Synthesis of Naturally Occurring Oxacycles and Their Derivatives

Dissertation submitted to Sikkim University in partial fulfilment of the requirements for award of the degree of

Master of Philosophy

Submitted by

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DECLARATION

I hereby declare that the dissertation entitled "**Synthesis of Naturally Occurring Oxacycles and Their Derivatives**" submitted to Sikkim University in partial fulfilment of the requirements for award of the degree of **Master of Philosophy** is my original work. This dissertation has not been submitted for any other degree of this University or any other University.

Samuzal Bhuyan

Date: 8/02/2016
Place: Tadong, Gangtok

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CERTIFICATE

This is to certify that the dissertation entitled "**Synthesis of Naturally Occurring Oxacycles and Their Derivatives**" submitted to Sikkim University in partial fulfilment of the requirements for award of the degree of **Master of Philosophy** in Chemistry embodies the result of bona fide research work carried out by **Samuzal Bhuyan** 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 the investigation have been duly acknowledged by him.

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Date:

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List of Abbreviations

CAN-	Cerium Ammonium Nitrate
DCC-	Dicyclohexylcarbodiimide
DCM-	Dichloromethane
de-	Distereomeric excess
DIPEA-	N,N-Diisopropylethylamine
DMAP-	4-Dimethylaminopyridine
DMSO-	Dimethyl sulfoxide
DNA-	Deoxyribonucleic Acid
EDGs-	Electron donating groups
ee-	Enantiomeric excess
FTIR-	Furier Transform Infra-red Spectroscopy
HMDS-	Hexamethyldisilazane
INC-	Intramolecular Nitrone Cycloaddition
INOC-	Intra Nitrile Ooxide-alkene Cycloaddition
LHMDS-	Lithium bis(trimethylsilyl)amide
LPS-	Lipopolysaccharide
MMC-	Methyl Methoxymagnesium carbonate
NBS-	N-Bromosuccinimide
NIS-	N-Iodosuccinimide
NMO-	4-Methylmorpholine N-oxide
NMR-	Nuclear Magnetic Resonence
NOS-	Nitric oxide synthase

PCC-	Pyridinium Chlorochromate
PNBPA-	4-Nitro-N-propylbenzylamine hydrochloride
PPTS-	Pyridinium p-toluenesulfonate
PyBroP-	Bromotripyrrolidinophosphonium hexafluorophosphate
RB-	Round Bottom (flask)
RCM-	Ring Closing Metathesis
TAIC-	Tandem acylation-intramolecular cycloaddition
TAMA-	Methylanilinium trifluoroacetate (trifluoroacetate de N-methylanilinium)
TBAF-	Tetrabutylammonium fluoride hydrate
TBDMSC-	Tert-Butyldimethylsilyl chloride
THF-	Tetrahydrofuran
TFAA-	Trifluoroacetic anhydride
TLC-	Thin layer chromatography

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Schemes:

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1.1 Introduction

Natural products have rich history of being inspiration for novel scaffold discovery of many new drugs.[1] 60% of today's drugs have been derived from natural products.[2] Thus natural products scaffolds became very important source for discovery of new drug molecules.[3] But the bioactive secondary metabolites present in them are of very low concentration and they always remain as a mixture of many other compounds which hinder its isolation, testing and commercial use. Therefore, chemical syntheses of these natural products and their derivatives have become an inevitable step in the drug discovery and commercialization process. Synthesis of natural products continues to be important as it provides new methodology, new reactions and techniques. It gives us the idea to synthesise many unnatural bioactive analogues.

Oxacycles, the heterocycles containing oxygen as a hetero atom have been shown to be a major component of many biologically important natural products.[4] Oxacycles constitute an important class of heterocycle as they are naturally abundant and have a diverse biological function.[5] More than 90% of the drugs available today are heterocycles and many of them contain oxygen.[6] Tetrahydrofuran and γ-butyrolactone derivative are very important synthetic target as they occur in numerous natural products and have a wide range of biological activities. They show antifungal,[7] antibacterial,[8] anti-inflammatory,[9] anticonvulsant,[10] herbicidal,[11] anti allergic,[12] anti viral,[13] and anticancer activities.[14] Many of today's drugs available in the market contain oxacycle. Some of the biologically active oxacycles and natural products have been shown below with their biological activity.

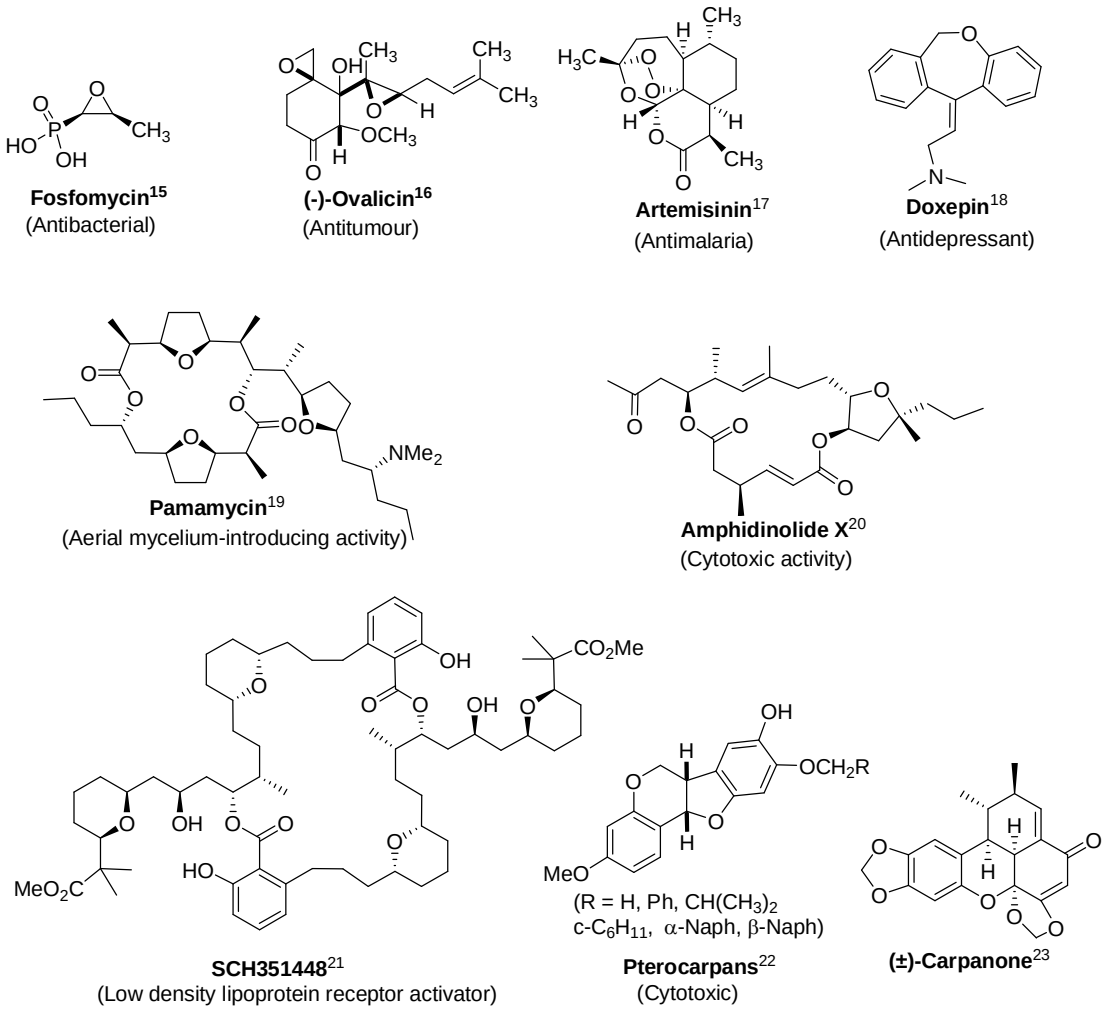


Figure 1.1: Oxacycles as Drugs

These days there is strong interest for synthesis of chiral molecules due to their selective binding advantage with chiral biological target site. Each enantiomer interacts differently in chiral environment of biological system.[24] When one enantiomer can show advantageous bioactivity other may not have any effect or some toxic effect. So, single enantiomer always has advantage over racemate.[25] In last ten to fifteen years due to considerable advancement in the chemical technologies in the field of synthesis, separation and analysis, stereoselective synthesis has become an area of considerable interest. Today in the world approximately 50% drugs are chiral and other 50% are mixture of their enantiomers.[25] Problem with stereoselective

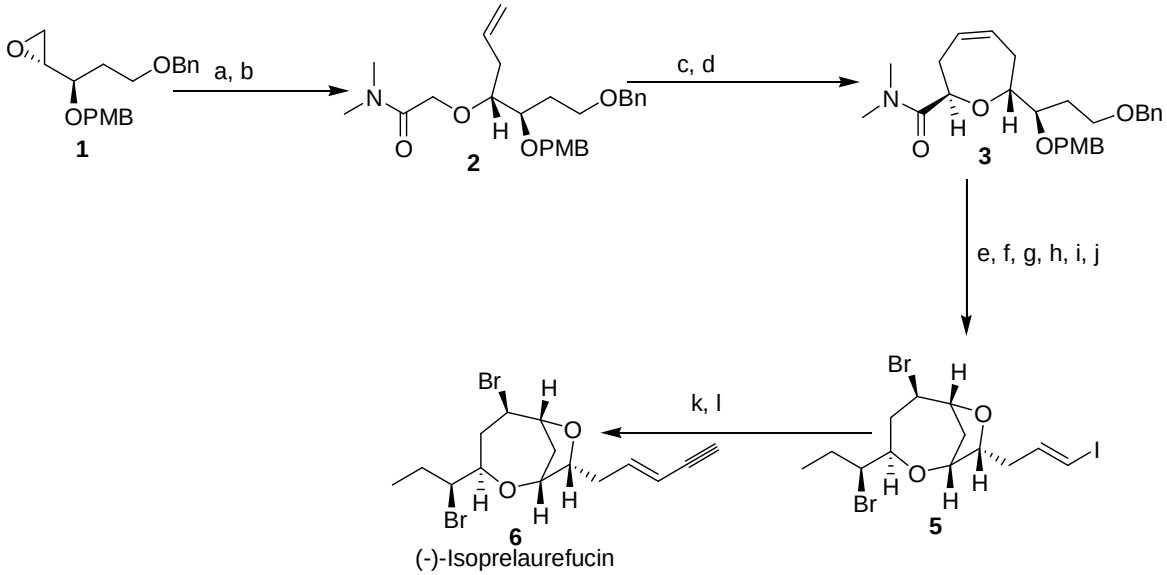
synthesis lies in the fact that it requires expensive chiral reagents and yields mixture of stereoisomers which are difficult to separate and thus consume considerable time and labour for separation. Instead, substrate control synthesis using easily available naturally occurring carbohydrate chiral pool with inexpensive common achiral reagents to obtain single stereoisomer bears great importance. Carbohydrates like D-Glucose contain six easily functionalizable chiral centres and thus mostly required inexpensive achiral reagent to generate any new chiral centre in almost stereo specific manner. Diacetone-D-glucose (1,2:5,6-di-O-isopropylidene-α-D-glucofuranose) is a cheap, stable and solid derivative of D-glucose which can be easily synthesise in laboratory in pure form and can be an excellent starting material for our synthesis.

The core objective of this research is synthesising oxacycles from sugar and to study their biological activity against various microbial strains, viral strains as well as anticancer activity in cell lines.

2.1 Literature Review

Due to their importance in drug industry and large presence in diverse natural product structures, synthesis of various oxacycles has become very important field among synthetic chemist.[18] Extensive research in this field yielded large number of important publications. Some of the most recent and relevant publications are summarised below.

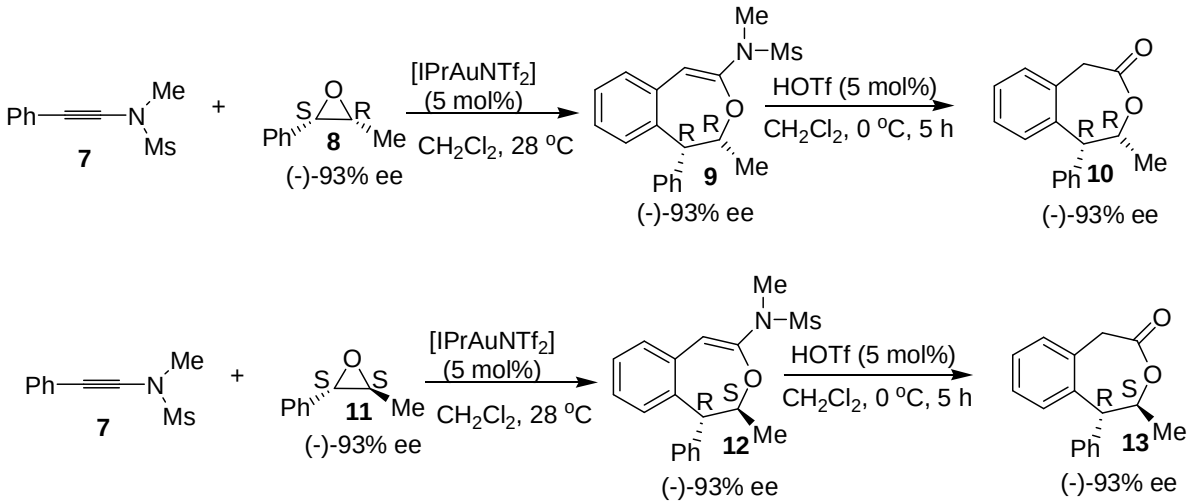
Hyunjoo *et al.*[26] reported the total synthesis of (-)-Isoprelaurefucin, a seven-membered oxacyclic marine natural product. They diastereoselectively synthesized R,R′-syn- and R,R′-anti-bis-alkenes, and subsequently did RCM to get the oxacyclic compound **3** from an epoxide **1**. The primary alcohol obtained by deprotection of **3** was then converted to an aldehyde by Dess-martin periodinane and introduction of the (E)-enyne moiety by Takai olefination protocol on the formed aldehyde resulted in the formation of the product **5**. Compound **5** was converted to the penultimate (E)-TMS-enyne by Sonogashira coupling with TMS-acetylene and further deprotection formed the seven membered oxacyclic marine product (-)-Isoprelaurefucin.



(a) CH_2=CHMgBr, CuI, -45 ^oC (b) $ClCH_2CONMe_2$, NaH, 0 ^oC (c) LHMDS, THF, -78 ^oC (d) Grubbs (I), 40 ^oC (e) EtMgBr, THF (f) L-Selectride, THF, -78 ^oC (g) CBr_4Oct_3P, 1-methylcyclohexane, (h) NBS, CH_3CN, (i) Dess-Martin periodiane (j) CH_3I $CrCl_2$, THF (k) TMS-acetylene, $Pd(Ph_3P)_4$, CuI Et_2NH (l) TBAF, THF

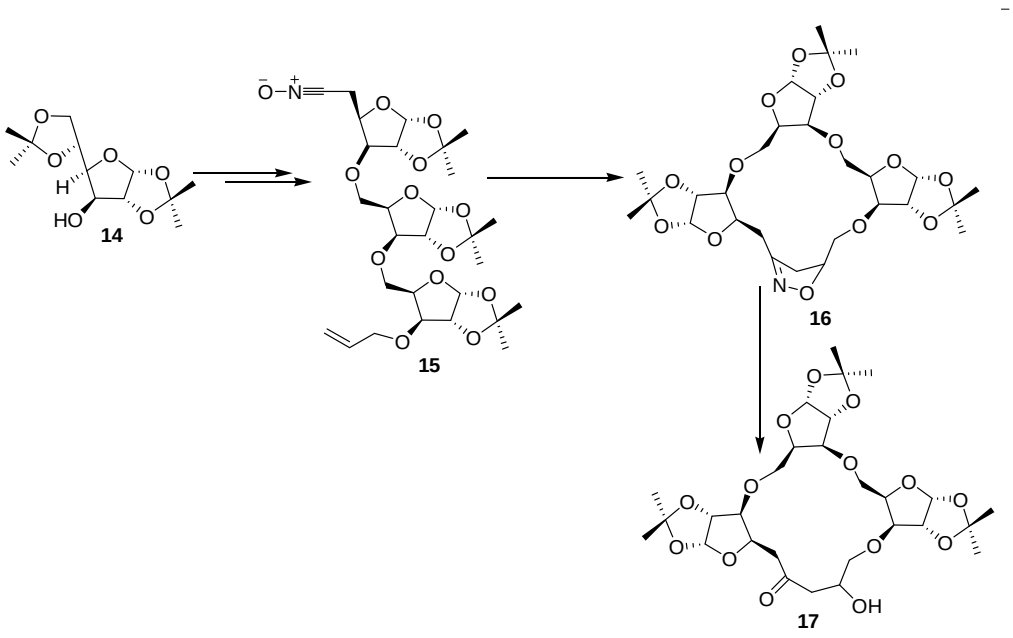
Scheme 2.1: Total synthesis of (-)-Isoprelaurefucin.

Karad *et al.*[27] reported a new synthesis of seven-membered oxacycles through a gold-catalyzed inter molecular [4+3] cycloaddition of arenynamides with epoxides. This cycloaddition is applicable for the synthesis of enantiopure oxacycle (**10**, 93% ee) using (2R, 3S)-(-)-2-methyl-3-phenyloxirane (**8**, 93% ee). Hydrolysis of oxacyclic adduct **9** formed the chiral oxacycle **10**. On using the enantiopure (2S, 3S)-(-)-2-methyl-3-phenyloxirane **11** (99% ee) and subsequent hydrolysis gave the corresponding chiral oxacycle **13**.



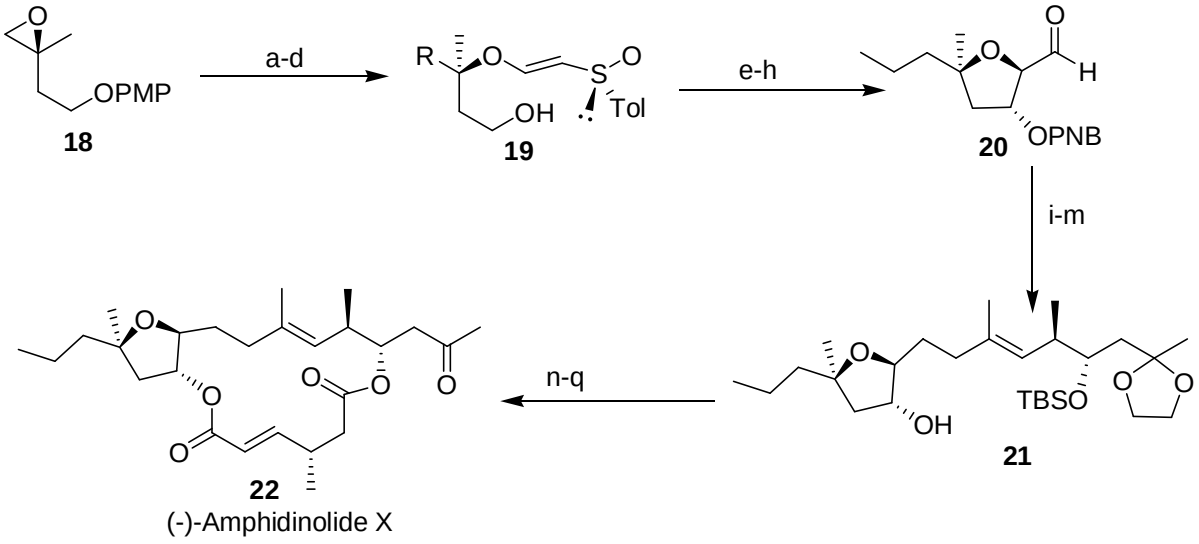
Scheme 2.2: Synthesis of enantiopure seven membered oxacycles.

Sengupta *et al.*[28] reported the synthesis of 3,5′-Ether-linked pseudo-oligopentose derivatives from carbohydrate precursors. Diacetone-D-glucose **14** was O-allylated at C-3 followed by deprotection at 5,6 position and mesylation gave a carbohydrate precursor for intramolecular cycloaddition of the nitrile oxides. That led to the diastereoselective formation of chiral isoxazolines fused 16-membered oxacycles.



Scheme 2.3: Synthesis of pseudo-oligosaccharide derivatives.

Jung *et al.*[29] reported the total synthesis of a marine natural oxacyclic product (-)-Amphidinolide X having considerable cytotoxic activity. Nucleophilic ring opening of chiral epoxide **18** followed by treatment with ethyl magnesium bromide and alkynyl sulfoxides result (E), (S)-β-alkoxyvinyl sulfoxide **19**. They utilized the chiral precursor **19** for their synthesis of (-)-amphidinolide X using SmI_2 mediated 5-exo cyclization and ring closing metathesis as vital step.

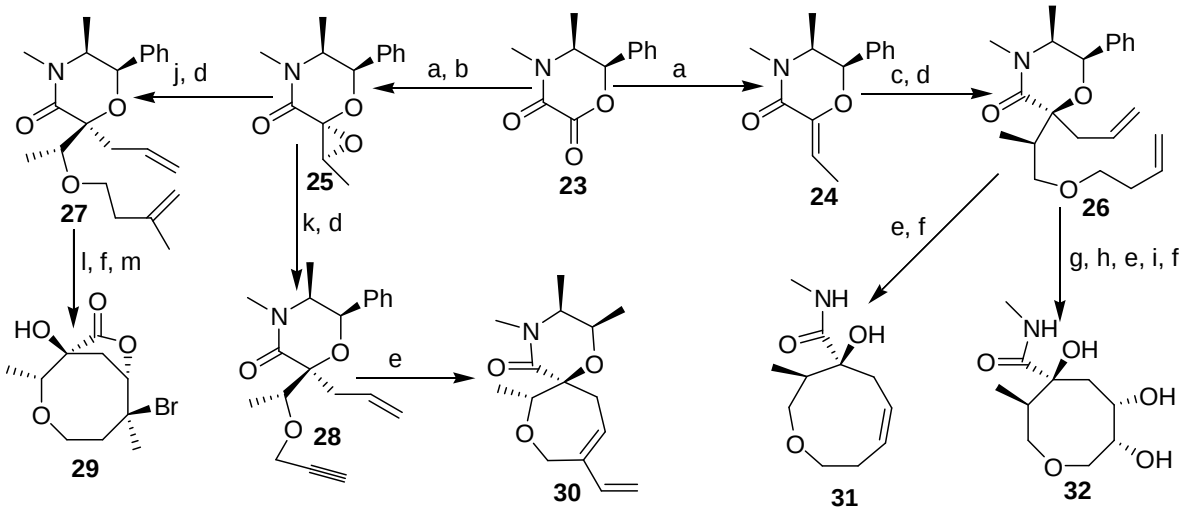


(a) EtMgBr, CuI,THF; (b) alkynyl sulfoxides, EtMgBr, LiCl, THF; (c) I_2, CH_2 Cl_2 THF (d) CAN, $MeCN/H_2O$ (e) DMP, CH_2Cl_2, (f) SmI_2, MeOH, THF (g) PNBA, DCC, DMAP, CH_2Cl_2; (h) TFAA, pyridine, MeCN; KOAc, H_2O; (i) $MeCOCH_2PO(OMe)_2$, DIPEA, MeCN; (j) H_2, Pd/C (k) $Ph_3PMe^+Br^-$, nBuLi, (l) LAH, diethyl ether; (m) H_2IMes_2 $(Cy_3P)Cl_2RuCHPh$, CH_2Cl_2, reflux; (n) $CH_2CHCOCl$, pyridine (o) AcOH, H_2O; (p) $(COCl)_2$,alcohol, DMAP, (q) 7 mol% (H_2IMes_2)-$(Cy_3 P)Cl_2RuCHPh$, reflux

Scheme 2.4: Total synthesis of (-)-Amphidinolide X **18**.

Pansare *et al.*[30] reported enantioselective synthesis functionalized seven, eight, and nine membered oxacycles. Their methodology included regioselective and diostereoselective transformations of an ephedrine-derived epoxy morpholinone to

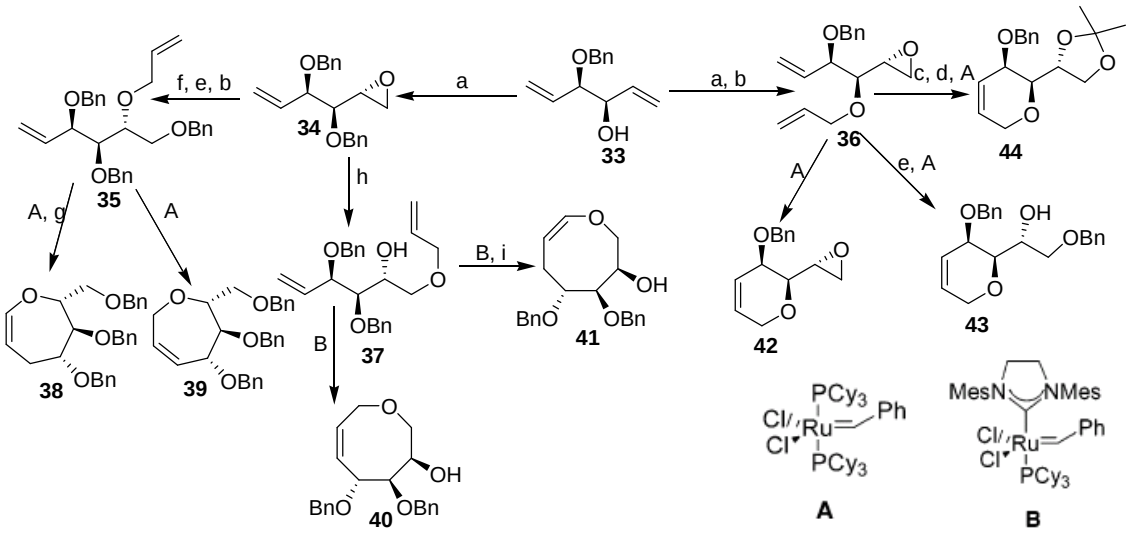
functionalized various diolefins or enynes and final cyclization through ring closing metathesis (RCM). They tethered olefinic and acetylinic moiety of different carbon chain length to synthesise medium size oxacycle of different ring sizes.



(a) $EtMgCl_2.Bf_3OEt_2$ (b) m-CPBA (c) aq HCHO, H_2SO_4, dioxane, (d) $CH_2=CHCh_2SiMe_3$, BF_3Et_2O (e) Grubbs I,(f) Na/NH_3, (g) BBr_3, CH_2Cl, (h) NaH. Allyl bromide, (i) OsO_4, NMO (j) $(CH_3)CH_2CCH_2CH_2OH$ (k) Propargyl alcohol (l) Grubbs II (m) NBS, THF,

Scheme 2.5: Stereoselective synthesis of medium size oxacycles.

Schmidt *et al.*[31] reported the stereoselective synthesis of six to eight membered oxacycles by ring closing metathesis and tandem RCM isomerisation. They used epoxide **34**, synthesized through stereoselective Sharpless epoxidation of **33**, as starting point for introduction of diolefins which on RCM reaction using catalyst A and B resulted in six to eight membered oxacycles related to heptoses.

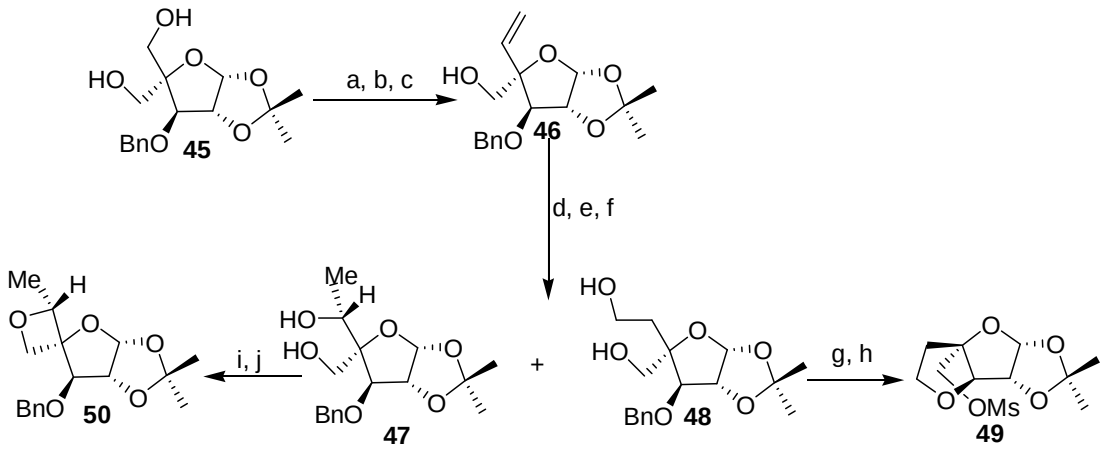


(a) $Ti(OPr)_4$, (+)-DET, (b) NaH, $H_2C{=}CHCH_2Br$, (c) H_2SO_4, THF/H_2O (d) $Me_2C(OMe)_2$, p-TSA

(e) $PhCH_2OH$, BF_3OEt_2 (f) NaH, BnBr (g) 2-propanol, NaOH (h) $H_2C{=}CHCH_2OH$, MeONa (i) $NaBH_4$

Scheme 2.6: Synthesis of unsaturated oxacycles by RCM and Tendem-RCM isomerism

Maity *et al.*[32] reported synthesis of spirocyclic, bicyclic nucleoside from D-Glucose derived substrate. They prepared precursor **45** in 5 steps from D-Glucose which was treated with imidazole then Swern oxidation followed by Wittig reaction gave the compound **46**. Oxidation of compound **46** in presence of peroxide gave both Markonikov and anti-Markonikov products **47**, **48** which on cyclization gave the corresponding products **49**, **50**.

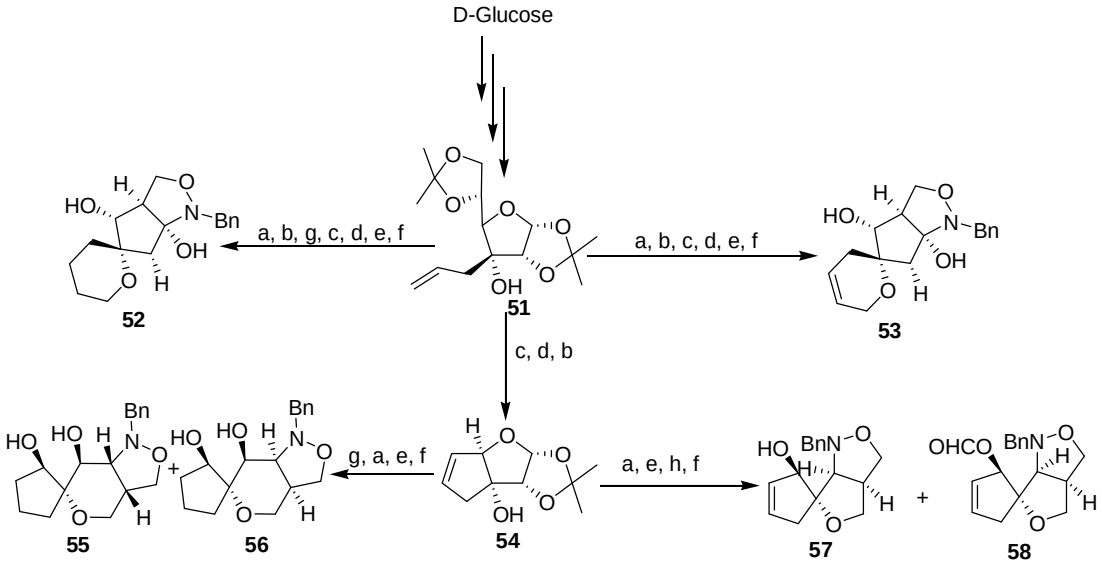


(a) Imidazole, TBDMSC, (b) Oxalyl chloride, DMSO, (c) Et_3N, H_2O (d) $Ph_3PCH3Br$, t-BuOK,

(e) B_2H_6, THF (f) H_2O_2, NaOH, (g) PPh_3, imidazole, I_2 (h) NaH, reflux (i) Py, MsCl (j) Na_2S, DMF

Scheme 2.7: Synthesis of oxacycle from glucose derived substrate.

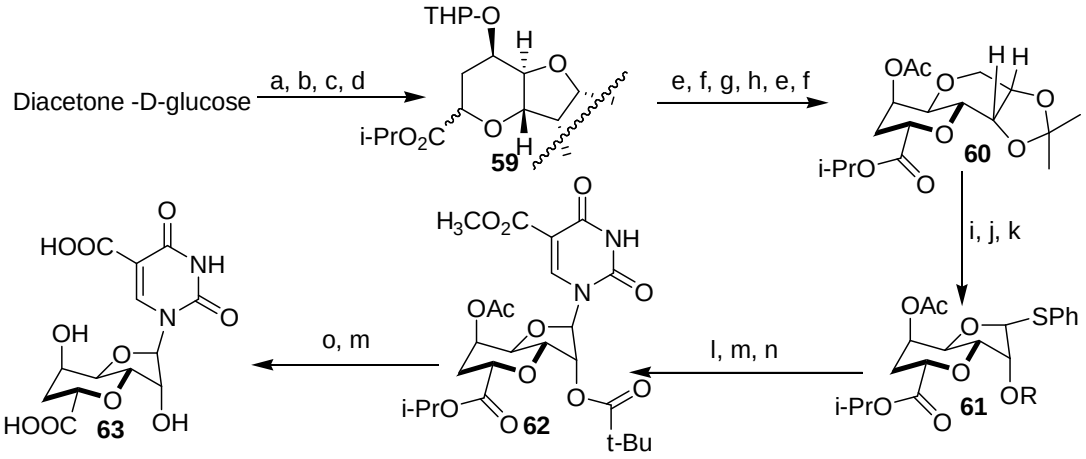
Sahabuddin *et al.* [33] reported the generation of oxacyclic nucleoside from D-Glucose derived precursor. They manipulated 1,2:5,6-di-O-isopropylidene-α- D -allofuranose to prepare suitable synthon which was converted to spirocycles and tricyclic oxacycle by applying ring closing metathesis (RCM) and intramolecular nitrone cycloaddition (INC) reactions. The formed oxacyclic rings were cleaved by transfer hydrogenolysis and generated nucleoside with 5-amino-4, 6-dichloropyrimidine.



