"Chiral Pool Synthesis of Swainsonine from Carbohydrate"

The thesis submitted in partial fulfillment for the requirement of

Master of Philosophy (M.Phil) Degree in Chemistry

Of

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2014

Declaration

I declare that the thesis "Chiral Pool Synthesis of Swainsonine from Carbohydrate" submitted for the award of Master of Philosophy (M.Phil.) Degree in Chemistry of Sikkim University is my original work. The content of this thesis is based on the experiments which I have performed myself. This thesis has not been submitted for any other degree to any other university.

Date: 15th July 2014

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We recommended the thesis for evaluation.

Signature of H.O.D./In-Charge	Signature of Supervisor	Signature of Joint-Supervisor
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Certificate

This is to certify that the thesis titled **"Chiral Pool Synthesis of Swainsonine from Carbohydrate"** submitted to **Sikkim University** in partial fulfillment of the requirement for degree of **Master of Philosophy (Chemistry)** is a result of original research work carried out by **Mrs. Anjali Sharma** under my guidance and supervision. No part of the thesis has been submitted for any other degree, diploma, associate-ship and fellowship.

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

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**Anjali Sharma**

CONTENTS

Chapter I

1.1 Introduction

Over the decades compounds isolated from natural resources played a very important role in the development and understanding of medicinal chemistry. Especially it-played a critical role in development of various life saving drugs and understanding of mechanism of various biological processes. Almost 70% of small molecule drugs available in the market today are inspired by the structures of various naturally isolated molecules.[1, 2] This was particularly evident in the area of cancer and other infectious diseases, where over 60% to 75% of these drugs respectively where shown to be of natural origin.[3] Thus natural products scaffolds became very important source for discovery of new drug molecules.[4] But presence of these bioactive secondary metabolite in very low concentration and always in a mixture of many other compounds hinder its easy isolation, testing and commercial use. Therefore, chemical syntheses of these natural product and their derivatives became an inevitable step in the drug discovery and commercialization process. Recent developments in high throughput screening created huge demand for new synthetic scaffold, which in turn gives a fresh impetus to the research of synthesis of natural product and their derivatives.

Our present study deals with synthesis of a biologically active naturally isolated indolizidine based alkaloid, Swainsonine **1** and its analogues. The indolizidine based alkaloid widely occurs in nature and have attracted great interests for the synthetic chemist because of their wide range of biological activities. Swainsonine (1, 2, 8-trihyroxyindolizidine) is one of the most well known members of this indolizidine family.[5] It was first isolated from the fungus *Rhizocotonia leguminicola* and subsequently has been found in several other plant and fungal sources.[5] Later it was also isolated from Australian legume *Swainsona canescens* and then identified in many *Astragalus* and *Oxytropis* species (Leguminosae).[6]

Swainsonine has proven anti-cancer activity with potential for treating glioma and gastric carcinoma. This is partially driven by the ability of (-)-swainsonine to inhibit Golgi α-mannosidase II, an enzyme involved in the processing of glycoproteins on the surface of

cancer cells.[7] This process has been associated with cancer metastasis and thus (-)-swainsonine and analogues are potentially useful anti-metastasis drugs for the treatment of cancer.[8] Swainsonine is also known to promote restoration of bone marrow damaged by some types of cancer treatments. Swainsonine is act as an appetite suppressant.[9, 10] Clinical trials with Swainsonine, as an anti-tumor drug, have shown obviously curative effects with well tolerance in the patients with advanced malignancies.[11, 12]

(-)-Swainsonine	L-(+)-Swainsonine	(-)-Swainsonine analogue
1	2	3
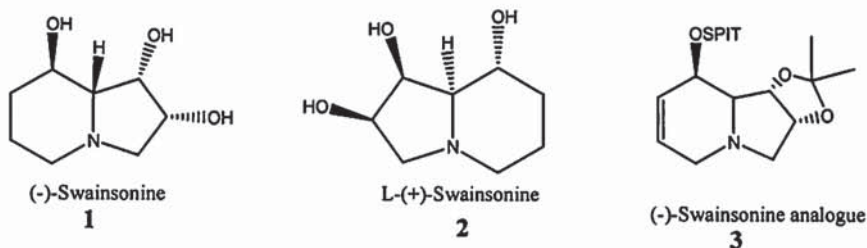
Total synthesis is an art of designing and creating molecular structure with desired activity using available synthetic methodology as tools. Better understanding of reactions, knowledge of available cheap reagents and substrate and judicious planning helps to scientists to achieve much shorter and more efficient newer methods. The main intent of any target oriented total synthesis is achieving it in cheap and in shortest possible time. Even little bit of increase in efficiency either in costing or time can reduce it market price of any drug drastically. Keeping this in mind we planned to use the cheapest available pure chiral sources of D-glucose as starting materials.

Before starting our work we have reviewed various previous synthetic procedure reported by other groups which is summarized in next chapter.

Chapter II

2.1 Literature Review

Due to its huge biological importance, since the first total syntheses in 1984,[13-16] many total synthesis of swainsonine has been reported.[17] Here we summarized some interesting recent approaches towards synthesis of swainsonine and its analogues.

H.G.Choi *et al* reported the formal synthesis of (-)-swainsonine from chiral aziridine. In this article they developed a new methodology for a formal synthesis of (-)-swainsonine starting from a readily available chiral aziridine-2-carboxylate by making use of an intramolecular cyclization to access the key intermediate in reasonably good yields (**Scheme 1**).[18] The synthesis of start with readily available (*2S*)-aziridine carboxylic acid (-)-menthol ester **4** reacted with Weinreb amide[19] to generated ketone **5**. The chelation-controlled reduction and ring-opening reaction[20] of **5** with AcOH in CH_2Cl_2 yielded compound **6**. The intramolecular cyclization[21] of **6** then replacement of methylbenzene group by Boc group,[22] swern oxidation[23] and wittig olefination reaction[24] gave product **7**. Gold (III)-catalyzed allene cyclization[25] of **7** constructed bicyclic intermediate **8** which on dihydroxylation gave the final product (-)-swainsonine **1**:
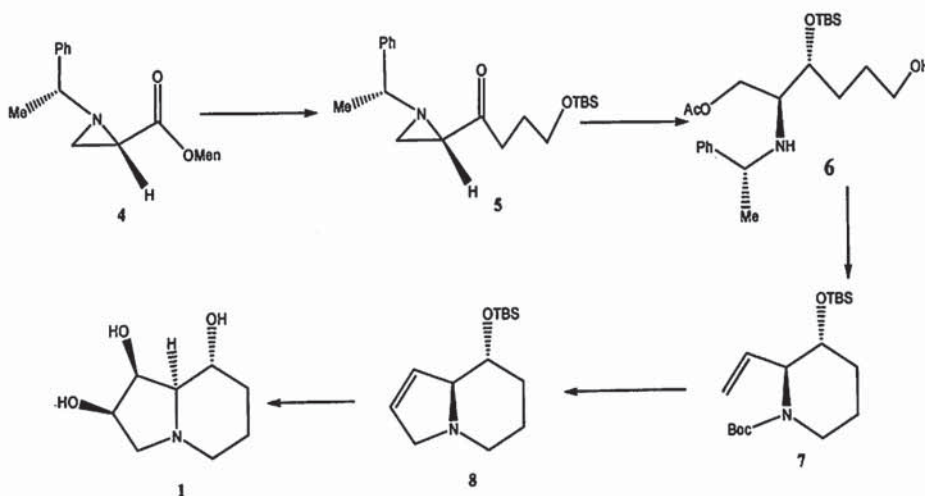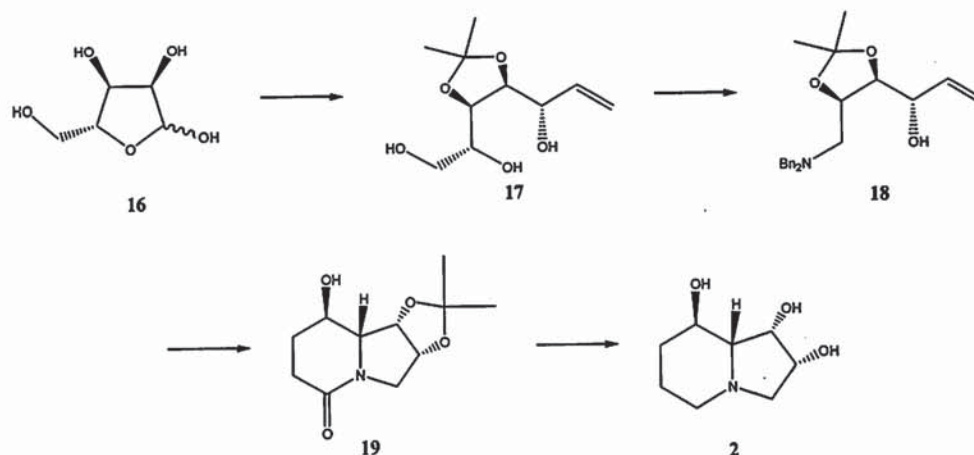

Scheme 1

Abrams *et al* introduced an enantioselective and diastereo controlled approach for synthesis of 8a-epi-D-swainsonine has been developed from achiral furfural **9** which underwent Grignard reagent with allyl magnesium chloride to afforded alcohol (**Scheme**

2).[26] This alcohol was converted into tosylate which was subsequently displaced with sodium azide to yield azide. Azide was reduced with triphenylphosphine to generate a primary amine which was protected with benzyl chloride to formed **10**. The furfural alcohol **10** underwent oxidative ring expansion to afford benyl protected pyranone **11**. Reaction of **11** by dihydroxylation of allylic alcohol under Upjohn condition[27] and selective acetonide protection of C-2/C-3 *cis*-hydroxyl group with 2, 2-dimethoxypropane and *p*-TsOH afford acetonide, which in turn was oxidized to provide acetonide ketone **12** under swern condition. The key step to one-pot procedure for the hydrogenolytic removal of two protecting groups and two intramolecular reductive amination reactions of **13** gave the product **14**. Finally acidic hydrolysis of **14** produced the desired product 8a-epi-swainsonine **15**.[26]
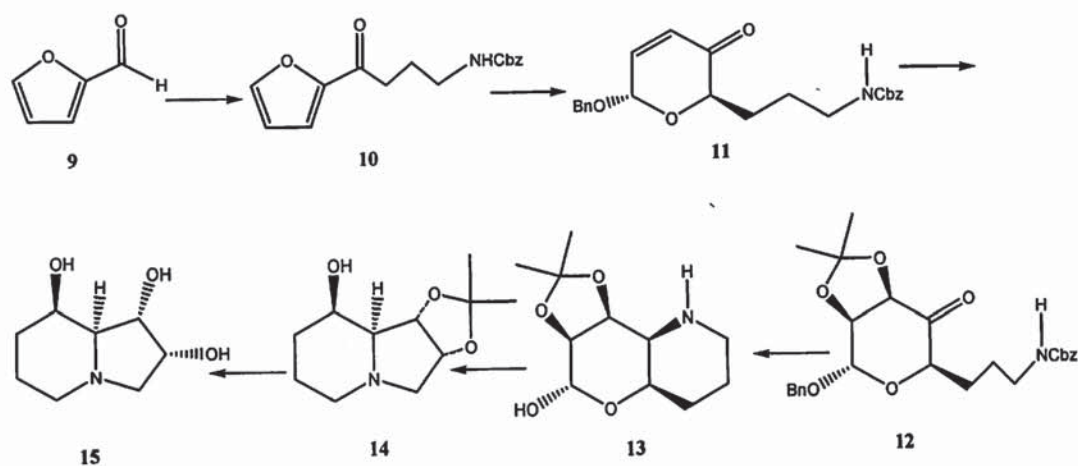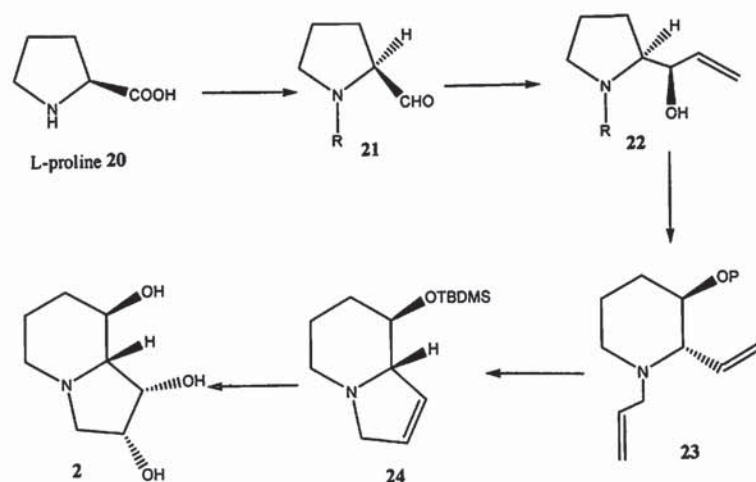

Scheme 2

Pearson *et. al.* has developed the synthesis of swainsonine with the starting material D-ribose (**Scheme 3**).[28] D-ribose **16** converted into acetonide in presence of acetone and acid, which was treated with vinyl magnesium bromide give the crude triol **17**. Oxidative cleavage of 1, 2-diol moiety and reductive amination reaction gave amino alcohol **18** which underwent a Johnson ortho ester Clasien rearrangement, osmium catalysed syn-dehydroxylation, conversion of hydroxyl group into mesylate and transfer hydrogenolysis of the N-benzyl groups gave the bicyclic lactum **19**. Bicyclic lactam is converted into swainsonine **2** by using borane tetrahydrofurane in 12% yield.

16 → **17** → **18**

19 → **2**

Scheme 3

Janine Cossy *et al* reported an efficient enantioselective formal synthesis of swainsonine has been achieved in 14 steps with 14% global yield using an enantioselective ring enlargement of a substituted prolinol and a ring-closing metathesis as the key steps (**Scheme 4**).[29] The synthesis of (−)-Swainsonine **2** was envisaged from the unsaturated bicyclic amino compound **24**, which synthesized by ring-closing metathesis applied to the amino diene **23**. This latter compound would be obtained by applying an enantioselective ring expansion to prolinol **22**, which will be synthesized by a diastereoselective addition of an organometallic species on prolinal **21**. This latter compound would be obtained from L-proline **20**.

