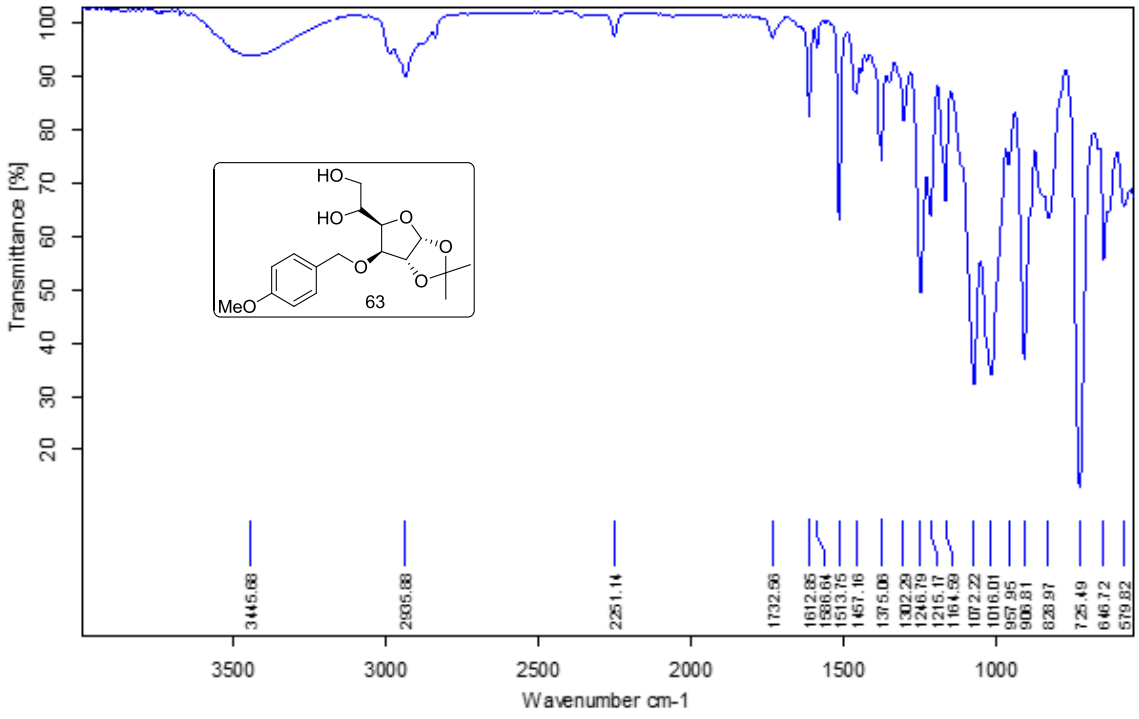
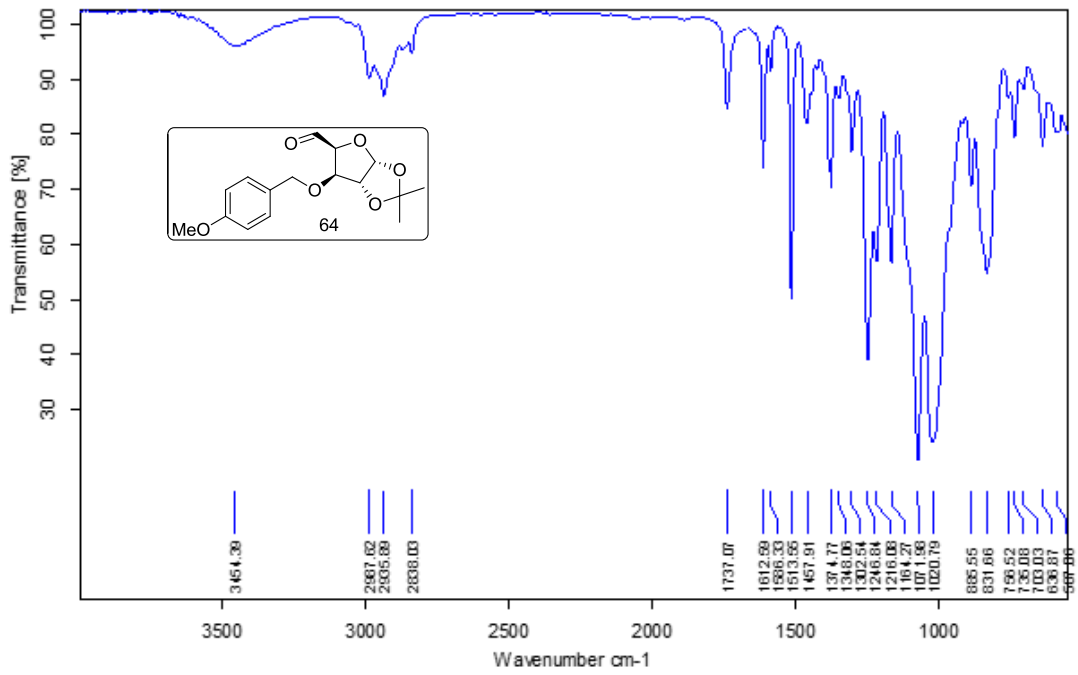
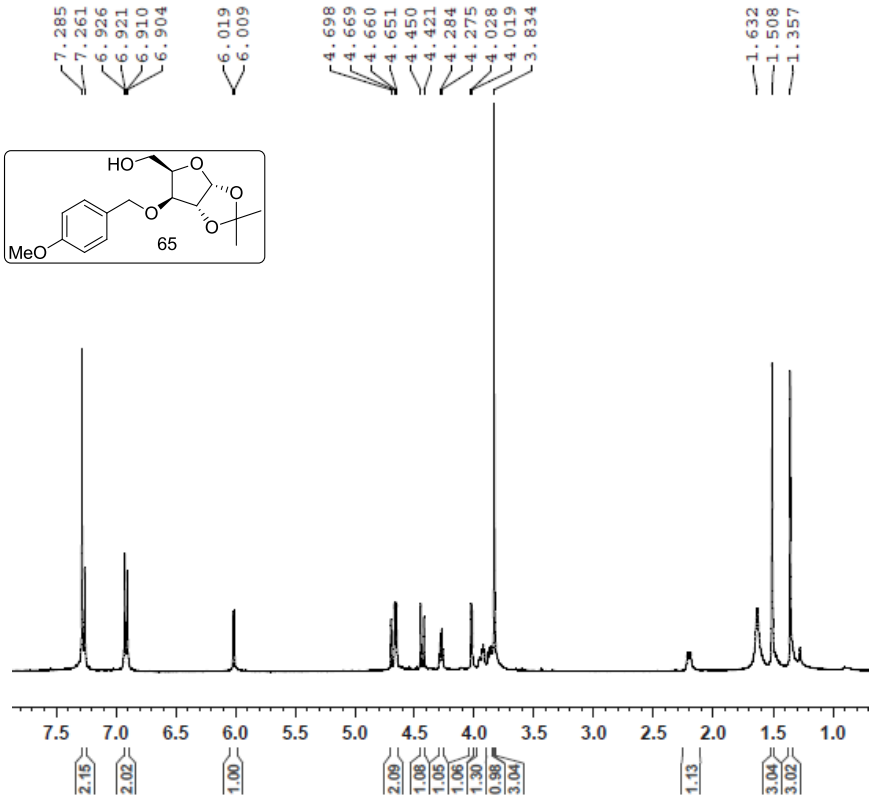


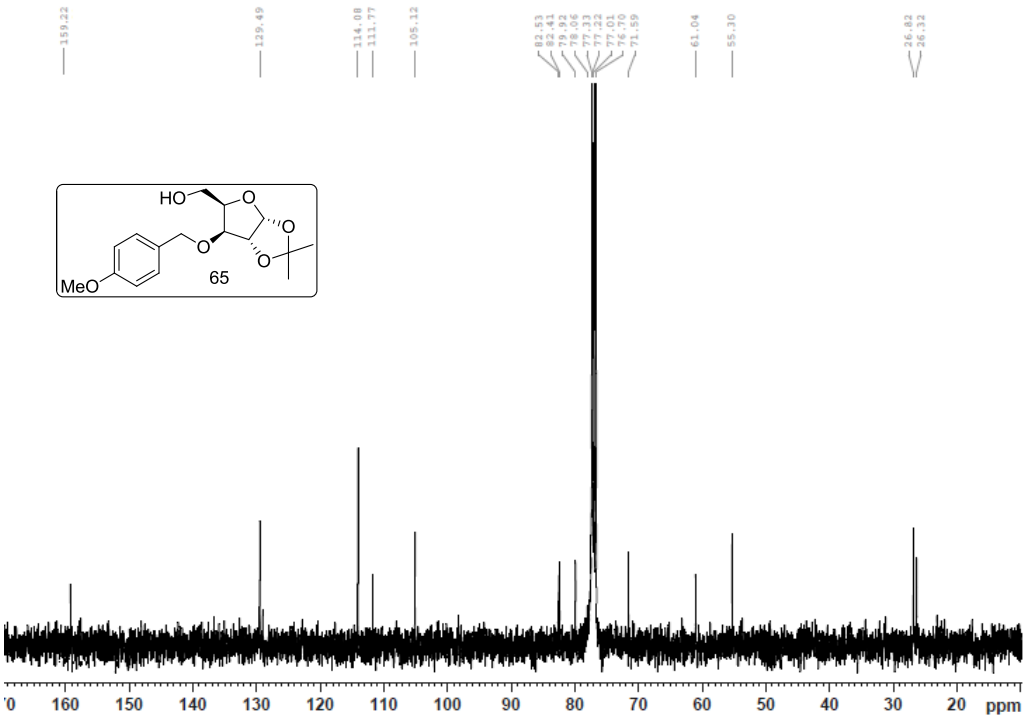
FTIR Spectrum: ν_{max} (neat)/cm^{-1} of Compound 63



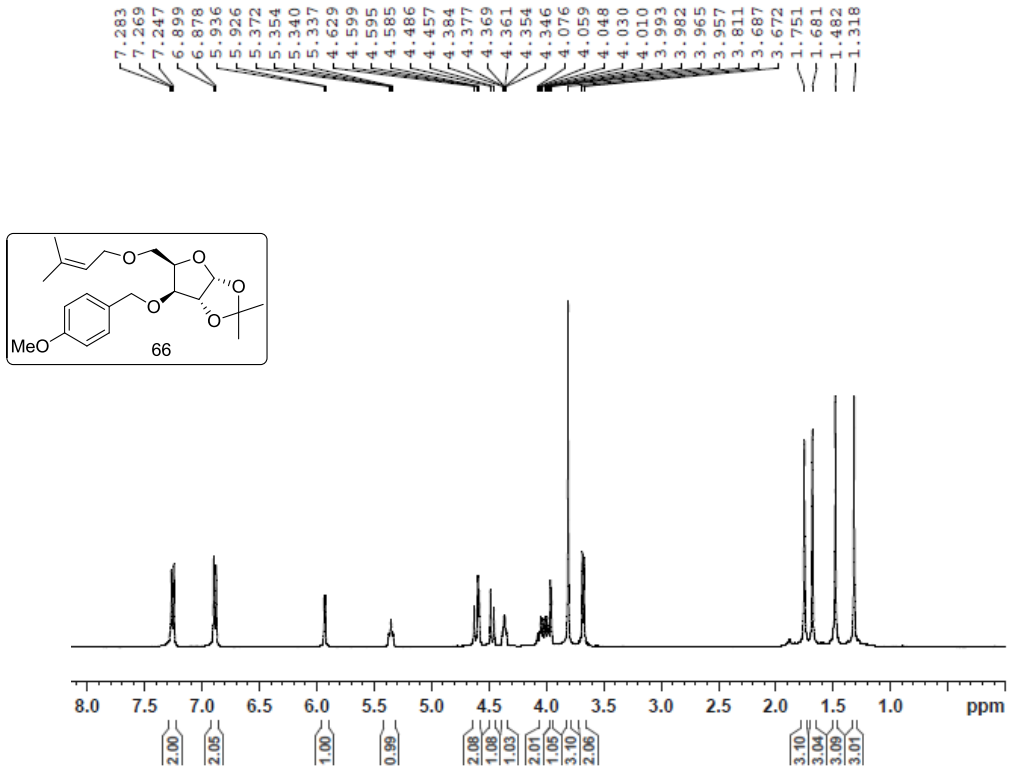
FTIR Spectrum: ν_{max} (neat)/cm^{-1} of Compound 64