Reagents and conditions: (a) NaH, allyl bromide, THF, reflux, 4 h; (b) $[Cl_2(Pcy_3)_2Ru=CHPh]$, CH_2Cl_2, rt, 6 h, N_2; (c) HOAc-H_2O (3:1), rt, overnight; (d) Ph_3P, imidazole, I_2, toluene, reflux, 6 h; (e) 4% H_2SO_4, CH_3CN-H_2O (3:1), rt, 24 h; (f) BnNHOH, dry EtOH, reflux, 4 h, N_2; (g) H_2-Pd/C (10%), EtOH, rt, 4 h; (h) $NaIO_4$ (aqueous), MeOH, 10 °C, 45 min.

Scheme 2.8: Synthesis of heterocyclic nucleoside by RCM and INC reaction.

Knapp, S. *et al.*[34] reported a short synthesis of octosyl nucleoside. The adenine analogue octosyl acid shows more pronounced biological activity. They converted commercially available 1,2:5,6-di-O-isopropylidene-α-D-allofuranose to a protected bicyclic octosyl acid thioglycoside donor in ten steps. Their synthesis focused on an intramolecular ester enolate alkylation, Glycosylation of N-benzoyladenine and methyl uridine-5-carboxylate.



(a) i-PrO_2CCH_2Br, (b) aq HOAc (c) I_2, PPh_3, CH_3CN, DMF, (d) DHP, PPTS, (e) aq HOAc, THF, (f) Ac_2O, Py, DCM, (g) t-BuOH, (h) i-PrI, NaH, (i) PhSH, $BF_3.OEt_2$, (j) $AgClO_4$, $NaHCO_3$, CH_3NO_2, (k) Piv-Cl, DMAP, (l) *N*-bemnzyladenine, HMDS, NIS, TfOH, (m) 1M aq LiOH (n) NH_4OH (o) methyl N,O-bis(trimethylsilyl)-uracil-5-carboxilate NIS, TfOH,

Scheme 2.9: Synthesis of octosyl nucleoside.

2.2 Aims and Objectives:

The objectives of this work are:

(i) Stereoselective synthesis of various oxacyclic natural products and their derivatives.

(ii) Development of new methodologies for the formation of oxacycles.

(iii) Structural and stereochemical elucidation of the synthesized oxacycles through spectroscopic techniques like ^{1}HNMR, ^{13}CNMR, Mass spectrometry, FTIR, Polarimeter etc.

(iv) Study of the biological activities of the synthesized oxacycles.

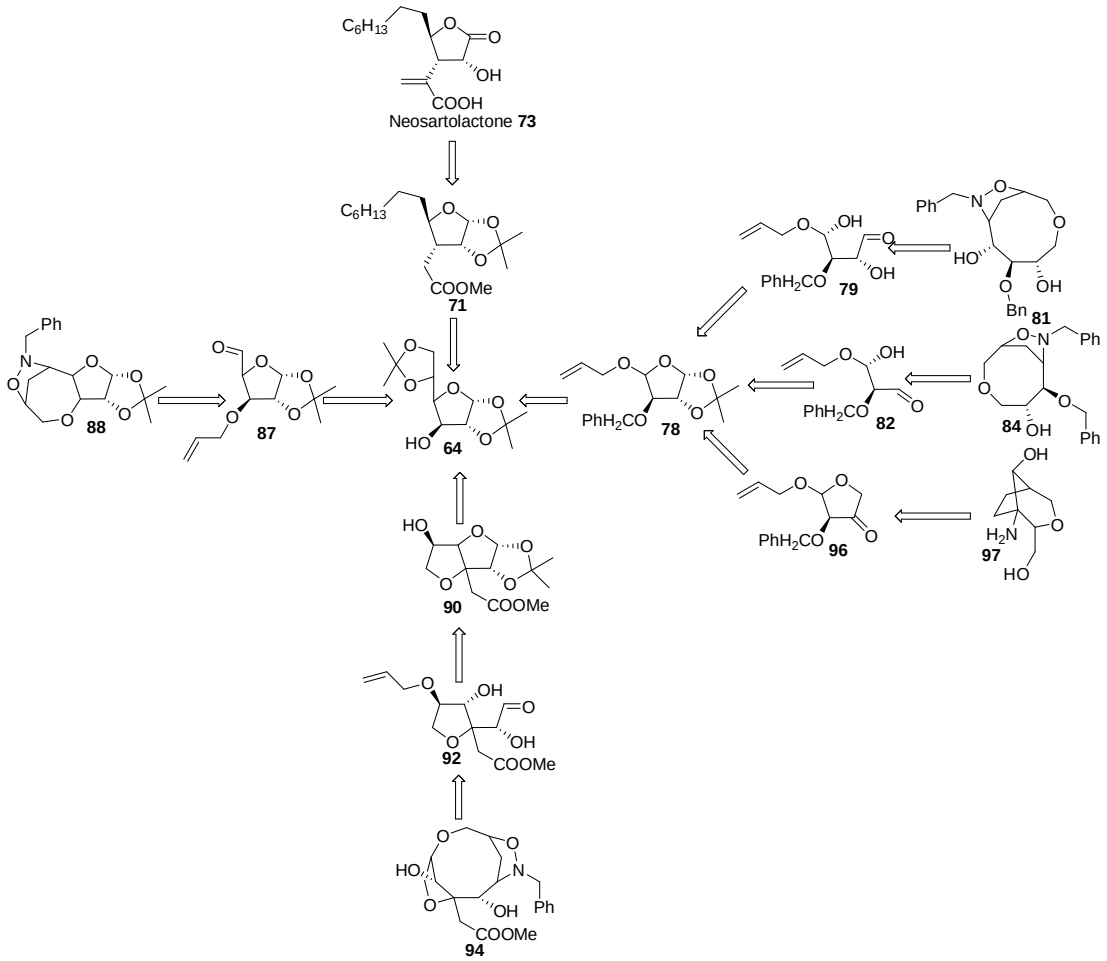
3. Materials and methods

3.1 Strategy for the Synthesis:

Strategies for the synthesis of different oxacycles were developed taking D-Glucose as a chiralpool starting material. Our strategy involves (i) C-1 nitrone and C-5 O-allyl, (ii) C-2 nitrone and C-5 O-allyl and (iii) oxa-Michael cyclization. The retrosynthesis followed by the synthetic route have been shown below.

3.1.1 Retrosynthesis

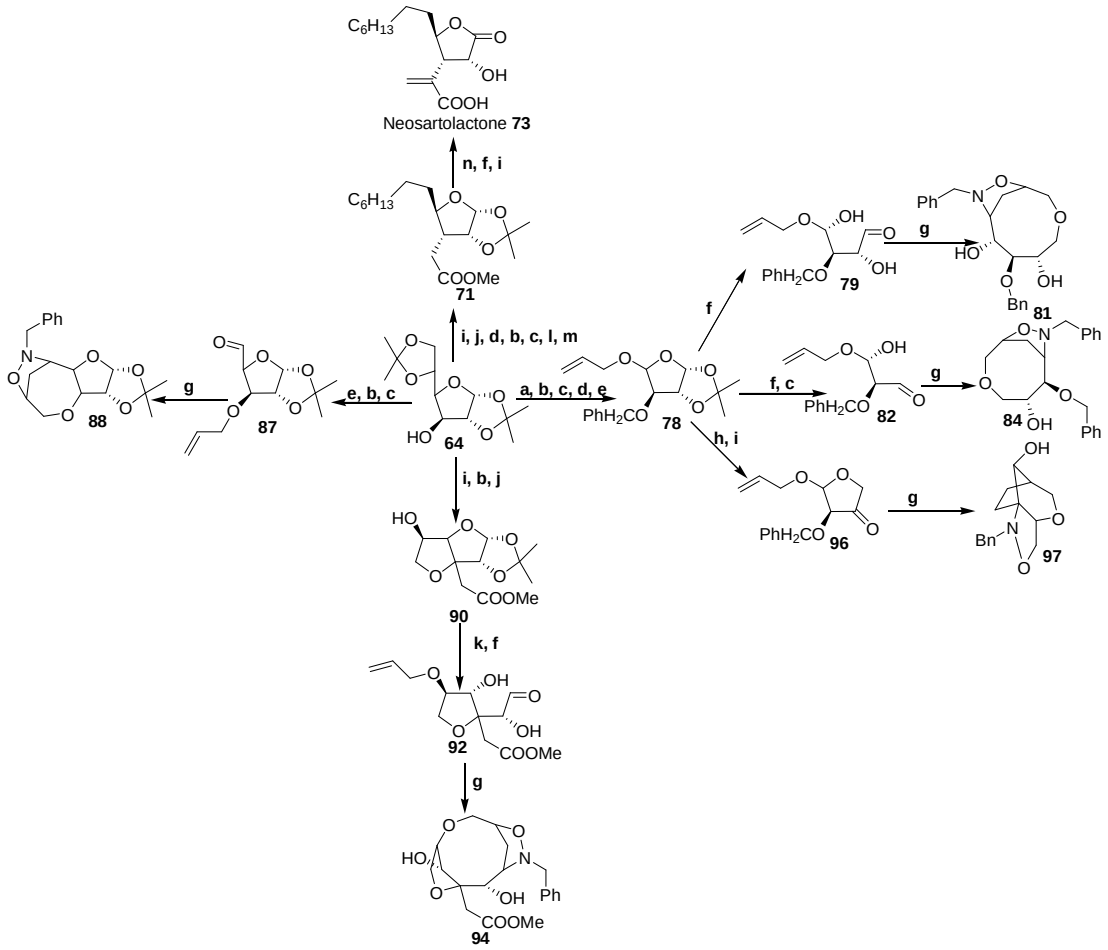
Following retrosynthesis was devised for the synthesis of *Neosartolactone* **73** and its 7-methyl ester analogue and bicyclic and tricyclic oxacycles **81**, **84**, **88**, **90**, **94** and **97** from Diacetone-D-glucose (1,2:5,6-di-O-isopropylidene-α-D-glucofuranose) which can be easily prepared from D-Glucose.[38] The total synthesis of *Neosartolactone* **73** and its 7-methyl ester analogue consist of nine steps from compound **64**. Synthesis of oxacycle **81** contains seven steps and synthesis of tricyclic oxacycle **90** contains three steps from compound **64**. Oxacycle **84** can be prepared from **79** in two steps. It takes four steps to synthesize compound **88** and five steps to synthesize the compound **94** from the compound **64**. Oxacycle **95** can easily be synthesized from compound **78** in three steps.



Scheme 3.1: Retrosynthetic analysis

3.1.2 Synthetic route

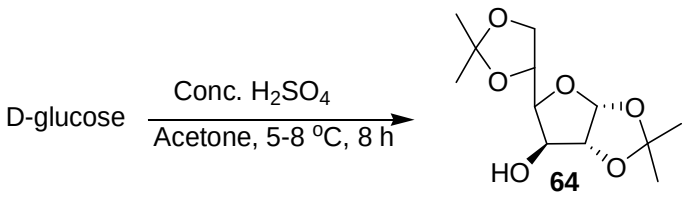
Following synthesis route was devised for the synthesis of *Neosartolactone* **73** and its 7-methyl ester analogue and bicyclic and tricyclic oxacycles **81**, **84**, **88**, **90**, **94** and **97**. The cyclization process involves intramolecular nitrone cycloaddition (INC) reaction by reacting with benzyl hydroxylamine. The reagents and the conditions for the syntheses have been given below the scheme.



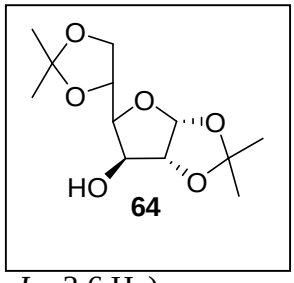
(a) BnBr, NaOH, $Bu_4N^+Br^-$, DCM, (b) 75% AcOH, (c) $NaIO_4$, Methanol, (d) $NaBH_4$, Methanol (e) Allylbromide, NaOH, $Bu_4N^+Br^-$ (f) 4% H_2SO_4 (g) BnNHOH, (h) BF_3Et_2O, Et_3SiH, DCM, (i) PCC, DCM, (j) $PPh_3CHCOOCH_3$, toluene, (k) NaH, Alylbromide, (l) $BrPPh_3C_7H_{15}$ (m) H_2/Pd-C (n) Na_2CO_3, HCHO

Scheme 3.2: Synthetic route

Synthesis of Diacetone-D-glucose (1,2:5,6-di-O-isopropylidine-α-D glucofuranose)



D-glucose (50 g, 0.28 mol) was dissolved in acetone and the reaction mixture was cooled to 0 ^{o}C in an ice bath. Conc. H_2SO_4 (40 ml) was added drop wise maintaining the temperature below 5-8 ^{o}C. The setup was allowed to stir vigorously maintaining the temperature between 5-8 ^{o}C for 8 h. Neutralization (pH = 7) of the acidic mixture by adding 50% NaOH solution maintaining the temperature below 20 ^{o}C was done. The acetone was taken out by rinsing thrice and dried in rotavapore in reduced pressure. The aqueous layer was taken in a separating funnel and the compound was extracted out by 3 x 20 ml portions of chloroform. The organic parts were combined and washed with brine and passed through anhydrous sodium sulphate to trap if little amount of water was left. Addition of pet-ether after concentrating the extracted organic part by drying resulted in the formation of white precipitate which on washing with pet ether gave pure solid compound 1,2:5,6-di-O-isopropylidene-α-D-glucofuranose **64** (44 g, 58%).



^{1}H NMR ($CDCl_3$, 400MHz): δ ppm 1.30 (s, 3H), 1.35 (s, 3H), 1.43 (s, 3H), 1.48 (s, 3H), 2.81 (d.1H, *J* = 3.6), 3.98 (dd, 1H, *J* = 5.2, 8.8 Hz), 4.05 (dd, 1H, *J* =2.4, 7.6), 4.15 (dd, 1H, *J* = 6.4, 8.4 Hz), 4.32 (m, 2H), 4.52 (d, 1H, *J* = 3.6 Hz) 5.93 (d, 1H, *J* = 3.6 Hz)

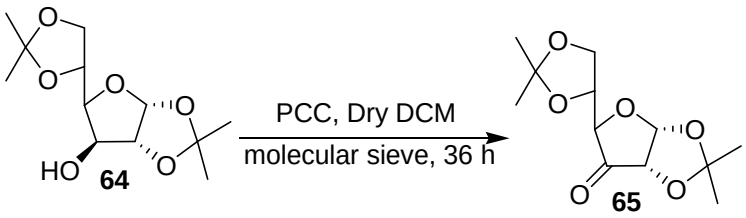
^{13}C NMR ($CDCl_3$, 100MHz): 25.1 (CH_3), 26.1 (CH_3), 26.7 (CH_3), 26.8 (CH_3), 67.6 (CH_2), 73.3 (CH), 75.0 (CH), 81.0 (CH), 85.5 (CH), 105.2 (CH), 109.6 (C), 111.8 (C).

FTIR Spectrum: ν_{max} (neat)/cm^{-1} 3425, 1373, 1218, 1063, 1004, 729

ESIMS, *m/z*: 260 $(M)^+$.

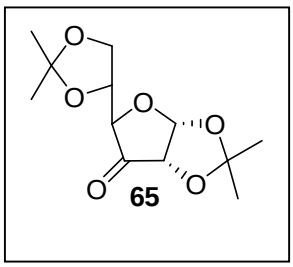
3.2 Towards the synthesis of Neosartolactone 73 and its 7-methyl ester analogue

Compound **73** is *Neosartolactone*, a γ-butyrolactone derivative which was originally extracted from the ethyl acetate extract of fermented broth of *Neosaryta sp.* by Sien-Sing Yang *et. al.*[35]. *Neosartolactone* is an anti inflammatory compound which inhibits the production of NO in Lipopolysaccharides (LPS) activated muriene macrophage. Towards the total synthesis of the compound a synthetic route was developed consisting nine steps from compound **64**. First seven steps have been successfully completed. Next step is introduction of methelene group for which a series of different reactions (shown below) have been performed but was not successful. Stepwise synthesis procedure and discussion of the spectroscopic data has been given below.

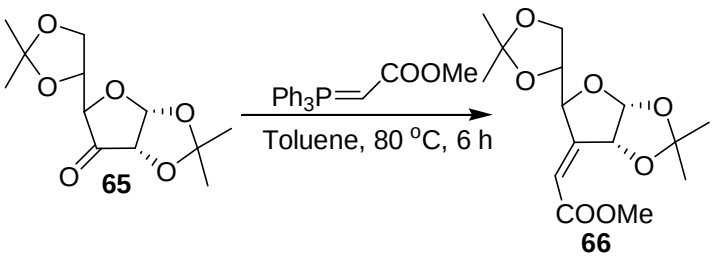


Diacetone D-glucose **64** (8.0 g, 30.1 mmol) was dissolved in dry dichloromethane (600 ml) and molecular sieve (15 g) was added with PCC (25 g) to the reaction mixture and stirred vigorously. A guard tube containing fused calcium chloride was connected ensuring no entry of H_2O and allowed to stir for 48 h. After completion of the reaction (confirmed by TLC) about 600 ml of pet-ether was added to the reaction mixture. Purification of the compound by column in Buckner funnel with silica gel yielded the white solid compound **65** (5.4 g, 68%).

^{1}H NMR ($CDCl_3$, 400MHz): δ ppm 1.36 (s, 3H), 1.38 (s, 3H), 1.52 (s, 3H), 1.56 (s, 3H), 3.89 (d, 1H *J* = 5.2 Hz), 4.02 (d, 1H, *J* = 6.4 Hz), 4.12 (m, 1H), 4.26 (d, 1H, *J* = 4.0 Hz), 4.44 (m, 1H), 5.83 (d, 1H, *J* = 3.6 Hz).

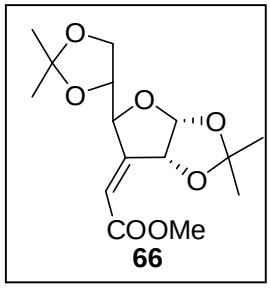


FTIR Spectrum: ν_{max} (neat)/cm^{-1} 2991, 1772, 1375, 1214, 1154, 1021, 845.

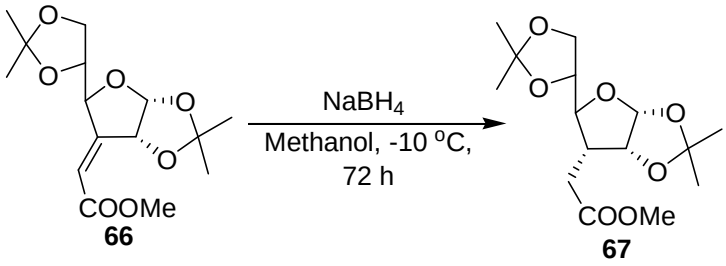


Compound **65** (4.0 g, 15.5 mmol) was dissolved in toluene and methyl (triphenylphosphoranylidene)acetate (6.18 g) was added. The reaction mixture was heated in an oil bath at 80 ^{o}C for 6 h with constant stirring. After completion of the reaction (confirmed by TLC) the toluene was dried in rotavapore under reduced pressure and extracted with dichloromethane (3 x 20 ml). The organic parts were combined and washed with brine, dried (anhydrous Na_2SO_4) and evaporated to obtain crude product. Purification of the crude by column chromatography afforded a thick oily compound **66** (4.6 g, 95%).

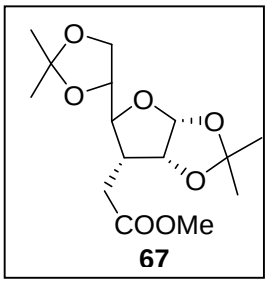
^{1}H NMR ($CDCl_3$, 400MHz): δ ppm 1.28 (s, 3H), 1.34 (s, 3H), 1.36 (s, 3H), 1.42 (s, 3H), 3.70 (s, 3H), 3.91-3.96 (m, 2H), 4.00-4.05 (m, 1H), 4.60 (dt, 1H, *J* = 1.6, 7.2 Hz), 5.67 (dt, 1H, *J* = 1.2, 5.2 Hz), 5.78 (d, 1H, *J* = 4.0 Hz), 6.29 (t, 1H, *J* = 1.6 Hz)



^{13}C NMR ($CDCl_3$, 100MHz): δ ppm 25.3 (CH_3), 26.7 (CH_3), 27.1 (CH_3), 27.3 (CH_3), 51.7 (CH_3), 67.2 (CH), 76.8 (CH), 78.3 (CH), 79.8 (CH), 104.9 (CH), 110.1 (C), 112.8 (C), 117.4 (CH), 156.1 (C), 165.5 (C=O).



To a methanolic solution of compound **66** (3.0 g, 9.5 mmol), $NaBH_4$ (435 mg, 11.4 mmol) was added slowly by cooling the reaction mixture to -10 ^{o}C and allowed to stir for 72 h. After the completion of the reaction (confirmed by TLC) $NaHCO_3$ (200 mg) has been added. Methanol was evaporated completely in low temperature under reduced pressure in rotavapore and the product was extracted with dichloromethane (3 x 20 ml). The combined extract was washed with water (2 x 15 ml), dried (anhydrous Na_2SO_4) and evaporated to an oily residue. The crude product was chromatographed over silica gel to afford **67** (2.7 g. 90%) as oily liquid.

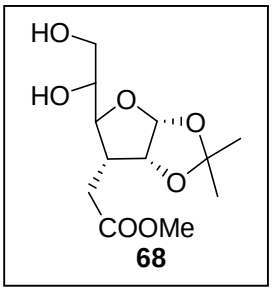


^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 1.29 (s, 3H), 1.31 (s, 3H), 1.39 (s, 3H), 1.48 (s, 3H), 2.28-2.35 (m, 1H), 2.65 (dd, 1H, *J* = 10.4, 17.2 Hz), 2.82 (dd, 1H, *J* = 4.0, 17.6 Hz), 3.64-3.73 (m, 1H), 3.69 (s, 3H), 3.90 4.01 (m, 2H), 4.06-4.11 (m, 1H), 4.79 (t, 1H, *J* = 4.0 Hz), 5.77 (d. 1H, J = 3.6 Hz)

^{13}C NMR ($CDCl_3$, 100MHz): δ ppm 25.2 (CH_3), 26.3 (CH_3), 26.6 (CH_3), 26.7 (CH_3), 29.7(CH_2), 44.5 (CH), 51.6 (CH_3), 67.9 (CH_2), 77.9 (CH), 80.9 (CH), 81.4 (CH), 105.0 (CH), 109.6 (C), 111.9 (C), 172.8 (C=O).

ESIMS, *m/z*: 316 $(M)^+$.

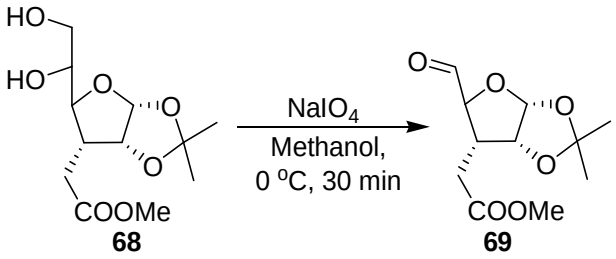
Compound **67** (2.5 g, 7.9 mmol) was dissolved in 25 ml aqueous AcOH (75%) and stirred for 24 h. The solvent was evaporated under reduced pressure and the last trace of AcOH was evaporated through azeotropic distillation with toluene to obtain the diol **68** as a thick colourless oily liquid (1.8 g, 82%).



68

^{1}H NMR ($CDCl_3$, 400MHz): δ ppm 1.04 (s, 3H), 1.45 (s, 3H), 2.37-2.45 (m, 1H), 2.76 (d, 1H, *J* = 5.6 Hz), 2.77 (s, 2H, broad), 2.78 (d, 1H, *J* = 6.4 Hz), 3.72 (s, 3H), 3.7-3.74 (m, 1H), 3.78-3.80 (m, 2H), 3.85-3.90 (m, 1H), 4.82 (t, 1H, *J* = 4 Hz), 5.81 (d, 1H, *J* = 3.6 Hz).

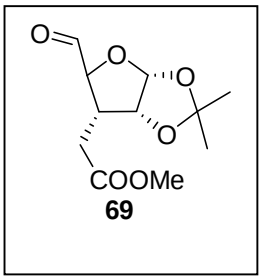
FTIR Spectrum: ν_{max} (neat)/cm^{-1} 3396, 1730, 1214, 1013



68 **69**

To a cooled (0 °C) methanolic solution (30 ml), compound **68** (2.5 g, 9.0 mmol) a saturated aqueous solution of $NaIO_4$ (2.6 g, 12.2 mmol) was added slowly and the mixture was allowed to stir for 30 min. The formed precipitate was filtered off, methanol was evaporated, and the residue obtained was extracted with dichloromethane (3 x 20 ml). The combined extract was dried (anhydrous Na_2SO_4) and solvent was evaporated to obtain the compound **69** (1.7 g, 76%).

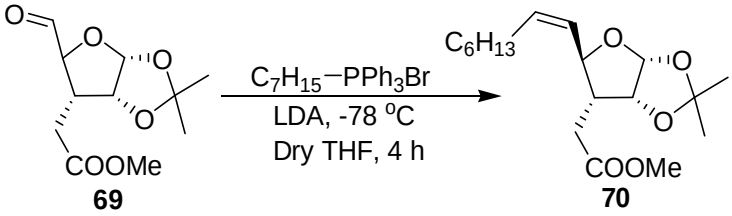
^{1}H NMR ($CDCl_3$, 400MHz): δ ppm 1.32 (s, 3H), 1.47 (s, 3H), 2.63 (m, 1H), 2.70 (dd, 2H, *J* = 5.6, 6.4 Hz), 3.70 (s, 3H), 3.73-3.84 (m, 1H), 4.81 (t, 1H, *J* = 4 Hz), 5.80 (d, 1H, *J* =3.6 Hz), 9.67 (d, 1H, *J* = 2.8 Hz)



69

^{13}C NMR ($CDCl_3$, 100MHz): δ ppm 26.7 (CH_3), 26.7 (CH_3), 28.8 (CH_2), 41.9 (CH), 51.9 (CH_3), 81.6 (CH), 83.4 (CH), 104.7 (CH), 111.8 (C), 173.0 (C=O), 200.3 (CHO)

FTIR Spectrum: ν_{max} (neat)/cm^{-1} 1779, 1005, 732

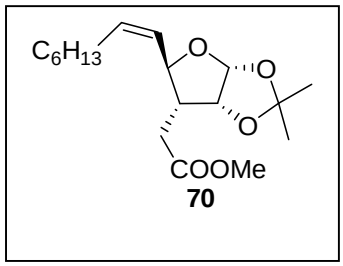


69 **70**

To a cooled, (-78 ^oC) nitrogen flushed dry tetrahydrofuran (30 ml) solution containing phosphorous ylide of bromoheptane (2.2 g, 4.9 mmol), t-butyl lithium (0.26 ml) was added and allowed to stir for 20 minutes. Compound **69** (1.0 g, 4.1 mmol) was added to the reaction mixture and kept for 5 h. After completion of the reaction (confirmed by TLC) few drops of water was added and solvent was dried in rotavapore under reduced pressure. The product was extracted with dichloromethane (3 x 20 ml). The combined extract was washed with water (2 x 15 ml), dried (anhydrous Na_2SO_4) and evaporated to an oily residue. The crude product was chromatographed over silica gel to afford pure compound **70** (0.97 g, 74%) as oily liquid.

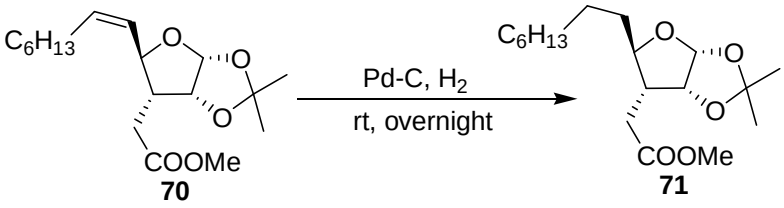
^{1}H NMR ($CDCl_3$, 400MHz): δ ppm 0.87 (t, 3H, *J* = 7.2 Hz), 1.24-1.34 (m, 8H), 1.33

(s, 3H), 1.43 (s, 3H), 2.02-2.13 (m, 3H), 2.27 (dd, 1H, *J* = 3.6, 16.8 Hz), 2.61 (dd, 1H, *J* = 10.8, 16.8 Hz), 3.68 (s, 3H), 4.52 (t, 1H, *J* = 10.0 Hz), 4.78 (t, 1H, *J* = 4.4 Hz), 5.66 (dt, 1H, *J* = 1.2, 11.6 Hz), 5.64-5.69 (m, 1H), 5.85 (d, 1H, *J* = 4 Hz).



70

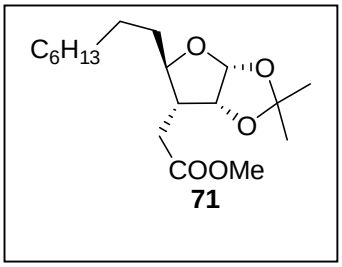
ESIMS, *m/z*: 326 $(M)^+$.



70 **71**

To an ethanolic solution of compound **70** (1.0 g, 3.1 mmol) activated Pd-C (60 mg) added. Connecting a balloon filled with H_2 gas with a three way connector the air inside the round bottom flask has been pumped out and H_2 gas from the balloon has been released to the round bottom flask thrice and allowed to stir overnight. After completion of the reaction (confirmed by TLC) the Pd-C has been filtered off and the solvent has been dried to obtain the compound **71** (0.98 g, 98%).

^{1}H NMR ($CDCl_3$, 400MHz): δ ppm 0.88 (t, 3H, *J* = 7.2 Hz), 1.22-1.40 (m, 14H), 1.31 (s, 3H), 1.49 (s, 3H), 2.02-2.07 (m, 1H), 2.31 (dd, 1H, *J* = 4.4, 17.2 Hz), 2.64 (dd, 1H, *J* = 10.4, 16.8 Hz), 3.71 (s, 3H), 3.73-3.77 (m, 1H), 4.75 (t, 1H, *J* = 4.4 Hz), 5.80 (d, 1H, *J* = 3.6 Hz)



71

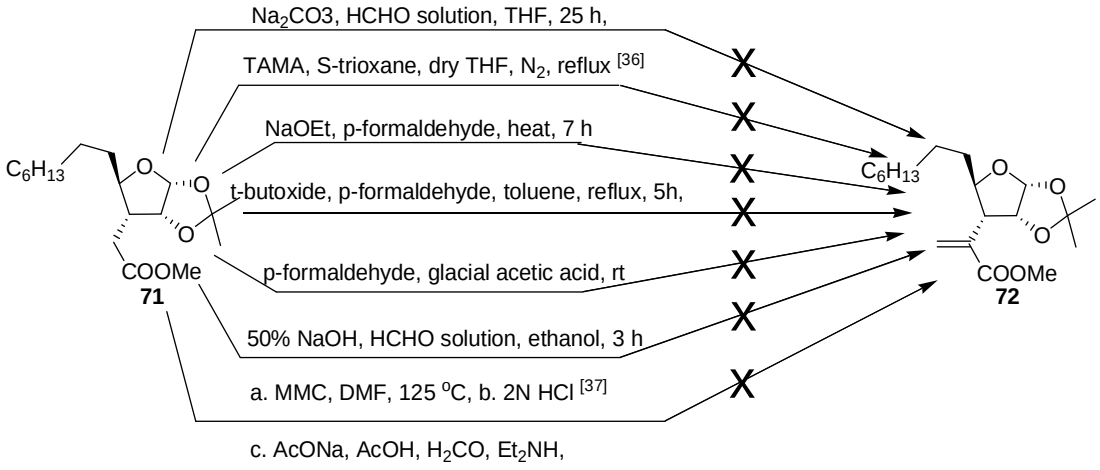
^{13}C NMR ($CDCl_3$, 100MHz): δ ppm 14.1(CH_3), 22.7 (CH_2), 26.1 (CH_2), 26.3 (CH_3), 26.5 (CH_3), 29.2 (CH_2), 29.5 (CH_2), 29.5 (CH_2), 29.8 (CH_2), 31.9 (CH_2), 32.6 (CH_2), 44.8 (CH), 51.8 (CH_3), 80.3 (CH), 81.0 (CH), 104.6 (CH), 111.2 (C), 172.7 (C=O).

DEPT135 ($CDCl_3$, 100MHz): δ ppm 22.7, 26.1, 29.2, 29.5, 29.5, 29.8, 31.9, 32.6

DEPT 90 ($CDCl_3$, 100MHz): δ ppm (peaks for CH only) 44.8, 80.3, 81.0, 104.6.

ESIMS, *m/z*: 328 $(M)^+$.

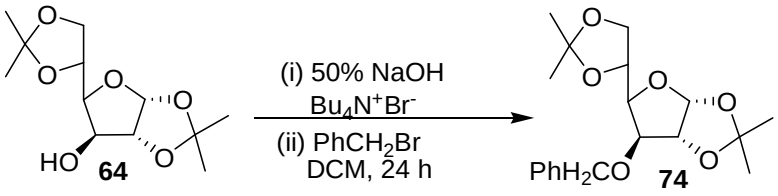
Many reactions have been carried out to prepare the compound **72** from compound **71** following different procedure using different reagents and reaction conditions as shown in the below scheme but the desired product has not been obtained.



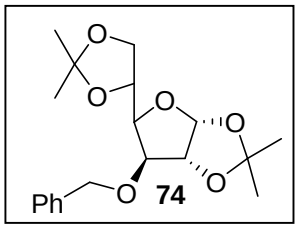
Scheme 3.2: Introduction of methelene group

3.3 Synthesis of oxacycle 81

The nine membered oxacycle **81** was prepared from compound **64** with an overall yield of 17% in seven steps. The stepwise preparation procedure with discussion of spectroscopic data has been discussed below.

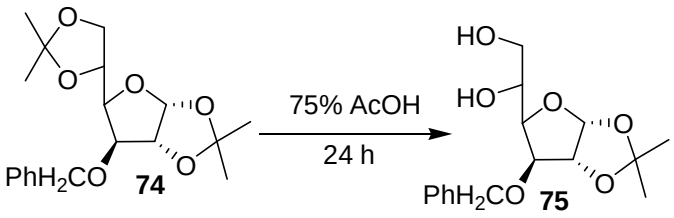


1,2:5,6-di-O-isopropylidene-α-D-glucofuranose **64** (5.0 g, 19.2 mmol) was dissolved in dichloromethane (DCM) and aqueous solution of 50% NaOH (30 ml) was added and allowed to stir vigorously for 10 minutes. Tetrabutylammoniumbromide ($Bu_4N^+Br^-$, 10 mol %) was added to the reaction mixture followed by Benzyl bromide (2.7 ml, 23.0 mmol) and allowed to stir vigorously for 24 h. After the completion of the reaction (confirmed by TLC) the organic layer has been separated by separating funnel and washed with brine, dried (anhydrous Na_2SO_4) and evaporated to obtain a crude product. The crude was subjected to column chromatography to obtain a oily liquid **74** (6.2 g, 92%).