L-proline **20** → **21** → **22**

24 ← **23**

2

Scheme 4

Pyne's synthesis of swainsonine involved as key steps, a stereoselective aminolysis reaction of a chiral vinyl epoxide to secure the correct C8, C8a stereochemistry of the target molecule, a ring-closing olefin metathesis reaction to form the pyrrolidine ring and a diastereoselective, *syn*-dihydroxylation reaction of an unsaturated indolizidine using the sharpless AD-mix reagents (**Scheme 5**).[30] Commercially available 4-pentyl-1-ol 25 was converted to *trans*-allyl alcohol 26. Catalytic asymmetric epoxidation, swern oxidation and wittig olefination of 26 gave vinyl epoxide 27.[30] Aminolysis of 27 and protection of amine via ring closing metathesis gave 2, 5-hydropyrrole derivative 28. *Syn*-dihydroxylation reaction of 28 using AD-mix reagents and catalytic hydrogenolysis formed the desired final product 2.[30] Thus the synthesis of (-)-swainsonine was achieved in 16 synthetic steps in an overall yield of just 4.5%.[30]
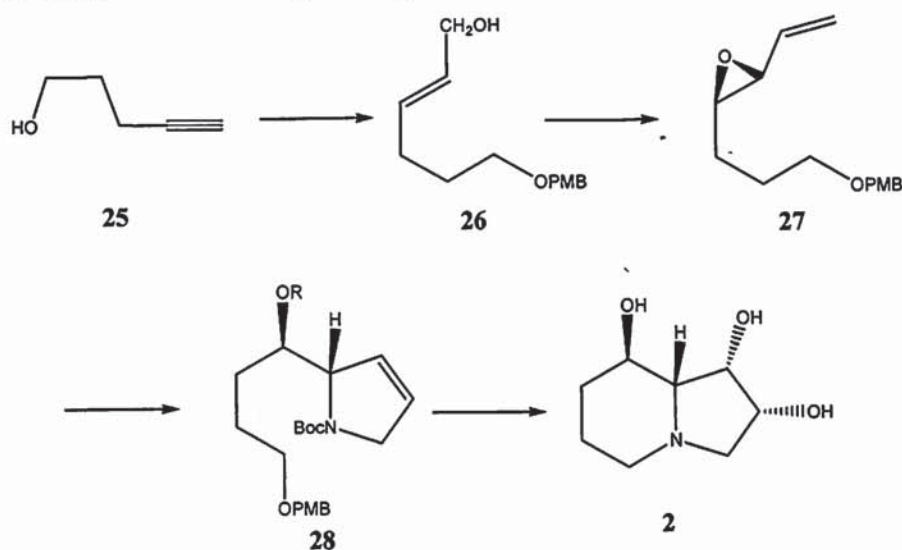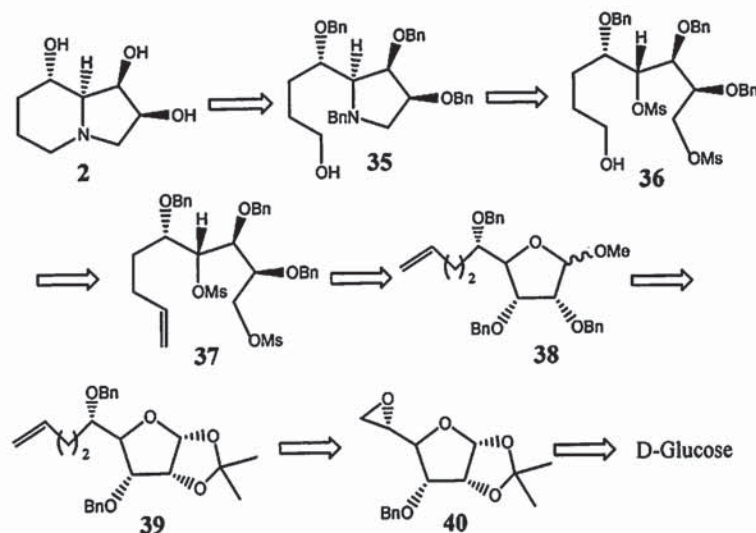

Scheme 5

Trost's synthesis synthesis of swainsonine analogue start with diol which was prepared from anthracene and benzoquinone (**Scheme 6**).[31] Trost's synthesis starts with the diol 29 that is readily prepared in 2 steps from anthracene and benzoquinone. Treatment of 29 with tosyl isonate gave the *meso*-bis-cabamate 30. Palladium-catalysed desymmetrization of 30 via Trost's chiral reagent afforded the oxazolidinone which was converted to 31 by syn-dihydroxylation with osmium catalyst. Base catalysed hydrolysis of the oxazolidinone ring of 31 and subsequent ozonolysis of this compound followed by reductive workup gave the diol 32. Regioselective cyclization of 32 under Mitsunobu

condition and oxidation gave aldehyde **33**. Consequently the aldehyde **33** was converted to enoate via Horner-Wadsworth-Emmons olefination reaction. Catalytic hydrogenation, reductive *N*-deprotection and borane reduction gave lactum **34** which was under acidic hydrolysis gave the desired product swainsonine. In this synthesis they were using tosyl isocynate, tris dibenzylideneacetonebis- palladium, chiral ligand *N, N'*-(1*R*, 2*R*)-1, 2-cyclohexanediylbis[2-(diphenylphosphino)benzamide reagent which are very expensive reagent in the market. This synthesis provided (-)-swainsonine in 17 overall steps from anthracene and benzoquinone in an overall yield of 13%. They are also using expensive reagent, taking long time reaction and not so good yield.[31]
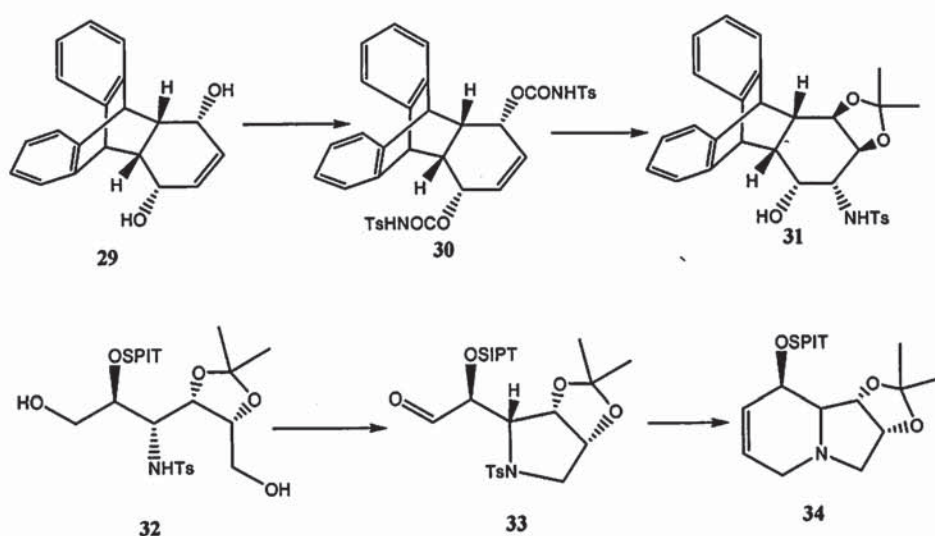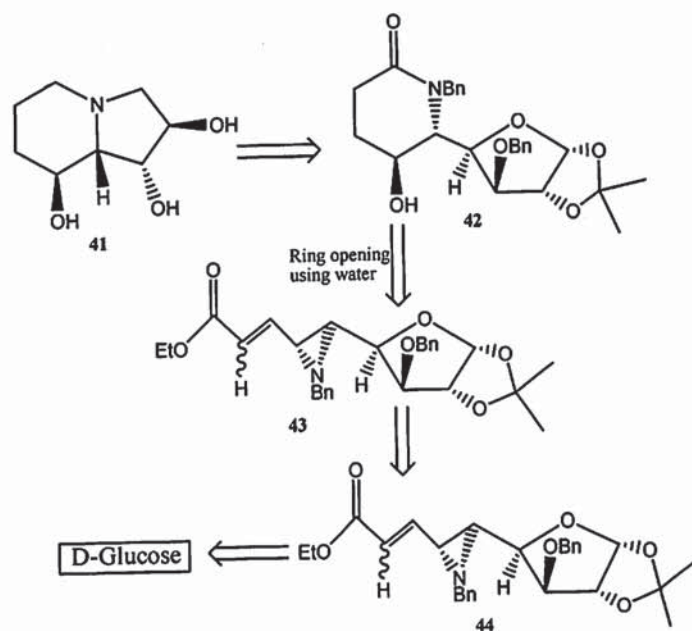

Scheme 6

Total synthesis of L-(+)-swainsonine is reported by starting from glucose in 17 steps in 17% yield with the key step was an intramolecular S_N2 reaction (**Scheme 7**). Retro synthetic analysis for L-(+)-swainsonine involved two crucial intramolecular S_N2 cyclizations leading to the formation of two rings successively.[32] The stereo chemically significant epoxide could be readily assembled from D-(+)-glucose by manipulation of the exocyclic 1, 2-diol unit. Regiospecific ring opening of epoxide gave alcohol. The free hydroxyl group of this alcohol was protected as benzyl ether by using NaH/benzyl bromide. Removal of the
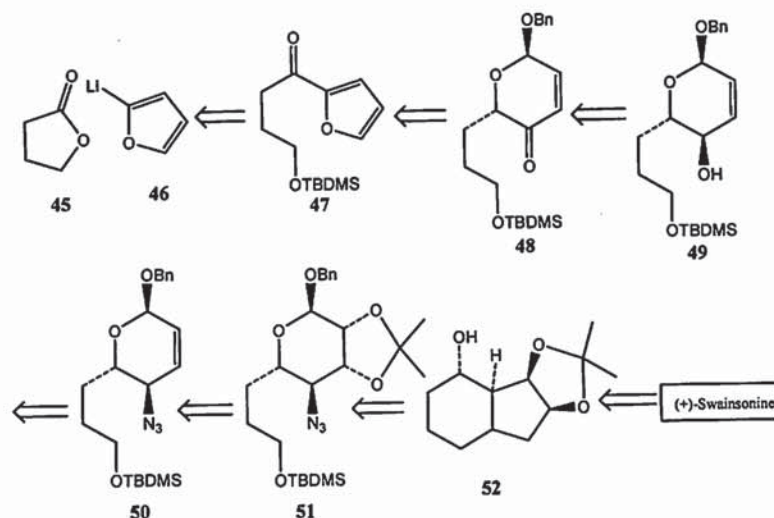
Scheme 7

Isopropylidene group and introduction of methoxy group at the anomeric carbon atom was done by treating **39** with HCL in methanol and free hydroxyl group is protected by benzyl ether formed compound **38**. The acetal group in comound **38** was deprotected by using 3% HCl in refluxing dioxane followed by the reduction of the hemiacetal group with NaBH$_4$ to form diol. Diol is converted into dimesylate **37** with mesyl chloride and Et$_3$N. Reduction of this aldehyde NaBH$_4$ gave hydroxyl dimesylate **36**. Thus **36** is heated with neat benzylamine at 90 °C for 12 hrs, which afforded compound **35**. In order to construct the second ring, alcohol **35** was treated with MsCl/Et$_3$N in CH$_2$Cl$_2$ which upon hydrogenolysis with 10 % Pd/C in MeOH gave desired compound **2**.[32]

The utility of a D-glucose-derived aziridine carboxylate was demonstrated for the synthesis of indolizidine alkaloids (**Scheme 8**).[33] The chemoselective reduction of **44** followed by two-carbon homologation by the wittig reaction afforded δ-aziridino-α,β-unsaturated ester **43**, which on regioselective nucleophilic aziridine ring opening either by using water as a nucleophile afforded δ-lactums **42** i.e., true synthons for the synthesis of four structurally different iminosugars, namely swainsonine **41**.[33]

Scheme 8

Guo and O'Doherty have reported a synthesis of both enantiomers of swainsonine by an enantio-divergent route (**Scheme 9**).[34] The key step to enantioselectivity was the catalytic transfer hydrogenation of **47** in the presence of the Noyori catalyst. Achmatowicz rearrangement of formed alcohol was effected with with N-bromosuccinimide to give the pyranone. The corresponding Boc-protected intermediate underwent palladium-induced coupling with benzyl alcohol to give **48**. The equatorial allylic alcohol **49** prepared by reduction **48** with sodium borohydride, was then transformed into the azide **50**. Dihydroxylation and protection of **50** to give the tetrahydropyran **51**, which was convert by means of a similar end-game into (+)-swainsonine via the ketal-protected intermediate **52**. The approach produced both enantiomers of swainsonine in about in about 17% overall yield.[35]

Scheme 9

Analogues of swainsonine synthesized during the period study include (-)-8-epi-swainsonine **53**[36] aand its triacetate,[37] both by routes involving ring-closing metathesis. New sulfonium ion analogues of swainsonine include the triols **54**[38] and **55**.[39]
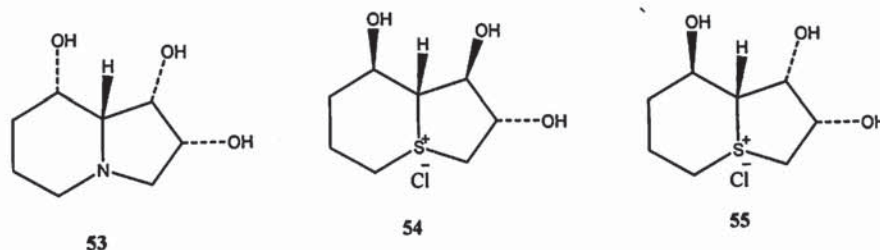
Though there many synthetic procedures reported for swainsonine, most of these methods are lengthy, time consuming and involve very expensive chiral reagents. The majority of published synthetic procedures also suffer from poor stereo-selectivity, and inefficient protecting group chemistry, especially with respect to handling of the amino residue. In this project we tried to synthesize Swainsonine and its analogues from cheapest available chiral pool of D-Glucose using fast, easy methods and inexpensive achiral reagents.