^{1}H NMR ($CDCl_3$, 400MHz) Spectrum of Compound 65



^{13}C NMR ($CDCl_3$, 100MHz) Spectrum of Compound 65



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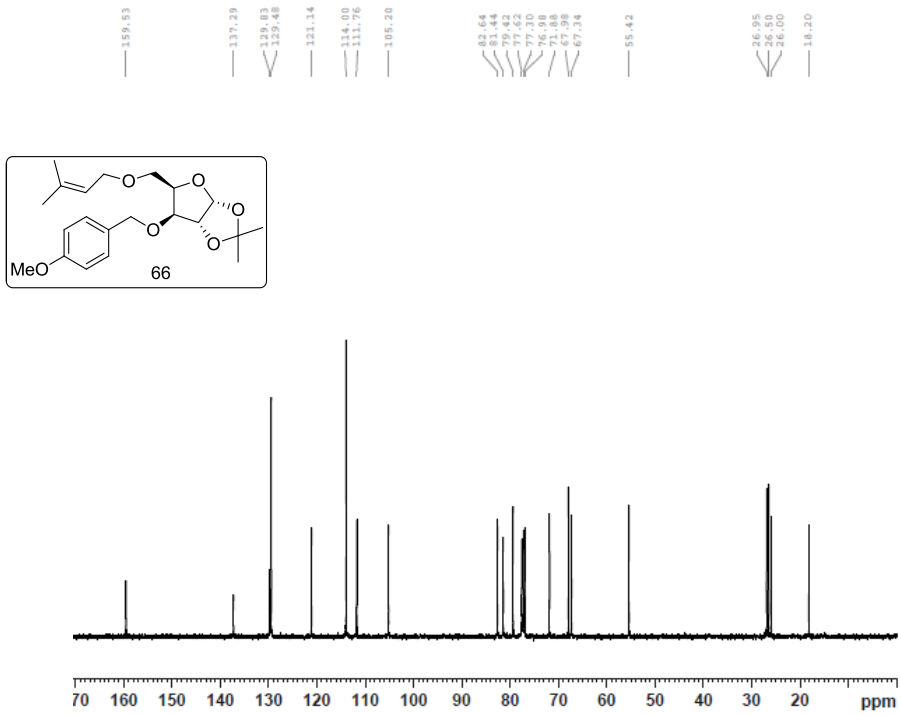
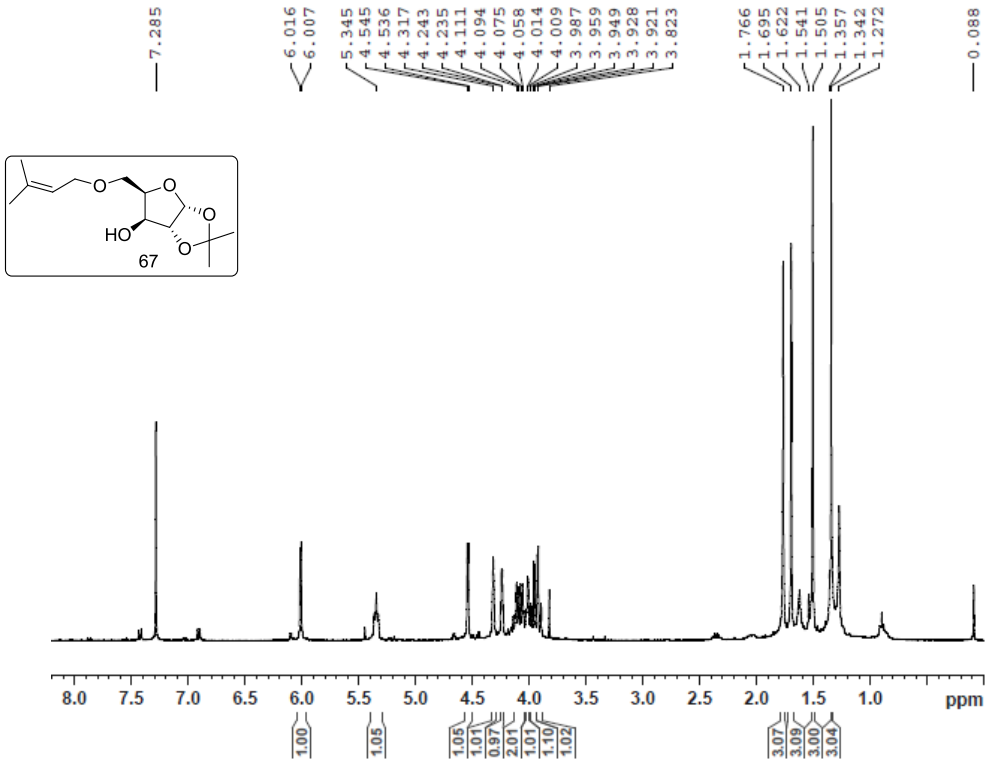


^{13}C NMR ($CDCl_3$, 100MHz) Spectrum of Compound 66



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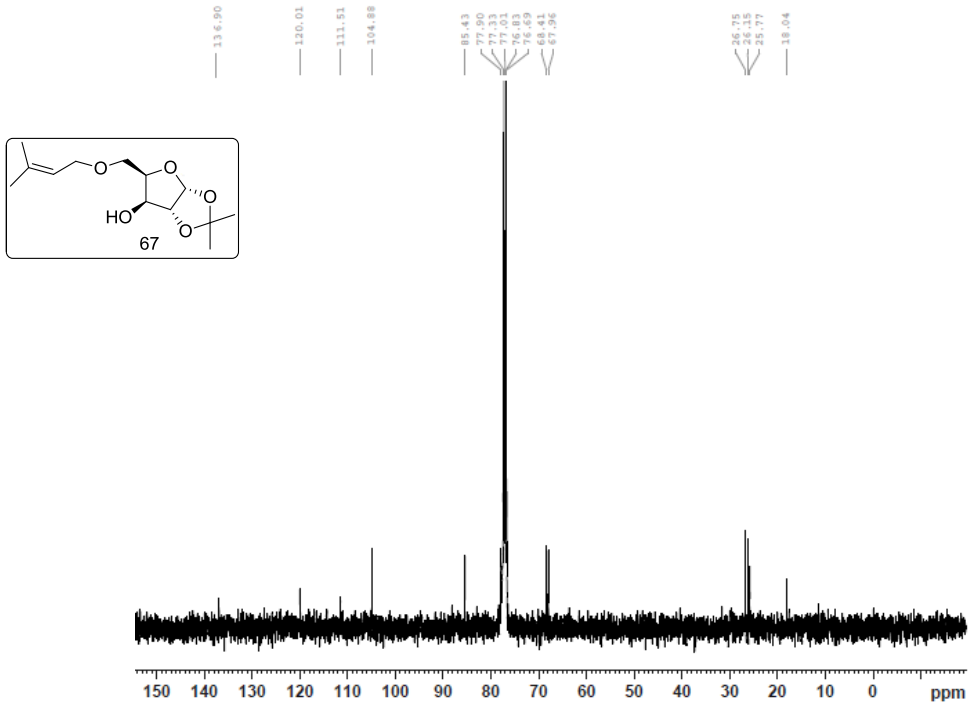
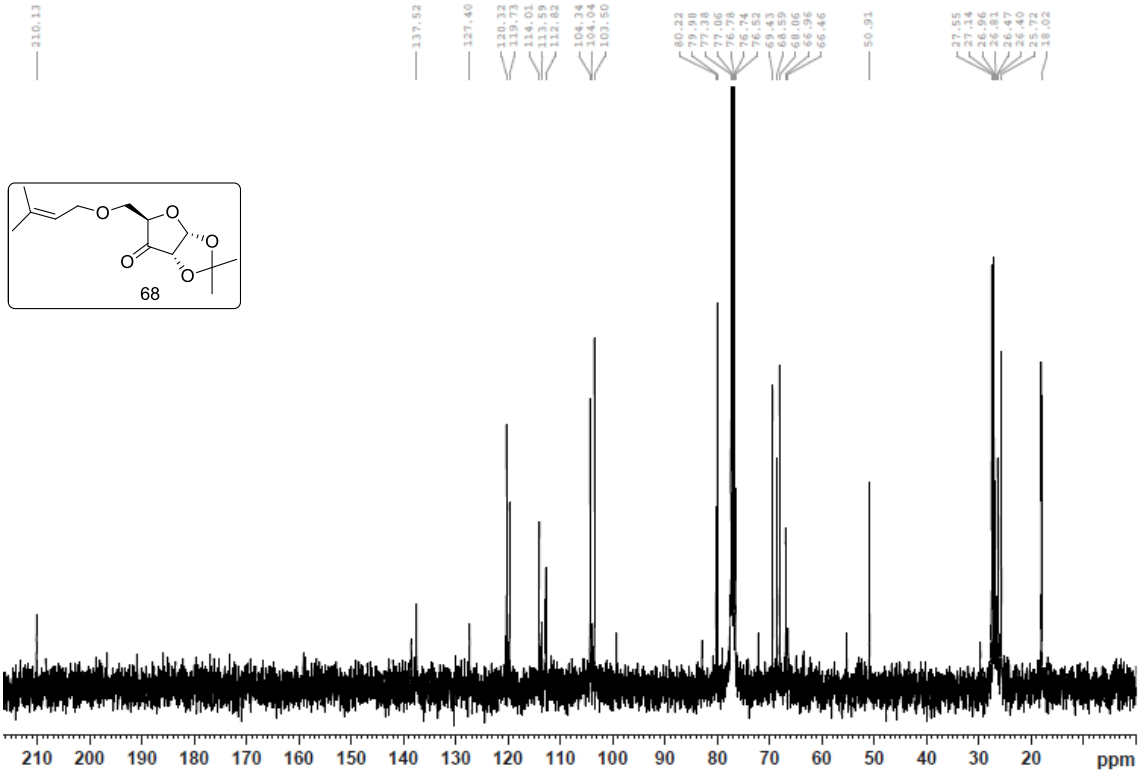


^{13}C NMR ($CDCl_3$, 100MHz) Spectrum of Compound 67



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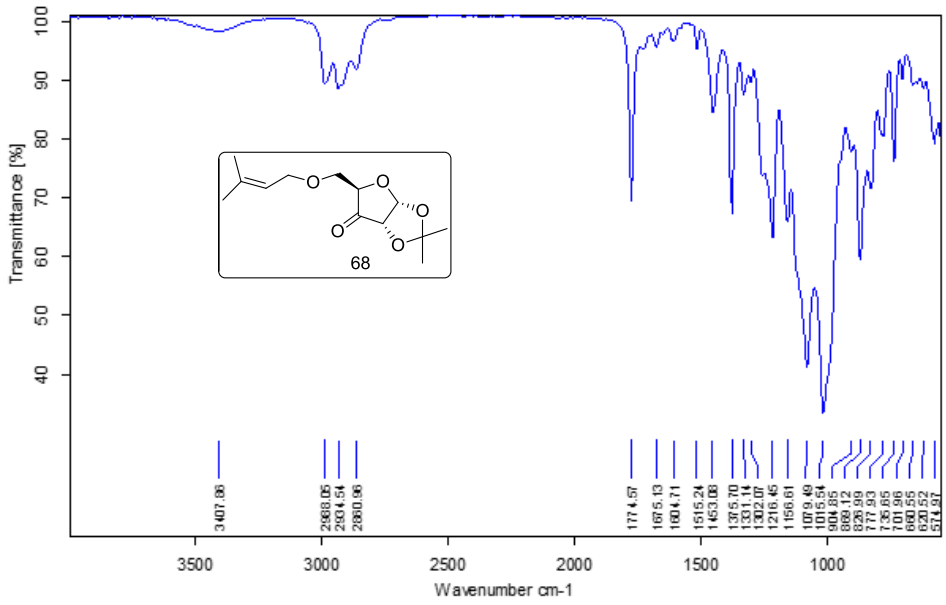
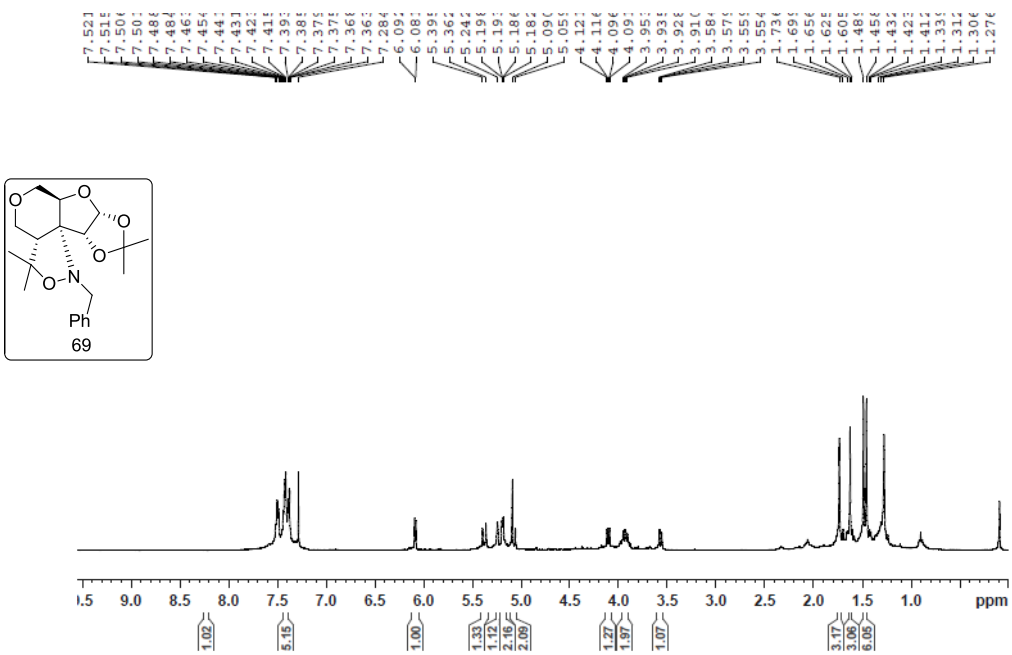
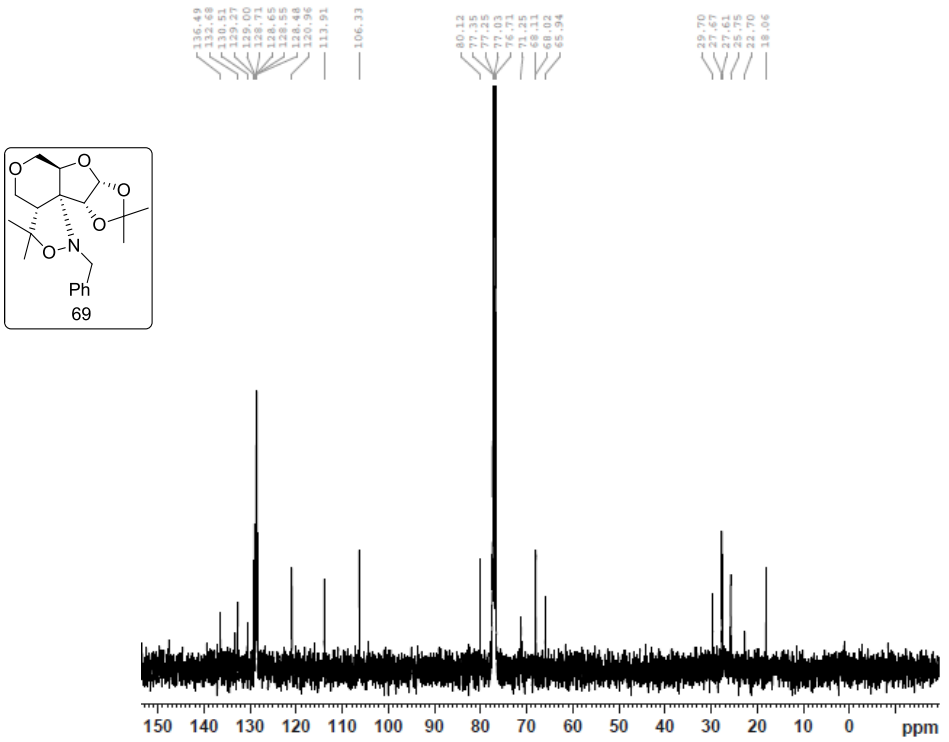