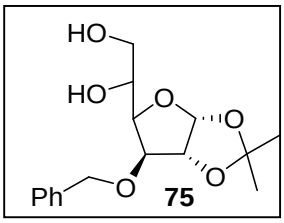


^{1}H NMR ($CDCl_3$, 400MHz): δ ppm 1.31 (s, 3H), 1.38 (s, 3H), 1.44 (s, 3H), 1.50 (s, 3H), 4.00-4.03 (m, 2H,), 4.11 (dd, 1H, *J* = 6.4, 8.8 Hz), 4.16 (dd, 1H, *J* = 3.2, 7.6 Hz), 4.39 (dd, 1H, *J* = 6.0, 13.6 Hz), 4.59 (d, 1H, *J* = 3.6 Hz), 4.64 (d, 1H, *J* = 11.6 Hz), 4.69 (d, 1H, *J* = 11.6 Hz), 5.90, (d, 1H, *J* = 3.6 Hz), 7.28-7.35 (m, 5H)

^{13}C NMR ($CDCl_3$, 100MHz): δ ppm 25.5 (CH_3), 26.3 (CH_3), 26.8 (CH_3), 26.9 (CH_3), 67.4 (CH_2), 72.4 (CH), 72.6 (CH_2), 81.4 (CH), 81.7 (CH), 82.7 (CH), 105.3 (CH), 109.0 (C), 111.8 (C), 127.7 (CH), 127.9 (CH), 128.4 (CH), 128.8 (CH), 129.0 (CH), 137.7 (C).

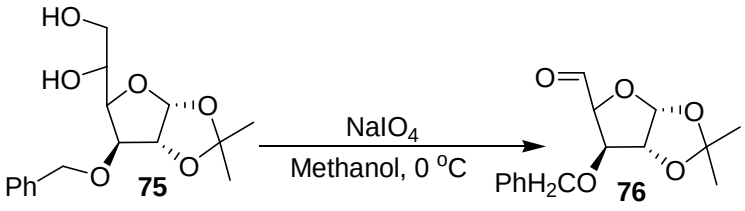


The benzylated compound **74** (2.0 g, 5.7 mmol) was dissolved in 75% acetic acid (40 ml) and allowed to stir for 24 h. After completion of the reaction (confirmed by TLC) the acetic acid was dried in reduced pressure in rotavapore at temperature 35 ^{o}C. Complete removal of acetic acid was insured by repeated addition of toluene (5 x 20 ml) to acetic acid solution to make azeotropic mixture. This gave the 5, 6 deprotected compound **75** (1.6 g, 90%) as colourless oil.



^{1}H NMR ($CDCl_3$, 400MHz): δ ppm 1.30 (s, 3H), 1.47 (s, 3H), 2.89 (s, Broad, 2H), 3.67 (dd, 1H, *J* = 5.6, 11.6 Hz), 3.80 (dd, 1H, *J* = 3.2, 11.6 Hz), 3.99-4.03 (m, 1H), 4.09-4.18 (m, 2H), 4.58 (d, 1H, *J* = 11.6 Hz), 4.61 (d, 1H, *J* = 3.6 Hz), 4.71(d, 1H, *J* = 11.6 Hz), 5.91 (d, 1H, *J* = 3.6 Hz), 7.26-7.46 (m, 5H).

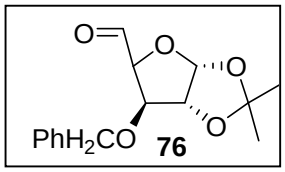
FTIR Spectrum: ν_{max} (neat)/cm^{-1} 3408, 1071, 1015, 731



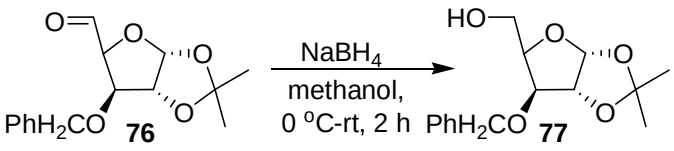
Methanolic solution (25 ml) of compound **75** (2.0 g, 6.5 mmol) was cooled to 0 ^{o}C by stirring in ice bath. Aqueous solution of $NaIO_4$ (3.8 g, 17.8 mmol) was slowly added to the reaction mixture with vigorous stirring for 30 minutes. White precipitate

appeared was filtered off by Buckner funnel and washed trice with methanol (3 x 3 ml). Solvent was evaporated under reduced pressure in rotavapore and extracted with dichloromethane (3 x 20 ml). The organic parts were combined, dried (Na_2SO_4) and evaporated to afford an oily liquid compound **76** (1.5 g, 83.3%).

^{1}H NMR ($CDCl_3$, 400MHz): δ ppm 1.30 (s, 3H), 1.47 (s, 3H), 4.16-4.32 (m, 2H), 4.54 (d, 1H, *J* = 11.6 Hz), 4.60 (d, 1H, *J* = 3.6 Hz), 4.71 (d, 1H, *J* = 11.6 Hz), 5.95 (d, 1H, *J* = 3.6 Hz), 7.23-7.36 (m, 5H), 9.67 (d, 1H, *J* = 1.6 Hz)

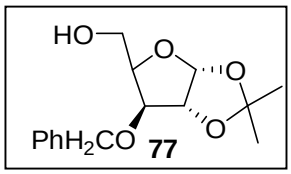


FTIR Spectrum: ν_{max} (neat)/cm^{-1} 1736, 1072, 1016, 730



To a cooled (0 ^{o}C) methanolic solution of compound **76** (1.5 g, 5.4 mmol), $NaBH_4$ (226 mg, 5.9 mmol) was added slowly and allowed to stir for 2 h at room temperature. After the completion of the reaction (confirmed by TLC) the solvents was dried in reduced pressure in rotavapore and extracted with dichloromethane (3 x 20 ml). The organic parts were combined, dried (Na_2SO_4) and evaporated to obtain the crude. The crude was chromatographed using silica gel to afford the pure compound **77** (1.3 g, 86.6%).

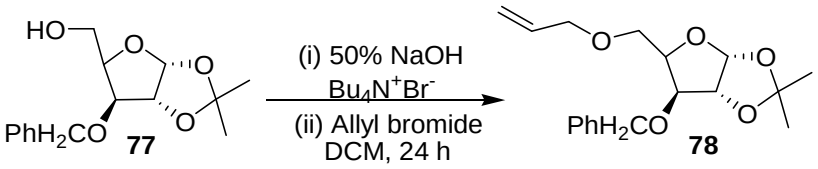
^{1}H NMR ($CDCl_3$, 400MHz): δ ppm 1.32 (s, 3H), 1.48 (s, 3H), 2.41 (s, 1H, broad), 3.85 (m, 1H), 3.91, 3.91 (dd, 1H, *J* = 5.2,



12.0 Hz), 4.01 (d, 1H, *J* = 3.6 Hz), 4.28 (dd, 1H, *J* = 4.8, 8.4 Hz), 4.50 (d, 1H, *J* = 12.0 Hz), 4.64 (d, 1H, *J* = 4.0 Hz), 4.72 (d, 1H, *J* = 12.0 Hz), 5.98 (d, 1H, *J* = 4.0 Hz), 7.26-7.36 (m, 5H)

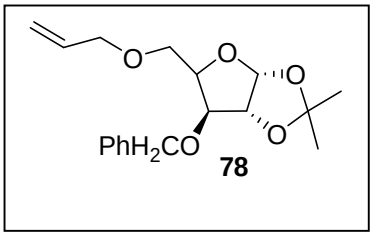
^{13}C NMR ($CDCl_3$, 100MHz): δ ppm 26.3 (CH_3), 26.8 (CH_3), 60.9 (CH_2), 71.9 (CH_2), 80.2 (CH), 82.4 (CH), 82.6 (CH), 105.0 (CH), 111.8 (C), 127.6 (CH), 127.8 (CH), 128.2 (CH), 128.4 (CH), 128.7 (CH), 137.1 (C).

ESIMS, *m/z*: 280 $(M)^+$.



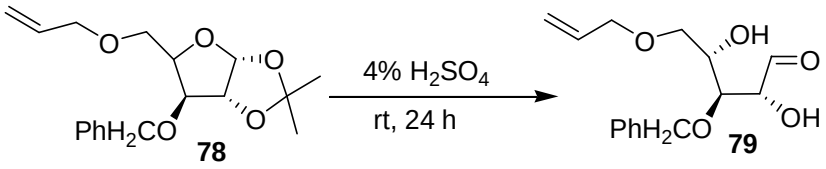
The compound **77** (1.3 g, 4.6 mmol) was dissolved in dichloromethane (30 ml) and aqueous solution of 50% NaOH (30 ml) was added and allowed to stir vigorously for 10 minutes. Tetrabutylammoniumbromide ($Bu_4N^+Br^-$, 10 mol %) was added to the reaction mixture followed by allyl bromide (0.47 ml, 5.6 mmol) and allowed to stir vigorously for 24 h. After the completion of the reaction (confirmed by TLC) the organic layer has been separated by separating funnel and washed with brine, dried (anhydrous Na_2SO_4) and evaporated to obtain a crude product. The crude was subjected to column chromatography to obtain an oily liquid product **78** (1.4 g, 91%).

^{1}H NMR ($CDCl_3$, 400MHz): δ ppm 1.34 (s, 3H), 1.51 (s, 3H), 3.73 (dd, 1H, *J* = 1.2, 6.4 Hz), 3.99 (d, 1H, *J* = 3.2 Hz), 4.08 (dd, 2H, *J* = 6.0, 17.6 Hz), 4.41 (dt, 1H,



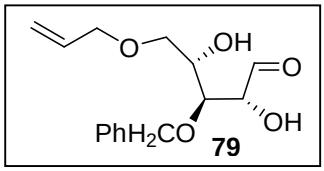
J = 3.2, 9.6 Hz), 4.56 (d, 1H, *J* = 12.0 Hz), 4.62 (d, 1H, *J* = 3.6 Hz), 4.68 (d, 1H, *J* = 12.0 Hz), 5.20 (dd, 1H, *J* = 1.2, 10.4 Hz), 5.30 (dd, 1H, *J* = 1.6, 17.2 Hz) 5.89-5.95 (m, 1H), 5.96 (d, 1H, *J* = 4.0 Hz), 7.28-7.39 (m, 5H).

^{13}C NMR ($CDCl_3$, 100MHz): δ ppm 26.3 (CH_3), 26.8 (CH_3), 67.5 (CH_2), 72.0 (CH_2), 72.4 (CH_2), 79.2 (CH), 81.7 (CH), 82.3 (CH), 105.1 (CH), 111.7 (C), 117.2 (CH_2), 127.6 (CH), 127.8 (CH), 127.9 (CH), 128.3 (CH), 128.5 (CH), 134.6 (CH), 137.5 (C).

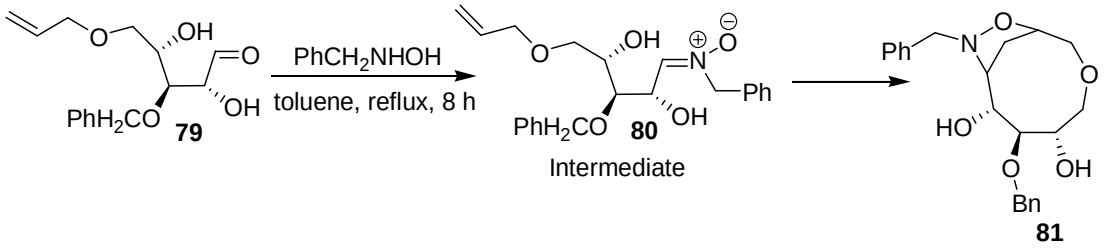


Compound **78** (1 g, 301 mmol) was dissolved in 4% H_2SO_4 (1:6:18 H_2SO_4, water and acetonitrile) and allowed to stir for 24 h. After completion of the reaction (confirmed by TLC) solid $CaCO_3$ was added to neutralize the reaction mixture (pH = 7) and filtered. The filtrate was evaporated, dissolved in dichloromethane and passed through Na_2SO_4 and dried to obtain the compound **79** (0.8 g, 93%).

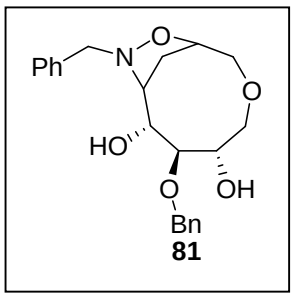
^{1}H NMR ($CDCl_3$, 400MHz): δ ppm 3.65 (d, H, *J* = 5.2 Hz), 3.72 (dd, 1H, *J* = 4.0, 5.6 Hz), 4.04 (m, 3H), 4.21 (t, 1H, *J* = 4.0 Hz), 4.53 (m, 1H), 4.57 (d, 1H, *J* = 12.0, Hz), 4.71 (d, 1H, *J* = 12.0 Hz), 5.20 (dd, 1H, *J* = 1.6, 10.4 Hz), 5.28 (dd, 1H, *J* = 1.6, 17.2 Hz), 5.87-5.94 (m, 1H), 7.31-7.38 (m, 5H).



^{13}C NMR ($CDCl_3$, 100MHz): δ ppm 69.0 (CH_2), 71.9 (CH_2), 72.7 (CH_2), 75.6 (CH), 83.5 (CH), 96.0 (CH), 103.3 (CH), 117.5 (CH_2), 127.6 (CH), 127.8 (CH), 128.4 (CH), 128.5 (CH), 134.2 (CH_2), 137.8 (C).



Compound **79** (0.5 g, 1.8 mmol) was dissolved in toluene and benzyl hydroxylamine (0.28g, 2.3 mmol) was added. The reaction mixture was refluxed with continuous stirring for 8 h. After completion of the reaction (confirmed by TLC) the solvent was dried and purified by column chromatography to obtain nine membered oxacycle **81** (0.3 g, 34%)

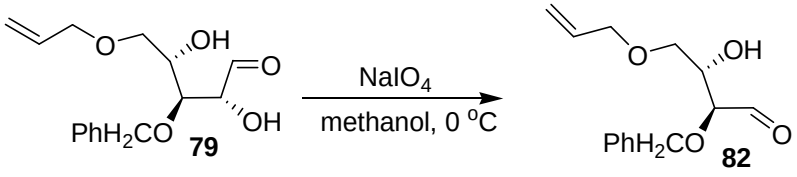


^{1}H NMR ($CDCl_3$, 400MHz): δ ppm 2.43 (d, 1H, *J* = 12.4 Hz), 2.66 (m, 1H), 3.41 (t-like, 2H, *J* = 8.0, 15.2 Hz), 3.59 (dd, 2H, *J* = 12.8,28.8 Hz), 3.81-3.93 (m, 1H), 3.99 (dd-like, 2H, *J* = 5.6, 10.0 Hz), 4.34 (d, 1H, *J* = 11.6 Hz), 4.41-4.43 (m, 1H), 4.45-4.51 (m, 2H), 4.98 (d, 1H, *J* = 8.8 Hz), 7.27-7.37 (m, 10H)

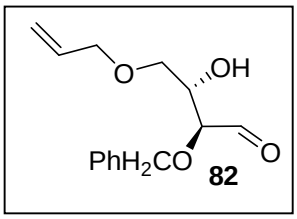
ESIMS, *m/z*: 385 $(M)^+$.

3.4 Synthesis of oxacycle 84

Compound **84** can be synthesised from compound **64** in 8 steps. Compound **79** was synthesised as discussed above. The stepwise procedure and spectroscopic data analysis is follows.

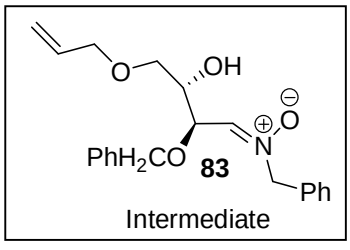


To a cooled to (0 ^{o}C) methenolic solution of compound **79** (1 g, 3.6 mmol), Aqueous solution of $NaIO_4$ (1.01 g, 4.7 mmol) was added. After 30 minutes the precipitate formed was filtered off and the methanol was evaporated under reduced pressure in rotavapore and extracted with dichloromethane (3 x 20 ml). The organic parts were combined, dried (Na_2SO_4) and evaporated to afford an oily liquid compound **82** (0.8 g, 86%).



^{1}H NMR ($CDCl_3$, 400MHz): δ ppm 3.56-3.79 (m, 2H), 3.90 (d, 1H, *J* = 4.0 Hz), 4.12 (d, 1H, *J* = 4.0 Hz), 4.61 (d, 1H, *J* = 11.6 Hz), 4.81 (d, 1H, *J* = 11.6 Hz), 5.21 (dd, 1H, *J* = 10.4, 18.0 Hz), 5.28 (dd, 1H, *J* = 1.2, 12.4 Hz), 5.39 (dd, 1H, *J* = 4.8, 9.6 Hz), 5.78-5.86 (m, 1H), 7.25-7.39 (m, 5H), 9.76 (d, 1H, *J* = 4.8 Hz).

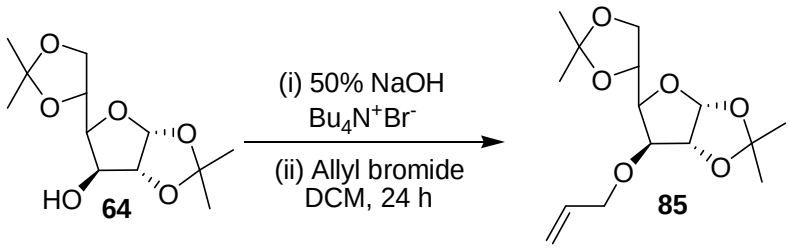
Compound **82** (0.5 g, 2.1 mmol) was dissolved in toluene and benzyl hydroxylamine (0.31 g, 2.5 mmol) was added to it. The reaction mixture was refluxed with continuous stirring for 8 h. Then the solvent was dried and purification by column chromatography afforded the intermediate compound **83** (0.3 g, 37%).



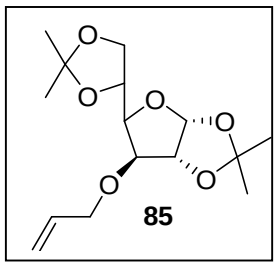
^{1}H NMR ($CDCl_3$, 400MHz): δ ppm 3.47 (dd, 1H, *J* = 4.4, 10.0 Hz), 3.56 (dd, 1H, *J* = 6.0, 10.0 Hz), 3.67 (m, 1H,), 3.95 (d, 1H, *J* = 5.6 Hz), 4.07 (dd, 1H, *J* = 4.4, 9.2 Hz), 4.50-4.55 (m, 2H) 4.65-4.69 (m, 1H), 5.13 (dd, 1H, *J* = 1.6, 17.2 Hz), 5.21 (dd, 1H, *J* = 1.6, 17.2 Hz) 5.78-5.85 (m, 1H), 7.25-7.52 (m, 10H)

3.5 Synthesis of oxacycle 88

Compound **88** was synthesised from compound **64** in four steps with an overall yield of 40%. The stepwise preparation procedure and the spectroscopic data analysis have been discussed below.



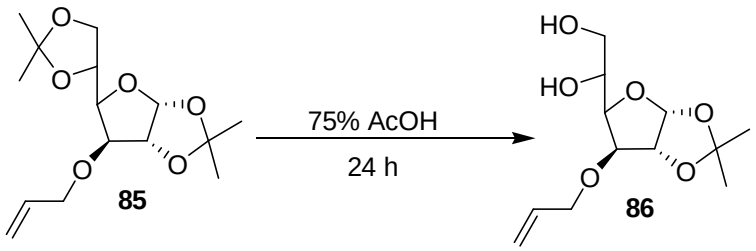
1,2:5,6-di-O-isopropylidene-α-D-glucofuranose **64** (5.0 g, 19.2 mmol) was dissolved in dichloromethane (DCM) and aqueous solution of 50% NaOH (30 ml) was added and allowed to stir vigorously for 10 minutes. Tetrabutylammoniumbromide ($Bu_4N^+Br^-$, 10 mol %) was added to the reaction mixture followed by allyl bromide (2.6 ml, 23.1 mmol) and allowed to stir vigorously for 24 h. After the completion of the reaction (confirmed by TLC) the organic layer has been separated by separating funnel and washed with brine, dried (anhydrous Na_2SO_4) and evaporated to obtain a crude product. The crude was subjected to column chromatography to obtain a oily liquid **85** (5.5 g, 96%).



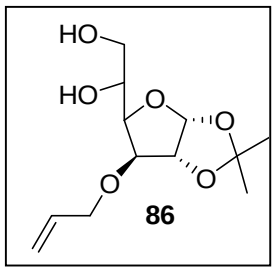
^{1}H NMR ($CDCl_3$, 400MHz): δ ppm 1.28 (s, 3H,), 1.31 (s, 3H), 1.39 (s, 3H), 1.46 (s, 3H), 3.91 (d, 1H, *J* = 3.2 Hz), 3.96 (dd, 1H, *J* = 5.6, 8.4 Hz), 4.03- 4.10 (m, 4H), 4.28 (dd, 1H, *J* = 6.0, 7.6 Hz), 4.50 (d, 1H, *J* = 3.6 Hz), 5.16 (dd, 1H, *J* = 1.6, 10.4 Hz), 5.27 (dd, 1H, *J* = 1.6, 17.2 Hz), 5.81- 5.85 (m, 1H) merged with 5.85 (d, 1H, *J* = 3.6 Hz)

^{13}C NMR ($CDCl_3$, 100MHz): δ ppm 25.4 (CH_3), 26.2 (CH_3), 26.8 ($2CH_3$), 67.2 (CH_2), 71.32 (CH_2), 72.4 (CH), 81.1 (CH), 81.3 (CH), 82.7 (CH), 105.2 (CH), 108.9 (C), 111.7 (C), 117.2 (CH_2), 134.1 (CH).

ESIMS, *m/z*: 300 $(M)^+$.

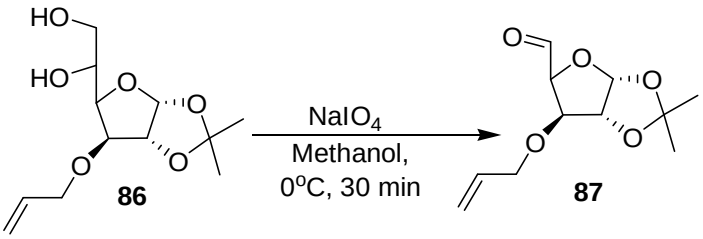


Compound **85** (2.0 g, 7.9 mmol) was dissolved in 25 ml aqueous AcOH (75%) and stirred for 24 h. The solvent was evaporated under reduced pressure and the last trace of AcOH was evaporated through azeotropic distillation with toluene to obtain the diol **86** as a thick colourless oily liquid (1.5 g, 87%).

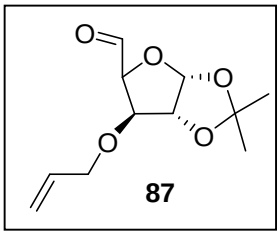


^{1}H NMR ($CDCl_3$, 400MHz): δ ppm 1.31 (s, 3H), 1.48 (s, 3H), 2.75 (s, 2H, broad), 3.73 (dd, 1H, *J* = 5.2, 11.6 Hz), 3.83 (dd, 1H, *J* = 3.6, 11.6 Hz), 3.99-4.07 (m, 3H), 4.13(dd, 1H, *J* = 3.2, 7.6 Hz), 4.18 (dd, 1H, *J* = 5.2, 12.8 Hz), 4.57 (d, 1H, *J* = 4 Hz), 5.22 (dd, 1H, *J* = 1.6, 10.8 Hz), 5.31 (dd, 1H, *J* = 1.6, 17.2 Hz), 5.86-5.93 (m, 1H), 5.92 (d, 1H, *J* = 4.0 Hz).

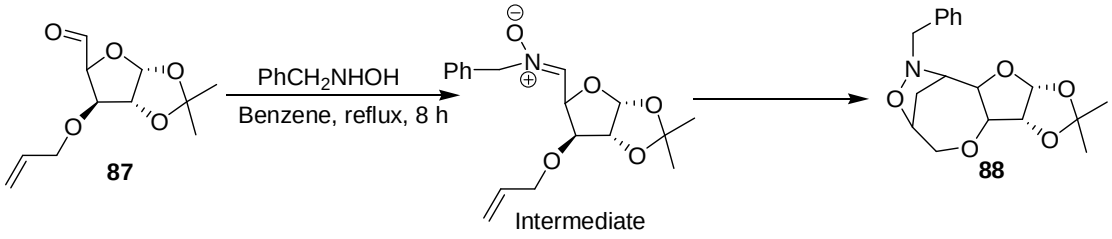
^{13}C NMR ($CDCl_3$, 100MHz): δ ppm 26.2 (CH_3), 26.7 (CH_3), 64.4 (CH_2), 69.4 (CH_2), 69.4 (CH), 71.1 (CH), 79.8 (CH), 82.1 (CH), 105.1 (CH), 111.8 (C), 118.2 (CH_2), 133.7 (CH).



To a cooled to (0 ^{o}C) methenolic solution of compound **86** (1.5 g, 5.8 mmol), aqueous solution of $NaIO_4$ (1.5 g, 7.1 mmol) was added. After 30 minutes the precipitate formed was filtered off and the methanol was evaporated under reduced pressure in rotavapore and extracted with dichloromethane (3 x 20 ml). The organic parts were combined, dried (Na_2SO_4) and evaporated to afford an oily liquid compound **87** (1.1 g, 84%).

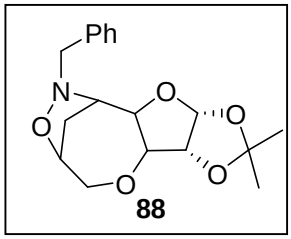


^{1}H NMR ($CDCl_3$, 400MHz): δ ppm 1.31 (s, 3H), 1.45 (s, 3H), 3.76, 3.81 (dd, 1H, *J* = 5.2 Hz), 3.86-3.89 (M, 1H,), 4.05-4.09 (m, 2H), 4.56 (d, 1H, *J* = 4.0 Hz), 5.21-5.73 (M, 1H,), 5.29-5.33 (m, 1H), 5.86-5.93 (m, 1H), 5.92 (d, 1H, *J* = 4.0 Hz), 9.66 (d, 1H, *J* = 1.6 Hz).



Compound **87** (0.5 g) was dissolved in toluene and benzyl hydroxylamine (1.2 equivalent, 0.3 g) was added to it. The reaction mixture was refluxed with continuous stirring for 8 h. After completion of the reaction (confirmed by TLC) the solvent was dried and purified by column chromatography. This gave an eight membered cyclised nitrone compound **88** (0.4 g, 57%).

^{1}H NMR ($CDCl_3$, 400MHz): δ ppm 1.21 (s, 3H), 1.44 (s, 3H), 2.32-2.39 (m, 1H), 2.37 (d, 1H, *J* = 12.4 Hz), 3.61 (m, 2H), 3.73 (m, 2H), 4.10 (m, 3H), 4.04 (d, 1H, *J* = 3.6 Hz), 4.61 (dd, 1H, *J* = 2.0, 8.4 Hz), 5.86 (d, 1H, *J* = 3.6 Hz), 7.21-7.40 (m, 5H).



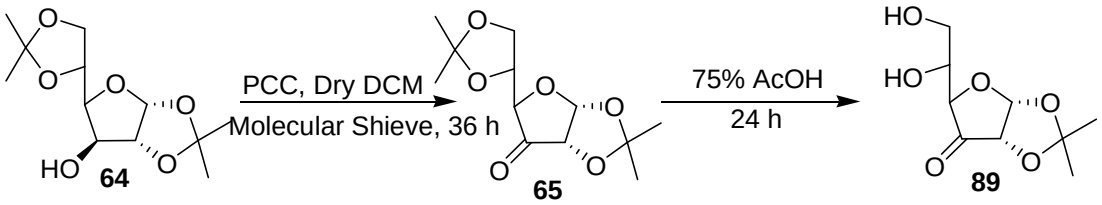
88

^{13}C NMR ($CDCl_3$, 100MHz): δ ppm 20.9 (CH_3), 21.5 (CH_3), 21.9 (CH_2), 57.0 (CH), 57.4 (CH), 67.3 (CH_2), 73.4 (CH), 74.5 (CH), 77.3 (CH), 79.5 (CH_2), 99.1 (CH), 106.5 (C), 122.6 (CH), 123.5 (2CH), 124.1 (2CH), 131.6 (C).

ESIMS, *m/z*: 333 $(M)^+$.

3.6 Synthesis of oxacycle 90

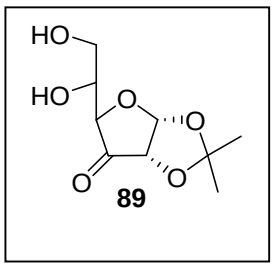
Compound **90** was synthesised from compound **64** in three steps. The cyclization occurred via base catalysed oxa Michael mechanism.



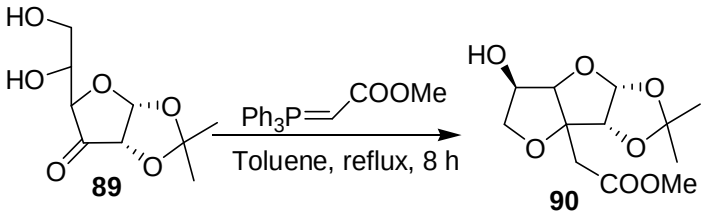
64 **65** **89**

Procedure for the synthesis of the compound **65** has been given in earlier step. For the synthesis of compound **89,** compound **65** (3.0 g, 11.6 mmol) was dissolved in 75% acetic acid (40 ml) and allowed to stir for 24 h. After completion of the reaction (confirmed by TLC) the solvent was evaporated in rotavapore in reduced pressure. The last trace of AcOH was evaporated through azeotropic distillation with toluene to obtain the diol **89** as a thick colourless oily liquid (2.3 g, 91%).

^{1}H NMR ($CDCl_3$, 400MHz): δ ppm 1.43 (s, 3H), 1.61 (s, 3H), 2.42 (s, 1H), 3.61 (s, 1H), 3.81 (q, 1H, *J* = 6.0 Hz), 4.32 (t, 1H, *J* = 6.8 Hz), 4.45 (s, 2H), 4.53 (t, 1H, *J* = 5.2 Hz), 6.00 (d, 1H, *J* = 3.2 Hz)

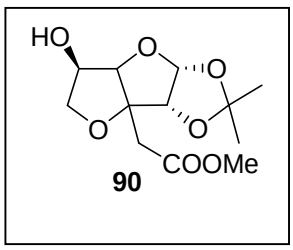


89



Compound **89** (2.0 g, 9.2 mmol) was dissolved in toluene and a pinch of NaOH was added to the mixture. Methyl (triphenylphosphoranylidene)acetate (4.1 g) was added to it and refluxed 8 h with constant stirring. After completion of the reaction (confirmed by TLC) the toluene was dried in rotavapore in reduced pressure and extracted with dichloromethane (3 x 20 ml). The organic parts were combined, dried (Na_2SO_4) and evaporated to afford an oily liquid compound **90** (2.1 g, 83%).

^{1}H NMR ($CDCl_3$, 400MHz): δ ppm 1.34 (s, 3H), 1.49 (s, 3H), 2.54 (d, 1H, *J* = 6.8 Hz), 2.68 (d, 1H, *J* = 15.6 Hz), 2.91 (d, 1H, *J* = 15.6 Hz) 3.44 (t, 1H, *J* = 8.8 Hz), 3.67 (s, 3H), 4.08 (t, 1H, *J* = 7.2 Hz), 4.37 (s, 1H), 4.55 (d, 1H, *J* = 4.4 Hz), 4.66 (d, 1H, *J* = 3.2 Hz), 5.88 (d, 1H, *J* = 3.6 Hz).

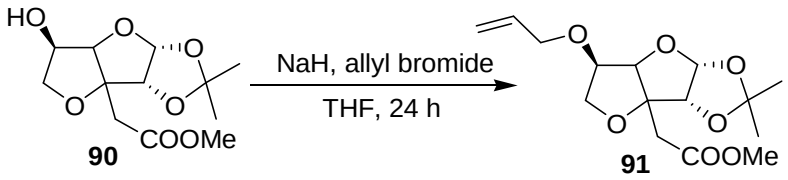


90

^{13}C NMR ($CDCl_3$, 100MHz): δ ppm 21.9 (CH_3), 22.5 (CH_3), 32.0 (CH_2), 46.8 (CH_3), 67.0 (CH_2), 67.1 (CH), 79.6 (CH), 81.5 (CH), 85.1 (C), 101.3 (CH), 108.3 (C), 165.1 (C=0).

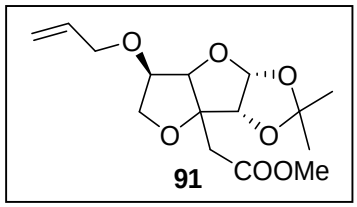
ESIMS, *m/z*: 274 $(M)^+$.

The tricyclic oxacycle **90** was further modified to synthesise a nine membered oxacycle **94** by INC reaction but cyclization step was not successful. The stepwise procedure and the analysis of the spectral data have been discussed below.

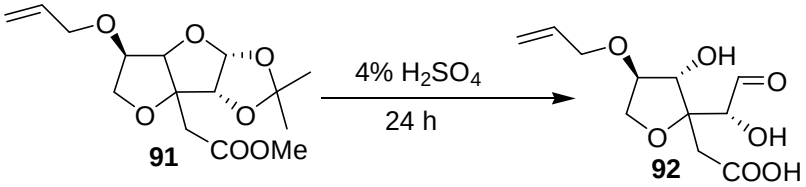


Compound **90** (2.0 g, 7.3 mmol) was been dissolved in THF and NaH was added to the mixture till effervescence stop coming. After 30 minute allyl bromide (1.05 ml, 8.8 mmol) was added to the reaction mixture and allowed to stir for 24 h. The completion of the reaction has been confirmed by TLC and the solvent has been dried. Extraction was done with dichloromethane (3 x 20 ml), washed with brine. Dried (Na_2SO_4) and solvent was evaporated to obtain the crude compound. Column chromatography with ethyl acetate and pet ether afforded pure compound **91** (2.0 g, 87%).