2.2 Aims and Objectives

Though there are several total and formal synthesis of swainsonine is already reported most of these methods are lengthy, time consuming and involve very expensive chiral reagents. The majority of published synthetic procedures also suffer from poor stereo-selectivity, and inefficient protecting group chemistry, especially with respect to handling of the amino residue. Swainsonine being a good candidate in advance phase clinical trial for cancer treatment as oligosaccharide processing inhibitor, it's cheaper and more efficient synthesis bears huge importance. Our target molecule is an interesting alkaloid having indolizidine moiety with four chiral centres. Chiral pool based synthesis using glucose will allow us reach desired chiral centers of target molecules using inexpensive achiral reagents in 12 steps. We started our work with following precise objectives.

1. **Fast, cheap synthesis of Swainsonine:** To achieve fast, efficient and cheap stereoselective synthesis of (-)-Swainsonine starting from cheapest available chiral pool of D-glucose using common achiral reagents.

2. **Optimization of reaction methods and conditions:** For each transformation there are numerous synthetic methodologies available in literatures. Correct choice of methodology and optimizing its condition for that particular substrate generally helps to increase yield and efficiency.

3. **Preparation of related analogues:** Little change in stereochemistry sometimes has huge impact on bioactivity. Not only Swainsonine but some of its diastereomeric analogues are also showed impressive bioactivities. That prompted us to think synthesizing some of its analogues.

4. **Spectroscopic confirmations of chemical structure:** Determination of structures with correct absolute stereochemistry is the most important practice in synthetic chemistry. We shall use NMR, IR and Mass spectroscopic techniques for determination of stereochemistry of target molecule.

Chapter III

3.1 Materials:

3.1.1 Chemicals

All the chemical composition was obtained from Merck Germany, Thomas Baker, Sigma Aldrich and SRL coppanies. The details of the materials and instrument used in this synthetic procedure are summarized below:

D-glucose - Sigma Aldrich, Dichloromethane – Rankem, Calcium Chloride – Merck, Sodium Hydroxide - Merck, TLC plate – Merck, Sodium Sulphate – Merck, Hydrochloric acid – Thomas Baker, Sulphuric acid – Thomas baker, Acetic acid – Merck, 3Å Molecular schieves - Acros Organics, Allylamine – Spectrochem, Benzyl chloroformate – Spectrochem, Toluene – Merck, Ethyl acetate - Merck, Petrolium ether – Merck, Chromium Trioxide - Thomas Baker, Pyridine – Thomas Baker, Sodium cynoborohydrode - Thomas Baker, Sodium Periodate - Thomas Baker, Phenylhydroxylamine – Sigma Aldrich, Silica gel - SRL

3.1.2 Instruments:

1. NMR Spectrometer: The ^{1}H and ^{13}C NMR spectra were taken from BRUKER-400 MHz NMR Spectrometer using $CDCl_3$ as solvent.

2. FT-IR Spectrometer: Bruker, Germany/Alpha FT-IR Spectrometer

3.1.3 Solution for TLC Stains

1. *Libermann Solution*: Acetic acid (5ml), Sulphuric acid (5ml), Methanol (40ml)

2. *Ninhydrin Solution*: Ninhydrin (1.5g), Propanol (100ml), Acetic Acid (3ml)

3. *Phosphomolybdic Acid Solution:* Phosphomolybdic Acid (5g), Ethanol (50ml)

3.2 Methodology:

### 3.2.1 Scheme 10 for synthesis of Swainsonine:

(-)-Swainsonine **1** has indolizidine structure with four chiral centers where five membered ring is substituted by two hydroxyl group at C-3 and C-4 position in cis fashion and six membered ring monosubstituted by hydroxyl group at C-5. If we analyze the structure retrosynthetically vicinal *cis* hydroxylation can be done easily using osmium tetroxide on compound **53**. Synthesis of **54** can be easily obtained by ring closing metathesis of compound **53**, which can be synthesized by Wittig reaction of masked aldehyde of hemiacetal generated by deprotecton of acetonide of **54**. Preparation of compound **55** is envisaged from **54** through deprotection of CBz followed by allylation. As understood **55** can be arrived by RCM of compound **54**, which can be reached from **56** by selective deprotection of C-5 and C-6 diol followed by their transformation to olefin. Synthesis of **56** can be achieved reductive amination of ketone obtained from oxidation C-3 hydroxyl group of Diacetone-D-glucose **57**.
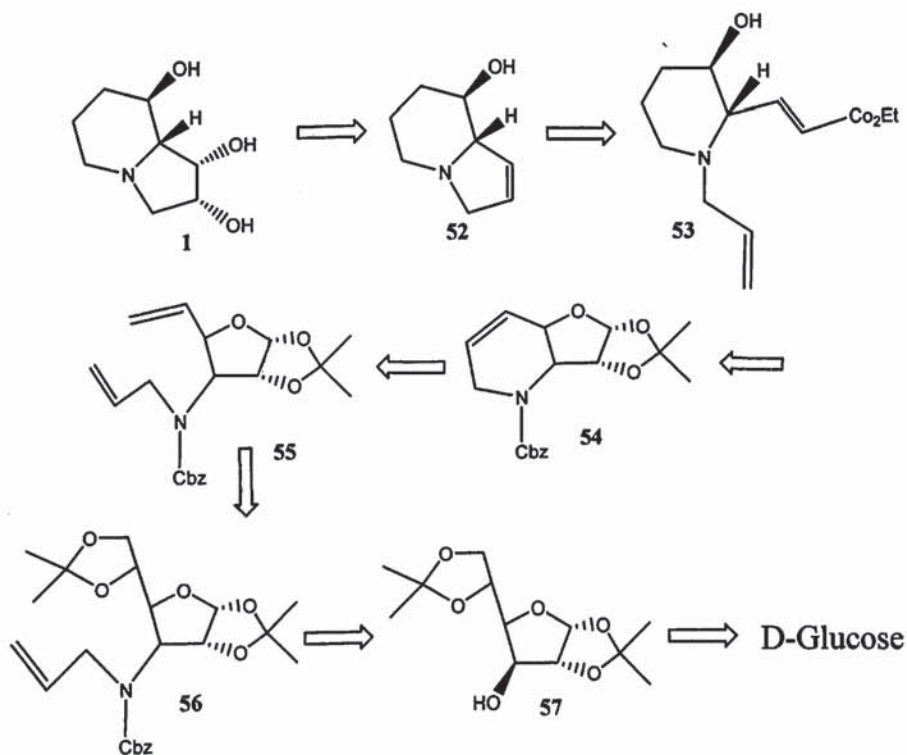
Scheme 10

3.2.2 Scheme 11 for synthesis of its analogues:

This scheme is started with same initial procedure of **Scheme 10** via formation of diacetone-D-glucose, oxidation with PCC, reductive amination reaction, deprotection of diol. Then compound **62** can be prepared by oxidation with $NaIO_4$ to form aldehyde at C-4 carbon. The simple strategy used in the formation of **64** involved a 1, 3-dipolar intramolecular cycloaddition reaction between C-5 nitrone and an allylamine moiety at C-3 instead of Grubb's reaction of **Schemes 10.** Synthesis of **65** can be done by Wittig reaction of masked aldehyde of hemiacetal generated by deprotecton of acetonide. Then ring closing metathesis of **65** generate new ring as compound **66.** Palladium-charcoal catalysed hydrogenolysis and *cis*-hydroxylation by using osmium tetroxide reagent generate desire analogue **67.**
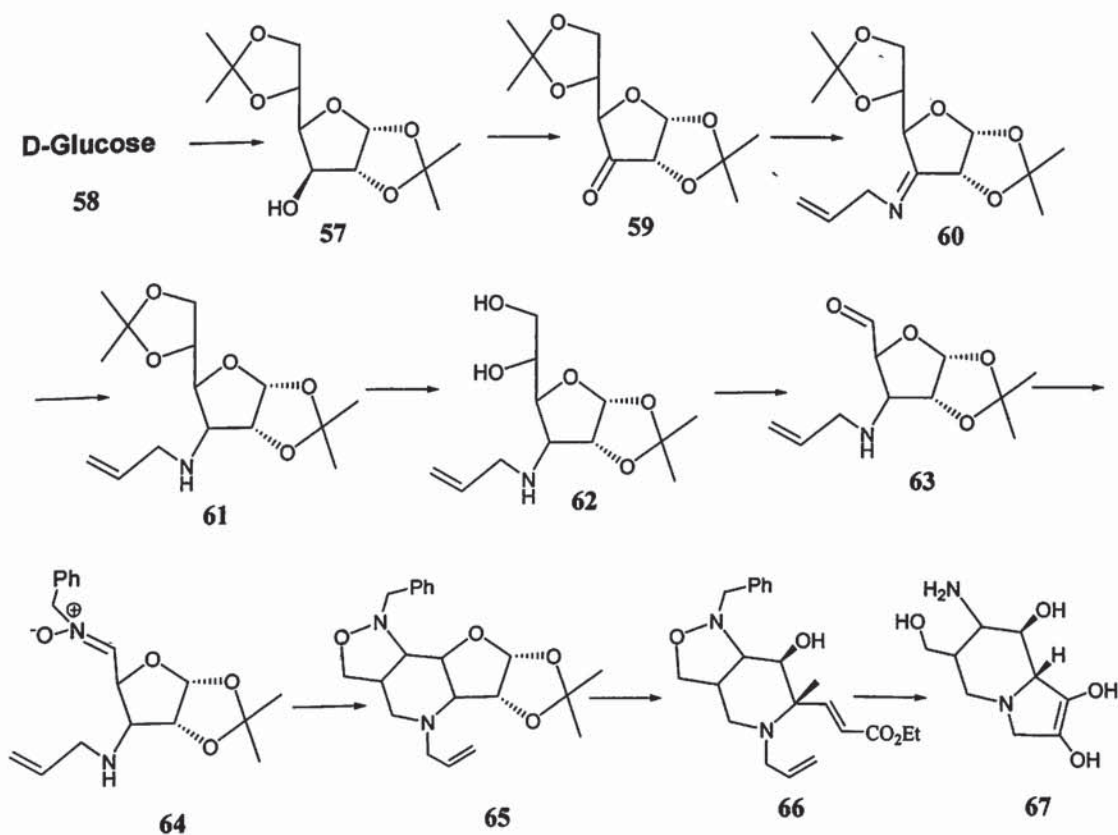

Scheme 11

According to our plan the total synthesis can be divided into following steps -

1. Conversion of D-glucose into 1,2:5,6-*O*-isopropylidine-D-glucofuranose

2. Oxidation of secondary alcohol at C-3 with PCC

3. Reductive amination of generated ketone at C-3 and Protection of amine

4. Selective deprotection of 5,6- vicinal diol and Transfomation of diol to olefin

5. Ring closing metathesis of diene

6. Deprotection of nitrogen and subsequent allylation

7. Deprotection of 1,2 diol followed by Wittig reaction

8. Ring closing metathesis and subsequent dihydroxylation by osmium tetroxide

1. Conversion of D-glucose into 1, 2: 5, 6-*O*-isopropylidine-D-glucofuranose:
Diacetone D-glucose can be synthesized by reaction between D-glucose and acetone in presence of concentrated sulfuric acid at low temperature (0-10°C).


58   57
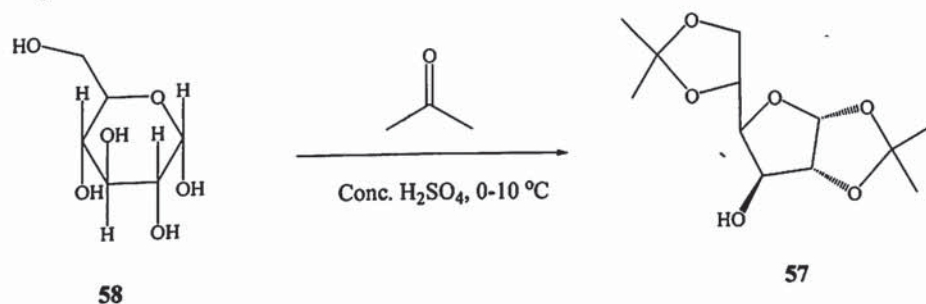
2. Oxidation of secondary alcohol at C-3 with PCC: Oxidation of C-3 hydroxyl group can be carried out using pyridinium chlorocromate (PCC). Reaction can be carried out in dry methylene chloride in presence molecular sieves 3A. Though there are many other oxidizing reagents available in market we prefer PCC due to it mildness to other groups and ambient reaction condition.


57   59
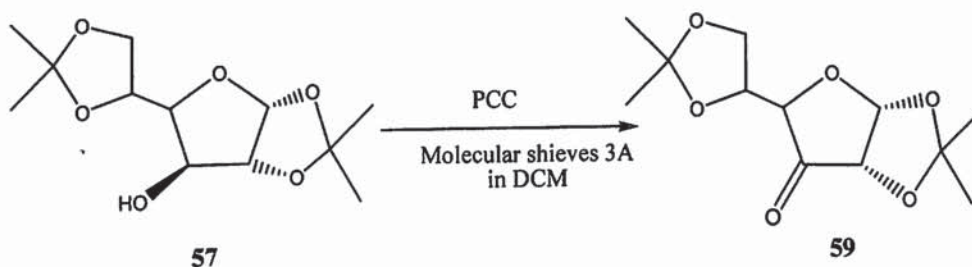
3. Reductive amination of generated ketone at C-3 and Protection of amine:

Reductive amination of ketone is a very well known technique. Here we can be use allyl amine to reach our desired target. For reduction of imine NaBH₃CN is used. Stereochemistry of attached allyl amine will be down only as approach of hydride to imine is not possible from back side due to the blockade by fused substituted five membered acetonide ring. This can be understood by NMR coupling constant of C-3 hydrogen with nearby C-2 and C-4 hydrogen. Protection of resulted secondary can be done using carboxybenzyl chloride.
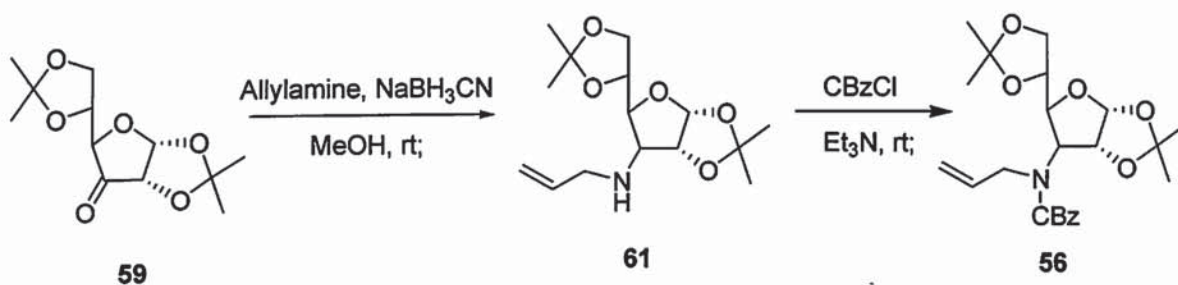