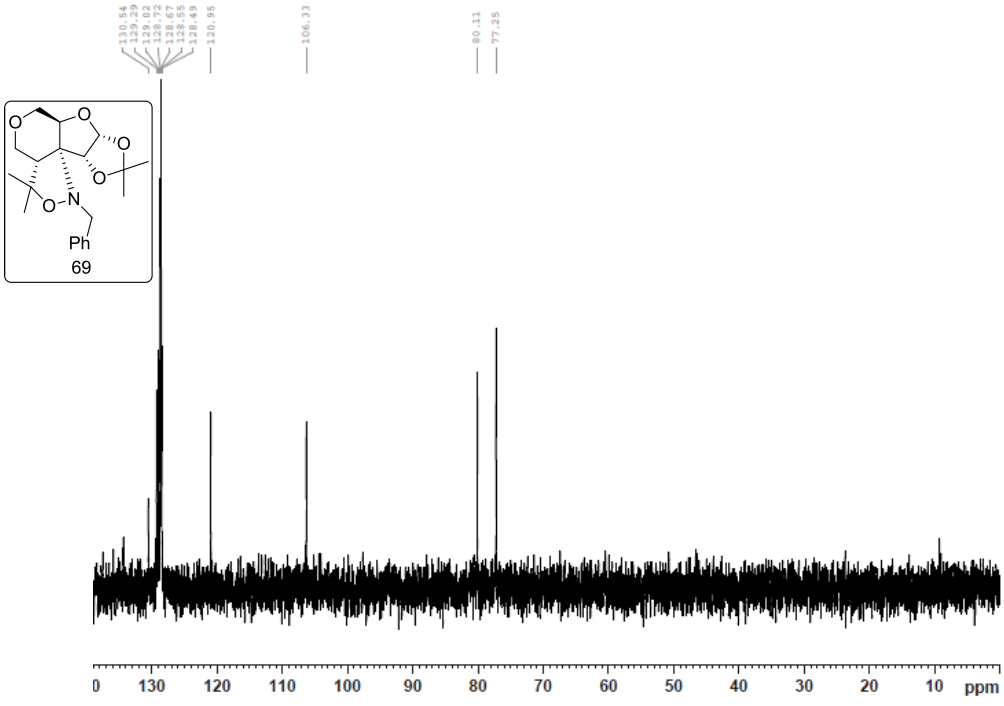
FTIR Spectrum: ν_{max} (neat)/cm^{-1} of Compound 68



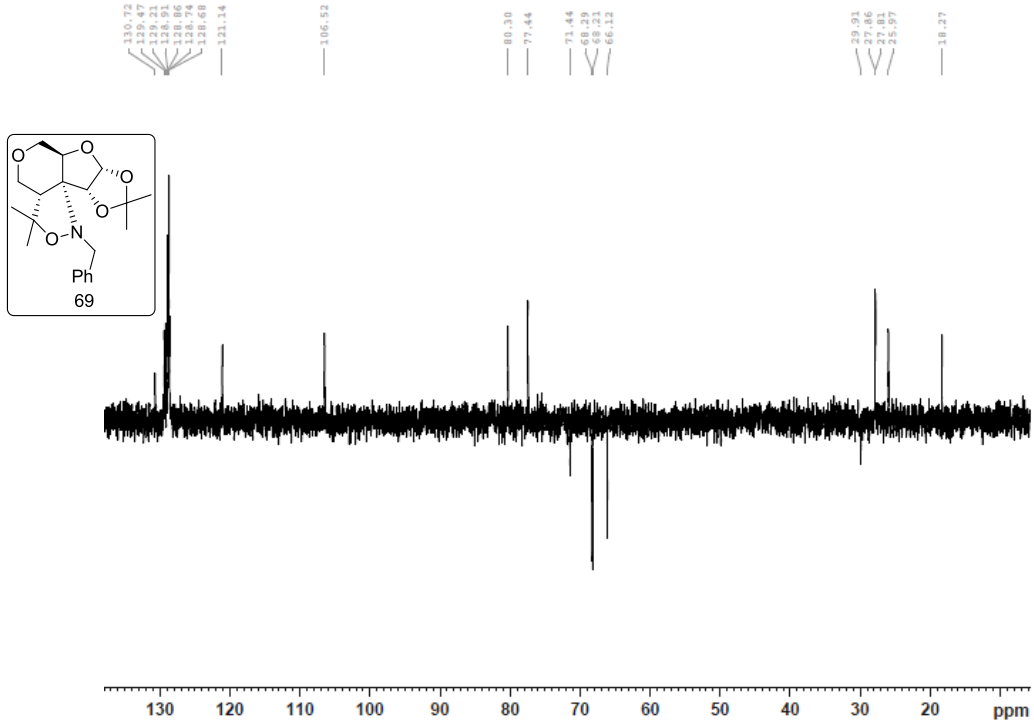
^{1}H NMR ($CDCl_3$, 400MHz) Spectrum of Compound 69



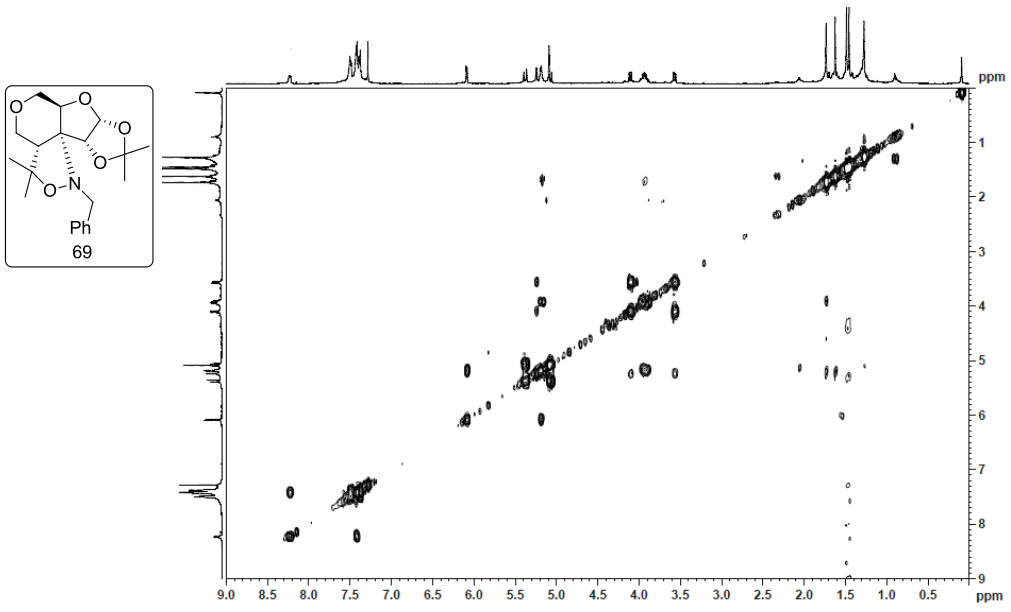
^{13}C NMR ($CDCl_3$, 100MHz) Spectrum of Compound 69



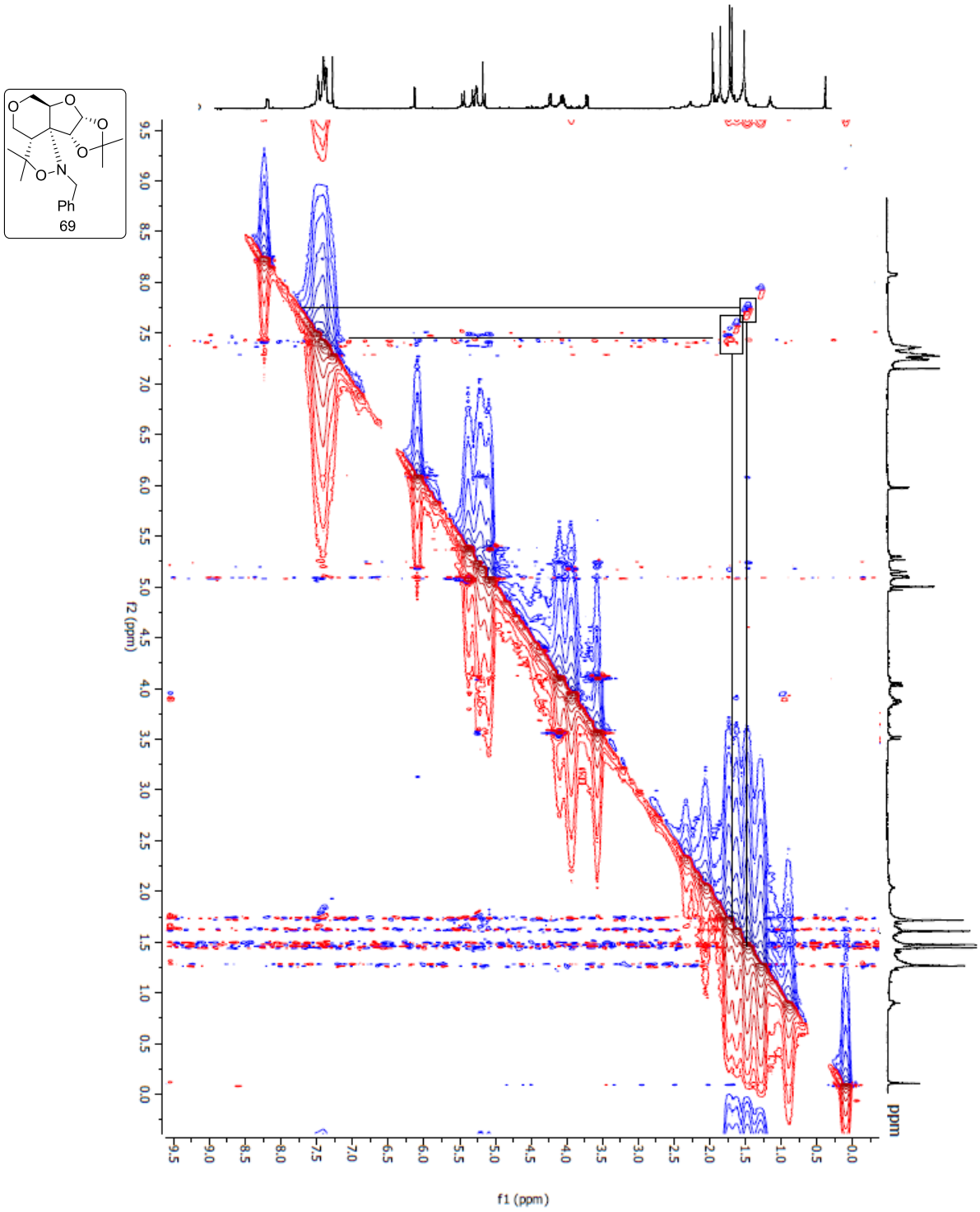
DEPT 90 ($CDCl_3$, 100MHz) Spectrum of Compound 69