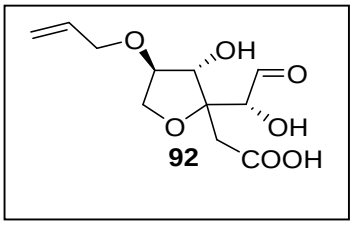
^{1}H NMR ($CDCl_3$, 400MHz): δ ppm 1.34 (s, 3H), 1.50 (s, 3H), 2.63 (d, 1H, *J* = 15.6 Hz), 2.93 (d, 1H, *J* =15.6 Hz), 3.62-3.69 (m, 1H), 3.96 (s, 3H), 4.00 (dd, 1H, *J* = 6.0, 12.4 Hz), 4.07-4.18 m (3H), 4.65 (dd, 2H, *J* = 3.2, 16.8 Hz), 5.21 (d, 1H, *J* = 10.4 Hz), 5.29 (d, 1H, *J* = 17.2 Hz) 5.88-5.95 (m, 1H), 5.97 (d, 1H, *J* = 2.8 Hz).



^{13}C NMR ($CDCl_3$, 100MHz): δ ppm 21.8 (CH_3), 22.4 (CH_3), 32.4 (CH_2), 46.8 (CH_3), 64.6 (CH_2), 66.57 (CH_2), 73.2 (CH_2), 77.8 (CH), 80.9 (CH), 85.7 (C), 101.7 (CH), 107.8 (C), 113.0 (CH_2), 129.1 (CH), 165.1 (C=O).



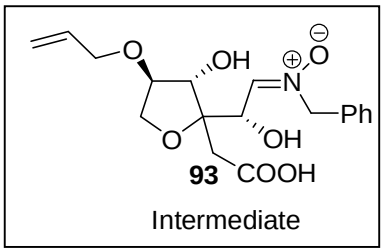
Compound **91**(1.0 g, 3.2 mmol) was dissolved in 4% H_2SO_4 (1:6:18 H_2SO_4, water and acetonitrile) and allowed to stir at room temperature for 24 h. After completion of the reaction (confirmed by TLC) solid $CaCO_3$ was added to neutralize the reaction mixture (pH = 7), precipitate was filtered off, solvents was evaporated. The crude was dissolved in dichloromethane and passed through Na_2SO_4, dried and obtained the compound **92** (0.6 g, 73%).



^{1}H NMR ($CDCl_3$, 400MHz): δ ppm 2.80 (d, 1H, *J* = 18.8 Hz), 3.01 (d, 1H, *J* = 18.8 Hz), 3.64 (t, 1H, *J* = 8.4 Hz), 4.00-4.11 (m, 3H), 4.16-4.26 (m, 1H), 4.66 (d, 1H, *J* = 5.2 Hz), 5.23 (dd, 1H, *J* = 0.8, 7.6 Hz), 5.33n (dd, 1H, *J* = 2.0, 14.0 Hz), 5.62-5.98 (m, 1H).

Compound **92** (0.5 g, 1.9 mmol) was dissolved in toluene in a round bottom flask and benzyl hydroxylamine (0.28 g, 2.3 mmol) was added to it. The reaction mixture was refluxed with continuous stirring for 12 h. The solvents was dried extracted with dichloromethane (3 x 20 ml), combined the organic parts, washed with brine and dried (Na_2SO_4) to afford the intermediate product **93** but cyclization did not occur to form the compound **94** (0.65 g, 92.8%).

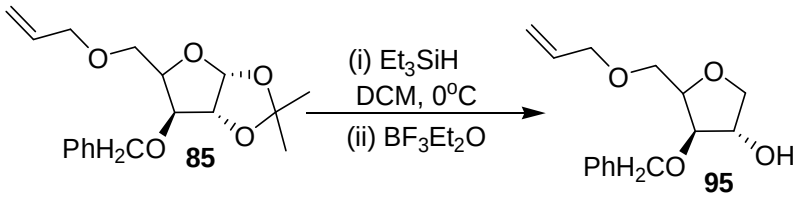
^{1}H NMR ($CDCl_3$, 400MHz): δ ppm 2.76-3.05 (m, 2H), 3.64 (t, 1H, *J* = 8.4 Hz), 4.00-4.11 (m, 3H), 4.16-4-4.26 (m, 1H), 4.55 (d, 1H, *J* = 12.0 Hz), 4.65 (d, 1H, *J* = 12.0 Hz), 4.66 (d, 1H, *J* = 7.6 Hz), 5.23 (dd, 1H, *J* = 2.4, 14.4 Hz), 5.34 (dd, 1H, *J* = 2.4, 17.2 Hz), 5.62-5.98 (m, 1H), 7.26-7.56 (m, 5H).



93
Intermediate

3.7 Synthesis of INC precursor 95

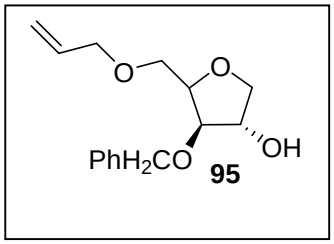
Precursor **95** can be easily prepared in six easy steps from compound **64** following same procedure up to compound **85**.



85 **95**

The compound **85** (1 g, 3.1 mmol) was dissolved in dry dichloromethane and cooled to 0 °C and triethylsilane (1.5 ml) was added and allowed to stir for 20 minutes. Then borontrifluoride etherate (0.8 ml) was added and stirred at room temperature for another 2 h. After the completion (confirmed by TLC) the mixture was neutralized with saturated solution of sodium bicarbonate and suction filtered. The filtrate was evaporated and extracted with dichloromethane (3 x 20 ml). The organic parts were combined, washed with brine and to dried (Na_2SO_4) to afford the crude which on purification by column chromatography afforded pure compound **95** (0.5 g, 61%).

^{1}H NMR ($CDCl_3$, 400MHz): δ ppm 2.35 (s, 1H, broad), 3.65-3.73 (m, 3H), 3.93 (dd, 1H, *J* = 1.2, 3.2 Hz), 4.02 (dd, 1H, *J* = 6.0, 12.8 Hz), 4.10 (dd, 1H, *J* = 5.6, 18.4



95

Hz), 4.16 (dd, 1H, *J* = 4.4, 10.0 Hz), 4.30 (dt, 1H, *J* = 5.2, 9.6 Hz), 4.37 (s, 1H), 4.58 (d, 1H, *J* = 12.0 Hz), 4.68 (d, 1H, *J* = 12 Hz), 5.20 (dd, 1H, *J* = 1.2, 9.2 Hz), 5.32 (dd, 1H, *J* = 1.6, 17.2 Hz), 5.88-5.97 (m, 1H), 7.28-7.39 (m, 5H).

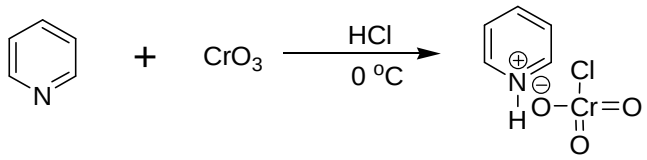
^{13}C NMR ($CDCl_3$, 100MHz): δ ppm 68.5 (CH_2), 72.2 (CH_2), 72.4 (CH_2), 73.6 (CH_2), 75.0 (CH), 79.2 (CH), 84.3 (CH), 117.2 (CH_2), 127.5 (2CH), 127.8 (CH), 128.5 (2CH), 134.7 (CH_2), 137.9 (CH).

FTIR Spectrum: ν_{max} (neat)/cm^{-1} 3400, 1266, 1072, 731

3.8 Preparation of reagents:

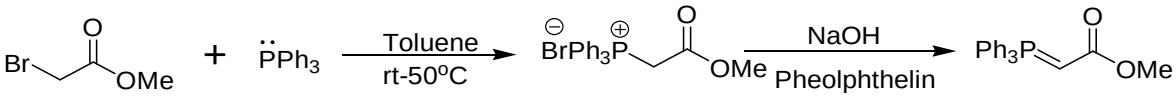
Many of the reagents used in the reactions have been prepared in the lab. The procedure and the spectroscopic data have been discussed below.

3.8.1 Preparation of PCC



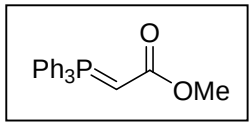
To a cooled (0 ^oC) mixture of chromium (IV) oxide (50 g, 0.5 mol) and 6 M HCl (92 ml), pyridine (48.88 ml) was added drop wise with continuous stirring and kept for 30 minutes in ice bath. The orange solid formed was filtered using Buckner funnel and washed with little amount of ice cold water and dried in desiccator to obtain PCC (67.1 g, 49.3%).

3.8.2 Synthesis of Methyl (triphenylphosphoranylidene)acetate (Wittig salt)



Triphenyl phosphine (10.2 g) was dissolved in toluene (100 ml) and methyl bromoacetate (3.85 ml) mixed with toluene (3 ml) was added drop wise by addition funnel. The reaction mixture was then heated to 50 ^{o}C. The white precipitate formed was filtered using Buckner funnel, washed with toluene (3 x 5 ml) and kept in desiccators overnight afforded phosphonium salt (10.43 g, 66%) as a white solid. The phosphonium salt was further reacted with 0.02 M NaOH by adding five drops of phenolphthalein as an indicator. The completion of the reaction was realized by appearance of pink colour. The precipitate was filtered by using Buckner funnel, dried which afforded methyl (triphenylphosphoranylidene)acetate as a white solid (8.42 g, 31.48% overall).

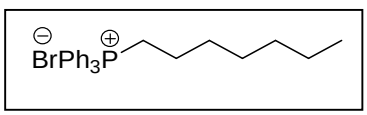
^{1}H NMR ($CDCl_3$, 400MHz): 3.50 (s, 3H), 7.22-7.95 (m, 16H).



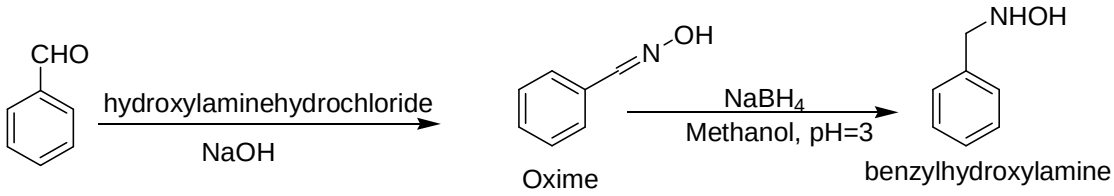
3.8.3 Synthesis of phosphonium ylide

Triphenyl phosphine (4.99 g) was dissolved in toluene bromoheptane (3 ml) was added. The reaction mixture was heated at 60-70 ^{o}C overnight and then allowed to cool. The oily substance formed was filtered using Buckner funnel. The white precipitate obtained was allowed to dry over P_2O_5 in desiccator yielded the product (7.5 g, 60.15%).

^{1}H NMR ($CDCl_3$, 400MHz): δ 0.79 (t, 3H, *J* = 2.8 Hz), 1.06-1.18 (m, 6H), 1.54 (m, 4H,), 3.56-3.62 (m, 2H), 7.62-7.75 (m, 15H)



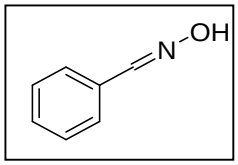
3.8.4 Preparation of benzyl hydroxylamine



Benzaldehyde (16.5 g) dissolved in 50% NaOH (15 ml) and hydroxylamine hydrochloride (7.5 g) was added slowly to the reaction mixture after 20 minutes. Upon cooling a crystalline mass of Na-derivative of oxime separated out. Water (30 ml) was added to it to form a clear solution and CO_2 gas was passed through it until saturated. The compound was extracted with ether (5 x 20 ml) and the organic parts were combined, washed with brine, dried (Na_2SO_4) afforded oxime (12 g, 63%).

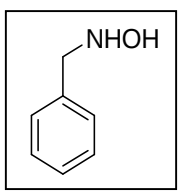
^{1}H NMR ($CDCl_3$, 400MHz): δ 7.40-7.47 (m, 3H), 7.59-7.63 (m, 2H), 8.21 (s, 1H,), 9.11 (s, 1H broad)

^{13}C NMR ($CDCl_3$, 100MHz): δ ppm 127.2 (CH), 128.5 (CH), 128.9 (CH), 130.2 (CH), 131.1 (CH), 131.8 (C), 150.6 (CH)

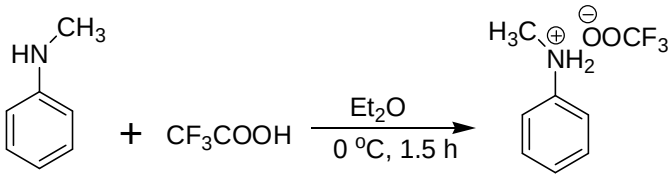


The oxime (12.0 g) was dissolved in methanol and pH was maintained at 3 by adding 2N HCl in methanol drop wise. $NaBH_4$ (5.0 g) was added to the reaction mixture slowly and kept stirring for three hours. After completion of the reaction methanol has been dried under reduced pressure in rotavapore. The residue was dissolved in distilled water (30 ml) and pH has been raised to 9 with 6N KOH solution saturated with NaCl. The crude was extracted with dichloromethane (3 x 20 ml), washed with brine, dried (Na_2SO_4) to obtain benzyl hydroxylamine (8.0 g, 66%).

^{1}H NMR ($CDCl_3$, 400MHz): δ 3.96 (s, 2H), 7.30-7.39 (m, 5H).



3.8.5 Preparation of TAMA



N-methyl aniline (2.8 g) was dissolved in Et_2O cooled to 0 ^oC. Trifluoro acetic acid (2 ml) was added to it and allowed to stir for 90 minutes. The formed precipitate has been filtered and washed with Et_2O and dried to obtain TAMA (3.2 g).

4.1 Results and discussions

1,2:5,6-di-O-isopropylidene-α-D-glucofuranose **64** was synthesised using reported procedure[38] from D-Glucose and dry acetone at 5-8 ^{o}C in presence of conc. H_2SO_4. Formation of **64** was confirmed from the appearance of four 3H singlets for methyl groups between δ 1.30-1.48 ppm of its ^{1}H NMR spectrum. Doublet at δ 2.81 ppm for one proton represents the C-3 hydroxyl group of **64**. Two doublets at δ 5.91 and 4.53 ppm for one proton each having equal *J* value of 3.6 Hz is representing adjacent protons of C-1 and C-2. Here C-2 proton giving doublet probably due to little or no coupling with trans oriented C-3 hydrogen. Two doublet of doublets peak at δ 3.98 and 4.05 ppm for one proton each are for the protons on the C-6. Triplet at δ 4.15 ppm for one proton is for the proton on C-3, where the hydroxyl group is attached. Multiplate at δ 4.32 ppm for two protons is for protons of C-4 and C-5. Doublets at δ 4.52 and 5.93 ppm for one proton each are for the protons at C-2 and C-1 respectively. ^{13}C NMR spectrum also corroborated its formation. Four peaks between δ 25.1-26.8 ppm can be attributed to the four 1, 2 and 5, 6 protected methyl groups. Peaks at δ 67.6, 73.3, 75.0, 81.0, 85.0 and 105.2 ppm are for the C-6, C-3, C-5, C-4, C-2 and C-5 respectively. The two peaks with smaller intensity at δ 109.6 and 111.8 ppm are for the tertiary carbons at 5, 6 and 1, 2 protected positions. FTIR peaks also corroborate the formation of the compound **64**.

The hydroxyl group of C-3 in **64** was oxidised to ketone by PPC to obtain the compound **65** (68%). The formation of **65** was confirmed by disappearance of hydroxyl peak at δ 2.81 ppm in ^{1}H NMR and appearance of peak at δ 207.7 ppm in ^{13}C NMR for the formed ketone. FTIR shows characteristic ketone peak at ν_{max} 1772 cm^{-1} for **65**. Wittig reaction of the compound **65** with methyl

(triphenylphosphoranylidene)acetate gave conjugated unsaturated ester **66**. Appearance of singlet peak at δ 3.71 ppm for three protons confirms the incorporation of methyl ester group. Triplet (1H) at δ 6.29 ppm is the olefin proton of conjugated ester showing long range coupling of 1.6 Hz with C-2 proton at 5.67 ppm and invisible 1.2 Hz coupling with C-4 hydrogen. Other proton have appeared with expected chemical shift and coupling constants values. Formation of conjugated ester **66** also confirmed by ester carbonyl peak at δ 165.5 and olefinic carbon peaks at δ 156.0 and 117.4 ppm and the ester methyl peak at δ 51.6 ppm in ^{13}C NMR spectrum. Our initial attempt to deprotect 5,6 acetonide of **66** resulted in formation of undesired product **90** through base catalyzed oxa-Michael reaction. Therefore it became necessary to selectively reduce only conjugated double bond without reducing the ester. The reaction was carried out at -10 ^{o}C because at above that temperature both double bond and ester of **66** was being reduced by $NaBH_4$. The formation of the compound **67** after $NaBH_4$ reduction was confirmed by the appearance of the multiplate at δ 2.28-2.36 ppm for C-3, 1H and doublet of doublet at δ 2.65 (J = 10.4, 17.2 Hz) ppm for 1H and at δ 2.81(J = 4.0, 19.2 Hz) for 1H in ^{1}H NMR. ^{13}C NMR peak δ 80.8 ppm for C-3 also confirms the reduction of the double bond in **67** (92%). Deprotection of **67** at 5,6- by treatment with 75% glacial acetic acid produced compound **68** (82%) where two methyl peaks between δ 1.26-1.29 ppm in ^{1}H NMR and δ 26.0-26.9 ppm in ^{13}C NMR disappears. Oxidative cleavage by sodium metaperiodate of the diol **68** resulted in the formation of an aldehyde **69** (76%).^{1}H NMR and ^{13}C NMR shows characteristic peak for the formed aldehyde at δ 9.67 ppm (d, 1H J = 1.6 Hz) and δ 200.3 ppm respectively. FTIR showed characteristics aldehyde peak at 1779 cm^{-1}. Wittig reaction of compound **69** with phosphorous ylide of bromoheptane at -78 ^{o}C, using t-butyl lithium produced the compound **70** (74%).

Disappearance of the aldehyde peaks both in ^{1}H NMR and ^{13}C NMR at δ 9.67 ppm and δ 200.3 ppm respectively and appearance of multiplate in the range of δ 1.24-1.34 ppm in ^{1}H NMR confirms the incorporation of the long carbon chain of heptane. A doublet of triplet at 5.66 (1H, *J* = 1.2, 11.6 Hz) and a multiplate in the range 5.64-5.69 for 1H in ^{1}H NMR corresponds to the olifinic carbon's protons in the long carbon chain which disappears on reduction of the double bond in the compound **70** with H_2/Pd-C to give the compound **71** (98%) and multiplate between δ 1.22-1.36 ppm appears. ^{13}C NMR showed eight peaks in the range of δ 14.1-32.6 ppm for the eight carbons in the chain.

The nine membered oxacycle **81** was synthesised in seven steps from compound **64** with an overall yield of 17%. O-benzylation of the C-3 hydroxyl in **64** was done to form **74**. The incorporation of the benzyl group in **74** was confirmed by disappearance of the broad hydroxyl singlet peak at δ 2.83 ppm and appearance of multiplate for the aromatic ring between δ 7.28-7.35 ppm and doublet of doublet at δ 4.65 ppm (*J* = 11.6, 20.6 Hz) for benzyl proton in ^{1}H NMR. ^{13}C NMR peaks between δ 127.6–137.6 and 72.5 ppm for aromatic carbons and the benzyl carbon also corroborate the formation of the compound **74** (92%). Compound **74** was deprotected by 75% acetic acid to obtain the compound **75** (90%) where two methyl peaks in the range of δ 1.32-1.50 ppm and δ 26.0-27.0 in ^{1}H NMR and ^{13}C NMR respectively disappeared. Peak for the hydroxyl group appeared at δ 2.43 ppm in ^{1}H NMR. The diol of the compound **75** was cleaved to an aldehyde by sodium metaperiodate at 0 ^{o}C. The formation of the aldehyde in compound **76** (83.3%) was confirmed by appearance of a doublet peak at δ 9.67 ppm, (*J* = 1.6 Hz) in ^{1}H NMR and a peak at δ 209.5 ppm in ^{13}C NMR. The aldehyde of the compound **76** was reduced to alcohol by sodium

borohydride to form the compound **77** (86.6%). Disappearance of the aldehyde peak both in ^{1}H NMR and ^{13}C NMR at δ 9.67 ppm and 209.5 ppm respectively and appearance of hydroxyl peak at δ 2.43 ppm in ^{1}H NMR confirms the formation of the compound **77**. O-allylation of the compound **77** was carried out by treatment with aq. NaOH to abstruct the hydroxyl proton and subsequent addition of allyl bromide and catalytic amount of Tetrabutylammoniumbromide ($Bu_4N^+Br^-$) as a phase transfer catalyst to obtain the compound **78** (91%). Introduction of the allyl group was confirmed by appearance of a multiplate at δ 5.89-5.96 ppm (1H) and a doublet of doublet at δ 5.20 ppm (1H, *J* = 1.2, 10.4 Hz) and at δ 5.30 (1H, *J* = 1.6, 17.2)in ^{1}H NMR for the terminal double bonded carbon's proton and peaks at δ 137.5, 117.2 ppm for the olifinic carbons in ^{13}C NMR. Deprotection of the compound **78** at 1, 2-position was done by 4% H_2SO_4 (1 ml H_2SO, 6 ml H_2O, and 18 ml CH_3CN). Formation of the compound **79** (93%) was confirmed by disappearance of the two singlet peaks in the range of δ 1.33-1.50 ppm in ^{1}H NMR and δ 26.3, 26.8 ppm in ^{13}C NMR for protected methyl groups and at δ 111.2 ppm for the tertiary carbon in ^{13}C NMR. Intermolecular nitrone cycloaddition (INC) reaction of the compound **79** by adding benzyl hydroxylamine and refluxing in toluene resulted in the formation of the nine membered oxacycle **81**. Characteristic doublet peak at δ 2.43 ppm (1H, *J* = 12.4 Hz) and multiplate between δ 2.62-2.68 ppm (1H) for bridged CH_2 in ^{1}H NMR confirmed the formation of the compound **81** (34%). The number of protons between δ 7.24-7.62 ppm in ^{1}H NMR increased by five, which is for the newly introduced phenyl group of the benzyl hydroxylamine. Disappearance of the aldehyde peak and the allyl peaks also confirmed the cyclization. An eight membered oxacycle also was expected but in our case we only obtained the nine membered oxacycle **81**. Oxidative cleavage of the compound **79** by sodium metaperiodate was carried out to obtain the

aldehyde compound **82** (86%). Disappearance of the doublet at δ 4.73 ppm for C-2 proton and appearance of clear doublet peak for aldehyde at δ 9.76 ppm in ^{1}H NMR which was not much clear in compound **79** because of hemi acetyl formation, confirmed the formation of the compound **82**. Intermolecular nitrone cycloaddition (INC) reaction of the compound **82** with benzyl hydroxylamine by refluxing in toluene resulted in the formation of the intermediate compound **83**. The non-occurrence of the cyclization can be attributed to the presence of bulky benzyl group near the aldehyde which sterically hindered the cyclization. Formation of the intermediate **83** was confirmed by the disappearance of the aldehyde peak at δ 9.76 ppm in ^{1}H NMR and increase in the proton count in the aromatic region for the newly introduced phenyl group of benzyl hydroxylamine. Another seven membered oxacyclic compound **88** was synthesised from compound **64** with an overall yield of 40 % in four steps. O-allylation of the compound **64** was carried out on treatment with aq. NaOH to abstruct the hydroxyl proton and subsequent addition of allyl bromide and catalytic amount of Tetrabutyl ammonium bromide ($Bu_4N^+Br^-$) as a phase transfer catalyst to obtain the compound **85** (91%). ^{1}H NMR shows characteristic doublet of doublet peaks for terminal allyl at δ 5.16 ppm (1H, J = 1.6, 10.4 Hz) and at δ 5.27 ppm (1H, J = 1.6, 17.2 Hz) and a multiplate at δ 5.81-5.86 ppm for 1H. Peaks at δ 117.2 and 134.3 ppm in ^{13}C NMR for the olifinic carbon also confirmed the introduction of the allyl group. The allylated compound **85** was deprotected at 5, 6-positions by 75% glacial acetic acid in water. Disappearance of two singlets in the range of δ 1.3-1.4 for 3H each in ^{1}H NMR for two methyl groups and disappearance of two peaks between δ 25.5-26.3 ^{13}C NMR for the same methyl groups confirmed the formation of the compound **86** (87%). Singlet peak at δ 2.73 ppm in ^{1}H NMR and a broad peak at 3426.8 cm^{-1} in FTIR appeared for the hydroxyl formed. Sodium

metaperiodate cleavage of the compound **86** was carried out to obtain an aldehyde compound **87** (84%), formation of which was confirmed by appearance of a doublet peak at δ 9.66 ppm (J = 1.6 Hz) in ^{1}H NMR. Intermolecular nitrone cycloaddition reaction (INC) of the aldehyde compound **87** with phenyl hydroxylamine by refluxing with toluene to obtain the seven membered oxacyclic compound **88** (57%) was done. ^{1}H NMR showed characteristic peaks for bridged CH_2 at δ 2.32–2.39 (m, 1H) and 2.63 ppm (d, 1H, J = 12.4 Hz). A peak at δ 21.6 ppm in ^{13}C NMR for the bridge CH_2 also confirmed the formation of the compound **88**. Base catalysed oxa-Michael cyclization afforded another five membered oxacyclic compound **90**. Deprotection at 5, 6 position of the compound **65** by 75% AcOH afforded the compound **89** (91%). Formation of the compound **89** was confirmed by the disappearance of two singlet methyl peaks in the range of δ 1.23-1.28 ppm in ^{1}H NMR. Wittig reaction of the compound **89** with (triphenylphosphoranylidene)acetate in toluene at a reflux temperature in presence of base afforded the cyclised compound **90**. Two quartets at δ 3.35 (1H, J = 8.8 Hz) and 4.08 (1H, J = 7.2 Hz) ppm in ^{1}H NMR for the C-6 protons and peaks at δ 32.0 and 66.9 ppm in ^{13}C NMR confirms the formation **90**. Towards the synthesis of one of the nine membered oxacyclic compound **94** through intermolecular nitrone cycloaddition (INC) reaction from compound **90**, O-allylation of the C-5 hydroxyl group was done by treatment with aqueous NaOH, Tetrabutyl ammonium bromide and allyl bromide for O-allylation to obtain compound **91** (87%). Appearance of characteristic doublet of doublet peak for terminal double bond of the allyl at δ 5.25 ppm (2H, J = 10.4, 30.4 Hz) and a multiplate at δ 5.88–5.97 ppm for 1H in ^{1}H NMR confirmed the formation of the compound. ^{13}C NMR also corroborated the formation of **91** from the appearance of the peaks at δ 129.0 and 113.0 ppm for the olifinic carbons. Compound **91** was

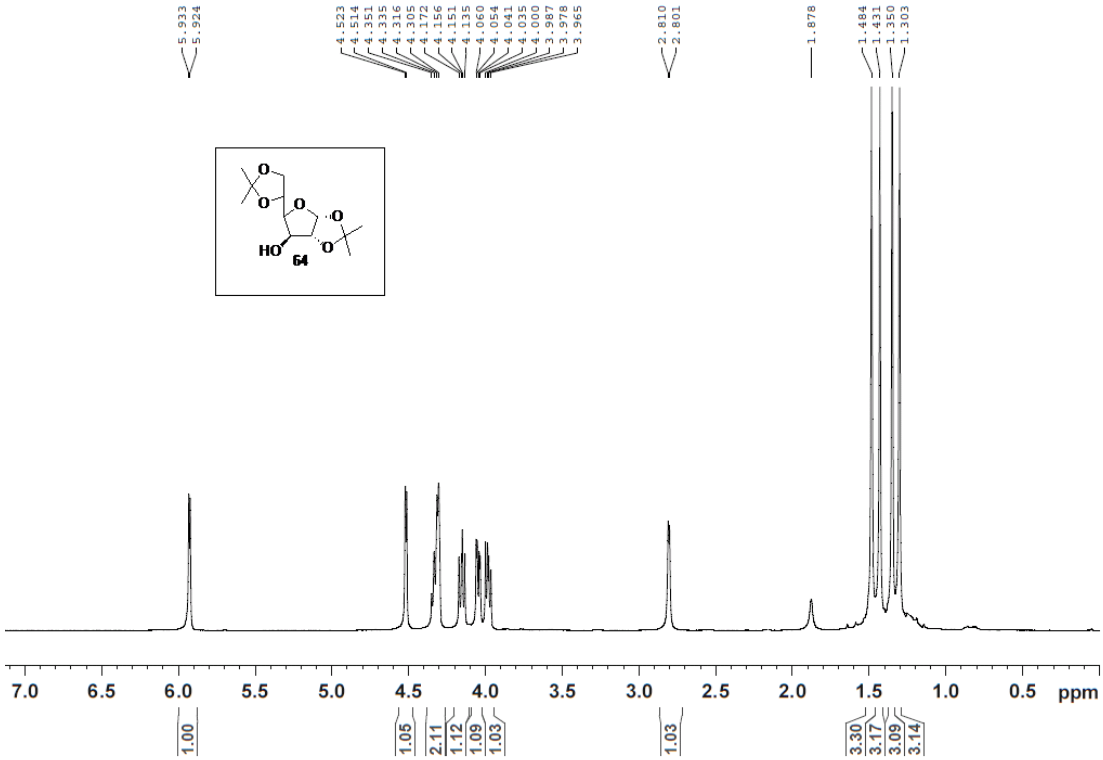
deprotected at 1, 2- position with 4% H_2SO_4 and intermolecular nitrone cycloaddition (INC) reaction by adding benzyl hydroxylamine was done in toluene in reflux temperature but cyclization was not successful to obtain compound **94**. The reason for this may be attributed to the steric and ring strain factor. The formation of the 1, 2 deprotected compound **92** was confirmed by disappearance of the singlet methyl peaks in the range of δ 1.24-1.27 ppm and appearance of doublet peak at δ 2.82 ppm for hydroxyl group in ^{1}H NMR. An inter nitrone cycloaddition (INC) precursor **95** (61%) was obtained from compound **78** on treatment with triethylsilane and borontrifluoride etherate. Disappearance of two singlet peaks at δ 1.41-1.43 ppm for the methyl groups and appearance of broad singlet at δ 2.35 ppm for one hydroxyl group and two doublet of doublet at δ 4.01 (J = 5.6, 18.4 Hz) and 4.10 (J = 6.0, 12.8 Hz) ppm in ^{1}H NMR for the C-1 proton confirms the formation of the compound **95**. ^{13}C NMR also confirms the formation of **95** as peaks at δ 26.2 and 26.5 and 111.2 ppm disappears which are for the two methyl groups and the tertiary carbon. Compound **95** will be oxidised with PCC and treated with benzyl hydroxylamine for INC reaction to obtain an oxacycle **97** in future. Many of the reagents like PCC, benzyl hydroxylamine, methyl (triphenylphosphoranylidene)acetate (Wittig salts), TAMA, phosphorous ylide of bromoheptane (Wittig salt) were prepared in the lab and used in the reactions by following reported procedures.

5.1 Conclusion

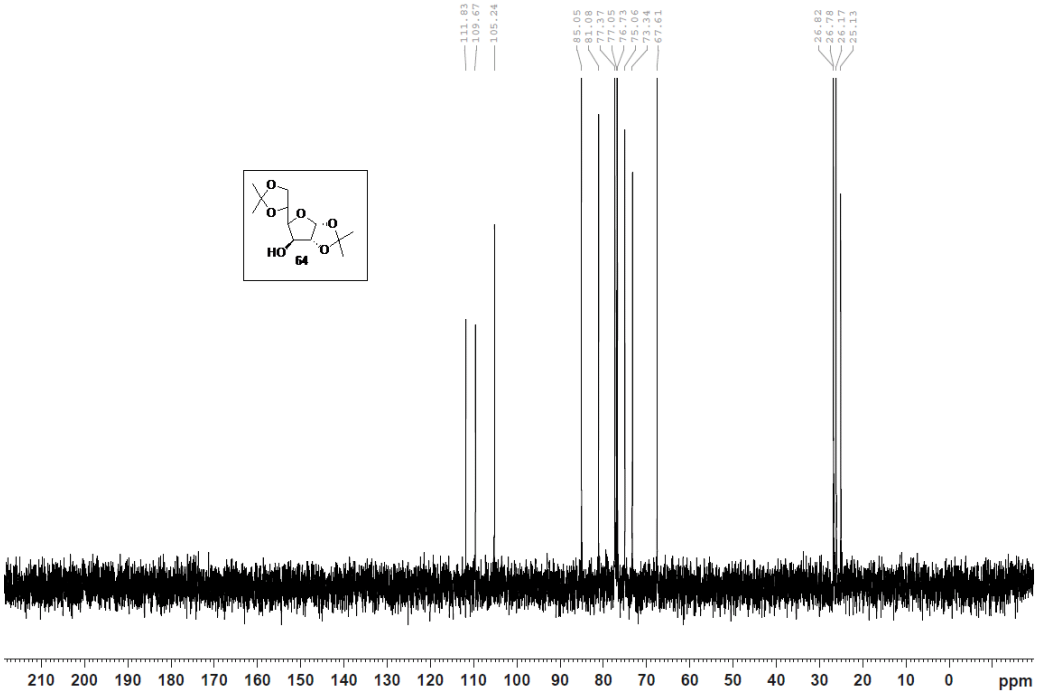
First seven steps among total 9 steps towards the synthesis of *Neosartolactone* **73** and its 7-methyl ester analogue was successfully achieved. For introduction of a methelene group in the compound **71** many reactions were tried without success. The remaining two steps of this total synthesis will be tried with other new methodologies. A nine membered bicyclic oxacycle **81** and a seven membered poly oxacycle **88** were synthesised from chiral pool D-Glucose as a starting material with a very good overall yield using intramolecular nitrone cycloaddition (INC) reaction. Another five membered poly oxacycle **90** was synthesised via base catalyse oxa-Michael cyclization using chiral pool D-Glucose which further was modified to make nitrone precursor **92**. An INC precursor **95** was synthesised successfully, which on INC reaction should give a locked oxacycle.