### 4. Selective deprotection of 5, 6- vicinal diol and Transfomation of diol to olefin:

Selective deprotection of 5, 6-O-isopropylidine can be done using 75% acetic as reported literature. 1, 2-O-isopropylidine deprotection required strong mineral acid. Diol generated by deprotection can be easily converted to olefin using reported procedure with PPh₃, iodine, imidazole. Mesylation can be followed by treatment of sodium iodide can also be used for the same purpose.
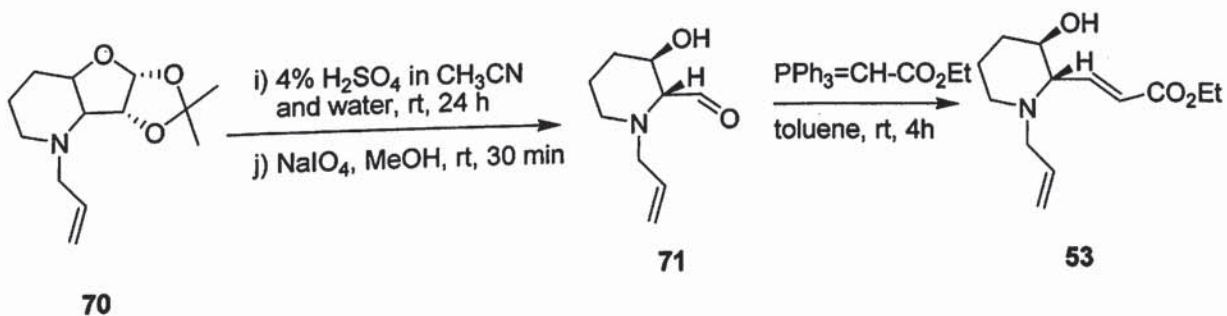

21
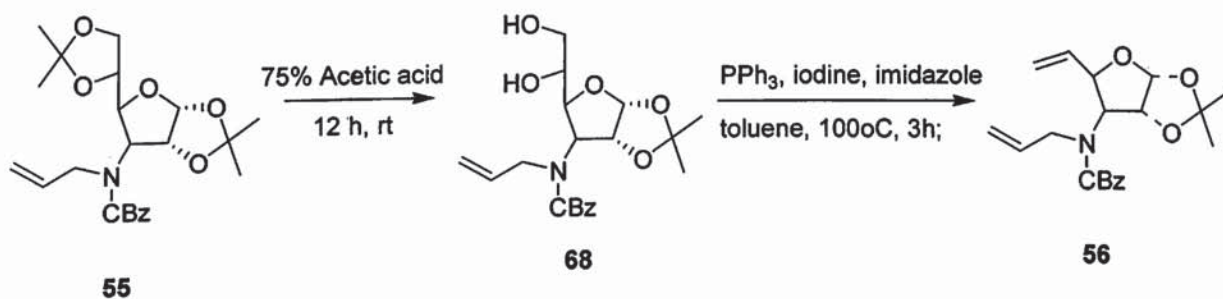
5. Ring closing metathesis of diene: This six member ring formation can be performed using first generation Grubb's catalyst.

Grubbs catalyst,
DCM, rt, 8-10 h

55   **54**
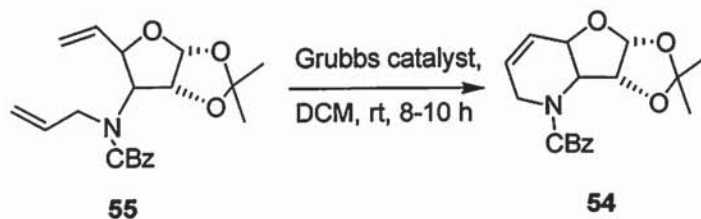
6. Deprotection of nitrogen and subsequent allylation: Deprotection and reduction of double bond can be simultaneously done by palladium-charcoal catalysed hydrogenolysis. After deprotection of amine allylation can be carried out using allyl bromide and aq. NaOH in dichloromethane with the help of phase transfer catalyst tetrabutyl ammonium bromide.


Pd-C, H_2
Ethanol, rt, 10 h

50% NaOH, allyl bromide,
TBAB, DCM, rt;

54   **69**   **70**
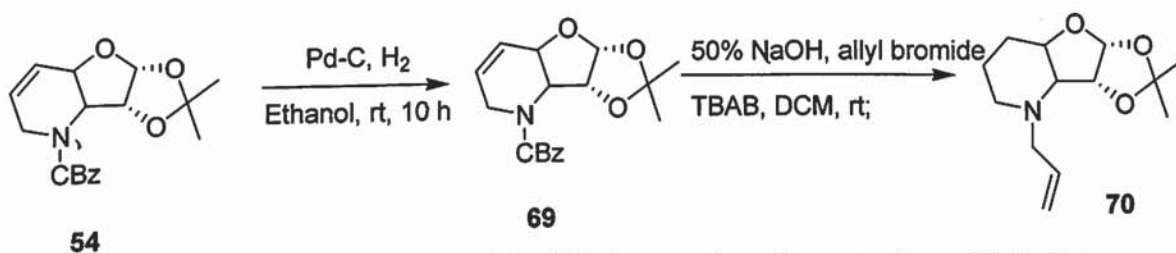
7. Deprotection of 1, 2 diol followed by Wittig reaction: Deprotection of 1, 2-diol can be done using mineral acid like 4% sulfuric acid. Metaperiodate cleavage of β-hydroxy aldehyde would yield aldehyde which can be used for Wittig reaction with ethyl acetate yilide to obtain unsaturaton in the desired position in the form of conjugated ester.


i) 4% H_2SO_4 in CH_3CN
and water, rt, 24 h

j) $NaIO_4$, MeOH, rt, 30 min

PPh_3=CH-CO_2Et
toluene, rt, 4h

70   **71**   **53**

8. Ring closing metathesis and subsequent dihydroxylation by osmium tetroxide: RCM reaction of diene using Grubb's catalyst followed by cis-dihydroxylation can result

the desired product (-) Swainsonine. In this step β-dihydroxide analogue can also be synthesize and these diastereomers can be separated using column chromatography. These analogues also can be very helpful to fully realize the stereochemistry of newly generated hydroxyl groups through NMR spectroscopic techniques.
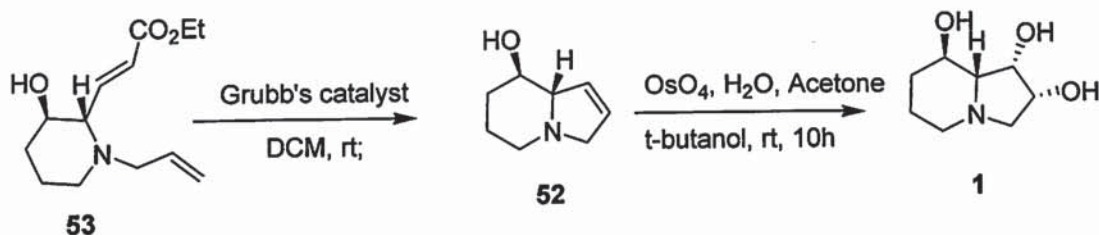
3.3 Experimental Details:

### 3.3.1 Conversion of D-glucose into 1, 2: 5, 6-O-isopropylidine-D-glucofuranose
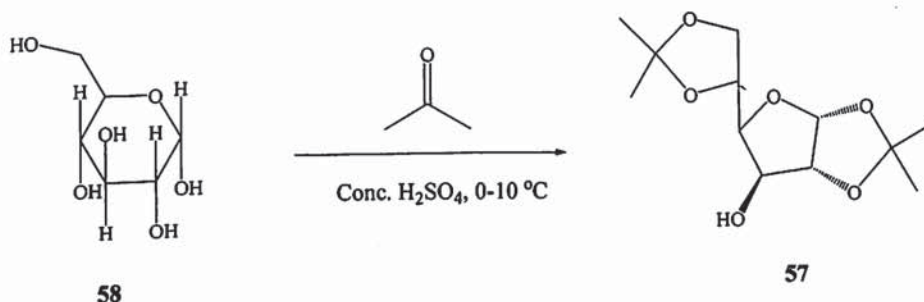
Synthesis Procedure

A suspension of D-glucose (50 g) in acetone, taken in the three necked flask fitted with a magnetic stirrer and an additional funnel, is cooled to 0 °C. Conc. H_2SO_4 (40 ml) is added to it portion wise so that the temperature remained inside the flask at 5-10 °C. After the addition the mixture is stirred for 5.5 hours at room temperature. It is then cooled at 10 °C and neutralized with the slow addition of NaOH solution (80 g in 80 ml of water) maintaining the temperature of reaction mixture <25 °C, finally $NaHCO_3$ (10 g) is added to it. Acetone is evaporated to give white solid which was then dissolved in dichloromethane and repeatedly washed with water (2 x 30 ml), brine (30 ml), dried with anhydrous Na_2SO_4 and the solvent is evaporated and obtained a white precipitate. It is

again dissolved in minimum amount of dichloromethane and placed in water bath, and the petroleum ether is added drop wise until the precipitation is started. After the entire product is precipitated out, it is removed from the water bath and filtered using Buckner funnel to obtain pure product as white solid (32.15g).
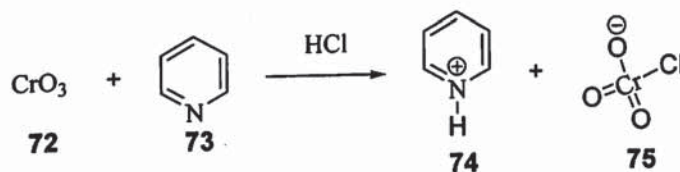
NMR Spectrum:

^{1}H NMR (CDCl$_3$, 400MHz): δ ppm 1.32 (s, 3H), 1.37 (s, 3H), 1.45 (s, 3H), 1.50 (s, 3H), 2.83 (s.1H), 4.00 (triplet like dd, 1H, J_1 = 6.0 Hz, J_2 = 7.6 Hz), 4.07 (d, 1H, J = 7.6 Hz), 4.19 (t, 1H, J = 14.8 Hz), 4.32 (triplet like dd, 2H, J_1 = 1.4 Hz, J_2 = 4.8 Hz), 5.92 (d, 1H, J = 4.4 Hz).
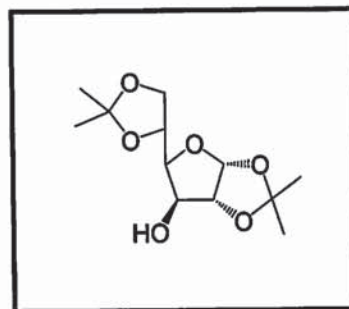
## Synthesis of Reagents:

(a)   Synthesis of Pyridinium Chlorochromate (PCC)

Synthesis Procedure

To 92 mL of 6M hydrochloric acid (1.1mol) is added 50 g of chromium (IV) oxide solution in water with continuous stirring. After 5 minutes the homogeneous solution is cooled to 0 °C. And 39.55 g (1mol) i.e. 40.27 ml of pyridine is carefully added over 12 minutes. Re-cooling the mixture to 0 °C give the yellow-orange solid which is collected on a sintered glass funnel and dried in vacuum yielded PCC (18.23 g).

3.3.2 Oxidation of secondary alcohol at C-3 with PCC

57   59
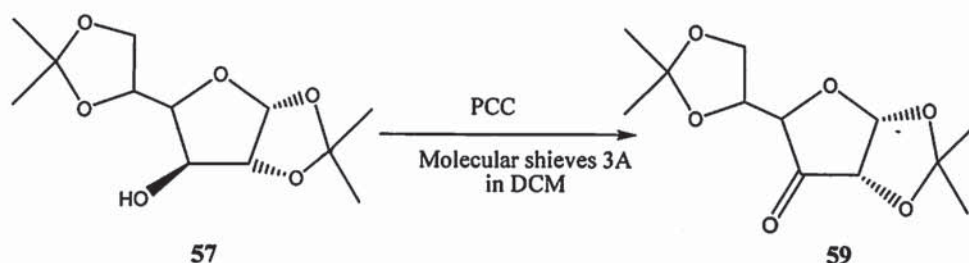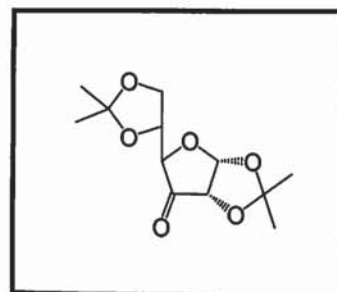
Synthesis Procedure

The glucofuranose **B** (1.5 g, 5.76 mmol) is taken in the round bottom flask and dichloromethane is added to it. Then it is stirred until the glucose is completely dissolved in the dichloromethane. Then molecular shieve (10 g) is added in the round bottom flask for the purpose of water absorption. Then PCC (10.1 g, 47.25 mmol) is added and placed on the magnetic stirrer and stirred continuously. The reaction mixture is left over night with constant stirring. The progress of the reaction is monitored using TLC in 2% methanol/dichloromethane, after it is confirmed by the checking TLC that the reaction is over, and then it is removed from the stirrer. Then next day the product is filtered silica gel in Buckner funnel. Again the filtrate TLC is done and it showed the product is a mixture. Then the product is further purified by column chromatography to obtain product (1.18 g, 72.94%) as a gummy liquid.
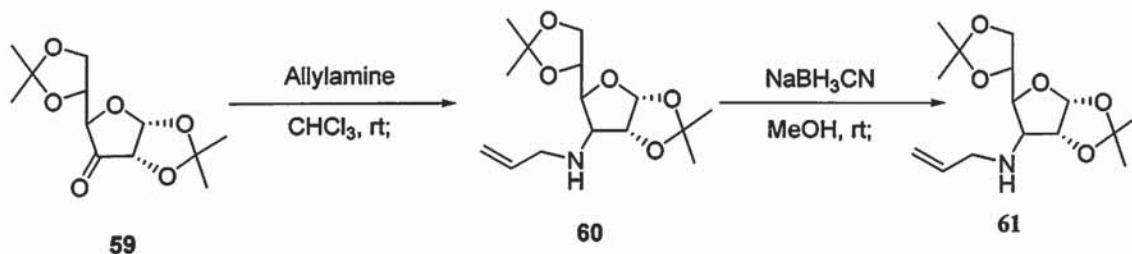
NMR Spectrum:

^{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).