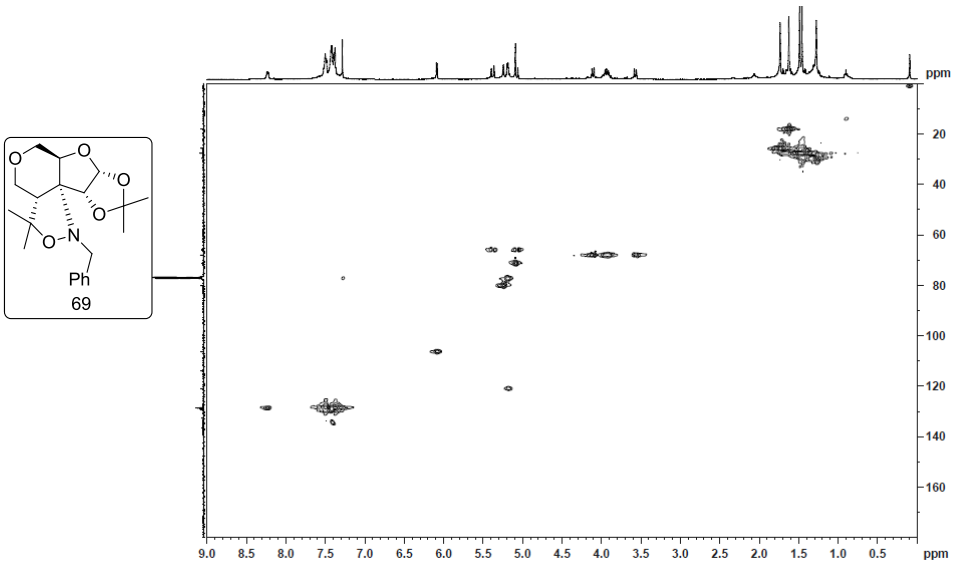
DEPT 135 ($CDCl_3$, 100MHz) Spectrum of Compound 69



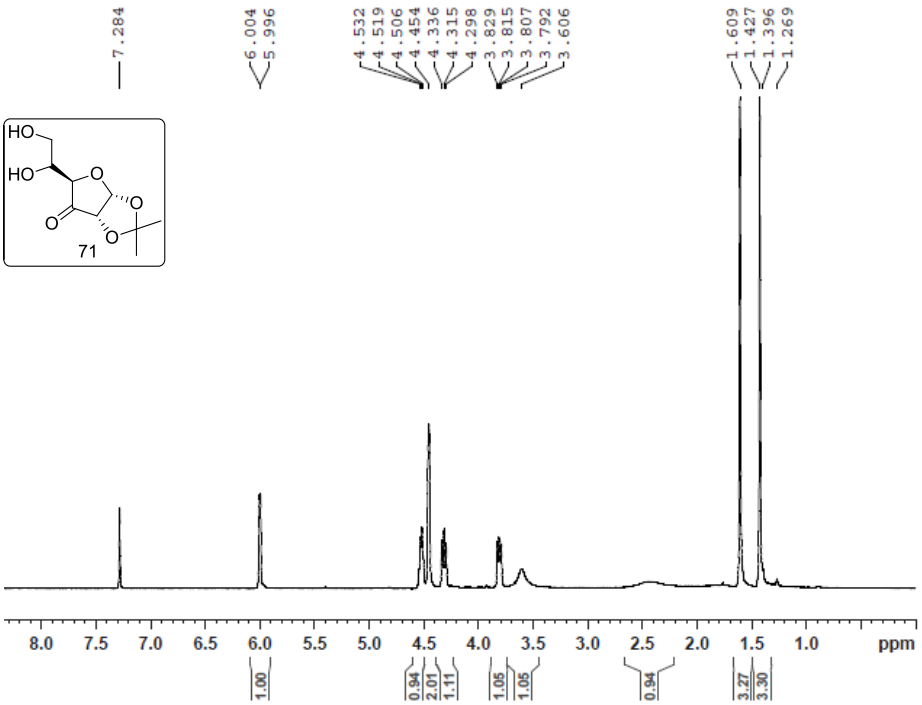
COSY ($CDCl_3$, 400MHz) Spectrum of Compound 69



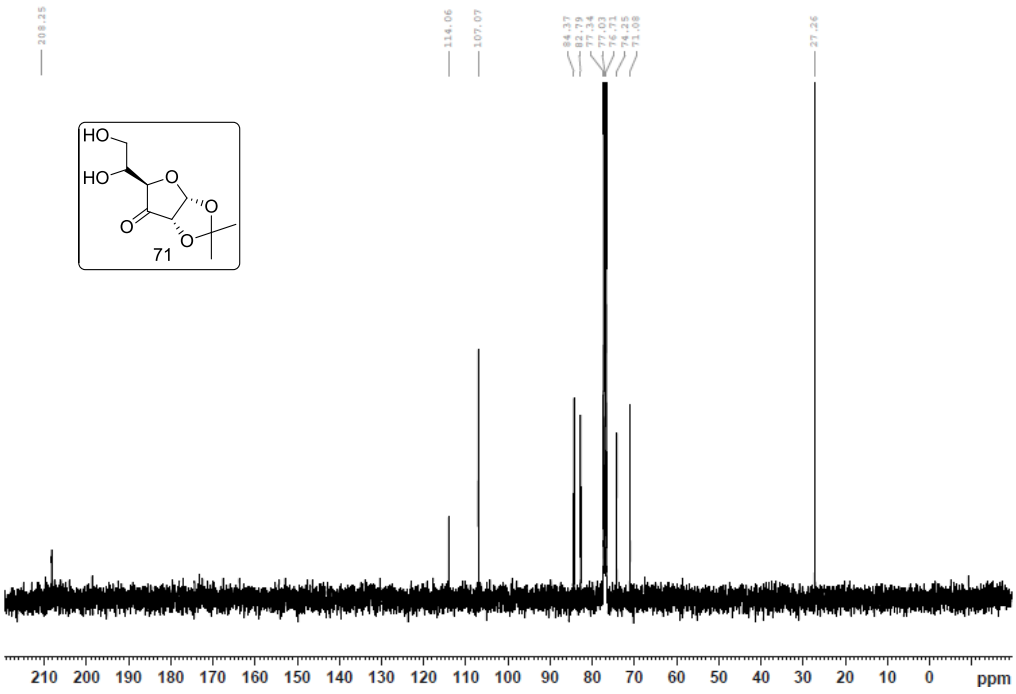
NOESY ($CDCl_3$, 400MHz) Spectrum of Compound 69



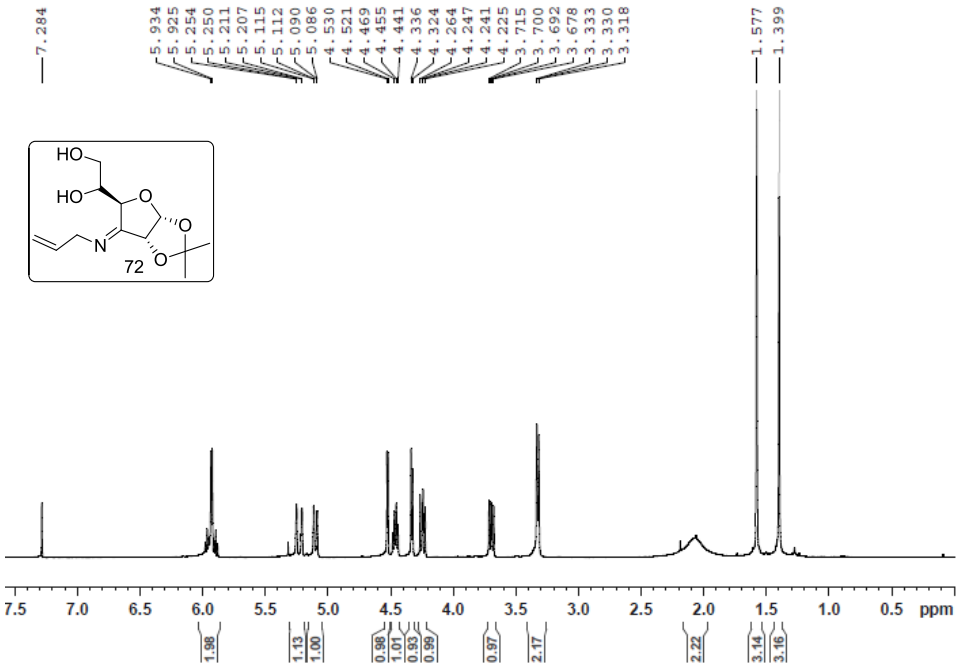
HMQC ($CDCl_3$, 100MHz) Spectrum of Compound 69



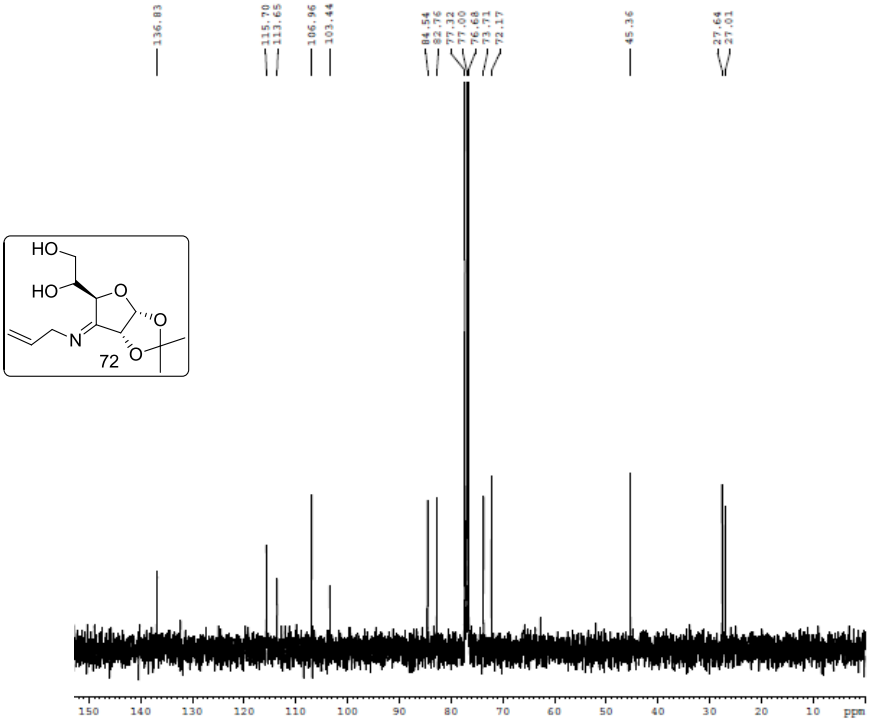
^{1}H NMR ($CDCl_3$, 400MHz) Spectrum of Compound 71



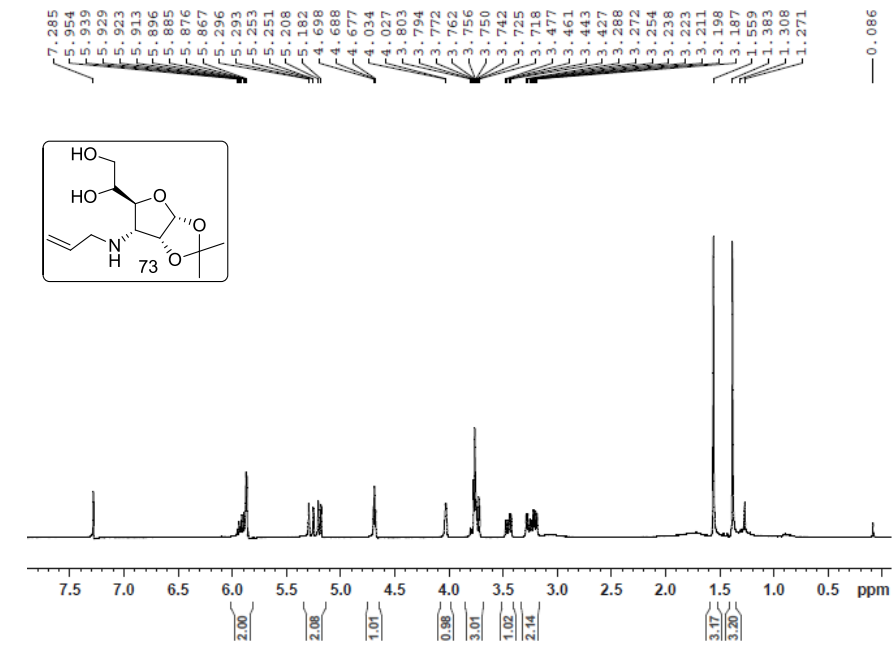
^{13}C NMR ($CDCl_3$, 100MHz) Spectrum of Compound 71