Compound produced in various steps were purified by column chromatography. The confirmation of the completion of the reaction was done by TLC. Characterization of all the compounds and intermediates formed was done by ^{1}HNMR, ^{13}CNMR, FTIR, Mass spectroscopy etc. wherever necessary.

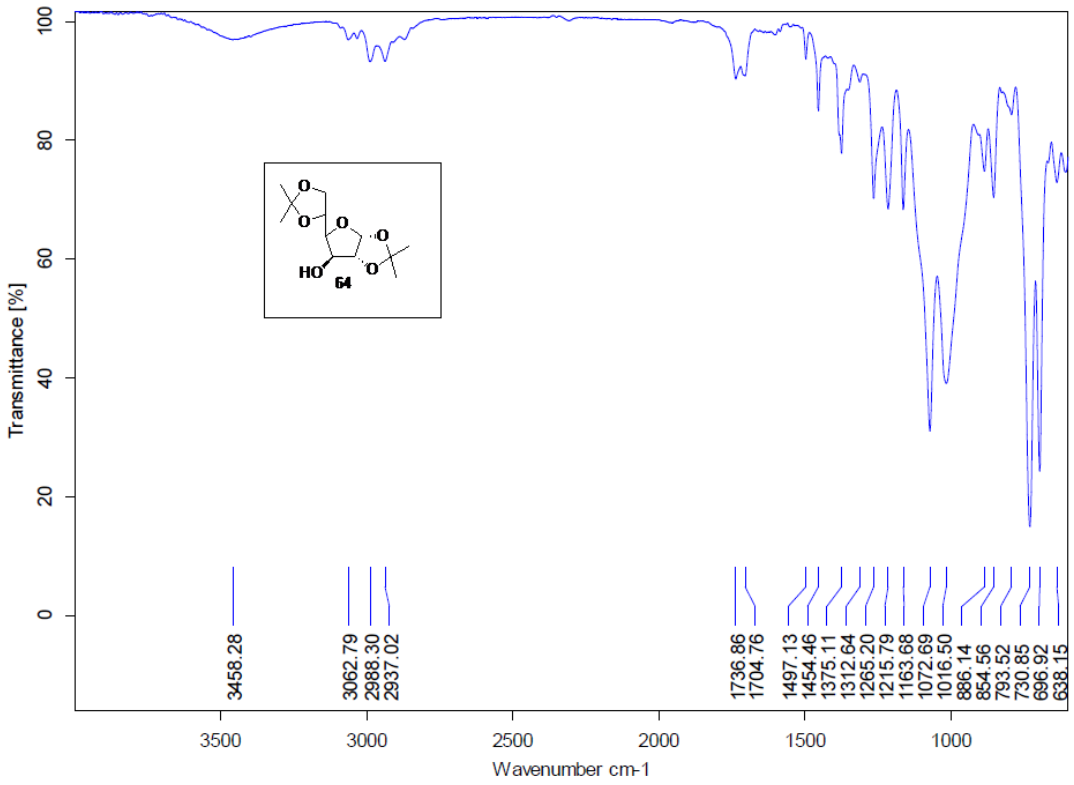
5.1 Spectra



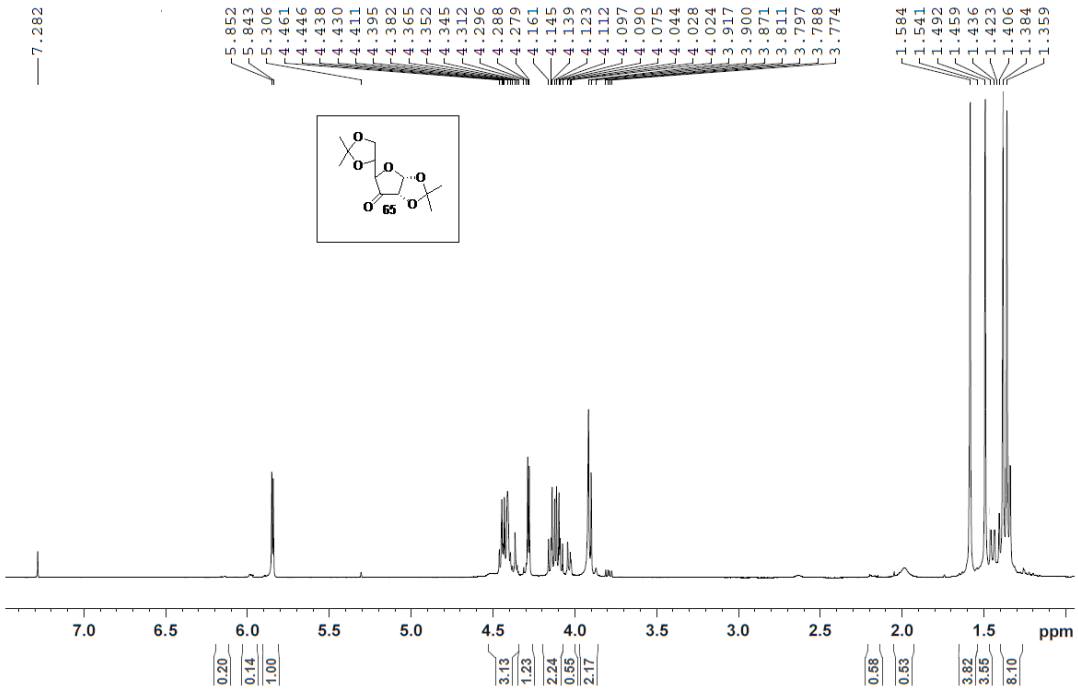
^{1}H NMR ($CDCl_3$, 400MHz) of 64



^{13}C NMR ($CDCl_3$, 100MHz) of 64



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



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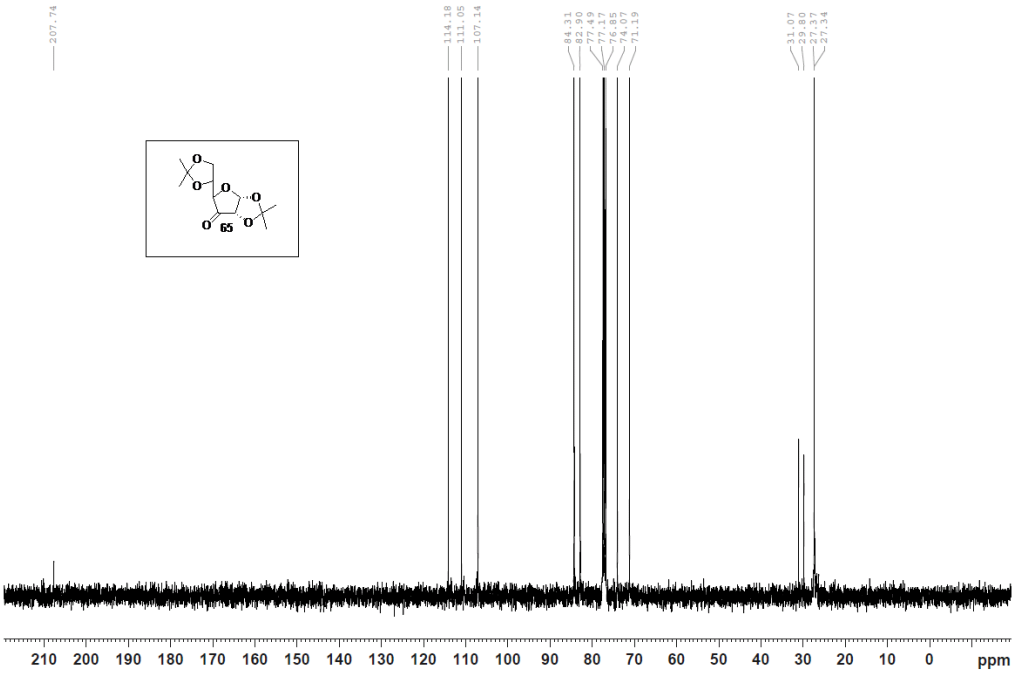

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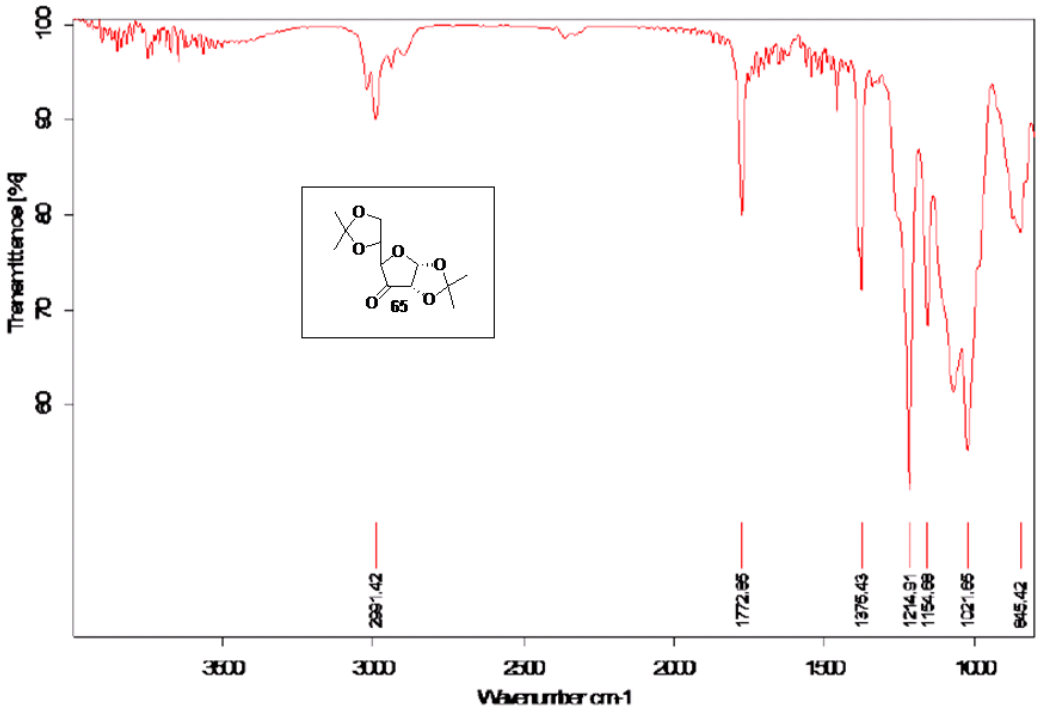
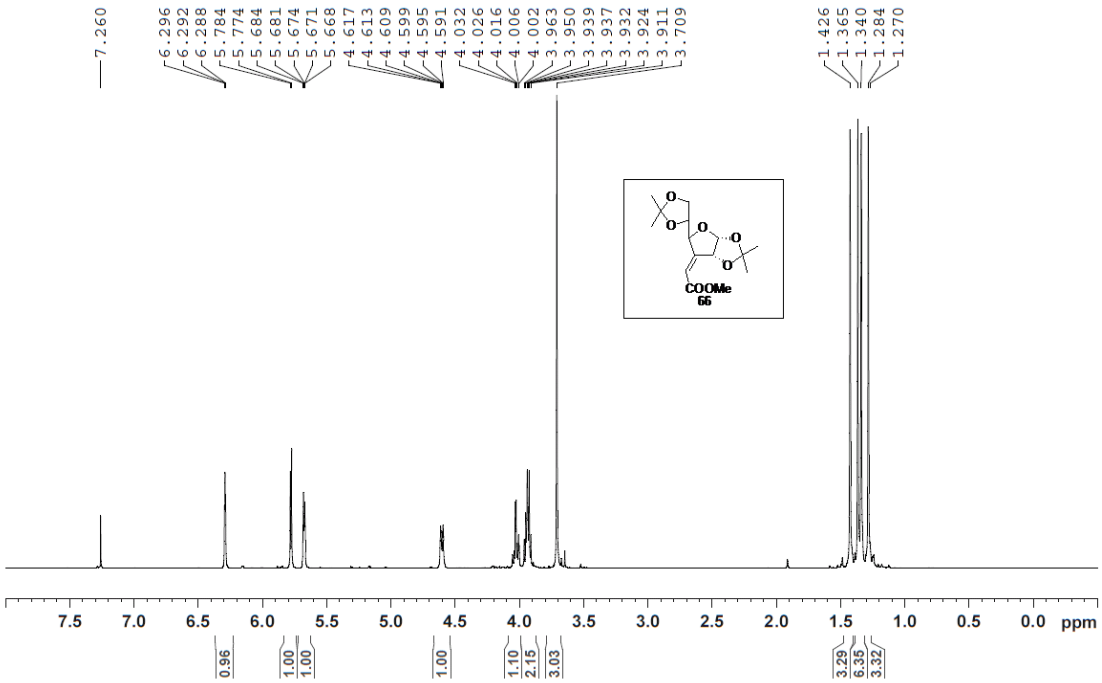


FTIR Spectrum: ν_{max} (neat)/cm^{-1} of 65



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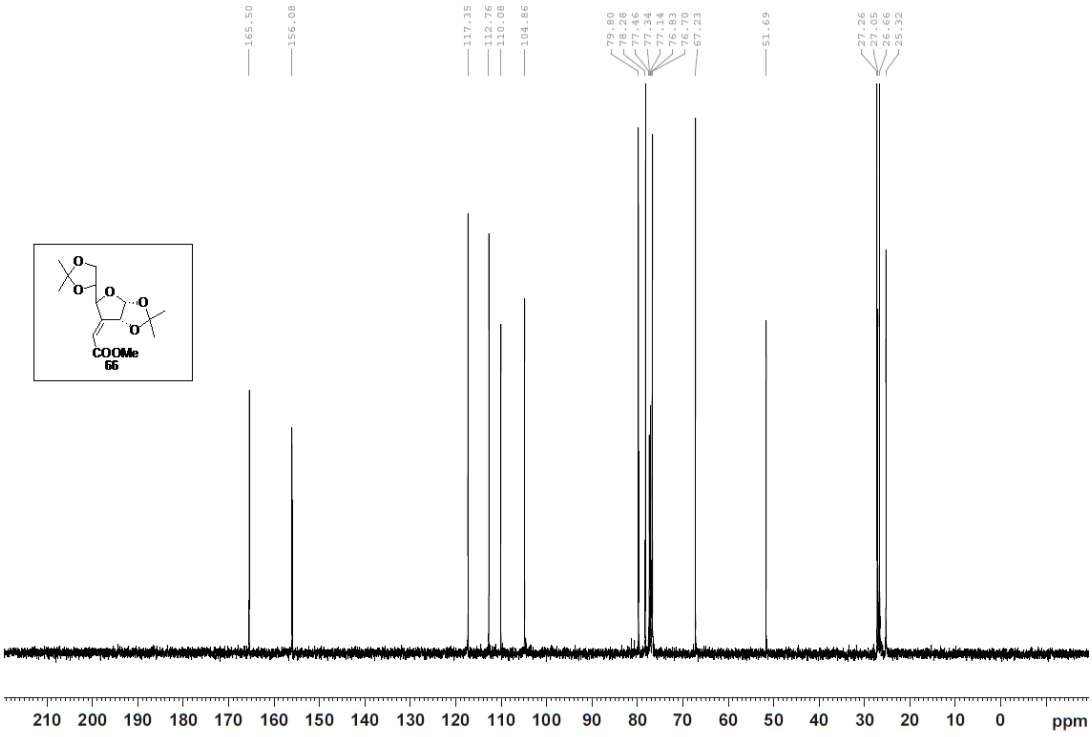

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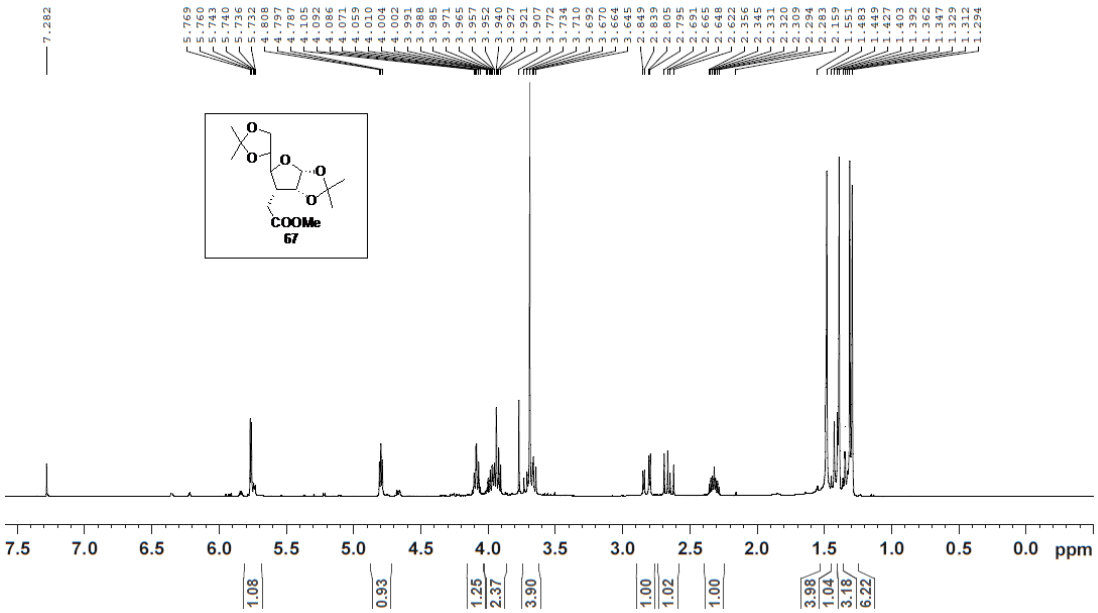

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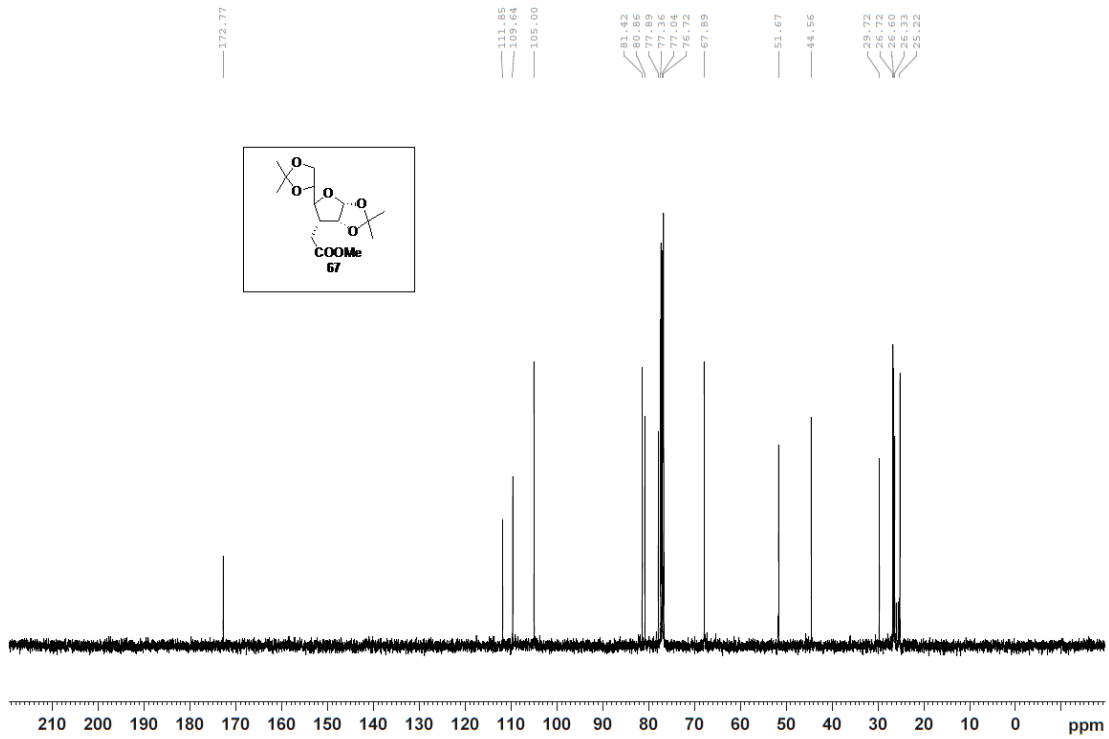
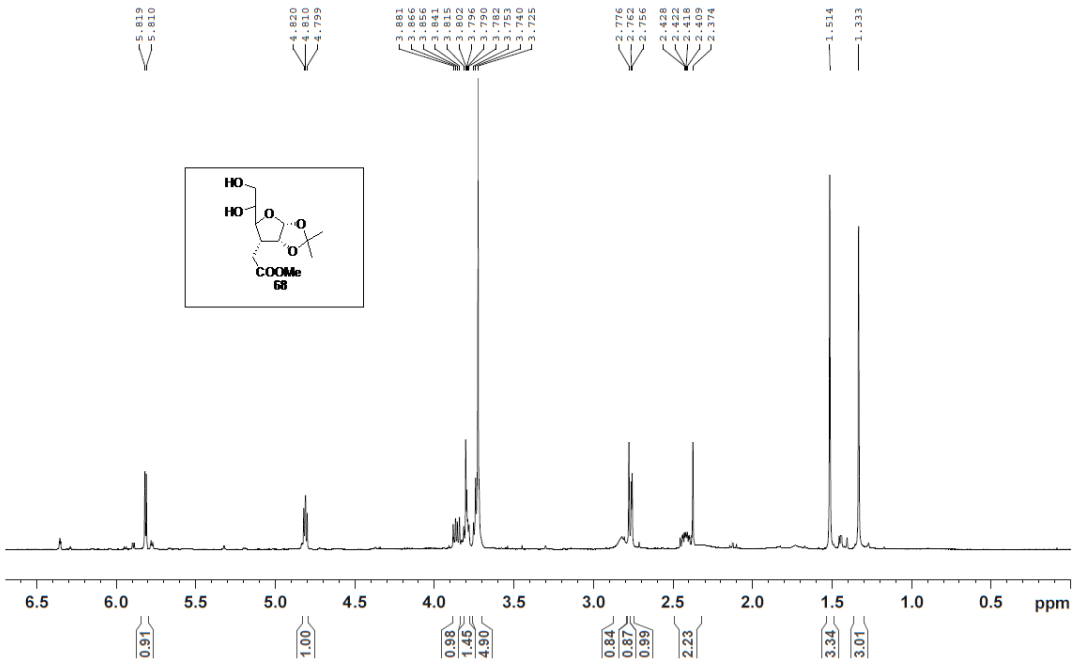


^{13}C NMR ($CDCl_3$, 100MHz) of 67



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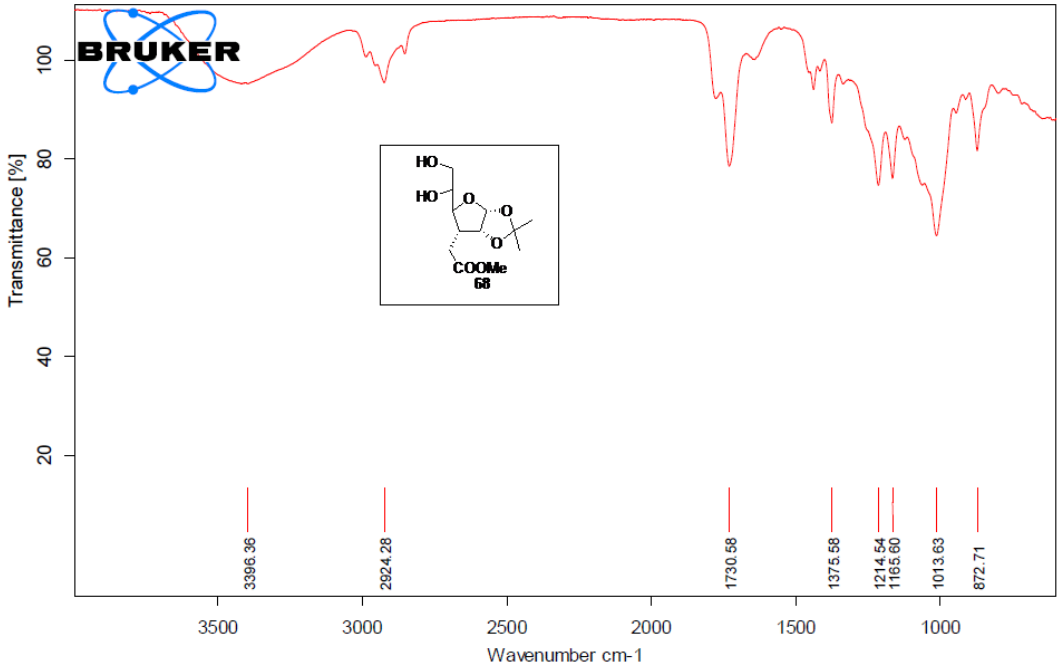
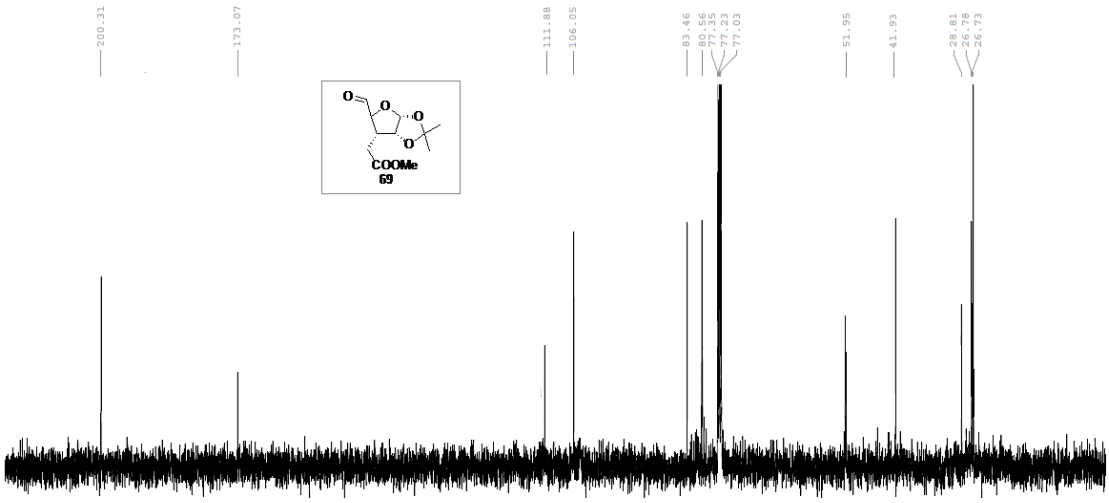
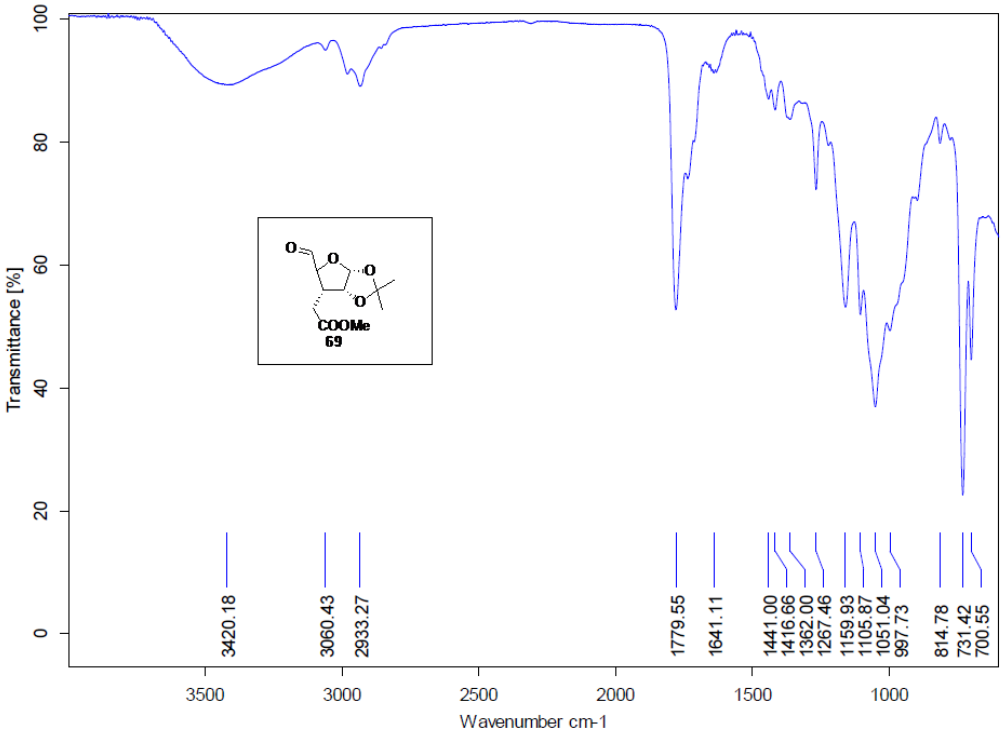


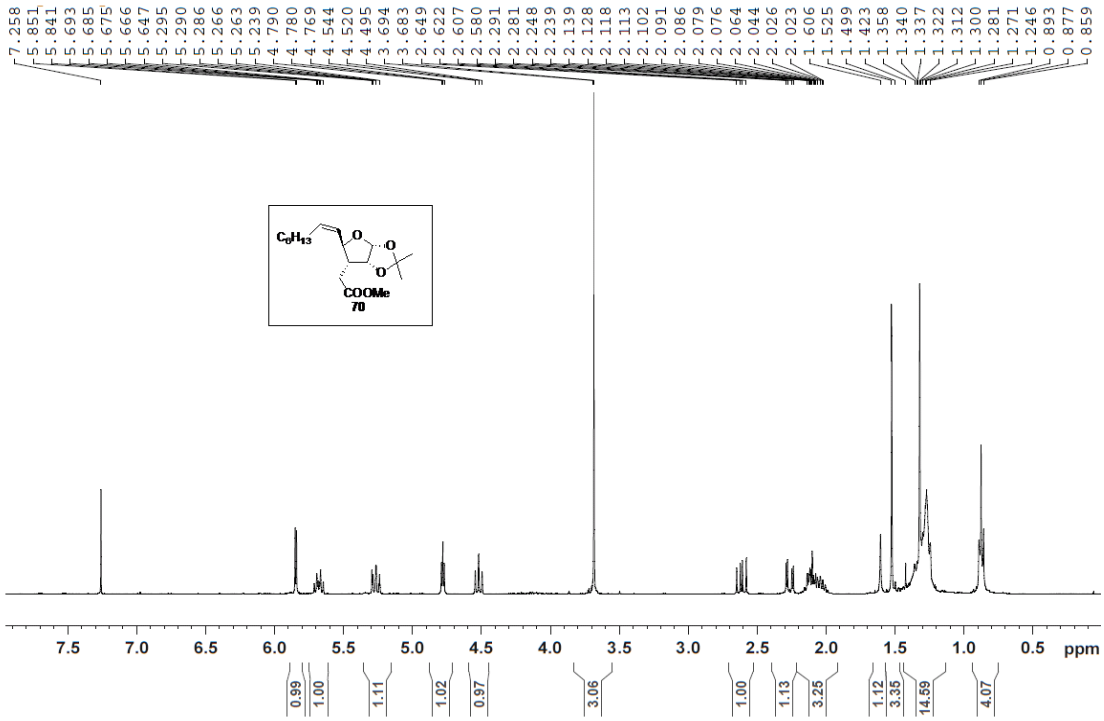
FTIR Spectrum: ν_{max} (neat)/cm^{-1} of 68