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

25

3.3.3 Reductive amination of generated ketone at C-3 and Protection of amine


Synthesis Procedure

The ketone **59** (0.3 g, 1.1 mmol) was taken in round bottom flask (50 ml) and added dry dichloromethane (10 ml) into it and dissolved it. After that added 1.2 equivalent of allylamine (104 µl, 1.38 mmol) and monitor the reaction and checked. TLC showed the complete consumption of reaction. Add 1 equivalent of NaBH₃CN (0.8 g) for reduction of compound containing allylamine group at C-3 position. This reaction was check by TLC. The compound was evaporated and the products were extracted with CHCl₃ (3 x 25 ml). The combined extract was washed with water (2 x 15 ml), brine solution (1 x 10 ml), dried (anhydrous Na₂SO₄) and evaporated to a gummy residue. The crude material was chromatographed over silica gel. Elution was made with petroleum ether-ethyl acetate (7:3) to afford the light yellowish gummy liquid **61** (0.22 g, 73 %).

NMR Spectrum:

^{1}H NMR (CDCl₃, 400MHz): δ ppm 1.34 (s, 3H), 1.35 (s, 3H), 1.43 (s, 3H), 1.57 (s, 3H), 3.40 - 3.43 (m, 1H), 3.52 (d, 1H, J = 5.2 Hz), 3.87 (d, 1H, J = 8.8 Hz), 4.01 (dd, 1H, J = 4.4 Hz, 8.8 Hz), 4.16 (triplet like dd, 1H, J = 6.4 Hz, 9.2 Hz), 4.36 (m, 1H), 4.75 (d, J = 3.6 Hz), 5.14 (dd, 1H, J = 1.6 Hz, 10.4 Hz), 5.27 (dd, 1H, J = 1.2 Hz, 18.4 Hz), 5.82 (d, 1H, J = 3.2 Hz), 5.95 (m, 1H).
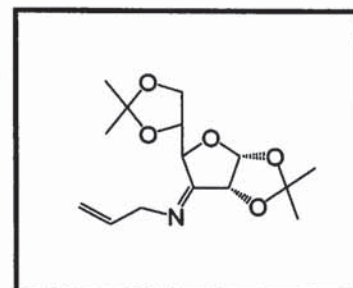
¹H NMR (CDCl₃, 400MHz): δ ppm 1.33 (s, 3H), 1.36 (s, 3H), 1.42 (s, 3H), 1.51 (s, 3H), 3.05 (dd, 2H, J = 4.8 Hz, 9.6 Hz), 3.25 (tdd, 1H, J = 2.8 Hz, 6.4 Hz, 14.0), 3.36 (tdd, 1H, J = 2.8 Hz, 5.6 Hz, 15.2 Hz), 3.80 (d, 1H, J = 4.0 Hz, 9.6 Hz), 3.99 (td, 1H, J = 6.8 Hz, 14.8 Hz), 4.17 (td, 1H, J = 7.2 Hz, 15.2 Hz), 4.34 (m, 1H), 5.10 (tdd, 1H, J = 1,2 Hz, 2.8 Hz, 10.4 Hz), 5.22 (tdd, 1H, J = 1.6 Hz, 3.6 Hz, 17.6 Hz), 5.77 (d, 1H, J = 3.6 Hz), 5.88 (m, 1H).
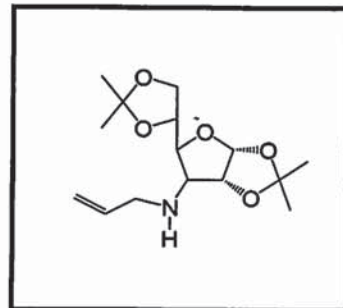
¹³C NMR (CDCl₃, 75 MHz): δ ppm 25.41 (CH₃), 26.30 (CH₃), 26.47 (CH₃), 26.75 (CH₃), 50.88 (CH₂), 61.42 (CH), 65.24 (CH₂), 75.86 (CH), 78.12 (CH), 79.07 (CH), 104.37 (CH), 109.52 (CH), 112.03 (CH), 116.10 (CH₂), 137.15 (CH).

IR Spectrum: ν_max (neat)/cm⁻¹ 2925, 1732, 1457, 1375, 1215, 1166, 1074, 841.

### 3.3.4 Selective deprotection of 5,6- vicinal diol
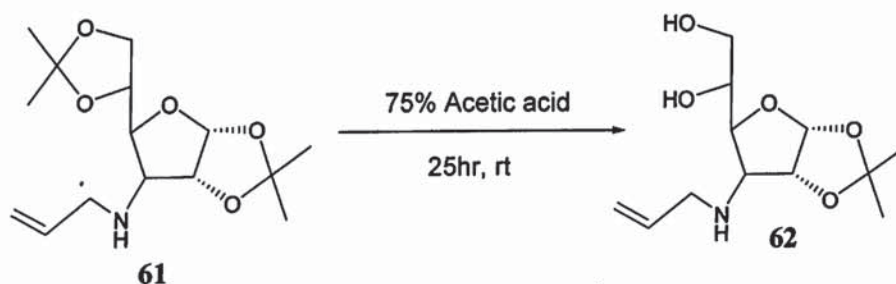
Procedure

De-protection of 5, 6-diol is started with 75% of acetic acid which was made by taking 15 ml of acetic acid in 5ml distilled water. Then this 75% acetic acid was added into the round bottom containing the sample **61** (0.4 g, 1.63 mmol) placed it on the magnetic stirred constantly for hours. The progress of the reaction was checked by TLC frequently. After it was confirmed that the reaction was over, the RB was removed from magnetic stirrer. The magnetic bar was washed by distilled water and did the work up for removal

27

of acetic acid by toluene. This reaction product is carried out successfully with the yield of 45% (0.18 g) as liquid form.

NMR Spectrum:

^{1}**H NMR** (CDCl$_3$, 400MHz): δ ppm 1.34 (s, 3H), 1.51 (s, 3H), 3.18 (d, 2H, J = 4.8 Hz), 3.24 (dd, 2H, J = 7.6 Hz, 14.0 Hz), 3.43 (dd, 1H, J = 6.4 Hz, 13.6 Hz), 3.75 (m, 3H), 3.99 (td, 1H, J = 2.8 Hz, 6.0 Hz), 4.65 (t, 1H, J = 8.4 Hz), 5.16 (dd, 1H, J = 1.2 Hz, 10.4 Hz), 5.25 (dd, 1H, J = 1.6 Hz, 17.2 Hz), 5.81 (d, 1H, J = 4.0 Hz), 5.85 (m, 1H).
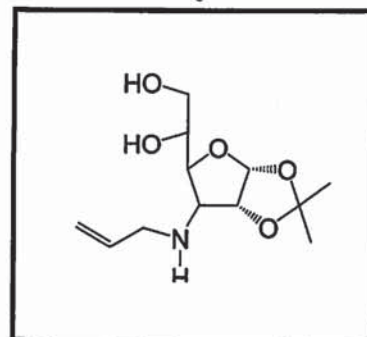
^{13}**C NMR** (CDCl$_3$, 75 MHz): δ ppm 26.51 (CH$_3$), 26.66 (CH$_3$), 50.34 (CH$_2$), 59.06 (CH), 63.11 (CH$_2$), 76.83 (CH), 77.47 (CH), 81.34 (CH), 104.68 (CH), 112.36 (CH), 117.73 (CH$_2$), 135.21 (CH).

IR Spectrum: v_{max} (neat)/cm^{-1} 2924, 1772, 1458, 1375, 1164, 1050, 873.

3.3.5   Oxidation by Sodium Periodide (NaIO$_4$)
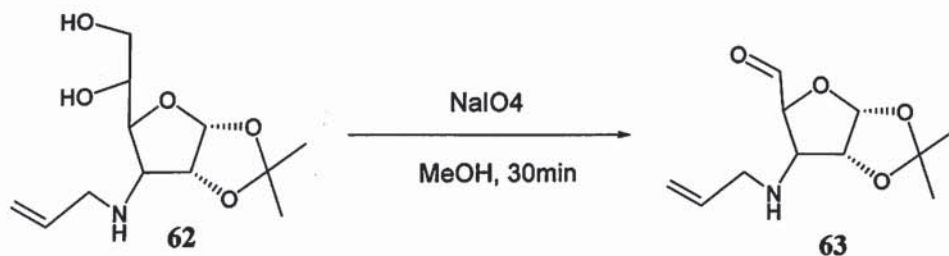
Synthesis Procedure

In oxidative cleavage reaction, the diol **62** (0.34 g, 1.34 mmol) is taken into small valve, dissolved in methanol and placed into the ice cold water. Then 1eq. sodium metaperiodate (0.28 g) is dissolved into distilled water and it is poured into the valve containing the sample. Small magnetic bar is also used to continuously stir the reaction mixture. It is then left for 30 minutes, after that the reaction is monitored by checking

TLC; it showed that the reaction is over. Firstly it is filtered using filter paper to separate the white precipitate; the filtrate is put into another valve. Then the methanol is evaporated out by using rotator evaporator. After methanol was evaporated, the aqueous solution was left. The washing of the aqueous solution is done with the chloroform (3 x 30 ml), brine solution (20 ml) is added to the organic/aqueous part and it is filtered using anhydrous Na_2SO_4. Then the filtrate is again put into the rotator evaporator for evaporated chloroform which afforded product (22 mg, 46.39%).

IR Spectrum: v_{max} (neat)/cm^{-1} 3374, 2924, 2854, 1646, 1456, 1376, 1015.

3.3.6 Nitrone reaction by N-benzylhydroxylamine
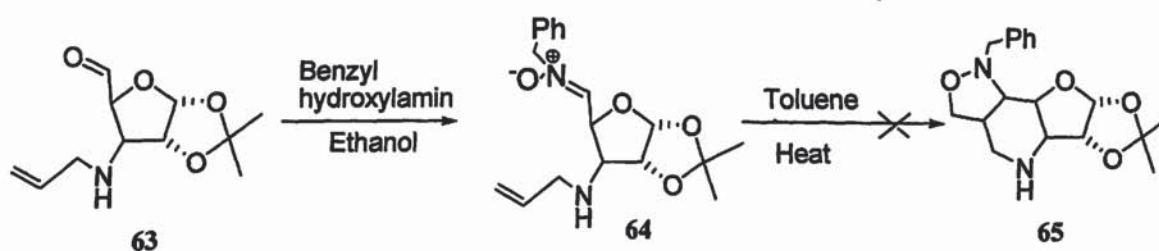

Synthesis Procedure

In nitrone cycloaddition reaction, the starting material **63** (0.18 g, 7.9 mmol) was taken into 50ml round bottom flask by keeping remaining material safely. Then the material was dissolved into ethanol and placed in magnetic stirrer. Two equivalent of benzylhydroxylamine (0.25 g, 1.58 mmol) was added and the lead of the round bottom flask was parafined. Then the reaction was monitored. After 4-5hrs reaction was checked by TLC. his reaction was check by TLC. The compound was evaporated and the products were extracted with $CHCl_3$ (3 x 20 ml). The combined extract was washed with water (2 x 15 ml), brine solution (1 x 10 ml), dried (anhydrous Na_2SO_4) and evaporated to a gummy residue. Dried the residue under decicator to afford the light yellowish gummy liquid **64** (0.134 g, 74 %).

NMR Spectrum:

^{1}**H NMR** (CDCl$_3$, 400MHz): δ ppm 1.41 (s, 3H), 1.50 (s, 3H), 3.39 (d, 2H, J = 1.2 Hz, 6.0 Hz), 3.88 (dd, 2H, J = 2.4 Hz, 12.8 Hz), 3.98 (dd, 1H, J = 3.6 Hz, 9.0 Hz), 4.64 (td, 1H, J = 2.4 Hz, 5.6 Hz), 4.85 (d, 1H, J = 3.6 Hz), 5.16 (d, 1H, J = 10.2 Hz), 5.25 (d, 1H, J = 16.0 Hz), 5.85 (m, 1H), 5.93 (d, 1H, J = 4.0 Hz), 7.32 (m, 5H), 8.2 (d, 1H, J = 7.0 Hz).
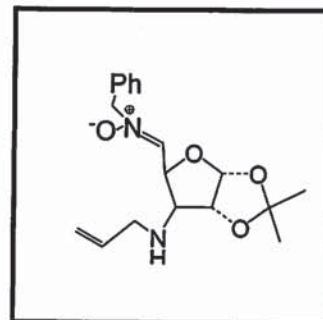
^{13}**C NMR** (CDCl$_3$, 75 MHz): δ ppm 26.79 (CH$_3$), 27.14 (CH$_3$), 47.04 (CH), 61.58 (CH$_2$), 71.52 (CH), 76.77(CH), 77.42(CH$_2$), 85.10 (CH) 106.61 (CH), 113.54 (CH), 117.60 (CH), 128.54 (CH), 128.72 (CH), 129.04 (CH), 129.33 (CH), 130.54 (CH).

IR Spectrum: ν$_{max}$ (neat)/cm^{-1} 2921, 2851, 1773, 1456, 1375, 1164, 1028, 907.

Chapter IV

4.1 Results And Discussion

Synthesis of diacetone-D-glucose **58** (1,2:5,6-di-*O*-isopropylidene-a-D-glucofuranose) a highly crystalline, stable and protected form of D-glucose which was prepared by treatment of D-glucose with acetone in presence of catalytic amount of concentrated H_2SO_4 at low temperature with the yield of 76%. Presence of four singlets for three protons each in the region of δ 1-2 ppm in proton NMR spectroscopy confirmed the structure of diacetone-D-glucose.

The hydroxyl group of **58** at C-3 position was then oxidized with PCC. TLC showed complete consumption of starting material. This reaction was also successful with the yield of 50% with the formation of ketone at C-3 position as compound **59**. In ^1H NMR spectrum the H-1 gave doublet at higher field (δ 5.83, $J = 3.6$ Hz) due to the high electro-negativity with oxygen atom. A doublet appearing at δ 4.26 ($J = 4.0$ Hz) was identified as the signal for H-2 proton. Formation of ketone at C-3 carbon is also confirmed by the presence of ketone carbonyl stretching absorption at v_{max} 1645 cm^{-1} in IR spectrum.