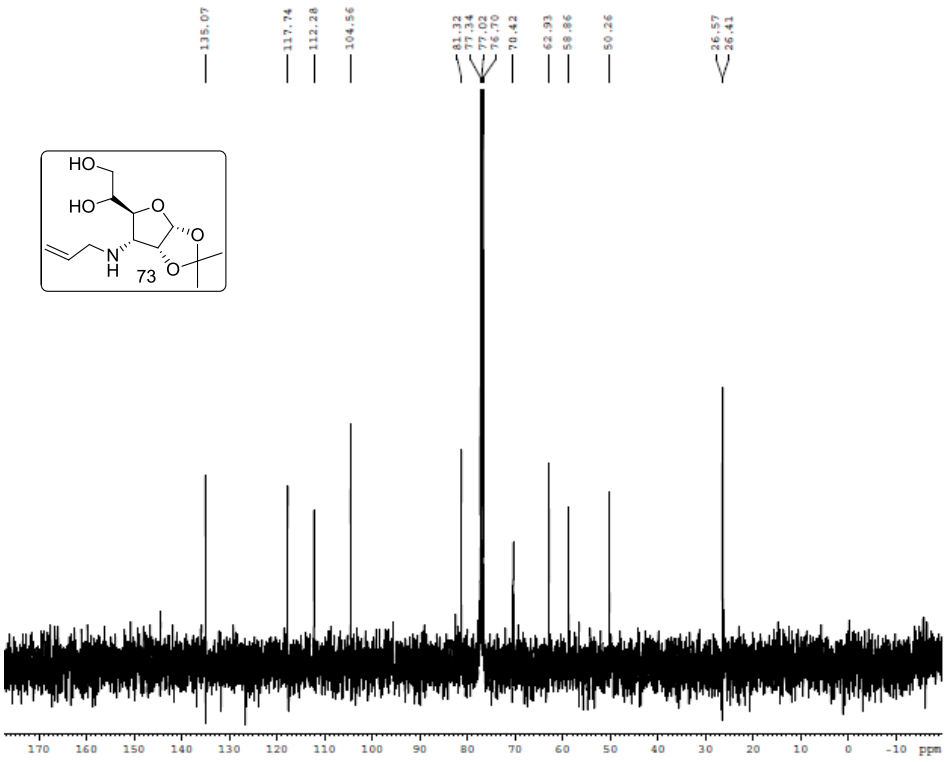
^{1}H NMR ($CDCl_3$, 400MHz) Spectrum of Compound 72



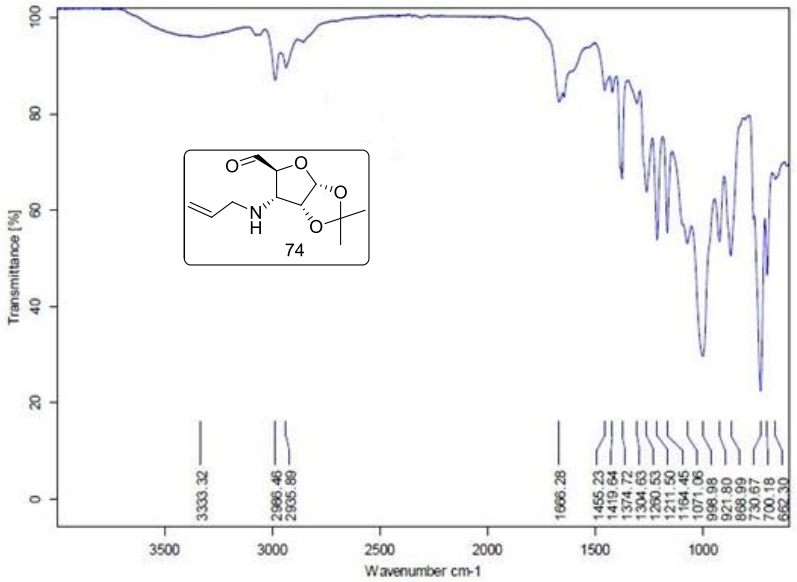
^{13}C NMR ($CDCl_3$, 100MHz) Spectrum of Compound 72



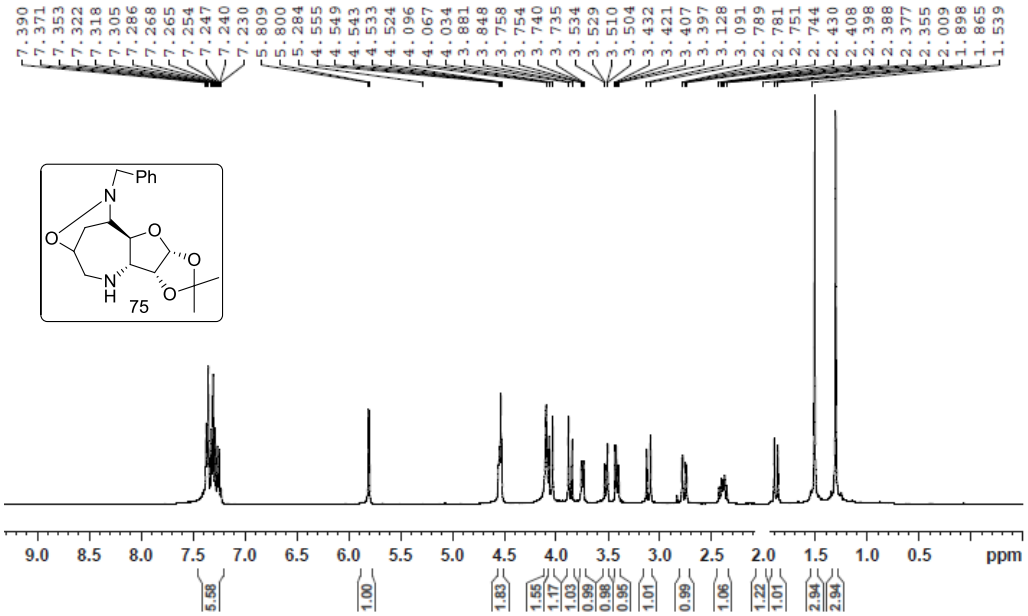
^{1}H NMR ($CDCl_3$, 400MHz) Spectrum of Compound 73



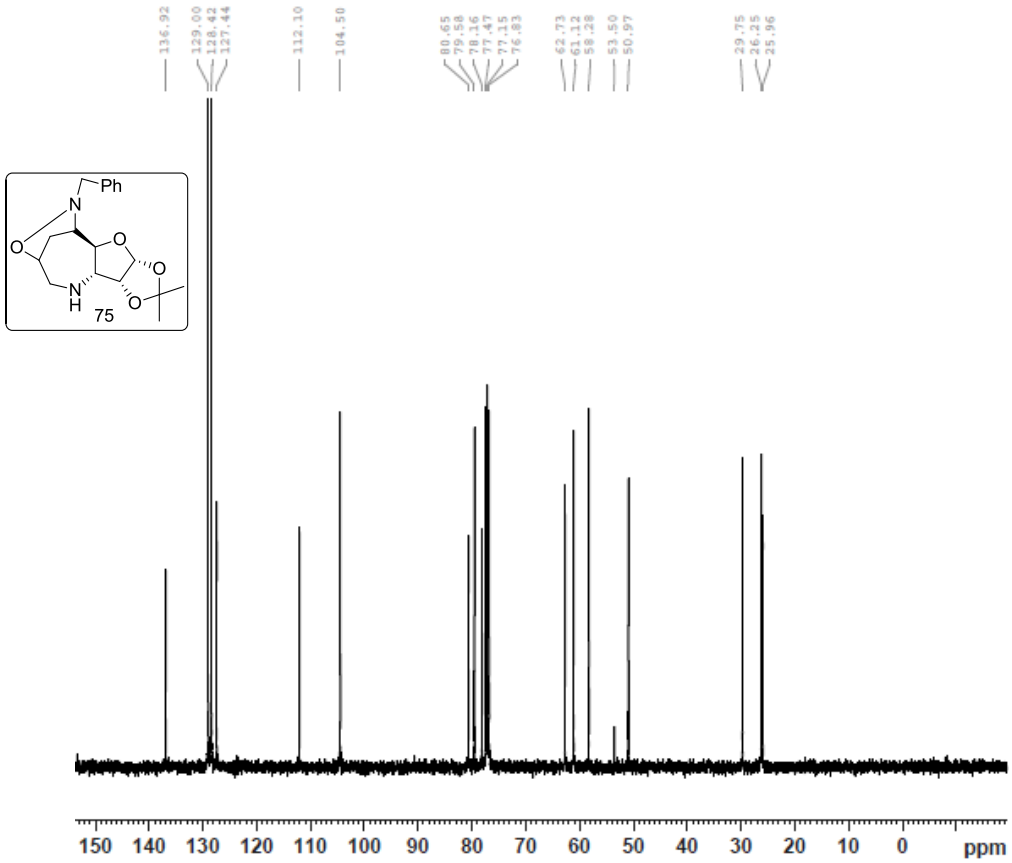
^{13}C NMR ($CDCl_3$, 100MHz) Spectrum of Compound 73



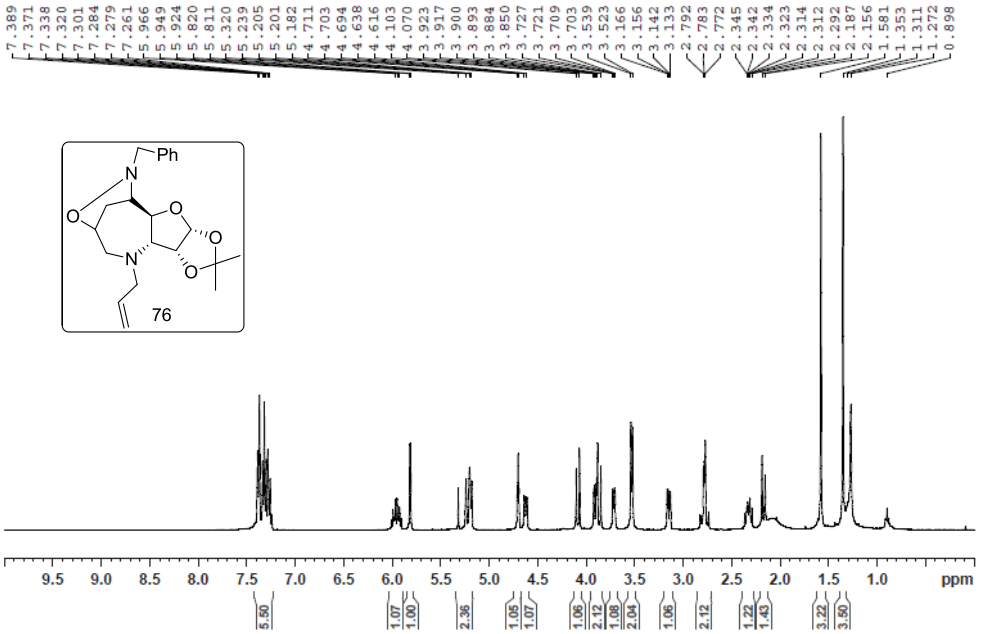
FTIR Spectrum: ν_{max} (neat)/cm^{-1} of Compound 74



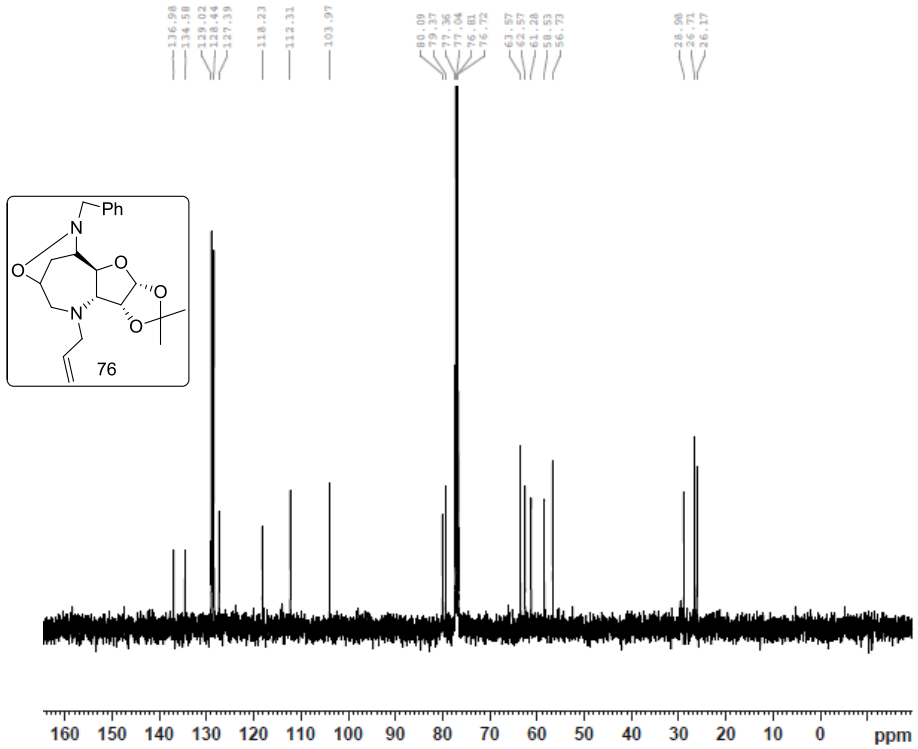
^{1}H NMR ($CDCl_3$, 400MHz) Spectrum of Compound 75