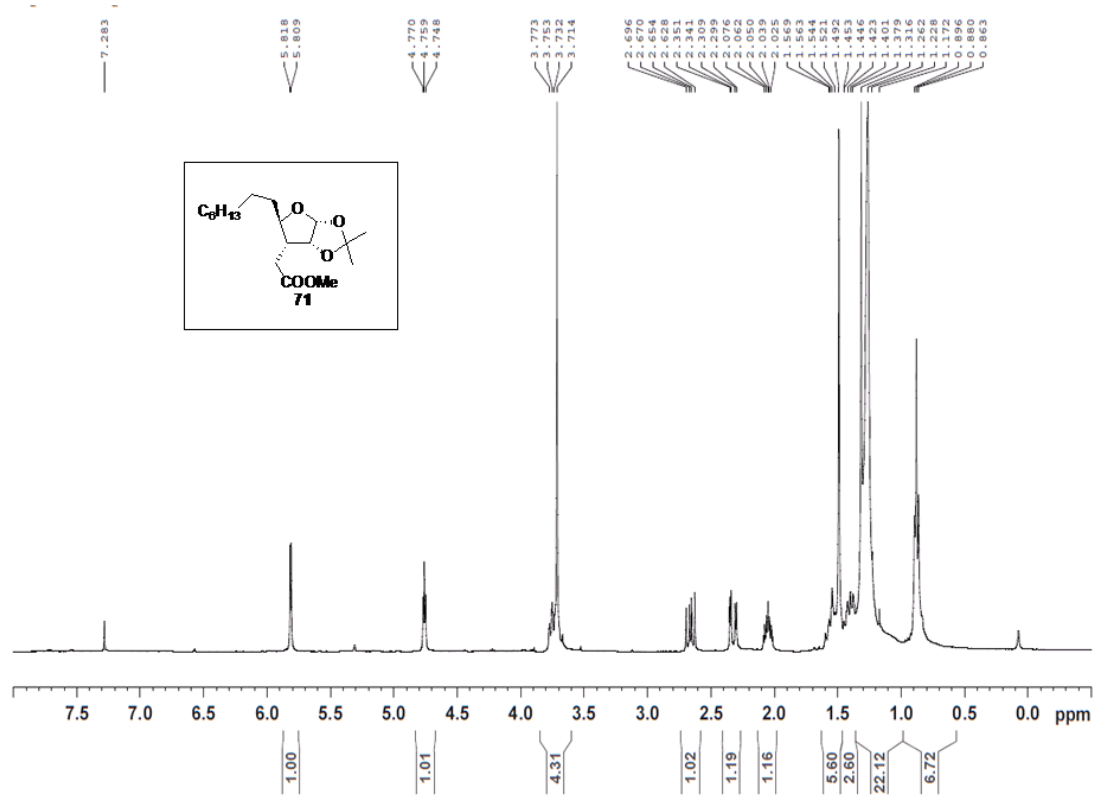
^{13}C NMR ($CDCl_3$, 100MHz) of 69



FTIR Spectrum: ν_{max} (neat)/cm^{-1} of 69



^{1}H NMR ($CDCl_3$, 400MHz) of 70



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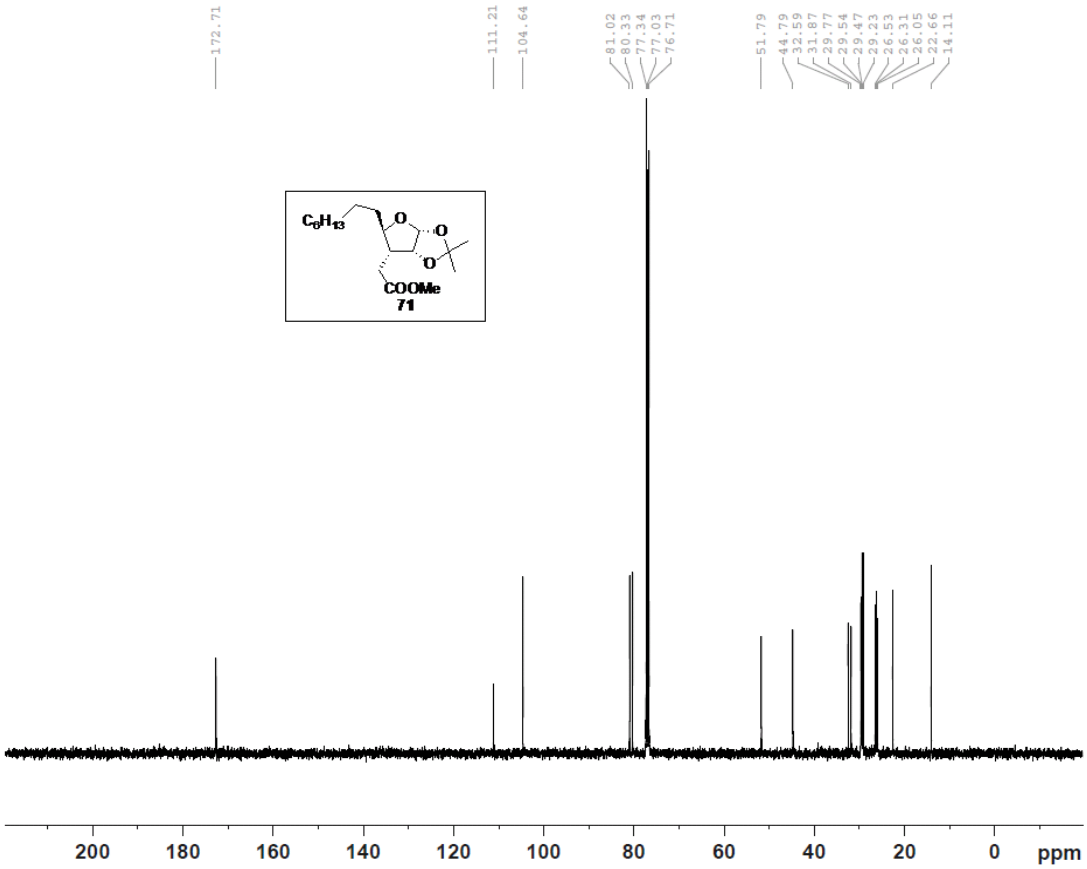
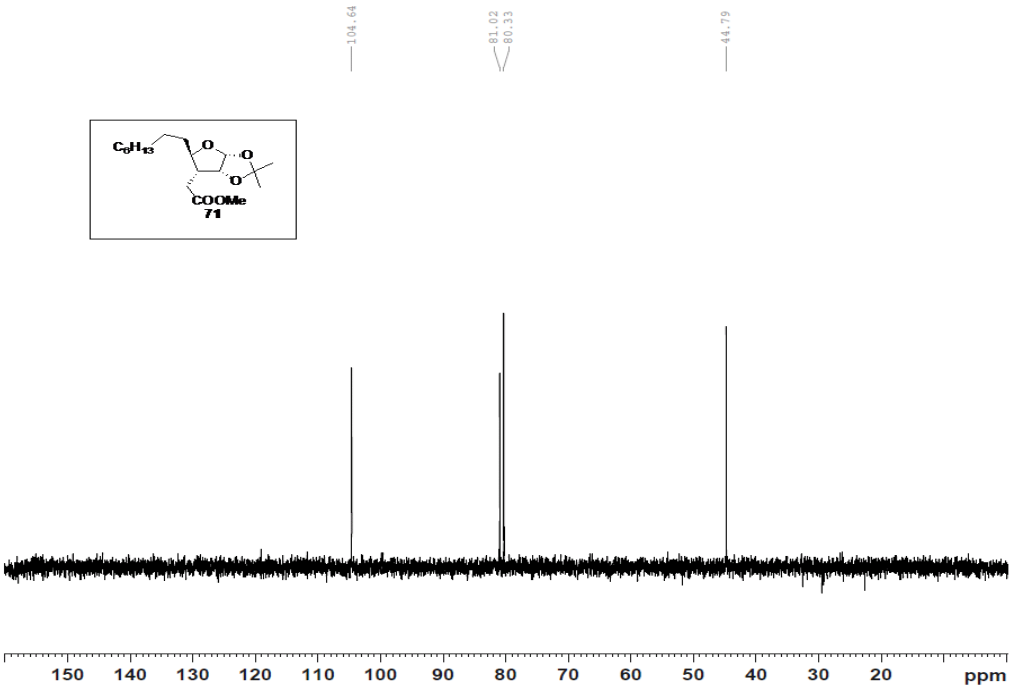
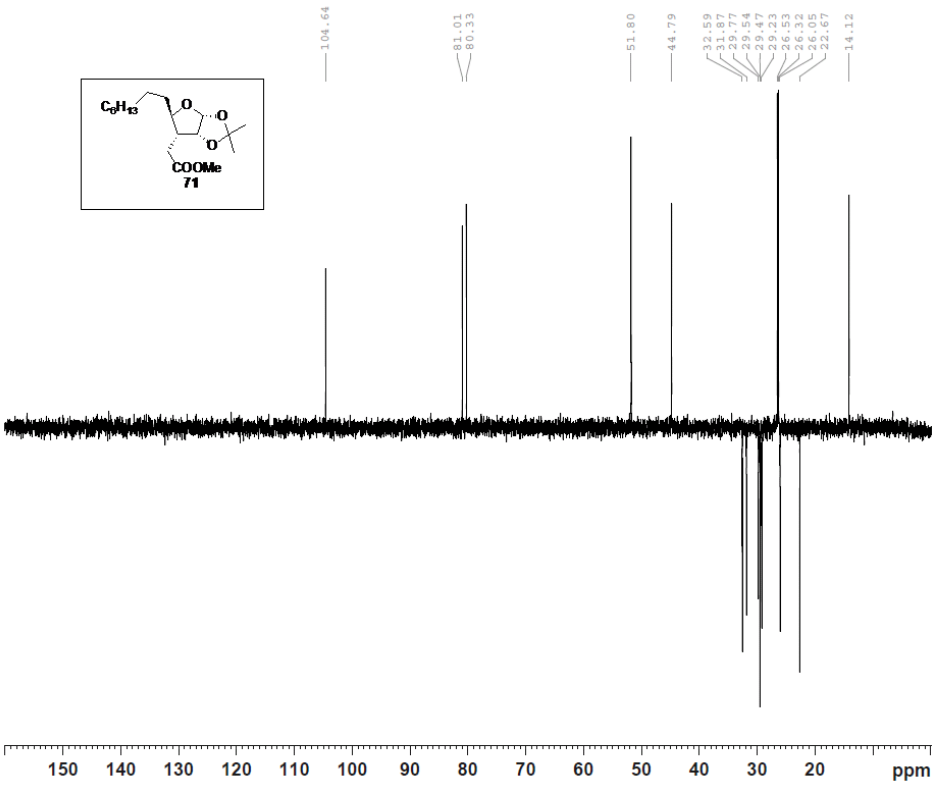


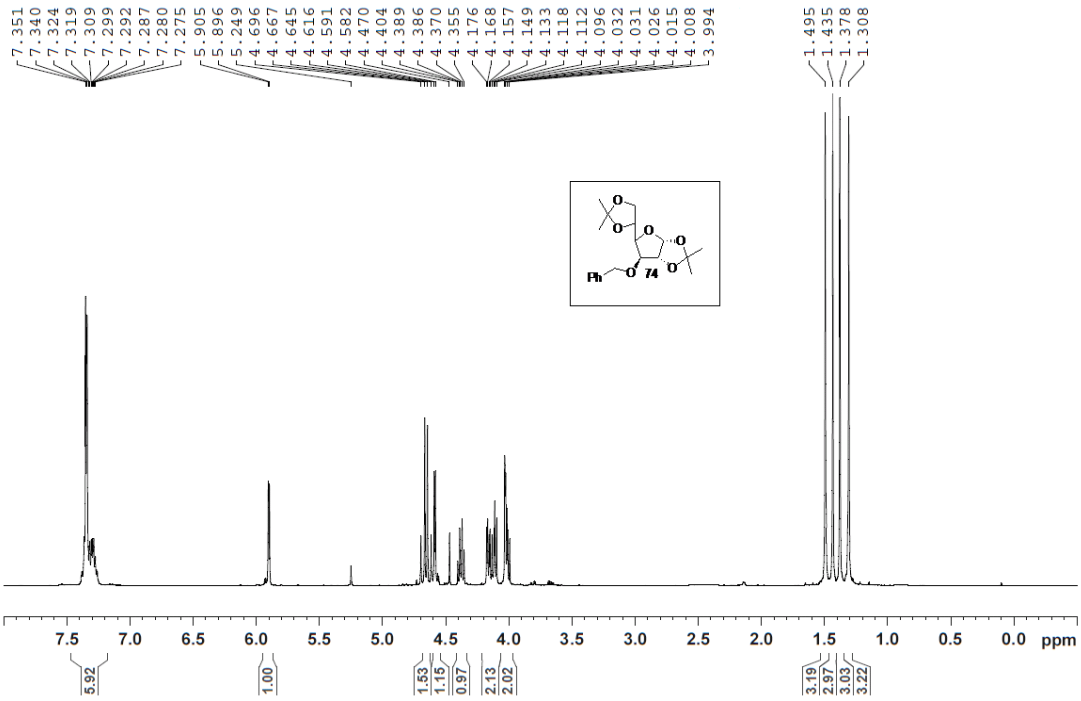
^{13}C NMR ($CDCl_3$, 100MHz) of 71



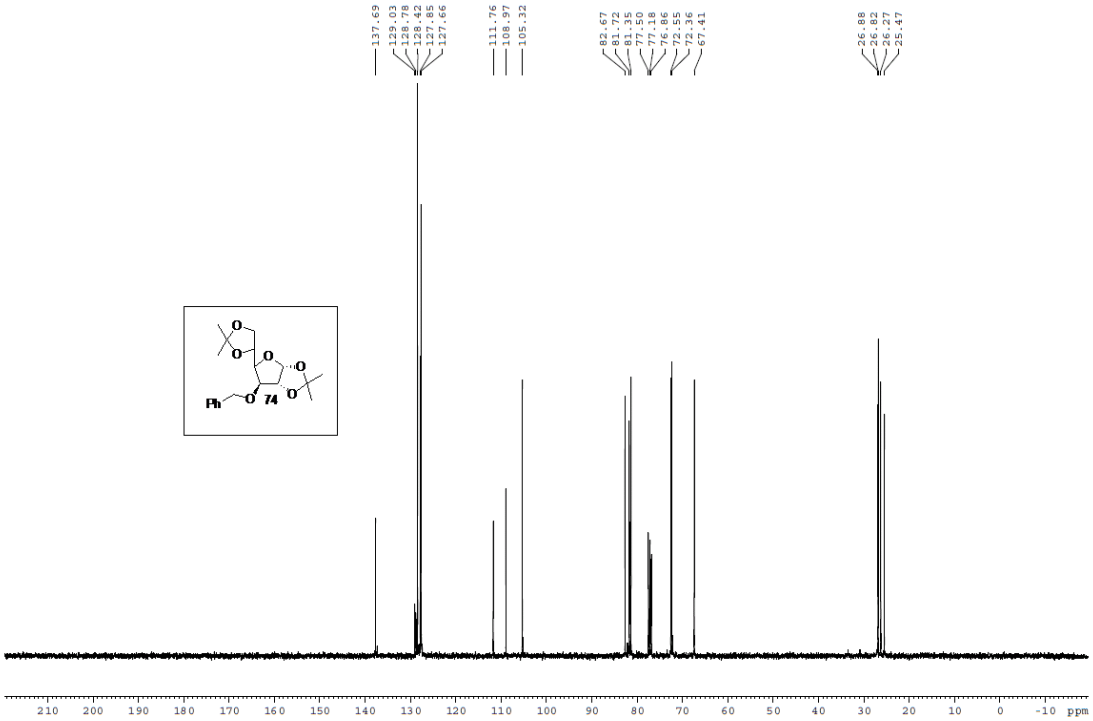
DEPT 90 ($CDCl_3$, 400MHz) of 71



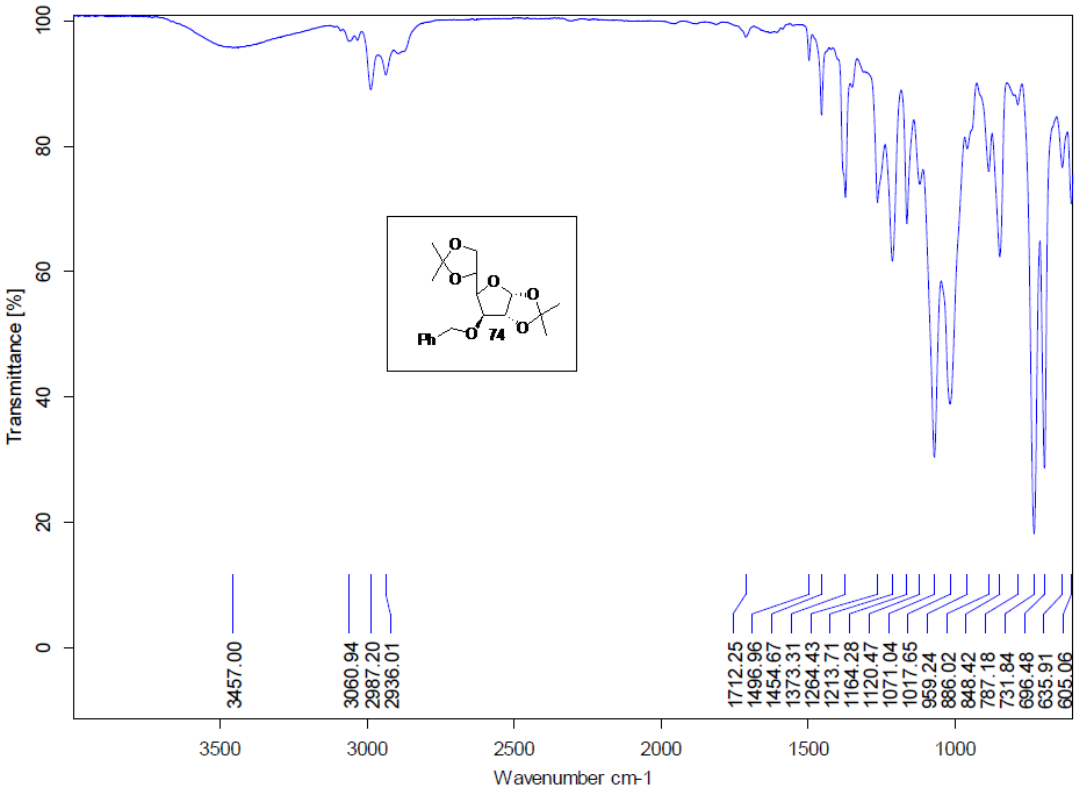
DEPT 135 ($CDCl_3$, 400MHz) of 71



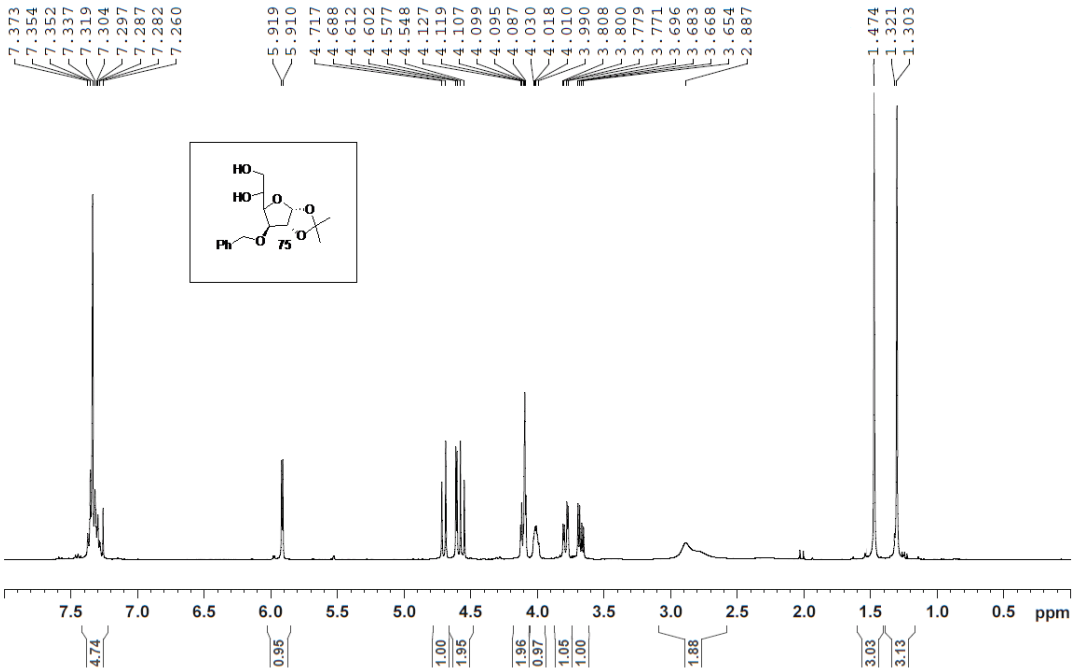
^{1}H NMR ($CDCl_3$, 400MHz) of 74



^{13}C NMR ($CDCl_3$, 100MHz) of 74



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



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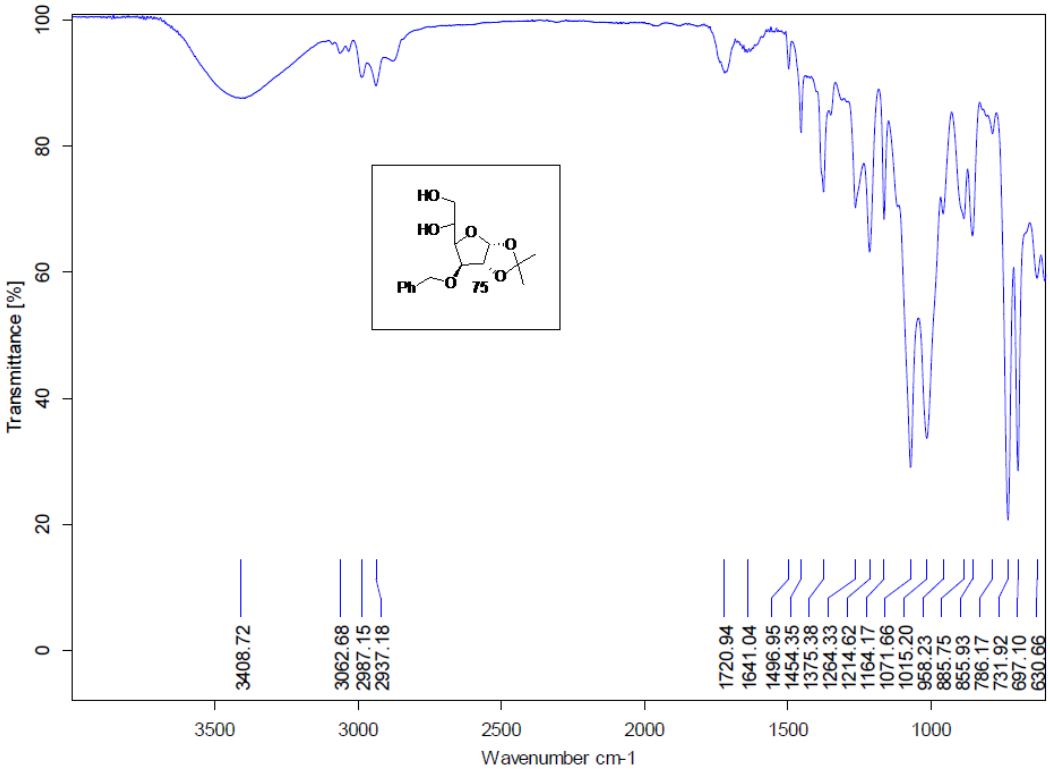

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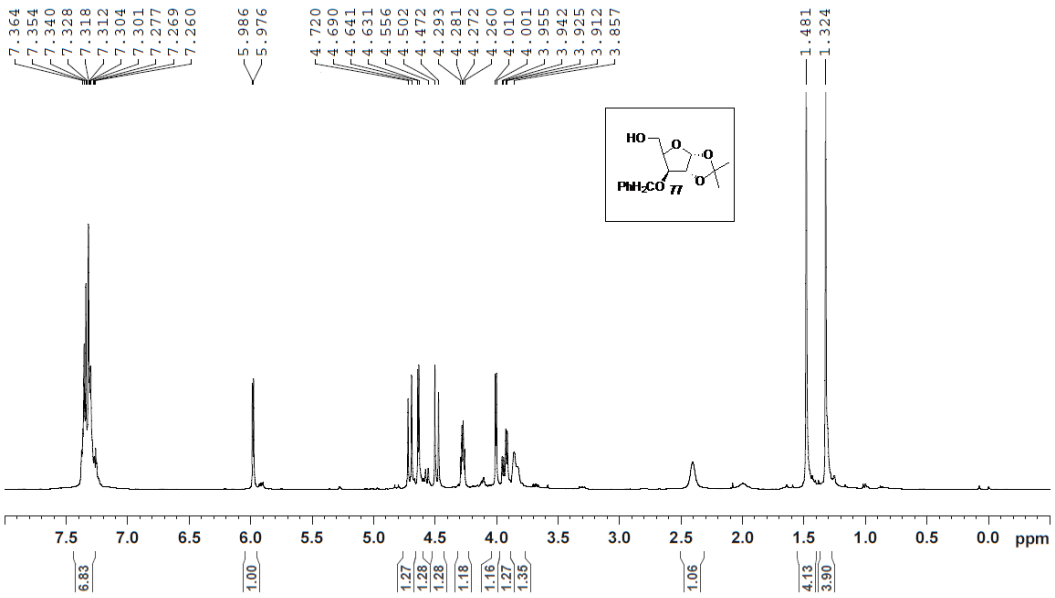

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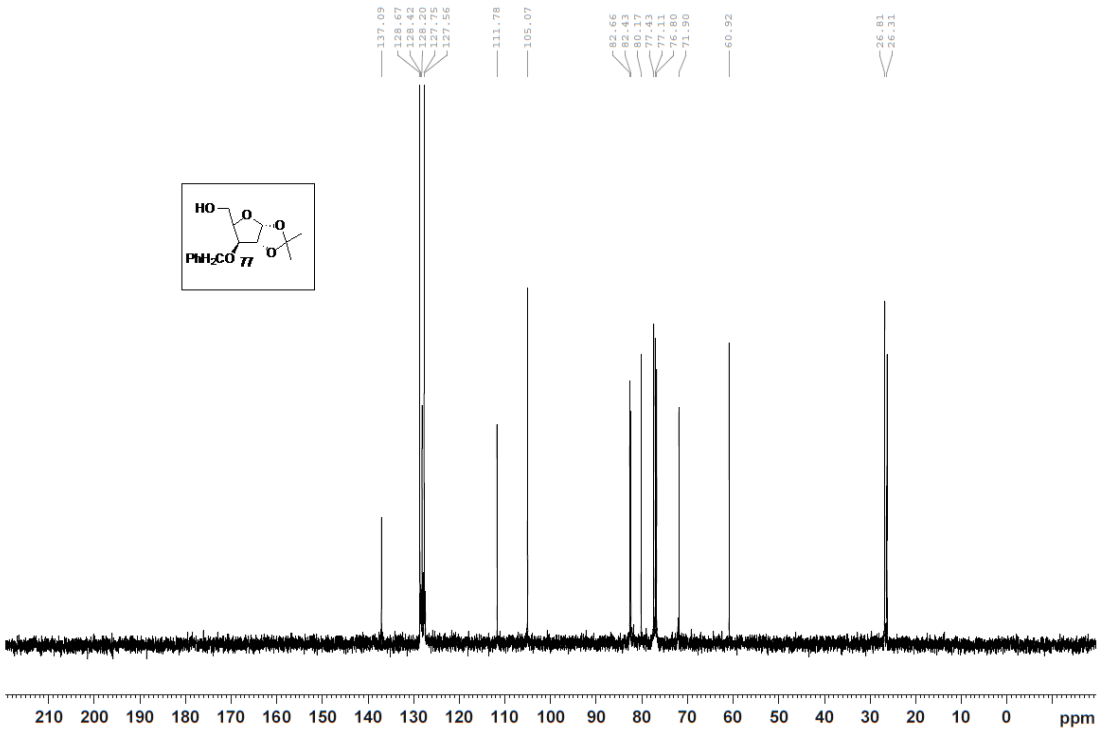

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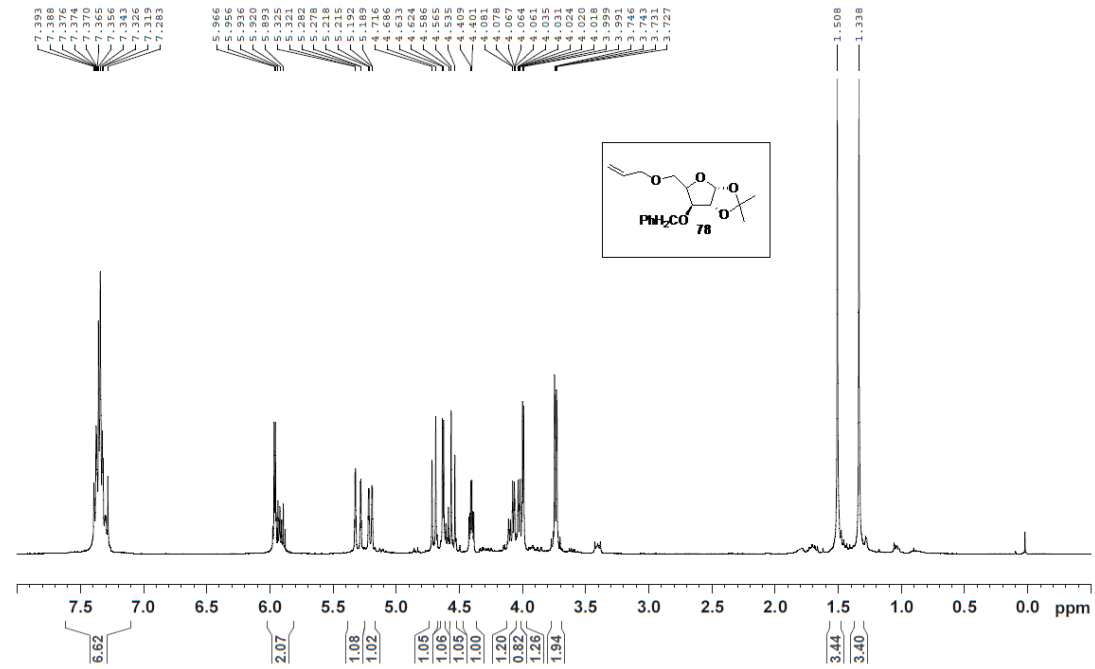

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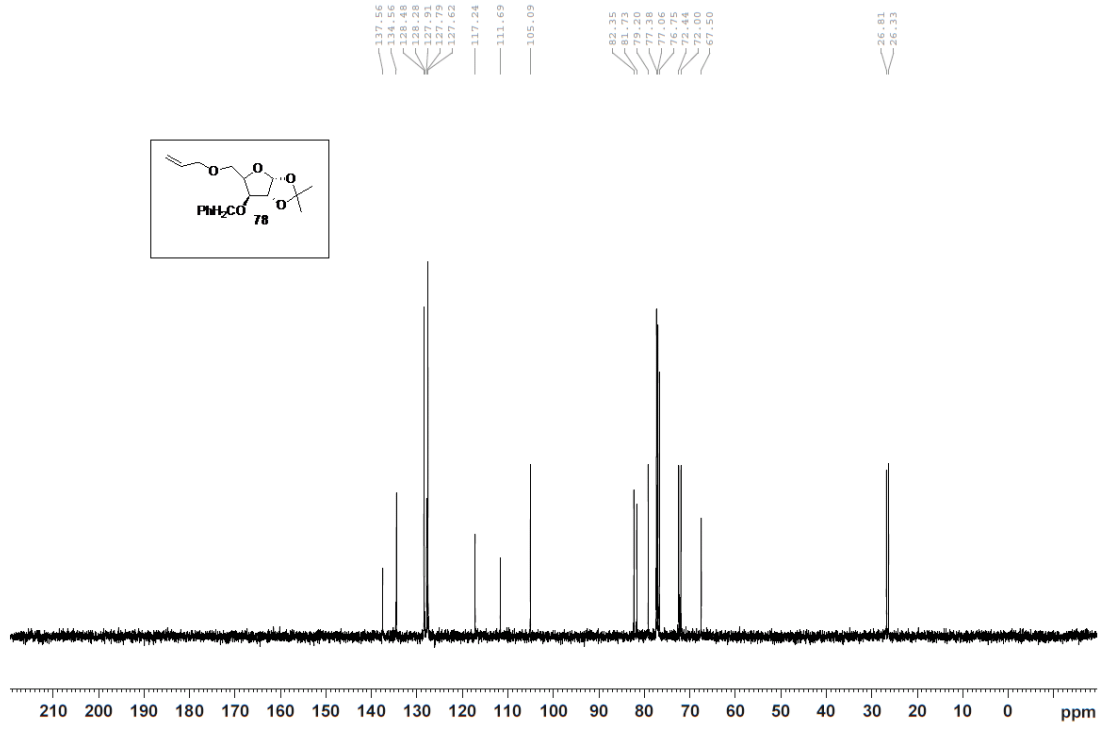

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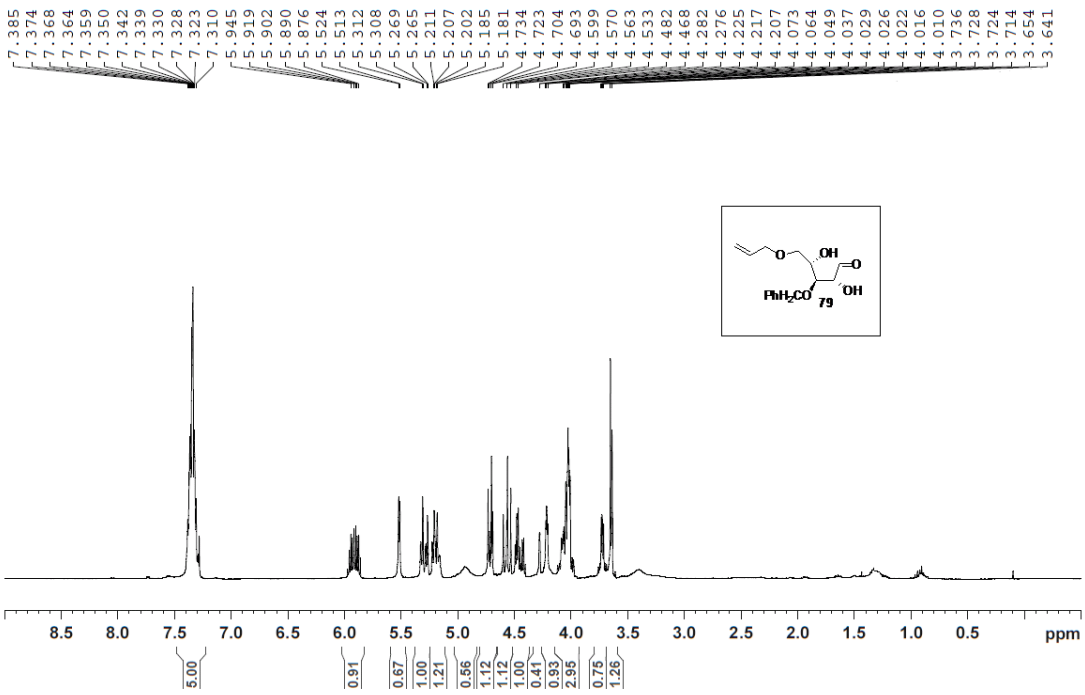

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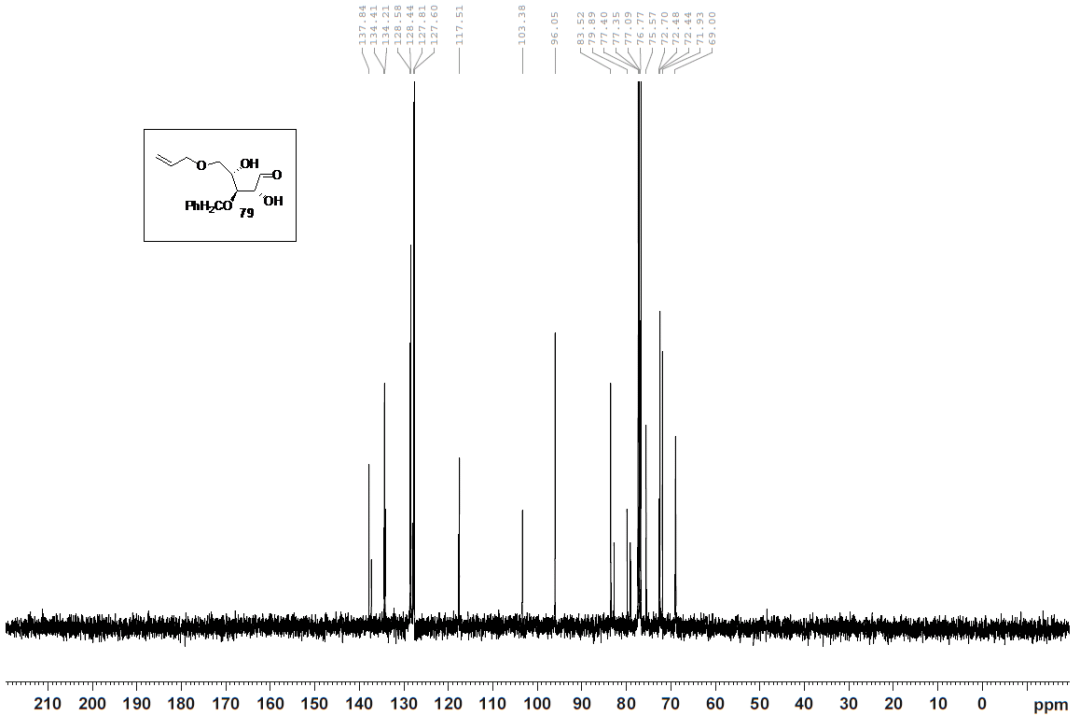