Reductive amination of this ketone with allylamine in dichloromethane resulted in formation of **60**. Incorporation of allyl moiety in **60** was confirmed by ^1H NMR signal viz. a characteristic multiplet for the olefinic methine proton at δ 5.95, upfield appearance of signal for two protons in the region of δ 5.14 (dd, $J = 1.6$ Hz, 10.4 Hz) and δ 5.27 (dd, $J = 1.2$ Hz, 18.4 Hz) indicated for vinylic protons and presence of doublet of doublet at the region of δ 3.52 (d, $J = 5.2$ Hz) and multiplet from δ 3.40- 3.43 to for two allylic protons. ^{13}C NMR spectrum also confirmed the allylamine moiety by the signal of δ 50.88 for aliphatic carbon and two upfield signals δ 116.10 and δ 137.15 for two ethylene carbons. In the reaction reductive amination of ketone we got two types of isomers of product in different reaction condition. In case of first isomer allylamine group was attach with C-3 carbon but at the position of C-3 diene was not reduced. This condition was confirmed by presence of doublet signal at δ 4.76 ($J = 3.6$ Hz) regions for H-2 proton. The presence of doublet showed that H-2 proton couples only with H-1 proton and by NMR spectrum we also got peaks for seventeen protons. Sodium cynoborohydride

reduction of **60** in methanol at room temperature yielded **61**. Formation of **61** can be understood from increase of a proton in 2-6 ppm region. Appearance of C-2 proton as triplet at δ 4.59 (J = 8.4 Hz) suggest that the hydride transfer from cyanoborohydride has taken place from up side of ribose ring forcing allylamine to go below the ring. The rationale behind the stereo-specificity arises from the unapprochability of the cyanoborohydride fron α-side due to blocking by steric crowding from fused five membered rings.

After that, compound **61** is treated with benzylcholoformate in presence of triethylamine for protection of amine group present in compound **61**. But this reaction was unsuccessful. So we tried to synthesized the indolizdiene moiety via opening of isopropylidine ring with 75% acetic acid, vicinal diol cleavage with sodium periodate and with nitrone reaction. Then compound **61** is treated with 75% acetic acid which was selectively opening of 5, 6-*O*-isopropylidine protection formed the diols **62** above the plane.

Removal of isopropylidene group was evident from the absence of two 3H singlet in ¹H NMR spectrum and presence of two methyl carbons at the region of δ 26.66 and δ 26.51 in ¹³C NMR spectrum. Here countinous presence of allylamine group was confirmed by presence of multiplet in upfield region at δ 5.85 for olefinic methine proton, two doublet of doublet at δ 5.25 (dd, J = 1.6 Hz, 17.2 Hz) and δ 5.16 (dd, J = 1.2 Hz, 10.4 Hz) for vinylic protons and two doublet of doublet at δ 3.43 (dd, J = 6.4 Hz, 13.6 Hz) and δ 3.24 (J = 7.6 Hz, 14.0 Hz) for methylene protons in ¹H NMR spectrum. Doublet of doublet signal is satisfied by the difference between two J values. ¹³C-NMR spectrum also ·dedicated by presence of δ 135.21 and δ 117.73 for vinylic carbon and signal at δ 50.34 for allylic carbon in allylamine moiety.

Oxidative cleavage of compound **62** was done by sodium periodate at low temperature and formation of aldehyde **63** at C-4 position was confirmed by the presence of aldehyde carbonyl stretching absorption at v_{max} 1646 cm⁻¹ in IR spectrum. Treatment of aldehyde with *N*-benzyl hydroxylamine in ethanol at room temperature produced a non isolable
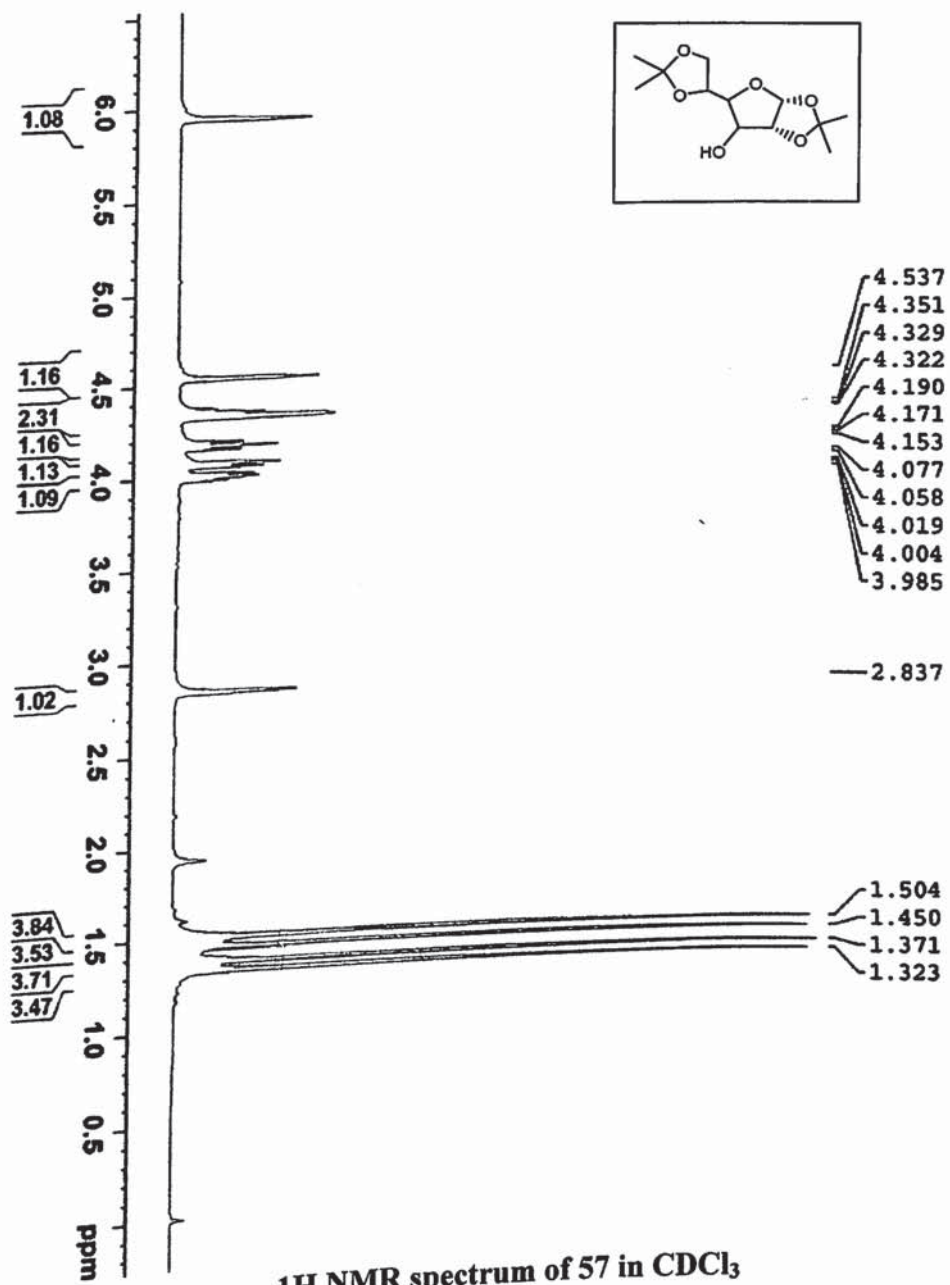
nitrone product **64**. Formation of compound **64** was evident by the characterstic peak of multiplet at δ 7.41 for five aromatic protons in *N*-benzyl hydroxylamine group. Here presence of doublet in upfield region at δ 8.20 ($J = 3.6$ Hz) for imine proton represents the attachment of nitrone at C-5 position. ^{13}C-NMR spectrum also detected the presence of five benzene carbons at the range between δ 129.33 to δ 128.32 values. So the spectrum of **64** clearly showed the attachement of benzylhydoxylamine to form nitrone successfully but there is no evidence for *in situ* cyclization with olefin of allyl group. Confirmation for unsuccessful cyclization is evident from no change in the pattern of chemical shift of vinyl protons. For further study we will be using ring closing metathesis (RCM) of **55** with Grubb's catalyst and intramolecular cyclo-addition reaction (INC) of **64** for synthesis of swainsonine and its analogues.
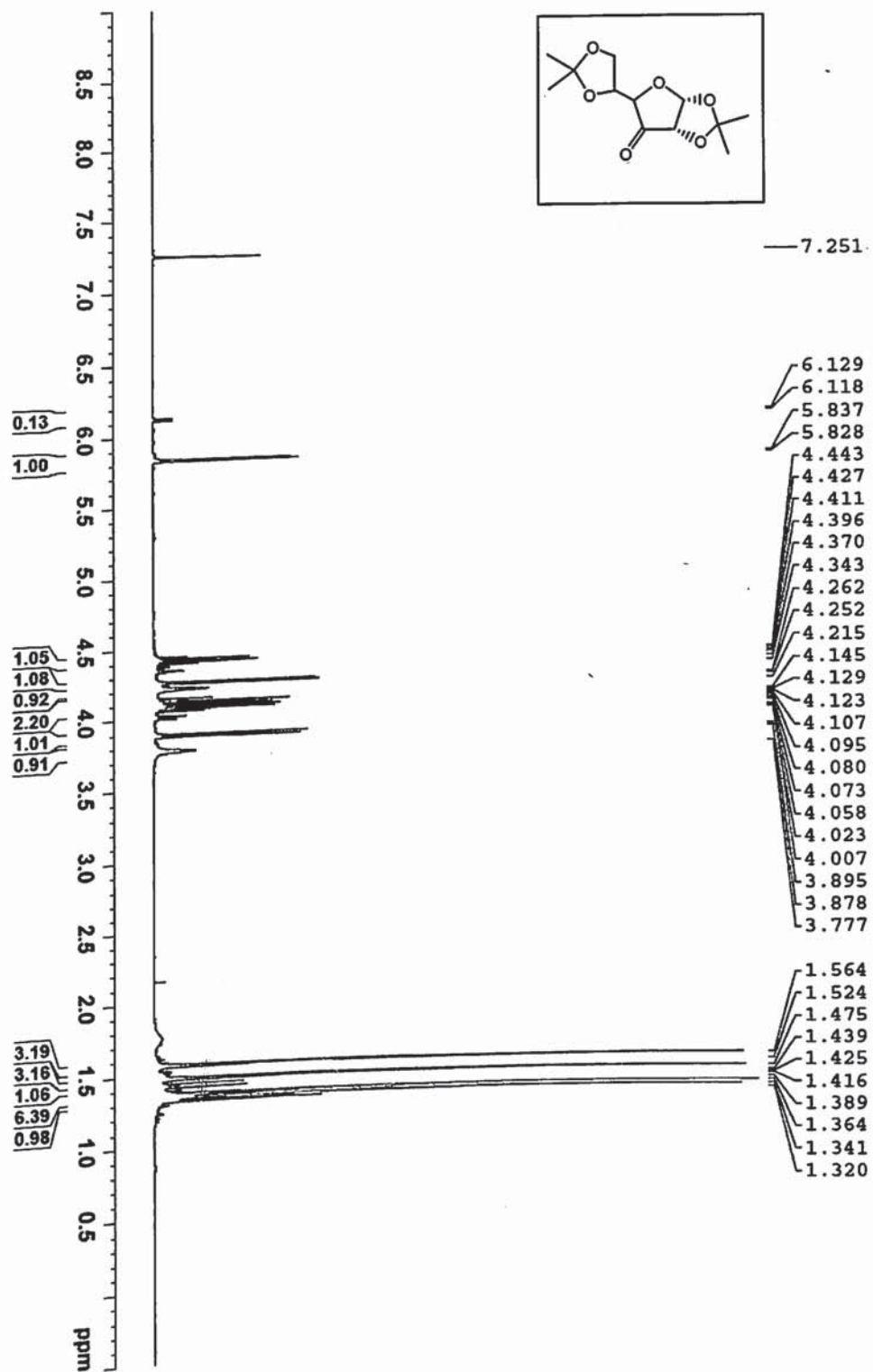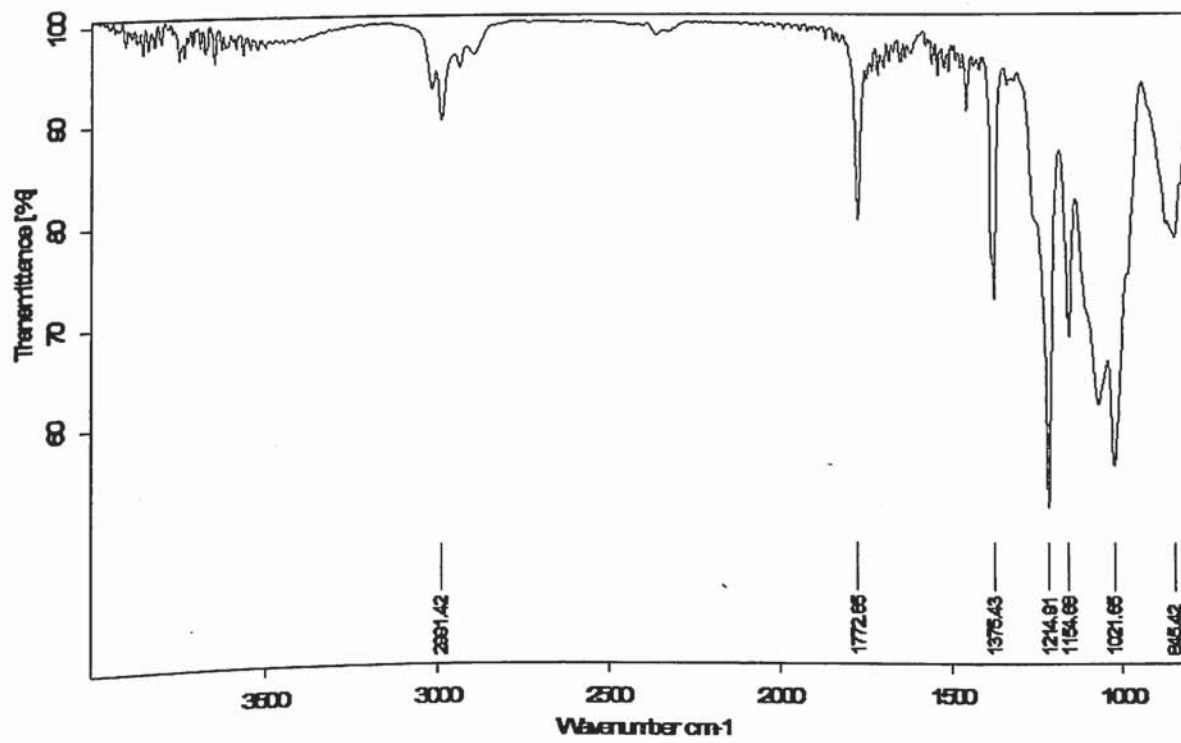
Chapter V