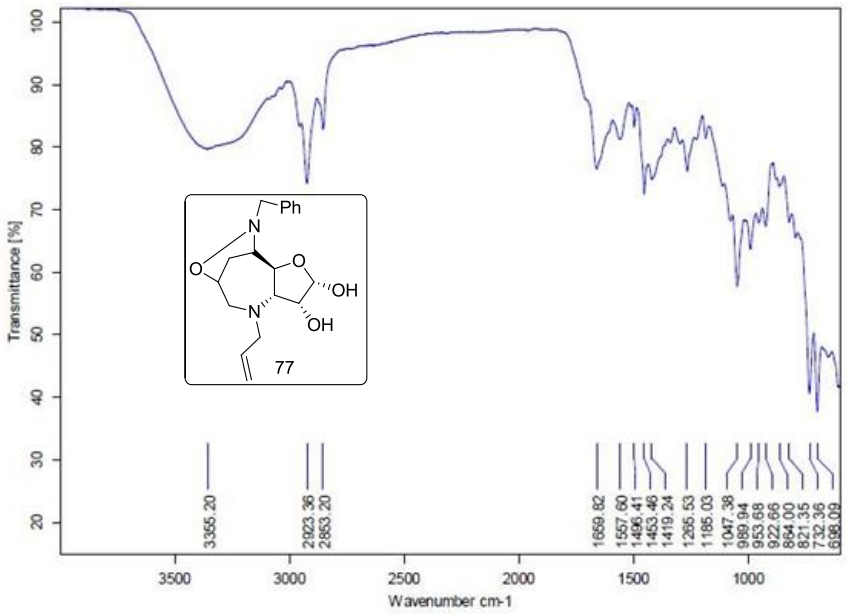
^{13}C NMR ($CDCl_3$, 100MHz) Spectrum of Compound 75



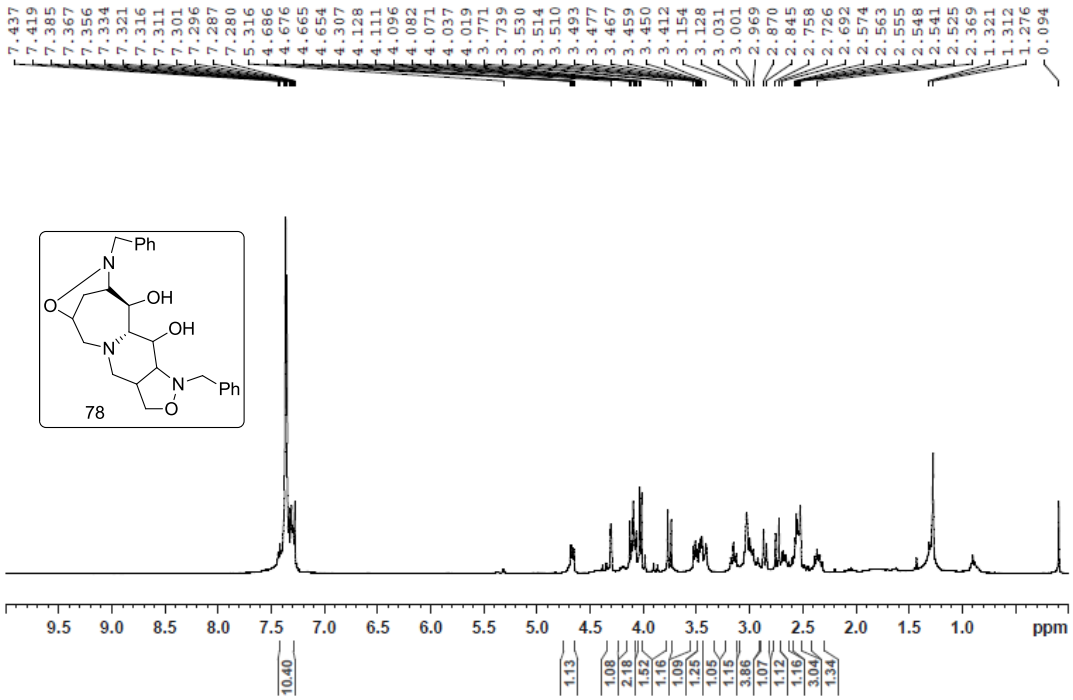
^{1}H NMR ($CDCl_3$, 400MHz) Spectrum of Compound 76



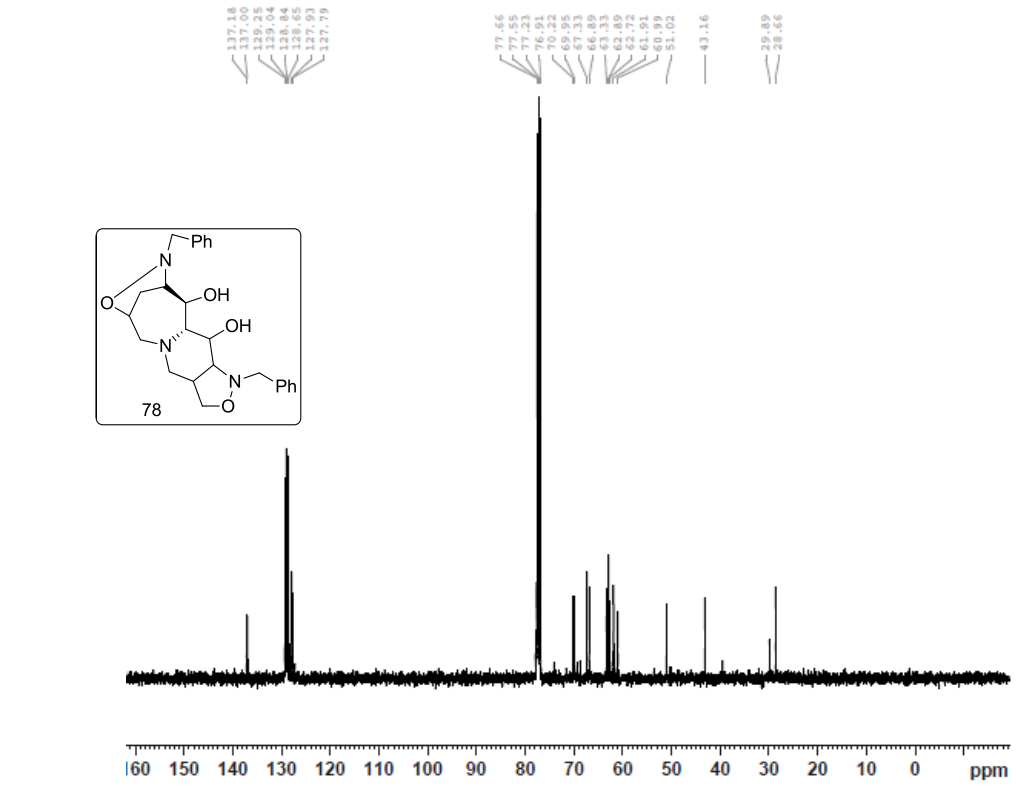
^{13}C NMR ($CDCl_3$, 100MHz) Spectrum of Compound 76



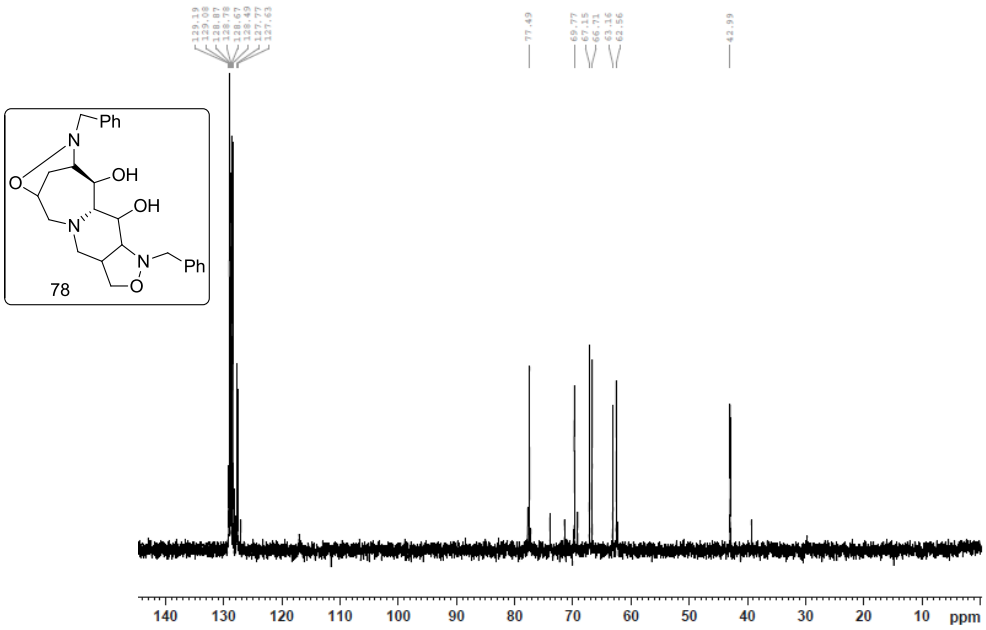
FTIR Spectrum: ν_{max} (neat)/cm^{-1} of Compound 77



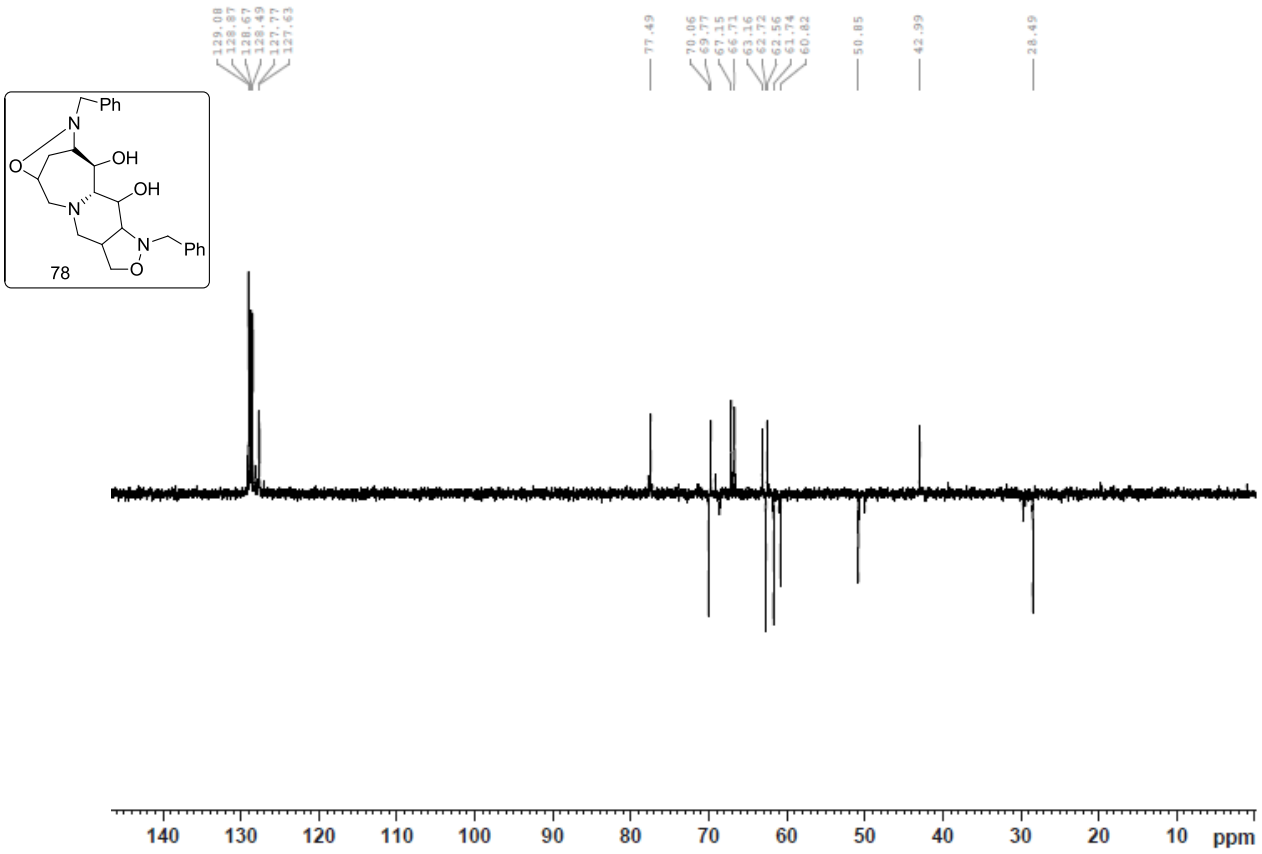
^{1}H NMR ($CDCl_3$, 400MHz) Spectrum of Compound 78