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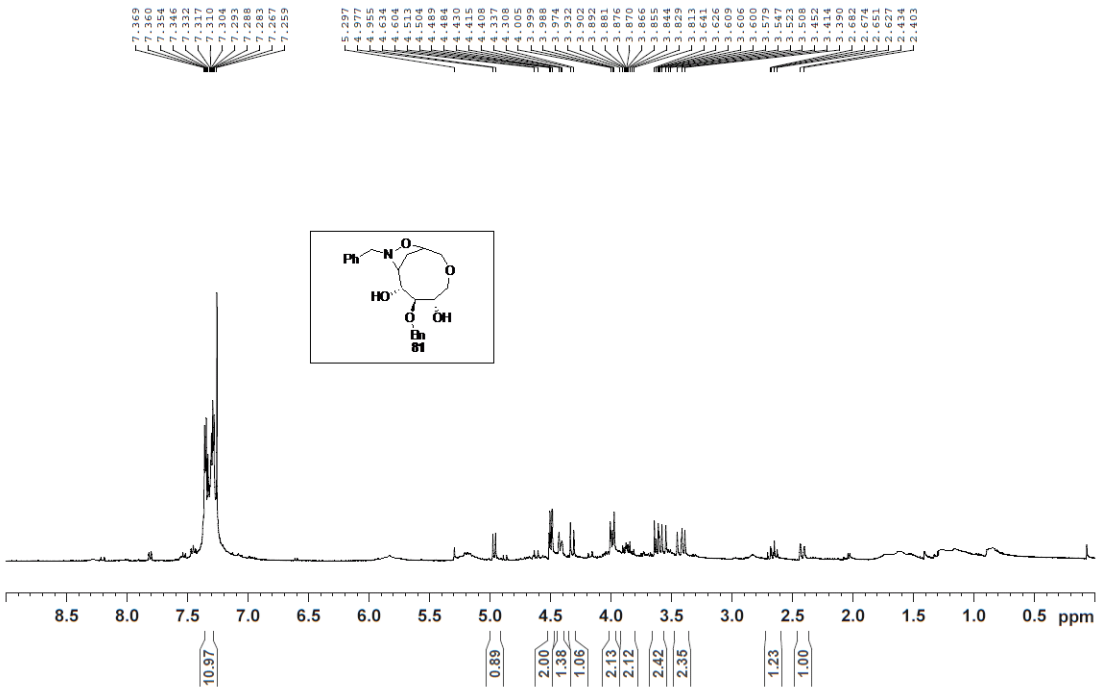

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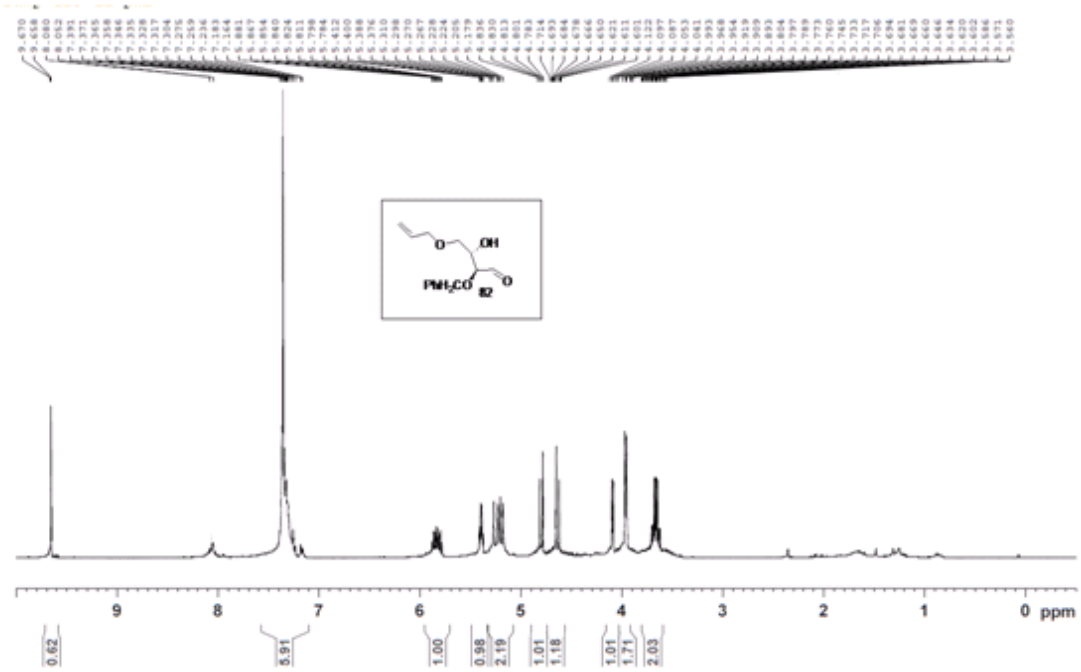

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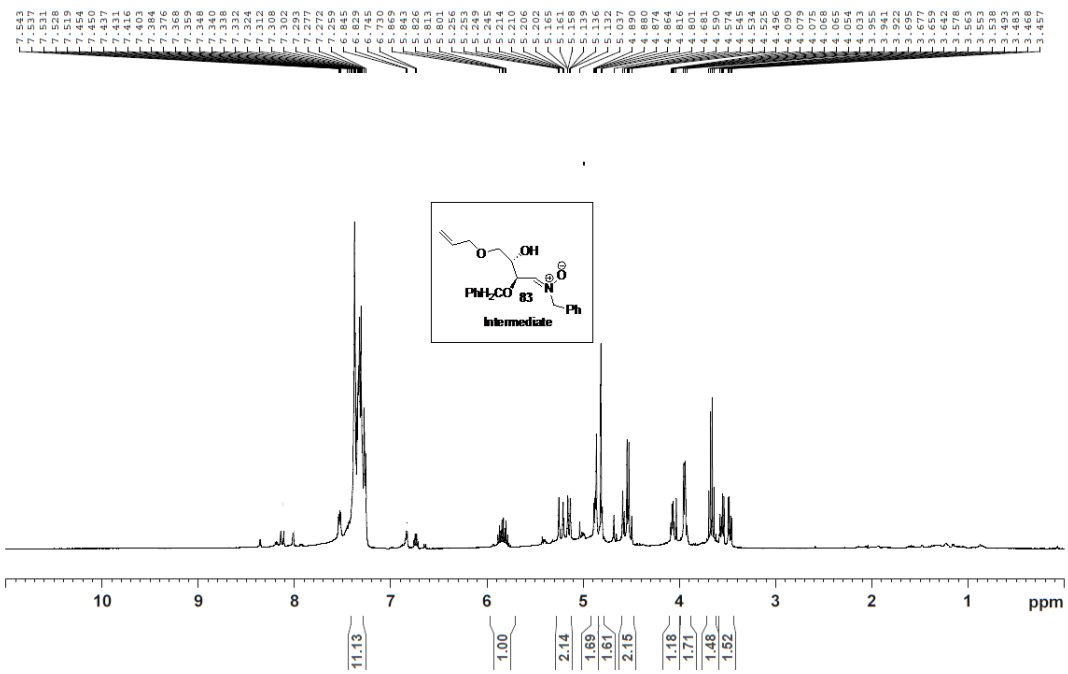
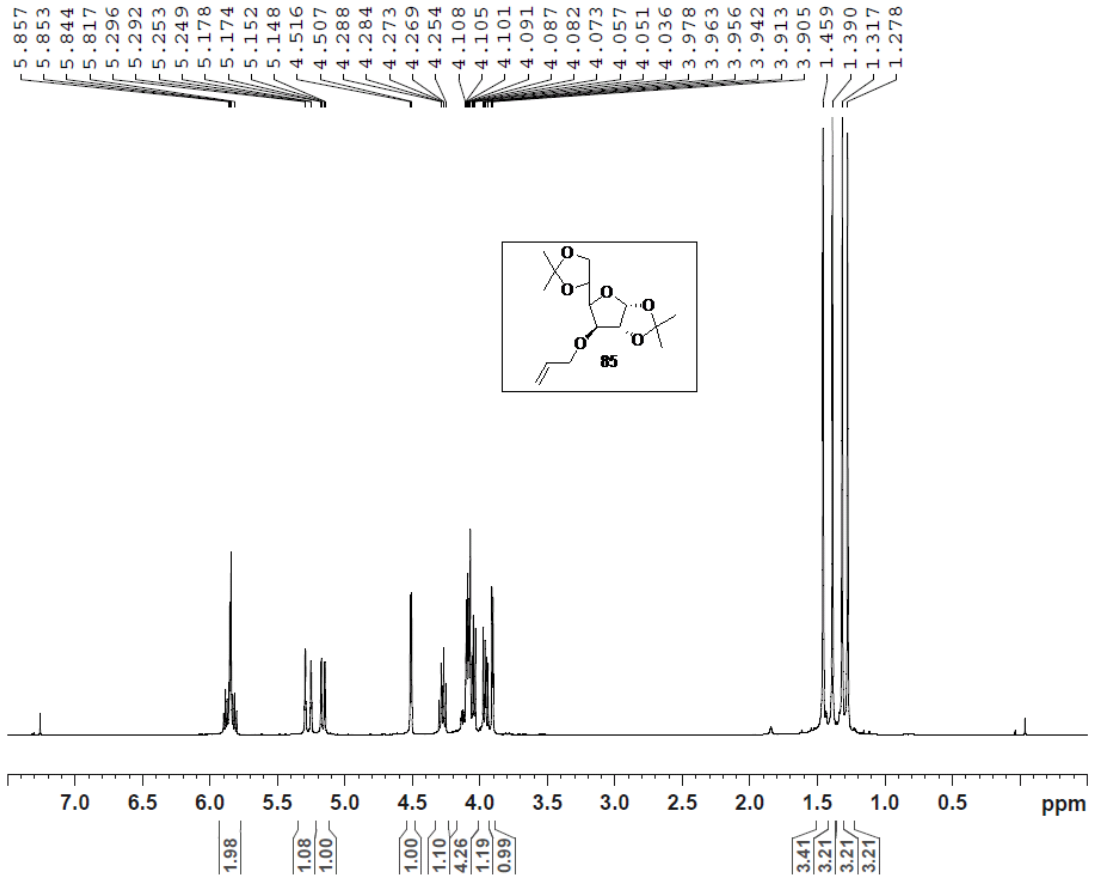
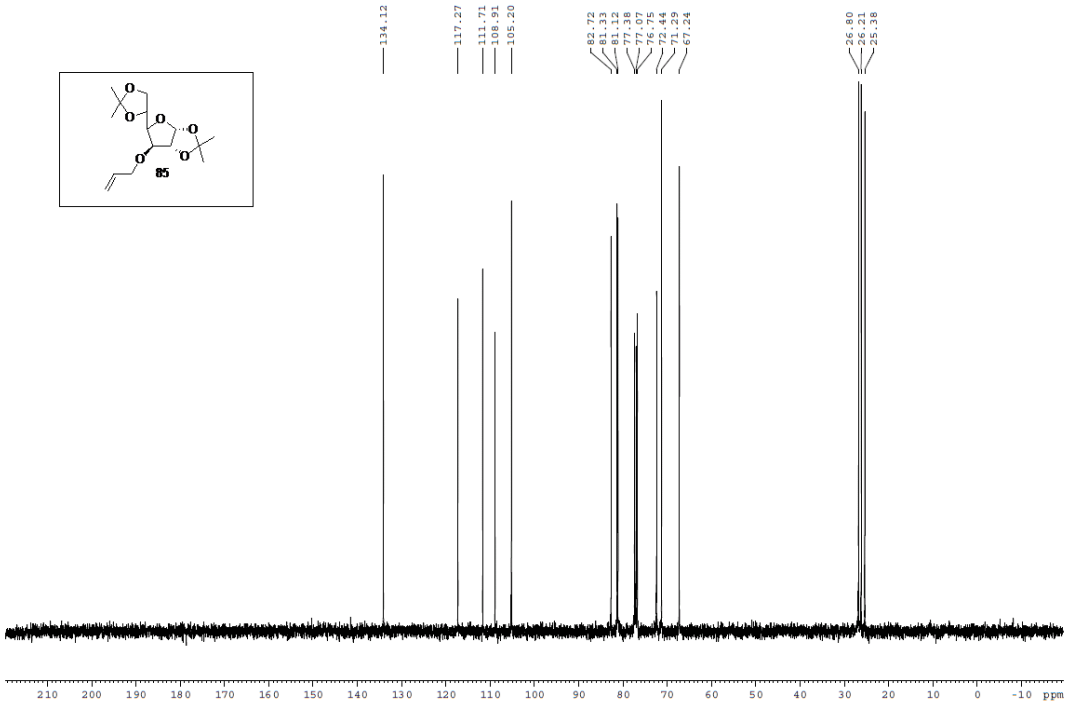


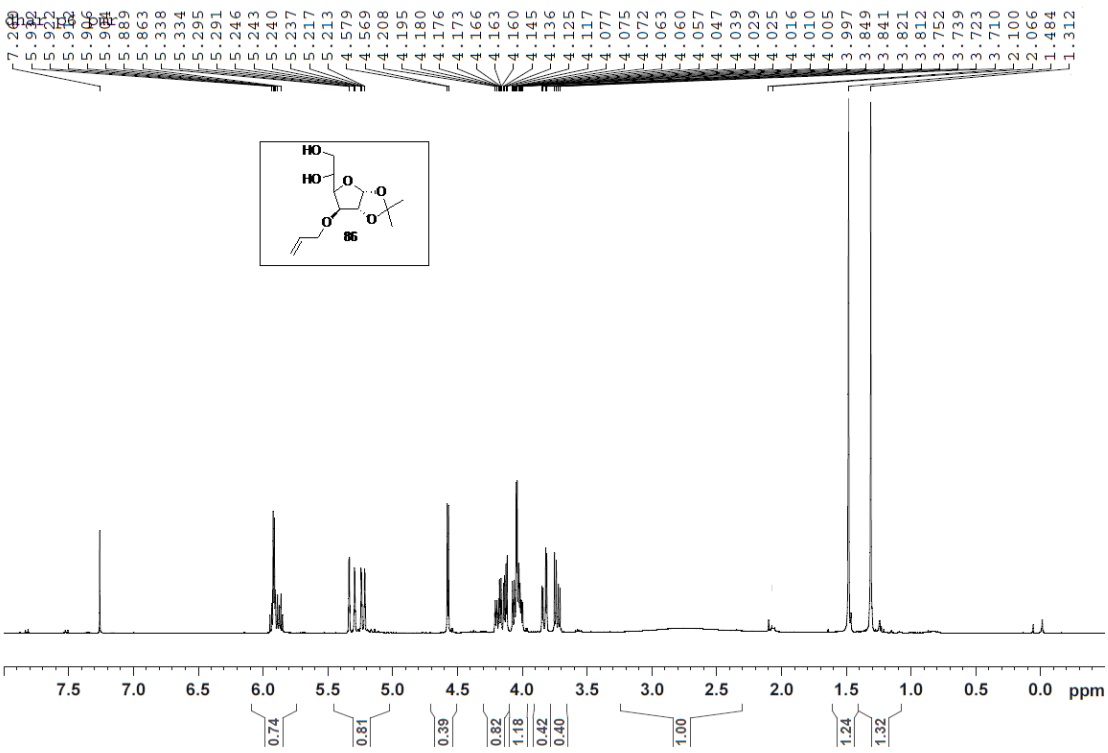
^{1}H NMR ($CDCl_3$, 400MHz) of 83



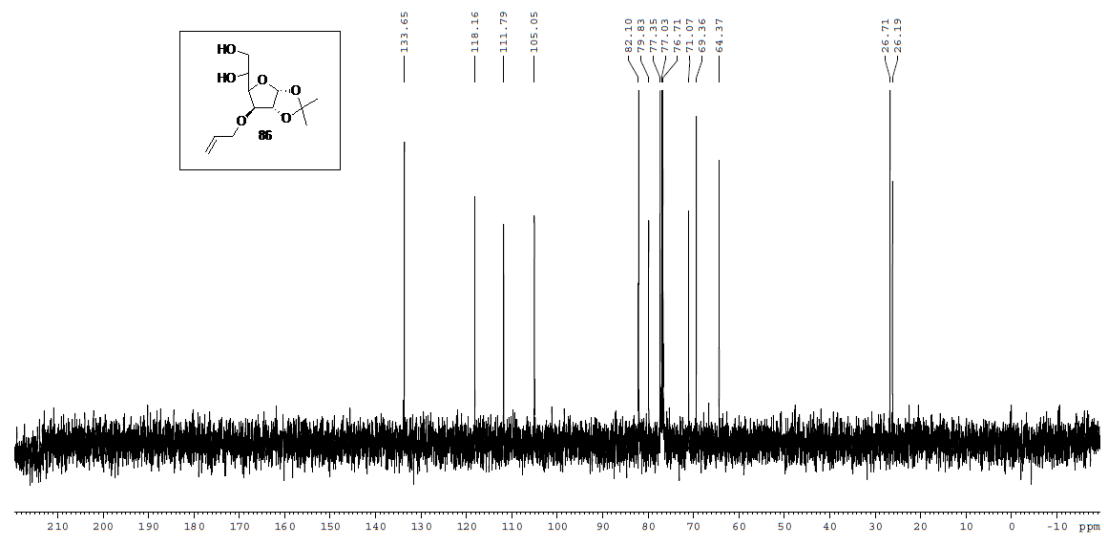
^{1}H NMR ($CDCl_3$, 400MHz) of 85



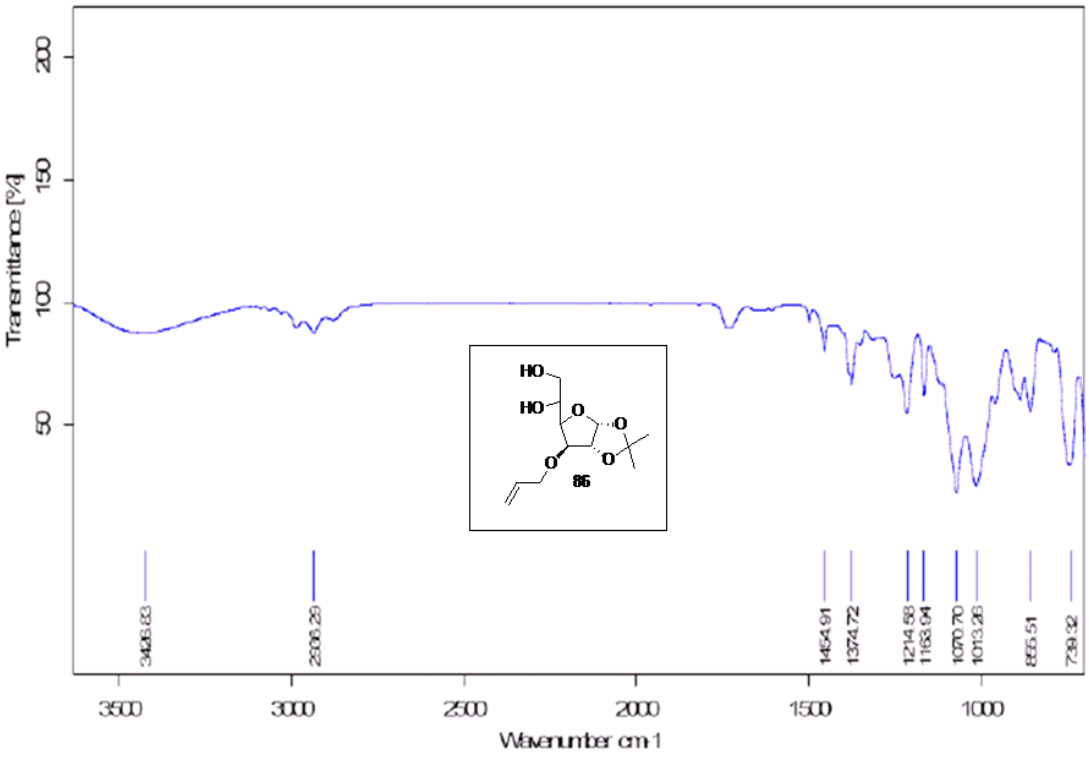
^{13}C NMR ($CDCl_3$, 100MHz) of 85



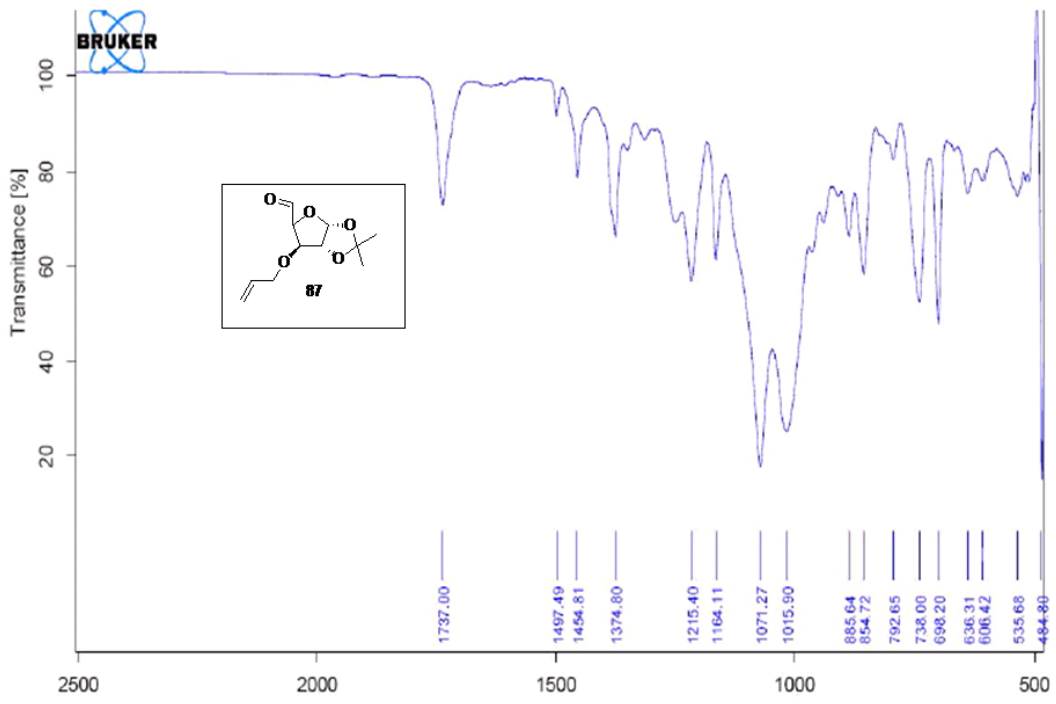
^{1}H NMR ($CDCl_3$, 400MHz) of 86



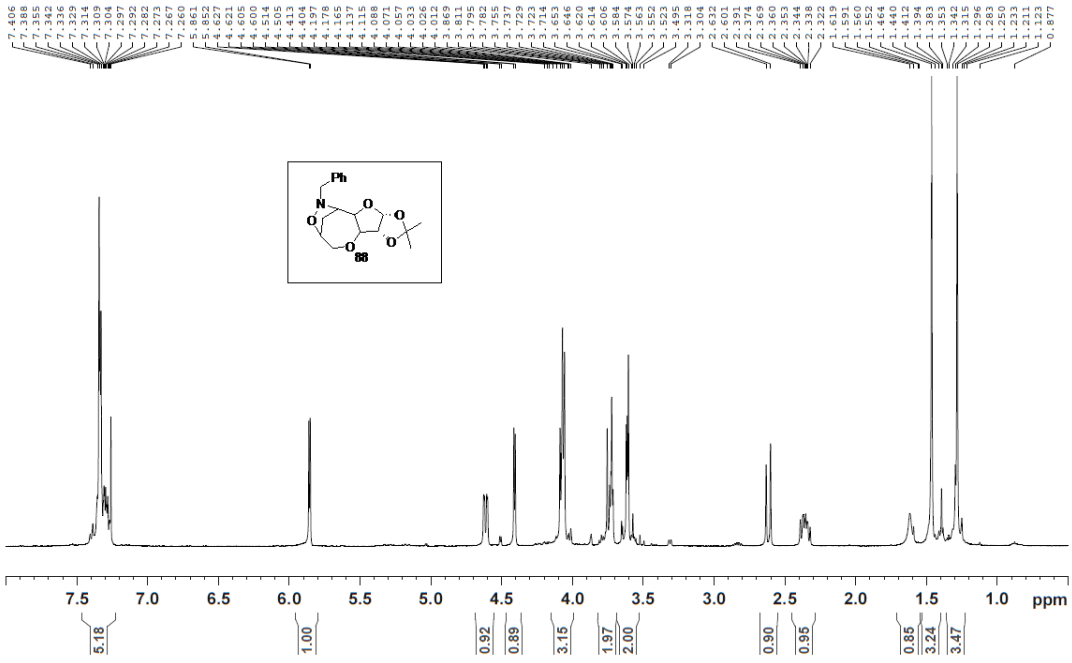
^{13}C NMR ($CDCl_3$, 100MHz) of 86



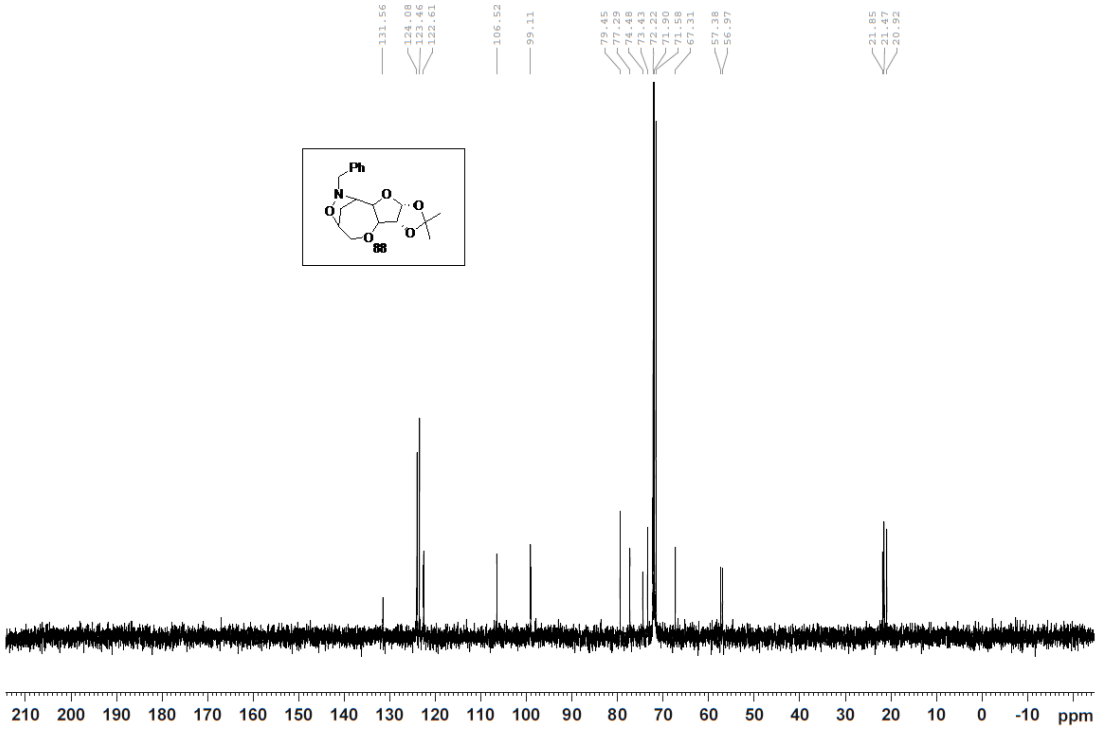
FTIR Spectrum: ν_{max} (neat)/cm^{-1} of 86



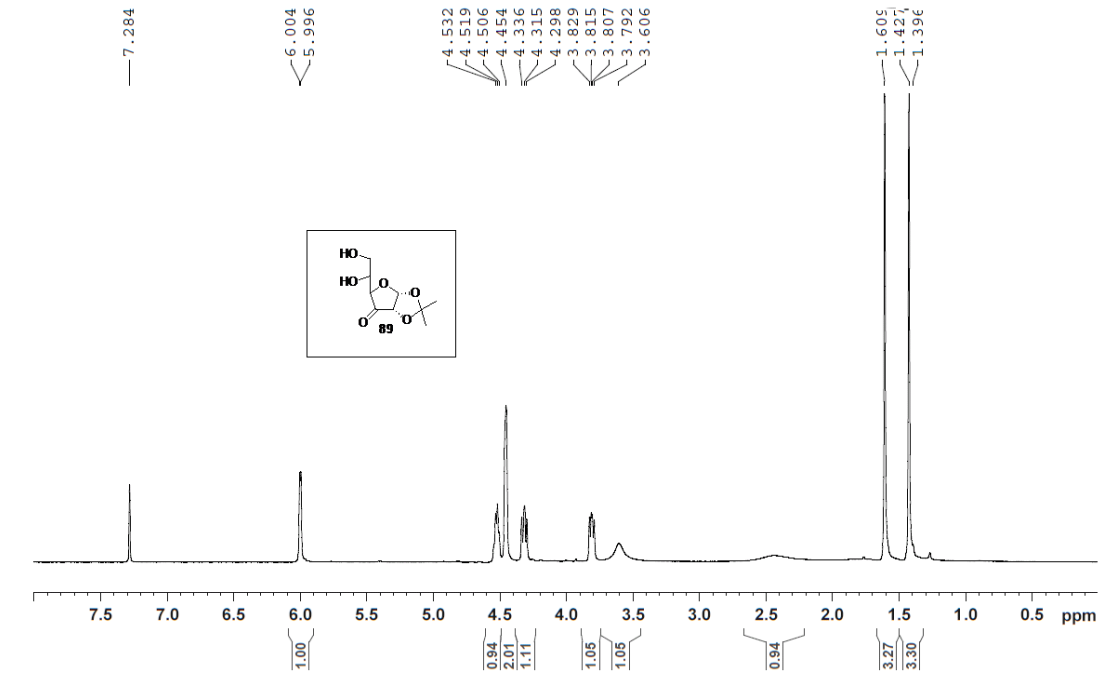
FTIR Spectrum: ν_{max} (neat)/cm^{-1} of 87