5.1 Conclusion

Six of the earlier important steps were successfully done. We started the scheme with conversion of D-glucose into 1, 2: 5, 6-*O*-isopropylidine-D-glucofuranose by reaction between D-glucose and acetone in presence of concentrated sulfuric acid at low temperature presence of acetone. Oxidation of the secondary alcohol at C-3 with PCC to formed ketone. Reductive amination of generated ketone at C-3 position generated imine product. Then selective deprotection of 5, 6-*O*-isopropylidine was done by using 76% acetic acid to formed 5, 6- vicinal diol. Transfomation of 5, 6- vicinal diol to aldehyde reaction were done successfully completed. Intramolecular nitrone cycloaddition reaction between aldehyde and diene was done by using *N*-benzyl hydroxylamine. In this reaction nitrone product is also synthesized but no evidence of cyclization is observed. Each of the steps are optimized and products are fully characterized by ^{1}H NMR, ^{13}C NMR and IR spectroscopy. In future we will be engaged in rest of the synthesis of swainsonine and its analogues using ring closing metathesis (RCM) and intramolecular cyclo-addition reaction (INC) reaction.
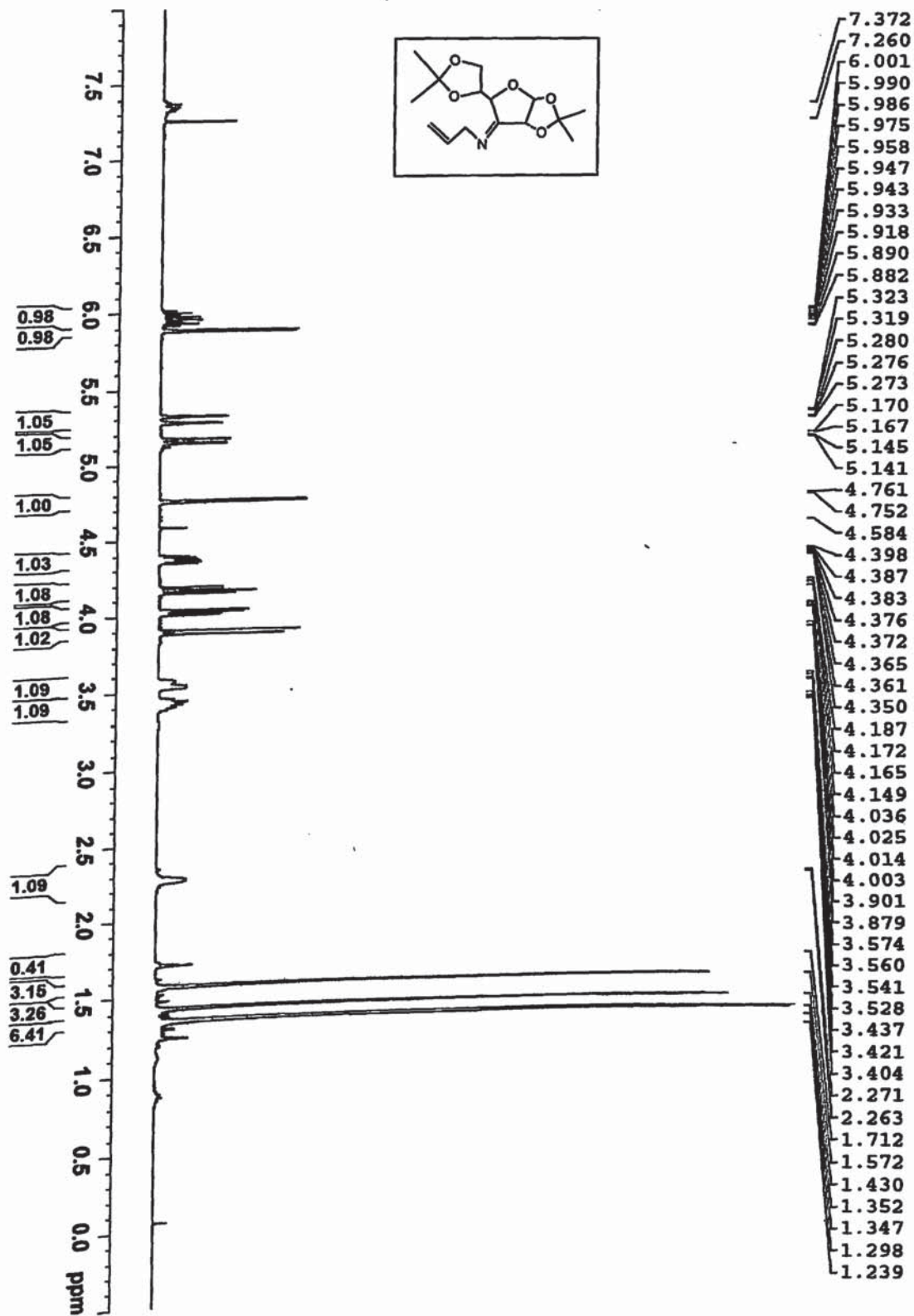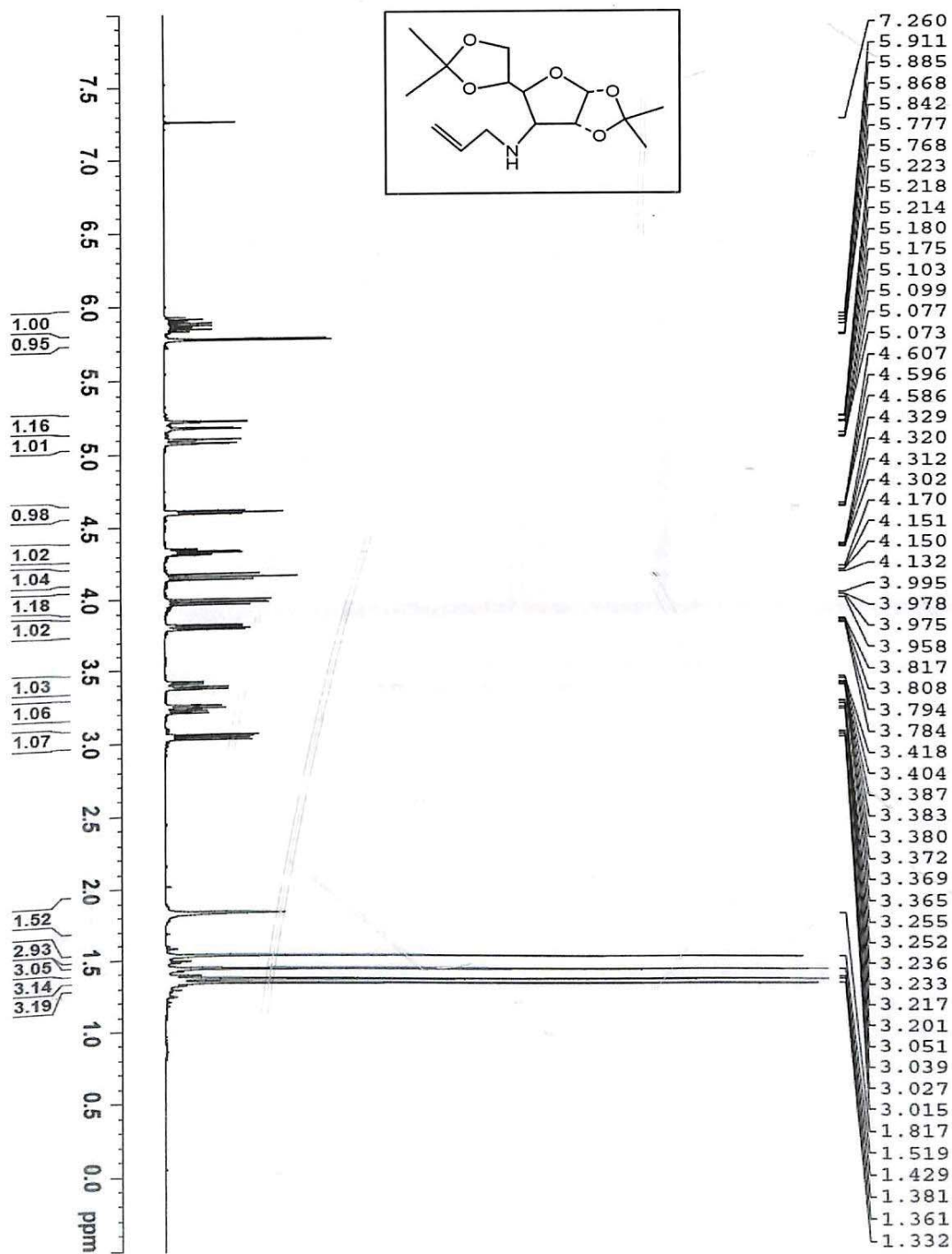
5.2 NMR and IR Spectra:

1H NMR spectrum of 57 in CDCl₃

—7.251

6.129
6.118
5.837
5.828
4.443
4.427
4.411
4.396
4.370
4.343
4.262
4.252
4.215
4.145
4.129
4.123
4.107
4.095
4.080
4.073
4.058
4.023
4.007
3.895
3.878
3.777

1.564
1.524
1.475
1.439
1.425
1.416
1.389
1.364
1.341
1.320

0.13
1.00

1.05
1.08
0.92
2.20
1.01
0.91

3.19
3.16
1.06
6.39
0.98

¹H NMR spectrum of 59

IR spectrum of 59

^{1}H NMR spectrum of 60

7.260
5.911
5.885
5.868
5.842
5.777
5.768
5.223
5.218
5.214
5.180
5.175
5.103
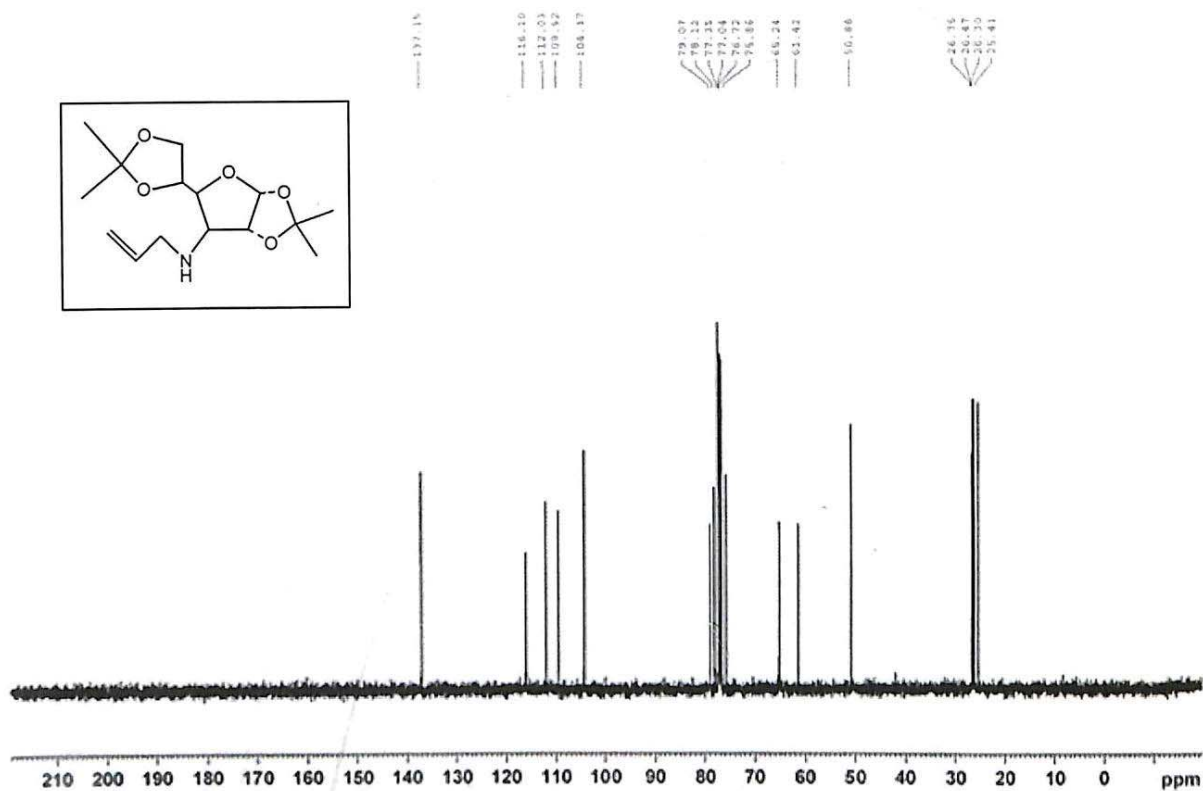5.099
5.077
5.073
4.607
4.596
4.586
4.329
4.320
4.312
4.302
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4.150
4.132
3.995
3.978
3.975
3.958
3.817
3.808
3.794
3.784
3.418
3.404
3.387
3.383
3.380
3.372
3.369
3.365
3.255
3.252
3.236
3.233
3.217
3.201
3.051
3.039
3.027
3.015
1.817
1.519
1.429
1.381
1.361
1.332

1.00
0.95

1.16
1.01

0.98

1.02
1.04
1.18
1.02

1.03
1.06
1.07

1.52
2.93
3.05
3.14
3.19

^{1}H NMR spectrum of 61

^{13}C NMR spectrum of 61

IR spectrum of 61

7.260

5.871
5.854
5.829
5.819
5.252
5.248
5.209
5.205
5.162
5.160
5.137
5.134
4.654
4.644
4.633
3.983
3.975
3.727
3.716
3.715
3.708
3.700
3.683
3.676
3.396
3.380
3.248
3.233
3.214
3.199
3.187
3.175
3.163
3.151