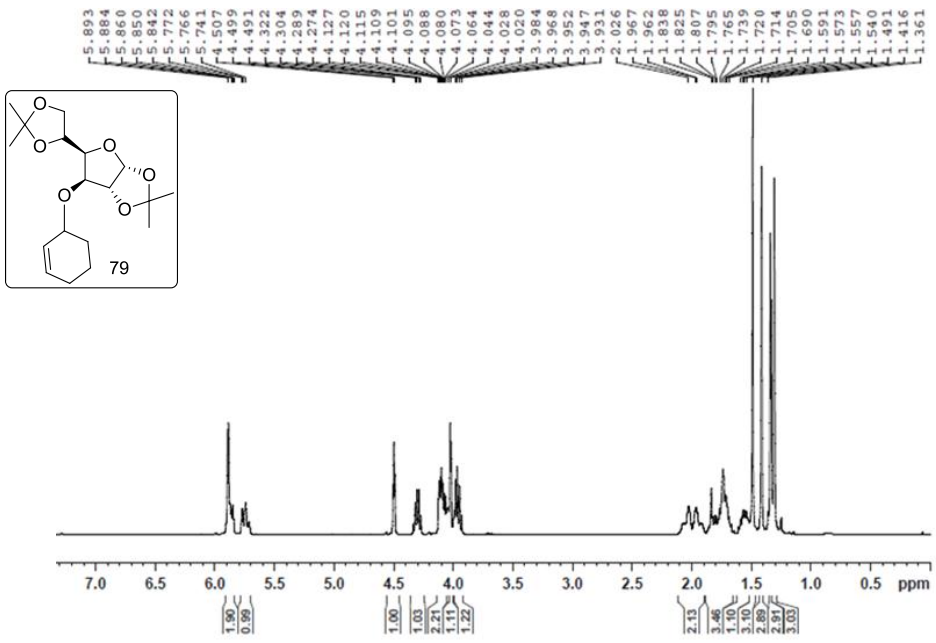
^{13}C NMR ($CDCl_3$, 100MHz) Spectrum of Compound 78



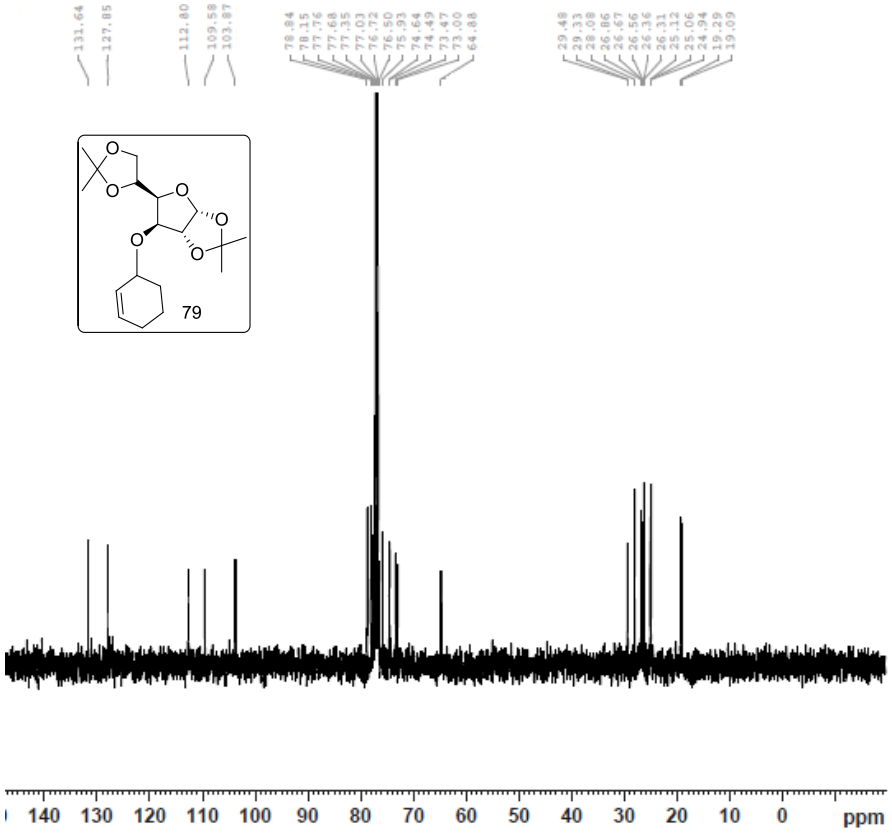
DEPT 90 ($CDCl_3$, 100MHz) Spectrum of Compound 78



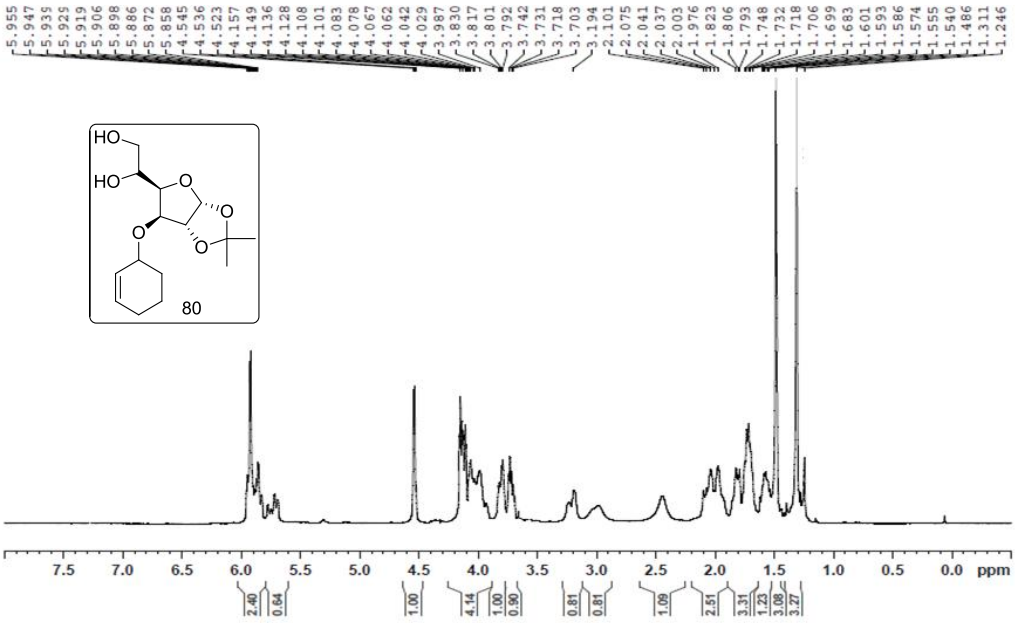
DEPT 135 ($CDCl_3$, 100MHz) Spectrum of Compound 78



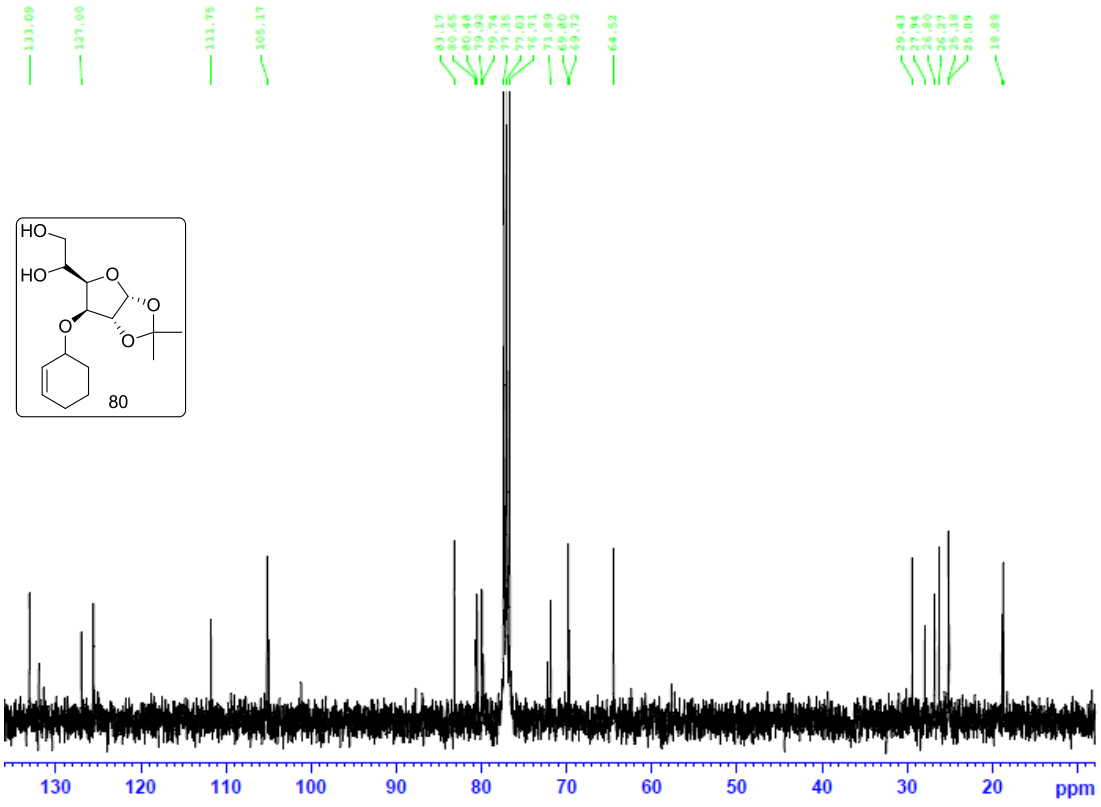
^{1}H NMR ($CDCl_3$, 400MHz) Spectrum of Compound 79



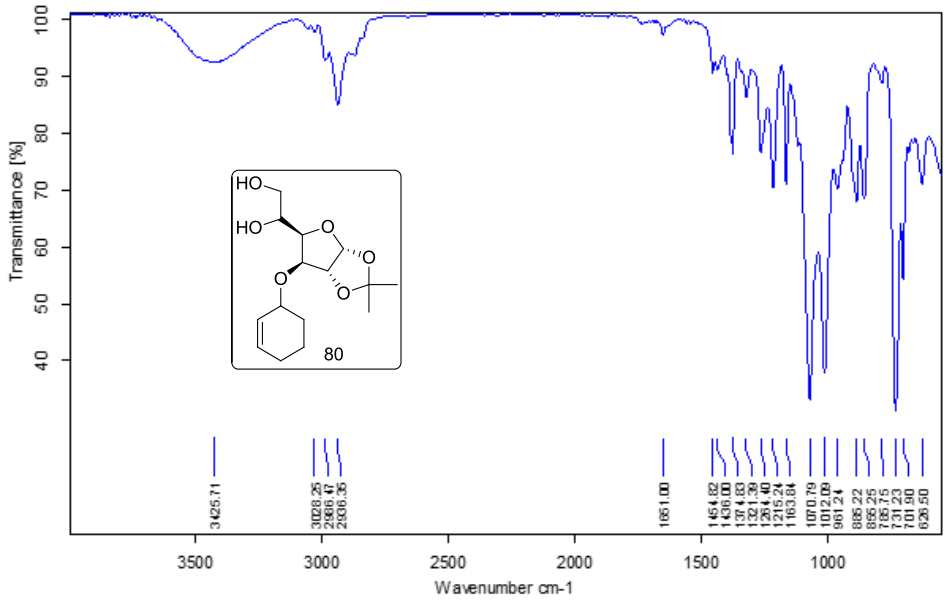
^{13}C NMR ($CDCl_3$, 100MHz) Spectrum of Compound 79



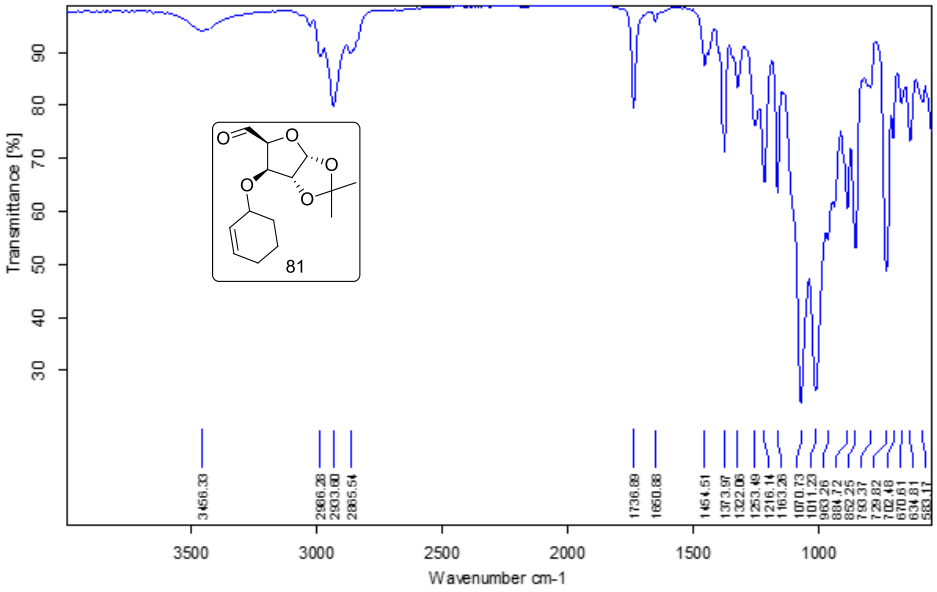
^{1}H NMR ($CDCl_3$, 400MHz) Spectrum of Compound 80