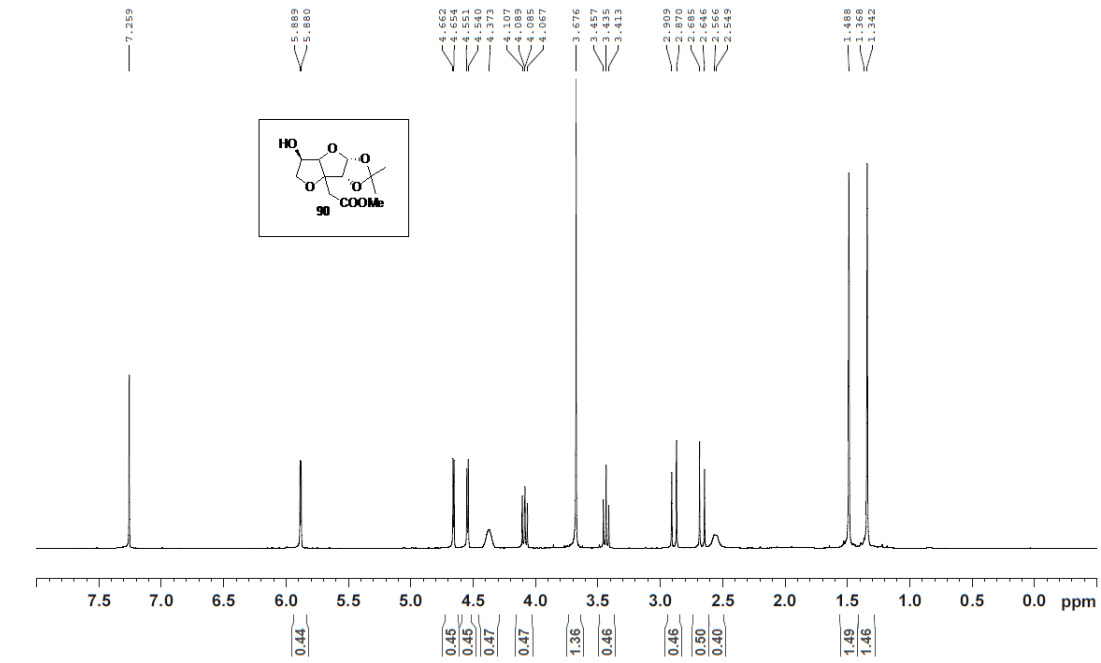
^{1}H NMR ($CDCl_3$, 400MHz) of 88



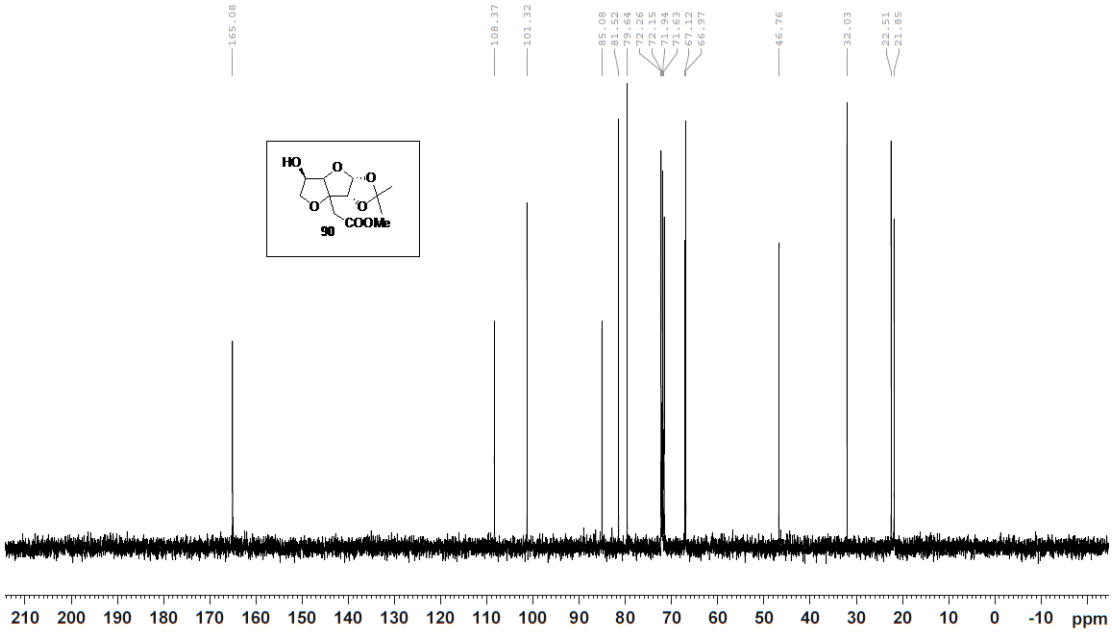
^{13}C NMR ($CDCl_3$, 100MHz) of 88



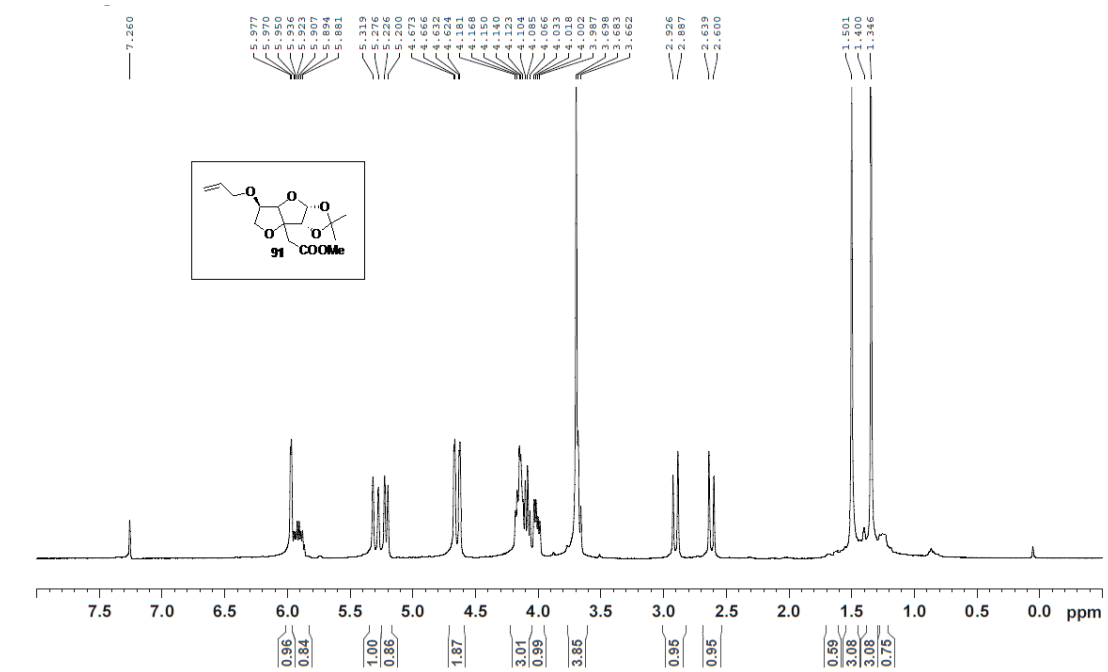
^{1}H NMR ($CDCl_3$, 400MHz) of 89



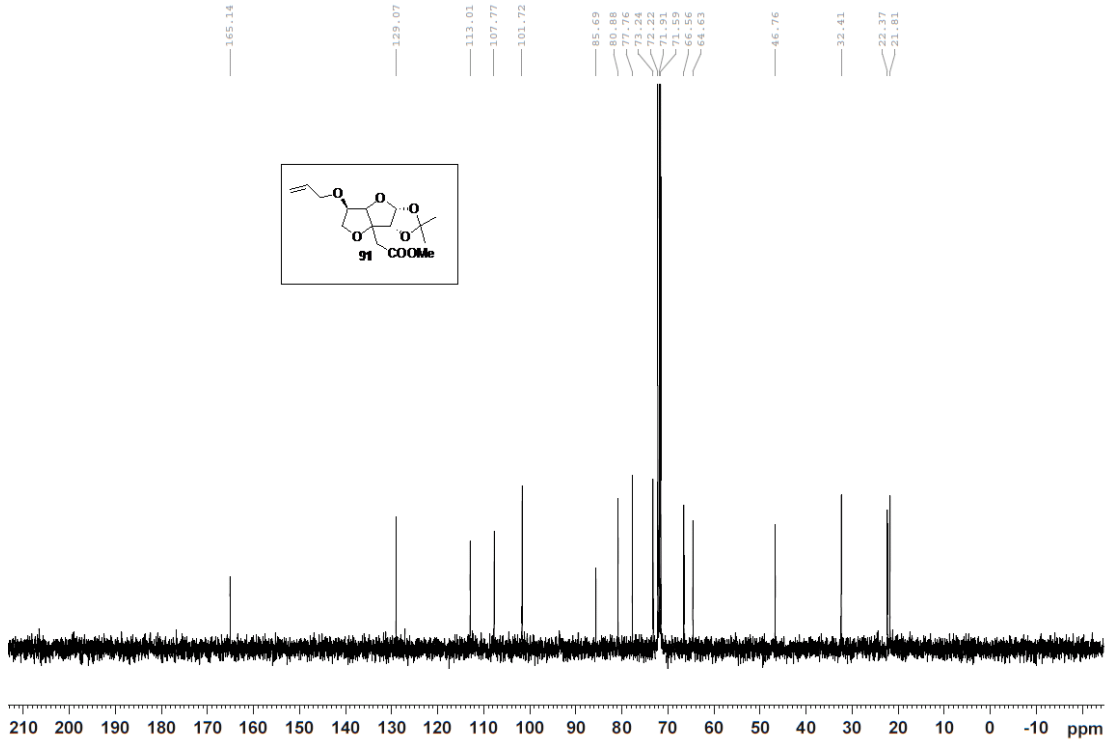
^{1}H NMR ($CDCl_3$, 400MHz) of 90



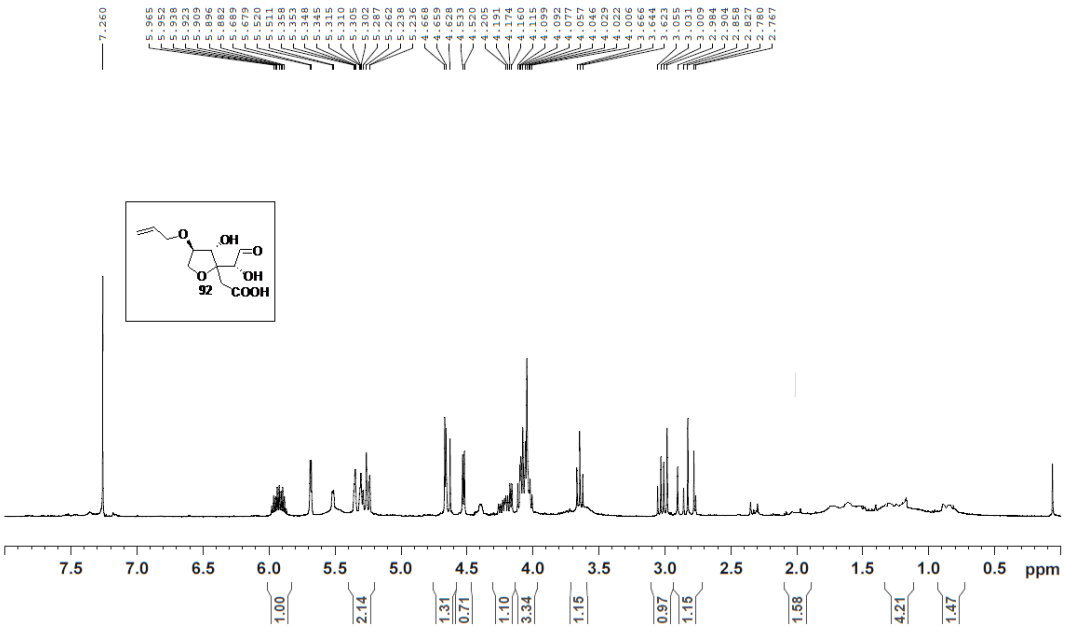
^{13}C NMR ($CDCl_3$, 100MHz) of 90



^{1}H NMR ($CDCl_3$, 400MHz) of 91



^{13}C NMR ($CDCl_3$, 100MHz) of 91



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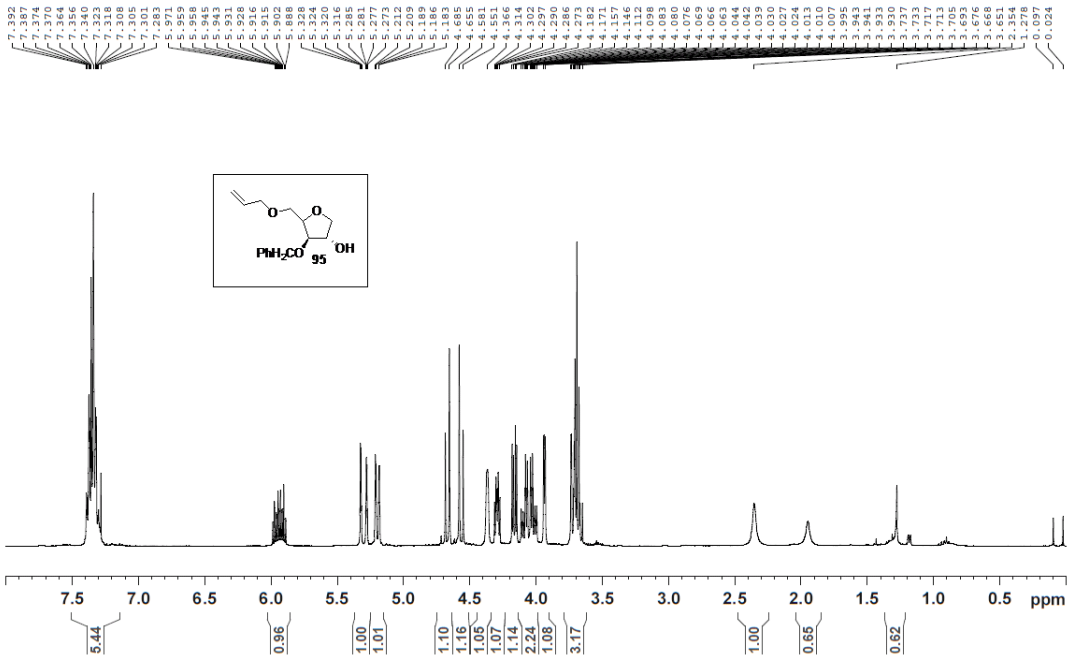
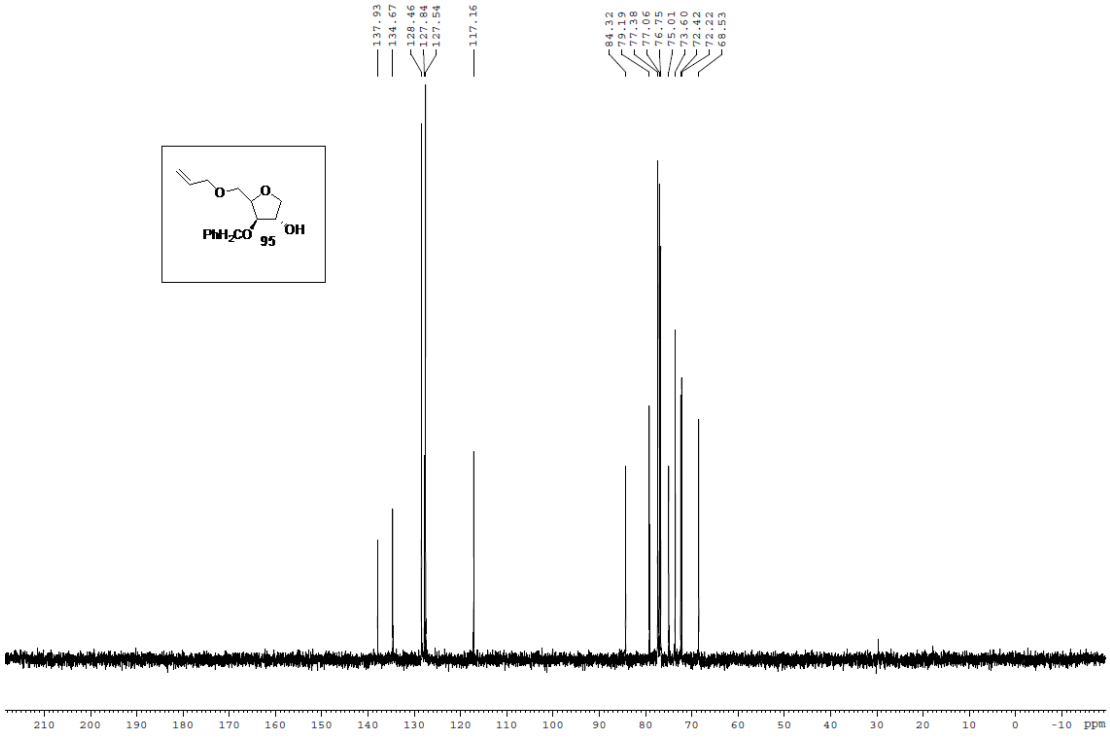
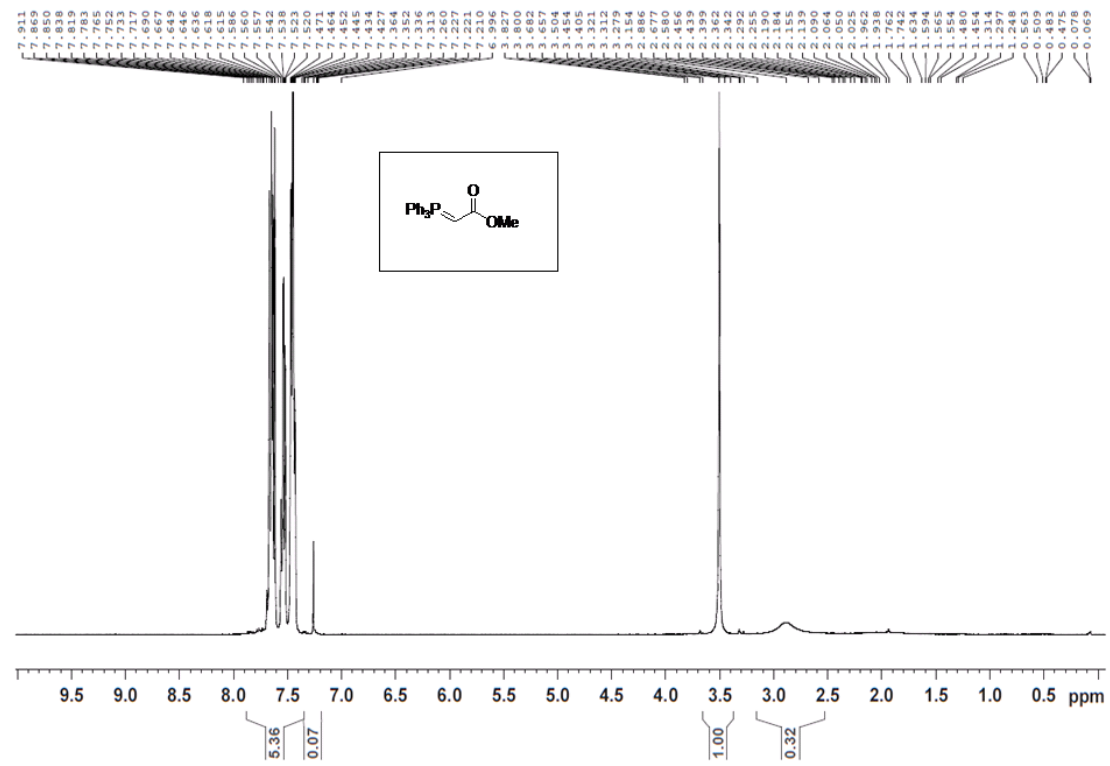


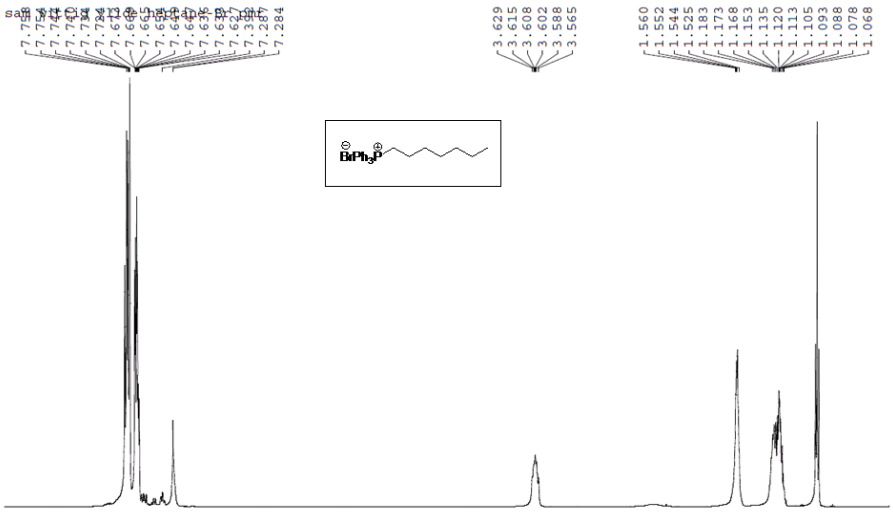
^{1}H NMR ($CDCl_3$, 400MHz) of 95



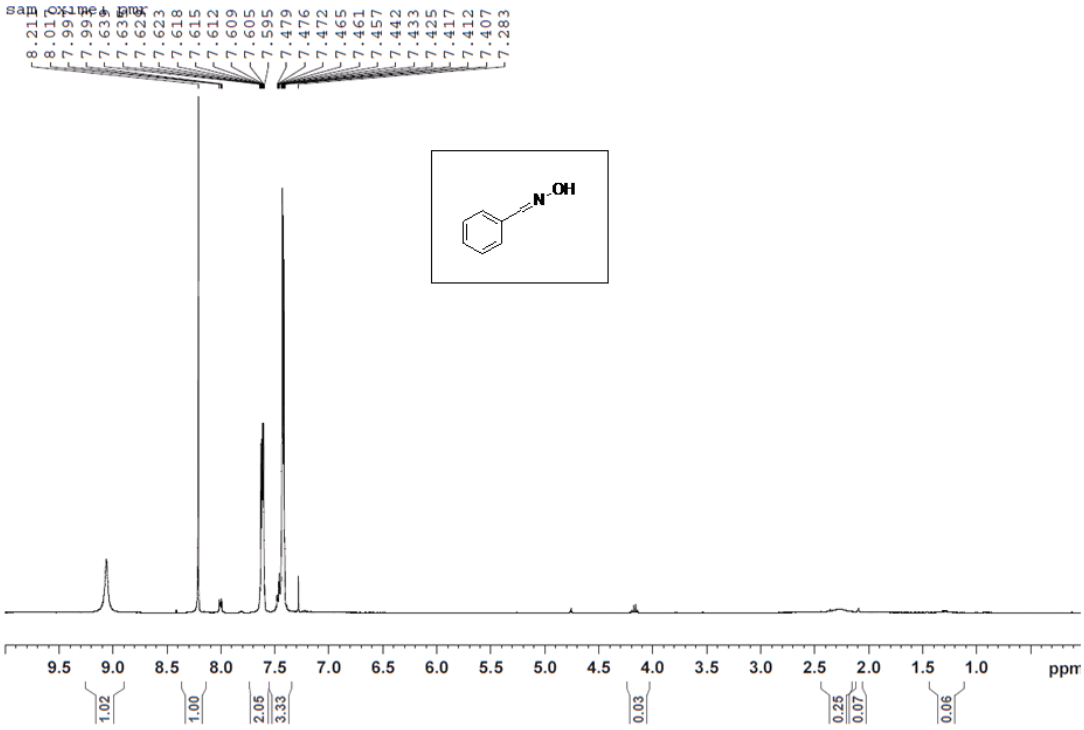
^{13}C NMR ($CDCl_3$, 100MHz) of 95



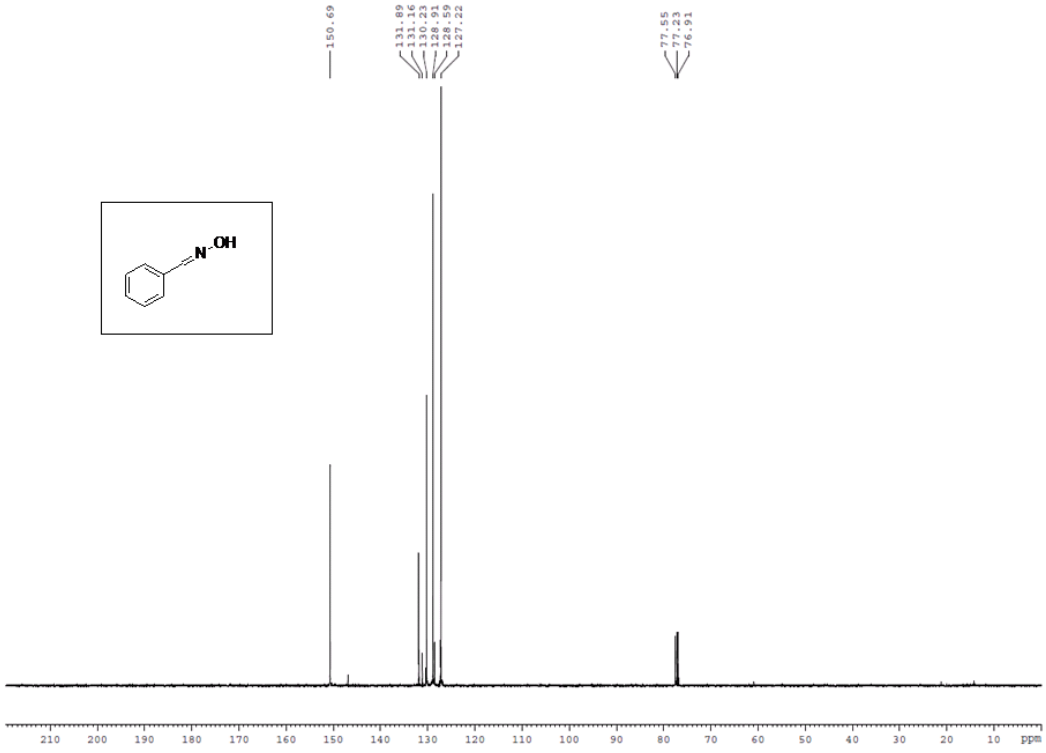
^{1}H NMR ($CDCl_3$, 400MHz) of Methyl (triphenylphosphoranylidene)acetate



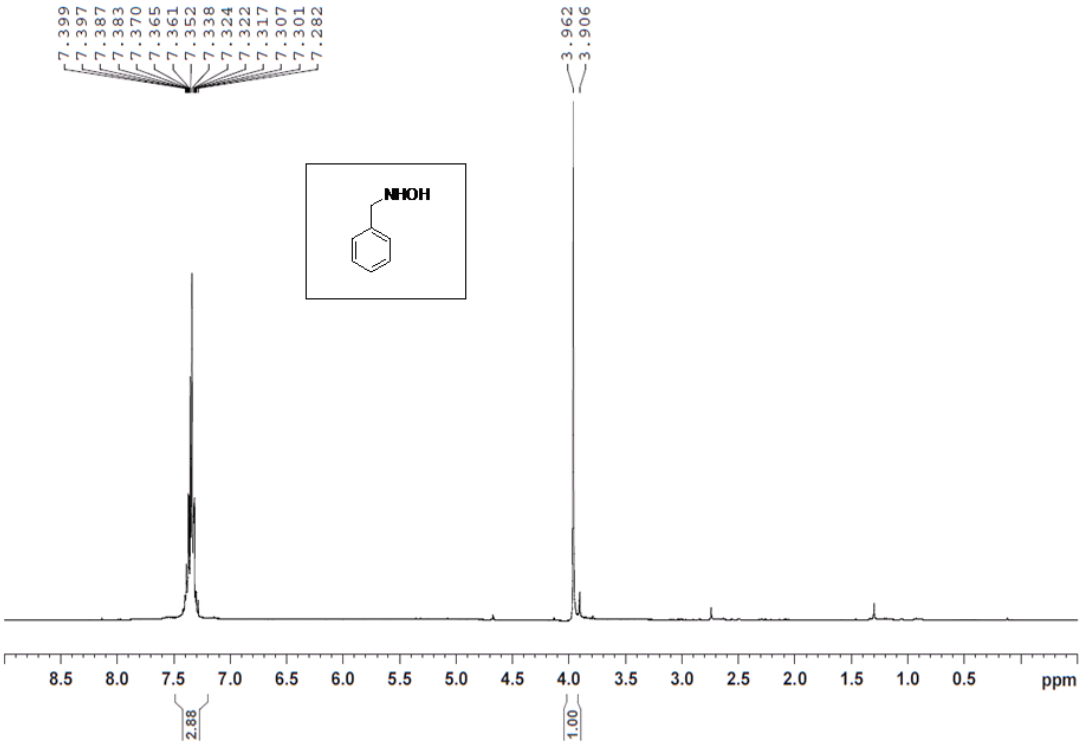
^{1}H NMR ($CDCl_3$, 400MHz) of phosphorous ylide of bromoheptane



^{1}H NMR ($CDCl_3$, 400MHz) of oxime



^{13}C NMR ($CDCl_3$, 100MHz) of oxime



^{1}H NMR ($CDCl_3$, 400MHz) of benzylhydroxylammine

5.3 References

1. a) Michael, J. P. *Nat. Prod. Rep*. **2004**, *19*, 625-649; b) Cragg, G. M.; Newman, D. J; Sander, K. M.; *J. Nat. Product*. **1997**, *60*, 52-60.
2. Newman, D. J.; Cragg, G. M.; Snader, K. M.; *J. Nat. Prod.* **2003**, *66*, 1022–1037.
3. Yang, S.; Wang, G. J.; Cheng, K. F.; Chen, C. H.; Ju, Y. M.; Tsau, Y. J.; Lee, T.; *Planta Med*. **2010**, *76*, 1701-1705.
4. Mukai, M.; Haruhisa, O.;Yamashita, and Kitagaki, .; *J. Org. Chem.* **2004**, *69*, 6867-6873.
5. Kaur, P.; Arora, R.; Gill, N.S.; *Indo American Journal of Pharmaceutical Research*, **2013**, *3*, 11.
6. Mukhtyar, S.; Saini, Kumar, A.; Dwivedi, J.; Singh, R.; *International Journal of Pharma Sciences and Research (IJPSR)* **2013**, *4*, 3.
7. Docampo, R.; Moreno, S.N.; *Drug Metab. Rev.;* **1990**, *22* (2–3), 161–178.
8. Rai, J.; Randhawa G. K.; Kaur, M.; *Int J Appl Basic Med Res.* **2013** ,*3(1)*, 3–10.
9. Ottani, A.; Leone, S.; Sandrini, M.; Ferrari, A.; Bertolini, A.; *European Journal of Pharmacology;* **2006**, *531*(1-3), 280–281.
10. Frigerio, F.; Chaffard, G.; Berwaer. M.; Maechler, P.; Chaffard; Berwaer; Maechler; *Biochem Pharmacol*,**2006,** *72 (8)*, 965–73
11. Box, F.; Html, F.F.H.; *Chin Med Journal*, **2008**, *121*, 26-26.
12. Nagai, H.; Teramachi, H.; Tuchiya, T.; *Allergol Recent advances in the development of anti-allergic drugs Int.*, 2006, *55*(1), 35-42.
13. Odani, S.; Tominaga, K.; Kondou, S.; *European Journal of* Biochemistry, **1999**, *262 (3)*, 915–23.
14. Lowe, J.; Li, H.; Downing, KH.; Nogales, E.; *Journal of Molecular Biology*, **2001**, *313* (5), 1045–57

15. Patel, S. S.; Balfour, J. A.; Bryson, H. M.; *Drugs*, 1997, *53* (4), 637–656.

16. Corey, E. J.; Dittami, J. P.; *J. Am. Chem. Soc.*, **1985**, *107* (1), 256–257.

17. Youyou, T.; *Nature Medicine*, **2011**, *17*, 1217–1220.

18. Jalander, L.; Oksanen, L.; Ahtinen, J.; *Synthetic Communications*, **1989** *19* (19), 3349-3352.

19. Eun, J.; Kang, J.; Taek, L.; Sung, S.; Hong, K.; Lee, E.; *J. Am. Chem. Soc.*, **2002**, *124* (49), 14655–14662

20. Total Synthesis of Amphidinolide X Lepage, O.; Kattnig, E.; Fürstner, A.; *J. Am. Chem. Soc.*, **2004**, *126* (49), 15970–15971.

21. Kang, E. J.; Cho, E. J.; Lee, Y. E.; Ji, M. K.; Shin, D. S.; Chung, Y. K.; Lee, E.; *J. Am. Chem. Soc.*, **2004**, *126* (9), 2680–2681.

22. Dawn, R.; Perrin; Bottomley, W.; *Nature*, 1961, *191*, 76 – 77.

23. Liron, F.; Fontana, F.; Zirimwabagabo, J. O.; Prestat, G.; Rajabi, J.; Rosa, C.; Poli, G.; *Org. Lett.*, **2009**, *11* (19), 4378–4381.

24. Sumithira G. *et al*; *Int J Ad Pharm Gen Res* **2013**, *1*(1), 1-19.

25. Peepliwal. A. K. *et al*.; *J Biomed Sci and Res.*, **2010**, *2* (1), 29-45.

26. Lee, H.; Kim, H.; Yoon,T.; Kim, B.; Kim, S.; Kim, H.; Kim, D.; *J. Org. Chem.* **2005**, *70*, 8723-8729.

27. Karad, S. N.; Bhunia, S.; Liu, R.; *Angew. Chem. Int. Ed.*, **2012**, *51*, 8722 –8726.

28. Sengupta, J.; Mukhopadhyay, R.; Bhattacharjya, A.; Bhadbhade, M.; Bhosekar, G. V.; *J. Org. Chem.* **2005**, *70*, 8579-8582.

29. Jung, J. H.; Lee, E.; *Angew. Chem. Int. Ed.*, **2009**, *48*, 5698 –5700.

30. Pansare, S. V.; Adsool, V. A.; *Org. Lett.*, **2006**, *8*, 25.

31. Schmidt, B.; Biernat, A.; *Org. Lett.*, **2008**, *10*, 1.

32. Maity, J. K.; Ghosh, R. P.; Drew, M. G. B.; Achari, B.; Mandal, S. B.; *J. Org. Chem.* **2008**, *73*, 4305–4308.

33. Sahabuddin, S.; Roy, A.; Drew, M. G. B., Roy, B. G.; Achari, B.; Mandal, *J. Org. Chem*, **2006**,*71*, 16.

34. Knapp, S.; Thakur, V. V.; Madduru, M. R.; Malolanarasimhan, K.; Morriello; Doss, G. A.; *Org. Lett.*, **2006**, *8*, 7.

35. Yang, S. S.; Wang, G., J.; Cheng, K. F.; Chen, C. H.; Ju, Y. M.; ; Tsau, Y. J.; Lee, T. H.; *Planta Med*, **2010**, *76*, 1701-1705.

36. Gras, J. L.; *Tetrahedron Letters*, **1978**, *24*, 2111 – 2114.

37. Danishefsky, S.; Bryson, T. A.; Puthenpurayil, J., *J. Org.* Chem., **1975**, *40*, 12.

38. Schmidt, O. T.; *Methods Carbohydr. Chem.* **1962**, *2*, 318-325.

39. Martin, J.; Watts, P. C.; Nson, F. *Chemical Communication* **1970**, *19*.

40. Perepogu, A. K.; Raman, D.; Murty, U. S. N.; Rao, V. J.; *Synth. Commun.* **2010**, *40*, 686– 696.

41. (a) Bella, V.; Margarita, V.; Orlando, C.; Orsini, M.; Parlanti, L.; Piancatelli, G. *Tetrahedron Lett.* **2000**, *41*, 561–565.

42. Sibi, M. P.; Ji, J. roccellaric acid. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 274–276.

43. Murta, M. M.; de Azevedo, M. B. M.; Greene, A. E.; *J. Org. Chem.* **1993**, *58*, 7537–7541.

44. Fernandes, R. A.; Chowdhury, A. K.; Eur. *J. Org. Chem*, **2011**, 1106-1112

45. Barros, M. T.; Maycock, C. D.; Ventura, M. R.; *Org. Lett*., **2003**,. *5*, No.22,

46. Crimmens. M. T, King. B. W, Tabet. E. A, J. Am. Chem. Soc, **1997**, *119*, 7883-7884

47. Ruck-Braun, K.; Freysoldt, T. H. E.; Wierschem, F.; *Chem. Soc. Rev.*, **2005**, *34*, 507-516

48. D. S. Tan, M. A. Foley, B. R. Stockwell, M. D. Shair and S. L. Schreiber, *J. Am. Chem. Soc*., **1999**, *121*, 9073-9087.

49. G. J. Kuster and H. W. Scheeren, *Tetrahedron Lett*., **1998**, *39*, 3613–3616.

50. G. J. Kuster and H. W. Scheeren, *Tetrahedron Lett.*, **2000**, *41*, 515–519.

51. Banerjee, S.; Ghosh, S.; Sinha, S.; Ghosh, S.; *J. Org. Chem.* **2005**, *70,* 4199-4202.

52. Sibi, M. P.; Ma, Z.; Jasperse, C. P.; *J. Am. Chem. Soc.*, **2004**, *126*, 718-719.

53. Sharma, P. K.; Nielsen, P.; *J. Org. Chem.* **2004**, *69*, 5742-5744

54. Aggarwal, K.; Roseblade, S. J.; Barrell, J. K.; Alexander, R.; *Org. Lett.*, **2002**, *4*, 7.