1.516
1.340

7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm

1.90
1.02
0.98
1.01
1.03
3.21
1.32
3.23
2.99
3.10

¹H NMR spectrum of 62

¹³C NMR spectrum of 62
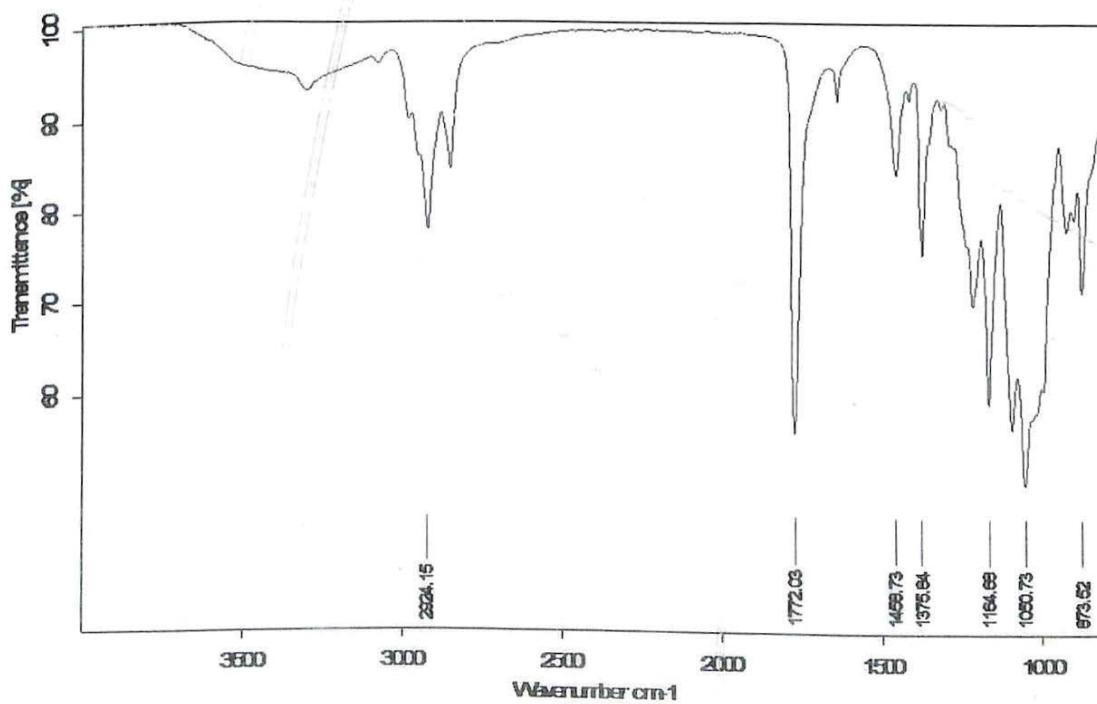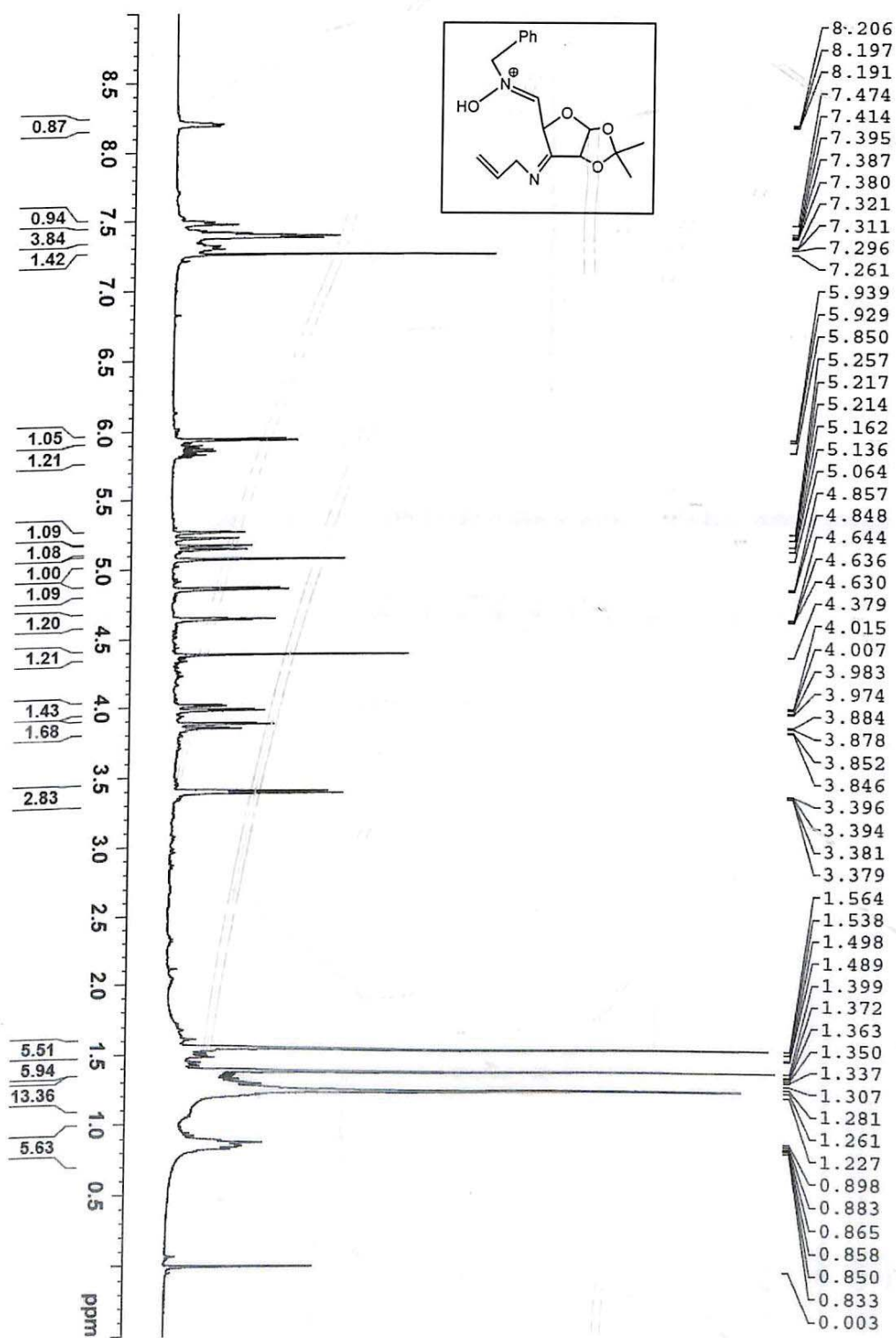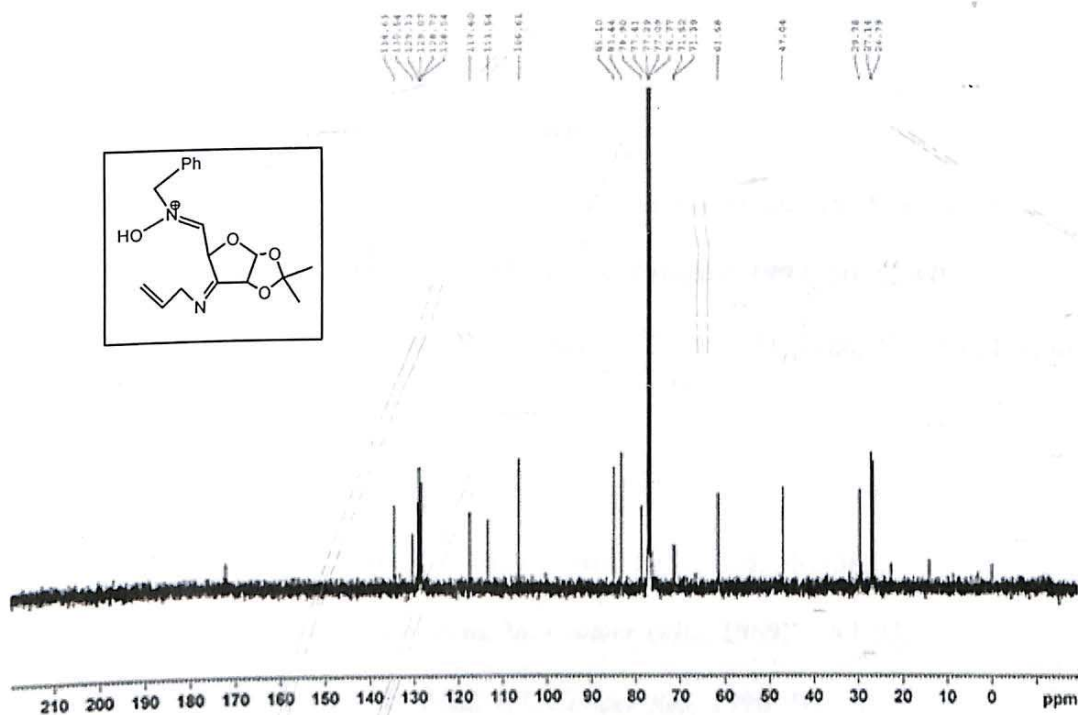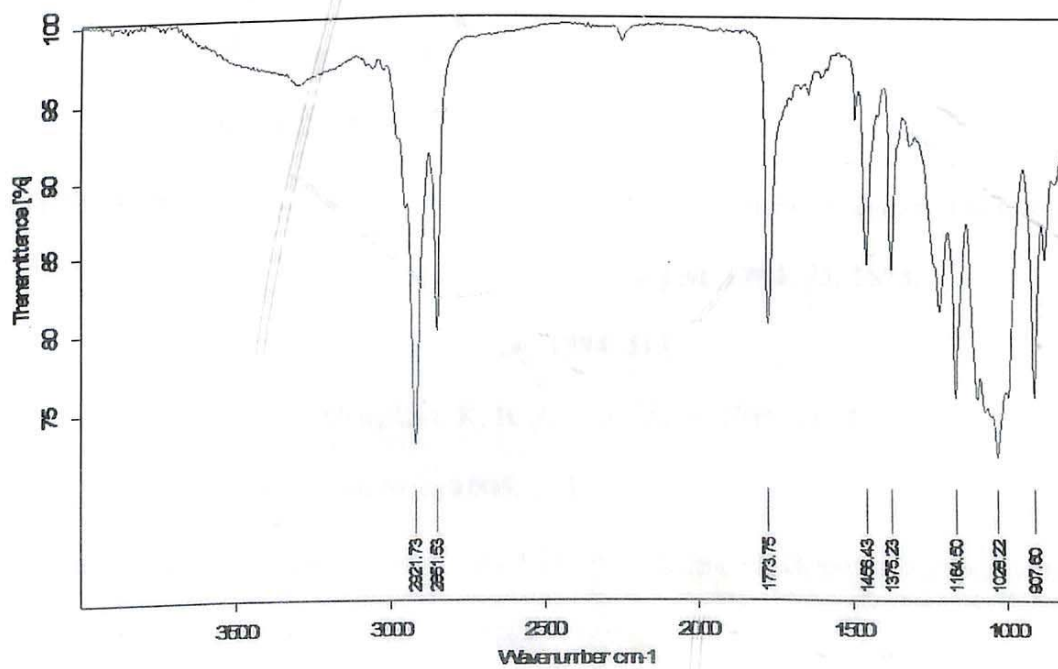

IR spectrum of 62
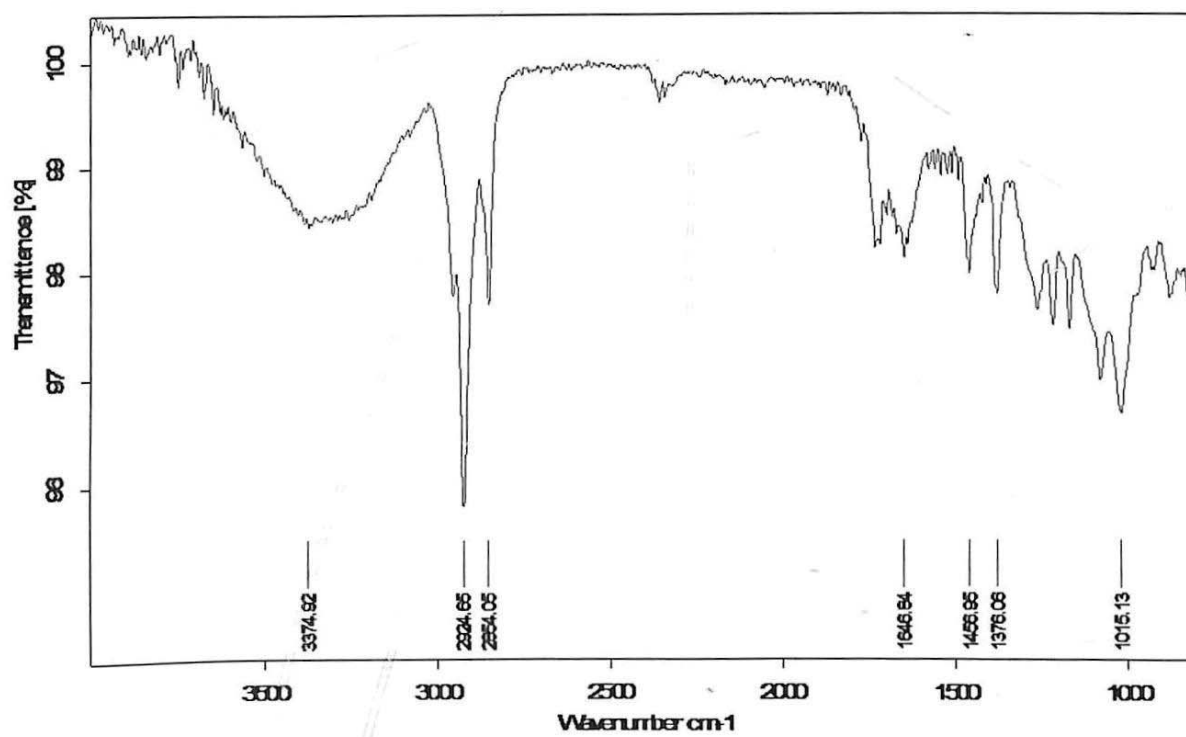
IR spectrum of 63

^{1}H NMR spectrum of 64

^{13}C NMR spectrum of 64

IR spectrum of 64

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