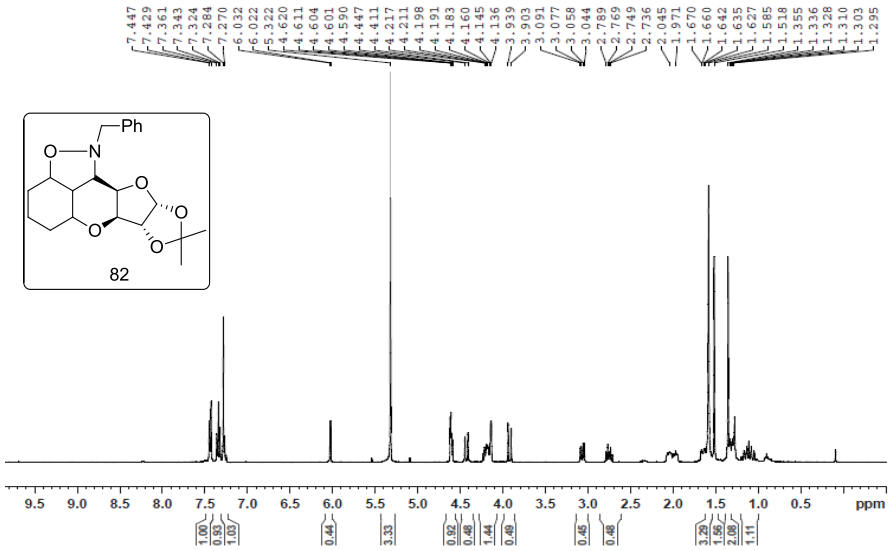
^{13}C NMR ($CDCl_3$, 100MHz) Spectrum of Compound 80



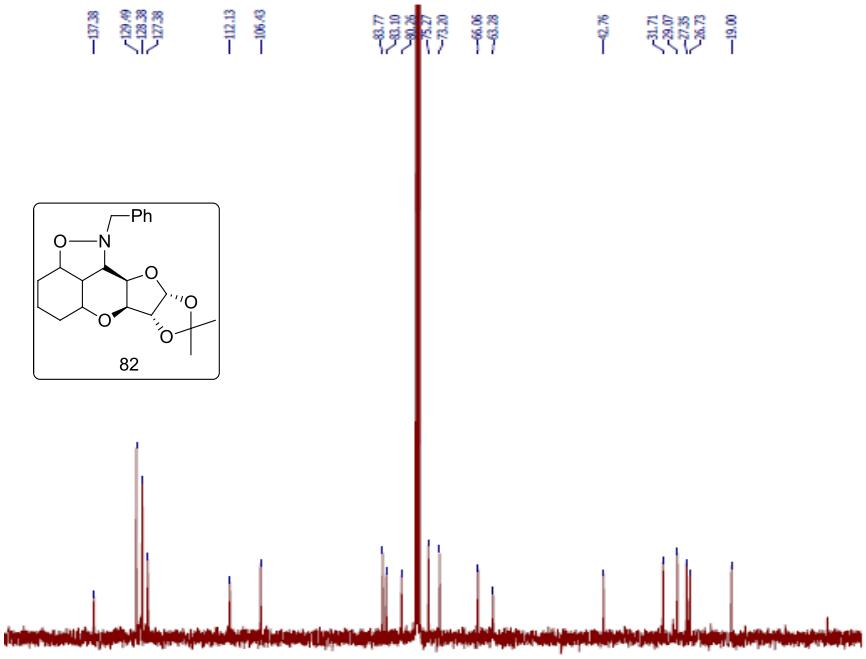
FTIR Spectrum: ν_{max} (neat)/cm^{-1} of Compound 80



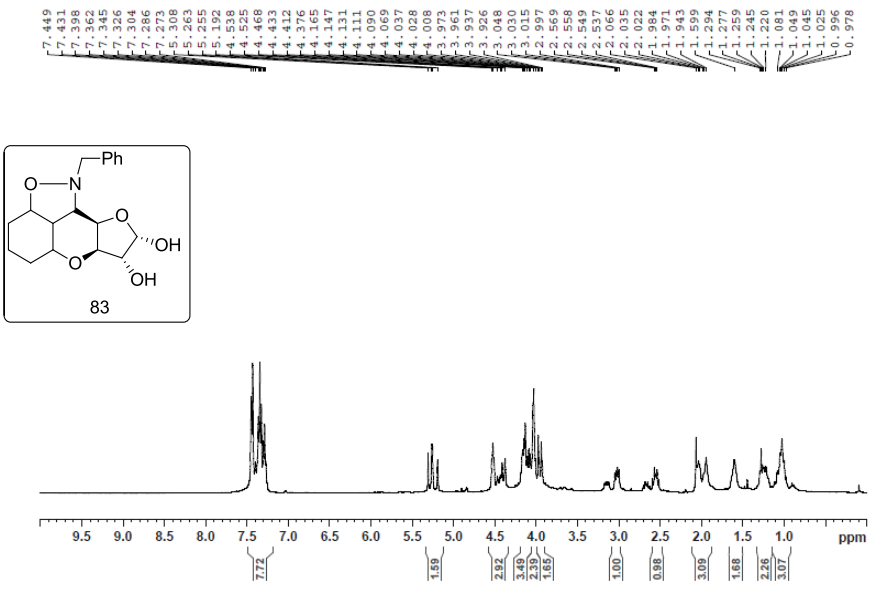
FTIR Spectrum: ν_{max} (neat)/cm^{-1} of Compound 81



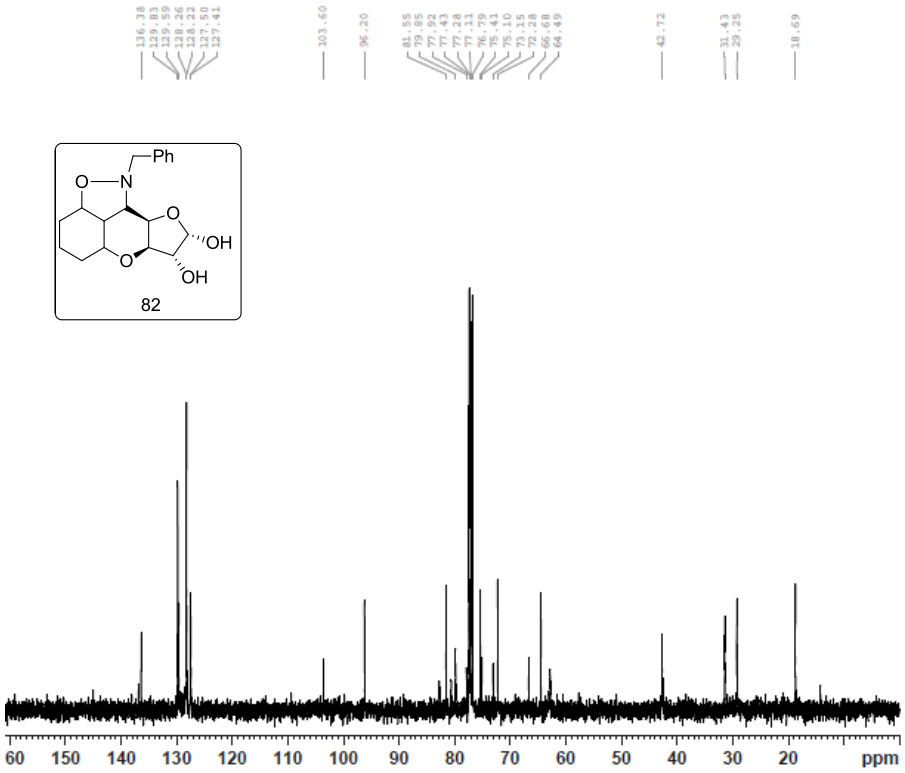
^{1}H NMR ($CDCl_3$, 400MHz) Spectrum of Compound 82



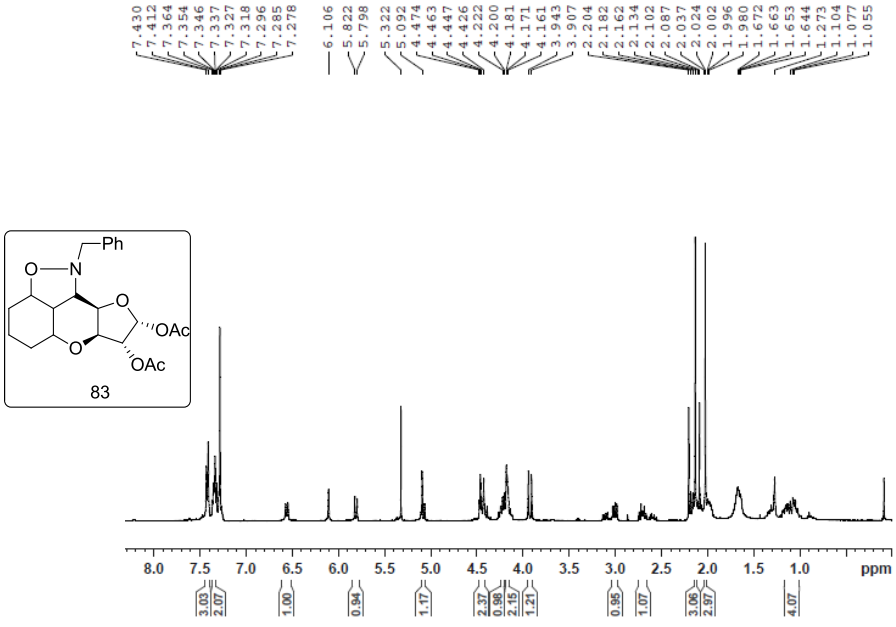
^{13}C NMR ($CDCl_3$, 100MHz) Spectrum of Compound 82



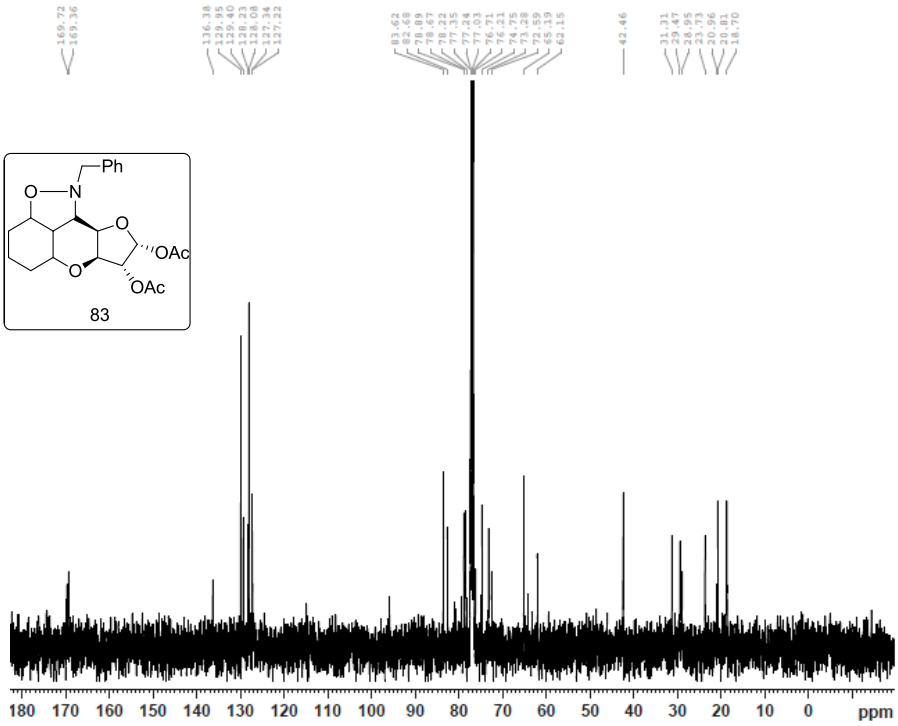
^{1}H NMR ($CDCl_3$, 400MHz) Spectrum of Compound 83



^{13}C NMR ($CDCl_3$, 100MHz) Spectrum of Compound 83



^{1}H NMR ($CDCl_3$, 400MHz) Spectrum of Compound 84



^{13}C NMR ($CDCl_3$, 100MHz) Spectrum of Compound 84

5.3 References

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